Strategies and Tactics in Organic Synthesis

Volume 3

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ACADEMIC PRESS, INC.
Harcourt Brace Jovanovich, Publishers

STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS

Volume 3

Edited by

Thomas Lindberg
The Upjohn Company

With a foreword by

Professor E. J. Corey
Nobel Laureate in Chemistry, 1990
Harvard University



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

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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 v. 3)

Strategies and tactics in organic synthesis.

Includes bibliographies and indexes.
1. Organic compounds--Synthesis. I. Lindberg, Thomas, date.
QD262.S85 1984 547'.2 83-15674
ISBN 0-12-450282-2 (v. 3)

PRINTED IN THE UNITED STATES OF AMERICA
91 92 93 94 9 8 7 6 5 4 3 2 1

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FOREWORD

This third volume of *Strategies and Tactics in Organic Synthesis*, edited by Thomas Lindberg, contains detailed accounts of thirteen unusually interesting recent developments in the field of synthesis. Like its predecessors, the book conveys much more of the history, trials, tribulations, surprise events (both negative and positive), and excitement of synthesis than can be found in the original publications of the chemical literature. One can even appreciate the personalities and the human elements that have shaped the realities of each story. But, above all, each of these chapters tells a tale of what is required for success when challenging problems are attacked at the frontiers of synthetic science.

Success depends on so many factors, even after the most thoughtful and intelligent planning: careful design, execution and analysis of experiments; persistence, imagination, and inventiveness in overcoming obstacles; dedication, patience, determination, and energy over a considerable period of time; altertness to new opportunities and openness to new ideas; appreciation and enjoyment of the adventure of synthesis; and not least, a happy working relationship between partners.

Those who have been involved with synthesis over a number of years know that failure is possible. In what human activity of any consequence is that not so? The courage to take on that risk of failure, to work on a problem of great difficulty with persistence and confidence, is a mark of a fine synthetic chemist.

The successful completion of a first-class synthesis is usually, in my opinion, underappreciated by all but a small fraction of chemists. Very few nonsynthetic chemists realize how formidable are the tasks of multistep synthesis—from finding the proper reactions, reagents, and conditions for individual steps to inventing new chemistry to fill gaps in existing synthetic methodology.

As time passes, synthetic chemistry becomes ever more sophisticated and powerful, and it is easy to think of the subject as mature. In fact, the more one is involved in chemical synthesis, the more one perceives that there is still much to be done. The chemistry of today will be viewed as primitive a century from now. So, it is very important that this practically and culturally valuable activity be continued at a high level by successive generations of bright young (and older) chemists. To that end, accurate and clear accounts of the events and ideas of synthetic chemistry, such as are found in this volume, will be of considerable importance.

E. J. COREY

PREFACE

It is a great pleasure to see Volume 3 of *Strategies and Tactics in Organic Synthesis* going to press. Volumes 1 and 2 were well received by the chemical community, and I am confident that this volume will also be well received.

This volume continues the theme set by Volumes 1 and 2: to give readers a "behind-the-scenes" look at organic synthesis. In the many elegant syntheses detailed in this book, one can see that the path leading to a synthetic target is never smooth and often contains numerous dead ends. Typically, it takes a mixture of creativity, perseverance, and hard work to reach the goal.

I would like to express my appreciation to the contributors. Without their hard work this book would not be a reality. I was also fortunate to enlist some chemists from the pharmaceutical industry. Drs. Robert Volkmann and Brian O'Neill (Pfizer) and Dr. R. P. Volante (Merck Sharp & Dohme) give a unique view of organic synthesis from an industrial perspective.

Finally, I would like to thank Professor E. J. Corey for kindly agreeing to write the foreword.

THOMAS LINDBERG

Chapter 1

REDOX GLYCOSIDATION: A STEREOSELECTIVE SYNTHESIS OF SUCROSE

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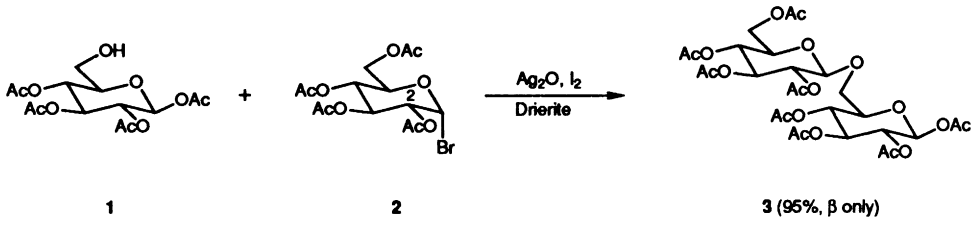
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I. Prologue

This story begins in 1972, long before I started independent research. At that time I was a second year undergraduate student in chemistry at Imperial College, London. Professor Leonard N. Owen was giving a very lucid and entertaining lecture course on carbohydrates. As a result, I became fascinated with the unusual properties of these substances: the mutarotation of glucose, the mysterious anomeric effect, and the subtle variations in reactions of aldohexoses and aldopentoses with acetone or benzaldehyde depending on stereochemistry. There were a few chemistry courses at Imperial College that were truly outstanding and Len Owen's carbohydrate course

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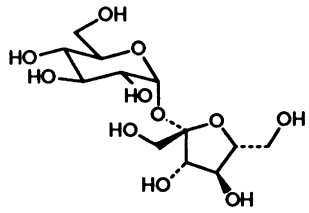
was undoubtedly one of them. I am certain that many of the students would have given Professor Owen a standing ovation had we been living in another culture more volatile than the English. Several years passed, I joined the faculty at Imperial College, and subsequently moved to Northwestern University. From time to time my research group used carbohydrates as starting materials, but we never attempted any projects that were truly carbohydrate in focus. There is a long-standing problem in carbohydrate chemistry. Oligosaccharides are biopolymers that contain aldose or ketose units iteratively linked together by glycosidic bonds. These bonds may be prepared by the Koenigs–Knorr reaction,[1] and this process is exemplified by the transformations in Scheme 1. In this process the carbohydrate alcohol **1** was reacted with a glycosyl bromide **2** in the presence of silver oxide as halide scavenger and iodine as activator to provide the disaccharide **3**.[2] The product **3** contains a single glycosidic bond between the anomeric center of one glucose unit (C_1) and the O_6 of the second glucose unit. It is clear that in order to prepare the disaccharide **3** cleanly, other hydroxyl groups in both **1** and **2** have to be protected and acetate esters are used for this purpose. The formation of the glycosidic bond is not mechanistically simple. These glycosidation reactions involve a mixed S_N1/S_N2 mechanism and the ratio of pathways depends upon the structures of the glycosyl donor and acceptor as well as the exact reaction conditions. In Scheme 1, the disaccharide **3** was formed as a single anomer with the β-stereochemistry. Clearly, the formation of β-**3** via an S_N2 reaction pathway was a straightforward inversion reaction. However, the competing S_N1 pathway also gave rise to β-**3** on account of neighboring group participation by the C_2 acetate via the intermediacy of an acetoxonium ion. Thus, both the yield and stereoselectivity of glycosidation of **3** are outstanding. However, this efficiency is not general. Frequently, glycosidation



1 2 3 (95%, β only)

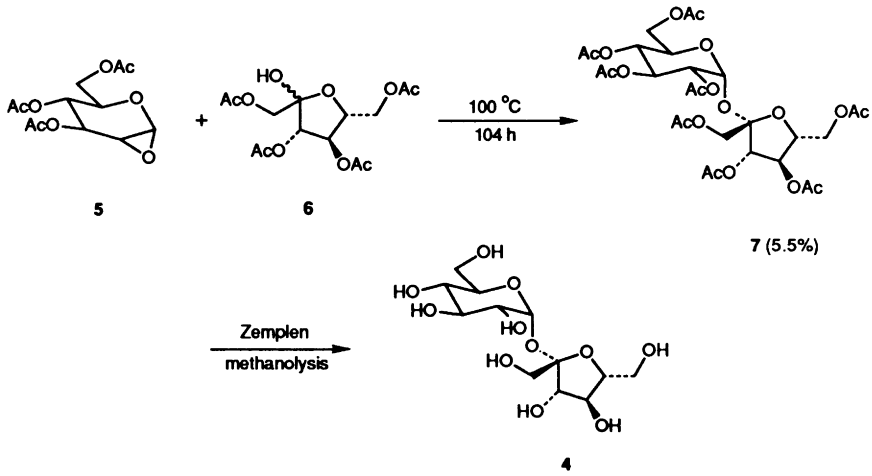
reactions proceed in much lower yields and give rise to mixtures of α- and β-glycosides. Clearly, the syntheses of oligosaccharides are experimentally very difficult and tedious unless each iteration proceeds both in high yield and with high anomeric stereoselectivity. In the near century of time since the discovery of the Koenigs–Knorr reaction, many variations on the reaction theme in Scheme 1 have been designed. A large variety of anomeric leaving groups and activating strategies have been introduced. In several cases, these strategies have simplified the synthesis of oligosaccharides of modest molecular weights.[3,4] Nonetheless, oligosaccharide synthesis is not yet simple and routine.

I had, on several occasions, thought about the design of new methods for the construction of glycosidic bonds. However, none of these ideas proved very compelling. In late 1987, I thought that it may be possible to prepare a molecule that contained a glycosidic bond via the intermediacy of a glycosyl ester. Such a strategy would have one major advantage: esters are easier to prepare than glycosides, particularly for hindered alcohols. However, the process would have one major problem: how exactly would the glycosyl ester be reduced in oxidation level to a glycoside without acyl oxygen bond cleavage? I chose sucrose (**4**) as an initial target, because this is a notoriously difficult substance to prepare stereoselectively in high yield. There are three problems with this venture. First, sucrose (**4**) is a nonreducing disaccharide containing a D-glucose and a D-fructose unit joined by a glycosidic bond linking both anomeric centers. Second, sucrose (**4**) contains a *cis*-α-D-glucopyranoside unit. In other words the C_2 hydroxyl and the anomeric C–O bond are *cis* on the six-membered ring. Third, the fructofuranoside β-anomeric oxygen is tertiary. As a result of these factors, sucrose (**4**) is a target of considerable difficulty, indeed infamy. In 1953, Lemieux and Huber reported the first total synthesis of sucrose (**4**) (Scheme 2).[5] These authors found that the Brigl anhydride **5** reacted with the alcohol **6** at 100°C to provide a mixture of products from which sucrose octaacetate (**7**) could be isolated. Zemplen methanolysis of the ester product **7** gave sucrose (**4**). This synthesis was a triumph since it clearly established the Brigl anhydride **5** as a useful glycosidation reagent for the construction of D-glucopyranosides. Additionally, the synthesis was a major achievement as Lemieux and Huber had succeeded where many others before had failed.[6] It is also remarkable that the



4

Lemieux–Huber synthesis has never been improved upon.[7] Thus I chose sucrose (**4**) as a target since it would be a useful system to assess any new methodology that we sought to develop. This new methodology was termed "redox glycosidation."[8]



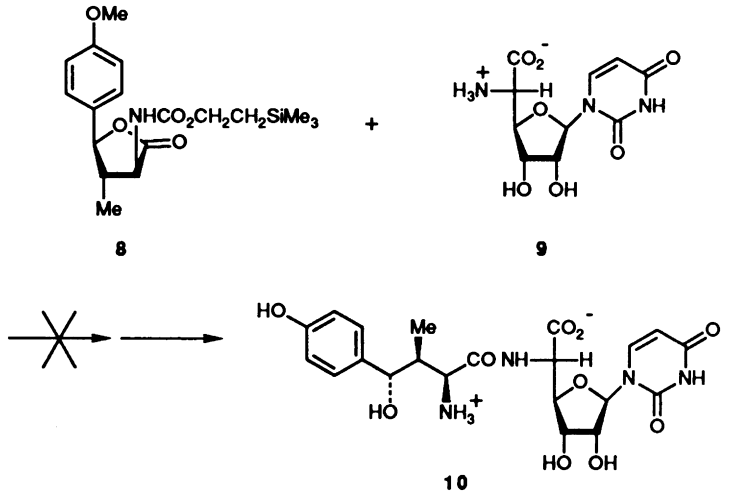
5 6 7 (5.5%) 4

SCHEME 2

II. Preparation of Selectively Protected γ- and δ-Hydroxy Acids

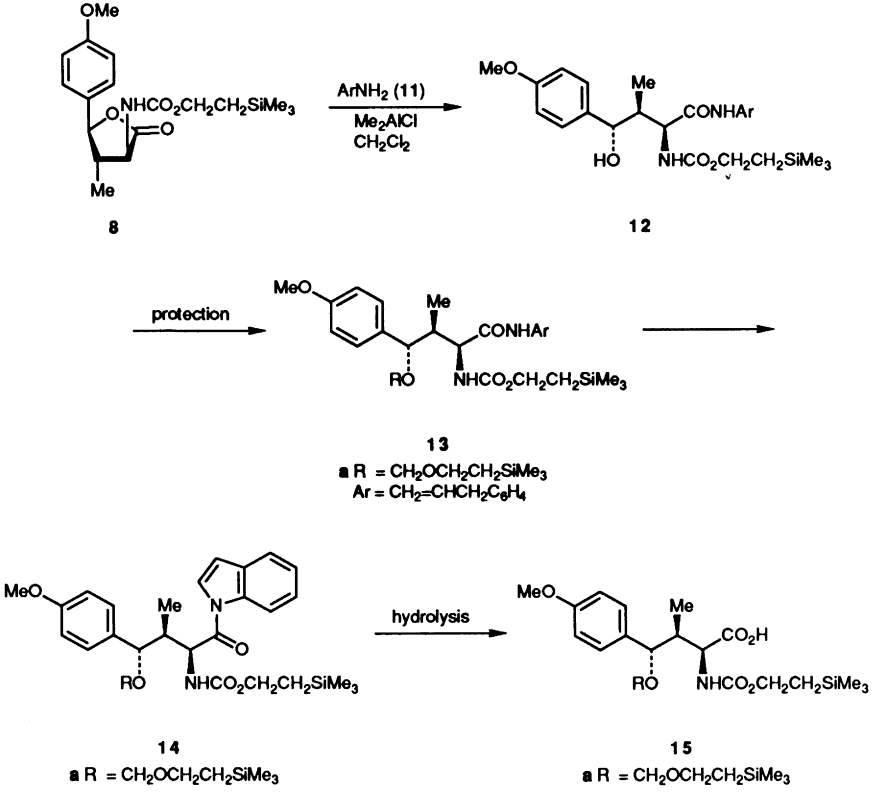
Both γ- and δ-hydroxy acids readily cyclize to produce the corresponding lactones. This process is very facile and the resultant γ- and δ-lactones are invariably stable compounds. As a result, attempted derivatization or protection of the γ- and δ-hydroxyl group in hydroxy acids may result in lactonization rather than the required protection process.[9] In fact, we encountered such problems some time before we initiated our studies in the area of redox glycosidation. At that time,

we were working on the total synthesis of the nikkomycins[10] and had chosen nikkomycin B (**10**) as a target. We had prepared both the γ-lactone **8**, using isoxazoline chemistry, and uracil polyoxin C (**9**). However, all our attempts to directly couple **8** and **9** and thereby produce a dipeptide precusor to nikkomycin B (**10**) were unsuccessful (Scheme 3). The lactone **8** was insufficiently electrophilic to *N*-acylate uracil polyoxin C (**9**) even in the presence of oxyphilic Lewis acids[11] and Bronsted bases or at high pressures. As a result of these failures, one of my postdoctoral research assistants, Dashyant Dhanak, sought to convert the lactone **8** into a protected γ-hydroxy acid and thereby prepare the key dipeptide precursor to nucleoside **10** by using an activated ester derivative such as the *p*-nitrophenyl ester.[12] However, he found that various routes to ring open the lactone **8** and protect the γ-hydroxy group were unsuccessful: either the starting lactone **8** was regenerated or the reaction gave intractable mixtures. Clearly, these failures were largely the result of the stability of the 5-membered lactone ring system. At this point, I became somewhat exasperated by the molecule and sincerely wanted revenge. I considered that perhaps we should be able to overcome these difficulties by using the stability of an alternative 5-membered ring species to help us in the derivatization of lactone **8**. In other words, we proposed to defeat the γ-lactone problem via the formation of another 5-membered ring species. The results were bittersweet.



SCHEME 3

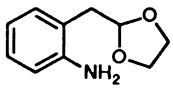
We sought to convert lactone **8** into an anilide derivative **12** by reaction with the corresponding aniline **11**. The resultant amide should have been sufficiently stable, due to the strength of the N–CO bond,[13] to permit clean γ-hydroxyl protection. In order to facilitate the release of the carboxylic acid group, the anilide **13** was to be converted into the corresponding *N*-acyl indole.[14] This species should have been easily hydrolyzed on account of the aromaticity of the indole ring system. Several years before our efforts on the nikkomycins, Sir Derek H. R. Barton had demonstrated that *N*-acyl indolines were easily hydrolyzed after oxidation to the corresponding *N*-acyl indoles.[14] Thus, the proposed strategy in Scheme 4 was a variation on this theme. Lactone **8** was smoothly condensed with aniline in the presence of dimethylaluminum chloride (Steven M. Weinreb's conditions[11]) to cleanly provide the corresponding stable anilide **12** (Ar = Ph, 86%). Encouraged by this result, anilines **16**, **17**, and **18**



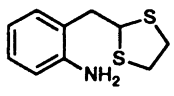
SCHEME 4

were each reacted with lactone **8** under Lewis acidic conditions.[11] Although amine **16** directly gave only indole and no anilide **12**, and although **17** reacted with **8** to give a complex mixture of products, 2-allylaniline (**18**) proved to be very useful. The amine **18** was allowed to react with lactone **8** and dimethylaluminum chloride to smoothly produce **12** (Ar = 2-CH_2=$CHCH_2$·CH_6H_4, 77%). In addition, protection of the alcohol **12** gave the corresponding adduct **13a** (100%). Both Dash Dhanak and I were particularly pleased that the lactone **8** was not reformed during the protection step. We were also delighted that ozonolysis of the alkene **13a** with a dimethyl sulfide work-up resulted in formation of the corresponding indole **14a** (77%). Clearly the intermediate aldehyde was readily cyclizing onto the anilide nitrogen. However, there was one problem with these transformations. The indole **14a** was not formed as a single compound. The ^{1}H NMR spectrum clearly showed that **14a** was obtained as a mixture of C_2 epimers (1 : 1.1). All our attempts to prevent epimerization and formation of both anilides **14a** and the epimer **19** were unsuccessful and, as a result, we abandoned the use of lactone **8** for the synthesis of nikkomycin B (**10**).[15,16] We did, however, examine the use of the anilide *N*-acyl indole strategy for the ring opening of other γ- and δ-lactones. This perseverance did indeed pay off since the process worked extremely well with all other lactones that we examined.

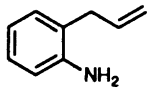
Both γ-butyrolactone (**20**) and δ-valerolactone (**25**) reacted cleanly with 2-allylaniline (**18**) in the presence of dimethylaluminum chloride to produce the corresponding anilides **21** (80%) and **26** (99%). These amides in turn were protected and the resultant alkenes **22** and **27** ozonolyzed with a dimethyl sulfide work-up to produce the *N*-acyl



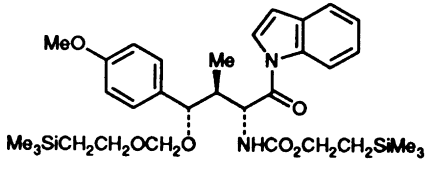
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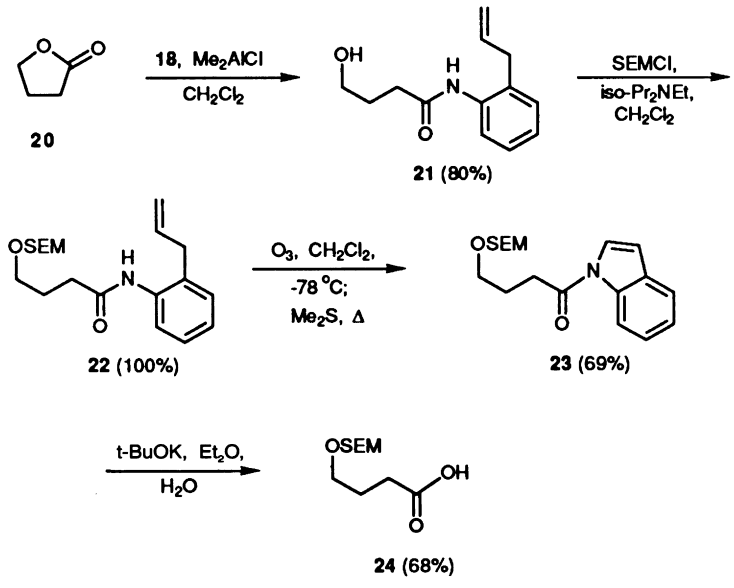
17



18



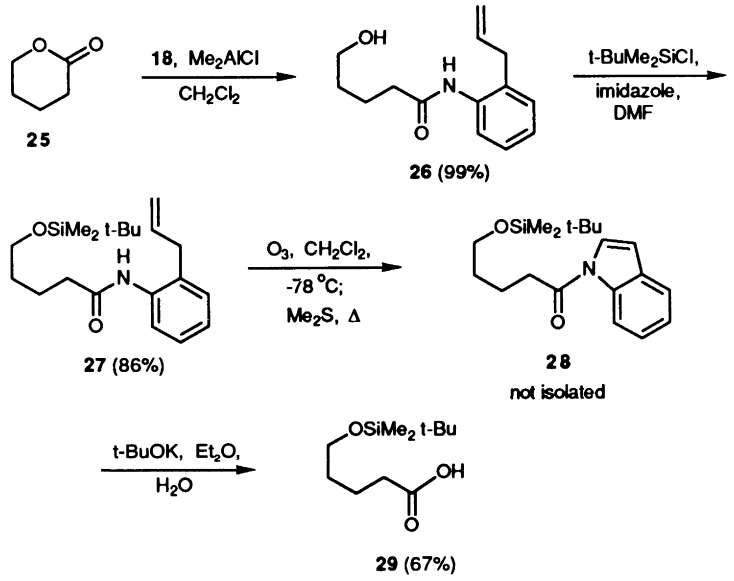
19



20 → **21** (80%) → **22** (100%) → **23** (69%) → **24** (68%)

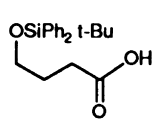
SEM = $CH_2OCH_2CH_2SiMe_3$

SCHEME 5

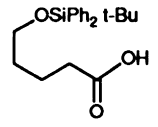


25 → **26** (99%) → **27** (86%) → **28** not isolated → **29** (67%)

SCHEME 6

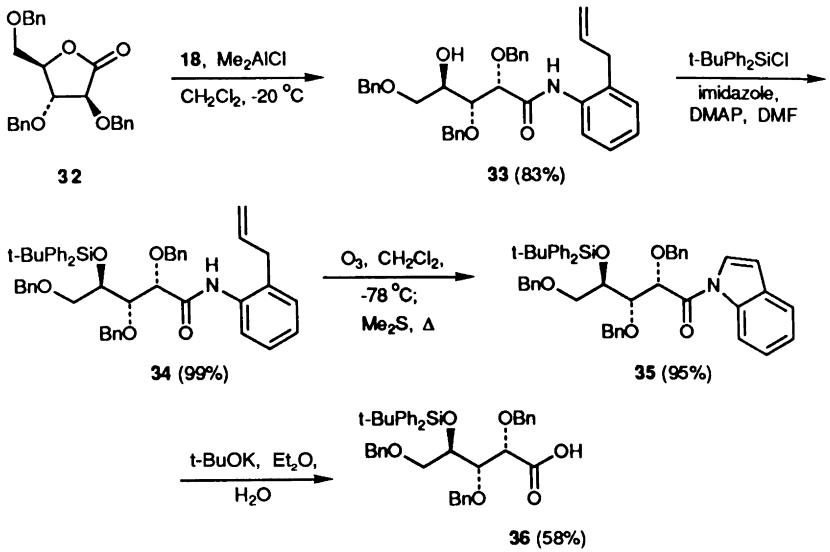


30



31

indoles **23** and **28**. As anticipated, these reactive amides were readily saponified to produce the corresponding carboxylic acids **24** and **29** by brief treatment with potassium *t*-butoxide in wet diethyl ether (Paul Gassman hydrolysis conditions)[17] (Schemes 5 and 6). The same sequence of transformations was also used to prepare the corresponding carboxylic acids **30** and **31**. Much to our delight, and in marked contrast to the nikkomycin system **14a**, this acyl–indole methodology was used to prepare several protected aldonic acid systems without any problems with C_2 epimerization. Indeed, we have only encountered one problem with such epimerization, ironically that observed with the prototype indole **14a** for which the whole procedure was first designed. Scheme 7 outlines the preparation of the arabinonic acid derivative **36**. All the various differentially protected aldonic acids used in further redox glycosidation procedures were successfully prepared from the γ- and δ-lactones via the corresponding *N*-acyl indoles.[18]



32

33 (83%)

34 (99%)

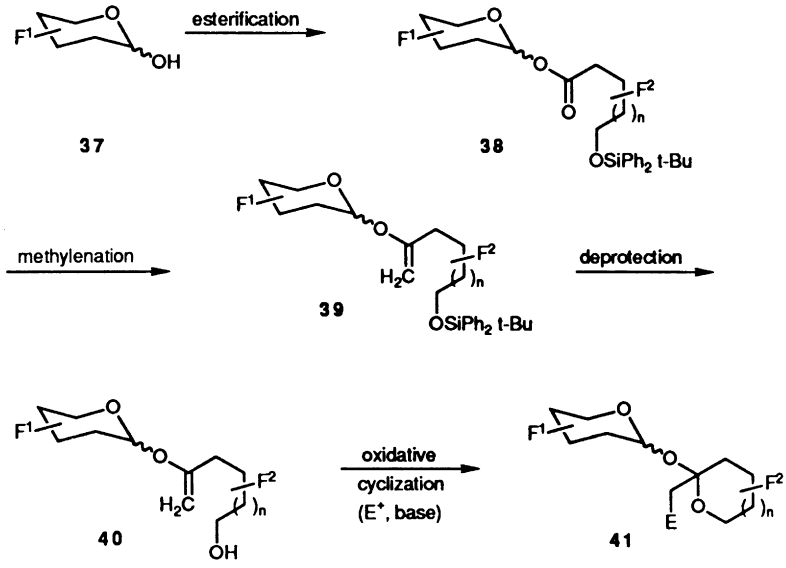
35 (95%)

36 (58%)

SCHEME 7

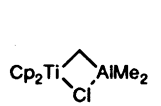
III. Development of a Redox Glycosidation Strategy via Ester Methylenation

In our first experiments on redox glycosidation, we sought to prepare a primitive glycoside **41** as outlined in Scheme 8. Mark A. Russell, a postdoctoral fellow in my group, elected to examine a strategy whereby an anomeric alcohol **37** would be derivatized to produce the corresponding ester **38**. This substance was expected to be easily converted into the corresponding vinyl ether **39** on methylenation using the Tebbe reagent **42**.[19] Desilylation of **39** was expected in turn to provide the alcohol **40**, which should prove to be an excellent precursor for cyclization. We hoped that epoxidation,[20] phenylselenenylation,[21] iodoetherification,[22] or oxymercuration[23] of alkene **40** should provide the nonreducing disaccharide **41**. Clearly, for such a process to be valid, all other hydroxyl groups in both the

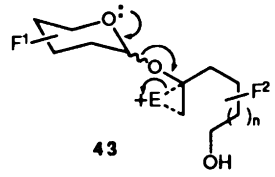


SCHEME 8

alkyl and acyl fragments of the ester **38** would have to be protected.[24] In spite of this rationalization, we were none-the-less concerned by several aspects of the proposed chemistry. First, if the method proved to be successful, we would need to develop two complementary stereoselective esterification reactions to respectively prepare α- and β-glycosyl esters. Second, we were concerned that the Tebbe methylenation reaction would fail since the resultant vinyl ether **39** would be sensitive to Lewis or Bronsted acid-catalyzed destruction. Third, we feared that all the cyclization reactions of alkene **40** would be complicated by a competitive fragmentation (see arrows on structure **43**). All of



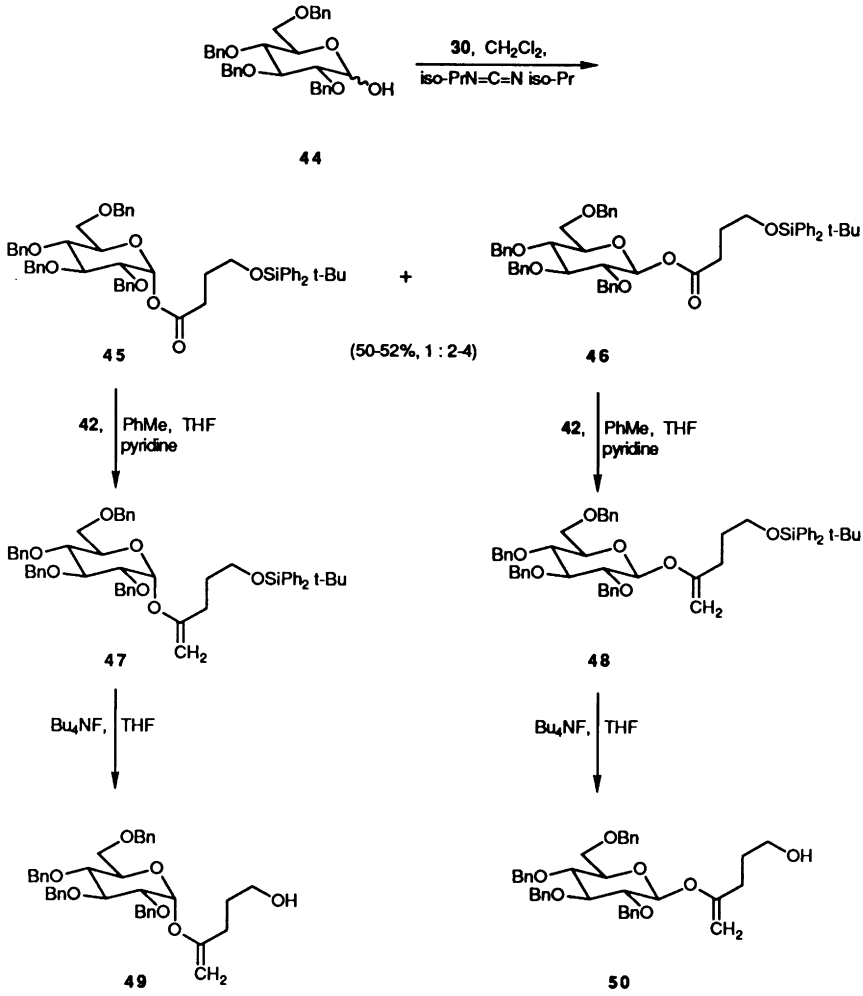
42



43

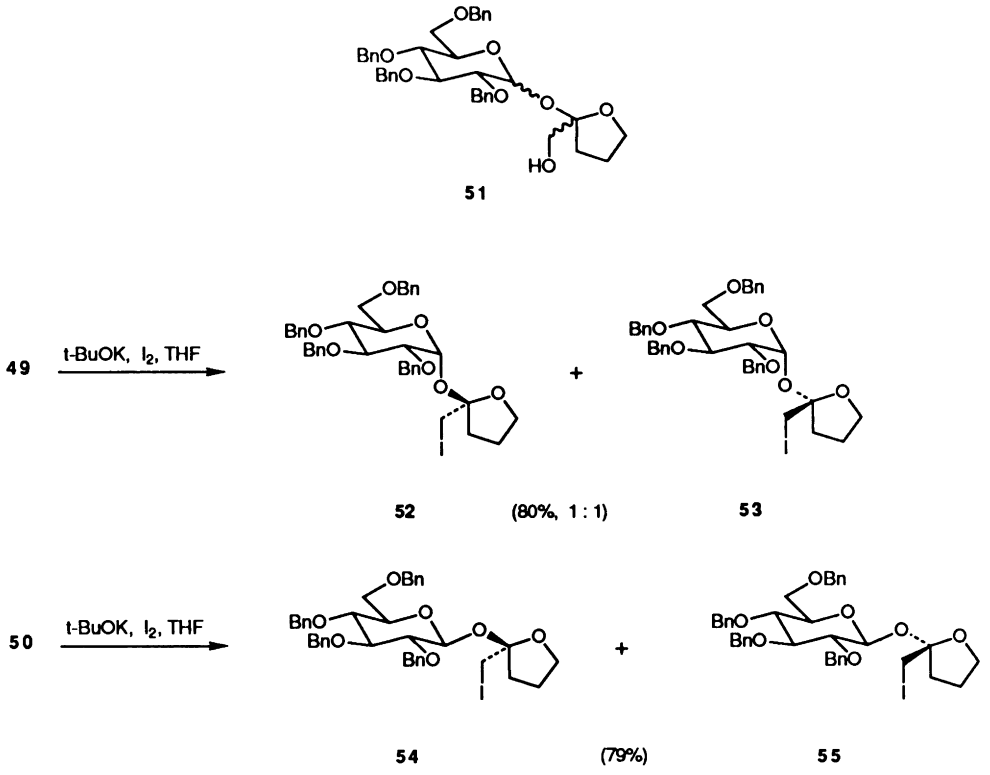
these anxieties proved to be unfounded. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**44**) was esterified with the protected γ-hydroxycarboxylic acid **30** using 1,3-diisopropylcarbodiimide as the dehydrating reagent.[25] Under these conditions, a mixture of α-**45** and β-esters **46** (50–52%,1 : 2–4) were obtained. This mixture of anomers was not separated but directly treated with the Tebbe reagent **42** in toluene–THF and pyridine to provide the mixture of alkenes **47** and **48**. After routine deprotection with tetrabutylammonium fluoride, the two anomers **49** and **50** were readily separated by chromatography (Scheme 9).

We were obviously very pleased that the Tebbe reaction worked well and the alkenes **47** and **48** were not degraded under the reaction conditions. However, this initial contentment was marred when we sought to cyclize the alkenes **49** and **50**. Much to our disappointment, attempted cyclization via oxymercuration chemistry using mercury(II)acetate, chloride, trifluoroacetate, or nitrate resulted in cleavage to regenerate the lactol **44**. Attempted selenoetherification of **49** and **50** using phenylselenenyl chloride in the presence of 2,6-di-*t*-butylpyridine or potassium carbonate also resulted in the unwanted cleavage reaction. The reaction of alkenes **49** and **50** with 3-chloroperoxybenzoic acid gave a mixture of products which consisted mostly of the lactol **44** but may have also contained the cyclized



SCHEME 9

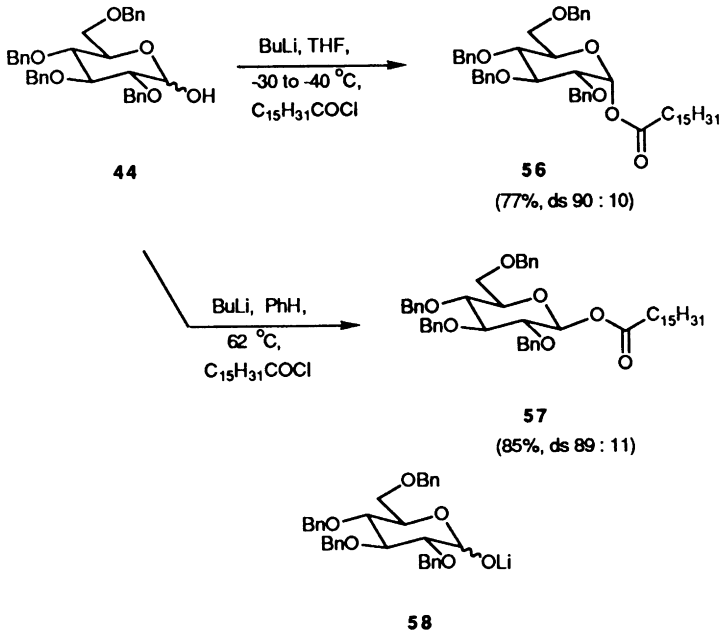
product **51**. At about the same time, Russell examined the use of iodine under basic conditions. Much to our considerable relief, iodine and potassium *t*-butoxide cleanly brought about the cyclization of the β-alkene **50** to provide the corresponding iodoethers **54** and **55** (79%). In exactly the same way, the α-isomer **49** was converted into the α-disaccharides **52** and **53** (80%) (Scheme 10). At this point in time, we were delighted that redox glycosidation was indeed a valid process for preparing a simple nonreducing disaccharide. There were,



SCHEME 10

however, many problems yet to be addressed. First, the aldonic esters **45** and **46** were formed with poor diastereoselectivity. Second, the cyclizations of both alkenes **49** and **50** gave mixtures of iodoethers. The two diastereomers **52** and **53** with the α-glucopyranose stereochemistry were easily separated by chromatography and each was formed in equivalent amounts.

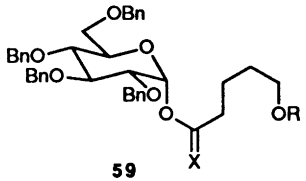
At this time Amy R. Howell joined my research group at Northwestern University and set out to extend Russell's initial work. We needed to improve the method for the preparation of the α- and β-glucosyl esters. Several years prior to our work, Pfeffer and co-workers had reported a curious method for the preparation of either the α- and the β-hexadecanoic esters of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose.[26] The Pfeffer results are summarized in Scheme 11. In THF at -30 to -40°C the lithium alkoxide derived from the



SCHEME 11

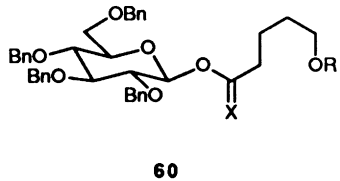
anomeric alcohol **44** gave predominantly the α-ester **56** on reaction with hexadecanoyl chloride. In contrast, alkoxide esterification in benzene at 62°C gave predominantly the β-esters **57**. These authors demonstrated that the anomeric composition of the alkoxide intermediate **58** did not vary much with solvent or with temperature.

Using these Pfeffer conditions, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**44**) was converted into the corresponding α- and β-glucosyl esters **59a** and **60a**. In complete agreement with the Pfeffer study, we found that the low temperature lithium alkoxide esterification in THF proceeded with good α-selectivity (13 : 1, 50%) whereas esterification in benzene at 60°C gave the β-anomer (40%, 6 : 1). Both esters **59a** and **60a** were smoothly methylenated using the Tebbe reagent **42** and desilylated to produce the vinyl ethers **59b** and **60b** respectively. Both substances were readily converted into the non-reducing disaccharides **61** and **62** on treatment with iodine and potassium *t*-butoxide. We were again very pleased by this result since it clearly demonstrated, at least for model systems, that redox glycosidation may be used to prepare both furanoside and pyranoside



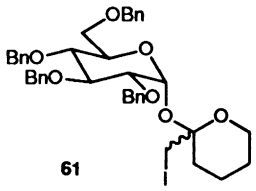
59

a X = O, R = t-BuPh$_2$Si
b X = CH_2, R = H



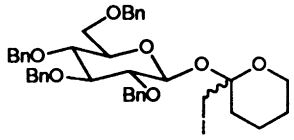
60

a X = O, R = t-BuPh$_2$Si
b X = CH_2, R = H



61

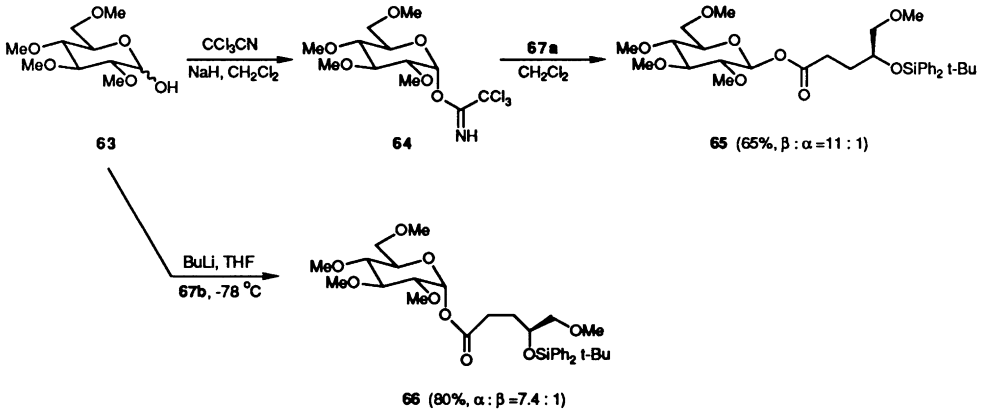
ds = 1.4 : 1



62

ds = 1 : 1

ring systems. At this point, Howell began to examine a thionester strategy to prepare glycosides (see Section IV) and the Tebbe reagent strategy was continued by Barend C. B. Bezuidenhoudt and Alan F. Gasiecki. Bezuidenhoudt was an academic visitor from the University of the Orange Free State and Al Gasiecki ("The Ace") a G. D. Searle employee who spent a three-month sabbatical in my laboratories at Northwestern University. Both of these gentlemen set out to extend redox glycosidation to "real" disaccharide systems. A variety of α- and β-glucopyranosyl aldonic esters were prepared stereoselectively. After some experimentation we found that the β-esters were most efficiently prepared via trichloroacetimidate activation. This process was previously introduced by Schmidt.[27] α-Esters in turn were most efficiently prepared by formation of the anomeric alkoxides using *n*-butyllithium and transesterification using 3-nitropyridine-2-thiol esters. Each of these processes are exemplified by the preparations of esters **65** and **66** (Scheme 12). The β-esters such as **65** were formed via the more stable α-trichloroacetimidate **64** and S_N2 displacement by the carboxylic acid. The origin of the α-diastereoselectivity in the formation of **66** is less straightforward to understand. Bezuidenhoudt found that the preparation of α-D-glucopyranosyl esters via alkoxide formation and transesterification with 3-nitropyridine-2-thiol esters was generally useful and a variety of esters were prepared in this way (Table I). It is particularly



SCHEME 12

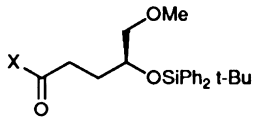
noteworthy that the method was successful for both D-glucose and D-mannose systems. It is reasonable to assume that under the reaction conditions, the α- and β-alkoxides were interconverting[28] and it is possible that the α-alkoxide has a dimeric structure **68** and the β-alkoxide the tetrameric structure **69**.[29,30] The dimeric species **68** may indeed be more reactive towards acylation than the β-tetramer **69**. In any case, irrespective of mechanistic speculation, Bezuidenhoudt and Gasiecki had identified preparatively useful, stereoselective methods for the preparation of either α- or β-esters.

The Tebbe methylenation and iodoetherification reactions also proceeded uneventfully and a variety of vinyl ethers were prepared

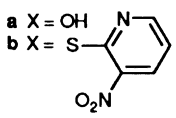
TABLE I

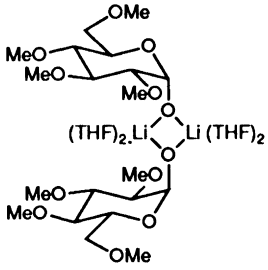
PREPARATION OF α-GLYCOSYL ESTERS USING THE ACYLATION OF ANOMERIC ALKOXIDES WITH 3-NITROPYRIDINE-2-THIOL ESTERS

Entry	Carbohydrate	Ester	Yield % (α : β)
1	**44**	**71a**	58 (16 : 1)
2	**44**	**71b**	73 (22 : 1)
3	**44**	**71c**	83 (20 : 1)
4	**44**	**72**	94 (9.5 : 1)
5	**44**	**73a**	65 (14 : 1)
6	**44**	**73b**	66 (6.5 : 1)
7	**63**	**74**	66 (18 : 1)
8	**63**	**75**	73 (11 : 1)
9	**70**	**76**	67 (α only)

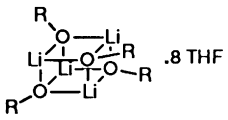


67

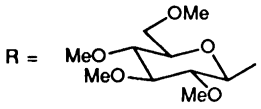


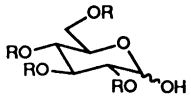


68

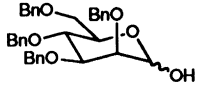


69

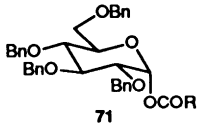




44 R = Bn
63 R = Me

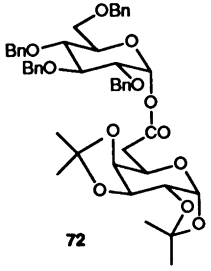


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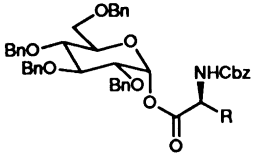


71

a R = Ph
b R = Me(CH2)6
c R = cyclohexyl

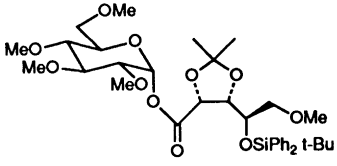


72

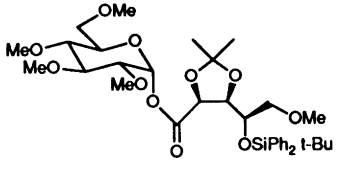


73

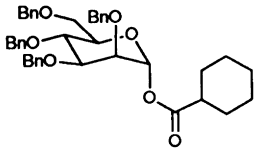
a R = iso-PrCH2
b R = iso-Pr



74



75

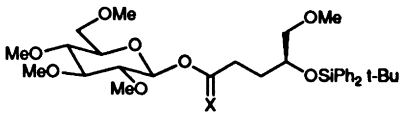
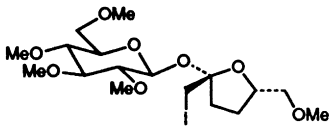
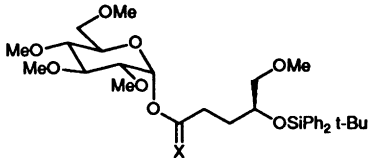
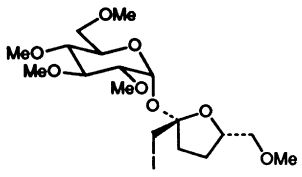
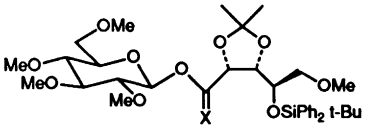
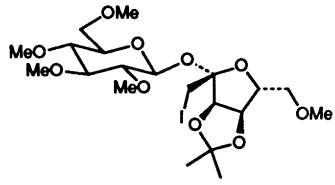
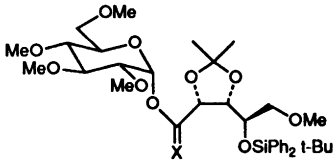
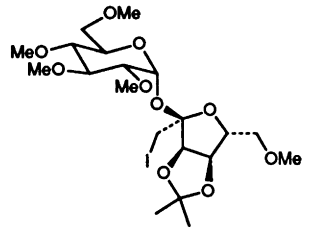
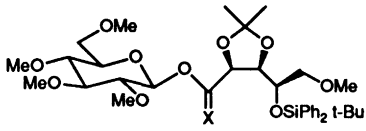
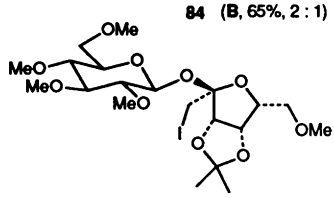


76

and cyclized using iodine and potassium *t*-butoxide in THF. These results are summarized in Table II. We were all greatly encouraged by all these examples. It was clear that the Tebbe methylenation reaction worked well for a variety of carbohydrate systems (Table II). Even the sterically hindered ribonic and lyxonic esters **81a**, **74**, **85a**, and **75** were cleanly methylenated without any complications from the isopropylidene groups. The vinyl ethers **77**, **79**, **81b**,

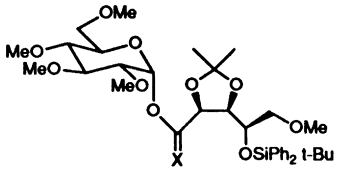
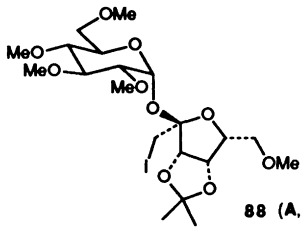
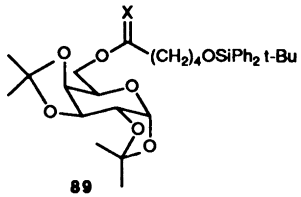
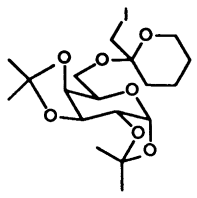
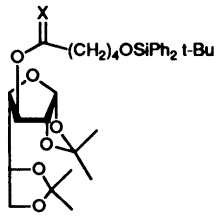
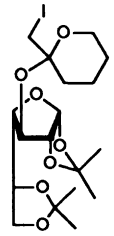
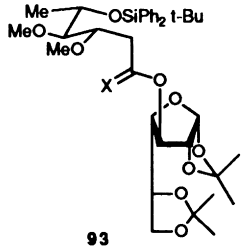
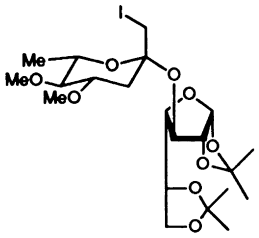
TABLE II

PREPARATION AND METHYLENATION OF GLYCOSYL ESTERS AND CYCLIZATION TO PRODUCE DISACCHARIDES

Entry	ESTER (YIELD % ds), VINYL ETHER (YIELD %)	MAJOR DISACCHARIDE (METHOD OF CYCLIZATION[a], YIELD %, ds)
1	 **65** X = O (65%, 11 : 1) **77** X = CH_2 (67%)	 **78** (A, 65%, 8 : 1)
2	 **66** X = O (80%, 7.4 : 1) **79** X = CH_2 (82%)	 **80** (A, 59%, >40 : 1)
3	 **81** **a** X = O (71%, 1 : 12) **b** X = CH_2 (72%)	 **82** (B, 69%, 5 : 1)
4	 **74** X = O (66%, 18 : 1) **83** X = CH_2 (84%)	 **84** (B, 65%, 2 : 1)
5	 **85** **a** X = O (83%, 10 : 1) **b** X = CH_2 (88%)	 **86** (B, 23%, 2 : 1)

(*continues*)

TABLE II (*continued*)

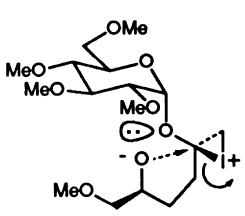
Entry	ESTER (YIELD % ds), VINYL ETHER (YIELD %)	MAJOR DISACCHARIDE (METHOD OF CYCLIZATION[a], YIELD %, ds)
6	 **75** X = O (67%, 11 : 1) **87** X = CH_2 (74%)	 **88** (A, 52%, >50 : 1)
7	 **89** **a** X = O (68%) **b** X = CH_2 (44%)	 **90** (A, 54%, 2 : 1[b])
8	 **91** **a** X = O (84%) **b** X = CH_2 (83%)	 **92** (A, 76%, 2 : 1[b])
9	 **93** **a** X = O (98%) **b** X = CH_2 (82%)	 **94** (C, 60%, 3 : 1)

[a] Methods for cyclization: (A) Bu_4NF, silica, I_2, t-BuOK, THF; (B) Bu_4NF, THF followed by I_2, t-BuOK, THF, −78 to −40°C; (C) Bu_4NF, THF followed by I_2, t-BuOK, THF, 0°C.

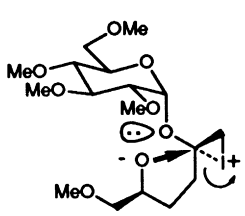
[b] The structure of the major diastereomer was not determined.

83, **85b**, **87**, **89b**, **91b**, and **93b** were converted into the corresponding disaccharides **78**, **80**, **82**, **84**, **86**, **88**, **90**, **92**, and **94** by desilylation using tetrabutylammonium fluoride and iodoetherification. These transformations were carried out in two distinct ways. In procedure A, the alkene silyl ether was reacted with tetrabutylammonium fluoride on silica, iodine and potassium *t*-butoxide in THF. Thus the iodoetherification was carried out *in the presence of silica.* In the second method, (procedures B and C) the silyl ether was first deprotected and the resultant alcohol purified and cyclized in a second step using iodine and potassium *t*-butoxide. At this point in time, neither I nor any of my co-workers attached any significance to the differences between the two methods. We were pleased to observe that several of the iodoetherification reactions proceeded with good diastereoselectivity.[31] It is clear that the substituents on the acyl fragment play a dominant role in determining stereoselectivity. The alkene **79** (entry 2) underwent cyclization with excellent diastereoselectivity. Presumably the stereocontrol was the result of both stereoelectronics (oxygen lone-pair antiperiplanar to the C–I bond) and minimization of steric congestion between the iodine and pyranose ring and between the methoxymethyl group and the anomeric oxygen. The structures of both intermediates **95** and **96** are stabilized by the anomeric oxygen lone pair. Cyclization via **96** would be favored since this avoids steric congestion between the methoxymethyl group and anomeric oxygen. This model would also explain the lower diastereoselectivity observed on the cyclization of the β-alkene **77** since the β-anomeric oxygen is less electron-rich due to the anomeric effect. In the ribose substituted examples **81b** and **83** (entries 3 and 4) presumably the steric biases of the methoxymethyl and isopropylidene rings are mismatched. The lyxose systems **85b** and **87** (entries 5 and 6) were both slow to undergo cyclization. In the β-case the yield of iodo ether **86** was low due to competitive destruction of the starting material. The α-anomer **87** was slowly cyclized to produce only the isomer **88**. It is possible, in this case, that cyclization took place via the conformation **97**. This species is favored by the stereoelectronic factors already mentioned, but more importantly it minimizes the severe congestion between the three *cis* substituents on the lyxose fragment and the pyranose ring.

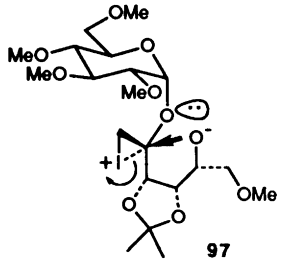
Entries 7 to 9 in Table II show that Tebbe methylenation followed by iodoetherification may be used to glycosylate hydroxyls other than those present at the anomeric center. Gasiecki prepared both alkenes



95



96

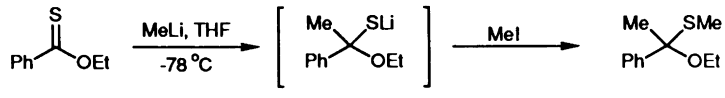


97

89a and **91b** and showed that redox glycosidation may be used to derivatize both the O-3 and O-6 atoms of D-galactose. In entry 9, Howell showed that redox glycosidation was appropriate for the attachment of an L-deoxyrhamnonic acid to D-galactose. We were particularly pleased that the iodoetherification of alkene **93b** proceeded with good diastereoselectivity favoring the axial iodomethyl compound **94**. This result was certainly a favorable auspice for the application of redox glycosidation in the sialic acid area.

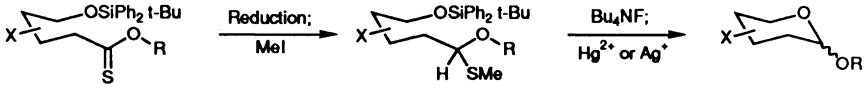
IV. Redox Glycosidation via Thionoester Intermediates

At an earlier stage in our work on the Tebbe methylenation chemistry, both Russell and myself had become concerned with one severe limitation of the method. An esterification, methylenation, iodoetherification sequence would be useless for the elaboration of the most common glycosidic bond: that between an alcohol and an aldose. About this time, K. C. Nicolaou and co-workers published a most interesting paper on the use of thionolactones in synthesis.[32] Nicolaou based his methodology upon pioneering observations by John S. Swenton, Lakshmi Narashimhan, and Robert Sanitra.[33] This group showed that organolithium reagents smoothly added to the carbon of thionoesters and the resultant tetrahedral intermediate was easily *S*-methylated to provide the corresponding monothioacetals. The process is exemplified by the conversion of **98** into **100** (Scheme 13).



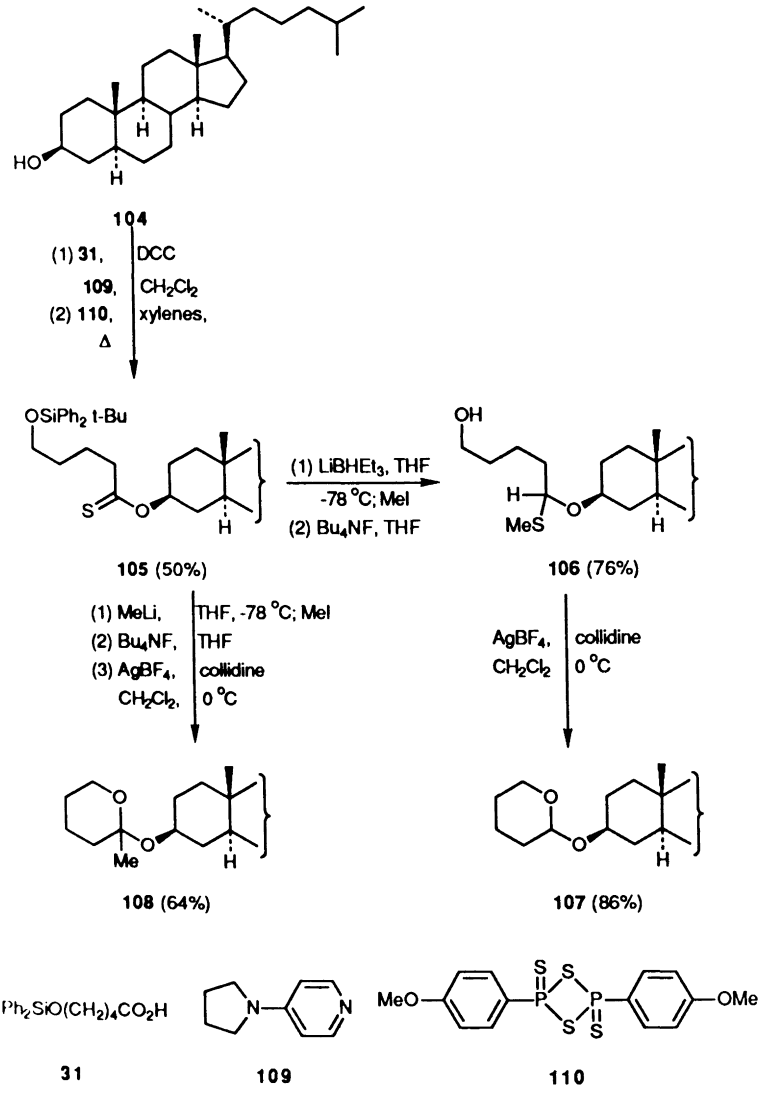
98 99 100

SCHEME 13



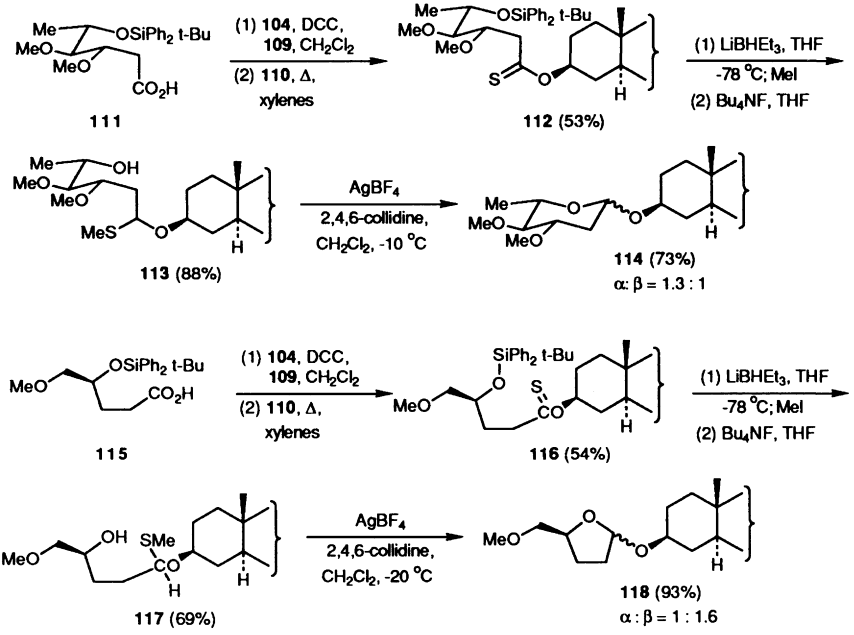
X = PROTECTED CARBOHYDRATE FUNCTIONALITY

SCHEME 14



SCHEME 15

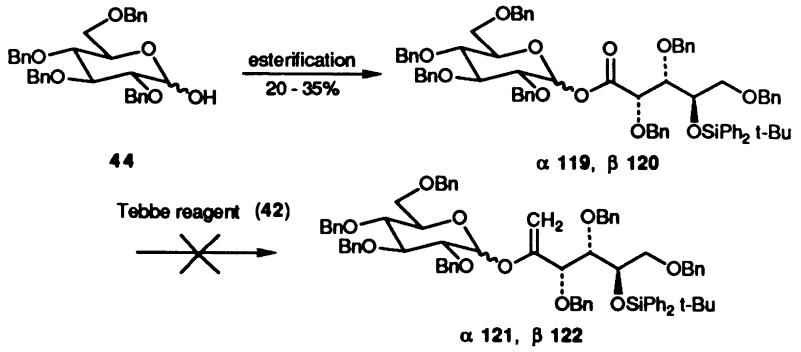
Russell suggested that such a process may be of use in the elaboration of glycosides (Scheme 14). He proposed that the thionoester **101** should give thioacetal **102** on reductive methylation and this species should undergo cyclization on treatment with tetrabutylammonium fluoride followed by a silver(I) or mercury(II) salt to provide the glycoside **103**. These predictions proved to be correct. Howell started the work by preparing a trivial derivative **107** of 5α-cholestan-3β-ol. The alcohol **104** was converted into the thionoester **105** via esterification with the acid **31** and thionation using the Lawesson reagent **110**.[34] Much to our considerable pleasure, the reductive methylation gave the thioacetal **106** and this species was cyclized to provide **107**. The final product **107** was identical with a sample prepared from **104** and dihydropyran.[24] These initial observations were extended by Howell, Bezuidenhoudt and Lee, and the method was used to prepare the steroidal glycosides **108**, **114**, and **118** (Schemes 15 and 16). It is clear from these results that thionoesters are useful intermediates for the construction of glycosides.[35] However, there is still the problem of anomeric stereocontrol—but that is another (incomplete) story.



SCHEME 16

V. The Synthesis of Sucrose

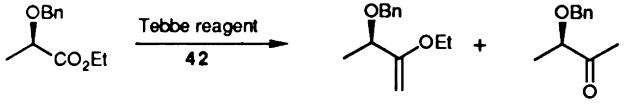
When we first directed our attention to sucrose (**4**) we had developed the acyl–indole methodology to prepare protected γ- and δ-hydroxy acids (Section II). In addition, we had shown that redox glycosidation via Tebbe methylenation worked well for the preparation of the simple model non-reducing disaccharides **52–55** (Scheme 10). At that time we had not developed the α-selective esterification methods (Scheme 12). Nonetheless, Russell and I decided that we should make sucrose (**4**). The selectively protected arabinonic acid **36** was readily prepared from 2,3,5-tri-*O*-benzyl arabinonic acid γ-lactone (**32**) (see Scheme 7). This substance **36** was esterified with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**44**) to produce the corresponding esters **119** and **120** (Scheme 17). Esterification under Mitsunobu conditions[36] using triphenylphosphine and diethyl azodicarboxylate gave both anomers **119** and **120** (4:3). Amos B. Smith III, in his elegant work on the phyllanthostatins, showed that Mitsunobu esterification may be used to prepare glycosyl esters stereoselectively, providing that the starting alcohol is a single anomer.[37] Alternatively esterification of **44** using 1,3-diisopropylcarbodiimide and 4-(dimethylamino)pyridine in dichloromethane gave mostly the β-ester **120** (ds ~ 9:1). However, both these procedures were inefficient and gave only poor yields of the corresponding esters **119** and **120** (20–35%). In spite of this inauspicious start, Russell persevered.



SCHEME 17

The mixture of anomeric esters **119** and **120** was treated with the Tebbe reagent **42** but, much to our disappointment, nothing happened. The number of equivalents of the reagent **42** was increased to 28. Nothing happened. At this point, I became concerned that perhaps the side products formed in the preparation of the Tebbe reagent **42** were too Lewis acidic and were chelating with one or more vicinal dialkoxy units in the esters **119** and **120**. Perhaps if we were to use the pure crystalline Tebbe reagent **42** rather than employing the *in situ* method, [19] the recalcitrant methylenation would take place. Thus, Russell prepared a quantity of multiply recrystallized Tebbe reagent **42** on our Schlenk line. As a general rule synthetic organic chemists dislike Schlenk apparatus but we overcame our prejudices in the face of necessity. The dark red crystalline Tebbe reagent **42** was added to a solution of the esters **119** and **120**. Nothing happened. I continued to be obsessed with chelation and as a result, Mark examined Tebbe olefination in the presence of various bidentate ligands in the hope of facilitating the wayward reaction. Thus, additives such as N,N,N′,N′-tetramethylethylenediamine and 1,10-phenanthroline were added to the methylenation reaction mixture. Nothing happened. At this time, we put the sucrose (**4**) project aside to allow time for reflection! Mark Russell did, however, convince me that there was nothing particularly wrong with the Tebbe methylenation of esters bearing α-benzyloxy groups (Scheme 18). He showed that the lactic acid derivative **123** smoothly provided the alkene **124** although the product was partially (10%) hydrolyzed to produce **125** on chromatography.

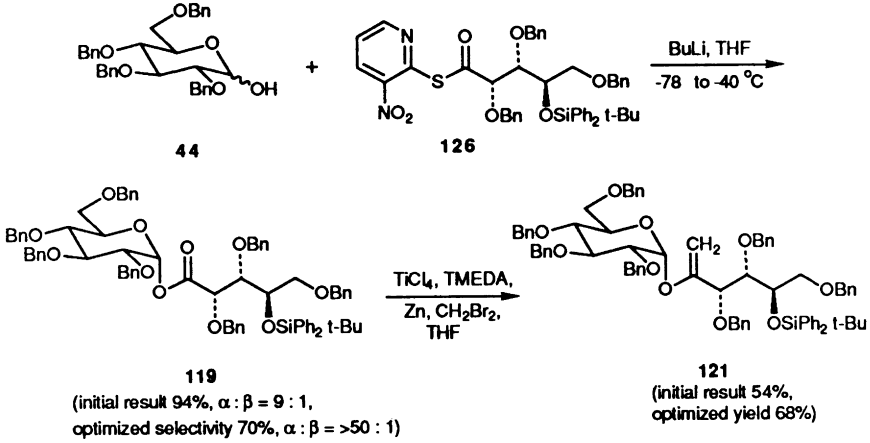
Some months later, I asked Amy Howell to reexamine the Tebbe methylenation of the esters **119** and **120**. Again in deference to my prejudices regarding chelation, the mixture of esters **119** and **120** was treated with **42** in the presence of 1,10-phenanthroline. Nothing happened and the esters **119** and **120** were recovered unchanged. Again, sucrose (**4**) was set aside.

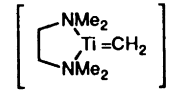


123 **124** (90%, 9 : 1) **125**

SCHEME 18

Several months passed and by this time, the redox glycosidation group had demonstrated that Tebbe methylenation and iodoetherification worked well for all the examples in Table 2. Surely, since the ribose **81a** and **74** and lyxose **85a** and **75** systems worked then the esters **119** and **120** must undergo methylenation. Ben Bezuidenhoudt was elected to reinvestigate this crucial process. Firstly, Ben applied his 3-nitropyridine-2-thiol ester chemistry to the stereoselective preparation of the α-glycoside **119**. Reaction of thionoester **126** with 2,3,4,6-tetra-O-benzyl-D-glucopyranose (**44**) and n-butyllithium in THF at $-78°C$ for 48 hours and $-40°C$ for 92 hours gave ester **119** and **120** (94%) with the required α-isomer **119** as the major component (9 : 1). Again the Tebbe reagent **42** was examined but without any significant success. Thus, Ben examined the use of the Nozaki-Takai reagent[38] to effect the methylenation. Much to our delight and my very considerable relief, the methylenation did indeed work and it smoothly provide the corresponding vinyl ether **121** (54%) (Scheme 19). The reagent cocktail, which presumably contains a carbene such as **127** or an equivalent dimetallocyclobutane, reacted





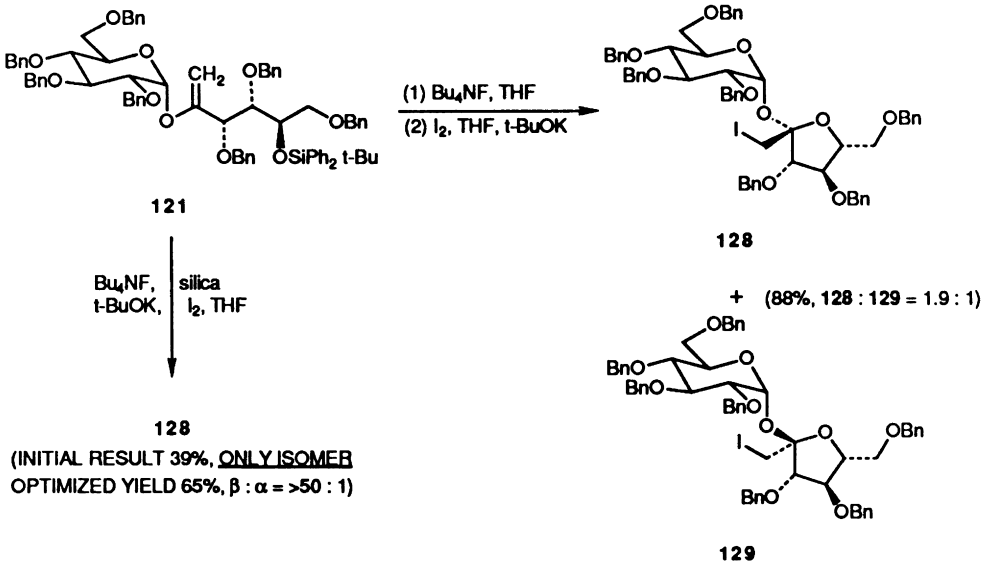
127

SCHEME 19

more rapidly with the α-ester **119** than the β-isomer **120**. Presumably, the Nozaki-Takai reagent worked because it is less Lewis acidic.

Ben rapidly examined the crucial iodoetherification reaction. Thus, the alkene **121** was desilylated and the resultant alcohol purified. As expected, this alkene was readily cyclized by reaction with iodine and potassium t-butoxide. Two disaccharides **128** and **129** were formed and the major (1.9 : 1) component **128** was shown to possess the sucrose configuration (Scheme 20). We were, of course, very pleased that the reaction did indeed work and we would have been satisfied to complete the synthesis even with this modest level of stereoselectivity (9 : 1 at the glucopyranoside center and 1.9 : 1 at the fructofuranoside center). However, both Ben and I still underestimated the pleasure and pain that awaited us.

One day Ben decided to take a shortcut. It is possible that a research meeting was imminent and he was concerned to maximize his productivity for the occasion. Anyway, Ben allowed the vinyl ether **121** to react with tetrabutylammonium fluoride on silica in THF. Subsequently, iodine and potassium t-butoxide were added to the reaction mixture. In other words, silica was present during the



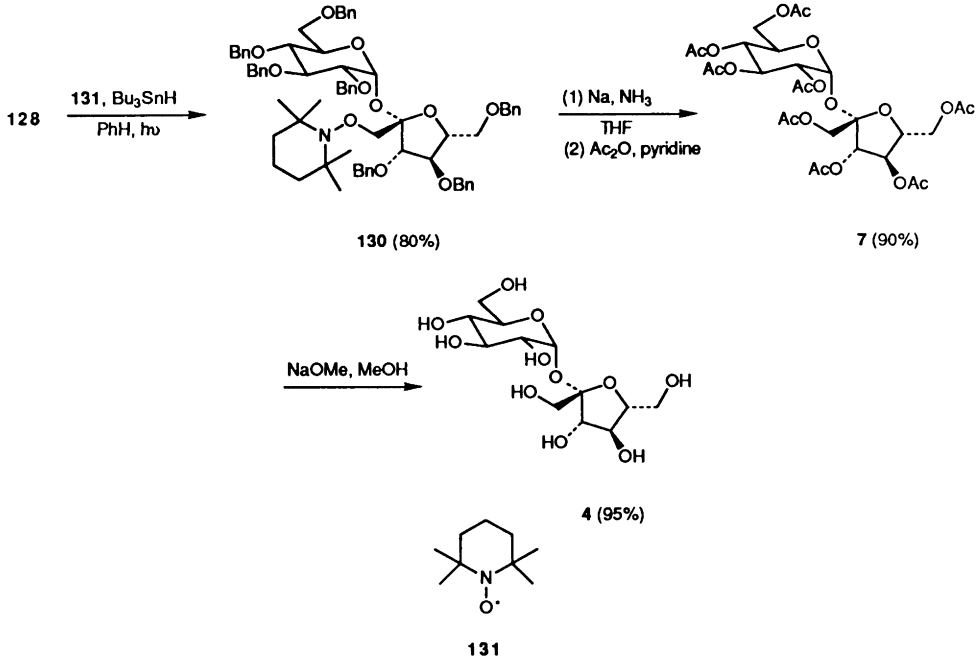
SCHEME 20

iodoetherification. A very curious result was observed and the notebook entry states cryptically "Only prod A of 1123!" The cyclization gave only the sucrose stereoisomer **128** albeit in very modest yield (39%) since considerable quantities of the starting alkene **121** remained. Clearly, silica was having a remarkable and fortuitous effect on the stereochemistry of ring closure. At this time, Ben was rushing to complete the project. His sabbatical at Northwestern University was drawing to a close and he needed to return to fulfill his obligations in his home university. Thus, he put aside the extraordinary silica effect and concentrated on converting the major isomer **128** into sucrose (**4**). However, he was destined to meet adversity again. The iodide **128** just did not react with various oxygen centered nucleophiles. Lithium benzyloxide or lithium hydroxide in THF did not displace the iodide. Neither did the "naked" anion potassium formate and 18-crown-6 in DMF, nor benzyl alcohol and silver salicylate, nor sodium benzyloxide and silver trifluoroacetate in the presence of 18-crown-6, nor potassium superoxide and 18-crown-6 in DMF and DMSO.[39] When several of these reagents were used at elevated temperatures only "junk" was obtained. Thus, it appeared we were to be defeated by a simple S_N2 displacement: a bitter end to a journey. The iodide **128** has both steric and stereoelectronic factors that disfavor nucleophilic displacement. It is neopentylic, with two β-oxygen substituents and is on an axial substituent.

On this rather disappointing note, Ben returned to Bloomfontein. However, I was certain that we should be able to complete sucrose (**4**) in short order. This naïve optimism was shared by several others in my research group and at least one unnamed vulture volunteered to complete the project in the anticipation of a publication for a minimum of work. In spite of this pressure, I asked another excellent group member, Laura Melcher to complete the sucrose work. I specifically asked her to optimize all the steps and to seek to complete the work by displacing the iodide **128** with some oxygen centered nucleophile. Her work, which was a modification and adaption of Ben's chemistry, at least as far as the iodide **128**, is summarized in Schemes 19 and 20. Firstly, the esterification process was optimized by carrying out the transesterification at $-78°C$ for 2 weeks! At this lower temperature the ratio of esters favored the α-anomer by at least 50 : 1. The Nozaki-Takai methylenation reaction was improved by ultrasonicating the reagent before but not after the addition of the ester **119**.

Finally, Laura improved both the conversion and yield of the iodoetherification reaction. Even at good conversions only the sucrose epimer **128** was observed (ds > 50 : 1). Additionally, she observed that the iodo compound with the epi-sucrose stereochemistry **129** was inert to the iodoetherification reaction conditions in the presence of silica. Thus, the diastereoselectivity was certainly kinetic in origin rather than due to selective destruction of the unwanted isomer **129**.

Laura still needed to cajole the iodide **128** into cooperation. I was still of the opinion that S_N2 displacement of the iodide **128** may have been possible. Thus Laura examined several additional reagents including prolonged reflux with excess potassium benzoate and 18-crown-6 in DMF. None of these approaches were successful. Either no reaction was observed or, under more forcing conditions, the iodide **128** was degraded. My research group owns a high pressure apparatus which we occasionally use to encourage bimolecular reactions to be cooperative. Unfortunately, in spite of many elegant applications of high pressure syntheses in the literature,[40] many members of my research group view the technique with suspicion. Indeed,



SCHEME 21

the apparatus is regarded with considerable disdain probably because I only suggest its use in times of trial and tribulation. Thus Laura Melcher set out to facilitate the S_N2 displacement reaction at elevated pressures. However, I finally became convinced of the futility of an S_N2 displacement when a solution of potassium benzoate or t-butylammonium formate and 18-crown-6 in DMF at 7000 atmospheres failed to displace the iodide **128**. Incidentally, the reputation of high pressure synthetic chemistry still remains at a low ebb in the Barrett group. Perhaps I should upgrade our apparatus to even higher pressures!

Clearly at this point, we had only one option for completing the synthesis: radical chemistry.[41] We considered that homolysis of the carbon iodine bond followed by oxidation of the resultant radical should provide the corresponding alcohol. Thus iodide **128** was photolyzed in hexane solution in the presence of hexabutyldistannane and oxygen. We were both pleased to note that the iodide **128** did indeed disappear and several products, which may have included the corresponding hydroperoxide, were formed. The reaction was neither clean nor preparatively useful. At this time, I attended the Royal Society of Chemistry International Symposium on "Transition Metals in Organic Synthesis" in St. Andrews, Scotland. One of the plenary lectures was given by Professor Gerry Pattenden and I was particularly pleased to attend his lecture for two reasons. Firstly, I anticipated a banquet of elegant chemistry presented in a lucid fashion. Secondly, Gerry had bought me a drink the night before and this was a very rare occurrence. As I expected, Gerry gave an excellent account of his recent studies of the radical chemistry of cobaloximes.[42] I was particularly impressed by his use of TEMPO (**131**) to efficiently trap alkyl radicals from the homolysis of cobalt (III) alkyls. I immediately asked Laura to examine **131** to trap the alkyl radicals formed on the photolysis of iodide **128**. Several years prior to our work, Professor Robert G. Bergman had employed both tributylstannane and TEMPO (**131**) in this way.[43] Thus iodide **128** was photolyzed in the presence of both these reagents and this provided the trialkylhydroxyamine (**130**). After considerable optimization, the yield of **130** was improved to 80% (Scheme 21).

Originally we planned to use global catalytic hydrogenolysis[24] to liberate sucrose (**4**). However, this reaction was not very clean. Thus **130** was converted into sucrose (**4**) by reduction using sodium in

ammonia and THF. The product was most conveniently isolated as the octaacetate **7** (90%). This sample was identical by m.p., TLC, $[\alpha]_D$, IR, 400-MHz ^1H NMR, 101 MHz ^{13}C NMR, and high resolution mass spectrometry with an authentic sample of sucrose octaacetate (**7**). Finally, Zemplen methanolysis[44] of **7** gave sucrose (**4**) and this sample was identical by TLC, m.p., $[\alpha]_D$, IR, 400-MHz ^1H NMR, 101 MHz ^{13}C NMR, and high resolution mass spectrometry with authentic material.

VI. Epilogue

At long last, we finally succeeded in preparing sucrose (**4**) with excellent diastereoselectivities at both anomeric centers. In a way the journey was over; a journey that was somewhat reminiscent of Odysseus' wanderings after the sacking of Troy. We are currently continuing to study redox glycosidation in the context of more complex systems. Both the methylenation and thionoester strategies continue to occupy our attention. The frustrations associated with the displacement of iodide **128** have led us into the area of organometallic chemistry on "The Island of Antimony." The synthesis of sucrose (**4**) is clearly just a start on a journey in carbohydrate chemistry. The analogy with Homer is presumptuous since Ithaca is still very, very far away.

I thank the National Institutes of Health (Grant GM-40949) and the G. D. Searle Company for generous support of this program of research. I am also grateful to the National Institutes of Health (Grants RR-02314 and RR-03245) for the purchase of a 400 MHz ^1H NMR spectrometer and a high resolution mass spectrometer used in these studies at Northwestern University. I also would like to sincerely thank all the co-workers named in this article. Dash Dhanak joined SKF in the U.K. when he left my research group. Mark Russell is now employed at G. D. Searle in Skokie, Illinois. Amy Howell emigrated from the U.S.A. to England to carry out postdoctoral work with Professor Gerry Pattenden in Nottingham. She is currently employed by Glaxo Group Research in Greenford. Amy is one of the very few people who have joined the "brain drain" but in the wrong direction. Ben Bezuidenhoudt returned to a faculty position in the University of the Orange Free State in South Africa. Al Gasiecki

returned to his position in medicinal chemistry at G. D. Searle where he continues to excel. Both Laura Melcher and Al Lee are still graduate students in my group. They both accompanied me west to Colorado. I thank both these students for generous help in the preparation of this manuscript.

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Chapter 2

SOLUTION OF COMPLEX STEREOCHEMICAL PROBLEMS WITH THE AID OF MOLECULAR MECHANICS-BASED MODELING: AN APPLICATION TO THE TOTAL SYNTHESIS OF (±)-PLEUROMUTILIN

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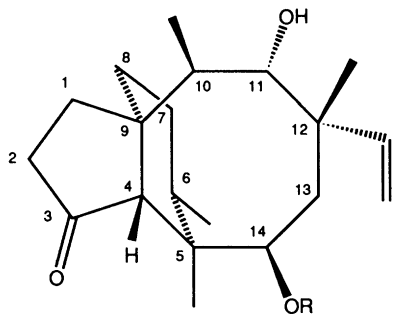
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I. Introduction

The development of computer-assisted molecular modeling with applications to a wide array of problems in organic and biological chemistry has been rapid since the early work of Westheimer[1] some 40

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years ago and subsequent studies of Hendrickson[2] and Allinger.[3] The molecular mechanics method has become a well-established tool with the development of accurately parameterized computer-based MM2 and other force field methods by Allinger as well as a number of other groups.[4–6] The method has proven quite useful as a means to evaluate the ground state energies and geometries of the various conformations in complex organic molecules, permitting the comparison of ground state properties and prediction of the equilibria between configurational isomers. The technique has now been extended with some modifications to the evaluation of transition state energies.[7]



1, R = - $C(O)CH_2OH$, pleuromutilin

2, R = - $C(O)CH_2S(CH_2)_2N(CH_2CH_3)_2$, tiamulin

3, R = - H, mutilin

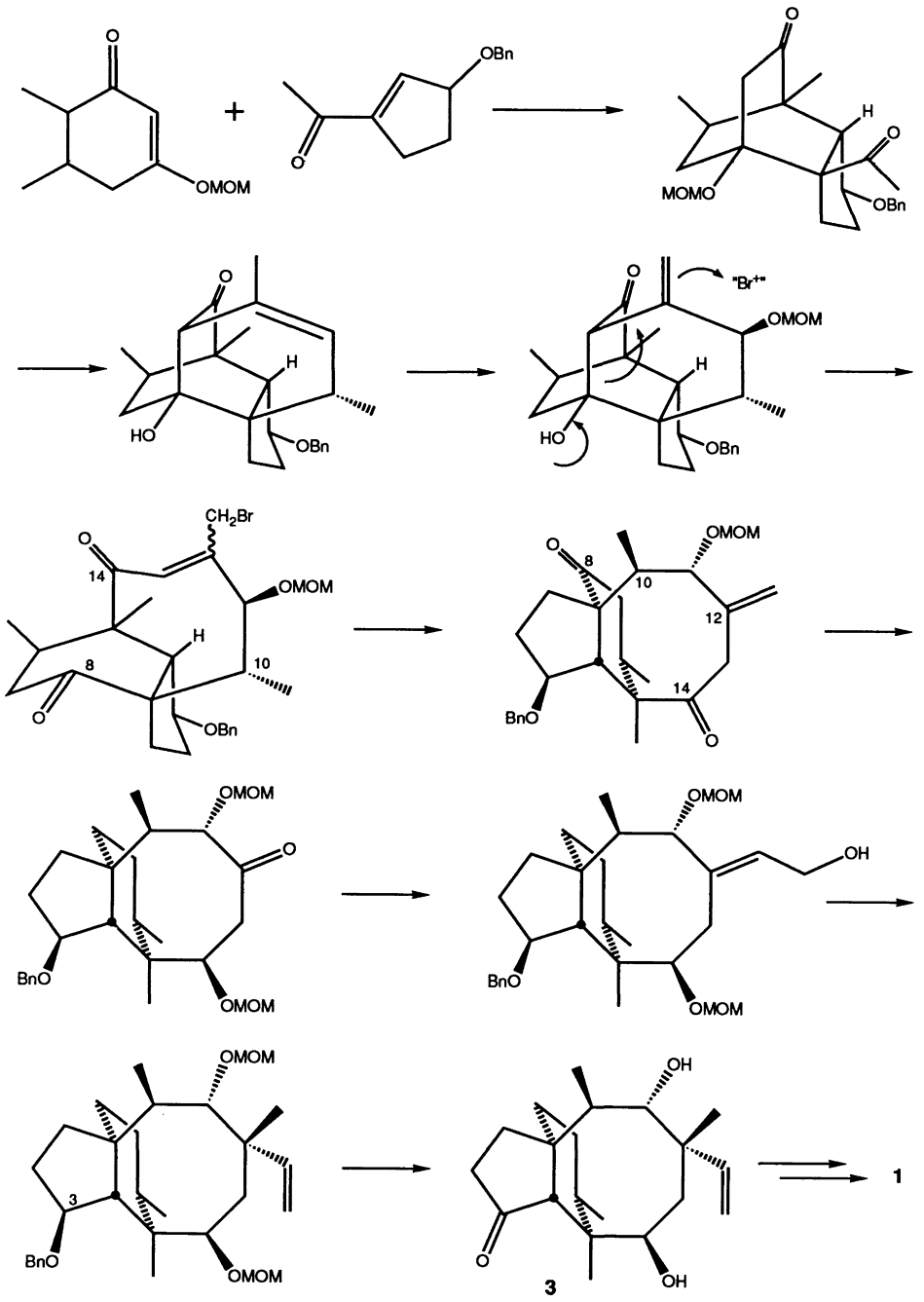
In 1980, at the inception of our work on (±)-Pleuromutilin (**1**), we were interested in determining the applicability and usefulness of the molecular modeling technique as an *apriori* assistance to strategic and tactical planning of a synthetic route to a stereochemically complex system. An ideal choice of a target appeared to be (±)-Pleuromutilin (**1**), a diterpene antibiotic whose derivative Tiamulin (**2**) has some commercial importance as an animal health product.[8] The structure of **1** had been known since the 1960's,[9,10] and **1** had been shown to exhibit a remarkable spectrum of unusual chemical transformations.

Those transformations are principally the result of the chemical (and probably conformational) properties of the 8-membered ring containing 7 stereogenic centers which is the centerpiece of the unique 5-8-6 ring system present in **1**.[9–12] Since 8-membered rings are among the most conformationally complex of the medium rings, an approach to **1** appeared to pose a formidable challenge in synthetic planning.

Although **1** has attracted the interest of a number of research groups,[12,13] at the beginning of our work, little was known regarding the accessibility of the tricyclic ring system since most chemistry which had been conducted upon **1** and its derivatives involved degradation and semisynthesis.[9–13] However, in 1982, Gibbons (working with Woodward at the time of his passing) described the first successful synthetic approach to **1** involving a typically elegant "Woodwardian" strategy of conformational restriction by rigidification *via* construction of a sterically strongly-biased ring system in the precursor(s). Using this template, the required stereogenic centers were installed prior to deconvolution to the pleuromutilin ring system (Scheme 1).[14,15] This type of strategy has, as its major drawback, an inherently lower efficiency since a more lengthy sequence must be employed as the result of the steps required for assembly and deconvolution of the rigid system on which the stereochemical control is based.

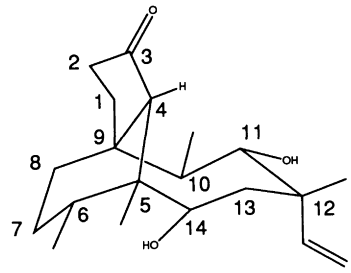
II. Conformational Analysis of Pleuromutilin Derivatives

Using MM2, we examined in detail the conformational properties of mutilin (**3**), the logical precursor of **1**, in order to determine the level of complexity of the problem. We were encouraged to find that a conformational search led to only two conformers, **4** and **5**, which were local energy minima (Scheme 2). Although it is possible that "twist" conformations may exist which involve C_{11}–C_{13} (Scheme 2), the conformational search suggested that if these "twist" conformations are populated, they maintain the overall ring topography of the 8-membered ring in the local minimum energy conformations **4** and **5**.[16] These findings were supported by the analysis of Hendrickson and later Still who found that even-membered medium and macrocyclic rings tend to exist in a few well-defined symmetrical conformations whereas odd-membered rings tend to have more complex

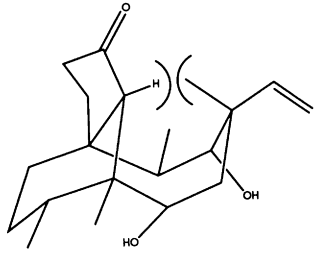


3

SCHEME 1



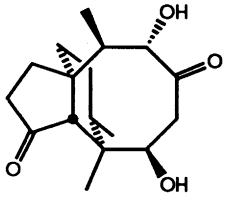
4
E_{rel}=0 Kcal/mol
boat-chair
(bc)



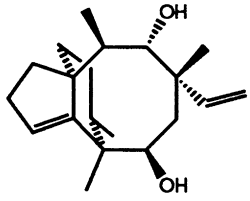
5
E_{rel}=13.1Kcal/mol
boat-boat
(bb)

SCHEME 2

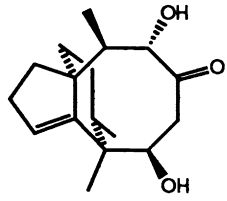
itineraries of conformations of often similar energies available to them.[17–19] The further conformational restriction imposed by bridging C_5 and C_9 in **1** eliminates the chair–chair (cc) conformation. As the energy difference (ΔE = 13.1 kcal/mol) indicates (Scheme 2), the boat–boat (bb) conformation is quite significantly destabilized by the prow interaction between the methyl group at C_{12} and the hydrogen at C_4 as well as by the necessity that the C_{11} hydroxyl group reside in an axial-like environment. Further analysis of the conformational properties of other related structures such as diketone **6**, olefin **7**, and keto olefin **8** was done based upon the expectation that the introduction of sp^2 centers at C_4 and C_{12} would lower the energy of the bb conformation relative to the boat–chair (bc) conformation. Still



6



7



8

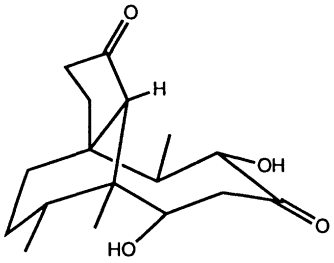
had observed such an effect in his studies.[19] The results shown in Scheme 3 indicated that the bb conformation would likely need to be considered only for early intermediates which are relatively unfunctionalized and possess sp^2 centers at both C_3 and/or C_4, and C_{12}.

Thus, the results of our conformational analysis led us to the conclusion that the 8-membered ring could be expected to adopt a well-defined low energy bc conformation in most intermediates whose local topography in the region of C_{10}–C_{14} could be expected to mimic the topography found in 6-membered rings (excepting systems which possess an endocyclic olefin). As a result, the substitution energies (*A* values) should roughly reflect those found in similar 6-membered ring structures. Therefore, it appeared one could employ a direct functionalization strategy which should result in significantly increased efficiency relative to other conceivable strategies, with the expectation that a reasonable level of stereoselection would be observed. With this background, we developed the two retrosynthetic schemes discussed below.

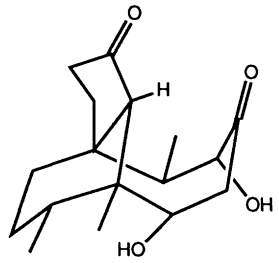
III. Retrosynthetic Analysis

Examination of the relative stereochemistry of the substituents in the low energy bc conformation of **1** shows that only the vinyl group at C_{12} exists in an axial or axial-like environment. Therefore, use of thermodynamic control to establish the relative stereochemistry of the other stereogenic centers appeared potentially feasible.

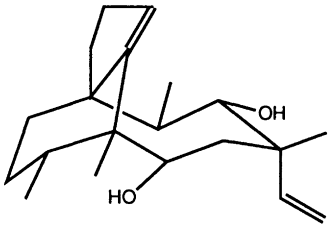
Further analysis suggested two potential dissections to arrive at a key keto olefin **9**, both of which were intended to systematically remove the functionality in the 8-membered ring. Rather than remove all the substituents, it was deemed desirable to retain one substituent



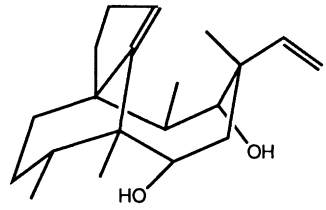
6
E_{rel}=2.1 Kcal/mol
(bc)



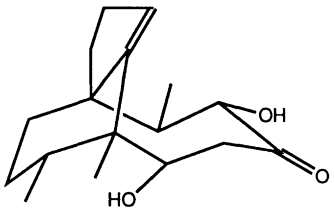
6
E_{rel}=0Kcal/mol
(bb)



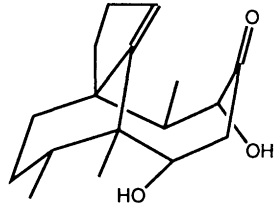
7
E_{rel}=0 Kcal/mol
(bc)



7
E_{rel}=8.7Kcal/mol
(bb)



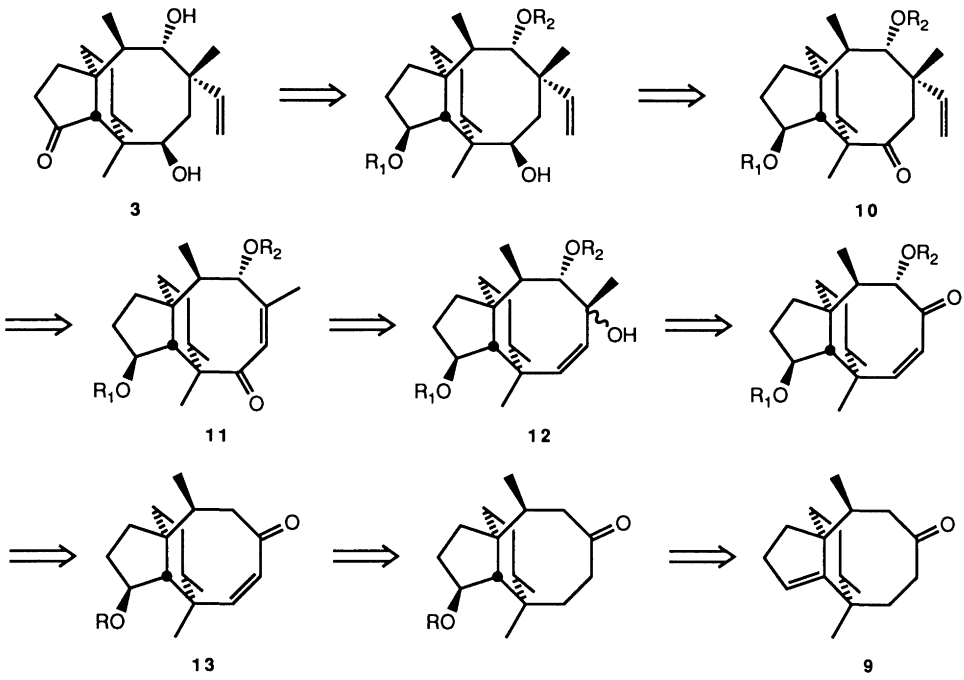
8
E_{rel}=4.0 Kcal/mol
(bc)



8
E_{rel}=0Kcal/mol
(bb)

SCHEME 3

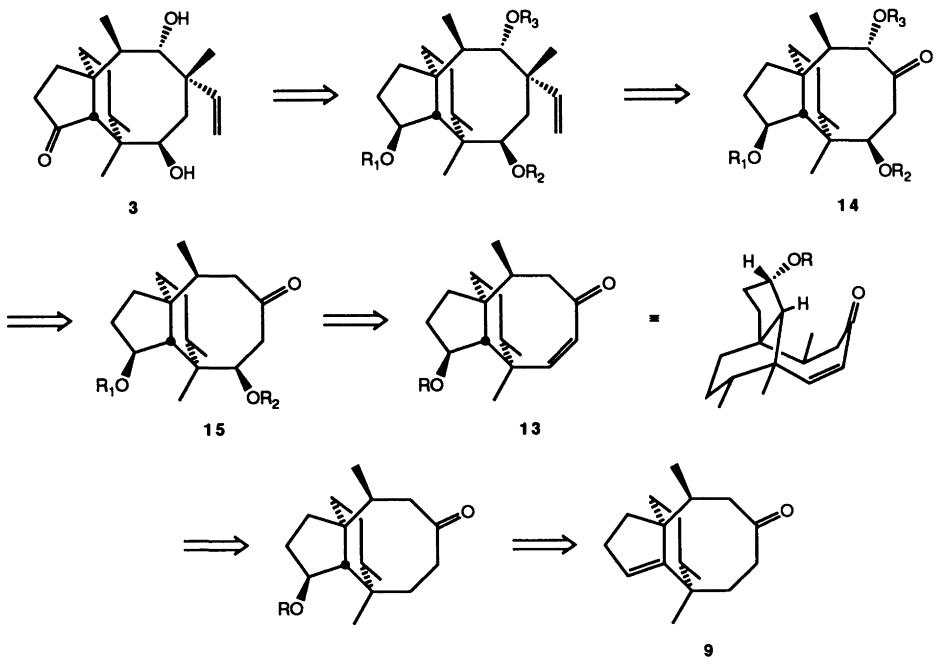
(the methyl group at C_{10} was selected) to impart additional conformational bias to the 8-membered ring. The first of these dissections is outlined in Scheme 4. Detailed evaluation of this route revealed several potential difficulties especially as the conformational properties of the projected intermediates were determined *via* MM2 calculations. After initial functional group manipulations to arrive at a differentially protected C_{14} alcohol, the substituents were envisioned to be removed successively from C_{12}, C_{11}, and $C_{14}(C_{13})$. Particularly noteworthy among these transformations is the need to reduce the C_{14} ketone in **10** from the α face. Hydride reduction was known to occur from the undesired β face in C_{14} keto pleuromutilin derivatives.[10,11] A thermodynamically controlled reduction appeared conceivable, but complications were known to occur during metal/ammonia reduction of pleuromutilin derivatives related to **10** which resulted, unexpectedly, in the concomitant reduction of the C_{12} vinyl group.[10] Although the desired reduction to the C_{14} β alcohol was subsequently realized by Gibbons,[14,15] this was considered a significant problem with the



SCHEME 4

analysis presented in Scheme 4. Enone **11** was expected to undergo well-precedented, stereoelectronically controlled α axial attack by lithium divinyl cuprate. However, the feasibility of the addition was questionable since the low energy conformation found for **11** had little or no overlap between the C_{14} carbonyl group and the C_{12}–C_{13} double bond. However, since other cyclooctenones, which appear to have comparable conformational properties, have been shown to undergo cuprate addition,[19,20] a higher energy, reactive, planar conformation might be responsible for the observed conjugate addition. Nevertheless, the population of this reactive conformation could be quite low possibly leading to greatly diminished reactivity. Introduction of the C_{14} ketone was envisioned to occur *via* oxidative rearrangement of 3° allylic alcohol **12**. In solvolytic studies, cyclooctenyl halides were found to be both sluggishly reactive, and to react without double bond isomerization.[21] However, this was considered to be a relatively minor issue since the mechanism for oxidative rearrangement likely involves a [3,3]-sigmatropic rearrangement rather than an S_N2' solvolysis.[22] The introduction of the C_{11} α-oxygen function by oxidation of the cross-conjugated enolate derived from **13** appeared plausible since the low energy conformation of the enolate was found to be distorted toward a bb conformation making the α-face sterically more accessible.[23] Functionalization of the olefin in **9** and installation of the C_{13}–C_{14} double bond were expected to be straightforward. In spite of these potential difficulties, some of the key elements of this sequence were tested experimentally as described below.

The second retrosynthetic analysis leading to ketoolefin **9** is outlined in Scheme 5 and has some similar elements but avoids some of the potential pitfalls. This scheme was evolved from that in Scheme 4 as difficulties were encountered in the implementation of the initial strategy. The primary differences reside first in the introduction of the C_{12} quaternary center by the appropriately ordered addition of methyl and vinyl units (depending on the realization of addition from the β face as dictated by the bc conformation of **14**) to a C_{12} ketone.[14,15,24] The second change was the introduction of the C_{11} α oxygen *via* the regiospecifically generated C_{11}–C_{12} enolate which was again expected to undergo α attack due to the adoption of a bb-like conformation by the C_{12}–C_{13} enolate derived from ketone **15**. The final modification was the introduction of the C_{14} β-oxygen *via* 1,4 addition to *cis* enone **13** in which the stereochemical control was to



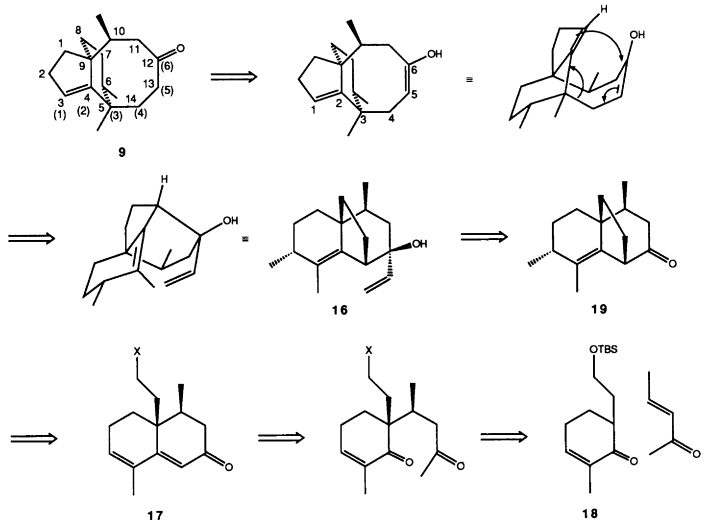
SCHEME 5

be imparted by the requirement for peripheral attack of the nucleophile on the lowest energy conformation of **13** (the C_{13}–C_{14} double bond is approximately perpendicular to the rough plane of the 6-membered ring, see Scheme 5). Enone **13** would be derived from **9** as in Scheme 4. The major potential difficulty is that the olefin and carbonyl groups in **13** will be insufficiently conjugated to undergo 1,4 addition at an appreciable rate. Furthermore, the nucleophile will possibly have to be a suitably protected hydroxyl group to avoid complications from retroaldol processes (vide infra).

All of the above analysis makes the fundamental assumption that the low energy conformations will likely be reasonably reactive and that no highly reactive minor conformations, possessing markedly different geometries, are likely to intervene. The assumption has been demonstrated to be valid in some cases.[19] In the cases examined above, the most likely instances where this assumption may not be valid are the reactions involving 1,4 addition to enones such as **11** and **13**. *Nevertheless, one must be cautious in the application of this assumption in cases where sizable populations of other*

reactive conformations are expected to be present in the conformational equilibrium. Also, implicit in this analysis is the assumption that stereocontrol will be dominated by nonbonded interactions or stereoelectronic effects arising predominantly from the substrate, and that the transition states for all kinetically controlled processes are rather early and reactant-like. This latter assumption is probably valid for most C–C bond-forming reactions, proton transfers, as well as those reactions involving highly reactive reagents (e.g., hydride reduction or peracid oxidation).

Both of the above analyses identify keto olefin **9** as a key intermediate. A retrosynthetic analysis for **9** is depicted in Scheme 6. The key features of this dissection are: first, the recognition of the latent 1,5 diene system in **9** (*via* its enol) leading to the oxy-Cope rearrangement from vinyl carbinol **16**; second, the stereoelectronically controlled 1,4 addition to dienone **17** and subsequent α alkylation; and third, the stereocontrolled Michael addition to the cross-conjugated enolate derived from **18**. This route is, in principle, highly stereocontrolled and extremely efficient. The postulated oxy-Cope rearrangement was quite attractive from the point of view of strategy, however at the outset, available precedent for successful rearrangement in hindered systems where one of the termini is disubstituted was very limited and not very encouraging.[25,26] However, the moderate energies of restricted ground-state geometries for **16**, approximating that required



SCHEME 6

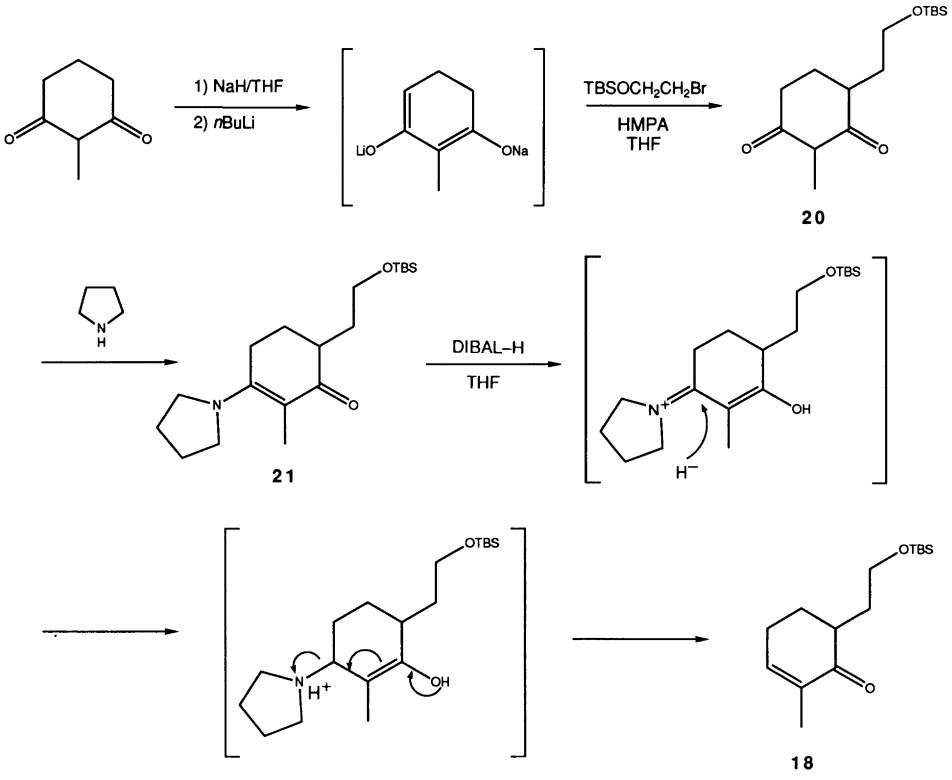
for rearrangement (derived from molecular modeling), and the lack of other reaction pathways for **16** leading to side reactions (such as the retro-ene process), as the result of the conformationally rigid allyl unit, encouraged us to pursue the implementation of this scheme.

IV. Synthesis of Keto-Olefin 9: Investigation of the Oxy-Cope Sequence

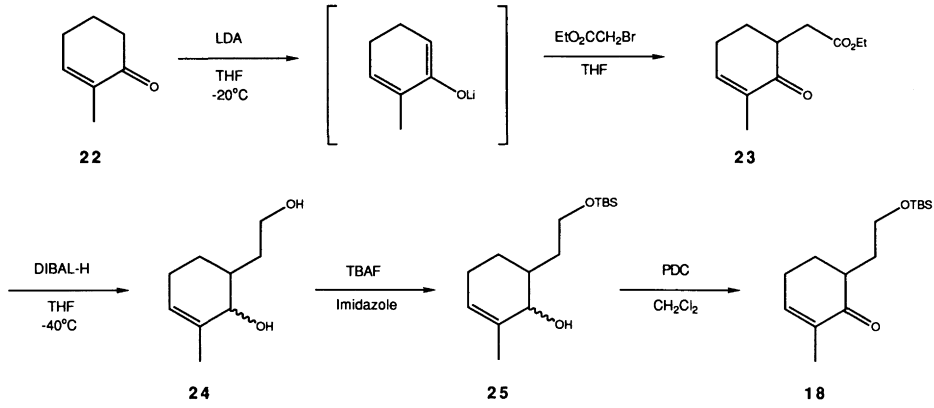
The sequence initially envisioned to prepare tricyclic ketone **19** (Scheme 6) required a Michael addition of the regiospecifically generated enolate derived from 2,3-dimethyl-6-(2-*t*-butyldimethylsilyloxyethyl) cyclohexanone with 3-penten-2-one. However, this approach was quickly abandoned when it was discovered that only a modest level of relative stereocontrol (2–3 : 1) was possible over the C_6 center (relative to C_3). It was clear that some independent (presumably stereoelectronically derived) control element would be required to achieve the desired relative stereochemistry at the pro C_6, C_9, and C_{10} centers, therefore, it was decided to construct β,γ-enone **19** by way of dienone **17**. We utilized the knowledge that cuprate addition would be expected to occur 1,6 and axial in the dienone **17** enforcing the required *trans* relationship between the 2-carbon bridge and the newly created secondary methyl group at C_6. This sequence also generates, regiospecifically, the enolate required for closure of the 2-carbon bridge. Literature precedent for related systems suggested that cyclization usually occurs exclusively *via* the kinetically formed cross-conjugated enolate under all reaction conditions,[27] so it was imperative in this instance to create the required linearly conjugated dienolate directly under kinetic control even though this enolate was expected to be the more thermodynamically stable.

With these considerations in mind, cyclohexenone **18** was prepared (Scheme 6). We developed several routes to the required intermediate enone **18**, however, the most direct routes *via* alkylation of the cross-conjugated enolate derived from **18** with a two carbon electrophile such as a t-butyldimethylsilyl (TBS) protected 2-halo ethanol or the mono TBS-protected ethanediol mono tosylate were unsuccessful. We attributed this failure to the known low electrophilicity of such alkylating agents, and the apparently low nucleophilicity of the cross-conjugated enolate derived from enone **18**. Consequently,

we developed the route depicted in Scheme 7, which employed the highly nucleophilic diketone dianion obtained by deprotonation of 2-methyl-1,3-cyclohexanedione. The dianion derived from this diketone reacted smoothly with TBS protected bromoethanol. Following quenching with pivalic anhydride (Pv_2O), hydrolysis afforded diketone **20** in high yield (79%). In order to effect regiospecific differentiation of the carbonyl groups, diketone **20** was treated with pyrrolidine which afforded exclusively the β amino enone **21** *via* attack at the less hindered carbonyl group (95%). Reduction of **21** with diisobutylaluminum hydride(DIBAL-H) then afforded the required enone **18** in acceptable yield (~50%) *via* reduction of the complexed enone at the iminium carbon and subsequent β elimination of pyrrolidine. While this route (Scheme 7) was suitable for preparation of gram quantities of **18**, upon scale-up, difficulties were encountered



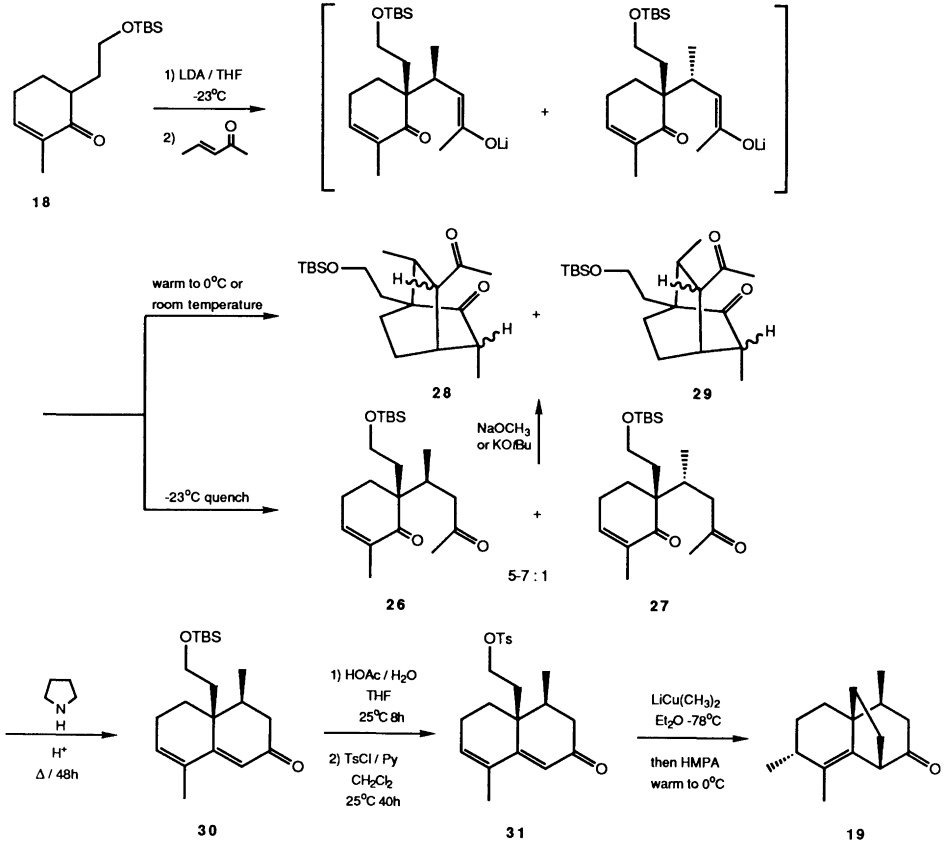
SCHEME 7



SCHEME 8

with the reduction step leading to diminished yields. Thus, we were led to develop the route shown in Scheme 8 for large scale preparation of enone **18**. Commercially available 2-methyl-2-cyclohexen-1-one (**22**) was alkylated with ethyl bromoacetate *via* the cross-conjugated enolate to afford keto ester **23** in high yield (91%). Simultaneous reduction of the two carbonyl groups afforded an inconsequential mixture of diastereomeric diols **24** (92%). After selective protection of the primary hydroxyl group, oxidation of the mixture of allylic alcohols **25** provided enone **18** (52%) in very good overall yield (45% from **22**). This route could be employed on a large scale and was used to secure 50–100 gram quantities of enone **18**, sufficient for our purposes.

Assembly of the bridged bicyclic β,γ-enone **19** (Scheme 9) was initiated by addition of the cross-conjugated enolate derived from enone **18** [lithium diisopropylamide (LDA)/THF/−23°C] to commercially available 3-penten-2-one with quenching at −23°C to afford a 5–7 : 1 mixture of enones **26** and **27** (73%) which were readily separated by chromatography and whose stereochemistry was tentatively assigned based on available literature precedent.[28] Temperature control and low temperature quenching were crucial to avoid the closure of the intermediate enolates to the bicyclic diketones **28** and **29**.[29] Closure of enedione **26** to dienone **30** was smoothly effected by treatment of chromatographically purified **26** with pyrrolidine in benzene in an acid-washed flask (trace acid catalysis was required) under a Dean–Stark water separator (78–98%). The use of very low acid concentra-

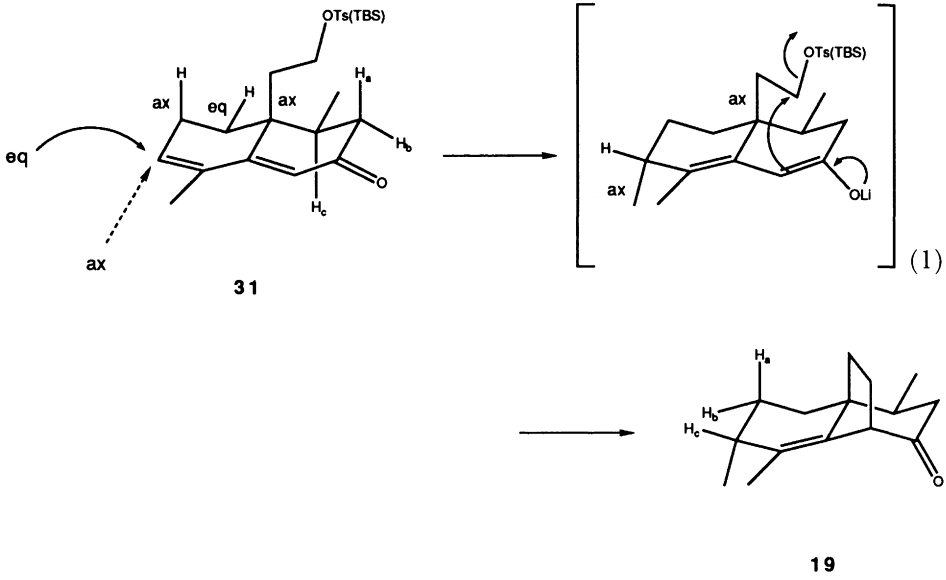


SCHEME 9

tions was required to minimize loss of the TBS protecting group (which accounts for the remainder of the isolated material). This material can, of course, be recovered by resilylation. As will be reinforced further below, pyrrolidine proved to be a fortuitous choice for cyclization in this case, since treatment of **26** with all other alkoxide and amide bases led primarily, if not exclusively, to closure to double Michael product(s) **28** and **29**. Analysis of **30** by ^{1}H NMR spectroscopy, including NOE experiments, confirmed the tentative stereochemical assignments for **26** and **27** [$J_{ac} = 14$ Hz, $J_{bc} = 5$ Hz (Eq. 1)].

Dienone tosylate **31**, the required substrate for the conjugate addition-alkylation sequence, was readily obtained *via* standard manipulations of silyl ether **30**. Deblocking of **30** in aqueous THF/HOAc for

8 hours at room temperature (87%) followed by tosylation of the resulting alcohol under standard conditions afforded tosylate **31** (85%) in excellent overall yield. With **31** in hand, we attempted the crucial conjugate addition–alkylation, a procedure which we had first described some years earlier.[30] Our expectations for the regiochemical and stereochemical outcome of this transformation were based upon the following considerations: (1) 1,6-addition should be favored over 1,4-addition owing to the substitution pattern in dienone **31** (β,β-disubstituted, δ-monosubstituted) as had been observed by Marshall;[31] (2) the incoming cuprate reagent should prefer stereoelectronically favored axial addition to the dienone system,[32] which in the conformationally restricted dienone **31** results in attack on the α face, since the geometry of the fused decalin requires that the angular substituent (CH_2CH_2OTs) occupy an axial environment with respect to ring B (Eq. 1); (3) the resulting linearly conjugated dienolate can

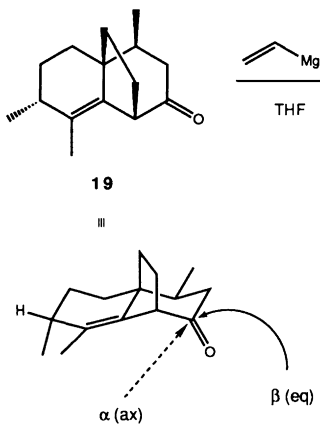


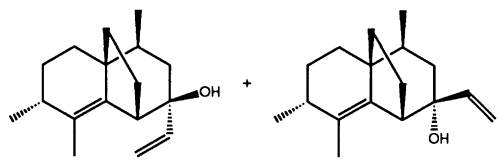
31 (1) **19**

readily undergo stereoelectronically favored axial alkylation (Eq. 1), with the α regiochemistry favored over γ on electronic grounds as well as by literature precedent.[27] Application of the standard protocol for such reactions, involving low temperature treatment of **31** with $LiCu(CH_3)_2$ in a relatively non-polar medium to accelerate conjugate

addition with respect to direct displacement of the tosylate followed by addition of excess HMPA (~17% by volume) and warming to 0°C, afforded the expected β,γ-enone **19** in excellent yield (93%). The regiochemical and stereochemical outcome was confirmed by ^{1}H NMR analysis of **19** which exhibited a vinyl methyl signal (s,3H) at δ 1.64 and coupling constants for the protons H_a, H_b and H_c whose magnitude (J_{ac} = 6 Hz, J_{bc} = 7 Hz) was consistent with H_c residing in a pseudoequatorial environment, thus placing the methyl group pseudoaxial as would result from axial addition of the cuprate reagent.

All that remained in order to access the vinyl carbinol **16** required for the oxy-Cope rearrangement was to effect stereoselective addition of a vinyl organometallic reagent to β,γ-enone **19** from the α face of the carbonyl group (Scheme 10). At this point we deviated from our normal practice, during this study, by failing to examine the conformational preferences of **19** as we had all other putative intermediates during the planning stages, since it appeared this transformation was quite straightforward. Enone **19** is rigid, and we based our expectation of attack on **19** from the desired α face of the carbonyl on the known preference of bicyclo [3.2.1] ketones to suffer attack *syn* to the 1-carbon bridge.[33,34] Thus, we treated **19** with vinylmagnesium bromide in THF at −23°C. We were surprised to find that a mixture of **16** and the epimeric vinyl carbinol **32** (whose stereochemistry was tentatively assigned based upon NOE measurements) was obtained in





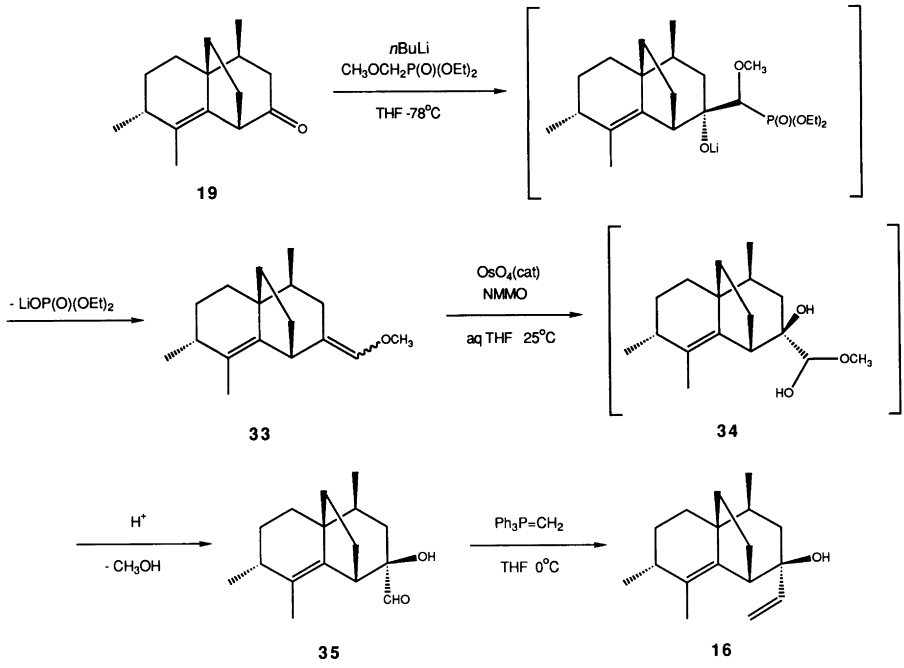
T(°C)	16	:	32	Total Yield (%)
25°C	5		4	84
0°C	1		2	82
-23°C	1		3	85
-78°C	1		6	90

SCHEME 10

which **32** predominated (3 : 1). Even more unexpectedly, the selectivity was increased upon going to −78°C (6 : 1), whereas the maximum selectivity (or lack thereof) was obtained at room temperature or higher (~1 : 1). A variety of other vinyl organometallics were examined (M = Li, Zn, Ce, Cu) with no significant improvement. We also examined the use of bulky aluminum-based Lewis acids to reverse the selectivity as had been demonstrated by Yamamoto, but we were unable to alter the selectivity in favor of **16**.[35] Use of sterically less-encumbered nucleophiles such as acetylide also did not improve the situation as might have been expected based upon observations by Stork.[36] Examination of the minimum energy conformation for **19** makes it clear, however, that we should have anticipated this problem. The most stable conformation of the carbonyl containing ring in **19** is the chair conformation reinforced by the rigidity imparted by the 2-carbon bridge, unlike the more flexible systems used as precedents.[34] Furthermore, it is well known that most organometallic reagents favor equatorial addition to cyclic ketones.[37] The alternative boat or boat-like conformation on the carbonyl containing ring ketone **19** which would permit equatorial attack on the α-face of the ring system is significantly destabilized by the eclipsing interaction between the 2-carbon bridge and the now axial-like C_{10} methyl group.

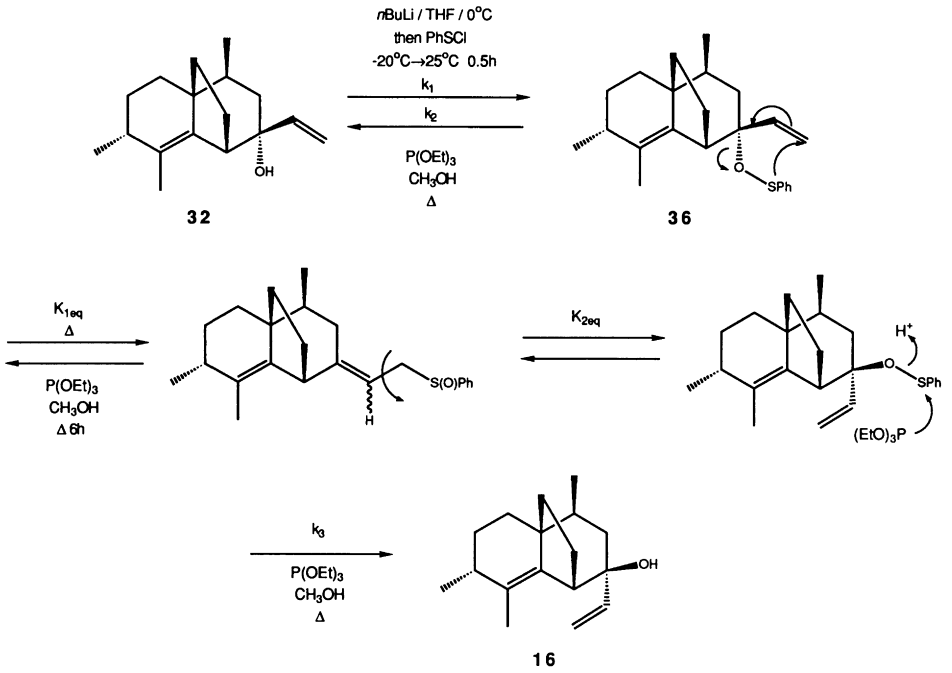
Once the nature of the difficulty was recognized, we devised two solutions to this problem. The first (Scheme 11) employs the well-recognized device of altering the order of addition of the substituents to the carbinol carbon to invert the stereochemical outcome.[38] This device relies on the observed inherent stereochemical preference for attack on an sp^2-hybridized carbon at C_2 from the β face in this ring system.

Treatment of ketone **19** with the lithium anion obtained by deprotonation of diphenyl methoxymethylphosphine oxide with LDA at −78°C to room temperature followed by exposure to NaH in THF afforded upon workup the methoxy olefin(s) **33** (47%). The olefin(s) **33** were directly oxidized with OsO_4 (cat)/NMO at room temperature in aqueous THF to afford primarily (5 : 1) the α hydroxy aldehyde **35** resulting from the expected β-face oxidation (85%). Finally, conversion of aldehyde **35** to **16** proceeded smoothly upon exposure of **35** to methylenetriphenylphosphorane at 0°C in THF (80%). Thus, we obtained **16** with complete stereoselectivity in three steps from **19** in an overall yield of 32% (unoptimized).



SCHEME 11

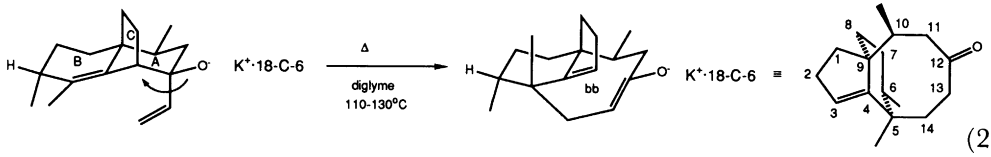
A somewhat shorter and more convenient solution for large scale work was also devised, although at the expense of chemical elegance (Scheme 12). Since the epimeric vinyl carbinols **16** and **32** were fortunately readily separable by chromatography, we considered a means to recycle the undesired carbinol epimer **32**. Such an interconversion could potentially be effected *via* an ionization, but it is possible that elimination and/or irreversible allylic isomerization would intervene. Alternatively, use of a mechanistically driven 1,3 interconversion of the heteroatom substituent precludes elimination, and with the proper choice of heteroatoms, the equilibrium can conceivably be driven in the desired direction. Isomerizations of this type had been previously effected by use of the sulfenate-sulfoxide [2,3]-sigmatropic rearrangement,[39] so we investigated this isomerization protocol in the case of carbinol **32**. Exposure of **32** to *n*-BuLi in THF at 0°C followed by PhSCl at −20 to 25°C smoothly afforded the expected sulfenate ester **36**, which, owing to its sensitivity, was not purified but directly



SCHEME 12

treated, after removal of the volatiles, with excess $P(OEt)_3$ in anhydrous CH_3OH at reflux for 6 hours. Workup afforded a mixture of **16** and **32** (1.2 : 1) in 81% total yield. In this way, the effective yield of **16** was increased to 74% after two cycles.

We then set out to investigate the crucial oxy-Cope rearrangement of carbinol **16** to **9** (Scheme 6). As was mentioned earlier, available precedent was limited and the observed yields very low.[25,26] Nevertheless, careful examination of the carbinol **16** revealed several features which led us to hope that the desired transformation would proceed smoothly (Eq. 2). First, only one degree of rotational freedom is present in **16**, the vinyl C–C single bond. Second, the geometry of the rigid AB ring system, which incorporates the allylic segment required



(2)

for the oxy-Cope, resembles a chair-like geometry. Thirdly, owing to the bridging ring C, the vinyl group is held rigidly axial, and no significant 1,3-nonbonded interactions appear to impede the required C–C bond rotation into the favorable chair-like transition state geometry. Thus, as is the case for enzymatic transformations, the reacting centers are partially preorganized in the starting carbinol **16** (with the exception of the vinyl group) and less additional energy is required to reach the transition state geometry thereby effectively lowering the activation energy for the conversion. Another way of considering this in energetic terms is that the preorganization which requires energy, effectively becomes incorporated in the ground state energy of carbinol **16** raising its energy with respect to the energy of the transition state which does not change significantly. Thus, the energy difference between the ground state of carbinol **16** and the transition state leading to **9** is decreased leading to a more facile reaction (Figure 1). Such a level of preorganization of the substrate was not present in the cases examined previously.[25,26]

One additional factor which we felt might play an important role in the successful outcome of the rearrangement is that the allylic fragment in **16** is imbedded within a rigid ring system. This structural feature precludes the intervention of an important reaction manifold involving retro-ene fragmentation (Eq. 3). Again, the cases examined

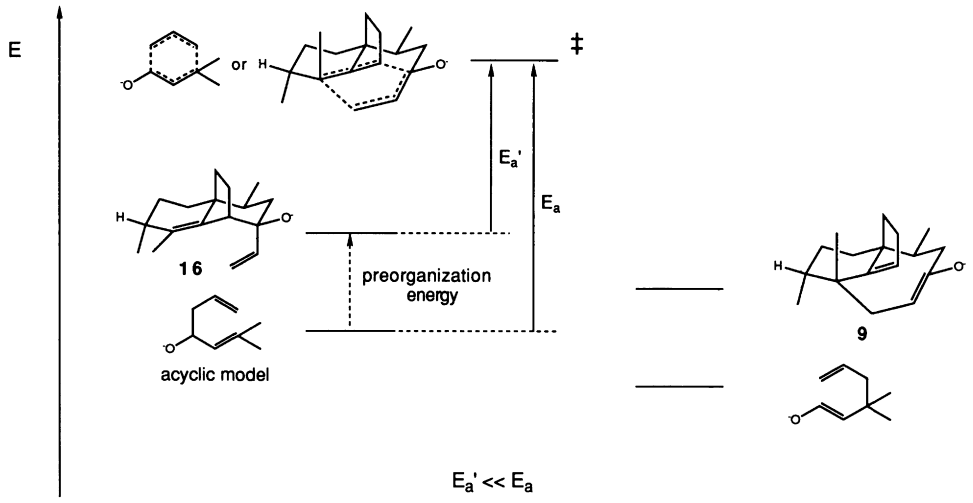
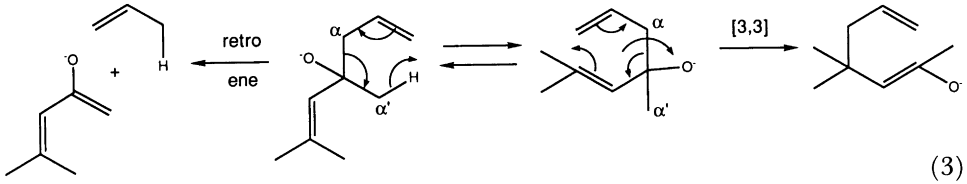


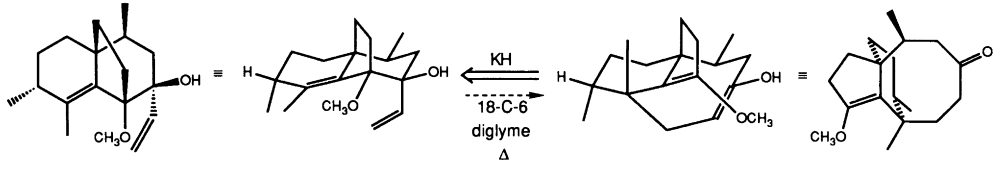
FIG. 1



(3)

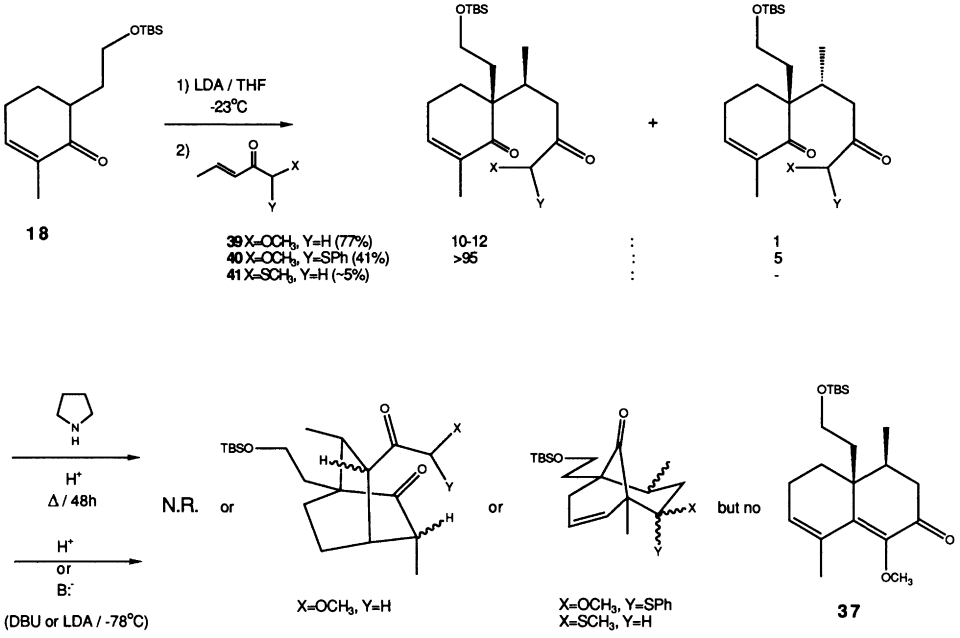
previously almost uniformly have the allylic unit as the acyclic component permitting access to the α' carbon and the transition state geometry required for the retro-ene fragmentation. Such a case is illustrated for a simple model substrate in Eq. 3. Very fortunately, this analysis was vindicated by experiment. Treatment of carbinol **16** with KH in diglyme at 25°C followed by addition of 1.5 equivalents of 18-Crown-6 and heating at 110–115°C for 1.5 hours led to a near quantitative conversion to the desired keto olefin **9** (99%) which required no further purification.[40] That this transformation proceeds *via* a concerted [3,3]-sigmatropic rearrangement mechanism is supported by the following experiments. First, thermolysis of the potassium alkoxide of **32** under identical conditions afforded **32** unchanged upon workup. Furthermore, at temperatures of up to 200°C, **32** failed to afford any **9** and was usually recovered intact. Second, thermolysis of the carbinols **16** and **32** or the related potassium alkoxides in the absence of 18-Crown-6, or the related trimethylsilyl ethers at temperatures up to 200°C failed to afford the rearrangement product **9**. These results are consistent with the expected acceleration of the oxy-Cope rearrangement provided by conversion of the carbinol to the free alkoxide as first observed by Evans,[40] and suggest strongly that the conversion of **16** to **9** proceeds *via* a concerted [3,3]-sigmatropic rearrangement mechanism.

With the key bicyclic keto olefin **9** in hand, we decided to investigate the incorporation of the required carbonyl oxidation state at C_3 prior to rearrangement by construction of the oxygenated carbinol **37** (similar to **16**) in hopes of effecting conversion to the bicyclic keto vinyl ether **38** (Eq. 4).



37 **38** (4)

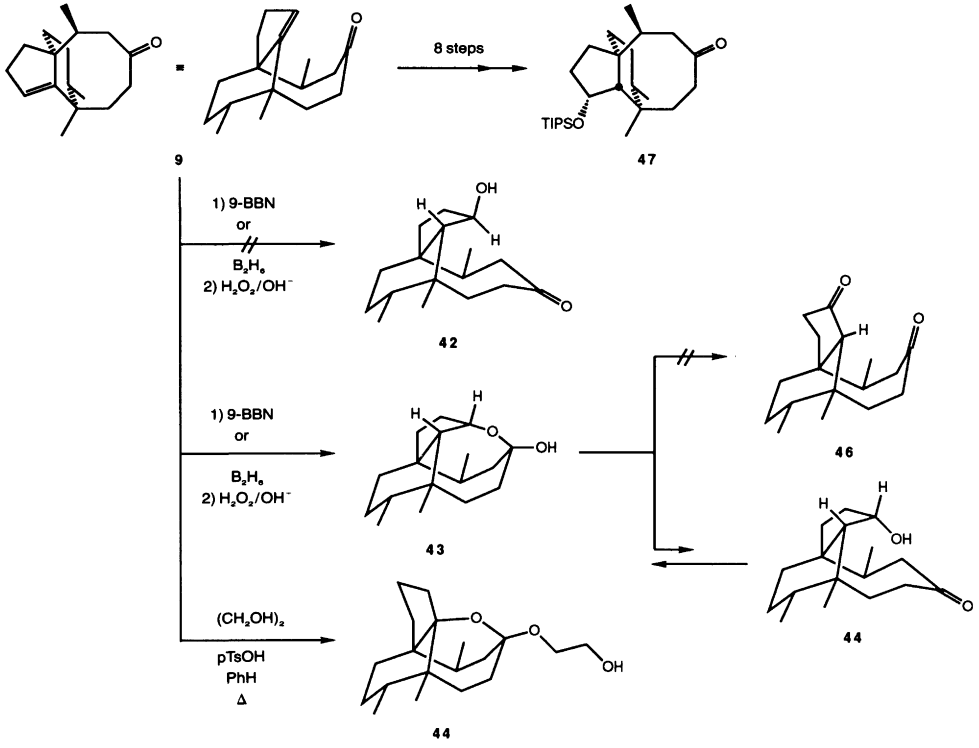
We were readily able to access a variety of functionalized Michael acceptors,[39–41] and to effect the required stereoselective 1,4-addition to the cross-conjugated enolate derived from **18** without complication from double Michael addition as shown in Scheme 13. The yields were widely variable but were not optimized since it was found that we were unable to effect the required ring closure to **37** under all conditions (both acidic and basic) investigated. In the case of the major adduct derived from **18** and **39**, only products of double Michael addition were obtained. When pyrrolidine (which was successful in the case of diketone **26**) was employed, no reaction was observed, possibly owing to the reluctance of these Michael adducts to form the requisite enamine intermediate. The more highly functionalized adducts derived from **18** and **40** or **41** afforded only products derived from enolization of the cyclohexenone unit, and condensation with the side-chain carbonyl group under strongly basic conditions. Therefore, we abandoned our attempts to procure **37** and concerned ourselves with further transformations of keto olefin **9**.



SCHEME 13

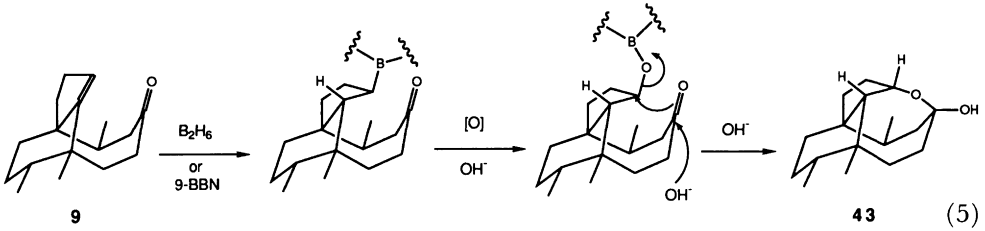
V. Functionalization of Ring A: Our First Encounter with Transannular Effects

Our first thought was to functionalize the double bond in **9** by means of a hydroboration/oxidation protocol with the intent to obtain ketol **42** (Scheme 14). At the time, we determined the most stable conformation of **9** by MM2. The results of this calculation indicated that the bb conformation was the more stable, although very close in energy to the bc conformer. Thus, it appeared that we might be able to effect stereoselective hydroboration by approach to the double bond from over the 6-membered ring. In practice, keto olefin **9** proved to react sluggishly with a variety of hydroboration reagents. However, exposure of **9** to excess 9-BBN or B_2H_6 in THF followed by the standard basic H_2O_2 workup afforded a product whose spectroscopic data indicated the desired hydroboration had occurred, since no



SCHEME 14

olefinic resonances were present in the ^1H NMR spectrum of this product. However, further evaluation of the spectral data showed them to be inconsistent with that expected for ketol **42**. After additional decoupling studies, we were able to assign the structure as ketol hemiketal **43**. Two mechanistic pathways could account for this result. In the first possibility, hydroboration could have unexpectedly occurred from the face of the olefin *syn* to the 8-membered ring with subsequent epimerization at C_4, where this ketol exists entirely in the cyclic hemiketal form **43** rather than open form **44**. This stereochemical outcome almost certainly requires reaction to occur with the bc conformer of **9** followed by an equilibration by a redox process conceivably involving a transannular hydride shift. Alternatively, hydroboration could have occurred from the expected olefin face *syn* to the 6-membered ring, but the intermediate borate ester obtained on oxidation suffered displacement with inversion by the hydrated carbonyl group during the oxidation leading to **43** (Eq. 5). We did not obtain experimental data which could distinguish between these or other possibilities.



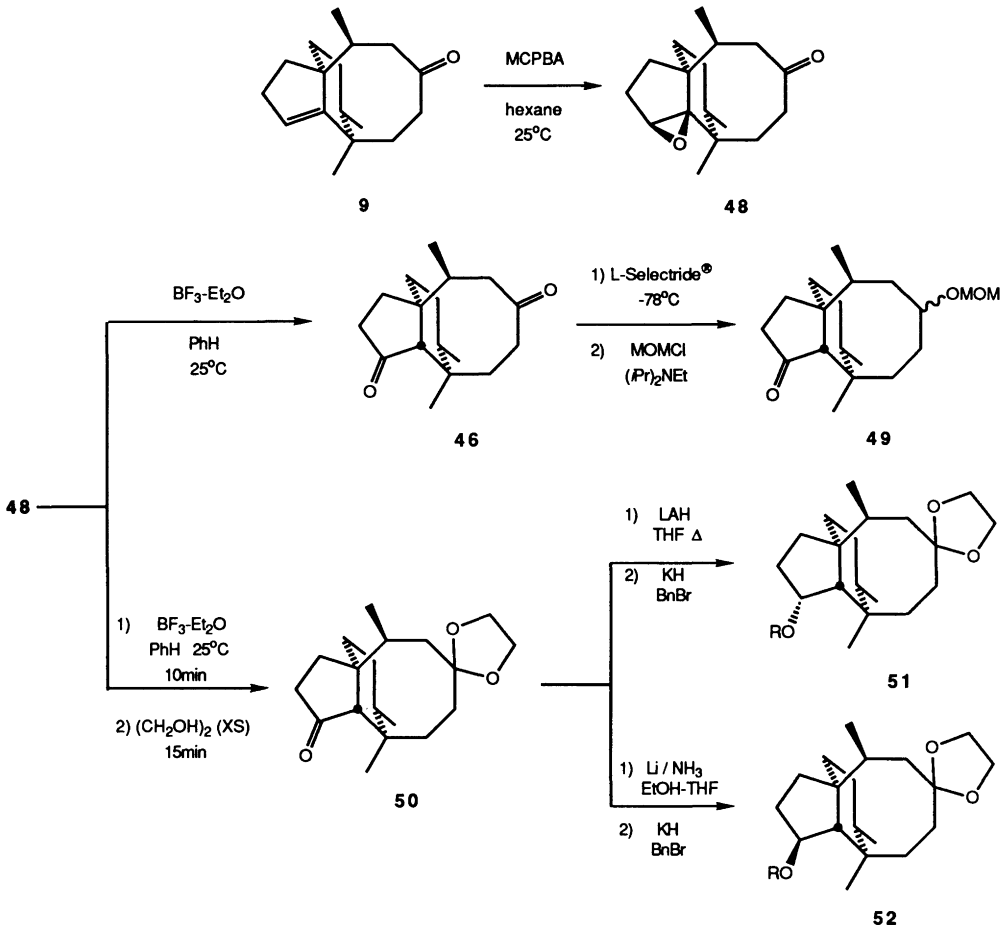
9 **43** (5)

Since participation of the 1,5 transannularly disposed carbonyl group appeared to be intimately involved mechanistically in this unusual apparent *trans* hydroboration, we attempted to block its participation by ketalization. Again, the accessibility of the bb conformer in **9** intervened to subvert the expected normal ketalization process. Treatment of **9** with excess ethylene glycol in benzene in the presence of acid afforded a very similar caged hemiketal **45** in which ethylene glycol served as the nucleophile to initiate a presumably acid-catalyzed ring closure of the intermediate hemiketal by attack on the protonated olefin at the 3° position. Unfortunately, hemiketal **43** did not prove to be a suitable intermediate, since ring opening and oxidation to diketone **46** could not be achieved in a synthetically useful yield.

In retrospect we should have been able to anticipate the magnitude of these transannular effects based on the ready accessibility and, indeed, the thermodynamic stability of the bb conformation of **9**. In no small part, this thermodynamic stability is probably also reflected in the facility of the oxy-Cope [3,3]-rearrangement which created the ring system. Unfortunately, while it is possible to assess the potential for interference by such effects qualitatively, we cannot currently predict their magnitude (relative rates kinetically) with any reasonable degree of accuracy, and therefore must rely on experiment.

We were ultimately able to achieve the required functionalization sequence to protected ketol **47** but only by means of a lengthy (8 step) and awkward sequence of functional group manipulations.[41] Therefore, in view of our inability to manipulate the double bond in **9** under acidic or basic conditions in the presence of nucleophiles, we reasoned that generation of the desired diketone **46** might be possible in the absence of nucleophiles which appeared to trigger the undesired chemistry by addition to the C_{12} carbonyl group. Furthermore, the facility with which the C_{12} carbonyl group reacted, and the reluctance of the C_3–C_4 double bond to undergo intermolecular addition suggested we might conceivably be able to differentiate the C_3 and C_{12} carbonyl groups in the projected diketone intermediate **46**. Epoxidation and Lewis acid-catalyzed rearrangement to the C_3 carbonyl group under aprotic, non-nucleophilic conditions appeared suitable.[42,43] However, the potential for 1,2 C–C bond migrations to the developing cationic center at C_4 during the rearrangement gave us considerable concern inasmuch as such a C–C bond migration would lead to a fundamental skeletal reorganization of the ring system which might not be readily detectable. Nevertheless, we chose to investigate this sequence.

Epoxidation of keto olefin **9** proceeded readily in the presence of m-chloroperbenzoic acid (MCPBA) in hexane and afforded a single crystalline epoxide, tentatively assigned as the β epoxide **48**, in 97% yield (Scheme 15).[44] Even more gratifyingly, exposure of **48** to BF_3–Et_2O at 25°C in benzene smoothly afforded the desired diketone **46**, with concomitant equilibration at C_4, in near quantitative yield.[43] To establish that no deep-seated skeletal reorganization had taken place, **46** was converted by L-Selectride® reduction at C_{12}(−78°C) and protection to a mixture of keto methoxymethyl (MOM) ethers **49**. This mixture was identical to the mixture of **49** obtained previously from **9** by a 4-step sequence involving (1) reduction, (2) protection,



SCHEME 15

(3) hydroboration/H_2O_2, and (4) PCC oxidation which was quite unlikely to have elicited such a rearrangement. The apparent ease with which we could differentiate the two carbonyl groups by reduction suggested a one pot conversion to ketal **50**. We were pleased to observe that brief treatment of **9** with BF_3–Et_2O at 25°C (10 minutes) followed by addition of excess ethylene glycol (15 minutes) afforded the crystalline C_{12} mono ketal **50** in 92% yield.

Since the carbonyl oxidation state at C_3 is ultimately required for pleuromutilin (**1**) we screened a number of possible carbonyl protecting groups. However the C_3 carbonyl group in **50** is apparently

remarkably hindered, and we were unable to induce oxime formation or conversion to a variety of other carbonyl derivatives. Consequently, we opted to effect reduction and protection. LAH reduction of **50** followed by benzylation afforded a single ketal benzyl ether **51** whose stereochemistry (α) was tentatively assigned based on steric approach considerations.[45] As expected, reduction of **50** with $Li/NH_3/EtOH$–THF afforded a separable 6 : 1 mixture of two alcohols, the minor of which was identical to the LAH derived product. Benzylation of the major isomer gave the β diastereomer, ketal ether **52** (68% overall from **50**). With ring A suitably functionalized, we were now in position to address functionalization of the 8-membered ring B.

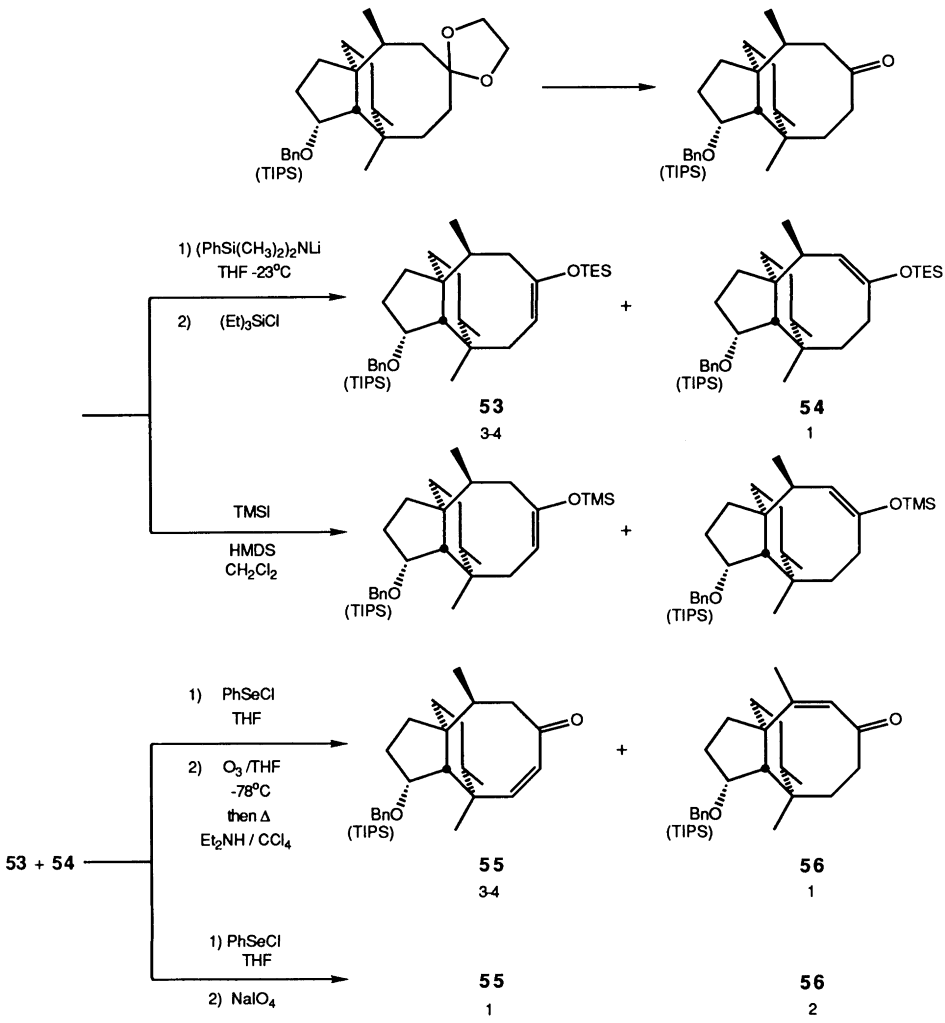
VI. Installation of the Stereogenic Centers Present on the 8-Membered Ring

A. Introduction of the C_{11} and C_{14} Oxygen Functions

Our studies in this phase of the synthesis began with the αC_3 *O*-benzyl ether **51** (Scheme 15) or the related *O*-triisopropylsilyl (TIPS) ether, although the majority of studies were done with the benzyl ether **51** since it was judged that the benzyl ether would prove to be a more suitable protecting group in the latter stages of the synthesis, and would permit structural correlation with intermediates in the Gibbons/Woodward synthesis.[15]

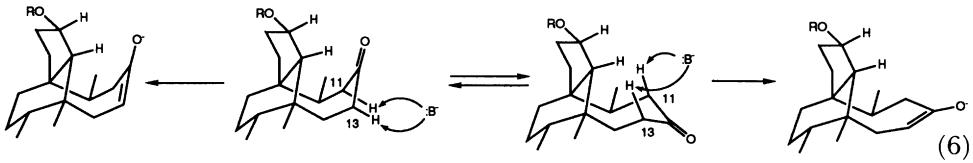
Our initial goal in this effort was the preparation of a $\Delta^{12,13}$ en-14-one **11** (Scheme 4), since we expected that addition of the requisite C_{12} vinyl unit would occur from the α face of **11** based upon conformational analysis of **11**. To acquire **11**, we wished to prepare a C_{12} methyl carbinol **12** and effect oxidative allylic rearrangement to **11**.[46] Therefore, this required preparation of a $\Delta^{13,14}$ en-12-one **13** and its related C_{11} α-hydroxylated derivative.

We first investigated the enolization tendencies of the C_{12} ketone derived from **51** (Scheme 16) with the objective of installation of the $\Delta^{13,14}$ unsaturation. Conformational analysis of the C_{12} ketone derived from **51** indicated that the bb conformation was preferred although the bc conformation should be accessible. Thus, enolization could in principle occur from either face of the ketone derived from **51** depending on the conformer which reacts, α on the bb conformer and β on the boat chair, since a proton exists in both conformations which



SCHEME 16

satisfies the stereoelectronic requirements of overlap with the carbonyl required for enolization (Eq. 6). Indeed, this analysis suggests that enolization may proceed via the bb conformer due to better steric accessibility. However, it also suggests that difficulties may be encountered in achieving regioselective enolization toward C_{13} as desired, since the C_{10} methyl group which is the distinguishing structural feature is on the opposite face and rather removed from the site



(6)

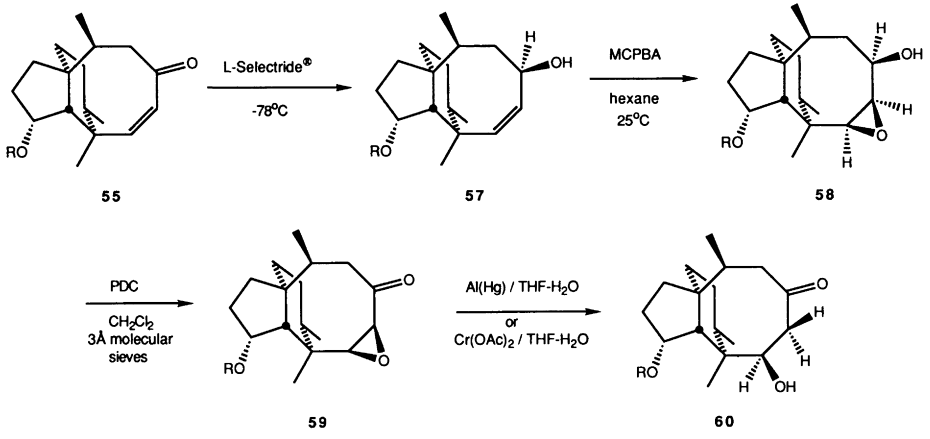
of attack by base. Thus, it was anticipated that a highly hindered base might be required. We also investigated the relative conformational energies of the two regioisomeric enolates (C_{11}–C_{12} and C_{12}–C_{13}) and found a rather small energy difference (~0.5 kcal/mol) in favor of the C_{11}–C_{12} enolate. Therefore, use of thermodynamic enolization techniques were not expected to be productive and these expectations were in part borne out by experiment.

Treatment with relatively strong relatively unhindered bases such as LDA gave at most 2 : 1 (C_{13} : C_{11}) selectivity. As the base became somewhat weaker and more hindered, the selectivity improved. For example, lithium hexamethyldisilazide (LiHMDS) gave ~3 : 1 (C_{13} : C_{11}), but the best selectivity we could achieve was ~3-4 : 1 with lithium bis(dimethylphenylsilazide) (Scheme 16).[47] In each case, the ratio was ascertained by trapping with triethylsilyl chloride (TESCl), due to instability of the TMS derivative, to afford the corresponding mixture of TES enol ethers **53** and **54**. This mixture was treated with phenylselenenyl chloride in THF to afford a corresponding mixture of regioisomeric selenenyl ketones which were directly oxidized with ozone followed by slow addition of the resulting crude selenoxide mixture to refluxing CCl_4 containing Et_2NH. Reich observed that these conditions were best for cyclooctanone itself and we confirmed that observation in this case.[48] The resulting mixture of enones **55** and **56** was obtained in 77% overall yield affording 58% of the desired enone **55** after separation by chromatography.

To check our prediction under conditions of thermodynamic enolization, we exposed the ketone derived from **51** to iodotrimethylsilane (TMSI) in hexamethyldisilazane, conditions known to provide the more stable enol ether isomer.[49] The resulting mixture of TMS enol ethers was directly carried through the selenenylation/oxidation sequence as before to afford a 1 : 2 mixture of enones **55** and **56**. Since, in previous experiments, this sequence did not result in equilibration of the silyl enol ethers, we believe that the ratio of **55** to **56** accurately reflects the ratio of enol ethers produced. Further confirmation of this

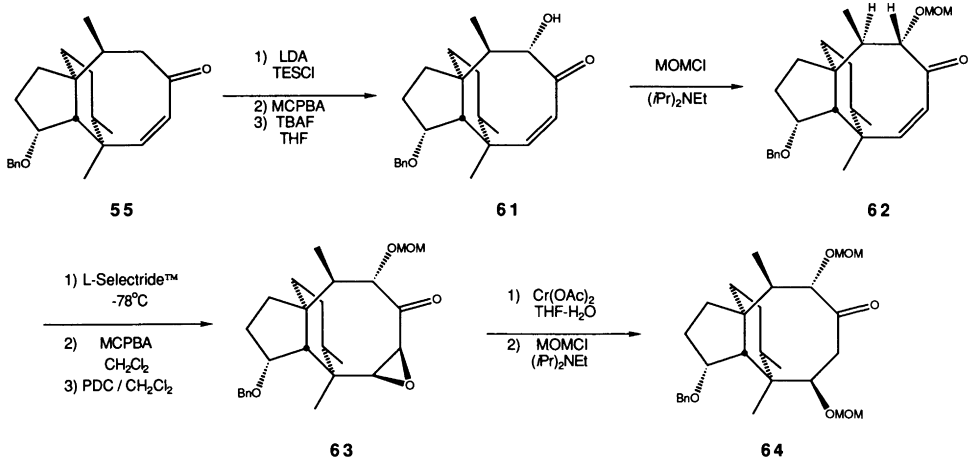
enolization tendency for **51** was obtained by direct selenenylation of the ketone derived from **51** followed by peracid oxidation/elimination to afford exclusively **56** (isolated material only) in modest yield (38%).

In spite of the relatively low yield conversion of **51** to **55**, we decided to press on to test the feasibility of stereoselective epoxidation of **55**. Conformational analysis of **55** suggested that poor conjugation exists between the C_{12} ketone and C_{13}–C_{14} double bond. Indeed, attempts to effect epoxidation of **55** under basic conditions (eg. Triton B/*t*-BuOOH) were fruitless, leading to complete recovery of **55**. Since the more stable conformation of **55** exposes only the β face of the C_{13}–C_{14} olefin to external reagents, we reasoned that electrophilic epoxidation might achieve our goal. Unfortunately **55** was inert to all manner of oxidizing agents of the peracid type most probably due to the inductive effects of the C_{12} carbonyl. Such inductive effects become dominant when conjugation is poor or absent. Therefore, a rather more awkward although generally straightforward sequence was employed (Scheme 17). The most stable conformation of **55**, based on MM2 calculations, suggested a major steric bias exists for approach of external reagents to C_{12} from the α face. Indeed, reduction of **55** at −78°C with L-Selectride® afforded a single allylic alcohol which we assigned as the expected βC_{12} alcohol **57**. The expected conformation of the 8-membered ring in **57** is only slightly different from that of **55**, so we anticipated epoxidation from the β face of **57**, possibly reinforced by hydrogen bonding from the C_{12} alcohol. We



SCHEME 17

were pleased to find that epoxidation of **57** proceeded smoothly upon exposure to MCPBA in CH_2Cl_2 to afford a single diasteromeric epoxide **58**, again assigned the β configuration based upon the preceding analysis. Oxidation of **58** with pyridinium dichromate (PDC) afforded a single epoxy ketone **59**. Reduction of **59** with either excess aluminum amalgam in aqueous THF or excess aqueous $Cr(OAC)_2$ in EtOH afforded a single product which was identified as the expected C_{14} β-hydroxy ketone **60**.[50–51] The stereochemistry of **60** was confirmed by analysis of the coupling pattern for the C_{14}–H which exhibited both a large ($J \cong 10$ Hz) and a small ($J \cong 1$ Hz) coupling constant which confirms that this hydrogen resides in an axial environment in a bc conformation, and therefore must be α. With this result in hand, we proceeded to explore the introduction of the C_{11} α hydroxy group via the cross-conjugated enolate derived from **55** (Scheme 18). Treatment of enone **55** with LDA at −78°C and trapping with TESCl followed by MCPBA oxidation of the resulting cross-conjugated dienol ether, and desilylation with tetra-*n*-butyl ammonium fluoride (TBAF) in THF afforded a single C_{11} α hydroxy enone **61** (39% overall).[52] Modeling of the intermediate dienol ether suggested that a flattened bc conformation was the energy minimum, and that there appeared to be a steric bias for approach of the epoxidizing agent from the α face away from the pseudoequatorial C_{10} methyl group. This stereochemical outcome could be confirmed by

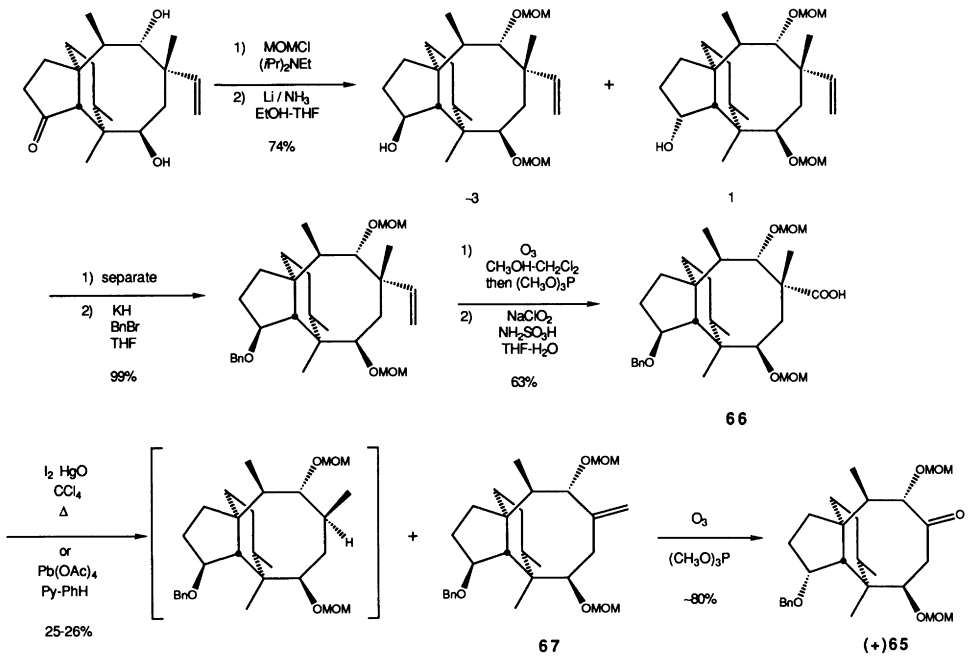


SCHEME 18

the observed small coupling constant for the C_{11} proton in **61** and the derived MOM ether **62** (~100% from **61**) which requires that the C_{11} proton reside in an equatorial-like environment in the bc conformation, and therefore the hydroxyl group resides in an axial-like position. Although we believe that this result accurately reflects the epoxidation stereoselectivity, we cannot rule out equilibration at C_{11} at some stage. We then applied an identical sequence to that described in Scheme 17 to afford MOM enone **62**. Reduction of **62** with L-Selectride®, in contrast to **55**, afforded a stereorandom mixture (1 : 1) of C_{12} allylic alcohols. The lack of selectivity in this reduction may at first glance seem surprising; however, when one considers the additional steric hindrance to reduction from the α face provided by a C_{11} MOM group, the lower observed selectivity appears consistent with the structural change imparted by the introduction of this group. Fortunately, the dominant control element in the subsequent epoxidation is the ring conformation since epoxidation of the C_{12} allylic alcohol mixture with MCPBA afforded a 1 : 1 mixture of only two epoxy alcohols. Oxidation of this mixture of epoxy alcohols afforded in 71% overall yield (from **62**) a single diastereomeric keto epoxide **63**; thus confirming that the stereochemistry of the diastereomers obtained from **62** differed only at C_{12}. Finally, $Cr(OAc)_2$ reduction of **63** in EtOH followed by exposure to MOMCl provided the bis(MOM) ether **64** in high yield. The stereochemistry of **64** was confirmed by examination of the coupling constants for the hydrogens at C_{11} and C_{14} which each exhibited one large (~10 Hz) coupling constant, consistent with the axial disposition of these protons in the bc 8-membered ring of **64**, and consistent with MM2 calculations on **64**. Bis(MOM) ketone **64** was also ultimately compared with a closely related intermediate in the Gibbons/Woodward synthesis and showed highly similar spectroscopic characteristics.[15]

Although the foregoing sequences (Schemes 16, 18) appear to provide a means to install the C_{11} and C_{14} stereogenic centers, the route is quite lengthy, and suffers from moderate yields and/or poor regio or stereoselectivity in the conversion of **51** to **55** and **55** to **61**. Therefore, we decided to explore alternative sequences for these interconversions.

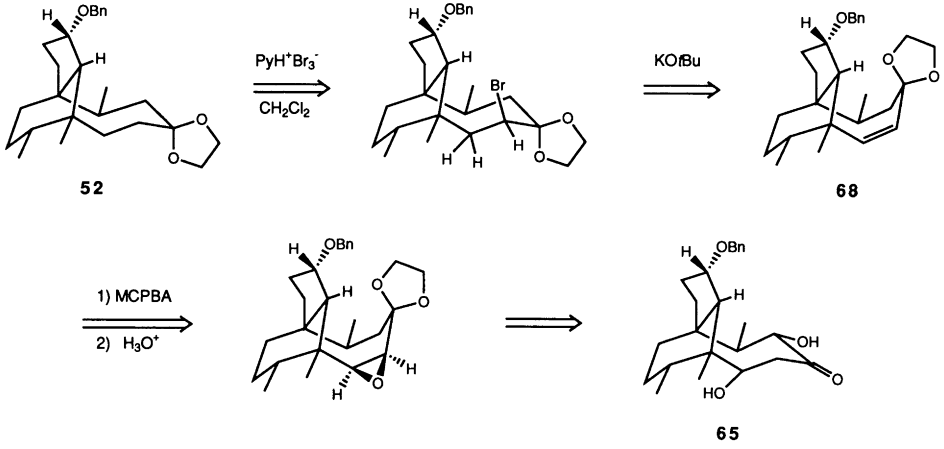
Since we felt it would be desirable to obtain a structural correlation with an advanced intermediate obtained by degradation, we selected ketone (+)**65**, whose preparation from (+)-mutilin was achieved as



SCHEME 19

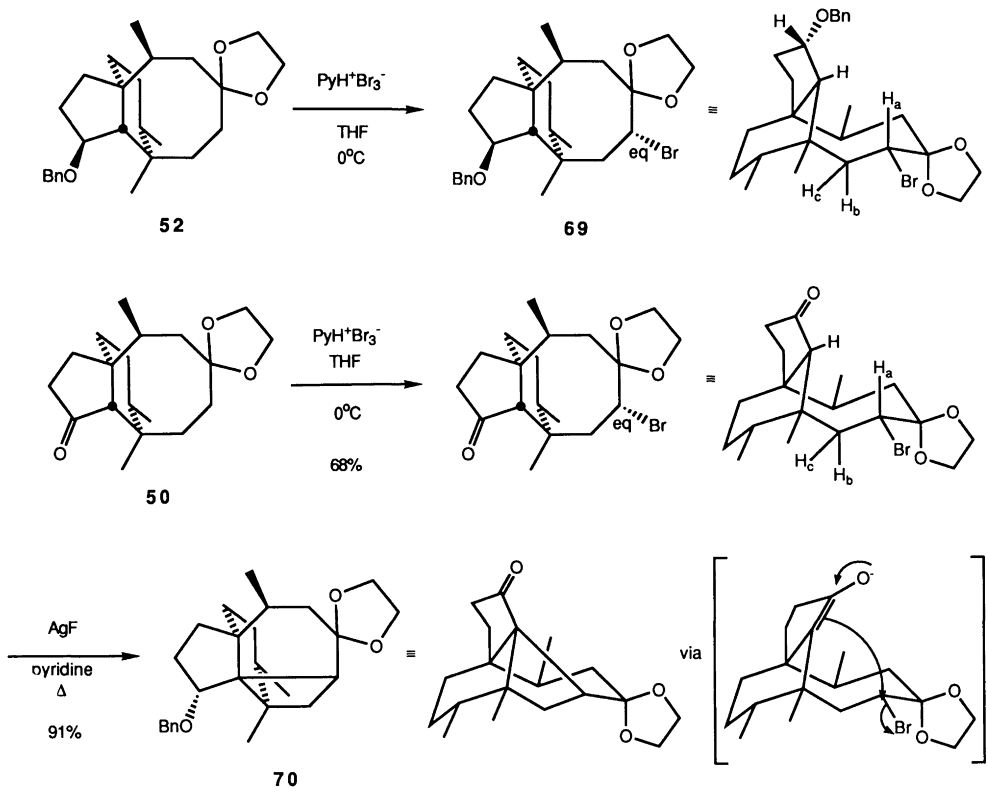
outlined in Scheme 19. The key step in this sequence is the oxidative decarboxylation of acid **66** to olefin **67** which could be accomplished by two modifications of the Hunsdiecker reaction, although in rather low yield.[53,54] Ketone (±)**65** had also by then appeared as an intermediate in the Gibbons synthesis, and thus its preparation would constitute a formal total synthesis of (±) pleuromutilin (**1**).[15]

The ketone (+)**65** possessed the β configuration at C_3; consequently we employed the C_3 β benzyl ether **52** (Scheme 15) in our synthetic sequence to (±)**65**. Our first objective was to devise an alternative to the selenenylation/oxidation sequence to provide the $\Delta^{13,14}$ en-12-one. Since **52** is a suitable substrate for a bromination under mild conditions, we explored the regioselective introduction of an α bromine atom into **52** with a view toward elimination to the olefinic ketal. If the bromination proceeded under kinetic control, we expected to obtain the β (axial) C_{13} bromide which would afford the *cis* C_{13}–C_{14} olefinic ketal **68** upon dehydrohalogenation (Scheme 20). Gratifyingly, exposure of **52** to pyridinium bromide perbromide



SCHEME 20

($PyH^+Br_3^-$) in THF at 0°C,[55] afforded a single regioisomeric bromoketal **69** in 92% yield, accompanied by a small amount of another substance of undefined structure which did not appear to be a regio or stereoisomer (Scheme 21). The stereochemistry of **69** was, however, established as the C_{13} α equatorial bromide by examination of the 3 proton spin system present at C_{13} and C_{14} (ABX). The predicted coupling constants [J_{ab} = 10.1 Hz, J_{ac} = 1.5 Hz(Macromodel (1988), Still)] and the observed coupling constants [J_{ab} = 9 Hz, J_{ac} = <1 Hz-(unresolved)] were in good agreement. Further support for this assignment was obtained upon treatment of **50** with $PyH^+Br_3^-$/THF followed by AgF in pyridine which afforded a keto cyclobutane ketal **70** (62% overall from **50**) by ring closure from C_4 to C_{13} which could only have occurred via S_N2 displacement of a C_{13} equatorial bromide (Scheme 21). One possible rationale for the production of a single regio and stereoisomer in this bromination is that bromination, which for ketals such as **52** is known to proceed *via* an enol derived by ring opening of the ketal,[55] occurs *via* the bb conformation of the enol as would be expected when sp^2 centers are present at C_{12} and C_{13}. The normal stereoelectronically preferred axial bromination is then observed; leading, upon reclosure of the ketal and ring conformational inversion to the bc conformer, to the observed equatorial configuration at C_{13} in bromide **69**. What is more difficult to understand is the high regiochemical preference for C_{13} over C_{11}, especially since thermodynamically controlled enolization appears to prefer C_{11} over C_{13}



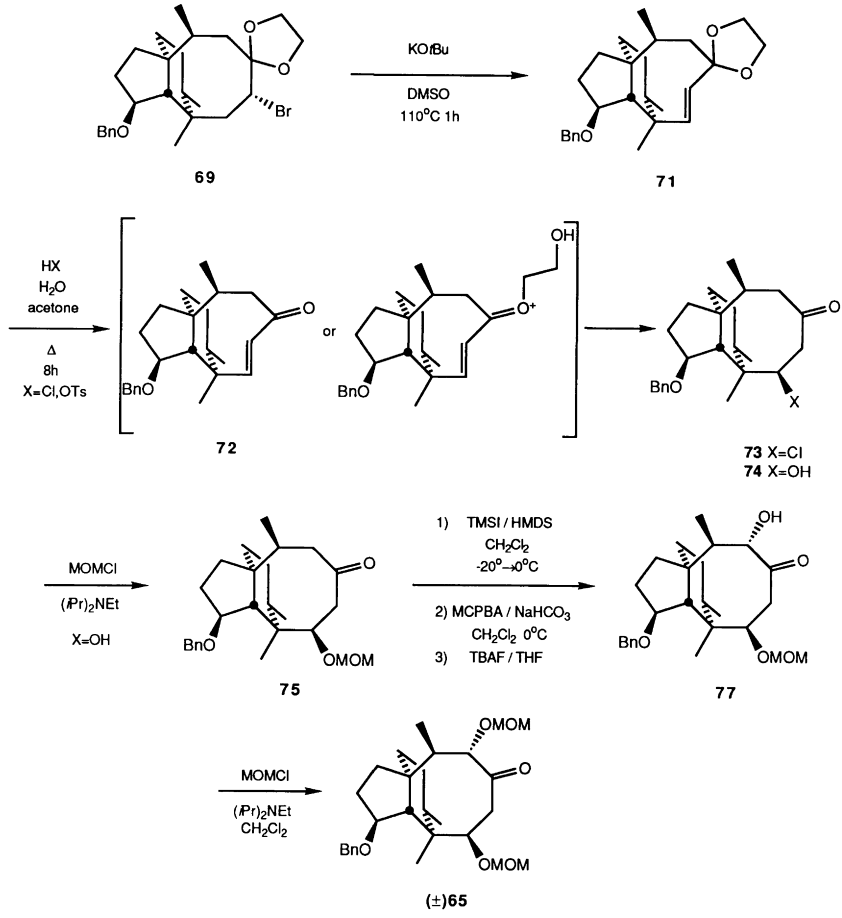
SCHEME 21

to a minor extent [2 : 1 (see Scheme 16)]. One possibility appears to be that reactions involving mild brominating agents such as $PyH^+Br_3^-$ are likely to have relatively more product-like transition state structures, thereby bringing the relatively bulky reagent into close proximity to the 8-membered ring and magnifying the steric interactions with the C_{10} methyl group which raises the transition state energy for the bromination of C_{11} enol regioisomer relative to the C_{13} enol regioisomer. Since the enols are in facile equilibrium *via* the ketal, the higher reactivity at C_{13} drives the equilibrium away from the thermodynamically preferred C_{11} enol. Of course, we cannot rule out other pathways including initial formation of a C_{13} β bromide followed by equilibration *via* the substituted $\Delta^{13,14}$ enol.

As a result of the formation of the C_{13} equatorial bromoketal **69**, we were obligated to revise our anticipated sequence to **65** (Scheme 20) since the formation of a *cis* $\Delta^{13,14}$ enone from **69** is precluded on

stereoelectronic grounds. However, the fact that the bc conformation appeared to be the primary conformation of the 8-membered ring in **69** suggested that the alternative *syn* elimination pathway might be realized. The C_{13} bromide and C_{14} β-proton (equatorial) have close to a 0° dihedral angle and a strictly 0° dihedral angle can be reached by a minor torsion about the C_{13}–C_{14} bond. Furthermore, since the resulting *trans* olefin is conformationally restricted, this group should suffer attack by external reagents from the desired β-face and the strain inherent in this group should enhance its reactivity.

Thus, we exposed bromo ketal **69** to KO*t*-Bu in DMSO at 110°C for 1 hour (Scheme 22). The rather vigorous conditions required

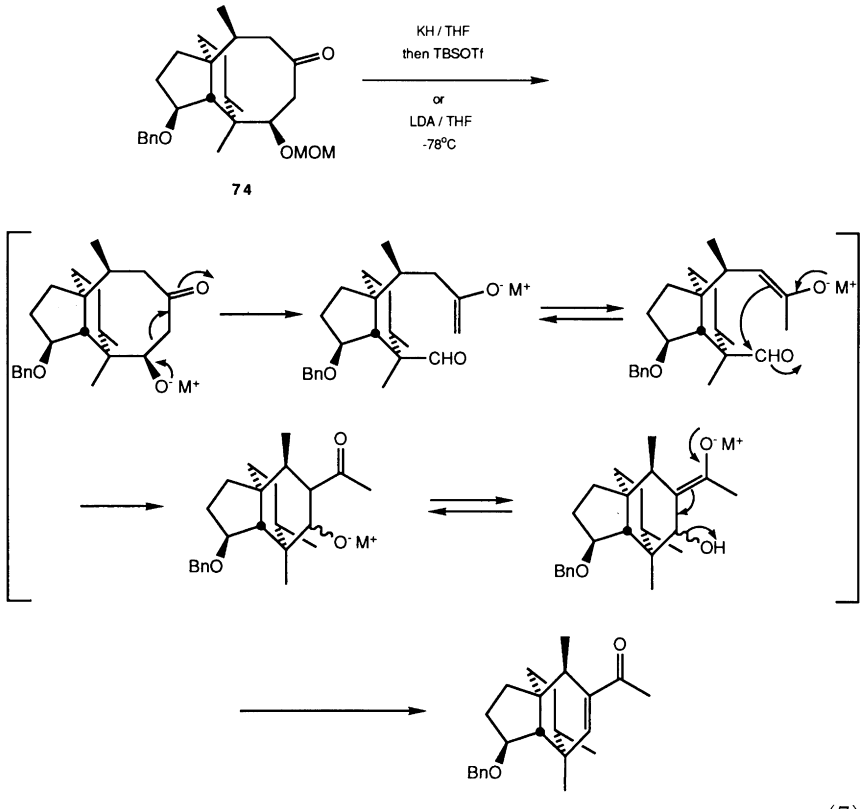


SCHEME 22

are evidence of the anticipated higher activation energy for *syn* elimination. Workup afforded the expected *trans* olefinic ketal **71** (J_{olefin} = 18 Hz) in ~73% yield, although in practice we did not purify bromoketal **69** but obtained **71** directly from **52** in 67% overall yield for 2 steps. Several options now existed for the introduction of the C_{14} β-hydroxyl group from ketal **71**. Although MM2 modeling of the *trans* enone **74** (derivable from **71**) indicated that overlap of the carbonyl and olefin was not ideal, it appeared a great deal better than the related *cis* enone. Therefore, we decided to attempt epoxidation of enone **72** after removal of the ketal since both electronically and sterically ketal **71** appeared to be a poor candidate for electrophilic epoxidation. We were surprised to find, however, that upon attempted hydrolysis of ketal **71** with aqueous HCl in acetone, a saturated ketone was produced, possibly indicating concomitant addition of a nucleophile to the strained *trans* enone **72**. Spectroscopic analysis of this compound led to assignment as the βC_{14} chloroketone **73**. This substance could arise by a number of possible pathways including 1,4 addition to a neutral or protonated enone derived from **72** or *via* S_N2' addition to the related vinylogous oxonium ion both from the expected peripheral β-face. However, such behavior is seemingly inconsistent with the intermediacy of the vinylogous oxonium ion formed by solvolysis of the ketal since it has been observed by Wiberg that upon solvolysis of optically active *trans* cyclooctenyl alcohols (as their *p*-nitrobenzoates) capture by nucleophiles occurs with near complete retention of configuration at the carbon which originally bore the leaving group.[21] However, Noyori has observed the thermal addition of alcohols to *trans* cyclooctenones such as **72**, so we are inclined to favor that pathway.[56] The facile formation of chloro ketone **73** led us to postulate that we might be able to substitute a non-nucleophilic acid for HCl and observe the addition of OH in an analogous manner. Consequently, we exposed the *trans* olefinic ketal **71** to *p*TsOH (1 equivalent) in hot aqueous acetone, and were pleased to obtain the corresponding βC_{14} hydroxy ketone **74** in 67% yield (Scheme 22). The stereochemistry of the C_{14} hydroxyl group was clearly assignable by NMR. The αC_{14} H appeared as a poorly resolved multiplet but the C_{13} methylene protons appear as a self coupled (J_{gem} = 15 Hz) doublet of doublets (J_{vic} = 12 Hz) and doublet (J_{vic} < 1 Hz) indicating one dihedral angle must approach 180° which is possible only if the αC_{14} proton occupies an axial environ-

ment in a bc or bb conformation. Some further evidence for the intermediacy of *trans* enone **72** in this process was obtained by exposure of the related *cis* enone **55** (Scheme 16) to the same conditions for **71**. *Cis* enone **55** proved inert and was recovered unchanged. The hydroxy ketone **74** was then smoothly converted to the protected ketone **75** upon treatment with MOMCl under standard conditions (98%). Application of the kinetic enolization/oxidation sequence developed earlier for the introduction of the αC_{11} hydroxyl group (**55–61**, Scheme 18) to ketone **75** followed by protection as the MOM ether did afford the desired αC_{11}, βC_{14} diol bis MOM ether (±)**65** (Scheme 22). However, regiocontrol over the enolization toward C_{11} was poor, leading to production of a mixture of (±)**65** and the regioisomeric αC_{13}, βC_{14} diol bis MOM derivative. Nevertheless, we were pleased that the spectroscopic data for (±)**65** proved identical in every respect to that reported by Gibbons,[15] therefore confirming the stereochemistry and completing a formal total synthesis of (±)-pleuromutilin (**1**). Since the final sequence to **65** was unsatisfactory, we explored ways of overcoming this lack of selectivity in enolization of **75**. One possibility appeared to be use of ketone **74** *via* formation of the dianion. Enolization of such β alkoxy ketones has been shown to prefer the α' site presumably due to electronic repulsions in the transition state.[57] Unfortunately, even at low temperatures, formation of the β alkoxide from **74** resulted in an exceedingly rapid conversion of **74** to 6-membered enone **76** (Eq. 7). Thus, it appeared that any base treatment of **74** would lead to such a ring contraction and therefore attention had to be focused on use of neutral or acidic conditions or use of C_{14} protected derivatives such as **75**. We initially explored enolization of **74** using t-butyldimethylsilyl triflate (TBSOTf) which smoothly afforded the expected bis(TBS) enol ether (unpurified), but which provided a ~1 : 1 mixture of C_{11} and C_{13} regioisomers on oxidation with MCPBA.

Our first hint of a solution came upon kinetic enolization of the C_{14} TMS ether derived from **74** with LDA at −78°C in the presence of excess TMSCl to prevent equilibration.[58] Upon oxidation with MCPBA, we obtained a 3 : 1 preference for C_{11} but in modest yield (44%). This result suggested: (1) that a relatively bulky C_{14} protecting group could direct reagent approach to C_{11} and (2) that some form of kinetic enolization conditions might be suitable if a sufficiently weak base were employed. Since we had previously observed some

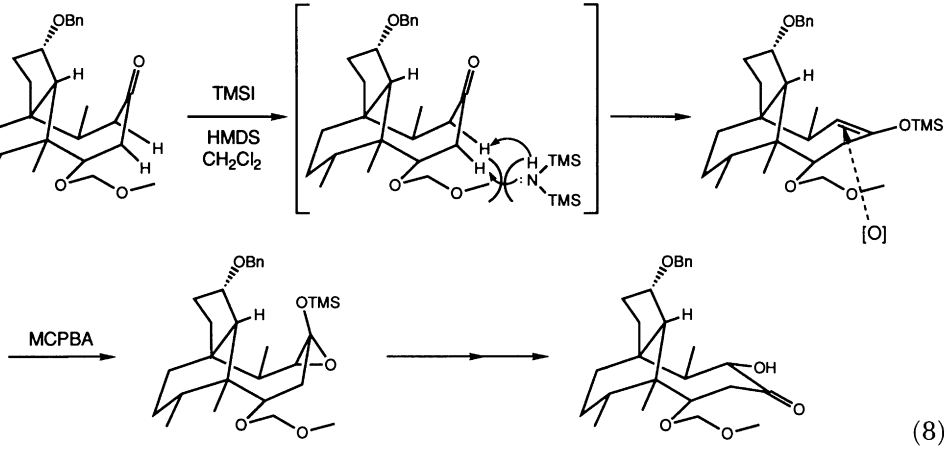


(7)

preference for enolization toward C_{11} when TMSI/HMDS was employed for enolization of ketone **51** (Scheme 16), we were encouraged to attempt such an enolization on C_{14} MOM protected ketone **75**. We were exceedingly pleased to find that treatment of **75** with TMSI/HMDS in CH_2Cl_2 followed by MCPBA oxidation and fluoride ion mediated desilylation provided a single regio and stereoisomeric C_{11} hydroxy ketone **77** in 63% overall yield from **75**. Protection of the C_{11} hydroxyl group in **77** proceeded under standard conditions in 90% yield to yield bis MOM ketone (±)**65** which was spectroscopically identical to (+)**65** obtained by degradation and to the Gibbons intermediate.[15]

With respect to the regio and stereochemical outcome in the transformation of **75** to **77**, MM2 calculations predicted a slight (2-3 : 1) preference for the C_{11} over the C_{13} ether. Clearly however, the regio-

selectivity was much higher than this calculation would predict. We ascribe this increased selectivity to the ability of the C_{14} MOM group to quite effectively shield the bottom face of the bb conformation in the intermediate silyl oxonium ion and to the weak and bulky base HMDS for which the transition state for proton transfer is relatively late along the reaction coordinate requiring the base to come into close proximity of C_{11} and C_{13} to effect proton transfer, thereby magnifying the steric effects of the MOM group. The C_5 quaternary center may also be responsible in part due to butressing of the C_{14} OMOM group and the fact that interactions with the C_5 methyl group orient the MOM chain toward C_{13} (Eq. 8). With respect to the C_{11} stereochemistry, the calculated minimum energy conformation of the $\Delta^{11,12}$ ether is a modified bb conformation since an sp^2 center exists at C_{12}. Thus, oxidation of this intermediate with MCPBA appears biased to occur from the more accessible α face (Eq. 8). We cannot, of course, rule out equilibration at C_{11} *via* the



(8)

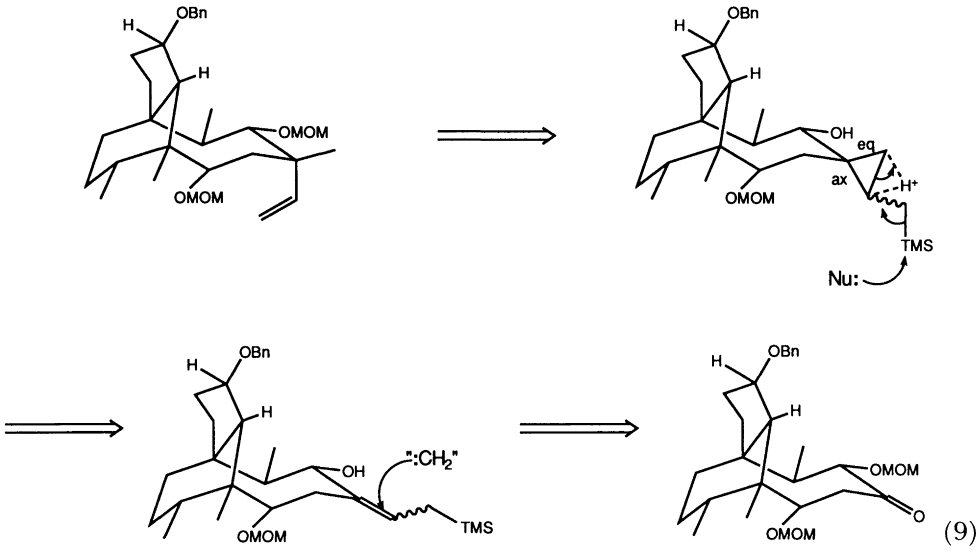
enol, but since such an equilibration could readily result in carbonyl transposition to C_{11} and since we observed no products of that type, we are inclined to exclude this possibility and presume that the stereochemistry at C_{11} arises *via* kinetic control in the epoxidation of the $\Delta^{11,12}$ silyl enol ether (Eq. 8). Having achieved the introduction of the C_{11} and C_{14} stereogenic centers, we were now prepared to address the completion of the total synthesis *via* creation of the C_{12} quaternary center.

B. Creation of the C_{12} Quaternary Carbon

Numerous difficulties attended the attempted construction of the C_{12} quaternary center beginning with bis MOM ketone (±)**65**.[14,15] Even the sequence eventually adopted by Gibbons suffers from relatively low yields and poor regio and stereoselectivity.[14,15] The available methodology which is effective for the creation of quaternary carbon centers is exceedingly limited,[59,60] and in the case of (±)**65** is further restricted by the fact that methods which result in the accumulation of significant negative charge at C_{12} in the intermediates or transition states leading to bond formation invariably result in ejection of the C_{11} oxygen function. Moreover, methods which result in the accumulation of positive charge at C_{12} also suffer difficulties possibly as the result of intervention of transannular hydride shifts from C_4 owing in part to the inductive destabilization of 2° or 3° C_{12} cations by the C_{11} and C_{14} oxygen functions. Consequently, we were encouraged to seek novel strategies and tactics to overcome these difficulties.

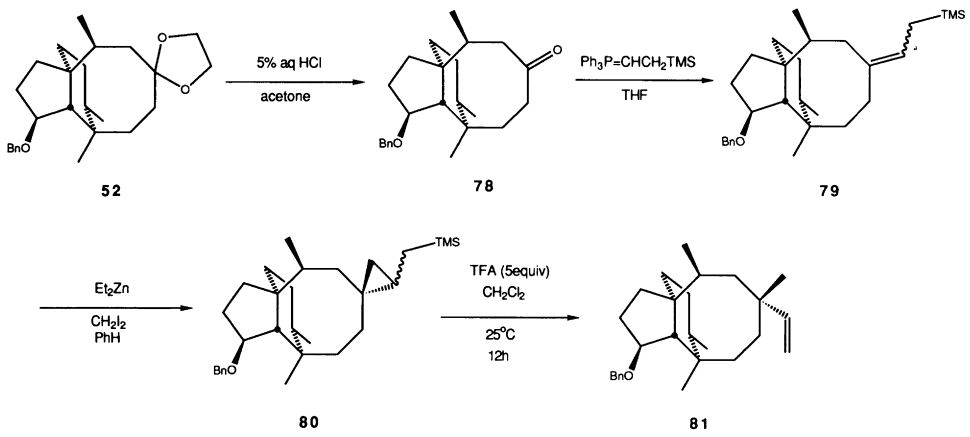
We were drawn to the possibility that regioselective cleavage of the less substituted bond in a spirocyclic cyclopropyl methyl silane might occur upon treatment with a relatively nucleophilic acid, by analogy to the reductive cleavage of cyclopropyl ketones or cyclopropyl methyl halides under acidic or basic reduction conditions.[61,62] Nucleophilic assistance in this process may play an important role along with stereoelectronic effects emanating from the 8-membered ring conformation adopted in the spirocyclic ring system and the resulting effects on the regioselectivity of cyclopropane ring protonation (Eq. 9). The requisite spirocyclic trimethylsilylmethyl cyclopropane should be available from (±)**65** *via* a two step process involving olefination to an allyl silane followed by sterically directed cyclopropanation (Eq. 9).[63] We felt use of a "carbenoid" to create the C_{12} quaternary carbon would avoid the aforementioned problems derived from accumulation of charge (+ or −) at C_{12} as the result of more or less concerted formation of both bonds of the cyclopropane. Also, the anticipated β face equatorial-like approach of the bulky carbenoid reagent to the C_{12} olefin in the postulated allyl silane intermediate (bc conformation) would appear to be favored on steric grounds thereby rendering the correct relative configuration at the C_{12} quaternary carbon center (Eq. 9).

We began our experimental work with a model study starting with



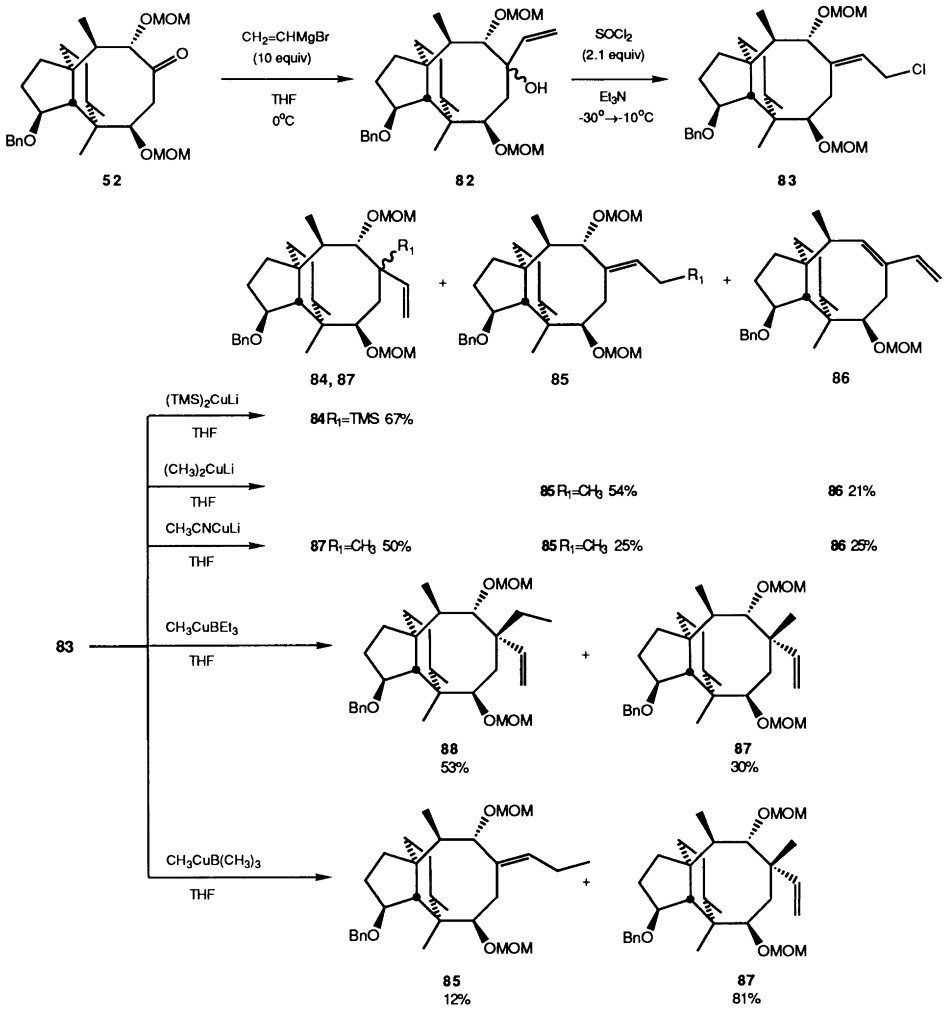
(9)

ketal benzyl ether **52** which afforded keto benzyl ether **78** upon hydrolysis in 90% yield (Scheme 23). Wittig reaction with 2-TMS ethylidene triphenylphosphorane delivered a ~4:1 mixture of geometric isomers of allyl silane **79** (34–63% unoptimized).[63] Cyclopropanation of **79** with a modified Simmons-Smith reagent afforded a ~4:1 mixture of stereoisomeric cyclopropanes **80** in 50–60% yield along with recovered allyl silanes **79**.[64] The stereoselectivity of cyclopropanation appeared very good and was assigned as the result of the expected β face attack of the carbenoid reagent, although the validity of this assignment was not established unequivocally. Rather, exposure of this mixture of cyclopropanes to trifluoroacetic acid (5 equivalents) in CH_2Cl_2 at 25°C for 12 hours afforded cleanly in >80% yield olefinic benzyl ether **81** possessing the desired vinyl methyl C_{12} quaternary center (stereochemistry based on **80**). Thus, we appeared to have in hand suitable methodology for completion of the sequence to (±)pleuromutilin (**1**). Unfortunately, the C_{12} center is remarkably hindered in (±)**65**, and use of forcing conditions are precluded by β elimination of the C_{14} oxygen substituent. All attempts to condense (±)**65** or its bis(TBS) ether analog with 2-TMS ethylidene triphenylphosphorane were fruitless leading to recovery of (±**65**) or elimination to the $\Delta^{13,14}$ en-12-one under forcing conditions.



SCHEME 23

Inasmuch as our efforts to obtain the fully substituted allyl silane were unsuccessful, we were forced to revise our strategy. We found it possible to add small nucleophiles, such as vinylmagnesium bromide, to (±)**65** in good yield. Thus, treatment of (±)**65** with excess vinyl magnesium bromide in THF at 0°C afforded a 7:1 mixture of stereoisomeric vinyl carbinols **82** in ~100% yield (Scheme 24). No effort was made to establish the stereochemistry of these carbinols, although addition of Grignard reagents from the equatorial direction to cyclic ketones is generally the rule, and the bc conformation of (±)**65** appears favored.[65] Smooth conversion of the mixture of alcohols **82** to a single related allylic chloride **83** occurred upon treatment of **82** with $SOCl_2$ (2.1 equivalents) and Et_3N at −30° to −10°C (64%). A first we attempted to procure the allyl silane from chloride **83** by treatment with $(TMS)_2CuLi$,[63] but to our surprise only γ alkylation affording a 1:1 mixture of the rather hindered quaternary allyl silanes **84** was observed (Scheme 24). On the other hand, treatment of **83** with $(CH_3)_2CuLi$ afforded a mixture of α alkylation product **85** (54%) and a reductive elimination product, diene **86**. Use of lithium cyanomethyl cuprate provided a mixture of 3 compounds, the desired γ alkylation product **87** (50%) as a single stereoisomer, α alkylation product **85** (25%) and elimination product **86** (25%). Some years earlier Suzuki and subsequently Yamamoto demonstrated that the regiochemistry of reactions with unsaturated substrates could be induced to favor γ substitution where complexes of CH_3Cu and BR_3



SCHEME 24

were employed.[66,67] Exposure of chloride **83** to CH_3CuBEt_3 provided a good yield (83%) of entirely γ alkylation products **88** and the desired **87** [1.8 : 1 (Et : CH_3)] in which both products had the desired C_{12} stereochemistry (Scheme 24). Consequently we turned to the use of $CH_3CuB(CH_3)_3$ which now afforded highly stereoselectively the desired C_{13} β methyl bis(MOM ether) **87** in 81% yield accompanied

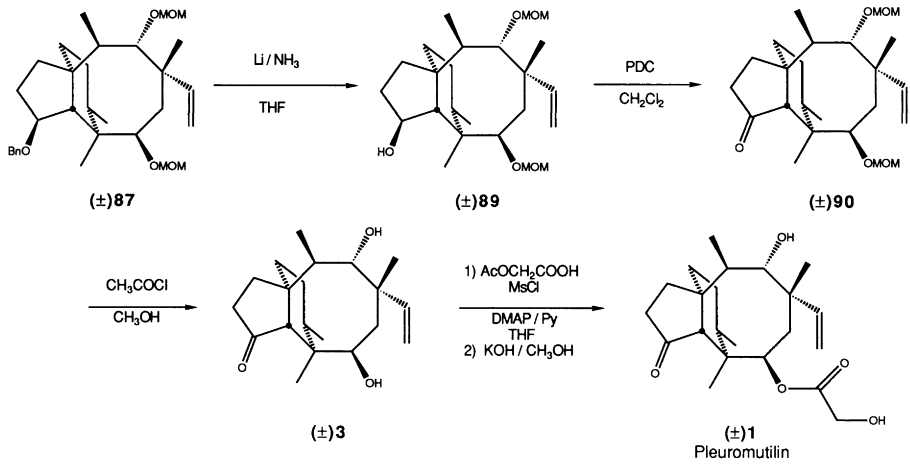
by a minor amount of α alkylation product **85** (12%). With the successful preparation of (±)**87**, assembly of the stereogenic centers on the 8-membered ring of (±)-pleuromutilin (**1**) was complete.

Regarding the stereoselectivity and regioselectivity exhibited by various organometallic reagents in their reaction with allylic chloride **83**, it does not appear possible to fully rationalize the outcome in all cases without additional information regarding the precise mechanism of these processes. However, it appears to us that the trialkyl boron–methyl copper complexes probably function as *ate* complexes. But one cannot rule out free radical reactions which also may account for the lack of loss of the C_{11} oxygen function since β elimination of β oxy radicals is slow.[66,68] The copper serves to activate the leaving group (halide). It is our best assessment that complexation with $Cu(I)^+$ initiates partial ionization of the allylic chloride. However, prior to loss of regiochemical integrity, donation of CH_3 from the ion-paired tetramethyl borate ion occurs to the least hindered β face of the incipient allylic cation. The donor ability of the various alkyl groups on boron seems directly related to the B–R bond strength ($B–C_2H_5 < B–CH_3$) accounting for the lower apparent reactivity of the $CH_3CuB(CH_3)_3$ reagent. Again, modeling of allylic chloride **83** had shown a distinct steric bias for approach from the β face of the more stable bc conformation of **83**.

VII. Conversion of the Fully Functionalized Intermediate to (±)-Pleuromutilin (1)

We examined several schemes which were designed to shorten the final sequence of steps to (±)-pleuromutilin (**1**) from (±)**87**. However, these studies met with failure due to the inability to selectively oxidize the C_3 alcohol in the presence of the C_{14} alcohol. As a result, we were forced to include additional protecting group manipulations. The strategy which was ultimately adopted was a variant of that of Gibbons.[14,15]

Treatment of benzyl ether (±)**87** with $Li/NH_3(l)$ provided the desired C_3 alcohol **89** (90%) as shown in Scheme 25. Oxidation of **89** with pyridinium chlorochromate (PCC) in CH_2Cl_2 smoothly gave the bis(MOM) ketone **90** (94%) which was cleaved with acetyl chloride in CH_3OH to produce crystalline (±)-mutilin (**3**) (mp 186.5–188°C) in 87% yield whose spectroscopic characteristics and thin-layer chro-



SCHEME 25

matographic behavior were identical to natural (+)-mutilin in every respect except optical rotation.

Finally, conversion of (±)**3** to (±)-pleuromutilin (**1**) was carried out by conversion to the bis acetoxy acetates *via* the mixed anhydride (repeated treatment due to low conversion) followed by selective hydrolysis in KOH/CH_3OH to afford (±)-pleuromutilin (**1**) (m.p. = 167–169.5°C) which was identical to natural (+)-pleuromutilin by all spectroscopic criteria except optical rotation as well as by TLC analysis in several solvent systems. This latter two step conversion was achieved in ~40% overall yield from (±)**3** on small scale with synthetic material and was not optimized.[14,15]

VIII. Summary

Our efforts to secure an efficient synthetic approach to (±)-pleuromutilin (**1**) were now complete. A 25-step sequence affords (±)-pleuromutilin (**1**) in an overall very highly stereoselective manner utilizing a novel strategy and several novel tactics including (1) a tandem 1,6 conjugate addition/alkylation, (2) a highly efficient oxy-Cope [3,3] sigmatropic rearrangement to construct the 8-membered ring of the pleuromutilin skeleton, and (3) the use of molecular mechanics based molecular modeling to assist the selection of a

strategy and to evaluate the tactics to be employed in the very direct functionalization sequence (7 steps) which installs three of the seven stereogenic centers present on the 8-membered ring.

Perhaps it is this latter accomplishment which was in the end most meaningful and rewarding, because it clearly articulates the potential for use of a new and potent tool in the planning and evaluation of synthetic sequences to highly functionalized, stereochemically complex molecules such as (±)-pleuromutilin (**1**). It is our hope that this effort will serve as an impetus to others to attempt to employ molecular mechanics based modeling in their own research to further define its potential to assist strategic planning and the selection of tactics for the synthesis of complex organic molecules.

Acknowledgments

The author wishes to thank Drs. Thomas R. Alessi and Dane M. Springer whose outstanding experimental skills, dedication and hard work, and many crucial observations and ideas contributed most significantly to the successful outcome of the studies described in this chapter. The author also wishes to thank the National Institute for General Medical Sciences (NIGMS) of the National Institutes of Health for a research grant (GM-29290) in support of the research described herein.

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24. As the number of substituents about the periphery of the 8-membered ring increases, and those substituents have the relative stereochemical arrangement which places them in equatorial or the equivalent environment in the boat-chair conformation, the 1,3-nonbonded interactions which occur in the boat-boat conformation increasingly favor the boat-chair conformation even when a carbonyl group is present at C_{12}.
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Chapter 3

TOTAL SYNTHESIS OF (±)-GINKGOLIDE B

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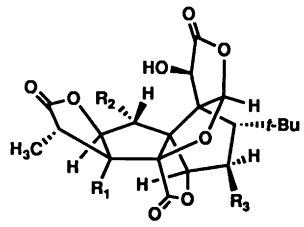
In 1987, Christmas arrived early for us; September found us celebrating the successful synthesis of one of the most complex organic natural products. This gave rise to a communication by Professor E. J. Corey outlining the first (and to this point only) total synthesis of racemic ginkgolide B (**2**).[1] It was our privilege to participate in this exciting endeavor; the educational experience was uniquely satisfying. We describe herein the scientific venture conceived and directed by Professor Corey which was amply filled with creativity, intuition, fortuitous developments and humbling events.[2]

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I. Introduction

Ginkgo biloba, or the *Ginkgo* tree, as it is commonly called, was unknown outside the Orient before the 18th century, but has now become common in North America and Europe.[3] The Ginkgo tree has always been part of the traditional Chinese and Indian pharmacopoeia. Specifically, the Chinese pharmacopoeia recommends inhalation of a decoction of *Ginkgo* leaves for the treatment of asthma. In India, the extract of the *Ginkgo* tree is one of the constituents of Soma, a mystical liquid thought to increase life span. In Japan it is called the Itcho tree and its fruit, known as the *Ginkgo* nut, is used in cooking. The crude extract of *Ginkgo* leaves is widely used in Europe under the trade names Tanakan® (France) and Tebonin® (Germany), to treat peripheral and cerebral ischemic disease.[4]

Not surprisingly, in light of its medicinal importance the Ginkgo tree has prompted systematic investigations, with the help of modern pharmacology, to correlate the claimed beneficial effects of its extracts to the active principles. In 1932 Professor Furukawa isolated four terpenoids from the bitter principles of *Ginkgo*, but their structure remained unsolved until the late 1960's. In 1967, Professor Nakanishi's group reported their structures and called them ginkgolide A (**1**), ginkgolide B (**2**), ginkgolide C (**3**) and ginkgolide M (**4**).[5] Their structures were further confirmed by independent X-ray crystallographic studies.[6]



	R_1	R_2	R_3
1	OH	H	H
2	OH	OH	H
3	OH	OH	OH
4	H	OH	OH

Asthma and bronchial hyperactivity against which *Ginkgo* extracts have been claimed to show beneficial effects are complex illnesses

involving many mediators. One of the important mediators has been suggested to be a phospholipid, platelet-activating factor (PAF). The research efforts of Dr. P. Braquet *et al.* have shown that the ginkgolides very selectively antagonize platelet aggregation induced by PAF. Ginkgolide B (**2**) is a very potent inhibitor of the binding of [^{3}H]-PAF to lung receptors, with a K_i value of 8.2 ± 4.3 nM.[4a]

Ginkgolides are among the most complex organic natural products. Their unique cage structure is built up very comfortably from six five-membered rings, half of which are present as lactone rings. Incorporated in this stable backbone are spiro[4.4]nonane and tetrahydrofuran rings. The cage structure is distinctively substituted with two or more hydroxyl groups and the uncommon *tert*-butyl group. The various ginkgolide compounds differ by the number and the position of hydroxyl groups. Biosynthetic pathways to ginkgolides have been elucidated by Professor Nakanishi; the first step is the cyclization of geranylgeranyl pyrophosphate to labdadienyl pyrophosphate, which subsequently undergoes extensive rearrangement and oxygenation to the ginkgolide backbone.[7] In the following account we outline the thought processes that led to the synthesis of the most potent PAF antagonist, ginkgolide B (**2**) in an investigation spanning three years.[8]

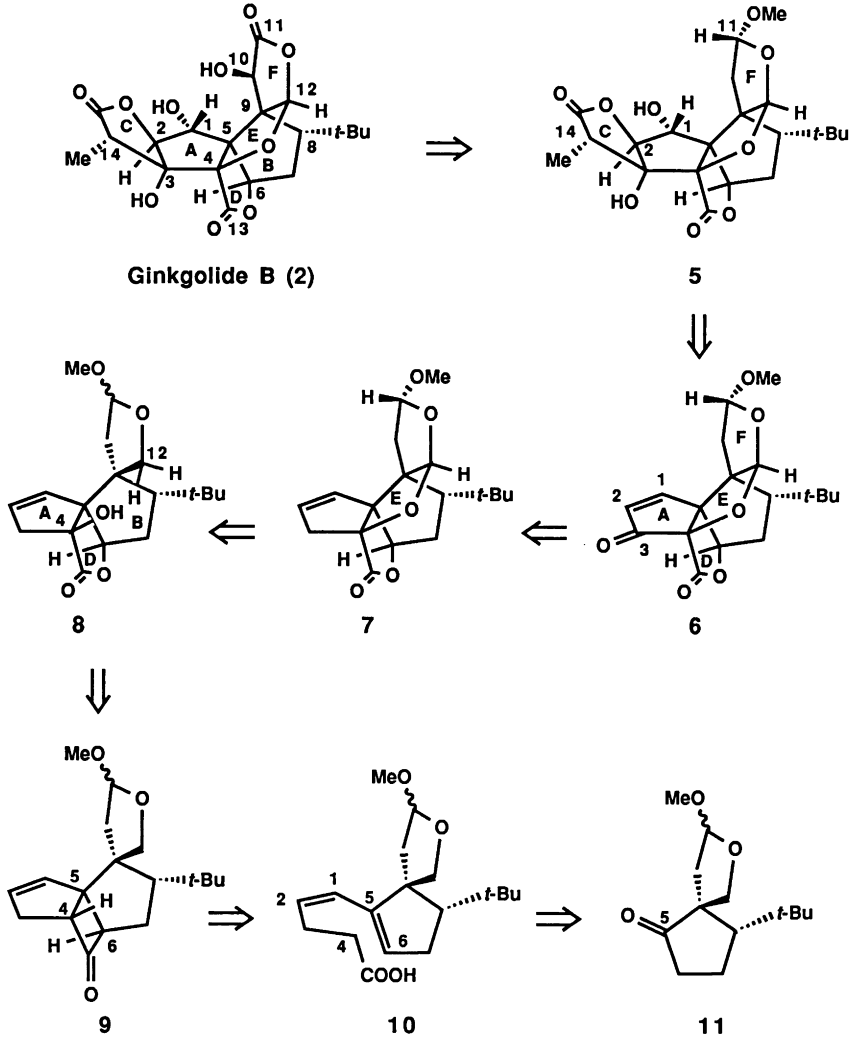
II. The Retrosynthetic Analysis

Three important features played a critical role in the retrosynthetic process of disconnecting the six rings of ginkgolide B (**2**); the hierarchical theme employed here has been widely chronicled in many syntheses of Professor Corey.[9] Essentially, rings A and B form the core of the molecule while four *oxacyclic* rings (C, D, E and F) spiral off of this central framework. Thus, disconnection of the spiro A-B system is most critical for the success of any retrosynthetic planning. Second, ring C is solely attached to ring A and thus is essentially an appendage. Finally, the most reactive functional groups are present in ring F. The approach dictated by these observations is that rings C and F are the first to be simplified. Oxacyclic rings D and E are disassembled next, leaving the spiro A-B ring system as our initial target.

Besides topographical complexity, there exists in the ginkgolides a high level of stereochemical complexity. It is most important that the

rings be disassembled in an order that allows the stereospecific creation of chiral centers. Specifically, the issue of creation of two adjacent quaternary centers, at the ring A–F is problematic. One particular retrosynthetic path which seems to address these daunting questions is outlined in Scheme 1.

In light of the foregoing discussion, the reactive functionality (α-hydroxy lactone) present in ring F can conceivably be generated from



SCHEME 1

the less reactive precursor **5** by multistep functional group transformations. For retrosynthetic planning, the stereochemistry of the C_{11} anomeric methoxy group is of no importance, and for convenience, its stereochemistry as shown in structures **5** to **7** is based on our synthetic studies. Next, ring C was disassembled; it is potentially available from intermediate **6** by a combination of aldol, epoxidation, and hydroxylactonization transformations. It was also felt that 1,2 addition of a *Z*-propionate enolate to **6** would establish the stereochemistry of the C_{14} methyl group.[10] However, an important question was whether the addition of the enolate anion to **6** would occur from the concave face formed by rings A, E and F (β-face) or that formed by rings A and D (α-face); this issue could not be resolved to our satisfaction in the absence of experimentation. Assuming the addition to take place from the β-face, epoxidation would occur from the α-face; intramolecular hydroxylactonization would then complete the ring C formation. This sequence of reactions would also serve to introduce the stereochemistry at the C_1 hydroxyl group present in ginkgolide B (**2**). Despite the ambiguity regarding facial selectivity of the addition reaction, it was difficult not to investigate this three step process which could introduce four chiral centers. Suffice it to say that the addition from the β-face indeed proved feasible in the end. The enone **6** can be envisioned to come from **7** by allylic oxidation. We regarded **7** as one of several critical intermediates because its transformation to ginkgolide B (**2**) would require only one C–C bond forming reaction: the remaining reactions are all relatively simple functional group transformations. Predictably enough, it was the transformation of **7** to **5** that proved most difficult.

Continuing our retrosynthetic analysis, ring E of **7** was viewed as arising from **8** *via* photolysis of the corresponding hypoiodite. This reaction has been studied in great detail and has found wide application in the steroid field, particularly in functionalization of the C_{10} angular methyl group; the success of such a reaction is dependent on the proximity of the oxygen radical and adjacent hydrogen.[11] We felt that abstraction of the C_{12} hydrogen would be favored because of its close proximity to the C_4 hydroxy group in **8**. Examination of models further supported this approach.

The carbocyclic rings A and B in **8** were the most challenging for disassembly. Our plan called for utilization of the intramolecular [2 + 2] ketene-olefin cycloaddition reaction. Rings A and B in intermediate **8** are held together by a γ-lactone (ring D) which can be

constructed *via* a Baeyer–Villiger reaction of cyclobutanone intermediate **9**. At this stage of planning, the regiochemical outcome of the Baeyer–Villiger reaction was uncertain. We believed, however, that the desired outcome could be managed through appropriate choice of reagents and reaction conditions.

Because of the remarkable regio and stereoselectivity of intramolecular [2 + 2] ketene-olefin cycloaddition reactions and their utility in the formation of spirocyclic ring systems, it was felt that the ketene generated from **10** would give **9**. Essential to the success of this reaction is the presence of the *Z* stereochemistry of the C_1–C_2 double bond in **10**. Specifically, it would provide for the eventual construction of ring C, and in addition serve to bring the ketene generated from **10** into close proximity with the C_5–C_6 double bond for the subsequent cycloaddition reaction.

This intramolecular [2 + 2] ketene-olefin cycloaddition reaction was really the pivotal step in our synthetic planning. In addition to constructing the core backbone of the two spiro carbocyclic rings, A and B, of ginkgolide B (**2**), it establishes the crucial stereochemistry at C_4, C_5 and C_6. The practicality of this cycloaddition reaction had been demonstrated by recently completed syntheses of retigeranic acid and *β-trans*-bergamotene.[12] Furthermore, these results testified to an asynchronous cycloaddition process.[13,14] We were confident about the regiochemical outcome of the reaction! The stereochemical course, however, could not be predicted with certainty. We instinctively felt that, in an asynchronous process, the product obtained from the reaction would be governed by conformational preferences established by the *tert*-butyl group, leading to the formation of **9**.

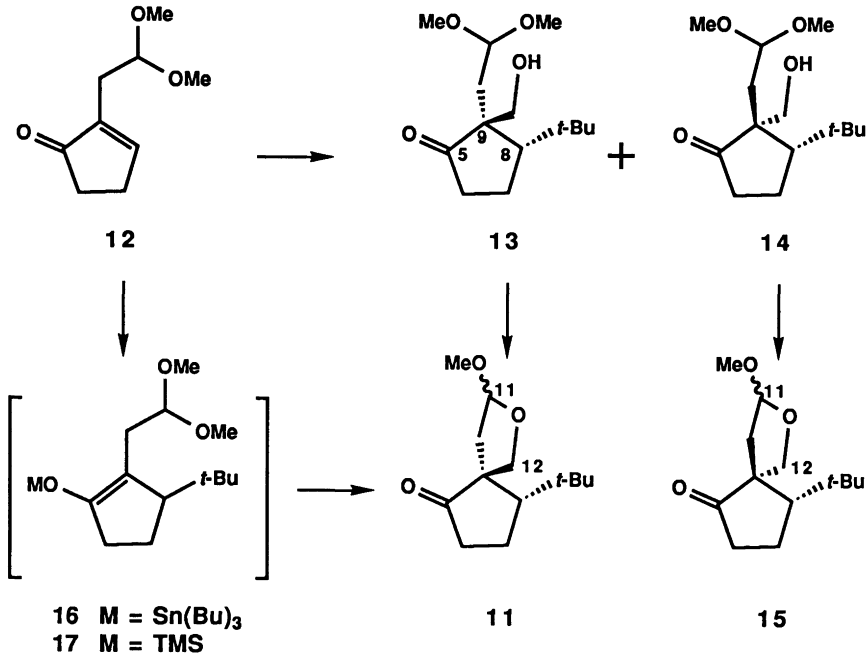
Thus, at the outset we regarded the feasibility of this route as hinging upon the favorable outcome of the intramolecular [2 + 2] ketene-olefin cycloaddition reaction [**10**→**9**]. Our first challenge was to prepare spiro-ketone **11**, the expected precursor to **10**.

III. Synthesis of Spirocyclic Intermediate 11

A key step envisioned in the synthesis of **11** was tandem vicinal difunctionalization of α,β-unsaturated carbonyl substrate **12**.[15] This was accomplished *via* 1,4-addition of a reactive higher order *tert*-butyl cuprate to enone **12**, followed by trapping of the resulting enolate with

formaldehyde at low temperature; it was expected that the *tert*-butyl group would direct the incoming electrophile to afford **13** (Scheme 2). The desirable feature of this strategy is that it permits both stereospecific generation of the C_9 quaternary center and incorporation of the *tert*-butyl group at C_8 in one step. Significantly, it also leaves a carbonyl group at the C_5 position for further elaboration to intermediate **10**.

The enone **12**, available in multigram quantity by a one-pot procedure, provided a convenient starting point for our synthesis. The reaction of 1-morpholinocyclopentene with dimethoxyacetaldehyde in toluene followed by acid-catalyzed dehydration/isomerization afforded **12** in 75% yield.[16] With a generous supply of enone **12** in hand, we next investigated the tandem vicinal difunctionalization reaction. Unfortunately, addition of the higher order organocuprate $(tert\text{-}Bu)_2Cu(CN)Li_2$ in either [−78°C→ −25°C] followed by quenching of the enolate with formaldehyde afforded a 1 : 1 ratio of **13 : 14**.[17]



SCHEME 2

There were now two issues confronting us: 1) how to determine their relative stereochemistry and 2) how to improve the product ratio.

To establish the stereochemistry, **13** and **14** were separated and converted individually to the corresponding spirocyclic ketones **11** and **15** as a mixture of diastereomers (2 : 1 ratio). We felt that an NOE experiment on **11** and **15** would reliably assign the stereochemistry. The isomer that on irradiation of the *tert*-butyl group showed 25% enhancement of the C_{12} proton signal was assigned structure **15**, whereas the other isomer, which showed no such NOE, was assigned structure **11**. The formation of a mixture at C_{11} was inconsequential, as this chiral center is nullified later on.

A complex combination of factors has been suggested to play a role in this tandem vicinal difunctionalization reaction.[15] However, a chance observation offered an explanation for the lack of stereoselectivity in this transformation. An accidental warming of the reaction during enolate trapping afforded *only undesired* **14**. The exclusive formation of **14** in this experiment was viewed as a consequence of equilibration of the kinetically formed β-oxido ketone intermediate *via* retroaldol and realdol to give the thermodynamically more stable **14**; warming of the reaction should facilitate such a process. Accordingly, we considered trapping the tin enolate **16** with formaldehyde at $-78° \rightarrow 10°C$, in the hope that the kinetically formed β-oxido ketone intermediate would be less prone to equilibration; this indeed improved the ratio of products **13 : 14** to 2 : 1. However, all attempts to further improve the product ratio were unsuccessful.

We were not very satisfied with the outcome of the reaction. At this point many options were available to us for improving the product ratio, but we were unwilling to further refine this transformation at this stage. Logistically, the thrust of the project at this point was to quickly confirm the feasibility of the intramolecular [2 + 2] ketene-olefin cycloaddition reaction [**10**→**9**] and the photolysis reaction [**8**→**7**]. Accordingly, it seemed practical to move forward, and address the development of a stereospecific route to **11** after establishing the feasibility of the key reactions. Thus, a sufficient supply of a mixture of **13 : 14** (~2 : 1) was produced from which pure **13** could be isolated in 55% yield by preparative HPLC (Prep 500). Treatment of **13** with p-toluenesulfonic acid in benzene (25°C, 2 hours) afforded the spirocyclic ketone **11** in 87% yield after chromatographic purification, as a 2 : 1 mixture of two diastereomers. In this manner **11** could be synthesized from **12** in 48% yield.

At a later time, the elusive stereospecific elaboration of **12** to **11** was eventually accomplished by trapping the enolate with trimethylsilyl chloride to furnish **17**, which was isolated by extractive work-up. Subsequent treatment of **17** with 1,3,5-trioxane and titanium(IV) chloride in methylene chloride at −78°C afforded *only* **11** as a 2:1 mixture of C_{11} anomeric methyl acetals.[18] The observed stereospecificity at C_9 can be attributed to trapping of the kinetic product by titanium chloride induced closure to the hemiacetal **11**. This shorter stereospecific route furnished **11** from **12** in 65% yield.

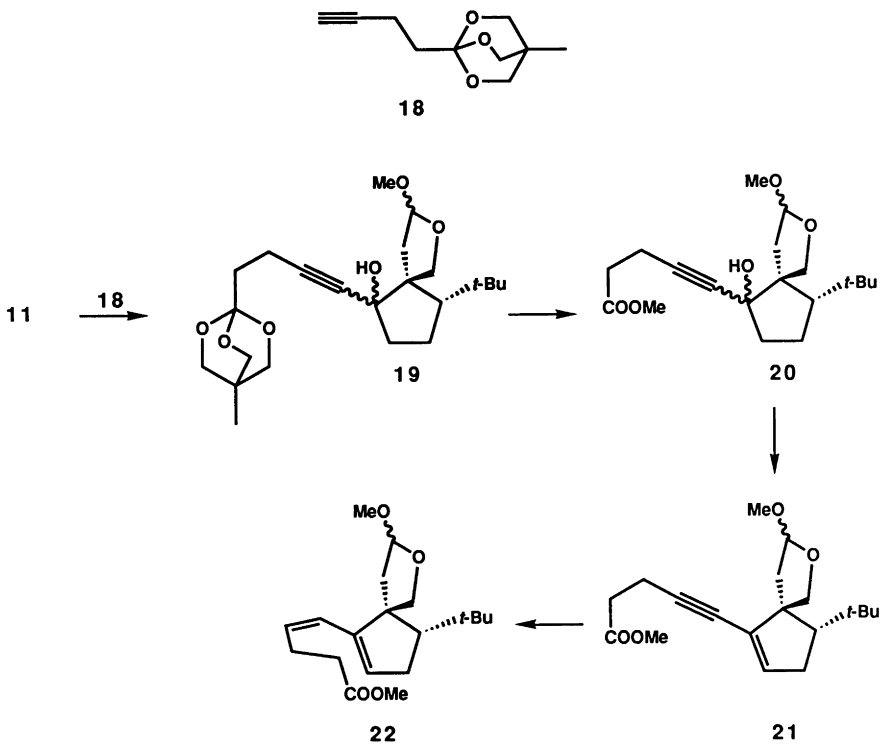
IV. Synthesis of Carboxylic Acid 10

With spiroketone **11** in hand, our immediate objective was its conversion to carboxylic acid **10**. Acetylene **18**, with a carboxylic acid group masked as an oxabicyclo[2.2.2]octyl (OBO) ester seemed an ideal material for carrying out the desired transformation.

Addition of the lithium acetylide anion derived from **18** to **11** gave an unacceptable yield of **19** (30–40%); 40–45% of **11** was recovered. This mediocre result was due to the ease of enolization of **11** and the high basicity of the lithium acetylide anion. Use of the less basic organocerium reagent, generated by reaction of the lithium acetylide of **18** with anhydrous cerium(III) chloride at −78°C, afforded **19** in 91% yield as a mixture of four diastereomers.[19] The carboxylic acid group was then liberated from the OBO ester and reprotected as the methyl ester (CH_2N_2) in quantitative yield.[20] The next step in the plan was dehydration of **20** to **21**, which proceeded uneventfully. Treatment of **20** with mesyl chloride in pyridine afforded **21** in 72% yield (Scheme 3).

Now it only remained to hydrogenate the triple bond and hydrolyze the methyl ester to obtain our key intermediate. Unfortunately, hydrogenation of enyne **21** turned out to be a troublesome reaction: 1.) the hydrogenation had to be stopped at 70% conversion to maximize the yield of **22**, 2.) the product was invariably contaminated with over reduced and 1,4-hydrogenated products, and 3.) diene **22** could not be isolated in high purity. In addition to the reduction problem, this approach incorporated cumbersome deprotection and reprotection of the carboxylic acid.

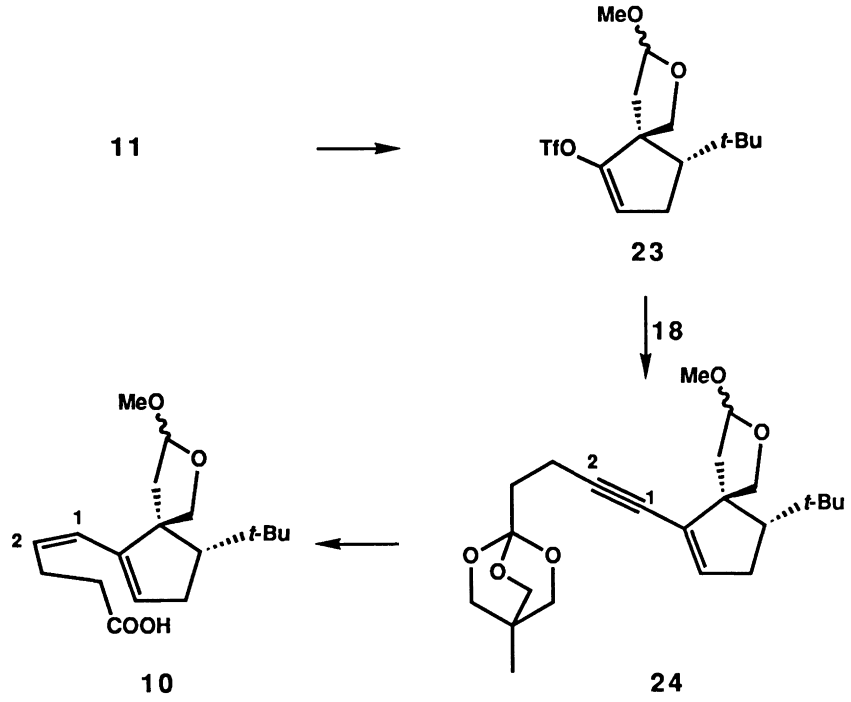
It should be mentioned at this stage that several options were available. The most attractive alternative to the nucleophilic



SCHEME 3

addition/dehydration route involved the palladium-catalyzed coupling of enol triflate **23** with an alkyne **18** (Scheme 4).[21] The *Z* stereochemistry of the C_1–C_2 double bond could then be generated by a chemoselective hydroboration/protonation sequence, thereby by-passing the troublesome hydrogenation step. Of particular note is that the appended carboxylic acid group would be unveiled during the standard work-up procedure of the hydroboration/protonation sequence.

Thus, treatment of spiroketone **11** with lithium diisopropylamide (LDA) in 1,2-dimethoxyethane at −78°C followed by reaction with N-phenyltriflimide, afforded crystalline **23** in 80% yield.[22] The coupling of **23** with **18** proceeded smoothly under the conditions of Sonogashira.[21] The reaction of a mixture of **23** and tetrakis-(triphenylphosphine)palladium(0) with **18**, n-propylamine and cuprous iodide afforded **24** in 76–84% yield. The conversion of **24** to



SCHEME 4

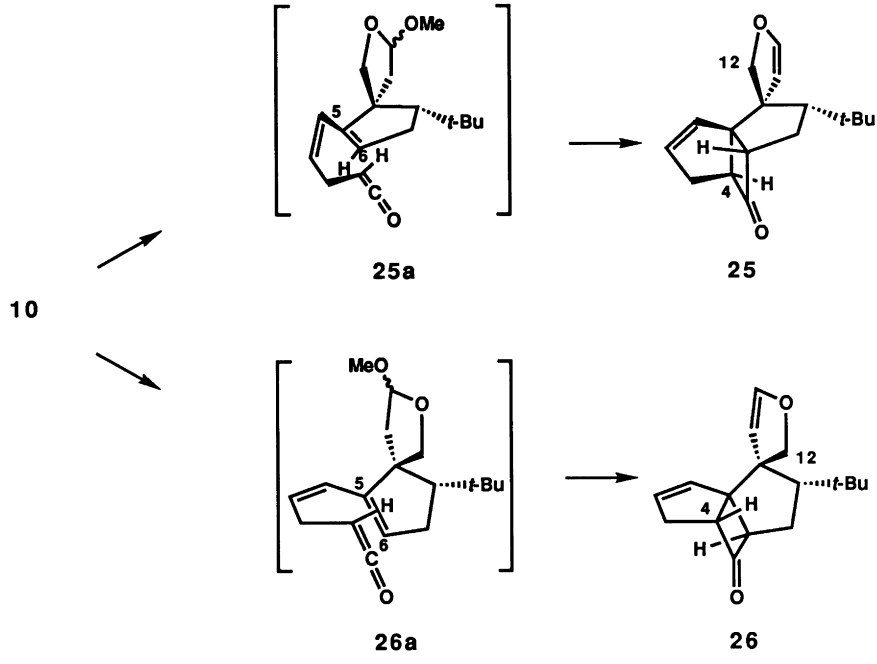
the desired carboxylic acid **10** was accomplished in 86% isolated yield by the following sequence of reactions: 1.) hydroboration with dicyclohexyl borane in THF (0°C, 3 hours), 2.) protonolysis by addition of excess acetic acid (23°C, 16 hours) and oxidation with 2N sodium hydroxide/30% aqueous hydrogen peroxide,[23] 3.) cleavage of the OBO ester unit by sequential adjustment of the pH of the reaction [pH 3 (23°C, 1 hour) → pH 11 (23°C, 1 hour) → pH 3]. In this fashion, the dienic carboxylic acid **10** was obtained in 58% overall yield from **11** (Scheme 4).

V. The [2 + 2] Ketene–Olefin Cycloaddition Reaction [10 → 9]

Up to this point we had enjoyed a period of steady progress. We now arrived at the first critical point in the synthesis: the intramolecular thermal [2 + 2] ketene-olefin cycloaddition reaction. The ketene

generated from **10** could approach either side of the C_5–C_6 double bond to produce **25** and/or **26**. When examining models of possible transition states for this cycloaddition reaction, it was difficult to predict the course of the reaction. However, we felt that approach to the C_6 carbon by the ketenic carbonyl carbon would occur *via* **26a**, due to the smaller number of non-bonding interactions; this should favor the formation of **26**. We could not, however, totally rule out the possibility of formation of **25** (Scheme 5). We thus approached this reaction with some anxiety, as it establishes the core of the molecule; formation of **25** or lack of stereoselectivity would require that we start over.

To our satisfaction, the cyclization proceeded with excellent selectivity. Treatment of the acid chloride of **10** with N,N-diisopropylethylamine in toluene at 120°C furnished a single cyclobutanone in 80% yield. One small surprise, evident from the ^{1}H NMR of the product, was that the diisopropylethylamine hydrochloride formed in the reaction led at high temperature to the elimination of the anomeric C_{11} methoxy group. This unexpected thermal dehy-



SCHEME 5

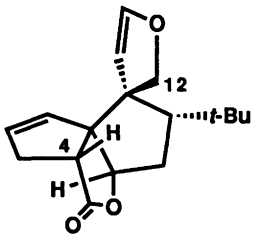
dromethoxylation proved very useful in the final stages of the synthesis for removal of the anomeric methoxy group.

The structure of the cyclobutanone could not be unequivocally assigned from the coupling constants in the ^{1}H NMR, since the dihedral angles between the critical protons in **25** and **26**, as derived from Drieding models, are almost identical. Unfortunately no significant NOE between the protons of interest was detected. Optimistically, we decided to proceed further by temporarily assigning structure **26** to the cyclobutanone. We hoped that critical evaluation of the ^{1}H NMR at every stage, in combination with consistency in the reactivity pattern of the molecule would provide sufficient data to establish the structure. The successful completion of retigeranic acid lent support to this strategy.[14]

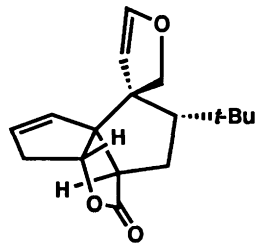
VI. A Startling Outcome in the Photolysis Reaction: Confirmation of Stereochemistry

Our attention now turned to investigation of the Baeyer-Villiger reaction of the cyclobutanone product tentatively assigned as **26**. Electrophilic reagents were unsuitable because of the presence of reactive double bonds in **26**; thus we turned to nucleophilic reagents, such as basic hydrogen peroxide. The success of such reagents in the Baeyer-Villiger reaction was demonstrated in connection with prostaglandin research.[24] In our initial attempt, reaction of **26** with sodium hydroxide/hydrogen peroxide afforded a 1 : 1 mixture of γ-lactones **27** and **28**. Our immediate task was thus to improve the product ratio to favor formation of **27**. Thus a systematic investigation of a variety of nucleophilic reagents and reaction conditions was undertaken. We soon discovered that the bulk of the reagent had a dramatic effect on the ratio of the products formed: *tert*-butyl hydroperoxide markedly improved the ratio to 3 : 1. An even bulkier reagent, triphenylmethyl hydroperoxide furnished *only* **27**, with virtual exclusion of **28**. The reaction protocol called for treatment of **26** with triphenylmethyl hydroperoxide and sodium hydroxide in acetone at −30°C for 6 hours furnishing **27** in 86% yield. We do not understand the origin of this regiospecificity, but suffice it to say that we were elated by the result.

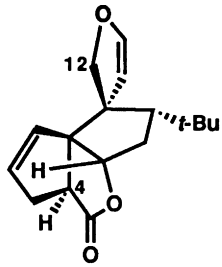
Ironically, though the desired regiochemical outcome in the Baeyer-Villiger reaction was successfully achieved *via* tuning of the reagent, the overall structure of the product remained in doubt at this



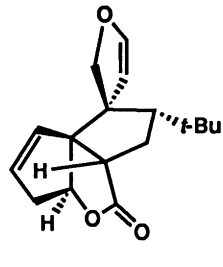
27



28



29

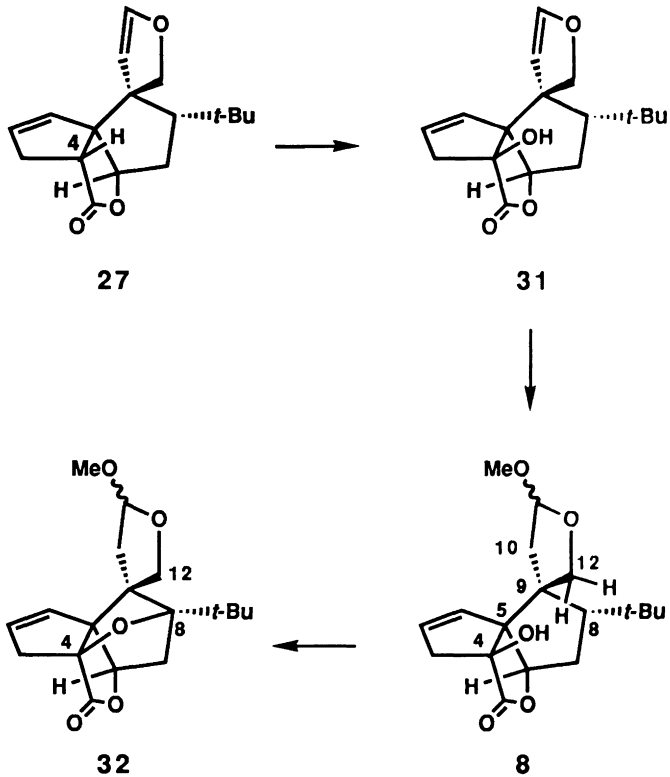


30

point. The regiochemistry of this ring expansion reaction was readily established by ^{1}H NMR; thus structures **28** and **30** were dismissed for the single Baeyer-Villiger product formed. Disappointingly, neither ^{1}H NMR nor NOE experiments were helpful in deducing the structure unequivocally. As a result there still remained a worrying possibility that we might be handling **29** even though we assigned structure **27** to the product. The lack of NOE observed between the C_{12} and C_4 protons concerned us the most. This suggested that the C_4 and C_{12} protons were not in close proximity and was consistent with structure **29**, arising from the undesired product of the [2 + 2] reaction. The C_4 and C_{12} protons are *anti* to each other in structure **29**. However, we reasoned that it was possible that the structure could still be **27**, if the molecule does not exist in a conformation that brings the C_4 and C_{12} protons into close proximity. If this was the case, we needed to be concerned about the outcome of the second key reaction, designed for the construction of ring E, the photolysis of the hypoiodite. This reaction would require close proximity between the C_4 oxygen radical and the C_{12} proton. In either case, we suspected that the era of constant progress would soon end; either the structure

of products **26** and **27** would have to be revised or we would have difficulty in forming ring E. In the absence of any solid evidence confirming the stereochemistry, we continued to execute our synthetic plan by provisionally assigning stereostructure **27** to the Baeyer–Villiger product. Deep in our hearts, we hoped that the next reaction would bring an end to our agonizing dilemma; these uncertainties were preventing us from making key strategic decisions. Obviously, at this stage we would have preferred an undesired outcome in the photolysis reaction rather than discovering that the Baeyer–Villiger product and cyclobutanone actually possessed structures **29** and **25**!

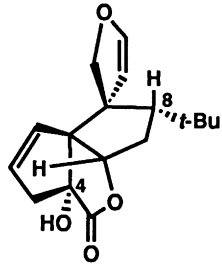
The conversion of lactone **27** to the hydroxylactone **8** therefore became our immediate objective and was achieved without incident as shown in Scheme 6. Treatment of lactone **27** with sodium hexamethyldisilazide at −50°C in tetrahydrofuran followed by



SCHEME 6

quenching of the anion with 2-(phenylsulfonyl)-3-phenyloxaziridine gave hydroxy lactone **31** in 73% yield.[25] Hydroxy lactone **31** on exposure to methanol and excess camphorsulfonic acid (CSA) at 25°C underwent addition of methanol to the dihydrofuran moiety to give **8** in 75% yield (Scheme 6).

The stage was now set for the test of our second key reaction: construction of ring E through intramolecular photolysis of the hypoiodite of **8**. Irradiation of **8** with a tungsten lamp (120 watts) in 1,2-dichloroethane in the presence of lead tetraacetate, pyridine and iodine at 25°C for 10 minutes afforded a single product (80%) which was assigned structure **32** on the basis of spectroscopic data. The ^{1}H NMR spectrum of the product clearly revealed the absence of the C_8 proton while indicating the presence of two protons on C_{12}. Additionally, the IR exhibited no hydroxyl group, forcing us to conclude that the oxygen bridge had formed between C_4 and C_8 by abstraction of the $C_8(\beta)$ proton by the C_4 oxygen radical. *The tactical significance of this result was enormous: the formation of* ***32*** *provided for the first time irrefutable stereochemical evidence for* ***26*** *and* ***27*** *as the products of the* [2 + 2] *ketene–olefin cycloaddition reaction and the Baeyer–Villiger reaction.* The formation of **32** is feasible only if the C_4 hydroxy group and the C_8 proton are *syn* to each other, as in **8**. The generation of **32** from **33** (the presumed structure for the hydroxylactone if the [2 + 2] cycloaddition reaction had yielded **25**) is impossible because the C_4 hydroxyl group and the C_8 proton are *anti* to each other in **33**.



33

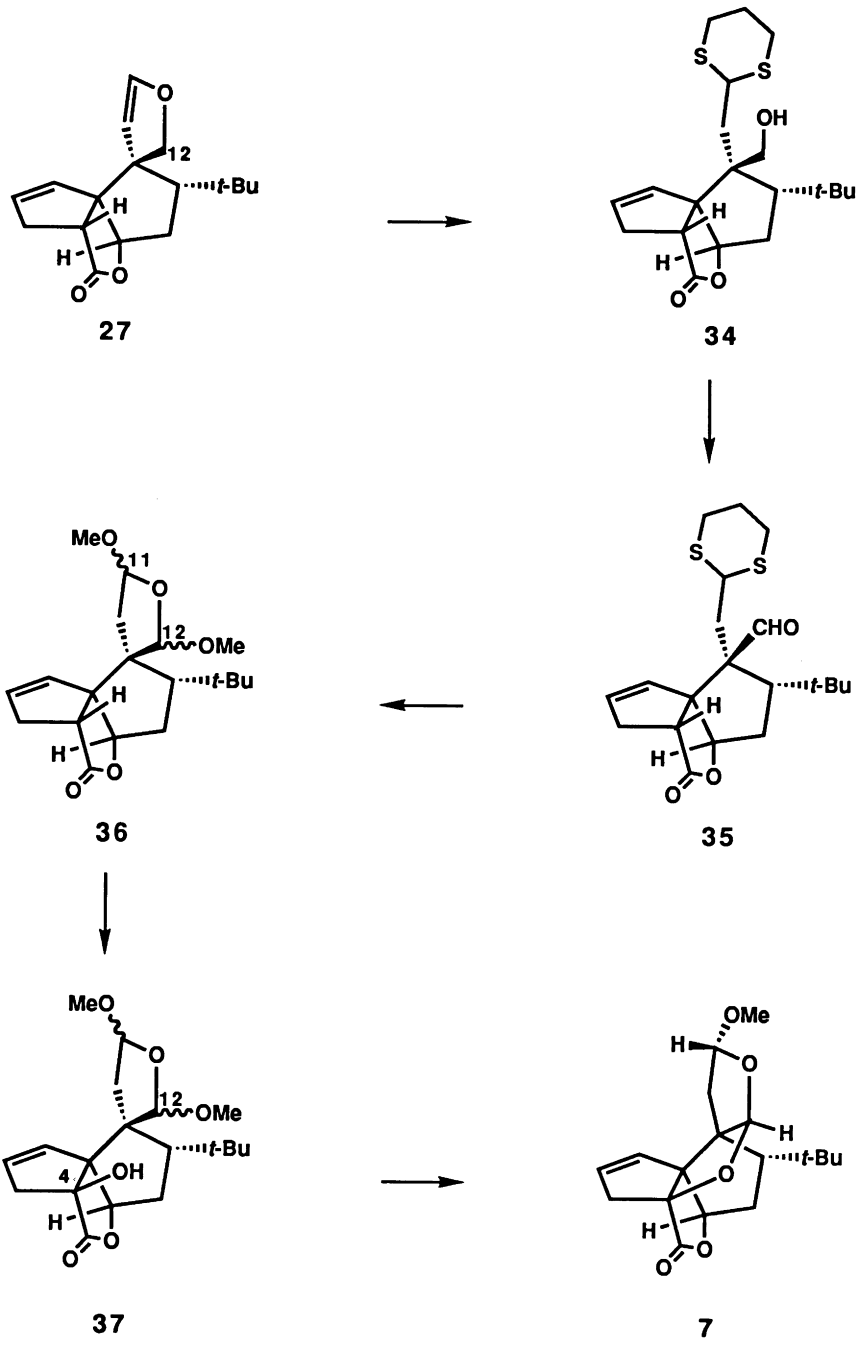
The formation of **32** rather than **7** could be explained by considering the ground state conformation of the intermediate **8**. Close proximity of the C_4 oxygen radical with the $C_{12}(\beta)$ proton, required for the formation of **7**, demands that all the C–C bonds around C_5

and C_9 be in the high-energy eclipsed conformation. In order to avoid these eclipsing interactions, the molecule adopts a puckered conformation, in which all the substituents on the C_5–C_9 bond are in a nearly staggered conformation. This brings the C_4 oxygen radical in proximity to the $C_8(\beta)$ proton, resulting in the formation of **32**. The puckered conformation also allows the *tert*-butyl group to occupy a pseudo-equatorial position thereby reducing unfavorable interactions with the C_{10} methylene protons. Recently, Professor Houk has reached a similar conclusion by analyzing the low energy transition structures for intermediate **8** *via* force field models.[26]

VII. Completion of Ring E: A Major Milestone Reached

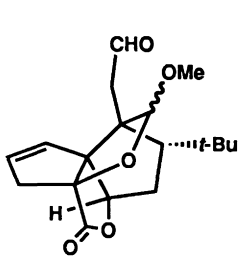
Although the formation of **32** ended our quandary regarding the structure of **26** and **27**, it was obviously not useful as a synthetic step for the construction of ring E. Strategically, the photolysis reaction was intended to bring C_{12} to the oxidation level of an aldehyde; our failure to do so necessitated development of an alternate approach. Ultimately, our successful plan for the conversion of **27** to pentacyclic intermediate **7** called for the straightforward multistep sequence shown in Scheme 7. Treatment of lactone **27** with 1,3-propanedithiol in methylene chloride in the presence of titanium (IV) chloride at 0°C gave **34** in quantitative yield.[27] We had some difficulty in our initial attempts to oxidize **34** to **35** in acceptable yield. Oxidation with pyridinium dichromate (PDC) under the usual conditions was slow (0°C, 6–8 hours) and afforded **35** in 55–60% yield.[28] The low yield was due to the formation of polar material, presumably formed by oxidation of the 1,3-dithiane moiety; we surmised that the long reaction time was contributing to this problem. Conveniently, the yield was improved to 75% by employing the accelerated PDC oxidation in the presence of acetic acid (0°C, 0.5 hour).[29] The dithiane group was then removed by treating **35** in a 1 : 1 mixture of methylene chloride and methanol with periodic acid under carefully controlled conditions (4 equivalents; −30°C, 20 minutes; 0°C, 20 minutes and 25°C, 20 minutes) to afford an anomeric mixture of **36** (2 : 1) which could be separated by flash chromatography (80%).[30]

Subsequent chemistry involving the conversion of **36** to **7** could be carried out on the mixture. In practice, however, it was found convenient to separate the two isomers and carry them individually to **7**.

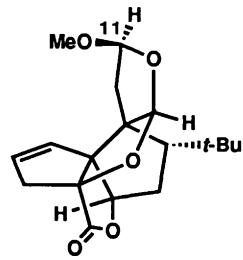


SCHEME 7

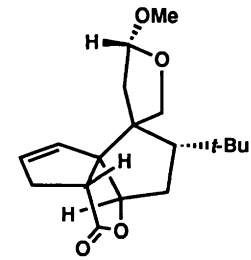
We believe these two products are isomeric at the C_{11} anomeric center and not at the C_{12} position; no effort was made to establish the relative stereochemistry at the anomeric methoxy groups. In the subsequent text these two isomers will be referred to as the major and minor isomers. Treatment of **36** (major or minor) with lithium diethylamide at 0°C (10 minutes) followed by quenching with 2-(phenylsulfonyl)-3-phenyloxaziridine afforded the corresponding hydroxylated products **37**, which could not be completely separated from the aromatic impurities arising from the reagent. In sharp contrast to the conversion of **27** to **31**, the use of sodium hexamethyldisilazide (–40°C) as base provided no hydroxylated product **37**; the presence of the additional methoxy group at C_{12} necessitates the use of the less hindered lithium diethylamide.



38



39



40

Now, with the correct oxidation states at C_4 and C_{12} in **37**, the oxygen bridge could be formed *via* treatment with CSA in an appropriate solvent. This ring E formation reaction was found to be very dependent on the choice of solvent. For example, upon ring closure under equilibrating conditions with CSA in methanol, **37** (major) afforded a 1 : 1 mixture of **7** and **38** while **37** (minor) furnished exclusively **38**. Fortunately, under non-equilibrating conditions, **37** (major) on treatment with CSA in methylene chloride (25°C, 6–12 hours) afforded only **7** (70%). In contrast **37** (minor) behaved rather differently under these conditions; it required a longer reaction time and afforded a mixture of C_{11} epimer **39** and **38** (3 : 1). Epimerization of the anomeric C_{11} methoxy group of **39** to **7** was achieved *via* treatment with CSA in methanol. Furthermore, the intermediate **38** could be converted to **7**. This transformation, however, required drastic conditions: 1.) Dioxane, CSA, sealed tube 120°C, 18 hours; 2.) MeOH, CSA, 25°C, 6 hours and was not investigated

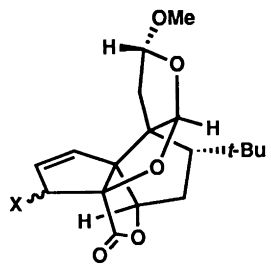
further. Using this method **27** was converted to **7** in 25–30% overall yield (Scheme 7).

The synthesis of pentacyclic intermediate **7** with proper topology and stereorelationships was a major milestone; not surprisingly our spirits were high. *The feasibility of the synthetic route was established, and we were now committed to the synthesis of ginkgolide B* (**2**) *through this pathway.* At this juncture the crucial issue was a logistic one: our ability to move forward depended on the availability of **7**. We diverted our resources for the rapid procurement of intermediate **7**; within three months 6.0 grams of pentacyclic intermediate **7** was synthesized (8% overall yield from **12**).

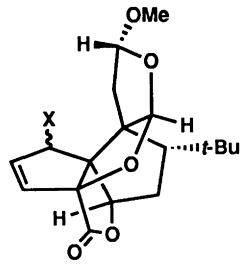
VIII. Allylic Oxidation of 7: The Problem Resolved

With this generous amount of intermediate **7** in hand, the allylic oxidation of **7** to **6** became our principal task. Our first experiment set the tone for the months to come: no reaction was observed upon treatment of **7** with *tert*-butyl hydroperoxide (TBTH) and copper(II) pivalate in benzene at 80°C for 48 hours.[31] To conserve the supply of **7** and to screen reagents more carefully with a higher degree of confidence, a series of model compounds such as α-pinene, β-amyrin benzoate, intermediate **40** and intermediate **36** were selected. Every reagent was first tested on one of the model compounds, and only after a successful transformation was obtained was the reaction repeated under identical or more forcing conditions on intermediate **7**. A wide variety of reagents such as CrO_3/3,5-dimethylpyrazole;[32] CrO_3/acetic acid/acetic anhydride,[33] TBTH/chromium hexacarbonyl,[34] TBTH/palladium acetate, TBTH/palladium bis(trifluoroacetate),[35] selenium dioxide,[36] and selenium dioxide/TBTH[37] were tested without success. In each case allylic oxidation proceeded in an acceptable manner with models but failed completely with **7**. The prospects for achieving the allylic oxidation looked very grim; we were now becoming thoroughly frustrated.

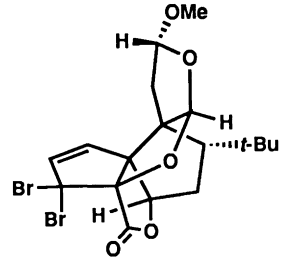
As is all too often the case in endeavors of this kind, a simple reagent provided a solution to this recalcitrant problem. Allylic bromination of **7** could be achieved with N-bromosuccinimide (NBS) in carbon tetrachloride (10°C, 6–7 hours), to afford a mixture (80%) of three products **41**, **42** and **43** (6 : 3 : 1). Unfortunately, direct allylic oxidation to **6** by irradiation with NBS in moist solvent[38] or oxidation of the bromide mixture with silver tetrafluoroborate in dimethyl-



41 X = Br
44 X = ONO_2
46 X = OH



42 X = Br
45 X = ONO_2



43

sulfoxide was unsuccessful.[39] Clearly, a less ambitious transformation was required; we began to investigate simple replacement of bromide by hydroxyl, bearing in mind that conversion of **42** to **6** would require S_N2' displacement. Initial results were not very encouraging. Treatment of the mixture of bromides with potassium superoxide in dimethylsulfoxide resulted in 30% reduction of the C–Br bond.[40] Finally, after considerable experimentation, the bromides were converted to the desired enone *via* a mosaic route. Exposure of the crude brominated mixture to 10M silver nitrate in acetonitrile (23°C, 15 min) furnished enone **6** (originating from bisbromide **43**) and the two nitrate esters **44** and **45**. The nitrate esters were separated and individually converted to allylic alochol **46**; reduction of **44** with zinc/acetic acid afforded **46** while regioisomer **45**, on S_N2' displacement with water in 10 : 1 benzene-methanol in the presence of DBU, afforded **46**. Oxidation of allylic alcohol **46** with PDC furnished **6**; overall, the bromination/nitrate ester route provided enone **6** in 50% yield.

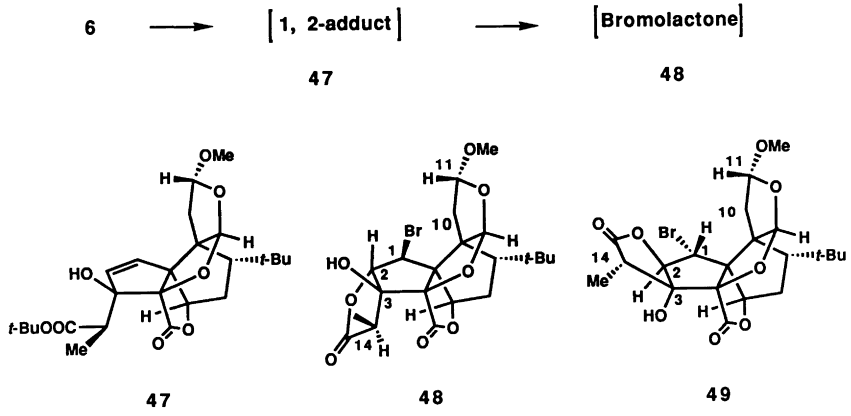
Grudgingly, we accepted this marginally efficient route for the allylic oxidation; this is indicative of the considerable gap which still exists in methodology for C–H activation. We were glad that this step was behind us; humbled by this struggle, we looked forward with optimism to assembling the C ring.

IX. Construction of Ring C: An Inventive Solution to a Recalcitrant Problem

We had now reached an advanced stage of our synthetic strategy; the goal remaining to be achieved was the formation of ring C. Crucial for success was creation of the C_3 chiral center *via* 1,2-addition of the

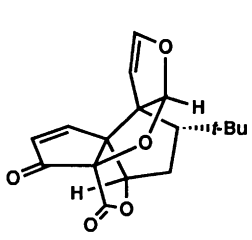
lithium enolate of an alkyl propionate to **6** from the concave face formed by rings A, E and F (β-face); the other chiral centers (C_{14} and C_2) of ring C would be fixed either by the reagents employed or by the nature of the stereoelectronics of the subsequent reactions. For instance, the correct stereochemistry of the C_{14} methyl group would be set during addition of the *Z* lithium enolate of *tert*-butyl propionate. Similarly, assuming that addition occurred from the β-face, epoxidation of the adduct would then be favored from the α-face; intramolecular hydroxylactonization *via trans*-diaxial epoxide opening would then control the C_2 stereochemistry as well as generating the C_1 hydroxyl group in the orientation present in ginkgolide B (**2**).[41] Thus, the success of ring C construction hinged upon the outcome of *tert*-butyl propionate enolate addition to **6**. We did not consider, 1,4-addition a major threat because of the unique shape of the molecule, but the issue of facial selectivity was of concern: would the addition occur from the α- or the β-face? This would depend on the relative accessibility of the two faces of the carbonyl group in **6**; the presence of many strategically located oxygen atoms, and the use of coordinating solvents such as hexamethylphosphoric triamide (HMPA) (necessary for the generation of the Z lithium enolate) made this difficult to predict. Not surprisingly, we approached this final C–C bond forming reaction with some trepidation.

Treatment of **6** with the anion formed from *tert*-butyl propionate and LDA in the presence of HMPA at $-78°C$ afforded a *single* aldol adduct **47** in 40% yield. Unfortunately, the stereochemistry at the newly created chiral centers could not be ascertained by ^1H NMR. Keeping in mind that our goal was the formation of ring C, we opted for moving forward, hoping that extensive NOE examination at an appropriate point would allow us to make the necessary stereochemical assignments. At this stage we decided to investigate bromolactonization of **47**, as debromination of the reaction product would lead to the synthesis of ginkgolide A (**1**). We planned to investigate epoxidation/hydroxylactonization of **47** at a later time, for the synthesis of ginkgolide B (**2**). Our spirits were very high; without further delay ring C formation *via* bromolactonization of **47** was investigated. Hydrolysis of *tert*-butyl ester **47** with trifluoroacetic acid, followed by bromolactonization in water/*tert*-butanol in the presence of sodium acetate afforded a hexacyclic bromolactone in 92% yield (Scheme 8). Since the facial selectivity in

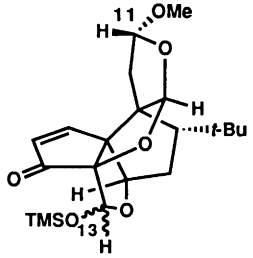


SCHEME 8

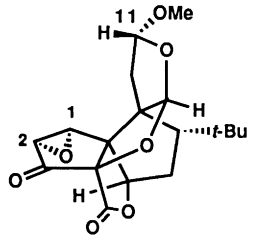
the addition was not established, the structure of the bromolactone could be either **48** or **49**. To our dismay, preliminary ^{1}H NMR analysis supported structure **48** for the bromolactone. In most of the intermediates the chemical shift for the β-proton on C_{10} is ~2.3 ppm; in case of bromolactone, however, it was 3.9 ppm. This can best be explained by the presence of the β-oriented bromine on C_1, pointing in the direction of the $C_{10}(\beta)$ proton; the $C_1(\alpha)$ bromine, as in structure **49**, should not have much influence on the chemical shifts of the $C_{10}(\beta)$ proton. Since the stereoelectronic requirement of the bromolactonization reaction demands an *anti* relationship between the bromine and the incoming oxygen nucleophile, assignment of the β-oriented bromine leads to structure **48**. The most convincing evidence supporting structure **48**, however, came from an NOE experiment. Irradiation of the C_{11} proton resulted in 21% enhancement of the signal due to the C_2 proton; this can only occur if the propionate attacked from the α-side (concave face formed by rings A and D). This was a major blow to our hopes of completing the synthesis in a few weeks. On a positive note, however, the NOE experiment provided the first positive evidence that the C_{11} methoxy group was *syn* to the *tert*-butyl group. Furthermore, irradiation of the C_1 proton led to an 18% enhancement of the C_{14} proton signal, establishing that use of the *Z*-enolate indeed fixes the desired stereochemistry of the C_{14} methyl group. The problem of ring C formation was thus narrowed down to securing enolate addition from the β-face.



50



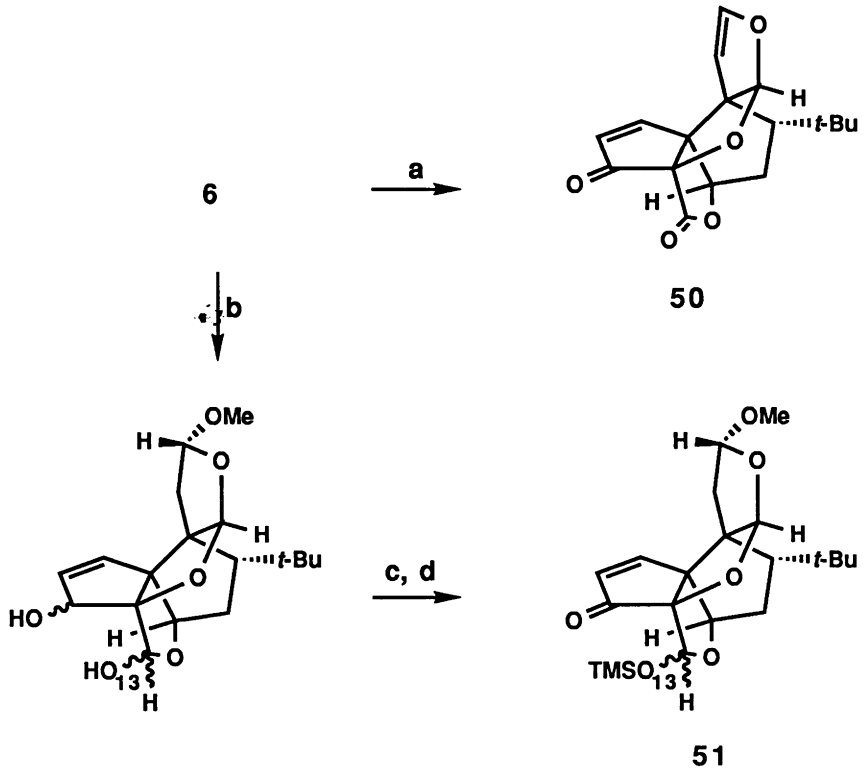
51



52

The unexpected formation of **47** indicated that the α-face of enone **6** is more accessible than the β-face. The reversal of the mode of addition would require making the β-face less hindered and/or the α-face more hindered. This line of reasoning suggested three options. To begin with, it was argued that the C_{11} proton of **6** might be interfering with the trajectory of enolate addition, thereby restricting approach from the β-face. In that case, removal of the C_{11} proton might favor β-face addition; therefore **50** became an interesting substrate. Alternatively, the α-face of the carbonyl group could be temporarily blocked by transforming C_{13} into a tetrahedral carbon. Thus, enolate addition to **51** appeared promising. Finally, yet another way to tease out a favorable outcome might be to investigate enolate addition to epoxide **52**. In this approach, epoxidation of the enone **6** would be expected to occur from the α-face to furnish **52**. The presence of an additional α-oxygen atom in the vicinity of the carbonyl group might tilt the steric balance in our favor.

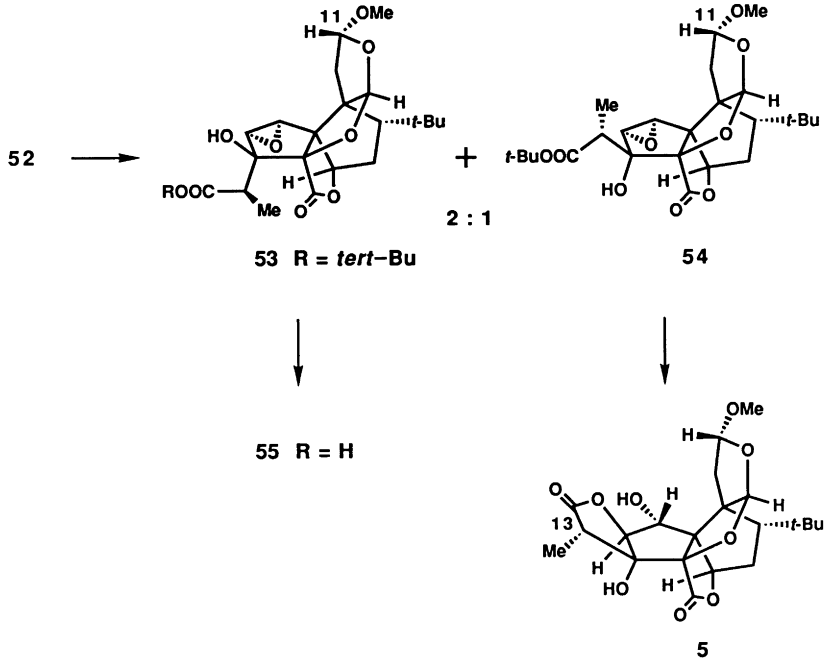
In line with our new objectives, we first synthesized **50** and **51** from enone **6** *via* functional group interconversion, as shown in Scheme 9. Of particular note is that the unexpected thermal dehydromethoxylation observed during the intramolecular [2 + 2] ketene-olefin cycloaddition reaction guided our selection of the reaction conditions (pyridinium *p*-toluenesulfonate, chlorobenzene, 135°C) for the elimination of the anomeric C_{11} methoxy group from **6**. With **50** and **51** in hand, we turned our attention to the crucial enolate addition. Much to our disappointment, even the addition of the sterically less demanding methyl acetate enolate to **50** occurred from the α-face while **51** resisted addition under a variety of conditions. The message was clear: removal of the C_{11} proton from **6** is not enough to reverse the mode of addition. The lack of reactivity of **51** from the α-face was understandable, but its unwillingness to react on the β-face was



SCHEME 9. Reagents and conditions: (a) PPTS, PhCl, Py, 135°C, 16 hours, 80%; (b) DIBAL-H, −78°C, 2 hours; (c) MnO_2, RT, 3 hours; (d) TMSOTf, 2,6-Lutidine, −78°C, 10 minutes.

puzzling: could the C_{11} proton in **51** be blocking addition from the β-face? We never investigated this question since we leaped into examining the seemingly straightforward third option: addition of the enolate to **52** (Scheme 10).

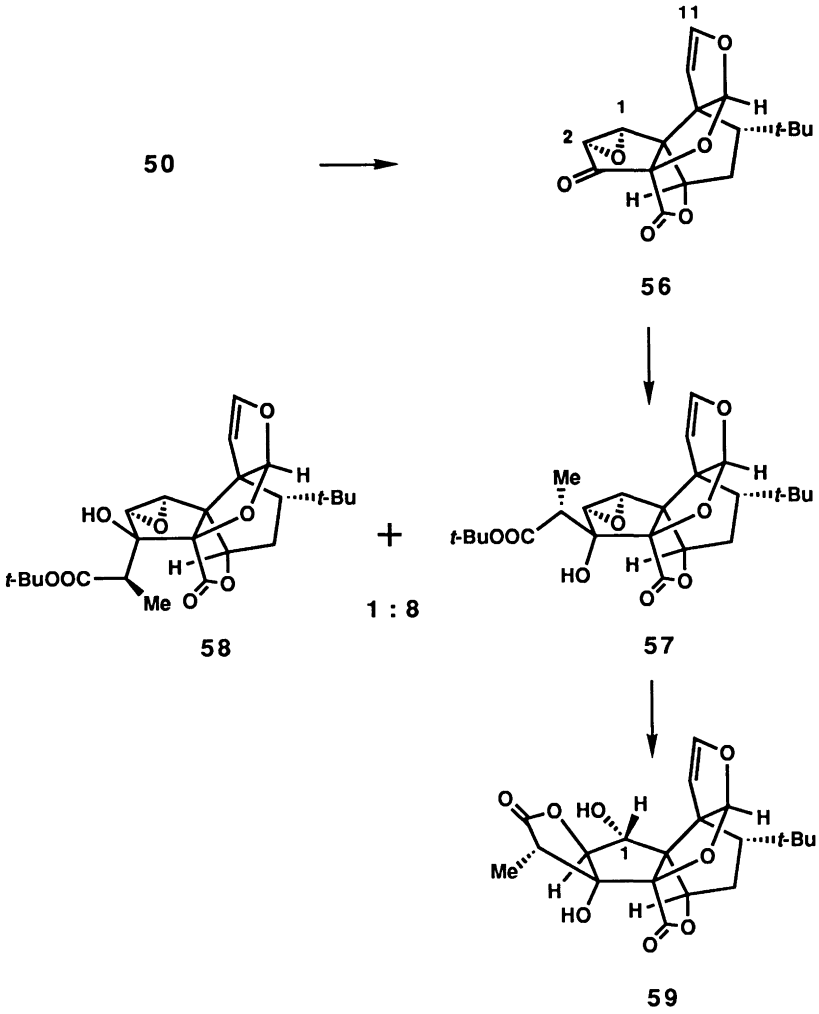
Attempts to prepare **52** *via* epoxidation were not initially successful;[42] reaction of **6** with *tert*-Butyl hydroperoxide and Triton B furnished the product formed by the 1,4-addition of *tert*-Butyl hydroperoxide. Once again, the bulkier peroxide came to our rescue; after considerable experimentation, we discovered that treatment of enone **6** with triphenylmethyl hydroperoxide in the presence of benzyltrimethylammonium methoxide in anhydrous THF afforded **52** in 68% yield. The stereochemistry of the epoxidation product was confirmed by an NOE experiment. With the synthesis of epoxide **52** in hand, we found ourselves at the threshold of the key enolate addition



SCHEME 10

experiment. To our initial satisfaction, reaction with the *Z* enolate of *tert*-butyl propionate ($-78°C \rightarrow -30°C$) provided a mixture of two diastereomers in a 2 : 1 ratio (53%). Since the stereochemistry at the newly created chiral center could not be ascertained by ^1H NMR, the two diastereomers were separated, and their structures established from their reactivity pattern on treatment with trifluoroacetic acid (TFA). The underlying assumption was that only the desired isomer possessed the necessary stereoelectronic arrangement to undergo hydroxylactonization.[41] When the minor isomer reacted with TFA, it underwent smooth hydroxylactonization to afford **5**, and thus was assigned structure **54**. In contrast, the major isomer under identical conditions provided the carboxylic acid **55**; it was therefore assigned structure **53**. This was indeed a welcome development. For the first time in more than nine months we saw some addition from the β-face; the synthesis of ginkgolide B (**2**) seemed imminent. We were not completely out of the woods, however: the poor β-selectivity of the enolate addition reaction was unacceptable. We surmised that this

could be improved *via* fine tuning of the reagent and/or substrate **52**. We first investigated addition to **52** of more than fifteen different esters and amides under a variety of conditions. No significant improvement in the facial selectivity was attained. We next considered making the β-face of the epoxide **52** less hindered. In line with our original theory that the C_{11} proton present in the cavity might be blocking the desired enolate trajectory, we turned our attention to preparing epoxide **56** (Scheme 11).



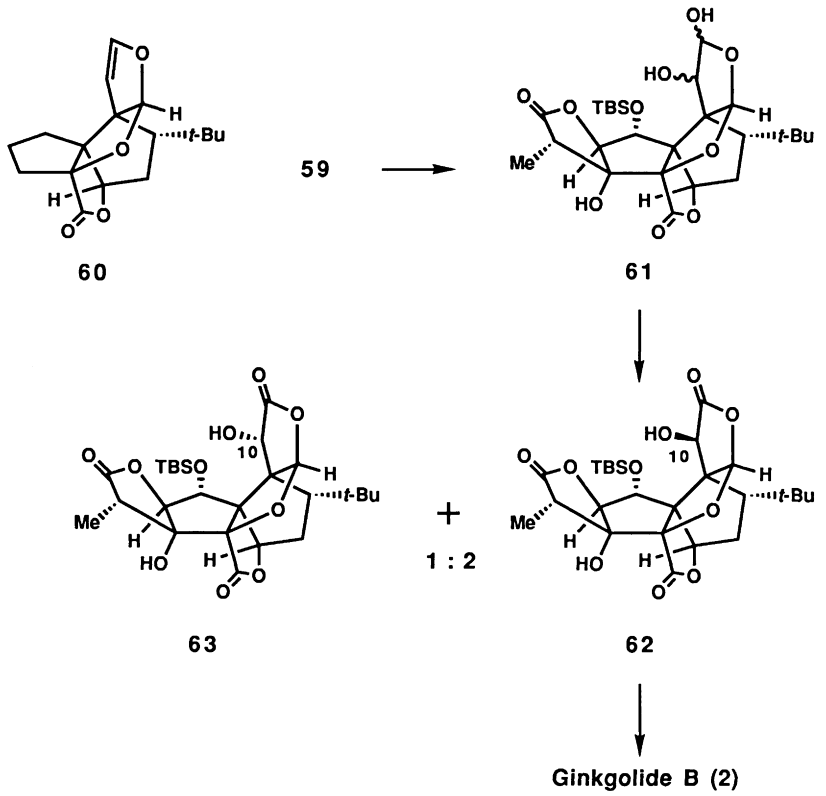
SCHEME 11

Somewhat to our surprise epoxidation of enone **50** by our previously established procedure furnished epoxide **56** in only 50% yield; the major side reaction was the competitive 1,4-addition of methoxide anion. The use of a sterically hindered base prevented this side reaction. The improved protocol called for the reaction of enone **50** with triphenylmethyl hydroperoxide (5.0 equivalents) and benzyltrimethylammonium isopropoxide in THF (0.5 equivalent) at −10°C, to furnish epoxide **56** in 72% yield. Once again we arrived at the pivotal enolate addition reaction; exposure of the epoxide **56** to the enolate derived from LDA and *tert*-butyl propionate in the presence of HMPA (−78°C → 30°C) afforded diastereomers **57** and **58** in an 8 : 1 ratio (68%). This was a decisive positive turn of events; for the first time the synthesis of ginkgolide B (**2**) seemed at hand. The major diastereomer underwent smooth hydroxylactonization to afford bis-lactone **59** in 92% yield. The problem of ring C annulation, with creation of four chiral centers was solved; the conversion of **6** to bis-lactone **59** could be accomplished in 36% overall yield.

X. Completion of the Synthesis of Ginkgolide B

At this point, all that remained to complete the synthesis was to functionalize the dihydrofuran moiety of bis-lactone **59**. This was achieved by the plan outlined in Scheme 12. All the transformations involved were initially investigated using **60** as a model system; it could be readily obtained from **7** *via* functional group interconversion; only experiments with **59** are described. Protection of the C_1 alcohol (TBDMS–OTf, 2,6-lutidine) followed by osmylation in pyridine at 60°C furnished a mixture of diols **61** in 65% yield.[43] Next, anomeric oxidation of diols **61** with iodine in the presence of calcium carbonate in methanol-water afforded epimeric hydroxy lactones **62** and **63** in a 2 : 1 ratio.[44] Finally, desilylation of **63** with excess boron trifluoride etherate in methylene chloride produced an 89% yield of (±)-ginkgolide B (**2**), displaying ^{1}H NMR, FT–IR and mass spectra identical to that of the natural sample provided to us by Dr. P. Braquet.[45]

Since the completion of the total synthesis of ginkgolide B (**2**), three important papers have emanated from the laboratory of Professor Corey.[46–49] Intimately tied to the research work described here is the



SCHEME 12

enantioselective synthesis of intermediate **27**[46] and the synthesis of ginkgolide A (**1**) from intermediate **59** and ginkgolide B (**2**).[47]

Most important, in view of the therapeutic potential of ginkgolides, the chemical route presented here offers a unique opportunity for determining the minimum structural features required for retaining the PAF antagonist activity. Indeed, simpler and more potent PAF antagonists have been developed as a result of this work.[48]

Acknowledgments

The authors owe a large debt of gratitude to Professor E. J. Corey for giving us the opportunity to participate in this exciting scientific venture. His insight, creativity, unceasing encouragement and guidance provided the crucial impetus to the completion of the project. Our experience in his group was memorable and rewarding.

Thanks are extended to Drs. Katherine E. Brighty and John A. Lowe for critically reviewing the manuscript.

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Chapter 4

SYNTHETIC STUDIES ON PENTACYCLIC QUASSINOIDS

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The making of molecules puts chemistry very close to the arts.
*We create the objects that we or others then study or appreciate.**

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The citation from Roald Hoffmann's marvelous essay, inspired by the great French chemist Marcellin Berthelot,[1] reminds us that there is an undeniable aesthetic appeal to synthetic chemistry that creates a close kinship between practitioners of synthesis on the one hand and artists, composers, writers and craftsmen on the other. Whether fully planned in advance by design, or shaped by chance and circumstance,

[†] Dedicated to the memory of my father, Emil Joseph Ganem, M.D., 1916–1990.

* Hoffman, Roald. "In Praise of Synthesis," *Negative Capabilities*, 10(⅔), 162(1990), Mobile, Alabama, 1990.

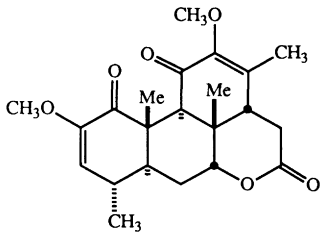
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the 'making of molecules' is an aspect of human creation whose often-pleasing intellectual harmonies and intuitive rhythms can be enjoyed over and over again.

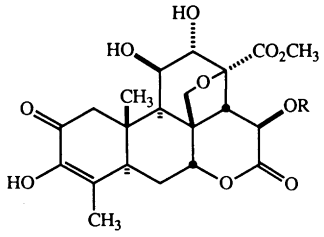
I. Introduction

The family of trees and shrubs known as *Simaroubaceae* comprises some thirty genera of woody plants found mostly in pantropical regions of Africa and North America.[2] For over a century, many of the more than two hundred species of this family were known to produce very low levels of intensely bitter substances collectively called "quassia." However, it took several decades before individual quassinoids (or simaroubolides) were completely characterized. For instance, the now classic representative *quassin* was not fully purified until 1937.[3] Twenty-four years later in 1961, its tetracyclic structure was finally identified as **1** (Scheme 1) by Valenta and co-workers.[4]

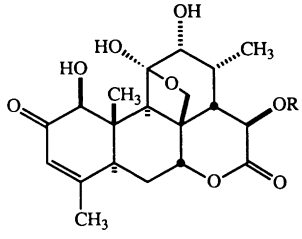
The quassinoids enjoyed a legendary reputation in herbal lore as treatments for a variety of illnesses.[5,6] In Europe during the mid-



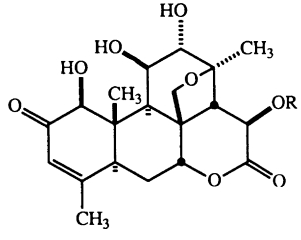
1 Quassin



2 Bruceolide R= H
3 Bruceantin R= OC-CH=CMe(i-Pr)



4 Glaucarubolone R= H
5 Glaucarubinone R= OC-C(OH)MeEt



6 Quassimarin R-OC-C(OAc)MeEt
7 Simalikalactone D R=OC-CHMeEt

SCHEME 1

eighteenth century, crude extracts of the wood of *Quassia amara* ("Surinam quassia") or *Picrasma excelsa* ("Jamaica quassia") in bitter tonic form were used as medicinal agents for the treatment of dyspepsia and dysentery.[7] Various quassia extracts found use as fly poison on flypaper.[8] For a time these bitter principles illegally replaced hops in beer,[9] and during World War II when Pacific naval blockades interrupted shipments of quinine to the West, quassin itself was for a time considered as a substitute in the production of quinine water.

Interest in the quassinoids suddenly exploded when in 1973 Kupchan and co-workers at the University of Wisconsin reported the isolation of several esters of the pentacyclic structure bruceolide **2** from *Brucea antidysenterica*, an Ethiopian plant long used in the treatment of cancers.[10,11] Other pentacyclic quassinoids, notably bruceantin **3** and esters of glaucarubolone **4** such as glaucarubinone **5**, displayed significant antileukemic, antimalarial, and antineoplastic activities.

The biological potency of pentacyclic quassinoids like **1–7** soon attracted the attention of scientists at the National Cancer Institute's Drug Development Program, whose mission is to track down and identify new chemical agents possessing chemotherapeutic value. A rather complex procedure for isolating bruceantin from stem bark of *B. antidysenterica*, the culmination of several years' work, was described in 1979 in which about 130 milligrams of **3** was obtained per kilogram of crude plant material.[12] This represented an overall yield of 0.013%.

The antitumor activity of bruceantin has since been shown to result from its ability to interfere with polypeptide synthesis, apparently by binding to the ribosomal peptidyltransferase center.[13–15] At high concentrations of the drug, peptide initiation seems to be inhibited. Bruceantin also disrupts nucleic acid synthesis, though to a lesser extent.[13]

II. Synthetic Philosophy and Goals

With the reported discovery of bruceantin's antineoplastic properties, we decided to initiate a program of research at Cornell aimed at devising a general strategy for the synthesis of biologically active quassinoids. The first problem we faced, to put it quite simply, was where to begin! Besides the C_{20} picrasane skeleton of quassin itself, a

wide variety of tetracyclic and pentacyclic quassinoids was known, embodying a number of different C_{18}, C_{19}, C_{20} and C_{25} degraded triterpene skeleta. Structures **1–7** in Scheme 1 only hint at the numerous oxidation states and substituent patterns observed in these compounds. Most quassinoids display simple combinations of these functional groups, nevertheless the occasional representative bearing a hydroxyl at C_6, C_{13} or C_{14} is known, and an exocyclic methylene may also replace the C_{13} methyl group (see Figure 1 for numbering). While β-glucoside derivatives are known as well,[16] most quassinoids are found in nature as free alcohols.

The vast majority of quassinoids may be classified into three main structural categories, depending on the oxidation state of the carbon substituent at C_8. The presence of a C_8 methyl group characterizes the simplest tetracyclic quassinoids which possess the basic *trans–anti–trans* tricarbocyclic ring system (Figure 1) found in many terpenes. One

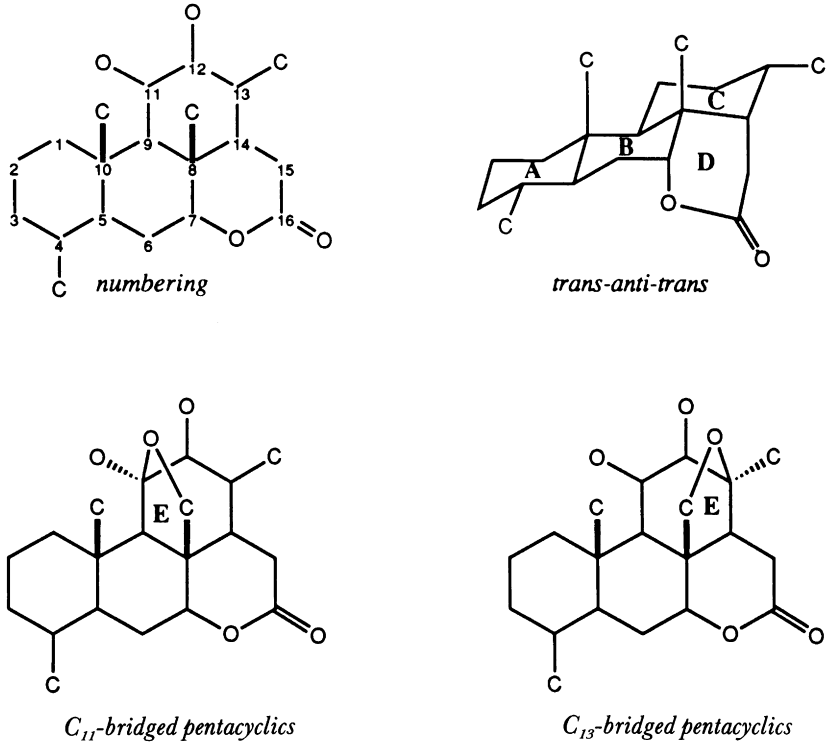


FIG. 1. Quassinoid Structure and Numbering.

class of pentacyclic quassinoids results when an oxidized hydroxymethyl group at C_8 exists in hemiketal form with a C_{11} ketone. Members of this category always possess a C_{12} α-hydroxyl group. Another principal subclass of pentacyclics, mostly found in the genus *Brucea*, features on oxymethylene bridge joining a C_8-hydroxymethyl group in ether linkage with C_{13}. Structure-activity relationships using semisynthetic quassinoids indicate that three structural features are absolutely required for potent biological activity: (i) a pentacyclic ring network, (ii) an electrophilic A-ring α,β–enone grouping, and (iii) a lipophilic C_{15} ester side chain. Two extensive reviews of the diversity of quassinoid structures by Polonsky serve as a useful guide for further detailed exploration.[17]

In spite of the overwhelming number of potentially attractive target molecules and the resulting sense of anxiety we experienced over which one(s) to tackle, certain key structural features stood out as among the most challenging for any total synthesis effort. In particular the 1,3-diaxial relationship of carbon substituents attached at C_8 and C_{10} posed the most serious stereochemical problem.

In this instance, biogenetic considerations were not particularly helpful in planning a synthesis. The quassinoids resemble in many aspects some of the bitter principles in the limonin family, another group of degraded triterpenoids closely related to the *Simaroubaceae*. Studies by Polonsky and coworkers suggest that both groups share a common biosynthesis from euphol (Figure 2).[17,18] In the case of the quassinoids, one of the C_4 methyl groups and four carbons of the side chain are lost. Moreover ring-D of the triterpene must undergo oxidative cleavage and the resulting carbon appendage then must reform a δ-lactone with an incipient C_7 α-hydroxyl. The key stereochemical relationship is established biogenetically by migration of the C_{14} methyl to C_8, perhaps triggered by protonation or oxidation of the Δ^7 double bond in euphol. Synthetically, that sort of approach might best be implemented by a Johnson-type biomimetic polyalkene cyclization.[19]

Most synthetic methods used to create a *trans-anti-trans* system with 1,3-diaxial substituents rely on the formation of one of the rings at either C_8 or C_{10}. Typical methods would result in forming the new bond from the less hindered face to generate the desired diaxial alignment. For example Ireland *et al.* carried out the intramolecular Friedel-Crafts alkylation of **8** and obtained the desired isomer **9** as the

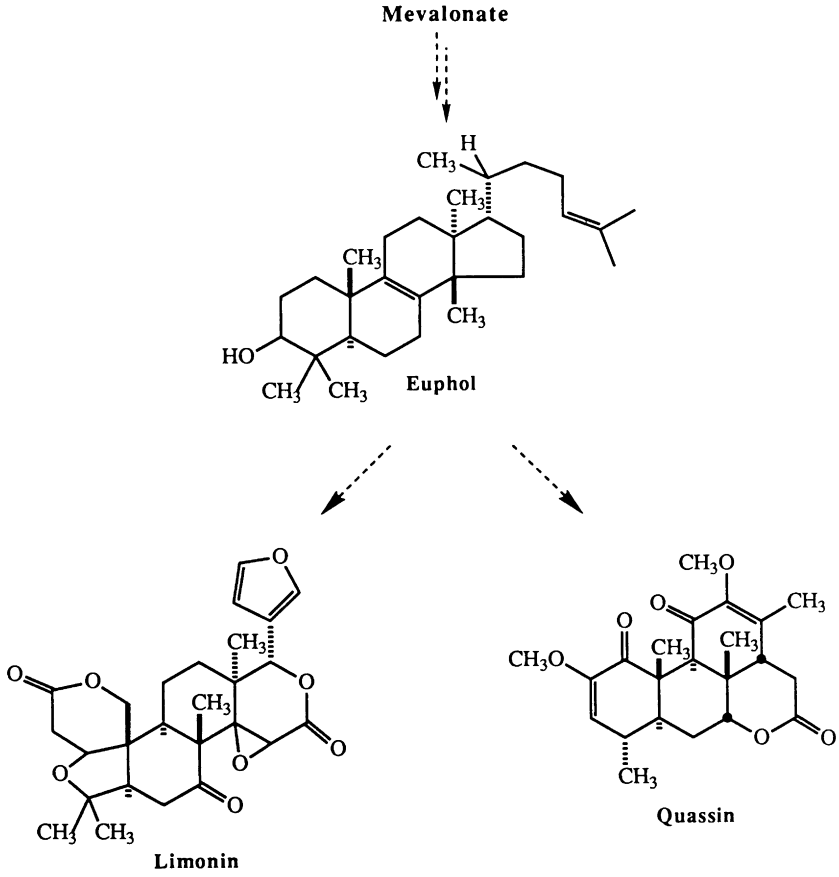
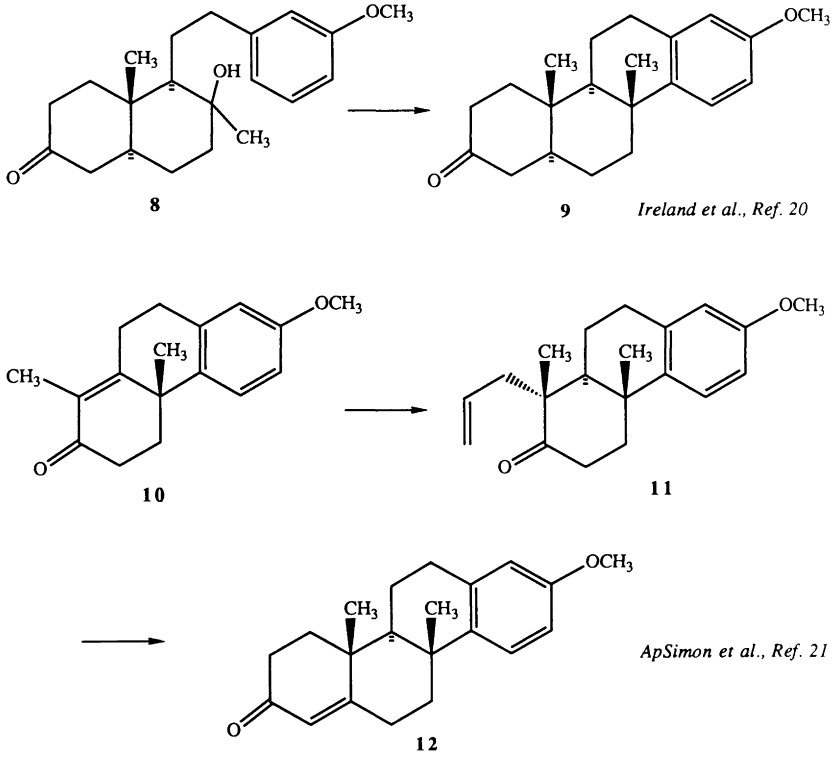


FIG. 2. Biosynthesis of Quassinoids.

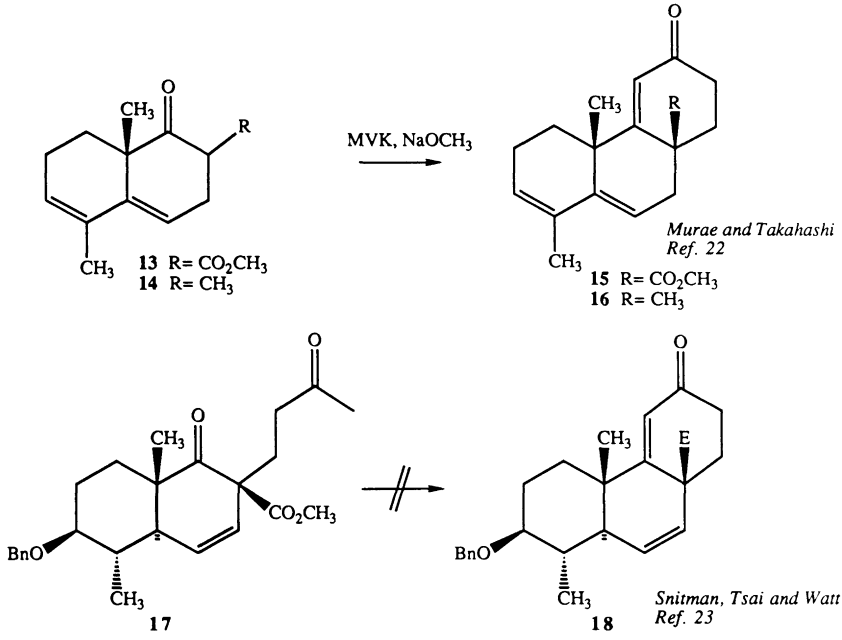
major product.[20] An alternative approach, based on similar stereochemical principles, was reported by ApSimon *et al.* in which reductive alkylation of **10** afforded **11**. Subsequent transformations produced **12** in 35% overall yield (Scheme 2).[21]

A similar strategy to construct ring-C of a tricyclic quassinoid precursor was successful[22] with **13** and **14** but in the case of **17**, the crucial aldol ring closure could not be completed,[23] suggesting that subtle conformational and stereoelectronic factors must influence the outcome of such Robinson annulations (Scheme 3).

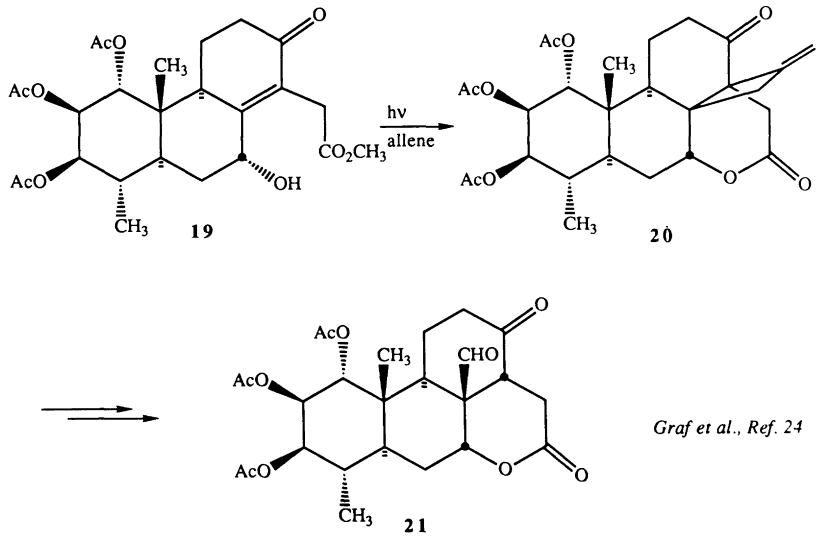


SCHEME 2

In planning for the difficult introduction of C_8 and C_{10} axial substituents we were also guided by several early model studies of Graf *et al.* in which steroids were employed as chiral synthetic precursors for quassin itself.[24] The key intermediate **19** (Scheme 4) was synthesized in approximately thirty steps from testosterone. A photochemically initiated [2 + 2] cycloaddition of allene furnished the 8β, 14β-methylenecyclobutane derivative **20** after spontaneous lactonization of the ester side chain. A degradation scheme followed this very clever ring-C construction to produce aldehyde **21** by an interesting, but unfortunately low-yielding route. In any event the advantages of partial synthesis seemed to be outweighed by the rather inefficient, multi-step reaction sequences required to transfigure the sterol ring network into that of the quassinoids.



SCHEME 3



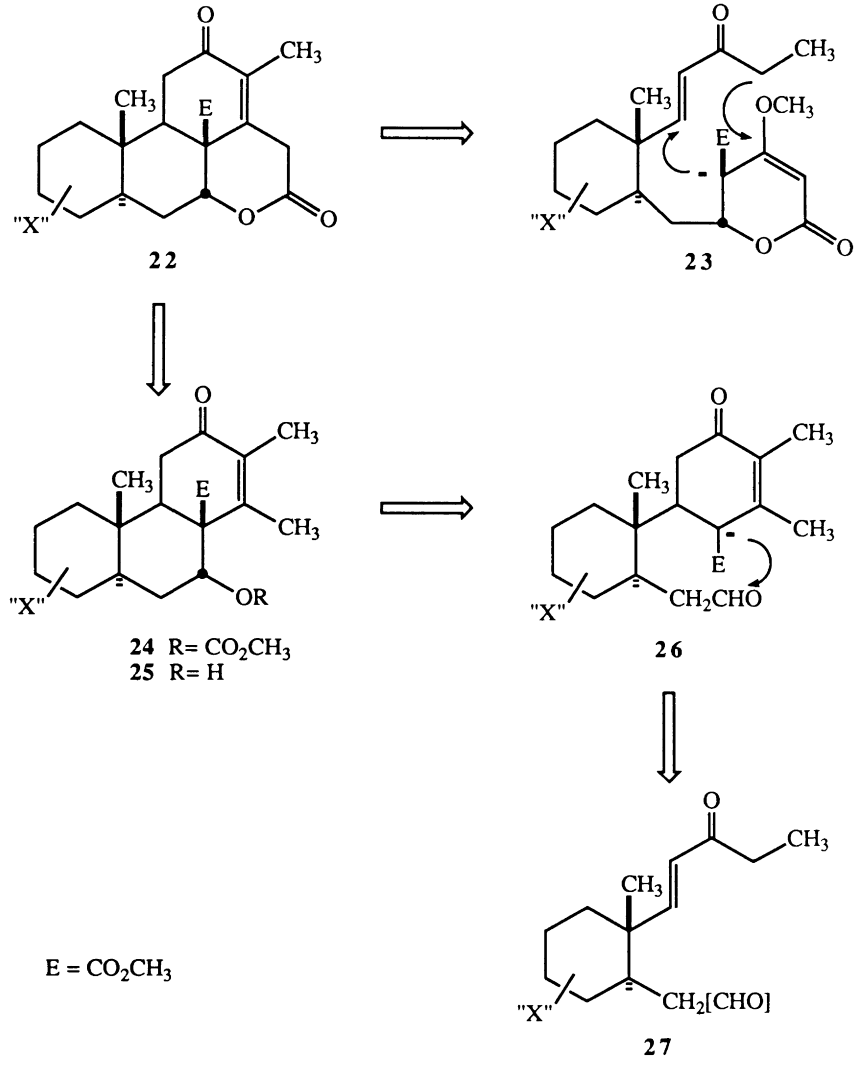
SCHEME 4

III. Overall Synthetic Strategy

The wide variety of high oxidation-state (and possibly reactive) substituent patterns found in the A-ring of most major quassinoids became another major planning issue. In the end it seemed prudent to adopt a strategy in which major stages of ring network construction, during which all the critical stereochemical relationships would be established, should be completed while ring-A remained relatively sparsely functionalized. By adorning the A-ring with one or two chemically stable but versatile functional groups capable of blossoming into highly oxidized arrays, we might leave some flexibility in the late stages of the synthesis for diverting synthetic material towards a great number of interesting metabolites. With these considerations in mind, structure **22** (Scheme 5) became a highly attractive prospective tetracyclic intermediate. An angular carboalkoxy substituent at C_8 could be useful in generating any of the three main classes of quassinoids. Moreover the rich chemistry offered by an α,β-unsaturated ketone in ring-C could provide the necessary methodology to control selective substitution, addition and/or hydroxylation reactions at either α-carbon of the carbonyl. The nature of 'X,' destined to serve as the A-ring functional handle, was undefined at this early stage of our retrosynthetic analysis, but would, needless to say, have to offer a multitude of reasonably well-precedented possibilities for accessing the targeted quassinoid.

Other, quite different, but reasonable retrosynthetic possibilities also presented themselves at the first level of analysis, however they were put aside for the moment. At least two further transforms of tetracyclic subtarget **22** were of special appeal.

First, a major simplification leading to the bicyclic intermediate **23** results by recognizing that intramolecular Michael addition of a highly stabilized vinylogous malonate anion to the well-situated α,β-enone as drawn would close to the quassinoid B-ring. Presumably in a one-pot reaction under the same basic conditions, subsequent deprotonation of the newly formed ethyl ketone and nucleophilic addition/elimination to the β-alkoxyvalerolactone moiety in **23** would then close ring-C. This Michael transform was a familiar one, since years earlier it had been used by the author as the cornerstone of a synthetic approach to the *Amaryllidaceae* alkaloid lycorine.[25] Of some concern, however, was the compatibility of the lactone ring in **23** with



SCHEME 5

the strongly basic conditions that might be required for cyclization. Furthermore, the proper stereochemical outcome of the Michael reaction required nucleophilic attack at the more hindered face of the electrophilic double bond, resulting in severe steric interactions between the angular substituents at C_8 and C_{10} as previously discussed.

An alternative transform, also outlined in Scheme 5, led to **24**. In this plan the final synthetic step would involve an intramolecular Claisen condensation between the γ-carbon of an extended enolate system and the carbonate function in **24**. Such a carbonate would be readily prepared from the corresponding C_7-alcohol in **25** (quassinoid numbering) which itself might arise by an internal aldol condensation in **26**. Moreover the nascent quassinoid C-ring in **26** could be assembled by means of the classical Hagemann's ester synthesis using acetoacetic ester and the α,β-enone **27**. Note that in this strategy, the pendant carbomethoxy group in **26**, destined to be the pivotal center for E-ring formation in the pentacyclic quassinoids, would also play an important role in enhancing the acidity of nucleophilic carbon centers responsible for B and C-ring formation as well.

Because of the potentially serious stereochemical problems associated with intermediate **23**, we decided to pursue the Claisen condensation transform (i.e. **24**) with stepwise assembly of rings from a monocyclic A-ring precursor. An enone like **27**, possessing the correct stereochemistry at C_5 and C_{10} and a masked aldehyde precursor (indicated by brackets) thus became a key synthetic objective.

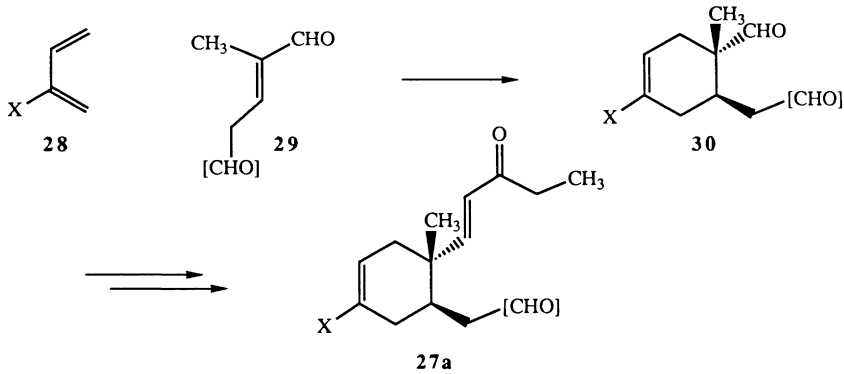
Clearly the nature of 'X' would also have to be defined at this juncture. In view of the numerous ring constructions that lay ahead, the latent functionality for ring-A must be expected to withstand relatively basic conditions, and must certainly be resistant to nucleophiles. Furthermore no unnecessary chiral centers should be created, if at all possible.

In weighing various contingency plans for 'X' it seemed inevitable that the development of a fully functionalized A ring, no matter which substitution pattern, would involve carbonyl chemistry to raise the oxidation state of the ring and, equally importantly, to introduce the requisite C_4-methyl substituent. In one of our most important early tactical decisions, we decided to defer installing the A-ring methyl group until late in the synthesis. While numerous opportunities presented themselves to reconsider this judgment, each time we reviewed the situation we concurred that the C_4-methyl group posed an unnecessary complication in the first stages of such a complex overall synthetic endeavor. It remains for the reader to determine the wisdom of our verdict on this point, although in synthetic chemistry, even hindsight can sometimes fall short of perfect 20/20 vision.

It is a common experience in synthetic chemistry that a truly optimal ordering of a synthetic route may not be possible in the planning stage, but may have to be determined experimentally. The precise information necessary for the complete and unambiguous evaluation of each step in a possible synthesis is hardly ever available.[26]

IV. The Diels–Alder Approach

The central 6-membered ring in candidates like **27** seemed like a prime candidate for assembly by means of a thermal [4 + 2] cycloaddition, a method long known for its excellent regio and stereochemical control. Use of a dienophile like **29** (Scheme 6) having one aldehyde group in protected form (brackets) should establish the correct relative configuration of C_5 and C_{10} and permit subsequent attachment of the enone comprising C_{11}–C_{13}. Furthermore, cycloaddition with a 2-substituted-1,3-butadiene such as **28** might provide an ideal 'handle' on the A-ring in the form of a functionalized alkene in **27a** for later manipulation. The possibility of choosing X to be a trimethylsilyl group was especially intriguing in the present context, since vinylsilanes are known to be versatile synthetic intermediates.[27] They are more tolerant of acid and base than other hetero-substituted alkenes such as enamines, enol ethers or enol esters, and can readily be converted into a variety of commonly used functional groups. Moreover vinylsilanes have been used as versatile precursors of aldehydes or ketones, and methods are known for installing the new carbonyl at either the silylated or nonsilylated end of the double bond.[28]



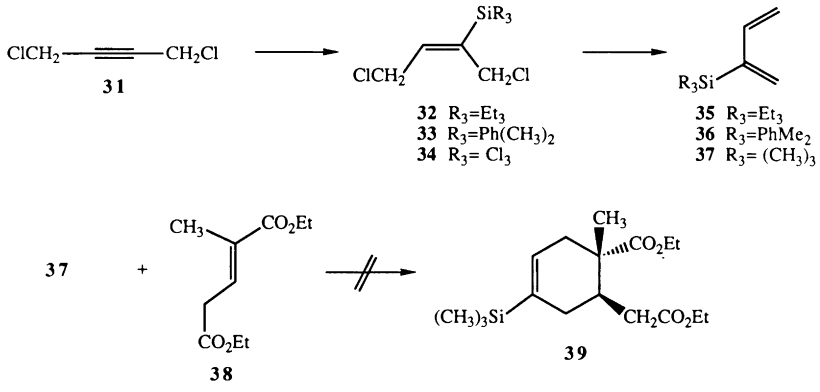
SCHEME 6

The requisite diene, 2-trimethylsilyl-1,3-butadiene, was unknown at the outset of our work. Other than an uncharacterized mixture of 1- and 2-silylated butadienes which was reported in 1960,[29] the only closely related compound known at the time was 3-methyl-2-triethylsilyl-1,3-butadiene.[30] No Diels–Alder reactions were mentioned in either report.[31] On the other hand, 1-trialkylsilylbutadienes were well-known at the time and participated in [4 + 2] cycloadditions to afford allylsilanes.[32–35]

In 1978 Douglas Batt, then a graduate student at Cornell, developed a versatile and practical synthesis of 2-silylated butadienes by the simple route shown in Scheme 7. Hydrosilylation of commercially available 1,4-dichloro-2-butyne **31** with an equimolar amount of triethylsilane catalyzed by H_2PtCl_2 afforded **32** in essentially quantitative yield. Reductive dehalogenation of the crude product using zinc powder gave diene **35** in 66% yield. In similar fashion, hydrosilylation of **31** with phenyldimethylsilane provided **33** and thence **36**.

The synthesis of 2-trimethylsilylbutadiene **37** required $(CH_3)_3SiH$ for the hydrosilylation step. However, the inconvenience of using pressurized reaction vessels when working with this gaseous silane led us to perform the hydrosilylation of **31** with trichlorosilane, a much less expensive liquid. When the initial adduct **34** was treated with excess methylmagnesium bromide, simultaneous methylation and reductive dechlorination led directly to **37** in 43% overall yield.[36]

Diels–Alder reactions of silyldienes **35–37** occurred smoothly with a variety of simple dienophiles. As expected, unsymmetrical dienophiles like methacrolein or ethyl acrylate produced mixtures of

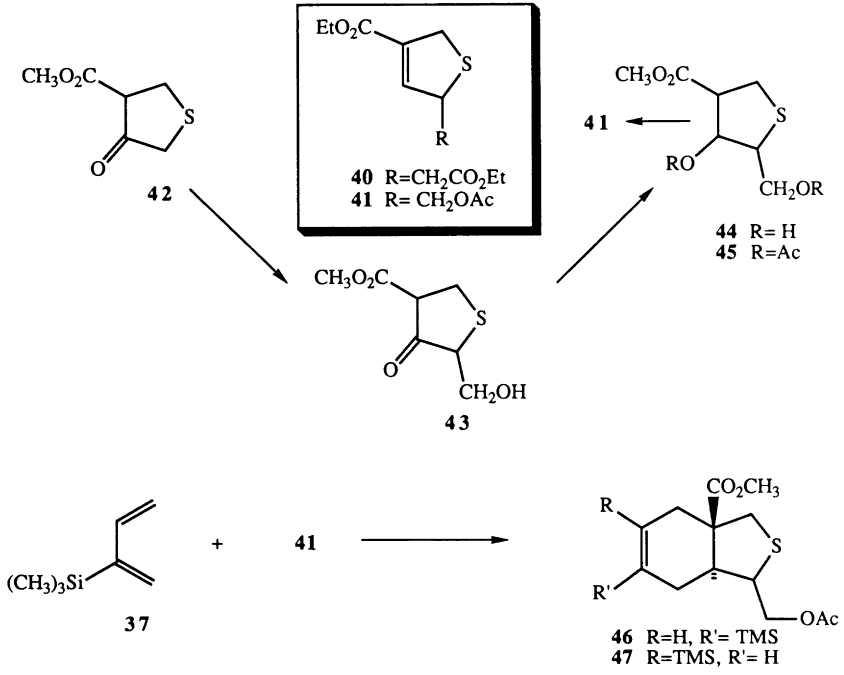


SCHEME 7

regioisomers, although regioselectivity was somewhat better than that reported for 1-trimethylsilyl-1,3-butadiene.[32–35] Lewis acid catalysts not only accelerated the reaction rate, but also enhanced the regioselectivity.

Next, the cycloaddition of **37** was studied with known diester **38**, which was chosen as a reasonable model for dienophiles like **29** (Scheme 6). Unfortunately **38** failed to undergo the desired Diels–Alder reaction in a preparatively useful manner. Even in the presence of $BF_3 \cdot Et_2O$ at 180°C a 2 : 1 mixture of adducts was obtained and in very poor yield. Moreover the Z-isomer of **38** was also recovered among the products, indicating that the dienophile's stereochemistry had been significantly eroded. Diester **38** also failed to react with 2-ethoxybutadiene. Apparently steric congestion about the trisubstituted alkene presented a formidable barrier to approach by the diene.

Several years earlier when confronted with a similar problem, Stork and Stotter designed diester **40** containing a sulfur bridge to restrict rotation of the flexible substituent and reduce crowding about the



SCHEME 8

dienophile (Scheme 8).[37] Later, Raney nickel reduction liberated the desired substituents. For the present synthesis we required **41** in which the differing oxidation states would later permit selective unmasking of aldehydes. The dianion of known[38] ketoester **42** was treated with gaseous formaldehyde to afford hydroxymethyl derivative **43**. Reduction with $NaBH_4$, then acetylation of **44** gave **45**. Treatment of **45** with DBU brought about elimination of acetic acid and thus furnished **41** in about 30% overall yield.

Cycloaddition of silyldiene **37** did occur, albeit sluggishly, with **41**. However, eight equivalents of diene at 150°C were required to obtain a 6 : 1 ratio of adducts **46 : 47** in 63% yield. The nontrivial synthesis of diene **41** coupled with modest yields in the key cycloaddition, especially at such an early synthetic stage, diminished the allure of this approach to the quassinoid A-ring. The Diels–Alder strategy was therefore abandoned in favor of a simpler, more efficient alternative.

V. The Conjugate Addition Approach

Kinetic conjugate additions of carbanions to 3,4-disubstituted-2-cyclohexenones[39] occur with high *trans*-stereoselectivity because the C_4-substituent adopts the pseudoaxial orientation (Figure 3) in order to avoid a near-eclipsing interaction with the C_3-group ($A_{1,2}$-strain).[40] Such excellent stereochemical control is obtainable with organocuprates, and had been exploited in numerous prostaglandin total syntheses.[41] The versatility of functionalized vinylic cuprates as synthetic reagents suggested a highly convergent approach to a key A-ring intermediate (Scheme 9). Michael acceptor **50** was prepared using the Stork-Danheiser method.[42] Thus enol ether **48** was kinetically deprotonated and alkylated with prenyl bromide to afford **49**. Without purification, **49** was treated with excess methyllithium and the product worked up with acid to produce α,β-enone **50** in excellent yield.

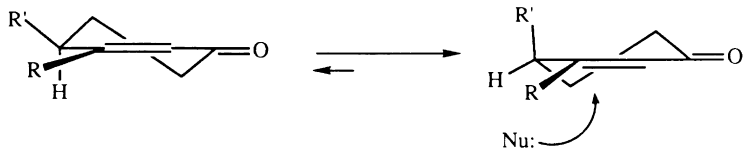
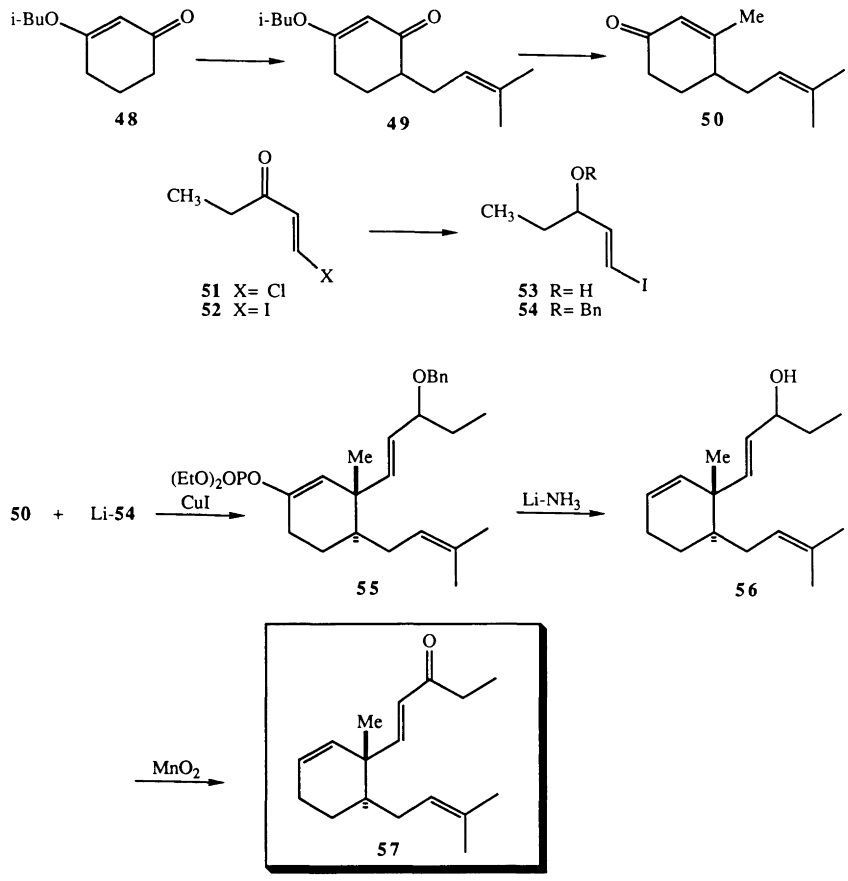


FIG. 3. Conformational Preference of 3,4-Disubstituted Cyclohexenones.



SCHEME 9

To make the cuprate precursor **54**, halogen exchange using NaI-acetone transformed chloroenone **51**[43] into iodide **52**. This ketone was then reduced ($NaBH_4$) to alcohol **53** and protected as its benzyl ether **54**. One-hundred-gram batches of **54** could easily be prepared in this fashion. Metal-halogen exchange (*n*-BuLi, −78°C) occurred smoothly to give the corresponding vinylic organolithium species.

When enone **50** was treated the simple cuprate (R_2CuLi) derived from **54**, and the intermediate enolate trapped with diethylchlorophosphate, excellent yields of the desired enol phosphate **55** were realized. Unfortunately, use of such homocuprates wastes one of the precious organic groups. This widely recognized shortcoming has led

to the development of many "mixed" cuprates bearing one inexpensive, nontransferrable ligand (e.g. alkoxide, thioalkoxide, cyanide). Contemporary with our own experiments in this area, Suzuki and Noyori and coworkers published a procedure for conjugate addition to enones using mono-organocopper reagents RCu in the presence of an excess of solubilizing ligand like tributylphosphine.[44] Indeed, when **50** was lithiated and combined with one equivalent of CuI-Bu_3P, then additional Bu_3P (1.6 equivalents) was added, the above mentioned conjugate addition-enolate trapping procedure on **54** led to adduct **55** in 60% yield.

Upon further reflection, it occurred to us that the intermediate enolate was probably a highly covalent, poorly soluble copper species, and thus unlikely to react well with diethylchlorophosphate. In fact the Noyori team noted that their intermediates underwent poor aldol condensations with benzaldehyde. We speculated that by adding one extra equivalent of *n*-BuLi to the enolate species resulting from conjugate addition, transmetallation of lithium for copper might form a more reactive enolate for the trapping stage. In the event we were gratified to see the overall yields of **55** rise to 85–90% routinely in 80–100 gram runs.

Debenzylation and reductive deoxygenation[45] of **55** to the olefinic alcohol **56** was achieved using lithium in liquid ammonia containing *t*-butyl alcohol, although a few percent of the corresponding deoxy product (not shown) resulting from allylic C–O cleavage could not be suppressed. Oxidation of alcohol **56** with MnO_2 or (better) pyridinium dichromate produced the targeted intermediate **57** in 75% yield from **55**.

In summary, a viable candidate for hypothetical target **27** outlined in the retrosynthetic analysis in Scheme 5 was obtained. Enone **57**, incorporating 14 of the 20 carbons present in most quassinoids, was prepared in five steps and 50–55% overall yield. Structural assignments for the *trans*-enone ($J = 16$ Hz) and the $\Delta^{1,2}$ alkene (clean ABX_2 spin system) were secured by NMR spectroscopy, while the assignment of relative stereochemistry at C_5 and C_{10} relied mostly on several precedents for the cuprate addition. Enone **57** thus incorporated a prenyl group as progenitor of a C_7-aldehyde, with the view that selective ozonolysis of the trisubstituted alkene ought to be possible under very mild conditions. The $\Delta^{1,2}$ alkene produced by reductive deoxygenation of the enol phosphate was to become a stable

yet useful handle ('X' in **27**) for elaborating whatever highly oxidized quassinoid A-ring pattern we might choose. With substantial quantities of **55** in hand, attention was focused on the construction of rings B and C leading to a tricyclic intermediate like **25**.

VI. Trouble at the Tricyclic Stage

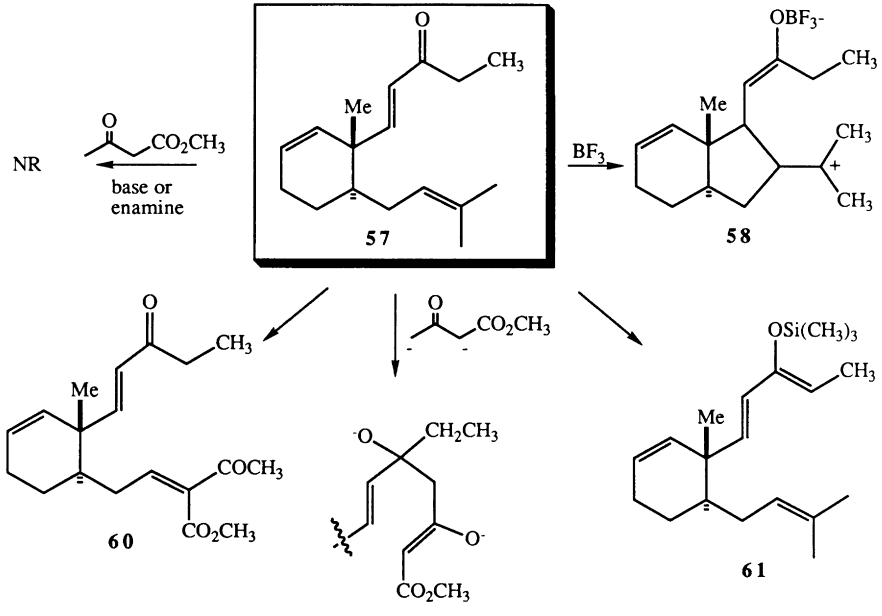
In the retrosynthetic analysis of Scheme 5, we planned to construct ring-C in **26** using a Hagemann's ester synthesis, *i.e.* conjugate addition/aldol condensation between methyl acetoacetate and **57** (Scheme 10). Unfortunately no reaction could be induced between these two partners using a variety of bases, including the pyrrolidine enamine method. The Michael addition also failed under acidic conditions. In the presence of $BF_3 \cdot Et_2O$, the enone and prenyl groups of **57** rapidly disappeared, suggesting the intervention of a cationic cyclization to **58** and products derived therefrom.[46]

In light of the failure of the Hagemann method, several quite different alternative approaches were explored of which three are noteworthy. In one variation, enone **57** was treated with the dianion of methyl acetoacetate,[47] hoping that an initial 1,2-addition product **59** (Scheme 10) might rearrange to the desired, more stable 1,4-adduct by the well-precedented oxy-Cope process. Unfortunately, however, no adducts were formed and **57** (probably just deprotonated by the dianion) was recovered in high yield.

Selective ozonolysis of **57** cleanly gave an aldehyde which was condensed with methyl acetoacetate under Knoevenagel conditions to make ketoester **60** (Scheme 10) as a mixture of geometric isomers in 60% yield. However, treatment of **60** with NaH (expected to generate an acetoacetate anion in close proximity to the electrophilic enone) led not to intramolecular conjugate addition, but instead to the deconjugated β,γ-unsaturated isomer of **60** (not shown).

In a third plan, Z-enol silyl ether **61** was prepared from **57** and subjected to a Diels–Alder reaction with methyl tetrolate. However no cycloaddition was detected after prolonged heating at 170°C.

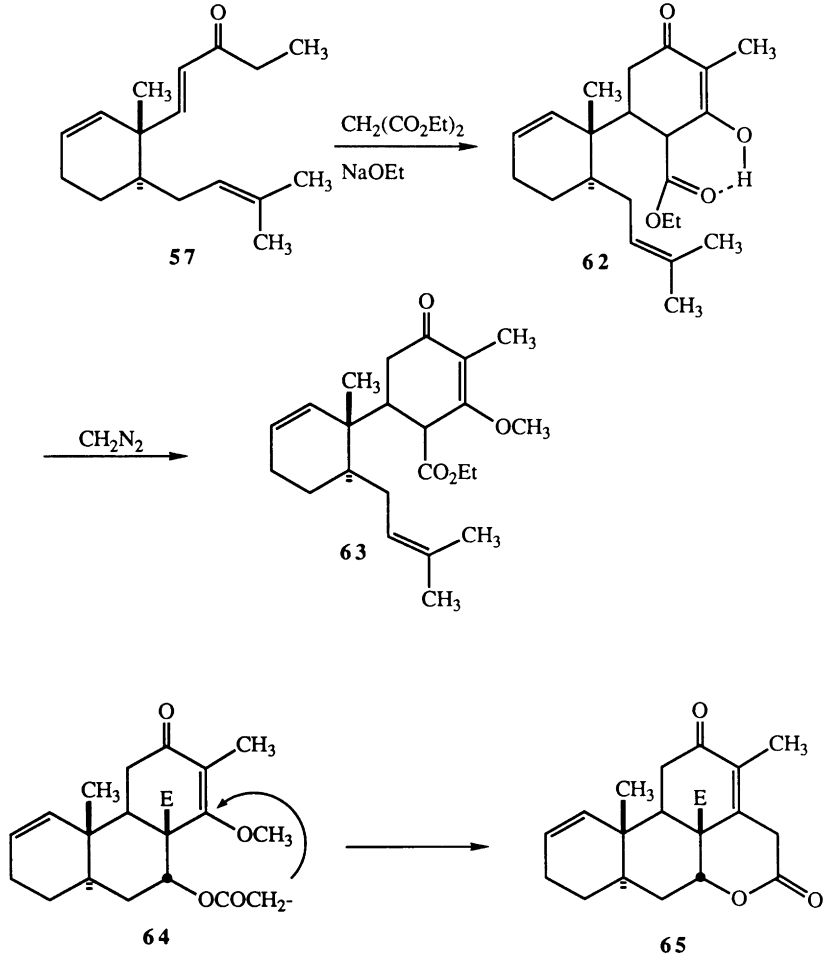
At this point, the reluctance of enone **57** to undergo β-alkylation seemed to have derailed our plan for ring-C construction. However in surprising contrast to methyl acetoacetate, diethyl malonate underwent a smooth conjugate addition *and cyclization* with **57** (Vorländer



SCHEME 10

synthesis) thus providing enolic diketoester **62** (Scheme 11) as a mixture of stereoisomers in nearly quantitative yield. Whether the enhanced nucleophilicity was due to the greater basicity[48] or higher carbanionic charge density of the malonate was unclear, although it might also be true that a favorable Claisen cyclization siphoned off the initial reversibly-formed Michael addition product in irreversible fashion, since **62** formed a very stable anion under the reaction conditions. Upon reaction with CH_2N_2, **62** formed a mixture of enol ethers **63**, which was separable into two groups of diastereomers (85 : 15) by careful chromatography. A total of six products were detected by HPLC, although only four were expected from the creation of two new chiral centers, indicating that O-methylation was not totally specific for the C_{14} oxygen. Nevertheless, *one diastereomer comprised two-thirds of the product!*

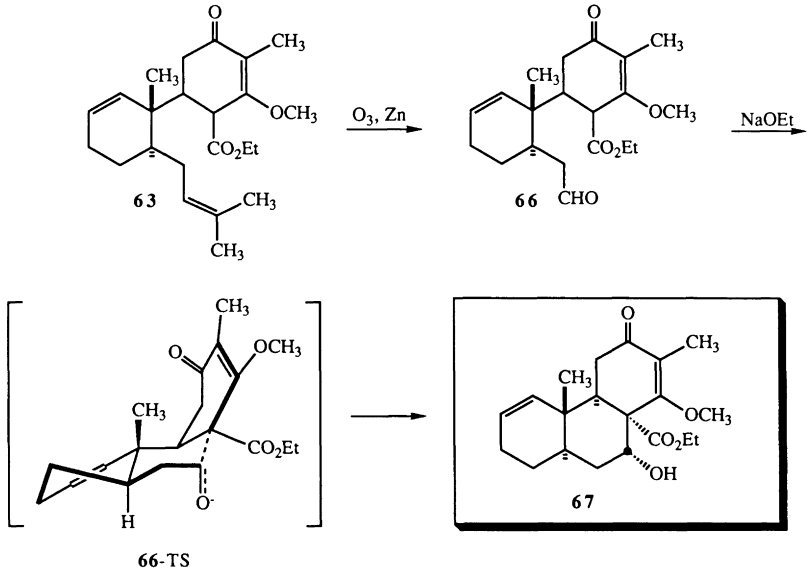
Despite the missing methyl which would comprise C_{15}, **63** possessed considerable potential as a key quassinoid intermediate. It bore a close resemblance to **26** in the retrosynthetic plan of Scheme 5 and



SCHEME 11

thus might be easily induced to close the B-ring. In one scenario, the missing carbon might later be inserted by a conjugate substitution reaction of the β-methoxyketone in **63**. Alternatively a C_{15} nucleophile might be delivered intramolecularly at the tricyclic stage (e.g **64**) from an acetate unit linked at the C_7-hydroxyl, thus converting ABC intermediate **64** to the ABCD tetracyclic lactone **65**.

Ozonolysis of **63** (as the unresolved stereoisomeric mixture) using a Rubin Ozonizer[49] followed by Zn-HOAc reduction gave a mixture of aldehydes **66** (Scheme 12) in 48% yield. The selectivity here was



SCHEME 12

poorer than with **57** because of competing attack at the electron-rich tetrasubstituted enone. However when **66** was treated with NaOEt/EtOH at room temperature, a mixture of tricyclic alcohols was formed in excellent yield. HPLC analysis of the oily semisolid product indicated that one stereoisomer comprised 50% of the mixture. Slow evaporative crystallization from CH_2Cl_2/hexane gave sharp-melting needles in 40–50% yield. While its 300 MHz ^1H NMR spectrum was well-resolved, the key stereochemistry at C_8 and C_9 could not be ascertained. From x-ray diffraction analysis the crystalline material was assigned structure **67**. Ironically, all the new chiral centers except for C_8 in **67** possessed the correct relative stereochemical configuration for pentacyclic quassinoids.

The preferred formation of the *trans-anti-cis* product **67**, however disappointing, could in retrospect be explained on steric grounds. Formation of the desired product having the β-carboethoxy group would give rise to a severe 1,3-diaxial interaction with the C_{10}-methyl substituent. In fact the transition state leading to the observed product (**66**-TS) appears to create two such interactions, with C_{12} and C_{14}, however the ease with which the relatively flat sp^2-hybridized C-ring can tilt away must dramatically alleviate steric compression.

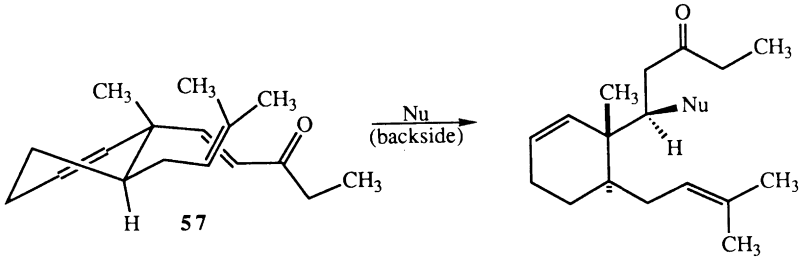


FIG. 4. Preferred Conformation of Enone 57 for Michael Additions.

Upon further reflection, two other facts gleaned from the crystal structure of **67** were most heartening. First, the *trans*-A,B-ring fusion had successfully been installed using the cuprate addition strategy. Moreover the correct configuration of C_9 observed in the major tricyclic product indicated that some measure of the desired stereoselectivity had been achieved in Michael additions to enone **57**. Assuming a preferred conformation in which the prenyl chain obstructed the approach of nucleophiles to the 'front' face of the enone **57**, attack by malonate from the 'rear' would result in the proper relative configuration of C_9 (Figure 4).

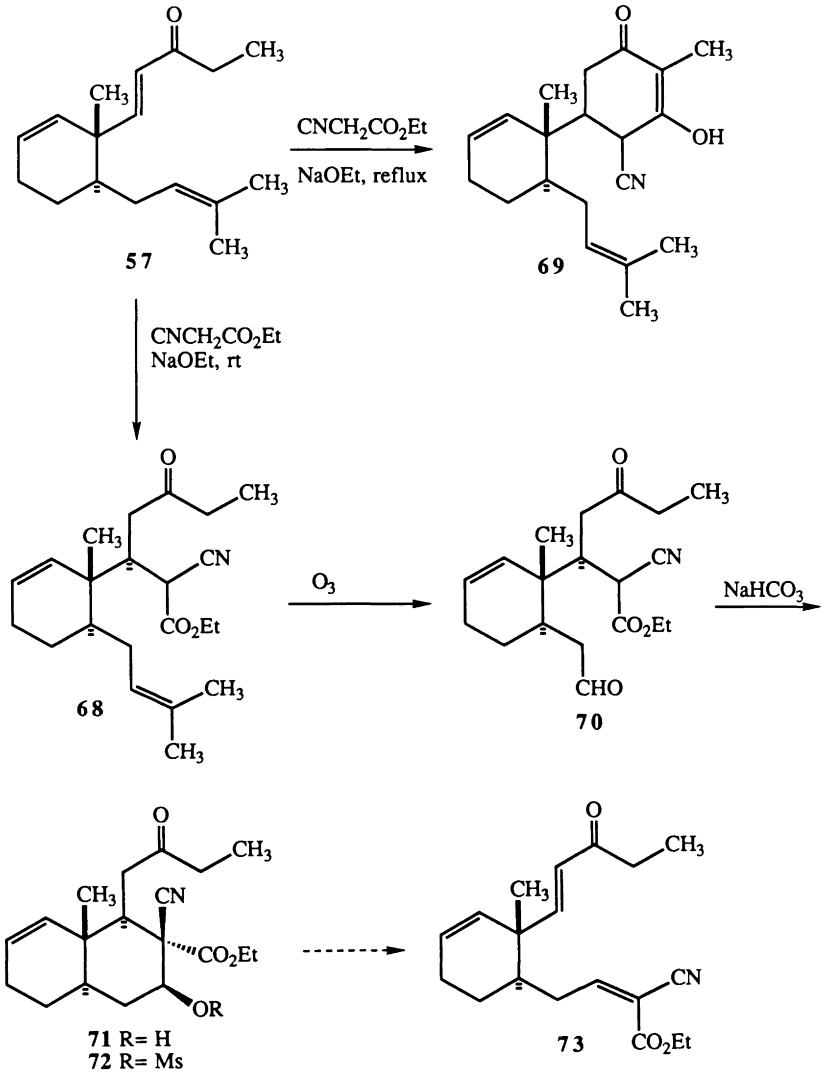
VII. A Tetracyclic Route Triumphs

If the stereochemistry of cyclization of **66** were largely governed by interactions of the bulky carboethoxy group, then replacing that ester with a sterically less demanding functional equivalent should improve prospects for success. The choice of a nitrile group seemed obvious, since it would similarly activate C_8 for B-ring closure by the aldol reaction, and would also serve as a viable precursor of a C_8 methyl or hydroxymethyl substituent. Moreover the nitrile (A = 0.2), being more slender than carboethoxy (A = 1.2),[50] should offer less steric resistance to the desired mode of cyclization.

Surprisingly, reaction of **57** with ethyl cyanoacetate under conditions which gave excellent yields of **63** (EtOH, NaOEt, room temperature) furnished only the simple Michael adduct **68** as an oil in 70% yield (Scheme 13). Apparently proton transfer to form the very stable product cyanoacetate salt greatly retarded ring-C formation by Claisen condensation. Although **69** was eventually obtained using

reflux conditions, the ready formation of **68** suggested an alternative strategy for network assembly in which ring-B would be closed *before* ring-C, thus simplifying the stereochemical factors influencing diaxial C_8 and C_{10} substituents.

NMR analysis of the oily sample of **68** indicated two diastereomers, however, the major isomer (45% overall yield) crystallized from

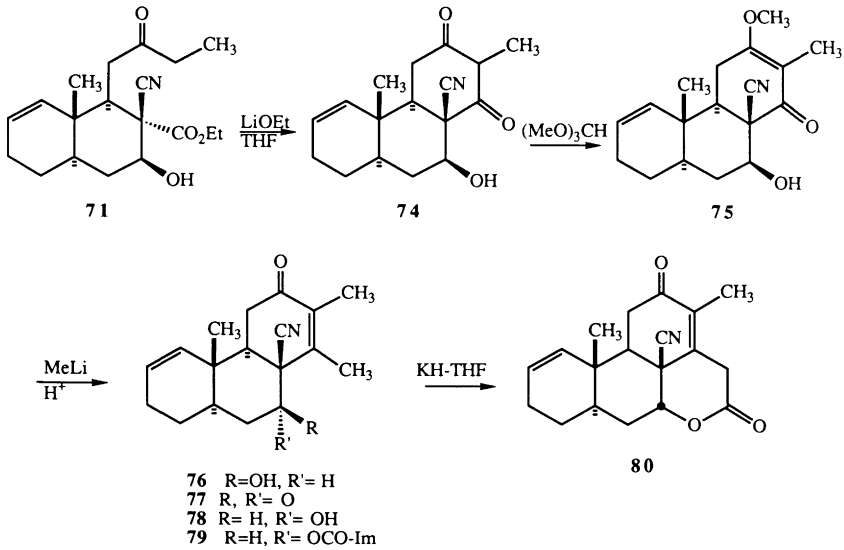


SCHEME 13

ethanol-water and was thus obtained pure. Selective ozonolysis of the prenyl group gave aldehyde **70** which could be cyclized during work-up in the presence of excess $NaHCO_3$ to a single bicyclic alcohol **71** in 86% yield. Its ^1H NMR spectrum revealed a slight deshielding of the C_{10} methyl group, consistent with an axial nitrile (an ester group would have shifted the methyl signal upfield)[51] and the equatorial C_7 hyroxyl stereochemistry was apparent from vicinal J-values in the corresponding acetate.

Attempts to create an axial OH group at C_7 in **71** by nucleophilic displacements on mesylate **72** failed with a variety of oxgyen nucleophiles, however the interesting fragmentation product **73** was detected. This triene most likely arose via a *trans*-antiperiplanar transition state, providing good indirect evidence for the equatorial orientation of the ketobutyl moiety in **71** (i.e. the correct configuration at C_9). We therefore decided to defer further operations on the B-ring until an operational route to a tricyclic ABC quassinoid intermediate could be established.

In fact, cyclization of **71** to the tricyclic dione **74** was readily achieved using lithium ethoxide at room temperature (Scheme 14). Since the highly enolic product was extremely polar and difficult to



76 R=OH, R'= H
77 R, R'= O
78 R= H, R'= OH
79 R=H, R'= OCO-Im

SCHEME 14

purify, **74** was converted directly to enol ether **75** which was obtained in 95% yield for the two steps. Although two regioisomeric enol ethers are in principle possible, only structure **75** explained the observed long-range coupling between protons at C_{11} and the C_{13} methyl hydrogens ($J = 1.5$ Hz).

Thus, our newly-evolved cyanoacetate strategy took a most serendipitous turn in the form of a modified A→AB→ABC strategy for ring assembly. Both ring-forming steps proved elegant in their simplicity. Notably closure of ring-C capitalized on the reversibility of nucleophilic additions to nitriles so as to direct cyclization via enolate attack at the carboethoxy group. The resulting Claisen condensation was then made irreversible by the subsequent deprotonation of **74**. If the stereochemistry at C_7 could be corrected, then the promise of completing a tetracyclic network as depicted in **64** → **65** (Scheme 11) might then be realized.

Like **71** before it, alcohol **75** resisted all attempts at stereochemical inversion. To circumvent this problem, **75** was treated with two equivalents of methyllithium and after acidic hydrolysis, the α,β-dimethylated enone **76** was obtained in excellent yield. Again, however, inversion of stereochemistry at C_7 by either the Mitsunobu reaction or mesylate displacement failed. Fortunately **76** was oxidized in good yield (albeit sluggishly) with excess Jones reagent, thus affording diketone **77**. Exhaustive reduction of **77** with diisobutylaluminum hydride (DIBAL) gave the expected diaxial diol (not shown) as judged by ^1H NMR coupling constants. Since we wished to preserve the ring-C carbonyl for future manipulations, the crude diol was worked up with MnO_2 to reoxidize the allylic alcohol and thus furnish hydroxyenone **78**. With **78** in hand, the stage was set for closure of the ring-D lactone by an intramolecular acylation. Carbonyldiimidazole combined with **78** in boiling THF to generate acylimidazole **79**. Using excess KH as base, the long sought-after tetracyclic lactone **80** was obtained in yields exceeding 80%. Overall the successful synthetic sequence to **80** carried out by Douglas Batt for his doctoral thesis involved fourteen steps from the enol ether of cyclohexane-1,3-dione **48**. Moreover the experimental execution paralleled rather closely our original retrosynthetic analysis outlined in Scheme 5. All of the essential elements needed in the projected key intermediate structure **22** were eventually realized in **80**: (i) an appropriate substituent at C_8 for pentacyclic formation, (ii) a C-ring enone for completing that ring's

functional array, and (iii) a stable yet versatile progenitor for the highly oxidized A-rings of targeted quassinoids. With ample supplies of tetracyclic material in hand, we designated the pentacyclic quassinoids quassimarin (**6**) and simalikalactone D (**7**) (Scheme 1) as our top-priority targets. These then became the immediate synthetic objectives of postdoctoral fellows Dr. Norio Takamura and Dr. Brian McKittrick.

VIII. Onward to Pentacyclics

Before we could close the fifth ring and complete the arrangement of C-ring *trans*-diol in these C_{13}-bridged quassinoids, one more critical stereocenter (C_{14}) at the C/D ring junction had to be locked in. Inspection of Dreiding models of **80** indicated that catalytic hydrogenation of the C-ring enone was unlikely to be selective. Moreover dissolving metal reductions of **80** might expel cyanide, and were further complicated by the enhanced acidity at C_{15} arising from its vinylogous ketolactone substructure. Some method of 'relaying' chirality to the remote location at C_{14} would be needed.

The important clue that eventually led to a solution came from the hydride reduction of **77** (Scheme 14). Ordinarily the C-ring allylic alcohol which formed was reoxidized during workup to afford **78**; however, closer inspection of its ^{1}H NMR spectrum revealed that the transient C_{12}-OH group was exclusively pseudoequatorial. That meant the hydroxyl was pointing in the same direction from which hydrogen atoms must be delivered to the enone in **80** (Figure 5).

Although the stereocontrolled hydrogenation of allylic alcohols using homogeneous iridium catalysts had not yet been invented, the $NaBH_3CN$-HOAc reduction of tosylhydrazones of α,β-enones seemed like an ideal solution to our problem.[52] This process was known to

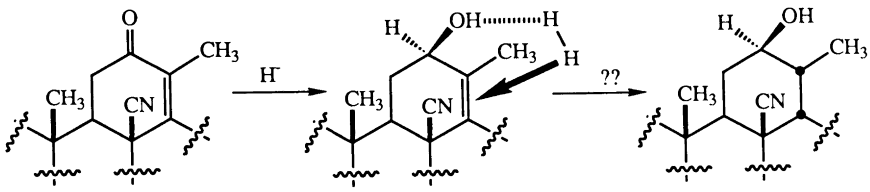
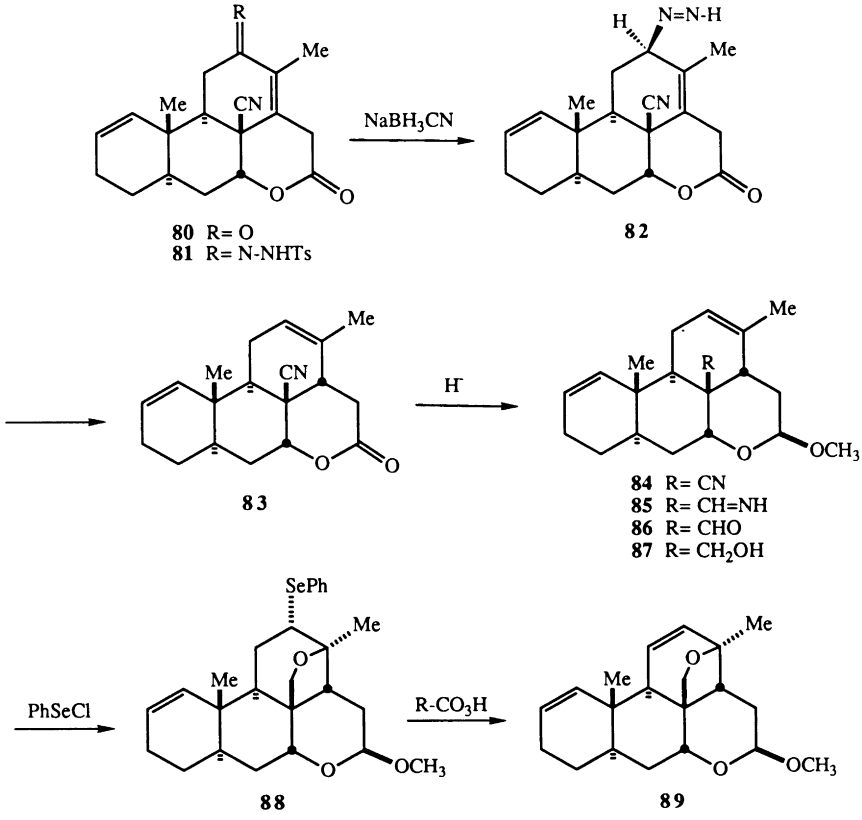


FIG. 5. Reduction of the C-ring Enone in 80 by Stereochemical Relay?

involve an initial 1,2-reduction and tosyl elimination. In the case of tosylhydrazone **81**, the resulting azo compound **82** then underwent the expected suprafacial 1,5-hydrogen shift with loss of N_2, to form rearranged trisubstituted $\Delta^{12,13}$ alkene **83** (55% yield from **80**) having the correct stereochemistry at C_{14}, as depicted in Scheme 15. Besides solving the stereochemical problem at C_{14}, this marvelous reductive rearrangement introduced a highly useful alkene for constructing the C_{13}-bridged E-ring tetrahydrofuran.

First, however, the angular nitrile at C_8 had to be reduced, and it was also evident that the D-ring lactone carbonyl would need some form of protection for most of the rest of the synthesis. Grieco, in his elegant synthesis of quassin,[53] found the acetal protecting group



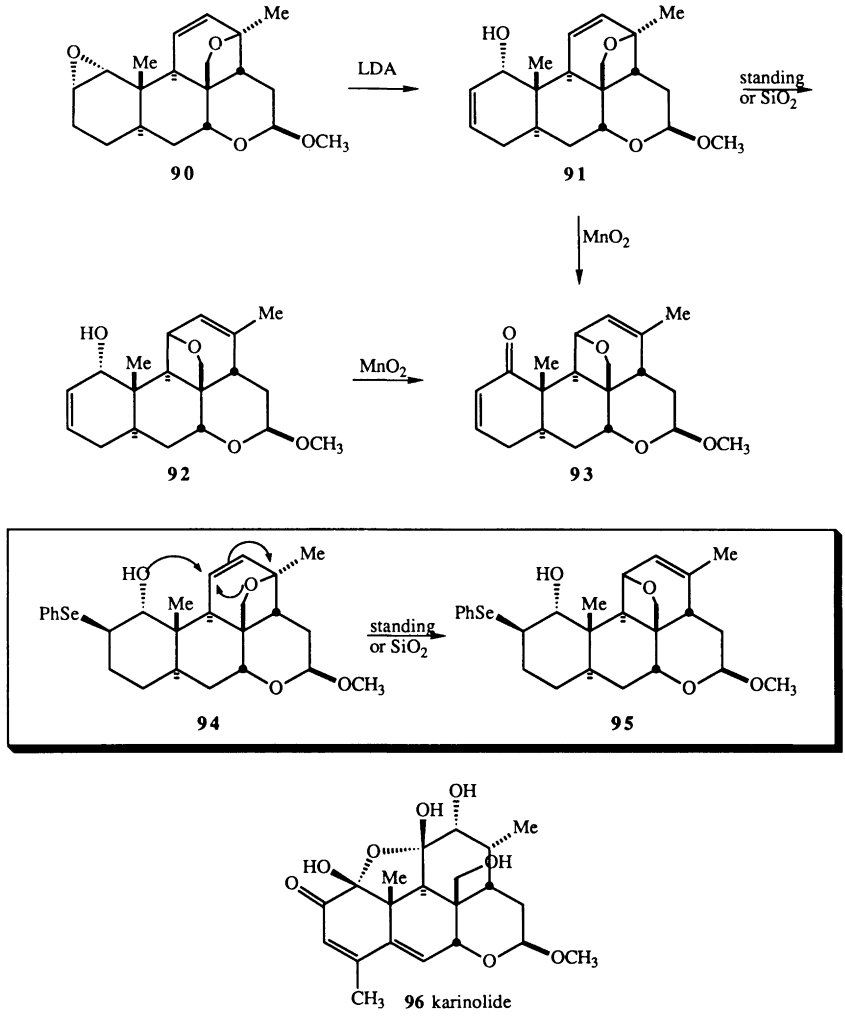
SCHEME 15

to be useful. Therefore, dienyllactone **83** was reduced with DIBAL (CH_3OH workup) to **84**, which set the stage for stepwise hydride additions to the hindered nitrile group. After some experimentation, this process could be streamlined into a one-pot reaction as follows. DIBAL reduction of **84** in toluene furnished imine **85** which was not isolated, but hydrolyzed *in situ* with HOAc-H_2O to aldehyde **86**. Enough CH_3OH was then added to homogenize the resulting aqueous toluene mixture, whereupon excess $NaBH_4$ was introduced to complete the reduction to alcohol **87**.

Hydroxydiene **87** proved to be an ideal candidate for ring closure using Nicolaou's method of selenoetherification.[54] Cyclization (PhSeCl, CH_2Cl_2) took place rapidly to furnish selenoether **88** which upon treatment with one equivalent of *m*-chloroperoxybenzoic acid (MCPBA) underwent oxidative elimination to diene **89** (62% overall). Fortunately at this stage, ^1H NMR analysis confirmed our expectations that the reduction of tosylhydrazone **81** had correctly configured C_{14}, since long-range coupling was observed between the C_{12} and C_{14} hydrogens. Such W-coupling would only occur if ring-D were diaxially fused to the ABC carbocyclic system.

At this point in the synthesis several decisions regarding the functionalization of rings A and C were dictated by the relative reactivity of alkenes in diene **89**. Molecular models clearly indicated the disubstituted ring-A alkene was less hindered, and in fact **89** could be regioselectively and stereoselectively monoepoxidized with MCPBA to **90** (Scheme 16). Rearrangement of the oxirane using either *n*-butyllithium or lithium diisopropylamide (LDA) transformed **90** into allylic alcohol **91**. *This substance proved rather unstable, and prolonged standing at room temperature or attempted chromatography on silica gel caused it to isomerize quite unexpectedly and virtually completely to the C_{11}-bridged quassinoid* **92**! Oxidation of either **91** or **92** using activated manganese dioxide furnished enone **93** in excellent yield, a pentacyclic quassinoid possessing two of the three necessary requirements for antileukemic or antineoplastic activity.

Our serendipitous discovery of this novel isomerization clearly warranted further study, since for the first time both structural classes of C_{11} and C_{13} bridging ethers became synthetically accessible from a common intermediate. Neither diene **89** nor epoxyalkene **90** showed any tendency to rearrange; however, hydroxyselenide **94** also isomerized quantitatively to the C_{11}-bridged **95**, thus implicating some sort of anchimeric assistance provided by the C_1 α-hydroxyl group. While



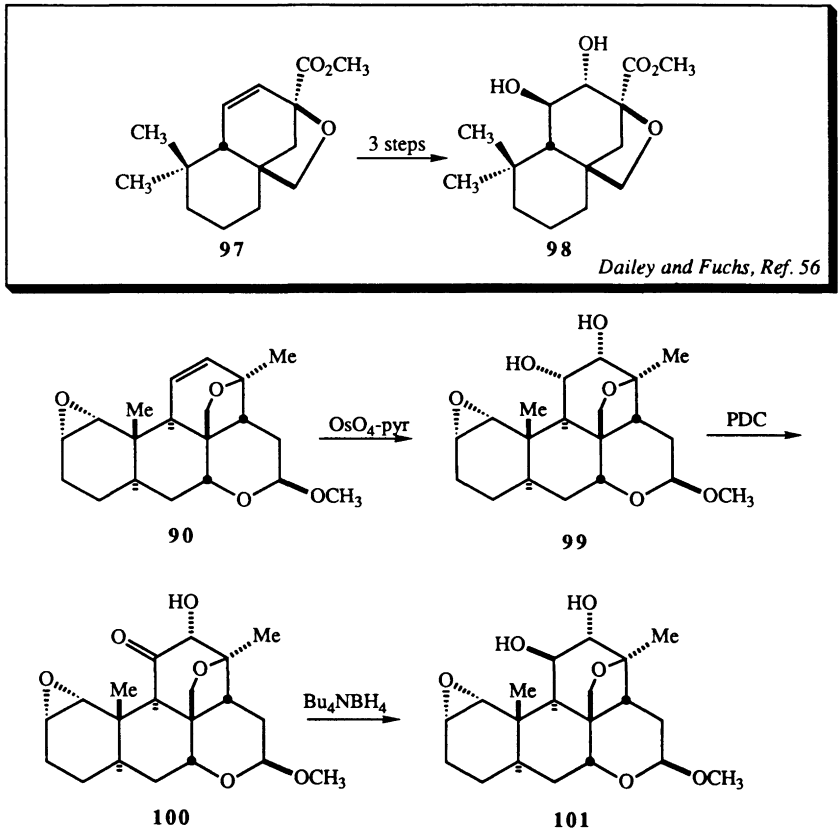
SCHEME 16

we were unaware of any naturally occurring quassinoid capable of similar rearrangement, our attention was drawn to the structure of karinolide **96**, whose internal mixed bis-hemiacetal[55] provided solid support for the potential nucleophilic attack by an axial OH group at C_1 on the π-system of a $\Delta^{11,12}$ alkene.

Now the reader can clearly see more and more key strategic decisions falling into place as the unusual chemistry of our system unfolded. With research on C_{13}-bridged structures **6** and **7** our top

priority, we decided to backtrack to epoxyalkene **90**. By first introducing the C_{11}–C_{12}-*trans*-diol functionality, we reasoned we could preclude any unwanted rearrangements of the bridging ether and at the same time complete the assembly of quassimarin's more stable C-ring, thus leaving the highly oxidized A-ring for last.

In undertaking the ring-C endeavor we were fortunate to be able to apply an extremely practical and efficient synthetic sequence developed by Professor P. L. Fuchs and his group at Purdue University for transforming alkene **97** into **98**, a rather good tricyclic BCE model system for the quassinoids (Scheme 17).[56] Thus, osmylation of epoxyalkene **90** from the less-hindered α-face afforded *cis*-diol **99** in 88% yield. Selective oxidation of the equatorial alcohol could be achieved



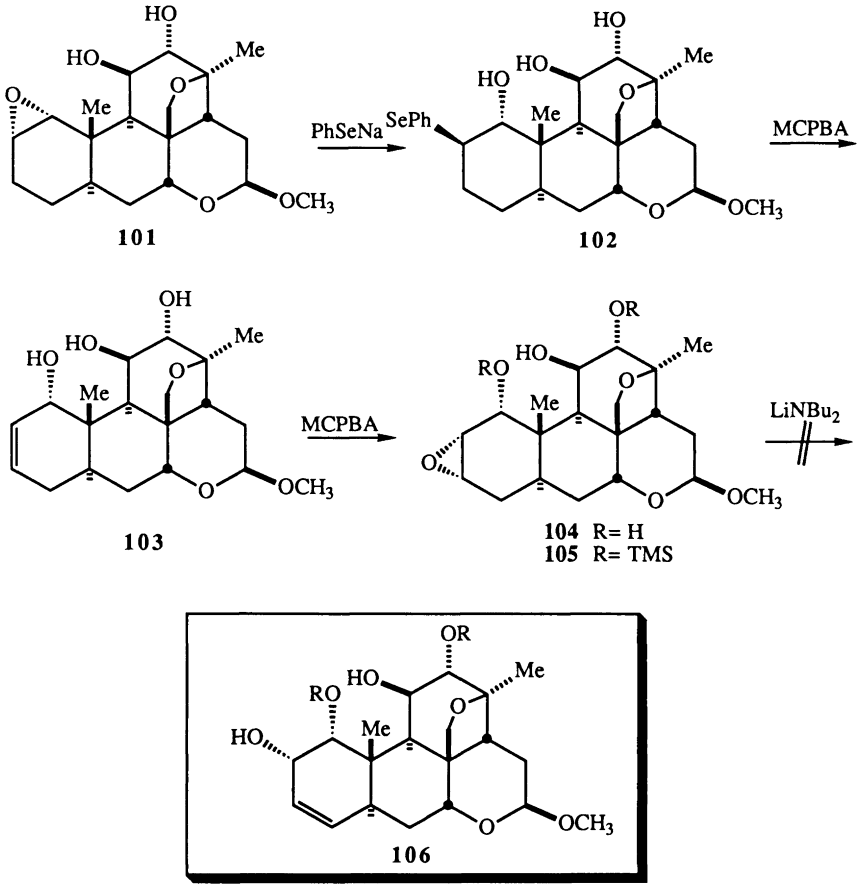
SCHEME 17

using DMSO-trifluoroacetic anhydride as was reported in the model series,[56] although we later found that pyridinium dichromate (PDC) worked more reliably and reproducibly. The sensitive hydroxyketone **100** was immediately reduced using Bu_4NBH_4 in ethyl acetate to furnish *trans*-diol **101**.

With the C-ring fully assembled and the E-ring locked in its C_{13}-bridged position, attention was turned to elaborating the complex A-ring oxidation state from epoxide **101**. Our plan was to utilize a consecutive series of 'counterclockwise' epoxide-to-allylic alcohol isomerizations that would functionalize C_2, C_3 and C_4, respectively, as in **106**. Such a procedure would pave the way for attaching the C_4-methyl substituent through a cuprate conjugate addition to the α,β-enone corresponding to **106**. Accordingly, allylic alcohol **103** (Scheme 18) was made in high overall yield by the straightforward reaction of PhSeNa with **101** and subsequent oxidative elimination of the hydroxyselenide **102** (85% for two steps). Then, as planned, **103** underwent *syn*-epoxidization using MCPBA to produce epoxyol **104**. At this stage we expected to rearrange **104** using Rickborn's lithium dialkylamide-ether procedure;[57] however, all attempts to prepare **106** with excess $LiNBu_2$ returned starting material. Since insoluble lithium alkoxides may have prevented reaction, triol **104** was first silylated to **105**. Nevertheless exposure of **105** to $LiNBu_2$/ether simply removed one or both of the TMS groups and no new alkenyl hydrogens were evident in the ^1H NMR spectrum of the product.

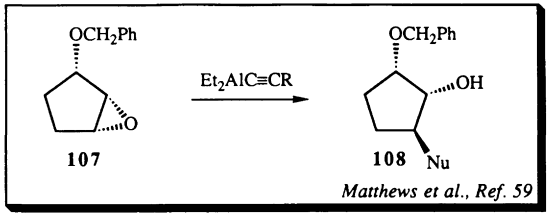
The unexpected reluctance of **104** to rearrange under strongly basic conditions left us in a quandary. Clearly the alternative PhSeNa opening/selenoxide elimination was no longer a viable alternative in this instance, since nucleophilic attack would result in *trans*-diaxial opening of **104** to furnish a 1,3-dihydroxy-2-selenide incapable of elimination to the requisite $\Delta^{3,4}$ alkene.

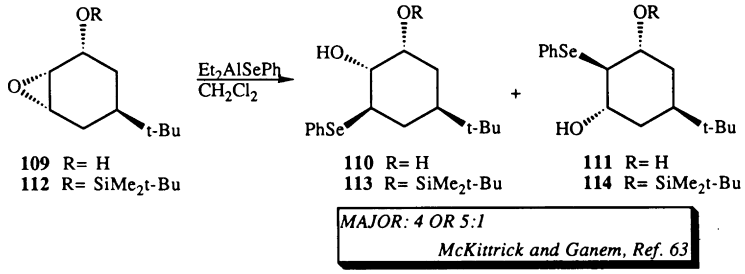
We reasoned that dialkylaluminum selenides might circumvent the absolute requirement for *trans*-diaxial opening of **104**, since the corresponding nucleophilic dialkylaluminum alkynes were known to attack acyclic or conformationally mobile 2,3-epoxy-1-ols regioselectively at C_3 (see for instance **107** to **108**, Scheme 19).[58,59] Although the nucleophilic properties of reagents like R_2AlSeR' were unknown, diisobutylaluminum phenylselenide had been reported to promote the Beckmann rearrangement of oxime sulfonates.[60] Also Kozikowski and Ames had used dimethylaluminum methylselenide to make active

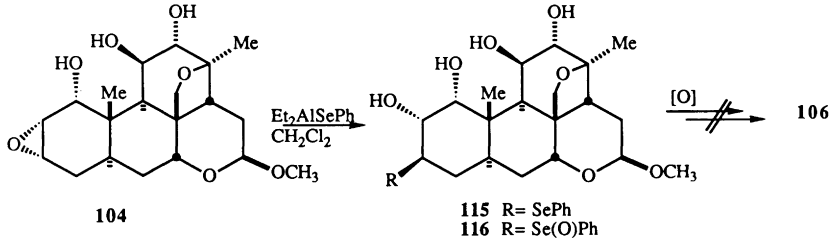


SCHEME 18

acyl transfer reagents.[61] Clearly success would require that the well-known chelation effects of trivalent aluminum species with epoxides[62] override the stereoelectronic preference for *trans*-diaxial opening. In fact model epoxyol **109** reacted with $Et_2AlSePh$ to afford a 4 : 1 mixture of **110** and **111**. The corresponding *tert*-butyldimethylsilyl ether **112** behaved similarly, affording **113** as the major product (5 : 1 ratio, Scheme 19).[63] The method also succeeded with epoxyol **104** producing the desired selenide **115** as the predominant product (2 : 1 mixture of regioisomers). Unfortunately, however, the corresponding selenoxide **116** could not be made to eliminate, once again thwarting our attempts to prepare allylic alcohol **106**.





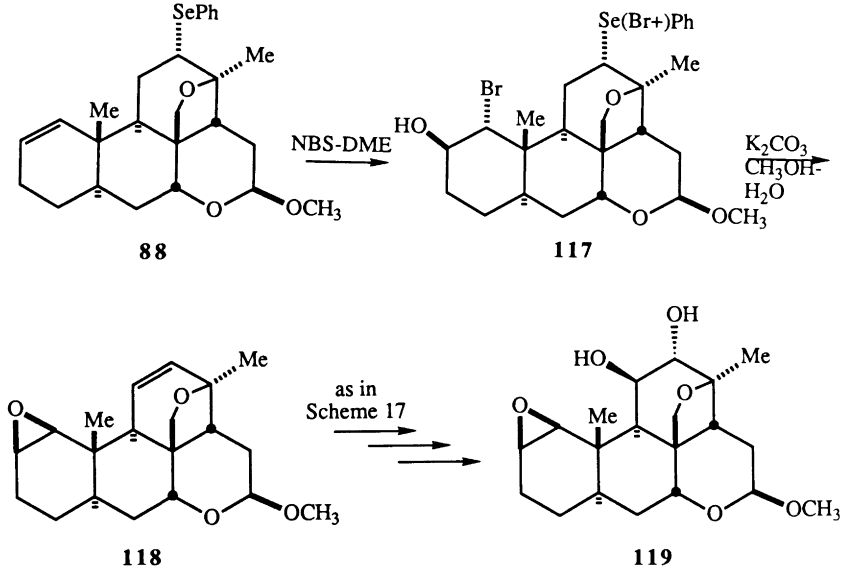


SCHEME 19

Many of the obstacles encountered while assembling the A-ring in this phase of the synthesis could be attributed to the unfavorable stereochemical alignments in products derived from the $C_1\alpha$–$C_2\alpha$-epoxide in **90**. Besides the regiochemical problems surrounding nucleophilic opening of α-epoxyol **104**, attendant difficulties in eliminating selenoxide **116** were likely caused by the β-equatorial orientation of the C_3-phenylselenenyl moiety. Finally it should be noted that quassimarin (**6**) and simalikalactone D (**7**) possess an equatorial (β) hydroxyl group at C_1 so that the synthesis of quassinoids from **90** would eventually require an inversion or equilibration (most likely via a C_2-ketone) at some stage of the plan.

It occurred to us that each of these obstacles might be surmounted by working with the more sterically hindered $C_1\beta$–$C_2\beta$-oxirane corresponding to **90**. Not only would the correct C_1-stereochemistry be installed directly, but subsequent *syn*-epoxyols would be more prone to nucleophilic attack from the more accessible α-face. In the absence of a potent directing group for peracids, the more hindered of two epoxide stereoisomers can usually be prepared by bromohydrin formation and based-promoted closure. We therefore decided to reinvestigate the oxidative elimination of selenoalkene **88** under different conditions.

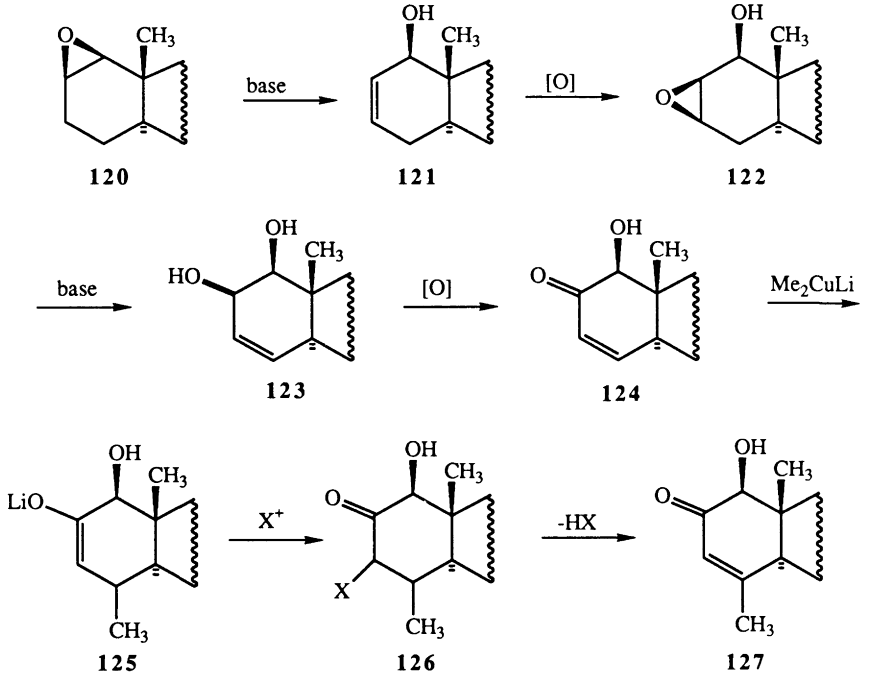
Dr. N. L. Reddy in our laboratory devised an elegant one-pot transformation of **88** to the desired β-epoxide by employing two equivalents of N-bromoacetamide in 1,2-dimethoxyethane (Scheme 20). That procedure oxidized both the selenide and the A-ring alkene. The intermediate selenonium species **117** was isolated once for purposes of characterization, but typically was exposed directly to aqueous base in the workup so as to promote selenoxide elimination and concomitant bromohydrin closure. In this fashion β-epoxyalkene **118** could be obtained in 82% overall yield. Although we were most anxious to explore the possibilities for A-ring modification, it was



SCHEME 20

clear from earlier studies that the ring-C *trans*-diol had first to be completed. The same sequence of osmylation, oxidation and reduction reactions earlier developed by Oliver and Fuchs[56] (Scheme 17) worked again beautifully to provide **119**.

With a good supply of the pentacyclic β-epoxide **119** in hand, we began a series of model studies to evaluate a strategy in which the C_1–C_2-epoxide would be used to 'bootstrap' the oxidation around ring A, creating in stepwise fashion the desired 1β-hydroxy-4-methyl-$\Delta^{3,4}$-2-one array. As can be seen from Scheme 21, a sequence of consecutive oxirane-to-allylic alcohol isomerizations was envisioned, leading to enediol **123**. Thereafter a selective oxidation of the allylic OH without *vic*-diol cleavage would be required to furnish hydroxyenone **124**. The final attachment of ring-A's C_4-methyl substituent could conceivably be achieved through the conjugate addition of some methyl cuprate species, and the resulting enolate either oxidized directly to **127** or in stepwise fashion *via* an intermediate α-halo or α-selenocyclohexanone.

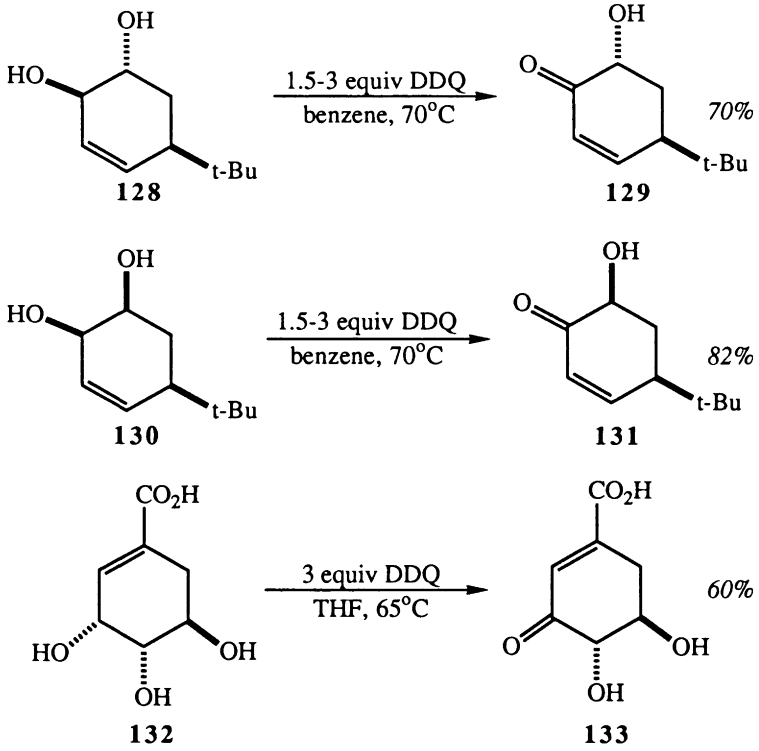


120 **121** **122** **123** **124** **125** **126** **127**

SCHEME 21

We were unaware at the time of any report describing a reagent selective enough to accomplish the partial oxidation of **123** to **124**. Most *cis*-enediols were very susceptible to overoxidation, giving diones (or even catechols, with MnO_2). However we found that 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) could selectively achieve the desired transformation in general fashion, as illustrated in Scheme 22.[63] Both *cis* and *trans*-enediols gave the expected hydroxyenones. Even shikimic acid **132** gave 3-dehydroshikimate in 60% yield, representing a major improvement over the rather capricious published procedure using Pt/O_2.

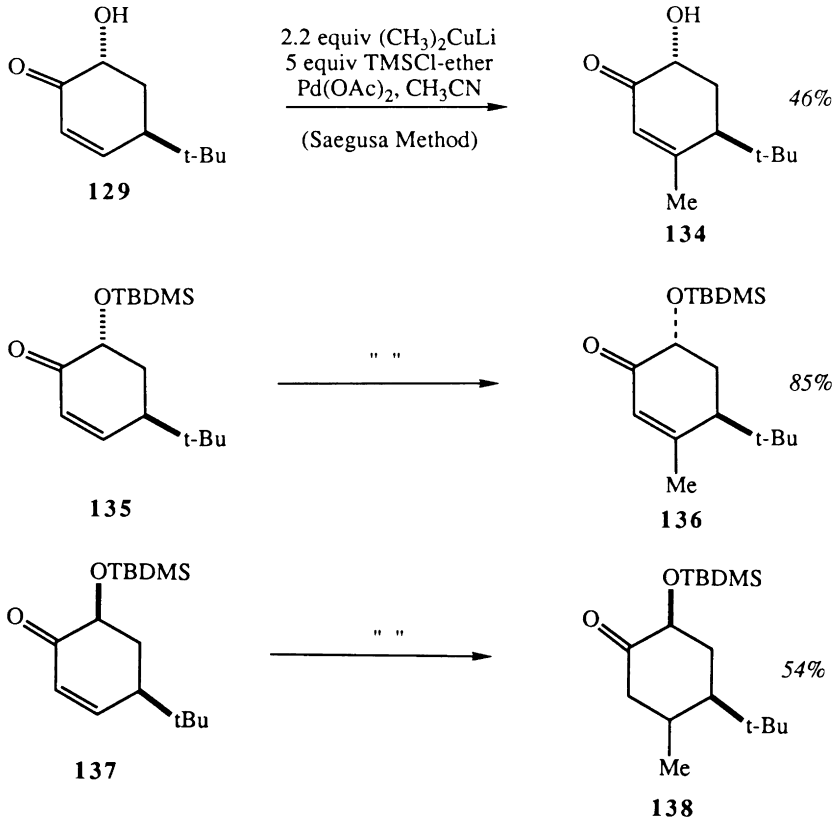
We also perfected a cuprate addition-oxidation protocol[63] in conformationally anchored monocyclic model systems (Scheme 23) based on Saegusa's palladium acetate oxidation of silyl enol ethers.[64] Hydroxyenone **129** or variations thereof (e.g. **135** and **137**) underwent a one-pot reaction involving conjugate methyl addition [$(CH_3)_2CuLi$]



SCHEME 22. DDQ oxidations of enediols.

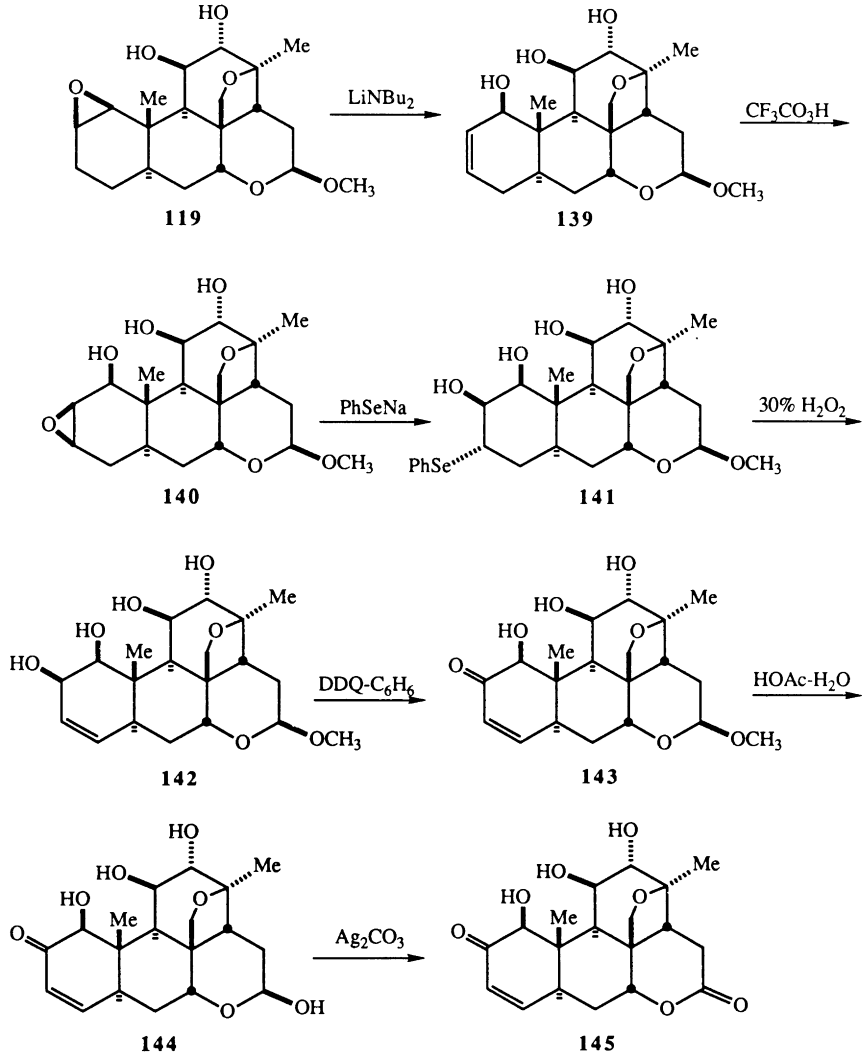
with enolate trapping [TMSCl, ether] and oxidation of the intermediate silyl enol ether [$Pd(OAc)_2$, CH_3CN] to furnish β-methylated enones **134**, **136** and **138**. Moreover, the latter two products could easily be desilylated with no detectable epimerization at the acidic α'-carbon.

Overall the two successful model studies described in Schemes 22 and 23 set the precedent necessary to apply our strategy for A-ring construction (broadly outlined in Scheme 20) to the specific case of pentacyclic epoxide **119** (Scheme 24). To begin this operation, the base-catalyzed epoxide opening of Rickborn[57] using $LiNBu_2$ in THF smoothly transformed **119** to **139** in 88% yield. Syn-epoxidation of the allylic alcohol was best accomplished with CF_3CO_3H in CH_2Cl_2 to give epoxyol **140** in 66% yield. Although this substance was quite



SCHEME 23. Ring A model alkylations.

stable and could easily be chromatographed, the Rickborn method of epoxide rearrangement gave a complex mixture of products. Instead, **140** was treated with PhSeNa in ethanol, whereupon the product hydroxyselenide **141** was obtained in high yield (93%). As we had hoped, the axial stereochemistry of this α-selenide made for a much more facile elimination of the corresponding selenoxide. In fact, treatment of **141** with H_2O_2 in THF-ethanol followed by heating at 65°C

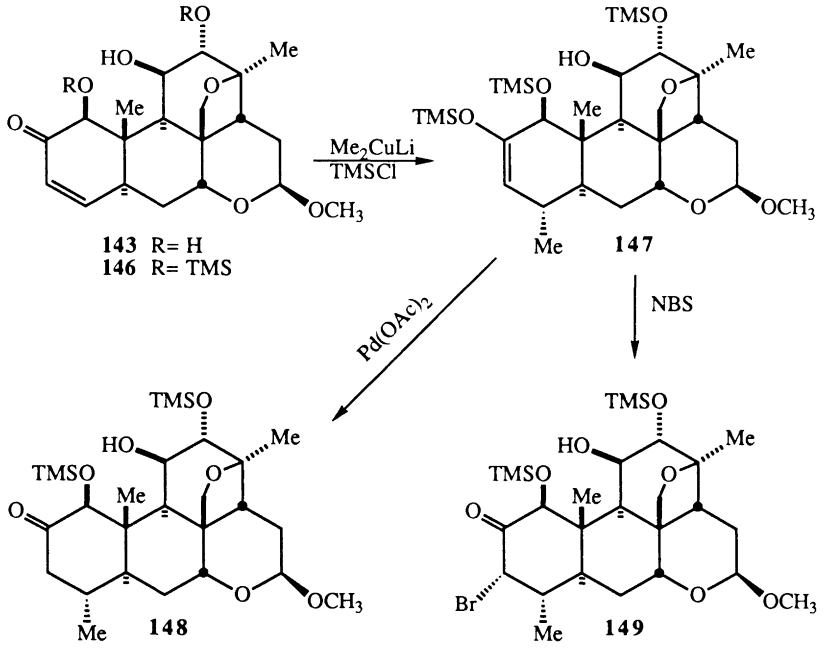


SCHEME 24

for 2 hours gave rise to the desired enediol **142** (89%). After heating **142** with DDQ (C_6H_6, reflux) we were gratified to observe the desired hydroxyenone **143** as the only new product (58%; 71% based on recovered starting material).

Before introducing the C_4-methyl group, we decided to establish the feasibility of deprotecting the D-ring mixed acetal and regenerating the lactone carbonyl for subsequent attachment of the C_{15} side chain. Therefore hydroxyenone **143** was converted to hemiacetal **144** in mild aqueous acid. Using Grieco's procedure[65] (Ag_2CO_3-Celite), **144** was smoothly oxidized in 74% yield to lactone **145**, our most advanced synthetic intermediate to date.

The current stage of our ongoing efforts towards the synthesis of quassimarin (**6**) and simalikalactone D (**7**) is summarized in Scheme 25. Initial attempts at the conjugate addition of $(CH_3)_2CuLi$ to **143** were complicated by alkoxide salt formation, therefore this trihydroxyenone was first partially silylated to **146** by means of hexamethyldisilazane-TMSCl. Apparently the C_{11}-hydroxyl was too sterically hindered to undergo silylation, an observation confirmed in model studies with several naturally-occurring quassinoids. Reaction



SCHEME 25

of $(CH_3)_2CuLi$ with enone **146** folowed by trapping of the intermediate did afford silyl enol ether **147**. However when **147** was exposed to $Pd(OAc)_2$ in anhydrous CH_3CN under the conditions reported in Scheme 23, a very sluggish reaction took place leading only to the saturated β-methylketone **148**. The equatorial stereochemistry assigned to the new C_4-methyl group was deduced from vicinal coupling constants in the ^1H NMR spectrum of **148**. To explain the failure of the Saegusa oxidation, we postulated that palladium coordinated to the less hindered α-face of silyl enol ether **147**, thus precluding oxidative addition into the β-C_4-hydrogen. To support this contention, **147** was oxidized instead with N-bromosuccinimide. A single bromoketone **149** was obtained whose structure indicated that bromination also occurred from the α-face of the enol ether.

IX. Summary

In summary, a conceptually attractive and appealing synthetic strategy for the assembly of pentacyclic quassinoids has been developed. Several serendipitous discoveries made along the way enhanced our insight into (and appreciation for) the beauty and complexity of these structures. Certain self-imposed synthetic challenges stimulated the development of new chemical methodology, while other unforeseen difficulties encountered in the experimental execution necessitated logical refinements and revisions of the original plan. Of course, the project has taken longer than expected! Nonetheless the thrill of the synthetic challenge, the challenge leading to each tactical achievement, and the achievements mastered in pursuit of excellence combine to make such endeavors interesting and exciting.

> *The synthetic chemist is more than a logician and strategist. He or she is an explorer strongly influenced to speculate, to imagine, and even to create. These added elements provide the touch of artistry which can hardly be included in a cataloguing of the basic principles of synthesis, but they are very real and extremely important.*[66]

Acknowledgments

I am greatly indebted to four enthusiastic and dedicated co-workers whose tireless efforts led to the results recorded in this chapter: Mr. (now Dr.) Douglas Batt, Dr. Norio Takamura, Dr. Brian McKittrick and Dr. N. Laxma Reddy. Their skillful experimental execution and thoughtful intellectual analysis during this project have been an inspiration to all the members of our reasearch group at Cornell. I also wish to acknowledge the National Institutes of Health for their generous financial support over the years.

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Chapter 5

TOTAL SYNTHESIS OF TAXUSIN: AN INITIAL STEP TOWARD TAXOL SYNTHESIS

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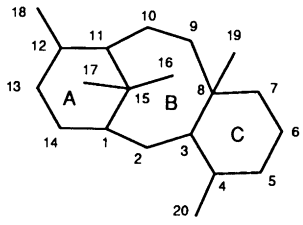
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I. Background: The Taxane Diterpenes

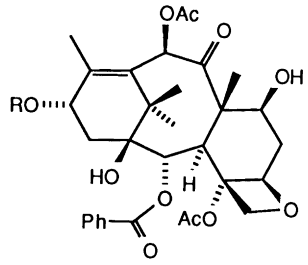
The taxane family of diterpenes is comprised of about thirty members, all of which possess the unique carbon skeleton **1**.[1] Two of them, taxol (**2**) and cephalomannine (**4**), have been found to be potent antitumor agents.

Taxol (**2**) was isolated from the yew *Taxus brevifolia*, and its structure was elucidated by a combination of chemical, spectroscopic and X-ray crystallographic techniques.[2] Taxol shows confirmed activity in the L-210, P-388 and P-1534 leukemia assays, in the WM-256

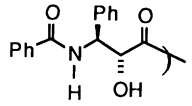
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Taxane Skeleton (1)

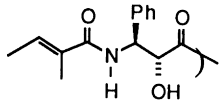


Taxol (2); R =



Baccatin III (3); R = H

Cephalomannine (4); R =



carcinosarcoma and 9KB cytotoxicity assays, in the B16 melanocarcinoma assays, in Colon 26, and in human colon, lung and mammary tumors carried as xenographs in nude mice.[1b,3]

Taxol entered Phase I clinical trials in 1981, and has been in Phase II clinical trials for about five years. It has recently entered Phase III clinical trials against ovarian cancer, due to the outstanding results obtained against refractory advanced ovarian cancer in the Phase II trials.[4] The related compound, cephalomannine (**4**), was isolated from *Taxus wallichiana* and also shows P-388 activity.[5]

One of the important features of taxol is that it exerts its antitumor activity in a novel and unique way. Taxol acts as a mitotic inhibitor,[6] but its mode of action is different from that of known antimitotic agents such as colchicine, podophyllotoxin, vincristine, and maytansine, which prevent the formation of microtubules.[7] It is bound to the microtubule in a stoichiometric fashion, one molecule of taxol per tubulin dimer unit. Taxol is a potent inhibitor of the replication HeLa and BALB/C fibroblast cells. HeLa cells treated with taxol accumulated in the G_2 and M phase of the cell cycle, and it has been suggested that taxol may exert its antitumor activity by preventing the cell from depolymerizing its microtubule cytoskeleton.[8] Because taxol operates in a novel way, the understanding of its mechanism of action is important to the understanding of cell mitosis. Taxol has become a useful tool for biologists studying cell mitosis, and many

publications describing such studies have appeared in the last few years.[9]

A few structure-activity relationships of taxol are known. Wall has shown that the taxol C_{13} side chain is necessary for activity, and that neither 10-deacetyl baccatin III, nor the side chain (free acid) are active.[2] Kingston has subsequently demonstrated that the $C_{2'}$ acetoxy derivative of taxol is inactive in vitro, but is active in vivo.[10] Kingston has also presented evidence that the oxetane ring is required for antitumor activity.[10b,11] Since cephalomannine has activity similar to that of taxol, the nature of the $C_{3'}$ amide substituent appears to be relatively unimportant.

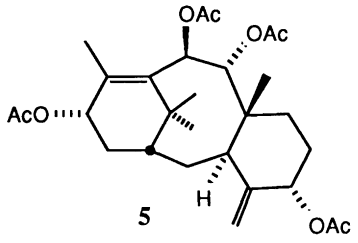
Unfortunately, progress in clinical trials involving taxol and studies of its mode of action have been retarded because a sufficient supply of the compound has not been available.[12] Taxol is obtained by extracting the bark of the pacific yew tree, *Taxus brevifolia*. To obtain the bark, the tree is sacrificed, and the yield of taxol from bark extractions has been in the range of .004% to .01%. Large scale isolations have yielded a few kilograms of taxol from several hundred thousand pounds of yew bark.

The problem is compounded by the fact that the pacific yew is a relatively small understory tree. It is found primarily in the virgin rain forests of the pacific northwest, and is scattered sparsely throughout the range of the rain forest. Large-scale harvests are even now beginning to threaten the existence of the yew and the virgin rain forests as well, and it is clear that sufficient supplies for the drug to be marketed cannot be obtained in this way. This has become a point of serious environmental concern.[13] Since the yew is an extremely slow-growing tree, it is not practical to consider cultivating stands of yew for harvest in future years.

A possible alternative source of taxol is chemical synthesis. The highly oxygenated tricyclic structures of the taxane diterpenes exhibit a high level of structural complexity and abundant stereochemical details. Prior to this work, synthetic efforts had not dealt with stereochemical issues, but, instead, had primarily concentrated on elaboration of the taxane carbon skeleton. Thus, among over twenty different approaches to the taxane diterpenes,[14] none of the natural products had yet been synthesized.

To develop chemical technology relevant to the synthesis of taxol, we embarked upon a program which had as its goals: 1.) an efficient

synthesis of the taxane ring system, 2.) the synthesis of taxusin (**5**),[15] the simplest member of the taxane family of diterpenes, and 3.) the synthesis of baccatin III (**3**) and its conversion into taxol. This interim report describes the first two stages of this program.

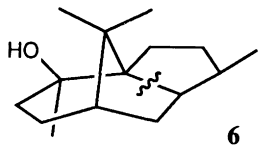


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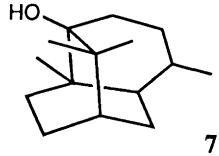
II. Synthesis of the Taxane Skeleton

A. Retrosynthetic Analysis: The Patchouli Connection

From the very beginning it was clear that a direct and very simple construction of the bicyclo[5.3.1] AB portion of the taxane ring system would be required, for, once a method for synthesis of the skeleton was realized, many other issues of reactivity and selectivity in this unknown setting would need to be addressed before any synthesis of the natural products could be contemplated. To this end, a wide variety of retrosynthetic pathways was entertained, but none offered sufficient simplicity until the "patchouli connection" was realized. The "patchouli connection" consisted of the recognition that the incorrect structure **6** for patchouli alcohol (the correct structure **7** was later determined by X-ray analysis)[16] proposed by Buchi,[17a,b] and subsequently confirmed by synthesis,[17c] differed from the bicyclo-[5.3.1] taxane AB ring system only in the existence of a bond



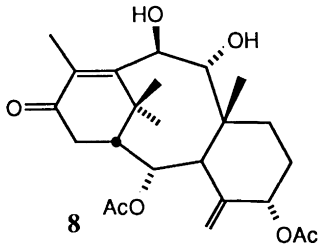
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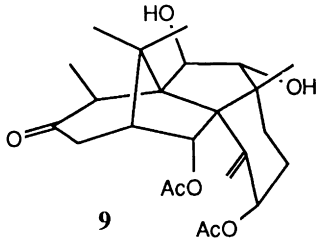
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between C_{11} and C_3 (taxane numbering). If a method could be found to cleave this bond, a simple synthesis of the taxane skeleton might be

achieved. In fact, the reverse of this desired transformation had already been accomplished by Nakanishi in the course of his elegant and extensive early studies on the structure of the taxanes. Photolysis of diacetate **8** derived from taxinine (**1**) quantitatively gave ketone **9**, the bridged bicyclic skeleton of which was identical to that of **6**.[18]

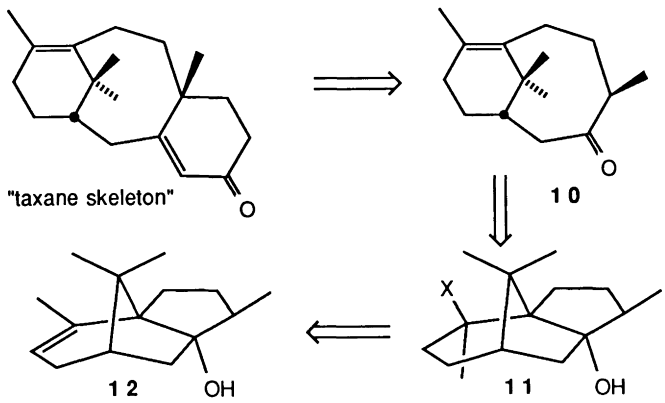


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Therefore, retrosynthetic analysis of the taxane ring system involved the attachment of the six-membered C-ring to the bicyclo[5.3.1] ketone **10** which would be formed via fragmentation of an appropriate substrate, such as **11**, having the bicyclo[3.2.1] skeleton fused to a five-membered ring. Several fragmentation substrates could possibly serve in this capacity, but they would probably all be derived from **12**, an intermediate which had been previously prepared by Buchi. Compound **11** would need the leaving group X situated in the β configuration so that the breaking bonds would be oriented anti and approximately coplanar. It was anticipated that the



difficult part of this sequence would be the synthesis of **10**, and that considerable experimentation would be required to identify and

prepare an appropriate fragmentation substrate **11**. The conversion of **10** to the taxane skeleton, on the other hand, was envisioned to be straightforward since it utilized well known annulation chemistry.

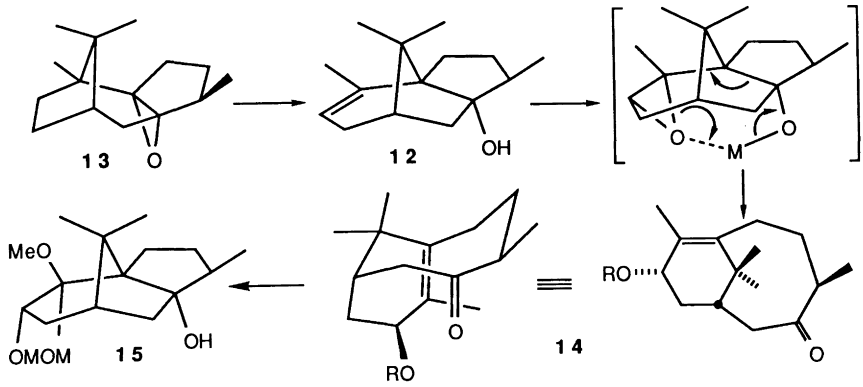
B. Discovery of the Key Fragmentation

The synthesis of **12** was carried out following the procedure of Buchi.[17] Patchouli alcohol (**7**) rearranged to β-patchouline in the presence of iodine in toluene, and β-patchouline readily underwent epoxidation to give the epoxide **13** in high yield. Later, it came to our attention that **13** is itself an article of commerce, marketed under the trade name "patchino," and the abundance of this material has served as the lifeblood for the work that follows.[19] In the presence of BF_3, **13** rearranged to give **12** in approximately 65% yield along with a variety of other products. Despite considerable adjustment of conditions, the yield of **12** could not be improved further.

After only a couple of abortive attempts to introduce an appropriate leaving group on the β-face of **12**, an objective from which our attention was permanently diverted, the directed epoxidation of **12** under Sharpless' conditions [*t*-BuOOH, $Ti(OiPr)_4$] was attempted. The presumed epoxide could be detected by TLC, but it was quickly replaced by two other substances. One of these, to our amazement and delight, turned out to be the hydroxy ketone **14** (R = H), and the other was the enone derived from further oxidation of **14**. The second time this reaction was attempted, dimethyl sulfide was added as soon as **12** had completely disappeared to prevent overoxidation of **14**. We were delighted to find that, under these conditions, **14** was formed in quantitative yield.

Interestingly, this key fragmentation featured the cleavage of bonds which were syn instead of anti. We suspect that this is a consequence of the excellent alignment of these bonds in the bicyclo[3.2.1] ring system, and we have since found that similar reactions take place readily in at least one other bicyclic ring system.[20]

One unusual property of keto alcohol **14** was that it could be detected with UV light on a TLC plate. It was protected as the corresponding (MOM) ether, whose UV spectrum exhibited a λ_{max} of 212 nm with an ϵ of 5355. This is a consequence of the conformation of the ring system in which the two sites of unsaturation in the molecule, the carbonyl group and the bridgehead olefin, experience through-space transannular conjugation.[21] This property is shared by



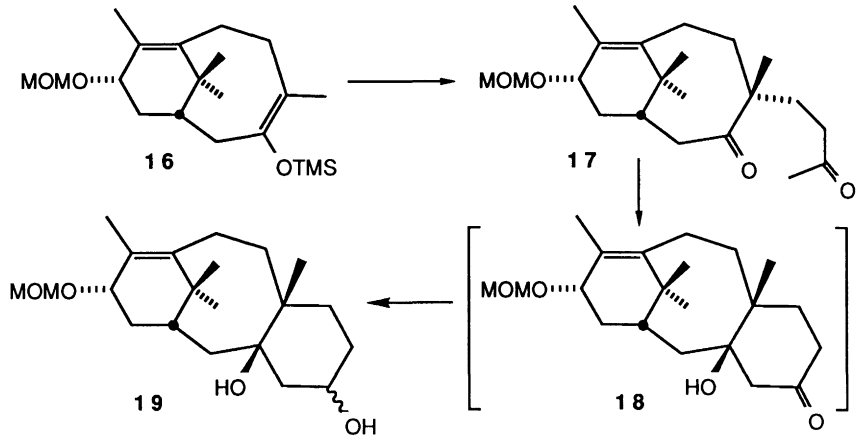
most of the compounds described herein containing these two functional groups.

Another consequence of the proximity of the olefin and the carbonyl group in **14** is that transannular cyclization occurs readily. When **14** (R = MOM) was treated with acidic methanol, it was rapidly converted to **15**, which has the same carbon skeleton as **11**. This process is formally the reverse of the originally planned fragmentation of **11** to **10**.

C. Annulation of the C-Ring

To complete the synthesis of the taxane skeleton, **14** (R = MOM) was converted through the utilization of bromomagnesium diisopropylamide (BMDA)[22] to the more substituted silyl enol ether **16** in quantitative yield. Generation of the lithium enolate from **16** was followed by the addition of trimethylsilyl methyl vinyl ketone exclusively from the α-face of the enolate to give **17** in 93% yield from **14**.

Aldol condensation of **17** to complete the formation of the tricyclic taxane skeleton was unexpectedly difficult. Under several different basic conditions, the cyclization of **17** proceeded to give **18** in varying amounts, but the ketol could not be isolated in pure form without contamination by **17**. In fact, repeated attempts to purify ketol **18** simply resulted in the production of greater amounts of diketone **17**. Under more vigorous conditions (*t*-BuOK, *t*-BuOH, reflux), **17** underwent retro-Michael cleavage to give **14** as a mixture of C_3 epimers. It appeared that the cyclization of **17** could be carried to completion at low temperature through the use of a chelating counterion, but upon isolation of the reaction product, some reversion to **17** occurred. Therefore, the cyclization was carried out at $-78°C$ using



BMDA in THF, and after thirty minutes at that temperature, the product was reduced by the addition of sodium bis(2-methoxyethoxy)aluminum hydride [Red-Al®]. In this way, **17** was converted to a mixture of diols **19**, epimeric at C_5, in 90% yield.

We decided that the formation of **19** was sufficient to claim the synthesis of the taxane skeleton, even though one carbon (C_{20}) was still absent. Undoubtedly, this carbon could have been included in some way, but rather than hack around in an attempt to include it, we decided to move on to our second objective, the synthesis of taxusin.

Despite the difficulties in the latter stage of the taxane skeleton synthesis, it still required only five steps and proceeded in an overall yield of approximately 55% from patchino.[23] This was quite remarkable, because the weakest link in the sequence was the 65% conversion of patchino to **12**. Nonetheless, large quantities of patchino were readily available, and we were able to prepare hundreds of grams of keto alcohol **14** in a relatively simple fashion. The availability of this material presented a great opportunity to explore various possibilities for taxusin synthesis.

III. Synthesis of Taxusin

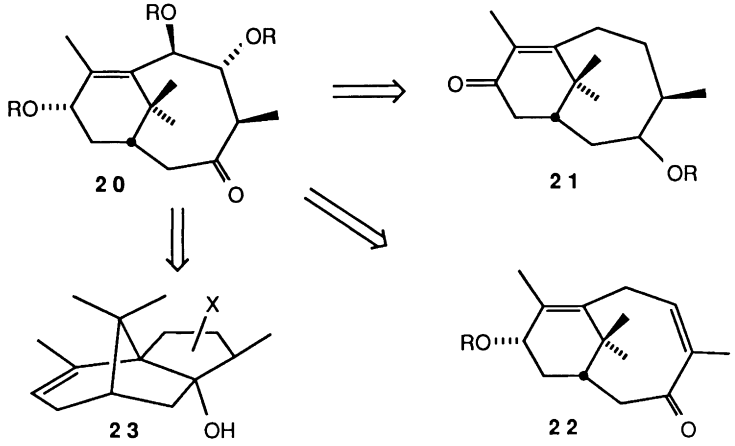
A. Functionalization of C_9 and C_{10}

1. *Initial Retrosynthetic Analysis*

Having received some indication that ketone **14** might possess unusual reactivity, we proceeded with caution in planning the approach to taxusin. We decided that it would be wise to explore the reactivity

of this system using several different approaches. The first objective in what we hoped would be a path toward taxusin was to find a way to introduce the trans diol functionality at C_9 and C_{10}. Therefore, we targeted the synthesis of diol **20** (or a suitably protected derivative).

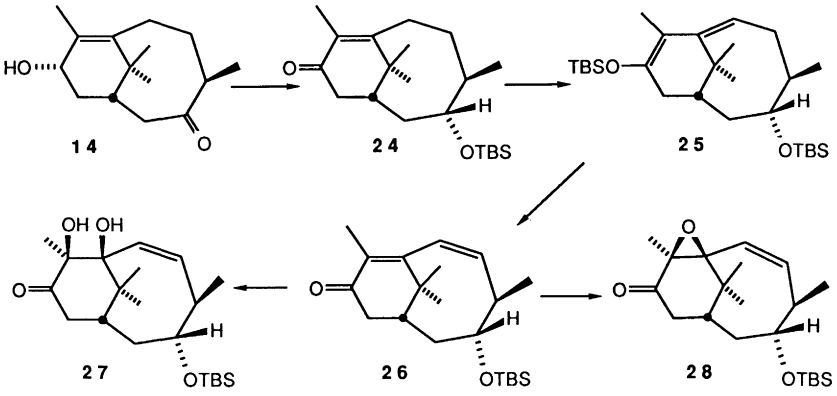
There were three obvious approaches to the functionalization of C_9 and C_{10}. Two of these involved utilization of the existing functionality in **14**. One possibility was to explore the deconjugation of a C_{13} ketone such as **21**. Another was to use the enol ether **16** to introduce unsaturation at C_8 and C_9 (and perhaps at C_9 and C_{10}) as in **22**. The second of these possibilities was more attractive, since it did not require that the already established stereochemistry of the C_{13} alcohol be destroyed. The third, and least palatable alternative would involve the introduction of some functionality at C_9 or C_{10} prior to fragmentation. This would require that we discover an alternative to the rearrangement of patchino to **12**, already a weak



step, and this was expected to present considerable difficulty. Since it was impossible at the time to judge which, if any, of these plans would prove successful, we set out to explore all three possibilities simultaneously.

2. *Introduction of the C_9 and C_{10} Hydroxyl Groups*

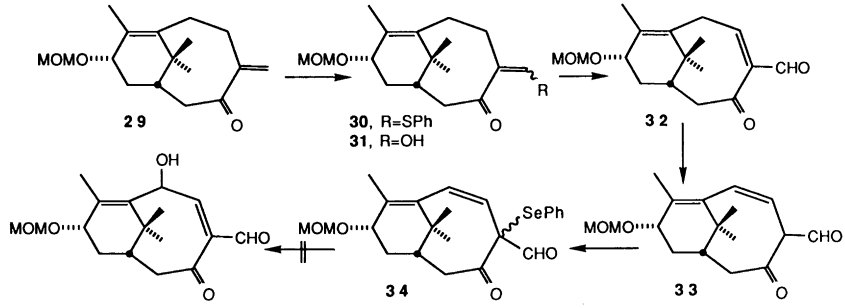
In the first approach,[24] ketone **14** was reduced with lithium aluminum hydride (LAH) to stereospecifically provide the C_3 α-diol. Oxidation of the allylic alcohol with manganese dioxide gave an enone which was protected as the *t*-butyldimethylsilyl (TBS) ether **24** (66% yield from **14**). In the presence of a slight deficiency of lithium



diisopropylamide (LDA), enone **24** was converted to a mixture of dienolates which were trapped as the TBS dienol ethers. Exposure of this mixture to silica gel resulted in the selective hydrolysis of the (minor) cross-conjugated dienol ether isomer, and in this way the through conjugated enol ether isomer **25** could be obtained in 95% yield at 52% conversion. Selenenylation of enol ether **25** (PhSeCl, 56%) was followed by oxidative elimination (mCPBA, $CHCl_3$, reflux; 88%) to provide dienone **26**. However, attempted oxygenation at C_9 and C_{10} was unsuccessful. For example, reaction of **26** with osmium tetroxide gave **27** in 74% yield, and no product of C_9–C_{10} hydroxylation could be detected. Furthermore, epoxide **28** was isolated from the epoxidation (mCPBA, $CHCl_3$, 25°C, 4 hours) of **26**, and a similar result was obtained from the corresponding C_3 alcohol.

Thus, it became clear that the C_{11}–C_{12} double bond of enone **26** is more reactive toward electrophilic reagents than the C_9–C_{10} double bond, even despite conjugation of the C_{11}–C_{12} double bond with the C_{13} carbonyl group. Examination of models suggests that the C_9–C_{10} double bond is exceptionally hindered, with the α-face being blocked by C_{18} and the β-face being blocked by C_{16}.

Meanwhile, the second approach,[25] utilizing the C_3 carbonyl in ketone **14**, commenced with the conversion of **14** (BMDA, TMSCl; MeLi, PhSeBr; $NaIO_4$; 80%) to enone **29**. Only the exocyclic enone isomer was obtained, with no trace of the endocyclic isomer having a C_8–C_9 double bond. Various attempts to isomerize **29** were completely unsuccessful. Therefore, conjugate addition of thiophenoxide to enone **29** was followed by oxidation with *N*-chlorosuccinimide to yield vinylogous thioester **30** in 74% yield from **29**. Hydrolysis ($AgNO_3$,



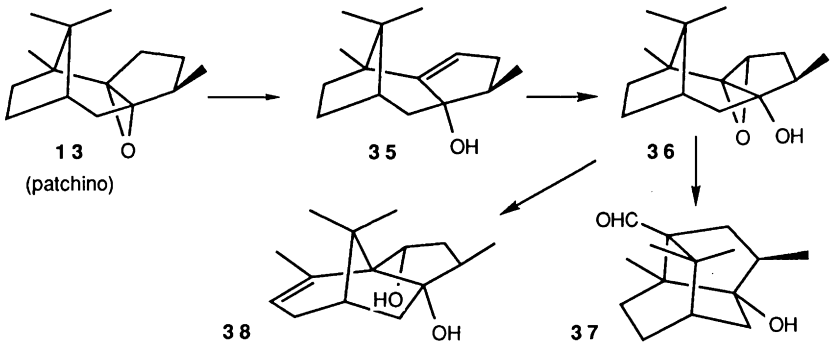
2,6-lutidine, THF-H_2O; 94%) provided β-keto aldehyde **31**, which underwent selenenylation followed by oxidative elimination (LDA, PhSeCl; mCPBA; 54%) to provide aldehyde **32**. Under basic conditions (DBU, THF; 100%), **32** underwent isomerization to give exclusively the C_9–C_{10} double bond isomer **33**. Selenenylation (*t*-BuOK, PhSeCl) of **33** gave a mixture of selenides **34**, which could be converted to the corresponding selenoxides. Unfortunately, neither selenoxide isomer underwent clean allylic rearrangement, but instead gave a complex mixture of products.

While this route did result in the successful introduction of the C_9–C_{10} double bond, it required a number of steps which definitely diminished its attractiveness. We did learn that, in this relatively unsubstituted version of the bicyclo[5.3.1] ring system, a C_9–C_{10} double bond is considerably more stable than the isomeric C_8–C_9 double bond. Although the introduction of a formyl group at C_8 presented some opportunities for further study, the third alternative route had by this time presented other more appealing opportunities.

The third approach to the installation of the C_9 and C_{10} hydroxyl groups had a dismal beginning. Over twenty different substrates were prepared to investigate the generality of rearrangements similar to the conversion of patchino (**13**) to **12** in only slightly more functionalized derivatives.[26] Absolutely none of these gave any encouragement at all, and a plethora of mixtures, unknown products, and bizarre and complicated rearrangements were encountered. In view of the complexity of this mess, the chemistry of only one of the many rearrangement substrates is described here.

Although it was quite sensitive to acidic conditions, patchino was relatively unreactive toward basic reagents. Treatment of patchino

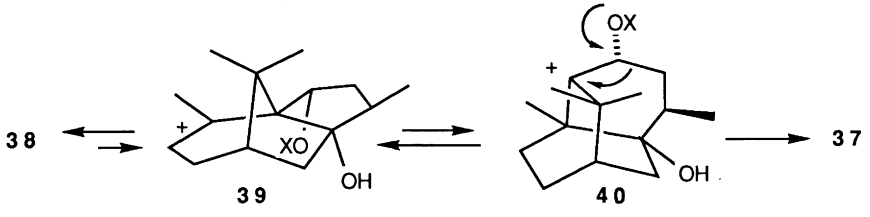
(**13**) with *t*-butyllithium under extremely vigorous conditions (hexane, reflux, 5 hours) gave the sensitive tertiary allylic alcohol **35**, which was epoxidized (*t*-BuOOH, $Ti(OiPr)_4$, CH_2Cl_2, 2 hours) without delay to give **36**. When the epoxidation was carried out sufficiently quickly without any attempt to purify **35**, **36** could be obtained in 98% yield from **13**. Under the usual rearrangement conditions ($BF_3 \cdot Et_2O$, 25°C), **36** was converted to many products, one of which was identified (with the aid of X-ray analysis) as the aldehyde **37**.[27] At lower temperatures (from −40 to 0°C) **37** could be obtained cleanly in reasonable yield, but none of the desired rearrangement product, diol **38**, was produced. This was puzzling, because models indicated that the migrating and breaking bonds in **36** were almost perfectly aligned for the desired migration to take place. After several frustrating failures to effect the rearrangement of other substrates, the reaction of **36** with $BF_3 \cdot Et_2O$ at −78°C was examined, and the desired diol **38** was detected for the first time.[26] After extensive experimentation,[27] conditions were developed ($BF_3 \cdot Et_2O$, CF_3SO_3H, CH_2Cl_2, −80°C, 22 hours) which converted **36** to diol **38** in 93% yield at 75% conversion. When the reaction was stopped at 75%



conversion, practically none of **37**, which was difficult to separate from **38**, was formed. If the reaction mixture was allowed to warm even to −70°C, a substantial amount of **37** contaminated diol **38**, and when **38** was treated with $BF_3 \cdot Et_2O$, it was converted to **37**. Since unreacted epoxy alcohol **36** could be easily separated from diol **38** by filtration through a plug of silica gel, and the recovered epoxy alcohol could then be recycled, we were able to prepare hundreds of grams of **38**.

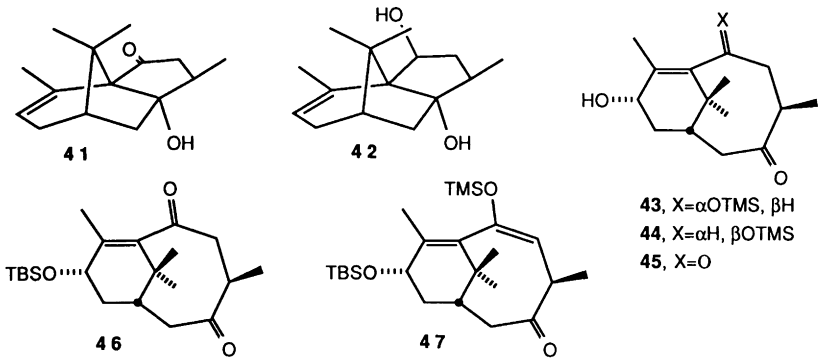
We rationalize these observations as follows. Epoxide **36** undergoes Lewis acid-mediated opening at low temperature with bond migration

to give cation **39**, which is in equilibrium with (the bridgehead) cation **40**. Cation **39** can lose a proton (reversibly) to give **38**. Cation **40** undergoes irreversible rearrangement to **37** by the indicated pathway, but, fortunately, this rearrangement is slower than proton loss from **39**.

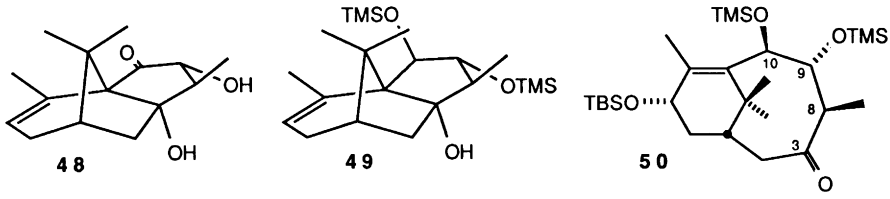


Oxidation of diol **38** (PDC, DMF, 3 hours, 25°C; 94%) furnished ketone **41**. It was gratifying to find that LAH reduction of **41** gave diol **42** stereospecifically, since we had predicted that reagents should approach **41** preferentially, if not exclusively, from the α-face. Furthermore, the mono trimethylsilyl (TMS) ethers of **38** and **42** as well as ketone **41** all underwent fragmentation (*t*-BuOOH, $Ti(OiPr)_4$, CH_2Cl_2, then DMS, reflux) without incident to give the keto alcohols **43** and **44**, and diketone **45**, respectively, in high yield.

Our attention was turned to addition of oxygen at C_9 of diketone **46**, which could be prepared (TBSOTf, pyridine, 0°C, 99%) from **45**. Diketone **46** readily underwent monodeprotonation exclusively at C_9, and the enolate could be trapped quantitatively as the enol ether **47**. Attempted oxygenations (mCPBA or BH_3 then H_2O_2, NaOH) of enol ether **47**, however, failed to provide a hydroxyl at C_9 and even the corresponding C_9–C_{10} enolate failed to react at C_9 with electrophilic agents.[26] Obviously, the C_9–C_{10} double bond was still quite unreactive, and it appeared that exploration of the introduction of both hydroxyl groups prior to fragmentation would be appropriate.



Introduction of the hydroxyl groups prior to fragmentation was accomplished easily. Ketone **41** was converted to the TMS enol ether (LDA, TMSCl) which was oxidized with peracid to give exclusively the α-alcohol **48**. LAH reduction then produced the desired trans diol which was converted to the bis (TMS ether) **49** (TMSCl, HMDS) in over 80% overall yield from diol **38**. Fragmentation of **49** then gave



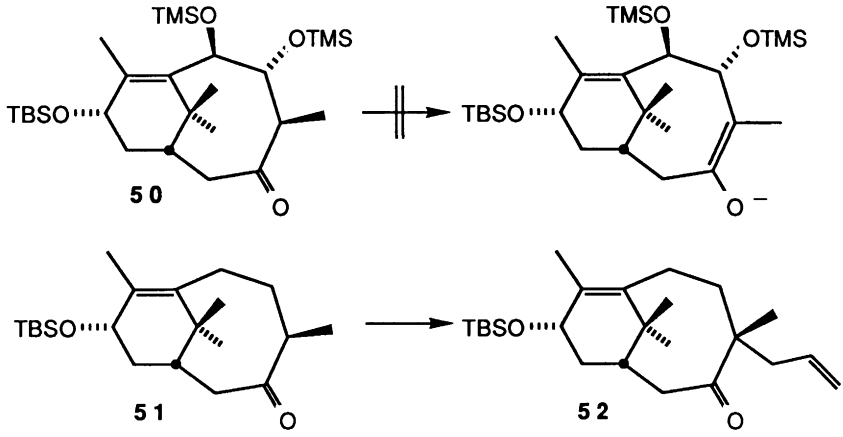
the bicyclo [5.3.1] ketone which was protected (TBSOTf, pyridine) as its TBS ether **50** (90% yield from **49**).[26] Finally, the C_9–C_{10} functionalization issue had been settled, and we were eager to complete the remainder of the taxusin synthesis, encouraged by the high yield preparation of **50** in just ten steps from patchino.

B. Attachment of the C-Ring Framework

1. *Initial Postfragmentation Attempts*[26]

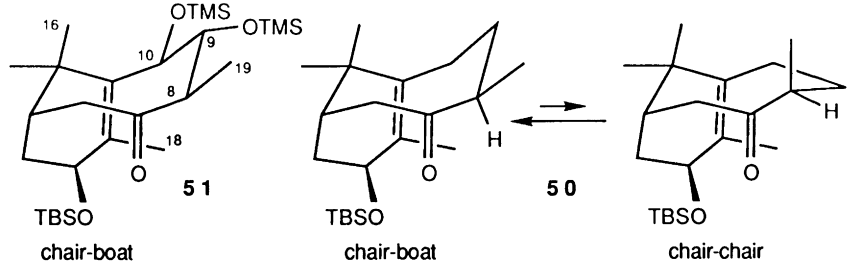
In order for **50** to be a useful taxusin intermediate, alkylation of C_8 was crucial. Also, before any serious synthetic planning could take place, it was necessary to know whether the C_3–C_8 enolate of an appropriately functionalized substrate having the bicyclo[5.3.1] skeleton could be utilized to introduce the necessary C-ring carbon chain with the proper stereochemistry. One might immediately be concerned about the possible β-elimination of the C_9 OTMS group from the C_3–C_8 enolate of **50**. We hoped, however, that this would not be a problem. We already knew that the C_8–C_9 double bond in **32** was not particularly stable, and examination of models indicated that the C_9 OTMS group would not be stereoelectronically aligned with the C_3–C_8 double bond for easy elimination to occur.

We did not expect what we found to be the case. We have been absolutely unable to prepare the C_3–C_8 enolate of **50** under any conditons; under most reasonable conditions, **50** simply is not deprotonated at C_8. We prepared **51**, the TBS ether of **14**, and this ketone



was found to undergo quantitative α-allylation (KO*t*Bu, allyl bromide) at C_8 to give **52**, while **50**, under identical conditions (reactions performed side by side), did nothing. It is possible to generate (LDA) the C_2–C_3 enolate of **50**, but this enolate has subsequently been found to possess unusual reactivity of its own. Furthermore, the C_2–C_3 enolate, while having some potential applications in taxol synthesis, was not useful for the synthesis of taxusin.

We invoke conformational preferences to explain the striking difference in the reactivity of **50** and **51**. The A-ring of both compounds is in a boat conformation. The B-ring of **50** prefers the chair-boat conformation, but the chair-chair conformation is only slightly (2 kcal or less) higher in energy than the chair-boat conformation, and the two conformers are in rapid equilibrium (ΔG^* = ca. 5 kcal). In the chair-boat conformer, the C_8 proton, which lies in approximately the same plane as the carbonyl group, is difficult to remove. In the chair-chair conformer, the C_8 proton is stereoelectronically aligned for removal, and it is from this conformation that deprotonation

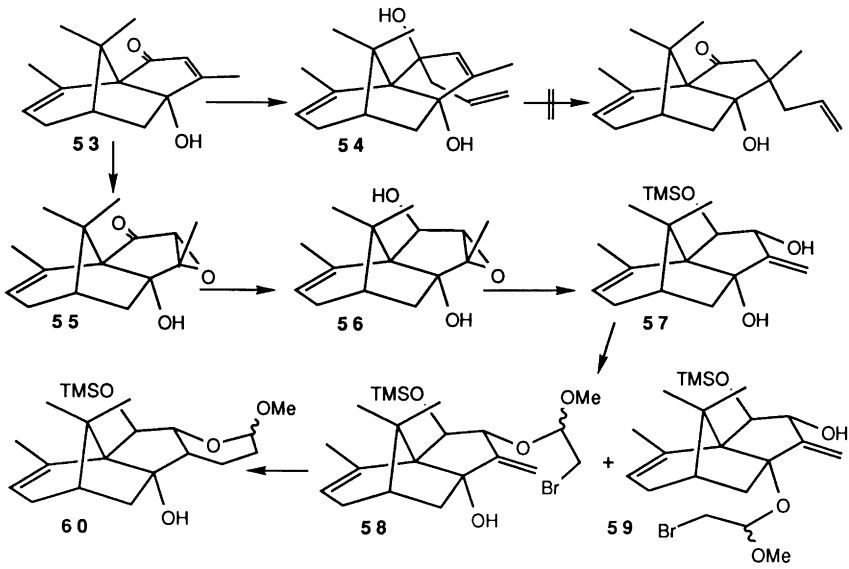


occurs. On the other hand, the B-ring of **51** is also in the chair–boat conformation, and the chair–chair conformation, which would have severe steric interactions between the C_{10} OTMS group and C_{16} and C_{19} methyl groups as well as between the C_9 OTMS group and the C_{18} methyl group, is energetically inaccessible. No other conformations are available to **51**, thus deprotonation at C_8 is difficult, if not impossible.

This observation is interesting, and it provides valuable insight into both the mechanism of ketone deprotonation and the conformational preferences of the taxane AB ring system. However, the failure of the alkylation of **51** did not help in our quest for a taxusin synthesis. In light of this development, we decided to investigate the incorporation of at least some of the C-ring carbons prior to fragmentation.

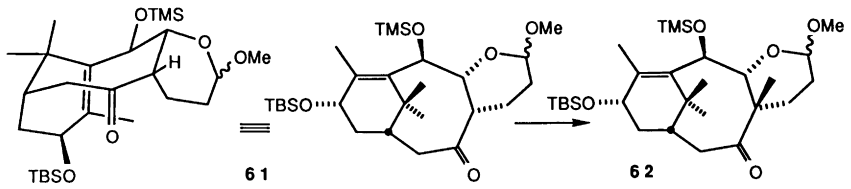
2. *Pre-fragmentation Introduction of Two C-Ring Carbons*

The TMS enol ether of ketone **41** readily underwent selenenylation and oxidative elimination of the phenyl selenide to give enone **53** in 95% yield from **41**. Attempted cuprate additions to enone **53** failed, although 1,2-addition of allyl Grignard gave diol **54**. The attempted oxy-Cope rearrangement of **54**, however, failed to give any of the desired product. Epoxidation of enone **53** (H_2O_2, NaOH, 25°C; 98%) provided epoxy ketone **55**, which could be reduced (LAH) stereo-



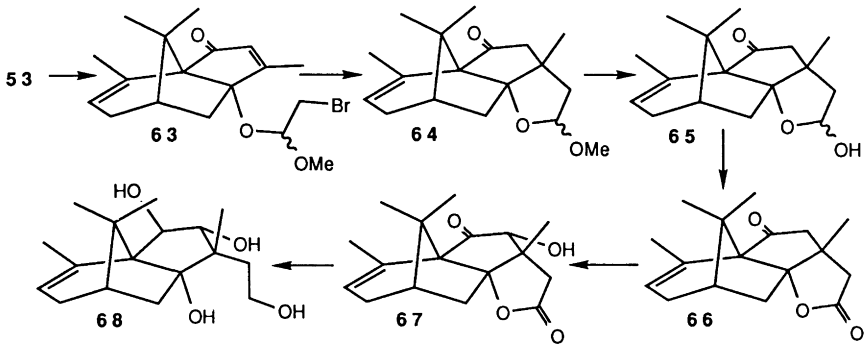
specifically to alcohol **56** in 90% yield.[25] The epoxy alcohol was protected as the TMS ether, and the epoxide was opened (LDA) to give allylic alcohol **57** in 92% yield. Bromoacetal **58** was obtained from **57** (1,2-dibromoethyl methyl ether, $PhNMe_2$) in only about 50% yield, along with tertiary bromoacetal **59** as the major (30%) byproduct, presumably from transacetalization. Radical cyclization[28] (Bu_3SnH, PhH, AIBN, reflux) of **58** failed to give any of the expected five-membered ring cyclization product, and, instead, the diastereomeric mixture of six-membered acetals **60** was isolated in about 50% yield, with the remainder being reduced material.

The mixture of acetals **60** underwent epoxidation-fragmentation to give **61** in over 90% yield.[26] Interestingly, NOE experiments revealed that the B-ring of **61** was in the chair–boat conformation (like **51**), and, in accord with the rationale advanced above, **61** underwent alkylation with methyl iodide (*t*-BuOK, THF) to give **62** quantitatively. Although **61** could potentially serve as a viable taxusin intermediate, it was a very costly material, since its preparation required two back-to-back 50% yield steps (25% for the two steps taken together). We were not willing to pay this price if we could avoid it, so we continued to search for a more economical route.



The appearance of bromoacetal **59** was not synthetically useful, since we could not quickly find a way of preparing **59** without the co-occurrence of **58**, but it did suggest that bromoacetals of tertiary alcohols could be prepared. Therefore, we decided to attempt the preparation of bromoacetal **63** from enone **53**. Three sequential additions of 1,2-dibromoethyl methyl ether (5 equivalents) and *N*,*N*-dimethylaniline (7 equivalents) to **53** over a 55 hour period provided bromoacetal **63** in 93% yield.[29] Upon radical cyclization (Bu_3SnH, AIBN, PhH, reflux), the anticipated tetracycle **64**, a mixture of diastereomers isomeric at the acetal carbon, was formed in 93% yield. Ketone **64** could be converted to the silyl enol ether, but the peracid oxidation of the diastereomeric mixture was problematic, probably

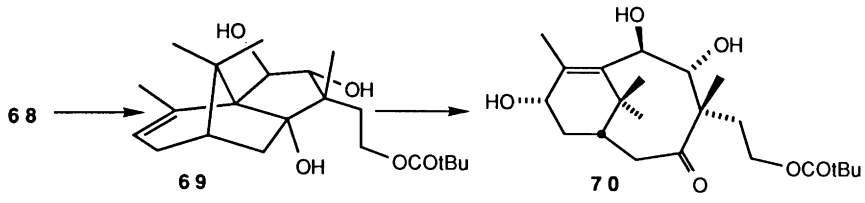
because the two diastereomers underwent oxidation at very different rates. Hydrolysis of **64** (*p*-TsOH, MeOH) readily gave the corresponding diastereomeric mixture of lactols **65**, which, unfortunately, did not undergo exchange with ethylene glycol to open the lactol ring and also did not undergo Wittig olefination. Therefore, **65** was oxidized (Jones; 99%) to lactone **66**, thereby converting the mixture to a single substance. With an excess of LDA and TMSCl, **66** was converted to the TMS enol ether-TMS ketene acetal, and the ketene acetal was hydrolyzed back to the lactone-TMS enol ether in an aqueous workup. Peracid oxidation then produced alcohol **67** in 92% yield, reduction of which (Red–Al®, PhH, reflux, 12 hours, 90%) revealed tetraol **68**.



At this stage, the epoxidation-fragmentation of tetraol **68** was of immediate concern. The factors controlling the rate of both fragmentation and epoxidation are not well understood, but it appears that subtle conformational changes can influence the rates dramatically. The high degree of substitution in tetraol **68**, therefore, was cause for some caution. It was convenient to protect the primary hydroxyl of tetraol **68** prior to attempting to epoxidize and fragment for two reasons. First, there would be no doubt that the incipient A-ring hydroxyl would be differentiated from the side chain hydroxyl, and second, tetraol **68** was an extremely polar substance and difficult to manipulate. Masking the primary hydroxyl would decrease this polarity. Under carefully controlled conditions, it was possible to differentiate the hydroxyls with a high degree of selectivity. Addition of two equivalents of pivaloyl chloride to a pyridine solution of tetraol **68** at 0°C followed by quenching into sodium bicarbonate no longer

than fifteen minutes later resulted in a near-quantitative yield of monopivalate **69**.

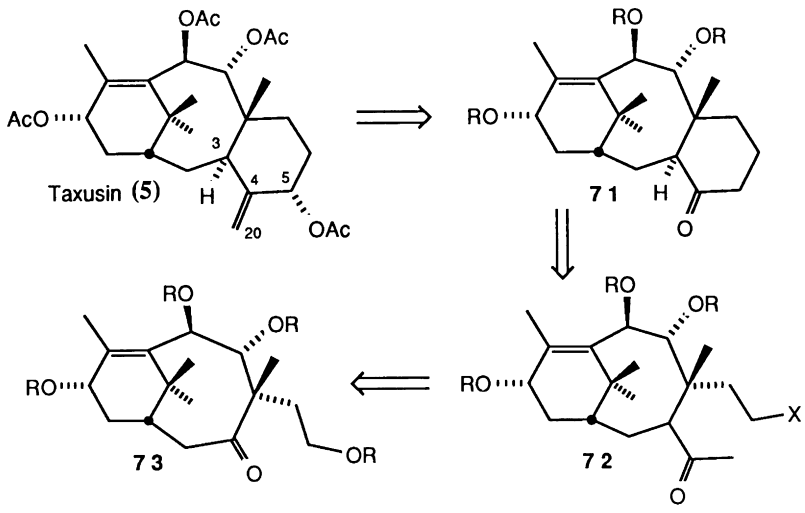
Unlike other similar substrates, Sharpless epoxidation of **69** was not effective. Apparently this is a consequence of having the pro-$C_8\alpha$ side chain attached. After some experimentation with additives in the



Sharpless epoxidation which failed to solve the problem, it was found that a large excess of anhydrous peracetic acid in methylene chloride solution was effective. The resulting epoxide was stable enough to obtain a ^1H NMR spectrum if it was run quickly, but this was not usually done. After workup with aqueous sodium thiosulfate to destroy excess peracid, the epoxide was typically subjected immediately to five equivalents of titanium tetraisopropoxide and the methylene chloride solution was heated to reflux for 45 minutes. In this manner a 90% yield of fragmented triol **70** could be realized.

3. *Retrosynthetic Analysis: The Remainder of the C-Ring*

To complete the synthesis of taxusin, we targeted intermediate ketone **71**. The C_4 carbonyl group of **71** was expected to be amenable to α-oxidation to introduce the C_5 acetoxy substituent as well as Wittig olefination to introduce C_{20}. In addition, it afforded the opportunity for epimerization at C_3, and, based upon the conformational information we had already obtained, the natural C_3 configuration was expected to be thermodynamically preferred. We planned to construct the C-ring of **71** via intramolecular aldol condensation or intramolecular alkylation of **72**. Since we expected the C_3 carbonyl group of a suitably protected derivative of **70**, represented as **73**, to be very hindered and quite resistant to nucleophilic attack, we planned to attempt the (hopefully irreversible) addition of a relatively unhindered but highly nucleophilic acyl anion equivalent to introduce the C_4 and C_5 carbons. Reductive removal of the C_3 tertiary hydroxyl group would then lead to **72**.

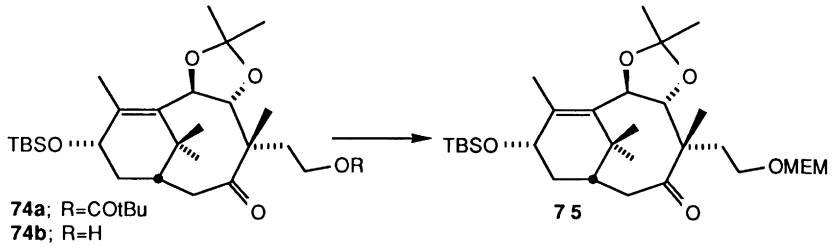


4. *Introduction of the Remaining C-Ring Carbons*[30]

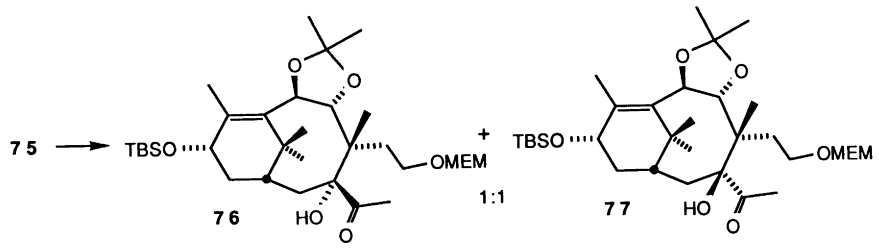
a. Methoxyvinyllithium Addition: Stereochemical Questions

It was necessary to protect triol **70** in order to add an acyl anion equivalent to the ketone carbonyl. To this end, **70** was treated with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid, resulting in rapid acetonide formation across the C_9–C_{10} hydroxyls, and C_{13} hydroxyl was protected (TBSOTf, pyridine) as the TBS ether to give **74a**. The pivalate group of **74a** was solvolyzed with methanolic sodium methoxide at reflux for two hours, providing the primary alcohol **74b** in 95% yield from **70**.

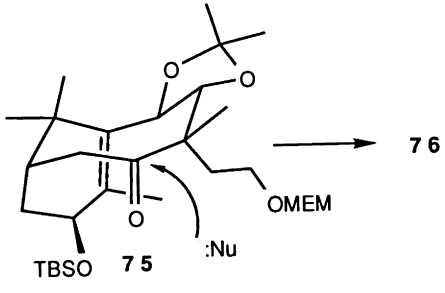
We chose α-methoxyvinyllithium[31] as the acyl anion equivalent. The choice of protecting group for the primary alcohol was critical. If the hydroxyl was left free, addition to the carbonyl was extremely slow, even at 0°C. The primary alcohol of **70** could be protected as a variety of acetals. However, the most interesting of these was the MEM ether **75**, produced in 99% yield by treatment of the alcohol with 2-methoxyethoxymethyl chloride and *N,N*-diisopropylethylamine in methylene chloride solution. Nucleophilic addition to the carbonyl was still slow; treatment of **75** with five equivalents of α-methoxyvinyllithium in THF solution for twelve hours at −13°C was necessary to effect complete consumption of starting material. Upon examination of the crude reaction mixture,



we were surprised to find a 1 : 1 mixture of diastereomeric enol ethers. This was confirmed by hydrolysis with aqueous acetic acid to provide the diastereomeric α-hydroxy ketones **76** and **77**, which were separable by flash chromatography.



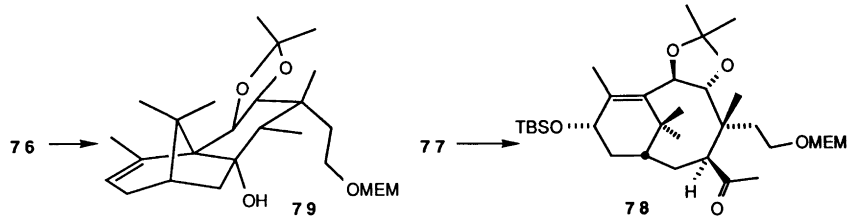
We certainly did not predict this result; given the chair-boat conformation for **75**, which was confirmed by NOE difference studies, one would expect the nucleophile to attack from outside the ring system, leading to **76** as the major, if not the exclusive, product. Since this is not the case, we reasoned that there must be a factor other than the conformation influencing the direction of the addition. The MEM ether was a possibility, since it could serve as a ligand for the lithium reagent. However, at this point we did not regard the mixture as a problem since the plan called for reductive removal of the hydroxyl substituent. This would give, in theory at least, an exocyclic methyl



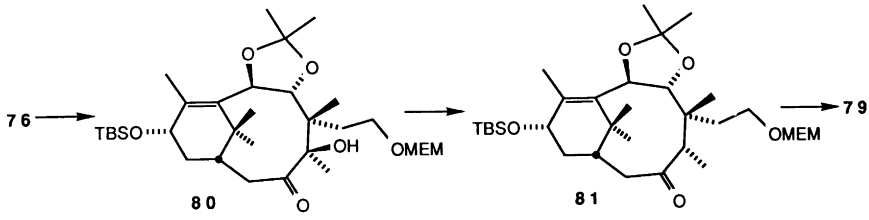
ketone, and the stereochemistry at C_3 could be controlled through epimerization. However, it rapidly became clear that we would need to address the stereoselectivity question in the α-methoxyvinyllithium addition.

b. An Unexpected Rearrangement[32]

Upon independently subjecting the two α-hydroxy ketones **76** and **77** to samarium diiodide (10 equivalents SmI_2, THF, 25°C, 2 hours) reduction,[33] two very different products were obtained. Isomer **77** (the one that we did not expect to obtain from methoxyvinyllithium addition to **75**) was reduced smoothly in 90% yield to a methyl ketone which was clearly the desired **78**, a single isomer, but we could not be certain of the stereochemistry at C_3. Ketone **78** underwent base-catalyzed deuterium exchange at C_3 without isomerization, and, since we could not obtain more conclusive evidence, we had to assume (an assumption which turned out to be correct) that we had obtained the desired C_3 stereochemistry. To our surprise, however, isomer **76** was reduced by samarium diiodide under the identical conditions to give tertiary alcohol **79** in 92% yield.



Under milder conditions (2 equivalents SmI_2, THF, 0°C, 1 hour), **76** was converted to a new compound, **80**, in 90% yield. The mass spectrum of **80** indicated that the molecular weight had not changed, so it was clear that **80** was a rearrangement product, not a reduction product. Further treatment of **80** with samarium diiodide (5 equivalents SmI_2, THF, 0°C, 2 hours) gave rise to the reductive dehydroxylation product **81** in 70% yield, together with small amounts of **80** and **79**. Finally, treatment of **81** with samarium diiodide (5 equivalents SmI_2, THF, 25°C, 2 hours) produced the initially observed tricyclic alcohol **79** in near quantitative yield. Alcohol **79** could be converted back to **81** by epoxidation with peracetic acid, fragmentation, and treatment with *t*-butyldimethylsilyl triflate, a fact



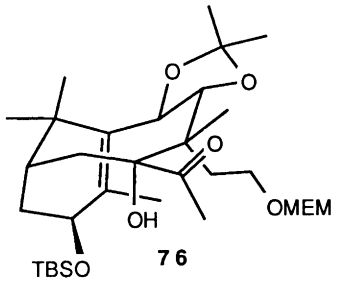
that was useful in determination of the structures of **79** and **81**, but was worthless for taxusin synthesis.

The stereochemistry of **79**, **80** and **81** was determined by NOE difference spectroscopy. The key in determining the stereochemistry of **80** was the fact that the methyl group adjacent to the carbonyl showed a positive NOE to one of the protons on the alkoxyethyl side chain but no NOE to protons of the β-face of the molecule. The methine proton adjacent to the carbonyl of **81** showed a positive NOE to both the β proton on the methylene adjacent to the carbonyl and the $C_9\beta$ proton (taxane numbering). The corresponding two protons in **79** are 1,3-diaxial and exhibit a positive NOE.

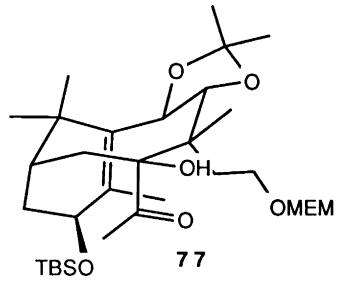
The first step of this process, skeletal rearrangement of **76** to **80**, is reminiscent of a pinacol rearrangement, and we anticipated that it should be subject to acid catalysis. Samarium(III) is Lewis acidic and is difficult to avoid when preparing SmI_2 due to the oxygen sensitivity of SmI_2. In fact, **76** rearranged quantitatively to **80** in the presence of Sm(III) alone. The rate of rearrangement, however, was dependent on how the Sm(III) was prepared. If SmI_2 was prepared in the usual fashion and then exposed to the atmosphere, the resulting Sm(III) caused rearrangement to take place in 24 hours at 25°C. This slow rate of rearrangement is quite possibly due to the presence of moisture, which would compete with **76** for Sm(III). Sm(III) prepared by oxidation of SmI_2 with di-*t*-butyl peroxide caused the rearrangement to proceed to 50% conversion in 2 hours at 0°C, while Sm(III) prepared by deoxygenation of cyclohexene oxide required 2 hours at 0°C to effect complete rearrangement. Given the difference in these rates, and the presence of Sm(II) in the original reaction, the nature of the active species must remain speculative at this point.

The question of why **76** undergoes this rearrangement at all while **77** does not still remains. We speculate that the answer lies in the conformation of the two molecules. The conformation of **76** is such that the p orbitals of the carbonyl group are perpendicular to the

carbon-oxygen σ bond of the hydroxyl group. The migrating carbon-carbon σ bond, however, is well-aligned with the carbonyl p orbitals. Rearrangement of **76** is thus favored over reduction. The situation is reversed in the case of **77**. Here the conformation, due to steric repulsion from the A-ring, is such that the p orbitals of the carbonyl group and the carbon-oxygen σ bond are perfectly aligned for reduction to occur.



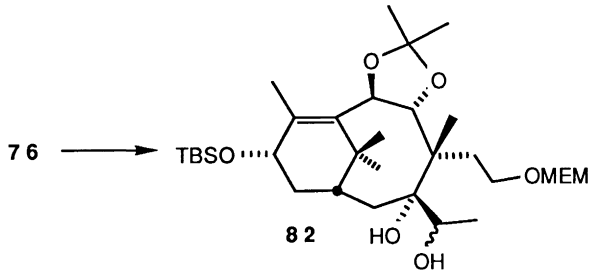
76



77

The next step in the process, the conversion of **80** to **81**, is simply reduction of an α-hydroxy ketone, but the final step, conversion of **81** to **79**, is non-trivial. It depends on close proximity between the carbonyl group and the A-ring bridgehead olefin. The phenomenon of transannular conjugation discussed earlier in the case of the bicyclo[5.3.1] compounds also occurs in the bicyclo[6.3.1] compounds. Evidence of this is provided by the UV spectrum of **81**, which showed a λ_{max} of 204 nm with an ε of 5736. One-electron reduction of **81** would give the corresponding samarium ketyl, which, because of its proximity to the olefin, could undergo radical cyclization followed by further electron transfer and loss of $TBSO^-$ to give **79**.

Further support for the notion of conformational control over the reactivity of these α-hydroxy ketones was obtained from the following experiment. We were interested in determining whether we could force the unfavorable reduction of **76** to take place (without rearrangement) to give **78**. To this end, we treated **76** with ten equivalents of SmI_2 in the presence of a large excess of triethylamine. In fact none of ketone **78** was obtained, but diol **82** was formed in good yield. This extraordinary result shows that even if the Lewis acid-catalyzed process is shut down, and the samarium ketyl is formed, the neighboring hydroxyl group is not expelled.



c. The Directed Methoxyvinyllithium Addition

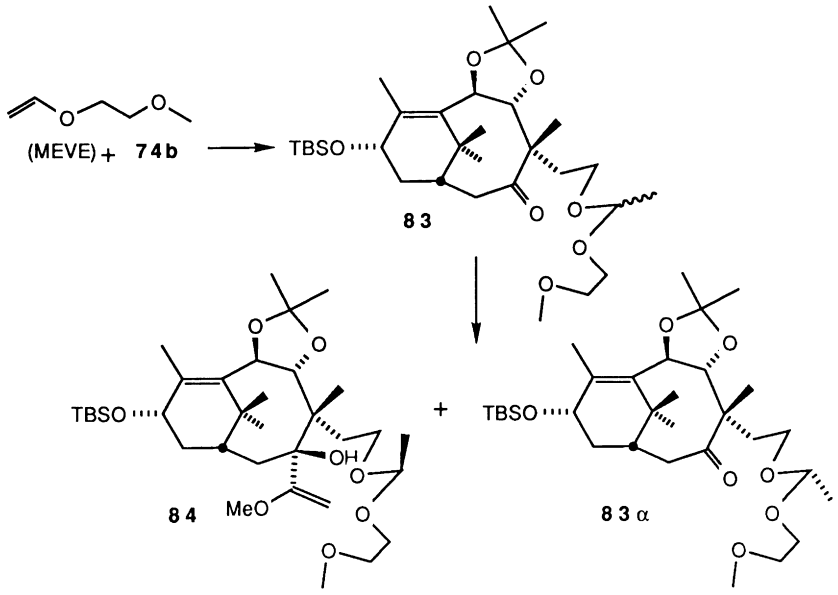
Since the divergent reduction of **76** appeared to represent a severe disruption in the synthetic path to taxusin, it became imperative to maximize the formation of **77** in the α-methoxyvinyllithium addition at the expense of **76**.

We had hypothesized that the MEM ether was acting as a ligand and thus directing the lithium reagent to the α-face of the molecule during the attack on ketone **75**. If this was true, then changing the solvent from THF, a coordinating solvent, to a hydrocarbon, unable to coordinate to lithium, should enhance this directing effect. We were most fortunate to find that this was in fact the case. Changing the solvent to hexane while keeping all other conditions identical resulted in the production of only (as determined by NMR analysis) one isomer, and α-hydroxy ketone **77** was obtained in 90% yield from **75** after hydrolysis of the enol ether. It proved possibe to reduce **77** to **78** with 2.3 equivalents of samarium diiodide at 0°C for 2 hours (90% yield), and this was the procedure subsequently used.

At this stage, one of our worst fears was realized: the MEM ether of **78** proved very resistant to cleavage under the usual ($ZnBr_2$; $TiCl_4$) conditions.[34] While we continued to search for conditions for the efficient cleavage of the MEM group, we also began a quest for protecting groups that would be easier to cleave and still have the directing effect of the MEM ether. We developed several of these, but only one gave sufficiently interesting results to warrant discussion. The corresponding EE ether reacted with α-methoxyvinyllithium to give a mixture of diastereomers in which the undesired isomer was predominant, i.e., essentially no directing effect was observed. Methoxyethyl vinyl ether (MEVE) was easily prepared from methoxy ethanol. Alcohol **74b** reacted (1% methanesulfonic acid/ether, 0°C)

with MEVE to give MEE ether **83** (ca. 1 : 1 mixture of diastereomers) in 98% yield.

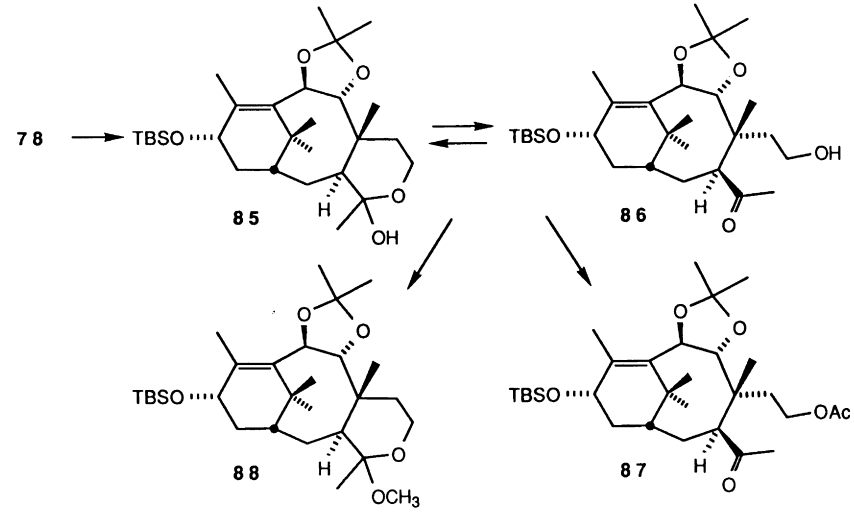
Addition of α-methoxyvinyllithium to **83** under the usual conditions gave a single vinyl ether diastereomer **84** in 56% isolated (flash chromatography) yield, along with 39% of the other diastereomer of the starting ketone (**83**α), which had not reacted. We have been unable to unambiguously confirm our stereochemical assignments at the acetal carbon in these two substances, but it is clear that excellent kinetic diastereoselectivity was observed in the reaction of **83** with α-methoxyvinyllithium. Whie **84** was not used in the synthesis of taxusin due to the low yield of its formation, the diastereospecificity observed in this case provides compelling evidence that groups able to coordinate to lithium on the side chain are involved in directing the stereochemistry of the α-methoxyvinyllithium addition.



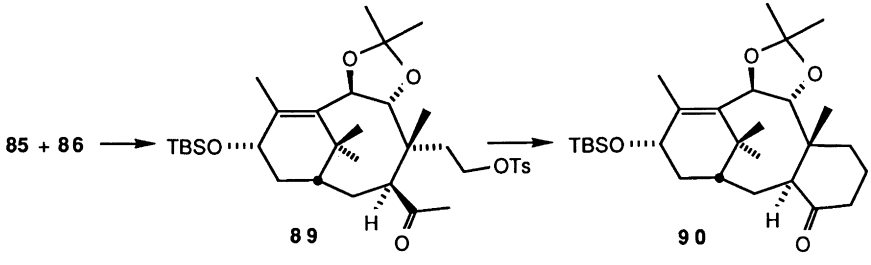
5. *Closure of the C-Ring*[29]

After many trials of various reagents and conditions, it was finally found that a catalytic amount of anhydrous $FeCl_3$ in acetic anhydride[35] at low temperature ($-45°C$) was very effective for the removal of the MEM group of ketone **78**. A mixture of acetate and acetoxy methyl ether was originally obtained, but in subsequent

experiments, the crude mixture was solvolyzed directly without isolation (K_2CO_3, MeOH) to give an equilibrium mixture of hemiketal **85** and hydroxy ketone **86** in 90% yield. For purposes of positive identification, the mixture was acetylated to give **87**. In addition, treatment of the mixture of **85** and **86** with acidic methanol produced ketal **88**.

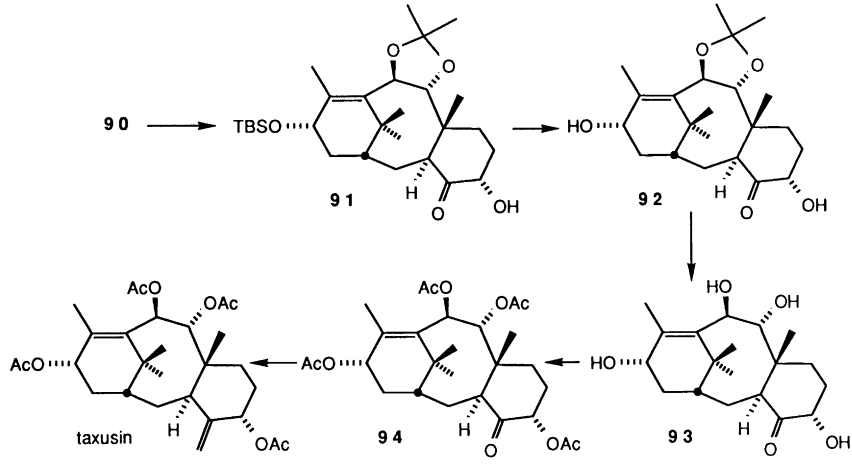


However, Swern oxidation of the mixture of **85** and **86** failed, and other methods of oxidation did not give a good yield of the corresponding aldehyde. Therefore, closure of the C-ring via an aldol condensation was not pursued. The mixture could, however, be converted (toluenesulfonic anhydride, pyridine) to the unstable tosylate **89**, which was directly cyclized (*t*-BuONa, THF) to furnish cyclic ketone **90** in 96% yield from the mixture of **85** and **86**. When potassium *tert*-butoxide was used as a base for the cyclization, a significant amount of enol ether resulting from O-alkylation was obtained.



C. Functionalization of the C-Ring

The final stage in the synthesis of taxusin simply required introduction of the C_5 hydroxyl group and C_{20}, an exocyclic methylene group. Both of these operations were easy compared with some of the difficulties we had previously experienced. Ketone **90** was converted (LDA, TMSCl) to the less substituted C_4–C_5 TMS enol ether, which underwent smooth epoxidation exclusively from the less hindered α-face to give hydroxy ketone **91** contaminated with a small amount of the corresponding TMS ether. Without purification at this stage, the silyl groups were removed through the action of tetrabutylammonium fluoride to provide diol **92**. The acetonide was then removed by hydrolysis with dilute aqueous acid, and the resulting tetraol **93** was acetylated to give tetraacetoxy ketone **94** in 83% yield from **90**. Both the silyl groups and the acetonide could be removed in the same operation by using aqueous HF/HCl, but the overall yield was slightly lower.



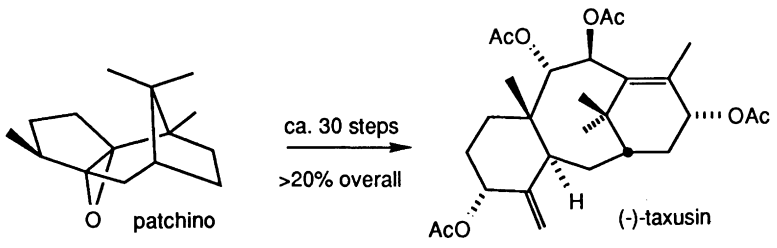
Wittig olefination was employed for the last step to introduce C_{20}. This reaction turned out to be nontrivial, for it required olefination of a relatively unreactive cyclohexanone in the presence of four esters. When **94** was treated with the ylide ($Ph_3P{=}CH_2$) in THF, ether, DME, or mixed solvents, yields were very low (< 20%). However, Wittig olefination of **94** with preformed ylide in a 1 : 1 mixture of toluene and hexane furnished (−)-taxusin in 70% yield. Presumably,

this solvent system provided a salt free ylide, and side reactions occurring from the four somewhat labile acetoxy groups were minimized. We were pleased with this result, although one might note that this seemingly simple reaction gave the lowest yield in the entire synthesis.

Synthetic taxusin exhibited ^{1}H NMR, ^{13}C NMR, and IR spectra and mp (125–127°C) identical with those of natural (+)-taxusin. However, the mixed melting point was depressed, and the optical rotation of synthetic taxusin was equal to that of natural taxusin but opposite in sign (natural, $[\alpha]^{25}_{Hg} + 120°$; synthetic, $[\alpha]^{25}_{Hg} - 120°$ ($CHCl_3$, c 0.16).[15]

IV. Summary and Outlook

I have described the first, and so far the only, total synthesis of a taxane diterpene. As might be expected for a first synthesis, it follows a conservative approach and requires approximately thirty steps for the conversion of patchino to (−)-taxusin. Despite its length, the synthesis is efficient, proceeding in greater than 20% overall yield, a tribute to the tenacious and meticulous effort of the dedicated co-workers who brought the synthesis to fruition.[36] Although the antipode of the natural product was actually obtained, the method is also applicable to the synthesis of (+)-taxusin, which would require a few additional steps for the preparation of (+)-patchino from (−)-camphor as previously described by Buchi.[17c]



Undoubtedly, a much shorter second generation synthesis of taxusin could now be developed. However, like most natural product syntheses, this is primarily an intellectual exercise, since there is no known practical utility for taxusin. The situation is quite different in

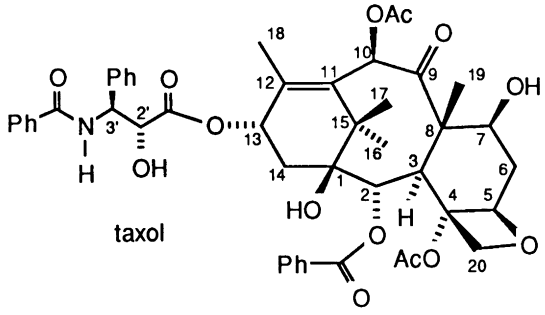
the case of taxol. The total synthesis of taxol presents an enormous intellectual challenge, but it is also a problem of great practical significance. The world awaits a solution to the taxol supply problem from the realm of synthetic organic chemistry.

The urgent need for taxol in large quantities (at least hundreds of kilograms per year) adds another dimension infrequently encountered by (academic) synthetic chemists. To successfully address the supply problem, the synthesis must be very short and economical, with each additional step increasing expense and diminishing practicality. We are still far away from attaining these goals.

Furthermore, the synthesis of taxol is not the only goal. An understanding of the mechanism by which taxol promotes the polymerization of tubulin at the molecular level is completely absent. A wide variety of taxol analogs will be needed to begin to gain some understanding of this process. Many of these analogs are also likely to be potent antitumor agents, and some of them might reasonably be expected to be even more effective than taxol. Only through synthetic organic chemistry can many important contributions in these areas be realized.

The synthesis of taxusin teaches that we must learn a great deal more about the chemistry of the taxane nucleus, particularly the influence of conformation on reactivity in the eight-membered B-ring. In fact, practically every step of the taxusin synthesis which involved chemistry of the eight-membered ring presented unexpected problems and produced unusual results. Therefore, an extensive exploration of the chemistry of the eight-membered ring will be necessary to provide the knowledge and understanding fundamental to any successful approach to the synthesis of taxol.

Upon inspection, taxol presents a number of issues which remain to be addressed. How can the oxygen functionality at C_1 and C_2 be introduced in a stereospecific fashion? How and when will the C_9 carbonyl group be introduced, and how can the readily epimerizable (through retro-aldol, realdol) C_7 hydroxyl group be dealt with? What method(s) for oxetane synthesis can be used in the setting of so much other functionality? How does one deal with the variety of esters present in taxol? Can a method for the efficient attachment of the C_{13} side chain, which is known to be extremely difficult,[37] be achieved?[38] How can we gain a more efficient entry into the natural enantiomeric series?



taxol

The search for answers to these questions continues. Difficulties remain, but opportunities abound.

Acknowledgments

I am deeply grateful to the fine group of co-workers whose dedication, diligence and enthusiasm made this work possible as well as exciting and enjoyable. I have attempted to indicate contributions of specific individuals at the appropriate places in the text. Dr. Shinya Harusawa and Dr. Sadamu Yogai contributed to the early stages of the taxusin synthesis, and it was through the persistence of Dr. Rouh-Rong Juo that the route from patchino to substituted bicyclo[5.3.1] compounds was discovered. Mr. Richard Lowenthal developed conditions which permitted this conversion to provide a sustained supply of material. The latter stages of the synthesis were carried out by Dr. Andrew D. Williams and Dr. Hyeong-Baik Kim, whose insight and careful experimentation brough the taxusin project to fruition.

Funding for the project was provided by the National Cancer Institute (CA 42031) and donors to the Taxol Research Fund. Special thanks are due to Dr. William Schrieber for providing an abundant supply of patchino.

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Chapter 6

THREE AND ONE-HALF APPROACHES TO THE SYNTHESIS OF PEDERIN

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I. Introduction

Our story begins in 1775 when the Danish entomologist Johann Christian Fabricius (1745–1808) first described the genus *Paederus* which at that time included only two species. In the ensuing two centuries, over 600 species have been found inhabiting all temperate and tropical climates including the chief protagonist in our account, the rather colorful and notorious beetle *Paederus fuscipes* (Figure 1) whose natural history deserves some mention.[1] *Paederus fuscipes* is about 8 mm long and reveals a black head and abdominal apex with

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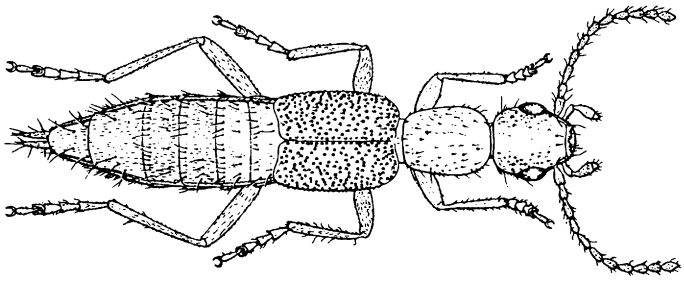


FIG. 1. *Paederus fuscipes.*

an orange thorax and abdominal base and iridescent blue elytra (wing case). It has an especially wide distribution: from central Asia its range extends westward to the British Isles, east to Japan, and southeast to Australia. Its habitat includes riverbanks, marshes, and irrigated fields where it feeds mainly on insects, mites, soil nematodes, and decaying vegetable matter. Like most members of the genus, *Paederus fuscipes* is a predator of arthropods with an important role in the natural regulation of the fly population. With only limited opportunity for human contact, we can usually regard the insect with beneficence; however, on warm spring and summer evenings, inadvertent contact with swarms of the insect attracted to artificial light can prove very painful.

The potent vesicant effects of *Paederus* first became known to Western science through a report by Vorderman (1901)[2] of personnel at the Anjet-Kidoel lighthouse in Java afflicted by severe dermatitis caused by small winged insects locally called *semoet-kalong*. Da Silva later (1912)[3] recorded a similar infestation suffered by agricultural workers in Brazil. The dermatitis is caused by crushing the insect on the skin and the eyes are particularly sensitive though the palms of the hand and the soles of the feet are resistant. In addition to lesions, severe symptoms such as fever, edema, neuralgia, arthralgia, and vomiting are observed with erythrema persisting for several months. Interestingly, hedgehogs, toads, and frogs are immune to the effects and chickens are less susceptible than mice, rats, and rabbits[1].

It has recently been suggested[1] that both the affliction and its causative agent were known to Chinese medicine over 1200 years earlier. An insect called *ch'ing yao ch'ung* was described in A. D. 739 by Ch'en: "It contains a strong poison and when it touches the skin it

causes the skin to swell up. It will take the skin off one's face and remove tattoo marks completely. It is used as a caustic for toxic boils, nasal polypi, and ringworm."

II. Isolation and Structure Proof

The active chemical agent responsible for the dermatitis caused by *Paederus fuscipes* was first isolated in crystalline form by Netolitzky in 1919[4]. The research which eventually led to the correct structure began in 1952 with Pavan and Bo[5] who named the toxic agent pederin and determined its melting point (112°C) on a sample derived from 25 million specimens (ca. 100 kg). The correct molecular formula ($C_{25}H_{45}O_9N$) established by Quilico and co-workers[6] in 1961 led to a detailed study of the chemical constitution of pederin and a structure, devoid of stereochemical definition, was proposed in 1965[7]. An independent investigation by Matsumoto's team at Sapporo gave corroborating evidence[8]. With one minor exception (*vide infra*) all the conclusions drawn from the degradation and ^1H NMR studies of Quilico and Matsumoto were later confirmed by an X-ray crystallographic analysis of pederin di-*p*-bromobenzoate[9] which also established the absolute and relative stereochemistry as shown in Figure 2. It is worth reviewing the very elegant degradation studies of the Quilico group since they were published with full experimental details[10] and contain a wealth of information on the stability of pederin and its degradation products which are relevant to all subsequent synthetic studies.

Pederin (**1**) and the hemiacetal pseudopederin (**2**) (Scheme 1) were both isolated from extracts of *Paederus fuscipes*. The compounds were interconvertible: warming an aqueous solution of pederin gave pseudopederin; methanolysis of pseudopederin gave pederin. Both reactions were highly stereoselective indicating that C_6 possessed

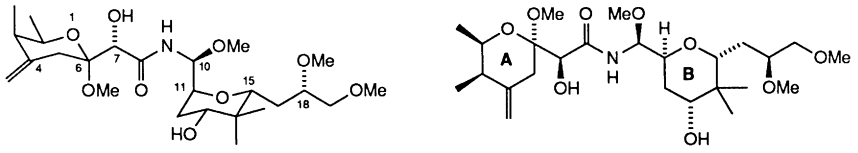
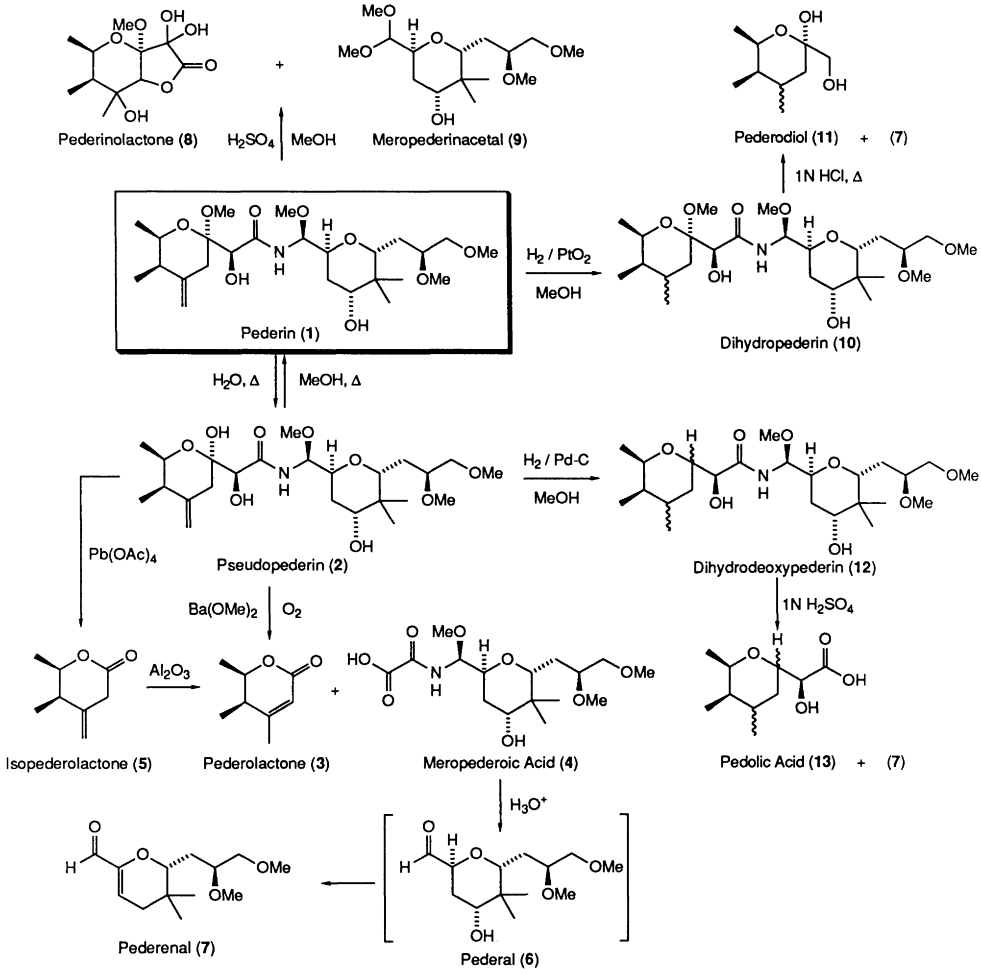


FIG. 2.



SCHEME 1

the more thermodynamically stable axial configuration as determined by the anomeric effect. Treatment of pseudopederin with barium methoxide in methanol in an oxygen atmosphere yielded pederolactone (**3**) and meropederoic acid (**4**) by a retroaldol/oxidation sequence of reactions. Alternatively, cleavage of pseudopederin with lead tetraacetate gave the unstable isopederolactone (**5**) which yielded **3** after column chromatography. The isolation of **4** under these conditions was significant since it demonstrated that the N-acyl

aminal moiety was stable to the neutral and basic conditions which decompose ring-A. Acidic hydrolysis of **4** gave pederal (**6**), oxalic acid, ammonia, and methanol, although under these conditions **6** was further degraded to pederenal (**7**). The ease of dehydration suggested that the ring-B hydroxyl function was located at C_{12} [i.e., β to the pendent carbonyl function at C_{11}] and led to misassignment of the structure. Subsequent studies have established the mechanism of the dehydration[11].

The Quilico group found that attempts to degrade the N-acyl aminal in **1** or **2** directly by acidic hydrolysis gave complex mixtures of products from which only pederenal (**7**) could be isolated. Acidic methanolysis of **1** in an oxygen atmosphere was more successful, yielding the acetal **9** and the oxidized lactone **8** in which the exocyclic methylene group at C_4 had been intramolecularly derivatized. Thus, the exocyclic methylene appeared to be the origin of the instability of the ring-A fragments to further degradation under non-oxidizing conditions or by acidic hydrolysis. This view was supported by studies on dihydropederin (**10**) and dihydrodeoxypederin (**12**) (Scheme 1). Acidic hyrolysis of the N-acyl aminal in **10** yielded a carboxylic acid which decarboxylated under the reaction conditions to give pederodiol (**11**), pederenal (**7**), ammonia, and methanol. In the deoxy-series, acidic hydrolysis of **12** gave efficient recovery of **7** and pedolic acid (**13**) which was resistant to decarboxylation.

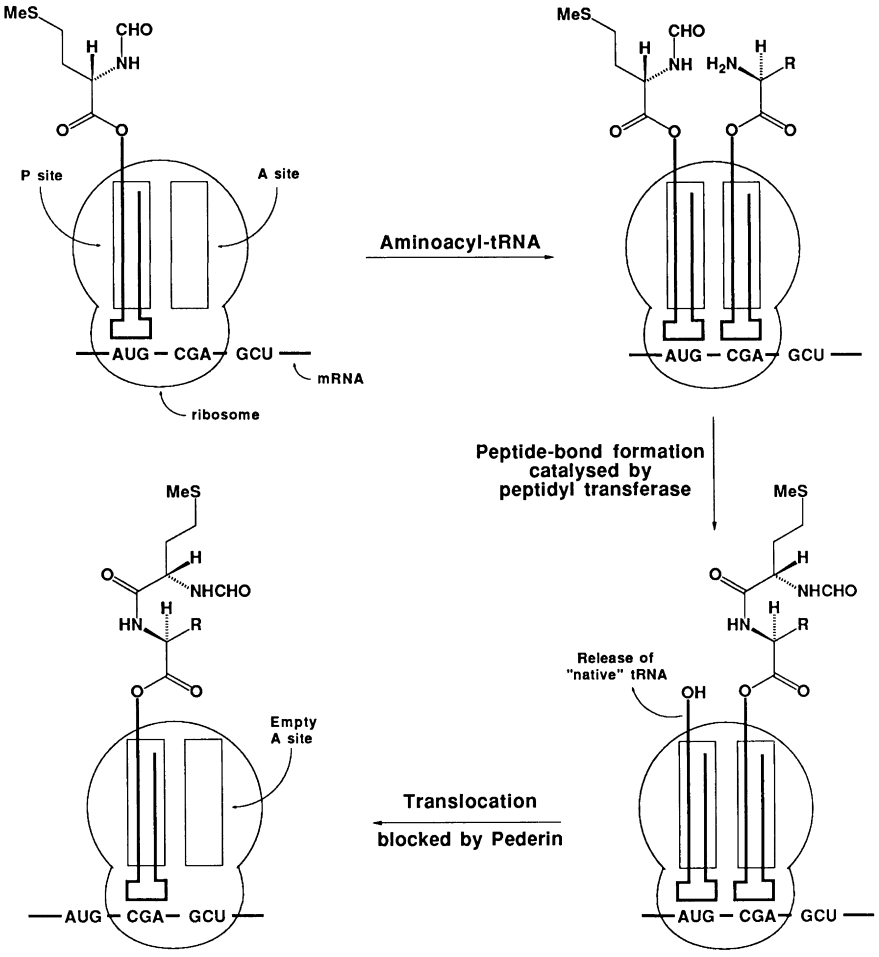
The degradation studies established that pederin harbored two functional groups that contributed to its instability. The exocyclic methylene greatly activated the homoallylic acetal making ring-A particularly fragile in acid. The N-acyl aminal was stable under neutral and basic conditions but it too was unstable towards acid. Any synthetic strategy would have to take account of these observations, particularly with respect to the final assembly of the molecule and the timing of the introduction of the labile functionality.

III. Biological Activity

Pederin is a very weak antibacterial agent but it is highly toxic to eukaryotic cells. Ingestion can cause severe internal damage and intravenous injection causes death at levels which suggest that it is more potent than cobra venom. The toxicity of pederin appears to be

related to its inhibition of protein biosynthesis and cell division. In order to appreciate how pederin works we must first consider the sequence of events by which a peptide chain is elongated (Scheme 2)[12].

The cellular apparatus required to assemble a peptide chain in a defined sequence involves the coordinated interplay of over a hundred macromolecules including mRNA, tRNAs, activating enzymes, and protein factors in addition to ribosomes. However, for the purposes of this discussion we will consider a highly simplified model involving a



SCHEME 2. Elongation cycle of protein biosynthesis.

ribosome, a molecule of mRNA incorporating transcripts of genetic code, and two molecules of functionalized tRNA (peptidyl-tRNA and aminoacyl-tRNA) that are coded to recognize a nucleotide triplet on the mRNA. Since peptide synthesis does not involve free amino acids, the functionalized tRNA also serves as an adapter which both binds an amino acid and delivers it in a coded sequence to the ribosome.

Ribosomes serve as templates which bind mRNA and tRNA. The peptidyl-tRNA bearing a peptide chain at the terminus is bound to the P-site of the ribosome. The aminoacyl-tRNA bearing a single amino acid at the terminus binds to the adjacent A-site. After peptide bond formation, the translocation step occurs in which peptidyl-tRNA occupying the A-site, now elongated by one amino acid, moves a distance of three nucleotides along the mRNA chain to the P-site (and in the process displaces "native" tRNA–i.e., tRNA minus its amino acid passenger) so that a new aminoacyl-tRNA can enter the A-site. These two tRNA binding sites on the ribosome are the key to understanding how the genetic code incorporated in the mRNA is translated into a specific amino acid sequence.

Using human tonsil ribosomes, Vazquez[13] studied the mechanism by which pederin inhibits protein biosynthesis. Pederin was shown to bind irreversibly to the ribosome, preventing translation of the mRNA. Inhibition occurred at the translocation step (Scheme 2) during the elongation cycle. After peptidyl transfer had occurred., the ribosome contained "native" tRNA on the P-site and dipeptidyl-tRNA on the A-site but the translocation step was blocked and chain elongation terminated.

The irreversible binding of pederin to ribosomes and its vesicant activity suggest it may function as an alkylating agent with the homoallylic acetal or N-acyl aminal as sites of potential reactivity. The biochemical and pharmacological activities may not be related, however, since the hydrogenated derivative dihydropederin (**10**) is not a vesicant though it remains a potent inhibitor of protein biosynthesis. Unfortunately, there have been very few attempts to evaluate the clinical potential of pederin. Pavan[14] demonstrated that elderly patients with chronic necrotic, purulent, and fetid sores completely recovered in some cases after treatment with minute amounts of pederin. A Russian study has also revealed a therapeutic effect on eczema and neurodermatitis with no complications[15]. Potential use as an anti-cancer agent has been suggested based on pederin's ability to

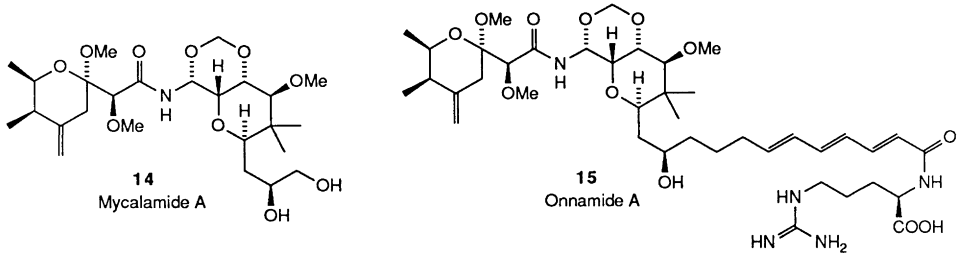


FIG. 3

block mitosis in normal and tumoral cells at doses of 1 ng/ml and reports that it inhibited sarcoma-180 tumors in mice[16].

For many years, pederin was considered to be structurally unique in the realm of natural products. However, the recent isolation of mycalamide A (**14**)[17] and onnamide A (**15**)[18] (Figure 3) from marine sources indicates that structures bearing two dihydropyran rings bridged by an N-acyl aminal are rather more common than hitherto supposed. The presence of **14** and **15** in marine organisms also casts further doubt on the defensive role previously assigned to pederin. It is significant that all three structures have potent biological activity: like pederin, mycalamide A and onnamide A are also inhibitors of protein biosynthesis and they show promising antiviral activity as well. Clearly, an efficient and flexible synthesis of pederin and close analogues would allow investigation of structure-activity relationships and further clarify its mode of action on eukaryotic ribosomes. Perhaps the recent isolation of the marine natural products will stimulate a serious effort to explore and evaluate the medical potential of pederin as well as its more complex relatives.

IV. Synthesis of Pederin

A. Anticipating Difficulties

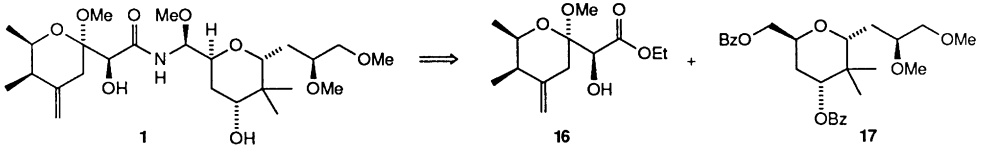
The novel architecture of pederin and its dense array of sensitive functionality poses a considerable synthetic challenge. The first three total syntheses of pederin adopted a very similar "sensible" strategy based on two considerations. First, all three appreciated that the N-acyl aminal bridge was a logical point of disconnection into ring-A and ring-B fragments of approximately equal complexity. Secondly,

all three syntheses were designed to avoid problems associated with the high acid-lability of the homoallylic acetal array in ring-A; therefore, the various ring-A fragments were constructed with this troublesome functionality present in latent form[19]. The first total synthesis of pederin was accomplished by Matsumoto and co-workers[19] who pioneered viable protocols for achieving the difficult task of constructing both the highly hindered N-acyl aminal bridge and the homoallylic acetal. Their work will be given detailed consideration later since the two subsequent syntheses by Nakata, Oishi, and co-workers[20] and the Southampton group[21] depend to a large extent on these Matsumoto protocols. We will begin our account of the Southampton synthesis of pederin with a prelude describing syntheses of the ring-A fragment (±)-ethyl pederate (**16**) and the ring-B fragment (+)-pederol dibenzoate (**17**)[22]. Although neither of these syntheses were efficient enough to warrant adoption into a total synthesis, they were profitable failures in that they stimulated new lines of productive research.

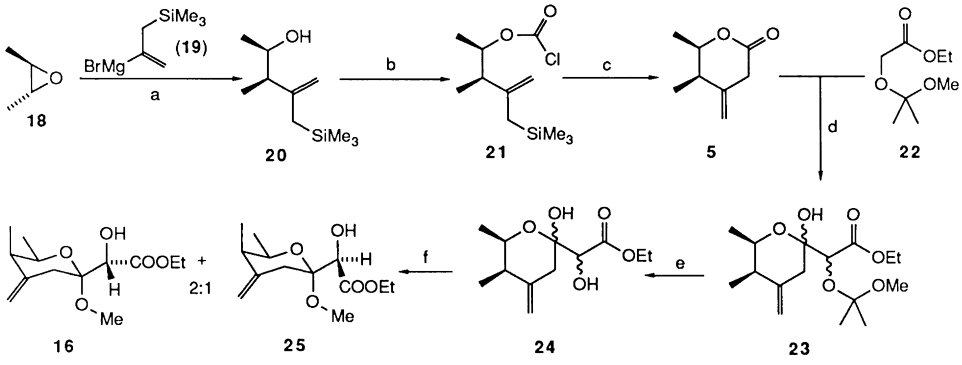
B. Playing with Silicon-Mediated Annulation Reactions

In light of the well-documented lability of the homoallylic acetal array, we made a decision which proved to be the very quintessence of maladresse: we proposed to unite a ring-A fragment bearing an intact C_4 methylene group derived from ethyl pederate (**16**) to a suitable ring-B fragment derived from pederol dibenzoate (**17**) (Scheme 3)[23]

Our short synthesis of ring A fragment (±)-ethyl pederate (**16**) (Scheme 4) was inspired by some contemporary work of Fleming and co-workers[24] who had demonstrated that electrophilic substitution reactions of allyl silanes provide a powerful method for the regiocontrolled introduction of exocyclic methylene groups. We began with nucleophilic scission of (±)-*trans*-2,3-epoxybutane (**18**) by the Grignard reagent **19** in the presence of CuI to give the homoallylic alcohol **20** in 47% yield. The corresponding chloroformate **21** cyclized on



Scheme 3



SCHEME 4: YIELDS AND REAGENTS

(a)	47%	THF, -30 to 0°C, 3 h;	(d)	37%	**22** + LDA / THF, -78°C; then add **5** at -78°C, 2 h;
(b)	88%	phosgene / toluene-pyridine, 0°C, 1 h;	(e)	------	conc. HCl / THF, rt, 30 min;
(c)	56%	1 eq. $SnCl_4$ / CH_2Cl_2, 0°C, 3 h;	(f)	45%	TsOH / MeOH, rt, 4 h.

SCHEME 4

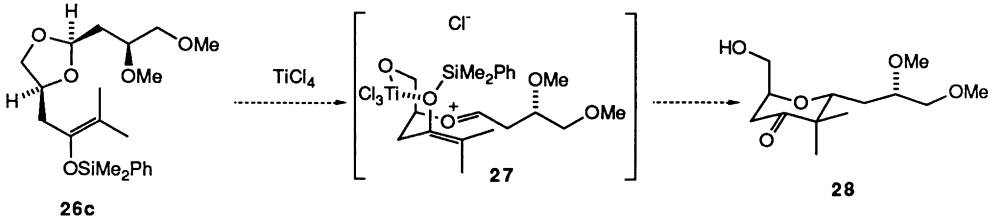
treatment with $SnCl_4$ to give the unstable β,γ-unsaturated lactone **5**. Considerable care had to be exercised in the purification and storage of **5** because it rearranged under the slightest provocation to the more stable α,β-unsaturated isomer **3** (Scheme 1). The conjugated lactone **3** could be converted back to **5** by conversion to the enolate with lithium diisopropylamide followed by kinetic protonation with acetic acid, but the recovery was poor and mixtures of **5** and its conjugated isomer **3** inevitably resulted.

The lactone **5** reacted with the lithium enolate prepared from the ethyl glycolate derivative **22** to give a mixture of hemiacetals **23** from which the hydroxyl protecting group was removed with acid. The resultant mixture of diastereomeric diols **24** was then treated with acidic methanol to give a 1 : 2 mixture of ethyl *epi*-pederate (**25**) and ethyl pederate (**16**) in 20% overall yield from **5**. The isomers were easily separated by column chromatography and their stereochemistry ascertained by ^1H NMR spectroscopy. Unfortunately, all attempts to effect base-catalyzed hydrolysis of ethyl pederate resulted in decomposition and it was just as susceptible to acid-catalyzed decomposition as pederin itself. The methyl ester proved no less tractable. The acid sensitivity of **16** was pronounced: it decomposed in dilute acetic acid or even on chromatography because the alkene function is able to stabilize an incipient oxonium ion formed on loss of the homoallylic axial methoxy group at C_6 thereby facilitating its de-

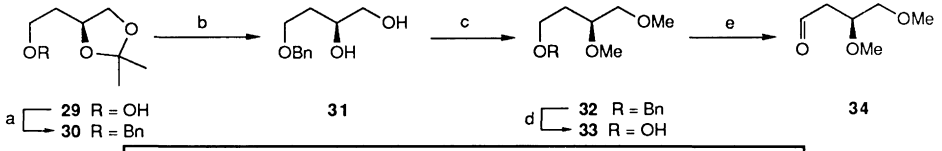
parture. Low yields and marginal stability led us to abandon development of our synthesis of ethyl pederate.

Our first approach to the ring-B fragment (+)-pederol dibenzoate (**17**) was conceived along the lines shown in Scheme 5 in which an intramolecular directed aldol reaction, in the variant developed by Mukaiyama and co-workers[25], was to play a crucial strategic role. Success depended on regioselective cleavage of the dioxolane **26c** giving a bridged (*E*)-oxonium ion intermediate **27** which would then suffer nucleophilic attack by a pendant enol silane from the *Si* face to generate the tetrahydropyranone **28** having the C_{11} substituent (pederin numbering) in an axial position. At the time these studies were launched (1981), there were very few examples of the intramolecular aldol condensation known[26] and thus no precedent for predicting the stereochemical course of the salient annulation reaction.

The dioxolane **26c** was constructed from two chiral fragments: diol **31** and aldehyde **34** (Scheme 6). These were synthesized efficiently on a substantial scale from the known (*S*)-butane-1,2,4-triol derivative **29**[27] using standard functional group manipulations. The only step in this sequence which caused concern was the Swern oxidation of the alcohol **33** to the aldehyde **34**. If triethylamine was used as prescribed



SCHEME 5



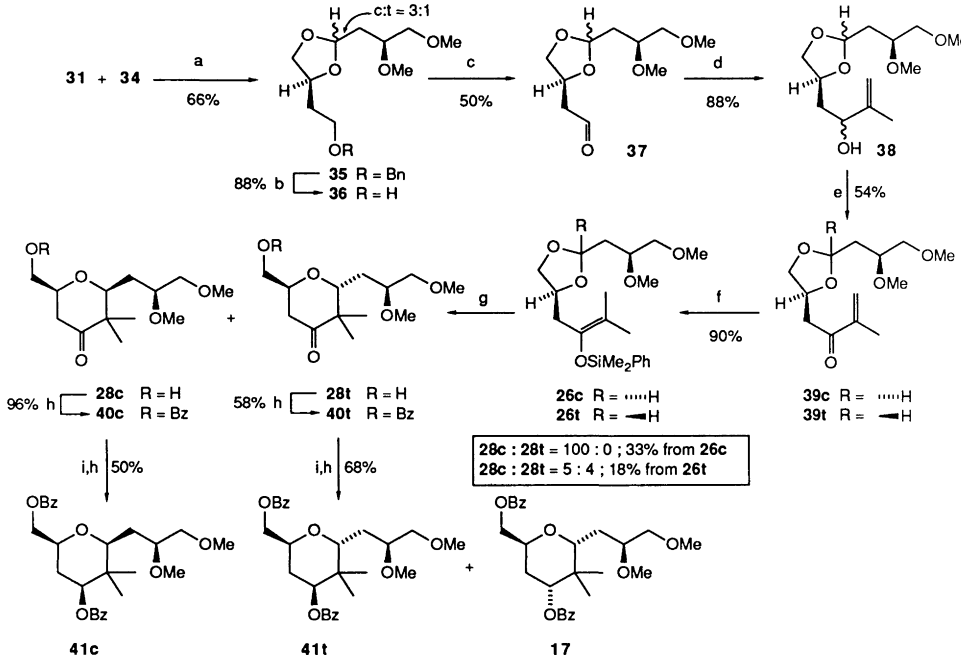
SCHEME 6: YIELDS AND REAGENTS

(a) 88% $PhCH_2Br$, NaH, NaI / THF, rt, 1 h;
(b) 100% aq. HCl, THF, reflux, 3 h;
(c) 93% MeI, NaH / THF, rt, 12 h;
(d) 96% H_2, Pd-C / EtOH;
(e) 98% Swern oxidation.

SCHEME 6

in the usual recipe, the product aldehyde **34** underwent easy β-elimination of MeOH. In order to circumvent this problem, the weaker base N-methylmorpholine was used in the decomposition of the intermediate sulfoxonium salt.

Condensation of aldehyde **34** with diol **31** (Scheme 7) gave an equilibrium mixture of the diastereomeric 1,3-dioxolanes **35** (*cis* : *trans* = 3 : 1) in only 66% yield. Once again the easy elimination of methanol from aldehyde **34** dictated the conditions used to form the dioxolane. Best results were obtained by treating a mixture of **34** and diol **31** in CH_2Cl_2 with *p*-toluenesulfonic acid at room temperature. Since the diastereomeric dioxolanes **35** were inseparable, the mixture was carried through the next four steps as outlined in Scheme 7. The base-sensitive enones **39c** and **39t** were then separated by tedious column chromatography and individually converted to the corresponding enol silanes **26c** and **26t** respectively using Rh(I)-catalyzed



SCHEME 7: REAGENTS

(a)	TsOH, $MgSO_4$ / CH_2Cl_2, rt, 48 h;	(d)	CH_2=C(Me)MgBr / THF, 0°C, 10 min;	(g)	$TiCl_4$ / CH_2Cl_2, -78°C, 1 h;
(b)	Na / NH_3(l)-Et_2O, -78°C;	(e)	PCC / CH_2Cl_2, rt, 3.5 h;	(h)	BzCl, DMAP (cat) / pyridine, rt;
(c)	PCC / CH_2Cl_2, rt, 2.5 h;	(f)	$PhMe_2SiH$, $[Ph_3P]_3RhCl$, 55°C, 1 h;	(i)	$NaBH_4$ / EtOH, rt, 2 h.

SCHEME 7

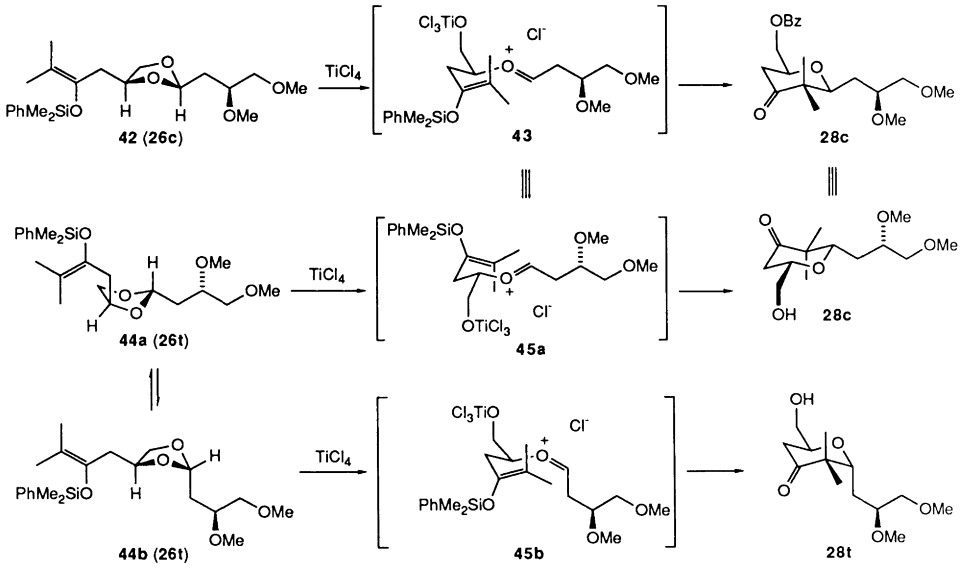
hyrosilylation[28]. This method was very mild and efficient (90% yield) and provided the desired enol silanes regiospecifically without the competing β-elimination which attended all the usual base-catalyzed silylation methods.

With isomerically pure **26c** and **26t** in hand, we next investigated the key intramolecular directed aldol reaction in considerable detail. The requisite 6-endo$_e$endo$_n$ annulation[29] was best achieved using 2 equivalents of $TiCl_4$ in CH_2Cl_2 at $-78°C$. Two equivalents of Lewis acid were necessary because the methoxy groups in the side chain formed a very stable complex with the $TiCl_4$ which prevented the desired reaction from taking place. The diastereomeric dioxolanes behaved differently in the cyclization reaction. The major *cis*-dioxolane **26c** gave the tetrahydropyranone **28c** as the sole identifiable annulation product in 33% yield whereas the minor *trans*-dioxolane **28t** gave a mixture of the tetrahydropyranones **28c** (10%) and **28t** (8%). In both cases several very minor products and polar material accounted for the balance of the mass.

To complete the synthesis of (+)-pederol dibenzoate (**2**), the keto group in **40t** was reduced and the resultant alcohol benzoylated in the usual way to give a 68% yield of a 1 : 1 mixture of **41t** and **17** which required HPLC to effect separation. The poor stereoselectivity in the reduction of **40t** probably reflects the steric hindrance to axial attack by hydride caused by the axial benzoyloxymethyl group since the isomeric tetrahydropyranone **40c** was reduced and benzoylated to give **41c** in which the expected[30] axial delivery of hydride had occurred exclusively.

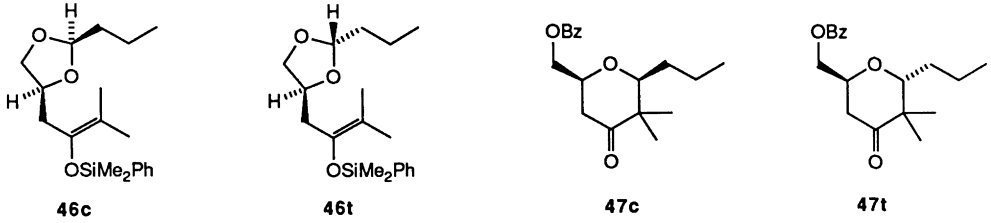
Scheme 8 attempts to rationalize the stereochemical course of the reaction. If we assume that the *cis*-dioxolane **26c** occupies a conformation **42** which undergoes cleavage of the dioxolane ring to form an (*E*)-oxonium ion, then cyclization *via* the chair-shaped intermediate **43** would generate the major tetrahydropyranone **28c**. Assuming the *trans*-dioxolane **28t** exists as an equilibrium mixture of the conformers **44a** and **44b** which undergoes cleavage of the dioxolane ring to (*E*)-oxonium ions, cyclization *via* chair-shaped intermediates **45a** and **45b** would account for the formation of the two observed tetrahydropyranones **28c** and **28t**.

In an attempt to gain some insight into the causes of the dreadful inefficiency of the key annulation reaction and its unfortunate stereochemical course, the model dioxolanes **46c** and **46t** (Figure 4) were prepared and their cyclization studied using a variety of Lewis



SCHEME 8

acid catalysts and conditions[29]. Under the conditions used to effect cyclization in the pederin series, the model *cis*-dioxolane **46c** gave the tetrahydropyranone **47c** exclusively in 65% yield whereas the *trans*-dioxolane **46t** gave a 1 : 1 mixture of the tetrahydropyranones **47c** and **47t** in 72% yield. Thus, the stereochemical course of the cyclization of the model compounds **46c** and **46t** paralleled that observed in the pederin series but the efficiency of the process was greatly improved. This difference in efficiency may reflect problems associated with the chelation of the side chain methoxyl groups to $TiCl_4$. Our failure to produce significant quantities of tetrahydropyranone **28t** indicated that the central premise of our approach to diastereocontrolled



46c **46t** **47c** **47t**

FIG. 4

annulation-coordination of the enol silane and dioxolane oxygens to an octahedral Ti(IV) complex was wrong and the route was abandoned.

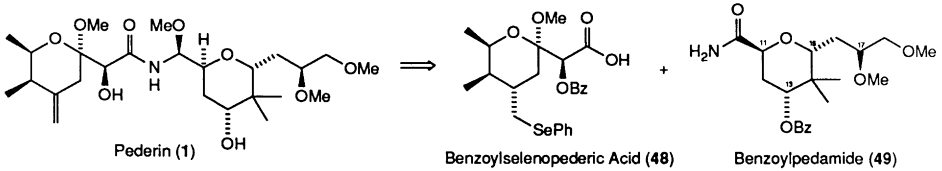
Our initial foray into the synthesis of pederin was motivated by a desire to exploit silicon-mediated annulation reactions in the synthesis of oxacyclic natural products. We were disappointed that ethyl pederate and pederol dibenzoate could not be nurtured beyond the stage of arrested saplings; however, transplanted to a new context, the intramolecular directed aldol chemistry did bear fruit in a novel synthesis of spiroacetals[31] and medium ring oxacycles[29].

C. Trials and Tribulations: The Imidate Ester Approach

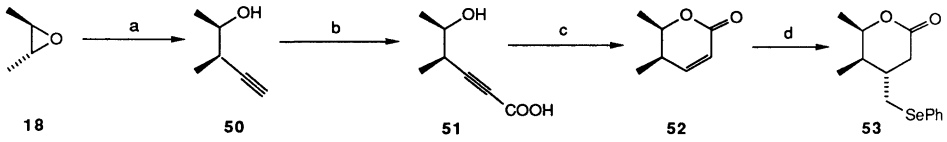
Experience had shown that any attempt to utilize a ring-A fragment with an intact C_4 methylene was likely to prove troublesome so we amended our strategy by constructing a ring-A fragment in which provision was made for the late introduction of the C_4 methylene under very mild conditions. The modified strategy (Scheme 9) depended on an efficient synthesis of the ring-A fragment (±)-benzoylselenopederic acid (**48**) and the ring-B fragment benzoylpedamide (**49**).

Our synthesis of (±)-benzoylselenopederic acid (**48**) required the selenolactone **53** (Scheme 10) which was prepared as a single diastereomer in one step by conjugate addition of phenylselenomethyl-lithium to the α,β-unsaturated lactone **52**. Though the successful conjugate addition was gratifying in this particular case, the reaction was not general since attempts to achieve similar additions to other α,β-unsaturated lactones lacking the branching substituent at C_3 (pederin numbering) failed to give useful yields of the desired selenolactones.

To complete the synthesis of **48**, the glycolate appendage had to be introduced onto the lactone **53** (Scheme 11). The lithium enolate **59**



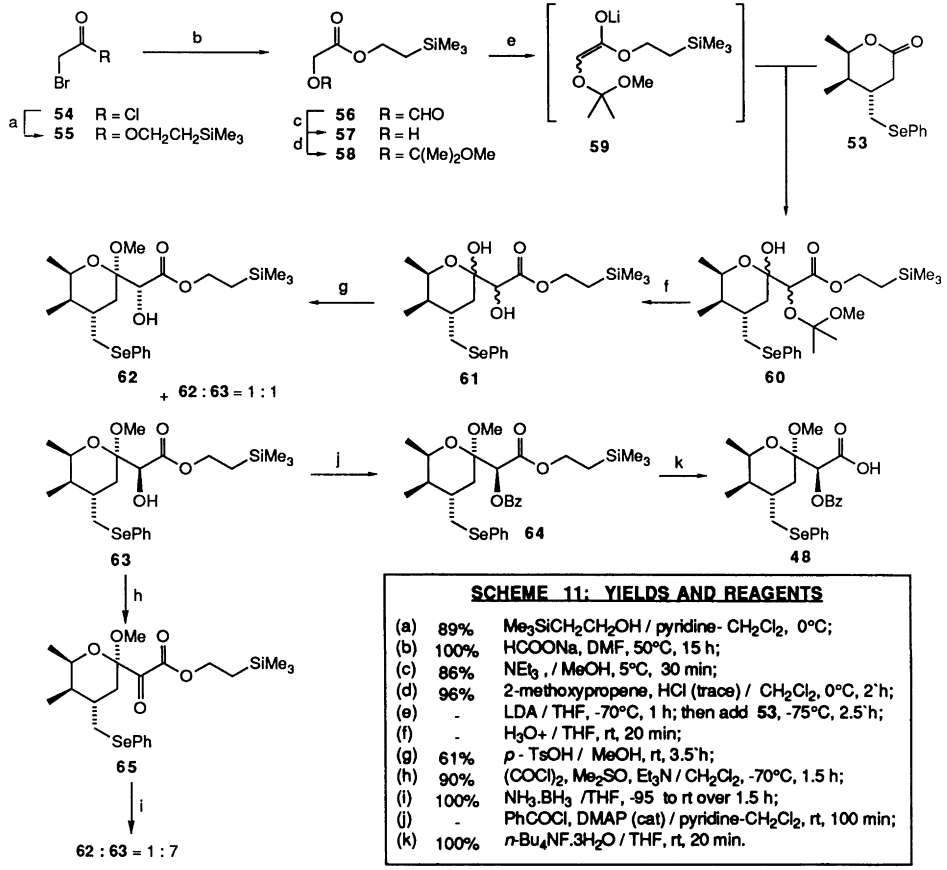
Scheme 9



SCHEME 10: YIELDS AND REAGENTS

(a) 82% lithium acetylide (3.6 eq) / HMPT, 20°C, 6 days;
(b) 96% *n*-BuLi followed by CO_2, -70°C, 20 min;
(c) 85% H_2, $Pd/BaSO_4$, quinoline followed by distillation;
(d) 89% $PhSeCH_2Li$ / THF - HMPA (1 : 1), -86°C, 1 h.

SCHEME 10



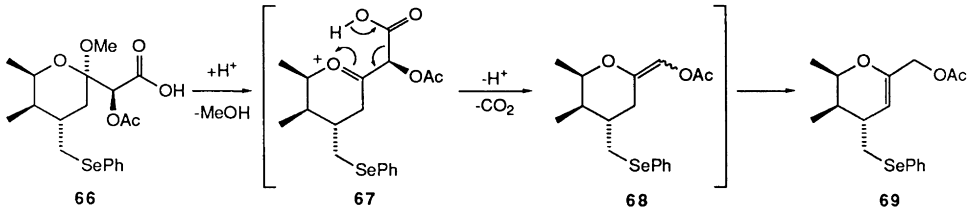
SCHEME 11: YIELDS AND REAGENTS

(a)	89%	$Me_3SiCH_2CH_2OH$ / pyridine- CH_2Cl_2, 0°C;
(b)	100%	HCOONa, DMF, 50°C, 15 h;
(c)	86%	NEt_3 , / MeOH, 5°C, 30 min;
(d)	96%	2-methoxypropene, HCl (trace) / CH_2Cl_2, 0°C, 2`h;
(e)	-	LDA / THF, -70°C, 1 h; then add **53**, -75°C, 2.5`h;
(f)	-	H_3O+ / THF, rt, 20 min;
(g)	61%	*p* - TsOH / MeOH, rt, 3.5`h;
(h)	90%	$(COCl)_2$, Me_2SO, Et_3N / CH_2Cl_2, -70°C, 1.5 h;
(i)	100%	$NH_3.BH_3$ /THF, -95 to rt over 1.5 h;
(j)	-	PhCOCl, DMAP (cat) / pyridine-CH_2Cl_2, rt, 100 min;
(k)	100%	*n*-$Bu_4NF.3H_2O$ / THF, rt, 20 min.

SCHEME 11

of ester **58** condensed cleanly with the lactone **53** though varying amounts of **53** were recovered owing to proton abstraction by the glycolate enolate competing with the desired nucleophilic addition. After two further steps, the alcohols **62** and **63** were isolated as a 1 : 1 mixture of isomers which were separable with difficulty by chromatography. However, it was more convenient to oxidize the mixture to the corresponding α-keto ester **65** followed by reduction *in situ* to give the diastereomers **62** and **63** in the more favorable ratio of 1 : 7. The ratio of diastereomers was strongly dependent on the reducing agent. In our hands, reduction of the α-keto ester with BH_3-NH_3 complex in THF at low temperature gave the best results. After removal of the undesired minor diastereomer by column chromatography, the alcohol function in **63** was converted to the crystalline benzoate derivative **64** and the relative stereochemistry firmly established by a single crystal X-ray analysis.

To complete the synthesis of benzoylselenopederic acid the carboxylic acid was unmasked by fluoride-induced fragmentation of the 2-(trimethylsilyl)ethyl ester **64** using tetra-*n*-butylammonium fluoride[32]. Initial attempts to recover the desired acid **48** by acidification of the resultant tetra-*n*-butylammonium salt was complicated by problems with decomposition. However, the free acid was fortuitously generated *without acidification* by simply partitioning the tetra-*n*-butylammonium salt between ether and water. Evaporation of the ether layer then gave the desired acid cleanly and efficiently with minimal contamination by decomposition products. This deprotection and isolation procedure was crucial to the successful isolation and purification of the labile acid **48**. Although the decomposition products derived from **48** were not characterized, the analogous acetate **66** underwent easy acid-catalyzed loss of CO_2 and MeOH to give the dihydropyran **69** (Scheme 12).



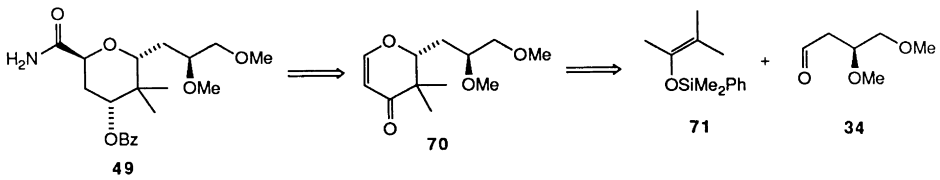
66 67 68 69

SCHEME 12

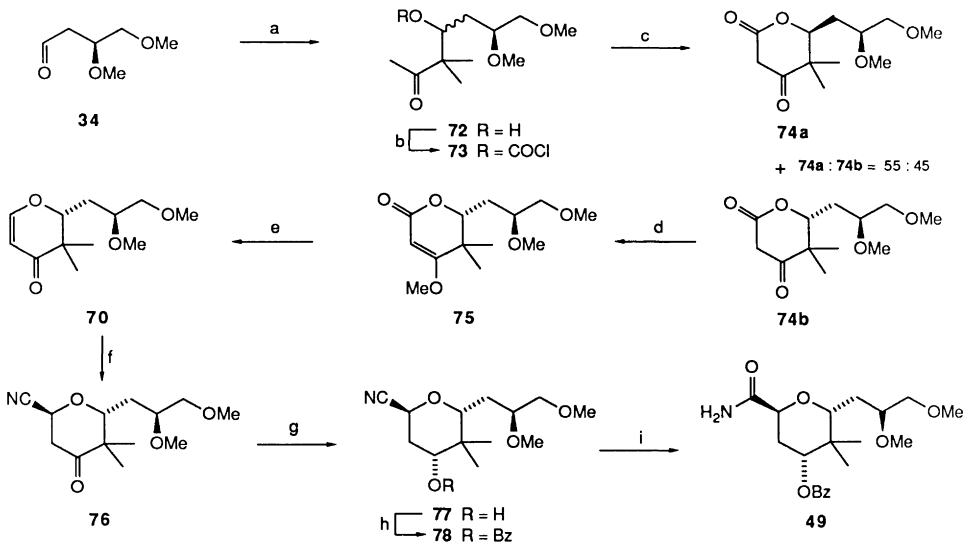
The overall strategy of our synthesis of (±)-benzoylpedamide (**49**) is outlined in Scheme 13. It has one feature in common with the synthesis of pederol dibenzoate (**17**): the stereogenic center on the ring at C_{15} was introduced by nucleophilic addition of an enol silane to an activated 3,4-dimethoxybutanal unit. Then, in subsequent steps, the dihydropyranone ring **70** was forged and the axial carboxamide unit introduced by a stereoselective conjugate addition reaction. However, once again the relative stereochemistry between C_{17} and C_{15} was to prove problematic.

Condensation of the enol silane **71** with (±)-3,4-dimethoxybutanal (**34**) (Scheme 14) provided the delicate aldol product **72** as an inseparable mixture of diastereomers in high yield but with varying diastereoselectivity depending on the Lewis acid catalyst and the precise reaction conditions (*vide infra*). The mixture was efficiently cyclized to the β-ketolactones **74a** and **74b** *via* intramolecular acylation of the enolate derived from treatment of the chloroformate **73** with lithium diisopropylamide (LDA). This reaction gave several byproducts but these were readily removed by extraction of the β-ketolactones **74a** and **74b** into aqueous $NaHCO_3$ followed by acidification. Upon cooling an ethereal solution of the mixture, the unwanted diastereomer **74a** crystallized out and concentration of the mother liquor gave the desired isomer **74b** as an oil of ca. 90% diastereomeric purity. Isomer **74b** was then converted to the dihydropyranone **70** using standard transformations and the isomeric impurities finally removed by chromatography.

Introduction of the axial carboxamide function at C_{11} was launched by a highly efficient and diastereoselective conjugate addition of Me_3SiCN to the dihydropyranone **70** to give the β-cyanoketone **76** in 95% yield after hydrolysis of the intermediate enol silane. Analysis of the crude product by NMR at 360 MHz gave no evidence of contamination by the corresponding equatorial nitrile. The one



SCHEME 13



SCHEME 14: YIELDS AND REAGENTS

(a) 91% **71**, $TiCl_4$ / CH_2Cl_2, -70°C, 1 h;
(b) 93% $COCl_2$ / pyridine, 0°C, 1 h;
(c) 80% LDA / THF, -70°C, 1 h;
(d) 99% Me_2SO_4, K_2CO_3 / acetone, reflux, 2 h;
(e) 70% DIBAL-H / toluene, 70°C, 3 h;
(f) 95% Me_3SiCN, BF_3OEt_2 / CH_2Cl_2, 0°C, 1.5 h;
(g) 99% $NaBH_4$, $CeCl_3$ / MeOH, -80°C, 0.5 h;
(h) 100% BzCl / pyridine, rt, 2 h;
(i) 74% H_2O_2, K_2CO_3 / EtOH, 70 min, rt.

SCHEME 14

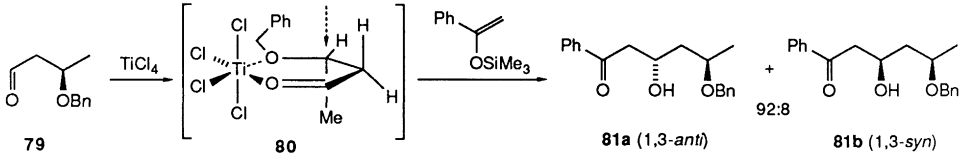
remaining stereogenic center at C_{13} was then introduced by reduction of the β-cyanoketone **76**. The stereoselectivity of this reaction depended on the conditions and the reducing agent. Both $NaBH_4$ and $LiBH_4$ were essentially non-selective even at low temperatures. Reduction with BH_3-NH_3 complex in THF at low temperature gave a 3 : 1 mixture of diastereomeric alcohols in which the desired equatorial isomer **77** was the major product. However, best results were obtained when β-cyanoketone **76** was reduced with $NaBH_4$ at −78°C in MeOH in the presence of $CeCl_3$. Under these conditions, the ratio of products was 25 : 1 in favor of the desired isomer **77** and the yield was essentially quantitative. To complete the synthesis, the alcohol function was benzoylated and the cyano function converted to the carboxamide giving (±)-benzoylpedamide (**49**) in 9 steps from aldehyde **34** in an overall yield of *ca.* 16%.

Before we proceed with a description of the imidate ester approach, we would like to digress and briefly discuss the stereochemistry of

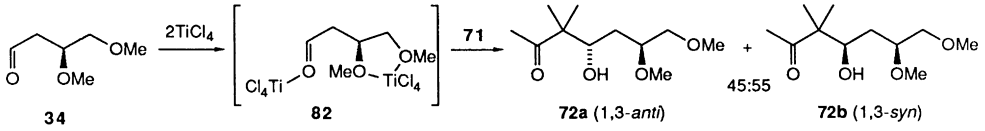
the directed aldol reaction to create the stereogenic center at C_{15} in benzoylpedamide. At the time the synthesis of benzoylpedamide was undertaken, we were not aware of any systematic study of the stereochemistry of the Lewis acid-catalyzed addition of C-nucleophiles to β-alkoxy aldehydes to guide us in predicting the stereochemistry of the initial aldol condensation between aldehyde **34** and enol silane **71**. That the reaction was essentially non-selective remains the prime blemish in an otherwise efficient and highly stereoselective synthesis of (±)-benzoylpedamide. In fact, the formation of aldol adduct **72** as a roughly 1 : 1 mixture of diastereomers was a blessing in disguise since the more recent work from the Reetz[33] and Heathcock[34] laboratories would suggest that the desired diastereomer should have been formed in only very minor amounts.

We would now like to consider the expected stereochemical course of an analogous aldol condensation between an enol silane and a β-alkoxy aldehyde, and then offer an explanation for the results we observed in the synthesis of aldol **72**. Scheme 15 shows the impressive diastereoselectivity obtained from the $TiCl_4$-catalyzed addition of the enol silane derived from acetophenone to the β-benzyloxyaldehyde **79**[35]. The marked bias in favor of the 1,3-*anti*[36] addition product **81a** was interpreted in terms of a chelation-controlled addition to an intermediate **80** in which the enol silane approached from the less hindered side of the ring opposite the *pseudo*-axial methyl group[37]. A substantial body of evidence now supports this view[38]. The diastereoselectivity in this case is typical of a wide range of similar additions involving other C-nucleophiles.

For the synthesis of benzoylpedamide, we required that nucleophilic addition of enol silane **71** to aldehyde **34** provide the 1,3-*syn* addition product **72b** (Scheme 16). This was achieved by a careful study of the various reaction parameters (Lewis acid, solvent, temperature). A slight bias in favor of the desired 1,3-*syn* adduct **72b** was best achieved by adding 2 equivalents of $TiCl_4$ to the aldehyde at low



SCHEME 15



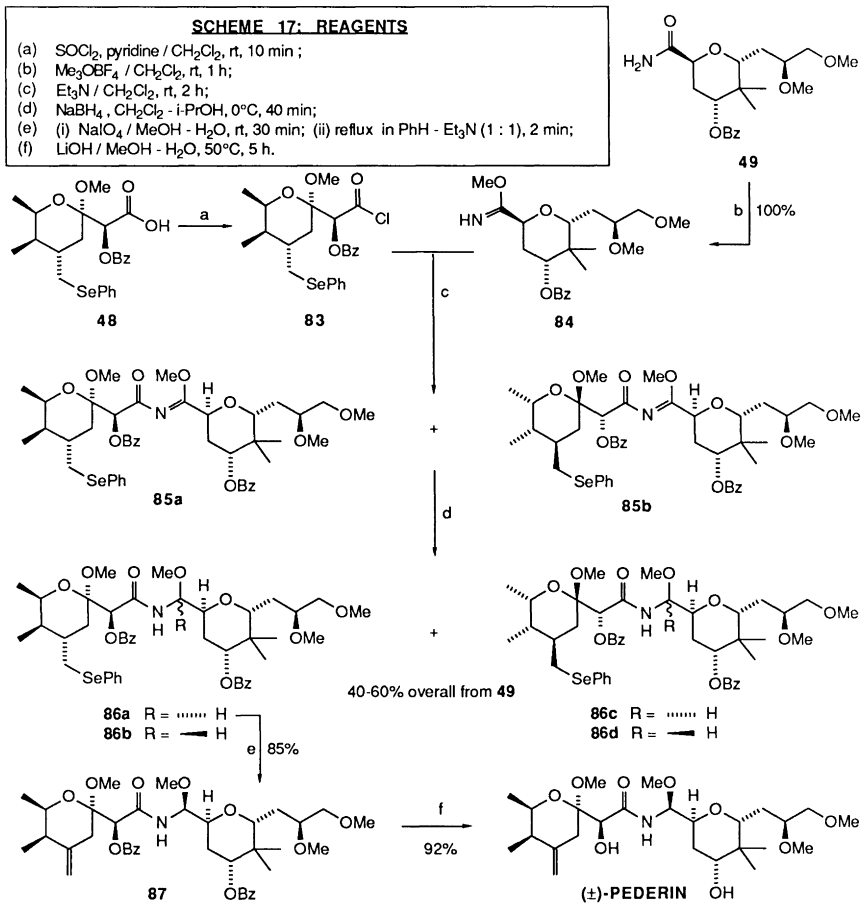
34 82 72a (1,3-*anti*) 72b (1,3-*syn*)

SCHEME 16

temperature followed by subsequent addition of the enol silane. We propose that the chelation-controlled model outlined in Scheme 15 is disrupted by initial coordination of the first molecule of $TiCl_4$ to the more basic methoxy oxygen atoms while the second molecule of $TiCl_4$ is required to activate the aldehyde towards diastereofacially indiscriminate addition to intermediate **82**. These results suggest that care must be exercised in predicting the stereochemistry of chelation-controlled addition to β-alkoxy aldehydes when other potential coordination sites are proximate.

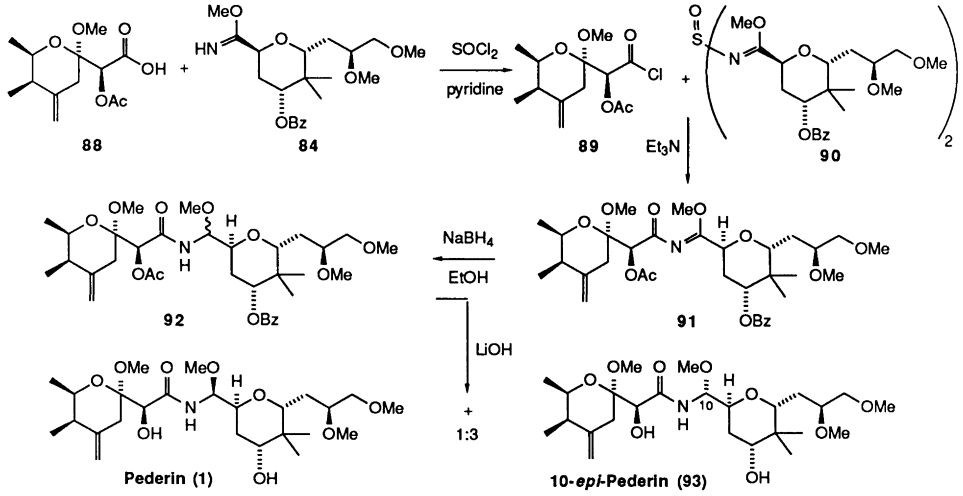
With adequate supplies of the racemic ring-A and ring-B fragments in hand, we were now in a position to construct the the N-acyl aminal bridge linking (±)-benzoylpedamide (**49**) with (±)-benzoylselenopederic acid (**48**) (Scheme 17). To that end we adopted the protocol developed in Matsumoto's laboratory[19] which had appeared while our work was in progress and which coincided with our intentions. Accordingly, the acid function in **48** was activated by conversion to the acid chloride **83** (*vide infra*) and the amide function in **49** was converted to the imidate ester **84**. These were condensed in the presence of base and thionyl chloride to give the diastereomeric N-acyl imidates (±)-**85a** and (±)-**85b** which were then immediately reduced to a mixture of the four N-acyl aminals **86a–86d** (and their enantiomers) in equimolar ratio. These were separated by HPLC and isomers **86a** and **86b** identified as belonging to the pederin and 10-*epi*-pederin series (diastereomeric at the aminal center) by comparison of their high field NMR spectroscopic data with related compounds[20]. Diastereomers **86c** and **86d** were derived from reduction of the N-acyl imidate **85b** which was an artifact of the coupling of the racemic ring-A and ring-B fragments. Two final efficient steps (selenoxide elimination and ester hydrolysis) transformed **86a** into (±)-pederin which was identical by high field ^{1}H NMR, IR, TLC, and MS with an authentic sample of natural (+)-pederin.

Before concluding our account of the imidate ester approach to pederin we would like to examine in greater detail the Matsumoto



SCHEME 17

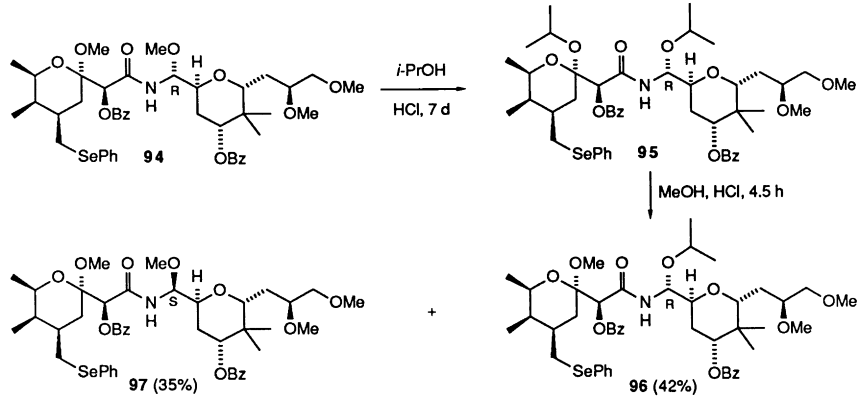
method for constructing the N-acyl aminal bridge. In particular, we wish to focus on the mechanism of imidate acylation and the stereochemistry of N-acyl imidate reduction. The Sapporo team showed that methyl imidate **84** (Scheme 18) could be condensed with the acid **88** after activation with thionyl chloride and pyridine. In model studies with simple unhindered acids, the reaction proceeded by *in situ* formation of the acid chloride followed by *rapid* acylation of the methyl imidate. However, with the pederic acid derivative **88** the acylation step required several hours and the reaction took a different but useful course: the sulfinyldiimidate **90** formed which itself



SCHEME 18

underwent fortuitous coupling with acid chloride **89** to give the desired N-acylimidate in 73% yield. Unfortunately, every path has its puddle and the stereochemistry of the metal hydride reduction of N-acylimidate **91** was unfavorable. After removal of the protecting groups pederin and 10-*epi*-pederin (**93**) were isolated in a ratio of 1 : 3 respectively. Despite the lack of stereocontrol in the reduction of **91**, the Matsumoto team were to be congratulated for achieving the first total synthesis of pederin.

Attempts to rectify the unfavorable stereocontrol in the N-acyl imidate reduction by epimerizing the 10-*epi*-pederin in acidic methanol were fruitless because of the acid lability of ring-A. However, partial resolution of the stereochemical problems at C_{10} was eventually achieved which gave further evidence of the lability of the N-acyl aminal group under acidic conditions. Treatment of dihydro-10-*epi*-pederin derivative **94** with acidic methanol under equilibrating conditions returned a mixture consisting of the 10R epimer **94** and the desired 10S epimer **97** in a ratio of 3 : 1 respectively. Thus thermodynamics provided no solace. However, **94** reacted with HCl in *i*-PrOH at room temperature for 7 days to give the unstable (10R)-diisopropoxy derivative **95**, which underwent methanolysis under *pseudo*-kinetic conditions (HCl in MeOH, room temperature, 4.5 hours) to give 42% of **96** along with 35% of **97** in which displacement of



SCHEME 19

the 10R-isopropoxy group had occurred mainly with inversion of configuration.

Conformational arguments were proffered to explain the *pseudo*-kinetic epimerization experiments described above. Matsumoto cited ^{1}H NMR data as well as X-ray structure data derived from pederin di-*p*-bromobenzoate as evidence for the thermodynamic preference of ground state conformation **99** over **98** in which an internal hydrogen bond stabilizes conformer **99**. Furthermore, he proposed that methanolysis occurred with inversion of configuration by direct displacement of *i*-PrOH from the unhindered face of conformer **99** (Figure 5). Whatever the explanation, it was clear from these studies that stereocontrol at the N-acyl aminal center was difficult to achieve either before or after the coupling of the ring-A and ring-B fragments[39].

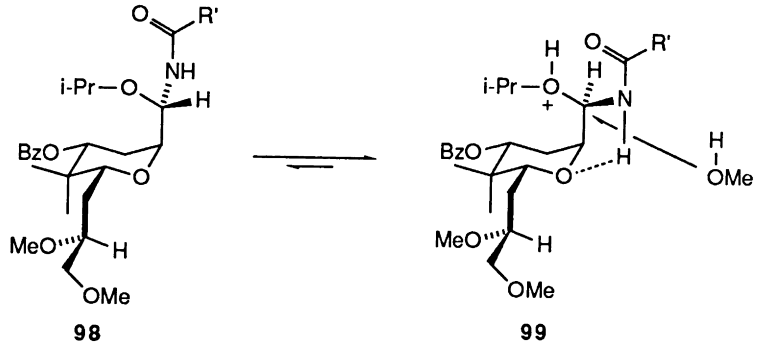


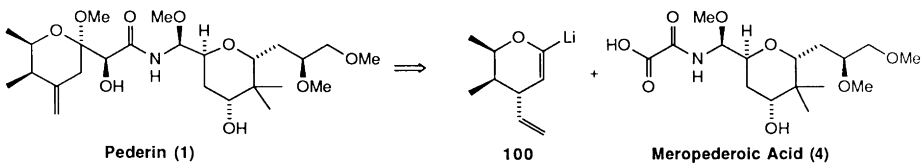
FIG. 5

A few comments about the closing stages of the Southampton synthesis are warranted. A great deal of effort was dissipated before the synthesis was successfully concluded because benzoylpederic acid and its activated derivatives such as **83** were unstable and the coupling reaction with imidate **84** was very slow. Furthermore, in our hands the reactions were messy and the products difficult to separate. Attempts to vary the method of carboxyl activation and increase the rate of coupling merely multiplied the complications and real improvements proved elusive. Taken together, these obstinate experimental facts created obstacles which could not be easily surmounted. Obviously the separation problems would have been simplified if homochiral ring-A and ring-B fragments, which could be readily prepared by trivial modifications to our routes, had been used in the coupling step. But the improvements were deemed to be too insignificant to warrant further investigation. Instead, we devised alternative methods for linking the two tetrahydropyran rings which culminated in our second synthesis of pederin outlined in the next section.

D. To Elevate a Shrub: The Metallated Dihydropyran Approach

> *We know that a few strokes of the axe will lop a cedar;*
> *but what art of cultivation can elevate a shrub?*
> *Samuel Johnson, 1750*

Pederin is far less robust than a cedar and it takes rather less violence than an axe to provoke its destruction. We have already seen how easily pederin can be lopped into various fragments (Scheme 1); for example, pseudopederin, the hydrolysis product of pederin, undergoes an easy retroaldol reaction on heating in base and in the presence of air to give meropederoic acid (**4**) wherein the *N-acyl aminal group is still intact.* These transformations run in reverse suggested to us a potential route for elevating meropederoic acid to the pederin skeleton which might circumvent the cascade of problems which beset the closing stages of our previous synthesis. This new strategy (Scheme 20) required a metallated dihydropyran (e.g., **100**) functioning as an acyl anion equivalent in a reaction with a suitably activated meropederoic acid derivative. There was good precedent for the ready formation of metallated dihydropyrans[40] and their efficient participation in C–C bond formation reactions is well-established[41] but no useful information was at hand which suggested ways of making the

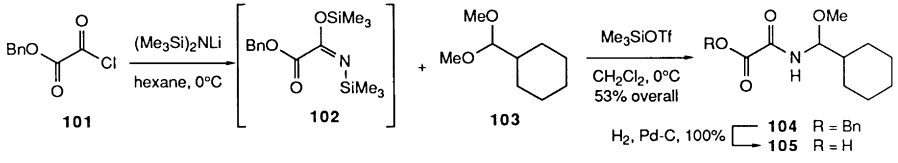


SCHEME 20

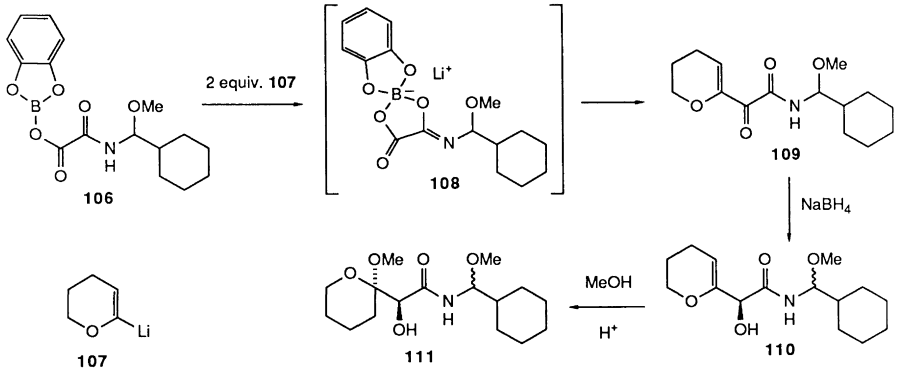
N-(1-alkoxy-1-alkyl)-oxalamide function of meropederoic acid. Therefore we turned to model studies to test some of our ideas.

Scheme 21 shows one approach to the simple model *N*-(1-alkoxy-1-alkyl)-oxalamide **105** in which the key step was a kind of directed aldol condensation between the *N,O-bis*-(trimethylsilyl)oxalamide ester **102**[42] and the acetal **103**. The *bis*-silyl amide **102** was generated from benzyl oxalyl chloride **101** and lithium hexamethyldisilazide in hexane solution and added to an equimolar mixture of the acetal and TMSOTf. By halting the reaction after a few minutes, a moderate yield (53%) of the adduct **104** was obtained along with 47% unreacted acetal. If the reaction times were increased, the isolation of the desired product was complicated by the formation of substantial amounts of by-products derived from further aldol reactions on the adduct **104**.

The next stage of these model studies required activation of the carboxylic acid function in the meropederoic acid analogue **105** toward nucleophilic attack by a suitable organometallic reagent. Unfortunately, all conventional protocols for the formation of acid chlorides, imidazolides, or mixed anhydrides failed. Successful activation of the carboxyl group was eventually achieved by reaction of acid **105** with one equivalent of catecholborane to give the mixed boric anhydride **106** (Scheme 22)[43]. On reaction with 2 equivalents of 6-lithio-dihydropyran **107**, the boric anhydride **106** gave a 71% yield of the desired acyl dihydropyran **109**. The first equivalent of **107**



SCHEME 21

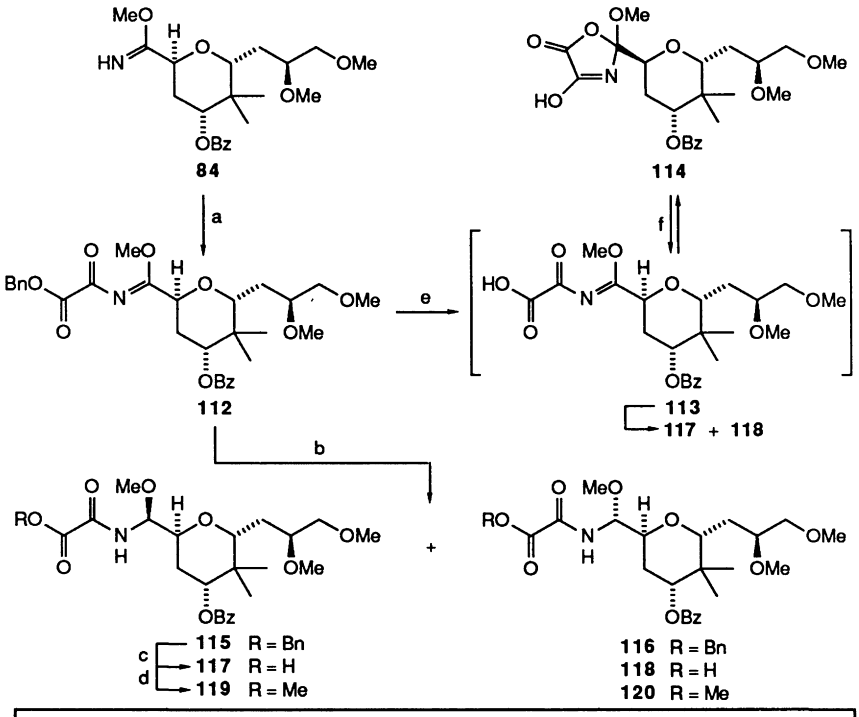


SCHEME 22

presumably generated the boronate intermediate **108** which then suffered attack by the second equivalent of the lithio-dihydropyran. Two further conventional steps served to convert **109** to a separable mixture of the two diastereomeric aminals **111** which differed in the relative stereochemistry at the aminal center.

The foregoing model experiments augured well for the success of the 'dihydropyran approach' and efforts were duly launched to synthesize the appropriate meropederoic acid derivative. Methyl 13-benzoylmeropederoate (**119**) (pederin numbering), a crucial advanced intermediate in our synthetic plan, was synthesized from the imidate ester **84** by two routes as shown in Scheme 23. In the first route, the N-oxalyl imidate ester **112** underwent reduction with borane ammonia complex (step b) to give a 1 : 1 mixture of the benzyl oxalate esters **115** and **116** which were readily separated by column chromatography. Poor as it was, the 1 : 1 ratio of reduction products was a minor triumph at this stage of the synthesis since all the other metal hydride reducing agents we examined gave **116** as the major product (*vide infra*). Hydrogenolysis of the more polar diastereomer afforded 13-benzoylmeropederoic acid **117** which was converted to methyl ester **119** in good yield. The preparation of **119** from **84** by using methyl oxalyl chloride in place of the benzyl derivative is an obvious abbreviation which was thwarted by the chromatographic inseparability of the methyl esters **119** and **120**.

In the second route, an attempt to produce meropederoic acid derivative **117** directly by catalytic reduction of the N-oxalyl imidate

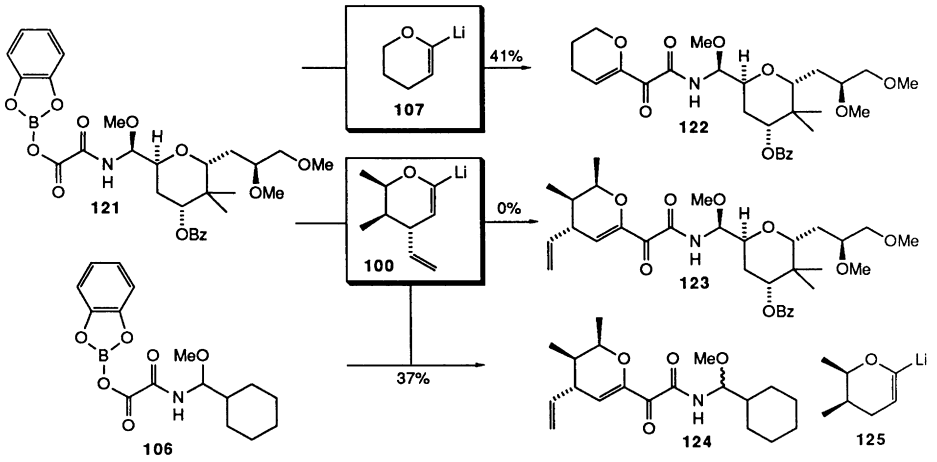


SCHEME 23: YIELDS AND REAGENTS					
(a)	-	$BnOOC\text{-}COCl$, Et_3N / CH_2Cl_2, 0°C	(d)	85%	CH_2N_2 / Et_2O
(b)	40%	$BH_3\text{-}NH_3$ / CH_2Cl_2, 0°C; separate	(e)	67%	H_2, Pd-C / EtOAc
(c)	97%	H_2, Pd-C / EtOAc	(f)	100%	$NaBH_3CN$ / HOAc-CH_2Cl_2

SCHEME 23

function in **112** gave instead the oxazolidindione derivative **114** owing to rapid hydrogenolysis of the benzyl ester followed by cyclization of the resultant carboxylic acid **113**. However, the cyclization was reversible: by treating **114** with $NaBH_3CN$ in acetic acid-CH_2Cl_2, 13-benzoylmeropederoic acid **117** and its diastereomer **118** were obtained in quantitative yield, but since they could not be readily separated the former route was preferred.

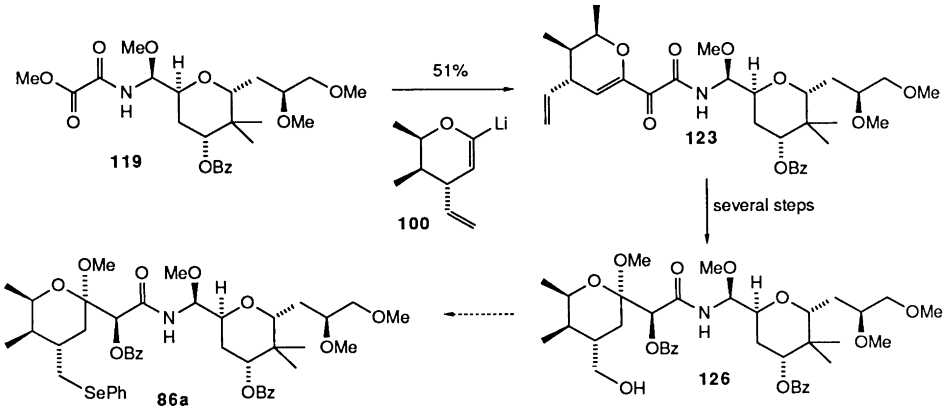
With the requisite B-ring meropederoic acid derivative **117** now available in gram quantities, the time was ripe to establish whether 'the dihydropyran approach', which had worked so well in the model (Scheme 22), was equally efficacious in a more complex system. Accordingly, the coupling of **117** with 6-lithio dihydropyran (**107**) was examined (Scheme 24) and once again the catecholborane activa-



SCHEME 24

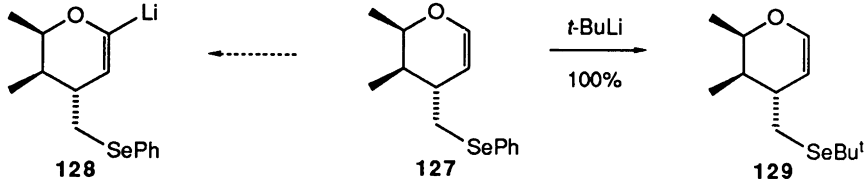
tion method proved its worth: the mixed anhydride **121** derived from treatment of **117** with 1.1 equivalents of catecholborane reacted with 2.2 equivalents of lithiated dihydropyran **107** to give the desired coupling product **122** in 41% yield. We were thus on the cusp between promise and fulfillment.

But fulfillment was to prove elusive. The A-ring fragment **100** would not react with **121** and varying solvent, temperature, stoichiometry, and borane activator proved fruitless. The lithium derivative **100** did react with model mixed anhydride **106** to give the adduct **124** in 37% yield. However, metallated dihydropyran **125** suffered the same fate as **100**: it would not react with anhydride **121**. It is not obvious why **121** should have been so adamant in its failure to undergo the desired coupling. We then widened the scope of carboxyl activation methods (e. g. thioesters, mixed anhydrides of phosphoric and sulfonic acids) and employed a larger repertoire of metals (zinc, magnesium, copper) in the metallated dihydropyran but they all proved to be cold coals to blow at. However, we eventually discovered the flint which rekindled our synthesis and allowed us to wrest victory from defeat—and by very simple means. The flint in question was none other than the quotidian methyl ester of 13-benzoylmeropederoic acid (**119**) which reacted with lithiated dihydropyran **100** in the presence of 1 equivalent of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) to give the desired adduct **123** in 51% yield (Scheme 25).



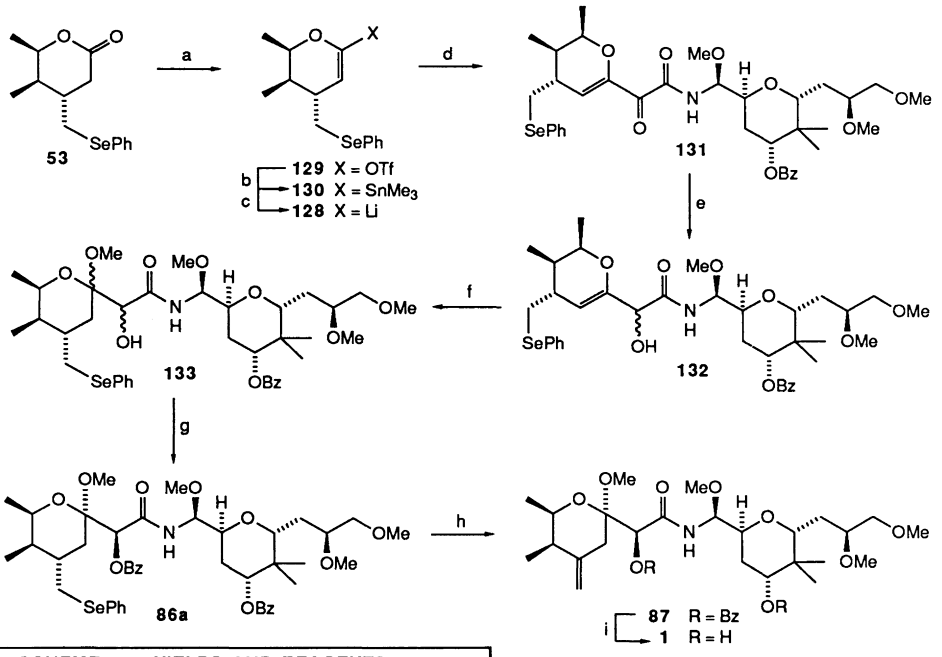
SCHEME 25

Unfortunately, our troubles were not yet over. The dihydropyran approach as originally conceived (Scheme 22) made use of lithiated dihydropyran **100** bearing a vinyl substituent at C_4 which would ultimately be transformed to a phenylselenylmethyl group *after* the A-ring and B-ring fragments had been conjoined. To that end we prepared alcohol **126** (Scheme 25) using standard procedures (*vide infra*) but we were unable to transform it to the requisite arylselenide **86a** under a variety of conditions. Progress, therefore, demanded that the phenylselenenyl group be introduced into the A-ring fragment *before* the N-acyl aminal bridge was constructed. Unfortunately this requirement jeopardized the dihydropyran strategy because all attempts to prepare the lithiated dihydropyran **128** (Scheme 26) in the usual way, by metallation of the corresponding dihydropyran **127** using *t*-BuLi[40] failed, owing to preferential reaction with the selenium atom[44] to give **129** in quantitative yield.



SCHEME 26

The last obstacle to our second synthesis of pederin was finally surmounted by the development of a new and efficient 3-step synthesis of the 6-(trimethylstannyl)-3,4-dihydropyran **129** (Scheme 27) *via* Pd(0)-catalyzed stannylation[45] of the enol triflate intermediate **130**. Transmetallation of **130** to the 6-lithio derivative **128** followed by reaction with meropederoic acid derivative **119** in the presence of TMEDA gave the keto amide **131** in 55% yield. TMEDA appeared to be an essential ingredient for the success of the coupling probably because it disrupted a tight lithium aggregate[46] or perhaps because it formed a ternary complex **133** incorporating the reactive partners.



SCHEME 27: YIELDS AND REAGENTS

(a)	78%	(i) $(TMS)_2NLi$ / THF, -80°C; (ii) $PhNTf_2$, -80 to rt;
(b)	69%	Me_6Sn_2, LiCl, $Pd[PPh_3)_4$ / THF, reflux, 12 h;
(c)	100%	*n*-BuLi / THF, -80°C, 15 min;
(d)	55%	**119**, TMEDA / THF, -80°C, 30 min;
(e)	100%	$NaBH_4$ / EtOH, 0°C, 30 min;
(f)	94%	CSA / MeOH-CH_2Cl_2 (5:95), rt, 4 h; add K_2CO_3;
(g)	-	BzCl, Et_3N, DMAP / CH_2Cl_2, rt, 12 h; separate;
(h)	85%	$NaIO_4$ / MeOH-H_2O; reflux in PhH;
(i)	92%	LiOH / MeOH, 50°C, 5 h.

SCHEME 27

To complete the synthesis of pederin, the keto group in **131** was reduced to give a 2 : 1 mixture of chromatographically inseparable diastereomeric alcohols **132** in which the major product possessed the incorrect stereochemistry. Some redress was derived in the next step: the dihydropyran ring in mixture **132** added methanol with a bias of *ca.* 2.5 : 1 in favor of the desired stereochemistry to give a mixture of 4 diastereomeric acetals **133** (*ca.* 2 : 1 : 6 : 3) which were separated by HPLC after benzoylation. Conversion of the desired diastereomer **86a** (*ca.* 15% of the mixture) to pederin proceeded as described previously and the second synthesis was successfully concluded[47].

E. The Triumph of Hope versus The Abbreviation of Time: Recent Improvements

What we call the beginning is often the end
And to make an end is to make a beginning.
The end is where we start from.

T. S. Eliot

Research problems, like teeth, can be divided into incisors and grinders. Pederin falls into the latter category. It took nearly three years of effort to finally realize the dihydropyran approach and now that our goal was grasped, we turned a cooler and more calculating eye on our achievement and identified three outstanding problems which still required attention: 1.) the poor yield and stereoselectivity in the reduction of the N-acyl imidate leading to meropederoic acid (step b, Scheme 23); 2.) the unfavorable stereochemistry in the reduction of the α-keto amide **131** (step e, Scheme 27); and 3.) the unsatisfactory stereoselectivity in the acid-catalyzed addition of MeOH to the dihydropyrans **132** (step f, Scheme 27). The third problem was deemed the easiest to correct and elementary conformational analysis gave the clue. Acetalization reactions are thermodynamically controlled processes in which product stability governs the course of the reaction. If we assume that the diastereomeric acetals **132** occupy conformations which benefit from maximum anomeric stabilization[48], two possible chair conformers **135** and **136** (Figure 6) are generated bearing the requisite axial methoxy groups. We can now understand why the addition of MeOH was not stereoselective since **135** and **136** are nearly equivalent in their disposition of the 5 ring substituents including rather similar 1,3-diaxial C–O interactions. However, by simply

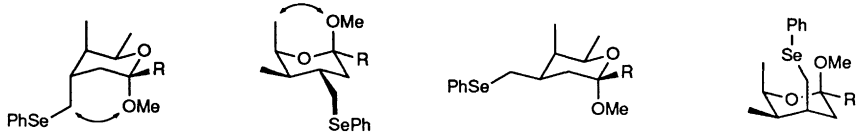
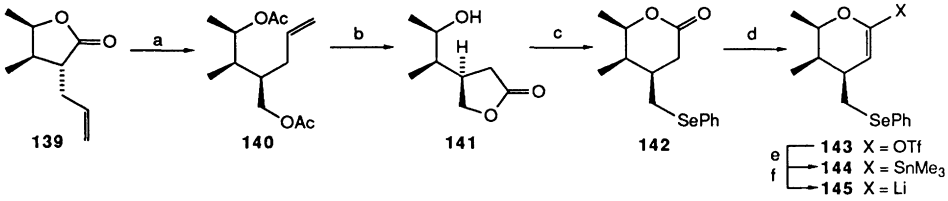


FIG. 6

inverting the stereochemistry of the phenylselenenylmethyl moiety, we can derive a much greater distinction in energy between the two conformers **137** and **138** leading to enhanced stereoselectivity in the addition of MeOH to the appropriate dihydropyran. The final assault on pederin described below will demonstrate the validity of these simple arguments and reveal solutions to the first and second problems as well.

The conformational arguments described above demanded a synthesis of the ring-A fragment **145** which was accomplished as outlined in Scheme 28. By this route, the known[22b] homochiral lactone **139** was converted to **145** in 39% overall yield.

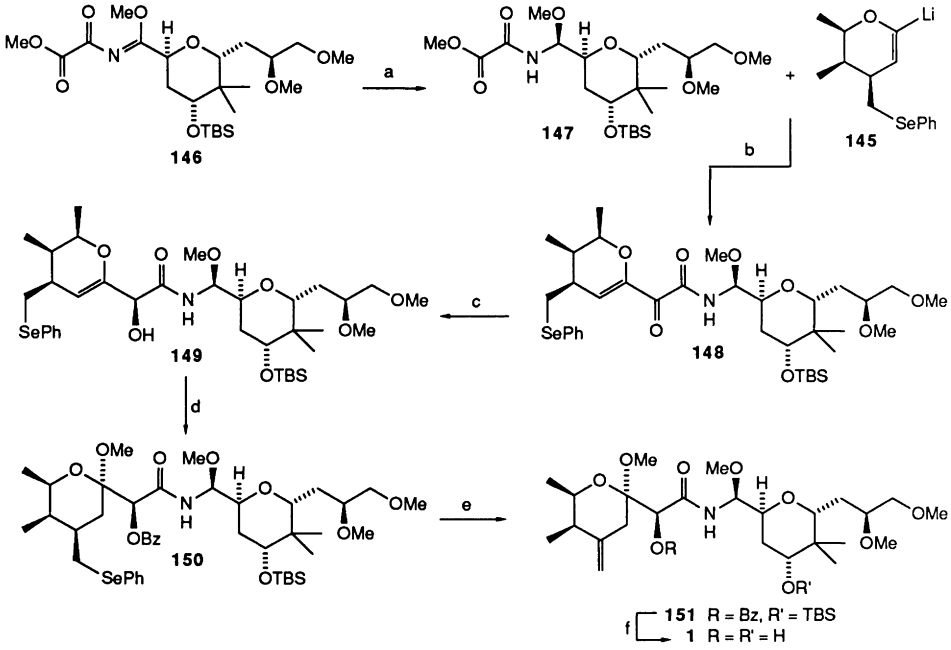
The first of our three goals was achieved after an extensive investigation of the reagents and conditions required to effect the reduction of N-acyl imidate **146** (Scheme 29). A wide variety of metal hydride reducing agents failed to generate the desired diastereomer **147** selectively: for example $NaBH_4$ or BH_3–NH_3 gave poor stereoselectivity whereas Bu_4NBH_4 was selective for the formation of the unwanted diastereomer. Indeed, one variable which impinged on our choice of



SCHEME 28: YIELDS AND REAGENTS

(a) 96% (i) $LiAlH_4$ / Et_2O, reflux, 3 h; (ii) Ac_2O, DMAP / pyr-CH_2Cl_2, rt, 24 h;
(b) 85% (i) O_3 / MeOH, -78°C; (ii) Me_2S; (iii) H_2CrO_4 / acetone; (iv) KOH / H_2O-MeOH, rt, 3 h; (v) HCl;
(c) 80% (i) PhSeNa, 18-crown-6 / THF, rt, 24 h; (ii) HCl;
(d) - (i) LHMDS / THF-HMPA; (ii) $PhN(Tf)_2$;
(e) 60% Me_6Sn_2, LiCl, $Pd[Ph_3P]_4$ / THF, reflux, 12 h;
(f) 100% *n*-BuLi / THF, -78°C, 15 min.

SCHEME 28



SCHEME 29: YIELDS AND REAGENTS

(a)	70%	catecholborane, $[Ph_3P]_3RhCl$ (5 mol%) / toluene, -80°C, 15 h;
(b)	53%	2.1 eq **145**, 2.1 eq TMEDA, 1 eq **147** / THF, -80°C, 30 min;
(c)	-	L-Selectride / THF, -80°C, 15 min;
(d)	53%	(i) CSA / MeOH-CH_2Cl_2, rt, 3 h; (ii) BzCl, DMAP /CH_2Cl_2-Et_3N;
(e)	77%	(i) $NaIO_4$ / MeOH-H_2O (3:1), rt, 20 min; (ii) reflux / Et_3N-PhH, 2 min;
(f)	60%	TBAF (5 eq) / 4A molecular sieves / THF, rt, 12 h.

SCHEME 29

the *t*-butyldimethylsilyl-protected N-acyl imidate **146** instead of the benzoate **112** used previously was the discovery that the protecting group at C_{13} significantly influenced the stereochemistry of the reduction with higher selectivities in favor of the desired isomer being observed with the silyl-protected derivative. It was therefore a major advance when we discovered that an efficient and highly stereoselective reduction could be accomplished using catecholborane in the presence of a catalytic amount of $[Ph_3P]_3RhCl$[49]. Under these conditions a 70% yield of a mixture of diastereomeric N-acyl aminals was obtained in which the desired isomer **147** predominated (10 : 1) and this could be substantially enriched by column chromatography. Thus, for the first time, efficient stereocontrol at C_{10} was achieved.

Fortunately the minor alterations wrought on the ring-A and ring-B fragments **145** and **147** did nothing to obstruct the crucial coupling reaction and the adduct **148** was obtained in 53% yield. Our second goal, namely stereoselective reduction of the α-keto amide, was accomplished by reduction of **148** with $LiBH(s\text{-}Bu)_3$. A mixture of 1,4- and 1,2-reduction products (1 : 4) was generated but again the stereoselectivity of the 1,2-process was favorable with the desired diastereomer **149** being the major product (3 : 1). No doubt further enhancements in the stereoselectivity of this step will emerge.

The third and final goal was realized when **149** was treated with acidic methanol: addition took place efficiently and with high stereocontrol [*ca.* 20 : 1 in favor of the desired isomer at C_6], as predicted. After benzoylation, the mixture of products carried through the last three steps was purified by column chromatography. To complete our third synthesis of pederin, we introduced the exocyclic methylene by selenoxide elimination from **150** as described previously and both protecting groups in **151** were removed in one operation with tetra-*n*-butyl ammonium fluoride.

V. Conclusion

Our synthesis of pederin required nearly ten years of subsultory effort before it was brought to a satisfactory conclusion. We presumed at the beginning that the task would be much simpler. But...

> *Presumption will soon be easily corrected. Every experiment will teach caution, and miscarriages will hourly shew, that attempts are not always rewarded with success. The most precipitate ardour will, in time, be taught the necessity of methodical gradation, and preparatory measures; and the most daring confidence be convinced that neither merit, nor abilities, can command events.*

So wrote Dr. Samuel Johnson in 1750 and they are fitting words with which to end our story.

Acknowledgments

We are grateful to Anna Marczak for her superb experimental assistance during the crucial later phases of our work and our gratitude extends to Dr. Simon F. Campbell of Pfizer Central Research (Sandwich), Dr. Kim Isaac, and Dr. Andrew Faller for their advice and assistance in the difficult early days. We are much obliged to Professor Dario Ghiringhelli of the Politechnico di Milano for generous samples of natural pederin and methyl meropederoate which had survived intact over 20 years of storage. Professor T. Nakata provided valuable spectroscopic

data which helped us to identify the structures of some of the diastereomers that plagued our second synthesis of pederin. We thank Professor M. Pavan (University of Pavia) for kind permission to reproduce the drawing of *Paederus fuscipes* and for valuable information garnered over a lifetime of study regarding the biological activity of pederin.

The treasure which sustained our work was generously provided by the Science and Engineering Research Council, the Wolfson Foundation, Pfizer Central Research (Sandwich) and Glaxo Group Research.

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Chapter 7

THE CHAMPAGNE ROUTE TO AVERMECTINS AND MILBEMYCINS

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I. Introduction

Much has been written on these pages of the challenge of organic synthesis and its comparison with conducting symphonies, playing chess, or creating other artistic forms. Some have remarked upon the immense intellectual challenges presented by the synthesis of complex structures and the elegance of the solution of these problems. More practical and realistic views have been expressed in terms of the frustrations, dead-ends, and even dropped flasks leading to the eventual joy of success. Others have commented that synthesis is a springboard for the discovery of new reactions and methods, as well as being the best training ground for young scientists who will go forward to make their own inventions and discoveries for the future benefit of

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all. While all of this is true, there is much more to the experience of being involved with synthesis. Only those who have been intimately absorbed will understand its truly creative element.

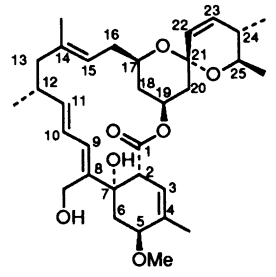
Some have the view that organic synthesis is a mature subject with little opportunity for new developments to be made. To the extent that we have come a long way in the last thirty years, this is true. We can now prepare complex target molecules in a relatively short period of time. We are at a point where we can use the tools of synthesis to powerful effect in the study of fundamental molecular problems in the areas of biology and material science. However, we are only just beginning to achieve the levels of selectivity in bond construction that are needed for tomorrow's problems. There is still so much more to discover.

In the next few pages we present our work on the synthesis of the avermectins and milbemycins, and unveil our thoughts, plans and philosophy in a roughly chronological order. Some of our approaches proved unsuccessful, but nevertheless triggered the new ideas and methods which eventually worked and led to the consumption of much champagne!

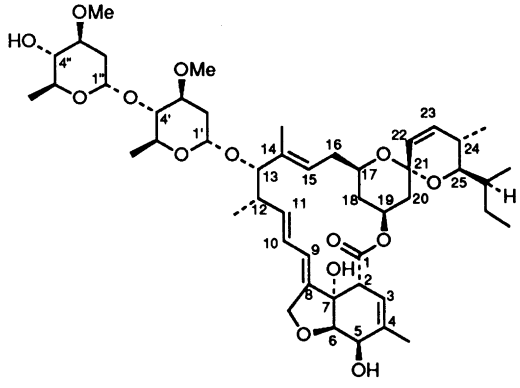
II. The Challenge

In the mid 1970's, workers in the Sankyo laboratories and the Kitasato Institute working with Merck, Sharp, and Dohme discovered the milbemycins and avermectins as a major new class of potent antiparasitic and insecticide agents.[1] Many new members of this series have been characterized since these early days, firmly establishing them as therapeutically and commercially important compounds. The architectural and biological novelty of these compounds soon made them popular targets for total synthesis.[2] In this chapter we discuss our efforts towards milbemycin β_1(**1**) and avermectin B1a(**2**), these being key representative examples of these macrolide natural products.

Although there is considerable structural diversity within the milbemycins and avermectins, there are several common features which need to be addressed in any synthetic program. Firstly, all contain a highly substituted spiroacetal fragment. This basic unit is also present in many other biologically active species, yet at the outset of our work,



Milbemycin β_1 (1)



Avermectin B1a (2)

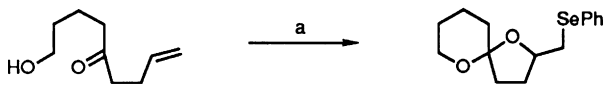
methodology for its formation was rather limited. Opportunities therefore presented themselves for new synthetic chemistry towards these groupings. The preparation of the sixteen-membered macrolactone ring was considered to be straightforward using existing methods, but this was only possible due to the significant advances made in large-ring synthesis in relatively recent times.[3] Careful synthetic planning would also be required to effect the introduction of the several stereocenters possessed by **1** and **2**. This would most reasonably be achieved using a convergent approach whereby isolated fragments containing groupings of asymmetric centers are coupled. The range of substituted double bonds in the avermectins and milbemycins obviously presents many problems to the synthetic chemist, and again, attention to these details early on should avoid frustration later. The "southern" C_1–C_{10} portion of these molecules would be expected to display a high tendency for aromatization, thus suggesting that these molecules may be susceptible to strongly acidic or basic conditions. The use of the terms "northern" and "southern", defining

portions of the molecules based on their common structural presentations, is used in this review. Although we recognize that it is not entirely satisfactory, it has become popular in the avermectin and milbemycin area. Finally, the high level of oxygen functionality needs careful attention when planning a synthesis to avoid unnecessary tactical problems of functional group elaboration and protection. When one superimposes these details with the desire to develop new synthetic methods and to adopt a novel approach, one is confronted by a challenging problem. Despite this, syntheses of milbemycin β_3,[4] milbemycin β_1,[5] milbemycin E,[6] avermectin A1a,[7] avermectin B1a[8] and the avermectin B1a aglycone[9] have all been reported. These syntheses amply demonstrate the versatility and imagination that is possible in natural product synthesis programs.

III. Initial Plans and Results

We began our studies in this area rather late as two groups in the USA, those of Smith[4e] and Williams[4a], had already reported their syntheses of milbemycin β_3, which is the simplest member of the series and possesses an aromatic southern portion. Undeterred, we set about devising some new routes to the inherent spiroacetal fragment since we believed that there was a need for improved procedures. The first method we investigated was prompted by our interest in selenium-mediated cyclization reactions of carbonyl compounds with double bonds.[10] We were able to show that hydroxyalkenyl ketones underwent spiroselenocyclization when treated with N-phenylselenophthalimide and zinc bromide (Scheme 1).[11] This reaction is an intramolecular version of a process first reported by Sharpless.[12]

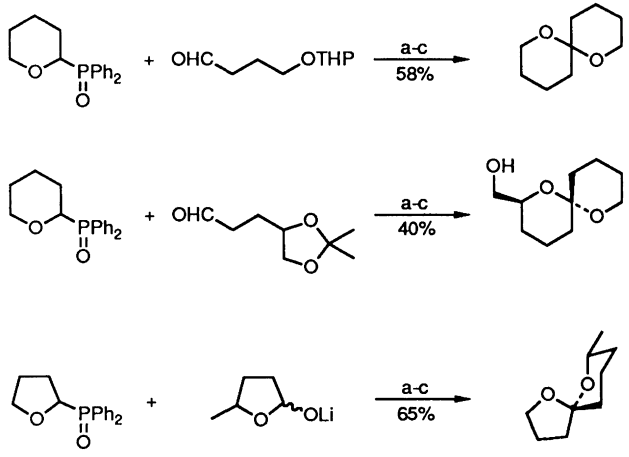
Although this method began our interest in the area and we were able to use the route for the preparation of some simple pheromone natural products, it was hardly sophisticated enough for the project in hand. At about this time our colleague at Imperial College, Tony



SCHEME 1. (a) *N*-(phenylseleno)phthalimide, $ZnBr_2$, 78%.

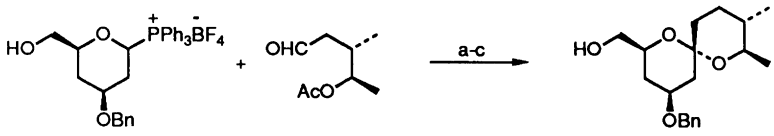
Barrett, had also begun synthetic studies on the milbemycins and avermectins, so it seemed reasonable that we should join forces and write a proposal to the Wolfson foundation to support our work. This was successful, and prompted the first champagne celebration. It also had the effect of concentrating our thoughts to improve the methods and to seriously begin the process of total synthesis. The problem of spiroacetal preparation[13] as we saw it related to the need for a simple procedure, but one which would be versatile and permit multifunctional substitution. We believed that by controlling stereochemistry in one preformed ring, we would have advantages over any acyclic process. The well known anomeric effect[14] would be expected to allow stereocontrol at the anomeric center. We thought it would be possible to make cyclic ether derivatives which would undergo a Wittig or Horner-Wittig reaction at the 2-position with aldehydes containing hydroxyl-substituted side-chains. The resulting enol ether should then close to give the spiroacetal simply on treatment with an acid.

It turned out to be an easy process to prepare both 2-triphenylphosphonium salts and 2-diphenylphosphinoxy cyclic ethers from lactols or dihydropyrans. As anticipated, these coupled well with aldehydes to give enol ethers which underwent cyclization on treatment with camphorsulfonic acid, giving spiroacetals.[15] A few examples of this process (Scheme 2) serve to illustrate its potential. Again,



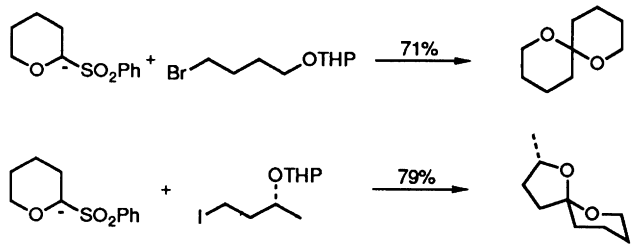
SCHEME 2. (a) LDA, THF, −78°C, then add aldehyde or lactol. (b) KO*t*-Bu, THF. (c) Cat. CSA, MeOH.

this sequence was used to prepare some pheromone natural products, from the olive fly *Dacus oleae* and the common wasp *Paravespula vulgaris*. Pleasingly, other groups have subsequently used our methods for spiroacetal preparation.[16] More importantly, however, these promising reactions could be applied to a simple synthesis of the spiroacetal fragment of the milbemycins,[17] giving us considerable encouragement (Scheme 3).



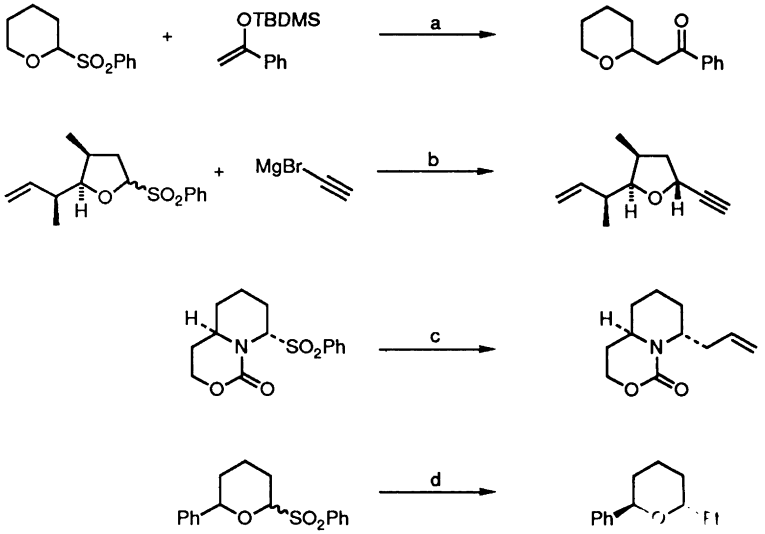
SCHEME 3. (a) 2 equivalents BuLi, THF, −78°C to 25°C. (b) NaOMe, MeOH. (c) 3M HCl, 36%.

This work had achieved not only a new spiroacetal preparation but also something we believed to be fundamentally more important; the formation of carbon-carbon bonds at the 2-position of cyclic ethers. Indeed, it was this realization that prompted the discovery of the final new method that we developed, one which has since proved to be extremely versatile and has opened up many new synthetic areas. This relates to the use of 2-benzenesulfonyl cyclic ethers. The phenylsulfone group was chosen to facilitate anion formation at the anomeric center much in the same way as we had used phosphonium salts and diphenylphosphine oxides. However, we anticipated that the anion would be more nucleophilic and might react with a wider variety of electrophiles, not only with aldehydes but also with ketones, halides and epoxides to effect carbon-carbon bond formation. Reductive desulfonylation would afford the substituted product, while elimination would give an enol ether. As before, if these enol ethers contained hydroxyl-substituted side chains, then cyclization under acidic conditions would provide spiroacetals. The crystalline and fairly stable sulfones were easily prepared from hydropyrans, lactols or lactol ethers by treatment with benzenesulfinic acid,[18] or alternatively by oxidation of the corresponding anomeric sulfides.[19] In the first experiments, we found these sulfones to be excellent precursors for spiroacetal preparation.[18] Following deprotonation with *n*-butyllithium at low temperature, the resulting anions reacted with halides to give a product which underwent spontaneous elimination of benzenesulfinic acid on warming to room temperature. Acidic work-



SCHEME 4

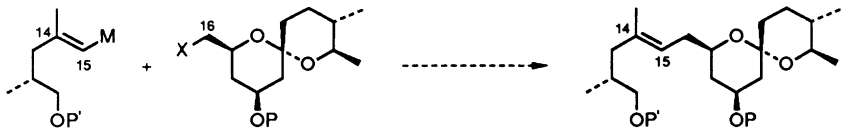
up gave spiroacetals in excellent yield (Scheme 4). The method turned out to be generally useful for the preparation of dihydropyran enol ethers. It was also found that direct substitution of the phenylsulfonyl group by organometallic reagents provided a simple new method for forming carbon-carbon bonds at the position adjacent to oxygen in cyclic ethers (Scheme 5).[20] Later work showed that we were also able to translate this substitution chemistry to cyclic amines, piperidines and pyrrolidines.[21] These additional bonuses that come as a result of developing methodology for natural product synthesis are very satisfying and one should always be prepared to take these opportunities as they arise.



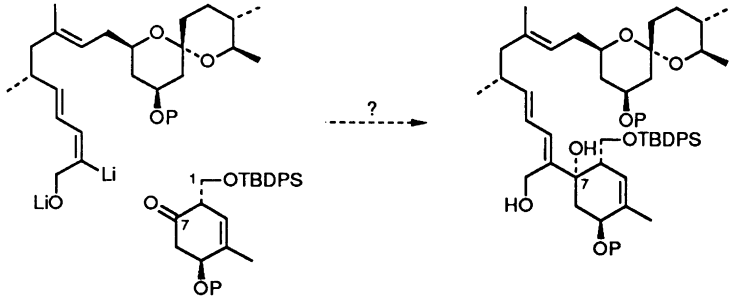
SCHEME 5. (a) $AlCl_3$, 90%. (b) $ZnBr_2$, THF, >95:5 *trans:cis*. (c) Allyltrimethylsilane, $AlCl_3$, 93%. (d) Et_2Zn, CH_2Cl_2, 25°C, 90%.

In spite of these successes, not all was going well with the other stages of the synthesis. For example, methods for introduction of an appropriate C_{10}–C_{15} alkene side chain into the previously synthesized spiroacetal fragment were proving unexpectedly difficult. Not only were attempts at displacement of C_{16}-leaving groups very sluggish owing to the β-oxygen effect of the neighboring pyran oxygen, but methods for controlling the *E*-geometry of the C_{14}–C_{15} double bond were also unsatisfactory (Scheme 6). Almost a year of hard work by Andrew Jackson gave very little to show for his efforts. Because of these difficulties, we were forced to rethink our strategy. In fact the solutions to these problems, which will be discussed later, greatly simplified the whole route to the northern hemisphere portion of these molecules and resulted in a unified approach to all members of the avermectin and milbemycin family. It is also interesting to note that while we were struggling with the formation of the C_{15}–C_{16} and C_{14}–C_{15} bonds, other groups[4d] were experiencing similar difficulties which they commented upon in subsequent publications.

In the meantime, we had begun to explore a route to milbemycin β_1 **1** in which we conceived a coupling of a northern fragment as an alkenyl anion reaction with a C_1–C_7 cyclohexanone southern region (Scheme 7). In this way, we would have a novel coupling approach

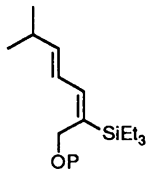


SCHEME 6

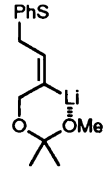


SCHEME 7

combined, we hoped, with a method of controlling the important C_7 angular hydroxyl configuration. This was an attractive approach but again, despite considerable effort by the student on the project, Paul Booth, we were unable to get very far, although some useful model studies were undertaken. For example, we were able to prepare protected dienol compounds such as **3** but these could never be converted to the required organometallic species for coupling. We were later able to obtain alkenyllithium reagents **4**, derived from 2-butyne-1,4-diol, but while these added to simple cyclohexanones, they failed to add to more highly substituted examples necessary for this work.



(3)

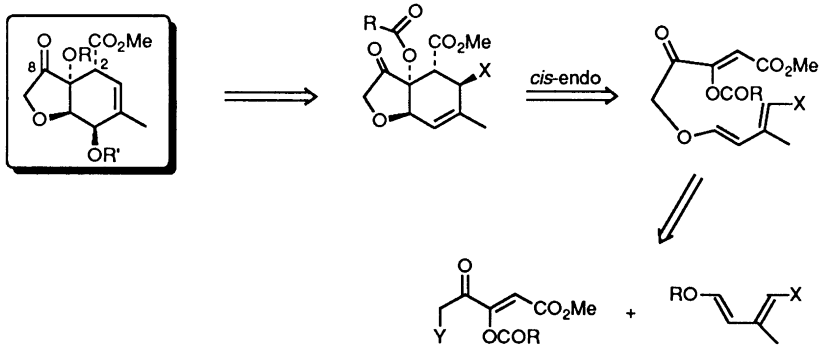


(4)

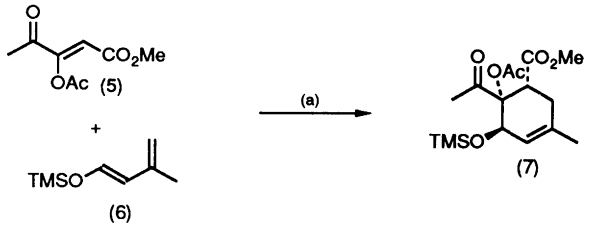
Concurrent with these early side chain and spiroacetal studies, we had also begun to address the issue of the synthesis of southern zone fragments. We planned to adopt a strategy which could be applied to both mono- and bicyclic southern units. On paper, we were most attracted by the Diels-Alder route which is shown retrosynthetically in Scheme 8. Although we eventually abandoned this approach, other groups (Ireland[22] and more recently Uang[23]) were much more successful, even though they have not yet used their fragments in total synthesis studies. Jung[24] has also reported a Diels-Alder approach to the avermectin hydrobenzofuran unit. Ian O'Neil, who examined our route,[25] did make significant progress, especially on model studies and in the preparation of appropriately substituted dienes, and these reactions are reported here. We eventually gave up this route mainly because the alternative sequence which we were developing was proving more versatile (*vide infra*). We were also becoming concerned about the configurational stability of the C_2 stereocenter and the liability of the 3,4-double bond to move into conjugation with the ester group.[26] Furthermore, we were worried that addition reactions to a hindered C_8 carbonyl group flanked by two heteroatoms would later prove problematic. Nevertheless, the nice feature of the

approach was the concise way the cyclohexene ring could be constructed with a predictable *cis-endo* selectivity to control relative stereochemistry. We also envisaged the use of a phenylselenenyl group in position X (Scheme 8), *via* its selenoxide and a [2,3]-sigmatropic shift, to set up the desired C_5 oxygen stereochemistry, simultaneously placing the double bond in the required 3,4-position. Crimmins has subsequently shown the viability of a related selenoxide migration process.[27]

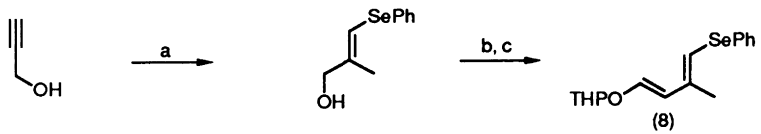
In model studies we were able to effect the Diels–Alder reaction of an acetoxy dienophile **5** with a substituted diene **6** to give the cycloaddition product **7** in 65% yield (Scheme 9). Disappointingly, all attempts to convert **7** to useful substrates for the synthesis by α-oxidation or direct nucleophilic addition to the C_8 ketone failed. Although we were also able to prepare a phenylselenenyl- substituted diene **8** by a short, stereoselective sequence (Scheme 10), it failed to react with **5** to give any cycloaddition product.



SCHEME 8



SCHEME 9. (a) 115°C, toluene, 72h, 65%.

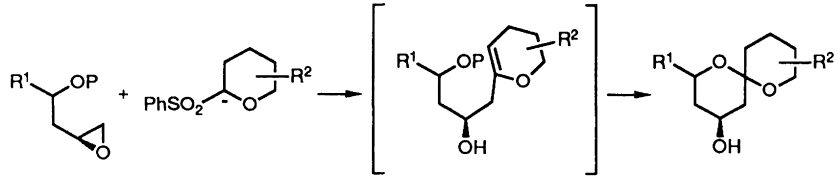


SCHEME 10. (a) Cp_2ZrCl_2, $AlMe_3$, $(CH_2Cl)_2$, then PhSeCl, 32%. (b) MnO_2, 95%. (c) (Tetrahydropyranyl)methylenediethylphosphonate, 48%.

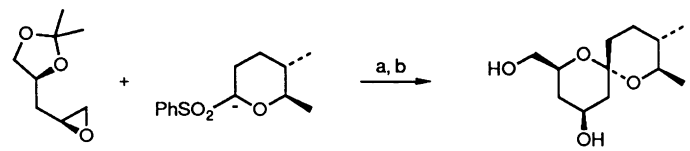
IV. The Next Stage

We now reached a stage where we had to consolidate our successes and rethink our strategy, particularly for the introduction of the diene side chain and the preparation of the southern hemisphere portion of the molecules. The next important step came when we were able to show that the anions derived from 2-benzenesulfonyl tetrahydropyrans react with epoxides.[28] This one reaction became the heart of all the remaining hydroxy-substituted spiroacetal syntheses leading to milbemycin β_1 (**1**) and avermectin B1a (**2**). In general terms, treatment of 2-benzenesulfonyl tetrahydropyrans with *n*-butyllithium effects formation of the anion, which then reacts with epoxides containing masked hydroxyl groups for later spirocyclization on treatment with acid (Scheme 11).

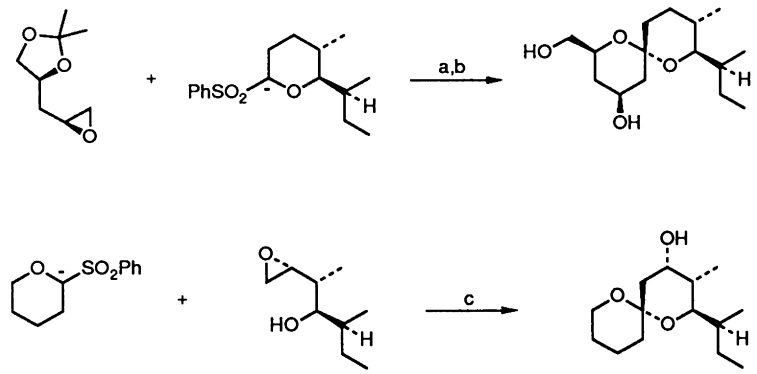
In a specific example, reaction of the anion from the sulfone **9** with the epoxide **10** gave the milbemycin spiroacetal **11** in 76% yield following treatment of the intermediate enol ether with camphorsulfonic acid[28] (Scheme 12). Similar reactions with other substrates afforded models for the avermectin spiroacetal, or, by reversing the coupling partners, gave the spiroacetal common to the avermectin 2 series (Scheme 13).[29] More recently, a modification of the same general method has allowed the preparation of unsaturated systems similar to those found in avermectin B1a.[30] The basis of this



SCHEME 11



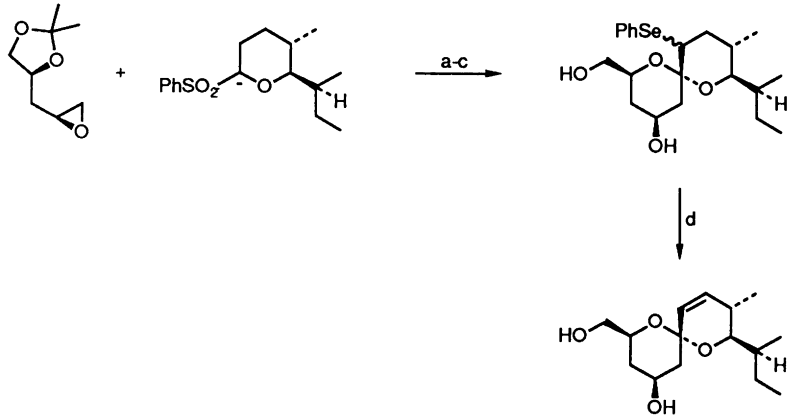
SCHEME 12. (a) BuLi, THF, −78°C. (b) CSA, MeOH, 25°C, 76%.



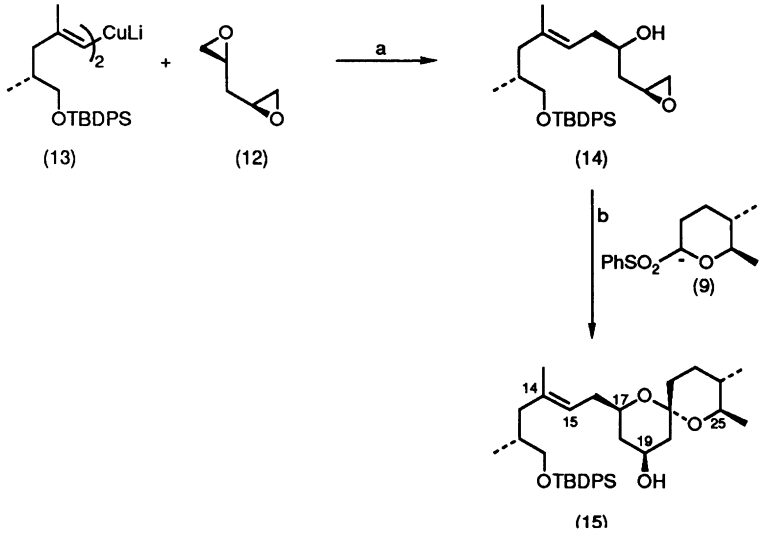
SCHEME 13. (a) BuLi, THF, −78°C, then add epoxide. (b) TsOH, 28%. (c) BuLi, THF, −78°C to 25°C, add epoxide, $Ti(OiPr)_4$, 56%.

modification relates to the trapping of the intermediate enol ether with a selenium electrophile. Spirocyclization gives selenium-containing spiroacetals. Oxidation and *syn*-elimination then provides the unsaturated systems (Scheme 14).

The success of the epoxide ring-opening process also stimulated another idea to solve the problem of the side chain introduction, and especially for controlling the *E*-geometry of the C_{14}–C_{15} bond. Since the configurations of the C_{17} and C_{19} centers are common to *all* avermectins and milbemycins, we conceived the idea of using the *bis*-epoxide **12** as a double electrophile. We had previously shown[31] that the milbemycin C_{14}–C_{15} *E* double bond could be constructed by opening epoxides using appropriately substituted alkenyl-metallic reagents. Indeed, when the *bis*-epoxide **12** was reacted with the vinyl cuprate reagent **13**, we obtained the addition product **14**. Reaction of **14** with the sulfone anion **9** in the presence of titanium (IV) isopropoxide, followed by an acidic work-up, gave the C_{11}–C_{25}



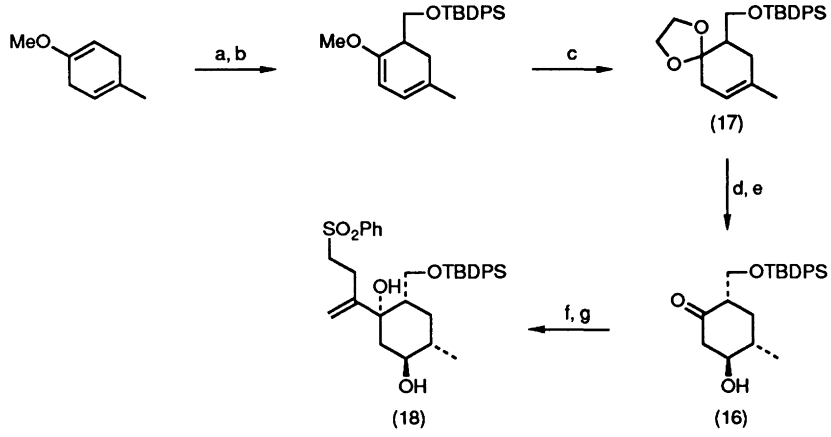
SCHEME 14. (a) BuLi, THF, −78°C to −50°C, then add epoxide. (b) PhSeCl, MeOH, Et_3N. (c) TsOH (cat.), CH_2Cl_2, 31%. (d) Camphor sulfonyl oxaziridine, CH_2Cl_2, 59%.



SCHEME 15. (a) −65°C, 4 hours, 53%. (b) Sulfone anion, $Ti(OiPr)_4$, THF, −78°C, then 5% aqueous H_2SO_4, 80%.

fragment **15** of the milbemycins (Scheme 15).[28] Conceptually, this route represents a most expedient and enormously versatile sequence to these northern hemisphere units, being capable of affording milbemycins, avermectins or novel analogues simply by appropriate choice of the various coupling components.

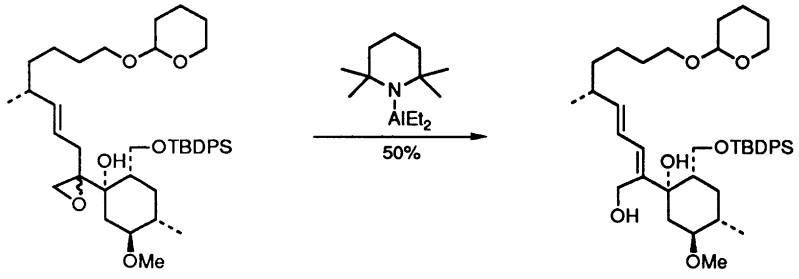
Along with these studies we were formulating a route to the southern portion of the natural products based upon a stereoselective alkenyl-anion addition reaction to a cyclohexanone derivative **16**, setting up the important C_7 angular hydroxyl stereochemistry. The choice of **16** was deliberate in that it should be readily available in the required optically active form, and all the functionalities can be readily manipulated to the desired materials, including the later opportunity for the preparation of the bicyclic hydrobenzofuran fragment needed in the avermectin synthesis. In this way, we would have a single, coherent route to all members of the milbemycin and avermectin family. Preparation of the necessary starting materials for this phase of the synthesis proceeded smoothly, and could be carried out on a 100-gram scale. Prins reaction[32] of 2,5-dihydro-4-methylanisole put together the carbon framework. Following silylation, reaction with ethylene glycol in the presence of pyridinium tosylate gave **17**; hydroboration and deprotection gave **16** in racemic form (Scheme 16). The deprotection step was not straightforward owing to problems of rapid β-elimination using conventional reagents, but use of the excellent Lipshutz method,[33] involving acetal exchange with acetone in the presence of Pd(II) salts, provided reproducible and high yields. Preparation of optically pure **16** will be discussed later.



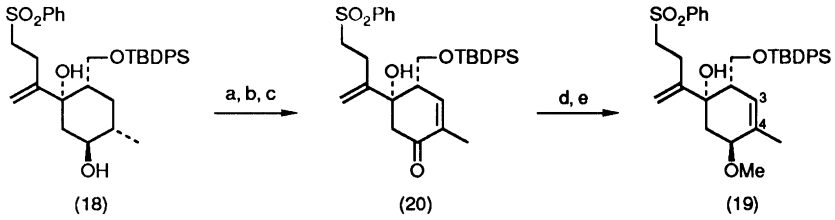
SCHEME 16. (a) Me_3Al, $(CHO)_n$, CH_2Cl_2, 0°C, 64%. (b) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, 98%. (c) Ethylene glycol, PPTS, C_6H_6, reflux, 16h, 88%. (d) $BH_3 \cdot Me_2S$, then aqueous NaOH, H_2O_2. (e) $PdCl_2(CH_3CN)_2$, acetone, 98%. (f) 2-lithio-4-phenylthio-but-1-ene, THF/ether, −78°C, 87%. (g) *m*CPBA, CH_2Cl_2, then Oxone®, MeOH/THF/H_2O, 88%.

In order to assess **16** as an eventual precursor for milbemycin β_1 synthesis, several further experiments were performed. Although we found that vinyl magnesium bromide would add to **16**, other vinyl side chains were less accommodating and not at all satisfactory (*vide supra*). Eventually, we found that 2-lithio-4-phenylthiobut-1-ene would add in excellent yield and with high selectivity. After oxidation with potassium peroxymonosulfate (Oxone®), the sulfone **18** was obtained (Scheme 16). We had planned that the phenylsulfone group in **18** could be used to effect coupling to the northern hemisphere fragment. At first sight, the C_8 methylene group in **18** appears to be wrongly placed in the side chain. However, we believed this could be a very desirable feature in that it could mask the *E,E*-dienol unit of milbemycin β_1 until a late stage, when hydroxyl-directed epoxidation and allylic rearrangement should produce the correct substitution pattern. This process was shown to be viable in a model study using diethylaluminum-2,2,6,6-tetramethylpiperidide[34] to effect the rearrangement (Scheme 17).

In another important series of transformations, **18** was elaborated to a unit **19** which contains many of the structural elements found in the natural product milbemycin β_1 (Scheme 18). Oxidation of the C_5 hydroxyl group of **18** was followed by regioselective selenenylation and *syn*-elimination to give **20**. C_7-hydroxyl-directed reduction with sodium triacetoxyborohydride and methylation with diazomethane in the presence of fluoroboric acid gave **19**. These last steps gave us encouragement for using this selenoxide elimination approach for the introduction of the C_3–C_4 double bond in the total synthesis studies, possibly at a very late stage of the synthesis. This could avoid anticipated problems[26] associated with epimerization at C_2 or the ready



SCHEME 17. (a) Diethylaluminum 2,2,6,6-tetramethylpiperidine, benzene, 50%.

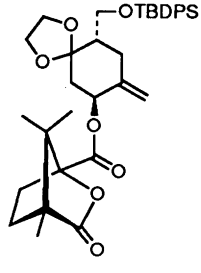


(18) (20) (19)

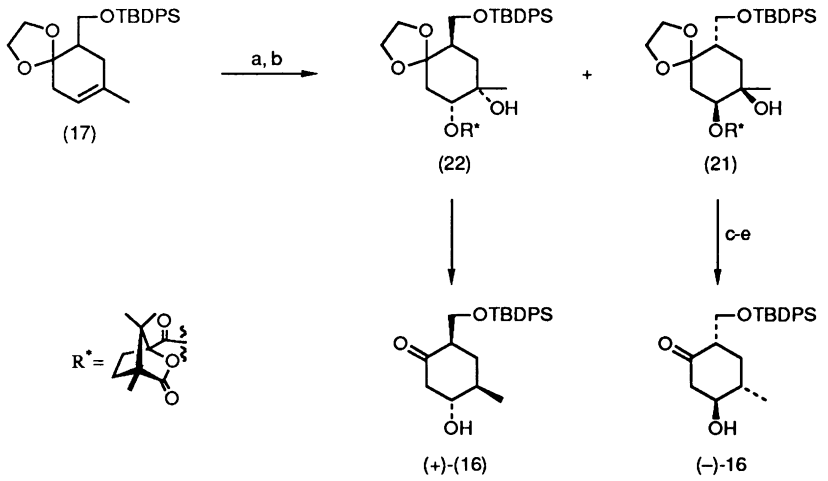
SCHEME 18. (a) $(COCl)_2$, DMSO, then Et_3N, CH_2Cl_2, 100% (b) PhSeCl, EtOAc, 25°C. (c) *m*CPBA, aqueous $NaHCO_3$, CH_2Cl_2, 96%. (d) $NaBH(OAc)_3$, AcOH, 25°C, 92%. (e) CH_2N_2, HBF_4, CH_2Cl_2, −78°C to 25°C, 94%.

isomerization of the double bond into conjugation on oxidation of the C_1 center.

The remaining problem to be solved was how to obtain this southern zone fragment in optically pure form for the synthesis of milbemycin β_1. Attempts of effect a kinetic resolution by asymmetric hydroboration[35] of the dioxolane **17** to give an optically enriched alcohol were moderately successful, but the reaction was very unreliable and could not be used on a preparative scale. We therefore had to resort to an alternative sequence. This involved initial catalytic osmium tetroxide *cis*-hydroxylation of **17** followed by reaction with (1S)-(−)-camphanic acid chloride to give the separable diastereomeric esters **21** and **22** (Scheme 19). These could be processed to (+)- and (−)-**17** by ester hydrolysis, formation of the orthoformates and conversion to the optically pure alkenes by treatment with acetic anhydride.[36] Hydroboration and deprotection were then performed as described earlier, to provide either enantiomer of **16**. Determination of the absolute configuration was achieved by X-ray crystallography on a derivative **23** obtained from **22** by dehydration using thionyl chloride and pyridine.



(23)



SCHEME 19. (a) OsO_4, NMO, *t*-BuOH/THF/H_2O, 71%. (b) 1S-(−)-camphanic acid chloride, Et_3N, DMAP, CH_2Cl_2. (c) K_2CO_3, MeOH, 88%; (d) $(MeO)_3CH$, PPTS, CH_2Cl_2, 100%; (e) Ac_2O, reflux, 64%, then as Scheme 16.

Not all was as straightforward as it seemed, however, as initially the absolute configuration was misassigned based upon the X-ray data and the reported structures for the (1S)-(−)-camphanic acid residue in the original Aldrich catalog[37] and in the review by J. W. Scott in Morrison's "Asymmetric Synthesis",[38] which as reported are actually incorrect! The error only became clear to us later when we began synthesizing the model compounds reported in the next section. Coupling to an optically pure northern hemisphere fragment afforded an isomeric milbemycin β_1 compound and caused us to reassign our diastereomeric esters **21** and **22**. This was a hard lesson to learn, but it points out that one should not always trust X-ray structure determinations and that not all you read in books is true!

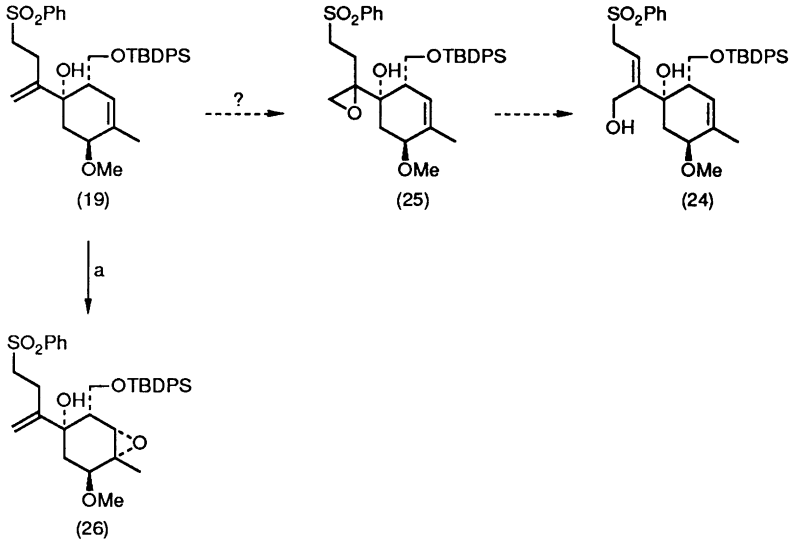
V. Synthesis of Model Compounds and Model Reactions

At this stage we were feeling fairly confident that our plans for the synthesis were beginning to be effective. A superstitious person when it comes to structures, the senior author is usually reluctant to write these down until the actual products are in hand. It was at about this time that, at his birthday party, he was presented with a sweater

made by some members of the group, with the completed structure of milbemycin β_1 emblazoned on the front. It was a further three years before the synthesis of milbemycin β_1 was completed!

The next phase of the work required us to devise coupling strategies and functional group manipulation. This involved model studies to avoid depletion of stocks of precious materials. Many questions still needed to be answered before we felt we could embark on the journey down the final road of using the correct enantiomerically pure fragments in coupling reactions. Since only a very small sample of milbemycin β_1 was available to us, we did not have the luxury of being able to study the relay work which is common practice in natural product synthesis. *De novo* synthesis of a complex molecule is a much more difficult task than learning to couple degraded fragments based on an adequate natural product supply.

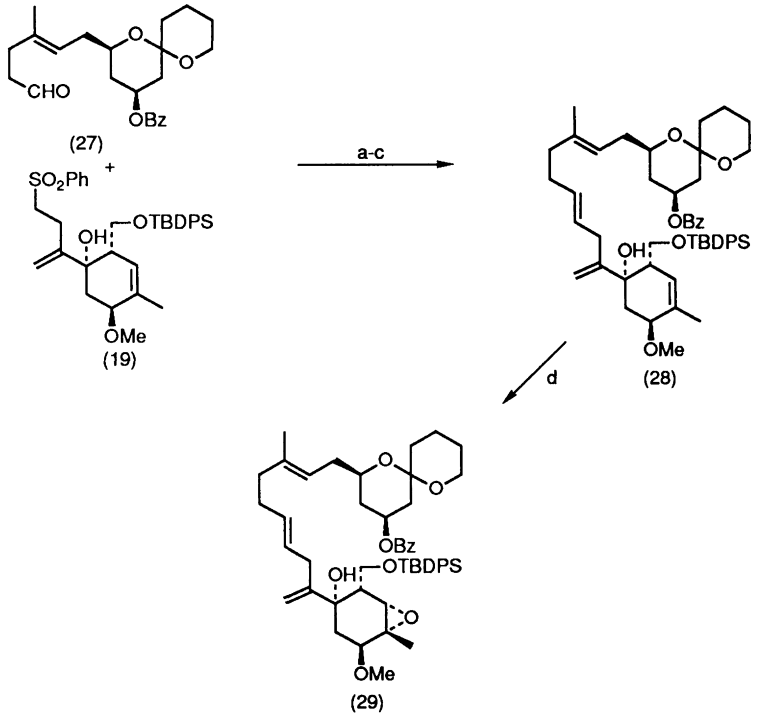
The problems that remained were to find a suitable method to create the side chain *E,E*-dienol portion of milbemycin β_1, and to establish a route to macrocyclic materials. We first attempted to modify the southern fragment **19** by directed epoxidation followed by allylic rearrangement to give a more suitable coupling unit **24** (Scheme 20). Surprisingly, when we used standard hydroxyl-



SCHEME 20. (a) $VO(acac)_2$, *t*-BuOOH, 66%.

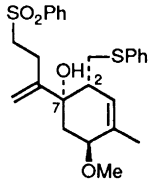
directed epoxidation with vanadyl acetylacetonate and *tert*-butyl hydroperoxide[39] or *m*-chloroperbenzoic acid, none of the allylic epoxide **25** was obtained. Rather, we obtained the homoallylic product **26** selectively and in high yield. We therefore decided to investigate some coupling reactions in the hope that the products would undergo the selective reactions we desired. By modification of the previously described methods, gram quantities of a northern hemisphere model spiroacetal **27** were prepared in just six steps. This was coupled with the dianion generated from **19** and, after reductive desulfonylation, the *E*-alkene **28** was obtained. Unfortunately, this too reacted under the Sharpless conditions to give the homoallylic epoxidation product **29** (Scheme 21).[40]

The coupled product **28** was then investigated as a model to study the macrolactonization reaction. Here too, we met with little success. Although **28** could be easily deprotected with fluoride to afford a

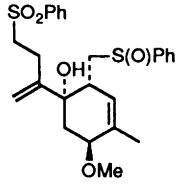


SCHEME 21. (a) 2 equivalents BuLi, THF/HMPA, then add (27). (b) PhCOCl. (c) 6% Na/Hg, THF/MeOH, Na_2HPO_4, 45%. (d) $VO(acac)_2$, *t*-BuOOH, 50%.

primary alcohol, *all* attempts, with a range of oxidizing reagents, failed to give either an aldehyde or the carboxylic acid necessary for macrolactonization. We also briefly studied a novel approach to macrocyclic ring construction involving an attempt to trap a Pummerer-type intermediate. As a model for this, we synthesized the sulfide **30**, and on treatment with *N*-chlorosuccinimide/iodine obtained a reactive intermediate iodide **31** which could be trapped with methanol to give the thioacetal **32**. Unfortunately, intramolecular cyclization to give the macrocyclic acetal **33** was never observed (Scheme 22). It could be argued that this was a poor model for the real system, so before abandoning the approach we also prepared the sulfide **34** and sulfoxide **35** as precursors. Under a variety of Pummerer conditions these suffered degradation *via* fragmentation of the C_2–C_7 bond assisted by the angular hydroxyl group.[40]

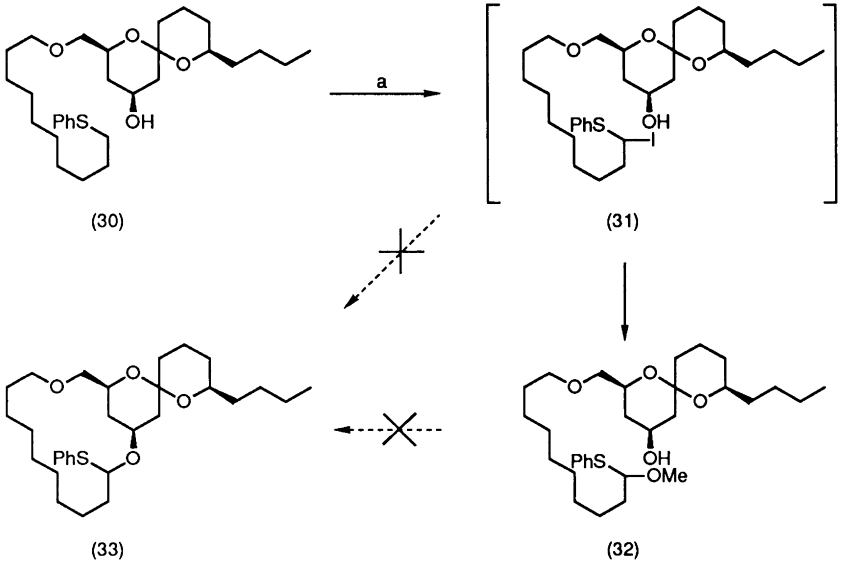


(34)



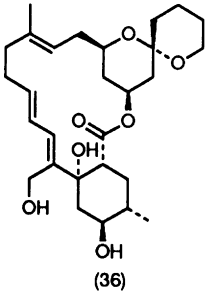
(35)

What we had learned from these studies was that early incorporation of the C_3–C_4 double bond caused many problems, as did attempts to effect directed epoxidation and rearrangement to establish *E,E*-dienol side chain groupings. To address these issues we decided to prepare a 3,4-dihydro model compound **36** as this has considerable skeletal homology with milbemycin β_1, and we envisaged introduction of the C_3–C_4 double bond using the selenium-based methodology established earlier. In this new approach, therefore, we reasoned that incorporation of the necessary oxygenation at the $C_{8'}$ position in the southern coupling fragment would overcome many of the difficulties encountered above. Hydroboration of **18**, the previously synthesized C_1–C_{10} unit, gave the diastereomeric alcohols **37** and **38** in a 2:9 ratio. Reaction of the major isomer **38** with benzaldehyde and pyridinium tosylate gave a separable 1:1 mixture of benzylidene acetals **39** and **40**. Only one of these, **39**, was carried through the synthesis, and the acetal **40** could be recycled by

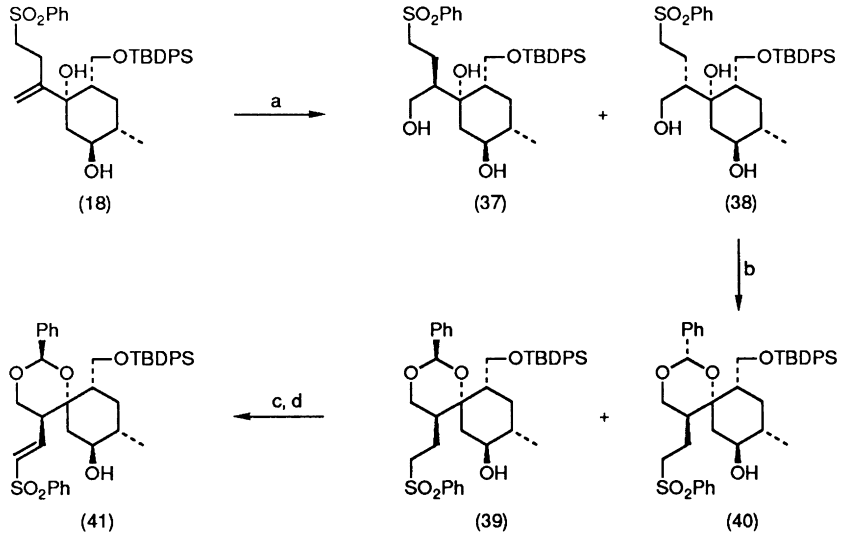


SCHEME 22. (a) *N*-Chlorosuccinimide, NaI, K_2CO_3, CCl_4, then MeOH, 33%.

re-exposure to the acetalization reaction conditions. Treatment of **39** with two equivalents of *tert*-butyllithium followed by quenching of the resulting α-sulfonyl carbanion with phenylselenenyl chloride, gave the intermediate selenides. Oxidation with *m*-chloroperbenzoic acid resulted in smooth *syn*-elimination of the selenoxides to give the *E*-vinylic sulfone **41** (Scheme 23). This was to be used as a coupling fragment in the synthesis of the model compound **36**, but also turned out to be the most suitable piece for the total synthesis of milbemycin β_1.

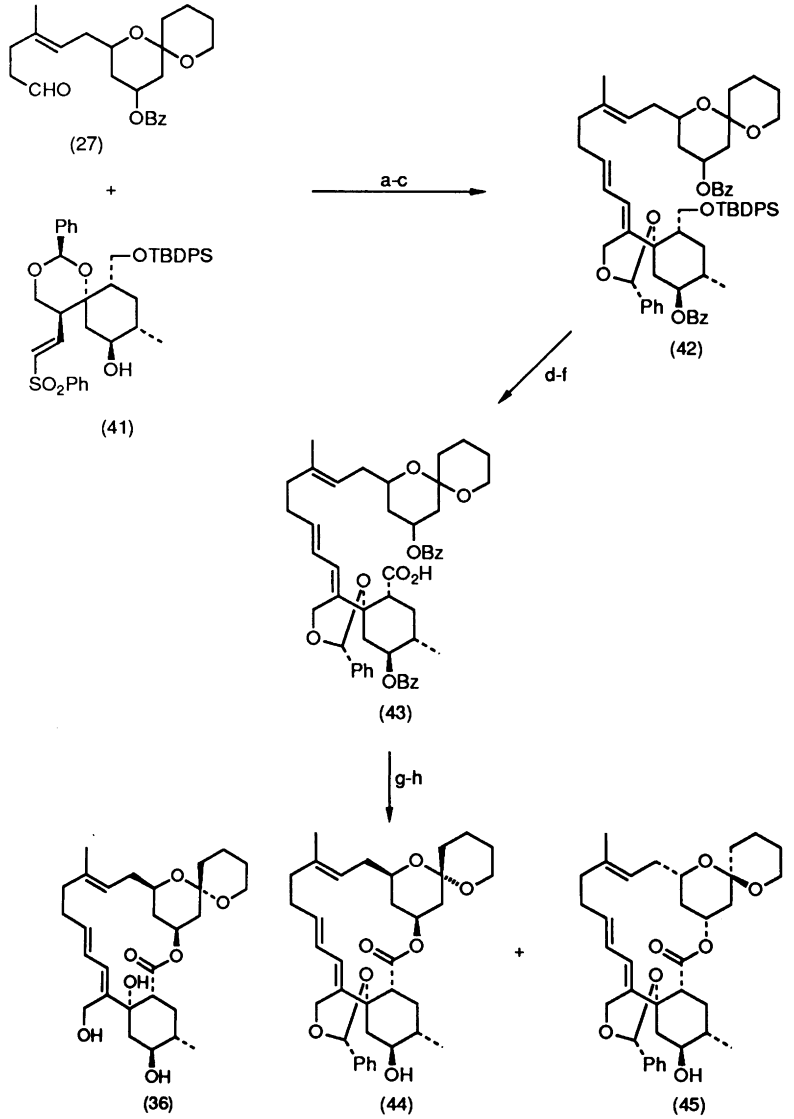


(36)



SCHEME 23. (a) $BH_3 \cdot Me_2S$, then aq. NaOH, H_2O_2. (b) PhCHO, PPTS, C_6H_6, reflux. (c) 2.2 eq. *t*-BuLi, THF, −78°C, then PhSeCl, 79%. (d) *m*CPBA, CH_2Cl_2/aqueous $NaHCO_3$, 99%.

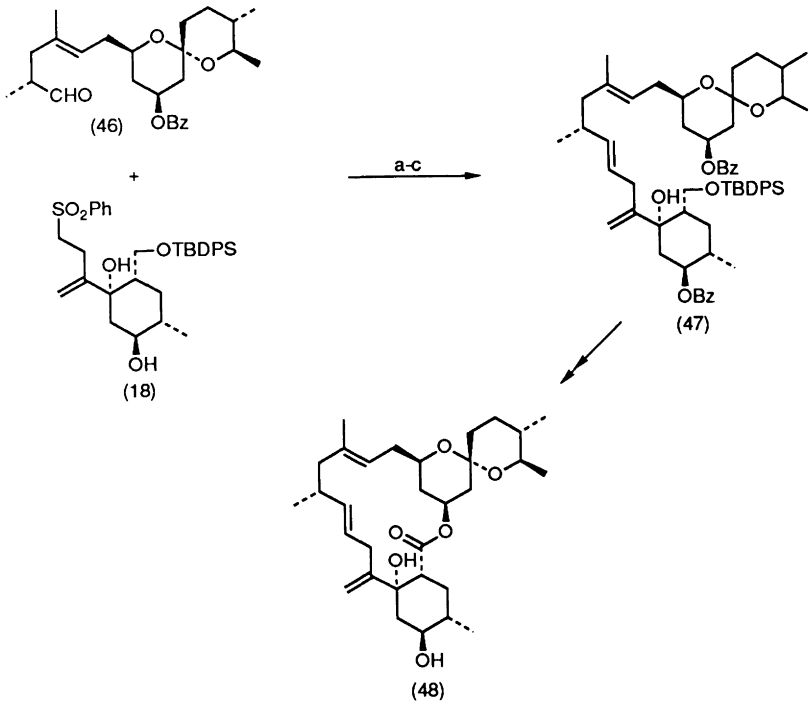
For the preparation of the model compound **36**, we proposed to couple the previously synthesized spiroacetal **27** with the dianion derived from **41**. We thought that **41** would undergo deprotonation with two equivalents of *tert*-butyllithium and that due to the conformation of the system it would remain sufficiently stable to react with **27** under Julia-type coupling conditions[41] *via* the deconjugated α-sulfonyl carbanion. Following benzoylation and reductive desulfonylation, the diastereoisomeric *E,E* dienes **42** were indeed obtained (Scheme 24). None of the other possible dienes were isolated, suggesting that steric effects may be operating in our favor in the coupling to give the desired C_8–C_9 double bond geometry. While it is difficult to predict this outcome we were nevertheless pleased and felt that this vindicated the use of a very sterically hindered group on C_1, which additionally had given us excellent control during the vinyl-anion addition reaction to set up the C_7 stereochemistry. The C_1 oxidation state in **42** was adjusted prior to macrolactonization. Thus, deprotection with tetra-n-butylammonium fluoride and two-stage oxidation using Swern conditions followed by immediate further oxidation with buffered sodium chlorite[42] gave the acids **43**. The



SCHEME 24. (a) 2 equivalents BuLi, THF, then add (27). (b) PhCOCl, −78°C to 25°C. (c) 6% Na/Hg, THF/MeOH, Na_2HPO_4, 25%. (d) TBAF, THF, 67°C, 77%. (e) $(COCl)_2$, DMSO, then Et_3N, CH_2Cl_2, 100%. (f) $NaClO_2$, KH_2PO_4, 100%. (g) NaOMe, MeOH. (h) 2-chloro-*N*-methyl pyridinium iodide, Et_3N, CH_3CN, reflux, 13% (44), 15% (45). (i) TFA, CH_2Cl_2.

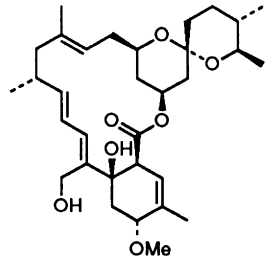
benzoyl groups were removed with sodium methoxide and the crude products subjected to macrolactonization using the Mukaiyama conditions.[43] As we were using racemic coupling partners, two diastereomeric sixteen-membered ring macrolide products **44** and **45** were expected. Removal of the benzylidene acetal protection from **44** gave the model compound **36** which, among other things, showed NMR characteristics for the olefin region very similar to β_1 (Scheme 24).[40,44] This route established the background for the eventually successful sequence to milbemycin β_1 (**1**).

In another model study,[45,46] we coupled the trianion generated from **18** with the C_{11}–C_{15} northern hemisphere fragment **46** which had been prepared previously by the 2-benzenesulfonyl tetrahydropyran technology. After benzoylation, reductive desulfonylation gave the C_{10}–C_{11} *E*-coupled product **47**. This was then processed by similar chemistry to that established in the previous model study to provide the macrolide **48** (Scheme 25). Unfortunately, due



SCHEME 25. (a) 3 equivalents BuLi, THF/toluene, then add (46). (b) PhCOCl. (c) 6% Na/Hg, THF/MeOH, Na_2HPO_4, 30%.

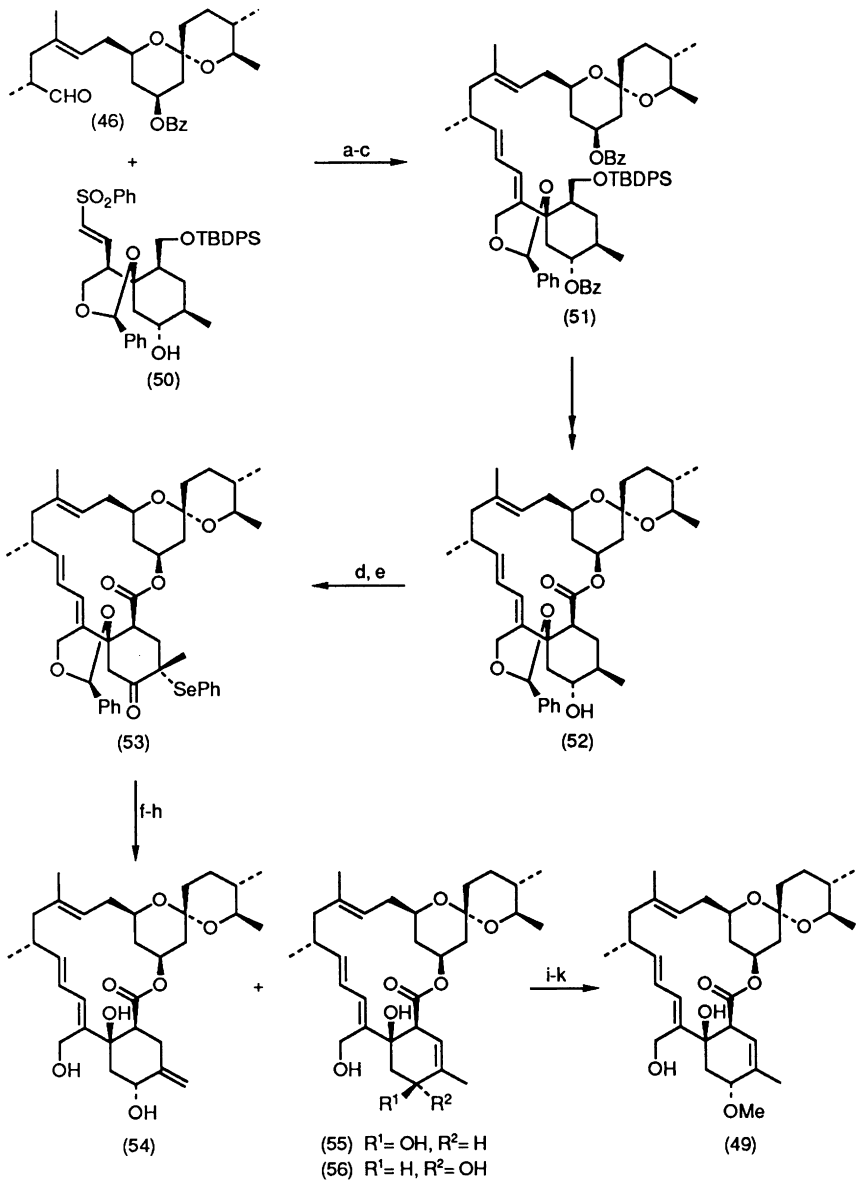
to lack of material at the end of this sequence owing to a rather modest yield (30%) in the coupling, we were unable to investigate selective epoxidation and rearrangement conditions for the installation of the *E,E*-dienol side chain. Nevertheless, the route showed that novel structures could be produced that potentially could be applied to β_1 synthesis.



(49)

The final model system we studied involved coupling of enantiomerically pure fragments. In this phase of the work we believed we were proceeding towards milbemycin β_1 itself, but as it turned out we prepared a novel isomer **49** owing to the initial misassignment of absolute stereochemistry of the southern C_1–C_{10} unit discussed earlier! This is just the sort of story that this series of books reveals but which goes unreported in other, more formal reviews. Compound **49** contains all the structural elements of milbemycin β_1, but consists of the correct C_{11}–C_{25} chirality while the C_1–C_{10} southern portion is antipodal to the natural product.[40]

The dianion from the antipodal unit **50** was added to the optically pure northern spiroacetal aldehyde **46**. Following benzoylation and reductive desulfonylation the *E,E*-diene **51** was obtained, albeit in a rather modest 29% yield (Scheme 26). Nevertheless, since we had good supplies of materials we were able to progress these compounds through to the final structures. Not all of the peripheral chemistry to this end is discussed; rather we will describe only the successful sequence as it was this route that set the stage for the natural product preparation. Compound **51** was converted to the macrolide **52** following essentially similar steps to those in the previous model studies. Following C_5 oxidation, the C_4–C_5 *tert*-butyldimethylsilyl enol ether was generated regioselectively. Attempts to generate enones directly from this intermediate silyl enol ether were not successful, but reaction with phenylselenenyl chloride gave the selenide



SCHEME 26. (a) 2 equivalents *t*-BuLi, THF, −78°C, then add (46), (b) PhCOCl, DMAP, pyridine, 25°C. (c) 6% Na/Hg, THF/MeOH, Na_2HPO_4, 29%. (d) $(COCl)_2$, DMSO, then Et_3N, CH_2Cl_2, 100%. (e) TBDMSOTf, Et_3N, CH_2Cl_2, then PhSeCl, −30°C, 92%. (f) TFA, CH_2Cl_2, −78C. (g) 2-phenylsulfonyl-1-3-(p-nitrophenyl)oxaziridine. (h) $NaBH_4$, $CeCl_3$. $7H_2O$, MeOH, 23% (54), 13% (55), 21% (56). (i) TBDMSCl, Et_3N, 0°C, CH_2Cl_2, 40%. (j) CH_2N_2, HBF_4, CH_2Cl_2, 70%. (k) HF/pyridine, 60%.

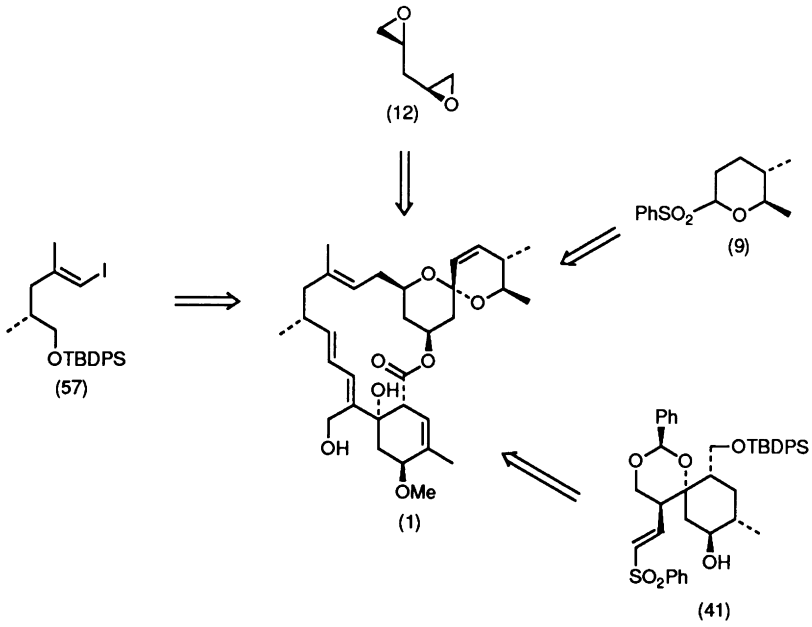
53. After some experimentation it was found that after deprotection of **53**, oxidation to the selenoxides using an oxaziridine reagent[47] and subsequent *syn*-elimination, followed by reduction under the Luche[48] conditions (sodium borohydride and cerium(III) chloride) three products **54**, **55**, and **56** could be obtained in 23%, 13% and 21% yields, respectively. **55** could also be recycled to **56** by oxidation and reduction. Other attempts to maximize the formation of the *endo* versus the *exo* methylene isomers in the *syn*-elimination step using chiral oxidizing agents or by utilizing alternative levels of hydroxyl group protection failed. Finally, **56** was converted to **49** by selective protection of the primary hydroxyl group using *tert*-butyldimethylsilyl chloride, methylation of the C_5 hydroxyl with diazomethane and fluoroboric acid as in the earlier model sequence, and finally deprotection with hydrogen fluoride. As these last steps were being completed, it became apparent from the NMR spectra that we were not producing milbemycin β_1 as we had hoped. From extensive additional NMR and molecular modeling work on **49**, we tentatively believed that we were producing a conformational isomer (atropoisomer) of β_1 around the C_7–C_{12} bonds caused by constraining this unit with the cyclic benzylidene acetal group earlier in the synthesis. We were unhappy with this explanation, as were Dick Stoodley after the Perkin Meeting in Manchester in April 1988 and Clay Heathcock later that year at the Sendai Meeting, although they were unable to suggest solutions to the problem. We continued to analyze the data until we realized the simple mistake associated with the X-ray structure determination of the absolute configuration discussed earlier. All then became clear—we had in fact coupled the antipodal southern zone. The synthesis of milbemycin β_1 should now be straightforward after paying the debt of one beer lost in the bet with Professor Stoodley.

VI. At Last, Milbemycin β_1: The Real Thing

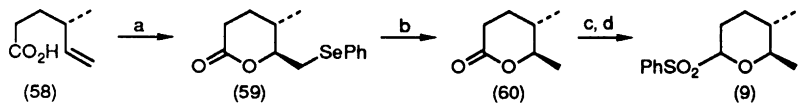
Based upon everything we had discovered so far, we could now define a synthetic plan to milbemycin β_1 (**1**) which we were extremely confident would be successful. This plan utilized the new chemistry for spiroacetal preparation and it employed the use of the *bis*-epoxide to link the side chain to the spiroacetal, with control of geometry and

configuration. It also used the coupling and macrolactonization sequences shown to be effective in the model compound syntheses. Furthermore, the plan was consistent with a general strategy which later also proved to be applicable to avermectin B1a synthesis (*vide infra*).

This highly convergent synthetic plan is presented in Scheme 27, showing the essential building blocks for the process. The preparation of **41** was described earlier; the alkenyl iodide **57** was obtained from *S*-(+)-methyl-3-hydroxy-2-methylpropionate, and the *bis*-epoxide **12** from ribonic acid-δ-lactone.[5] The sulfone **9** was derived from the known carboxylic acid **58**[4b] using a modified selenolactonization procedure under thermodynamic conditions with *N*-phenylselenophthalimide (NPSP) and tin(IV) chloride in boiling dichloromethane to give **59** as the major product. These conditions were used during our other selenium-mediated cyclization chemistry reported earlier.[11] Reductive removal of the phenylselenenyl group from **59** gave the lactone **60** which was converted to **9** by treatment with diisobutylaluminum hydride then benzenesulfinic



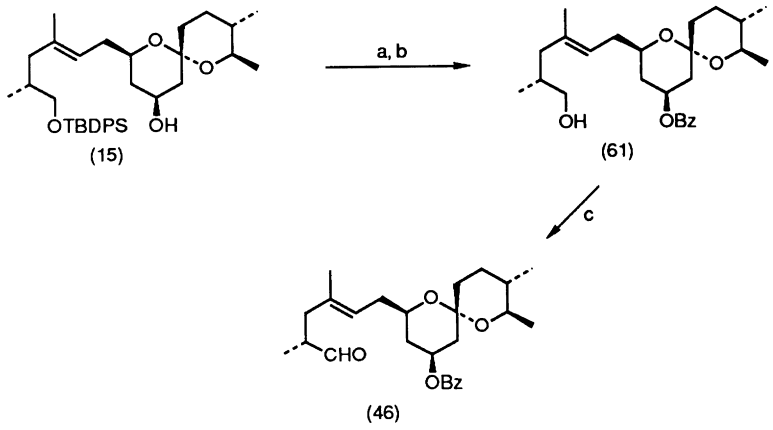
SCHEME 27



SCHEME 28. (a) *N*-(phenylseleno)phthalimide, $SnCl_4$, CH_2Cl_2, reflux, 78%. (b) Bu_3SnH, AIBN, DME, 80°C, 87%. (c) DIBAL, toluene, −78°C, 94%. (d) $PhSO_2H$, CSA, CH_2Cl_2, 91%.

acid (Scheme 28). Efficient coupling of **57**, **12**, and **9** to give the C_{11}–C_{25} northern hemisphere fragment **15** was discussed earlier (Scheme 15). Compound **15** was elaborated to the aldehyde **46** by benzoylation and fluoride treatment to give the alcohol **61**, which was then oxidized using tetra-n-propyl ammonium perruthenate, TPAP[49] (Scheme 29). This reagent, which is a new room temperature, catalytic oxidant for alcohols, has served us well in many of our synthetic programs.

Coupling of the northern C_{11}–C_{25} unit **46** to the southern C_1–C_{10} fragment **41** was examined next, following the general procedures shown to be successful in the model studies. Treatment of **41** with two equivalents of *tert*-butyllithium gave the dianion which again reacted with **46** through its C_{10} carbon atom to give the coupled material in good yield (84%). Reductive elimination and benzoylation afforded the *E*,*E*-diene **62** (Scheme 30). Deprotection of **62** with tetra-n-butyl-ammonium fluoride gave the C_1 alcohol **63**. This

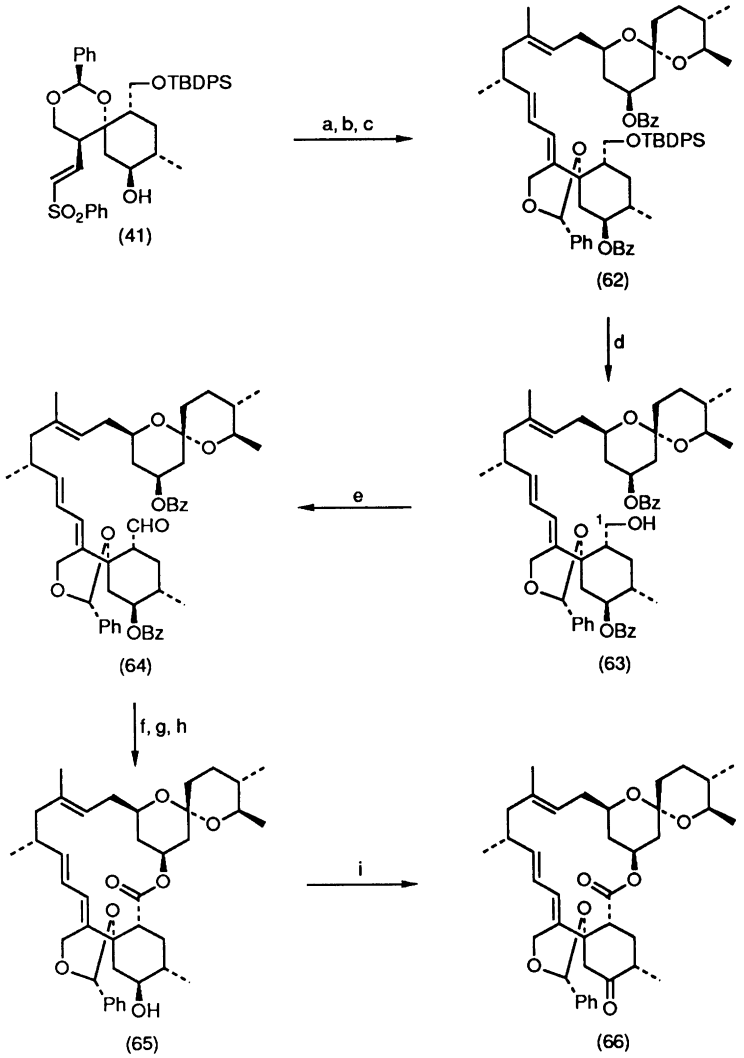


SCHEME 29. (a) PhCOCl, DMAP, pyridine, 85%. (b) TBAF, THF, 95%. (c) TPAP, NMO, 4Å ground sieves, CH_2Cl_2, 85%.

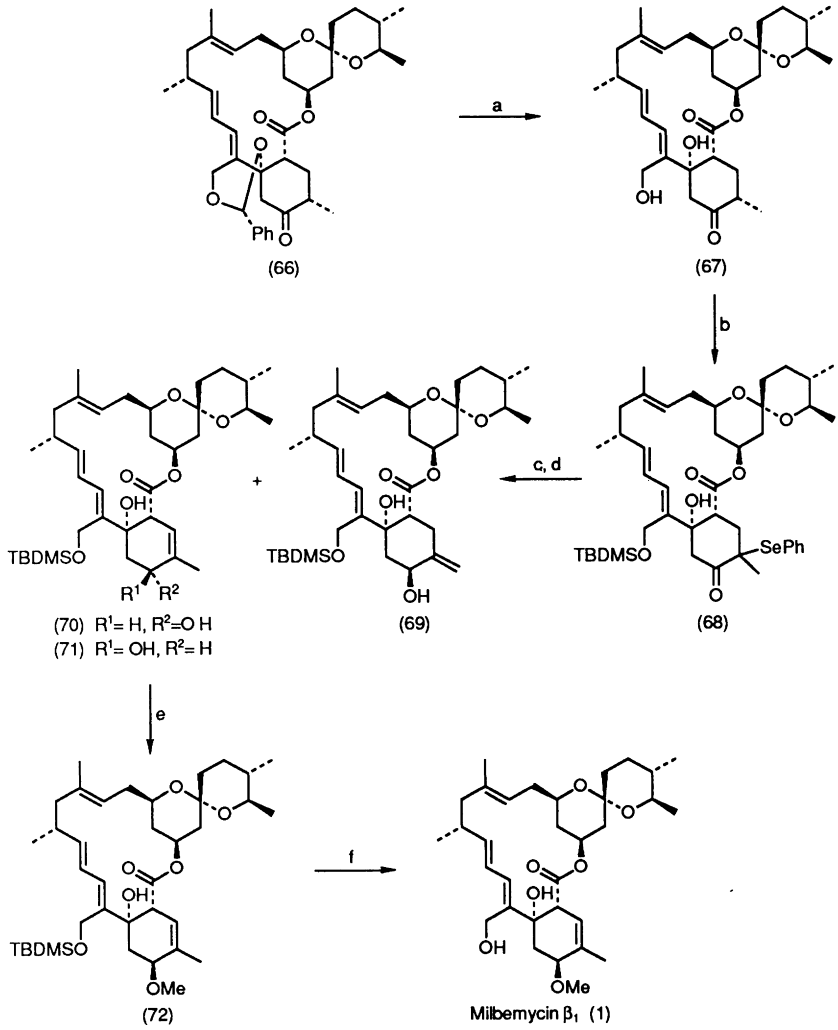
was oxidized in two steps, using the TPAP reagent to provide the aldehyde **64** followed by reaction with sodium chlorite to give the acid, which, after removal of the benzoate groups, was subjected to macrolactonization to give **65** (Scheme 30).

For the final steps of the synthesis the C_5 hydroxyl group in **65** was oxidized to the carbonyl compound **66** using TPAP. At this stage we decided to deviate from the model studies by removing the benzylidene acetal protection in the hope that we would avoid any possible conformational problem associated with this ring constraint. This was achieved by brief exposure to trifluoroacetic acid. The product diol **67** reacted with *tert*-butyldimethylsilyl triflate and triethylamine, followed by addition of phenylselenenyl chloride, to give the selenide **68**. Thus, in this one reaction we had effected regioselective selenenylation simultaneous with protection of the primary hydroxyl group. Oxidation of **68** with the Davis oxaziridine reagent[47] gave the intermediate selenoxides which underwent spontaneous *syn*-elimination at room temperature to give a mixture of *exo* and *endo* products in a 1 : 2 ratio by ^{1}H NMR. Owing to the possibility of aromatization of these compounds, they were most conveniently handled by work-up of this mixture with cerium(III)chloride/sodium borohydride to give the alcohols **69**, **70**, and **71** in a 1 : 1 : 1 ratio, in excellent overall yield. The compound **70** could be recycled to **71** by oxidation (TPAP) and reduction as above. Finally, methylation of **71** with methyl iodide and silver oxide under ultrasonication[50] gave **72**. Treatment with HF/pyridine gave us the long sought-after natural product milbemycin β_1 (**1**) (Scheme 31). The synthetic sample was identical by ^{1}H NMR, ^{13}C NMR, IR, mass spectrum, optical rotation and TLC (3 solvent systems) to an authentic sample kindly provided by the Sankyo company.[51]

The day was Friday, January 27, 1989, and we celebrated with three jeroboams of champagne, which were consumed by the group in as many minutes! We then spent the next two months repeating the work and bringing material through to complete all our data and to optimize yields to tidy up the work for publication. The paper was written and submitted on March 28, just after Easter. You can imagine our surprise when, shortly afterwards, we received a referee's comment on the work: "Preliminary reporting of organic synthesis should not be allowed to degenerate into uncheckable claims to priority. I would



SCHEME 30. (a) 2.2 equivalents *t*-BuLi, THF, −78°C, then add (46), 84%. (b) 6% Na/Hg, Na_2HPO_4, 3 : 1 THF:MeOH, −40°C. (c) PhCOCl, DMAP, pyridine/CH_2Cl_2, 29% (d) TBAF, THF, reflux, 91%; (e) TPAP, NMO, 4Å ground sieves, CH_2Cl_2, 76%. (f) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*-BuOH/H_2O. (g) NaOMe, MeOH. (h) 2-chloro-l-methyl-pyridinium iodide, Et_3N, CH_3CN, reflux, 9 hours, 49% from (64). (i) TPAP, NMO, 4Å ground sieves, 83%.



SCHEME 31. (a) TFA, CH_2Cl_2, 92%. (b) TBDMSOTf, Et_3N, CH_2Cl, then PhSeCl, CH_2Cl_2, 50%. (c) 2-(Phenylsulfonyl)-3-(*p*-nitrophenyl) oxaziridine, $CDCl_3$, r.t. (d) $NaBH_4$, $CeCl_3.7H_2O$, MeOH. (e) MeI, Ag_2O,))), 73%. (f) HF, pyridine, CH_3CN, 75%.

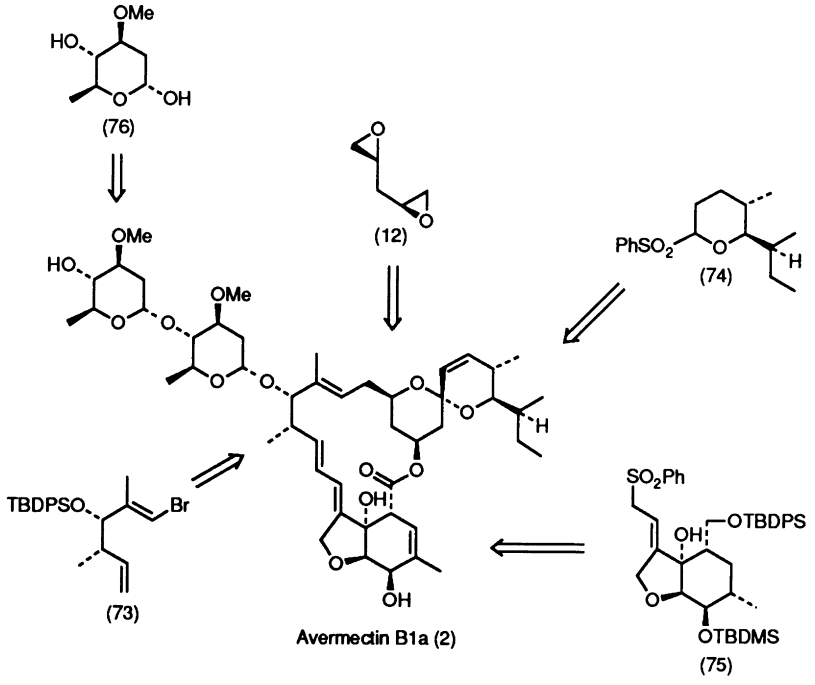
much rather see this work described in two notes...". The referee also commented .. "it sets a bad example in that there is entirely inadequate characterization of all new compounds."

We were obviously very angry at these comments, since it was not our policy to unduly fragment work. Details of two key compounds were provided, as was a statement to the fact that all compounds had

been fully characterized by spectroscopic and microanalytical or accurate mass data. We modified the paper[52] by adding six extra words and appealed to the Editor for his sense of fair play. Our appeals were immediately accepted, but with a "revised" submission date of April 25, 1989.

VII. The Final Celebration: Avermectin B1a Synthesis

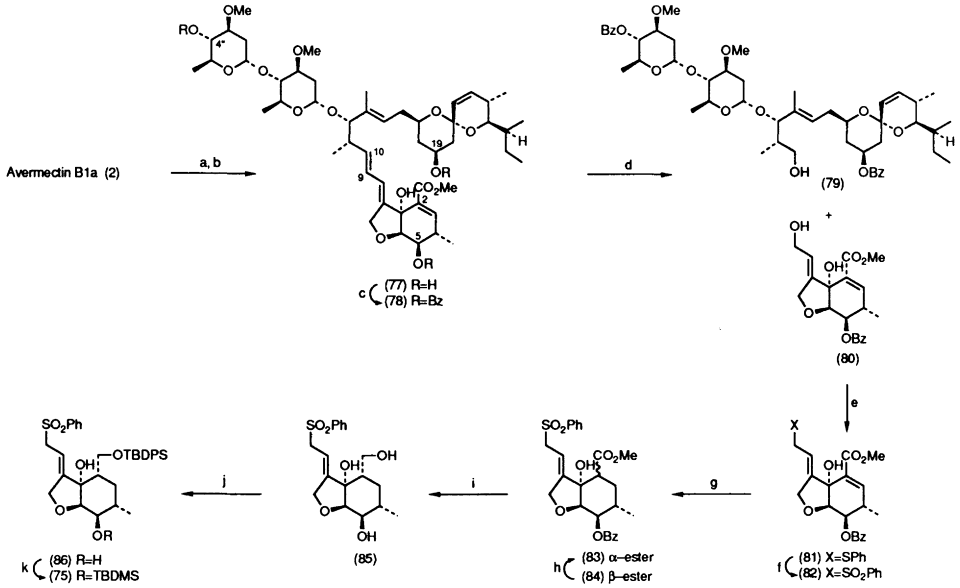
The prize of this area of synthesis must be avermectin B1a (**2**) as it contains all the structural challenges of the series and also plays the central biological role. Throughout our work we endeavored to formulate a general strategy to these molecules. Indeed, the highly convergent route which evolved for milbemycin β_1 synthesis can also be adapted broadly to encompass the synthesis of **2**. Following a similar convergent plan, we envisaged coupling of five key fragments (Scheme 32).



SCHEME 32

We retained the idea of constructing the spiroacetal portion through coupling of a side chain fragment derived from **73** and a hydropyran sulfone **74** with the *bis*-epoxide **12**. The reduced hydrobenzofuran C_1–C_{10} unit **75** was chosen following our previous experience for introducing the 3,4-unsaturation at a late stage in the synthesis. The carbohydrate residue oleandrose **76** needed for the coupling differentiates the avermectins from the milbemycins, which lack the *bis*-saccharide at the C_{13} position. Synthesis of the *bis*-epoxide **12** was commented upon earlier, although the remaining pieces of the puzzle in Scheme 32 are new. Another important difference from the work on milbemycin β_1 was the availability of generous supplies of the natural product for degradation and relay studies.[53] This was an enormous advantage, giving us the opportunity to match synthetic fragments with material obtained by degradation and manipulation. The complication for some of this work was that the natural product supply additionally contains approximately 5% avermectin B1b, the C_{25} isopropyl avermectin, which needs to be removed by tedious HPLC prior to some studies to ensure really clean samples and spectra. While we have used some similar degradation reactions to those described in the literature, many discussed here are new and have not been reported elsewhere.

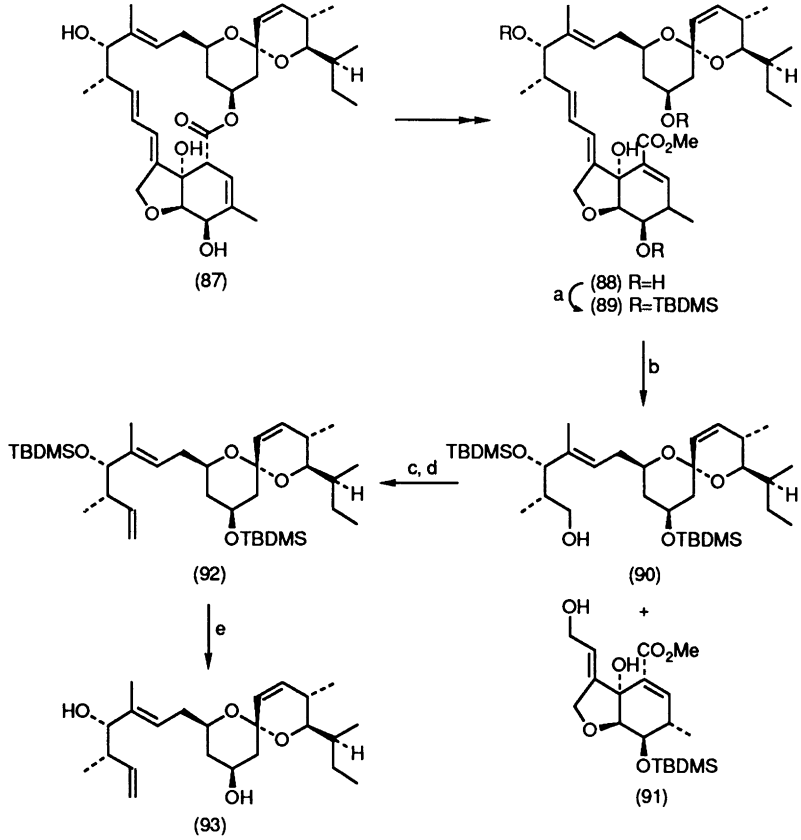
The first of our degradation studies was aimed at providing material for the southern C_1–C_{10} fragment **75** (Scheme 33). Here avermectin B1a (**2**) was converted to the C_2-conjugated ester **77** using the Hanessian protocol.[54] The free hydroxyl groups at C_5–C_{19}, and $C_{4''}$ were benzoylated to give **78** prior to selective C_9–C_{10} double bond cleavage by ozonolysis in the presence of Sudan Red 7B as an indicator to detect excess ozone. Reductive work-up with sodium borohydride afforded the two fragments **79** (92%) and **80** (78%). The southern unit **80** was converted to the required coupling fragment *via* conversion of the primary hydroxyl group to the sulfide **81** using diphenyldisulfide and triphenylphosphine. Oxidation of the sulfide with Oxone® gave the sulfone **82**. This, on conjugate reduction with an excess of sodium borohydride, gave a 1.4 : 1 mixture of esters **83** and **84**. However, the β-isomer **84** was readily converted to **83** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 70% yield. Reduction of **83** with lithium aluminum hydride gave the triol **85** which could be protected selectively with *tert*-butyldiphenylsilyl chloride to give **86**. This material was



SCHEME 33. (a) Aqueous KOH, DME. (b) CH_2N_2. (c) PhCOCl, DMAP, pyridine, 80% from (2). (d) O_3, −78°C, CH_2Cl_2/EtOH, then $NaBH_4$, 92% (79), 78% (80). (e) PhSSPh, Bu_3P, THF, 95%. (f) Oxone®, MeOH/aqueous pH 4 buffer, 99%. (g) $NaBH_4$, MeOH, 73%. (h) DBU, CH_2Cl_2, 3 days, 70%. (i) $LiAlH_4$, THF, 0°C, 70%. (j) TBDPSCl, Et_3N, CH_2Cl_2, 72%. (k) TBDMSOTf, Et_3N, CH_2Cl_2, 100%.

obtained in a reasonable 10% overall yield from avermectin B1a. Silylation afforded **75**, identical to material prepared later by synthesis (*vide infra*).

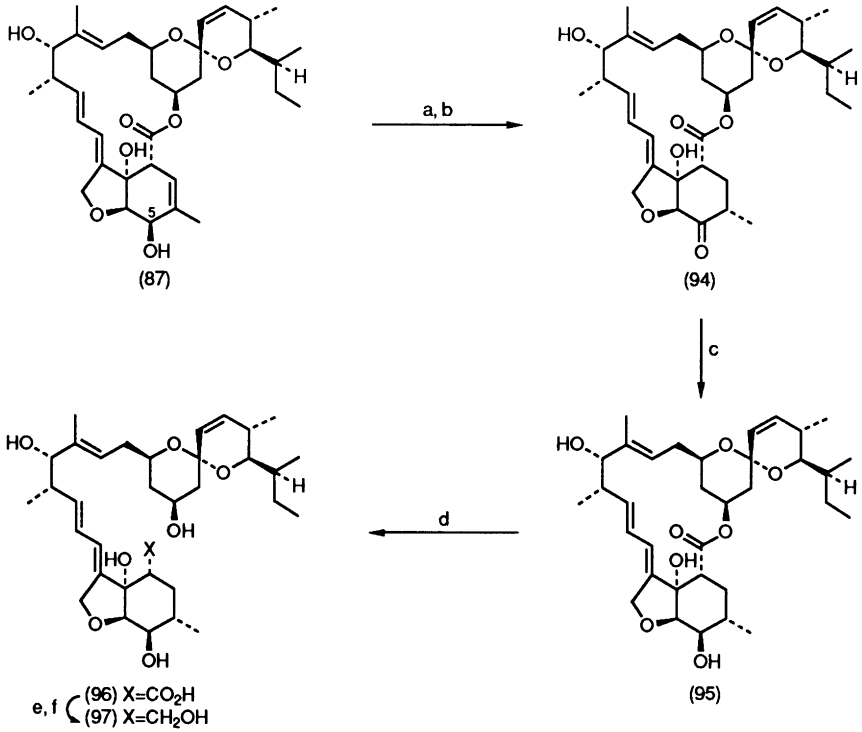
In related degradation studies, the avermectin B1a aglycone (**87**), obtained from **2** by acidic glycolysis,[55] was hydrolyzed using potassium hydroxide to open the macrolide and effect migration of the C_3 double bond into conjugation (Scheme 34). Methylation with diazomethane gave **88**, which was subjected to silylation with *tert*-butyldimethylsilyl chloride to give **89**. In a similar fashion to the previous degradation study, this was selectively ozonized to provide the C_{11}–C_{25} northern fragment **90** (87%) as well as a C_1–C_{10} segment **91** (85%). Both of these could be used in relay studies. For example, oxidation of **90** with the Swern reagent followed by methylenation with dibromomethane/zinc/titanium tetrachloride[56] gave **92** in 93% overall yield. Compound **92**, after deprotection



SCHEME 34. (a) TBDMSCl, imidazole, DMAP, DMF, 75%. (b) O_3, −78°C, CH_2Cl_2–EtOH, then $NaBH_4$, 87% (90), 85% (91). (c) $(COCl)_2$, DMSO, then Et_3N, CH_2Cl_2. (d) CH_2Br_2, Zn, $TiCl_4$, 93% from (90). (e) HF/CH_3CN, 90%.

with HF in acetonitrile, afforded **93**. This was also identical to the material targeted for synthetic studies (*vide infra*).

Among many other degradation and relay studies that we investigated,[57] one final sequence (Scheme 35) provided key compounds which, we planned, would lie on the total synthesis pathway. Here we were able to show that the aglycone **87** could be selectively oxidized at the C_5 position with manganese dioxide before conjugate reduction with sodium dithionite ($Na_2S_2O_4$)[58] to give **94**, albeit in a rather modest 35% overall yield. Nevertheless, this sequence could be used to prepare several other important compounds in the pro-

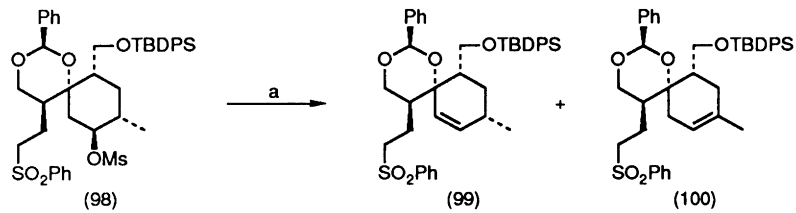


SCHEME 35. (a) MnO_2. (b) $Na_2S_2O_4$. (c) $NaBH_4$, MeOH, 30% from (87). (d) KOH, DME, Δ. (e) CH_2N_2, 88%. (f) $LiAlH_4$, Et_2O, 68%.

posed synthesis pathway and could conceivably be a route to novel avermectin analogues. Reduction with sodium borohydride gave the triol **95** which could be hydrolyzed to the acid **96** using potassium hydroxide in methanol. This compound was used in the later macrolactonization studies. Reduction of **96** with lithium aluminum hydride afforded the pentol **97** which also featured as a pivotal compound in the total synthesis.

These degradation and relay studies played a major role in facilitating a rapid conclusion to the avermectin B1a synthesis compared to the previous *de novo* synthesis of milbemycin β_1. However, although the groundwork that was covered during the β_1 synthesis served us well, and most of our plans towards avermectin B1a worked, as with any major synthetic program it was not easy. We first tackled the problem of the preparation of the C_1–C_{10} sulfone **75**. As it turned

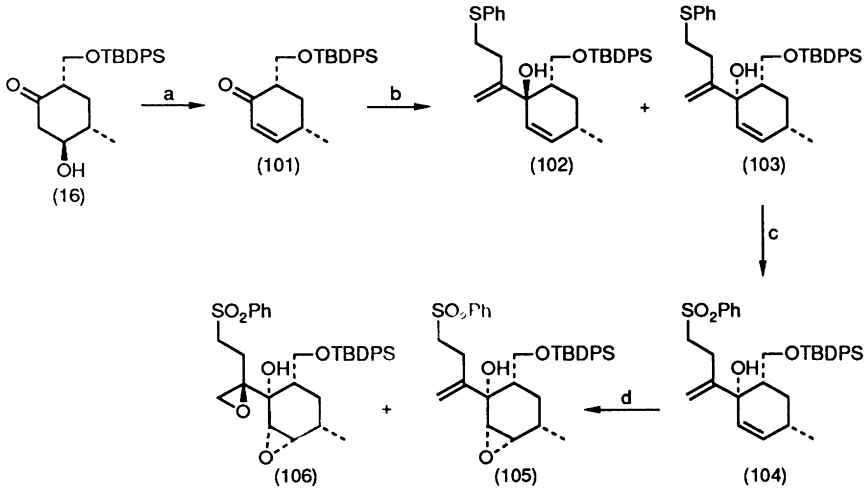
out, this was one of the most difficult problems to solve. We had set our goals high in that we wished to use a consistent strategy which would be widely applicable; from a common precursor, we hoped to prepare both the monocyclic southern zone fragments of milbemycin β_1 and the bicyclic hydrobenzofuran unit which occurs in so many avermectins and milbemycins. With regard to manipulation of intermediates used in the synthesis of the milbemycin southern hemisphere, the major task to be faced was the introduction of oxygen functionality at C_6. The obvious possibility of α-oxygenation of a C_5-carbonyl group was generally thwarted by the ready β-elimination of a protected C_7-hydroxyl group upon deprotonation at C_6. In view of this problem, a C_5–C_6 olefin appeared to be potentially the most flexible precursor to oxygenation at these two positions. In addition to the possibility of direct oxidation, the large number of methods that would allow cyclization of a $C_{8'}$-hydroxyl group onto this double bond was appealing. The regioselective elimination of the C_5-hydroxyl group present in most of the milbemycin southern hemisphere intermediates prepared to date would provide the most direct route to C_5–C_6 unsaturation. Initial results were promising; it was found that the mesylate **98**, prepared from the corresponding alcohol **39**, gave a 6:1 mixture of the olefin **99** and its C_4–C_5 isomer **100** after stirring overnight with basic alumina in carbon tetrachloride (Scheme 36).[59] Unfortunately, we had difficulties in removing the benzylidene acetal protecting group from **99** due to problems with elimination of the tertiary hydroxyl group. More seriously, stocks of the particular batch of Woelm basic alumina that we had been using in these elimination reactions were running low, and we were unable to repeat the good elimination ratios with other samples. We therefore decided to investigate the introduction of the C_5–C_6 double bond *before* addition of the C_8–C_{10} side chain. We found that the hydroxycyclohexanone



SCHEME 36. (a) Woelm basic alumina, CCl_4, 12h, 80%, 6:1 (99):(100).

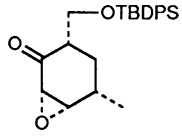
16 could easily be dehydrated using methanesulfonyl chloride and triethylamine in dichloromethane to provide the cyclohexenone **101**. However, rather disappointingly, this reacted with our favorite side chain, 2-lithio-4-phenylthiobut-1-ene,with poor selectivity, giving a 1 : 1 mixture of addition products **102** and **103** (Scheme 37). This ratio appeared to be insensitive to changes of temperature or solvent. Oxidation of the desired sulfide **103** gave the corresponding sulfone **104**. We then spent a considerable period of time trying to effect selective olefin functionalization with this compound. We were particularly interested in the possibility of selective osmium tetroxide *cis*-hydroxylation of the ring double bond, or selective hydroboration of the terminal methylene. Only one of the many transformations attempted, however, gave acceptable selectivity. Hydroxyl-directed epoxidation using the Sharpless conditions of vanadyl acetylacetonate and *tert*-butyl hydroperoxide provided predominantly the ring epoxide **105** (69%), along with the *bis*-epoxide **106** (22%). This *bis*-epoxide proved suitable for X-ray structure determination, allowing rigorous proof of stereochemistry at C_7 and C_5.

Since the ring epoxide **105** was the only compound we were able to obtain selectively, it became the focal point for further synthetic



SCHEME 37. (a) MsCl, Et_3N, CH_2Cl_2, 100%. (b) 2 equivalents 2-lithio-4-phenylthio-but-1-ene, 1 : 1 ether/THF, −78°C, 44% (102), 50% (103). (c) Oxone®, 1 : 1 : 1 THF/MeOH/pH 4 aqueous buffer, 89%. (d) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 69% **105**, 22% **106**.

transformations. The major blemish in the synthesis of **105** was the lack of stereocontrol in the side chain addition to the enone **101**. As an alternative route, it was envisaged that nucleophilic addition to the epoxy ketone **107** should occur with good stereoselectivity. Tony Barrett, by this time working at Northwestern University, had shown the utility of similar epoxy ketones in the synthesis of avermectin model systems.[60] Unfortunately, attempts to perform direct epoxidation of our enone **101** under basic conditions resulted in facile β-elimination of *tert*-butyldiphenylsilanol. Reduction gave predominantly the C_7-β-alcohol, precluding the use of a hydroxyl-directed epoxidation sequence to establish the C_5–C_6 stereochemistry. At around this time, several reports began appearing in the literature describing the power of dioxiranes in organic synthesis.[61] The observation by Murray[62] that a dilute (*ca.* 0.1 M) solution of dimethyldioxirane (**108**) could be distilled over from a basic mixture of acetone and Oxone® was particularly interesting, since this provided a powerful, anhydrous oxidant.[63] Pleasingly, reaction of such a dioxirane solution with enone **101** gave a readily separable 5 : 1 mixture of epoxides in favor of the desired isomer **107** (Scheme 38). The stereoselectivity of this reaction is not easily rationalized, but, as in every multi-step synthesis, the occasional piece of hard-earned good fortune is very welcome! We were also delighted to find that addition of 2-lithio-4-phenylthio-but-1-ene to **108** occurred with excellent diastereoselectivity. Oxidation of the sulfide **110** gave the sulfone **105**, identical to the compound prepared by the previous route.

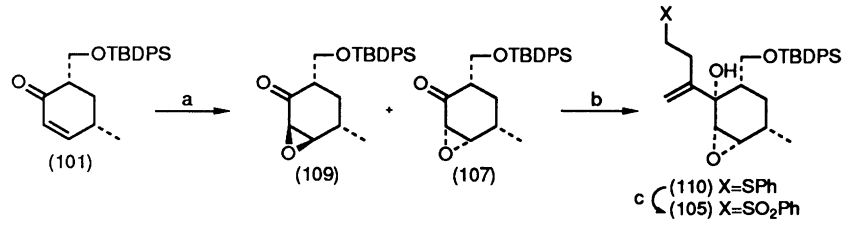


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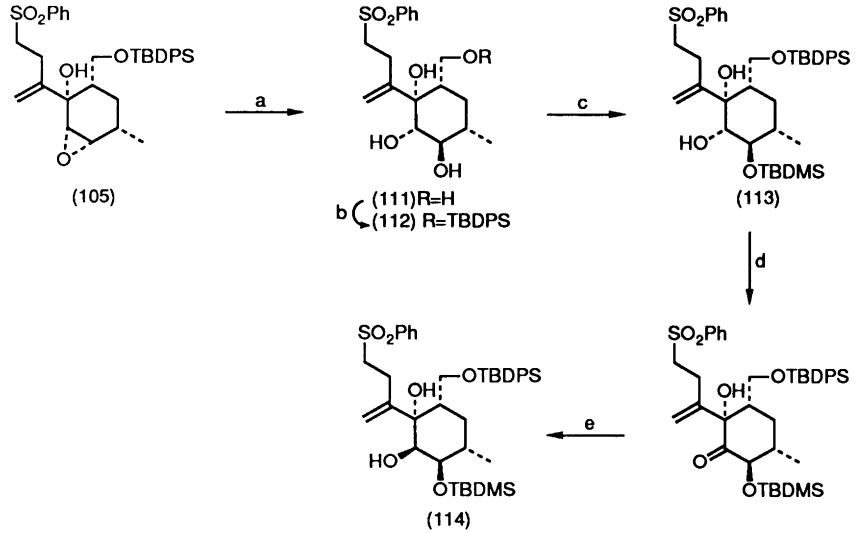


(108)

We considered several options for continuing the synthesis from **105**. Attempts to functionalize the terminal methylene group being unsuccessful, we examined many methods for epoxide opening with an oxygen nucleophile. Unfortunately, cleavage of the *tert*-butyldiphenylsilyl group always preceded epoxide opening. The conditions that we settled upon for this step are shown in Scheme 39;



SCHEME 38. (a) Dimethyldioxirane, acetone/CH_2Cl_2, 11% (109), 64% (107). (b) 2-lithio-4-phenylthio-but-1-ene, THF, −78°C, 95%. (c) Oxone®, 1:1:1 THF/MeOH/pH 4 aqueous buffer, 88%.



SCHEME 39. (a) 1:1 15% H_2SO_4:THF, 60°C, 12h, 80%. (b) TBDPSCl, imidazole, DMF, 91%. (c) TBDMSOTf, Et_3N, CH_2Cl_2, 91%. (d) $(COCl)_2$, DMSO, then Et_3N, 73%. (e) $NaBH_4$, MeOH, 79%.

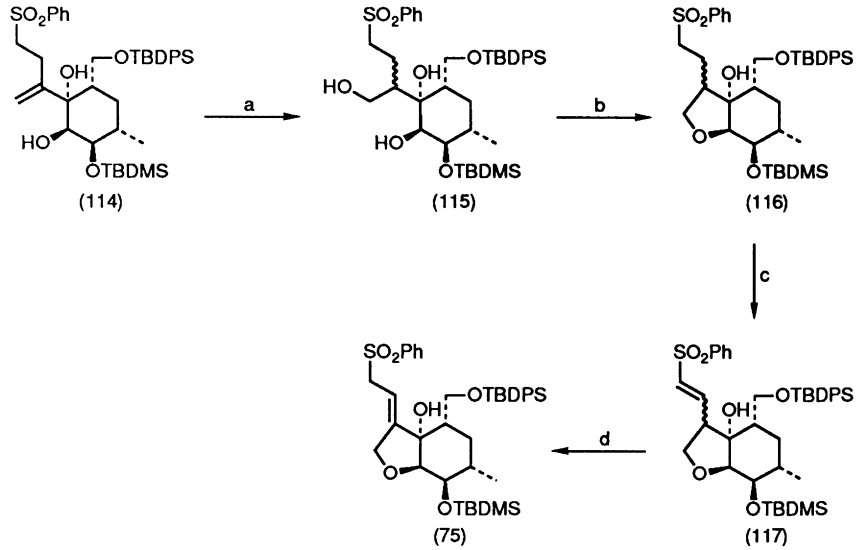
selective re-protection of the primary hydroxyl group of tetraol **111** was inconvenient but trivial. Surprisingly, the diequatorial product of epoxide opening was obtained rather than the expected diaxial isomer.

The triol **112** now in hand possessed the correct C_5-stereochemistry, but inversion of the C_6 alcohol was necessary. Application of an oxidation-reduction procedure to this problem would require prior protection of the C_5-hydroxyl. Fortunately, it was found

that treatment with *tert*-butyldimethylsilyl triflate and triethylamine in dichloromethane gave **113** in excellent yield. This selectivity suggests that the C_6-hydroxyl group is very hindered, and indeed, difficulties were experienced in oxidizing this alcohol. Best results were achieved using an excess of the Swern reagent at higher temperature (− 35°C) than is usual. Sodium borohydride reduction then gave the desired C_6-epimer **114**.

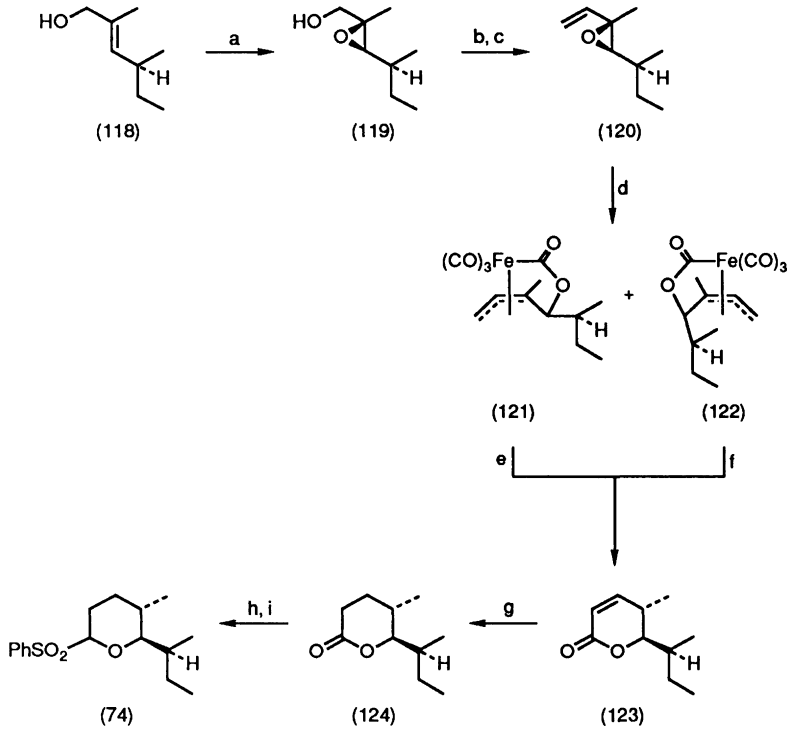
We then tried to effect a selenium-mediated cyclization[64] of the C_6 alcohol of **114** onto the terminal double bond, since this would not only close the furan ring, but the resulting C_8-selenide would be a precursor to a C_8–C_9 double bond. This transformation could not be achieved, although a variety of conditions were examined. Turning instead to chemistry similar to that used in the preparation of the milbemycin southern hemisphere, the methylene group in **114** was subjected to hydroboration using borane–dimethyl sulfide followed by work-up with basic hydrogen peroxide to give the alcohols **115** as a 2:1 mixture of C_8 isomers (Scheme 40). While separation was possible, and the remaining steps of the synthesis were performed initially on the separate isomers, it was more convenient to perform the reaction on the mixture since both isomers converge in the later steps of the synthesis. Formation of the tetrahydrofurans **116** proceeded in 78% yield simply using *p*-toluenesulfonyl chloride and pyridine at 50°C. The final steps to the required southern zone fragment **75** involved treatment of **116** with 2.2 equivalents of *n*-butyllithium in THF at − 78°C, quenching with phenylselenenyl chloride, followed by oxidation of the selenides with *m*-chloroperbenzoic acid and *syn*-elimination of the resulting selenoxides to afford the vinylic sulfones **117**. Treatment of this mixture with *tert*-butyllithium resulted in proton abstraction from the position α- to the sulfone rather than from the γ-position. However, under thermodynamic conditions, the vinylic sulfones mixture **117** was converted cleanly and stereoselectively to the *E*-allylic sulfone fragment **75** using DBU in acetonitrile at room temperature.[65] The synthetic compound **75**[66] was spectroscopically identical to the sample obtained by degradation and manipulation of natural avermectin B1a.[57]

The next key compound required for the synthesis was the hydrobenzofuran sulfone **74**. While there are many conventional routes to this material that one could use, we chose to exploit a more



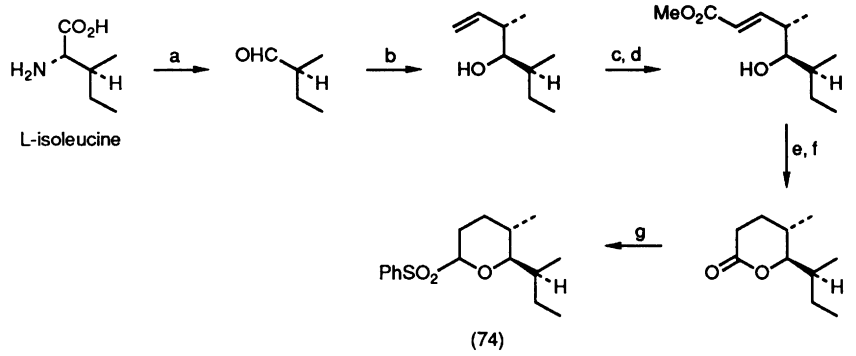
SCHEME 40. (a) $BH_3{\cdot}Me_2S$, THF, then NaOH, H_2O_2, 66%. (b) *p*TsCl, py, 16h, r.t., 20h, 60°C, 78%. (c) BuLi, THF, then PhSeCl, 65% (+30% starting material). (d) DBU, CH_3CN, 3.5h, 77%.

interesting synthetic procedure based on π-allyltricarbonyliron lactone complexes which we had developed in our laboratories. We found that the allylic alcohol **118**, readily available from (*S*)-2-methylbutanal,[67] underwent asymmetric epoxidation using the excellent Sharpless procedure[67] to give **119** (Scheme 41). This was oxidized and methylenated to give the vinyl epoxide **120** as the precursor for the iron carbonyl chemistry. Reaction with diiron nonacarbonyl gave the readily separated diastereomeric tricarbonyliron lactone complexes **121** and **122**. These could be transformed separately to the same unsaturated δ-lactone **123** under previously established, high pressure carbonylation conditions.[69,70] These reactions also afforded small amounts of other unsaturated lactone isomers which had to be removed by column chromatography. The double bond in **123** was removed by hydrogenation using hydrogen and platinum(IV) oxide to give **124**. This was then readily transformed to the desired sulfone **74** by diisobutylaluminum hydride reduction and treatment with benzenesulfinic acid as in the earlier work. Since we required a double bond in this ring in the



SCHEME 41. (a) $Ti(OiPr)_4$, *t*-BuOOH, D-(−)-diethyl tartrate, −23°C, CH_2Cl_2, 81%. (b) $(COCl)_2$, DMSO, then Et_3N, 80%. (c) Ph_3PCHBr, KHMDS, THF, 85%. (d) $Fe_2(CO)_9$, THF, 74%, *ca.* 1 : 1 **121** : **122**. (e) CO, 240 atm., 140°C, benzene, 40%. (f) CO, 250 atm., 50°C, benzene, 65%. (g) H_2, PtO_2, EtOAc, 100%. (h) DIBAL, −78°C, toluene, 93%. (i) $PhSO_2H$, $CaCl_2$, CH_2Cl_2, 85%.

final product, one might question why we removed this bond by hydrogenation. This is reasonable question, and indeed we did attempt to effect coupling reactions with this bond in place, but without success. We also examined other approaches to the sulfone **74** in order to guarantee supplies and to effect correlations for absolute configuration determination. One of these routes gave **74** in just seven steps from L-isoleucine (Scheme 42). The key reaction in this sequence involved Brown's allyldiisopinocampheyl borane chemistry[71] which worked extremely well to set up two of the stereocenters. The sulfone obtained by these reactions was also subjected to X-ray crystallography to confirm the relative configuration and also the absolute configuration as a result of incorporating one

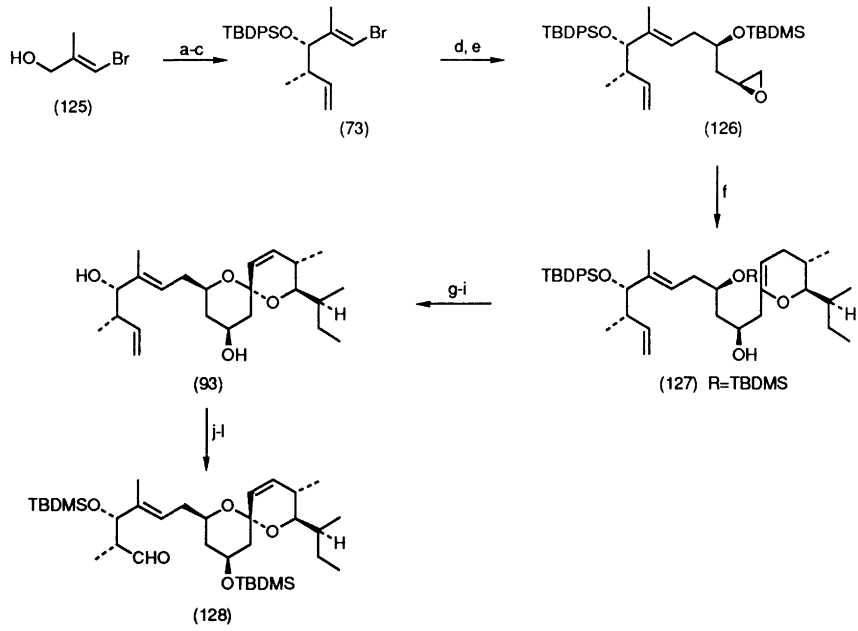


(74)

SCHEME 42. (a) Ninhydrin, 65%. (b) *E*-Crotyldi-(+)-isopinocampheyl borane, −90°C to −78°C, then NaOH, H_2O_2. (c) O_3, −78°C, then PPh_3. (d) Ph_3PCHCO_2Me, 72%. (e) H_2, Pd/C. (f) Amberlyst 15 resin, 83%. (g) As Scheme 41.

known stereocenter. This is also a route which we have not previously published.

The remaining fragment of the original general plan needed before we could begin coupling studies was the side chain alkenyl bromide **73**. We investigated many routes to related units based on our knowledge from the milbemycin work, but none was entirely satisfactory due to low yields or because of long, inelegant sequences. It was at about this time that Danishefsky[7] reported his beautiful synthesis of avermectin A1a and we were attracted by, among other things, the way he established the C_{12} and C_{13} stereocenters. We believed that his approach, once again based on Brown's allylborane chemistry, could be adapted to our synthesis. We found that the hydroxy vinylbromide **125**, after oxidation with TPAP, reacted smoothly with (+)-IPC-but-2-enyl borane. Protection of the alcohol as its silyl ether in the usual way gave **73** in 51% overall yield (Scheme 43). All was now set up to study the coupling reactions. Metal exchange of **73** with *tert*-butyllithium and trimethylaluminum gave a presumed intermediate aluminate which once again reacted with the *bis*-epoxide **12** to give the product alcohol. Silylation afforded **126**. Reaction of **126** with the anion derived from the 2-benzenesulfonyl pyran **74**, prepared earlier, in the presence of boron trifluoride etherate, gave the rather labile enol ether **127** on work-up. Using chemistry we had established on model systems, **127** was subjected to selenenylation, spirocyclization, elimination and deprotection to provide the northern

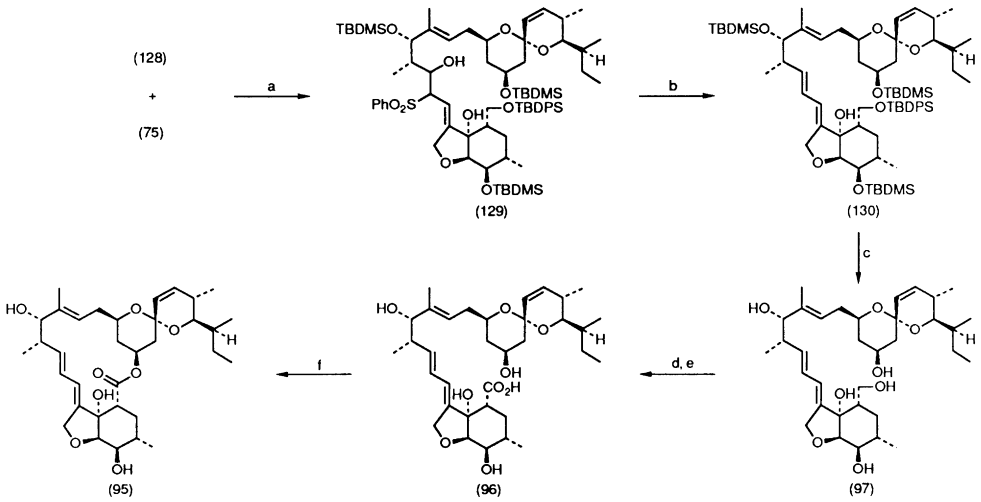


SCHEME 43. (a) TPAP, NMO, 4Å ground sieves, CH_2Cl_2, 74%. (b) *E*-Crotyldi-(+)-isopinocampheyl borane, THF-Et_2O, −90°C, 75%. (c) TBDPSCl, imidazole, DMAP, DMF, 50°C, 92%. (d) *t*-BuLi, Me_3Al, −78°C to 0°C, then add (12), −30°C to 0°C, 82%. (e) TBDMSCl, DMAP, Et_3N, DMF, 94%. (f) Sulfone anion, $BF_3{\cdot}OEt_2$, 45%. (g) PhSeCl, MeOH, Et_3N, CH_2Cl_2, then CSA, MeOH/CH_2Cl_2, 66%. (h) 2-(Phenylsulfonyl)-3-(*p*-nitrophenyl) oxaziridine, $CHCl_3$, 50°C, 77%. (i) TBAF, THF, Δ, 91%. (j) TBDMSCl, imidazole, DMF, 95%. (k) OsO_4, NMO, *t*-BuOH/THF/H_2O, 71%. (l) $NaIO_4$, KH_4PO_4, H_2O/MeOH, 86%.

hemisphere **93** of avermectin B1a without purification of intermediate compounds. These reactions all proceeded in good yield. We believe this to be an extremely expedient route, comparing extremely well with any existing synthesis of similar fragments.[72] It should be remembered that **93** was also available by natural product degradation and modification from the relay studies. Finally, **93** was converted to the aldehyde **128** suitable for coupling with the southern C_1–C_{10} carbon skeleton **75** by protection and subsequent oxidative cleavage of the terminal methylene group.[73]

The stage was now set to perform the final couplings and head towards avermectin B1a itself. Treatment of **75** with two equivalents of *tert*-butyllithium at − 78°C followed by reaction with the aldehyde

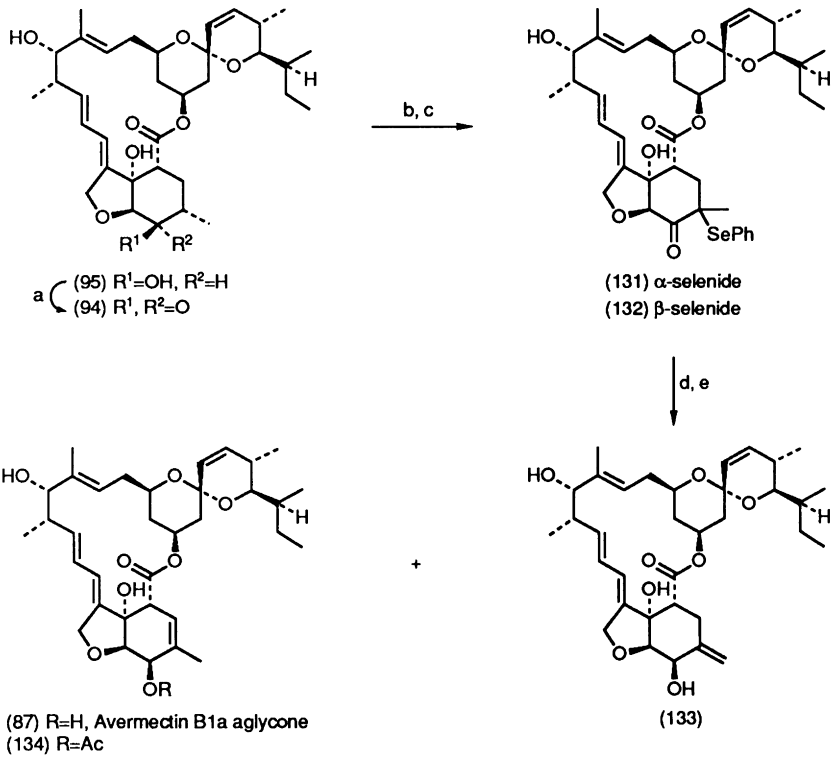
128 successfully effected the important coupling of the two major components, giving the hydroxysulfones **129**. Following reductive elimination, the *E*, *E*-diene **130** was obtained (Scheme 44). We then decided to take a very bold step and remove all the protecting groups by reacting **130** with tetra-n-butylammonium fluoride to give the pentol **97**. We hoped that by exploiting the reactivity differences of the various hydroxyl groups in **97** we would be able to prepare the avermectin B1a aglycone **87** *without the need for further protection.* This turned out to be the case and the reader will now recognize the importance of the relay and modification studies we performed earlier as these underpin the next sequence of reactions. Selective primary alcohol oxidation of **97** under the Oshima conditions[74] gave an intermediate aldehyde which was immediately oxidized further to the C_1-acid **96**. We believed that this would undergo intramolecular macrolactonization rather than any intermolecular coupling process and indeed, treatment with 2-chloro-1-methylpyridinium iodide gave **95**. The next selective transformation which had to be achieved was the oxidation of the secondary C_5 hydroxyl group in the presence of the C_{13} allylic secondary hydroxyl group. On the face of it, this task



SCHEME 44. (a) 2.2 equivalents *t*-BuLi, THF, −78°C, then add **128**, 74%. (b) 6% Na/Hg, THF/MeOH, Na_2HPO_4, 34%. (c) TBAF, THF, Δ 94%. (d) $RuCl_2(PPh_3)_3$, benzene. (e) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*-BuOH/H_2O, 29% from **97**. (f) 2-chloro-l-methyl-pyridinium iodide, Et_3N, CH_3CN, reflux, 9 hours, 47%.

appears to be a difficult one, but from molecular modeling studies and other chemistry we believed the C_{13} position to be more hindered than C_5 and therefore thought that it was worth a try.[75] We found that by using our TPAP reagent stoichiometrically at 0°C we could achieve this transformation, giving **94** in 60% yield (Scheme 45).

Installation of the carbonyl group at the C_5 position now gave access to the chemistry discovered in the milbemycin work for introduction of the important 3,4-double bond. Once again, this was achieved by selenenylation of an intermediate, regioselectively produced enol ether, to give the α and β selenides **131** and **132** in a 1 : 1 ratio. *Syn*-elimination of the selenoxides from **131** using the Davis oxaziridine reagent gave the avermectin B1a aglycone (**87**)

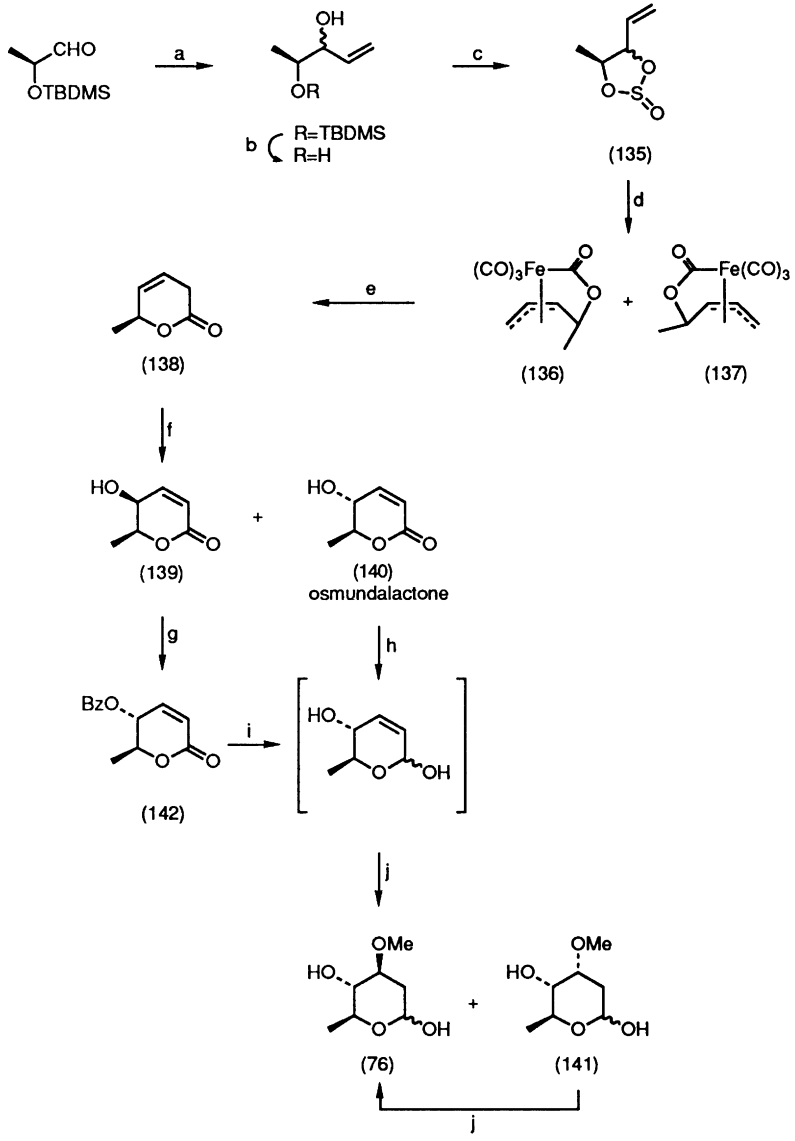


SCHEME 45. (a) TRAP, CH_2Cl_2, 60%. (b) TMSOTf, Et_3N, CH_2Cl_2, 0°C, 93%. (c) PhSeCl, CH_2Cl_2, −78°C, 90%, then HF, CH_3CN, 88%, 1:1 131/132. (d) 2-phenylsulfonyl-3-(*p*-nitrophenyl)oxaziridine, $CHCl_3$, 25°C. (e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH. 35% **87**, 23% **11**. (f) CH_3COCl, pyridine, 97%.

(35%) and the *exo*-methylene derivative **133** (23%) after reaction with cerium(III) chloride and sodium borohydride.[76] The synthetic aglycone was, of course, identical in all respects to the material obtained from the natural product by glycolysis. The formation of the *exo*-methylene isomer **133** in these eliminations is annoying and we have not yet found a method either to produce the *endo*-isomer exclusively or to convert **133** to **87**. Similar elimination of the β-selenide **132** gives only the *exo*-product. We are continuing to study these reactions until we solve this step to our satisfaction.

Having prepared the aglycone we could have declared a formal total syntheses of avermectin B1a since the coupling of the *bis*-oleandrosyl disaccharide unit was known,[7,8,77,78] but we had come a long way and could not give up so easily. It seemed to us that there were still challenges left in this molecule that were worthy of study. In particular, new methods for the preparation of 2-deoxy sugars would be useful, as would alternative glycosidation reactions. These could find applications in many other areas.

Although syntheses of oleandrose have been reported,[7,77,78,79] we chose to adopt a new approach, using π-allyltricarbonyliron lactone complexes. We had shown that alkenyl cyclic sulfites served as novel, non-volatile precursors for complex formation.[80] We therefore prepared the cyclic sulfite **135**, configurationally defined at the important C_4 center (Scheme 46). This was reacted with diiron nonacarbonyl in benzene under ultrasonic conditions to give the two diastereoisomeric complexes **136** and **137**. Carbonylation of these compounds in the presence of acrolein as an iron carbonyl scavenger to minimize double bond migration gave the β,γ-unsaturated lactone **138**. Owing to volatility this was generally isolated in yields of around 50%, although in one run a 98% yield was recorded. The lactone **138** was then treated with dimethyldioxirane to give a mixture of unstable epoxides which were best not isolated but reacted with 2% triethylamine in pyridine to give the two hydroxy lactones **139** and **140**. In fact, **140** is the natural product osmundalactone which had been prepared previously by somewhat longer synthetic sequences.[81] In our original communication[82] only one of these lactones, **140**, had been converted to oleandrose. However, we have now devised a convergent route which also transforms the other isomer **139** to oleandrose. These unsaturated lactones are separable but because of their instability it is necessary to use silica gel columns

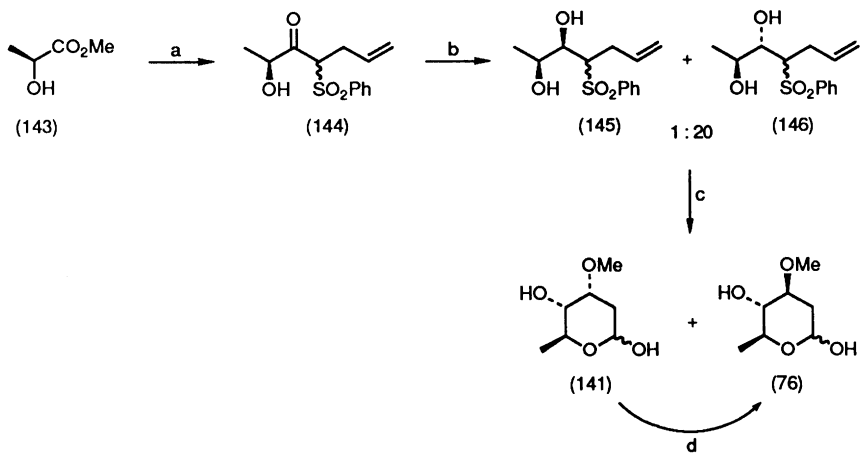


SCHEME 46. (a) Allylmagnesium bromide, THF, −60°C to 25°C, 74%. (b) Catalytic TsOH, MeOH, 92%. (c) $SOCl_2$, CCl_4, 100%. (d) $Fe_2(CO)_9$, benzene,))), 65%. (e) CO, Δ, acrolein, pressure, benzene, 51%. (f) Dimethyldioxirane, acetone, 0°, then 2% Et_3N/pyridine, 75%, 2:1 **139**:**140**. (g) Diethyl azodicarboxylate, PPh_3, Et_2O, $PhCO_2H$, 92%. (h) DIBAL, THF, −78°C. (i) DIBAL, toluene, −78°C. (j) 1% DBU, MeOH.

which have been doped with pyridine. Diisobutylaluminum hydride reduction of **140** in THF gave an unstable intermediate, presumably a lactol or a ring-opened equilibrating mixture. The crude product was immediately treated with DBU in methanol at room temperature to give oleandrose **76** and cymarose **141**. We believe these are produced under these conditions as an equilibrium mixture by ring opening, β-elimination and readdition, followed by ring closure. Indeed, re-exposure of cymarose **141** to the reaction conditions rapidly establishes the 7 : 3 ratio of **76** to **141** which facilitates a recycling process to permit isolation of more oleandrose *via* Florisil chromatography.

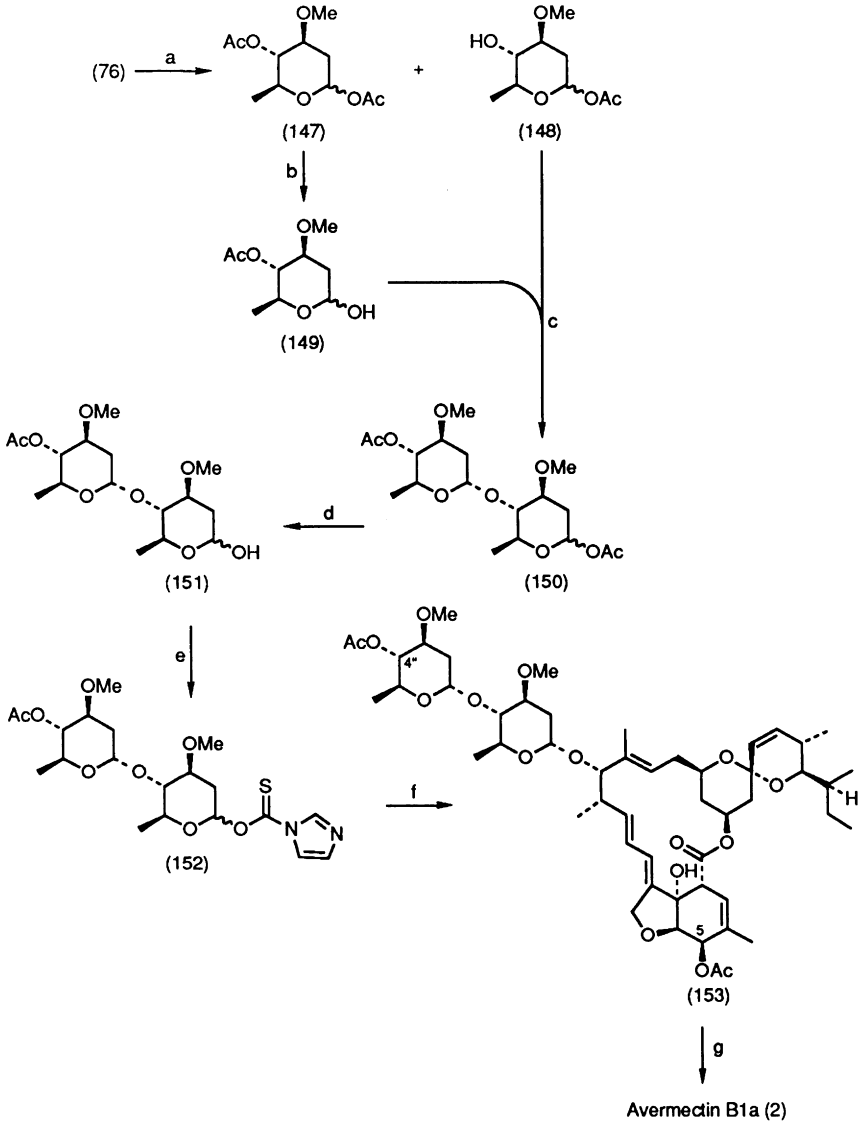
The other hydroxyl lactone isomer **139** required an inversion of configuration prior to its conversion to oleandrose. This was readily achieved by reaction under Mitsunobu conditions to give the benzoate **142**. Similar reduction of this compound with diisobutylaluminum hydride in toluene gave entry to the same intermediate lactol which was converted to the oleandrose/cymarose mixture. As we are using a convergent route to oleandrose it is appropriate to describe a combined yield for the process from the lactone **138** of 40% following one recycle of the cymarose. This novel route further exemplifies the use of tricarbonyliron lactone complexes for synthesis.

Since these studies we have also developed a new, three-step preparation of oleandrose from (*S*)-(−)-methyl lactate **143** which employs the conjugate exchange process and gives access to multigram quantities of this useful sugar derivative (Scheme 47).[83] The process involves addition of an excess of (3-butenylsulfonyl) benzene dianion to (*S*)-(−)-methyl lactate **143** to give the keto sulfones **144** as 1 : 1 mixture of diastereomers. Chelation-controlled reduction of **144** with ethereal zinc borohydride furnished the diols **145** and **146** in a 1 : 20 ratio. The high stereoselectivity appears to be unaffected by the mixture of stereoisomers present in **144**. The final step in the synthesis involved oxidative cleavage, elimination of benzenesulfinic acid and conjugate addition of methanol in the presence of DBU to the resulting α,β-unsaturated aldehyde, followed by ring closure. All these reactions are carried out in one pot and this leads to oleandrose **76** and cymarose **141** as in the previous sequence. Following one recycle of cymarose under the re-equilibration conditions, a total yield of 55% of oleandrose can be realized from S-(−)-methyl lactate **143**.



SCHEME 47. (a) 2 equivalents of the anion derived from (3-butenylsulfonyl)benzene, THF, −78°C, 87%. (b) $NaBH_4$, $ZnBr_2$, 94%. (c) O_3, MeOH, then Me_2S, 32% **141**, 48% **76**. (d) DBU, MeOH, 60%.

We next studied dimerization reactions of oleandrose derivatives to provide the disaccharide, using a new glycosidation method which we had developed.[84] We preferred to follow this pathway rather than simply adopt existing methods. We believe our new route also has practical advantages and has proved to be both efficient and reliable. Reaction of oleandrose **76** with acetic acid activated by carbonyldiimidazole gives a 1 : 1 mixture of diacetate **147** and the first coupling partner, the C_1 monoacetate **148**, in excellent yield (Scheme 48). The mixture here was especially useful and was a designed part of the plan to afford differentiated materials for the coupling procedure. Treatment of the diacetate **147** with lithium triethylborohydride at −78°C cleanly afforded the C_4 monoacetate **149** which is the second coupling unit. Conversion of **149** to its imidazoylylcarbonyl glycoside and coupling with the C_1 monoacetate **148** activated by the addition of silver perchlorate in ether at 40°C gave the disaccharide diacetate **150** in 62% yield after separation of a small amount of the $C_{1'}$ β-anomer. Once again, selective deprotection of **150** worked extremely well at −78°C using 2.5 equivalents of lithium triethylborohydride to give **151**. In contrast to the previous coupling, compound **151** had to be converted to the imidazoylylthiocarbonyl glycoside **152** by treatment with thiocarbonyldiimida-



SCHEME 48. (a) Carbonyldiimidazole, AcOH, CH_2Cl_2, 93%, 1 : 1 mixture, (b) 2.5 equivalents $LiBHEt_3$, THF, −78°C, 95%. (c) Carbonyldiimidazole, THF, $AgClO_4$, 62%. (d) 2.5 equivalents $LiBHEt_3$, −78°C, 98%. (e) Thiocarbonyldiimidazole, THF, 57%. (f) **134**, $AgClO_4$, K_2CO_3, THF/toluene, 64%. (g) $LiBHEt_3$, THF, −78°C, 90%.

zole in THF since the corresponding imidazoylyl carbonyl derivative failed to undergo coupling with the very hindered C_{13} hydroxyl group of the avermectin aglycone. On the other hand, reaction of avermectin B1a aglycone C_5 monacetate **134** with **152** in the presence of silver perchlorate and potassium carbonate in THF/toluene gave **153** in 65% yield. A small amount of contaminating β-anomer always produced in these glycosidations was readily removed by chromatography. Finally, removal of the two acetate groups, from C_5 and $C_{4''}$, was achieved by treatment with an excess of lithium triethylborohydride, to give the macrolide anthelmintic agent avermectin B1a (**2**), identical in all respects to the natural product. Champagne time!

Acknowledgments

We thank a large number of people: N. J. Anthony, P. M. Booth, M. G. Brasca, D. S. Brown, D. Culshaw, D. Díez-Martín, M. J. Ford, C. Greck, P. Grice, I. A. O'Neil, A. Jackson, A. B. Jones, J. G. Knight, H. C. Kolb, B. Lygo, A. Madin, S. Mukherjee, A. N. Shaw, G. Strange, S. Vile, A. D. White, A. Wonnacott and M. Woods, all of whom have contributed so much to the success of this project. Not all have been rewarded with publications although their names are mentioned in the text and their efforts are duly acknowledged. We also thank the SERC, Ministerio de Educacion y Ciencia (Spain), the British Council, SmithKline Beecham for a CASE award, Farmitalia Carlo-Erba, and NATO for their support of this work. Finally, little of this work would have been possible had it not been for the generous financial contributions from ICI Strategic Research Fund, Merck, Sharp and Dohme and, especially, Pfizer Central Research.

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Chapter 8

THE TOTAL SYNTHESES OF (±)-NEOLEMNANE AND (±)-14-DEOXYISOAMIJIOL: "THE REST OF THE STORY"[§†]

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Athens, Georgia

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I. Introduction

Because cycloheptane and cyclooctane rings are more difficult to form than the corresponding five- or six-membered carbocycles, the synthetic strategy for making these medium-sized rings requires

[§] A daily occurrence throughout much of the nation is the broadcast of the news and commentary by Paul Harvey, a colorful, enthusiastic and extremely conservative journalist who includes in his reports a tersely worded news item recently featured by one of the major wire services and then proceeds to tell "the rest of the story ..." This chronicle of our total syntheses of the sesquiterpenes neolemnane and neolemnanyl acetate and the dolastane diterpene 14-deoxyisoamijiol has been prepared in this spirit and is largely based on the Ph.D. dissertations of Kenneth Hull (University of Georgia; Athens, 1989), Derric Lowery (University of Georgia; Athens, 1989) and Clay Ringold (University of Georgia; Athens, 1989).

[†] Dedicated to Professor Paul A. Grieco on the occasion of his receipt of the *1991 Award for Creative Work In Synthetic Organic Chemistry (ACS)*.

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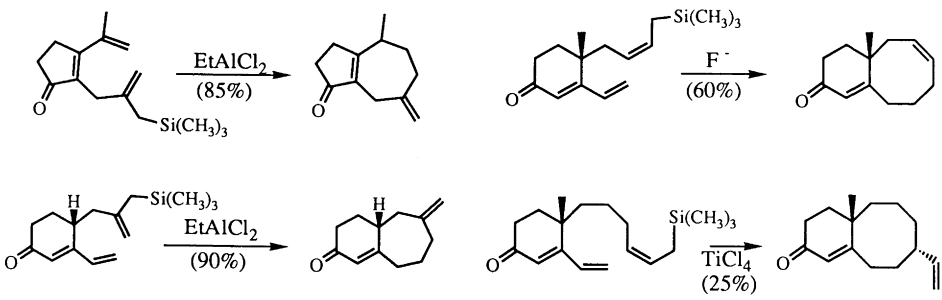


CHART 1

new methodology, rather than adaptations of techniques suitable for smaller rings.

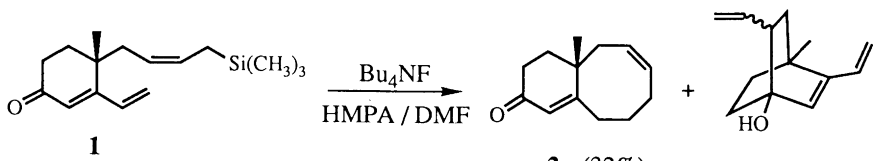
Reactions of allylsilanes are becoming increasingly popular as a method for inter- and intramolecular carbon-carbon bond formation, due to their remarkable versatility and broad synthetic utility.[1,2] Our major contributions in this active field have focused on developing new procedures using allylsilane chemistry to annulate seven- or eight-membered rings (Chart 1).[3,4]

Allylsilane-based cyclizations are useful for the synthesis of polycyclic natural products because the cyclization precursors are easy to prepare and the cyclized products contain most of the carbocyclic skeleton with few sensitive functional groups present. These cyclizations can also proceed with high stereoselectivity, establishing quaternary carbons and chiral centers early in the synthesis.

The following analysis of our syntheses of three marine natural products typifies our use of intramolecular allylsilane cyclizations.

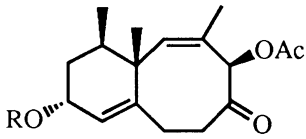
II. (±)-Neolemnane

In the Spring of 1984 I presented the annulation shown in Eq. (1) at the first "Latest Trends in Organic Synthesis Symposium.[5]" During the discussion period I was asked what—if any—cyclooctanoid natural product I intended to synthesize. I mentioned numerous sesquiterpenes which possessed novel structures as well as significant biological potential to showcase the utility of our cyclooctane annulation procedure and indicated that a suitable candidate had not yet been selected. Later on fellow conferee Professor Robert Gadwood



1 2 (32%) 3 (35%) (1)

informed me of an irregular terpenoid having a 6,8-framework. From a search of the literature, we learned of the structures for neolemnanyl acetate (**4**) and neolemnane (**5**) (Figure 1).[6] Fused cyclooctane **2** obviously has many of the salient features of these sesquiterpenes. Closer scrutiny reveals that the functionality of the six-membered ring

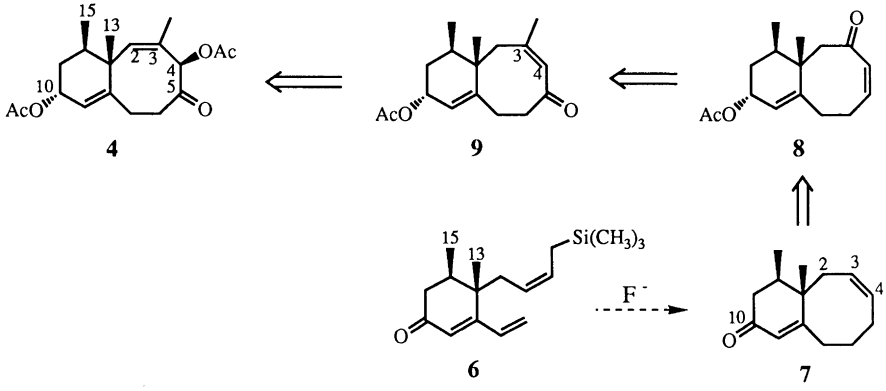


neolemnanyl acetate (4) R = Ac

neolemnane (5) R = H

FIG. 1

requires only the stereospecific reduction of the C_{10} carbonyl and the introduction of the *cis*-vicinal methyl group (Scheme 1).[7] Neither of these problems were anticipated to be difficult. Based on retrosynthetic analysis, we expected that *tri*-substituted enone **9** would permit

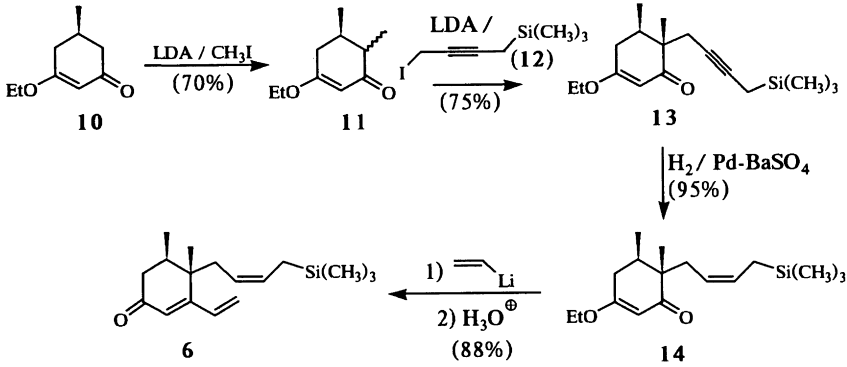


SCHEME 1

the efficient migration of the C_3-C_4 olefin to C_2-C_3 and facilitate the stereospecific introduction of a C_4 hydroxyl group. Moreover, we were confident that the C_3-C_4 double bond of **7** would allow the preparation of *tri*-substituted enone **9**. We chose to synthesize neolemnanyl acetate first and therefore delayed the need to differentiate the C_4 and C_{10} hydroxyls which a neolemnane synthesis requires.[8]

Our first priority was the construction of trienone **6**, the cyclization precursor leading to the neolemnanyl skeleton.[9] The starting material for the synthesis of **4** was enol ether **10**, conveniently prepared from dihydroorcinol (Scheme 2).[10] Based on the work of Stork and Danheiser,[11] we knew that the *cis*-$C_{13}-C_{15}$ dimethyl relationship found in trienone **6** could be achieved by successive alkylations and that the relative stereochemistry of the asymmetric centers could be established by the alkylation order. Thus, methylation of **10** under kinetic conditions yielded enol ether **11**. The silicon-containing iodide **12** was prepared in 74% overall yield from 4-trimethylsilyl-2-butyn-1-ol[12] by means of the Finkelstein method. Enol ether **11** was alkylated under kinetic conditions with **12** to yield an 8:1 mixture of diastereomers of which **13** was the major isomer. Enone **13** was isolated by column chromatography as a viscous oil in 75% yield.

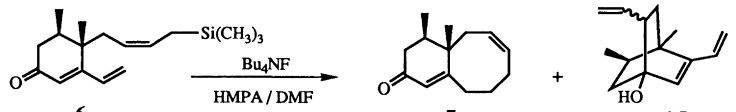
Selective reduction of the acetylenic functionality to a *cis*-olefin with a modification of the traditional Lindlar procedure afforded **14** in 95% yield. Conversion of **14** to dienone **6** was achieved through the 1,2-addition of vinyllithium to the carbonyl group, followed by subse-



SCHEME 2

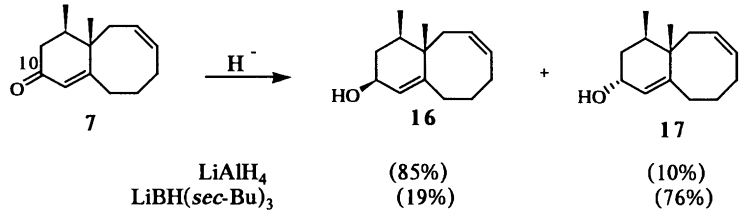
quent hydrolysis of the diastereomeric alcohols to yield the target enone in 88% yield. Yields for the analogous procedure with vinylmagnesium bromide are approximately 10% lower.

Cyclization of 4-butenyl-dienone[13] **6** under fluoride ion catalysis yielded the 6,8-fused bicyclic enone **7** in 60% yield (Equation 2) while bicyclic alcohol **15**, resulting from the 1,2-addition of the allylsilane, accounted for 10% of the isolated reaction products. The yield of this annulation was improved when the DMF was removed by distillation (instead of aqueous workup) prior to column chromatography. This modification allowed the reaction to be carried out on up to seven grams of substrate with yields consistent to within ± 5%.



6 → **7** (60%) + **15** (10%) (2)

The next objective was to generate the axial allylic alcohol from the cyclohexenone system. In accordance with the observation of Henbest[14a] and Dauben[14b] we expected the reduction of **7** with $LiAlH_4$ to provide only **16** on the basis that rigid cyclic α,β-unsaturated ketones afford the thermodynamically more stable equatorial alcohol upon reduction. Indeed, treatment of enone **7** with $LiAlH_4$ provided the equatorial stereoisomer (e.g., **16**) in 85% yield (Scheme 3). It was clear that the introduction of the axial allylic alcohol (e.g. **17**) would require a more sterically active hydride source.[15] The use of L-Selectride afforded a 4 : 1 ratio (axial : equatorial) of the C_{10} epimeric alcohols in 95% combined yield. These alcohols were separable via column chromatography.



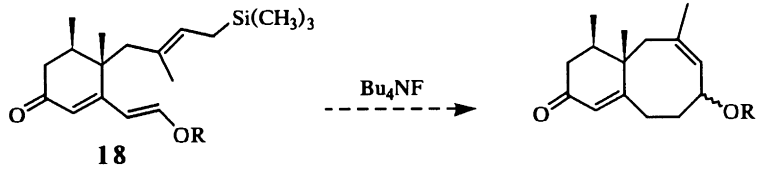
7 → **16** + **17**

	16	**17**
$LiAlH_4$	(85%)	(10%)
$LiBH(sec\text{-}Bu)_3$	(19%)	(76%)

SCHEME 3

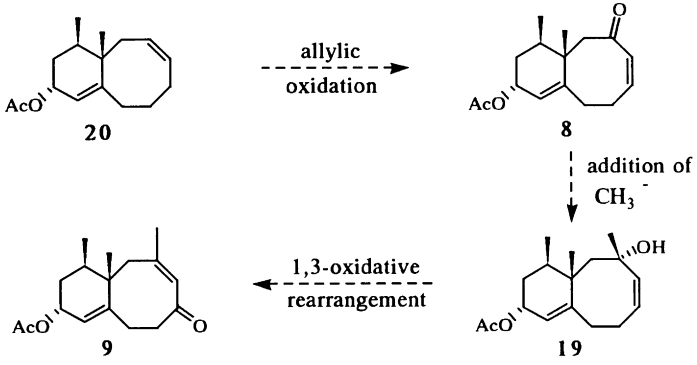
Since the reduction described above gave a 19% yield of **16**, we attempted to invert the C_{10} stereochemistry of this material. However, subjection of **16** to the Mitsunobu methodology[16] yielded a 1 : 1 mixture of allylic esters, presumably through solvolysis of the intermediate allylic oxyphosphonium salt. Additionally, conversion of **16** to the corresponding allylic mesylate followed by treatment with cesium acetate gave similar results,[17] which suggests that the axial allylic acetate is prone to solvolysis. Nevertheless, we were satisfied that gram quantities of **17** could be prepared in less than two weeks in only eight steps.

Initially we thought of cyclizing a highly functionalized precursor, such as **18** in Eq. (3). However, this approach was rejected since the *tri*-substituted allylsilane unit required was not readily accessible[18] and we were wary of the stability and reactivity of the enol ether unit.[19,20]



18 (3)

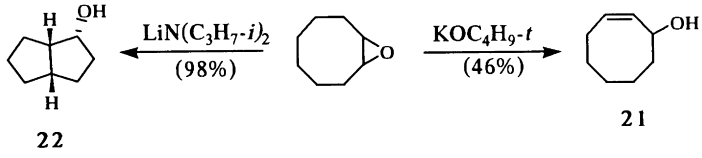
Invoking retrosynthetic analysis, we reasoned that *tri*-substituted enone **9** could be prepared by an oxidative rearrangement of tertiary allylic alcohol **19** derived from cyclooctenone **8** (Scheme 4). There are several ways by which a cycloalkene can be converted into a cycloalkenone, hence cyclooctenone **8** became our next objective.



SCHEME 4

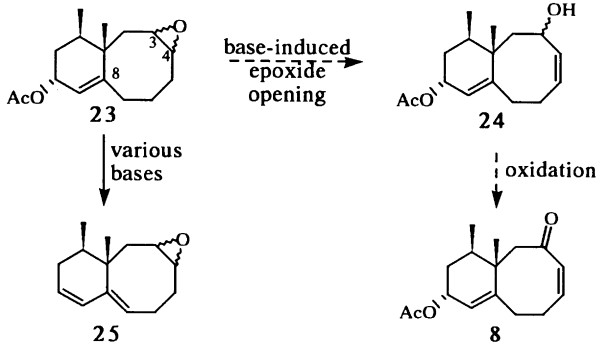
The first strategy we examined to prepare **8** seemed straightforward in that the isomerization of epoxides to allylic alcohols in medium-sized rings is known. For example, *cis*-cyclooctene epoxide reacts with weak bases such as potassium *t*-butoxide to give allylic alcohol **21** (Scheme 5). However, this isomerization is sensitive to the choice of catalyst since strong bases, such as lithium diisopropylamide, result in a transannular cyclization to give a 5,5-fused alcohol (**22**).[21] In light of this precedent, we were confident that a C_3–C_4 epoxide could be opened. Also, the unsaturated nature of C_8, in our case, precluded the transannular side reaction thus enabling us to control the regiochemistry of the opening by using sterically hindered bases (cf. **23** → **24**, Scheme 6). Subsequent oxidation of alcohol **24** would furnish enone **8**.

Epoxide **23** was prepared and subjected to a variety of basic conditions. Unfortunately, it either decomposed, failed to react, or produced diene **25**, through an E_2 elimination process. These results were independent of the nature of the C_{10} hydroxy protecting group.

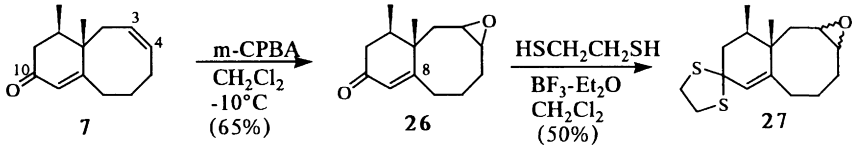


SCHEME 5

In order to avoid this side reaction, we oxidized the C_3–C_4 double bond of enone **7** using *m*-chloroperbenzoic acid prior to masking the C_{10} carbonyl (Scheme 7). Subsequent thioketalization of **26**



SCHEME 6

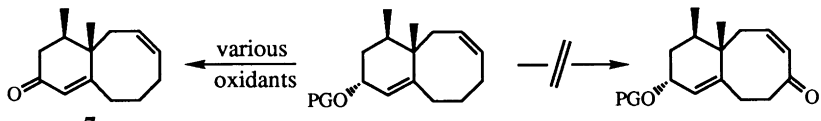


7 26 27

SCHEME 7

furnished substrate **27**, albeit in only 33% overall yield. Although the competing elimination was precluded, epoxide **27** failed to react under any conditions.

The failure of the epoxide-opening strategy led us to investigate the selective oxidation of the C_5-allylic methylene (Scheme 8). However, all attempts to oxidize acetate **20** or other protected variants (i.e., **28** and **29**) with common procedures [SeO_2, PCC, PDC or $Cr(CO)_6$] resulted in the facile regeneration of the original cyclization product **7**.



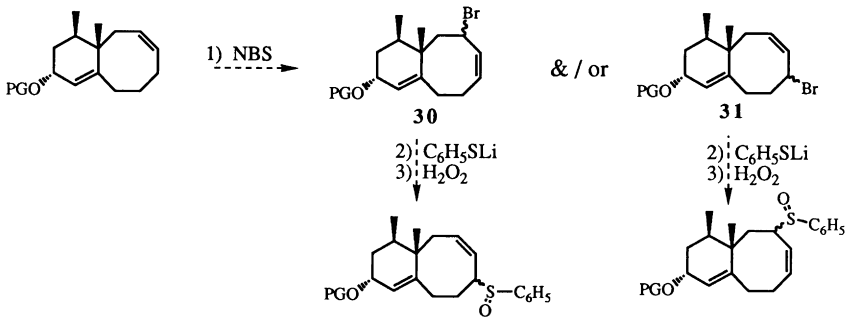
7 28

PG = Ac (**20**)
= $CH_2C_6H_5$ (**28**)
= THP (**29**)

SCHEME 8

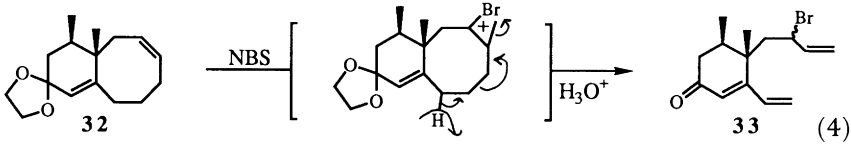
By this point the neolemnane project began to have a stigma attached to it. My students delighted in calling to my attention the difficulties others preparing cyclooctanoid natural products encountered and openly joked that everyone was expected to "pay their dues" by first working on "*neo*" before getting a "*real*" project.

In April of 1988 Derric Lowery, then a third year graduate student, volunteered to complete a synthesis of neolemnanyl acetate. To keep his enthusiasm high I mentioned that I only had two ideas left for functionalizing the eight-membered ring. The first relied on an allylic bromination to produce either **30** or **31**. Ideally, a single bromide would predominate; thereby permitting subsequent elaborations using Evan's allylic sulfoxide chemistry (Scheme 9).[22] Shortly thereafter, Derric walked into my office and calmly informed me that he had been successful in preparing an allylic bromide from ketal **32**.



SCHEME 9

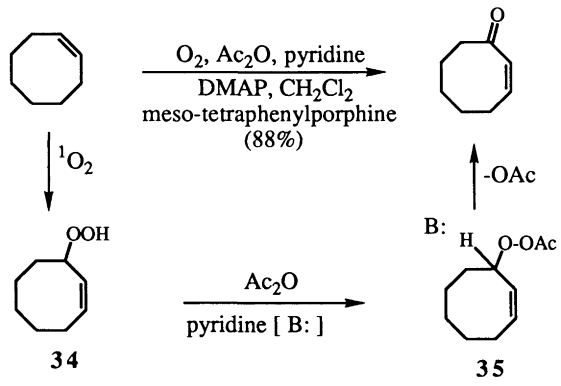
Unfortunately, as he had correctly identified, the allylic bromide he had prepared corresponded to **33**, the product of a bromonium ion-promoted fragmentation (Equation 4). Undaunted Derric then investigated the second alternative.



(4)

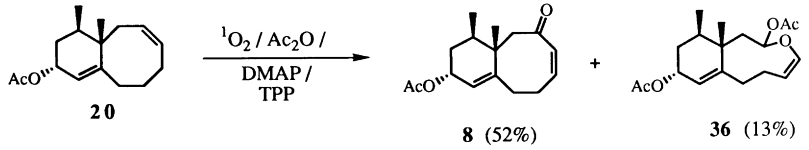
The use of singlet oxygen is an attractive method for oxidizing aliphatic or cyclic olefins to the corresponding α,β-unsaturated enones.[23] This conversion is usually carried out in a stepwise fashion and involves the isolation of either the hydroperoxide or the allylic alcohol, prior to further oxidation. Problems caused by isolating the oxidized intermediates can be avoided by means of an *in-situ* photooxygenation-elimination procedure developed by Mihelich and Eickhoff (Scheme 10).[24] This one-pot procedure is typified by the oxidation of cyclooctene to cyclooctenone as illustrated in Scheme 10. Reaction of cyclooctene with singlet oxygen, produced using *meso*- 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) as the photosensitizer, gives allylic hydroperoxide **34**, which is acetylated *in situ* to provide an allylic peracetate (e.g. **35**). Base-promoted fragmentation of this peracetate intermediate furnishes cyclooctenone in 88% yield.

I was dubious of the applicability of the Mihelich/Eickhoff procedure to our system. Nevertheless, Derric found that photooxygenation of acetate **20** afforded enone **8** in 52% yield, along with 20% of



SCHEME 10

unreacted **20** and a 13% yield of enol ether **36**, the product of a Hock fragmentation (Equation 5).[25]

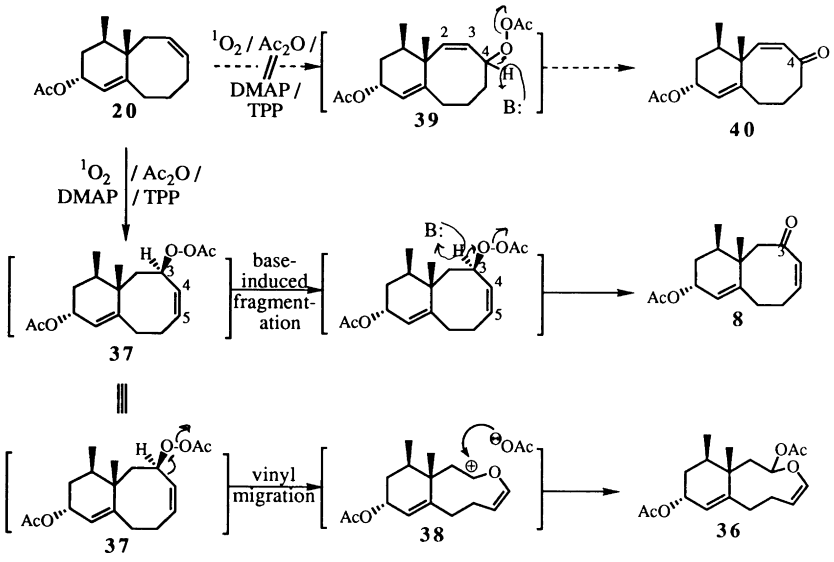


(5)

This oxidation warrants further comment. In Mihelich and Eickhoff's original study, the regiospecificity of the oxidation is not an issue. Such selectivity, however, becomes a concern when more complex substrates are studied. Because singlet oxygen photooxidations often proceed through a concerted ene-reaction mechanism,[26] oxidation of **20** can occur at either C_3 or C_4 (cf. **37**→**8** and **39**→**40**, Scheme 11). However, we felt that formation of peracetate **39** was unlikely due to steric effects of the C_{13} methyl and this was experimentally observed.

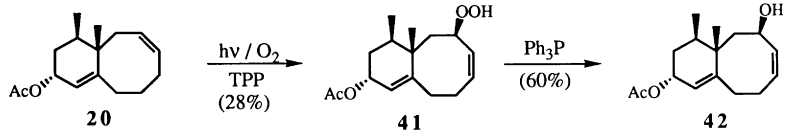
The origin of enol ether **36** can also be traced to peracetate **37** in which a migration of the vinyl unit, analogous to that in the Baeyer-Villiger reaction, generates an oxygen-stabilized carbonium ion species (e.g. **38**) that is eventually trapped by the acetate ion in solution to afford the nine-membered acetal. The formation of **36** was significantly decreased using minimal solvent while the use of excess (or stronger) base had little influence on the product distribution.

In view of the Hock fragmentation product resulting from rearrangement of the allylic peracetate intermediate, we investigated the



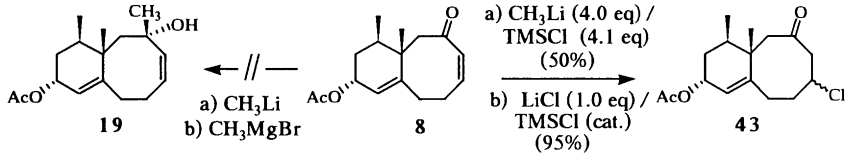
SCHEME 11

stepwise conversion of **20** to **8**. Standard photooxidation of **20** afforded hydroperoxide **41** in 28% yield (Scheme 12) while reduction of **41** with triphenylphosphine in ether at 0°C gave allylic alcohol **42** in 60% yield. Although oxidation of **42** gave enone **8** in 95% yield, this three-reaction sequence was less efficient and therefore deemed impractical.



SCHEME 12

Preparation of *tri*-substituted enone **9**, the next pivotal synthetic intermediate, required the seemingly trivial, 1,2-addition of a methyl anion equivalent to the C_3 carbonyl of **8**, followed by the oxidative rearrangement of tertiary allylic alcohol **19**. Since methyllithium readily adds to cyclooctenone, we expected enone **8** to behave similarly. However, treatment of **8** with excess methylithium or methylmagnesium bromide [>four equivalents] under conditions ranging from −78°C to lengthy periods of reflux failed to provide **19** (Scheme

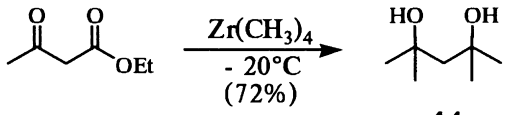


SCHEME 13

13). Astonishingly, the C_{10} acetate was stable under these vigorous conditions.

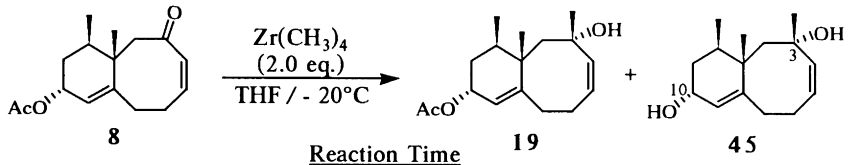
This lack of reactivity of **8** was puzzling because Dreiding stereomodels indicated the C_3 carbonyl was unhindered. We therefore assumed that enolization of the enone was precluding 1,2-addition and to test this, we reacted **8** with 4.0 equivalents of methyllithium at room temperature for four hours and then quenched the reaction with 4.1 equivalents of chlorotrimethylsilane (TMSCl). However, the isolated product was not the expected silyl enol ether, but ketone **43** resulting from the Michael addition of chloride ion (produced by the reaction of TMSCl with methyllithium). Moreover, the excess TMSCl promotes the Michael reaction as was confirmed by treating enone **8** with one equivalent of lithium chloride and a catalytic amount of TMSCl. We also examined whether cerium chloride, lithium perchlorate or boron trifluoride etherate could activate enone **8** towards 1,2-addition. Nevertheless, these activating agents either had no influence or caused **8** to decompose.

In the past decade, organotitanium and organozirconium reagents[27] have been shown to be superior to traditional Grignard reagents for additions to sterically hindered and/or enolizable ketones. The high reactivity and low basicity of these zirconium reagents is illustrated by the efficient conversion of ethyl acetoacetate to diol **44**, whereas exposure to typical Grignard reagents only results in enolization (Equation 6).



(6)

We were pleased to find that reaction of enone **8** with tetramethylzirconium gave tertiary alcohol **19** in high yield (Scheme 14). This conversion was empirically observed to require two equivalents of the

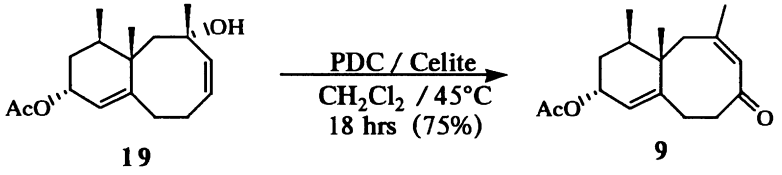


Reaction Time	19	45
20 seconds	86%	---
30 seconds	77%	13%
5 minutes	---	50%

SCHEME 14

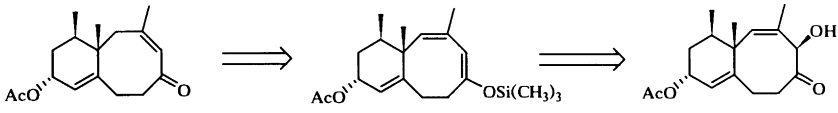
zirconium reagent to proceed to completion, however reaction times in excess of thirty seconds also led to deacetylation of the C_{10} alcohol (cf. **45**). Formation of diol **45** was inconsequential since the secondary C_{10} alcohol could be selectively acetylated using standard conditions to regenerate **19** in quantitative yield. It is noteworthy that the cyclic nature of organozirconium reactions[27c] precludes conjugate addition of the methyl group in the preparation of **19** and accounts for the stereochemistry of the newly formed C_3 chiral center.

The final step in preparing enone **9** was the oxidative rearrangement of **19**. This oxidation proceeds smoothly using pyridinium dichromate to furnish *tri*-substituted enone **9** in 75% yield (Equation 7).[28]



(7)

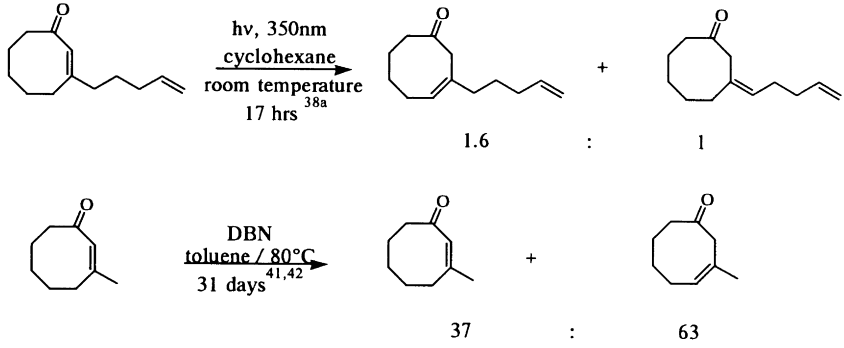
Three manipulations remained to complete our neolemnanyl acetate synthesis: the migration of the C_3–C_4 olefin to C_2–C_3; the stereospecific hydroxylation of C_4; and acetylation of the C_4 hydroxyl group. Our initial strategy relied on the generation of through-conjugated silyl dienol ether **46** (Scheme 15). In previous research photolysis of 3-alkyl-cyclooctenones[29] and the base-promoted isomerizations of 3-methylcycloalkenones[30] afforded the corresponding β,γ-substituted cyclooctenones (Scheme 16). These studies suggested that deconjugation of **9** would lead to β,γ-enone **48**, which contains a relatively acidic allylic methylene unit positioned



9 46 47

SCHEME 15

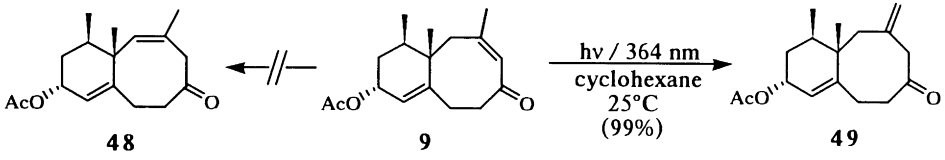
next to the carbonyl, thus facilitating the specific formation of dienol silyl ether **46** (e.g. **48**→**46**). With this strategy in mind enone **9** was irradiated (365 nm, 7 hours in cyclohexane) at ambient temperature



SCHEME 16

to yield a single product, identified as the exocyclic isomer (e.g. **49**, Scheme 17). This result was confusing because photoisomerizations proceed via free radical pathways and the exocyclic olefin is clearly the result of the less stable primary radical.[31] Identical results were obtained whether the allylic alcohol in the six-membered ring was protected or not.

The formation of the exocyclic olefin under photolytic conditions led us to study base-catalyzed isomerizations. Attempts to generate

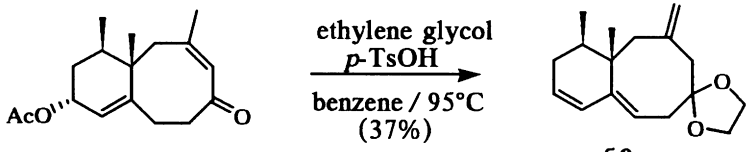


48 9 49

SCHEME 17

and trap the endocyclic dienolate derived from **9** using standard thermodynamic conditions also failed.[32] For example, subjection of **9** to excess 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in refluxing benzene for up to five days afforded only recovered starting material.

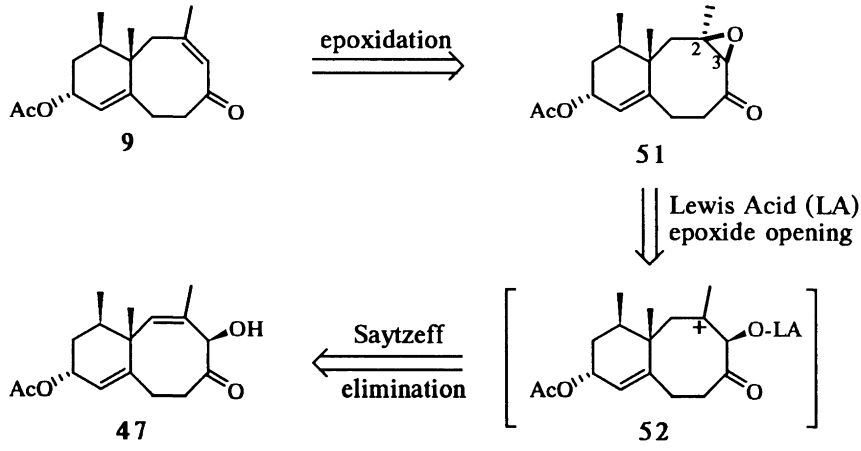
Babler and others discovered that ketalization of cyclic enones occurs with the deconjugation of the starting enone.[33] Ketalization of **9** using ethylene glycol in refluxing benzene with a catalytic quantity of *p*-toluenesulfonic acid did migrate the C_3–C_4 double bond; however, the only isolated product (**50**) contained not only an exocyclic olefin but also a heteroannular diene (Equation 8). Ketalization conditions could not be developed to avoid the elimination of the C_{10} acetate. We examined whether preparing the ketal derived from 1,3-propanediol would result in a different distribution of exo/endo olefins (Equation 8). This speculation proved to be wrong. Thus, we were forced to devise another route to complete the functionalization of the eight-membered ring.



9 **50** (8)

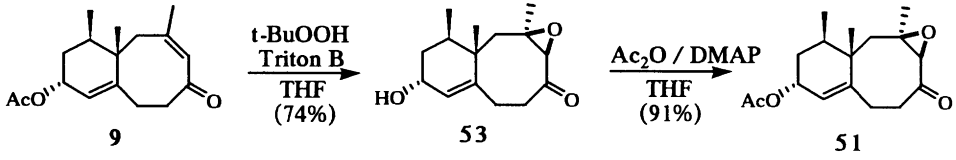
I was teaching E_1/E_2 elimination reactions of alcohols to our premedical and professional chemistry majors when, during the lecture, it dawned on me that an E_1 elimination represented *the* solution to our dilemma. More specifically, if enone **9** was stereospecifically epoxidized from the β-face, this epoxide (**51**) could be opened with a Lewis acid to form a tertiary carbonium ion (e.g. **52**), capable of producing the more substituted C_2–C_3 double bond upon Saytzeff elimination (Scheme 18).

Soon afterwards we found that epoxidation of **9** using *t*-butyl hydroperoxide and N-benzyltrimethylammonium hydroxide (Triton-B) yielded a single epoxide. We assumed that epoxidation had occurred from the peripheral face of the enone (i.e., **53**, Scheme 19) since the *t*-butyl hydroperoxide anion is known to be strongly influenced by steric effects.[34] Although the acetate protecting group was lost because of the basic conditions used, reprotection of the epoxy-alcohol posed no difficulty.



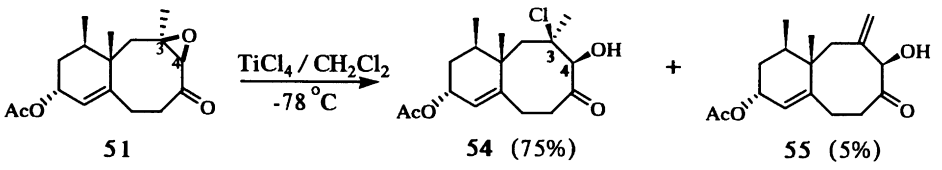
SCHEME 18

On several occasions we noted that the C_{10} acetate was sensitive to moderately acidic or basic conditions; hence, we felt the safest approach to open the C_3–C_4 epoxide would be to begin with



SCHEME 19

mild Lewis acids and to proceed accordingly. Although we tried weak Lewis acids such as $(CH_3)_3Al$, ZnI_2, $MgBr_2$, $Ti(i\text{-}OPr)_4$, TMSI/DBU, and $EtAlCl_2$ + TMP, only strong Lewis acids, such as titanium tetrachloride or ethylaluminum dichloride, were effective. For example, treatment of epoxide **51** with excess titanium tetrachloride in tetrahydrofuran at −78°C led to the formation of chlorohydrin **54** as a single diastereomer in 75% yield (Scheme 20) with allylic alcohol **55** isolated as a minor side product (≤5%). The relative stereochemistry of the chlorine in **54** is based on the assumption that the substitution occurs via an S_N1 mechanism from the sterically more accessible face of **54** or via an S_Ni displacement of the C_3-oxygen bond by the chlorine ligand of the coordinated Lewis acid as illus-



SCHEME 20

trated in Figure 2.[35] The failure of chlorohydrin **54** to regenerate epoxide **51** upon treatment with various bases supports our stereochemical assignment.

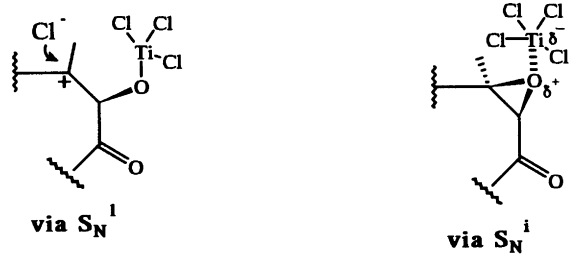
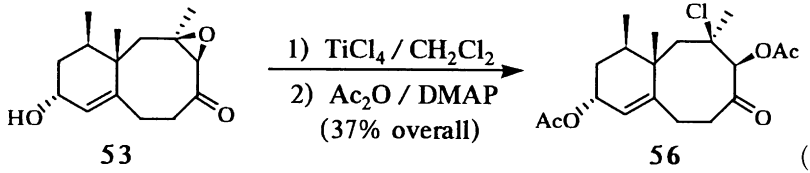


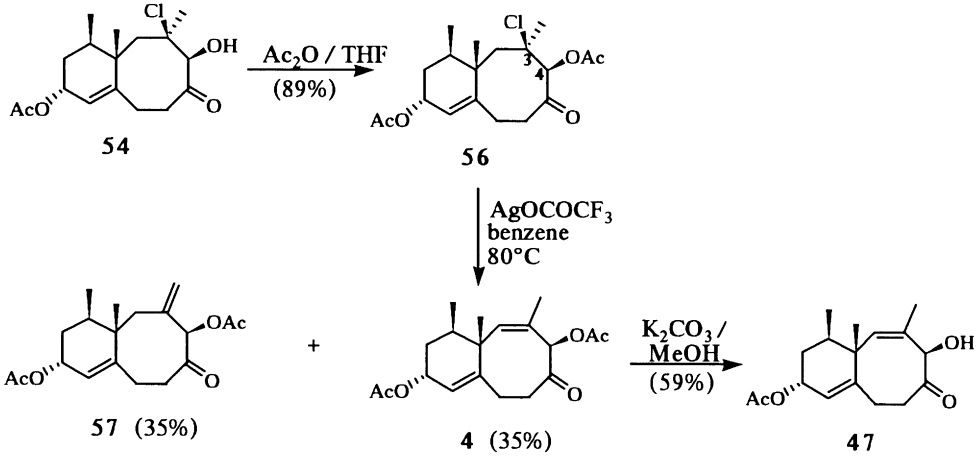
FIG. 2

The formation of allylic alcohol **54**, although seemingly a setback, substantiated our belief that formation of a tertiary carbonium ion *in the absence of nucleophiles* would undergo an E_1 elimination. We therefore decided to use silver salts to form carbonium ion **52**. The real question, in light of the preference of cyclooctenones to exist out of conjugation, was whether the olefin formed would be endocyclic or exocyclic. As a precaution the C_4 hydroxyl group was acetylated (i.e., **56**, Scheme 21).

Bis-acetate **56** could also be prepared from alcohol **53** in two steps. Regrettably, this alternative process occurred in only 37% overall yield, presumably due to the sensitivity of the C_{10} alcohol to acids (Equation 9).



(9)



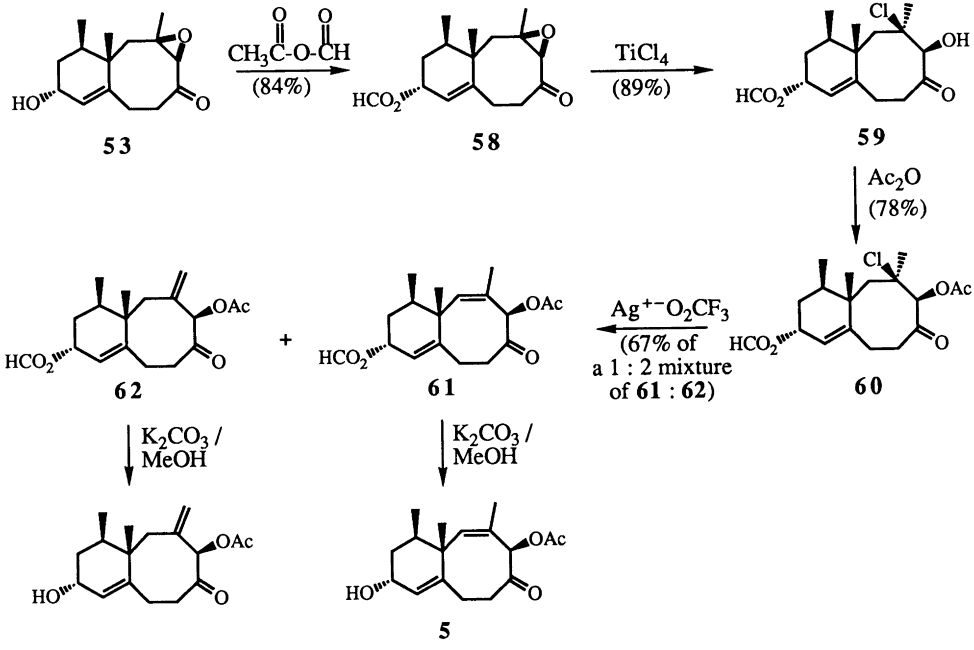
SCHEME 21

Four silver salts of varying strengths were investigated. Reaction of chloride **56** with silver nitrate afforded only recovered starting material,[36a] whereas silver tetrafluoroborate[36b] and silver trifluoromethanesulfonate[36c] proved to be too harsh and resulted in either decomposition of **56** or the formation of multiple products, none of which was shown to be neolemnanyl acetate. In contrast, treatment of **56** with silver trifluoroacetate in refluxing benzene furnished a separable mixture of neolemnanyl acetate **4** in 35% yield along with an equal amount of the exocyclic isomer **57** (Scheme 21). The spectral and chromatographic properties of synthetic (±)-neolemnanyl acetate were identical to those of an authentic sample prepared by acetylating neolemnane. In an attempt to isomerize the exocyclic double bond, a 1 : 1 mixture of **4** and **57** was treated with rhodium trichloride and heated.[37,38] Although the isomer ratio was not affected, prolonged reaction times resulted in elimination of the C_{10} acetate unit.

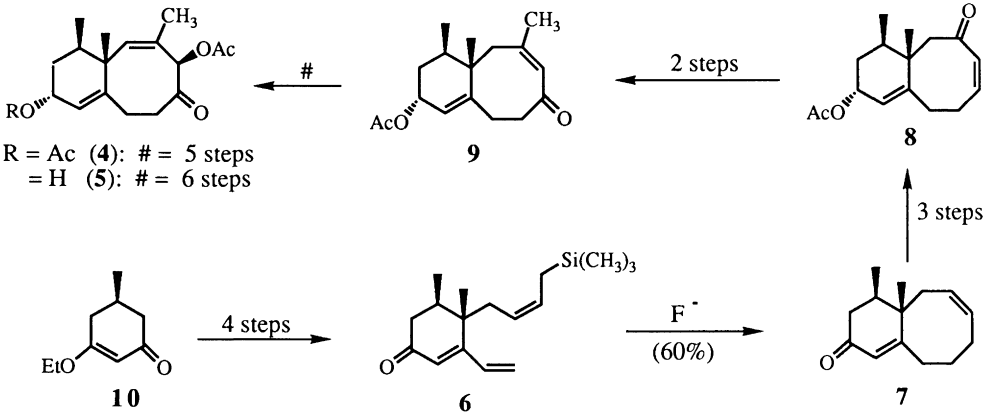
Having prepared neolemnanyl acetate, our attention turned to neolemnane (**5**). Dr. Vikram Khetani, a stalwart contributor in our synthesis of neolemnanyl acetate, assumed the responsibility for completing this synthesis.

Although selective deprotection of the C_{10} acetate of neolemnanyl acetate would directly afford neolemnane, this hydrolysis gives only alcohol **47** (Scheme 21). The use of protecting groups to differ-

entiate the C_4 and C_{10} allylic alcohols ultimately permitted the preparation of neolemnane (Scheme 22). We found that trialkylsilyl or benzyl ethers were incompatible with these requirements. The formate protecting group was chosen based on its compatibility with titanium tetrachloride [necessary for opening the C_2–C_3 epoxide] and its capability to be removed selectively even in the presence of the C_4 acetate.[39] Addition of epoxy-alcohol **53** to acetic-formic anhydride, prepared from anhydrous formic acid and acetic anhydride, gave formate ester **58** in 95% yield after stirring at room temperature for 28 hours. These mild conditions precluded solvolysis of the C_{10} alcohol and preserved the stereochemistry of this chiral center. Reaction of epoxide **58** with $TiCl_4$ gave chlorohydrin **59** in good yield. The C_4 hydroxyl group was then acetylated in 75% overall yield from epoxide **58**. Dehydrohalogenation of tertiary chloride **60** with silver trifluoroacetate yielded a separable mixture of cyclooctenones **61** and **62** in 67% yield and a disheartening 1 : 2 ratio, respectively. Despite much effort, Vikram was unable to improve upon this ratio. Finally, the formate protecting group was selectively removed



SCHEME 22



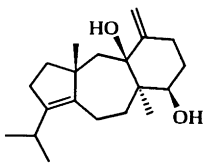
SCHEME 23

with K_2CO_3/aqueous methanol to afford neolemnane. The ^1H NMR (300 MHz), infrared and mass spectra as well as the chromatographic properties of synthetic (±)-neolemnane were identical with those of a sample kindly furnished by Professor William Fenical, thus confirming the first total synthesis of this sesquiterpene.

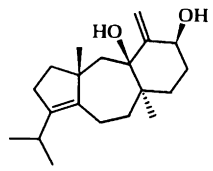
The major difficulty encountered during our syntheses of neolemnanyl acetate and neolemnane was functionalizing the cyclooctane ring. Once this obstacle was overcome, the remainder of the synthesis was straightforward (Scheme 23).

III. (±)-14-Deoxyisoamijiol

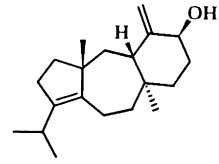
The dolastanes are comprised of over twenty known marine diterpenes. An interesting feature of the dolastanes, as represented by amijiol (**63**), isoamijiol (**64**), and 14-deoxyisoamijiol (**65**), is their distinctive 5-7-6 linear fused tricyclic framework depicted in Figure 3.[40]



amijiol (63)



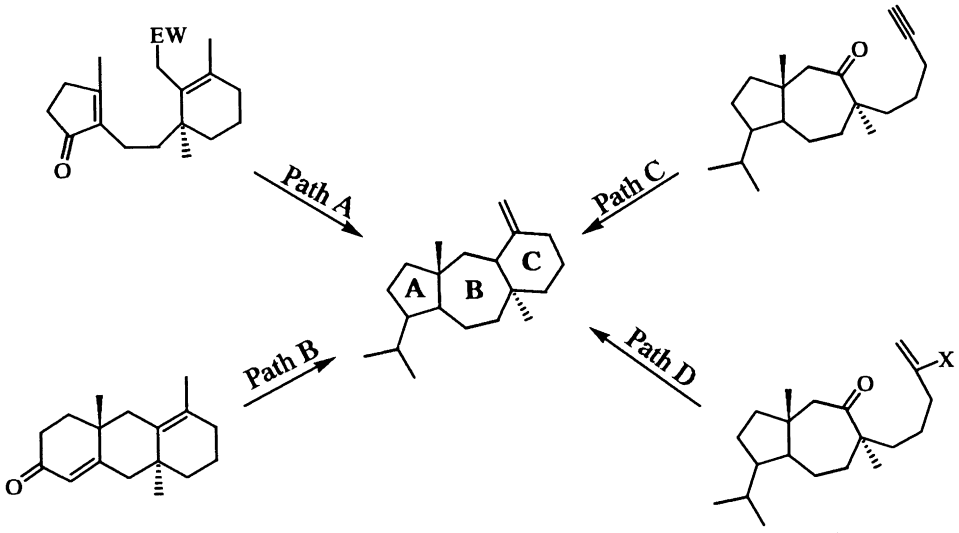
isoamijiol (64)



14-deoxyisoamijiol (65)

FIG 3

To date four different approaches to the dolastanes have been reported. One of the first strategies, devised by Paquette and coworkers, involved an intramolecular Michael addition to form the central cycloheptane ring as the final step in an "A + C → ABC" approach (path A, Scheme 24).[41] When this strategy proved unsuccessful, Paquette performed a concomitant ring expansion-ring contraction of a functionalized hydroanthracene precursor to generate the tricyclic nucleus (path B).[42] The third strategy for the construction of

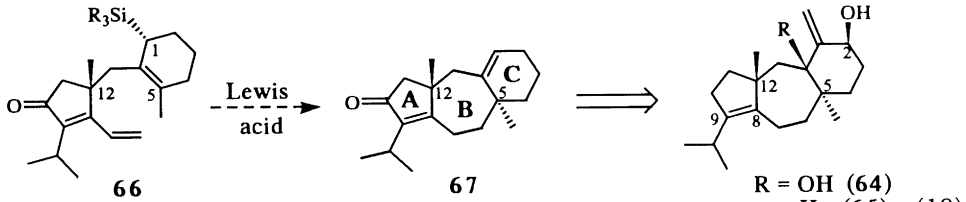


SCHEME 24

the dolastane framework involves cyclohexane annulation of a preformed perhydroazulene nucleus (paths C and D). Pattenden's synthesis,[43] as well as Mehta's enantioselective route,[44] feature a cyclohexane annulation using the intramolecular reductive coupling of a terminal acetylenic ketone (path C). Similarly, an annulation sequence developed by Piers employs the intramolecular addition of a regiospecifically generated vinyl anion to a ketone to give an allylic alcohol (path D.)[45]

The story behind our synthesis of 14-deoxyisoamijiol began in December of 1987.[46] I was anxious to apply our annulation procedures to polycyclic natural products and had identified the dolastanes, many of which exhibit promising biological activity, as an

appropriate test for our methodology. Since many of our cyclizations proceed with remarkable diastereoselectivity,[47] I expected that cyclization of **66** would not only assemble the basic dolastane skeleton but also establish the correct stereochemical relationship between the C_5 and C_{12} quaternary carbon atoms as shown in Equation 10. Moreover, sufficient functionality exists in the "A" and "C" rings of enone **67** to permit a dolastane synthesis. Paquette's statement that "any dependence upon penultimate construction of the medium ring appears ill-fated"[41] posed a challenge for our chemistry.

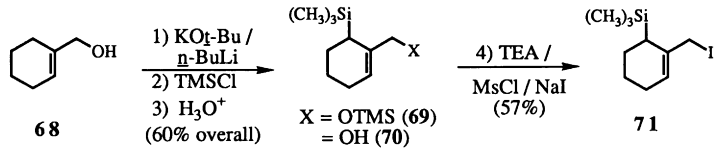


66 **67** R = OH (**64**) = H (**65**) (10)

At the time Clay Ringold was in the process of writing up the syntheses of three perforanes for his Masters degree and had decided to continue working towards a Ph.D. One day I asked Clay to photocopy a few dolastane references while he was at the library. Later he showed how we could prepare the dolastane framework using the very reaction illustrated in Eq. 10 and then convinced me that he was the logical one to work on this project. After I begrudgingly agreed (!) we chose to synthesize first isoamijiol (**64**) and then prepare 14-deoxyisoamijiol (**65**).

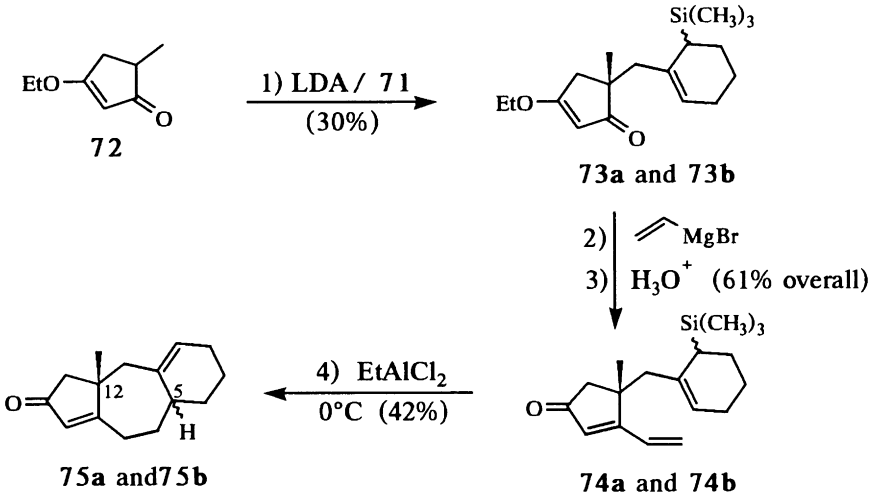
In order to test the viability of our "A + C → ABC" approach, it was necessary to prepare a cyclic allylsilane [the "C" ring] to couple with an appropriately functionalized "A" ring using the Stork/Danheiser protocol.[11] The first cyclic allylsilane synthesized was iodide **71**, which was prepared in five steps from 1-hydroxymethylene-1-cyclohexene (**68**) (Eq. 11). We initially attempted C-silylation of this allylic alcohol using the conditions developed by Trost and co-workers.[48] However, treatment of **8** with excess *n*-butyllithium for prolonged reaction times failed to generate any of the desired dianion, producing only the silyl ether as a result of oxygen-silylation. Fortunately an earlier method developed by Carlson[49] was applicable to alcohol **68**. Reaction of **68** with two

equivalents of potassium *tert*-butoxide and two equivalents of *n*-butyllithium for 14 hours generated the requisite dianion which was *bis*-silylated (cf. **69**) by quenching with excess trimethylchlorosilane. The silyl ether of **69** was selectively hydrolyzed with dilute acid to give the carbon-silylated allylic alcohol **70** in 60% overall yield. Transformation of this alcohol into iodide **71** was accomplished in 57% overall yield by a modification of the procedure originated by Finkelstein.



68 **71** (11)

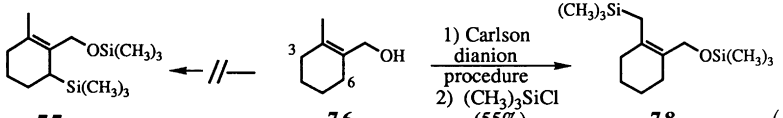
After preparing iodide **71**, we coupled the "A" and "C" rings. For the sake of expediency we postponed the introduction of the C_9 isopropyl and instead reacted **71** with the kinetic enolate derived from 3-ethoxy-5-methyl-2-cyclopenten-1-one (**72**) (Scheme 25). The 3 : 1 mixture of alkylation diastereomers formed were inseparable. Since this model study was intended only to determine whether we could



SCHEME 25

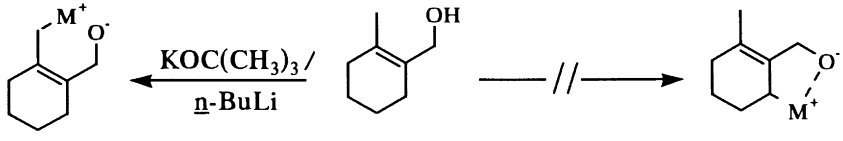
form a linearly fused tricyclic nucleus, this alkylation was not optimized and the absolute stereochemistry of the diastereomers was not established. Therefore, enol ethers **73a** and **73b** were treated with vinylmagnesium bromide and the crude allylic alcohols thus obtained were subjected to dilute acid-catalyzed allylic rearrangement to give conjugated dienones **74a** and **74b**. Treatment of **74a** and **74b** with ethylaluminum dichloride at 0°C gave two 5-7-6 tricyclic dienones in a 3 : 1 ratio. Although enones **75a** and **75b** were separable by chromatography, no attempt was made to determine the relative stereochemistry of either isomer. Nevertheless, formation of these tricyclic enones confirmed that the dolastane framework could be generated using our approach. Of equal importance was the observation that enones **75a** and **75b** were produced in the same ratio as were formed in the alkylation step, which implied that the cyclization occurred stereospecifically. A more sophisticated model study was needed wherein cyclization generates a tricyclic structure with angular methyl groups at C_5 and C_{12}.

We expected that the preparation of a cyclic allylsilane with a vinylic methyl group, such as **77**, would be an extension of our earlier work (Eq. 12). However, reaction of alcohol **76** using Carlson's dianion conditions silylated at the vinylic methyl giving ether **78**. In



77 **76** **78** (12)

retrospect, dianion formation at the C_6 methylene position involves a five-membered lithium chelate (cf. **i**, Eq. 13), whereas dianion formation at the vinylic methyl position proceeds through a more stable six-membered lithium chelate (cf. **ii**). A different approach was necessary to introduce a vinylic methyl group into the cyclic allylsilane.

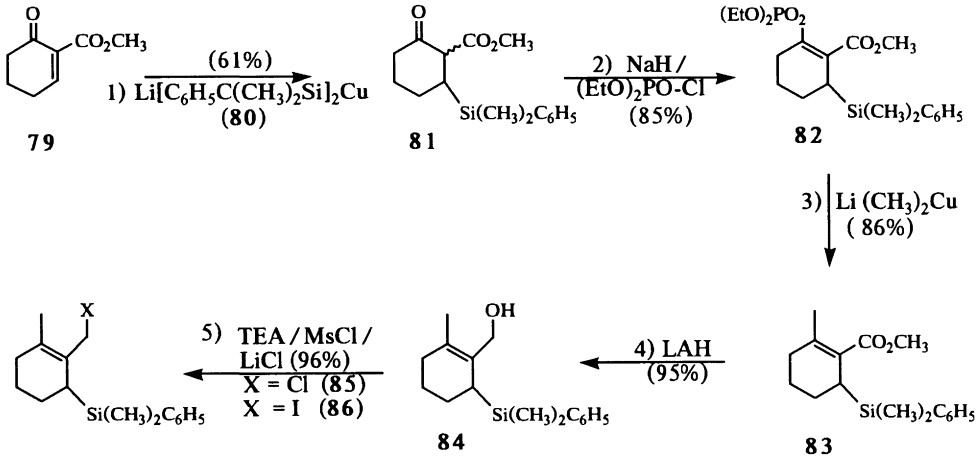


ii **76** **i** (13)

Since silyllithium reagents add in conjugate fashion to α,β-unsaturated ketones in the presence of HMPA or copper(I) iodide,[50] we hoped to add phenyldimethylsilyllithium (**80**) to 2-carbethoxy-2-cyclohexen-1-one (**79**) and then introduce the vinylic methyl group through the reaction of the corresponding enol phosphonate with lithium dimethylcuprate. Dimethylphenylsilyllithium was also chosen because it was easy to prepare and it was expected to favorably influence the diastereoselectivity in the coupling step.

2-Carbethoxy-2-cyclohexen-1-one was prepared using chemistry developed by Reich and co-workers in 1975.[51] Our purification of this doubly activated Michael acceptor proved to be troublesome: chromatography over silica gel or distillation at reduced pressure resulted in acid-promoted tautomerization to give a mixture of 1-hydroxy-2-carbethoxy-1,3-cyclohexadiene and **79** in a 2 : 1 ratio. Therefore, this material was used crude.

To a solution of the cuprate derived from **80** was added crude enone **79**. Workup and distillation afforded the Michael adduct **81** in 55% yield. Enol phosphonate **82** was obtained in 85% yield by the addition of **81** to a suspension of sodium hydride, followed by trapping the enolate upon the addition of diethylchlorophosphate. Addition of the enol phosphonate **82** to a solution of lithium dimethylcuprate at −78°C efficiently introduced the vinylic methyl group to provide β-methyl ester **83** in 86% yield. Reduction of this ester with lithium aluminum hydride gave allylic alcohol **84** in 95%



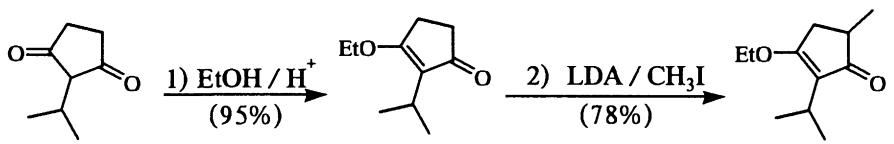
SCHEME 26

yield. Jee-Seop Song, a talented second year graduate student, scaled up this four-step sequence so that twenty grams of alcohol **84** could be prepared per batch.

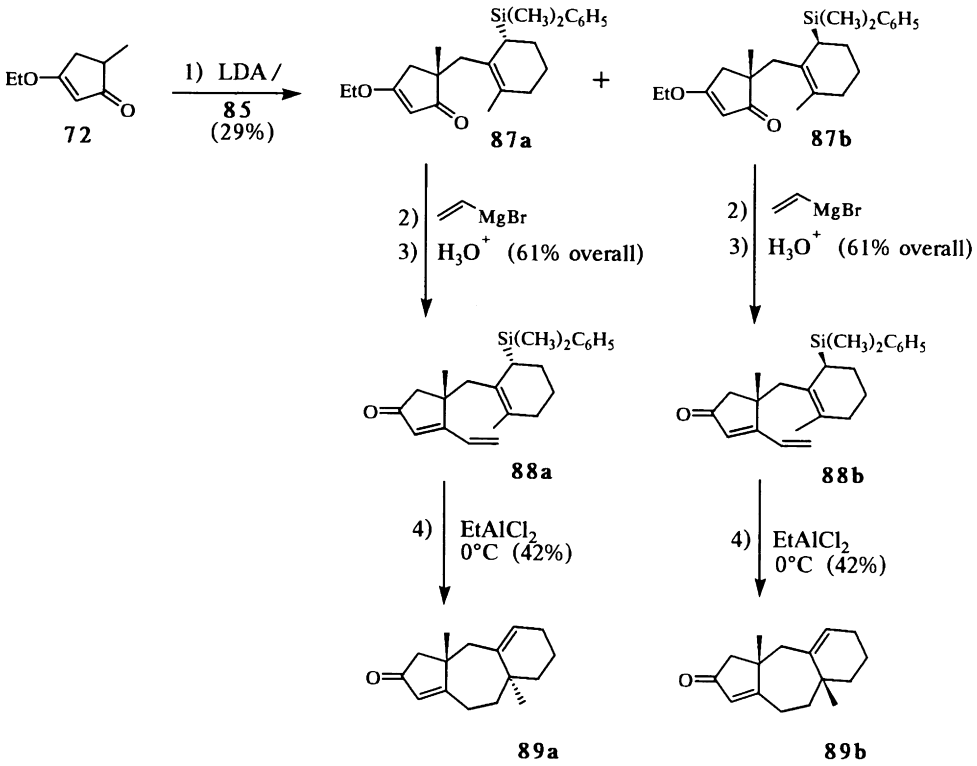
It was originally intended to convert alcohol **84** into the corresponding allylic iodide using a Finkelstein displacement. To this end, **84** was treated with triethylamine at 0°C and methanesulfonyl chloride was added dropwise. However, these conditions gave chloride **85**,[52] along with a small amount of the expected methanesulfonate. Anhydrous lithium chloride was added to the reaction mixture to maximize the yield of **85**.[53] Although attempts to prepare allylic iodide **86** via a halogen exchange reaction were successful, this iodide decomposed rapidly, while chloride **85** proved to be stable indefinitely when stored at −10°C.

The alkylation of **72** with chloride **85** gave two separable diastereomeric products (**87a** and **87b**) in a 1 : 1.8 ratio, in an unoptimized 29% yield. Enol ethers **87a** and **87b** were converted to trienones **88a** and **88b** in the usual manner. To our satisfaction, the Lewis acid-catalyzed cyclization of both **88a** and **88b** proceeded with complete stereospecificity to produce the diastereomeric 5-7-6 tricyclic dienones **89a** and **89b** in which one isomer enjoys a cis-relationship of the angular groups, and the other isomer enjoys a trans-relationship of the angular methyl groups. Although simple high field NMR experiments [i.e., difference NOE, COSY or NOSY] would have readily differentiated these isomers, this was not available to us as the department's JEOL 270 MHz NMR was broken and I was adamantly opposed to paying $67/hour for time on a colleague's instrument. Because the cyclizations of **88a** and **88b** occurred stereospecifically, a moratorium was declared on further models.

In order to achieve a dolastane synthesis we required a cyclization precursor with an isopropyl at the α-position of the dienone unit. 2-Isopropylcyclopentane-1,3-dione (**90**), first reported more than eighty years ago (Eq. 14),[54] was readily transformed into enol ether **91** in 95% yield using Fischer esterification conditions. Methylation



90 **91** **92** (14)

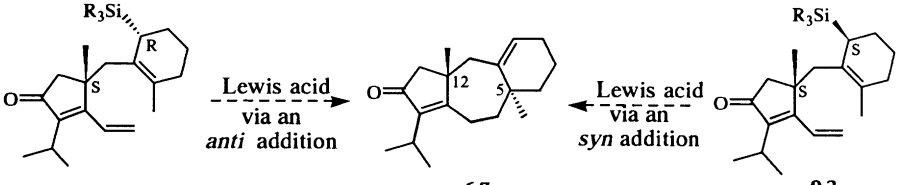


SCHEME 27

of this compound was performed in the usual manner to give enone **92** in 78% yield. A small amount (11%) of 5,5-dimethyl-3-ethoxy-2-isopropyl-2-cyclopenten-1-one was also produced, but was readily separable from **92**.

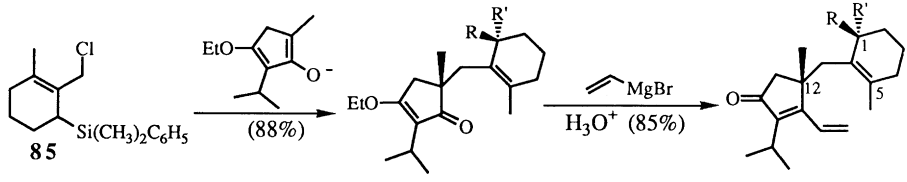
The next step was to couple our functionalized "A" ring, enone **92**, with the "C" ring as represented by chloride **85**. Since our model annulations led us to believe that formation of the dolastane skeleton occurs stereospecifically, a specific cyclization precursor was required. Despite the wealth of knowledge available regarding the trajectory requirements for Michael additions[55,56] as well as the stereochemical requirements for electrophilic substitution reactions of allylsilanes,[57–59] we were uncertain that the cyclization of **66** would produce a tricyclic product with the correct stereochemical relationship between the C_5 and C_{12} quaternary carbon atoms.

Trajectory requirements demand that the two reactive planar units achieve a parallel orientation in order for Michael addition to occur. When this relationship is obtained in trienone **66**, the silyl moiety of the allylsilane is positioned opposite the reactive centers; *anti* addition therefore results in a *trans* configuration of the angular methyl groups (Eq. 15). This analysis is consistent with Kumada's and Fleming's intermolecular findings regarding the stereochemistry of electrophilic substitution reactions of *acyclic* allylsilanes.[57] However, work with *cyclic* allylsilanes by Fleming *et al.* showed that electrophiles can add *syn* to the silyl moiety through either coordination of the electrophile with the silicon atom or because of simple steric factors.[58] Thus trienone **93** could produce enone **67** via a *syn* addition. Although we favored *anti* addition, *syn* addition could not be ruled out. We reasoned that the preparation and cyclization of both trienones (**66** and **93**) would resolve this question.



66 **67** **93** (15)

Coupling of **92** with chloride **85**, using the Stork-Danheiser procedure, produced enol ethers **94** and **95** in good yield as an inseparable mixture of diastereomers (Eq. 16). The diastereoselectivity of this reaction was dependent on the scale of the reaction. For example, enol ethers **94** and **95** were prepared in a 3 : 1 ratio, respectively, on reactions using less than 50 mg of chloride **85** while a 1.6 : 1 ratio, respectively, was obtained when the alkylation is carried out using 5 grams of electrophile.

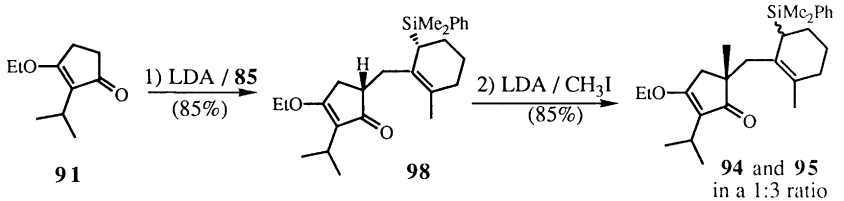


85

R = H; R' = $Si(CH_3)_2C_6H_5$ (**94**)
R = $Si(CH_3)_2C_6H_5$; R' = H (**95**)

R = H; R' = $Si(CH_3)_2C_6H_5$ (**96**)
R = $Si(CH_3)_2C_6H_5$; R' = H (**97**) (16)

Attempts to improve the diastereoselectivity using enolates other than lithium were unsuccessful. The order of alkylation was also inverted with the aim of increasing the yield of **94**. Although alkylation of **91** with chloride **85** afforded a single diastereomer (presumably enone **98**), methylation of this enone under kinetically controlled conditions gave a 1 : 3 mixture of **94** and **95**, respectively (Eq. 17).



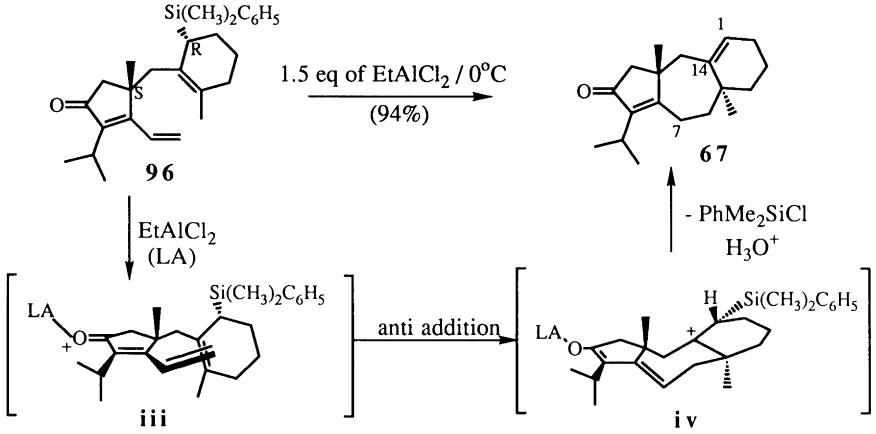
91 **98** **94** and **95** in a 1:3 ratio (17)

Though the resurrection of our NMR capabilities at the University of Georgia had been hopelessly delayed, Clay had already prepared conjugated dienones **96** and **97** from enones **94** and **95** using the standard procedure and was studying the cyclizations. I therefore assigned enone **94**, the major isomer, with the structure shown based on optimism and the premise that the addition of the electrophile to the enolate would be highly influenced by the bulky dimethylphenylsilyl moiety.

About this time, Professor Douglas Smith invited me to present a research seminar at the University of Toledo and was kind enough to put me in touch with Dr. Gregory Nemeth, their Research Instrumentation Manager. Greg viewed our spectroscopic needs as a means to further hone his NMR skills and requested samples of the cyclized products and their precursors. The following discussion benefits from his expertise and structural assignments.[60,61]

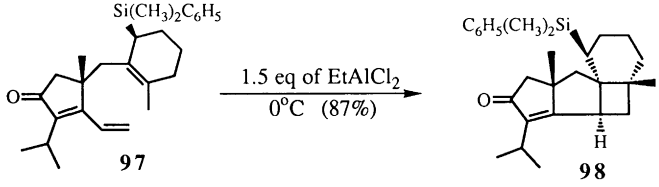
Treatment of trienone **94** with 1.5 equivalents of ethylaluminum dichloride at 0°C afforded tricyclic dienone **67**, with a trans relationship of the C_5 and C_{12} quaternary centers, in 93% yield (Scheme 28). Attack from the less sterically hindered face of the allylsilane—via an *anti* addition—generated cationic intermediate **iv**. Loss of chlorodimethylphenylsilane from this reactive intermediate formed the C_1–C_{14} double bond.

In contrast, reaction of trienone **97** under identical conditions furnished an unknown polycyclic enone (**98**) in 87% yield (Eq. 18). For once luck seemed to be with us. The department had just received



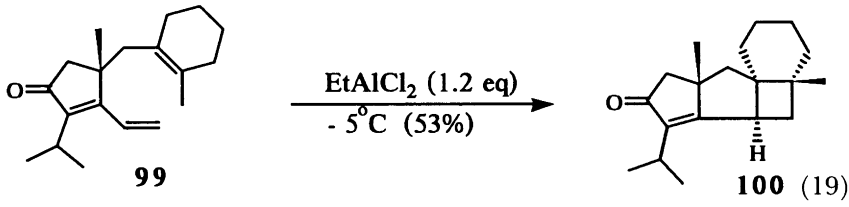
SCHEME 28

a grant to purchase a 400 MHz instrument and was evaluating the capabilities of various instruments. In an effort to be helpful, one of the manufacturers volunteered to run an INADEQUATE experiment [**I**ncredible **N**atural **A**bundance **D**oubl**E** **QUA**ntum **T**ransfer **E**xperiment] on unknown **98** for us. Since an INADEQUATE experiment reveals the C—C connectivity of a molecule, we did not question the structure shown in Eq. 18 which we received. Indeed, other arguments supported this polycyclic cyclobutane. Several research groups—including ours—have reported silicon-containing byproducts with cyclobutane rings in various intermolecular Sakurai allylations.[62] In addition, concurrent with our dolastane work, Dr.



(18)

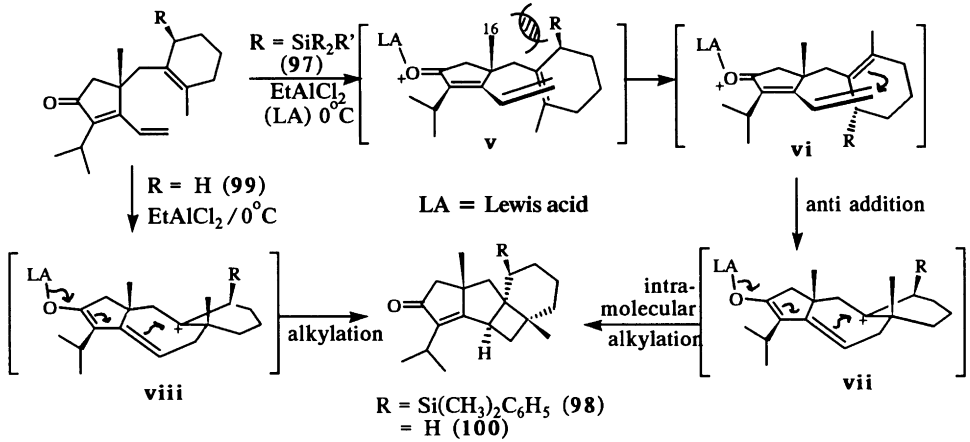
Vikram Khetani, recognized earlier for his neolemnane contributions, was studying cationic cyclizations in which unactivated alkenes react with 3-vinylcycloalkenones to form fused cyclobutanes.[63] Vikram found that treatment of **99** with 1.2 equivalents of ethylaluminum



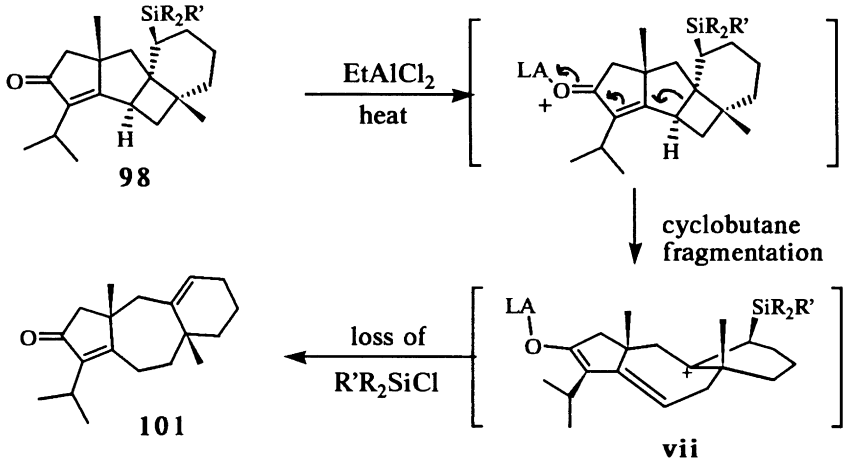
dichloride at −5°C afforded tetracyclic enone **100**, containing a cyclobutane ring (Eq. 19).

The structural similarities and mechanistic origins between tetracycles **98** and **100** are obvious (Scheme 29). In the case of enone **97**, steric repulsion between the silyl group and the C_{16} methyl group (cf. **v**) favors conformer **vi**, in which steric interactions have been minimized. Cyclization, again via an *anti* mechanism, produced cationic intermediate **vii** in which the angular methyl groups are *cis* to one another. Intramolecular alkylation of the aluminum dienolate accounts for cyclobutane formation.[64] Unlike the cyclizations of **97**, tertiary cation **viii** formed upon cyclization of **99** is unstabilized and is trapped to afford tetracycle **100**.

Once, instead of monitoring the cyclization of trienone **97** and working up the reaction when appropriate, the reaction was allowed



SCHEME 29

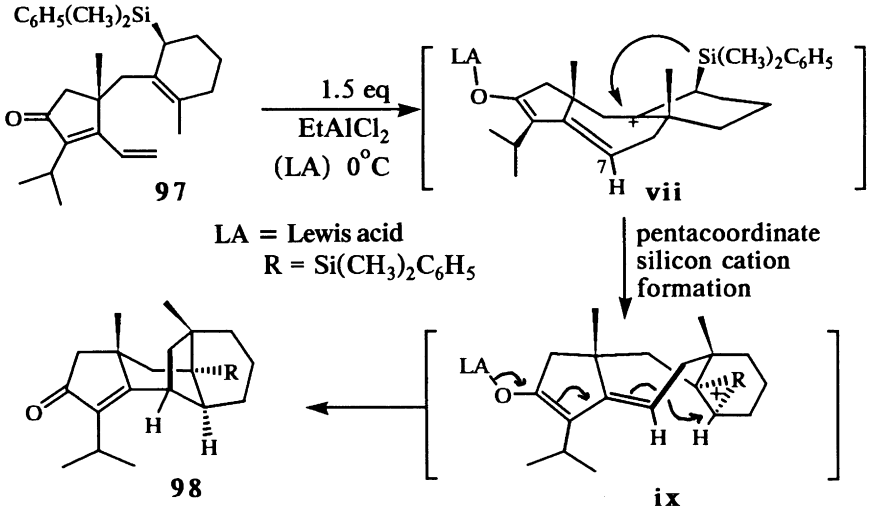


SCHEME 30

to stir overnight at room temperature. Subsequent workup afforded a small amount of tricyclic enone **101**. We immediately recognized that resubmission of **98** to Lewis acid catalysis would regenerate intermediate **vii**, and that irreversible loss of silyl group would result in the formation of tricycle **101** (Scheme 30). Indeed, treatment of **97** with 1.5 equivalents of ethylaluminum dichloride at 65°C afforded enone **101** in 91% yield. This fragmentation could also be achieved at room temperature with two equivalents of ethylaluminum dichloride in 66% yield. Trienone **35** could be cyclized directly to **101**—without the isolation of **98**—by doing the reaction with excess Lewis acid at 65°C.

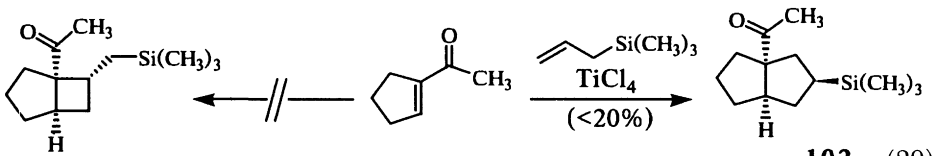
Thus, the observation of other silicon-containing cyclobutanes in allylsilane reactions, the formation of fused cyclobutane **100** and the fragmentation study supported the INADEQUATE-based assignment of **98**.

Because enone **98** contained the silyl group at C_1—with its original chirality intact—we wanted to determine its stereochemistry to resolve the *syn/anti* addition question. To our chagrin an X-ray diffraction study revealed that the INADEQUATE-based structure for enone **98** was wrong! Instead of a tetracyclic cyclobutane, enone **98** contains a silylcyclopentane in which the silyl moiety has migrated (Scheme 31).[65]



SCHEME 31

Our revised mechanistic rationalization is presented in Scheme 31 and begins with the intermediacy of cation **vii** from trienone **97** (cf. Scheme 30). Ordinarily, this cation would lose chlorodimethylphenylsilane to generate a double bond or be trapped by alkylation of the aluminum dienolate as we originally thought. However, formation of a bridged non-classical pentavalent silicon cation, such as **ix**, affords a new six-membered ring—instead of a cyclobutane—and thus enone **98** by means of an intramolecular alkylation. The intermediacy of hypervalent silyl cations during allylsilane additions was first postulated by Jarvie and Eaborn[66a,b] and has recently been proven by Knolker.[66c] In a reinvestigation of the Sakurai reaction of 1-acetylcyclohexene, Knolker and co-workers found that the minor silicon-containing byproduct previously assumed to be a cyclobutane ring[62a] is actually a silylcyclopentane (cf. **102**, Eq. 20).[66c] Our determination that **98** also contains a silylcyclopentane augments Knolker's findings.



102 (20)

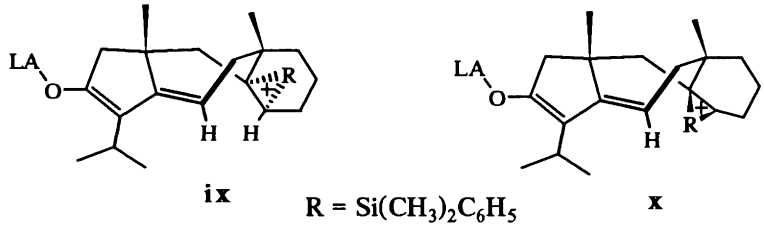
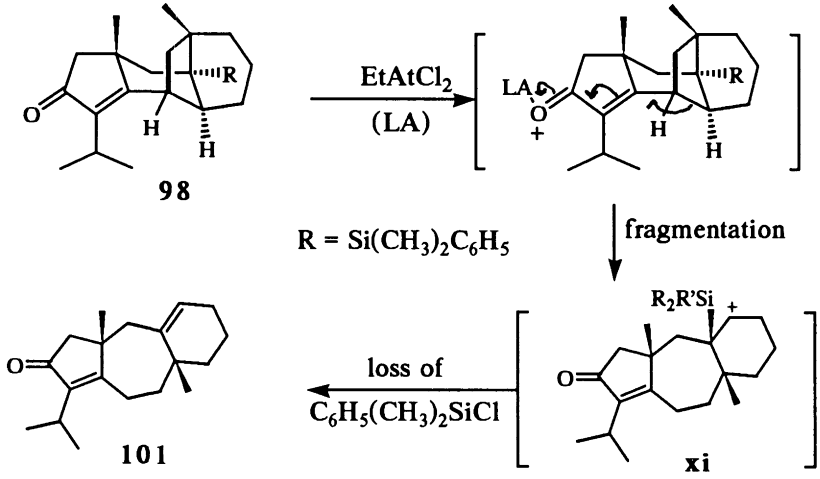


FIG. 4

A silylcyclopentane system can form only if the pentavalent silicon cation is on the β-face of **ix** (Figure 4) since a pentavalent silicon cation with the silyl moiety on the α-face of this molecule (cf. **x**) precludes intramolecular alkylation leading to desilylation and formation of enone **67**. This means that the silyl group must have been on the β-face of the molecule and dictates that allylsilane addition occurs via the *anti* mechanism we favored.

Scheme 32 illustrates how silylcyclopentane **98** fragments to generate tricycle **101** under conditions of thermodynamic control.

To summarize, the cyclizations of both trienone **96** and **97** occurred with complete stereospecificity. Tricyclic enone **67**, prepared from the major trienone **96**, has the required *trans* stereochemical relationship



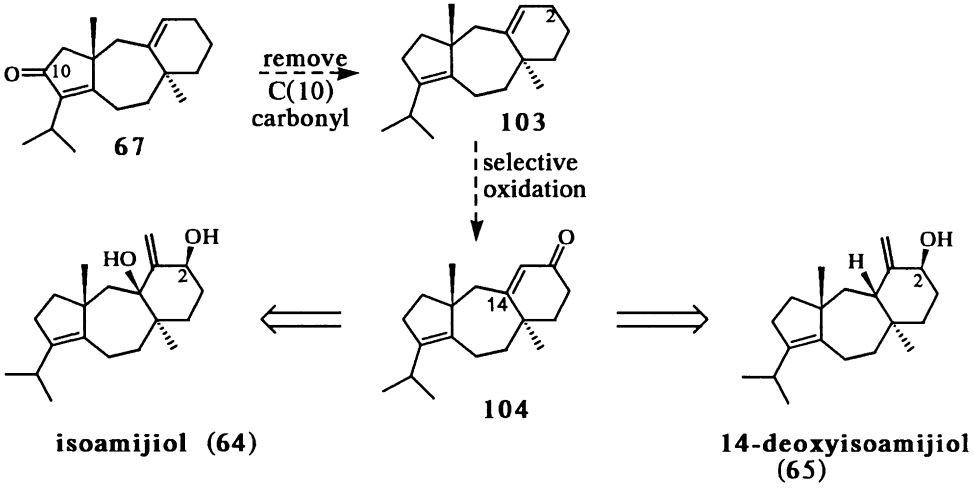
SCHEME 32

between the C_5 and C_{12} quaternary carbon atoms, while trienone **97** gave a kinetic tetracycle (**98**) with a *cis*-relationship between the C_5 and C_{12} quaternary carbon atoms, which we mistakenly assigned as having a central cyclobutane. Since **98** was not an intermediate in our synthesis, this error was inconsequential. Nevertheless, determining the correct structure for **98** allowed us to establish that the allylsilane cyclizations were occurring via an *anti* addition mechanism.

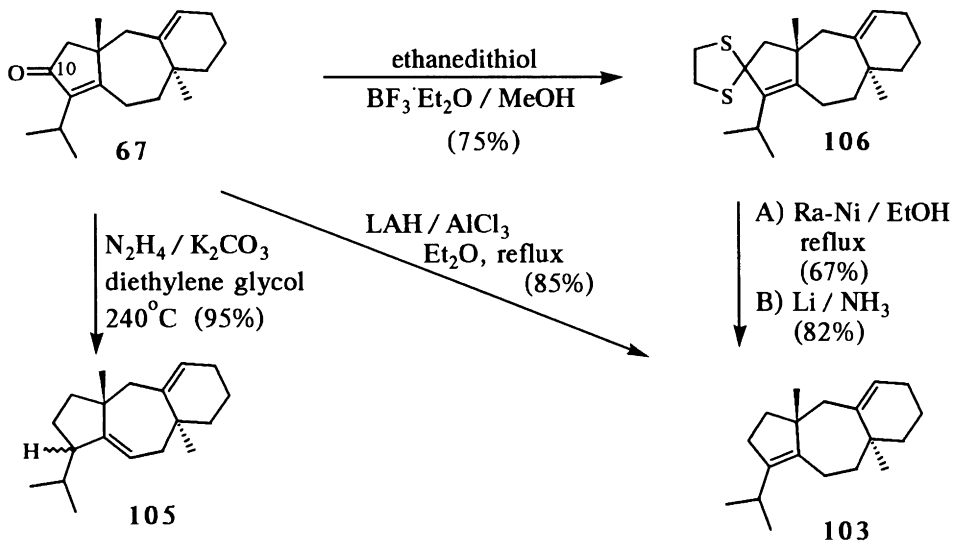
With dienone **67** in hand we wanted to convert it into diene **103**, followed by a regiospecific allylic oxidation at C_2 to give dienone **104**. This dienone was an attractive intermediate for both an isoamijiol and a 14-deoxyisoamijiol effort[67] since both targets have a C_2 β-allylic hydroxyl group (Scheme 33).

Reduction of the cyclopentenone carbonyl using Wolff-Kishner conditions resulted not only in removal of the C_{10} carbonyl, but also in migration of the cyclopentene double bond (cf. **105**, Scheme 34). Although modifications of the Wolff-Kishner reduction designed to prevent isomerization of the enone double bond were examined,[68] this double bond shift could not be suppressed.

We had previously used a two-step sequence for the reduction of cycloalkenone carbonyls without double bond isomerization in a



SCHEME 33

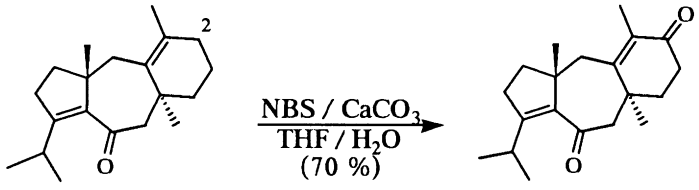


SCHEME 34

synthesis of (±)-valencene.[69] This procedure relies on the dithioketalization of a cycloalkenone using 1,2-ethanedithiobis(trimethylsilane)[70] and a mild Lewis acid, followed by desulfurization of the dithioketal. However, no reaction occurred when dienone **67** was treated with 1,2-ethanedithiobis(trimethylsilane), presumably due to the steric bulk of the reagent and the steric crowding of the cyclopentenone carbonyl moiety by the α-isopropyl appendage. Reaction of 1,2-ethanedithiol and a stoichiometric quantity of boron trifluoride etherate provided thioketal **106** in 75% yield without a shift of the cyclopentene double bond.[71] Addition of dithioketal **106** to an excess of freshly prepared Raney nickel (W-6) in refluxing ethanol afforded diene **103** in 67% yield.[72] The yield of this desulfurization was improved by the addition of the **106** to a solution of lithium dissolved in liquid ammonia to afford an 82% yield of **103** and in a 61% overall yield from **67**.[73] Ultimately, we were able to prepare **103** directly from **67** in 85% yield using aluminum trichloride and lithium aluminum hydride.[74]

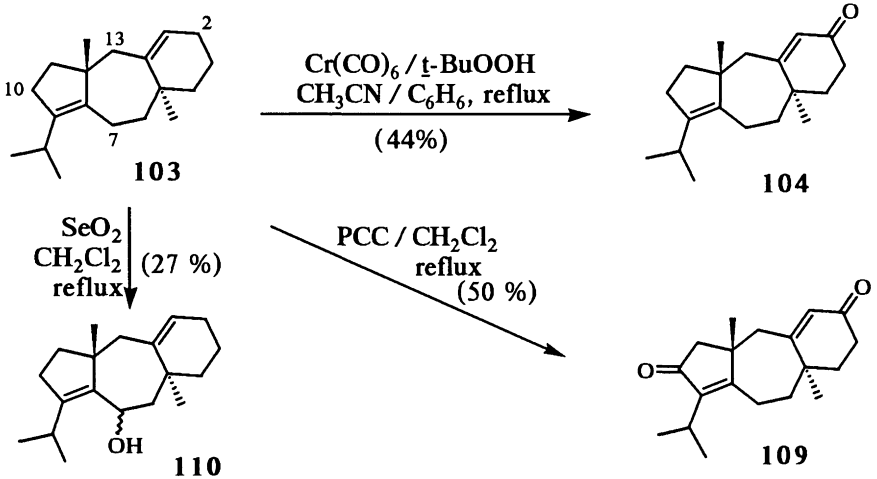
Our route to functionalize the cyclohexene ring called for an allylic oxidation at C_2. Even though there are four allylic sites in **103**, we were confident that C_2 was the most reactive position based on

Paquette's observation[42] that allylic bromination of enone **107** gave *bis*-enone **108** in high yield (Eq. 21). Equally important was our realization that cyclohexenes are oxidized more rapidly with chromium hexacarbonyl than are the analogous cyclopentenes,[75] which



107 **108** (21)

suggested that a substrate having both a cyclopentene and cyclohexene moiety would be selectively oxidized. Indeed, treatment of **103** with a catalytic amount of chromium hexacarbonyl and an excess of *tert*-butyl hydroperoxide in refluxing acetonitrile and benzene (10 : 1) selectively oxidized the C_2 position to provide the desired cyclohexenone **104** in 44% actual yield or 75% yield based on recovered **103**. Prolonged reaction times generated *bis*-enone **109** in good yield (Scheme 35). Other oxidants showed different selectivity. For example, treatment of **103** with selenium dioxide resulted in oxidation of

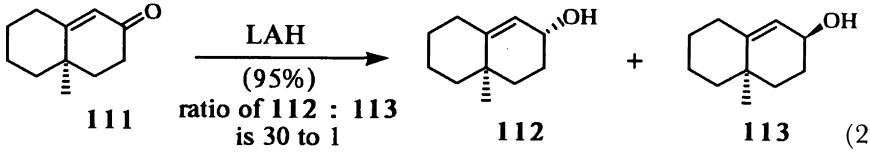


103 **104** **110** **109**

SCHEME 35

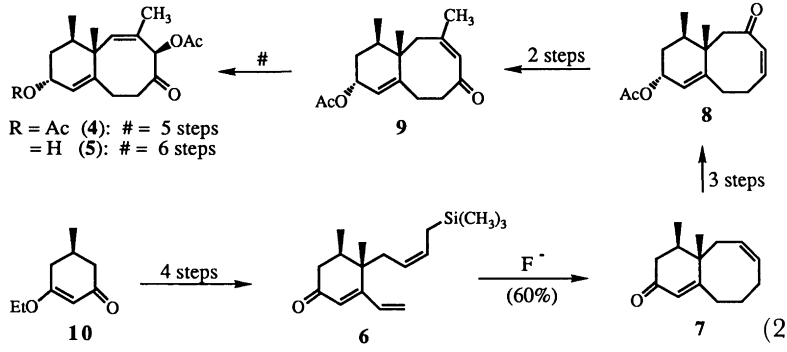
the cycloheptane ring at C_7 to give allylic alcohol **110**, while PCC or PDC favored oxidation of both the C_2 and C_{10} methylenes to furnish **109**.

We expected the reduction of dienone **104** with lithium aluminum hydride to provide an α-allylic alcohol based on the known reduction of octalone **111** (Eq. 22), which upon reduction with $LiAlH_4$ yields the thermodynamically more stable equatorial α-allylic alcohol **112**.[76]



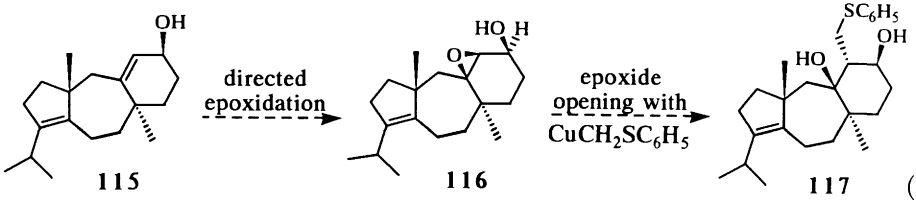
111 **112** **113** (22)

Also, molecular mechanics calculations performed on dienone **104** showed that conformation **xii** represents the minimum energy conformation and that hydride attack would occur from the more accessible β-face of the enone moiety (Eq. 23). In fact, treatment of **104** with lithium aluminum hydride in ether at $-15°C$ provided only α-allylic alcohol **114** in 95% yield. The use of bulky reducing agents produced small quantities of the β-oriented isomer (**115**).



(23)

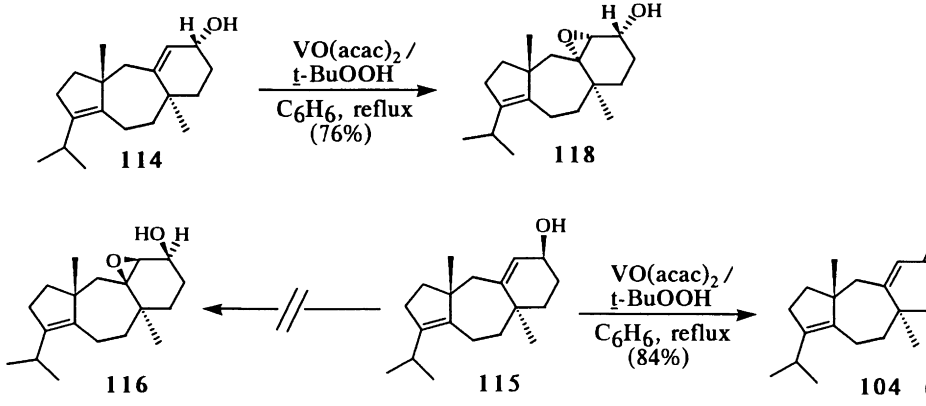
Before optimizing the preparation of desired alcohol **115** by means of Mitsunobu inversion, we first examined whether its epoxidation would be stereospecific. We wanted to prepare α-epoxide **116** since its reaction with the cuprate derived from phenylthiomethyllithium would produce an isoamijiol precursor (cf. **117**, Eq. 24).



115 116 117 (24)

Peroxyacid epoxidations of double bonds proceed under the directive influence of allylic hydroxyls; however, it is known that the introduction of a hydroxyl group into the allylic position in fact reduces the rate of peroxyacid epoxidation compared with the parent olefin.[77] Therefore, it was expected that an mCPBA epoxidation of **114**, or **115**, would result in epoxidation of both double bonds. Indeed, all attempts to selectively epoxidize the cyclohexene double bond of alcohol **114** resulted in *bis*-epoxidation using mCPBA. However, epoxidations of allylic alcohols using a catalytic amount of vanadyl acetylacetonate [Vo(acac)$_2$] and an excess of *tert*-butyl hydroperoxide in refluxing benzene exhibit a rate enhancement as well as an allylic hydroxyl directing control.[78] It was anticipated that this directing control and rate enhancement due to the allylic hydroxyl would allow the stereoselective epoxidation of the cyclohexene double bond of alcohols **114** and **115**.

Epoxidation of α-allylic alcohol **114** using the conditions mentioned above gave good yields of α-epoxy alcohol **118** with complete stereospecificity (Eq. 25). Unfortunately, reaction of **115** under identical conditions resulted only in dehydrogenation to provide dienone



114 118

116 115 104 (25)

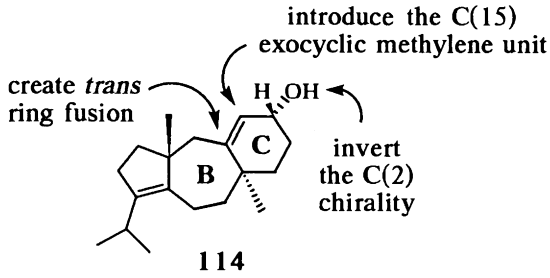


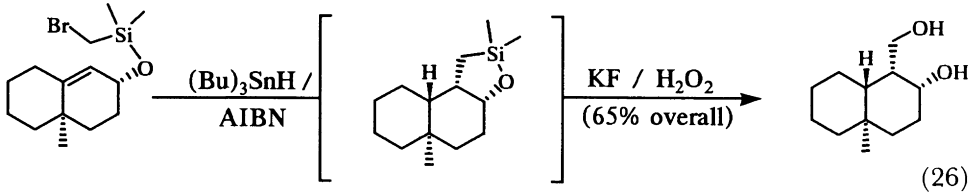
FIG. 5

104. Others have observed similar limitations in epoxidizing hindered allylic alcohols.

These setbacks prompted us to synthesis 14-deoxyisoamijiol first and then to devise a means to introduce the C_{14} hydroxyl group needed for isoamijiol.

Three functionalizations were required to complete a synthesis of **3** from alcohol **114**: establisment of the *trans*-B/C ring fusion; introduction of an exocyclic methylene at C_1; and conversion of the C_2 carbonyl to a β-oriented alcohol (Figure 5). While several routes could achieve these conversions, a newly discovered process would insure that a hydrogen atom would be introduced at C_{14} on the β-face of the molecule.

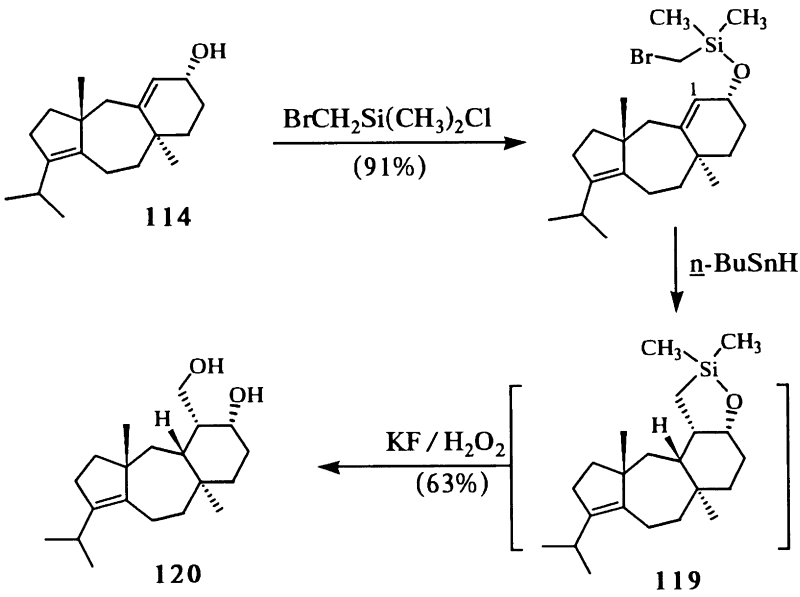
In 1985 Stork and Kahn reported that bromomethylsilyl ethers, readily derived from allylic alcohols, add in intramolecular fashion to produce siloxanes in which addition of a hydrogen atom occurs *anti* to the newly formed carbon–carbon bond (Eq. 26.)[79] Moreover, oxidative cleavage of the carbon–silicon bond culminates in diol formation.



(26)

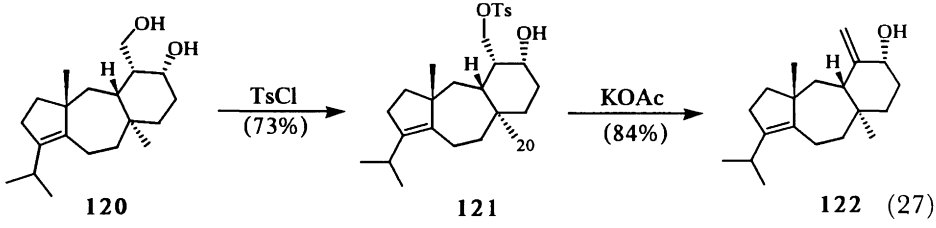
This methodology was ideally suited to our synthesis since a *trans*-ring fusion is generated and a hydroxyl methyl group would be added at C_1, facilitating the introduction of the C_{15} exomethylene unit.

We had already established that reduction of enone **104** with $LiAlH_4$ gave only α-allylic alcohol **114**. Silylation of **114** followed by radical-promoted cyclization and workup of siloxane **119** with KF and hydrogen peroxide gave diol **120** in 57% overall yield (Scheme 36).



SCHEME 36

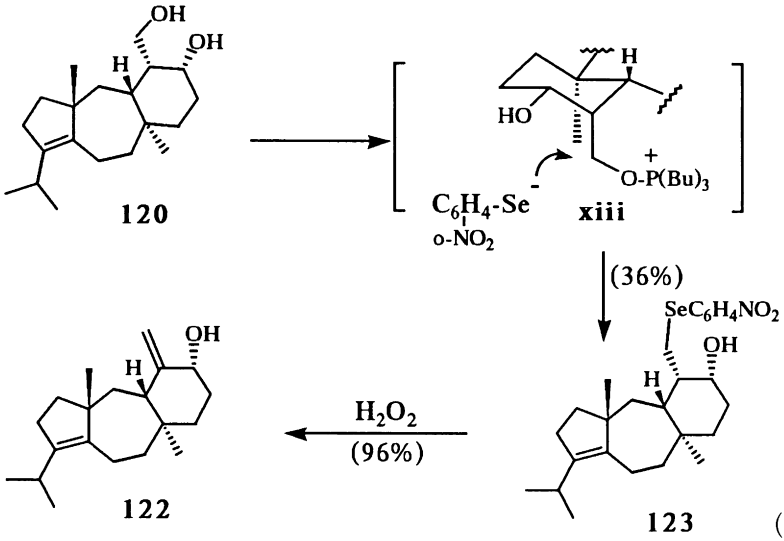
The final elaboration of the cyclohexane ring was achieved in three reactions. Selective *mono*-tosylation of the primary hydroxyl group, followed by base-promoted 1,2-elimination, gave allylic alcohol **122** in 61% overall yield (Eq. 27).



(27)

This elimination approach was superior to more recent means of converting alcohols into double bonds. For example, although conversion of alcohols into selenides, followed by oxidative elimination, is an

extremely useful and popular method,[80] this chemistry was of limited utility in converting diol **120** into allylic alcohol **122**, since selenide formation (cf. **123**) was severely hampered by the 1,3-diaxial relationship imposed by the C_{20} methyl group (cf. **xiii**, Eq. 28).



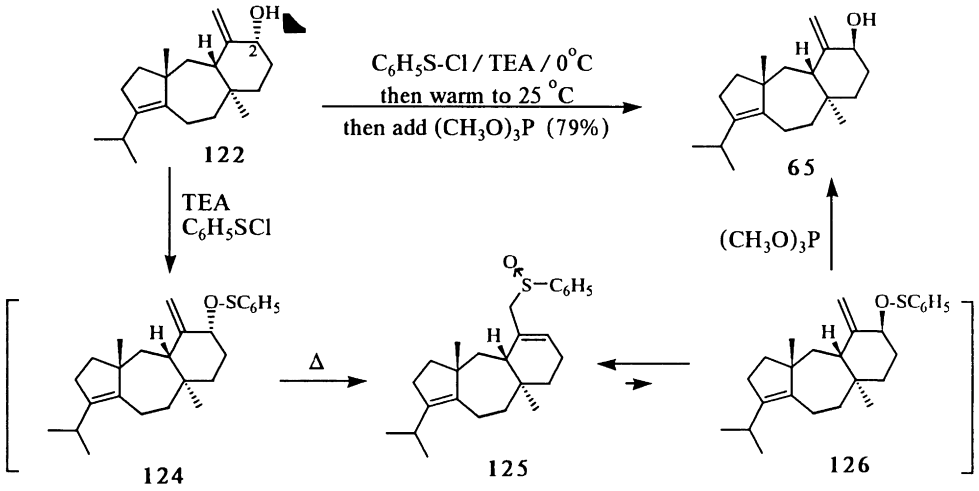
(28)

All that remained to complete our synthesis was to invert the stereochemistry of C_2. While a Mitsunobu inversion[16] achieved this inversion in 30% overall yield, we favored a less obvious procedure. The synthetic utility of the sulfoxide–sulfenate rearrangement has been rigorously established by Evans and others.[22,81] In general the equilibrium between a sulfenate ether and the corresponding allylic sulfoxide decidedly favors sulfoxide formation. However, introduction of a thiophile to this system results in consumption of the sulfenate ether so that an allylic alcohol is formed. We felt that the steric effects of the C_{20} methyl group would destabilize the sulfenate, derived from allylic alcohol **122**, so that the sulfoxide would strongly predominate. In addition, the steric effect of the C_{20} methyl would lead to an epimeric sulfenate (cf. **126**) once the sulfenate–sulfoxide equilibrium was reestablished. Addition of a thiophile after sulfoxide formation had occurred would therefore consume the new, thermodynamically favored sulfenate resulting in production of 14-deoxyisoamijiol. This type of inversion strategy was first used to control the C_{15} chirality of PGE_1 by Untch and co-workers.[82]

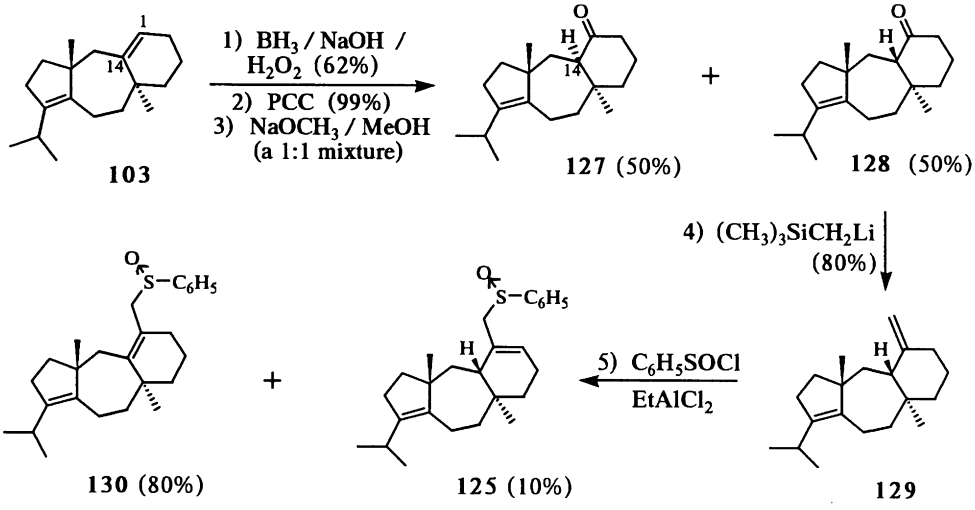
Treatment of **122** at 0°C with freshly prepared phenylsulfenyl chloride immediately resulted in formation of a sulfenate (cf. **124**, Scheme 37), which rearranged to sulfoxide **125** at room temperature. We were pleased to find that addition of trimethyl phosphite to **125** directly afforded 14-deoxyisoamijiol (**65**). The NMR (300MHz), infrared, and mass spectra of synthetic racemic **65** were identical to those published.[67]

In an attempt to shorten this synthesis we explored the sequence of steps depicted in Scheme 38. This time, rather than oxidize the C_2 methylene, we sought to oxidize C_1 by means of a hydroboration/oxidation sequence. Although *syn* addition of the borane would produce a *cis*-B/C ring fusion, subsequent oxidation of this alcohol would lead to a ketone capable of isomerizing the C_{14} methine. Ketone **128** was viewed as an attractive dolastane precursor since olefination would produce an exocyclic double bond which could react with arylsulfinyl halide to generate sulfoxide **125** *in situ*.[83] Alternatively, diene **129** could also be oxidized using selenium dioxide and *tert*-Butyl hydroperoxide to give **65** in less than 10% yield.[84]

Execution of this strategy proved troublesome. Hydroboration of diene **103** occurred in modest yield. To our surprise equilibration of ketone **127** using either acid or base catalysis gave an inseparable 1 : 1 mixture of **127** and **128**. Fortunately, reaction of this mixture with a

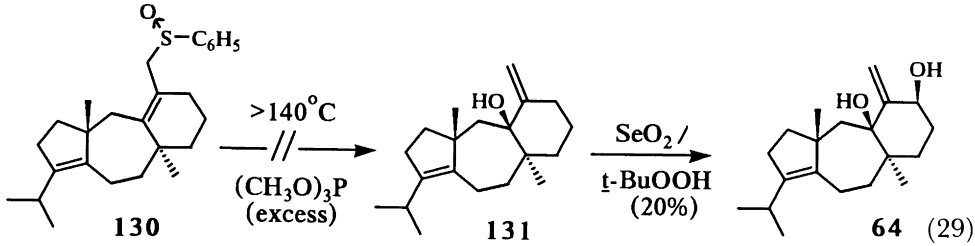


SCHEME 37

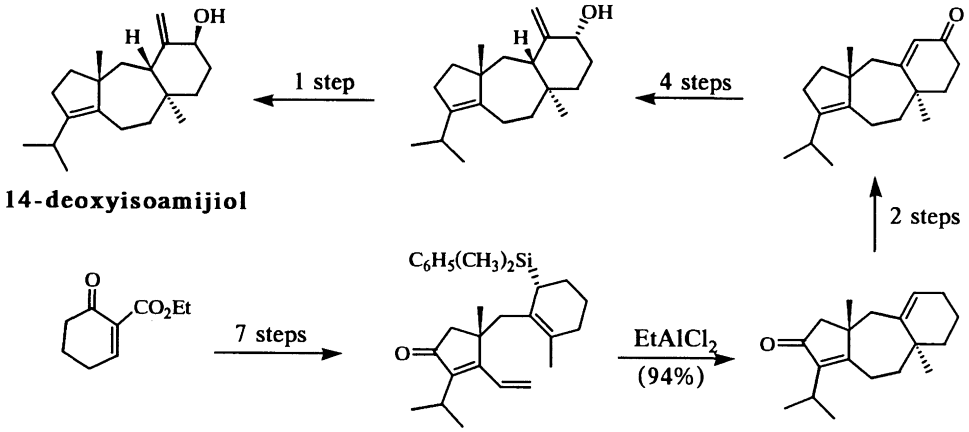


SCHEME 38

stoichiometric quantity of Peterson reagent[85] gave only olefin **129** with a *trans*-B/C ring fusion, along with unreacted ketone **127**. While less than desirable, this was nevertheless an effective means of preparing usable amounts of **129**. Unfortunately, reaction of diene **129** with toluenesulfinyl chloride and Lewis acid catalysis gave only trace quantities of allylic sulfoxide **125**. The major product of this reaction was the tetrasubstituted sulfoxide **130**, which although useless for a (14)-deoxyisoamijiol synthesis, was ideal for an isoamijiol synthesis (Eq. 29). In particular, we were hopeful that sulfoxide **130** would rearrange and thereby produce allylic alcohol **131**, an intermediate in both Mehta's and Pattenden's syntheses of isoamijiol.[43,44] To our disappointment, sulfoxide **130** failed to rearrange under a variety of drastic conditions. Clearly the C_{16} methyl group shields the C_1–C_{14} double bond preventing isomerization.



(29)



SCHEME 39

Scheme 39 summarizes the sixteen steps needed to achieve a stereoselective synthesis of (±)-14-deoxyisoamijiol. This synthesis features a highly selective allylic oxidation reaction and novel applications of the Stork/Kahn and Untch reactions. To date, we have elected not to complete an isoamijiol synthesis.

IV. Summary

The above syntheses of neolemnanyl acetate, neolemnane and 14-deoxyisoamijiol demonstrate the power of allylsilane-based strategies to assemble—with stereochemical control—polycyclic systems not readily accessible using more traditional annulation strategies. In future studies, we intend to incorporate more functionality into our cyclization precursors, thereby reducing the number of steps needed to complete a given synthesis.

Acknowledgment

I am indebted to many students and a single postdoctoral associate whose efforts and enthusiasm made this work possible. The first student in my group to work on neolemnane was Kenneth Hull who prepared bicyclic enone **7**, functionalized the cyclohexane ring and suffered through our early attempts to functionalize the cyclooctane ring. Clay Ringold developed the use of propargyl iodide **12** in order to facilitate the preparation of the cyclization precursor and endured the disappointments encountered in the failed expoxide opening studies. Although Derric Lowery and Dr. Vikram Khetani ultimately achieved syntheses of neolemnanyl acetate and neolemnane, credit must also be given to Jee-Seop Song, who as a first year graduate

student prepared five grams of enone **7** to guarantee the completion of this project. In the preparative work, Jee-Seop carried out the fluoride ion-promoted cyclization of **6** to **7** on more than seven grams of trienone.

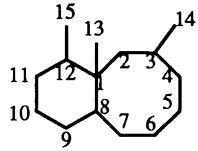
Our synthesis of 14-deoxyisoamijiol was the result of the work of Clay Ringold and Jee-Seop Song. Clay began this project and carried it through the first ten steps to the preparation of key enone **104**, while Jee-Seop completed this synthesis only two months later.

Support for both projects was received from the National Institute of General Medical Sciences through research grant 1 R01 GM39752 and is gratefully acknowledged.

The principal author also expresses his gratitude to Professor William Fenical for an authentic sample of neolemnane, Dr. Christopher Shiner for helpful discussions regarding the preparation of silane **70**, Dr. Gregory Nemeth, Research Instrumentation Manager at the University of Toledo for his invaluable spectroscopic assistance and Dr. M. Gary Newton for the X-ray study to clarify the structure of "unknown" **98**.

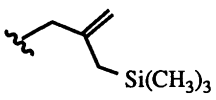
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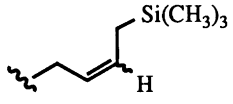


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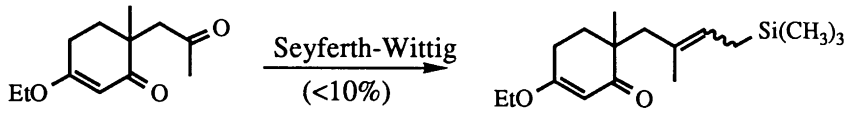


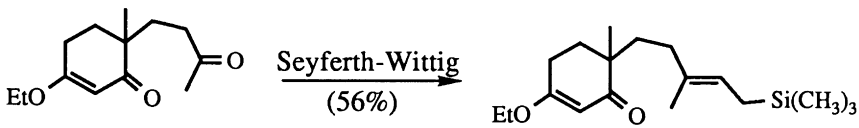
isoalkenyl



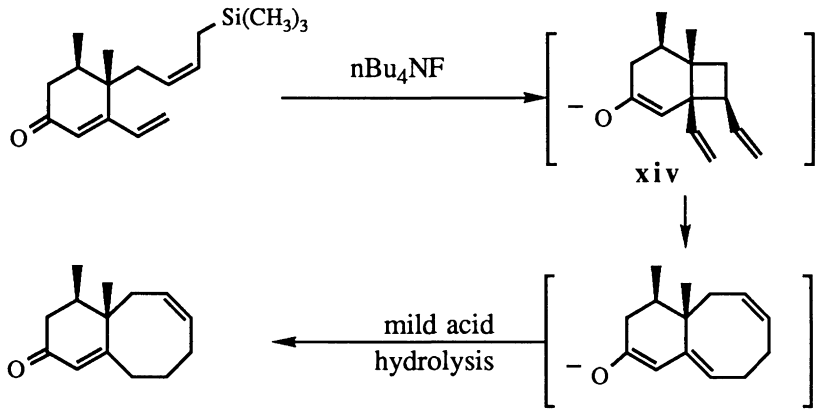
***n*-alkenyl**

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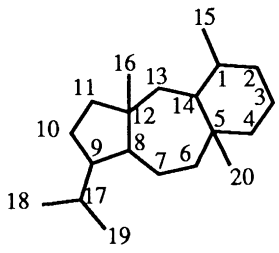


19. Although a detailed discussion of the mechanism of this cyclooctane annulation can be found elsewhere,[20] the key steps are summarized below. 1,4-Addition of the allylsilane via an S_E2' pathway to the dienone moiety forms divinylcyclobutane **xiv** which then undergoes an enolate-accelerated Cope rearrangement resulting in cyclooctane formation.



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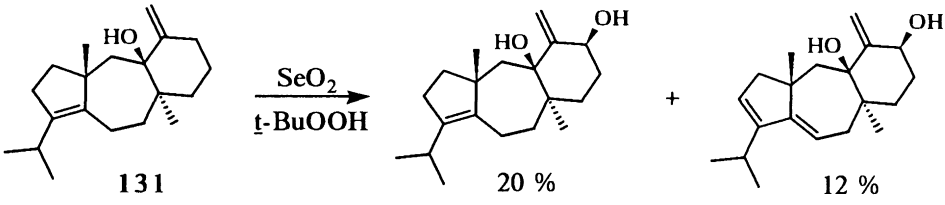
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131 20 % 12 %

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Chapter 9

SYNTHESIS OF CEMBRANOID NATURAL PRODUCTS BY INTRAMOLECULAR S_E' ADDITIONS OF ALLYLIC STANNANES TO YNALS

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I. Introduction

The family of diterpenes now known as "cembranes" was formalized in 1962 following structure elucidation of the hydrocarbon cembrene (**I**) from pine oleoresins,[1,2] and the diols **II** and **III** (stereochemistry unassigned) from tobacco.[3] In the intervening years

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hundreds of cembranes have been isolated, mainly from three sources-tobacco, Caribbean gorgonians, and Pacific soft corals. Cembranes are the most widely occurring diterpenes in Nature.[4,5] Some representative examples are depicted in Figure 1.[6–11] In general, the lactonic cembranes come from marine sources.

A range of biological activities has been reported for cembranes. Most of the marine derived compounds are highly toxic to fish suggesting that they serve as chemical deterrents against predators for their otherwise defenseless host organisms. The tobacco cembranoids α and β-CBT are effective inhibitors of tumor promotion and most α-methylene lactonic cembranes are potent cytotoxic agents.[12]

In the late 1970s we became interested in cembranes as synthetic targets. We were intrigued by their novel structures and diverse

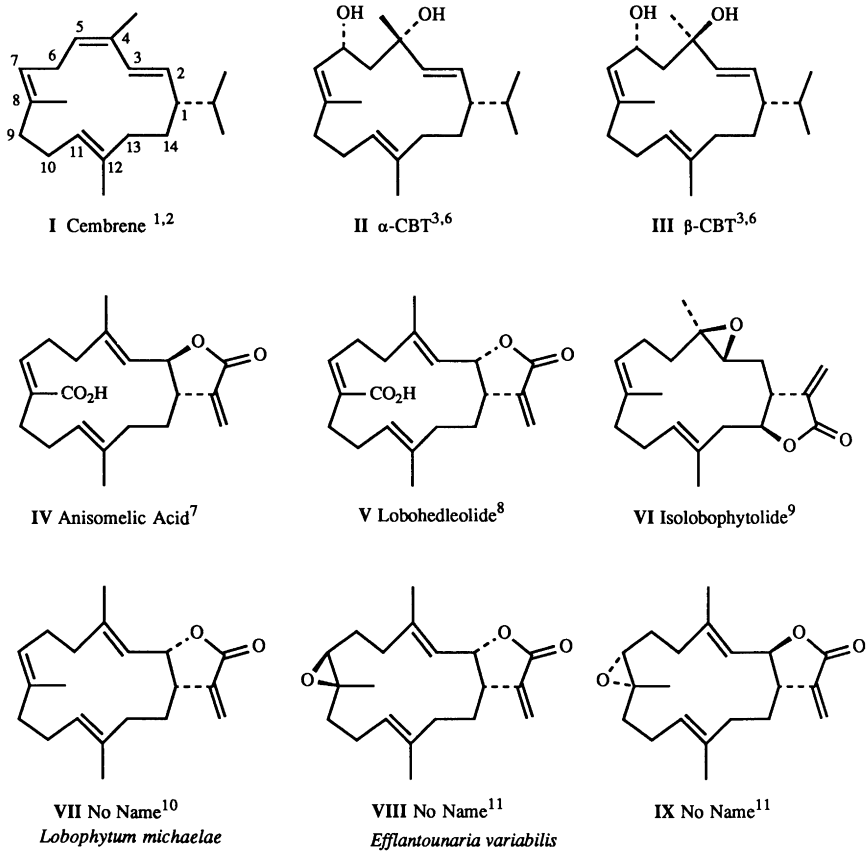


FIG. 1. Representative Cembrane diterpenes.

biological profiles.[12,13] Furthermore, the general area of macrocyclic synthesis seemed ripe for exploration.[13] Our then current work on the chemistry of betweenanenes had enhanced our awareness of the unique conformational properties of (*E*)-cycloalkenes. Thus, we viewed the cembrane ring system, with multiple (*E*)-double bonds, as a potentially rigid array having well-defined conformations. We planned to develop strategies based on acyclic stereocontrol to assemble likely precursors and then utilize macrocyclic conformational analysis, with the help of molecular modeling, to guide further manipulations of cyclic intermediates.[14] One of our foremost considerations was devising suitable methodology for closure of the 14-membered ring.[13] A number of different approaches were examined and considerable effort was invested in fashioning stereochemically unambiguous routes to suitable acyclic precursors. The methodology to be discussed in this chapter evolved from a planned synthesis of lobohedleolide (**V**) initiated in 1983 with graduate student Brad DeHoff.

II. Preliminary Studies—S_E' Additions and Horner-Emmons Condensations

The plan, as outlined in Figure 2, was appealing because it offered two ring closure options, both involving strategic bond formation. Furthermore, literature precedent could be found for both cyclizations. Thus, Stork[15] and Nicolaou[16] had just established the viability of the intramolecular Horner-Emmons reaction, at least for the formation of macrocyclic lactones, in support of **XI** → **X**. Precedent for the alternative cyclization, **XII** → **X**, could be found in Still's ingenious synthesis of asperdiol, published that same year, in which an *in situ* generated allychromium species underwent smooth intramolecular S_E' addition to an enal moiety.[17] An additional attractive feature of our plan was its modularity, requiring only two closely related subunits **XIII/XIV** and **XV/XVI**.

After considering various options for M in **XII** or **XV**, we chose the Bu_3Sn derivative for the following reasons: (1) allyl stannanes were known to be stable isolable intermediates,[18] (2) Lewis-acid promoted additions of allyl stannanes to aldehydes were known to proceed under mild conditions and in high yield,[19] (3) BF_3-catalyzed additions were known to be highly *syn* selective, independent of double bond geometry,[19] and (4) additions leading to *anti* products could be effected through *in situ* transmetallation of the allyl stannane with

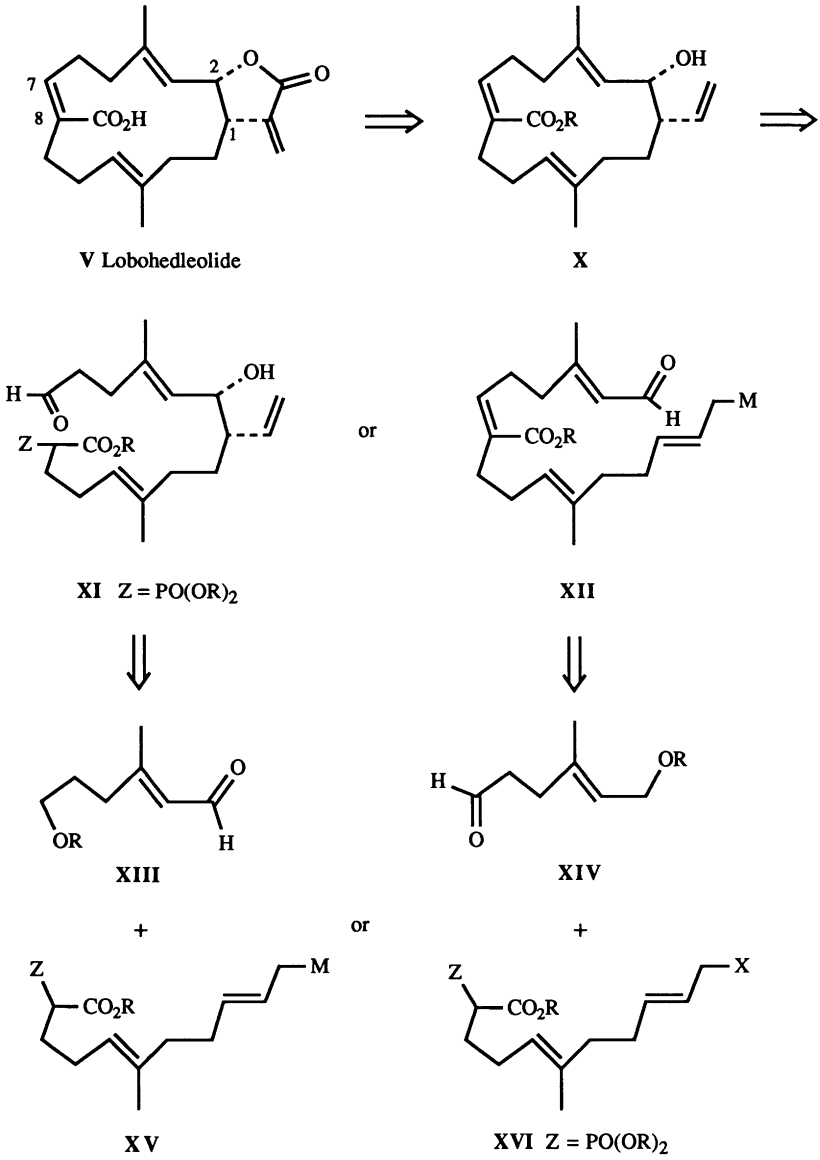
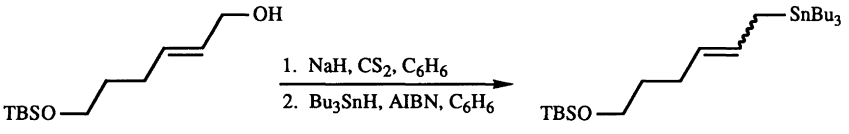


FIG. 2. Synthetic plan for lobohedleolide.

$TiCl_4$.[20] This last point was of interest for the synthesis of *trans* fused cembranolides such as anisomelic acid (**IV**).[7]

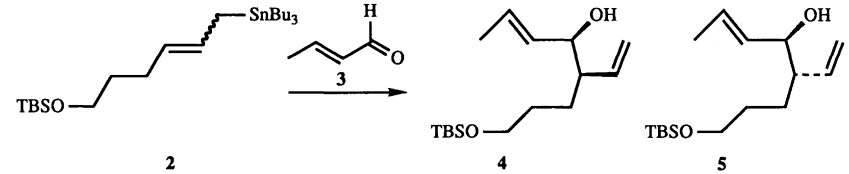
We initiated our investigations with a series of model studies designed to probe the applicability of allyl stannane additions to aldehydes similar in structure to our intended application. We felt this was necessary because prior examples of these additions had employed relatively simple reaction partners.[19] We selected allyl stannane **2**, easily prepared from the allylic alcohol **1** by the method of Ueno *et al.*, as our model system (Eq. 1).[21] BF_3 promoted addition of this stannane to *trans*-crotonaldehyde (**3**) proceeded readily affording a 90 : 10



(1)

1 **2**

mixture of *syn* and *anti* products **4** and **5** (Eq. 2). The $TiCl_4$-promoted addition yielded the same two adducts with the *anti* isomer **5** predominating 95 : 5.[22] The lower yield of the latter addition may result from partial cleavage of the OTBS group by the Lewis acid.



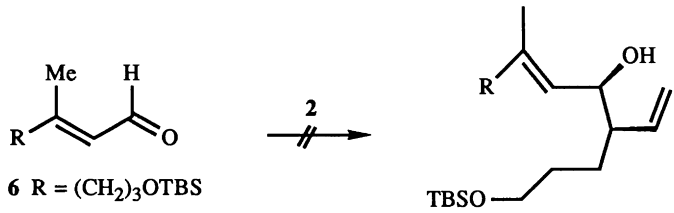
(2)

2 **4** **5**

Conditions	Yield	4:5
1.1 eq BF_3•OEt_2, CH_2Cl_2, -78°C	73%	90:10
1.1 eq $TiCl_4$/**2** followed by **3**, -78°C	47%	5:95

Surprisingly, the seemingly trivial extension of this addition to the β,β-disubstituted aldehydes **6** and **7** failed completely (Eq. 3). At −78°C, even with a large excess of $BF_3 \cdot OEt_2$ and long reaction times, only starting materials were recovered. At temperatures between −30°C and 0°C, decomposition of the reactants was observed.

These results were quite discouraging and could well have signaled the end of this approach and possibly our involvement with allylstannane chemistry. However, my co-worker Brad DeHoff decided to



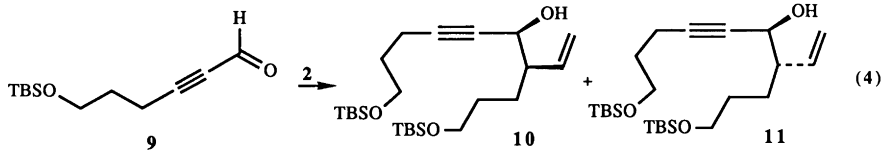
(3)

6 R = $(CH_2)_3OTBS$
7 R = $(CH_2)_2CH{=}CMe_2$

8

Conditions	Result
2 - 10 eq. $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78°C to -30°C	no reaction
2 - 10 eq. $BF_3{\cdot}OEt_2$, CH_2Cl_2, -30° to 0°C	decomposition

examine acetylenic aldehyde **9** as the electrophilic partner (Eq. 4). This addition was extremely rapid giving rise to mainly *syn* or *anti* adduct **10** or **11**, depending upon reaction conditions.

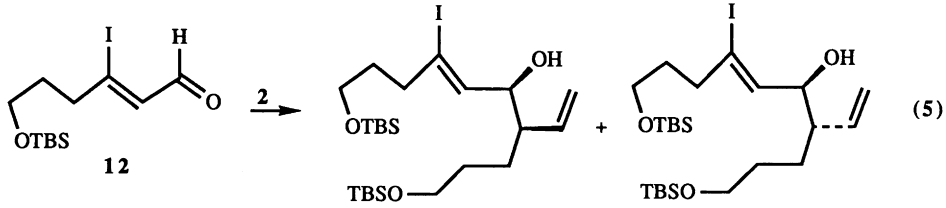


(4)

9 10 11

Conditions	Yield	10:11
1.1 eq. $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78°C	81%	90:10
1.1 eq. $TiCl_4$/2 followed by 9, CH_2Cl_2, -78°	60%	5:95

Interestingly, the β-iodo enal **12** afforded the adducts **13** and **14** with allyl stannane **2** (Eq. 5). Thus, β-substituents *per se* do not disfavor the addition.

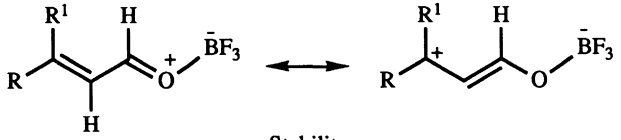


(5)

12 13 14

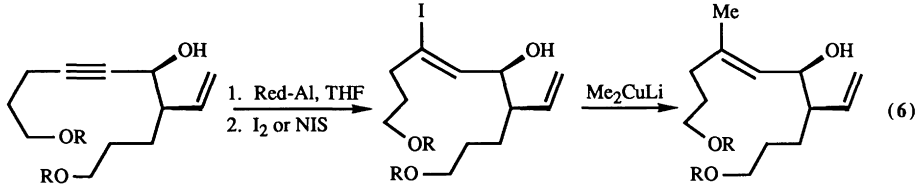
Conditions	Yield	13:14
1.1 eq. $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78°C	57%	75:25

The unreactivity of aldehydes **6** and **7** relative to **3**, **9** and **12** may stem from inductive stabilization of the aldehyde–BF_3 complex **A** by



A

the second β-alkyl substituent in the former leading to decreased electrophilic character. In any case, success with aldehydes **9** and **12** revived our approach, as the adducts obtained from these enals could be converted to the requisite β-methyl compounds by known methodology, as illustrated in Eq. 6.



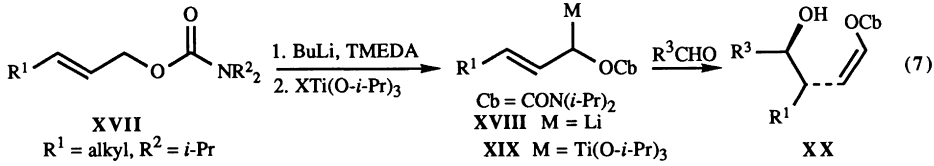
(6)

10 R = TBS
15 R = Bn

13 R = TBS
16 R = Bn

8 R = TBS
17 R = Bn

Although the foregoing results showed promise, we temporarily turned our attention from allylstannane chemistry to investigate an ongoing parallel strategy utilizing condensations of α-(alkoxy)allyl titanium reagents, as reported by Hoppe and co-workers, to construct a precursor such as **XI**(Figure 2).[23] Hoppe found that allylic carbamates **XVII** can be lithiated with n-BuLi and then treated with $Ti(O\textit{i}\text{-}Pr)_3$ to afford transient allyl Ti species **XIX** which react *in situ* with aldehydes to afford mainly anti products **XX** (Eq. 7).



(7)

XVII
R^1 = alkyl, R^2 = *i*-Pr

Cb = $CON(\textit{i}\text{-}Pr)_2$
XVIII M = Li
XIX M = $Ti(O\text{-}\textit{i}\text{-}Pr)_3$

XX

In view of the conditions required to obtain the allyl titanium intermediate **XIX**, we felt that intramolecular applications of the Hoppe reaction would not succeed. We therefore decided to utilize Hoppe's allyl titanium methodology to couple fragment **XXI** with **XIII** and carry out the ensuing ring closure by intramolecular Horner-Emmons condensation. The known *anti* diastereoselectivity of the Hoppe addition made anisomelic acid (**IV**) the ideal synthetic target. Our approach is illustrated in Figure 3. The synthesis was achieved according to plan as shown in Scheme 1.[24] Not surprisingly, the key cyclization step **22**→**23**, the first of its kind for cembrane synthesis, was found to be concentration dependent. At 0.004 *M* as much as 27% of a cyclic dimer (28-membered ring!) was formed in addition to 42% of the desired product **23**. Under optimized conditions **23** could be obtained in 71% yield.

Interestingly, the cyclization led to a 9:1 mixture of conjugated esters favoring the (*Z*)-isomer **23**. The analogous intermolecular Horner-Emmons condensation gave mainly the (*E*)-product by an 85:15 preference.[25] Evidently conformational factors exert a major

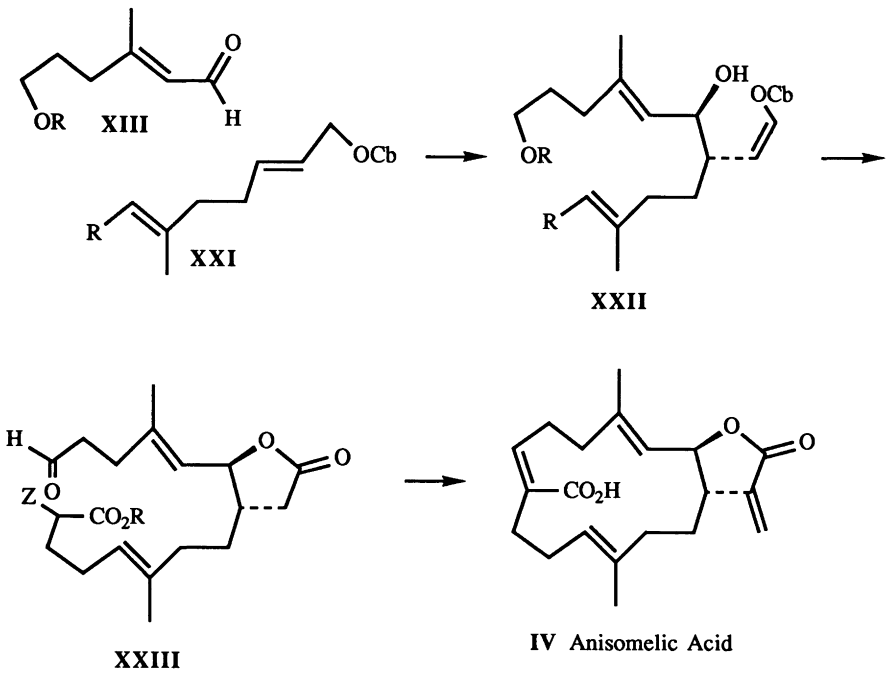
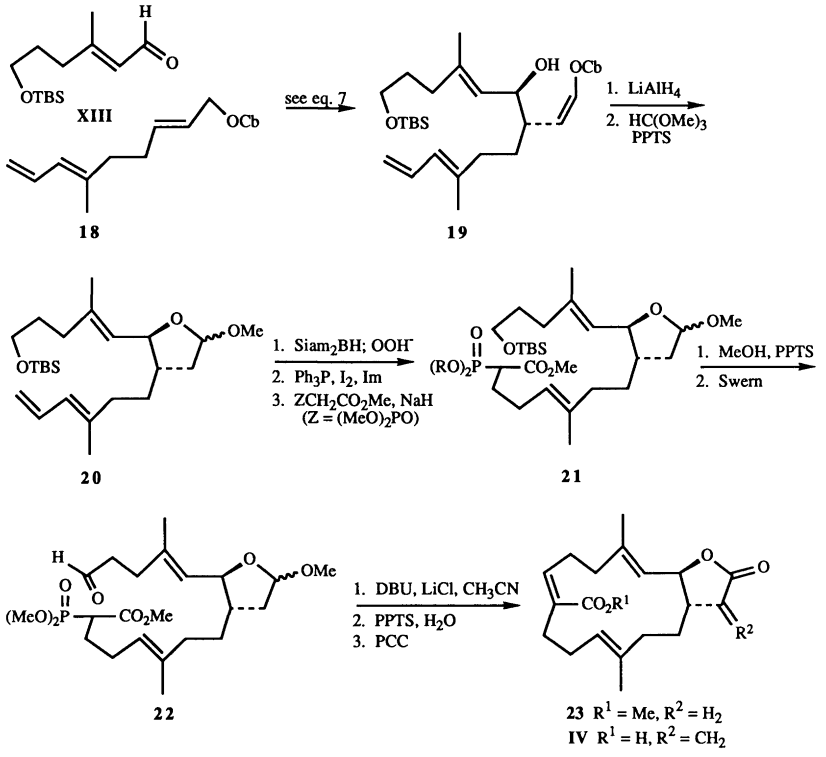


FIG. 3. Synthetic plan for anisomelic acid (**IV**).



SCHEME 1. Total synthesis of (±)-anisomelic acid.

influence on the stereochemistry of the condensation. This turns out to be an important general phenomenon but, because of current limitations in transition state modeling, it is one that is difficult to predict. We shall encounter other examples as our story proceeds.

III. α-(Alkoxy)allyl Stannanes—Efficient S_E' Partners in Cyclizations Leading to Cembranoids

The foregoing synthesis, though relatively efficient and straightforward, suffers from a number of drawbacks as a general strategy. Foremost, the Horner-Emmons cyclization does not readily accommodate the vast majority of cembranolide natural products with a C_8-CH_3 substituent. Furthermore, the route is not readily amenable to the synthesis of optically active cembranes. As a possible solution to both problems we turned to a modified version of our

initial plan in which cyclization would be effected with an α-(alkoxy)allyl stannane (Figure 4).

This plan offers several important advantages over our initial one. Foremost, it opens up the possibility for asymmetric synthesis by virtue of the stereogenic (starred) α-(alkoxy) center in the stannane precursor **XXIV** or **XXVI**. In addition, the oxidation state of the enol ether side chain is more closely matched to that of the eventual lactone target.

α-Hydroxy stannanes are readily prepared by the method of Still.[26] Thomas was able to resolve the hydroxy stannane derived from crotonaldehyde by separation of the diastereomeric *O*-(menthyl)oxymethyl ethers. He utilized these stannanes in highly stereoselective thermal additions to aldehydes leading to δ-(alkoxy)homoallylic alcohols (Eq. 8).[27] However, such additions had not been attempted under Lewis acid catalysis. Accordingly, we began our investigations with some model studies.[28]

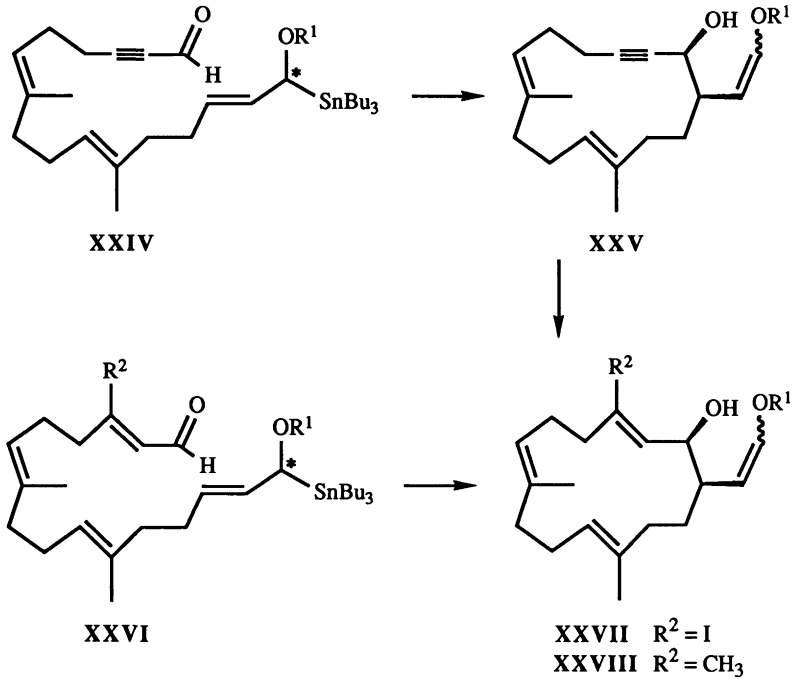
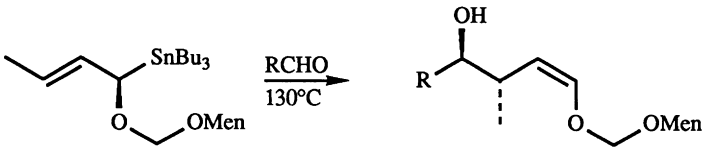


FIG. 4. Cembranolide synthesis by intramolecular S_E' addition of α-(alkoxy)allyl stannanes to aldehydes.

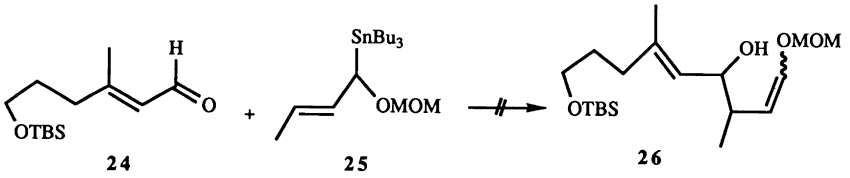


(8)

XXX Men = (-)-menthyl **XXXI**

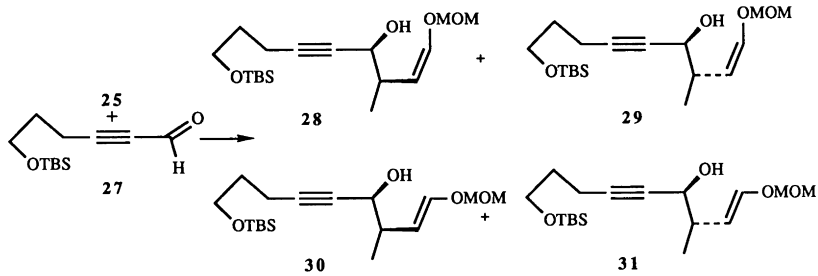
a R = Ph (70-80%)
b R = c-C_6H_{11} (80%)
c R = PhCH=CH (68%)

Addition of the racemic α-(alkoxy)crotyl stannane **25** to enal **24** was not successful under thermal or Lewis acid conditions. In the former case prolonged heating caused decomposition of the reactants. With $BF_3 \cdot OEt_2$, starting aldehyde was recovered after extended treatment at -78 to -30°C while higher temperatures caused decomposition (Eq. 9). Recalling our earlier experience with allyl stannane



24 **25** **26** (9)

2, we carried out the same reactions on acetylenic aldehyde **27**. Both additions were successfully achieved. The thermal reaction, complete within 5 minutes, gave a 1 : 1 mixture of syn and anti diastereomers **28** and **29** (Eq. 10). The BF_3 reaction was also facile. Addition took place



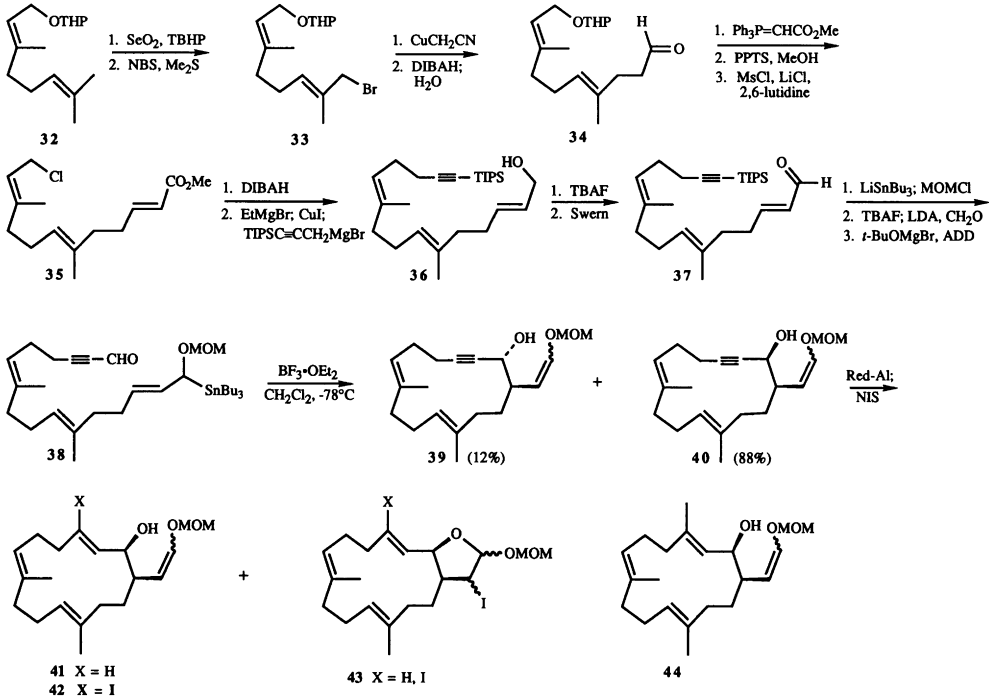
(10)

Conditions	28	29	30	31	syn:anti
140°C, 5 min	45%	55%			45:55
$BF_3 \cdot OEt_2$, CH_2Cl_2, -78°C, 1 h	35%	15%	35%	15%	70:30

at −78° within 1 hour leading to the four isomeric products **28–31** in high yield.

Although the ease of the foregoing additions to ynal **27** was highly encouraging, the poor stereoselectivity was of some concern. However, we felt that conformational factors would play the major role in controlling the stereochemistry of the intramolecular addition, as was the case with the Horner-Emmons cyclization (Scheme 1). We therefore set this concern aside and proceeded to the next stage of our investigation.

An appropriate cyclization precursor was prepared by Brad DeHoff and postdoctoral collaborator Stephen Crooks, as shown in Scheme 2, starting from the readily available tetrahydropyranyl (THP) ether of geraniol (**32**).[28] Highly selective allylic oxidation followed by bromide formation, cyanomethylcopper[29] homologation and nitrile reduction led to aldehyde **34**. Horner-Emmons condensation, then THP



SCHEME 2. Synthesis of the cembrane skeleton by intramolecular S_E' addition of an α-(alkoxy)allyl stannane to an ynal.

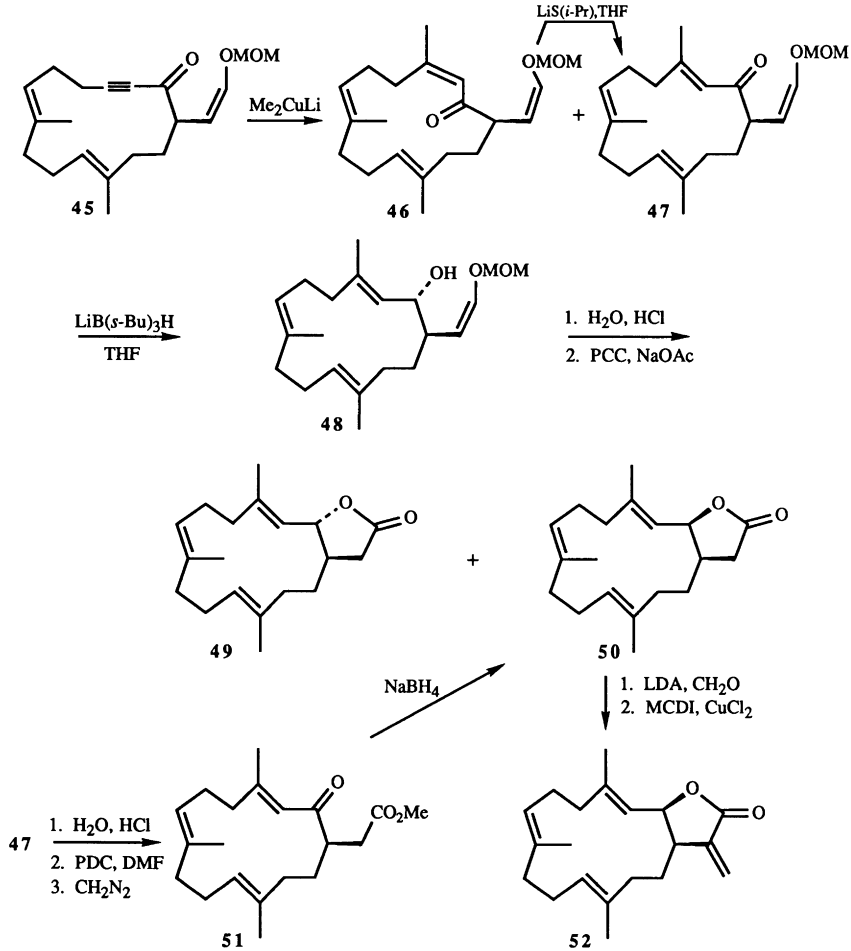
ether cleavage, and allylic chloride formation afforded **35** which was reduced and coupled as the magnesium alkoxide with the triisopropylsilyl (TIPS) protected propargylmagnesio cuprate to give the alcohol **36**. The TIPS grouping sterically prevents S_N' coupling at the propargylic triple bond.[30] Significant amounts of allenic byproducts were formed when the unprotected propargylic cuprate was used in this step.

Desilylation and oxidation led to aldehyde **37** which was readily converted to the alcohol precursor of allyl stannane aldehyde **38**. However, oxidation of that alcohol proved quite problematical. Cr(VI) reagents caused complete decomposition of the stannane moiety and Swern oxidation proceeded in low yield. Denmark[31] found the Mukaiyama protocol employing 1,1′-(azodicarbonyl)dipiperidine (ADD)[32] to be effective for oxidations of alcohols containing allylic stannane groupings. This methodology served admirably for the production of aldehyde **38** (81% yield). Cyclization of this ynal was readily effected by $BF_3 \cdot OEt_2$ at −78°C to give an 88 : 12 mixture of racemic syn and anti alcohols **40** and **39** in 88% yield. This cyclization is one of the most efficient yet reported for cembranoid systems.[13]

IV. Elaboration of the Cembranoid System—Synthesis of a Racemic Cembranolide

At this point our goal seemed assured as we had only to apply the hydroalanation–iodination–methylation sequence,[33] as in our model system (Eq. 6), to reach the cembrane carbon skeleton and then perform the straightforward conversion of the δ-(alkoxy)homoallylic alcohol array to a fused γ-lactone. Unfortunately, we underestimated the nucleophilic reactivity of the enol ether double bond. Hydroalanation of the alkyne proceeded readily, as evidenced by the conversion of propargylic alcohol **40** to the (*E*)-allylic alcohol **41** upon treatment with Red-Al® followed by aqueous quench. However, iodination of the intermediate alanate with I_2 or N-iodosuccinimide (NIS) gave the vinyl iodide **42** in only 15% yield. A mixture of products **43** arising from iodoetherification of the enol ether double bond accounted for the remainder of the material. Moreover, treatment of the purified vinyl iodide **42** with Me_2CuLi gave none of the desired methylated product **44** even with a tenfold excess of cuprate.

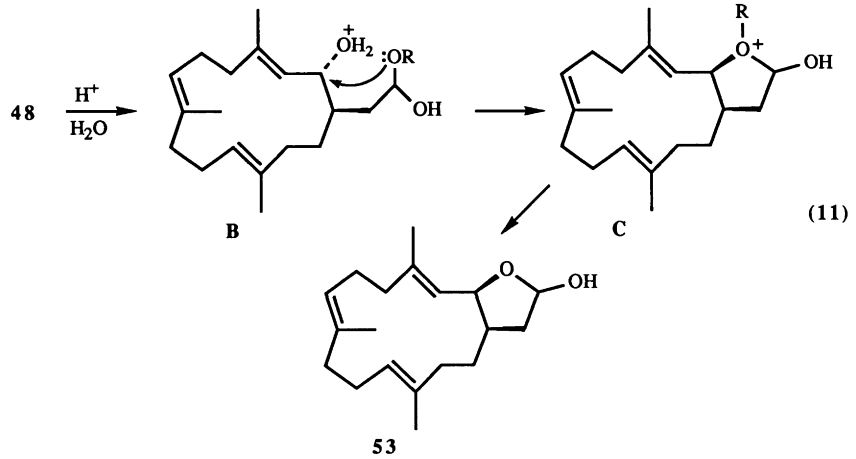
The apparent unreactivity of iodide **42** forced us to devise an alternative means for methylation of alkyne **40**. It also gave us an opportunity to examine conformationally directed reactions in macrocarbocyclics, one of the initial goals of our cembrane program. To that end, the mixture of *syn* and *anti* alcohols **40** and **39** was oxidized to ketone **45**. Addition of Me_2CuLi afforded a nearly 1 : 1 mixture of (*Z*) and (*E*) 1,4-adducts **46** and **47** (Scheme 3).[34] Molecular mechanics calculations indicated that the (*E*) isomer **47** should be of lower energy.[14] In fact, equilibration of the mixture with



SCHEME 3. Final methylation-reduction sequence leading to (±)-cembranolide **52**.

LiS-*i*Pr in THF afforded the (*E*) isomer **47** exclusively. Reduction of ketone **47** with L-Selectride gave a single diastereomeric alcohol **48**. Molecular mechanics calculations show that the local environment of the ketonic grouping in **47** is similar for the major low energy conformers and conducive to stereoselective additions of nucleophiles.

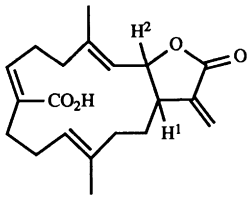
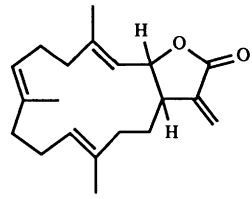
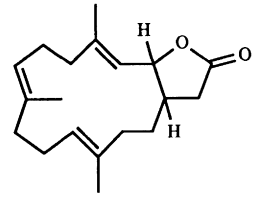
At the threshold of our objective, we were once again diverted by a subtle unforeseen neighboring group effect. Thus, acidic hydrolysis of the enol ether **48** and subsequent oxidation of the intermediate lactols afforded varying mixtures of *trans* and *cis* lactones **49** and **50** even though the starting alcohol **48** was stereochemically homogeneous. Evidently, the allylic alcohol, or the derived lactol, is prone to solvolytic dissociation with possible participation by a side chain oxygen substituent (Eq. 11).



(11)

In order to avoid this unwanted epimerization, we effected enol ether hydrolysis at the ketone stage. Subsequent oxidation of the resulting keto aldehyde and esterification of the derived acid with CH_2N_2 gave the keto ester **51**. Reduction with $NaBH_4$ was stereoselective producing a 9 : 1 mixture of the *cis* and *trans*-lactones **50** and **49** directly. Stereochemistry was readily assigned from the characteristic chemical shift and J values of the carbinyl protons (Table I). Interestingly, the reductions of ketones **47** and **51** show opposite stereoselectivity. This unexpected result must reflect subtle conformational differences between the two as reduction of ketone **47** with $NaBH_4$ afforded a 1 : 1 mixture of epimeric alcohols.

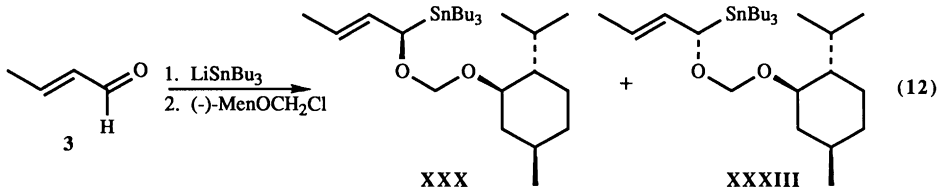
TABLE I
δH^2 ($J_{2,1}$) FOR FUSED CEMBRANE LACTONES.

	 V/IV	 VII/XXXII	 50/49
cis	5.44 (7.5)	5.39 (7.5)	5.19 (7.0)
trans	4.86 (4.1)	4.86 (3.5)	4.70 (2.0)

Lactone **50** was hydroxymethylated by treatment with lithium diisopropylamide (LDA) and formaldehyde. Dehydration of the derived hydroxymethyl lactone was effected with the water soluble diimide 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (MCDI),[35] affording the racemic lactone **52**. Spectroscopic comparison of racemic **52** with the optically active natural product **VII** confirmed their identity.

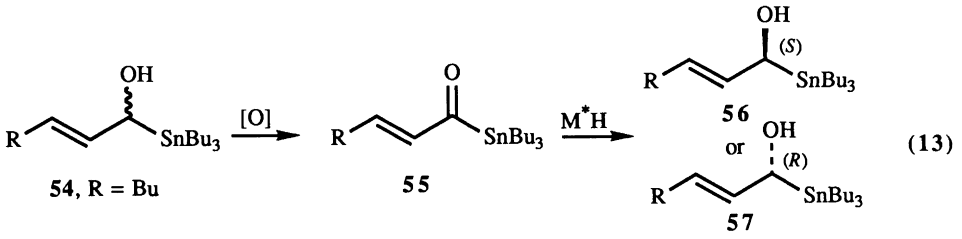
V. Optically Active α-(Alkoxy)allyl Stannanes—Preparation and S_E' Chemistry

Although the foregoing synthesis suffered from a number of shortcomings, it showed the cyclization methodology to be highly efficient and stereoselective. Accordingly with the help of postdoctoral associate Benjamin (Wei) Gung, we turned our attention to the preparation of nonracemic α-(alkoxy)allyl stannanes hoping to synthesize optically active cembranolides. As previously noted, Thomas had prepared the optically active α-(menthyloxy)crotyl stannane **XXX** by etherification of the α-(hydroxy)allyl stannane with (−)-(menthyloxy)methyl chloride and separation of the diastereomeric ethers by careful column chromatography (Eq. 12).[27] We examined this approach with several alkyl homologs of **XXX** but were unable to separate the diastereomeric (−)-(menthyloxy)methyl ethers. We then decided to explore a route to enantioenriched α-hydroxy stannanes by asymmetric synthesis, thus bypassing an intrinsically inefficient optical resolution.



(12)

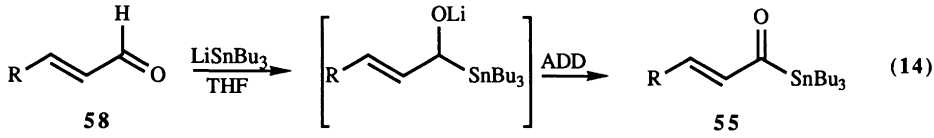
The preparation of optically active alcohols by reduction of ketones with chiral hydride reagents is well known.[36] Furthermore, a selection of such reagents is available for the synthesis of both (*S*) and (*R*) alcohols. It therefore seemed reasonable to apply this methodology to an acyl stannane such as **55** (Eq. 13).



(13)

Our first task was to develop a general route to acyl stannanes. These compounds were virtually unknown at the onset of our work and published routes to the few examples were not well suited to our purpose.[37] A seemingly straightforward but previously unexplored approach through oxidation of readily available α-hydroxy stannanes such as **54**, was appealing in its simplicity. However, the instability of α-hydroxy stannanes to acid and base and the lability of the acyl stannane products to further oxidation caused complications. A number of the more common oxidizing agents for alcohols were examined but none was suitable. Recalling our problems with oxidation of the (alkoxy)allyl stannane alcohol precursor of aldehyde **38**, we turned to the Mukaiyama reagent *t*-BuOMgBr–ADD.[32] The results were highly promising. We eventually developed a one-step protocol in which the lithio (alkoxy)allyl stannane adduct was directly treated with ADD thereby circumventing isolation of the unstable hydroxy stannane intermediate (Eq. 14).

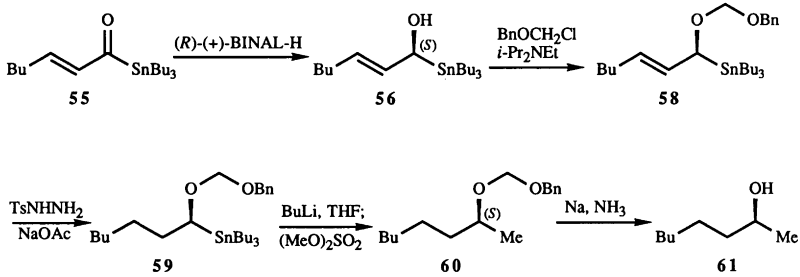
Reduction of the acyl stannane **55** was readily effected with Noyori's (*S*) and (*R*)-BINAL-H reagents.[38] In each case hydroxy



(14)

stannane **56** or **57** of >90% ee was obtained. The configuration of these α-hydroxy stannanes was surmised from the characteristic chemical shift differences of the vinylic protons in the ^{1}H NMR spectra of the (*S*)-α-(methoxy)phenylacetic ester derivatives.[39] In addition, the (*S*)-isomer **56** was converted to (*S*)-2-octanol (**61**) of high enantiomeric excess (ee) along the lines of Thomas by the sequence outlined in Scheme 4.[27] It is well established that α-(alkoxy)alkyl stannanes can be lithiated with retention of configuration and the derived lithio species are configurationally stable.[40]

We found that reduction of acyl stannane **55** with (*R*)-(+)-BINAL-H affords the (*S*)-carbinol **56**. This outcome was contrary to prediction based on Noyori's findings that enones are converted to (*R*)-carbinols by the (*R*) reagent.[38] The disparity can be attributed to chelation between the Bu_3Sn and alkoxy ligand of the BINAL-H reagent in the transition state **E** as illustrated in Figure 5. Noyori postulates that, for vinylic ketones, transition state **D** with an axial R^2 and an equatorial vinyl group is favored over the epimeric axial vinyl/equatorial R^2 arrangement because of electronic repulsion between an axial vinyl grouping and the unshared electron pair on the BINAL oxygen in the latter. The alternative (flipped) chair with axial R^2/equatorial vinyl suffers from steric interactions between R^2 and one of the napthalene rings of the BINAL ligand. In our case, transi-



SCHEME 4. Correlation of α-hydroxy stannane **56** with (*S*)-(+)-2-octanol (**61**).

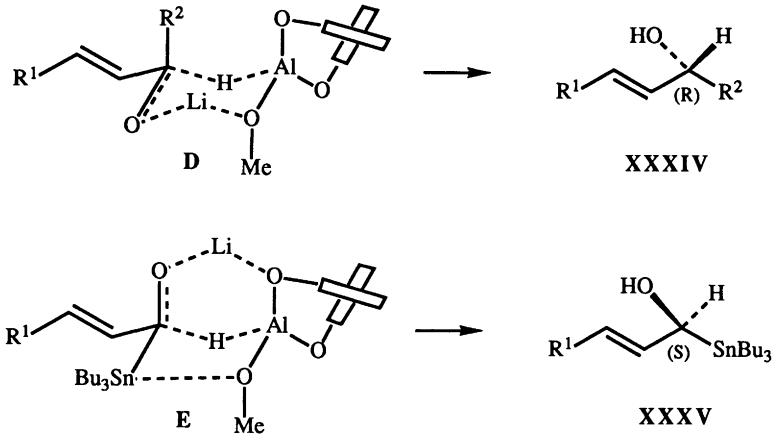
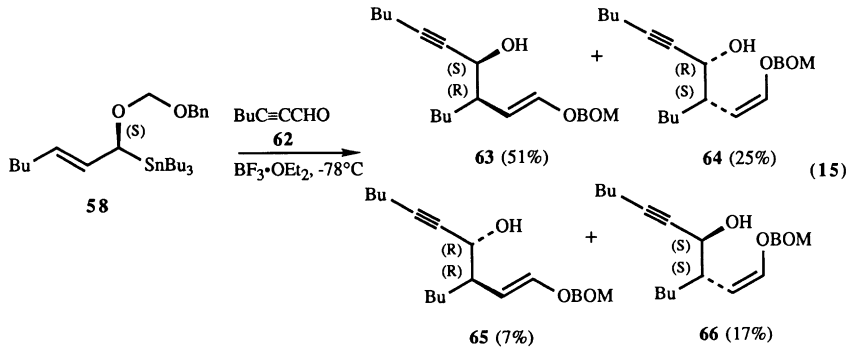


FIG. 5. Transition states for the reduction of unsaturated ketones and acylstannanes with (*R*)-(+)-BINAL-H.

tion state **E** enables the electropositive Sn to associate with the basic OMe oxygen.

Addition of the (*S*)-α-(benzyloxy)methoxy allylic stannane **58** to the model aldehyde 2-heptynal (**62**) afforded four products **63–66** in 88% yield (Eq. 15). In each case the relationship between the enol ether geometry and the allylic sp^3 stereocenter was consistent with exclusive *anti* S_E' addition of the allylstannane to the aldehyde, as illustrated in Figure 6 for the adduct **64**.[41] This finding together with our previous cyclization result virtually assured a successful outcome for our planned synthesis of enantioenriched cembranoids.



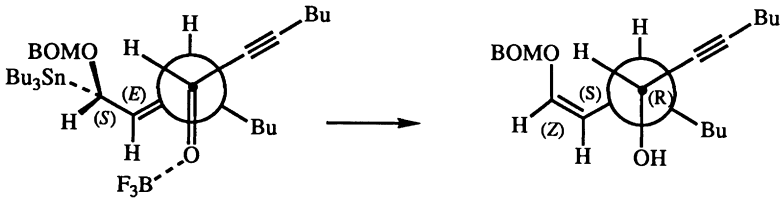
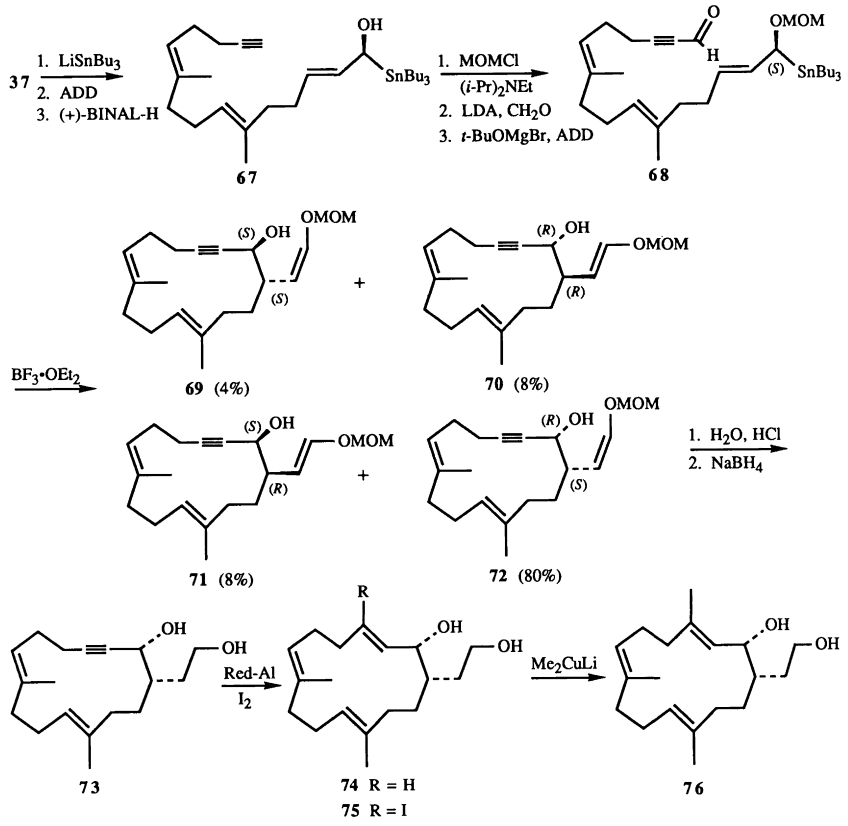


FIG. 6. Anti S_E' transition state for addition of (*S*)-α-(alkoxy)allyl stannane **58** to 2-heptynal (**62**).

VI. A Stereorational and Highly Enantioselective Cembranolide Synthesis

Cyclization of the racemic α-(alkoxy)allyl stannane ynal **38** afforded the *cis* (*Z*) isomer **40** (*Z* enol ether) as the major product (Scheme 2). Thus, following an anti S_E' pathway, the (*S*) enantiomer of **58** would expectedly lead to the (1*S*, 2*R*) isomer corresponding to **64** as the major cyclization product. The absolute configuration of our target, the unnamed cembranolide **VII**, had not been established but considering its genesis from South Pacific soft coral we suspected it to be (1*S*).[4] We therefore reduced the acyl stannane obtained from aldehyde **37** with (*R*)-(+)-BINAL-H to secure the (*S*) α-(hydroxy)allyl stannane **67** (Scheme 5). The methyloxymethyl (MOM) ether derivative **68** readily cyclized upon treatment with $BF_3 \cdot OEt_2$ at −78°C to a mixture of four products **69–72**. These could be separated by careful column chromatography and analyzed for ee and absolute configuration by means of the ^1H NMR spectra of the *O*-methyl mandelates. As expected, the double bond geometry and allylic sp^3 configuration of these products show the same relationship as those of intermolecular addition (Eq. 15), consistent with an anti S_E' process. However, the ratios of products are significantly different. Thus, as previously noted, conformational constraints imposed by the connecting carbon chain profoundly influence the preferred transition state geometry. However, these constraints do not alter stereoelectronic preferences.

In our previous synthesis of the racemic cembranolide **52** ((±)-**VII**), we converted the cyclization products to the ynone **45** prior to introduction of the C_4 methyl substituent by 1,4-addition (Scheme 3). In the present case we wished to preserve both of the stereocenters produced in the cyclization. We therefore elected to re-examine the Corey hydroalanation-iodination-methylation sequence for introduc-



SCHEME 5. Stereoselective synthesis of cembranolide precursor **76** by S_E' cyclization of the (*S*)-α-(alkoxy)allyl stannane ynal **68**.

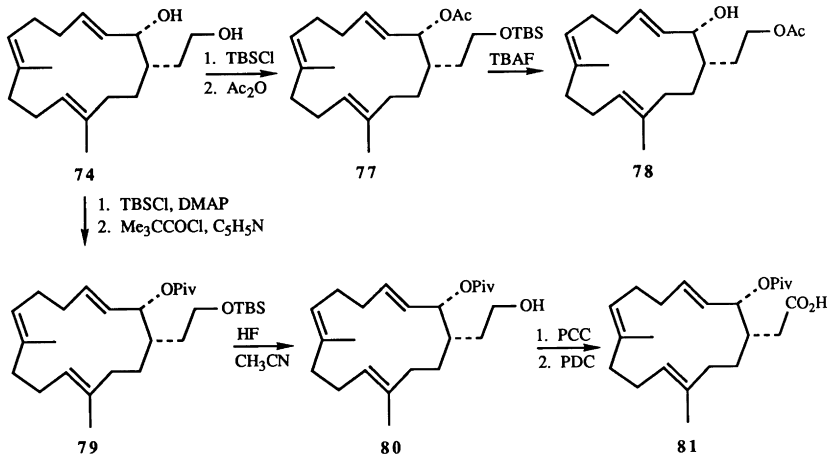
tion of this substituent.[33] To avoid the disastrous iodoetherification side reaction, we converted enol ether **72** to diol **73** by hydrolysis and reduction. Diol **73** was smoothly transformed to a 7 : 1 mixture of vinyl iodide **75** and protonolysis product **74** in 80% yield. Treatment of the former with Me_2CuLi afforded the methylated product **76** in 85% yield. This reaction was significantly slower than its acyclic counterpart (Eq. 6). However, in view of our failure to methylate iodide **42**, we were pleased with the outcome.

Preliminary investigations on the conversion of diol **76** to the required γ-lactone were carried out on the protonolysis product **74** as a model system. Attempts to effect this conversion in one step by

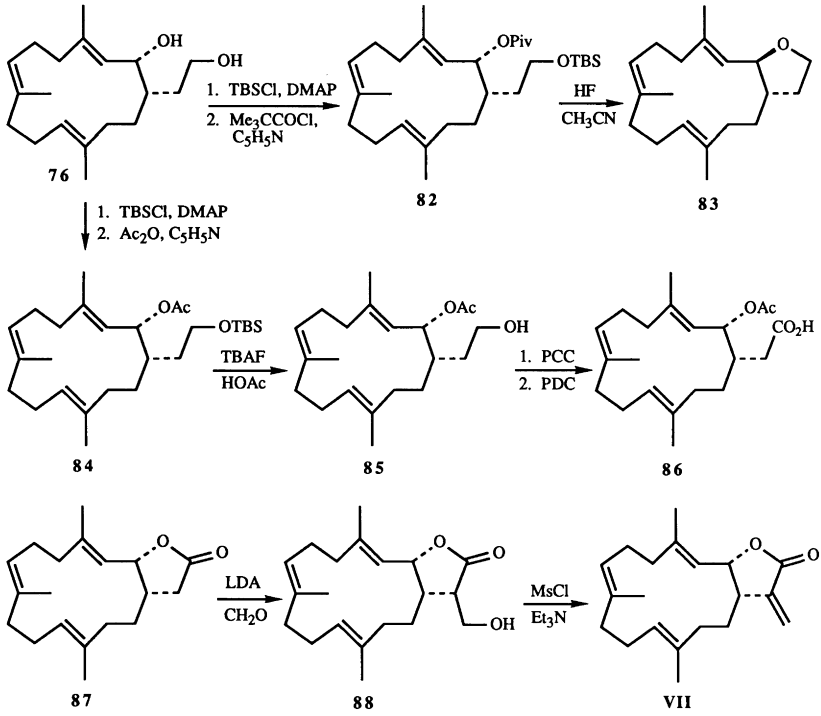
selective oxidation with various oxidizing agents were unsuccessful. We therefore explored a protecting group approach (Scheme 6).

Selective silylation followed by acetylation afforded the t-butyldimethylsilyl (TBS) ether acetate **77**. Removal of the TBS protecting group with tetra-n-butyl ammonium fluoride (TBAF) unexpectedly gave the primary acetate **78**. Apparently the basic desilylation conditions are conducive to transacetylation. To avoid this unwelcome complication we employed the less reactive pivalate derivative **79** and effected desilylation with HF. The desired primary alcohol **80** was thereby secured in high yield. Two stage oxidation, first with pyridinium chlorochromate (PCC) then pyridinium dichromate (PDC), gave the carboxylic acid **81**.

The foregoing sequence was next applied to diol **76** (Scheme 7). However, cleavage of the TBS ether **82**, the methyl homologue of **79**, with HF–CH_3CN led not to the expected alcohol but afforded the fused tetrahydrofuran **83** instead. This product presumably arises by an assisted S_N' solvolysis of pivalate **82** (*cf.* **B** → **C**, Eq. 11). The contrasting behavior of the close analogs **79** *vs* **82** can be attributed to enhanced inductive stabilization of the polarized transition state for the S_N' reaction by the methyl substituent of **82** (*cf.* **A**). The problem was easily circumvented. In fact, it was unnecessary to employ the pivalate grouping. The protected acetate **84** underwent TBS cleavage without transacetylation or furan formation upon treatment with TBAF in the presence of acetic acid. The alcohol **85** was subjected to



SCHEME 6. Model studies for side chain oxidation.



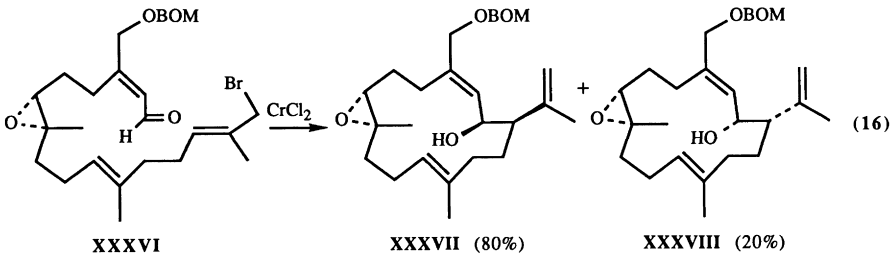
SCHEME 7. Conversion of diol **76** to the unnamed cembranolide **VII**.

a two-stage oxidation to give acid **86** in 60% yield. Acetate cleavage and lactonization were then carried out without isolation of the intermediate hydroxy acid. The final steps of the synthesis involved hydroxymethylation of the lactone **87** and dehydration *via* the mesylate derivative. The synthetic lactone **VII** showed a rotation of +78° in close agreement with the value reported for the natural product. Thus, the absolute configuration is established as shown.

VII. Extensions, Disappointments, and Pleasant Surprises

A. Remote Diastereocontrol

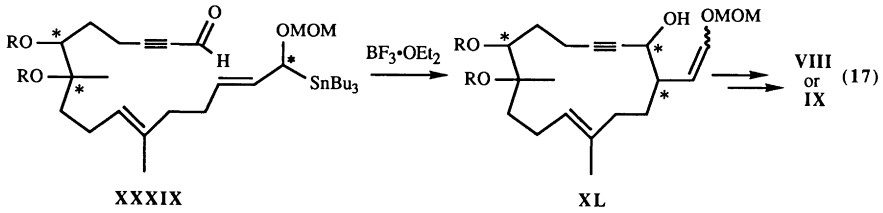
In 1983 Still and Mobilio reported that the racemic epoxy enal **XXXVI** cyclizes upon treatment with $CrCl_2$ to an 80:20 mixture of diastereomers **XXXVII** and **XXXVIII** (Eq. 16).[17] This observation suggests that remote substituents can exert significant influence on



(16)

XXXVI XXXVII (80%) XXXVIII (20%)

diastereomeric transition states in such cyclizations. With a view toward an eventual synthesis of the unnamed epoxy cembranolides **VIII** and **IX**, graduate student Jay Markwalder set out to examine an α-(alkoxy)allyl stannane version of the Still-Mobilio cyclization (Eq. 17). Initially we were concerned that the $BF_3 \cdot OEt_2$ catalyst might promote unwanted reactions of the epoxide so we formulated our

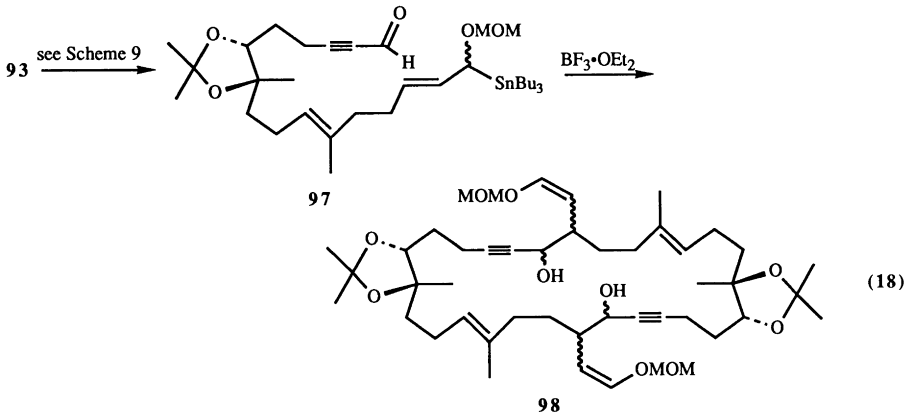


(17)

XXXIX XL

first plan around the acetonide **97**. This intermediate was prepared from diol **93** along the lines shown in Scheme 8 and Scheme 9.[42] The optically active epoxy alcohol **92** of high ee was readily secured through Sharpless kinetic resolution of allylic alcohol **90**. Coupling of this epoxy alcohol with the anion derived from allylic sulfone **96** was markedly assisted by prior formation of the bromomagnesio alkoxide.[43]

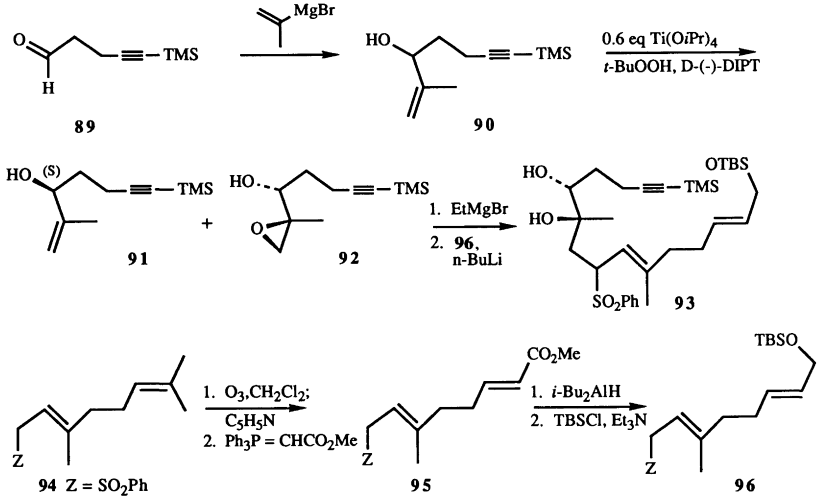
For our preliminary cyclization trials we employed a 1 : 1 mixture of diastereomeric alkoxy stannanes **97**. Treatment with $BF_3 \cdot OEt_2$ for short periods afforded a product (~50% yield) with the expected spectroscopic properties but the mass spectrum showed it to be dimeric (Eq. 18). None of the monomeric cyclic product could be



(18)

found. We speculate that conformational constraints imposed by the acetonide ring of **97** prevent favorable alignment of the aldehyde and allylstannane moieties in the cyclization transition state. Consequently, bimolecular coupling occurs preferentially. The resultant intermediate, with its greater conformational flexibility, can attain the requisite geometry for ring closure to the 28-membered cyclic product **98**. It is worth noting that a ring of this size can be so easily formed by the allylstannane methodology.

Recalling our success with the unsaturated analogue of **97** (Scheme 2, **38**→**39**) we decided to employ the geometrically similar epoxy derivatives **102** and **104** despite misgivings about epoxide

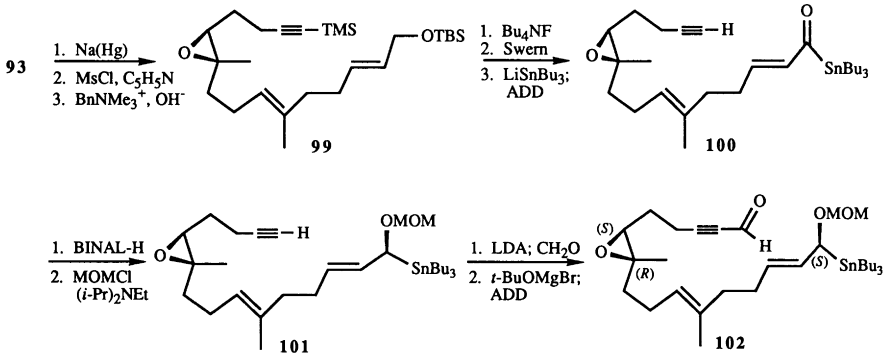


SCHEME 8. Synthesis of the diol precursor **93** to acetonide **97** and epoxide **102**.

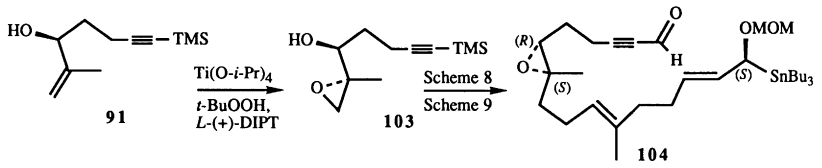
stability. Accordingly, diol **93** was desulfonylated and converted to epoxide **99** *via* the secondary mesylate derivative (Scheme 9). Desilylation followed by Swern oxidation, addition of Bu_3SnLi and *in situ* oxidation of the hydroxy stannane adduct with ADD afforded the keto stannane **100**. Conversion to the (*S*)-α-(alkoxy)allyl stannane **102** was effected as previously described for the des-epoxy analogue **68** (Scheme 5).

The diastereomeric (*R*,*S*,*S*) epoxy α-(alkoxy)allyl stannane aldehyde **104** was similarly prepared (Scheme 10) from the unepoxidized allylic alcohol **91** recovered from the Sharpless resolution of racemic **90** (Scheme 8).

We were pleased to find that both allylic stannanes **102** and **104** cyclized with retention of the epoxy function upon treatment with $BF_3 \cdot OEt_2$ at −78°C (Figure 7). As expected the two diastereomers gave rise to different ratios of *cis* products indicative of a matched and mismatched pairing of stereocenters. The *S*, *R*, *S* isomer **102** afforded a 2.3 : 1 mixture of *cis*-(*Z*) and *cis*-(*E*) products **105** and **106** in 60%



SCHEME 9. Enantioselective synthesis of the (*S*, *R*, *S*) alkoxy stannane epoxy aldehyde cyclization substrate **102**.



SCHEME 10. Enantioselective synthesis of the (*R*, *S*, *S*) alkoxy stannane epoxy aldehyde cyclization substrate **104**.

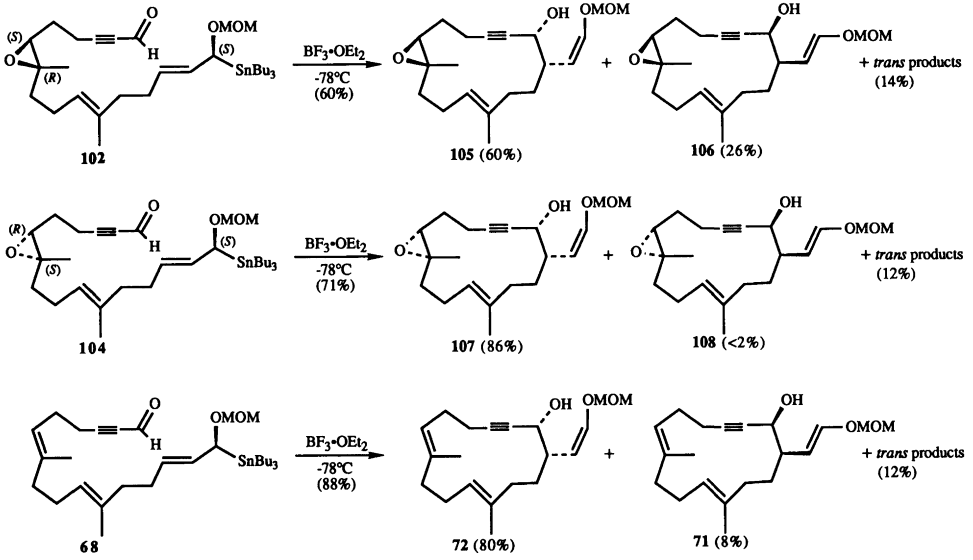


FIG. 7. Diastereodifferentiation in cyclizations of α-(alkoxy)allyl stannane aldehydes.

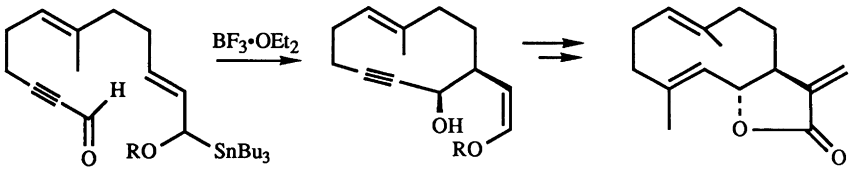
yield whereas the *R*, *S*, *S* isomer **104** cyclized to a > 40 : 1 mixture of products **107** and **108**. In comparison the unsaturated analog **68** gave the products **72** and **71** as a 10 : 1 mixture in 88% yield. In all three cases *trans* products accounted for *ca.* 12–14% of the cyclized material. The lower overall yield obtained with the matched epoxy stannane **104** *vs* the unsaturated counterpart **68** may result from Lewis-acid promoted side reactions of the epoxide grouping.

Epoxy alcohol **107** is a likely precursor for the unnamed cembranolide **IX** (Figure 1) following a sequence analogous to that employed for **VII** (Scheme 7). We have found that Mitsunobu inversion of propargylic alcohols such as **107** can be effected in high yield.[44]

B. Applications to Other Ring Sizes—An Unexpected Isomerization

The remarkable efficiency of the α-(alkoxy)allyl stannane cyclization, as applied to cembranes, encouraged our examination of other ring sizes. Historically, 10-membered rings have been the most difficult to prepare. This ring system is most commonly encountered in

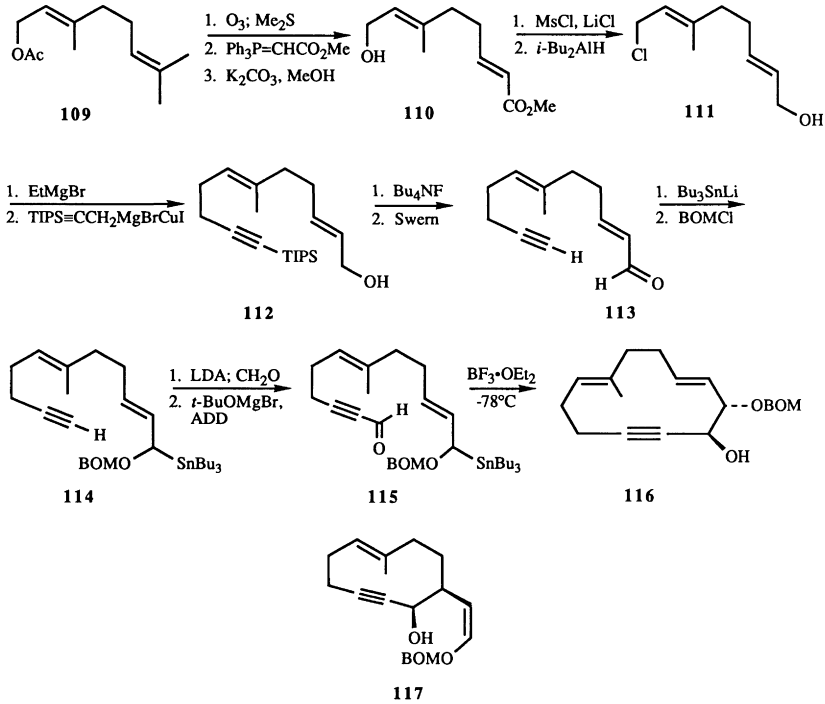
the widespread germacrane class of terpenic natural products. Post-doctoral Benjamin (Wei) Gung began our investigations into this area with a planned synthesis of costunolide **XLIII** (Eq. 19).



(19)

XLI **XLII** **XLIII**

Our synthesis of the cyclization substrate **XLI** followed a route similar to that used for our cembranolide precursors. Selective ozonolysis of geranyl acetate (**109**) followed by Wittig condensation and methanolysis afforded the hydroxy ester **110** (Scheme 11).[45] Coupling



SCHEME 11. Synthesis of a potential germacranolide precursor, alkoxy stannane aldehyde **115**, and its unexpected cyclization to the 1,2-diol derivative **116**.

of the derived chloride **111** with the TIPS propargyl cuprate led to dienyne **112**. The previous sequence of desilylation, Swern oxidation, stannylation and alkyne homologation smoothly led to the requisite stannyl alkynal **115** in racemic form.

Cyclization of aldehyde **115** proceeded slowly to give not the expected cyclodecynol **117**, but the cyclododecynol **116** in 25% yield along with unidentified decomposition products. We suspected that conformational and geometric constraints must prevent the alkoxy stannane double bond from attaining the proper alignment with the ynal carbonyl. Hence decomposition and bimolecular addition can compete with cyclization. The formation of cyclododecynol **116** suggested that 1,3-isomerization of the α-(alkoxy)allyl stannane had taken place and that the resulting intermediate was more favorably disposed toward ring closure (Figure 8). In support of this postulate we could isolate small amounts of the γ-(alkoxy)allyl stannane **118** after brief exposure of the α-isomer **115** to $BF_3 \cdot OEt_2$ at $-78°C$.

At this point we decided to examine the Co-complexed alkynal **120** as a possible cyclization substrate hoping that the bending of the linear alkyne linkage by the bridging Co atoms would place the

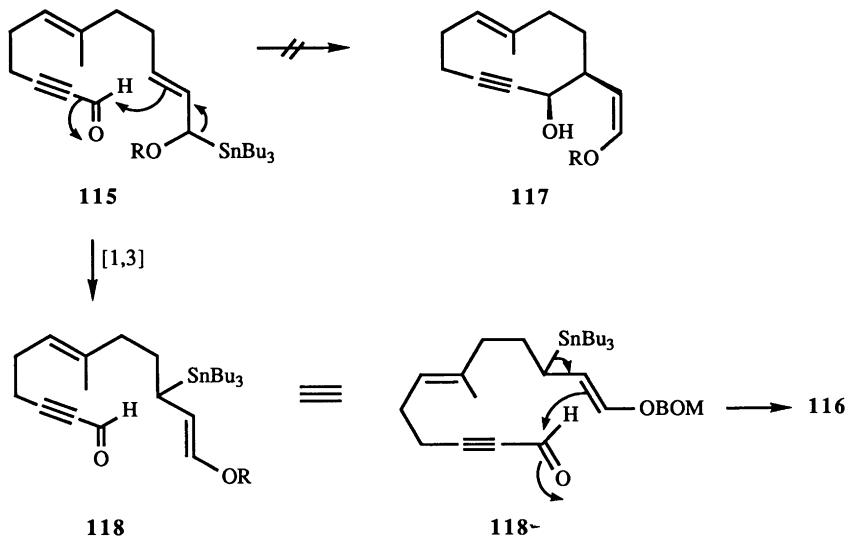
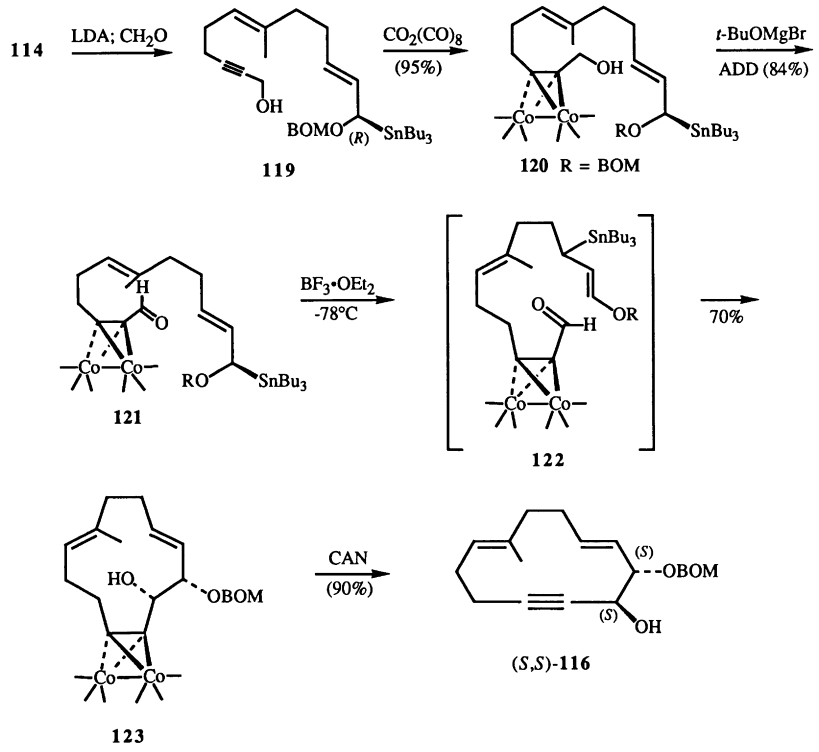


FIG. 8. Cyclization of α-(alkoxy)allyl stannane **115** to cyclododecynol **116** *via* γ-(alkoxy)allyl stannane **118**.

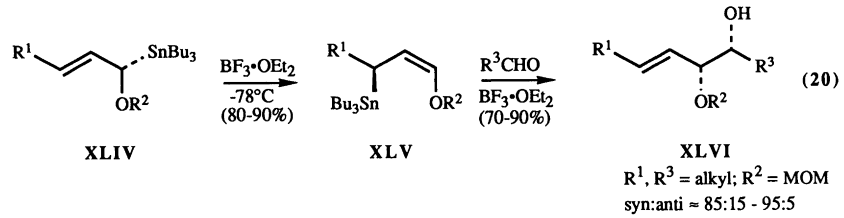


SCHEME 12. Cyclization of the $Co_2(CO)_6$ complex **120** of alkynal **115**.

carbonyl group into more favorable juxtaposition with the allylstannane double bond.[46] We were uncertain as to how readily such an intermediate could be prepared and if the aldehyde carbonyl would be sufficiently reactive to undergo addition by the weakly nucleophilic allylstannane. Both concerns proved unwarranted. The propargylic alcohol **119** afforded the complex **120** in 95% yield upon mixing with $Co_2(CO)_8$ following close literature precedent.[47] Oxidation to the aldehyde **121** proved somewhat problematical but, happily, the Mukaiyama protocol again saved the day.[32] Slow addition of aldehyde **121** to a cold solution of $BF_3 \cdot OEt_2$ in CH_2Cl_2 afforded a cyclization product in 70% yield. However, upon oxidative removal of the bridging Co moieties only the previously obtained alkynol **116** was obtained. Thus, bending the alkyne triple bond appears to improve the transition state geometry, but not sufficiently to allow 10-membered ring formation.

Interestingly, when the foregoing sequence was repeated with (*R*)-α-(alkoxy)allyl stannane **119** of 60% ee the (*S*,*S*) product **116** of 60% ee was obtained. Thus, the presumed 1,3-isomerization of **121** to **122** must be highly stereoselective, if not stereospecific.

Although it is beyond the scope of this chapter we might mention that in subsequent studies we have found the 1,3-isomerization of α-(alkoxy)allyl stannanes to be a general reaction which can be used to prepare γ-(alkoxy)allyl stannanes (Eq. 20).[48] Contrary to our expectation, the reaction proceeds by a stereospecific *intermolecular anti*



process. γ-(Alkoxy)allyl stannanes undergo S_E' additions to aldehydes affording monoprotected syn 1,2-diols with high stereoselectivity. This methodology, currently under investigation by co-workers Greg Welmaker and George Luke, has excellent potential for the synthesis of acyclic and cyclic polyols.

VIII. Summary

The impetus for the research described in this chapter was to devise an efficient route to cembranoid natural products. A major goal was to develop effective strategies for the conversion of acyclic precursors to the 14-membered cembranoid system with control of relative and absolute stereochemistry. The α-(alkoxy)allyl stannane/ynal cyclization admirably fulfills both objectives. With this methodology the cembrane ring system is assembled efficiently and two crucial stereocenters are introduced with predictable absolute stereochemistry. Once formed, the cembranolide intermediates can be modified and additional stereocenters can be introduced stereoselectively. Of equal or greater interest, the enantioenriched α-(alkoxy)allyl stannanes undergo facile stereospecific isomerization to γ-(alkoxy)allyl stannanes. These novel reagents condense with aldehydes to afford

monoprotected 1,2-diols with high stereoselectivity. Furthermore, the addition can be used to form cyclic 1,2-diol derivatives. These serendipitous findings considerably extend the scope of the methodology to include cyclic and acyclic polyol natural products.

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Chapter 10

SYNTHESIS OF A CANCER GROWTH-INHIBITING DITERPENE: SPATOL

Robert G. Salomon

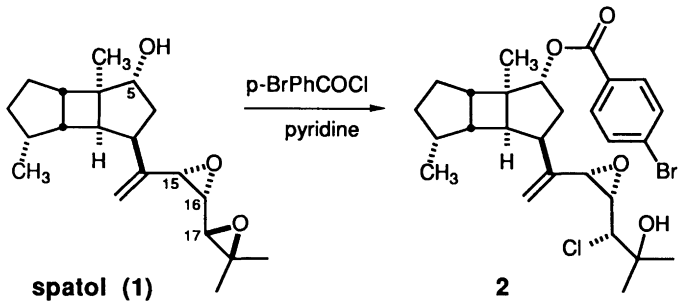
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Spatol (**1**), a structurally and functionally complex minor metabolite produced by a tropical marine alga,[1] shows potent cytotoxicity against skin and brain tumor cells, completely inhibiting cell division in human T242 melanoma and 224C astrocytoma neoplastic cell lines at 16 μg/ml. The unique allylic vicinal diepoxide in **1** constitutes by far the most challenging aspect of any synthetic approach to this target. The high electrophilicity of this functional array is evidenced by the epoxide ring opening reaction with a chloride nucleophile

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which accompanies esterification upon treatment of **1** with *p*-bromobenzoyl chloride and pyridine producing **2**.

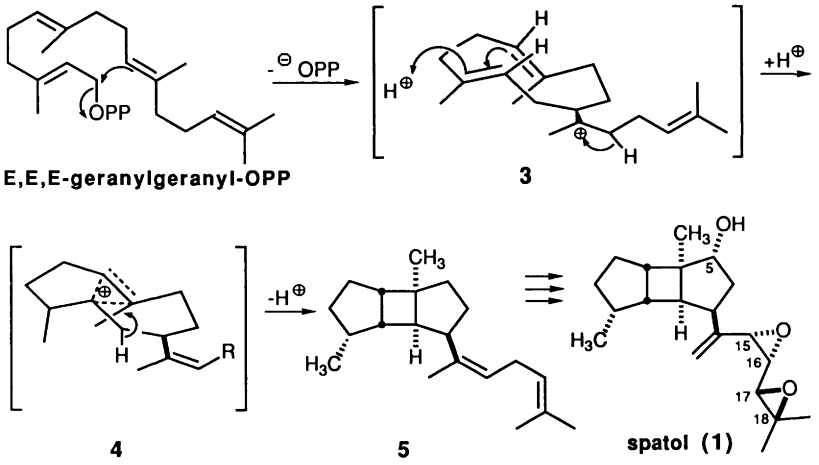


spatol (1) **2**

In the present chapter, the evolution and execution of our plan for the total synthesis of spatol will be described in the context of other strategies for achieving this same goal. As for all natural products, a successful synthetic strategy for spatol existed before any human endeavor. It is always interesting to examine Nature's strategy because an analogous approach, a biomimetic strategy, can be effective in the laboratory. A consideration of other strategies, including Nature's, can lead to a deeper appreciation of the strengths and weaknesses of a particular approach.

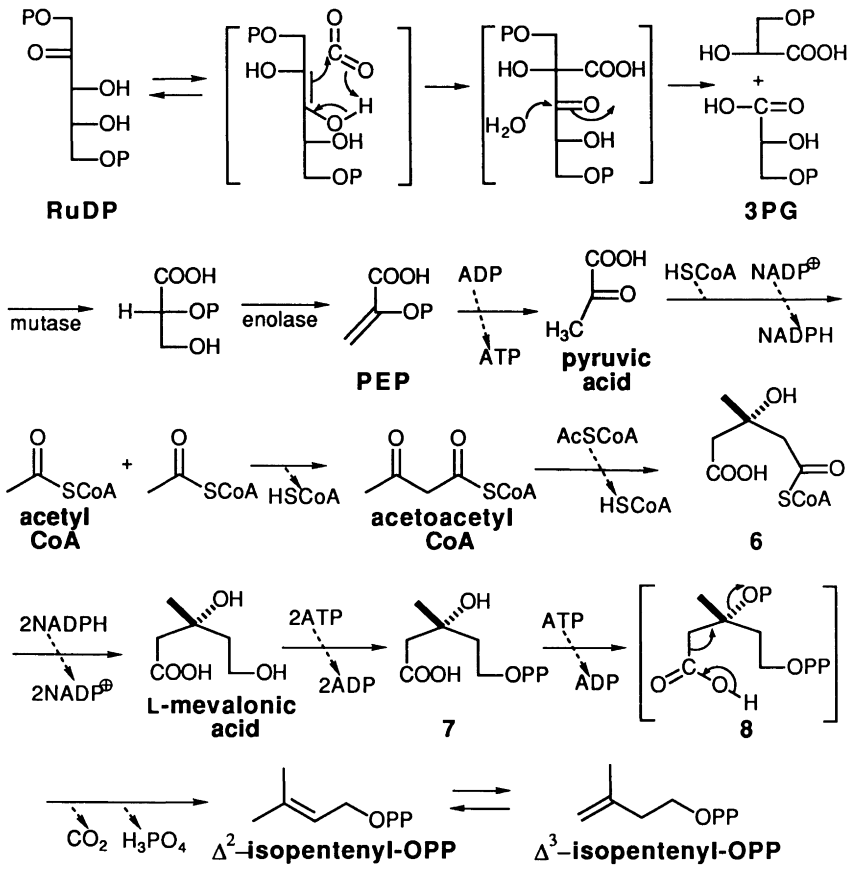
I. Nature's Strategy

Diterpenes are derived in nature from *E,E,E*-geranylgeranyl pyrophosphate or its geometrical isomers. Intramolecular electrophilic addition of the allylic pyrophosphate to the trisubstituted C=C bonds can lead to various mono- and multicyclic carbocations (e.g., **3**). Carbocationic electrophiles can also be generated by protonation of C=C bonds. A hypothetical pathway for the biosynthesis of spatol (**1**) involves protonation of a C=C bond and intramolecular electrophilic addition to produce a cyclobutane **5** by proton loss from **4**. This hypothesis derives support from the natural occurrence of **5**.[2] The oxygen functionality in spatol (**1**) is presumed to arise from oxidative metabolism of **5** by the marine organisms which produce this tricyclic diene and a wide variety of other oxygenated metabolites with the spatane carbon skeleton. Particularly remarkable is the introduction of a hydroxyl group at the 5-position. Such functionaliza-



tion at aliphatic carbon, remote from potential activating or stereodirecting functionality, is common in biosynthesis. Although not entirely unknown in chemical synthesis, it is unusual for such reactions to be employed in the total synthesis of structurally and functionally complex organic molecules.

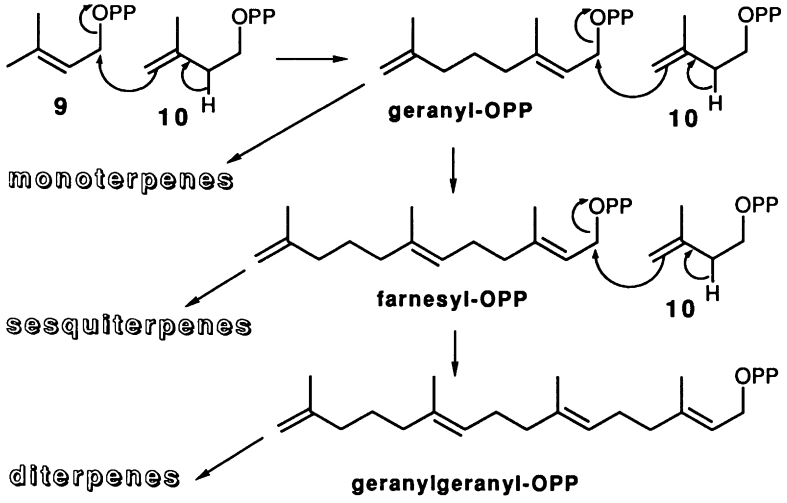
The biosynthetic strategy is not designed with a focus on avoiding chemically difficult steps or on the efficient assembly of a particular terpenoid natural product. It is focused instead on versatility in generating a vast array of $(C_5)_n$ structures from a single starting material, CO_2. From this perspective, the biosynthetic strategy is elegantly simple. Biosynthesis of a monomeric C_5 intermediate (Scheme 1) begins with the fixation of CO_2 by condensation with ribulose diphosphate (RuDP) generating two molecules of 3-phosphoglyceric acid (3PG). Through a remarkable sequence of reactions, known as the Calvin Cycle, RuDP becomes a catalyst for the reductive *trimerization of* CO_2 into 3PG. Thus, the fixation of six molecules of CO_2 by reaction with six molecules of RuDP generates 12 molecules of 3PG. But the 30 carbons contained in 10 of these molecules of 3PG are reshuffled and reduced by 10 NADPH to regenerate 6 molecules of RuDP. 3PG is generally stored as glucose which is formed reversibly by a reductive (NADPH) dimerization. Subsequent decarboxylative conversion of 3PG into a 2-carbon building block, acetyl CoA, *generates the activating (ATP) and reducing (NADPH) reagents* required in the subsequent reductive *trimerization of acetyl CoA* to produce the monomeric C_5 intermediate, Δ^2-isopentenyl



SCHEME 1

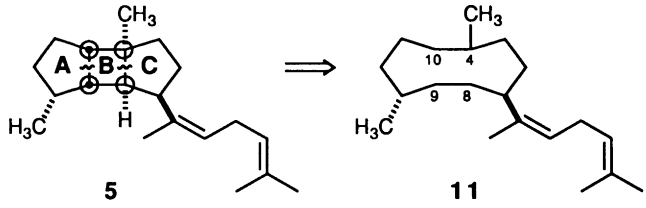
pyrophosphate (PP). Prototropic shift delivers Δ^3-isopentenyl-OPP. The acyclic precursor (*E*, *E*, *E*-geranylgeranyl-OPP) containing all the carbon atoms of spatane diterpenes is produced by *tetramerization of* Δ^2*-isopentenyl-OPP* (Scheme 2).

Thus, the biosynthetic strategy is efficient in its utilization of a single starting material (CO_2) which is oligomerized to generate a key intermediate building block 3PG which also is oligomerized to generate other building blocks, the isopentenyl pyrophosphates. These are, in turn, oligomerized to generate an acyclic C_{20} precursor containing all the carbons of spatane (and many other) diterpenes. The biosynthetic strategy is also environmentally safe since the byproducts, CO_2 and phosphate, are nontoxic and recyclable.

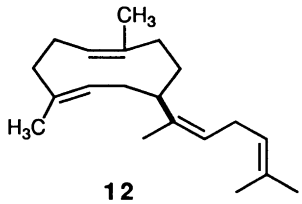


SCHEME 2

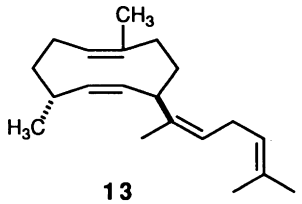
Topological analysis of the biosynthetic strategy reveals another important feature. In the topological approach to synthetic planning, attention is first directed to "an exhaustive analysis of the topological properties of the carbon network to define the range of possible precursors . . . from which the desired skeleton can be produced by the establishment of one or two connecting bonds."[3] In many cases, the most synthetically useful dislocations[4] result from removing one bond between ring-member atoms, called "common atoms", which are bonded to three or four other ring-members (but not two).[3] The tricyclo [5.3.0.$0^{2,6}$], decane nucleus of the spatane diterpenes incorporates 4 common atoms (circled in **5**), the four atoms of the B-ring. Application of the heuristic protocol of removing bonds between common atoms suggests monocyclic precursors from which the tricyclic synthetic target can be generated by the formation of bonds between two sets of common atoms, 4–8 and 9–10. In the second



stage of the topological approach, functionalized synthetic equivalents[5] of the topological synthon[6] are formulated. For the synthon **11**, one synthetic equivalent, **12**, is suggested by our biogenetic hypothesis. Another synthetic equivalent, **13**, is suggested by the possibility of an intramolecular $2\pi + 2\pi$ cycloaddition.



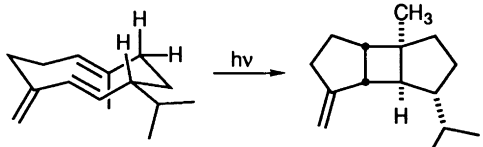
12



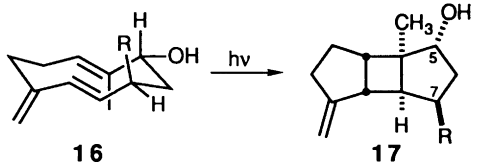
13

II. Prior Art

Prior art for the chemical synthesis of terpenoid tricyclo [5.3.0.$0^{2,6}$] decanes concerns the bourbonenes. An expeditious synthesis[7] of β-bourbonene (**15**) exploits intramolecular photocycloaddition of germacrene D (**14**) an intermediate analogous to **13**. UV evidence ($\lambda_{max} = 259$ mμ, $\epsilon = 4500$ in *n*-hexane) indicates a significant transannular interaction between the two endocyclic C=C bonds in the sesquiterpene **14**. Thus, **14** probably prefers a conformation in which the two endocyclic C=C bonds are situated parallel and face to face with each other, and the isopropyl substituent occupies the less sterically hindered equatorial configuration. Thermodynamic control assures the proper configuration at the isopropyl bearing carbon while stereoelectronic control assures the correct *cis,anti,cis* configurations



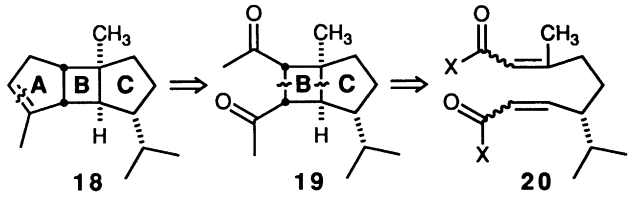
14 **15**



16 **17**

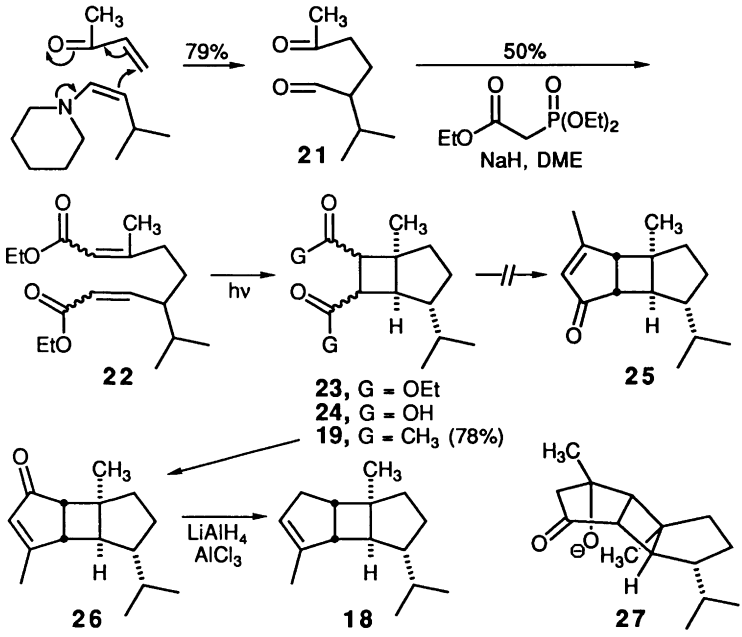
at the cyclobutane stereocenters. An analogous photocyclization to generate a precursor **17** for spatol is not favorable since a substituent R which is to become the side chain must occupy a more sterically encumbered axial position as in **16**.

Another strategy exploiting intramolecular photocycloaddition was applied by Brown[8] to the total synthesis of (±)-α-bourbonene (**18**). However, the strategy differs topologically from the **16** to **17** conversion which generates the ABC-ring system from a monocyclic precursor. In Brown's synthesis the last skeletal connection generates the A-ring on a preformed BC-ring intermediate **19** which is generated, in turn, from an acyclic precursor **20** by intramolecular $2\pi + 2\pi$ cycloaddition.



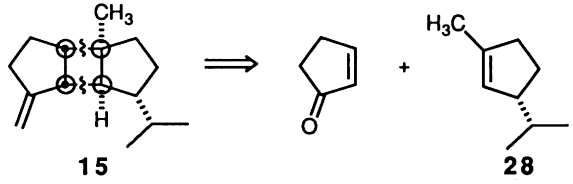
18 **19** **20**

This approach is attractive since the photobicyclization substrate **22** is readily available by Wadsworth-Emmons olefination of ketoaldehyde **21** which, in turn, is readily available by Michael condensation of the piperidine enamine of isovaleraldehyde with methyl vinyl ketone (Scheme 3). Photobicyclization of **22** occurs stereoselectively producing **23** with the isopropyl substituent in the required sterically least encumbered exo configuration. Saponification affords **24** which is transformed in good yield into diketone **19** by sequential treatment with $SOCl_2$, CH_2N_2, HCl, and KI–Zn in acetic acid. Thermodynamic control provides the correct configurations at the remaining B-ring stereocenters owing to epimerizability α to the acyl substituents and a preference for the sterically less congested cis,anti,cis arrangement. Notably, aldol condensation of **19** occurs with complete regioselectivity to afford **26**. Apparently, the alternative cyclization to **25** is disfavored by steric hindrance by the cyclobutyl methyl group which interferes with generation of the aldolate **27** required to produce **25**. The use of such a strategy to generate a precursor for spatol must anticipate inverting the configuration of a photocycloadduct analogous to **23**. Thus, for spatol, the required stereochemistry at position 7 is opposite to that favored in the photobicyclization of **22**.

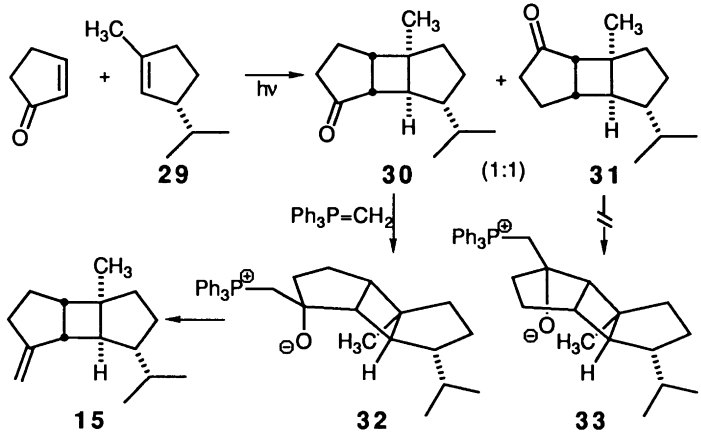


SCHEME 3

A third topologically unique strategy exploiting skeletal construction by the conjunction of two pairs of common atoms (circled) was used in White's synthesis of β-bourbonene (**15**).[9] In fact, $2\pi + 2\pi$ photocycloaddition of cyclopent-2-en-1-one with 3-isopropyl-1-methylcyclopentene (**28**) is favorably stereoselective. Owing to steric



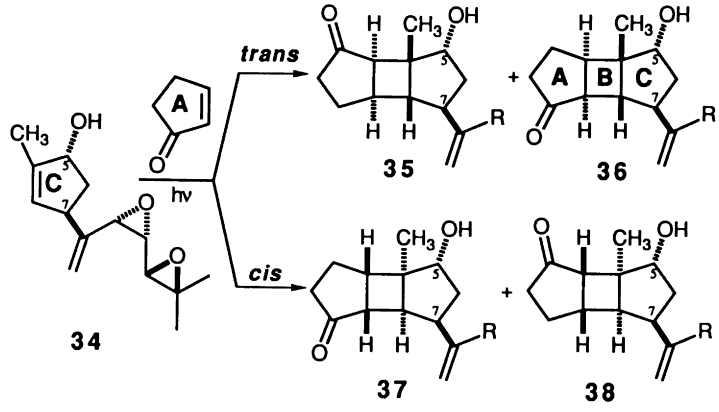
approach control, cycloaddition occurs from the face of the cyclopentene ring opposite the isopropyl substituent and with the requisite cis,anti,cis disposition of the ring fusions. Unfortunately, the cycloaddition is orientationally nonselective producing a 1 : 1 mixture of the desired ketone **30** and its structural isomer **31** (Scheme 4). While



SCHEME 4

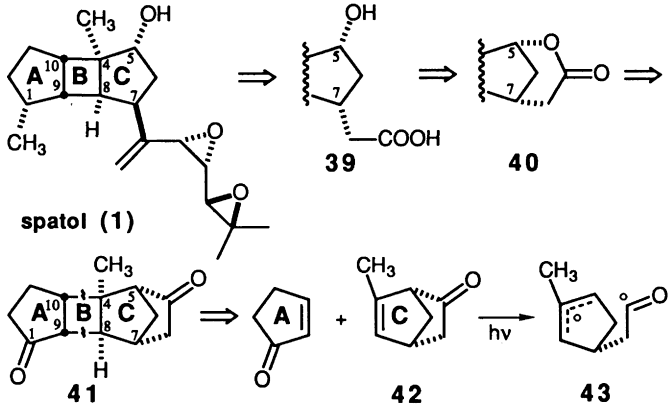
separation of such an isomeric mixture by physical means might prove a redoubtable task, a profound difference in reactivity between the carbonyl groups of **30** and **31** made separation of the mixture unnecessary. Thus, treatment of **30** with methylenetriphenylphosphorane affords β-bourbonene (**15**). On the other hand, ketone **31** is recovered unchanged after exposure to the Wittig reagent owing to steric congestion between the alkoxide oxygen and the bridgehead methyl substituent which would develop in **33** upon addition of the ylide to the carbonyl carbon of **31**.

Thus, prior art for assembling the terpenoid tricyclo [5.3.0.$0^{2,6}$] decane ring system, including the presumed biosynthesis of spatol, exploits strategic connections between pairs of common atoms located in the cyclobutane ring. Of all these strategies, a convergent[10] approach analogous to White's is particularly attractive for a total synthesis of spatol since the tricyclic nucleus is assembled from two fragments. These could be readily modified to prepare derivatives of the natural product for the structure-activity studies needed to develop medicinal applications. However, in spatol (**1**) the orientation of the allylic diepoxide side chain is *cis* to the cyclobutane in contrast with the *trans* isopropyl group in **15**. The allylic diepoxide side chain or its precursor in a cyclopentene intermediate **34** is expected to favor the wrong stereoselectivity in a photocycloaddition with cyclopent-2-en-1-one favoring **35** or **36** rather than the desired adduct **37** or its structural isomer **38**. Furthermore, none of the previous strategies



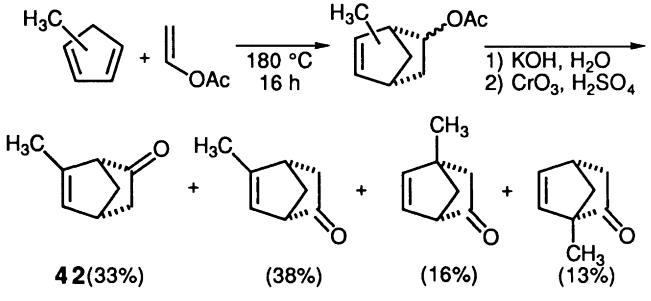
provide an obvious solution to another challenge which must be met by any plan for a synthesis of spatol's tricyclic nucleus, namely the stereocontrolled introduction of a hydroxyl substituent at the 5-position. This feature of the synthetic target captivated our attention and was the focus for our strategy.

I vividly recall the moment of inspiration. Groggy and nearly asleep, I was suddenly wide awake with a possible solution to the puzzle. How could one face of the C=C bond in a C-ring precursor be blocked so photocycloaddition of cyclopent-2-en-1-one would occur only from the face opposite an allylic hydroxyl substituent? I knew that photocycloadditions to norbornene occur stereoselectively from the exo face of the C=C bond.[11] In effect, an ethano bridge acts as a blocking group which controls the facial selectivity of the photocycloaddition. Could an ethano bridge somehow be the precursor of a hydroxyl substituent? The answer to this question prompted the surge of adrenaline that aroused me from somnolence. The oxygen required for the hydroxyl substituent could be inserted between a carbon of the ethano bridge and the 5-position in the C-ring by a Baeyer-Villiger oxidation. Photocycloaddition of norbornenone **42** with cyclopent-2-en-1-one should deliver a cyclobutane **41** by exo addition. Baeyer-Villiger oxidation to lactone **40** followed by hydrolysis would deliver an intermediate **39** containing the correct stereochemical relationships between an hydroxyl substituent at the 5-position and the stereocenters of the B-ring cyclobutane. Furthermore, a carbonyl group at the 1-position could facilitate introduction of the A-ring methyl substituent, and the acetic acid substituent on the C-ring of **39**



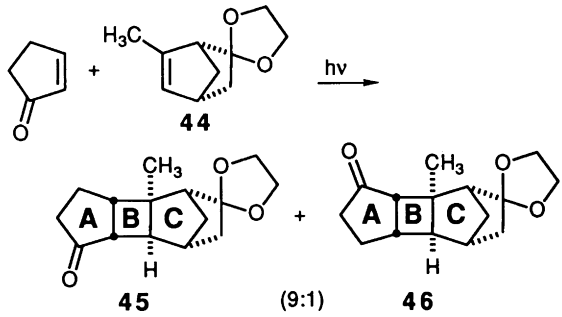
could serve as a precursor of the side chain at the 7-position in spatol (**1**).

This strategy had one obvious flaw. The strained bicyclic homoallylic ketone **42** is expected to readily undergo photoinduced cleavage to diradical **43**.[12] However, masking of the carbonyl in **42** would circumvent this problem and facilitate differentiation between the two carbonyl groups in the photocycloadduct **41**. Also, the configuration at the 7-position in **39** would have to be inverted to provide the requisite configuration at this stereocenter in spatol. Fortunately, a synthesis of 6-methylbicyclo [2.2.1] hept-5-ene-2-one (**42**) from vinyl acetate and methyl-1,5-cyclopentadiene was known.[13] A Diels–Alder reaction of these starting materials produces a mixture of structural isomers. Saponification followed by Jones oxidation gives a mixture of isomeric ketones. We found that Swern oxidation doubles the yield of this three step synthesis. Most importantly, separation of **42** from its isomers can be achieved by spinning band distillation.[14]

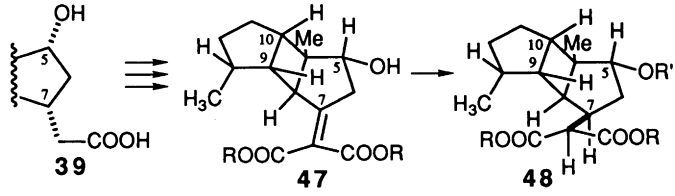


III. Pilot Studies

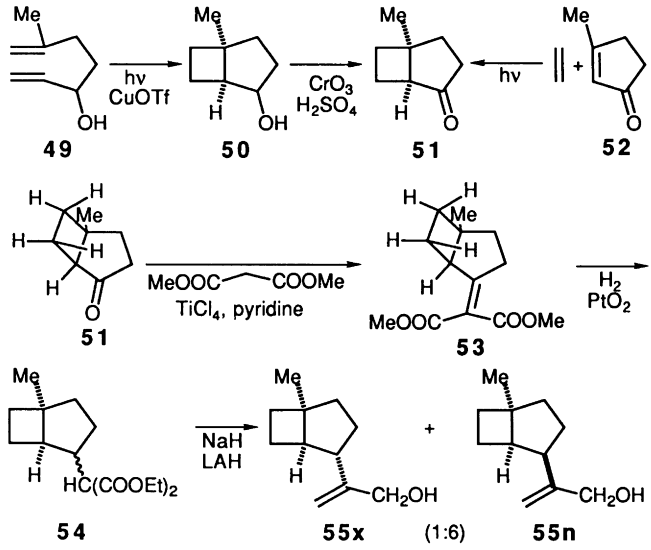
A series of preliminary experiments supported the viability of our plan. We were delighted to discover that photocycloaddition of the ethylene ketal **44** (from **42**) with cyclopent-2-en-1-one is entirely stereoselective producing only **45** and **46** with cyclobutyl B-rings *trans* to the temporary bridge across the α-face of the C-ring. An additional benefit of the temporary bridge was a structural selectivity favoring the desired isomer **45** over the useless byproduct **46** by 9 : 1 in contrast with the 1 : 1 ratio of **30** and **31** produced in the photocycloaddition of the unbridged 1-methylcyclopentene **29** (Scheme 4).



Since the substituent at position 7 in **45** is part of a temporary bridge, the derived carboxymethyl substituent in the subsequent intermediate **39** will have an α configuration. However, a β configuration is required for the spatol side chain. We envisioned conversion of the carboxymethyl in **39** into an alkylidene malonic ester as in **47**. Subsequent reduction of this intermediate with steric approach control of hydrogen delivery was expected to favor generation of **48**.



To test this hypothesis, the model alkylidene malonic ester **53** was prepared (Scheme 5). In connection with another study, we previously prepared bicyclic ketone **51** from 6-methylhepta-1,6-dien-3-ol

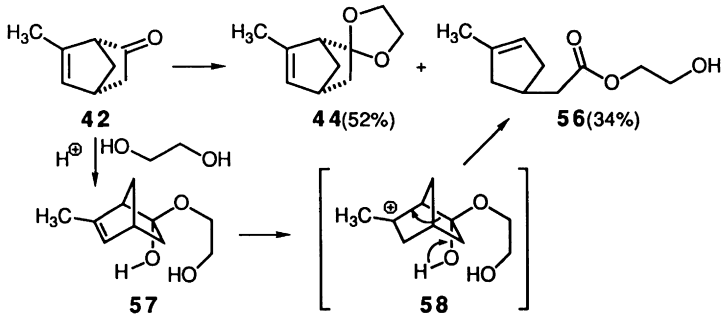


SCHEME 5

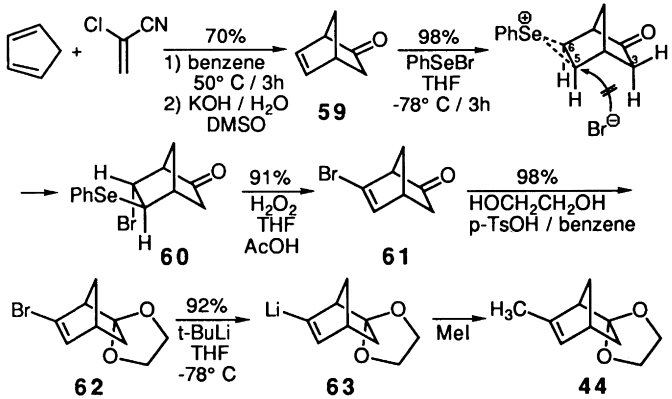
(**49**) by copper(I) triflate-catalyzed photobicyclization[15] followed by oxidation of the resulting bicyclic alcohol **50**. Ketone **51** is also readily available by photocycloaddition of ethylene with 3-methyl-cyclopent-2-en-1-one (**52**).[16] A modified Knoevenagel reaction[17] of **51** with diethyl malonate affords **53**. Catalytic hydrogenation followed by Marshall reduction[18] of the resulting malonic ester **54** delivered an epimeric mixture of allylic alcohols. These were shown by ^{1}H NMR studies with the Eu(fod)$_3$ shift reagent to be the undesired *exo* and desired *endo* epimers **55x** and **55n** in a 1 : 6 ratio, respectively.

IV. A Structurally Selective Synthesis of C-Ring Precursor 44

Masking of the carbonyl group in **42** proved unexpectedly difficult. Only a moderate yield of the ethylene ketal **44** was available by acid-catalyzed ketalization of **42** under conditions which give an excellent yield of ketal[19] from the 6-unsubstituted analogue, bicyclo [2.2.1] hept-5-en-2-one, owing to a competing fragmentation to **56**. The proclivity of **42** toward this fragmentation undoubtedly arises from the relative stability of the tertiary carbocation **58** and the relief of ring strain attending conversion of **57** to **56**.



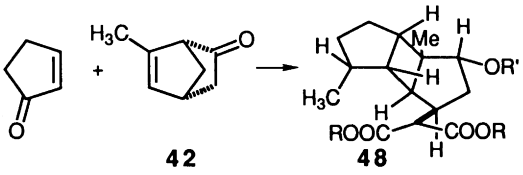
A structurally selective synthesis of ethylene ketal **44** from bicyclo [2.2.1] hept-5-en-2-one (**59**) was achieved[20] by exploiting a regioselective bromoselenenylation reaction (Scheme 6). Thus, reaction of **59** with phenylselenenyl bromide delivered **60** in virtually quantitative yield. The orientational selectivity of the **59** to **60** conversion presumably arises from steric approach control during attack by bromide on an intermediate selenonium ion. Reaction at the 5-position is hindered by the *endo* hydrogen at position 3. Alternatively, the selectivity may result from homoconjugative stabilization by the carbonyl group of positive charge at the 6-position.[21] As expected, oxidative deselenenylation of **60** delivered bromoalkene **61** which showed no proclivity toward fragmentation during acid-catalyzed ketalization affording **62**. Lithium-bromine exchange with t-butyllithium followed by methylation of the intermediate vinyllithium **63** delivered the masked ketone **44** directly.



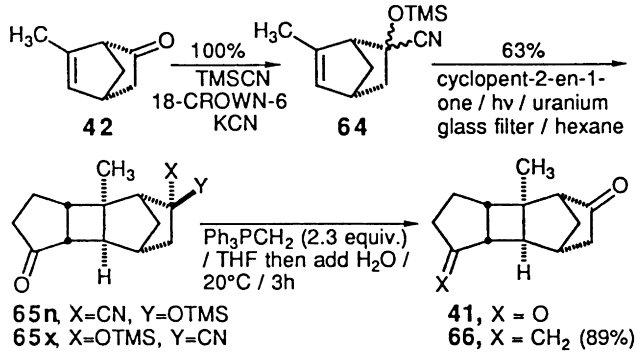
SCHEME 6

V. First Synthesis of a Tricyclic Malonic Ester Intermediate

The first synthesis[22] of the tricyclodecylmalonic ester intermediate **48** (R = CH_3, R′ = H) began with the photocycloaddition of cyclopent-2-en-1-one to a masked derivative of ketone **42**. An unusual choice for the masking group was developed during a search for a group which could be introduced under nonacidic conditions. Thus, ketone **42** is converted quantitatively into an epimeric mixture of

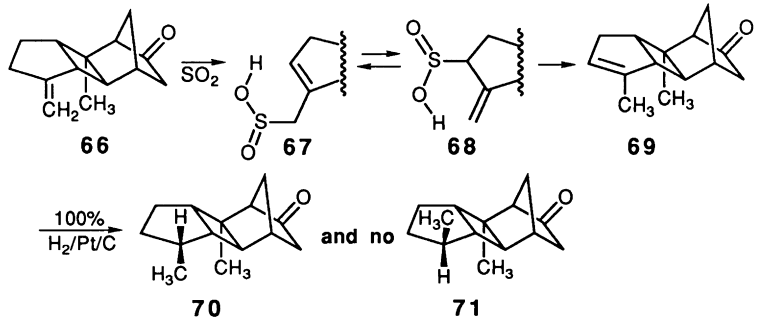


cyanohydrin silyl ethers **64** by reaction with trimethylsilyl cyanide. While the use of an unsymmetrical masking group might seem unwise since this leads to epimeric mixtures of several intermediates, this is a small price to pay for the otherwise ideal characteristics of the cyanohydrin silyl ether masking group. Thus, photocycloaddition with cyclopent-2-en-1-one delivered two epimeric adducts **65x** and **65n** with high stereo (cis, anti, cis ring fusions and exo addition to the bicyclohept[2.1.1]ene) and orientational (cyclopentane carbonyl remote from the bridgehead methyl group) selectivity. Serendipitously, the major adduct **65x** crystallized from the photoreaction mixture together with the dimer of cyclopentenone from which it was readily separated by trituration with hot hexane leaving behind pure dimer. Pure **65x** (m.p. 109–111°C) was then obtained in 51% yield, based



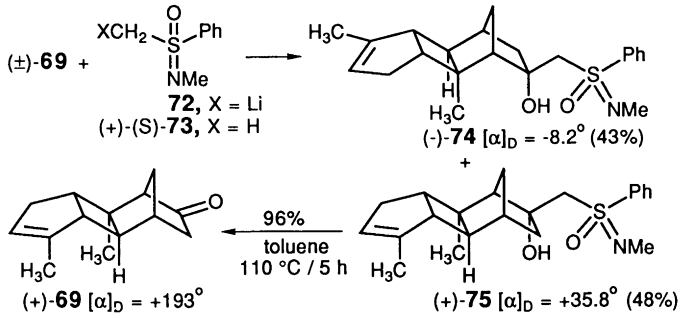
on **64**, by elution of the partially purified product through a column of silica gel with ethyl acetate-hexane. Column chromatography of the hexane soluble photoproduct afforded a fraction from which nearly pure minor cycloadduct **65n** crystallized together with a little **65x**. This mixture is suitable for Wittig olefination to produce methylidene ketone **66**, *vide infra*. The combined isolated yield of **65x** plus **65n** exceeds 60%. A sample of pure **65n** (m.p. 116–118°C) was obtained by HPLC. The epimeric relationship between **65x** and **65n** was demonstrated by production of the same diketone **41** upon hydrolysis of the cyanohydrin silyl ether masking group. The epimeric relationship between **65x** and **65n** was also proven by production of the same methylidene ketone **66** upon reaction with methylenetriphenylphosphorane followed by hydrolysis of the cyanohydrin silyl ether. The conversion of **65** into **66** was performed as a one-pot procedure affording pure **66** in 89% overall yield. The utility of the cyanohydrin silyl ether masking group in the above transformations is noteworthy. It is introduced under mild neutral reaction conditions. It is sufficiently robust to survive UV irradiation, chromatography on silica gel, and Wittig olefination; but it is readily converted to a carbonyl group by the aqueous base generated upon addition of water to the Wittig reaction mixture.

Catalytic hydrogenation of **66** favored the required epimer **70** over the useless byproduct **71** by 10 : 1 owing to steric approach control by the methyl group in **66**, which shields the α-face of the A-ring. However, separation of **70** from the mixture could not be achieved by any method except fractional crystallization, and this only allowed isolation of the desired epimer in fair yield. To circumvent this separation problem, **66** was isomerized to the endocyclic alkene **69** by SO_2.[23] This clean, quantitative isomerization presumably involves ene ad-

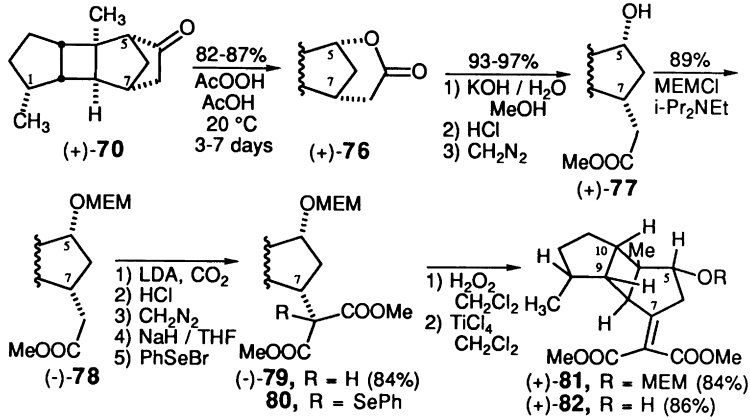


dition of SO_2 to **66** producing **67**. Subsequent [1,3]-sigmatropic rearrangement of sulfur affords **68** which undergoes retro ene fragmentation delivering **69**. Catalytic hydrogenation of **69** delivers **70** cleanly and quantitatively. Apparently the closer proximity of the endocyclic C=C bond to the bridgehead methyl group in **69** than the exocyclic C=C to the methyl group in **66** results in greater steric hindrance in **69** than in **66** to α hydrogen delivery.

Efficient, virtually quantitative resolution[14] of ketone **69** was readily achieved by flash chromatography and crystallization of the 1,2-adduct with chiral lithiosulfoximine **72**.[25] Retro ene elimination of the less soluble dextrorotatory diastereomer (+)-**75** delivers ketone (+)-**69** (m.p. 67–68°C) which was correlated with (+)-spatol by conversion to a degradation product from natural spatol (*vide infra*). The sulfoximine (+)-(*S*)-**73** was recovered in 95.9% yield.

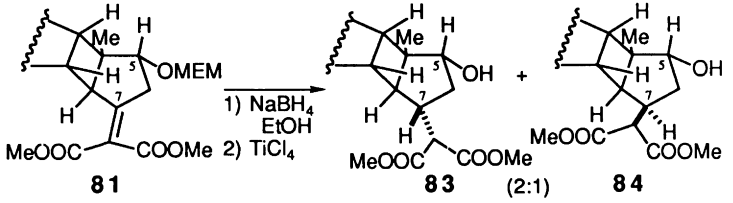


Catalytic hydrogenation of (+)-**69** provided ketone (+)-**70**. Introduction of oxygen at position 5, cleavage of the temporary bridge, and inversion of configuration at the 7-position were accomplished as outlined in Scheme 7. Thus, Baeyer-Villiger oxidation to give lactone (+)-**76**, saponification, and methylation of the resulting acid provided alcohol (+)-**77**. Masking of the 5-hydroxyl provided (−)-**78** which was carboxylated to give malonic ester (−)-**79**. Epimerization at the 7-position was initiated by selenenylation followed by oxidative deselenenylation of the resulting **80** to deliver alkylidene malonic ester **81**. Reduction of **81** with $NaBH_4$ followed by removal of the MEM protecting group with $TiCl_4$ afforded a 2 : 1 mixture respectively of the *cis* hydroxy malonic ester **83** and its C-7 epimer, the desired *trans* hydroxy malonic ester **84**. This disappointing result suggested that the 2-methoxyethoxymethoxy (OMEM) substituent at the 5-position

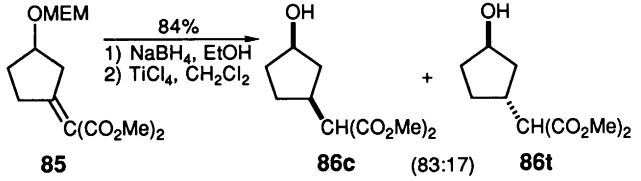


SCHEME 7

sterically hinders hydride delivery to the α-face of the C=C bond in **81**.



In a model study, borohydride reduction of MEM protected alkylidene malonic ester **85** followed by removal of the MEM group with $TiCl_4$ affords the *cis* epimer **86c** with a 5 : 1 preference over the corresponding *trans* epimer **86t**. Here also the MEM ether substituent functions as a bulky steric hindrance to syn approach of the



hydride. Most significantly for our synthetic approach to spatol, the stereochemical outcome was reversed by first removing the MEM

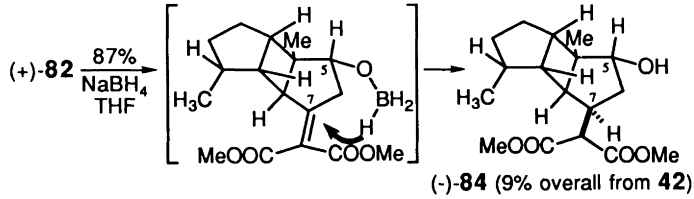
TABLE I
HYDRIDE REDUCTION OF **87**

Entry	Reagent	Solvent	**86t:86c**	Yield(%)
1	$LiAl(OMe)H_3$	THF	1:1	100
2	$LiAl(O\text{-}s\text{-}Bu)H_3$	THF	1:1	92
3	$LiAl(O\text{-}t\text{-}Bu)_3H$	THF	1:1	90
4	$NaBH_4$	EtOH	3:2	92
5	$NaBH_4$	THF	3:1	86
6	NaH then BH_3	THF	4:1	60

protecting group in **85** followed by treatment of the hydroxy alkylidene malonic ester **87** with $NaBH_4$. Reduction of **87** with various hydride reagents is summarized in Table I. The slight preference for hydride delivery *syn* to the hydroxyl, evident with $NaBH_4$ in ethanol (entry 4), is amplified in aprotic solvent (entry 5). Thus the remote hydroxyl group fosters *syn* hydride delivery. Presumably this involves a preference for pseudointramolecular hydride delivery via an alkoxyborohydride intermediate. Exploiting an alternative method for generating an alkoxyborohydride intermediate, reaction of the sodium alkoxide from alcohol **87** with BH_3 affords an even greater preference for *syn* hydride delivery (entry 6); however the overall yield with this protocol is unsatisfactory. It is noteworthy that aluminum hydrides (entries 1–3) do not react stereoselectively presumably because replacement of a hydride by the alkoxy substituent derived from **87** deactivates the hydride donor so that pseudointramolecularity no longer provides sufficient benefit to compete effectively with intermolecular hydride delivery from the starting hydride reagent (Table I, entries 1 and 2). However, replacement of a hydride in $NaBH_4$ by an alkoxy substituent activates the hydride donor.[26] Thus, pseudointramolecularity provides little benefit for $NaBH_4$ reduction of **87** in ethanol where $Na(EtO)_nBH_{4-n}$ competes intermolecularly. In THF, however, intermolecular hydride delivery by $NaBH_4$ is somewhat less effective than pseudointramolecular reaction via an alkoxyborohydride.

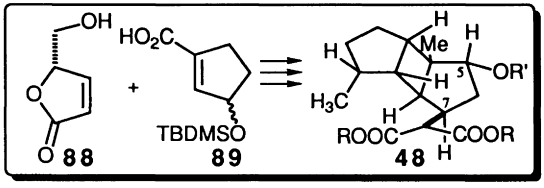
The hydroxy alkylidene malonic ester intermediate (+)-**82**, required for our total synthesis of spatol, was prepared from the MEM ether (+)-**81** (Scheme 7). Hydride reduction provided the desired

trans hydroxy malonic ester (−)-**84** (=48, R = Me, R′ = H) completely stereoselectively in *9% overall yield from C-ring precursor* **42** *in 21 steps including the resolution.*

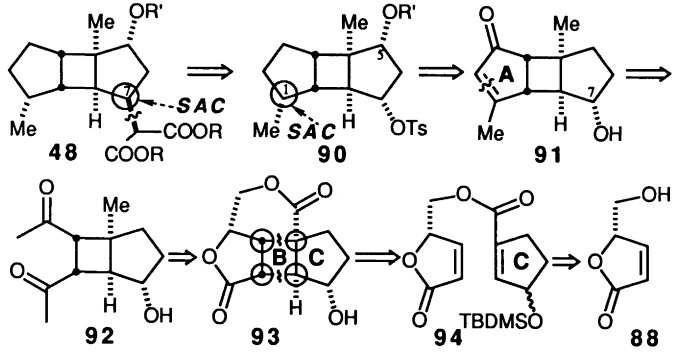


VI. Koga's Enantiospecific Synthesis of a Tricyclic Malonic Ester Intermediate

A different synthesis[27] of the homochiral tricyclodecylmalonic ester intermediate **48** (R = Et, R′ = MOM) was designed with a focus on exploiting butenolide **88** as a chiral auxiliary to establish the correct absolute configuration during generation of the B-ring by a $2\pi + 2\pi$ photocycloaddition with C-ring precursor **89**. Homochiral butenolide **88** is readily available from L-glutamic acid. An allylic oxygen substituent in **89** provides a point of attachment for the malonic ester side chain and activation for the introduction of oxygen at the 5-position.



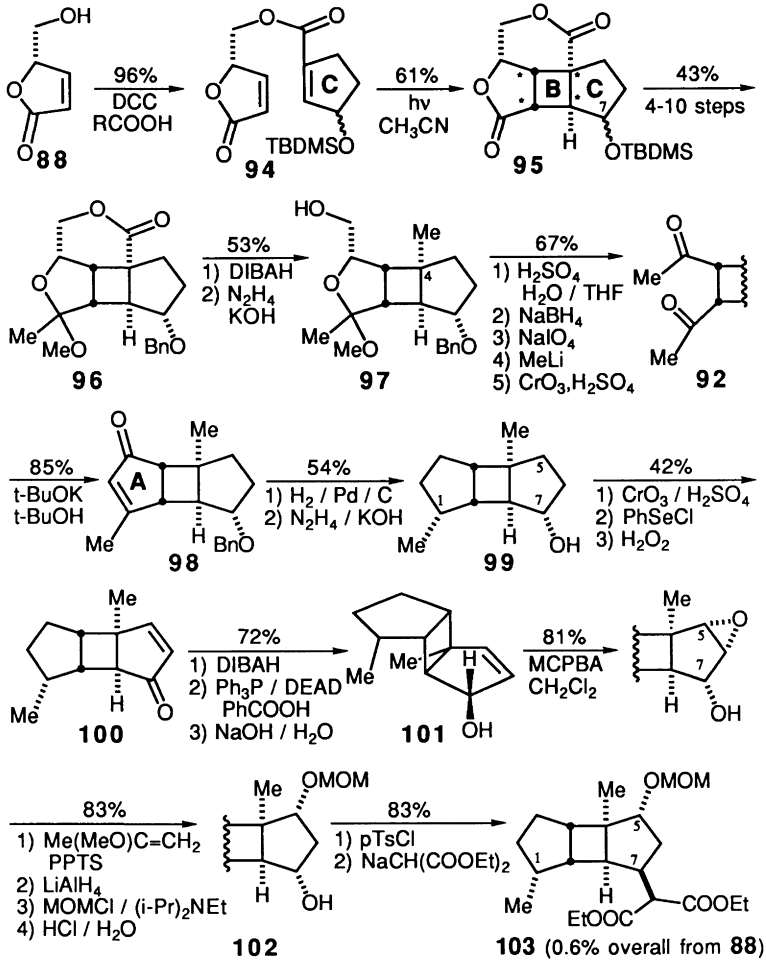
In a retrosynthetic format, the strategy envisions attachment of the malonic ester last by a stereospecific S_N2 alkylation with **90**. Since the chiral auxiliary **88** does not provide the cyclopentane ring required for the A-ring of **48**, this ring will have to be generated after the photocycloaddition of **88**. A dione **92** is an especially attractive precursor since the **19** to **26** conversion cited earlier (Scheme 3) allows the prediction of an entirely regioselective aldol condensation to provide **91**. Steric approach control should favor β-delivery of hydrogen during reduction of **91** to give the requisite configuration at



position 1 in **90**. The proper orientation during generation of the B-ring can be assured by a temporary bridge, an ester, between **88** and the C-ring precursor **89**. The synthesis is summarized in Scheme 8.

Intramolecular photocycloaddition of the ester **94** from the chiral auxiliary **88** delivered cyclobutane **95**. Addition of a methyl group (the one carbon needed to complete the A-ring) required 4–10 steps depending on the configuration of the C-7 substituent in **95**. Reduction of the remaining ester in **96** then provided the methyl group at position 4 in **97** which had been functionalized solely to allow construction of the temporary bridge in **94**. Functional group manipulation then provided dione **92** which underwent completely selective aldol condensation affording **98**. Stereoselective hydrogenation of **98** created the stereocenter at position 1 and removed the benzyl protecting group. Wolff-Kishner reduction of the resulting saturated ketone delivered **99**. Introduction of the 5-hydroxyl and 7-malonic ester substituents then required oxidation to **100**, reduction and Mitsunobu inversion to give **101**, stereoselective epoxidation followed by hydride reduction, protection, and deprotection to deliver **102** and nucleophilic substitution which provided malonic ester **103** (i.e., **48**, R = Et, R′ = MOM) in *0.6% yield overall from **88** in 29-35 steps.*

The overall yield of homochiral malonic ester (−)-**84** (i.e. **48**, R = Me, R′ = H) from (±)-**42** was more than an order of magnitude higher than the yield of homochiral malonic ester **103** (i.e., **48**, R = Et, R′ = MOM) from homochiral **88**. Two factors contribute to the success of using resolution to introduce asymmetry in the first synthesis. The resolution is performed very early in the synthesis and



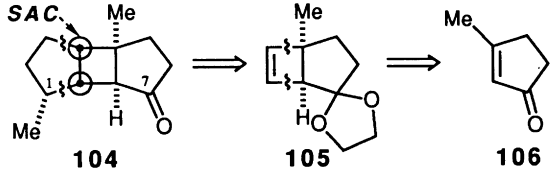
SCHEME 8

Johnson's sulfoximine method is spectacularly effective. The advantages of the clever plan to exploit the readily available chiral auxiliary **88** to introduce asymmetry into the second synthesis cannot overcome the penalty arising from the absence of a methyl group at position 4 or a hydroxyl group at position 5, and the lack of an A-ring in the photocycloadduct **95** from **88**. The first synthesis is more **convergent** than the second. Thus, two large fragments are constructed which contain most or all of the skeletal atoms and functionality of the target and these fragments are then united. Such an approach has several

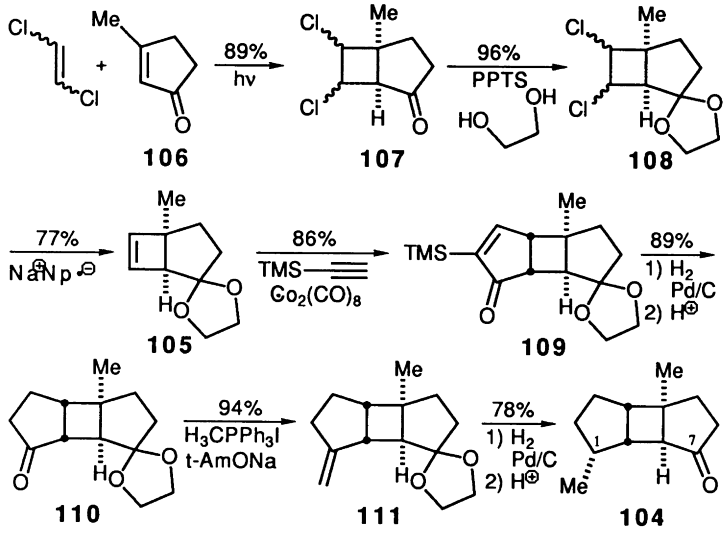
advantages over a **linear** synthesis, that is, one in which the molecule is constructed by sequentially uniting many small fragments or introducing functionality after skeletal construction is complete. A convergent synthesis is more efficient as measured by overall yield. If the average yield of an n-step synthesis is X%, then the overall yield will be $100(X/100)^n$%. A 21-step ***linear synthesis*** with an average 95% yield will have an overall 34% yield, or an overall 11% with an average 90% yield, or *an overall 0.9% with an average 80% yield.* In contrast for a ***convergent synthesis*** which combines two intermediates each prepared by 10-step synthesis (i.e., a total of 21 steps), the overall yield will be 56% with an average 95% yield, or an overall 31% with an average 90% yield, or *an overall 9% with an average 80% yield.* In effect the convergent synthesis is only 11 steps.

VII. Dauben's More Convergent Approach

A further example of the benefits of greater convergence is provided by an alternative synthesis of tricyclic ketone **104**, an intermediate in Koga's spatol synthesis (Scheme 8: **104** is produced by oxidation of **99**). The A-ring is assembled by a cobalt-assisted annulation which creates two bonds in a single step. The correct relative configurations of the newly generated stereocenters at the AB-ring junction are assured by steric approach control to the less congested face of the C=C bond in **105**. Assembly of the B-ring is also accomplished by creating two bonds in a single step by a $2\pi + 2\pi$ cycloaddition to cyclopentenone **106**. The synthesis is outlined in Scheme 9.[28]

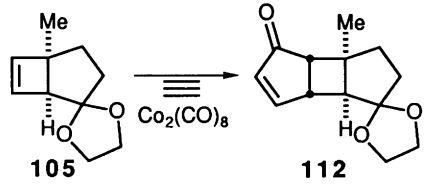


Particularly noteworthy is the fact that the key Pauson-Khand annulation of cyclopentenone **109** is entirely orientationally selective. This selectivity can be attributed to the ethynyl trimethylsilyl substituent which acts an orientational control element. Thus, Pauson-Khand annulation with *acetylene* gives the isomeric cyclopentenone **112** with the opposite orientational selectivity. The *less convergent*



SCHEME 9

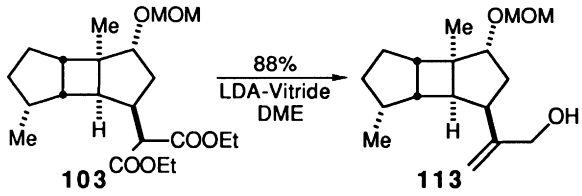
approach of Scheme 8 generates homochiral **104** in 17–23 steps and about 4% overall yield. The *more convergent* approach of Scheme 9 provides racemic **104** in 9 steps and 37% overall yield. With the optimistic but reasonable assumption that the racemic ketone can be



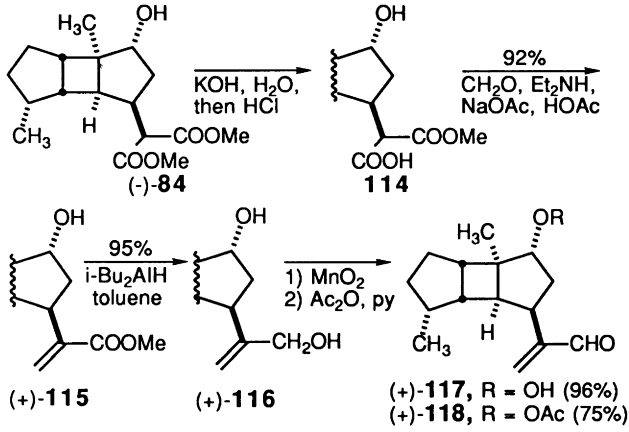
quantitatively resolved by Johnson's sulfoximine method, the more convergent approach would deliver homochiral **104** in 18% overall yield in 11 steps. However, for a total synthesis of spatol, the problem of introducing the hydroxyl substituent at the 5-position in the A-ring must yet be addressed. The difficulty encountered in introducing that substituent during the **99** to **104** to **102** conversion (Scheme 8) underscores the importance of its presence, albeit in latent form, in our key intermediate, photocycloadduct **65** and its precursor, bicyclic ketone **42**.

VIII. The Allylic Diepoxide Spatol Side Chain

The malonic ester group in the intermediates (−)-**84** and **103** was intended to provide a three-carbon allylic precursor of the spatol side chain. Koga succeeded in converting **103** into allylic alcohol **113** by a modified Marshall reduction.[27] However, our attempted one-step



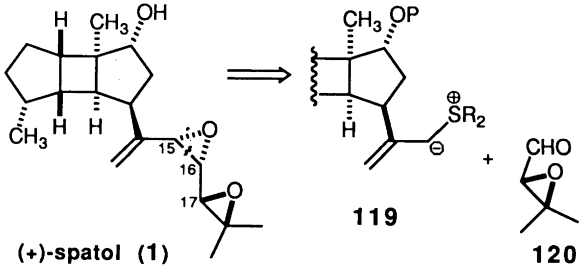
conversion of (−)-**84** into the allylic alcohol **116** by the Marshall reduction, i.e. LAH reduction of the sodium enolate, failed completely. Therefore, this transformation was accomplished by monosaponification to **114** and decarboxylative aldol condensation with formaldehyde to provide acrylic ester (+)-**115**. Hydride reduction then delivered allylic alcohol (−)-**116** which was selectively oxidized with MnO_2 to the aldehyde (+)-**117**. To correlate our synthetic intermediates with the natural product, (+)-**117** was acetylated. The totally synthetic acetate showed $[\alpha]_D^{22} = +25.1°$ which compares well with the naturally derived acetate which showed $[\alpha]_D^{22} = +26.5°$.[1]



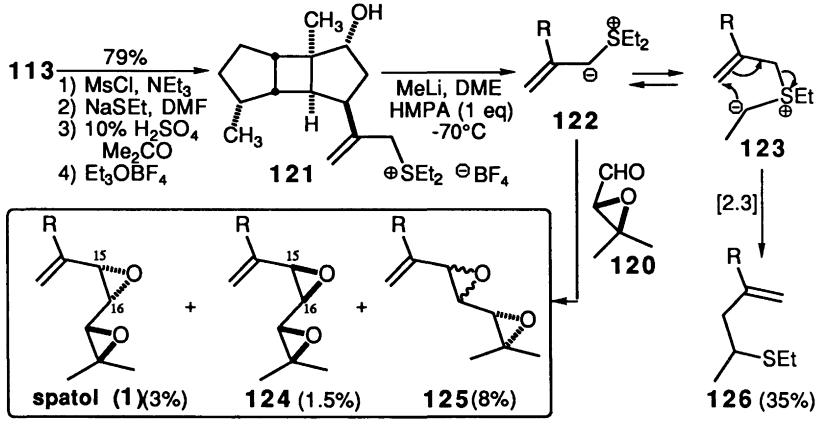
SCHEME 10

A. First Total Synthesis of Spatol

A convergent strategy for construction of the allylic diepoxide side chain of spatol (**1**) generates the connection between carbons 15 and 16 by reaction of a homochiral C_{15} ylide **119** with a homochiral C_5 aldehyde **120**.[29] Although the ultimate in brevity, this strategy provides no control over the stereochemistry at positions 15 and 16. The

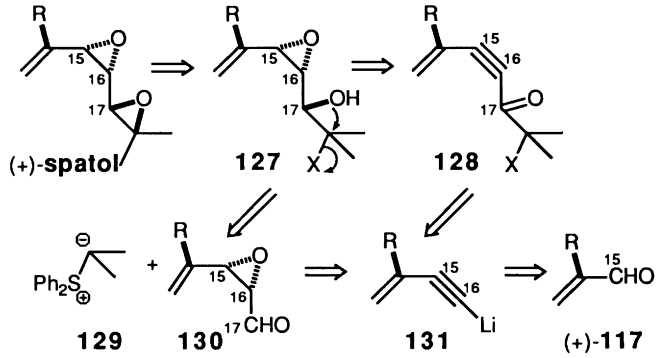


ylide **122** was prepared from the allylic alcohol **113** through an intermediate sulfonium salt **121**. Reaction of ylide **122** with aldehyde **120** produced spatol (**1**) in only 3% yield together with the isomeric allylic *cis* diepoxide **124** (1.5%) and a mixture of *trans* diepoxides **125** (8%). Moreover, **122** exists in equilibrium with an alternative ylide **123** which undergoes [2,3]-sigmatropic rearrangement producing the homoallylic sulfide **126** (35%) as the major product of the reaction.

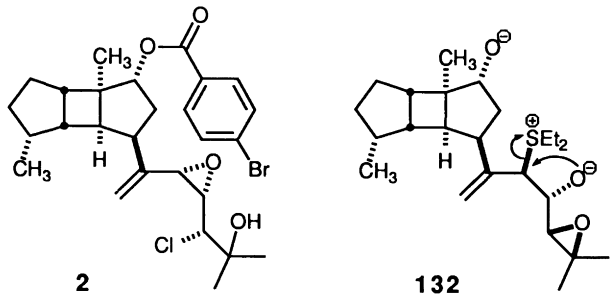


B. The Epoxydiol Strategy

Two major routes to epoxides are epoxidation of C=C bonds and intramolecular vicinal alkylation of an alkoxide. The last step in the reaction of ylide **122** with aldehyde **120** is an example of the latter process. The reaction of aldehyde **130** with ylide **129** is a related strategy. The epoxy aldehyde **130** might be available from aldehyde

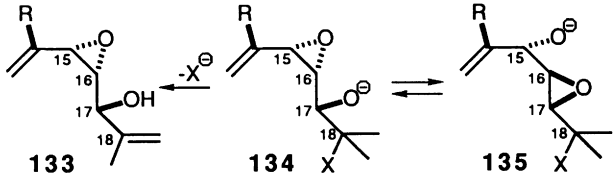


(+)-**117** by Corey-Fuchs alkynylation to give **131**, homologation with formaldehyde, Lindlar reduction of the resulting propargyl alcohol, asymmetric epoxidation of the derived allylic alcohol, and Swern oxidation of the resulting epoxy alcohol. Alternatively, **131** might be homologated to **128**. Then, after asymmetric reduction of this propargyl ketone, Lindlar reduction, and $VO(acac)_2$-catalyzed epoxidation, heterocyclization of the resulting **127** might deliver (+)-spatol. Neither of these early ideas was pursued primarily because they are too long. The NIH study section considering a request for support of our efforts concurred with this view and their comments inspired an alternative strategy. "*A more convergent type of approach for this task would have been desirable but such a route is not obvious. Ring closures of intermediates such as...[**127**] seem unlikely considering the potential for pinacol rearrangement, E-1 elimination, homoallylic solvolysis and...transepoxidation.*" Furthermore, the sensitivity of the target diepoxide to intermolecular nucleophilic opening *appeared* to be amply precedented by the reaction with chloride leading to chlorohydrin **2**. At the time, Koga's synthesis involving the similar cyclization of an intermediate **132** had not been reported.



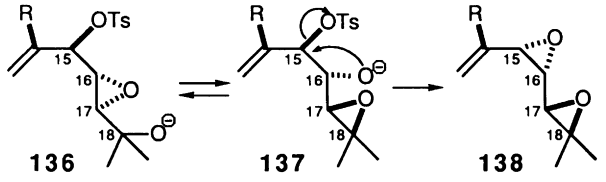
2 132

In fact, intramolecular attack of the alkoxide in **134** at the 16-position to give **135** rather than at the 18-position to give spatol seemed reasonable. Such trans-epoxidation reactions (Payne rearrangements) are well known.[30] However, the rearrangement is reversible while heterocyclization of **134** would be irreversible. Nevertheless, E1 elimination to give **133** seemed a reasonable concern.



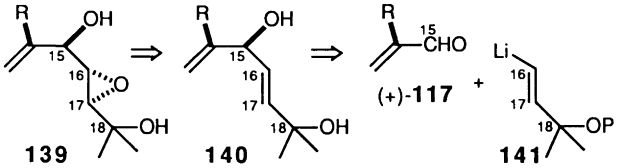
133 134 135

The inspiration for an alternative strategy was sparked by the question: what if we generate an epoxy alkoxide **136** similar to **135** but with the positions of the nucleofuge and alkoxide exchanged? Payne rearrangement should produce **137** and the *trans* stereochemistry of the epoxide in **136** should virtually preclude direct attack of the alkoxide at the 15-position to produce a tertrahydrofuran. The allylic electrophile at position 15 in **137** should be particularly effective in alkylating the neighboring alkoxide producing an allylic diepoxide **138**. Furthermore, a *convergent* strategy for assembling an epoxydiol precursor **139** for **136** seemed feasible. Thus, **139** should be available

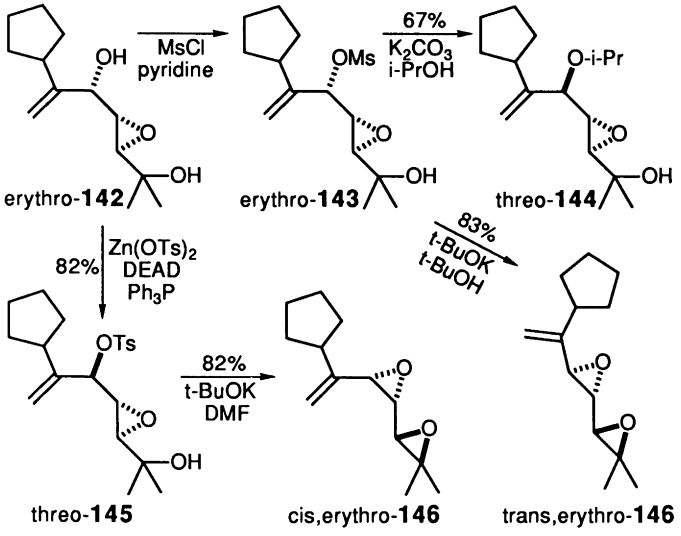


136 137 138

by regioselective epoxidation of **140** which should, in turn, be available by the union of a C_{15} electrophile (+)-**117** with a C_5 nucleophile **141**. This plan won the enthusiatic support of an NIH study section and financial support of the project by NCI.



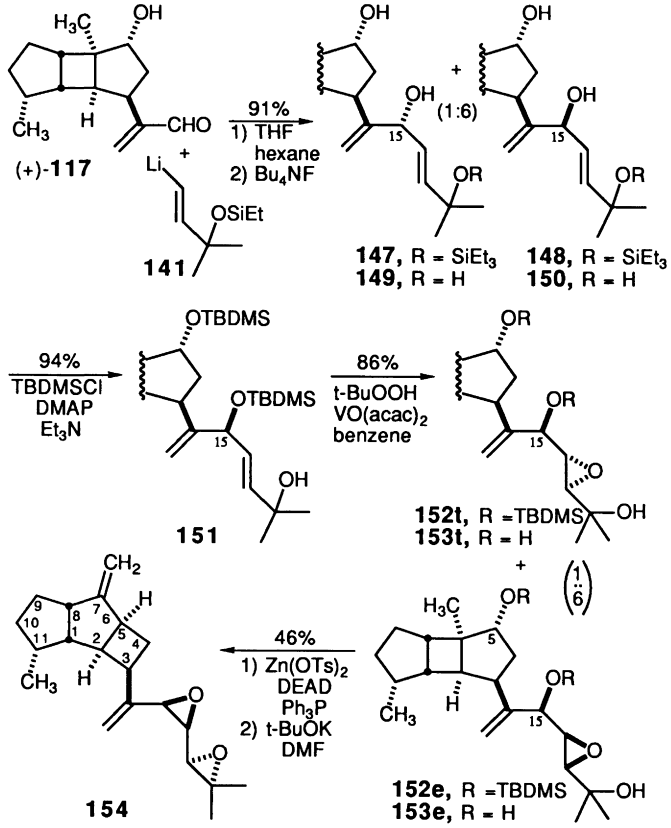
A model study confirmed that, under appropriate reaction conditions, the allylic diepoxide array of the spatol side chain can be produced in high yield from appropriately activated derivatives of epoxydiol **139**. Thus, activation of erythro-**142** as a mesylate, erythro-**143**, followed by treatment with solid K_2CO_3 in boiling isopropanol delivered *threo*-**144** by intermolecular S_N2 displacement rather than a vicinal diepoxide by Payne rearrangement followed by heterocyclization. Since the tertiary hydroxyl group in erythro-**143** is apparently not sufficiently nucleophilic to displace the epoxy leaving group, conditions were sought which would generate an alkoxide from the tertiary hydroxyl. Treatment with *t*-BuOK in *t*-BuOH promoted a clean, stereospecific rearrangement and heterocyclization to deliver



the diepoxide *trans,erythro*-**146**. A route from the *erythro* epoxy alcohol **142** to an activated derivative of the *threo* epoxy alcohol requires activation with concomitant inversion of configuration. This can be accomplished by the Still modification of the Mitsunobu reaction.[31] Treatment of erythro-**142** with $Zn(OTs)_2$, diethyl azodicarboxylate, and triphenylphosphine, gave the inverted tosylate threo-**145** which, upon treatment with *t*-BuOK in DMF, afforded the allylic diepoxide *cis,erythro*-**146** in 82% yield.

Considering the substitution reaction of mesylate *erythro*-**143** with isopropanol to give *threo*-**144**, we expected a similar substitution with tetrabutylammonium hydroxide. Instead, a high yield of diepoxide *trans,erythro*-**146** was obtained. The unexpected stability of this allylic diepoxide product toward hydroxide is especially interesting in view of the epoxide cleaving substitution reaction of spatol with the less nucleophilic chloride anion to give chlorohydrin **2** (*vide supra*). Apparently, the latter reaction is an *acid-catalyzed epoxide opening induced by pryridinium hydrochloride*, a byproduct of the acylation with *p*-bromobenzoyl chloride in the presence of pyridine. It remains an interesting question why chloride attacks the 17-position in spatol to generate **2** rather than inducing cleavage of the presumably weaker allylic C–O bond at position 15. That the reactivity of the side chain functionality is important for spatol's biological activity is supported by the fact that both of the isomeric allylic diepoxides **146** are biologically active. The ability of these allylic diepoxides to inhibit microtubule assembly and the mitosis of sea urchin eggs was examined. *Cis,erythro*-**146** showed: 36% inhibition at 16 μg/mL in the sea urchin egg assay and 74% inhibition of microtubule assembly at 70 μg/mL; *trans,erythro*-**146** showed: 28% inhibition at 16 μg/mL in the sea urchin egg assay and 64% inhibition of microtubule assembly at 70 μg/mL.[32] In comparison, spatol (**1**) showed 50% inhibition at 1.2 μg/ml in the sea urchin egg assay.[1] Apparently the lipophilic tricylic nucleus of spatol amplifies its biological potency by at least an order of magnitude.

In our first attempt to implement the plan (Scheme 11), addition of vinyllithium **141** to aldehyde (+)-**117** provided a 1:6 mixture of triols **149** and **150** respectively after desilylation of the intermediate monosilylethers **147** and **148**. To control the regioselectivity of epoxidation, the triol **150** was selectively disilylated. Vanadium-catalyzed epoxidation of **151** was then directed to the 16,17-C=C bond by the

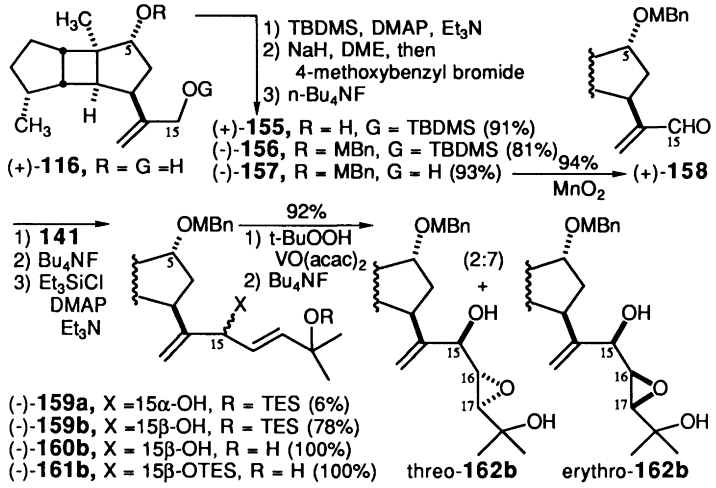


SCHEME 11

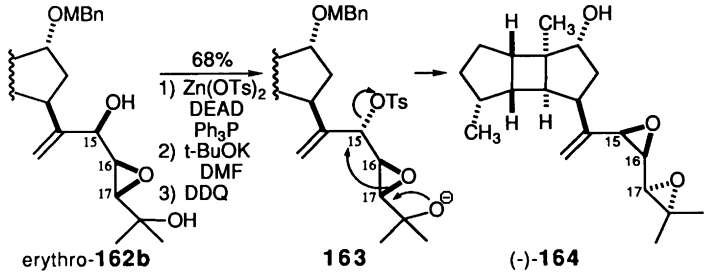
remaining allylic hydroxyl. Since the major epoxide product was the erythro derivative **152e**, selective activation of the less hindered 15-hydroxyl in the corresponding triol **153e** was accomplished with inversion of configuration by the Still modification of the Mitsunobu reaction. However, treatment with base produced an allylic diepoxide **154** with a rearranged tricyclic nucleus. The *cis,anti,cis*-tricyclo[5.3.0.$0^{2,5}$]decane nucleus of **154** is formed by a Wagner-Meerwein rearrangement of the *cis,anti,cis*-tricyclo[5.3.0.$0^{2,6}$]decane nucleus of **152e**, apparently owing to unintended activation of the 5-hydroxyl that accompanied the desired activation of the hydroxyl at the 15-position.

These results suggested that derivatives of epoxy triols **153e** and **153t** with the hydroxyl at position 5 masked would be desirable for generation of the spatol side chain without accompanying rearrangement of the tricyclic nucleus. The lability of the allylic diepoxide array in spatol (**1**) under acidic conditions limited the choice of derivatives to those with masking groups which would be removable under neutral or basic reaction conditions. The further requirement for stability towards a vinyllithium reactant and the presence of unsaturation in the synthetic target agreed with the choice of p-methoxybenzyl (MBn) ether derivatives. The MBn masking group is removable under mild conditions by oxidative cleavage with DDQ.[33] The MBn derivatives *erythro*-**162b** and *threo*-**162b** of **153e** and **153t** were prepared from diol (+)-**116** as outlined in Scheme 12.

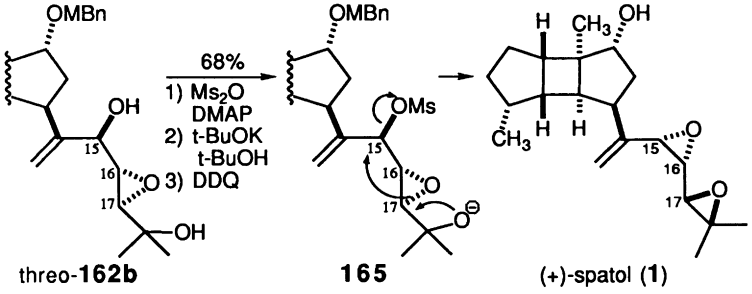
Actually, no basis was available for distinguishing between the epimers **159**. The conclusion that the major epimer (−)-**159b** has the *S* absolute configuration at the 15-position is based on correlation with natural (+)-spatol (*vide infra*). Epoxidation of the derived silyl ether (−)-**161** provided a 2:7 mixture of *threo* and *erythro* epoxides **162b**. The major isomer, erythro-**162b**, was converted into a *cis,erythro* diepoxide (−)-**164** by conversion to a *threo* tosylate with inverted configuration at the 15-position followed by base-induced Payne rearrangement-heterocyclization, and completed by deprotection of the



SCHEME 12



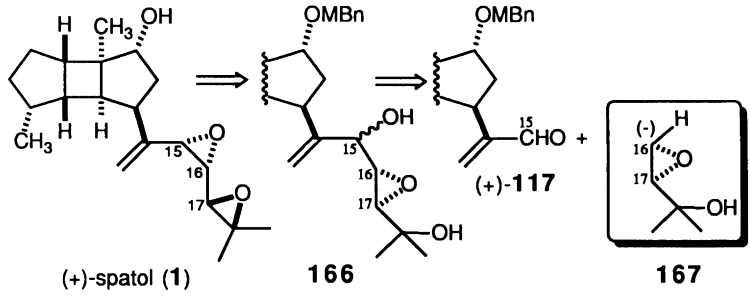
5-hydroxyl. That (−)-**164** was not spatol (**1**) was evident from its optical activity, $[\alpha]_D = -10.0°$ in contrast with $[\alpha]_D = +45.6°$ reported for the natural product. Small chemical shift differences (e.g., vinyl ^{1}H NMR resonances at δ5.14 and 5.09) confirmed that (−)-**164** is epimeric at positions 15, 16, and 17 with (+)-spatol (**1**) which exhibits vinyl resonances at δ5.13 and 5.02. The minor isomer, threo-**162b**, was converted into a *cis,erythro* diepoxide (+)-spatol (**1**) by conversion to a *threo* 15-monomesylate followed by base-induced Payne rearrangement-heterocyclization, and deprotection of the 5-hydroxyl. Each resonance in the ^{1}H NMR spectrum of synthetic (+)-spatol (**1**) coincided within 0.01 ppm with a spectrum of an authentic sample of natural spatol.[34]



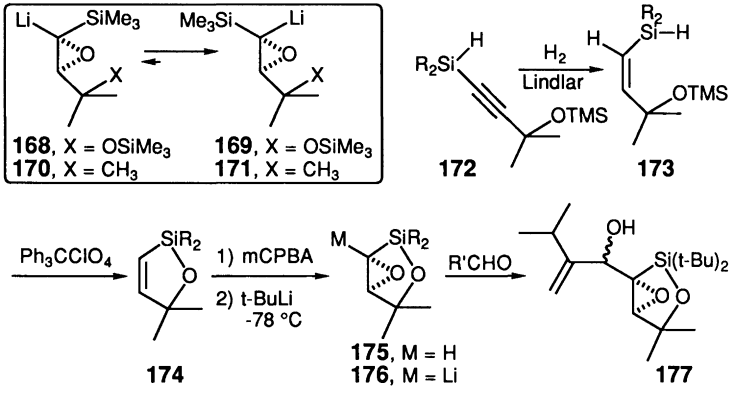
C. A Proposed α-Lithioepoxide Strategy for Spatol

Since the epoxydiol route to the allylic diepoxide side chain allows the stereospecific conversion of *either* epimer of epoxydiol **166** into spatol, stereocontrol at the 15-position is unimportant for an efficient total synthesis. A convergent, stereocontrolled strategy envisions assembly of the spatol skeleton in **166** from the homochiral C_{15} aldehyde (+)-**117** and a homochiral C_5 α-epoxy nucleophile **167**.

Since α-silyl epoxides are readily hydrodesilylated by moist fluoride with complete retention of configuration[35], a possible synthetic equivalent of synthon **167** is the silyl-stabilized α-lithioepoxide **168**.



A serious flaw could sabotage this strategy. While α-lithioepoxides are generally configurationally stable, the α-lithioepoxide **170**, a close analogue of **168**, exhibits an unusual configurational instability rearranging completely to **171** owing, no doubt, to steric strain which is relieved upon *trans–cis* isomerization.[36] A similar isomerization of **168** to **169** would derail the synthesis since the *trans* configuration of the epoxide in **166** is absolutely essential. This flaw can be circumvented by a temporary bridge between the *C*-silyl substituent and neighboring oxygen as in **176**. In fact, racemic **176** (R = *t*Bu) is readily available from **172** through epoxidation of vinyl silane **174**. Reaction of **176** with 2-isopropylacrolein delivered **177**. Thus, intramolecular *O*-silylation precludes isomerization of the carbanion **176** obtained by metallation of **175**. One challenge remains. For an efficient synthesis of (+)-spatol, the requisite enantiomer of epoxide **175** must be prepared.



Acknowledgments

This research was assisted financially by grants CHE8205122 from the National Science Foundation and CA31595 from the National Cancer Institute of the National Institutes of Health. This project was a collaborative effort that succeeded through the patience and hard work of many students. The primary participants in chronological order were: Navser D. Sachinvala, Subhas Roy, and Basudeb Basu. Also contributing were Swadesh R. Raychaudhuri, Donald B. Miller, Ram B. Sharma, Kasturi Lal, Bruce S. Levison, and Khrishna K. Murthy.

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Chapter 11

TOTAL SYNTHESIS OF THE FK506/FKBP COMPLEX

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Harvard University,
Cambridge, Massachusetts

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I. Introduction

In August 1987, the structure of FK506, a new natural product possessing remarkable immunosuppressive activity,[1] was reported in the *Journal of the American Chemical Society*.[2] By October of 1989, this molecule had been used to prevent the rejection of transplanted organs in humans; these preliminary results were promising enough to warrant a front page *New York Times* article.[3] Not surprisingly, reports of progress towards the synthesis of this molecule began to appear in the chemical literature as early as January of 1988.[4] In February of 1989, a communication of the first total synthesis of this molecule was reported by Shinkai's group at Merck Process Development;[5] the full paper reporting our total synthesis of FK506 was submitted in December of 1989.[6]

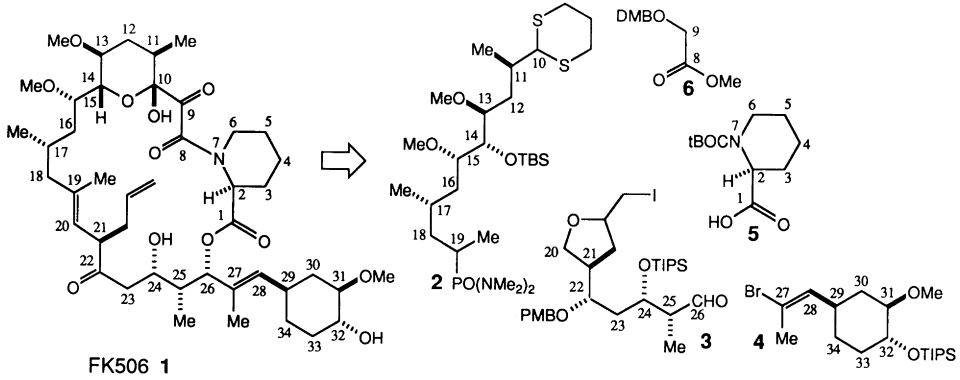
It is popular in some circles to discuss the possibility that the art of organic synthesis has reached such a highly developed state that, given enough time and resources, any structure that can be drawn on paper can be prepared in the laboratory. While those of us who actually practice organic synthesis favor applying such grandiose generalizations on a molecule-by-molecule basis, this particular compound does provide an example where the question was not one of *whether or not* the molecule could be synthesized, but rather of *when* it would be synthesized. As our research program in the molecular recognition of protein receptors hinged on the availability of synthetic samples of slight variants of FK506 (*vide infra*), achieving a practical total synthesis of the natural product itself was of paramount importance. As it turns out, our synthetic skills tested our patience, yet did not fail us. The problems that were posed by this molecule, and the partial conquering of these problems as described herein, should demonstrate that organic synthesis is a maturing science, but not necessarily a mature one.[7] We also hope to clearly illustrate the power of synthetic chemistry in research programs aimed toward solving biological problems. In combination with the methods available for the synthesis of proteins, *via* the synthesis of engineered DNA, the techniques of organic synthesis allow entire receptor–ligand ensembles to be prepared. It is this research accomplishment that we chronicle in the pages that follow.

With the appeal of a remarkable and complex structure, FK506 excited a large part of the chemical community, but it was of particu-

lar interest to us because of its immunosuppressive activities. The new field of immunoorganic chemistry was just beginning to blossom at Yale, where projects relating to cyclosporin A (CsA, **77**), an immunosuppressant with a spectrum of activity that paralleled FK506's, were well underway. FK506 was a molecule that offered us the opportunity to begin to bridge the gap between organic synthesis and immunology, as it posed great challenges for practitioners of both arts. Our synthetic efforts toward FK506 also bridged the group's move from Yale to Harvard in August of 1988; for both of these reasons, the story behind our total synthesis of this molecule should be an interesting one.

II. Retrosynthetic Analysis

Scheme 1 outlines the retrosynthetic analysis of FK506 that culminated in our successful synthesis of this molecule. In the spirit of honesty, we acknowledge that the retrosynthesis shown below was not the first that we conceived (or pursued). In fact, with the exception of the C_{10}–C_{19} phosphonamide, our initial ideas for the coupling partners were quite different from those presented in Scheme 1. However, the general strategy of disconnecting at or near the two trisubstituted olefins was adopted from the beginning of the project. This provided three subunits that corresponded roughly to C_{10}–C_{19}, C_{20}–C_{26}, and C_{27}–C_{34} (the latter was referred to as the cyclohexyl moiety). We never adopted the practice of affixing geographic labels to the various



SCHEME 1

subunits (e.g., "the northern half," or "the southern hemisphere"), probably due to the confusion that reigned in the early stages of the project regarding the most aesthetically pleasing way to draw the molecule. As can be seen by examining certain publications in the FK506 synthetic literature, the molecule can be quite difficult to draw without some awkward bond stretching and bending. Thus, exactly what portion of the molecule one meant by "the northern segment" was changing on a weekly basis in the early stages of our synthetic effort; our rendering of FK506 went through several changes before we finally arrived at the perspective shown in Scheme 1.

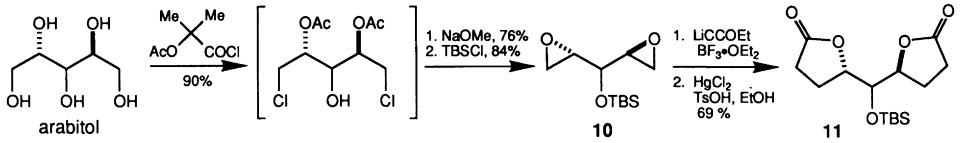
One motivation for disconnecting at the two olefins was our anticipation that these linkages would be relatively easily synthesized. As will be shown, however, this was not the case; if anything, controlling the relative and absolute stereochemistry of the individual pieces was an easier task than forming the two trisubstituted olefins. This is an interesting comment on the state of the art in asymmetric synthesis: at least in this synthetic endeavor, acyclic stereocontrol was relatively straightforward, while the regio- and stereoselective formation of the trisubstituted olefins was a much more challenging problem. This would certainly not have been the case just ten years ago.[8]

III. Early Success: The Application of the Class C Two-Directional Chain Synthesis Strategy to the C_{10}–C_{19} Portion

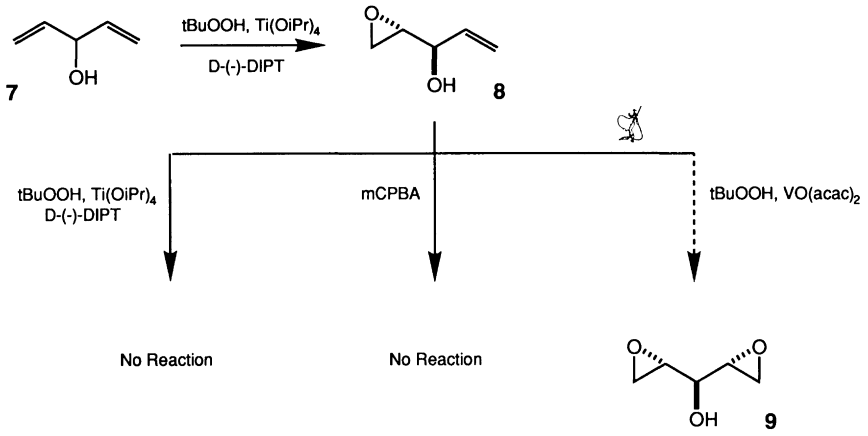
At an early stage of our synthetic studies, we learned of a similar interest in FK506 by Professor Samuel Danishefsky and members of his research team. As the interactions between our groups have always been amicable, it was quite natural to agree to work out our independent synthetic schemes in an atmosphere of cooperation. There is little doubt that our research proceeded with greater efficiency following our agreement to share both the successes and pitfalls of our efforts.

An important goal from the beginning of our efforts was to prepare each of the coupling partners in chiral, nonracemic form *without the use of stoichiometric chiral auxiliaries*. As will be discussed later, catalytic asymmetric induction was utilized for the C_{20}–C_{26} and C_{27}–C_{34} subunits. For the C_{10}–C_{19} portion, however, our recognition of the pseudo C_2-symmetry of this region made the class C two-directional chain synthesis strategy[9] an attractive approach. Our initial idea was

to make use of bis-epoxide **10** (Scheme 2). Although one might consider a double Sharpless epoxidation as a route to this compound, in fact we knew from unpublished work of Dave Smith in our group that the second epoxidation of divinyl carbinol[10] was exceedingly sluggish, and that side reactions destroyed the mono-epoxide before useful amounts of any bis-epoxide were formed (Scheme 3).[11] As the charter member of the FK506 team, Tarek Sammakia initiated our efforts in this area in March of 1987; one of his first experiments was to study the achiral epoxidation of monoepoxide **8** with achiral reagents,[12] in the hope that a separable mixture of the *meso* and C_2-symmetric epoxides would be formed. He found that olefin **8** was completely unreactive toward *m*-chloroperbenzoic acid (*m*CPBA), presumably due to the electronic effects of the adjacent oxygen functionality. Epoxidation with *t*-BuOOH/VO(acac)$_2$[13] was considered, but would be expected to provide the *meso* bis-epoxide **9**, if it proceeded at all. Several unsuccessful pathways were investigated until Tarek realized that the desired bis-epoxide could be derived from



SCHEME 2

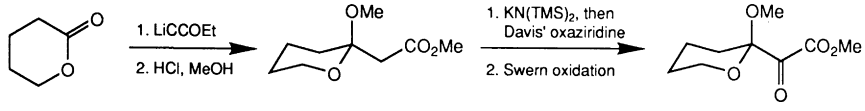


SCHEME 3

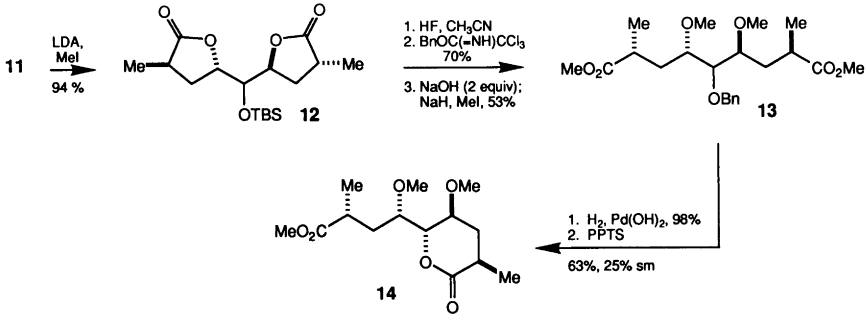
arabitol, as shown in Scheme 2. Thus, treatment of arabitol with the Moffatt reagent[14] was followed by acetate hydrolysis and silylation to provide **10** in 57% overall yield.

Homologation of bis-epoxide **10** was effected with the lithium anion of ethoxyacetylene in the presence of boron trifluoride etherate. Following acidic workup, bis-lactone **11** was isolated in 69% overall yield. An interesting outgrowth of this reaction sequence was the use of ethoxyacetylene in several other areas of the growing FK506 synthetic effort in the Schreiber group. Dave Smith and John Ragan had joined the project in August of 1987, and each succeeded in putting this versatile two-carbon component to good use. Dave utilized it in our approach to the cyclohexyl fragment (*vide infra*), and John developed the chemistry outlined in Scheme 4 as an approach to the tricarbonyl moiety. The feeling among group members at the time was that we were rapidly diminishing the Aldrich Chemical Company's supply of this valuable reagent.

Generation of the dianion of bis-lactone **11** and treatment with MeI provided **12** as the predominant diastereomer in excellent yield (Scheme 5). Desilylation and benzylation provided the corresponding benzyl ether. This seemingly superfluous protecting group switch was necessary because the benzyl ether was found to lower the yield of the



SCHEME 4

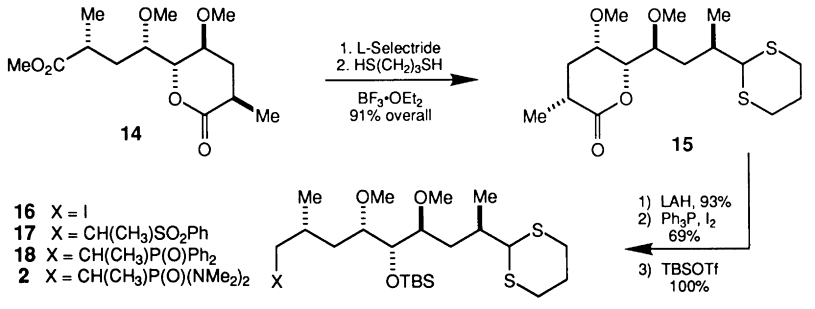


SCHEME 5

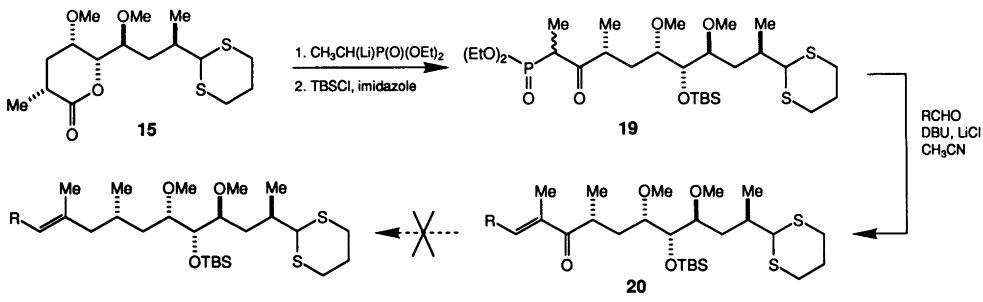
epoxide opening/lactonization (**10** to **11**) substantially, as well as that of the double alkylation (**11** to **12**), while the *t*-butyldimethylsilyl (TBS) ether migrated in the following transformation. Needless to say, discovery of this optimal sequence involved no small degree of frustration, as reactions that had worked well with one protecting group failed with a different one. Treatment of the benzyl ether with two equivalents of NaOH and exhaustive methylation in DMF provided bis-methyl ester **13**.

Hydrogenation of **13** provided the alcohol substrate for the diastereotopic group-selective lactonization. Treatment of this alcohol with pyridinium *p*-toluenesulfonate in CH_2Cl_2 containing a small amount of water provided the desired lactone **14** in 63% yield, plus 25% recovered starting material. Several experimental protocols designed to drive this lactonization to completion were investigated, but none were as efficient as the sequence described above. These lactonization studies were performed in collaboration with Dr. Annabella Villalobos of the Danishefsky group, who had prepared the same lactonization substrate by a completely different route. (Annabella was actually the first person to study this lactonization.)[15c] The identity of our lactone ester **14** with the material prepared in the Danishefsky group reassured us that our stereochemical assignments up to this point were correct.

Having differentiated the two ester groups via lactonization, we next investigated selective reduction of the lactone (Scheme 6); L-Selectride® (lithium tri-*sec*-butylborohydride) proved to be an ideal reagent for this transformation, providing a mixture of two lactol anomers, which upon treatment with propanedithiol and $BF_3 \cdot Et_2O$ gave lactone dithiane **15** in 91% overall yield from **14**. Elaboration to



SCHEME 6



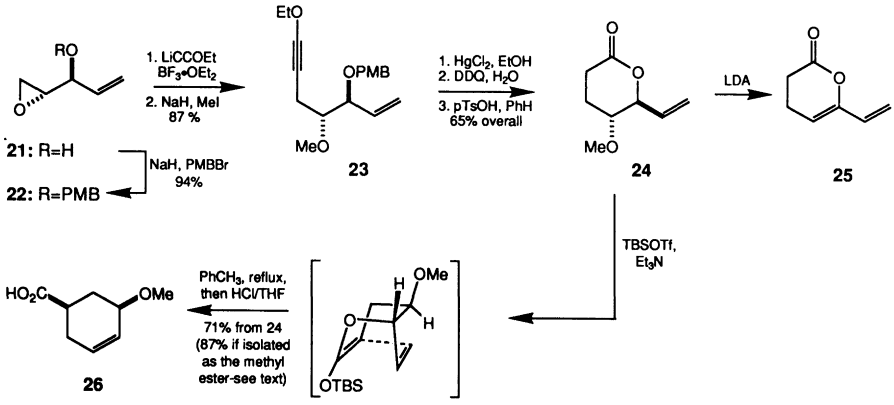
SCHEME 7

iodide **16** was accomplished by the three step sequence of $LiAlH_4$ reduction, iodination, and silylation (64% overall yield). Iodide **16** was converted into a series of compounds **17**, **18**, and **2**, which were utilized in model studies with isobutyraldehyde to determine potential methods for forming the C_{19}–C_{20} olefin; from these initial studies, phosphonamide **2** emerged as the optimal coupling partner.

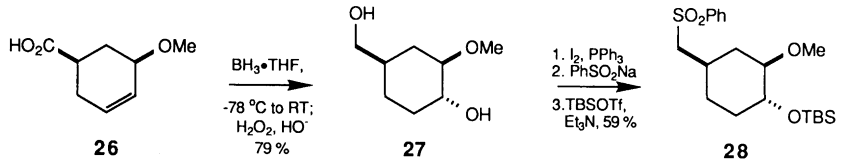
An interesting approach to the C_{19}–C_{20} olefin was pursued by David Uehling, who had joined the FK506 group in September of 1987, following his graduate studies with Clayton Heathcock, and who developed much of the chemistry described above. (Tarek had foolishly thought he could escape by moving to Harvard to work with Professor David Evans; little did he know that we would be following him in less than a year.) As outlined in Scheme 7, this involved conversion of lactone **15** into β-keto phosphonate **19**, followed by a Horner-Wadsworth-Emmons type coupling to provide an *E* enone such as **20**. Were R in **20** to be a suitable derivative of the C_{21}–C_{34} portion of FK506 (e.g., **62** in Scheme 21), then deoxygenation would provide the equivalent of dithiane **63** (Scheme 23). David found that the chemistry up to enone **20** (with R = isopropyl or cyclohexyl) worked well, but deoxygenation conditions could not be found that left the dithiane and trisubstituted olefin intact.

IV. Preparation of the Cyclohexyl Portion and Model Sulfone Couplings: The First Generation Approach to the C_{27}–C_{28} Trisubstituted Olefin

Investigations into the preparation of the cyclohexyl moiety had been initiated by Dave Smith in August of 1987. The approach outlined in Schemes 8 and 9 was particularly appealing to us be-



SCHEME 8



SCHEME 9

cause it symbolized the interactive spirit between ourselves and the Danishefsky group by combining elements of each research program; that is, the group- and face-selective epoxidation of divinyl carbinol[10] and an Ireland-Claisen rearrangement of a δ-lactone-derived silyl ketene acetal.[16] The latter rearrangement allowed us to transfer the C–O chirality from a Sharpless epoxidation into the cyclohexyl chirality required for the C_{28}–C_{34} subunit of FK506. Epoxide **21** was a compound of some familiarity to Dave from his earlier research efforts,[10,17] and its conversion to acid **26** is outlined in Scheme 8. Exposure of PMB ether **22** (PMB = *para*-methoxybenzyl) to lithioethoxyacetylene followed by methylation with sodium hydride and methyl iodide provided acetylene **23**, which was hydrated, deprotected, and cyclized to provide lactone **24**.

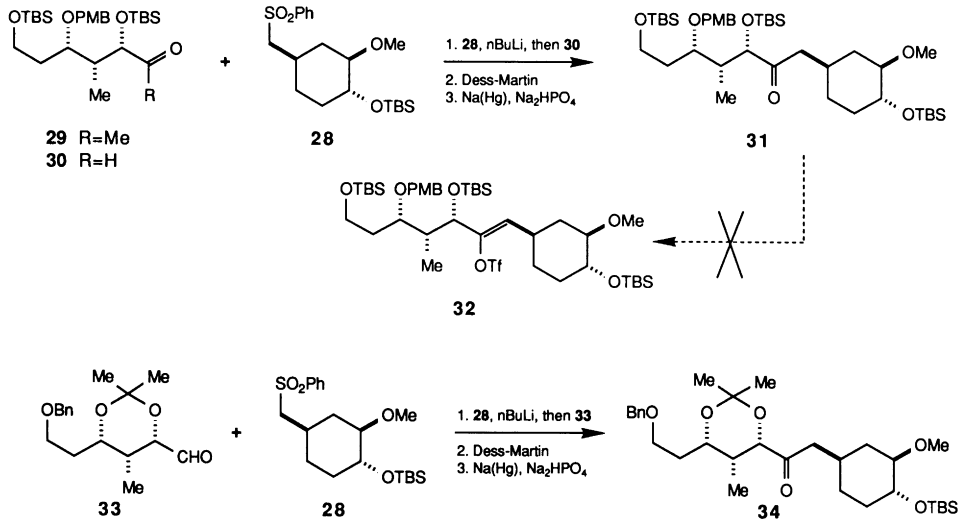
Initial investigations of the Ireland-Claisen rearrangement involved treatment of **24** with lithium diisopropylamide (LDA); this resulted in methoxide elimination to the corresponding 1,3-diene

(**25**). When **24** was exposed to less basic enolization conditions (*t*-butyldimethylsilyl triflate and triethylamine) and then to refluxing toluene, the desired [3,3]-sigmatropic rearrangement took place. Hydrolysis of the silyl ester provided acid **26** in 71% yield; however, isolation of the methyl ester following direct treatment of the crude acid with diazomethane was even more efficient, providing methyl ester **54** (Scheme 19) in 87% overall yield. A comment concerning the reliability of this reaction is warranted: as with any key reaction in a synthetic sequence, the issue of how well the reaction can be scaled up is critical to processing large quantities of material. While the Claisen rearrangement described here was initially run in a sealed NMR tube (10–20 mg scale), it was eventually run in a 1-liter flask (1–2 gram scale) *with the same or better yield.* Experienced chemists will recognize the value of a reaction that scales up so reliably.

Treatment of acid **26** with excess borane effected regio- and stereoselective hydroboration of the olefin plus reduction of the acid to provide, after oxidative workup, diol **27** in 79% yield. That this compound possessed the stereochemistry required for the cyclohexyl moiety of FK506 was confirmed by comparing its ^{1}H NMR spectrum with that reported for a degradation product of FK506 corresponding to **27**.[2] Elaboration of the diol to sulfone **28** occurred without incident as shown in Scheme 9. We were now ready to investigate couplings to form the C_{27}–C_{28} trisubstituted olefin.

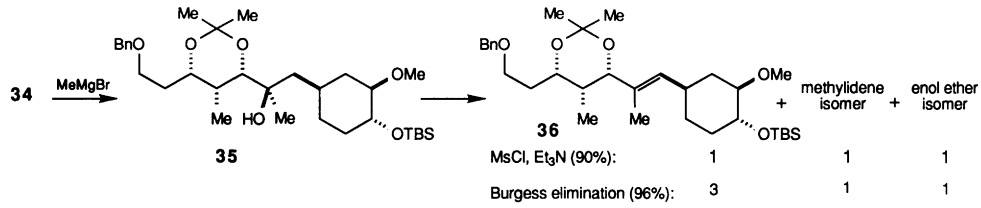
Efforts by our colleagues in the Danishefsky group had produced ketone **29** and aldehyde **30**,[15e] and several protocols for joining these compounds with sulfone **28** were investigated (Scheme 10). Attempted coupling of ketone **29** with the lithium anion of our sulfone met with repeated failure; however, sulfone addition to aldehyde **30** could be achieved in good yield. Oxidation with the Dess-Martin periodinane[18] followed by reductive desulfonylation provided ketone **31**. Several attempts were made to convert **31** into enol triflate **32**, but this transformation could not be achieved.[19] The sulfone anion could also be added to aldehyde **33**, which we had prepared as a model for investigating various routes to the required trisubstituted olefin. Oxidation and desulfonylation then provided ketone **34**, which proved to be our first successful substrate for formation of the C_{27}–C_{28} trisubstituted olefin.

Since additions to methyl ketone **29** had met with failure, our plan was to couple *via* an aldehyde (e.g., **30** or **33**), elaborate to a ketone



SCHEME 10

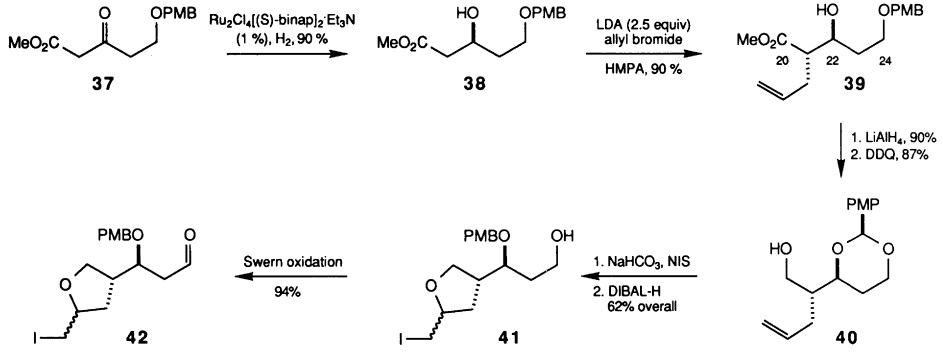
such as **34**, and then add a methyl group and attempt to find conditions to effect regio- and stereoselective elimination to olefin **36**. Indeed, addition of methylmagnesium bromide occurred smoothly to provide the tertiary alcohol **35**, as predominantly (>20 : 1) one isomer (the isomer depicted in Scheme 11 is that predicted for a chelation-controlled addition, although this stereochemistry was never rigorously proven). Treatment with methanesulfonyl chloride and triethylamine provided a mixed result: the alcohol had indeed suffered elimination, but the product was a 1 : 1 : 1 mixture of the three possible regioisomers. Several attempts were made to equilibrate these isomers, with no success. When the same elimination was performed with the Burgess reagent,[20] a more promising result was realized. The desired trisubstituted olefin was formed as the major component of a 3 : 1 : 1 mixture with the two isomers observed earlier, one of which (the enol ether isomer) could be removed by chromatography. Thus a method was in hand that allowed for the coupling of sulfone **28** with a suitable aldehyde and elaboration to a 3 : 1 mixture of two olefins in which the desired isomer predominated. While we were not completely satisfied with this coupling protocol, it was suitable for initial forays into couplings with a more fully functionalized aldehyde whose preparation was already underway.



SCHEME 11

V. Preparation of the C_{20}–C_{27} Portion: Acyclic Stereocontrol via Substrate-Controlled Reactions

As demonstrated in the Shinkai group's synthesis of FK506,[5] the stereochemistry found in the C_{20}–C_{27} region can be efficiently constructed by a series of Evans aldol reactions. However, we were interested in preparing this fragment without the use of chiral auxiliaries and in a fashion amenable to a convergent synthesis; therefore we chose Noyori's ruthenium BINAP-catalyzed asymmetric hydrogenation of β-keto esters.[21] As outlined in Scheme 12, this reduction was used to set the C_{22} stereochemistry as *S* (e.g., compound **39**), and this center was then used in a series of substrate-controlled reactions to set the stereocenters at C_{21}, C_{24}, and C_{25}. Note that the C_{22} stereocenter will eventually be returned to an achiral, trigonal center, as this carbon is a ketone in FK506; thus the decision to make this center *S* was simply one of convenience for setting the other three stereocenters.



SCHEME 12

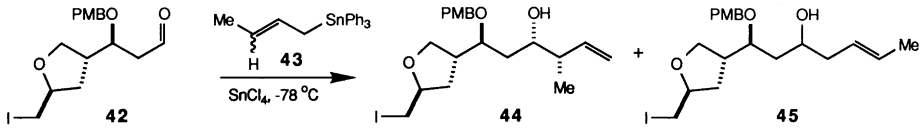
The dianion of hydroxy ester **38** was formed with 2.5 equivalents of LDA and treated with allyl bromide to provide ester **39** in excellent yield;[22] only one diastereomer was detected in the crude reaction mixture. The success of this reaction was critically dependent on the method by which the LDA was prepared. With the standard procedure (diisopropylamine and *n*-BuLi in THF), little if any alkylation product was detected, and substantial quantities of the starting material *as its n-butyl ester* were recovered. This apparently arose from lithium *n*-butoxide in the *n*-BuLi, presumably due to oxygen contamination. Several attempts at this reaction with various bottles of *n*-BuLi from different suppliers were made, but all failed. Much to our good fortune, a related alkylation was being investigated at the same time elsewhere in the Schreiber group; first-year graduate student Chris Poss (who is now nearing the completion of his doctoral studies) and post-doctoral fellow Scott Rychnovsky (who is now an Assistant Professor of Chemistry at Minnesota) were working on the synthesis of mycoticins A and B,[23] and Chris had discovered that the use of LDA prepared from diisopropylamine, lithium metal, and α-methyl styrene[24] avoided the problems associated with alkoxide contaminants found in commercial *n*-BuLi. When our alkylation was attempted with this modification, the reaction worked beautifully. This provides a good example of how the interaction among chemists in a research group working on a wide range of problems can lead to productive crossfertilization of ideas, and how one person's solution to a problem seemingly specific to his own project can benefit other projects as well.

Elaboration of ester **39** to aldehyde **42** proceeded remarkably smoothly. Reduction with $LiAlH_4$ followed by oxidation with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided benzylidene acetal **40** (PMP = *para*-methoxyphenyl).[25] The terminal olefin and the primary alcohol were masked by iodoether formation with either iodine or *N*-iodosuccinimide, and the acetal was reduced with diisobutylaluminum hydride to give alcohol **41**.[26] Swern oxidation then provided aldehyde **42**, which would serve as a substrate for the Lewis-acid mediated addition of a crotylstannane reagent. This transformation would prove to be particularly troublesome.

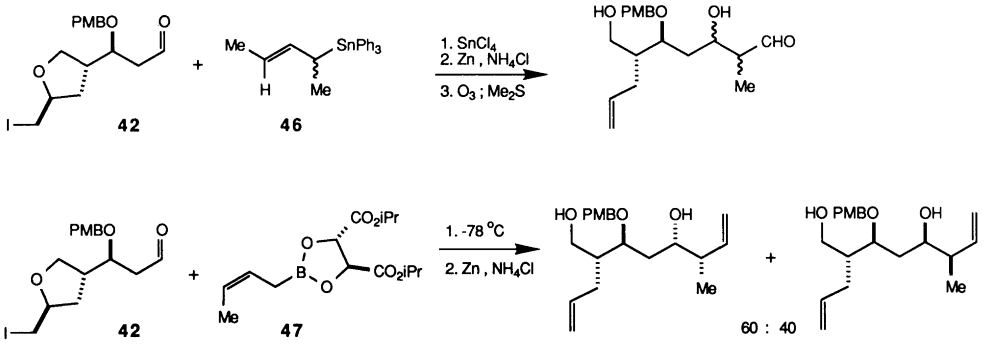
Armed with ample literature precedent for this reaction (most notably the work of Keck),[27] we began to investigate a variety of Lewis acids to effect the chelation-controlled union of aldehyde **42**

and triphenylcrotylstannane **43**. While some Lewis acids (e.g. $MgBr_2 \cdot Et_2O$, $SiCl_4$) gave low diastereofacial selectivity and sluggish reactions, others (e.g., $TiCl_4$, $EtAlCl_2$) were too harsh and caused deprotection of the *p*-methoxybenzyl (PMB) ether. $SnCl_4$ provided a happy medium; it was sufficiently mild to leave the PMB ether untouched at −78°C, but potent enough to effect complete reaction within 60 to 90 minutes (Scheme 13). Furthermore, the diastereofacial selectivity was quite high (opening of the iodoether with Zn/NH_4Cl and acetylation provided a bis-acetate that was >95% isomerically pure by 250 MHz NMR). The downfall of this procedure was the formation of internal olefin isomer **45** as a substantial byproduct (20–40% of the reaction product); this isomer was difficult to separate from the desired product, and necessitated several tedious chromatographic cycles, which made the sequence difficult to scale up efficiently.

We were not satisfied with this procedure, although it was the best available to us for almost a year. Shortly after our move to Harvard in August of 1988, we began a concerted effort to find a more practical solution to this reaction, which had become a significant bottleneck in the flow of material. Several Lewis acids were reinvestigated with various orders of addition and precomplexation protocols, and the use of tributylcrotylstannane as well as isomerically enriched (>85% *E*) triphenylcrotylstannane was studied. Two of the more interesting potential solutions are outlined in Scheme 14. Chuck Stankovic, then a fourth-year graduate student in the Schreiber group, pointed out a literature reference[28] for the addition of α-methyl triphenylcrotylstannane **46** to aldehydes, which can give rise to only one olefin regioisomer; the added methyl group at the olefin terminus would be of no consequence, as this double bond was to be oxidatively cleaved by ozonolysis. Treatment of aldehyde **42** and this stannane with $SnCl_4$ followed by iodoether opening and ozonolysis showed a *ca.* 1 : 1 mixture of aldehyde diastereomers; apparently the addition was not



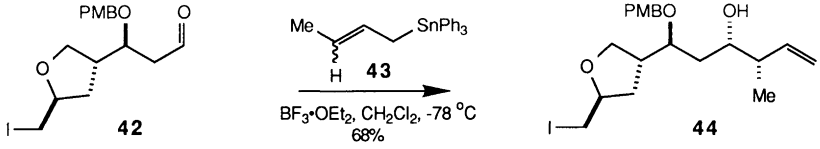
SCHEME 13



SCHEME 14

facially selective with our substrate. We also investigated Roush's chiral crotylboronate **47**,[29] but this reagent gave only a 3 : 2 mixture of addition diastereomers following iodoether opening; this indicates that aldehyde **42** must have a strong intrinsic selectivity for formation of the β-carbinol in this reaction, as **47** typically exhibits 3–13 : 1 enantiofacial selectivity for the isomer corresponding to the α-carbinol.

The current solution to this problem was achieved when Dave Smith examined the work of Reetz on allylsilane additions to β-alkoxy aldehydes.[30] Reetz observed predominant (95 : 5) formation of the 1,3-*anti* isomer expected for a chelation-controlled addition with $TiCl_4$ and $SnCl_4$; surprisingly, however, $BF_3 \cdot Et_2O$ also gave useful levels of selectivity (91 : 9) in the "chelation-controlled" sense. Because of Reetz's results with allylsilanes, we decided to study the use of $BF_3 \cdot Et_2O$ with our crotylstannane addition; indeed, exposure of aldehyde **42** and triphenylcrotylstannane **43** (As a 55 : 45 mixture of olefin isomers) to $BF_3 \cdot Et_2O$ at $-78°C$ provided the desired isomer **44** as the major component of a 4 : 1 mixture (Scheme 15). Of significant practical advantage, this isomer could be isolated in 45–55% yield

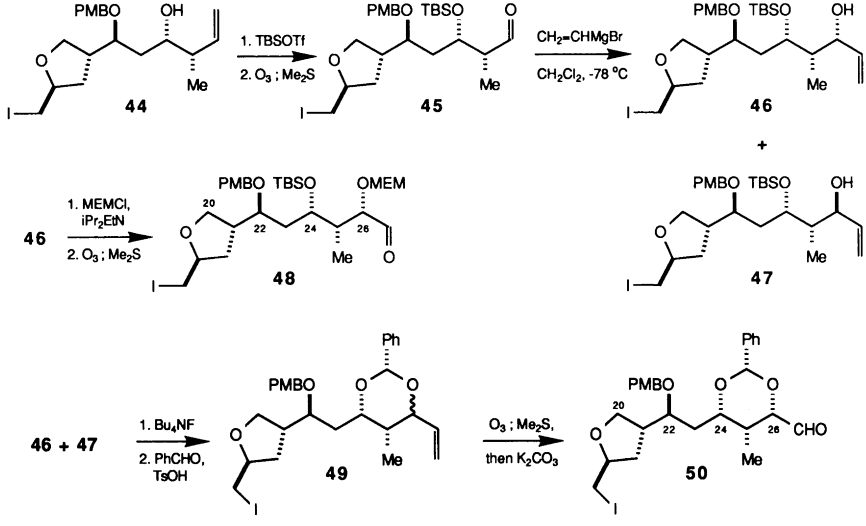


SCHEME 15

after one chromatographic cycle; after several recycles of mixed fractions, the isolated yield could be raised to 68%. A practical solution to the troublesome crotylstannane addition was finally at hand.

VI. The Burgess Elimination Route to the C_{20}–C_{34} Portion: A Tedious Coupling Procedure

While the above studies on optimization of the crotylstannane addition were in progress, advancement from homoallylic alcohol **44** was taking place (Scheme 16). Silylation with *t*-butyldimethylsilyl triflate and ozonolysis provided aldehyde **45**, which was treated with vinyl magnesium bromide to provide a mixture of allylic alcohols in which the Cram isomer **46** predominated. Our initial plan was to control the stereochemistry at C_{26} *via* equilibration of aldehyde **50** (ancillary stereocontrol),[31] so the degree of Cram-selectivity was considered inconsequential. However, the serendipitous discovery that this reaction was moderately Cram-selective (**46**:**47** = 2–3 : 1, with the highest selectivity being obtained in CH_2Cl_2) was crucial to our later development of the vinyl bromide approach to the C_{27}–C_{28} olefin. The mixture of allylic alcohol isomers (**46** + **47**) was treated

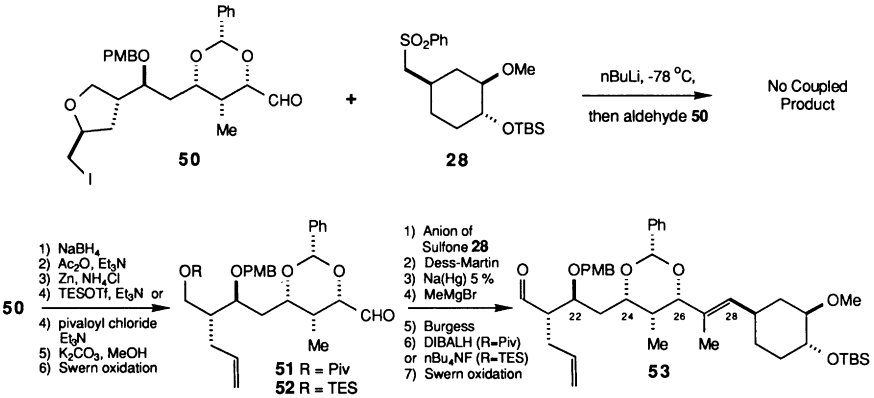


SCHEME 16

with Bu_4NF, and the resulting 1,3-diols were exposed to benzaldehyde and catalytic *p*-toluenesulfonic acid to form acetals **49**. Ozonolysis of the terminal olefin and *in situ* equilibration with K_2CO_3 provided the 1,3-*syn* acetal **50** as the major isomer (>12 : 1).

With the exception of Schemes 14 and 15, the chemistry described up to this point was developed at Yale University during our very productive interactions with Sam Danishefsky and his co-workers. The fact that two large synthetic research programs were able to work interactively on a molecule of such great current interest is a favorable testimony to the interactive nature of the Yale Chemistry Department. The work achieved during this period was reported in a series of five communications that were submitted at the time of our move to Harvard.[15a–e] Our desire to tie up any loose ends prior to the submission of these communications led to some rather frantic experiments during our last few weeks at Yale; for example, aldehyde **48** was prepared and characterized less than 24 hours before the movers arrived to begin packing our lab equipment for the move to Harvard.

Several attempts to couple aldehyde **50** with sulfone **28** met with complete failure; no products incorporating both coupling partners could be isolated (Scheme 17). Although we never isolated products corresponding to iodether opening of aldehyde **50**, we reasoned that this functionality was the most likely culprit for the reaction's failure. Thus, a tedious and rather lengthy detour was undertaken to convert **50** into aldehydes **51** and **52**, in which the iodoether was replaced by a pivaloyl ester or triethylsilyl ether, respectively. Indeed, the sulfone



SCHEME 17

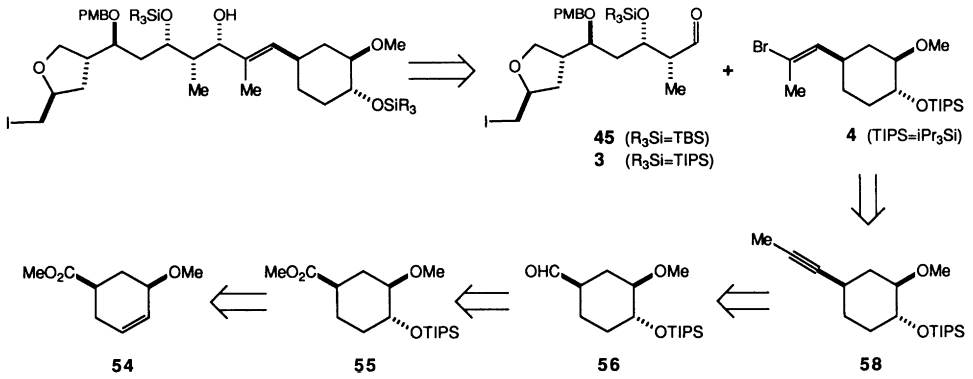
anion coupled smoothly with both of these aldehydes; apparently our sulfone coupling procedure was incompatible with the iodoether functionality. Aldehyde **53**, which represents the C_{20}–C_{34} portion of FK506, was prepared by the sequence shown in Scheme 17. *However, we ascertained that a practical total synthesis simply could not be achieved by this route.* The large number of transformations (13 steps from aldehyde **50**) prevented the material processing that would be necessary to work out the completion of our planned synthesis. An alternative solution had to be found.

VII. The Vinyl Bromide Coupling: A More Efficient Second Generation Approach to the C_{27}–C_{28} Olefin

In addition to a weekly group meeting, the Schreiber group gathers each week for "Show and Tell," in which group members present their most recent research results and gather advice from other group members on any particularly troublesome experiments they're working on. It was during one such meeting in January of 1989 that the vinyl bromide approach was originally conceived. Masashi Nakatsuka, a postdoctoral fellow from the Sumitomo Pharmaceutical Company in Japan, had joined the project the previous September, and was bringing up substantial quantities of material through the sequence outlined in Scheme 12. John Ragan, then a fourth-year graduate student, was likewise bringing material through the Claisen route to the cyclohexyl subunit (Scheme 8). Frankly, however, we realized that we had no good way to join these two pieces; our prospects for achieving a total synthesis of FK506 in the near future were grim.

Armed with the knowledge that the vinyl Grignard addition to aldehyde **45** is moderately Cram-selective, and blessed with the lethargy of mind induced by a Friday morning group meeting, John began to scribble down some structures, and happened upon vinyl bromide **4**. Had we ever considered a subunit such as this for the cyclohexyl moiety? The answer was that we had, but had ruled it out as being incompatible with coupling partners such as **29** or **30**, which we had originally been striving to utilize in order to maximize our interactions with the Danishefsky group (Scheme 10). Given the rather dismal state of affairs with the current sulfone coupling, however, this idea now seemed worthy of investigation.

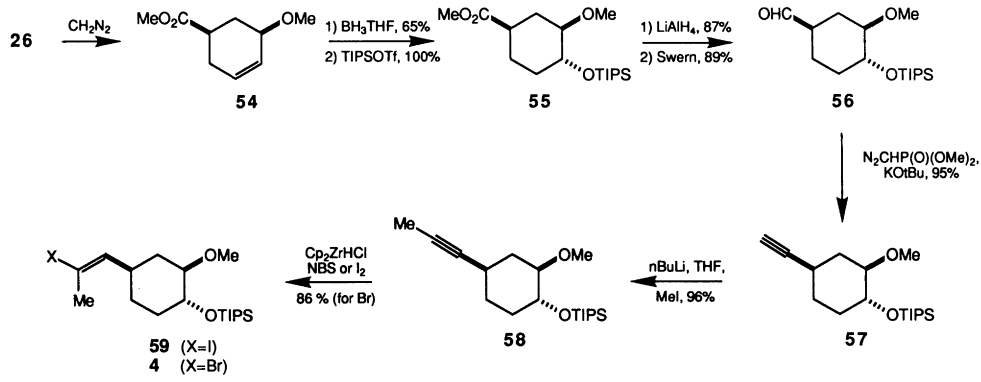
We had been at Harvard for just over four months, and in retrospect, it seems quite appropriate that the vinyl bromide route was conceived at this time. The precedent of a similar vinyl halide coupling was in Corey's landmark syntheses of erythronolides A[32] and B,[33] and details of this work (which involved hydrozirconation of a methyl acetylene) were readily available in Ph.D. theses in the Chemistry Department Library. This led retrosynthetically to acetylene **58** (Scheme 18), which could be prepared from aldehyde **56** by known methods.[34] Aldehyde **56** could in turn be prepared by a minor modification of the cyclohexyl synthesis. It is interesting to note how three serendipitous findings were juxtaposed and led to this development: our previous observation of moderate Cram-selectivity in additions to aldehyde **45**, Corey's precedent for the regio- and stereoselective hydrozirconation of a methyl acetylene closely related to **58**, and the fact that such an acetylene could be prepared from an intermediate on our current synthetic pathway. (Indeed, the Claisen rearrangement leading up to aldehyde **56** had been set up the previous evening.) In addition, we already had a Gilbert reagent $[N_2CHP(O)(OMe)_2]$[34d] in hand as a gift from Dr. Jim Hauske of Pfizer, a longtime friend, and the Cp_2ZrHCl necessary for the proposed hydrozirconation[35] was available from Bruce Dorsey, a postdoctoral fellow in the group, who had prepared ample quantities of the reagent for his own project. Our initial optimism for this new route was quite high, and was only to be increased as the strategy was successfully implemented.[36]



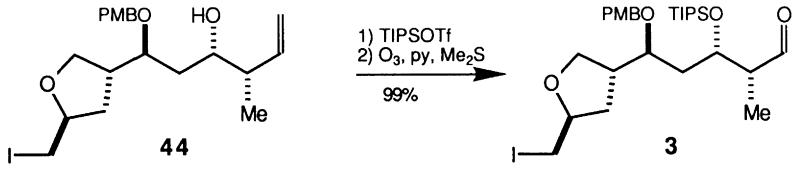
SCHEME 18

The preparation of vinyl halides **4** and **59** proceeded smoothly (Scheme 19); vinyl iodide **59** was in hand within three weeks. Aldehyde **3** was also readily prepared by the two-step sequence shown in Scheme 20; it should be noted that performing the ozonolysis in the presence of pyridine greatly improved the yield (from 50–60% to 99% for the two step sequence). Not surprisingly, development of an efficient coupling protocol was a more challenging task.

We first investigated lithiation of the vinyl iodide with a variety of reagents (*n*-BuLi, *sec*-BuLi, *t*-BuLi, Li metal, and Li·naphthalenide). These methods met with some encouraging success on model systems such as cyclohexane carboxaldehyde but did not provide acceptable coupling yields with aldehyde **3**. We were soon to find that the iodoether was again causing problems. In the course of the coupling investigations, we had also prepared vinyl bromide **4**. Using this compound, Masashi found that upon metallation with *t*-BuLi and addition of aldehyde **3** he recovered unreacted aldehyde, the olefin resulting from protonation of the vinyllithium reagent, *and vinyl iodide* ***59***. Clearly, the iodoether was quenching the vinyllithium species.



SCHEME 19

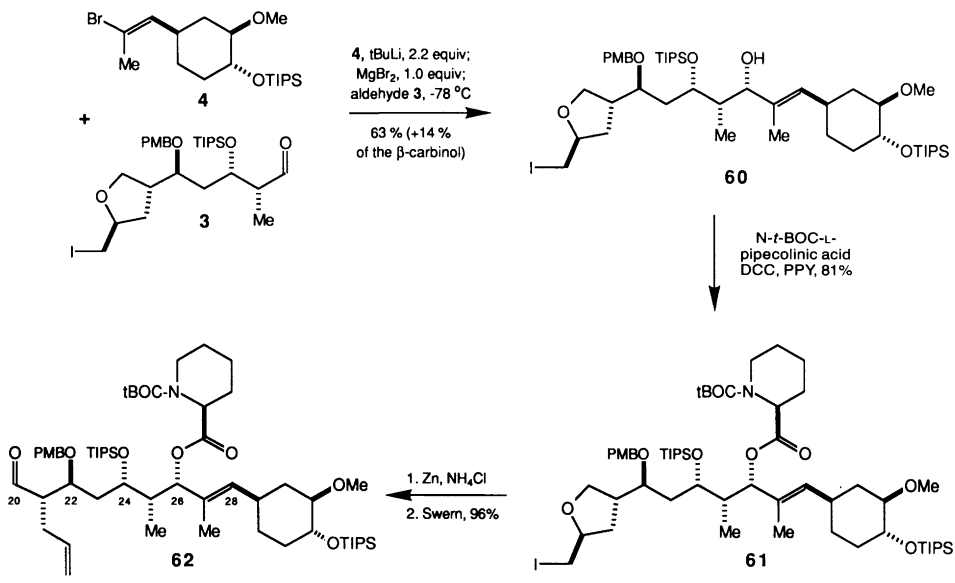


SCHEME 20

This was hardly an encouraging result, as it was all too reminiscent of the failed sulfone couplings which we had earlier attributed to the iodoether functionality. Fortunately, we soon discovered that treatment of the vinyllithium species with anhydrous $MgBr_2$ (freshly prepared from magnesium metal and 1,2-dibromoethane) generated the corresponding Grignard reagent, which added smoothly to aldehyde **3** to give a 4.5 : 1 ratio of two readily separable allylic alcohols in 77% yield. We were quite confident that the major isomer was the α-carbinol resulting from a Cram-selective addition; indeed, this was shown to be the case by correlation with material prepared by the earlier sulfone route, wherein the C_{26} stereochemistry was controlled *via* ancillary stereocontrol.

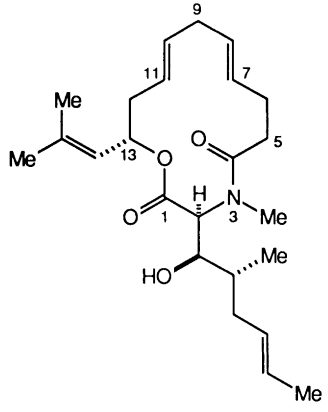
In addition to providing a substantially more efficient coupling of the C_{20}–C_{26} and C_{27}–C_{34} fragments (this route shaved 18 steps off of our earlier synthesis *via* aldehyde **53**), the vinyl bromide strategy allowed for easy differentiation of the C_{24} and C_{26} alcohols. This was an advantage we truly appreciated, for differentiation of these two oxygens in compounds such as **53** (Scheme 17) had been a source of no small trepidation for us. We initially considered some type of protecting group for the allylic alcohol in our new coupling product **60** but then realized that acylation with the pipecolinyl moiety found in FK506 would offer a more direct approach to the natural product. Although sluggish, the desired acylation could be effected with excess *N-t*-BOC-L-pipecolinic acid, DCC, and 4-pyrrolidinopyridine in CH_2Cl_2 at $-20°C$ over 20 to 30 hours to provide ester **61** (Scheme 21). We were concerned about racemization of the pipecolinic acid (which had been resolved *via* its D-tartaric acid salt). That this was not occurring was confirmed by running the reaction with racemic *N-t*-BOC-pipecolinic acid; two products were observed and were separable by careful silica gel chromatography. The second isomer observed in the racemic coupling was clearly absent from the nonracemic coupling.

Introduction of the pipecolinyl moiety at this stage was actually a major conceptual departure from our original strategy, in which we had planned to form the FK506 ring system by a macrolactonization between the C_{26} alcohol and the C_1 ester. Introduction of the pipecolinyl unit at this stage, however, was consistent with a strategy in which the FK506 ring system would be formed by a macrolactamization between the N_7 amine and C_8 carbonyl. Some unpublished



SCHEME 21

observations of Bruce Dorsey (who is now employed at Merck in West Point) played a critical role in this revision of our macrocyclization strategy. Bruce had been investigating the preparation of the macrolide shown in Scheme 22 and found that macrolactonization (i.e., formation of the C_{13} oxygen-C_1 lactone) was difficult to achieve,



SCHEME 22

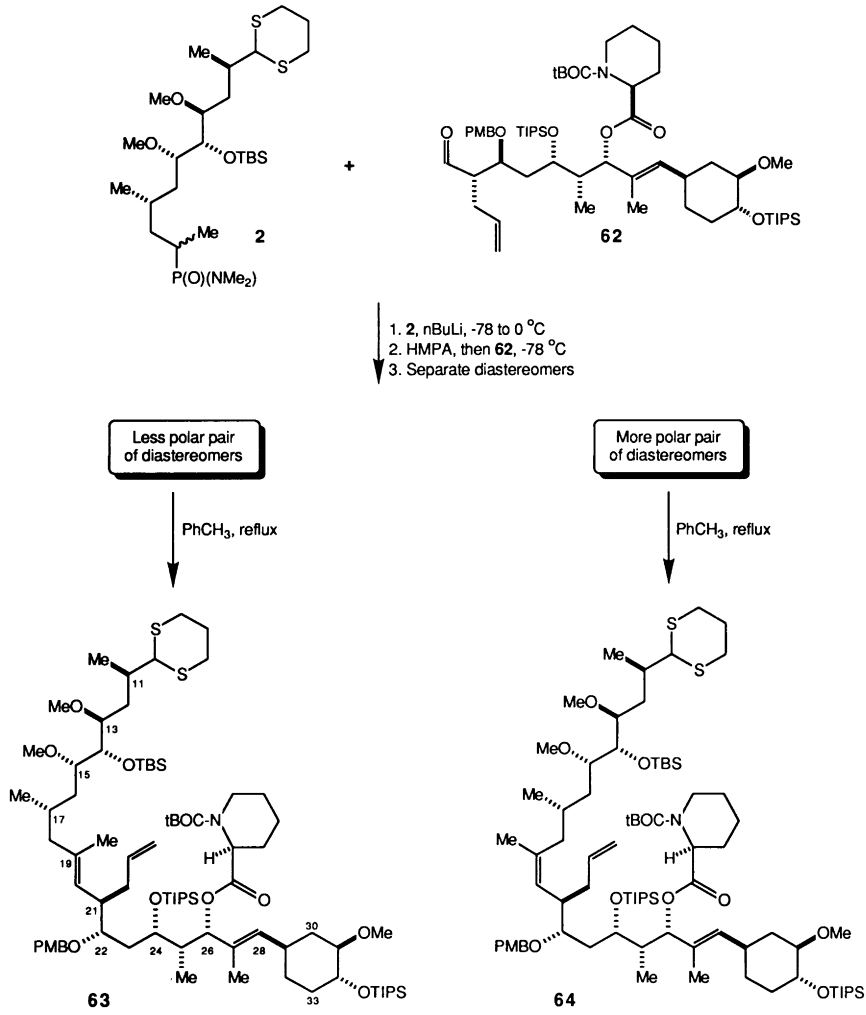
whereas macrolactamization (i.e., formation of the N_3–C_4 lactam) occurred readily. The relevance of these observations to the FK506 project was not lost on us, and in fact the sluggish acylation of alcohol **60** indicates that a macrolactonization approach to FK506 might indeed be especially challenging.

Opening of the iodoether **61** occurred smoothly with Zn/NH_4Cl and Swern oxidation of the resulting alcohol provided aldehyde **62**. We were now ready to study the coupling with phosphonamide **2** to form the C_{19}–C_{20} olefin.

VIII. The Phosphonamide Coupling: Preparation of the C_1–N_7/C_{10}–C_{34} Dithiane

In a series of model couplings of compounds **17**, **18**, and **2** with isobutyraldehyde (Scheme 6), phosphonamide **2** had emerged as the optimal coupling partner. Thus, our first investigations into formation of the C_{19}–C_{20} olefin used this compound (Scheme 23). Treatment of the phosphonamide with a slight excess of *n*-BuLi at 0°C for 30 minutes generated a deep yellow solution of the α-lithiophosphonamide. Cooling to −78°C and treatment with aldehyde **62** over 1–2 hours provided two pairs of hydroxyphosphonamide diastereomers by TLC, which were readily separable by chromatography. Treatment of the separated pairs of diastereomers with refluxing toluene for 6–8 hours cleanly provided two different C_{19}–C_{20} olefin isomers, in overall yields ranging from 50 to 70% (i.e., 25 to 35% for each olefin).

The assignment of olefin geometry to the two isomers was made on the basis of their ^{13}C NMR spectra. Careful examination of the $\delta 0$ to 50 ppm region of the two spectra showed a fairly clear correlation of all but two of the signals; the olefin formed from the less polar pair of diastereomers had a unique signal at 16.0 ppm, and the olefin formed from the more polar pair of diastereomers had a unique signal at 23.5 ppm. The Shinkai group had assigned the C_{19}–C_{20} olefin geometry of a similar dithiane on the basis of the C_{19}-methyl group resonance, which occurred at 16.6 ppm for the *E* isomer and 23.6 ppm for the *Z* isomer.[4] Although nothing was rigorously proven, we were nevertheless confident that the signal at 16.0 ppm arose from the C_{19}-methyl group of the desired *E* isomer **63**. Rigorous confirmation of this assignment came from the subsequent conversion of this compound into FK506.



SCHEME 23

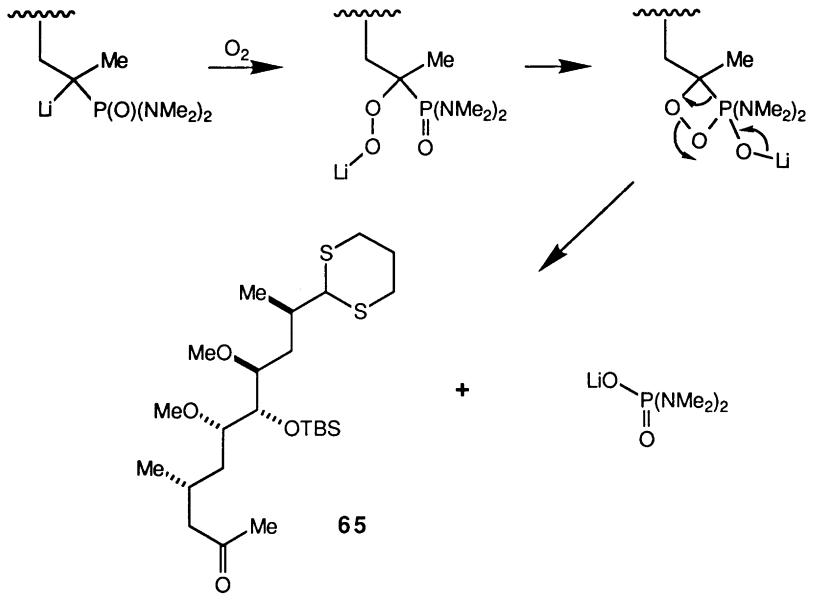
The phosphonamide coupling procedure described above was developed during the late spring and summer of 1989 by David Uehling, who had just accepted a position at Glaxo Pharmaceuticals. David left Harvard in August to start his new job, and shortly thereafter, we realized just how valuable he had been to the FK506 project; although the coupling had been completely reproducible in David's hands, our subsequent attempts to repeat this reaction failed completely. Had we

been trying to reproduce such a reaction from a literature report, we probably would have simply written our failure off to an incomplete description of the reaction conditions. But this reaction was developed within our own group, had been meticulously documented in David's notebook, and had been performed in our own laboratory on several occasions; clearly, something was amiss. After many detailed discussions with David over the telephone and a total of three failed coupling attempts, it was clear that our material was too precious to risk a fourth attempt. The only feasible solution was to fly David back to Cambridge and take advantage of his now mythical laboratory technique.

David flew into Boston on a Saturday night in October, and spent the evening tracking down glassware and syringes for his vacated lab bench. On Sunday morning the entire FK506 team gathered in David's lab to observe him perform the critical coupling reaction. Allow us to summarize a few very tense few hours in the lab by stating that the reaction worked beautifully; the most likely culprit for our previous failed attempts was an argon tank which contained unacceptable levels of oxygen. (David ran the reaction under house nitrogen, and this was the only difference we could ascertain between the successful and failed reactions.) Oxygen also seemed a likely culprit on the basis of our isolation of methyl ketone **65** from the failed couplings; a possible mechanism for the formation of this byproduct is presented in Scheme 24. We have subsequently been able to repeat this reaction on many occasions, even with David in North Carolina. Running the reaction under nitrogen seems to be the key factor.

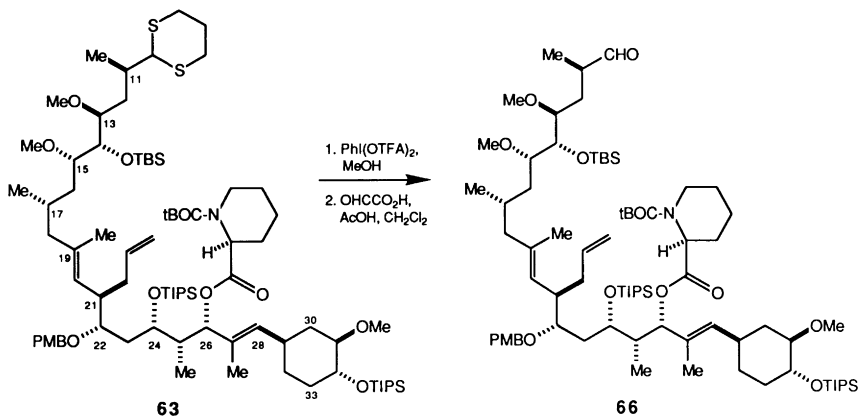
The events described above demonstrate the fragility of communicating laboratory procedures. We should have had at least one other group member perform this key reaction prior to David's departure so that any problems could be addressed while he was still present. Fortunately it all worked out smoothly, but those of us involved with this project will never take for granted the ability of one scientist to repeat another scientist's work on the basis of just a written record, however detailed.

Dithiane **63** corresponds to C_1–N_7 and C_{10}–C_{34} of FK506. In other words, all but two of the carbon atoms present in the natural product are present in this molecule. Hydrolysis of the dithiane to aldehyde **66** proved to be problematic, with several of the standard conditions (MeI, THF, aqueous CH_3CN; $PhI(OTFA)_2$, THF, aqueous CH_3CN;



SCHEME 24

$AgNO_3$, NCS, collidine, THF, aqueous CH_3CN) giving unacceptably low yields (25–35%). A two-step procedure was thus employed that utilized the Stork reagent [$PhI(OTFA)_2$, MeOH, CH_2Cl_2][37] to provide the dimethyl acetal, which in turn was hydrolyzed to the aldehyde in 59% overall yield (Scheme 25). We were now at a stage where the



SCHEME 25

last two carbon atoms of FK506 could be installed, and the final cyclization/deprotection sequence could be investigated. While we appeared to be quite close to our target, these remaining tasks would prove to be unexpectedly challenging.

IX. Macrolactamization and Challenging Protecting Group Removal: The Total Synthesis of FK506

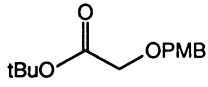
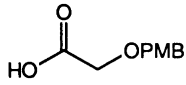
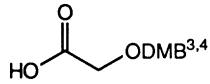
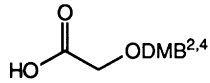
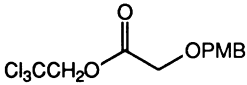
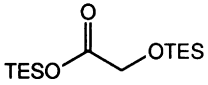
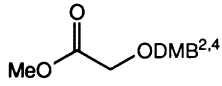
We commenced this final stage of the synthesis in the late spring of 1989, and thus were armed with the details of the Shinkai group's FK506 synthesis, which had appeared in the *Journal of the American Chemical Society* earlier that year. These workers had prepared an aldehyde that was related to compound **66** and elaborated it *via* an Evans aldol reaction followed by a macrolactamization to form the complete FK506 carbon framework. We had decided to follow a similar approach, but with an achiral aldol reaction to install the last two carbons (C_8 and C_9), consistent with our aim to minimize the use of complex reagents throughout the course of the synthesis. Of course, the reader will note in regard to the aldol reaction of interest that the stereochemistry at C_9 and C_{10} is eventually removed following oxidation of these centers.

Table I summarizes a few of the glycolate esters that we investigated to achieve this two carbon homologation. The identity of the alcohol protecting group turned out to be critical to subsequent transformations: PMB and 3,4-DMB (DMB = dimethoxybenzyl) ethers were difficult if not impossible to remove after macrolactamization. It should be noted that consultations with Professor Yoshito Kishi proved invaluable to us at this stage of the project. His expertise in this area is remarkable, as he demonstrated in the late stages of his palytoxin synthesis.[38] After a substantial amount of experimentation, methyl-2,4-dimethoxybenzyl glycolate **67** was identified as the optimal reagent. This compound was prepared from α-bromoacetic acid, which is commercially available in doubly ^{13}C-labeled form, allowing ready incorporation of ^{13}C labels at C_8 and C_9.

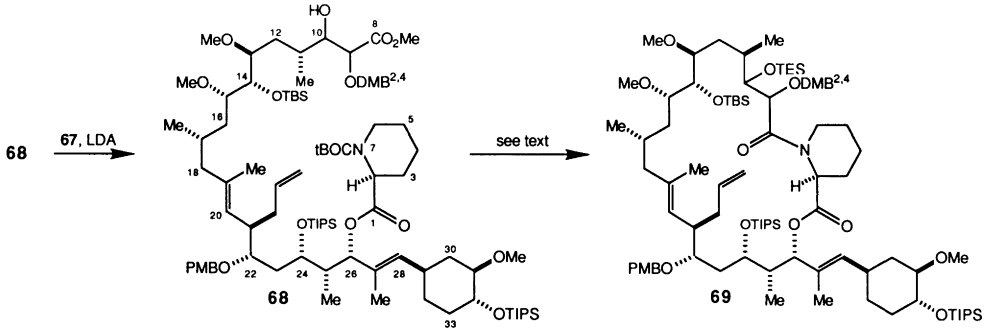
Treatment of aldehyde **66** with an excess of the lithium enolate of ester **67** provided a mixture of four diastereomeric aldol products **68** (Scheme 26). This mixture was then converted into macrolactams **69** (four diastereomers) by the following sequence: (i) 1 N LiOH, to effect selective saponification of the methyl ester, (ii) triethylsilyl

TABLE I

GLYCOLATE ESTERS USED IN ACHIRAL ALDOL REACTION

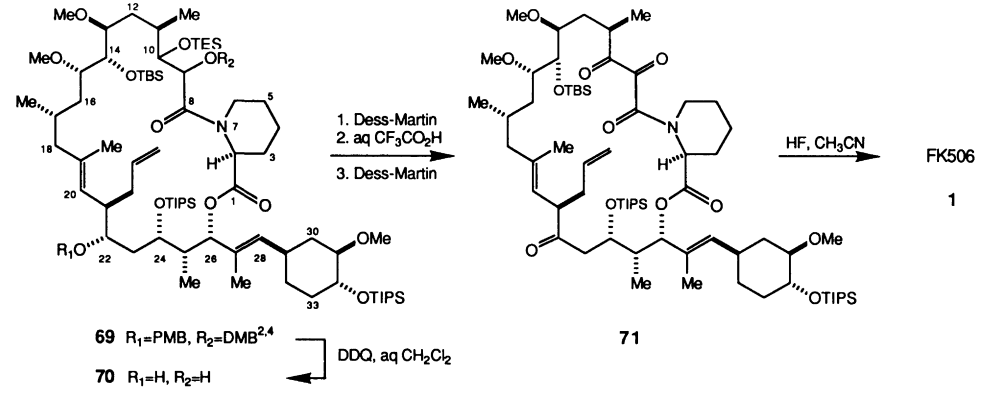
Two Carbon Aldol Reagent	Comments
	Aldol reaction OK, but tBu ester could not be removed.
	Aldol reaction (with dianion) and subsequent cyclization OK, but PMB could not be removed.
	Aldol reaction (with dianion) and subsequent cyclization OK, but DMB removal was low yielding (<20%).
	Unstable; 2,4-DMB labile to acid.
	Trichloroethyl ester unstable to LDA.
	Aldol reaction OK, but TES ether was unstable to silica gel aging (see text).
 **67**	Best reagent studied. See text.

triflate (TESOTf), to form the C_{10} TES ether and C_8 TES ester, and to convert the *t*-butyl carbamate to the corresponding TES carbamate; (iii) silica gel, with aging for 60 minutes prior to standard flash chromatography, to remove the TES ester and carbamate, leaving the corresponding amino acid; (iv) Mukaiyama reagent (2-chloro-1-methylpyridinium iodide), to effect macrolactamization. The four diastereomers were either separated or carried on directly, as described below.



SCHEME 26

Our first preparation of FK506 involved a deprotection sequence that was low-yielding but nevertheless provided enough material to reach the natural product. This sequence is summarized in Scheme 27. The four isomers of the macrolactamization product **69** were separated, and the behavior of each towards DDQ was investigated. The observation of both *p*-methoxybenzaldehyde (from the C_{22} PMB ether) and 2,4-dimethoxybenzaldehyde (from the C_9 2,4-DMB ether) by TLC indicated that deprotection was occurring, but the reaction was exceedingly slow, and a variety of byproducts was observed. Similar behavior was observed for each of the four diastereomers, so it appeared not to be a stereochemical or conformational effect. (This had caused us some concern, for it was possible that in the Merck



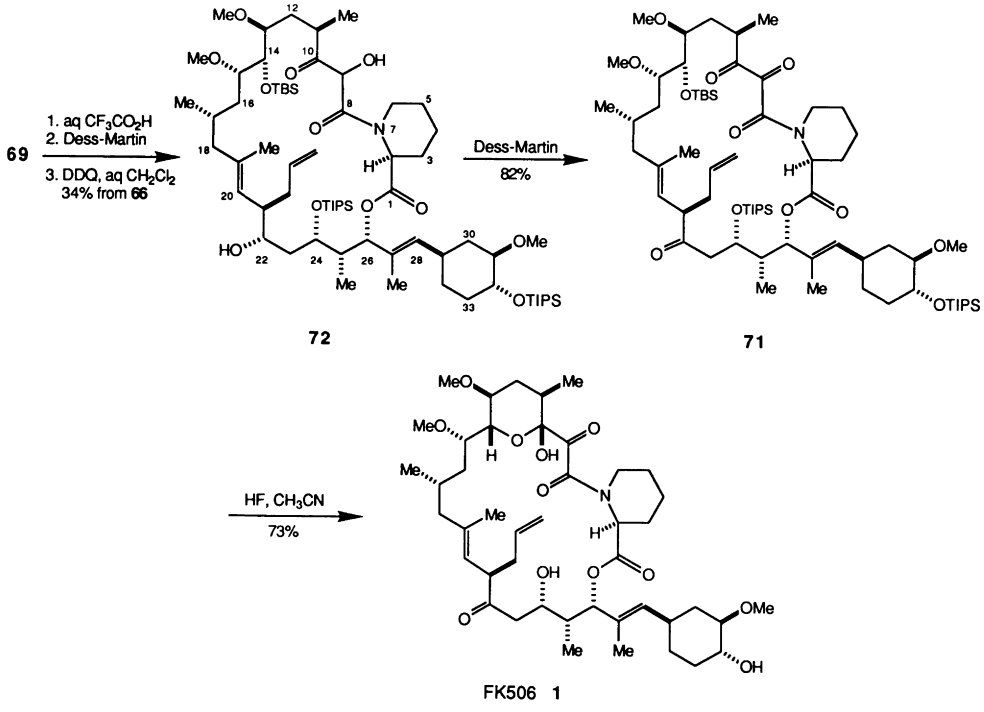
SCHEME 27

synthesis of FK506, which employed a PMB ether, only the isomer obtained by the Evans aldol reaction was readily deprotected for some steric or conformational reason.) These deprotections did provide a small amount of the desired C_9–C_{22} diol **70** (<20% yield), and this material was carried on as shown in Scheme 26 to provide a small amount (*ca.* 0.1 mg) of synthetic FK506. Although the sequence clearly had to be optimized, *there was little doubt from the 500-MHz ^1H NMR spectrum that our synthetic material was identical to natural FK506.*

The presence of several byproducts that had lost the triethylsilyl ether in the above debenzylation led us to conclude that this functionality was unstable to the DDQ deprotection. Thus, the remaining macrolactam **69** was treated with aqueous trifluoroacetic acid to remove the C_{10} TES ether and was then oxidized with the Dess-Martin periodinane (DMP) to provide the β-keto lactam (Scheme 28). Treatment of this compound with DDQ gave a much cleaner reaction by TLC and provided the C_9, C_{22} diol **72** in 34% overall yield from aldehyde **66** (for an average yield of 85.7% per step over the seven step sequence). Oxidation with the Dess-Martin reagent provided triketone **71**; treatment of this compound with 3N HF in CH_3CN for several hours again provided FK506 [the C_{32} triisopropylsilyl (TIPS) ether and C_{14} *t*-butyldimethylsilyl (TBS) ether are removed within 1–2 hours, while the C_{24} TIPS ether requires 12–18 hours for complete deprotection]. This sequence provided *ca.* 0.5 mg of synthetic FK506, and the 500 MHz ^1H NMR spectrum of this material overlapped completely with that of the natural product.

A third preparation of FK506 incorporated ^{13}C-labels at C_8 and C_9 through the use of methyl-2,4-dimethoxybenzyl (1,2-^{13}C)glycolate. The sequence of reactions was exactly the same as described above (Scheme 28), except that we could now readily obtain ^{13}C NMR data for C_8 and C_9 with just milligram quantities of material. This allowed us to monitor the oxidation state at these two carbons [e.g., in the bis-benzyl ether precursor to **72**, the C_9 signals (two rotamers) are at 91.5 and 84.7 ppm, while in triketone **71** they come at 188.4 and 186.6 ppm]; most importantly it allowed ^{13}C NMR analysis of the C_8 and C_9 carbonyls in FK506 in the presence of its biological receptor, FKBP.

A fourth preparation of FK506 was on a substantially larger scale, which allowed for the optimized yields shown in Scheme 28. Using unlabeled glycolate ester **67**, 45.0 mg of aldehyde **66** was carried

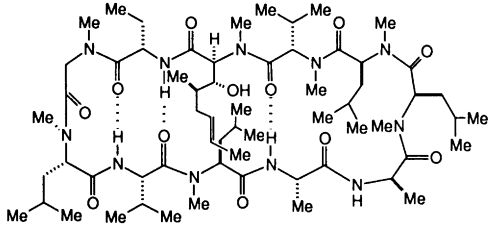


SCHEME 28

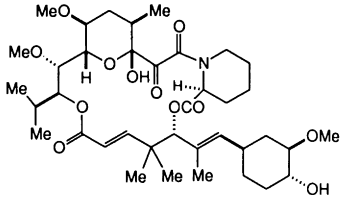
through the sequence to provide 5.2 mg of synthetic FK506, whose rotation,[39] spectroscopic properties (IR, ^{1}H NMR, and ^{13}C NMR), and chromatographic mobility in a variety of solvent systems were identical to those of natural FK506. This final reaction sequence also uncovered an interesting observation on the final desilylation: Masashi discovered that performing this deprotection in a polypropylene reaction vessel rather than a glass one substantially improved the isolated yield of FK506 (from 30–35% to the 73% yield shown in Scheme 28). This type of creativity and meticulous attention to detail is representative of Masashi's laboratory technique; it should also be noted that he alone was responsible for the development of all of the chemistry described above from aldehyde **66** through FK506. The final sequence of the total synthesis consisted of a total of 56 transformations; the emphasis on convergency resulted in a longest linear sequence of 32 reactions (from divinyl carbinol, *via* vinyl bromide **4**), and the overall yield was 0.21%.

X. Discovery of an FK506 and Rapamycin Binding Protein (FKBP)[40,41]

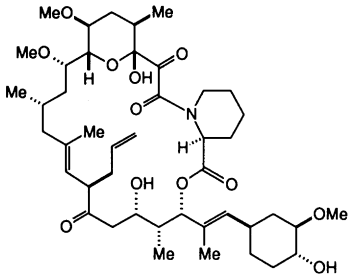
In the fall of 1988, David Uehling's talents were temporarily diverted from the FK506 total synthesis to the preparation of an FK506 affinity matrix, meaning FK506 covalently attached to a polymeric support. The object, of course, was to isolate an FK506 binding protein from a crude tissue extract containing thousands of proteins. Because FK506 itself is unreactive toward the commerical supports, a suitably functionalized tether had to be added, and the most obvious attachment point was one of the hydroxyls on FK506. After simple derivatization (acylation) procedures failed because FK506 either failed to react or decomposed, David discovered that if he first reduced the C_{22} ketone of FK506 with L-Selectride®, he could acylate the cyclohexyl hydroxyl specifically with β-azidopropionyl chloride. Subsequent reduction of the azide with 1,3-propanedithiol gave the free amine, which was found to react directly with the active *N*-hydroxysuccinimide esters of Affi-Gel 10. More recently, David's



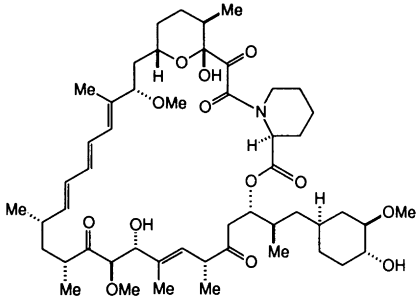
Cyclosporin A (CsA) **77**



506BD **78**



FK506 **1**

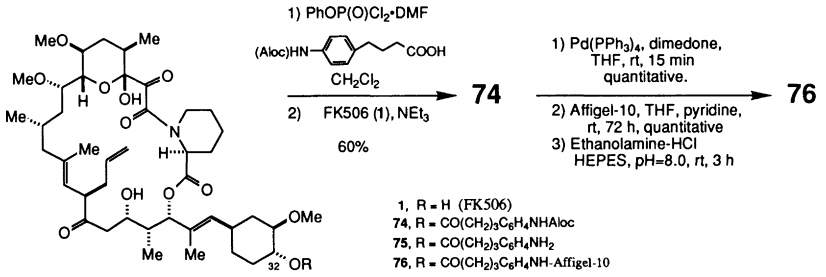


Rapamycin **73**

SCHEME 29

procedure has been modified by postdoctoral fellow Heinz Fretz. Heinz's procedure (Scheme 30) allowed direct acylation of the cyclohexyl hydroxyl of FK506 and also worked well with rapamycin (**73**, Scheme 29), a structurally related immunosuppressant.[42]

The affinity matrix was studied by Andrzej Galat, a postdoctoral associate in our laboratory, and by Matt Harding, then an Assistant Professor at the Yale Medical School (and who remains a close personal friend of S.L.S.). After incubating the matrix with extract of calf thymus or of human spleen and washing it, they batch-eluted with either FK506 or rapamycin. The predominant protein in the eluate from both drugs, estimated by its SDS–PAGE mobility to have a molecular weight of 14 kDa, was dubbed *fujiphilin* in analogy to cyclophilin (CyP), the predominant binding protein for the immunosuppressant cyclosporin A (CsA, **77**, Scheme 29). (Ultimately, the name was dropped in favor of FKBP when an editor objected that the protein might be confused with a nearly homonymic photographic medium, and the molecular weight was eventually found to be 11.8 kDa.) The most pressing issues regarding this protein were whether it was a new one, and more specifically, whether it was a relative or a modification of CyP. Though precious little material could be had from affinity chromatography, there was enough for N-terminal sequencing by Edman degradation. The 20 amino acids of sequence so obtained showed conclusively that our protein was indeed a new one, and one very different from CyP in its N terminus, but the possibility remained that homology would be found in the C-terminal end. (None was). John Siekierka and co-workers at the Merck, Sharp, and Dohme Research Laboratories independently isolated the same protein, and the two groups published their findings back-to-back.[40,41]



SCHEME 30

XI. Molecular Cloning[43,44] and Overexpression[43] of FKBP

We soon concluded that we needed to develop a procedure for larger-scale isolation, a task Matt and Andrzej would share, but that we should also undertake the molecular cloning of this new protein, meaning we should find and sequence the complementary DNA (cDNA) that encoded it. Cloning would not only give us the sequence of the protein, it would afford the opportunity to avoid the isolation bottleneck by overexpressing the human protein in the bacterium *E. coli*. Success in that endeavor promised yields measured in milligrams instead of micrograms and a purification procedure taking days instead of weeks. In fact, the physical and structural studies we envisioned would be impossible without cloned protein. It also seemed to us that we should do the cloning in house, despite our minimal experience in cloning proteins (to put it charitably). For expertise, we relied on Greg Verdine, an assistant professor specializing in bioorganic chemistry, on his group, and on Kurtis MacFerrin, a Schreiber student who had begun experiments in molecular biology under Greg's tutelage and who was meeting with good success. Bob Standaert, a graduate student who had been working on an unrelated synthetic project, was then offered the most unusual project of his career.

Our initial cloning strategy was based on the polymerase chain reaction (PCR), a new chemical method for amplifying a selected DNA sequence by more than 10^7-fold in an afternoon.[45,46] Those unfamiliar with the technique are referred to a *Chemical and Engineering News* cover story for an introduction.[47] While PCR has created a revolution in molecular biology, we take some comfort in viewing it as a type of enzymatic organic synthesis, with the starting material being a pair of synthetic oligonucleotides (15–50mers, typically), the reagent being a blend of all four monomeric deoxynucleotide triphosphates, and the catalyst being a DNA polymerase. We do not wish to stretch this analogy to the point where we feel justified in providing a "retrosynthetic" strategy for our PCR experiments or in giving an in depth analysis of our misadventures in cloning, but a brief explanation lacking technical details is helpful. To amplify a desired piece of DNA, one needs information only about the ends of that piece (20 bases is adequate) to prepare the oligonucleotide "primers"; in our case, the protein sequence and the universal genetic code formed the basis of an educated guess. The other necessity is a template to

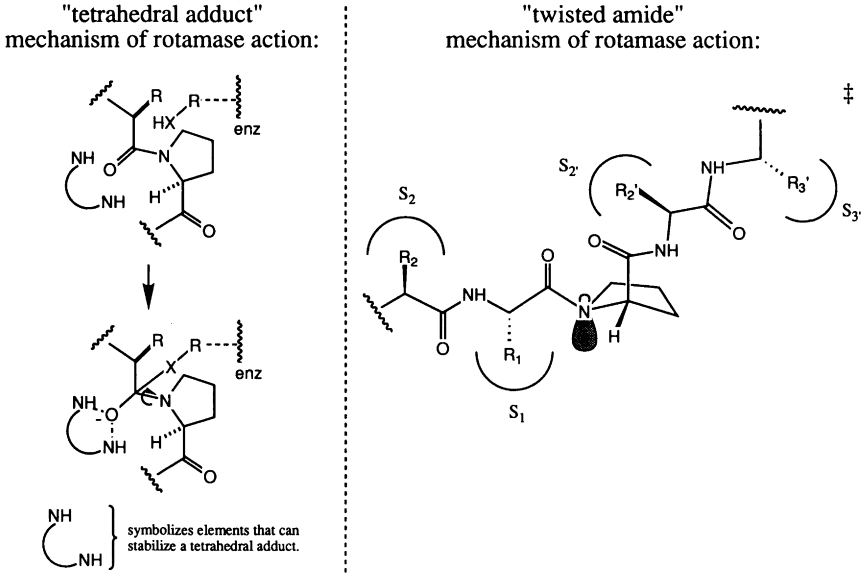
amplify, and this is provided by a cDNA *library*, which in simplest terms is an ensemble of DNA molecules representing, ideally, all of the proteins being made in the tissue from which it was derived.

Bob set about designing and making "oligos," and in April 1989, set about running PCRs. Initial efforts managed to amplify nothing, and later efforts amplified something worse: non-FKBP DNA (junk DNA, as far as we were concerned). PCR's great virtue, extreme sensitivity, can also be a great drawback. Sequences having a reasonable homology to the target sequence can be amplified, and if they are more abundant than the target, can be amplified predominantly. Aside from wasting time, isolating and sequencing junk DNA produces a chagrin comparable to that of an organic chemists's upon isolating, purifying, and exhaustively characterizing extract of Tygon tubing. Fortunately, Andrzej had in the meantime improved the isolation procedure for bovine FKBP, and with each new batch came more sequence information, first to 30, and then to 42 amino acids of the N terminus in July 1989. This information was quickly put to good use in the cloning effort, and in September Bob succeeded in amplifying the complete human FKBP cDNA. He began forthwith an effort to express the protein in *E. coli* using the expression cassette PCR (ECPCR) procedure, which had recently been developed in a collaborative effort by Kurtis MacFerrin of our group and Mike Terranova of the Verdine group.[48] Expressing a functional human protein in bacteria can be a time-consuming and frustrating task that sometimes borders on the impossible, and we were extremely fortunate that the second expression system Bob tried yielded a reasonable level of expression. Andrzej developed a quick and effective purification procedure that yielded 5–10 mg of pure, fully active protein from a litre of bacterial culture (we had never before had more than 0.5 mg of FKBP), and just before Christmas, we had our first large samples of recombinant protein in hand.

XII. (8,9-^{13}C)FK506 and Its Application to Investigations of the FK506/FKBP Complex[49]

In characterizing FKBP, Matt and Andrzej, and also the Siekierka group, had shown that FKBP was a rotamase, that is, an enzyme that catalyzes interconversion of the *cis* and *trans* rotamers of a peptidyl-prolyl bond.[40,41] This was a very intriguing observation because

cyclophilin is also a rotamase,[50,51] and furthermore, FK506 and CsA each inhibited the rotamase activity of its own respective binding protein but not that of the other. The shared catalytic activity of the two binding proteins, or immunophilins, had immediate (and deceptive) implications for the mechanisms of the drugs' immunosuppression, and it heightened our interest in mechanistic studies of the rotamase activity of FKBP. Amide resonance is the cause of the large (15–20 kcal/mol) barrier to rotation in amides; as rotation occurs, resonance stabilization is lost, and a complete loss of stabilization occurs when the carbonyl is twisted 90° out of the original amide plane. An enzyme catalyzing rotation must either disrupt amide resonance or else mitigate it. Two plausible mechanisms correspond to these alternatives (Scheme 31). In the first, a nucleophilic residue of the enzyme (or water activated by the enzyme) adds to the peptidyl carbonyl, and the resulting tetrahedral adduct is free to rotate about the former amide bond; after rotation, the nucleophile is eliminated, leaving the rotated amide. In the second, the enzyme simply stabilizes the normal, twisted, transition state conformation of the substrate through non-covalent interactions; alternately, it might destabilize



SCHEME 31. Mechanistic Hypotheses for the Catalysis by Rotamases.

the planar conformation, but the net effect would be the same: the barrier to rotation would be reduced.

On examining the structure of FK506, any organic chemist would note the unusual hemiketal–ketocarbonyl amide, and many, including us, suspected it of playing a role in the inhibition of rotamase activity. In particular, the pipecolinic acid residue looks a lot like proline, and the ketocarbonyl dyad looks electrophilic and thus would be a fine trap for an enzyme-bound nucleophile; the enzyme would be foiled because the tetrahedral adduct would be stable and the nucleophile would not readily be eliminated. Intuition thus would support the protease-like tetrahedral adduct mechanism, and it was this hypothesis we planned to test with the (8,9-^{13}C)FK506; nucleophilic attack would cause a large and unmistakable upfield shift in one of the carbonyl ^{13}C NMR signals.

It was perhaps unreasonably optimistic to undertake the total synthesis of (8,9-^{13}C)FK506 with the expectation that enough FKBP would be available for NMR spectroscopy when, in fact, we had not yet managed to find the cDNA for FKBP, let alone express it in *E. coli*. It must be considered an instance of remarkable good fortune that the preparation of the first batches of pure recombinant protein coincided perfectly with the completion of the total synthesis of labeled FK506. The time had come to perform the crucial experiment, but we approached it with as much trepidation as excitement because we could expect just one opportunity. Our sample of (8,9-^{13}C) FK506 amounted to about 0.6 mg, just enough to get a high quality ^{13}C NMR spectrum overnight, and it was priceless. If we destroyed it, we could not expect to get more for at least several months, and we did not know if complexation or merely excessive manipulation would prove fatal for protein or ligand. None of us had ever taken an NMR spectrum of a protein, but Mike Rosen, then a second-year graduate student, had been studying peptides by NMR and was fast becoming the NMR expert of the chemistry department, although he couldn't foresee the depth of his plight then. So, Mike was brought on board for the planning and execution of the total synthesis of the complex of FK506 and FKBP. After a string of meetings and discussions where we poured forth all the dread complications we could think of and laid out an experimental plan, Mike began the background work. First, he recorded ^{13}C NMR spectra of natural FK506 in (deuterated) methanol and methanol–water mixtures and saw no evidence of hydration

or hemiketal formation. He also discovered that the drug came out of solution if the water content was raised above about 40% and that no ^{13}C NMR signal whatsoever could be measured in pure water (D_2O), even with the labeled material.

Before consummating the experiment, Mike tested the strategy for preparing the complex with natural FK506 and a small sample of recombinant protein. A methanol solution of drug was added in small portions to a slight excess of recombinant protein in aqueous buffer, and with each addition came a cloudiness that disappeared quickly upon mixing. Addition of the entire sample in this way produced a completely homogeneous solution of complex. Feeling almost secure, he carefully added the precious (8,9-^{13}C)FK506 to another sample of recombinant FKBP and was met with something unexpected and alarming—a precipitate. We isolated it by centrifugation and found it to be completely insoluble in chloroform and water. Its identity remains a mystery, but we could at least show that it was not FK506 or FKBP. Somewhat shaken, we put the supernatant back in an NMR tube and started scanning. At first, we transformed the spectra after every hundred or so scans, but saw nothing conclusive and eventually tired of this and went home. The spectrum we had the next morning was something of a mystery; there were new upfield peaks, not at all where we expected them, and the FK506 signals were still present, but with an important difference: What in chloroform had been two pair of doublets, corresponding to the *cis* and *trans* rotamers of FK506, was now a single pair of doublets, corresponding to a single rotamer. We suspected that the upfield peaks might be from contaminants in our protein sample because their chemical shifts were not consistent with a tetrahedral adduct or any other reasonable modification of FK506. Glycerol, used liberally in the protein purification procedure, proved to be the culprit and had to be removed. Nervously, we removed our sample from the NMR tube and subjected it to ultrafiltration.[*] In this technique, the protein solution is concentrated by forcing it against a membrane that allows only small molecules (MW <3000 for our membrane) to pass through. Several cycles of concentration and dilution with fresh buffer were performed to remove all low molecular weight contaminants. Our greatest worry about this process was that sample losses can be significant, and we were particularly worried about loss of FK506 through the membrane, but our

fears proved unfounded. Once again, we placed the sample in the NMR tube and started collecting data. The new spectrum showed only the single pair of doublets at δ168.7 and 198.4 ppm (about 2–4 ppm downfield from either rotamer of the free drug in chloroform). There was no trace of the upfield signal that would arise for a tetrahedral adduct, and we had to conclude that, in the complex, FK506 existed intact and as a single rotamer (Figures 1 and 2). Moreover, the FK506 could be recovered completely by denaturing the protein and extracting the drug into chloroform.

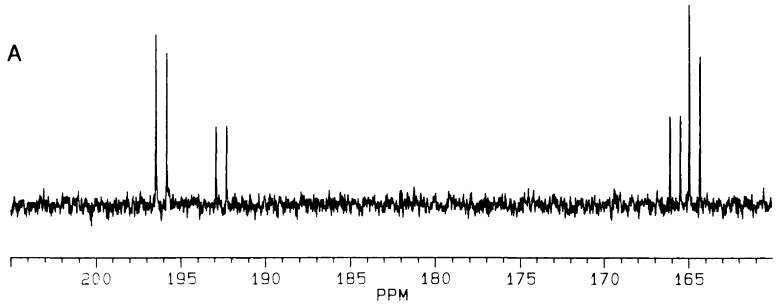


FIG. 1a. ^{13}C-NMR spectrum of (8,9-^{13}C)FK506 in chloroform-*d*, illustrating the existence of two rotamers about the C_8–N_7 amide bond. The spectrum was recorded at 125.8 MHz in $CDCl_3$; the region δ 160–210 ppm is displayed (J_{major} = 64 Hz, J_{minor} = 61 Hz; C_{8major} = 164.6 ppm, C_{8minor} = 165-8 ppm, C_{9major} = 196.1 ppm, C_{9minor} = 192.6 ppm; $CDCl_3$ reference).

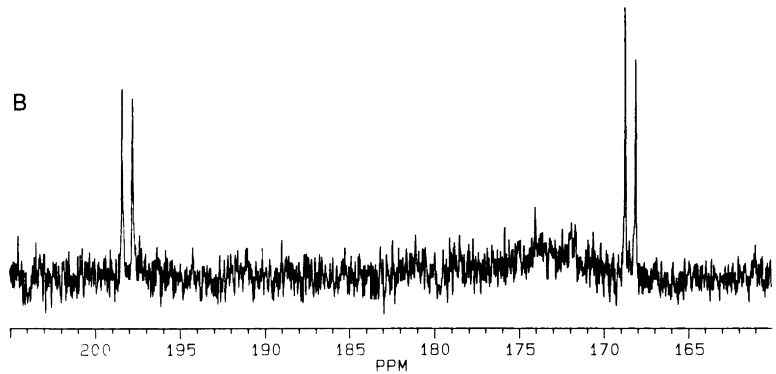


FIG. 1b. ^{13}C–NMR spectrum of the (8,9-^{13}C)FK506/FKBP complex, illustrating the existence of a single rotamer about the C_8–N_7 amide bond. The spectrum was recorded at 100.61 MHz in 9 : 1 D_2O/10 mM potassium phosphate buffer (pH 7.3, 25°C); the region δ160–210 ppm is displayed (J = 61 Hz; C_8 = 168.7 ppm, C_9 = 198.4 ppm; dioxane reference).

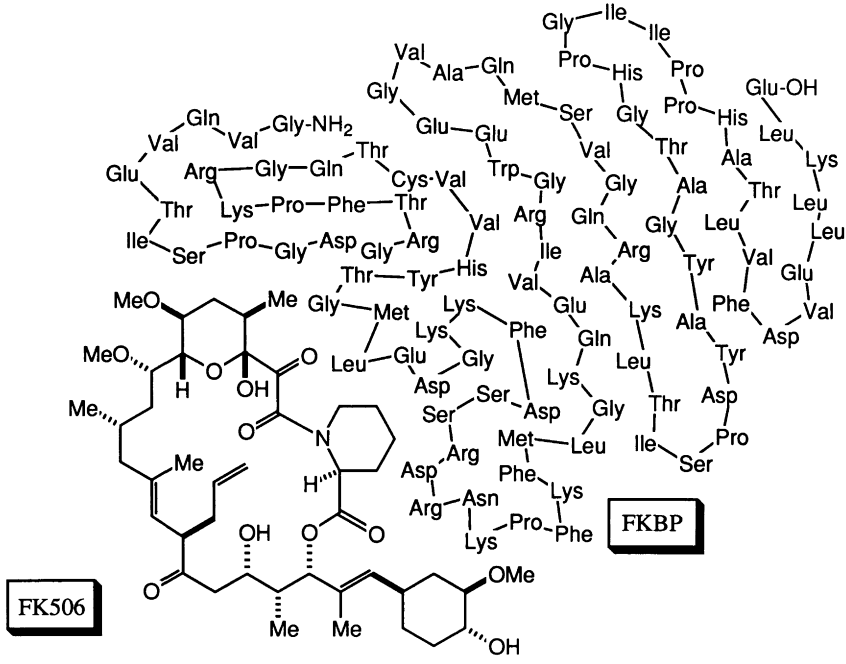
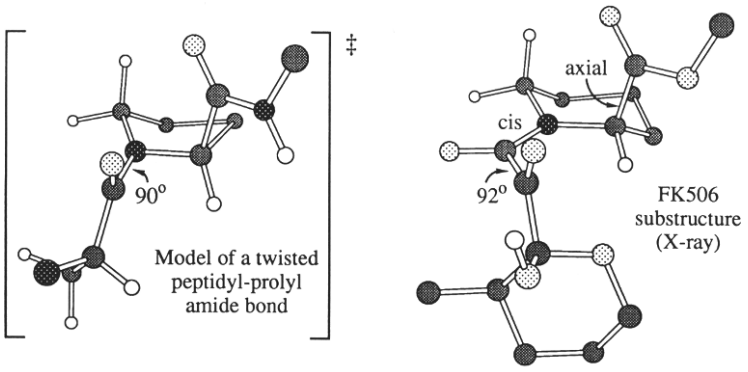


FIG. 2. Structure of the FK506/FKBP complex consistent with all but recent data.

A little intuition, it seems, is a dangerous thing. Having our hubristic, intuitive theory dashed on the rocks of experiment has proved beneficial, though, for it at least gave us a necessary humbling and at last forced us to *think* about how FK506 might inhibit the rotamase activity of FKBP. NMR spectroscopy lent strong support to the twisted amide mechanism, and when we viewed the other available data in this light, a new picture emerged. The X-ray crystal structure of FK506[2] shows quite clearly that the keto and amide carbonyls are essentially orthogonal (dihedral angle = −89°). Such an arrangement places the keto carbonyl in a plane orthogonal to the pipecolinyl amide, a position very like that of the amide carbonyl of a twisted (90°) peptidyl–prolyl bond. (Scheme 32). If FK506 were appropriately oriented, the keto carbonyl could occupy the site that is occupied during catalysis by an out of plane peptidyl carbonyl. Thus, we surmised that the conformational biases of the ketoamide make it an excellent twisted amide surrogate.



SCHEME 32

XIII. Conclusion

That ^{13}C NMR spectrum offered the first glimpse of the FK506–FKBP complex, but it also stands as a milestone for our group. A project that began as the total synthesis of a natural product had grown to encompass its receptor and had, along the way, initiated the growth and diversification of the group into a multidisciplinary unit. When we undertook the total synthesis of FK506, we could not have foreseen the number and scope of projects related to FK506, FKBP, and their complex that have sprung forth. Synthetic technology developed for the FK506 total synthesis is being applied to the total synthesis of rapamycin (**73**), a structurally related macrolide that also binds to FKBP and inhibits its rotamase activity. The same technology has already been applied to the synthesis of some very interesting FKBP ligands, such as "506BD" (**78**), a molecule designed to include only the FKBP-binding domain of FK506.[52] Studies with 506BD have given important insight into the biological actions of FK506 and rapamycin. Investment in improving the FK506 (and rapamycin) affinity matrix synthesis has been rewarded with the discovery of several new FKBPs, which we are in the process of characterizing. Our FKBP-overproducing strain of *E. coli* has been distributed to over ten laboratories in three countries, and it has been working overtime for various members of our own group. Recombinant FKBP has been used in our laboratory in studies of kinetics, binding, and biology,[53] but by far the biggest use has been in NMR studies, which have

recently provided the three-dimensional solution structure of FKBP.[54,55] Among the interesting variants of FKBP produced for these and other studies are ones labeled with ^{2}H, ^{13}C, ^{15}N, ^{35}S, and Se.[56]

Each extension of the FK506 project has required us to adopt techniques not traditionally associated with organic chemistry, and incremental expansion of our repertoire has made our group home to a diverse set of talents. More than anything else, each foray into a new area has required an open mind, particularly in regard to our own abilities; we certainly would not restrict a synthesis to include only reactions we had run before, and by the same token, we will not allow arbitrary stereotypes to prevent us from approaching an interesting problem. The same spirit of open-mindedness has led us into a number of symbiotic collaborations in the FK506 area, mostly on the cell biological aspects of this research, where each group contributes its own special skills and intellectual perspective. Through it all, we have found that our synthetic efforts and our backgrounds as organic chemists with a structural and mechanistic inclination have created or inspired new undertakings and have served us well in their execution; we are convinced that good things will come to the organic chemist with an intrepid spirit and an open mind.

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Chapter 12

TOTAL SYNTHESIS OF (−)FK506

R. P. Volante

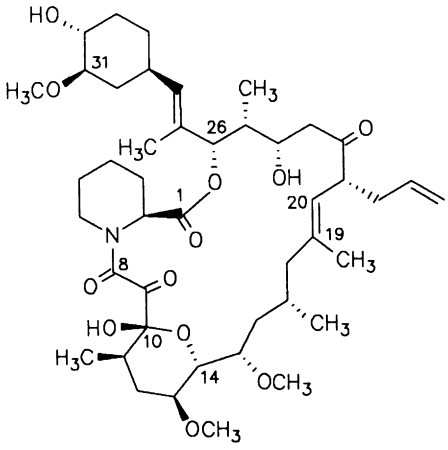
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I. Introduction

In late 1987 scientists at the Fujisawa Pharmaceutical Corporation reported the discovery and isolation of a novel 21-membered macrolactam (FK506, **1**) from a fermentation broth of a soil organism *Streptomyces tsukubaensis* No. 9993.[1,2] In a separate publication FK506 (**1**) was reported to possess immunosuppressive activity, including the

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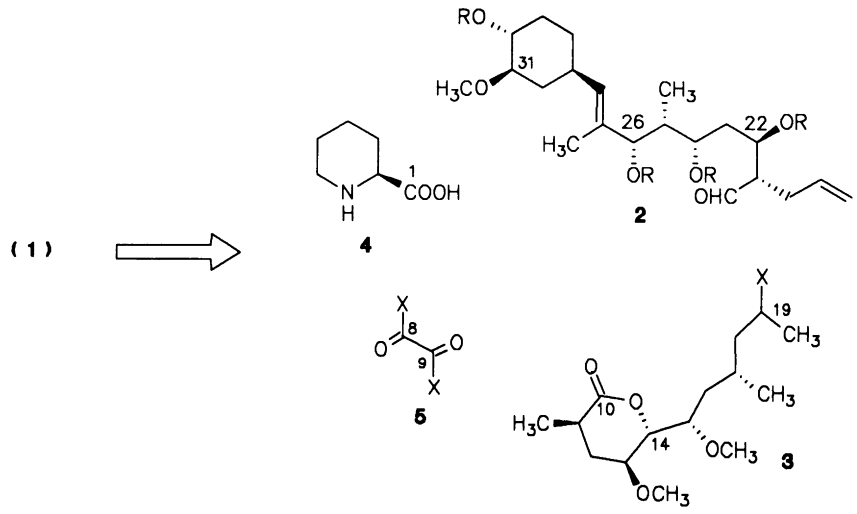


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inhibition of lymphocyte production (IL-2, IL-3, IFN), at levels 100-fold lower than cyclosporin A (CsA) in a number of autoimmunity models.[3–6] This discovery made FK506, or a derivative thereof, a primary candidate for clinical allotransplantation in humans. In addition, the vast structural differences between FK506 and CsA both gave immunologists a new biological probe of the immune response system and raised many new questions concerning the mechanism of action of these two compounds. These factors coupled with the challenging structural features of FK506, in particular the unusual hemiketal masked α,β-diketo amide linkage (C_8–C_{10}), made it a primary target for total synthesis. Furthermore, it was expected that the vast arsenal of chemical knowledge that would be obtained in the course of the total synthesis would provide ready access to a number of analogous compounds that would be generally useful for the determination of the minimum structural requirements necessary for immunosuppression. Since the completion of this work, considerable insight and knowledge has been gained concerning the mechanism of action of FK506 and the biological events leading to immunosuppression.[7,8] This research has been further catalyzed by the announcement of the extraordinarily effective and apparently safe use of FK506 for the prevention of organ rejection following liver and kidney transplantation in humans.[9,10]

II. The General Plan

Our retrosynthetic analysis of the FK506 molecule (**1**) consisted of four primary disconnections and divided the molecule into four fragments: the C_{20}–C_{34} "northern hemisphere" (**2**), the C_{10}–C_{19} "southern hemisphere" (**3**), the commercially available C_1–N_7 (*S*)-pipecolic acid section (**4**) and the C_8–C_9 oxalate unit (**5**). In the forward



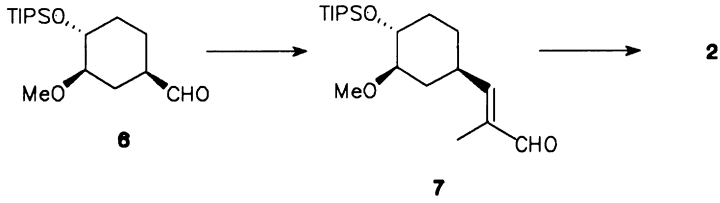
direction, the northern and southern hemisphere fragments **2** and **3** would be individually prepared with each stereocenter set in its correct optical configuration. At this point we envisioned installation of the key C_8–C_{10} tricarbonyl array by acylation of a C_{10} acyl anion equivalent (e.g., a dithioacetal or cyanohydrin) with an appropriately functionalized two carbon electrophile (e.g., diethyl oxalate).[11] This type of transformation was well precedented in the chemical literature and was expected to provide the desired tricarbonyl unit in its correct oxidation state (protected at C_{10}). Finally, insertion of the commercially available (*S*)-pipecolic acid unit (**4**) would complete construction of the macrocyclic ring system. The strategy for final ring construction was left open at this stage as there were two schools of thought concerning whether a "macrolactonization" or "macrolactamization" approach would be more efficient for formation of the 21-membered ring system. In either case, a point of major concern

was the possibility of epimerization of the pipecolic acid derived stereocenter at C_2 during acylation of the somewhat hindered C_{26} secondary hydroxyl function.

We also recognized that the selection of protecting groups for the various hydroxyl functions and the timing for introduction of the C_{22} ketone functionality were critical decisions that would play a major role in determining the eventual success or failure of the proposed synthetic strategy. In particular, the C_{22} ketone of FK506 is flanked by both a potentially epimerizable stereocenter at C_{21} (allylic and alpha to the ketone) and a sensitive beta hydroxyl group at C_{24} (prone to both elimination and retro-aldol ring cleavage reactions).[1b] Thus, we chose to focus our efforts on a strategy that would introduce the C_{22} oxygen functionality at the alcohol oxidation state. The less sensitive C_{22} hydroxyl center could then be differentially protected and carried through the synthesis as such. Final deprotection and oxidation to reveal the more sensitive ketone functionality would then be accomplished at the latter stages of the synthesis.

III. The C_{20}–C_{34} Northern Hemisphere: Strategy

Our strategy for the synthesis of the C_{20}–C_{34}, northern fragment **2** was focused on an initial preparation of the chiral, nonracemic C_{28}–C_{34} cyclohexane carboxaldehyde **6**. The cyclohexane carboxaldehyde **6** would first be converted to a C_{26}–C_{34} aldehyde, e.g., **7**, by a stereoselective Wittig olefination and then homologated to the desired C_{20}–C_{34} fragment **2** by a series of diastereoselective aldol reactions. This strategy, although somewhat iterative in nature, would



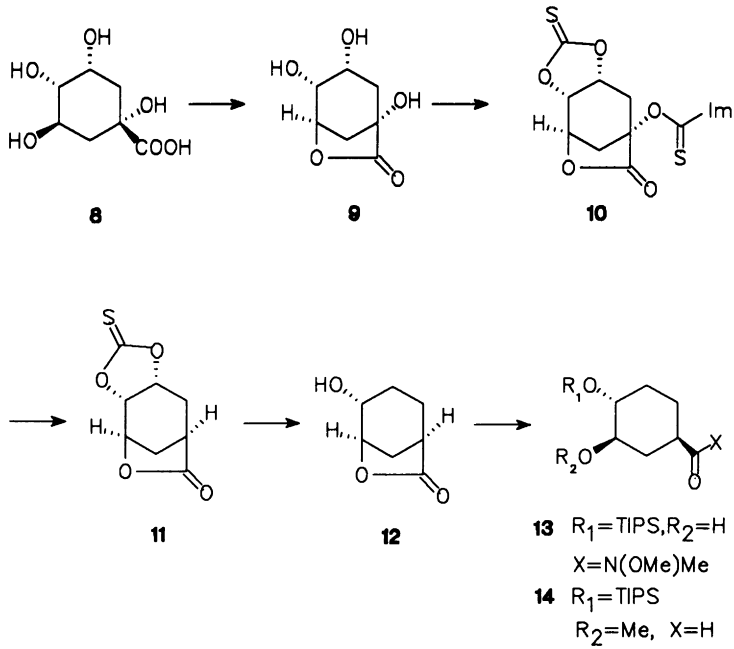
allow for differential protection of the corresponding hydroxyl functions at C_{22}, C_{24}, and C_{26}. As was pointed out earlier, the selection of the proper protecting groups for each of these hydroxyl functions

was envisioned as a key feature of the synthetic strategy for this highly functionalized segment of the molecule. For maximum efficiency in the latter stages of the synthesis, our strategy required hydroxyl protecting groups that could be selectively removed in the following order: $C_{26} > C_{22} > C_{24} = C_{34}$. More specifically this translates, in the forward direction, to a macrolactamization strategy that involves: (1) initial deprotection of the C_{26} hydroxyl; (2) acylation with the pipecolic acid moiety (**4**); and (3) macrocyclization to the FK506 ring system by formation of the N_7–C_8 lactam bond. Selective deprotection of the C_{22} hydroxyl, oxidation to the requisite C_{22} ketone and concomitant deprotection of the C_{24} and C_{34} hydroxyls would then complete the synthesis.

IV. The C_{20}–C_{34} Northern Hemisphere: Synthesis of the Cyclohexanecarboxaldehyde

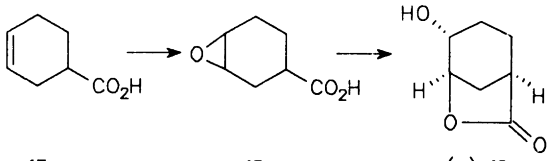
First, we recognized that the requisite C_{29}, C_{31}, and C_{32} stereocenters of the C_{28}–C_{34} cyclohexane carboxaldehyde fragment **6** could, in principle, be derived from naturally occurring (1*R*, 3*R*, 4*R*, 5*R*)-quinic acid (**8**) by a regio- and stereospecific reductive cleavage of the C_1 and C_5 (quinic acid numbering) hydroxyl groups. Thus, quinic acid (**8**) was treated with Amberlite-15 in benzene/DMF (with azeotropic removal of water) to give the known bicyclic lactone **9** in 64% isolated yield.[12] Lactone **9** was then converted to the bis-thiocarbonyllactone **10** (74% yield) by treatment with thiocarbonyldiimidazole in 1,2-dichloroethane. Reduction of **10** with Bu_3SnH in xylenes at 140°C then effected selective removal of the quinic acid C_1 hydroxyl to give lactone **11** (75–85% yield, ^1H NMR). Lactone **11** was isolable; however, direct treatment of the crude reaction mixture with additional Bu_3SnH in the presence of AIBN gave nonracemic **12** more efficiently (40% overall isolated yield from **8** after workup and purification). Protection of the remaining hydroxyl group as its triisopropylsilyl (TIPS) ether and subjection of the crude reaction mixture to methylchloroaluminum N-methoxy-N-methylamide, following the Weinreb protocol, then gave amide **13** in 85% yield.[13] Methylation of the 4-hydroxyl (methyltriflate/2,6-di-t-butyl-4-methylpyridine) and reduction with diisobutylaluminum hydride (DIBAL) gave the desired nonracemic, cyclohexanecarboxaldehyde **6** in 85% yield. All attempts to effect selective methylation of

the 4-hydroxyl group of silyl ether **13** by treatment with more standard, less reactive, methylating reagents resulted in migration of the TIPS ether protecting group and formation of significant amounts of the C_{32} methyl ether by-product **14**.



Although we were able to prepare gram quantities of nonracemic aldehyde **6** via this methodology, it became evident that this route would not be amenable to the preparation of the multihundred gram quantities of material that we envisioned as necessary for completion of the total synthesis. Thus, development of an alternate, more efficient synthesis of racemic **6** was initiated. Treatment of racemic 3-cyclohexane carboxylic acid **15** with m-chloroperbenzoic acid gave a mixture of syn- and antiepoxides **16**. High dilution thermolysis of the crude epoxide mixture in dichlorobenzene then effected selective cyclization of the antiepoxide to give racemic bicyclic hydroxylactone **12**. The acidic, uncyclized cis-epoxyacid was readily removed by extraction with bicarbonate and lactone **12** was isolated by crystallization (30% yield from **15**). Lactone **12** was then converted to racemic aldehyde **6** via the previously described protocol. This proce-

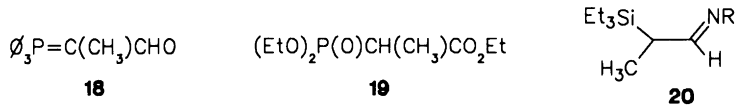
dure was easily adaptable to large scale operation and hundred gram quantities of racemic aldehyde **6** were ultimately prepared by this procedure. However, all attempts to extend this methodology to the preparation of similar quantities of chiral **6** were unsuccessful due to our inability to efficiently resolve the starting cyclohexene carboxylic acid. Thus, in an effort to conserve our supply of optically pure **6** from the quinic acid approach, we decided to continue developmental studies using racemic **6** as a model aldehyde.



15 **16** (±) **12**

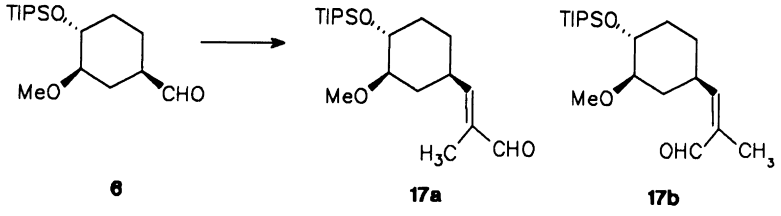
V. The C_{20}–C_{34} Northern Hemisphere: Homologation to the C_{26} Aldehyde

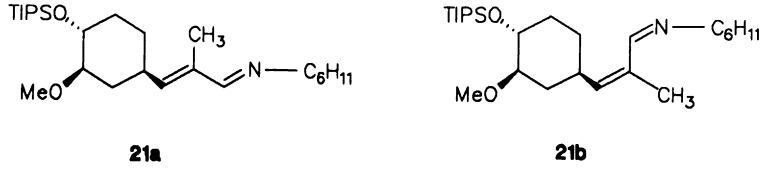
Our initial attempts to extend racemic cyclohexanecarboxaldehyde **6** to the *E*-enal **17a** were centered around the use of standard Wittig type olefination reagents such as ylide **18** and phosphonate **19**. However, attempted condensation of aldehyde **6** with the highly stabilized ylide **18** resulted mainly in epimerization of **6** and gave only trace amounts of olefinic products. Condensation of **6** with the more reactive lithio-anion of phosphonate **19** resulted in the desired homologation; however, the ratio of *E*:*Z* alpha–beta unsaturated olefins produced was poor (ca. 1 : 1). As an alternative, we then turned our attention to the silyl imine olefination procedure of Corey[14] as modified by Schlessinger.[15] However, purification of the starting t-butyl imine **20** (R = t-bu) proved difficult in our hands and use of impure material usually returned 7–15% of unreacted starting aldehyde after olefination. A second, more serious concern was that the ratio of the product *E* and *Z* unsaturated aldehydes **17a** and **17b** usually varied



18 **19** **20**

between 2:1 and 10:1. The first problem was readily solved by substitution of the t-butyl group of **20** with the higher molecular weight cyclohexyl group. A single distillation of cyclohexylimine **20** (R = cyclohexyl) consistently provided high purity reagent that in turn gave high, reproducible yields in the olefination. The solution to the second problem was not as straightforward. However, during the course of our developmental work we noticed that the variability of the *E*:*Z* olefin ratios was critically dependent on the exact conditions of the aqueous oxalic acid workup or hydrolysis procedure. We thus decided to investigate the source of product ratio variability by examining the individual steps of the olefination procedure. First, we found that quenching the condensation reaction with water did not lead to any appreciable hydrolysis of the intermediate imines **21a** and **21b** (which were easily quantified by ^{1}H NMR; —C**H** for *E* at 7.78 ppm and for *Z* at 8.31 ppm). The ratio of imines was also found to be somewhat dependent on the condensation reaction conditions (temperature, etc.), but was typically in the range of 2:1 to 5:1. Subsequent hydrolysis of the imine mixtures under the standard aqueous oxalic acid conditions typically led to ratios of enals that were consistent with the ratio of the starting imines. However, enhancements of the ratios (up to 10:1) were observed by slight variation of both the amount of acid and the amount of water added in the hydrolysis. This observation led us to the conclusion that the unsatu-

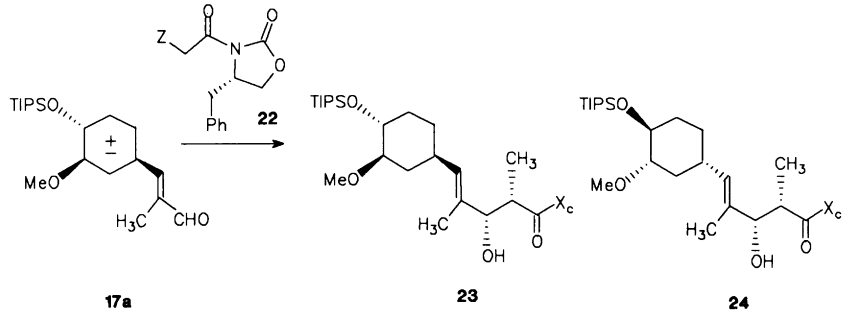


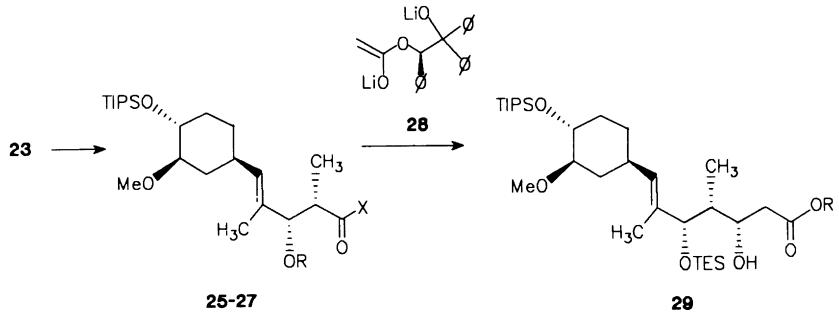


rated imines were undergoing isomerization to the desired *E*-imine **21a** in competition with hydrolysis to the corresponding aldehydes. Indeed, treatment of crude imine mixture with anhydrous trifluoroacetic acid led to essentially complete conversion to the *E*-imine **21a** ($E:Z > 100:1$). Addition of water to the mixture then effected hydrolysis to racemic *E*-aldehyde **17a** ($E:Z > 100:1$).[16]

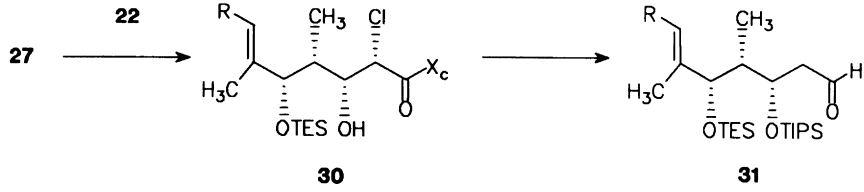
VI. The C_{20}–C_{34} Northern Hemisphere: Homologation to C_{20}: The Aldol Sequence

The first aldol sequence was carried out without incident. Racemic aldehyde **17a** was treated with the propionic acid derived imide **22** ($Z = Me$), following the standard Evans protocol[17] (n-Bu_2BOTf, N,N-diisopropylethylamine, methylene chloride, −78°C to 0°C) to give a 1 : 1 mixture of the diastereomeric syn alcohols **23** and **24** (syn diastereoselectivity >99 : 1). The formation of two diastereomeric products was a result of the racemic nature of aldehyde **17a**. After diastereomer separation and purification by silica gel chromatography, imide **23** was converted to the corresponding Weinreb amide **25**, the C_{26} hydroxyl was protected as the triethylsilyl (TES) ether **26**, and the amide function was reduced with DIBAL to give optically pure aldehyde **27** (X = H, R = TES, 88% yield from racemic **17a**). Conversion to the corresponding C_{22}–C_{34} homologue **29** was initially accomplished via a diastereoselective addition of the dilithioacetate enolate **28**[18] to aldehyde **27** (60% yield; C_{24}, S : R = 5 : 1). Pure C_{24} (S) diastereomer was obtained after purification via silica gel chromatography.



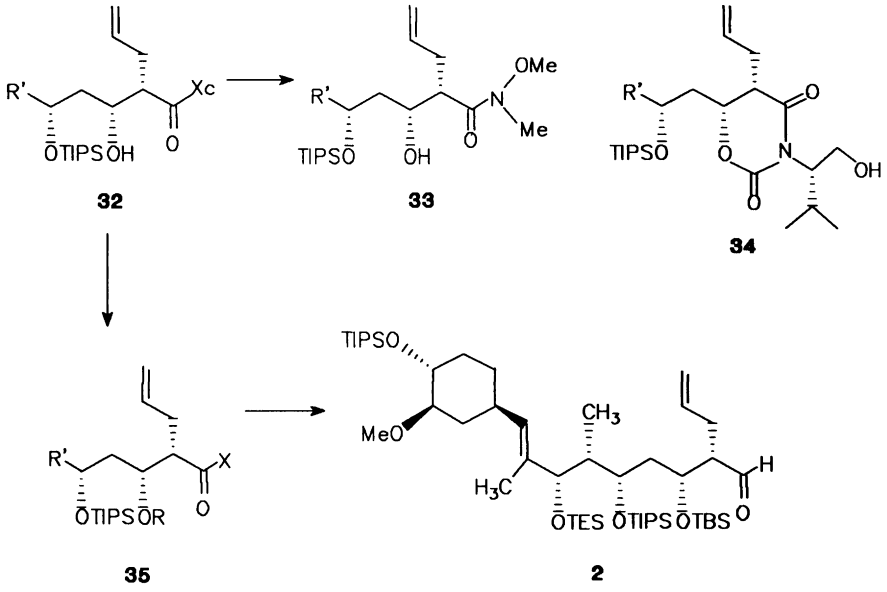


Subsequently, we found this transformation could be more readily accomplished by treatment of aldehyde **27** with chloroimide **22** ($Z = Cl$) via the Evans' boron enolate aldol technology.[19] The resultant C_{22}–C_{34} chloro-alcohol **30** was obtained as a single diastereomer (C_{24} S : R = 99 : 1) in 92% yield. Zinc reduction, transamination to the methoxymethyl amide, protection of the C_{24} hydroxyl as its TIPS ether (TIPSOTf, 2,6-lutidine) and reduction (DIBAL) gave the fully protected C_{22}–C_{34} aldehyde **31** (76% yield from **30**).



The final aldol transformation was carried out by treatment of **31** with the 4-pentenoic acid derived imide **22** [$Z = (CH_2—CH=CH_2)$], again following the Evans' procedure,[17] to give **32** in 95% yield (single diastereomer). However, attempted formation of the corresponding C_{20} Weinreb amide following the standard protocol (methylchloroaluminum N-methoxy-N-methyl amide) gave only a 26% yield of the desired product **33** in addition to significant amounts of the cyclic carbamate **34**. Similarly, attempts to selectively remove the C_{20} imide auxiliary by saponification with aqueous base failed due to competitive attack and hydrolysis of the imide carbonyl to give ring opened compounds. Fortunately for us, Evans had just developed the highly efficient LiOOH technology for selective removal of the imide auxiliary.[20] Application of this methodology

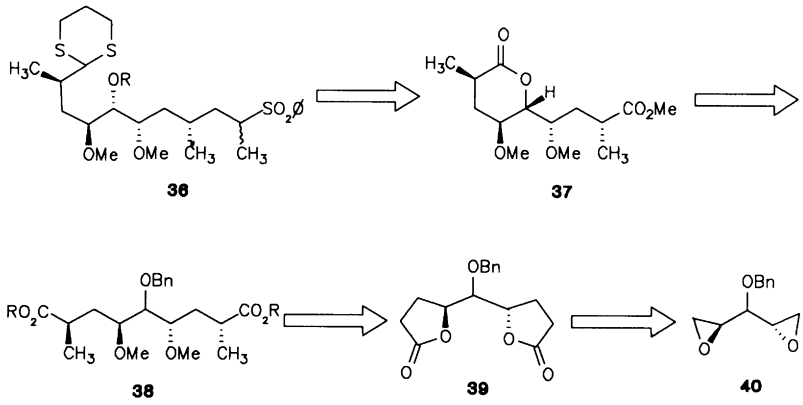
to **32** gave clean conversion to the desired free acid **35** ($X = OH$). Amide formation (carbonyldiimidazole activation followed by treatment with N-methyl-N-methoxy amine), protection of the C_{22} hydroxyl as its t-butyldimethylsilyl (TBS) ether and reduction (DIBAL) then gave the fully protected C_{20}–C_{34} "Northern" aldehyde **2** (86% yield from **32**).[21]



VII. The C_{10}–C_{19} Southern Hemisphere: Strategy

Our initial synthetic target for the C_{10}–C_{19} "Southern" fragment of FK506 was the dithiane-sulfone **36**. Recalling our retrosynthetic analysis, the alpha-methyl sulfone functionality at C_{19} of **36** would be coupled with the C_{20} aldehyde unit of **2** to give a C_{10}–C_{34} fragment with the C_{19}–C_{20} trisubstituted olefinic linkage in place. Acylation of the corresponding C_{10} lithio-dithiane with a C_8–C_9 electrophile (diethyl oxalate) would then provide ready access to a C_8–C_{34} homologue with the tricarbonyl array intact. Retrosynthetically, the C_{10}–C_{19} subunit **36** should be readily derived from C_{10}–C_{18} lactone **37** via standard transformations. We envisioned lactone **37** to be available from the pseudo C_2-symmetric diacid or diester **38** via a diastereoselective lactonization process.[22] The C_{11} and C_{17} methyl

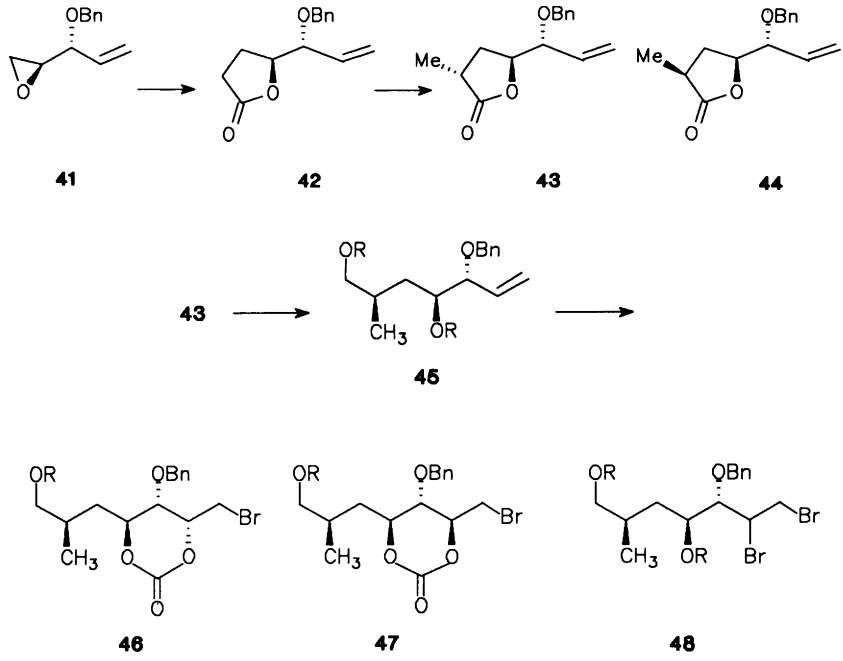
substituents of **38** would be introduced by simultaneous, diastereoselective methylation of the nonracemic bis-lactone **39**.[23] Bis-lactone **39** could conceivably be prepared from a bis-epoxide such as **40** by benzylation, simultaneous acetate enolate alkylation, and lactonization. The chiral, nonracemic bis-epoxide **40** could be obtained, in principle, from 1,4-pentadien-3-ol by a bis-Sharpless epoxidation.[24] However, to simplify the problem of product structure determination we chose to first investigate a simplified approach wherein the stereocenters would be created sequentially. This type of iterative approach also would provide direct access to a selectively protected species, and obviate the need for additional terminus differentiation methodology.



VIII. The C_{10}–C_{19} Southern Hemisphere: Synthesis

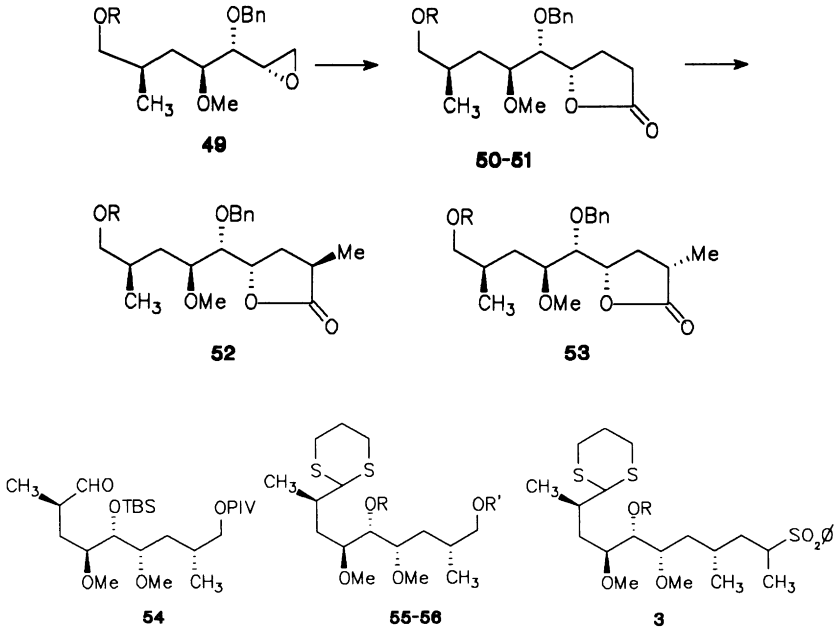
Standard Sharpless epoxidation of divinyl carbinol followed by benzyl ether formation gave epoxide **41** in 75% yield.[24,25] Treatment of **41** with lithioacetonitrile followed by lactonization then gave lactone **42** (76% isolated yield).[26] Methylation of **42** (1.0 equivalent LDA, −78°C to −50°C, 1 hour; MeI, −78°C, 1 hour) resulted in a mixture of lactones **43** and **44** (91%) with the desired lactone **43** predominating (**43** : **44** = 87 : 13). Reduction of **43** with lithium aluminum hydride (LAH) followed by treatment with excess 2-(t-butoxycarbonylimino)-2-phenylacetonitrile (BOC-ON) gave **45** [R = t-butyloxycarbonyl(t-BOC)]. Treatment of **45** with bromine in the presence of potassium carbonate at −80°C produced a mixture of

the bromocarbonates **46** and **47** (R = t-BOC, 74% overall yield from lactone **43**; **46** : **47** = 11 : 1 as determined by ^{1}H NMR) as well as the dibromide by-product **48** (ca. 23%).[27,28] The stereochemistry of the bromocarbonates was easily determined by NOE difference spectroscopy. The desired bromocarbonate **46** was readily isolated as a single diastereomer by crystallization. Furthermore, dibromide by-product **48** could be recycled to the bis-carbonate **45** by treatment with sodium iodide.



Selective saponification of the cyclic carbonate (NaOMe/MeOH) followed by O-methylation of the resultant hydroxy-epoxide gave **49** (65% overall yield from **46**). Epoxide **49** (R = COOt-bu) was converted to lactone **50** (R = H) as before and the C_{10} hydroxyl (FK506 numbering) was protected as its TBS ether **51** (57% from epoxide **49**). Trans selective methylation of **51** then gave lactones **52** and **53** (R = TBS) in 93% yield (**52** : **53** = 94 : 6). Transformation of **52** to the C_{10} aldehyde **54** was then accomplished by a series of standard functional group interconversions (LAH reduction, selective protection of the C_{18} hydroxyl as its pivaloyl ester, methylation of the C_{15}

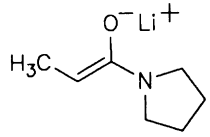
hydroxyl, hydrogenolysis of the C_{14} benzyl ether and reprotection as the C_{14} OTBS ether, selective hydrolysis of the C_{10} primary TBS, and Swern oxidation; 62% yield from **52**). Treatment of aldehyde **54** with 1,3-propanedithiol in the presence of boron trifluoride etherate gave dithiane **55** (R = H, R′ = pivaloyl). Resilylation of the C_{14} hydroxyl and reductive removal of the C_{18} pivaloyl group with LAH gave **56** (R = TBS, R′ = H). Finally, the C_{18} hydroxyl was activated as its benzenesulfonate and displaced with lithioethylphenyl sulfone to give the desired fully functionalized C_{10}–C_{19} "Southern" fragment **3** (82% from **54**).



IX. The C_{10}–C_{19} Southern Hemisphere: The Propionamide Enolate–Epoxide Approach

While in the midst of the above approach, it occurred to us that it should be possible to diastereoselectively convert epoxides **41** and **49** directly to the methyl lactones **43** and **52** by alkylation of a propionate enolate equivalent with the respective epoxides. The stereochemistry of the hydroxyl centers would be set by the stereochemistry of the ep-

oxides and the resultant methyl stereochemistry should be controlled by both the regiochemistry of the propionate enolate and the facial selectivity of the enolate with respect to the approach of the incoming epoxide electrophile. Thus, in principle, the epoxide chirality could control the enolate approach. However, we found that alkylation of the achiral *Z*-lithiopropionamide enolate **57** with epoxide **41** gave rise to, at best, a 60 : 40 mixture of lactones **43** and **44**, after lactonization.



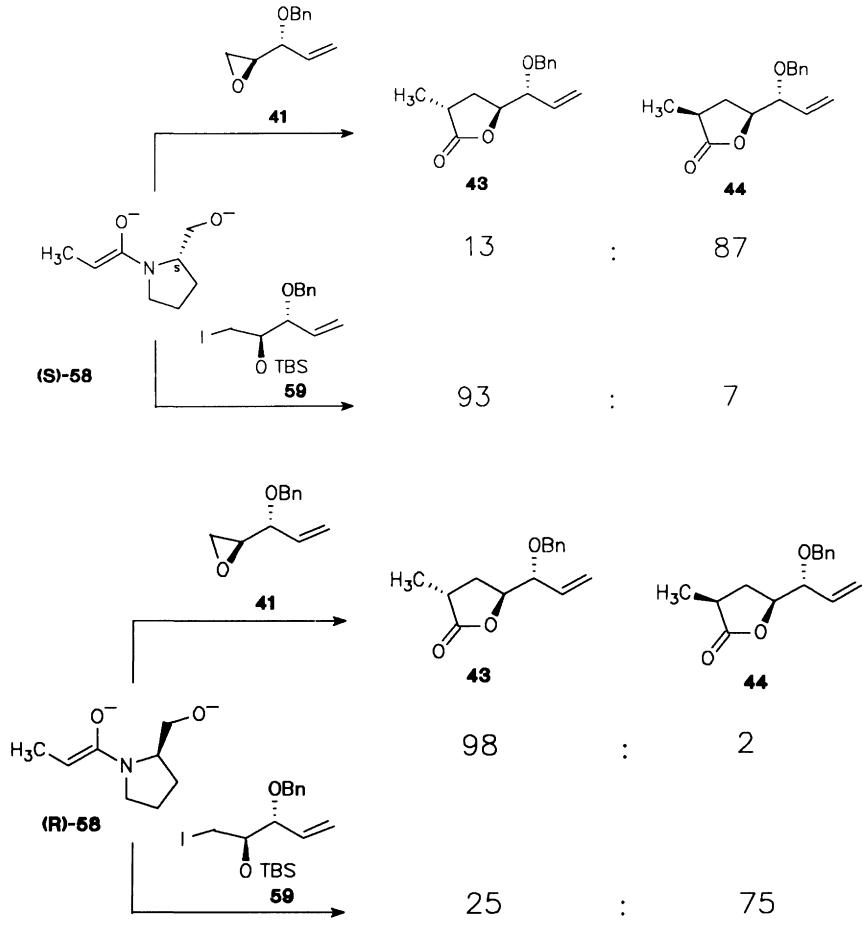
57

Thus, in this example, the epoxide exerted very little influence on the stereochemistry of the newly formed methyl center. We then chose to introduce a chiral center on the amine portion of the amide enolate, in hopes of further enhancing the facial selectivity of the epoxide approach.

We first chose to investigate the enolate derived from the nonracemic prolinol amides **58**. The alkylation of chiral, nonracemic prolinol amide enolates with achiral and chiral alkyl halide electrophiles was well documented in the literature and the stereochemistry of such alkylations was readily predictable.[29] Treatment of **41** with 5 equivalents of enolate (**S**)-**58**, which possesses a very strong facial bias toward alkylation from the pro-2(*R*) face (anti to —CH_2OLi) followed by hydrolysis and lactonization gave lactones **43** and **44** (85%). Surprisingly, the undesired *cis*-lactone **44** was obtained as the major species (**43** : **44** = 13 : 87). This result implied attack on the epoxide by enolate (**S**)-**58** from the more hindered pro-2(S) face (syn to —CH_2OLi).

Similarly, alkylation of the antipodal (**R**)-**58** enolate with **41** gave reversed facial attack from the pro-2(R) face, affording almost exclusively (98 : 2) the desired lactone **43** in 90% yield. To further probe the effect of the electrophile in this reaction, epoxide **41** was converted to the corresponding silyl protected iodohydrin **59**. Alkylation of enolate (**S**)-**58** with **59** followed by lactonization gave rise to lactones **43** and **44** (**43** : **44** = 93 : 7). This corresponds to attack of the electrophile from the least hindered pro-2(R) face as typically predicted for such alkylations (anti to —CH_2OLi). Similarly, alkylation of

enolate (**R**)-**58** with iodohydrin **59** occurred from the least hindered face to give rise to lactones **43** and **44** (**43** : **44** = 25 : 75).

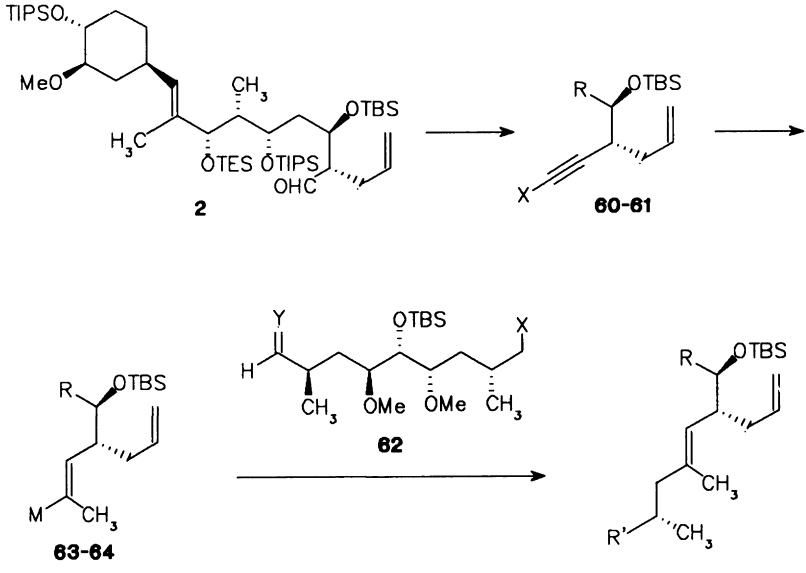


Alkylation of the more advanced epoxide intermediate **49** with the enolate (**S**)-**58**, followed by hydrolysis, provided mainly the desired trans-lactone **52**, although the selectivity was poor (**52** : **53** = 70 : 30). It should be noted that although the configuration of the epoxide center in **49** is (S), it has the opposite relationship with the benzyloxy substituent (syn) compared to epoxide **41** (trans). The exact reason for the unexpected reversal in selectivity for the alkylation of epoxides vs alkyl halides remains unclear. However, one possibility for the

reversal is that intermolecular chelation of the basic epoxide oxygen to the lithio-alkoxymethyl group directs alkylation from the apparently more hindered face of the enolate.

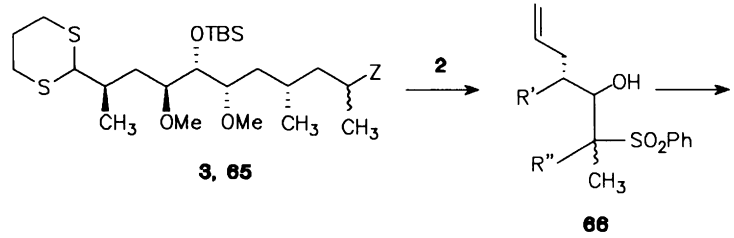
X. Coupling: The C_{19}–C_{20} Trisubstituted Olefin

Our first attempts to stereoselectively introduce the C_{19}–C_{20} trisubstituted olefinic linkage were focused on a two step sequence involving hydrometalation of methyl acetylene **61** followed by stereoselective coupling with an appropriately functionalized C_{10}–C_{18} electrophile such as **62**. Acetylene **61** (X = Me) was prepared from aldehyde **2** by a two step process consisting of conversion to the terminal acetylene **60** (X = H) and alkylation with methyl iodide.[30] Two metals, zirconium and boron, were explored for the hydrometalation. First, in the case of zirconium, all attempts at selective hydrozirconation of **61** led to selective reaction at the terminal olefin functionality in preference to the methyl acetylene.[31] In the case of boron, hydroboration with dibromoborane methyl sulfide did provide predominantly the desired olefin isomer **63**.[32] Olefin **63** (M = R_2B) could be transformed to the desired vinyl iodide **64** (M = I, low yield); however, all attempts to directly convert **63** to either a more

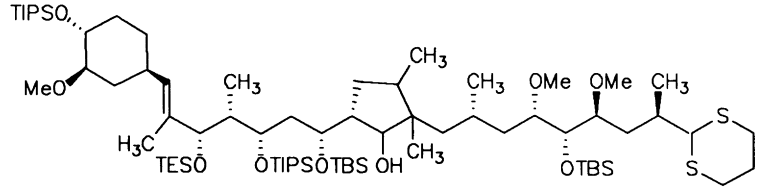


reactive coupling reagent such as a boron "ate" complex or a cuprate were unsuccessful.

At this point our efforts were switched to more classical Wittig or Julia olefination procedures. Sulfone **3** (Z = SO_2Ph) and phosphine oxide **65** (Z = $P(O)Ph_2$, prepared from the benzenesulfonate of **56** by standard alkylation procedures) were selectively metalated and added to the C_{20}–C_{34} protected aldehyde **2** to give the corresponding adducts **66** (as a mixture of diastereomers). In the case of the sulfone adducts, the crude mixture was acylated with acetic anhydride and subjected to standard reductive elimination conditions (Na/Hg at −30°C). Surprisingly, no olefinic products were formed and the major reaction products isolated were the cyclopentanes **67**. Apparently, the radical generated by cleavage of the carbon-sulfur bond cyclizes with the terminal olefin of the allylic side chain in preference to elimination of the acetoxy group (note: this problem was subsequently solved by Danishefsky by use of the more labile trifluoroacetoxy leaving group).[33]



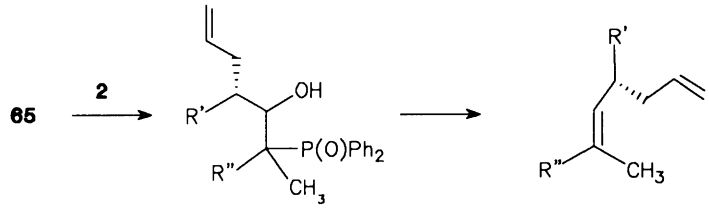
3, 65 **66**



67

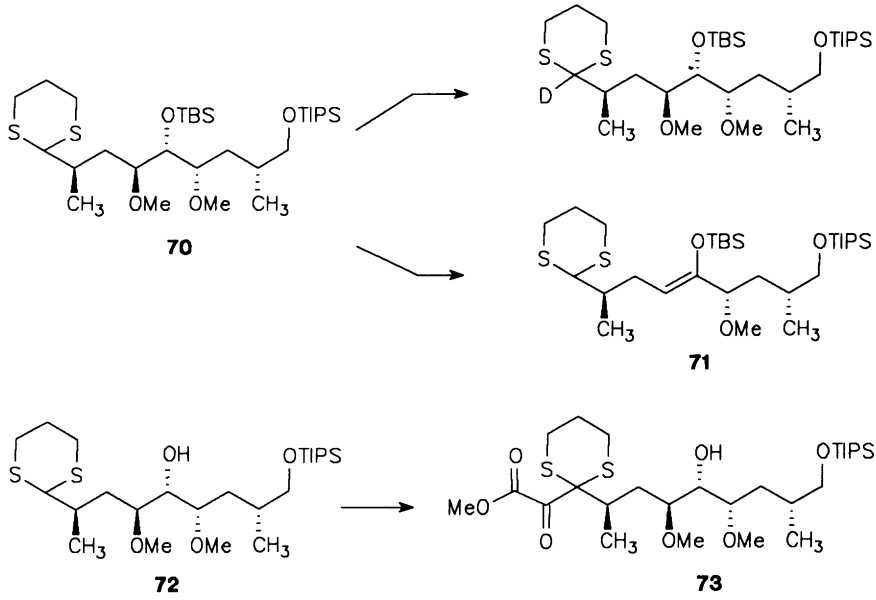
In the analogous phosphine oxide case, three of the four possible diastereomeric adducts (**68**) were formed. The adducts were separated by silica gel chromatography and then individually eliminated to the corresponding *E* and *Z* olefins by treatment with lithium hexamethyldisilazide (32 and 30% yields respectively from aldehyde

2).[34] The olefin geometry was assigned by the ^{13}C chemical shift of the C_{19} CH_3 (16.6 ppm vs. 23.6 ppm for the *E* and *Z* olefins respectively).[35] We realized at the time that this coupling was not particularly efficient or aesthetically pleasing; however, it was workable and we were able to prepare relatively large amounts of the desired *E*-olefin **69** (ca. 1.0 gram) by this procedure. In addition, we had hopes of recycling the undesired phosphine oxide adducts (those leading to *Z* olefin) to the desired adducts by a sequence involving oxidation and selective reduction. At this point the pressure to complete the synthesis was increasing from both external and internal sources and we were forced to forge ahead.

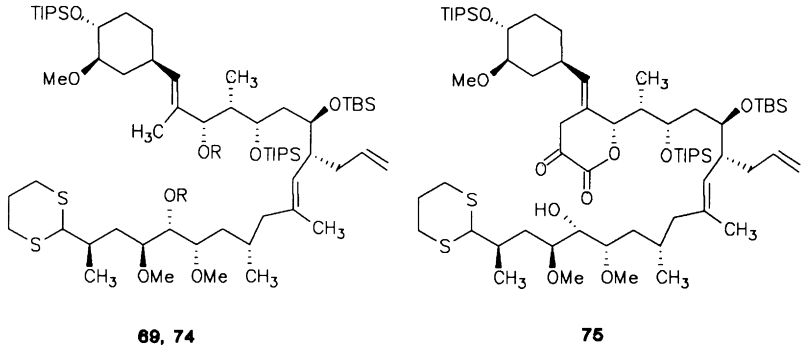


XI. Tricarbonyl Introduction: The Dithiane Approach

With the C_{10} terminus of **69** functionalized as a dithiane acetal, we were now poised for introduction of the tricarbonyl array following the Corey protocol (selective deprotonation of the C_{10} dithiane followed by acylation with diethyl oxalate).[11] However, before exposing our precious, fully functionalized C_{10}–C_{34} fragment to this sequence, we decided to first explore the chemistry using the C_{10}–C_{18} fragment **70** as a model. A number of low temperature ^1H NMR experiments were then performed in an attempt to determine the optimal deprotonation/acylation conditions. First, we found that **70** was readily deprotonated with n-butyllithium in d_8-THF (containing two equivalents of HMPA) to form the desired C_{10} acyl anion; however, this anion rapidly abstracted a deuterium from the solvent to give back C_{10} deuterated **70**. This problem was overcome by changing the solvent to d_{10}-DME; however, under these conditions abstraction of the C_{14} methine proton (most likely via initial C_{10} proton abstraction followed by intramolecular proton transfer from C_{14}) and elimination of the C_{13} methoxyl occurred to give olefin **71** as the major product.

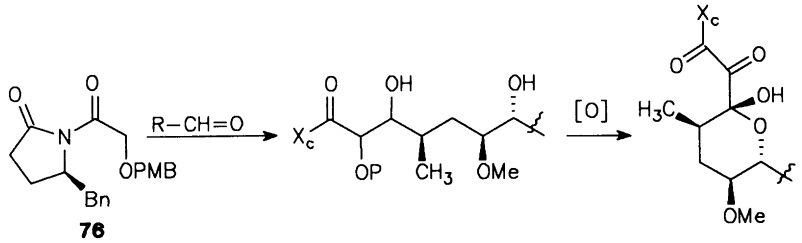


Undaunted by this result, we moved to the unprotected C_{14} hydroxyl substrate **72**. We felt that the *in situ* formation of the C_{14} lithium alkoxide would serve as an efficient means of protecting the C_{14} methine proton from abstraction. Attempted dianion formation on **72** failed in THF; however, deprotonation in neat TMEDA followed by treatment with diethyl oxalate gave the desired acylated dithiane **73** in 64% isolated yield. Unfortunately, application of these conditions to the C_{14}–C_{26} dihydroxy C_{10}–C_{34} substrate **74** (R = H) gave primarily C_{27} acylated material **75** and only trace amounts (8%) of the desired C_{10} acylated product.



XII. Tricarbonyl Introduction: C_{10} as an Electrophile

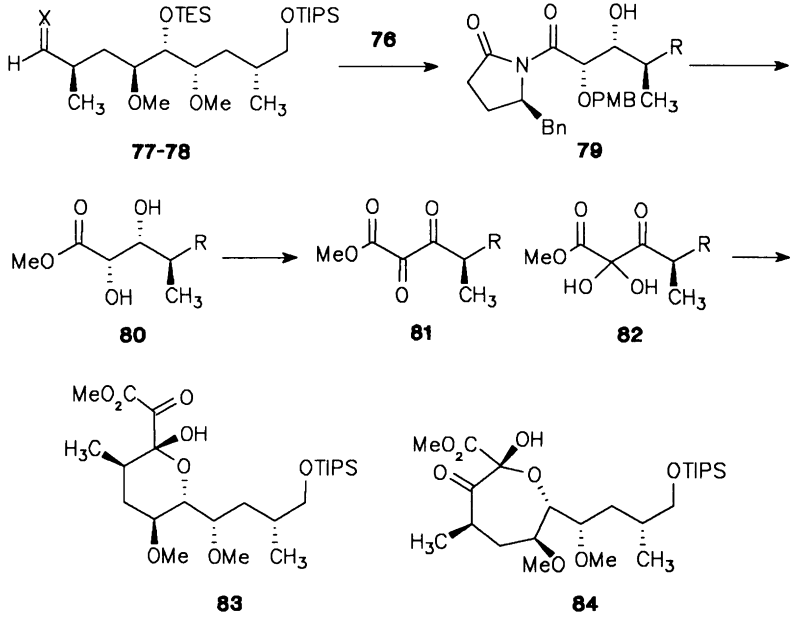
At this point we were convinced that the dithiane acylation approach was not likely to be practical and efforts were focused on an alternative approach, wherein, the C_{10} carbon would serve as an electrophile. More specifically, we envisioned the addition of a protected two carbon hydroxy imide (e.g., **76**) to a C_{10}–C_{34} aldehyde to generate a C_9, C_{10} dihydroxy tricarbonyl precursor. Bis-oxidation of the C_9, C_{10} dihydroxyl array and deprotection of the C_{14} hydroxyl would then reveal the FK506 hemiketal-tricarbonyl. The use of the asymmetric imide **76**, in principle, was not necessary (subsequently



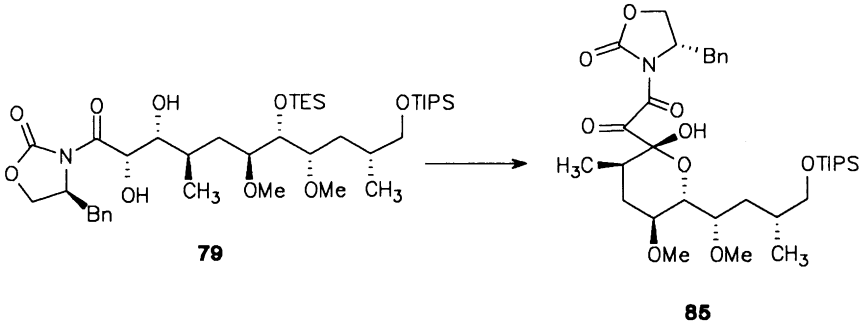
76

demonstrated by Schreiber);[36] however, we felt the advantages of the boron aldol approach (mild, high yields and diastereoselectivity) outweighed those of the corresponding glycolate ester systems. The selection of the alcohol protecting group of **76** (PMB = p-methoxybenzyl) was based on orthogonality to the other protecting groups. A number of alcohol protecting groups were explored (TBS, TES, and 3,4-dimethoxybenzyl); however, they were not useful as all were removed during enolization.

Addition of the boron enolate of imide **76** to model aldehyde **78** (X = O; prepared from dithiane **77**, X = $-S(CH_2)_3S-$), following the standard Evans protocol, gave adduct **79** as a single diastereomer (90% yield). Treatment of **79** with methoxy magnesium bromide and subsequent hydrogenolysis of the C_9 p-methoxybenzyl protecting group provided diol **80** in 63% isolated yield. Bis-Swern oxidation then gave a 1–3 : 1 mixture of the desired tricarbonyl ester **81** and its C_9 (FK506 numbering) hydrate **82**. Treatment of the crude reaction mixture with aqueous trifluoroacetic acid effected selective removal of the C_{14} TES ether and concomitant cyclization to a 1–4 : 1 mixture of hemiketals **83** and **84**. However, all attempts to effect equilibration

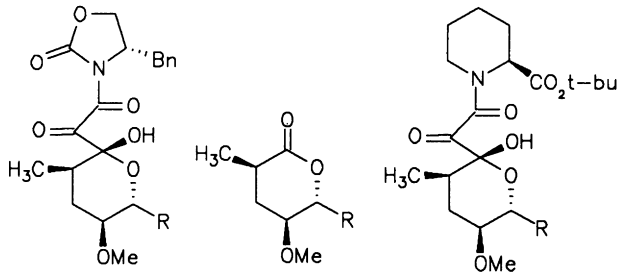


of the hemiketal mixture to the desired 6-membered ring hemiketal **83** were ineffective. This result was not actually unexpected. The C_9 carbonyl is the most electrophilic center in the molecular; thus, competitive hemiketalization at this center is not unreasonable. Surprisingly, direct deprotection of the imide adduct **79** followed by bis-Swern oxidation and subsequent C_{14} TES removal resulted in exclusive formation of the desired 6-membered ring hemiketal **85**.



This result was rationalized by inspection of model systems. It appears that an amide or imide functionality at C_8 can effectively screen the C_9 carbonyl from nucleophilic attack and thus enhances

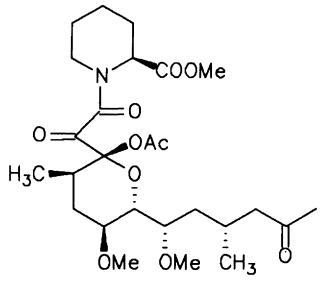
the selectivity for ring closure to the desired 6-membered ring hemiketal system. However, all attempts to hydrolyze the imide functionality of **85** were discouraging. First, treatment with LiOOH effected clean cleavage of the C_9–C_{10} bond to give the C_{10}–C_{18} hydroxy-lactone **86**. Aqueous alkaline hydrolysis of **85** gave a crude mixture of product acids which when treated with the t-butyl ester of pipecolic acid and Mukaiyama's reagent (2-chloro-N-methylpyridinium iodide) gave only a 30% yield of the desired tricarbonyl **87**. Upon closer examination of this sequence we concluded that the low overall yield was due to an apparent instability of the tricarbonyl imide system of **85** under the alkaline hydrolysis conditions. This result was particularly surprising since the original Fujisawa workers had reported that the tricarbonyl system of FK506 was stable to aqueous base. In fact they had reported the isolation of an intact C_1–C_{19} tricarbonyl fragment after a sodium hydroxide based degradation of FK506. At this point we decided that it would be prudent to further investigate the chemistry of the FK506 tricarbonyl system with respect to both its stability and chemical reactivity prior to continuation of the critical end game chemistry.



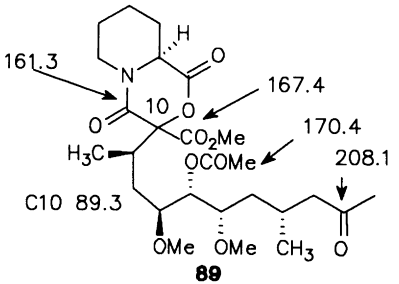
XIII. Degradation and Rearrangement of FK506

Repetition of the Fujisawa FK506 degradation sequence gave us a C_1–C_{19} derived fragment with spectroscopic characteristics (^1H and ^{13}C NMR) identical to those reported in the literature.[1b] However, careful examination of the ^{13}C NMR shift data for the degradate relative to both FK506 and our synthetic fragment **87** revealed the conspicuous absence of the characteristic C_9 carbonyl shift at ca. 196–197 ppm. This signal was replaced in the degradate

by an ester carbonyl signal at 167.4 ppm. Additional ^{1}H and ^{13}C NMR investigations unequivocally supported the structure of the degradation product to be the rearranged pyridooxazinedione **89** and not the originally proposed tricarbonyl **88**.[37] This evidence, in addition to the reported tendency of vicinal polyketones to undergo a facile



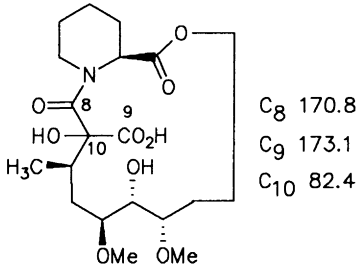
88



89

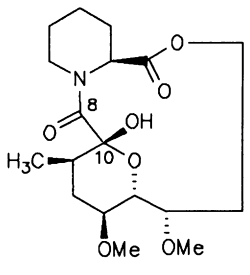
hydroxide induced 1,2-acyl migration,[38] led us to interpret that pyridooxazinedione **89** was most likely formed from FK506 by one of two mechanisms: (1) a sequence involving nucleophilic addition of LiOH to the C_9 ketone followed by C_{10} hemiketal opening and migration of C_8 to C_{10}; or (2) a hydroxide mediated C_{11} to C_9 acyl migration to give a ring expanded lactone, which would be saponified to acid **90**. Further documentation of the facility of this process and the structure of the rearranged product was obtained by exposure of C_{24}, C_{32} bis-TIPS FK506 to LiOH (1.03 equivalents at 0°C). The product acid **90** was then oxidatively decarboxylated with $Pb(OAc)_4$ to give des-C_9 keto FK506 **91** (93% overall yield from bis-TIPS FK506).[39]

This sequence also provided an excellent means to distinguish between our two proposed rearrangement mechanisms. In the first



90

C_8 170.8
C_9 173.1
C_{10} 82.4



91

sequence, the C_8–C_{10} migration would give rise to a product acid **90** wherein the acid carbon and the tetrasubstituted hydroxyl bearing carbon would arise from the FK506 C_9 and C_{10} carbons, respectively. In contrast, the C_9–C_{11} acyl shift pathway would give rise to carboxylic acid and tetrasubstituted carbons from the FK506 C_{10} and C_9 carbons, respectively.

Toward this end, C_{24}, C_{32} bis-triethylsilyl (TES) FK506 (^{13}C-labeled at C_9) was prepared. Treatment of an admixture of 99 atom % bis-TES-FK-506 and unlabeled bis-TES-FK506 with aqueous LiOH gave, after workup, the corresponding bis-TES rearranged hydroxy acid **90** bearing the ^{13}C label at the acid carbon. The isomer of **90** bearing the ^{13}C label at the quaternary carbon could not be observed at this point. Decarboxylation of **90** gave the nor-C_9 analog **91** bearing only a small amount of the original label at the hemiketal carbon. More extensive ^{13}C NMR work indicated that approximately 3% of the original label was present at the hemiketal carbon of **91**, implying 3% of the rearrangement by the unexpected C_9–C_{11} acyl shift mechanism (b). Thus, the major pathway of the rearrangement appeared to be via the expected C_8–C_{10} rearrangement pathway (a).[40]

Our general conclusion from this work was that introduction of the tricarbonyl system should be postponed until as late as possible in the synthesis due to its extreme sensitivity towards rearrangement. Thus, we chose to pursue a strategy where the final oxidation to the tricarbonyl array would be delayed until after pipecolic acid introduction and macrocyclic ring formation.

XIV. Pipecolate Chemistry and Macrocyclization

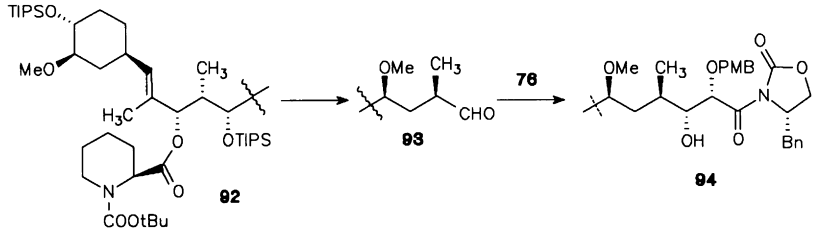
Our next strategic decision concerned the sequence of reactions for introduction of the C_1–N_7 pipecolic acid moiety and construction of the macrocyclic ring. As was pointed out earlier in our retrosynthetic analysis, two options were available for ring formation: macrolactonization and macrolactamization. Model studies involving simple acylation of the somewhat hindered C_{26} hydroxyl group with N-BOC-pipecolic acid demonstrated that significant epimerization at C_2 was possible under typical macrolactonization conditions (high dilution and prolonged reaction times). Therefore, we chose to pursue

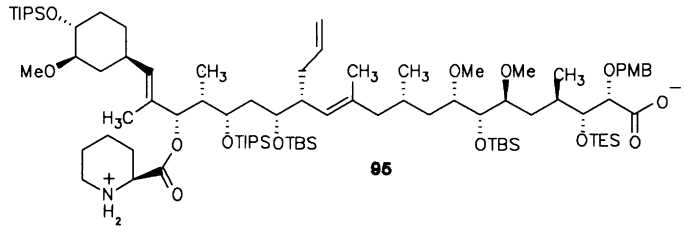
a macrolactamization strategy wherein the critical C_{26} hydroxyl acylation could be done intermolecularly using an excess of N-BOC-pipecolic acid under highly concentrated reaction conditions. Macrocyclization would then be performed using the previously defined Mukaiyama salt procedure for formation of the N_7–C_8 linkage.

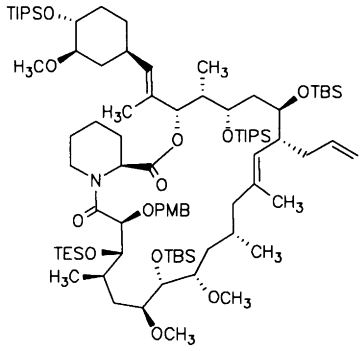
XV. Completion of the Synthesis

Prior to execution of the aldol sequence on the fully protected C_{10}–C_{34} segment **69**, it was first necessary to acylate the C_{26} hydroxyl with (S)-N-BOC-pipecolic acid and then convert the C_{10} dithiane functionality to an aldehyde. Selective hydrolysis of the C_{26} OTES group (TFA/THF/H_2O) and acylation with the pipecolic acid (10 equivalents, DCC, DMAP, −15°C) gave **92** (93% yield). Less than 1% racemization was detected (NMR analysis). The C_{10} dithiane of **92** was then converted to aldehyde **93** by a two step procedure. Modified Corey conditions[41] ($AgNO_3$, NCS, 2,6-lutidine, CH_3OH, THF) transformed the dithiane to a dimethyl acetal, which was hydrolyzed to aldehyde **93** (glyoxylic acid hydrate, HOAc, CH_2Cl_2,) in 67% overall yield from **92**. Addition of aldehyde **93** to the boron enolate of imide **76** gave **94** as a single diastereomer (88% yield). Removal of the imide auxiliary (LiOOH) and treatment of the resulting hydroxy acid with excess triethylsilyltriflate simultaneously formed a silyl ether at C_{10} a silyl ester at C_8 and transformed the BOC group to a silylcarbamate.[42] Exposure of this intermediate to silica gel effected simultaneous hydrolysis of both the silyl ester and carbamate groups to give the unstable amino acid **95** (80% yield from **94**).

Macrocyclization to **96** (P = PMB, R′ = TES) was best accomplished by immediate treatment of **95** with Mukaiyama's chloropyridinium salt[43] under high dilution conditions (81–85% yield). It is interesting to note that macrocycle **96** exists in predominantly one rotameric form. Treatment of **96** with DDQ gave a mixture of the C_9-OH, C_{10}-OTES macrocycle **97** (P = H, R′ = TES) and the desired diol **98** (P = H, R′ = H).[44] Exposure of this mixture to aqueous trifluoroacetic acid effected clean conversion to diol **98**, which was obtained in 74% isolated yield. Until this point assignment of the macrocyclic structure to the fully protected Mukaiyama product **96** had been accomplished only by analogy of spectroscopic data to

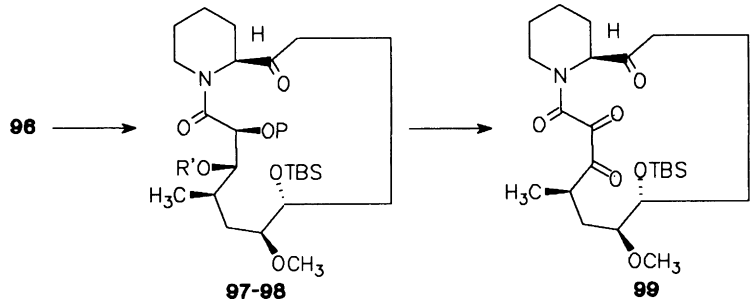


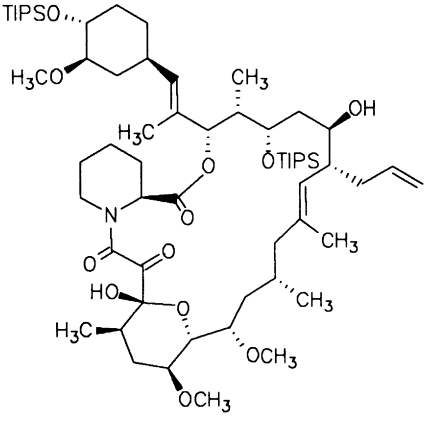




acyclic cases. However, NOE difference spectroscopy on the C_9-OH, C_{10}-OTES macrocycle provided conclusive spectroscopic evidence for the formation of the lactam: NOE difference spectroscopy on the C_9-OH, C_{10}-OTES macrocycle revealed a 5% NOE from H_9 to H_2 (in the major amide rotamer). Diol **98** was then oxidized to **99** by a bis-Swern procedure. Treatment under the standard Swern conditions typically produced a mixture of the desired diketone **99** and monooxidized products; however, reoxidation of this mixture following the same protocol gave the yellow tricarbonyl **99** in 80% yield.

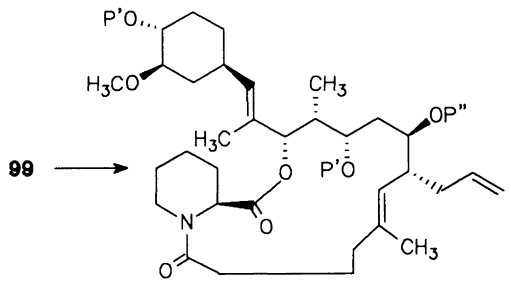
At this point our protecting group strategy for selective removal of the C_{14} and C_{22} TBS ethers broke down. All attempts to convert **99** to hemiketal **100** by selective removal of the C_{14} and C_{22} TBS groups



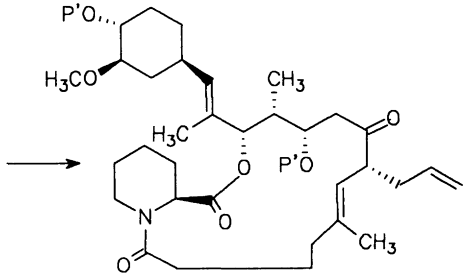


100

failed. It was possible to selectively remove the more labile C_{14} OTBS group in the presence of the C_{22} group; however, more extensive hydrolysis resulted in a complex mixture of partially desilylated products. Thus, our only option was to effect complete desilylation (HF/CH_3CN, 81% yield) to dihydro FK506 (**101**, P′ = P″ = H) and then attempt a selective reprotection of the less hindered C_{24} and C_{34} hydroxyls. Fortunately, selective silylation was readily accomplished by treatment with triethylsilyltriflate to give **102** (P′ = TES, P″ = H) in 70% yield. Finally, oxidation of the C_{22} hydroxyl with the Dess-Martin periodinane reagent[45] gave bis-TES-FK506 (**103**, P′ = TES, 61% yield) and deprotection with HF/acetonitrile gave (−)FK506 (**1**) (81%) which was identical to natural material by ^1H NMR, COSY-45, ^{13}C NMR, optical rotation at six wavelengths, and TLC in several solvent systems.[46,47]

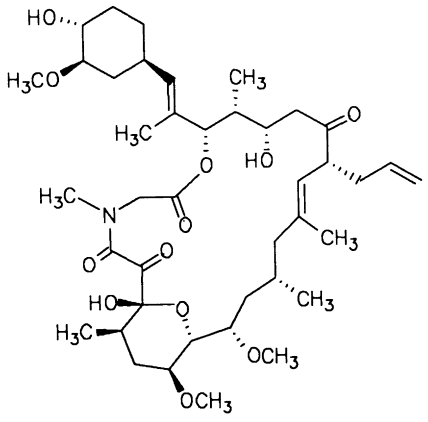


101-102

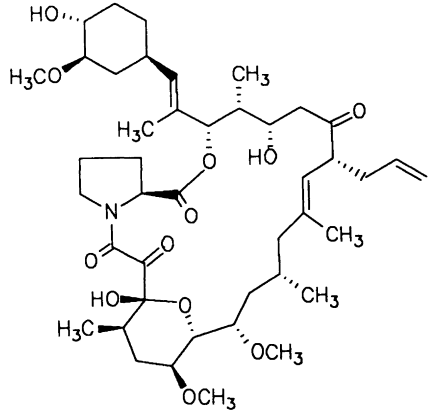


103, (1)

Finally, the generality of our macrocyclization and tricarbonyl formation methodology was demonstrated by preparation of the novel sarcosine **104** and proline **105** (FK525) analogues.[48,49]



104



105

Acknowledgments

The successful total synthesis of FK506 described herein was possible because of the combined efforts of an exceptionally talented and devoted group of co-workers. Drs. David Askin, Sander G. Mills, Todd K. Jones, and David Tschaen; Mr. Rich Desmond, Mr. Robert Reamer, Mr. Ken Ryan, Mr. Wm. Laswell, and Ms. Daisy Joe were all key members of the Process Research team responsible for the design and excecution of this synthesis. In addition I would like to thank Dr. Ichiro Shinkai for his continuous leadership, support, and chemical insight throughout the completion of the project.

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Chapter 13

AN INDUSTRIAL PERSPECTIVE ON TOTAL SYNTHESIS; PENEM ANTIBACTERIAL CP-70,429

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Groton, Connecticut

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I. Introduction: Discovery of Penem Antibacterial CP-65,207 (7)

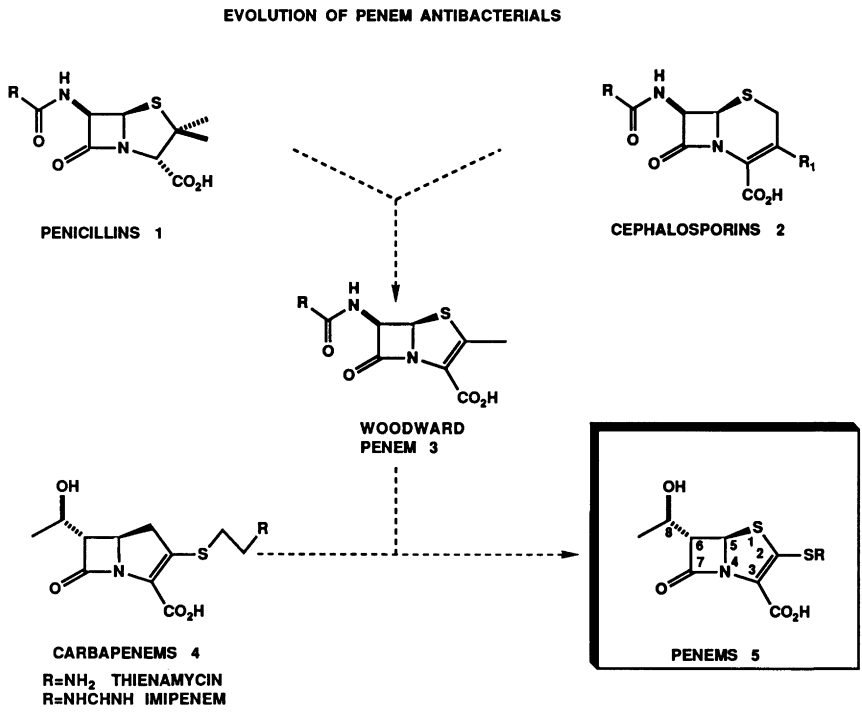
Penicillin (**1**) and cephalosporin (**2**) antibiotics have established an unparalleled record of safety and reliability in the treatment of infectious disease during the last half of this century. A consequence of widespread clinical acceptance of these β-lactam antibiotics has been

* The authors wish to dedicate this chapter to the memory of our friend and colleague, David Lindner.

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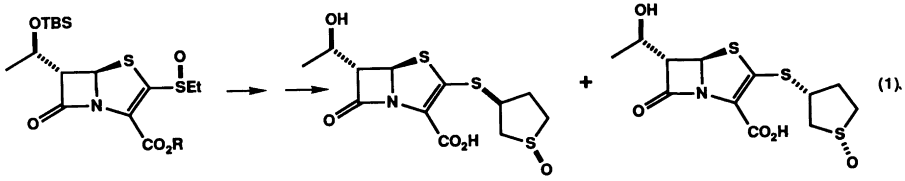
an increase in resistance by target bacteria thus compromising the efficacy of many of these drugs. Bacterial resistance, coupled with the need to widen the spectrum of these agents, has fueled the search for novel therapeutics from both synthetic and natural sources. The discovery of penems and carbapenems, two new families of β-lactam antibacterials, was an outgrowth of these efforts.

In 1976, the Woodward/Ciba group prepared the first penem (**3**)[1], a structural hybrid of penicillins and cephalosporins. The antibacterial activity of these novel 6-acylaminopenems was disappointing; however, the Merck discovery of the broad-spectrum carbapenem, thienamycin (**4**)[2], from fermentation sources, demonstrated that novel β-lactams, devoid of key penicillin and cephalosporin structural features, would be capable of potent antibacterial activity. The structural relationship between carbapenems and penems suggested a further refinement of the penem structural class in the form of 2-thioalkylpenems **5** which displayed an impressive antibacterial



profile. The commercial implications of this discovery were obvious. As a result, Mike Kellogg, Ernie Hamanaka, Bob Rosati, and coworkers at Pfizer initiated a synthetic program aimed at the discovery of potent penem antibacterials. By no means were they alone in their chemical efforts as an explosion in β-lactam research occurred in other laboratories at the same time as a result of the carbapenem/penem discoveries.

The seminal contributions by individuals in early penem/carbapenem research are too numerous to mention at this juncture. Certainly synthetic methodology developed by the Woodward/Ciba group and also at Schering, Merck, Sankyo, Bristol-Myers, Farmitalia Carlo Erba, and other companies factored into our drug discovery efforts.[3] In 1983 Dave Johnson and Bob Martingano, working with Ernie Hamanaka, prepared a series of 2-thioalkylpenems by treatment of known enantiomerically pure intermediate **6**[4] with a series of racemic heterocyclic thiolates. They were convinced that polar substituents appended to the carbapenem/penem skeleton (such as the β-aminoethylsulfide moiety in thienamycin) were responsible for the breadth (gram negative activity) of spectrum and balance of potent antibacterial activity of these compounds. The most notable substance generated from their synthetic efforts was CP-65,207 (**7**)[5], a diastereomeric mixture of *cis*-thiophanesulfoxide-containing penems with a remarkably well-balanced antimicrobial spectrum (Eq. 1). Because of its impressive biological credentials, CP-65,207 (**7**) was nominated in 1984 as a candidate for clinical development at Pfizer.



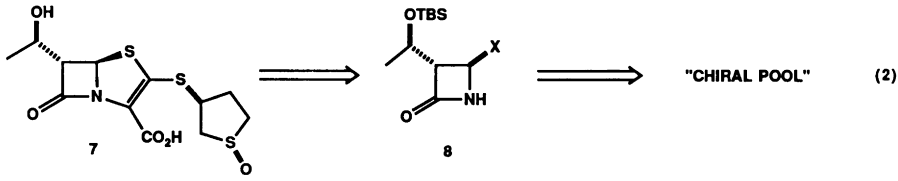
6 7 (CP 65,207) (1)

It was about this time when the project team was confronted by the sobering realities of pharmaceutical development. Initial cost estimates for the production of CP-65,207 (**7**) and other members of the series were astronomical. We were not alone in the realization that the commercial potential of the penem/carbapenem class would depend

on the development of highly efficient syntheses. Merck had already responded aggressively to the challenge of drug development by uncovering a more stable analog of thienamycin, imipenem, and developing a commerical process for its synthesis. Our course was also clearly defined and we began to evaluate, in earnest, possible synthetic routes to CP-65,207 (**7**).

II. Retrosynthetic Analysis: Identification of a General Strategy for Penem Synthesis

Our reading of previous penem and carbapenem methodology suggested several attractive options for the preparation of CP-65,207 (**7**). Based on our analysis, no single process emerged as the overwhelming choice for the eventual commerical production of our penem candidate. However, a general strategy for penem synthesis was clearly evident (Eq. 2): The β-lactam portion of the molecule was best assembled at an early stage, in the form of azetidinone **8**, which would establish the three contiguous penem stereocenters. A number of synthetic avenues could subsequently be employed to fashion the CP-65,207 penem skeleton from this template.

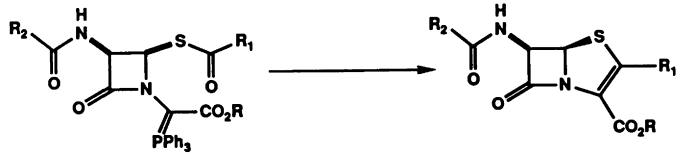


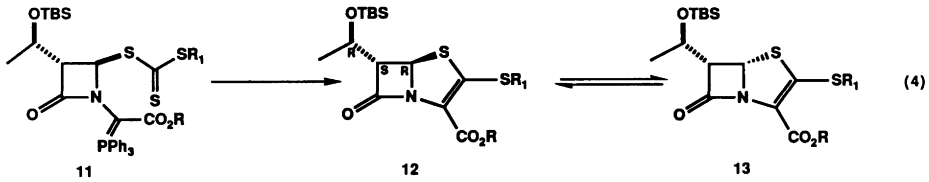
Our process and medicinal discovery teams now joined forces with the goal of using this strategy to develop an efficient, cost effective process which would be amenable to kilogram scale processing. Results of these efforts are the subject of this chapter.

III. Background: The Original Synthesis of CP-65,207 (7)

Many distinct processes had been developed for the preparation of 2-substituted-6-hydroxyethyl penems **5** which rely on 3-(1-hydroxyethyl)-azetidin-2-one intermediate **8** to establish the three contiguous penem stereogenic centers. The 2-carbon substituted penem antibacterials were initially prepared by the Woodward

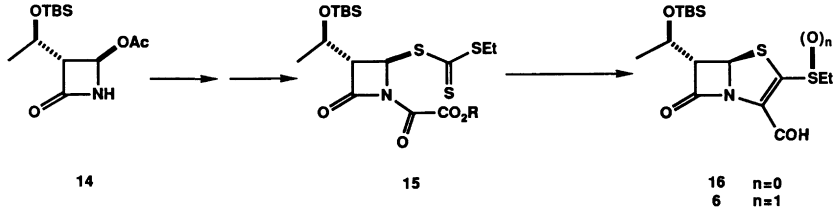
approach,[1] which depends on the intramolecular Wittig reaction of **9** to assemble the strained bicyclic penem framework **10** (Eq. 3). The possibility that an analogous intramolecular phosphorane condensation might provide a route to 2-alkylthiopenems **12** was realized soon thereafter with the less reactive trithiocarbonate moiety of **11**.[6] 2-Alkylthiopenem acids **12** (R = H) (having the requisite 5*R*, 6*S*, 8*R* stereochemistry) generated using this methodology proved to be potent antibacterials. However, in addition to **12** (R = allyl), an undesired isomeric penem **13** (R = allyl) was also produced in this reaction, through thermal epimerization at C_5 under the Wittig conditions (Eq. 4).[6b,6c,7]





In 1982, a novel carbene mediated cyclization was reported simultaneously by Afonso and co-workers at Schering and Yoshida, *et al.* at Sankyo (Eq. 5).[8] This procedure employed mild cyclization conditions (the addition of triethylphosphite to a refluxing chloroform solution containing oxalimide **15**) and the C_5 epimerization problem which plagued the intramolecular Wittig condensation was avoided.

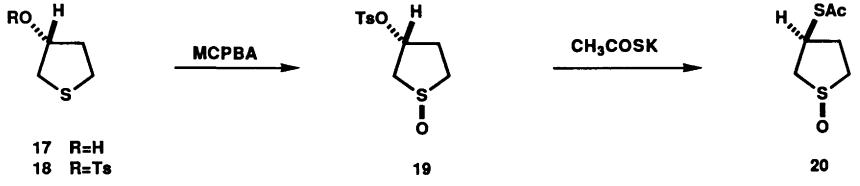
The oxalimide-based penem approach became the most desirable method for the preparation of 2-alkylthiopenems (**5**) and was our choice for the preparation of CP-65,207 (**7**) for toxicological studies. In this synthesis, oxalimide **15** [R = p-nitrobenzyl (PNB)] was generated in two steps by addition of sodioethyltrithiocarbonate to acetoxyazetidinone **14** followed by acylation of the resultant azetidinone trithiocarbonate with p-nitrobenzyloxalyl chloride. Treatment



(5)

of **15** in refluxing chloroform with triethylphosphite (2.2 equivalents) over an 18 hour period afforded S-ethyl penem **16** (R = PNB) in 65% yield. DiNinno *et al.*[4] had previously described the utility of 2-ethylsulfinyl **6** for the preparation of 2-alkylthiopenems by demonstrating that the sulfinyl group could be displaced with a variety of thiols in the presence of N,N-diisopropylethylamine. We utilized this reaction in our early discovery efforts and later for the synthesis of CP-65,207 (**7**). Penem **16** was therefore oxidized with 1 equivalent of m-chloroperbenzoic acid (MCPBA) resulting in a selective (9 : 1) oxidation of exocyclic : endocyclic penem sulfur atoms providing in 65% yield **6**[4], as a mixture of diastereomeric sulfoxides.

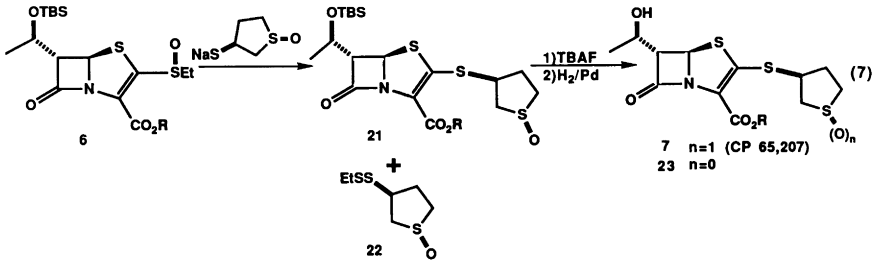
The CP-65,207 sulfoxide side chain thioacetate **20** was assembled in a straightforward fashion. Tosylation of racemic 3-hydroxythiophane **17** gave **18** which was oxidized with MCPBA to give a mixture (82 : 18) of *trans* and *cis* sulfoxides. Treatment of the major *trans* sulfoxide **19** with potassium thioacetate provided side chain thioacetate **20** (Eq. 6).



(6)

Saponification of **20** and Michael addition of the intermediate thiolate to **6** at − 60°C generated the fully functionalized bis-protected penem **21** in 65% yield (Eq. 7). In addition, disulfide **22** was also generated, resulting from a competitive thiolate condensation with the ethylsulfenic acid produced in the sulfoxide displacement. Removal of the t-butyldimethylsilyl (TBDMS) alcohol protecting group of **21** with tetrabutylammonium fluoride followed by reductive

(H_2/10% Pd/Celite®/$NaHCO_3$) removal of the PNB acid protecting group provided after purification by Sephadex chromatography CP-65,207 (**7**) as its sodium salt in 50% yield. Varying amounts (5–15%) of **23**, resulting from sulfoxide reduction were also produced in the hydrogenation step.

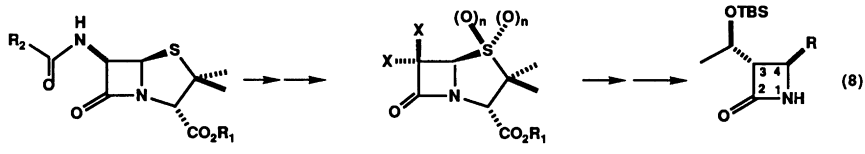


In the early stages of biological evaluation of CP-65,207 (**7**), this synthetic scheme with its inherent problems served us well in providing the necessary supplies of drug. Clearly, however, a more efficient and cost effective process would be required for the progression of this antibacterial agent. We therefore turned our attention to some of the more obvious problems associated with the current process and in particular the difficulties associated with removal of the PNB acid protecting group, the synthesis of azetidinone precursors, and the overall lengthy synthesis of CP-65,207 resulting from the replacement of the S-ethyl side chain with our own. Solutions to these problems, we hoped, would at a minimum provide for a more efficient preparation of CP-65,207 (**7**) and if we were fortunate would provide the potential for the identification of a commercial CP-65,207 (**7**) process.

IV. The Azetidinone Problem: A Penicillin-Based Approach

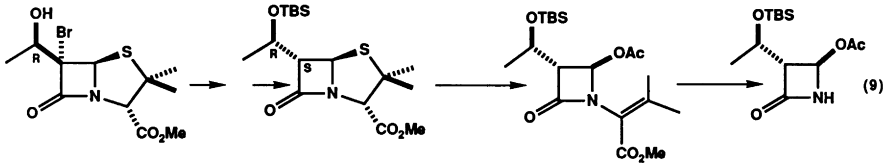
From the start, we recognized that the substituted azetidinone moiety would be the major contributor to the overall cost of CP-65,207 (**7**). For this reason, we decided to evaluate several processes for the synthesis of enantiopure 4-substituted-3-[(R)-1-hydroxyethyl]-azetidin-2-ones **28** (bearing a leaving group in the 4 position) which are ideally suited as penem/carbapenem intermediates. Even though

penicillins **24** have structurally little in common with **28**, we were biased toward a penicillin based route[7,9] largely because of the availability in our laboratories of kilogram quantities of penicillin-derived dibromopenicillinic acid **25** ($R_1 = H$) and sulfone **26** ($R_1 = H$), intermediates in the commerical synthesis of Pfizer's β-lactamase inhibitor, sulbactam **27** ($R_1 = H$) (Eq. 8).[10] In addition, we knew a great deal about the chemistry of these compounds.



24 25 n=0,X=Br 26 n=1,X=Br 27 n=1,X=H 28 (8)

DiNinno[11], *et al.*, demonstrated previously that the Grignard reagent derived from **25** (R_1 = Me) undergoes aldol addition with acetaldehyde to afford a mixture of products with the major one (**29**) having the requisite 8R penem stereochemistry. Establishment of the 6S penem stereocenter was achieved by catalytic hydrogenolysis of the major aldol product **29** to invert the hydroxyethyl side chain. Subsequent alcohol protection afforded penicillinate **30** as the major product. Mercuric acetate treatment of **30** to generate acetoxyazetidinone **31** followed by olefin oxidation and oxalimide hydrolysis provided the desired acetoxyazetidinone **14**. This literature scheme (Eq. 9) provided us with a convenient preparative means for the generation of substantial amounts of **14** for laboratory work.

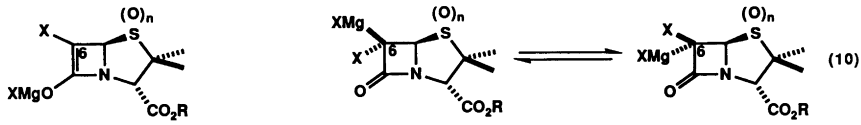


29 30 31 14 (9)

The lack of stereospecificity in the aldol condensation to generate **29** (ca. 20% of undesired isomeric aldol products are produced) and in the subsequent reduction of **29** (ca. 10% of the undesired 6R isomer is generated) coupled with the need for using toxic mercuric

acetate on a large scale to convert **30** to **31** encouraged us to explore other azetidinone routes.

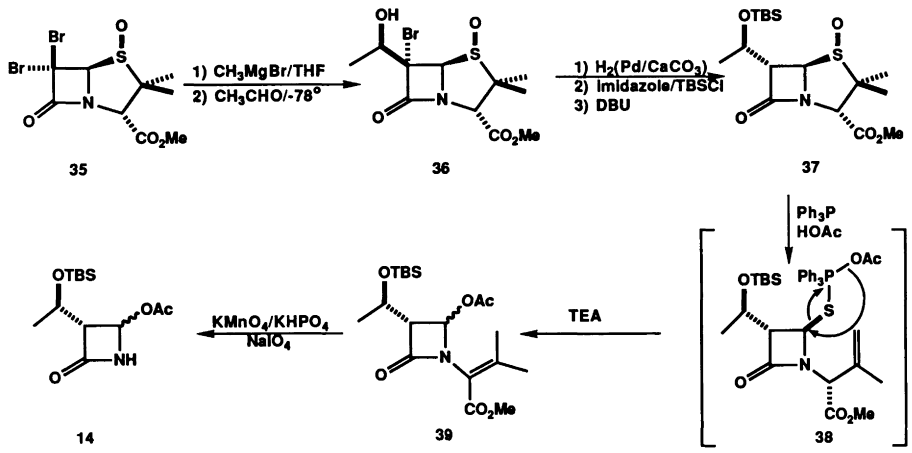
Our attention remained focused on penicillin-based azetidinone syntheses, all of which would employ the penicillin Grignard reaction to set the (8*R*)-hydroxyethyl penem stereochemistry. Attempts to improve the aldol stereoselectivity of **25** (R_1 = Me) by solvent,[12] counterion[12] and substituent manipulations[13,14] (replacing the C_6 bromine atoms) were not successful. Only three aldol products are obtained in significant amounts in THF from **25** (R_1 = Me). The major desired (8*R*) isomer is generated in 77% yield by acetaldehyde addition from the more hindered β-face of the penicillinate Grignard while mixtures of 8*R* and 8*S* isomers are produced upon addition from the α-face of the β-lactam. Even though a specific solution to this aldol stereoselectivity problem was not obvious, our strategy was. We would need to devise a way to improve the facial selectivity (β vs. α) of the anion additions since only one hydroxyethyl diastereomer is produced upon addition from the β-face. The actual reason for the preferred β-facial selectivity of the penicillin Grignard is not known and we were not comfortable with previous explanations that suggested the intermediacy of magnesium enolate **32**. We felt that tetrahedral penicillin carbanions **33** and **34** were more likely intermediates (Eq. 10). To test this hypothesis, we have recently prepared ^{13}C labeled (C_6) dibromopenicillanates **25** and **26** (R_1 = Me) from ^{13}C labeled ethylbromoacetate by modifying published procedures.[10,15] Our intent is to examine Grignard and additionally organolithium (^6Li) reagents derived from these by ^{13}C NMR.



32 **33** **34**

If the reaction were to proceed via a tetrahedral carbanion, we would predict the aldol diastereoselectivity to be higher in the case of the Grignard reagent derived from β-sulfoxide **35** due to carbanion stabilization by the proximal sulfoxide moiety. Such a reaction could be particularly useful in azetidinone syntheses since the sulfoxide moiety would serve a dual role in setting the side chain stereochemistry and facilitating the ultimate destruction of the thiazolidine ring via

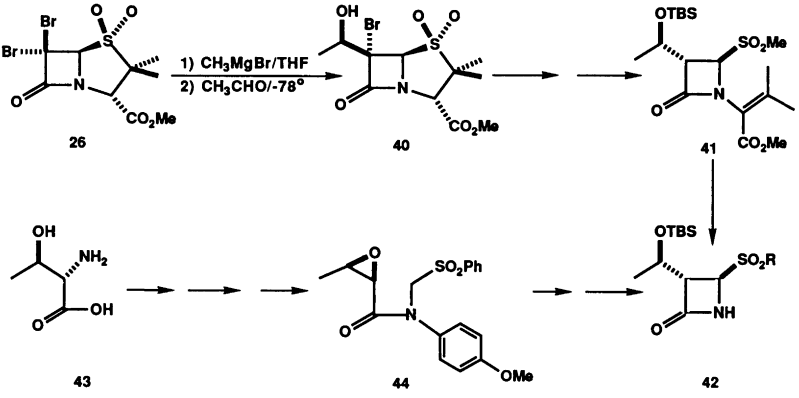
a sulfenic acid rearrangement. To examine this possibility, Brad Brown and Paul Merrigan treated the Grignard reagent derived from **35** with acetaldehyde (Scheme 1). To our delight, 8*R* alcohol **36** was generated in high yield with greater than 98% diastereoselectivity. Catalytic hydrogenolysis of alcohol **36** followed by silylation of the resultant product under standard conditions generated a mixture which without isolation was treated with 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) to afford the desired 6*S* silyloxyethyl side chain. Sulfoxide **37** was produced in moderate (70%) yield. We next investigated the propensity of penicillin sulfoxides to undergo a sulfenic acid elimination[16] as a means of rupturing the thiazolidine ring. We understood from previous work of Lombardi, Kellogg, Hatfield, and Alpegiani that reductive acylation of sulfenates derived from penicillinate sulfoxides is useful in generating functionalized azetidinones.[16] Accordingly, sulfoxide **37** was treated with triphenylphosphine in acetic acid followed by triethylamine to isomerize the expected β,γ-unsaturated ester. Acetoxyazetidinone **39** was cleanly produced. The precise mechanistic events leading to **39** are not known; certainly the results are consistent with the intermediacy of penta-coordinate phosphorus intermediate **38**. Oxidative cleavage of **39** afforded azetidinone **14**. This sulfoxide-based approach clearly solved the aldol diastereoselectivity problem and provided a route to **14**. We unfortunately were never able to generate **35** in high isolated yields (via diazotization/bromination of



SCHEME 1

6-aminopenicillinic acid sulfoxide-methyl ester) nullifying the benefits of this route. As a result we turned our attention to a conceptually similar sulfone-based azetidinone approach (Scheme 2).

Dibromopenicillanate sulfone **26** was treated with methylmagnesium bromide in THF (−78°) followed by acetaldehyde to afford hydroxyethylsulfone **40** in high yield (79%; 89:11 **40**:undesired isomers) which could be crystallized from the reaction mixture. Using a procedure developed at Sankyo by Hirai, *et al.*,[9e] and independently developed in our laboratories by George Quallich[17] and co-workers, **40** was hydrogenated to afford a mixture of C_6 isomers which were silylated under standard conditions. The inductive effect of the sulfone coupled with its propensity for elimination could simultaneously be exploited for the preparation of azetidinone **42** (R = Me). The *t*-butyldimethylsilyloxyethyl side-chain was isomerized completely with DBU (~1 min at 25°C) thereby removing the severe torsional strain caused by the β-(6R)-silyloxyethyl group. The sulfone residue then underwent a facile base-catalyzed β-elimination and was alkylated *in situ* with methyl iodide to afford α,β-unsaturated ester **41**. Conventional oxidative cleavage of unsaturated ester **41** with sodium metaperiodate and catalytic potassium permanganate gave desired azetidinone **42** (R = Me) in 35% overall yield over six steps from **26**. No chromatography of intermediates was required. A related sulfone **42** (R = Ph) was generated *via* a threonine-derived route involving epoxide **44** which was reported earlier by workers at Sankyo[18] and



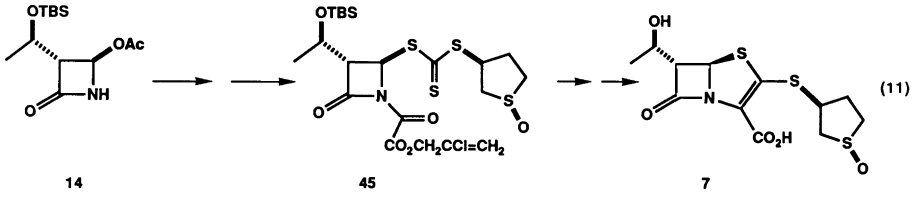
SCHEME 2

examined in our laboratories by Bob Dugger. Unfortunately our enthusiasm for the utility of sulfones **42** (R = Me or Ph) was short-lived as we would soon discover that these sulfones are less reactive than acetoxyazetidinone **14** to nucleophilic addition of the CP-65,207 (**7**) side chain trithiocarbonate.

We were still confident that further improvements in our existing syntheses of azetidinone intermediates could be made and several alternatives were under consideration; however, acetoxyazetidinone **14** became commercially available from the Kanegafuchi and Takasago companies at this time. Bulk quantities of **14** were obtained, albeit at high cost, and while the need for an economic azetidinone synthesis remained, the urgency for its development disappeared. The penicillin-based syntheses had nonetheless served a valuable role in providing azetidinone intermediates for the synthesis of all our clinical CP-65,207 supplies. Our attention, however, was now directed to other aspects of penem synthesis and specifically to the key conversion of **14** to CP-65,207 (**7**).

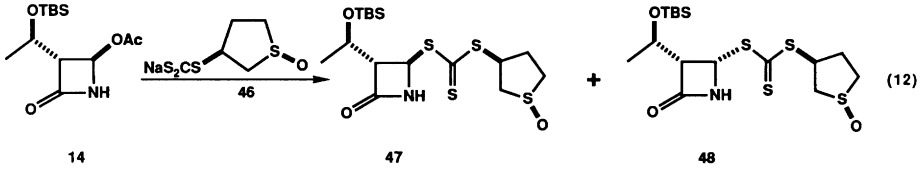
V. Problems in Penem Synthesis: The Oxalyl Fluoride Solution

Of the synthetic options for streamlining conversion of acetoxyazetidinone **14** to CP-65,207 (**7**), the phosphite mediated cyclization route involving oxalimide **45** (Eq. 11) appeared the most promising since it would eliminate two steps from the existing synthesis shown in Eq. 7. We decided at the same time to replace the PNB ester with an allylic acid protecting group because of the sulfoxide reduction problems associated with PNB removal. The mild palladium(0)-mediated transesterification conditions reported by McCombie and Jeffrey[19] were selected for allyl ester removal. Because of the putative intermediacy of a carbene in the phosphite mediated cyclization, we settled on the chloroallyl ester moiety to discourage internal cyclopropanation of the allyl protecting group. Our most experienced β-lactam experi-



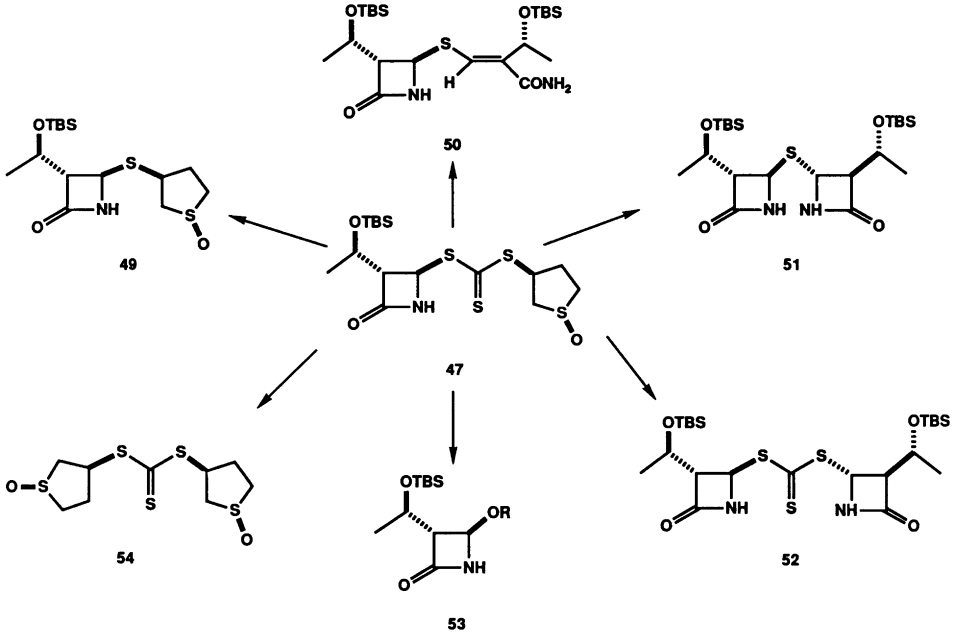
(11)

mentalist, John Jasys, explored this "straightforward" synthesis shown in Eq. 12 and employed standard methodology (sodium ethoxide mediated saponification of thioacetate **20**, carbon disulfide trapping of the intermediate thiolate to give trithiocarbonate **46** followed by the addition of **46** to acetoxyazetidinone **14**) to generate trithiocarbonate **47** (*trans* **47**: *cis* **48** = 92 : 8) (Eq. 12).



14 47 48

Yields were uniquely low (30–50%) for this addition as unreacted **14** in addition to a number of structurally diverse by-products **49–54** were obtained. To shed some light on this problem, desired trithiocarbonate **47** was subjected to a series of stability studies (Scheme 3). By merely dissolving trithiocarbonate **47** in ethanol, alkoxyazetidinone **53** (R = Et), trithiocarbonate **54** along with minor amounts of



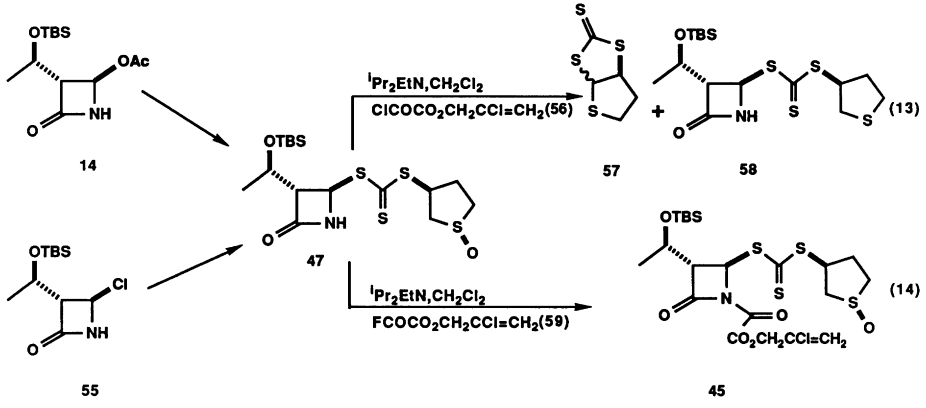
SCHEME 3

49 and **51** were generated. A similar decomposition occurred with *i*-propanol, albeit at a slower rate. In the presence of base (Et_3N/CH_2Cl_2), **47** lost CS_2 to generate mainly **49** along with **50**, **51**, **52** and **54**. To make matters worse, the formation of **47** was reversible; NMR studies in deuterated *i*-propanol showed that **47**, upon treatment with potassium acetate, generated predominantly **49**, and minor amounts of **14**.

We soon discovered that sodiotrithiocarbonate **46** could be precipitated as its THF solvate. By using isolated **46**, condensation yields improved. Trithiocarbonate **47** could be obtained in 65% yield with ca. 7% of **48** via the condensation of a 10–15% excess of **14** with **46** in *i*-propanol at −5–0°C (at temperatures >5°C, **49** is produced in significant amounts). Attempts to further improve this transformation with counterion/solvent/temperature manipulations were not successful. Nonetheless, this procedure was scaled up to provide multigram quantities of **47**.

Up to this point, we had only explored the addition of **46** to acetoxyazetidinone **14** and sulfone **42** (R = Me) because of their bulk availability. As mentioned earlier methylsulfone **42** was not as reactive as **14** and in fact did not react with sodiotrithiocarbonate **46** using conditions described above. P-Nitrophenylsulfone **28** ($R = SO_2PhNO_2$) however, did undergo addition suggesting more reactive azetidinones would have promise. Later in our development efforts, Dave Hageman targeted 4-chloroazetidinone **55** for synthesis to test this hypothesis. A remarkably stable yet reactive chloroazetidinone **55**[20] was prepared as described by Endo[21] (via chlorination of sulfide **28** ($R = S^iPr$)) and treated with equimolar amounts of **46** in acetone (0°) to provide **47** in >95% yield!

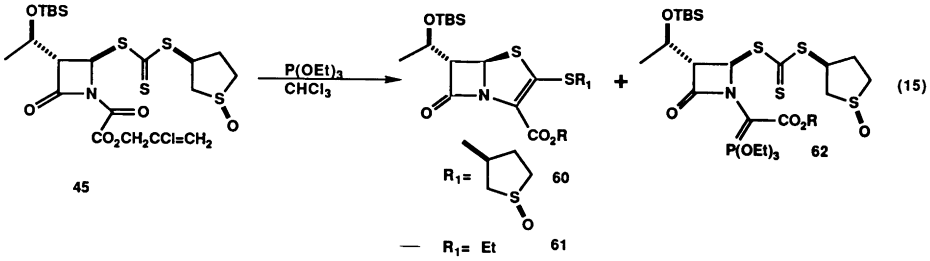
Standard acylation conditions (Et_3N/oxalyl chloride **56**/CH_2Cl_2, −5°–0°C) were first employed to convert **47** to oxalimide **45**. Unfortunately concerns on our part over the possibility of competitive sulfoxide acylation were justified as little if any product was obtained. The sulfoxide side-chain was the culprit as evidenced by our isolation of bicyclic trithiocarbonates **57** (Pummerer by-products of **47**) and trithiocarbonate **58**, resulting from sulfoxide reduction (Eq. 13). We shared our synthetic frustrations with Professor E. J. Corey, a consultant on the project. He suggested the use of oxalyl fluoride **59** as a possible way to avoid this problem. Little was known in the literature at the time about the reactivity of acyl fluorides, (recent reports however describing the stability of fluoroformates in



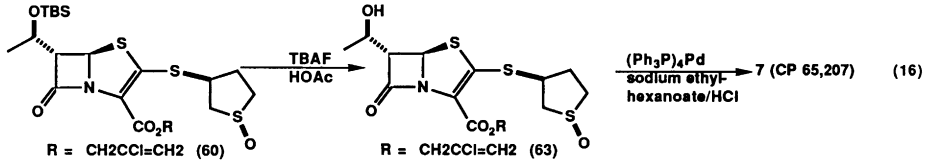
DMSO and chemoselectivity of acyl fluorides have appeared).[22] There was some skepticism in our ranks about the ability of oxalyl fluorides to solve our chemoselectivity problem but we were obviously in no position to eliminate possible solutions since the success of the early side chain introduction approach was at stake. As a result, we set off to prepare oxalyl fluoride **59**. We discovered that **59** could be smoothly generated by treatment of **56** with cesium fluoride/CH_3CN. Reaction progress was monitored by IR spectroscopy. Dropwise addition of N,N-diisopropylethylamine to a CH_2Cl_2 solution ($-50°$) containing **47** and **59** provided, after workup, the desired **45** in *>95% isolated yield* (Eq. 14). Remarkably, no by-products indicative of sulfoxide acylation were isolated and we assumed, in our excitement, that all our synthetic problems were now behind us.

Once acylated, the azetidinone trithiocarbonates were considerably more stable. Treatment of **45** in EtOH-free $CHCl_3$ heated to a gentle reflux under nitrogen with 2.2 equivalents of $(EtO)_3P$ over an 18 hour period provided two major penem products, desired penem **60** (56%) and triethylphosphite-derived S-ethyl penem **61** (7%) along with phosphite ylide **62** (Eq. 15). A minor amount of product (<3%) resulting from sulfoxide reduction was also obtained. In our hands, the overall yield of **60** was somewhat lower than that obtained in the original S-ethyl penem synthesis developed by Schering.[8a] They obviously benefited from the S-ethyl penem-producing side reaction (formation of **61**) since in their case the side product **61** and desired product are one and the same!

Standard conditions were employed for the removal of the *t*-butyldimethylsilyl alcohol (TBAF/HOAc/THF)[8] and chloroallyl



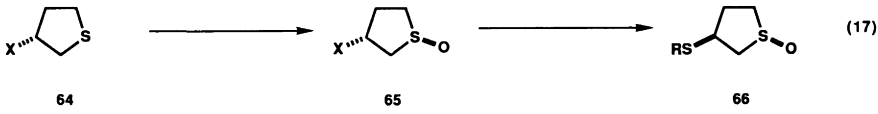
(Ph_3P/(Ph_3P)$_4$Pd/sodium ethylhexanoate) acid protecting groups. An aqueous solution of this crude penem sodium salt was then treated with activated charcoal to remove any residual palladium impurities and was converted to crystalline free acid **7** by treatment with 6N HCl (Eq. 16).



VI. Problems in the Clinic: A Call for Both Penem Diastereomers

At this time, we received disturbing news from our clinial colleagues that the urine of patients treated with CP-65,207 (**7**) had a pungent, skunklike odor. As a result human trials were halted and our enthusiasm was all but destroyed. In retrospect, this result was not totally unexpected as penems and carbapenems are prone to degradation by renal dehydropeptidase. In the case of the marketed carbapenem, Imipenem, this problem is so severe that an inhibitor, cilastatin, is co-administered with the drug. In our case a possibility, albeit somewhat remote, existed that one of the CP-65,207 diastereomers was more susceptible to enzymatic destruction and primarily responsible for a malodorous metabolite in the urine especially since the urinary recovery of one of the CP-65,207 diastereomers was almost twice the other. Our only hope was to test such a hypothesis; to do so, we obviously needed to prepare the pure diastereomers using the corresponding enantiomerically pure tetrahydrothiophene (thiophane) sulfoxide side chains.

We were confident that if we could access enantiomerically pure 3-substituted thiophanes **64** (in which X is a leaving group) we would be able to employ the identical strategy we had used earlier for side chain synthesis (Eq. 17).

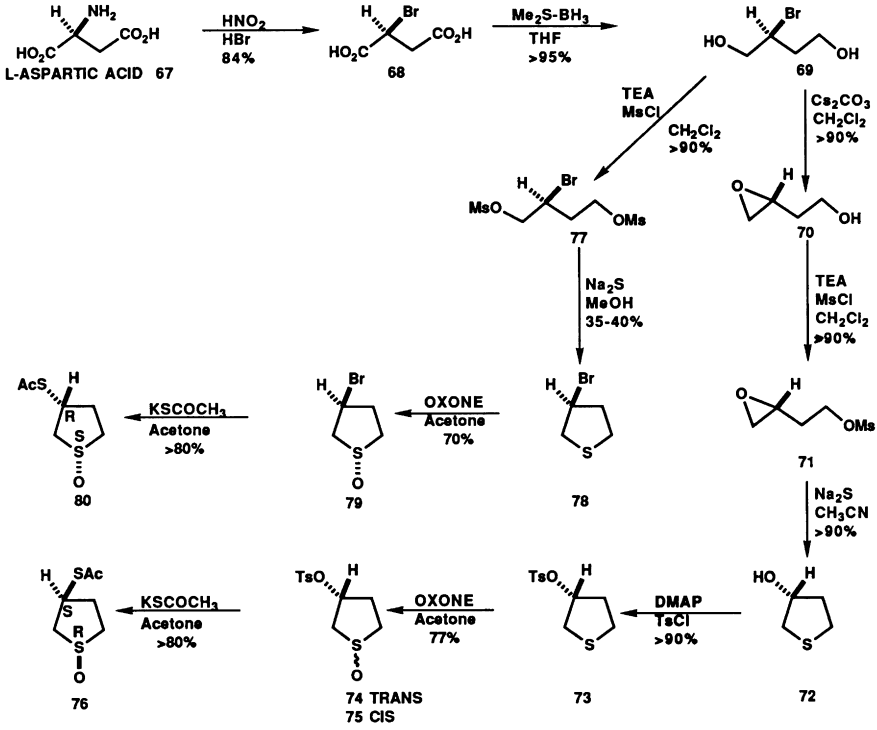


64 65 66 (17)

Enantiomerically pure 3-hydroxythiophane **64** (X = OH) had been prepared by Brown[23] *et al.* via a diisopinocampheylborane-mediated asymmetric hydroboration of 2,3-dihydrothiophene. We opted for an alternate approach amenable to large scale synthesis using L-aspartic acid **67** as a synthon for thiophane ring construction (Scheme 4). Paul Kelbaugh and Deane Nason set out to prepare both sulfoxide side chains using this starting material.

Bromodiacid **68**[24], obtained by diazotization/acid treatment of L-aspartic acid **67**, had been converted by Sugimura and co-workers[25] to (*R*)- and (*S*)-3-mercaptopyrrolidines. We envisioned a similar strategy, i.e., the preparation of homochiral (*R*)- and (*S*)-3-mercaptothiophanes. Attempts to convert bromodiacid **68** to diol **69**[25] and epoxide **70**[25,26] were frustrated by water solubility of these intermediates. As a result, we sought to eliminate the aqueous work-ups in these reactions. Problems in the diborane reduction workup were obviated by addition of methanol and azeotropic removal of trimethylborate. Additional problems in the ensuing epoxidation step were circumvented by treatment of diol **69** with cesium carbonate in dichloromethane to afford epoxide **70** in high yield. Following the removal of cesium salts by filtration, the crude reaction mixture could then be treated directly with Et_3N/mesyl chloride to afford epoxymesylate **71** in high yield. Sodium sulfide treatment of **71** afforded (*R*)-3-hydroxythiophane **72** (>90% overall yield from **68**) which was cleanly converted to tosylate **73**. Oxidation of **73** with potassium peroxymonosulfate (Oxone®)[27] (1 equivalent) yielded the desired *trans* sulfoxide **74** in 77% yield in addition to minor amounts of the undesired *cis* isomer **75**. Potassium thioacetate treatment of **74** provided optically active (1*R*, 3*S*) targeted thioacetate **76** in >80% yield.

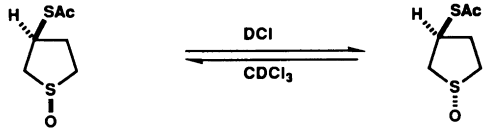
To access the other side chain enantiomer, diol **69** was smoothly converted to bismesylate **77**. The presence of the secondary bromide



SCHEME 4

substituent in **77** raised concerns about regiospecific sulfide addition and episulfide formation. These concerns were justified as bromide **78** was obtained in only 35–40% yield. Fortunately **78** was the only material obtained in appreciable amounts during distillation of the crude reaction mixture. Standard oxidation/thioacetate displacement conditions were employed to generate optically active (1*S*, 3*R*) thioacetate **80**.

Gram quantities of **76** and **80** were produced in our discovery laboratories using this L-aspartic acid derived route. In examining the ^{1}H NMR of **76** obtained in a large scale synthesis by our pilot plant colleagues, we were shocked to see a 9 : 1 mixture of *cis* : *trans* thioacetatesulfoxides **76** and **81** since we had never run into problems with this sequence (Eq. 18). An ensuing ^{1}H NMR (24 hrs later) showed the ratio to be even worse (3 : 2) implicating the stability of thiophane sulfoxides. In fact, Fava and co-workers[28] have shown that 5-membered ring sulfoxides are particularly prone to an acid mediated



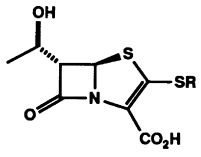
76 81 (18)

stereomutation (presumably via nucleophilic halide addition to the protonated sulfoxide).[29] Indeed the HCl present in the $CDCl_3$ we used for the ^1H NMR was apparently the culprit. Reexamination of the ^1H NMR spectrum of the same sample of **76** using another source of $CDCl_3$ showed only desired product. We obviously had initially jumped to the wrong conclusion in implicating problems in scale up when we first examined the NMR of **76**. Moreover, this experience demonstrated the susceptibility of these sulfoxides to acid-catalyzed isomerizations and encouraged us to carefully monitor all our sulfoxide-containing reactions and product isolations.

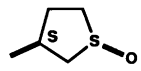
VII. Sweet Smell of Success: The Emergence of CP-70,429 (82)

Thioacetates **76** and **80** were converted to penems **82** and **83** in a straightforward fashion using our existing methodology. Fortunately, from a process standpoint, nearly all the penem intermediates are crystalline. Penem **82** (CP-70,429) was significantly more stable than **83** to human (2x) and porcine (1.3x) renal dehydropeptidase, a result which was consistent with its higher urinary recovery in our first human trial. Midst a sea of skepticism, CP-70,429 (**82**) was selected for clinical follow-up, and prepared in multigram amounts. The key determinant of the proposed study would be urine smell with CP-65,207 (**7**) containing the mixture of diastereomers serving as the control. We had invested a great deal of time and energy into penem research up to this point and wanted to be convinced of the outcome of the study. The fate of CP-70,429 (**82**) and future penem research was at stake. We therefore accompanied our clinical colleagues to a Providence hospital on a beautiful Saturday afternoon in the Fall of 1987 for the key "smell off." To our delight, the urine samples from

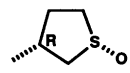
those who were administered CP-70,429 (**82**), had no significant odor while the CP-65,207 (**7**) samples did. A CP-70,429 urine sample was inadvertently spilled on the clothes of one of us providing a satisfying reminder of our conquest of the smell problem. CP-70,429 (**82**) became the penem candidate and our chemistry efforts continued.



82 (CP 70,429)



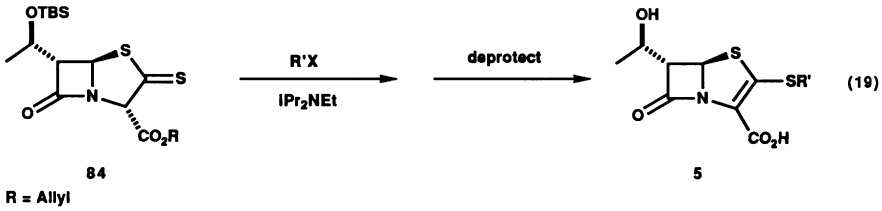
83 (CP 81,054)



VIII. A Convergent Approach to Side-Chain Addition: The Dithiolactone (84) Connection

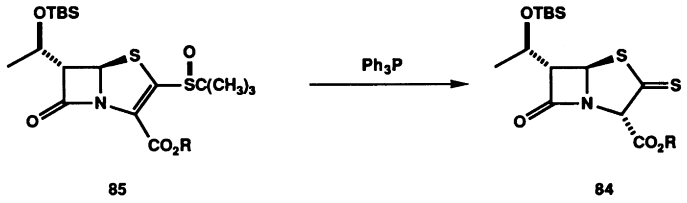
After the breakthrough in clinical studies, chemistry efforts were refocused on the pilot plant process. In retrospect, we had relied on carbene based methodology to successfully carry the penem into development but the low overall yield of the process was still cause for concern. In addition, we felt uneasy with the timing of side-chain insertion especially now that enantiomerically pure substrate[30] was required. The group was confident that simple efficiency problems in the carbene route could be solved through process development efforts but we became convinced that a new strategy, focusing on late side-chain addition, would ultimately be needed to substantially lower our overall process cost. Much effort had been expended to bring the carbene process on line and so the call went out for us to identify an alternative route for scale-up of CP-70,429 (**82**).

In 1983, workers at Merck and Schering reported the utility of novel thione **84** as an intermediate for the preparation of 2-alkylthiopenems **5** (Eq. 19).[9b,31] Several penems were prepared through a N,N-diisopropylethylamine mediated S-alkylation with simple halides. We felt that **84** would offer a satisfactory solution to our side-chain addition problems, provided that the key alkylation was *straightforward and high yielding* with our substrate. We were optimistic that a short and efficient synthesis of key intermediate **84** was an achievable goal, thus making the overall plan quite attractive.



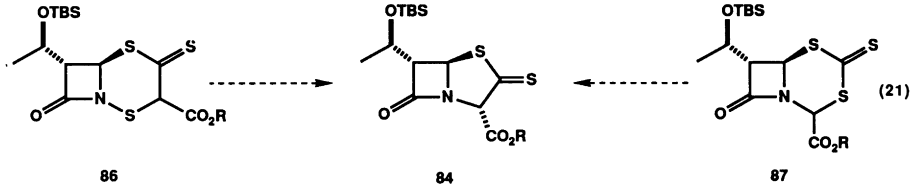
(19)

Previous syntheses of thione **84** involved assembly of a functionalized β-lactam followed by attachment of the dithiolactone ring. Thione **84** had been prepared early on in our laboratory using a lengthy process previously described by workers at Sandoz. In the final step a thermal rearrangement of 2-t-butylsulfinyl penem **85** was employed to generate **84** (Eq. 20).[32] In search of a shorter, more efficient route, we entertained two conceptually unique and admittedly



(20)

more speculative sulfur extrusion-based processes to **84**. Our intent was to obviate problems associated with direct assembly of the strained[3.2.0]bicyclic penem ring system since we felt the inefficiencies of the carbene based method were due to difficulties in thiazoline ring formation in the key cyclization step. Our plan was to generate less strained[4.2.0]bicyclic β-lactams and use these intermediates as templates for subsequent ring contraction/sulfur extrusion to generate thione **84** (Eq. 21). Azadithiobicyclo[4.2.0]octanes **86** and **87** appeared to be attractive candidates for sulfur extrusion and were, as a result, targeted for synthesis.

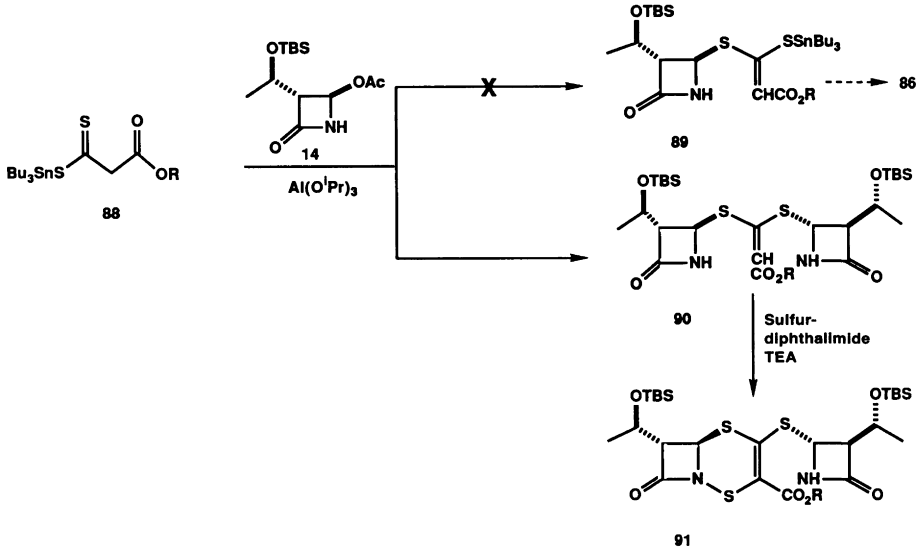


(21)

IX. Some Confusion about Sulfur Extrusion: A Synthesis of Dithiolactone (84)

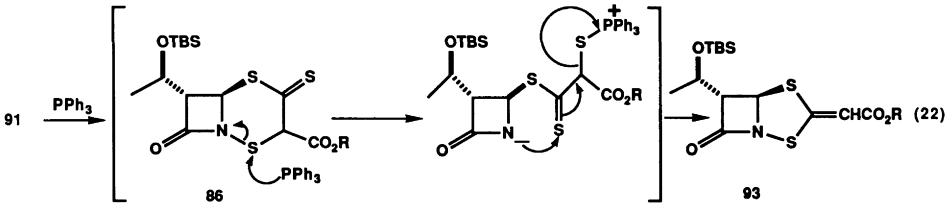
To explore the first of these options, we planned to generate dithioketeneacetal **89** and convert it directly to sulfenamide **86** by addition of an appropriate sulfur-containing electrophile (Scheme 5). Accordingly, John Jasys treated acetoxyazetidinone **14** with dithiostannyl ester **88** in the presence of aluminum isopropoxide. None of the desired dithioketeneacetal **89** was generated utilizing these conditions. Instead bisazetidinone **90** (in which our inexpensive tributyltin sulfur protecting group had been replac by an expensive azetidinone moiety) was obtained. Even though **90** was not our intended product, we felt it should still provide us with the same synthetic opportunities as **89**. As a result, we proceeded forward with bisthioketeneacetal **90** to probe the viability of our approach. Treatment of **90** with sulfur diphthalimide[33] generated sulfenamide **91** in 79% yield. We were obviously pleased with this result since we were in position to probe the first of our sulfur extrusion routes.

Treatment of **91** with triphenylphosphine in THF afforded a new compound which by mass spectral analysis had a molecular ion identical to that of the desired **84**. However, our excitement was short-lived as additional spectral data (^{13}C and ^{1}H NMR) confirmed



SCHEME 5

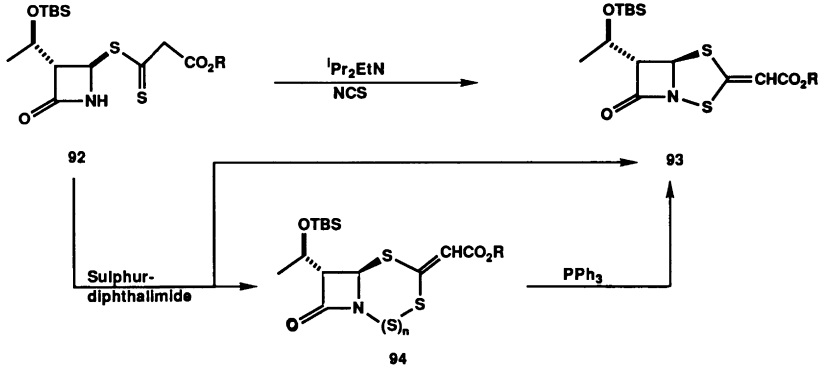
that this new compound in fact was a mixture of two isomers, neither of which was the desired thione **84** (Eq. 21).



(22)

Additional information on the identity of **93** was garnered by treatment of **92** (which could be obtained by the addition of the sodium salt of **88** to **14**) with sulfur diphthalimide (Scheme 6). A mixture of products was produced, one of which was our mystery compound **93**. Upon treatment with triphenylphosphine, the other products **94** (n = 1,2) of this reaction, which were thought to contain one or two additional sulfur atoms as evidenced by mass spectral analysis, also generated **93**! In fact, **93** was produced in all of our attempts to prepare **84** from **91** or **92**! All the evidence suggested that **93** is an isomeric mixture of novel β-lactam-containing sulfenamides shown in Scheme 6. Mike Kellogg suggested a simple experiment to verify its structure. Accordingly, a methylene chloride solution of **92** containing N,N-diisopropylethylamine was treated with N-chlorosuccinimide to generate **93** in >90% yield (Scheme 6).

Our sulfenamide-based sulfur extrusion route was obviously doomed. In all likelihood we had in fact generated from **91** our intended target, sulfenamide **86**, which upon exposure to triphenylphosphine did not produce the desired thione **84** but had selected a

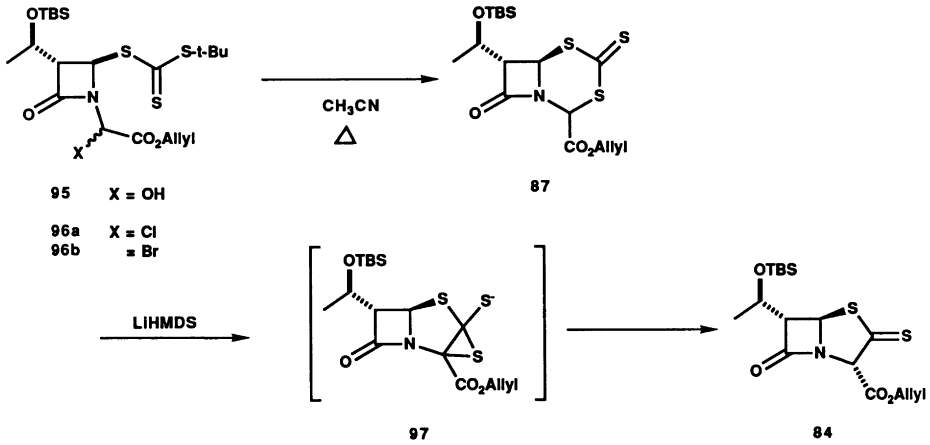


SCHEME 6

different (albeit lower energy) pathway to provide **93**. A possible mechanism is shown in Eq. 22. Attempts to salvage the approach by a photolytic conversion of **93** to **84** were not successful. As it turned out, our synthetic efforts were not a total loss as **93** was submitted to a variety of biological assays and found to be an extremely potent inhibitor of human leukocyte elastase, a serine proteinase that is responsible for the destruction of lung tissue in emphysema patients.

In exploring the second of the sulfur extrusion approaches, Katherine Brighty outlined a synthesis of **84** based upon ring contraction of the novel [4.2.0] trithiocarbonate system **87**.[34] Synthesis of compound **87** was achieved rapidly by a four step process from acetoxyazetidinone **14** (Scheme 7). Accordingly, addition of sodium *t*-butyltrithiocarbonate[35] to **14** followed by condensation with allyl glyoxylate afforded alcohol intermediate **95** (86%). Bromination (or chlorination) to generate **96** and subsequent heating of this product in acetonitrile under mild conditions effected ring closure to intermediate **87** in 55% yield.

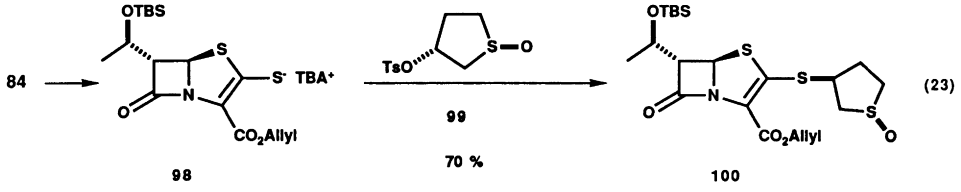
Following suggestions made earlier by Mike Kellogg, thiocarbonate **87** was primed for ring contraction under conditions related to the well known Eschenmoser sulfide contraction.[36] Naturally, Brighty and co-workers were operating on a system somewhat different from the usual thioamide substrate described by the Swiss group; however, in concert with this approach was the expected formation of an episulfide intermediate **97**, collapse of which, under the influence of a



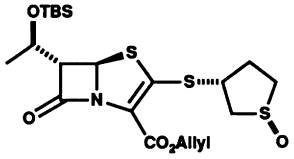
SCHEME 7

thiophile, was expected to provide the desired penem **84**. With **87** in hand, ring contraction was first attempted with lithium hexamethyldisilazide at −78°C. Interestingly, dithiolactone **84** was obtained directly in 64% yield as the sole product! Unlike corresponding Eschenmoser and the previously described Schering-Sankyo methodology, the presence of a phosphorous-based thiophile was not necessary for the collapse of intermediate **97**.

The success of the approach rapidly provided a long sought after opportunity for preparation of our penem system. Accordingly, intermediate **84** was subjected to base-mediated alkylation in the manner described by Leanza *et al.*[9b] To our disappointment, readily available tosylate **99** was relatively unreactive in the presence of N,N-diisopropylethylamine under these published conditions. Even worse, we found that alkali-metal enolates were also poor nucleophiles toward the tosylate. With much on the line, we prepared the related tetra-butylammonium (TBA) enolate **98**, since this counterion had served us well in other difficult alkylations. Reaction between **98** and tosylate **99** afforded **100** in a modest 70% yield (Eq. 23).

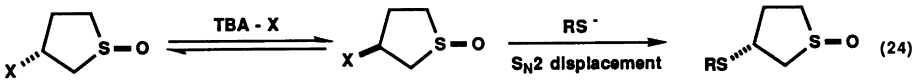


Other 3-substituted thiophanesulfoxide substrates such as the 3-(*R*)-iodide or bromide (**102**, Eq. 24) provided **100**, again in moderate yield. Unfortunately, in these cases, the product was contaminated by an unexpected isomer, shown from spectroscopic data to be the *trans* isomer **101** (% **101** from Br; 13–15%, I; 3–5%).



101

The fact that **101** was a minor by-product whose formation depended upon the leaving group (**102**; X = I or Br but X ≠ OTs) suggested to us that our halogen substituted side-chain had undergone isomerization prior to nucleophilic attack. This in turn pointed to the existence of a unique halide epimerization process, initiated once formation of bis-protected **100** was underway. It became clear that the reaction by-product TBA-Br (or TBA-I) had launched a competitive nucleophilic attack on **102** affording epimeric 3-(*S*)-halide **103** (simultaneously with formation of **100**). The resulting *cis* orientation of **103** provided unhindered access for attack by thiolate and thus displacement of this isomer resulted in formation of the *trans* diastereomer **104**.



102 X = I, Br

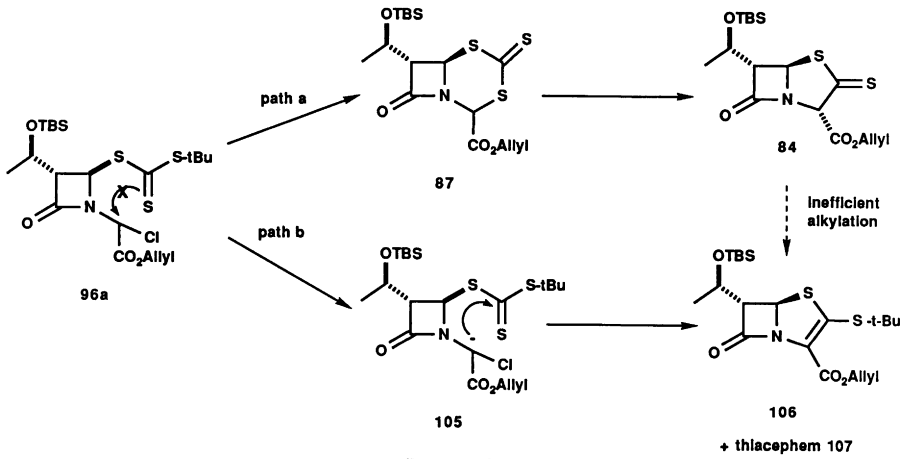
103

104 R = penem

In summary, our hopes for an alkylation-based process had been foiled. The superior reactivity of the TBA enolate toward displacement was compromised by its role in the epimerization of the side-chain halides. Additionally, the moderate alkylation yields afforded with the tosylate were not sufficient for production of CP-70,429 (**82**). Our final attempts to generate the triflate derivative (**102**, X = OTf), a substrate which would combine excellent leaving group ability and low nucleophilicity, proved fruitless. None of this material was ever obtained, ending in the demise of the plan.

X. Trithiocarbonate Ring Contraction: An Interesting Synthetic Excursion

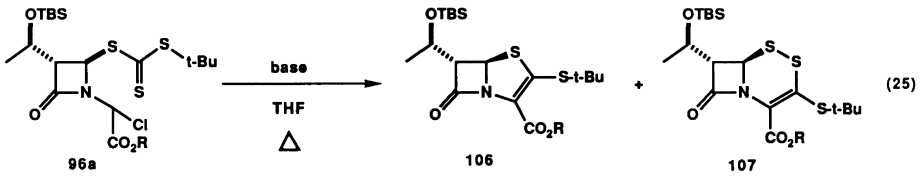
The value of dithiolactone **84** and in a broader sense our entire sulfur extrusion strategy was severely undermined by our inability to overcome alkylation-based problems. As a result, we were leaning toward total abandonment of the trithiocarbonate ring contraction approach until the following result was obtained. In contrast to the expected trithiocarbonate **87**, treatment of **96a** in refluxing acetonitrile with 1,8-bis(dimethylamino)napthalene produced S-alkylpenem **106** now as the



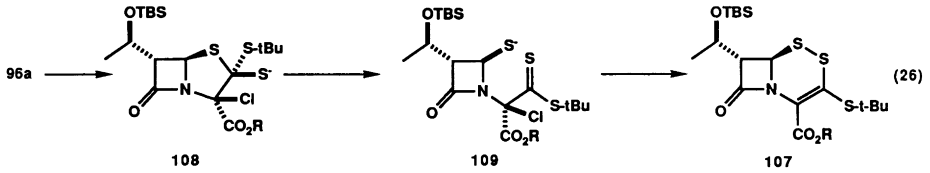
SCHEME 8

only identifiable product (Scheme 8, path b)! Base-mediated cyclization conditions were initially selected by Brighty to improve the yield of **87** (path a) after suspicions were raised that the desired product (**87**) had suffered an acid-catalyzed decomposition in the refluxing solvent. The level of acidity in path a (Scheme 8) was controlled to some extent by the generation and trapping of HCl with isobutylene, as both were reaction by-products; however, the efficiency of this process could not be insured in the refluxing solvent.

The concerns eventually led her to buffer the reaction mixture with a molar equivalent of base. We were obviously aware of the significant ramifications that base might have beyond the intended role of acid scavenger; however, the absolute delicacy of the original cyclization (path a) had not been completely appreciated. Further increase in the strength of the base by employment of sodium hydride afforded **106** as the major product (49%) and also effected the formation of a second compound identified as thiacephem derivative **107** (36% yield, Eq. 25).

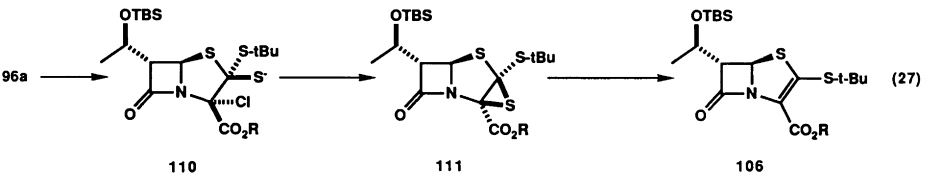


Based upon isolated products, a possible mechanistic rationale is depicted in Eqs. 26 and 27. Base-induced ester enolization of **96a** and intramolecular Darzens-like condensation with the thiocarbonyl residue results in the formation of two diastereomeric chlorothiolates **108** and **110**. The syn isomer **108**, unable to collapse to an episulfide by a stereoelectronically allowed process, suffers an overall migration of the dithioformate moiety. Subsequent intramolecular attack by the thiolate and release of chloride would provide thiacephem **107**.[37]



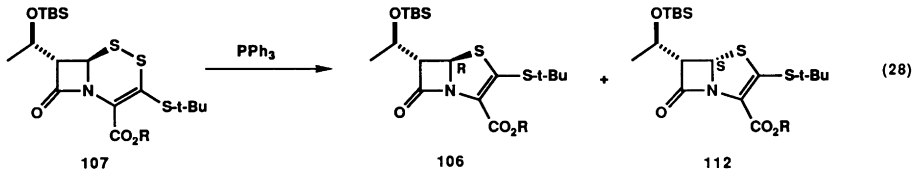
Simultaneously, anti-diastereomer **110** (Eq. 27), suitably arranged for episulfide formation, suffers ring closure–desulfurization to form the penem ring system directly. Although the intimate mechanistic details of the overall reaction scheme are not known, it is clear that enolate formation outpaces halide displacement by sulfur, providing a direct entry into fully protected penems. It was deemed unlikely that investigation of reaction conditions would lead to a unification of the two processes and increase selectivity for penem **106**.

We recognized that the diastereoselectivity problem (**108** vs. **110**), in principle, could be circumvented if a method for the conversion of thiacephems to penems (i.e., **107** to **106**) were available. For this reason, we investigated thiacephem desulfurization with phosphorous based reagents (Eq. 28). Desulfurization of **107** was accomplished with triphenylphosphine using solvents of differing polarity.



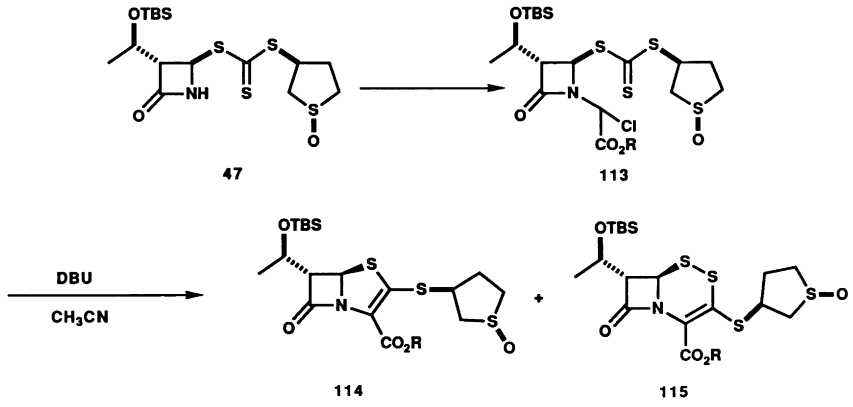
Consistant with previous findings,[38] the reduction unfortunately led to the formation of two diastereomers at C_5; however, by choice of solvent the ratio of diastereomers could be shifted to favor the biolo-

gically active 5-R penem ring system **106**. Interestingly, the use of non-polar solvents such as hexane favored retention of configuration (5 : 1 ratio of **106** : **112**) whereas the use of methanol or DMSO led to inversion of configuration. The "one pot" methodology was then applied to the synthesis of our fully elaborated penem.



(28)

In light of our previous experiences with penem model studies we certainly were not about to assume that the chemistry of chloroazetidinone **113** containing the Pfizer side chain would be identical to that of **96a**. Trithiocarbonate **47**, prepared earlier, was transformed into chloroazetidinone **113** under previously described conditions. The heavily functionalized substrate was subjected to modified ring closure conditions in acetonitrile using DBU as base (Scheme 9). The combination of substrate and base changes brought about an increase in overall yield (79%) but now favored the production of thiacephem **115** (5 : 1 ratio with **114**)! In all likelihood, the reversal in selectivity stems from the added influence of the newly introduced thiophane chirality with increased preference for the syn-isomer akin to intermediate **108**.



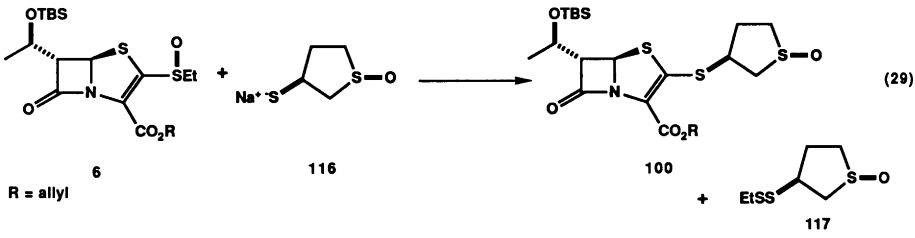
SCHEME 9

Desulfurization of **115** was accomplished with triphenylphosphine, but the trend towards 5-R isomer formation in solvents of low polarity did not emerge in this case. The best conditions involved reduction with triphenylphosphine in acetonitrile (6:1 5R:5S; 90%). Other phosphines were less effective in this regard.

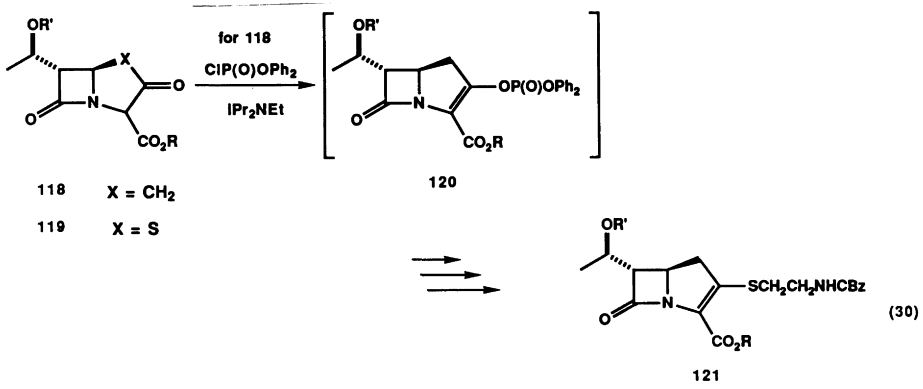
In summary, the trithiocarbonate ring contraction chemistry provided us with additional experience in assembling the penem skeleton. Unfortunately, the key conversion of trithiocarbonate **47** to bis-protected penem **114** containing the fully assembled side-chain was not selective (Scheme 9) and as a result was not an ideal solution to our penem problem. While we were obviously disappointed with the outcome of the ring contraction chemistry, we were at least consoled by the fact that a novel synthetic entry to dithiolactone **84**, still a relevant intermediate in penem synthesis, had been achieved.

XI. Michael Addition–Elimination: The Triflate Process

Our recent experience with side-chain alkylation/sulfur extrusion ended in disappointment and we began looking for a fresh approach. As an alternative, we decided to reverse the roles of the two substrates and concentrate our efforts on a Michael addition process with thiolate **116**. The plan paralleled earlier studies by DiNinno *et al.*[4] which we previously had used for the preparation of bis-protected CP-65,207 (**100**; Eq. 29). We later abandoned this approach when coupling yields could not be optimized. Part of the problem centered on the latent reactivity of the sulfenic acid leaving group which effected partial conversion of the thiolate to disulfide **117** (Eq. 29). Several avenues were briefly explored to circumvent this dilemma but we were more optimistic that the problem could be solved through selection of an inert leaving group.

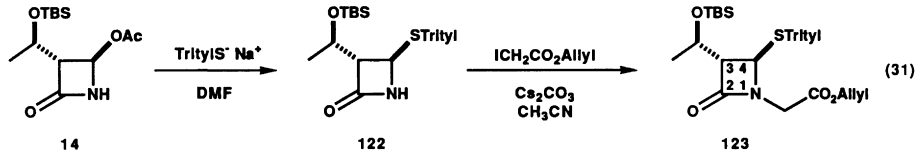


Ample precedent from the carbapenem field established Michael addition to sulfonate or phosphate esters such as **120** as the preferred method for preparation of 2-alkylthiocarbapenems.[39] As an example, enolphosphate activation of β-ketoester **118** followed by Michael addition of a thiol afforded excellent yields of thienamycin precursor **121**. The obvious convergency of this process convinced us to pursue this avenue as a way to enhance our overall yield and facilitate scale-up. We set out to prepare the related thiolactone **119**[9d] to test this hypothesis.



(30)

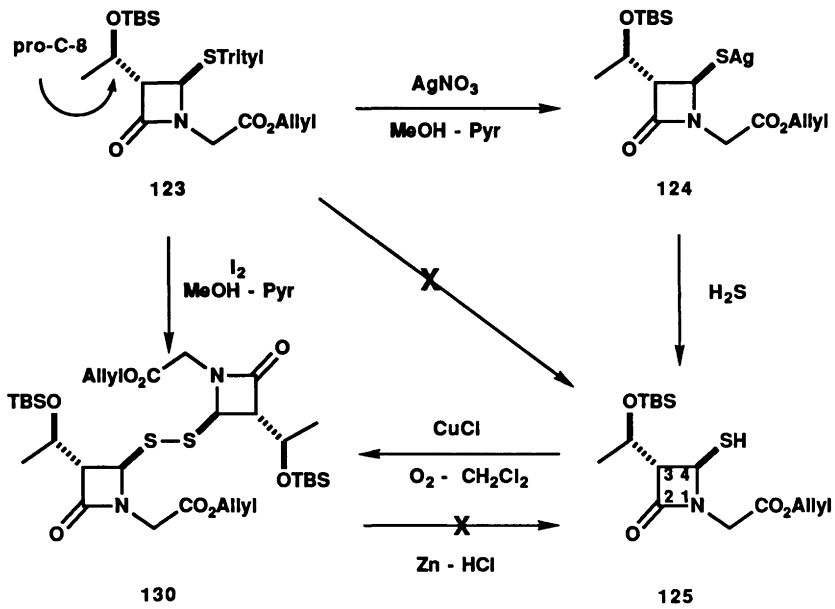
Synthesis of thiolactone **119** was initiated from the large stock of acetoxyazetidinone **14** currently in-house. Our plan was to culminate with Dieckmann cyclization of seco-derivative **126** or **127** (Eq. 32) by a process patterned after the Merck-Schering synthesis of dithiolactone **84**, although some modification of the intervening steps was anticipated.[9b,31] The known S-trityl-N-substituted azetidinone **123** (Eq. 31), was generated in two steps by addition of sodium tritylthiolate to **14** followed by alkylation of the ring nitrogen. This approach provided exclusively the desired *trans* arrangement at carbons C_3 and C_4.



(31)

Treatment of **123** (Scheme 10) with various combinations of acidic reagents and metals did not result in successful removal of the trityl group while prolonged treatment afforded the desilylated derivative or product degradation.[40,41] Other potential solutions (Li-NH_3, Et_3SiH/TFA and n-Bu_3SnH) were likewise ineffective. However, some success was achieved in a stepwise approach precedented by the known oxidative deprotection of *S*-tritylcysteines in peptide systems.[42] Treatment of tritylsulfide **123** with one equivalent of iodine in methanol-pyridine provided a more polar material which clearly lacked the aromatic residue. We were able to assign the structure of this compound as the disulfide **130** through use of NMR and mass spectrometry.

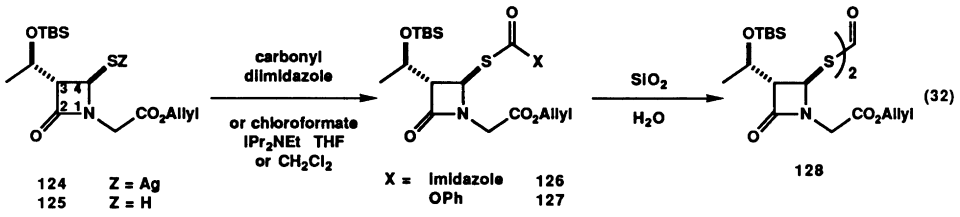
Unfortunately, we were unable to effect selective reduction of the disulfide bond without concomitant removal of the silyl group or continued degradation of the molecule. It appears in hindsight that this transformation is somehow intertwined with the state of functionalization of the alcohol moiety at pro-C_8. With the free alcohol, disulfide cleavage is found to proceed smoothly with zinc and strong acid; however, silyl protection of the alcohol effectively blocked disul-



SCHEME 10

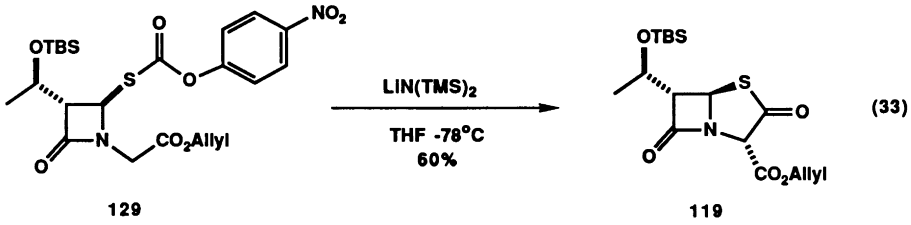
fide cleavage under mild conditions. Subsequently, we became aware of an independent study conducted by D. Hou and co-workers at Schering[43] which confirmed our observations of disulfide formation and trityl deprotection.

Standard sulfide deprotection (silver-mediated methanolysis with formation of **124**[9b,31] Scheme 10), already known for intermediate **123**, worked exceedingly well and after one hour, clean formation of the silver thiolate was accomplished. To facilitate later work, the silver salt was treated with hydrogen sulfide to release thiol **125** in essentially quantitative yield. Deuterium exchange experiments, monitored by ^1H NMR, confirmed a vicinal coupling of 9 Hz between the mercaptan SH and the methine at C_4. Treatment of **125** with copper (I) salts, in air, resulted in formation of disulfide **130**, identical to that prepared above. As expected, acylation of **125** with chloroformates or acylimidazoles (Eq. 32) cleanly produced the desired thiocarbonates **126** and **127**. However attempted isolation by chromatography partially degraded these intermediates to the dithiocarbonate **128**.



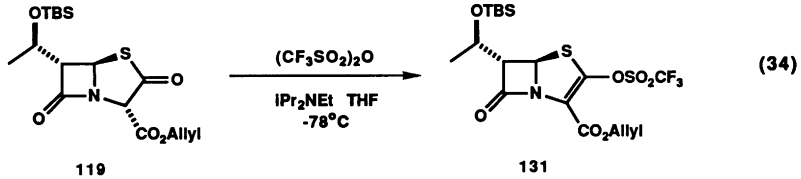
(32)

We were able to avert this problem by simply avoiding the isolation of the thiocarbonate. However, more troublesome was our discovery of the poor reactivity of these substances to base-mediated ring closure.[9b,31] Low yields of the desired thiolactone **119** were obtained by the treatment of **126** and **127** (generated *in situ*) with a variety of disilylamide bases or lithium diisopropylamide. Fortunately, this problem was overcome by employing the highly electrophilic para-nitrophenylthiocarbonate **129**, suggested by Jim Hauske. Doug Phillips demonstrated the acylation of thiol **125** with *p*-nitrophenylchloroformate and the resulting solution of **129** was charged to 1 molar lithium hexamethyldisilazide in THF stirring at −78°C. The reaction, as it turned out, worked reasonably well to give **119** and provided us with a satisfactory resolution of the synthetic problem (Eq. 33).



129 119 (33)

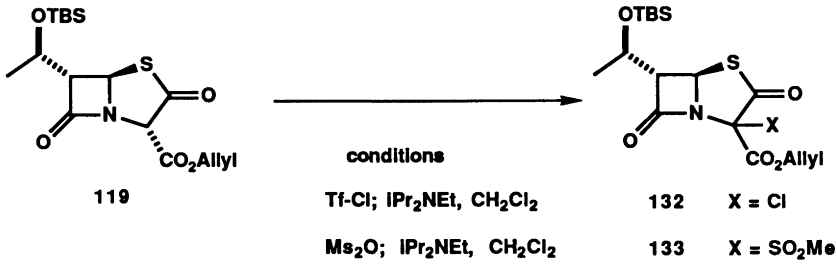
We had assembled substantial quantities of thiolactone **119** and were quite excited about the prospects for successful transformation to the penem. Activation of **119** would derive from enol-ester formation as discussed previously. We expected most sulfonate or phosphate leaving groups to provide some measure of usefulness but decided to prepare the enol triflate initially since it offered a higher probability for an efficient coupling and avoided generation of reactive by-products. Not escaping our attention was the fact that the electronics of our enol triflate system would be unlike that of the corresponding carbapenem system due to the additional presence of the ring sulfur atom. We were obviously not sure what effect this would have on coupling. When a solution of **119** and diisopropylethylamine at −78°C was treated with triflic anhydride, there was obtained a quantitative conversion of **119** to the novel triflylthioketene acetal **131** as observed by thin layer analysis (Eq. 34).[44]



119 131 (34)

Triflate **131** was sufficiently stable to allow isolation by chromatography although in fairness this operation had to be conducted rapidly to avoid substantial losses. The resulting solid could be recrystallized from pentane (−20°C) and stored for periods of several hours. The stability of intermediate **131** was higher than that of the related carbapenem enol-triflate which has not as yet been isolated.[39d] Interestingly, an entirely different result was obtained when we acylated **119** with triflic chloride under otherwise similar conditions (Eq. 35). In this case, α-chlorothiolactone **132**, possessing three carbonyl infrared absorptions, was the only product obtained. The chlorination of

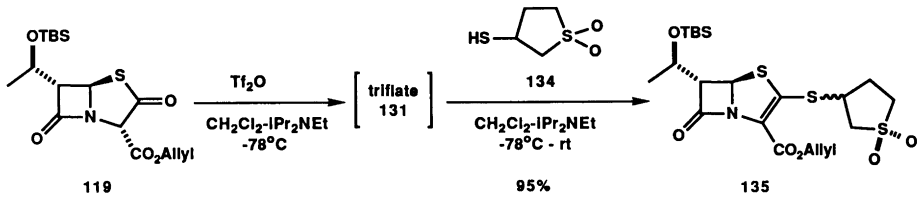
β-ketoesters and malonates by triflic chloride was precedented by the work of George Just[45]; however, we were surprised by the results of subsequent experiments designed to prepare the corresponding O-tosylate and O-mesylate derivatives. In these cases, attempted tosylation resulted in the formation of the α-chloride **132** while attempted mesylation provided the interesting α-methylsulfone derivative **133**.



(35)

Not surprisingly, α-chlorinated compound **132** was easily reduced with triphenylphosphine, to return thiolactone **119** in quantitative yield.[46] This result provided some evidence of structure for this compound but more importantly signaled the intermediacy of an O-triphenylphosphonium salt as a possible intermediate during reduction. We have tried on several occasions to trap this moiety with a mercaptan, but have been unable to prepare the penem system by this method.

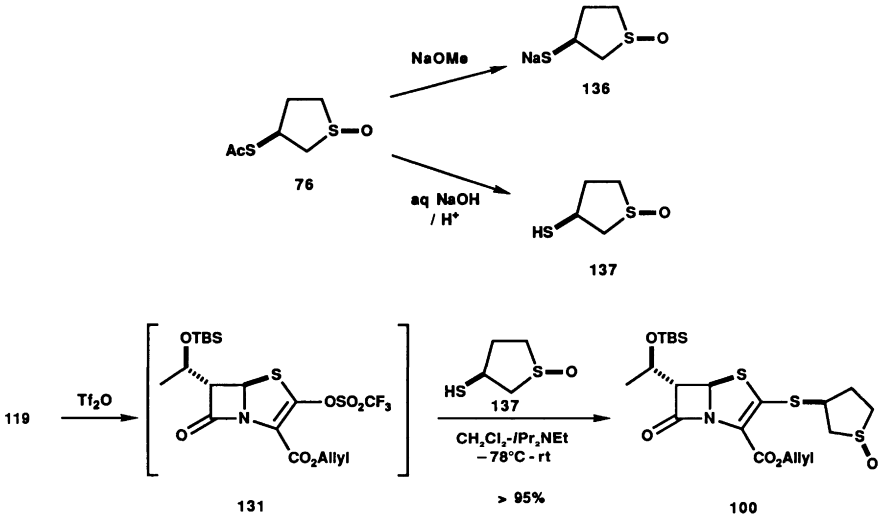
The suitability of triflate **131** as a key penem intermediate was assessed by its condensation with thiosulfone **134**[47], a stable, readily available thiol which was a remnant of our drug discovery efforts. Triflate **131**, prepared *in situ* at −78°C in methylene chloride, underwent a very efficient Michael addition by the thiol **134** to provide an excellent yield of diastereomeric penems **135** (Eq. 36).



(36)

With the model study complete, assembly of our penem candidate from a derivative of sulfoxide **76** was attempted. Deacylation of the

thioacetate with sodium methoxide produced the sodium thiolate **136** as previously discussed. However, Michael addition of this substrate was unsuccessful; the highly nucleophilic thiolate mainly degraded triflate **131** and we observed a poor yield of bis-protected penem **100**. Significant amounts of thiolactone **119** were recovered, suggesting nucleophilic attack on the sulfonate group was competitive with conjugate addition. As a means of lowering the reactivity of our nucleophile we examined the thiol itself. We had little experience with free thiol **137**; however mild aqueous hydrolysis of the thioacetate **76** followed by neutralization and repeated extraction provided this thiol which was used directly without isolation.



Gratifyingly, reaction of thiol **137** at low temperature with the preformed triflate **131** afforded an excellent yield of penem **100**. Careful attention to the exact stoichiometry of the preformed reagents, generated simultaneously (*in situ*), was necessary to realize a quantitative yield of the desired penem. In preparative runs, on greater than 100 gram lots, only slight diminution of penem yields were observed. We successfully corroborated that penem generated by this process was identical to that prepared previously. This extremely satisfying result demonstrated the usefulness of the Michael addition-elimination strategy in penem synthesis and provided an attractive alternative for the synthesis of CP-70,429 (**82**).

XII. Concluding Remarks

Having made substantial progress on the synthetic front, the fate of our penem candidate was placed in the hands of our clinical colleagues. We felt justifiably optimistic that a commercial synthesis of CP-70,429 (**82**) would be an achievable goal and we reflected positively on our role in this synthetic adventure. The penem had provided a deceptively simple target, functionalized with an array of challenging and fragile architecture; but, along with synthetic obstacles in this drug's development, lay a more serious responsibility to provide significant material for biological evaluation. Our selection of key chemical transformations always mirrored our concerns for reproducibility and brevity. Hard lessons, learned during scale-up runs, were an unavoidable consequence of early manufacturing campaigns. A select few of these will continue to enrich our memory in the future. Fortunately, seemingly insurmountable problems were eventually overcome and bulk material was prepared.

Our goal in presenting this chapter has been to describe the experiences of a team of medicinal and process chemists brought together to develop an economic synthesis of a penem antibacterial and to share some of the excitement and frustrations of their work. While the difficulties encountered were unique to CP-70,429 (**82**), the synthetic questions are certainly no different than those faced by many others in the pharmaceutical industry today. The challenges posed by novel therapeutic agents of the future will likewise demand innovative, imaginative and yet practical solutions from organic chemists involved in pharmaceutical development.

Acknowledgments

In addition to our colleagues mentioned in the text, the authors wish to acknowledge the intellectual and synthetic contributions of Frank Urban, Frank Busch, Ken Chausse, Susumu Nakanishi, Dennis Godek, Brad Guarino, Larry Vincent, Mike Dee, Don Pirie, Ed Kobelski, Dave Lindner, Tom Crawford, Buzz Cue, Bob Kaye, John Rogers, Bill Lackey, Bernie Moore, Ralph Breitenbach, Gerg Young, Bob Sysko, Joe Selvidio, Terry Sinay, Mark Barrila, Jim Weeks, Paul Weeks, Rick Lehner, Vinod Parikh, Magda Wroblewska-Adams, Peter Morrissey, Mark Elliott, Isao Nagakura and Alex Grodski. Special thanks are extended to Tom Gootz and colleagues in the Infectious Disease Group, to John Jasys for his critical review and to Doreen Gale for help in preparing this manuscript.

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