# Strategies and Tactics in Organic Synthesis

## Volume 2

Edited by

THOMAS LINDBERG

With Contributions by

*Dale L. Boger*
*Steven D. Burke*
*Bruce D. Dorsey*
*Thomas A. Engler*
*Bert Fraser-Reid*
*Michael N. Greco*
*Paul Helquist*
*Peter A. Jacobi*
*Michael E. Jung*
*Alan P. Kozikowski*
*Stephen F. Martin*
*William R. Rous*
*Amos B. Smith III*
*Daniel D. Sternbach*
*Ray Tsang*
*David R. Williams*

ACADEMIC PRESS, INC.
Harcourt Brace Jovanovich, Publishers

# STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS

## Volume 2

*Edited by*

Thomas Lindberg
*The NutraSweet Company*
*Mt. Prospect, Illinois*

*With a foreword by*

Sir Derek Barton
*Nobel Laureate in Chemistry*

ACADEMIC PRESS, INC.
*Harcourt Brace Jovanovich, Publishers*
San Diego New York Berkeley Boston
London Sydney Tokyo Toronto

ACADEMIC PRESS, INC.
San Diego, California 92101

*United Kingdom Edition published by*
ACADEMIC PRESS LIMITED
24-28 Oval Road, London NW1 7DX

**Library of Congress Cataloging-in-Publication Data**

(Revised for volume 2)

Strategies and tactics in organic synthesis.

Includes bibliographies and indexes.
1. Chemistry, Organic—Synthesis. I. Lindberg, Thomas, Date.
QD262.S85 1984 547'.2 83-15674
ISBN 0-12-450280-6 (v. 1) (alk. paper)
ISBN 0-12-450281-4 (v. 2) (alk. paper)

PRINTED IN THE UNITED STATES OF AMERICA
88 89 90 91 9 8 7 6 5 4 3 2 1

# CONTRIBUTORS

Numbers in parentheses indicate the pages on which the authors' contributions begin.

DALE BOGER *(2), Department of Chemistry, Purdue University, West Lafayette, Indiana 47907*

STEVEN D. BURKE *(57), Department of Chemistry, University of Wisconsin-Madison, Madison, Wisconsin 53706*

BRUCE D. DORSEY *(415), Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, 19104*

THOMAS A. ENGLER *(91), Department of Chemistry, University of Kansas, Lawrence, Kansas 66045*

BERT FRASER-REID *(123), Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706*

MICHAEL N. GRECO *(263), Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260*

PAUL HELQUIST *(163), Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556*

PETER A. JOCOBI *(191), Department of Chemistry, Wesleyan University, Middletown, Connecticut 06457*

MICHAEL E. JUNG *(221), Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90024*

ALAN P. KOZIKOWSKI *(263), Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260*

STEPHEN F. MARTIN *(291), Department of Chemistry, The University of Texas, Austin, Texas 78712*

WILLIAM R. ROUSH *(323), Department of Chemistry, Indiana University, Bloomington, Indiana 47405*

AMOS B. SMITH III *(370), Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104*

DANIEL D. STERNBACH *(415), Glaxo Research Laboratories, Research Triangle Park, North Carolina 27709*

RAY TSANG *(123), Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706*

DAVID R. WILLIAMS *(439), Department of Chemistry, Indiana University, Bloomington, Indiana 47405*

# FOREWORD

The first volume of *Strategies and Tactics in Organic Synthesis*, edited by Thomas Lindberg, was inspired by an article by Dr. I. Ernest, of the Woodward Institute, on the real story behind the late R. B. Woodward's synthesis of prostaglandin. We learned that Nature did not always do what R. B. Woodward told it to do!

Candor in explaining how one really reached one's synthetic target is a virtue not shared by most academic chemists when they publish in learned journals. There are two reasons for this. One is that space restrictions discourage the presentation of negative, or misleading, experiments. The second is that R. B. Woodward, and many others who have followed, chose to publish as if all the steps in a synthesis had been so carefully planned beforehand that the final product was bound to be obtained—provided, of course, that the effort applied was sufficiently diligent and skillful. At the beginning, before the academic community realized that long-planned Woodwardian syntheses were possible, this attitude was stimulating to the advance of organic chemistry. However, now that so many synthetic chemists are able to emulate the early Woodwardian achievements, one must ask the question, Is it worth the effort? It is worth the effort if new principles emerge—like orbital symmetry control, or new reactions such as Eschenmoser's elegant photochemical cyclization in the second synthesis of vitamin $B_{12}$, or new reagents. But a synthesis, however long and difficult, which uses known principles, known reactions, and known reagents can only contribute to chemistry by accident. This is a costly way to be original. It is much more cost effective to think more and do less.

This second volume of *Strategies and Tactics in Organic Synthesis* continues the same, healthy theme as the first. In showing more frankly

how academic synthetic work is really done, an important service is rendered to all chemists. Our friends in inorganic and physical chemistry can also learn from these articles because the point of view of those outside organic chemistry is that because we pretend that organic synthesis can be planned, it cannot be research anymore and therefore is not worth doing.

An academic chemist who begins a long synthesis soon learns about the importance of a high yield in each step. However, in presenting work later, the yields are not always mentioned and, in particular, the overall yield is not given. It can often be nearly zero. Fortunately, our friends in industry are always conscious of the yield problem. Contact with the real chemical life of industry helps the academic chemist to purge his intellectual system of false pride.

This second volume is as good, or better, than the first. I can strongly recommend it to all who are interested in synthetic chemistry, and especially to those who think that the subject is dull and uninteresting.

DEREK H. R. BARTON
*Texas A&M University*
*College Station, Texas*

# PREFACE

It is indeed a pleasure to be writing the preface to the second volume of *Strategies and Tactics in Organic Synthesis.* The theme of the second volume is the same as that of the first: to give students a "behind-the-scenes" look at organic synthesis from the perspective of outstanding organic chemists.

Students can easily get a mistaken impression of organic synthesis by reading the primary journals—long syntheses of natural products look easy and straightforward. Synthetic dead-ends, blind alleys, and difficulties are rarely mentioned, partly because of space limitations. As both of these volumes illustrate, syntheses rarely turn out the way they were initially planned. In reality, one can plan a reasonable, rational, "paper" synthesis only to go into the lab and discover that the reactions don't want to work the way they should. One then starts changing variables—solvent, temperature, pressure, catalysts—until the reaction is made to work. If the reaction refuses to work, the synthetic route has to be modified. Perseverance is certainly a quality that organic chemists should have.

I owe a special debt of gratitude to the contributors for making this book possible. It is my special pleasure to welcome Amos Smith back for an encore. I hope that readers find the second volume as interesting and informative as the first.

THOMAS LINDBERG

*Chapter 1*

# DIELS–ALDER REACTIONS OF HETEROCYCLIC AZADIENES: DEVELOPMENT OF A STRATEGY FOR THE TOTAL SYNTHESIS OF STREPTONIGRIN, LAVENDAMYCIN, AND SYNTHETIC QUINOLINE-5,8-QUINONES

*Dale L. Boger*

*Department of Chemistry*
*Purdue University*
*West Lafayette, Indiana*



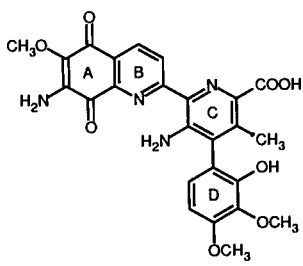


STRATEGIES AND TACTICS
IN ORGANIC SYNTHESIS, VOL. 2

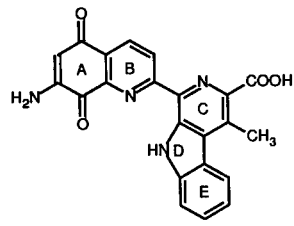
## I. Introduction

At the onset of much of our work we have elected to select synthetic targets which possess a significant or contemporary synthetic challenge and which possess biological properties which merit further investigation. At the very least we hope to develop or apply new synthetic methodology that is especially suited for application in the total synthesis of the structure under consideration and, concurrent with these efforts, to design and prepare structurally related compounds which would permit us to address or define the structural characteristics of the naturally occurring material that are responsible for and/or potentiates the observed biological properties. These latter considerations are facilitated if we or others have previously studied or speculated on the agent's *chemical* mechanism of action that is responsible for the observed or expressed biological effects.

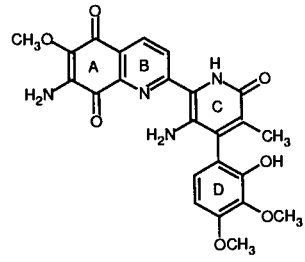
Streptonigrin (**1**),[1] lavendamycin (**2**),[2] and streptonigrone (**3**)[3] are three structurally and biosynthetically related antitumor antibiotics isolated from *Streptomyces flocculus, Streptomyces lavendulae*, and an unidentified *Streptomyces* species (IA-CAS isolate No. 114), respectively. Each possesses a characteristic, highly functionalized 7-aminoquinoline-5,8-quinone AB ring system and a fully substituted pyridyl C ring central to its structure. Consequently, the effective assemblage of the pentasubstituted pyridyl C ring of **1–3** coupled with a divergent approach to the introduction of the streptonigrin/lavendamycin quinoline-5,8-quinone AB ring systems was formulated initially as the key to the total synthesis of members of this class of naturally




1 Streptonigrin




2 Lavendamycin




3 Streptonigrone

occurring antitumor antibiotics. Based largely on the work in progress in our laboratories as well as information available from the extensive investigations of Professors Sauer[4] and Neunhoeffer,[4] our approach to the construction of the pentasubstituted pyridyl component of the naturally occurring materials was expected to be addressed with the implementation of inverse electron demand Diels–Alder reactions of electron-deficient heterocyclic azadienes.

Streptonigrin was first identified and characterized in 1959,[1a] its structure was correctly determined in 1963[1b] using a combination of classical chemical degradative studies coupled with the application of the then emerging spectroscopic techniques of infrared, $^1$H NMR, and mass spectrometry, and subsequently was confirmed in 1975 with a single-crystal X-ray structure determination.[1c] Since the initial structure determination, streptonigrin has been the subject of extensive synthetic, biosynthetic, and biological investigations which have resulted from a continued interest in its confirmed antimicrobial, cytotoxic, and antitumor properties.[5] In no small part, the synthetic challenges posed by the streptonigrin structure, which include its concentrated array of reactive functionality and the presence of stable CD biaryl atropisomers,[1e] investigations on the chemical mechanism by which streptonigrin expresses its biological effects,[4,6] efforts to define the essential structural features required for observation of this activity,[4–7] and revealing biosynthetic investigations account for the continued interest in this structure.[4,8] Information and work derived from the completed total syntheses[9,10] of streptonigrin [Weinreb *et al.* (1980) and Kende *et al.* (1981); cited in Chart I] and from the extensive preliminary investigations[4,11,12] of Cheng, Rao, Lown, Kametani, Martin,[13] Kende, Weinreb, and Cushman contributed substantially in the planning and execution of our own efforts.[14]

The structure identification of lavendamycin (**2**), which was disclosed in 1981,[2] rested exclusively on extensive spectroscopic studies on a limited supply of naturally occurring material which were guided by biosynthetic considerations. It is a tribute to the advances in modern spectroscopic techniques that lavendamycin was initially and correctly identified with the available naturally occurring material using principally $^1$H/$^{13}$C NMR information, ultraviolet and infrared spectroscopy, and high-resolution mass spectral exact mass determinations, guided correctly by prior biosynthetic postulates for intermediates potentially involved in the biosynthesis of streptonigrin.[8,15] Thus, in contrast to the earlier structure elucidation of streptonigrin (**1**), classical chemical degradative studies played little apparent role in the structure identification of lavendamycin. Unambiguous confirmation of the proposed lavendamycin structure was accomplished by subsequent total syntheses.[16,17] Most notably, Kende's approach to lavendamycin, which has been concurrently pursued by the Hibino and Rao

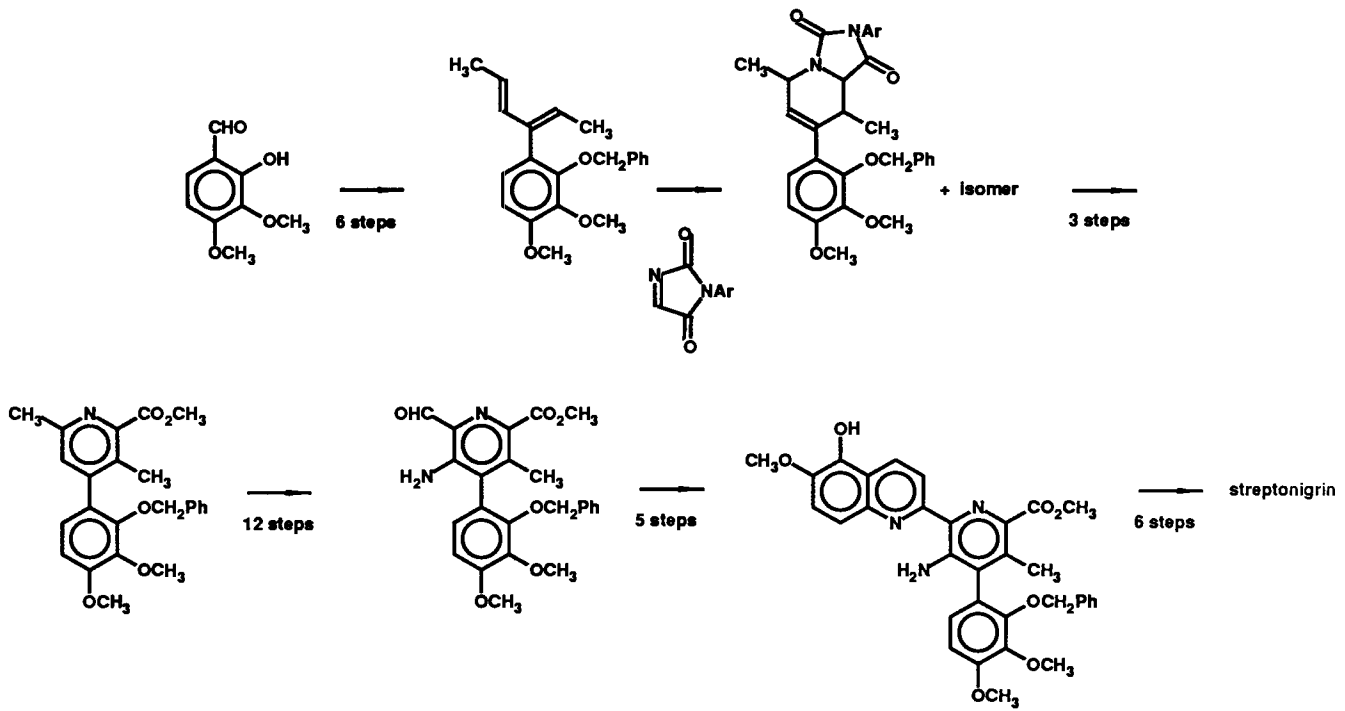



CHART 1. Summary of streptonigrin total syntheses. Top, Ref. 9; Bottom, Ref. 10.

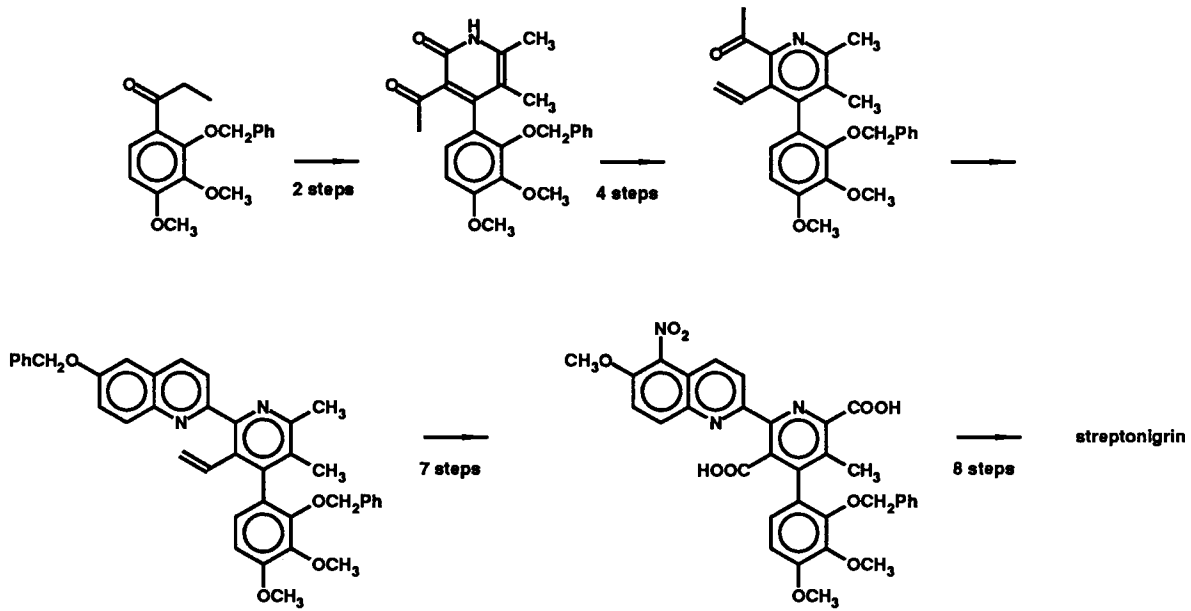


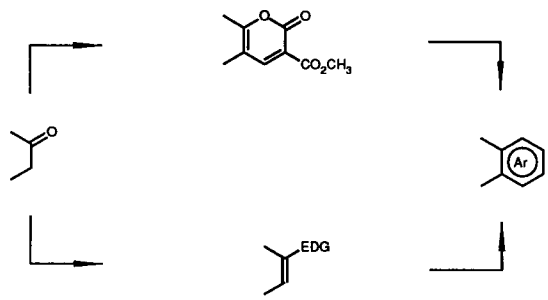

CHART 1 (*continued*).

groups, is based on a Bischler–Napieralski cyclodehydration and subsequent *in situ* dehydrogenation of amides derived from β-methyltryptophan en route to the construction of the β-carboline unit of lavendamycin in a process mimicking the transformations involved in the biosynthesis of lavendamycin.[16] A recent comparative study of the antimicrobial, cytotoxic, and antitumor properties of lavendamycin and streptonigrin has been conducted.[18]

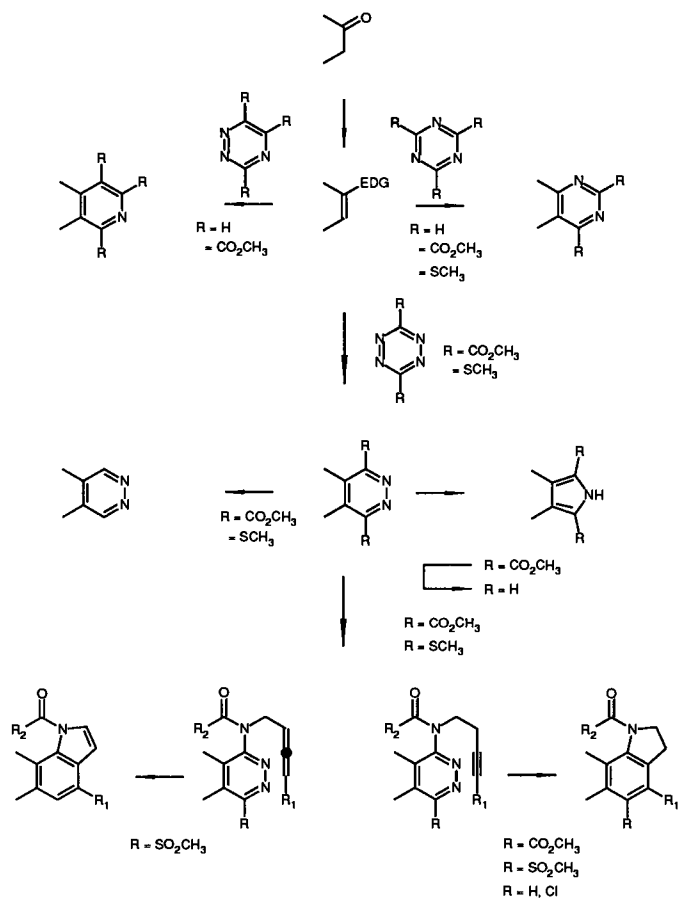
The structure identification of streptonigrone (**3**), which was disclosed in 1985,[3] was based exclusively on extensive spectroscopic studies including high-resolution chemical ionization mass spectrometry for exact mass determination. Streptonigrone was shown to possess the 2-pyridone structure **3** identical with that of streptonigrin (**1**), lacking only the C-2′ carboxylate. Unambiguous confirmation of the streptonigrone structural assignment by total synthesis or single-crystal X-ray analysis remains to be completed. Importantly, streptonigrone lacks the potent antimicrobial, cytotoxic, and antitumor properties associated with streptonigrin, and consequently this recent observation underscores the importance previously attributed to the streptonigrin C-2′ carboxylate for observable biological activity.[3,4]

## II. Methodology Development. Inverse Electron Demand Diels–Alder Reactions of Electron-Deficient Azadienes: 1,2,4-Triazines, 1,3,5-Triazines, 1,2,4,5-Tetrazines, 1,2-Diazines

Preceding and concurrent with our efforts on the total syntheses of streptonigrin, lavendamycin, streptonigrone, and structurally related synthetic quinoline-5,8-quinones we have been engaged in efforts designed to investigate and develop the synthetic utility of the inverse electron demand Diel–Alder reactions of electron-deficient heterocyclic azadienes. A basic premise of this work has been the development and implementation of methods which would permit the divergent introduction of aromatic and heteroaromatic systems onto preexisting aliphatic substrates, thereby facilitating the preparation of a series of structurally similar agents, Eq. (1). In addition, we chose to adopt the use of aliphatic substrates bearing a carbonyl group, where the carbonyl group would serve as the necessary functionality to permit or direct the aromatic introduction. For this purpose there are two potential approaches by which the inverse electron demand Diels–Alder reaction may be implemented for such an aryl annulation. The first, and perhaps most evident, involves conversion of the carbonyl group into an electron-rich olefin followed by its participation in a [4 + 2] cycloaddition reaction with an electron-deficient diene in a process suitable for aryl introduction. A second, and perhaps less obvious, approach relies on the conversion of the substrate bearing a carbonyl group into a substrate bearing



(1)

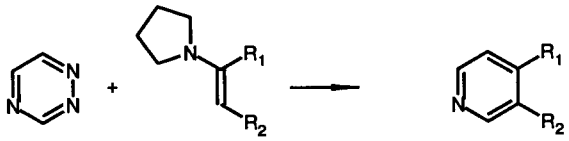


an electron-deficient diene and its subsequent participation in a [4 + 2] cycloaddition reaction with an electron-rich dienophile in a process suitable for the aryl introduction. The former process has proved to be particularly well suited for the introduction of heteroaromatic systems employing electron-rich olefins (dienophiles) typically derived from ketones, e.g, enol ethers, enamines, in inverse electron demand Diels–Alder reactions with electron-deficient heteroaromatic azadienes[4] including 1,2,4-triazines,[19a] 1,3,5-triazine,[19b] 1,2,4,5-tetrazines,[19c] and electron-deficient 1,2-diazines.[19d] Consequently, the use of a single aliphatic substrate bearing a carbonyl group permits the preparation of a complete range of heteroaromatic systems by the implementation of a series of complementary inverse electron demand heteroaromatic azadiene Diels–Alder reactions, Eq. (1).

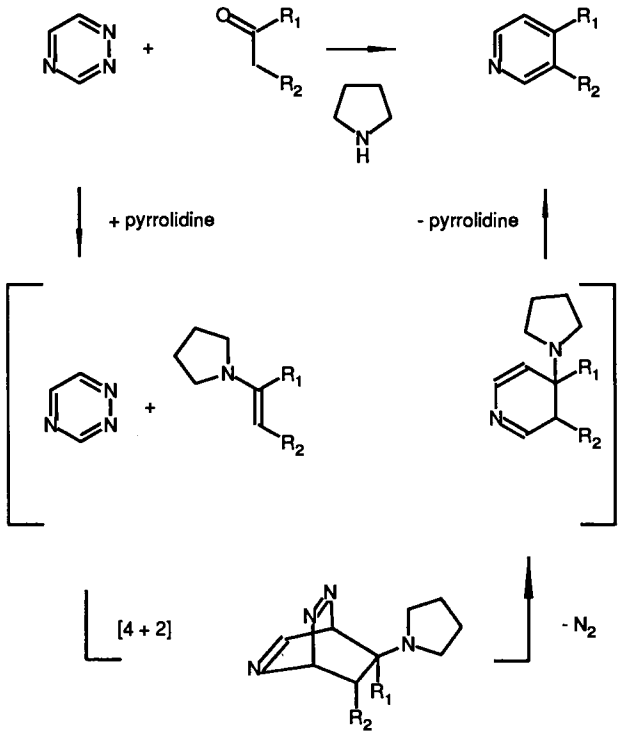
Of importance to the investigations on the total synthesis of streptonigrin and lavendamycin, pyrrolidine or morpholino enamines derived from ketones participate in regioselective [4 + 2] cycloaddition reactions with 1,2,4-triazine to provide 3,4-disubstituted pyridines. Cycloaddition occurs exclusively across C-3/C-6 of the 1,2,4-triazine nucleus and the nucleophilic carbon of the electron-rich dienophile adds exclusively to C-3 of the 1,2,4-triazine, Eq. (2).[19a] The reduction of this process to a catalytic Diels–Alder reaction with the *in situ* generation of the pyrrolidine enamine does not alter these observations, Eq. (2).[19a] In many instances of the Diels–Alder cycloaddition reactions of electron-deficient heteroaromatic azadienes, including the [4 + 2] cycloaddition of 1,2,4-triazines with pyrrolidine (morpholine) enamines, the slow or rate-determining step of the reaction sequence is not the initial [4 + 2] cycloaddition reaction but the final aromatization step involving the loss of pyrrolidine (morpholine).

## III. Formal Total Synthesis of Streptonigrin

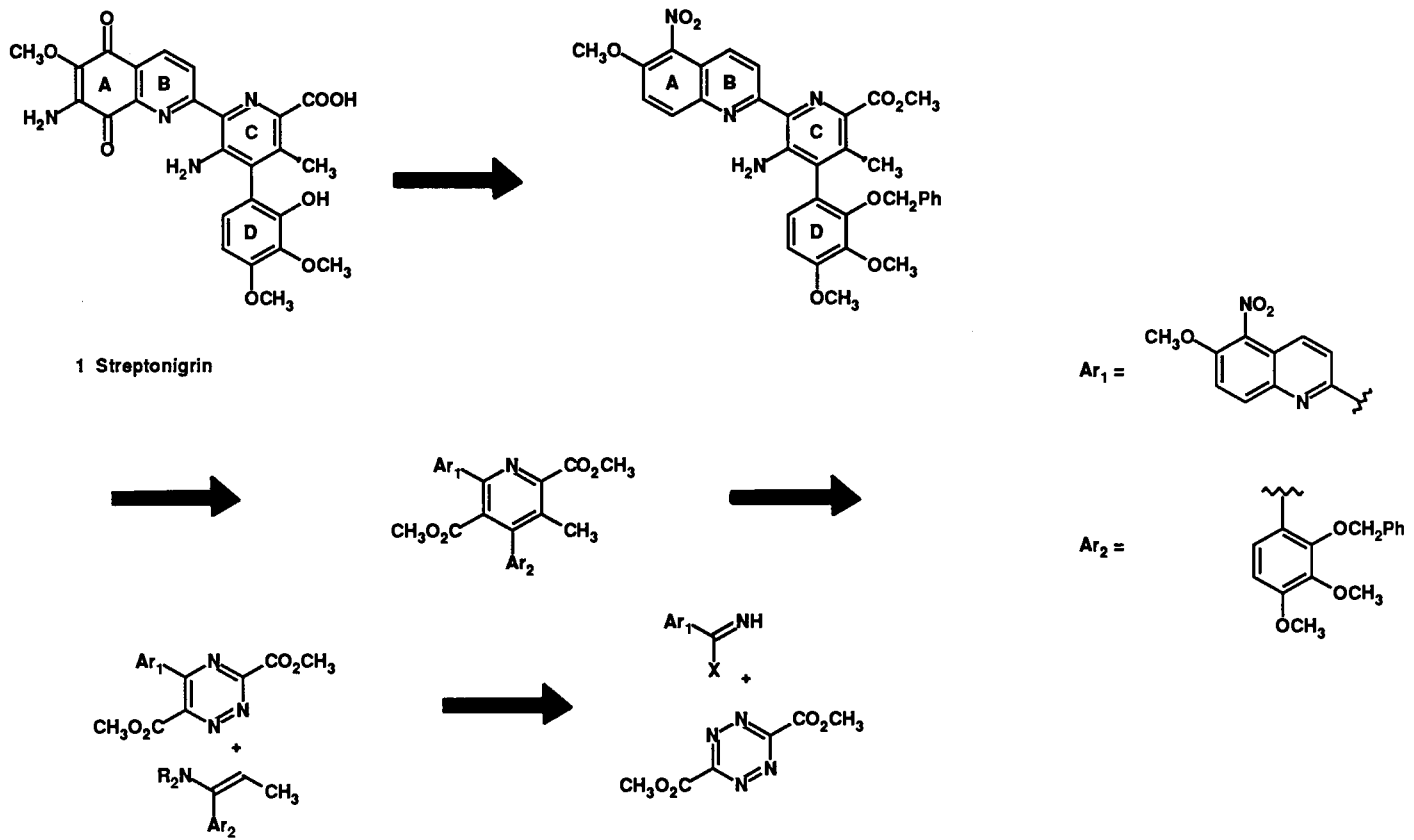
Our initial formulated approach to the total synthesis of streptonigrin is summarized in Scheme 1 and was based on the potential of implementing two sequential heterocyclic azadiene inverse electron demand Diels–Alder reactions for the preparation of the pentasubstituted pyridyl C ring of streptonigrin *and* for the assemblage of the carbon framework of streptonigrin. The demonstrated ability of the 6-methoxy-5-nitro-2-quinolyl system to serve as an appropriate precursor to the 6-methoxy-7-aminoquinoline-5,8-quinone streptonigrin AB ring system[10] and the ability of a C-5′ carboxylate to serve as potential functionality for the streptonigrin C-5′ pyridylamine introduction, Chart I,[10] simplified the planning and implementation of our



(2)



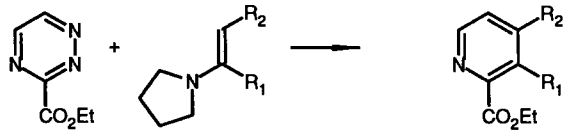

approach. Moreover, this convergent approach to the total synthesis of streptonigrin, in which the carbon framework of the natural product is established in two sequential steps, appeared especially attractive since structural analogs possessing modified AB and/or D ring systems conceivably could be assembled without the concerns which generally accompany a linear synthesis.




SCHEME 1. Initial strategy for the total synthesis of streptonigrin (**1**).

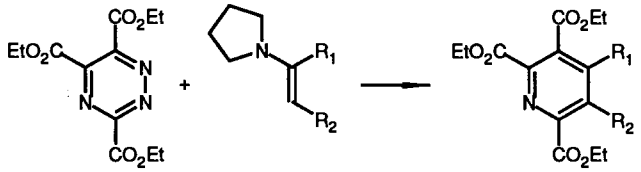
## A. Streptonigrin Biaryl CD Ring Construction: Reactivity and Regiocontrol of 1,2,4-Triazine Inverse Electron Demand Diels–Alder Reactions

In order to test the feasibility of this approach to streptonigrin we first investigated the potential of the enamine/1,2,4-triazine Diels–Alder reaction for application in the construction of the streptonigrin biaryl CD ring system. Of immediate concern was the effect the substitution of the 1,2,4-triazine nucleus with electron-withdrawing groups would have on the rate and regiocontrol of the proposed [4 + 2] cycloaddition. For this reason we took the opportunity to investigate the viability, rate, and regioselectivity of the [4 + 2] cycloaddition reactions of the readily available 3-ethoxycarbonyl-1,2,4-triazine [**4**, Eq. (3)] and 3,5,6-triethoxycarbonyl-1,2,4-triazine[19f] [**5**, Eq. (4)] with electron-rich olefins. Both the position and number of




(3)

4




(4)

5

electron-withdrawing substituents present on the 1,2,4-triazine nucleus were found to control the reactivity as well as the observed regioselectivity of the Diels–Alder reaction without altering the observed mode of cycloaddition. Cycloaddition of pyrrolidine enamines with 3-ethoxycarbonyl-1,2,4-triazine (**4**) was found to proceed across C-3/C-6 of the 1,2,4-triazine nucleus with the nucleophilic carbon of the electron-rich dienophile attaching to C-6, Eq. (3). Thus, the mode of cycloaddition of **4** was found to be identical to that of the parent 1,2,4-triazine but proceeded with the opposite regioselectivity. Moreover, the overall reactivity of **4** was found to be diminished relative to that of 1,2,4-triazine despite the additional electron-withdrawing character of the ethoxycarbonyl group. In contrast, 3,5,6-triethoxycarbonyl-1,2,4-triazine (**5**) was found to participate in rapid, often exothermic, [4 + 2] cycloaddition reactions with enamines with addition

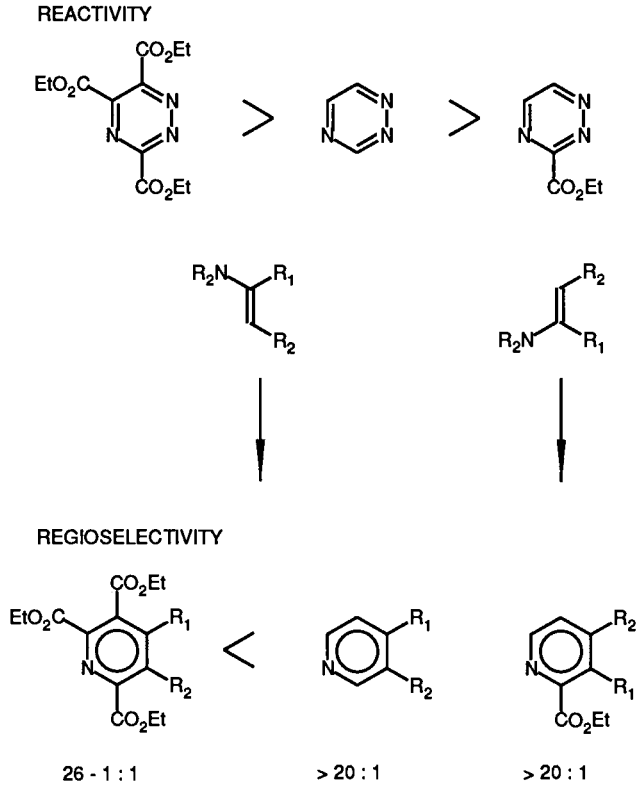



FIG. 1

occurring across C-3/C-6 of the 1,2,4-triazine nucleus and with the nucleophilic carbon of the electron-rich olefin preferring attachment to C-3. This is qualitatively the same as the behavior exhibited by the parent 1,2,4-triazine, Eq. (2), with the exception that the overall reactivity has been enhanced and the extent of the observed regioselectivity was occasionally diminished. For example, the trimethylsilyl enol ether derived from acetophenone was found to be sufficiently reactive to participate in a [4 + 2] cycloaddition with 3,5,6-triethoxycarbonyl-1,2,4-triazine (**5**) but failed to react with 1,2,4-triazine itself.[11] Figure 1 summarizes our observations on the 1,2,4-triazine substituent effects on the rate and regioselectivity of their inverse electron demand [4 + 2] cycloaddition reactions.[11,19]

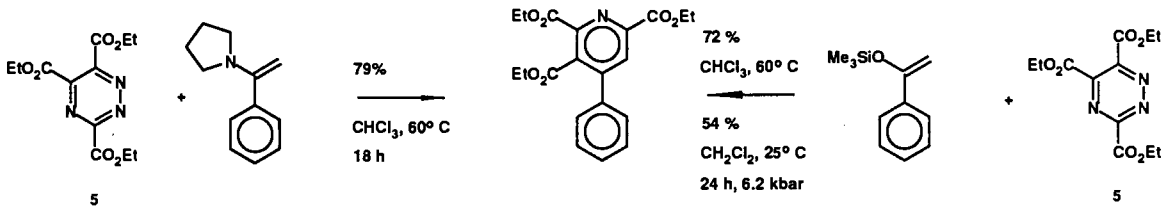
Of immediate concern was the viability of this approach for the construction of the CD biaryl ring system found in streptonigrin. Consequently, the reaction of the electron-rich olefins derived from acetophenone, propiophenone, and 2-benzyloxy-3,4-dimethoxypropiophenone with 3,5,6-

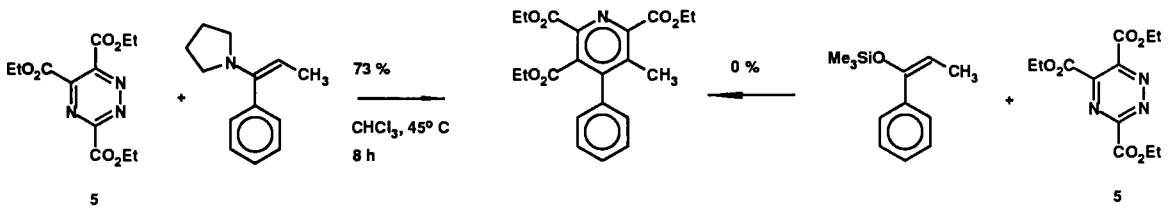
triethoxycarbonyl-1,2,4-triazine (**5**) was investigated and found to provide the desired 4-arylpyridines, Eq. (5). In the case of pyrrolidine enamines, the initial cycloaddition was exothermic and was accompanied by the initial evolution of nitrogen. A final aromatization step involving the loss of pyrrolidine account for the required reaction conditions detailed in Eq. (5). With these observations, the viability of the approach to the preparation of the streptonigrin CD biaryl ring system utilizing an enamine/1,2,4-triazine [4 + 2] cycloaddition reaction was firmly established; cf. **6**.[14a].

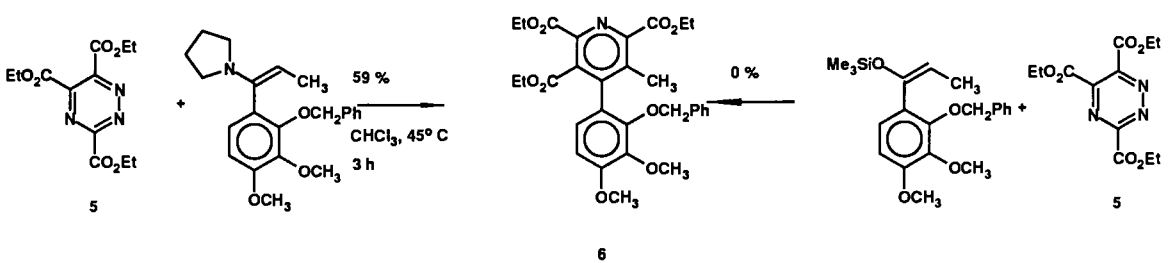
In many instances the initial reaction of enamines with substituted 1,2,4-triazines, especially 3,5,6-triethoxycarbonyl-1,2,4-triazine (**5**), was found to occur at a satisfactory rate at room temperature and was accompanied by the evolution of nitrogen. The slow or rate-determining step for the formation of the pyridine products was the final aromatization step involving the loss of secondary amine. In instances when the initial [4 + 2] cycloaddition was slow, efforts to promote a low-temperature [4 + 2] cycloaddition reaction of enamines with substituted 1,2,4-triazines by the addition of conventional Lewis acids were unsuccessful. In contrast, in the instances when the [4 + 2] cycloaddition did not proceed at a satisfactory rate, the use of pressure-promoted Diels–Alder reaction conditions[20] has proven useful in increasing the rate of cycloaddition. Thus, many sensitive, electron-rich olefins can be induced to participate in [4 + 2] cycloaddition reactions with unreactive 1,2,4-triazines at mild reaction temperatures which ensure their stability (6.2–14 kbar, 25°C), Eq. (5).[11] This proved to be a key feature of the 1,2,4-triazine Diels–Alder reaction implemented in the formal total synthesis of streptonigrin.

### B. Streptonigrin ABC Ring Construction: 1,2,4-Triazine Preparation via the Inverse Electron Demand Diels–Alder Reaction of 1,2,4,5-Tetrazines with C=N Dienophiles

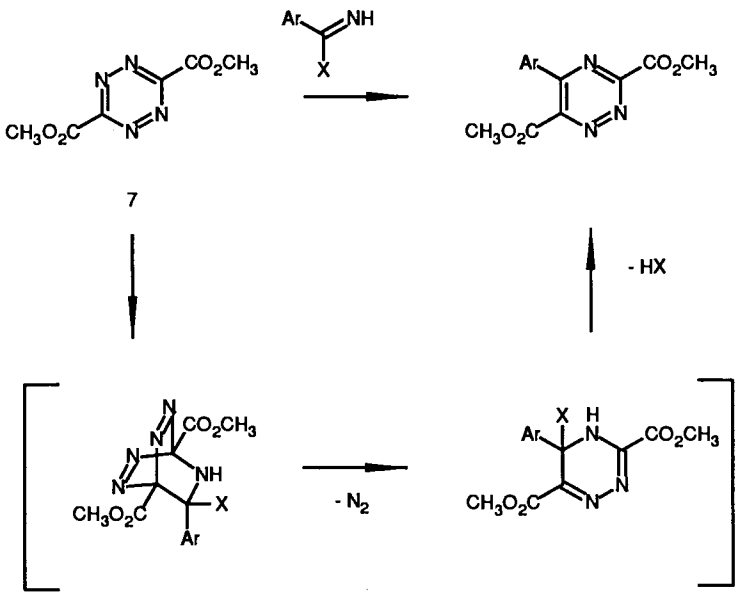
Assured that the [4 + 2] cycloaddition reaction of an appropriately substituted 1,2,4-triazine with an enamine derivative of 2-benzyloxy-3-4-dimethoxypropiophenone could serve as an effective approach to the construction of the streptonigrin biaryl CD ring system, the potential use of a second inverse electron demand Diels–Alder reaction for the preparation of the required 1,2,4-triazine was investigated, Eq. (6). Studies of the thermal cycloaddition reactions of substituted 1,2,4,5-tetrazines with heterodienophiles have been detailed[4] and short accounts of their reactions with aryl imidates and amidines[21] suggested the potential of this approach for the preparation of 1,2,4-triazines. However, the successful examples of such reactions were limited and had been reported concurrently with an equal number of unsuccessful attempts. Moreover, in the instances where the desired cycloaddition had been observed, competing and/or subsequent


79%
CHCl3, 60° C
18 h
72 %
CHCl3, 60° C
54 %
CH2Cl2, 25° C
24 h, 6.2 kbar
5
5


73 %
CHCl3, 45° C
8 h
0 %
5
5


59 %
CHCl3, 45° C
3 h
0 %
5
6
5

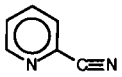
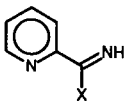
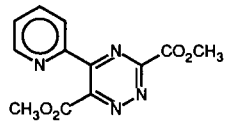
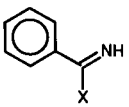
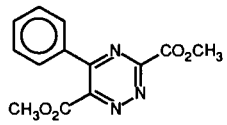
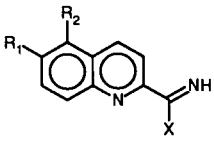
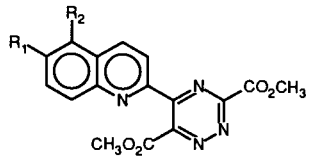
cycloaddition reactions of the product 1,2,4-triazines had been observed. Table I details our investigations of the cycloaddition reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**7**)[19g] with nucleophilic dienophiles possessing a carbon–nitrogen double bond, which defined the importance of the nucleophilic character of the dienophile as well as a previously unappreciated importance of the leaving group ability of X, Eq. (6).[14b]




Our initial efforts employing aryl nitriles and aryl amidines were unsuccessful. 2-Cyanopyridine failed to react with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**7**) and no identifiable products were isolated from the reaction of **7** with aryl amidines despite an initial exothermic reaction which was accompanied by the evolution of nitrogen. Aryl imidates did provide the desired 1,2,4-triazine products,[21] albeit in modest yields. In contrast, aryl *S*-methyl thioimidates provided the desired 1,2,4-triazine cycloaddition products in dependable, reproducible yields under mild, controllable reaction conditions. In no instance was there evidence of product 1,2,4-triazine participating or competing with **7** in subsequent Diels–Alder reactions with unreacted *S*-methyl thioimidate. Consequently, the success of the [4 + 2] cycloaddition reaction of the aryl *S*-methyl thioimidates with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate can be attributed to the optimal combination of the nucleophilic character of the C=N dienophile (amidine, *N,N*-dialkylamidine > *S*-methyl thioimidate ≅ ethyl imidate) and the leaving group ability of X ($-SCH_3 > -OEt > -NH_2, -NR_2$), Eq. (6).

TABLE I

DIELS–ALDER REACTION OF DIMETHYL 1,2,4,5-TETRAZINE-3,6-DICARBOXYLATE (**7**) WITH C=N HETERODIENOPHILES

| Dienophile | Conditions: Temperature, °C (time, h)[a] | Product | % yield |
|---|---|---|---|
|  | 80–100 (15–42) | | —[b] |
|  | |  | |
| X = $SCH_3$ | 80 (20) | | 68 |
| = OEt | 80 (8–12) | | 37 |
| = $NH_2$ | 25 (5) | | 0[c] |
| = $NEt_2$ | 25–50 (25) | | 0 |
|  | |  | |
| X = $SCH_3$ | 80 (24) | | 64 |
| = OEt | 60 (10) | | 27 |
| = $NH_2$ | 25 (1) | | 0[c] |
|  | |  | |
| $R^1 = R^2 = H$ | 80 (4) | | 70 |
| X = $SCH_3$ | 80 (20) | | 33 |
| = OEt | | | |
| $R^1 = OCH_3$ $R^2 = H$ | | | |
| X = $SCH_3$ | 80 (4) | | 78 |
| $R^1 = OCH_3$ $R^2 = NO_2$ | | | |
| X = $SCH_3$ | 80 (20–24) | | 82[d] |

[a] All reactions were run in dry dioxane under an atmosphere of nitrogen (0.1–0.3 *M* in substrate) in the presence of 2.0 equivalents **7** unless otherwise noted.

[b] No detectable reaction.

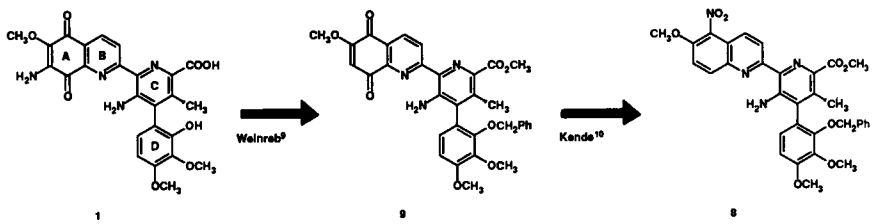
[c] Rapid, exothermic reaction accompanied by the evolution of nitrogen; no detectable 1,2,4-triazine product.

[d] 1.3 equivalents of **7** was employed.

## C. Formal Total Synthesis of Streptonigrin: Unexpected Observations on the Reactivity and Regioselectivity of 1,2,4-Triazine Inverse Electron Demand Diels–Alder Reactions

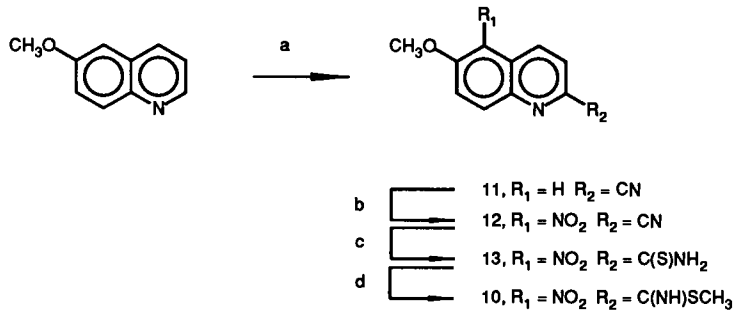
Since Kende had demonstrated that the 5-nitro-6-methoxy-2-quinolyl unit found in **8** serves as a useful precursor to the 6-methoxyquinoline-5,8-quinone unit of **9**, a key intermediate in Weinreb's total synthesis of streptonigrin, Eq. (7), we selected 5-nitro-6-methoxy-2-quinolyl *S*-methyl thioimidate **10** as the required starting dienophile for our synthetic efforts.

(7)

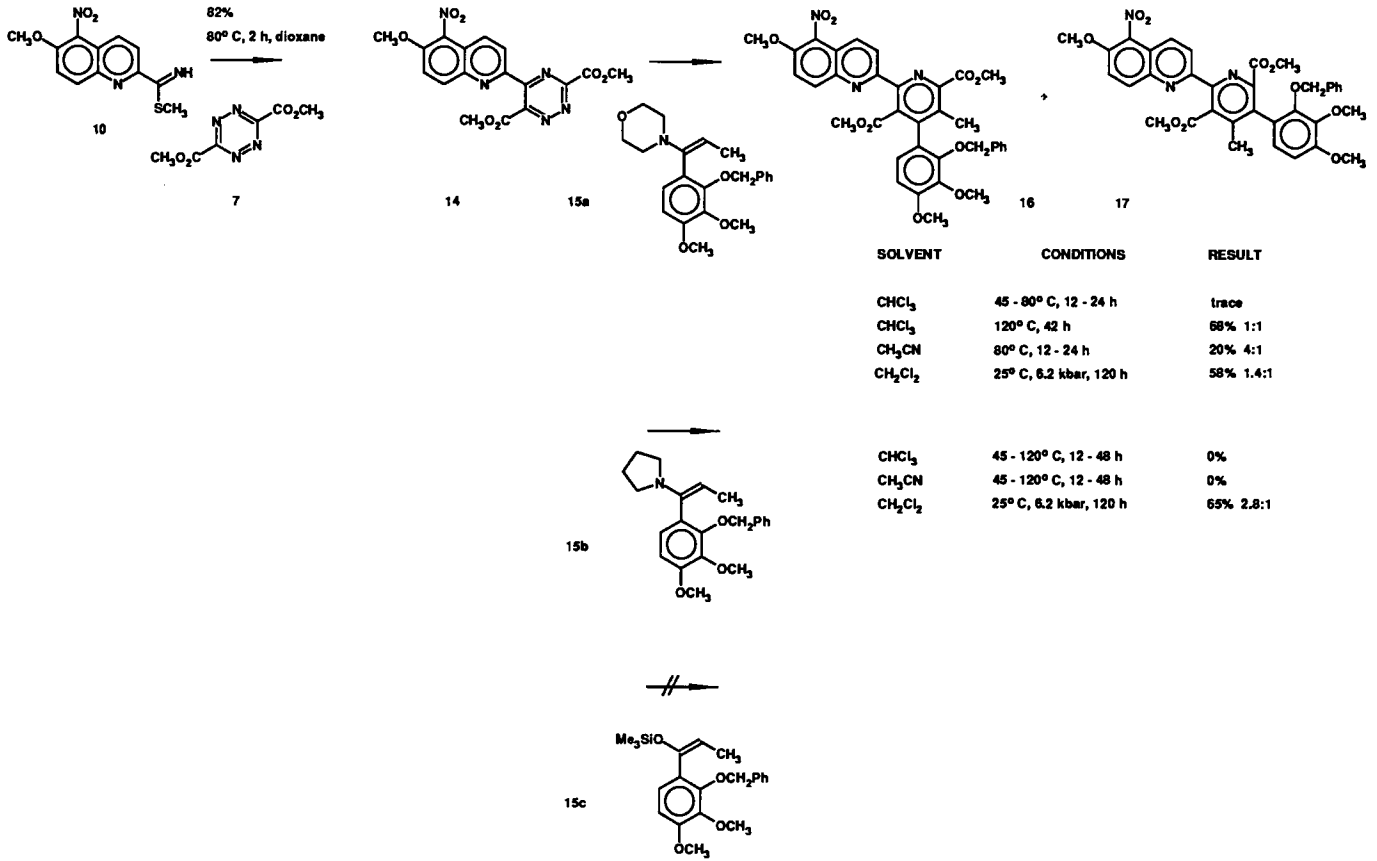



1 9 8

The *S*-methyl thioimidate **10** was prepared in four steps from commercially available 6-methoxyquinoline as detailed in Scheme 2. Treatment of 6-methoxyquinoline with *p*-toluenesulfonyl chloride–potassium cyanide in a methylene chloride–water two-phase reaction mixture for an extended reaction period afforded 2-cyano-6-methoxyquinoline (**11**) directly without the isolation of the Reissert intermediate. The generality of this method for the direct one-step preparation of 2-cyanoquinolines as well as its extension to the preparation of 1-cyanoisoquinolines was subsequently investigated,[22a] and it proved equally useful in the generation of intermediates utilized in our




Scheme 2. Preparation of starting material for the total synthesis of streptonigrin. (a) 1.6 equivalents of *p*-TsCl, 3.0 equivalents of KCN, $CH_2Cl_2$–$H_2O$, 25°C, 120 hours, 81%. (b) 1.5 equivalents of 70% $HNO_3$, $H_2SO_4$, 25°C, 82%. (c) $H_2S$, catalytic $Et_2NH$, dioxane, 0–25°C, 24 hours, 75–88%. (d) 2–4 equivalents of $CH_3I$, $CH_3CN$, 80°C, 2 hours; saturated aqueous $NaHCO_3$–$CHCl_3$, 25°C, 15 min, 56%.




SCHEME 3. Construction of the carbon skeleton of streptonigrin.

concurrent efforts on the divergent total syntheses of the azafluoranthene alkaloids rufescine and imeluteine.[22b] Careful nitration of **11** (<25°C) provided **12** cleanly. If the nitration of **11** was carried out at temperatures higher than 25°C, hydration of the nitrile accompanied the C-5 nitration. Conversion of the nitrile to the *S*-methyl thioimidate **10** via the thioamide **13** completed the preparation of our starting material.

Treatment of *S*-methyl thioimidate **10** with dimethyl 1,2,4,5-tetrazine-3-6-dicarboxylate (**7**) provided the dimethyl 5-quinolyl 1,2,4-triazine-3-6-dicarboxylate **14** in excellent yield (82%), Scheme 3. After considerable experimentation, it was found that treatment of **14** with the morpholino enamine of 2-benzyloxy-3,4-dimethoxypropiophenone **15a** provided a regioisomeric mixture of [4 + 2] adducts **16** and **17**, of which the preferred cycloadduct **16** proved to contain the carbon framework of streptonigrin, Scheme 3.

Table II details representative results of our full investigations to introduce the streptonigrin biaryl CD ring system via the participation of 1,2,4-triazine **14** in a [4 + 2] cycloaddition reaction. In agreement with our earlier observations, the morpholino enamine **15a** cycloadds exclusively across C-3/C-6 of the 1,2,4-triazine nucleus of **14**. However, an unanticipated decreased reactivity of **14** toward cycloaddition relative to 3,5,6-triethoxycarbonyl-1,2,4-triazine (**5**) and the thermal instability of the morpholino enamine **15a** required a select set of conditions for observable cycloaddition. As the results detailed in Table II illustrate, the nucleophilic

TABLE II

[4 + 2] CYCLOADDITION REACTIONS OF 1,2,4-TRIAZINE **14** WITH **15a–c**: PREPARATION OF THE KEY STREPTONIGRIN INTERMEDIATE **16**

| Electron-rich olefin (equiv) | Conditions | % yield (**16**:**17**) | |
|---|---|---|---|
| **15a** (4.0) | $CH_3CN$, 80°C, 12–24 h | 15–26 | (4:1) |
| (2.0) | $CH_3CN$, 120°C, 16 h | 30 | (1:1) |
| (2.0–6.0) | $CHCl_3$, 45–80°C, 12–48 h | Trace | (—) |
| (2.0) | $CHCl_3$, 120°C, 16 h | 30 | (1:1) |
| (4.0) | $CHCl_3$, 120°C, 42 h | 68 | (1:1) |
| (4.0) | $CH_2Cl_2$, 25°C, 120 h, 6.2 kbar | 58 | (1.4:1) |
| (4.0) | $CH_3CN$, 25°C, 96 h, 6.2 kbar | 0 | |
| **15b** (2.0–4.0) | $CHCl_3$, 60–120°C, 12–48 h | 0 | |
| (2.0–4.0) | $CH_3CN$, 60–120°C, 12–48 h | 0 | |
| (2.0) | $CH_2Cl_2$, 25°C, 120 h, 6.2 kbar | 37 | (2.8:1) |
| (4.0) | $CH_2Cl_2$, 25°C, 120 h, 6.2 kbar | 65 | (2.8:1) |
| **15c** (2.0–4.0) | $CHCl_3$, 60–120°C, 12–48 h | 0 | |
| (2.0–4.0) | $CH_3CN$, 60–120°C, 12–48 h | 0 | |
| (2.0–4.0) | $CH_2Cl_2$, 25°C, 120 h, 6.2 kbar | 0 | |

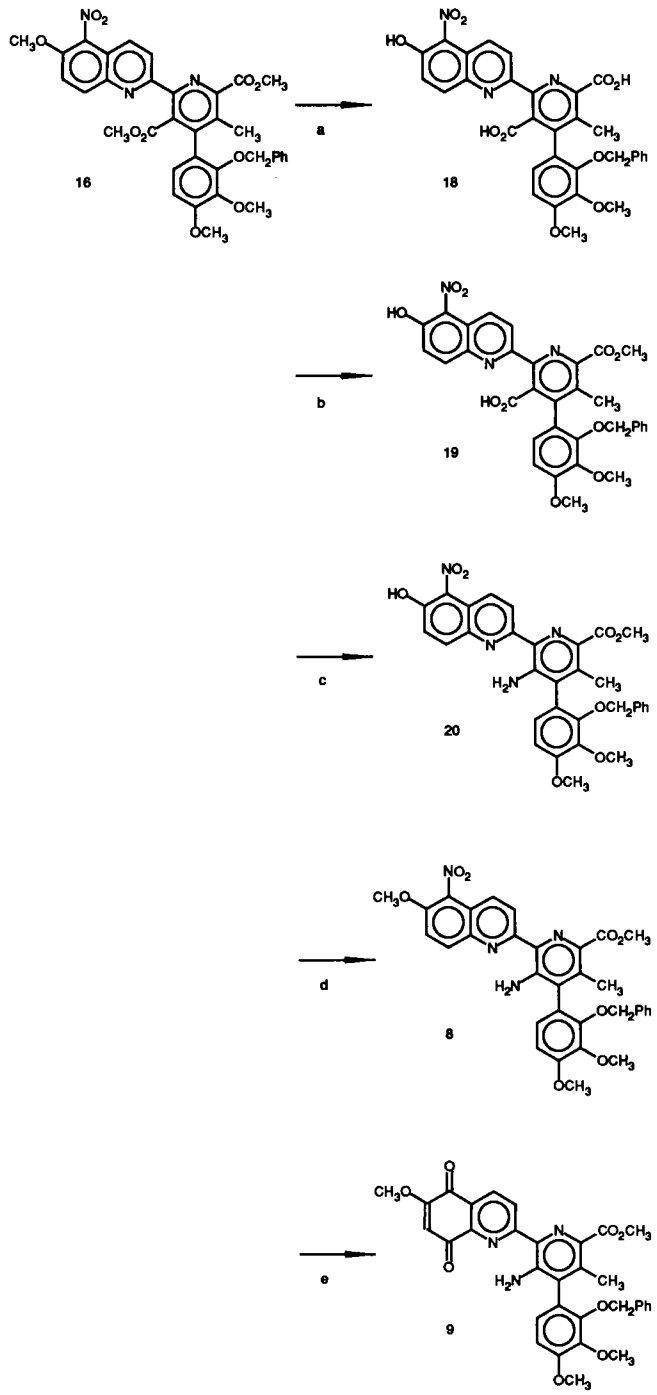
carbon of the electron-rich dienophile preferred attachment to C-3 of 1,2,4-triazine **14**, results consistent with the studies of 3,5,6-triethoxycarbonyl-1,2,4-triazine [**5**, Eq. (4)], but the vigorous conditions required for complete reaction eliminated the observed regioselectivity. Thus, the choice of reaction conditions was found to determine the relative amount of **17** produced in the cycloaddition reaction. While we do not have a conclusive argument which explains these observations, it is not unlikely that the 5-(6-methoxy-5-nitro-2-quinolyl) group of the 1,2,4-triazine **14** is a sufficiently stronger electron-withdrawing substituent than an ethoxycarbonyl group (e.g., in **5**) that its C-5 positioning on the 1,2,4-triazine nucleus is responsible for the diminished rate of cycloaddition (**5** versus **14**) *and* the observed decreased regioselectivity.

All efforts to promote the [4 + 2] cycloaddition of the morpholino enamine of 2-benzyloxy-3,4-dimethoxypropiophenone (**15a**) or the corresponding pyrrolidine examine **15a** with **14** by the use of conventional Lewis acid [e.g., $AlCl_3$, $BF_3{\cdot}OEt_2$, $Cu(BF_4)_2$, $Cu(AcAc)_2$] or radical cation catalysis[23] were unsuccessful and promoted only the decomposition of the electron-rich olefin without Diels–Alder catalysis. Moreover, efforts to promote the reaction of pyrrolidine enamine **15b** with **14** under thermal conditions were unsuccessful due to the thermal instability of **15b**.

Convinced that the expected regioselectivity of the 1,2,4-triazine **14** Diels–Alder reaction would be observed provided mild reaction conditions could be devised for effecting the [4 + 2] cycloaddition of **15a**, **15b**, or **15c** with **14**, pressure-promoted Diels–Alder reaction conditions were examined.[20] Moreover, as a result of observations made in concurrent efforts on the total synthesis of lavendamycin, we anticipated that the successful use of pyrrolidine enamine **15b** would provide a significant increase in the observed regioselectivity of the cycloaddition with **14** when compared to the corresponding morpholino enamine **15a** provided that mild thermal conditions could be maintained. Consistent with these expectations, the pressure-promoted (6.2 kbar, 25°C) cycloaddition of **15a** and **15b** provided the cycloadducts **16/17** with a preference for the predicted and desired regioisomer **16** (1.4 : 1 and 2.8 : 1, respectively) in acceptable yields. Under the optimum conditions examined, the [4 + 2] cycloadduct **16** was isolated in nearly 50% yield from the reaction of **15b** with **14** (6.2 kbar, 25°C, $CH_2Cl_2$, 120 h, 65–70%; **16** : **17**, 2.8 : 1)

As anticipated from our prior observations, the trimethylsilyl enol ether of 2-benzyloxy-3,4-dimethoxypropiophenone **15c** failed to undergo [4 + 2] cycloaddition with **14** under thermal or pressure-promoted Diels–Alder reaction conditions, Scheme III and Table II.

The final conversion of **16** to Kende's streptonigrin advanced intermediate **8** is detailed in Scheme 4 and proved more challenging than anticipated.




SCHEME 4. Completion of the formal total synthesis of streptonigrin. (a) 5.0 equivalents of NaSePh, THF–HMPA, 70°C, 21 hours. (b) 10% HCl, $CH_3OH$, 25°C, 18 hours. (c) 10 equivalents of $(PhO)_2P(O)N_3$, $C_6H_6$, 80°C, 2.5 hours; $H_2O$–$C_6H_6$, 80°C, 1 hour, 40% from **16**. (d) $CH_3I$, $K_2CO_3$, THF, 65°C, 21 hours, 94%. (e) See reference 10: $Na_2S_2O_4$, THF–$H_2O$, reflux, 3 hours; Fremy's salt, acetone–0.05 *M* $Na_2HPO_4$, 25°C, 12 hours, 70%.

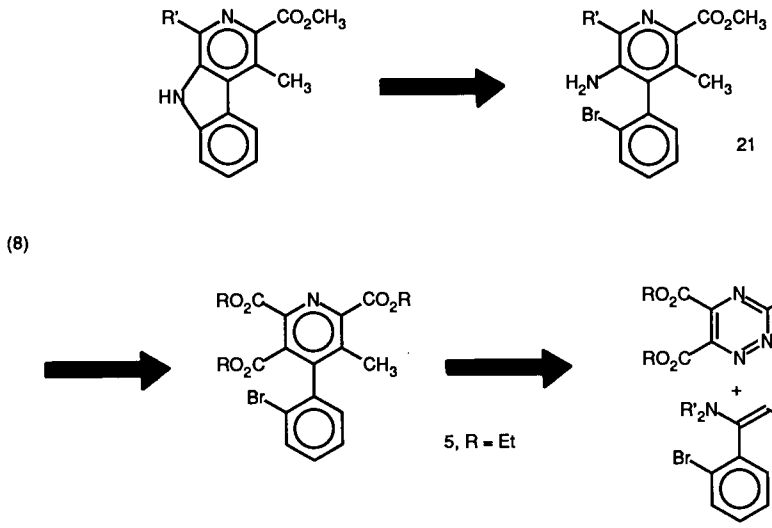
Formally, the preparation of **8** from **16** required the conversion of the pyridyl C-5′ carboxylate to an amino group and Kende had previously described the use of a modified Curtius rearrangement of the free pyridyl C-5′ carboxylic acid to effectively provide a comparable conversion.[10] The initial plan to hydrolyze both methyl esters of **16** (pyridyl C-2′ and C-5′) followed by selective reesterification of the unhindered C-2′ carboxylate proved far more difficult than anticipated. All direct hydrolytic methods of deesterification requiring nucleophilic attack at the ester carbonyl carbon failed to effect hydrolysis of the hindered C-5′ methoxycarbonyl group. Moreover, methods of dealkylative deesterification which were found to be satisfactory for effecting the C-5′ methoxycarbonyl to C-5′ carboxylic acid transformation were found to preferentially demethylate the C-6 aryl methoxy group ortho to the electron-withdrawing C-5 nitro group (C-2′ carboxylate demethylation > C-6 *O*-demethylation > C-5′ carboxylate demethylation). Consequently, treatment of **16** with the sodium salt of phenylselenol (5.0 equiv) under the conditions described by Liotta[24] afforded **18**, resulting from C-2′/C-5′ carboxylate demethylation *and* C-6 *O*-demethylation. Simple, and selective, Fischer esterification of the unhindered C-2′ carboxylate provided **19**. Conversion of the C-5′ carboxylate to the pyridyl C-5′ amine following Kende's protocol[10] using the Shiori–Yamada reagent, diphenylphosphoryl azide,[25] followed by menthylation of the free C-6 phenol provided Kende's advanced streptonigrin intermediate **8**. Interestingly, attempts to *O*-methylate the free phenol of **20** with diazomethane provided competitive C-5′ amine *N*-methylation, highlighting the *acidic* character of the C-5′ pyridyl amine. As detailed later, we took advantage of this recognized nonnucleophilic, nonbasic nature of the C-5′ pyridyl amine in the total synthesis of lavendamycin methyl ester.

The tetracyclic amine **8** proved identical in all comparable respects ($^1$H NMR, IR, electron-impact MS, high-resolution-MS, TLC: EtOAc, 50% EtOAc–hexane, 30% EtOAc–hexane, 1% $CH_3OH$–$CHCl_3$) with a sample of synthetic material previously described in the work of Kende and co-workers.[10] Two-step conversion of the 6-methoxy-5-nitro-2-quinolyl unit of **8** to the 6-methoxyquinoline-5,8-quinone **9** as described by Kende and co-workers[10] provides Weinreb's advanced streptonigrin intermediate **9**,[9] thus completing our formal total synthesis.

## IV. Total Synthesis of Lavendamycin Methyl Ester

Our initial success in the application of the inverse electron demand [4 + 2] cycloaddition reactions of substituted, electron-deficient 1,2,4-triazines with $\alpha$-aryl enamines to provide substituted 4-aryl pyridines

suggested that a complementary approach for the introduction of the lavendamycin CDE ring system could be devised provided a suitable β-carboline preparation/closure could be formulated and successfully implemented. It was anticipated that conventional protocols for nitrogen–aryl carbon bond formation[26] would permit the closure of an appropriately substituted 3-amino-4-(2′-bromophenyl)-pyridine, e.g., **21**, to provide the corresponding β-carboline and thereby permit the construction of the lavendamycin CDE ring system, Eq. (8). The required substituted 3-amino-4-(2′-bromophenyl)-pyridine in turn was expected to be prepared from the [4 + 2] cycloaddition product derived from the reaction of 3,5,6-triethoxycarbonyl-1,2,4-triazine (**5**) and the pyrrolidine enamine of 2-bromopropiophenone provided suitable differentiation of the pyridyl C-2, C-5, and C-6 ethoxycarbonyl groups could be devised, Eq. (8).



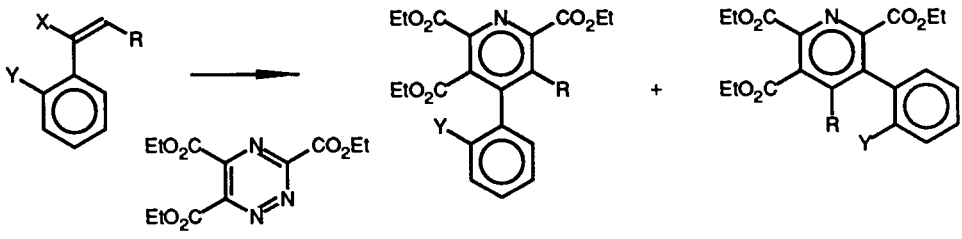

## A. Lavendamycin CDE β-Carboline Formation: Additional Observations on the Regioselectivity and Reactivity of 1,2,4-Triazine Diels–Alder Reactions and the Development of a Palladium (0)-Mediated β-Carboline Preparation

Initial efforts on the development of a synthetic approach to lavendamycin focused on demonstrating the feasibility of lavendamycin CDE β-carboline preparation from a requisite 4-aryl pyridine. Thermal cycloaddition of the pyrrolidine enamine of 2-bromopropiophenone (**25**) with 3,5,6-triethoxycarbonyl-1,2,4-triazine (**5**) *proceeded at room temperature* to provide predominantly 4-(2-bromophenyl)-5-methyl-2,3,6-triethoxycarbonylpyridine (**26a**) accompanied by a small amount of the isomeric 3-aryl pyridine **26b**.

The desired 4-aryl pyridine cycloadduct **26a** arose from the expected cycloaddition of **25** across C-3/C-6 of the 1,2,4-triazine nucleus of **5** with the nucleophilic carbon of the electron-rich olefin attaching to C-3. The minor 3-aryl pyridine cycloadduct, 5-(2-bromophenyl)-4-methyl-2,3,6-triethoxycarbonylpyridine (**26b**), similarly arises from cycloaddition across C-3/C-6 of **5** but with the nucleophilic carbon of the electron-rich olefin attaching to C-6 of the 1,2,4-triazine. Consequently, the observed addition and preferred regioselectivity of this [4 + 2] cycloaddition were in full agreement with the observations detailed in our prior investigations with the exception that the [4 + 2] cycloaddition and subsequent aromatization proceeded under milder conditions than anticipated or previously observed. We attribute this to the enhanced reactivity of the pyrrolidine enamine of 2-bromopropiophenone to the presence of the large ortho substituent and partial loss of the stabilizing aryl–olefin conjugation. Table III summarizes representative results of a study of this [4 + 2] cycloaddition reaction which illustrate three additional important observations. Modest increases in the [4 + 2] cycloaddition reaction temperature decreased the observed regioselectivity of the [4 + 2] cycloaddition, and this observation is consistent with expectations and the prior observations made en route to streptonigrin, cf. Table II. In addition, the morpholino enamine of 2-

TABLE III

[4 + 2] CYCLOADDITION REACTIONS OF **5** WITH SELECTED α-STYRYL ENAMINES




**5**

| X | Y | R | Equivalents | Conditions | Result |
|---|---|---|---|---|---|
| Pyrrolidine | H | H | 2.0 | $CHCl_3$, 60°C, 18 h | >26:1 79% |
| Pyrrolidine | H | $CH_3$ | 2.0 | $CHCl_3$, 45°C, 8 h | 9:1 73% |
| Pyrrolidine | Br | $CH_3$ | 1.5 | $CHCl_3$, 60°C, 19 h | 3.1:1 51% |
| | | | | $CH_2Cl_2$, 40°C, 22 h | 6.5:1 51% |
| | | | | $CH_2Cl_2$, 25°C, 24 h | 7.5:1 50% |
| Morpholine | Br | $CH_3$ | 2.0 | $CHCl_3$, 45°C, 24 h | — Trace |
| | | | | $CHCl_3$, 60°C, 20 h | 1:1 58% |

bromopropiophenone was less reactive than the corresponding pyrrolidine enamine *and* participated in the [4 + 2] cycloaddition with **5** with less (no) regioselectivity under reaction conditions required for complete reaction. Although this behavior was unanticipated, it is consistent with our prior observations on the reactivity and regioselectivity of the [4 + 2] cycloaddition reactions of the pyrrolidine versus morpholine enamines of 2-benzyloxy-3,4-dimethoxypropiophenone which were made in our streptonigrin work. At present we attribute this general observation to the increased size of morpholine enamines and consequently their reduced ability to cyloadd through a preferred endo transition state. A third important feature of the [4 + 2] cycloaddition reactions of 1,2,4-triazines with $\alpha$-styryl enamines that was derived from these and the preceding streptonigrin study was the decrease in rate and regioselectivity which generally accompanies alkyl substitution of the $\beta$-styryl position of the $\alpha$-styryl enamines. Figure 2 summarizes our observations on the effect the structure of the electron-rich dienophile has on the rate and regioselectivity of [4 + 2] cycloaddition reactions of electron-deficient 1,2,4-triazines.

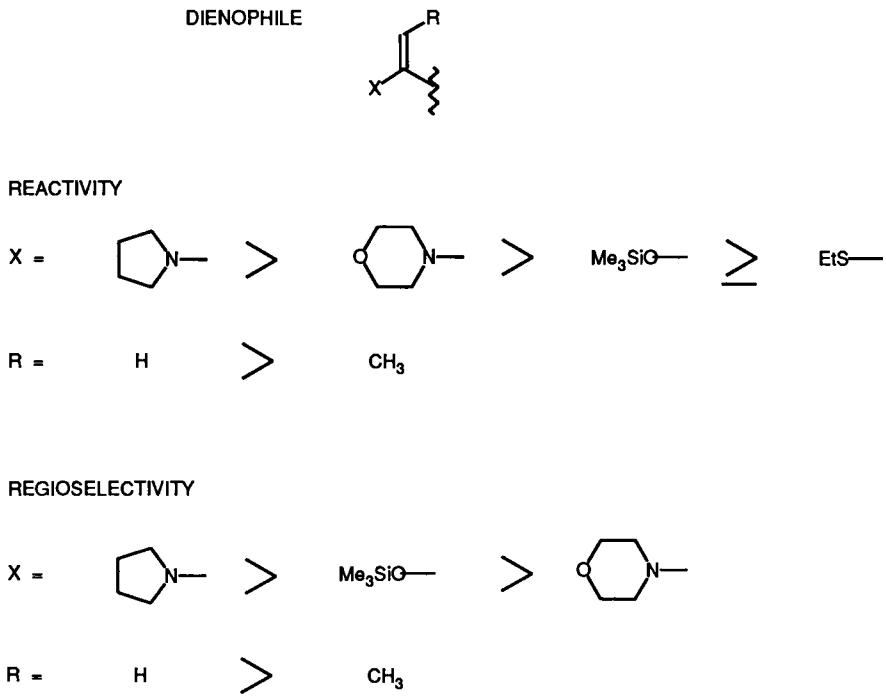
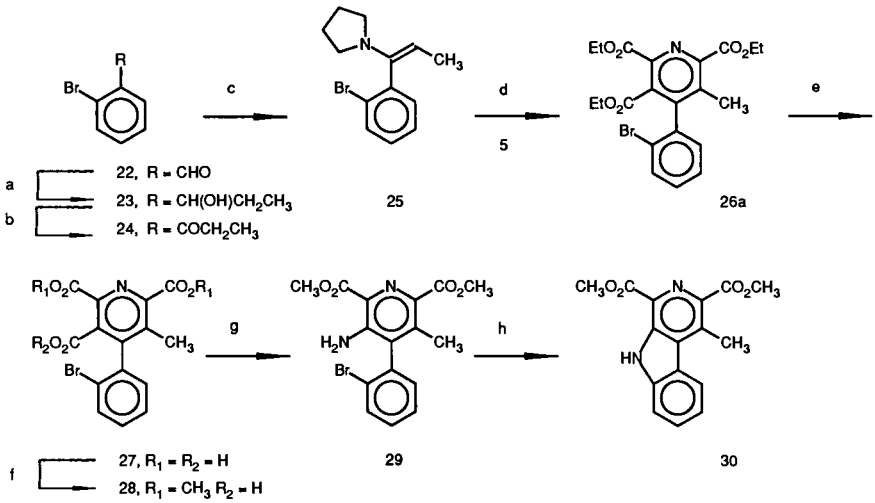



FIG. 2

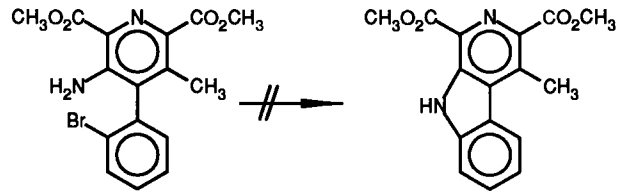



SCHEME 5. (a) 1.0 equivalent EtMgBr, THF, −78 to 25°C, 3.5 hours. (b) 1.2 equivalents $H_2CrO_4$, $Et_2O$, 25°C, 3 hours, 94% from **22**. (c) 4.0 equivalents pyrrolidine, 0.5 equivalent $TiCl_4$, $Et_2O$, 0–25°C, 12–16 hours, 80–88%. (d) Table III. (e) 15 equivalents LiOH, THF–$CH_3OH$–$H_2O$ (3 : 2 : 1), reflux, 28–30 hours. (f) 10% HCl–$CH_3OH$, 25°C, 18–20 hours. (g) 2.2 equivalents $(PhO)_2PON_3$, 2.2 equivalents $Et_3N$, $C_6H_6$, 80°C, 2.5 hours; $H_2O$–$C_6H_6$, 80°C, 2 hours, 72%. (h) 1.5 equivalents $(Ph_3P)_4Pd$, dioxane, 100°C, 24 hours, 80%.

As a result of the observations made in the prior efforts on streptonigrin,[10,12] the introduction of the C-3 pyridyl amine, which would precede the β-carboline closure, was anticipated to be accomplished through a modified Curtius rearrangement of a free pyridyl C-3 carboxylate. This required an effective differentiation of the hindered C-3 ethoxycarbonyl group from the accessible C-2/C-6 ethoxycarbonyl groups of **26a**, and as a result of observations and protocols developed in the synthetic efforts on streptonigrin this was expected to be addressed by selective esterification of tricarboxylic acid **27**, Scheme 5. Exhaustive ester hydrolysis of **26a** followed by room temperature, selective Fischer esterification of the accessible C-2/C-6 pyridyl carboxylates of **27** afforded 4-(2-bromophenyl)-2,6-bis(methoxycarbonyl)-5-methylpyridine-3-carboxylic acid (**28**). Subsequent conversion of the free pyridyl C-3 carboxylate to an amine using a modified Curtius rearrangement with the Yamada–Shiori reagent, diphenylphosphoryl azide,[25] afforded **29**, Scheme 5.

We had expected that conventional methods for the formation of an aryl–nitrogen bond would provide the final β-carboline closure to the lavendamycin CDE ring system, and consequently we were duly concerned when *all* such attempts were uniformly unsuccessful, Eq. (9).[26] No trace of the desired β-carboline product **30** could be detected in the reaction

(9)

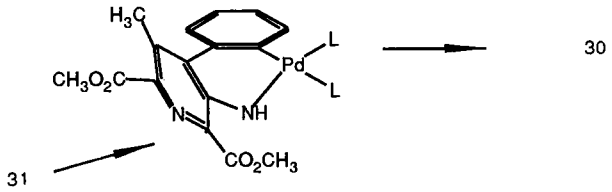



29 30

NaH, CuBr (ref. 26a)
$K_2CO_3$, CuI (ref. 26b)
$K_2CO_3$, Cu(Zn) (ref. 26c)
tBuOK, $Me_2SO$ (ref. 26e)
LDA (ref. 26d)

mixtures. It was thought that the failure of these methods to provide the desired β-carboline might be due to the noncoplanarity of the biaryl ring system of **29**, the result of two ortho substituents forcing the 4-aryl ring into a perpendicular arrangement relative to the pyridyl ring, and the resultant inability of the pyridyl 3-amine to approach the 4-phenyl 2′-position required for β-carboline formation. Consequently, we reasoned that an approach to the β-carboline ring closure which would proceed through a six-centered, versus five-centered, intermediate might be capable of promoting the desired nitrogen–carbon bond formation. Moreover, we had previously recognized the nonnucleophilic, nonbasic nature of similarly substituted C-3 pyridyl amines, the consequence of C-2/C-6 methoxycarbonyl delocalization, and anticipated pyridyl C-3 amine chemical behavior atypical of amines. Palladium(0) treatment of **29** under conditions conducive to oxidative insertion into aryl halide bonds provided the β-carboline **30** smoothly. The rationale for the study of this process, which may account for the success, was the potential and accessible formation of the six-centered intermediate **31** which may precede a reductive elimination with formation of the aryl–nitrogen bond and β-carboline generation, Eq. (10). Table IV

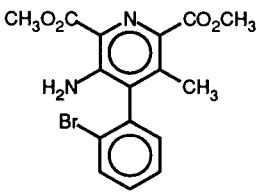
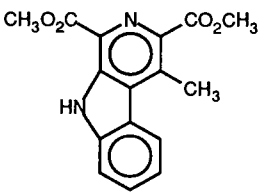
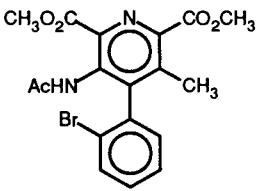
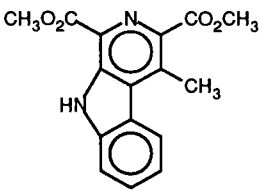
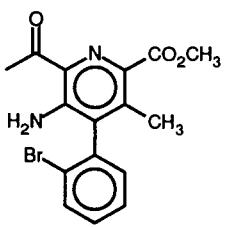
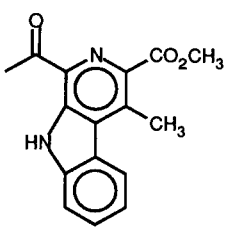
(10)




details representative results of our study of this reaction. The rate of the palladium(0)-promoted β-carboline cyclization reaction is comparable to the rate of oxidative addition reactions of palladium(0) with aryl bromides, [27] suggesting that the reaction proceeds via an initial and rate-determining

TABLE IV

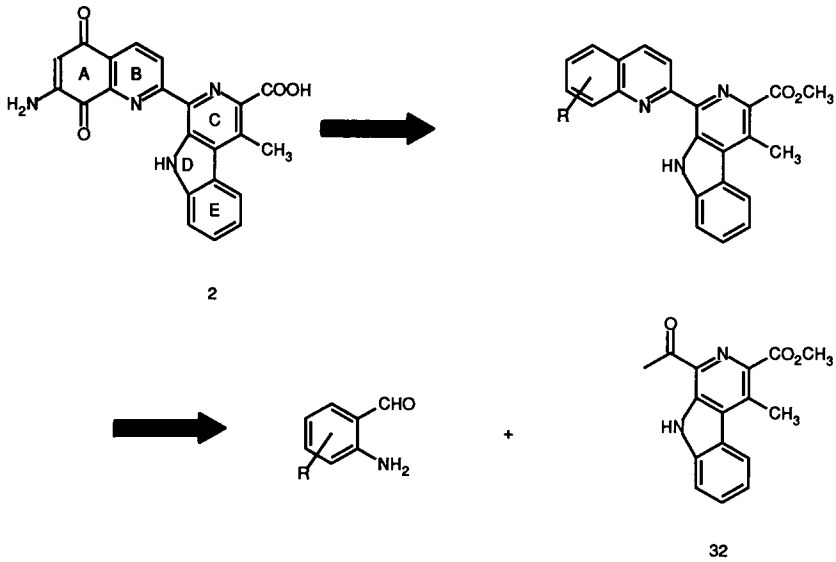
PALLADIUM(0)-MEDIATED β-CARBOLINE SYNTHESIS

| Substrate | Conditions: Equivalents $(Ph_3P)_4Pd$, solvent, temperature, time | Product | % yield |
|---|---|---|---|
|  | 1.0, THF, 80°C, 20 hours |  | 50 |
| | 1.2, THF, 80°C, 21 hours | | 81 |
| | 1.5, THF, 80°C, 21 hours | | 84 |
| | 1.2, dioxane, 100°C, 20 hours | | 50 |
| | 1.5, dioxane, 100°C, 24 hours | | 80 |
| | 1.2, toluene, 100°C, 24 hours | | 43 |
| | 0.01, THF, 80°C, 24 hours | | 0 |
| **29** | | **30** | |
|  | 1.2, dioxane, 100°C, 22 hours |  | 50 |
| | | **30** | |
|  | 1.4, dioxane, 100°C, 10 hours |  | 60 |
| | 1.5, dioxane, 100°C, 36 hours | | 87 |

oxidative addition with the generation of an aryl–palladium(II) intermediate, e.g., **31**. A trace amount (0–10%) of debromo substrate was isolated[28] if the cyclization reactions were quenched prior to complete consumption of substrate, thus substantiating this expectation. A subsequent reductive elimination of **31** with nitrogen–carbon formation would provide **30**. Thus, the palladium(0)-promoted β-carboline preparation detailed in Table IV may involve the first example of a nitrogen–palladium(II) reductive elimination with nitrogen–carbon bond formation, and the successful observation of such a process may be attributed to the reduced basicity of the pyridyl C-3 amine and a weakened N–Pd coordination.[29]

## B. Development of an Approach for the Introduction of the Lavendamycin 7-Aminoquinoline-5,8-quinone AB Ring System

Assured that the lavendamycin CDE ring system could be prepared from the 4-aryl pyridine **26a** generated with the use of the inverse electron demand [4 + 2] cycloaddition reaction of 3,5,6-triethoxycarbonyl-1,2,4-triazine (**5**) with the pyrrolidine enamine of 2-bromopropiophenone, our efforts turned to the introduction and preparation of the lavendamycin AB ring system. Because of the anticipated sensitivity of the 7-aminoquinoline-5,8-quinone, we elected to delay the introduction of the lavendamycin AB ring system to a late stage of the total synthesis. Moreover, we elected to prepare the AB ring

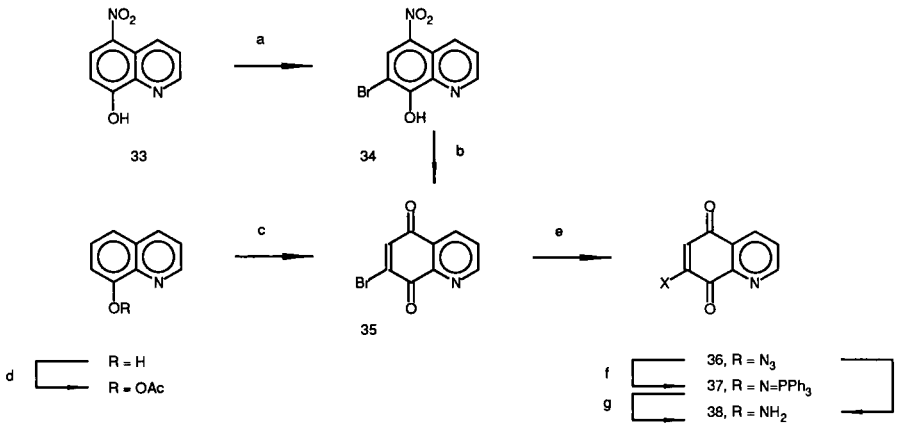



Scheme 6. Plan for the final stages of the total synthesis of lavendamycin.

system from an appropriately substituted quinoline precursor, which was to be introduced by a Friedlander condensation[30] of a suitably functionalized 2-aminobenzaldehyde with the 2-acetyl-β-carboline **32** possessing the fully constructed lavendamycin CDE ring system, Scheme 6.

Initial studies conducted with 7-bromoquinoline-5,8-quinone (**35**) secured the suitability of one such approach for the preparation of the lavendamycin 7-aminoquinoline-5,8-quinone ring system which was based on the prior studies of Sturgeon[31] and Kuo,[32] Eq. (11). Treatment of 7-bromoquinoline-5,8-quinone with sodium azide under carefully controlled reaction conditions followed by reduction of 7-azidoquinoline-5,8-quinone (**36**) with triphenylphosphine[33] and mild, aqueous acid hydrolysis of the resultant triphenylphosphine imine **37** provided 7-aminoquinoline-5,8-quinone (**38**). We did find that the use of excess sodium azide in the displacement reaction led to the predominant formation of 7-amino-6-azidoquinoline-5,8-quinone and that the dissolution of the sodium azide in water or methanol prior to its addition to **35** resulted in a noticeable increase in the isolated yield of **36**. Moreover, under these conditions the displacement reaction was found to proceed much more rapidly (6 min, EtOH-$H_2O$, 25°C, 87%; 12 min, THF-$H_2O$, 25°C, 91%) than the prior[31,32] or concurrent studies might indicate. Initial attempts to effect the standard sodium hydrosulfite[31,32] reduction of **36** failed to provide 7-aminoquinoline-5,8-quinone (**38**) in

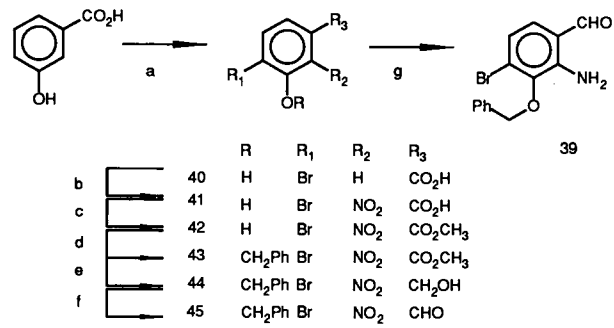
(11)



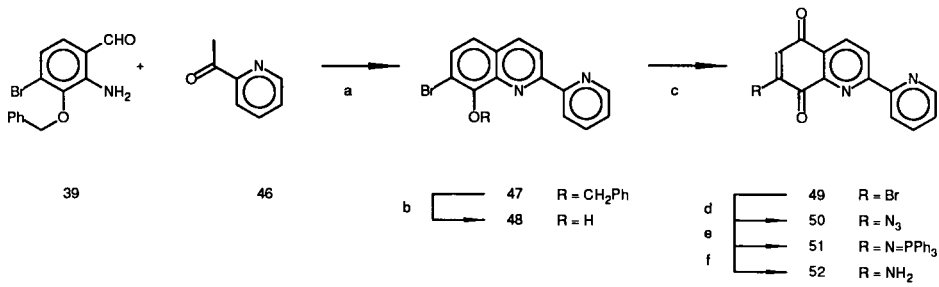

(a) 1.05 equivalents NBS, THF, cat. $H_2SO_4$, 25°C, 2.5 hours, 88%. (b) 5.0 equivalents $Na_2S_2O_4$, THF–$H_2O$, 60°C, 10 min, 74%; 2.0 equivalents $K_2Cr_2O_7$, $CH_2Cl_2$–5% aq. $H_2SO_4$, 25°C, 30 min, 64%. (c) R = H, 4.0 equivalents NBS, HOAc–$H_2O$, 76°C, 0.4 hour, 18%. (d) $Ac_2O$, 100°C, 12 hours, 91%. (e) 1.1 equivalents $NaN_3$, THF–$H_2O$, 25°C, 0.2 hour, 91% **36** and 3% **38**. (f) 1.1 equivalents $Ph_3P$, $CH_2Cl_2$, 25°C, 1 hour, 79%. (g) HOAc–$H_2O$–THF (3:2:1), 25°C, 10 min, 93%. (h) 1.0–5.0 equivalents $Na_2S_2O_4$, THF–$H_2O$, 25–60°C, 2–24 hours, 10–30%.

acceptable yields (10–30%). However, the use of stoichiometric triphenylphosphine in the conversion of **36** to the triphenylphosphine imine **37** followed by mild, aqueous acid hydrolysis (HOAc : $H_2O$ : THF, 3 : 2 : 1, 25°C; 10 min, 93%; 3 h, 48%) proceeded in excellent overall yield without competitive quinone-to-hydroquinone reduction. Importantly, the direct C-7 azide displacement of 7-bromoquinoline-5,8-quinone, versus C-6 addition–elimination, was established and confirmed by comparison of **38** with authentic material of unambiguous structure.[34]

Fully convinced that a 7-bromoquinoline-5,8-quinone could serve as the immediate precursor for introduction of the lavendamycin AB ring system, our attention turned to the preparation of a suitably functionalized 2-aminobenzaldehyde for use in a Friedlander condensation and to serve as a suitable precursor for introduction of the intermediate 7-bromoquinoline-5,8-quinone. After considerable deliberation and additional unsuccessful experimentation,[35] 2-amino-3-benzyloxy-4-bromobenzaldehyde (**39**) was selected for this purpose. The selection of **39** for use in the Friedlander condensation and subsequent lavendamycin AB ring introduction was based on the recognition that 6-substituted 2-aminobenzaldehydes, agents which possess two substituents ortho to the aryl aldehyde, participate in Friedlander condensations in only low to modest yields.[30] Thus our selection of **39** represents one in which the 2-aminobenzaldehyde possessed suitable functionality for introduction of the 7-aminoquinoline-5,8-quinone and one in which its participation in a Friedlander condensation would be expected to proceed well. The preparation of **39** is detailed in Scheme 7 and was based in part on the past efforts of Seela.[35]




SCHEME 7. Preparation of 2-amino-3-benzyloxy-4-bromobenzaldehyde (**39**) and studies on the introduction of the lavendamycin AB ring system. (a) $Br_2$, HOAc.[35] (b) $HNO_3$, $H_2SO_4$.[35] (c) HCl, $CH_3OH$.[35] (d) 1.2 equivalents NaH, DMF, 0°C, 10 min; 1.1 equivalents $PhCH_2Br$, 25°C, 20 hours, 85%. (e) 3.0 equivalents $LiBH_4$, THF, 25°C, 21 hours, 97%. (f) 1.5 equivalents PDC, $CH_2Cl_2$, 25°C, 11 hours, 83%. (g) 5.0 equivalents $Na_2S_2O_4$, THF–$H_2O$, 60°C, 0.5 hours, 93%.




SCHEME 7 (*Continued*). (a) 4 equivalents Triton B [$PhCH_2(Me)_3N^+OH^-$], THF, 25°C, 18 hours, 90%. (b) HBr(g), $C_6H_6$, 60°C, 7 hours, 98%. (c) 20 equivalents Fremy's salt [$\cdot ON(SO_3K)_2$], acetone–0.5 *M* $KH_2PO_4$, 25°C, 2 hours, 77–100%. (d) 1.1 equivalents $NaN_3$, $CH_2Cl_2$–$H_2O$, 23 hours, 25°C, 85% **50** and 8% **52**. (e) 1.1 equivalents $PPh_3$, $CH_2Cl_2$, 1 hour, 25°C, 51–65%. (f) HOAc–$H_2O$–THF (3 : 2 : 2), 25°C, 0.3 hour, 98%.

Consistent with expectations, condensation of **39** with 2-acetylpyridine (**46**) provided 8-benzyloxy-7-bromo-2-(2′-pyridyl)quinoline (**47**) in excellent yield, Scheme 7. Deprotection of the phenol of **47**, which was most effectively accomplished using anhydrous hydrogen bromide in benzene or methylene chloride, provided **48**. Initial efforts to cleave this benzyl ether with trifluoroacetic acid were equally effective (90–98%) but on occasion did provide substantial or predominant amounts of an additional by-product which was tentatively identified as the pyridinium *N*-benzyl derivative of **48**. Efforts to minimize or prevent the generation of this by-product by conventional techniques[36] were not successful and our subsequent efforts relied on the anhydrous hydrogen bromide benzyl ether cleavage. Direct conversion of **48** to the 7-bromoquinoline-5,8-quinone **49** was accomplished with the use of Fremy's salt, potassium nitrosodisulfonate,[37] in an oxidation that was not especially sensitive to substrate concentration. Since this oxidation was anticipated to be a key and potentially problematic step in the total synthesis of lavendamycin, we took this opportunity to investigate a range of reagents and reaction conditions for effecting the direct oxidation.[38] The results are summarized in Table V. Given the range of experimental conditions for successfully conducting the direct oxidation of **48**, we felt confident of its direct extension to the lavendamycin series. Nonetheless, given the variability of potassium nitrosodisulfonate oxidations and the potential of a competing Fremy's salt β-carboline oxidation in the lavendamycin efforts, we did assure ourselves that adequate, albeit less direct, alternatives existed for the preparation of a 7-bromoquinoline-5,8-quinone from a 7-bromo-8-hydroxyquinoline.[39] Conversion of the reactive and sensitive bromoquinone **49** to 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone (**52**) followed the protocol described beforehand and is detailed in Scheme 7.

Consistent with our earlier observations, treatment of *suspensions* of the

TABLE V

REPRESENTATIVE REAGENTS AND CONDITIONS EXAMINED FOR THE DIRECT OXIDATION OF 7-BROMO-8-HYDROXYQUINOLINE **48** TO 7-BROMOQUINOLINE-5,8-QUINONE **49**

| Reagent (equiv) | Conditions | Result |
|---|---|---|
| $\cdot ON(SO_3K)_2$ (20.0) | 0.0015 *M* **48**, acetone–0.05 *M* $KH_2PO_4$, 25°C, 1.5 hours | **49**, 100% |
| | 0.030 *M* **48**, acetone–0.05 *M* $KH_2PO_4$, 25°C, 2.0 hours | **49**, 75–85% |
| | 0.010 *M* **48**, $CH_3OH$–0.05 *M* $KH_2PO_4$, 25°C, 2.5 hours | **49**, 53% |
| | 0.10 *M* **48**, $CH_2Cl_2$–$H_2O$, 1.0 equivalent $(nBu)_4NHSO_4$, 25°C, 3.5 hours | **49**, 70%[a] |
| $\cdot ON(SO_3K)_2$ (10.0) | 0.01 *M* **48**, THF–0.05 *M* $KH_2PO_4$, 25°C, 2–10 hours | No reaction[b] |
| $HIO_4$ (1.5) | $CH_3OH$–$CHCl_3$ (2 : 1), 25°C, 20 hours | No reaction[b] |
| $(NH_4)_2Ce(NO_3)_6$ (2.0–6.0) | THF–$H_2O$; $CH_3OH$–$H_2O$; acetone–$H_2O$; 25°C, 0.5–5 hours | 0%[c] |
| $K_2Cr_2O_7$ (1.0–5.0) | 5% aq. $H_2SO_4$ or 5% aq. $H_2SO_4$–$CH_2Cl_2$ | 0%[d] |

[a] For the introduction of the two-phase Fremy's salt oxidation, see reference 16a.

[b] For related, successful oxidations, see K. V. Rao and H.-S. Kuo, *J. Heterocycl. Chem.* **42**, 232 (1978).

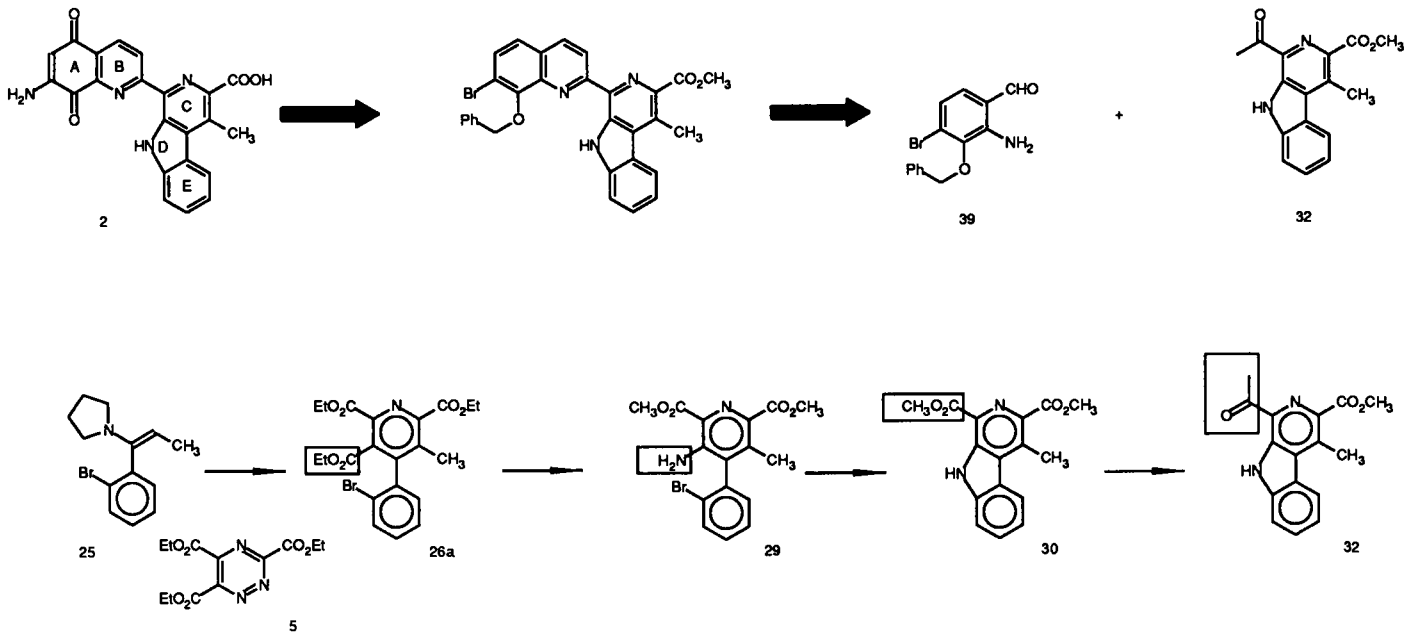
[c] For a related, successful oxidation, see S. Hibino, M. Okazaki, K. Sato, and I. Morita, *Heterocycles* **20**, 1957 (1983).

[d] V. Petrow and B. Sturgeon, *J. Chem. Soc.*, 571 (1954). See also reference 16a.

insoluble 7-bromoquinoline-5,8-quinone **49** in tetrahydrofuran, methanol, dimethylformamide, or hexamethylphosphoric triamide with 1 equivalent of predissolved sodium azide (methanol or water) afforded predominantly 7-amino-6-azido-2-(2′-pyridyl) quinoline-5,8-quinone and is the result of reaction conditions containing effective concentrations of sodium azide in excess of 1 equivalent. The desired C-7 azide displacement to provide **50** was accomplished with use of a two-phase reaction mixture ($CH_2Cl_2$-$H_2O$, 1 : 1, 1.1 equivalents $NaN_3$) in order to minimize the effective concentration of sodium azide present in the organic phase (<1.0 equivalents), and which additionally permitted the reaction to be conducted under conditions where **49** was soluble. Reduction of the 7-azidoquinoline-5,8-quinone **50** with triphenylphosphine and subsequent mild, aqueous acid hydrolysis of the resultant triphenylphosphine imine **51** provided 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone (**52**).

## C. TOTAL SYNTHESIS OF LAVENDAMYCIN METHYL ESTER

Assured that our approach to construction of the lavendamycin AB and CDE ring systems was on firm foundation, we mounted our final efforts on the natural product. Our intent was to pursue the Friedlander condensation

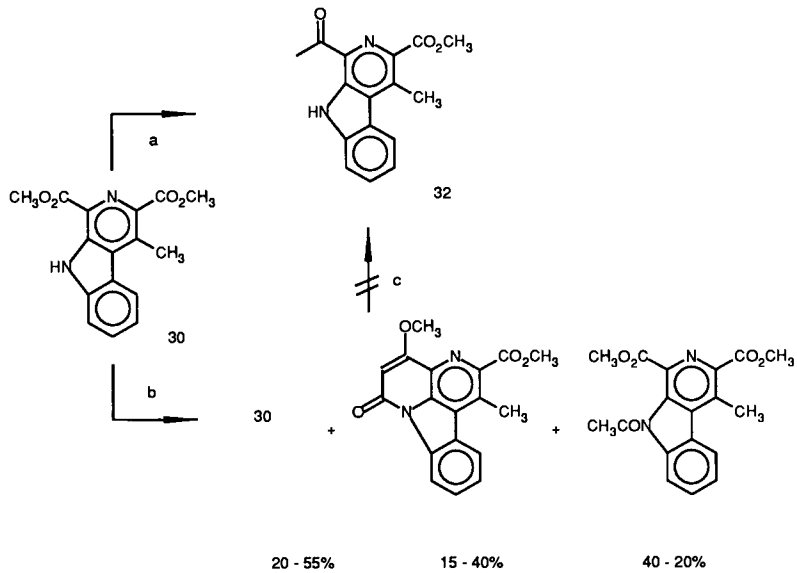

A
B
C
D
E
COOH
CH3
HN
N
O
H2N
Br
Ph
CO2CH3
CHO
NH2
2
39
32
25
26a
29
30
5
EtO2C
CO2Et
CH3O2C
H2N

SCHEME 8.

of 2-amino-3-benzyloxy-4-bromobenzaldehyde **39**, the 2-aminobenzaldehyde possessing suitable functionality for introduction of the lavendamycin 7-aminoquinoline-5,8-quionone AB ring system, with 1-acetyl-3-methoxycarbonyl-4-methyl-β-carboline (**32**), a 1-acetyl-β-carboline constituting the fully functionalized CDE ring system of lavendamycin, (Scheme 8).

In studies detailed in a preceding section we had completed the preparation of 1,3-bis(methoxycarbonyl)-4-methyl-β-carboline (**30**) from triethyl 4-(2-bromophenyl)-5-methylpyridine-2,3,6-tricarboxylate (**26a**), the product of a regioselective inverse electron demand [4 + 2] cycloaddition of 3,5,6-triethoxycarbonyl-1,2,4-triazine. A key to the implementation of this approach to the functionalized 4-aryl-3-aminopyridine **29** utilized in the β-carboline preparation was the effective differentiation of the hindered C-3 carboxylate from the accessible, unhindered C-2/C-6 carboxylates of **26a**. A final differentiation of the remaining C-1/C-3 methoxycarbonyl groups of 1,3-bis(methoxycarbonyl)-4-methyl-β-carboline **30** was anticipated to provide the final stage of the CDE ring construction necessary for implementation in the total synthesis of lavendamycin (Scheme 8). Initial efforts to convert **30** to 1-acetyl-β-carboline **32** directly or with the assistance of *N*-functionalization of the β-carboline proved unsuccessful, Eq. (12). No

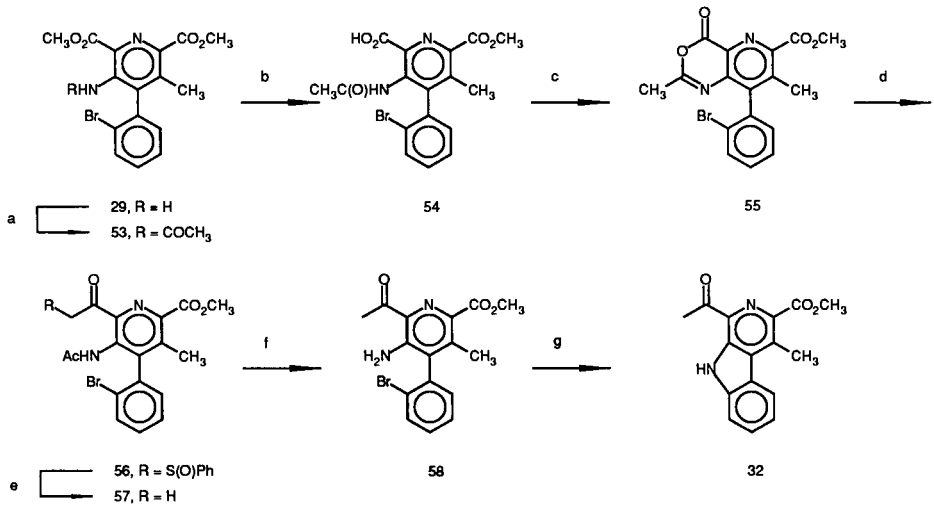
(12)




(a) MeLi; MeMgBr; $(CH_3)_2Al(CH_2)ClTi(Cp)_2$. (b) 1.1 equivalents NaH, 15 min, 25°C; 1.1 equivalents $CH_3COCl$, THF, 25°C, 24 hours. (c) LiOH, $H_2O$ THF, 25–100°C; 1 *N* aq. HCl or 1 *N* aq. HCl–dioxane, (1:1), 100°C.

appropriate reagent was found to successfully complex to the β-carboline nitrogen and selectively direct a reaction to the proximal C-1 carboxylate. Related efforts to functionalize the β-carboline nitrogen with derivatives capable of directing selective, intramolecular reaction to the C-1 carboxylate were not encouraging, Eq. (12). These and related efforts with simple systems suggested that the carboxylate differentiation may be best conducted at the amino diester **29** stage (C-2/C-6 methoxycarbonyl differentiation) in which the pyridyl C-3 amine could serve as the necessary functionality to direct reaction to the proximal C-2 carboxylate.[40]

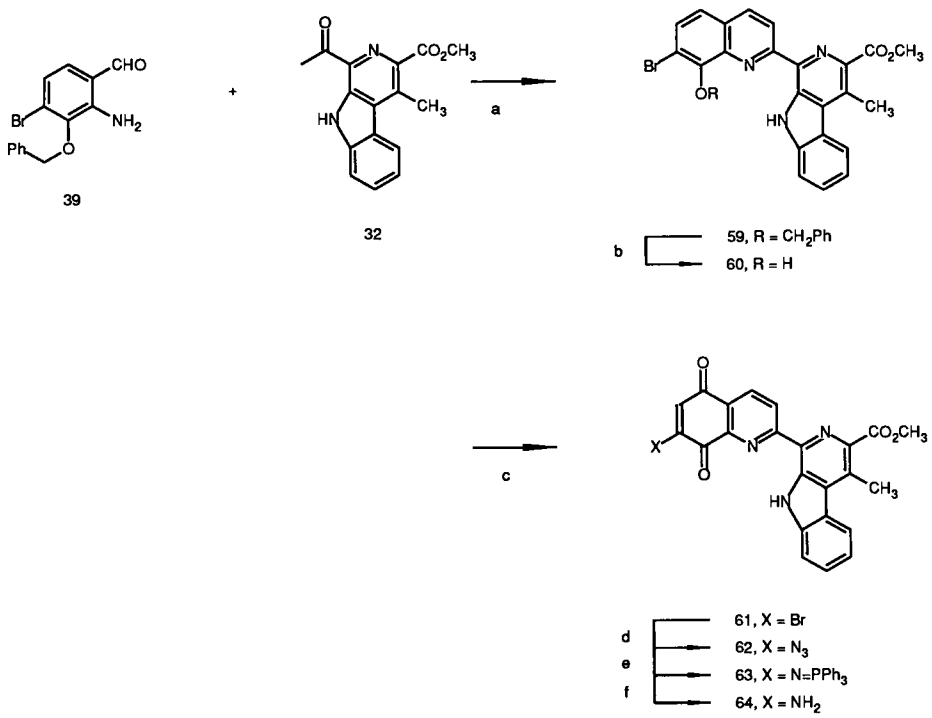
*N*-Acylation of dimethyl-3-amino-4-(2-bromophenyl)-5-methylpyridine-2,6-dicarboxylate (**29**) followed by base-catalyzed closure of **53** to the oxazinone **55** and aqueous workup afforded **54**, Scheme 9, thus affording a selective hydrolysis of the C-2 methyl ester of **29** and providing the required, selective C-2/C-6 carboxylate differentiation. Reclosure of **54** to the oxazinone **55** under strict anhydrous conditions followed by treatment with α-lithiomethyl phenyl sulfoxide[41] and subsequent reductive desulfinylation[41,42] of the β-keto sulfoxide **56** provided **57**. An extensive number of direct, one-step alternatives to this two-step conversion of oxazinone **55** to methyl ketone **57** were investigated and proved less successful.[40] Selective amide hydrolysis and palladium(0)-promoted closure of the free amine **58** provided the desired 1-acetyl-β-carboline **32** constitut-




SCHEME 9. Preparation of the lavendamycin CDE ring system. (a) 6.0 equivalents $CH_3COCl$, 8 equivalents $K_2CO_3$, THF, 50°C, 22 hours, 88%. (b) 1.2 equivalents NaH, THF, reflux, 4 hours; $H_2O$, 98%. (c) 1.0 equivalent DCC, $CH_2Cl_2$, 0°C, 7 hours, 95–100% from **53**. (d) 2.6 equivalents $LiCH_2S(O)Ph$, THF, −78°C, 40 min. (e) 10 weight equivalents Al(Hg), wet THF, −15°C, 41% from **53**. (f) 10% HCl–$CH_3OH$, 60°C, 6 hours, 76%. (g) 1.5 equivalents $(Ph_3P)_4Pd$, dioxane, 100°C, 36 hours, 89%.

ing the CDE ring system of lavendamycin. The *N*-acetyl amine **57** could be employed for the β-carboline closure and provided **32** directly (54%), presumably with hydrolysis of the labile β-carboline amide occurring upon workup and purification.

Friedlander condensation of **32** with 2-amino-3-benzyloxy-4-bromobenzaldehyde (**39**) provided **59** and completed the assemblage of the carbon skeleton of lavendamycin, Scheme 10. Cleavage of the benzyl ether with anhydrous hydrogen bromide in methylene chloride (85%) provided **60**. Subsequent *p*-quinone formation was effected only by direct oxidation of **60** with potassium nitrosodisulfonate (5.0–25.0 equivalent Fremy's salt) and with the use of Kende's two-phase reaction system[16a] (1 : 1 $CH_2Cl_2$ : 0.05 *M* $KH_2PO_4$, 25°C, 4 hours) in the presence of a phase transfer catalyst [1.0 equivalent $(n\text{Bu}_4)_4\text{NHSO}_4$] providing the red, crystalline 7-bromoquinnoline-5,8-quinone **61** identical in all respects with authentic material.[43]



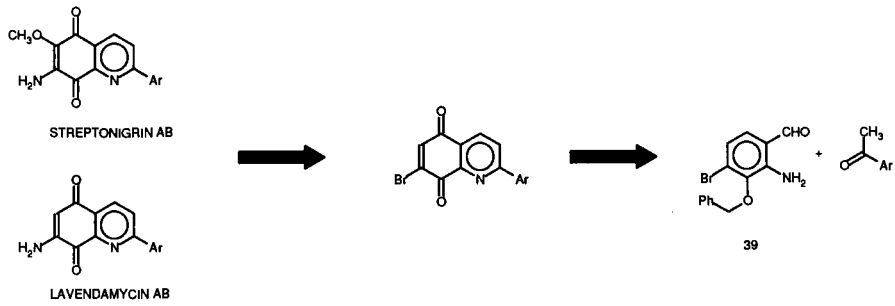

SCHEME 10. Total synthesis of lavendamycin methyl ester. (a) 2.0 equivalents Triton B [$PhCH_2(Me)_3N^+OH^-$], THF, 25°C, 18 hours, 52–58%. (b) HBr(g), $CH_2Cl_2$, 0°C, 20 min, 85%. (c) 10 equivalents $\cdot ON(SO_3K)_2$, $CH_2Cl_2$–0.05 *M* $KH_2PO_4$, 1.0 equivalent $(n\text{Bu})_4\text{NHSO}_4$, 25°C, 4 hours, 50–72% from **59**. (d) 1.1 equivalents $NaN_3$, THF–$H_2O$, 25°C, 21 hours. (e) 1.1 equivalents $PPh_3$, $CH_2Cl_2$, 25°C, 2 hours. (f) HOAc–$H_2O$–THF (3 : 2 : 1), 25°C, 3 hours, 31–42% from **61**.

In practice, the execution of these last two steps without the purification of **60** and with the rapid purification of the sensitive bromoquinone provided **61** in yields as high as 72% for the combined two steps. An anticipated major concern of ours for effecting the direct oxidative conversion of **60** to **61** was the potential competing Fremy's salt oxidation of the β-carboline,[30] and perhaps for this reason, our attempts to carry out this oxidation in a single phase (2.0–20.0 equivalent Fremy's salt, acetone–0.05 *M* $KH_2PO_4/CH_3OH$–0.05 M $KH_2PO_4$, 1–18 h) were unsuccessful. Conversion of **61** to lavendamycin methyl ester was accomplished employing the sequence described in Kende's work, implementing the modifications we had previously investigated. Carefully controlled conditions for C-7 azide displacement, subsequent triphenylphosphine-promoted reduction of the azide **62**, and mild, aqueous hydrolysis of the triphenylphosphine imine **63** provided lavendamycin methyl ester (**64**) (Scheme 10).[44]

## V. Divergent Introduction of the Streptonigrin/Lavendamycin Quinoline-5,8-quinone AB Ring Systems

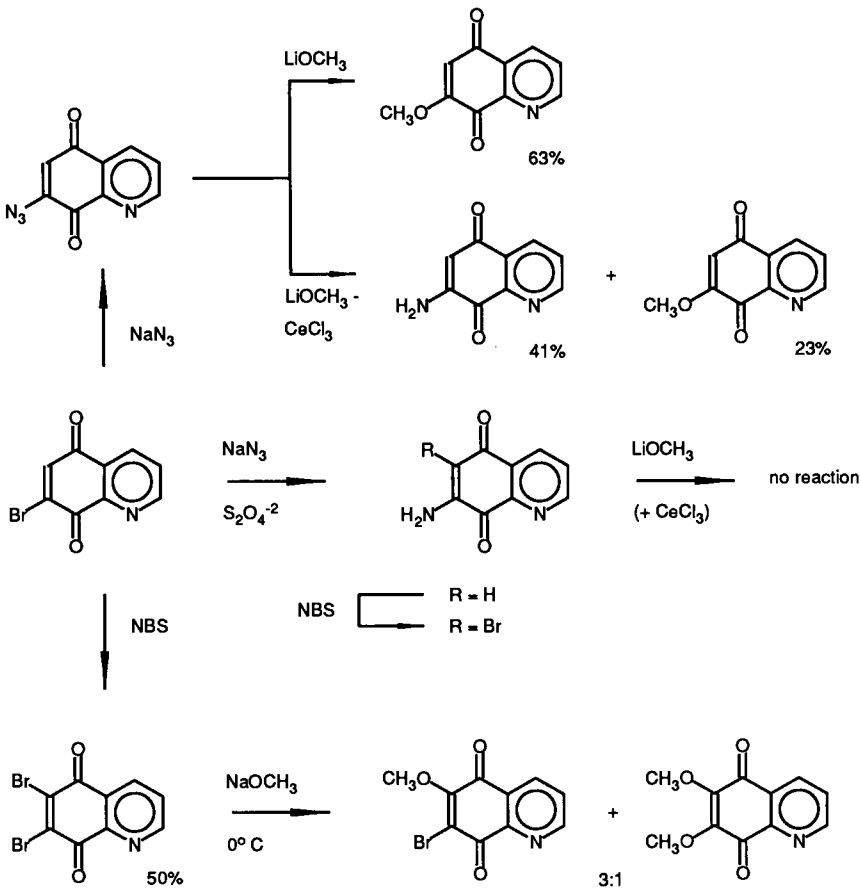
Early efforts on streptonigrin and more recent efforts on lavendamycin have confirmed that the minimal structural component of the naturally occurring antitumor antibiotics that is required for observable *in vitro* cytotoxic or antimicrobial activity consists of the characteristic functionalized quinoline-5,8-quinone AB ring systems[5]. However, no comparative study has conclusively defined the additional structural features of the naturally occurring materials which potentiate the cytotoxic and antimicrobial properties of the functionalized quinoline-5,8-quinones.[43,44] Consequently, in efforts to reduce the extent of our synthetic efforts required to generate the comparative series of synthetic agents possessing *both* the streptonigrin and lavendamycin AB ring systems, we elected to examine a modified, divergent approach for the introduction of the 7-amino-6-methoxyquinoline-5,8-quinone (streptonigrin) and 7-aminoquinoline-5,8-quinone (lavendamycin) ring systems. Moreover, we elected to investigate

(13)



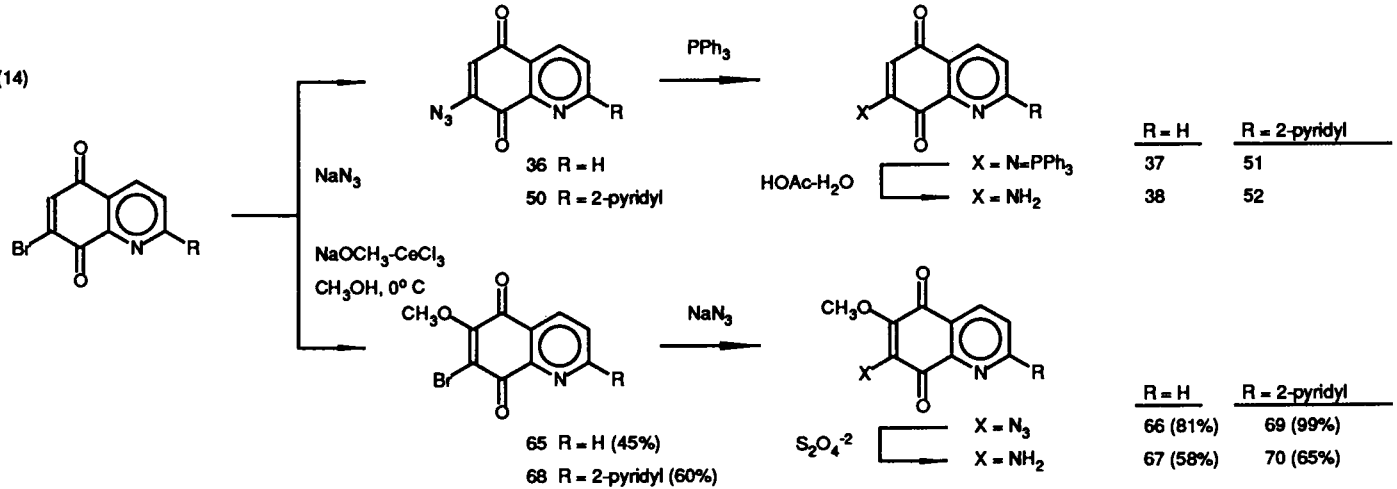
the potential of preparing the streptonigrin 7-amino-6-methoxyquinoline-5,8-quinone ring system from intermediates derived from 7-bromo-8-benzyloxyquinolines, the Friedlander condensation products of 2-amino-3-benzyloxy-4-bromobenzaldehyde (**39**), thereby permitting the divergent introduction of the streptonigrin *or* lavendamycin AB ring systems from a common advanced intermediate we knew we could readily prepare, Eq. (13).

After a number of unsuccessful efforts (Scheme 11)[45] the direct, controlled nucleophilic substitution of the 7-bromoquinoline-5,8-quinone ring system, was found to provide the necessary divergent AB quinoline-5,8-quinone introduction. As detailed earlier, the direct C-7 azide displacement of a 7-bromoquinoline-5,8-quinone followed by triphenylphosphine-promoted reduction, which proceeds without competing quinone-to-hydroquinone




SCHEME 11

(14)

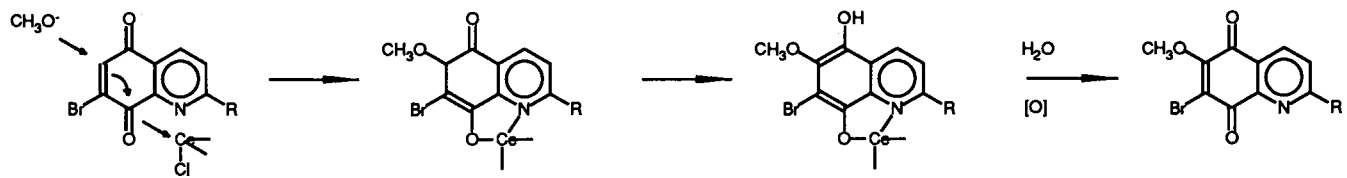



36 R = H
50 R = 2-pyridyl

65 R = H (45%)
68 R = 2-pyridyl (60%)

| | R = H | R = 2-pyridyl |
|---|---|---|
| X = $NH_2$ | 37 | 51 |
| X = $NH_2$ | 38 | 52 |
| X = $N_3$ | 66 (81%) | 69 (99%) |
| X = $NH_2$ | 67 (58%) | 70 (65%) |

(15)




65, R = H
68, R = 2-pyridyl

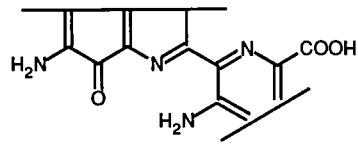
reduction and with the generation of a stable and isolatable triphenylphosphine imine, permitted the introduction of the lavendamycin 7-aminoquinoline-5,8-quinone system, Eq. (14). In a complementary sequence, treatment of a 7-bromoquinoline-5,8-quinone with cerium(III) methoxide in methanol was found to provide C-6 methoxy substitution. Cerium(III) cation coordination with the substrate apparently serves to direct nucleophilic attack to C-6 *and* serves to stabilize the initial C-6 addition product, Eq. (15).[45] This stabilization of the hydroquinone addition product prevents the characteristic C-6 addition–elimination reactions normally observed when conventional conditions (sodium methoxide–methanol) are employed; cf. Scheme 11. The C-6 nucleophilic substitution proceeded at a decelerated and controlled rate in the presence of cerium(III) and its presence did not accelerate the rate of nucleophilic addition.[45]

This divergent approach to the introduction of the streptonigrin/lavendamycin AB ring systems was utilized for the preparation of a complementary series of quinoline-5,8-quinones detailed in the following section.

## VI. Structure–Activity Studies: Experimental Probes of the Chemical Mechanism of Action of Streptonigrin, Lavendamycin, and Synthetic Quinoline-5,8-quinones

Streptonigrin exhibits potent, broad-spectrum antimicrobial properties against Gram-positive, Gram-negative, and acid-fast bacteria and fungal organisms in addition to its confirmed broad-spectrum antitumor activity against sarcoma 180, adenosarcoma 755, Lewis Lung carcinoma, Ridgway osteogenic carcinoma, Walker 256 carcinosarcoma, mouse mammary carcinoma, and human herpes simplex 1 grown in rats.[5,46–49] It has been shown to inhibit the growth of viral tumors including Rauscher murine, Friend leukemia, and thymic lymphoma and it has been demonstrated to inhibit the replication of oncornavirus *in vitro* and *in vivo*.[5,47,48] The tolerated dose of streptonigrin is approximately 2 mg per course of a treatment, and it is this potent toxicity which has prevented its clinical use.

Early and limited structure–activity studies on streptonigrin indicated that the 6-methoxy-7-aminoquinoline-5,8-quinone, the pyridyl C-2' carboxylate, and perhaps the pyridyl C-5' amine structural components of the natural product were necessary for potent cytotoxic and antimicrobial activity[5] and led Rao[46] to propose **71** as the active pharmacophore of the naturally occurring material. Moreover, results obtained in the initial but limited studies with derivatives of streptonigrin have led to the conclusion that major modification of the streptonigrin structure, including major structural reductions or simplifications, would reduce or diminish the potent




71

cytotoxic or antimicrobial activity.[5,46–49] Extensive investigations focusing on simple, substituted quinoline-5,8-quinones,[5,12,51] related naphthoquinones,[46,50] and a series of related heterocyclic-fused *p*-benzoquinones[5,51–52] have confirmed and defined the cytotoxic, antimicrobial, and potential antitumor properties of the simple and substantially less potent systems. In most instances, an excellent correlation of the reduction potential of the quinone system with the extent of cell-free single-strand DNA cleavage has been observed,[12,51,53] and in many series a correlation has been found with the cytotoxic potency of the agents.[5,52,53] None, however, have been described to possess cytotoxic, antimicrobial, and antitumor potency comparable to that of streptonigrin despite their comparable or enhanced redox properties.

Additional efforts have shown that the streptonigrin cellular toxicity may be attributed to the depletion of NADPH/NADH, the uncoupling of oxidative phosphorylation, and/or the formation of single-strand cleavage of DNA. This latter effect, which has been studied in cell-free systems, has been actively pursued as the mechanism of streptonigrin antitumor activity.[5,46–48]

At the risk of unjustly summarizing an extensive series of investigations,[5,47,48] streptonigrin-induced cell-free single-strand cleavage of convalently closed circular DNA (*ccc*-DNA) requires: (1) *in situ* reduction (NADH activation) of the AB quinoline-5,8-quinone presumably to the corresponding hydroquinone or semiquinone radical, (2) the presence of trace metal cations including Cu(II) and Fe(II),[12f,48] (3) is completely inhibited by the addition of ethylenediaminetetraacetic acid (EDTA), (4) requires the presence and activation of molecular oxygen, and (5) is inhibited by superoxide oxidoreductase (EC 1.15.1.1) and hydrogen peroxide oxidoreductase (EC 1.11.1.6). Conflicting reports of direct and indirect experimental evidence which suggest the (lack of) association of streptonigrin with double-stranded DNA in the (absence) presence of divalent metal cations continue to cloud the potential mechanism for streptonigrin-induced double-stranded DNA cleavage. Consequently, two mechanisms for the streptonigrin cellular toxicity and single-strand cleavage of DNA based on this information have been advanced: the participation of streptonigrin in the reductive generation of free, diffusible superoxide ($O_2^{\cdot-}$) or hydroxyl ($HO^{\cdot}$) radical from molecular oxygen distal or proximal to DNA[47,53] or the direct, covalent interaction of an intermediate streptonigrin semiquinone radical with DNA.[54] One interpretation of the chemical mechanism that follows from this information is summarized in

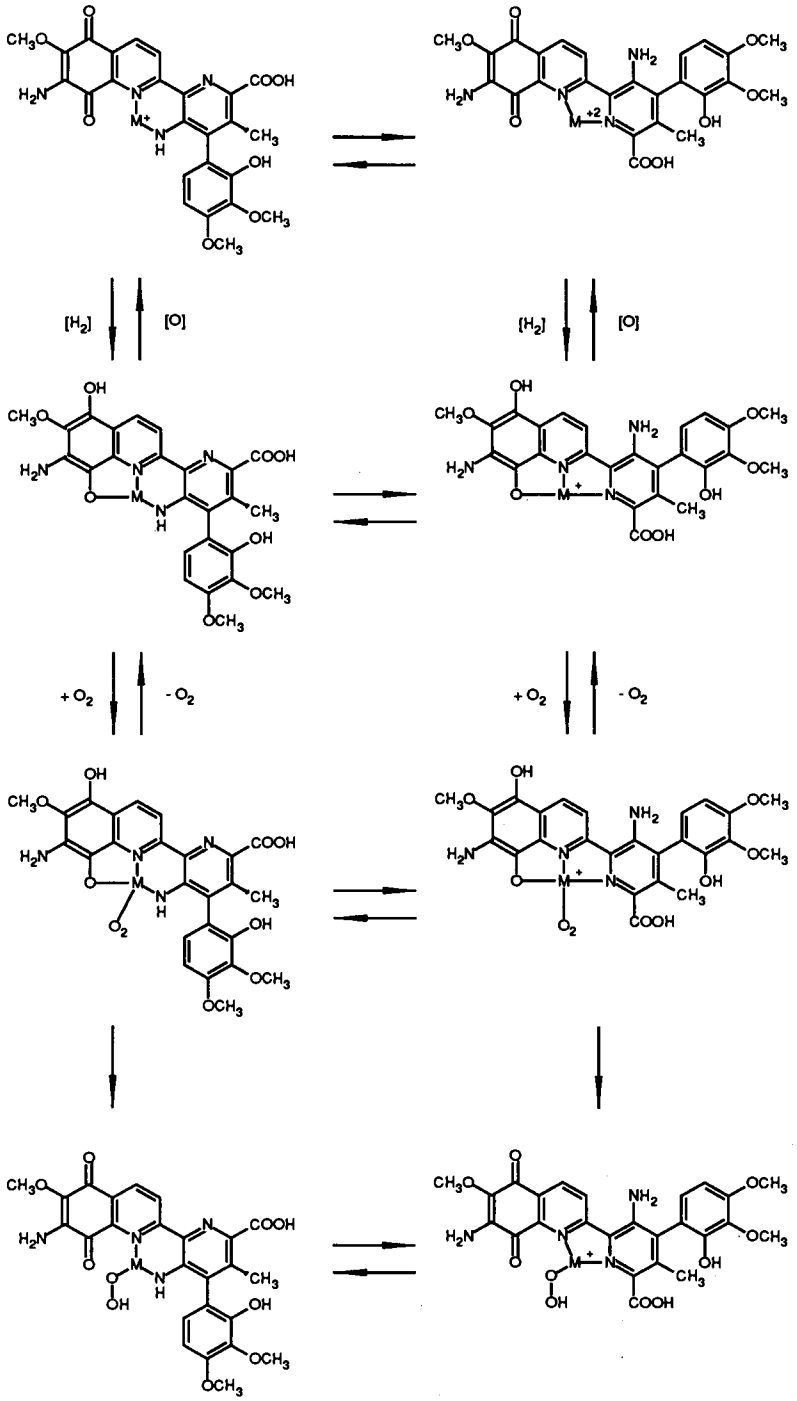
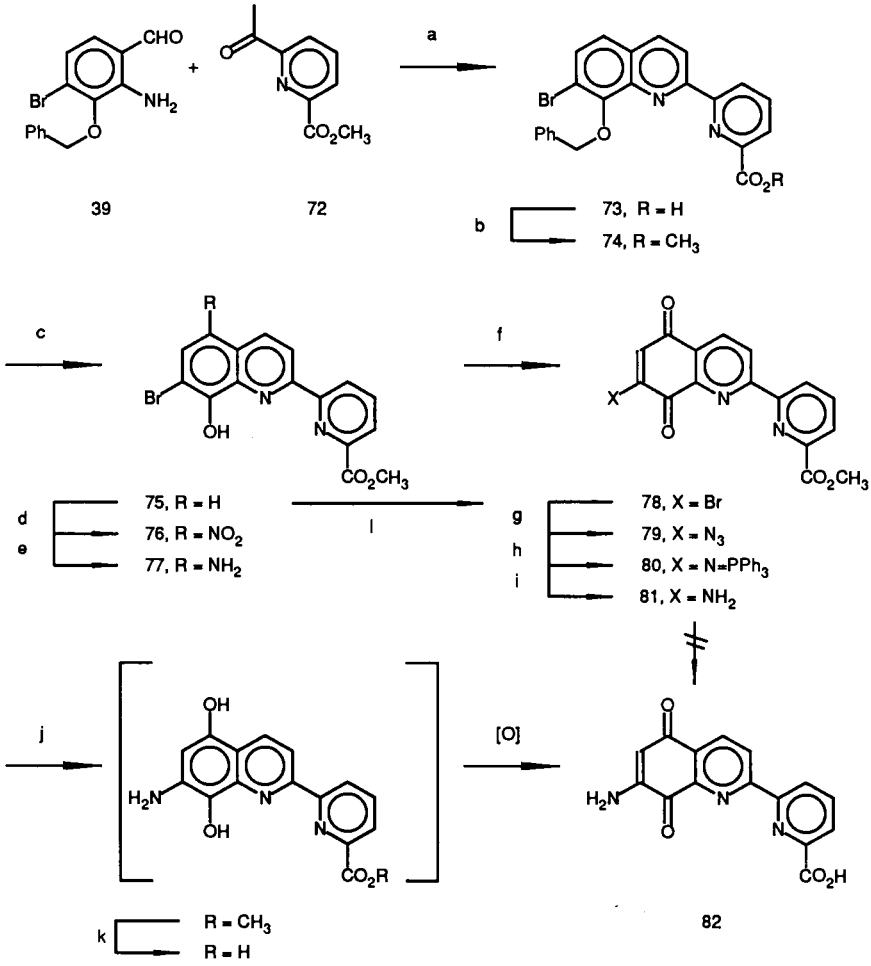


FIG. 3

Fig. 3. The effective ability of 8-hydroxyquinolines (cf. streptonigrin/lavendamycin quinoline-5,8-quinone → 5,8-dihydroxyquinoline) to complex metal cations and the feasible potentiation of the 8-hydroxyquinoline metal chelation, oxygen activation process by the streptonigrin/lavendamycin pyridyl N-1′/C-2′ carboxylate or acidic C-5′ pyridyl amine provide an attractive explanation for the observed cytotoxic potency and cell-free single-strand DNA cleavage efficacy of streptonigrin. A particularly attractive, and perhaps unique, feature of this mechanism of metal cation oxygen activation is the ligand (streptonigrin hydroquinone) participation (oxidation) in the activation (reduction) of molecular oxygen.

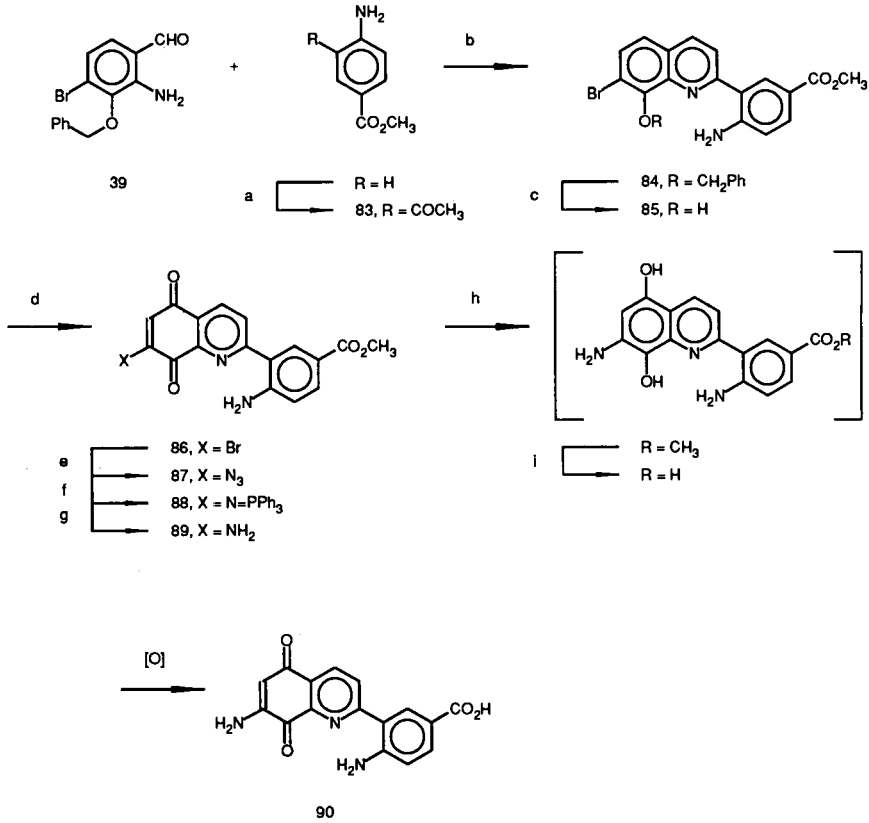



SCHEME 12

The metal-chelating agent, an 8-hydroxyquinoline, may be reoxidized to the 7-aminoquinoline-5,8-quinone by stepwise single-electron or two-electron oxidation, concurrent with the reduction of molecular oxygen to a metal hydroperoxide species which may serve as a powerful oxidizing agent in its own right or as an intermediate en route to the generation of free, diffusible superoxide ($O_2^{\cdot-}$) or hydroxyl ($HO^{\cdot}$) radical. Consequently, the groups capable of potentiating or facilitating the quinoline-5,8-quinone metal chelation, oxygen activation process are the pyridyl N-1′ nitrogen/C-2′ carboxylate *or* the nonnucleophilic, nonbasic pyridyl C-5′ amino groups. The well-established potentiation of the cytotoxic, antimicrobial, and antitumor properties which may be attributed to the streptonigrin C-6′ carboxylic acid ($CO_2H \gg CO_2CH_3 \cong CONHNH_2$),[5,46,55] the recognized metal complexation properties of related 2,2′-bipyridyl systems, and the recent demonstration of the affinity, specificity, and nuclease oxidative cleavage of native and synthetic polynucleotides promoted by 1,10-phenanthroline metal complexes suggested indirectly that it may be the streptonigrin, lavendamycin C-ring N-1′/C-6′ carboxylates which are responsible for the enhanced efficacy of the naturally occurring materials. Therefore, we initially investigated the feasibility of potentiation of the antimicrobial and cytotoxic effects of the quinoline-5,8-quinones via the introduction of the N-1′/C-2′ carboxylate into simple systems bearing the streptonigrin and lavendamycin AB quinoline-5,8-quinone ring systems as a test of the validity of this chemical mechanism for antitumor activity, Schemes 12 and 13.

The *in vitro* cytotoxic and antimicrobial testing results of synthetic quinoline-5,8-quinones which were prepared to explore the validity of this hypothesis and to define the structural components of streptonigrin and lavendamycin which potentiate the biological properties of substituted quinoline-5,8-quinones are detailed in Table VI. In initial, direct comparisons of antimicrobial and cytotoxic properties of the synthetic quinoline-5,8-quinones, the 7-aminoquinoline-5,8-quinone ring system (lavendamycin AB ring system) proved more potent than the 7-amino-6-methoxyquinoline-5,8-quinone ring system (streptonigrin AB ring system), (Table VI: **38** versus **67**; **52** versus **70**). Consistent with past observations, both the 7-amino- and 7-amino-6-methoxyquinoline-5,8-quinone ring systems proved substantially more potent than alternative, substituted quinoline-5,8-quinones including the 6-aminoquinoline-5,8-quinone ring system.[57] Contrary to initial expectations, the results suggest that the enhanced potency of streptonigrin (**1**) versus lavendamycin (**2**) is due not to the intrinsic potency of the AB quinoline-5,8-quinone ring systems but to a substantial potentiation of the cytotoxic properties attributable to the peripheral streptonigrin CD versus lavendamycin CDE ring systems.

The fully elaborated streptonigrin CD and lavendamycin CDE ring




SCHEME 13. (a) Reference *65b*. (b) 4.0 equivalents of Triton B [$PhCH_2(Me)_3NOH$], THF, 0–25°C, 6 hours, 81%. (c) HBr(g), $CH_2Cl_2$, 60°C, 10 hours, 87%. (d) 10 equivalents of $\cdot ON(SO_3K)_2$, 1 : 1 $CH_2Cl_2$ : 1.0 *M* phosphate buffer ($KH_2PO_4/Na_2HPO_4$ = 1), 1.0 equivalent $(n\text{-}Bu)_4NHSO_4$, 25°C, 20 hours. (e) 1.0 equivalent of $NaN_3$, THF–$H_2O$, 25°C, 0.5 hours, (89% overall from **85**). (f) 1.0 equivalent of $Ph_3P$, $CH_2Cl_2$–MeOH, 25°C, 1.5 hours, 65%. (g) HOAc:$H_2O$:THF (3:2:3), 25°C, 0.2 hour, 99%. (h) 5.0 equivalents of $Na_2S_2O_4$, THF–MeOH–$H_2O$ (3 : 2 : 1), 25°C, 0.5 hour. (i) 10 equivalents of LiOH, 50°C, 35 hours, 66% from **89**.

systems (Table VI,[56] **92** and **30**, **32**, respectively) as well as a number of related synthetic structures proved inactive in the antimicrobial and cytotoxicity assays. The observed lack of activity with the intact streptonigrin CD ring system **92** has been detailed in the early investigations of Cheng.[5,12,46]

Streptonigrin (**1**) proved substantially more potent than streptonigrin methyl ester (**91**), as previously detailed, as well as lavendamycin (**2**)[18] and lavendamycin methyl ester (**64**).

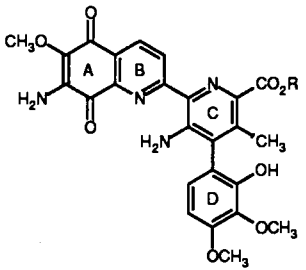
Evaluation of the synthetic agents bearing the streptonigrin C-ring N-1′ pyridyl nitrogen provided by introduction of the 2-(2′-pyridyl) unit onto the

## TABLE VI

*In Vitro* Antimicrobial and Cytotoxic Activity [56]

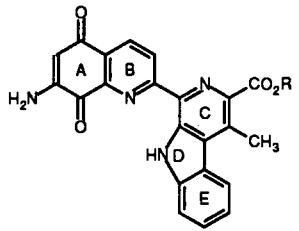
| | Antimicrobial (MIC, μg/ml)[a,b] | | | | | | | Cytotoxic ($IC_{50}$, μg/ml)[b,c] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* ATCC 13709 | *E. coli* ATCC 9637 | *S. gallinarum* ATCC 9184 | *K. pneumoniae* ATCC 10031 | *M. smegmatis* ATCC 607 | *C. albicans* ATCC 10231 | *P. aeruginosa* ATCC 27853 | CCRF-CEM[d] | L-1210[e] | B16[f] | 9PS(P388)[g] | 9KB[h] |
| **1** | <0.1 | 6.25 | 1.56 | 0.1 | 1.56 | 12.5 | 6.25 | 0.00017 | 0.61 | 0.48 | 0.045 | 0.0025 |
| **91** | >100 | >100 | >100 | >100 | >100 | >100 | >100 | 0.017 | 3.1 | 1.5 | 0.26 | 0.53 |
| **2** | (0.16)[18] | (1) | — | (>125) | — | (16) | (16) | — | 0.9 | 1.1 | — | — |
| **64** | — | — | — | — | — | — | — | — | 2.2 | 3.1 | — | — |
| **82** | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >2.1 | >20 | >20 | >10 | >10 |
| **81** | 6.25 | >50 | >50 | 50 | 6.25 | >50 | >50 | 0.1 | 0.4 | 0.9 | 3.9 | 0.17 |
| **90** | >50 | >50 | >50 | >50 | >50 | >50 | >50 | 14.6 | >20 | >20 | 5.0 | >10 |
| **89** | >50 | >50 | >50 | >50 | >50 | >50 | >50 | 0.4 | 0.6 | 0.4 | 0.2 | 2.7 |
| **38** | 12.5 | 50 | 25 | 50 | 12.5 | 50 | >100 | 0.3 | 0.34 | 0.14 | 0.19 | 0.74 |
| **67** | 6.25 | >50 | >50 | 50 | 50 | 50 | >50 | 0.2 | 1.0 | 1.2 | 0.22 | 1.9 |
| **52** | 3.12 | >100 | 100 | 100 | 0.78 | 50 | >100 | 0.09 | 0.42 | 0.26 | 0.0023 | 0.10 |
| **70** | 1.56 | >100 | >100 | 25 | 1.56 | 3.12 | >100 | 0.5 | 0.30 | 0.45 | 0.034 | 0.33 |
| **92** | >50 | >50 | >50 | >50 | >50 | >50 | >50 | — | >20 | >20 | >10 | >10 |
| **30** | >50 | >50 | >50 | >50 | 50 | >50 | >50 | 16.8 | >25 | >25 | — | — |
| **32** | >50 | >50 | >50 | >50 | >50 | >50 | >50 | — | >25 | >25 | — | — |

[a] Minimum inhibitory concentration (MIC).
[b] American Type Culture Collection (ATCC).
[c] Inhibitory concentration for 50% cell growth relative to untreated control ($IC_{50}$).
[d] Human lymphoblastic leukemia cell culture.
[e] L-1210 mouse lymphocytic leukemia cell culture.
[f] B16 mouse melanoma cell culture.
[g] P388 mouse leukemia cell culture.
[h] Human epidermoid carcinoma of the nasopharynx.



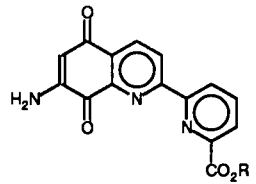
1, R = H streptonigrin

91, R = $CH_3$ streptonigrin methyl ester



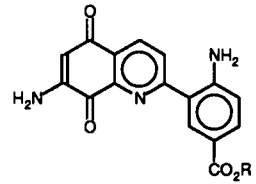
2, R = H lavendamycin

64, R = $CH_3$ lavendamycin methyl ester



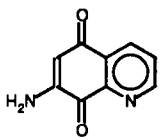
82, R = H

81, R = $CH_3$

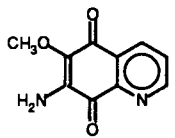


90, R = H

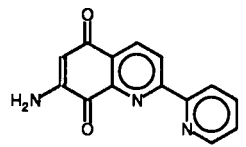
89, R = $CH_3$



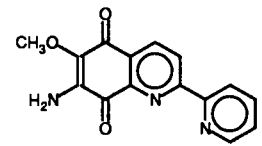
38



67

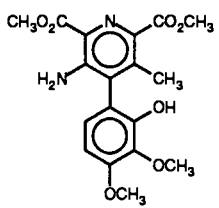


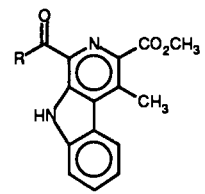
52



70

92





30, R = $OCH_3$

32, R = $CH_3$

7-amino- or 7-amino-6-methoxyquinoline-5,8-quinone ring system revealed agents with increased cytotoxic potency (Table VI: **52** versus **38**; **70** versus **67**). 7-Amino-2-(2′-pyridyl)quinoline-5,8-quinone (**52**) proved to be comparable in cytotoxic potency to streptonigrin, albeit with altered selectivity. Streptonigrin was found to be exceptionally potent in the CCRF-CEM and 9KB cell culture assays ($IC_{50}$ = 0.17 and 2.5 ng/ml, respectively), while **52** displayed potent cytotoxic activity in the 9PS (P388) cell culture assay ($IC_{50}$ = 2.3 ng/mL).

Evaluation of the synthetic agents **82** and **81** provided the opportunity to probe the role the streptonigrin C-ring N-1′/C-6′ carboxylate may play in the streptonigrin antimicrobial/cytotoxic activity. The cytotoxic properties of 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone-6′-carboxylate as its methyl ester **81** proved comparable to those of the parent 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone (**52**) with the exception of a marked decrease in 9PS (P388) cytotoxic activity. A loss of antimicrobial and cytotoxic activity was observed with the free carboxylic acid derivative **82** (inactive) which accompanied the introduction of the C-6′ carboxylic acid onto the potent, parent 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone. Thus, in contrast to observations associated with streptonigrin in which the C-6′ carboxylic acid potentiates the antitumor, antimicrobial, and cytotoxic activity of the naturally occurring quinoline-5,8-quinone, the C-6′ carboxylic acid of **82** diminishes the observed antimicrobial and cytotoxic properties of the parent 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone. Consequently, these comparative results suggest that the streptonigrin C-ring N-1′/C-6′ carboxylate does not potentiate the properties of a 7-aminoquinoline-5,8-quinone by a productive participation of the C-6′ carboxylic acid in metal complexation.

Evaluation of the synthetic agents **89** and **90** (lacking the streptonigrin C-ring N-1′ pyridyl nitrogen) provided the opportunity to probe the role the streptonigrin C-ring C-3′ pyridyl amine/C-6′ carboxylate may play in potentiating the antimicrobial/cytotoxic properties of streptonigrin. 7-Amino-2-(2′-aminophenyl)quinoline-5,8-quinone-5′-carboxylate as its methyl ester **89** proved comparable to the parent 7-aminoquinoline-5,8-quinone (Table VI: **89** versus **38**) but less potent than the 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone systems bearing the streptonigrin C-ring N-1′ nitrogen (Table VI: **89** versus **81**, **52**, **70**). A loss of antimicrobial and cytotoxic activity was observed with the free carboxylic acid **90**. Thus, in contrast to the observations on streptonigrin, the introduction of the free carboxylic acid further diminished the cytotoxic properties of the parent 7-aminoquinoline-5,8-quinone (Table VI: **90** versus **38**) and abolished the marginal cytotoxic properties of the 7-amino-2-(2′-aminophenyl)quinoline-5,8-quinone system (**90** versus **89**).

A comparison of the results on the antimicrobial and cytotoxic properties of the synthetic streptonigrin and lavendamycin partial structures, Fig. 4, suggests a prominent role for the streptonigrin C-ring N-1′ nitrogen in potentiating the cytotoxic potency of the 7-amino-(6-methoxy)-quinoline-5,8-quinone ring system and a minimal direct participation in the potentiation of the properties by the streptonigrin C-ring C-3′ pyridyl amine/C-6′ carboxylate. While the mechanism of streptonigrin cellular toxicity may require metal complexation and a subsequent role in oxygen activation, the potentiation of the antimicrobial and cytotoxic properties of the streptonigrin/lavendamycin 7-aminoquinoline-5,8-quinone AB ring system is not due to enhanced metal complexation properties introduced by the streptonigrin peripheral C-ring substituents. Moreover, the unrecognized origin of the well-established potentiation of the cytotoxic, antimicrobial, and antitumor properties of streptonigrin which may be attributed to the streptonigrin C-6′ carboxylic acid appears to override the diminished intrinsic activity which the addition of this group imparts to structurally related, synthetic 7-aminoquinoline-5,8-quinones.

The investigations which I have tried to summarize, and which have led to our development of a formal total synthesis of streptonigrin and a total synthesis of lavendamycin methyl ester based on the implementation of

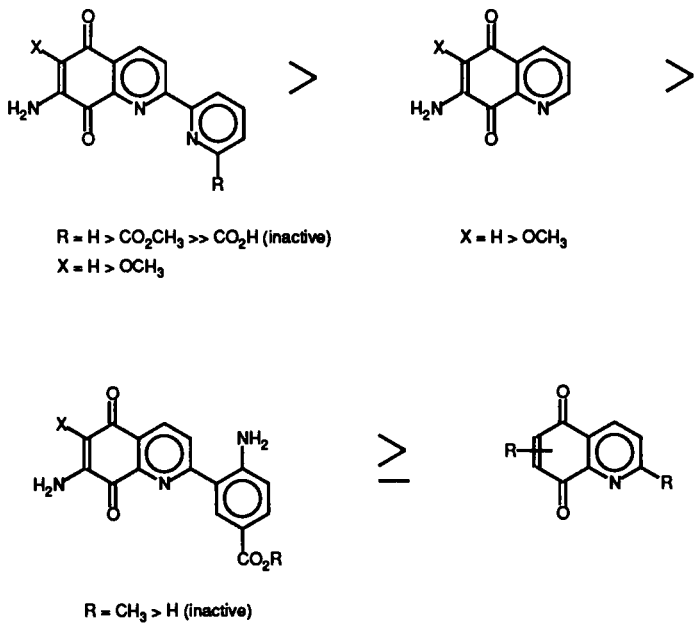



FIG. 4. Summary of *in vitro* cytotoxic activity.

heterocyclic azadiene inverse electron demand Diels–Alder reactions as well as our participation in current investigations on the chemical mechanism of action of the naturally occurring and synthetic quinoline-5,8-quinones, proved more fruitful and rewarding than the original or initial proposed studies. This may be attributed to the enthusiasm and intellectual contributions brought to the work by those who have been responsible for its completion: Professor James S. Panek, Dr. Masami Yasuda, and Dr. Steven R. Duff.

## Acknowledgments

I would like to gratefully acknowledge the financial support of our work provided by the National Institutes of Health (CA 01134/42056), the Searle Scholars Program, and the Alfred P. Sloan Foundation.

I am indebted to the students and postdoctoral colleagues whose efforts and enthusiasm for our work are well illustrated by the studies detailed herein. In addition to the direct efforts of Professor J. S. Panek, Dr. M. Yasuda, and Dr. S. Duff, the daily suggestions and participation of Dr. M. Mullican, Dr. C. Brotherton, M. Patel, D. Yohannes, and R. Coleman contributed to the enjoyment and success of the studies.

## References

1. (a) Streptonigrin isolation: K. Rao and W. P. Cullen, *Antibiot. Annu.* p. 950 (1959–1960); (b) Structure determination: K. V. Rao, K. Biemann, and R. B. Woodward, *J. Am. Chem. Soc.* **85,** 2532 (1963); (c) X-ray structure determination: Y.-Y. H. Chiu and W. N. Lipscomb, *J. Am. Chem. Soc.* **97,** 2525 (1975); (d) Identical with bruneomycin: H. G. Brazhnikovo, V. I. Ponomarenko, I. N. Kovsharova, E. B. Kruglyak, and V. V. Prashiyakova, *Antibioti ki (Moscow)* **13,** 99 (1968); (e) Streptonigrin atropisomers: S. Dholakia and R. D. Gillard, *Tetrahedron* **37,** 2929 (1981).
2. Lavendamycin structure determination: T. W. Doyle, D. M. Balitz, R. E. Grulich, D. E. Nettelton, S. J. Gould, C.-h. Tann, and A. E. Moews, *Tetrahedron Lett.* **22,** 4595 (1981).
3. Streptonigrone isolation, structure determination; biological properties: A. J. Herlt, R. W. Rickards, and J. P.-Wu, *J. Antibiot.* **38,** 516 (1985).
4. H. Neunhoeffer and P. F. Wiley, *Chem. Heterocycl. Compd.* **33,** 226 (1978); H. Neunhoeffer, in "Comprehensive Heterocyclic Chemistry," Vol. 3, pp. 421–429, (A. J. Boulton and A. McKillop, eds.). Pergamon, London, 1984; D. L. Boger, *Tetrahedron* **39,** 2912 (1983); D. L. Boger, *Chem. Rev.* **86,** 781 (1986).
5. S. J. Gould and S. M. Weinreb, *Fortschr. Chem. Org. Naturst.* **41,** 77 (1982).
6. N. I. Nissen, T. Pajak, I. Glidewell, H. Blom, M. Flaherty, D. Hayes, R. McIntyre, and J. F. Holland, *Cancer Treat. Rep.* **61,** 1097 (1977); see also I. A. Shaikh, F. Johnson, and A. P. Grollman, *J. Med. Chem.* **29,** 1329 (1986); R. Cone, S. K. Hasan, J. W. Lown, and A. R. Morgan, *Can. J. Biochem.* **54,** 219 (1976); J. W. Lown, S.-K. Sim, and H.-H. Chen, *Can. J. Biochem.* **56,** 1042 (1978); N. R. Bachur, S. L. Gordon, M. V. Gee, and H. Kon, *Proc. Natl. Acad. Sci. USA* **76,** 954 (1979); see also references 46–48.
7. K. V. Rao, *Cancer Chemother. Rep., Part 2* **4,** 11 (1974).
8. Streptonigrin biosynthesis: S. J. Gould and D. E. Cane, *J. Am. Chem. Soc.* **104,** 343 (1982); S. J. Gould and C. C. Chang, *J. Am. Chem. Soc.* **99,** 5496 (1977), **100,** 1624 (1978), **102,** 1702 (1980); S. J. Gould and D. S. Darling, *Tetrahedron Lett.* p. 3207 (1978); S. J. Gould, C. C. Chang, D. S. Darling, J. D. Roberts, and M. Squillacote, *J. Am. Chem. Soc.* **102,** 1707 (1980).

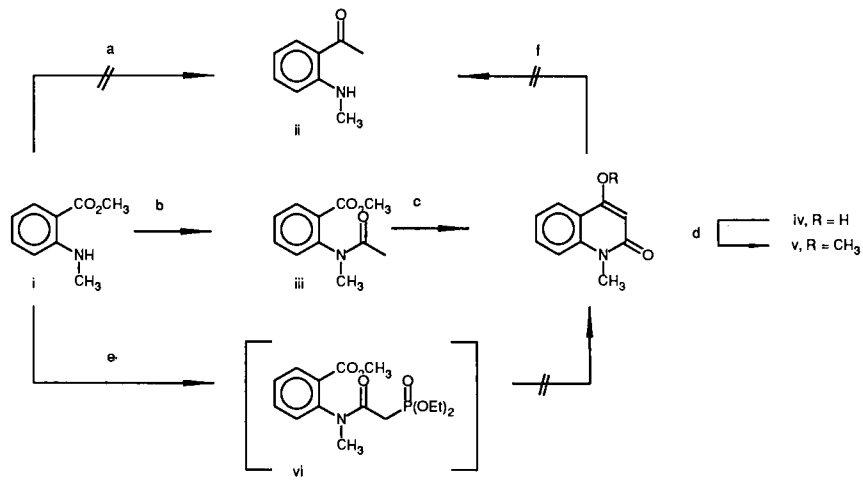
9. Streptonigrin total synthesis: S. M. Weinreb, F. Z. Basha, S. Hibino, N. A. Khatri, D. Kim, W. E. Pye, and T.-T. Wu, *J. Am. Chem. Soc.* **104,** 536 (1982); F. Z. Basha, S. Hibino, D. Kim, W. E. Pye, T.-T. Wu, and S. M. Weinreb, *J. Am. Chem. Soc.* **102,** 3962 (1980). For a detailed account, see S. M. Weinreb, *in* "Strategies and Tactics in Organic Synthesis" (T. Lindberg, ed.), Vol. 1, Chap. 12. Academic Press, Orlando, Florida, 1984.
10. Streptonigrin total synthesis: A. S. Kende, D. P. Lorah, and R. J. Boatman, *J. Am. Chem. Soc.* **103,** 1271 (1981). For a detailed discussion of the Rochester route to the total syntheses of streptonigrin and lavendamydin, see A. S. Kende, F. H. Ebetino, R. Battista, R. J. Boatman, D. P. Lorah, and E. Lodge, *Heterocycles* **21,** 91 (1984).
11. D. L. Boger and J. S. Panek, *J. Am. Chem. Soc.* **107,** 5745 (1985); D. L. Boger and J. S. Panek, *J. Org. Chem.* **48,** 621 (1983).
12. For a prior account of the synthetic studies on streptonigrin, see reference 5. For recent efforts, see (a) S. Hibino, *Heterocycles* **6,** 1485 (1977); (b) T. K. Liao, W. H. Nybert, and C. C. Cheng, *Angew. Chem. Int. Ed. Engl.* **6,** 82 (1967); T. K. Liao, P. J. Wittek, and C. C. Cheng, *J. Heterocycl. Chem.* **13,** 1283 (1976); P. J. Wittek, T. K. Liao, and C. C. Cheng, *J. Org. Chem.* **44,** 870 (1979); (c) K. V. Rao and P. Venkateswarlu, *J. Heterocycl. Chem.* **12,** 731 (1975); K. V. Rao, *J. Heterocycl. Chem.* **14,** 653 (1977); K. V. Rao and H.-S. Kuo, *J. Heterocycl. Chem.* **16,** 1241 (1979); (d) D. Kim and S. M. Weinreb, *J. Org. Chem.* **43,** 121, 125 (1978); S. Hibino and S. M. Weinreb, *J. Org. Chem.* **42,** 232 (1977); (e) M. Cushman and J. Mathew, *J. Org. Chem.* **46,** 4921 (1981); (f) J. W. Lown and S.-K. Sim, *Can. J. Chem.* **54,** 2563 (1976); (g) A. S. Kende and P. C. Naegely, *Tetrahedron Lett.* p. 4775 (1978); (h) T. Kametani, A. Kozuka, and S. Tanaka, *Yakugaku Zasshi* **91,** 1068 (1971), **90,** 1574 (1970), and references cited therein.
13. For initial studies on a related approach to streptonigrin based on the implementation of 1,2,4-triazine Diels–Alder reactions, see J. C. Martin, *J. Org. Chem.* **47,** 3761 (1982); J. C. Martin, *J. Heterocycl. Chem.* **17,** 1111 (1980).
14. Streptonigrin synthetic studies: (a) D. L. Boger and J. S. Panek, *J. Org. Chem.* **48,** 3763 (1982); (b) D. L. Boger and J. S. Panek, *Tetrahedron Lett.* **24,** 4511 (1983).
15. Lavendamycin biosynthesis: W. R. Erickson and S. J. Gould, *J. Am. Chem. Soc.* **107,** 5831 (1985).
16. Lavendamycin total synthesis: (a) A. S. Kende and F. H. Ebetino, *Tetrahedron Lett.* **25,** 923 (1984); (b) S. Hibino, M. Okazaki, M. Ichikawa, K. Sato, and T. Ishizu, *Heterocycles* **23,** 261 (1986); (c) D. L. Boger, S. R. Duff, J. S. Panek, and M. Yasuda, *J. Org. Chem.* **50,** 5790 (1985); (d) A. V. R. Rao, S. P. Chavan, and L. Sivadasan, *Tetrahedron* **42,** 5065 (1986); (e) For the preparation of desmethyllavendamycin and related studies, see S. Hibino, M. Okazaki, K. Sato, I. Morita, and M. Ichikawa, *Heterocycles* **20,** 1957 (1983); A. V. R. Rao, S. Chavan, and L. Sivadasan, *Indian J. Chem., Sect B* **23B,** 496 (1984).
17. Lavendamycin synthetic studies: (a) D. L. Boger and J. S. Panek, *Tetrahedron Lett.* **25,** 3175 (1984); (b) D. L. Boger, S. R. Duff, J. S. Panek, and M. Yasuda, *J. Org. Chem.* **50,** 5782 (1985).
18. Lavendamycin biological activity: D. M. Balitz, J. A. Bush, W. T. Bradner, T. W. Doyle, F. A. O'Herron, and D. E. Nettelton, *J. Antibiot.* **35,** 259 (1982).
19. (a) D. L. Boger and J. S. Panek, *J. Org. Chem.* **46,** 2179 (1981); D. L. Boger, J. S. Panek, and M. M. Meier, *J. Org. Chem.* **47,** 895 (1982); (b) D. L. Boger, J. Schumacher, M. D. Mullican, M. Patel, and J. S. Panek, *J. Org. Chem.* **47,** 2673 (1982), D. L. Boger and Q. Dang, *Tetrahedron* **44,** in press (1988); (c) D. L. Boger, R. S. Coleman, J. S. Panek, and D. Yohannes, *J. Org. Chem.* **49,** 4405 (1984); D. L. Boger, and M. Patel, *Tetrahedron Lett.* **28,** 2499 (1986); *J. Org. Chem.* **53,** 1405 (1988); D. L. Boger and S. Sakya, *J. Org. Chem.* **53,** 1415 (1988); (d) D. L. Boger and R. S. Coleman, *J. Org. Chem.* **49,** 2240 (1984), **51,** 3250 (1986); D. L. Boger and R. S. Coleman, *J. Am. Chem. Soc.* **109,** 2717 (1987); (e) For the com-

plementary use of 3-methoxycarbonyl-2-pyrones, see D. L. Boger and M. D. Mullican, *J. Org. Chem.* **49,** 4033 (1984); D. L. Boger and M. D. Mullican, *Tetrahedron Lett.* **23,** 4551 (1982), and references cited therein; (f) D. L. Boger, J. S. Panek, and M. Yasuda, *Org. Synth.* **66,** 142, (1987); (g) D. L. Boger, R. S. Coleman, J. S. Panek, F. X. Huber, and J. Sauer, *J. Org. Chem.* **50,** 5377 (1985).

20. W. G. Dauben and A. P. Kozikowski, *J. Am. Chem. Soc.* **96,** 3664 (1974); W. G. Dauben and H. Krabbenhoft, *J. Org. Chem.* **42,** 282 (1977); N. S. Isaacs, "Liquid Phase High Pressure Chemistry." Wiley (Interscience), New York, 1981; K. Matsumoto, *Synthesis* p. 999 (1986). Pressure reactions (6.2 kbar) were conducted in an AGP-10002 pressure generator available from Leco Corporation, Tem-Pres Division (Bellefonte, PA 16823) in a glass-plug-sealed, heat-shrinkable Teflon tubing. For a description of the apparatus, see P. DeShong, C. M. Dicken, J. J. Perez, and R. M. Shoff, *Org. Prep. Proced. Int.* **14,** 369 (1982).
21. P. Roffey and J. P. Verge, *J. Heterocycl. Chem.* **6,** 497 (1967); H. P. Figeys and A. Mathy, *Tetrahedron Lett.* **22,** 1393 (1981).
22. (a) D. L. Boger, C. E. Brotherton, J. S. Panek, and D. Yohannes, *J. Org. Chem.* **49,** 4056 (1984); (b) D. L. Boger and C. E. Brotherton, *J. Org. Chem.* **49,** 4050 (1984).
23. For example, see R. A. Pabon, D. J. Bellville, and N. L. Bauld, *J. Am. Chem. Soc.* **105,** 5158 (1983).
24. D. Liotta, W. Markiewicz, and H. Santiesteban, *Tetrahedron Lett.* p. 4365, 4369 (1977); D. Liotta, U. Sunay, H. Santiesteban, and W. Markiewicz, *J. Org. Chem.* **46,** 2605 (1981).
25. T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.* **94,** 6203 (1972); K. Ninomiya, T. Shioiri, and S. Yamada, *Tetrahedron* **30,** 2151 (1974).
26. (a) T. Kametani, T. Ohsawa, and M. Ihara, *Heterocycles* **14,** 277 (1980); (b) T. Kametani, T. Ohsawa, M. Ihara, and K. Fukumoto, *J. C. S. Perkin I* p. 460 (1978); T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *J. C. S. Perkin I* p. 389 (1976); (c) R. B. Miller and J. G. Stowell, *J. Org. Chem.* **48,** 886 (1983); (d) T. Kauffmann and H. Fischer, *Chem. Ber.* **106,** 220 (1973); (e) M. R. V. Sahyun and D. J. Cram, *Org. Synth.* **45,** 89 (1965).
27. P. Fitton, M. P. Johnson, and J. E. Mckeon, *J. C. S. Chem. Commun.* p. 6 (1968); P. Fitton and E. A. Rick, *J. Organomet. Chem.* **28,** 287 (1971).
28. The debromo substrate, dimethyl 3-amino-5-methyl-4-phenylpyridine-2,6-dicarboxylate, was fully characterized.[17b]
29. L. S. Hegedus and J. M. McKearin, *J. Am. Chem. Soc.* **104,** 2444 (1982); L. M. Venanzi and B. Pugin, *J. Organomet. Chem.* **214,** 125 (1981).
30. C. C. Cheng and S.-J. Yan, *Org. React.* **28,** 37 (1982).
31. V. Petrow and B. Sturgeon, *J. Chem. Soc.* p. 570 (1954).
32. H. S. Kuo and S. Yoshina, *Yakugaku Zasshi* **97,** 827 (1977).
33. For example, see W. S. Mungall, G. L. Greene, G. A. Heavner, and R. L. Letsinger, *J. Org. Chem.* **40,** 1659 (1975); E. J. Corey, B. Samuelsson, and F. A. Luzzio, *J. Am. Chem. Soc.* **106,** 3682 (1984).
34. (a) Authentic 7-aminoquinoline-5,8-quinone was prepared from 8-hydroxyquinoline by (i) 70% $HNO_3$, $H_2SO_4$, 0–25°C, 1 hour, 75% (5,7-dinitro-8-hydroxyquinoline); (ii) $H_2$, 5% Pd/C, THF–EtOH, 25°C, 48 hours (5,7-diamino-8-hydroxyquinoline); (iii) 10 equivalents Fremy's salt, $CH_3OH$–0.05 *M* $K_2HPO_4$, 25°C, 14–48 hours, 10–35% overall (7-aminoquinoline-5,8-quinone). (b) Further confirmation of these observations was derived from the work detailed in a total synthesis of lavendamycin methyl ester which was published[16a] subsequent to our initial studies.
35. F. Seela, *J. Med. Chem.* **15,** 684 (1972).
36. J. P. Marsh, Jr. and L. Goodman, *J. Org. Chem.* **30,** 2491 (1965); Y. Kiso, H. Isawa, K. Kitagawa, and T. Akita, *Chem. Pharm. Bull.* **26,** 2562 (1978).
37. H. Zimmer, D. C. Lankin, and S. W. Horgan, *Chem. Rev.* **71,** 229 (1971).

38. (a) J. A. Luly and H. Rapoport, *J. Org. Chem.* **46,** 2745 (1981); (b) K. V. Rao and H.-S. Kuo, *J. Heterocycl. Chem.* **42,** 232 (1979).
39. For example, see Eq. (11) and Scheme XII for efforts on the preparation of 7-amino-2-[2′-(6′-methoxycarbonyl)pyridyl]quinoline-5,8-quinone.
40. For a detailed account of many of the unsuccessful efforts, see reference 16c, supplementary material. Unsuccessful efforts related to our attempts to directly functionalize the β-carboline **30** are detailed below in Eq. (16).

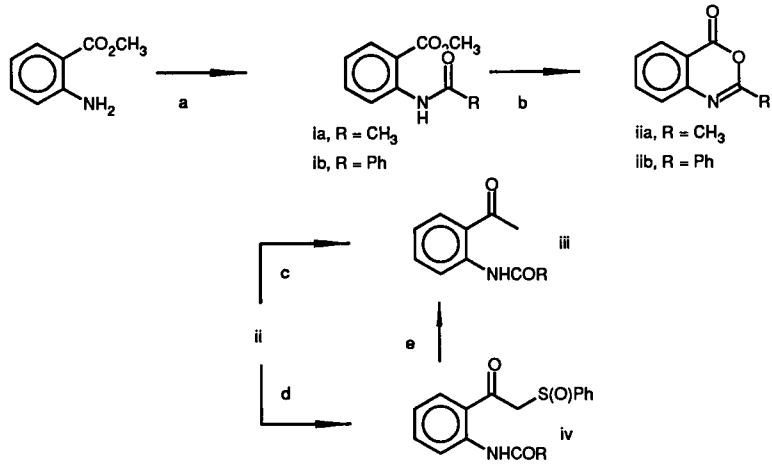
(16)




(a) 1.2–2.2 equivalent $(CH_3)_2Al(CH_2)(Cl)Ti(Cp)_2$, toluene–pyridine, −78 to 25°C, 24–48 hours, no reaction. (b) 1.2 equivalents NaH, THF, 0–25°C, 0.5 hour; 1.2 equivalents $CH_3COCl$, 25°C, 5 hours, 86%. (c) 2.5 equivalents LDA, THF, −78°C, 0.3 hours, 54%. (d) $CH_2N_2$, $Et_2O$, 25°C, 95%. (e) 1.2 equivalents $(EtO)_2P(O)COCl$, base ($Et_3N$, pyridine, DBU, NaH, *t*BuOK), no **v**. (f) Excess LiOH, $H_2O$–(THF), 25–100°C; 1 *N* aq. HCl or 1 *N* aq. HCL–dioxane (1 : 1), no **ii**.

Initial, preliminary studies which provided the basis for the decision to conduct the C-2/C-6 carboxylate differentiation at the stage of the amino diester **29** are detailed in Eq. (17).

41. E. J. Corey and M. J. Chaykovsky, *J. Am. Chem. Soc.* **87,** 1345 (1965).
42. A. I. Meyers, J. L. Durandetta, and R. Marava, *J. Org. Chem.* **40,** 2025 (1975).
43. $^1H$ NMR, IR, MS, and HRMS of **61** were in agreement with that previously disclosed for synthetic material.[10,16a] A direct comparison of a copy of the $^1H$ NMR (400 MHz) spectrum of authentic synthetic material[16a] with that of **61** (300 MHz) confirmed that the materials were identical.
44. Synthetic **64** displayed spectroscopic properties identical to those reported for authentic material.[2,5,10,16a] A direct comparison of a copy of the $^1H$ NMR (300 MHz) of authentic lavendamycin methyl ester[16a] with that of **64** confirmed that the materials were identical. A sample of authentic synthetic or natural lavendamycin or lavendamycin methyl ester was not available for direct comparison.
45. (a) D. L. Boger and M. Yasuda, *Heterocycles* **24,** 1067 (1986); (b) For prior use of cerium(III)-promoted additions to quinones and quinoline-5,8-quinones, see Y. T. Pratt, *J. Org. Chem.* **27,** 3905 (1962); H. S. Kuo and S. Yoshina, *Yakugaku Zasshi* **97,** 827 (1977).




(a) For **ia**: 3.0 equivalents $CH_3COCl$, 3.4 equivalents $K_2CO_3$, 25°C, 14 hours, 85%. For **ib**: 1.1 equivalents PhCOCl, pyridine, 0°C, 5 min, 100%. (b) For **iia**: 1.3 equivalents LiOH, THF–$H_2O$ (3:1), 25°C, 1.5 hours, 94%; 1.0 equivalent DCC, $CH_2Cl_2$, 25°C, 0.5 hour, 97%. For **iib**: 1.3 equivalents LiOH, THF–$H_2O$ (3:1), 25°C, 2 hours, 100%; 1.0 equivalent DCC, $CH_2Cl_2$, 25°C, 0.75 hour, 74%. (c) For **iia**: $Me_2(CN)CuLi_2$, $Et_2O$, −78°C, 0.5 hour, 36%. (d) For **iia**: 3.1 equivalents $LiCH_2S(O)Ph$, THF, −78°C, 2 hours, 83%. (e) R = $CH_3$, 10 equivalents Al(Hg), wet THF, −15°C, 2 hours, 80%.


46. K. V. Rao, *Cancer Chemother. Rep., Part 2* No. 4, 4, 11 (1974).
47. J. W. Lown, *Mol. Cell. Biochem.* **55,** 17 (1983); K. T. Douglas, *Chem. Ind. (London)* p. 766 (1984); N. S. Mizuno, *in* "Antibiotics V-2" (F. E. Hahn, ed.), pp. 372–384. Springer-Verlag, Berlin and New York, 1979.
48. J. Hajdu, "Metal Ions in Biological Systems," Chaps. 3, Vol. 19, pp. 53. Academic, New York, 1985.
49. B. K. Bhuyan, *in* "Antibiotics I. Mechanism of Action" (D. Gottlieb and P. D. Shaw, eds.), pp. 173–180. Springer-Verlag, Berlin and New York, 1967.
50. E. M. Hodnett, C. Wongwiechintana, W. J. Dunn, III, and P. Marrs, *J. Med. Chem.* **26,** 570 (1983).
51. I. A. Shaikh, F. Johnson, and A. P. Grollman, *J. Med. Chem.* **29,** 1329 (1986).
52. J. Renault, S.-G. Renault, M. Baron, P. Mailliet, C. Paoletti, S. Cros, and E. Voisin, *J. Med. Chem.* **26,** 1715 (1983).
53. R. Cone, S. K. Hasan, J. W. Lown, and A. R. Morgan, *Can. J. Biochem.* **54,** 219 (1976).
54. N. R. Bachur, S. L. Gordon, M. V. Gee, and H. Kon, *Proc. Natl. Acad. Sci. USA* **76,** 954 (1979).
55. (a) T. Miyasaka, S. Hibino, Y. Inouye, and S. Nakamura, *J. C. S. Perkin Trans. I* p. 479 (1986); (b) Y. Inouye, H. Okada, S. K. Roy, T. Miyasaka, S. Hibino, N. Tanaka, and S. Nakamura, *J. Antibiot.* **38,** 1429 (1985).
56. Minimum inhibitory concentrations (MIC, μg/mL) were determined by the agar dilution/streak method [see L. A. Mitscher, R.-P. Leu, M. S. Bathala, W.-N. Wu, J. L. Beal, and R. White, *Lloydia* **35,** 157 (1972)] by Mr. Steven D. Drake, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045–2500. $IC_{50}$ (μg/mL, inhibitory concentration for 50% cell growth relative to untreated control) values for B-16 mouse

melanoma and L-1210 mouse leukemia cell culture (ATCC CCL-219) were determined by Professor Paul Kitos, Department of Biochemistry, University of Kansas, Lawrence, KS 66045–2500, using a previously detailed procedure [see D. L. Boger, L. A. Mitscher, M. D. Mullican, S. D. Drake, and P. Kitos, *J. Med. Chem.* **28,** 1543 (1985)]. The $IC_{50}$ ($\mu$g/mL) values for P388 mouse leukemia (9PS) and human epidermoid carcinoma of the nasopharynx (9KB) were determined under the supervision of Linda Jacobsen, Purdue Cancer Center Cell Culture Laboratory Purdue University, West Lafayette, IN 47907, following the protocols established by the National Institutes of Health, National Cancer Institute.

57. D. L. Boger, M. Yasuda, L. A. Mitscher, S. D. Drake, P. A. Kitos, and S. C. Thompson, *J. Med. Chem.* **30,** 1918 (1987).

*Chapter 2*

# STUDIES IN SESQUITERPENE SYNTHESIS: (±)-QUADRONE AND (+)-PHYLLANTHOCIN

*Steven D. Burke*
*Department of Chemistry*
*University of Wisconsin–Madison*
*Madison, Wisconsin*



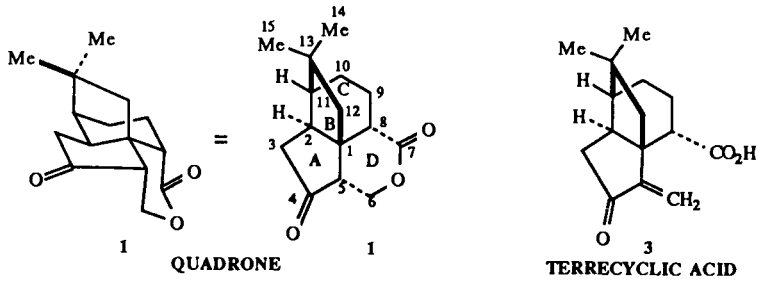
## I. Introduction

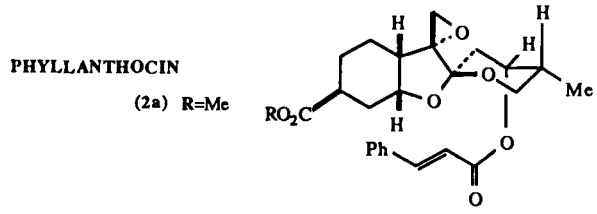
The skeletal and functional diversity of sesquiterpene natural products has provided synthetic chemists with decades of intellectual and technical challenge.[1] Current standards for carbocycle construction, stereocontrol, functional group manipulation, and computer-assisted synthetic analysis owe much to developments inspired by sesquiterpene targets. Even recently, when macrolide, polyether, and polyene structures (*inter alia*) have rightly drawn much attention, novel terpenoid structures with purported biological activity have still attracted considerable effort from the synthetic community.

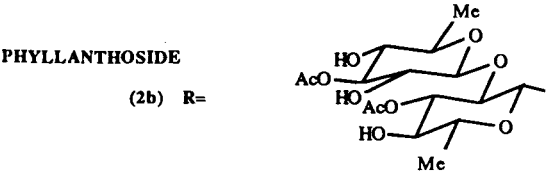
The isolation and characterization of two such targets, quadrone (**1**) and phyllanthocin (**2a**), coincided roughly with the inception of our independent research effort at the University of South Carolina in 1978. These substances possessed an irresistible combination of novel structure, respectable (but not daunting) complexity, and biomedical potential. The fact that *fourteen* groups

have since reported quadrone total syntheses[2] and that phyllanthocin has been synthesized via *five* different routes[3] signifies the intensity of the pursuit of these targets. Although outside the scope of this chapter, a comparison of the competing synthetic routes to these reveals an astonishing strategic diversity and notable tactical agility.

As is the style of the contributions to this and the preceding volume,[4] there is presented here an unlaundered account of our studies culminating in total syntheses of (±)-quadrone and (+)-phyllanthocin. Primary responsibility and full credit for these efforts must go to my first and seventh Ph.D. students, Bill Murtiashaw (Ph.D., 1983) and Jeff Cobb (Ph.D., 1985), whose dissertations[5] provide the basis for the ensuing discussion, and to their colleagues named in the literature citations.




Two reports on the isolation, structure, and biological properties of quadrone (**1**) emanated from the laboratories of the W. R. Grace Co. in 1978.[6] Butanol extracts of cultures of the soil fungus *Aspergillus terreus*

exhibited significant biological activity and yielded upon purification a crystalline substance which was reported to have cell growth inhibitory activity *in vitro* against human epidermoid carcinoma of the nasopharynx (KB, $ED_{50}$ = 1.3 $\mu$g/ml) and *in vivo* against P388 lymphocytic leukemia in mice. A relatively low general toxicity (intraperitoneal $LD_{50}$ value in mice >340 mg/kg) and a high yield of this substance from the fermentation broth (0.2 mg/ml) made characterization and further study imperative.

Standard spectroscopic and chemical analysis revealed cyclopentanone, $\delta$-lactone, and geminal dimethyl constitutional subunits and direct single-crystal X-ray analysis established **1** as the structure of this *quadr*icyclic ket*one*. The absolute configuration of natural (−)-quadrone was assigned in 1984 by Smith and Konopelski,[2k] who synthesized the unnatural antipode.

Cursory inspection of the quadrone structure renders the observed cytotoxic properties somewhat surprising, in that the molecule is devoid of the electrophilic functionality common in sesquiterpene antitumor agents. Published speculation[2d,q] that quadrone might serve via $\beta$-elimination as the source of the $\alpha$-methylene ketone **3**, a more plausible cytotoxic agent, presaged the isolation of this substance from a different strain of *A. terreus*.[7] In fact, the two syntheses of (±)-quadrone completed before ours proceeded via the substance **3**,[2d,e] prior to its isolation from nature and christening as terrecyclic acid. Significantly, terrecyclic acid is substantially more toxic than is quadrone. Unfortunately, neither of these substances has any apparent clinical potential.

Biosynthetic studies by Cane involving $^{13}C$-labeled acetate incorporations suggest that quadrone is derived from a mevalonate → farnesyl pyrophosphate → humulenyl cation (CC-conformation) → a fused triquinyl cation route, which provides the quadrone/terrecyclic acid skeleton after a series of 1,2-shifts.[8] No examples of this sesquiterpene architecture were previously known.

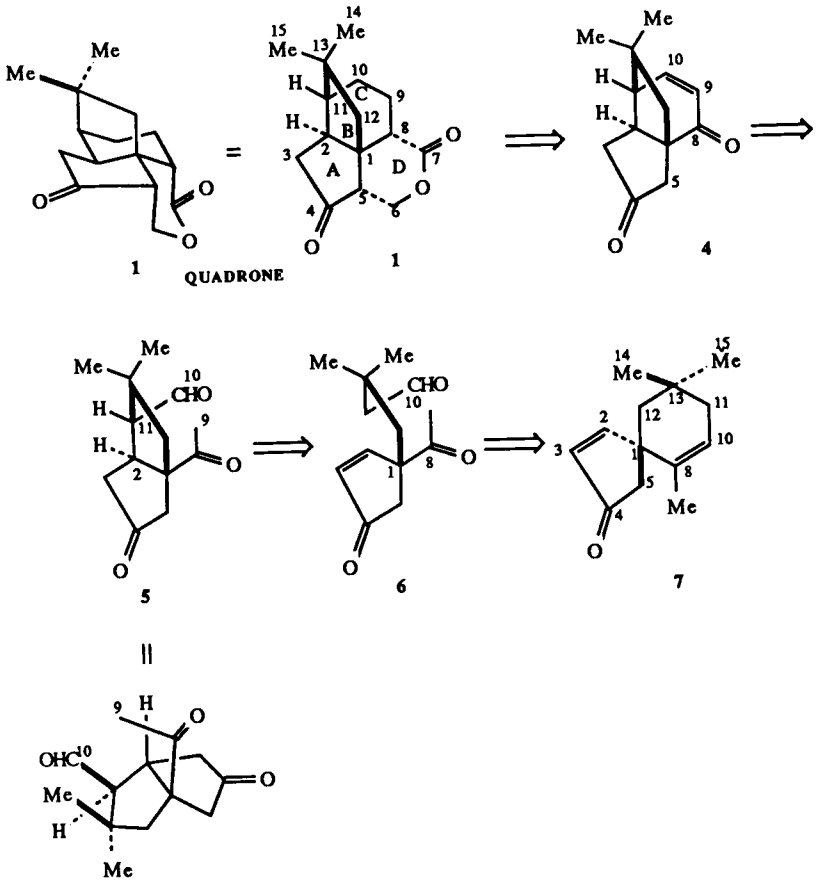
The isolation and structural analysis of (+)-phyllanthocin (**2a**) were reported in 1977 from the laboratories of the late Professor S. M. Kupchan.[9] As part of the U.S. National Cancer Institute's search for new antineoplastic agents from plants, the U.S. Department of Agriculture collected in Costa Rica roots of a tree believed to be *Phyllanthus brasiliensis* Muell. The genus *Phyllanthus* has a history of human medicinal usage, including the primitive treatment of cancer.[10] The Kupchan report described a new bisabolane glycoside from ethanol extracts of these roots, exhibiting significant *in vitro* cytotoxicity against KB cell culture and *in vivo* activity against murine 388 lymphocytic leukemia (PS). Methanolysis of the biologically active glycoside phyllanthoside (**2b**) afforded phyllanthocin (**2a**), the constitution and relative stereochemistry of which were determined by single-crystal X-ray analysis. This aglycone retains none of the biological activity of the parent glycoside.

Unlike quadrone, the biological imperative associated with phyllanthoside grew with time and necessitated substantial further study. This was impeded by the death of Professor Kupchan in 1976 and by the loss of the original samples of phyllanthoside and phyllanthocin. There remained 19 kg of plant material from the original collection, but this proved to be insufficient for the reisolation of phyllanthoside. Further attempts to reisolate phyllanthoside from the plant source were hampered when USDA scientists realized that *P. brasiliensis* is *not* indigenous to Central America. However, they were able to identify the original plant source as the closely related *Phyllanthus accuminatus* Vahl. A sample (150 kg) of root material was collected.

Guided by the PS assay, Professor G. R. Pettit was able to isolate and characterize four very similar glycosides from $MeOH/CH_2Cl_2$ extracts of these roots.[11] One of these was the Kupchan product, phyllanthoside, and the remaining three antineoplastic glycosides were designated as phyllanthostatins 1, 2, and 3. Phyllanthoside and phyllanthostatins 1 and 2 have in common the phyllanthocin bisabolane sesquiterpene aglycone (**2a**). To accommodate the testing needs of the National Cancer Institute, Pettit devised a large-scale isolation protocol for phyllanthoside.[11] For example, after a sequence of extraction and chromatography procedures, 1.56 metric tons of the chipped stems of *P. accuminatus* yielded 215.6 (0.014%) of phyllanthoside (**2b**). Recent biological interest has focused on the differential cytotoxicity toward breast tumors in the human tumor colony-forming assay (50% response rate at 1 $\mu$g/ml), although the rapid metabolism of phyllanthoside in rodents has hampered *in vivo* preclinical studies.[12]

## II. Quadrone

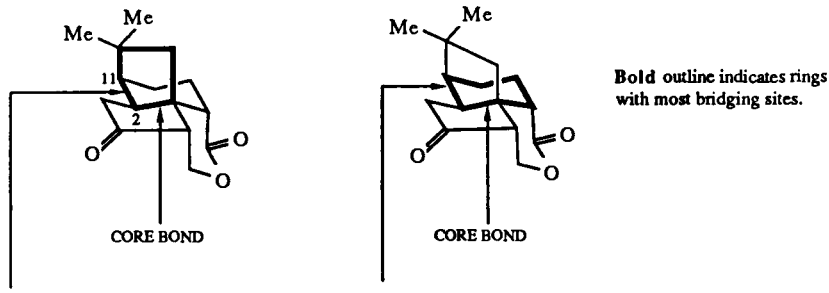
The antithetic simplifications in Scheme 1 reveal the strategic plan for the synthesis of (±)-quadrone (**1**). Our attention was focused upon the carbocyclic framework, wherein two bicyclooctane structural subunits are present. A diquinane moiety[13] is apparent in the cis-fused bicyclo[3.3.0]octane AB ring system, while rings BC define a bicyclo[3.2.1]octane skeleton. The C-8–C-10 propano bridge across the exo face of the diquinane and the C-3–C-5 fusion to the one-carbon bridge of the bicyclo[3.2.1] subunit are distinctive features, although these basic subunits are widely distributed among natural products of the cedrane, gibberellane, gymnomitrane, hirsutane, isocomane, and kaurane skeleta. In quadrone (**1**) there are five asymmetric centers distributed evenly such that the four rings contain three, three, four, and three stereocenters, respectively. Of the five asymmetric carbon atoms, four are neopentyl and the fifth (C-1) is quaternary and is common to each of the four rings. Excision of the D-ring $\delta$-lactone from **1** in a retrosynthetic sense leads




SCHEME 1

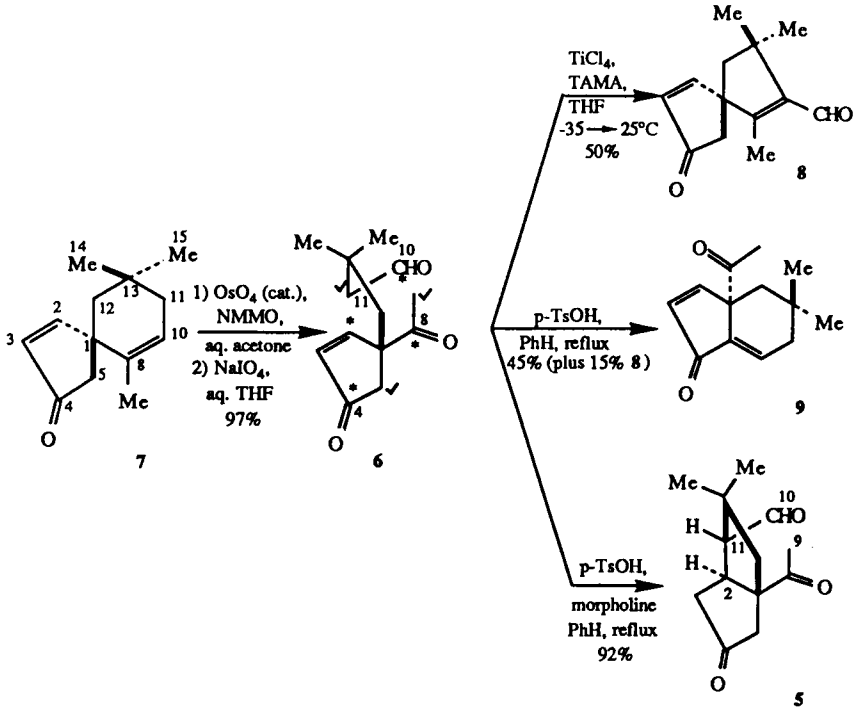
to the tricyclic enedione **4**, with the inclusion of a synthetically expedient C-9–C-10 unsaturation. It seemed likely at the planning stage that C-8 carbonyl homologation and C-5 hydroxymethylation in **4** would provide a simple end game for the synthesis. This supposition was grossly in error (*vide infra*). A retro aldol C-9–C-10 disconnection leads to the functionalized cis-fused bicyclo[3.3.0]octane system **5**, redrawn to highlight the fact that the formation of the C-9–C-10 bond in **4** would require an aldol closure bridging the exo face of the cis-fused diquinane. This idea, contained in one of my first research proposals, was described by one reviewer as "unlikely"; a less generous reviewer described it as "impossible." (The first comment was wounding, the second challenging.) Application of a retro-Michael transform

to **5** disconnects C-2 and C-11, leading to the $\delta,\delta$-disubstituted cyclopentenone **6** with the C-1 quaternary center in place. Finally, upon antithetic connection of the C-8 and C-10 carbonyls, the spiro[4.5]-decadienone **7** emerges as the 13-carbon precursor to the key tricyclic enedione **4**. Coincidentally, a vinylsilane-mediated spiroannulation sequence had been developed in our laboratories that provided efficient access to synthetically useful quantities of **7**.[14]




An *ex post facto* evaluation of this plan by application of Corey's "strategic bond" analysis provides gratifying support for the intramolecular Michael addition step for the formation of the C-2–C-11 bond.[15] Following Corey's guidelines, the quadrone B and C rings (boldly outlined) turn out to have the most bridging sites. Based on the published guidelines, one can identify the core bond in the structure and a strategic bond common to both of the outlined primary rings. Thus the C-2—C-11 bond-forming strategy is more than just intuitively appealing, in that a systematic synthetic planning protocol ratifies the choice.

The overall transmutation of the spiro[4.5]decadienone **7** to the tricyclic enedione **4** via **6** required a selective oxidative cleavage of one of two olefinic bonds. Specifically (Scheme 2), the C-8–C-10 trisubstituted olefin was the desired site. Fortunately, since most reagents for cleaving double bonds are electrophilic in nature, it seemed apparent that the cyclopentenone $\alpha,\beta$-unsaturation would not interfere. Much literature precedent existed for the use of $O_3$ or $OsO_4$ in related selective alkene cleavages.[16] Following a procedure by Slomp and Johnson[17] in which pyridine improved the selectivity of an ozonolysis in a substance with an isolated and a conjugated olefin, we were able to secure samples of **6** which were ~95% pure. However attempted purification on silica gel was not successful. More satisfactory results were obtained by a two-step procedure involving vicinal diol formation followed by oxidative cleavage. Thus treatment of **7** with a catalytic amount of $OsO_4$ and any of a variety of reoxidants [$NaIO_4$, $NaClO_3$, or (most



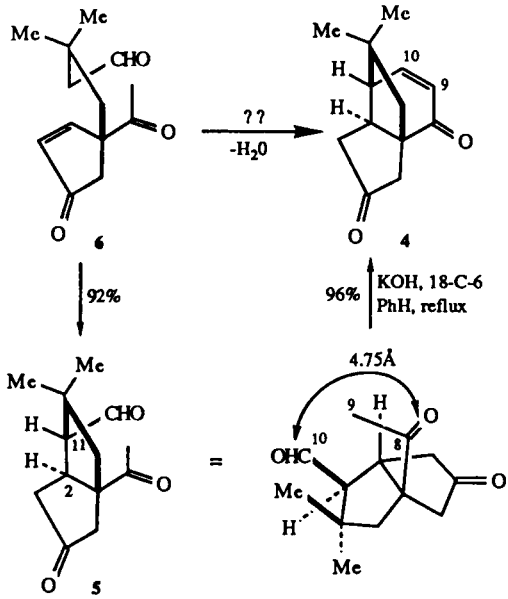

SCHEME 2

effectively) *N*-methylmorpholine *N*-oxide[18]] gave a crystalline mixture of diastereomeric *vic*-diols which suffered oxidative cleavage with $NaIO_4$ in aqueous tetrahydrofuran. The crude product thus formed could be chromatographed rapidly on silica gel to give a 97% yield of pure monocycle **6**.

We had hoped, naively, that the conversion of **6** to the tricyclic enedione **4** would follow directly via a one-pot Michael addition/aldol cyclization sequence with a net dehydration. This never happened. The conversion of **7** into **6** unleashed a smorgasbord of nucleophilic (√) and electrophilic (*)sites (Scheme 2) with possible pairings more numerous than suggested by the optimistic conformational drawing, and much trouble ensued.[19] Seeking simultaneous activation of the functionality in **6** as enamine (C-8, C-10) and imminium salt (C-4) derivatives, we settled on a mixture of $TiCl_4$ and *N*-methylanilinium trifluoroacetate (TAMA)[20] as a likely combination for effecting the Michael addition/aldol condensation to transform **6** into **4**. Treatment of a solution of **6** in THF at −35°C with 1 equivalent of $TiCl_4$ followed by 2 equivalents of TAMA gave, after warming slowly to room temperature, the crystalline spiro[4.4]nonadienone **8** (mp 108–111°C) as the

sole isolable product in 50% yield. Resulting from condensation between C-11 and C-8, this product of net dehydration was isomeric with the desired tricyclic enedione **4**. Similarly unsatisfying was the formation of a second crystalline dehydration product (**9**, mp 65–67°C) in 45% yield along with **8** (15%) upon treatment of **6** with catalytic *p*-toluenesulfonic acid in refluxing benzene. Fortunately, the course of conversion of **6** could be selectively guided along yet a third pathway; the functionalized diquinane Michael addition product **5** (mp 68–70°C) was formed in 92% yield on heating a solution of **6** with 2 equivalents of morpholine and catalytic *p*-TsOH in benzene at reflux with azeotropic removal of water.

Several dozen failed attempts to effect the C-9–C-10 aldol closure across the convex face of the cis-fused bicyclo[3.3.0]octane system followed. An X-ray crystallographic analysis of **5** provided a good news/bad news dichotomy.[21] Our fears that the C-11-formyl residue might not be on the exo face as formulated in **5** proved unfounded. However, the X-ray data provided an alternative explanation for the lack of success in the aldol closure (Scheme 3). The distance between the exo-oriented C-8 and C-10 carbonyls in the crystal was 4.75 Å, leaving the C-9 and C-10 carbons a closest approach of about 3.25 Å without deformation of the diquinane. The previously mentioned gloomy projections of the proposal referees regarding this closure were being strongly supported by structural data and repeated experimental failure.

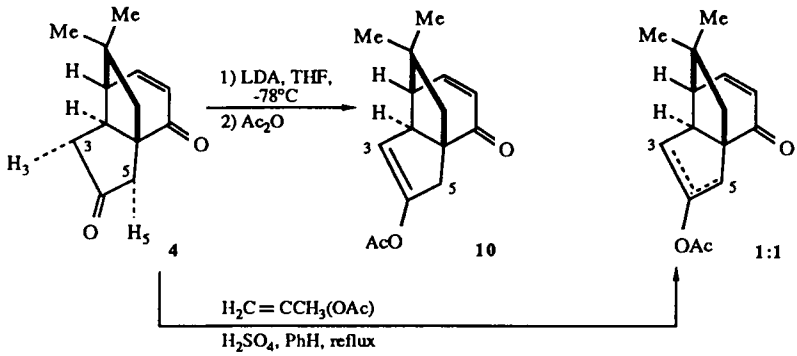



SCHEME 3

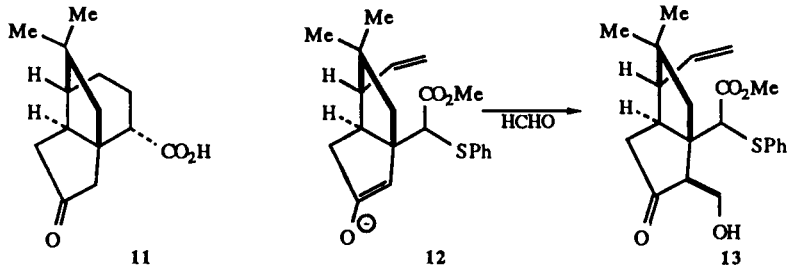
Standard aldol condensation conditions left **5** unaffected. No evidence for the formation of the tricyclic enedione **4** could be seen with secondary amine/acetic acid combinations or with numerous alkoxide and hydroxide bases in hydroxylic solvents. Of course, these conditions all afforded opportunity for retro-aldolization, which one might consider favorable given the nature of the desired closure between C-9 and C-10.

Treatment of **5** with LiOH solubilized in refluxing benzene with a phase transfer catalyst (Adogen 464)[22] provided in modest yield a new UV-active crystalline substance (mp 59–61°C) with distinctive spectral data. Carbonyl stretches in the infrared spectrum were observed at 1740 and 1680 $cm^{-1}$. A prominent parent ion at *m/e* 204 in the mass spectrum corresponded to a dehydration of **5**. The $^1H$ NMR was notably lacking resonances due to formyl and methyl ketone moieties. Olefinic resonances at $\delta$ 7.29 (1H, dd, $J$ = 9.6, 9.3 Hz) and $\delta$ 5.90 (1 H, d, $J$ = 9.6 Hz) confirmed the formation of the tricyclic enedione **4.** Several modified sets of conditions which also led to the successful aldol condensation/dehydration shared the following general features: alkali metal alkoxide (LiOH, NaOH, or KOH) in refluxing benzene with either phase-transfer or crown ether catalyst present. An optimum set of conditions (KOH, dibenzo-18-crown-6, high dilution in refluxing benzene) allowed the conversion **5** → **4** in 96% yield.[23]

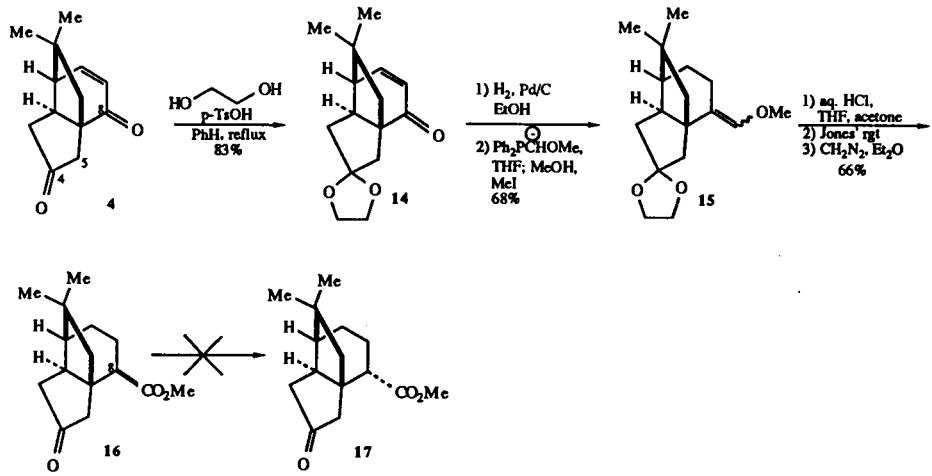
The tricyclic endione **4** seemed to us to be ideally suited for selective functionalization at C-5 and/or C-8 in that the two carbonyls would be easily differentiable by enolate formation. Enolization of the cyclohexenone moiety would be proscribed by the bridgehead nature of the intermediate dienol(ate).[24] One could, in principle, do selective electrophilic addition to a derived cyclopentanone enolate, or selective nucleophilic addition to the C-8 carbonyl by protecting the C-4 carbonyl as an enolate. Furthermore, we were able to (wrongly) convince ourselves, on the basis of a stereoelectronic argument, that of the presumably more accessible $\alpha$-oriented protons at C-3 and C-5, the latter should have the greater kinetic acidity.[25] In the event, kinetic deprotonation of **4** with LDA in THF at −78°C followed by an acetic



anhydride quench gave a single, undesired, $\Delta^{3,4}$-enol acetate **10**. Enol acetylation under thermodynamic conditions [$H_2C{=}CCH_3(OAc)$, $H_2SO_4$, benzene, reflux] gave a 1 : 1 mixture of the $\Delta^{3,4}$ and $\Delta^{4,5}$-enol acetates, a result considered not synthetically useful. It is noteworthy that Danishefsky had also encountered the selective formation of the undesired $\Delta^{3,4}$-enolate in his related system **11**[2d] and that Helquist, after generating by conjugate nucleophilic addition the $\Delta^{4,5}$-enolate **12**, observed unexpected endo (concave) face addition of formaldehyde to give **13**.[2e] Manifestations of the subtle and mischievous behavior of the quadrone ring system have been recorded in many laboratories.[2]

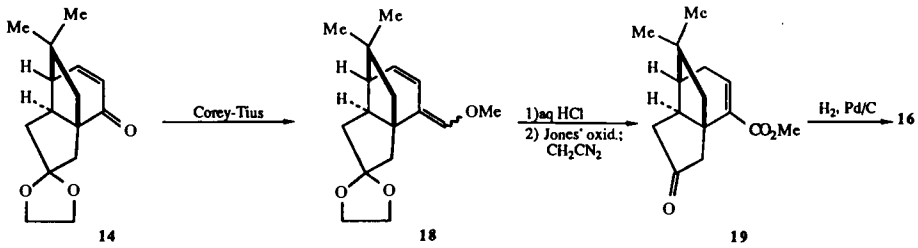



Having failed to selectively functionalize C-5, we turned to the homologation of the C-8 carbonyl (Scheme 4). Protection of the C-4 ketone as the ethylenedioxy ketal proceeded selectively under standard conditions to give **14**. Saturation of the C-9–C-10 olefin gave in near-quantitative yield the



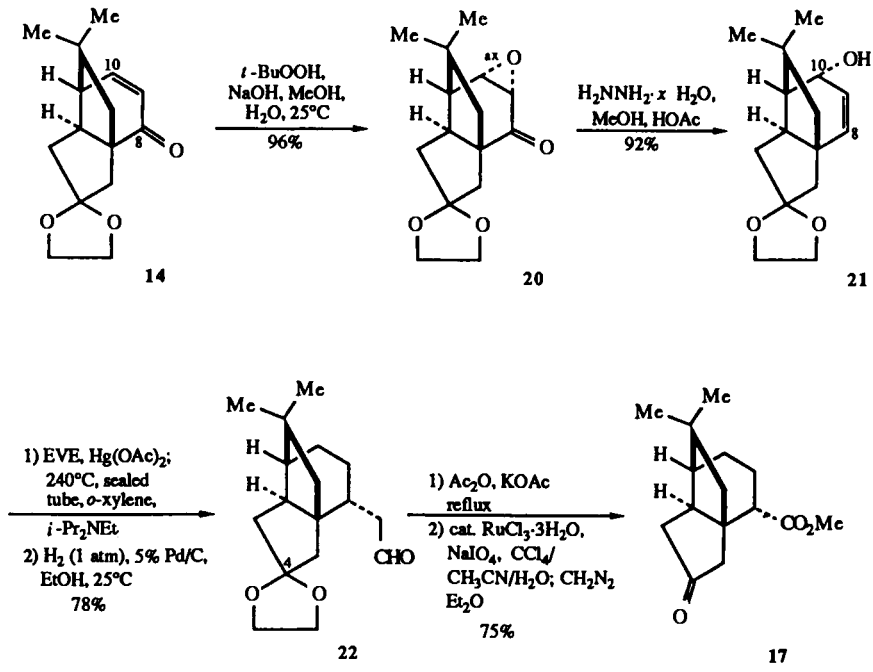

SCHEME 4

crystalline cyclohexanone (mp 58–60°C). The neopentyl C-8 carbonyl in both the enone **14** and the derived saturated ketone proved to be resistant to attack by numerous nucleophilic homologating agents; 2-lithio-2-trimethylsilyl-1,3-dithane,[26] methoxymethylenetriphenylphosphorane,[27] dimethylsulfonium methylide,[28] and chloro(trimethylsilyl)methyllithium[29] all failed to react. However, l-(diphenylphosponio)-l-methoxymethyllithium[30] proved to be a competent nucleophile in these systems. Reaction of this reagent with the saturated derivative of **14** followed by quenching and quaternization by the Corey-Tius protocol gave in 68% yield the enol ethers **15** plus 32% recovered ketone, presumably a result of competing enolate formation. Hydrolysis of the enol ether and ketal moieties gave in near-quantitative yield a single keto aldehyde with indeterminate C-8 stereochemistry. Oxidation with Jones' reagent and diazomethane esterification gave a single ester diasteromer **16** as an oil. That the C-8 stereochemistry in **16** was, as depicted, wrong became apparent on comparing the 400-MHz $^1$H NMR spectrum of our oily ester **16** with that of Danishefsky's crystalline ester **17**.[31] Numerous attempts to effect epimerization at C-8 in **16** failed; in fact, we found no evidence by $D_2O$ quenching experiments that deprotonation at the C-8 position ever occurred when **16** was treated with excess strong base.




A last attempt to homologate at C-8 involved the direct use of the enone **14** in the Corey–Tius homologation.[30] Now, absent the enolization possibility, **14** was completely consumed by the reagent, leading to the dienol ethers **18**. Hydrolysis with aqueous HCl gave the $\alpha,\beta$-enal ketone, which in turn gave the $\alpha,\beta$-unsaturated ester **19**. Catalytic hydrogenation of **19** gave the undesired keto ester **16** with equatorially oriented carbomethoxy group. Thus the seemingly ideal quadrone precursor **4** was proving to be less accommodating than anticipated. Attempts to directly functionalize C-5 and C-8 were halted.

Within the group we had developed an appreciation for intramolecular reactions for C—C bond formation,[32] especially methods by which carbon–heteroatom bonds could be parlayed into carbon–carbon bonds by sigmatropic rearrangement. Specifically (Scheme 5), it was felt that an $\alpha$-oriented




SCHEME 5

C-10 hydroxyl in a transposed allylic alcohol derived from **14** could serve to intramolecularly deliver a carbon in the contrathermodynamic C-8 axial orientation. This was the ultimately successful strategy for the completion of the formal and total syntheses of (±)-quadrone (**1**).[2a–c]

Successive allylic transpositions accomplished the C-8 functionalization, beginning with a Wharton rearrangement.[33] Conjugate epoxidation of **14** with basic *t*-BuOOH in aqueous methanol[34] afforded in 96% yield the crystalline epoxy ketone **20**. The sterically occlusive dimethylethano bridge in **14** served not only to lock the conformation of the C-ring enone but also to ensure α-epoxidation.

Of the several cantankerous reactions encountered during the course of this synthesis, the Wharton rearrangement converting **20** to the allylic alcohol **21** proved to be the most exasperating. High yields (92%) were obtained on a small scale (13 mg of **20**) under a very precise experimental protocol. Drastic reduction in yield accompanied all scale-up attempts. Some alleviation of this logistical bottleneck was possible by simultaneously executing 15–20 reactions in vials containing 13 mg each of the epoxy ketone **20**. To each vial was added 160 μl of reagent grade methanol and 0.5 ml

of glacial acetic acid, and the solution was frozen at −78°C. Upon removal from the bath, 32 μl of 64% aqueous hydrazine hydrate was added just as the solid began to melt. The contents of all the vials were then combined for workup and purification. It was possible in this way to process 1 g of epoxy ketone **20** per day to produce the crystalline allylic alcohol **21** (mp 69–71°C).

Initial attempts to effect the second allylic transposition focused on delivery of a single carbon to the C-8 α-position in **21** via a [2,3] sigmatropic rearrangement. Still's method[35] for the conversion of allylic alcohols to transposed homollylic alcohols was unsuccessful in this case, as was Buchi's method[36] for the conversion of allylic alcohols to β,γ-unsaturated amides. Attempted application of Nakai's method[37] involving the dianion of the α-allyloxyacetic acid derived from **21** also failed. The conformational rigidity in the bridged cyclohexene unit common to all of these [2,3] rearrangement substrates is the likely cause of these problems.

Delivery of a two-carbon subunit to the C-8 α-position in **21** was investigated next. Frustration mounted as various [3,3] sigmatropic rearrangement methods also failed in this substrate. Claisen rearrangement variants developed by Meerwein and Eschenmoser (amide acetal)[38] and by Johnson (orthoester)[39] gave no desired product. Attempted application of Whitesell's enolate Claisen rearrangement[40] of the methoxy acetyl derivative of **21** gave only fragmentation, regenerating **21**.

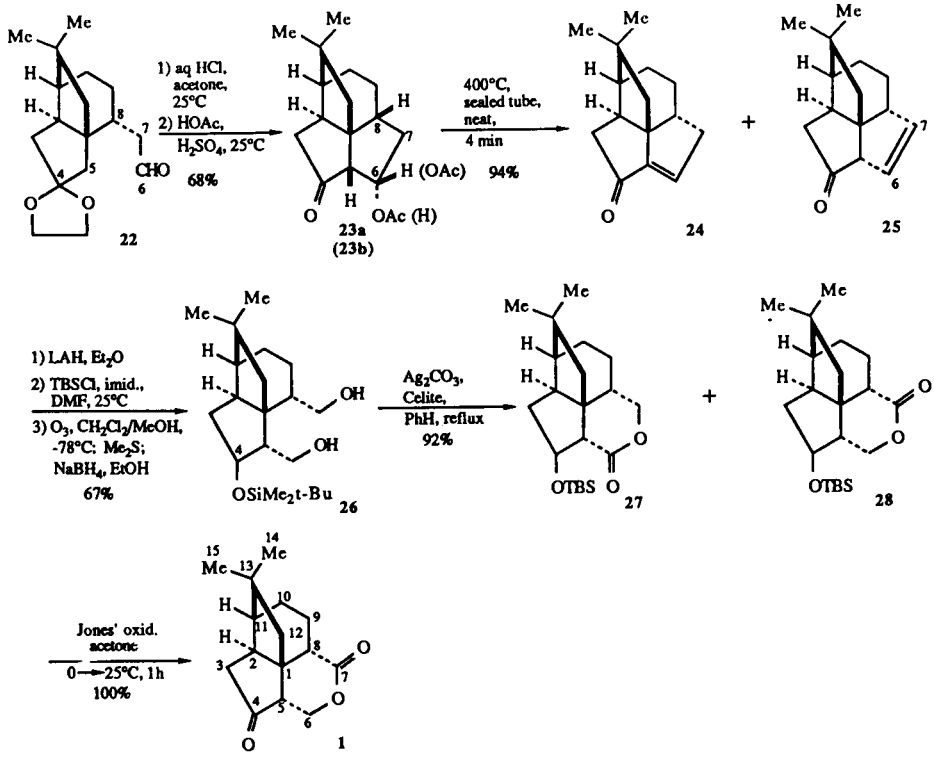
Finally, success was achieved by applying the most classical form of the Claisen rearrangement.[41] Vinyl ether exchange converted **21** to the corresponding allyl vinyl ether, which was thermolyzed at 240°C in xylene solution with Hunig's base (*N,N*-diisopropylethylamine) in a sealed tube. Catalytic hydrogenation of the resultant C-9–C-10 unsaturation gave the acetaldehyde derivative **22** in 78% overall yield from **21**.

With the recalcitrant C-8 axial carbon substituent unambiguously emplaced, a formal total synthesis of (±)-quadrone was at hand. Net oxidative decarbonylation and deketalization of **22** to give Danishefsky's intermediate **17** was accomplished in two ways. A common first step in these routes involved the enol acetylation of aldehyde **22** with $Ac_2O/KOAc$.[42] The dehomologous aldehyde was produced (60%) on oxidative cleavage with $NaIO_4/OsO_4$.[43] Jones oxidation was accompanied by deketalization to afford, after treatment with ethereal diazomethane, the keto ester **17** (mp 48–50°C; lit.[2d] 49–51°C) in 60% overall yield. This proved to be identical with an authentic sample from the Danishefsky laboratories by the usual spectroscopic and chromatographic criteria. A more efficient and aesthetic conversion of the enol acetates from **22** involved reaction with $RuCl_3 \cdot H_2O/NaIO_4$ in $CCl_4/CH_3CN/H_2O$.[44] This resulted in oxidative cleavage of the enol acetate double bond, upward adjustment to the

carboxylic acid oxidation state, *and* deketalization. Diazomethane esterification of the crude acid so derived gave in 79% overall yield the keto ester **17**.

Although serviceable for the completion of the formal synthesis, this dehomologation sequence had an annoying aspect. Discounting the ketal, the tricyclic aldehyde **22** has 15 carbons, exactly as needed for the natural product. To excise one carbon from **22** only to face the nontrivial introduction of the nascent C-6 residue at the difficulty accessible C-5 $\alpha$-site was not very attractive. It seemed reasonable to us that the aldehyde residue in **22** was suitably positioned for delivery to the C-5 $\alpha$-site via an internal aldol condensation, thus offering an unforced solution to the regio- and stereochemical problems encountered by others[2d,e] in the $\alpha$-functionalization of the C-4 carbonyl. This solution was predicated on our ability to adjust the C-7 and C-6 oxidation states and to effect their disconnection and reattachment through oxygen to give the requisite D-ring $\delta$-lactone in **1**.

Treatment of **22** with aqueous HCl in acetone effected deketalization to give the keto aldehyde (mp 77–79°C) in 86% yield (Scheme 6). On




SCHEME 6

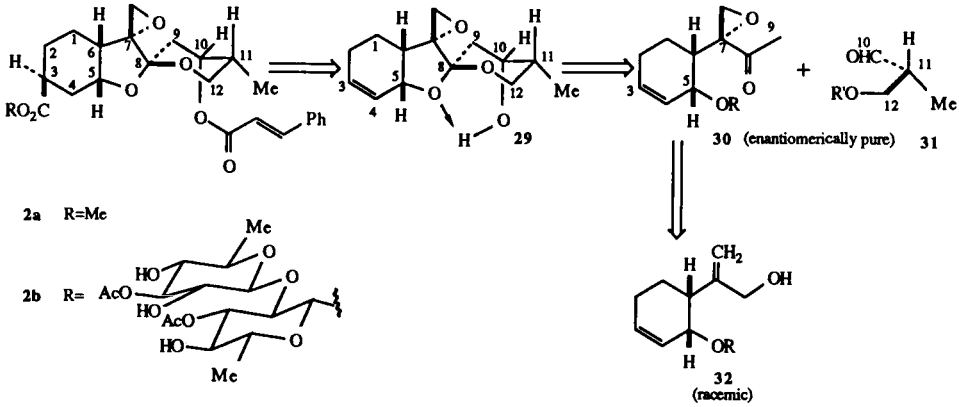
exposure to glacial acetic acid containing a trace of $H_2SO_4$, this keto aldehyde underwent intramolecular aldol cyclization to give the $\beta$-acetoxy ketones **23a,b** in a 4 : 1 ratio (79%). Pyrolysis of this mixture in a sealed tube at 400°C for 4 minutes gave a mixture of the desired $\beta,\gamma$-unsaturated ketone **25** (61%) and the conjugated enone **24** (33%). [Base-catalyzed aldolization and acetylation ($K_2CO_3$, MeOH, 25°C; $Ac_2O$) reversed the ratio to 1 : 2, and thermolysis of this mixture gave **24** as the predominant product.] Reduction of the carbonyl in the major isomer **25** and protection as the *t*-butyldimethylsilyl (TBS) ether[45] gave a single diastereomer of indeterminate configuration at C-4. Ozonolysis of the C-6–C-7 olefinic linkage followed by reductive workup gave the diol **26** (mp 139–140°C) in good overall yield. Unfortunately, the nearly symmetrical nature of this diol prevented a regioselective oxidation to cleanly give the quadrone $\delta$-lactone isomer. Oxidation with $Ag_2CO_3$ on Celite (Fetizon's reagent)[46] in refluxing benzene gave in 92% yield a 1 : 1 mixture of lactone regioisomers **27** and **28**. Attempts to improve on this oxidation regiochemistry with pyridinium chlorochromate,[47] pyridinium dichromate,[48] nickel(II) benzoate/$Br_2$,[49] and $PtO_2/O_2$[50] all failed to enhance the **28/27** ratio. Treatment of **28** with Jones' reagent in acetone at 0 → 25°C for 1 hour effected silyl ether hydrolysis and oxidation to provide (±)-quadrone (**1**) (mp 139–140°C; lit.[2d] 140–142°C) in quantitative yield. Comparison of our sample with one provided by Professor Danishefsky[31] confirmed that we had reached the synthetic objective.

The overall conversion of the spirodienone **7** to the natural product required 19 synthetic steps and proceeded in an overall yield of 6.2%. Notable in retrospect is the fact that experimental reality forced us to employ a synthetic route in which *all* new carbon–carbon bond-forming reactions were *intramolecular*.

## III. Phyllanthocin

An inspection of the stereofunctional attributes of phyllanthocin (**2a**) reveals a broad distribution of seven asymmetric centers about the tetracyclic nucleus. Attention is drawn immediately to the C-8 spiroketal as a key structural feature (Scheme 7). Notable also is a fused tetrahydrofuran wherein all carbons in this heterocyclic subunit are stereogenic. The C-7 spiro epoxide moiety has an *endo*-oriented oxygen relative to the cis-fused C-1–C-8 bicyclic subunit, thus negating on steric grounds a standard C-7 olefin epoxidation tactic.

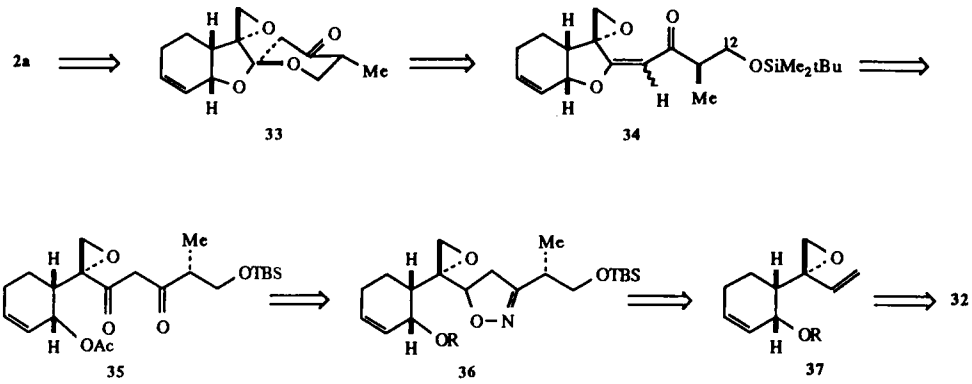
We pursued two synthetic approaches to (+)-phyllanthocin (**2a**) as the enantiomerically pure, natural antipode. The ultimately successful route is outlined antithetically in Scheme 7.[3d,e] A functionally simplified tetracyclic




SCHEME 7

framework **29** illustrates two key features of this strategy. First, we believed that the desired C-8 spiroketal configuration would prevail under thermodynamic control. The favorable combination of anomeric stabilization,[51] the indicated intramolecular hydrogen bond, and the equatorially oriented C-11 methyl group would not be sustained in the alternative C-8 epimer. Second, we sought to avoid the complication of accommodating the C-3 carbomethoxy group and the attendant stereochemical issue until the latest stages of the synthesis. This required the development of a means for the regioselective functionalization of the olefinic carbons C-3 and C-4 in **29** with oxidized carbon and hydrogen atoms, respectively. A convergent route to **29** was envisioned via a directed aldol coupling[52] of the enolate derived from the epoxyketone **30** and the now-familiar aldehyde **31**. High enantiomeric purity for both coupling partners would be required to avoid the formation of a complex diastereomeric mixture. Moreover, the compatibility of the electrophilic epoxide moiety in **30** with the generation and elaboration of the neighboring C-8–C-9 enolate was a serious concern. In fact, this strategy was based on an application of Sharpless' asymmetric epoxidation method[53] on the racemic allylic alcohol **32** for the control of the C-5, C-6, and C-7 stereocenters. Thus the sensitive 1,1-disubstituted epoxide was to be put in place at an early stage and carried through numerous functional manipulations.

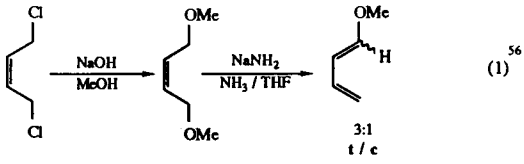
An alternative approach, which will be briefly described later, was based on the retrosynthesis detailed in Scheme 8. Access to the vinylogous ester **34** was expected via a $\pi$-allyl palladium species[54] derived from **35**; nucleophilic attack by the $\beta$-diketone would complete a double inversion process to give the spiroketal precursor **34**. Coupling of enantiomerically pure fragments analogous to **30** and **31** (Scheme 7) via a nitrile oxide [3 + 2] dipolar



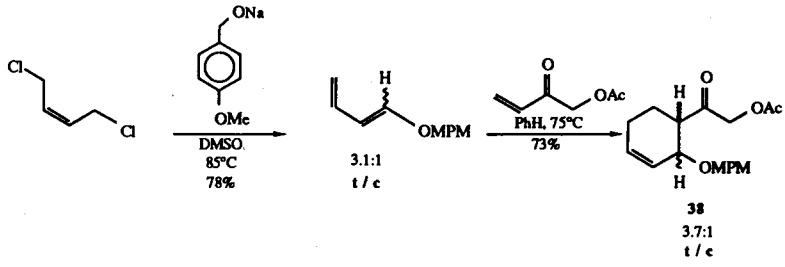

SCHEME 8

cycloaddition[55] was expected to give the $\Delta^2$-isoxazoline **36** as a $\beta$-diketone precursor. The ultimate failure of this route rested with the mutual incompatibility of the C-7 spiro epoxide and 1,3-dicarbonyl moieties (*vide infra*).

The initial need for a functionalized cyclohexene derivative such as **32** suggested a Diels–Alder route to the C-1–C-6 ring. As shown in Eq. (1), Everhardus *et al.* had described a 1,3-dienyl ether synthesis from *cis*-1,4-dichloro-2-butene.[56] We needed a dienyl ether wherein an ether → alcohol deprotection could ultimately be effected in a highly functionalized molecule (e.g., **42**) under neutral oxidative conditions. The *p*-methoxybenzyl [or *para*-*m*ethoxy*p*henyl*m*ethyl (MPM)] ether[57] promised to be ideal and was incorporated in the 1,3-diene by a modification of the Everhardus procedure [Eq. (2)]. Attempted formation of the bis-ether from *cis*-1,4-dichloro-2-butene and either lithium or sodium *p*-methoxybenzyloxide in THF gave no



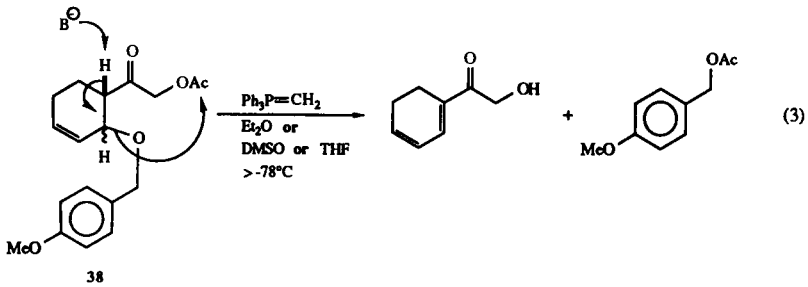

(1)[56]




(2)

product. However, reaction of the sodium alkoxide with the alkylating agent in DMSO at room temperature gave the pure *E*-dienyl ether in 25% yield. Apparently the alkoxide is a strong enough base in DMSO to effect elimination of the mono- or bis-ether to give the diene. A higher yield (78%) is available at the expense of stereoselectivity (3.1 : 1 *E*/*Z*) by conducting the reaction at 85 °C. The minor *Z*-isomer is recovered quantitatively from a Diels–Alder cycloaddition with acetoxymethyl vinyl ketone [58] and the diene mixture in benzene at 75°C; only the *E*-dienyl ether reacted under these conditions to give a 3.7 : 1 mixture of diastereomeric racemates **38** arising from competing endo and exo transition states.

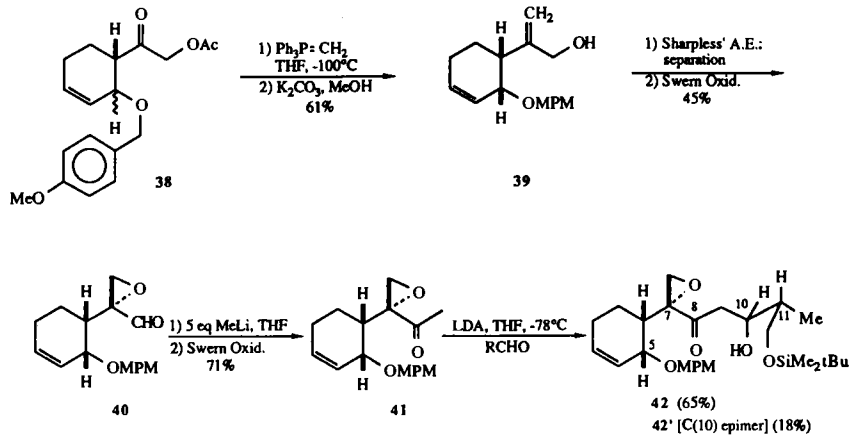
A Wittig methylenation of the ketone **38** was initially plagued by the β-elimination/transacylation process illustrated in Eq. (3). Fortunately, this




38 (3)

pathway could be minimized by conducting the Wittig reaction in THF at −100°C, with a beneficial enhancement of the cis/trans ratio from 3.7 : 1 in **38** to 5.9 : 1, presumably occurring via selective eliminative destruction of *trans*-**38.** After cleavage of the acetate with methanolic $K_2CO_3$, the racemic allylic alcohol **39** was available in 61% overall yield.

The tartrate-mediated Ti(IV)-catalyzed asymmetric epoxidation procedure of Sharpless[53] was applied to this allylic alcohol in two contexts. Epoxidation to complete consumption of **39** with (*L*)-(+)-diethyl tartrate/Ti(O-*i*-Pr)$_4$/*t*-BuOOH in methylene chloride at −23°C gave the (difficultly) separable diastereomeric epoxy alcohols along with 10–15% of isopropoxide-opened epoxide. Sharpless later noted the likelihood of this side reaction in the epoxidation of allylic alcohols similar to **39** in structure.[59] Under his revised conditions using Ti(O-*t*-Bu)$_4$ the combined yield of diastereomeric expoxides was 95%; also isolated was 4% of epoxide-opened product which had incorporated the *t*-butoxide ligand. Repetitive chromatography on silica gel separated the desired and undesired epoxide diastereomers, which by $^1$H NMR analysis at 400 MHz of the derived Mosher's esters [60] had enantiomeric excesses of ≥95% and 91%, respectively. The identity of the desired epoxide (mp 73–73.5°C) was secured by a chemical correlation and by



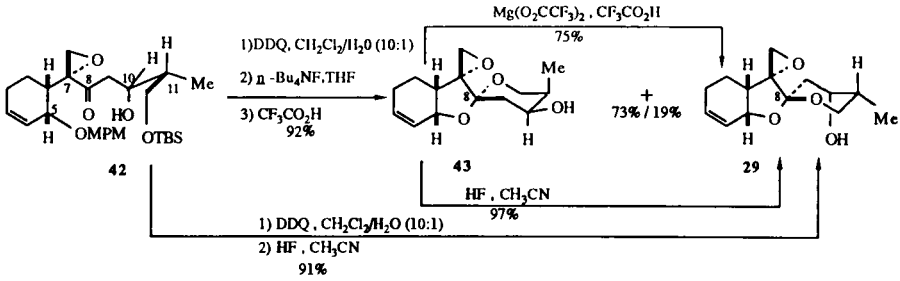

SCHEME 9

single-crystal X-ray diffraction studies [21] of a derivative of the unwanted isomer. Swern oxidation[61] of the purified epoxy alcohol with the correct absolute configurations at C-5, C-6, and C-7 gave the epoxy aldehyde **40** in quantitative yield.

A kinetic resolution[62] of the racemic allylic alcohol **39** was also attempted using the Sharpless asymmetric epoxidation. The reaction was stopped at approximately 50% completion to give in 45% yield the diastereomeric epoxides in a desired/undesired ratio of 1 : 4. Thus, although the enantiomers of **39** did epoxidize at different rates, the difference was insufficient for synthetic exploitation.

With aldehyde **40** available in multigram quantities in a state of high enantiomeric purity, completion of the synthesis of the directed aldol coupling partner (Scheme 9) was accomplished by the addition of MeLi in excess, which was always necessary to get complete consumption of **40.** Swern oxidation[61] of the resulting 2° alcohol gave in 71% overall yield the crystalline epoxy ketone **41** (mp 86–86.5°C).

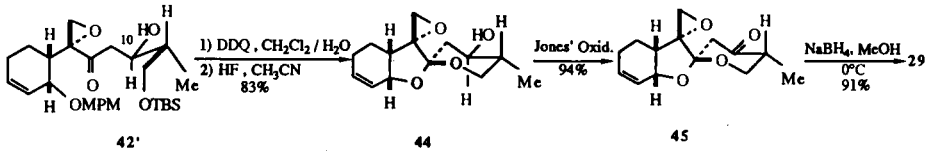
The required aldehyde **31** (Scheme 7, R′ = $SiMe_2t$-Bu) for the crossed aldol coupling was readily obtained in 85% yield by standard procedures from commercially available (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate.[63] Generation of the enolate of **41** with LDA in THF at −78°C followed by the addition of the C-10−C-12 aldehyde gave an easily separable 3.6 : 1 mixture of aldol products in 83% yield, plus 11% recovered ketone **41**. Thus concerns about the ability of the 1,1-disubstituted epoxide moiety in **41** to withstand the conditions of this coupling were unfounded. The major aldol product **42** has the correct C-10 stereochemistry and corresponds to a "Cram-cyclic" addition reminiscent of observations by Masamune[64] in a related condensation.



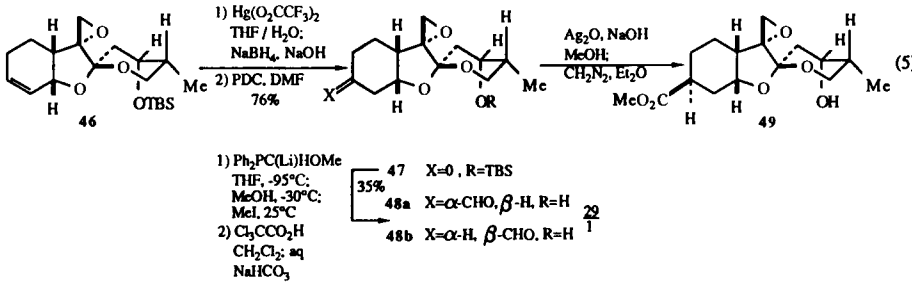

SCHEME 10

Construction of the C-8 spiro ketal moiety was initiated by cleavage of the MPM ether under mild oxidative conditions with DDQ (Scheme 10),[57] producing a mixture of hemiacetals. Direct treatment with *n*-$Bu_4NF$ cleaved the TBS ether, and cyclization with $CF_3CO_2H$ gave a 3.8 : 1 mixture of spiro ketals **43** and **29** in 92% overall yield. Analysis of the $^1$H-NMR and IR data for these isomers clearly identified the major product as the undesired diastereomer **43**. Subjection of this isomer to a variant of Williams' procedure[3b] for isomerizing a closely related spiroketal gave the desired diastereomer **29** in 75% yield. A substantial improvement in this sequence involved cleavage of the C-12 *t*-butyldimethysilyl (TBS) ether with 5% aqueous HF in acetonitrile. Under these conditions, spiroketalization occurred directly under equilibrium control to give the desired product **29** in 91% overall yield from **42**. Although the presence of **43** was detected at short reaction times (~3 min), the clean production of **29** was complete within 10 minutes at 25°C. Finally, subjection of the undesired diastereomer **43** to the $HF/CH_3CN$ conditions led to complete conversion (97% isolated yield) to the desired C-8 epimer **29**.

A high-yielding sequence by which the minor diastereomer **42'** from the crossed aldol condensation was also converted to **29** is detailed in Eq. (4). Deprotection and spiroketalization gave in 83% yield the C-10 equatorial alcohol **44**, which by oxidation and $NaBH_4$ reduction was inverted to the axial isomer **29** (**29** : **44** = 10.5 : 1).




After protection of the C-10 axial alcohol as the *t*-butyldimethylsilyl ether [**46**, Eq. (5)],[45] we were set for the task of regioselective functionalization of




(5)

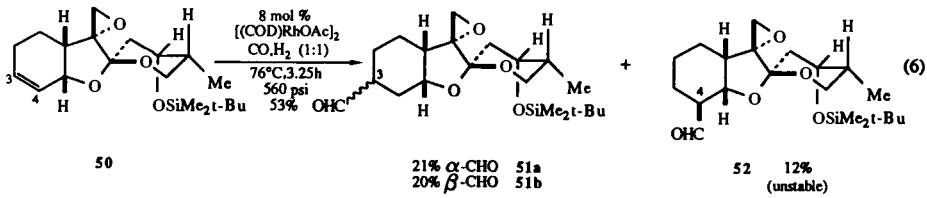
the cyclohexene subunit. Hopeful that a steric preference for C-3 metalation would outweigh the olefin polarization induced by the allylic oxygen, we first examined a hydrozirconation/carbonylation tactic.[65] Under Schwartz's usual reaction conditions [$(Cp)_2Zr(H)Cl$, PhH, alkene, 25°C], the substrate **46** was simply unreactive. Under more forcing conditions (65°C), extensive degradation of the substrate was the result. Similarly, no reaction could be effected between the spiroketal olefin **46** and 9-BBN,[66] within the framework of an attempted hydroboration/carbonylation. Possible explanations for this low reactivity credit the multiple Lewis basic sites in **46** with competing effectively but unproductively for the electrophilic reagents, or implicate the conflicting steric and electronic features of the allylic ether moiety.

With lowered expectations, **46** was subjected to oxymercuration/demercuration [Eq. (5)].[67] Reaction with mercuric trifluoroacetate in aqueous THF followed by reduction with $NaBH_4$ under alkaline conditions gave a 1.7 : 1.0 mixture of epimeric C-3 alcohols, which converged in 76% overall yield to a single ketone **47**. Much like the attempted ketone homologation in our quadrone efforts (*vide supra*), several attempts here were similarly unsuccessful. Methoxymethylenetriphenylphosphorane,[27] chloro-(trimethylsilyl)methyllithium,[68] and 2-lithio-2-trimethylsilyl-1,3-dithiane[26] gave no useful product. Limited success was again achieved with the Corey–Tius procedure,[30] converting **47** to the homologous methyl enol ether mixture in yields varying from 0 to 35%. Hydrolysis afforded quantitatively the C-3α- and β-formyl compounds **48a** and **48b** in a ratio of 29 : 1. Oxidation of **48a** with $Ag_2O$ in alkaline MeOH[69] was accompanied by epimerization to give, after esterification with $CH_2N_2$, a 2 : 1 mixture of descinnamoylphyllanthocin (**49**) and its C-3 epimer. Although formally completing a synthetic route to (+)-phyllanthocin,[3b] this method for introducing the C-3 carbomethoxy was unattractive and unreliable; we thus returned to investigating a more direct olefin functionalization method.

In principle, catalytic hydroformylation[70] offered a most attractive solution to the task at hand. Of course, the hydroformylation substrate **50** [(Eq (6)] represented an unusually complicated test in terms of functionality and

stereochemistry for this method. Typically, hydroformylation involves the rhodium- or cobalt-catalyzed addition of hydrogen and carbon monoxide to a linear terminal olefin, producing a mixture of branched and straight-chain saturated aldehydes. The ratio of linear to branched isomers is influenced by a number of factors, including catalyst, temperature, pressure, concentration, and solvent. Notably, the presence of excess phosphine ligand generally increases the linear/branched ratio in hydroformylation.

Much experimentation led to the result in Eq. (6), wherein usable C-3$\alpha$- (**51a**) and C-3$\beta$-formyl (**51b**) products could be obtained in a combined yield of 41%. Since **51a** could be epimerized with NaOMe/MeOH to **51b**,




(6)

both C-3-formyl products were useful for the production of (+)-phyllanthocin, as described in the original report.[3d] The undesired C-4-formyl product **52** was useless for our purposes; unfortunately, most attempts to improve the yield, regioselectivity, and stereoselectivity of this hydroformylation step led to preferential formation of **52**. After approximately 50 attempts to improve on the result in Eq. (6) by varying catalysts ($[COD)RhCl]_2$, $Rh_6(CO)_{16}$, $Rh_4(CO)_{12}$, $Rh_2O_3$, $(Ph_3P)_3RhCl$, $(CO)(Ph_3P)_2RhCl$, $[Rh(OAc)_2]_2$, $[(CO)_2RhCl]_2$, $(Ph_3P)_3Rh(CO)(H)$, $[(Ph_3P)_2Rh(CO)_3]^+ClO_4^-$, $Co_2(CO)_8/Ru_3(CO)_{12}$, $Co_2(CO)_8$, $(Ph_3P)_3Ir(CO)(H)$) and conditions (temperature, pressure, time, presence of excess phosphine or phosphite ligands, solvent), the following conclusions were reached:

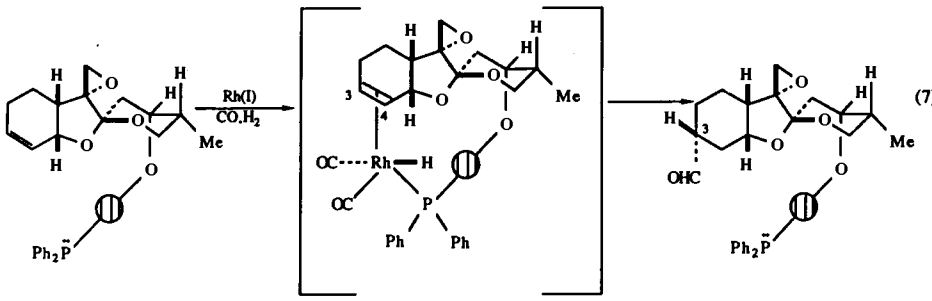
(1) Neither changes in temperature nor changes in solvent greatly affected the regioselectivity.

(2) Higher pressures promoted the formation of the unwanted regioisomer.

(3) The presence of phosphine or phosphite ligands greatly affected the regiochemistry in favor of the wrong regioisomer **52**, while making the reactions cleaner and faster.

(4) For the purpose at hand, the original conditions outlined in Eq (6) remained the best.

The positive aspects of the "added phosphine effect" leading to the comparatively clean and selective production of the unwanted C-4 regioisomer were the most promising of this discouraging list. It was felt that a

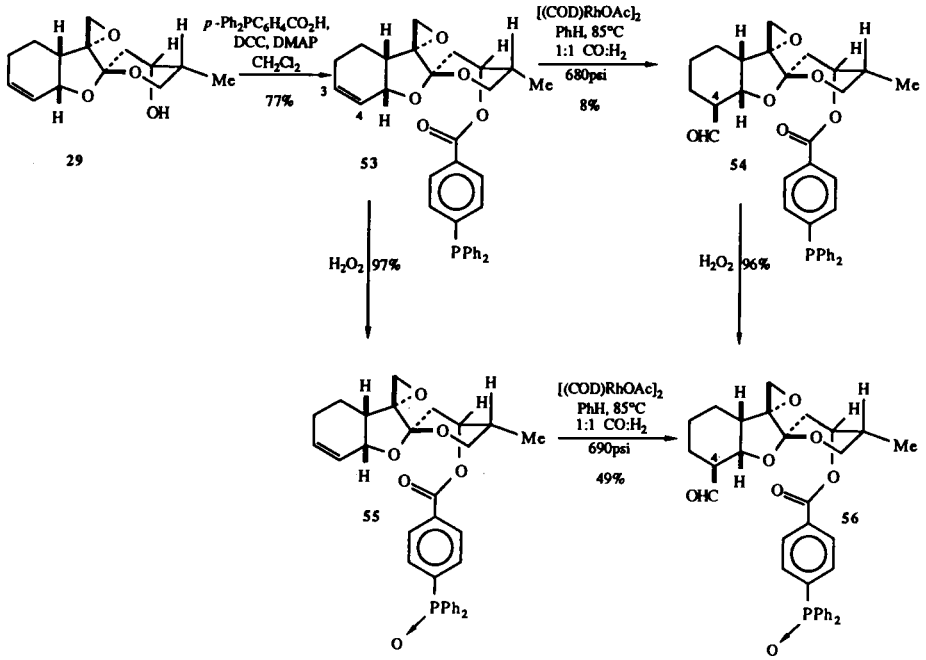



(7)

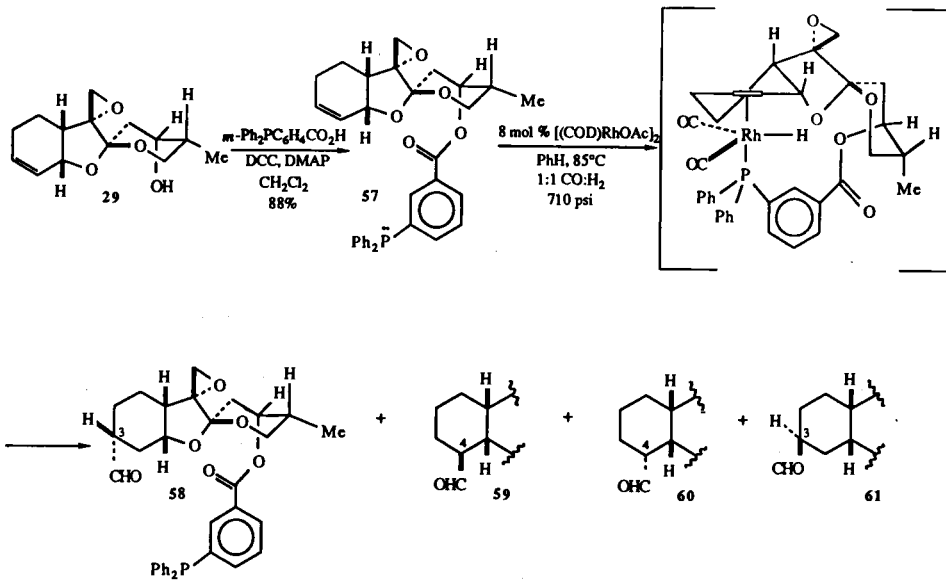
phosphine ligand could be incorporated into the hydroformylation substrate via a tether of suitable geometry so that the inherent regioselectivity could be reversed, illustrated generally in Eq. (7).[71] By linking the phosphine to the C-10 axial oxygen through a rigid spacer, it was hoped that the bracketed intermediate $\pi$-complex would proceed through the C-3 rhodium acyl, leading, after reductive elimination, to the C-3$\alpha$-formyl product. The phosphine would then have to give up the substoichiometric Rh(I) catalyst to another substrate phosphine for the process to continue. Although this "intramolecular hydroformylation" would necessarily give the opposite C-3 stereochemistry to that in phyllanthocin, the needed epimerization of the contrathermodynamic, endo-oriented C-3$\alpha$-formyl seemed assured.

Examination of molecular models suggested that the *p*-diphenylphosphinobenzoate auxiliary would have the necessary spatial characteristics for the intramolecular delivery to the concave face of the C-3—C-4 olefin. Coupling of the known carboxylic acid[72] to **29** (Scheme 11) gave in 77% yield the substrate **53**. Subjection of this to the hydroformylation conditions shown did result in a very clean reaction, with recovery of starting material in 84% yield. Hydroformylation had occurred in only 8% yield to provide **54**, in which the regiochemical outcome was wrong. Moreover, the formyl residue had been delivered to the face of the olefin opposite to where the phosphine was held. An enlightening sequence involved the conversion of **53** to the corresponding phosphine oxide **55** with 30% aqueous $H_2O_2$ in $Et_2O$.[73] Hydroformylation of this substrate, wherein there was no longer a phosphine ligand, had more "normal" characteristics. The reaction was messy, all starting material was consumed, and the C-4$\beta$-formyl product **56** was isolated in 49% yield, with which **54** was correlated by oxidation. This suggested that the phosphine moiety in **53** was indeed serving as a ligand for the Rh(I) catalyst, but that this association was largely prohibiting hydroformylation. To the small extent that reaction of **53** was occurring, the mode of hydroformylation was clearly *not* intramolecular.

Speculating that the ligand/spacer combination in **53** was too long, serving only to push the catalyst beyond the olefin locale, we chose the

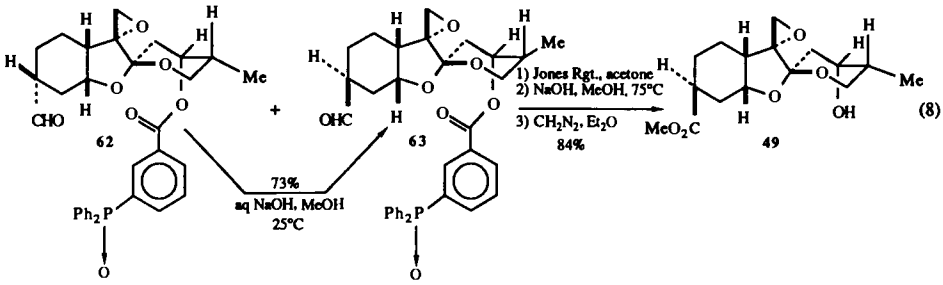



SCHEME 11




SCHEME 12

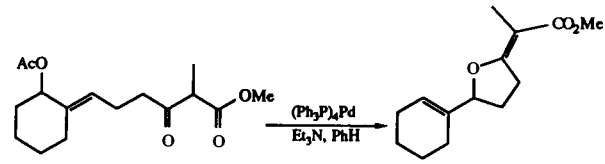
*m*-diphenylphosphinobenzoate **57** (Scheme 12) as a shortened ligand/spacer group. Coupling of the known *m*-diphenylphosphinobenzoic acid[74] to **29** by the Steglich procedure[75] afforded the substrate **57** in 88% yield. Subjection to the indicated hydroformylation conditions gave, via the presumed bracketed intermediate, a mixture of aldehydes **58**, **59**, **60**, and **61** in a ratio of 7.7 : 1 : 1 : 0.3.[76] Following a workup procedure involving removal of the rhodium catalyst with bis(1,3-diphenylphosphino)propane and oxidation (*t*-BuOOH) to the phosphine oxides, these aldehydic products were separated. The combined yield of desired C-3-formyl isomers **62** and **63** [Eq. (8)]

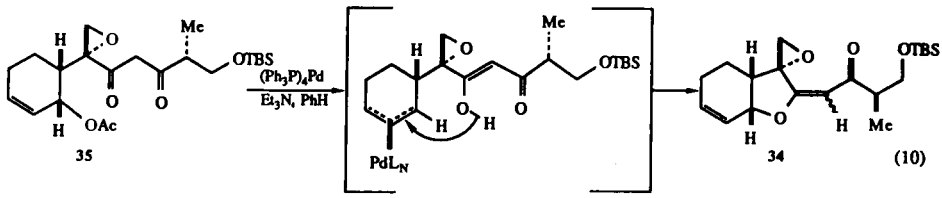



was 72% Equilibration of **62** with aqueous NaOH/MeOH at 25°C gave in 73% yield **63** (plus 18% recovered **62**). Oxidation of **63** to the acid with Jones' reagent, cleavage of the C-10 benzoate ester with aqueous NaOH in MeOH at 75°C, and esterification with ethereal diazomethane gave in 84% overall yield the crystalline hydroxy ester **49** (mp 130–130.5°C). Cinnamoylation of this material by the procedure of Williams[3b] gave (+)-phyllanthocin, mp 129–129.5°C, $[\alpha]_D^{25}$ +27.2° (*c* 2.04, $CHCl_3$),[77] in 82% yield. The synthetic objective was thus attained in 17 steps including an early introduction of the spiro epoxide moiety via a Sharpless asymmetric epoxidation protocol and a novel intramolecularly guided hydroformylation step.

It would be misleading, however, to leave the impression that the C-7 epoxide moiety was relatively inert. In fact, any exposure of the various epoxide-containing substances in the preceding discussions to acids such as HX or $ZnX_2$ (X = Cl, Br) invariably led to halohydrin formation. The failure of a synthetic strategy (Scheme 8) investigated in parallel to that just discussed can be directly blamed on the electrophilicity of the epoxide unit.

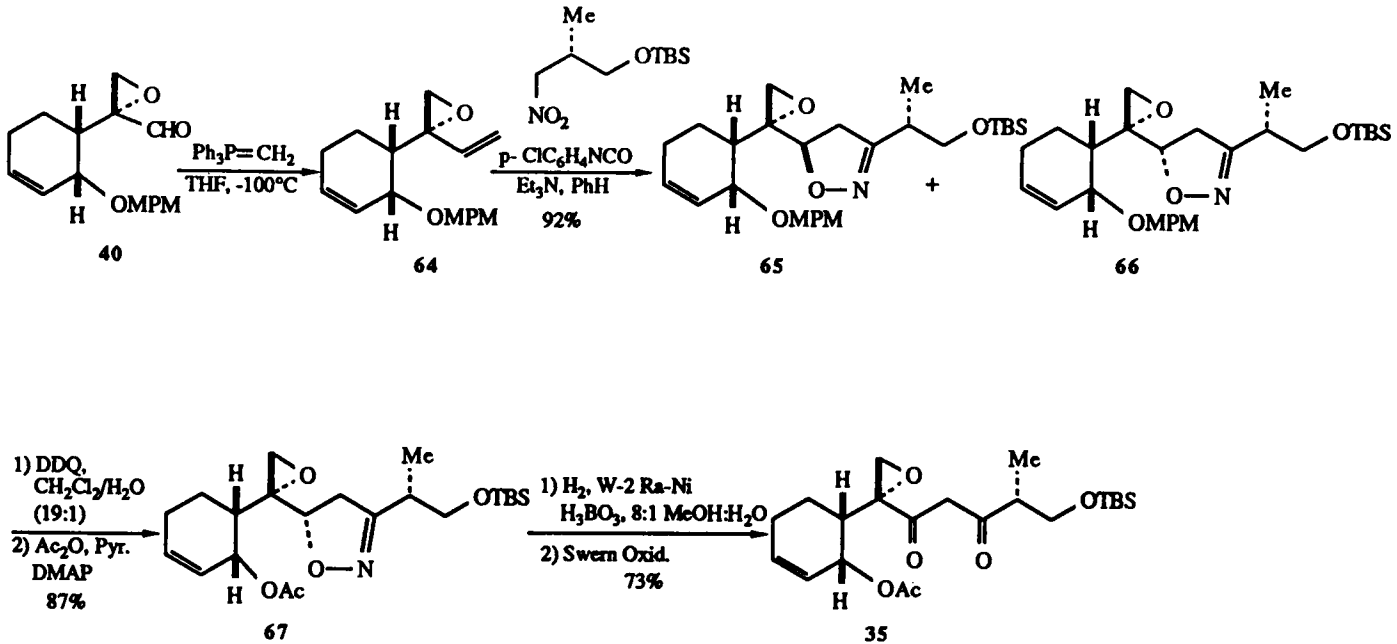
On the basis of a 1979 report by Trost[78] in which an intramolecular variant of his palladium-catalyzed allylic alkylation gave *O*-alkylated product [Eq. (9)], we had formulated a plan in which substrate **35** [Eq. (10)] would be similarly transformed. Double inversion via the $\pi$-allyl palladium species in brackets to the cyclized vinylogous ester **34** was expected to provide a viable precursor to the spiroketal **33** (Scheme 8).



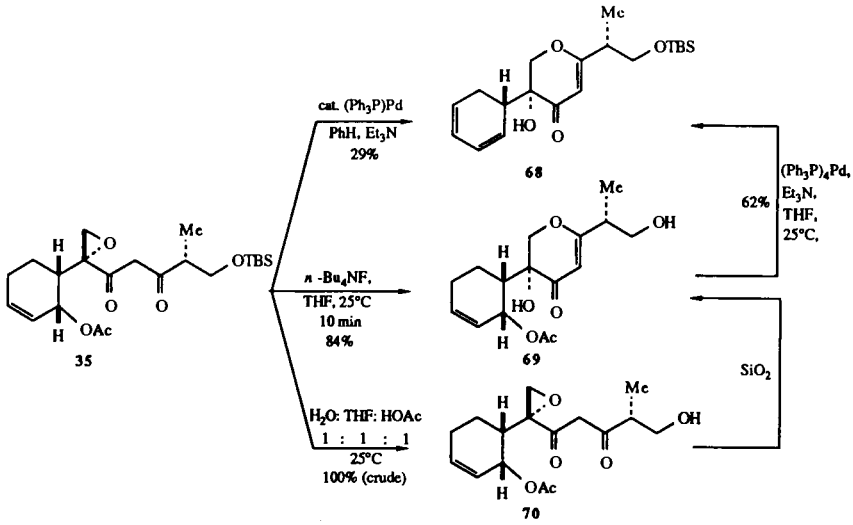




The synthesis of the β-diketone **35** is outlined in Scheme 13. The epoxy aldehyde **40** was available from the corresponding alcohol via Swern oxidation, [61] as described before. Wittig methylenation then gave the olefin **64** in 71% overall yield from the epoxy alcohol. Dehydration of the indicated nitro compound[79] *in situ* with *p*-chlorophenylisocyanate in *refluxing* benzene (Mukaiyama's conditions)[80] in the presence of the olefin **64** led to little [3 + 2] dipolar cycloaddition. Instead, the intermediate nitrile oxide had dimerized to give the corresponding furoxane.[81] However, the desired [3 + 2] cycloaddition pathway between **64** and the generated nitrile oxide did proceed smoothly when the reaction was run at room temperature, although a full 2 equivalents of the nitroalkane were required. The desired $\Delta^2$-isoxazolines **65** and **66** (1 : 2.6)[82] were formed in 92% combined yield, and both were carried forward independently. For example, conversion of the *p*-methoxybenzyl ether in **66** to the allylic acetate **677** proceeded uneventfully. Reductive cleavage of the isoxazoline N—O bond using Curran's buffered Raney Ni conditions[83] and *in situ* hydrolysis gave the corresponding β-hydroxyketone. Oxidation[84] with the trifluoroacetic anhydride version of the Swern oxidation gave in 73% overall yield the β-diketone **35**.

The key step in this strategy, an intramolecular palladium-catalyzed allylic *O*-alkylation, was at hand. Treatment of **35** under Trost's conditions[78] (Scheme 14) led to the dienic dihydropyrone **68** in 29% yield. The β-diketone nucleophile had eschewed the π-allyl palladium unit in favor of the epoxide electrophile. Base-induced elimination is a common fate of π-allyl Pd species in the absence of a nucleophile, leading to dienes.[85] Attempted desilylation of **35** with a variety of fluoride sources always gave in high yield the dihydropyrone **69** or its 1° *t*-butyldimethylsilyl (TBS) ether. Pyrone formation was always faster than deprotection. In the hope that pyrone formation would be reversible under the conditions of π-allyl Pd complex


Me
OTBS
NO2
H
O
CHO
OMPM
Ph3P=CH2
THF, -100°C
p- ClC6H4NCO
Et3N, PhH
92%
O—N
+
40
64
65
66
1) DDQ,
CH2Cl2/H2O
(19:1)
2) Ac2O, Pyr.
DMAP
87%
OAc
67
1) H2, W-2 Ra-Ni
H3BO3, 8:1 MeOH:H2O
2) Swern Oxid.
73%
35

SCHEME 13



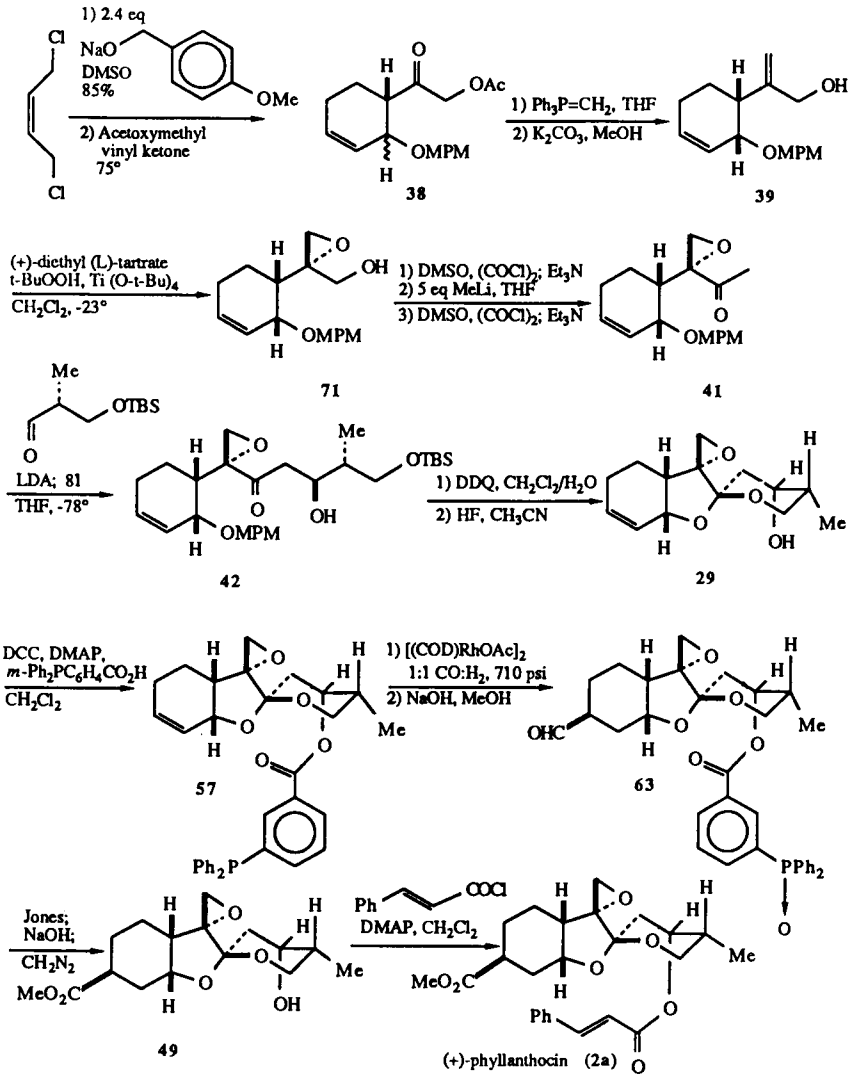

SCHEME 14

formation, **69** was so treated, leading only to **68**. Finally, conditions were found for desilylating **35**; treatment with 1 : 1 : 1 $H_2O$ : THF : HOAc gave the labile hydroxy diketone **70**, but attempted purification on silica gel led to clean production of the dihydropyrone **69**. Thus the electrophilic reactivity of the C-7 epoxide in **35** served to halt the pursuit of the nitrile oxide strategy of Scheme VIII.[86]

The linear sequence of 17 steps leading from *cis*-1,4-dichloro-2-butene to (+)-phyllanthocin (**2a**) is recapitulated in Scheme 15. From the optically pure, single diastereomer **71** through the 12 remaining steps to (+)-phyllanthocin the overall yield, not counting recovered and recycled material, was 13.4%. Thus, the early concessions to diastereomer separation in the steps leading to the epoxy alcohol **71** were compensated by average yields of approximately 85% in each of the final 12 steps.

## IV. Summary

The students of these chapters and the scientists who pursue synthetic organic chemistry will realize that the investigative trails leading to the syntheses of stereofunctionally complex molecules are never so direct as implied by primary literature accounts. Prominent synthetic chemists have eloquently stated the dangers of projecting such a misimpression[87] and have made compelling cases for the continued central role of synthesis in chemistry and related disciplines.[88] In this context, a degree of critical




SCHEME 15

introspection will help focus the future attention of synthetic chemists on timely issues of fundamental and practical importance.

It is likely and appropriate that synthetic chemistry will continue to evolve beyond terpenoid structural targets. Nevertheless, synthetic studies such as those herein leading to (±)-quadrone (**1**) and (+)-phyllanthocin (**2a**) provide intriguing and realistic challenges for the most current of organic chemical theory and methodology.

## Acknowledgments

The enthusiasm and tenacity shown by the researchers who did this work was inspirational. In addition to Charles W. (Bill) Murtiashaw and Jeffery E. Cobb, others who made substantial contributions to these studies are M. S. Dike, J. A. Oplinger, J. O. Saunders, S. M. S. Strickland, R. W. Sutton, and J. K. Takeuchi. This work was generously supported by the National Science Foundation, the National Institutes of Health, and the Alfred P. Sloan Foundation.

## References

1. (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In "The Total Synthesis of Natural Products" ApSimon, J., Ed.; Wiley: New York, 1983; Vol. 5, p. 1; (b) Heathcock, C. H. In "The Total Synthesis of Natural Products," ApSimon, J., Ed.; Wiley: New York, 1973; Vol. 2, p. 197.
2. (a) Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Dike, M. S. *J. Am. Chem. Soc.* **1982,** *104*, 872; (b) Burke, S. D.; Murtiashaw, C. W.; Oplinger, J. A. *Tetrahedron Lett.* **1983,** *24*, 2949; (c) Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Oplinger, J. A.; Dike, M. S. *J. Am. Chem. Soc.* **1984,** *106*, 4558; (d) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am Chem. Soc.* **1981,** *103*, 4136; (e) Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *J. Am. Chem. Soc.* **1981,** *103*, 4647; (f) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982,** *104*, 5805; (g) Takeda, K.; Shimono, Y.; Yoshii, E. *J. Am. Chem. Soc.* **1983,** *105*, 563; (h) Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983,** *48*, 1146; (i) Dewanckele, J. M.; Zutterman, F.; Vandewalle, M. *Tetrahedron* **1983,** *39*, 3235; (j) Wender, P. A.; Wolanin, D. J. *J. Org. Chem.* **1985,** *50*, 4418; (k) Smith, A. B., III; Konopelski, J. P. *J. Org. Chem.* **1984,** *49*, 4094; (l) Funk, R. L.; Abelman, M. M. *J. Org. Chem.* **1986,** *51*, 3247; (m) Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987,** *52*, 1483; (n) Kon, K.; Ito, K.; Isoe, S. *Tetrahedron Lett.* **1984,** *25*, 3739; (o) Piers, E.; Moss, N. *Tetrahedron Lett.* **1985,** *26*, 2735; (p) Iwata, C.; Yamashita, M.; Aoki, S.; Suzuki, K.; Takashi, I.; Arakawa, H.; Imanishi, T.; Tanaka, T. *Chem. Pharm. Bull.* **1985,** *33*, 436; see also Imanishi, T.; Matsui, M.; Yamashita, M. *J. Chem. Soc. Chem. Commun.* **1987,** *1802*; (q) Scarborough, R. M., Jr.; Toder, B. H.; Smith, A. B., III. *J. Am. Chem. Soc.* **1980,** *102*, 3904; see also reference 16.
3. (a) McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982,** *104*, 4496; (b) Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* **1984,** *106*, 2949; (c) McGuirk, P. R.; Collum, D. B. *J. Org. Chem.* **1984,** *49*, 843; (d) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1985,** *50*, 3420; (e) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986,** *27*, 4237; (f) Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987,** *109*, 1269; (g) Smith, A. B., III; Rivero, R. *J. Am. Chem. Soc.* **1987,** *109*, 1272; see also Smith, A. B., III; Hale, K. J; Vaccaro, H. A. *Tetrahedron Lett.* **1987,** *28*, 5591. (h) Martin, S. F.; Dappen, M. S.; Dupre, B.; Murphy, C. J. *J. Org. Chem.* **1987,** *52*, 3706.
4. "Strategies and Tactics in Organic Synthesis," Lindberg, T., Ed.; Academic Press: Orlando, Florida, 1984.
5. (a) Murtiashaw, C. W. Ph. D. Thesis, Univ. of South Carolina, Columbia, 1983; (b) Cobb, J. E. Ph. D. Thesis, Univ. of South Carolina, Columbia, 1985.
6. (a) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978,** 499; (b) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978,** *31*, 38.
7. (a) Nakagawa, M.; Hirota, A.; Sakai, H.; Isogai, A. *J. Antibiot.* **1982,** *35*, 778; (b) Hirota, A.; Nakagawa, M.; Sakai, H.; Isogai, A. *J. Antibiot.* **1982,** *35*, 783. The intraperitoneal $LD_{50}$ value in mice was found to be between 125 and 63 mg/kg.
8. Cane, D. E.; Whittle, Y. G.; Liang, T.-C *Tetrahedron Lett.* **1984,** *25*, 1119; *Bioorg. Chem.* **1986,** *14*, 417.

9. Kupchan, S. M.; La Voie, E. J.; Branfman, A. R.; Fei, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1977,** *99*, 3199.
10. (a) Usher, G. "A Dictionary of Plants Used By Man," Constable Press: London, 1974; p. 455; (b) Pettit, G. R.; Cragg, G M.; Gust, D.; Brown, P. *Can. J. Chem.* **1982,** *60*, 544.
11. Pettit, G. R.; Cragg, G. M.; Suffness, M. I.; Gust, D.; Boettner, F. E.; Williams, M.; Saenz-Renauld, J. A.; Brown, P.; Schmidt, J. M.; Ellis, P. D. *J. Org. Chem.* **1984,** *49*, 4258, and references cited therein.
12. These data were provided to us in January 1987 by Dr. Gordon M. Cragg, Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, NIH, Bethesda, Maryland. We thank him for his encouragement and assistance.
13. (a) Paquette, L. A. "Recent Synthetic Developments in Polyquinane Chemistry," Topics in Current Chemistry; Springer-Verlag: Berlin and New York, 1984; Vol. 119; (b) Paquette, L. A.; Doherty, A. M. "Polyquinane Chemistry, Syntheses and Reactions," Springer-Verlag: Berlin and New York, 1987.
14. Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Strickland, S. M. S.; Saunders, J. O. *J. Org. Chem.* **1981,** *46*, 2400.
15. Corey, E. J.; Howe, W. J.; Orf, H. W.; Pensak, D. A.; Petersson, G. *J. Am Chem. Soc.* **1975,** *97*, 6116.
16. For selective ozonolyses on polylefinic substrates, see (a) Pelletier, S. W.; Iyer, K. N.; Chang, J. W. J. *J. Org. Chem.* **1970,** *35*, 3535; (b) Heyl, F. W.; Herr, M. E. *J. Am. Chem. Soc.* **1950,** *72*, 2617; (c) Herr, M. E.; Heyl, F. W. *J. Am. Chem. Soc.* **1952,** *74*, 3627; (d) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980,** p. 807; (e) For an example of a selective osmylation, see Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952,** *74*, 4223.
17. Slomp, G.; Johnson, J. L. *J. Am. Chem. Soc.* **1958,** *80*, 915.
18. Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976,** p. 1973.
19. Burke, S. D.; Murtiashaw, C. W.; Dike, M. S. *J. Org. Chem.* **1982,** *47*, 1349.
20. Gras, J.-L. *Tetrahedron Lett.* **1978,** p. 2111.
21. We are indebted to Dr. Lukasz Lebioda for this structure determination.
22. Kieczykowski, G. R.; Pogonowski, C. S.; Richman, J. E.; Schlessinger, R. H. *J. Org. Chem.* **1977,** *42*, 175.
23. Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem. Int. Ed. Engl.* **1986,** *25*, 960.
24. (a) Buchanan, G.-L. *Chem. Soc. Rev.* **1974,** *3*, 41; (b) Köbrich, G. *Angew. Chem. Int. Ed. Engl.* **1973,** *12*, 464.
25. (a) Stork, G.; Still, W. C.; Singh, J. *Tetrahedron Lett.* **1979,** p. 5077. For a similar example, see (b) Reference 7 in Quallich, G. J.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979,** *101*, 7627.
26. Gröbel, B.-T.; Seebach, D. *Synthesis* **1977,** p. 357.
27. (a) Levine, S. G. *J. Am. Chem. Soc.* **1958,** *80*, 6150; (b) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961,** *94*, 1373.
28. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965,** *87*, 1353.
29. Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977,** *99*, 4536.
30. Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980,** *21*, 3535.
31. We are grateful to Professor Danishefsky (Yale University) for providing spectra and authentic samples.
32. The case for intramolecular synthetic processes has been convincingly stated by Eschenmoser. See Eschenmoser, A. *Q. Rev. Chem. Soc.* **1970,** *24*, 366.
33. Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961,** *26*, 3615.
34. Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958,** *80*, 5845.
35. Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978,** *100*, 1927.

36. Büchi, G.; Cushman, M.; Wüest, H. *J. Am. Chem. Soc.* **1974,** *96*, 5563.
37. Nakai, T.; Mikami, K.; Taya, S.; Kimura, Y.; Mimura, T. *Tetrahedron Lett.* **1981,** *22*, 69.
38. (a) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969,** *52*, 1030; (b) Meerwein, H.; Florian, W.; Schön, N.; Stopp, G. *Justus Liebigs Ann Chem.* **1961,** *641*, 1.
39. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970,** *92*, 741.
40. Whitesell, J. K.; Helbing, A. M. *J. Org. Chem.* **1980,** *45*, 4135.
41. For reviews of the Claisen rearrangement, see (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975,** *22*, l; (b) Ziegler, F. E. *Acc. Chem. Res.* **1977,** *10*, 227.
42. Bedoukian, P. A. "Organic Syntheses," Wiley: New York, 1955; Collect. Vol. III, p. 127.
43. Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956,** *21*, 478.
44. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981,** *46*, 3936.
45. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972,** *94*, 6190.
46. Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975,** *31*, 171.
47. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975,** p. 2647.
48. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979,** p. 399.
49. Doyle, M. P.; Bagheri, V. *J. Org. Chem.* **1981,** *46*, 4806.
50. Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973,** p. 3899.
51. For an excellent discussion of the anomeric effect, see Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry," Pergamon: Oxford, 1983; Chap. 2.
52. For recent reviews of stereoselective aldol reactions, see (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982,** *13*, l; (b) Mukaiyama, T. *Org. React. (N. Y.)* **1982,** *28*, 203; (c) Heathcock, C. H. In "Comprehensive Carbanion Chemistry," Durst, T.; Buncel, E., Eds.; Elsevier: Amsterdam, 1984; Vol. II; (d) Heathcock, C. H. In "Asymmetric Synthesis," Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p. 111.
53. Katsuki, T.; Sharpless, K. B. *J. Am Chem. Soc.* **1980,** *102*, 5974; (b) Rossiter, B. E. In "Asymmetric Synthesis," Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p. 193.
54. For a general overview, see Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. "Principles and Applications of Organotransition Metal Chemistry," Univ. Sci. Books: Mill Valley, California, 1987; p. 881.
55. For a general review of this area, see "1,3-Dipolar Cycloaddition Chemistry," Padwa, A., Ed.; Wiley: New York, 1984; Vols. 1 and 2.
56. Everhardus, R. H.; Peterse, A.; Vermeer, P.; Brandsma, C.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1974,** *93*, 90.
57. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982,** *23*, 885.
58. Hennion, G. F.; Kupiecki, F. P. *J. Org. Chem.* **1953,** *18*, 1601.
59. Lu, L. D.-L.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984,** *49*, 728.
60. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968,** *90*, 3732.
61. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978,** *43*, 2480.
62. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981,** *103*, 6237.
63. Aldehyde **31** was produced from the indicated propionate by the following sequence: (a) TBSCl, imidazole, DMF; (b) Dibal, $CH_2Cl_2$, −23°C; (c) Swern oxidation. The aldehyde was used without purification, as it suffered partial racemization during chromatography or distillation.
64. Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982,** 104, 5526.
65. (a) Bertelo, C. A.; Schwartz, J. *J. Am. Chem. Soc.* **1975,** *97*, 228; (b) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1979,** *101*, 3521.

66. (a) Brown, H. C.; Hubbard, J. L.; Smith, K. *Synthesis* **1979,** p. 701; (b) Kabalka, G. W.; Delgado, M. C.; Kunda, U. S.; Kunda, S. A. *J. Org. Chem.* **1984,** *49*, 174.
67. Brown, H. C.; Geoghegan, P. J., Jr.; Kurek, J. T. *J. Org. Chem.* **1981,** *46*, 3810.
68. Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977,** *99*, 4536.
69. Campaigne, E.; LeSuer, W. M. "Organic Syntheses," Wiley: New York, 1963; Collect. Vol. IV, p. 919.
70. Pino, P.; Piacenti, F.; Bianchi, M. In "Organic Syntheses Via Metal Carbonyls," Wender, I.; Pino, P., Eds., Wiley: New York, 1977; Vol. II.
71. Conceptually related precedent for this work is available in the "remote functionalization" of the steroid nucleus by Breslow and co-workers and in the process of metal-mediated intramolecular C–H activation (cyclometalation). For key recent references, see (a) Breslow, R.; Mehta, M. P. *J. Am. Chem. Soc.* **1986,** *108*, 2485; (b) Bruno, J. W.; Smith, G. M.; Marks, T. J.; Fair, C. K.; Schultz, A. J.; Williams, J. M. *J. Am. Chem. Soc.* **1986,** *108*, 40; (c) Latesky, S. L.; McMullen, A. K.; Rothwell, I. P.; Huffman, J. C. *J. Am. Chem. Soc.* **1985,** *107*, 5981.
72. Baldwin, R. A.; Cheng, M. T.; Homer, G. D. *J. Org. Chem.* **1967,** *32*, 2176.
73. Buckler, S. A. *J. Am. Chem. Soc.* **1962,** *84*, 3093.
74. Gilman, H.; Brown, G. E. *J. Am. Chem. Soc.* **1945,** *67*, 824.
75. Neises, B.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978,** *17*, 522.
76. In the crude product mixture, the eight resonances due to the C(3) or C(4) methines and the associated formyl protons were distinguishable in the 400-MHz $^1$H NMR spectrum, thus providing a reliable means of relative quantitation of the four isomeric aldehydes.
77. The literature values for the mp and $[\alpha]_D$ of (+)-phyllanthocin are as follows: mp 126–127°C. 126–127°C, $[\alpha]_D^{24}$ + 25.2° (*c*2.00, $CHCl_3$, [9]mp 120–121°C, $[\alpha]_D^{33}$ + 23.81° (*c*1.26, $CHCl_3$); [11]mp 118–120°C, $[\alpha]_D^{24}$ + 24.9° (*c*1.86, $CHCl_3$).[3b]
78. Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1979,** *102*, 2840.
79. Prepared in 62% overall yield from (*R*)−(−)-methyl 3-hydroxy-2-methylpropionate via the following sequence: (a) *t*-$BuMe_2SiCl$, imidazole, DMF; (b) Dibal; (c) *p*-TsCl, pyridine; (d) NaI, acetone; (e) $NaNO_2$, DMSO.
80. Mukaiyama, T.; Hoshino, J. *J. Am. Chem. Soc.* **1960,** *82*, 5339.
81. Gasco, A.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1981,** *29*, 251.
82. Tentative stereochemical assignments of isomers **65** and **66** were made by $^1$H NMR in analogy to similar systems studied by Kozikowski. See Kozikowski, A. P.; Ghosh, A. R. *J. Org. Chem.* **1984,** *49*, 2762.
83. Curran, D. P. *J. Am. Chem. Soc.* **1982,** *104*, 4024.
84. Smith, A. B., III; Levenberg, P. A. *Synthesis* **1981,** p. 567.
85. Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979,** p. 2301.
86. Professor Stephen Martin (University of Texas at Austin) recently reported a successful approach to (+)-phyllanthocin via a nitrile oxide dipolar cycloaddition (see reference 3). For a phyllanthocin model study using such a reaction, see Kozikowski, A. P.; Li, C.-S. *J. Org. Chem.* **1985,** *50*, 778.
87. Fraser-Reid, B. *Acc. Chem. Res.* **1985,** *18*, 323.
88. (a) Danishefsky, S. J. *Aldrichimica Acta* **1986,** *19*, 59; (b) Deslongchamps, P. *Aldrichimica Acta* **1984,** *17*, 59; (c) Whitesides, G. M.; Wong, C.-H. *Angew, Chem. Int. Ed. Engl.* **1985,** *24*, 617; (d) Trost, B. M. *Science* **1985,** *227*, 908.

*Chapter 3*

# THE TOTAL SYNTHESIS OF RETIGERANIC ACID

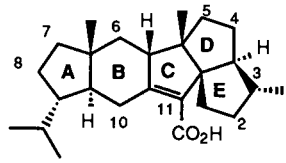
*Thomas A. Engler*
*Department of Chemistry*
*University of Kansas*
*Lawrence, Kansas*



## I. Introduction

Retigeranic acid, **1**,* is a novel member of the relatively rare sesterterpene class of plant products.[1] Since its structure was unveiled in 1972,[2] the molecule has captured the imagination of synthetic chemists because of its unique network of rings and stereogenic centers, which present formidable challenges to current synthetic methodology.[3] In late January 1982, the

* The Chemical Abstracts numbering scheme and the ring designations shown in **1** have been adopted for this account.

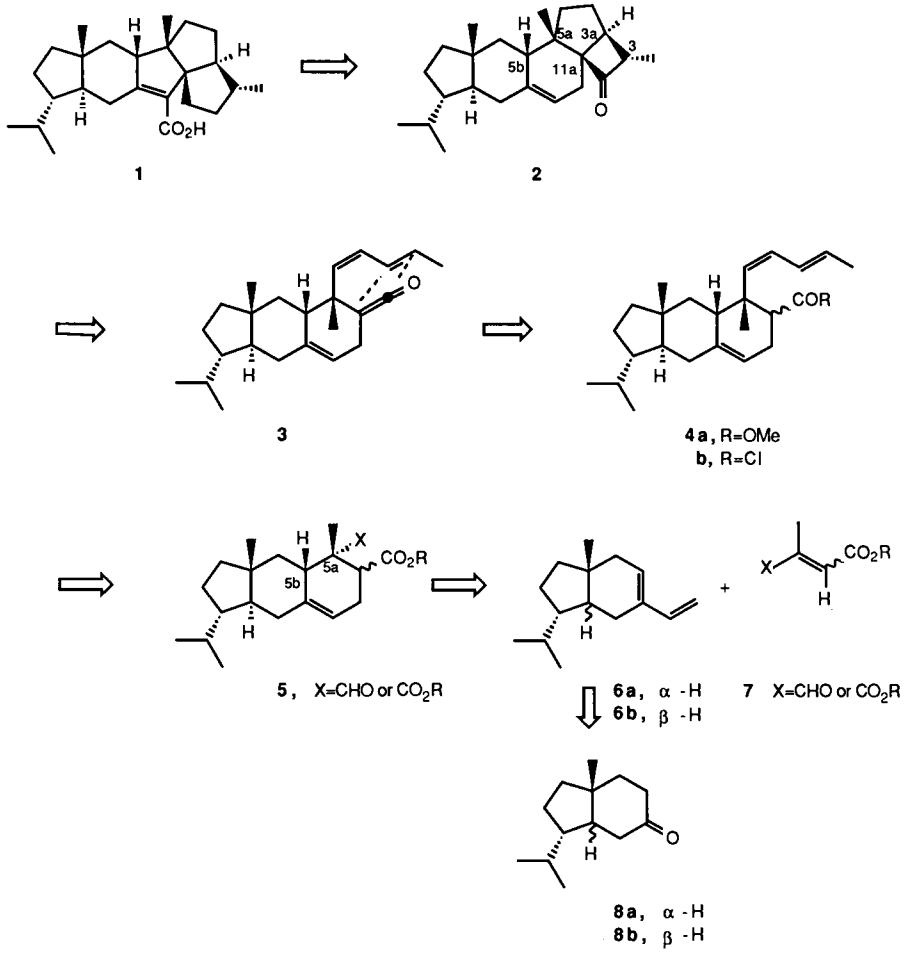



1

quest for an efficient laboratory synthesis of **1** was launched in the laboratories of Professor E. J. Corey and the venture was successfully completed 3 years later—nearly to the day.[4,5] In the following account, I describe this journey chronologically and attempt to detail our thoughts and aspirations as the venture progressed.

## II. Retrosynthetic Analysis: The Initial Plan

Retigeranic acid incorporates three structural features which have posed long-standing synthetic problems: (a) a *trans*-hydrindane unit,[6] (b) adjacent quaternary stereogenic centers,[7] and (c) an angularly fused triquinane unit (the CDE fragment). Because of their interesting topology, angularly fused triquinane moieties have attracted much attention recently[8] and, in fact, most reported synthetic approaches to **1**[3,5] have focused on annulation of the hydrindane moiety onto a preformed di- or triquinane unit. Our approach was quite different. The initial plan (Scheme 1) was to form the triquinane unit late in the synthesis from cyclobutanone intermediate **2** via a sequence of ring-E expansion and ring-C contraction. The reason to conceal ring C as a cyclohexene and ring E as a cyclobutanone was to set up two powerful cycloaddition processes: an intramolecular ketene–olefin cycloaddition to form the cyclobutanone moiety, i.e., **3** → **2**, and a Diels–Alder reaction to construct the cyclohexene moiety, i.e., **6** + **7** → **5**. Because of the remarkable stereoselectivity of Diels–Alder reactions and their utility in the formation of quaternary centers,[7] it was felt that the reaction of **6** and **7** to give **5** would occur with predictable selectivity and properly put in place the eventual C-5a and C-5b stereogenic centers of **1**. In addition, it was anticipated that the intramolecular 2 + 2 cycloaddition of **3** would be controlled by the stereochemistry of the dienyl side chain at C-5a and stereospecifically form **2**, which incorporates the future stereogenic centers at C-3, C-3a, C-5a, C-5b, and C-11a of **1**. Thus, at the outset, the Diels–Alder reaction of **6** and **7** was identified as a means to control all of the stereochemistry in the CDE fragment of **1**. (As detailed below, the failure of the intramolecular ketene–olefin cyclization as shown in Scheme 1 prevented the realization of this goal




SCHEME 1

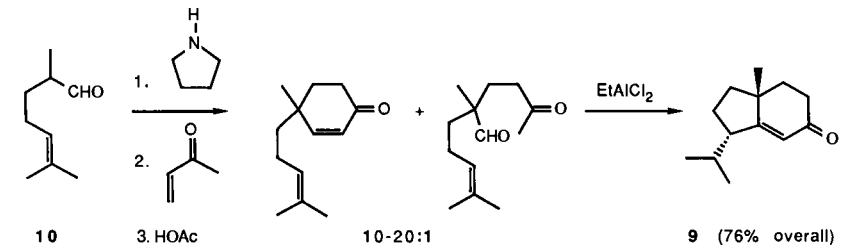
as originally formulated. However, a plan for a similar, successful intramolecular 2 + 2 cycloaddition resulted from the studies of the reactions of **3**. In the latter plan, good stereochemical control was achieved in the formation of four of the five stereogenic centers in the CDE fragment.

Our first challenge was to prepare *trans*-hydrindanone **8a**, the expected precursor to diene **6a**. This turned out to be more difficult than anticipated. However, as is often the case, the problems encountered in reaching a difficult synthetic goal offer an opportunity to investigate new and interesting chemistry.

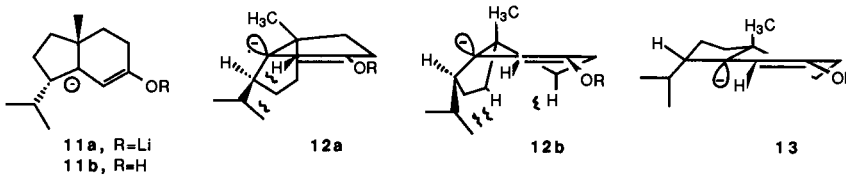
## III. The *trans*-Hydrindane Problem: Rapid Progress and False Hope

The very short stereospecific synthesis of hydrindenone **9** reported by Snider[9] (Scheme 2) provided a convenient starting point for the preparation of **8**. A generous supply of melonal, **10**, was donated to us by Dr. M. Manowitz of the Givaudan Co. and using Snider's method >100 g of hydrindenone **9** was prepared.

The method of choice for the transformation of **9** to **8** appeared to us to be a dissolving metal reduction, although the stereochemical outcome at the ring fusion was not considered immediately obvious. In the experiment (3 equivalent Li/1 equivalent *t*-BuOH/$NH_3$, −78°C only *one* hydrindanone product was obtained in 76% yield and we felt that there was good reason to believe that it was the desired *trans*-isomer **8a**. The stereochemistry of dissolving metal reductions of enones can generally be predicted by consideration of the relative stabilities of the various conformations of an allylic anion intermediate; in this case **11a** or **11b**.[10] Assuming a tetrahedral configuration for the β-carbanionic center in **11** and that the developing β-CH bond in the transition state for protonation of **11** prefers to overlap with the adjacent π system, three conformations of **11** should be considered. Conformations **12a** and **12b**, which would result in a cis ring juncture on protonation, suffer from severe steric interactions between the vinyl hydrogen and the *i*-propyl appendage or between the *i*-propyl group and axial hydrogens on the concave face of the molecule. Thus, conformer **13** may be favored and protonation of **13** with retention of configuration would afford trans-isomer **8a**. At the time we

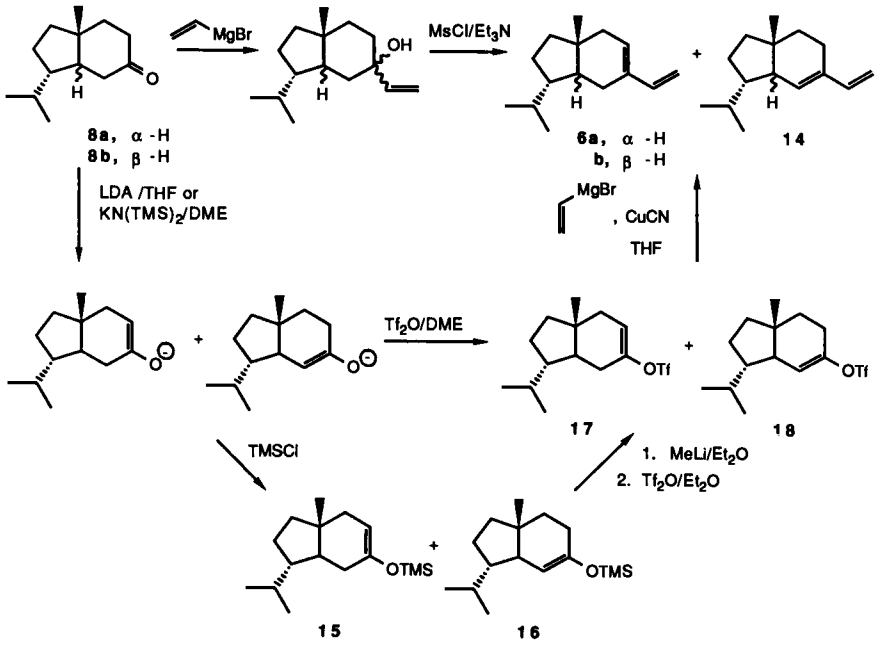



SCHEME 2



had no direct evidence for the configuration of the carbons at the ring fusion in the hydrindanone product; X-ray analysis was precluded since good crystals of the hydrindanone product could not be obtained. We decided to continue with the synthetic plan and confirm the stereochemistry of the hydrindane unit when a suitable intermediate was available.

The next step in the plan was the conversion of hydrindanone **8** to diene **6** (Scheme 3). Addition of vinylmagnesium bromide to **8** followed by dehydration of the resulting allylic alcohols via their mesylates[11] gave an unacceptable 1 : 1 mixture of dienes **6** and **14**. However, kinetic deprotonation/silylation of **8** (LDA/TMSCl/THF, −78°C) was highly regioselective and a 9 : 1 ratio of an inseparable mixture of trimethylsilyl enol ethers **15** and **16** was formed. Conversion of **15/16** to vinyltriflates **17/18** was effected by the standard literature procedure,[12] i.e., reaction of enol ethers **15/16** with methyllithium in ether to regenerate the enolates and then treatment with triflic anhydride. This circuitous route from **8** to **17/18** demanded a search for a way to directly trap the enolate formed by deprotonation of **8**. After considerable experimentation, it was discovered that deprotonation of **8** with potassium hexamethyldisilazide in 1,2-dimethoxyethane (DME) at −78°C followed by addition of triflic anhydride gave **17** and **18** in good yield



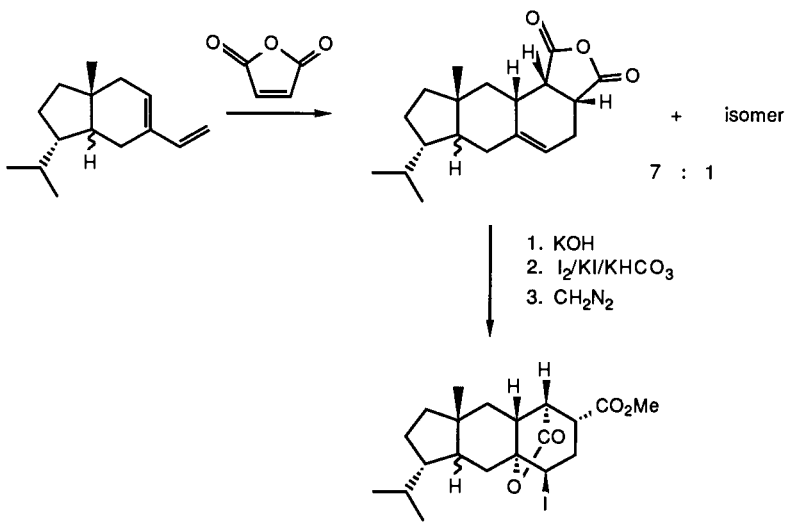

SCHEME 3

(84%) and in an acceptable 9:1 ratio, respectively.[13] Coupling of vinyltriflates **17/18** with the cuprate derived from copper(I) cyanide and 2 equivalents of vinylmagnesium bromide produced dienes **6** and **14** in a 9:1 ratio (92%).[14]

We were at the threshold of exploring the Diels–Alder reactions of **6**, a vital reaction in the synthetic plan. We had arrived at this point within 3 months of the start of the project and we proceeded with great confidence.

## IV. The Diels–Alder Reaction: Revealing an Error

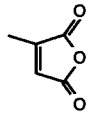
Our first experiment on a Diels–Alder reaction utilizing diene **6** did not dispel our high expectations. The reaction of **6** with maleic anhydride was examined in order to determine the facial selectivity of this dienophile toward diene **6**. Under thermal conditions an encouraging 7:1 ratio of 4 + 2 adducts was obtained (Scheme 4). To establish stereochemistry of the major adduct, it was converted to iodolactone **19** in 93% overall yield by the sequence (1) hydrolysis to a diacid, (2) iodolactonization of the diacid, and (3) diazomethane esterification. Because of the rigidity of the bicyclic structure, we felt that NMR coupling constants would be reliable for the assignment of the stereochemistry in the iodolactone unit and all spectral data were consistent with structure **19**. Thus, it appeared that the Diels–



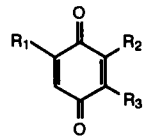

SCHEME 4.

Alder reaction of **6** with maleic anhydride was occurring via endo addition of the dienophile to the $\alpha$-face of **6**. This explanation seemed to support the assignment of a trans ring juncture in diene **6** since, with this configuration, the angular methyl group should shield the $\beta$-face of the diene and favor cycloaddition to the $\alpha$-face as observed. The next series of experiments would contradict this hypothesis.

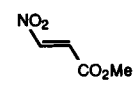
In our synthetic strategy, we planned to construct the C-5a quaternary center of **1** via the Diels–Alder reaction of **6** with an appropriately methyl-substituted dienophile. In fact, reactions of **6** with eight dienophiles, **20–27**, were examined. In each case good yields of 4 + 2 adducts were found under thermal and/or Lewis acid-catalyzed conditions; however, to our dismay, the reactions produced mixtures of two to six isomeric products in unacceptable ratios.



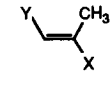
**20**



**21**, $R_1$=$R_2$=$CH_3$, $R_3$=H
**22**, $R_1$=$CH_3$, $R_2$=$OCH_3$, $R_3$=H
**23**, $R_1$=$CH_3$, $R_2$=H, $R_3$=$OCH_3$

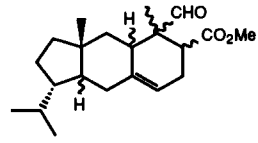


**24**

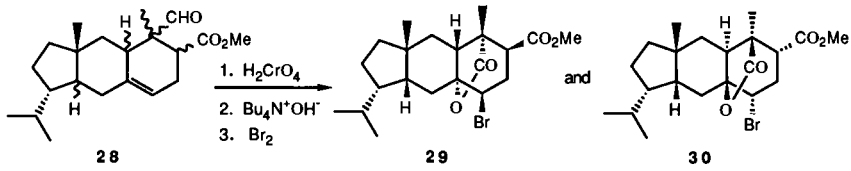


**25**, X=CHO, Y=CN
**26**, X=CHO, Y=$CO_2$t-Bu
**27**, X=CHO, Y=$CO_2CH_3$

Two explanations could account for these observations. Either Diels–Alder reactions of **6a** were not facially selective (which, if true, would require a drastic change in synthetic strategy) or the diene possessed a cis- fused hydrindane structure, **6b**, in which case dienophiles would not be expected to demonstrate a preference for cycloaddition to the $\alpha$-face of the diene. It became imperative that the structure of diene **6**, or of a derivative, be unequivocally established. To do this we chose to examine the 4 + 2 adducts from thermal reaction of **6** with **27**.[15] This decision was made for several reasons: (1) the Diels–Alder reaction gave a 1 : 1 mixture of two major adducts (75%; two minor isomers were also present in <5% combined yield), (2) these adducts were stereoisomers with structure **28**, rather than regioisomers, which allowed for more direct spectral comparison of the two, and (3) the two major adducts were separable. Finally, crystalline derivatives of both major adducts could be formed quickly and efficiently.



**28**



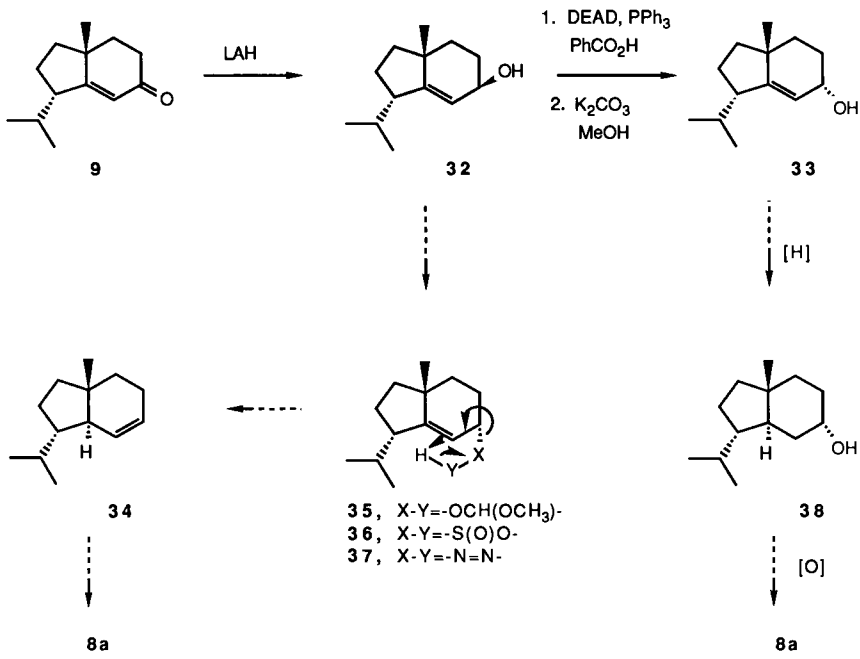

28 29 30

SCHEME 5.

Thus, the isomeric adducts **28** were each converted to crystalline isomeric bromolactones by chromic acid oxidation of the aldehyde group and bromolactonization of the resulting acid (Scheme 5). Crystals of the bromolactone whose $^1$H-NMR spectrum best fit the desired stereochemistry in the B/C ring were chosen for X-ray analysis. The result revealed structure **29**.[16] While the stereochemistry of the C ring was as expected, the hydrindane unit in **29** was cis-fused. The structure of the second bromolactone was assigned as **30** based on spectral evidence. Thus, the hydrindanone formed in the dissolving metal reduction of enone **9** was cis-fused hydrindanone **8b**. Apparently, the stereochemistry of the reduction is controlled by kinetic and steric factors associated with the approach of the protonating species to the allylic anion intermediate.

## V. The *trans*-Hydrindane Problem: Multiple Solutions

Although relieved to have found the reason for the nonselective Diels–Alder reactions, we were again faced with the problem of preparing the *trans*-hydrindanone **8a**. Enone **9** was still considered a convenient starting point and a variety of methods to reduce the enone functionality were explored. We quickly found that metal hydride reduction of **9** was stereoselective and gave allylic alcohol **32** in >99% yield (Scheme 6). Inversion of the alcohol center in **32** was effected via the Mitsunobu procedure[17] and gave **33** in 89% yield. This immediately suggested the development of a protocol in which the hydroxyl group in **33** is enlisted to control the stereochemistry of the reduction of the olefin and/or one in which stereochemistry at the alcohol carbon is transferred to the remote carbon of the olefin. Two methods came to mind (Scheme 6). The first employed a hydroxyl-directed hydrogenation of **33** utilizing a soluble iridium(I) catalyst that had been introduced recently by Crabtree[18] and Stork.[19] The second involved a retro-ene fragmentation process with internal hydrogen delivery to the carbon at the ring fusion and double bond migration to give olefin **34**. The second method had ample literature precedent in the thermal decomposition of allylic acetals (**35**),[20] sulfenic acids (**36**),[21] and diazenes (**37**).[22]

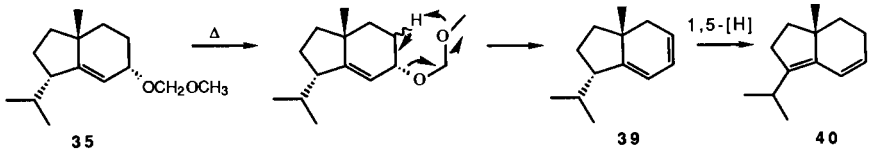



SCHEME 6.

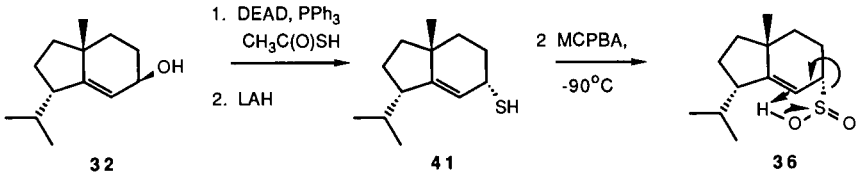
Unfortunately, hydrogenation of **33** with $[Ir(COD)P(c\text{-}Hx)_3Py]^+PF_6^-$ as catalyst in $CH_2Cl_2$ was not satisfactory.[6b] Low yields of saturated alcohol **38** were obtained even at high (>30 mol %) catalyst concentrations. Considerable quantities of unidentified nonpolar products were found. At the time we were unable to explain the failure of this method other than to postulate that the *i*-propyl substituent in **33** shielded the olefin moiety and prevented effective binding to the catalyst. Later we were to uncover a more likely explanation.

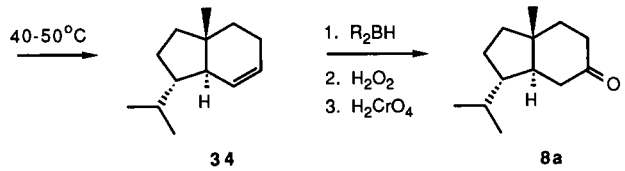
Our attention turned to the investigation of the fragmentation strategies. Methoxymethyl ether **35** was prepared and thermolyzed at 400–500°C through a glass tube pretreated with $(Me_3Si)_2NH$ (Scheme 7). Dienes **39** and **40** resulted, perhaps via a fragmentation process followed by a sigmatropic 1,5-hydrogen shift as shown or by complex processes occurring on the glass surface. Again, the the failure of this method was attributed to shielding of the olefin moiety in **35** by the *i*-propyl substituent.

The sulfenic acid fragmentation route proved successful (Scheme 8).[6b] Thiol **41** was prepared in 78% yield by a Mitsunobu procedure employing alcohol **32** and thiolacetic acid[23] followed by reduction of the resulting thiol acetate with lithium aluminum hydride. Oxidation of **41** with 2 equivalents




SCHEME 7



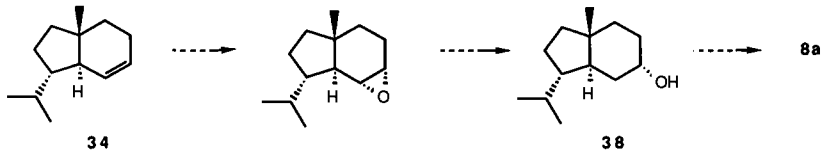




SCHEME 8

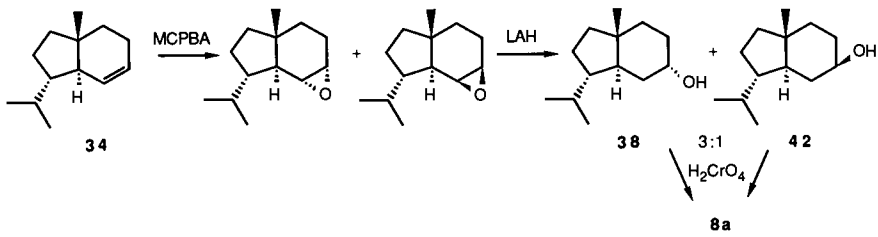
of *m*-chloroperoxybenzoic acid in dichloromethane[24] at −90°C gave **36**, which underwent thermal fragmentation on removal of solvent by distillation at atmospheric pressure to produce olefin **34** in 80% overall yield from thiol **41**. Hydroboration of **34** with 9-BBN (9-Borobicyclo[3.3.1]nonane) or dicyclohexylborane followed by oxidation of the intermediate boranes with basic hydrogen peroxide and then chromic acid regioselectively gave *trans*-hydrindanone **8a**. The AB ring fusion was set.

However, the transformation of olefin **34** to hydrinanone **8a** was not without disadvantages. Hydroborations of **34** with 9-BBN or dicyclohexylborane in THF or DME were sluggish (1–3 days, 23–60°C) and smaller hydroboration reagents were not completely regioselective. In addition, the overall yield under the best conditions was 55–61%.

A second route from alkene **34** to hydrindanone **8a** was designed (Scheme 9). We reasoned that if expoxidation of **34** occurred selectively from the more open α-face, then the resulting epoxide should undergo stereospecific trans-diaxial ring opening on treatment with a nucleophilic hydride reagent and afford alcohol **38**, which could be oxidized to **8a**. Reaction of



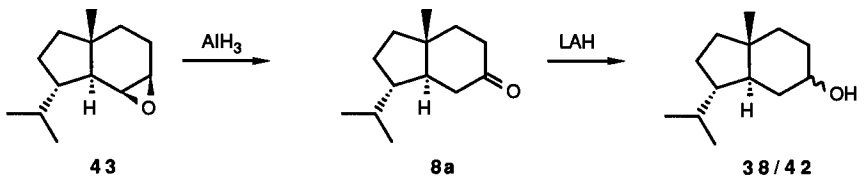

SCHEME 9.




SCHEME 10.

**34** with *m*-chloroperoxybenzoic acid gave an initially disappointing inseparable 3 : 1 mixture of epoxides (Scheme 10) and treatment of this mixture with lithium aluminum hydride gave two alcohols in a similar 3 : 1 ratio. However, to our surprise, oxidation of the mixture of alcohols with chromic acid gave one product—*trans*-hydrindanone **8a**—in 89% overall yield from **34**. Of course, this indicated that the two alcohols were epimers and not regioisomers! Based on $^1$H NMR, the major isomer was identified as **38** and the minor isomer as **42**.

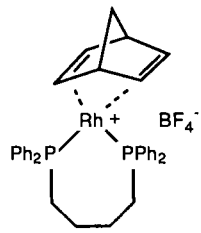
Obviously, the rule[25a] of stereospecific trans-diaxial ring cleavage of epoxides via an $S_N2$ mechanism could not be rigorously applied to the reaction of lithium aluminum hydride with the mixture of epoxides derived from **34**. One rational explanation for this observation is that epoxide **43** undergoes $AlH_3$-catalyzed rearrangement to ketone **8a**,[25b] followed by reduction. Recent experiments on the epoxide ring-opening reaction of cyclohexene oxide with lithium aluminum deuteride indicate that the mechanism is more complex than simple $S_N2$ displacement and products from non-trans-diaxial ring opening may be found.[25c]



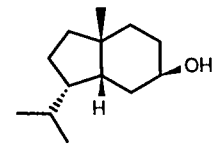
Whatever the mechanistic details may be, a workable route to **8a** was in hand. Although the transformation of hydrindenone **9** to hydrindanone **8a** required a number of steps, the individual steps were clean, efficient, and simple to perform. In practice, the sequence of reactions from thiol **41** to **8a** was conducted without separation or purification of intermediates and gram quantities of **8a** were prepared in this manner in 71% overall yield from **41**.

At this time Professor David Evans arrived at Harvard, and he and his co-worker Michael Morrissey told us of their successful work in effecting stereospecific hydroxyl-directed hydrogenations of unsaturated alcohols with soluble rhodium(I) catalysts.[26] Encouraged by their results, and with their support as readily available consultants, we reinvestigated the hydrogenation of allylic alcohol **33**, this time with Evans' rhodium (I) catalyst.

The results of our initial experiments with this system were disappointingly similar to the experiments utilizing the iridium(I) catalyst. Hydrogenation of **33** in $CH_2Cl_2$ at one atmosphere of $H_2$ and with [Rh(NBD) (DIPHOS-4)]$^+BF_4^-$, **44**,[26a] as catalyst gave mainly mixtures of nonpolar materials including diene **39**. At high pressures of $H_2$ (550–650 psi), reasonable amounts (60–65%) of saturated alcohol products were found from either alcohol **32** or its epimer **33**. However, in each of the latter experiments, subsequent oxidation with chromic acid produced mixtures of hydrindanones **8a** and **8b**. Contrary to the results obtained by Evans and Morrissey in reductions of a number of allylic alcohols, the reductions of **32** or **33** appeared to be nonstereospecific. We redoubled our efforts to find a reasonable explanation.

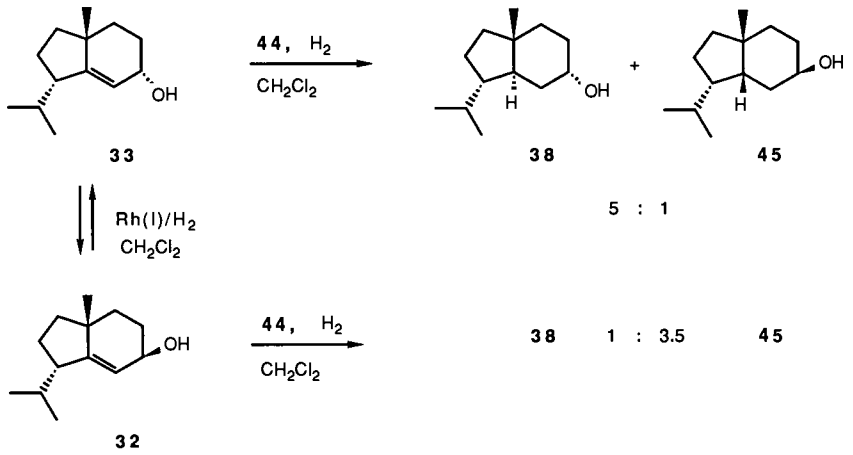



**44**




**45**

It is noteworthy that at this time we had in our possession authentic samples of saturated alcohols **38**, **42**, and **45** [from Ir(I)-catalyzed hydrogenation of **32**]. Careful capillary chromatography and $^1H$ NMR analysis of the product mixture from reduction of **33** with catalyst **44** (7.5 mol %) and $H_2$ (50 psi) showed it to consist of **38** and **45** in a 5:1 ratio (Scheme 11). Similarly, the mixture from reduction of **32** was composed of **38** and **45** in a 1:3.5 ratio. Of particular note was that **42** was not detected in the latter experiment. These results implied that the




SCHEME 11

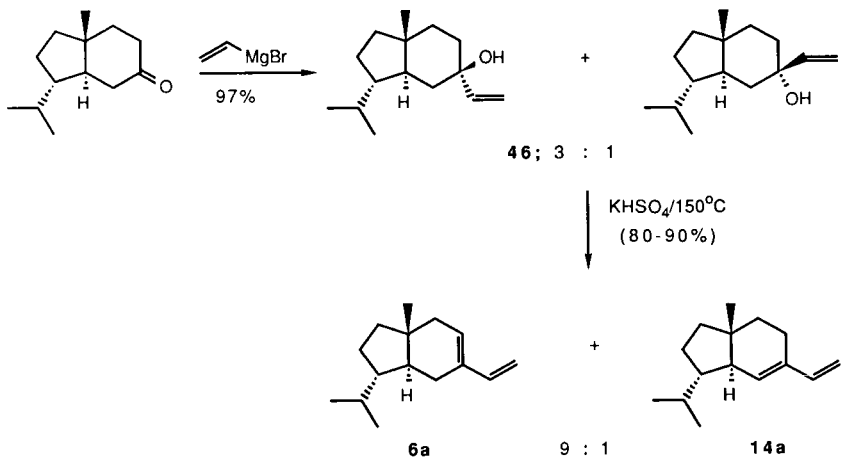
failure in our system may not be to nonspecific hydrogenation; rather, epimerization of the allylic alcohols was occurring prior to reduction. Evidence which supported this hypothesis was obtained in the following experiment. The catalyst **44** was reduced to Rh(DIPHOS-4)$^+$ by exposure to $H_2$ and then evacuation of the $H_2$ atmosphere and replacement with argon. A solution of isomerically pure **32** was added under argon (catalyst:alcohol ratio = 1 : 5) and after 30 minutes an approximately 1 : 1 mixture of **32** and **33** was detected by TLC and NMR.

We reasoned that the epimerization of **32** to **33** may be due to the Lewis acidic properties of Rh(I) in dichloromethane or perhaps to trace amounts of hydrogen chloride liberated from the interaction of the catalyst with dichloromethane in the presence of $H_2$.[27] In either event, we surmised that a change to a less polar, nonhalogenated solvent would alleviate the problem. In fact, hydrogenations of either **32** or **33** with the Rh(I) catalyst **44** in THF worked very well indeed.[26a] Reaction of an 81 : 1 mixture of **33** and **32** with $H_2$ (900 psi) in THF with **44** as catalyst (5.4% by weight with respect to the starting alcohols) followed by direct Jones oxidation of the resulting crude alcohol gave a 70 : 1 mixture of **8a** and **8b**, respectively, in 93% yield. In a similar manner, a 1 : 21 mixture of **33** and **32** gave a 1 : 70 mixture of **8a** and **8b**, respectively, in 86% yield (the apparent discrepancy in the ratio of the starting isomers compared with the ratio of the product isomers was probably due to faster reduction of **32** and removal of unreacted starting material on product isolation). The high degree of specificity found in the reductions of sterically congested substrates **32** and **33** impressively demonstrates the utility of the Evans Rh(I) catalyst **44** in hydroxyl-directed hydrogenations of alkenes.

Thus, *trans*-hydrindanone **8a** was available in four steps from enone **9** via the sequence **9** → **32** → **33** → **38** → **8a**. The procedure was easily scaled up (18–20 g/reaction), the yields for each step were consistently high (>80%), and catalyst concentrations as low as 1.8% were effective in the hydrogenation step. When this sequence was scaled up, small amounts (1–5%) of the *cis*-hydrindanone **8b** were found to contaminate the desired end product **8a**. Isomer **8b** originated from erosion in the stereospecificity of the Mitsunobu reaction **32** → **33** on scaleup. This minor impurity was removed effectively by recrystallization of the hydrindanone product mixture from pentane at –45°C, and **8a** was obtained which was of >99% isomeric purity by capillary VPC. Using this sequence, >50 g of isomerically pure **8a** was prepared.

Conversion of **8a** to a 9 : 1 mixture of dienes **6a** and **14a** was effected in a straightforward manner (Scheme 12) by addition of vinylmagnesium bromide followed by dehydration of the resulting allylic alcohols **46**. The dehydration was achieved via distillation of **6a**/**14a** from a mixture of **46** and an excess of potassium hydrogen sulfate.[28] The ratio of dienes **6a** and **14a** obtained was independent of the ratio of starting allylic alcohols **46**, although the pressure and temperature employed in the distillation were critical in attaining diene yields of 80–90%. This dehydration procedure was suggested to us by Professor A. W. Burgstahler and was found to be superior to treatment of the mixture of allylic alcohols **46** with methanesulfonyl chloride/$Et_3N$.[11]

We were again at the threshold of the key Diels–Alder reaction.

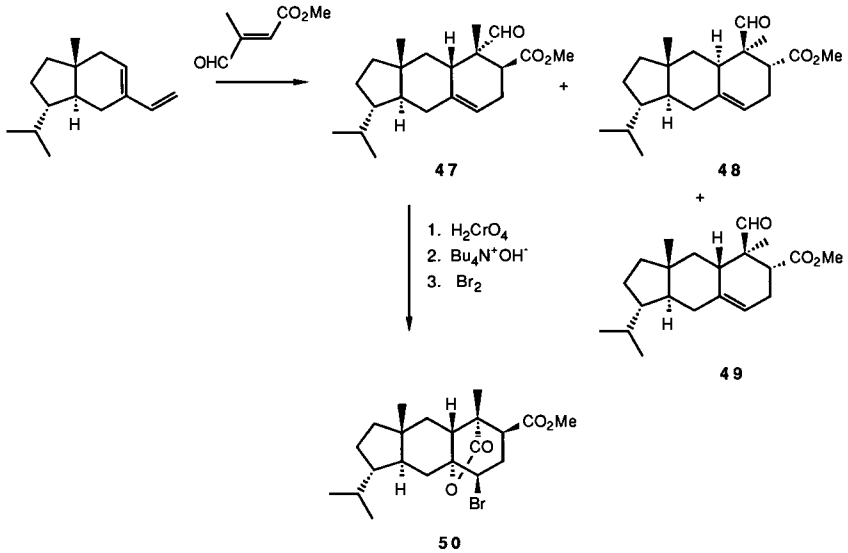



SCHEME 12

## VI. Success of the Diels–Alder Reaction: Construction of a Tricyclic Intermediate

Through our experience with diene **6b**, we knew that Diels–Alder reactions of dienophile **27** were moderately regio- and stereoselective and we felt that the expected adduct from cycloaddition of **6a** and **27** would fit nicely into the synthetic plan to **1**. The thermal reaction of **6a** and **27** (5 equivalents **27**, neat, 98–105°C) worked admirably well (Scheme 13), a 5.3 : 1.3 : 1 mixture of three products **47–49**, respectively, was obtained in 75% yield and the major isomer was separable by HPLC. Attempts to catalyze the Diels–Alder reaction with Lewis acids were not successful. The minor diene isomer **14a** did not interfere in this step.

That the three Diels–Alder adducts, **47–49**, possessed the proper substitution pattern in the C ring was apparent by $^1$H NMR; however, the stereochemical orientation of these substituents was not obvious. Since the Diels–Alder reaction was planned to establish the stereogenic centers which would control the stereochemistry of the formation of the C–D–E ring junctures of **1** (Scheme 1), it was essential that the structure of the major Diels–Alder adduct be established with certainty. Therefore the major Diels–Alder adduct was converted to a bromolactone in 81% overall yield by the series of reactions shown in Scheme 13. Single-crystal X-ray analysis of this bromolactone[16] confirmed its structure as **50**, which established that the



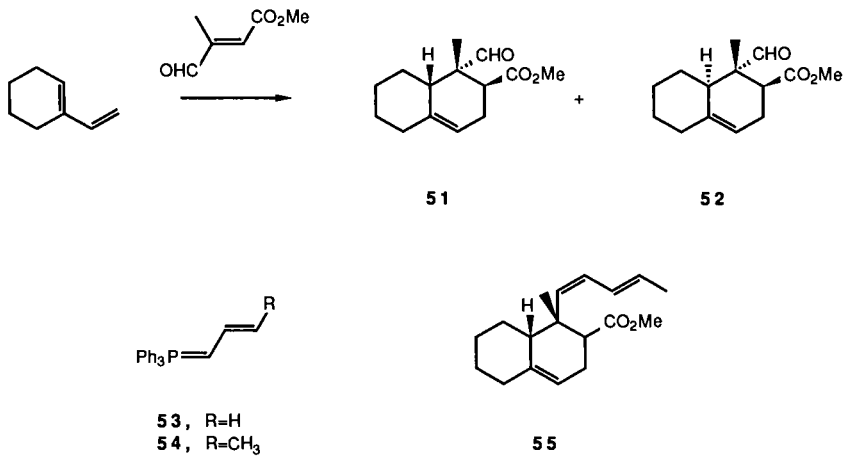

SCHEME 13

structure of the major Diels–Alder adduct was **47**. The minor 4 + 2 adducts from **6a** and **27** were assigned structures **48** and **49** based on $^1$H NMR. Thus, the key Diels–Alder reaction of **6a** with **27** was reasonably stereo- and regioselective and the major product **47**, which incorporates five of the eight stereogenic centers of **1**, was available in nine steps with good control of stereochemistry.

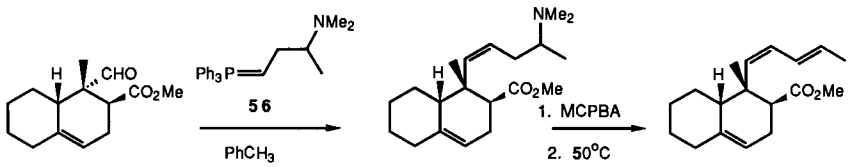
In practice, the Diels–Alder reaction was the bottleneck in the synthesis since the isolation of the major isomer required separation by HPLC. However, conditions were found utilizing a Du Pont 8800LC system with a 21.2 mm × 25 cm Du Pont Zorbax silica column which allowed 500 mg of the crude Diels–Alder reaction mixture to be processed in a single injection (retention time = ~40 min) and the purified yield of **47** was 61%. In this manner, 6 g of **47** was stockpiled, which was enough material for the remaining steps of the synthesis.

## VII. Reversible 2 + 2s: A Change in Strategy

In order to conserve our supply of **47**, a model system similar to **47** was prepared by Diels–Alder reaction of **27** with 1-vinylcyclohexene which afforded an 8 : 1 ratio of aldehydes **51** and **52** in 78% yield (Scheme 14). The optimum conditions for most of the remaining reactions in the synthesis were developed using this mixture. Conversion of the aldehyde group of **51** to a butadienyl side chain was attempted first via Wittig reactions with allylidenetriphenylphosphoranes **53** and **54**. However, the reactions of these




SCHEME 14.



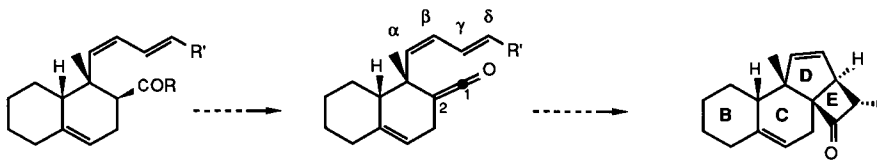

51 57 55

SCHEME 15

ylides with neopentyl aldehyde **51** were slow, gave low yields of diene products, and were complicated by the reactivity of the γ-carbon of the ylides, a problem which has been noted by other researchers.[29,30]

A more reactive nonconjugated ylide was required. An additional demand was that this ylide incorporate appropriate functionality such that, after Wittig reaction of the ylide with **51**, the resulting cis-alkene could be easily converted to the desired diene **55**. The ylide **56** derived from 3-dimethylaminobutyltriphenylphosphonium bromide fit these criteria nicely, and it reacted with **51** under salt-free conditions to afford **57** stereoselectively in 82% yield (Scheme 15). The amine **57** was converted to **55** in 65% overall yield by oxidation to the amine oxide and thermal Cope elimination. This three-step sequence represented a new, efficient, and reliable method for the preparation of 1,3-*Z*,*E* dienes.[31]

We now faced the imposing intramolecular ketone–olefin cyclization, which would be tested first on model system **60** → **61** (Scheme 16). We did not approach this step without some trepidation. When examining models of possible transition states for this cycloaddition,[32,33] it is difficult to align the terminal olefin of the butadienyl side chain in **60** with both carbons of the ketene moiety in the proper geometry for a synchronous $\pi_a^2 + \pi_s^2$ transition state.[34] However, a considerable body of evidence exists which suggests that intramolecular ketene–olefin cyclizations may not require the synchronous




**55**, R=OMe, R'=Me
**59**, R=Cl, R'=Me
**62**, R=Cl, R'=H

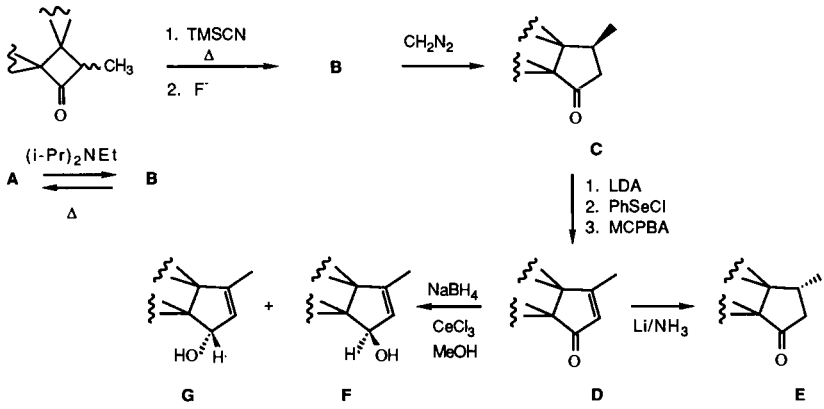
**60** **61**

SCHEME 16

formation of two new bonds.[35] Instead, these cycloadditions may occur via a concerted asynchronous mechanism in which bonding between the ketenic carbonyl carbon and the most nucleophilic carbon of the alkene (in the Markovnikov sense) is considerably advanced over the development of the second bond. In a Dreiding model of ketene **60**, C-1 and C-$\delta$ can approach each other without severe molecular deformation and bond formation between these carbons may greatly facilitate bond development between C-2 and C-$\gamma$.

With this idea in mind, we prepared acid chloride **59** and treated it with diisopropylethylamine in toluene. High temperature (120°C) was required to effect a reaction and, to our surprise, two cyclobutanone products, **A** and **B**, were produced. The structures of the cyclobutananones **A** and **B** could not be deduced from spectral data; therefore they were subjected to a series of experiments designed to gain structural information. A fascinating road map problem in structure elucidation resulted (Scheme 17) and the answer revealed that an extraordinary atomic reorganization had occurred in the formation of **A** and **B** from **59**.

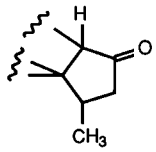
Cyclobutanones **A** and **B** could be interconverted by heating with Etn($i$-Pr)$_2$ in toluene and, at first, it was postulated they were epimers at the methyl-bearing carbon $\alpha$ to the ring-E carbonyl group in **61**. However, this was shown to be unlikely by experiments with desmethyl-acid chloride **62**, which also gave two cyclobutanones on treatment with EtN($i$-Pr)$_2$. Reaction of a mixture of **A** and **B** with trimethylsilyl cyanide/KCN/18-crown-6[36] at 155°C gave a mixture of two trimethylsilyl cyanohydrins, which on treatment with fluoride ion gave only **B**. On reaction with diazomethane in the presence of methanol,[37] cyclobutanone **B** gave a



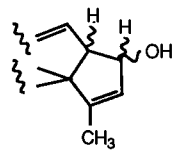

SCHEME 17

cyclopentanone **C**, which was transformed into a cyclopentenone **D** by the sequence (1) LDA, (2) PhSeCl, and (3) MCPBA.[38] Dissolving metal reduction of **D** regenerated **C** along with an isomer **E**. Finally, reduction of **D** with sodium borohydride/$CeCl_3$[39] afforded a mixture of two allylic alcohols, **F** and **G**.

A great deal of spectral data was now available from compounds **A–G**. The most revealing aspects of these data were that **C** and **E** were $\beta$-methylcyclopentanones and that the methyl-bearing carbon $\beta$ to the carbonyl group was bonded to a quaternary center (the methine proton $\beta$ to the carbonyl group was coupled only to the geminal $CH_3$ and the $\alpha$ methylene protons in the proton NMR spectra). Thus, partial structure **63** was indicated for **C** and **E**. In the $^1H$ NMR spectrum of one of the allylic alcohols, **F**, the proton on the hydroxylated carbon was coupled to a vinyl proton and an allylic methine proton, thus suggesting partial structure **64**. Before proceeding, the reader may find it challenging to suggest structures for **A–G** and propose a mechanism for their formation.



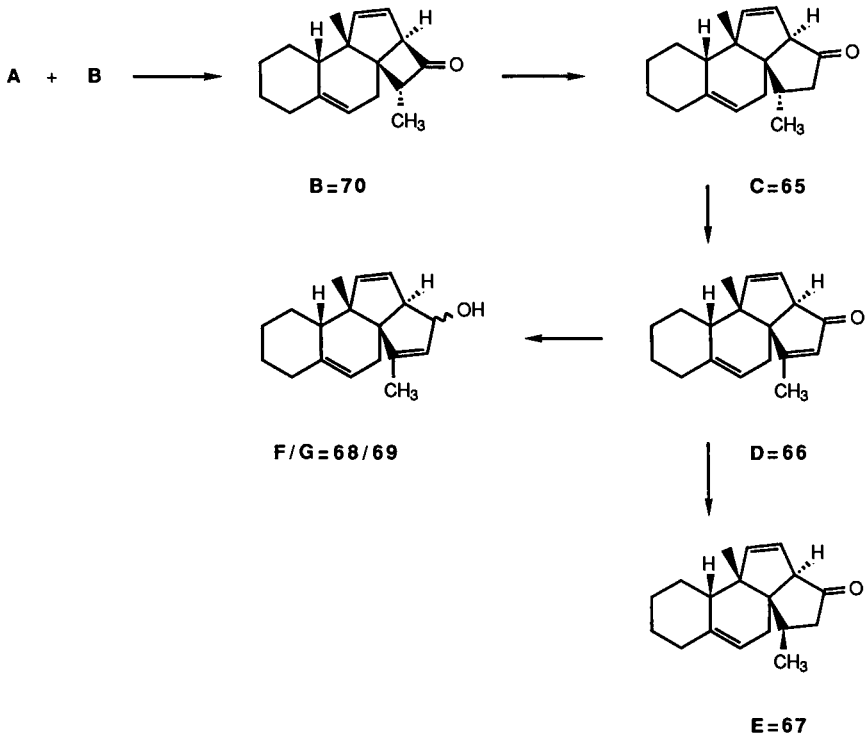

**63**




**64**

Clearly, the data were not compatible with products expected from **61**, the desired cyclobutanone from the intramolecular 2 + 2 cycloaddition of ketene **60**. The spectral evidence could be explained, however, with structures **65–69** for **C–F**, respectively (Scheme 18). Structure **70** was thus required for **B** which obviously could not result directly from intramolecular cycloaddition of ketene **60**.

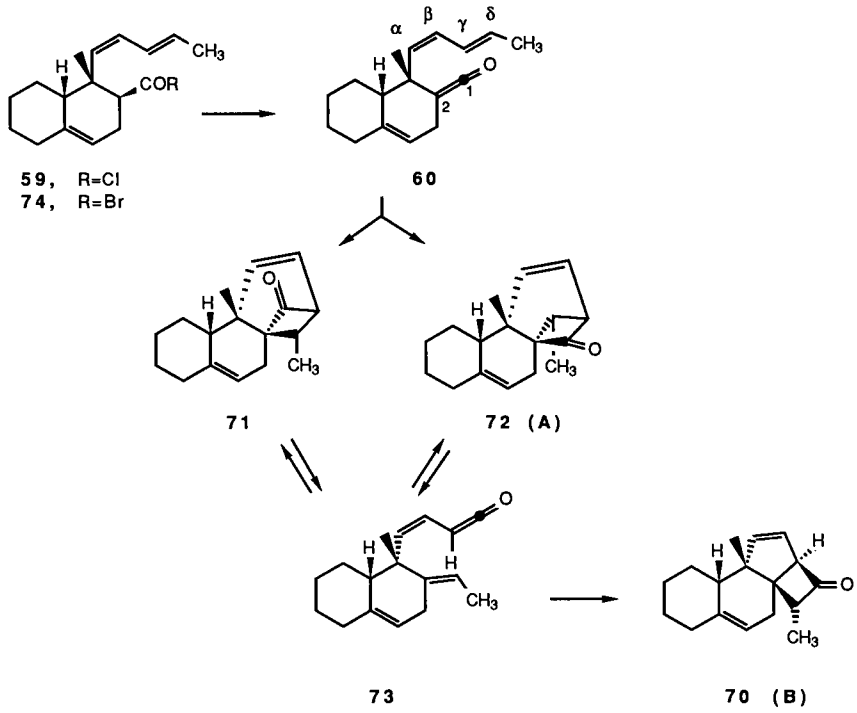
We now believe that ketene **60** produced the isomeric bridged cyclobutanones **71** and **72** (Scheme 19). Under the reaction conditions (120°C), the more highly strained isomer **71** undergoes a 2 + 2 cycloreversion to ketene **73**, which then recloses to fused cyclobutanone **70** (**B**). Isomer **72** (**A**) also fragments to **73**, but at a lower rate, and this accounts for the thermal interconversion of **70** and **72**. Evidence to support this scenario was obtained by generating ketene **60** at 55°C from acid bromide **74** (formed from the free acid and oxalyl bromide) and $EtN(i\text{-}Pr)_2$ in DME which gave **71**, which had not been previously observed, and **72**. Apparently, due to geometrical constraints in **60** bond formation between C-$\gamma$ and C-1 is favored over bond development between C-$\delta$ and C-1.




SCHEME 18

On the surface it may appear that this was a disastrous turn of events. To the contrary, the recognition of ketene **73** as an intermediate in the rearrangement of **71** to **70** became the guiding force behind a new synthetic strategy detailed in Scheme 20.[40] It suggested that a related ketene, **77**, should readily give cyclobutanone **78**, a viable precursor to **1**. In a Dreiding model of ketene **77**, the ketenic carbon (C-$\delta$) and the ring-C exo-methylene carbon (C-1) can be brought much closer to one another than can the kenetic carbon and C-2. In addition, an asynchronous transition state model for the ketene–olefin cycloaddition would predict that the electrophilic ketenic carbon in **77** should bond to the C-1 carbon of the exo-methylene unit. Thus, the formation of fused cyclobutanone products from **77** should be preferred over the formation of bridged cyclobutanones.

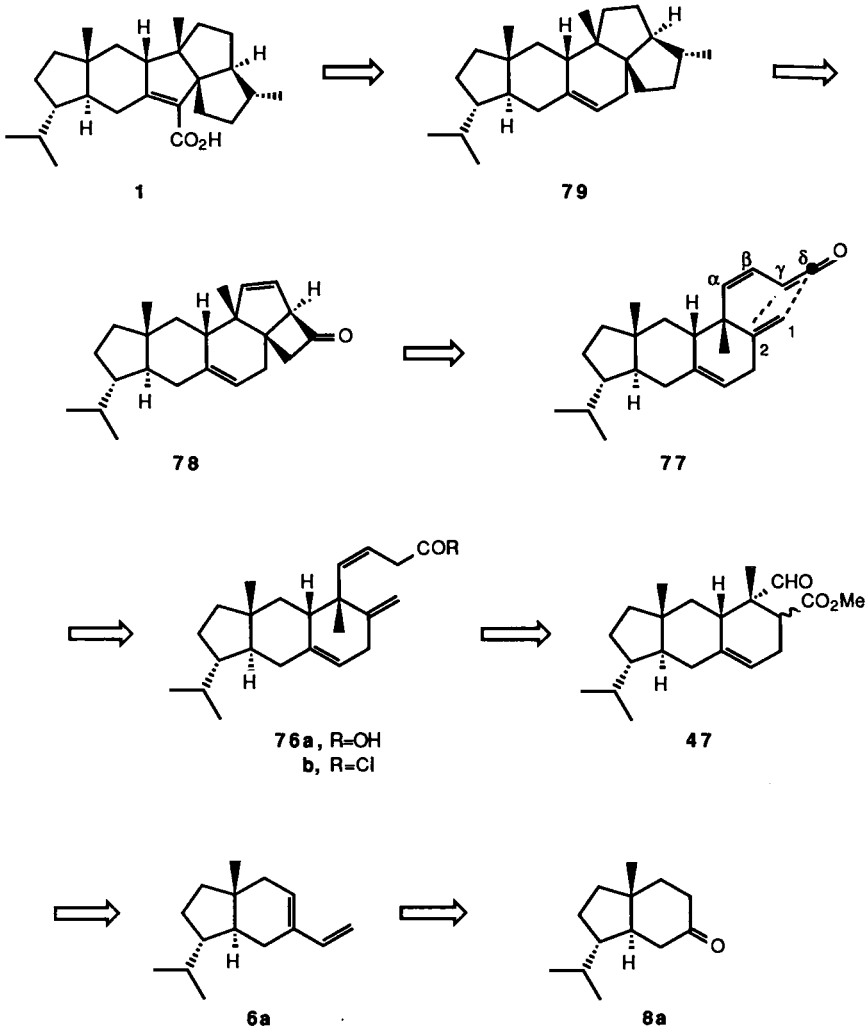
The strategy outlined in Scheme 20 was attractive for another reason. In the formation of ketene **60**, high temperatures were required, probably to overcome steric factors associated with the deprotonation of the neopentyl




SCHEME 19

position in acid chloride **59**. These conditions may have contributed to the failure of ketene **60** to demonstrate facial selectivity in the intramolecular cycloaddition to the C($\gamma$)–C($\delta$) double bond of the dienyl side chain and isomeric cyclobutanones **71** and **72** resulted. However, in acid halide **76b**, the precursor to ketene **77**, the $\alpha$-hydrogens are readily accessible and activated by an additional $\pi$ system. Thus, generation of **77** from **76b** may be possible under mild conditions and ketene **77** may be more selective in addition to the exo-methylene unit in the C ring. In addition, an equilibrium between bridged and fused cyclobutanones may be avoided under mild conditions.[32g]

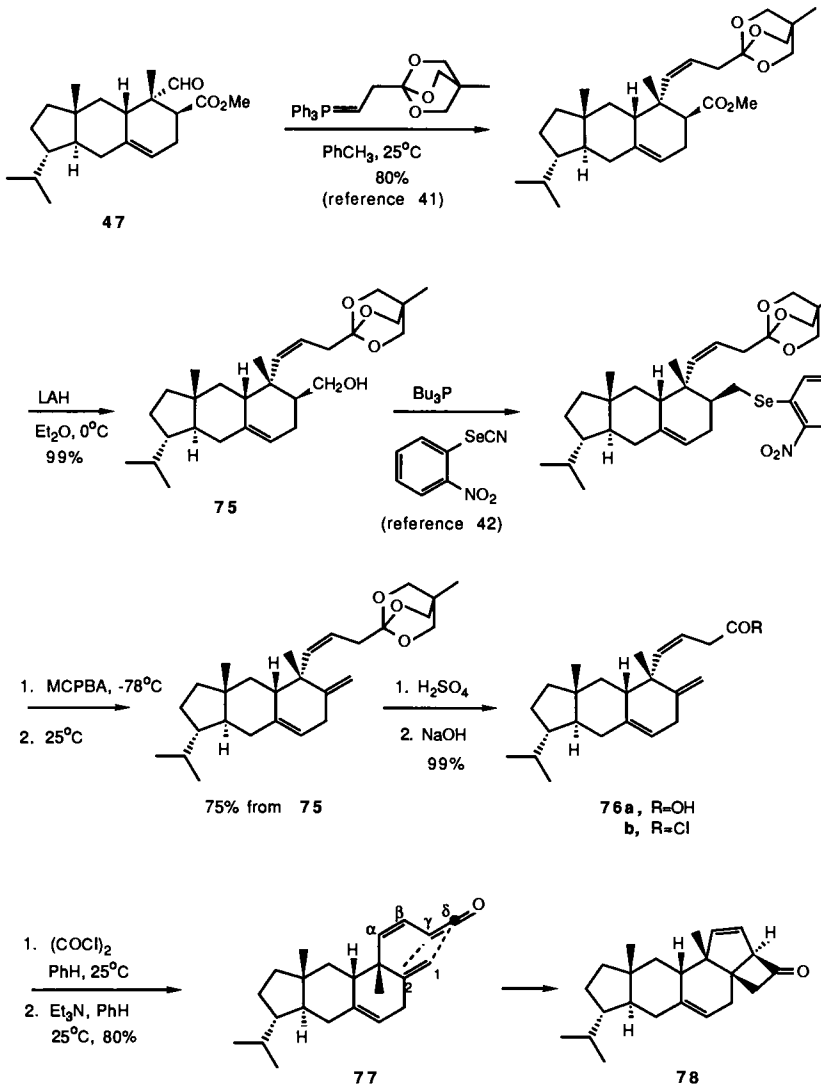
The transformation of cyclobutanone **78** to **79** would require (1) expansion of the E ring, (2) introduction of the ring-E methyl substituent, and (3) removal of the carbonyl functionality. The method of choice for introduction of the ring-E methyl group was clearly dependent on the mode of expansion of the E ring. This could not be predicted with any confidence from models of **78**, and at this stage our plan for the conversion of **78** to **79** was not completely formulated.




SCHEME 20

## VIII. Success of the Intramolecular 2 + 2: Construction of a Pentacyclic Intermediate

In practice, the plan outlined in Scheme 20 worked exceptionally well. Although most of the experiments described below were initially investigated using the model system from **51**, only the successful experiments with the "real" system **47** are described in this section.




SCHEME 21

Conversion of aldehyde **47** to acid **76a** proceeded efficiently and without incident and will not be discussed in detail here (Scheme 21). To our considerable satisfaction, the transformation of **76a** to **78** worked exceedingly well; treatment of the acid with oxalyl chloride followed by triethylamine gave only one cyclobutanone product in 80% yield. In glaring contrast to reactions of ketene **60**, the formation of ketene **77** and its intramolecular

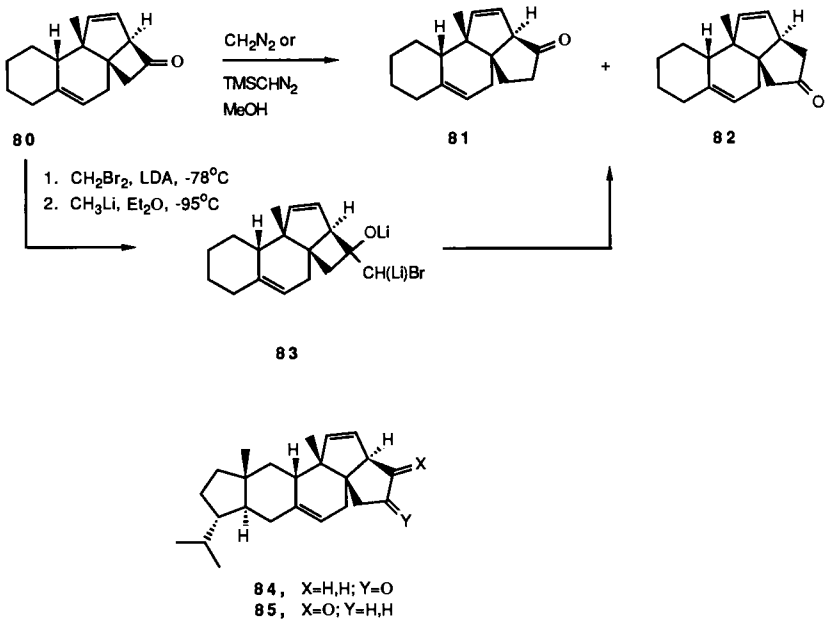
cycloaddition to give cyclobutanone **78** occured in less than 5 minutes at room temperature![43] These observations are especially instructive since they again testify to an asynchronous cycloaddition process.[40] As with ketene **60**, a reasonable molecular geometry for a synchronous $\pi_s^2 + \pi_a^2$ transition state seems unattainable for ketene **77**. However, the ketene carbon in **77** and the exo-methylene carbon on ring C can be brought within bonding distance with little molecular deformation, and the formation of this bond may promote bond formation between C-2 and C-$\gamma$.

A pentacyclic framework **78** with the proper topology and stereorelationships for the synthesis of retigeranic acid was now assembled. It remained to modify the sizes of rings C and E and introduce the ring-E methyl substituent. As is often the case in the synthesis of complex molecules, once an appropriate advanced intermediate is in hand the remaining steps of the synthesis are completed with surprising swiftness. Such was the case in this project; cyclobutanone **78** was converted to **1** within a few months.

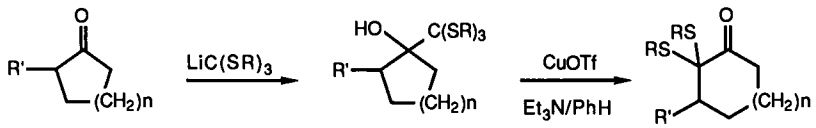
## IX. Ring Expansions and Contractions: The Total Synthesis of Retigeranic Acid

To probe the ring expansion of the E ring in **78**, we resorted to model system **80** (Scheme 22), which was prepared from aldehyde **51** in model studies of the transformations shown in Scheme 21. Once again, problems were encountered in our initial experiments. Reaction of **80** with diazomethane or trimethylsilyl diazomethane[44] under a variety of conditions (MeOH; $BF_3 \cdot Et_2O$, etc.) produced a 1 : 1 mixture of the two cyclopentanones **81** and **82** (Scheme 22). The same product mixture was found with ring expansion processes involving $\beta$-oxido carbenoid intermediates **83**.[45] These results were not considered catastrophic since, in principle, the products resulting from application of these reactions to **78**, i.e., **84** and **85**, could both be converted into **1**. However, two separate routes would be required for maximum utilization of **84** and **85**.

A unified route for both the ring expansion and methyl group introduction was considered more aesthetically appealing and efficient. A protocol to effect this transformation was suggested by the reports of Cohen[46] and Knapp[47] (Scheme 23). They reported that $\alpha$-hydroxy-trithio-orthoesters **86**, formed by addition of trithioalkyl(or phenyl)-methyllithium to cyclic ketones, yield ring-expanded $\alpha,\alpha$-dithioalkyl(or phenyl) cycloalkanones **87** on treatment with copper(I) triflate/$Et_3N$. Furthermore, these reactions were highly regioselective with preferential migration of the more highly substituted alkyl group in intermediates **86** derived from unsymmetrical ketones.

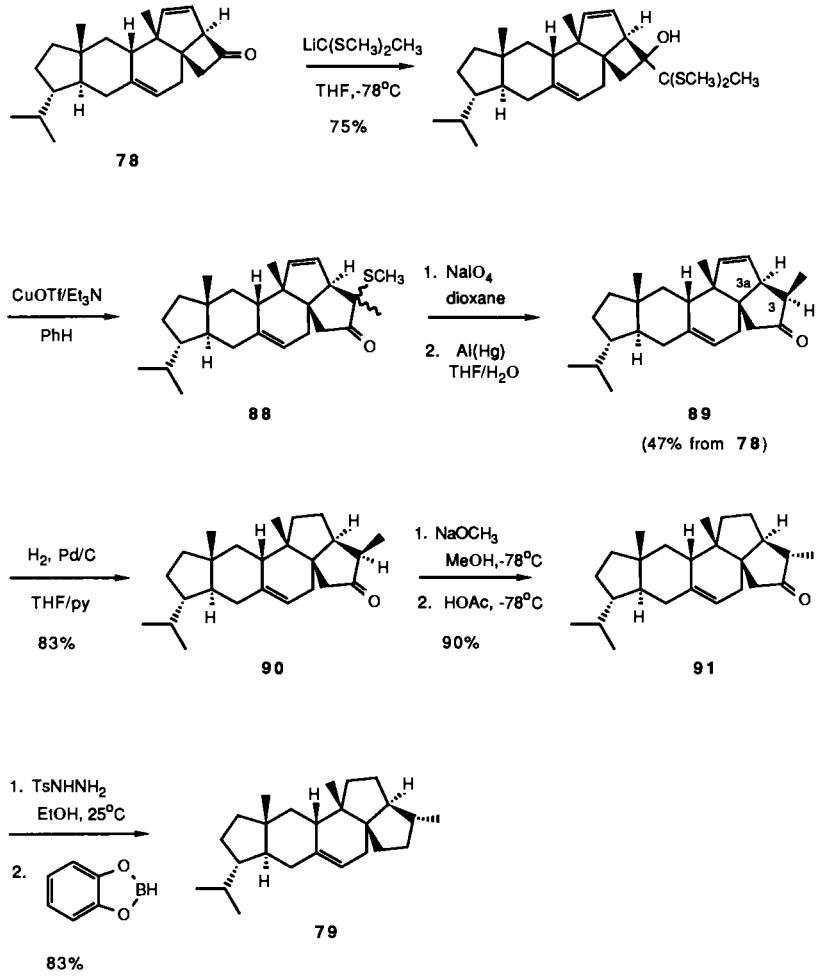



SCHEME 22



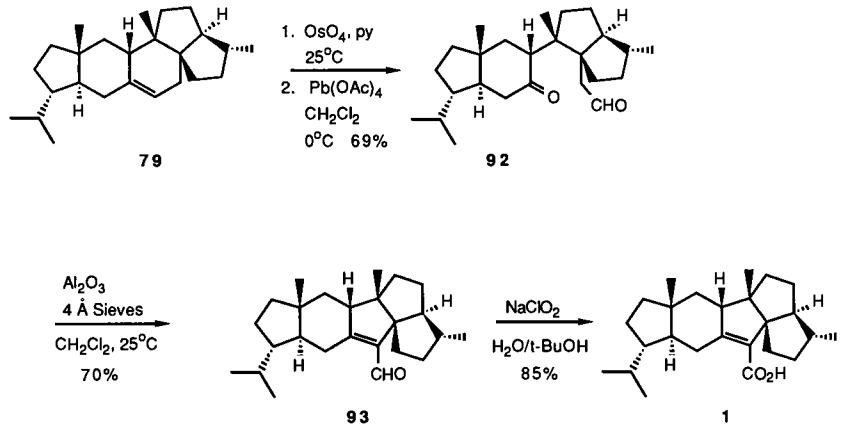

SCHEME 23

The application of this methodology to the ring expansion of cyclobutanone **78** required that α-hydroxy-dithioketals react with CuOTf/$Et_3N$ in a manner similar to the α-hydroxy-trithio-orthoesters **86**, a matter which could not be taken for granted in the absence of prior practical experience. Fortunately, this was in fact found to be the case, and conversion of **78** to **88** (Scheme 24; the stereochemistry of **88** was not determined) was effected by the sequence (1) addition of 1-lithio-1, 1-(dithiomethyl)ethane and (2) treatment with CuOTf/$Et_3N$/benzene. Desulfurization of **88** via its sulfone gave




SCHEME 24

cyclopentanone **89** in 47% overall yield from **78**. A large $J_{H3-H3a}$ of 8.5 Hz in the $^1H$ NMR spectrum of **89** indicated a $\beta$ orientation of the methyl group in ring E. The stereochemistry at this position was corrected to that of naturally occurring **1** after selective hydrogenation of the disubstituted double bond in **89** which afforded **90**. With the increased steric bulk on the $\beta$ face of **90**, in comparison to **89**, epimerization of the methyl group in ring E to the more stable configuration in **91** was readily effected by treatment of **90** with 1 equivalent of sodium methoxide in methanol at $-78°C$ followed by addition of acetic acid at that temperature. Deoxygenation of ketone **91** to hydrocar-




SCHEME 25

bon **79** was accomplished by catechol–borane reduction of the tosylhydrazone derivative.[48] In order to ensure that epimerization of the ring-E methyl group had not occurred during the reduction sequence, an identical series of reactions was duplicated with **90**, which resulted in a hydrocarbon product clearly different from **79**. The latter series of reactions with **90** was necessitated by the lack of distinguishing proton resonances in the $^1$H NMR spectrum of **79**, which prevented assignment of the stereochemistry in ring E.

The final steps from **79** to **1** were (Scheme 25) (1) oxidative cleavage of the C ring in alkene **79** by $OsO_4$ hydroxylation[49] and $Pb(OAc)_4$ glycol fission to give keto-aldehyde **92**, (2) internal aldol cyclization to aldehyde **93**, effected with neutral alumina/4 Å molecular sieves,[50] and (3) $NaClO_2$ oxidation[51] of **93** to **1**. The methods used to effect the reactions in Scheme 25 were chosen because of their use of mild and nearly neutral conditions. In particular, the sodium chlorite oxidation had been successfully employed in the oxidation of sensitive aldehydes encountered in other projects in Professor Corey's laboratories.[51b]

The total synthesis of a molecule we believed to be retigeranic acid was complete.

## X. The Natural Product: Retigeranic Acid-A and Retigeranic Acid-B

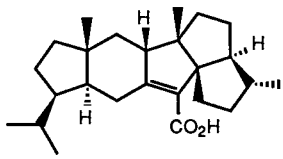
The ultimate indication of success in any natural product synthesis is direct comparison of the synthetic material with the natural product itself. A sample of naturally occurring retigeranic acid was kindly supplied by

Professor Shibata and a favorable TLC comparison was made with our synthetic (±)-**1**. However, some "extra" peaks were observed in the 270-MHz $^1$H NMR of the natural product when compared to the NMR of synthetic (±)-**1**. Diazomethane esterification of the natural product and analysis by HPLC revealed that this sample was a mixture of two acids, **1-A** and **1-B**.* The methyl esters of the two components were isolated and the methyl ester of **1-A** was found to be identical in all respects to the methyl ester of synthetic (±)-**1**. The ester of the second component, **1-B**, was clearly different. Thus, the molecule synthesized in our laboratory was indeed a component of natural retigeranic acid.

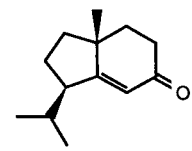
However, a final task remained. In the original report on retigeranic acid, the structure was based on an X-ray crystal structure determination of a *p*-bromoanilide derivative. Apparently, during preparation of the derivative for X-ray analysis, crystals of a *p*-bromoanilide derivative of **1** were obtained by fractionation of an isomeric mixture. We were faced with a dilemma since we could not be sure which component of natural retigeranic acid, **1-A** or **1-B**, gave rise to the crystal of the *p*-bromoanilide derivative used in the X-ray study. In particular, we were concerned that components **1-A** and **1-B** were stereoisomers differing only at the methyl-bearing carbon in the E-ring, a postulate which was supported by biosynthetic considerations. If the assignment of ring-E stereochemistry in the synthetic intermediate **79** or **91** was wrong, then our synthetic (±)-**1** might have the opposite configuration at the methyl-bearing carbon in ring E.

Professor Shibata again came to our aid and supplied a sample of the *p*-bromoanilide derivative of retigeranic acid from which the crystal was taken for the X-ray study. This sample was compared by HPLC to the *p*-bromoanilide derivatives of **1-A**, **1-B**, and synthetic (±)-**1**. The derivatives of **1-A** and synthetic (±)-**1** were identical with the X-ray sample, whereas the derivative of **1-B** was undoubtedly different.

After our report on the synthesis of retigeranic acid, Professor Shibata communicated to us that he had isolated both components of natural retigeranic acid and determined their structures by X-ray crystallography.[52]




**94**




**95**

*The nomenclature was suggested by Professor Shibata.[52]

Component **A** indeed has structure **1** and component **B** differs in stereochemistry at the isopropyl-bearing carbon in the A ring; i.e., **94**. It is perhaps noteworthy that hydrindenone **95** has been previously prepared[53] and in principle could be used as a starting point for a synthesis of retigeranic acid **B** utilizing a strategy similar to the one outlined above.

## Acknowledgments

It was a great pleasure to share this project (and a laboratory, with a superb chemist and a great individual, Dr. Manoj C. Desai. I also thank him for the use of his research reports, from which I have borrowed liberally (and literally). Of course, the project could not have been completed without the expert planning, guidance, and encouragement of Professor E. J. Corey. My experience in his research group was rewarding and memorable and I thank him for presenting me with the opportunity to be a part of that stimulating environment.

## References

1. (a) Rao, P. S.; Sarma, K. G.; Seshardri, T. R. *Curr. Sci.* **1965,** *34*, 9; (b) *Curr. Sci.* **1966,** *35*, 147.
2. (a) Kaneda, M.; Takahashi, R.; Iitaka, Y.; Shibata, S. *Tetrahedron Lett.* **1972,** 4609; (b) Kaneda, M.; Iitaka, Y.; Shibata, S. *Acta Crystallogr., Sect. B* **1974,** *B30*, 358.
3. Several preliminary reports have appeared: (a) Fallis, A. G.; Attah-Poku, S. K.; Chau, F.; Yadav, V. *J. Org. Chem.* **1985,** *50*, 3418; (b) Sternbach, D. D.; Hobbs, S. H. *Abstr. Pap., 188th Nat. Meet. Am. Chem. Soc.; Philadelphia* **1984,** ORGN 52; (c) Roberts, R. A.; Schüll, V.; Paquette, L. A. *J. Org. Chem.* **1983,** *48*, 2076; (d) Hudlicky, T.; Short, R. P. *J. Org. Chem.* **1982,** *47*, 1522.
4. Corey, E. J.; Desai, M. C.; Engler, T. A *J. Am. Chem. Soc.* **1985,** *107*, 4339.
5. Recently, the total synthesis of **1** has been accomplished by two other groups; (a) Paquette, L. A.; Wright, J.; Drtina, G. J.; Roberts, R. A. *J. Org. Chem.* **1987,** *52*, 2960; (b) Hudlicky, T. Personal communication.
6. For leading references, see reference 3a; (b) Corey, E. J.; Engler, T. A. *Tetrahedron Lett.* **1984,** 149; (c) Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1982,** *47*, 5042; (d) Tsuda, T.; Kawamoto, T.; Kumamoto, Y.; Saegusa, T. *Synth. Commun.* **1986,** *16*, 639; (e) Snider, B. B.; Karras, M. *J. Am. Chem. Soc.* **1980,** *102*, 7951; (f) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984,** *49*, 153. (g) Fukuzaki, K.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett* **1984,** 3591.
7. Martin, S. F. *Tetrahedron* **1980,** *36*, 419.
8. (a) Dauben, W. G.; Hart, D. J. *J. Org. Chem.* **1977,** *42*, 3787; (b) Pirrung, M. C. *J. Am. Chem. Soc.* **1979,** *101*, 7130; (c) Oppolzer, W.; Bättig, K.; Hudlicky, T. *Tetrahedron* **1981,** *37*, 4359; (d) Wender, P. A.; Dreyer, G. B. *Tetrahedron* **1981,** *37*, 4445; (e) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981,** *46*, 1103; (f) Oppolzer; W.; Bättig, K. *Helv. Chim. Acta* **1981,** *64*, 2489; (g) Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1983,** *105*, 7358 (h) **1982,** *104*, 4504; (i) Paquette, L. A; Leone-Bay, A. *J. Am. Chem. Soc.* **1983,** *105*, 7352; (j) Wenkert, E.; Arrhenius, T. S. *J. Am. Chem. Soc.* **1983,** *105*, 2030; (k) Mehta, G.; Rao, K. S. *Tetrahedron Lett.* **1984,** 3481. For recent reviews, see (l) Paquette, L. A. *Top. Curr. Chem.* **1979,** *79*, 41; (m) **1984,** *119*, 1.
9. Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980,** *102*, 5872.
10. Caine, R. *Org. React.* **1976,** *23*, 20.
11. Servis, K. L.; Crossland, R. K. *J. Org. Chem.* **1970,** *35*, 3195.

12. (a) Stang, P. J.; Mangum, M. G.; Fox, D. P.; Haak, P. *J. Am. Chem. Soc.* **1974,** *96*, 4562, (b) Treatment of **8** with $Tf_2O$ and 2,6-di-*t*-butyl-4-methylpyridine in $CH_2Cl_2$ gave a 1 : 1 mixture of **6** and **13** in 88% yield; for this method to prepare vinyltriflates, see Stang, P. J.; Dueber, T. E. *Org. Synth.* **1974,** *54*, 79; Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982,** 85, and references cited therein.
13. After this research was completed, $(Tf)_2NPh$ was reported as a useful reagent to trap kinetically formed enolates as their triflates; See McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983,** 979.
14. (a) McMurry, J. E.; Mohanraj, S. *Tetrahedron Lett.* **1983,** 2723, and references cited therein; (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984,** *40*, 5005.
15. Formed in 92% yield by managanese dioxide oxidation of methyl *trans*-4-hydroxy-3-methyl-2-butenoate, which was prepared by the method of Epstein; see Epstein, W. W.; Sonntag, A. C. *J. Org. Chem.* **1967,** *32*, 3390. Several syntheses of **27** or closely related esters have appeared recently: (b) Curley, R. W., Jr.; Ticoras, C. J. *J. Org. Chem.* **1986,** *51*, 256; (c) Curley, R. W., Jr.; Ticoras, C. J. *Synth. Commun.* **1986,** *16*, 627; (d) Yoshii, E.; Takeda, K.; Shibata, Y.; Sagawa, Y.; Urahata, M.; Funaki, K.; Hori, K.; Sasahara, H. *J. Org. Chem.* **1985,** *50*, 4673; (e) Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984,** 820.
16. Corey, E. J.; Engler, T. A.; Berg, J M. *Acta Crystallogr., Sect. C* **1985,** *C41*, 289.
17. Mitsunobu, O. *Synthesis* **1981,** 1.
18. (a) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983,** *2*, 681; (b) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979,** *168*, 183.
19. Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983,** *105*, 1072.
20. Oppolzer, O. *Helv Chim. Acta* **1973,** *56*, 1812.
21. (a) Mock, W. L.; Nugent, R. M. *J. Org. Chem.* **1978,** *43*, 3433, and references cited therein; (b) Rogić, M. M.; Masilamani, D. *J. Am. Chem. Soc.* **1977,** *99*, 5219; (c) Sharpless, K. B.; Hori, T.; Singer, S. P. *J. Org. Chem.* **1978,** *43*, 1456.
22. (a) Greene, A. E. *J. Am. Chem. Soc.* **1980,** *102*, 5337; (b) Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978,** *43*, 2299; (c) Kabalka, G. W.; Yang, D. T. C.; Baker, J. D., Jr. *J. Org. Chem.* **1976,** *41*, 574; (d) Djerassi, C.; Taylor, E. J. *J. Am. Chem. Soc.* **1976,** *98*, 2275; (e) Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975,** *40*, 923; (f) Hutchins, R. O..; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973,** *95*, 3662.
23. Volante, R. P. *Tetrahedron Lett.* **1981,** 3119.
24. Filby, W. G.; Günther, K.; Penzhorn, R. D. *J. Org. Chem.* **1973,** *38*, 4070.
25. (a) March, J. "Advanced Organic Chemistry," 3rd Edition; Wiley (Interscience): New York, 1985; p. 394; (b) Carey, F. A.; Sundberg, R. J. "Advanced Organic Chemistry, Part B," 2nd Edition; Plenum: New York, 1983; pp. 498–500; (c) Schwab, J. M. *J. Org. Chem.* **1983,** *48*, 2105, and references cited therein.
26. (a) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984,** *106*, 3866; (b) Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985,** 6005; (c) Evans, D. A.; Morrissey, M. M. *Tetrahedron Lett.* **1984,** 4637; see also (d) Brown, J. M.; Naik, R. G. *J.C.S. Chem. Commun.* **1982,** 348.
27. Collman, J. C.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry," Univ. Sci. Books: Mill Valley, California, 1980; p. 328.
28. Overberger, C. G.; Saunders, J. H. "Organic Syntheses," Wiley: New York, Collect. Vol. III, p. 204.
29. (a) Büchi, G.; Wüest, H. *Helv. Chim. Acta* **1971,** *54*, 1767; (b) Dauben, W. G.; Hart, D. J.; Ipaktschi, J.; Kozikowski, A. *Tetrahedron Lett.* **1973,** 4425.
30. The reagents (1-diphenylphosphino)allyltitanium and (*E*)-1-trimethylsilyl-1-propene-3-pinacolboronate were also unsuccessful; see reference 31.
31. Corey, E. J.; Desai, M. C. *Tetrahedron Lett.* **1985,** 5747.

32. For previous examples of intramolecular ketene–olefin cyclizations, see (a) Beereboom, J. J. *J. Am. Chem. Soc.* **1963,** *85,* 3525; (b) *J. Org. Chem.* **1965,** *30,* 4230; (c) Masamune, S.; Fukumoto, K. *Tetrahedron Lett.* **1965,** 4647; (d) Bates, R. B.; Onore, M. J.; Paknikar, S. K.; Steelink, C.; Blanchard, E. P. J. *J.C.S. Chem. Commun.* **1967,** 1037; (e) Yates, P.; Fallis, A. G. *Tetrahedron Lett.* **1968,** 2493; (f) Baldwin, S. W.; Page, E. H., Jr. *J. S. Chem. Commun.* **1972,** 1337; (g) Smit, A.; Kok, J. G. J; Geluk, H. W. *J.C.S. Chem. Commun.* **1975,** 513; (h) Moon, S.; Kolesar, T. K. *J. Org. Chem.* **1974,** *39,* 995; (i) Becker, D.; Nagler, M.; Birnbaum, D. *J. Am. Chem. Soc.* **1972,** *94,* 4771; (j) Murray, R. K., Jr.; Goff, D. L.; Ford, T. M. *J. Org. Chem.* **1977,** *42,* 3870; (k) Ireland, R. E.; Aristoff, P. A. *J. Org. Chem.* **1979,** *44,* 4323; (l) Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thaisrivongs, S. *J. Org. Chem.* **1984,** *49,* 1001.

33. Many recent papers describing intramolecular ketene–olefin cyclizations have appeared; see (a) Snider, B. B.; Kulkarni, Y. S. *J. Org. Chem.* **1987,** *52,* 307; (b) Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *J. Am. Chem. Soc.* **1985,** *107,* 2194, and earlier papers in this series; (c) Markó, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985,** *107,* 2192; see also reference 40.

34. (a) Woodward, R. B.; Hoffman, R. "The Conservation of Orbital Symmetry," Verlag Chemie: Weinheim, 1970; (b) Zimmerman, H. E. *Acc. Chem. Res.* **1971,** *4,* 272; (c) Fleming, I. "Frontier Orbitals in Organic Chemical Reactions," Wiley: New York 1976; pp. 143–147.

35. (a) Corey, E. J.; Arnold, Z.; Hutton, J. *Tetrahedron Lett.* **1970,** 307; (b) Holder, R. W.; Graf, N. A; Duesler, E.; Moss, J. C. *J. Am. Chem. Soc.* **1983,** *105,* 2929; (c) Bertrand, M., Gras, J.-L.; Goreé, J. *Tetrahedron Lett.* **1972,** 1189; (d) Fletcher, V. R.; Hassner, A. *Tetrahedron Lett.* **1970,** 1071, 5053; (e) Katz, T. J.; Dessau, R. *J. Am. Chem. Soc.* **1963,** *85,* 2172; see also reference 40.

36. Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974,** *39,* 914.

37. (a) Paquette, L. A.; Cox, O.; Oku, M.; Henzel, R. P. *J. Am. Chem. Soc.* **1974,** *96,* 4892; (b) Greene, A. E.; Deprés, J.-P. *J. Am. Chem. Soc.* **1979,** *101,* 4003.

38. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975,** *97,* 5434.

39. Gemal, A. L., Luche, J.-L. *J. Am. Chem. Soc.* **1981,** *103,* 5454.

40. This ketene–olefin cyclization also became the seminal idea for a short synthesis of *β-trans*-bergamotene; Corey, E. J.; Desai, M. C. *Tetrahedron Lett.* **1985,** 3535.

41. Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983,** 5771.

42. Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976,** *41,* 1485.

43. In fact, the analogous reaction with the ketene derived from model compound **51,** i.e., devoid of the A ring, proceeded in 2 hours at -20°C.

44. Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980,** 4619.

45. Taguchi, H., Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977,** *50,* 1588, 1592, and references cited therein.

46. Cohen, T.; Kuhn, D.; Falck, J. R. *J. Am. Chem. Soc.* **1975,** *97,* 4749.

47. (a) Knapp, S.; Trope, A.; Ornaf, R. M. *Tetrahedron Lett.* **1980,** 4301; (b) Knapp, S.; Trope, A. F.; Theodore, M. S.; Hirata, N.; Barchi, J. J. *J. Org. Chem.* **1984,** *49,* 608.

48. Kabalka, G. W.; Chandler, J. H. *Synth. Commun.* **1979,** *9,* 275.

49. Baren, J. S. *J. Org. Chem.* **1960,** *25,* 257.

50. Tanabe, K.; Morisawa, Y. *Chem. Pharm. Bull.* **1963,** *11,* 536.

51. (a) Bal'B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981,** *37,* 2091; (b) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985,** *107,* 5574.

52. Professor S. Shibata, personal communication to Professor E. J. Corey June 10, 1986.

53. (a) Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1977,** 3107; (b) Allard, M.; Levisalles, J.; Rudler, H. *Bull. Soc. Chim. Fr.* **1968,** 303.

*Chapter 4*

# CARBOCYCLES FROM CARBOHYDRATES: THE "ANNULATED SUGAR" APPROACH

*Bert Fraser-Reid and Ray Tsang*

*Department of Chemistry*
*Paul M. Gross Chemical Laboratory*
*Duke University*
*Durham, North Carolina*



## I. Introduction

The explosive impact of carbohydrate chemistry on the practice of synthetic organic chemistry during the past 15 years is an interesting piece of chemical sociology.[1–3] Hitherto, the former area had exploited and benefited greatly from developments in the latter, but the reverse was not the case. Apart from fringe areas which dealt with mechanistic and stereochemical investigations, traditional synthetic organic chemistry had remained in splendid isolation from traditional carbohydrate chemistry.

A number of factors converged in order to bring about this change. One, undoubtedly, was a growing insistence on the preparation of biologically important compounds in optically active forms. Exploitation of the "chiral pool"[4] therefore seemed logical, and attention was necessarily focused on sugars, the most abundant component(s) thereof. A second factor arose from some simple developments in organic chemistry which turned out to be of paramount importance. Thus, the recent wealth and variety of gentle protecting groups were particularly felicitous for carbohydrate manipulations. Indeed, many of them were developed in that domain.[5–8] The same holds true for gentler methods of oxidation[9] and deoxygenation,[10–14] processes which are invariably featured in any carbohydrate-based synthesis.

Allied with these has been the emergence of NMR spectroscopy,[15] a tool which was nurtured[16] in the realm of carbohydrate chemistry. Structure proof has become routine because of this, and the earlier well-justified fear of the reluctance of sugars to crystallize is now largely irrelevant because adequate characterization can be ensured by the use of a battery of spectroscopic tools.

From the standpoint of chemistry, a pivotal point was undoubtedly the landmark studies of Masamune, which culminated in the first synthesis of a macrolide.[17] In the rush that was triggered by this monumental achievement, sugar-based strategies were logical,[18] in view of the polyoxygenated nature of both the starting materials and targets. Indeed, this connectivity had already been recognized in the seminal studies of Celmer.[19]

Many macrolides, or segments thereof, can be regarded as higher-carbon sugars.[20] Erythronolide has held a central place among the macrolides, probably because of Woodward's famous comment 30 years ago that "erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers".[21]

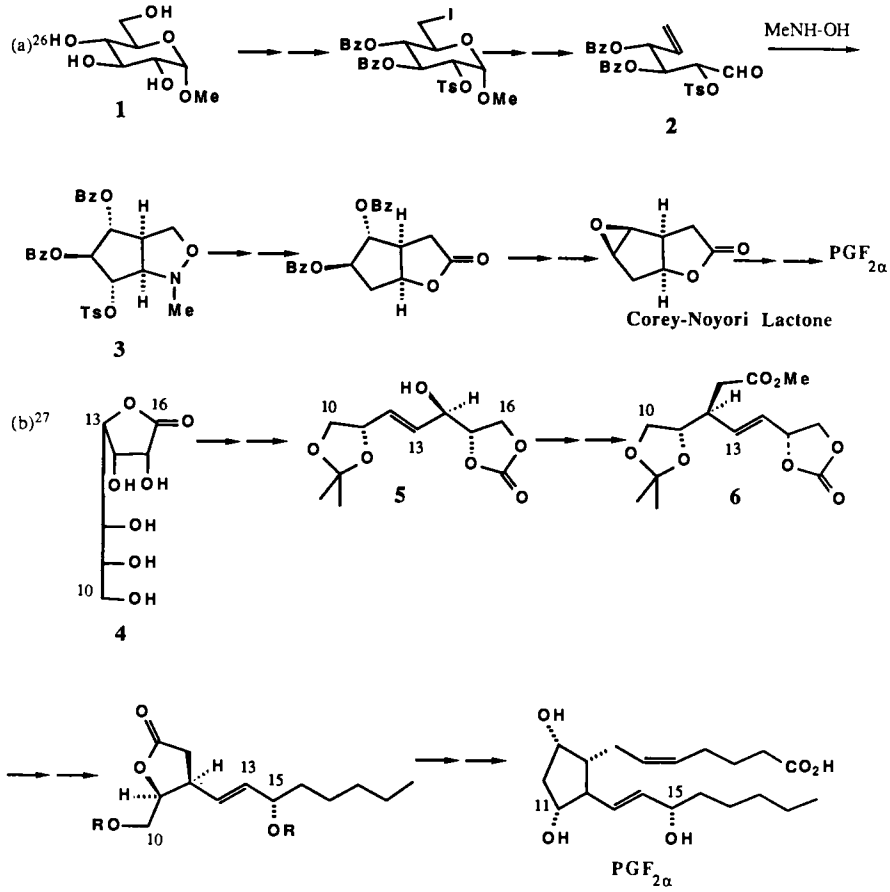
Although the first literature report of a sugar-based approach to erythronolide came, not from a "carbohydrate chemist", but from Miljkovic and co-workers,[22] the most extensive studies culminating in an advanced intermediate were from the Hanessian group.[23] Ironically, in spite of a number of approaches since then,[24] a sugar-based synthesis of erythronolide was only recently completed by the Russian team lead by Kochetkov.[25]

## II. The General Protocol

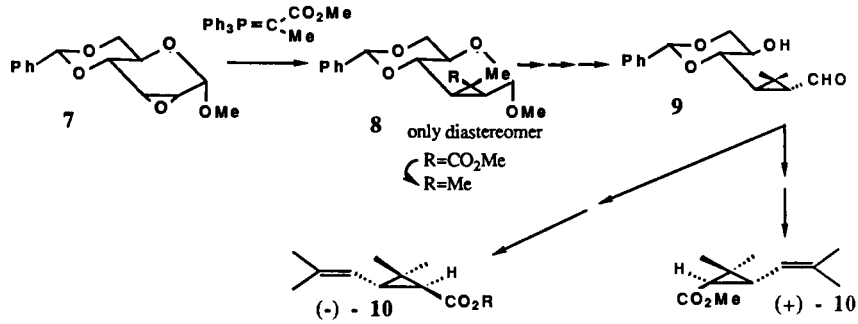
The challenges of the macrolides notwithstanding, the interest in our research group was drawn toward the development of strategies for the preparation of carbocycles from carbohydrates. Unlike the macrolides, there is no obvious *visual* connection between carbocycles and carbohydrates. For

example, how would a sugar be converted into a prostaglandin? The approach of Ferrier is shown in Scheme 1a, in which the key step was the intramolecular cycloaddition **2** → **3**. The nitrone was developed from the anomeric (aldehydic) carbon, while the double bond was obtained by reductive elimination of the 5,6-diol of methyl α-D-glucopyranoside, **1**.[26]

Stork's earlier synthesis of $PGF_{2\alpha}$[27] remains an elegant achievement for the use it made of the entire starting material, D-*glycero*-D-*gulo*-heptono-1,4-lactone, **4** (Scheme 1b). All seven carbons were utilized beautifully. Achiral centers in the starting material and the products were programmed to correlate, and of the five secondary hydroxyl groups, two were used for the stereospecific creation of the trans double bond (in **5**), two survived in the final product (at C-11 and C-15), and one was transferred to carbon




SCHEME 1




SCHEME 2.[30]

asymmetry by means of a Claisen rearrangement (**5** → **6**). Therefore, all centers of the starting material were utilized with both functional and stereochemical economy.

The approach pursued in our laboratory also grew out of a desire to make fullest use not only of the functional aspects of the sugar but also of its topographical features. Thus, as we noted in a very early publication,[28] the conformational bias of sugars fosters (a) high stereoselectivity in chemical reactions and (b) easy proof of structure of the products arising therefrom. Our wish, therefore, was to utilize these attributes repeatedly and then to destroy the sugar only after they had been fully exploited. The "annulated pyranoside" concept[29] was devised for this purpose, and it is demonstrated with the synthesis of both enantiomers of chrysanthemic acid [(+) and (−) **10**] from a common intermediate **9** (Scheme 2).[30]

The success of the chrysanthemic acid syntheses (Scheme 2) suggested a general protocol for the preparation of carbocycles from carbohydrates.

(1) The topographical features of the sugar derivative would be used to engender stereoselective formation of the annulus (e.g., **7** → **8**).

(2) NMR analysis, aided by the known, fixed geometry of the sugar moiety, would give details regarding the stereochemical features of the resulting "annulated sugar" (e.g., **8**).

(3) Structural manipulations on the annulus would then be undertaken on the assumption of conformational inflexibility of the annulated sugar, and stereoselectivity of the various transformations would be monitored by NMR.

(4) Having served its purpose, the carbohydrate moiety would be destroyed and/ or modified (e.g., **8** → **9**), according to the requirements of the synthetic target.

## III. Synthetic Design

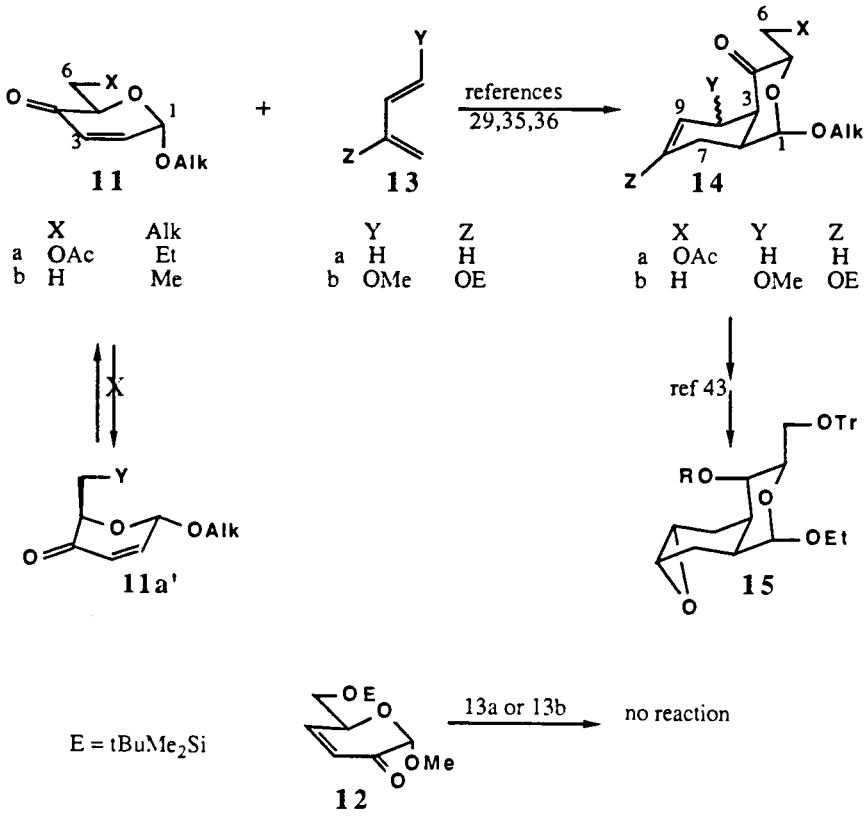
In pursuing the annulated sugar approach, it is clear that our main preoccupation is to utilize the sugar for its *stereochemcial* advantages and not merely because of its *chirality*. Chirality comes from nature (usually via Aldrich!!), and chemists do not, indeed they cannot, *create* it—although they can destroy it! This being the case, they can take no credit for it. On the other hand, chemists move chirality around, and the objective is to do so efficiently, whether by use of chirons, chiral auxiliaries, asymmetric induction, or other means. In this context, efficiency can be equated with stereoselectivity, and as such it is the direct outcome of the synthetic design. The latter ultimately is a test of creativity and, if successful, credit can be taken, for credit is due.

## IV. Actinobolin

The plan devised for the synthesis of actinobolin, **16a** (Scheme 4), grew out of an initial interest in carbohydrate $\alpha$-enones, such as **11**[31] and **12**,[32] as substrates for synthesis of branched-chain sugars. Simple conjugate additions (e.g., $LiR_2Cu$[33] or $R\dot{C}HOH$[34]) had worked smoothly, and hence Diels–Alder reactions were an obvious avenue for exploration. Thermal addition of butadiene (**13a**) to **11a** (Scheme 3) was unfruitful; but with Lewis acids at low temperatures, yields of 80–90% of **14a** could be obtained.[29] We were pleasantly surprised that the addition had occurred at all, given the generally poor record of Diels–Alder additions of butadiene to unsubstituted cyclohexenones.

Our initial rationalization for this favorable circumstance was that the acceleration was due, somehow, to the ring oxygen. However, this assessment had to be abandoned when it was found, subsequently, that the regioisomeric enone **12** failed to yield a product with butadiene. It was this surprising result that caused us to examine Danishefsky's diene **13b**.[35,36] Similar trends in reactivity (and unreactivity!) prevailed and these, coupled with some anomalies which we had observed in the addition of $R\dot{C}HOH$ to $\alpha$-enone,[34] caused us to launch a broadly based investigation into the general reactivity of carbohydrate versus carbocyclic $\alpha$-enones. Some aspects of this study were recently published.[37]

Our initial report on the exclusive formation of $\beta$-face Diels–Alder adducts was based on 60 MHz $^1$H-NMR spectroscopy,[29] and it is gratifying to know that these observations have been upheld, even at 400 MHz,[38] and with a much wider assortment of dienes.[35,36,39] Enone **11a** has one axial and one

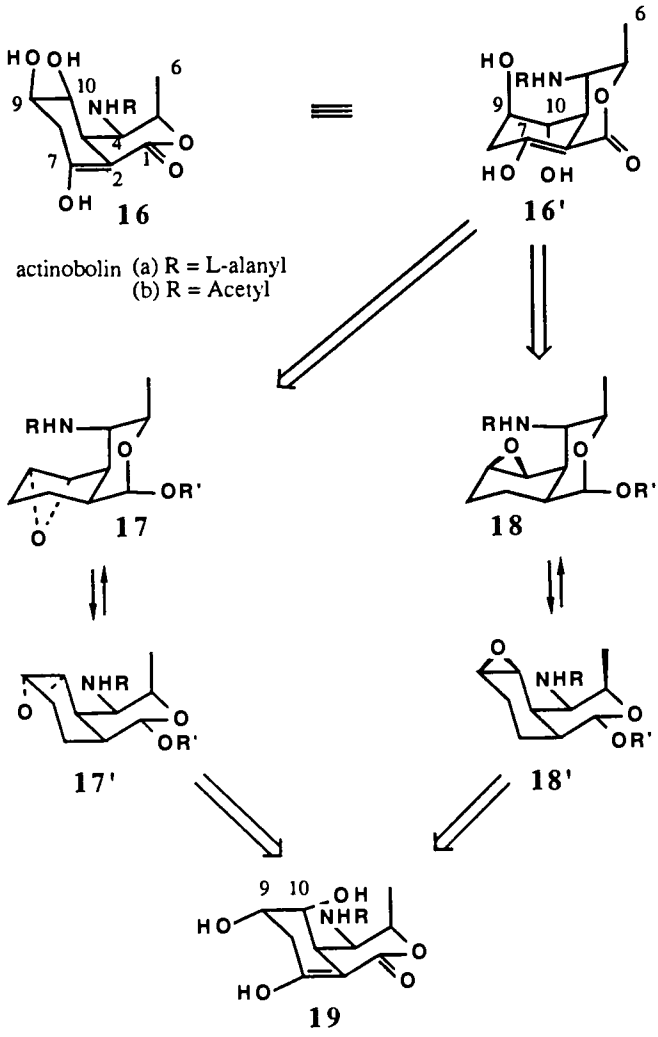



SCHEME 3

equatorial substituent, as does its other conformer **11a'**. At the outset, we knew that the axial OEt would be favored in **11a** because of the anomeric effect.[40] Since then, the work of Eliel has shown that the conformational preference of a carbon substituent $\alpha$ to the oxygen of a pyran ring (e.g., $CH_2X$ in **11**) is much greater than in a corresponding carbocycle.[41]

Thus, both substituents in **11a** are in their preferred orientations and, although we are sensitive to the Curtin–Hammett principle,[42] we note that the enone appears to react only from this conformation. That the product was indeed the $\beta$-face adduct **14a** was immediately obvious from the unsplit appearance of the signal for H-1.[29] Had addition occurred cis to the OAlk group, the H-1 signal of the product would have been a clear doublet.[29b]

The topographical characteristics of the annulated pyranoside **14a** suggested that the molecule should display a high degree of stereoselectivity in




SCHEME 4

its reactions. Indeed, a single epoxide, assigned as **15**, was obtained from it.[43] Thus, the high facial selectivity which had been found in the reactions of the simple pyranoside **11a** had been carried over into the more complex annulated pyranoside **14a**.

This observation provided a basis for tackling one of the problems of synthesis posed by actinobolin **16a**, namely the 9,10-diol moiety. It is known that the molecule exists in the trans-diequatorial arrangement shown.[44]

However, from a synthetic standpoint, the trans-diaxial arrangement (**16′**) should be more readily secured through hydrolysis of *either* an exo or endo epoxide, **17** or **18**, respectively—whichever was easier to obtain.

That trans-diaxial opening of **17** or **18** would give the desired product **16** (≡ **16′**) is obvious. However, the situation was not trivial because if the reactive species were the conformers **17′** and **18′** (instead of **17** and **18**), *trans-diaxial cleavage would lead to diol* ***19****, which is the diastereomer of* ***16***!

It seemed to us that the axial anomeric OAlk group might lock the bicyclic system in the desired conformation, **17** or **18**, by virtue of the anomeric effect.[40] However, once the glycosidic center of **17** or **18** was destroyed (e.g., by oxidation to a lactone), the molecule would be free to relax into its favored conformation (e.g., **16** ⋙ **16′**).

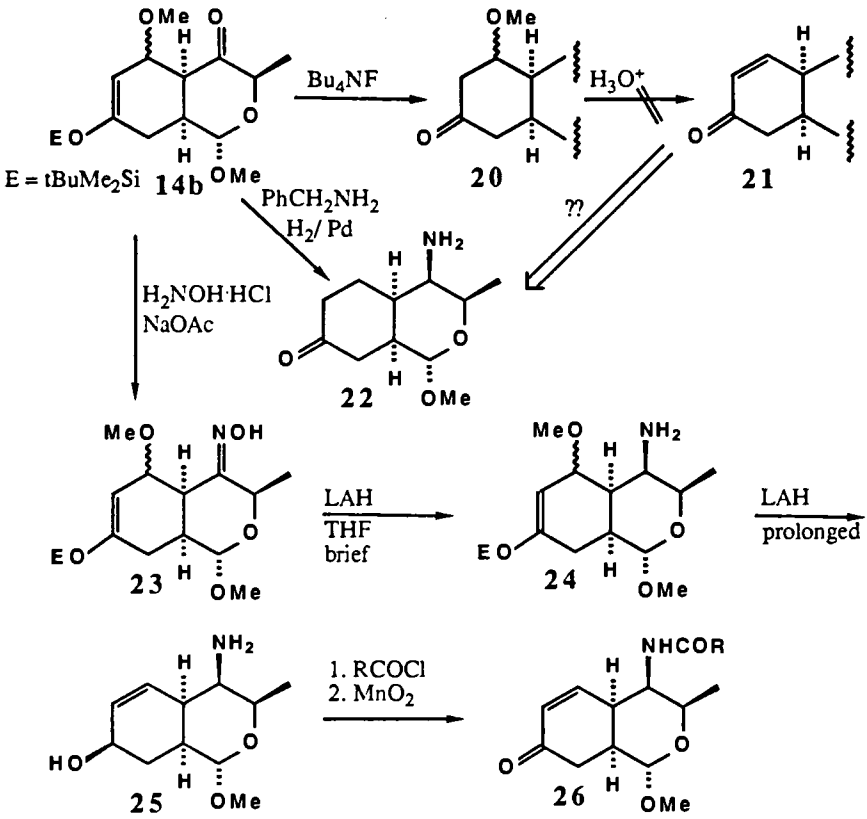
*Poor Prospects*

(1) However, was this a feasible retrosynthetic plan? The most generous estimates of the anomeric effect are in the region of 1.5 kcal/mol.[40b] Would this be enough to lock the molecule in conformation **17** or **18**? An assessment of nonbonded interactions was not encouraging, but we decided not to be dissuaded by this "poor prospect," but to see to what extent the anomeric effect would have predictability for such a system.

(2) A second poor prospect came from our difficulty in unravelling the Diels–Alder adduct from Danishefsky's diene[45] (e.g., **13b**). There was already evidence in the literature to show that unraveling to give the $\alpha,\beta$-unsaturated ketones (e.g., **14b** → **21**, Scheme 5) could be problematic.[46,47] Indeed, treatment of **14b** with tetra-*n*-butylammonium fluoride could not be taken beyond the $\beta$-methoxy ketone **20**, and attempts to eliminate methanol by use of acid caused, not surprisingly, severe decomposition.

The latter poor prospect was overcome by a surprising twist of fate which occurred while we were focusing attention on the efficient installation of the C-4 amino function. Reductive amination using ammonium acetate and sodium cyanoborohydride[48] failed, and an alternative procedure using benzylamine and 5% Pd/C[49] gave the saturated ketone **22**. If this unexpected product could be converted into enone **21**, then the problem of unraveling of **14b** could be obviated.

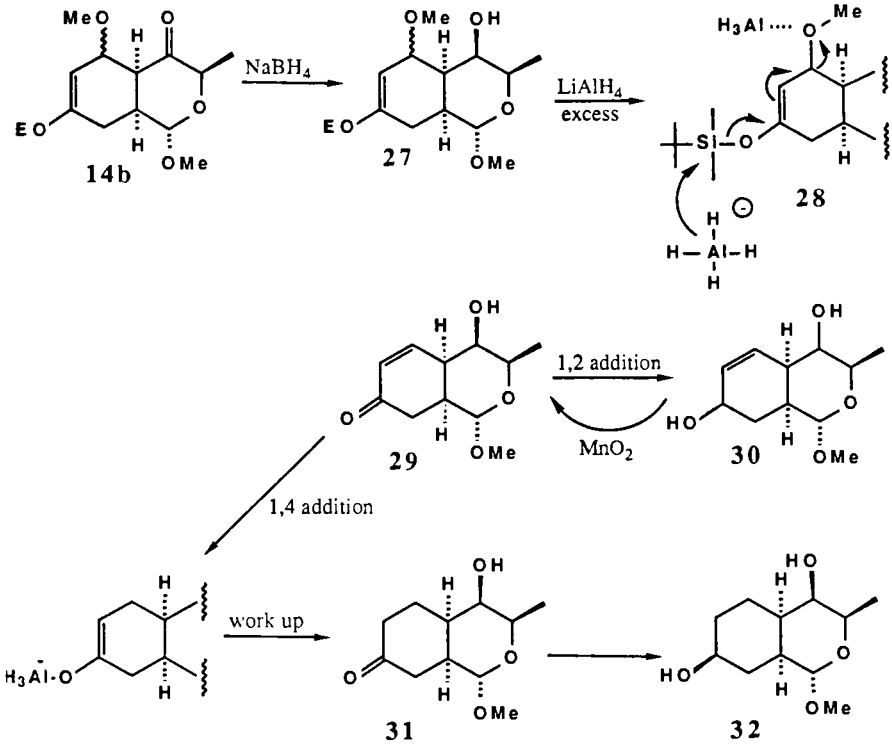
Promising though this idea appeared, it was never pursued because of an even more propitious occurence. The oxime **23** had been obtained in 95% yield under basic conditions. Reduction with lithium aluminum hydride for a short time at room temperature gave "the expected product" **24**—but only in moderate yield since "other" products were also formed. It was then found that prolonged standing with lithium aluminum hydride at room temperature, or for shorter periods at reflux, produced a mixture in which the amino alcohol **25** predominated.[35]



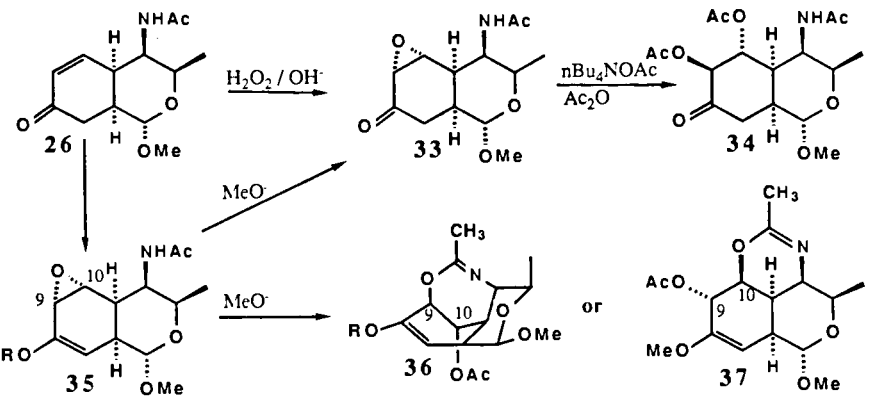

SCHEME 5

The generality of this unraveling process and some of the mechanistic details were then tested with the alcohol **27** (Scheme 6), which was obtained cleanly by reduction of **14b** with sodium borohydride.[36] Treatment of **27** with lithium aluminum hydride in THF for 18 hours gave **30, 31**, and **32** in a 10 : 1 : 1 ratio. Rationalization for the formation of these products is implied in **28** (Scheme 6), and a full account of our reasoning has been published.[36] Manganese dioxide oxidation of **30** (and **25**) then afforded the desired $\alpha$-enones **29** (and **26**), respectively.

With the fortunate discovery of this facile two-step procedure for unraveling the Danishefsky diene adducts,[35,36] it was now possible to turn our attention to the other poor prospect, the opening of the epoxide (e.g., **17** or **18**, Scheme 4). Simultaneously, we were concerned about how to introduce the C-7 oxygen of actinobolin. The presence of a C-8 carbonyl presented several options. First, it should provide convenient activation of both




SCHEME 6.[35,36]




(a) R=t BuMe$_2$Si
(b) R=Me

SCHEME 7

neighboring sites—C-7 for $\alpha$-oxygenation and C-9 for $S_N2$ attack. Accordingly, the enone **26** was epoxidized (Scheme 7), the exo orientation of **33** being confirmed by a 600-MHz spectrum. However, treatment of **33** with a wide variety of oxygen nucleophiles either left the starting material unreacted or caused decomposition.

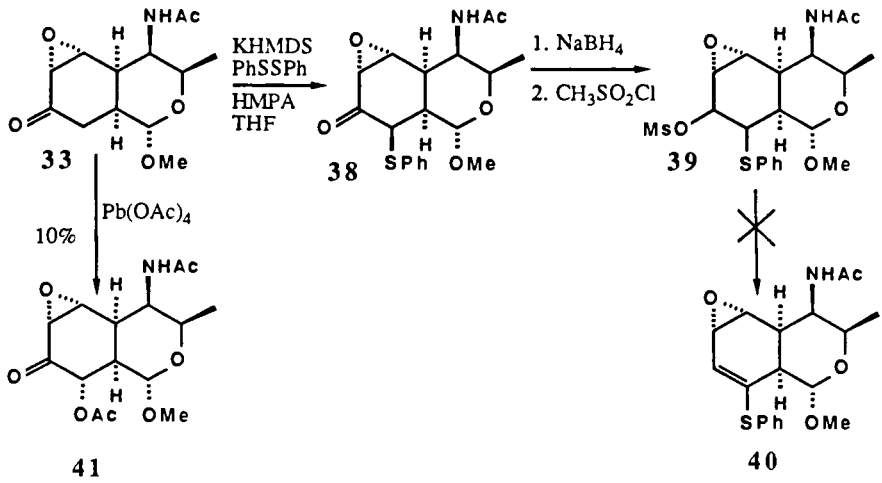
We had been aware all along that cleavage of the epoxides, such as **33**, would require an external nucleophile to approach from the concave surface—certainly an unfavorable option. However, the molecule had a conveniently positioned "internal" nucleophile in the guise of the C-4 amido group. There are ample precedents in the carbohydrate literature which indicate that the process depicted in Eq. (a) is feasible.[50] The question, then, was the regiochemistry of epoxide opening in our system.


(a)[50]

Attack at C-9 could probably be induced by opening that center vis-à-vis C-10, for example, by making C-9 allylic in the enol ether **35**. However, although the enol silane **35a** did react with a variety of oxygen nucleophiles, the product was the regenerated epoxy ketone **33**. This indicated that the preferred site for attack was silicon rather than C-9. Presumably, this could be avoided by changing silicon for carbon, and hence the methyl analog **35b** was prepared. Solvolysis with sodium methoxide did, indeed, cause the welcome disappearance of the infrared absorption for amide, raising our hopes that the desired reaction might have occurred. Regrettably, a 600-MHz spectrum showed that the product was not **36**, as desired, but was the oxazine **37**. Evidently, the activation offered at the allylic C-9 site of **35b** was not enough to overcome the tendency to form a six-membered ring.

In spite of this discouraging result, the prospect of using the C-8 carbonyl group for introducing the C-7 oxygen was still an available option. One possibility was $\alpha$-carbonyl transposition. The dense functionality of the molecule precluded most of the usual methods. Although the Trost process[51] could be applied to epoxy ketone **33** and taken to the sulfonate **39** (Scheme 8), elimination to the enol thioether **40** could not be effected.

If $\alpha$-carbonyl transposition was not possible, $\alpha$-oxygenation was yet another option. Of various non basic procedures available,[52] the lead tetraacetate procedure of Ellis[53] was chosen because it operates in neutral conditions. However, our best result in the reaction of **33** with this reagent



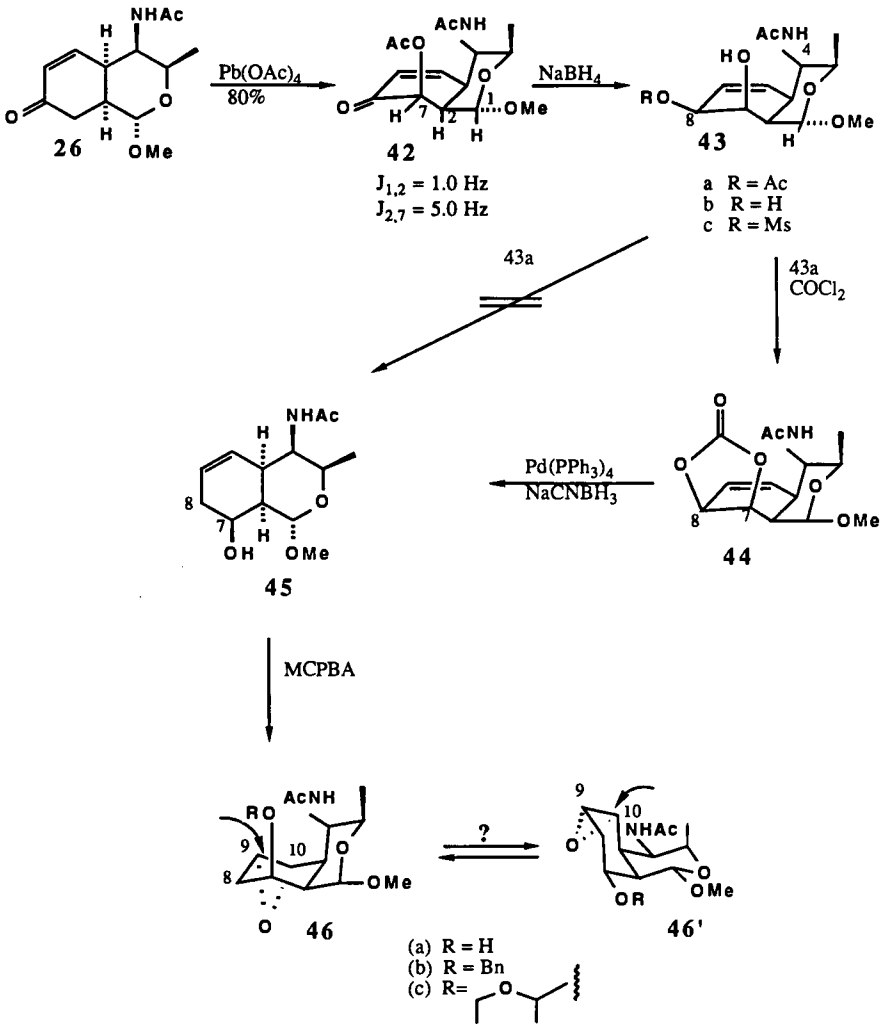

SCHEME 8

afforded only 10% of the α-acetoxy derivative **41** (Scheme 8). We surmised that our problem might be due in part to the presence of the epoxide, and this was presumably true for the α-enone **26** (Scheme 9) gave an 80% yield of **42**, the stereochemistry being indicated by the NMR parameters shown.

Having served its purpose, the C-8 carbonyl could be removed, and palladium-catalyzed deoxygenation of allylic acetates[54,55] seemed plausible. The appeal of this option was enhanced by the fact that upon sodium borohydride reduction of **42**, the acetyl group migrated cleanly to the newly created C-8-OH to give **43a** (Scheme 9). Models showed that there were severe interactions between a C-7-OAc and C-4-NHAc, which could be relieved by the migration of the acetyl group. In this context, it is interesting to note that sulfonation of the diol **43b** occurred only at C-8 to give the mesylate **43c**.

However, Pd(0) deoxygenation of **43a** failed. Fortunately, a timely communication by Sutherland[56] reported that deoxygenation of allylic carbonates was a very facile process. The cyclic carbonate **44** was readily formed, the conformational properties being indicated by virtue of the NMR parameters. The Sutherland deoxygenation then proceeded smoothly to give the alcohol **45**.

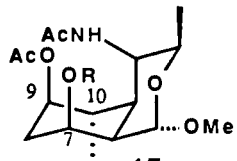
The conformation of **45** made it certain that exo-epoxidation would occur from the exo face, and the problem discussed above in connection with **17/17′** (Scheme 4) now had to be faced; i.e., what would be the reacting conformation—**46** or **46′**? Clearly, the approach to C-9 of **46** was hindered; indeed, the benzylated derivative **46b** failed to react, the congestion within



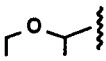

SCHEME 9

the cavity being evident from the fact that the $NHCOCH_3$ resonated at abnormally high field (1.20 ppm) because of shielding by the aromatic ring.

However, with the $\alpha$-ethoxyethyl analog **46c** ($NHCOCH_3$ being normal at 2.00 ppm) acetolysis occurred in 70% yield, leading to compound **47** (Scheme 10). The fact that (a) the epoxide had been cleaved in the desired sense and (b) molecule **47** existed in the conformation shown was evident from the NMR parameters for H-1 and H-9 (Scheme 9).



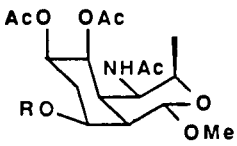

47

a R= 

b R=H

$J_{9,10}$ = 5 Hz

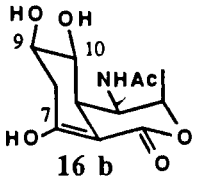
H1 = singlet




47'

more stable by 10+ Kcal

ref. 57




16 b

N-acetyl actinobolin

SCHEME 10

Compound **47** had hitherto been established as a relay intermediate by preparation from, and reconversion into, *N*- acetyl actinobolin.[57] Hence, the synthesis was complete.

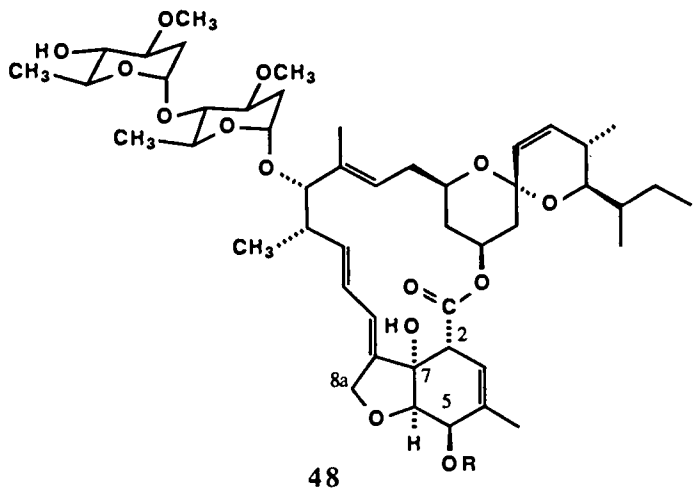
In summary, the actinobolin study showed that annulated pyranosides of type **14** (Scheme 3) exist in, and react from, conformations which have the benefit of the anomeric effect. This guarded statement is not intended to imply that the anomeric effect *provides* a conformational lock. Indeed, it is interesting to speculate on what is responsible for the conformational bias. In the case of **47**, $^1$H NMR parameters reveal that the molecule exists in the conformation shown in Scheme 10—in spite of the fact that it is *less* stable than the conformational isomer **47'** by 10 ± 3 kcal. An investigation of this and similar inconsistencies is under way in our laboratory.

## V. The Oxahydrindene Moiety of Avermectins

The actinobolin example demonstrated how the pyranoside ring could be used to achieve the four objectives outlined in the general protocol, (see Section II). It was the further exploitation of this concept that attracted us to our work on the avermectins, e.g., **48**,[58] (Scheme 11), and in so doing we widened our horizons from the restrictive "annulated *pyranoside*" to the more encompassing strategy involving "annulated *sugars*."

The key feature of the "northern half" of avermectin **48** is the spiroketal, and the basic science required for its construction is rooted in an understanding of the anomeric effect.[40] On this basis Evans had carried out seminal early studies,[59] and subsequent accomplishments, notably the first syntheses of milbemycin,[60,61] made the groundwork secure. Not surprisingly, several synthetic approaches to the northern half of avermectin were quickly forthcoming.[62]

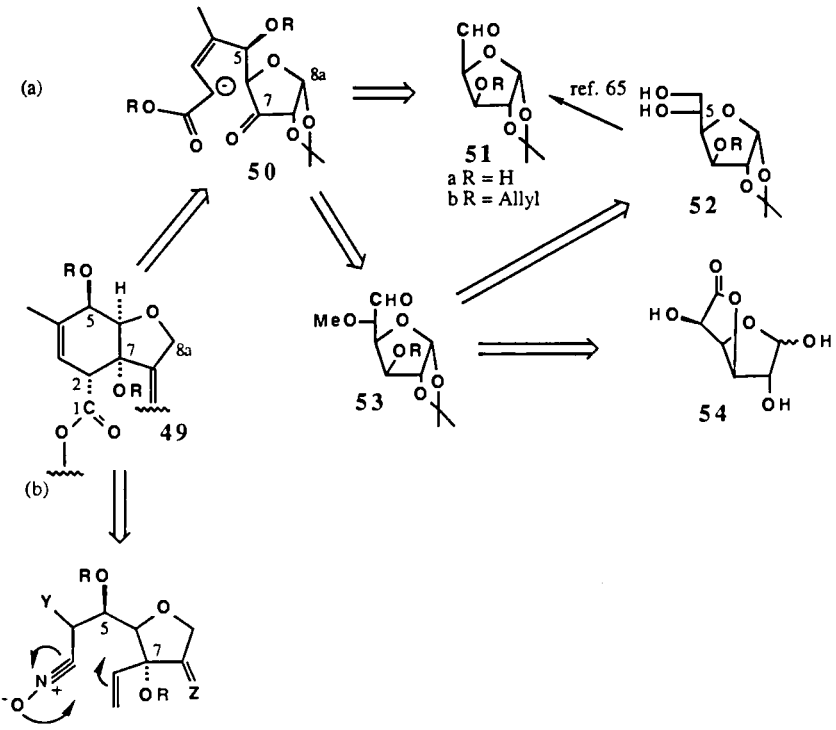
The "southern half"[63,64] contained a number of key structural features which are essential for biological activity. These include the "natural" orientations at C-2 and C-5, the presence of the $\Delta^3$ olefinic center, and the tertiary C-7-OH. From the standpoint of stability, two $\beta$-eliminations would cause aromatization leading to an isobenzofuran. Furthermore, prototropic shift of the double bond to the the $\Delta^2$ position would destroy the biological




**48**

R = H or Me

SCHEME 11

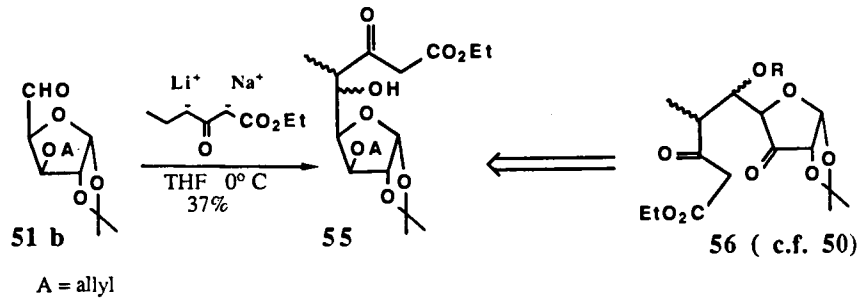



SCHEME 12

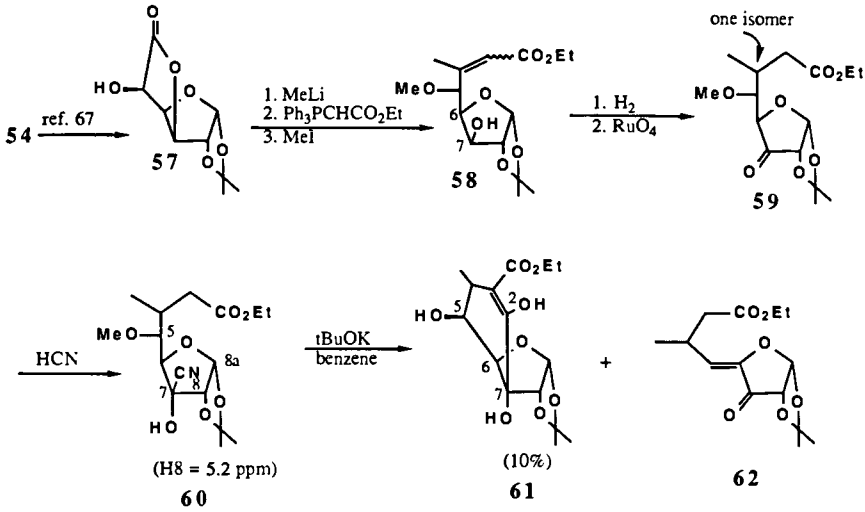
activity. There were, therefore, several challenges which faced a stereocontrolled synthesis.

*Retrosynthesis.* Representation of the southern half, as in **49** (Scheme 12), emphasizes the connectivity of the furan moiety with a furanose sugar. The tertiary C-7-OH could then be obtained by intramolecular addition to a ketose (e.g., **50**). One approach (Scheme 12a) would then proceed through aldehydes, such as **51** which are readily prepared from monoacetone glucose **52.**[65] Indeed, application of the Weiler methodology[66] brought about the condensation of a $\beta$-keto ester with aldehyde **51b** to give **55** in 37% yield (Scheme 13). We could then have proceeded toward **56** (≡ **50**) in the hope of effecting an intramolecular condensation, as proposed in Scheme 12a. However, this approach was plagued by (a) the low yield and (b) the (not unexpected) low stereoselectivity in which **55** had been obtained.

Furthermore, simple analysis made it obvious that the C-5-OH configuration of **49** was congruent with the C-5 center in monoacetone glucose **52.** It therefore seemed judicious not to tamper with it, even if its preservation




SCHEME 13




SCHEME 14

required the expenditure of additional steps. Accordingly, aldehyde type **53** (Scheme 12b) seemed a more suitable starting point.

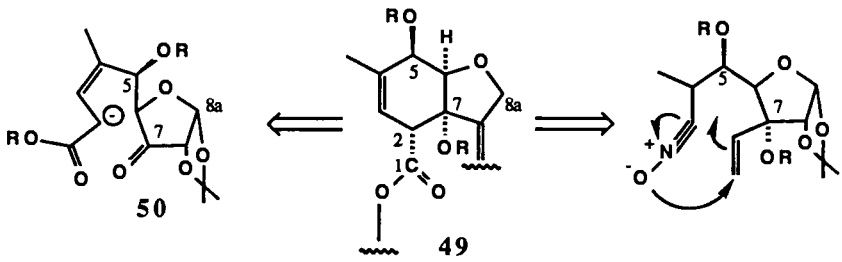
On the basis of this revised plan (i.e., Scheme 12b), a convenient starting material was glucofuranolactone **54**, compound **57**[67] (Scheme 14) being an excellent equivalent of synthon **53**. A number of standard transformations then afforded ester **58**.

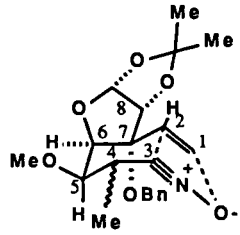
With compound **58** in hand, we now had the option of going toward a 7-keto derivative (**59**) and carrying out the intramolecular addition (e.g., **50** → **49**, Scheme 12). However, our handling of these derivatives, in the interim, had made us fearful of the possibility of epimerization at C-6, so we

elected to pursue a more secure path involving the cyanohydrin **60** (Scheme 14). We were confident that the C-7-OH of **59** had been generated in the desired $\alpha$-orientation because its H-2 signal matched well that of the major product obtained from a comparable sequence, beginning with diacetone glucose itself (5.3 versus 4.7 ppm).[68]

Cyclization was effected, but compound **61** was obtained in only 10% yield, the major product being the conjugated ketone **62**. The latter obviously results from regeneration of ketone **59**, followed by $\beta$-elimination, an outcome that confirmed our fears about working with this type of compound.

With intermediate **61** in hand, the annulus had indeed been formed by the intramolecular condensation; but subsequent creation of the C-2 center with stereocontrol did not seem promising. Clearly, a preferred approach would be to secure the C-5 *and* C-7 centers (as in **60**), but then to establish the "annulus" in such a way as to ensure proper orientation at C-2. For this outcome, we needed to rely on the topographical features of the sugar to elicit the desired stereochemical choice. This is exactly what had been accomplished in the *inter*molecular Diels–Alder reactions involving the pyranoside **11** (Scheme 3). However, while some sort of *inter*molecular condensation did not seem appropriate to the case at hand, an *intra*molecular process was more appealing.




**63**

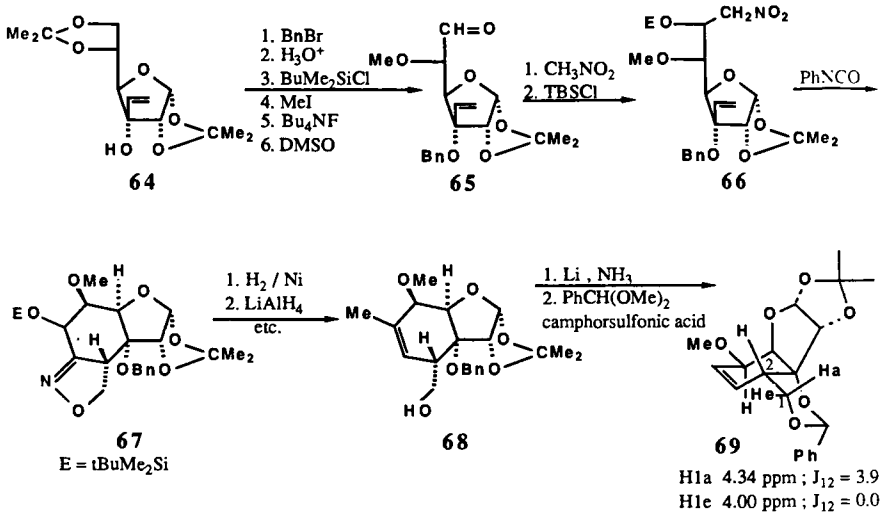
SCHEME 15

The intramolecular nitrile oxide cycloaddition (INOC) reaction, as popularized by Kozikowski[69] and Curran,[70] seemed most appropriate. Thus, as indicated in Scheme 15, the condensation implied in **50** differed from the INOC approach with respect to the bond being formed at C-2. The major advantage of the INOC approach was the opportunity it offered for stereochemical induction. In this connection, it was gratifying to note that in the chair-transition state **63** (Scheme 15), the developing C-2 center had H-2 trans to the C-7-OH as desired.[63]

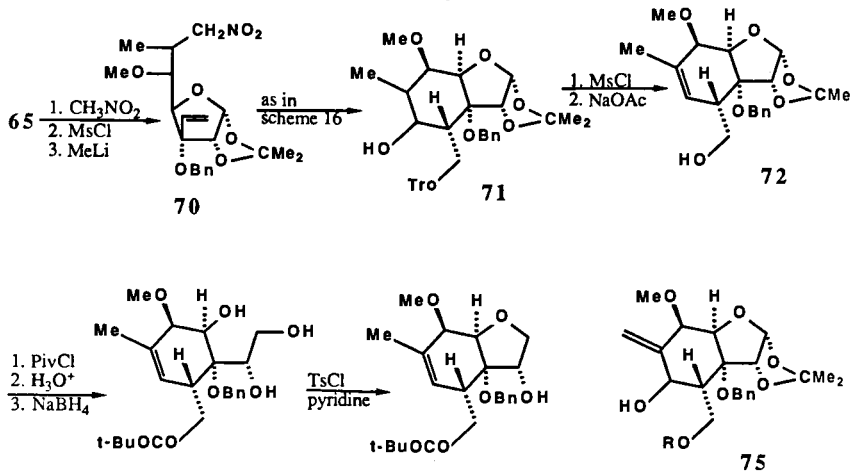
The furanose precursor for the new route (Scheme 16) was the known allylic alcohol **64**,[71] and standard processing led to the aldehyde **65**. Application of the Henry reaction for the formation of nitro sugars was well precedented,[72] and the path to the key intermediate **66** was based on these precedents.

The INOC reaction was highly successful, giving a single substance, presumed to be **67**. However, this result obviously had to be confirmed. NMR assignment of **67** did not prove availing, and hence the adduct was processed in the hope of obtaining a more compatible candidate. This was achieved in compound **68**, and the benzylidene derivative **69** enabled a clear decision to be made. Thus, the H-2 parameters shown in Scheme 16 could be accommodated only by the structure shown. (A benzylidene derivative of the C-2 epimer would have shown ~10-Hz splitting.)

With this "vote of confidence" for the INOC route, the C-4-$CH_3$ could be installed, as in **70** (Scheme 17), and subjected to the same sequence, as in Scheme 16. This led to the alcohol **71** and thence alkene **72**.




SCHEME 16




SCHEME 17

Having served its purpose, the furanose ring was destroyed by formation of triol **73**, which upon sulfonation underwent *in situ* etherification to afford **74**.

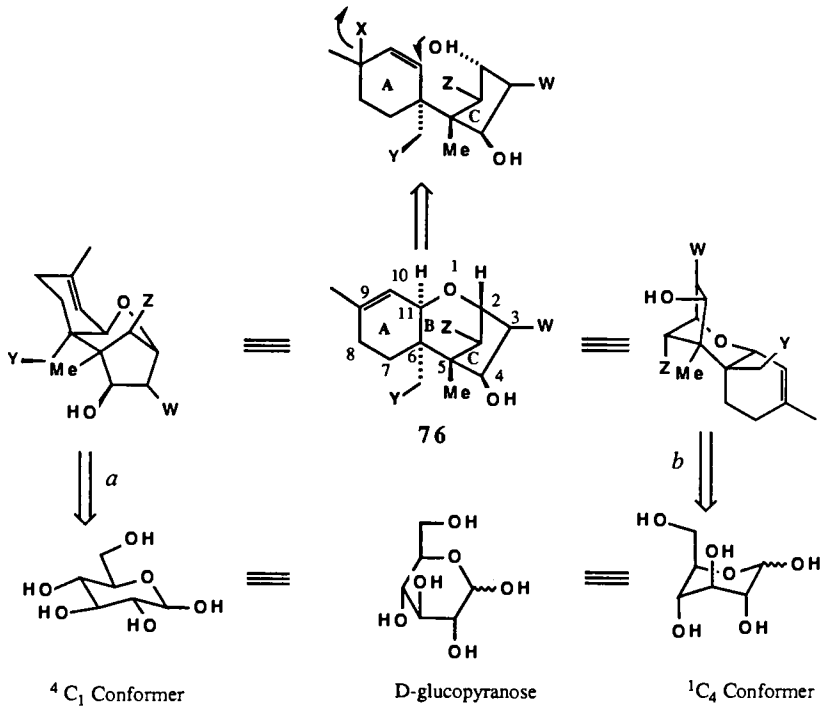
Our subsequent studies suggested that **74** was, in fact, not a good precursor for the "southern half" and that the exocyclic olefin **75** is preferable.[73]

However, the avermectin southern half represented another example of the annulated sugar concept being utilized with great advantage to achieve a highly (completely!) stereocontrolled operation with the entire sugar moiety being incorporated into the synthetic target.

## VI. The Trichothecane System

The majority of trichothecane syntheses[74] have mimicked the proposed biosynthetic pathway[75] in which preformed A and C rings are cyclized to give the B ring, as illustrated in Scheme 18. Our approach to the trichothecane system, **76**, by pyranosidic annulation was easily visualized, since verrucarol resembles a "bis-annulated C-pyranoside." Thus, the pyranose moiety would remain intact, while its conformational bias and stereoelectronic attributes would be exploited throughout the synthesis.

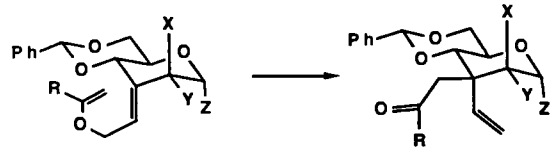
The stereochemical local $C_2$ axes of symmetry at C-2 and C-11 (with respect to the pyran B ring) allow for two different modes of bis-annulation to a D-hexopyranose (e.g., D-glucose), depending on which conformation is employed. Path *a* requires the persistence of the $^4C_1$ conformation while the



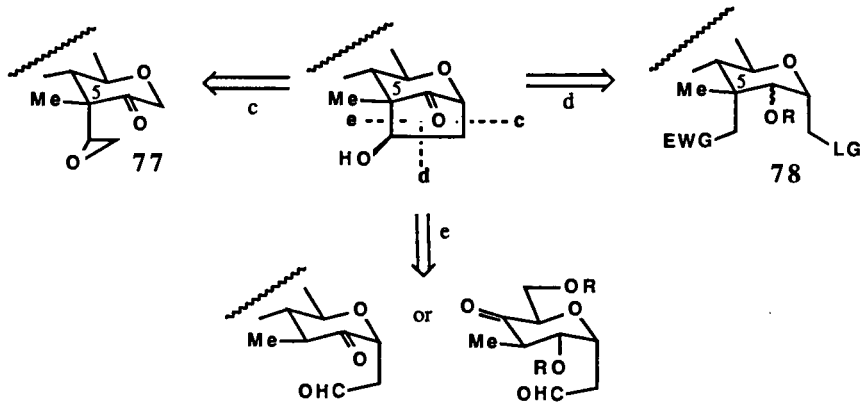

SCHEME 18

A and C rings are established at the "back" and "front," respectively, of the pyranose. On the other hand, path *b* necessitates that the pyranose adopt a $^1C_4$ conformation with the A and C rings being developed at the "front" and "back," respectively.

The synthetic challenge of the trichothecene skeleton stems from the requirement for stereoselective alkylation at numerous sites, particularly the quaternary centers at C-5 and C-6. For this reason, geminal alkylation by spiro-Claisen rearrangement [exemplified by Eq. (b)] was studied at various positions of the pyranoside ring.[76] The excellent stereoselectivity and the creation of two differently functionalized geminal centers offered a high degree of versatility for our synthetic endeavors.

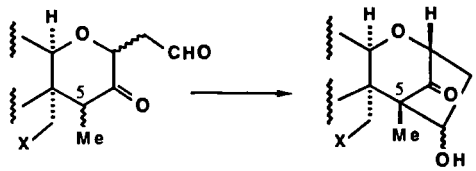



eq. (b).




SCHEME 19

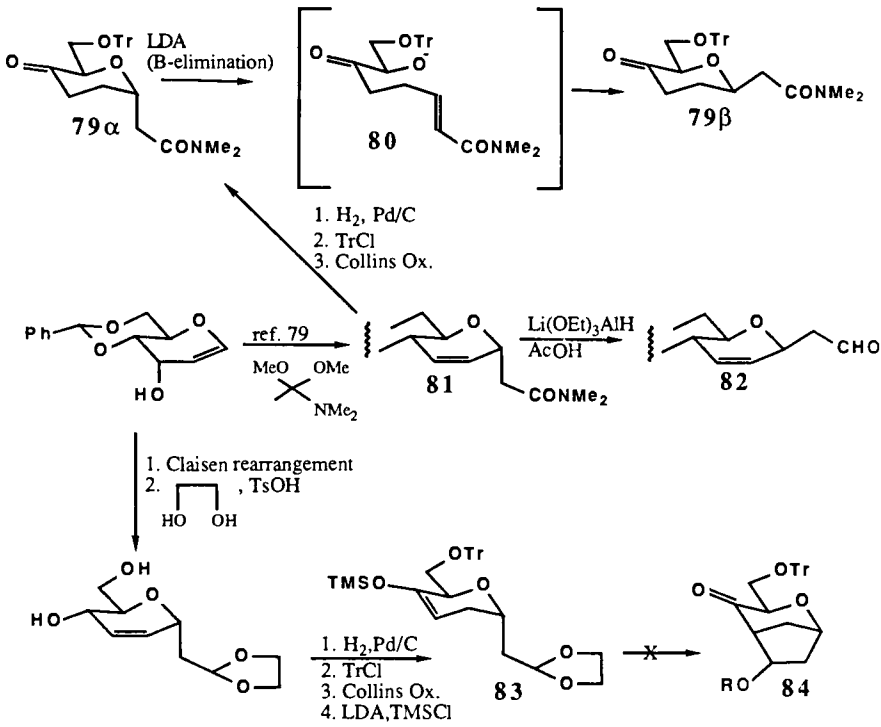
In Scheme 19, we indicate three options for developing the bridging five-membered ring at the front of the pyranose. Options c and d require prior formation of the quaternary C-5 center—hopefully by the spiro-Claisen rearrangement shown in Eq. (b). However, option e takes cognizance of the fact that the quaternary center is at a ring junction, and hence quaternization and annulation can be achieved in one step with complete stereocontrol. Indeed, such a strategy was employed in the landmark synthesis of trichodermol by Colvin and Raphael[77] to construct the bridged five-membered C ring [Eq. (c)].




eq. (c)[77]

Our early attempts are shown in Scheme 20. Prior work in our laboratories showed that treatment of precursors such as **79**$\alpha$[78] with base led only to anomerization to **79**$\beta$, presumably through intermediate **80** (Scheme 20). Such facile anomerization was also demonstrated by reduction of the amide **81**[79] to aldehyde **82**.[78*] Lewis acid-catalyzed processes were therefore attempted on precursors such as **83**, but nothing corresponding to **84** was detected.

* Note that subsequent work has shown that this problem is not encountered if commercially available reagent is used, rather than the homemade variety used in our original studies. We are grateful to Professor Kozikowski for this information.

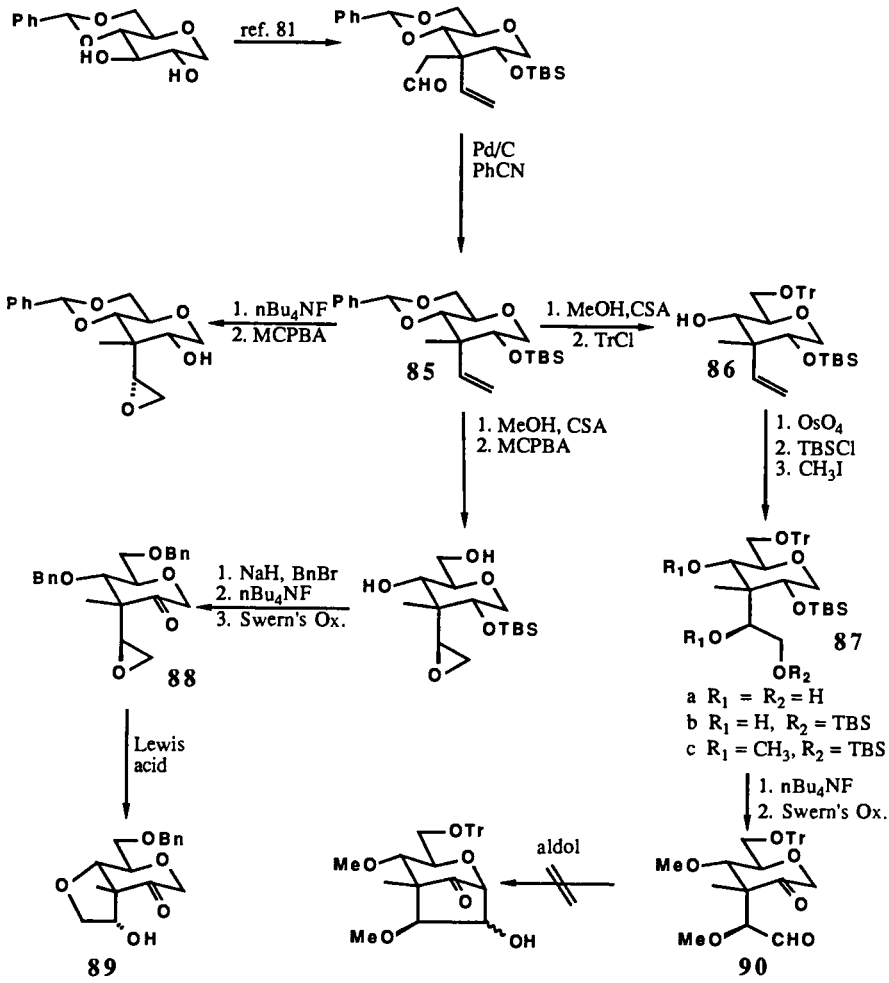



SCHEME 20

Difficulties involved in the formation of bond e (Scheme 19) led us to examine the other modes of bond connection for the construction of the C ring. Bond c connection through epoxide **77** was an attractive possibility, since the epoxidation of olefin **85** (Scheme 21) was found to be highly stereoselective, giving rise exclusively to one diastereomer or the other, depending on which hydroxyl group, C-2 or C-4, was free.[80] However, cyclization of **88** could not be induced under a wide variety of conditions. Treatment with base led only to decomposition, while acidic conditions resulted in formation of the furan **89**.

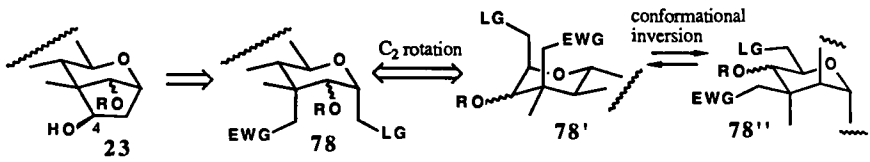
Hydroxylation of the olefin **86** with $OsO_4$ was found to be equally stereoselective to give **87a**, which was processed to the keto-aldehyde **90** (Scheme 21). However, attempted aldol reaction of the keto-aldehyde **90** did not lead to any isolable products.

Path d (Scheme 19) was the only remaining option, and it was by far the most interesting. First, precursor **78** required an electron-withdrawing group, (EWG), which also had to be a latent hydroxyl function. The geminal substitution at C-5 could clearly be obtained by *spiro*-Claisen rearrangement




SCHEME 21

[Eq. (b)]. Second, a functionalized one-carbon residue ($CH_2LG$) was required at C-3 (≡ C-1) in syn relationship to the EWG group. A synthetic sequence could undoubtedly have been devised for this one-carbon residue. However, perceptive analysis showed that because of the local C-2 axis of symmetry in the B ring (see Scheme 18), the C-6 residue of a D-hexopyranose has the same stereochemical (and functional) requirements as the $CH_2LG$ group in **78**. Furthermore, since the *spiro*-Claisen rearrangement generated two differently functionalized branched chains, one or the other could be




SCHEME 22

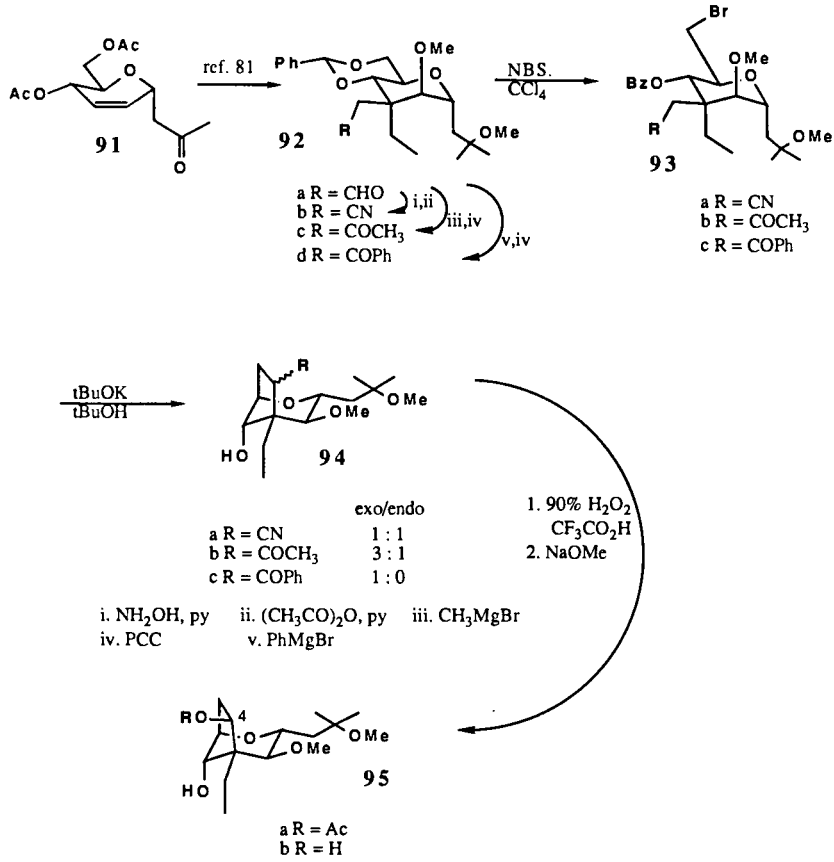
processed to give the EWG-bearing residue at C-3. So a more gratifying, radically different approach emerged, as depicted in Scheme 22, in which **78** and **78′** are related by a $C_2$ rotation, while **78′** and **78″** are related by conformational inversion.

The practicality of this approach would be highly dependent on the conformational flexibility of the pyranose ring. The EWG group was envisioned as a carbonyl function, since the predominance of the exo-isomer at the newly created C-4 stereocenter could be induced by equilibration. The desired C-4 hydroxyl function could be subsequently obtained with retention of configuration by a Baeyer–Villiger oxidation.

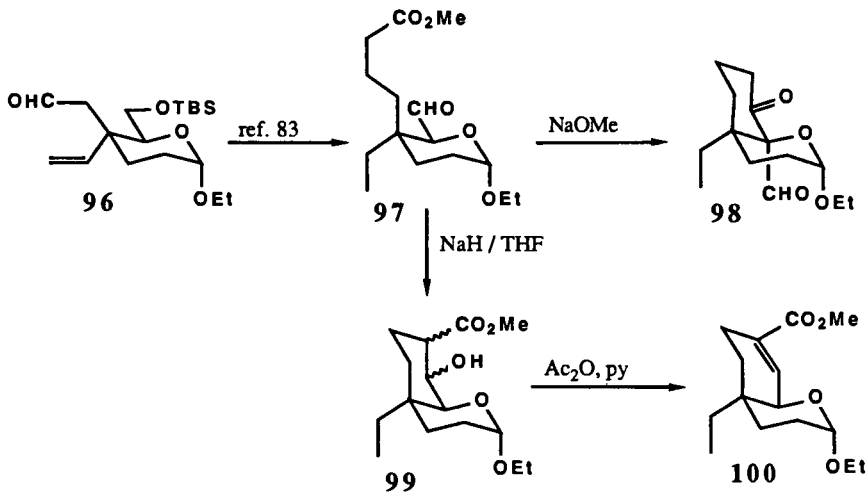
Several model systems were devised to test this plan. The aldehyde **92a**,[81] obtained through spiro-Claisen rearrangement, was transformed by standard steps into a nitrile (**92b**) or into a methyl or phenyl ketone (**92c** and **92d**, respectively) (Scheme 23). The Hanessian–Hullar[82] reaction unraveled the benzylidene acetal to give C-6 bromides (**93a–c**), which on treatment with base underwent facile cyclization to give **94a–c** in varying exo/endo ratios.

Although the phenyl ketone **94c** was obtained as the desired exo-isomer exclusively, Baeyer–Villiger oxidation was unsuccessful. With the methyl ketone (exo **94b**), the Baeyer–Villiger oxidation could be achieved only with the strongest of peracids, trifluoroperoxy acetic acid. Configuration at the newly created C-4 stereocenter in **95** was firmly established by comparison of $^1$H NMR coupling constants with those of naturally occurring trichothecenes.

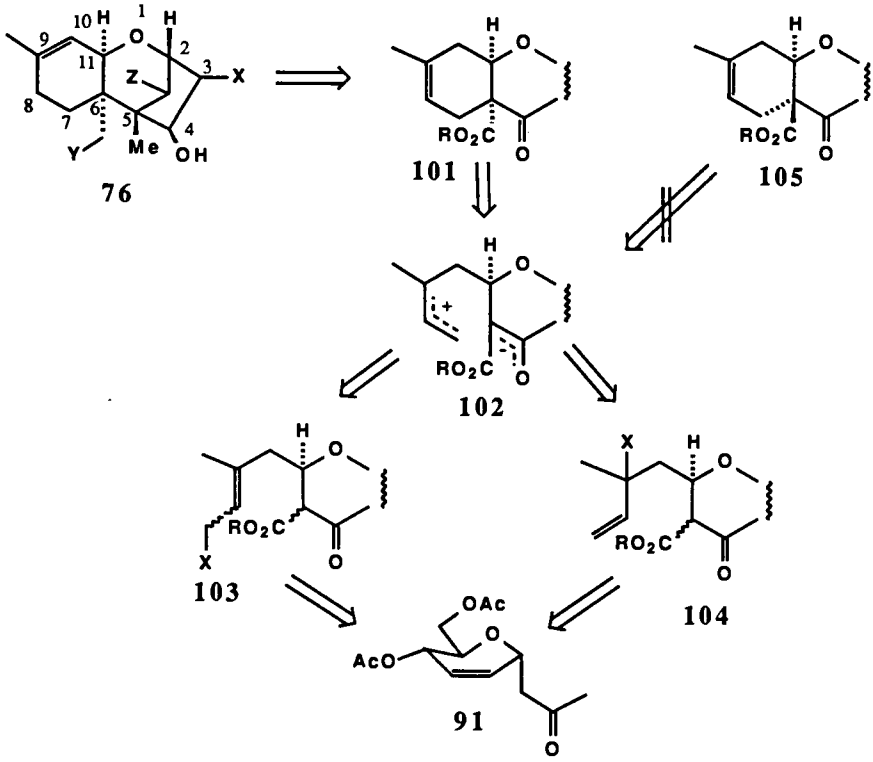
Synthetic sequences devised for the construction of the A-ring were less onerous. Our initial plan involved annulating a cis-fused six-membered ring at the "back" of the pyranoside (path *a*, Scheme 18), and this was indeed achieved, as depicted in Scheme 24. Spiro-Claisen rearrangement at C-4 of pyranosides was found to be stereoselective[76b] to give **96**. Claisen condensation on the acetaldehyde side chain, followed by oxidation at C-6, provided compound **97**.[83] Treatment of the latter with sodium methoxide gave the undesired ketoaldehyde **98**; however, the desired mode of cyclization in **99** was attained by use of sodium hydride. Dehydration of **99** was effected with acidic anhydride and pyridine to give the cyclohexene **100**.




SCHEME 23




SCHEME 24



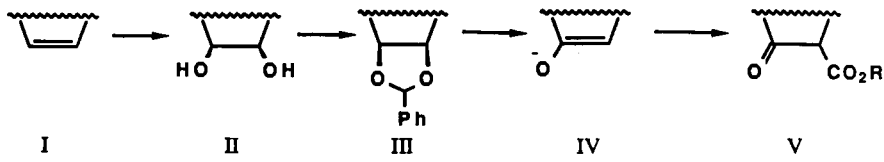

SCHEME 25

Unfortunately, this synthetic route (Scheme 24) for the A ring had been devised when the plan was for the C ring to be annulated at the front of the pyranoside (i.e., path *a*, Scheme 18). Since the disposition of the A and C rings was now to be reversed in light of the development in Scheme 23, a plan had to be devised for construction of the A ring at the front of the pyranose.

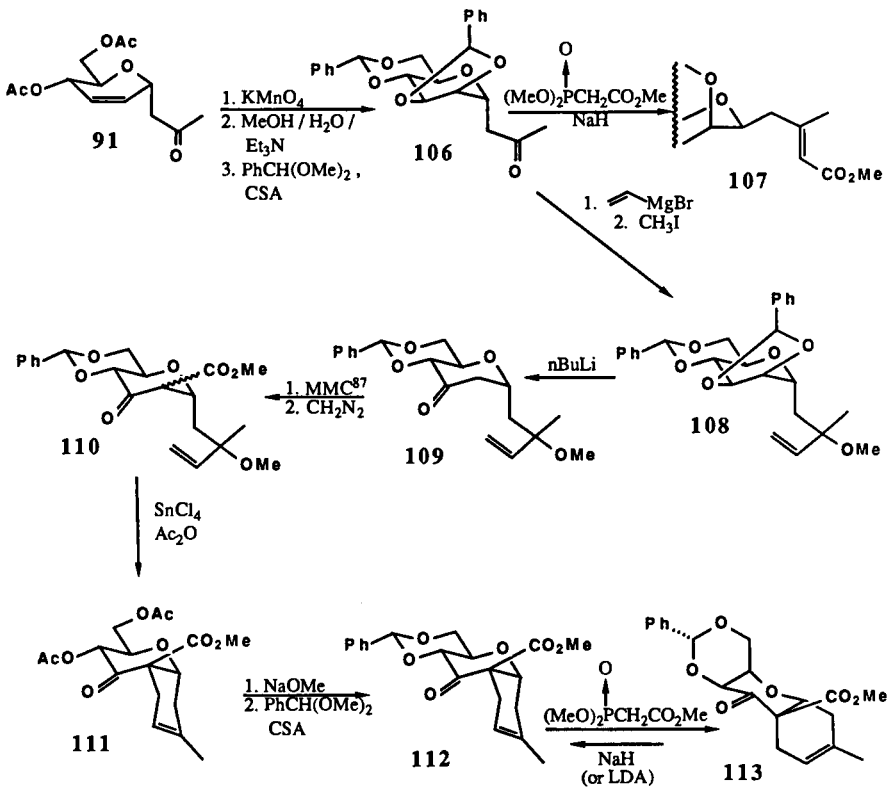
We envisioned a C-6—C-7 bond connection which would generate the A ring and quaternary center at C-6 simultaneously. In our retrosynthetic analysis (Scheme 25), the C-9–C-10 unsaturation was shifted to the C-8–C-9 position, as in **101**, so that the C-6–C-7 bond could be established through an allyl cation synthon, **102**. This strategy would obviate the necessity of generating the C-9–C-10-olefin stereoselectively in the acyclic precursor. Subsequent translocation of the double bond could then be achieved by a variety of chemical procedures. A bonus of this approach was that the C-8–C-9 unsaturation enabled the introduction of functionality at C-8, which some trichothecenes possess.

Both allylic structures **103** and **104** were suitable synthons for **102**, and the C-glycoside **91**[84] was chosen as our ultimate starting material.

However, a threatening scenario was that cyclization of **102** would lead, instead, to the trans-fused annulated pyranoside **105**. A way to make this option impossible was simply to place a 4,6-*O*-benzylidene ring on the




SCHEME 26




SCHEME 27

precursor **110** (Scheme 27), so as to impose conformational inflexibility. Obviously, this plan meant that the A ring had to be affixed to the pyranose *before* the C ring.

Incorporation of the β-keto ester moiety of **103** or **104** was envisioned as occurring through a vicinal diol type II, as depicted in Scheme 26. Fragmentation[85] of dioxolanes of type III is known to generate an enolate (IV), which can then be acylated to give the desired β-keto ester V.

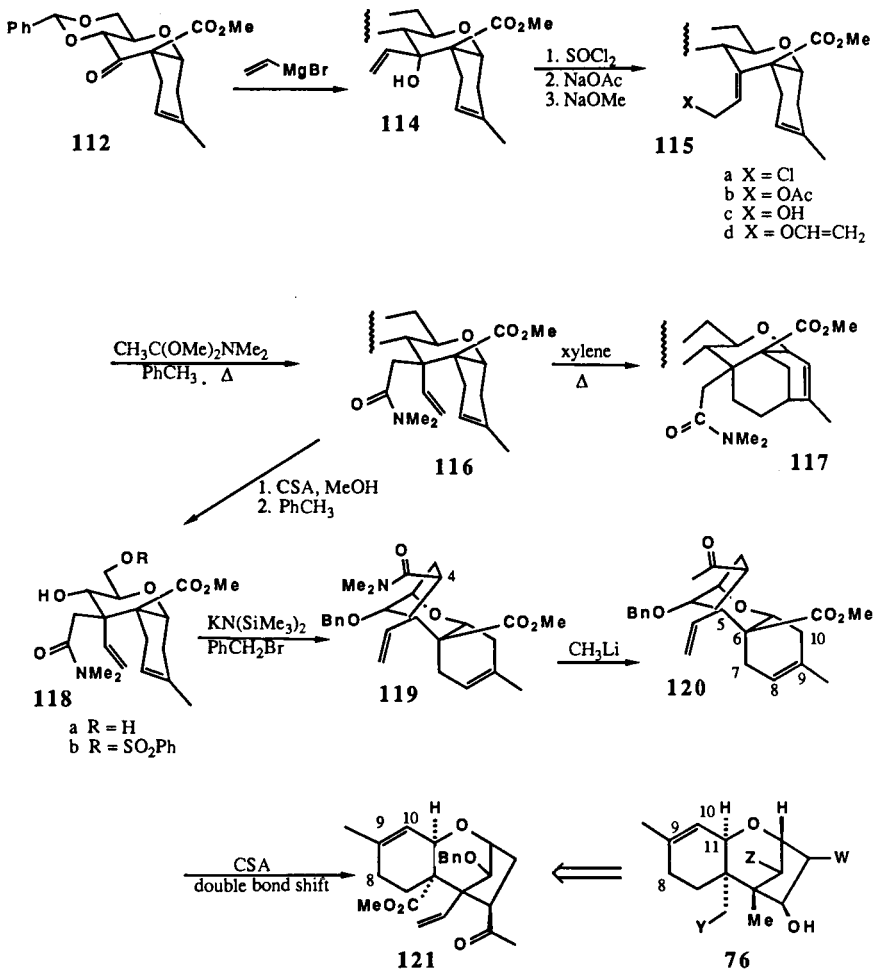
The readily obtained α-*C*-glycopyranoside **91**[84] underwent hydroxylation exclusively from the β face, and, after deesterification, the resulting tetrol was converted into the bis-benzylidene ketone **106** (Scheme 27). The ketone **106** was inert toward stabilized Wittig reagents. Olefination could be carried out with a Horner–Emmons reagent, but the product was the undesired β-C-glycoside **107**. (Such facile anomerizations had been witnessed earlier—see Scheme 20). As an alternative, the allylic moiety of **108** was installed.

Chemo- and regiospecific cleavage of the dioxolane ring of **108** was effected by treatment with *n*-butyllithium, as presented by Klemer and Rodemeyer.[85] However, *in situ* acylation of the resulting enolate led only to *O*-acylation under a wide variety of conditions.[86] Thus, the ketone **109** was carboxylated with Stiles' reagent[87] to give the required β-keto ester **110**, after esterification with diazomethane. Although Pd(0)-assisted ring closure of **110** was not successful, cyclization could be induced with Lewis acids. This, of course, caused concomitant debenzylidination, and the most efficient course proved to be the isolation of the corresponding diacetate **111**.

The benzylidene acetal was reinstalled in **112** to provide conformational rigidity of the pyran ring and thereby ensure stereoselectivity in the upcoming spiro-Claisen rearrangement (Scheme 28). But the hindered carbonyl group now posed a dilemma. No reaction was observed with stabilized Wittig reagents, and the more basic Horner–Emmons reagents caused only epimerization at C-4 to give a 1 : 2 mixture of **112** and **113**.

Thus, in a modification of our previous protocol, ketone **112** was treated with vinylmagnesium bromide and the resulting alcohol **114** (Scheme 28) was rearranged through the chloride **115a** into the desired allylic alcohol **115c**. Although the allyl vinyl ether **115d** could be prepared, thermal treatment caused only extensive decomposition. On the other hand, with the Eschenmoser modification[88] in refluxing toluene, a slow reaction was realized, leading to **116**. Attempts to accelerate the rearrangement by use of refluxing xylene caused tandem ene reaction of **116** to give the polycyclic compound **117**.

Acid hydrolysis of **116** gave the diol **118a**, which was selectively sulfonated, and treatment of the product, **118b**, with 2 equivalents of $KN(SiMe_3)_2$ afforded the desired cyclized material. Quenching of the reaction




SCHEME 28

mixture with benzyl bromide before workup provided the tricyclic compound **119** as a single diastereomer.

The amide group of **119** was therefore a mask for the C-4-OH present in many trichothecanes and, to this end, we wished to convert it into a methyl ketone as a prelude to a Baeyer–Villiger reaction. Differentiation of the amide from the carbomethoxy group was simple because of the sterically hindered location of the latter. Accordingly, reaction with methyllithium occurred chemoselectively to give ketone **120**.

In an attempt to protect the methyl ketone as a dioxolane, compound **120** was treated with ethylene glycol in the presence of camphorsulfonic acid. It was found that prototropic shift of the double bond occurred, giving the $\Delta^9$ isomer **121** in ~60% conversion.

Thus, a serendipitous avenue for isomerization of the olefin was uncovered, and this was fortunate because attempts to achieve this result by using palladium catalysts were unavailing. Juxtaposition of compound **121** and the generalized trichothecene **76** (Scheme 28) shows that the functional groups of **121** are compatible with the transformations required to proceed further.

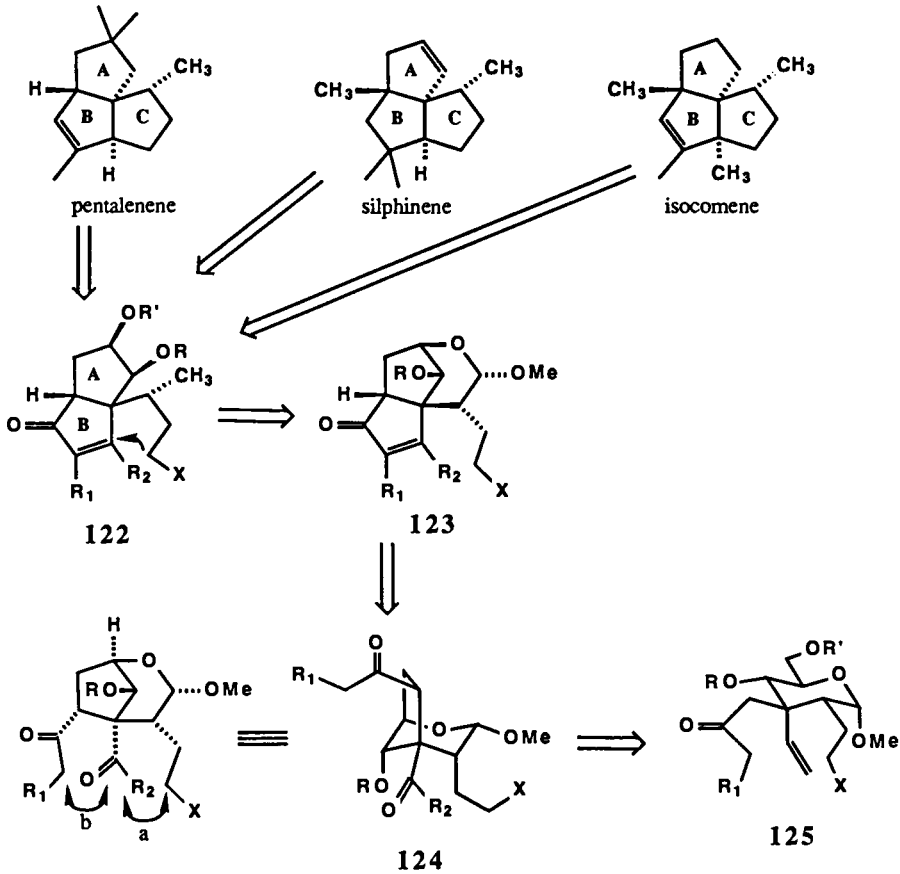
However, for the purposes of the present chapter, it is sufficient to note that the bis-annulated pyranoside strategy for assembly of the trichothecane skeleton was successful. The two annulations, which were both executed stereoselectively, took advantage of different conformations of the pyran ring. In the first (Scheme 28), the $^4C_1$ conformation was secured by means of the 4,6-*O*-benzylidene ring to enable the cis-fused cyclohexenyl ring to be established at the front of the sugar. This placed a carbon substituent at the anomeric center, thereby facilitating the second annulation, **118b** → **119** (Scheme 28), since there was no anomeric effect to overcome in going to the abnormal $^1C_4$ conformation required to make the bridging five-membered ring at the back of the sugar.

## VII. The Triquinane System

The bis-annulation of the pyranose nucleus achieved in Part VI was a promising strategy, and the ease of formation of the bridging five-membered C ring (Scheme 28) prompted us to consider its synthetic utility for other cyclopentanoid natural products. The angular triquinanes (Scheme 29) pose an interesting synthetic challenge because three fused cyclopentane rings share a common quaternary carbon. The representative examples shown were chosen to illustrate their structural similarities.

Based on our trichothecane precedent (Schemes 27, 28, and 29), one approach would be to prepare an intermediate, such as **124** (cf. **119**, Scheme 28), and to carry out the cyclizations depicted as a and b, sequentially. Our retrosynthetic approach therefore envisioned the highly functionalized diquinane **122** as a common precursor (Scheme 29), the C ring being formed by the conjugate addition depicted. The omnipresent $CH_3$ on the C ring is masked as the anomeric carbon of **123**, and the 2-cyclopentenone moiety is obtained by intramolecular aldol condensation of **124**. The latter can be obtained by intramolecular enolate alkylation of **125** by the methods developed for the trichothecene synthesis.

The general plan for syntheses of intermediates such as **125** is illustrated in

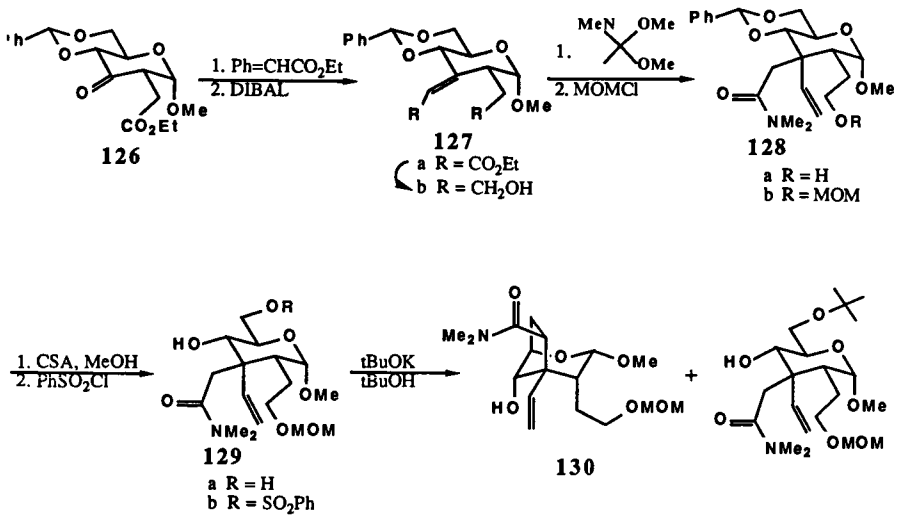



SCHEME 29

Scheme 30. The readily available keto-ester **126**[89] reacts with stabilized Wittig reagents to give the bis-ester **127a**, which is then reduced to the diol **127b**. Eschenmoser–Claisen rearrangement[88] affords the desired hydroxy amide **128a**, which is then processed to give the cyclization precursor **129b**.

Treatment of **129b** with potassium hexamethyldisilazide under the conditions employed in the trichothecene synthesis (Scheme 28) did not induce formation of **130**. However, with potassium *tert*-butoxide, some of the latter (35%) was obtained.

It is interesting to speculate on the reasons for the differences in reactivities of **129b** versus **93** and **118b** (Schemes 22 and 28). In all three cases, conformational changes of the pyranoid ring ($^4C_1 \rightarrow {}^1C_4$) are required in



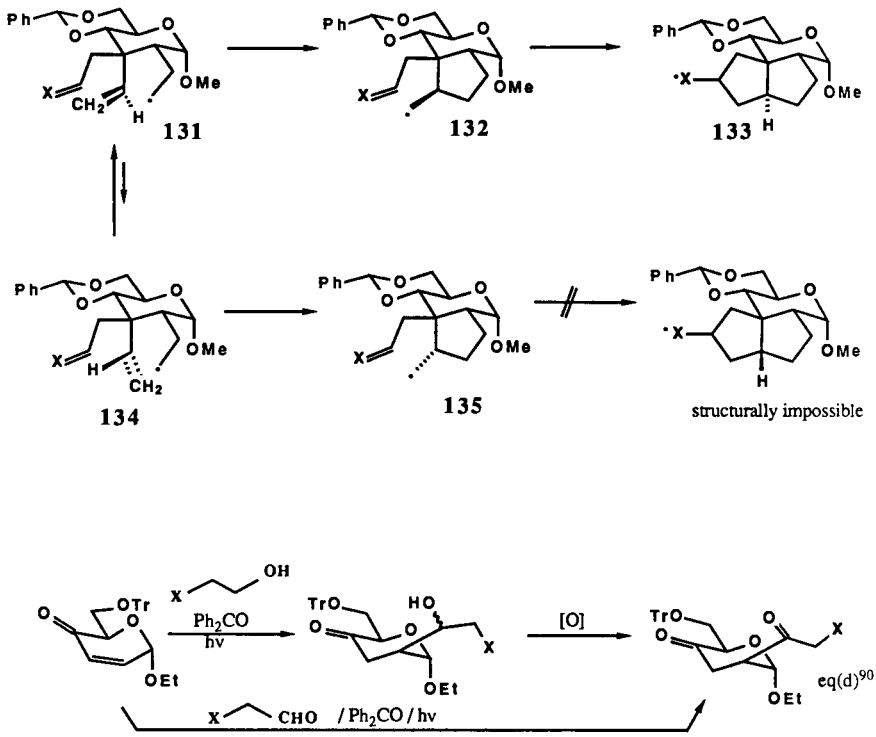

SCHEME 30

order for the intramolecular $S_N2$ displacement to succeed. However, unlike **93** and **118b**, compound **129b** has to relinquish the stabilization due to the anomeric effect of the axial methoxyl group, a situation which is compounded by the fact that the C-2 substituent becomes axial in **130**.

Could these adverse factors be avoided? Unfortunately, the orientation at C-2 is necessary to ensure the configuration of the C-ring $CH_3$ groups in the triquinanes shown in Scheme 29. With regard to the anomeric center, we could conceivably have employed a $\beta$-glycoside as a precursor, in which case the reactive $^1C_4$ conformer would enjoy the anomeric effect. However, with respect to the latter change, the extent of stereoselectivity in the spiro-Claisen rearrangement of $\beta$-glycosides was unknown, and rather than explore this territory it was decided to postpone annulation of the A ring until *after* the pyranoside ring had been destroyed.

How could the B–C rings be annulated on a pyranoside? The highly functionalized "branches" highlighted in **128** (Scheme 30) contain all of the carbons necessary for the B–C moiety, and we envisioned that a serial radical cyclization involving **131** → **132** → **133** (Scheme 31) could be induced. The suitability of radical reactions for carbohydrate transformations, as exemplified in Eq. (d), has long been championed by us,[90] and therefore recent precedents by Curran,[91] Beckwith,[92] and Stork[93] were appealing.

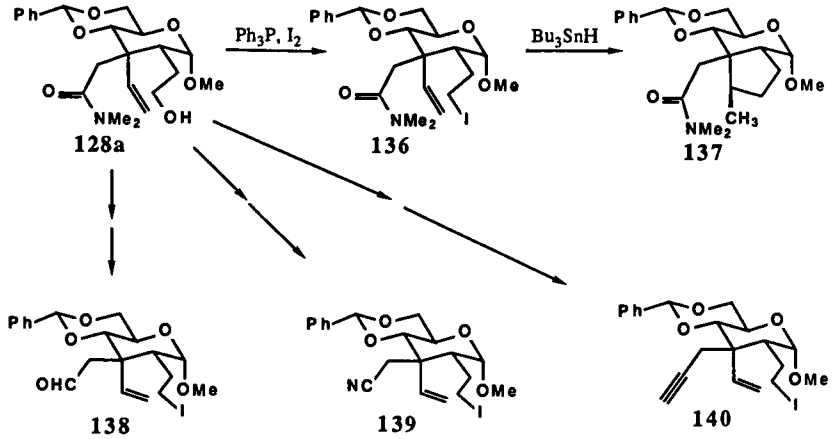
We anticipated that a radicaloid species, **131**, generated at the terminus of the C-2 ethyl branch, would cyclize onto the C-3 vinyl group in a 5-exo mode



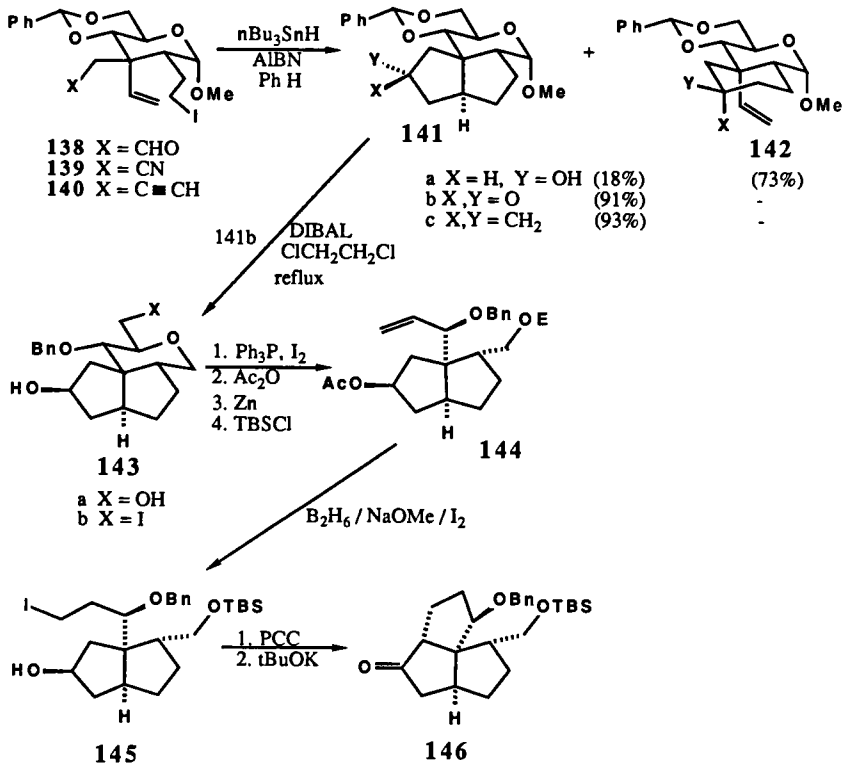

SCHEME 31.

to produce a primary radical, **132**, on the cis-fused cyclopentane ring (Scheme 31). The newly generated radical could thereafter add to a suitable radical acceptor on the equatorial C-3 branch, also in a 5-exo mode, to give the bis-annulated pyranoside **133**. Clearly, success of the second cyclization would depend on the stereoselectivity of the first, since an endo methyl radical (e.g., **135**) would be unable to cyclize further. Our experience with epoxidations of pendant vinyl substituents in similar systems predicted that the vinyl group would react entirely via the "exo" rotamer[94] **131** and not from the endo counterpart **134**.

Although amides or esters were generally known to be poor radical acceptors, we examined their cyclizations because they were so readily accessible. Accordingly, the alcohol **128a** was converted into an iodide **136** (Scheme 32), which upon treatment with tributyltin hydride afforded the cyclopentane derivative **137**. The first cyclization had succeeded, but not the second, and in order to determine whether different radical acceptors would be more auspicious, the amide was processed to give the aldehyde **138**, the




SCHEME 32. (For details of these transformations, see ref. 95.)




SCHEME 33

nitrile **139**, and the alkyne **140**.[95] Results of the serial cyclizations are illustrated in Scheme 33.

The nitrile **139** and the alkyne **140** underwent serial cyclizations efficiently, as expected, to give **141b** and **141c**, respectively, whereas the major product from the aldehyde **138** was the cyclohexanol **142**. This was a surprising result in that the rate of cyclization of the aldehyde to give the cyclohexanol **142** had obviously surpassed that of the 5-hexenyl radical.

(This surprisingly efficient intramolecular addition of carbon radicals to aldehyde groups to give cycloalkanols has been found by us to be a general reaction[96] and, in another study, these aldehyde cyclizations have been shown to compete successfully with olefins.[97] These results are revealing.)

A procedure for elaboration of the bis-annulated pyranoside **141b** into the triquinane skeleton has been explored, as outlined in Scheme 33. High-temperature reduction with diisobutylaluminum hydride cleaves both acetals,[98] and the C-6-OH of the product **143a** is converted into an iodide, **143b**. Reductive elimination then leads to the alkene **144**, and after hydroboration and due processing, the keto iodide **145** is set for intramolecular alkylation. The triquinane **146** is thereby obtained, and comparison with the naturally occurring samples in Scheme 30 make it obvious that the readily prepared multibranched sugars, such as **138**, **139**, and **140**, are promising candidates for realization of the triquinane skeleton.

## VIII. Conclusions

The progression from Part IV → V → VI → VII has shown an evolution in the "annulated sugar" concept from the relatively simple origins with the chrysanthemic acids (Scheme 2). The four cases reviewed have imposed different demands on the sugars, from the standpoint of both functionality and stereoselectivity. The "sugar moiety" has been represented variously as a δ-lactone, a furan, a pyran, and a secondary $CH_3$ in Parts IV, V, VI, and VII, respectively. Nevertheless, in all cases, the entire sugar has been incorporated, and the general principles outlined above (see General Protocol, Section II) have been upheld.

The examples show that, although stereocenters of the original sugar are sometimes destroyed in order to prepare suitable intermediates, full recovery is possible by utilizing the topographical feature of the sugars. The Diels–Alder reactions in Scheme 3 and the preparation of the multibranched chained sugars, **128** (Scheme 30), are notable examples. The overall stereochemical audit is therefore excellent, and this general strategy for carbohydrate → carbocycle conversion has much to recommend it.

## Acknowledgments

The achievements reported in this chapter were due largely to the skillful efforts of Mohammed Abdur Rahman, Drs. David Kelly and Prasad Ravi (actinobolin), Drs. Kemal Deen Pallie and Mahavir Prashad (avermectin), Deen Tulshian, Robert Dawe, and Ray Tsang (trichothecanes), and Ray Tsang (triquinanes). However, the groundwork on which they built had been well laid by a previous generation of graduate students, particularly Dave Hicks, Robert C. Anderson, John Primeau, and Brian Fitzsimmons. We are grateful to them all for their contributions.

Funding that made the early studies possible was obtained from the National Research Council of Canada. The work in the United States was funded by the National Institutes of Health, the National Science Foundation, the Petroleum Research Fund, and Merck Sharp & Dohme.

Finally, we thank Ms. Mary Aker for her help in preparing this manuscript and Mr. Jeffrey Skatoff for executing the diagrams.

## References

1. Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980,** *39*, 1.
2. Hanessian, S. "Total Synthesis of Natural Products: The Chiron Approach," Pergamon: New York, 1983.
3. Inch, T. D. *Tetrahedron* **1984,** *40*, 3161.
4. Seebach, D. and Hugerbühler, E., 91 Verlag Sauerländer Salzburg In "Modern Synthetic Methods," Scheffold, R., Ed.; Verlag: Frankfurt, 1980; Vol. 2.
5. Hanessian, S.; Lavallee, P. *Can J. Chem.* **1977,** *55*, 562.
6. Cunningham, J.; Gigg, R.; Warren, C. D. *Tetrahedron Lett.* **1964,** p. 1191; Gigg, R.; Warren, C. D. *J. Chem. Soc. C.* **1969,** p. 2367.
7. Gelas, J.; Horton, D. *Carbohydr. Res.* **1978,** *67*, 371.
8. Zehavi, U.; Amit, B.; Patchornik, A. *J. Org. Chem.* **1972,** *37*, 2281; Zehavir, U.; Patchornik, A. *J. Org. Chem.* **1972,** *37*, 2285.
9. Garegg, P. J.; Samuelson, B. *Carbohydr. Res.* **1978,** *67*, 267.
10. Garegg, P. J.; Samuelson, B. *Synthesis* **1979,** p. 813.
11. Heyns, K.; Paulsen, H. In "Newer Methods of Preparative Organic Chemistry," Foerst, W., Ed.; Academic Press: New York, 1963; Vol. 2, p. 303.
12. Barton, D. H. R.; McCombie, S. W. *J. C. S, Perkin I* **1975,** p. 1574.
13. (a) Eastwood, F. W.; Harrington, K. J.; Josan, J. S.; Pura, J. L. *Tetrahedron Lett.* **1970,** p. 5223; (b) Hanessian, S.; Bargiotti, A.; La Rue, M. *Tetrahedron Lett.* **1978,** p. 737.
14. Horton, D.; Thomson, J. K.; Tindall, C. G., Jr. *Methods Carbohydr. Chem.* **1972,** *6*, 297.
15. See, e.g., Pfeffer, P. E. *J. Carbohydr. Chem.* **1984,** *3*, 613; Hall, L. D. *ACS Symp. Ser,* **1979,** *103*, 123.
16. Lemieux, R. U.; Kulling, R. K.; Bernstein, H. J.; Schneider, W. G. *J. Am. Chem. Soc.* **1957,** *79*, 1005; Lemieux, R. U.; Kulling, R. K.; Bernstein, H. J.; Schneider, W. G. *J. Am. Chem. Soc.* **1958,** *80* 6098.
17. Masamune, S.; Kim, C. U.; Wilson, K. E.; Spesard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975,** *97*, 3512; Masamune, S.; Yamamota, H.; Kamamata, S.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975,** *97*, 3513.
18. For a recent review, see Patterson, J.; Mansuri, M. M. *Tetrahedron* **1985,** *41*, 3569.
19. Celmer, W. D. *Pure Appl. Chem.* **1971,** *28*, 413.
20. The name of the seco-acid of erthyronolide is 2,4,7,8,10,14,15-heptadeoxy-2,4,6,8,10,12-hexa-*C*-methyl-*D-erythro*-l-ido-pentadec-9-ulosonic acid. We are indebted to Professor Derek Horton of Ohio State University for verifying this name.

21. Woodward, R. B. In "Perspectives in Organic Chemistry," Todd, A., Ed.; Wiley (Interscience): New York, 1956, p. 155.
22. Miljkovic, M.; Gligorijevic, M.; Satoh, T.; Miljkovic, D. *J. Org. Chem.* **1974,** *39*, 1379.
23. Hanessian, S.; Rancourt, G. *Can. J. Chem.* **1977,** *55*, 1111; Hanessian, S.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* **1978,** *56*, 1843.
24. For leading references, see Wakamatsu, T.; Nakamura, H.; Nishikimi, Y.; Yoshida, K.; Noda, T.; Taniguchi, M. *Tetradedron Lett.* **1986,** *27*, 6071.
25. Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S.; Kochetkov, N. K. *Tetrahedron Lett.* **1987,** *28*, 3835, 3839.
26. Ferrier, R. J.; Prasit, P. *J.C.S, Chem. Commun*, **1981,** p. 983.
27. Stork, G.; *et al. J. Am. Chem. Soc.* **1976,** *98*, 1583; **1978,** *100*, 8272.
28. Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1975,** *97*, 3870.
29. (a) Primeau, J. L.; Anderson, R. C.; Fraser-Reid, B. *J.C.S. Chem. Commun*, **1980,** p. 6; (b) Primeau, J. L.; Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1983,** *105*, 5874.
30. Fitzsimmons, B. J.; Fraser-Reid, B. *Tetrahedron* **1984,** *40*, 1279.
31. Fraser-Reid, B.; McLean, A.; Usherwood, E. W. *J. Am. Chem. Soc.* **1969,** *91*, 5392.
32. Holder, N. L.; Fraser-Reid, B. *Can. J. Chem.* **1973,** *51*, 3357.
33. Plauman, D. E.; Yunker, M. B.; Fraser-Reid, B. *Can. J. Chem:* **1977,** *55*, 4002.
34. Fraser-Reid, B.; Holder, N. L.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* **1977,** *55*, 3978; Fraser-Reid, B.; Anderson, R. C.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* **1977,** *55*, 3986.
35. Fraser-Reid, B.; Rahman, M. A.; Kelly, D. R.; Srivastava, R. M. *J. Org. Chem.* **1984,** *49*, 1835.
36. Rahman, M. A.; Kelly, D. R.; Srivastava, R. M.; Fraser-Reid, B. *Carbohydr. Res.* **1985,** *136*, 91.
37. Fraser-Reid, B.; Underwood, R.; Osterhout, M.; Grossman, J. A.; Liotta, D. *J. Org. Chem.* **1986,** *51*, 2152.
38. Prasad, J. S.; Clive, D. L. J.; da Silva, C. V. J. *J. Org. Chem.* **1986,** *51*, 2717.
39. Chew, S.; Ferrier, R. J. *J.C.S, Chem. Commun.* **1984,** p. 911.
40. (a) Lemieux, R. U.; Chu, N. J. *Abstr. Pap., Am. Chem. Soc.* **1958,** *133*, 31N; (b) Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen", New York: Springer-Verlag, 1983.
41. Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, M. *J. Am. Chem. Soc.* **1982,** *104*, 3635.
42. Seeman, J. *Chem. Rev.* **1983,** *83*, 86.
43. Anderson, R. C. Ph.D. Thesis, Univ. of Waterloo, Waterloo, Ontario, 1978.
44. Wetherington, J. B.; Moncrief, J. W. *Acta Crystallogr., Sect. B* **1975,** *B31*, 501; Von Dreele, R. B. *Acta Crystallogr., Sect B* **1976,** *B32*, 2852.
45. Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974,** *96*, 7801.
46. Jackson, D. A.; Stoodley, R. J. *J.C.S, Chem. Commun*, **1981,** *478*.
47. Vaya, J.; Anathasubramanian, L. *J. Am. Chem. Soc.* **1980,** *102*, 5983.
48. Rosen, G. M. *J. Med. Chem.* **1974,** *17*, 358; Boutique, M.-H.; Jacquesy, R. *Bull. Soc. Chim. Fr.* **1973,** p. 750.
49. Schmitt, J.; Panouse, J. J.; Hallot, A.; Cornu, P.-J.; Pluchet, H.; Comoy, P. *Bull. Soc. Chim. Fr.* **1962,** p. 1855
50. For typical examples, see Gent, P. A.; Gigg, R.; May, S.; Conant, R. *J.C.S, Perkin I* **1972,** p. 2748; Gross, P. H.; Brenda, K.; Zimmerman, H. K.; Jr. *Justus Liebigs Ann. Chem.* **1964,** *680*, 155; Horner, M. W.; Hough, L.; Richardson, A. C. *J. Chem. Soc. C* **1971,** p. 99.
51. Trost, B. M.; Hiroi, K.; Kurozumi, S. *J. Am. Chem. Soc.* **1975,** *97*, 438.
52. Reitsema, R. H. *J. Am. Chem. Soc.* **1957,** *79*, 4465; Zalkow, L. H.; Ellis, J. W.; Brennan, M. R. *J. Org. Chem.* **1963,** *28*, 1705; Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984,** p. 5839; Williams, G. J.; Hunter, N. R. *Can. J. Chem.* **1976,** *54*, 3830.

53. Ellis, J. W. *J. Org. Chem.* **1969,** *34*, 1154.
54. Hutchins, R. O.; Learn, K.; Fulton, R. P. Tetrahedron Lett. **1980,** p. 27; Trost, B. M. *Acc. Chem. Res.* **1980,** *13*, 385.
55. Tsuji, J. "Organic Synthesis with Palladium Compounds," Springer-Verlag: New York, 1980.
56. Sutherland, J. K.; Tolmetzki, G. B. *Tetrahedron Lett.* **1984,** p. 881.
57. Rahman, M. A.; Kelly, D. R.; Ravi, P.; Fraser-Reid, B. *Tetrahedron* **1986,** *49*, 2409.
58. For a recent thorough review, see Davies, H. G.; Green, R. N. *Nat. Prod. Rep.* **1986,** *3*, 87; Chabala, J. C.; Mrozik, H.; Tolman, R. L.; Eskala, P.; Lusi, A.; Peterson, L. H.; Woods, M. F.; Fisher, M. H.; Campbell, W. C.; Egerton, J. R.; Ostlin, D. A. *J. Med. Chem.* **1980,** *23*, 1134.
59. Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979,** *101*, 6789.
60. Smith, A. B.; III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982,** *104*, 4015.
61. Williams, D. R.; Barnes, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982,** *104*, 4708.
62. Hanessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem.* **1983,** *48*, 4427; Baker, R.; Hugh, O.; Boyes, R.; Mark, P.; Broom, D.; Alastair, D. J.; Swain, C. J. *J.C.S, Chem. Commun.* **1983,** p. 829; Culshaw, D.; Grice, P.; Ley, S. V.; Strange, G. A. *Tetrahedron Lett.* **1985,** *26*, 5837; Kocienski, P.; Street, S. D. A. *J.C.S, Chem. Commun,* **1984,** 571; Crimmins, M. T.; Hollis, W. G., Jr.; Bankaitis-Davis, D. M. *Tetrahedron Lett.* **1987,** *28*, 3651.
63. Prashad, M.; Fraser-Reid, B. *J. Org. Chem.* **1985,** *50*, 1564.
64. Crimmins, M. T.; Hollis, W. G., Jr.; Lever, J. G. *Tetrahedron Lett.* **1987,** *28*, 3647; Crimmins, M. T.; Lever, J. G. *Tetrahedron Lett.* **1986,** *27*, 291.
65. Wolfrom, M. L.; Thomas, G. H. S. *Methods Carbohydr. Chem.* **1963,** *2*, 32.
66. Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974,** *96*, 1082.
67. Shafizadeh, F.; Wolfrom, M. L. *J. Am. Chem. Soc.* **1955** *77*, 2568.
68. Rosenthal, A.; Cliff, B. L. *Can. J. Chem.* **1976,** *54*, 543.
69. Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984,** *49*, 2301; Kozikowski, A. P. *Acc. Chem. Res.* **1984,** *17*, 410.
70. Curran, D. P. *J. Am. Chem. Soc.* **1983,** *105*, 5826.
71. Baker, D. C.; Brown, D. K.; Horton, D.; Nickol, R. G. *Carbohydr. Res.* **1974,** *32*, 299.
72. Grosheintz, J. M.; Fischer, H. O. L. *J. Am Chem. Soc.* **1948,** *70*, 1479.
73. Unpublished results from the authors' laboratory.
74. (a) Still, W. C.; Tsai, M.-Y.; *J. Am. Chem. Soc.* **1980,** *103*, 3654; (b) Brooks, D. W.; Grothans, P. G.: Mazdiyashi, H. *J. Am. Chem. Soc.* **1983,** *105*, 4472; (c) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982,** *104*, 1116; (d) Trost, B. M.; McDougal, P. G.; Haller, K. J. *J. Am. Chem. Soc.* **1984,** *106*, 383; (e) Roush, W. R.; D'Ambra, T. E. *J. Am. Chem. Soc.* **1983,** *105*, 1058.
75. (a) Machida, Y.; Nozol, S. *Tetrahedron* **1972,** *28*, 5113; (b) Masuoka, N.; Kamikawa, T.; Kubota, T. *Chem. Lett.* **1974,** p. 751; (c) Masuoka, N.; Kamikawa, T. *Tetrahedron Lett.* **1976,** p. 1691.
76. (a) Fraser-Reid, B.; Tsang, R.; Tulshian, D. B.; Sun, K. M. *J. Org. Chem.* **1981,** *46*, 3764; (b) Tulshian, D. B.; Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **11984,** *49*, 2347; (c) Fraser-Reid, B.; Tulshian, D. B.; Tsang, R.; Lowe, D.; Box, V. G. S. *Tetrahedron Lett.* **1984,** p. 9579.
77. (a) Colvin, E. W.; Raphael, R. A.; Roberts, J. S. *J.C.S, Chem. Commun,* **1971,** p. 858; (b) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J.C.S. Perkin I* **1973,** p. 1989.
78. Tulshian, D. B.; Fraser-Reid, B. *J. Org. Chem.* **1984,** *49*, 518.
79. Fraser-Reid, B.; Dawe, R. D.; Tulshian, D. B.; *Can. J. Chem.* **1979,** *57*, 1746.
80. Tsang, R.; Fraser-Reid, B.; McPhail, A. T. *J. Carbohydr. Chem.* **1986,** *5*, 513.

81. Tsang, R. Ph.D. Thesis, Duke Univ., Durham, North Carolina, 1985.
82. Hanessian, S. *Methods Carbohydr. Chem.* **1972,** *6*, 183.
83. Tulshian, D. B.; Fraser-Reid, B. *Tetrahedron* **1984,** *40*, 2083.
84. Grynkiewicz, G.; BeMiller, J. N.; *J. Carbohydr. Chem.* **1982,** *1*, 121.
85. Klemer, A.; Rodemeyer, G. *Chem. Ber.* **1974,** *107*, 2612.
86. Tsang, R.; Fraser-Reid, B. *Chem. Commun*, **1984,** p. 60.
87. Finkbeiner, H. L.; Stiles, M. *J. Am. Chem. Soc.* **1963,** *85*, 616.
88. Wick, A. E.; Felix, D.; Stern, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964,** *47*, 2425.
89. Chapleur, Y. *J.C.S, Chem. Commun*, **1983,** p. 141.
90. Fraser-Reid, B.; Walker, D. L. *Can. J. Chem.* **1980,** *58*, 2694.
91. Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985,** *107*, 1448.
92. Beckwith, A. L. J.; Roberts, D. H.; Schiesser, C. H.; Wallner, A. *Tetrahedron Lett.* **1985,** *26*, 3349.
93. Stork, G.; Mook, R.; Jr. *J. Am. Chem. Soc.* **1983,** *105*, 3720.
94. Tsang, R.; Fraser-Reid, B.; McPhail, A. T. *J. Carbohydr. Chem.* **1986,** *5*, 513.
95. Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986,** *108*, 2116.
96. Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986,** *108*, 8102.
97. Tsang, R.; Dickson, J. K., Jr.; Pak, H.; Holton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987,** *109*, 3484.
98. See, e.g., Liptak, A. *Carbohydr. Res.* **1978,** *63*, 69.

*Chapter 5*

# δ-VALEROLACTONE ANNULATION: APPLICATION TO THE TOTAL SYNTHESIS OF QUADRONE

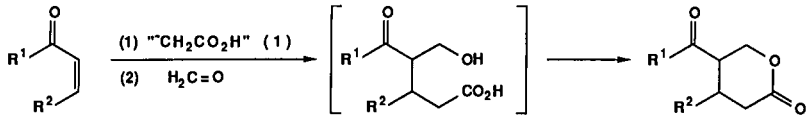
*Paul Helquist*
*Department of Chemistry*
*University of Notre Dame*
*Notre Dame, Indiana*



## I. Introduction

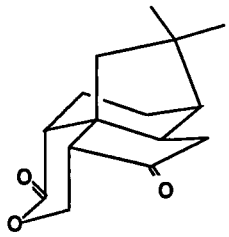
Over the years, many of the efforts of the author's research group have been directed toward the development of new methods for the direct annulation of various ring systems onto preexisting acyclic or cyclic organic frameworks. These annulations have involved the formation of both carbocyclic and heterocyclic systems. Included among the former have been three-, four-, five-, six-, and seven-membered rings,[1–5] whereas the latter have included isoquinolines, oxazoles, and γ-butyrolactones.[5–7] Also of interest were procedures for forming six-membered lactones because of the occurrence of numerous important natural products containing the α-pyrone unit and various reduced forms of this ring system, including the tetrahydro derivatives, i.e., the δ-valerolactones.

Therefore, an effort was initiated to find means of effecting the direct lactone annulation shown in simple terms in Eq. (1). One of the basic ideas was to employ a synthetic equivalent of the acetic acid carbanion synthon **1** in a conjugate addition reaction with $\alpha,\beta$-unsaturated ketones, followed by trapping of the intermediate enolate with formaldehyde and subsequent lactonization. The exact nature of the individual steps would be dependent on the specific choice of synthetic equivalents for **1**.




(1)

Ironically, shortly after the initial studies of developing this methodology had begun, tremendous excitement was generated in the synthetic organic community by the report of a newly isolated, $\delta$-valerolactone-containing natural product simply called quadrone (**2**).[8,9] This compound combined the very attractive points of having a fascinating structure and exhibiting antitumor activity.



**2**

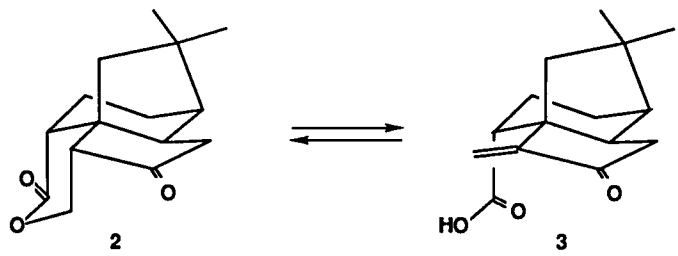
Very quickly, the synthesis of quadrone became an irresistible goal of several research groups. Although the author's research group had more commonly emphasized the development of new synthetic reactions rather than actual total syntheses, quadrone was recognized as a very timely and appropriate target on which to focus the study of the proposed lactone annulation procedures.

## II. Background

The isolation of quadrone was first reported by Calton, Ranieri, and Espenshade of W. R Grace & Co. in 1978.[8,9] It was isolated from the fungus *Aspergillus terreus*, and it was found to have activity against human epidermoid carcinoma of the nasopharynx (KB cell cultures) and P388

lymphocytic leukemia in mice (PC). The structure of quadrone (**2**) was determined by single-crystal X-ray diffraction,[9] and the absolute configuration was established by correlations employing materials obtained from synthetic sources.[10,11] Biosynthetic studies by Cane and co-workers indicated a pathway involving a farnesyl pyrophosphate cyclization as the origin of quadrone in nature.[12,13]

A number of closely related natural products have been reported more recently. These compounds include terrecyclic acid A (**3**),[11,14,15] terrecyclol,[16] isoquadrone,[17] 6-hydroxyquadrone,[17] and 8-hydroxyquadrone. The first of these compounds, **3**, is particularly interesting in that before it was found as a naturally occurring compound, it had been employed as the final intermediate in several syntheses of quadrone. Furthermore, because of its obvious structural relationship to the α-methylene γ-butyrolactone-containing natural products having antitumor activity **3** has been considered to be possibly the form in which quadrone actually exhibits its activity; the chemical equilibrium between **2** and **3** is easily perceived [Eq. (2)].[11,14,15]



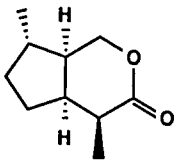

**2** **3** (2)

Not at all surprising is the vast amount of effort that has been directed toward the synthesis of quadrone and related compounds. Preliminary investigation of various approaches to quadrone and associated studies have been reported by the research groups of Danishefsky, Paquette, Burke, Monti, Pattenden, Piers, Smith, Schuda, and Hua,[18–26] and stereoelectronic considerations pertaining to quadrone approaches have been presented by De Clercq.[27] The first actual synthesis of quadrone was achieved by Danishefsky's group.[28,29] Subsequent total or formal syntheses have been reported (in chronological order) by the author's group [30] and from the laboratories of Burke, Kende, Yoshii, Schlessinger, Vandewalle, Smith, Iwata, Piers, Wender, Funk, and Magnus.[10,31–42] Much of this work has been reviewed by Kreiser [43] and by Paquette.[44]

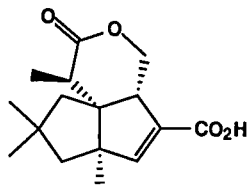
In addition to syntheses of quadrone and its very close relative terrecyclic acid A[11] (often concurrently), syntheses have also been achieved for descarboxyquadrone,[45–49] descarboxydesdimethylquadrone,[50] a spiro analog of

quadrone,[51] and some fused ring derivatives.[52] Also, microbiological reduction products of quadrone have been obtained.[53]

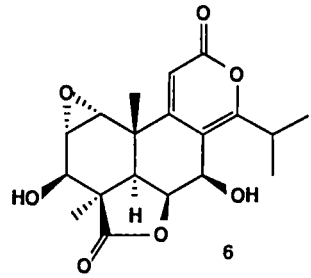
Briefly mentioned in the Introduction was that the occurrence of many types of natural products containing six-membered lactone ring systems served as the original impetus for the author's entry into this area. A few specific examples of these lactone derivatives include iridomyrmecin (**4**),[54] pentalenolactone E (**5**),[19,55] and nagilactone C (**6**).[56] A structural feature to be noted in these and several other compounds is that the lactone ring is fused to various types of carbocyclic systems. Therefore, the need was recognized for methods that would permit annulation of lactones onto preexisting ring systems.




4




5

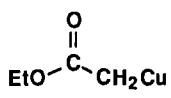



6

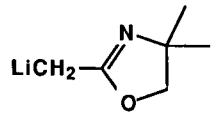
## III. Methods for δ-Valerolactones and α-Pyrones

Various approaches to these lactones were investigated as portions of the dissertion projects of a series of graduate students in the author's former laboratory at the State University of New York at Stony Brook. The principal contributors to these studies were doctoral students John Ponton, Walter K. Bornack, and Shripad S. Bhagwat,[57–59] and some earlier, preliminary studies were carried out by Anthony Marfat and Steven Brandt.[60,61] Because the work of these co-workers began as investigations of basic synthetic methods for six-membered lactone systems in general, and because the isolation of quadrone was reported after the initial studies of these methods had begun, the results of this basic development work will be presented before the synthetic studies of quadrone itself are discussed.

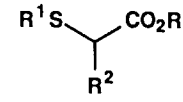
One of the basic approaches to δ-valerolactones has already been presented in the Introduction [Eq. (1)]. This approach is dependent on the availability of appropriate synthetic equivalents of the acetic acid synthon **1**. When this work was begun, possibly useful equivalents included ethoxycarbonylmethylcopper (**7**),[62] metalated 2-methyloxazoline derivatives (e.g., **8**),[63] and 2-(alkylthio) carboxylic acid derivatives (**9**)[64–78] among others. Alternatively, various equivalents of the acetaldehyde synthon **10** could be employed in modifications of Eq. (1) requiring appropriate adjustment of



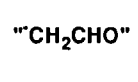
7



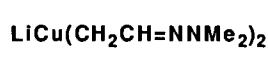
8



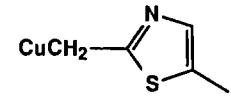
9



10



11

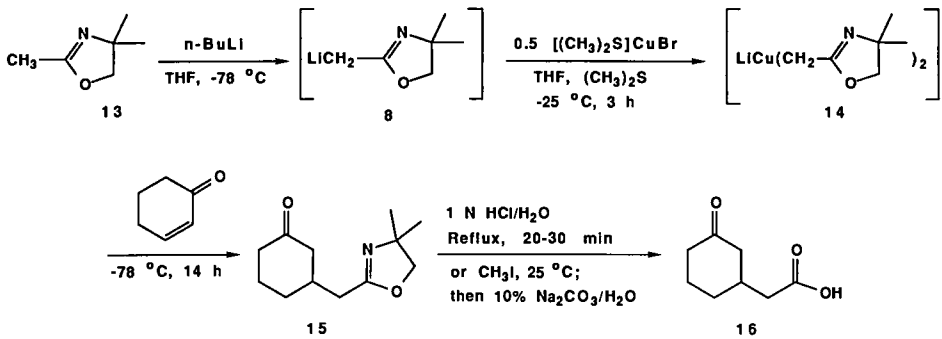


12

oxidation states. Among the acetaldehyde equivalents that were available at the time were the dimethylhydrazone derivative **11**,[79] the thiazole derivative **12**,[60,61,80] and several others.

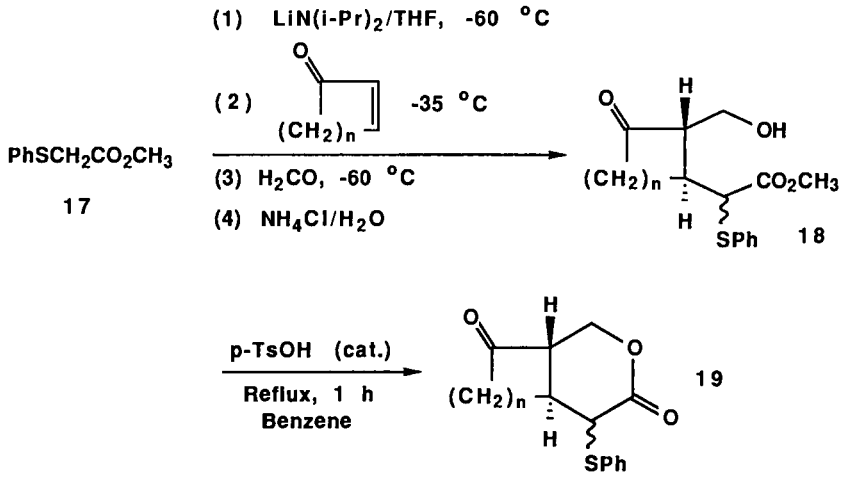
To begin the lactone annulation studies, the ethoxycarbonylmethylcopper reagent **7** was prepared from the lithium enolate of ethyl acetate according to the literature procedure,[62] with the exception that the dimethyl sulfide complex of cuprous bromide[81] was used in place of cuprous iodide as the source of copper. Also, reagents having the supposed formulation of the homocuprates $LiCu(CH_2CO_2R)_2$ (R = Et or *t*-Bu) were generated by reaction of two equivalents of the corresponding lithium ester enolates with one equivalent of $[CH_3)_2S]CuBr$. However, when each of the resulting organocopper species was allowed to react with 2-cyclohexenone, complex mixtures of products were obtained.

Next to be investigated were metalated oxazoline derivatives (Scheme 1). Based in part on the work of Wollenberg with related oxazines,[82] the trimethyloxazoline **13** was metalated with *n*-butyllithium in the usual manner.[63] Reaction of 2 equivalents of the resulting **8** with 1 equivalent of $[(CH_3)_2S]CuBr$ gave the supposed cuprate **14**, which underwent conjugate




13 8 14 15 16

SCHEME 1

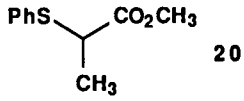



SCHEME 2

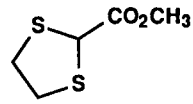
addition to 2-cyclohexenone to give **15** in 64% yield after purification (85% yield determined by gas chromatography (GC) analysis of the crude mixture). Simple acid hydrolysis[63] gave the ketoacid **16** in 69% yield. Alternatively, the same product could be obtained under milder conditions by first forming the methiodide salt followed by hydrolysis with aqueous sodium carbonate.[63]

The conjugate addition reaction of **14** did not prove to be very general. Substrates such as 3-methyl-2-cyclohexenone and mesityl oxide, which are more hindered than 2-cyclohexenone, underwent primarily 1,2,-addition, even at higher temperatures (e.g., −25°C) and even in the presence of cosolvents such as hexamethylphosphoric triamide. Another limitation in using **14** is that although the enolate resulting from addition to 2-cyclohexenone could be trapped moderately well with reactive alkylating agents such as methyl iodide and allyl bromide, trapping with acetaldehyde or benzaldehyde led to very complex product mixtures. (An important exception to these difficulties is discussed below as part of the synthesis of quadrone.)

2-(Alkylthio) carboxylic acid derivatives (**9**)[64–78] were next studied with greater success. First of all, methyl 2-(phenylthio)acetate (**17**), as its lithium enolate, was found to undergo conjugate addition to 2-cyclohexenone followed by quenching with anhydrous formaldehyde[83] to give the adduct **18**. Acid-catalyzed lactonization then gave the desired lactone **19** (Scheme 2). Analogous reaction sequences were performed with other $\alpha,\beta$-unsaturated ketones and with other sulfur-substituted ester enolates, including those derived from **20** and **21**. The results are summarized in Table I.



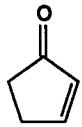
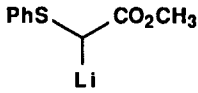
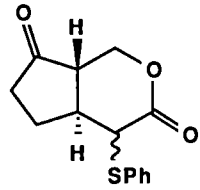
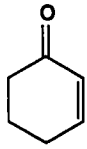
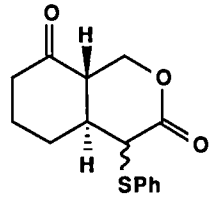
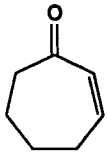
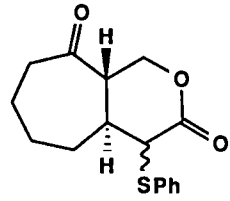
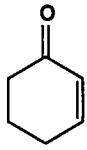
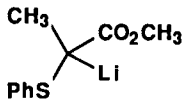
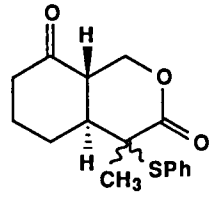
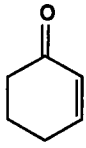
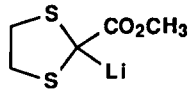
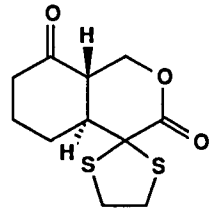

20



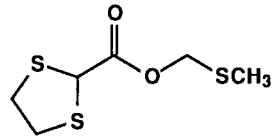

21

TABLE I

SYNTHESIS OF δ-VALEROLACTONES USING 2-(ALKYLTHIO) ESTERS, α,β-UNSATURATED KETONES, AND FORMALDEHYDE

| Enone | Ester enolate | Product | Overall yield (%) |
|---|---|---|---|
|  |  17 |  | 44 |
|  | 17 |  | 30 |
|  | 17 |  | 31 |
|  |  |  | 70 |
|  |  |  | 25 |

In a further modification of this approach, the conjugate addition of the ketene silyl acetal, $H_2C{=}C(OCH_3)OSi(CH_3)_2t\text{-}Bu$,[84] to 2-cyclohexenone was investigated, but the yield of the adduct was only 25% at best. Also attempted was the use of the methylthiomethyl ester **22** in a sequence employing conjugate addition, *S*-methylation to give a sulfonium salt, and subsequent intramolecular alkylation involving enolate displacement of dimethyl sulfide to give lactones, but this approach and a few of its variations failed to give the desired products.

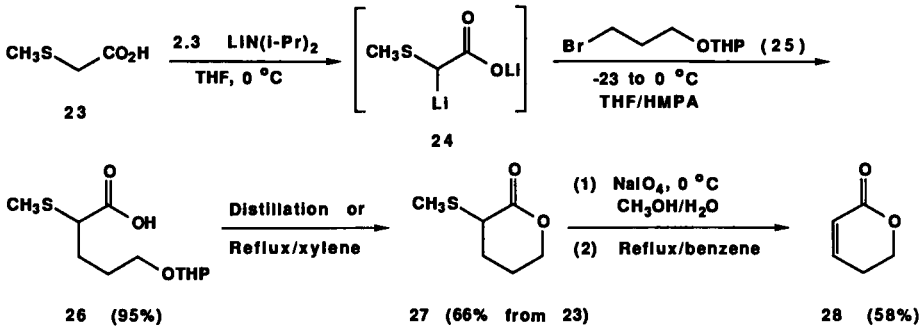



**22**

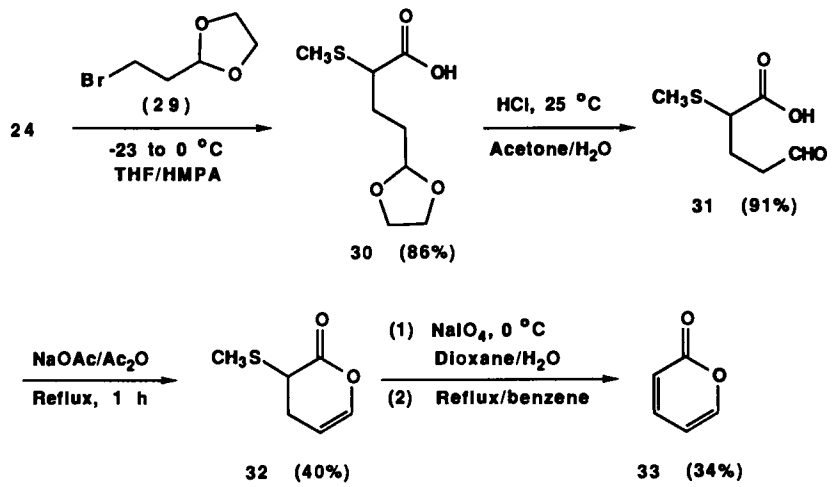
Other modifications of the above approaches were more successful. For example, (methylthio)acetic acid (**23**) was converted to the dianion **24**,[69] which underwent reaction with 3-bromopropyl tetrahydropyranyl ether (**25**)[85] to give the alkylation product **26**. Heating of **26** accomplished both removal of the THP group and lactonization, and when the resulting lactone **27** was subjected to oxidative elimination of the sulfur substituent,[86] the dihydropyrone **28** was obtained (Scheme 3).

A closely related pathway employing 2-(2-bromoethyl)-1,3-dioxolane (**29**)[87] gave the acetal derivative **30** as the initial alkylation product, the aldehyde **31** on hydrolysis, the dihydropyrone **32** on enol lactonization,[88] and finally the parent $\alpha$-pyrone (**33**) in low yield on oxidative elimination (Scheme 4).

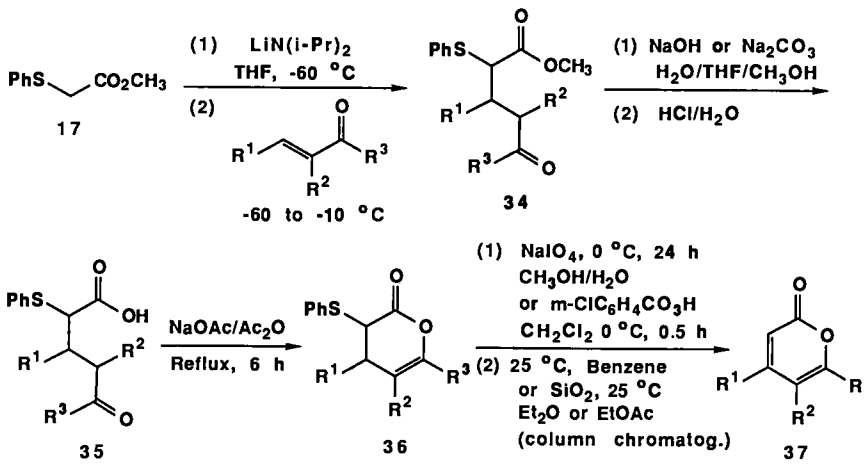
A more general route leading to substituted $\alpha$-pyrones went back to the use of methyl 2-(phenylthio) acetate (**17**) in conjugate addition reactions once again (Scheme 5). However, in place of the formaldehyde trapping that




SCHEME 3



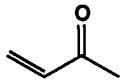
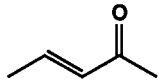
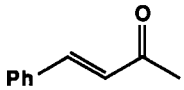
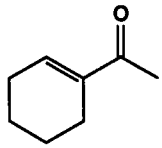
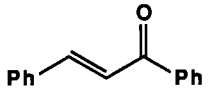

SCHEME 4




SCHEME 5

was employed earlier (Scheme 2), the adducts **34** were hydrolyzed to the ketoacids **35**, which were then subjected to enol lactonization. The resulting 3-(phenylthio)dihydropyrones **36** were then oxidized, and the resulting sulfoxides underwent the desired elimination either on standing in solution at 25°C or during silica gel chromatography to give the substituted α-pyrones **37**. The results of this more attractive sequence are summarized in Table II.

TABLE II
SYNTHESIS OF α-PYRONES ACCORDING TO SCHEME 5

| Enone | Product yields (%) | | | |
|---|---|---|---|---|
| | **34** | **35** | **36** | **37** |
|  | 59 | 93 | 81 | 82 |
|  | 90 | 94 | 82 | 70 |
|  | 77 | 96 | 56 | 88 |
|  | 70[a] | 88 | 0[b] | — |
|  | No reaction | — | — | — |

[a] This reaction was done with THF/HMPA as solvent.
[b] Extensive decomposition occurred to give a complex mixture in this case.

When an attempt was made to extend this approach to the use of unsaturated aldehydes in place of enones, only 1,2-addition of the enolate of **17** occurred with crotonaldehyde as a test case. Also unsuccessful were attempts to use methyl iodide for trapping the initial adducts of the enolate of **17** to enones, attempts to perform enolate alkylations of the dihydropyrones **36**, and attempts to effect lithium/halogen exchange of *cis*-3-iodoacrylic acid to give *cis*-LiCH=CHCO$_2$Li. The last of these species would have provided very direct access to α-pyrone derivatives.

In other studies, the thiazolylmethylcopper derivative of **8** was found to undergo efficient conjugate addition to 2-cyclohexenone, but its further use was overshadowed by the other successful results described above.

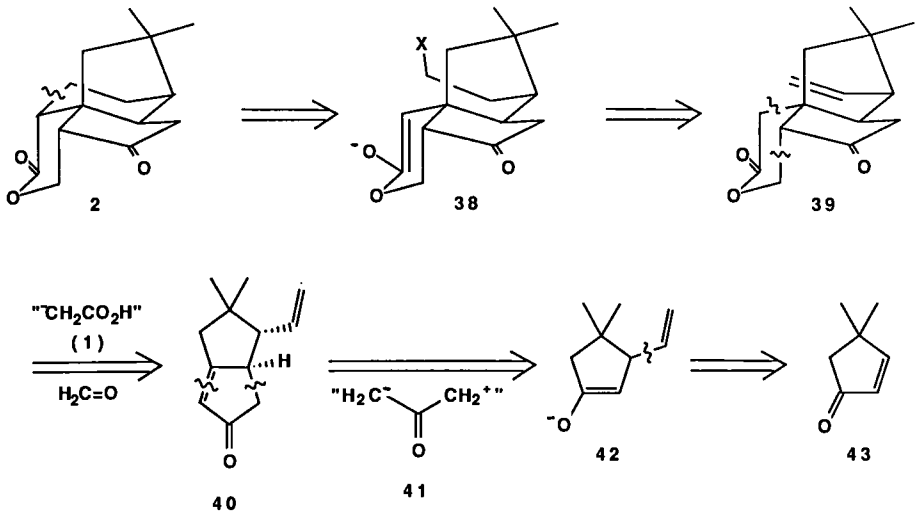
Aside from the application to the synthesis of quadrone (*vide infra*), the preceding reaction sequences were not pursued in greater detail, largely

because of considerable overlap with concurrent studies by Uda,[72] Yee and Schultz,[73] Yoshii,[74] and Yoshida.[78a] In addition, closely related studies have been reported by Welzel.[78b]

## IV. Basic Strategy for Quadrone

The basic strategy used for the synthesis of quadrone in the author's laboratory had an interesting origin. In early 1978, John Ponton, who was the first of three graduate students to work in this area, faced a graduate school requirement of writing and orally defending an independent research proposition. John's need to meet this requirement coincided with the first report of the isolation and structure of quadrone,[8,9] and he quickly recognized that the design of a synthesis of this compound combined with the proposal of new methods for lactone annulation would provide an attractive basis for his proposition. Not being aware of the approach that John was pursuing, the author also set about to design a synthesis of quadrone. To our great surprise, our two routes turned out to be nearly identical. In hindsight, the extremely close similarity of the two routes should not have been unexpected in light of the great interest in certain types of annulation reactions in the author's laboratory at the time.

The basic strategy that resulted from these efforts provided for a rapid assembly of the complex polycyclic skeleton of quadrone (Scheme 6). Based




SCHEME 6

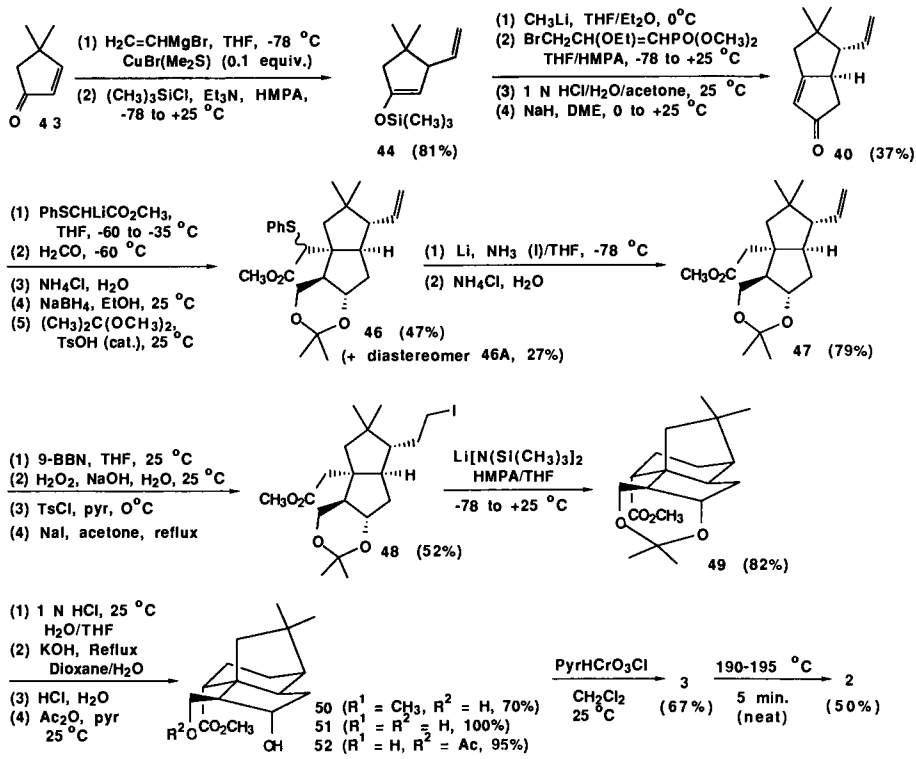
on this retrosynthetic analysis, the final bond-forming step would provide quadrone by an intramolecular lactone enolate alkylation of intermediate **38**. The 2-haloethyl side chain of this species would arise from straightforward functional group manipulations (hydroboration, etc.) of the vinyl group in the ketolactone **39**. The key part of the strategy was the application of the new lactone annulation procedures to the bicyclo[3.3.0]oct-1-en-3-one **40**. In turn, this enone would arise by reaction of any of several available synthetic equivalents of the acetone synthon **41** (*vide infra*) with the cyclopentanone enolate **42**, which in turn would be generated by conjugate addition of a vinylcopper species to the readily available cyclopentenone **43**.[89,90] An important point to be noticed about this approach is that in its original form, it not only was very short (perhaps as few as six or seven actual laboratory operations) but also may have avoided the use of any protecting groups.

Of course, few syntheses are completed according to the originally planned pathway, and this synthesis was no exception. For the most part, though, the final synthesis remained fairly faithful to the original plan except for a reordering of the intramolecular enolate alkylation and the lactone ring closure and for the need to use a few simple protecting groups. As will be discussed in the next section, the need for the reordering of steps arose because of an unexpected stereochemical problem in the application of the new lactone annulation procedures to the bicyclic enone **40**. In the end, however, the occurrence of this difficulty was actually fortunate; if the originally planned order of steps had been followed, and if the intermediate **38** had been reached, a more severe difficulty would probably have been encountered in the intramolecular lactone enolate alkylation as reported by Paquette[19] after completion of the synthesis described below.

## V. Synthesis of Quadrone

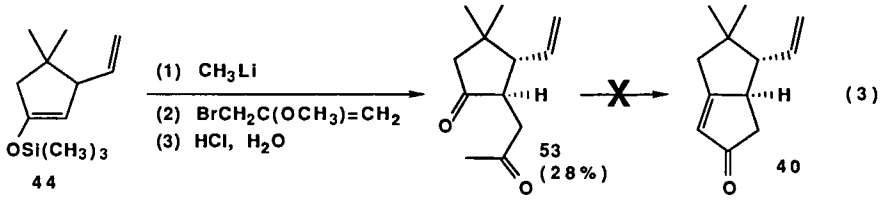
The overall route to quadrone is shown in its entirety in Scheme 7, but its discussion will be divided into certain logical stages. The first stage that was accomplished was the construction of the bicyclo[3.3.0]oct-1-en-3-one **40** (Scheme 7). Next came the introduction of the basic elements of the $\delta$-valerolactone ring, but the actual lactonization step was postponed to the end of the synthesis. After a protecting group scheme was adopted, the intramolecular enolate alkylation was accomplished, and the lactone construction was finally completed to give quadrone itself.

To begin the synthesis, copper-catalyzed conjugate addition of vinylmagnesium bromide to 4,4-dimethyl-2-cyclopentenone (**43**) and enolate trapping with trimethylsilyl chloride proceeded smoothly to give the silyl enol ether **44**. However, the initial attempts to introduce the second five-membered



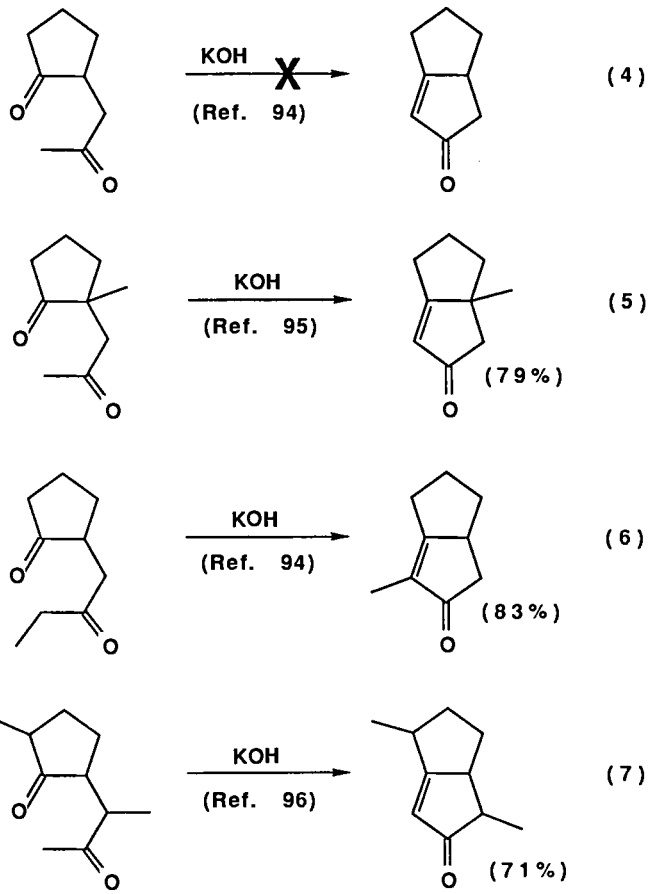

SCHEME 7

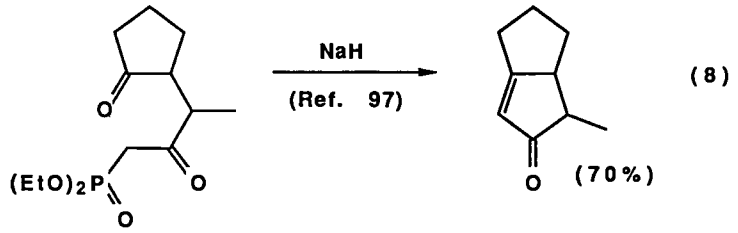
ring through the use of various synthetic equivalents of the acetone synthon **41** were not successful. For example, reaction of **44** with 2-nitropropene and tin tetrachloride[91] gave a complex mixture of products containing no detectable quantities of the desired 2-acetonylcyclopentanone **53**. On the other hand, the use of 3-bromo-2-methoxy-1-propene[92] in the alkylation of the enolate derived from silyl enol ether **44** did lead to the formation of **53**, but all attempts to effect intramolecular condensation of this 1,4-diketone to give the key bicyclo[3.3.0]oct-1-en-3-one **40** met with failure [Eq. (3)]. Among the



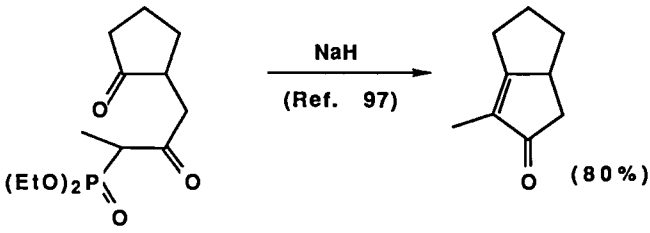
conditions employed were potassium hydroxide in ethanol, potassium *tert*-butoxide in *tert*-butanol, lithium diisopropylamide in THF, aqueous sodium carbonate, *p*-toluenesulfonic acid in toluene at reflux, and anhydrous hydrogen chloride in methanol.

This type of cyclization is expected to be difficult on the basis of stereoelectronic principles,[93] and indeed there have been many cases reported in which relatively simple 2-acetonylcyclopentanones fail to undergo aldol cyclization. Somewhat contradictory, however, is that some more highly substituted substrates undergo cyclization quite efficiently.[94–99] Some examples that illustrate this varying behavior of 2-acetonylcyclopentanones are shown in Eqs. (4)–(10). Note in the last of these examples that the cyclization product undergoes rapid dimerization, probably via a double Michael ad-

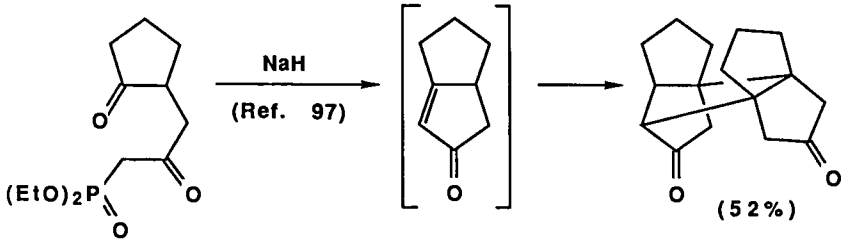





(8)



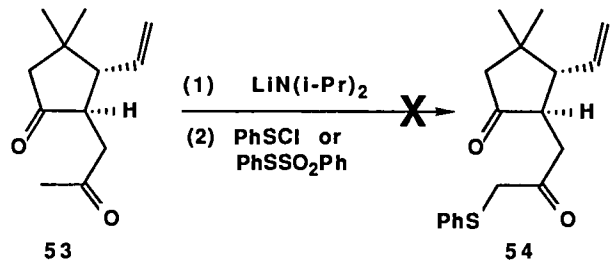

(9)




(10)

dition sequence, resulting in the isolation of a complex polycyclic product [Eq. (10)].

In the case of the particular 2-acetonylcyclopentanone **53**, kinetic enolate formation at the methyl group was also attempted, followed by trapping with various electrophilic reagents. Among the reagents that were employed were benzenesulfenyl chloride[100] and phenyl benzenethiosulfonate[101] with the goal of obtaining the α-(alkylthio)ketone **54** [Eq. (11)], which in turn would be employed in rather obvious transformations leading to appropriate

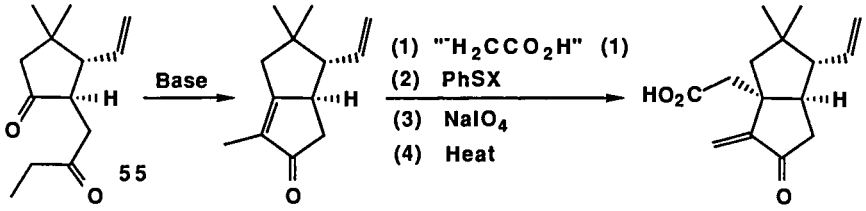



53 54

(11)

bicyclo[3.3.0]oct-1-en-3-ones. In all cases, only complex mixtures of products were obtained.

Next to be considered was the synthesis of the 1,4-diketone **55**, a one-carbon homolog of **53**, which would be employed as shown in Eq. (12). For this purpose, a reaction of silyl enol ether **44** was attempted with 2-nitro-1-butene and either tin tetrachloride or titanium tetrachloride,[91] but diketone **55** was not obtained.



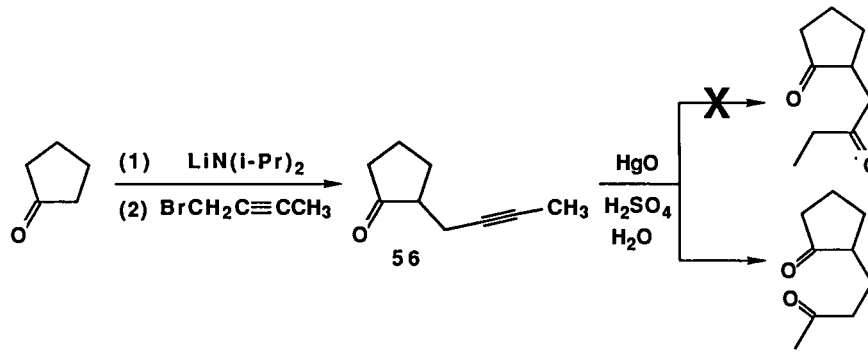

(12)

Also briefly pursued was the preparation of $BrCH_2C(OCH_3)=CHCH_3$ as an alkylating agent in place of that used for conversion of silyl enol ether **44** to **53** in Eq. (3). 1-Bromo-2-butanone underwent acid-catalyzed reaction with trimethyl orthoformate to give the corresponding dimethyl ketal, but pyrolytic cracking failed to give the desired enol ether.

In a model study for diketone **55**, the lithium enolate of cyclopentanone itself was subjected to alkylation with 1-bromo-2-butyne to give substituted ketone **56**. However, instead of giving the 1,4-diketone **57**, subsequent mercury-promoted hydration produced the 1,5-diketone **58** [Eq. (13)].

Among other ideas that were pursued briefly without success for the synthesis of **55** were alkylations of the enolate derived from silyl enol ether **44** with 1,2-epoxybutane followed by oxidation, alkylation of the enolate with 1-bromo-2-butanone, and alkylation with ethyl bromoacetate.

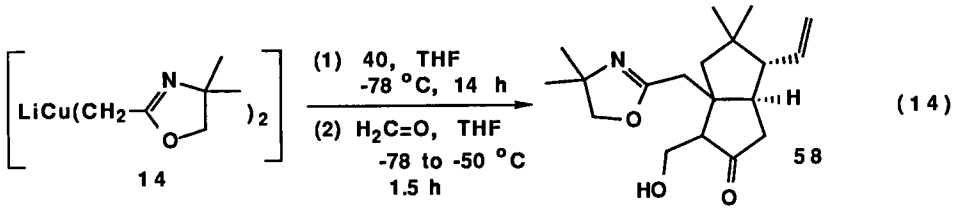
After all of these unsuccessful attempts to forge beyond silyl enol ether **44** as only a very early intermediate in the quadrone synthesis, the students




(13)

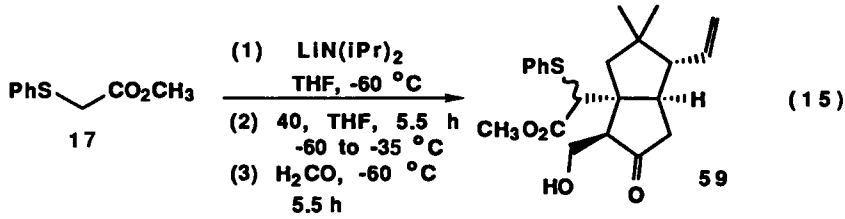
working on this project were justifiably becoming very depressed and unoptimistic. Fortunately, at this very low point in the students' morales, Professor Piers happened to report the use of 3-bromo-2-ethoxypropenephosphonate (**45**) as a new reagent for cyclopentenone annulation.[102] In light of this very promising development, further pursuit of the several approaches described above was abandoned. With the help of further valuable information that was generously provided by Professor Piers,[103] the new reagent finally provided a solution to the problem of converting **44** into the desired bicyclo[3.3.0]oct-1-en-3-one **40** (Scheme 7).

The next phase of the synthesis was the introduction of the elements of the δ-valerolactone ring. Based on one of the earlier approaches discussed in Section III, a reaction was performed between the bicyclic enone **40** and the oxazolinylmethylcuprate **14**. After the reaction mixture was quenched with aqueous ammonium chloride, the conjugate addition product was obtained in 77% yield. When formaldehyde was added before the quenching, the adduct **58** was obtained, but the yield was only 45% of material having a purity of 60–80%. This material proved to be very difficult to purify further. In addition, all attempts to effect hydrolysis of the oxazoline moiety to the corresponding carboxylic acid or lactone were unsuccessful.




(14)

Without further delay, the analogous reaction sequence was performed with the enolate of methyl (phenylthio)acetate (**17**). On addition of formaldehyde, the adduct **56** was isolated in 68% yield [Eq. (15)].

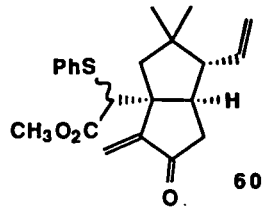



(15)

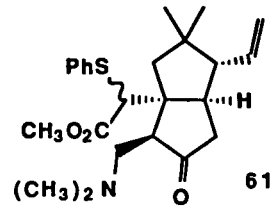
Because of the highly folded nature of bicyclo[3.3.0]octane systems, the assumption had been made that the formaldehyde condensation would occur on the convex surface of this ring system, i.e., cis to the (phenylthio)acetate group, despite the bulkiness of this angular substituent and despite the

several reports of overall trans addition in conjugate addition/alkylation sequences starting with monocyclic 2-cyclopentenones.[104] Spectroscopic studies were not useful in determining the stereochemistry of **59**. Also, aside from the expected formation of epimers at the center bearing the phenylthio group, there was no clear evidence of whether a stereochemically homogeneous product had been obtained. The first indication that the above assumption may have been incorrect was given when efforts to effect lactone formation from **59** met with repeated failure. Instead, under a variety of acidic and basic conditions, the dehydration product **60** was obtained. That the conjugate addition/formaldehyde condensation sequence may have resulted in at least predominant trans addition was a distinct possibility, but the actual stereochemistry of **59** was not established until considerably later when an X-ray crystal structure was determined for a more advanced intermediate (*vide infra*).

In order to minimize this tendency for elimination, formaldehyde was replaced by Eschenmoser's salt, $H_2C{=}N^+(CH_3)_2I^-$,[105] in the previous reaction sequence for the purpose of obtaining the amine **61**; its quaternized derivative was to have been employed in a lactonization reaction similar to that reported by Holton.[106] However, **61** could not be isolated and, again, the elimination product **60** was obtained.



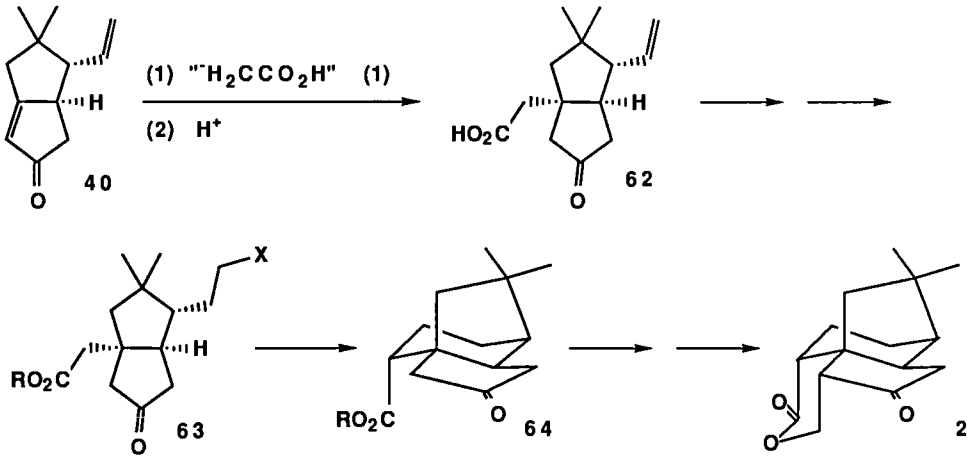

**60**




**61**

The high reactivity of the $\alpha$-methylenecyclopentanone moiety of **60** precluded carrying this functionality through further steps of the synthesis. For example, attempted hydroboration of the vinyl substituent of **60** and subsequent oxidation with alkaline peroxide led to very complex reaction mixtures, most likely due to competing reactions of the $\alpha$-methylene ketone unit.

For a time, consideration was given to the possibility of reordering the steps of the synthesis in such a manner that introduction of the troublesome, dehydration-prone hydroxymethyl group would be postponed until later in the synthesis. For example, the acetic acid synthon **1** could conceivably have been added to bicyclo[3.3.0]oct-1-en-3-one **40** using methyl (phenylthio)acetate (**17**), or even simpler synthetic equivalents such as malonates, followed by simple protic quenching to give adduct **62** (Scheme 8). Conversion of the vinyl substituent to a 2-haloethyl group and, if necessary, esterification would give a substrate **63** for intramolecular alkylation leading to tricyclic



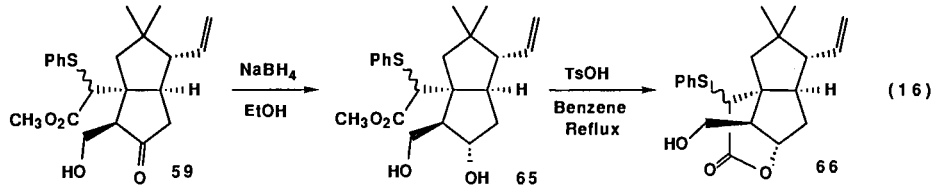

SCHEME 8

intermediate **64**. Regioselective hydroxymethylation or equivalent operations on the cyclopentanone moiety would then lead to quadrone (**2**).

Fortunately, before this alternative approach ever proceeded beyond the rough planning stages, Danishefsky published the preliminary report of the first synthesis of quadrone.[30] Indeed, the Danishefsky synthesis employed the alternative strategy described in the preceding sentences, but a stumbling block turned out to be lack of the required regioselectivity in the hydroxymethylation of an intermediate analogous to **64**. Therefore, going back to the original tandem conjugate addition/formaldehyde condensation sequence appeared to be particularly advantageous in light of the regiochemical problems encountered by Danishefsky. However, at this point the realization was made that the initial plan of avoiding the use of protecting groups would need to be abandoned.

Several reactions were performed in attempts to convert the ketone **59** into a ketal derivative, but none of these experiments were successful. Not surprisingly, the acid catalysis used in these reactions often promoted the formation of dehydration products again. Therefore, a protecting group strategy was adopted in which the oxidation state of the cantankerous (hydroxymethyl)cyclopentanone group was modified temporarily.

Reduction of **59** with sodium borohydride gave the 1,3-diol **65**, which upon acid catalysis was converted into a lactone **66**, still containing a free hydroxymethyl group according to a tentative structure assignment [Eq. (16)]. Therefore, lactonization had apparently involved the ring hydroxyl rather than the hydroxymethyl side chain. This result provided a

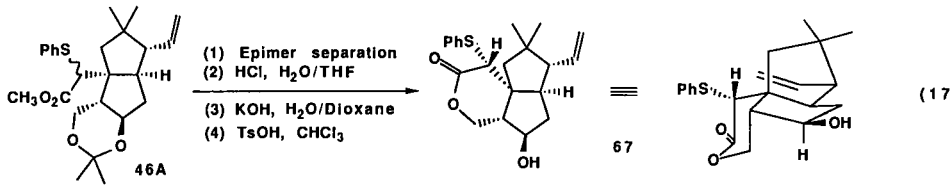



(16)

further indication that the conjugate addition/formaldehyde sequence leading to **59** had occurred at least predominantly in the trans rather than the desired cis fashion. According to a study of molecular models, lactonization involving the hydroxymethyl group trans to the carboxylate side chain of **65** would have given a more strained product than the apparently observed lactone **66**, whereas if the hydroxymethyl group had been cis as planned, participation of this group in the lactonization might have been favored over the ring hydroxyl group. Again, though, the actual determination of stereochemistry awaited an X-ray analysis of a later intermediate.

The diol **65** was employed further in the synthesis on conversion to the acetonide **46** (Scheme 7). At this stage of the synthesis, the first clear indication was given that the conjugate addition/condensation sequence had occurred to produce a mixture of diastereomers; chromatographic purification of **46** gave two pairs of diastereomers in overall yields of 47 and 27% from the bicyclo[3.3.0]oct-1-en-3-one **40**. Each pair apparently consisted of epimers about the phenylthio-substituted center. When the major pair (1.5 : 1 mixture according to $^1$H NMR) was subjected to reductive cleavage of the phenylthio group, a single, pure product was obtained. The X-ray analysis performed on a later intermediate demonstrated that the reductive cleavage product had stereo structure **47**. Surprisingly, though, the minor pair of diastereomers proved to be resistant to the same conditions of reductive cleavage.

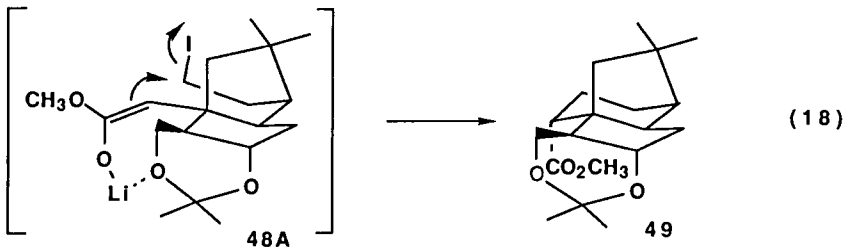
Based on further studies, the most likely structure of the minor pair of diastereomers was **46A**. The higher $R_f$ component of this pair was separated by silica gel chromatography and was then subjected to hydrolysis of the acetonide and ester groups and then to lactonization. Detailed 300-MHz $^1$H NMR analysis permitted the assignment of stereo structure **67** to the resulting lactone [Eq. (17)].




(17)

Quite obvious is that a route could conceivably have been devised to convert the minor diastereomer **46A** or the derived lactone **67** into quadrone, in which case the overall yield of the synthesis would have been increased significantly (note the combined yield of 74% for the conjugate addition/condensation/reduction/ketalization sequence leading to **46** and **46A**). A principal requirement would have been to avoid employing the intramolecular enolate alkylation of the type of fused lactone system seen in **67**. We note once again that although this means of cyclization had been part of our original strategy (see **38** in Scheme 6), it proved to be unattainable in Paquette's approach to quadrone.[19]

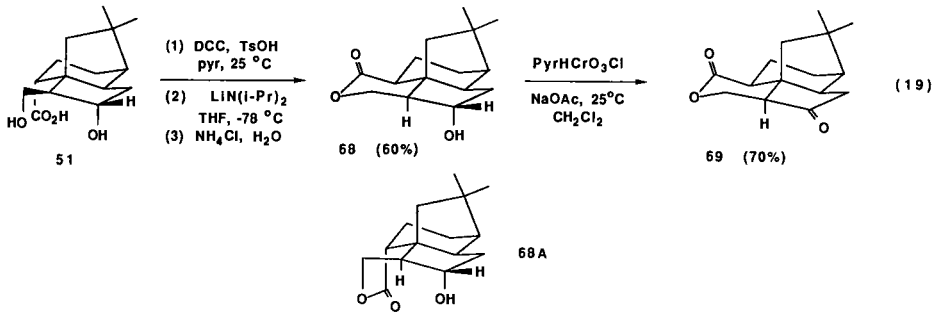
Because a quite straightforward route was also apparent for further use of **47** arising from the major diastereomer, only this material was carried all the way through the synthesis. The vinyl group was converted to a 2-iodoethyl substituent by the sequence of hydroboration, oxidation, tosylation, and Finkelstein exchange to give **48** (Scheme 7). In a crucial step, this compound was subjected to intramolecular ester enolate alkylation on treatment with lithium hexamethyldisilazide. Only one diastereomer of the cyclization product **49** could be detected. Although the conclusive proof of stereochemistry of this product needed to await the X-ray analysis of the next key intermediate, Danishefsky had reported predominantly an endo orientation of the carbomethoxy group in the closely analogous cyclization employed in his synthesis.[30,31] One of the possible rationales for this stereochemical outcome in the present case of **48** is that in the transition state for the alkylation (see **48A**), the enolate group is held in the endo orientation by chelation of the enolate counterion by an oxygen atom of the fused acetonide ring [Eq. (18)]. Fraser-Reid has more recently invoked a similar explanation in a related reaction,[107] whereas a quite different explanation was given by Danishefsky for his result.[31]




(18)

Removal of the acetonide group of **49** gave a dihydroxy ester **50** (Scheme 7) which resisted lactonization by means of intramolecular transesterification catalyzed by *p*-toluenesulfonic acid. This result gave yet another indication that the earlier conjugate addition/condensation sequence had not occurred predominantly in the desired cis fashion. Ester hydrolysis of

**50** gave the corresponding dihydroxy acid **51**, which on recrystallization was obtained as well-formed, colorless needles. This compound was again resistant to lactonization under several sets of conditions, but, finally, reaction with dicyclohexylcarbodiimide and *p*-toluenesulfonic acid in pyridine[108] gave a mixture of two diastereomeric lactones. Treatment of this mixture with lithium diisopropylamide followed by aqueous ammonium chloride resulted in epimerization, leaving just one hydroxylactone isomer **68**. Oxidation of the hydroxyl function with pyridinium chlorochromate[109] gave a product **69** [Eq. (19)] that appeared to be identical to a sample of natural quadrone supplied by Dr. R. L. Ranieri[8,9] on direct comparison by thin layer and gas–liquid chromatography. However, analysis of 300-MHz $^1$H NMR spectra revealed that the product **69** was not quadrone but in fact possessed the diastereomeric structure shown below. In turn, hydroxylactone **68** could be assigned the indicated structure, and the initially obtained mixture of diastereomeric hydroxylactones must have consisted of the epimeric compounds **68** and **68A** before treatment with base to give the single epimer **68**. Apparently, the lactonization of dihydroxy acid **51** produced epimer **68A** as the initial product, but being quite strained, this isomer underwent partial epimerization under the conditions of the lactonization. The strain of **68A** also explains the difficulties that were encountered in attempts to form lactones at earlier points in the synthetic pathway.




In order to confirm the various preceding stereochemical assignments once and for all, advantage was taken of the beautiful crystalline form in which dihydroxy acid **51** was obtained. A single-crystal X-ray structure determination was performed in collaboration with Professor Joseph W. Lauher at Stony Brook. The resulting ORTEP diagram for **51** is shown in Fig. 1 along with a standard line drawing for convenience in identifying each of the atoms (note the reversal of enantiomeric representation relative to the other drawings in this chapter). Clearly, the crucial conjugate addition/

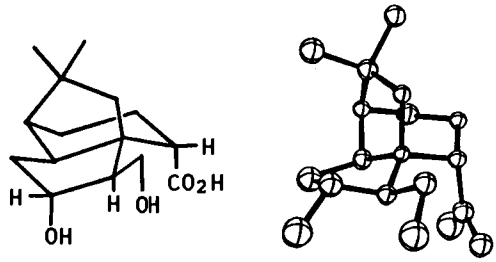



FIG. 1. Structure of dihydroxy acid **51** as determined by X-ray diffraction.

condensation sequence had occurred predominantly with net trans-addition to the bicyclo[3.3.0]oct-1-en-3-one **40**, and finally a firm stereochemical basis was provided for explaining several of the subsequent reactions performed in this synthesis.

The synthesis of quadrone was then completed rather straightforwardly. The primary hydroxyl group of **51** was protected as the acetate **52** (Scheme 7). This derivative was obtained in nearly quantitative yield as a sharp-melting crystalline solid and quite clearly as a single diastereomer according to $^1$H NMR analysis. Oxidation of the secondary hydroxyl group of **52** with pyridinium chlorochromate[109] was accompanied by elimination of the acetate group to give the exocyclic methylene cyclopentanone derivative **3**, subsequently isolated from natural sources and named terrecyclic acid A.[10,12,14,15] Recrystallization gave highly pure material having a $^1$H NMR spectrum identical to that of the same compound prepared by Danishefsky. As in the Danishefsky synthesis, heating pure **3** without solvent in a nitrogen-filled flask at 190–195°C for 5 minutes produced quadrone (**2**), which was identical to the natural material supplied by Dr. Ranieri[8,9] on direct comparison by TLC, GLPC, IR, $^1$H NMR, and MS.

The overall yield for the 16 steps of this synthesis was 0.7%, although hypothetically the yield could have been increased to 1.2% if the minor diastereomeric material **46A** from cis-conjugate addition/condensation had also been carried through the synthesis. The pathway permitted direct control of the relative configurations of four of the five stereogenic centers of quadrone, and the fifth was corrected by means of the acetate elimination/carboxylate addition sequence (**52** → **3** → **2**). Furthermore, this route allowed for complete regiochemical control in the functionalization of each of the rings of the quadrone system. In particular, the conjugate addition/condensation sequence for introduction of the elements of the δ-valerolactone ring avoided the regiochemical difficulties encountered by several others in functionalization of the cyclopentanone ring of quadrone.

## VI. Conclusion

The original objective of this research was the investigation of new methods for the synthesis of δ-valerolactones and α-pyrone derivatives in general. However, this work became focused in more specific directions as the result of the very timely report of the isolation and structure of quadrone and the subsequent adoption of this compound as a goal for total synthesis. Consequently, this research has had two important outcomes. One is that a synthetic pathway to quadrone was completed in which a reasonably high level of stereo- and regiochemical control was exercised. The second outcome is that these studies have successfully led to the development of several reactions that should be of general use and that may serve as leads for the exploration of yet further methods in synthetic organic chemistry.

As is very frequently the case in synthesis, this second outcome is probably the more important in the longer term. Synthetic organic chemists have demonstrated that they are able to synthesize ever-increasingly complex compounds, and a given compound such as quadrone may ultimately be synthesized by several groups of workers using several different routes. A given synthesis may have certain advantages over others, such as proceeding with better stereochemical control, having greater overall efficiency, or being more economical. However, these syntheses are often most significant when they contribute new knowledge of general use to the scientific community. Foremost among these contributions in many cases are new reactions that may be employed by others in unforeseen applications in the future.

### Acknowledgments

The author wishes to acknowledge, first of all, Drs. John Ponton, Walter K. Bornack, and Shripad S. Bhagwat, who as graduate students contributed their excellent talents and efforts in accomplishing the work that is described in this chapter. Special acknowledgement is made to Dr. Ponton also for his important contributions to the original design of the quadrone synthesis, to Drs. Anthony Marfat and Steven Brandt for their preliminary studies of early aspects of the new reactions, to Professor Joseph W. Lauher (SUNY at Stony Brook) for his assistance in the X-ray crystal structure determination, to Dr. R. L. Ranieri (W. R. Grace & Co.) for providing a sample of natural quadrone, and to Professor Samuel Danishefsky (Yale University) for providing spectroscopic data for synthetic quadrone and some of its precursors. The author also wishes to thank the National Institutes of Health, the National Science Foundation, the Petroleum Research Fund administered by the American Chemical Society, and the State University of New York at Stony Brook for providing the financial support for the several phases of this research.

### References

1. J. Ponton, P. Helquist, P. C. Conrad, and P. L. Fuchs, *J. Org. Chem.* **46,** 118 (1981).
2. S. A. Bal, A. Marfat, and P. Helquist, *J. Org. Chem.* **47,** 5045 (1982).
3. J. T. Carey, C. Knors, and P. Helquist, *J. Am. Chem. Soc.* **108,** 8313 (1986).

4. E. J. O'Connor, S. Brandt, and P. Helquist, *J. Am. Chem. Soc.* **109,** 3739 (1987).
5. D. J. Jakiela, P. Helquist, and L. D. Jones, *Org. Synth.* **62,** 74 (1984).
6. R. Connell, F. Scavo, P. Helquist, and B. Åkermark, *Tetrahedron Lett.* **27,** 5559 (1986).
7. L.-C. Yu and P. Helquist, *J. Org. Chem.* **46,** 4536 (1981).
8. G. J. Calton, R. L. Ranieri, and M. A. Espenshade, *J. Antibiot.* **31,** 38 (1978).
9. R. L. Ranieri and G. J. Calton, *Tetrahedron Lett.* p. 499 (1978).
10. A. B. Smith, III and J. P. Konopelski, *J. Org. Chem.* **49,** 4094 (1984).
11. K. Kon, K. Ito, and S. Isoe, *Tetrahedron Lett.* **25,** 3739 (1984).
12. D. E. Cane, Y. G. Whittle, and T.-C. Liang, *Tetrahedron Lett.* **25,** 1119 (1984).
13. D. E. Cane, Y. G. Whittle, and T.-C. Liang, *Bioorg. Chem.* **14,** 417 (1986).
14. M. Nakagawa, A. Hirota, H. Sakai, and A. Isogai, *J. Antibiot.* **35,** 778, 783 (1982).
15. A. Hirota, M. Nakagawa, H. Hirota, T. Takahashi, and A. Isogai, *J. Antibiot.* **39,** 149 (1986).
16. M. Nakagawa, H. Sakai, A. Isogai, and A. Hirota, *Agric. Biol. Chem.* **48,** 117 (1984).
17. M. Nakagawa, H. Sakai, A. Isogai, and A. Hirota, *Agric. Biol. Chem.* **48,** 2279 (1984).
18. S. Danishefsky, K. Vaughan, R. C. Gadwood, K. Tsuzuki, and J. P. Springer, *Tetrahedron Lett.* **21,** 2625 (1980).
19. L. A. Paquette, G. D. Annis, and H. Schostarez, *J. Am. Chem. Soc.* **104,** 6646 (1982).
20. S. D. Burke, C. W. Murtiashaw, and M. S. Dike, *J. Org. Chem.* **47,** 1349 (1982).
21. S. A. Monti and T. R. Dean, *J. Org. Chem.* **47,** 2679 (1982).
22. K. Cooper and G. Pattenden, *J.C.S. Perkin I* p. 799 (1984).
23. E. Piers, G. L. Jung, and N. Moss, *Tetrahedron Lett.* **25,** 3959 (1984).
24. A. B. Smith, III, B. A. Wexler, C.-Y. Tu, and J. P. Konopelski, *J. Am. Chem. Soc.* **107,** 1308 (1985).
25. P. F. Schuda, J. L. Phillips, and T. M. Morgan, *J. Org. Chem.* **51,** 2742 (1986).
26. D. H. Hua, W.-Y. Gung, R. A. Ostrander, and F. Takusagawa, *J. Org. Chem.* **52,** 2509 (1987).
27. P. J. De Clercq, *Tetrahedron* **37,** 4277 (1981).
28. S. Danishefsky, K. Vaughan, R. C. Gadwood, and K. Tsuzuki, *J. Am. Chem. Soc.* **102,** 4262 (1980).
29. S. Danishefsky, K. Vaughan, R. C. Gadwood, and K. Tsuzuki, *J. Am. Chem. Soc.* **103,** 4136 (1981).
30. W. K. Bornack, S. S. Bhagwat, J. Ponton, and P. Helquist, *J. Am. Chem. Soc.* **103,** 4647 (1981).
31. S. D. Burke, C. W. Murtiashaw, J. O. Saunders, and M. S. Dike, *J. Am. Chem. Soc.* **104,** 872 (1982).
32. A. S. Kende, B. Roth, P. J. Sanfilippo, and T. J. Blacklock, *J. Am. Chem. Soc.* **104,** 5808, (1982).
33. K. Takeda, Y. Shimono, and E. Yoshii, *J. Am. Chem. Soc.* **105,** 563 (1983).
34. R. H. Schlessinger, J. L. Wood, A. J. Poss, R. A. Nugent, and W. H. Parsons, *J. Org. Chem.* **48,** 1146 (1983).
35. J. M. Dewanckele, F. Zutterman, and M. Vandewalle, *Tetrahedron* **39,** 3235 (1983).
36. S. D. Burke, C. W. Murtiashaw, and J. A. Oplinger, *Tetrahedron Lett.* **24,** 2949 (1983).
37. S. D. Burke, C. W. Murtiashaw, J. O. Saunders, J. A. Oplinger, and M. S. Dike, *J. Am. Chem. Soc.* **106,** 4558 (1984).
38. C. Iwata, M. Yamashita, S. Aoki, K. Suzuki, I. Takahashi, H. Arakawa, T. Imanishi, and T. Tanaka, *Chem. Pharm. Bull.* **33,** 436 (1985); C. Iwata, K. Suzuki, S. Aoki, K. Okamura, M. Yamashita, I. Takahashi, and T. Tanaka, *Chem. Pharm. Bull.* **34,** 4939, 4947 (1986); C. Iwata, M. Yamashita, S. Aoki, K. Suzuki, H. Arakawa, and T. Tanaka, *Chem. Pharm. Bull.* **34,** 4947 (1986).

39. P. A. Wender and D. J. Wolanin, *J. Org. Chem.* **50,** 4418 (1985).
40. E. Piers and N. Moss, *Tetrahedron Lett.* **26,** 2735 (1985).
41. R. L. Funk and M. M. Abelman, *J. Org. Chem.* **51,** 3248 (1986).
42. P. Magnus, L. M. Principe, and M. J. Slater, *J. Org. Chem.* **52,** 1483 (1987).
43. W. Kreiser, *Nachr. Chem. Tech. Lab.* **29,** 868 (1981).
44. L. A. Paquette, *Top. Curr. Chem.* **119,** 97 (1984).
45. A. B. Smith, III, B. A. Wexler, and J. Slade, *Tetrahedron Lett.* **23,** 1631 (1982).
46. K. Kakiuchi, T. Nakao, M. Takeda, Y. Tobe, and Y. Odaira, *Tetrahedron Lett.* **25,** 557 (1984).
47. K. Kakiuchi, M. Ue, T. Tadaki, Y. Tobe, and Y. Odaira, *Chem. Lett.* p. 507 (1986).
48. G. Mehta, K. Pramod, and D. Subrahmanyam, *J.C.S. Chem. Commun.* p. 247 (1986).
49. T. Imanishi, M. Matsui, M. Yamashita, and C. Iwata, *Tetrahedron Lett.* **27,** 3161 (1986).
50. N. Ida, H. Koike, and A. Kanai, Jpn. Pat. 61, 78, 721 [86, 78, 721] (1986); *C.A.* **105,** 72682h (1986).
51. K. Kakiuchi, T. Tadaki, Y. Tobe, and Y. Odaira, *Chem. Lett.* p. 1565 (1985).
52. Y. Ohira, Jpn. Pat. 61, 227, 522 [86, 227, 522] (1986); *C.A.* **106,** 113541c (1987).
53. J. M. Beale, Jr., J. M. Hewitt, and J. P. Rosazza, *Enzyme Microb. Technol.* **6,** 543 (1984).
54. R. S. Matthews and J. K. Whitesell, *J. Org. Chem.* **40,** 3312 (1975).
55. D. E. Cane and T. Rossi, *Tetrahedron Lett.* p. 2973 (1979).
56. Y. Hayashi, S. Takahashi, H. Ona, and T. Sakan, *Tetrahedron Lett.* p. 2071 (1968).
57. J. Ponton, Ph.D. Thesis, State Univ. of New York at Stony Brook, 1980.
58. W. K. Bornack, Ph.D. Thesis, State Univ. of New York at Stony Brook, 1981.
59. S. S. Bhagwat, Ph.D. Thesis, State Univ. of New York at Stony Brook, 1983.
60. A. Marfat, unpublished results of Ph.D. thesis research, State Univ. of New York at Stony Brook, 1978.
61. S. Brandt, Ph.D. Thesis, State Univ. of New York at Stony Brook, 1979.
62. I. Kuwajima and Y. Doi, *Tetrahedron Lett.* p. 1163 (1972).
63. A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Am. Chem. Soc.* **98,** 567 (1976).
64. J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, *J. Am. Chem. Soc.* **95,** 7923 (1973).
65. J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.* p. 2599 (1973).
66. K. Iwai, M. Kawai, H. Kosugi, and H. Uda, *Chem. Lett.* p. 385 (1974).
67. A. G. Schultz and Y. K. Yee, *J. Org. Chem.* **41,** 4044 (1976).
68. H. Kotake, K. Inomata, S. Aoyama, and H. Kinoshita, *Chem. Lett.* p. 73 (1977).
69. B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.* **99,** 3101 (1977).
70. H. Paulsen and H. Bünsch, *Chem. Ber.* **111,** 3484 (1978).
71. A. A. Jaxa-Chamiec, P. G. Sammes, and P. D. Kennewell, *J.C.S. Chem. Commun.* p. 118 (1978).
72. S. Yamagiwa, N. Hoshi, H. Sato, H. Kosugi, and H. Uda, *J.C.S. Perkin I* p. 214 (1978).
73. Y. K. Yee, Ph.D. Thesis, Cornell Univ., Ithaca, New York, 1978.
74. Y. Takeuchi, Y. Makino, K. Maruyama, and E. Yoshii, *Heterocycles* **14,** 163 (1980).
75. K. Ogura, S. Furukawa, and G. Tsuchihashi, *J. Am. Chem. Soc.* **102,** 2125 (1980).
76. T. R. Hoye and M. J. Kurth, *J. Org. Chem.* **45,** 3549 (1980).
77. J. R. Donaubauer and T. C. McMorris, *Tetrahedron Lett.* **21,** 2771 (1980).
78. (a) T. Yoshida and S. Saito, *Chem. Lett.* p. 1587 (1982). (b) H. W. Hoppe, M. Kaiser, D. Müller, and P. Welzel, *Tetrahedron* **43,** p. 2045 (1987).
79. E. J. Corey and D. Enders, *Tetrahedron Lett.* p. 11 (1976).
80. L. J. Altman and S. L. Richheimer, *Tetrahedron Lett.* p. 4709 (1971).
81. H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.* **40,** 1460 (1975).
82. R. H. Wollenberg, Ph.D. Thesis, Harvard Univ., Cambridge, Massachusetts, 1976.
83. Solutions of anhydrous formaldehyde were prepared by a modification of the procedure of

M. Schlosser and D. Coffinet, *Synthesis* p. 380 (1971). Paraformaldehyde (200 g, 66.7 mmol) was suspended in THF (60 mL) under nitrogen, and boron trifluoride etherate (20 drops) was added. The vigorously stirred mixture was heated in an oil bath at 80–85°C, and the resulting vapor was passed through a well-insulated distillation apparatus (no cooling water was used) and was condensed at −78°C in a receiver flask having a side arm equipped with a rubber septum. This operation required about 1.5 hours. The resulting solution, which was assumed to be about 0.8 *M* in formaldehyde, was prepared immediately before use and was transferred into the subsequent reaction vessel with a dry ice-cooled syringe.

84. Y. Kita, J. Segawa, J. Haruta, H. Yasuda, and Y. Tamura, *J.C.S. Perkin I* p. 1099 (1982).
85. L. A. Paquette and M. K. Scott, *J. Am. Chem. Soc.* **94,** 6751 (1972).
86. B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.* **95,** 6840 (1973).
87. G. Büchi and H. Wuest, *J. Org. Chem.* **34,** 1122 (1969).
88. P. H. Begemann, V. Lamberti, and W. T. Weller, *Recl. Trav. Chim. Pays-Bas* **86,** 1335 (1967).
89. D. E. Ryono and G. M. Loudon, *J. Am. Chem. Soc.* **98,** 1889 (1976).
90. R. V. Stevens, R. E. Cherpeck, B. L. Harrision, J. Lai, and R. Lapalme, *J. Am. Chem. Soc.* **98,** 6317 (1976).
91. M. Miyashita, T. Yanami, and A. Yoshikoshi, *J. Am. Chem. Soc.* **98,** 4679 (1976).
92. R. M. Jacobson, R. A. Raths, and J. H. McDonald, *J. Org. Chem.* **42,** 2545 (1977).
93. J. E. Baldwin, *J.C.S. Chem. Commun.* p. 734 (1976).
94. H. Paul and I. Wendel, *Chem. Ber.* **90,** 1342 (1957).
95. See reference 91 for this and related aldol cyclizations.
96. T. Sakan, A. Fujino, F. Murai, A. Suzui, and Y. Butsugan, *Bull. Chem. Soc. Jpn,* **33,** 1737 (1960); A. Suzui, Ph.D. Thesis, Osaka City Univ., 1959; T. Sakan, personal communication, Inst. Food Chem., Osaka, 1979.
97. M. J. Begley, K. Cooper, and G. Pattenden, *Tetrahedron Lett.* **22,** 257 (1981).
98. D. K. Klipa and H. Hart, *J. Org. Chem.* **46,** 2815 (1981).
99. B. M. Trost and D. P. Curran, *J. Am. Chem. Soc.* **102,** 5699 (1980).
100. D. Seebach and M. Teschner, *Chem. Ber.* **109,** 1601 (1976).
101. B. M. Trost and G. S. Massiot, *J. Am. Chem. Soc.* **99,** 4405 (1977).
102. E. Piers, B. Abeysekera, and J. R. Scheffer, *Tetrahedron Lett.* p. 3279 (1979).
103. E. Piers, personal communication, Univ. of British Columbia, 1979.
104. For leading references, see M. Suzuki, A. Yanagisawa, and R. Noyori, *J. Am. Chem. Soc.* **107,** 3348 (1985).
105. J. Schreiber, M. Haag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **10,** 330 (1971).
106. R. A. Holton, *J. Am. Chem. Soc.* **99,** 8083 (1977).
107. K. M. Sun, B. Fraser-Reid, and T. F. Tam, *J. Am. Chem. Soc.* **104,** 367 (1982).
108. K. Holmberg and B. Hansen, *Acta Chem. Scand., Ser. B* **B33**, 410 (1979).
109. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.* p. 2647 (1975).

*Chapter 6*

# THE TOTAL SYNTHESIS OF SAXITOXIN

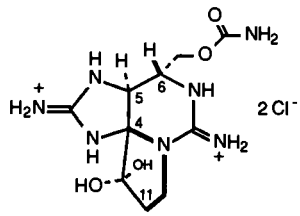
*Peter A. Jacobi*
*Department of Chemistry*
*Wesleyan University*
*Middletown, Connecticut*



## I. Introduction

### A. A Colorful History

Saxitoxin (**1**), the paralytic agent of the Alaskan butter clam *Saxidomus giganteus*, has a long and notorious history as one of the most toxic of the nonprotein poisons known (Fig. 1).[1-4] With an $LD_{50}$ in mice of ~8 $\mu$g/kg, it




Saxitoxin (1)

FIG. 1

has been estimated that a single dose of 0.2–1.0 mg would prove fatal in humans. It is thus about 100 times more poisonous than strychnine, 200 times more potent than mushroom toxins, almost 1000 times more deadly than a typical synthetic nerve gas, and 2000 times more toxic than sodium cyanide.[5]

Saxitoxin was first isolated in the pure state in 1957 by Schantz *et al.* from clams and mussels collected on the west coast of the United States,[6] and more recently from clams collected on the east coast which were feeding on certain marine dinoflagellates.[7] When conditions of temperature and light are right, these organisms reproduce (or bloom) so rapidly as to discolor the sea, producing a so-called red-tide. Shellfish, especially clams and mussels, feeding on the dinoflagellates at this time become poisonous to humans, causing paralytic shellfish poisoning. This poisoning is due to **1** being ingested by the shellfish, which is stored for weeks in mussels and for many months in clams. Symptoms of poisoning in humans begin with a numbness in the lips, tongue, and fingertips within a few minutes after ingestion. This is rapidly followed by weakness in the legs, arms, and neck, which progresses to a general muscular incoordination. Death occurs from respiratory paralysis.

With such properties, it is perhaps not surprising that the Central Intelligence Agency (CIA) began experimenting with saxitoxin in the 1950s, reportedly using the poison in suicide pills provided to its agents (including U-2 pilot Francis Gary Powers). The agency is also said to have developed dart guns and other means to deliver the poison to troublesome guard dogs when entering embassies or other buildings. In 1970, President Nixon ordered the CIA to destroy its supply of saxitoxin under the terms of a United Nations agreement to ban biological weapons. But in 1975, CIA Director William Colby revealed to Congress that 10.9 g of saxitoxin, isolated in secrecy over a period of 10 years, remained in its laboratories in downtown Washington, D.C. Since the CIA held nearly the entire world's

supply of saxitoxin, the scientific community was relieved when the agency decided to distribute the substance to medical researchers under the auspices of the National Institutes of Health.

## B. Mode Of Action And Importance In Medical Research

Saxitoxin acts by selectively blocking the entrance to sodium channels in neuron membranes, thereby preventing the transient $Na^+$ ion conductance increases associated with action potentials.[8] The presence of **1** appears to have no effect on $K^+$ or $Cl^-$ ion currents or on acetylcholine release. The blockage of the sodium channel, although very strong, is also totally reversible, and in fact **1** and common local anesthetics can act synergistically to give complete, long-lasting, and reversible nerve blocks at very low concentration.[9] Of greater importance, however, the toxin's physiological behavior makes it ideally suited for use as a probe of normal and afflicted tissue, and it is an excellent tool for the study of synaptic and neuromuscular transmissions.[10] Medical researchers have used this agent for the labeling, characterization, and isolation of sodium channel components, which has opened new avenues in the study of various nerve disorders.[11]

Establishing a structure for **1** was complicated by the nonvolatile and noncrystalline nature of its salts. Extensive chemical degradations were carried out by Rapoport at Berkeley,[12] but the correct structure was determined in 1975 by X-ray analysis of crystalline derivatives, carried out independently by Clardy and Schantz[13] and Rapoport.[14] Since compound **1** has both an unusual structure and potential medical importance, it became an attractive target for synthesis as soon as its structure was firmly established.

## C. Early Encounters

My initial interest in the structure and synthesis of **1** arose out of a change meeting with Professor Yoshito Kishi in the late summer of 1972. At that time, Professor Kishi was a visiting faculty member at Harvard, and he was introduced to me as a person who might be helpful in obtaining a postdoctoral fellowship with R. B. Woodward. On his blackboard was a drawing of the most recently proposed structure for **1**,[12] and he explained to me in some detail why the structure in question could not be reconciled with the observed $pK_a$ values of 8.24 and 11.60. I found his arguments to be convincing and I made a mental note to keep track of any future developments in this area. As it happened, three years later I was in a position to write a modest research proposal to the Petroleum Research Fund when the

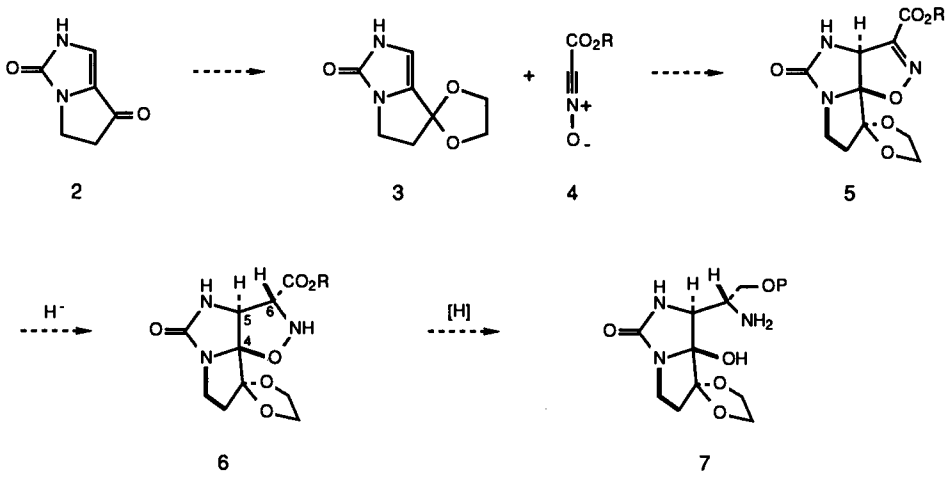
correct structure for **1** was announced.[13,14] The synthesis of **1** would be my first project as an assistant professor at Wesleyan, to be initiated by Mr. Allen Brownstein.

## II. The Nitrile Oxide Route to Saxitoxin

### A. The Strategy in Brief

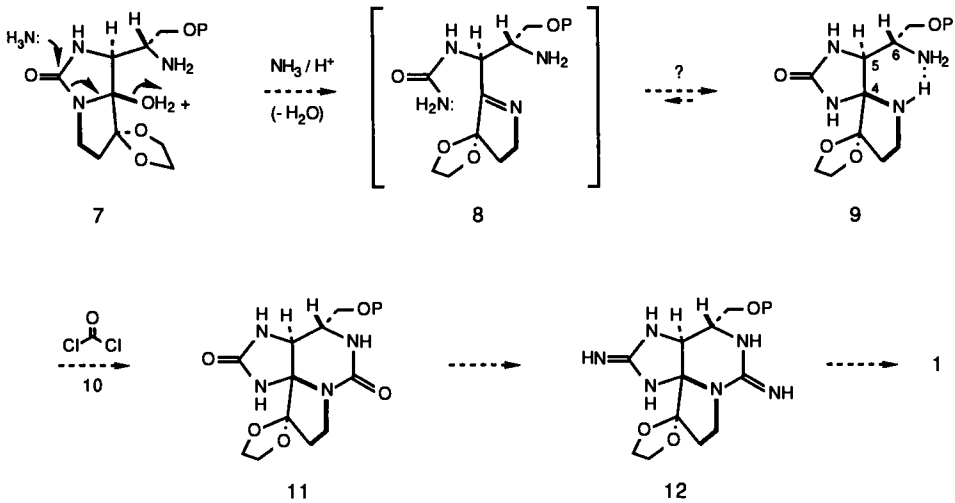
It is interesting to note that every carbon atom in **1**, with the exception of C-11, is directly bonded to a heteroatom. This relationship suggested many possibilities for both bond making and bond breaking, and it had an important influence on our retrosynthetic analysis. In addition, three structural features of **1** required special consideration. First, it was clear from the outset that both guanidine groups would have to be introduced at the very last stage of the synthesis, since there could be little hope of carrying out selective transformations in the presence of such highly polar functionalities. Second, the unusual hydrated ketone at C-12 would have to be carried through most of the synthesis in protected form. And finally, a major challenge in the synthesis of **1** resided in the control of relative stereochemistry at C-4, C-5, and C-6. From the X-ray data it was known that the carbamate functionality at C-6 occupied a pseudoaxial position,[13] and therefore the requisite $\alpha$-configuration could not be established under thermodynamic control.

As one strategy, it occurred to us that an attractive route to **1** might be developed through the intermediacy of the isoxazoline derivative **5**, itself derivable via dipolar addition of the nitrile oxide **4** to the pyrroloimidazolone **3** (Scheme 1). It was our premise, in particular, that the stereochemical relationship between C-5 and C-6 might be more efficiently controlled in **5**, as compared to **1**, because of its well-defined concave and convex surfaces (bicyclo[3.3.0] versus bicyclo[4.3.0] ring system). This geometric bias might be exploited in either of two ways. First, it seemed plausible that hydride reduction of **5** might be governed by initial complexation at the $\beta$-face of the imidazolone ring, thereby producing the desired stereoisomer **6** under kinetic control. And second, if kinetic control was impractical, we were confident that the $\alpha$-configuration at C-6 would be favored at thermodynamic equilibrium. Thus, the "unnatural" configuration at C-6 not only would require that the ester group be confined to a highly concave surface but also would lead to strongly eclipsing interactions between the substituents at C-5 and C-6 (saxitoxin numbering). Finally, reductive modification of **6** might then produce the hemiaminal species **7**, in which the stereogenic centers at C-5 and C-6 had been secured.

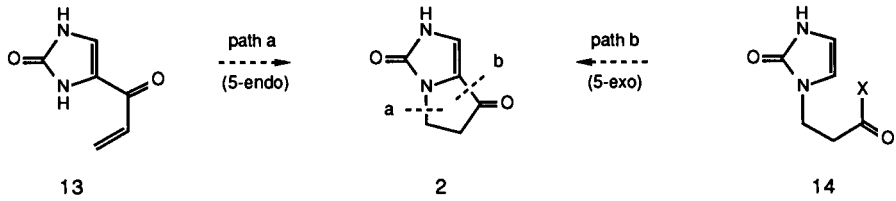



SCHEME 1

It was our intention, now, that **7** might be directly converted to the spirocyclic pyrrolidine **9** by a sequence of steps involving acid-catalyzed fragmentation to afford the open-chain imine **8**, followed by intramolecular capture of the newly produced urea (Scheme 2). This transformation would generate the remaining stereogenic center at C-4, and at first glance it might appear to be somewhat ambiguous. One could argue, for instance, that such




SCHEME 2




13 2 14

FIG. 2

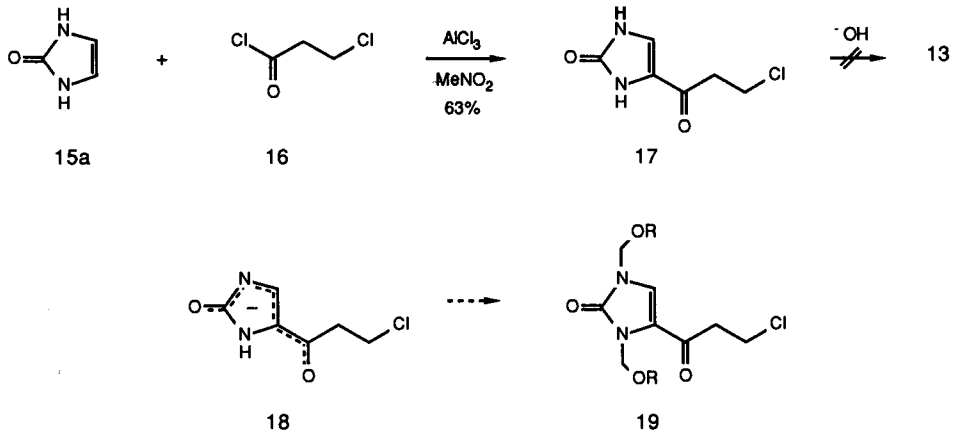
a process would most likely proceed under equilibrium control and that many products, including the C-4 epimer of **9**, might be formed. However, it was our hope that **9** might represent a "thermodynamic well" along the reaction pathway, since it should derive considerable stabilization from the hydrogen bonding indicated. Once in hand, ring closure of **9** with phosgene (**10**) would complete the synthesis of the perhydropurine **11**, which embodies the entire carbon skeleton of saxitoxin (**1**) with all of its stereogenic centers. The remaining steps necessary for the conversion of **11** to **12**, and finally to **1**, appeared to be straightforward.

In order to test this strategy, it was first necessary to devise an efficient synthesis of the pyrroloimidazolone starting material **2**, and as summarized below, two routes were explored to accomplish this goal (Fig. 2).

## B. Path A. To The Starting Pyrroloimidazolone: Floundering On "Baldwin's Rules"

We initially envisioned that the desired pyrroloimidazolone **2** might be prepared by an intramolecular Michael addition of the imidazolone-enone **13** (path a), itself derived from a suitably functionalized ketone. Toward this end, we eventually found that 4-imidazolin-2-one (**15a**) could be cleanly converted to the $\beta$-chloroketone **17** by Friedel–Crafts acylation with 3-chloropropionyl chloride (**16**) (Scheme 3).[15] Interestingly, however, **17** was completely stable under the strongly alkaline conditions which we expected would bring about elimination to **13**. With hindsight, this result can be rationalized by the fact that initial deprotonation at N-1 would produce the highly stabilized vinylogous imide anion **18**, and subsequent elimination by way of either an ElcB or E2 mechanism would then be energetically unfavorable.

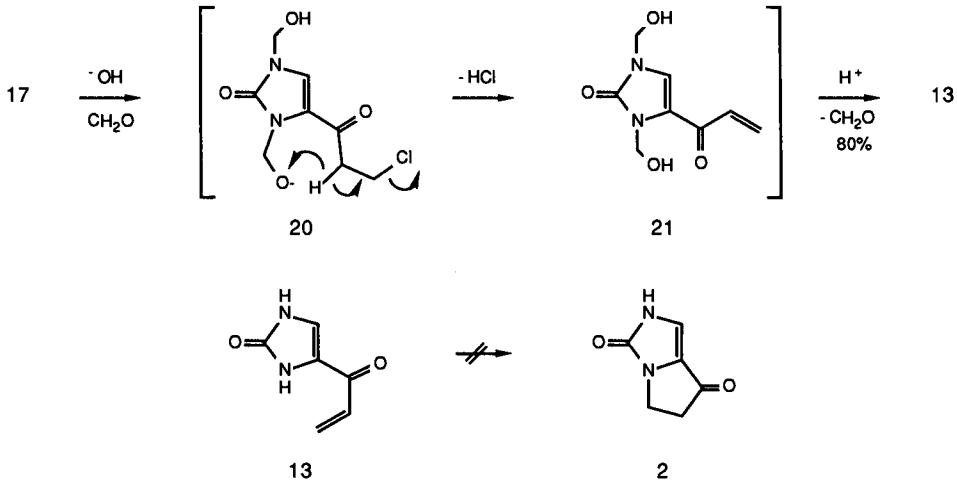
In order to circumvent this difficulty, we next focused our attention on the preparation of *N*-methylol derivatives of general structure **19** (R = H, alkyl), in which both N–H bonds would be protected. Intermediates of this type have been widely reported in the literature,[16] and they are frequently prepared by base-catalyzed condensation with formaldehyde followed by acidification in anhydrous alcohol. In the present case, however, we were




SCHEME 3

delighted to find that alkaline solutions of **17** were instantly converted to the elusive enone **13** in the presence of a slight excess of aqueous formaldehyde (Scheme 4). This transformation most likely proceeds through the intermediacy of the bis-*N*-methylol **20**, and it is tempting to postulate that elimination is facilititated by intramolecular proton abstraction. The resulting enone **21** would then afford **13** and formaldehyde upon workup.

With ample quantities of **13** thus secured, experiments to effect the ring closure of **13** to **2** were undertaken with some degree of confidence. Despite our most intensive efforts, however, this transformation could not be

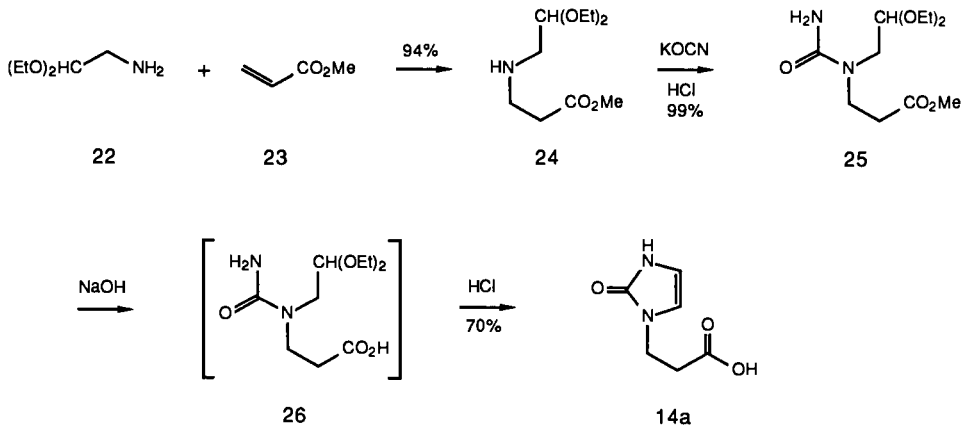



SCHEME 4

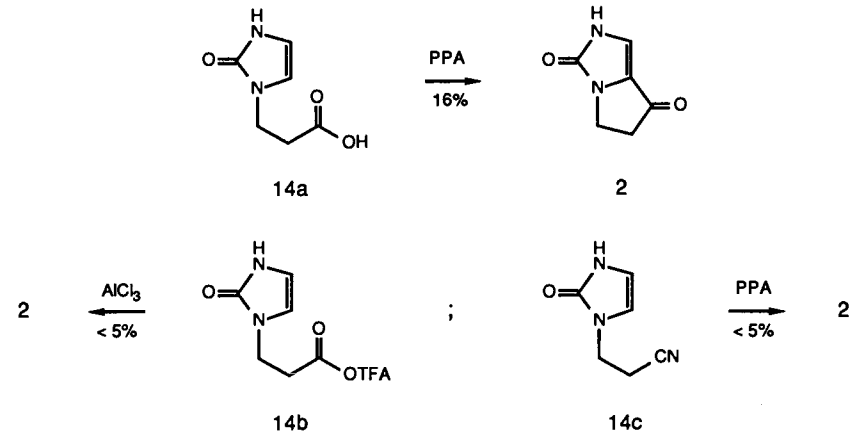
accomplished. Why should such a simple reaction present such an insurmountable barrier? The answer was put forward on January 30, 1976 by Professor Jack E. Baldwin, then of MIT, during the course of a seminar he was presenting at Wesleyan. On this occasion, Professor Baldwin spoke on his observations pertaining to nucleophilic trajectory and the relative facility of ring closure at atoms of differing geometry. These observations, which later became famous as "Baldwin's rules,"[17] provided a timely explanation for our frustrations in the conversion of **13** to **2**, since the desired transformation would require an unfavorable 5-endo-trigonal ring closure.[17b]

## C. Path B. A Modest Success

During the course of the work described above, we were also actively engaged in experiments directed toward the synthesis of imidazolone-acid derivatives of general structure **14** (see Fig. 2). As previously noted, intermediates of type **14** might be converted to **2** via an intramolecular Friedel–Crafts acylation (path b), and we drew encouragement from the fact that this transformation could (now!) be classified as a favorable 5-exo-trigonal ring closure.[17b] In the event, we were pleased to find that the parent acid **14a** could be prepared in excellent overall yield following the route outlined in Scheme 5. Thus, Michael addition of aminoacetaldehyde diethyl acetal (**22**) to methyl acrylate (**23**) gave a 94% yield of the desired adduct **24**, which on treatment with aqueous potassium cyanate in 6 *N* HCl was quantitatively converted to the ureide derivative **25**. Alkaline hydrolysis of **25** to the corresponding acid **26**, followed by *in situ* aldehyde deprotection and cyclization, then gave the target acid **14a**.




Scheme 5




SCHEME 6

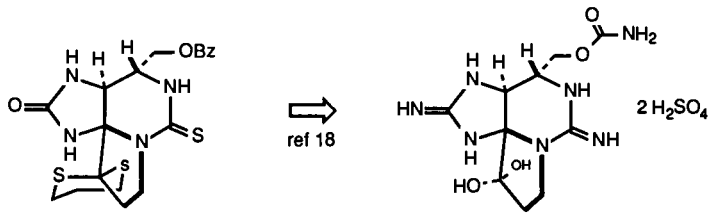
Surprisingly, however, we were unable to effect the cyclodehydration of **14a** to **2** in preparatively useful quantities. Reagents investigated for this purpose included $ZnCl_2$, fuming sulfuric acid, fluorosulfonic acid, hydrofluoric acid, $NaAlCl_4$, and "polyphosphate ester" (PPE), all of which have been utilized as effective cyclodehydration agents in related transformations. In the present case, none of the desired product **2** could be detected. Eventually, limited success was achieved with hot polyphosphoric acid (PPA), which afforded a 16% yield of **2** accompanied by extensive decomposition. Trace amounts of **2** were also obtained from the mixed anhydride **14b** and the nitrile analog **14c** (Scheme 6). Compound **14c** was prepared from **22** and acrylonitrile in a manner similar to that described for **14a**.

In summary, the synthesis of the key pyrroloimidazolone derivative **2** proved to be a greater challenge than anticipated, and we reluctantly concluded that the nitrile oxide route to saxitoxin (**1**) would have to be abandoned. Fortunately, however, new developments in the preparation and chemistry of a class of 1,3-dipoles known as azomethine imines opened the way for a related approach to **1** which eventually proved to be successful.

## III. The Azomethine Imine Route to Saxitoxin

### A. A New Strategy Emerges

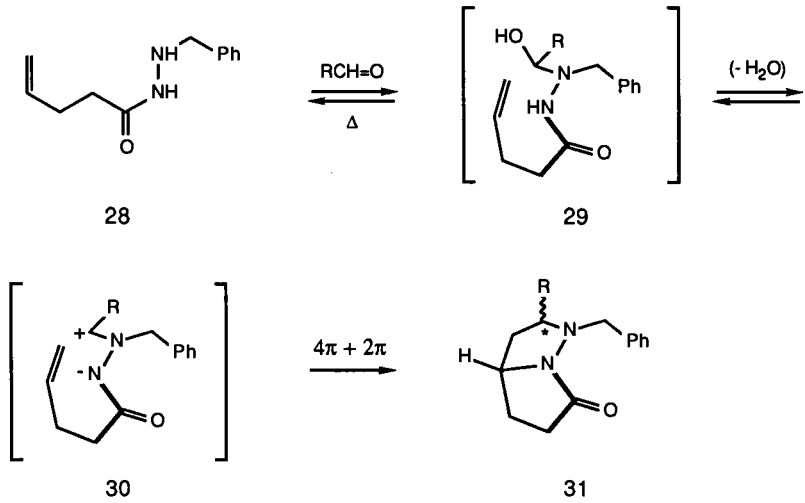
Early in 1977, two publications appeared which had a critical impact on our program to synthesize saxitoxin (**1**). One of these was the pioneering paper by Kishi *et al.* which described the first total synthesis of **1** and




27 1

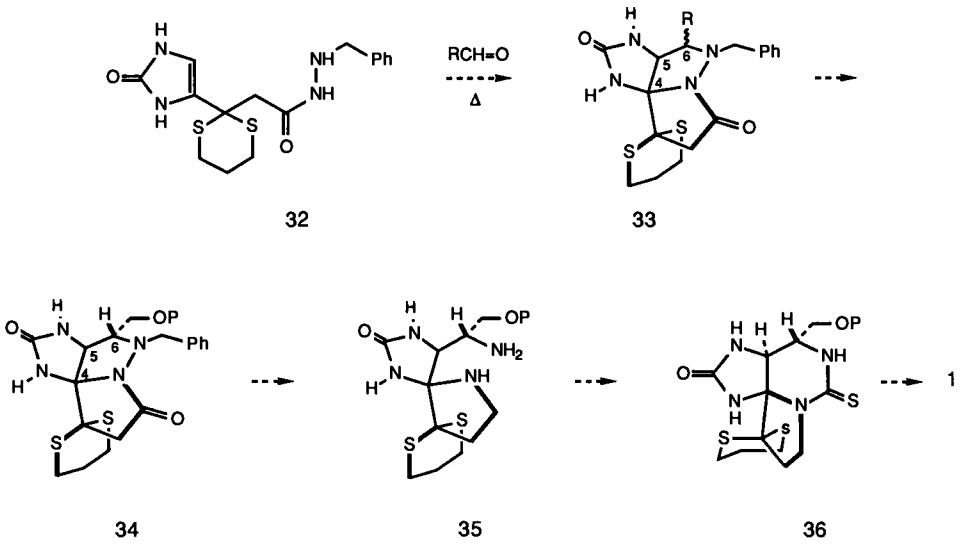
FIG. 3

provided invaluable assistance in charting our own course.[18] As indicated, a key intermediate in the Kishi synthesis of **1** was the thiourea–dithiane derivative **27** (Fig. 3). The second paper, by Professor Wolfgang Oppolzer, was a review article surveying "Intramolecular [4 + 2] and [3 + 2] Cycloadditions in Organic Synthesis," and it included many examples from the author's elegant studies of intramolecular 1,3-dipolar cycloadditions.[19a] In particular, we were intrigued by his finding that the vinylhydrazide **28** could be smoothly converted to azomethine imines of type **30**, which, without isolation, underwent an intramolecular 1,3-dipolar cycloaddition to give adducts of type **31** in excellent overall yield (Fig. 4).[19b] The significance of this work in relation to our own studies was readily apparent. By analogy, one might reasonably expect that the closely related hydrazide **32** would afford adducts of general structure **33** on condensation with aldehydes, and




28 29 30 31

FIG. 4



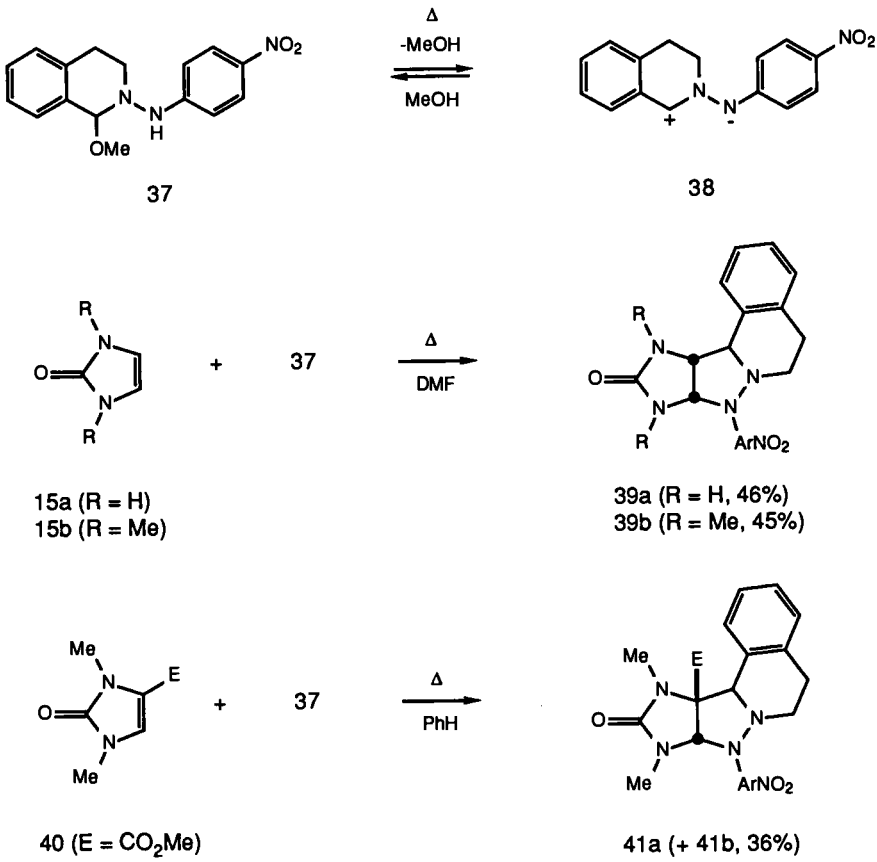

SCHEME 7

we were confident that **33** could be further elaborated to pyrazolidine derivatives of type **34** using standard methodology (Scheme 7). Compound **34** contains all of the stereogenic centers of **1** in their proper relative configuration, and it became the pivotal target in our second strategy for the synthesis of **1**. Once in hand, there was ample precedent for the sequential reductive cleavage of **34** to **35** under nonepimerizing conditions,[20] and it seemed likely that **35** could be directly converted to thiourea derivatives of type **36** by bridging with thiocarbonyldiimidazole.[21] If such were the case, then our projected synthesis might converge with that of Kishi *et al.* (cf. **27** in Fig. 3).[18]

At the outset, however, there were two questions which remained to be settled. First, we could find no information pertaining to the reactivity of imidazolones as 1,3-dipolarophiles; and second, although **34** was clearly in the thermodynamically most favored configuration (*vide supra*), the stereochemical outcome of such dipolar additions under kinetic control was far from certain (cf. C-6 in **33**).[19b]

## B. Intermolecular Trials

For practical reasons, our initial studies were carried out with intermolecular trials, where advantage could be taken of the ready availability of various 1,3-dipolar species. Thus, dihydroisoquinoline **37** served as a stable, convenient, and neutral source of the highly reactive azomethine imine




SCHEME 8

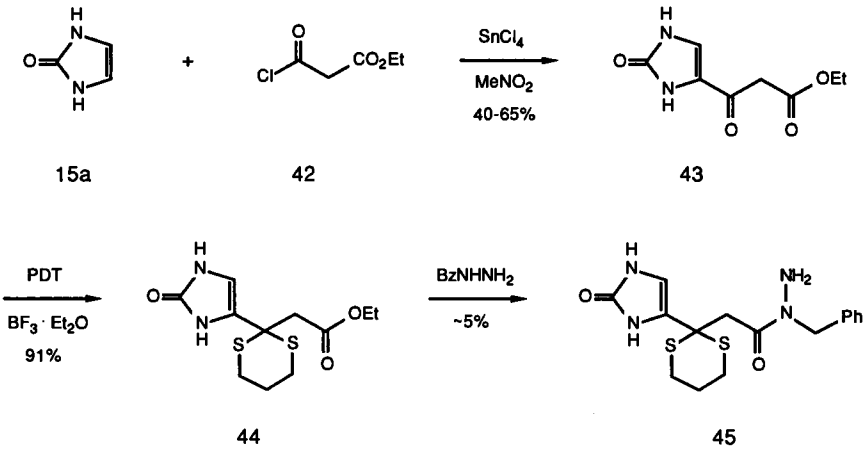
**38**[22,23] and model studies were undertaken with 4-imidazolin-2-one (**15a**), *N*,*N*-dimethyl-4-imidazolin-2-one (**15b**), and the methyl ester **40** in a variety of polar and nonpolar solvents (Scheme 8). As indicated, **39a** and **39b** were formed in moderate yield after chromatographic purification, while the less electron-rich **40** afforded a 36% combined yield of regioisomers **41a** and **41b** in a 4 : 1 ratio.

Large solvent effects were observed in all of these model studies. Both **15a** and **15b** gave appreciable amounts of **39** ony in dipolar aprotic solvents, while **40** reacted exclusively in benzene. In solvents other than noted for each individual case, unreacted dipolarophile and dimeric material derived from **38** were the only products recovered. Many examples of such solvent effects have been reported,[24] and Kadaba has postulated that they are a result of specific interactions between a partially charged transition state and solvent

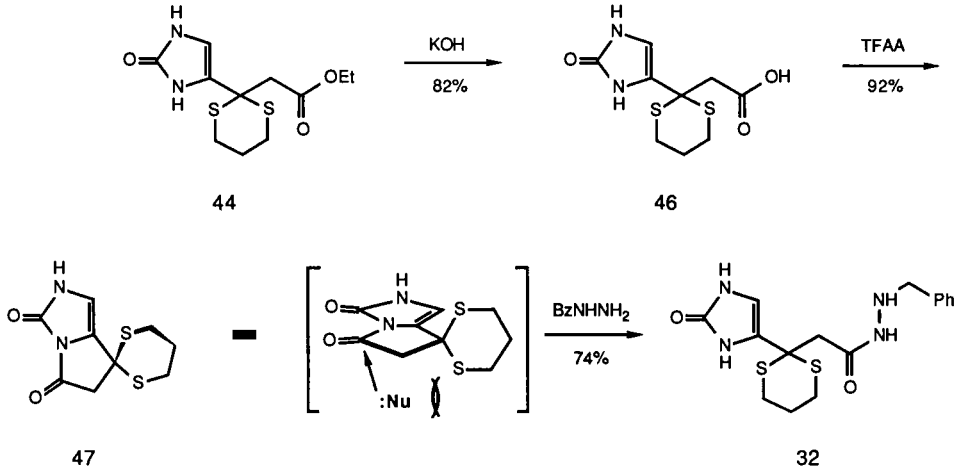
molecules.[25] For our purposes, however, the primary importance of these model studies lay in the demonstration that imidazolones can function as dipolarophiles with azomethine imines, and they also provided insight into the possible experimental conditions and solvents required in our intramolecular studies.

## C. Synthesis Of The Key Hydrazide 32

We next turned our attention to the question of stereochemical control, a factor which would be of crucial importance in the preparation of **34** but which was not investigated in our intermolecular studies. In order to address this issue, it was first necessary to develop a practical synthesis of the requisite hydrazide **32**, and our initial experiments in this direction were encouraging. Thus, 4-imidazolin-2-one (**15a**) could be cleanly acylated with ethyl malonyl chloride (**42**), and the resulting ketone **43** was readily protected to afford the dithiane-ester **44** (Scheme 9). Unfortunately, however, all attempts at the direct conversion of **44** to **32** led to complex mixtures of products containing only traces of the desired **32** (<1%), in addition to larger amounts (~5%) of the regioisomeric hydrazide **45** (**32**:**45** ≈ 1 : 10). This failure was partly due to the unreactive nature of **44**, which rapidly decomposed under the forcing conditions required for ester aminolysis (a strong propanedithiol odor was evident). Of equal importance, however, the regiochemical outcome of this reaction would have to be reversed, such that primary acylation would predominate over the normally more favored pathway involving acylation at the secondary nitrogen.[26]

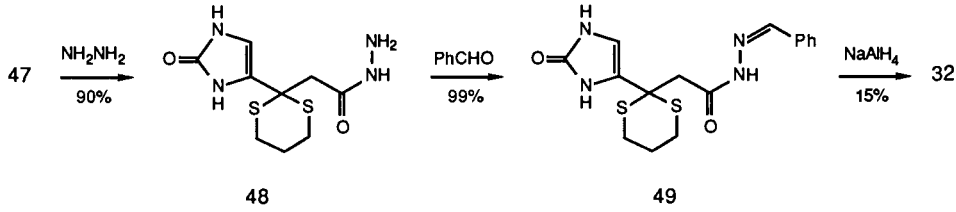



Scheme 9




SCHEME 10

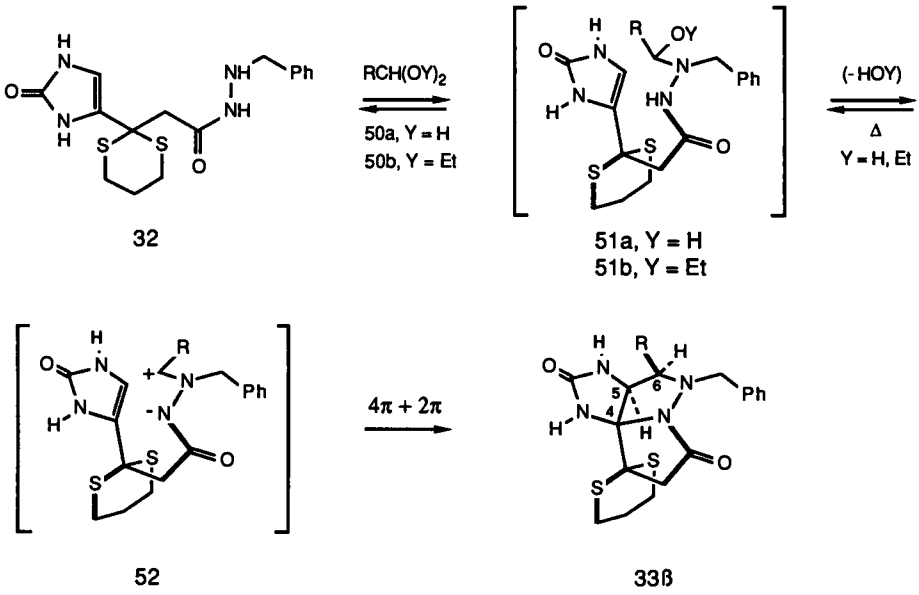
An efficient solution to these difficulties was eventually uncovered in the form of the bicyclic imide **47**, which was readily prepared from **44** by hydrolysis to the dithiane-acid **46** followed by cyclodehydration (Scheme 10). There could be little doubt that **47** would function as an exceedingly reactive acylating agent. Furthermore, we reasoned, in this case the nucleophilic trajectory of benzyl hydrazine *must* pass in close proximity to the spirocyclic dithiane ring,[17] leading, in turn, to considerable steric crowding and possibly to a more favorable outcome in the regiochemical course of reaction. In agreement with this hypothesis, we were pleased to find that **47** and benzyl hydrazine reacted smoothly at ambient temperature, and the desired isomer **32** separated cleanly from the reaction mixture. That **32** was indeed in hand was unequivocally demonstrated by direct comparison with the material obtained by the alternative, but far less efficient, synthesis outlined in Scheme 11.




SCHEME 11

## D. Intramolecular Cycloadditions. A Stereospecific Process

We had considerable difficulty in our initial attempts at generating dipolar species of type **52** (Scheme 12). Under the usual conditions, for example, we could find no evidence for the desired reaction between **32** and benzaldehyde (**50a**, R = phenyl), obtaining in every case a quantitative return of starting materials (Ph—CH=O, refluxing toluene, continuous removal of water).[19] Furthermore, this outcome was unaffected by a variety of modifications in the experimental parameters, and we found a similar lack of reactivity with other aldehydes which had previously been employed with marked success in simpler model systems.[19] A contributing factor in these difficulties was the highly insoluble nature of **32** in all but the most polar of organic solvents. However, solubility properties alone were probably not a crucial factor, since we had previously found that equally insoluble derivatives readily combined, in an *inter*molecular fashion, with suitably generated azomethine imines (cf. Scheme 8). More likely, this lack of reactivity was due to an extremely unfavorable equilibrium between **32** and **51a**, which would have an inhibiting effect on the required 1,3-elimination of water. In order to circumvent this problem, we focused our attention next on the potential utility of aminoacetals of type **51b**, in which an equilibrium process of the type suggested for **51a** would be untenable (cf, also **37** in Scheme 8).




32 51a, Y = H 51b, Y = Et

52 33ß

Scheme 12

In fact, we were pleased to find that excellent yields of adducts of general structure **33β** could be obtained under conditions which strongly implicate the intermediacy of aminoacetals **51b**.[27] As a typical example, a mixture of 1.0 equivalent of hydrazide **32** and 1.25 equivalents of benzaldehyde diethyl acetal (**50b**, R = phenyl) was heated at 80°C, with vigorous stirring, in freshly distilled DMF containing a catalytic amount of TsOH (careful exclusion of moisture). Solution was complete within 1 hour and after a total of 5 hours the reaction was concentrated and chromatographed to afford an 83% yield of adduct **33β-1** (R = phenyl) as a colorless crystalline solid. Similarly prepared were the following (compound, R, % yield): **33β-2**, *p*-methoxyphenyl, 90%; **33β-3**, *p*-methylphenyl, 91%; **33β-4**, *p*-nitrophenyl, 52%; **33β-5**, 2-furyl 68%; **33-β-6**, 2-thienyl, 80%; **33β-7**, H, 64%; **33β-8**, benzyl, 17%. All of these reactions were highly dependent on the nature of the solvent, proceeding only moderately well in acetonitrile and not at all in glyme or less polar solvents.[25] Furthermore, they failed completely in the absence of TsOH. We believe that TsOH serves mainly in the capacity of bringing about an initial ionization of the aldehyde acetal, which is subsequently trapped by the strongly basic nitrogen of hydrazide **32** to give **51b**. In agreement with this hypothesis, the relative rates for these conversions varied in a manner fully consistent with the ability of R to stabilize a developing cationic center (i.e., **33β-2, 33β-5 > 33β-1, 33β-3, 33β-6 > 33β-7 > 33β-4**). Aliphatic acetals either failed to react under these conditions or gave much lower yields of adducts (17% with phenylacetaldehyde diethyl acetal to give **33β-8**).

The stereochemical assignments for these adducts followed readily from their highly characteristic NMR spectra, which invariably contained two features that are worthy of special comment. One of these is the extremely low field of absorption exhibited by $H_5$ (4.9–5.3 ppm), which undoubtedly derives from the strongly deshielding environment provided by a proximate dithiane ring. In this regard, it is interesting to note that a similar effect is operative in saxitoxin (**1**) itself ($H_5$; 4.77 ppm).[13] Second, in every case the observed coupling between $H_5$ and $H_6$ was in full accord with an expected dihedral angle of approximately 40° ($J$ = 4.8–5.2 Hz). For a representative example, **33β-1**, these assignments were completely verified by single-crystal X-ray analysis, and in no case could we detect a measurable quantity of adduct having the "natural" configuration at C-6.

The extraordinary selectivity of these reactions, although not predicted, can be readily understood on the basis of severe nonbonded interactions in exo transition state **A** (Fig. 5). As indicated, the required trans relationship between $H_5$ and $H_6$ is rendered highly unlikely by concomitant eclipsing interactions between R and R′, and as a result, *path b* becomes the reaction route of choice. Having arrived at this juncture, there were two

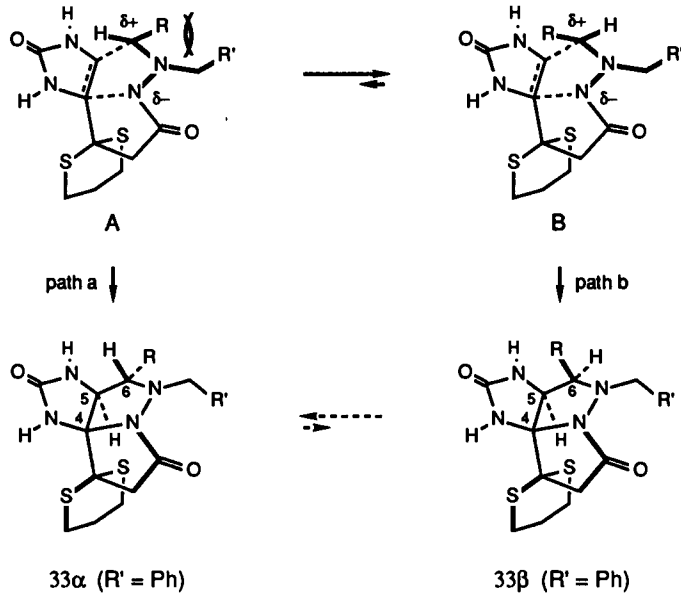



FIG. 5

possible means of altering the undesired stereochemical outcome. One of these would involve a modification of the 1,3-dipolar addition process such that kinetic control might lead directly to adducts of proper stereochemistry. In principle, at least, this goal might be achieved either by drastically reducing the steric bulk of both R and R′ or by joining together R and R′ in such a fashion as to ensure the necessary trans relationship between $H_5$ and $H_6$ (cf. path a, Fig. 5). Alternatively, an epimerizable group at C-6 should allow for a facile thermodynamic equilibration to the more stable isomer **33α**. Each of these approaches was explored in turn.

## E. Kinetically Controlled Processes

In a noteworthy series of papers, Grigg *et al.* have described the tautomeric interconversion of phenylhydrazones of type **53** with azomethine imines **54**, the latter materials being efficiently trapped with *N*-phenylmaleimide (NPMI) to afford pyrazolidines of general structure **55** (Fig. 6).[28] These results suggested that a similar equilibrium might be established between the benzyloxyhydrazone **56**, itself derived in 89% yield by condensation of hydrazide **48** with benzyloxyacetaldehyde, and the azomethine imine **57** (Scheme 13). If such were the case, then steric interactions in the transition state leading to cycloaddition might be sufficiently minimized that a

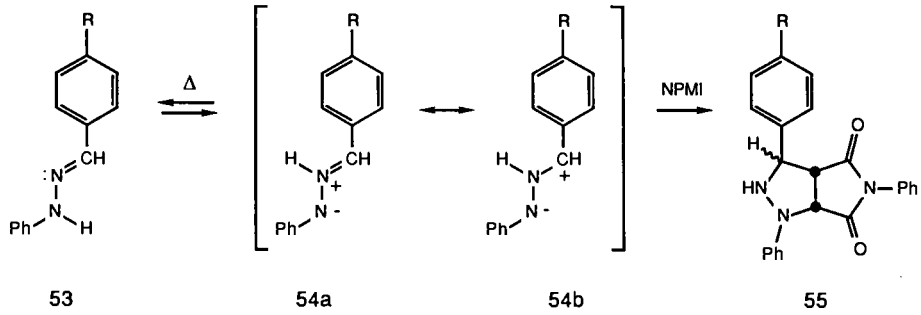
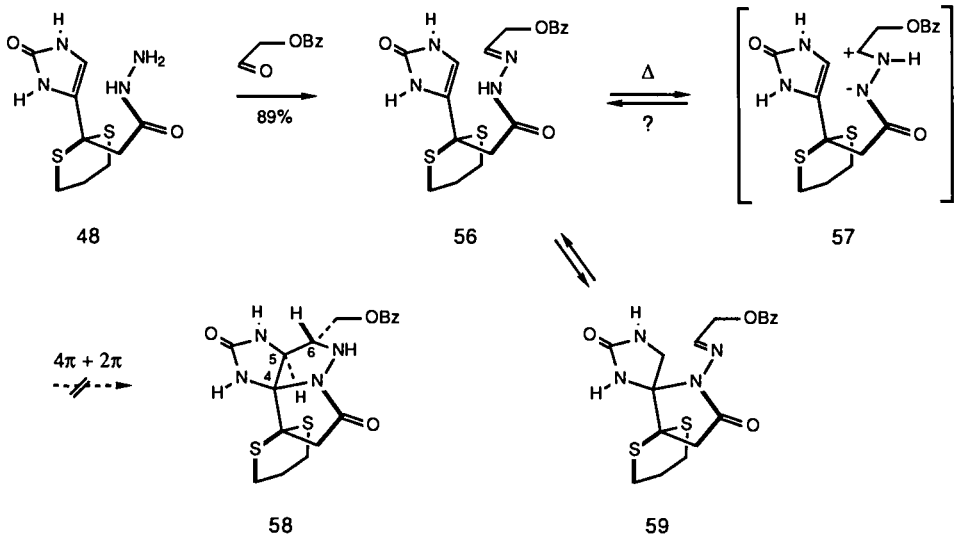


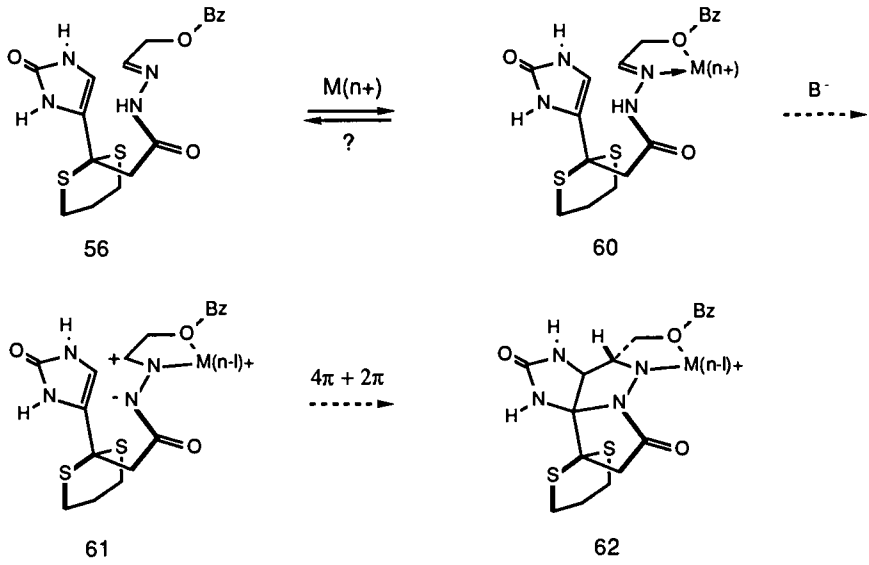

FIG. 6




SCHEME 13

favorable ratio of the desired $\alpha$ product **58** could be obtained (cf. **A** in Fig. 5, $-CH_2R' = H$). This plan was highly appealing in terms of its overall simplicity, and it also had the potential of intersecting with the Kishi synthesis.[18] In practice, however, all attempts at the direct conversion of **56** to **58** led mainly to the reversible formation of the lactam derivative **59**, and no trace of either the desired adduct **58** or its 6-$\beta$-isomer could be detected in the crude reaction mixtures. Evidently, the required proton transfer to afford the dipolar species **57** had not occurred.

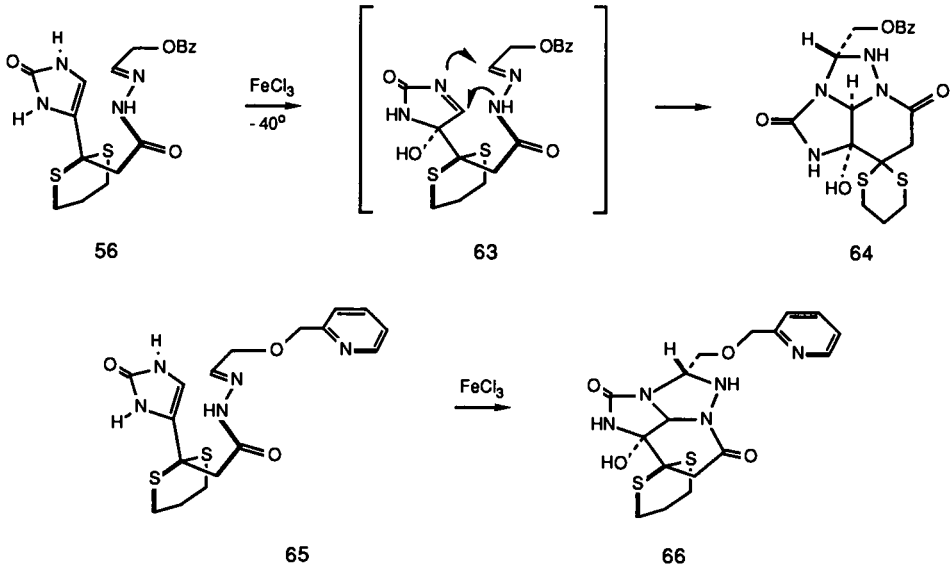
In an effort to facilitate this process, attention was next focused on the possible utility of chelated derivatives of type **60**, in which M ($n$+) might




SCHEME 14

serve as an auxiliary for the redistribution of electron density leading from **56** to the dipolar species **61** as well as a template for the control of cycloaddition stereochemistry (Scheme 14). Along these lines, an exhaustive study was carried out in which M corresponded to Be, Mg, Ca, Mo, Mn, Fe, Co, Ni, Cu, Zn, Ga, Cd, Pd, Pt, and Hg in various oxidation states. Suitable changes in solvent, reaction conditions, and counterions were also investigated. In most cases, either no reaction was observed or total decomposition of **56** occurred at ambient temperatures and below. This is perhaps not surprising in view of the many sites available for coordination. In one experiment ($FeCl_3$), however, a smooth conversion to the tricyclic species **64** was observed even at −40°C (Scheme 15).[29] Since **64** most likely arises from an initial oxidation of **56** to **63**, followed by a stepwise ring closure as indicated, the pyridyl ether **65** was subsequently prepared in an attempt to achieve greater selectivity in binding. Unfortunately, however, the results obtained with **65** exactly paralleled those described for **56**.

Finally, in a related series of experiments, we briefly explored the possibility that an intramolecular alkylation might be employed as a means of generating the requisite dipolar species (Scheme 16). Such an approach was previously utilized in the synthesis of azomethine imines (cf., for example, **38** in Scheme 8),[22,23] and, if successful, it should be geometrically biased in favor of adducts having the "natural" configuration at C-6 (cf. **68** → **69**). This hypothesis was readily tested with a number of hydrazones **67**, and in

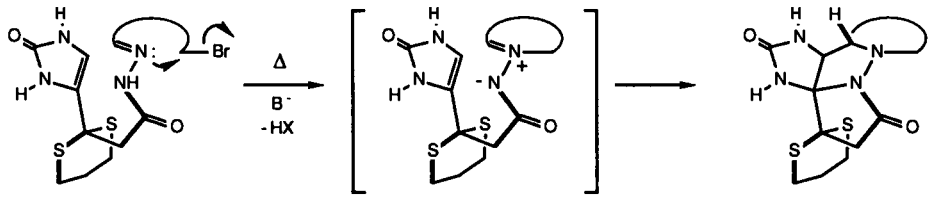



56 63 64

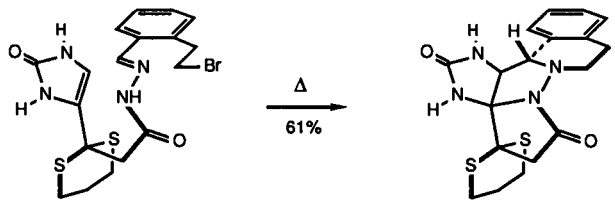



65 66

SCHEME 15

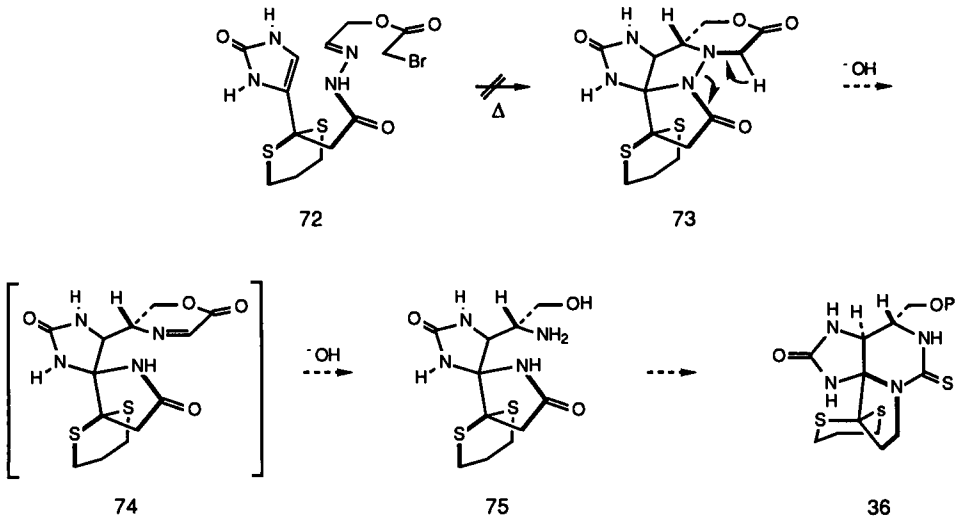



67 68 69




70 71

SCHEME 16

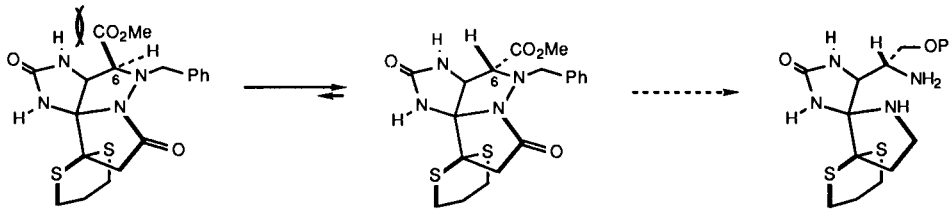



SCHEME 17

certain cases the results obtained were quite encouraging. Hydrazone **70**, for example, gave an excellent yield of the corresponding adduct **71** merely on warming in anhydrous DMF at 80°C. However, the success of these reactions was highly dependent on the nature of the bridging alkyl halide, and satisfactory results were obtained only when this appendage incorporated a benzene ring. In particular, hydrazone **72** gave none of the expected adduct **73**, a species which we believed could be readily converted to **74**, and subsequently to **75**, *via* an internal redox reaction followed by hydrolytic cleavage (Scheme 17). In view of these results, increasing attention was devoted to processes which would establish the crucial stereochemistry at C-6 under thermodynamic control. At this stage of the project, it was my good fortune to obtain the services of Mr. Michael Martinelli, a first-year graduate student from Professor Richard F. Smith's group at SUNY, Geneseo. Michael is a gifted experimentalist and a tireless worker and deserves most of the credit for the successful conclusion which follows.

## F. THERMODYNAMIC CONTROL. THE DESIRED STEREOCHEMISTRY AT LAST

As previously noted, the thermodynamically most favored configuration for adducts having an epimerizable group at C-6 would be the desired $\alpha$ orientation. Thus, the $\beta$-ester **76** clearly suffers from strongly eclipsing



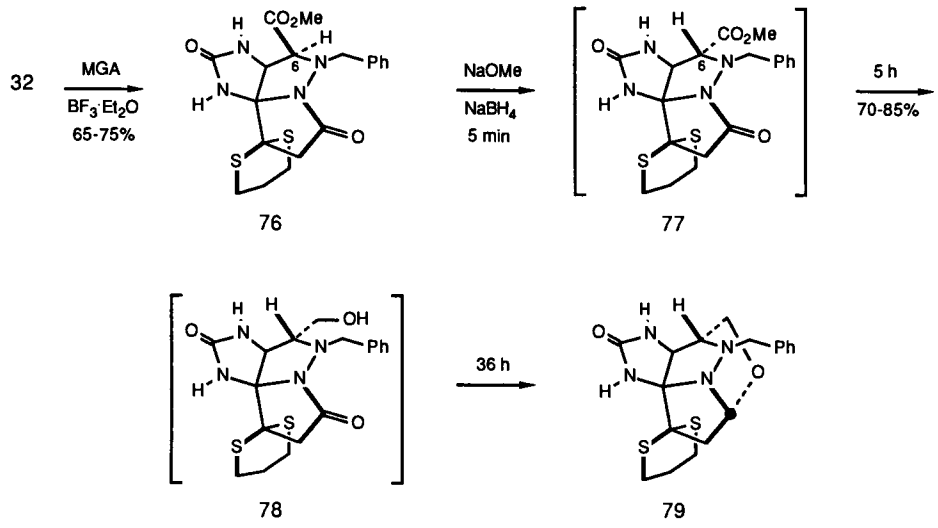
76 77 35

SCHEME 18

interactions at positions **5**, **6**, and **7** of the pyrazolidine ring (saxitoxin numbering), as well as considerable torsional strain (Scheme 18). Destablizing forces of this type are readily discernible in the X-ray crystal structure of **33β-1**, which adopts a highly distorted geometry about C-6 in order to accommodate the C-5–C-7 substituents in a syn relationship. Ester **77**, on the other hand, can assume a perfectly staggered configuration and should be greatly favored at equilibrium. It was our intention that **77** would ultimately be converted to the desired target compound **35** through a series of reductive transformations.

In our initial efforts, however, we were disappointed to find that **76** could not be prepared using our previously developed conditions (TsOH/DMF, 80°C; see also reference 19). Thus, various combinations of hydrazide **32** with methyl glyoxylate (MG),[30] methyl glyoxylate hemimethylacetal (MGA),[31] or methyl glyoxylate dimethylacetal (MGDA) either failed to react (MGA, MGDA)[32] or led to total decomposition of starting materials (MG). The latter difficulty was clearly a result of random condensation reactions involving the highly electrophilic aldehyde group in MG. Eventually, however, we were pleased to find that the desired adduct **76** could be obtained in a 65–75% yield on treatment of **32** with 2.0 equivalents of 1 : 1 MGA/$BF_3 \cdot Et_2O$ in dry acetonitrile at reflux (Scheme 19). These more forcing conditions presumably expedite what is undoubtedly an unfavorable ionization leading to the 1,3-dipolar species, and on several occasions, in fact, stable aminocetals of general structure **51** could be isolated from the crude reaction mixtures (cf. Scheme 12, R = $CO_2Me$, Y = Me).

Once in hand, the desired epimerization of **76** to **77** could be cleanly accomplished with NaOMe/MeOH under carefully defined conditions (**77** : **76** > 99 : 1). Not surprisingly, enolization at C-11 played a competing role in this transformation, and it quickly became apparent that the enolate anion **80** was in equilibrium with the enone **81** derived by a retro-Michael opening of the dithiane ring (Fig. 7). Thus, in the presence of air **81** was irreversibly trapped in the form of its oxidative dimer **82**, and this was a




SCHEME 19

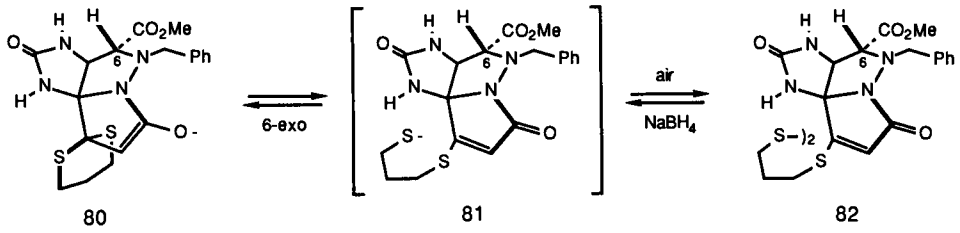
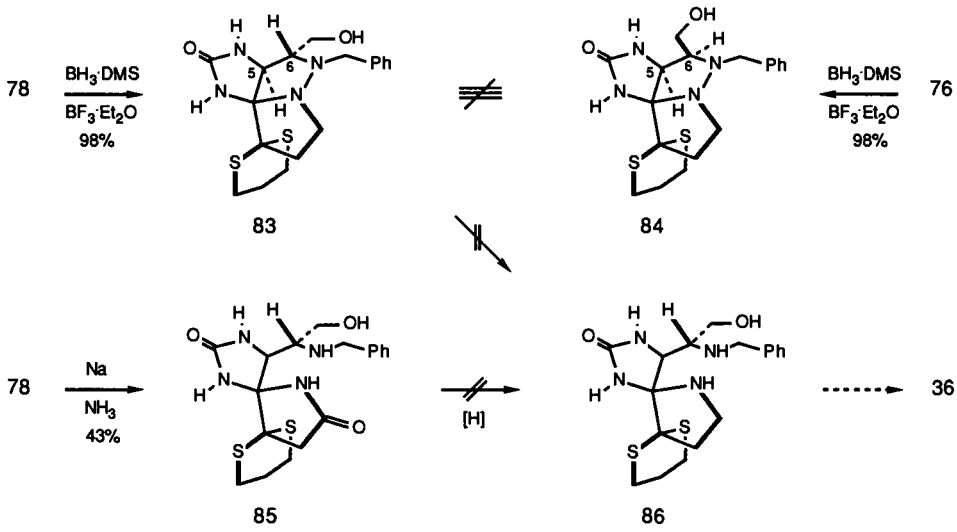



FIG. 7

source of some initial difficulties. Fortunately, however, oxidative dimerization was completely eliminated through the addition of equivalent amounts of $NaBH_4$. Under these conditions, the disulfide bond in **82** was rapidly cleaved to regenerated **80** by a 6-exo-dig-cyclization,[17b] and **77** could be isolated in excellent overall yield. The epimeric relationship of **77** and **76** was clearly evident from their $^1H$ NMR spectra, which had $J_{5,6}$ = 1.6 Hz for **77** and $J_{5,6}$ = 4.8 Hz for **76**.

Next, we were pleased to find that **76** could also be directly converted to the amino-alcohol **78** on somewhat longer exposure to $NaBH_4$/NaOMe (Scheme 19). On a preparative scale this transformation was routinely carried out on multigram scales, under exceedingly mild conditions, to afford **78** in 70–85% yield after crystallization (5 hours, 10 equivalents $NaBH_4$, room temperature). It is well known that such highly polarized esters fre-




SCHEME 20

quently can be reduced with $NaBH_4$ at ambient temperatures and below,[33] and therefore this result offered little occasion for surprise. Of perhaps greater interest, however, after 36 hours or longer **78** afforded the novel hemiaminal species **79** by partial reduction of the lactam ring followed by intramolecular cyclization; and ultimately, **79** was further reduced to the pyrrolidine derivative **83** in the presence of Lewis acid catalysts (cf. also Scheme 20 below).[34]

For large-scale work this final conversion of **78** to **83** was more conveniently carried out with the reagent system $BH_3 \cdot DMS/BF_3 \cdot Et_2O$, which afforded **83** in 98% yield after crystallization (Scheme 20).[35] The material thus obtained was identical in all respects with that prepared as described above and was directly compared to the isomeric compound **84** derived by reduction of the $\beta$-ester **76** under nonepimerizing conditions [$BH_3 \cdot DMS/BF_3 \cdot Et_2O$, THF, reflux; $J_{5,6}$(**83**) = 3.2 Hz as opposed to $J_{5,6}$(**84**) = 6.8 Hz]. With a ready supply of **77**, **78**, and **83** thus secured, the suitability of each of these materials for the synthesis of **1** was carefully examined.

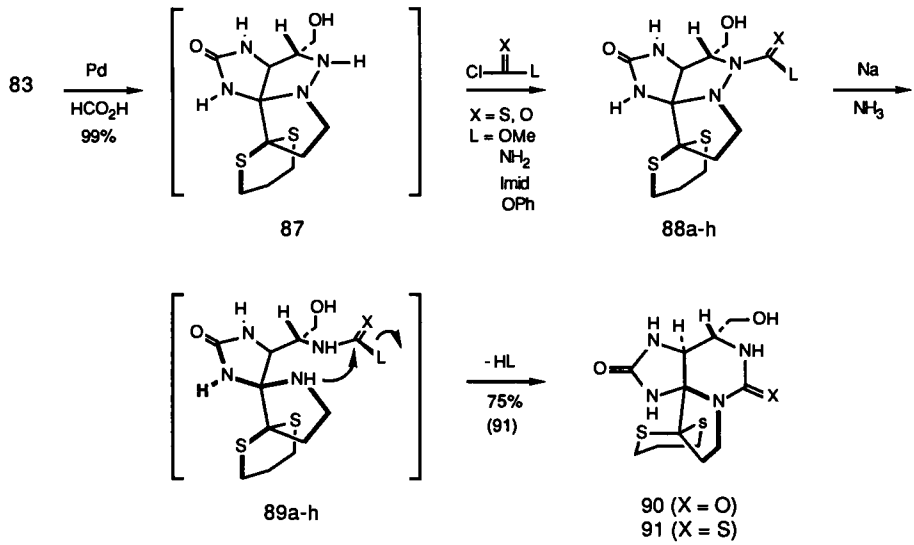
## G. Final Success

Our preliminary experiments were carried out with the lactam-alcohol **78**, and we quickly discovered that this material could be selectively cleaved, in good yield, to afford the spirocyclic intermediate **85** ($Na/NH_3$, −78°C,

Scheme 20).[36] Unfortunately, however, all attempts at the further reduction of **85** to **86** gave only complex mixtures of products containing none of the desired material.[37] This result was rather surprising in view of the extraordinary ease of conversion of **78** to **83** and is most likely due to an inherent lack of stability of compounds of type **86** rather than a lack of chemoselectively. On several occasions, in fact, decomposition products arising from **86** could be detected in the crude reaction mixtures.

Furthermore, similarly discouraging results were obtained on attempted reductive cleavage of **83** to give the target compound **86** directly. In this case, the pyrazolidine N–N bond is not activated by acylation and a variety of reagents failed to bring about the desired transformation. For example, **83** was virtually inert to $Na/NH_3$ in the absence of a proton donor (−78°C), and with added alcohol it was rapidly converted to desulfurized products, as well as mixtures derived from Birch reduction of the aromatic ring. In no case could we isolate products corresponding to the desired **86**, and also, simple *N*-debenzylation was never observed under dissolving metal conditions.

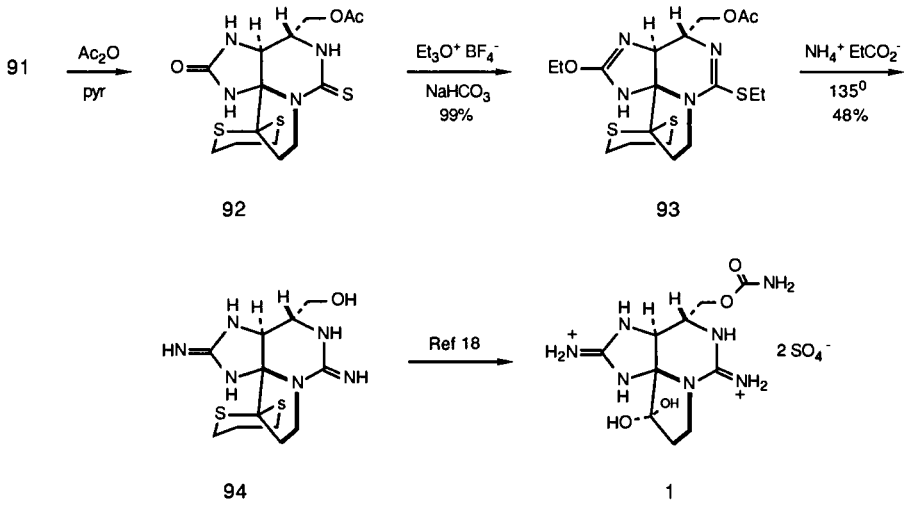
As an alternative approach, however, we found that **83** could be smoothly debenzylated to **87** by catalytic transfer hydrogenation (Pd, HOAc, $HCO_2H$),[38] and **87** was selectively acylated to give a range of *regio*isomerically activated species **88a–h** in excellent overall yield (Scheme 21). It was our hope, in this scheme, that intermediates of type **89** might undergo an intramolecular ring closure at a rate competitive with decomposition. Along




SCHEME 21

these lines, the reaction of a variety of carbamates **88** with the reagent system $Na/NH_3$ or $Pd/HOAc/HCO_2H$ followed diverse reaction pathways. With **88a** (X = S, L = OMe), transfer hydrogenation served only to regenerate the parent system **87**, a phenomenon which was also observed with **88c–d** (X = S; L = imidazole, OPh). Compound **88e** (X = O, L = OMe), on the other hand, readily underwent N—N bond reduction to give the expected intermediate **89e** (X = O, L = OMe), but this latter material was only marginally stable and could not be cyclized to **90**. Finally, however, we found that with X = S the desired reductive cleavage could be smoothly accomplished under dissolving metal conditions (1.25 equivalents $Na/NH_3$, −78°C),[39] and the resulting solutions were carefully monitored for the presence of **91** (TLC). By way of summary, with **88a** (X = S, L = OMe) and **88b** (X = S, L = $NH_2$) the derived intermediates **89a** and **89b** slowly decomposed at temperatures of 0°C and above, and no evidence could be found for the desired cyclization. With the more reactive **88d** (X = S, L = OPh), however, the initially formed **89d** cleanly cyclized at −30°C, and **91** was isolated by direct crystallization in 75% overall yield. That **91** was actually in hand was unequivocally demonstrated by all of the usual methods of characterization (NMR, IR, UV, MS, etc.) as well as by its subsequent conversion to saxitoxin (**I**).

Thus, **91** was next acylated to give the protected derivative **92**, which on careful reaction with $Et_3O^+BF_4^+/NaHCO_3$ afforded a virtually quantitative yield of the bis-pseudourea **93** (Scheme 22).[18] Compound **93** then gave a 48% yield of the known bis-guanidine **94** on brief thermolysis in strictly



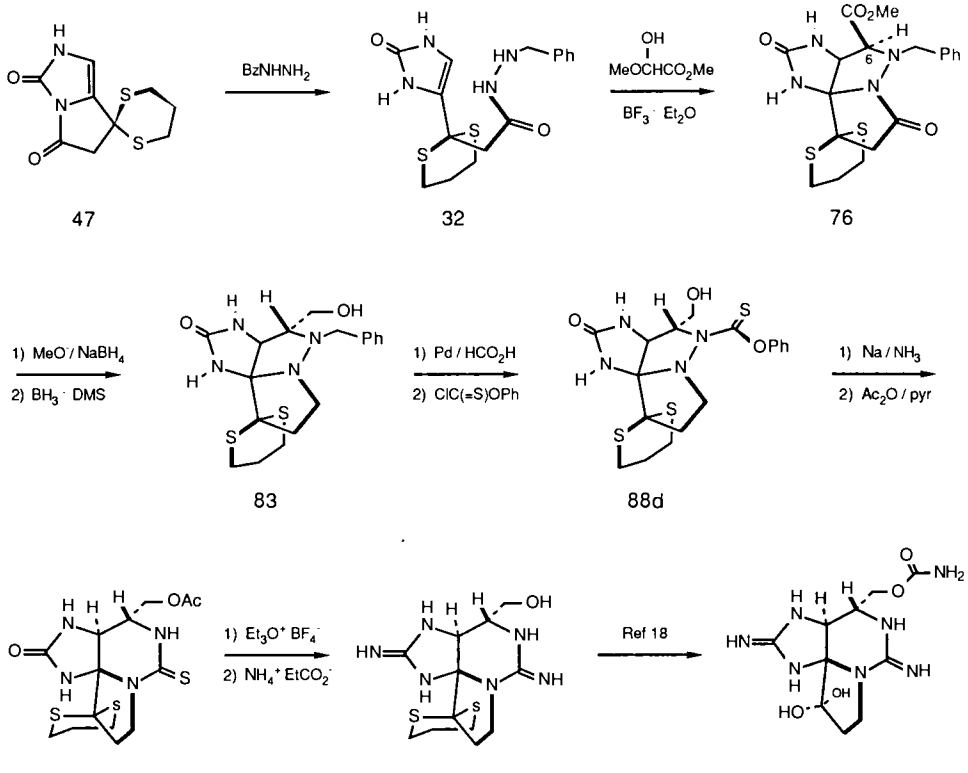

92 93 94 1

SCHEME 22

anhydrous $NH_4^+EtCO_2^-$,[18] thereby completing the formal total synthesis of saxitoxin (±)-**1**. Finally, deprotection and carbamoylation, as previously described by Kishi *et al.*,[18,40] afforded (±)-**1** as an amorphous solid which was indistinguishable from the natural product by TLC[41] and NMR analysis.[42,43]

## IV. Summary

In the interest of clarity, the final reaction sequence leading from the bicyclic imide **47** to (±)-saxitoxin (**1**) is summarized below in its entirety, much as it appeared in our original publication (Scheme 23).[44] As a measure of efficiency, it was eventually possible to prepare the key intermediate **92** on 0.5–1.0-g scales with no chromatographic separations. This achievement is a tribute to the skill and dedication of my co-workers. To readers of this




SCHEME 23

volume, however, it will not go unnoticed that the synthesis of (±)-**1** as initially reported was conspicuously more direct than the story which unfolded on the preceding pages.

**Acknowledgements**

I gratefully acknowledge the efforts of Dr. Allen Brownstein and Dr. Michael Martinelli, who carried out the vast majority of the work described in this chapter. Valuable contributions were also made by Professor Slovenko Polanc, on leave from E. Kardelj University, Ljubljana, Yugoslavia, and Dr. Karl Grozinger, on leave from Boehringer Ingelheim Ltd. Financial support of this work was provided by the Petroleum Research Fund (8706-G1), administered by the American Chemical Society, and the National Institutes of Health (GM29540).

**References**

1. For a comprehensive listing of sources for the isolation of saxitoxin (**1**), see Ghazarossian, V. E.; Schantz, E. J.; Schnoes, H. K.; Strong, F. M. *Biochem. Biophys, Res. Commun.* **1974,** *15,* 1219.
2. Murtha, E. F. *Ann. N.Y Acad. Sci.* **1960,** *90,* 820.
3. Schantz, E. J. *Ann. NY. Acad. Sci.* **1960,** *90,* 843.
4. Schantz, E. J. *Can. J. Chem.* **1961,** *39,* 2117.
5. Mosher, H. S.; Fuhrman, F. A.; Buchwald, H. D.; Fisher, H. G. *Science* **1964,** *144,* 1100.
6. Schantz, E. J.; Mold, J. D.; Stanger, D. W.; Shavel, J.; Riel, F. J.; Bowden, J. P.; Lynch, J. M.; Wyler, R. S.; Riegel, B.; Sommer, H. *J. Am Chem. Soc.* **1957,** *79,* 5230.
7. (a) Schantz, E. J. *Pure Appl. Chem.* **1979,** *52,* 183; (b) Schantz, E. J. *Environ. Sci. Res.* **1981,** *20,* 25.
8. Kao, P. N.; James-Kracke, M.R.; Kao, C. Y. *Pfluegers Arch.* **1983,** *398,* 199, and references therein.
9. Takman, B. H.; Boyes, R. N.; Vassallo, H. G. "Principles of Medicinal Chemistry," Foye, W. O., Ed.; Lea & Febiger: Philadelphia, Pennsylvania, 1974; p.316.
10. Ritchie, J. M.; Rogart, R. B. *Proc. Natl. Acad. Sci. USA* **1977,** *74,* 211.
11. Henderson, R; Ritchie, J. M.; Strichartz, G. R. *J. Physiol. (London)* **1973,** *235,* 783.
12. (a) Wong, J. L.; Osterlin, R.; Rapoport, H. *J. Am. Chem. Soc.* **1971,** *93,* 7344; (b) Wong, J. L.; Brown, M. S.; Matsumoto, K.; Osterlin, R.; Rapoport, H. *J. Am. Chem. Soc.* **1971,** *93,* 4633.
13. Schantz, E. J.; Ghazarossian, V.E.; Schnoes, H. K.; Strong, F. M.; Springer, J. P.; Pezzanite, J. O.; Clardy, J. *J. Am. Chem. Soc.* **1975,** *97,* 1238.
14. Bordner, J.; Thiessen, W. E.; Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1975,** *97,* 6008.
15. Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc.* **1946,** *68,* 2350.
16. Walker, J. F. "Formaldehyde," Reinhold: New York, 1964.
17. (a) Baldwin, J. E. *J. C. S. Chem. Commun.* **1976**, p. 734; (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. C. S. Chem. Commun.* **1976,** p. 736; (c) Baldwin, J. E. *J. C.S. Chem. Commun.* **1976,** p. 738.
18. (a) Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977,** *99,* 2818; (b) Kishi, Y. *Heterocycles* **1980,** *14,* 1477; (c) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983,** *48,* 3833.
19. (a) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1977,** *16,* 10; (b) Oppolzer, W. *Tetrahedron Lett.* **1972,** p. 1707.

20. (a) "Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings," Wiley, R. H., Ed.; Wiley (Interscience): New York, 1967; (b) Stetter, H.; Spangerberger, H. *Chem. Ber.* **1958,** *91*, 1982; (c) Stetter, H.; Findeisen, K. *Chem. Ber.* **1965,** *98*, 3228; (d) Feuer, H.; Brown, F., Jr. *J. Org. Chem.* **1970,** *35*, 1468; (e) Kemp, D. S.; Sidell, M. S.; Shortridge, T. J. *J. Org. Chem.* **1979,** *44*, 4473; (f) Wasserman, H. H.; Robinson, R. P., Matsuyama, H. *Tetrahedron Lett.* **1980** p. 3493; (g) Rylander, P. N. "Catalytic Hydrogenation in Organic Synthesis," Academic Press: New York, 1979; p. 299.
21. Sharma, S. *Synthesis* **1978,** *30*, 803.
22. (a) Rieche, A.; Schmitz, E. *Chem. Ber.* **1956,** *89*, 1254; (b) Schmitz, E. *Chem. Ber.* **1958,** *91*, 1495.
23. Huisgen, R.; Grashey, R.; Laur, P.; Leitermann, H. *Angew. Chem.* **1960,** *72*, 416.
24. (a) Kadaba, P. K. *Synthesis* **1973,** p. 71; (b) Kadaba, P. K.; Edwards, J. O. *J. Org. Chem.* **1961,** *26*, 2331; (c) Kadaba, P. K. *Tetrahedron* **1966,** *22*, 2453.
25. Kadaba, P. K. *Tetrahedron* **1969,** *25*, 3053.
26. Hinman, R. L.; Fulton, D. *J. Am. Chem. Soc.* **1958,** *80*, 1895.
27. Howard, J. C.; Gever, G.; Wei, P. H. L.. *J. Org. Chem.* **1963,** *28*, 868.
28. Grigg, R.; Kemp, J.; Thompson, N. *Tetrahedron Lett.* **1978,** p. 2827, and references therein.
29. This experiment was carried out by Profesor Slovenko Polanc, of E. Kardelj University, Ljubljana, Yugoslavia. The structure of **64** was unequivocally proved by X-ray analysis.
30. Kelly, T. R.; Schmidt, T. E. Haggerty, J. G. *Synthesis* **1972,** p. 544.
31. Bernstein, Z.; Ben-Ishai, D. *Tetrahedron* **1977,** *33*, 881.
32. In the absence of a sufficiently reactive carbonyl component, hydrazide **32** underwent an acid-catalyzed spirocyclization to give an *N*-aminopyrrolidine derivative in exact analogy to the conversion of **56** to **59** (Scheme 13).
33. Schenker, E. "Newer Methods of Preparative Organic Chemistry," Verlag Chemie: Weinheim, 1968; Vol. 4, pp. 196–335.
34. Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956,** *78*, 2582.
35. (a) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981,** p. 966; (b) *J. Org. Chem.* **1982,** *47*, 3153.
36. See, e.g., references 20e and 20f.
37. A partial listing of reagents attempted for this transformation includes $NaBH_4$, $BH_3$·THF, $BH_3$·DMS/$BF_3$·$Et_2O$, $NaBH_4$/$Co(OAc)_2$, $NaBH_4$/$Sm_2O_3$, DIBAH, LAH, $NaBH_4$/$PrCl_3$, LAH/$AlCl_3$, $Et_3O^+BF_4^-$/$NaBH_4$, $NaBH_4$/HOAc, $NaBH_4$/NaOMe, $Na_2S_2O_4$/pH 7, $Bu_4N^+BH_4^-$, and others.
38. (a) ElAmin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979,** *44*, 3442; (b) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzoigraki, C.; Meienhofer, J. *J. Org. Chem.* **1978,** *43*, 4194; (c) Greenstein, J. P.; Winitz, M. "The Chemistry of Amino Acids," Wiley: New York, 1961; p. 1233.
39. Hartwig, W. *Tetrahedron* **1983,** *39*, 2609.
40. We are grateful to Professor Yoshito Kishi of Harvard University for providing us with copies of spectral data (NMR, IR, UV, mass spectrum) and TLC data for compound **94** (as the hexaacetate derivative **95**) and other pertinent intermediates, as well as providing us with experimental details for the conversion of **94** to (±)−**1**.
41. Ghazarossian, V. E.; Schantz, E. J.; Schnoes, H. K.; Strong, F. M. *Biochem. Biophys. Res. Commun.* **1974,** *59*, 1219, and references therein.
42. Ghazarossian, V. E.; Schantz, E. J.; Schnoes, H. K.; Strong, F. M. *Biochem. Biophys. Res. Commun.* **1976,** *68*, 776.
43. We are grateful to Professor Allan Berlind of Wesleyan University for providing us with an authentic sample of saxitoxin (**1**).
44. Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984,** *106*, 5594.

*Chapter 7*

# PROBLEM SOLVING IN ORGANIC SYNTHESIS: THE FALSE STEPS, FAILED PATHWAYS, AND ULTIMATELY SUCCESSFUL ROUTE TO THE BOTTOM HALF OF IVERMECTIN

*Michael E. Jung*
*Department of Chemistry and Biochemistry*
*University of California*
*Los Angeles, California*



## I. Introduction

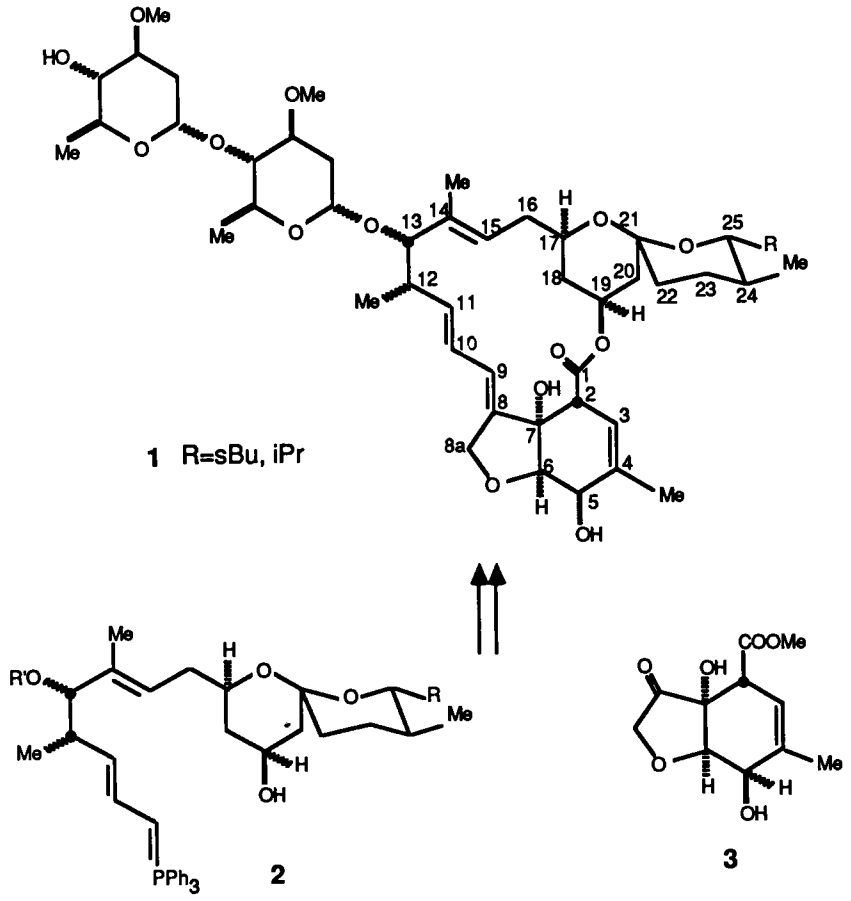
Many metaphors have been used to describe the total synthesis of natural products—the intricacies of a chess match; the theme and variations of a musical composition; a long, tortuous, and unpredictable journey; the creation of a work of art. The title of this series uses a military analogy in its description of the practice of organic synthesis, with the implied use of well-developed tactics in an overall sound strategic plan. While all of these are certainly appropriate, to me it has always seemed a problem-solving contest. Nature presents us with the basic problem in the form of a novel

molecular structure. We then further define the problem by adding certain artificial parameters. For example, we might limit the maximum number of steps or try to heighten the efficiency of bond construction. But most importantly, in each synthesis we try to guarantee the development of new and hopefully general synthetic methods along the way, because a synthesis which uses all known chemistry does not contribute greatly to the overall knowledge of the field. Once the problem is defined, we look for a solution, or rather several solutions, since in the abstract we can't be sure that the first, or indeed any, will work. This continuing contest with nature, this attempt at solving a particular problem, is what generates, for me, the intellectual excitement and fervor of research in organic synthesis. Lastly, at least in the best of all worlds, the final solution should fulfill one additional requirement, one that is really a matter of taste: the synthesis should be elegant, or beautiful, or clever. Just as masterpieces of art or music have a certain undefinable quality that sets them apart, so should the truly great achievements of organic synthesis. This eminent goal, though often unattainable, is nonetheless worth striving for.

I wish to thank the editor and publisher for producing this series of books in which the story of a synthetic effort can be explained in full. I agree completely with the thoughts expressed in the preface to the first volume, that students and chemists who want to learn about synthesis must see more than just the positive results that appear in brief communications. They must be made aware of the whole picture—why certain routes were chosen, why some failed, and why new and different approaches were selected. Otherwise, the magnitude of the challenge can be misunderstood and the real accomplishments of the synthesis underestimated. The student or chemist is often left with the wholly incorrect impression that organic synthesis is already such a mature, well-developed field that no further studies in synthesis are necessary. However, there are still numerous unsolved major problems in the synthesis of important molecules. I hope those who read this account will enter this richly stimulating field of science and join in the problem solving.

## II. The Problem

In 1981 I became aware of the structures of a group of strongly antiparasitic compounds, namely the avermectins and milbemycins.[1] Of particular interest both biologically and synthetically was the commercial anthelmintic agent 22,23-dihydroavermectin $B_{1a}$, also called ivermectin (**1**). After several years of letting various "paper" synthetic routes simmer, we finally began a synthetic effort in this area in earnest in early 1984. Our original synthetic plan involved the fairly obvious disconnection of the

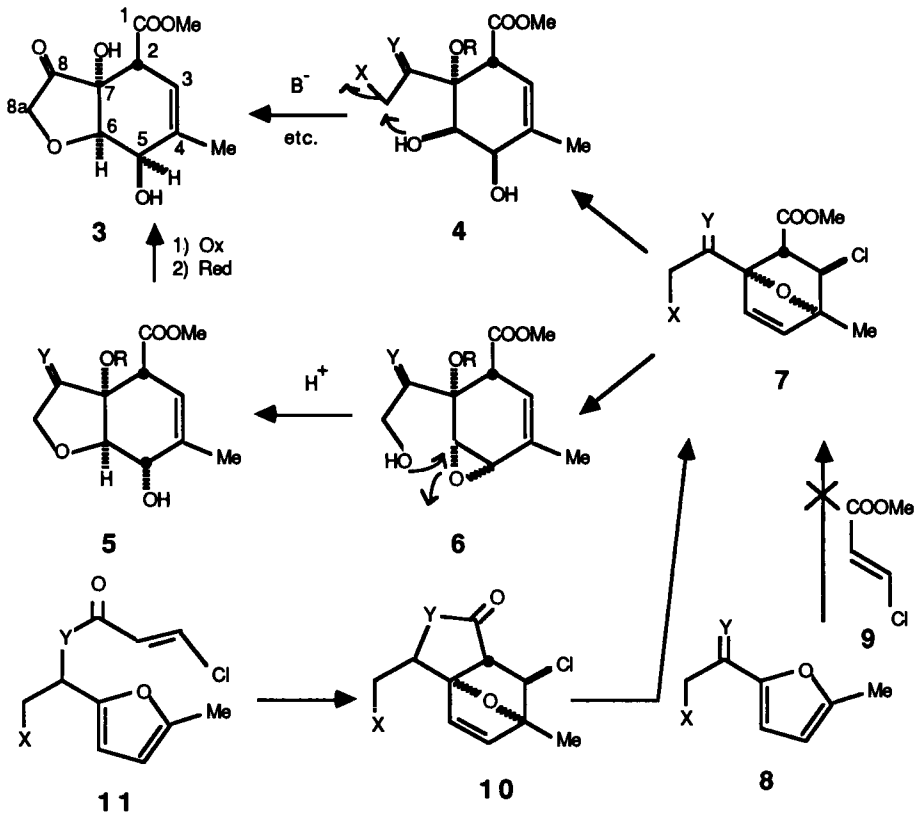



molecule into two smaller portions, e.g., **2** and **3**, which could be reconnected by a sequence of some type of Wittig reaction and macrocyclic lactonization, or the alternative route of esterification and intramolecular Wittig-type olefination. Several other groups already had synthetic programs under way aimed at the total synthesis of these molecules using a similar type of disconnection. Quite often the two compounds **2** and **3** or their analogs were described as "northern" and "southern" "hemispheres," "segments," or "subunits." Being somewhat more laid back in Los Angeles, we refer to **2** and **3** as the top and bottom halves, respectively. Since I had funds[2] and space for only one co-worker on this project, we decided to attempt to synthesize what for us was the more interesting of the two halves, namely the bottom half **3**. This compound is a highly functionalized small molecule (6 oxygen atoms for only 11 carbons) in which there are four contiguous

asymmetic centers and each carbon atom (with the exception of the allylic methyl group at C-4) is functionalized. It would be expected to be relatively unstable since it could lose 2 moles of water fairly easily (being both a $\beta$-hydroxy ester and a vinylogous $\beta$-hydroxy ester) to give an aromatic ring (a benzofuranone). Thus we thought this highly functionalized, potentially quite labile small molecule would be a quite attractive synthetic target.

We examined various possible disconnections of **3** and initially zeroed in on the following approach (Scheme 1). We hoped that **3** might be available from a diol such as **4** by base-catalyzed cyclization with loss of a leaving group (X = OTs, halide, etc.) and eventual deprotection where necessary. One would expect to obtain the fused five-membered ring system rather than the alternative bridged six-membered ring. It should be pointed out in passing that our "paper" synthetic musings were put on a firm basis when Fraser-Reid published the first synthesis of a bottom half component similiar to **3** in which just such a cyclization of a molecule very similar to **4** was successfully carried out.[3] An alternative approach to **3** would be via the C-5 epimer (in its protected form) **5**, which could be oxidized to the enone and reduced from the $\alpha$ face to give the required 5$\beta$-alcohol and thereby, after deprotection, **3**. A very similar inversion of the 5$\alpha$-alcohol to the 5$\beta$-alcohol via an analogous oxidation–reduction sequence had already been reported in the milbemycin D series,[4] and thus the conversion of **5** to **3** had literature precedent. As we will see much later, this transformation turned out to be more difficult than we had been led to expect from the literature results. We hoped that **5** would be available by the acid-catalyzed cyclization of the epoxy alcohol **6**. Again in this case, recent results have shown that our early hypothesis was sound, since Barrett has reported the acid-catalyzed cyclization of a slightly less functionalized epoxy alcohol to give a product analogous to **5**.[5] The cyclization of **6** to **5** would still be worth testing since there is the possibility that the 3,4-olefin might promote attack at C-5 (which is now allylic) to give the bridged six-membered system rather than attack at C-6 to give the desired fused five-membered system.

A potential common precursor to both **4** and **6** would be the corresponding 5,6-olefin, which would clearly be too unstable toward aromatization (via loss of the 7-alkoxy function) to be useful in a synthetic approach. Therefore we chose in our synthetic strategy to protect the 3,4-olefin and the 7-hydroxyl group jointly as a cyclic trans-chloro ether, e.g., **7**. This compound should be much more stable to acid and base and should be convertible into **4** and **6** by a sequence of stereospecific hydroxylation or epoxidation, respectively, followed by reductive elimination of the trans-chloro ether. An obvious synthetic route to this substituted oxanorbornene **7**, namely an intermolecular Diels–Alder reaction between the substituted furan **8** and methyl




SCHEME 1

β-chloroacrylate **9**, was quickly eliminated from consideration, since a mixture of four compounds (both regio- and stereoisomers) would be expected. Indeed, in the desired isomer **7** the ester group has the less favorable exo stereochemistry (cis to the bridging oxygen) and thus would probably be a very minor component. This potentially thorny problem of regio- and stereochemistry could be neatly solved by tying together the ester of the dienophile to the Y function of the diene, namely by choosing **10** as the immediate precursor of **7**. Now the key Diels–Alder reaction has been made intramolecular, which (if it can be made to work) guarantees both the desired regiochemistry (only one isomer is now possible) and stereochemistry (the five-membered ring can only be bridged via an exo substituent)! Thus our ultimate precursor in this route to **3** was the simple β-chloroacryloyl

derivative of the furfuryl system, **11**, in which X could be a hydrogen or, better, a protected hydroxyl group and Y, at least theoretically, could be any heteroatom (O,NR,S), easily convertible to a ketone function. With this initial synthetic design, then, we began our efforts toward a synthesis of **3**.

## III. Intramolecular *N*-Furfurylacrylamide Diels–Alder Approach[6]

Initially we decided to prepare compounds **11** with X = H for three reasons: they were easier to make, they would serve as good models for the desired cycloaddition, and the adducts derived from them might be hydroxylated at a later stage. The choice for Y in **11** was more limited since Parker had reported that compounds with an ester linkage (Y = O) or a secondary amide linkage (Y = NH) would not cyclize to give the desired adducts.[7] For this reason we originally chose Y = NR in **11** and began with the highly activating *o*-hydroxyphenyl substituent which Mukaiyama had used (as the magnesium salt) to force even quite hindered acrylamides to cyclize.[8] 2-Acetyl-5-methylfuran **12a** was reductively aminated with *o*-hydroxyaniline and sodium cyanoborohydride to give the amine **13a**, which was acylated with β-chloroacryloyl chloride to give the *N*-furfurylacrylamide **14a**. Heating **14a** at 110°C in toluene for 12 hours gave a 74% yield of a 5 : 1 mixture of diastereomers **15a** and **16a**. Thus we were able to carry out this key cycloaddition in good yield without having to use the magnesium salt. Because of the difficulties associated with the removal of the *o*-hydroxyphenyl

TABLE I

INTRAMOLECULAR DIELS–ALDER REACTION OF **14** to Give **15** and **16**[a]

| Compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Time (h) | Yield (%) | **15 : 16** |
|---|---|---|---|---|---|---|---|---|
| a | Me | H | Me | $o$-$HOC_6H_4$ | Cl | 12 | 74 | 5 : 1 |
| b | Me | H | Me | $CH_2Ph$ | Cl | 1.1[b] | 100 | >95 : <5 |
| c | Me | H | Me | $CH_2Ph$ | H | 1 | 100 | >95 : <5 |
| d | H | H | Me | $CH_2Ph$ | Cl | 1 | 100 | >95 : <5 |
| e | Me | H | H | $CH_2Ph$ | Cl | 8 | 67 | |
| f | Me | OMe | Me | $CH_2Ph$ | Cl | <10 min[c] | 100 | 1 : 1 |
| g | Me | H | Me | H | Cl | 48[d] | 0 | |
| h | Me | H | Me | Ac | Cl | (4)[e] | 100 | >95 : <5 |

[a] All reactions were carried out at 100°C in toluene solution.

[b] This reaction could also be run at 25°C proceeding in 65% yield in 6 days.

[c] This reaction was complete in 12 hours at 25°C, also providing a 1 : 1 diastereomer mixture.

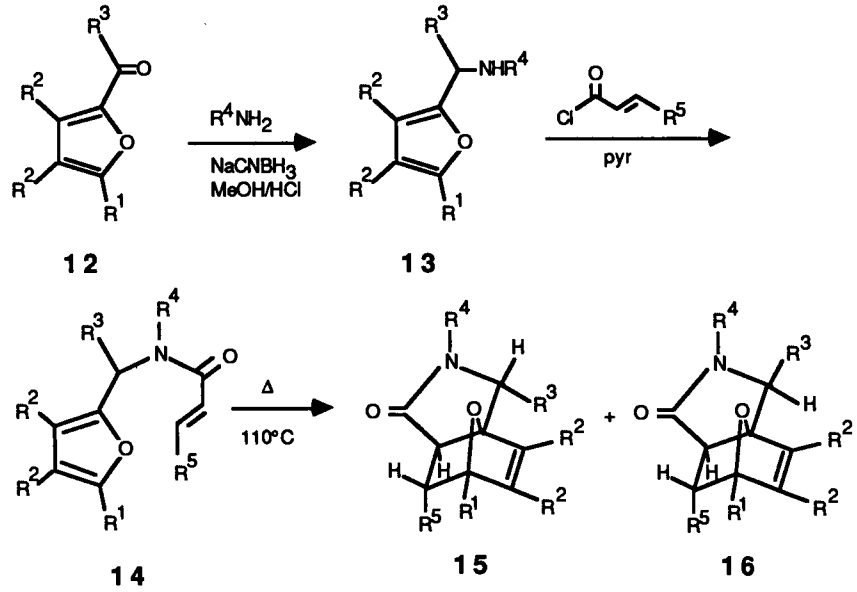
[d] Starting material was recovered unchanged.

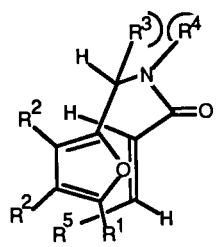
[e] This reaction was carried out at 153°C by heating **14g** in acetic anhydride for 4 hours, effecting both acetylation and cyclization.

group from the nitrogen, we decided to investigate the cyclization of other N-substituted derivatives of **14**, as well as other structurally modified analogs. All of the *N*-furfurylacrylamides **14** were prepared by the analogous sequence of reductive amination and acylation. The results of their thermal cycloadditions are shown in Table I.

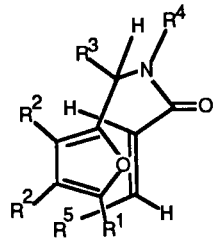
A large amount of interesting information concerning these cycloadditions can be derived from a close scrutiny of Table I, as follows. (1) The *N*-benzyl compounds are much more reactive than the corresponding *N*-(*o*-hydroxyphenyl) compound (**14b** versus **14a**) and are more diastereoselective. The structures of the diastereomers were assigned by analogy to **15b**, which was analyzed by X-ray crystallography. (2) The methyl on the chain linking the diene and dienophile greatly accelerates the reaction (reaction of **14b** is complete in 1.1 hours while **14e** is only 67% reacted after 8 hours). This acceleration is probably a special case of the *gem*-dimethyl effect.[9] (3) By raising the electron density of the furan system, one can greatly speed up cyclization (**14f**). Now, however, a 1 : 1 mixture of diastereomers is formed since the normally favored endo isomer now suffers strong steric interaction with the adjacent methoxy group. (4) Finally, the secondary amide **14g** does not give the desired cycloadduct **15g** (or**16g**) under these conditions, thus confirming Parker's results.[7]

Three interesting points should be made regarding these data. First, the diastereoselectivity is probably due to steric hindrance between the alkyl group $R^3$ on the chain and the N-substituent ($R^4$) in the transition state **17x**





**17x**



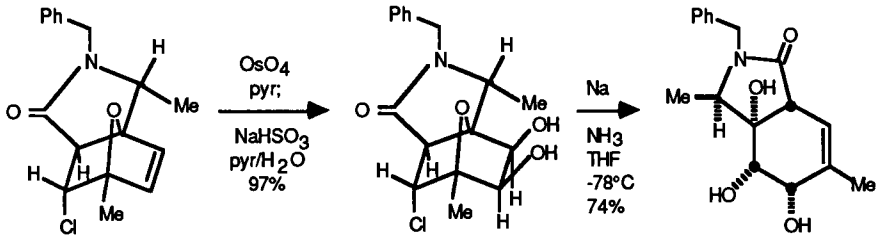
**17n**

leading to **16**, which is not present in the transition state **17n** leading to **15**. Only when $R^2$ = OMe does the interaction of $R^2$ and $R^3$ in **17n** become sufficient to offset the $R^3$, $R^4$ interaction in **17x** and a 1 : 1 mixture results. This diastereoselectivity is of no value in this synthesis since that center of chirality is destined to be destroyed (by reconversion to a ketone), but this could prove useful in other natural product syntheses.

Second, the reason given most often for the reluctance of secondary amides to cyclize is a kinetic one, namely that the ground state greatly prefers the s-trans conformation about the N—CO partial double bond, which cannot cyclize, rather than the s-cis conformation required for cyclization. While this may well be the case, we have now shown that there is also a thermodynamic bias against cyclization of secondary amides. Heating of **14g** gives none of the product **15g**. However, by heating **14g** in acetic anhydride, we can prepare the adduct **15h**, which on hydrolysis (HCl/EtOH) gives **15g**. When **15g** is heated in toluene, it slowly reverts back to **14g**, thus indicating that **14g** is more stable thermodynamically than **15g** and that the reaction is reversible at this temperature. The surprising fact is that the N-substituted cases lie totally on the side of the adducts, while the N-unsubstituted case lies far on the side of the starting furan! The reasons for this difference in stability have not yet been clarified.

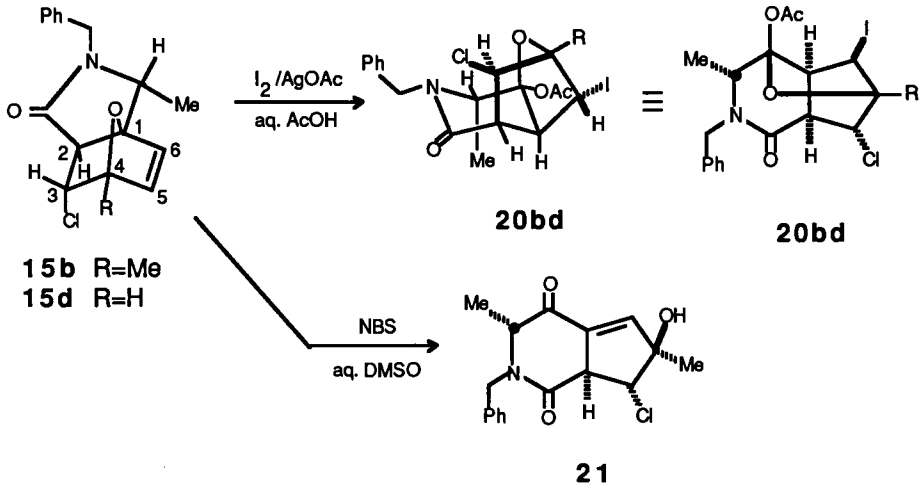
Finally, the acceleration of cyclization due to substituents on the connecting chain, while not of great value here, might find significant use in other systems, especially ones which are slow to cyclize. In these cases, a thioalkyl group or dithioacetal unit could be placed on the chain connecting the diene and dienophile to facilitate cycloaddition due to the *gem*-dimethyl effect and then removed after after serving its purpose to regenerate the unsubstituted connecting chain.

To return to the synthesis, we decided to test our key reductive elimination step.[10] The olefin of **15b** was hydroxylated to give **18**, which could be cleaved with sodium in liquid ammonia and THF to give the triol lactam **19** in good yield. Thus we felt that we had a chance of carrying out this important step in later, more functionalized derivatives.




**15b** **18** **19**

Although **19** has the correct functionality for eventual conversion to our target intermediate **4**, the stereochemistry of the 5,6-diol is opposite to that needed, namely it must be trans to the oxygen at C-7. In order to use this approach for the preparation of a molecule which could lead to **4**, we required a cis hydroxylation of the oxanorbornene system from the more hindered endo direction, an unknown transformation in this system. We attempted to use the Woodward method for cis hydroxylation from the more sterically hindered direction.[11] However, we could only isolate the products of a novel structural rearrangement. Treatment of **15bd** under Woodward's conditions ($I_2$, AgOAc, aq. AcOH) gave the rearranged products **20bd** in 60% yield, while treatment of **15b** with NBS in aqueous DMSO gave the similar structurally rearranged product **21**, also in 60% yield.[12] The proposed mechanism involves migration of the C-1—C-2 bond to the halonium ion derived from addition of the positive halogen species ($I^+$ or

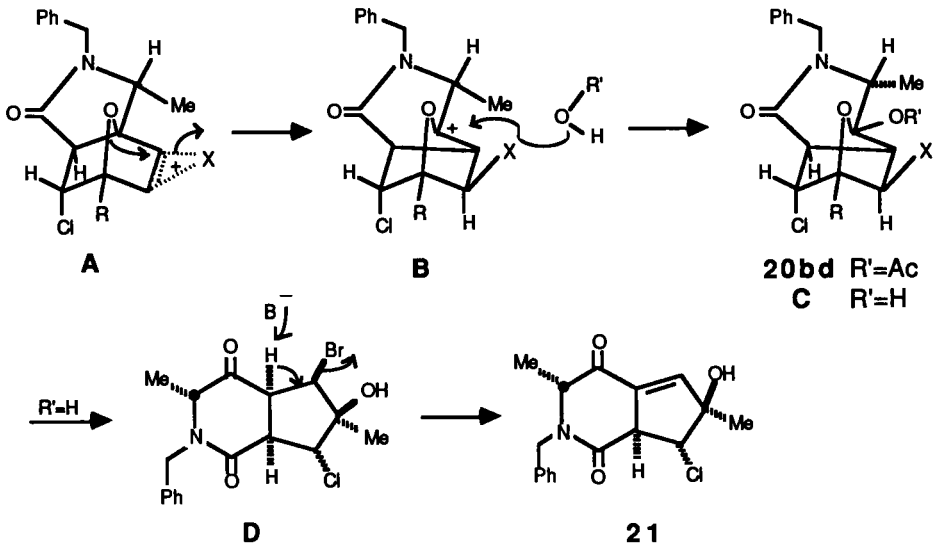



**15b** R=Me
**15d** R=H

**20bd** **20bd**

**21**

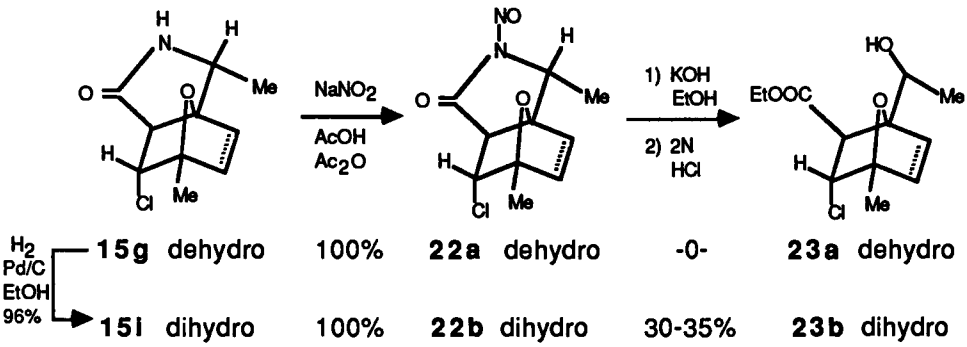
$Br^+$) to the exo face of the olefin, **A**, followed by trapping of the cation of **B** with solvent (AcOH or $H_2O$) to give **20bd** (R′ = Ac) or **C** (R′ = H). Opening of the hemiketal **C** to **D** and base-catalyzed elimination of HBr would give **21**.[12]



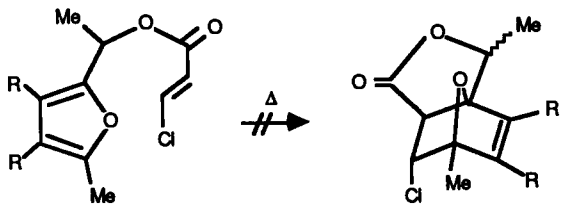

Although these compounds might be of value in the synthesis of other natural products, they were clearly of no use in the construction of intermediates such as **4** for the synthesis of the ivermectin bottom half **3**. There are other potential routes to cis-endo-hydroxylated oxanorbornenes—for example, hydride reduction of the α-diketone derived from oxidation of the diol **18**, from the less hindered exo direction, or perhaps catalytic hydrogenation of the dibenzyloxy analog of **15f** from the exo face. However, we decided to abandon, at least temporarily, all routes to **3** which passed via **4** and to concentrate our efforts on the epoxide route via **6**.

We also examined in this series methods for regeneration of the ketone functionality at what becomes C-8 in the final product. Nitrosation of **15g** and its hydrogenated analog **15i** gave the *N*-nitroso lactams **22ab** in good yield. Cleavage of these compounds under Mukaiyama's conditions[8b] gave essentially no product in the case of **23a** and only 30–35% of **23b**. Clearly, a better method of ketone regeneration would have to be developed in order to use this approach.

We thought that perhaps the accelerating effect of the methyl on the chain might make it possible to use the ester linkage in the cyclization.



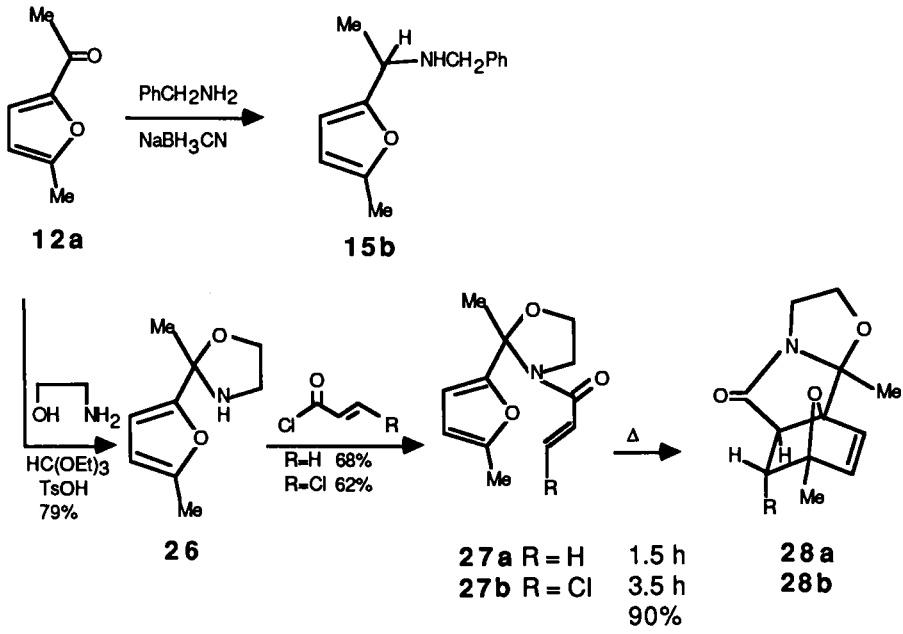

Clearly, the lactone of the cycloadducts would be readily hydrolyzed under base-catalyzed conditions to give the hydroxy ester and thence the desired keto ester. However, all attempts at cyclizing the furfuryl β-chloroacrylates **24ab** under thermal or Lewis acid conditions afforded none of the desired cycloadducts **25ab**, giving back only starting materials in the absence of Lewis acids and decomposition in their presence.



**24a** R=H
**24b** R=OMe

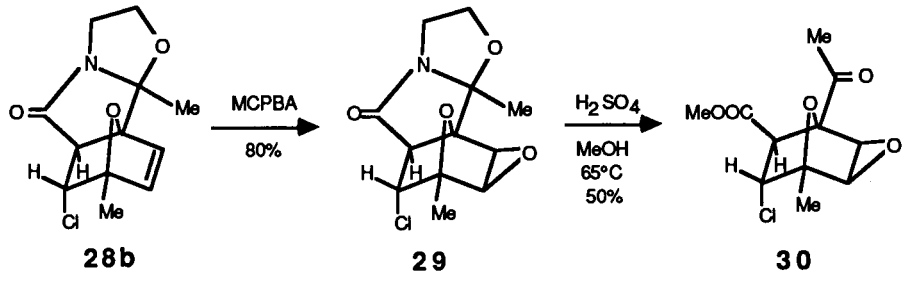
**25a**
**25b**

During any total synthesis, you have to step back from time to time and look at the overall sequence to see if, by pushing hard on one tack, you've allowed any foolish or uneconomical procedures or assumptions to slip in. We now did this here and decided that we had, and right at the very beginning too! The first step of the synthesis was the reductive amination of the furyl ketone **12a** to give the amine **15b**. In the first step we had taken the correct oxidation state and reduced it, thereby necessitating a reoxidation step later in the synthesis. It's true that we needed a nitrogen atom to append the acryloyl group to effect the cyclization, but perhaps this nitrogen could be part of an aminal, so that the oxidation state is retained. The aminal **26** was prepared and acylated to give **27ab**, which could be readily cyclized to the tetracyclic adducts **28ab** in excellent yield. Thus we could keep this carbon

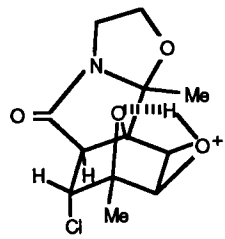



at the ketone oxidation state and still effect the intramolecular Diels–Alder reaction, thereby eliminating the problem of oxidation of the secondary amine to ketone mentioned above.

To continue the approach, epoxidation of **28b** occurred as expected completely from the exo face to give the epoxide **29** in good yield. Hydrolysis–methanolysis of the lactam aminal of **29** proved quite difficult. Although the C—O bond of the aminal was readily cleaved, the lactam was quite resistant to hydrolytic opening, due presumably to a Thorpe-Ingold-like effect (the intermediate amino carboxylic ester would be expected to cyclize very readily since the groups are held very close together). However, under forcing conditions—10% sulfuric acid in methanol at 65°C

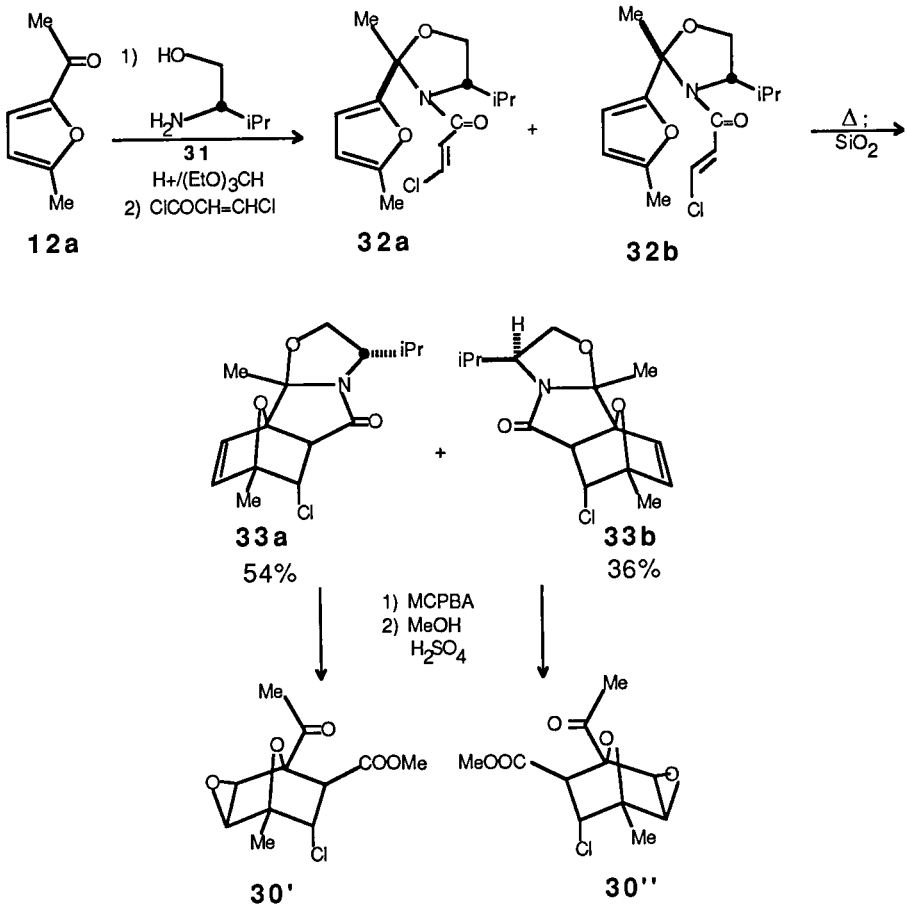


for 14 hours—a 50% yield of the desired ester **30** was obtained. It is somewhat surprising that the strongly acidic conditions do not cause skeletal rearrangement of the epoxide similar to that seen for the halonium ions derived from **15bd**. Perhaps the protonation of the epoxide oxygen occurs syn to the bridging oxygen so that a strong internal hydrogen bond can occur, e.g., **E**. This species would be much less prone to rearrangement since migration of the C—C bond is made somewhat unfavorable due to both resonance and inductive effects.[12]



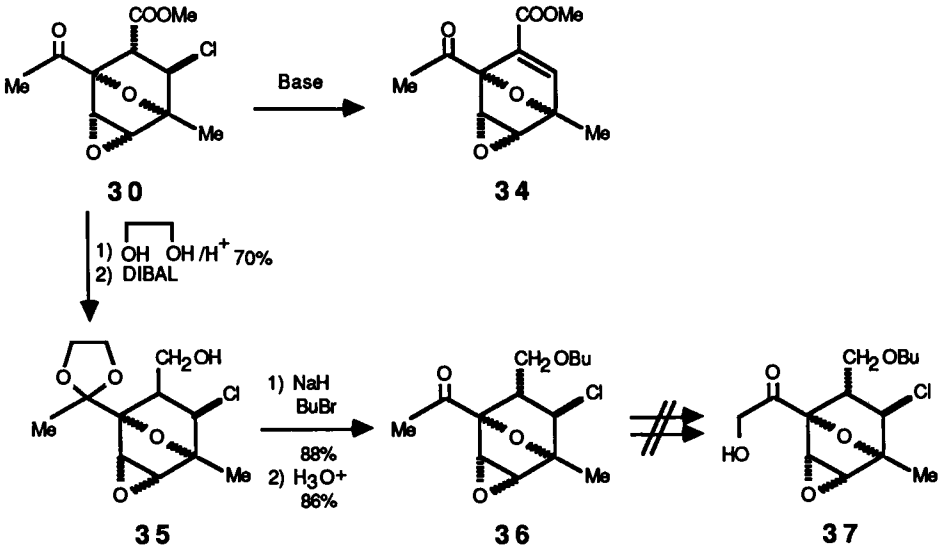

**E**

The successful use of simple aminals derived from 2-aminoethanol prompted us to investigate the possibility of preparing optically active material by use of the readily available amino alcohols derived from natural amino acids. The use of L-valinol **31** illustrates this approach. Reaction of **12a** with L-valinol **31** followed by acylation with $\beta$-chloroacryloyl chloride furnished a 1.5 : 1 mixture of diastereomers **32ab** which could be separated chromatographically only with difficulty. The structures of these compounds were assigned on the basis that under the equilibrating conditions, the more stable diastereomer (**32a** with isopropyl cis to methyl and trans to furan) should be the major product.[13] However, thermolysis of the mixture produced a 90% yield of the adducts **33ab**, which could be very easily separated by flash chromatography to give 54% of **33a** and 36% of **33b**. These compounds were then separately converted into the two enantiomers of **30** (**30′** and **30″**) by epoxidation and hydrolysis as described above. The L-valinol can be easily isolated in the workup of the hydrolysis step. Thus L-valinol serves as a recyclable resolving agent for the chromatographic separation of diastereomers. The enantiomer required for the synthesis of the natural products is the minor isomer **30″**, although it could be made the major component by using the unnatural D-amino alcohol in the first step. However, the facility of this resolution and the fact that the undesired cycloadduct **33a** can be reconverted into **12a** and L-valinol **31** by hydrolysis and thermolysis (retro Diels–Alder reaction) make it quite useful for preparing the optically pure material **30″**.

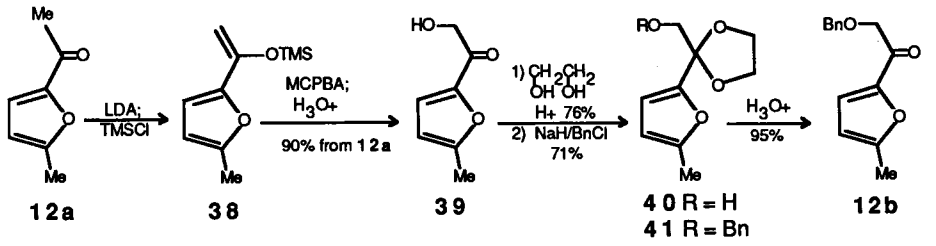



To return to the synthesis, attempts to hydroxylate the methyl ketone of **30** under basic conditions were unsuccessful due to rapid elimination of HCl from the $\beta$-chloroester leading to the $\alpha,\beta$-unsaturated ester **34**. Therefore the ester was reduced to the primary alcohol, which was protected as its benzyl ether **36** in four steps via the hydroxy ketal **35**. However all attempts to $\alpha$-hydroxylate **36** via its enolate or silyl enol ether failed to afford the desired $\alpha$-hydroxy ketone **37**, giving either recovered **36** or decomposition, depending on the conditions. The reasons for our failure to produce **37** in this matter are not well understood and perhaps with more investigation might be overcome. But at this juncture we were left with no choice but to abandon this particular route in favor of the following alternative.

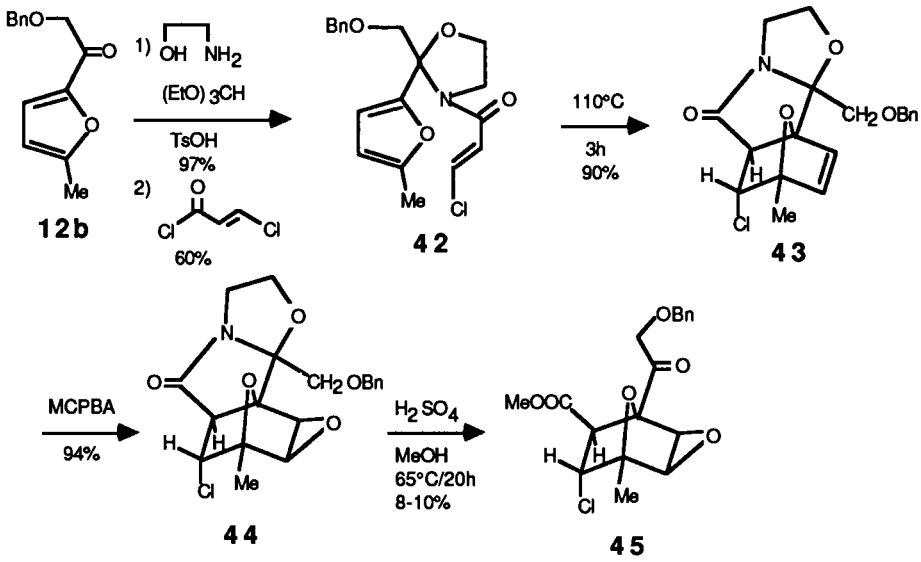
Since there were difficulties associated with $\alpha$-hydroxylation of the acetyl group at a late stage in the synthesis, we pursued the alternative of per-




forming this functionalization at the very outset of the synthesis. Treatment of **12a** with 1 equivalent of LDA in THF followed by trapping of the enolate with trimethylsilyl chloride produced the silyl enol ether **38**, which was oxidized with MCPBA to produce after hydrolysis in 90% yield the $\alpha$-hydroxy ketone **39**. Ketalization with ethylene glycol afforded **40**, which was then benzylated under the normal conditions to give **41** in 54% yield for the two steps. A final acidic hydrolysis (95%) furnished the desired $\alpha$-benzyloxy ketone **12b**, thus making it available in 46% overall yield from **12a**.[13]

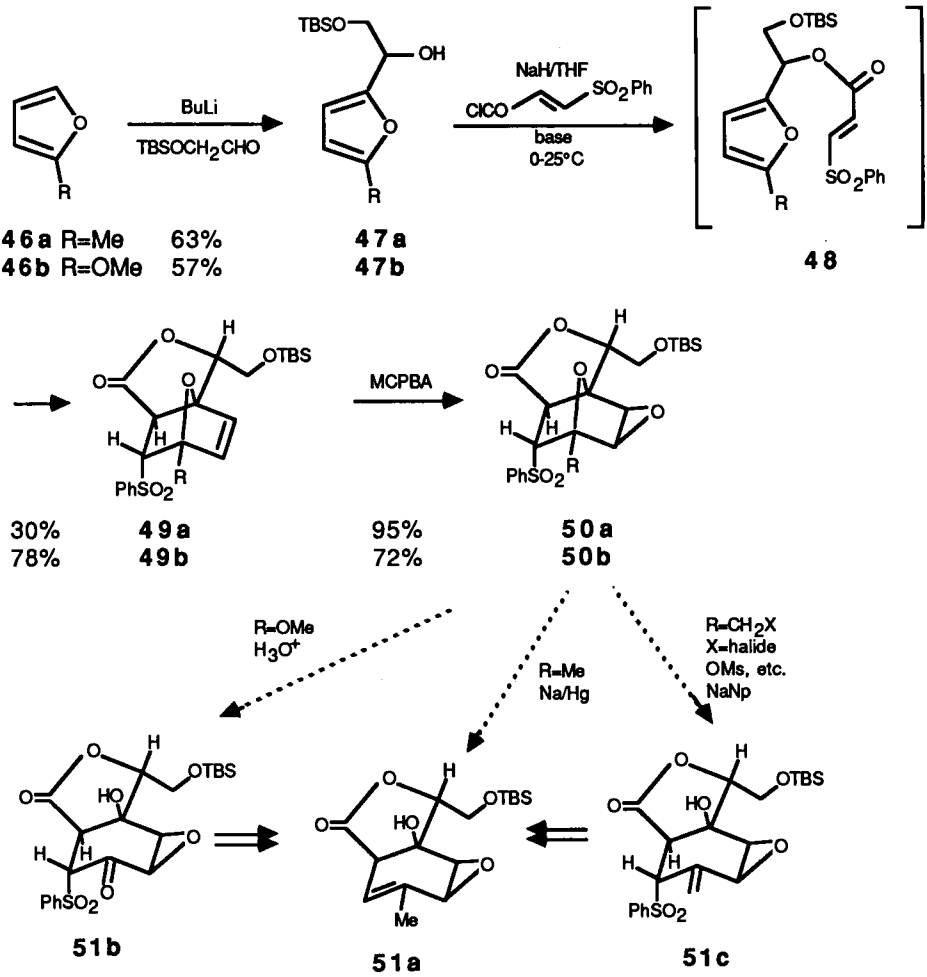



Reaction of **12b** with 2-aminoethanol, triethyl orthoformate, and *p*-toluenesulfonic acid produced in 97% yield the aminal, which was immediately acylated with $\beta$-chloroacryloyl chloride to furnish **42** in 60% yield. Refluxing a solution of **42** in toluene for 3 hours produced a 90% yield of the cycloadduct **43** as a single stereoisomer. Epoxidation of the olefin of **43** with




1 equivalent of MCPBA in dichloromethane at 0°C furnished in 94% yield the epoxide **44**, which was then subjected to acidic methanolysis (10% $H_2SO_4$ in MeOH, reflux, 20 hours) to afford the desired epoxy ester **45** in a yield of only 8–10%, although occasionally higher yields (~35%) were obtained. Our inability to carry out this hydrolysis consistently in reasonable yield was the death for all routes proceeding via intramolecular *N*-furfurylacrylamide cycloaddition and prompted us to seek totally different approaches.

Before leaving this area completely, I want to point out some interesting preliminary results which may permit the resurrection of this approach.[14] Metalation of the 2-substituted furans **46ab** with *n*-butyllithium followed by trapping with the silyloxy acetaldehyde produces the alcohols **47ab**. Reaction of the anion of these alcohols with *E*-β-phenylsulfonylacryloyl chloride afforded the intramolecular Diels–Alder adducts **49ab** directly via the esters **48ab**. Thus if one activates sufficiently the β-carbon atom of the acrylate system, then ester linkages can be utilized successfully in these internal cycloadditions. In both cases a mixture of diastereomers is obtained with the endo silyloxymethyl isomer shown as the major component (structure again assigned by X-ray crystallographic analysis of **49a**). These can be easily separated by flash chromatography and the more abundant endo isomer epoxidized to give **50ab**. We are attempting to utilize these sulfones to produce the hydroxylactone **51a** as follows: reductive elimination of **50a** should give directly **51a**, while hydrolysis of **50b** should produce **51b**, which could potentially be used to prepare **51a**. Finally, the analog of **50** with

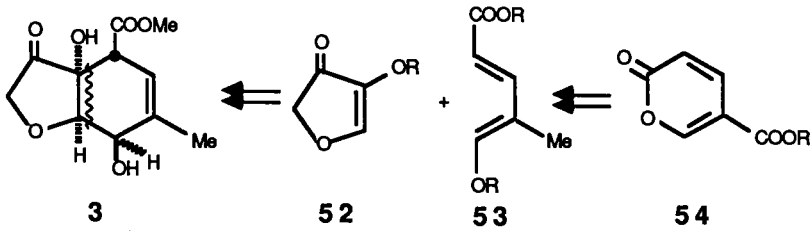



R = $CH_2X$, where X is an easily reduced group, might also be reductively eliminated to give the exocyclic olefin **51c**, which might be convertible to **51a**. Results in this area will be reported in due course.[14]

## IV. Background for Choosing Alternative Approach

From the very first time I examined the structure of the ivermectin bottom half **3**, I had always tried to come up with the simple disconnection shown, namely in the formal sense, a Diels–Alder cycloaddition between the dienophile **52** and the diene **53**. As drawn, this would give the epimer at C-5

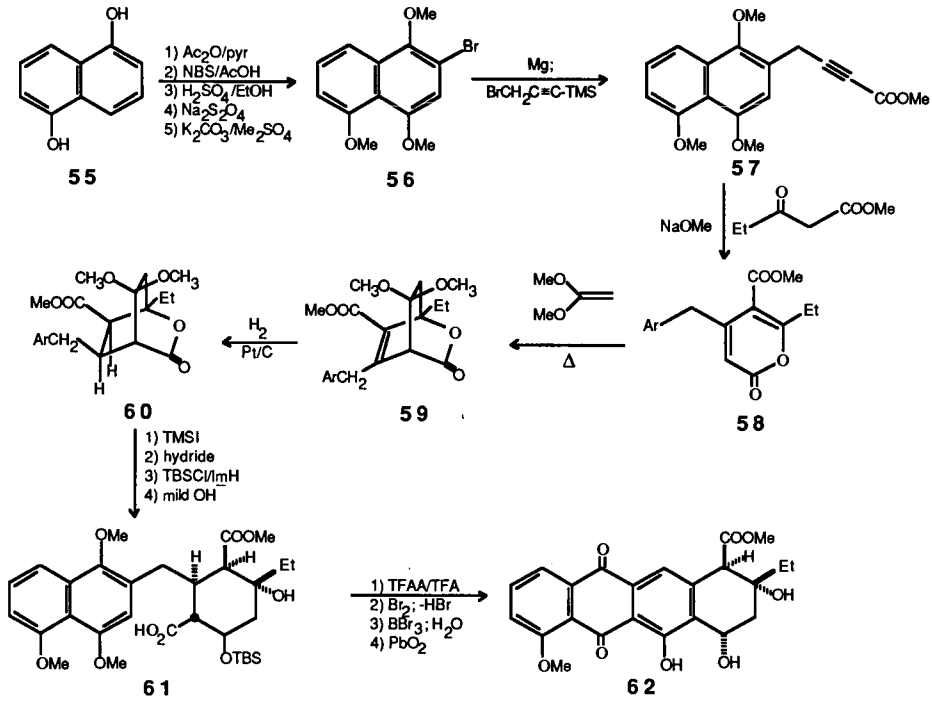
but, as discussed earlier, we felt that this stereochemistry could be inverted late in the synthesis. However, this disconnection always seemed quite problematic for the following reasons. Through the work of many synthetic chemists (Danishefsky, Suzuki, Normant, Negishi, Trost, Zweifel, Kishi, and others), we can now prepare almost any diene one can imagine and therefore the preparation of **53** should present no great difficulty. The problem arises with the dienophile for this cycloaddition, the furanone **52**. Although the electron-withdrawing carbonyl group lowers the electron density of the double bond, the two ethereal oxygen atoms make the olefin electron-rich and therefore presumably much less reactive in the normal electron demand Diels–Alder reactions. There are several examples with $\alpha$-acyloxy or $\alpha$-silyloxy enones reacting in normal cycloadditions but very few with $\beta$-alkoxy enones and none to my knowledge with both $\alpha$ and $\beta$-alkoxy substituents. In effect, the furanone **52** is too electron-rich for the cycloaddition with the diene **53**. Because of this fact, we chose to shelve this approach at the beginning of our studies.




**3** **52** **53** **54**

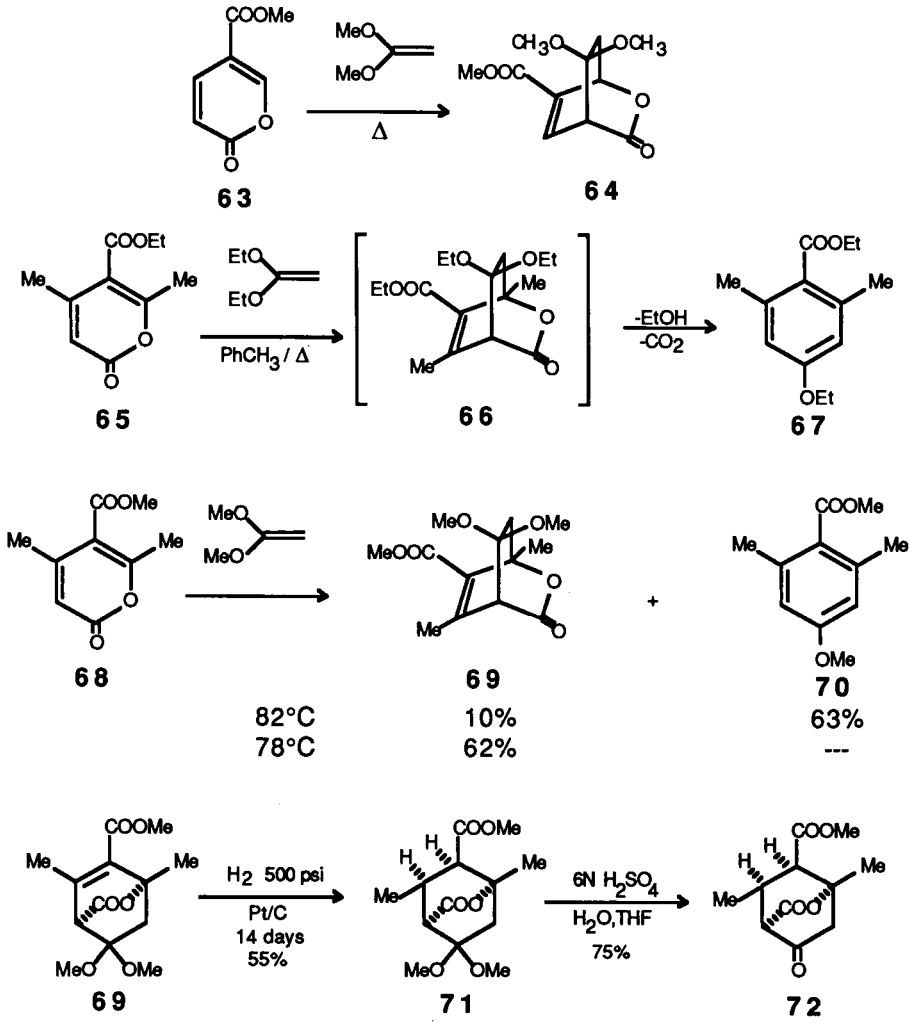
As often happens in a large research group where students are working on widely different projects, another ongoing project aimed at a totally different molecule gave us, at least theoretically, a solution to the problem of the use of the electron-rich dienophile **52** in this approach to **3**. The real trick was in getting the cross-fertilization of research ideas to occur, to realize that by making fairly small changes, we could apply the chemistry involved in a completely different project to this approach to the ivermectin bottom half **3**. I want to briefly summarize the work we had been doing on the cycloaddition of coumalates **54** with electron-rich olefins to give the reader an indication of why we chose this molecule as a replacement for the diene **53** in our successful approach to **3**.

Sometime earlier we had carried out cycloadditions with electron-rich 6-alkoxy pyrones[15] in approaches to the anthracycline antitumor agents. More recently[16] we had investigated the cycloadditions of benzopyrones with electron-rich olefins as a route to AB-ring analogs of the same natural products. However, the project ongoing in the group at the time of the

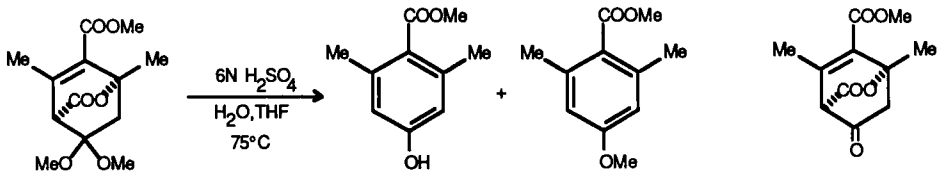



SCHEME 2

ivermectin work involved the approach to aklavinone **62** outlined in Scheme 2.[17] The key step of this sequence involved the cycloaddition of the 4,6-disubstituted coumalate **58** (prepared from **55** as shown) with dimethyl ketene acetal to give the bicyclic lactone **59**, which would then be reduced to give **60** (and thence **62**). Before beginning chemistry on the real system, we carried out some model studies.[18] Behringer and Heckmaier[19] had reported in 1969 that methyl coumalate (**63**) reacted with dimethyl ketene acetal to give the bicyclic lactone **64**. However, the corresponding lactone **66** could not be isolated from the cycloaddition of the 4,6-dimethyl derivative **65** with diethyl ketene acetal; rather it lost carbon dioxide and ethanol to give the aromatic product **67**. By carefully controlling the temperature of this reaction, we were able to isolate good yields of the corresponding lactone **69** from the reaction of the corresponding methyl coumalate **68** with dimethyl ketene acetal. However, if the temperature is raised slightly, the aromatic ester **70** becomes the major product. This lactone **69** could be hydrogenated to give the saturated lactone **71** in fair yield under vigorous conditions. This

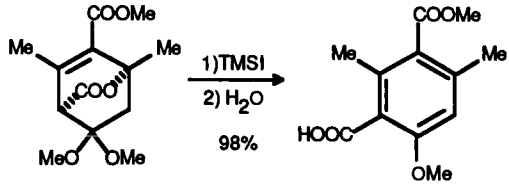



hydrogenation is difficult due to severe steric hindrance of the tetrasubstituted olefin (although the strain of the bicyclic system should increase its reactivity) and the electron-withdrawing ester on the double bond. But reaction at 500 psi over 14 days gave a reasonable yield of **71**. The ketal of the lactone **71** could then be hydrolyzed to produce the keto lactone **72**. Attempted hydrolysis of olefinic lactone **69** gave predominately the *p*-hydroxybenzoate **73** with some of the *p*-methoxybenzoate **70** also being formed, indicating that hydrolysis to the desired ketone **74** is probably




**69** **73** 56% **70** 38% **74**

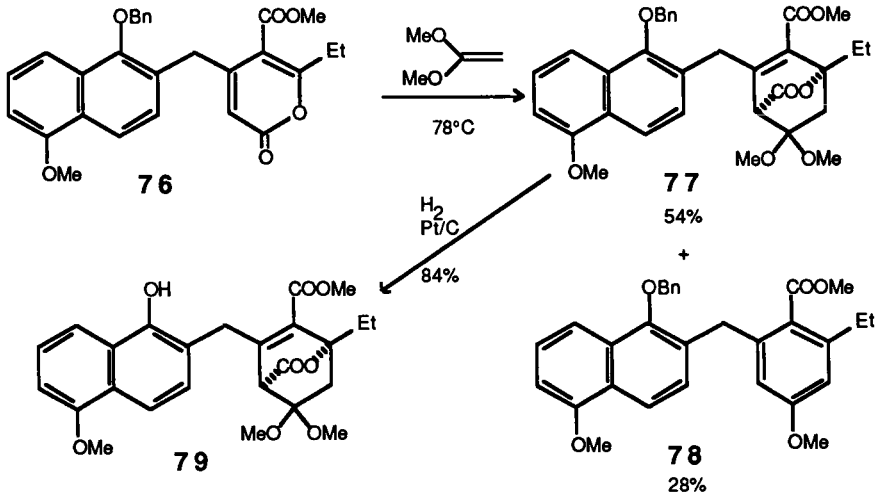
occurring but that it is too unstable with respect to enolization and loss of carbon dioxide to be isolated. It is interesting that the use of trimethylsilyl iodide for this hydrolysis produced, in nearly quantitative yield, the pentasubstituted aromatic ester **75**, presumably by preferential reaction with the lactone, cleavage of the tertiary allylic C—O bond, deprotonation, and loss of methanol. This may prove to be a useful method for the synthesis of pentasubstituted aromatic compounds and potentially (by the use of 1,1-dimethoxyalkenes in place of the ketene acetal) even hexasubstituted aromatics.



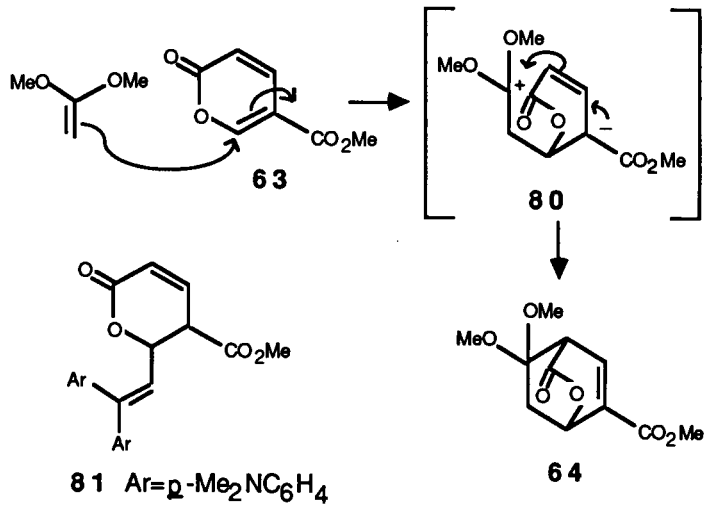

**69** **75**

This approach to aklavinone **62** eventually foundered on our inability to reduce the double bond in a very closely related bicyclic lactone. Thus the cycloaddition of **76** (a close analog of **58**, prepared as outlined in Scheme 2) with dimethyl ketene acetal afforded a 54% yield of the bicyclic lactone **77** (with 28% of the aromatic ester **78** also being produced). However, all attempts to reduce the olefin of **77** furnished only the debenzylated phenol **79** with no evidence for double-bond hydrogenation. Presumably the extra steric hindrance of an ethyl group (versus a methyl in **69**) and a naphthylmethyl group in **77** (also versus a methyl in **69**) causes the double bond to be too unreactive to hydrogenate under these conditions. But this unsuccessful foray into aklavinone synthesis via coumalate–ketene acetal cycloadditions suggested a potentially useful alternative in the ivermectin series.

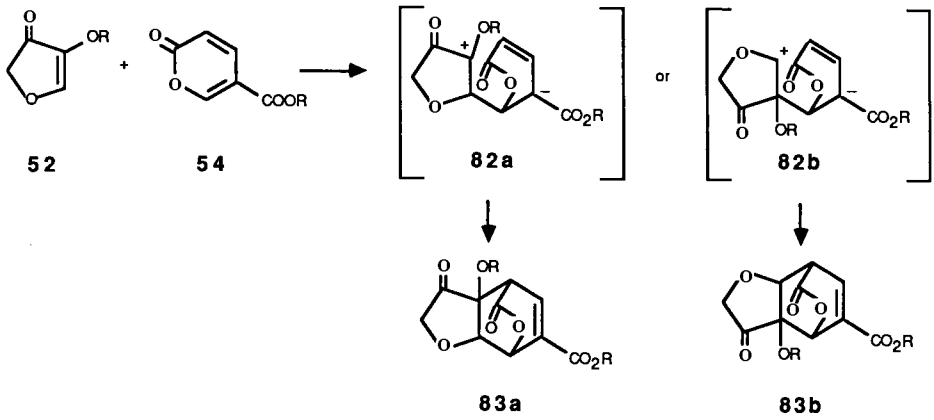
To return to the synthesis of the ivermectin bottom half **3**, we now



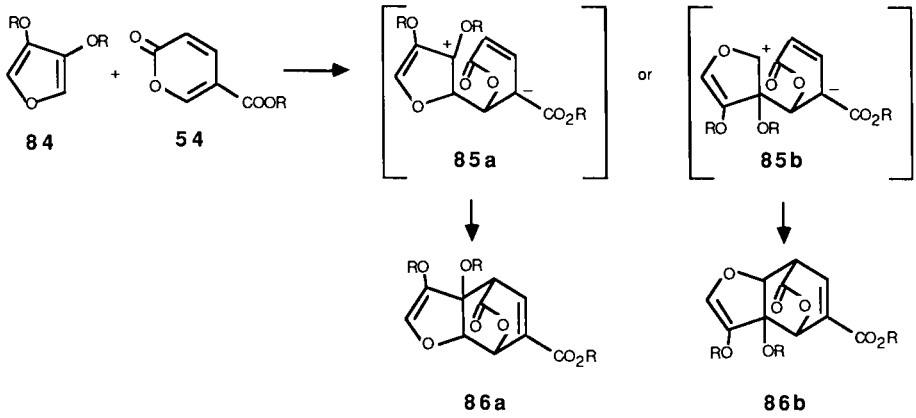

proposed that reaction of a coumalate **54** with the electron-rich olefin **52** might be expected to proceed based on the analogies given above. However, the furanone **52** is not a ketene acetal (as our earlier dienophiles were) and thus might be expected to be somewhat less reactive. More serious, however, was the fact that it was a 1,2-dioxygenated olefin rather than a 1,1-dioxygenated olefin and thus could lead to a mixture of regioisomers. Behringer proposed that the ketene acetal–coumalate cycloaddition was a



two-step process (rather than a concerted cycloaddition) proceeding via a zwitterionic intermediate, e.g., **80**, which then closes to the bicyclo[2.2.2] octane system **64**. The nonsynchronous mechanism was supported by the isolation of **81** in 92% yield from the reaction of the corresponding 1,1-diarylethylene with **63**.[19] In the reaction of **52** with **54**, two intermediates **82ab** are possible. An unbiased observer would clearly predict the latter, **82b**, to be the more stable since although both **82ab** are $\alpha$-oxygenated carbonium ions, the former, **82a**, has the destabilization of a carbonyl group (with $\delta+$ on the carbon atom) $\alpha$ to the positive charge. Therefore this route seemed destined to lead to the regioisomer of **3** via **83b** rather than the correct natural subunit via **83a**. Even if the cycloaddition is concerted (rather than proceeding via a zwitterionic intermediate), one would make the same prediction based on partial formation of bonds in the transition state. Thus wherever we have invoked a zwitterionic intermediate, one could equally well substitute an asymmetric transition state with nonsynchronous bond formation.

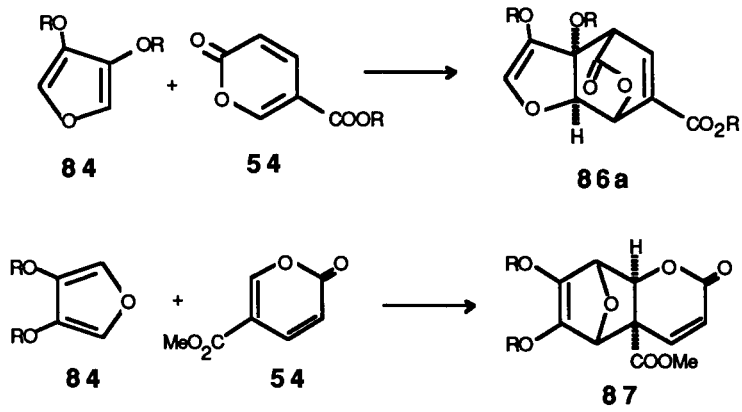



Faced with this regiochemical difficulty, we suggested a small alteration in the dienophile which might alleviate the problem. It is true that we eventually need a carbonyl at what becomes C-8 of **3** but it doesn't have to start out life that way. For example, it could be any type of protected carbonyl and, in particular, an enol ether, e.g., the 3,4-dialkoxyfuran **84**. Now an analysis of the proposed zwitterionic intermediates **85ab** of the cycloaddition of **84** with **54** suggests that the desired regioisomer **85a** would be the more stable due to the increased resonance stability of the carbonium ion. One would then expect **86a** to be the major regioisomer formed. Thus was born our alternative, ultimately successful, approach to the synthesis of **3**.

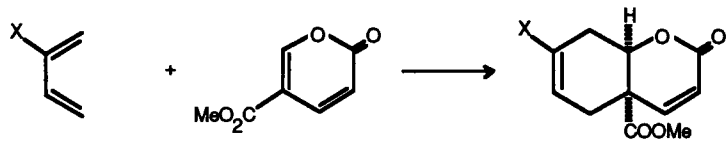



## V. Furan–Coumalate Diels–Alder Approach[20]

There are times when you hope that your co-worker has read everything the literature has to offer concerning a certain key reaction to learn not only the directly related but also any ancillary information. And there are times when you hope that your co-worker will take your prediction of sure success for a certain reaction on faith and will not hunt up discouraging or contradictory counterexamples in the literature (which might weaken his resolve to force the reaction to work). The furan–coumalate cycloaddition was a clear example of the latter. Although there was good precedence in our own work for the reaction to occur in the desired manner, e.g., **84** acting as dienophile and **54** serving as diene to give **86a**, there was equally good precedence for the alternative reaction mode, namely **84** as diene and **54** as dienophile to give a completely different cycloadduct, the 7-oxabicyclo [2.2.1]heptene **87**. Several groups [21] had carried out cycloadditions of the



latter type with coumalates **54** and several simple dienes, e.g., butadiene, isoprene, and 2-ethoxybutadiene **88abc**, to give the adducts **89abc**. Thus a strong argument could be made, based on literature precedent, that the 3,4-dialkoxyfuran would serve as diene rather than dienophile versus coumalate and lead to **87** rather than the desired **86a**. Only experiment could settle this question of chemoselectivity.



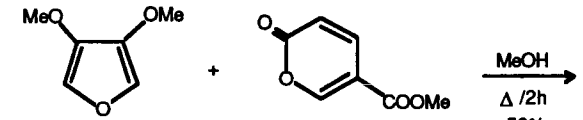

**88a** X = H
**88b** X = Me
**88c** X = OEt

**54**

**89a** X = H
**89b** X = Me
**89c** X = OEt

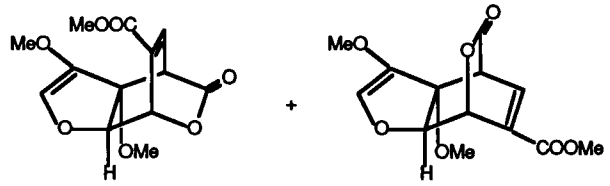
Therefore, there were four possible problems with the reaction of **84** with **54**: (1) chemoselectivity: would **86a** or **87** be favored? (2) regioselectivity: would **86a** or **86b** be favored? (3) stereoselectivity: we have not even discussed endo versus exo selectivity of the desired mode of cycloaddition; and finally (4) the crucial question of reactivity, namely, would **84** and **54** react at all? Consider that in this reaction the aromaticity of two nonbenzenoid aromatic systems must be broken in a single thermal reaction under mild conditions. It might well have been the case that the loss of resonance energy in the transition state was too great to permit the reaction to occur at all.

As it turned out, we won on three of the four possible problems and tied on the last one. The two components *reacted*, with the right *chemoselectivity* and complete *regioselectivity* but with no *stereocontrol*. We tested the reaction first on a model system, namely the reaction of 3,4-dimethoxyfuran **90**[22] with methyl




**90**

**63**




**91n**

**91x**

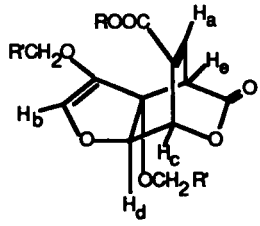
coumalate **63**.[23] Refluxing a solution of these two components in methanol gave, after silica gel chromatography, the two pure stereoisomers **91nx** in approximately equal amounts in a combined yield of 52%.

The high-field $^1$H NMR spectra of the isolated isomers (Table II) clearly indicated that the isomers possessed the same regiochemistry and differed only in their stereochemistry. This was obvious from the splitting patterns of $H_c$ and $H_e$, the protons $\alpha$ to the oxygen and carbonyl of the lactone, respectively. $H_c$ appeared as a doublet of doublets, coupled both to $H_d$ and via allylic coupling to $H_a$, while $H_e$ appeared as a simple doublet in each isomer. This could be the case only if the cycloadditions had occurred with the expected regiochemistry as shown. The stereochemistry of the adducts could not be determined simply from their NMR spectra. However, the less polar fraction from the chromatography, the exo isomer **91x**, proved to be nicely crystalline, so its structure could be assigned as exo by a single-crystal X-ray crystallographic analysis.

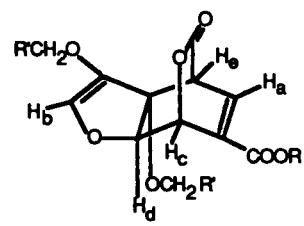
The reasons for the chemoselectivity are not obvious. One reasonable

TABLE II

SELECTED $^1$H NMR DATA FOR CYCLOADDUCTS[25]



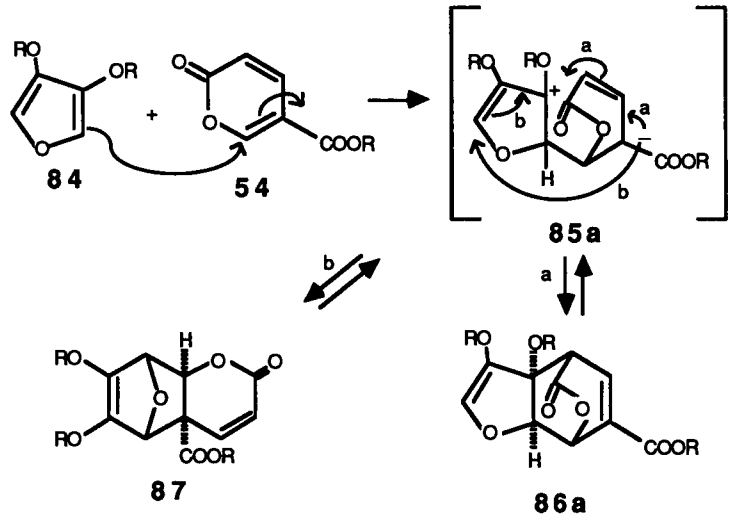

**n**




**x**

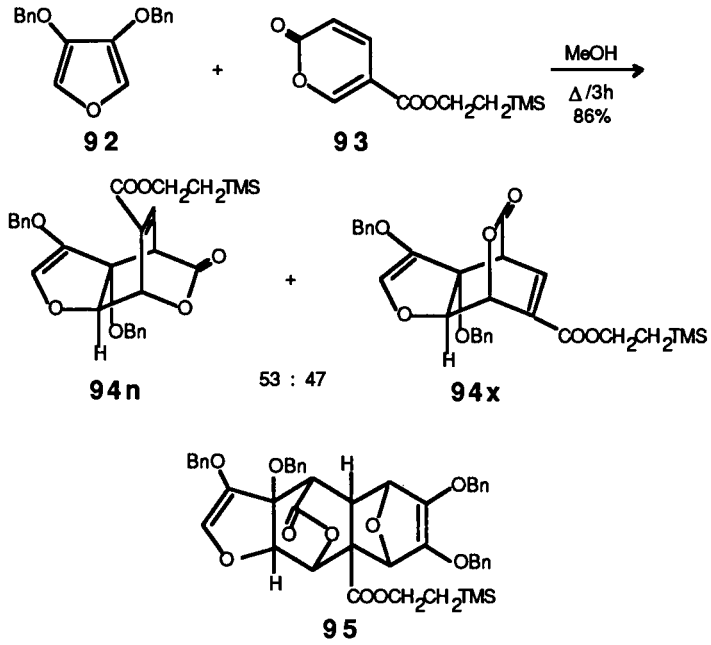
| | Compound | | | |
|---|---|---|---|---|
| | **91n** | **91x** | **94n** | **94x** |
| R | Me | Me | $(CH_2)_2TMS$ | $(CH_2)_2TMS$ |
| R' | H | H | Ph | Ph |
| $H_a$ | 7.26 | 7.35 | 7.17 | 7.30 |
| $H_b$ | 5.95 | 6.20 | 6.01 | 6.25 |
| $H_c$ | 5.79 | 5.84 | 5.78 | 5.84 |
| $H_d$ | 4.77 | 4.33 | 4.81 | 4.39 |
| $H_e$ | 4.00 | 4.12 | 4.17 | 4.27 |
| $J_{ae}$ | 6.75 | 6.1 | 6.85 | 6.2 |
| $J_{cd}$ | 4.7 | 2.0 | 4.7 | 2.2 |
| $J_{ac}$ | 2.4 | 1.75 | 2.3 | ~1.0 |

hypothesis is that with these particular reagents, both cycloaddition reactions are not concerted but rather proceed via the same zwitterionic intermediate **85a**, which can then close reversibly to either **86a** or **87**. The ratio of products would then be determined by thermodynamics, namely the difference in the stability of the two structural isomers. One would predict that the bicyclo[2.2.2]octene system of **86a** would be much more stable than the bicyclo[2.2.1]heptene system of **87**, and thus **86a** would be expected to predominate in the thermodynamic equilibrium.[24]



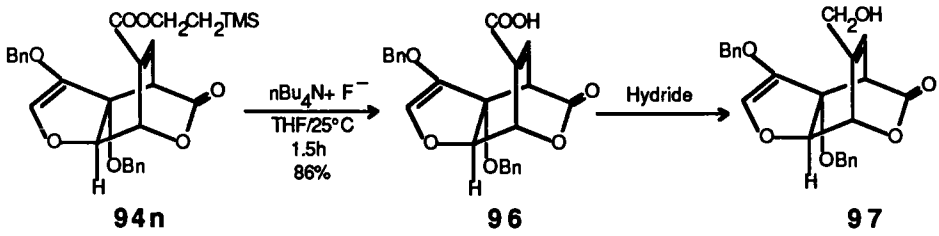

The isolation of only the desired regioisomers implies that our original proposal concerning the stability of the zwitterionic intermediates **85ab** (or the corresponding asymmetric transition states) must have some validity. The fact that a 1 : 1 mixture of stereoisomers is obtained is not surprising, since there is reasonable secondary orbital overlap in both the endo and exo transition states.

Now that the key step of the synthesis had been carried out successfully in a model series, we turned to preparing the starting materials for the real system, choosing 3,4-bis(benzyloxy)furan **92** and 2-(trimethylsilyl)ethyl coumalate **93** as the two components. The furan **92** was prepared in five steps from diglycolic acid by a slight modification of the literature route,[22] while the coumalate **93** was made in three steps from inexpensive DL-malic acid via coumalic acid and its acid chloride.[23] Reaction of **92** and **93** in refluxing methanol for 3 hours gave a 1 : 1 mixture of **94n : 94x** in 38% yield with approximately 20% of a 2 : 1 furan : pyrone adduct being formed for



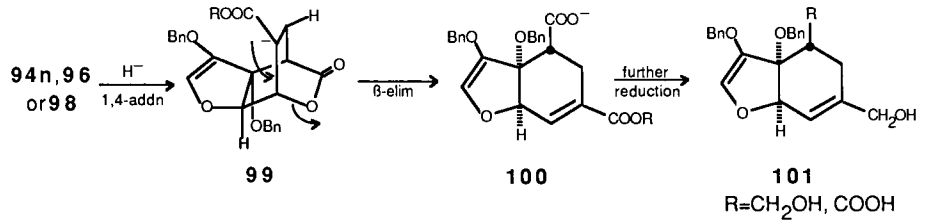

which the structure **95** (mixture of stereoisomers) has been assigned. This latter compound **95** is presumably formed by a Diels–Alder addition of the electron-rich furan **92** to the strained acrylate unit of the initial cycloadducts **94nx**. However, a simple modification of the reaction conditions as follows permitted us to overcome this obstacle. Refluxing a methanol solution containing 10 equivalents of **93** and 1 equivalent of **92** for 3 hours followed by silica gel chromatography afforded an 86% yield of **94n** and **94x** in a ratio of 53 : 47 with only a trace of **95** being produced. In addition, this simple chromatography returned 86% of the unreacted coumalate **93** in pure form for use in further cycloadditions. The structures of the endo and exo adducts **94n** and **94x** were assigned by the close similarity of their $^1$H NMR spectra to those of **91n** and **91x**, respectively, especially the coupling constants of $H_c$ and $H_e$ (Table II).

Although both stereoisomeric adducts **94nx** are potentially useful intermediates for the synthesis of **3**, the possible difficulties associated with isomerization at C-2[26] led us to initially examine only the conversion of the endo adduct **94n** to **3**. It should be pointed out that this readily available compound **94n** possesses the entire molecular skeleton of the desired target **3** with functionality at all the necessary positions but with two major problems, namely an ester at C-4 instead of a methyl group and the incorrect stereochemistry at C-5.




**94n** **96** **97**

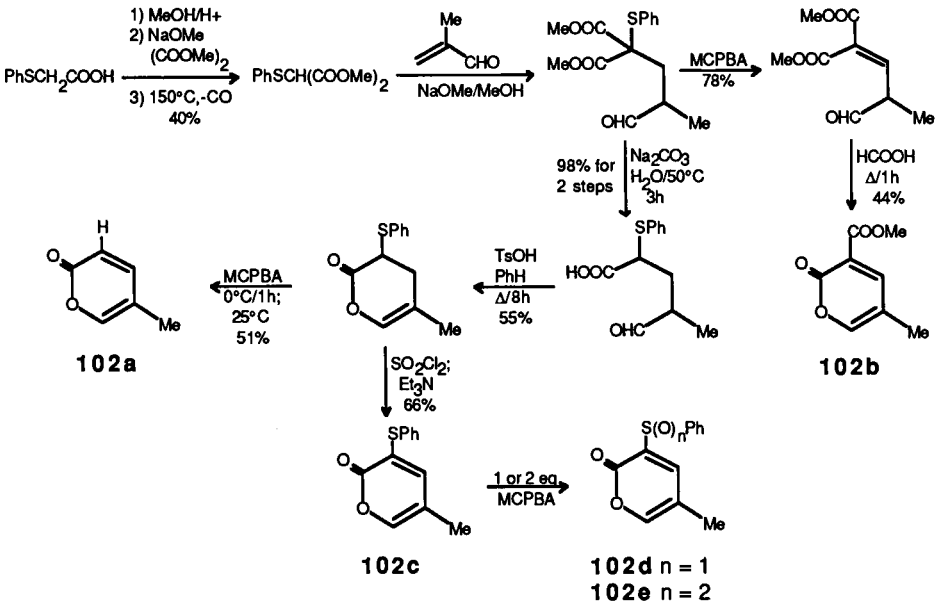
We first corrected the functionality at C-4 as follows. Fluoride-promoted hydrolysis of the silylethyl ester of **94n** furnished the crystalline acid **96** in 86% yield. Many methods were attempted to reduce this acid or the corresponding silylethyl and methyl esters to the desired allylic alcohol **97**, including the following: borane (and several complexed boranes) on the acid **96**; sodium and zinc borohydride on the derived mixed anhydride **98**; lithium ethoxyaluminum hydride on the ester **94n**; DIBAL on the methyl ester; and lithium triethylborohydride on various esters. Although in a few cases (e.g., the first two mentioned above) we could obtain low yields of **97** (20–25%), the preferred reaction pathway generally involved 1,4-addition of hydride to the acrylate moiety to produce an intermediate carbanion **99**, which then opened the strained lactone via β-elimination to give ring-opened allylic alcohols such as **101**, with either an acid or hydroxymethyl function at



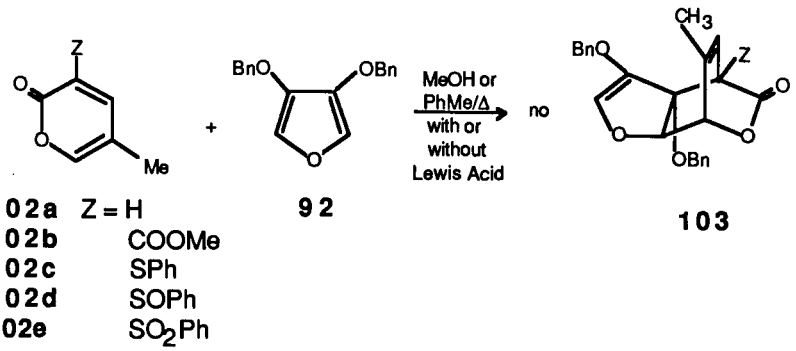

**99** **100** **101**

R=$CH_2OH$, COOH

C-2. While attempting to find other reduction methods to overcome this difficulty, we decided to try a different approach. Since we eventually wanted a methyl group at C-4 of **3**, we wondered if we could use a pyrone in the initial cycloaddition which already had a methyl group at C-5 of the pyrone. For this reason we prepared several 5-methylpyrones **102a–e**, the parent and several analogs with electron-withdrawing substituents at C-3 (in order to stabilize the full or partial negative charge of the zwitterionic intermediate such as **85a**). The preparation of these compounds is shown in Scheme 3. However, reaction of **102a–e** with **92** in methanol or toluene at various temperatures up to reflux with or without Lewis acids gave none of the desired cycloadduct **103**. Without Lewis acid, starting materials were recovered; with Lewis acids, the pyrone was recovered but the furan was

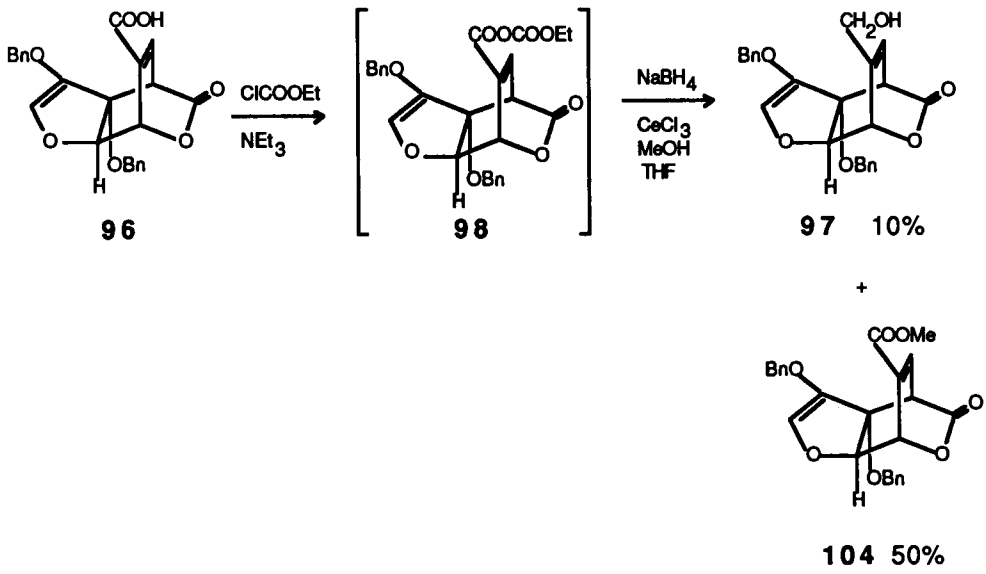



SCHEME 3



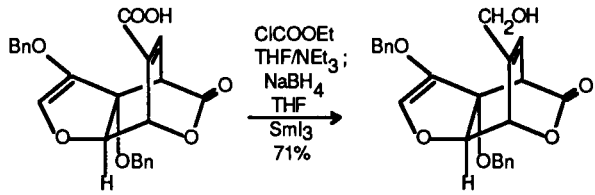

decomposed. Thus it seems that if C-5 of the pyrone bears an electron-donating group, even a methyl group, production of the desired cycloadduct, e.g., **103,** is totally suppressed.

It should be pointed out that even if this alternative approach had worked, the overall savings, in terms of the total number of steps in the synthesis, would really have been small. The silylethyl coumalate **93** is available in three steps from malic acid, while the 5-methylpyrones **102a–e** require anywhere from six to nine steps to prepare. Thus the benefit of not having to



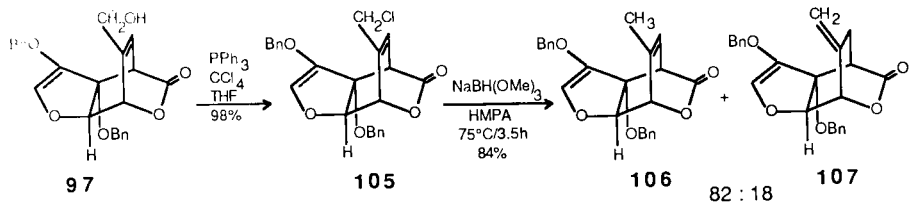

convert ester to methyl would have been offset by a longer sequence in making the starting materials.

The solution to our problem of selective reduction came from a modification of the work of Luche[28] on the 1,2-reduction of enones using sodium borohydride in the presence of trivalent lanthanide salts. Although Luche has not looked extensively at other functionalities, we thought that the principle of modifying the borohydride reagent to favor 1,2- over 1,4-reduction might apply as well to other $\alpha,\beta$-unsaturated carbonyl or carboxyl groups. Therefore we treated the mixed anhydride **98**, prepared *in situ* from **96**, with methanolic sodium borohydride in the presence of dissolved $CeCl_3$. Although about 10% of the desired alcohol **97** was produced, the major product was the corresponding methyl ester **104**, the not-unexpected product of methanolysis of the mixed anhydride **98**. Clearly it was necessary to find a trivalent lanthanide salt which was soluble in aprotic solvents. At this point, we began a tour of the lanthanide series of the periodic table. After several unsuccessful attempts to use various erbium and cerium salts, we finally succeeded by using samarium triiodide, which is partially soluble in THF. Thus, addition of the anhydride **98**, prepared *in situ* from **96**, to a suspension of samarium triiodide in THF at 0°C followed by slow addition of sodium borohydride at 5–15°C produced the desired alcohol **97** in 71% yield. Thus, by using an organic-soluble trivalent lanthanide salt, we could induce sodium borohydride to effect 1,2-reduction rather than 1,4-reduction of the reactive mixed anhydride. We are currently attempting to use this




**96** **97**

alcohol **97** for the preparation of the bottom halves of the milbemycins ($\alpha_9$, $\alpha_{10}$, and F), which have an acyloxymethyl group at C-4. Conversion of the hydroxymethyl group of **97** to methyl was attempted by several different methods, including various hydride reductions of the corresponding primary bromide, chloride, or sulfonate; tributyltin hydride/AIBN reduction of the primary bromide or chloride; and cupric sulfate/DMF reduction of the bromide. All of these met with somewhat mixed results, generally giving only fair yields of the desired methyl compound. The best method proved to be reduction of the chloride **105** (prepared in 98% yield from the alcohol **97** by treatment with triphenylphosphine and carbon tetrachloride) with sodium (trimethoxy)borohydride in warm HMPA to give an 82:18 mixture ($^1$H NMR integration) of the desired endocyclic olefin **106** and its exocyclic isomer **107** in 84% yield. We were unable initially to separate these isomers and thus used the mixture in separate steps. Later we found that **106** could be crystallized from the mixture. We have not yet been successful in isomerizing the exocyclic isomer **107** into the endocyclic **106** via various metal-catalyzed processes.

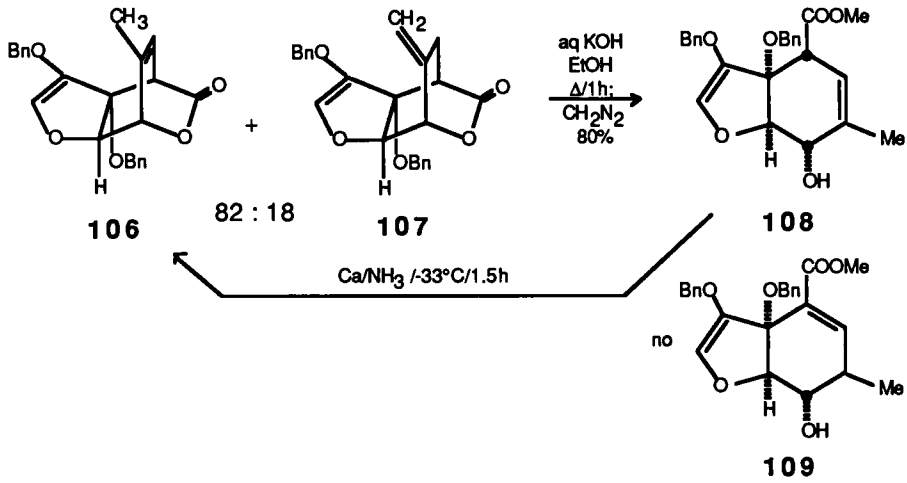



**97** **105** **106** 82 : 18 **107**

Having surmounted one of the two major synthetic hurdles, namely the conversion of the ester at C-4 into the desired methyl group, we turned our attention to the final synthetic challenge, namely the inversion of the alcohol stereochemistry at C-5. All along, from the very beginning of our synthetic planning, we had assumed that the sequence of allylic alcohol oxidation to the enone followed by sodium borohydride reduction would give the desired

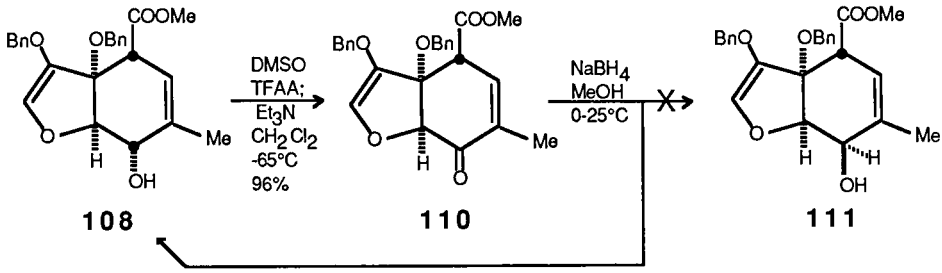
5$\beta$-alcohol, as in the natural series.[4] Therefore we attempted to put this planning into practice.

The first step involved hydrolysis of the mixture of lactones to give the opened hydroxy acid. We initially tried to carry out this transformation under very mild conditions in order to avoid any potential problems associated with C-2 epimerization or conjugation of the resulting $\beta,\gamma$-unsaturated acid to the $\alpha,\beta$-unsaturated acid. This type of epimerization and conjugation in base has been seen often in both the natural series[27a] and simpler bottom half analogs.[27b] However, our inability to open the lactone of our system under mild conditions forced us to use more vigorous conditions. Hydrolysis of the 82 : 18 mixture of lactones **106** and **107** with potassium hydroxide in refluxing aqueous ethanol for 1 hour produced the hydroxy acid, which was immediately esterified with diazomethane to give the hydroxy ester **108** in 80% overall yield. We don't know if the undesired isomer **107** is converted into **108** or if the product is derived solely from **106**, although we suspect the latter to be true (with any products derived from **107** being destroyed under these conditions). We observe none of the corresponding $\alpha,\beta$-unsaturated ester **109** in this reaction. The $\beta,\gamma$-unsaturated ester **108** is stable indefinitely at 25°C and can be purified by silica gel chromatography without conjugation to the $\alpha,\beta$-unsaturated isomer **109**. We could also show that no epimerization at C-2 had occurred by recyclization of **108** to give back the lactone **106** during an attempted reduction of the benzyl groups by treatment with calcium in ammonia. For this to occur, the hydroxyl and ester groups must both still have the $\alpha$-stereochemistry. Thus our system differs significantly with regard to

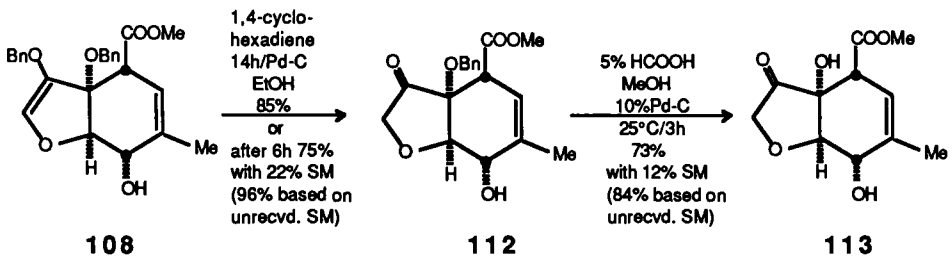


epimerization and conjugation from the natural material and the structurally similar one of Fraser-Reid,[27b] presumably because of differences in the relative energies of the isomers due to the presence of the benzyl enol ether and benzyl ether.

We next attempted to correct the C-5 stereochemistry. Oxidation of the allylic alcohol **108** under modified Swern conditions, using trifluoroacetic anhydride, DMSO, and triethylamine in dichloromethane at −65°C, afforded the enone **110** in 96% yield. However, disaster struck when we reduced this enone **110** with sodium borohydride in methanol at 0°C to 25°C, the conditions used for the conversion of 5-oxomilbemycin D to milbemycin D.[4] Only the starting 5$\alpha$-alcohol **108** was obtained, with none of the desired, and expected, 5$\beta$-alcohol **111** being produced! Thus it appears that the free hydroxyl group at C-7 is required to direct this simple reduction from the $\alpha$ face of the molecule. The reaction that we had been depending on from the start, based on reasonable literature precedent, had completely failed us in the end!

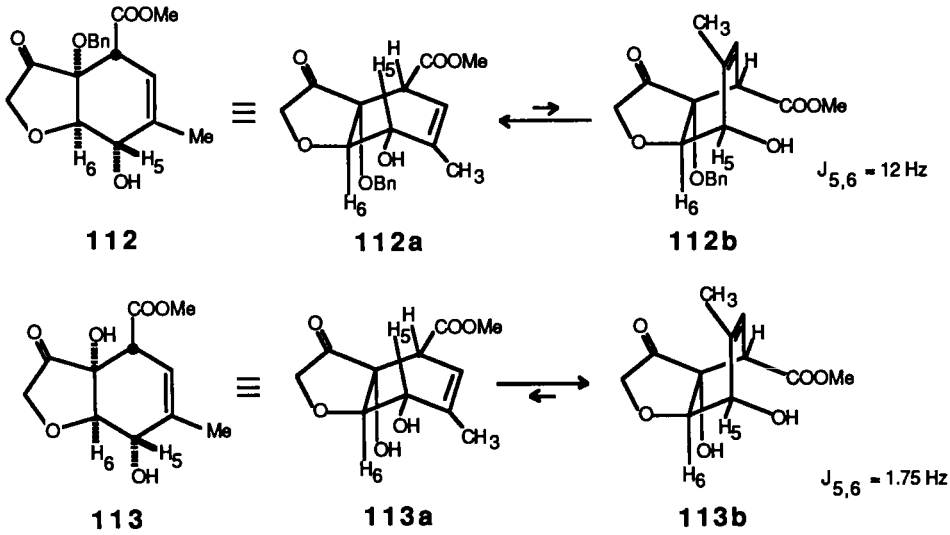



We originally tried to get around this difficulty by trying other totally different approaches, namely inversion of stereochemistry by the Mitsunobu reaction or by displacement of the corresponding mesylate of **108** by various nucleophiles, including cesium acetate and formate and potassium acetate in the presence of crown ethers. None of these methods proved satisfactory. We then decided to try to free the hydroxyl at C-7 by removing the benzyl protecting groups so that our enone would be even closer to the natural system and perhaps would reduce correctly. Many methods for benzyl ether removal proved unsuccessful (lithium or calcium in ammonia, chromate oxidation to benzoate and hydrolysis, benzylic bromination and hydrolysis, triarylaminium radical oxidation–hydrolysis, simple catalytic hydrogenation). However, palladium-catalyzed transfer hydrogenation of the benzyl ethers could be successfully carried out. Treatment of **108** with 1,4-cyclohexadiene and palladium on carbon in ethanol gave an excellent yield of the ketone **112**, in which the more sterically accessible benzyl enol ether has

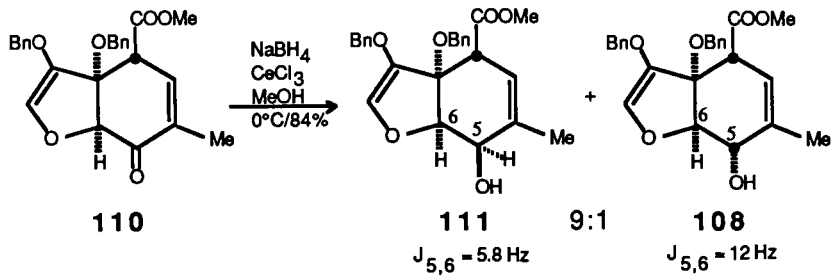



**108** **112** **113**

been cleaved. Further treatment under these conditions did not remove the more hindered tertiary benzyl ether. But switching to the more reactive hydrogen source, formic acid, effected the desired removal of the tertiary benzyl ether to give the ketodiol **113** in good yield. However, the coupling constants of the H-5 and H-6 protons in the $^1$H NMR of **113** gave us a real shock and convinced us initially that maybe we had isomerized the alcohol at C-5 by solvolysis under the acidic conditions! In all of these compounds, the six-membered ring is forced to adopt a boatlike conformation (as shown by both simple Dreiding models and more sophisticated MM2 calculations). In **112**, $J_{5,6}$ was 12 Hz, indicating that the molecule probably exists predominately in the conformation **112a** rather than **112b** (with the alcohol and ester groups occupying the flagpole–bowsprit positions). However, in **113**, $J_{5,6}$ was only 1.75 Hz! Thus, either the change from benzyl ether to alcohol forced the molecule to now exist in a totally different conformation (**113b** rather than **113a**) or the stereochemistry at C-5 had been inverted to give the desired final product **3**! We originally could not see any strong reason for the molecule **113** to adopt a different conformation from that of **112** and thus initially favored the idea that inversion at C-5 occurred via the allylic cation (our critical faculties were clearly clouded by a lot of wishful thinking at this point). We soon realized that this was not the case. First, one could argue that in **113b** the C-7 hydroxyl could now form a strong internal hydrogen bond to the ester, which was not possible in **113a** or indeed in the benzyl ether **112**. Thus it was very likely, on this basis alone, that epimerization had not occurred. Second, a coupling constant of 1.75 Hz was inconsistent for the expected $J_{5,6}$ for **3** since in most of the known natural avermectins and milbemycins and their close synthetic analogs, $J_{5,6}$ was about 5–6 Hz. The final evidence for the structure of **113** came from comparison of its $^1$H NMR with that of the known 5-epi avermectins prepared by Mishima and co-workers,[4] which had $J_{5,6}$ = 1.5 Hz. Thus it was clear that the ketodiol had the structure **113**. However, we had obviously developed a mild method for the selective removal of the benzyl groups in good yield and had prepared the bottom half synthon **113** for the 5-epi avermectins. All that remained was the nagging problem of correcting the C-5 stereochemistry.

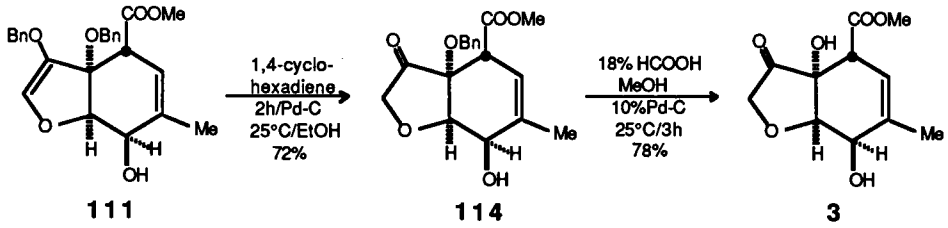



The solution to this problem had been before our eyes for some time but we hadn't looked closely enough. In fact, this synthesis is essentially a paean to the value of lanthanide salts in organic chemistry. Luche[28] had shown that added lanthanide salts not only favor 1,2- over 1,4-reduction of enones but also have an effect on the stereoselectivity of the reduction. In cyclohexenones one generally favors the equatorial alcohol by the use of lanthanide-modified hydride reagents, although there are some notable exceptions (with piperitone the axial alcohol is favored). We hoped that the presence of lanthanide salts would help promote complexation of the 7$\alpha$-benzyl ether with the borohydride reagent to internally deliver hydride from the $\alpha$ face. This turned out to be the case. Reduction of the enone **110** with sodium borohydride and $CeCl_3$ in methanol at 0°C furnished a 9 : 1 mixture of the desired 5$\beta$-alcohol **111** and the starting 5$\alpha$-alcohol **108** in 84% yield. The stereoselectivity is greatly lowered by trace amounts of DMSO left over from



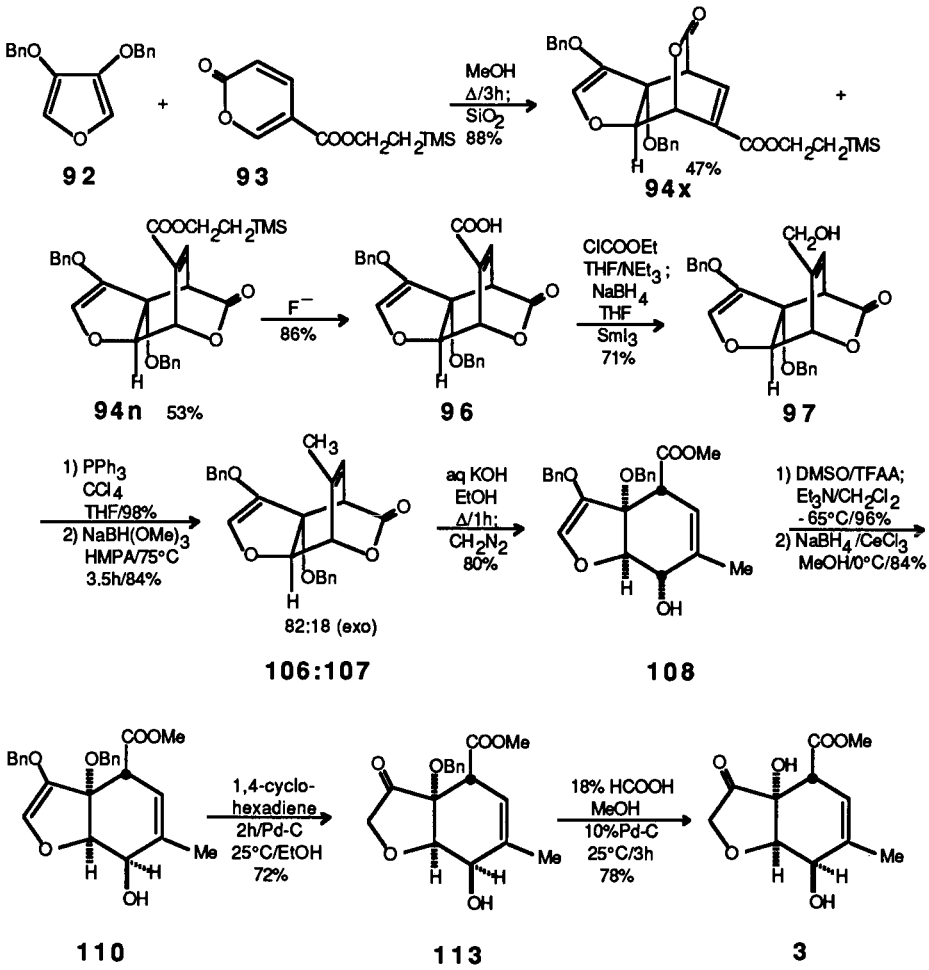
the preparation of **110** from **108**. That the 5$\beta$-alcohol **111** had indeed been formed was inferred from the 500-MHz $^1$H NMR, in which the coupling constant between the hydrogens at C-5 and C-6, $J_{5,6}$, was calculated to be 5.8 Hz; in the starting alcohol **108** $J_{5,6}$ is 12 Hz. Thus by the simple expedient of adding $CeCl_3$ and carrying out the reduction at 0°C, we were able to completely invert the stereoselectivity of the reduction from producing totally **108** to giving a 9:1 mixture favoring **111**.

The synthesis of **3** was completed in two steps of transfer hydrogenation, analogous to those carried out earlier for the C-5 epimer **108**. Reduction of the sterically more accessible benzyl enol ether of **111** with 1,4-cyclohexadiene and palladium on carbon in ethanol at 25°C for 2 hours furnished the cyclopentanone **114** in 72% yield. Removal of the more hindered tertiary benzyl ether of **114** required a more reactive hydrogen source. Treatment of **114** with 18% formic acid and palladium on carbon in methanol at 25°C for 3.5 hours afforded the desired target molecule **3** in 78% yield (based on unrecovered starting material). Carrying out this final transfer hydrogenation until all of the starting material disappeared resulted in the formation of a substantial amount of the overreduced product in which the 3,4-double bond has also been reduced. The structure assignment of **3** is again based on spectroscopic data—IR, MS, and especially 500-MHz $^1$H NMR, which indicates that the $J_{5,6}$ is 5.6 Hz, a value that corresponds well with those of the natural product and its derivatives.[4]




**111** **114** **3**

Thus we have finally reached our goal of a rapid and efficient total synthesis of the bottom half of ivermectin **3**. Although this account of the synthesis has necessarily rambled a bit to examine all of the false steps and failed pathways on the way to **3**, the overall synthesis is in fact quite concise, as is shown in Scheme 4. The synthesis of **3** requires only 10 steps from **92** and **93** and proceeds in an overall yield of 9%. The 5-epimer **113** is available in only eight steps and 17% overall yield.[29] We believe this represents a really excellent construction of a very functionalized and oxygenated substructure of a complex natural product and hope that others will view it as somehow elegant, beautiful, or clever.




SCHEME 4

## VI. Conclusion

With the completion of the synthesis of **3**, the descriptive part of this account is finished. However, it is instructive to review briefly what new synthetic methods or principles have come forth from this work and to consider what our further goals are. We have (1) provided new information on intramolecular Diels–Alder cyloadditions of furfuryl systems (especially amides and esters); (2) determined that there is a thermodynamic bias against cycloaddition of secondary *N*-furfurylacrylamides and for tertiary *N*-furfuryl

acrylamides; (3) exposed a novel and perhaps useful *gem*-dimethyl effect in these intramolecular cyclizations; (4) discovered and explained the reasons for the diastereoselectivity of side-chain substituents in these cycloadditions; (5) developed a new method for the conversion of these furan cycloadducts into cyclohexenol derivatives; (6) discovered new, interesting rearrangements in the reactions of 7-oxanorbornene systems with electrophiles; (7) developed a useful method for the easy introduction of asymmetry into the cycloadducts by the use of L-valinol as a chiral auxiliary; (8) explored in detail the preparation of unsymmetrical 4,6-disubstituted pyrones and their cycloadditions with electron-rich olefins; (9) developed a good method for the synthesis of highly functionalized bridged olefinic lactones and showed that they are good precursors of tetra-, penta-, and perhaps even hexasubstituted aromatic systems; (10) produced the first example of the cycloaddition of two nonbenzenoid aromatic systems (furan and pyrone) in which the aromaticity of both is lost in one step under mild conditions; (11) developed a new method for the 1,2-reduction of acids to allylic alcohols using a samarium triiodide-modified borohydride reagent; (12) provided an additional example of the utility of lanthanide salts in controlling the stereoselectivity of the 1,2-reduction of enones; and (13) determined the preferred conformation of close analogs of **3** by $^1$H NMR measurements—all in addition to accomplishing the primary goal of synthesizing **3**. For the future, we hope to (1) investigate the use of compounds such as **97** for the preparation of the natural materials (milbemycins $\alpha_9$, $\alpha_{10}$, and F) with a (2-pyrroloyl)oxymethyl group at C-4;[30] (2) develop a method for transforming the exo adduct **94x** into the ivermectin bottom half **3**; (3) study the reaction of the 7-keto derivatives of **3** (with the alcohols protected) with various nucleophiles; (4) extend this synthesis to the preparation of the natural products themselves and several simpler macrocyclic analogs; and (5) further study the use of the furfuryl acrylate cycloadducts for the preparation of these and other natural products.

## Acknowledgments

I want to thank my excellent co-workers: Jeffrey Hagenah, who developed the synthesis of unsymmetrical coumalates, studied their cycloadditions, and attempted the synthesis of aklavinone; Leslie Street, who began the ivermectin project, prepared the *N*-furfurylacrylamide cyloadducts and studied their further chemistry, and carried out the initial furan coumalate cycloaddition; Yoshi Usui, who picked up the alternate approach and by careful and hard work carried it through to the synthesis of the 5-epi compound; Truc Vu, who studied the furfuryl acrylate cycloadditions, took over the second approach, and completed the synthesis of **3**; and finally David Head and Jackie Gervay, who are continuing to work on aspects of this project. I am also very grateful to the rest of my research group at UCLA for their intellectual and material input. Finally, I must thank the agencies who supported this research: in its early stages, the Agricultural Research Division of the American Cyanamid Company; and since then, the Institute of General Medicine of the National Institutes of Health via grant GM 31349.

## References


1. H.G. Davies and R. H. Green, *Nat. Prod. Rep.* **3,** 87 (1986).
2. The early funding for this project was provided by a grant from the Agricultural Research Division of American Cyanamid Co. We gratefully thank them for this support and their continuing interest and helpful discussions.
3. M. Prashad and B. Fraser-Reid, *J. Org. Chem* **50,** 1564 (1985).
4. H. Mishima, J. Ide, S. Muramatsu, and M. Ono, *J. Antibiot.* **36,** 980 (1983). For the reduction, see also J. C. Chabala, A. Rosegay, and M. A. R. Walsh, *J. Agric. Food Chem.* **29,** 881 (1981).
5. A. G. M. Barrett and N. K. Capps, *Tetrahedron Lett.* **27,** 5571 (1986).
6. A preliminary communication on this approach has been published. M. E. Jung and L. J. Street, *J. Am. Chem. Soc.* **106,** 8327 (1984).
7. K. A. Parker and M. R. Adamchuk, *Tetrahedron Lett.* p. 1689 (1978).
8. (a) T. Mukaiyama, T. Tsuji, and N. Iwasawa, *Chem. Lett.* p. 697 (1979); (b) T. Mukaiyama and N. Iwasawa, *Chem. Lett.* p. 29 (1981).
9. (a) A similar, though much weaker, effect has been observed in the cyclization of substituted 2-(4-pentenyl) furans. D. D. Sternbach and D. M. Rossana, *Tetrahedron Lett.* p. 303 (1982). (b) Experiments have been carried out to determine the reasons for this effect using furfuryl methyl fumarates and indicate that the higher population of reactive rotamers on substitution is more important than the decrease in the furyl-C-X bond angle. M. E. Jung and J. Gervay, *Tetrahedron Lett.*, in press (1988).
10. Other similar reductive eliminations of chloroethers are well known. For leading references, see P. G. Sammes and L. J. Street, *J.C.S. Chem. Commun.* p. 666 (1983).
11. (a) R. B. Woodward and F. V. Brutcher, Jr., *J. Am. Chem Soc.* **80,** 209 (1958); (b) C. A. Bunton and M. D. Carr, *J. Chem. Soc.* p. 770 (1963); (c) F. D. Gunstone, *in* "Advances in Organic Chemistry" (R. A. Raphael, E. C. Taylor, and H. Wynberg, eds.), Vol 1, p. 103. Wiley (Interscience), New York, 1960.
12. M. E. Jung and L. J. Street, *Tetrahedron Lett.* p. 3639 (1985).
13. M. E. Jung and L. J. Street, *Heterocycles*, **26,** 45 (1988). Molecular mechanics (MM2) calculations predict a 0.5-kcal energy difference favoring the amine leading to **32a** over that leading to **32b.**
14. M. E. Jung and C. T. Vu, submitted for publication.
15. M. E. Jung, J. A. Lowe, III, M. A. Lyster, M. Node, R. W. Pfluger, and R. W. Brown, *Tetrahedron* **40,** 4751 (1984).
16. M. E. Jung, R. W. Brown, J. A. Hagenah, and C. E. Strouse, *Tetrahedron Lett.* **25,** 3659 (1984).
17. M. E. Jung and J. A. Hagenah, *J. Org. Chem.* **52,** 1889 (1987).
18. M. E. Jung and J. A. Hagenah, *Heterocycles* **25,** 117 (1987).
19. H. Behringer and P. Heckmaier, *Chem. Ber.* **102,** 2835 (1969).
20. M. E. Jung, L. J. Street, and Y. Usui, *J. Am. Chem. Soc.* **108,** 6810 (1986).
21. (a) T. Imagawa, M. Kawanisi, and K. Sisido, *J.C.S. Chem. Commun.* p. 1292 (1971); (b) T. Imagawa, N. Sueda, and M. Kawanisi, *J.C.S. Chem. Commun.* p. 388 (1972); (c) T. Imagawa, N. Sueda, and M. Kawanisi, *Tetrahedron* **30,** 2227 (1974); (d) T. Imagawa, T. Nakagawa, M. Kawanisi, and K. Sisido, *Bull. Chem. Soc. Jpn.* **52,** 1506 (1979); (e) Y. Nakahara and T. Tatsuno, *Chem. Pharm. Bull.* **28,** 1981 (1980); (f) G. A. Kraus and K. Frazier, *J. Org. Chem.* **45,** 4820 (1980); (g) G. A. Kraus and B. Roth, *J. Org. Chem.* **45,** 4825 (1980); (h) J. D. White, T. Matsui, and J. A. Thomas, *J. Org. Chem.* **46,** 3376 (1981); (i) T. Matsui, T. Inoue, M. Nakayama, and J. D. White, *Bull. Chem. Soc. Jpn.* **56,** 647 (1983).
22. (a) P. X. Iten, A. A Hofmann, and C. H. Eugster, *Helv. Chim. Acta* **61,** 430 (1978); (b) E. McDonald, A. Suksamrarn, and R. D. Wylie, *J.C.S. Perkin I* p. 1893 (1971).

23. Methyl coumalate: J. H. Boyer and W. Schoen, "Organic Syntheses", Collect. Vol. 4, p. 532. Wiley, New York, 1963; Coumalic acid: R. H. Wiley and N. R. Smith, "Organic Syntheses", Collect. Vol. 4, p. 201.Wiley, New York, 1963.
24. Molecular mechanics calculation (MM2) predict that **86a** (R = Me) is much more stable than **87.**
25. Chemical shift data are given in parts per million downfield from internal tetramethylsilane and coupling constants are in hertz. The spectra were recorded at 500 MHz. Other resonances in the spectra are as follows: **91n,** 3.82 (3 H, s), 3.57 (3, H, s), 3.35 (3 H, s); **91x,** 3.83 (3 H, s) 3.61 (3 H, s), 3.24 (3 H, s); **94n,** 7.40–7.26 (10 H, m), 4.69 (2 H, AB, q, $J$ = 11.2 Hz), 4.65 (2 H, s), 4.30 (2 H, m), 1.05 (2 H, m), 0.06 (9 H, s); **94x,** 7.40–7.24 (10 H, m), 4.74 (2 H, s), 4.55 (2 H, d, $J$ = 11.5 Hz), 4.46 (2 H, d, $J$ = 11.5 Hz), 4.31 (2 H, m), 1.05 (2 H, m), 0.06 (9 H, s).
26. Pivnichny and co-workers [27a] report that the avermectins (2$\beta$-H) isomerize first to the 2-epimer (2$\alpha$-H) and then to the conjugated isomer ($\Delta^2$) on treatment with hydroxide in aqueous methanol. Fraser-Reid[27b] has questioned Hanessian's early work[27c] on the deconjugation of the $\Delta^2$-olefin to give the $\Delta^3$-olefin with the correct stereochemistry at C-2 under kinetic protonation, although Hanessian's latest paper[27d] contains $^1$H NMR data that seem consistent with his claim.[31]
27. (a) J. V. Pivnichny, J.-S. K. Shim, and L. A. Zimmerman, *J. Pharm. Sci.* **72,** 1447 (1983); (b) B. Fraser-Reid, H. Wolleb, R. Faghih, and J. Barchi, Jr., *J. Am. Chem. Soc.* **109,** 933 (1987); (c) S. Hanessian, A. Ugolini, D. Dubé, P. J. Hodges, and C. André *J. Am. Chem. Soc.* **108,** 2776 (1986); (d) S. Hanessian, A. Ugolini, P. J. Hodges, P. Beaulieu, D. Dubé, and C. André, *Pure Appl. Chem.* **59,** 299 (1987).
28. (a) J.-L. Luche, *J. Am. Chem. Soc.* **100,** 2226 (1978); (b) A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.* **103,** 5454 (1981); (c) J.-L. Luche, L. Rodriguez-Hahn, and P. Crabbé, *J.C.S. Chem. Commun.* p. 601 (1978).
29. M. E. Jung, Y. Usui, and C. T. Vu, *Tetrahedron Lett.* **28,** 5977 (1987).
30. We have just recently been able to convert **97** into the hydroxymethyl analog of **3** by an adaptation of the route described using a benzyl ether as a protecting group with its eventual removal by transfer hydrogenation. M. E. Jung and D. B. Head, unpublished results.
31. Since this manuscript was submitted, Hanessian has published an article which clears up this controversy. He showed that $\Delta^2$-avermectin $B_{1a}$ can be converted into 2-epiavermectin $B_{1a}$ and then by partial isomerization in the presence of imidazole into a 1:1 mixture of avermectin $B_{1a}$ and its 2-epimer, along with 10–20% of the $\Delta^2$ isomer. S. Hanessian, D. Dubé, and P. J. Hodges, *J. Am. Chem. Soc.*, **109,** 7063 (1987).

*Chapter 8*

# SYNTHESIS OF THE INDOLE ALKALOID α-CYCLOPIAZONIC ACID (αCA) BY TWO SULFUR-MEDIATED REACTIONS: DISCOVERY OF A USEFUL DIORGANOZINC REACTION

*Alan P. Kozikowski and Michael N. Greco*

*Department of Chemistry*
*University of Pittsburgh*
*Pittsburgh, Pennsylvania*



## I. Introduction

The mycotoxins (from the Greek work μύκης, meaning fungus) are a group of secondary metabolites of fungal origin.[1] As the name itself suggests, the mycotoxins are toxic substances elaborated by aggressively growing molds which are responsible for such diseases as alimentary toxic aleukia, yellow rice toxicoses (Japan), and facial eczema (New Zealand). The molds, unlike many antibiotic-producing organisms such as Streptomycetes, directly compete with humans for foodstuffs.

TABLE I

MYCOTOXINS AS REPRESENTATIVE OF THE MAIN BIOSYNTHETIC CATEGORIES OF SECONDARY METABOLITES[a]

| Biosynthetic category | Representative mycotoxins |
|---|---|
| Polyketides | |
| Tetra- | Patulin, penicillic acid, chlorflavonin |
| Penta- | Citrinin, ochratoxins |
| Hexa | Maltoryzine |
| Hepta- | Viriditoxin, cytochalasins, rugulosin, etc. |
| Octa- | Ergochromes |
| Nona- | Zearalenone, viridicatumtoxin |
| Deca- | Aflatoxins, austocystins, erythroskyrine |
| Tetronic/tetramic acids | Tenuazonic acid, cyclopiazonic acid, cytochalasins |
| Diketopiperazines | |
| Simple | Aspergillic acid, echinulins |
| Modified | Brevianamides, sporidesmins, fumitremorgens, oxaline |
| Peptides | Tentoxin, ergotamine, tryptoquivaline |
| $C_6C_3$ products | Chlorflavonin, xanthocillin, terphenyllin |
| Terpenes | |
| Mono- | Viridicatumtoxin |
| Sesqui- | Trichothecenes |
| Di- | Paspaline |

[a] From J. D. Bu'lock (1980). Reproduced with permission from Academic Press.

Aflatoxin $B_1$, a metabolite of *Aspergillus flavus*, has, in fact, been found to be one of the most potent hepatocellular carcinogens to be identified.[2] Demographic studies have associated the occurrence of aflatoxins in food supplies with a high incidence of human liver cancer in underdeveloped nations.[3]

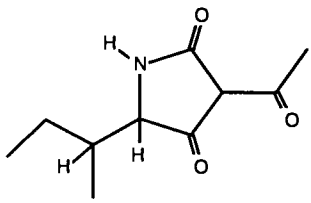
The mycotoxins are made up of a diverse class of compounds which cannot be classified readily based on any commonality of structural features. As shown in Table I, the mycotoxins are best classified in terms of the biosynthetic pathways by which they are created.[4]

In the category of tetramic/tetronic acids, one can find the compound $\alpha$-cyclopiazonic acid. This product is produced by *Penicillium cyclopium* Westling, a fungus that has been isolated from stored grain and cereal products worldwide.[5] Several outbreaks of a disease which occurred after ingestion of grain products contaminated with *P. cyclopium* have been reported by Wilson and Harrison.[6] Holzapfel was the first to isolate a major toxic metabolite from a strain of *P. cyclopium* found growing on ground nuts.[5] The toxin, designated $\alpha$-cyclopiazonic acid, was isolated by extraction with chloroform–methanol with subsequent chromatographic purification on cellulose powder followed by ion exchange chromatography.

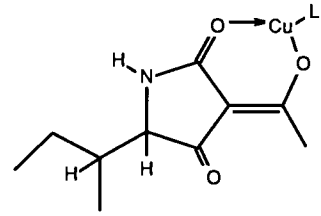
The toxicity of $\alpha$-cyclopiazonic acid ($\alpha$CA) has been investigated by

Purchase. Changes in the liver, heart, spleen, kidney, and pancreas were observed as well as necrosis of the bile duct cells in the liver.[7]

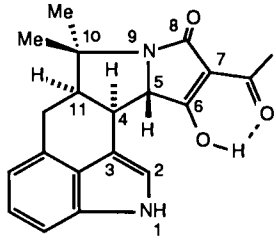
As an aside, it is pertinent to note that the first example of a naturally occurring tetramic acid was, in fact, reported as early as 1959 by Stickings.[8] This compound was obtained from a strain of *Alternaria tenuis* Auct. and has been designated tenuazonic acid. As can be discerned from its structure **1**, tenuazonic acid is probably derived biosynthetically from isoleucine. Compound **1** readily forms complexes **2** with metal cations like copper, calcium, and magnesium through its tautomeric enol form.[9]



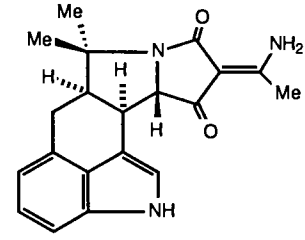
Tenuazonic acid (1)



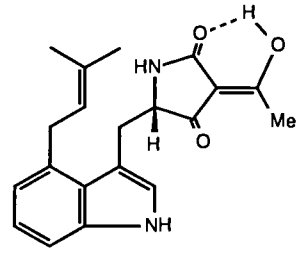
Copper bistenuazonate (2)



α-Cyclopiazonic acid (3)



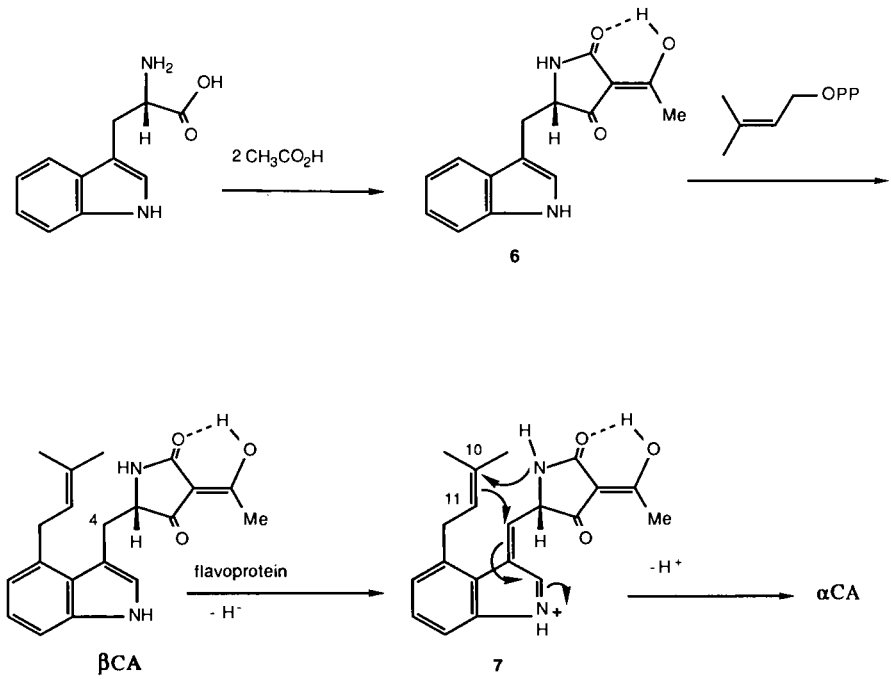
Cyclopiazonic acid imine (4)



β-Cyclopiazonic acid (5)

Holzapfel was able to determine the structure of αCA on the basis of NMR, IR, UV, and mass spectral analysis. While αCA was originally assigned the enol structure **3**, a more recent $^{13}C$ NMR study indicates that it probably exists as a mixture of three enol tautomers.[10] The toxicity of αCA, like that of tenuazonic acid, may be related to its ability to chelate trace metals *in vivo*. In addition to αCA, two other chemically related metabolites have been identified from *P. cyclopium*. These compounds are cyclopiazonic acid imine (**4**) and bissecodehydrocyclopiazonic acid **5** (also called β-cyclopiazonic acid, βCA).[11]

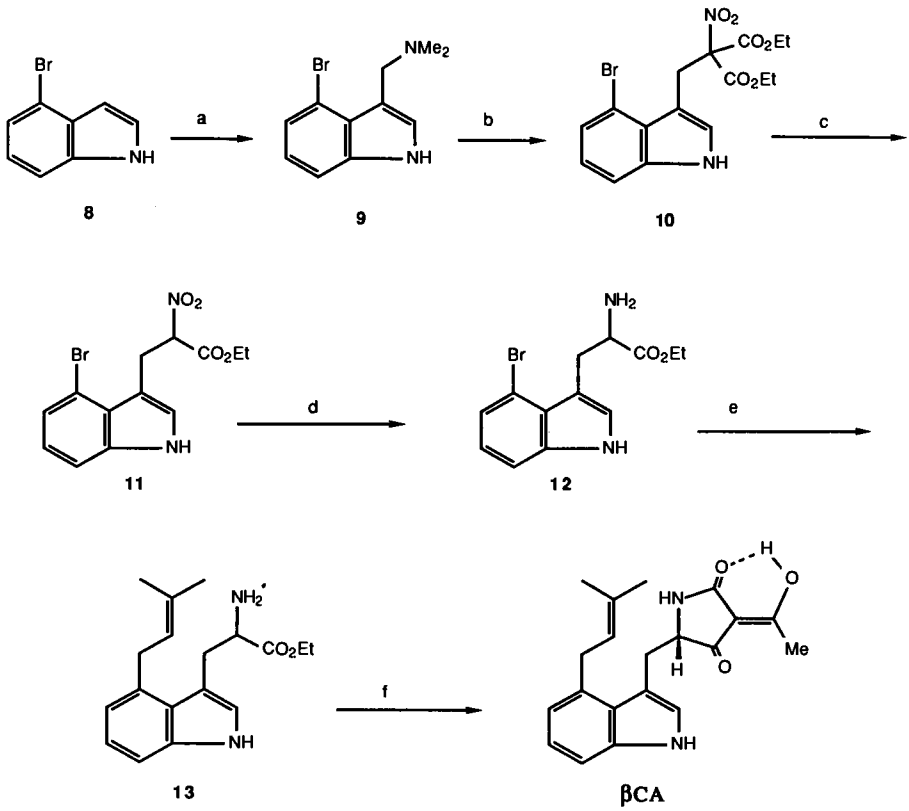
Biosynthetically, it has been shown that βCA is the direct precursor to αCA, for [1-$^{14}C$]acetate-labeled βCA was converted by *P. cyclopium* into αCA which contained 64% of the label. βCA itself is probably derived by a process involving the initial conversion of tryptophan to cycloacetoacetyl-L-tryptophan **6** followed by isoprenylation of the 4-position of the indole ring by dimethylallyl pyrophosphate (Scheme 1). The precise mechanism by which the isoprenylation reaction takes place still remains a mystery, much as it does in the biosynthesis of the ergot alkaloids. The successful execution of an alkylation reaction at the least nucleophilic position of the indole ring




SCHEME 1. A possible biosynthesis pathway to αCA from L-tryptophan.

may, however, be related quite simply to nature's clever design of an enzyme binding pocket.

The mechanism by which βCA undergoes oxidative cyclization to αCA has been proposed to involve in the first stage proton removal from C-4 (αCA numbering system) followed by an electron transfer reaction (the overall result being equivalent to a hydride ion transfer process) to provide the 3*H*-indolyidene cation **7**. Next, cyclization of this intermediate by a route involving attack of the π electrons of the C-10, C-11 double bond on the C-4 center would produce a stabilized 3° carbocation at C-10. Lastly, the nitrogen atom of the tetramic acid ring can attack the 3° cationic center to give αCA upon proton loss.[5,12]




SCHEME 2. Holzapfel–Gildenhuys synthesis of βCA. (a) $CH_2O$, $HN(Me)_2$, $CH_3CO_2H$-$H_2O$; (b) $HC(NO_2)(CO_2Et)_2$, cat. KOH, toluene, 130 °C; (c) i, NaOEt, 1 : 1 EtOH-$Et_2O$, rt, 4 h; ii, $H^+$; (d) $Na_2S_2O_4$, 1 : 1 DMF-$H_2O$, 60°C, 15 min; (e) π-(3,3-dimethylallyl)nickel (I) bromide, DMF, 60 °C, 12 h; (f) i, diketene, EtOH, -5 °C to 0 °C, 12 h; ii, NaOMe, benzene reflux, 6 h; iii, $H^+$.

Because of the structural uniqueness of αCA, the unanswered questions concerning its biosynthesis,[13] and the need to learn more about the molecular basis of its biological actions, we were encouraged to develop a total synthesis approach to this molecule.

At the time we undertook our efforts, the only published synthetic endeavor directed toward the cyclopiazonic acids was a successful synthesis of βCA. Holzapfel and Gildenhuys were able to construct this 3,4-disubstituted indole through a scheme beginning with the elaboration of 4-bromoindole (**8**) to its tryptophan derivative **12** by the use of fairly conventional methodology. Thus, 4-bromoindole was converted to its gramine derivative **9**, a displacement reaction was then carried out using diethyl nitromalonate, and the resulting diester **10** was decarboethoxylated to provide **11**. After nitro group reduction, the dimethylallyl unit was introduced by means of π-(3,3-dimethylallyl)nickel(I) bromide. Lastly, the tetramic acid unit was assembled by reaction of **13** with diketene to afford an intermediate acetoacetamide, which was cyclized under basic conditions. Holzapfel's route to βCA is summarized in Scheme 2.[14]

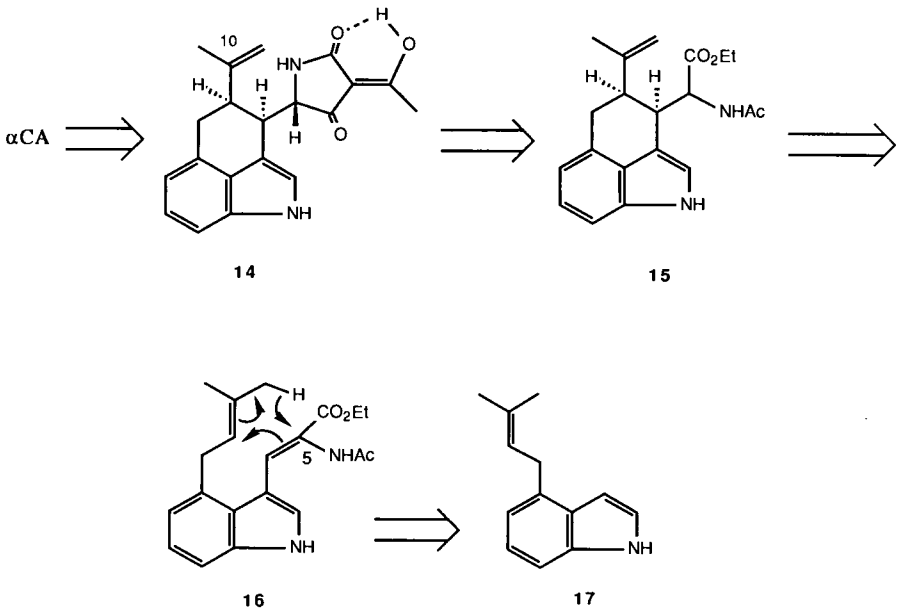
In the following section, we turn to a description of our own synthetic endeavors in this area. As we shall see, these studies proved most rewarding, for they led to the discovery of a rather unusual diorganozinc reaction.

## II. Synthesis of αCA

### A. An Ene Approach to αCA

In the initial stages of our synthetic investigations of αCA, we were taken with the notion of carrying out a biosynthetically patterned synthesis of the molecule. If we cleave the C-9, C-10 bond of αCA to form the tricycle **14** (Scheme 3), one might well imagine reconstruction of this bond by a process involving, like the proposed biosynthesis itself, formation of a carbocation at C-10. We envisioned the use of mercury(II) as our "super-proton" source for the induction of this ring closure. Further simplification of **14** by excision of acetoacetic acid from the tetramic acid unit and by rupture of the C-4, C-11 bond of **15** leads to the 1,7-diene **16**. From such a structure, the possibility of an intramolecular ene process with an amidoacrylate as the enophile becomes apparent. Additionally, should **16** be protonated at the C-5 carbon center, then an indolyidene cation evolves which is structurally akin to the cation **7** proposed as a likely intermediate in the biosynthesis of αCA.

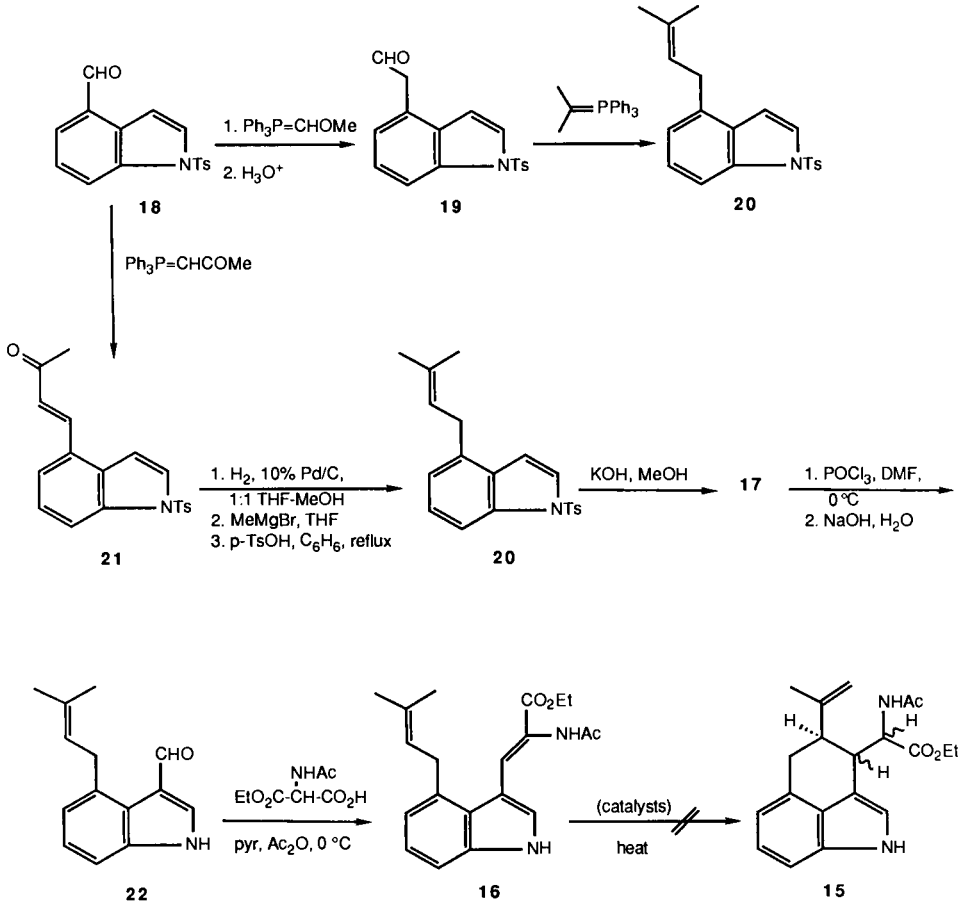
To investigate the feasibility of constructing the C ring of αCA by the intramolecular ene process, we first needed to prepare suitable quantities of 4-(γ,γ-dimethylallyl)indole. The *N*-tosyl derivative of **17** had been made




SCHEME 3. An ene reaction based retrosynthetic analysis of αCA.

by Plieninger for use in studies related to the biosynthesis of the ergot alkaloids.[15] His scheme made use of a novel transformation of α-naphthylamine to indole-4-acetaldehyde, which was converted to the dimethylallylindole by straightforward methods.

Since in our own laboratories a multigram scale method had been developed for the preparation of 4-formylindole,[16] we chose to use this versatile intermediate as the starting point for the elaboration of αCA. The *N*-tosyl derivative **18** of this aldehyde was readily converted to the Plieninger aldehyde **19** by reaction with methoxymethylenetriphenylphosphorane followed by acid hydrolysis (Scheme 4). A second Wittig reaction with isopropylidenetriphenylphosphorane then yielded **20**. The sequence of three steps, while simple enough to execute, was relatively disappointing in terms of overall yield (at best, 20%). A better "Wittig-based" solution was reached by first reacting **18** with 1-triphenylphosphoranylidene-2-propanone to produce the enone **21**. Next, the double bond was hydrogenated, the ketone carbonyl was reacted with methylmagnesium bromide, and the tertiary alcohol was dehydrated with *p*-toluenesulfonic acid in refluxing benzene. This sequence of reactions was again straightforward with the added advantage of being high yielding (75% overall yield from **18**). The tosyl




SCHEME 4. Synthesis of the 3,4-disubstituted indole required to test the ene reaction.

group could be cleaved from **20** in quantitative yield by potassium hydroxide–methanol treatment.

To now install an amidoacrylate unit at the 3-position of the indole nucleus, use of $\alpha$-nitro-$\beta$-ethoxyacrylate[17] was attempted. Reaction of indole **17** with this reagent under a variety of reaction conditions failed, however, to provide workable amounts of the 3,4-disubstituted indole. Fortunately, the aldehyde **22** formed on Vilsmeier–Haack formylation[18] of indole **17** reacted with ethyl acetamidomalonate in the presence of acetic anhydride and pyridine to provide the desired amidoacrylate **16** by way of a decarboxylative condensation process.[19]

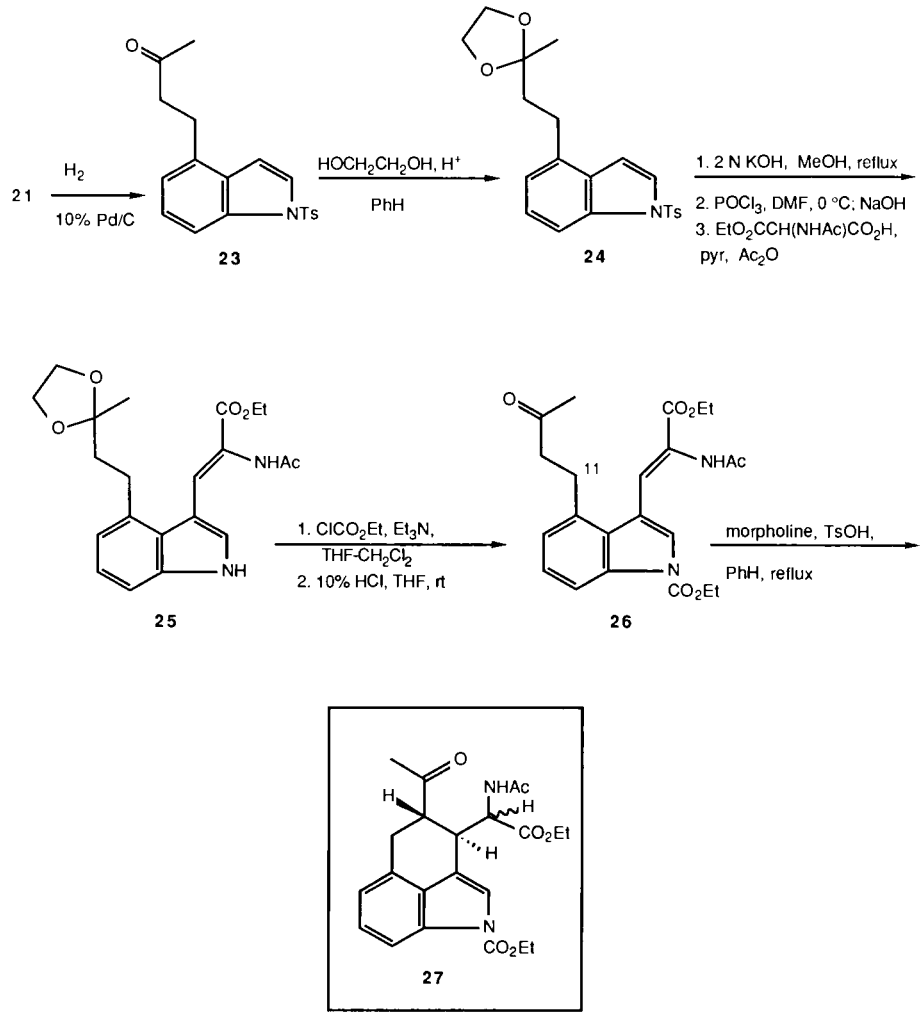
While a host of reaction temperatures, solvents, and catalysts were examined to induce **16** to undergo the ene process, *none* of the desired tricyclic compound **15** could be isolated. While one might question whether the amidoacrylate unit is sufficiently electron deficient to engage in the ene process, for certainly the electron release furnished by the indole ring will have the effect of raising its LUMO energy, the failure probably relates more to geometric factors. The presence of the rigid indole ring separating ene from enophile makes achievement of a parallel plane arrangement of these groups rather difficult. While various Lewis acid conditions were investigated as well in order to impart a greater degree of nonsynchroneity to the reaction process, thus perhaps alleviating in part such geometric barriers, again none of the desired product was isolated.

While one can imagine other possible "corrections" in the ene strategy which might make it feasible, such as the replacement of the acetamido group of **16** by a more powerfully electron-withdrawing nitro group or the appendage of an electron-withdrawing group to the indole nitrogen, such modifications were not examined. A more direct route involving formation of the C-4, C-11 bond by way of a Michael reaction was, in fact, thought of during the initial discouraging studies of the ene reaction. This Michael addition strategy was thus quickly put to the test and found to yield some encouraging results.

## B. A Michael Reaction Approach to αCA

The Michael addition strategy requires the use of a substrate structurally related to that used in the attempted ene route. Indeed, the Michael precursor is derived from the 1,7-diene **16** by simply transforming one of the methyl groups of the indole C-4 appendage to a hydroxyl group. To prepare the ketone **26** required to examine this altered approach, the enone **21** was hydrogenated to provide the saturated ketone **23** (Scheme 5). The carbonyl group was now protected as its ethylene ketal, and the *N*-tosyl group was cleaved by methanolic potassium hydroxide treatment. Next, the amidoacrylate unit was introduced at the C-3 position of the indole ring by the two-step process used previously: Vilsmeier–Haack formylation followed by decarboxylative condensation of the aldehyde with the half ester of acetamidomalonate.[20] A single amidoacrylate **25** resulted which was assigned the Z stereochemistry based solely on literature precedent.[19]

The indole nitrogen was now protected by *N*-carboethoxylation and the ketal protecting group was removed by acid hydrolysis to provide the keto acrylate **26**, the key compound required for testing the Michael reaction process.




SCHEME 5. A Michael reaction for C-ring closure.

A host of bases were examined under a variety of reaction conditions in order to induce bond formation between carbon atoms 4 and 11 ($\alpha$CA numbering). Bases such as potassium *t*-butoxide, sodium ethoxide, pyrrolidine, piperidine, triethylamine, DBU, and sodium hydroxide were employed in both catalytic and stoichiometric amounts at temperatures ranging from 0 to 200°C. Both protic and polar aprotic solvents were used. Under such conditions, only starting material, polymerized product, or the

*N*-decarboethoxylated product (resulting from simple cleavage of the indole nitrogen protecting group) could be isolated.

Finally, use of push–pull reaction conditions comprising 2 equivalents of morpholine and a catalytic amount of *p*-toluenesulfonic acid provided the desired Michael product **27** as a single isomer of undefined stereochemistry at C-5 in 60% yield.

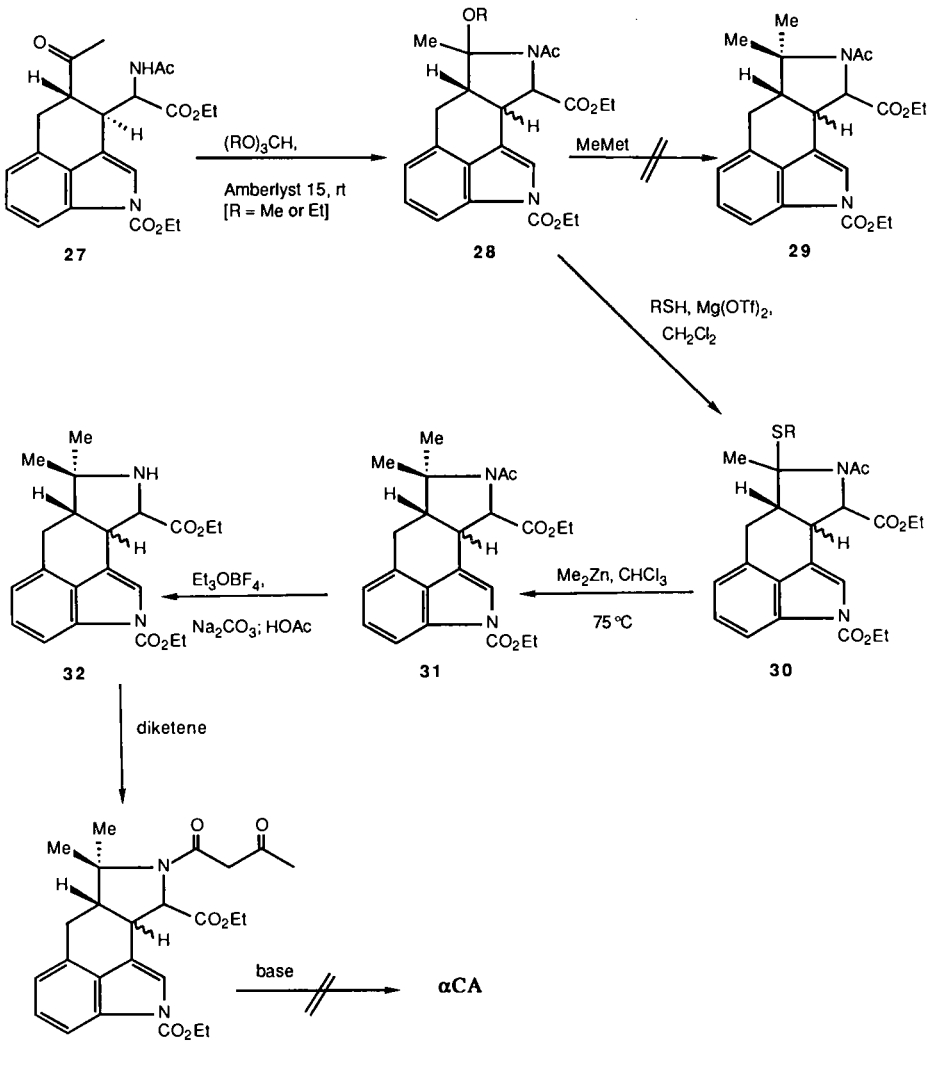
At this point in the synthesis scheme, we were essentially at a stage akin to that which would have been reached had the initial ene process worked. Compounds **15** and **27** are related by the simple exchange of the C-10 methyl group of the former by a hydroxyl group.

To form the D ring of αCA, it now became desirable to examine methods for the intramolecular addition of the amino group at C-5 to the C-10 carbonyl group. One likely sequence involved the protection of this carbonyl group as its ketal, and then hydrolytic cleavage of the *N*-acetyl group followed by imine formation. It was our hope that equilibration of the C-11 stereocenter might take place during this imine-forming step, a hope based on both kinetic and thermodynamic considerations.

On reacting **27** with either trimethyl or triethyl orthoformate and Amberlyst 15 ion exchange resin, a single product resulted which was not the anticipated ketal (Scheme 6).[21] Rather, the product was found to be the ring-closed hemiaminal **28** (the stereochemistry at C-5 was assigned at a later stage). The proximity of the amide nitrogen to the C-10 carbonyl center greatly favors formation of the five-membered ring structure in lieu of the amido ketal.

While the $^1$H NMR spectrum of **28** appeared to indicate the trans-fusion of the C and D rings ($J_{H4,H11}$ = 11.9 Hz; this coupling constant is ~6 Hz in αCA), we were still somewhat **naively** hopeful that epimerization of the C-11 stereocenter might have taken place. Even if the stereochemistry of the C,D-ring juncture was incorrect, intermediate **28** provided us, for the moment, with a readily available substance for examining the methodology required to install the additional methyl group at C-10. While this transformation appeared at the outset to be a reasonably straightforward one, we were soon disappointed to find that a host of organometallic regents[22–27] simply failed to react with the hemiaminal **28** to provide the required gem-dimethyl derivative **29**. As is apparent from an examination of Table II, attempts to carry out this transformation in the presence of Lewis acids led to the isolation of the product of D-ring opening. Of course, the Lewis acid was incorporated in the reaction medium in hope that it would complex to the C-10 alkoxy group thereby triggering formation of an acyliminium ion intermediate.

Since no success could be achieved with the hemiaminal intermediate **28**, we decided to examine the reaction profile of the thiohemiaminal derivatives




SCHEME 6. D-Ring construction by aid of a diorganozinc reaction.

instead. Our rationale for doing this rested on both the weaker nature of the C—S bond and the possibility of activating the sulfur group for departure in ways "radically" different from those used for activation of the alkoxy group.

The methylthio, ethylthio, and phenylthio derivatives **30** were formed easily from the methoxy or ethoxy amides **28** by reaction with the appropri-

TABLE II

| Reagent | Conditions | Product |
|---|---|---|
| 1) $CH_3MgBr$ | −78°C → 0°C, THF | Starting material and decomposition products |
| 2) $TiCl_2Me_2$[22] | −30°C, $CH_2Cl_2$ | **27** |
| 3) $Me_2Zn$[23] | 0°C → r.t., $CH_2Cl_2$ | Starting material |
| 4) $MeCu \cdot BF_3$[24] | −78°C → r.t., THF | **27** |
| 5) $CH_3MgBr$, $BF_3 \cdot Et_2O$ | −70°C → 0°C, THF | **27** |
| 6) $(CH_3)_2CuLi$ | −55°C → 0°C, $Et_2O$–$CH_2Cl_2$ | Starting material |
| 7) $CH_3Ti(OiPr)_3$[25] | −50°C → 65°C, THF | Starting material |
| 8) $CH_3MgBr$, $Mg(OTf)_2$[26] | −78°C → 0°C | **27** |
| 9) $AlMe_3$, tol[27] | 0°C → 75°C sealed tube | Starting material and decomposition products |

ate thiol in the presence of magnesium triflate.[26] Analysis of these sulfur compounds by $^1H$ NMR still indicated a trans-fusion of the C,D rings by virtue of the large coupling constant (12 Hz) between the C-4 and C-11 hydrogens.

Treatment of these sulfur compounds with the same methylmetallics tried in the case of the hemiaminals led to similar results. Ring opening with isolation of the keto amide **27** was observed using the reaction conditions summarized in entries 2, 4, 5, and 8 of Table II. This transformation presumably proceeds through the acyliminium ion intermediate, which is simply attacked by water during the workup process.

In an effort to replace the thio substituent by a methyl group under radical conditions, the phenylthio derivative **30** (R = Ph) was heated in the presence of excess dimethylmercury and AIBN (catalytic amounts of tributyltin hydride were also added in later experiments). Unfortunately, the starting material was largely recovered along with trace amounts of the desulfurized product. Subjection of the phenythio derivative **30** to tetramethyltin in the presence of AIBN also failed to provide any new products.

Finally, in a fit of serendipity, the phenylthio derivative was heated with dimethylzinc in chloroform at 75°C in a sealed tube. *These reaction conditions led to the clean conversion of the sulfur compound to the desired gem-dimethyl derivative* **31** *in a good yield!*

A thorough examination of the literature failed to reveal any precedent for this type of transformation. The only marginally related example of similar chemistry we were able to locate at the time of the discovery was the

conversion of a tertiary chloride to a quaternary carbon compound by the action of dimethylzinc.[23] No example of the use of diorganozinc reagents in the replacement of a sulfur substituent by an alkyl fragment could be found. While the mechanistic aspects of this unusual replacement reaction appeared to be somewhat mysterious during the initial stages of the discovery, all became rather more clear when the reaction was extended to carbohydrate substrates. These studies are delineated in the last section of this chapter.

At this juncture in the synthesis, we could now pin down the precise stereochemical nature of the C,D-ring fusion, for if everything was correct, we anticipated that αCA could be produced in but a few additional steps. The *N*-acetyl group, having served its protecting group role, was now removed from **31** by the action of Meerwein's salt in the presence of potassium carbonate followed by an acetic acid quench.[28] Attempts to cleave the acetyl group by acid or base treatment proved unsuccessful.

Next, the newly freed amine **32** was reacted with diketene in absolute ethanol at 0°C. This reaction provided the desired acetoacetamide intermediate **33** (Scheme 6). It was hoped that subjection of **33** to basic conditions would result in ring closure to provide the tetramic acid unit of αCA. Subsequent or concomitant deprotection of the indole nitrogen would then provide the target structure.

Disappointingly, when **33** was exposed to a variety of bases under a variety of reaction conditions, formation of the tetramic acid ring system could not be observed. While a product was obtained which possessed a similar TLC mobility to αCA, NMR analysis of this product proved impossible due to extensive line broadening. The mass spectrum of the compound was also uninformative.

Accordingly, we backtracked in our synthesis a bit and obtained some good crystals of **31** for X-ray analysis. It was not surprising, but nonetheless disappointing, that the X-ray analysis (Fig. 1) confirmed that the C,D-ring fusion was indeed trans. Treatment of **27** with ethyl or methyl orthoformate to effect D-ring formation had not proceeded with epimerization at C-11. Since the coupling constants between H-4 and H-5 and H-4 and H-11 remained quite constant throughout the reaction sequence from structures **28** through **33**, the stereochemistry can now be assigned rigorously for the C-4, C-5, and C-11 stereocenters of these structures.

A means for properly constituting the C,D-ring fusion stereochemistry of our αCA intermediate now became the main objective of our efforts. Several protocols were envisioned for accomplishing this goal using the trans-fused product **31**. One seemingly straightforward strategy involved the conversion of **32** to its *N*-chloroamine derivative **34**. Dehydrohalogenation to the pyrroline and subsequent acylation of the imine might next produce **35**, an

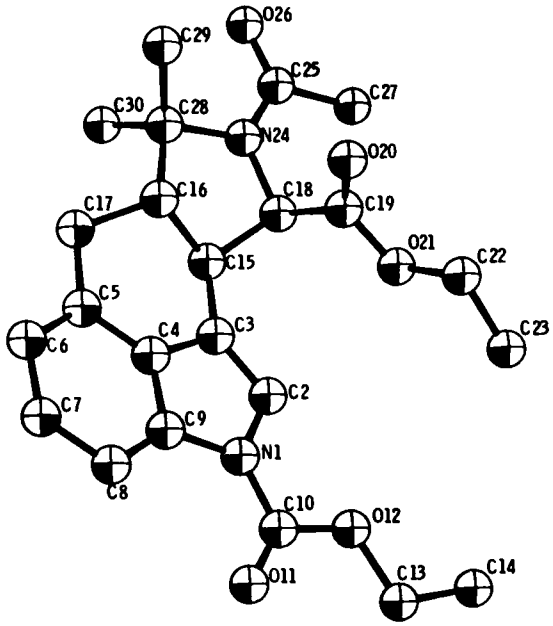


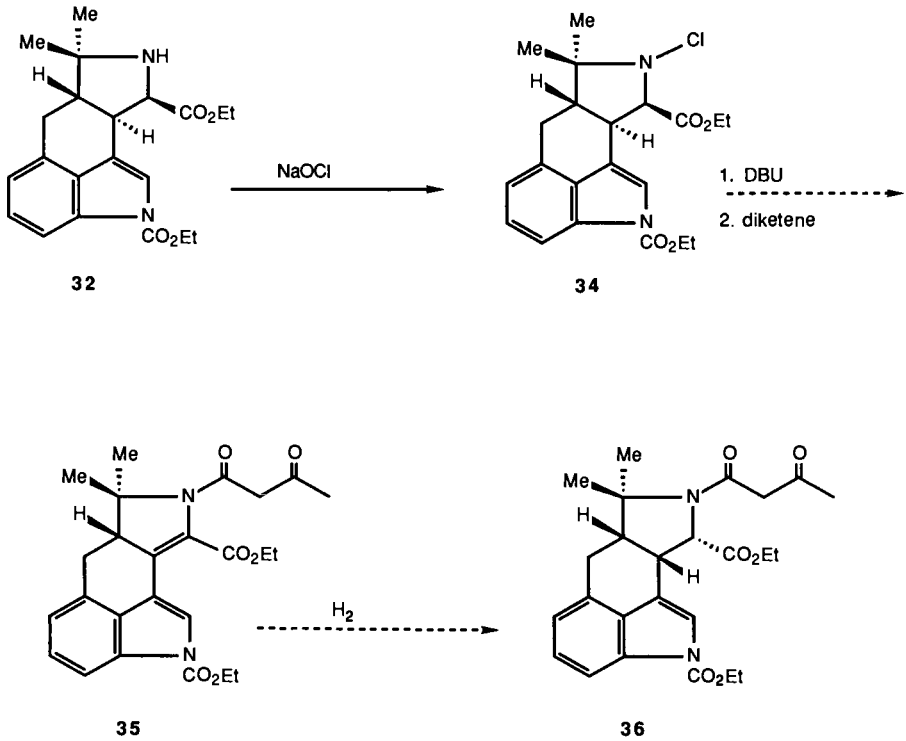

FIG 1. An X-ray structure of **31** with hydrogen atoms omitted for clarity.

intermediate which we anticipated could be hydrogenated to afford the cis-fused product **36** (Scheme 7).

In the event, **32** was chlorinated with 5.25% sodium hypochlorite solution[29] to afford the crystalline chloroamine. Much to our chagrin, this compound failed to cleanly undergo the desired dehydrohalogenation process when reacted with a variety of bases. Since complex mixtures generally resulted, attempts were also made to trap the putative pyrroline intermediate by carrying out the dehydrohalogenation reaction in the presence of diketene. Again, however, the results were not encouraging.

While efforts were also made to purposefully isomerize the starting trans-disubstituted tricycle **27** to the cis compound via the formation of various thermodynamic enol derivatives, a solution to the present problem was eventually found by modifying the opening Michael reaction itself. We imagined that if this Michael reaction could be executed with some suitable leaving group at C-11 (αCA numbering) of the Michael reaction precursor **26**, then removal of this group at a later stage by a radical scission process might offer access to the desired stereoisomer.

The ketone **26** was converted to its thermodynamic enol silyl ether by

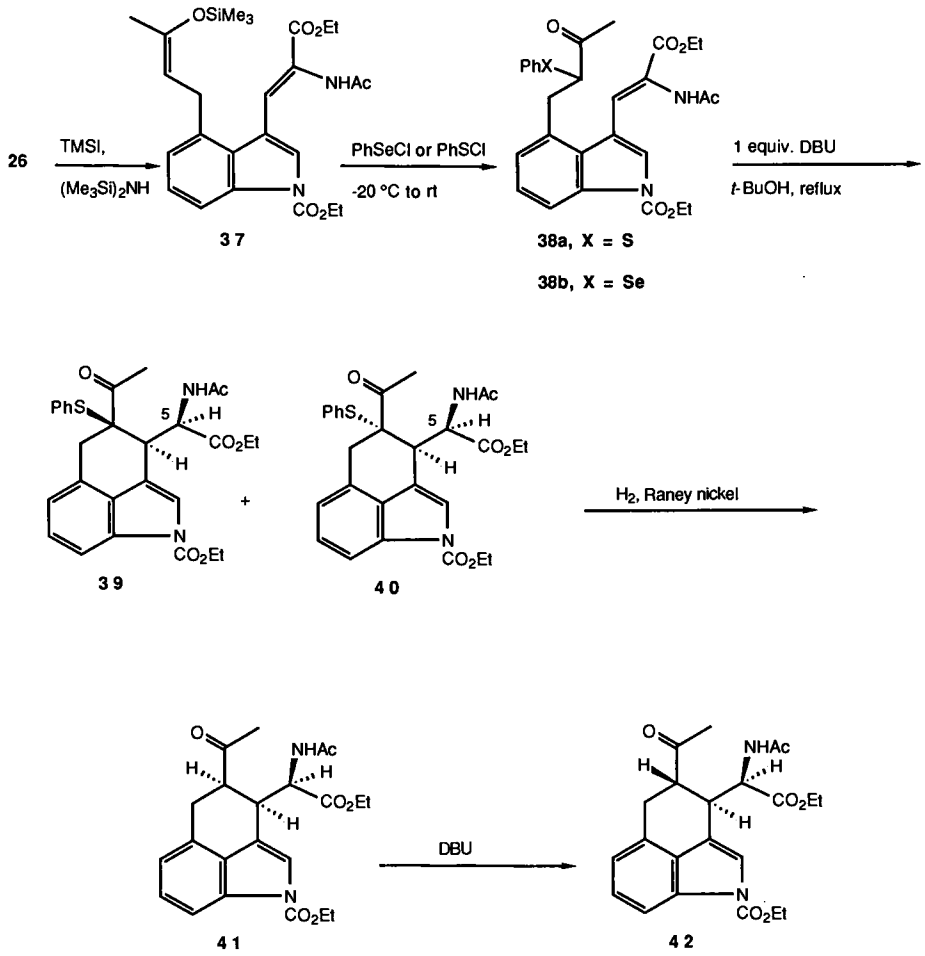



SCHEME 7. A waylayed attempt to fix the C,D-ring fusion stereochemistry.

reaction with hexamethyldisilazane and trimethylsilyl iodide.[30] The crude silyl enol ether was reacted in turn with either phenylsulfenyl chloride or phenylselenenyl chloride to provide the desired substituted ketones **38a** and **38b** (Scheme 8).

Unfortunately, all attempts to induce the selenylated ketone **38b** to undergo the Michael reaction met with failure. Even the morpholine, *p*-toluenesulfonic acid conditions which worked so well for **26** offered no solace.

On the other hand, when a solution of the sulfenylated ketone **38a** was refluxed in *t*-butanol in the presence of DBU, the desired Michael reaction took place to provide a 1 : 1 mixture of **39** and **40**. The relative stereochemistry of isomer **39** was determined by a single-crystal X-ray analysis (Fig. 2). Since the assignment of stereochemistry to the C-5 center of isomer **40** became possible after subsequent chemical correlation with isomer **39** (*vide infra*; **39** and **40** possess the same relative stereochemical relationship between the C-4 and C-5 stereocenters), isomer **40** must differ from **39** by




SCHEME 8. Michael reaction of the sulfenylated ketone **38a**.

possessing a cis relationship between its C-4 hydrogen and the phenylthio group.

Subjection of each of the isomers **39** and **40** individually to trimethyl orthoformate and Amberlyst 15 ion exchange resin failed to effect D-ring formation. Consequently, attempted desulfurization of the tricyclic compounds themselves appeared to constitute a worthwhile experiment. In principle, desulfurization of either **39** or **40** could be expected to proceed

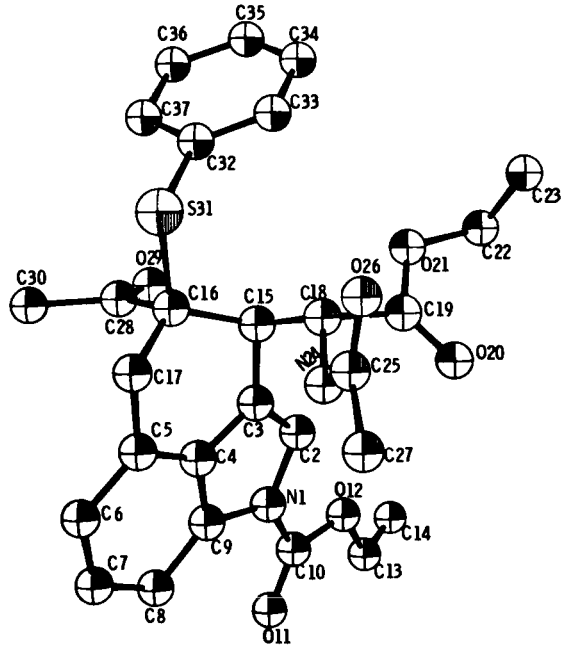
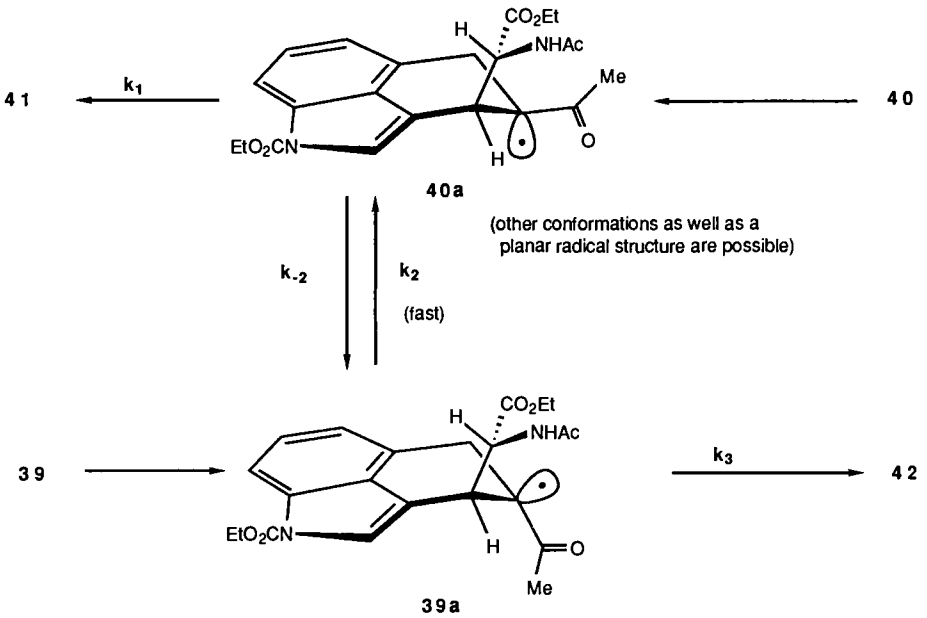



FIG. 2. An X-ray structure of **39** with hydrogen atoms omitted for clarity.

with formation of a stabilized tertiary radical at C-11. Since such tertiary radicals are believed to undergo rapid inversion of configuration,[31] addition of hydrogen could then occur from the sterically more accessible face to provide the cis-disubstituted tricycle **41** in each case.

To test this notion, the isomers **39** and **40** were each exposed separately to excess Raney nickel at room temperature under 1 atmosphere of hydrogen for 4 to 6 hours. Much to our delight, each isomer gave the cis-fused ketone **41** with approximately 92% stereoselectivity. That the major new compound **41** constituted the kinetic product of the desulfurization reaction was made apparent on exposing it to DBU in THF at room temperature, for isomerization occurred to provide a new product possessing a coupling constant between H-4 and H-11 of a magnitude ($J$ = 10.1 Hz) indicative of their trans stereochemical relationship.

These remarkable results can be rationalized by assuming that the desulfurization process occurs via the commonly accepted mechanistic pathway involving production of a radical intermediate.[32] While scission of the carbon–sulfur bond of **39** and **40** would be expected to provide initially the radical intermediates **39a** and **40a** (drawn as slightly pyramidalized), subsequent delivery of hydrogen from the catalyst surface to these intermedi-

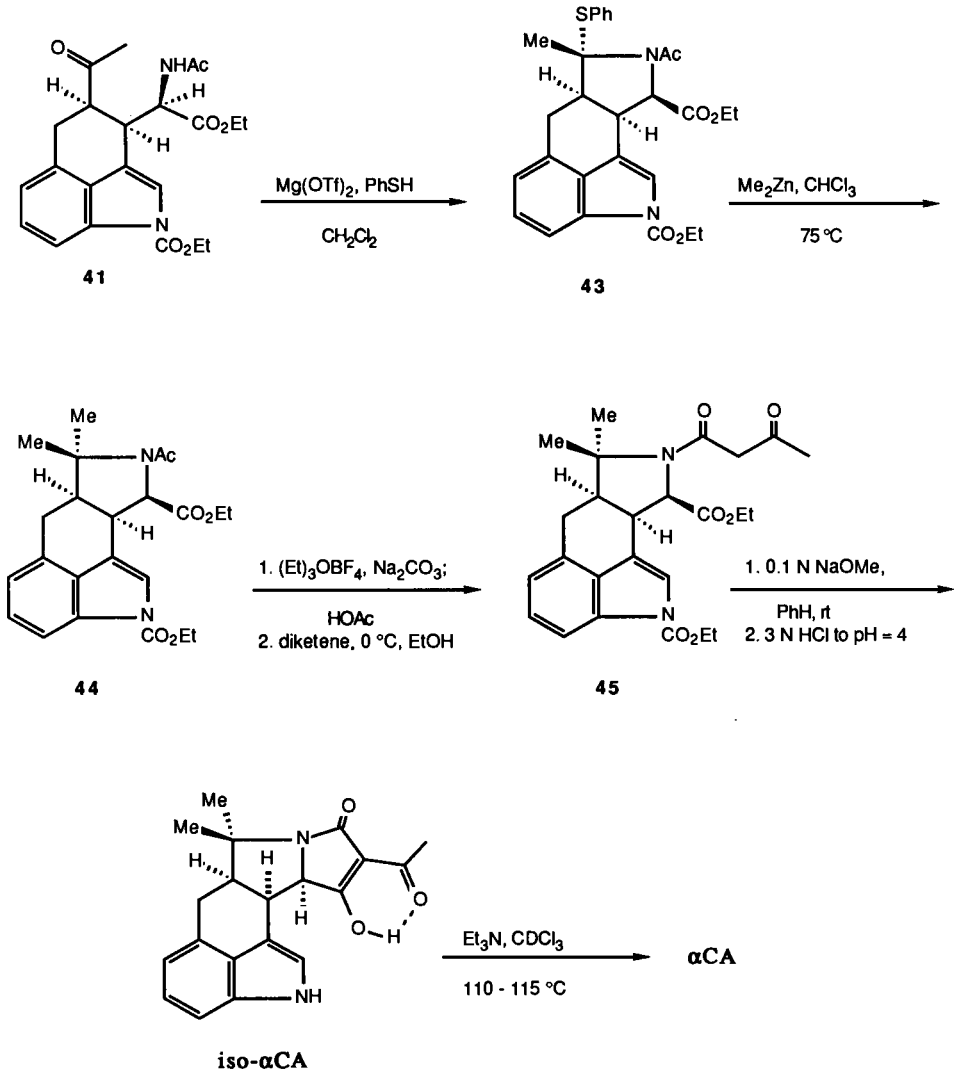



SCHEME 9. Raney nickel desulfurization of **39** and **40**.

ates must be controlled by steric factors (Scheme 9). Equilibration between the radical intermediates must therefore be fast, with intermediate **40a** exhibiting a greater facility for hydrogen atom capture by virtue of revealing a molecular surface unencumbered by carbon appendages ($k_1 > k_3$). While other explanations of these results involving nickel intermediates or a planar radical structure can also be advanced, the end point, the "contrathermodynamic" nature of the reaction process, must remain undisputed. Additionally, the fact that **39** and **40** both gave rise to **41** as the major product provides definitive support for our assignment of stereochemistry to the C-5 center of **40**, for epimerization at this stereocenter is unlikely under the reaction conditions.

At this stage, much of the same chemistry which had been explored using the trans C,D-ring fused compound **28** could now be called into play. During some of the earlier studies we had also discovered that the keto amide **27** could be more efficiently transformed to the sulfur-bearing tetracycle **30** by simply reacting it with thiophenol and magnesium triflate in methylene chloride.

By applying the same reaction conditions [$Mg(OTf)_2$, PhSH, $CH_2Cl_2$] to the cis-disubstituted tricycle **41**, the desired cis C,D-ring fused tetracycle **43** resulted with $J_{H4,H11}$ = 6.06 Hz (Scheme 10). No epimerization at C-11 was




SCHEME 10. Completion of the αCA synthesis.

detectable in the reaction process. As was made apparent from a subsequent X-ray analysis (Fig. 3) of **43**, thiophenol had added to the presumed acyliminium ion intermediate from the more accessible convex face of the butterfly-shaped intermediate. Furthermore, the stereochemistry at C-5 was retained, therefore locating the carboethoxy group on the concave surface of the molecule.

Having properly attended to the creation of the cis-fused C,D-ring system,

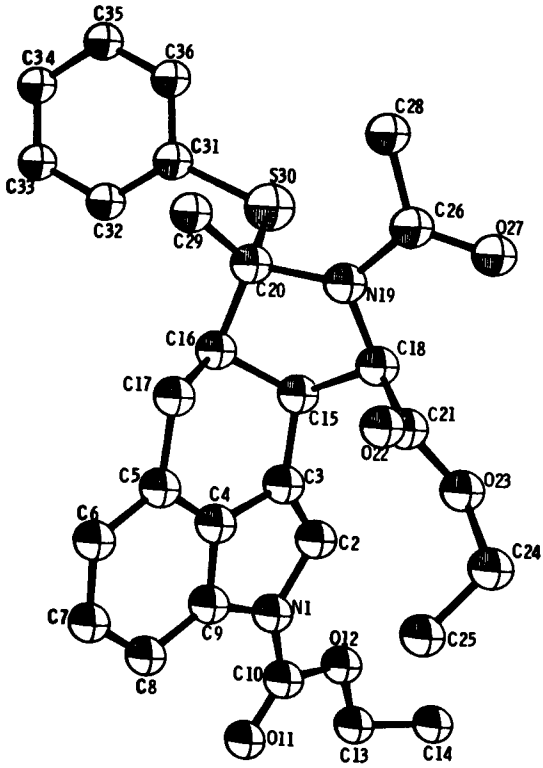



FIG. 3. An X-ray structure of **43** with hydrogen atoms omitted for clarity.

we could now complete installation of the geminal dimethyl grouping of αCA by exploiting the diorganozinc reaction discovered earlier. The reaction of **43** with dimethylzinc in chloroform proceeded smoothly to afford **44** in 82% yield. The *N*-acetyl group was next cleaved by the Meerwein salt procedure and the free amine treated with diketene to yield the desired acetoacetamide **45**.

This acetoacetamide was stirred with an excess of 0.1 N sodium methoxide in benzene at room temperature, and the resulting sodium salt was extracted with water. The aqueous layer was acidified with 10% HCl at 0°C and was extracted with chloroform. Upon drying and concentrating the chloroform extracts, a crude residue was obtained whose mass spectrum was nearly identical to that of natural αCA.

Although the product also displayed similar behavior on TLC to that of natural αCA (heavy tailing, blue stain with Ehrlich's reagent), the $R_f$ of the product was slightly higher than that of the authentic sample with 4:1 chloroform–methanol as the developing solvent. While one can rationalize such differences as stemming perhaps from the incorrect stereochemistry at

C-5, we were appalled to find that the $^1$H NMR of this product comprised an incomprehensible set of hills and valleys containing little in the way of fine structure. Attempted purification by either alumina or silica gel chromatography simply made matters worse. After numerous attempts to purify the product by other methods such as reverse phase and ion exchange chromatography and recrystallization, the reaction itself was simply repeated, but this time some changes in the workup procedure were implemented.

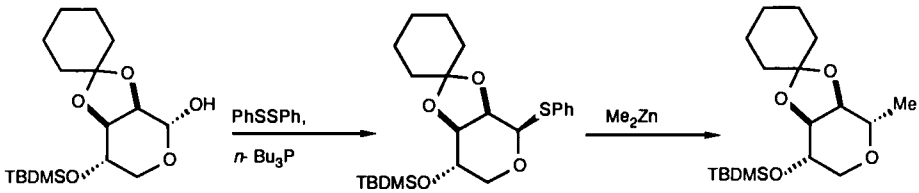
After partitioning the presumed sodium salt of the tetramic acid into water, acidification was carried out with 3 N HCl at 0°C to bring the pH to slightly less than 4. The resulting solution was then extracted with chloroform and concentrated **without** the use of a drying agent. This time $^1$H NMR analysis of the crude product clearly indicated the presence of iso-$\alpha$-cyclopiazonic acid. The result could, of course, be expected based on the X-ray structure of intermediate **43**, for if no epimerization occurs at C-5 during formation of the tetramic acid ring system, only iso-$\alpha$CA should result.

In the original structure elucidation studies Holzapfel had found that treatment of $\alpha$CA with excess aqueous sodium hydroxide under reflux conditions (10 hours) resulted in formation of a 3:2 mixture of $\alpha$CA and iso-$\alpha$CA.[33] We found that by simply heating our sample of iso-$\alpha$CA in deuterochloroform in a sealed NMR tube at 115°C for 8 hours a 3:1 mixture of $\alpha$CA and iso-$\alpha$CA was produced. Since numerous attempts to effect the complete isomerization of iso-$\alpha$CA to $\alpha$CA only generated similar product mixtures, isomer separation was required. To this end the formamide–oxalic acid-impregnated paper chromatography system reported by Holzapfel was used to our advantage.[33] By this technique we were able to procure milligram amounts of pure (racemic) $\alpha$CA in 37% overall yield from **45**. The synthetic material was identical in all respects to samples kindly provided by Doctors Richard Cole and C. W. Holzapfel.

While the synthesis of $\alpha$CA had thus been brought to a successful stage of completion,[34] we still remained somewhat puzzled by the mechanistic aspects of the diorganozinc reaction we had stumbled upon. In an effort to better understand the nature of the reaction process, we attempted its application to various phenylthio glycoside derivatives. These studies are summarized in the final section of this chapter.

## III. Application of the Zinc Reaction to Phenylthio Glycosides: A New C-Glycoside Synthesis

In order to further probe both the synthetic and mechanistic aspects of this new diorganozinc reaction, we decided to try to extend the chemistry to phenylthio glycosides. Our purpose in choosing carbohydrates as substrates was twofold: (a) these substrates were expected to provide valuable stereo-



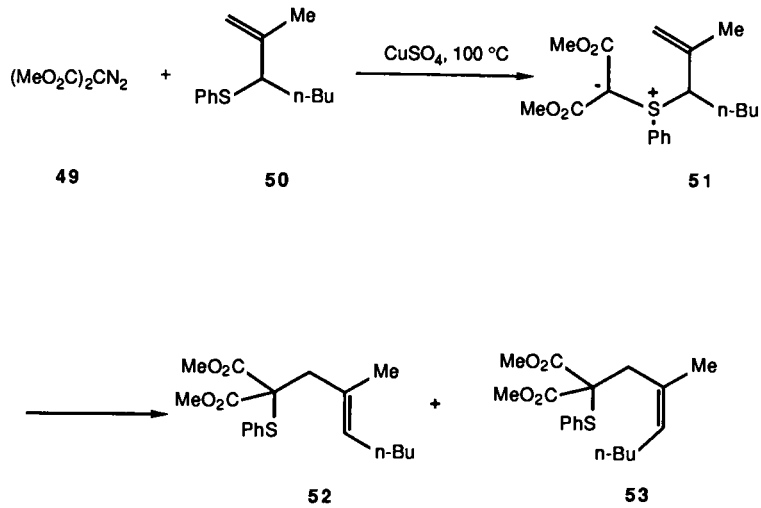

46 47 48

SCHEME 11. Application of the zinc reaction to a phenylthio glycoside.

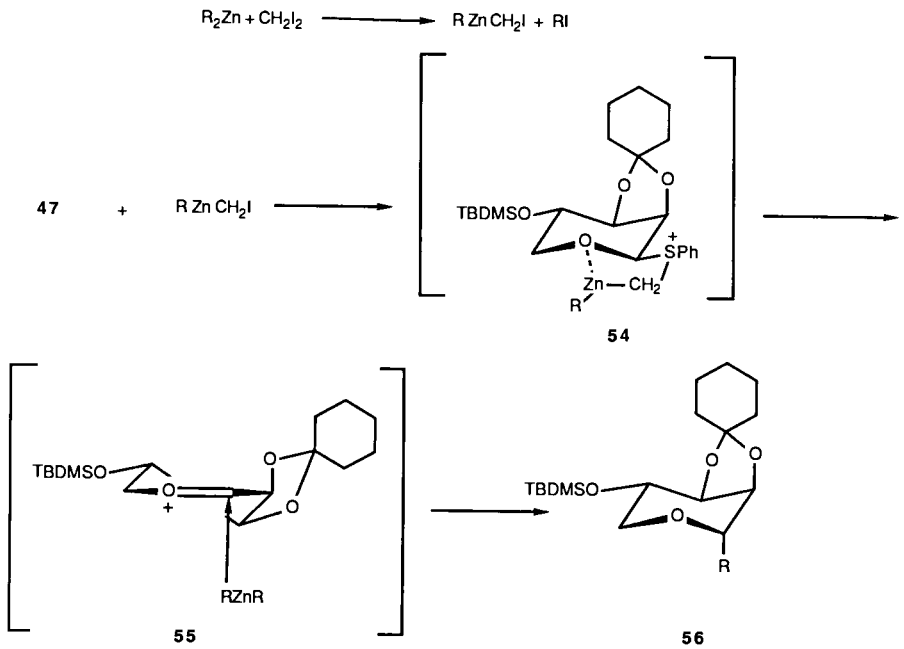
chemical information on the course of the zinc reaction; and (b) if the yields and stereoselectivity observed in this reaction were good, then a new entry to an important class of natural product substances, the *C*-glycosides, would be at hand.[35] We further take note of the fact that such carbohydrate derivatives resemble our cyclopiazonic acid intermediate in that the phenylthio group is located on a carbon atom which bears an additional heteroatom. The importance of this feature will become apparent as we proceed.

On reacting the phenylthio glycoside **47**, prepared from the protected lyxose derivative **46**, with dimethylzinc in chloroform at 75°C in a Kimax tube for 12 hours, a single less polar product **48** was obtained (Scheme 11). Rather dramatically, when the same reaction was carried out in toluene, benzene, or hexanes, in the absence of chloroform, no *C*-methyl glycoside was formed. Additionally, when a toluene solution of **47** was treated with 5 equivalents of methylene iodide and 10 equivalents of diethylzinc at 65°C for 2 hours, the *C*-ethyl glycoside was obtained in an isolated yield of 78%. Likewise, by substituting carbon tetrachloride for the methylene iodide, the *C*-ethyl glycoside was again obtained, but under a milder set of reaction conditions (35°C for 2 hours).

Early on in our studies of this zinc reaction we thought that the dialkylzinc might complex to the sulfur substituent to rupture the C—S bond with formation of an oxonium (or iminium) ion intermediate. However, the findings regarding the necessity of the halocarbon additives logically suggest that the dialkylzinc is performing a dual role. First, it must react with the methylene iodide or carbon tetrachloride to deliver a carbenoid, a reaction which represents a well-known variant of the standard Simmons–Smith cyclopropanation procedure.[36] Subsequently, the zinc carbenoid interacts with the sulfur substituent to generate a sulfonium ion intermediate (which can also be viewed as a sulfur ylid). The direct formation of sulfur ylids by the reaction of sulfides with carbenes is, of course, well documented. The copper-catalyzed decomposition of dimethyl diazomalonate in the presence of the allyl sulfide **50** leads, for example, to the [2,3]-sigmatropic rearrangement products **52** and **53** via the intermediacy of the sulfur ylid **51** (Scheme 12).[37]



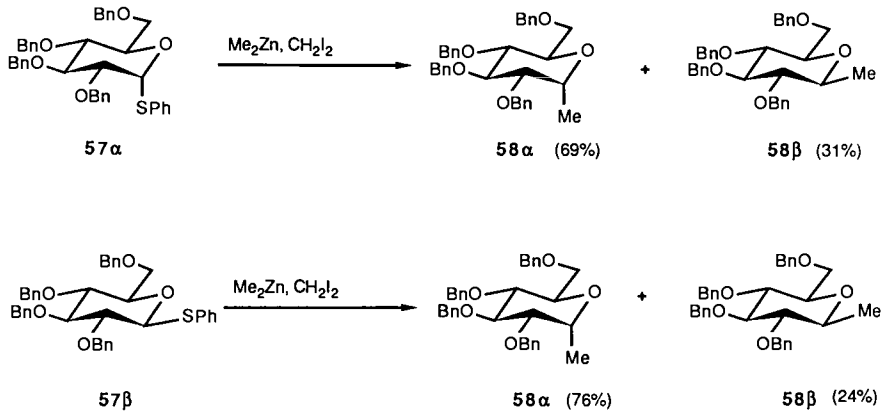

SCHEME 12. Sulfur ylid formation.




SCHEME 13. A mechanism for C-glycoside formation.

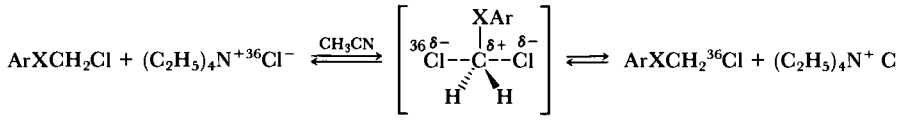
For the carbohydrate substrates, once the organozinc–sulfur complex has formed, it presumably reacts with the excess diorganozinc reagent present to provide the *C*-glycoside by way of an oxonium ion intermediate (Scheme 13).

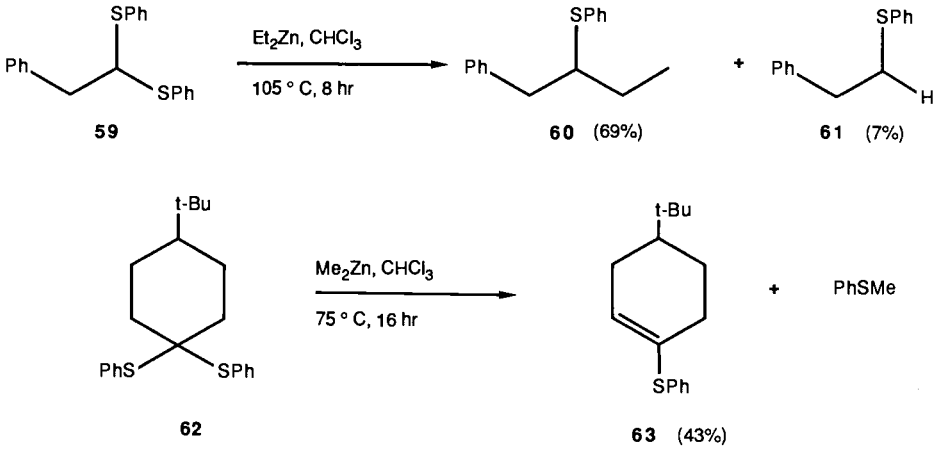
Such a cyclic oxonium ion intermediate would best explain the stereochemical result obtained for the lyxose derivative, for conformational energetics and the kinetic anomeric effect combine to favor axial addition of the incoming alkyl group.[38] While a direct displacement mechanism might also be suggested in the lyxose case, the production of an oxonium ion intermediate derives further support from the experiments using both the α- and β-phenylthio anomers of glucose. If an oxonium ion intermediate is formed, then compounds **57α** and **57β** should give similar product ratios. Indeed, as shown in Scheme 14, **57α** and **57β** gave rise to nearly identical product ratios when reacted with dimethylzinc and methylene iodide. The major isomer is that arising again from the preferred axial addition mode.




SCHEME 14. Application of the diorganozinc reaction to the α and β-phenylthio derivatives of glucose.

While our zinc reaction has been applied to a host of other carbohydrate substrates, it is important to note that this diorganozinc reaction fails when alkyl phenyl sulfides are employed as the substrates. Apparently, some degree of stabilization of the carbocationic intermediate by a neighboring heteroatom is required for C—S bond rupture. From solution solvolysis data the order of cation-stabilizing ability of a heteroatom is known to be α-amino > α-oxy > α-thio.[39]






SCHEME 15. Application of the zinc reaction to thioacetals.

On this basis one might suspect that thioacetals and thioketals could also serve as possible substrates for the zinc reaction but that such transformations would require more vigorous reaction conditions. Indeed, the thioacetal of phenylacetaldehyde reacted with diethylzinc in chloroform as solvent at 105°C (8 hours) to give the alkyl substitution product **60** along with the reduction product **61** (Scheme 15). In other cases (e.g., **62** → **63**) elimination products were found to predominate. Due to the extreme variability in product outcome, the applicability of the zinc reaction to thioacetals would appear to be of limited utility.[40]

## IV. Conclusions

The work described in this chapter provides a useful illustration of how a total synthesis effort can spur the development of new ideas with the creation of new and useful synthetic tools. The present studies may furthermore prove valuable to efforts aimed at unraveling the complexities of the biosynthesis of the cyclopiazonic acids, for such biosynthetic studies often require the preparation of labeled compounds considered to be possible intermediates along the biosynthetic pathway.

### Acknowledgments

We are indebted to Dr. Toshiro Konoike and Mr. Allen Ritter for studies pertaining to the application of the zinc reaction to carbohydrate substrates. We thank Dr. James Springer for carrying out the X-ray analyses described herein. Financial support for this work was provided by the National Institutes of Health.

## References


1. B. Franck, *Angew. Chem., Int. Ed. Engl.* **23,** 493 (1984).
2. L. A. Goldblatt, "Aflatoxin," Academic Press, New York, 1969.
3. R. J. Cole and R. H. Cox, "Handbook of Toxic Fungal Metabolites," Academic Press, New York, 1981.
4. J. D. Bu'lock, *in* "The Biosynthesis of Mycotoxins—A Study in Secondary Metabolism" (P. S. Steyn, ed.), pp. 1–16. Academic Press, New York, 1980.
5. C. W. Holzapfel, *in* "The Biosynthesis of Mycotoxins—A Study in Secondary Metabolism" (P. S. Steyn ed.), pp. 327–355. Academic Press, New York, 1980.
6. J. Harrison, *Trop, Sci.* **13,** 57 (1971); B. J. Wilson, *in* "Mycotoxins in Human Health" (J. F. H. Purchase, ed.), pp. 223–229. Macmillan, New York, 1971.
7. I. F. H. Purchase, *in* "Mycotoxins" (I. F. H. Purchase, ed.), pp. 149–162. Elsevier, Amsterdam, 1974.
8. C. E. Stickings, *Biochem. J.* **72,** 332 (1959).
9. A. Dippenaar, C. W. Holzapfel, and J. C. A. Boeyens, *J. Cryst. Mol. Struct.* **7,** 189 (1977).
10. P. S. Steyn and P. L. Wessels, *Tetrahedron Lett.* **47,** 4707 (1978).
11. C. W. Holzapfel, R. D. Hutchinson, and D. C. Wilkins, *Tetrahedron* **26,** 5239 (1970).
12. C. W. Holzapfel and D. C. Wilkins, *Tetrahedron* **10,** 351 (1971); J. C. Schabort, D. C. Wilkens, C. W. Holzapfel, D. J. J. Potgrieter, and A. W. Neitz, *Biochim. Biophys. Acta* **250,** 311 (1971).
13. P. S. Steyn, R. Vleggaar, N. P. Ferreira, G. W. Kirby, and M. J. Varley, *J. C. S. Chem. Commun.* p. 465 (1975).
14. C. W. Holzapfel and P. J. Gildenhuys, *S. Afr. J. Chem.* **30,** 125 (1977).
15. H. Plieninger, C. Wagner, and H. Immel, *Liebigs Ann. Chem.* **743,** 95 (1971).
16. A. P. Kozikowski, *Heterocycles* **16,** 267 (1981).
17. N. I. Aboskalova, K. K. Babievskii, V. M. Belikov, V. V. Perekalin, and A. S. Polyanskaya, *J. Org. Chem. USSR (Engl. Transl.)* **9,** 1082 (1973).
18. G. F. Smith, *J. Chem. Soc.* **76,** 3842 (1954).
19. U. Hengartner, D. Valentine, K. K. Johnson, M. E. Larscheid, F. Pigott, F. Scheidl, J. W. Scott, R. C. Sun, J. M. Townsend, and T. H. Williams, *J. Org. Chem.* **44,** 3741 (1979).
20. H. Hellmann, K. Teichmann, and F. Lingens, *Chem. Ber.* **91,** 2427 (1958).
21. S. A. Patwardhan and S. Dev, *Synthesis* p. 348 (1974).
22. M. T. Reetz, J. Westermann, and R. Steinbach, *Angew. Chem., Int. Ed. Engl.* **19,** 900 (1980).
23. M. T. Reetz, B. Wenderoth, R. Peter, R. Steinbach, and J. Westermann, *J. C. S. Chem. Commun.* p. 1202 (1980).
24. K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.* **99,** 8068 (1977).
25. K. Clauss, *Liebigs Ann. Chem.* **711,** 19 (1968); B. Weidmann and D. Seebach, *Helv. Chim. Acta* **63,** 2451 (1980).
26. E. J. Corey and K. Shimoji, *Tetrahedron Lett.* **24,** 169 (1983).
27. A. Meisters and T. Mole, *J. C. S. Chem. Commun.* p. 595 (1972).
28. S. Hanessian, *Tetrahedron Lett.* **16,** 1549 (1967).
29. J. Hausler and U. Schmidt, *Liebigs Ann. Chem.*, 1881 (1979); M. M. Joullie and R. F. Nutt, *J. Am. Chem. Soc.* **104,** 5852 (1982); A. V. Brossi, F. Schenker, and W. Leimgruber, *Chem. Ber.* **47,** 2089 (1964).
30. R. D. Miller and D. R. McKean, *Synthesis* p. 730 (1979).
31. T. H. Lowry and K. S. Richardson, "Mechanism and Theory in Organic Chemistry," pp. 468–470. Harper & Row, New York, 1976.
32. G. R. Pettit and E. E. van Tamelen, *Org. React. (N.Y.)* **12,** 356 (1962).
33. C. W. Holzapfel, *Tetrahedron* **24,** 2101 (1968).
34. A. P. Kozikowski and M. N. Greco, *J. Am. Chem. Soc.* **106,** 6873 (1984). The stereochemistry

shown for the ester-bearing center of the tetracyclic intermediates drawn in this paper is incorrect and should be amended in accord with Figure 3 of this chapter.
35. R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley (Interscience), New York, 1970; R. J. Suhadolnik, "Nucleosides as Biological Probes," Wiley (Interscience), New York, 1979.
36. H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.* **81,** 4256 (1959).
37. W. Ando, S. Kondo, K. Nakayama, K. Ichibori, H. Kohoda, Y. Yamato, I. Imai, S. Nakaido, and T. Migita, *J. Am. Chem. Soc.* **94,** 3870 (1972).
38. A. J. Kirby, "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen," Springer-Verlag, Berlin and New York, 1982.
39. E. Block, "Reactions of Organosulfur Compounds," pp. 128–175. Academic Press, New York, 1978.
40. For a related elimination process, see A. D. Rodriguez and A. Nickon, *Tetrahedron* **41,** 4443 (1985).
41. For the application of this zinc reaction to a greater range of carbohydrate substrates, see A. P. Kozikowski, T. Konoike, and A. Ritter, *Carbohydr. Res.* **171,** 109 (1987).

*Chapter 9*

# A UNIFIED STRATEGY FOR THE SYNTHESIS OF ALKALOIDS OF THE YOHIMBOID, HETEROYOHIMBOID, AND CORYNANTHEIOID FAMILIES

*Stephen F. Martin*
*Department of Chemistry*
*University of Texas at Austin*
*Austin, Texas*



## I. Introduction

One of the major and continuing challenges in synthetic organic chemistry is the development of general and efficient strategies for the construction of complex natural products. One paradigm that has been effectively employed for the design of such synthetic strategies requires the recognition of those

structural subunits that are common to the molecular frameworks of similar substances belonging to a selected class. The initial step in the conceptualization of a strategy involves the generation of an overall logistical plan for the assemblage of the target molecule by the creative fabrication and union of these individual subunits. Once the basic approach has been formulated, the specific tactics that will be required to achieve the requisite constructions and refunctionalizations must be devised, and oftentimes it is necessary to invent new protocols for effecting certain chemical transformations. Ideally, the evolution of successful new strategies for the preparation of complex targets will be accompanied by the innovative applications of known tactics coupled with fresh developments in synthetic methodology.

Several important criteria may be utilized to assess the basic merits of a particular synthetic plan, and a brief discussion of these, in no pedagogical order, is warranted. First, the development of a concise route to the selected target is a laudable goal that is realized by maximizing the efficiency of bond formations and functional group interconversions. Judicious selection of starting materials, reagents, and chemical reactions is required. Furthermore, processes that result in the creation of more than one new bond in a single reaction are especially significant, whereas sequences involving mere protective and deprotective operations that do not simultaneously result in some useful structural manipulation or modification should be avoided whenever possible. Control of stereochemistry in both a relative and an absolute sense, which is typically realized by a combination of reagent- and substrate-based techniques, is another crucial requirement, and the most effective means for achieving this objective must be carefully and critically evaluated. The overall synthetic plan should provide maximal opportunities for the discovery of novel chemistry and the invention and development of new, useful methodology. Finally, the synthesis of the chosen molecule should be practical and economical.

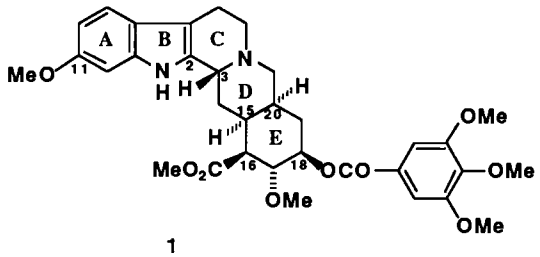
The selection of a particular strategy and sequence of tactics for the preparation of the designated target will ultimately be governed by the subjective and objective assessment of the relative importance of each of the aforementioned standards within the overall framework of the specific scientific goals. For example, the desired substance may be required to explore the scope and limitations of new synthetic methods or perhaps to test a mechanistic or biological hypothesis, or it may possess some commercial importance. Alternatively, the target may have been selected to serve simply as a platform for teaching or expressing the art of organic chemistry. Given these considerations, a variety of unique approaches to any given problem may be initially defined, but frequently the manner in which the actual synthetic target is eventually obtained bears only faint resemblance to the original plan. This is a consequence of the experimental and sometimes

unpredictable nature of the science, and it further underscores our present lack of a detailed understanding of chemical reactivity and selectivity in certain circumstances.

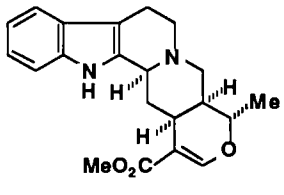
## II. Formulation of the Strategy

The structurally diverse alkaloids of the indole family[1] exhibit a wide range of biological activities, and they have long attracted the attention of synthetic organic chemists. Although there are a number of classes of indole alkaloids, the three important subgroups that are biosynthetically derived from the union of tryptophan and an unrearranged secologanin skeleton are the yohimboid, heteroyohimboid, and corynantheioid alkaloids. Representative members of these groups include reserpine (**1**)[2] (yohimboid), tetrahydroalstonine (**2**)[3] (heteroyohimboid), and geissoschizine (**3**)[4] (corynantheioid). Inasmuch as a major focus of research in our laboratories over the past several years has been directed toward the design and development of general strategies for the total synthesis of alkaloids, it was inevitable that we should become intrigued by the considerable challenge of inventing a new entry to these complex alkaloids.

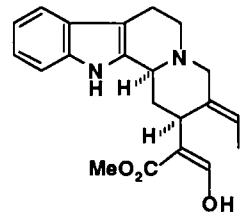
A cursory comparison of the structures of the natural bases **1–3** with other related alkaloids of the indole group reveals the existence of key skeletal



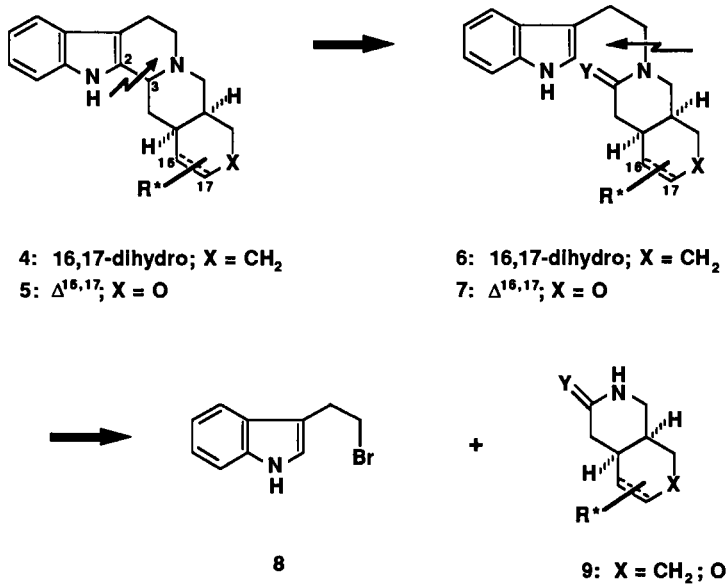

1




2




3

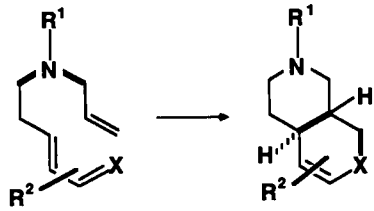



SCHEME 1

subunits that comprise characteristic architectural features of the various classes. For example, reserpine (**1**) is endowed with a *cis*-hydroisoquinoline as the D/E ring system, whereas tetrahydroalstonine (**2**) incorporates a *cis*-oxahydroisoquinoline ring system as the D/E moiety. On the other hand, geissoschizine (**3**) lacks the E ring and possesses instead a highly substituted piperidine as the D ring. Recognition of these commonalities evokes the synthetic strategy D(E) ⇒ ABD(E) ⇒ ABCD(E), which has been widely exploited in the area of indole alkaloid chemistry. This approach is adumbrated in a retrosynthetic sense in Scheme 1 for the hypothetical pentacyclic yohimboid and heteroyohimboid models **4** and **5**, respectively, wherein R* collectively represents the substituents appended to the E ring. According to this plan, the final synthetic step required for the construction of the intact nucleus typically proceeds via nucleophilic attack of the indole moiety onto an electrophilic site at C(3) of an intermediate that is generated from a 2,3-seco derivative such as **6** or **7** (Y = O, $H_2$). Compounds of the general type **6** and **7** are readily accessible upon coupling of a tryptophyl synthon **8** with either an intact *cis*-hydroisoquinoline or *cis*-oxahydroisoquinoline **9** (X = $CH_2$ or O, respectively). If the general strategy depicted in Scheme 1 is adopted as a format for the invention of new approaches to the pentacyclic

indole alkaloids, the fundamental task may then be formulated within the simpler context of developing novel methods for the efficient construction of *cis*-hydroisoquinolines and *cis*-oxahydroisoquinolines. The further extension of the plan to the synthesis of the corynantheioid alkaloids would then require an added operation to effect the cleavage of the E ring of a suitably functionalized intermediate.

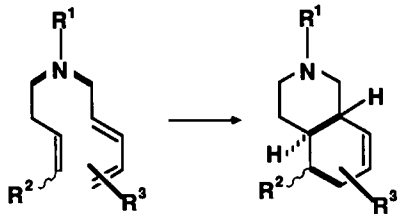
It occurred to us that one appealing tactic for the construction of D/E ring fragments related to **9** (X = $CH_2$ or O) would entail the intramolecular Diels–Alder reaction[5] of trienes possessing a nitrogen atom in the chain linking the dienic and dienophilic moieties [Eqs. (1) and (2)]. For example, the thermally induced cyclization of **10a** would afford **11a**, whereas the related $\alpha,\beta$-unsaturated aldehyde **10b** would undergo a [4 + 2] cycloaddition to generate **11b**. One may further envisage that the incorporation of additional substituents and functionality at propitious sites on **10a,b** would lead to the correspondingly substituted cycloadducts **11a,b**, which might be then suitably disposed for eventual elaboration to the yohimboid and heteroyohimboid alkaloids. Access to the corynantheioid alkaloids would necessitate scission of a carbon–oxygen bond in the E ring of an intermediate derived from the cycloadduct **11b**. In a similar fashion, the transformation illustrated in Eq. (2) allows the construction of the isomeric hydroisoquinolines **13** from the triene **12**. There is a practical element inherent in the




(1)

**10a,b** **11a,b**

**Series a: X = $CH_2$**
**b: X = O**




(2)

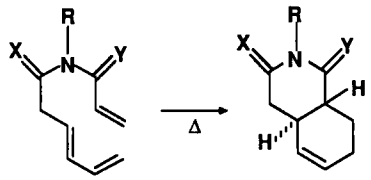
**12** **13**

application of Eqs. (1) and (2) to the fabrication of the bicyclics **11a** and **13** that should be clearly recognized. Namely, the requisite trienes **10a,b** and **12** would be readily available by either of two different connective modes (darkened bonds) that exploit the relative facility with which carbon–nitrogen bonds may be constructed. This bimolecular coupling reaction nicely sets the stage for the simultaneous formation of two new bonds (darkened) in **11a,b** and **13** by an entropically favored intramolecular [4 + 2] cycloaddition.

## III. Preliminary Model Studies

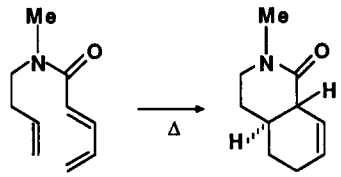
The feasibility of effecting the cyclizations of trienes related to **10a** and **12** to produce the corresponding hydroisoquinolines **11a** and **13** was not held seriously in question owing to the existence of adequate precedent in similar systems lacking the nitrogen atom in the chain connecting the diene and the dienophile.[5] However, the preferential stereochemical course of the intramolecular [4 + 2] cycloadditions of such trienes could not be accurately predicted *a priori*, and it was necessary to engage in several exploratory model studies to assess the stereochemical issues inherent in such cyclizations. On the other hand, whereas intermolecular and intramolecular hetero Diels–Alder reactions have been extensively documented,[6–8] at the outset of our experiments there were no examples of thermal, intramolecular variants of this process that involved heterotrienes such as **10b** in which $\alpha,\beta$-unsaturated aldehydes lacking additional activating substituents served as the $4\pi$ component.[8] Thus, in this latter venture, it was necessary to establish the underlying viability of applying intramolecular hetero Diels–Alder reactions to the construction of fused hydropyrans prior to evaluating the more subtle stereochemical aspects of the reaction.

In order to examine the stereochemistry of the intramolecular [4 + 2] cycloadditions of nitrogen-linked trienes of types **10a** and **12**, a representative series of simple substrates that included **15a–g** and **18** was prepared. (Scheme 2). The thermolyses of these trienes preferentially formed the *cis*-hydroisoquinolines **16a–g** and **19**, respectively.[9] Although the cyclizations of **15a–e** and **18** produced the corresponding cis-cycloadducts with only modest (1.1–2 : 1) selectivity, the acrylamides **15f,g**, both of which possessed activated dienophilic partners, underwent intramolecular Diels–Alder reactions via endo transition states with synthetically acceptable levels of diastereoselectivity (7–8 : 1) to furnish the *cis*-hydroisoquinolines **16f,g**. Access to the yohimboid nucleus was also readily achieved by the transformation of the *cis*-hydroisoquinoline **16c** into $\Delta^{16,17}$-didehydroalloyohimbane (**21**)




15 16: α-H
17: β-H

Series a: R = H; X = O; Y = $H_2$
b: R = Me; X = O; Y = $H_2$
c: R = $CH_2CH_2$-3-Indolyl; X = O; Y = $H_2$
d: R = Me; X = Y = $H_2$
e: R = $CO_2Me$; X = Y = $H_2$
f: R = Me; X = $H_2$; Y = O
g: R = H; X = $H_2$; Y = O

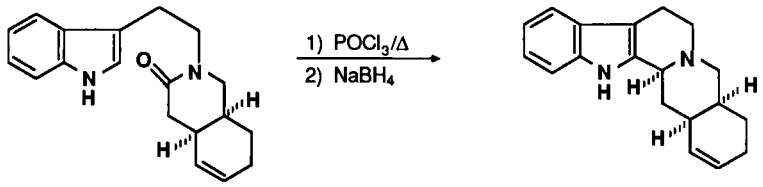



18 19: α-H
20: β-H

SCHEME 2

in a straightforward fashion using a Bischler–Napieralski cyclization followed by the hydride reduction of the intermediate iminium salt [Eq. (3)].[10]

Thus, these preliminary investigations unequivocally established that the intramolecular Diels–Alder reactions of certain nitrogen-linked trienes could be employed for the efficient construction of *cis*-hydroisoquinolines. Although the feasibility of elaborating the pentacyclic nucleus of the yohimboid alkaloids was also successfully demonstrated, these model studies did not in themselves provide compelling assurance that one could efficaciously apply such cyclizations to the total syntheses of selected members of the indole




(3)

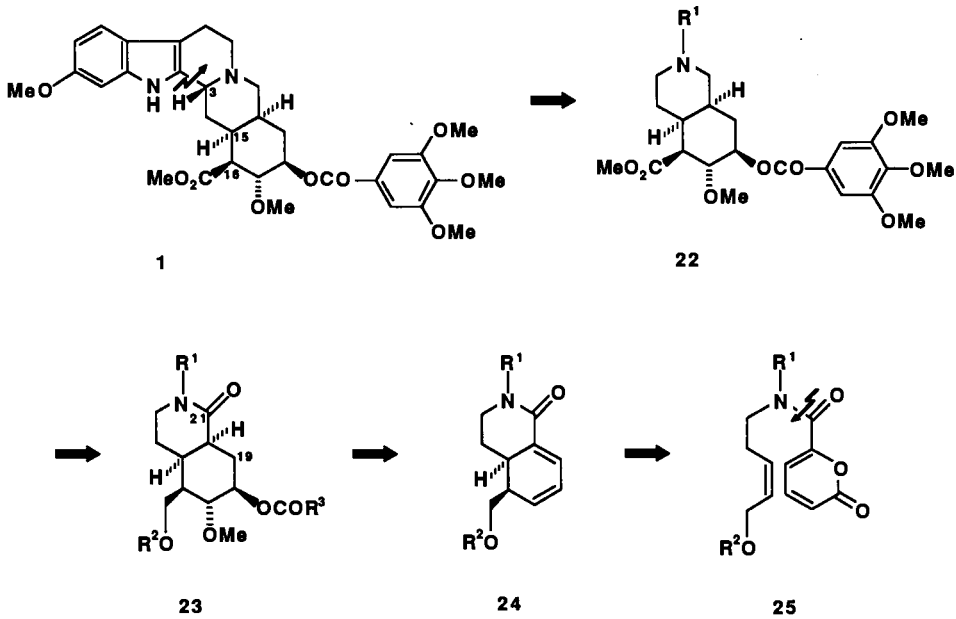
16c 21

alkaloid family. Since reserpine (**1**) is the stereochemically and functionally most complex member of the yohimboid subgroup, it followed that the total synthesis of **1** would represent the most demanding test of the basic strategy embodied in Scheme 1 and Eqs. (1) and (2).

## IV. The First-Generation Approach

### A. Total Synthesis of (±)-Reserpine (1)

With our preliminary model studies serving as the essential background, the strategy for the total synthesis of reserpine (**1**)[2d] that eventuated is outlined in Scheme 3. The ultimate subgoal of this ambitious venture required



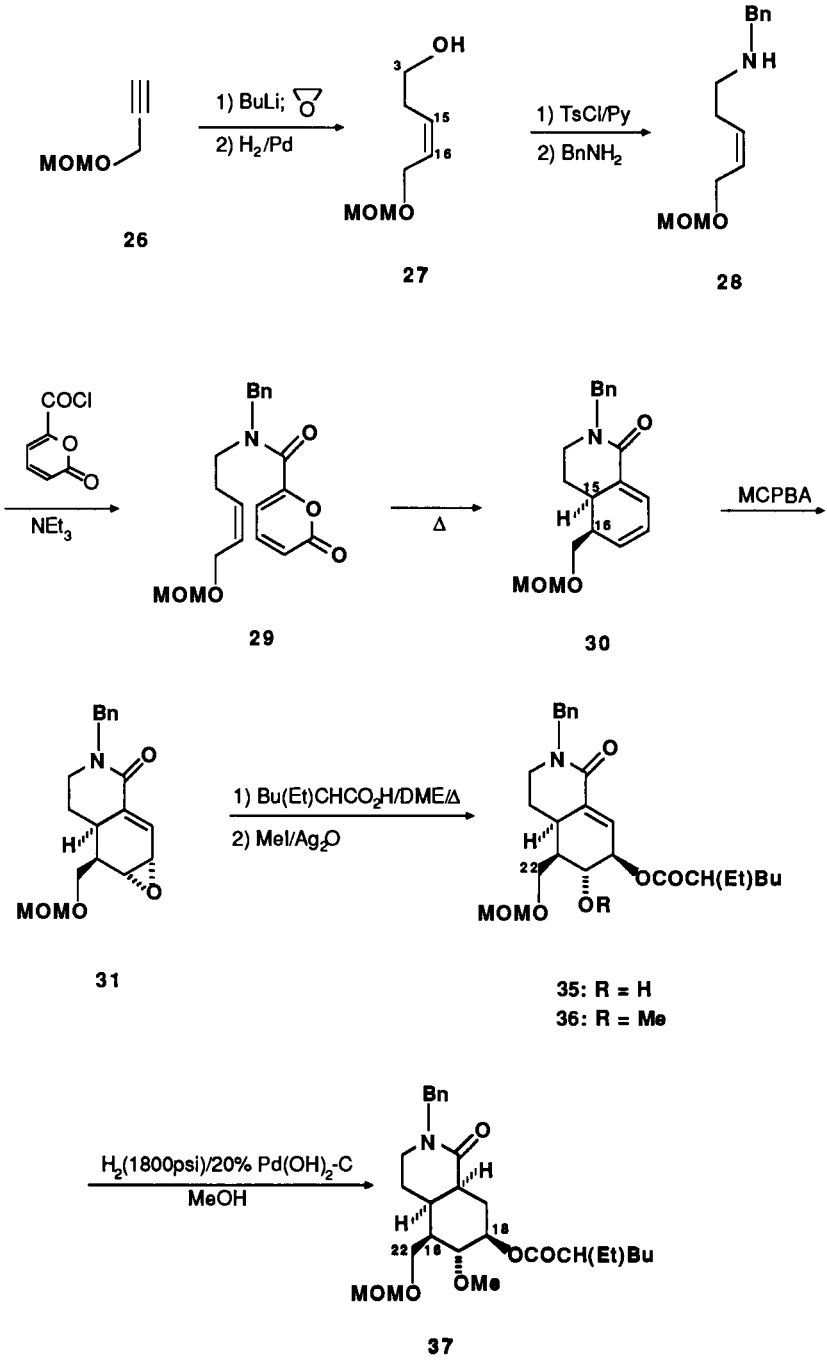
1 22 23 24 25

Scheme 3

the stereoselective elaboration of the fully intact D/E ring subunit **22** ($R^1$ = H). Formation of **22** would involve the refunctionalization of **23**, which incorporates the full complement of stereochemical features present in **22**. After considering a number of possibilities for elaborating the *cis*-hydroisoquinoline ring of **23**, we concluded that an intramolecular Diels–Alder reaction of the type depicted in Eq. (2) would provide the most attractive access to a suitable precursor of **23**. Since we had previously noted that the cyclization of the unsubstituted triene **18** proceeded with only a modest level of cis-diastereoselectivity, the stereoselective reduction of a $\Delta^{19,20}$-dehydro derivative of **23** was envisaged as a convenient tactic that would guarantee the obtention of the requisite cis-ring fusion present in **23**. If the hydrogenation of this double bond did not ensue in a highly stereoselective fashion, the favorable placement of the lactam carbonyl group at C(21) would allow base-induced epimerization at C(20) to afford the thermodynamically more stable *cis*-hydroisoquinolone **23**. In view of these considerations, the cycloadduct **24**, which would be obtained on intramolecular Diels–Alder reaction of **25**, appeared to be ideally suited for conversion to **23**. The final stage of the total synthesis of reserpine (**1**) would then entail the *N*-alkylation of **22** ($R^1$ = H) with a tryptophyl synthon followed by the oxidative closure of the C ring according to established methodology.[11,12] Although the 6-methoxyindole moiety could have been incorporated at an earlier stage, the susceptibility of this highly reactive ring system to oxidation and electrophilic attack appeared to render such a tactic problematic.

The first objective was the construction of the triene **29**, and it was assembled in 89% yield upon coupling the dienophilic subunit **28** with 2-oxopyran-6-carbonyl chloride (Scheme 4). The unsaturated amine **28** was readily prepared from propargyl alcohol by *O*-protection to give the methoxymethyl ether **26**, which was then converted into **27** by a straightforward sequence involving metallation, two-carbon extension, and catalytic semihydrogenation. The *Z*-double bond in **27** was essential since this $sp^2$ stereochemistry would be transferred into the $sp^3$ stereogenic centers at C(15) and C(16) of **30** and reserpine (**1**). The exchange of the hydroxyl function for an amino group was smoothly effected by the transformation of **27** into the corresponding tosylate, which then underwent reaction with benzylamine in dimethyl sulfoxide in the presence of a catalytic amount of sodium iodide to provide **28** in 60% overall yield from propargyl alcohol. When the triene **29** was heated in xylene at reflux, a facile [4 + 2] cycloaddition ensued with concomitant loss of carbon dioxide from the primary cycloadduct to furnish **30** in excellent yield.

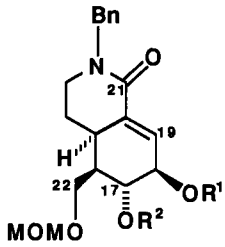
Refunctionalization of the D/E ring subunit then commenced with the introduction of the 1,2-dihydroxy array at C(17) and C(18), and a protocol involving the trans-diaxial opening of an epoxide was envisioned.


1) BuLi;
2) $H_2$/Pd
1) TsCl/Py
2) $BnNH_2$
MOMO
OH
Bn
NH
26
27
28
COCl
$NEt_3$
Δ
MCPBA
29
30
1) Bu(Et)$CHCO_2H$/DME/Δ
2) MeI/$Ag_2O$
31
35: R = H
36: R = Me
$H_2$(1800psi)/20% $Pd(OH)_2$-C
MeOH
OCOCH(Et)Bu
OMe
OR
37

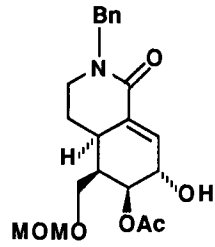
SCHEME 4

The regioselective and stereoselective monoepoxidation of **30** with *m*-chloroperbenzoic acid (MCPBA) at the more nucleophilic carbon–carbon double bond distal to the carbonyl group occurred as expected from the less hindered $\alpha$ - face to give **31** in 82% yield; none of the other possible isomeric monoepoxides were isolated. In order to establish the desired vic-glycol array, it was necessary to induce the opening of the epoxide moiety exclusively at the allylic terminus at C(18). Such a mode of attack was predicated not only on the reasonable supposition that the allylic terminus of the epoxide would be electronically activated but also on the expectation that the protected hydroxymethyl substituent at C(16) would offer a considerable steric impediment to the approach of a nucleophile on the trajectory required for the alternative attack at C(17). In agreement with these conjectures, we discovered that the reaction of **31** with AcOH/AcONa in THF at reflux provided a readily separable mixture (approximately 85 : 15) of the 1,2-hydroxy acetate **32** together with its regioisomer **33**. Unfortunately, **32** suffered unexpectedly facile isomerization via 1,2-acyl transfer to give **34**, a deleterious event that severely compromised the suitability of **32** as a viable substrate for further manipulation. On the other hand, scission of the epoxide moiety at the allylic terminus proceeded in a highly selective fashion when the more sterically hindered carboxyl group of 2-ethylhexanoic acid was employed as the nucleophilic reagent, and the resulting vic-hydroxy ester **35** exhibited little tendency toward isomerization. The extent to which the protected hydroxymethyl substituent at C(16) served as a crucial stereo- and regiochemical control element during the functional group interconversions at C(17) and C(18) of the E ring was noteworthy. Subsequent methylation of the secondary alcohol group at C(17) of **35** with neat methyl iodide in the presence of silver(I) oxide then afforded **36** in 88% overall yield from **31**.

With four of the five stereogenic centers present on the E ring now secured, only the ostensibly trivial task of reducing the $\Delta^{19,20}$-double bond of **36** to

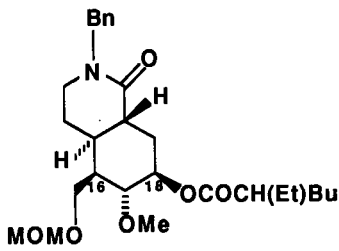



**32:** $R^1$ = Ac; $R^2$ = H
**34:** $R^1$ = H; $R^2$ = Ac

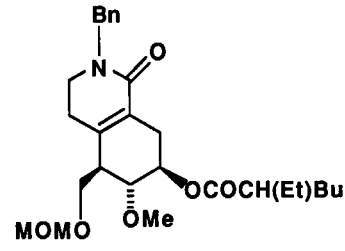



**33**

furnish **37** remained to address the major stereochemical issues posed by reserpine. As mentioned previously, if the delivery of hydrogen from the $\alpha$-face did not occur with a high degree of selectivity, the juxtaposition of a lactam carbonyl group at C(21) would allow the base-induced epimerization at C(20) of any *trans*-hydroisoquinolone **38** that might be produced to afford the more stable *cis*-hydroisoquinolone **37**, wherein each of the three substituent groups at C(16)–C(18) occupies an equatorial orientation on the E ring in its chair conformer. In the energetically less favorable trans-isomer **38**, the E ring would be compelled to reside in a twist boat or a related conformation in order to avoid the severe 1,3-diaxial interactions that would be incurred by the simultaneous placement of these three substituents in axial orientations.

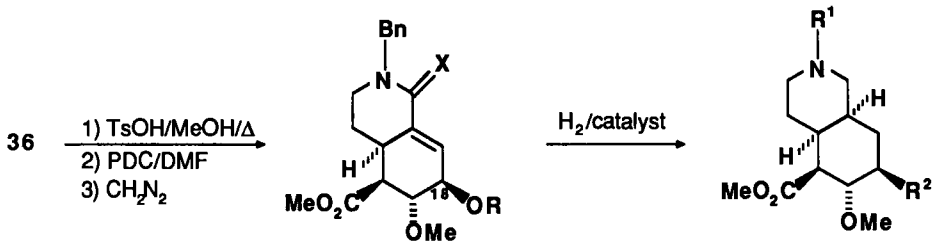



**38**




**39**

Notwithstanding this prior analysis, we were thoroughly frustrated in our initial efforts to reduce the trisubstituted, conjugated double bond present in **36** by catalytic hydrogenation because the competing isomerization of **36** to **39** ensued preferentially under a wide variety of standard conditions. Several attempts to engage dissolving metal or other conjugate reductions on the $\alpha,\beta$-unsaturated lactam array of **36** and the corresponding C(18) alcohol or alkoxide were also unavailing, with extensive cleavage of the allylic carbon–oxygen bond being a major side reaction. As is all too often the case in endeavors of this kind, the ultimate solution to the problem proved to be astonishingly simple. Namely, when the reduction of **36** was performed in methanol under high hydrogen pressure in the presence of Pearlman's catalyst, the *cis*-hydroisoquinolone **37**, which contains all of the stereochemical features present in the D/E ring subunit of reserpine (**1**), was isolated in 90% yield; only minor amounts of other diastereoisomers were detected. Although it was possible to reduce the tetrasubstituted double bond in **39** under these forcing conditions, an unacceptable mixture of stereoisomers was obtained.



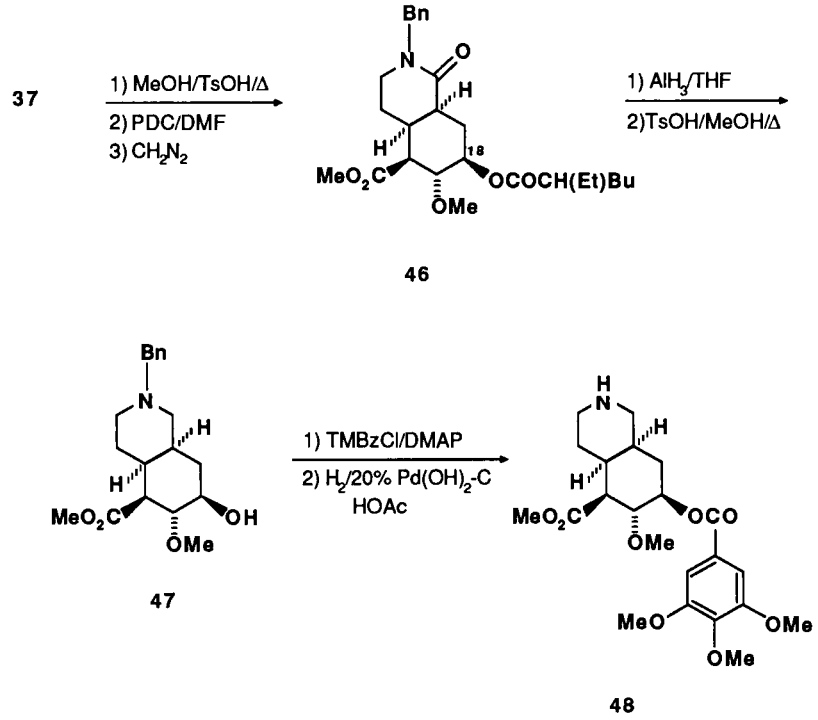

**40**: X = O; R = COCH(Et)Bu
**41**: X = $H_2$; R = COCH(Et)Bu
**44**: X = $H_2$; R = H

**42**: $R^1$ = Bn; $R^2$ = H
**43**: $R^1$ = $R^2$ = H
**45**: $R^1$ = Bn; $R^2$ = OH

SCHEME 5

During the course of our investigations to develop a practical protocol to achieve the stereoselective reduction of **36**, we ventured into several side excursions (Scheme 5). Since one such odyssey led to an interesting discovery that would be later implemented in the synthesis of α-yohimbine (*vide infra*), a brief diversion is warranted. It occurred to us that the carbonyl function located at C(21) might be playing some role, perhaps electronic, in facilitating the preferential isomerization relative to reduction of the $\Delta^{19,20}$-carbon–carbon double bond in **36**, and the possibility that its removal might attenuate this deleterious process was considered. In order to avoid any complications that might be encountered during the adjustment of the oxidation state at C(22) in the presence of a tertiary amine, **36** was converted to the methyl ester **40** in 77% overall yield prior to effecting the selective reduction of the amide moiety of **40** with alane to furnish **41**. Although the reduction of the double bond in **41** by catalytic hydrogenation then proceeded smoothly without apparent isomerization, extensive hydrogenolysis of the allylic ester function at C(18) intervened as an offending side reaction. Depending on the reaction conditions and the catalyst employed, mixtures containing variable quantities of **42** and **43** as the major products were typically isolated. Whereas catalytic hydrogenation of the derived alcohol **44** proceeded largely without hydrogenolysis, a mixture of products was formed with the desired **45** being isolated in only about 40% yield. Based on the foregoing results, it was apparent that the carbonyl group at C(21) was critical for the preservation of the hydroxyl function at C(18) during reduction of the $\Delta^{19,20}$-double bond, but it was less important for the control of the stereocenter at C(20) than was originally presumed.

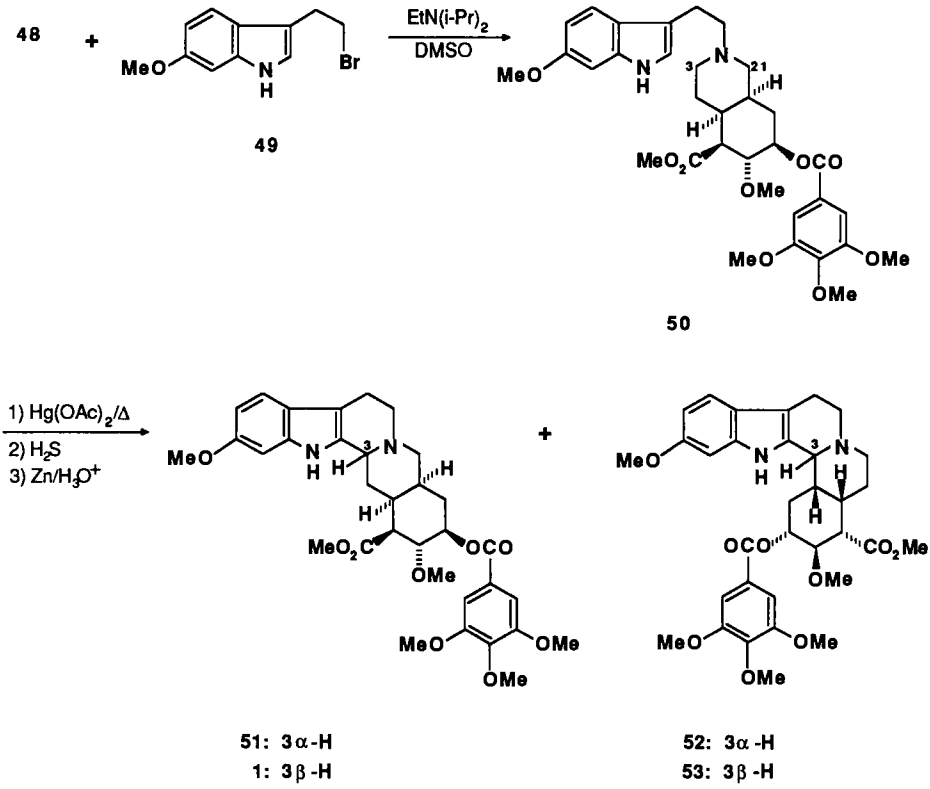
The conversions required for the final refunctionalization of **37** to the fully elaborated D/E ring subunit **48** were then executed as summarized in




SCHEME 6

Scheme 6. The methoxymethyl protecting group was first removed from the hydroxyl group at C(22) of **37**, and the intermediate primary alcohol was transformed into the corresponding methyl ester to give **46** in 75% overall yield. The chemoselective hydride reduction of the lactam carbonyl group proceeded smoothly under carefully controlled conditions, and subsequent deprotection of the hydroxyl function at C(18) by acid-catalyzed transesterification in methanol furnished **47** in 65% yield. The attempted cleavage of this hydroxyl protecting group by base-induced saponification was accompanied by extensive degradation of the E ring via $\beta$-elimination of the methoxy group at C(17) and subsequent aromatization. Reacylation of the hydroxyl group at C(18) of **47** with trimethoxybenzoyl chloride followed by the removal of the *N*-benzyl substituent by catalytic hydrogenolysis provided **48**.

The completion of the total synthesis of reserpine was then achieved in two quick moves (Scheme 7). The *cis*-hydroisoquinoline **48** was first coupled with **49** to deliver *seco*-dihydroreserpine **50**, and the final oxidative cyclization of **50** was performed according to a modification of the procedure previously developed by Sakai[11,12] to furnish (±)-reserpine (**1**) (35%) and (±)-



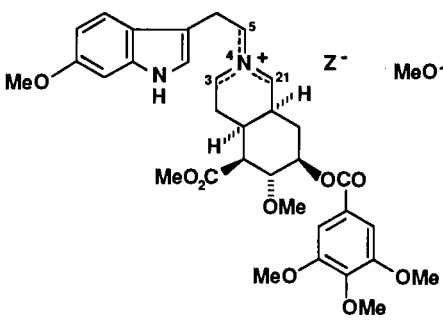

SCHEME 7

isoreserpine (**51**) (8%) together with the two corresponding inside derivatives **52** (18%) and **53** (4%) and starting **50** (10%). Thus, the total synthesis of racemic reserpine (**1**) from propargyl alcohol required a longest linear sequence of only 20 chemical operations and proceeded in approximately 4% overall yield.

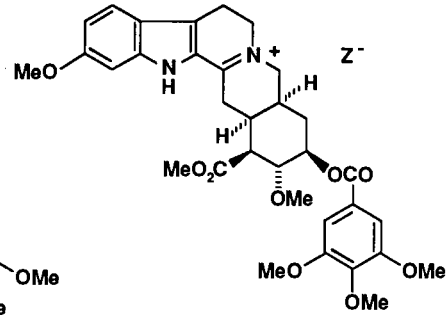
Meriting brief comment are the regiochemical and stereochemical consequences of the chemical transformations that resulted in the conversion of **50** into a mixture of **1** and the isomeric substances **51–53**. Namely, an analysis of the ratio of the products obtained revealed that the mercuric ion-induced oxidation of **50** delivered a mixture (approximately 2 : 1) of the two trisubstituted iminium salts **54**, which led to reserpine (**1**) and isoreserpine (**51**), and **55**, which afforded the corresponding inside isomers **52** and **53**. There was no conclusive evidence for the formation of **56**, but minor amounts of products derived therefrom would not have been isolated. An oxidative route to some related iminium salts has been reported using the

Polonovski reaction,[12f] and although the scope and limitations of this methodology have not been extensively explored, this alternative tactic did not appear *a priori* to offer any significant improvements over the mercuric ion-mediated oxidations and was not examined. Thus, the relatively low degree of regiochemical control that was encountered in the formation of the key iminium salt **54** from **50** was viewed as an inevitable consequence inherent in any approach to the pentacyclic nucleus of the yohimboid and heteroyohimboid alkaloids that involved the oxidative cyclization of 2,3-seco-precursors.[11,12] It would be necessary to redress this deficiency in the development of second generation variants of this strategy.

The production of the epimers **1** and **51** may be attributed to the modest stereoselection observed in our hands during the dissolving metal reduction[13,14] of the dehydroreserpine (**57**) that was produced *in situ* by the mercuric ion-induced oxidation of the **1** and **51** initially formed. In this regard, we presently believe that the cyclization of **54** delivered **1** as the

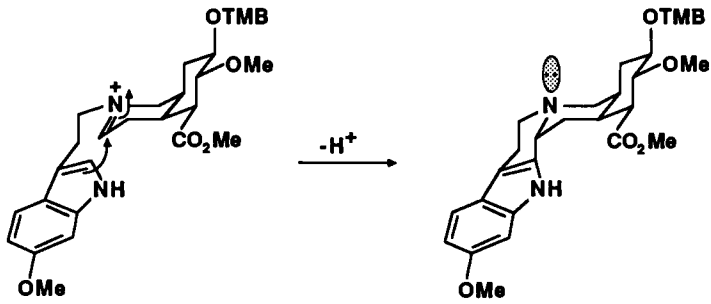



54: $\Delta^{3,4}$
55: $\Delta^{4,21}$
56: $\Delta^{4,5}$




57

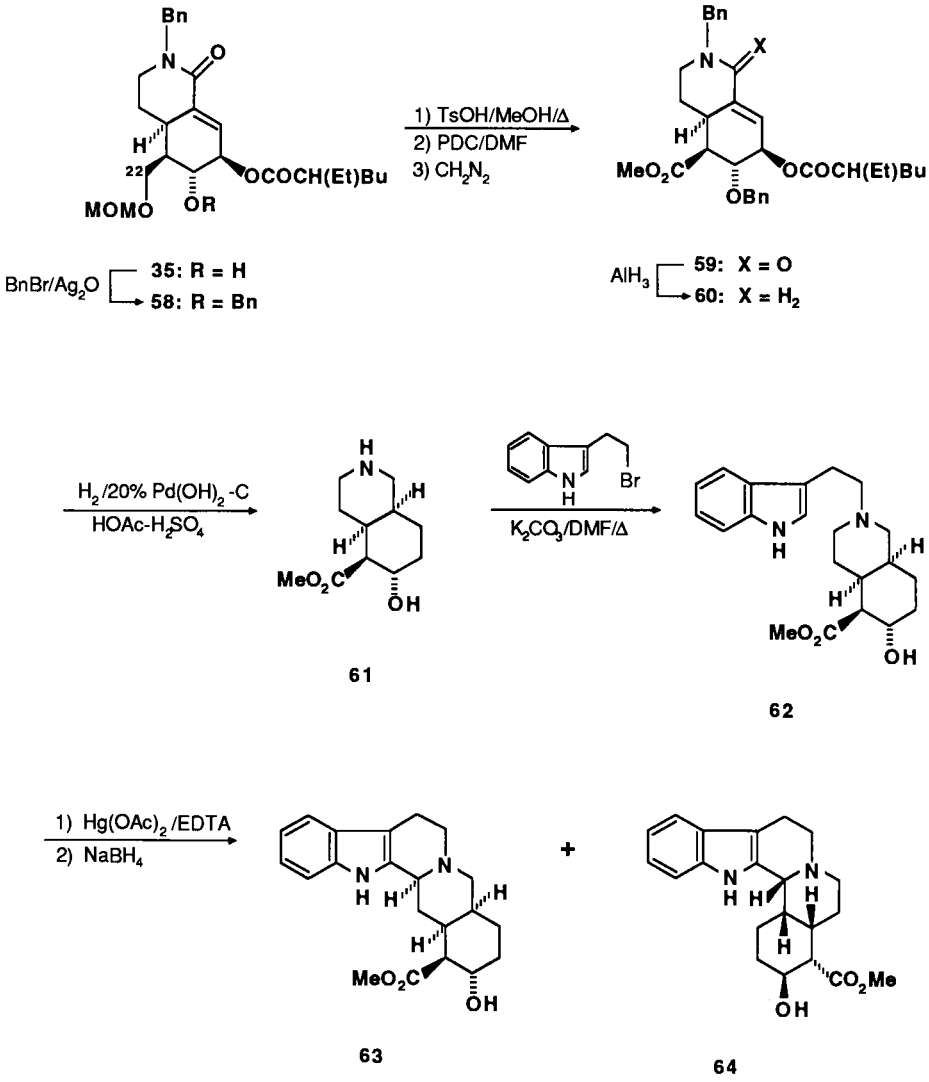
major kinetic product by a process involving the axial addition of the indole ring to the cyclic iminium salt moiety of the D/E ring system residing in its most stable half-chair/chair conformation as illustrated in Eq. (4). The importance of this stereochemical control element in the nucleophilic additions to cyclic iminium salts was recognized previously by others.[15] The alternative mode of closure of **54** to produce **51** must proceed via a transition state involving a higher energy boatlike or twist boat conformation. Although cyclization by this latter topology should be energetically less favorable, it is not possible to exclude completely its occurrence.




(4)

## B. Total Synthesis of (±)-α-Yohimbine (**63**)

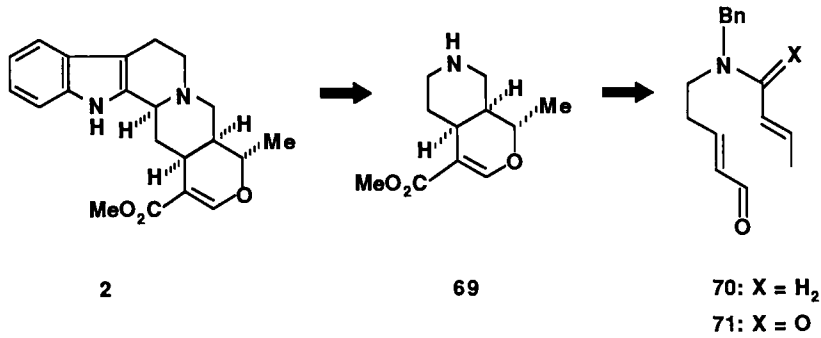
The close structural relationship between reserpine (**1**) and α-yohimbine (**63**)[16] suggested that one of the intermediates required for the synthesis of **1** might also be exploited for the construction of the D/E ring subunit of **63**. Our serendipitous discovery that the oxygen function at C(18) of the amine **41** could be efficiently removed by catalytic hydrogenolysis provided further encouragement and impetus to the undertaking of this new project. While a variety of possibilities may be envisioned, one highly satisfactory solution to the problem commenced with the *O*-benzylation of the C(17) hydroxyl function of **35** followed by installation of the carbomethoxy group at C(22) according to prior art (Scheme 5) to afford **59** in very good overall yield (Scheme 8). Chemoselective reduction of the lactam carbonyl of **59** with alane furnished the unsaturated tertiary amine **60** in 89% yield. Stirring a solution of **60** under an atmosphere of hydrogen in the presence of Pearlman's catalyst in glacial acetic acid containing a trace of concentrated sulfuric acid then resulted in the *simultaneous* hydrogenolyses of the allylic oxygen function at C(18), the *N*-benzyl and *O*-benzyl groups, as well as the stereoselective reduction of the $\Delta^{19,20}$-double bond to give **61**, which comprised the intact D/E ring subunit of α-yohimbine. Alkylation of **61** with tryptophyl bromide then provided 2,3-*seco*-α-yohimbine (**62**) in very good overall yield. After treatment of **62** with mercuric ion in the presence of the disodium salt of ethylenediaminetetraacetic acid (EDTA), the crude mixture thus obtained was reduced with sodium borohydride to deliver α-yohimbine (**63**) (31%) together with the corresponding inside isomer **64** (31%). The obtention of both **63** and **64** from this process further underscored the regiochemical difficulties associated with present methods for constructing the C ring of the pentacyclic yohimboid nucleus by the regioselective, oxidative cyclization of 2,3-seco derivatives.




SCHEME 8

## C. FORMAL SYNTHESIS OF (±)-TETRAHYDROALSTONINE (2)

Having successfully demonstrated that the cis-D/E ring subunit common to several yohimboid alkaloids could be rapidly assembled through the aegis of an intramolecular Diels–Alder reaction, we focused on the considerable challenge of further extending the general strategy outlined in Scheme 1 to

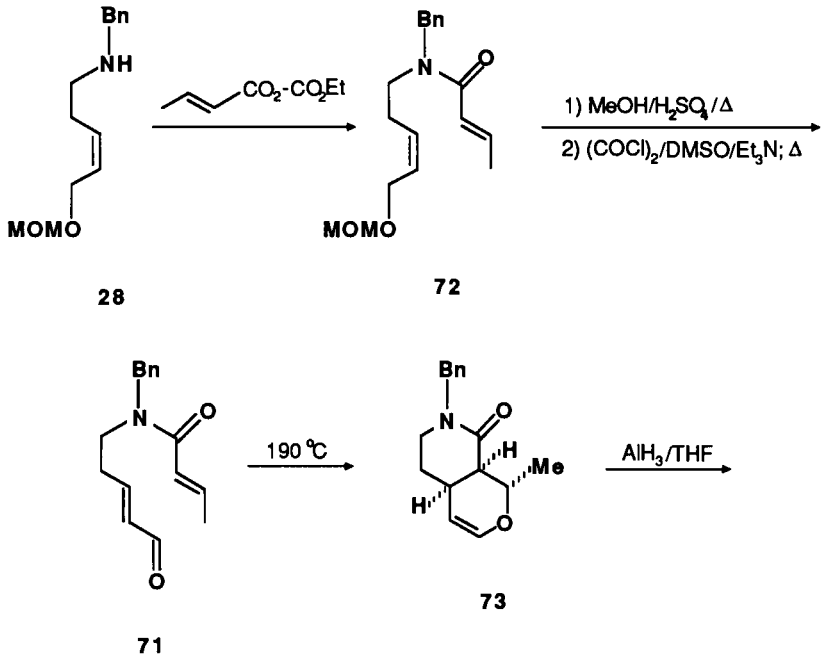



**2** **69** **70: X = $H_2$** **71: X = O**

SCHEME 9

the synthesis of the heteroyohimboid alkaloid tetrahydroalstonine (**2**) (Scheme 9). The crucial issue to be addressed at the outset of this enterprising venture was whether the intramolecular hetero Diels–Alder reaction of a triene related to **70** or **71**, in which an unactivated $\alpha,\beta$-unsaturated aldehyde served as the dienic partner, would deliver a *cis*-oxahydroisoquinoline that could then be elaborated into the requisite bicyclic intermediate **69**. One may envisage straightforward methods for converting the unsaturated amine **28** into the heterotrienes **70** and **71**, and since **28** was already available from previous work, we elected to test the feasibility of the key hetero Diels–Alder reaction directly without executing the usual model studies.

In the event, acylation of the amine **28** provided the crotonamide **72**, and successive deprotection of the allylic hydroxyl group and Swern oxidation afforded an intermediate *Z*-enal that suffered surprisingly facile acid-catalyzed isomerization to furnish the *E*-enal **71** in 64% overall yield from **28** (Scheme 10). The *E*-enal **71** could also be obtained directly on oxidation of the *Z*-allylic alcohol derived from **72** using manganese dioxide or pyridinium dichromate (PDC), reagents that do not normally induce double-bond isomerization, but the overall yield using the Swern procedure was superior. Thermolysis of **71** at 190°C provided a readily separable mixture (5 : 1) of the cis- and trans-cycloadducts **73** and **74** from which the requisite **73** was isolated in 73% yield. It is interesting to note that the intramolecular nature of the cyclization of **71** enforces a regiochemistry on this hetero Diels–Alder reaction that is *opposite* to that which would be expected on purely electronic grounds.[6] Based on the available precedent in the literature,[5] one would anticipate that the thermolysis of the *Z*-enal isomer of **71** should furnish the desired *cis*-oxahydroisoquinoline **73** as the exclusive product. However, several preliminary efforts to effect the thermal cyclization of the *Z*-enal were attended by some decomposition and extensive geometric isomerization to



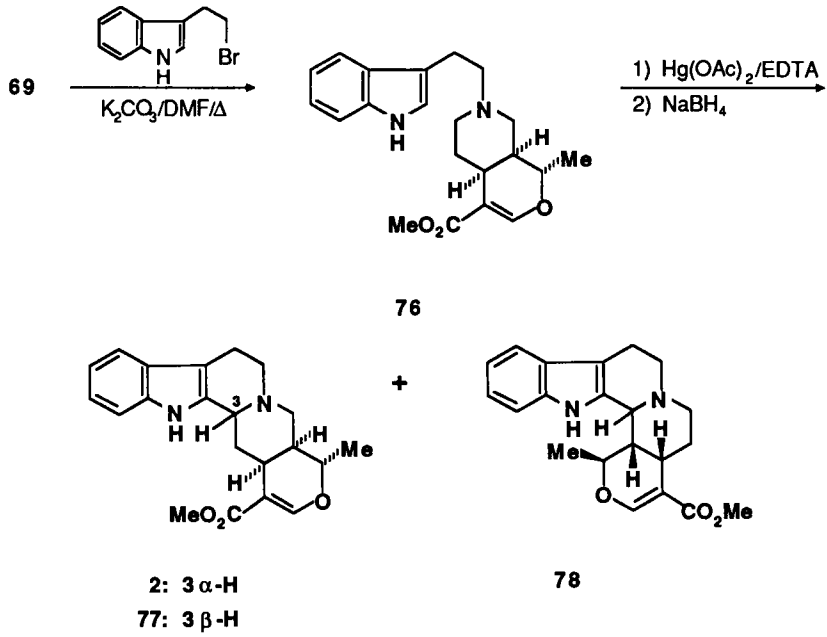

28 72 71 73 69 74

SCHEME 10

give the *E*-isomer **71**, and a mixture of **73** and **74** was thus obtained, albeit in somewhat lower yield. Although the related and unstable heterotriene **70** could be prepared from **28** by sequential alkylation with crotyl bromide, hydroxyl deprotection, and oxidation with PDC, initial attempts to induce its cyclization were unavailing, and once again decomposition pathways predominated.

Having unequivocally established the fundamental viability of this novel intramolecular hetero Diels–Alder reaction for the construction of *cis*-oxahydroisoquinolines, it remained to complete the synthesis of tetrahydroalstonine (**2**). Hydride reduction of the lactam moiety of **73** gave the tertiary amine **75**. Subsequent installation of the carbomethoxy function at C(16) of **75** was achieved by an efficient two-step process entailing the initial acylation of the enol ether moiety with trichloroacetyl chloride[17] followed by the methanol-induced, haloform-type cleavage of the intermediate α-trichloromethyl carbonyl group to deliver **76** in 73% overall yield from **73**. This novel protocol for the construction of a vinylogous carbonate array from a cyclic enol ether should prove to be of general utility. The synthetic task was then consummated when the *N*-benzyl group of **76** was excised by catalytic hydrogenolysis to afford **69**, the D/E ring subunit of **2**.

Since Uskoković[3c,d] had previously converted **69** into **2** by the two-step procedure depicted in Scheme 11, the present route to **69**, which required a




SCHEME 11

linear sequence of only 13 chemical operations and proceeded in 18% overall yield from propargyl alcohol, constituted a formal total synthesis of **2**. However, it is again relevant to the discussion of some future developments in the area (*vide infra*) to reiterate that the oxidation of the 2,3-seco derivative **76** with mercuric ion followed by the treatment of the resulting mixture of pentacyclic iminium salts with sodium borohydride gave a mixture of tetrahydroalstonine (**2**) and akuammigine (**77**) in a 4.3 : 1 ratio *together* with unspecified quantities of the corresponding inside derivative(s) **78**.

Based on the aforementioned results and discussions, it is evident that the intramolecular Diels–Alder and hetero Diels–Alder reactions of selected nitrogen-linked trienes may be expeditiously applied to the total syntheses of complex indole alkaloids, and efficient and concise entries to reserpine (**1**), α-yohimbine (**63**), and tetrahydroalstonine (**2**) serve as compelling testimonials to the viability of the basic strategy. However, at this time it is appropriate to critically evaluate the current state of the art and to examine what possible refinements and modifications of the present strategy and tactics might result in the design and development of improved, second-generation approaches to these and related naturally occurring bases.

## V. The Second-Generation Approach

One drawback that appears inherent in the strategy depicted in Scheme 1 is a direct consequence of the requirement to employ oxidative cyclizations of seco derivatives such as **6** and **7** (Y = $H_2$) (e.g., **50**, **62**, and **76**) to effect the closure of the C ring as the final step in the construction of the pentacyclic ring system of the target alkaloids. The oxidations of these and related tertiary amines to cyclic iminium salts typically proceeded with modest levels of regioselectivity[12] at best, and mixtures of the desired skeleta (*e.g.*, **1**, **2**, **51**, and **63**) together with significant amounts of the corresponding inside derivatives (*e.g.*, **52**, **53**, **64**, and **78**) were invariably obtained. Since there are presently no solutions to this dilemma, an alternative approach to the pentacyclic nucleus is required that avoids such oxidative processes for the formation of the C ring. A further issue that arises at this juncture is whether the aforementioned entries to reserpine (**1**), α-yohimbine (**63**), and tetrahydroalstonine (**2**) might be modified and then implemented to access members of the corynantheioid family and perhaps the even more complex alkaloids of the *Strychnos* class. Finally, the important concern of producing the target alkaloids in enantiomerically pure form remains to be addressed, and potential solutions to this problem must be devised.

In accordance with the above considerations, we have recently designed a second-generation entry to the indole alkaloids that may be formulated as an

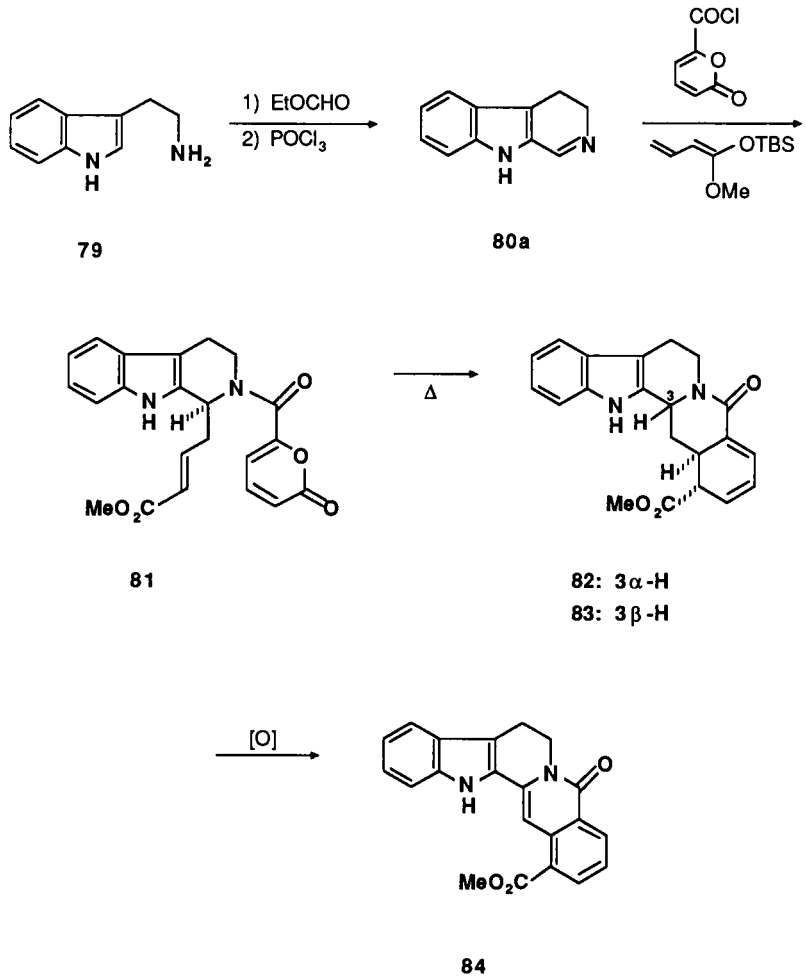
ABC ⇒ ABCDE approach, since the requisite dienic and dienophilic partners were appended to a preexisting ABC ring subunit prior to the pivotal intramolecular Diels–Alder reaction. The following discussion will unveil the obvious merits of this modified strategy, which has resulted in the extraordinarily concise syntheses of several indole alkaloids.

### A. Total Synthesis of Oxogambirtannine (**84**)

One instructive example of the seductive simplicity inherent in this new approach may be found in a facile synthesis of oxogambirtannine (**84**).[18] Thus, *N*-formylation of tryptamine (**79**) followed by a Bischler–Napieralski cyclization afforded the known dihydrocarboline **80a**. When **80a** was allowed to react with 2-oxopyran-6-carbonyl chloride in the presence of a vinyl ketene acetal derived from methyl crotonate, the triene **81** was produced in approximately 70–75% yield via a process that presumably proceeded by the nucleophilic addition of the terminus of the vinyl ketene acetal to an intermediate *N*-acyl iminium salt (Scheme 12). Subsequent thermolysis of **81** then furnished a mixture of the epimeric pentacyclic lactams **82** and **83**. Thus, an exceedingly concise, linear sequence of reactions transforms inexpensive, commercially available starting materials into the pentacyclic nucleus characteristic of the yohimboid alkaloids. Oxidation of the mixture of **82** and **83** with benzoquinone then delivered oxogambirtannine (**84**). In other experiments, we discovered that the transformation of **81** into **84** could be more expeditiously executed upon thermolysis of **81** in the presence of atmospheric oxygen or benzoquinone.

### B. Total Syntheses of (±)-Tetrahydroalstonine (**2**) and (±)-Cathenamine (**90**)

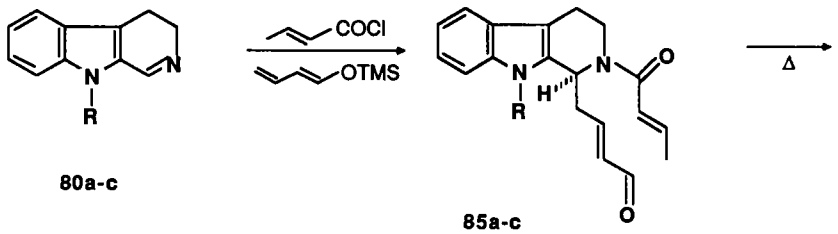
Another striking demonstration of the efficacy of this modified ABC ⇒ ABCDE strategy is its application, in tandem with a hetero Diels–Alder reaction, to the design of a succinct entry to the heteroyohimboid alkaloids (Scheme 13). Since at the outset of these studies it was not possible to predict accurately whether *N*-protection would be required for the indole nucleus, we initially elected to explore three possibilities in parallel investigations in which the nitrogen atom of the indole ring was unprotected (Series a) or protected with either an electron-withdrawing substituent ($CO_2Me$) (Series b) or an alkyl group ($CH_2OMe$) (Series c). It is noteworthy that **80b** and **80c** could be conveniently prepared *in situ* from **80a** immediately prior to the formation of **85b** and **85c**. Ultimately, we discovered that these prior concerns regarding the need to protect the indole ring or the indolic N—H bond were unwarranted, and each of the reactions involving unprotected




SCHEME 12

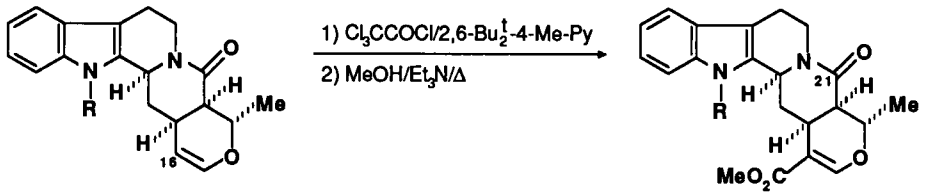
indoles proceeded without event under suitably defined conditions. Inasmuch as any protective measures unnecessarily added to the number of synthetic operations, our experimental efforts were concentrated on the unprotected indoles of Series a, and the ensuing discussion will be focused accordingly with specific comment regarding the *N*-protected intermediates only when justified.

Although a variety of potential entries to the key hetero triene **85a** might be imagined, one simple and highly effective route was analogous to that previously described for the preparation of **81** (Scheme 12). Thus,



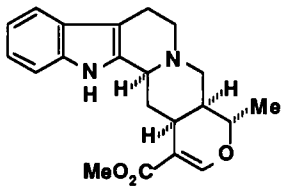

80a-c

85a-c

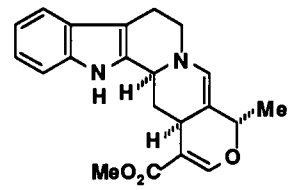



86a-c

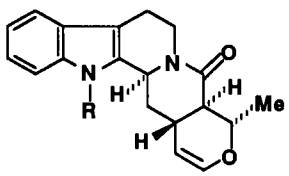
89a-c



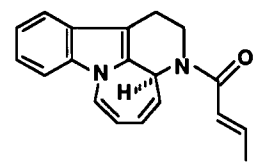
2



90



87a-c



88

**Series a: R = H**
**Series b: R = $CO_2Me$**
**Series c: R = $CH_2OMe$**

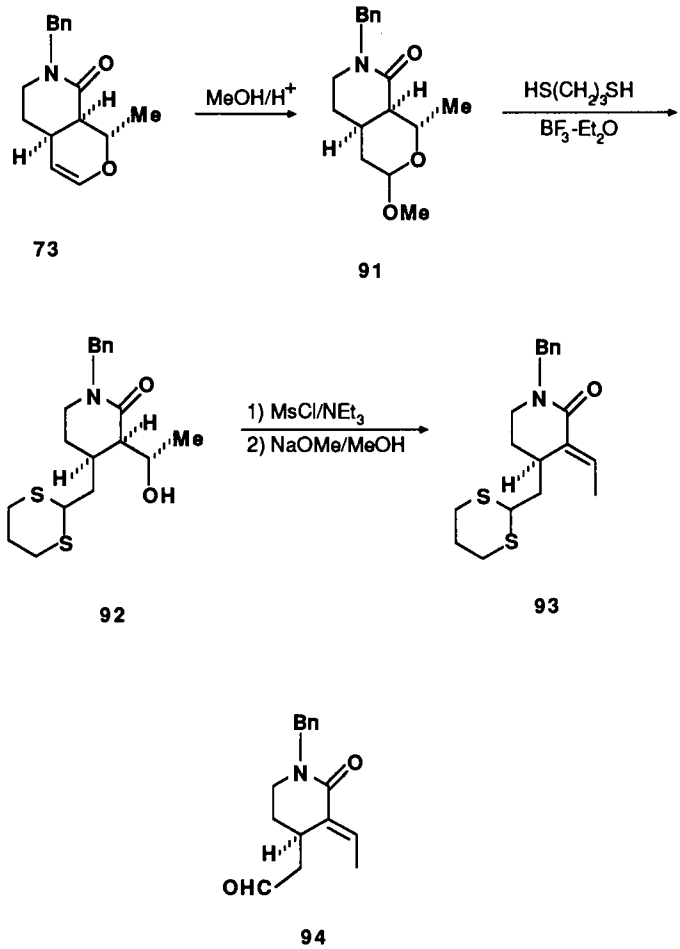
SCHEME 13

the reaction of **80a** with crotonyl chloride in the presence of 1-trimethylsilyloxybutadiene provided **85a** in approximately 80% yield (Scheme 13). Rapid elaboration of the heteroyohimboid skeleton was then achieved by the thermolysis of **85a**, which proceeded to afford a separable mixture (approximately 9 : 1) of the cis- and trans-cycloadducts **86a** and **87a**, respectively, in a combined yield of 87%. Whenever the thermolysis of **85a** was executed without exercising extreme care to exclude acid, variable but significant quantities of the novel dienamine **88** were isolated. The installation of the carbomethoxy group into C(16) of **86a** to furnish **89a** (ca. 70% overall yield) was then achieved by slight modification of the experimental conditions in the two-step protocol previously described for the preparation of **76** (Scheme 10). In a similar fashion, the *N*-protected analogs **89b,c** were prepared from **80b,c**, respectively, but these conversions were not fully optimized.

Completion of the total synthesis of tetrahydroalstonine (**2**) merely entailed the chemoselective addition of 2 equivalents of hydride to the lactam moiety at C(21) of **89a**. Alternatively, it was also possible to effect the selective delivery of a single equivalent of hydride to the lactam function of **89a** using lithium triethoxyaluminum hydride to provide the unstable and biosynthetically important alkaloid cathenamine (**90**).[19] Thus, the heteroyohimboid alkaloids **2** and **90** are now readily accessible from a longest linear sequence involving only seven steps from commercially available tryptamine, and it presently appears that this strategy will be eminently suited for the design of efficacious syntheses of other members of this important class of natural products.

### C. Total Synthesis of (±)-Geissoschizine (3)

A brief comparison of the structures of **86a** and **89a** with that of the corynantheioid alkaloid geissoschizine (**3**) revealed the tantalizing possibility that these intermediates might also be exploited as precursors of **3**. The critical issue at this juncture regarded the feasibility of effecting the $\beta$-elimination of the hydropyran oxygen atom of either **86a** or **89a** to provide a ring-opened derivative bearing the requisite *E*-ethylidene array at C(20). That this tactic was indeed meritorious was quickly verified in two preliminary model studies (Scheme 14). In the first, the cis-cycloadduct **73**, which was available from our initial work in the tetrahydroalstonine arena (Scheme 10), was converted in two steps to the 3,4-disubstituted-2-piperidone **92**. After transformation of the secondary hydroxyl group of **92** into the corresponding mesylate, base-induced $\beta$-elimination afforded the *E*-$\alpha,\beta$-unsaturated lactam **93** as the sole product.[20] In the second

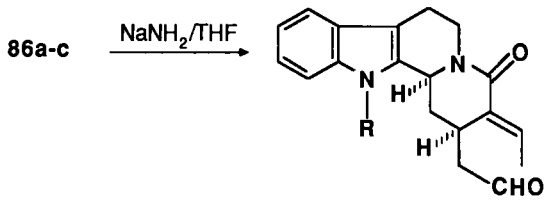



73 91 92 93 94

SCHEME 14

study, a simplified solution to the problem was developed. Namely, when **73** was treated directly with excess sodium amide, the hydropyran ring suffered cleavage via $\beta$-elimination to furnish **94** in good yield. The stage was therefore set to apply these discoveries to the total synthesis of geissoschizine (**3**).

In initial experiments, we discovered to our considerable chagrin that **86a** did not undergo clean $\beta$-elimination to give **95** when treated with base under a variety of conditions. This behavior is apparently due to the presence of the free indolic N–H, since the related *N*-methoxymethyl derivative **86c** was readily converted to **96** on exposure to excess sodium amide (Scheme 15);

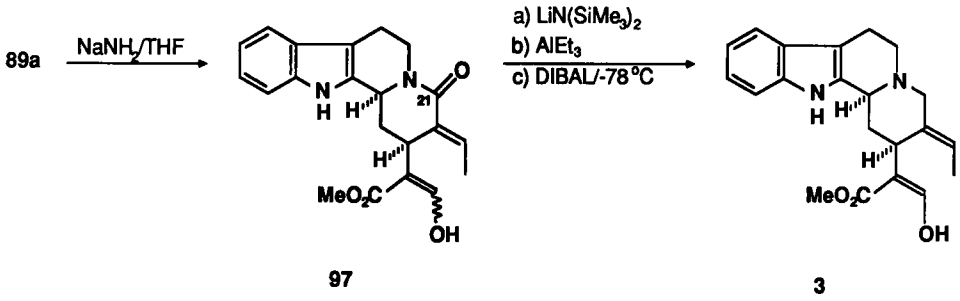



**95: R = H**
**96: R = $CH_2OCH_3$**

SCHEME 15

none of the corresponding *Z*-ethylidene isomer was detected. On another front, the *N*-carbomethoxy derivative **86b** suffered $\beta$-elimination with competing *N*-deprotection under identical conditions, and a mixture (ca. 1 : 1) of **86a** and **95** was obtained. Inasmuch as one of the principal goals of the overall project was to minimize superfluous protection/deprotection routines during the syntheses of these complex molecules, the requirement to protect the indolic nitrogen in order to realize efficient $\beta$-elimination was ruled as unacceptable, and a more direct tactic was sought.

We reasoned that **89a** should be a superior substrate for a base-induced cleavage of the E ring, since the leaving group in this instance would be the stabilized enolate of an $\alpha$-formyl ester rather than the more basic enolate of an aldehyde as in the cases of **86a–c**. In agreement with this hypothesis, treatment of **89a** with sodium amide resulted in the smooth $\beta$-elimination of the ring oxygen atom to give in 95% yield, the *E*-ethylidene lactam **97** as a variable mixture of geometric isomers about the enol double bond; none of the isomeric *Z*-exocyclic olefin was isolated (Scheme 16). At this stage only the superficially straightforward task of reducing the lactam carbonyl group at C(21) of **97** to a methylene remained to complete the total synthesis of geissoschizine (**3**). However, given the highly functionalized nature of the substrate **97**, we anticipated that we might experience some difficulty in defining suitable conditions to achieve this "simple" transformation. Our pessimistic view of the situation was all too accurate, and it was necessary to expend considerable effort before finding a satisfactory experimental solution to the problem. Ultimately, we discovered that when the $\alpha$-formyl ester array of **97** was protected *in situ* as an enolate, the selective reduction of the lactam moiety using diisobutylaluminum hydride under strictly controlled conditions did ensue to deliver geissoschizine (**3**) in good yield. Thus, the total synthesis of **3** was readily accomplished by a linear sequence requiring only eight chemical steps from commercially available tryptamine.

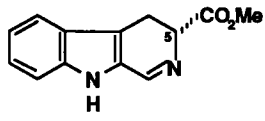



SCHEME 16

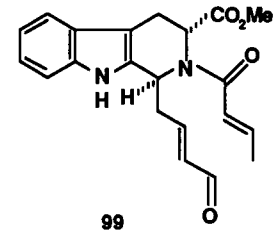
## VI. Conclusions and Future Directions

A general strategy for the total syntheses of indole alkaloids of the yohimboid, heteroyohimboid, and corynantheioid classes has been designed and developed, and the efficacy of the overall approach has been convincingly established by the successful completion of the concise syntheses of reserpine (**1**), α-yohimbine (**63**), tetrahydroalstonine (**2**), geissoschizine (**3**), oxogambirtannine (**84**), and cathenamine (**90**). The salient feature of this novel entry to the indole alkaloids is the intramolecular [4 + 2] cycloaddition of nitrogenlinked trienes of the general form **12** and heterotrienes of the general type **10b** to provide facile access to the *cis*-D/E ring subunits present in the yohimboid and heteroyohimboid alkaloids. Cleavage of the hydropyran ring of the cycloadducts obtained upon cyclization of the heterotrienes **10b** then provided a convenient path to the corynantheioid alkaloids.

There remain, however, further obstacles to be challenged and problems to be solved. For example, it is intriguing to consider the possibility that **98**, which is accessible from D-tryptophan, might be employed for the preparation of diastereomerically pure **99**, a potentially useful intermediate for the asymmetric syntheses of the heteroyohimboid and corynantheioid alkaloids according to the general plans outlined in Schemes 13 and 15; efforts in this




98




99

important direction are now under careful scrutiny. Significantly, the carboxyl group at C(5) in **98** need not serve merely to provide a stereochemical bias for subsequent constructions since it may also act as a critical functional handle at C(5) to allow entry to certain of the architecturally more complex indole alkaloids such as ajmaline.[21] Additional tests of the merits of the strategy and tactics described herein will be encountered as we embark on the syntheses of members of other classes of the indole family. The trials and tribulations encountered in these future investigations will doubtless offer additional opportunities for the discovery and development of new chemistry and the invention of novel synthetic methods.

## Acknowledgments

I wish especially to thank my highly dedicated group of co-workers for their extensive intellectual, creative, and technical contributions to the overall success of the work presented herein. These individuals include B. Benage, Dr. S. P. Brown, L. S. Geraci, Dr. S. Grzejszczak, Dr. J. E. Hunter, Dr. H. Rüeger, and S. A. Williamson. I am also grateful to the National Institutes of Health (GM 25439) and the Robert A. Welch Foundation for their generous support of this research. Finally, we thank Dr. M. R. Uskoković (Hoffmann–LaRoche, Inc.) and Professor E. Wenkert (University of California, San Diego) for samples of authentic tetrahydroalstonine and Professor H. Rapoport (University of California, Berkeley) for an authentic sample of geissoschizine.

## References

1. For leading references and reviews of the monoterpenoid alkaloids of the indole family, see (a) "The Alkaloids, Chemistry and Physiology," Manske, R. H. F., Ed.; Academic Press: New York, 1981; Vol. XX; (b) Saxton, J. E. in "Specialist Periodical Reports, the Alkaloids"; Royal Soc. Chem.: London, 1983; Vol. 13, pp. 221–237 (see also in Vols. 1–12); (c) Cordell, G. A. "Introduction to Alkaloids, a Biogenetic Approach"; Wiley (Interscience): New York, 1981; pp. 574–832.
2. For total syntheses of reserpine, see (a) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956,** *78*, 2023, 2657; *Tetrahedron* **1958,** *2*, 1; (b) Pearlman, B. A. *J. Am. Chem. Soc.* **1979,** *101*, 6398, 6404; (c) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980,** *102*, 6157; *Heterocycles* **1987,** *25*, 263; (d) Martin, S. F.; Grzejszczak, S.; Rüeger, H.; Williamson, S. A. *J. Am. Chem. Soc.* **1985,** *107*, 4072, **1987,** *109*, 6124; (e) Stork, G.; Goodman, B. A. *Am. Chem. Soc. Nat. Meet., 192nd, Anaheim, Calif.* **1986,** ORGN 136.
3. For total syntheses of tetrahydroalstonine, see (a) Winterfeldt, E.; Radunz, H.; Korth, T. *Chem. Ber.* **1968,** *101*, 3172; (b) Brown, R. T.; Leonard, J.; Sleigh, S. K. *J.C.S. Chem. Commun.* **1977,** p. 636; (c) Uskoković, M. R.; Lewis, R. L.; Partridge, J. J.; Despreaux, C.W.; Pruess, D. L. *J. Am. Chem. Soc.* **1979,** *101*, 6742; (d) Gutzwiller, J.; Pizzolato, G.; Uskoković, M. R. *Helv. Chim. Acta* **1981,** *64*, 1663; (e) Martin, S. F.; Benage, B.; Williamson, S. A.; Brown, S. P. *Tetrahedron* **1986,** *42*, 2903.
4. For total syntheses of geissoschizine, see (a) Yamada, K.; Aoki, K.; Kato, T.; Uemura, D.; van Tamelen, E. E. *J.C.S. Chem. Commun.* **1974,** p. 908; (b) Hachmeister, B.; Thielke, D.; Winterfeldt, E. *Chem. Ber.* **1976,** *109*, 3825; (c) Benson, W.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1979,** *18*, 862; (d) Wenkert, E.; Vankar, Y. D.; Yadav, J S. *J. Am. Chem. Soc.*

**1980,** *102*, 7971; (e) Banks, B. J.; Caverley, M. J.; Edwards, P. D.; Harley-Manson, J. *Tetrahedron Lett.* **1981,** *22*, 1631; (f) Bohlmann, C.; Bohlmann, R.; Rivera, E. G.; Vogel, C.; Manandhar, M. D.; Winterfeldt, E. *Liebigs Ann. Chem.* **1985,** p. 1752; (g) Overman, L. E.; Robichaud, A. J. *Am. Chem. Soc. Nat. Meet., 194th, New Orleans, La.* **1987,** ORGN 148.

5. For excellent reviews of the intramolecular Diels–Alder reaction, see (a) Ciganek, E. *Org. React. (N.Y.)* **1984,** *32*, 1; (b) Taber, D. F. *React. Struct. Concepts Org. Chem.* **1984,** *18*, 1; (c) Fallis, A. G. *Can J. Chem.* **1984,** *62*, 183.
6. For a review of hetero Diels–Alder reactions, see Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975,** *75*, 651.
7. For some recent examples of intramolecular heterodiene Diels–Alder reactions, see (a) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1981,** *22*, 4437; (b) Tietze, L.-F.; von Kiedrowski, G.; Berger, B. *Angew. Chem., Int. Ed. Engl.* **1982,** *21*, 221; (c) Tietze, L.-F.; Stegelmeier, H.; Harms, K.; Brumby, T. *Angew. Chem., Int. Ed. Engl.* **1982,** *21*, 863; (d) Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984,** *49*, 3671; (e) Takano, S.; Satoh, S.; Ogasawara, K. *Heterocycles* **1985,** *23*, 41; (f) Tietze, L. F.; Brand, S.; Pfeiffer, T.; Antel, J.; Harms, K.; Sheldrick, G. M. *J. Am. Chem. Soc.* **1987,** *109*, 921; (g) Tietze, L. F.; Bratz, M.; Machinek, R.; von Kiedrowski, G. *J. Org. Chem.* **1987,** *52*, 1638.
8. (a) Snider, B. B.; Duncia, J. V. *J. Org. Chem.* **1980,** *45*, 3461; (b) Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986,** *108*, 8274; (c) Denmark, S. E.; Sternberg, J. A. *J. Am. Chem. Soc.* **1986,** *108*, 8277.
9. Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983,** *48*, 5170, and references therein.
10. Williamson, S. A. Ph.D. Thesis, Univ. of Texas, Austin, 1985.
11. Sakai, S.; Ogawa, M. *Heterocycles* **1978,** *10*, 67.
12. For some related examples of oxidative cyclizations, see (a) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1962,** *84*, 4914; (b) Morrison, G. C.; Cetenko, W.; Shavel, J., Jr., *J. Org. Chem.* **1967,** *32*, 4089; (c) Husson, H.-P.; Chevolot, L.; Langlois, Y.; Thal, C.; Potier, P. *J.C.S. Chem. Commun.* **1972,** p. 930; (d) Aimi, N.; Yammanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron* **1973,** *29*, 2015; (f) Sakai, S.; Saito, N.; Nirose, N.; Yamanaka, E. *Heterocycles* **1982,** *17*, 99; (g) Fujii, T.; Ohba, M.; Sasaki, N. *Heterocycles* **1984,** *22*, 1805. **1982,** *17*, 99; (g) Fujii, T.; Ohba, M.; Sasaki, N. *Heterocycles* **1984,** *22*, 1805.
13. *cf.* (a) Blaha, L.; Weichet, J.; Zvacek, J.; Smolik, S.; Kakac, B. *Collect. Czech. Chem. Commun.* **1960,** *25*, 237; (b) Weichet, J.; Pelz, K.; Blaha, L. *Collect. Czech. Chem. Commun.* **1961,** *26*, 1529; (c) Jilek, J. O.; Ernest, I.; Novak, L.; Rajsner, M.; Protiva, M. *Collect. Czech. Chem. Commun.* **1961,** *26*, 687.
14. Since high levels of stereoselectivity for this reduction have been reported, the stereochemical outcome may be sensitive to the precise conditions of the reaction. See (a) Velluz, L.; Muller, G.; Joly, R.; Nomine, G.; Mathieu, J.; Allais, A.; Warnant, J.; Valls, J.; Bucourt, R.; Jolly, J. *Bull. Soc. Chim. Fr.* **1958,** p. 673; (b) see in reference 13c.
15. (a) Morrison, G. C.; Cetenko, W.; Shaval, J. Jr., *Org. Chem.* **1967,** *32*, 4089; (b) van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1969,** *91*, 7315; (c) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972,** *94*, 5109; (d) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973,** *95*, 7146; (e) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976,** *98*, 3645; (f) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982,** *104*, 1054; (g) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983,** *105*, 5373; (h) Stevens, R. V. *Acc. Chem. Res.* **1984,** *17*, 289, and references therein.
16. For previous syntheses of $\alpha$-yohimbine, see (a) Töke, L.; Honty, K.; Szabo, L.; Blaskò, G.; Szántay, C. *J. Org. Chem.* **1973,** *38*, 2496; (b) Töke, L.; Gombos, Z.; Blaskò, G.; Honty, K.;

Szabo, L.; Tamas, J.; Szántay, C. *J. Org. Chem.* **1973,** *38*, 2501; (c) Szántay, C.; Honty, K.; Töke, L.; Szabo, L. *Chem. Ber.* **1976,** *109*, 1737; (d) Martin, S. F.; Rüeger, H. *Tetrahedron Lett.* **1985,** *26*, 5227.

17. See (a) Effenberger, F.; Maier, R.; Schonwalder, K.-H.; Ziegler, T. *Chem. Ber.* **1982,** *115*, 2766; (b) Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1986,** *108*, 4974.
18. Merlins, L.; Mondelli, R.; Nasini, G.; Hesse, M. *Tetrahedron* **1967,** *23*, 3129.
19. (a) Stöckigt, J.; Husson, H. P.; Kan-Fan, C.; Zenk, M. H. *J.C.S. Chem. Commun.* **1977,** p. 164; (b) Brown, R. T.; Leonard J. *J.C.S. Chem. Commun.* **1979,** p. 877; (c) Stöckigt, J. *Phytochemistry* **1979,** *18*, 965; (d) Heinstein, P.; Stoeckigt, J.; Zenk, M. H. *Tetrahedron Lett.* **1980,** *21*, 141; (e) Kan, D.; Kan, S.-K.; Lounasmaa, M.; Husson, H. P. *Acta Chem. Scand., Ser. B.* **1981,** *B35*, 269.
20. For a related transformation, see reference 4e.
21. See in van Tamelen, E. E.; Oliver, L. K. *J. Am. Chem. Soc.* **1970,** *92*, 2136.

*Chapter 10*

# EVOLUTION OF A STRATEGY FOR THE SYNTHESIS OF OLIVOMYCIN A: DEVELOPMENT OF METHODOLOGY FOR THE DIASTEREO- AND ENANTIOSELECTIVE SYNTHESIS OF CARBOHYDRATES FROM ACYCLIC PRECURSORS

*William R. Roush*

*Department of Chemistry*
*Indiana University*
*Bloomington, Indiana*



## I. Introduction

This account of the evolution of our strategy for the synthesis of olivomycin A and our work on acyclic diastereoselective synthesis as applied to carbohydrates begins in 1979, when I was a second-year assistant professor at

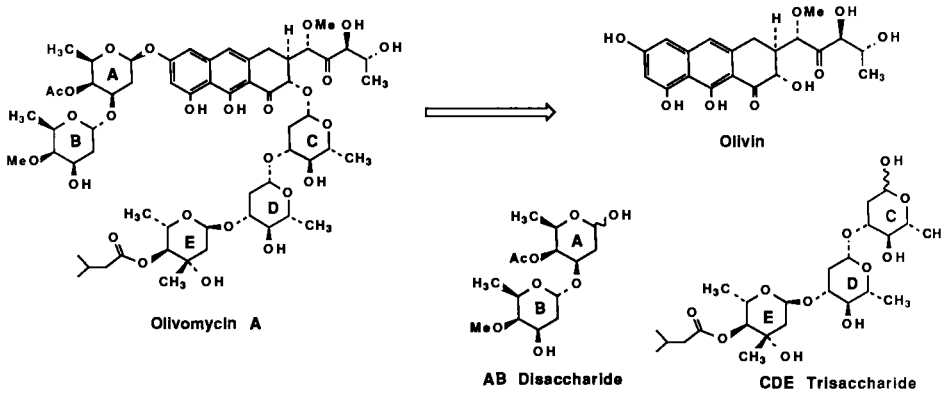



FIG. 1

the Massachusetts Institute of Technology. The decision to initiate work on this formidable target (Fig. 1) was based on a growing awareness that acyclic diastereoselective techniques would become an increasingly important component of organic synthesis and that carbohydrate chemistry would also see a resurgence of interest from the synthetic organic community. Hindsight clearly shows both premises to be correct.[1,2] At the time, however, I knew relatively little about either topic and consequently initiated studies on the synthesis of olivomycin A partly as a means of learning these important areas of research.

Olivomycin A, of course, is also a highly attractive target for organic synthesis. It is a member of the aureolic acid group of antitumor antibiotics, several members of which—including olivomycin A itself—have found application in the clinical treatment of human cancers.[3] The toxicity of these antibiotics, however, has limited their use in chemotherapy. We viewed this problem to be an opportunity for research, since a program in total synthesis might prove useful in the development of analogs with improved therapeutic efficacy.

We have always attempted to develop or showcase new chemistry in every total synthesis that we have pursued. Sometimes a natural product target is selected to illustrate a type of chemistry that we have developed, while in others it emerges as a consequence of observations made along the way. In these cases a synergism frequently develops between the total synthesis and methodology development efforts, with one significantly influencing the direction and evolution of the other. In the most successful examples, the new area of chemistry grows to the point that it is spun off into a separate, totally independent research program.

Our work on olivomycin A provides a good example of this interplay of

target-oriented research and methodology development in my laboratory. Our program on allylboronate chemistry[4] is an outgrowth of initial studies on the synthesis of olivin where the first highly diastereoselective reaction of a chiral aldehyde and an allylboronate was observed. This program has evolved to the point where our tartrate ester-modified allylboronates have made a significant impact on the synthesis of propionate-derived natural products.[4h,i] As will be shown subsequently, the allyboron methodology now also plays a central role in our work on the synthesis of the monosaccharide components of the di- and trisaccharides of olivomycin A. Thus, allylboron chemistry promises to make a significant contribution toward the synthesis of polyglycolates in general and the ultimate completion of the olivomycin A project in particular.

An up-to-date account of these investigations, with emphasis on the events that influenced the strategies and tactics employed, constitutes the subject of this chapter.

## II. A Highly Stereoselective Total Synthesis of the Natural Enantiomer of Olivin

We begin by discussing our work on the synthesis of olivin, which was recently completed in our laboratories at Indiana University.[5,6] Our strategy from the outset called for the carbohydrate-like side chain to be assembled in the form of a differentially protected D-fucose derivative (**3**, Fig. 2), the

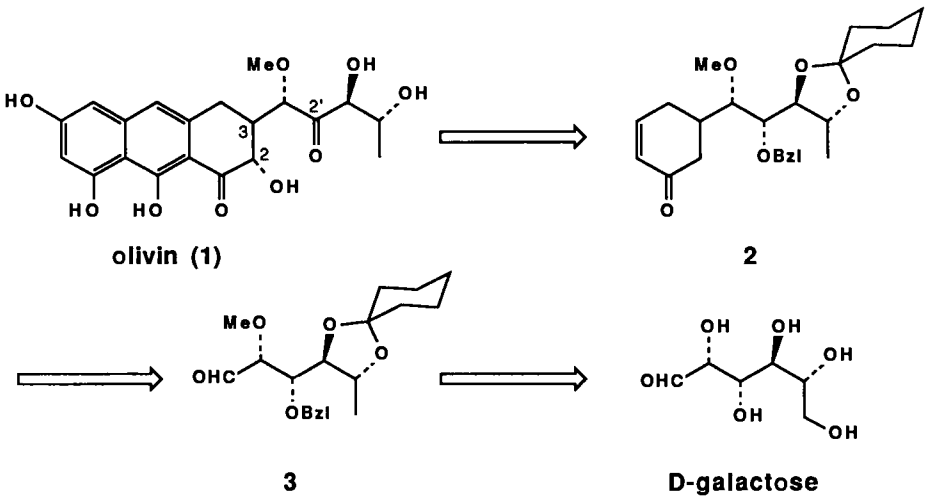



FIG. 2

resident chirality of which would be used to induce the correct stereochemistry at C(3) of **1** in a subsequent C—C bond-forming reaction. Because the side-chain fragment would be carried through a major portion of the synthesis, we decided that the potentially sensitive C(2′) carbonyl unit of **1** would be masked in **3** as an alcohol derivative. We also envisaged that cyclohexenone **2** would serve as the key intermediate in an annelation sequence leading to the establishment of the anthracenone nucleus of **1**. Finally, we regarded the stereochemistry of the hydroxyl group at C(2) of **1** to be strategically insignificant since it is trans to the side chain at C(3) and presumably could be controlled either by kinetic or thermodynamic experimental conditions.

## A. Synthesis of a Functionalized D-Fucose Derivative

The first problem to be solved was how to synthesize D-fucose derivative **3** in an efficient manner. It is ironic that while our goal upon initiation of this project was to develop useful acyclic diastereoselective synthetic methodology, intermediate **3** was first synthesized in our laboratory via a classical "chiron" approach using D-galactose as the ultimate starting material.[7] At the time this chemistry was initiated, it was not at all obvious to us that *any* diastereoselective synthesis could be more efficient than one originating from readily available hexose. In fact, we initially regarded D-galactose as the ideal starting material since each of the six carbon atoms and four chiral centers mapped directly into **3**; only the hydroxyl group at C(6) would need to be removed. This seemed to be a situation where a chiron approach was clearly called for.

Commercially available methyl β-D-galactopyranoside was converted into the known compound **5** by using modifications of Vasella's published procedures (Fig. 3).[8] The free hydroxyl group at C(2) was then methylated and the C(6)-bromomethyl group reduced with $LiAlH_4$ to give **6**. After hydrolysis of the acetonide unit, the axial C(3)-hydroxyl group of **7** was selectively benzylated via the intermediacy of a 3,4-dibutylstannylene derivative.[9] At this stage, we had hoped to perform Wittig reactions on the free sugars prepared from either **7** or **8** (e.g., **10**) as a means of generating unsaturated esters (e.g., **11**) or enones desired for subsequent C—C bond-forming reactions. Unfortunately, attempts to condense **10a** with $Ph_3P{=}CHCO_2Me$ under a variety of conditions led to a mixture of pyran and furan derivatives, **12p** and **12f**, respectively,[10] while **10b** failed to react to any significant extent even when benzoic acid was added to catalyze the reaction (Fig. 4).[10a]

These problems were avoided by protecting the C(5), C(6) diol prior to the unmasking of the aldehyde unit (Fig. 3). Thus, treatment of **10b** (a mixture of pyranose and furanose anomers prepared by hydrolysis of **8**

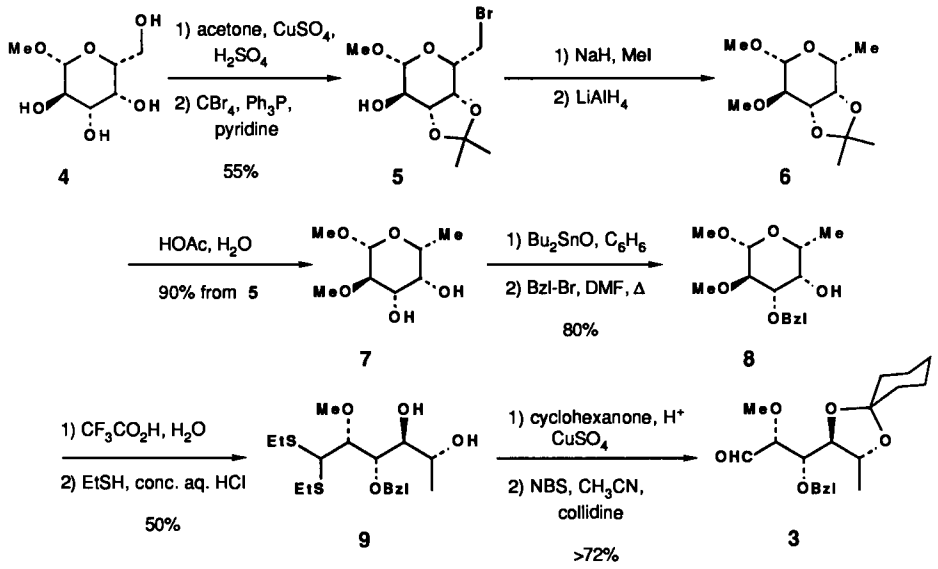

1) acetone, CuSO4, H2SO4
2) CBr4, Ph3P, pyridine
55%
1) NaH, MeI
2) LiAlH4
HOAc, H2O
90% from 5
1) Bu2SnO, C6H6
2) BzI-Br, DMF, Δ
80%
1) CF3CO2H, H2O
2) EtSH, conc. aq. HCl
50%
1) cyclohexanone, H+ CuSO4
2) NBS, CH3CN, collidine
>72%
4
5
6
7
8
9
3

FIG. 3

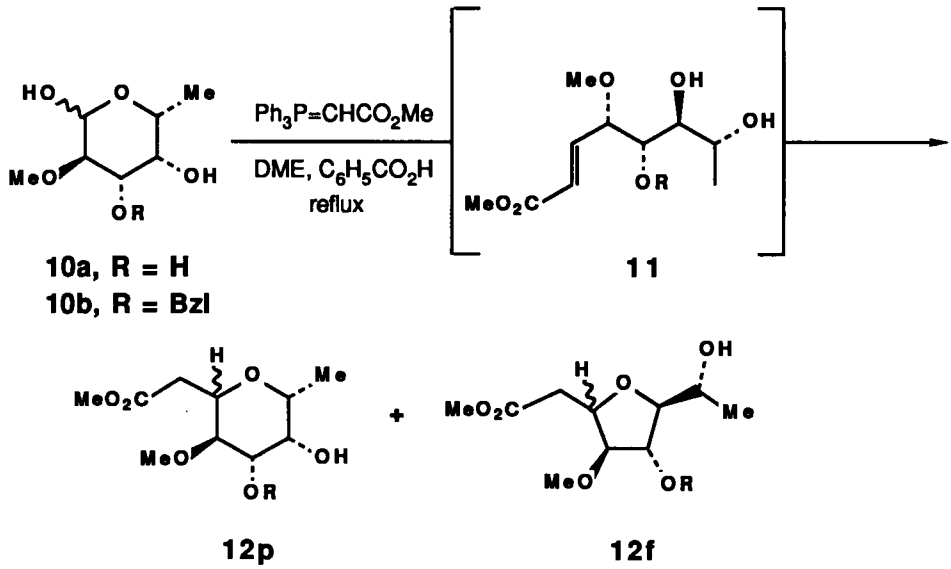

Ph3P=CHCO2Me
DME, C6H5CO2H
reflux
10a, R = H
10b, R = BzI
11
12p
12f

FIG. 4

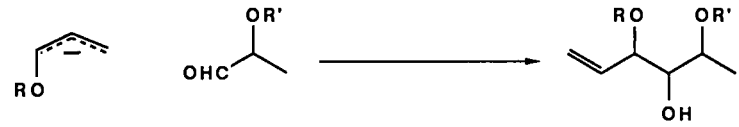



FIG. 5

with aqueous trifluoroacetic acid) with excess EtSH and concentrated HCl (as solvent) at 0°C[11] provided dithioacetal **9** in 50% yield, along with 25% of a mixture of thiopyranosides and thiofuranosides that could be recycled to **10b** in high yield by treatment with $HgCl_2$ and $CaCO_3$ in aqueous $CH_3CN$. Finally, the diol unit was protected as a cyclohexylidene ketal, and then the thioacetal was hydrolyzed under oxidative conditions[12] to arrive at the key intermediate **3**.

Although we had reached the desired subgoal, and while we were able to prepare sufficient quantities of this and related intermediates to begin exploring methods for inducing the critical C(3) stereocenter in more advanced olivin precursors, we were not satisfied with what we had accomplished. First of all, this synthesis required 11 steps, including the conversion of D-galactose to the $\beta$-methyl pyranoside **4** that was performed for us by Sigma, and was not nearly as efficient as we would have liked (14% yield overall from **4**). Second, we had developed no new chemistry. And, finally, the brutally harsh conditions[11] required for the conversion of **8** to **9** suggested that more desirable protecting groups for C(3)-OH (e.g., silyl ethers) would not be compatible with this route. As will be shown subsequently, intermediates containing a *t*-butyldimethylsilyl (TBDMS) ether at this position ultimately were used in completing the olivin synthesis.

We thus began to consider alternative strategies for synthesizing D-fucose derivative **3**. Particularly attractive was the idea that carbohydrates could be constructed via the reaction of an allyl ether anion equivalent and an $\alpha$-alkoxyaldehyde (Fig. 5).[13,14] For this approach to be successful, it would be necessary (i) to control the regioselectivity of the reaction of the allyl ether anion,[13] (ii) to control the syn (threo) or anti (erythro) relationship generated in concert with the new C—C bond, and (iii) to be able to control this new syn or anti relationship with respect to the chiral center already present in the aldehydic component.

Fortunately, solutions to problems (i) and (ii) were at hand by virtue of studies by Hoffmann and Wuts on the reactions of $\gamma$-alkoxyallylboronates with *achiral* aldehydes (Fig. 6).[14–16] At the time that we decided to examine the applicability of this methodology toward the olivin synthesis, however, relatively little information was available regarding the stereochemistry of such reactions with chiral aldehydes. Hoffmann had published several examples of reactions of (*E*)- and (*Z*)-crotylboronates (methyl replacing

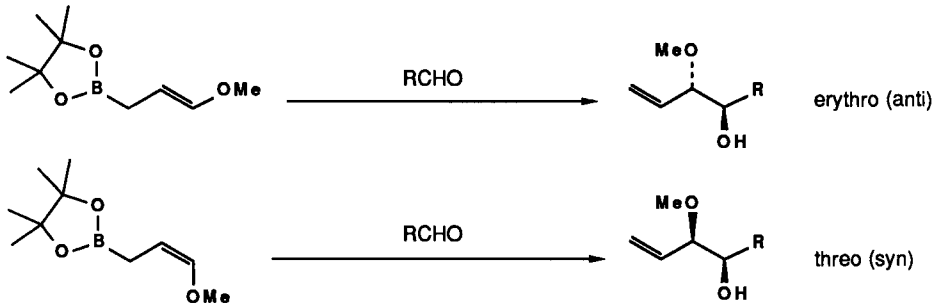
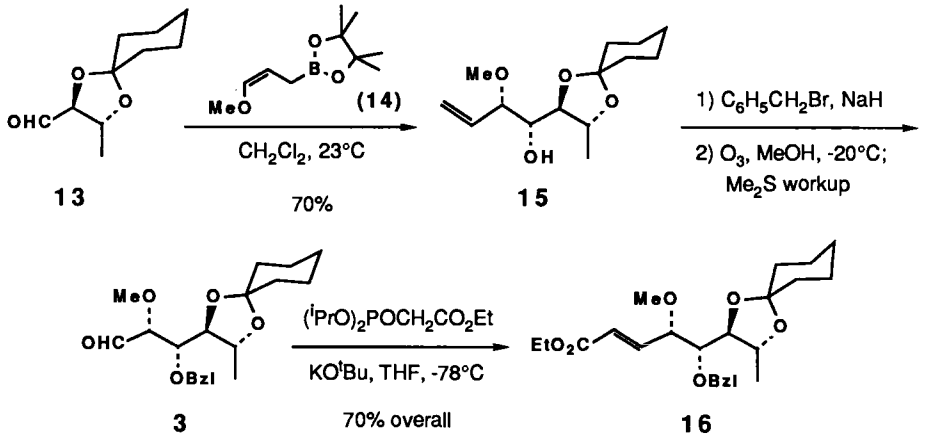



FIG. 6

OMe in Fig. 6) with chiral aldehydes such as 2-methylbutanal, but the best diastereofacial selectivity that had been reported was only 83 : 17.[17] Thus, it was by no means certain that the chemistry summarized in Fig. 7 would be successful.[4a]

Aldehyde **13**, readily prepared by a four-step synthesis from L-threonine (ca. 50% yield overall),[4a,18] was treated with the known (*Z*)-γ-methoxyallylboronate **14**[15a,c] in hexane or $CH_2Cl_2$. This reaction, like other reactions of pinacol allylboronates, was relatively slow and required 24–48



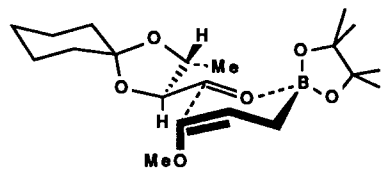




FIG. 7

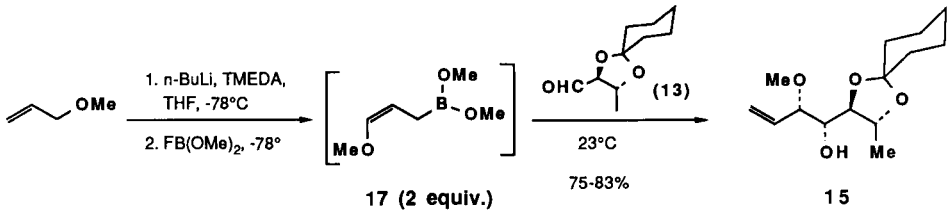



FIG. 8

hours at room temperature to reach completion. To our surprise, however, it was extremely selective and provided homoallyl alcohol **15** in 70% yield with greater than 95% diastereoselectivity. The stereochemistry of this compound was quickly verified by conversion to **3** as shown in Fig. 7.[4a]

Thus, an interesting synthesis of **3** had emerged that was relatively brief (seven steps from L-threonine) and considerably more efficient (25% overall) than the D-galactose-based synthesis described at the outset. One problem with this new sequence, however, was the synthesis of reagent **14**, which, in our hands, was low yielding, tedious, and not readily amenable to scale-up.[15a,c] On the other hand, use of *in situ* generated dimethyl (*Z*)-γ-methoxyallylboronate (**17**)[13b,19] was extremely convenient and actually provided **15** in higher yield (75–83%) than the original method involving **14** (Fig. 8). It is this modified procedure that is now used for all large-scale work.

## B. A Brief Detour into Allylboronate Chemistry

The great success of the reaction of aldehyde **13** and γ-methoxyallylboronate **14** had an immediate and profound influence on the evolution of my research program. We were intrigued by the high level of selectivity and realized that if it were general we would be able to synthesize a wide range of carbohydrate- and propionate-derived materials. We immediately initiated studies, therefore, on the reactions of allyl- and crotylboronates with D-glyceraldehyde acetonide (**18**) and the threonine-derived aldehyde **13**. Much to our surprise, however, we found that high diastereoselectivity was unique to reactions involving (*Z*)-crotyl- or (*Z*)-γ-alkoxyallylboronates. Stereoselectivity diminished or disappeared altogether as the C(3) substituent was removed (allyl reagent **20**) or inverted [(*E*)-crotylboronate **21**]. Results of this investigation using D-glyceraldehyde acetonide are summarized in Fig. 9.[4e]

This observation that diastereofacial selectivity is dependent on the substitution pattern and geometry of the allylboron reagent appears to be

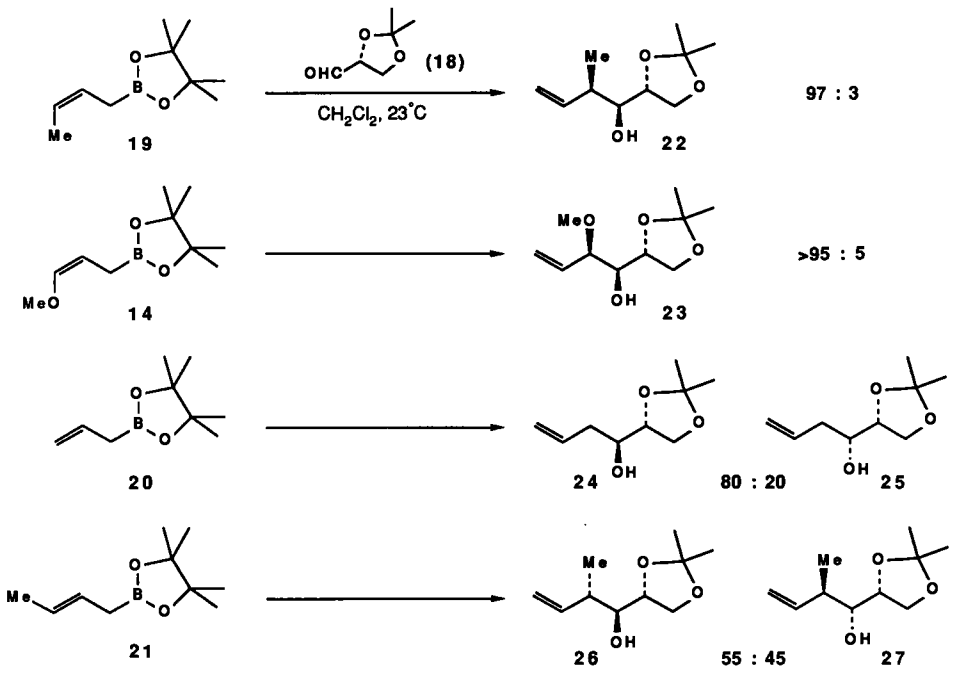



FIG. 9

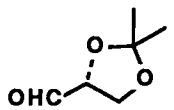
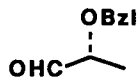
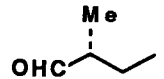
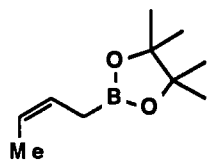
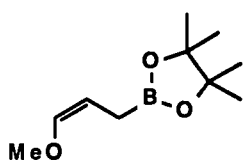
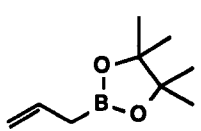
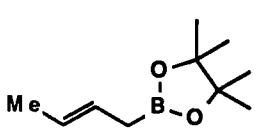
general. Table I summarizes additional results published by Hoffmann and Wuts that support this thesis.[20] These data show further that diastereofacial selectivity also depends on the electronic makeup of the aldehyde reaction partner.[4e,20a]

While this stereochemical picture is certainly intriguing, these results are disappointing from the perspective of potential applications in synthesis. Without recourse to an efficient chiral reagent, high diastereofacial selectivity (>20 : 1) can be counted on only in reactions of $\alpha,\beta$-dialkoxyaldehydes and (*Z*)-allylic boronates (e.g., **14**, **19**),[4e,20b] and, as shown by Hoffmann, in reactions of certain $\alpha$-methyl chiral aldehydes with (*E*)-crotylboronates, but only when the second $\alpha$-alkyl substituent (R) is quite bulky.[20a] It was extremely fortunate, therefore, that the first allylboronate reaction that we performed (e.g., **13** + **14**, Fig. 7) was one that fell into the "high selectivity" group.

In spite of the poor diastereoselectivity realized in reactions with chiral aldehydes, allylboronates are highly attractive reagents for organic synthesis.[4,14,15,20] Most are easily prepared in large quantities, and all are very convenient to use. They are nonbasic, relatively nonnucleophilic, and hence highly chemoselective in their reactions. The pinacol esters are notable for

TABLE I

REPRESENTATIVE DIASTEREOFACIAL SELECTIVITIES (ANTI : SYN) IN REACTIONS OF ALLYL BORONATES AND CHIRAL ALDEHYDES

| |  (18) |  (28) |  (29) |
|---|---|---|---|
|  (19) | 97 : 3 | — | 70 : 30 |
|  (14) | >95 : 5 | 90 : 10 | — |
|  (20) | 80 : 20 | 55 : 45 | 38 : 62 |
|  (21) | 55 : 45 | — | 17 : 83 |

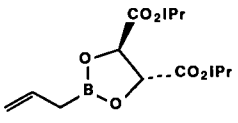
their stability[22]—most are easily purified by distillation and the isomeric purity of the crotyl reagents can be determined by capillary GC analysis.[4e] From all perspectives they are well-behaved chemical entities.

Fortunately, the poor diastereoselectivity realized in the reactions of most chiral aldehydes and achiral allylboronates appeared to be a problem that could be solved by recourse to the strategy of double asymmetric synthesis.[23] Our studies on the chemistry of allylboronates thus moved into this new arena of asymmetric synthesis, our objective being the development of a chiral allylboron reagent capable of controlling the stereochemical outcome of reactions with chiral aldehydes independent of any diastereofacial preference on the part of the aldehydic component.

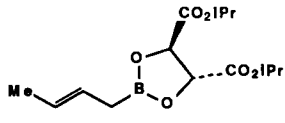
Here, too, our work was preceded by that of Hoffmann, who had examined a number of terpene-derived chiral diols[24] and had shown that allylboronates incorporating *endo*-3-phenyl-*exo*-2,3-bornandiol as auxiliary were moderately successful in increasing the diastereofacial selectivity of several aldehyde addition reactions (matched cases).[17,20b] This auxiliary, however, was not sufficiently enantioselective to be effective in mismatched double asymmetric reactions—cases in which the stereochemical preferences dictated by the auxiliary and chiral aldehyde are dissonant.[25] Since $C_2$ symmetric diols had not been explored, we decided to focus our efforts on reagents incorporating this strategically significant symmetry element.[26]

The use of tartrate esters was an obvious place to start, especially since both enantiomers are readily available commercially and had already found widespread application in asymmetric synthesis (e.g., Sharpless asymmetric epoxidation).[27,28] We have since found that reagents **30–32** (Fig. 10) are easily prepared and are reasonably enantioselective in reactions with achiral aliphatic aldehydes (typically 82–88% e.e.).[3c,h] Surprisingly, however, all other $C_2$ symmetric diols that we have examined (2,3-butanediol, 2,3-pentanediol, 1,2-diisopropylethanediol, hydrobenzoin, and mannitol diacetonide, among others) are relatively ineffective in comparison to the tartrate esters.[29]

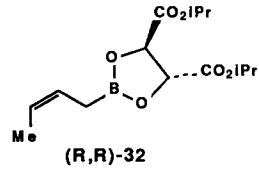
It is beyond the scope of this presentation for us to review all of the studies that have been performed with **30–32**. We note, however, that these reagents are especially useful in the context of double asymmetric synthesis.[4c,d,h,i] For




(R,R)-30




(R,R)-31




(R,R)-32

FIG. 10

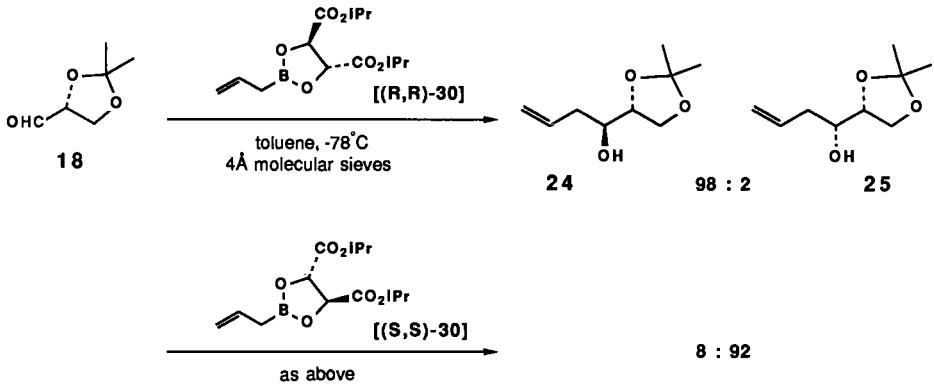



FIG. 11

example, whereas the reaction of D-glyceraldehyde acetonide (**18**) and pinacol allylboronate (**20**) provides the erythro diastereomer (**24**) as the major component of an 80:20 mixture (Fig. 9), the reaction of **18** and (*R,R*)-**30** provides this same product with up to 98:2 selectivity (matched case).[3c,30] When (*S,S*)-**30** is used, however, the diastereoselectivity is reversed (mismatched combination) and the threo diastereomer **25** is the major component of a 92:8 mixture (Fig. 11).[4d,30]

Thus, as this example clearly shows, reagent **30** is sufficiently enantioselective to control the stereochemical outcome of reactions with aldehydes that possess only modest intrinsic diastereofacial preferences. The consequences of this increased selectivity for organic synthesis are obvious. In the present case, compounds **24** and **25** are each now easily prepared with excellent selectivity from readily available precursors. Additional applications of this methodology in the synthesis of carbohydrates will be presented later in this chapter. For now, however, we return to a discussion of the chemistry leading to the completion of the olivin synthesis.

## C. Establishment of the C(3) Stereocenter of Olivin

The next critical hurdle in this approach to olivin involved devising a diastereoselective method for introducing the C(3) stereocenter in intermediates suitably functionalized for elaboration to the natural product. As mentioned previously, our original intention was to proceed by way of a cyclohexenone intermediate such as **2**. This, in turn, suggested that the conversion of D-fucose derivative **3** to **2** might involve a Wittig olefination followed by a Diels–Alder reaction with Danishefsky's diene or, alternatively, a diastereoselective 1,4-addition of an acetaldehyde equivalent and a subsequent aldol ring closure (Fig. 12).

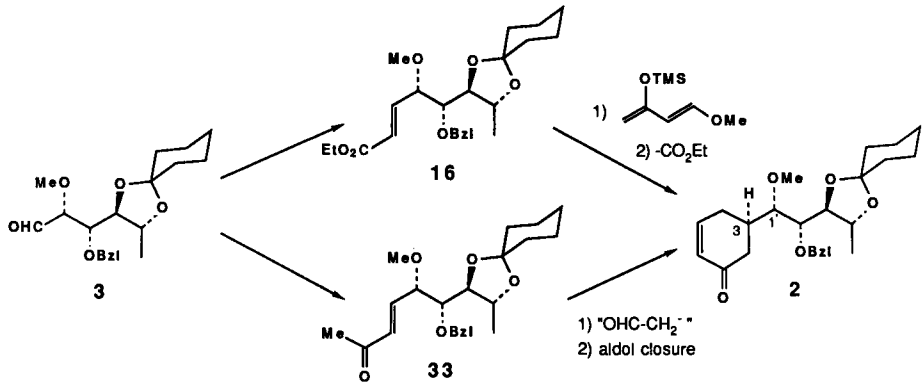



FIG. 12

Exploratory studies were initiated with enoate **34** and enone **35**, which were prepared from diol **9** (Fig. 3) and were available before the syntheses of **3** in Fig. 3 and 7 had been completed. Surprisingly, however, these compounds failed to react smoothly with the well-known diene **36**[31] under a variety of conditions, even when **36** was used as solvent in a sealed tube at 170°C (see Fig. 13). Enoate **16** similarly failed to yield detectable quantities of the desired cycloadduct from thermal or Lewis acid-mediated experiments. This unexpected lack of reactivity, together with Franck's publication[32] of a very similar approach to olivin, persuaded us to discontinue this line of investigation. Interestingly, Franck subsequently reported a synthesis of a cyclohexenone related to **2** via the Diels–Alder reaction of **36** and an *unsaturated lactone* as dienophile[33] but has not yet completed an olivin synthesis from this intermediate.[6b]

We turned instead to an examination of methodology for construction of cyclohexenone **2** via the 1,4-addition of an acetaldehyde equivalent to **35**.

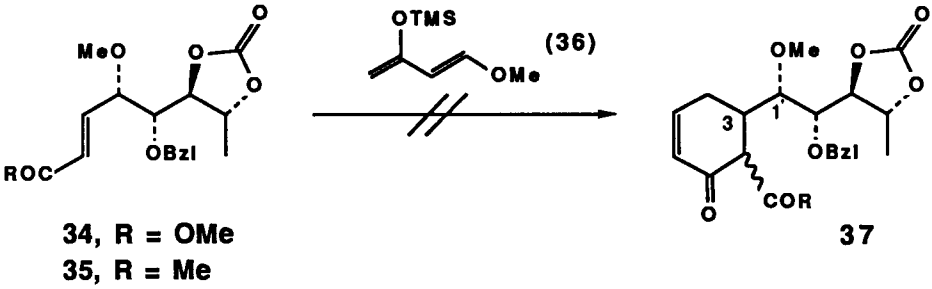



FIG. 13

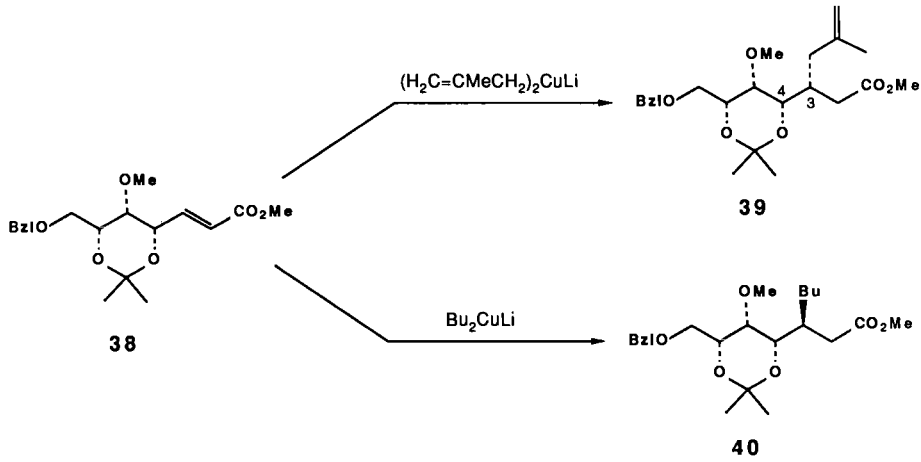



FIG. 14

When this research was initiated, relatively little was known about the diastereoselectivity of the 1,4-additions of organometallic reagents to γ-alkoxy-α,β-unsaturated carbonyl systems. Isobe had reported several examples of highly diastereoselective additions of alkyllithium reagents to γ-alkoxy-α-trimethylsilyl-α,β-unsaturated sulfones that apparently proceed by way of chelated intermediates,[34] and Nicolaou had shown that dimethallylcuprate reacted with carbohydrate derivative **38** to give **39** with very high selectivity (Fig. 14).[35] This result also could be rationalized by invoking chelated reaction intermediates (Fig. 15) and was very interesting for our purposes since the stereochemical relationship between C(3) and C(4) of **39** was exactly that needed for C(3) and C(1′) of cyclohexenone **2**. On the other hand, the generality of this process was unclear, since Ziegler had reported that the stereochemistry of this reaction was completely reversed when $Bu_2CuLi$ was used (**38** → **40**, Fig. 14).[36] We proceeded cautiously, therefore, into investigations of diastereoselective 1,4-addition reactions with enone **35**.

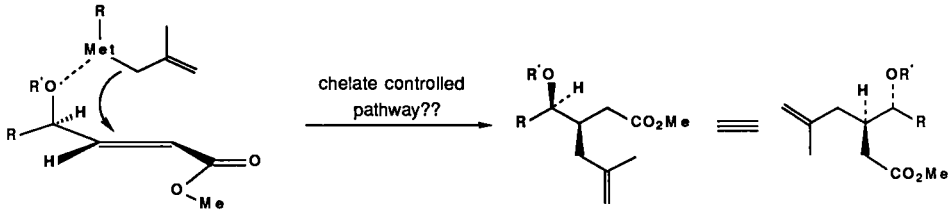



FIG. 15

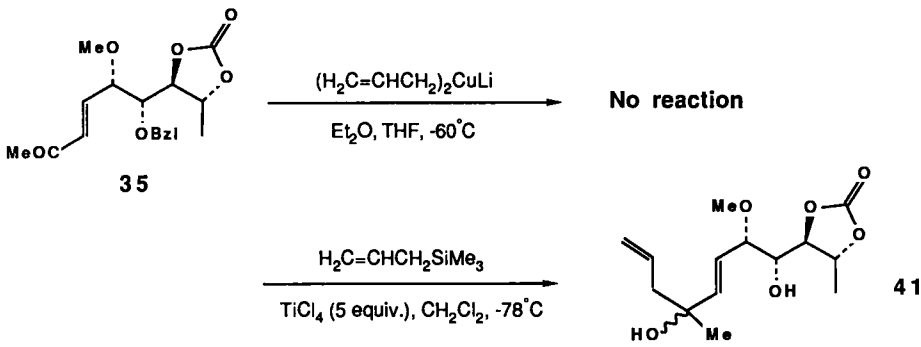



FIG. 16

Preliminary experiments involving the reaction of **35** and diallylcuprate were unsuccessful (Fig. 16). Evidently, our technique for generating and handling this sensitive reagent[37] was flawed, since attempts to perform the 1,4-allylation of cyclohexenone likewise failed. When $CH_2$=$CHCH_2MgBr$ and $CuBr(Me_2S)$ were employed with **35**, only products of 1,2-addition were detected.

In light of these negative results, we briefly examined the applicability of the Sakurai reaction to this problem (Fig. 16).[38] Surprisingly, no reaction occurred when 1–2 equivalents of $TiCl_4$ and allyltrimethylsilane were employed. Evidently, the Lewis acid was binding preferentially to the ethereal or carbonate carbonyl oxygen atoms, thereby precluding reaction at the enone. When a much greater excess of the reagents was employed, a mixture of products was obtained, including **41** resulting from carbonyl 1,2-addition and benzyl ether cleavage.

Success was finally realized in the reactions of **35** and divinylcuprate (Fig. 17).[39,40] Only one diastereomer (**42**) could be detected by NMR analysis of the crude reaction product, but small quantities of the second diastereomer (**43**) were isolated by chromatography. Similar results were subsequently achieved with enone **33**. Interestingly, the stereochemistry of this reaction proved insensitive to the geometry of the enone, an important observation since mixtures of enone and enoate isomers frequently are obtained in the olefination reactions of carbohydrate derivatives.

The stereochemistry of the C(3) center in adducts **42**, **43**, and **45** was assigned according to the studies summarized in Fig. 18. Hydrolysis of the carbonate units afforded diols **46** and **47**, respectively, which cyclized upon treatment with $FeCl_3$ in $CH_2Cl_2$[41] to give bicyclic acetals **48a** and **49**. Acetal **48a**, which was also obtained directly from **45** by exposure to 98:2 TFA–$H_2O$ (77% yield), was converted to **48b** by hydrogenolysis and

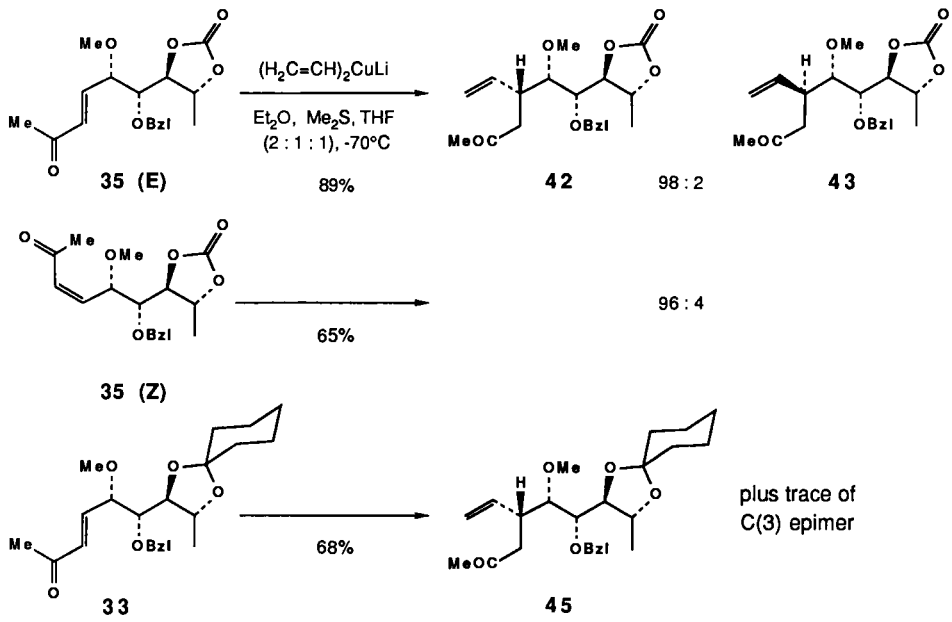



FIG. 17

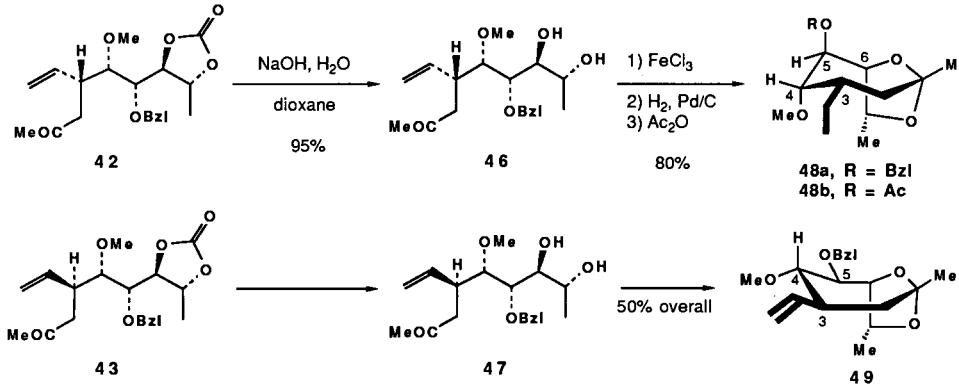



FIG. 18

acylation in order to ensure first-order behavior of the H(4)–H(5) and H(5)–H(6) spin systems. The observation of a W-couple ($J_{4,6}$ = 1.7 Hz) in **48b** and its absence in **49**, together with the presence of two large coupling constants for H(4) in **49** ($J_{3,4}$ = 10.7 Hz; $J_{4,5}$ = 7.9 Hz; in addition, $J_{5,6}$ = 0 Hz) versus very small values in **48b** ($J_{3,4}$ = 0 Hz, $J_{4,4}$ = 3.5 Hz,

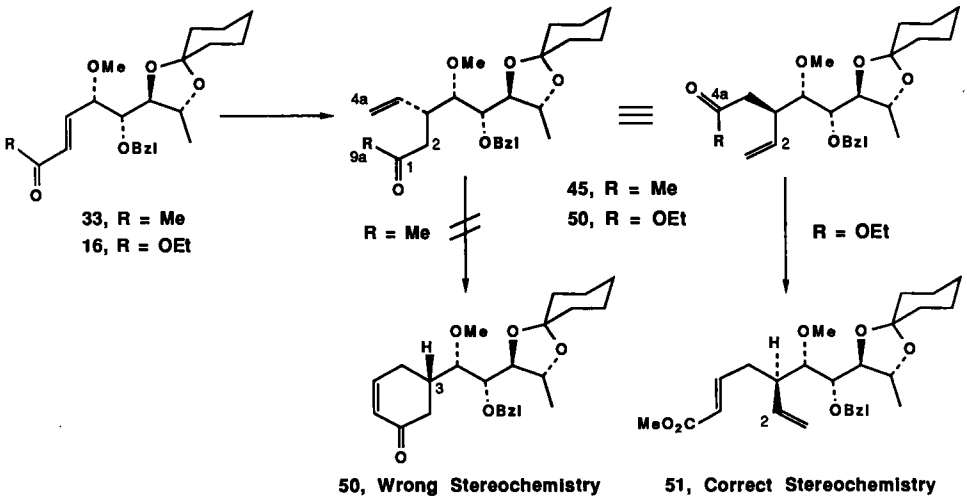



FIG. 19. Revised synthetic plan.

and $J_{5,6}$ = 1.7 Hz), enables the conformations and stereochemistry of **48** and **49** to be assigned as indicated in Fig. 18. It was evident, therefore, that adducts **42** and **45** possess the wrong stereochemistry at C(3) for use in this approach to olivin.

In view of these results, a reevaluation of our synthetic plan was called for. Although cyclohexenone **50**, the C(3) epimer of **2**, would be produced if a bond were constructed between C(4a) and C(9a) of **45** (olivin numbering system), it was readily apparent that 1,4-adducts **50** prepared from enoate **16** could be used if the plan to proceed via **2** was abandoned (Fig. 19). That is, we envisaged that the roles of the vinyl and acetic ester appendages in subsequent C—C bond-forming reactions could be reversed. For example, reduction of the ester unit in **50** to the corresponding aldehyde followed by a Wittig olefination would give **51**. The unsaturated ester unit would provide a handle for constructing the naphthalene core of the aglycone, while the vinyl appendage ultimately would contribute C(2) to the natural product structure.

Fortunately, for our purposes, the stereochemical outcome of the reactions of vinyl cuprates with enoates such as **16** proved to be the same as with enones **33** and **35**.[39] As shown in Fig. 20, the reaction of **16** and $(CH_2{=}CH)_2CuLi$ at −35°C yielded **50** as a 10 : 1 mixture of C(3) epimers. The major product was then smoothly elaborated to **51** as summarized in the figure.

While this sequence appeared to solve the problem concerning the establishment of the C(3) stereocenter in olivin precursors, it proved

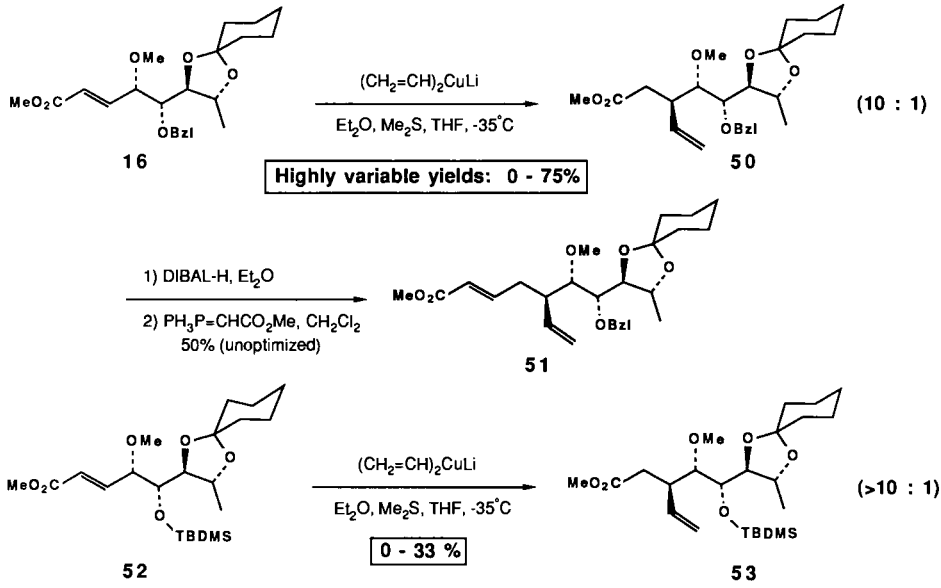



FIG. 20

unsatisfactory on two counts. First of all, the yield of **50** proved to be highly variable (0–75%) and very poor results were obtained on attempted scale-up. Second, the benzyl ether unit, an artifact of the original synthesis of aldehyde **3** from D-galactose (Fig. 3), was regarded as an unsatisfactory protecting group for later stages of the synthesis. In a parallel series of experiments, therefore, TBDMS ether **52** was prepared from **15**, which, in turn, was synthesized via the allylboronate chemistry summarized in Fig. 7. While compound **52** also displayed excellent diastereoselectivity (>10:1) in the reaction with $(CH_2{=}CH)_2CuLi$, this compound proved to be even less reactive than **16** and the best yield of **53** ever obtained was 33%.

The poor reactivity of **16** and **52** as cuprate acceptors[37] together with the sensitivity of the vinyl cuprate toward $O_2$ and $Cu^{2+}$ impurities presumably contributed to these poor results. The reagent rapidly decomposed (visual evidence) when the reactions were attempted at temperatures above −35°C, and enoates **16**/**52** were too unreactive for the experiments to be performed at temperatures below −40°C. Attempts to improve the situation by using $(CH_2{=}CH)_2CuLi/BF_3$,[42] $CH_2{=}CHCu/BF_3$,[43] or $(CH_2{=}CH)_2Cu(CN)$-$Li_2$[44] gave equally unsatisfactory results.

Fortunately, these problems were solved by using unsaturated aldehyde **54** as the electrophilic component in this reaction (Fig. 21).[45] The greater reactivity of the enal as opposed to an enoate permitted this transforma-

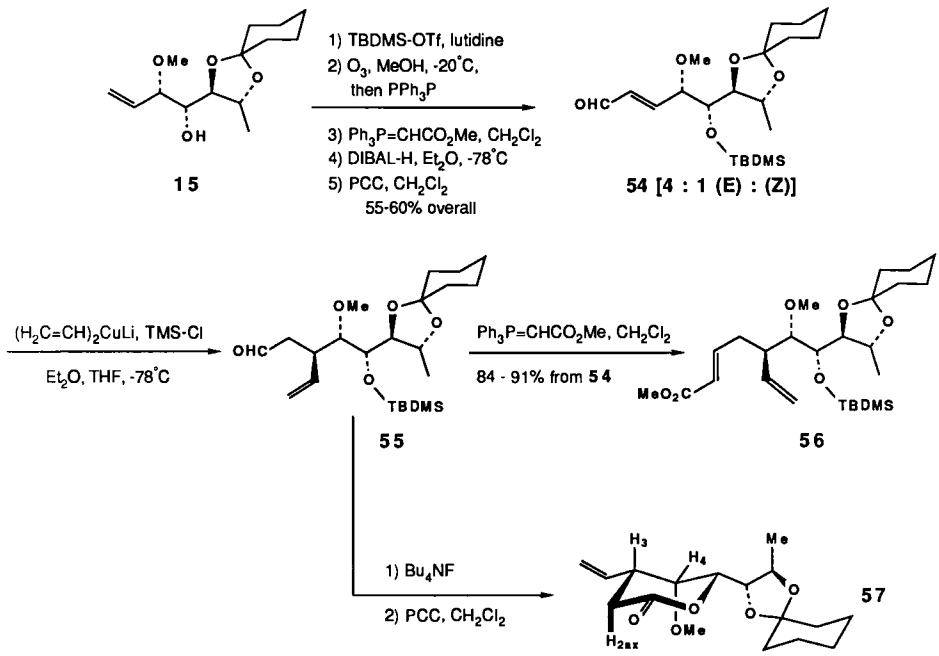



FIG. 21

tion to be performed at −78°C, conditions under which the stability of $(CH_2{=}CH)_2CuLi$ was not an issue. This reaction is highly stereoselective (a single diastereomer was observed), high yielding (>84–91%), and highly reproducible, and multigram quantities of **56** have been prepared in this way. It should be noted that this cuprate reaction is performed in the presence of trimethylsilyl chloride (TMS-Cl); when omitted, the reaction is still successful and provides **56** in 75% yield.[46] In addition, it is worthy of mention that the stereoselectivity of this step was not influenced by the isomeric purity of **54** (used in most cases as a mixture of olefin isomers).

The stereochemistry of **55** was assigned following conversion to lactone **57**. In particular, the multiplicity of H(4) (broad t, $J$ = 2 Hz) and the diaxial coupling constant ($J$ = 10 Hz) between H(3) and $H(2_{ax})$ require that the stereochemistry of C(3) must be as indicated in Fig. 22.

In summary, it is interesting to note that the stereochemical outcome of the vinyl cuprate additions to enones **33** and **35**, enoates **16** and **52**, and enal **54** is the same. The stereochemistry in these cases is consistent with the addition of the organometallic reagent anti to the allylic C—O bond from a rotamer in which the smallest allylic substituent, H, lies in the plane of the C–C double bond (Fig. 22). This is termed a "vinylogous Felkin-type

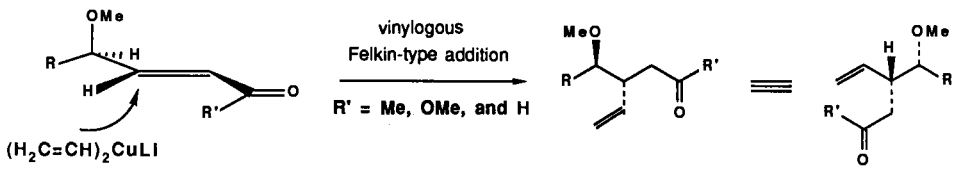



FIG. 22

addition" to reflect the absence of chelation in the reaction transition state and to emphasize the role that stereoelectronics undoubtedly play.[47] The alternative allylic rotamer in which R eclipses the C=C is presumably disfavored for steric reasons and is especially bad when the double bond is (*Z*). While we recognize that the allylic rotamer indicated in Fig. 22, reflecting the energetically favored ground state conformation, may not actually be the reactive species in the transition state,[48] this picture is consistent with our observation that both olefin isomers of enone **35**, enoate **33**, and enal **54** give rise to the same (anti) diastereomer in the 1,4-addition reactions. Additional examples have been published that are consistent with this model.[49] The only organometallic 1,4-addition reactions that deviate markedly from the results reported here involve allylic cuprates,[35,36] allyllithium reagents,[35c,36,49a] and the additions of $RCu-BF_3$ to (*Z*)-enoates.[48] In each of these cases, the observed diastereoselectivity is consistent with a chelated transition state as depicted in Fig. 15. Further experimentation is clearly called for to resolve the striking differences that exist, for example, in the behavior of allylic versus vinylic cuprates.

## D. Completion of the Olivin Synthesis

With a highly selective and efficient solution to the major stereochemical problems well in hand (Figs. 7 and 21), we turned our attention to the construction of the anthracenone nucleus of olivin. Two related methods for elaborating **56** to naphthoate **59** were envisaged (Fig. 23). First, the reaction of **56** with an orsellinate derivative **57** (X = SPh, $SO_2Ph$, SePh, etc.) was regarded as a reasonable approach to this problem since several laboratories had previously reported syntheses of simpler naphthoates via the reactions of sulfur- or selenium-substituted toluate anions with unsaturated esters.[50] Alternatively, we imagined that phthalide anion **58** could also be used as the nucleophilic component of an aromatic annulation sequence.[51] Because the toluate anion method leads directly to the desired aromatic system—an extra dehydration step is required in the phthalide approach[51]—and because the reported yields were generally higher, we concentrated first on the orsellinate anion chemistry.

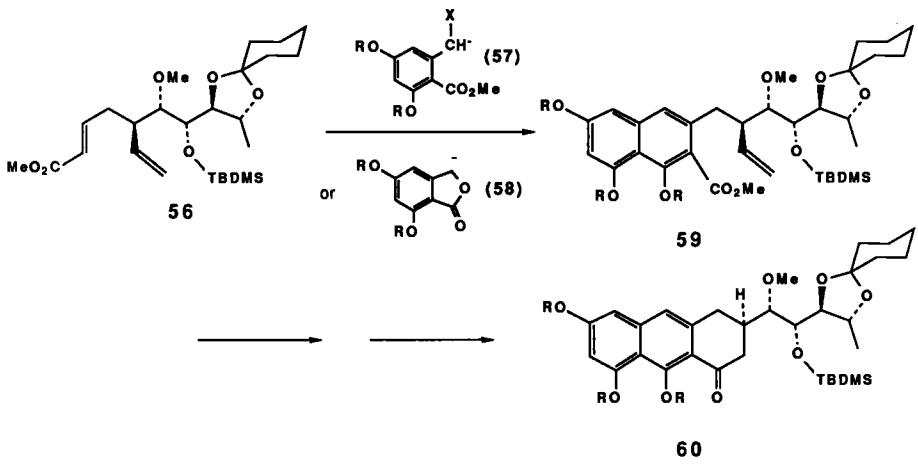
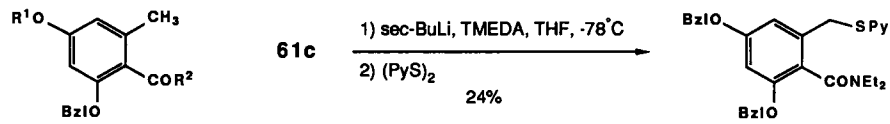



FIG. 23

Unfortunately, however, we were unable to develop an efficient synthesis of a suitably protected reagent. In spite of considerable literature precedent,[52] all attempts to functionalize orsellinates **61a–c** with $(PhS)_2$, $(PyS)_2$, PhSCl, NBS, $I_2$, and related oxidants after treatment with bases such as LDA, LiTMP, LiHMDS, or *sec*-BuLi (in the cases where $R^2$ = OH or $NEt_2$) in THF at −78°C led to low yields of the desired product, some recovered starting material, dimeric products,[52a] and occasionally products in which one of the benzyl ether protecting groups had been removed. The greatest success was realized by using amide **61c** as the substrate, but the yields were very low, as illustrated in Fig. 24 by the reaction with dipyridyl disulfide. Attempts to brominate **61a** ($R^2$ = OMe) by direct reaction with NBS (2.2 equivalents)[53] were nonselective and gave a mixture of four products in comparable amounts.

We turned, therefore, to an examination of the phthalide route for preparing naphthoate **59**. Phthalide **62** was prepared by a four-step sequence in 50% overall yield starting from methyl 3,5-dihydroxybenzoate (Fig. 25).[54]




**61a, $R^1$ = Bzl, $R^2$ = OMe or H**
**61b, $R^1$ = MEM, $R^2$ = OMe or H**
**61c, $R^1$ = Bzl, $R^2$ = $NEt_2$**

FIG. 24

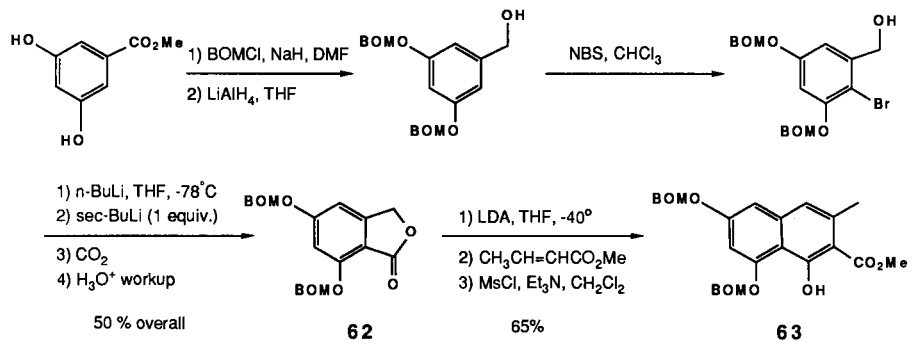



FIG. 25

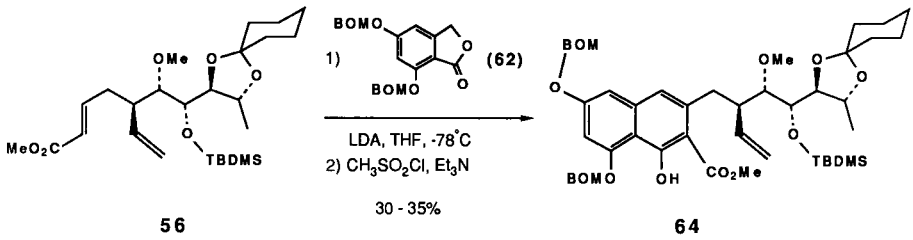



FIG. 26

The lithium anion, generated by using 3 equivalents of LDA in THF at −40°C, readily condensed with methyl crotonate (used in excess) to give an intermediate hydroxytetralone that smoothly aromatized upon exposure to methanesulfonyl chloride (1.1 equivalents based on **62**) and $Et_3N$. In this way, naphthoate **63** was obtained in 65% yield. We elected not to use the aromatization conditions described by Sammes ($CF_3CO_2H$ or $BF_3$–$Et_2O$), since we were concerned that the acid-labile protecting groups present in **62** and enoate **56** might not survive these conditions.

A similar protocol was used for the coupling of phthalide **62** and enoate **56** with the exception that **56** and **62** were used in equimolar amounts (Fig. 26). This reaction provided naphthoate **64** in 30–35% yield together with 5–10% of the corresponding phenolic mesylate. While the efficiency of this step is lower than we would like, and efforts to optimize it are continuing, sufficient quantities of **64** were prepared to permit completion of the synthesis (Fig. 27).

The free phenol of **64** was protected as a benzyloxymethyl (BOM) ether, and then the vinyl appendage was oxidized via aldehyde **65** to diester **66**. Of the numerous methods examined, only Masamune's recently introduced procedure for oxidation of aldehydes was suitable for the efficient oxidation of **65** (85%).[55] This set the stage for formation of the final C—C bond of

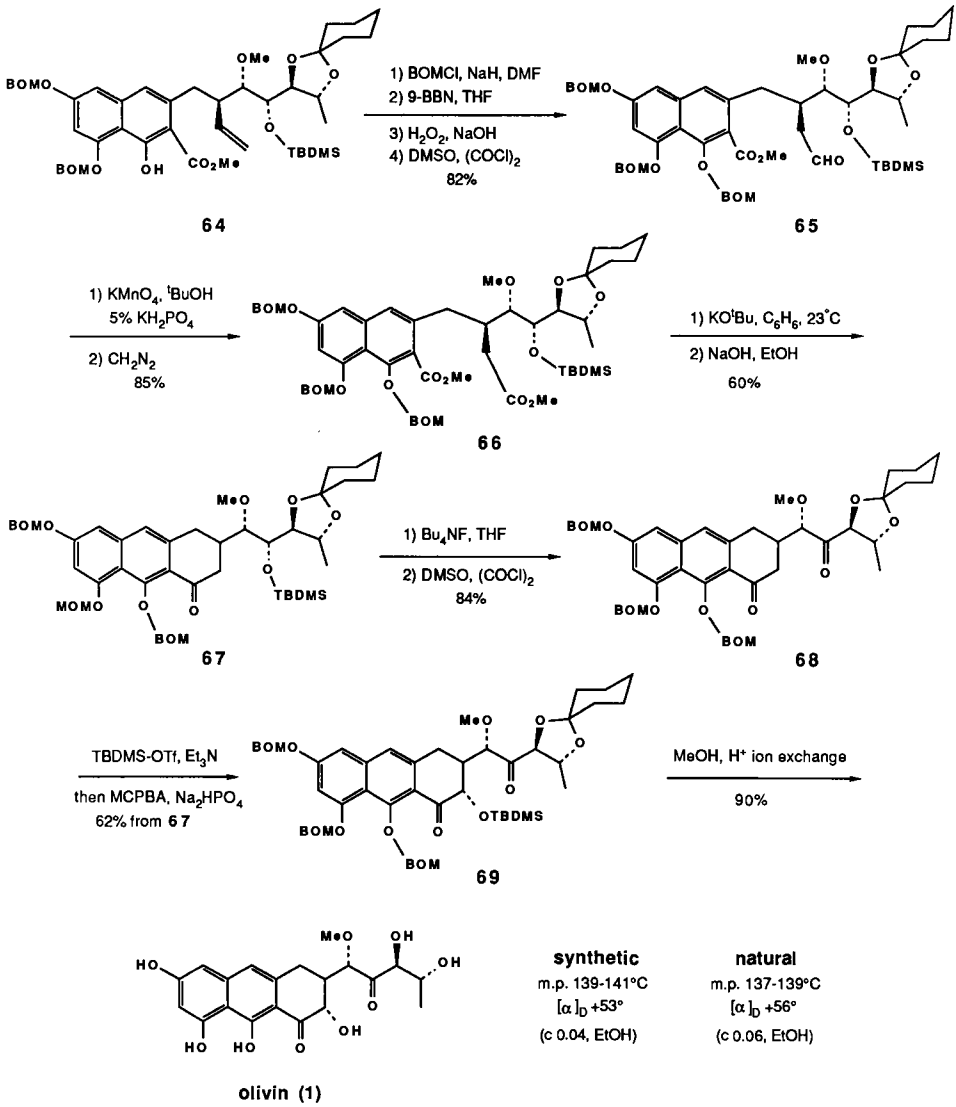



FIG. 27

olivin by treatment of **66** with an excess of KO*t*Bu in $C_6H_6$. Subsequent exposure of the Dieckmann product to 0.4 *M* NaOH in aqueous EtOH at reflux thereby provided anthracenone **67** in 60% yield.

The side-chain TBDMS ether of **67** was next cleaved by treatment with $Bu_4NF$ in THF (93%) and the resulting hydroxyl group oxidized to the C(2′) ketone via a standard Swern procedure (90%).[56] Selective conversion

of the C(1) carbonyl to the corresponding TBDMS enol ether was smoothly accomplished according to Mander's method,[57] thus setting the stage for the oxidative conversion to **69** (76%). The success of this last step was dependent on the purity of the TBDMS enol ether, and it proved necessary to filter this intermediate through silica gel before exposure to MCPBA. Finally, all five protecting groups in **69** were removed by treatment with Dowex 50W-X8 $H^+$ resin in MeOH at 23°C. Direct crystallization of the crude reaction product from ether–hexane provided synthetic olivin, mp 139–141°C, in 90% yield. Synthetic **3** so obtained was identical by all the usual criteria with an authentic sample prepared by acidic methanolysis of olivomycin A.[58]

Thus, a highly diastereoselective synthesis of the natural enantiomer of olivin has been completed. This also happens to be the first synthesis of this molecule in unprotected form.[6] Progress toward the completion of an olivomycin A synthesis is discussed in the following sections of this chapter.

## III. Progress Toward the Synthesis of Olivomycin A

Olivomycin A is a formidable synthetic target (Fig. 1). In order to complete a total synthesis of this molecule, it will be necessary to prepare the individual monosaccharides in suitably protected form and develop technology for constructing the five glycosidic bonds with acceptable levels of efficiency (yield) and stereoselectivity. While we are still a long way from having solved the β-2-deoxy glycosidic linkage problem—note that three such linkages occur in olivomycin A—we have made considerable progress toward the synthesis of the monosaccharide precursors[59,66] and have developed an efficient synthesis of the AB disaccharide unit.[60] Because a detailed discussion of the as yet unsolved β-2-deoxy glycoside problem falls outside of the theme of this chapter, we restrict the following discussion to a review of our work on the synthesis of monosaccharides from acyclic precursors.

### A. Synthesis of the AB Disaccharide Unit

Our strategy for synthesis of the oligosaccharide chains, unlike that of Thiem, who has performed significant pioneering studies on the structure[61] and synthesis[62] of these important structural units, calls for the 2,6-dideoxyhexoses or the corresponding glycals to serve as precursors for both α- and β-glycosidation reactions. If a selective β-glycosidation protocol can be developed, then in principle *any* structural isomer or analog of the natural product can be assembled from a common set of monosaccharide precursors. That is, we envisage that our approach will prove useful in the synthesis of

structurally modified oligosaccharide analogs with improved therapeutic efficacy.[63]

Each of the sugar residues in olivomycin A was known at the time our studies were initiated, and syntheses of each from commercially available carbohydrate precursors had been recorded.[59b,64] We elected not to synthesize these materials via literature procedures, however, since we felt that totally synthetic methods might prove to be a more convenient and general solution, particularly in the context of a program where the synthesis of structurally modified oligosaccharides was a long-range goal. We were also aware that several of these monosaccharides occur naturally (as glycosides of antibiotics) in both enantiomeric series,[64] and we realized that a route involving asymmetric synthesis would provide equal access to either enantiomeric series. Perhaps the most important influence on this decision, however, was an intellectual one. We realized that acyclic stereoselective methods were becoming increasingly important in organic synthesis and sensed that methodology for synthesizing polyhydroxylated sugarlike acyclic systems could in fact compete with chiron-based strategies in many instances; our work on the synthesis of D-fucose derivative **3** is but one example (refer to Figs. 3 and 7). That is, we decided to embark on a program of monosaccharide synthesis from acyclic precursors as a means of developing methodology that would be useful to the organic chemist in a wide range of contexts.[1,2]

In our initial work on the synthesis of the olivomycin A sugar residues, epoxy alcohols prepared by the Sharpless kinetic resolution/enantioselective epoxidation technology served as the key synthetic intermediates.[65] Our most important contribution was the development of methodology for controlling the regioselectivity of nucleophilic substitution reactions of the epoxy alcohol intermediates.[59] Figure 28 summarizes two complementary, highly regioselective procedures for substitution reactions with oxygen nucleophiles. As is apparent in the digitoxose synthesis, the reaction of 2,3-epoxy alcohols with aqueous acid proceeds with very high selectivity for attack of the nucleophile (water in this case) at the $\beta$-position—the epoxide carbon farthest away form the carbinol center. In order for attack to occur at $C_\alpha$, as required here for the synthesis of olivose (**72**), it is necessary for the nucleophile to be delivered intramolecularly. We have found that phenylurethanes are the best source of "tethered" oxygen nucleophiles and that these neighboring group-assisted reactions are best performed in the presence of Lewis acid catalysts (e.g., $Et_2AlCl$).[59]

This methodology has been used in syntheses of D-olivose (**72**, Fig. 28), which appears in olivomycin as the C and D monosaccharide units, as well as D-oliose, which is homochirally related to the A and B residues of the natural product target. Interestingly, these syntheses compare favorably in terms of both steps and yield to routes originating from D-glucose and D-galactose.[59b]

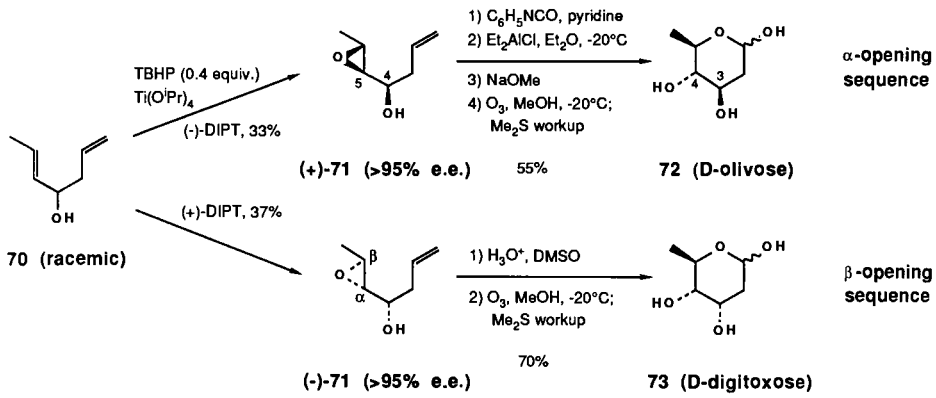



FIG. 28

Nevertheless, this approach suffers from several major drawbacks: (i) since a resolution is involved, the maximum yield of usable chiral, nonracemic intermediates is 50%, and the separation of epoxy alcohol from the unreacted, kinetically resolved allylic alcohol is tedious, especially for large-scale work; (ii) the generality of this method is restricted since the efficiency of the kinetic resolution (e.g., the relative rate of epoxidation of the two allylic alcohol enantiomers) and the diastereoselectivity of the epoxidation step are poor for secondary (*Z*)-allylic alcohols, an important class of substrates; and (iii) the $\alpha$-opening methodology is unattractive in cases where the intended role of the carbohydrate fragment is as an intermediate in subsequent chemical transformations (e.g., glycosidations). That is, the intrinsic differentiation of the C(4) and C(5) oxygen functionality in the epoxy alcohol substrate is lost in the course of the $\alpha$-opening process (see **71** to **72**, Fig. 28). This is undesirable since sugars with undifferentiated hydroxyl groups at C(3) and C(4) are produced; introduction of a suitable set of protecting groups into D-olivose (**72**), for example, as the first step in studies on the $\beta$-glycosidation problem has proved nontrivial.[66]

The important conclusion from an operational point of view is that if sugars are to be synthesized *de novo*, it is imperative that the method be direct, efficient, completely general, and provide access to intermediates in which all of the hydroxyl functionality is completely differentiated for use in subsequent synthetic schemes.

Our development of the tartrate ester-modified allylboronates[4c,h] made it possible for us to consider that many of these problems might be avoided by using the reaction of a chiral aldehyde and a chiral allylboronate ("double asymmetric synthesis") as a means of establishing the stereochemistry of the sugar backbone. It is this strategy that has been used in our synthesis of the AB disaccharide unit of olivomycin A (Figs. 29, 30).[4f]

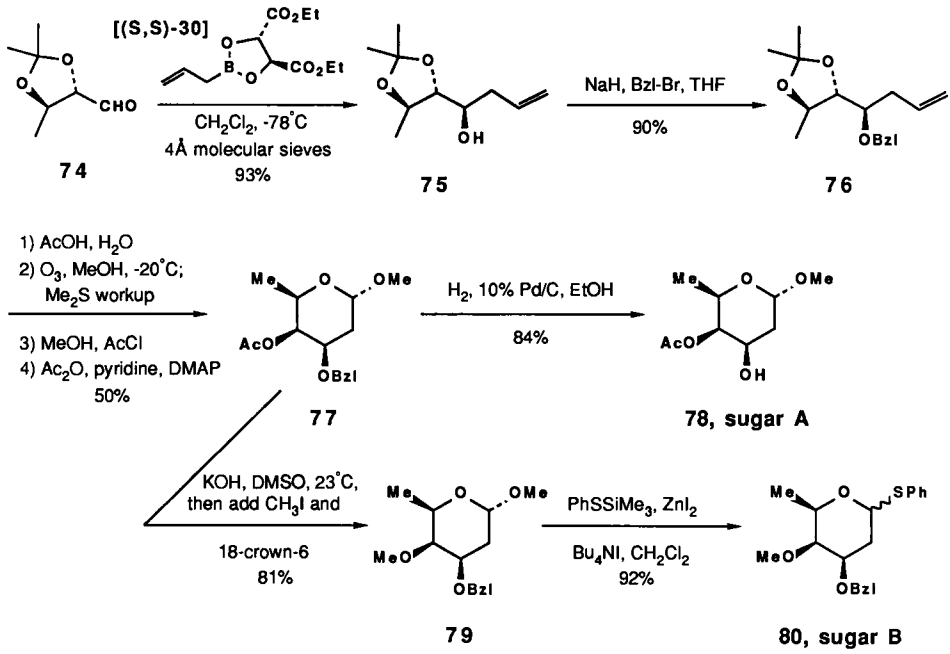

[(S,S)-30]
CO2Et
CO2Et
CHO
74
CH2Cl2, -78°C
4Å molecular sieves
93%
OH
75
NaH, Bzl-Br, THF
90%
OBzl
76
1) AcOH, H2O
2) O3, MeOH, -20°C;
Me2S workup
3) MeOH, AcCl
4) Ac2O, pyridine, DMAP
50%
Me
OMe
AcO
OBzl
77
H2, 10% Pd/C, EtOH
84%
OH
78, sugar A
KOH, DMSO, 23°C,
then add CH3I and
18-crown-6
81%
MeO
79
PhSSiMe3, ZnI2
Bu4NI, CH2Cl2
92%
SPh
80, sugar B

FIG. 29

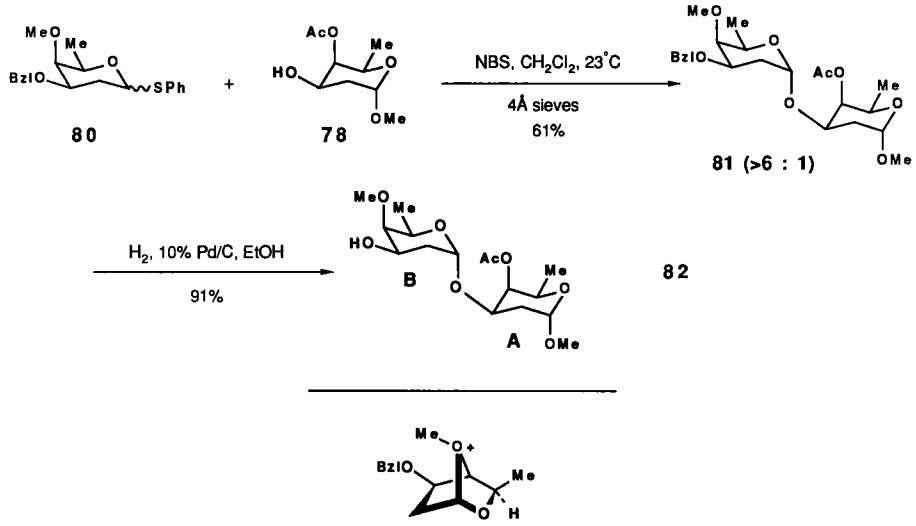

MeO
Me
BzlO
SPh
80
AcO
HO
OMe
78
+
NBS, CH2Cl2, 23°C
4Å sieves
61%
81 (>6 : 1)
H2, 10% Pd/C, EtOH
91%
B
A
82
Me
BzlO
H

FIG. 30

Syntheses of monosaccharides **78** and **80**, corresponding to the A and B sugar residues, respectively, commenced with the reaction of aldehyde **74** (prepared from L-threonine)[4a,18] and (*S,S*)-**30** that provided **75** in 93% yield and with 300 : 1 stereoselectivity. By way of comparison, when pinacol allylboronate (**20**) was used, diastereomer **75** was the major component of a 90 : 10 mixture. Benzylation of **75** under standard conditions provided **76** which was hydrolyzed by treatment with 4 : 1 HOAc–$H_2O$ (98%). Ozonolysis of the resulting diol then provided 3-O-benzyl-2,6-dideoxy-D-*lyxo*-hexose (72%) as a mixture of pyranose and furanose anomers that was directly converted to the corresponding mixture of methyl glycosides by treatment with methanol containing acetyl chloride as a source of HCl. This mixture was most conveniently separated following acylation. In this manner the desired $\alpha$-pyranoside **77** was obtained as the major product in 36% yield along with an unseparated mixture of the $\beta$-pyranoside and the $\alpha,\beta$-furanosides. The latter mixture was recycled three times [(i) MeOH, AcCl; (ii) $Ac_2O$, pyridine, DMAP; (iii) chromatographic separation], bringing the total yield of **77** to 71%.

Intermediate **77** served as precursor to both of the monosaccharide units in disaccharide **82**. Thus, the A-ring sugar **78** was prepared in 84% yield by hydrogenation of **77** in EtOH over 10% Pd/C. Alternatively, treatment of **77** with powdered KOH in DMSO followed by excess $CH_3I$ and catalytic 18-crown-6 gave **79** in 81% yield. This intermediate was then converted into thiosugar **80** as a mixture of anomers in 92% yield by using the method described by Hanessian.[67] Coupling of these two units (Fig. 30) was smoothly accomplished by treatment of a mixture of **78** and **80** (1.1 equivalents with NBS (1.2 equivalents) and 4-Å molecular sieves in $CH_2Cl_2$.[68] Although a mixture of anomers was anticipated at the outset,[69,70] we were pleased to find that this method provided **81** in 61% yield as a >6 : 1 mixture in which the $\alpha,\alpha$-anomer predominated. It is interesting to speculate that the selectivity in this case, which greatly exceeds that previously reported for glycosidations of 2-deoxyglucose derivatives (arabino configuration), may be the consequence of neighboring group assistance as suggested at the bottom of Fig. 30. Finally, hydrogenation of **81** gave disaccharide **82**, the spectroscopic properties of which were in excellent agreement with literature values.[62b]

## B. A General Synthetic Approach to Monosaccharides

The synthesis of AB disaccharide **82** described in the previous section is quite efficient (10 steps from **74**, 17% overall yield) and is readily amenable to scale-up. In contemplating extensions of this chemistry to the synthesis of differentially protected derivatives of D-olivose (e.g., **83**, Fig. 31) needed for construction of the CDE trisaccharide, however, it became apparent that this

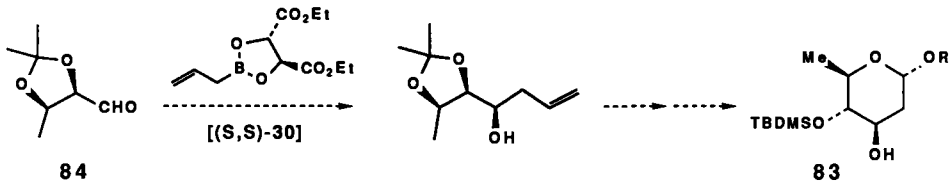



FIG. 31

synthetic strategy is not appropriate for construction of olivose derivatives because the required starting material, **84**, formally deriving from D-*allo*-threonine, is not readily accessible.[70]

This prompted us to begin exploratory studies of a truly general approach to monosaccharides that would not rely on the accessibility of specific chiral pool precursors. This approach, outlined in Fig. 32, relies on two powerful asymmetric transformations: (i) the Sharpless asymmetric epoxidation,[27] which can be used to prepare the epoxy allylic alcohol precursors to the indicated epoxy aldehydes, and (ii) the asymmetric allylboration reaction, which can be used to achieve diastereoface selection in the addition of allyl or γ-alkoxyallyl units to the epoxy aldehydes. Control of stereochemistry at C(3) relative to C(4) in **88** should be possible by selection of the appropriate reagent **86** or **87**. Given the ability to rationally manipulate the epoxide functionality (e.g., Fig. 28), all possible hexoses of either absolute configuration should be easily accessible. Note also that as long as β-epoxide opening reactions are employed, the intrinsic differentiation of the C(4) and C(5)

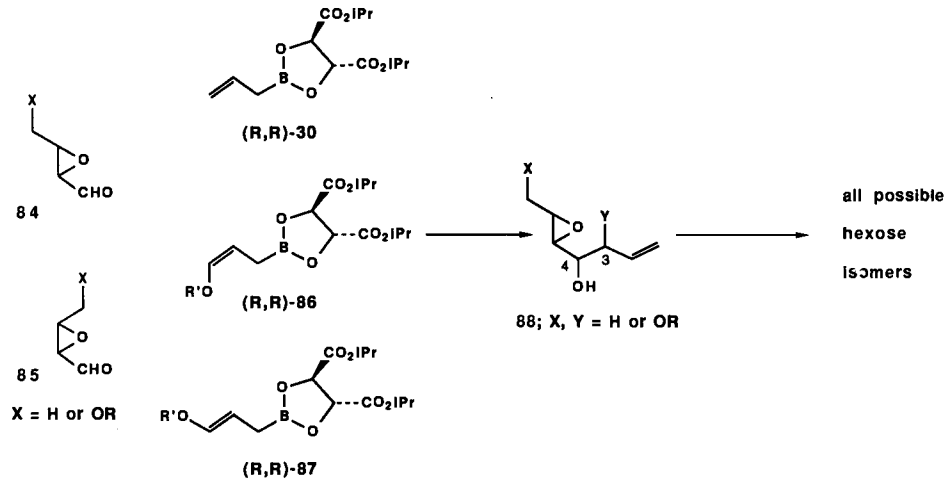
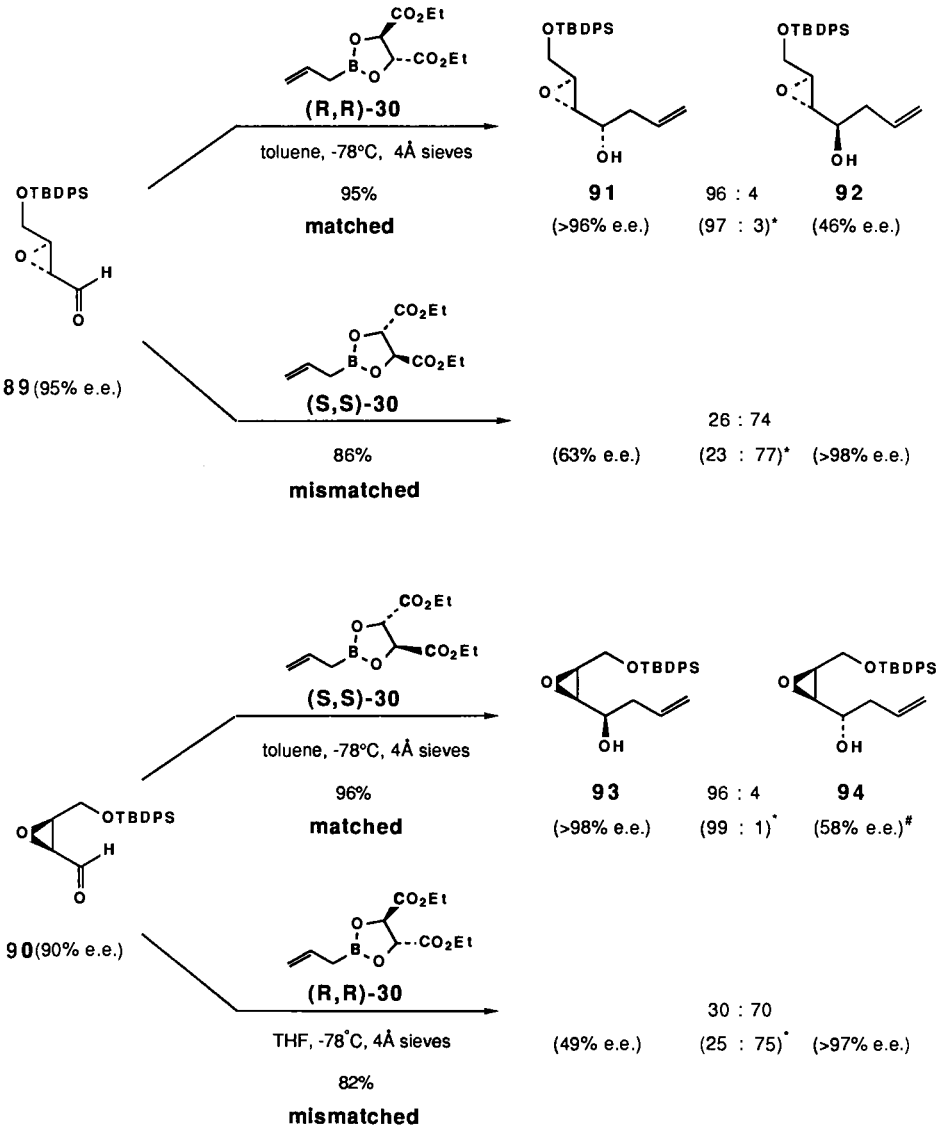



FIG. 32. PROPOSAL FOR A GENERAL CARBOHYDRATE SYNTHESIS.




*Selectivity expected if epoxyaldehyde is 100% e.e.

#The major enantiomer in this case derives from the minor epoxyaldehyde enantiomer.

FIG. 33

oxygen functionality in **88** can be carried through to the target hexose. Finally, this monosaccharide synthesis promises to be shorter and more practical than those based on iterative asymmetric epoxidation cycles.[71]

We began by studying the reactions of epoxy aldehydes **89** and **90** with both enantiomers of tartrate allylboronate **30** (Fig. 33).[66,72] The aldehydes were prepared by oxidation of the corresponding epoxy allylic alcohols with NaOAc-buffered PCC (92–95% yield). When **89** was treated with *achiral* pinacol allylboronate (**20**), erythro epoxy alcohol **91** was produced as the major component of a 60:40 mixture. The reaction of **89** with (*R,R*)-**30**, therefore, constitutes a matched pair since the selectivity for **91** is increased to 96:4. Erythro epoxy alcohol **93** similarly is the major product (96:4) of a matched double asymmetric reaction of cis-epoxy aldehyde **90** and (*S,S*)-**30**. Thus, two of the four epoxy alcohol diastereomers are available with exceptional diastereoselectivity. The second pair of diastereomers, namely threo-epoxy alcohols **92** and **94**, are available with lower selectivity (70–74:30–26) via the mismatched double asymmetric reactions indicated in Fig. 33. While we had hoped that the selectivity in these cases might have been higher, these reactions may still be useful synthetically, at least in cases such as this where the two diastereomers are very readily separated chromatographically.

A very interesting aspect of the chemistry reported in Fig. 33 concerns the enantiomeric purity of the two product diastereomers, which in every case are different. This is a consequence of a kinetic resolution involving distinctly different pathways for the reaction of **30** with the two epoxy aldehyde enantiomers, both of which are present since the Sharpless epoxidation provides the epoxy alcohol precursors to **89** and **90** in only 95 and 90% e.e., respectively. For example, while the reaction of **89** with (*R,R*)-**30** is a matched pair and leads preferentially to **91**, the reaction of *ent*-**89** with (*R,R*)-**30** is a mismatched combination and leads preferentially to *ent*-**92** (Fig. 34). That is, the minor enantiomer of the epoxy aldehyde (e.g., *ent*-**89**) is converted preferentially to the minor product diastereomer (e.g., *ent*-**92**), causing the enantiomeric purity of the major reaction product to be much greater than that of the epoxy aldehyde precursor, while the enantiomeric purity of the minor diastereomer becomes significantly less so. This is perhaps most strikingly demonstrated by the reaction of **90** and (*S,S*)-**30**, where the *major* enantiomer of the minor reaction product **94** in fact derives from the *minor* enantiomer of **90**.

This phenomenon has important ramifications in organic synthesis, since it clearly suggests that products with very high enantiomeric purity can be prepared by linking multiple double asymmetric transformations in a synthetic pathway. This point has also been demonstrated by Hoye[73] and Schreiber[74] in studies of asymmetric epoxidations of bisallylic alcohols. It is

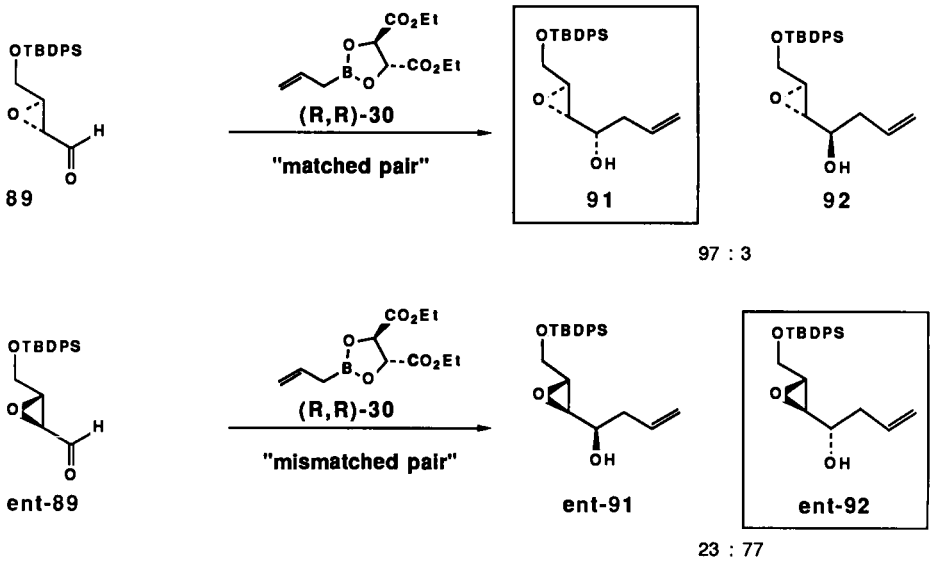



FIG. 34

interesting to speculate further that this principle may also operate in biosynthesis, where any stereochemical infidelity (diastereo- or enantiomeric) in a given transformation may be corrected by a kinetic substrate selectivity in the next.

The epoxy allylic alcohols prepared in this way are very useful precursors to 2-deoxyhexoses or their immediate precursors (Fig. 35). We illustrate the flexibility of this chemistry by summarizing here the use of the two epoxy alcohol products of matched double asymmetric reactions (**91**,**93**) in the preparation of all four 2-deoxyhexose series. The $\alpha$-opening reactions of **91** (to **95**, and thence to 2-deoxy-L-glucose) and **93** (to **97**) involve the $\alpha$-opening technology developed previously in our laboratory and require no additional comment. As far as the $\beta$-opening reactions are concerned, two different methods have been employed. In the conversion of **91** to **96**, the silyl ether protecting group was first removed and then the resulting diol was treated with NaOH under conditions where epoxide migration can occur (see Fig. 36).[75] Monosubstituted epoxide **100** is the most reactive species present under these conditions, and nucleophilic attack occurs at C(7) of **100** to produce **95** with excellent regioselectivity. When diol **101** (prepared from **93**) was subjected to these conditions, however, tetrahydrofuran **104** and not tetraol **98** was the major product.[66] Evidently, two epoxide migration pathways are accessible to **101**, and the cyclization of **103** to **104** is faster than the intermolecular attack of hydroxide on **102**. We subsequently found

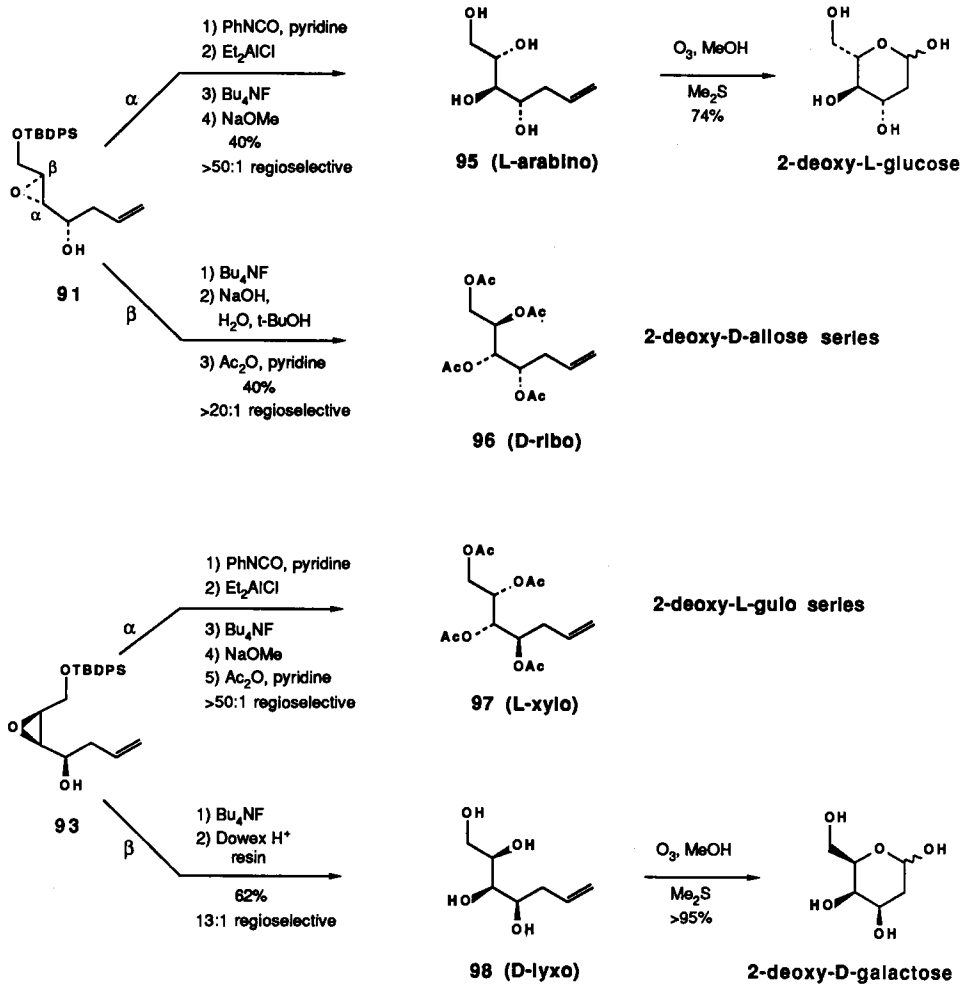



FIG. 35

that tetrahydrofuran formation also competes to a limited extent (ca. 15%) in the alkaline hydrolysis of **99**. This problem has been solved in the case of **101** by using acidic hydrolysis conditions (Fig. 35), which provided the desired tetraol **98** as major component of a 13 : 1 diastereomeric mixture (no tetrahydrofuran was seen in this case). The regioselectivity in this case presumably is dictated by the different steric environments at C(6) and C(5), since the electronic makeup of the two epoxide carbons should be comparable due to the oxygen substituents at each adjacent position. It remains to be seen how general this acid hydrolysis will be with epoxy alcohols **99**, **92**,

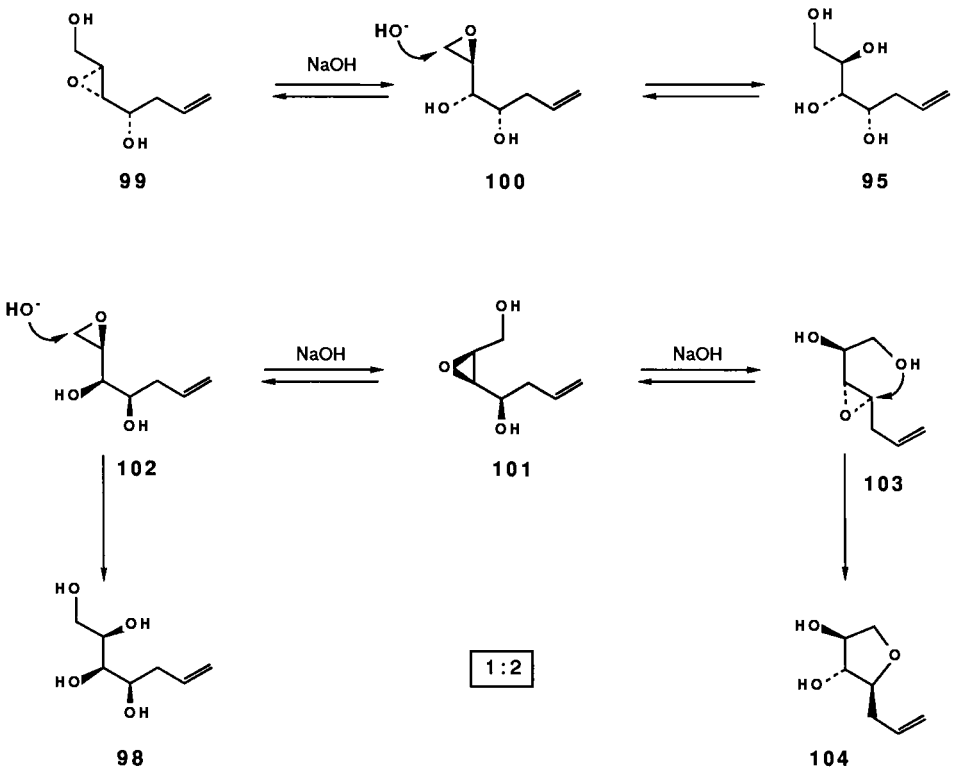
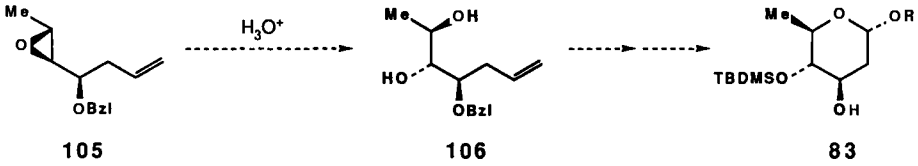



FIG. 36

and **94**. We note in passing that the alkaline β-opening protocol has also been applied to the diols corresponding to **92** (10:1 regioselectivity; no tetrahydrofuran) and **94** (>20:1 regioselectivity; no tetrahydrofuran) and that efforts to further optimize the β-opening sequence with all four epoxy alcohol substrates are continuing.

We began these studies with the intention of applying this tandem asymmetric epoxidation/asymmetric allylboration sequence toward the synthesis of D-olivose derivative **83**. Once again, however, we realized that this new methodology, at least in its current state of development, is not suited for this task (Fig. 37). A threo-epoxy alcohol derivative such as **105** is required if a β-opening sequence (**105** to **106**) is to be used, but **105** will of course derive from a mismatched double asymmetric reaction of reagent (*S,S*)-**28** with (2*R*,3*S*)-epoxybutanal. Since that reaction is not expected to proceed with greater than 75% selectivity, it is questionable whether this route is preparatively feasible.

No further work has been performed on the development of a practical synthesis of **83**. This and the synthesis of the olivomycin CDE trisaccharide



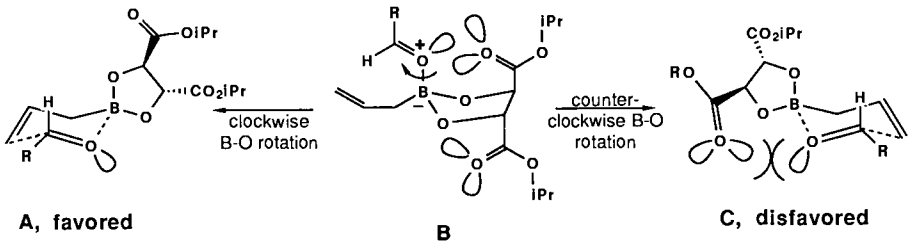

105 106 83

FIG. 37

remain unsolved problems for future exploration. Because it is the enantioselectivity of the tartrate ester allylboronates that has limited the success of the mismatched double asymmetric reactions reported here, as well as in several other cases published from our laboratory,[4h] the focus of our work on chiral allylboronates has shifted away from synthetic applications and toward the development of a more highly enantioselective chiral auxiliary. One such auxiliary has been developed, as described below.

## C. *N,N'*-Dibenzyl-*N,N'*-ethylene Tartramide, a Rationally Designed Chiral Auxiliary for the Allylboration Reaction

To put this work into proper perspective, it is appropriate to begin with a discussion of our thoughts on the origin of asymmetry with tartrate allylboronates **30–32**.[4c,d] Our results are consistent with major product formation occurring via transition state **A** (Fig. 38); the olefinic substituents of **31/32** are omitted for clarity. Reagents prepared from (*R,R*)-tartrate invariably induce the (*S*) configuration at the carbinol center, assuming that *R* has priority over the allyl group that is transferred. The level of asymmetric induction, however, is difficult to explain by simple steric interactions alone because the aldehydic R group is too far removed to interact strongly with the ester substituents and because selectivity is not influenced by the identity of the ester group itself (Me, Et, iPr, adamantyl, cyclodecyl, and 2,4-dimethyl-3-pentyl tartrate esters have been studied, and all give essentially identical levels of enantioselectivity). That conventional




A, favored B C, disfavored

FIG. 38

steric effects are probably not the dominant stereochemically determining factor is supported by our observation that the tartrate esters are substantially more enantioselective than any other $C_2$ symmetric diols examined to date (e.g., butanediol, 1,2-diisopropylethanediol, hydrobenzoin, mannitol diacetonide, 0–40% e.e.), all of which presumably do have a steric origin of enantioselection.[29]

These considerations, among others, prompted us to suggest early on that transition state **A** is favored as a consequence of *n*/*n* electronic repulsive interactions between the aldehydic oxygen atom and the β-face ester group that destabilizes **C** relative to **A**.[4c] These interactions are possible since an easily accessible and frequently favored conformation of α-heteroatom-substituted carbonyl systems is one in which the heteroatom and carbonyl are syn-coplanar.[76] Toluene appears to be particularly effective among nonpolar solvents in stabilizing this conformation[77] and, interestingly, also happens to be the solvent in which **30–32** generally display the greatest enantioselectivity.

For this mechanism to be correct, it is also necessary for the dioxaborolane to exist in conformation **B** with the two -$CO_2$iPr units pseudoaxial. In any other conformation about the C—$CO_2$iPr bond or in the dioxaborolane system, the ester and aldehydic oxygen atoms are too far removed to interact. It should be noted further that reasonable transition states for C—C bond formation are inaccessible if the aldehyde is symmetrically disposed with respect to the dioxaborolane system. Counterclockwise rotation about the B—O bond as indicated in **B** moves the aldehyde nonbonding lone pair away from the proximate ester carbonyl and leads to the favored transition state **A**. Rotation of the B—O bond in the reverse direction increases the *n*/*n* interactions and leads to disfavored transition state **C**.

These arguments imply that the aldehyde to boronate complexation step (a Lewis acid/Lewis base reaction) is the critical enantioselectivity-determining event, since conformation **B** most probably represents the ground state Lewis acid aldehyde complex. This conformation may be stabilized by a boron-centered anomeric effect ($n_O$–$\sigma^*$ interactions between the axial lone pairs of the ring oxygens and the B—O=CHR single bond).[78] The actual transition state for the allyl transfer probably occurs during a flipping motion of the dioxaborolane O—B—O unit that moves the allyl group toward a pseudoaxial position with development of two anti $n_O$–$\sigma^*_{B-C}$ interactions that facilitate cleavage of the B—C bond.

One further point is worthy of brief mention. While we have focused on lone pair/lone pair repulsive interactions that destablilize transition state **C**, it is conceivable that **A** is actually stabilized relative to **C** by a favorable charge–charge interaction between the ester carbonyl ($\delta^-$) and the aldehydic carbonyl carbon ($\delta^+$) owing to the proximity of these groups in **A**. While it is not yet possible to resolve the relative contributions of these distinct

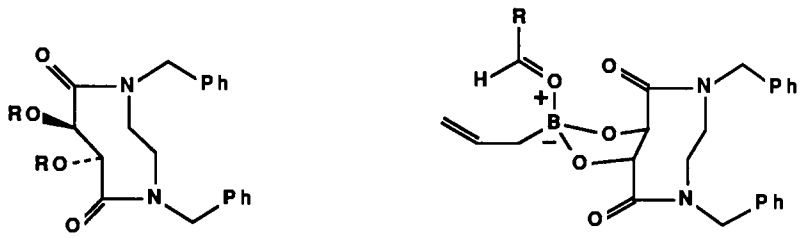



FIG. 39

stereoelectronic effects, it is clear that our mechanistic proposal explains the experimental results only if the dioxaborolane and the C—$CO_2$iPr bonds exist in the conformations indicated in **B**. Any conformational infidelity at either site would be expected to lead to diminished enantioselectivity.

We have performed a number of studies designed to probe this and other mechanistic hypotheses.[29] The most pertinent for the present purposes concerns our decision to explore conformationally restricted auxiliaries such as **107** (Fig. 39).[79] We recognized that as long as the tartrate unit is held within an eight-membered ring, the critical conformational features discussed for **B** become structural constants in **D**. If our mechanistic hypothesis was correct, we expected reagent **108** to be substantially more enantioselective than the parent tartrate allylboronate **30**.[80]

Bislactam (*R,R*)-**107** was readily synthesized from benzylidene tartrate (**109**) and *N,N'*-dibenzyl ethylenediamine (**110**) by a three-step sequence in 40–42% overall yield (Fig. 40). It is noteworthy that the Mukaiyama salt-mediated[81] amidation–lactamization step proceeds in a preparatively useful yield (52–56%) in view of the poor results previously reported for the synthesis of eight-membered lactams from ω-amino acid precursors.[82] Reagent **108** was then prepared by treatment of **107** with triallylborane.[4c]

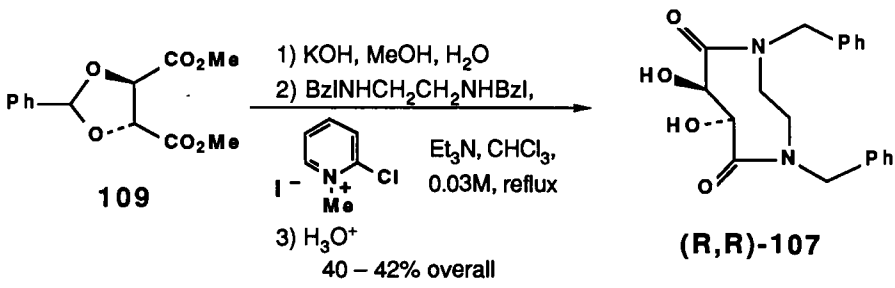
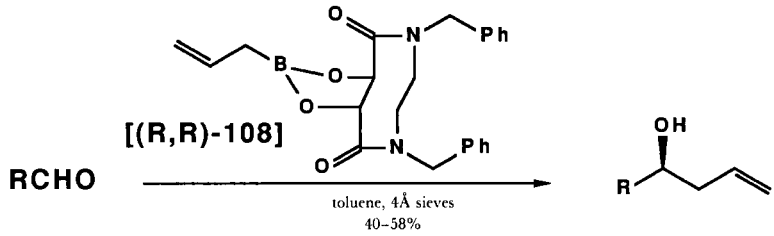



FIG. 40

TABLE II

REACTIONS OF (*R,R*)-**108** AND ACHIRAL ALDEHYDES




| RCHO | Temp. (°C) | Selectivity (% e.e.) | $\Delta\Delta G^{\ddagger}$ (kcal mol$^{-1}$) |
|---|---|---|---|
| $C_6H_{11}CHO$ | −78 | 97 (87)[a] | −1.61 (−1.03)[a] |
| $C_6H_{11}CHO$ | −50 | 94 (—) | −1.53 (—) |
| $C_6H_{11}CHO$ | +25 | 87 (50) | −1.57 (−0.65) |
| $t$-$C_4H_9CHO$ | −78 | 96 (86) | −1.50 (−1.00) |
| $TBDPSOCH_2CH_2CH_2CHO$ | −78 | 94 (84) | −1.34 (−0.94) |
| $BzlOCH_2CHO$ | −78 | 85 (60) | −0.97 (−0.53) |
| $C_6H_5CHO$ | −78 | 85 (60) | −0.97 (−0.53) |

[a] Values in parentheses are data obtained by using the parent DIPT reagent (**30**) under identical reaction conditions.

Table II summarizes results obtained in the reactions of (*R,R*)-**108** with several representative achiral aldehydes. Also included are comparative reference data (in parentheses) obtained in reactions with the parent tartrate allylboronate **30**. In every instance it is readily apparent that **108** greatly outperformed its predecessor. The reactions of **108** with cyclohexanecarboxaldehyde, pivaldehyde, and 4-*t*-butyldimethylsilyloxybutanal proceed with 94–97% e.e., versus 84–87% e.e. with DIPT reagent **30**, a very significant improvement. Even benzyloxyacetaldehyde and benzaldehyde, which were very poor substrates for **30** (60% e.e), now each give homoallyl alcohols with acceptable levels of enantioselection (85% e.e.). In energetic terms ($\Delta\Delta G^{\ddagger}$ data), the new reagent is at least 50% more enantioselective on a case-by-case basis. Also significant are the observations that **108** is as selective in reactions at 25°C as is **30** at −78°C (entries 1,3); the $\Delta\Delta G^{\ddagger}$ of reactions of **108**, but not **30**, are independent of temperature within experimental error (entries 1–3); and the sense of asymmetric induction with **108** and **30** is the same.

The increased enantioselectivity of **108** pays the expected dividends in reactions with chiral aldehydes (Fig. 41). β-Alkoxypropionaldehydes **111** were relatively poor substrates when **30** was used.[4h] The best selectivity ever

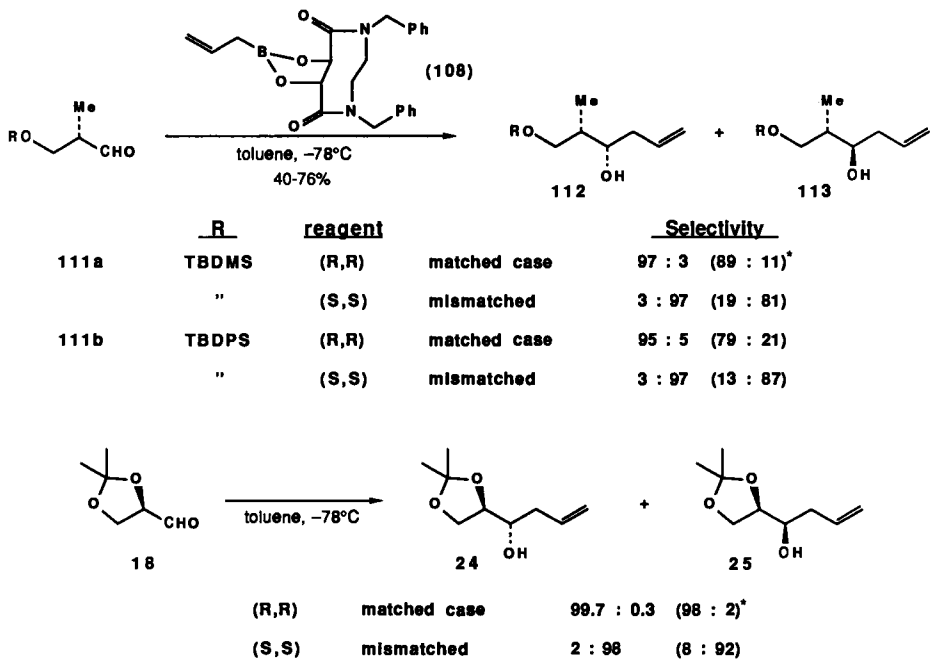



FIG. 41

obtained for syn diastereomer **112** in the matched double asymmetric reactions was 89 : 11 [(*R*,*R*)-**30** and **111a**], whereas the best selectivity for anti diastereomer **113** was 87 : 13 [reaction of **111b** and (*S*,*S*)-**30**]. In contrast, the allylborations of **111a,b** with the new reagent **108** now proceed with up to 97 : 3 selectivity for either product diastereomer. Even more impressive results were obtained with glyceraldehyde acetonide (**18**): the matched double asymmetric reaction leading to **24** now proceeds with 300 : 1 diastereoselectivity, while the mismatched combination leading to **25** proceeds with 50 : 1 selectivity.

These data strongly support our original thesis regarding the origin of asymmetry with reagents **30–32** and establish **108** as the most highly enantioselective allylmetal reagent yet devised.[25,83] It should be further noted that the increased enantioselectivity with **108** is not simply the consequence of the ester to lactam functional group modification, since a series of acyclic tartramides have been examined (e.g., bis-*N*,*N*-dibenzyl

tartramide), and their allylboron derivatives are *significantly* less enantioselective than even **30**. Consequently, these studies emphasize the important geometric relationships that must be present in the favored allylboration transition state and, further, suggest that the convergence of functional groups toward a metal center can be an exceedingly useful strategy for achieving a topological bias in the enantioselective functionalization of a carbonyl group.[84]

Although **108** is substantially more enantioselective than **30**, it is not, unfortunately, a superior reagent for organic synthesis. Compound **108** suffers from poor solubility in toluene, especially at low temperatures, causing the reactions summarized in Table II and Fig. 41 to be rather sluggish and require long reaction times for reasonable conversions.[79] We regard **108** as a prototype of an improved auxiliary and are actively striving to develop a reagent that combines the reactivity of **30** with the enantioselectivity and ease of preparation of **108**. If we are successful in these endeavors, then we will have an auxiliary that will greatly increase the utility of allylboronates in organic synthesis, especially in the context of mismatched double asymmetric reactions.

## IV. Concluding Remarks

One of our objectives in initiating this program was to make a contribution to the area of acyclic diastereoselective synthesis. Even though the total synthesis has not yet been completed, I feel that we have been successful, particularly in view of the allylboron chemistry that has emerged. The course of events detailed in this chapter has led ultimately to the discovery of a new stereoelectronic effect that may find broad applicability in asymmetric synthesis, another line of inquiry that is a direct descendant of the olivomycin story. Thus, our decision to embark on this total synthesis has had a significant impact on the evolution of my research program, a process that has not yet reached its zenith.

### Acknowledgments

I am indeed grateful to acknowledge the intellectual and experimental contributions of the many students and postdoctoral associates who participated in the research described in this chapter. They are, in alphabetical order: Dr Luca Banfi, Richard J. Brown (now Dr.), Dr. Wesley K. M. Chong, Dr. David J. Harris, Dr. Brigitte Lesur, Michael R. Michaelides, Julie A. Straub (now Dr.), and Dr. Dar-Fu Tai. Without the contributions of these individuals there would be no story to tell. Thanks are also extended to the following group members for their contributions toward the development of the tartrate allylboronates as practical reagents for organic synthesis: Michael A. Adam (now Dr.), Dr. Kaori Ando, Dr. Ronald L. Halterman, Lee K. Hoong, Alan

D. Palkowitz, Michelle A. J. Palmer, and Alan E. Walts (now Dr.). Finally, I would like to thank the National Institutes of Health (CA 29847, GM 26782, and AI 20779) for their continued support of my research program.

## References

1. For a general review of acyclic diastereoselective synthesis, see Bartlett, P. A. *Tetrahedron* **1980,** *36*, 2.
2. For recent reviews of syntheses of carbohydrates from noncarbohydrate precursors, see (a) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987,** *26*, 15; (b) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984,** *3*, 125; (c) Zamojski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982,** *40*, 1.
3. For reviews, see (a) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley (Interscience): New York, 1979; Chap. 3; (b) Skarbeck, J. D.; Speedie, M. K. *In* "Antitumor Compounds of Natural Origin: Chemistry and Biochemistry," Aszalos, A., Ed. CRC Press: Boca Raton, Florida, 1981; Chap. 5.
4. (a) Roush, W. R.; Harris, D. J., Lesur, B. M. *Tetrahedron Lett.* **1983,** *24*, 2227; (b) Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984,** *49*, 3429; (c) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985,** *107*, 8186; (d) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986,** *108*, 294; (e) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986,** *108*, 3422; (f) Roush, W. R.; Straub, J. A. *Tetrahedron Lett.* **1986,** *27*, 3349; (g) Roush, W. R.; Michaelides, M. R. *Tetrahedron Lett.* **1986,** *27*, 3353; (h) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987,** *52*, 316; (i) Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987,** *109*, 953; (j) Roush, W. R.; Coe, J. W. *Tetrahedron Lett.* **1987,** *28*, 931.
5. Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987,** *109*, 7575.
6. Two syntheses of tri-O-methyl olivin have been reported previously: (a) Dodd, J. H.; Starrett, J. E.; Weinreb, S. M.; *J. Am. Chem. Soc.* **1984,** *106*, 1811; (b) Franck, R. W.; Bhat, V.; Subramaniam, C. S. *J. Am. Chem. Soc.* **1986,** *108*, 2455.
7. D-Fucose also could have been selected as starting material. If so, the synthesis of **3** would have been shortened by two steps. We viewed D-fucose, however, as an unreasonable starting material on the basis of cost ($11 per gram, versus $0.04 per gram for D-galactose; 1987 Aldrich prices).
8. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979,** *62*, 2411.
9. (a) Auge, C.; David, S.; Veyrieres, A. *J.C.S. Chem. Commun.* **1976,** p. 375; (b) Nashed, M. A. *Carbohydr. Res.* **1978,** *60*, 200.
10. (a) Buchanan, J. G.; Edgar, A. R.; Power, M. J.; Theaker, P. D. *Carbohydr. Res.* **1974,** *38*, C22; (b) Zhdanov, Y. A.; Alexeev, Y. E.; Alexeeva, V. G. *Adv. Carbohydr. Chem.* **1972,** *27*, 227.
11. Zinner, H.; Ernst, B.; Kreienbring, F. *Chem. Ber.* **1962,** 95, 821. Attempts to use milder conditions were less successful. Some cleavage of the benzyl ether was also observed.
12. Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971,** *36*, 3553.
13. 1-Alkoxyallyllithiums react with electrophiles preferentially at the $\gamma$ position, so use of a metal additive [e.g., $(RO)_2BX$] to reverse the regioselectivity of the reaction would be necessary: (a) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974,** *96*, 5560; (b) Still, W. C.; Macdonald, T. L. *J. Am. Chem. Soc.* **1974,** *96*, 5561.
14. For a review of the diastereoselective addition of allylmetal compounds to aldehydes, see Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1982,** *21*, 555.

15. (a) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1982,** *23*, 845, **1981,** *22*, 5263; (b) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1982,** *47*, 2498; (c) Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Liebigs. Ann. Chem.* **1985,** 2246.
16. For other γ-alkoxyallylmetal reagents see (a) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987,** *28*, 139; (b) Koreeda, M.; Tanaka, Y.; *Tetrahedron Lett.* **1987,** *28*, 143; (c) Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987,** *52*, 957; (d) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985,** *292*, 311; (e) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1982,** p. 237, **1981,** p. 1005, **1979,** p. 1279; (f) Koreeda, M.; Tanaka, Y. *J.C.S. Chem. Commun.* **1982,** p. 845.
17. Hoffmann, R. W.; Zeiss, H. J.; Ladner, W.; Tabche, S. *Chem. Ber.* **1982,** *115*, 2357.
18. Servi, S. *J. Org. Chem.* **1985,** *50*, 5865.
19. Fujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982,** *65*, 1258.
20. (a) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985,** *118*, 3966; (b) Hoffmann, R. W.; Endesfelder, A.; Zeiss, H. J. *Carbohydr. Res.* **1983,** *123*, 320; (c) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1983,** *48*, 3489.
21. (a) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981,** *103*,7690; (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979,** *12*, 63.
22. Dimethyl allylboronates (e.g., **17**) are sensitive to hydrolysis, and the allylboronic acids are unstable in the presence of $\mathbf{O}_2$.
23. For a review, see Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985,** *24*, 1.
24. (a) Herold, T.; Schrott, U.; Hoffmann, R. W.; Schnelle, G.; Ladner, W.; Steinbach, K. *Chem. Ber.* **1981,** *114*, 359; (b) Hoffmann, R. W., Herold, T. *Chem. Ber.* **1981,** *114*, 375.
25. For leading references to other classes of chiral allylmetal compounds, see (a) Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986,** *119*, 2013; (b) Hoffmann, R. W.; Dresely, S. *Angew. Chem. Int. Ed. Engl.* **1986,** *25*, 189; (c) Ditrich, K.; Bube, T.; Sturmer, R.; Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1986,** *25*, 1028; (d) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986,** *51*, 432; (e) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986,** *108*, 5919; (f) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987,** *52*, 3701, 319; (g) Midland, M. M.; Preston, S. B. *J. Am. Chem. Soc.* **1982,** *104*, 2330; (h) Jephcote, V. J.; Pratt, A. J.; Thomas, E. J. *J.C.S. Chem. Commun.* **1984,** p. 800; (i) Mukaiyama, T.; Minowa, N.; Oriyama, T.; Narasaka, K. *Chem. Lett.* **1986,** p. 97; (j) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982,** *104*, 4962; (k) Roder, H.; Helmchen, G.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1984,** *23*, 898.
26. An important consequence of the use of a $C_2$ symmetric auxiliary is that the number of competing transition states is reduced from four (as in the case of Hoffmann's bornandiol reagents) to two, thereby increasing the probability that a single, selective pathway will be found.
27. For recent reviews, see (a) Rossiter, B. E. *In* "Asymmetric Synthesis"; Morrison, J. D.; Academic Press: New York, 1985; Vol 5, p. 193; (b) Finn, M. G.; Sharpless, K. B. *In* "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p. 247.
28. Use of tartrate esters as chiral auxiliaries in the asymmetric reactions of allenyl boronic acid has been reported: Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986,** *108*, 483; Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982,** *104*, 7667.
29. Roush, W. R.; Banfi, L. Unpublished research results.
30. Roush, W. R.; Palmer, M. A. J. Unpublished optimized data.
31. Danishefsky, S. *Acc. Chem. Res.* **1981,** *14*, 400.
32. (a) Franck, R. W.; John, T. V. *J. Org. Chem.* **1980,** *45*, 1170; (b) Franck, R. W.; John, T. V.; Olejniczak, K.; Blount, J. F. *J. Am. Chem. Soc.* **1982,** *104*, 1106.

33. Franck, R. W.; Subramaniam, C. S.; John, T. V.; Blount, J. F. *Tetrahedron Lett.* **1984,** *23*, 2439.
34. Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979,** 3465; **1980,** *21*, 4727.
35. (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981,** *103*, 1224; *Tetrahedron Lett.* **1979,** 2327; (b) see also Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982,** *104*, 2027; (c) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981,** *22*, 3997.
36. Ziegler, F. E.; Gilligan, P. J. *J. Org. Chem.* **1981,** *46*, 3874.
37. House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978,** *43*, 2443.
38. Hasomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977,** *99*, 1673.
39. Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983,** *24*, 2231.
40. House, H. O.; Chu, C. Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975,** *40*, 1460.
41. Singh, P. P.; Gharia, M. M.; Dasgupta, F.; Srivastava, H. C. *Tetrahedron Lett.* **1977,** 439.
42. Smith, A. B., III; Jerris, P. J. *J. Am. Chem. Soc.* **1981,** *103*, 194.
43. Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978,** *100*, 3240.
44. Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985,** *285*, 437.
45. For studies of the reactions of enals and organocuprates, see (a) Liu, H. J.; Browne, E. N. C. *Can. J. Chem.* **1978,** *56*, 306; (b) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1981,** *37*, 1385.
46. For recent studies on the use of TMS-Cl in organocuprate conjugate additions, see (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985,** *26*, 6015, 6019; (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986,** *27*, 1047; (c) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986,** *27*, 4025; (d) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986,** *27*, 4029.
47. (a) Che'rest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968,** p. 2199; (b) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977,** *1*, 61.
48. For cases in which stereoselectivity is dependent on the double bond geometry, see Yamamoto, Y.; Nishii, S.; Ibuka, T. *J.C.S. Chem. Commun.* **1987,** p. 464.
49. (a) Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987,** *28*, 2525; (b) Cha, J. K.; Lewis, S. C. *Tetrahedron Lett.* **1984,** *25*, 5263; (c) Salomon, R. G.; Miller, D. B.; Raychaudhuri, S. R.; Avasthi, K.; Lal, K.; Levison, B. S. *J. Am. Chem. Soc.* **1984,** *106*, 8296; (d) Heathcock, C. H.; Kiyooka, S.; Blumenkopf. T. A. *J. Org. Chem.* **1984,** *49*, 4214; **1986,** *51*, 3252.
50. (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978,** *43*, 178; (b) Wildeman, J.; Borgen, P. C.; Pluim, H.; Rouwette, P. H. F. M.; van Leusen, A. M. *Tetrahedron Lett.* **1978,** p. 2213; (c) Dodd, J. H.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1982,** *47*, 4045.
51. Broom, N. J. P.; Sammes, P. G. *J.C.S. Perkin. I* **1981,** p. 465.
52. (a) Carpenter, T. A.; Evans, G. E.; Leeper, F. J.; Staunton, J.; Wilkinson, M. R. *J.C.S. Perkin I* **1984,** p. 1043; (b) Hauser, F. M.; Rhee, R. P.; Prasanna, S.; Weinreb, S. M.; Dodd, J. M. *Synthesis* **1980,** p. 72.
53. Datta, S. C.; Franck, R. W.; Noire, P. D. *J. Org. Chem.* **1984,** *49*, 2785.
54. The corresponding dimethyl ether has been prepared by related procedures: (a) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981,** *103*, 6885; (b) Noire, P. D.; Franck, R. W. *Synthesis* **1980,** p. 882.
55. Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986,** *27*, 4537.
56. Mancuso, A. J.; Swern, D. *Synthesis* **1981,** p. 165.
57. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984,** *25*, 5953.
58. Berlin, Y. A.; Esipov, S. E.; Kolosov, M. M.; Shemyakin, M. M.; Brazhnikova, M. G. *Tetrahedron Lett.* **1964,** p. 1323. These authors report mp 189–191°C and $[\alpha]_D^{25}$ +60.5° (c 0.5, EtOH) for natural olivin.

59. (a) Roush, W. R.; Brown, R. J.; DiMare, M. *J. Org. Chem.* **1983,** *48*, 5083; (b) Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1983,** *48*, 5093; (c) Roush, W. R.; Hagadorn, S. M. *Carbohydr. Res.* **1985,** *136*, 187; (d) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985,** *50*, 3752.
60. Roush, W. R.; Straub, J. A. *Tetrahedron Lett.* **1986,** *27*, 3349.
61. (a) Thiem, J.; Meyer, B. *J.C.S. Perkin II* **1979,** p. 1331; (b) Thiem, J.; Meyer, B. *Tetrahedron* **1981,** *37*, 551; (c) Thiem, J.; Schneider, G. *Angew. Chem., Int. Ed. Engl.* **1983,** *22*, 58.
62. (a) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985,** *50*, 954; (b) Thiem, J.; Meyer, B. *Chem. Ber.* **1980,** *113*, 3058; (c) Thiem, J.; Gerken, M. *J. Carbohydr. Chem.* **1982–1983,** *1*, 229; (d) Thiem, J.; Elvers, J. *Chem. Ber.* **1981,** *114*, 1442, **1980,** *113*, 3049; (e) Thiem, J.; Meyer, B. *Chem. Ber.* **1980,** *113*, 3067; (f) Thiem, J.; Gerken, M.; Snatzke, G. *Liebigs Ann. Chem.* **1983,** p. 448.
63. Available structure–activity correlation data, reviewed in reference 3, clearly indicate that the oligosaccharide fragments have a marked effect on the biological properties of the aureolic acid antibiotics.
64. (a) Horton, D.; Wander, J. D. *In* "The Carbohydrates," 2nd Edition; Academic Press: New York, 1980; Vol. 1B, p. 643; (b) Williams, N. R.; Wander, J. D. *In* "The Carbohydrates," 2nd Edition; Academic Press: New York, 1980; Vol. 1B, p. 761; (c) Butterworth, R. F.; Hanessian, S. *Adv. Carbohydr. Chem. Biochem.* **1971,** *26*, 279.
65. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981,** *103*, 6237.
66. Straub, J. A., Ph.D. Thesis, MIT, Cambridge, Massachusetts, 1987.
67. Hanessian, S.; Guindon, Y. *Carbohydr. Res.* **1980,** *86*, C3.
68. Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983,** *105*, 2430.
69. For leading references to other glycosidation methods involving thio sugars, see reference 20 c and (a) Hanessian, S.; Bacquet, C.; Lehong, N. *Carbohydr. Res.* **1980,** *80*, C17; (b) Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. *Carbohydr. Res.* **1973,** *27*, 55.
70. The (L) enantiomer of **84,** but not **84** itself, is available from cinnamaldehyde via an asymmetric hydroxylation reaction involving fermenting baker's yeast: Fronza, G.; Fuganti, C.; Grasselli, P. *J.C.S. Chem. Commun.* **1980,** p. 442.
71. (a) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science* **1983,** *220*, 949; (b) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982,** *104*, 1109.
72. For other recent studies of diastereoselective nucleophilic additions to epoxy aldehydes, see (a) Howe, G. P.; Wang, S.; Procter, G. *Tetrahedron Lett.* **1987,** *28*, 2629; (b) Takeda, Y.; Matsumoto, T.; Sato, F. *J. Org. Chem.* **1986,** *51*, 4728.
73. (a) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985,** *107*, 5312; (b) Hoye, T. R., Suhadolnik, J. C. *Tetrahedron* **1986,** *42*, 2855.
74. Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987,** *109*, 1525.
75. (a) Payne, G. B. *J. Org. Chem.* **1962,** *27*, 3819; (b) Katsuki, T.; Lee, A, W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982,** *47*, 1373.
76. (a) Kroon, J. *In* "Molecular Structure and Biological Activity," Griffin, J. F.; Duax, W. L., Eds.; Elsevier: New York, 1982; p. 151; (b) Karabatsos, G. J.; Fenoglio, D. J. *Top. Stereochem.* **1970,** *5*, 167.
77. (a) Karabatsos, G. J.; Fenoglio, D. J.; Lande, S. S. *J. Am. Chem. Soc.* **1969,** *91*, 3572; (b) Karabatsos, G. J.; Fenoglio, D. J. *J. Am. Chem. Soc.* **1969,** *91*, 3577; (c) Brown, T. L. *Spectrochim. Acta.* **1962,** *18*, 1615.
78. For a previous example of a boron-centered anomeric effect, see Shiner, C. S.; Garner, C. M.; Haltiwanger, R. C. *J. Am. Chem. Soc.* **1985,** *107*, 7167.
79. Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* (in press).

80. Eight-membered dilactones have also been considered, but so far we have been unable to synthesize these materials.
81. (a) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976,** p. 49; (b) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975,** p. 1163.
82. (a) Steliou, K.; Poupart, M. A. *J. Am. Chem. Soc.* **1983,** *105*, 7130; (b) Collum, D. B.; Chen, S. C.; Ganem, B. *J. Org. Chem.* **1978,** *43*, 4393.
83. Reagent **108** also ranks among the most highly enantioselective chiral acetate aldol enolate equivalents: (a) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987,** *26*, 24, and literature cited therein; (b) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986,** *108*, 8279.
84. The significance of convergent functional groups for the design of molecular receptors and clefts has been described: (a) Rebek, J., Jr.; Askew, B.; Ballester, P.; Doa, M. *J. Am. Chem. Soc.* **1987,** *109*, 4119; (b) Rebek, J., Jr.; Askew, B.; Nemeth, D.; Parris, K. *J. Am. Chem. Soc.* **1987,** *109*, 2432; (c) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987,** *109*, 2426.

*Chapter 11*

# EVOLUTION OF A SYNTHETIC STRATEGY, PART II: TOTAL SYNTHESIS OF (−)-CASBENE AND (−)-BERTYADIONOL

*Amos B. Smith III* and Bruce D. Dorsey*

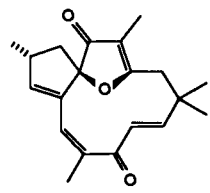
*Department of Chemistry,*
*Laboratory for Research on the Structure of Matter*
*and Monell Chemical Senses Center*
*University of Pennsylvania*
*Philadelphia, Pennsylvania*



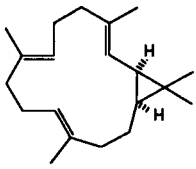
* Camille and Henry Dreypus Teacher Scholar, 1978–1983; National Institute of Health (National Career Institute) Career Development Awarder, 1980–1985; and J. S. Guggenheim Fellow, 1985–1986.

## I. Introduction

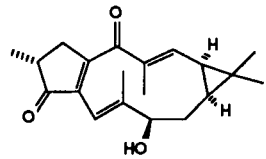
In the inaugural volume of *Strategies and Tactics in Organic Synthesis* we recorded the development of a synthetic program which culminated in the first total synthesis of the diterpene antitumor agent jatrophone (**1**).[1] As noted in the introduction to that chapter, it was obvious in retrospect that the unique architecture and functionality of the jatrophone molecule had influenced the evolution of a major portion of the research that we undertook during those early years (ca. 1976–1981). The impact of the jatrophone program continues today. Our most recent exploits have concerned casbene (**2**) and the closely related lathyranes known as bertyadionol (**3**) and the jolkinols (**4,5**). In keeping with the informal spirit of this collection of essays



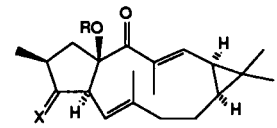

JATROPHONE
1




CASBENE
2




BERTYADIONOL
3




4 JOLKINOL C R = H X = O
5 JOLKINOL D R = Ac X = β-OH, α-H

SCHEME 1

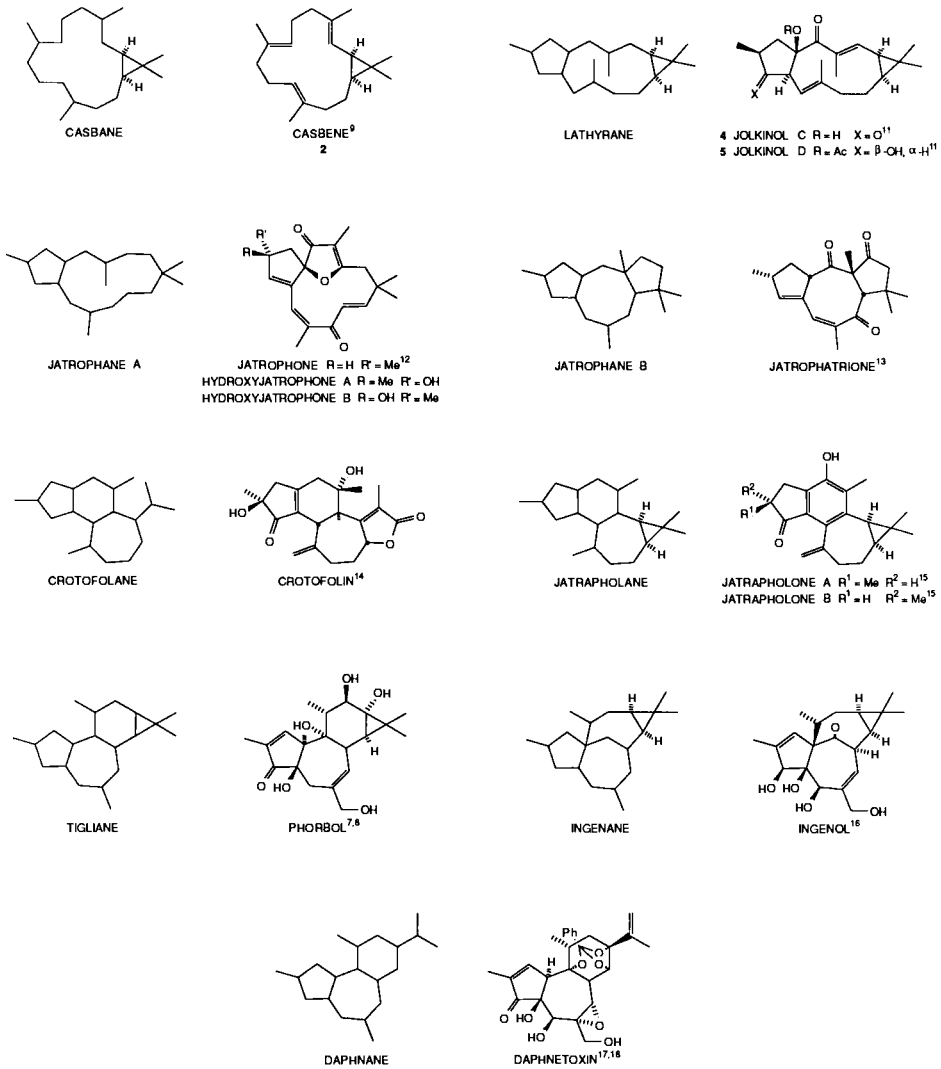
on the development and execution of synthetic strategies, we will present here in chronological order a fairly complete account of the evolution of the ideas, spin-offs, and setbacks of what we now refer to as the casbene–bertyadionol era (1981–1986). We note in advance the major accomplishments that have emanated from the casbene–bertyadionol synthetic venture:

1. An efficient, enantioselective total synthesis of (−)-casbene: the putative biosynthetic precursor of the lathyrane diterpene natural products isolated from Euphorbiaceae and Thymeleaceae.[2]
2. The total synthesis of (−)-bertyadionol, the first and to date only lathyrane diterpene to succumb to total synthesis.[3]
3. A unified synthetic strategy for the casbene–lathyrane diterpenes, currently being exploited for the synthesis of the jolkinols.[2]
4. The preparation, reactivity, and spectroscopic properties of 1,3-dioxin vinylogous esters: versatile β-ketovinyl cation equivalents.[4]
5. A unified synthetic strategy for the hydroxyjatrophones.[5]
6. The development of an effective resolution of (−)-*cis*-chrysanthemic acid.[6]

These accomplishments notwithstanding, the reader will recognize that much remains to be discovered before a truly efficient entry to the lathyrane diterpenes will be at hand. Indeed, the strategies and tactics presented below comprise only an initial attack on this most intriguing class of natural products. The evolution of the lathyrane problem in our laboratory now permits us to contemplate a second assault (*vide infra*).

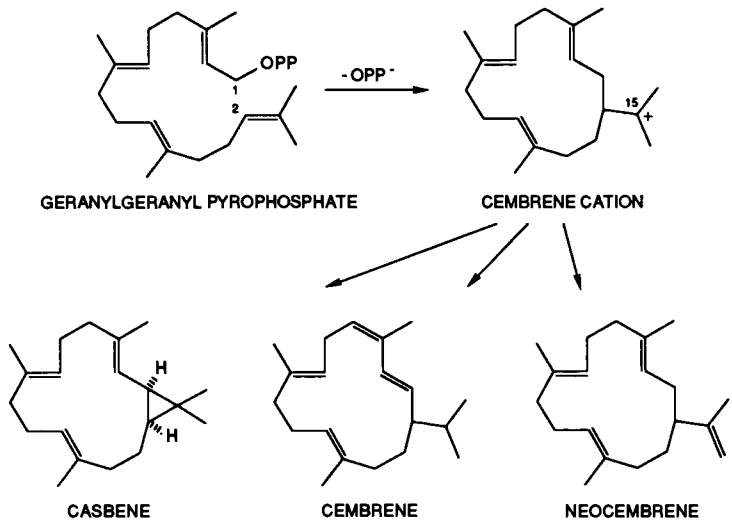
## II. General Background: A Continuing Fascination with the Diterpenes

Nature provides the synthetic chemist with a plethora of architecturally diverse diterpenes, many of which possess important biological properties. The Euphorbiaceae and Thymeleaceae plant families are particularly rich in both attributes. Interest in these plants intensified dramatically after the isolation and structure elucidation in the mid-1960s of the tumor-promoting phorbol esters.[7,8] The carbon frameworks of phorbol and other polycyclic diterpenes (Scheme 2), isolated from the Euphorbiaceae and Thymeleaceae families, are quite similar and can be categorized in the following groups: casbane (casbene[9]), lathyrane (bertyadionol,[10] jolkinols[11]), jatrophane A (jatrophone[12]), jatrophane B (jatrophatrione[13]), crotofolane (crotofolin[14]), jatropholane (jatropholone A and B[15]), tigliane (phorbol[7,8]), ingenane (ingenol[16]), and daphnane (daphnetoxin[17,18]).




SCHEME 2.

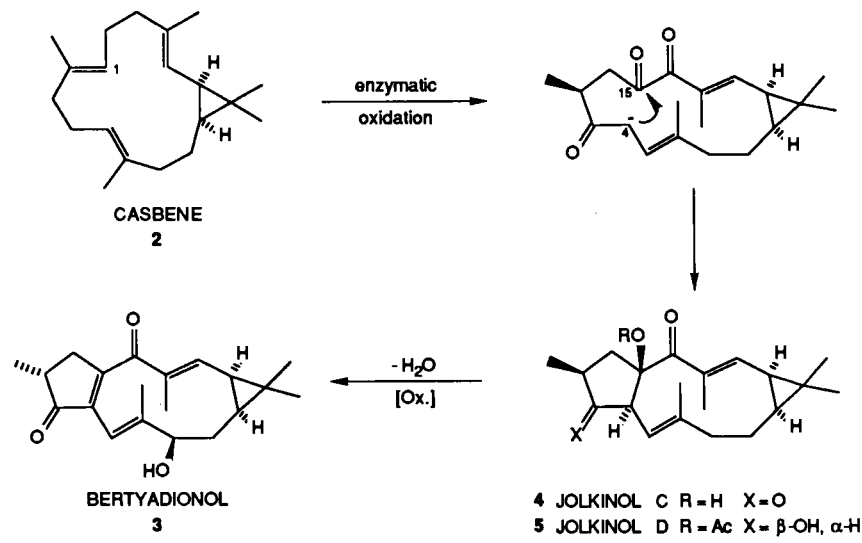
proposed biosynthetic mechanism for casbene involves cyclization via the loss of pyrophosphate (Scheme 3). The resultant cembrene carbocation can then either lead to casbene via proton loss, undergo hydride shifts followed by proton loss to generate cembrene, or simply eliminate a proton to afford neocembrene.[21,22]



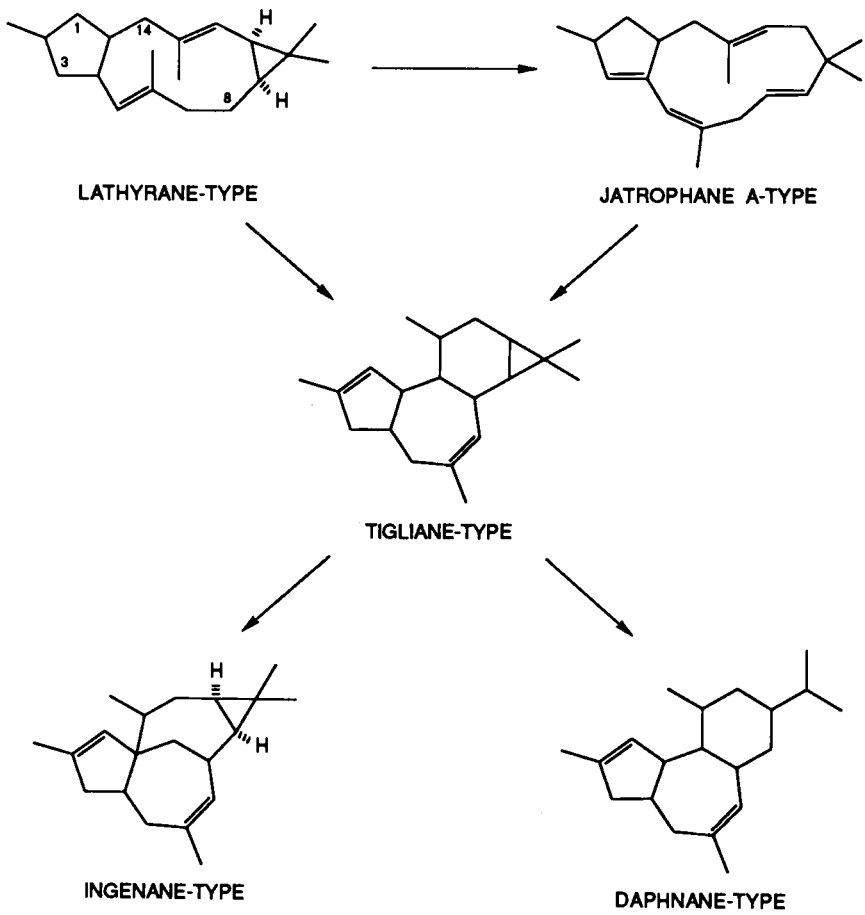

SCHEME 3

Casbene, structurally the simplest of the polycyclic diterpenes, is produced from either geranylgeranyl pyrophosphate or mevalonic acid by cell-free extracts from seedlings of the castor bean *Ricinus communis* L.[9,19,20] The

Although the biosynthesis of casbene has been investigated in detail, the biogenetic interrelationships between casbene and the other macrocyclic diterpenes have yet to be established. In 1977 Adolf and Hecker[19] put forth a theory suggesting that many bicyclic and tricyclic diterpene skeletons are formed biosynthetically from casbene. In support of this theory, now known as the Adolf–Hecker postulate, several tigliane and daphnane diterpenes have been isolated from both the Euphorbiaceae and Thymeleaceae plant families. This co-occurrence of structural type provides strong circumstantial evidence that many of these natural products originate from similar, if not identical, precursors. For example, casbene could undergo closure between C(4) and C(15) to create a cyclopentane ring and thereby generate the lathyrane skeleton. This process, outlined in Scheme 4, is envisioned to occur through a series of enzymatic oxidations, followed by an aldol reaction to generate the jolkinols. Dehydration at C(15) and oxidation at C(7) would then afford bertyadionol (**3**). The lathyrane-type skeleton once formed could then undergo either bond cleavage at C(9) to afford the jatrophane skeleton (Scheme 5) or ring closure between C(8) and C(14) to access the tigliane family. The latter in turn would lead to the daphnanes via cyclopropyl opening and proton loss, or to the ingenanes by carbon bond migration.[19]




SCHEME 4

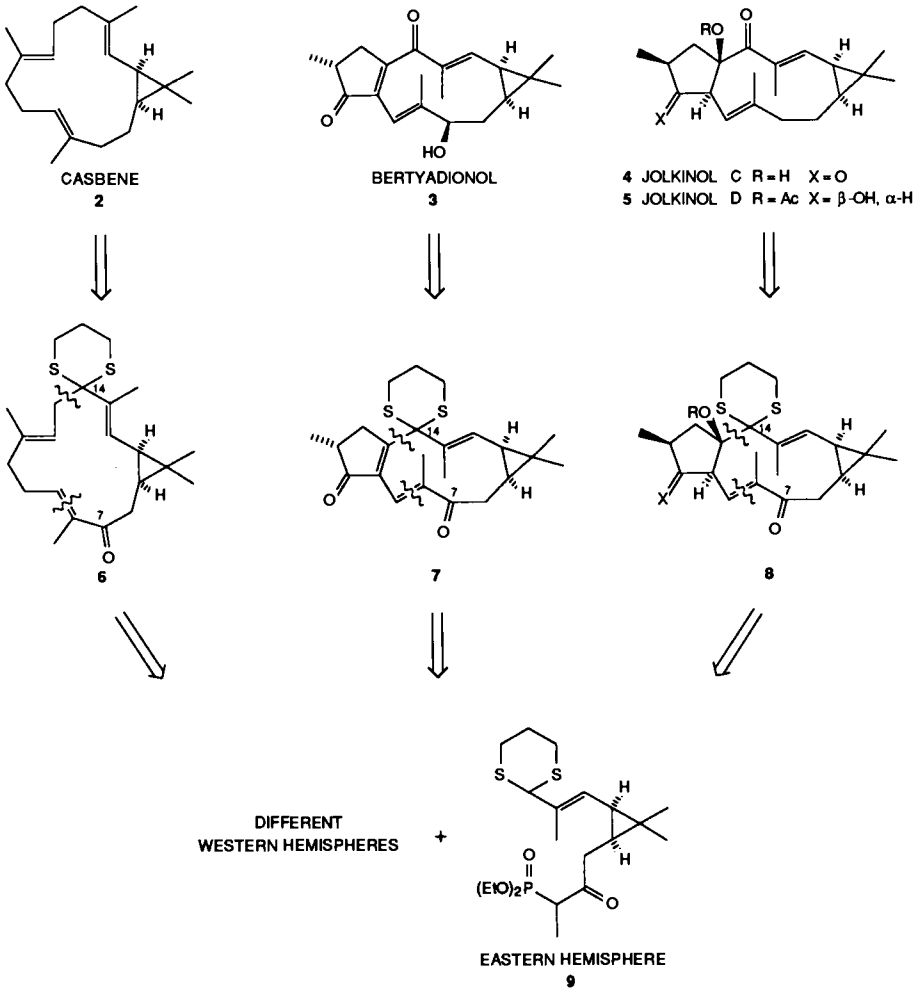



SCHEME 5

## III. Development of a Unified Approach to Casbene and the Lathyrane Diterpenes: The Cornerstone of This Synthetic Venture

The supposition of the biosynthetic interrelationships among the Euphorbiaceae–Thymeleaceae diterpenes suggested the possibility of developing a unified synthetic strategy that would provide access to a number of important diterpene targets. A central theme in this laboratory has been (and will continue to be) the development of efficient synthetic strategies that are not single-target oriented, but rather will permit construction of entire classes of natural products.[23] We believe that the development and execution of such a strategy, starting with casbene as the initial target and expanding to the lathyranes (i.e., bertyadionol and the jolkinols), amply demonstrate this philosophy.[23]

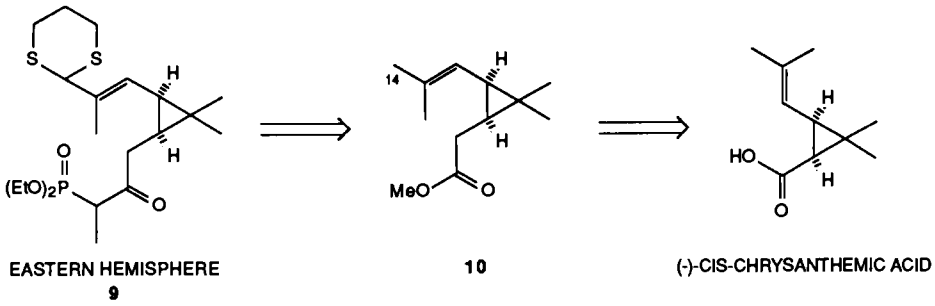
From the outset the core structural feature of casbene and the lathyrane diterpenes was perceived to be the cyclopropyl ring, *cis*-fused to a macrocyclic skeleton (Scheme 6). Also noteworthy from the synthetic viewpoint was the array of *E*-trisubstituted olefins that punctuate the periphery of the macrocyclic ring. To conjoin these structural features, we proposed in retrosynthetic fashion the incorporation of a dithiane unit at C(14) and a carbonyl group at C(7), thereby generating advanced intermediates **6–8**. These functional group additions in turn would permit strategic bond disconnections at C(5,6) and C(14,15), the immediate result being a common eastern hemisphere (i.e., **9**) for all targets. In the synthetic sense, the dithiane unit was seen as an acyl anion equivalent[24] for an as yet undefined electrophilic site on the western hemisphere, the latter unique for each target system. The ketophosphonate functionality was selected to permit macrocyclic ring formation via condensation with an aldehyde unit, present at least in latent form on the western hemisphere. This choice was prompted by the elegant work of Nicolaou, Stork, and Rosen,[25] who by the outset of our studies had clearly demonstrated the utility of the Horner–Emmons protocol for the construction of large-ring systems (13- to 19-membered). Equally important, we could be reasonably confident of high *E*-configurational selectivity at the newly generated 5,6-trisubstituted olefin.[25] However, application of this protocol for the construction of medium-sized rings (8- to 11-membered) was unprecedented. Particularly worrisome here would be the severe transannular interactions expected during medium-sized ring formation. We were nonetheless guardedly optimistic, given the number of $sp^2$-hybridized carbons as well as the *cis*-fused cyclopropane ring present in each target, as we anticipated that these structural features would markedly reduce transannular interactions.




SCHEME 6

Continuing with this analysis, methyl ester **10** (Scheme 7) was viewed as an ideal precursor for the proposed common eastern hemisphere (**9**). Allylic oxidation followed by thioketalization with 1,3-propanedithiol would lead to a dithiane unit at C(14),[26] and addition of the anion of diethyl ethylphosphonate[27] to the ester carbonyl would produce β-ketophosphonate **9**. Ester **10** in turn was envisioned to arise from *cis*-chrysanthemic acid via a one-carbon homologation.

The required absolute stereochemistry for the common eastern hemisphere derived from the combined work of Crombie and Jefferies. In




SCHEME 7.

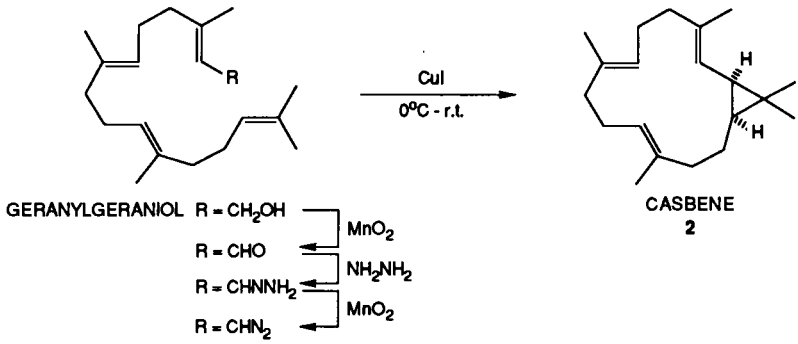
particular, Crombie,[20] through the total synthesis of (−)-casbene, and Jefferies,[10] via degradation of bertyadionol, established that both natural products have the 9*S*,11*S* configuration. That the jolkinols and other lathyrane diterpenes should also share the 9*S*,11*S* stereogenicity follows from the Adolf–Hecker postulate.[19] Inspection of the literature revealed that (−)-*cis*-chrysanthemic acid, the less readily available enantiomer, possesses the requisite absolute stereochemistry.[28]

## IV. Casbene: The Initial Target

In 1970 West and Robinson[9] isolated and characterized (−)-casbene, one of five hydrocarbon diterpenes found in the cell-free extracts of young seedlings of the castor bean. Their study revealed that casbene possessed significant antifungal activity and also served as a phytoalexin[9b] that protected the growth of the beans. Thus, for example, if the bean seedlings are exposed to potentially pathogenic fungi (e.g., *Rhizopus stolonifer* or *Aspergillus niger*) prior to incubation, the production of casbene is greatly enhanced.[9]

The structural assignment of casbene was initially based on careful analysis of $^1$H NMR and mass spectral data.[9] Although elegant, this assignment could only be considered tentative because of the minute amount of casbene available. In 1976 Crombie *et al.* verified West's 1970 structure by total synthesis.[20] Their synthesis substantiated both the structure and absolute configuration, but the approach lacked regiocontrol and proceeded in poor overall yield.

More recently, a short biomimetic synthesis of racemic casbene has been completed by Takahashi (Scheme 8).[29] This four-step route, starting with geranylgeraniol and proceeding in about 14% overall yield, is outlined




SCHEME 8

below. While elegant in both design and execution, the synthesis does not permit construction of homochiral material or allow access to the lathyrane or related diterpenes.

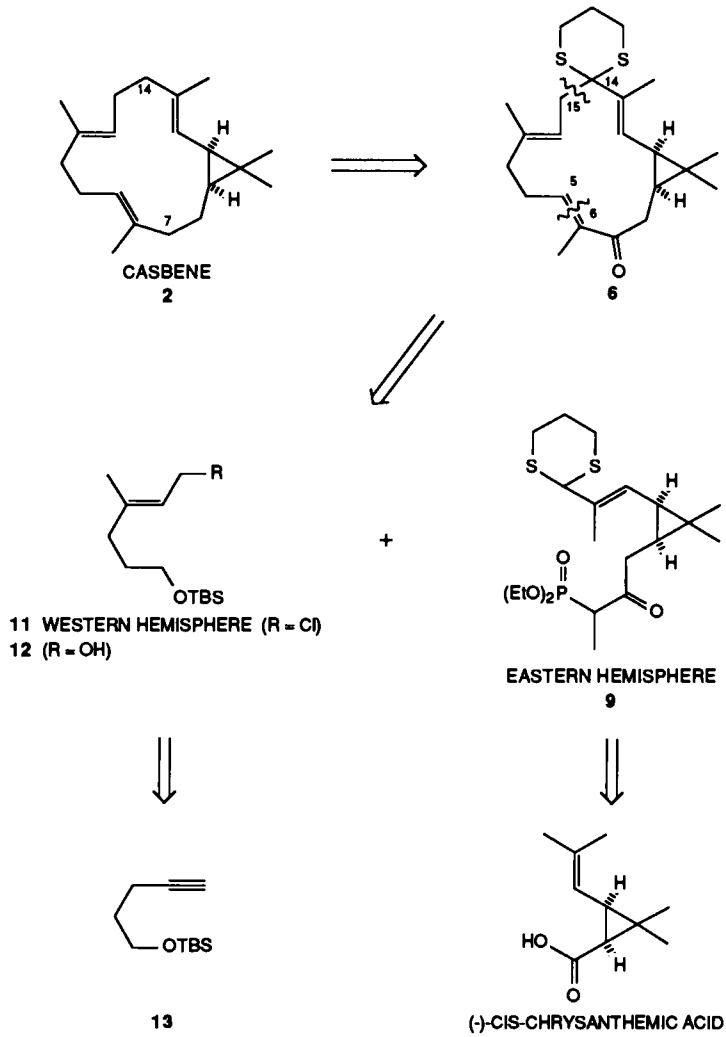
## A. Casbene from the Retrosynthetic Perspective: The Western Hemisphere

As suggested in our general analysis of the Euphorbiaceae–Thymeleaceae diterpenes,[1] addition of functionality at C(7) and C(14) of casbene would serve two purposes (Scheme 9). First, it would enable us to use efficient carbon–carbon bond-forming reactions to assemble the hydrocarbon skeleton. Second, it would permit the generation of a common eastern hemisphere building block and thereby provide a unified strategy for both casbene and the lathyrane diterpenes.

With these considerations in mind, disconnection at C(5,6) and C(14,15) leads to allylic chloride **11** as the western hemisphere for (−)-casbene. This allylic chloride would in turn arise from a protected version of commercially available 4-pentyn-1-ol (**13**).

## B. Execution of the (−)-Casbene Total Synthesis: Preparation of the Common Eastern Hemisphere

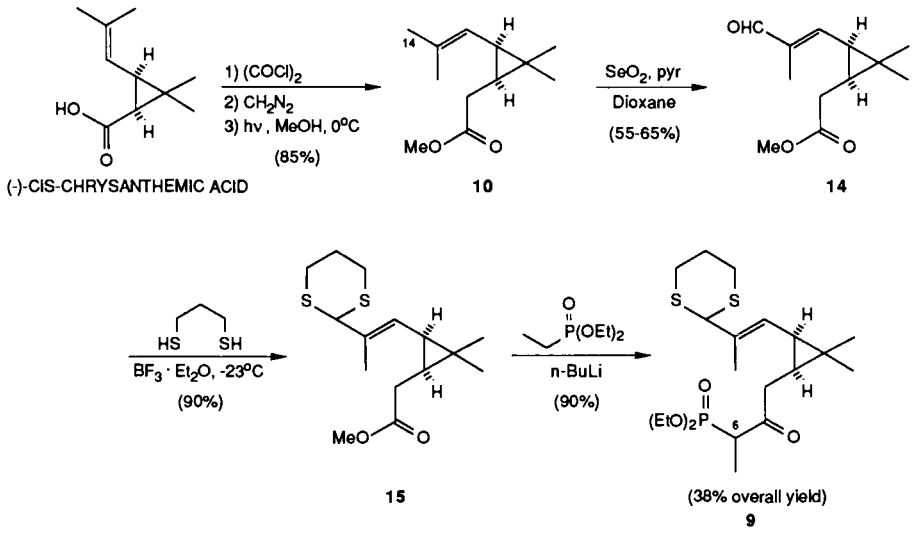
Eastern hemisphere **9** was prepared on a large scale beginning with (−)-*cis*-chrysanthemic acid,[1] obtained via resolution of the racemic *cis*-acid with (−)-*N*-methylephedrine, following an extensively modified procedure of Pavan and Bulidon.[28] Crystallization of the diastereomeric salts from diisopropyl ether, followed by filtration, provided the (−)-*cis*-chrysanthemic acid-*N*-methylephedrine salt, which upon acid decomposition and distillation afforded pure (−)-*cis*-chrysanthemic acid. The enantiomeric purity was




SCHEME 9

shown to be 88–92%, via formation of the Mosher[30] esters of the derived primary alcohol followed by NMR analysis.

A photochemical version of the classic Arndt–Eistert[31] protocol was then employed to homologate the acid (Scheme 10). Toward this end, the acid chloride obtained with oxalyl chloride was treated with excess ethereal diazomethane. Rearrangement of the derived diazoketone via photolysis in methanol (0°C) resulted in **10**, with an overall yield for this three-step

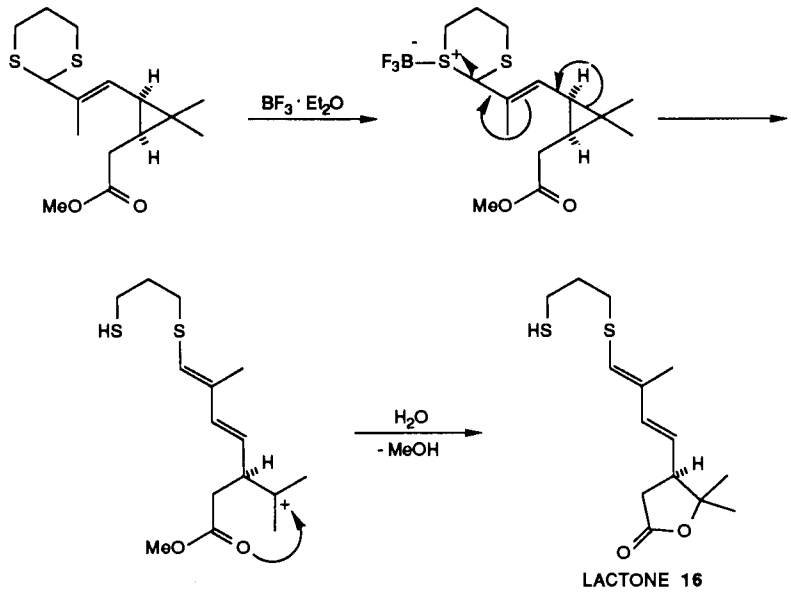



SCHEME 10

sequence of 85%. As is often the case, the photochemical Wolff rearrangement proved to be superior to various metal ion-promoted protocols.[32]

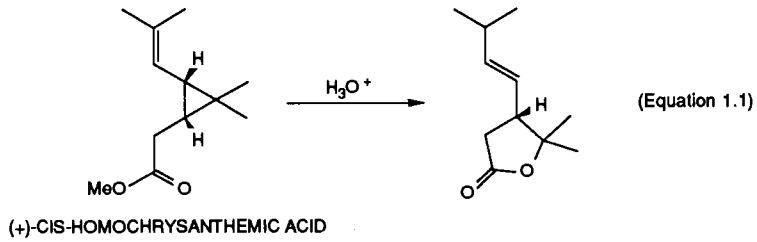
We next introduced oxygen regioselectively at C(14) (casbene numbering) with selenium dioxide. Best results were obtained when the reaction was buffered with pyridine.[33] Without buffer, the yield of **14** decreased to less than 30%, due presumably to the acid-sensitive nature of the aldehyde. The propensity to undergo acid-promoted decomposition was observed again during formation of thioacetal **15**. In this case, exposure of aldehyde **14** to 1,3-propanedithiol and $BF_3 \cdot Et_2O$ in methylene chloride at or below $-23°C$ led to the desired thioacetal in 90% yield. However, higher reaction temperatures promoted formation of lactone **16** (Scheme 11). This transformation presumably involves coordination of the Lewis acid with a sulfur atom, resulting in opening of the dithiane ring to generate a vinylogous cyclopropyl carbinyl cation,[34] which in turn undergoes cyclopropyl ring opening and capture by the ester oxygen to afford lactone **16**. Similar acid-promoted transformations have been described by Crombie[Eq. (1.1), Scheme 12][28b] The propensity for such acid-promoted cyclopropyl ring openings foreshadowed significant complications for our proposed (−)-bertyadionol synthesis (*vide infra*).

Continuing with the casbene synthesis, condensation of **15** at $-78°C$ with 2 equivalents of the anion derived from diethyl ethylphosphonate yielded a 1 : 1 diastereomeric mixture (90% yield) of eastern hemisphere **9** (Sch-




SCHEME 11

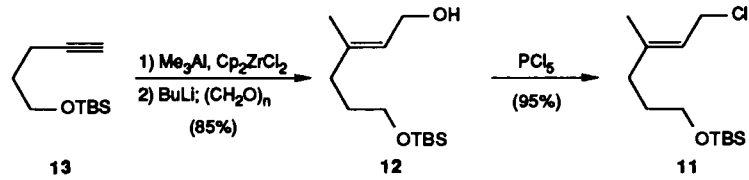
eme 10). Since C(6) was destined to become an $sp^2$ center, formation of diastereomers was perceived to be inconsequential. The overall yield for this four-step sequence was 38%. Equally important, the preparation of **9** was amenable to large-scale work; 20 gram lots of **9** could be prepared in approximately 2–3 days from (−)-*cis*-chrysanthemic acid.




SCHEME 12

## C. CONSTRUCTION OF THE WESTERN HEMISPHERE

With substantial quantities of **9** in hand, we turned to the construction of **11**, the western hemisphere for casbene. This sequence begins with commercially available 4-pentyn-1-ol and requires the stereo- and regiocontrolled




13 12 11

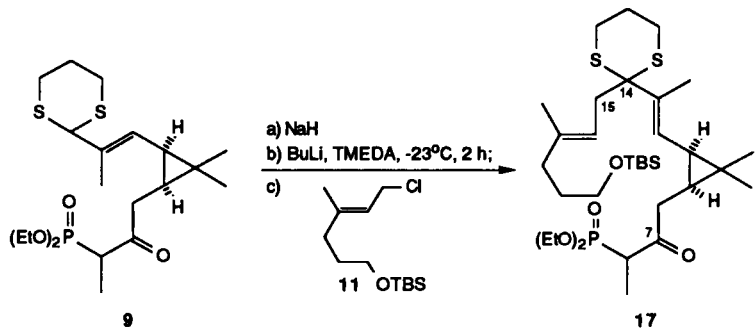
SCHEME 13

introduction of a trisubstituted *E*-olefin (Scheme 13). The zirconium-mediated carboalumination protocol of Negishi[35] appeared ideally suited for our purpose. Thus, the *t*-butyldimethylsilyl ether of 4-pentyn-1-ol (**13**) was treated with $Me_3Al$–$ZrCp_2Cl_2$ to create a carbometalated intermediate. Generation of the ate complex via addition of *n*-BuLi, followed by trapping with paraformaldehyde, produced allylic alcohol **12** with the required *E*-configuration. The derived alcohol was then converted to the chloride with phosphorus pentachloride, thereby affording **11** in three steps. The overall yield from 4-pentyn-l-ol was 66%.

## D. ASSEMBLY OF THE CASBENE SKELETON

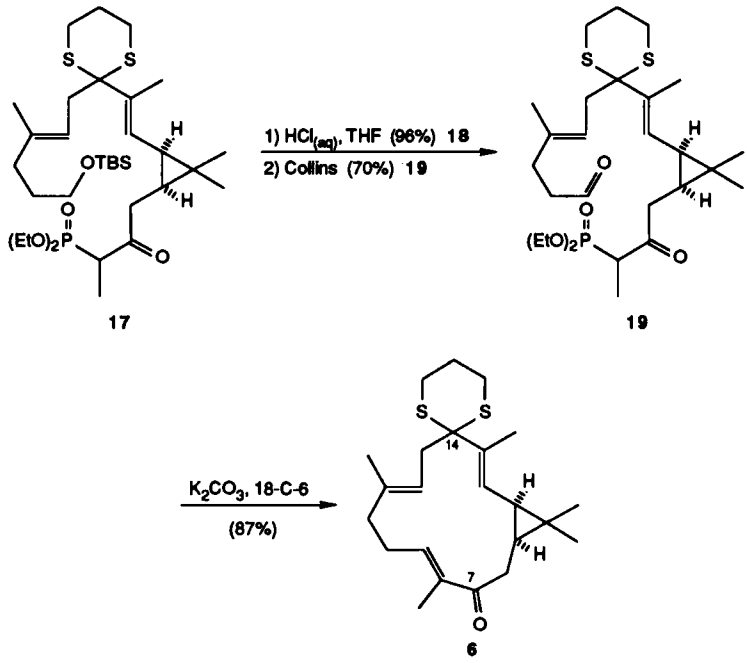
For union of the eastern and western hemispheres, ketophosphonate **9** was first treated with 1.2 equivalents of sodium hydride, followed by reaction with 1.2 equivalents of *n*-BuLi/TMEDA complex at −23°C for 2 hours (Scheme 14). The presumed dianon was then immediately treated with **11** to afford the coupled product **17** in 64% yield.

Having created the key C(14,15) $\sigma$-bond, all that remained to complete (−)-casbene was macrocyclization[25] followed by removal of the extraneous




9 17

SCHEME 14

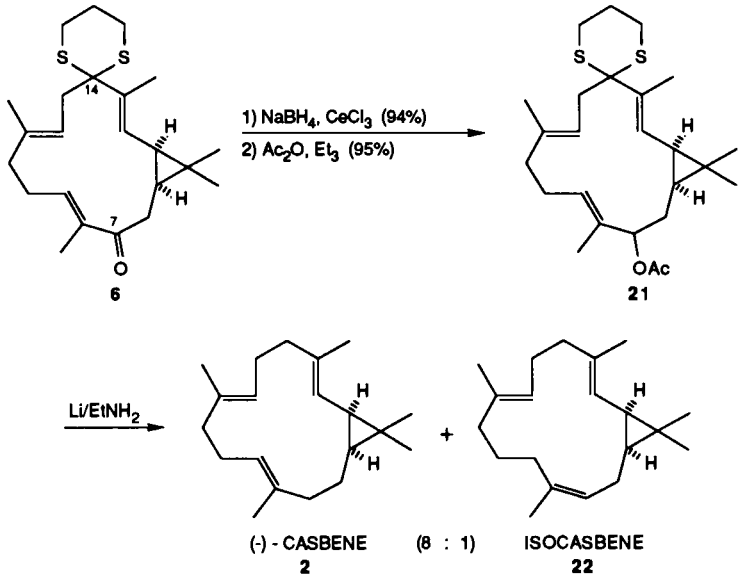



SCHEME 15

functionality at C(7) and C(14). To prepare for macrocyclization, we first removed the silyl group with mild acid (Scheme 15) and then performed a Collins oxidation.[36] The resultant aldehyde **19**, available in 64% yield, was subjected to Horner–Wittig macrocyclization. Gratifyingly, the reaction proved highly stereoselective and proceeded in 87% yield. Somewhat more surprising was the fact that the macrocyclization could be conducted *without* resort to high-dilution techniques (i.e., 0.2 *M* in toluene, 6 equivalents $K_2CO_3$, 13 equivalents 18-crown-6) with absolutely no indication of dimer formation.[25]

## E. COMPLETION OF (−)-CASBENE

To liberate (−)-casbene from **6**, we initially investigated the formation of a second dithiane unit at C(7). Reductive cleavage of both dithianes would then provide the target. However, all attempts to effect thioketalization of the C(7) carbonyl proved fruitless; apparently the problematic generation of a vinylogous cyclopropyl carbinyl cation once again intervened. One possible alternative appeared to be the reductive removal of an allylic acetate at C(7)




6 21

SCHEME 16

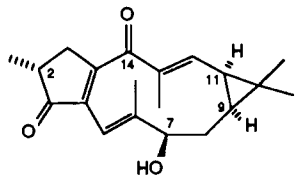
via the Linstead protocol ($Li/EtNH_2$).[37] It was even conceivable that such a procedure would also remove the dithiane. To set the stage for this reaction, enone **6** was reduced with $NaBH_4/CeCl_3$ in MeOH at −23°C,[38] followed by acetylation; acetate **21** was produced in 89% yield for the two steps (Scheme 16). Following this sequence, **21** was added to a solution of lithium dissolved in ethylamine at −78°C. To our delight, reductive removal of both the dithiane and allylic acetate groups took place smoothyl to afford (−)-casbene **2** (75%), admixed with 9.2% of isocasbene **22**, the latter apparently arising from olefin migration during the reduction. Separation via preparative TLC, using $AgNO_3$-impregnated silica gel, afforded pure (−)-casbene [$[\alpha]_D = 114°$ ($c = 0.28$, $CHCl_3$); lit.[20] $[\alpha]_D = 114°$ ($c = 0.30$, $CHCl_3$)]. That synthetic (−)-casbene was indeed in hand was demonstrated by careful comparison with published spectra (IR, $^1H$ NMR, $^{13}C$ NMR, and high-resolution MS).[20]

In summary, our approach to (−)-casbene proved to be highly efficient (7% overall yield), reasonably economic (13 steps), and enantiospecific, in that (−)-*cis*-chrysanthemic acid served as the starting material. Of particular interest was the development and utilization of eastern hemisphere **9**. Further exploitation of this common building block will now be presented in connection with the total synthesis of (−)-bertyadionol, the first and, to this point, the only lathyrane diterpene to succumb to total synthesis.

## V. Total Synthesis of (−)-Bertyadionol: A More Challenging Target

### A. Isolation, Structure Determination, and Chemical Reactivity

Bertyadionol (**3**), a lathyrane diterpene isolated in 1970 by Jefferies and co-workers[10] from *Bertya cupressoidea* (Euphorbiaceae), a plant indigenous to Western Australia, represents the first member of this structural type to be isolated from the Euphorbiaceae subfamily *Ricinocarpoideae*. A preliminary report, including a tentative structure, appeared in 1970.[10a] Several years later the relative and absolute stereochemistries were secured through a combination of degradation and double-resonance NMR experiments.[10b]

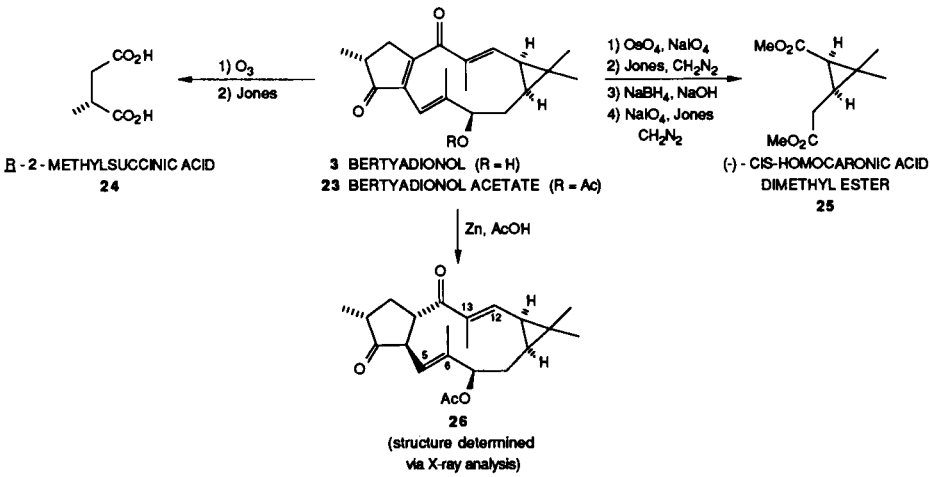



(-) - BERTYADIONOL
**3**

Specifically, ozonolysis of (−)-bertyadionol, followed by oxidative workup, led to the isolation of (*R*)-(+)-2-methylsuccinic acid **24** (Scheme 17).[39] The configuration at C(2) was thus designated as *R*. The absolute configuration of the cyclopropyl carbons (i.e., 9*S*, 11*S*) was also determined by chemical degradation, in this case employing (−)-bertyadionol acetate (**23**). Here a series of oxidations and reductions led to the dimethyl ester of (−)-*cis*-homocaronic acid (**25**),[40] again a known compound with known absolute stereochemistry.

The elegant structure elucidation work of Jefferies was corroborated in 1975 by White and co-workers[10d] through a single-crystal X-ray analysis of a derivative of (−)-bertyadionol acetate (i.e., **26**), obtained by reduction with zinc and acetic acid (Scheme 17). This work revealed that the disposition of the carbinol group was $\beta$ and that the configurations of the C(5,6)- and C(12,13)-olefins were *E*.

Of considerable importance vis-a-vis any synthetic program was Jefferies' report that bertyadionol is *extremely* reactive toward mild acid, base, and ultraviolet light, as well as to various nucleophiles and electrophiles.[10] As will become apparent, the instability of bertyadionol proved to be a major factor during the final staging of our synthesis.




B-2-METHYLSUCCINIC ACID
**24**

**3** BERTYADIONOL (R = H)
**23** BERTYADIONOL ACETATE (R = Ac)

(-)-CIS-HOMOCARONIC ACID DIMETHYL ESTER
**25**

**26**
(structure determined via X-ray analysis)

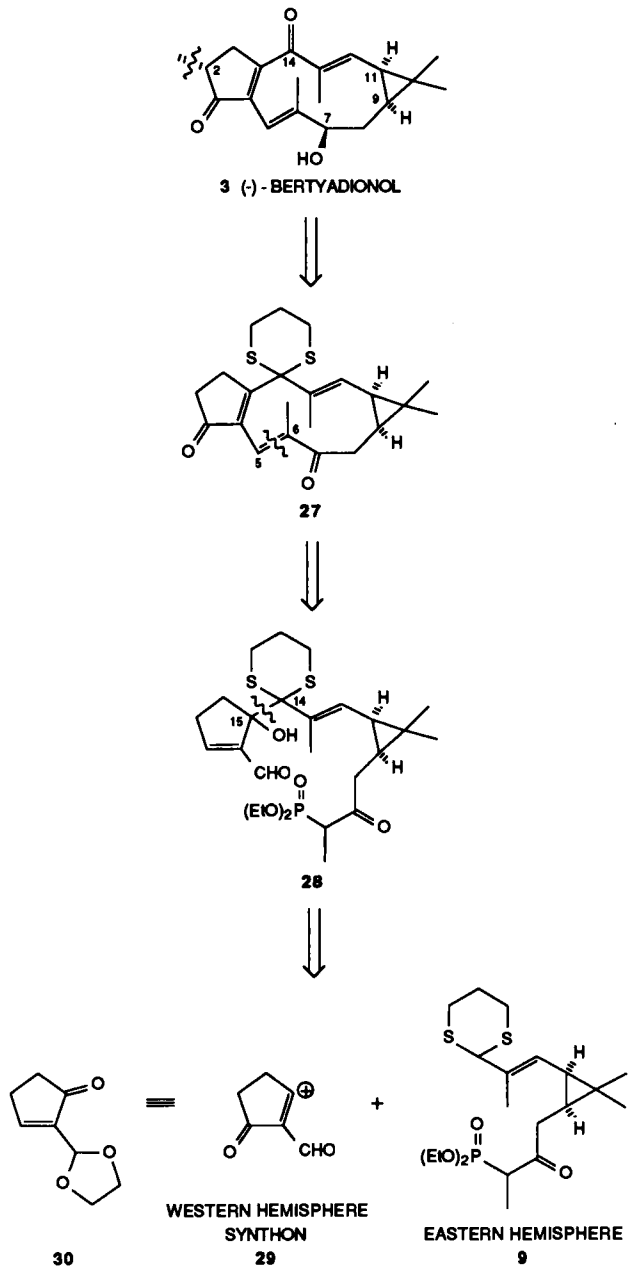
SCHEME 17

## B. BERTYADIONOL FROM THE RETROSYNTHETIC PERSPECTIVE

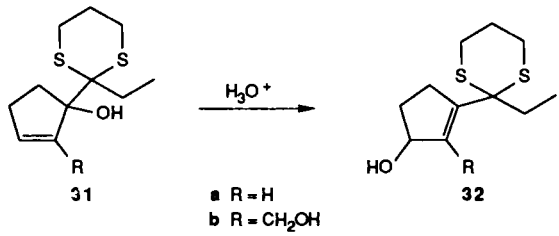
With this background, we turn next to an analysis of bertyadionol in the context of our unified synthetic strategy, in particular the design of an appropriate intermediate to serve as the western unit. A crucial consideration in this analysis involves the stereochemistry of the C(2)-methyl substituent. From the outset of the casbene-bertyadionol program, we suspected that stereochemical control at C(2) would be problematic, given the extreme ease with which bertyadionol was known to undergo epimerization. For example, we found that treatment of authentic bertyadionol[41] even with a half-saturated solution of $NH_3$ in methanol led to immediate epimerization, followed by total decomposition upon prolonged contact. With this in mind, retrosynthetic cleavage of the C(2)-methyl group (Scheme 18), introduction of a dithiane at C(14), and oxidation of the C(7)-alcohol would generate dienone **27**, an advanced intermediate from which to stage the final assault on bertyadionol. Application of our unified strategy to **27** by disconnections at C(5,6) and at C(14,15) leads to **29** as the western synthon. The eastern hemisphere, of course, remains the same as in the casbene effort.

For closure of the macrocyclic ring, we again planned to take advantage of the intramolecular Horner–Wittig reaction. Allylic rearrangement of the C(15)-hydroxyl group either before or after macrocyclization would then introduce the C(4,15)-tetrasubstituted olefin and an oxygen function at C(3), the latter permitting eventual addition of the C(2)-methyl group.

Precedent for the proposed allylic rearrangement derives from our jatrophone program, wherein we discovered that treatment of either **31a**


3 (-) - BERTYADIONOL
27
28
WESTERN HEMISPHERE
SYNTHON
EASTERN HEMISPHERE
30
29
9

SCHEME 18.




SCHEME 19.

or **31b** with mild acid led efficiently to 1,3-transposed alcohols **32a** and **32b** (Scheme 19).

Continuing with this analysis (Scheme 18), we envisioned that cyclopentenone **30** would nicely serve as the synthetic equivalent for synthon **29**. Addition of the dianion of **9** would then afford **28**. The required cyclopentenone **30** in turn would be prepared by exploiting our $\alpha$-ketovinyl anion methodology, also developed in connection with our jatrophone[42] and cyclopentenoid antibiotic[43] program and discussed in detail in our previous contribution to *Strategies and Tactics in Organic Synthesis* (Chapter 9).[1]

Given this synthetic plan, three major structural problems were immediately discernible; two were stereochemical in nature, and the third involved the general difficulty anticipated in closing an 11-membered ring. We will first consider the potentially problematic macrocyclization. Whereas the Horner–Emmons protocol is well documented for the formation of small- and large-ring systems (i.e., $C_5$–$C_7$ and $C_{12}$–$C_{18}$),[5,44] this tactic had not been employed for medium-sized ring construction. However, as alluded to earlier, the presence of five $sp^2$ hybridized carbons, in conjunction with the cyclopropyl ring, was expected to limit the number of transannular interactions and also restrict the number of possible conformations, thereby facilitating formation of the requisite 11-membered ring.

Assuming the viability of the macrocyclization and allylic rearrangement, two stereochemical problems would require attention. In the synthetic direction, the first would be the introduction of the C(7) $\beta$-hydroxyl group. Inspection of Dreiding models suggested that the ground state of advanced intermediate **27** is best depicted by the conformation shown in Fig. 1. Peripheral approach[45] of a reducing reagent in this case would afford the undesired $\alpha$-hydroxyl at C(7) and thereby necessitate an inversion at C(7) to arrive at bertyadionol.

The second stereochemical problem would arise in introducing the C(2) methyl group with the correct $\alpha$ configuration. Here careful analysis of Fig. 1 suggested that electrophiles would approach the C(3) kinetic enolate from the $\beta$ face. Assuming this to be the case, one possible scenario for controlling

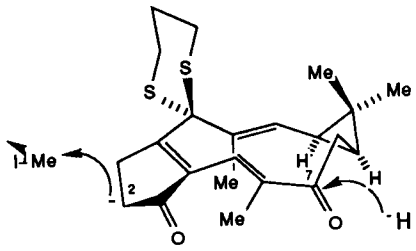


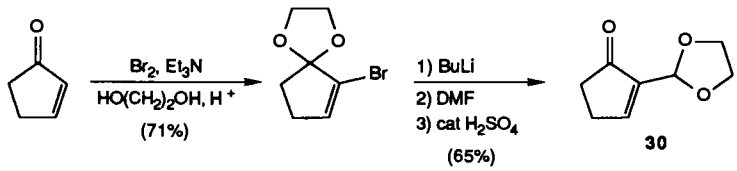

FIG. 1

the C(2) center would involve incorporation of the C(2) methyl without regard to stereochemistry, followed by regeneration of the C(3) enolate and kinetic $\beta$-protonation. If a mixture of epimers resulted, we would attempt to effect equilibration to enhance the yield of of the desired $\alpha$-isomer. There was, however, no guarantee that either tactic would prove successful. Thus, from the inception of the bertyadionol project, we recognized that introduction of the C(2) stereochemical center was at best a high-risk operation.

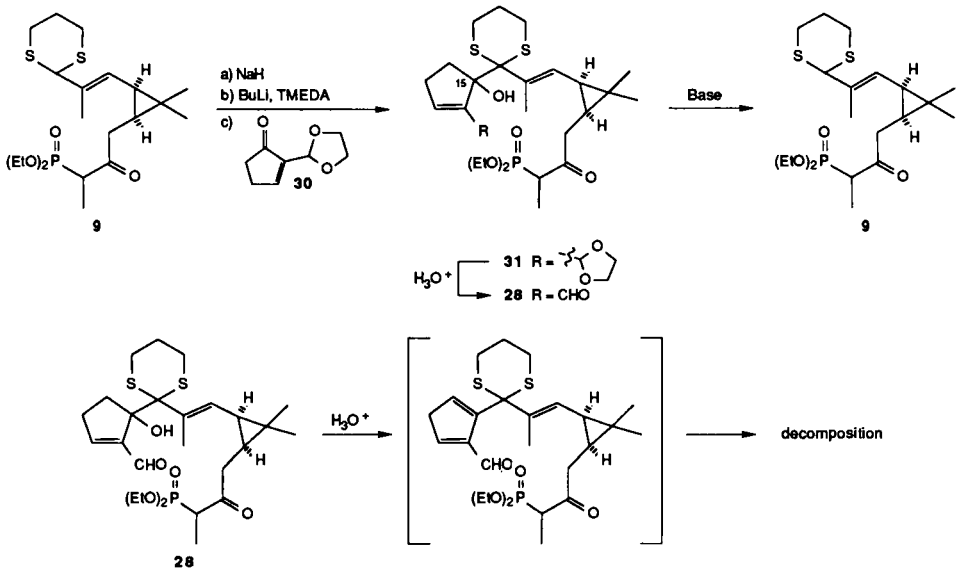
## C. THE INITIAL ASSAULT ON BERTYADIONOL

As noted, cyclopentenone **30** was envisioned as the cyclopentenyl synthon. Its preparation took advantage of the $\alpha$-ketovinyl anion methodology outlined in Scheme 20. Noteworthy here was the facile ketal–acetal interchange that occurred in the final step. The overall yield from cyclopentenone was 46%.

The dianion of **9** was then generated as in the casbene synthesis and added to cyclopentenone **30** (Scheme 21). *In situ* hydrolysis of the acetal furnished ketophosphonate **28**, which was poised for macrocyclization. Unfortunately, all attempts to effect the Emmons modification of the Wittig reaction,[25] employing a wide variety of bases, solvents, and temperature regimes, proved fruitless. The major difficulty was believed to involve the C(15) tertiary carbinol, which in the presence of base at high temperatures led to




SCHEME 20

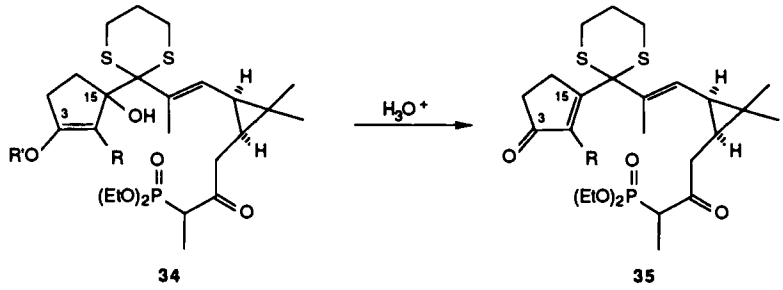



SCHEME 21

fragmentation, regenerating **9** and destroying the cyclopentenone unit. An obvious solution to this problem would be to protect the hydroxyl functionality, but this also proved problematic. In fact, all attempts to silylate or esterify alcohol **28** were totally unsuccessful. Another potential solution would be to effect the "well-precedented" 1,3-allylic alcohol transposition prior to macyclization (*vide supra*). Again, success proved elusive in that mild acid treatment led either to starting material or to elimination of the tertiary alcohol, affording an unstable cyclopentadiene system which readily decomposed. Completely frustrated by all attempts to proceed with the synthesis, we were forced to reevaluate our choice of the western hemisphere.

## D. Development of a Revised Western Hemisphere: a Major Spin-Offs from the Casbene–Bertyadionol Project

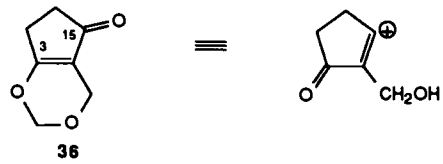
The obstacles encountered in our initial approach to bertyadionol suggested an alternative tactic. Although the carbonyl moiety in **30** served as an excellent electrophilic partner for dianion **9**, our efforts to manipulate the tertiary hydroxyl group (i.e., by protection and/or 1,3-transposition) were not fruitful. To circumvent these problems, we reasoned that an enol ether already in position at C(3) of **34** (Scheme 22) might facilitate direct introduction of the requisite C(3) carbonyl and the C(4,15)-tetrasubstituted olefin by treatment with acid. In light of this conjecture, vinylogous ester **36**




SCHEME 22

(Scheme 23) appeared ideal as an equivalent for the western synthon for bertyadionol.

Two questions required immediate attention. First, could we prepare **36** in a preparatively useful fashion; second, would the dianion of **9** add to the less electrophilic vinylogous ester carbonyl?

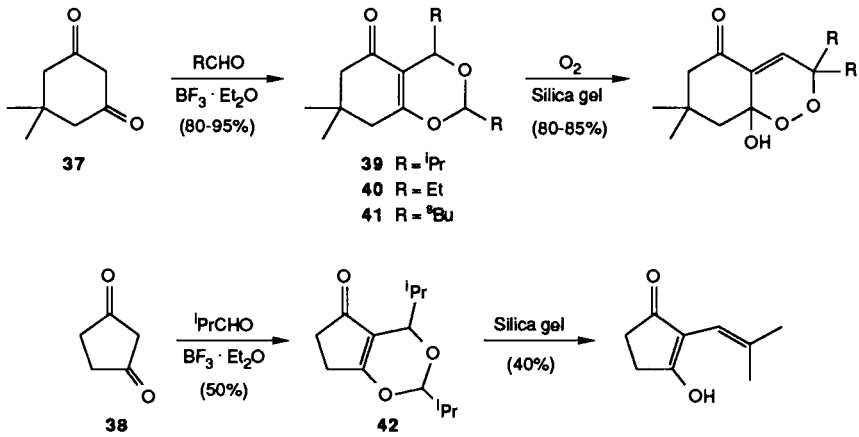



SCHEME 23

1. *The Prins Reaction of Cyclic 1,3-Diketones with Formaldehyde: An Extremely Useful Reaction*

In 1982 Crow and co-workers[46] recorded the preparation of several substituted 1,3-dioxins (**39–42**). In particular, they observed that treatment of cyclic 1,3-diketones **37** and **38** with aliphatic aldehydes in the presence of $BF_3 \cdot Et_2O$ led in good to excellent yields to substituted 1,3-dioxins (Scheme 24). However, the resultant diastereomeric mixtures were found to be inseparable, due in part to their propensity to rearrange and/or react with oxygen adsorbed on silica gel.[46]

For our purposes, we required that formaldehyde or an equivalent thereof serve as the electrophile. Toward this end, treatment of a mixture of 1,3-cyclopentanedione **38**[47] and powdered paraformaldehyde (3 equivalents) with $BF_3 \cdot Et_2O$ (0.33 equivalent) in methylene chloride at ambient temperature, according to the Crow protocol, did afford **36** as a white crystalline solid, but the yield was quite low (ca. 10%). To maximize the efficiency of the process,




SCHEME 24

a systematic investigation was undertaken; the results are illustrated in Table I. The key to improving this reaction involved use of a larger excess of paraformaldehyde, as well as increasing the $BF_3$-a2.5 $Et_2O$-to-paraformaldehyde ratio. Best results were obtained when 6 equivalents of paraformaldehyde and 3 equivalents of $BF_3 \cdot Et_2O$ were employed; under these conditions, dioxin **36** was produced in 70–75% yield. Importantly, **36** was quite stable; it could be conveniently purified via silica gel flash chromatography without noticeable reaction with oxygen (*vide supra*).

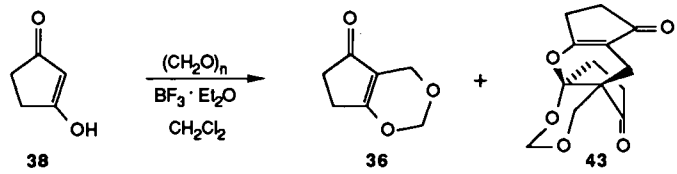
In addition to vinylogous ester **36**, a small amount (ca. 10%) of a novel crystalline propellane (**43**) was formed. The structure of the propellane, initially quite obscure on the basis of spectral data alone, was established via single-crystal X-ray analysis.[48]

Having optimized the Prins reaction with 1,3-cyclopentanedione **38**, we expanded the study to include six- and seven-membered 1,3-diketones **44** and **45**. As illustrated in Table II, application of the aforementioned conditions to 1,3-cyclohexanedione (**44**) led to the corresponding six-membered ring vinylogous ester (**46**) in 40% yield (entry 3). Again, a small amount (9%) of an analogous propellane (**47**) was obtained. A substantial improvement in the yield of **46** was realized when trioxane was substituted for paraformaldehyde. Further progress (i.e., 84% yield) was achieved when a syringe pump was employed to add the 1,3-diketone (Table II, entry 4). A modest improvement in yield (74–78%) was also noted in the case of 1,3-cyclopentanedione (**38**) when the trioxane–syringe pump protocol was employed (Table II, entry 2).

Turning next to 1,3-cycloheptanedione (**45**),[49] best results were obtained

TABLE I

PREPARATION OF 6,7-DIHYDROCYCLOPENTA-1,3-DIOXIN-5(4*H*)-one **36**: Exploratory Studies




| Entry | **38** (mmol) | $(CH_2O)_n$ (equiv) | $BF_3 \cdot Et_2O$ (equiv.) | Solvent (ml) | Yield (%) **36** | **43** |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 0.33 | 12 | 10 | — |
| 2 | 2 | 5 | 1.2 | 12 | 11 | — |
| 3 | 2 | 6.6 | 2.4 | 12 | 59 | 4 |
| 4 | 2 | 6.6 | 2.4 | 25 | 59 | 6 |
| 5 | 2 | 6.6 | 2.4 | 12[a] | 13 | — |
| 6 | 2 | 6 | 4 | 12 | 66 | 8 |
| 7 | 20 | 6 | 3 | 120 | 73 | 9 |

[a] $CH_2Cl_2Et_2O$ (1 : 1).

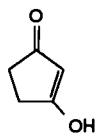
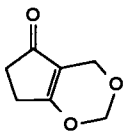
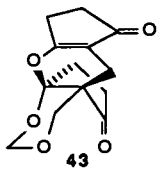
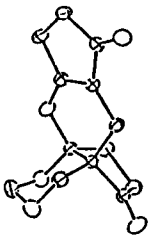
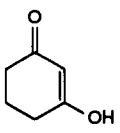
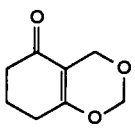
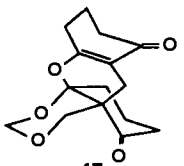
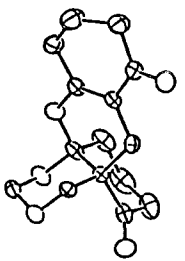
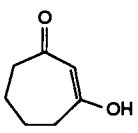
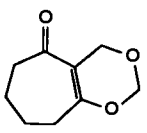
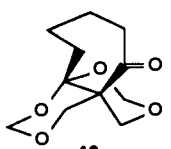
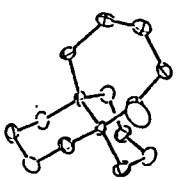
with paraformaldehyde and $BF_3 \cdot Et_2O$ (Table II, entry 5). In this case vinylogous ester **48** was obtained in 72% yield, again accompanied by a small amount of a crystalline propellane. Elemental composition data quickly indicated that the latter was not a simple analog of the previous two propellanes, but instead involved condensation of 1,3-cycloheptanedione (**45**) with 4 equivalents of formaldehyde. X-ray analysis revealed structure **49**.[48] Vinylogous ester **48** apparently undergoes a second Prins reaction, and the resultant intermediate reacts with an additional equivalent of formaldehyde.

## 2. *The Chemical Reactivity of the Dioxin Vinylogous Esters*

Having developed effective syntheses of dioxins **36**, **46**, and **48**, we set out to explore their reactivity. In view of our ongoing bertyadionol synthetic program and related efforts, we were particularly interested in two types of reactivity: (A) reductive and alkylative 1,3-carbonyl transpositions,[24] and (B) regioselective alkylation with carbon[50] and oxygen electrophiles.[51] We anticipated that such transformations, if successful, would not only prove useful for our program but also would promise general utility of the dioxin vinylogous ester system for complex molecule synthesis.

TABLE II

PREPARATION OF 1,3-DIOXIN VINYLOGOUS ESTERS.

| Entry | Substrate | Conditions[a] | Time (h) | Products | | |
|---|---|---|---|---|---|---|
| |  **38** | | |  **36** |  **43** | ≡  |
| 1 | | A | 38 | 73% | 9% | |
| 2 | | B | 30 | 78% | 4% | |
| |  **44** | | |  **46** |  **47** | ≡  |
| 3 | | A | 32 | 40% | 9% | |
| 4 | | B | 18 | 84% | 16% | |
| |  **45** | | |  **48** |  **49** | ≡  |
| 5 | | A | 2 | 72% | 9% | |
| 6 | | B | 5 | 49% | 44% | |

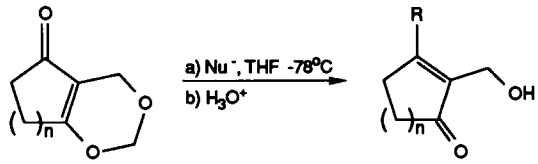
[a] Conditions A: Paraformaldehyde (6 equiv) and $BF_3 \cdot Et_2O$ (3 equiv), diketone 0.16 *M* in $CH_2Cl_2$. Conditions B: Trioxane (6 equiv) and $BF_3 \cdot Et_2O$ (3 equiv), diketone 0.02 *M* in $CH_2Cl_2$.

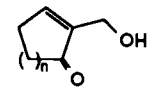
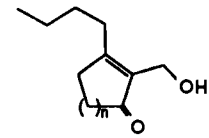
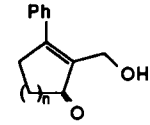
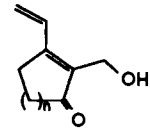
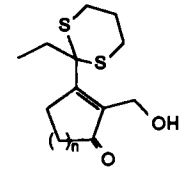
### 3. *Reductive and Alkylative 1,3-Carbonyl Transpositions: An Important Element of the Revised Bertyadionol Strategy*

Reductive and alkylative 1,3-carbonyl transpositions of vinylogous esters are well precedented.[24,50] To explore the feasibility of such processes with dioxins **36**, **46**, and **48**, we selected a number of readily available nucleophiles. Our results are listed in Table III. Several comments are in order.

TABLE III

REDUCTIVE AND ALKYLATIVE 1,3-CARBONYL TRANSPOSITION OF 1,3-DIOXIN VINYLOGOUS ESTERS.



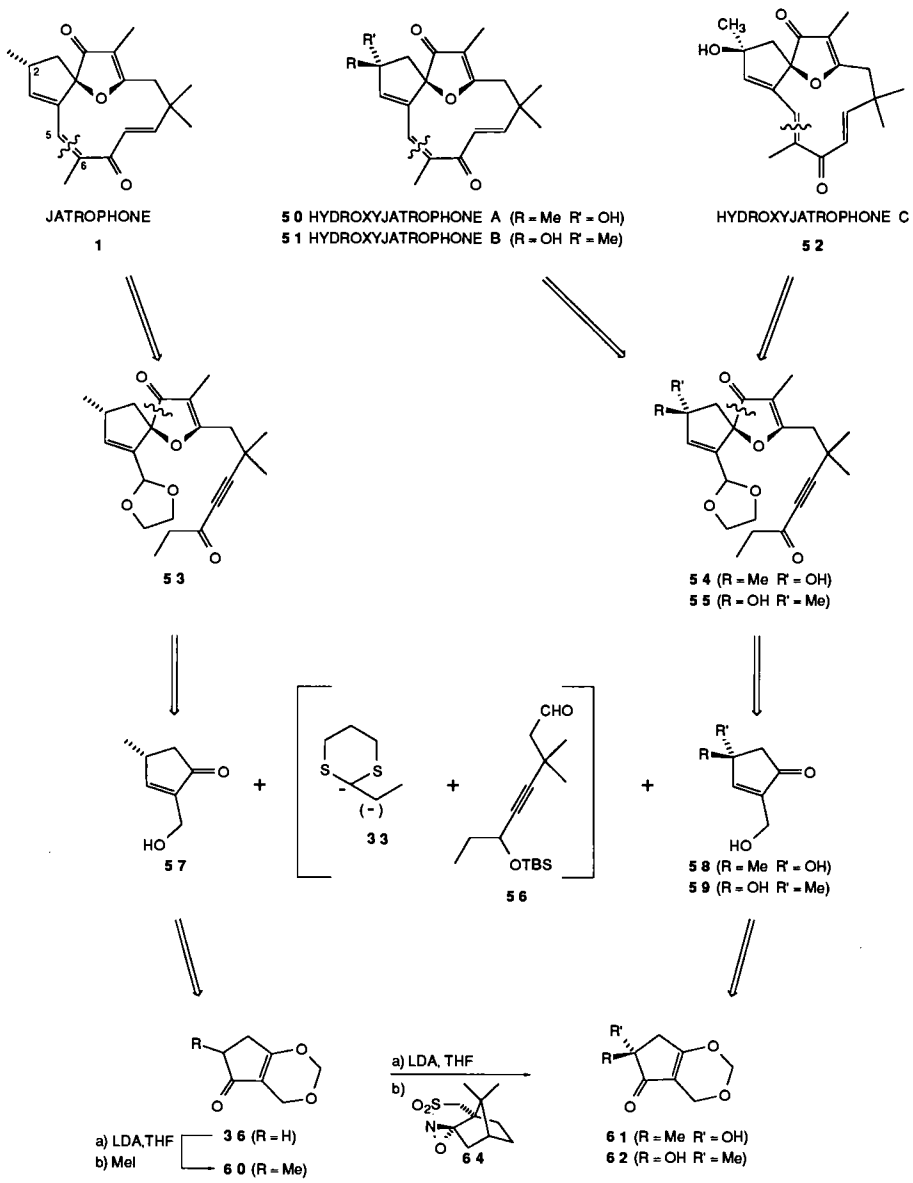

| Entry | Nucleophile | *n* | Yield (%) | Product |
|---|---|---|---|---|
| 1 | DIBAL | 1 | 91 |  |
| 2 | | 2 | 91 | |
| 3 | | 3 | 84 | |
| 4 | LAH | 1 | 81 | |
| 5 | BuLi | 1 | 95 |  |
| 6 | | 2 | 66 | |
| 7 | | 3 | 89 | |
| 8 | PhLi | 1 | 78 |  |
| 9 | | 2 | 93 | |
| 10 | | 3 | 87 | |
| 11 | | 1 | 94 |  |
| 12 |  | 2 | 76 | |
| 13 | | 3 | 86 | |
| 14 |  | 1 | 81 |  |
| 15 | | 2 | 93 | |
| 16 | | 3 | 74 | |

First, a variety of simple $\beta$-substituted or unsubstituted $\alpha$-hydroxymethyl enones can be prepared efficiently in two operations from the corresponding 1,3-diketones. The economy of this approach should be contrasted with the multistep procedures previously developed in our laboratory for the construction of simple $\alpha$-hydroxymethyl enone systems (e.g., 2-hydroxymethylcyclopentenone and -cyclohexenone).[52] Second, entries 11–13 highlight a variety of dienes now readily available for possible use in Diels–Alder reactions. Third, acyl anion equivalents (see entries 14–16) provide access to latent 1,4-enedione units, the latter encountered in the structure of bertyadionol and related natural products. Finally, it should be emphasized that the specific nucleophiles chosen for this study represent only a fraction of those that could be employed.

### 4. *The Jatrophone Problem Revisited: A Synthetic Strategy for the Hydroxyjatrophones A, B, and C*[5]

During the course of the above diversion, we realized that vinylogous ester **36** held considerable potential as starting material for other synthetic ventures ongoing in our laboratory. As illustrated from the retrosynthetic perspective in Scheme 25, vinylogous esters **60**, **61**, and **62** could serve as starting materials for jatrophone[12] and the hydroxyjatrophones.[53] Note again the common theme of a unified synthetic strategy. Specifically, carbon–carbon bond disconnection at the C(5,6) olefin of each jatrophone affords a similar 3(2*H*) furanone (i.e., **53**, **54**, or **55**). We envisioned that these advanced intermediates could arise via addition of a propionyl anion synthon (e.g., **33**) to an appropriately protected cyclopentenone **57**, **58**, or **59**. In the forward sense, unmasking of the ketone followed by condensation with aldehyde **56** would then afford, after further functional group interchange, advanced intermediates **53–55**. Macrocyclization exploiting the intramolecular version of the Mukaiyama acetal condensation, followed by elimination of the elements of ethylene glycol, would then afford the jatrophone targets. For the hydroxyjatrophones, key elements of this synthetic strategy derive from the total synthesis[1] already completed in our laboratory. The requisite enantiomeric hydroxymethyl cyclopentenones would be accessible via hydride reduction of the suitably alkylated 1,3-dioxin vinylogous esters **61** and **62**.

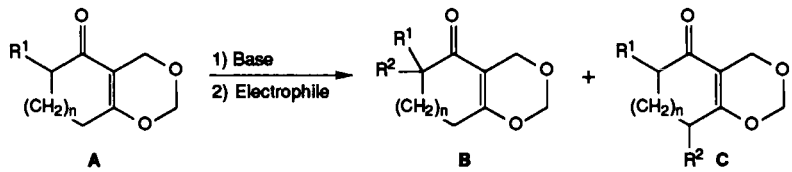
In light of this analysis, we examined the reactions of the enolates derived from vinylogous esters **36**, **46**, and **48**. As electrophiles we selected methyl iodide and the Davis oxaziridines, to introduce respectively a carbon and oxygen substituent at C(2) (jatrophone numbering).[51] Our results are outlined in Table IV; yields, although not optimized, were good. Best results were obtained by using THF as solvent. Importantly, the regiochemical


JATROPHONE
1
50 HYDROXYJATROPHONE A (R = Me R' = OH)
51 HYDROXYJATROPHONE B (R = OH R' = Me)
HYDROXYJATROPHONE C
52
53
54 (R = Me R' = OH)
55 (R = OH R' = Me)
57
33
56
58 (R = Me R' = OH)
59 (R = OH R' = Me)
a) LDA,THF
b) MeI
36 (R = H)
60 (R = Me)
a) LDA, THF
b)
64
61 (R = Me R' = OH)
62 (R = OH R' = Me)

SCHEME 25.

TABLE IV

ALKYLATION OF VINYLOGOUS ESTERS **36**, **46**, **48**.



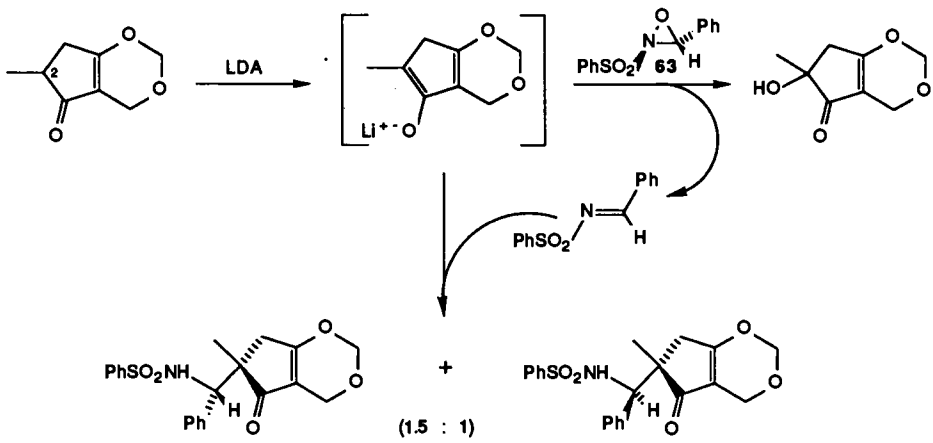

**A** **B** **C**

| Entry | $n$ | $R^1$ | Base | Solvent | Electrophile | Product $R^2$ | Yield (%) B | Yield (%) C |
|---|---|---|---|---|---|---|---|---|
| 1 (**36**) | 0 | H | LDA | THF | MeI | Me | 61 | 3 |
| 2 | 0 | H | NaHMDS | THF | MeI | Me | 53 | <5 |
| 3 | 0 | H | LDA | DME | **63** | OH | 33[a] | 6[a] |
| 4 | 0 | H | NaHMDS | THF | **63** | OH | 35[a] | 36[a] |
| 5 | 0 | Me | LDA | THF | **63** | OH | 51 | 0 |
| 6 | 0 | Me | LDA | DME | **63** | OH | 57 | 0 |
| 7 | 0 | Me | NaHMDS | THF | **63** | OH | 4 | 76 |
| 8 | 0 | H | LDA | THF | **64** | OH | 45[a] | 4[a] |
| 9 | 0 | Me | LDA | THF | **64** | OH | 68 | 4 |
| 10 | 0 | Me | NaHMDS | THF | **64** | OH | 3 | 28 |
| 11 (**46**) | 1 | H | LDA | THF | MeI | Me | 78 | 0 |
| 12 | 1 | H | LDA | DME | **63** | OH | 58 | 0 |
| 13 | 1 | H | NaHMDS | THF | **63** | OH | 49 | 37 |
| 14 (**48**) | 2 | H | LDA | THF | MeI | Me | 73 | 0 |
| 15 | 2 | H | LDA | DME | **63** | OH | 54 | 0 |
| 16 | 2 | H | NaHMDS | THF | **63** | OH | 51 | 37 |

[a] Based on recovered starting material

outcome was found to depend on both the choice of amide base and the substitution pattern of the vinylogous ester. For example, treatment of **36**, **46**, or **48** with 1.1 equivalents of LDA in THF led to the presumed kinetic enolate (i.e., $\alpha'$), which upon reaction with either methyl iodide or the Davis oxaziridines afforded the corresponding $\alpha'$ derivative as the major product. In the case of **36** only, small amounts (3–5%) of both $\gamma$-monomethylated and $\alpha,'\gamma$-dimethylated products were obtained. Surprisingly, lithium bis-(trimethylsilyl)amide resulted in essentially the same $\alpha' : \gamma$ ratio (entry 2), whereas use of sodium bis(trimethylsilyl)amide led to a significant increase in $\gamma$-alkylation. High $\gamma$-selectivity was observed only when the $\alpha$-position was substituted; entry 7 ($R^1$ = Me, $n$ = 0) best illustrates this point.

In several cases (entries 5, 6, 12, and 15), the hydroxylations were complicated by a side reaction involving addition of a vinylogous ester enolate to the sulfonimide derived from 2-(phenylsulfonyl)-3-phenyloxa-

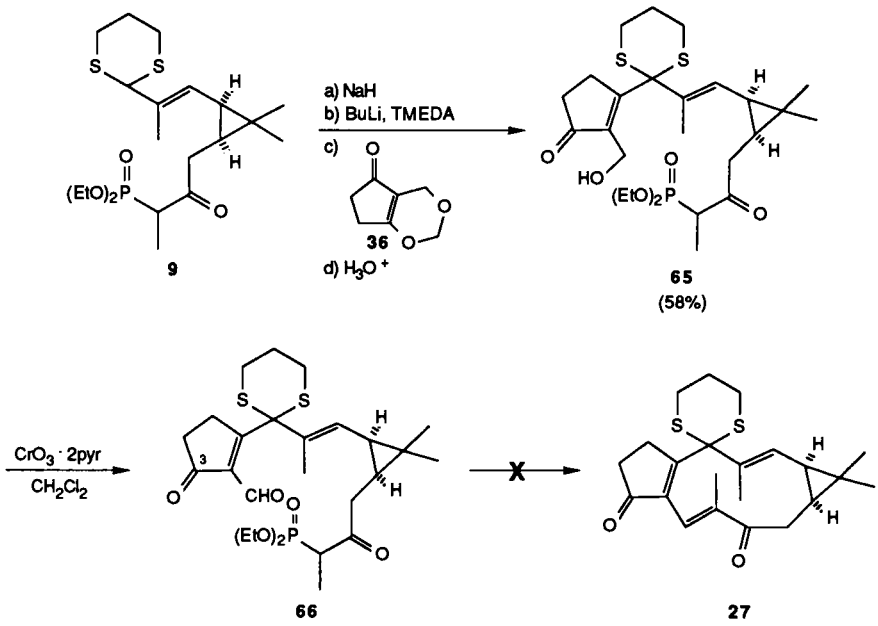



SCHEME 26

ziridine (**63**), affording a diastereomeric mixture (ca. 1 : 1) of imino–aldol products (Scheme 26). In one example (entry 6), the assigned structures of both diastereomers of these imino–aldol adducts were confirmed by single-crystal X-ray analyses.[48] This minor complication can be conveniently circumvented through use of the camphorsulfonyl oxaziridine **64**, which as Davis[54] has noted, does not give rise to the amino–aldol side products in enolate hydroxylations (entries 8, 9, 10). Unfortunately, only low levels of asymmetric induction were observed with this homochiral reagent.

### E. Return to the Bertyadionol Synthesis: A Viable Union of the Eastern and Western Hemispheres

With ample quantities of the now revised western hemisphere (**36**) in hand, we turned again to the bertyadionol synthesis. As before, generation of the dianion of **9** followed by addition to **36** resulted in a 1,2-adduct. Although this intermediate could be isolated and characterized, it was expedient to expose the reaction mixture to mild acid, thereby directly generating **65** (58% yield), which possessed the requisite C(3) carbonyl and tetrasubstituted olefin functionalities (Scheme 27). Collins oxidation[36] of the allylic hydroxyl provided the functionality required for the Horner–Emmons[25] macrocyclization. However, progress again was thwarted; aldehyde **66** proved to be quite unstable, as even silica gel chromatography led to its complete destruction. Attempted macrocyclization of unpurified material was also unsuccessful. The problem at this juncture appeared to be the considerable susceptibility of the cyclopentenone–aldehyde system to nucleophilic attack.

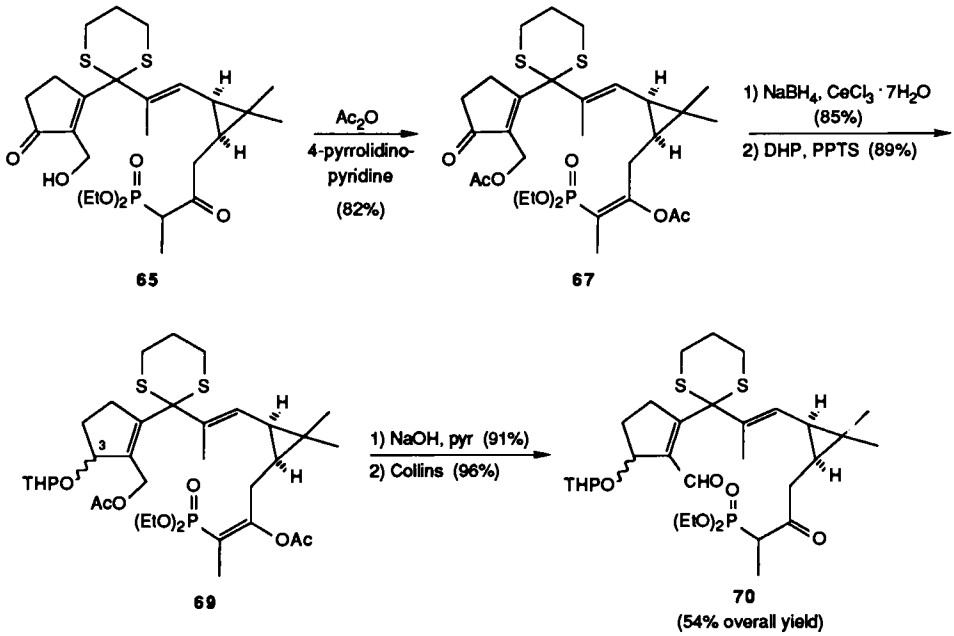



SCHEME 27

To reduce the propensity for nucleophilic addition, the oxidation state at C(3) of **66** was adjusted. This required a five-step synthetic sequence (Scheme 28), beginning with acetylation of **65** to generate diacetate **67**. The latter was subjected to Luche reduction ($NaBH_4$, $CeCl_3 \cdot 7H_2O$),[38] followed by protection of the resultant hydroxyl group as the tetrahydropyranyl ether (DHP, PPTS), to afford a mixture of diastereomeric allylic ethers (**69**). We presumed that the mixture at C(3) would be of little consequence because this carbon was destined to become a carbonyl in the final target. Hydrolysis of the acetates and Collins oxidation generated enal **70**, which was poised for macrocyclization. This five-step sequence afforded **70** in 54% overall yield.

## F. Macrocylization: A Difficult Transformation

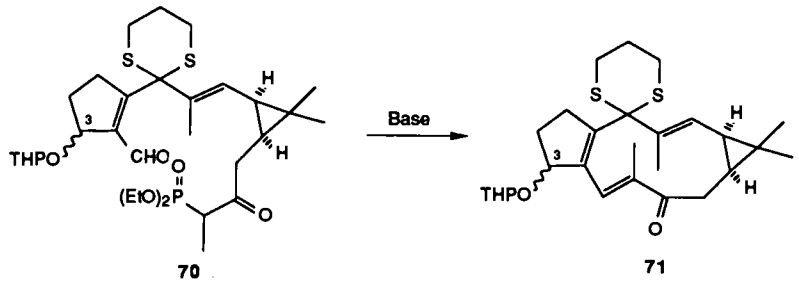
After moderating the nucleophilic susceptibility of the cyclopentenyl system, we again turned to the macrocyclization. The question we confronted was whether the increased stability of the enal system would now permit us to overcome inherent transannular ring strain (enthalpy) and entropy problems associated with medium-sized ring construction. After considerable experimentation, we found that ring closure was possible; the best conditions




SCHEME 28

TABLE V

ATTEMPTED MACROCYCLIZATIONS.

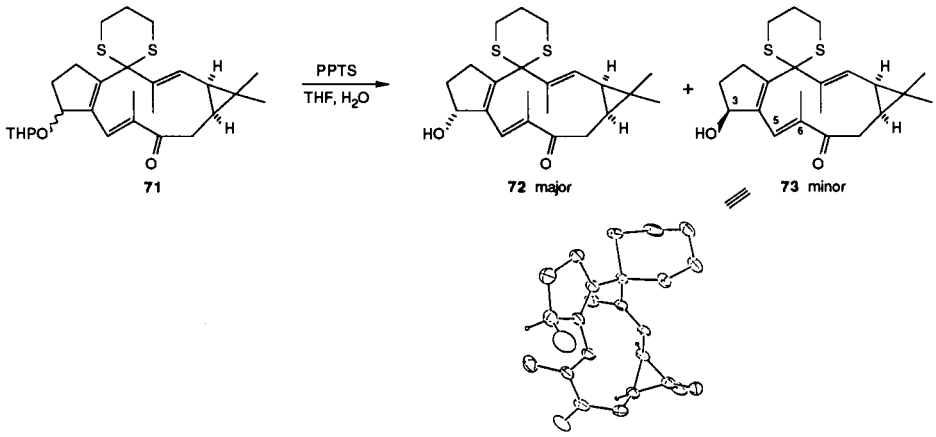



| Conditions | Results |
|---|---|
| 1) NaH, 45–50°C, PhMe, 9 hours add'n | 28–42% |
| 2) LiO$^i$Pr, THF, HMPA | Decomposition |
| 3) DBU, LiCl, MeCN | <5% plus by-products |
| 4) NaH, LiCl, PhMe | 18% |
| 5) NaOH (2 equiv), 50°C, 14 hours | 13.3% |

involved slow addition (syringe pump) of enal **70** to an excess (5 equivalents) of sodium hydride in warm toluene over a 9-hour period. The only product isolated was enone **71**; the yield ranged from 28 to 42%. Table V describes our attempts to improve the yield. In general, enal **70** also proved to be quite unstable, especially to base.

One notable fact observed with the NaH–toluene protocol was that the C(3) diastereomers of **70** did not undergo macrocyclization with equal efficiency. This difference in reactivity became apparent when we observed that the original 1 : 1 diastereomeric mixture at C(3) afforded a 5 : 1 mixture at C(3) in **71** (Scheme 29); that is, hydrolysis of the tetrahydropyran ether (PPTS, aqueous THF, 93%) and chromatographic separation afforded a 5 : 1 mixture of alcohols **72** and **73**. The minor isomer (**73**) crystallized from EtOAc : hexane (mp 166–171°C decomp.), to produce a crystal suitable for single-crystal X-ray analysis.

The derived ORTEP plot[48] illustrates two important points. First, it confirmed that we had indeed closed the 11-membered ring and that the requisite *E*-configuration at C(5,6) was secure. Second, it demonstrated that the minor product possesses the $\beta$-configuration at C(3). We presume that the $\beta$-THP ether in **70** sterically hinders ring closure and that unproductive pathways intervene to change the C(3) diastereomeric ratio.

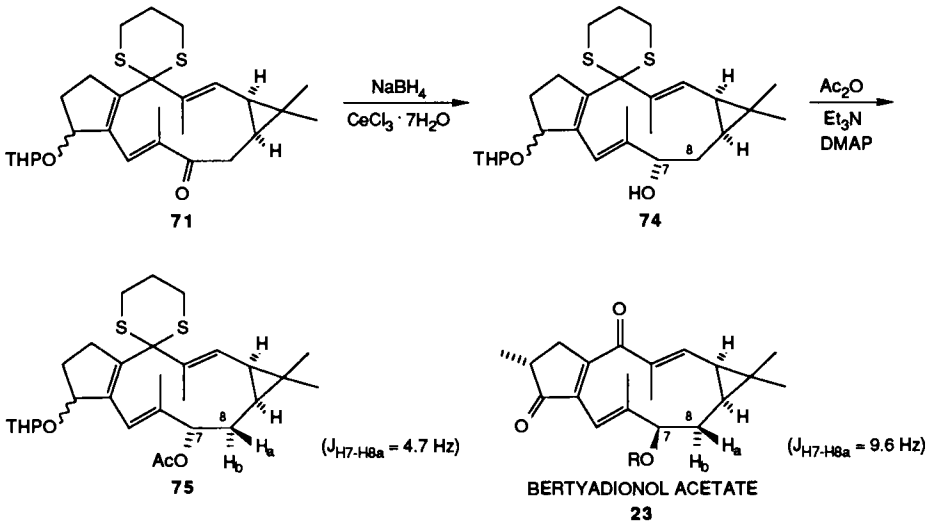



SCHEME 29

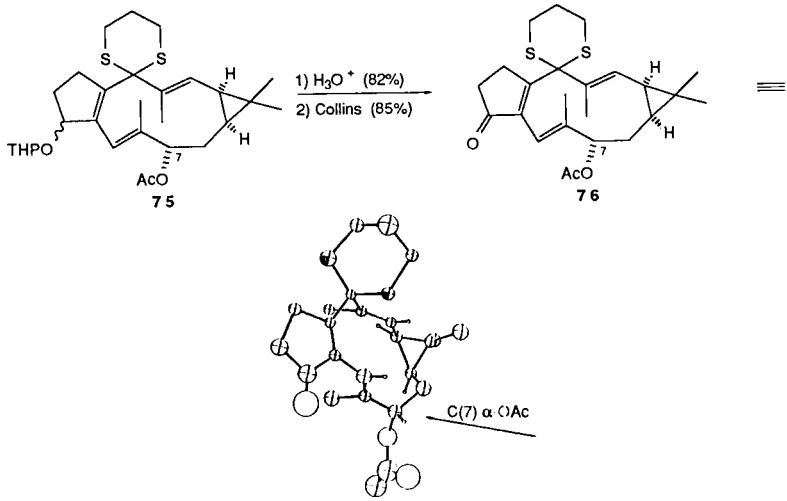
At this point we took the opportunity to examine the enantiomeric purity of our advanced intermediates. To this end, alcohol **72** was converted to the corresponding Mosher esters[30] and the latter were analyzed by both $^{19}F$ NMR and HPLC. The indicated enantiomeric purify of 88–92% was commensurate with that of the starting (−)-*cis*-chrysanthemic acid.

## G. INTRODUCTION OF THE C(7) β-HYDROXYL GROUP: AN EXERCISE IN MACROCYCLIC CONFORMATIONAL ANALYSIS

To complete the synthesis of bertyadionol, three major operations were required: introduction of the C(7) hydroxyl, addition of the C(2) methyl group, and hydrolysis of the dithiane moiety. The first two required stereochemical control. As indicated earlier, generating the β-configuration at C(7) would necessitate stereoselective reduction of the carbonyl group. However, inspection of the X-ray structure of **73** suggested that peripheral attack[45] by hydride at C(7) would generate the undesired α-carbinol, as previously anticipated from molecular models. In the event, Luche reduction ($NaBH_4$, $CeCl_3 \cdot 7H_2O$)[38] of enone **71** afforded a single C(7) alcohol in 92% yield, which in turn furnished acetate **75** in 92% yield (Scheme 30). The stereochemistry at C(7) was tentatively assigned as α by comparison of the C(7) methine coupling constant in **75** ($J_{7-8a}$ = 4.7 Hz) with the value reported by Jefferies for the C(7) acetate of natural bertyadionol ($J_{7-8a}$ = 9.6 Hz). To confirm this assignment, we again sought a crystalline compound for X-ray analysis. Toward this end, hydrolysis of the THP ether in **75** and Collins oxidation of the derived alcohol afforded **76** (64% yield for the two steps) as a crystalline solid (mp 188–190°C; Scheme 31). The crystal structure[48] confirmed that the C(7) hydroxyl indeed possessed the α-configuration.




SCHEME 30

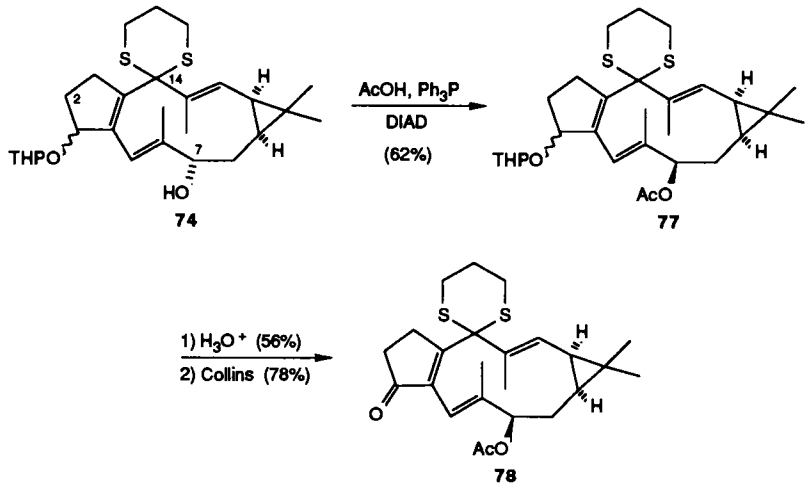



SCHEME 31

## H. THE BERTYADIONOL END GAME: DEVELOPMENT OF A VIABLE DITHIANE HYDROLYSIS

Given the undesired α-configuration at C(7) in **74**, inversion of the allylic hydroxyl group via a Mitsunobu reaction[55] appeared to be the obvious solution. However, it was not clear which carboxylic acid would prove optimal for this process, because of the known instability of bertyadionol and the potential problems associated with subsequent ester group hydrolysis (*vide infra*). We also anticipated that hydrolysis of the dithiane moiety at C(14) could be problematic, and as noted earlier, we recognized that stereochemical problems could arise in the introduction of the C(2) methyl group. Accordingly, we decided first to synthesize C(2)-normethyl bertyadionol, an exercise which would require only five functional group manipulations: (1) Mitsunobu inversion of the α-C(7)-carbinol, (2) hydrolysis of the THP ether, (3) oxidation of the C(3) hydroxyl to a ketone, (4) hydrolysis of the dithiane moiety, and (5) removal of the ester unit at C(7).

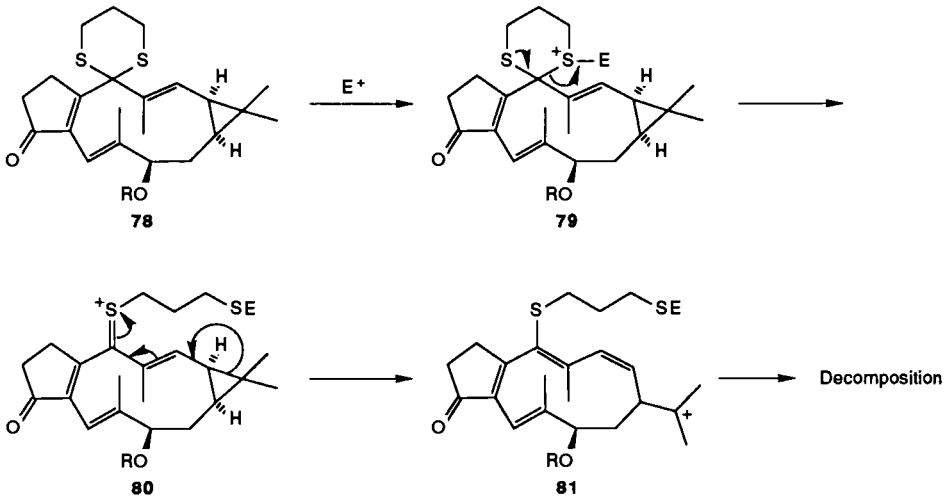
To explore the feasibility of this end game, and in particular to evaluate the carboxylic acids that might be employed in the Mitsunobu reaction, we prepared the benzoate of natural bertyadionol[41] and examined its hydrolysis. This effort proved remarkably unsuccessful. Fortunately, bertyadionol acetate[41] proved more amenable to hydrolysis. In this case, treatment with excess potassium carbonate in MeOH, carefully maintaining the reaction




SCHEME 32

temperature between −4 and 0°C for 1.25 hours, led in 55% yield to a mixture of (−)-bertyadionol and 2-epibertyadionol, in what we believed to be the thermodynamic ratio (45 : 55). We concluded that acetic acid would be suitable for use in the Mitsunobu reaction. In the event, treatment of alcohol **74** with dry acetic acid, triphenylphosphine, and diisopropyl azodicarboxylate afforded acetate **77** in 62% yield (Scheme 32). Of course, the material was still a diastereomeric mixture at C(3). To rectify this problem, we first hydrolyzed the THP ether, carefully avoiding prolonged exposure to acid, which leads to elimination of the C(3) hydroxyl. Collins oxidation[36] then generated enone **78** as a single compound in 43% yield for the two steps. Comparison of the C(7)-methine proton coupling constant ($J_{7-8a}$ = 9.6 Hz) strongly suggested that the C(7) hydroxyl group now possessed the required $\beta$-configuration.

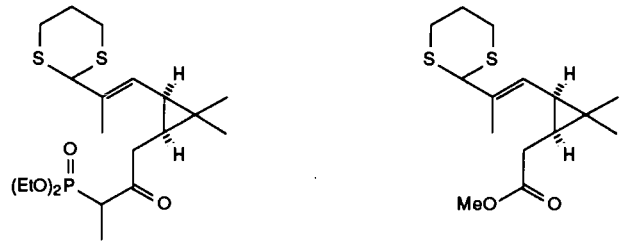
Having established that the acetate of bertyadionol could be hydrolyzed and that the C(7) hydroxyl in **74** could be inverted, we turned to the hydrolysis of the C(14) dithiane unit. Again the synthesis ran into a major impasse. All attempts to hydrolyze the dithiane, which encompassed the use of most, if not all, of the known procedures (ca. 23),[56] proved useless! Similar efforts to remove the dithiane unit in selected intermediates also failed dismally. It quickly became evident that the problem was once again related to the generation of a carbocation at C(14), which was vinylogously $\alpha$ to the cyclopropane ring (i.e., a cyclopropyl carbinyl system). The scenario depicted in Scheme 33 best explained our results and suggested a possible solution. Initial coordination of various Lewis acids with the sulfur atom

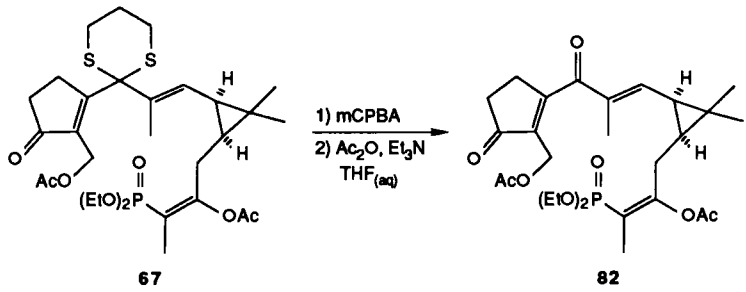



SCHEME 33

leads to a thionium ion **80**. The latter, before it can be trapped by water, undergoes cyclopropyl ring opening to generate the tertiary carbocation **81**, leading to decomposition.

To rectify this problem, it would be necessary to find a nucleophile that could intercept transient cation **80** before cyclopropyl ring opening could occur. Intramolecular rearrangements are often faster than their intermolecular counterparts; accordingly, we recognized that our best prospects for success would involve the use of an *intramolecular* trapping agent. For initial studies, we required an appropriate model system. Clearly, the best "model" system would be **78** itself; this material, however, was quite precious. On the other other hand, ketophosphonate **9** and thioacetal methyl ester **15** could be obtained in gram quantities, but these did not appear to be particularly good model systems in that they did not possess the latent cross-conjugated $\pi$-system found in **78**. A better choice appeared to be





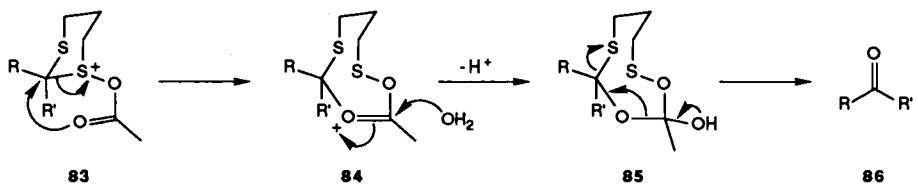

SCHEME 34

diacetate **67**, which was readily available in gram quantities and also possessed the desired $\pi$-array.

We were by this time not unaware that dithiane monosulfoxides undergo hydrolysis more readily than the corresponding parent dithianes.[56] Particularly attractive here was the notion of exploiting the sulfoxide oxygen for attachment of a nucleophilic unit which might intercept the thionium ion prior to cyclopropyl ring opening. To explore this scenario, we subjected **67** to the "Pummerer-like" conditions[57] of $Ac_2O$, $Et_3N$, and aqueous THF (Scheme 34). Having by now experienced several months of disappointment, we were delighted to obtain enedione **82** in 55–60% yield.

Mechanistically the reaction pathway outlined in Scheme 35 nicely accommodates this result. First, the monosulfoxide is activated by O-acetylation, thereby weakening the C—S $\sigma$-bond. Anchimeric assistance by the second sulfur atom leads to the thionium ion, which is rapidly captured *intramolecularly* by the resident acetyl group, thereby suppressing entry into the vinylogous cyclopropyl carbinyl cation manifold. In effect, this operation rapidly removes the positive charge from the bertyadionol skeleton. Capture of the resultant acylium ion by water then leads to hemi-ortho ester **85**, which can collapse as illustrated to afford ketone **86**.

In an attempt to improve this dithiane hydrolysis protocol, the reaction conditions were systematically varied. Changing the solvent from dioxane to DME and then to acetonitrile increased the solvent dielectric constant,




SCHEME 35

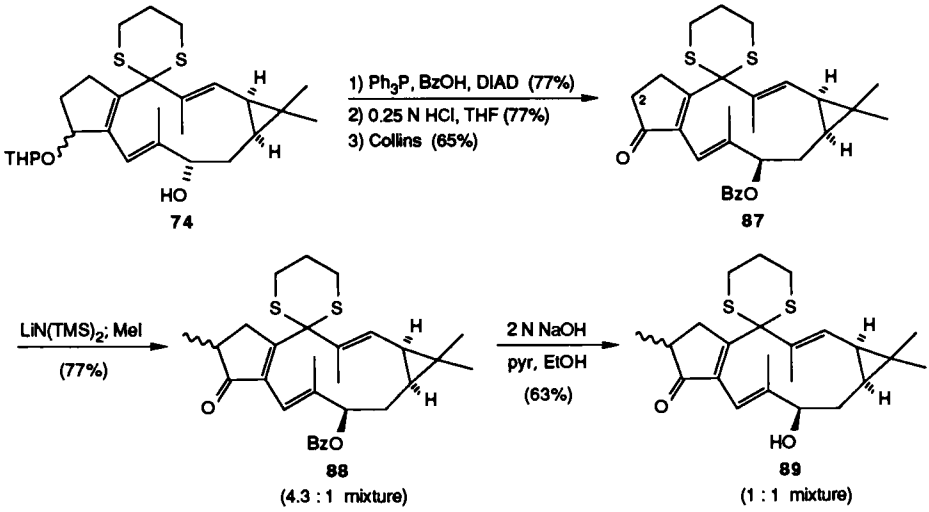
whereupon the overall yield of the reaction diminished. Triethylamine and water were both found to be essential; exclusion of either prevented hydrolysis. Finally, changing the electrophilic reagent from acetic anhydride to either trifluroacetic anhydride or methyl chloroformate resulted only in decomposition of the starting material.

## I. Application of the Dithiane Hydrolysis Protocol: Completion of the (−)-Bertyadionol Synthetic Venture

Nearly all major synthetic endeavors are continually plagued with the problem of material advancement, and decisions regarding model studies, analog systems, and reevaluation of goals must be made constantly. At this juncture we were faced with such a choice. Given the value of our advanced material, in conjunction with the fact that our "end game" now appeared feasible, we decided to abandon the synthesis of the model normethyl bertyadionol and proceed with the synthesis of the natural product. One problem remained: introduction of the C(2) methyl group. In this context, we were particularly concerned about possible deprotonation of the acetate unit under the strongly basic conditions required for C(2) alkylation. A tactical solution would involve substitution of benzoic acid for acetic acid in the Mitsunobu reaction. Experimentally, benzoic acid often affords higher yields and is easier to handle. Furthermore, the derived benzoate would not posses acidic protons. We were, of course, cognizant of our inability to convert bertyadionol benzoate to bertyadionol, which might necessitate a benzoate–acetate interchange late in the synthesis. On the other hand, it might be possible to remove the benzoate group prior to dithiane hydrolysis. No information concerning the feasibility of the latter maneuver, however, was available.

In the event, the change from acetic to benzoic acid proved highly beneficial. Indeed, the enhanced stability of the benzoate increased the yield of every reaction. For example, the Mitsunobu[55] inversion proceeded in 77% yield, and the hydrolysis of the THP ether and oxidation of the allylic alcohol afforded **87** in a combined yield of 65% (Scheme 36).

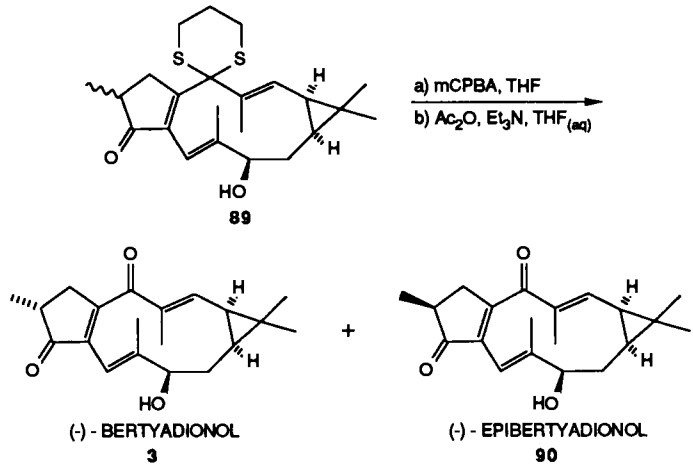
Turning to the introduction of the C(2) methyl group, kinetic deprotonation of the C(3) carbonyl with $LiN(TMS)_2$ (THF, −78°C), followed by alkylation with methyl iodide, generated a 4.3 : 1 mixture of monomethylated products (**88**). The major epimer was assumed to possess the $\beta$-configuration, as originally suggested by the conformation in Fig. 1. However, we did not attempt to assign the C(2) stereochemistry unequivocally, inasmuch as the conditions required for hydrolysis of the benzoate ester were also expected to epimerize the C(2) center, assuming that the hydrolysis could be effected at all. Fortunately, treatment of **88** with sodium hydroxide and pyridine in ethanol then gave a 1 : 1 diastereomeric mixture of allylic




SCHEME 36

alcohols (**89**). Separation of this mixture was likewise not attempted, because the conditions for dithiane removal would again almost certainly re-epimerize the C(2) methyl group.

At this point we were hopeful, but not certain, that the free hydroxyl at C(7) would not adversely affect hydrolysis of the C(14) dithiane moiety. To our delight, oxidation of **89** with *m*-CPBA, followed by treatment with a mixture of acetic anhydride, triethylamine, and aqueous THF for 25 hours at 40°C, afforded bertyadionol and epibertyadionol as a 45 : 55 diastereomeric mixture (Scheme 37). The yield ranged from 28 to 37%. Separation by




SCHEME 37

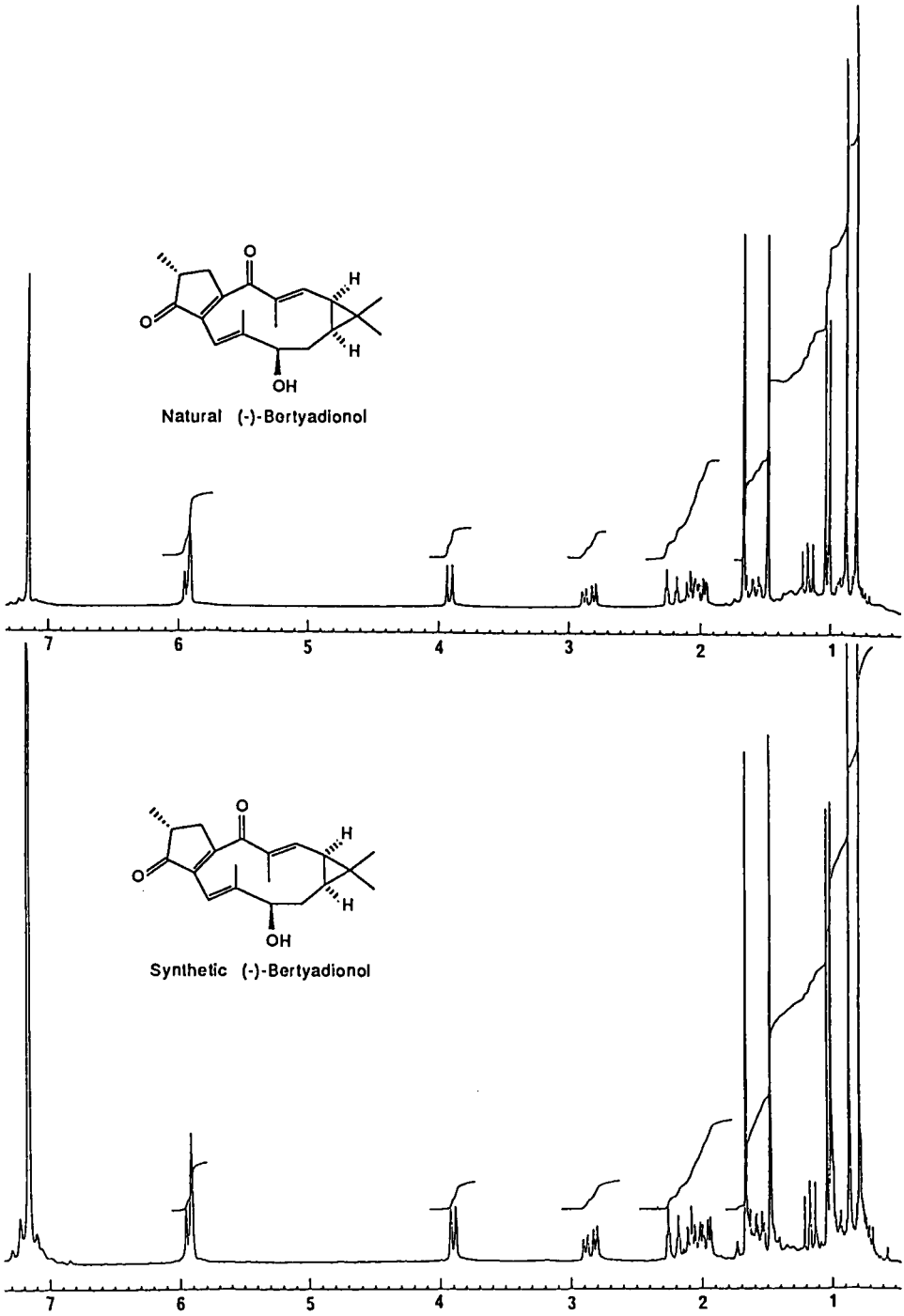



FIG. 2. Comparison of synthetic and natural (−)-bertyadional, 250-MHz $^1$H NMR.

HPLC afforded pure (−)-bertyadionol, identical in all respects ($^1$H NMR, TLC, HPLC, mp, mmp, and GC/MS) with an authentic sample of natural material kindly provided by Professor Jefferies.[41] The 250-MHz $^1$H NMR spectra of both synthetic and natural bertyadionol are illustrated in Fig. 2.

## VI. Summary

In this chapter we recorded the evolution of a unified synthetic strategy, which to date has led to the total synthesis of (−)-casbene and (−)-bertyadionol, the latter the first lathyrane diterpene to yield to total synthesis. Of particular interest from the strategic viewpoint is the rapid assembly of the carbon skeletons, in conjunction with the use of (−)-*cis*-chrysanthemic acid to deliver the targets in homochiral form. In the bertyadionol synthesis, major tactical problems were encountered in the intramolecular ketophosphonate construction of the 11-membered ring and in removal of the dithioketal unit employed to couple the eastern and western hemispheres. Efforts to exploit this unified strategy for the synthesis of the jolkinols and other compounds in this class will require reevaluation of these tactics. Progress toward these objectives will be reported in due course.

## Acknowledgments

The senior author is greatly indebted to the many students and postdoctoral colleagues whose dedication and enthusiasm for chemistry are best illustrated by the results recorded in this chapter. Foremost here were Michael Malamas, Tetsuya Maeda, Masashi Ohba, and Andrew T. Lupo, Jr. who contributed greatly to our overall research program, and Paul Sprengeler, who assisted in the preparation of this chapter. I also thank Professor Christopher S. Shiner (University of Colorado) for his critical reading and helpful suggestions.

It is a pleasure to acknowledge the continuing support of the National Institutes of Health (National Cancer Institute and the Institute of General Medical Sciences) and the National Science Foundation (Chemical Instrumentation Program). Finally, I wish to thank Drs. George Furst, Patrick Carroll, John Dykins, and John Yates, the directors of the University of Pennsylvania NMR, X-ray, MS, and computer facilities, for their generous help.

## References

1. Smith, A. B., III. *in* "Strategies and Tactics in Organic Synthesis," Lindberg, T., Ed; Academic Press: New York, 1984; pp. 224–254.
2. Malamas, M.; Maeda, T. Dorsey, B. D. Unpublished results.
3. Smith, A. B., III; Dorsey, B. D.; Visnick, M.; Maeda, T.; Malamas, M. S. *J. Am. Chem. Soc.* **1986,** *108*, 3110.
4. Smith, A. B., III; Dorsey, B. D.; Ohba, M.; Lupo, A. T. Jr.; Malamas, M. *J. Org. Chem.*, (in press).
5. *Note Added in Proof.* Since submission of this manuscript, we have successfully completed the first stereocontrolled total synthesis of (+)-hydroxyjatrophone B (**51**), exploiting the

synthetic strategy outline here. A complete account of this effort, as well as progress toward the total synthesis of hydroxyjatrophones A and C (**50** and **52**) will be forthcomming.
6. Maeda; T. Unpublished results.
7. Hecker, E. *Naturwissenschaften* **1967,** *54*, 282; Hecker, E.; Bartsch, H.; Bresch, H.; Gschwendt, M.; Harle, E.; Kreibich, G.; Kubinyi, H.; Schairer, H. U.: Szezpanski, C. von; Thielmann, H. W. *Tetrahedron Lett.* **1967,** p. 3165; Hecker, E.; Schmidt, R. *Prog. Chem. Org. Nat. Prod.* **1974,** *31*, 377.
8. Crombie, L.; Games, M. L.; Pointer, D. J. *J. Chem. Soc. C* **1968,** p. 1347.
9. (a) Robinson, D. R.; West, C. A. *Biochemistry* **1970,** *9*, 70, 80; (b) Sitton, D.; West, C. A. *Phytochemistry* **1975,** *14*, 1921; (c) Stekoll, M.; West, C. A. *Plant Physiol.* **1978,** *61*, 38.
10. (a) Ghisalberti, E. L.; Jefferies, P. R.; Payne, T. G.; Worth, G. K. *Tetrahedron Lett.* **1970,** p. 4599; (b) Ghisalberti, E. L.; Jefferies, P. R.; Payne, T. G.; Worth, G. K. *Tetrahedron* **1973,** *29*, 403; (c) Ghisalberti, E. L.; Jefferies, P. R.; Toia, R. F.; Worth, G. K. *Tetrahedron* **1974,** *30*, 3269; (d) Maslen, E. N.; Toia, R. F.; White, A. H.; Willis, A. C. *J.C.S. Perkin II* **1975,** 1684; (e) Ghisalberti, E. L.; Jefferies, P. R.; Toia, R. F. *Tetrahedron* **1978,** *34*, 233.
11. Uemura, D.; Nobuhara, K.; Nakayama, Y.; Shizuri, Y.; Hirata, Y. *Tetrahedron Lett.* **1976,** 4593.
12. Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1976,** *98*, 2295.
13. Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Beavers, W. A.; Cutler, R. S. *J. Org. Chem.* **1976,** *41*, 1855.
14. Chan, W. R.; Prince, E. C.; Manchand, P. S.; Springer, J. P.; Clardy, J. *J. Am. Chem. Soc.* **1975,** *97*, 4437.
15. Purushothaman, K. K.; Chandrasekharan, S.; Cameron, A. F.; Connolly, J. D.; Labbé, C.; Maltz, A. Rycroft, D. S *Tetrahedron Lett.* **1979,** p. 979.
16. Uemura, D.; Hirata, Y. *Tetrahedron Lett.* **1971,** p. 3673; Uemura, D.; Hirata, Y. *Tetrahedron Lett.* **1973,** p. 881.
17. (a) Stout, G. H.; Balkenhol, W. G.; Poling, M.; Hickernell, G. L. *J. Am. Chem. Soc.* **1970,** *92*, 1070; (b) Ronlán, A.; Wickberg, B. *Tetrahedron Lett.* **1970,** p. 4261.
18. Sakata, K.; Kawazu, K.; Mitsui, T.; Masaki, N. *Tetrahedron Lett.* **1971,** p. 1141.
19. Adolf, W.; Hecker, E. *Is. J. Chem.* **1977,** *16*, 75.
20. Crombie, L.; Kneen, G.; Pattenden; G.; Whybrow, D. *J.C.S. Perkin I* **1980,** p. 1711; Crombie, L.; Kneen, G.; Pattenden, G. *J.C.S. Chem. Commun.* **1976,** p. 66.
21. Dueber, M. T.; Adolf, W.; West, C. A. *Plant Physiol.* **1978,** *62*, 598.
22. Guilford, W. J.; Coates, R. M. *J. Am. Chem. Soc.* **1982,** *104*, 3506.
23. For references to other unified synthetic strategies developed in our laboratory, see (a) Cyclopentenoid antibiotics: Scarborough, R. M., Jr.; Smith, A. B., III. *J. Am. Chem. Soc* **1977,** *99*, 7085; Branca, S. J.; Smith, A. B., III *J. Am. Chem. Soc.* **1978,** *100*, 7767; Scarborough, R. M., Jr.; Toder, B. H.; Smith, A. B., III *J. Am. Chem. Soc.* **1980,** *102*, 3904; Smith, A. B., III; Pilla, N. N. *Tetrahedron Lett.* **1980,** *21*, 4691; Boschelli, D.; Smith, A. B., III *Tetrahedron Lett.* **1981,** *22*, 3733; Boschelli, D.; Smith, A. B., III; Jenkins, R. H., Jr.; Stringer, O. D.; Davis, F. A. *Tetrahedron Lett.* **1981,** *22*, 4385; Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982,** *47*, 1855; Wexler, B. A.; Toder, B. H.; Smith, A. B., III *J. Org. Chem.* **1982,** *47*, 3333; Smith, A. B., III; Boschelli, D. *J. Org. Chem.* **1983,** *48*, 1217; (b) The paniculides: Smith, A. B., III; Richmond, R. E. *J. Org. Chem.* **1981,** *46*, 4814; Smith, A. B., III; Richmond, R. E. *J. Am. Chem. Soc.* **1983**, *105*, 575; (c) The mycorrhizin fungal metabolites: Smith, A. B., III; Koft, E. R. *J. Am. Chem. Soc.* **1982,** *104*, 2659; Smith, A. B., III; Huryn, D. M. *J. Org. Chem.* **1985,** *50*, 1342; Smith, A. B., III; Yokoyama, Y.; Huryn, D. M.; Dunlap, N. K. *Tetrahedron Lett.* **1987**, *28*, 3659; Smith, A. B., III; Yokoyama, Y.; Dunlap, N. K.; Hadener, A.; Tamm, C. *Tetrahedron Lett.* **1987,** *28*, 3663;

Smith, A. B., III; Koft, E. R.; Huryn, D. M.; Dunlap, N. K.; Yokoyama, Y. Submitted for publication; (d) The phyllanthoside family of antibiotics: Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987,** *109*, 1269; Smith, A. B., III; Rivero, R. A. *J. Am. Chem. Soc.* **1987,** *109*, 1272; Smith, A. B., III; Hale, K. J.; Vaccaro, H. A. *J.C.S. Chem. Commun.* **1987,** 1026; Smith, A. B.; III; Hale, K. J.; Vacarro, H. A. *Tetrahedron Lett.* **1988,** *28*, 5591.

24. Corey, E. J.; Crouse, D. *J. Org. Chem.* **1968,** *33*, 298; Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973,** *38*, 1775; Quesada, M. L.; Schlessinger, R. H. *Synth. Commun.* **1976,** *6*, 555; Tobin, P. S.; Basu, S. K.; Grosserode, R. S.; Wheeler, D. M. S. *J. Org. Chem.* **1980,** *45*, 1250.
25. Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978,** *100*, 7069; Stork, G.; Nakamura, E. *J. Org. Chem.* **1979,** *44*, 4010; Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P.; Petasis, N. P. *J. Org. Chem.* **1979,** *44*, 4011; Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982,** *104*, 2027.
26. Seebach, D.; Jones, N. R.; Corey, E. J. *J. Org. Chem.* **1968,** *33*, 300.
27. For preparation of ketophosphonates, see Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.: Sakai, T. *Tetrahedron Lett.* **1984,** *25*, 2183; see also reference 19c.
28. (a) Pavan, C.; Bulidon, J. *Chem. Abst.* **1982,** *96*, 85798W; (b) Crombie, L.; Crossley, J.; Mitchard, D. A. *J. Chem. Soc.* **1963,** p. 4957.
29. Toma, K.; Miyazaki, E.; Murae, T.; Takahashi, T. *Chem. Lett.* **1982,** p. 863.
30. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969,** *34*, 2543.
31. Arndt, F.; Eistert, B.; Partale, W. *Ber. Dtsch. Chem. Ges.* **1927,** *60*, 1364; Arndt, F.; Amende, J. *Ber. Dtsch. Chem. Ges.* **1928,** *61*, 1122; Arndt, F.; Eistert, B.; Amende, J. *Ber. Dtsch. Chem. Ges.* **1928,** *61*, 1949; Ardnt , F.; Eistert, B. *Ber. Dtsch. Chem. Ges.* **1935,** *68*, 200; for a comprehensive review of this area, see Dave, V.; Warnhoff, E. W. *Org. React.* (*N.Y.*) **1970,** *18*, 217; Kirmse, W. *Prog. Org. Chem.* **1964,** *6*, 164; Kirmse, W. "Carbene Chemistry"; Academic Press: New York, 1971; Jones, M., Jr.; Moss, R. A. "Carbenes"; Wiley: New York, 1973; Burke, S. D.; Grieco, P. A. *Org. React.* (*N.Y.*) **1979,** *26*, 361.
32. On a number of occasions we have found that the photochemical Wolff rearrangement first introduced by Horner *et al.* (Horner, L.; Spietschka, E.; Gross, A. *Justus Liebigs Ann. Chem.* **1951,** *573*, 17; see also Horner, L.; Spietschka, E. *Chem. Ber.* **1952,** *85*, 225) is considerably more efficient than the thermal or metal-catalyzed variants; see Smith, A. B., III; Toder, B. H.; Branca, S. J. *J. Am. Chem.* **1984,** *106*, 3995.
33. Camps, F.; Coll, J.; Parente, A. *Synthesis* **1978,** p. 215.
34. For a discussion of the cyclopropyl carbinyl cation, see Lowry, T. H.; Richardson, K. S. In "Mechanism and Theory in Organic Chemistry," Wasserman, M.; Castellano, E., Eds.; Harper & Row: New York, 1981, pp. 403–413.
35. Okukado, N.; Negishi, E. *Tetrahedron Lett.* **1978,** *28*, 2357.
36. Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968,** 3363.
37. Hallsworth, A. S.; Henbest, H. B.; Wrigley, T. I. *J. Chem. Soc.* **1957,** p. 1969.
38. Luche, J.-L. *J. Am. Chem. Soc.* **1978,** *100*, 2226.
39. McPhail, A. T.; Sim, G. A.; Asher, J. D. M.; Robertson, J. M.; Silverton, J. V. *J. Chem. Soc. B*, **1966,** 18; Fredga, A. *Tetrahedron* **1960,** *8*, 126; Frega, A.; Jennings, J. P.; Klyne, W.; Scopes, P. M.; Sjoberg, B.; Sjoberg, S. *J. Chem. Soc.* **1965,** p. 3928.
40. Matsui, M.; Yashioka, H.; Sakamoto, H.; Yamada, Y.; Kitahara, T.; *Agric. Biol. Chem.* **1967,** *31*, 33; Cocker, W.; Lauder, H. St. J.; Shannon, P. V. R. *J.C.S. Chem. Commun.* **1972,** p. 684.
41. We wish to thank Professor Jefferies (University of Western Australia) for the generous samples of (−)-bertyadionol ar$^2$ (−)-bertyadionol acetate.
42. Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T.

W. *J. Am. Chem. Soc.* **1981,** *103*, 219; Smith, A. B., III; Malamas, M.; *J. Org. Chem.* **1982,** *47*, 3442.

43. (a) Branca, S. J.; Smith, A. B., III *J. Am. Chem. Soc.* **1978,** *100*, 7767; (b) Smith, A. B., III; Pilla, N. N. *Tetrahedron Lett.* **1980,** *21*, 4691; (c) Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982,** *47*, 1855.
44. Dauben, W. G.; Robbins, J. D. *Tetrahedron Lett.* **1975,** p. 151; Lang, M.; Prasad, K.; Holick, W.; Gosteli, J.; Ernest, I.; Woodward, R. B. *J. Am. Chem. Soc.* **1979,** *101*, 6296; Ernest, I.; Gosteli, J.; Ernest, I.; Woodward, R. B. *J. Am. Chem. Soc.* **1979,** *101*, 6301; Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980,** *102*, 5699; Aristoff, P. A. *Synth. Commun.* **1983,** *13*, 145.
45. (a) Still, W. C.; *J. Am. Chem. Soc.* **1979,** *101*, 2493; (b) Vedejs, E.; Dolphin, J. M.; Mastalerz, H. *J. Am. Chem. Soc.* **1983,** *105*, 127.
46. Bolte, M. L.; Crow, W. D.; Yoshida, S. *Aust. J. Chem.* **1982,** *35*, 1411.
47. Available from Aldrich Chemical Co.; see also Lick, C.; Schank, K. *Chem. Ber.* **1978,** *111*, 2461.
48. Carroll, P. Unpublished results, Univ. of Pennsylvania X-Ray Crystallographic Facility.
49. Bhushan, V.; Chandrasekaran, S. *Synth. Commun.* **1984,** *14*, 339.
50. (a) Stork, G.; Danheiser, R. L.; Ganem, B. *J. Am. Chem. Soc.* **1973,** *95*, 3414; Koreeda, M.; Liang, Y.; Akagi, H. *J.C.S. Chem. Commun.* **1979**, p. 449; Koreeda, M.; Mislankar, S. G. *J. Am. Chem. Soc.* **1983,** *105*, 7203.
51. Davis, F. A.; Hague, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986,** *51*, 2402; Davis, F. A.; Vishwakarma, L. C. *Tetrahedron Lett.* **1985,** p. 3539; Evans, D. A.; Morrisey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985,** *107*, 4346.
52. Guaciaro, M. A.; Wovkulich, P. M.; Smith, A. B., III *Tetrahedron Lett.* **1978,** p. 4661; Smith, A. B., III; Branca, S. J.; Pilla, N. J.; Guaciaro, M. A. *J. Org. Chem.* **1982,** *47*, 1855; see also Smith, A. B., III; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Org. Synth.* **1983,** *61*, 65.
53. Smith, A. B., III; Taylor, M. D.; Furst, G. T.; Gunasekura, S. P.; Bevelle, C. A.; Cordell, G. A.; Farnsworth, N. R.; Kupchan, S. M.; Uchida, H.; Branfman, A. R.; Dailey, R. G., Jr.; Sneden, A. T. *J. Am. Chem. Soc.* **1983,** *105*, 3177.
54. Davis, F. Personal communication, Drexel Univ.
55 Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972,** *94*, 679; Mitsunobu, O.; Eugchi, M. *Bull. Chem. Soc. Jpn.* **1971,** *44*, 3427; Mitsunobu, O. *Synthesis* **1981,** p. 1.
56. For a review on dithiane hydrolysis methods, see Grobel, B.-T.; Seebach, D. *Synthesis* **1977,** p. 357; see also Stahl, I.; Apel, J.; Manske, R.; Gosselck, J. *Angew. Chem., Int. Ed. Eng.* **1979,** *18*, 165; Herrmann, J. L.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973,** *14*, 3267.
57. For reviews, see Russell, G. A.; Mikol, G. J. "Mechanisms of Molecular Migrations," Thyagarajan, B. S.; Wiley: New York, 1968; Vol. 1, pp. 157–207; Durst, T. *Adv. Org. Chem.* **1969,** *6*, 356; see also Kociensky, P. J. *Chem. Commun.* **1980,** p. 1096; Mander, L. N.; Mundill, P. H. C. *Synthesis* **1981,** p. 620.

*Chapter 12*

# A New Strategy for the Synthesis of Polyquinanes

*Daniel D. Sternbach*
*Glaxo Research Laboratories*
*Research Triangle Park, North Carolina*



## I. Introduction

It is rare that one has the chance to outline the genesis of an idea leading to a chemical synthesis. In this chapter I hope to describe how my thoughts started and developed into a general strategy for the synthesis of polyquinanes.

During my graduate studies I worked on trying to develop a synthetic method that would allow for the formation of five-membered carbocyclic rings by a route that derived from the 1,3 dipolar cycloaddition. On mechanistic grounds these dipolar additions will always lead to heterocycles with one or more heteroatoms. Extending this idea to carbocyclic ring formation requires the addition of an allyl anion, or its equivalent, to an olefin. Work in this area never produced a satisfactory method.



STRATEGIES AND TACTICS
IN ORGANIC SYNTHESIS, VOL. 2

During my postdoctoral years the intramolecular Diels–Alder reaction was coming of age. In particular, Roush[1] was using the intramolecular Diels–Alder to form hydrindanes (a five–six fused ring system) with great success. Since I was interested in using the concerted nature of the Diels–Alder reaction to form a five-membered ring, the six-membered ring that is always part of the Diels–Alder product was of no particular importance; however, the bridging chain needed to be three carbons in length and the stereochemistry of the addition had to be well defined. These criteria were met in the intramolecular Diels–Alder reaction with furan as a diene, and the strategy was developed from there.

## II. Furan Diels–Alder Reactions

Initially our interest in forming five-membered carbocyclic rings centered on intramolecular Diels–Alder reactions using furan as the diene (Fig. 1). In this case a three-carbon chain was used to connect the furan(diene) with the dienophile. Earlier work[2] had demonstrated this concept particularly when a nitrogen is part of the bridging chain. When we started our work only one example of an intramolecular Diels–Alder reaction with furan as the diene and concomitant five-membered carbocyclic ring formation was known[2e] (Fig. 2). The yield at equilibrium in refluxing benzene in this case was only 40%.

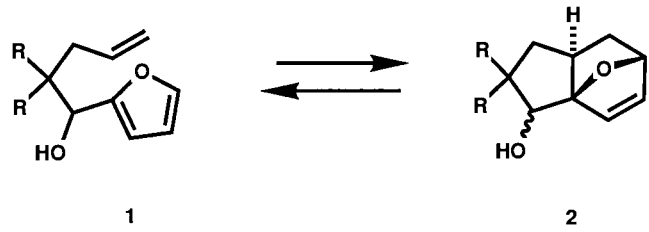



FIG. 1

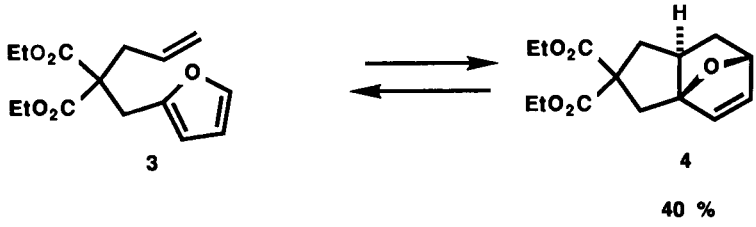



FIG. 2

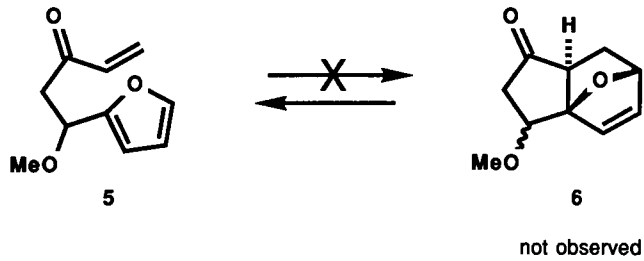



FIG. 3

This result pointed out the potential problem with this approach. That is, the reactions were readily reversible. We discovered that the success of this reaction was highly dependent on the substitution pattern of the bridging chain. Thus, at 80°C the reaction depicted in Fig. 1 did not occur when R = H, but when R = OEt a yield at equilibrium of better than 90% was obtained.[3] Intermediate yields were obtained when R was alkyl or thioalkyl. It is noteworthy that electron-withdrawing groups on the dienophile were not particularly helpful (Fig. 3).[4]

It is apparent that these reactions are only likely to give a single regiochemical outcome with respect to the dienophile. It is not as obvious why the stereochemical outcome where the bridging chain is "exo" (See Fig. 4) is observed, since analogous Diels–Alder reactions where the diene is not in a five-membered ring frequently give mixtures of exo and endo products. A plausible rationale for these results can be seen by focusing on

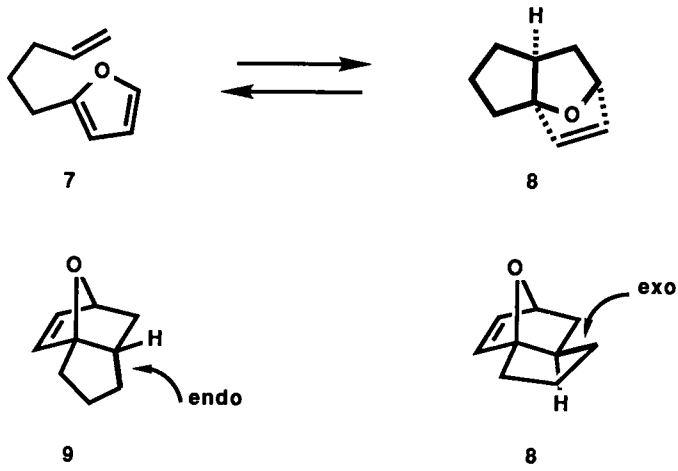



FIG. 4

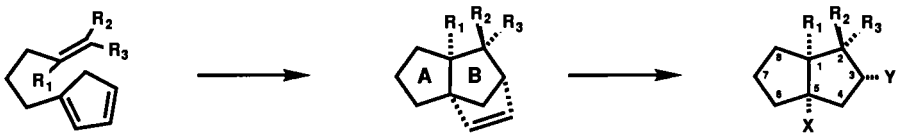
the two five-membered rings (boldface in **8**) that are formed during the cyclization. In the exo approach (i.e., the bridging chain is exo) the incipient [3.3.0] ring system is cis fused, while with the endo approach these rings are trans fused. In the parent bicyclic [3.3.0] hydrocarbon the trans compound is about 6–7 kcal less stable than the cis.[5] It is presumably this difference in energy that is reflected in the transition state for the intramolecular Diels–Alder reaction that causes the exo approach to dominate.

We had originally planned to use the furan intramolecular Diels–Alder reaction for a synthesis of prostaglandin intermediates. When the required substrate, **5**, failed to undergo the intramolecular Diels–Alder reaction we abandoned this approach. We are still using the furan intramolecular Diels–Alder reaction in an ongoing approach to the synthesis of phorbol[6] wherein full advantage is taken of these stereochemical preferences.

## III. Extension to the Synthesis of Fused Five-Membered Carbocyclic Rings

The above analysis points out the fact that two new five-membered rings are formed during the intramolecular Diels–Alder reaction (while there are three five-membered rings in the intramolecular Diels–Alder reaction products, only two of them are new) these are indicated in boldface in **8**. Thus, if cyclopentadiene is used as a diene instead of furan this reaction would result in the formation of two fused five-membered carbocyclic rings (a diquinane). In addition, one would expect the product to be more thermodynamically favored since no loss of aromaticity is involved in this cyclization.

If the double bond in this Diels–Alder product is cleaved, only the two new five-membered rings are left (Fig. 5). The use of other Diels–Alder precursors (with varying substituents on the bridging chain) could lead to diquinanes with substituents at almost any or all of the carbons. In addition, the relative stereochemistry at carbons 1 and 2 in the diquinane (see **12** for numbering) is predetermined by the stereochemistry of the dienophile




10 11 12

FIG. 5

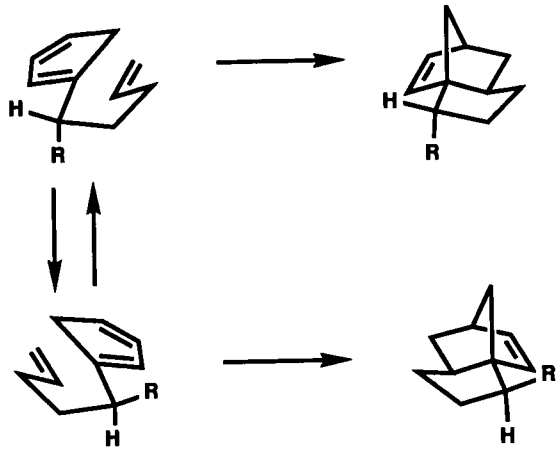



FIG. 6

double bond, and the stereochemistry of the X and Y groups relative to the R groups is determined by the exo nature of the intramolecular Diels–Alder reaction. Thus, four stereo centers on the B ring are completely controlled.

Substituents could also be included on the A ring, but the stereochemistry in these cases would be less certain since two diastereomeric transition states (corresponding to approach on either face of the diene) would result in different diastereomers (Fig. 6; for clarity, only one enantiomer is depicted).

Substitution would be difficult at the 4 position. This carbon arises from the $sp^3$ carbon of cyclopentadiene. Under the conditions needed for cyclization rapid 1,5 hydride shifts are occurring on the cyclopentadiene ring. Since this position is interchanging with the other ring positions, a substituent located there would be scrambled during the reaction (compare **13** and **14** in Fig. 7).

One might wonder why Diels–Alder reactions resulting from other isomers of the starting cyclopentadiene are not formed. Recently, Dreiding[7] found that if the 5-substituted cyclopentadiene could be made at low temperature and if the cyclization could be induced to occur at temperatures where 1, 5 hydride shifts were slow (in this case an aldehyde-activated dienophile was used to facilitate the cyclization) some compounds with carbon frameworks like **16** would be observed. Compounds like **15** and **16** are not formed at higher temperatures.

Another synthetic advantage of this type of intramolecular Diels–Alder reaction is its utility in forming quaternary carbons. All of these intramolecular Diels–Alder reactions form at least one quaternary center. In principle, up to three contiguous quaternary carbons can be formed in one step if a tetrasubstituted dienophile is used. In practice, two quaternary centers are

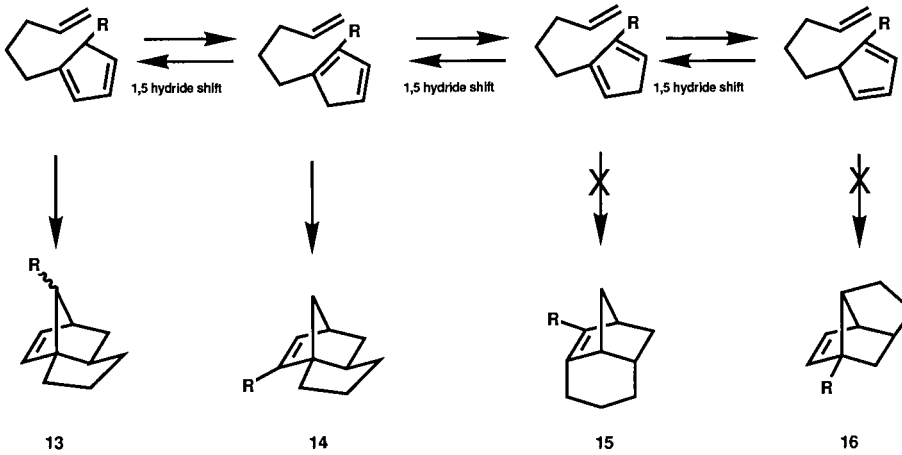



FIG. 7

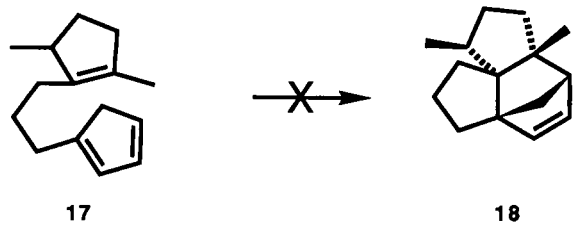


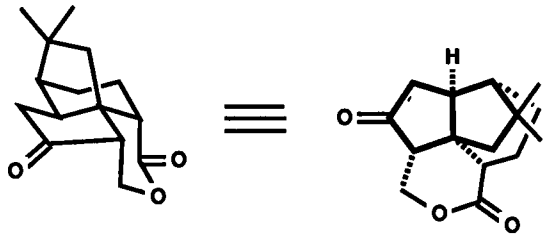

FIG. 8

easily formed (*vide infra*). A solitary attempt to form three contiguous quaternary centers failed (Fig. 8) even under forcing conditions.[8]

To summarize, the advantages of an intramolecular Diels–Alder approach for the formation of quinanes are (1) the well defined stereochemistry obtainable at four carbons in the nascent diquinane, (2) the ease of formation of quaternary carbons, and (3) the ability to introduce substituents at all but one of the diquinane carbons.

## IV. Approach to the Synthesis of Quadrone

Our initial thoughts on using this strategy for the synthesis of diquinanes were directed toward the synthesis of the cytotoxic tetracyclic keto–lactone quadrone (Fig. 9). The structure of quadrone is depicted in Fig. 9 with a projection that highlights the diquinane moiety. Quadrone was recently isolated from the fungus *Aspergillus terreus*[9] and was found to have some




**Quadrone**

FIG. 9

antitumor activity. At the time our work began only one total synthesis of quadrone had been reported[10]; however, a total of 13 syntheses have since been described.[11]

Our retrosynthetic analysis is illustrated in Fig. 10. In this original strategy 13 of the 15 carbons needed for the skeleton of quadrone (all the carbons save the geminal methyl groups) would be assembled in a highly

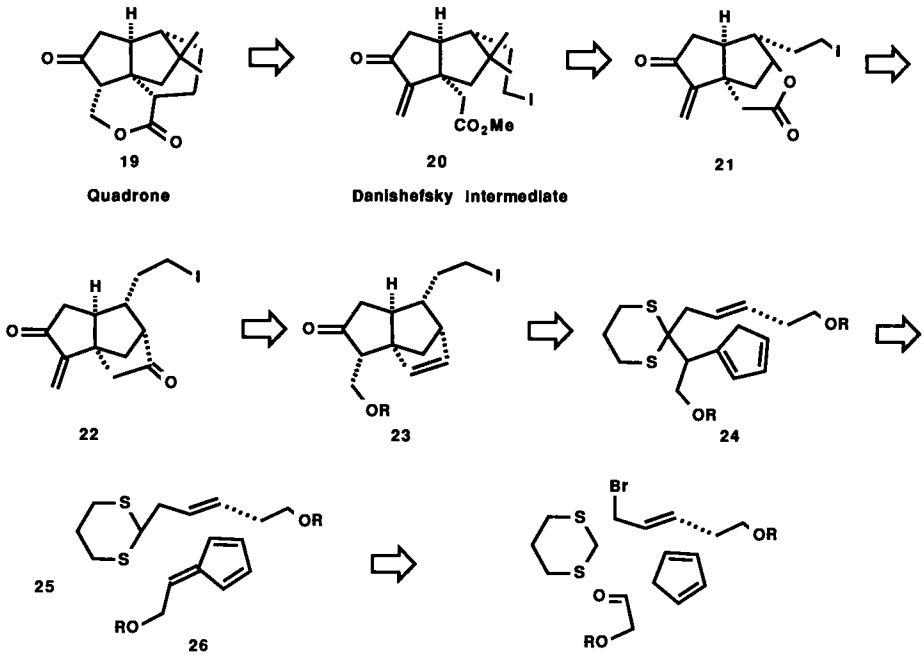
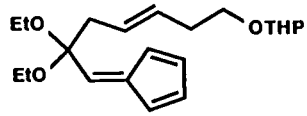
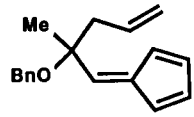
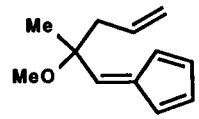
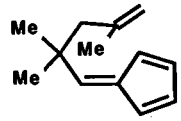
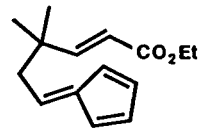



FIG. 10

TABLE I

ADDITIONS OF NUCLEOPHILES TO FULVENES

| Nucleophile | Fulvene | Yield (%) |
|---|---|---|
| $LiAlH_4$ |  | 28 |
| MeLi | " | 61 |
| $CH_2{=}C(OEt)Li$ |  | 71 |
| $CH_2{=}C(CH_3)Li$ | " | 94 (crude) |
| $CH_2{=}C(CH_3)Li$ |  | 93 |
| $CH_2{=}C(OEt)Li$ |  | 80 |
| $CH_2{=}C(CH_3)Li$ | " | 71 |
| $LiAlH_4$ | " | 84 |
| $DIBAL/LiAlH_4$ |  | 98 (ester is also reduced) |

convergent manner by addition of the anion generated from dithiane **25** to **26**. After the Diels–Alder reaction the double bond in **23** could be hydroborated and manipulated as in Fig. 10 to generate a diquinane that was very similar to the intermediate that Danishefsky used in the first synthesis of quadrone.[10]

The success of this strategy required an efficient method for synthesizing the Diels–Alder precursors. Simple alkylation of cyclopentadiene anion has

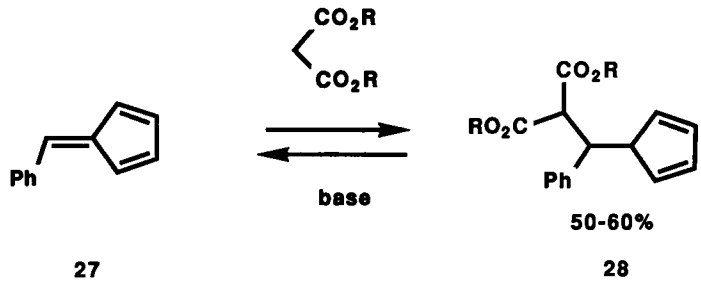



FIG. 11

been used with some degree of success by others in the past. These reactions usually work best on primary halides. Some of the substrates would require alkylation at extremely hindered neopentylic centers. To circumvent this potential problem we set out to explore the addition of nucleophiles to fulvenes. Only a few of these additions were known.[12] Some of our results that expand the scope of this reaction are depicted in Table I.[13] The addition works well for alkyl lithiums and hydride (i.e., reduction of the exocyclic fulvene bond with $LiAlH_4$). High yields are obtained even with hindered substrates. In general, enolates failed to add to fulvenes derived from ketones. In some cases malonates could be added to aldofulvenes as depicted in Fig. 11.[14] In this example a yield of 50–60% was reached at equilibrium. With this particular fulvene the anion generated from *t*-butyl acetate could also be added in 63% yield.

In general, one can view the polarized fulvene exocyclic double bond as carbonyl-like in its reactivity (Fig. 12). Since cyclopentadiene has approximately the same $pK_a$ as an alcohol, this comparison is fairly accurate. Therefore it is not surprising that addition of enolates is reversible (similar to the reversibility of some aldol reactions). Furthermore, the addition of nucleophiles to hindered ketofulvenes may result in deprotonation of the fulvene instead of addition.

For the quadrone synthesis aldofulvene **26** was necessary. Several attempts to synthesize it failed, probably due to its high reactivity. As an


FIG. 12

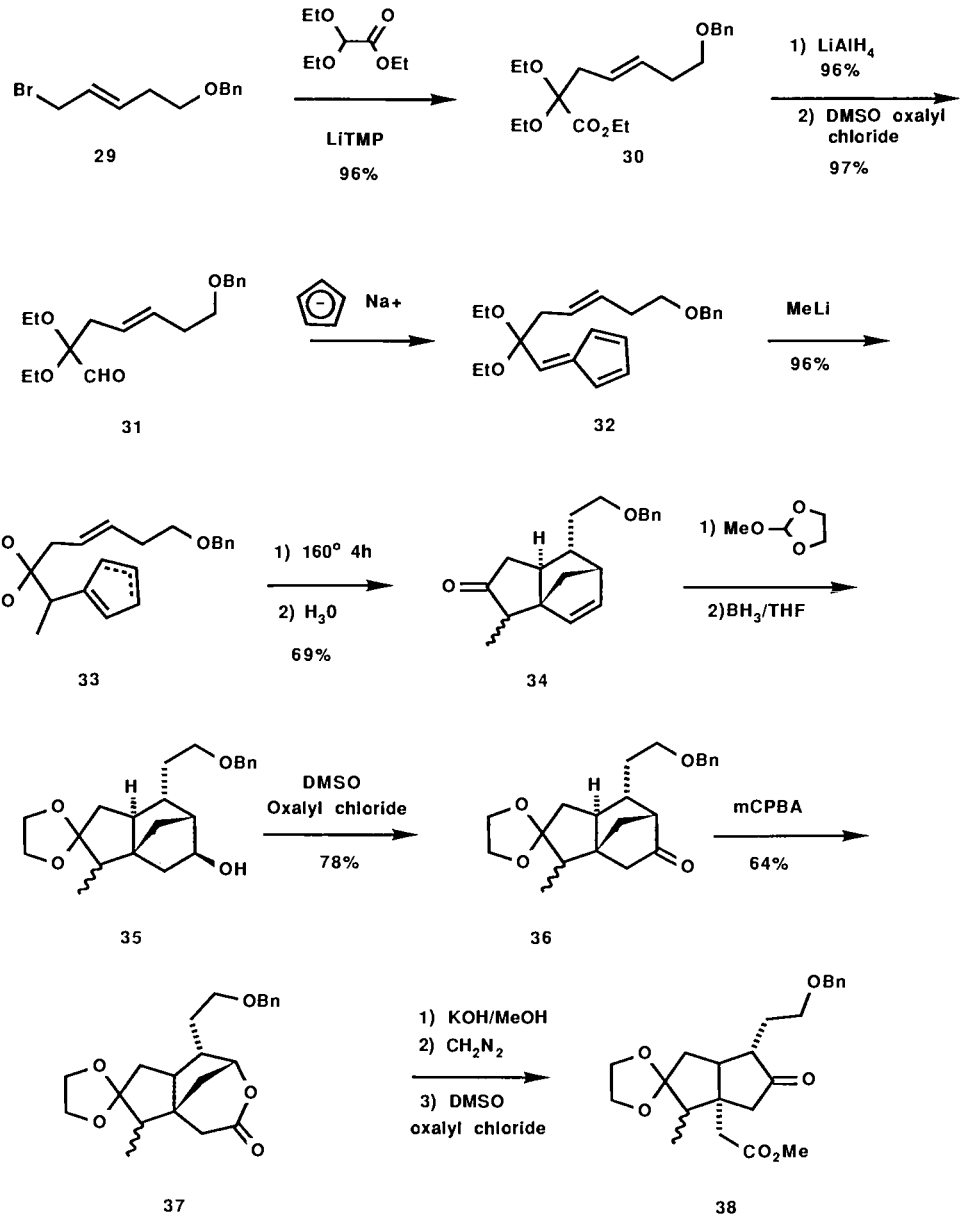

Br
OBn
29
EtO
O
EtO
OEt
LiTMP
96%
OBn
EtO
EtO
CO2Et
30
1) LiAlH4
96%
2) DMSO oxalyl
chloride
97%
OBn
EtO
EtO
CHO
31
Na+
EtO
OBn
EtO
32
MeLi
96%
EtO
OBn
EtO
33
1) 160° 4h
2) H30
69%
H
OBn
O
34
1) MeO
O
O
2)BH3/THF
H
OBn
O
O
OH
35
DMSO
Oxalyl chloride
78%
H
OBn
O
O
O
36
mCPBA
64%
OBn
O
O
O
O
37
1) KOH/MeOH
2) CH2N2
3) DMSO
oxalyl chloride
OBn
O
O
O
CO2Me
38

FIG. 13

alternative strategy the more hindered aldofulvene **32** (Fig. 13) was employed. This fulvene proved to be stable, probably due, in part, to the absence of acidic protons. Ideally, for the execution of the quadrone synthesis an $\alpha$-heteroatom-substituted anion such as $MeOCH_2Li$ would be added to the fulvene. Many attempts with different $\alpha$-heteroatom-substituted anions (e.g., *t*-butoxy methyllithium, methoxymethylmagnesium chloride, phenylthiomethyllithium, and dimsyl lithium) met with failure. Finally, in order to test the rest of the strategy a model compound (**33**) was synthesized by adding methyllithium to the fulvene **32**.

The stage was now set to try the key intramolecular Diels–Alder reaction. In the event, the cyclization of **33** afforded a high yield of products after heating at 160°C for 4 hours. Under these conditions some ethanol was eliminated, making it expedient to hydrolyze the reaction mixture directly, which afforded the ketone **34** in 69% overall yield as a 57 : 43 ratio of methyl epimers. Reprotection of the carbonyl as the ethylene ketal was necessary for the next steps. One could use the ethylene ketal from the outset, and here the cyclization occurred after only 1 hour of heating at 160°C in 77% yield without any destruction of the ketal. Some of the yields en route to this Diels–Alder precursor were lower, however, offsetting any advantage in using it. Another annoying feature of this reaction was the lack of stereoselectivity with respect to the methyl group. While the actual stereochemistry of the methyl group did not matter since it would ultimately be converted to an exocyclic methylene in the Danishefsky intermediate, **20**, the problem of dealing with this mixture made interpretations of subsequent reactions more difficult.

Selective hydroboration of the double bond with borane–THF yielded **35**, which was subjected to the Swern oxidation to afford a 78% yield of **36**. A regiospecific Baeyer–Villiger reaction produced **37**. This lactone could be hydrolyzed, esterified, and oxidized to give **38**. Although this intermediate is similar to the Danishefsky intermediate, we were discouraged because of the mixture of methyl epimers (even when samples enriched in one epimer were used, subsequent protection and deprotection steps led to epimerization) and chose to abandon this synthesis in favor of exploring an extension of the intramolecular Diels–Alder strategy for the synthesis of triquinanes.

## V. Triquinane Strategy

At some point in the synthesis of quadrone we realized that the same strategy could be utilized for the synthesis of triquinanes. This extension, depicted in Fig. 14., required that the Diels–Alder precursor be suitably functionalized. The Diels–Alder product double bond could be cleaved and

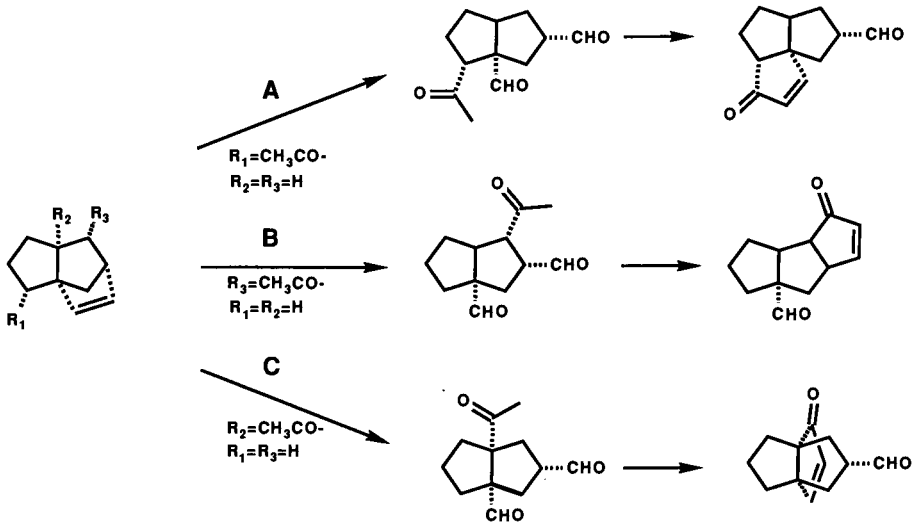
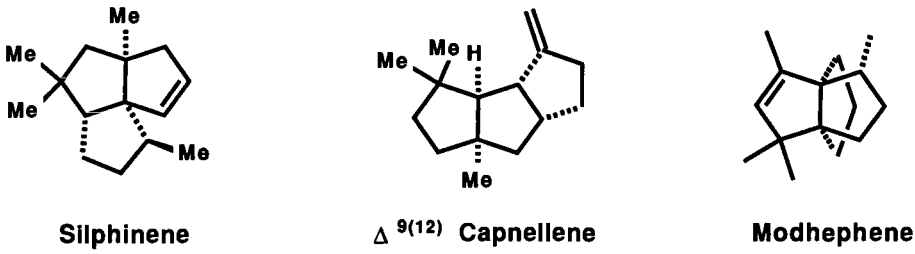



FIG. 14




**Silphinene** **$\Delta^{9(12)}$ Capnellene** **Modhephene**

FIG. 15

the resulting dialdehyde cyclized (by aldol condensation with a suitably placed methyl ketone) to form a third five-membered ring, which would produce an angularly fused system as in path A, a linearly fused triquinane via path B, or a propellane skeleton as in path C. There are a number of polyquinane natural products with these skeletons; an example of each is depicted in Fig. 15.

The required Diels–Alder precursors for schemes A, B, and C are shown in Fig. 16. The angularly fused triquinanes (path A) would require an acyl substituent at the first carbon of attachment to the cyclopentadiene (**39**), while the linearly fused (path B) and propellanelike (path C) triquinanes

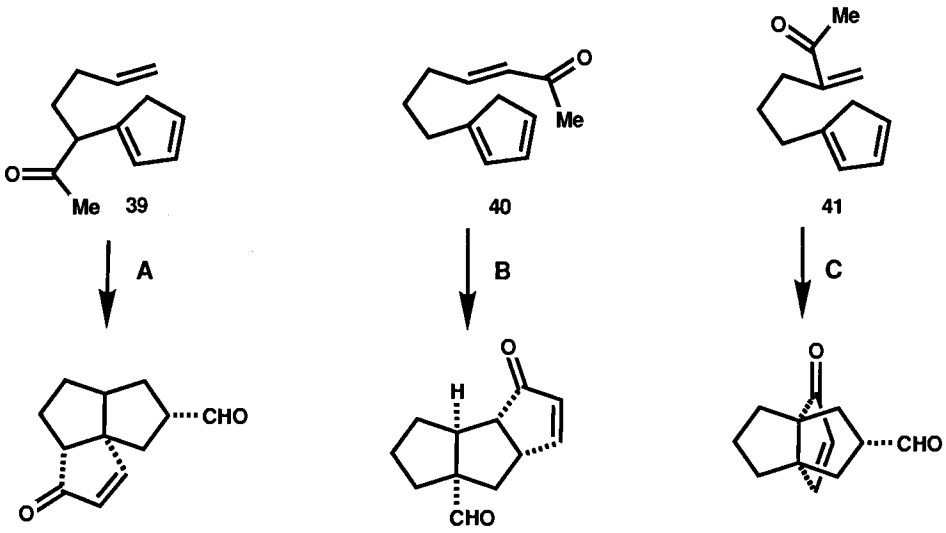
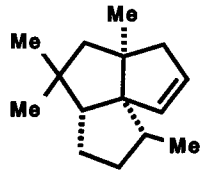



FIG. 16

would both require an acyl group on the dienophile (**40** and **41**, respectively), which would serve to activate the olefin toward the Diels–Alder reaction. To demonstrate the feasibility of these approaches we set out to synthesize a linearly fused and an angularly fused triquinane natural product.

## VI. Synthesis of Silphinene, and Angularly Fused Triquinane

Silphinene (Fig. 17) was first isolated by Bohlmann[15] in 1980 from the roots of *Silphium perfoliatum* L. The structure of silphinene, determined by NMR analysis, is highlighted by an angularly fused triquinane skeleton with four stereogenic centers, including two quaternary carbons. Five total syntheses of silphinene have been reported,[16] including our own.[17]




**SILPHINENE**

FIG. 17

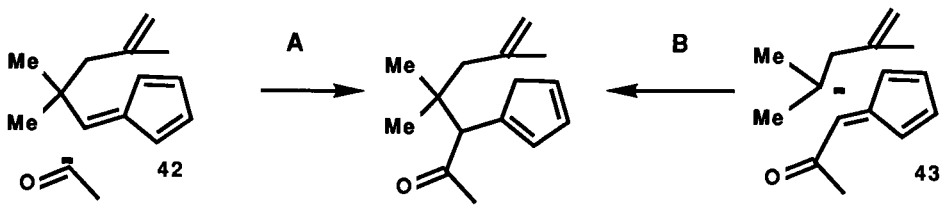



FIG. 18

To utilize the strategy mentioned above in the synthesis of silphinene a precursor for path A (like **39**) would be required. This intermediate could in turn be synthesized by addition of an appropriate nucleophile to a fulvene. In this case the choice of which component was better suited as a fulvene was straightforward (Fig. 18). In one case a tertiary carbanion is required to add to a fulvene that contains a latent ketone, **43**; alternatively, a carbonyl anion equivalent is required to add to a fulvene with a quaternary center near the electrophilic center, **42**. Here the quarternary center is actually advantageous since it prevents deprotonation of the fulvene. As a carbonyl anion equivalent we chose to use the alkenyllithium generated from ethyl vinyl ether.

The readily available pentenal **44** (synthesized from isobutyraldehyde and methally bromide) was reacted with sodium cyclopentadienide to form the fulvene **42** in 75% yield (Fig. 19). Addition of the anion generated from ethyl vinyl ether and *t*-butyllithium produced the substituted cyclopentadiene **45** as a mixture of double-bond isomers. Cyclization of this intermediate was complete after heating at 160°C for 2 hours in benzene (sealed tube). Here again the reaction mixture was best hydrolyzed before purification. Surprisingly, the reaction yielded a 10:1 mixture of acetyl epimers (**47**:**48**, 69% total yield) as compared with the approximately 1:1 ratio of methyl epimers found in the intramolecular Diels–Alder reaction for quadrone. Presumably this stereoselectivity resulted from the unfavorable interaction of the angular methyl group and the latent acetyl group in the minor isomer (Fig. 20). Further support for this stereochemical result comes from an epimerization study that resulted in the slow conversion of **48** to **47** but not **47** to **48**, even though deprotonation was occurring as evidenced by deuterium exchange. Note that the major isomer does not have the desired stereochemistry. This stereochemical result was irrelevant as far as the silphinene synthesis was concerned since either isomer could be used (*vide infra*), but it served to illustrate some of the controlling elements in the cyclization.

Ozonolysis of the mixture of isomers led to the dialdehyde **49** as a mixture of hydrates. This dialdehyde was treated with base directly to effect the aldol

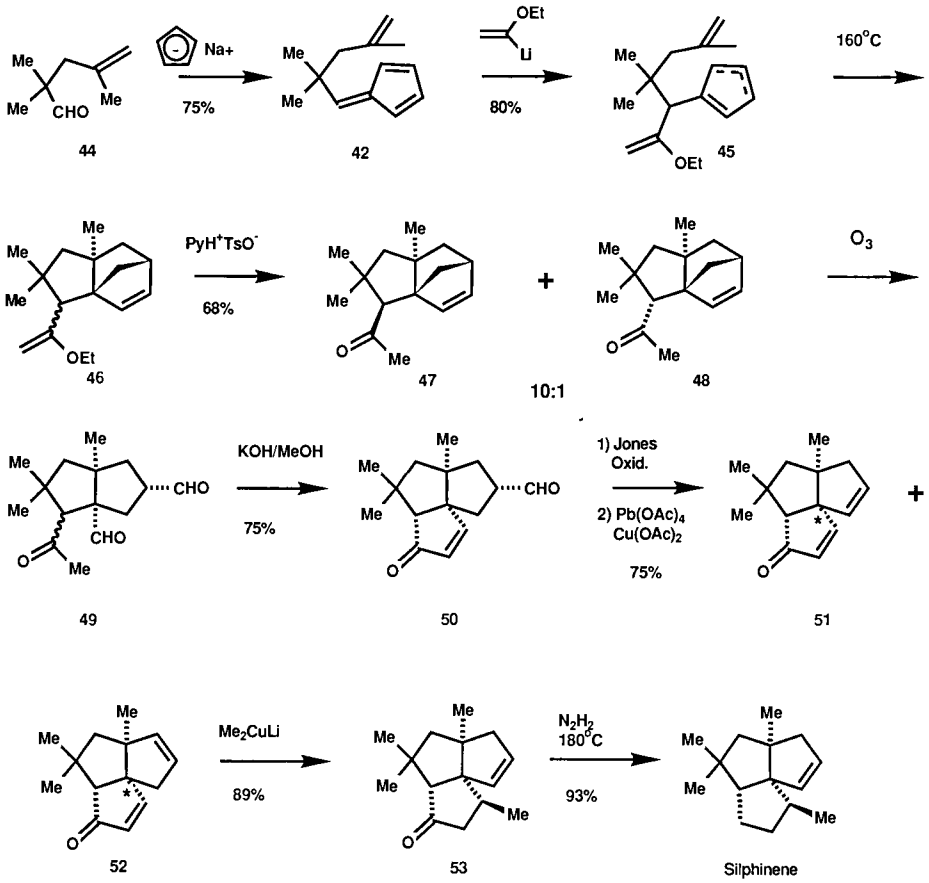
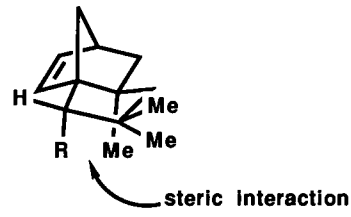



FIG. 19




**minor isomer**

FIG. 20


FIG. 21

condensation. It was gratifying to learn that each of the methyl ketone epimers underwent aldol condensation to give triquinane **50**. This meant that epimerization must be occurring before cyclization in the case of the major isomer. In addition to the aldol product **50** (obtained in 75% yield), about 10% of the corresponding acid, resulting from oxidation of the remaining aldehyde, was obtained. This unexpected result, probably due to oxidation with adventitious oxygen, was not a problem since our strategy called for the oxidation of this aldehyde to an acid anyway. This was accomplished in high yield with the Jones reagent. The oxidative removal of the carboxylic acid carbon to form a double bond was the next hurdle. Even though one could venture some handwaving arguments as to why the double-bond location in silphinene (Fig. 21A) is more stable than its regioisomer (Fig. 21B), we were unsure of the direction in which the elimination would occur. In the stereo view shown in Fig. 21 the $\alpha$-methyl group clearly has more space if it is near the $sp^2$ center as in A, as opposed to being next to the $sp^3$ center as in B. We anticipated that in the worst case double-bond equilibration could be carried out on the final product. In order to take advantage of this stereochemical effect it is necessary to introduce the methyl group before oxidatively removing the carboxyl group. However, after a few unsuccessful attempts to add dimethylcopper lithium to the enone aldehyde **50** and to the corresponding acid derivative, we decided to remove the carboxyl group first.

Oxidative decarboxylation following Kochi's[18] procedure led to two isomeric alkenes **51** and **52** in a 7:3 ratio. The yield was 75% with the remainder being unreacted starting material. Taking into account the recovered starting material, the yield rose to 97%. All attempts to coerce this reaction to completion failed. The $^{13}C$ NMR spectrum of each isomer reconfirmed our assignment. The major isomer **51** had a quaternary carbon which resonated at 74.6 ppm, while he corresponding carbon in the minor isomer **52** resonated at 66.6 ppm (these carbons are marked by asterisks in Fig.19). Fortunately, the double-bond isomers could be separated of flash chromatography.

To complete the synthesis of silphinene, dimethylcopper lithium was added to the enone to yield a single product in 89% yield. The $\beta$

stereochemistry of this methyl was predicted by examination of Dreiding models and from close precedent in the literature.[19]

All of the carbons of silphinene were now in place, and the completion of the synthesis required only reductive removal of the carbonyl group. A Wolff–Kishner reduction at high temperature (200–250°C) in triethylene glycol afforded a 93% yield of silphinene along with a small amount of a compound that was tentatively identified (GC-MS analysis) as dihydrosilphinene.

## VII. Synthesis of $\Delta^{9(12)}$-Capnellene; a Linearly Fused Triquinane

To demonstrate the utility of the intramolecular Diels–Alder strategy for the synthesis of linearly fused triquinanes, we investigated the synthesis of $\Delta^{9(12)}$-capnellene. $\Delta^{9(12)}$-Capnellene was isolated from the soft coral *Capnella imbricata*[20] and is the parent hydrocarbon of a family of sesquiterpene alcohols designated as the capnellanes. This compound has been synthesized by several groups.[21] Our retrosynthetic strategy toward the simplest member of this family is shown in Fig. 22.

At the outset we thought that this strategy was ideally suited for the capnellanes for two reasons. First, the Diels–Alder precursor required a carbonyl in a position that would also serve to activate the dienophile. Second, synthesis of the precursor could in principle be accomplished by simply alkylation of cyclopentadiene, since this alkylation would take place at a primary center (thus the fulvene strategy would not be needed).

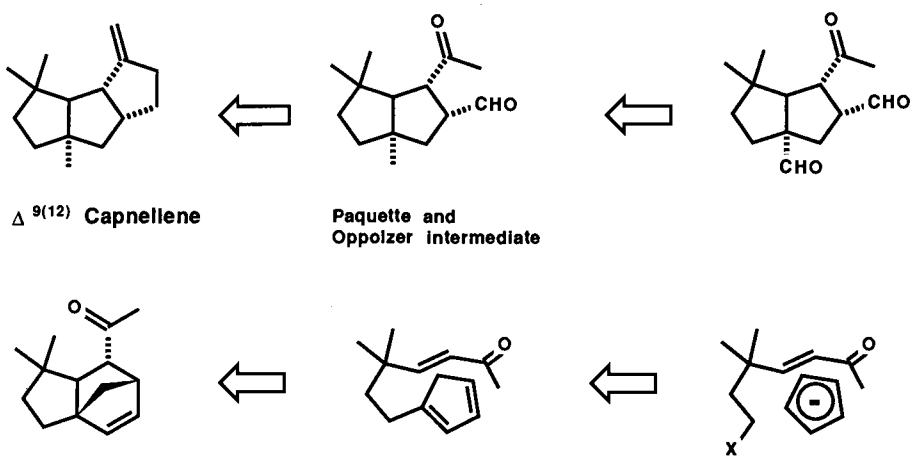



FIG. 22

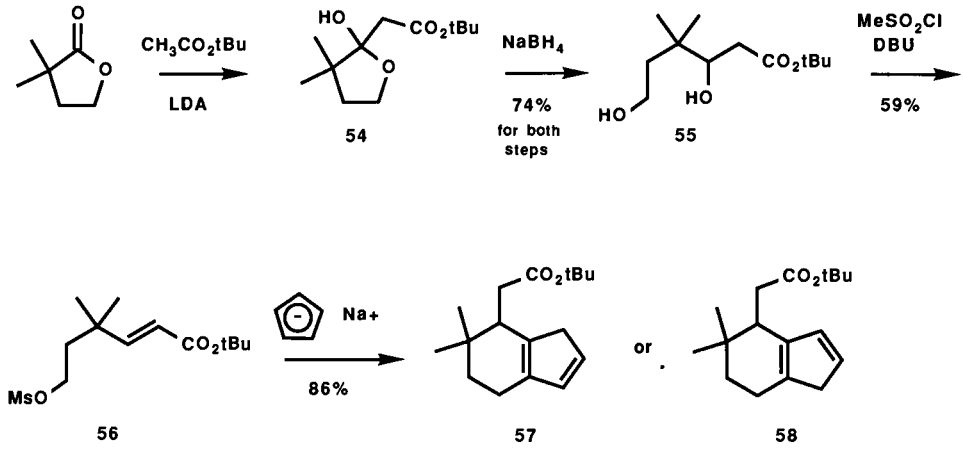



FIG. 23

In our initial attempt, a suitable alkylating agent was easily prepared starting with 2,2-dimethylbutyrolactone (Fig. 23). Addition of the lithium enolate of *t*-butyl acetate to 2,2-dimethylbutyrolactone produces hemiketal **54**, which can be reduced with sodium borohydride to diol ester **55**. Upon mesylation, spontaneous elimination of the secondary hydroxyl and formation of the desired unsaturated ester mesylate (**56**) occur.

All of our attempts to alkylate cyclopentadienide with **56** led to the high-yield formation of a six–five fused-ring system with a structure of either **57** or **58**. Thus, while alkylation had occurred, there was a concomitant Michael addition to the $\alpha,\beta$-unsaturated ester group. At the outset we had realized that this was a possibility but we had thought that the reactivity of the unsaturated ester **56** would be diminished because of the sterically demanding adjacent carbon bearing the geminal methyl groups. Since alkylation consumes the base and the Michael reaction requires only a catalytic amount of base, one might surmise that if the cyclization was the result of a facile alkylation at the primary mesylate followed by a very rapid intramolecular Michael reaction, carefully controlling the amount of base present could achieve a better result. Numerous attempts to vary the amount of base (e.g., inverse addition) did not improve the results. Evidently the relative rates of cyclization and alkylation are such that improvement was not possible with either sodium or lithium cyclopentadienide.[22]

An alternative strategy that avoided alkylation of cyclopentadiene with an $\alpha,\beta$-unsaturated ester is depicted in Fig.24. While alkylation of these two substrates (**63** and **64**) preceeded smoothly, the subsequent intramolecular Diels–Alder trials led to unrecognizable products. We finally fell back on the

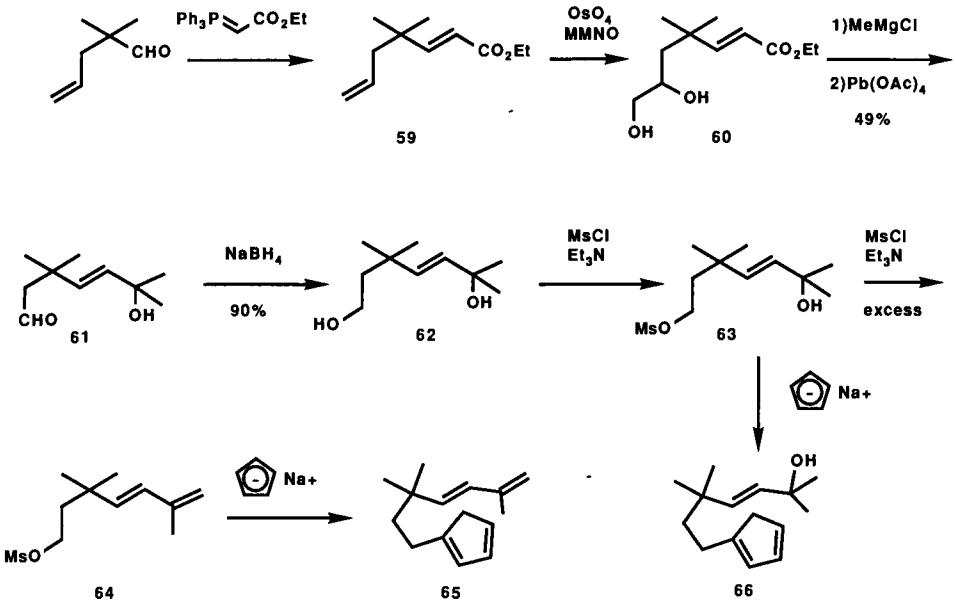



FIG. 24

fulvene strategy as shown in Fig. 25. Starting with diolefin **59**, selective osmylation of the terminal double bond followed by lead tetraacetate cleavage of the vicinal diol led to the aldehyde ester **67**. Formation of the fulvene **68** uncomplicated by Michael addition products could be accomplished by using diethylamine as base.[23] Reduction of the fulvene exocyclic bond without concomitant reduction of the ester group was not possible, and several reducing agents led to complicated product mixtures. Good results were finally achieved when the ester was deliberately reduced first with diisobutylaluminum hydride (DIBAL) followed directly in the same pot by reduction of the fulvene exocyclic double bond with $LiAlH_4$.

It is interesting to note that cyclization of **69** occurred at 160°C but, unlike the previous examples, required 24 hours to reach completion. Presumably the lower rate was due in part to the fact that the dienophilic double bond was sterically more hindered than in the previous examples. In addition, there was no geminal substitution at the middle carbon of the bridging chain. All the prior examples had geminal substitution at this carbon, and as we found in the furan Diels–Alder reaction, this substitution could make or break the reaction (*vide supra*).

Oxidation of the intramolecular Diels–Alder product **70** followed by addition of MeLi produced the methyl ketone **72** via the acid. Ozonolytic

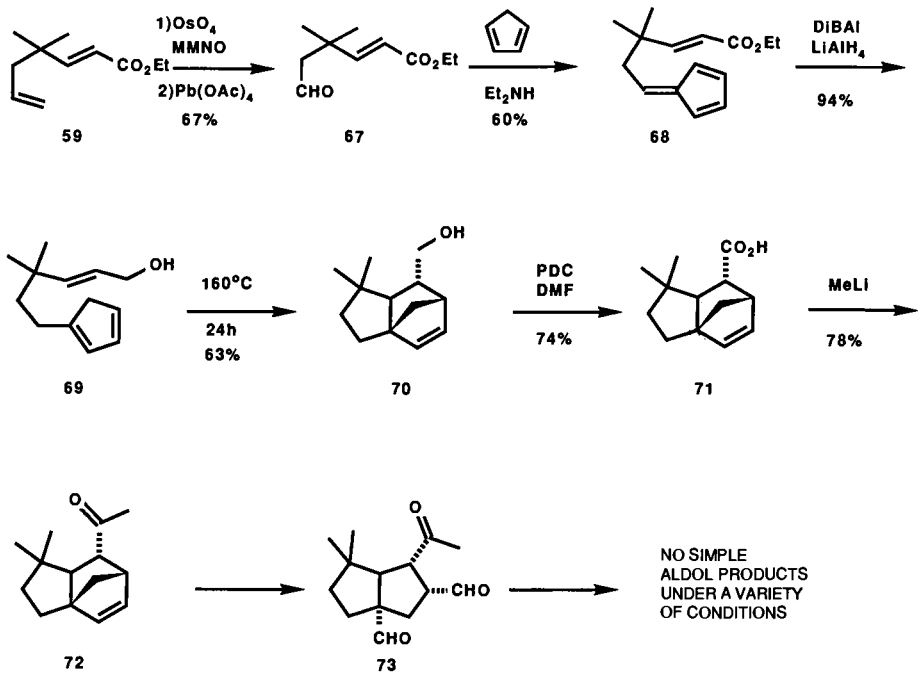



FIG. 25

cleavage of **72** led to an intermediate that differed from the Paquette–Oppolzer intermediate only in the oxidation state of the angular aldehyde (see Fig. 22). This difference proved to be crucial in that all our attempts at aldol condensation failed. We now had to backtrack and try to converge on the exact Paquette–Oppolzer intermediate.

Our first thought was to try to differentially protect the two aldehydo groups in **73**. This could be accomplished in a satisfactory manner by treating the crude ozonolysis product with trimethyl orthoformate to afford **75** in 75% yield (Fig. 26). In this compound one of the aldehydes could be liberated under basic conditions, leaving the other protected. Indeed, we hoped to liberate this aldehyde under the conditions necessary for cyclization of the third ring. To this end, the lactone acetal was reacted with 2 equivalents of dimethyllithiomethyl phosphonate, which on the first attempt produced a tantalizing trace of the desired enone **77** (presumably via the intermediacy of the beta ketophosphonate) along with recovered starting material. Unfortunately, trying to improve the yield of the cyclization by varying the amounts of the phosphonate met with little success, producing overaddition products or resulting in recovered starting material.

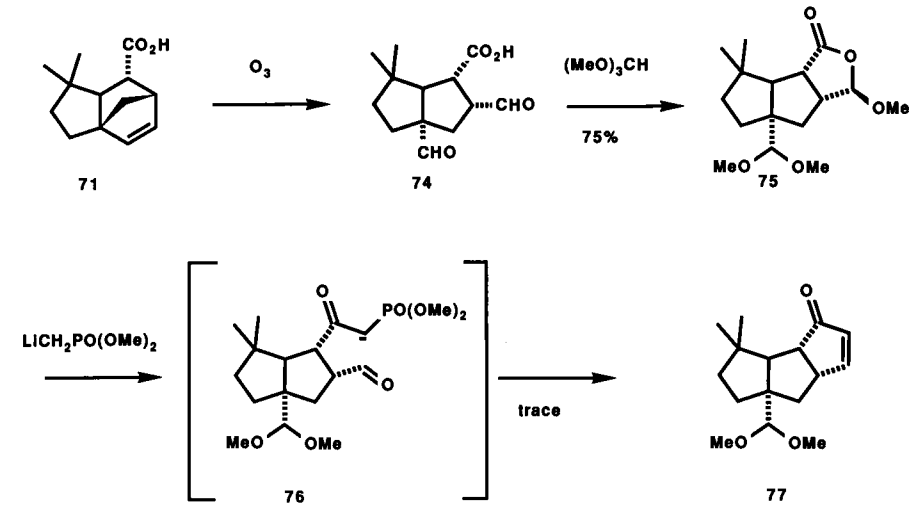



FIG. 26

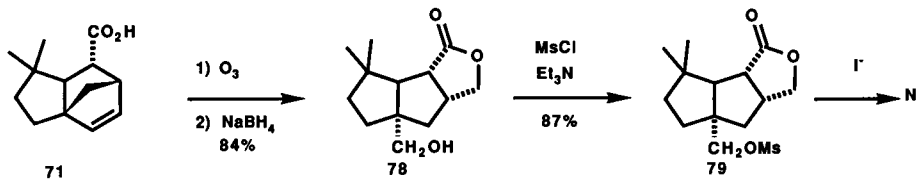



FIG. 27

Once again we were forced to backtrack to **71**. This time the plan was to use a reductive workup in the ozonolysis and differentiate the two resulting alcohols by forming a lactone with one of them (Fig. 27). Thus, treating the ozonolysis product with sodium borohydride yielded the hydroxy lactone, **78**. Rather than protect the other hydroxyl we elected to remove it to generate the angular methyl group of capnellene. Formation of the mesylate could be readily accomplished, but further reactions to form the iodide or direct reduction of the mesylate failed. It was not too surprising that iodide failed to displace the extremely hindered neopentylic mesylate. Interestingly, formation of the neopentylic iodide could be accomplished in high yield (87%) by using an adaptation of the Mitsunobu protocol (Fig. 28).[24] The success of this reaction may well be attributed to the fact that the initial charged adduct, the oxyphosphonium iodide salt, goes to the uncharged products on heating in benzene. In contrast to the usual $S_N2$ conditions

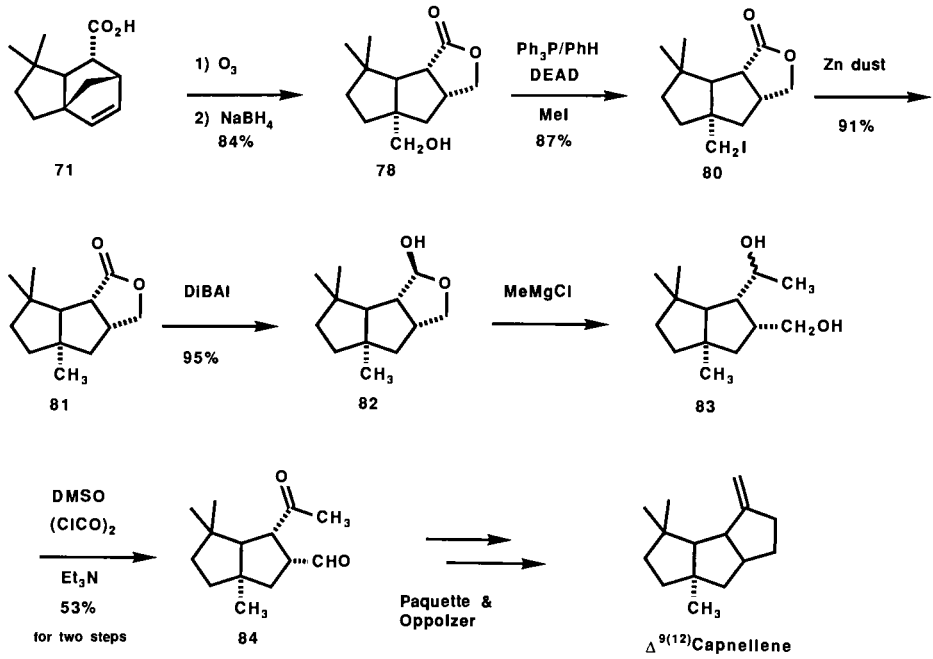



FIG. 28

that benefit by a polar aprotic solvent because the structure of the transition state is more charge separated than that of the starting material, this reaction benefits by the use of a nonpolar solvent since the charged starting material is en route to uncharged products. In addition, the final substitution reaction is unimolecular. Reductive removal of the iodide in **80** was accomplished with Zn dust in 91% yield.

To complete a formal total synthesis of $\Delta^{9(12)}$-capnellene the addition of one more carbon was required. To this end the lactone **81** was reduced with DIBAL to yield the hemiacetal. This compound was reacted with MeMgCl to yield a mixture of diol epimers, which in turn were oxidized with DMSO/oxalyl chloride to produce a ketoaldehyde, which partially isomerized on silica gel to yield an isomer that was spectroscopically identical to the penultimate precursor in Oppolzer's synthesis of $\Delta^{9(12)}$-capnellene.[21d,25]

## VIII. Conclusion

I have tried to show how a strategy for the synthesis of polyquinanes evolved from early concepts. This strategy can lead to the assembly of complex polyquinanes in a highly convergent manner. Much was also learned along the way about the requirements for successful intramolecular

Diels–Alder reactions. While we have outlined approaches to or syntheses of a diquinane, an angularly fused triquinane, and a linearly fused triquinane, there has been no attempt to use this strategy to synthesize a propellane skeleton.

## Acknowledgments

I would like to acknowledge the hard work of the two graduate students who carried out most of this work: Debby Rossana, who started the work on the intramolecular Diels–Alder reaction of furans, and Jeffrey Hughes, who pioneered the polyquinane work. The donors of the Petroleum Research Fund administered by the American Chemical Society and the Research Corporation must also be acknowledged for partial support of these projects. I would also like to thank my colleagues at Glaxo for their help in proofreading this manuscript. The bulk of this work was carried out while the author was at Duke University, Durham, North Carolina.

## References

1. Roush, W. R. *J. Am. Chem. Soc.* **1978,** *100*, 3599.
2. (a) Bilovic, D.; Stojanac, Z.; Hahn, V. *Tetrahedron Lett.* **1964,** p. 2071; (b) Bilovic, D. *Croat. Chem. Acta* **1968,** *40*, 15; (c) Torossian, G. H.; Paravian, S. L.; Mkrtchian, R. S.; Tahmazian, K. T.; Babayan, A. T. *Chem. Abst'.* **1978,** *92*, 76234z; (d) Klepo, Z.; Jakopcic, K. *Croat. Chem. Acta* **1975,** *47*, 45; (e) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978,** p. 1689.
3. Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1982,** *23*, 303; Sternbach, D. D.; Rossana, D. M.; Onan, K. D. *Tetrahedron Lett.* **1985,** *26*, 591.
4. Rossana, D. M. Ph.D. Thesis, Duke Univ., Durham, North Carolina, 1983.
5. Corey, E. J.; Glass, R. S. *J. Am. Chem. Soc.* **1967,** *89*, 2600.
6. Sternbach, D. D.; Ovington, O.; Smith, G. *Abst'. Pap., Am. Chem. Soc. Nat. Meet., 190th, Chicago, Ill.* **1985,** ORGN 98.
7. Wallquist, O.; Rey, M; Dreiding, A. S. *Helv. Chim Acta* **1983,** *66*, 1891.
8. Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Forstot, R. M. *Tetrahedron Lett.* **1983,** *24*, 3295.
9. Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978,** p. 499; Ranieri, R. L.; Calton, G. J.; Espenshave, M. A. *J. Antibiot.* **1978,** *31*, 38.
10. Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981,** *103*, 4136.
11. (a) Helquist, P.; Bornack, W.K.; Bhagwat, S. S.; Ponton, J. *J. Am. Chem. Soc.* **1981,** *103*, 4647; (b) Burke, S. D.; Murtiashaw, C. W.; Saunder, J. O.; Dike M. S. *J. Am. Chem. Soc.* **1982,** *104*, 872; (c) Kende, A. S.; Roth, B.; Sanfilippo, P J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982,** *104*, 5808; (d) Takeda, K.; Shimono, Y.; Yoshii, E. *J. Am. Chem. Soc.* **1983,** *105*, 563; (e) Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983,** *48*, 1146; (f) Dewanckele, J. K.; Zutterman, F.; Vandewalle, M. *Tetrahedron* **1983,** *39*, 3235; (g) Smith, A. B., III; Konopelski, J. P. *J. Org. Chem.* **1984,** *49*, 4094; (h) Iwata, C.; Yamashita, M.; Aoki, S.; Suzuki, K.; Takahashi, I.; Arakawa, H.; Imanishi, T.; Tanaka, T. *Chem. Pharm. Bull.* **1985,** *33*, 436; (i) Wender, P. A.; Wolanin, D. J. J. *Org. Chem.* **1985,** *50*, 4418; (j) Piers, E.; Moss, N. *Tetrahedron Lett.* **1985,** *26*, 2735; (k) Funk, R.L.; Abelman, M.M. *J. Org. Chem.* **1986,** *51*, 3247; (l) Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987,** *52*, 1483.
12. (a) Little, W. F.; Koestler, R. C. *J. Org. Chem.* **1961,** *26*, 3247; (b) Ziegler, K.; Gellet, H. G.; Martin, H.; Schnider, J. *Justus Liebigs Ann. Chem* **1954,** *589*, 91; (c) Know, G. R.; Pauson, R. L. *J. Chem. Soc.* **1961,** p. 4610; (d) Buchi, G.; Berthet, D.; Decorzant, R.; Grieder A.; Hauser, A. J. *J. Org. Chem.* **1976,** *41*, 3208.

13. Sternbach, D. D.; Hughes, J. W.; Burdi, D. F. *J. Org. Chem.* **1984,** *49*, 201.
14. Sternback, D. D.; Ensinger C. L. Unpublished results.
15. Bohlmann, F; Jakupovic, J. *Phytochemistry* **1980,** *19*, 259.
16. (a) Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983,** *24*, 83; (b) Paraquette, L. A.; Leone-Bay, A. *J. Am. Chem Soc.* **1983,** *105*, 7352; (c) Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985,** *26*, 2625; (d) Crimmins, M. T.; Mascarella, S. W. *J. Am. Chem. Soc.* **1986,** *108*, 3435.
17. Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Banks, B. A. *J. Am. Chem. Soc.* **1985,** *107*, 214.
18. (a) Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968,** *24*, 2215; (b) Ito.; Tomiyoshi, N.; Nokamura, K.; Azuma, S.; Izawa, M.; Maruyamz, F.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron* **1984,** *40*, 225.
19. Paquette, L. A.; Hfan, Y.-K. *J. Am. Chem. Soc.* **1981,** *103*, 1835.
20. Ayanoglu, E.; Gebreyesus, T.; Beechan, C. M.; Djerassi, C.; Kaisin, M. *Tetrahedron Lett.* **1978,** p. 1671.
21. (a) Little, R. D.; Carroll, G. L. *Tetrahedron Lett.* **1981,** *22*, 4389; (b) Stevens, K. E.; Paquette, L. A. *Tetrahedron Lett.* **1981,** *22*, 4393; (c) Birch, A. M.; Pattenden, G. *Tetrahedron Lett.* **1982,** *23*, 991; (d) Oppolzer, W.; Baettig, K. *Tetrahedron Lett.* **1982,** *23*, 4669; (e) Huguet, J.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982,** *65*, 241; (f) Mehta, G.; Reddy, D. S.; Murty, A. N. *J.C.S. Chem. Commun.* **1983,** p. 824; (g) Piers, E.; Karunaratne, V. *Can. J. Chem.* **1984,** *62*, 629; (h) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984,** *106*, 7500; (i) Stille, J. R.; Grubbs, R. *J. Am. Chem. Soc.* **1986,** *108*, 855; (j) Liu, H. J.; Kulkarni, M. G. *Tetrahedron Lett.* **1985,** *26*, 4847; (k) Curran, D. P.; Chen, M. H. *Tetrahedron Lett.* **1985,** *26*, 4991.
22. Grubbs and Stille (see reference 21i) have recently reported a successful alkylation of this substrate with cyclopentadienylmagnesium chloride. They have also confirmed our cyclization results when other counterions for cyclopentadiene are used.
23. Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981,** *103*, 2744.
24. Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976,** *59*, 2100.
25. We thank Prof. Oppolzer for sending copies of the spectra of this intermediate for comparison.

*Chapter 13*

# EXPLORATIONS TOWARD PSEUDOMONIC ACID C

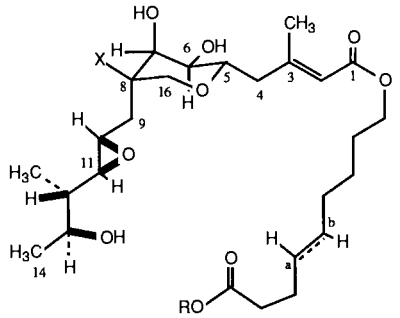
*David R. Williams*
*Department of Chemistry*
*Indiana University*
*Bloomington, Indiana*

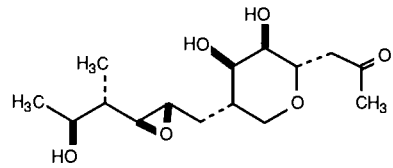


## I. Introduction

The pseudomonic acids consist of a small group of four closely related metabolites, originally isolated from submerged cultures of *Pseudomonas fluorescens* (NCIB 10586). Structural elucidation of the major component, pseudomonic acid A (**1**), was first communicated in 1974.[1] Detailed analysis of spectral data and key degradative characterizations of methyl pseudomonate A (**1a**) were reported in 1977, along with extensive proton-decoupling experiments, which allowed assignments of relative stereochemistry at C-5, C-6, C-7, and C-8.[2] In the following year, support for the *E*-configuration of the trisubstituted alkene of **1**, together with an X-ray diffraction of the *ortho*-bromophenylhydrazone of the degradation product **2**, completed formulation of the molecular structure and provided absolute stereochemistry at the eight chiral centers.[3] During this period, the structure of the minor component, pseudomonic acid B (**1b**), was also reported. The tertiary C-8 hydroxyl substituent was assigned as the $\beta$-equatorial alcohol based on the

equivalence of chemical shifts observed for the diastereotopic hydrogens at C-16.[4]





2

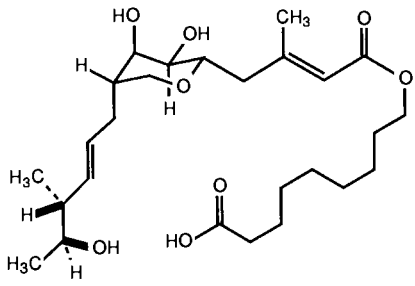
1 X = H ; R = H
$C_a$-$C_b$ = $C_2H_4$

1a X = H ; R = $CH_3$
$C_a$-$C_b$ = $C_2H_4$

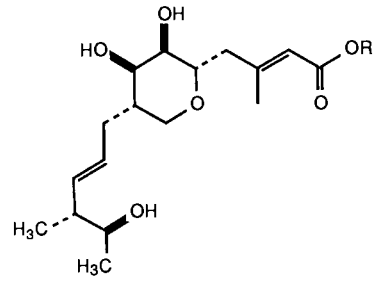
1b X = OH ; R = H
$C_a$-$C_b$ = $C_2H_4$

1d X = H ; R = H
$C_a$ - $C_b$ = E-C=C

The characterization of pseudomonic acid C (**1c**) was communicated in 1980.[5] Saponification led to the $\alpha,\beta$-unsaturated acid **3a**, which was given the trivial name monic acid C. Furthermore, the major metabolite **1** was converted into pseudomonic acid C in high yield. Unambiguous confirmation of the structure was achieved via X-ray diffraction studies of the crystalline ethyl monate C (**3b**).[6] Finally, the isolation of a new minor component, designated as pseudomonic acid D (**1d**), demonstrated the presence of an *E*-carbon double bond at C-4′ in a 9-hydroxynonenoic acid side chain.[7]



1c



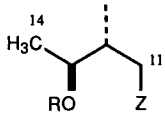
3a R = H
3b R = $C_2H_5$

## II. General Strategy and Objectives

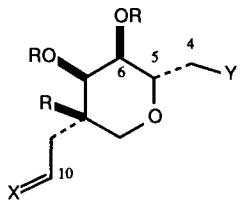
In 1980 we had authored a proposal for synthesis of the pseudomonic acid antibiotics. However, the disclosure of our successful total synthesis of pseudomonic acid C bears little resemblance to those early plans.[8] This is due to the natural evolution of ideas and our responses to the new opportunities which are presented by every unanticipated result, both positive and negative. I find it humorous that we chemists often identify those reaction schemes stemming from unprecedented discovery in the desired direction as examples of "good strategy," whereas pathways which evolve in response to unprecedented negative results are clearly "tactical victories." This observation merely leads us to conclude that most organic chemists are optimists, at least in retrospect. Perhaps we could define *strategy* as the *proposed* course in an uncharted area of organic synthesis. This seems reasonable since practitioners of the art of total synthesis commonly recognize that a *strategic* (proposed) intermediate is truly the next unknown compound of the sequence (the one you have not been able to prepare). Of course, any plan worthy of its weight will contain ample discussion of formation of *strategic* bonds and *strategic* disconnections. It seems the term has evolved to denote some kind of *pending* impending significance. Does this mean that our results must be *tactical* in nature? For some reason, the term *strategic results* clearly has a more impressive ring.

In retrospect, I am unsure which segments of our successful synthesis are attributable to strategy and which components are tactical. However, we initially had a number of fundamental objectives, which I will briefly summarize.

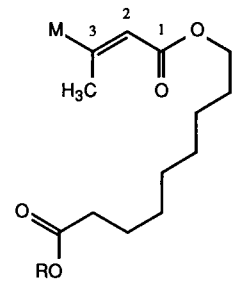
The pseudomonic acids, A, B, and C, were roughly dissected into three components **4**, **5**, and **6**. Our rationale was to first focus on the more




5



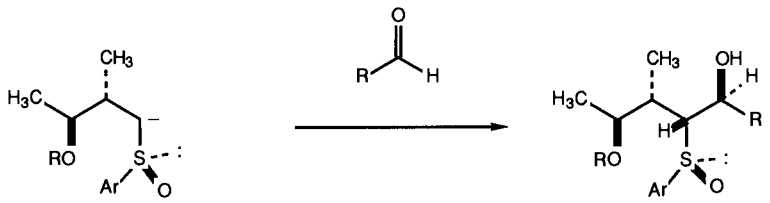

4




6

interesting tetrahydropyranyl system, followed by addition of the short, chiral carbon chain (C-11 → C-14) as a point of convergence with C-10 → C-11 bond formation. With the appropriate choice of an electron-

withdrawing group ($Z$) we could form the trans ($E$)-alkene of pseudomonic acid C (**1c**), or with acyclic stereocontrol we might obtain the desired trans-$\beta$-epoxide at C-10 → C-11 as required for pseudomonic acids A (**1a**) and B (**1b**). The latter possibility was clearly suggested by our earlier studies of stereocontrolled additions of $\alpha$-sulfinyl carbanions **7** to aldehydes, affording **8**.[9]




7 8

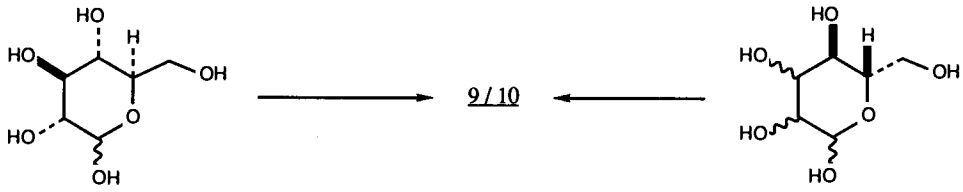
The final stages of the synthesis would extend the carbon chain at C-4, allowing a stereospecific introduction of the trisubstituted olefin originating via nucleophilic addition of some organometallic reagent, which would permit further elaboration for attachment of the carbon chain as required for net incorporation of **6**.

We identified two tetrahydropyrans, **9** and **10**, as key objectives leading to **4**. These would be prepared as chiral materials with **9** as an intermediate for pseudomonic acid C and **10** for pseudomonic acid B. Furthermore, we hoped that each of these would share a common origin for the beginning stages of the synthesis.


9 10

Although my developing research group had high levels of enthusiasm, we had little in-house expertise in the area of carbohydrate chemistry. I was keenly aware of the carbohydrate "chiron" concepts as advanced by Hanessian, Fraser-Reid, and others.[10] Thus, an intangible benefit of our involvement with the pseudomonic acids was to provide a learning experience which would allow us to develop techniques and an appreciation of the carbohydrate literature.

It was readily apparent that the tetrahydropyranyl systems **9** and **10** resembled hexose derivatives. However, the stereochemistry at C-5 was opposite to that available from the common D-hexoses, such as D-glucose (**11**). As starting materials, the related L-sugars **12** were prohibitively expensive.



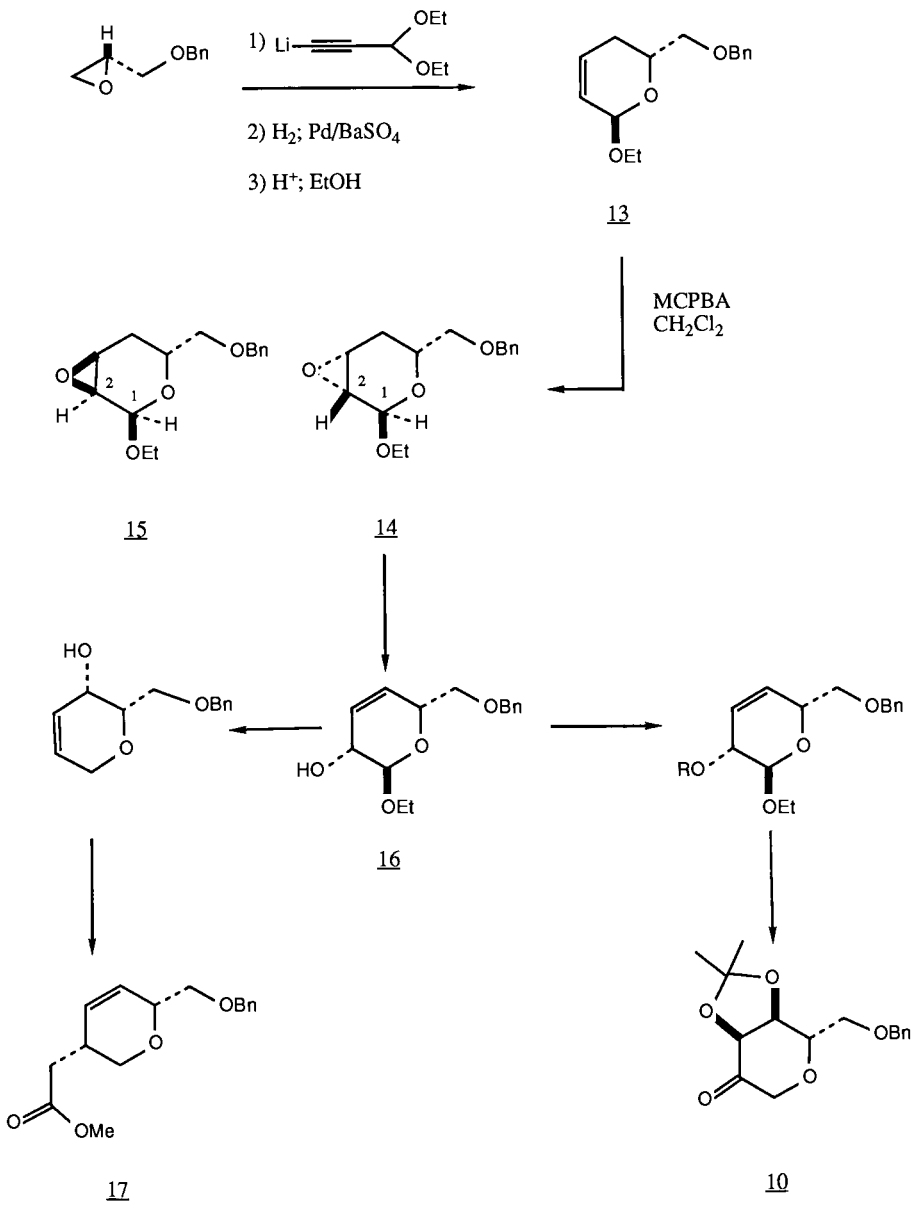

11 12

As a result, we began contemplating the preparation of hexose derivatives in the L-series as an immediate goal which could afford information and techniques to be put to general use for the synthesis of polyhydroxylated natural products.

In April 1982, after 2 years of reading and writing, we began in earnest our studies toward pseudomonic acid C. During this period, vigorous development of the pseudomonic acids in the Beecham Pharmaceuticals Laboratories drew attention to the potential for commercialization.[11] In addition, Kozikowski and co-workers had communicated the first synthesis of racemic **1c** followed by conditions for conversion of methyl pseudomonate C to pseudomonic acid A.[12] These studies provided a wealth of information. However, our resolve was to complete a synthesis of (+)-pseudomonic acid C while exploring *new* opportunities for construction of the molecule. At this point, I seem to recall that the most difficult part of a total synthesis is usually finishing it. Our commitment was total.

## III. Difficult Beginnings: Stereocontrol in Tetrahydropyrans

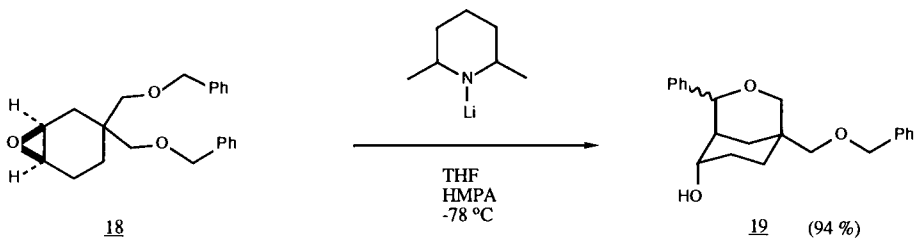
We developed a straightforward preparation of the chiral dihydropyran **13** as shown in Scheme 1. The reagents were inexpensive, and **13** was stable, available in multigram quantities, and easily purified. Epoxidation proceeded in high yield to give approximately a 3 : 1 ratio of two isomers, which were conveniently separated by flash chromatography. The major compound was shown to be the desired $\alpha$-epoxide **14** as recognized by the characteristically small vicinal proton coupling $J_{1,2}$, which was 0.6 Hz for **14**, whereas the minor $\beta$-isomer **15** displayed $J_{1,2}$ = 3.0 Hz.[13] Our plan called for a base-induced isomerization of **14** to the allylic alcohol **16**. Reduction of the


1) Li
OEt
OEt
2) $H_2$; Pd/$BaSO_4$
3) $H^+$; EtOH
OBn
OEt
13
MCPBA
$CH_2Cl_2$
15
14
HO
RO
16
17
10
OMe

SCHEME 1

anomeric C-1 carbon followed by a series of standard protections and oxidations could lead to **10** for the synthesis of **Ib**. On the other hand, reduction of the acetal and 1,3-transposition of the allylic alcohol would produce a substrate for a 3,3-sigmatropic Claisen process to the ester **17**. Thus, the allylic alcohol **16** could function as our common intermediate to both pseudomonic acids B and C.

Although closely related examples of base-catalyzed isomerizations of oxiranes were known,[14] all of the usual reagents and conditions led to decomposition of **14** without formation of **16**.[15] To some extent, our troubles were traced to the choice of the O-benzyl protecting group, as we soon discovered that the analogous carbocycle **18** produced an intermediate benzylic carbanion under the strongly basic conditions with intramolecular nucleophilic oxirane opening to yield **19**.[16]




18 19 (94 %)

Using trimethylsilyl triflate in the presence of 2,6-lutidine in toluene at −78°C, the α-epoxide **14** was transformed to the bicyclic system **20** in excellent yield (86%).[17] Mechanistically, we suggest intermediate formation of the triflate **21** with ring inversion allowing intramolecular displacement to **20** with subsequent debenzylation. Notably, the β-epoxide **15** was stable to these conditions at -78°C, but underwent complete decomposition upon gradual warming. Diaxial opening of **15** to the triflate **22** was expected to be sluggish owing to the powerful inductive effects at C-1. However, direct cyclization of **15** was never observed. A structural elucidation of **20** was feasible by a systematic decoupling study of the proton NMR, leading to the assignments shown in Fig. 1.

These difficulties were overcome as illustrated in Scheme 2, beginning with a two-step process involving trans antiperiplanar opening of the epoxide **14** with sodium phenylselenide in ethanol, yielding **23** (87%). Subsequent oxidation with syn elimination of the corresponding selenoxide at ambient temperature produced the desired allylic alcohol **16** (96%). Benzoylation furnished **24**, and subsequent reduction with triethylsilane in trifluoroacetic acid at 0°C with addition of boron trifluoride etherate (1 equivalent) gave the dihydropyran **25** in 72% isolated yield. The product was readily identified

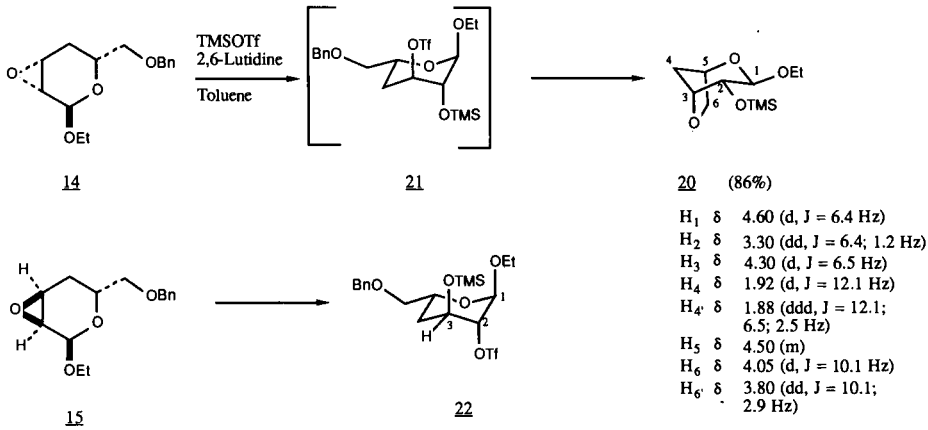
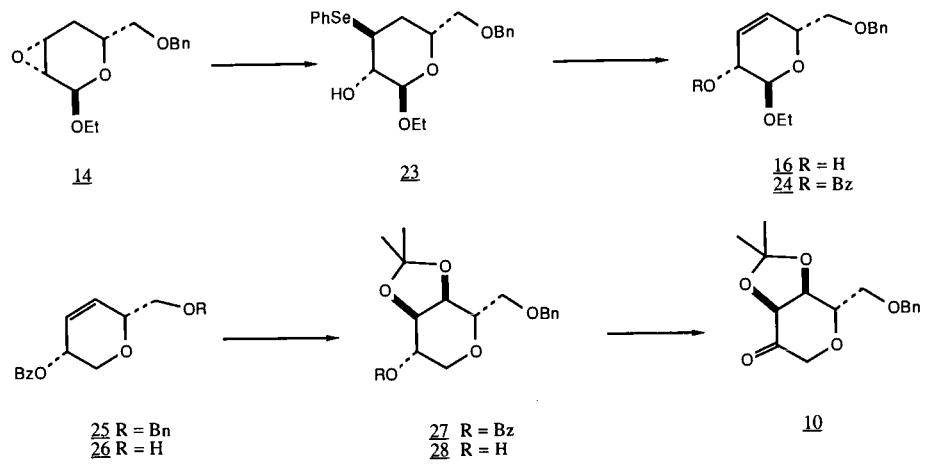
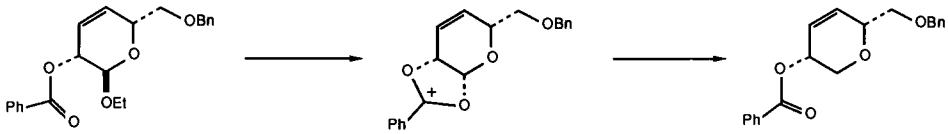



FIG. 1




SCHEME 2

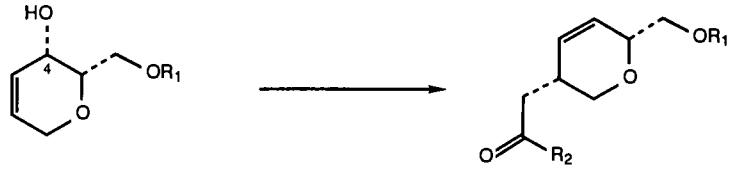
by new signals in the proton NMR data assignable to the methylene group at C-1. One hydrogen at $\delta$4.24 was seen as a broadened doublet ($J_{gem}$ = 12.9 Hz) resulting from long-range and geminal interactions, whereas the other C-1 hydrogen at $\delta$3.91 was clearly a doublet of doublets ($J_{gem}$ = 12.9; $J_{vic}$ = 2.8 Hz). Small amounts of the primary alcohol **26** were obtained as the only side product of this reaction, a particularly satisfying result when one considers the possibilities for silane reduction of the intermediate carbocation **25a**.



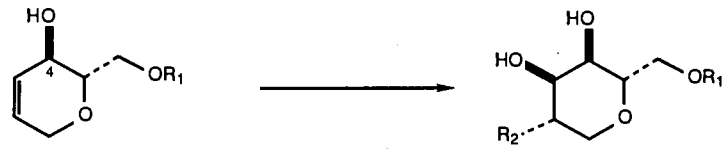

24 25a 25

Routine cis hydroxylation of **25** and transketalization of the diol using 2,2-dimethoxypropane gave solely the acetonide **27**. Hydrolysis to the secondary alcohol **28** was followed by oxidation to the intermediate ketone **10** as necessary for our future studies.

We had recognized that a plan permitting a stereocontrolled introduction of a hydroxyl at C-4 would circumvent the rather nonselective epoxidation of Scheme 1 and further eliminate the necessity of a 1,3-transposition. In fact, either $\alpha$- or $\beta$-hydroxyl stereochemistry seemed serviceable since the $\alpha$-alcohol **29** would be used as a substrate for 3,3-sigmatropic rearrangements to **17**, whereas the $\beta$-alcohol **30** could lead to the trans diaxial introduction of the C-2 alkyl chain and the C-3 hydroxyl as shown in **31**. This latter possibility was a significant step in our thinking because it stimulated us to consider plans for construction of the vicinal diol by methodology other than cis hydroxylation of an olefin.

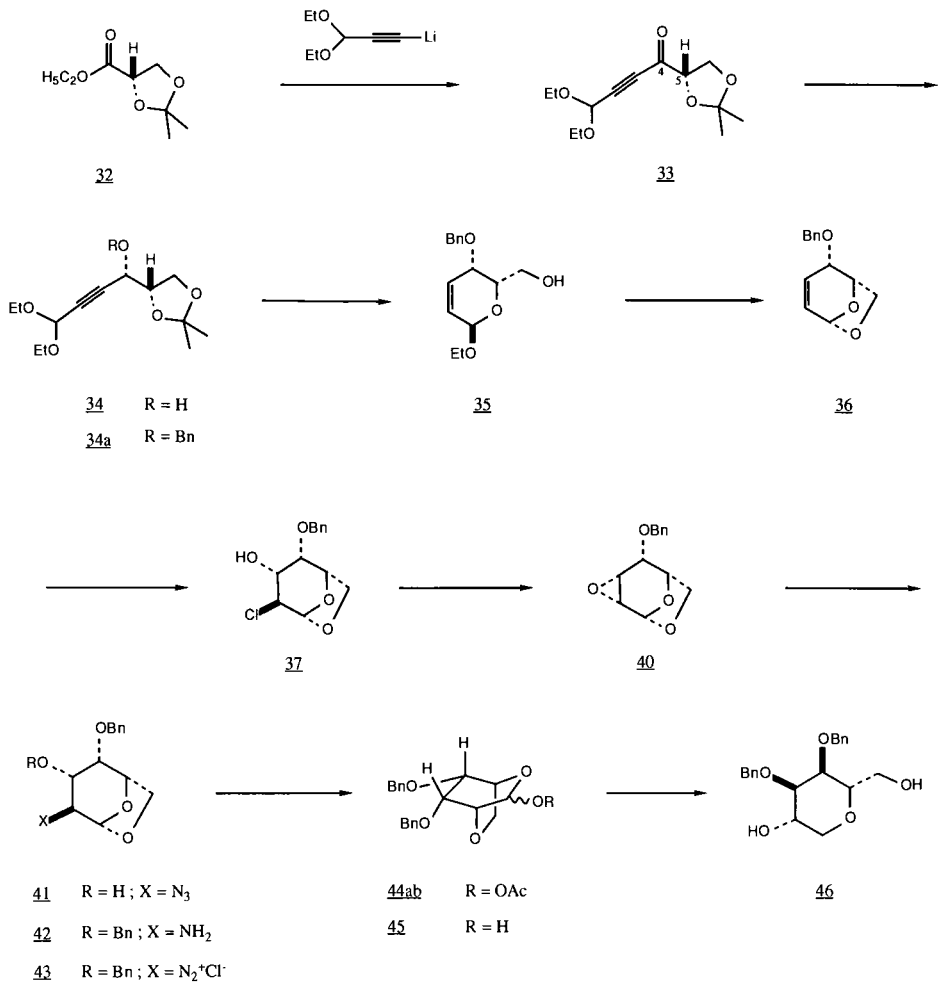



29 17




30 31

Our early investigations in this direction are displayed in Scheme 3, starting with the chiral acetonide **32**, which was prepared by diazotization of L-serine.[18] Nucleophilic substitution using 1-lithio-3,3-diethoxypropyne in tetrahydrofuran at -78°C gave the acetylenic ketone **33** (50% yield) after column chromatography. We needed a diastereoselective reduction of the



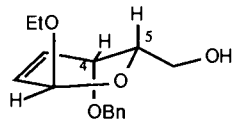

SCHEME 3

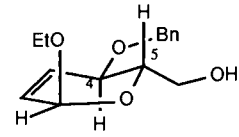
carbonyl at C-4 to produce a single stereoisomer relative to the adjacent chiral center at C-5. All reagents and conditions gave rise to mixtures of diastereomeric alcohols as summarized by the examples in Table 1. However, use of the chirally modified borane, (*R*)-Alpine Borane®,[19] resulted in good conversion to the $\alpha$-alcohol **34**, demonstrating the same enantiofacial preference as predicted by the Midland model.[20] By contrast, the antipodal (*S*)-Alpine Borane® was adversely affected by the adjacent asymmetric center at C-5, and reductions produced approximately a 1 : 1 mixture of diastereomeric alcohols.

TABLE I
CARBONYL REDUCTIONS OF *33*

| Hydride reagents | Yield (%) | Product ratio ($\beta$-OH) | Product ratio ($\alpha$-OH) |
|---|---|---|---|
| L-Selectride, THF, −78°C | 94 | 40 | 60 |
| $Zn(BH_4)_2$, ether, 0°C | 72 | 30 | 70 |
| DIBAL, THF, $CH_2Cl_2$, −78°C | 48 | 40 | 60 |
| DIBAL, $CH_2Cl_2$, −78°C | 66 | 55 | 45 |
| $LiBH_4$, THF | 78 | 57 | 43 |
| *S*-Alpine Borane | 93 | 54 | 46 |
| *R*-Alpine Borane | 91 | 10 | 90 |

Benzylation and partial hydrogenation of **34** was followed by treatment with a catalytic amount of *p*-toluenesulfonic acid in absolute ethanol to yield the ethyl hexopyranoside **35** as a single isomer which was assumed to be the $\alpha$-anomer.[21] Furthermore, our analysis of the proton NMR data for the pure major and minor pyranosides **35a** and **35b** allowed clear assignments of stereochemistry at C-4 for reductions of the acetylenic ketone **33**.



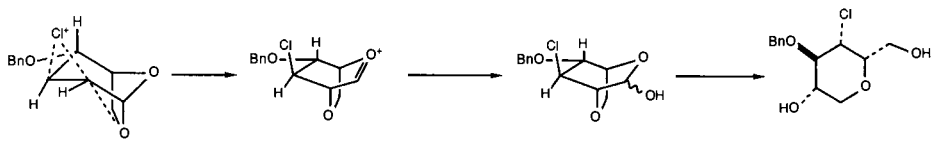




35a $J_{4,5}$ = 2.8 Hz

35b $J_{4,5}$ = 9.1 Hz

Noting that the available hydroxyl configuration at C-4 was opposite to that required for the natural products, we needed to accomplish a C-4 inversion as well as a reduction of the anomeric center at C-1. Internal ketalization of **35** to the 1,6-anhydro sugar **36** was driven by acid catalysis with azeotropic removal of ethanol in benzene at reflux. Reaction of **36** with freshly prepared *tert*-butylhypochlorite in acetone–water (3 : 1 by volume) at -25°C (bath temperature) gave two major products and traces of benzaldehyde arising from benzylic oxidation of our protecting group. Electrophilic attack on the exo face of the carbon double bond and addition of water in a trans diaxial fashion afforded the chlorohydrin **37** (47% yield). A more polar product **38** was obtained in nearly equal amounts (45% yield), displaying anchimeric assistance and subsequent migration of the trans coplanar oxymethylene bridge with formation of the stabilized oxonium species **38a**. Lithium borohydride reduction of the lactols **38** cleanly produced the tetrahydropyran diol **39**. Thus, we had demonstrated, albeit prematurely, the inversion

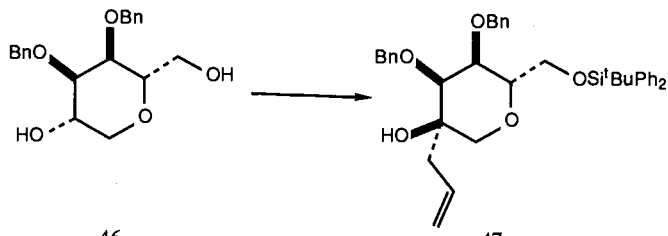
of the carbohydrate skeleton with concomitant reduction of the anomeric carbon.



38a 38 39

Treatment of chlorohydrin (Scheme 3) with sodium hydride in tetrahydrofuran at 22°C gave the expected α-epoxide **40**. Our structural assignment of **40** was supported by direct epoxidation of the alkene **36** using *meta*-chloroperbenzoic acid, which afforded solely the corresponding β-oxirane. Ring opening of **40** with sodium azide required harsh (HMPA, 2-methoxyethanol, 100°C) conditions, resulting in a 3 : 1 ratio of predominantly the desired azido-sugar **41** complicated by alternative attack at C-3 to give some of the diequatorial isomer. Benzylation of **41** followed by catalytic reduction at atmospheric pressure produced the requisite amine **42** in quantitative yield. Diazotization was performed in glacial acetic acid at 10°C by addition of a concentrated aqueous solution of sodium nitrite. Thus, the intermediate diazonium salt **43** allowed for the facile 1,2 shift of the antiperiplanar oxymethylene bridge with concomitant loss of nitrogen. Chromatography led to the isolation of the novel dioxabicyclo[2.2.2]system in 86% yield with purification of the α-and β-acetates **44a** (35%) and **44b** (21%), respectively, as well as the lactols **45** (30%). Reduction of these products, individually or as a mixture, with lithium borohydride afforded 80–87% yields of the desired optically active tetrahydropyran diol **46**. The net result of this sequence has been to turn the starting hexose inside out. In effect, the C-1 position of the anhydro sugar **36** has become C-6 of **46**, with the C-6 assignment at C-1. In the process, each chiral center of **46** has, in effect, undergone inversion relative to the starting monosaccharide.

Further elaboration of **46** by silylation of the primary alcohol, oxidation at C-2, and subsequent addition of allyl Grignard at −78°C supplied the tertiary alcohol **47** as a potential intermediate for pseudomonic acid B.



46 47

However, our efforts toward pseudomonic acid C had been stifled, and opportunities for reduction of the anomeric C-1 carbon of **35** were questionable. Moreover, during this period, reports from other laboratories had documented the 1,3-O→C transposition as incorporated in our Claisen rearrangement pathway to **1c**.[22] In view of the difficulties we had encountered, we began to reformulate our plans for the tetrahydropyranyl system of **1c**. In the next section we will see how synthesis of the tetrahydropyran moiety evolved from a study of relative stereocontrol on a ring template to an investigation of acyclic diastereoselection.

## IV. Phase Two: Stereoselective Synthesis of the Tetrahydropyran Component

Our efforts of Scheme 3 had developed an approach to introducing the cis-C-6–C-7 diol with stereocontrolled placement of each hydroxyl independently. A more straightforward protocol would incorporate the required C-6 hydroxyl in the starting chiron. Consequently, we began considering nucleophilic additions for the C-7 → C-8 bond connection. Such a plan, as illustrated in Fig. 2, required (a) the availability of an appropriate four-carbon chiron **48**, (b) addition with diastereofacial selectivity at C-7, (c) stereoselective placement of an alkyl substituent at C-8 as in **49** to provide future elaboration as the C-9 → C-14 side chain, and (d) a means for ring closure of the tetrahydropyranyl system, of which C—O bond formation by intramolecular alkoxide displacement of an effective leaving group from the primary site (C-16) in **50** seemed most reasonable. A related alternative for C → O bond closure was also considered. For example, backside displacements using the primary alkoxide **51** could secure the necessary stereochemistry at C-5. However, this route required nucelophilic attack to occur at the more hindered secondary carbon versus the favorable situation in **50**. In addition, we anticipated further deactivation toward nucleophilic alkylations at C-5 owing to the inductive effects of the vicinal alkoxy functions at C-4 and C-6. Although the epoxide **52** might be expected to negate, to some degree, the disadvantages cited above, this 1,3-diol could undergo competing four-, five-, or six-membered oxacycle formation. We chose first to explore pathways which established the correct C-5 asymmetry at the earliest possible juncture.

Our strategy for synthesis of the tetrahydropyran component of pseudomonic acid C had become a problem of acyclic stereoselection. First, we needed a readily available, optically active, four-carbon precursor. With modifications of known procedures, we had previously developed an efficient route to the L-threitol **53** beginning with L-ascorbic acid[23] or via the

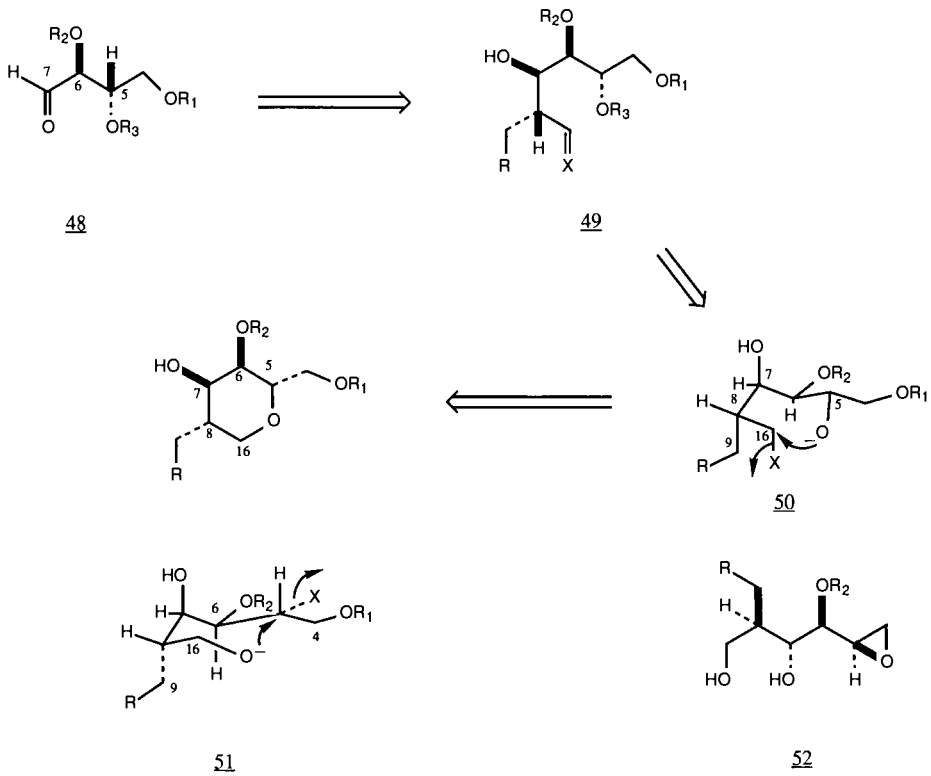



FIG. 2

L-tartrate.[24] Likewise, the D-erythritol **54** was produced from D-isoascorbic acid. Unfortunately, we required the enantiomeric L-erythritol for preparation of chirons corresponding to **48**. In principle, this could be achieved by a wise choice of protecting group manipulations which would, in effect, reverse the C-1 and C-4 positions of **54**. One could also consider a scheme for inversion of hydroxyl stereochemistry at C-2 of the threo diastereomer **53**. In practice, our requirement of a convenient large-scale preparation of the L-erythritol was accomplished by a three-step sequence using D-glucose.[25] Although the crystalline diol **55** was easily obtained and stable, it was not appropriately functionalized to meet our needs. Formation of the trityl ether of **55**, benzylation of the secondary alcohol, and acid-catalyzed hydrolysis gave a crude triol, which was selectively protected as the five-membered acetonide **56** in 50% overall yield (Fig. 3). Swern oxidation conditions using oxalyl chloride and dimethyl sulfoxide in methylene chloride at −78°C followed by addition of anhydrous triethylamine led to 85–92% yields of the desired aldehyde **57**. However, approximately 2% of the diastereomer

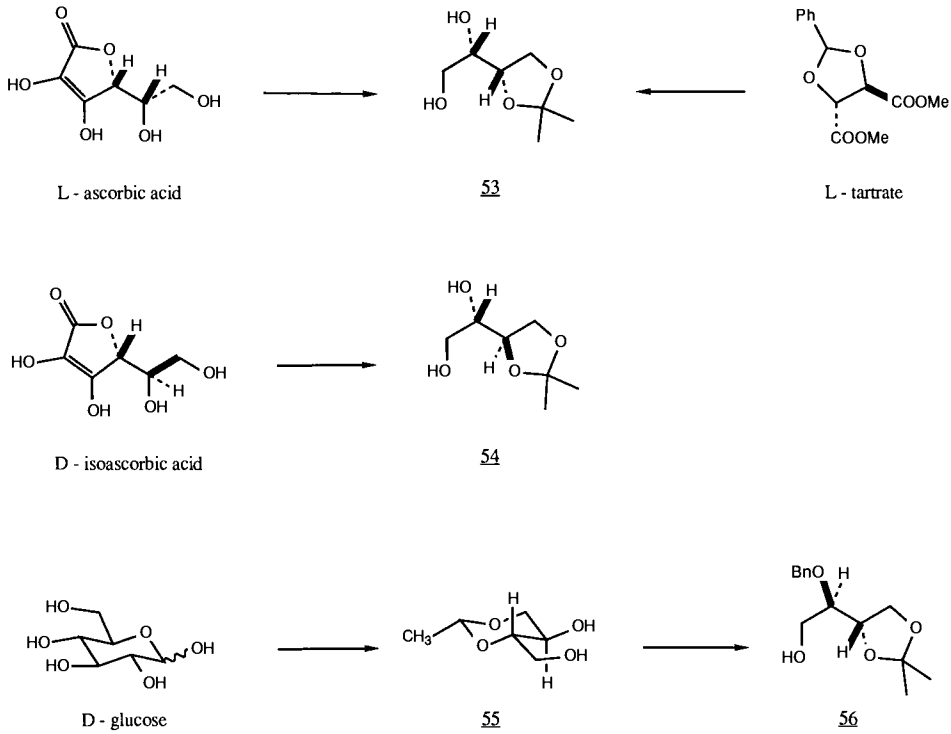
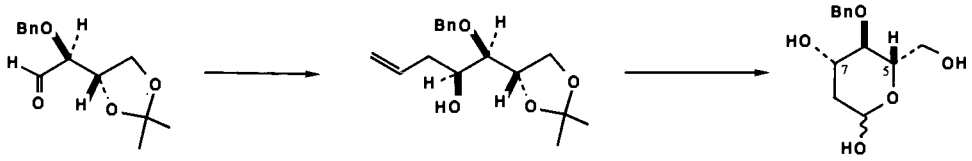


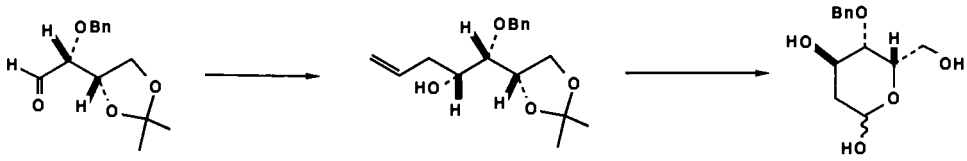

FIG. 3

resulting from C-2 epimerization was evident by high-field proton NMR. Pyridinium chlorochromate oxidations of **56** at ambient temperature gave lower yields (70–75%) of **57** without detectable isomerization.

We were now prepared to evaluate our chances for stereoselective additions to the $\alpha,\beta$-dialkoxyaldehyde **57**. Reactions with a variety of allylic organometallic reagents exhibited nearly indiscriminate diastereofacial selectivity, providing a pair of homoallylic alcohols. The magnesium bromide-catalyzed addition of allyltrimethylsilane to aldehydes **57** and **58** proved to be a significant exception, affording greater than 98% stereocontrol.[26] The products **59** and **60** confirm the controlling influence of the stereochemistry of the $\alpha$-benzyloxy substituent and support a strong $\alpha$-chelation effect. Transformations of **59** and **60** to the tetrahydropyrans **61** and **62** clearly indicated that we had selectively obtained the undesired epimer at C-7. If we were to have any chance of achieving the required stereochemistry at C-7, our analysis clearly indicated that we would need a counterion which would not engage in $\alpha$- and/or $\beta$-chelation events to direct nucleophilic addition.



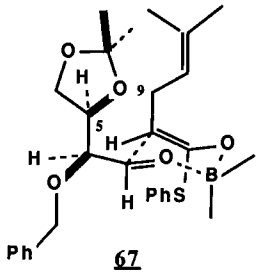
57 59 61



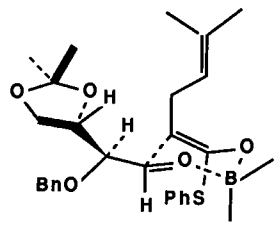
58 60 62

This study failed to take into account the effects of alkyl substitution and the stereocontrol required at C-8, as illustrated for **49** in our plan. Of course, the most direct pathway for constructing a 1,3-diol beginning with the chiral aldehyde **57** would evoke an aldol condensation strategy. Extensive studies of the aldol reaction had led to the development of several valuable techniques, all resulting in excellent stereoselectivity.[27] However, very little stereochemical information was available for such condensations with $\alpha,\beta$-dialkoxyaldehydes. Using the aldol methodology as developed by Masamune,[28] we transformed the phenylthio ester **63** of Scheme 4 into the corresponding *Z*(*O*)-boron enolate **64**. Our choice of the boron-mediated aldol was particularly significant. On a large scale we could readily generate a single enolate geometry, and the 9-borabicyclo[3.3.1]non-9-yl derivative **64** offered only one additional site for coordination as a Lewis acid. Subsequent addition of aldehyde **57** at -78°C gave two diastereomers, which were separated by flash chromatography and later assigned as the 2,3-syn–3,4-anti isomer **65** (79%) and the corresponding 2,3-syn–3,4-syn product **66** (5%). The observed diastereofacial selectivity of **65** is predicted by the Felkin–Ahn model **67** with attack from the *re*-face of the aldehyde through the chairlike cyclic transition state. This outcome may be fortuitous in light of the steric interactions of the allyl chain (C-9) and the acetonide (C-5). Nonbonded interactions are relieved by the alternative Cornforth-like transition state **68**. Assessing all of the possible electronic and steric interactions presented in the numerous conformational arrangements available to our aldol transition state is a difficult task. Recent developments by Hoffmann[29] and by Roush[30] suggest that we may cautiously consider our boron enolate in

much the same way as reactions of (*Z*)- and (*E*)-crotylboronates with chiral aldehydes. The intrinsic diastereofacial tendency of the chiral aldehyde component is determined predominantly by the absolute configuration of the $\alpha$-carbon. The relative configuration of the $\beta$-alkoxy substituent of **57** is of minor influence. Finally, the geometry of our *Z*(*O*)-boron enolate may directly affect the sense of asymmetric induction as a result of nonbonded interactions in a tight transition state. A detailed comparative study of stereoselectivities for the Masamune aldol procedure using a variety of $\alpha,\beta$-dialkoxy-substituted aldehydes is not available.



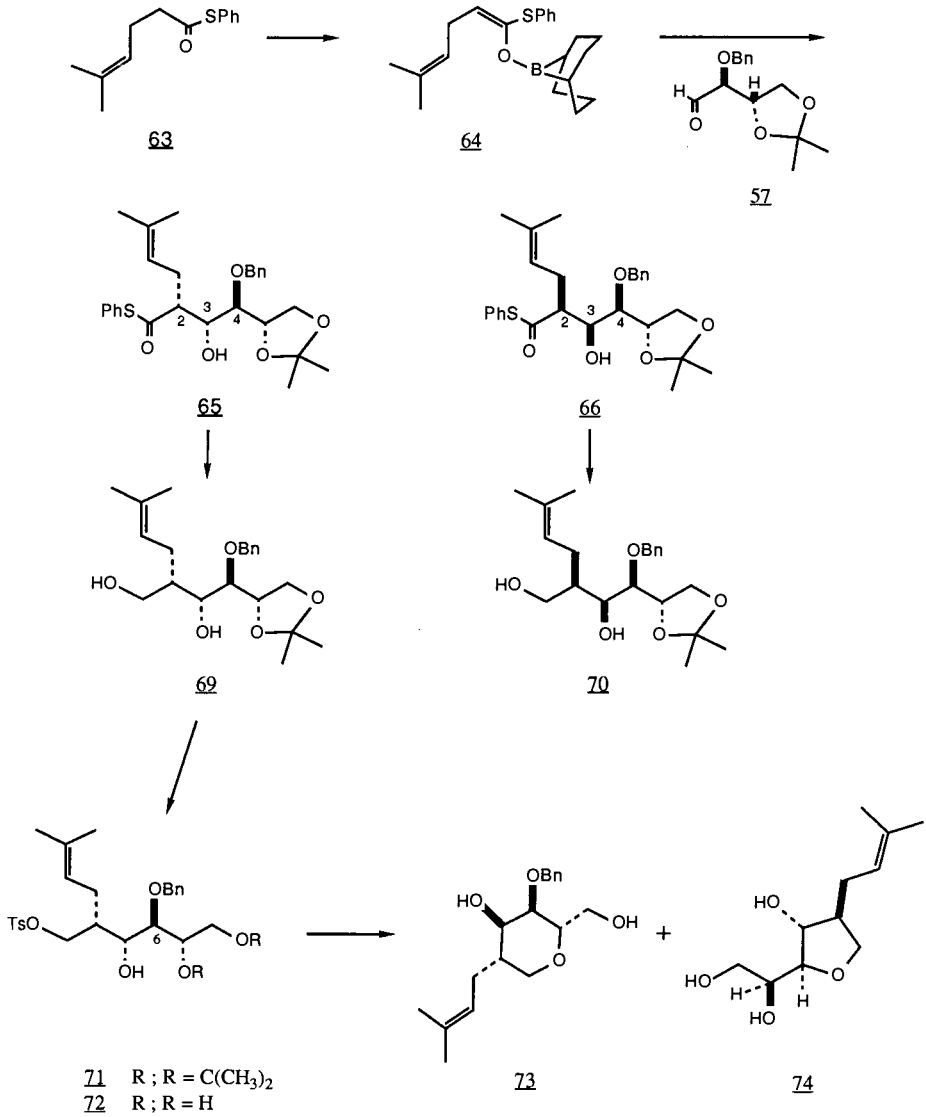

67




68

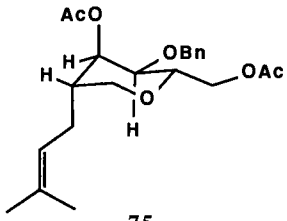
Lithium aluminum hydride reduction of each of the thioesters **65** and **66** at 0°C in ether afforded the pure 1,3-diols **69** and **70**. Selective conversion of **69** to the primary tosylate **71** was followed by acid-catalyzed hydrolysis of the ketal to give the crude triol **72**. Immediate addition of methanolic sodium methoxide resulted in ring closure to the desired tetrahydropyran **73** (80%) along with small amounts of another cyclization product, which was subsequently identified as the tetrahydrofuran **74** (5%) (Scheme 4). A number of bases were used without dramatically altering the course of the cyclization. Although we had recognized the possibility of competing oxetane formation, it was difficult to assess the influence of conformational preferences of the starting acyclic triol **72**. Participation of the benzyl ether (at C-6) led to displacement of the sulfonate and formation of an oxonium ion, which underwent subsequent dealkylation to **74**. This process was initiated prior to the introduction of strong bases, and fortunately it proceeded at a relatively low rate compared to the internal alkoxide displacement. Rigorous stereochemical assignments of the two isomeric aldol products **65** and **66** were possible after conversion to the tetrahydropyrans in each series. Formation of the diacetates **75** and **76** permitted a clear analysis by proton-decoupling studies.

We had reached a critical intermediate in our synthetic planning. The chiral tetrahydropyran diol **73** had been achieved with good overall stereocontrol. This component was readied for a convergent linkage to the

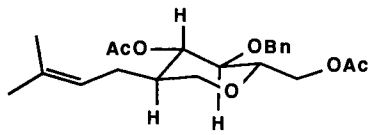



SCHEME 4

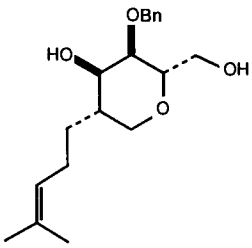
C-11–C-14 carbon segment by three steps. Formation of the *tert*-butyldiphenylsilyl ether and subsequent benzylation of the secondary hydroxyl was followed by ozonolysis in methylene chloride containing pyridine at −78°C. This procedure selectively led to the desired aldehyde **77** without




75




76

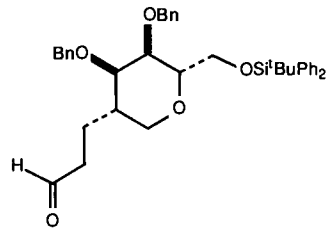



73

1) $Ph_2{}^tBuSi\text{-}Cl$
$CH_2Cl_2$; DMAP

2) BnBr; NaH
THF

3) $O_3$; $CH_2Cl_2$
pyr at -78 °C
then DMS

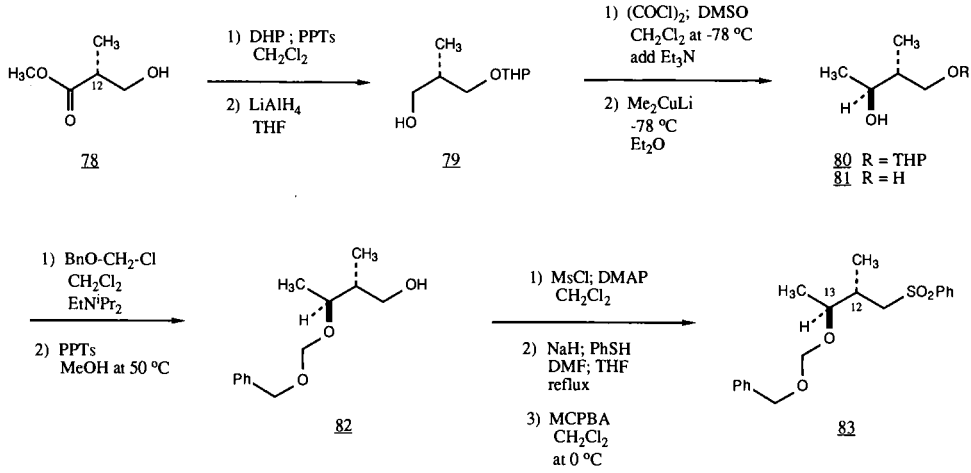



77 (82.3% overall yield)

competing oxidation of the benzyl ethers to their corresponding benzoates. In the final section we will discuss plans and problems which had to be overcome for completion of our total synthesis..

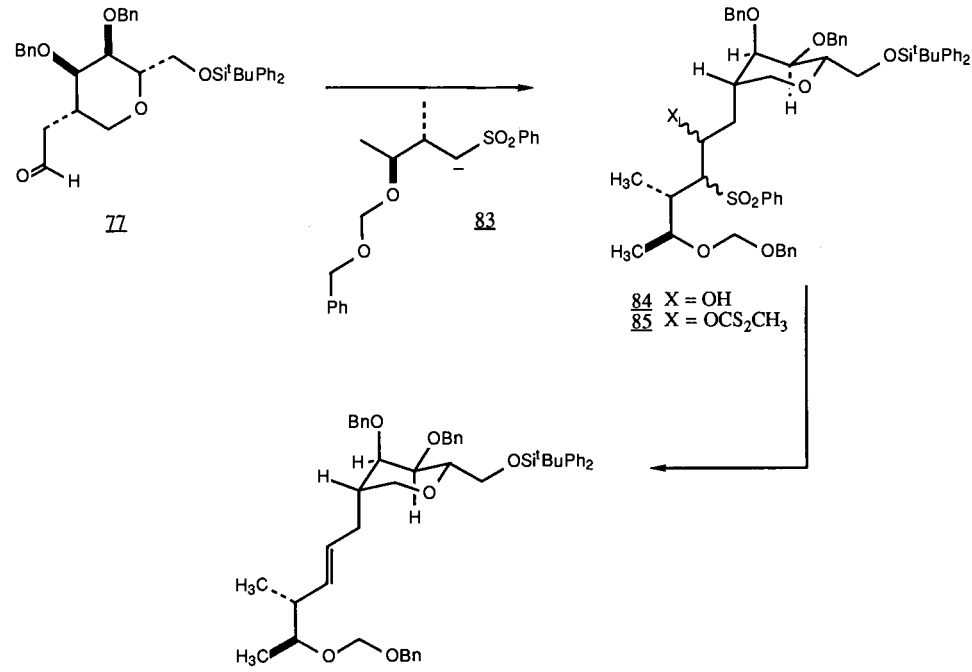
## V. The Final Stages: It's Never Over Until It's Over

Preparation of the C-11–C-14 carbon segment required chiral materials to prevent production of an unwanted diastereoisomer after attachment to the tetrahydropyran **77**. We chose to begin with the correct C-12 chirality using methyl (*R*)-(−)-3-hydroxy-2-methylpropionate (**78**). Protection as the tetrahydropyranyl ether and direct reduction with lithium aluminum hydride gave alcohol **79** in quantitative yield. Swern oxidation and addition of an ethereal solution of lithium dimethylcuprate at -70°C proceeded with excellent relative stereocontrol.[31] Deprotection of **80** using pyridinium *p*-toluenesulfonate (PPTS) in methanol gave 82% of the known chiral diol **81**.[32] Once we had established the enantiomeric purity of **81**, the secondary alcohol **80** was protected as its benzyloxymethyl ether and selective removal of the THP unit gave a 93% yield of **82**. Conversion to the mesylate, displacement with sodium thiophenolate, and oxidation afforded the desired sulfone **83**.



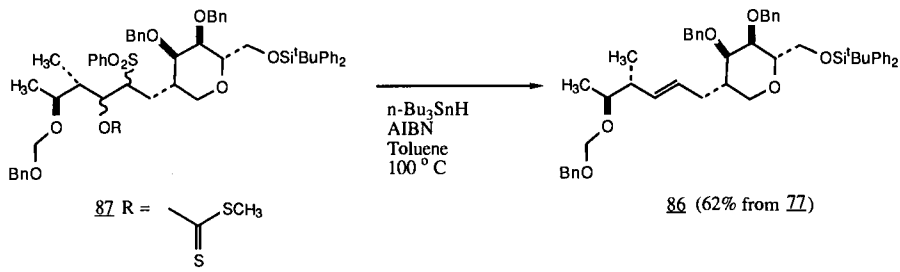

78 79 80 R = THP 81 R = H 82 83

Our strategy called for use of the Julia procedure for construction of the C-10–C-11 carbon double bond.[33] Deprotonation of **83** using lithium diisopropylamide in THF at -60°C gave a bright yellow solution of the $\alpha$-sulfonyl carbanion, which was quenched by addition of the aldehyde **77**.

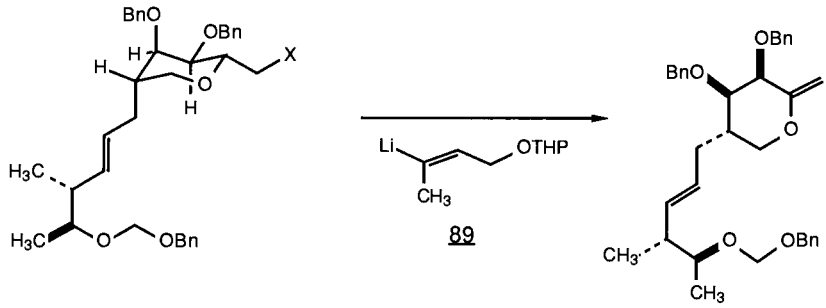


77 83 84 X = OH 85 X = $OCS_2CH_3$ 86 (83% from 77)

Excellent yields of diastereomeric mixtures of the β-hydroxysulfone adducts **84** were obtained, and these were converted into their corresponding acetates, benzoates, and mesylates for reductive eliminations using 6% sodium amalgam in ethanol. Our substrates were recovered unaffected under the usual reductive conditions. However, more vigorous attempts afforded saponification to the β-hydroxysulfones and further cleavage to the starting sulfone **83**.[34] Fortunately, we were able to adapt an alternative procedure briefly reported by Lythgoe and Waterhouse.[35] Quenching our addition reactions with carbon disulfide and methyl iodide provided the diastereomeric β-sulfonyl xanthates **85**. After flash chromatography, reductive elimination with tri-*n*-butyltin hydride in toluene at 100°C gave an 86% yield of the desired olefin **86** as the major component of the thermodynamic process (*E*/*Z* ratio 85:15). The reacting partners were also reversed to give the xanthates **87**, which underwent tin hydride reduction to **86** in 62% overall yield for the three-step condensation–elimination pathway. Since many functional groups are not affected by tin hydrides, the process may prove useful for connective constructions in complex molecules.




Fluoride-induced deprotection of the pure *E*-alkene **86** gave the primary alcohol **88** in 85% yield. We had hoped to elongate the carbon chain with formation of the C-3–C-4 single bond of pseudomonic acid C via an alkylation reaction which would ensure retention of the geometry of the trisubstituted olefin. This point is significant since the corresponding *Z*-α,β-unsaturated ester has greatly reduced antibiotic activity.[36] Furthermore, Wittig processes afforded construction of the unsaturation as an *E*/*Z* mixture, requiring a difficult separation of the desired isomer.[37] The known vinyllithium reagent **89** was prepared from its vinyl bromide by exchange using *tert*-butyllithium,[38] and several procedures were followed to examine the related cuprates and mixed Gilman reagents derived from **89**. Alkylation attempts using the primary mesylate, triflate, bromide, or iodide obtained from the alcohol **88** all resulted in elimination to the vinyl ether **90**. Although nucleophilic displacements with sodium cyanide were feasible, lithium acetylides also provoked the characteristic elimination process.



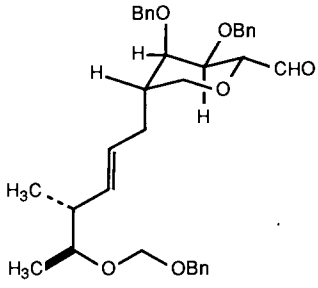

86 X = OSi$^t$BuPh$_2$
88 X = OH

90

To circumvent this difficulty, we needed to consider a more electrophilic site for carbon–carbon bond formation. This was achieved via a pyridinium dichromate (PDC) oxidation of **88** in methylene chloride, yielding a separable mixture (4 : 1) of **91** and the isomeric aldehyde **92**. On the other hand, Swern oxidation conditions at −78°C led to a 1 : 3 ratio favoring the thermodynamically more stable epimer **92**. Our initial attempts to condense the vinyllithium **89** with **91** led to substantial amounts of $\beta$-elimination of the C-6 benzyloxy substituent, affording mixtures of the desired alcohols **93** and the $\alpha,\beta$-unsatured aldehyde **94**. We sought to reduce the basicity of the nucleophilic component via *in situ* formation of the corresponding organocerium reagent.[39] Thus, a suspension of anhydrous cerium(III) iodide in THF was added dropwise to **89** at −100°C, followed by slow introduction of the aldehyde to produce a 65% isolated yield of the allylic alcohols **93** as a 3 : 1 mixture of C-4 epimers, without effecting $\beta$-elimination.

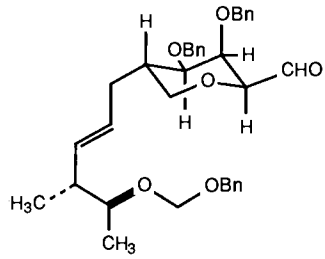
We were forced to deal with yet an additional problem. The unwanted C-4 hydroxyls of **93** had to be replaced by hydrogen without loss of regio- or stereochemical integrity of the adjacent trisubstituted alkene and without reductive ring opening of the tetrahydropyran. Transformation of **93** to the allylic bromides **95** was accomplished using carbon tetrabromide–triphenylphosphine, buffered with barium carbonate to prevent cleavage of the tetrahydropyranyl protecting unit. Our NMR data indicated that this substitution occurred with inversion, maintaining a 1 : 3 ratio of bromides. Reaction with tri-*n*-butyltin hydride in toluene at 60°C afforded solely the desired olefin **96** in 82% yield. The allylic radical had been reduced with complete regiocontrol; perhaps as a result of Lewis acid coordination of tin hydride with the neighboring tetrahydropyranyl oxygen or the benzyl ether oxygen at C-6 to effect an intramolecular hydrogen delivery.

Finally, our journey was nearing its end. Removal of the tetrahydropyranyl ether yielded the allylic alcohol **97**, which served as an ideal substrate for manganese dioxide oxidations. Upon detection of the conjugated alde-

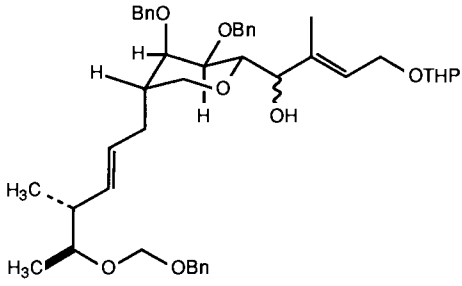



91

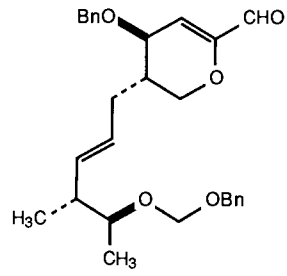
+



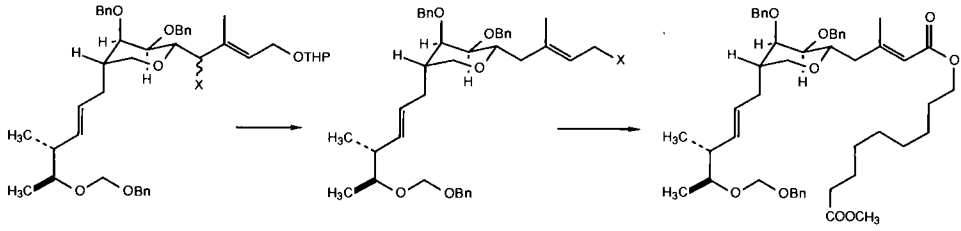

92




93




94




93 X = OH
95 X = Br

96 X = OTHP
97 X = OH
98 X = O

99

hyde **98**, a second allylic oxidation[40] was initiated by the *in situ* addition of 9-hydroxynonanoate methyl ester with sodium cyanide and glacial acetic acid, affording nearly quantitative conversion to the protected methyl pseudomonate **99**. Deblocking was conveniently achieved with boron trichloride at -90°C in methylene chloride for 2 minutes followed by treatment of the residue with 1 *M* lithium hydroxide in aqueous methanol (10 minutes). Reacidification using acetic acid led to a 97% yield of synthetic (+)-pseudomonic acid C (**1c**).

## VI. Conclusion

My story of pseudomonic acid C is but a glimpse into the vast field of organic synthesis. While this chapter is intended to present the evolution of our successful synthetic strategy, a significant proportion of research is based on observations of the infinite uniqueness nature has to offer. Indeed, it is the foundation of our scientific method: meaningful observation, logical rationale, and experimentation.

Today, chemistry as a discipline has come under increasing pressure to adopt various management skills toward planned scientific discovery. In both academia and industry, directors strive for some unit measure of individual scientific productivity and some quantitative definition of progress toward a selected goal. Lest we forget, as in all creative endeavors, the number of insightful solutions is at least as great as the number of potential problems. We are encouraged by the words of the late Professor R. B. Woodward.[41]

> Not infrequently, Nature is more knowledgeable and artful than the chemist, and devises combinations between, or transformations of, reacting molecules which the designer had not anticipated at all. Some such surprises may be unpleasant ones, in that the unanticipated course of events may require serious modification of the synthetic plan, or even its abandonment. But in other cases, such happenstances may facilitate the work, and render easier than had been expected some difficult passage. In either event, the unexpected is always important, and its study should be welcomed.

### Acknowledgments

I am greatly appreciative of the individual effort and skills dedicated to the early stages of this project by Jonathan Grote, William Bennett, and Dr. Minoru Yamada. We express our gratitude to Jimmie L. Moore for his determined efforts, which led to the total synthesis. The support of the Alfred P. Sloan Foundation and the National Institutes of Health (NIH Al 17674) is also gratefully acknowledged.

## References


1. E. B. Chain and G. Mellows, *J.C.S. Chem. Commun.* p. 847 (1974).
2. E. B. Chain and G. Mellows, *J.C.S. Perkin I* p. 294 (1977).
3. R. G. Alexander, J. P. Clayton, K. Luk, N. H. Rogers, and T. J. King, *J.C.S. Perkin I* p. 561 (1978).
4. E. B. Chain and G. Mellows, *J.C.S. Perkin I* p. 318 (1977).
5. J. P. Clayton, P. J. O'Hanlon, and N. H. Rogers, *Tetrahedron Lett.* p. 881 (1980).
6. J. P. Clayton, P. J. O'Hanlon, N. H. Rogers, and T. J. King, *J.C.S. Perkin I* p. 2827 (1982).
7. P. J. O'Hanlon, N. H. Rogers, and J. W. Tyler, *J.C.S. Perkin I* p. 2655 (1983).
8. D. R. Williams, J. L. Moore, and M. Yamada, *J. Org. Chem.* **51,** 3916 (1986).
9. D. R. Williams, J. G. Phillips, and J. C. Huffman, *J. Org. Chem.* **46,** 4101 (1981); D. R. Williams, J. G. Phillips, F. H. White, and J. C. Huffman, *Tetrahedron* **42,** 3003 (1986); D. R. Williams and J. G. Phillips, *Tetrahedron* **42,** 3013 (1986).
10. S. Hanessian, "Total Synthesis of Natural Products: The 'Chiron' Approach." Pergamon, New York, 1983.
11. The pseudomonic acids are used as topical antibiotics, marketed under the name Mupirocin.
12. A. P. Kozikowski, R. J. Schmiesing, and K. L. Sorgi, *J. Am. Chem. Soc.* **102,** 6577 (1980); A. P. Kozikowski, R. J. Schmiesing, and K. L. Sorgi, *Tetrahedron Lett.* **22,** 2059 (1981).
13. A. Banaszek and A. Zamojski, *Rocz. Chem.* **45,** 2089 (1971); A. Konowal, A. Zamojski, M. Masojidkova, and J. Kohoutava, *Rocz. Chem.* **44,** 1741 (1970).
14. A. Banaszek and A. Zamojski, *Carbohydr. Res.* **25,** 453 (1972); U. P. Singh and R. K. Brown, *Can. J. Chem.* **49,** 3342 (1971).
15. For review, see J. K. Crandall and M. Apparu, *Org. React. (N.Y.)* **29,** 345 (1983).
16. D. R. Williams, and J. Grote, *J. Org. Chem.* **48,** 134 (1983).
17. R. Noyori, S. Murata, and M. Suzuki, *Tetrahedron* **37,** 3899 (1981).
18. C. M. Lok, J. P. Ward, and D. A. vanDorp, *Chem. Phys. Lipids* **16,** 3115 (1976).
19. M. M. Midland, *in* "Asymmetric Synthesis" (J. D. Morrison, ed.), Vol. 2, Part A, p. 45–69. Academic Press, New York, 1983.
20. M. M. Midland, D. C. McDowell, R. L. Hatch, and A. Tramontano, *J. Am. Chem. Soc.* **102,** 867 (1980); M. M. Midland, A. Tramontano, A. Kazubski, R. S. Graham, D. J. S. Tsai, and D. B. Cardin, *Tetrahedron* **40,** 1371 (1984).
21. R. U. Lemieux and S. Kato, *Tetrahedron* **30,** 1933 (1974).
22. G. W. J. Fleet, M. J. Gough, and T. K. M. Shing, *Tetrahedron Lett.* **24,** 3661 (1983); D. P. Curran, *Tetrahedron Lett.* **23,** 4309 (1982).
23. M. E. Jung and T. J. Shaw, *J. Am. Chem. Soc.* **102,** 6304 (1980).
24. K. Fugita, H. Nakai, S. Kobayashi, K. Inoue, S. Nojima, and M. Ohno, *Tetrahedron Lett.* **23,** 3507 (1982).
25. R. Barker and D. L. MacDonald, *J. Am. Chem. Soc.* **82,** 2301 (1960).
26. D. R. Williams and F. D. Klinger, *Tetrahedron Lett.* **28,** 869 (1987).
27. C. H. Heathcock, *in* "Asymmetric Synthesis" (J. D. Morrison, ed.). Vol. 3 p. 111–212. Academic Press, New York, 1984; D. A. Evans, J. Bartroli, and T. L. Shih, *J. Am. Chem. Soc.* **103,** 2127 (1981); D. A. Evans and J. Bartroli, *Tetrahedron Lett.* **23,** 807 (1982).
28. S. Masamune, *Heterocycles* **21,** 107 (1984); S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.* **24,** 1 (1985).
29. R. W. Hoffmann and U. Weidmann, *Chem. Ber.* **118,** 3966 (1985).
30. W. R. Roush, M. A. Adam, A. E. Walts, and D. J. Harris, *J. Am. Chem. Soc.* **108,** 3422 (1986).
31. W. C. Still and J. A. Schneider, *Tetrahedron Lett.* **21,** 1035 (1980).

32. The diol **81** and its trimsylate were previously prepared from L-arabinose, see G. W. J. Fleet and T. K. M. Shing, *Tetrahedron Lett.* **24,** 3657 (1983).
33. M. Julia and J.-M. Paris, *Tetrahedron Lett.* p. 4833 (1973); P. J. Kocienski, B. Lythgoe, and S. Ruston, *J.C.S. Perkin I* p. 829 (1978); P. J. Kocienski, B. Lythgoe, and I. Waterhouse, *J.C.S. Perkin I* p. 1045 (1980).
34. Coincident with our investigations, Keck and co-workers had extensively explored the Julia methodology for introduction of the C-10–C-11 alkene with similar difficulties. See G. E. Keck, D. F. Kachensky, and E. J. Enholm, *J. Org. Chem.* **50,** 4317 (1985).
35. B. Lythgoe and I. Waterhouse, *Tetrahedron Lett.* p. 4223 (1977).
36. M. J. Crimmin, P. J. O'Hanlon, and N. H. Rogers, *J.C.S. Perkin I* p. 549 (1985).
37. J. P. Clayton, K. Luk, and N. H. Rogers, *J.C.S. Perkin I* p. 308 (1979); S. Coulton, P. J. O'Hanlon, and N. H. Rogers, *J.C.S. Perkin I* p. 729 (1982).
38. E. J. Corey, M. G. Bock, A.P. Kozikowski, and A. V. Rama Rao, *Tetrahedron Lett.* p. 1051 (1978).
39. For preparation of anhydrous cerium (III) iodide, see T. Imamoto, T. Kusumoto, and M. Yokoyama, *J.C.S. Chem. Commun.* p. 1042 (1982).
40. E. J. Corey, N.W. Gilman, and B. E. Ganem, *J. Am. Chem. Soc.* **90,** 5616 (1968).
41. R. B. Woodward, "Pointers and Pathways in Research," p. 3–21. Ciba of India, Bombay, 1963.

# GLOSSARY OF ABBREVIATIONS

**BBN:** 9-Borabicyclo[3.3.1]nonane
**BOM:** Benzyloxymethyl
**DBU:** 1,8-Diazabicyclo[5.4.0]undec-7-ene
**DHP:** Dihydropyran
**DMAP:** *N,N*-Dimethylaminopyridine
**DME:** Dimethoxyethane
**DMSO:** Dimethylsulfoxide
**HMPA:** Hexamethylphosphoric triamide
**HPLC:** High-performance liquid chromatography
**IR:** Infrared spectroscopy
**LDA:** Lithium Diisopropylamide
**LiHMDS:** Lithium hexamethyldisilazide
**LiTMP:** Lithium tetramethylpiperidide
**MCPBA:** *m*-chloroperbenzoic acid
**MS:** Mass spectroscopy
**NBS:** *N*-Bromosuccinimide
**NMR:** Nuclear magnetic resonance spectroscopy
**PCC:** Pyridinium chlorochromate
**PDC:** Pyridinium dichromate
**PPTS:** Pyridinium *p*-toluenesulfonate
**TBS** or **TBDMS:** *t*-Butyldimethylsilyl chloride
**THF:** Tetrahydrofuran
**TLC:** Thin layer chromatography
**TMEDA:** Tetramethylethylenediamine
**TMSCl:** Trimethylsilyl chloride
**TMSI:** Trimethylsilyl iodide

# INDEX

## Q



## R



## S



## T



## V



## W



## Y



## Z