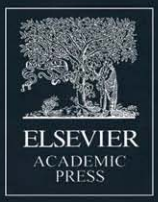

Strategies and Tactics in Organic Synthesis

Volume 4

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STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS

Volume 4

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STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS

Volume 4

Edited by

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University of Missouri – Columbia

With a foreword by

Professor Paul A. Wender
Stanford University

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FOREWORD

Chemistry is a gateway to the future of science. It provides the tools and understanding needed to analyze and often predict structure and function at the molecular level and to design and synthesize new structures of value. This uniquely important molecular expertise is now driving remarkable advances in a wide range of disciplines. From molecular medicine to molecular biology, materials, paleontology and even art, the tools and theories of chemistry are creating revolutionary changes, enabling a range of products including new therapeutic agents, materials, devices, and sensors that impact virtually every aspect of our existence. We are indeed in the midst of a molecular revolution that is transforming our world, our sense of self, our environment, our technology, our economy, our past and our future.

One of the major activities of chemistry is synthesis. Through synthesis we advance our understanding of chemistry and especially structure and mechanism, address supply, validate or correct structural assignments of known molecules and create new molecules that often transform, if not create new fields of research. Synthesis has evolved significantly in the last half century. Fifty years ago, it was not clear whether some targets could be made. That uncertainty gave way to the challenge of whether targets could be made selectively. In 2003, more than one total synthesis per day will be reported. The issues of "can it be made" and "can it be made selectively" are now increasingly incorporated into a new generation of challenges calling for the design of functional molecules that can be prepared in a practical fashion. Function-oriented syntheses and step-economical syntheses are goals of great significance.

Synthetic chemists are uniquely situated to meet these challenges, as they are skilled in translating function into structure and structure into a viable if not practical plan of synthesis.

Professor Harmata has impressively collected in this volume of *Strategies and Tactics in Organic Synthesis* a brilliant series of contributions from the leaders in the field. To the student and practitioner alike, this volume serves up engaging and informative insights into the inner workings of synthesis design and execution that are not found in most publications. It illustrates beautifully and broadly the thought processes, surprises, frustrations and achievements involved in synthesis and the many advances that make the field so exciting and important. The range of synthetic problems and strategies in this volume and the richness of its chemical information combine with the human element supplied by experts behind the scenes to provide the reader with a treasure of educational experiences. The coverage is unique and provides a window into the world of design, function and synthesis that is at the leading edge of the molecular frontier. It is a wonderful source of information, insight and inspiration.

PAUL A. WENDER
Stanford University, CA
November 2003

Preface

Research is teaching. It as not as obvious as it sounds. Indeed, in academics, our workloads are typically divided into research, teaching and service. This is nonsense, in the big picture, but apparently necessitated by omnipresent administrative forces that appear to be inescapable.

As an exercise in teaching, research is also an exercise in learning. Whether conducted within an academic or industrial setting, research necessarily leads to learning among all the participants.

The first volumes of Strategies and Tactics in Organic Synthesis served this concept well, allowing readers to get a glimpse of the story behind the story. Research is not just a matter of results, but a process through which results are obtained. In the world of organic synthesis in particular, it involves the use of tools and concepts from all branches of chemistry, as well as the incorporation of principles from the humanities, arts and philosophy. Most importantly, it involves people.

I undertook the editorship of this and at least several future volumes of this series in the hope that I could produce a set of books that would further served to educate, challenge and inspire both those who are well acquainted with organic synthesis and those who are just beginning their trek into this wonderful world of creation. It is with the help of many talented scientists that this vision will be achieved. This volume is the fruit of our initial efforts. Another volume will follow shortly.

My thanks go out to the authors. It was a pleasure to share in their description of the adventure of discovery. Thanks to people at Elsevier for their willingness to give new life to this series. Special thanks are due to Tamsin Kent and Ian Salusbury.

This volume was assembled with the able help of Mr. Tom Rhodelander to whom I am extremely grateful.

I appreciate the receipt of constructive criticism and helpful suggestions that can lead to a better product. Feel free to contact me regarding how this series might be improved.

Finally, without a research program of my own, there would not be time to invest in "synergistic activities" like book editing. My thanks go out to the National Science Foundation and the Petroleum Research Fund for their continuing support of our work.

Michael Harmata

Dedication

This volume is dedicated with heartfelt congratulations, gratitude and love to Andrew and Bernadine Harmata, on the occasion of their fiftieth wedding anniversary; June 6, 2003.

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STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 1

METHODOLOGY VALIDATION AND STRUCTURE CORRECTION BY TOTAL SYNTHESIS: THE CASE OF THE CLERODANE DITERPENOID, SACACARIN

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I. Introduction

Scientists who pursue the total synthesis of natural products may choose a target compound for several reasons. The target may be chosen because it has potentially useful properties in biological systems (antibiotic, anticancer, etc.); because of unique structural elements that make its synthesis particularly challenging, so that its structure can be confirmed; or because it has structural elements that make it particularly amenable to synthesis by a newly developed synthetic methodology.

The total synthesis described in the following account was a product of the last motivation. Our group had developed a synthetic methodology, a suite of reactions that we called double annulation, and we sought to apply it to the synthesis of a naturally-occurring compound.

The target that we chose was sacacarin, whose structure was reported to be **1** (Figure 1).[1] We chose this compound simply because, among all the natural products we found when we sifted through the literature, its structure was best suited to our methodology. However, the achievement of the synthesis resulted in a correction of the structure of the natural product to **2**,[2] showing that, despite all the powerful spectroscopic methods available to chemists today, total synthesis is sometimes still the ultimate structural proof.

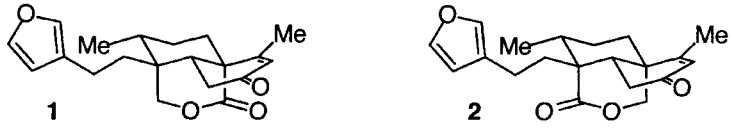
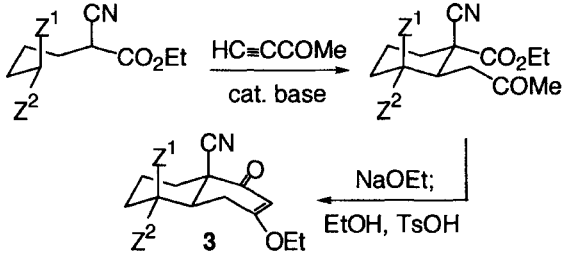


FIGURE 1. The originally reported structure of sacacarin (**1**) and its corrected structure (**2**).

II. The Search for a Synthetic Target for Double Annulation

Our story begins in 1999, when our group had completed several projects showing that the double annulation sequence provided a convenient, stereoselective route to *trans*-decalins, **3**, featuring two quaternary centers decorated with three functionalized, one-carbon substituents (Scheme 1).[3,4] The double annulation was originally conceived as a potential route to the insect antifeedant, azadirachtin (Figure 2), which features just such a *trans*-decalin moiety.[5] However, it was clear to us that azadirachtin's very complex structure would make it a poor choice for our first total synthesis effort. In fact, despite the efforts of some large and very talented synthetic groups across the world,[6] azadirachtin has yet to succumb to total synthesis.



3	Z^1	Z^2
a	CN	CO_2Et
b	CO_2Et	CN
c	CO_2Et	CO_2Et
d	Me	NO_2

SCHEME 1

Azadirachtin is a tetranortriterpenoid; i.e., it has a C_{26} skeleton that is built up from six isoprene units ($C_5 \times 6$) followed by the removal of four

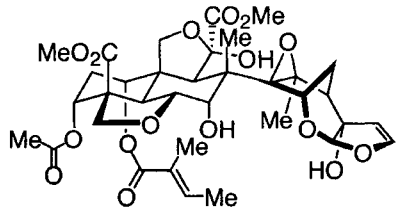


FIGURE 2. Azadirachtin, the inspiration for the double annulation.

C atoms. Many other terpenoids are known whose skeletons, like azadirachtin, contain *trans*-decalin moieties similar to the one present in **3** (Figure 3). These terpenoids include sesquiterpenoids such as the drimanes, diterpenoids such as the labdanes, clerodanes, kauranes, atisanes, and abietanes, and higher terpenoids such as the lanostanes. Because of their simpler structures, we chose to focus our search among the drimane, labdane, and clerodane terpenoids. Specifically, we sought terpenoids in these classes in which as many of the C(4) and C(10) substituents [C(5) and C(9) in clerodanes] as possible were functionalized, because we wanted to incorporate as much as possible of the functionality that was present in **3** into the final target. We also preferred to see functionalization at C(7) [C(2) in clerodanes] and none at C(1–3) [C(6–8) in clerodanes]. Finally, we preferred that our target had biological activity.

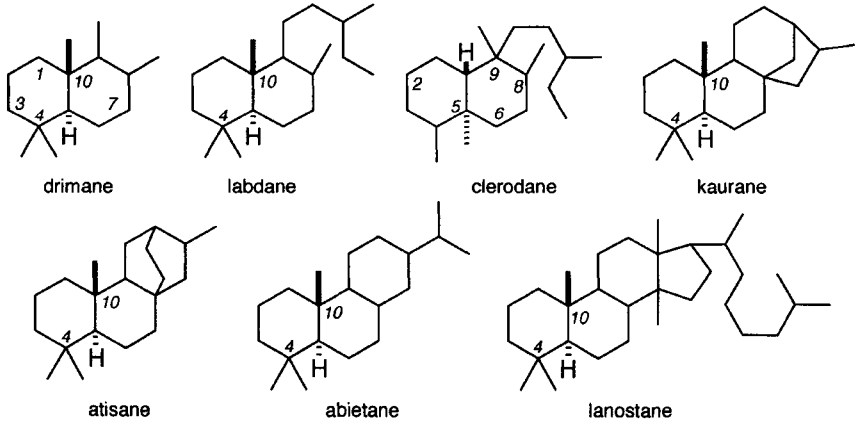
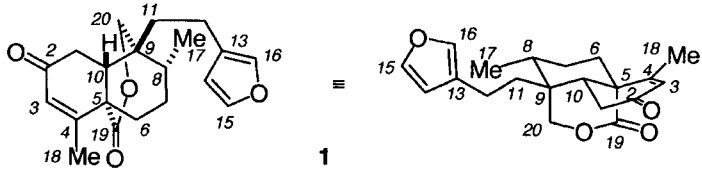


FIGURE 3. Skeletons of some terpenoids that contain *trans*-decalin moieties.

The strictures that we placed on our search eliminated most natural products from consideration. The most suitable compound, **1**, was the one recently reported to be the structure of the clerodane, sacacarin (Figure 4).[1] With respect to the C(5) and C(9) substituents, **1** was function-

alized at both C(19) and C(20), and, although it was not functionalized at C(11), we could easily imagine attaching C(12–16) to a synthetic precursor via a functionalized C(11). Furthermore, **1** was functionalized at C(2) and was unfunctionalized at C(6–8). Finally, although sacacarin had not been tested for biological activity, most of the clerodanes isolated from natural sources have been shown to have insect antifeedant and other biological activities.[7] Sacacarin itself was isolated from the bark of a Brazilian tree, known locally as sacaca, that was used for various medicinal purposes,[8] although it constituted only about 0.0015% by weight of the dry bark.

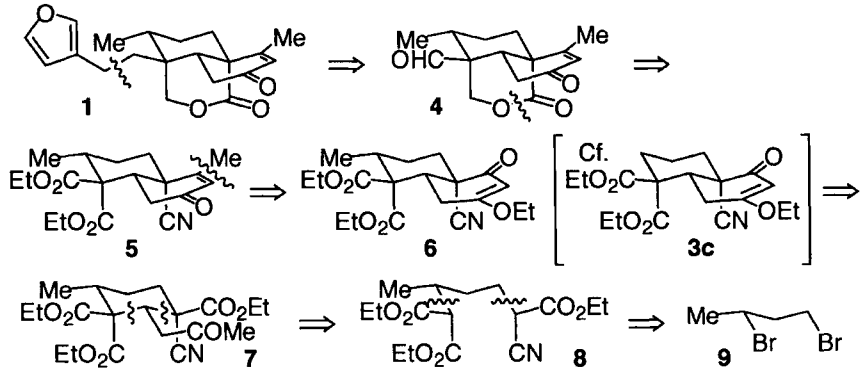


1

FIGURE 4. Compound **1** and its numbering system.

III. Retrosynthetic Analysis and Synthetic Design

With a target chosen, the next task was a retrosynthetic analysis (Scheme 2). We envisioned attaching the C(12–16) side chain of **1** via a Wittig reaction of tricyclic aldehyde **4**. We envisioned the lactone of **4** as being prepared by cyclization of a cyano alcohol, which could be prepared from diester **5**. Finally, we presumed that the C(18) Me group of **5** could be installed by addition of MeLi to the β-ethoxyenone group of **6**. Our retrosynthetic analysis ended at this point, because **6** was very similar to



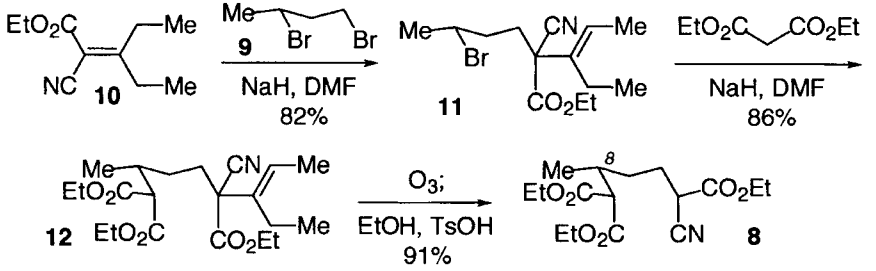
SCHEME 2

3c, a compound we had already prepared in our previous work.[3] Following that precedent, **6** would be prepared from **7** by a regioselective Dieckmann reaction, **7** would be prepared from **8** by a diastereoselective double Michael reaction, and **8** would be prepared from **9** by alkylation of diethyl malonate and ethyl cyanoacetate with 1,3-dibromobutane.

We wanted to incorporate several features into our synthetic design. First, like all clerodanes, **1** had four contiguous stereocenters, and we wanted our synthesis to be highly diastereoselective and amenable to enantioselective modification. Second, we wanted to avoid protecting group manipulations wherever possible. Protecting groups must sometimes be used in a synthesis, but they are the bane of organic synthesis. Many a synthetic effort has foundered on the shoals of an injudicious or merely unlucky choice of protecting group. Protecting groups also introduce extra steps into a synthesis, entailing costs of material loss and consumption of time and effort. We wanted to show that seemingly identical functional groups within densely functionalized intermediates such as **5**, **6**, and **7** could be differentiated without resorting to protecting group manipulations. Third, we wanted to use simple, inexpensive, off-the-shelf reagents to carry out these manipulations. Fourth, we wanted to maximize the proportion of C–C bond-forming steps in the total synthesis, keeping the overall synthesis as short as possible. Fifth, we wanted our synthetic approach to differ significantly from previous synthetic approaches to the clerodane diterpenoids.[9]

IV. First-Generation Approach: Synthesis of Tethered Diacid

The starting materials for double annulation are compounds that we have dubbed "tethered diacids." They consist of two carbon acids (malonate derivatives, nitro compounds, and the like) connected by a tether. Tethered diacid **8** was easily prepared by the methodology we had previously reported for preparing such compounds (Scheme 3).[10] Knoevenagel adduct **10** was deprotonated with NaH and then alkylated with dibromide **9**. Only the 1° alkyl bromide of **9** reacted with the nucleophile, and **11** was obtained in 82% yield. In this reaction, **10** acted as if it were ethyl cyanoacetate with one of its two acidic hydrogens blocked. If ethyl cyanoacetate itself had been used instead, a four-membered ring would probably have been obtained. A polar aprotic solvent was used for this alkylation because, in alcohol solvents, alkylated Knoevenagel compounds tended to undergo retro-Claisen reactions, with loss of a CO_2Et group. In the second step, diethyl malonate was uneventfully alkylated with **11** to



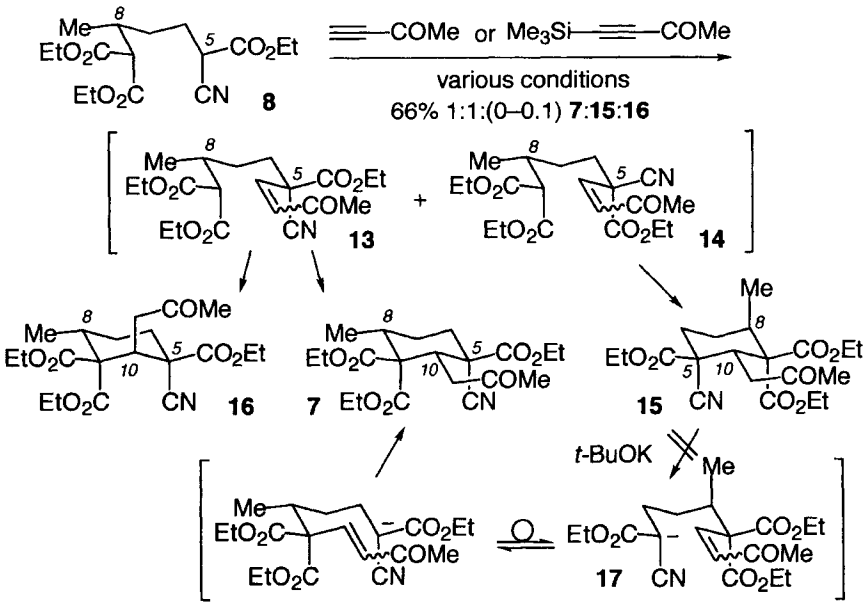
SCHEME 3

give **12** in 86% yield. Finally, the alkenyl group of **12** was replaced with H by ozonolyzing **12** and subjecting the ozonide to refluxing acidic EtOH. Under the latter conditions, the ozonide decomposed to the ketone, which underwent a retro-Claisen reaction to deliver **8** (and ethyl propionate) in 91% yield. No reductive workup of the ozonolysis was required; the extra equivalent of O in the ozonide was consumed by the ozonolysis by-product, acetaldehyde, to give ethyl acetate.

Although **8** consisted of two diastereomers, only one of the stereocenters in **8**, C(8), was to be preserved beyond the next stage of the synthesis. As a result, the synthesis of **1** could have been rendered enantioselective by beginning with enantiopure **9** or, for example, the ditosylate of enantiopure 1,3-butanediol. At this stage, however, we did not feel that it was necessary to pursue an enantioselective synthesis of **1**.

V. First-Generation Approach: Diastereoselectivity Problem in Double Michael Reaction

The double Michael reaction of **8** and 3-butyn-2-one catalyzed by 10 mol% *t*-BuOK in CH_2Cl_2 provided two of the four possible diastereomeric double Michael adducts, **7** and **15**, as a 1:1 mixture in 66% yield (Scheme 4). A similar result was obtained when **8** was combined with the more readily available 4-trimethylsilyl-3-butyn-2-one[11] in THF containing catalytic TBAF (desilylation occurred under the reaction conditions); in this case, ca. 10% of the product consisted of a third diastereomer, **16**. Compounds **7** and **15** had the same C(5,10) relative stereochemistry (clerodane numbering), with an axial CN group and an equatorial acetonyl group, but they differed in their C(5,8) relative stereochemistry. This result was not unexpected: the first, intermolecular Michael reaction of **8** proceeded at the more acidic C(5), and because the existing C(8) stereocenter had no influence over the newly forming C(5) stereocenter, a 1:1



SCHEME 4

mixture of mono-Michael adducts **13** and **14** was formed. Nascent 1,3-diaxial interactions in the TSs leading from **13** and **14** to **7** and **15** then placed the acetonyl group exclusively in the equatorial position and the CN group exclusively axial, producing the same C(5,10) relative stereochemistry in **7** and **15**.

We had several options to deal with the expected 1:1 diastereomeric mixture of **7** and **15**, but none of them was in the end satisfactory. We had previously found that diastereomeric mixtures of certain other double Michael adducts (Figure 5) could be converted to thermodynamic mixtures upon treatment with base, presumably by a retro-Michael–Michael process.[3,4] In the case of **7** and **15**, the hope was that the two isomers could be equilibrated via a retro-Michael reaction to **17**, internal bond rotation, and reclosure by a Michael reaction. Unfortunately, **7** and **15**

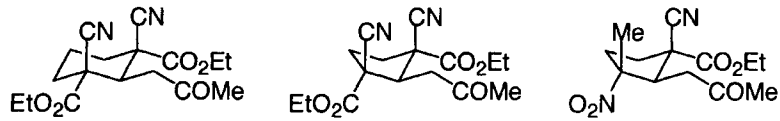
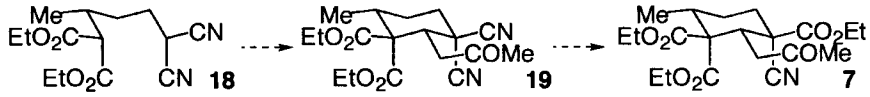


FIGURE 5. Double Michael adducts that undergo diastereomer equilibration via retro-Michael–Michael reactions.

underwent other reactions instead of equilibration. Another plan was to find conditions under which **13** cyclized preferentially over **14**; we did find such conditions (10% $KF{\cdot}2H_2O$, EtOH, rt), but the dr of **7** obtained in this way was still only 5:1, the minor amount of **15** could still not be removed, and the yield was limited to about 25–30% because the unreacted **14** was discarded. After these plans failed, we decided to separate the two diastereomers and carry them on individually to **1** and to 8-*epi*-**1**. Unfortunately, **7** and **15** were inseparable, and when the mixture was carried forward in the synthesis, the diastereomeric mixtures of later intermediates were also inseparable.

The failure of these strategies to provide **7** or later intermediates in diastereopure form spurred us to design a new route that avoided the generation of a stereocenter in the first Michael reaction (Scheme 5). Specifically, we realized that tethered diacid **18** would undergo a double Michael reaction in which the stereochemistry-determining step would be the second, ring-closing Michael reaction, and, in this step, 1,3-diaxial interactions would be expected to give double Michael adduct **19** in largely stereopure form. However, this solution raised a new question: could the equatorial CN group in **19** be converted into a CO_2Et in **7** without affecting the axial CN group? We were optimistic that it could, as we had previously found that the hydrogenation of double Michael adducts containing both axial and equatorial CN groups affected only the latter,[3,12] but only experiment would tell for sure.

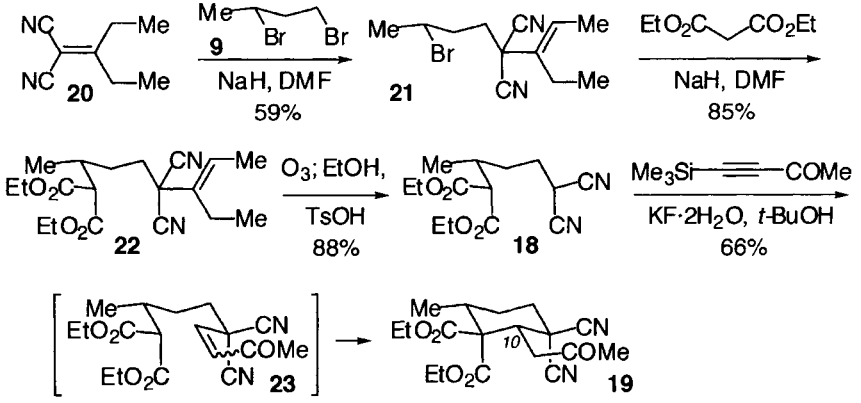


SCHEME 5

VI. Second-Generation Approach: The Double Michael, Pinner, and Dieckmann Reactions

Tethered diacid **18** was as easily prepared as **8** was (Scheme 6).[10] Knoevenagel adduct **20** was deprotonated with NaH and then alkylated with dibromide **9** to give **21** in 59% yield. Alkylation of diethyl malonate with **21** gave **22** in 85% yield, and ozonolysis of **22** and acidic alcoholysis delivered **18** in 88% yield.

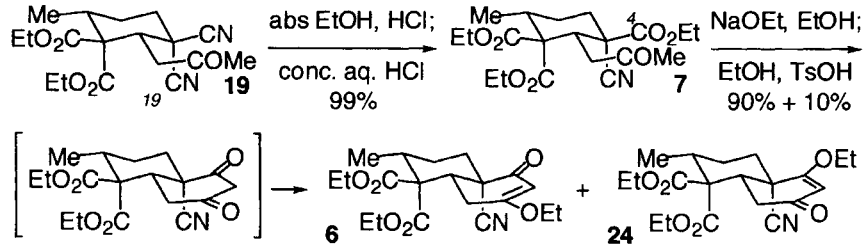
The double Michael reaction of **18** was first executed with 4-trimethylsilyl-3-butyn-2-one and catalytic $KF{\cdot}2H_2O$ in EtOH, but side products derived from addition of EtOH to the CN groups of the intermediate **23**



SCHEME 6

motivated us to change the solvent to *t*-BuOH. Under these conditions, the desired double Michael adduct **19** was obtained in about 5:1 dr. This dr was close to the thermodynamic dr of 5.6:1 that was roughly calculated from accepted values for gauche and 1,3-diaxial interactions in substituted cyclohexanes,[13] as would be expected from a kinetically controlled reaction with a product-like transition state. (The difference in energy between **19** and its 10-*epi* isomer was relatively small because **19** had two fewer 1,3-diaxial interactions but two more gauche interactions.) Moreover, **19** crystallized selectively from the reaction mixture; after workup of the supernatant, partial evaporation of the solvent, and further crystallization, **19** was obtained in 60:1 dr and 66% isolated yield. X-ray crystallography confirmed its stereochemistry.

When dinitrile **19** was subjected to Pinner reaction conditions, and the imidate was then hydrolyzed, the desired **7** was obtained quantitatively and as a single diastereomer (Scheme 7). Only the equatorial CN group of **19** underwent the Pinner reaction; the axial CN group remained complete-



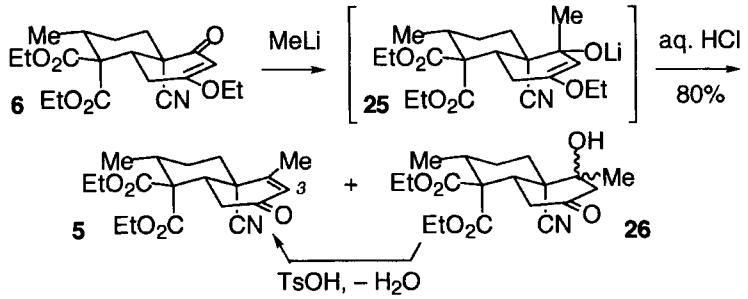
SCHEME 7

ly undisturbed. The difference in reactivity between the two CN groups was attributed to the increased 1,3-diaxial interactions that would result from converting C(19) from sp to sp^2 hybridization. The diastereopure **7** that was obtained from **18**, unlike the impure **7** that had been prepared previously, was a low-melting, crystalline solid.

A Dieckmann reaction of **7** and enol etherification provided *trans*-octalone **6** in 90% yield. An additional 10% of the transposed β-ethoxyenone **24** was also isolated. Compound **24** could easily be removed chromatographically (the first chromatography of the synthesis) and could be isomerized back to the 9:1 mixture in favor of **6** by resubjection to the etherification conditions. Compound **7** had three different CO_2Et groups, yet only the one adjacent to the CN group was attacked by the nascent ketone enolate. This selectivity, attributed to the effect of the powerfully electron-withdrawing CN group, was expected, as it was observed previously in the preparation of **3c**.[3] The selectivity of the enol ether formation was also expected from previous work.

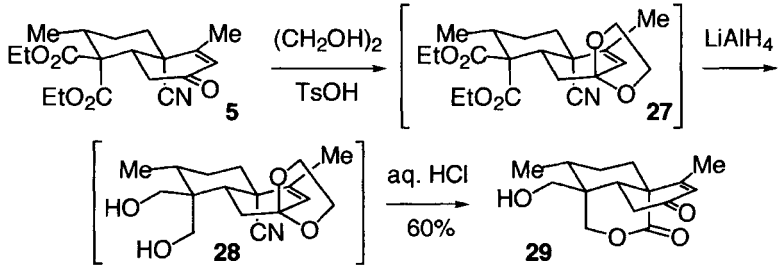
VII. Methylation, Reduction, and Lactonization

At this point our synthesis entered unknown territory. Addition of MeLi to the C(4) ketone of **6** gave adduct **25** without any addition to the CO_2Et groups (Scheme 8), and acidic hydrolysis of **25** gave the desired **5** admixed with surprisingly large amounts of **26**. Fortunately, **26** could be slowly converted to **5** by treatment with TsOH in benzene with azeotropic removal of H_2O, providing **5** in 80% overall yield after recrystallization. The formation of **26** was explained by the destabilizing effect of the axial, electron-withdrawing CN group on the already electron-poor alkenone of **5**. (In fact, a Hückel calculation showed that the energy of the LUMO of **5** was almost as low as if the CN group were on C(3)!)



SCHEME 8

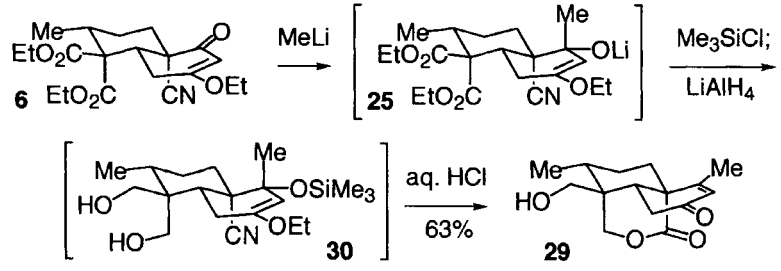
Ketone **5** was converted to acetal **27** with ethylene glycol (Scheme 9), and **27** was reduced with $LiAlH_4$. The diol **28** was then boiled in concentrated aqueous HCl to provide the tricyclic lactone **29** in ca. 60% yield. The selectivity of the $LiAlH_4$ for the esters over the CN group was noteworthy. Another nice feature of this step was the lactonization, which served to differentiate the two CH_2OH groups in **28**.



SCHEME 9

Although we were able to obtain the desired **29** in this way, there were several aspects of the last few steps that troubled us. One flaw was the requirement for azeotropic removal of H_2O in two consecutive steps: the dehydration of **26** to **5** and the acetalization of **5** to **27**. Another flaw was that the acetal protecting group, discarded immediately after its use here, needed to be reinstalled before the last step of the synthesis (see below). Although ethylene glycol was very inexpensive, it seemed that this duplication of effort should have been avoided, if possible.

It occurred to us that the C(2) ketone of **5** was already protected in **25**, the immediate product of MeLi addition to **6**. As a result, we decided to add $LiAlH_4$ directly to **25** (Scheme 10). Solubility problems prevented the reduction of **25** from proceeding smoothly, but when Me_3SiCl was added to **25** and then $LiAlH_4$ was added, the reduction proceeded smooth-



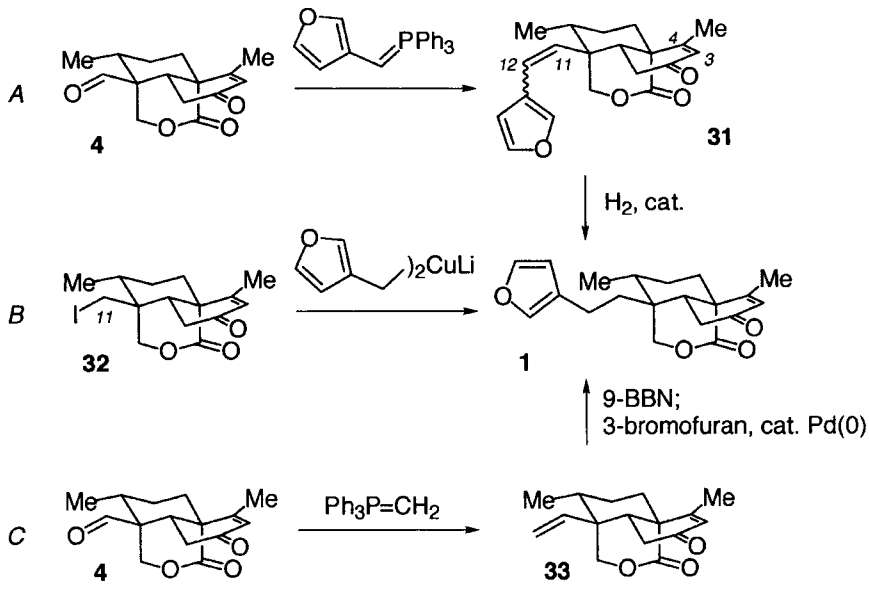
SCHEME 10

ly to give **30**. Acidic hydrolysis of **30** followed by chromatographic purification then gave tricyclic lactone **29** in 63% yield from **6**.

With the implementation of this improvement, the synthesis at this point stood at seven steps with no protecting groups and only two chromatographic purifications (**6** and **29**).

VIII. Introduction of the Side Chain

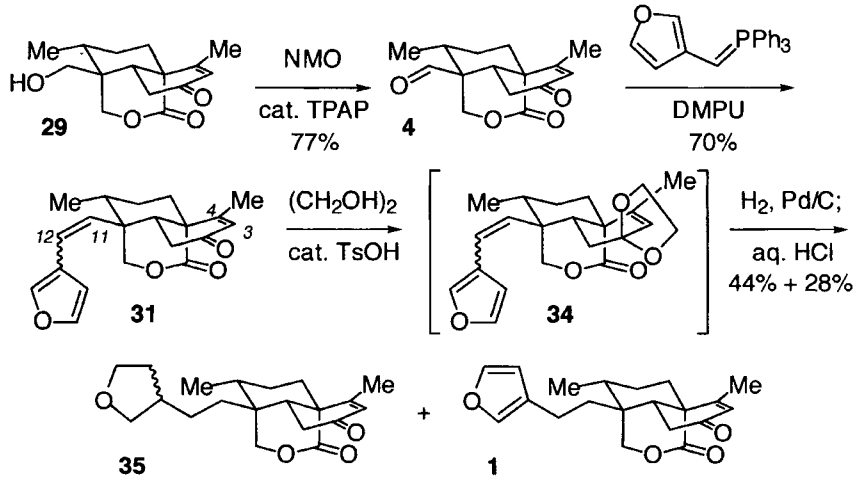
The final stage of the synthesis required attachment of the side chain to the core tricyclic portion of the molecule. Several strategies were conceived, each with its own potential drawbacks (Scheme 11). The first-conceived strategy involved a Wittig reaction of aldehyde **4** with (3-furyl)CH=PPh_3[14] to give alkene **31**, followed by reduction to final target **1** (path A). This strategy required selective reduction of the extremely hindered C(11–12) π bond of **31** over the more electron-poor C(3–4) π bond and the more electron-rich furan ring. A second strategy involved a transition-metal-mediated or -catalyzed cross-coupling between iodide **32** and a 3-furylmethyl cuprate or comparable nucleophile to give **1** directly (path B). This strategy required an S_N2-type substitution of the extremely hindered alcohol to obtain the iodide. A third strategy involved conversion of the aldehyde of **4** to terminal alkene **33**, followed by



SCHEME 11

hydroboration and Suzuki coupling to 3-bromofuran to give **1** (path C). Although Suzuki couplings to 3-bromofuran had been reported previously, none involved an alkylborane as the nucleophile.

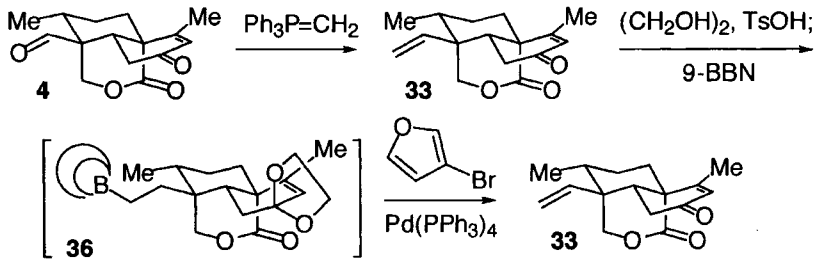
We decided that path A offered the best hope of success. As a result, alcohol **29** was oxidized to the aldehyde **4** with NMO and catalytic TPAP (Pr_4N^+ RuO_4^-) in 77% yield (Scheme 12). The aldehyde could be purified simply by filtration through a short plug of silica gel. The Wittig reaction of **4** with (3-furyl)CH=PPh_3 did not proceed well in THF, presumably because of solubility reasons, but the same reaction in DMPU afforded alkene **31** in 70% yield as a 4:1 mixture of isomers in favor of the *Z*-isomer. The selectivity of the Wittig reaction for the exceedingly hindered aldehyde over the completely unhindered ketone was notable. In order to protect the C(3–4) π bond from reduction, ketone **31** was converted to acetal **34**, which was then subjected to hydrogenation over Pd/C. After acetal hydrolysis, the desired **1** was obtained in 28% yield. Compound **35**, the undesired furan reduction product, was also obtained, and in 44% yield, but it was easily separated from **1**.



SCHEME 12

Many other methods for reducing **34** were explored, but none gave more satisfactory results. The best alternative used 1400 psi H_2 over Lindlar catalyst; under these conditions, furan reduction was suppressed, but reduction of the C(3–4) π bond occurred to some extent, and this by-product was inseparable from the desired **1** and unreacted **31**.

We briefly explored path C. The reaction of **4** with $Ph_3P{=}CH_2$ proceeded uneventfully to give terminal alkene **33** (Scheme 13). Compound **33** was subjected to acetal formation and was then hydroborated with 9-BBN to give borane **36** (confirmed by NMR). However, when **36** was combined with 3-bromofuran and catalytic amounts of $Pd(PPh_3)_4$, instead of **1**, alkene **33** was reisolated! The most likely explanation was that after transmetallation of **36** to the furyl–palladium complex, reductive elimination from the furyl–palladium–alkyl catalytic intermediate was slow, providing an opportunity for β-hydride elimination to occur instead to give **33**. Suzuki alluded to just such a possibility in the paper that originally described the use of 9-alkyl-9-BBN compounds in Pd-catalyzed coupling reactions.[15]



SCHEME 13

IX. Revision of the Target Structure

We would probably have invested more effort in perfecting the synthesis of **1** by either path A or C, but when we first isolated **1**, we discovered that our natural product was not the natural product! The NMR spectra of **1** differed significantly from those reported for saca-

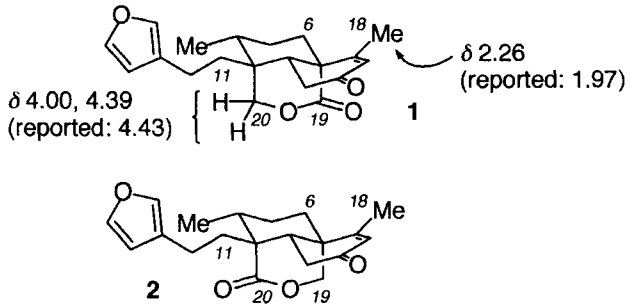


FIGURE 6. Reported (**1**) and actual (**2**) structures of sacacarin.

carin.[1] Most notably, in $CDCl_3$ the two lactone H atoms of **1** appeared at δ 4.00 and 4.39, whereas those of sacacarin resonated isochronously at δ 4.43 (Figure 6). Also, the H(18) methyl group appeared at δ 2.26 in **1**, whereas it resonated at δ 1.97 in sacacarin. The upfield shift of H(18) in sacacarin as compared to **1** was best explained by assigning structure **2** to sacacarin: in **2**, C(18) was further from the deshielding lactone carbonyl group than it was in **1**. Structure **2** was also more consonant with the structures of previously isolated C(19,20)-lactone-bridged clerodanes, which had the carbonyl group at C(20).[1]

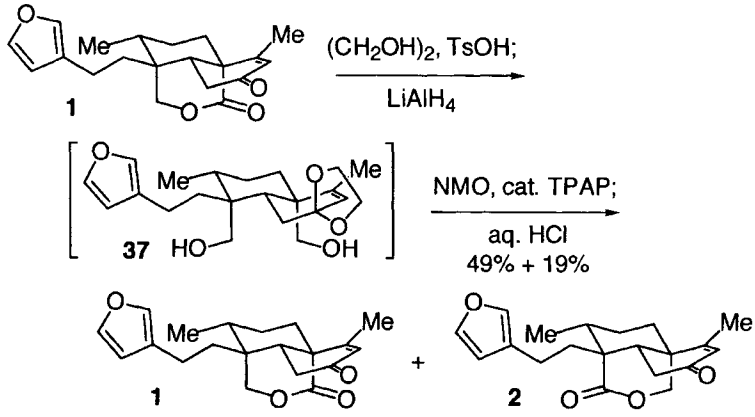
With all of the spectroscopic techniques available to modern chemists, how could such a misassignment have been made? In fact, in their paper describing sacacarin's isolation and structure determination,[1] Maciel et al. considered both **1** and **2** as possible structures for sacacarin. Their assignment of **1** as the structure of sacacarin rested on the observation of a cross-peak between a ^{13}C NMR resonance at δ 35.2, assigned to C(11), and a ^{1}H NMR resonance at δ 4.43, assigned to the lactone CH_2 group, in the COLOC (long-range heteronuclear coupling) NMR spectrum. This piece of evidence placed the lactone CH_2 group close to C(11), as in **1**. The ^{13}C NMR resonance was assigned to C(11) because it showed cross-peaks to ^{1}H NMR resonances at δ 2.31 and 1.68 in a HETCOR (one-bond heteronuclear coupling) spectrum, and these latter resonances that were assigned to H(11). However, the cross-peaks in the HETCOR spectrum were about 0.2 ppm wide along the ^{1}H NMR axis, and the resonances of the two H(6) atoms overlapped significantly with those of H(11). The evidence suggested that the ^{13}C NMR resonance at δ 35.2 that Maciel assigned to C(11) should actually have been assigned to C(6). As a result, the COLOC experiment should have placed the lactone CH_2 group close to C(6), as in **2**.

X. Proof of the Revised Structure

Although we had achieved the synthesis of our target, **1**, we were distraught when we realized we had made an unnatural product, not a natural one. Moreover, a very small possibility remained that we had misinterpreted the structural evidence provided by our synthesis, and that Maciel's interpretation of the NMR data was correct. As a result, we decided that we needed to synthesize compound **2** so that we could compare its NMR spectra to those of sacacarin.

We chose a route that, while unselective for **2** over **1**, would provide rapid access to sufficient **2** for characterization (Scheme 14). Compound

1 was protected as its ketal and reduced with $LiAlH_4$ to diol **37**. Reoxidation with NMO and catalytic TPAP provided a mixture of lactones, and deprotection and separation gave 49% **1** and 19% **2**. The spectral features of the synthetic **2** were identical to those of sacacarin.[1]



SCHEME 14

XI. Conclusion

Our synthesis of **1** accomplished many of the objectives we had defined at the onset.

- The synthesis was very short, requiring only ten steps, six of which were C–C bond-forming steps, to prepare the twenty-carbon target **1**.
- The synthesis was stereoselective, establishing all four stereocenters of **1** with good to excellent diastereoselectivity. Although the synthesis of **1** was not enantioselective as executed, an enantioselective synthesis could easily be achieved by replacing **9** with the ditosylate of (*S*)-1,3-butanediol.
- The chemical information inherent in densely functionalized intermediates such as **18** was used to direct transformations with remarkably high chemo-, regio-, and stereoselectivity. Only the final step failed to achieve a high level of selectivity.
- The synthesis required only simple, inexpensive reagents.
- The synthesis proceeded with a high level of atom-economy.
- Only three intermediates (**6**, **29**, and **31**) and the final product **1** were purified chromatographically. Even these intermediates were crystalline, so further refinements might obviate two or more of these chromatographies.

• Only one protecting group was used in the entire synthesis, and that only in the last step.

• Of all the stoichiometric organic waste products — ethyl acetate and propionate (step 3), Me_3SiOR (steps 4 and 7), ethanol (steps 6 and 7), *N*-methylmorpholine (step 8), Ph_3PO (step 9), and ethylene glycol (step 10) — all but one were removed simply upon workup or evaporation.

Our synthesis of **1** also achieved some unexpected results. We were able to show that sacacarin had the structure **2**, we discerned the origin of the structural misassignment, and we prepared **2** from **1** and confirmed the new structural assignment.

Finally, our synthesis of **1** demonstrates the importance of choosing one's target carefully if one is hoping to validate a new methodology. An inappropriate target can make a new methodology look clumsy and ineffectual. An appropriate target, on the other hand, can showcase a new methodology in a most attractive way.

Acknowledgements

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References

1. Maciel, M. A. M., Pinto, A. C., Brabo, S. N., da Silva, M. N. *Phytochemistry* **1998**, *49*, 823.
2. Grossman, R. B., Rasne, R. M. *Org. Lett.* **2001**, *3*, 4027.
3. Grossman, R. B., Varner, M. A., Skaggs, A. J. *J. Org. Chem.* **1999**, *64*, 340.
4. Grossman, R. B., Rasne, R. M., Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7173.
5. Ley, S. V., Denholm, A. A., Wood, A. *Nat. Prod. Reports* **1993**, 109.
6. (a) Durand-Reville, T., Gobbi, L. B., Gray, B. L., Ley, S. V., Scott, J. S. *Org. Lett.* **2002**, *4*, 3847. (b) Fukuzaki, T., Kobayashi, S., Hibi, T., Ikuma, Y., Ishihara, J., Kanoh, N., Murai, A. *Org. Lett.* **2002**, *4*.
7. (a) Merritt, A. T., Ley, S. V. *Nat. Prod. Reports* **1992**, 243. Rodríguez-Hahn, L., Esquivel, B., Cárdenas, J. *"Clerodane Diterpenes in* Labiatae*"* in *"Progress in the Chemistry of Organic Natural Products,"* Eds. Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C. Springer-Verlag: New

York, 1994, vol. 63, p. 107. (b) Piozzi, F. *Heterocycles* **1994**, *37*, 603. (c) Piozzi, F., Bruno, M., Rosselli, S. *Heterocycles* **1998**, *48*, 2185.

8. Maciel, M. A. M., Pinto, A. C., Arruda, A. C., Pamplona, S. G. S. R., Vanderlinde, F. A., Lapa, A. J., Echevarria, A., Grynberg, N. F., Côlus, I. M. S., Farias, R. A. F., Costa, A. M. L., Rao, V. S. N. *J. Ethnopharmacology* **2000**, *70*, 41.
9. Tokoroyama, T. *Synthesis* **2000**, 611.
10. Grossman, R. B., Varner, M. A. *J. Org. Chem.* **1997**, *62*, 5235.
11. Komarov, N. V., Yarosh, O. G. *J. Gen. Chem. USSR (Engl. Transl.)* **1967**, *37*, 247.
12. Grossman, R. B., Pendharkar, D. S., Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7178.
13. Carroll, F. A. *"Perspectives on Structure and Mechanism in Organic Chemistry,"* Brooks/Cole Publishing Co.: Pacific Grove, CA, 1998.
14. van Altena, I. A., Miller, D. A. *Aust. J. Chem.* **1989**, *42*, 2181.
15. Miyaura, N., Ishiyama, T., Ishikawa, M., Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 6369.

STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 2

TOTAL SYNTHESIS OF (±)-CYLINDROSPERMOPSIN

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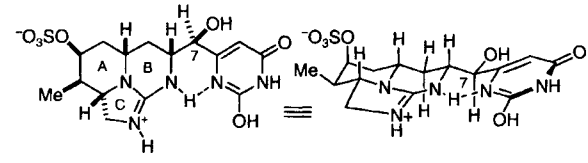
I. Introduction

Cylindrospermopsin (**1**)[1] was isolated from the cyanobacterium *Cylindrospermopsis raciborskii* by Moore and shown to be the causative agent of a 1979 outbreak of hepatoenteritis in Australia.[2,3] Feeding studies indicated that cylindrospermopsin is an acetogenin with guanidinoacetic acid serving as the starter unit of the polyketide chain.[4] The structure of cylindrospermopsin was determined spectroscopically. The relative stereochemistry of the ring carbons was assigned based on analysis of the coupling constants.[2,3] The stereochemistry of the side chain alcohol was tentatively, and incorrectly, assigned as that of 7-epicylindrospermopsin (**2**), based on the coupling constants, NOEs and the unusual behavior of the uracil carbons in the ^{13}C NMR spectrum. 7-Epicylindrospermopsin (**2**)[5] and 7-deoxycyclindrospermopsin (**3**)[6] have recently been isolated. Weinreb's stereocontrolled synthesis of structure **2**, which was completed after the work described in this chapter was published, formed 7-epicylindrospermopsin, not cylindrospermopsin, necessitating a revision of the stereochemical assignment of the side chain alcohol.[7,8]

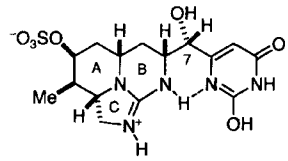
Cylindrospermopsin has also been isolated from *Umezakia natans* and *Aphanizomenon ovalisporum.* Algal blooms that produce cylindrospermopsin are widespread in tropical waters where occurrences of gastro-

intestinal diseases of unknown origin are common. The toxicological effects of cylindrospermopsin, analytical techniques for its detection in drinking water and management strategies to minimize its harmful effects have been the subject of more than 100 publications.[9]

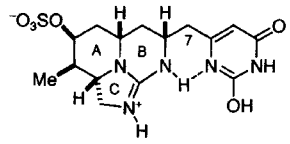


cylindrospermopsin (**1**)
(proposed structure of 7-epicylindrospermopsin)

cylindrospermopsin (**1**)



7-epicylindrospermopsin (**2**)
(proposed structure of cylindrospermopsin)



7-deoxycylindrospermopsin (**3**)

The novel structure of cylindrospermopsin, with a guanidine embedded in a tricyclic system, six chiral centers, and polar sulfate, uracil and guanidine functional groups, makes its synthesis challenging. Its potent toxicity makes the synthesis of cylindrospermopsin an important problem that has been the subject of intense interest.[1,7,8]

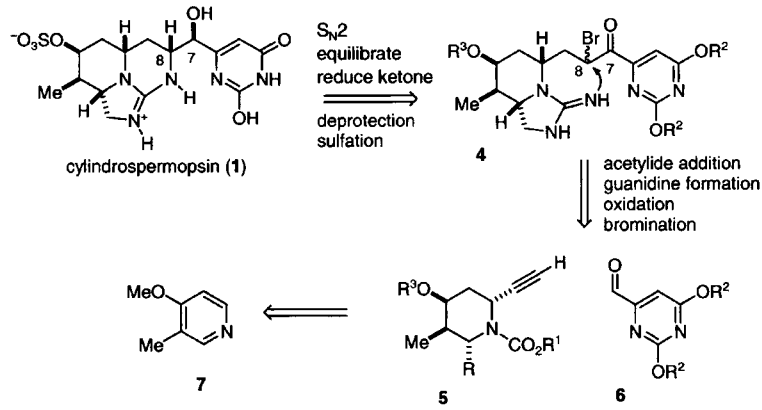
II. Retrosynthetic Analysis

The polar functionality presents a major problem in the synthesis of cylindrospermopsin because the natural product cannot be extracted into organic solvents, making its separation from water-soluble reagents difficult. Clearly, the sulfate ester should be introduced in the last step. The guanidine should also be introduced late in the synthesis and should be protected as a less basic acyl guanidine until as late as possible. Finally, the uracil is also polar and so must be either introduced late in the synthesis or protected as a dialkoxypyrimidine.

We envisioned that the B ring of cylindrospermopsin (**1**) could be prepared by an intramolecular S_N2 reaction of the guanidine of **4** on the bromoketone. Equilibration would provide the desired equatorial side chain. Reduction of the ketone, deprotection and sulfation would complete the synthesis of cylindrospermopsin. Addition of acetylene **5** to pyrimidine

carboxaldehyde **6** would provide a convergent and efficient approach to **4**. Acetylene **5** should be available by addition of trimethylsilylacetylide to pyridine **7** and further modification to introduce the R group.

There were several concerns about late stages in this synthetic scheme. The formation of guanidine-containing rings by the S_N2 reaction with an α-bromoketone was novel and there were stereochemical concerns about side chain equilibration, which would control the stereochemistry at C_8, and ketone reduction, which would control the stereochemistry at C_7. There were also questions about the choice of protecting groups for the pyrimidine ring of **6**. We decided that these questions were best answered by a model study using a modified A ring lacking the methyl group, oxygen substituent, and one-carbon side chain needed for ring C.

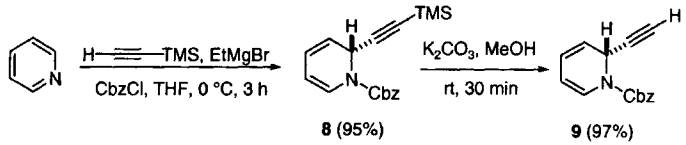


III. Model Study for Closure of the B-ring

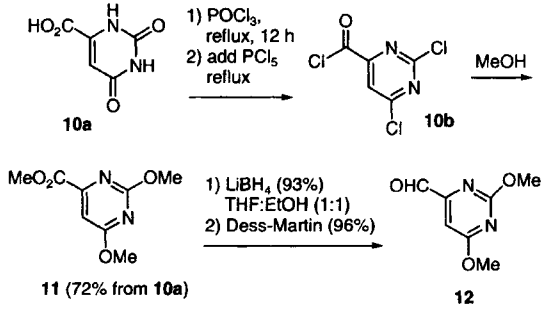
Acetylene **9**, the model for acetylene **5**, was prepared concisely by the procedure of Yamaguchi by addition of trimethylsilylethynylmagnesium bromide to pyridine and benzyl chloroformate to give 95% of **8**, followed by desilylation with K_2CO_3 in MeOH to give 97% of **9**.[10] Methyl 2,6-dimethoxy-4-pyrimidinecarboxylate (**11**) was prepared by the procedure of Gershon.[11] Orotic acid (**10a**) was refluxed in $POCl_3$ and then in $POCl_3/PCl_5$ to give 2,6-dichloropyrimidine-4-carbonyl chloride (**10b**), which was stirred in MeOH overnight to give **11**. Reduction of the ester with $LiBH_4$ in THF afforded 93% of the primary alcohol, which was oxidized with Dess-Martin periodinane to provide 96% of aldehyde **12**.[12]

We chose methyl groups to protect the pyrimidine ring of **12** because they were easily introduced by treatment of **10b** with excess MeOH. For

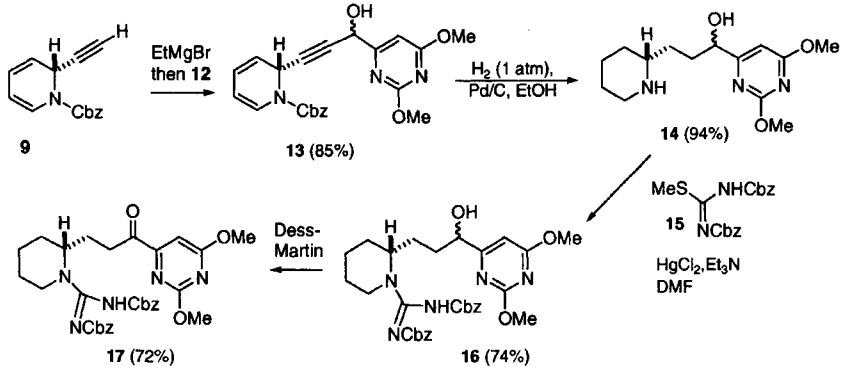
instance, introduction of benzyl protecting groups by treatment of the dichloropyrimidine with only three equivalents of benzyl alcohol was not



clean, and use of excess benzyl alcohol caused separation problems. Methyl protecting groups were also likely to be stable throughout the synthetic sequence. However, we suspected that we might not be able to remove the methyl groups at the end of the sequence, in which case we would have to react **10b** with a different alcohol to introduce a less robust protecting group in lower yield.



Addition of acetylene **9** to aldehyde **12** afforded 85% of propargylic alcohol **13** as a mixture of diastereomers. Hydrogenation reduced the triple bond and both double bonds and cleaved the Cbz groups providing 94%



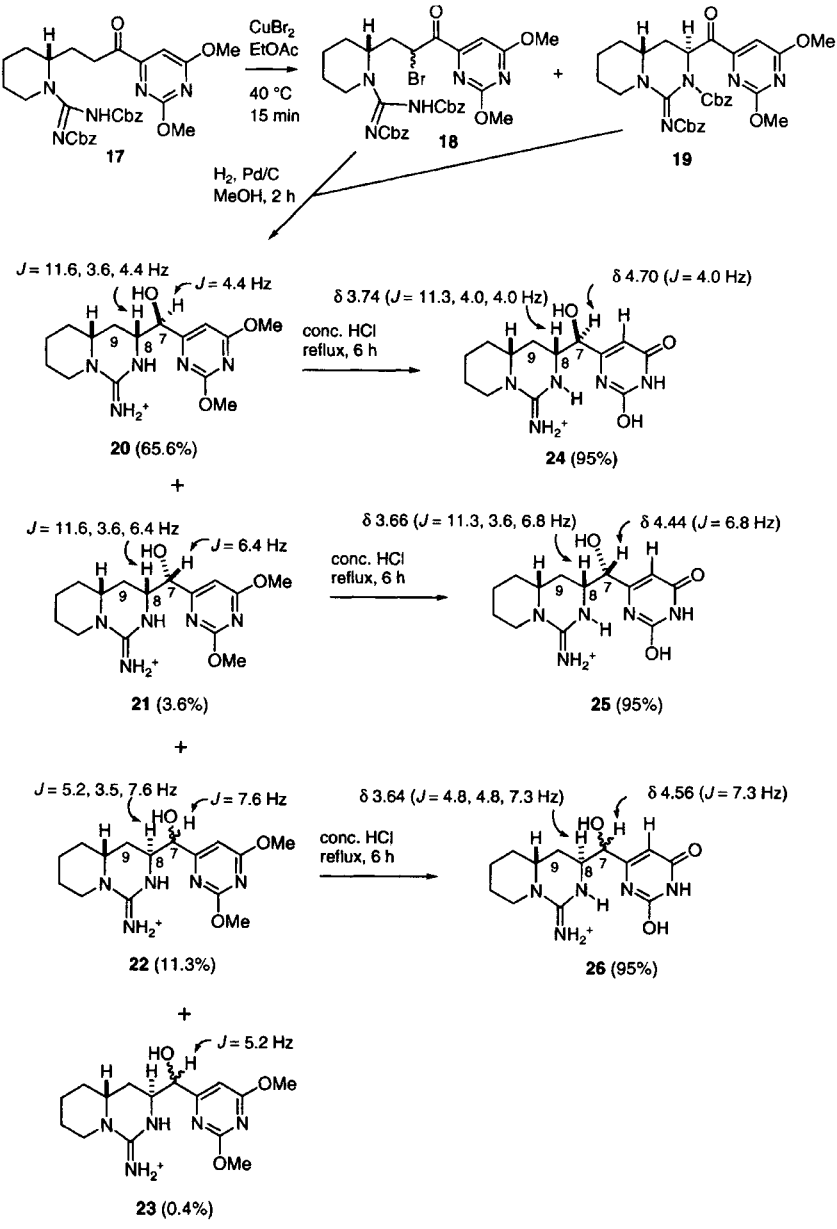
of piperidine **14**. Guanylation of **14** with **15** afforded 74% of **16**, which was oxidized with the Dess-Martin periodinane to give 72% of ketone **17**.

α-Bromination of ketone **17** was unsuccessful with common brominating reagents. Bis carbamates of guanidines are non-polar and easy to isolate and purify, but are somewhat sensitive to acid and base because one of the carbamates is easily cleaved. Successful α-bromination was eventually achieved by treatment of **17** with $CuBr_2$[13] in EtOAc for 15 min at 40 °C to provide unstable bromoketone **18**, which appeared to contain a small amount of bicyclic ketone **19**. Hydrogenolysis of the Cbz groups should lead to the free guanidine, which should undergo a rapid S_N2 reaction to form the B ring. However, the α-bromoketone is also susceptible to hydrogenolysis, which must be slower than hydrogenolysis of the Cbz groups if this sequence was to be successful.

We were therefore delighted to find that hydrogenolysis of the crude mixture of **18** and **19** over Pd/C in MeOH liberated the free guanidine, which underwent an intramolecular S_N2 reaction to form the B ring of cylindrospermopsin model **25**. As an unexpected added bonus, the ketone was also hydrogenated[14] under these conditions to give 65.6% of the desired hydroxy guanidine **20**, 3.6% of **21** with 7-epicyclindrospermopsin stereochemistry, 11.3% of **22** with the wrong stereochemistry at C_8 and 0.4% of **23** with the wrong stereochemistry at C_8. The spectral data indicated that the hydroxymethyluracil side chains of **20** and **21** are equatorial. The ring methine hydrogens (H_8) absorb at δ 3.81 (ddd, 1, J = 11.4, 4,4, 3.6, Hz) and 3.74 (ddd, 1, J = 11.6, 6.4, 3.6 Hz), respectively, with a large 11.6 Hz coupling constant between the anti-periplanar axial H_9 and H_8. In **22**, H_8 absorbs at δ 3.65 (ddd, 1, J = 7.6, 5.2, 3.5 Hz). The absence of a large coupling to H_{9ax} indicates that H_8 is equatorial.

The side chain hydrogen (H_7) absorbs at δ 4.61 (d, 1, J = 4.4 Hz) in **20** and at δ 4.38 (d, 1, J = 6.4 Hz) in **21**. H_7 absorbs at δ 4.70 (d, 1, J = 4.0 Hz) in cylindrospermopsin (**1**), suggesting that the major product **20** probably has the same stereochemistry as cylindrospermopsin. However, the structural differences between the uracil of cylindrospermopsin and the dimethoxypyrimidine of **20** and **21** precluded definitive assignment at this point.

We therefore turned our attention to deprotection of the dimethoxypyrimdine. Very harsh conditions are typically required and our situation was further complicated by the polarity of the product, which would make purification troublesome. The use of 6 M hydrochloric acid[15] to cleave the methyl groups was therefore appealing because excess reagent could



be removed by evaporation under reduced pressure. Refluxing **20** in 6 M hydrochloric acid for 5 h did not affect cleavage, but at least did not cause any decomposition. We then refluxed **20** in concentrated (12 M)

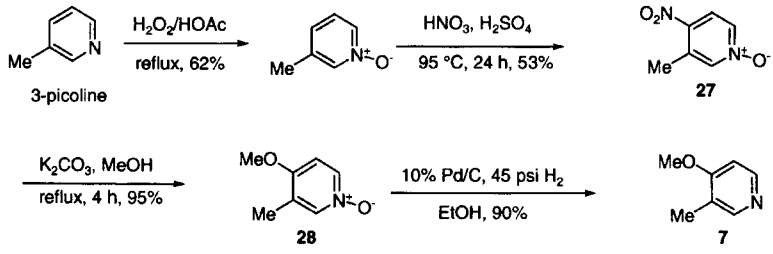
hydrochloric acid for 6 h, which cleaved both methyl groups to provide 95% of the desired model **24**. Apparently, the protonated guanidine and uracil ring protected the alcohol from solvolysis, a process which would result in the formation of a trication. Although hydrolysis of guanidines to ureas is known to proceed very slowly in strong acid at high temperature,[16] we confirmed that the guanidine was still present by HRMS. Similar hydrolyses of **21** and **22** afforded **25** and **26**.

The spectral data of **24** are very similar to those of the right half of cylindrospermopsin (**1**), while those of **25** are quite different. For instance, the absorption of the side chain methine hydrogen H_7 of **24** at δ 4.70 (d, 1, J = 4. 0 Hz) is identical to that of cylindrospermopsin and very different from that of **25** at δ 4.44 (d, 1, J = 6.8 Hz). Therefore, we concluded that **24** has the same stereochemistry as cylindrospermopsin. The spectral data for **25** was later used to support the structural assignment of 7-epicylindrospermopsin (**2**) in which the side chain hydrogen absorbs at δ 4.50 (d, 1, J = 6.6 Hz).[5]

The stereochemistry at C_7 was introduced by the hydrogenation of the ketone. Although this hydrogenation was very selective for the desired stereoisomer, the process provided no information to confirm or refute the tentative stereochemical assignment at this center, which remained incorrectly assigned until Weinreb completed a stereocontrolled synthesis of 7-epicylindrospermopsin in 2001.[7a]

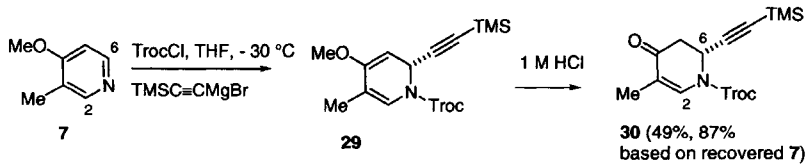
IV. Preparation of Acetylene 35

Having established that the end game of the proposed synthesis of cylindrospermopsin (**1**) from bromoketone **4** was viable, we turned our attention to the preparation of acetylene **5** from 4-methoxy-3-methylpyridine (**7**). 4-Methoxy-3-methylpyridine (**7**) was prepared by modifications of the literature procedure.[17,18] 3-Methyl-4-nitropyridine *N*-oxide (**27**),[19] was treated with K_2CO_3 in methanol at 70 °C to displace the nitro group to



afford **28**.[18] Hydrogenolysis of crude **28** over 10% Pd/C under 45 psi H_2 for a week reduced the *N*-oxide to provide **7** in 83% yield from **27**.

We now needed to add the appropriate chloroformate to pyridine **7** and then add trimethylsilylethynylmagnesium bromide to give **29** by Comins' procedure.[20] Although addition of trimethylsilylethynylmagnesium bromide could occur at either C_2 or C_6, we anticipated that the 3-methyl group would block C_2, so that addition should occur regioselectively at C_6 even with a sterically undemanding acetylide nucleophile. Investigation of conjugate additions to **30** (see below) indicated that a vinyl group was a suitable latent aminomethyl group. Therefore, benzyl chloroformate could not be used to activate the pyridine to nucleophilic attack as in the synthesis of **9** because the Cbz group could not be removed without reduction of the vinyl group. Treatment of **7** with Cl_3CH_2OCOCl (TrocCl) and then trimethylsilylethynylmagnesium bromide at –30 °C afforded dihydropyridine **29**, which was hydrolyzed with hydrochloric acid to afford 49% (87% based on recovered **7**) of **30** and 2-3% of the regioisomer resulting from addition at C_2.

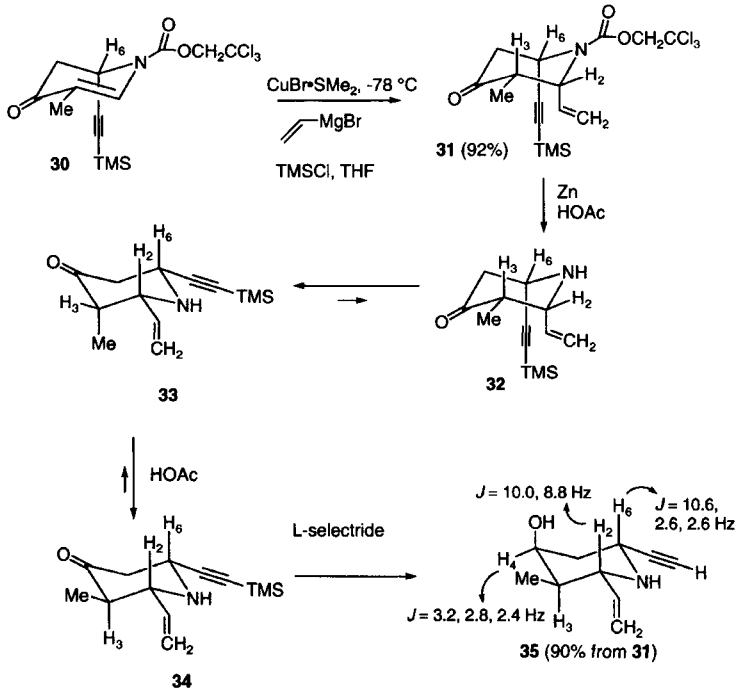


7 **29** **30** (49%, 87% based on recovered **7**)

Reaction of **30** with Et_2AlCN afforded <20% of the desired 1,4-adduct. Other procedures for cyanide addition were even less successful. We then examined the copper-catalyzed addition of vinylmagnesium bromide to **30** because Comins has shown that cuprates add to C_2 cis to a substituent at C_6 in a wide variety of *N*–carboalkoxy-5,6-dihydro-4-pyridones.[20] Piperidone **31** was generated in 66% yield by treatment of **30** with vinylmagnesium bromide and BF_3•Et_2O in the presence of a catalytic amount of CuBr•Me_2S at –78 °C in THF. The yield of **31** was improved to 92% by utilizing TMSCl[21] instead of BF_3•Et_2O to activate the cuprate addition. Due to $A^{(1,3)}$ strain between the alkynyl and *N*-acyl group of **30**, dihydropyridone **30** adopts the chair conformation with an axial alkynyl group. Stereoelectronically preferred axial attack by the organocuprate reagent at C_2 led to the desired isomer **31** with cis axial alkynyl and vinyl substituents as observed by Comins in related examples.[20] The stereochemistry of the methyl group adjacent to the carbonyl group was controlled by axial protonation of the enolate, which gives the more stable equatorial methyl group. Attempted equilibration of **31** in K_2CO_3/MeOH

gave only recovered starting material, confirming that **31** is the thermodynamic product.

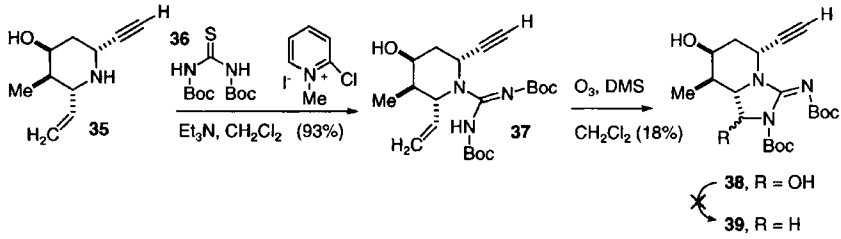
Cleavage of the Troc group of **31** with zinc dust in acetic acid for 30 min afforded the free piperidone **32**, which flipped to give the more stable conformer **33** with equatorial vinyl and alkynyl substituents and an axial methyl group. The methyl group adjacent to the ketone equilibrated under the acidic reaction conditions over an additional 5 h to give the thermodynamically more stable isomer **34** with all three substituents equatorial. Reduction of **34** with L-Selectride in THF at – 78 °C and basic hydrolysis afforded the axial alcohol and cleaved the alkynylsilane providing the desired piperidine **35** in 90% yield from **31** with control of all four chiral centers on the A ring. The stereochemistry of **35** was confirmed by analysis of the coupling constants. Large diaxial coupling constants, $J_{6\text{-}5ax}$ = 10.6 Hz and $J_{2\text{-}3}$ = 10.0 Hz, established that the methyl, ethynyl and vinyl substituents were equatorial. The absence of large diaxial coupling constants for H_4, J = 3.2, 2.8, 2.4 Hz, indicated that the hydroxy group was axial.



V. Unsuccessful Approaches to Ketone 58

Conversion of **35** to bromoketone **4** required (1) addition of the acetylene to aldehyde **12**, (2) guanylation of the piperidine nitrogen, and (3) oxidative cleavage of the vinyl group to an aminomethyl group, which will form the C-ring of cylindrospermopsin. A priori, it was not obvious which of these steps should be carried out first. Because addition of the acetylide to aldehyde **12** generates a mixture of diastereomers that will complicate spectroscopic analysis, we decided to investigate this last.

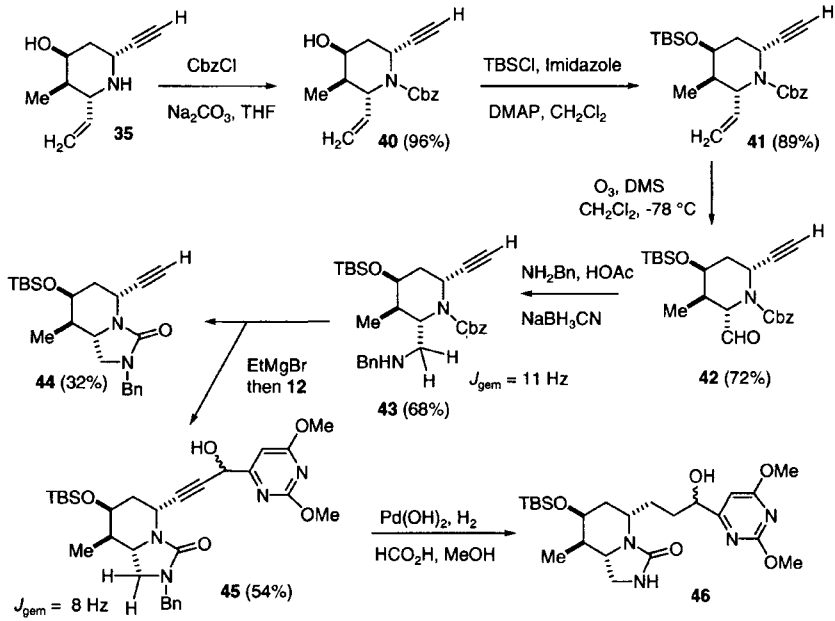
Coupling of the nitrogen of **35** with a variety of guanylating agents was unsuccessful. Eventually we found that treatment of **35** with protected thiourea **36**, Et_3N, and Mukaiyama's reagent afforded 93% of **37**.[22] Ozonolysis and reduction of the ozonide with Me_2S afforded 18% of **38**, which could not be reduced to give the desired imidazolidine **39**.



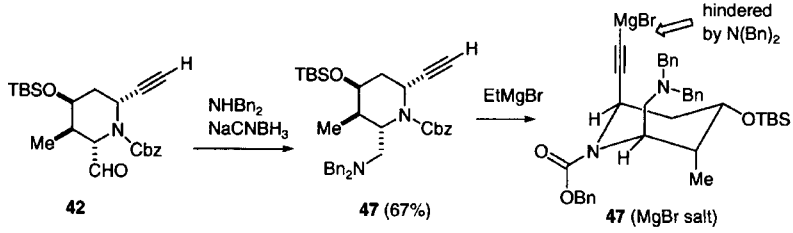
We next investigated the cleavage of the alkene before the introduction of the guanidine. Protection of the amine of **35** with benzyl chloroformate afforded 96% of **40**. *t*-Butyldimethylsilylation afforded 89% of **41**. Ozonolysis of the alkene and reduction with Me_2S afforded 72% of aldehyde **42** without cleavage of the alkyne.[23] Reductive amination[24] of **42** with $BnNH_2$ and $NaBH_3CN$ afforded 68% of benzylamine **43**. Much higher yields were obtained with $BnNH_2$ than with NH_3. We expected that the benzyl group would be hydrogenolyzed during the hydrogenation of the acetylene after coupling with aldehyde **12** so that we wouldn't need an extra step to remove the benzyl group.

We added the acetylene to aldehyde **12** now because this step is not compatible with a protected guanidine. Treatment of **43** with EtMgBr to form the acetylide and addition of aldehyde **12** afforded 54% of **45** and 32% of **44**. Under the basic conditions, the secondary amine adds to the carbamate to form the oxazolidinone ring. The decrease in the geminal coupling constant of the methylene hydrogens adjacent to the nitrogen from 11 Hz in **43** to 8 Hz in oxazolidinone **45** is characteristic of the

formation of a five-membered ring.[25] Hydrogenation and hydrogenolysis of **45** over $Pd(OH)_2$ afforded **46** cleanly, but initial attempts to convert the urea to a guanidine were not promising.



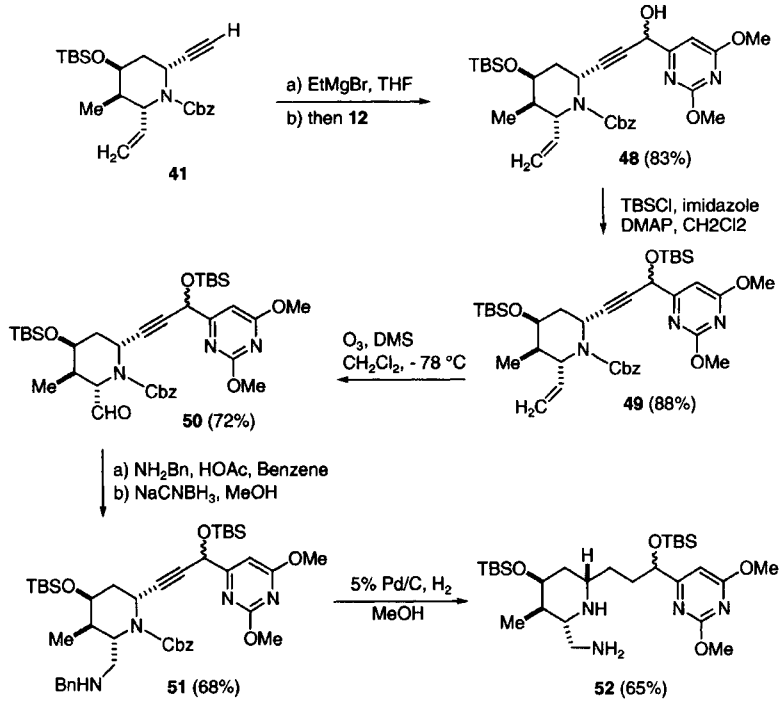
We thought that reductive amination of **42** with Bn_2NH would prevent the formation of the oxazolidinone. Treatment of **42** with Bn_2NH and $NaBH_3CN$ afforded 67% of **47**. Unfortunately, to our surprise, we were unable to add the acetylide from **47** to aldehyde **12**. $A^{(1,3)}$ strain with the Cbz group forces both the acetylide and Bn_2NCH_2 substituents to be axial. Apparently, the second benzyl group significantly increased the steric hindrance of the magnesium acetylide as shown below.



VI. Synthesis of Ketone 58

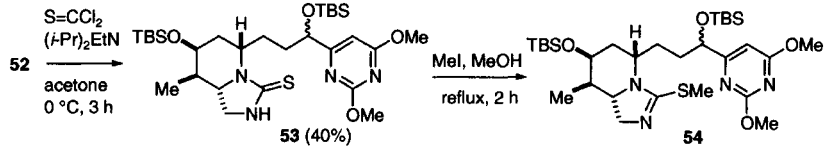
Because addition of the acetylene to the aldehyde proved difficult after the introduction of the aminomethyl side chain, we decided to carry out this addition first, even though this generates a mixture of stereoisomers that has to be carried through several steps before they reconverge in the oxidation of alcohol **57** to ketone **58**. This mixture is therefore of no consequence, although it complicates purification of the products and interpretation of the NMR spectra.

Treatment of **41** with ethylmagnesium bromide formed the alkynylmagnesium bromide, which was treated with **12** to yield 83% of alcohol **48** as a 1:1 mixture of diastereomers. Ideally, the side chain alcohol of **48** should be protected with a group that can be cleaved in the presence of a TBS group. The triethylsilyl group proved to be too unstable. Acetal protecting groups are unstable to ozonolysis conditions and ester groups might be displaced by the free secondary amine after it was liberated. We therefore chose to introduce a second TBS group, with the expectation that the benzylic-type alcohol on the side chain could be selectively oxidized with MnO_2.

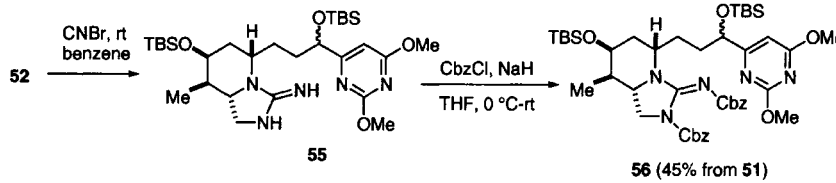


Protection of the alcohol of **48** with TBSCl, imidazole and a catalytic amount of DMAP in CH_2Cl_2 gave 88% of **49**. Ozonolysis of **49** for 20 min cleaved the double bond providing 72% of aldehyde **50** after reductive workup with Me_2S. Lower yields were obtained at longer reaction times. The NMR spectrum of **50** was very broad and not very informative due to the mixture of diastereomers and slow rotation about the Cbz amide bond. Condensation of aldehyde **50** with benzylamine in benzene, followed by reduction of the resulting imine with $NaCNBH_3$[24] afforded 68% of benzylamine **51**. Hydrogenation (1 atm) of **51** over 5% Pd/C in MeOH reduced the triple bond and hydrogenolyzed the benzyl and Cbz groups to afford 65-75% of crude diamine **52**.

Conversion of the diamine of **52** to a guanidine proved very challenging. Reaction of **52** with thiophosgene[26] afforded cyclic thiourea **53** in only 40% yield and initial attempts to convert **53** to the guanidine were unsuccessful. Reaction with methyl iodide in MeOH at reflux afforded isothiourea **54**, which did not form the desired guanidine on treatment with ammonia in MeOH.



Eventually we found that slow addition of 1 equiv of cyanogen bromide[27] to **52** in dilute toluene solution gave the primary cyanamide which cyclized to form guanidine **55**. Use of excess cyanogen bromide led to the bis cyanamide. In the model study, bromination of ketone **17** was achieved with the guanidine protected with two Cbz groups. The guanidine of **55** was therefore protected with CbzCl and NaH in THF at rt for 8 h to afford **56** in 45% overall yield from **51** and 10% of a byproduct in which one Cbz group and one benzyl group are attached to the guanidine.



Presumably, reaction of chloride ion with benzyl chloroformate formed benzyl chloride.

Desilylation of **56** with TBAF in THF at rt overnight gave 83% of **57**, which was oxidized with MnO_2 in CH_2Cl_2 to form 87% of ketone **58**. Because the nine steps from **41** to **58** were carried out with a mixture of diastereomers, the structure and stereochemistry of ketone **58** was carefully confirmed spectroscopically as shown in Figure 1. The coupling constants between H_{13} and H_{14}, J = 11.0 Hz, and H_{10} and H_{11ax}, J = 11.6 Hz, demonstrated that H_{10}, H_{13} and H_{14} are axial. H_{12}, with a very narrow half width, is equatorial. The small geminal coupling constant for H_{15}, J = 10.0 Hz, established that the five-membered C ring had been formed.

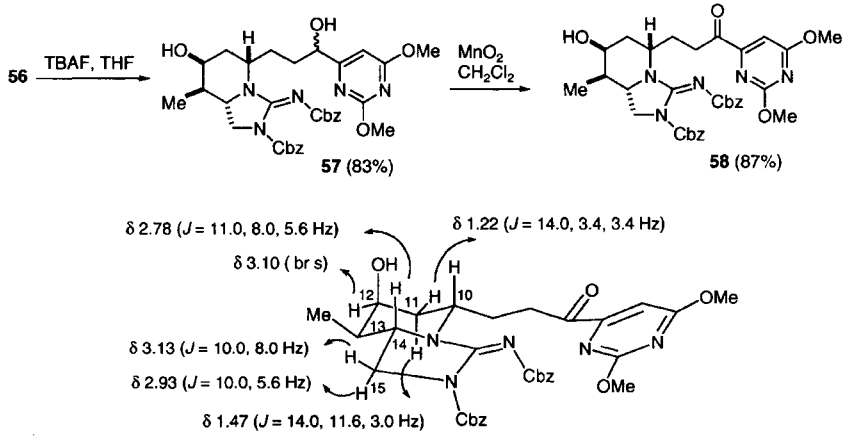
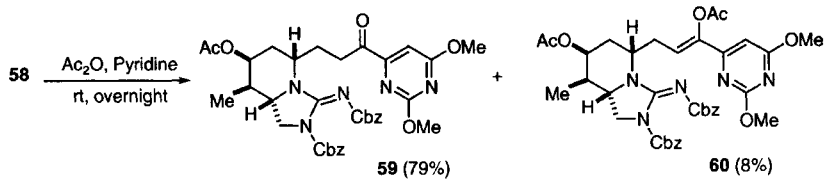


Figure 1. ^1H NMR Spectral data of **58** in benzene-d_6

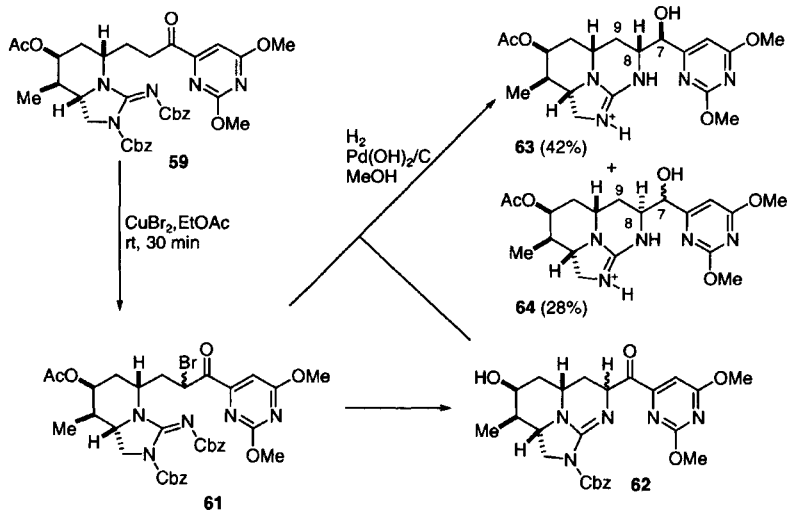
VII. Completion of the Synthesis of Cylindrospermopsin (1)

Bromination of ketone **58** could not be accomplished. The alcohol was therefore acetylated with acetic anhydride in pyridine at rt, which gave 87% of a 9:1 mixture of **59** and enol acetate **60**. The enol acetate was the



only product when DMAP was added to the reaction mixture. Basic hydrolysis of the enol acetate with $KHCO_3$ in methanol also cleaved one of the Cbz groups, so the 9:1 mixture was used because both the ketone and enol acetate should form the same bromoketone.

Bromination of the mixture of acetoxy ketone **59** and enol acetate **60** with $CuBr_2$ in EtOAc at rt for 30 min gave an unstable mixture of bromoketone **61** and tricycle **62** in which one of the Cbz groups had been lost and the S_N2 reaction had taken place. Immediate hydrogenation of this mixture over 5% Pd/C in methanol provided a 1:3 mixture of the desired product **63** and stereoisomer **64**. Fortunately, hydrogenation over 20% $Pd(OH)_2/C$ gave an easily separable 3:2 mixture of **63** and **64** in 72% yield from the mixture of acetoxy ketone **59** and enol acetate **60**. Hydrogenolysis of the Cbz groups afforded the free guanidine, which underwent an intramolecular S_N2 reaction to form the third ring. We expected that hydrogenation of the ketone should be the slowest step. Equilibration of the ketone side chain before hydrogenation should favor the desired isomer **63** with an equatorial side chain. We therefore carried out the hydrogenation in the presence of bases such as K_2CO_3, Et_3N, and $KHCO_3$, and acids such as formic acid and HCl. Unfortunately, none of the acids improved the ratio of **63** to **64**. Much lower yields were obtained in the presence of the bases.



The stereochemistry of the newly formed six-membered ring of **63** was assigned based on the coupling constant, $J_{9ax\text{-}8}$ = 11.6 Hz, which is very

similar to that of **1** ($J_{8\text{-}9ax}$ = 11.4 Hz) (see Figure 2). This established that H_8 is axial as in **1**. The absorption for H_7 in **63**, δ 4.68 (d, J = 3.7 Hz) corresponds closely to that of cylindrospermopsin, δ 4.70 (d, J = 3.9 Hz) suggesting that hydrogenation of the ketone afforded the correct stereochemistry at C_7. Stereoisomer **64** has the opposite C_8 stereochemistry because the coupling constant, $J_{8\text{-}9ax}$ = 5.5 Hz, indicates that H_8 is equatorial. Only a single alcohol isomer was formed, but the stereochemistry at C_7 in **64** could not be assigned. Alcohols **63** and **64** correspond to the two major products, **20** and **22**, in the model study. Although the selectivity for **63** is not as good as that for **20**, this still provides a practical route to cylindrospermopsin, since two stereocenters and the final ring are constructed in this step.

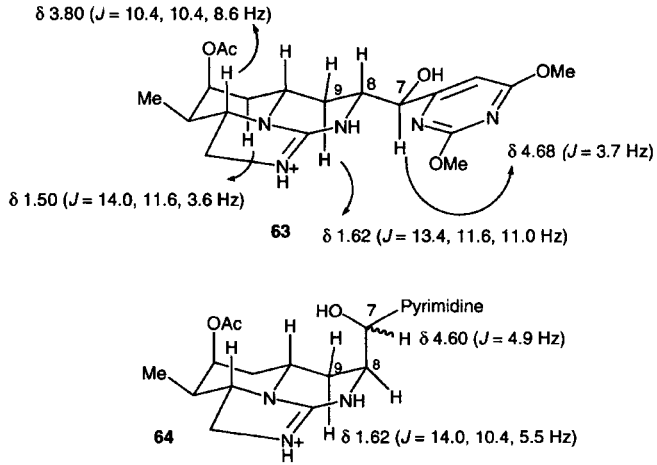
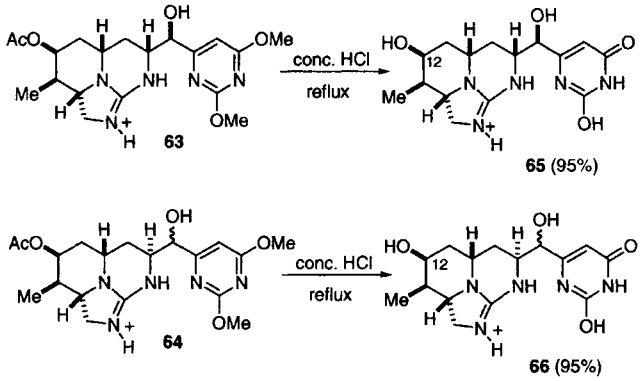
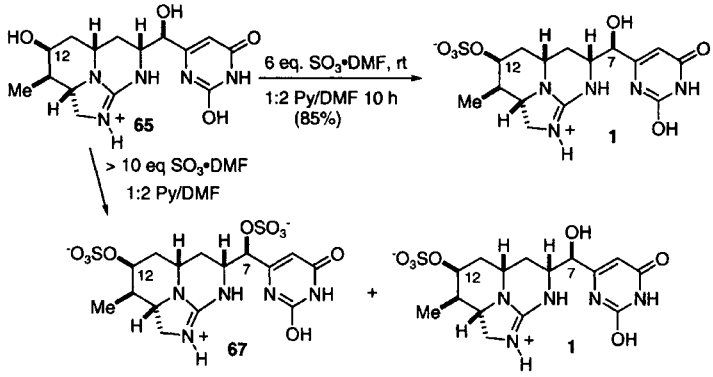


Figure 2. ^{1}H NMR Spectral data for **63** and **64**

Hydrolysis of **63** in concentrated hydrochloric acid at 100 °C for 6 h afforded 95% of uracil diol **65** with ^{1}H and ^{13}C NMR spectral data virtually identical to those of cylindrospermopsin except for the protons and carbons close to C_{12}. A similar hydrolysis of **64** provided 95% of **66**. This hydrolysis is perhaps the most remarkable step in the synthesis. Very harsh conditions are needed to hydrolyze the dimethoxypyrimidine to the uracil. However, the reaction is remarkably clean, accompanied only by the desired hydrolysis of the acetate ester, but no decomposition or epimerization at any of the stereocenters. Presumably, the protonated guanidine and uracil make it hard to protonate either alcohol and solvolyze to form a trication.



Monosulfation[28-30] of the ring alcohol of **65** was needed to complete the synthesis. Because both alcohols are secondary, it was not obvious which would be more reactive. Reaction of **65** with 10 equiv of SO_3•DMF in anhydrous pyridine and DMF overnight and concentration in vacuum gave a mixture of cylindrospermopsin (**1**) and bis sulfate ester **67** containing some DMF and pyridine, indicating that the ring alcohol is more reactive. We were delighted to find that reverse phase chromatography on C_{18}-silica gel using D_2O as the eluent and NMR spectroscopy to monitor fractions gave pure bis sulfate ester **67** followed by pure **1**. Sulfation of **65** with 6 equivalents of SO_3•DMF gave 60-80% of cylindrospermopsin after purification. The ^1H and ^{13}C NMR spectral data of **1** were identical to those reported for the natural product.[1] The absorption for H_{12} shifts downfield to δ 4.60 in **1** from δ 4.03 in **65**, while the absorption for H_7 at δ 4.72 in **1** was virtually identical to that of **65** at δ 4.78. H_{12} of bis sulfate **67** also absorbs at δ 4.61, while H_7 was now also shifted downfield to δ 5.20, and H_8 was shifted downfield from δ 3.87 in **1** to δ 3.99 in **67**.



The toxicities of model diol **20**, diol **65**, and synthetic cylindrospermopsin ((±)-**1**) were compared to that of natural (–)-**1** in the previously reported *in vitro* hepatocyte assay.[31] Natural **1** has been shown to cause depletion of the cellular antioxidant glutathione (GSH) in heptatocytes. This loss always precedes cell death. Racemic diol **65** is more potent than racemic **1** and as least as potent as the natural toxin clearly demonstrating that the sulfate group is not necessary for either biological activity or entry into the cell. Diol **20** is not toxic, indicating that the A-ring functionality and/or C ring are needed for activity.

VIII. Conclusion

In conclusion, the first total synthesis of the novel hepatotoxin (±)-cylindrospermopsin (**1**) was accomplished in 20 steps from 4-methoxy-3-methylpyridine (**7**) in 3.5% overall yield as summarized in Figure 3. The substituted piperidine A ring **35** was generated stereospecifically by a four-step sequence using the addition of trimethylsilylethynylmagnesium bromide to **7** to give **30** and stereospecific addition of vinylcuprate to **30** to form **31**. The reaction of diamine **52** with cyanogen bromide produced the cyclic guanidine C ring of **55**.

The key step in the synthesis was bromination of ketone **59**, followed by hydrogenation to liberate the free guanidine, which underwent an intramolecular S_N2 reaction to form the tetrahydropyrimidine ring B. Further hydrogenation reduced the ketone to yield 42% of **63** containing the fully functionalized tricyclic system and protected hydroxymethyluracil side chain of cylindrospermopsin. Hydrolysis of the pyrimidine of **63** in concentrated hydrochloric acid at reflux and selective monosulfation completed the synthesis of cylindrospermopsin.

This hydrogenation gave predominantly the side chain alcohol with the cylindrospermopsin stereochemistry. However, it provided no information about the relative stereochemistry. Therefore, although we successfully completed the first synthesis of cylindrospermopsin, we did not realize that the stereochemistry of the side chain alcohol had been misassigned.[1c] The following year, Weinreb reported a stereocontrolled synthesis that was designed to produce the originally assigned structure of cylindrospermopsin (**2**).[7a] To everyone's surprise, the compound he obtained with structure **2** was 7-epicylindrospermopsin, not cylindrospermopsin, necessitating a revision of the cylindrospermopsin structure to **1**.

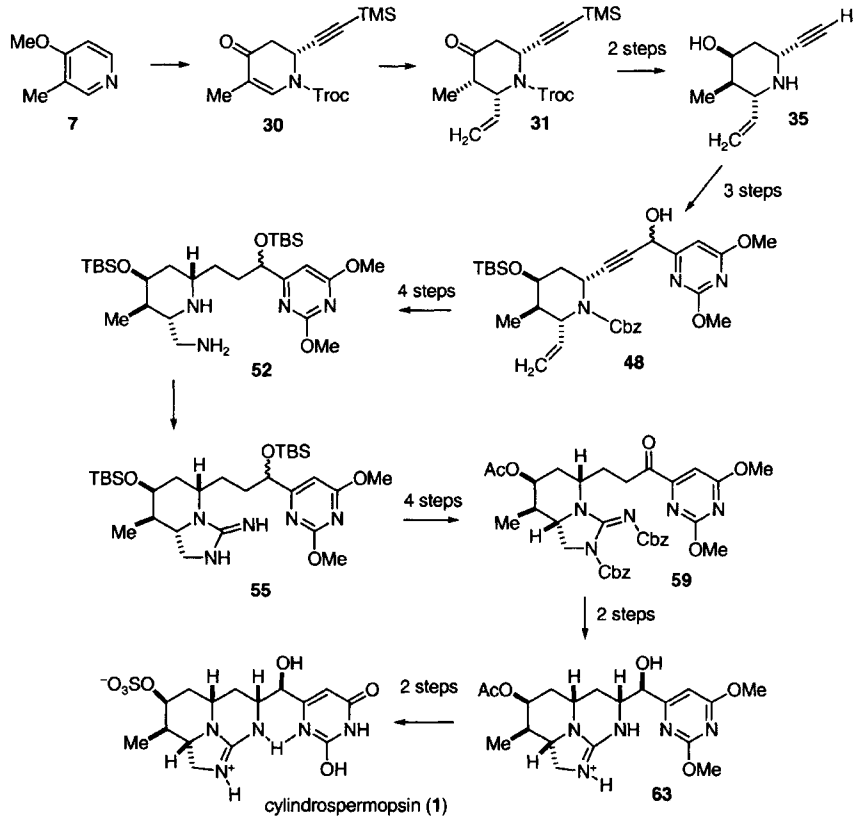


Figure 3. Overview of the synthesis of cylindrospermopsin (**1**)

Acknowledgments

We are grateful to the National Institutes of Health (GM-46470) for financial support. We thank Dr. Christine Hofstetter for assistance in obtaining NMR data and Dr. Thomas C. Harvey for carrying out preliminary experiments on another route to cylindrospermopsin.

References and Footnotes

1. For the primary reports of the synthesis described in this chapter see: (a) Snider, B. B., Harvey, T. C., *Tetrahedron Lett.* **1995**, *36*, 4587. (b) Snider, B. B., Xie, C., *Tetrahedron Lett.* **1998**, *39*, 7021. (c) Xie, C., Runnegar, M. T. C., Snider, B. B.,

J. Am. Chem. Soc. **2000**, *122*, 5017. (d) Xie, C., Ph. D. Thesis, Brandeis University, 2000.

2. Ohtani, I., Moore, R. E., Runnegar, M. T. C., *J. Am. Chem. Soc.* **1992**, *114*, 7941.
3. Moore, R. E., Ohtani, I., Moore, B. S., De Koning, C. B., Yoshida, W. Y., Runnegar, M. T. C., Carmichael, W. W., *Gazz. Chim. Ital.* **1993**, *123*, 329.
4. Burgoyne, D. L., Hemscheidt, T. K., Moore, R. E., Runnegar, M. T. C., *J. Org. Chem.* **2000**, *65*, 152.
5. Banker, R., Teltsch, B., Sukenik, A., Carmeli, S., *J. Nat. Prod.* **2000**, *63*, 387.
6. Norris, R. L., Eaglesham, G. K., Pierens, G., Shaw, G. R., Smith, M. J., Chiswell, R. K., Seawright, A. A., Moore, M. R., *Environ. Toxicol.* **1999**, *14*, 163.
7. (a) Heintzelman, G. R., Fang, W.-K., Keen, S. P., Wallace, G. A., Weinreb, S. M., *J. Am. Chem. Soc.* **2001**, *123*, 8851. (b) Heintzelman, G. R., Fang, W.-K.; Keen, S. P., Wallace, G. A., Weinreb, S. A., *J. Am. Chem. Soc.* **2002**, *124*, 3939.
8. For another synthesis of 7-epicylindrospermopsin see: White, J. D., Hansen, J. D., *J. Am. Chem. Soc.* **2002**, *124*, 4950. For other synthetic work see: (a) Heintzelman, G. R., Parvez, M., Weinreb, S. M., *Synlett* **1993**, 551. (b) Heintzelman, G. R., Weinreb, S. M., Parvez, M., *J. Org. Chem.* **1996**, *61*, 4594. (c) McAlpine, I. J., Armstrong, R. W., *Tetrahedron Lett.* **2000**, *41*, 1849. (d) Keen, S. P., Weinreb, S. M., *Tetrahedron Lett.* **2000**, *41*, 4307. (e) Djung, J. F., Hart, D. J., Young, E. R. R., *J. Org. Chem.* **2000**, *65*, 5668. (f) Looper, R. E., Williams, R. M., *Tetrahedron Lett.* **2001**, *42*, 769.
9. For recent reviews see: (a) Murphy, P. J., Thomas, C. W., *Chem. Soc. Rev.* **2001**, *30*, 303. (b) Griffiths, D. J., Saker, M. L., *Environ. Toxicol.* **2003**, *18*, 78.
10. (a) Yamaguchi, R., Nakazono, Y., Kawanisi, M., *Tetrahedron Lett.* **1983**, *24*, 1801. (b) Yamaguchi, R., Nakazono, Y., Matsuki, T., Hata, E-I., Kawanisi, M., *Bull. Chem. Soc. Jpn.* **1987**, *60*, 215.
11. Gershon, H., *J. Org. Chem.* **1962**, *27*, 3507.
12. Stogryn, E. L., *J. Heterocycl. Chem.* **1974**, *11*, 251.
13. Matsumoto, M., Ishide, Y., Watanabe N., *Heterocycles* **1985**, *23*, 165.
14. (a) Bettoni, G., Cellucci, C., Ferorelli, S., Perrone, R., Tortorella, V., *Tetrahedron* **1986**, *42*, 2117. (b) Tramontini, M., *Synthesis* **1982**, 605.
15. (a) Takahashi, T., Kotsubo, H., Koizumi, T., *J. Chem. Soc., Perkin Trans. 1* **1991**, 1677. (b) Wada, A., Yamamoto, J., Hase, T., Nagai, S., Kanatomo, S., *Synthesis* **1986**, 555. (c) Uno, H., Terakawa, T., Suzuki, H., *Synthesis* **1989**, 381. (d) Khan, M. W., Kundu, N. G., *J. Chem. Res., Synop.* **1999**, 20. (e) Griengl, H., Wanek, E., Schwarz, W., Streicher, W., Rosenwirth, B., De Clercq, E., *J. Med. Chem.* **1987**, *30*, 1199. (f) Kundu, N. G., Choudhuri, L. N., Das, B., *J. Chem. Soc., Perkin Trans. 1* **1989**, 1165. (g) Maruyama, T., Kimura, S., Honjo, M., *Org. Prep. Proced. Int.* **1988**, *20*, 485.

16. Murray, K., Rasmussen, P. S., Neustaedter, J., Luck, J. M., *J. Biol. Chem.* **1965**, *240*, 705.
17. Profft, E., Schulz, G., *Arch. Pharm.* **1961**, *294*, 292.
18. Profft, E., Krueger, W., Kuhn, P., Lietz, W., Ger. Pat. (East) 69,126; *Chem. Abstr.* **1970**, *72*, 90309w.
19. Taylor, E. C., Jr., Crovetti A. J., In *Organic Syntheses Collective Volume IV*, Rabjohn, N., Ed., Wiley: New York, 1963, pp 654-656.
20. (a) Comins, D. L., Brown, J. D., *Tetrahedron Lett.* **1986**, *27*, 4549. (b) Comins, D. L., Weglarz, M. A., O'Connor, S., *Tetrahedron Lett.* **1988**, *29*, 1751. (c) Brown, J. D., Foley, M. A., Comins, D. L., *J. Am. Chem. Soc.* **1988**, *110*, 7445. (d) Comins, D. L., Joseph, S. P., Goehring, R. R., *J. Am. Chem. Soc.* **1994**, *116*, 4719. (e) Comins, D. L., Dehghani, A., *J. Org. Chem.* **1995**, *60*, 794. (f) Comins, D. L., Joseph, S. P., Hong, H., Al-awan, R. S., Foti, C. J., Zhang, Y.-M., Chen, X., LaMunyon, D. H., Weltzien, M. G., *Pure Appl. Chem.* **1997**, *69*, 477. (g) Comins, D. L., LaMunyon, D. H., Chen, X., *J. Org. Chem.* **1997**, *62*, 8182.
21. (a) Corey, E. J., Boaz, N. W., *Tetrahedron Lett.* **1985**, *26*, 6015. (b) Alexakis, A., Berlan, J., Besace, Y., *Tetrahedron Lett.* **1986**, *27*, 1047. (c) Bertz, S. H., Miao, G., Rossiter, B. E., Snyder, J. P., *J. Am. Chem. Soc.* **1995**, *117*, 11023.
22. Yong, Y. F., Kowalski, J. A., Lipton, M. A., *J. Org. Chem.* **1997**, *62*, 1540.
23. (a) Lee, S. Y., Niwa, M., Snider, B. B., *J. Org. Chem.* **1988**, *53*, 2356. (b) Veysoglu, T., Mitscher, L. A., Swayze, J. K., *Synthesis* **1980**, 807.
24. Borch, R. F., Bernstein, M. D., Durst, H. D., *J. Am. Chem. Soc.* **1971**, *93*, 2897.
25. Bordner, J., Thiessen, W. E., Bates, H. A., Rapoport, H., *J. Am. Chem. Soc.* **1975**, *97*, 6008.
26 (a) Schmidtchen, F. P., Oswald, H., Schummer, A., *Liebigs Ann. Chem.* **1991**, 539. (b) Dyson, G. M., George, H. J., Hunter, R. F., *J. Chem. Soc.* **1927**, 436.
27. (a) Siddiqui, S., Begum, S., Siddiqui, B. S., *Z. Naturforsch.* **1982**, *37b*, 1481. (b) Siddiqui, S., Haider, S. I., Ahmad, S. S., Siddiqui, B. S., *Z. Naturforsch.* **1985**, *40b*, 546. (c) Ahmad, S. S., Haider, S. I., Fatima, I., *Synth. Commun.* **1987**, *17*, 1861.
28. Mulder, G. R., Ed. *"Sulfation of Drugs and Related Compounds"* CRC Press: Boca Raton, FL, 1981, p 51.
29. Lubineau, A., Lemoine, R., *Tetrahedron Lett.* **1994**, *35*, 8795.
30. Futaki, S., Taike, T., Yagami, T., Ogawa, T., Akita, T., Kitagawa, K., *J. Chem. Soc., Perkin Trans. 1* **1990**, 1739.
31. Runnegar, M. T., Kong, S.-M., Zhong, Y.-Z., Ge, J. L., Lu, S. C., *Biochem. Biophys. Res. Commun.* **1994**, *201*, 235.

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STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

CHAPTER 3

THE TOTAL SYNTHESIS OF (-)-ARISUGACIN A.

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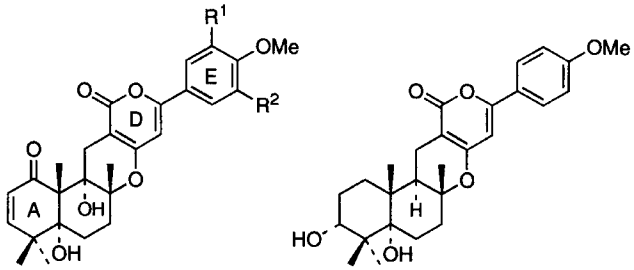
I. Introduction

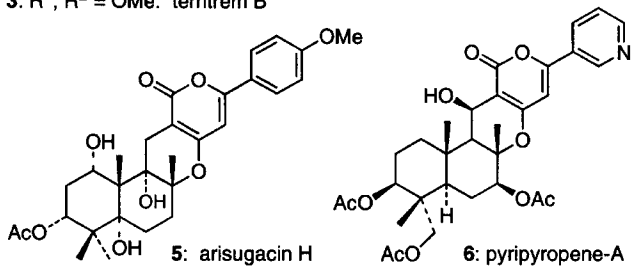
Arisugacin A [**1**], isolated from *Penicillium Sp.* Fo-4259 by Õmura, is a potent and selective inhibitor of acetylcholinesterase [AChE] with an IC_{50} of 1 nM,[1] thereby possessing significance in treatment of dementia diseases such as Alzheimer's disease [AD].[2,3] The entire arisugacin family [i.e., arisugacin B: **2**, E: **4**, and H: **5**] features a unique meroterpenoidal structure, or a hybrid of polyketide and terpenoid, that resembles other medicinally important natural products such as the territrems [**3**][4] and pyripyropenes [**6**: pyripyropene A] which is a potent inhibitor of acyl-CoA cholesterol acyltransferase (ACAT)[5] [Figure 1].

FIGURE 1



1: R^1 = H; R^2 = OMe: arisugacin A
2: R^1, R^2 = H: arisugacin B
3: R^1, R^2 = OMe: territrem B

4: arisugacin E



5: arisugacin H **6**: pyripyropene-A

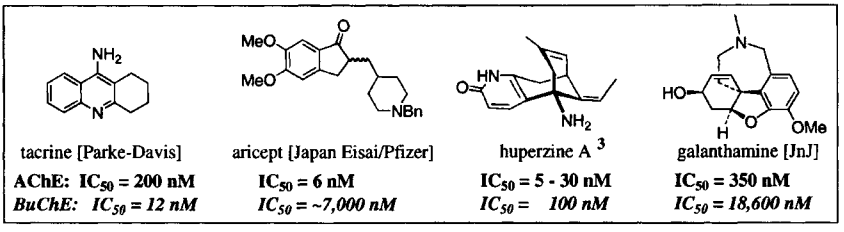
Dementia Diseases. AD affects almost 5 million people in America today,[2,3] representing one of the most degenerative and devastating syndromes characterized by severe loss of memory and cognitive abilities especially among the geriatric population. The exact pathogenic mechanism of AD is still not well understood because the pathogenic analysis has focused mainly on a single postmortem point. However, the cholinergic deficiency hypothesis[6,7] has been established as the most rational as well as consistent approach for the therapeutic treatment of AD. This hypothesis links AD to the loss of acetylcholine, a neurotransmitter responsible for memory and cognitive functions at the hippocampal and cortical levels.[6,7] Thus, to maintain concentrations of acetylcholine in AD patients, one of the most promising treatments involves the use of reversible and competitive inhibitors of AChE, the enzyme that catalyzes the hydrolysis of acetylcholine.

Only four inhibitors of AChE have been approved as therapeutic drugs for combating dementia diseases. The very first is tacrine or Cognex [Figure 2] from Parke-Davis[8] and the second is aricept from Eisai [Japan] and Pfizer [U.S.].[9] A third inhibitor available is huperzine A, a "nootropic" agent isolated from a Chinese folk medicine and used by Chinese for centuries to improve memory.[10] Other known reversible AChE inhibitors

are physostigmines[11] and galanthamine.[12] The latter, sponsored by JnJ, was just approved by FDA in February of 2003. Administration of these therapeutic drugs has demonstrated improvement in memory and cognitive functions of AD patients at early stages by maintaining the concentration of available acetylcholine. However, as the disease progresses, these drugs lose their therapeutic effects as neurons continue to be destroyed. Therefore, efforts in searching for more potent and selective inhibitors of AChE will remain highly significant in the therapeutic treatment of AD.

FIGURE 2

Other Known Therapeutics for Anti-Dementia Diseases

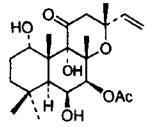


tacrine [Parke-Davis]	aricept [Japan Eisai/Pfizer]	huperzine A [3]	galanthamine [JnJ]
AChE: IC_{50} = 200 nM	**IC_{50} = 6 nM**	**IC_{50} = 5 - 30 nM**	**IC_{50} = 350 nM**
BuChE: IC_{50} = 12 nM	***IC_{50} = ~7,000 nM***	***IC_{50} = 100 nM***	***IC_{50} = 18,600 nM***

Arisugacin not only demonstrates impressive potency in inhibiting AChE with an IC_{50} value of 1 nM, but more importantly, it is highly selective for AChE since >18 μM is required to inhibit butyrylcholinesterase [BuChE]. In contrast, tacrine and other inhibitors are less selective for AChE. In the case of tacrine, it is actually more selective for BuChE with an IC_{50} value of 12 nM, thereby raising concerns about its potential in liver damage.[13]

The scarcity of arisugacin from the natural resource severely hinders meaningful explorations of its potential therapeutic significance in the treatment of AD. Therefore, developing efficient synthetic pathways leading to arisugacin should not only provide a solution to the availability problem, but more significantly, should lead to discovery of various unique or unexplored synthetic methodologies for the synthesis of natural products with biological relevance.

Structural analysis reveals that arisugacin A [**1**] contains five rings, two of which are heterocycles, and four contiguous stereocenters, two of which bear angular hydroxyl groups. Arisugacin A [**1**] is clearly a close structural analog of pyripyropene-A [**6**] and the ABC tricyclic frame of arisugacin closely resembles the skeleton of forskolin [see left], an agonist of adenylyl cyclase.[14] These structural features provide fertile ground for developing new methodologies.



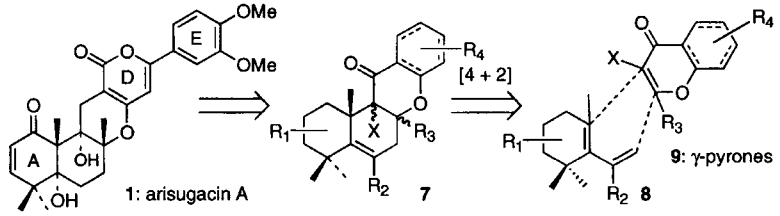
forskolin

II. Retrosynthetic Analysis

A. A DIELS-ALDER APPROACH

Cycloaddition and annulation reactions are among the most powerful methods in organic synthesis, owing to their ability to provide multiple bond formations with regio- and stereochemical control leading to polycyclic carbocycles and heterocycles through a concerted, stepwise, or sequential process. Our very first approach toward the synthesis of arisugacin A [**1**] involved [4 + 2] cycloaddition reactions using γ-pyrones **9** as dienophiles, and when dienes **8** [Scheme 1] could be used, such a cycloaddition would provide a convergent approach for constructing angularly fused tetracyclic frame of arisugacins shown as **7**. This strategy could serve as a useful entry to a wide range of structural analogs.

SCHEME 1



It is noteworthy that there had been very few reports of [4 + 2] cycloaddition reactions using γ-pyrones as dienophiles when our studies commenced.[15] The only examples of 4-*H*-benzopyran-4-ones employed as dienophiles were 3-acylchromones reported by Wallace,[16] while the first examples of 3-acyl-4-*H*-pyran-4-ones in [4 + 2] cycloaddition reactions were described in the preparation of reduced flavones.[17]

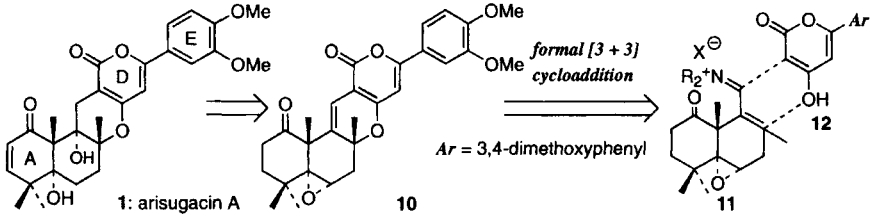
We focused on 3-cyanochromone derivatives, for the dienophilic reactivity of these compounds has gone unnoticed.[18] In addition, these 3-cyanochromones could serve as excellent model systems for exploring the potential of our strategy and investigating the scope [i.e. regio- and stereoselectivity] of γ-pyrones in [4 + 2] cycloadditions. As a result, this cycloaddition also became a subject of research by other groups.[19]

B. A FORMAL [3 + 3] CYCLOADDITION APPROACH

Despite the fact that the [4 + 2] cycloaddition strategy was intriguing and novel, it posed serious limitations in achieving an efficient total

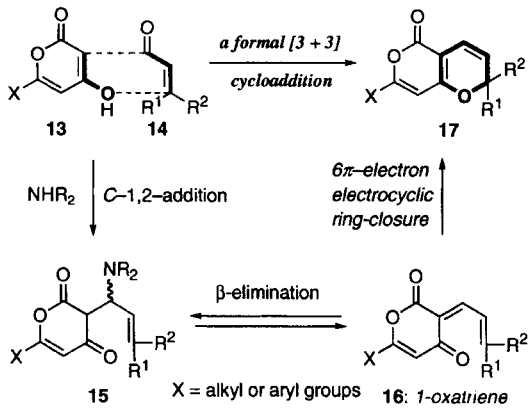
synthesis. Our ultimate total synthesis of arisugacin A [**1**] employed a formal [3 + 3] cycloaddition method[20] that involved condensing α,β-unsaturated iminium salts **11** with 6-aryl-4-hydroxy-2-pyrones **12** [Scheme 2].

SCHEME 2



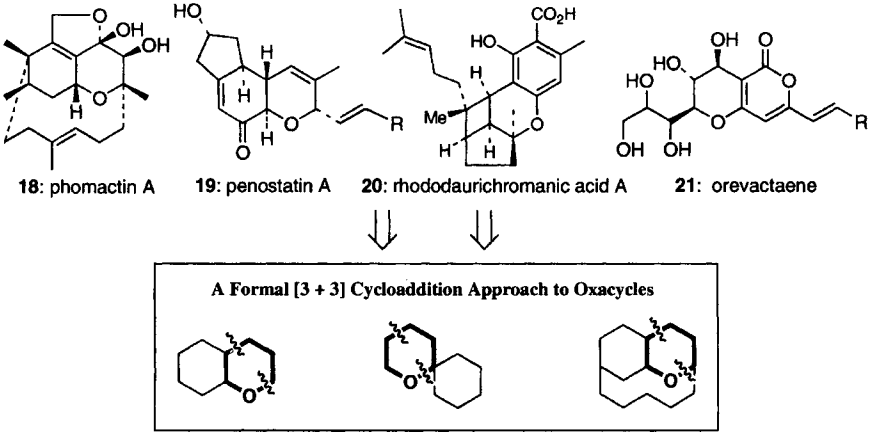
This annulation reaction was first cited by Link[21] in 1944 specifically involving 4-hydoxy-coumarins and later was studied in detail by Moreno-Mañas.[22] Mechanistically, this annulation reaction has been proposed to involve a sequence that consists of a *C*-1,2-addition of 6-alkyl- or 6-aryl-4-hydroxy-2-pyrones **13** to the iminium salt generated *in situ* from α,β-unsaturated aldehydes **14** and a secondary amine, followed by β-elimination to give an 1-oxatriene **16** [Knoevenagel condensation], and concluded with a 6π-electron electrocyclic ring-closure of **16** [Scheme 3].[23] This results in the formation of two σ-bonds and a new stereocenter adjacent to the oxygen atom, thereby constituting a tandem anionic-pericyclic process [or tandem Knoevenagel condensation-pericyclic ring-closure sequence] that is formally equivalent of a [3 + 3] cycloaddition,[24-25] a term described in Seebach's carbo-annulation of nitroalkenes with enamines.[25]

SCHEME 3

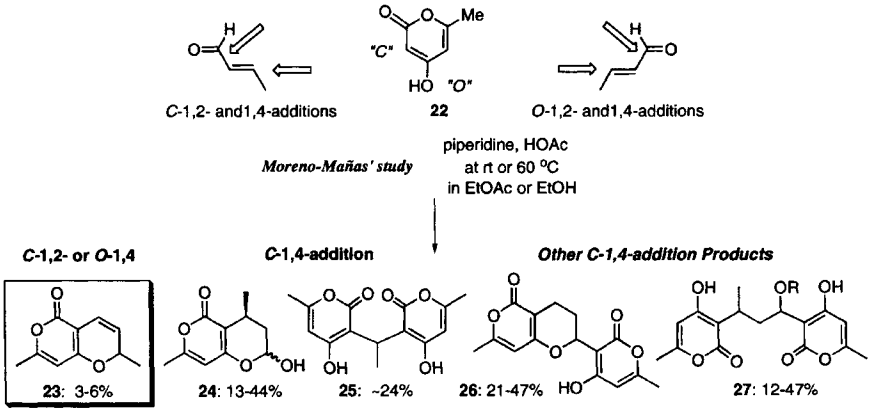


The significance of tandem strategies in natural product synthesis has been elegantly reviewed.[26] This particular formal cycloaddition strategy should provide a unique approach to 1-oxadecalins and oxa-spirocycles that are well represented in biologically relevant natural products such as phomactin A [**18**],[27-29] penostatin A [**19**],[30] rhododarichromanic acid A [**20**],[31] and orevactaene [**21**][32] [Figure 3] in addition to arisugacins.

FIGURE 3



SCHEME 4



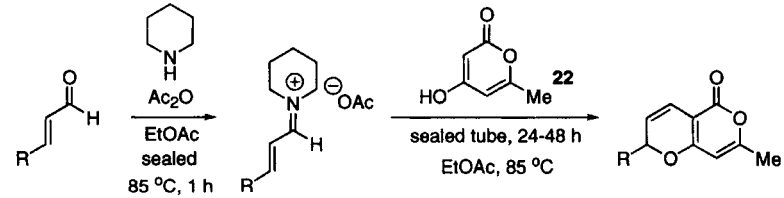
Despite the obvious synthetic potential of this formal cycloaddition or annulation reaction, its application has remained little known because of the competing reaction pathways due to 1,2- versus 1,4-addition as well as *C*-addition versus *O*-addition [Scheme 4]. Moreno-Mañas reported a

detailed study featuring reactions of 6-methyl-4-hydroxy-2-pyrone **22** and crotonaldehyde.[22] A variety of products such as **23-37** were identified and isolated in various amounts, resulting from these competing reaction pathways. The synthetically useful product **23** was found in low yields.

Although the use of cyclic enals improved the overall product distribution by suppressing the 1,4-addition pathway,[33,34] a general solution remained elusive. To solve the competing reaction pathway problem or to improve the pathway that would ultimately lead to the 2*H*-pyran **33** involved extensive experimental modifications. Our solution eventually involved the utilization of preformed α,β-unsaturated iminium salts instead of generating them *in situ.*[35-38]

As shown in Scheme 5, respective enals [**28a-c**] were incubated in the presence of 1.0 equiv of piperidine and 1.0 equiv of Ac_2O in EtOAc (added at -10 °C) at 85 °C in a sealed flask for 45 min to 1 h. The solution containing the iminium salt **29a-c** was then transferred without cooling to a solution of pyrone **22** in EtOAc. After stirring at 85 °C in a sealed flask for an additional 24-48 h, the 2*H*-pyrans **23**, **30b**, and **30c** were obtained in good yields.[35,37]

SCHEME 5

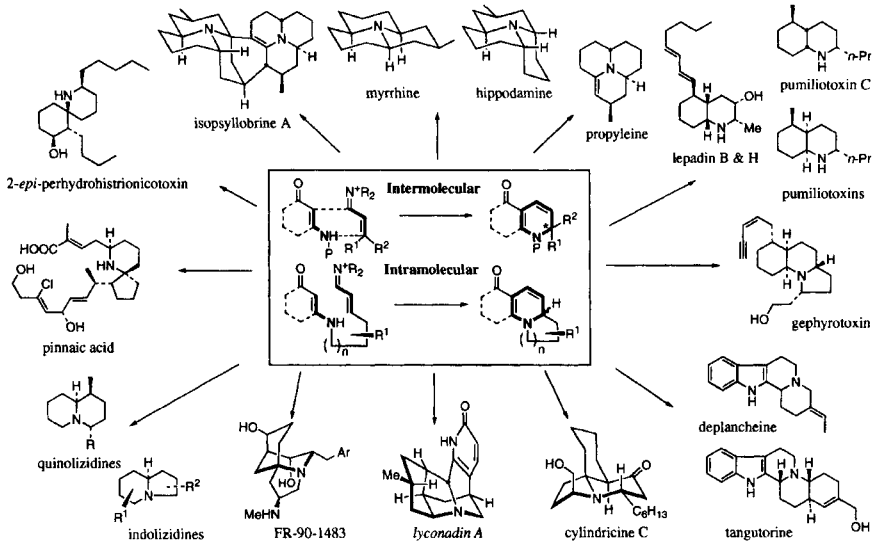


The usage of α,β-unsaturated iminium salts clearly represents a general and efficient solution leading to 2*H*-pyranyl products exclusively via the *C*-1,2-addition pathway. The reaction of the pyrone **22** led to the pyran product **23** in a much-improved yield relative to Moreno-Mañas's study, and also gave previously unknown products **30b** and **30c** under these reaction conditions [Scheme 5]. The significance of using preformed α,β-unsaturated iminium salts to control regioselectivity of this formal cycloaddition reaction was recently validated in an account reported by Cravotto.[39]

As a final note in this retrosynthetic analysis, arisugacin A [**1**] represents a structure that is unique but modest in complexity.

Nevertheless, this endeavor has brought on a number of methodological developments.

FIGURE 4



For our research group, the eventual reward was that this formal [3 + 3] cycloaddition strategy was extended to include the use of vinylogous amides, leading to stereoselective constructions of 1,2-dihydropyridines [Figure 4].[40-44] That ultimately led to a productive research program entailing stereoselective total syntheses of natural alkaloids via a formal aza-[3 + 3] cycloaddition strategy [Figure 4][42,43] and the first stereoselective electrocyclic ring closure of 1-azatrienes.[41,45,46]

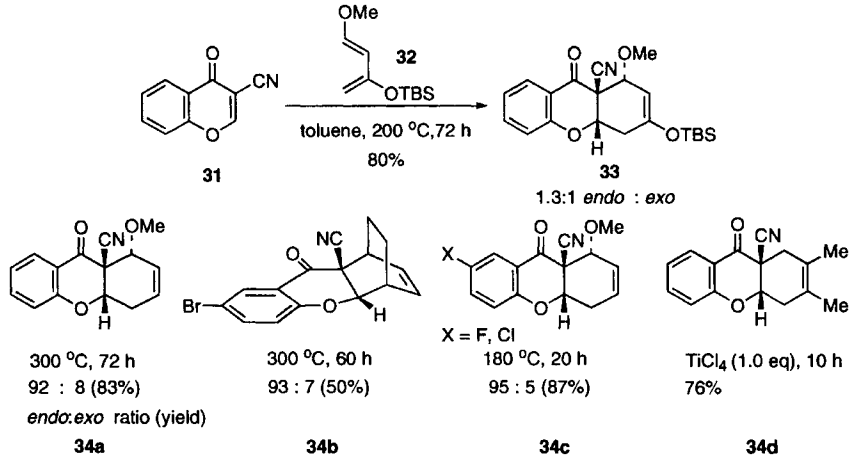
III. A Diels-Alder Approach

To demonstrate the feasibility of Diels-Alder cycloaddition using γ-pyrones as dienophiles,[47-50] the reaction of 3-cyanochromone **31** with diene **32** in toluene proceeded at 200 °C in a sealed tube for 72 h to give the desired cycloadduct **33** in 80% yield [Scheme 6] without observing any inverse electron demand [4 + 2] cycloadducts.[51] However, the *endo* : *exo* ratio was only 1.3:1 as determined by ^{1}H NMR with the stereochemistry assigned using nOe experiments.

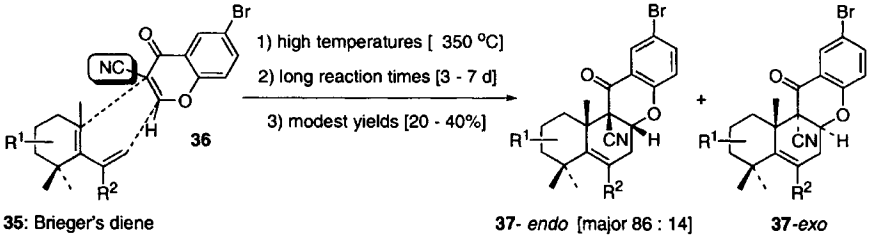
The compound **33** could be hydrolyzed to the corresponding methoxyketone in high yields using 3*N* HCl without any complications

involving aromatization or destruction of the pyrone ring as was observed for cycloadducts derived from 3-acylchromone.[16] Hence, nitrile substituted γ-pyrone systems could provide more useful dienophilic protocols for these cycloadditions since dehydrocyanation did not occur readily, allowing further manipulations of the newly formed six-membered ring without destroying the new stereocenters. In summary, these reactions can be highly stereoselective using other dienes that would lead to cycloadducts such as **34a-d**, and Lewis acids such as $TiCl_4$ could be useful for non-oxygenated dienes.[47]

SCHEME 6

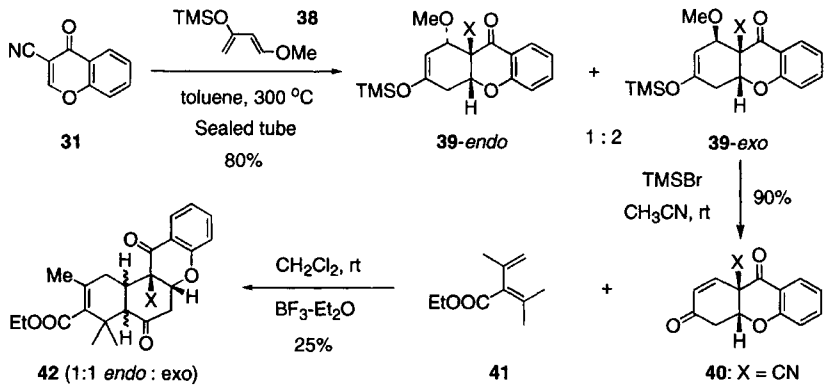


SCHEME 7



To examine the potential of this reaction in developing a convergent strategy for constructing the ABC tricyclic frame of arisugacin A [**1**], the diene **35** was reacted with 2.0 equiv of 6-bromo-3-cyanochromone **36**[50] at 350 °C in toluene for 7 d to give the desired adduct **37** in 32% yield with an *endo* : *exo* ratio of ≥ 86 : 14 [Scheme 7].[47] The stereochemistry here was assigned according to nOe experiments.

SCHEME 8



In another attempt, we reached the tetracyclic structure **42** via two consecutive [4 + 2] cycloaddition reactions. Reaction of 3-cyano-4-benzopyrone **31** with Danishefsky's diene **38** in toluene at 300 °C for 96 h provided the desired cycloadduct **39** in 80% yield with an *endo* : *exo* ratio of 1:2 [Scheme 8]. Hydrolysis of the silyl enol ether in **39** using TMSBr in CH_3CN at room temperature proved to be feasible but slow, and afforded the enone **40** in 90% yield. Reaction of diene **41** with enone **40** in the presence of 2.5 equiv of BF_3–Et_2O yielded tetracycle **42** in 25% yield with an *endo* : *exo* ratio of 1 : 1 after 120 h at room temperature.[49]

The very success of achieving these cycloaddition reactions at the methodological level also brought on the recognition that this would not be the best approach for an efficient total synthesis of arisugacin A [**1**], with long reaction times and high temperatures being required just to achieve low yields of the tetracyclic skeleton. This allowed us to focus on the formal [3 + 3] cycloaddition strategy for an eventual total synthesis of arisugacin A [**1**].[35a]

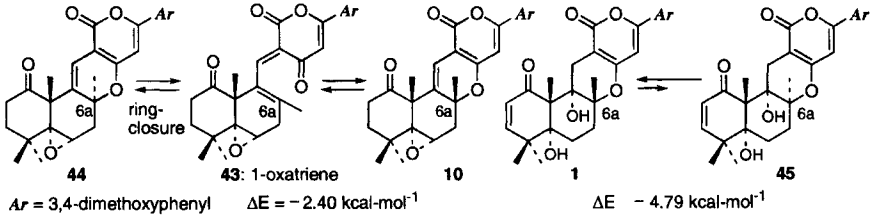
IV. A Formal [3 + 3] Cycloaddition Approach

Although the proposed route in **Scheme 2** can be feasible based on our understanding of the key formal [3 + 3] cycloaddition step [**11** + **12** → **10**],[20,35,37] there are two major uncertainties that could still render this effort futile.

First, sterically congested α,β-unsaturated iminium salts such as **11** [Scheme 2] can impede the formal [3 + 3] cycloaddition.[20] Secondly, and more significantly, there had been no successful stereoselective examples[36]

of this particular formal cycloaddition using chiral α,β-unsaturated iminium salts except in one isolated case.[33] Thus, the ability to control the stereochemistry at C6a through this key formal [3 + 3] cycloaddition reaction remained speculative.

FIGURE 5



However, because the 6π–electron electrocyclic ring-closure of the respective 1-oxatriene **43** has been found to be reversible,[20,37,41] a favorable diastereoselectivity could still be achieved leading to the thermodynamically more stable isomer **10**, in which the C6a methyl is β, in the event that **44** is the initial major product. The pentacycle **10** is more favored than its C6a-epimer **44** [the C6a methyl is α] by about 2.40 kcal mol^{-1} using PM3 calculations [Spartan™]. In addition, calculations showed that arisugacin A **1** itself is more stable with a β-C6a-methyl than the isomer **45** [C6a methyl is α] by ~ 4.79 Kcal mol^{-1} [Figure 5].

V. The Epoxy Diol Route

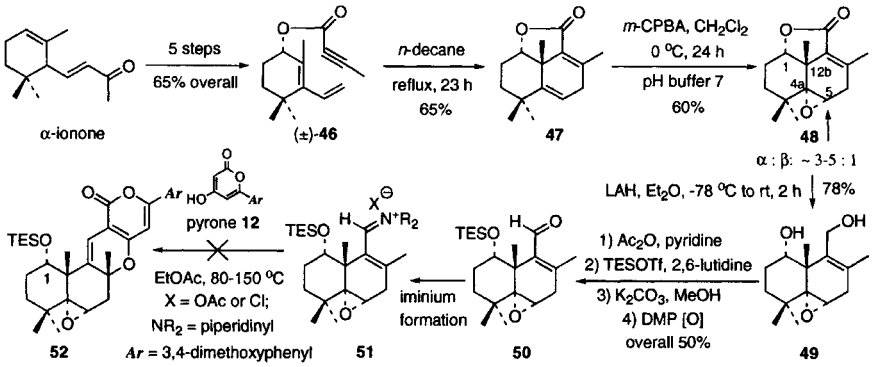
Encouraged by this calculation, the racemic ester **46** was prepared readily in 5 steps from α-ionone in 65% overall yield via a known sequence used in the synthesis of forskolin [Scheme 9].[14] The subsequent intramolecular Diels-Alder reaction of **13** in refluxing *n*-decane gave the tricyclic lactone **47** in 65% yield.[52]

Epoxidation of **47** using buffered *m*-CPBA led to α-epoxy lactone **48** in 60% yield. The corresponding β-epoxy isomer was also isolated in 10-20% yield but could be readily separated from α-epoxy isomer **48**. The relative stereochemistry of **48** was assigned using nOe experiments.

It is noteworthy that stereochemical control of the two new stereogenic centers at C4a and C12b ultimately stems from the stereochemistry at C1 through the intramolecular Diels-Alder reaction. Hence, an optically pure **46** should lead to an enantioselective preparation of α-epoxy lactone **48**, thereby ultimately leading to an enantioselective synthesis of arisugacin A [**1**]. LAH reduction of (±)-α-epoxy lactone **48** led to epoxy diol **49** in 78%

yield with the epoxide remaining intact when the reaction was carried out at low temperature. Standard functional group manipulations provided aldehyde **50** in 4 steps with an overall yield of 50%.

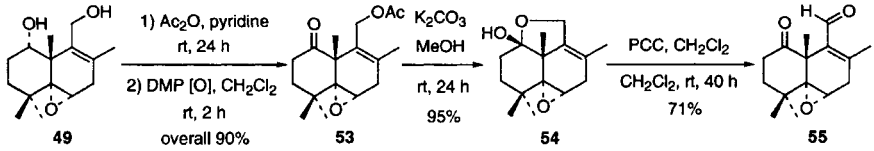
SCHEME 9



However, under our conditions[20,35,37] as well as a variety of other conditions,[53,54] the formal [3 + 3] cycloaddition reaction of the iminium salt **51** with pyrone **12** failed to provide any desired pentacycle **52**. This failure prompted us to think that **51** might be sterically too demanding, thereby obstructing the reaction pathway.

Molecular models revealed that if either the C1 carbon was sp^2 hybridized or the C1 hydroxyl group was unprotected, such a steric congestion could be alleviated. We chose the former option as shown in Scheme 10.

SCHEME 10

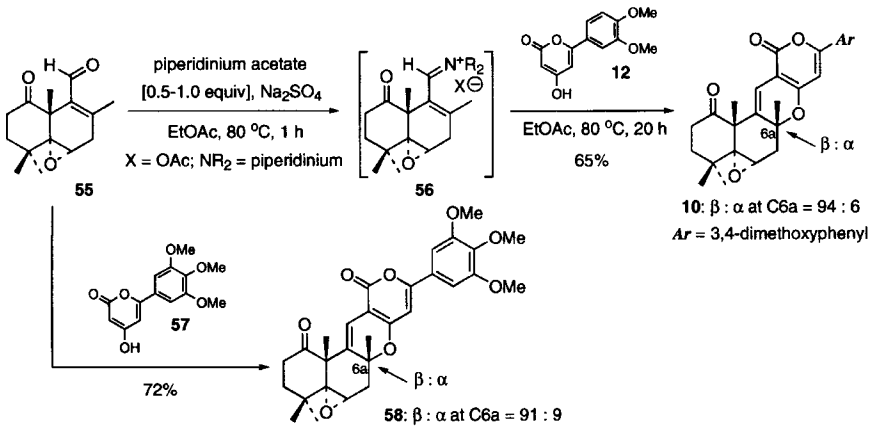


Acetylation of epoxy diol **49** followed by Dess-Martin periodinane [DMP] oxidation afforded epoxyketone **53** in 90% overall yield. Deacetylation of **53** led to the formation of epoxy lactol **54**, and PCC oxidation successfully oxidized **54** to give the desired keto-aldehyde **55** in 71% yield. Attempts to go from **49** to **55** directly via a double Swern oxidation were not successful.

Keto-aldehyde **55** proved to be suitable for constructing the pentacycle **10**.[55] The iminium salt intermediate **56** was generated from **55** using 0.5-1.0 equiv of piperidinium acetate in the presence of Na_2SO_4 at 80 °C for 1

h [Scheme 11]. The subsequent reaction of **56** with pyrone **12** in EtOAc at 80 °C for 20 h led to the isolation of pentacycle **10** in 65% yield with a diastereomeric ratio of 94 : 6.[55,56] The angular methyl at C6a was established as β for the major isomer of **10** and α for the minor isomer **44** by using nOe experiments.

SCHEME 11

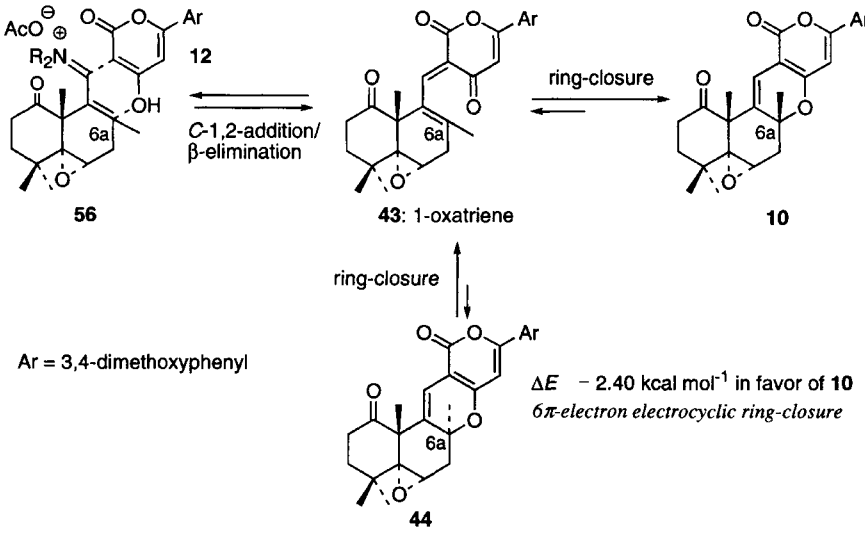


By using pyrone **57**[57] under the same conditions, pentacycle **58** was obtained in 72% yield with a diastereomeric ratio of 91 : 9 in favor of the same major isomer. The compound **58** contains the desired E-ring of territrem B [**3**]. This current formal [3 + 3] cycloaddition approach also proves to be superior to another related variation of this cycloaddition using acid chlorides[58] instead of α,β-unsaturated iminium salts.

Reversibility of 6π-Electron Electrocyclic Ring-Closure. The high diastereoselectivity obtained in these reactions here is likely a result of the reversible 6π-electron electrocyclic ring-closure.[20,37,41] The best evidence for the reversibility of this ring-closure is described in Scheme 12. We were able to isolate both the desired major isomer **10** and the minor isomer **44** from the formal cycloaddition reaction of the iminium salt **56** with pyrone **12**.

With the pure minor isomer **44** in hand, it was possible to equilibrate **44** quantitatively to the desired major isomer **10**.[37] This successful equilibration strongly suggests the reversibility of the ring-closure via the 1-oxatriene intermediate **43**, thereby leading to the final product **10** that is thermodynamically more stable than **44** by about 2.40 kcal-mole^{-1} from PM3 calculations using Spartan Model™.

SCHEME 12

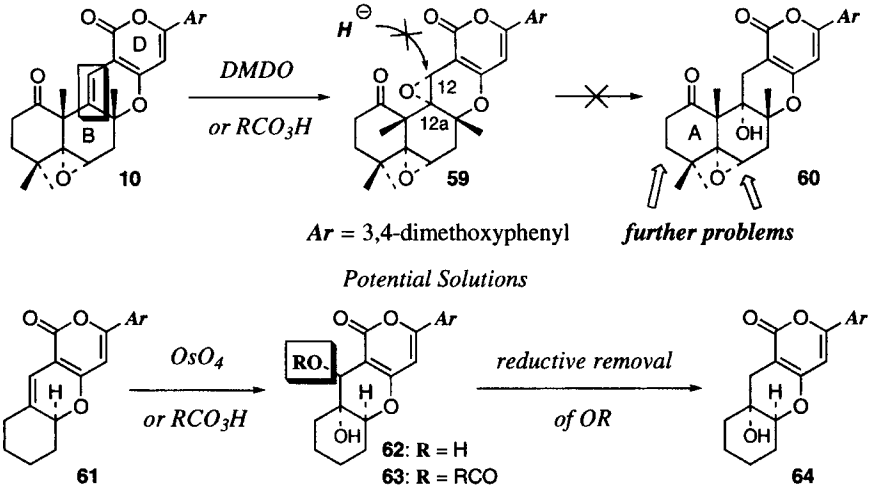


VI. Problems with the Epoxy Diol Route

The 13-step preparation of pentacycle **10** in 9% overall yield from α-ionone firmly establishes the feasibility of the formal [3 + 3] cycloaddition reaction as an approach to arisugacin A [**1**] and its family members as well as structural analogs. However, a major challenge lay ahead that led to a 14-month investigation involving installation of the C12a hydroxyl group in the C-ring.[59] The sequence of epoxidation-reduction was met with difficulties because ring opening of the C12a-C12 epoxide in **59** by various nucleophilic species precluded the addition of hydride [Scheme 13]. The desired product **60** was never isolated.[59]

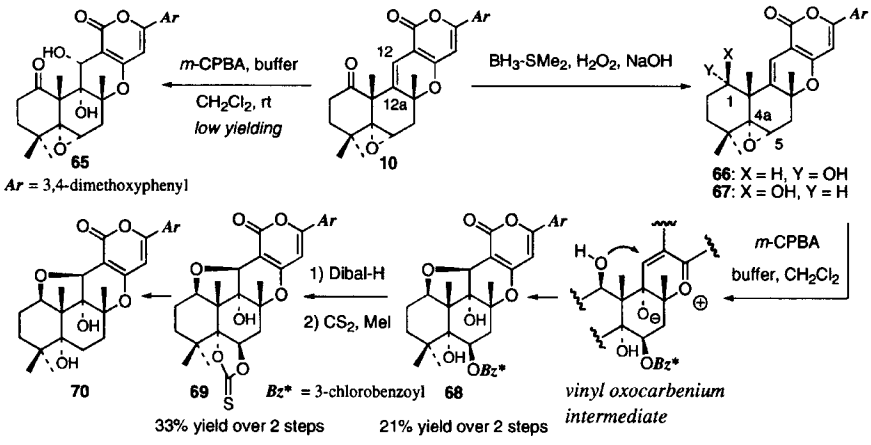
To solve this problem, bisoxygenation or dihydroxylation of the model tetracycle **61** was carried out followed by removal of the more activated secondary oxygen functionality in **62** or **63** using reductive methods that we had developed for these specific systems [Scheme 13].[59,60] The effort in developing this methodology [**61** → **64**] turned out to be significant not only in this synthetic endeavor, but also for future total syntheses employing the formal [3 + 3] cycloaddition reaction.

SCHEME 13



Based on our model study [**61** → **64**],[60] the C12-C12a olefin in the C-ring of epoxy pentacycle **10** was subjected to a variety of epoxidation and dihydroxylation conditions but all failed. The only discernable product arising from these attempts was the diol **65** in only 8-21% yield when using *m*-CPBA, but this result was also difficult to reproduce [Scheme 14]. Attempts to hydroborate the same C12-C12a olefin in **10** using BH_3–SMe_2 gave exclusively the alcohol **67** with β-C1-OH based on nOe experiments. The alcohol **67** was also obtained when **10** was reduced using Dibal-H or $NaBH_4$.

SCHEME 14



Epoxidation of **67** using *m*-CPBA buffered with $NaHCO_3$ led to the hexacycle **68** in 21% overall yield starting from **10**.[61,62] The stereochemistry of the hexacycle **68** was assigned using nOe experiments. This indicates that not only epoxidation of the C12-C12a olefin had taken place, but also the ring opening of the C12-C12a epoxide had occurred. This presumably took place through a vinyl oxocarbenium intermediate that was trapped intramolecularly by the β-C1-OH, leading to the new furan ring, although such an event could also take place without involving the proposed zwitterion. Furthermore, C4a-C5 epoxide in the B-ring had surprisingly ring-opened at the same time

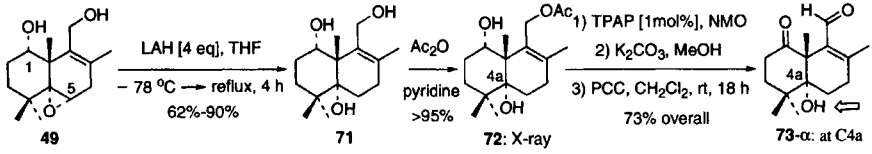
Reductive removal of the 3-chlorobenzoyl group [*Bz**] in **68** using Dibal-H [63% yield] led to a free alcohol at C5 that was subjected to xanthate formation [CS_2, MeI, 52% yield] to give xanthate **69**.[61,62] However, the subsequent Barton deoxygenation proceeded to give **70** only in very low yield in removing the C5 oxygen functionality. Ultimately, there were additional problems associated with ring opening of the C4a-C5 epoxide, thereby suffocating this route.

The most significant result in this endeavor turned out to be the recognition in hindsight that the C1-OH group has to be β to allow successful functionalization of the C12-C12a olefin in the C-ring.

VII. The Triol Route

To avoid the C4a-C5 epoxide issue, a new route to the keto enal "**73**-α" was pursued [Scheme 15]. Triol **71** could be attained via LAH reduction of epoxy diol **49**, and acylation of **71** would lead to the acetate **72** whose stereochemistry was assigned by X-ray analysis. The subsequent TPAP oxidation of **72** followed by deacylation and PCC oxidation led to the keto-enal "**73**-α" in 73% overall yield.

SCHEME 15



It was not readily apparent that the assignment of keto enal "**73**-α" was incorrect until we pursued the subsequent formal [3 + 3] cycloaddition of the alleged "**73**-α"with pyrone **12**. The reactions of keto enal "**73**-α" with

12 could only proceed at high temperatures using the more reactive piperidinium hydrochloride salt[53] leading to the pentacycle **74** with low yield and poor diastereoselectivity [Scheme 16].

An X-ray structural analysis [Figure 5] disturbingly showed while the connectivity was correct, it was not the keto enal "**73**-α" but **73**-β that had led to the wrong pentacycle **74** and not the desired pentacycle **75** with *trans*-fused AB-ring.[61,62]

SCHEME 16

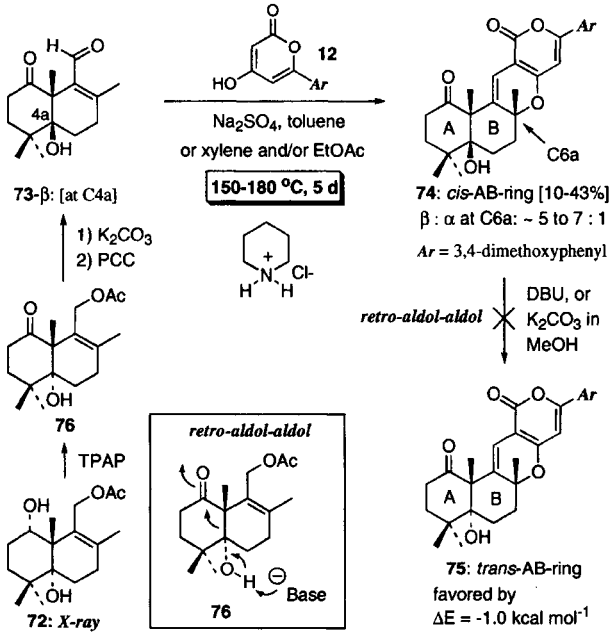
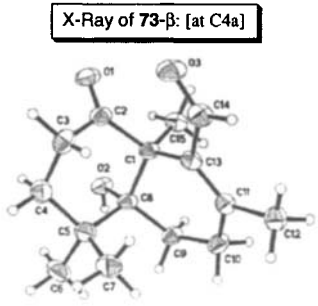


FIGURE 5



It is reasonable to propose that a *retro-aldol-aldol* sequence had occurred during the attempted preparation of **73**-α at the stage of

deacylation of **76** using K_2CO_3/MeOH [see the box in Scheme 16]. Calculations [AM1-Spartan^{TM}] showed that *cis*-fused decalin motif in **73**-β is actually more stable than **73**-αby ~1.5 kcal mol^{-1} presumably due to the severe interactions between the two axial methyl groups in the *trans*-decalin motif of **73**-α.

On the other hand, the desired pentacycle **75** was calculated [AM1-Spartan^{TM}] to be more stable than **74** by ~1.0 kcal mol^{-1}, but attempts using K_2CO_3/MeOH or DBU to equilibrate **74** to **75** via another *retro-aldol-aldol* sequence failed .[62]

SCHEME 17

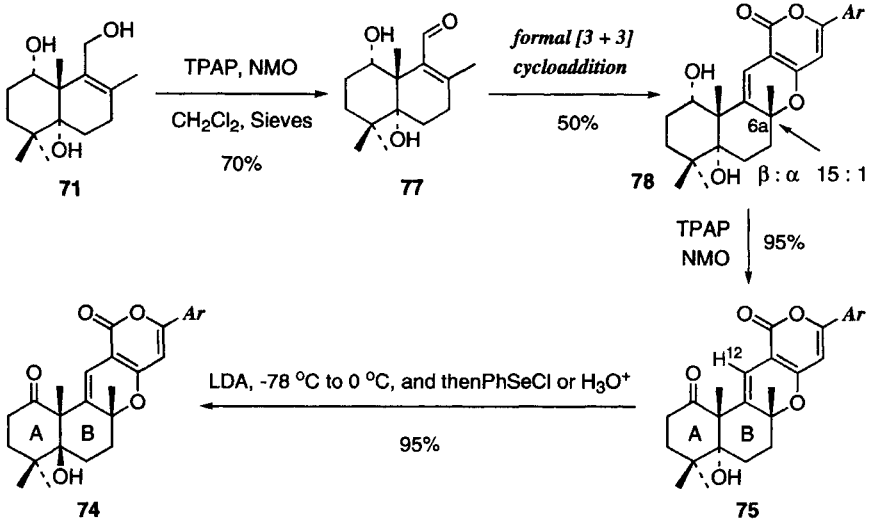
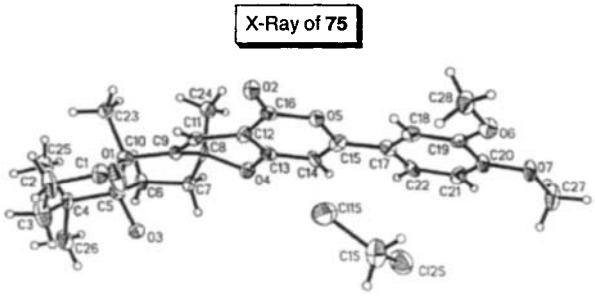


FIGURE 6



To avoid this unexpected *retro-aldol-aldol* predicament, the desired pentacycle **75** was prepared via yet another route. As shown in Scheme 17, the triol **71** was oxidized using Ley's TPAP oxidation without protecting

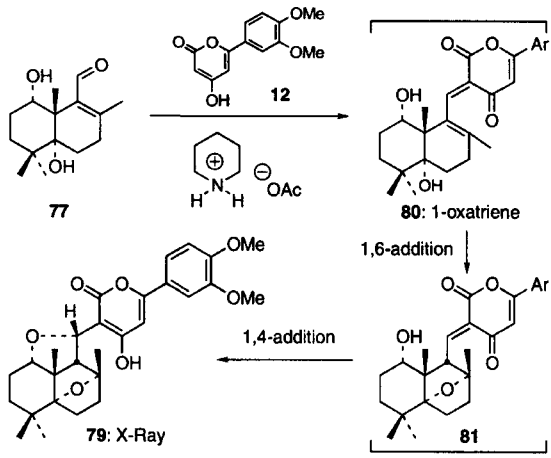
either the C1- or C4a-hydroxyl group to give enal **77** in 70% yield. This chemoselectivity likely was a result of a shorter reaction time in favor of the more reactive primary allylic alcohol. Enal **77** surprisingly did not lactolize right away unless it was subjected to elevated temperatures or acidic conditions, in which case it also decomposed.

Reaction of enal **77** with **12** under the standard [3 + 3] conditions led to the desired pentacyle **78** essentially as a single diastereomer with an improved 50% yield. Subsequent oxidation of **78** using Ley's TPAP afforded the pentacycle **75** in 95% yield. The relative stereochemistry was unambiguously confirmed using X-ray analysis [Figure 6]. The X-ray structure of **75** also explains the unusually downfield shifted olefinic ^{1}H in the C-ring [7.43 ppm], whereas the same olefinic ^{1}H in **74** is at the expected region [6.09 ppm]. The ^{1}H in **75** experiences a diamagnetic anisotropic effect due to its close proximity to the A-ring carbonyl oxygen.

When the pentacyle **75** was treated with 2.0 equiv of LDA followed by addition of PhSeCl, **75** was found to have isomerized completely to the pentacycle **74** likely via a similar *retro-aldol-aldol* sequence [Scheme 17]. The propensity of **75** to epimerize to **74** back to implies that **74** could actually be the thermodynamically more stable structure.

Finally, we isolated hexacycle **79** from reaction of enal **77** with pyrone **12** using piperidinium acetate salt [Scheme 18]. Although hexacycle **79** was found as a minor product initially when the reaction was terminated in 2 h, the yield of **79** could be as high as 60-70% if the reaction time for was extended to 18-24 h.

SCHEME 18

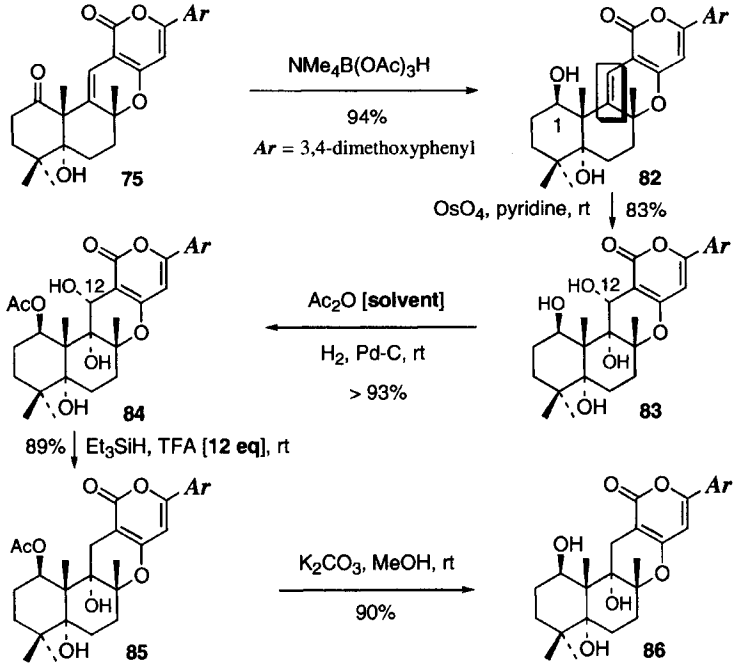


The unambiguous assignment of **79** via X-ray structural analysis suggests the formation of the 1-oxatriene intermediate **80**. Two consecutive intramolecular trappings of **80** by the two hydroxyl groups in 1,6- and 1,4-additions should lead to **79** through the initial intermediate **81**. Given that hexacycle **79** was formed as a single diastereomer, it is also very reasonable to suggest that the stereochemical predisposition of two hydroxyl groups in **80** controls the stereochemical outcome of the two conjugate additions.

VIII. Commencement of the Synthesis of (±)-Arisugacin A

Advanced pentacycles **75** and **78** provided new opportunities in achieving a total synthesis of (±)-arisugacin A [**1**]. However, attempts at oxidizing the C-ring olefin in **78** using various protocols all failed. These failures suggest that the stereochemistry of the C1-OH group likely plays a significant role sterically.

SCHEME 19

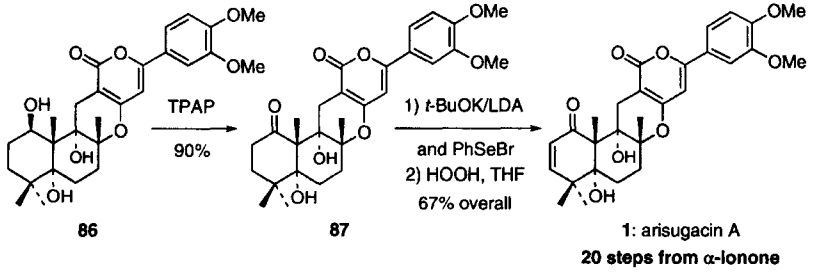


Given our earlier success in epoxidizing the epoxy pentacycle **67** having the β-C1-OH [see Scheme 14], the pentacycle **75** was subjected to directed reduction using $NMe_4B(OAc)_3H$ in AcOH to give exclusively diol **82** in 94% yield with β-C1-OH [Scheme 19].[61]

Dihydroxylation[60] of **82** using a stoichiometric amount of OsO_4 in pyridine gave the desired tetraol **83** in 83% yield as a single diastereomer. The removal of the C12-OH in **83** using the Et_3SiH protocol[60] gave an undesired hexacycle structurally similar to **68**.[63,64] Hydrogenation of **83** using Ac_2O as solvent[60] gave instead triol acetate **84** in > 93% yield, suggesting that acylation of the C1-OH had taken place. Triol acetate **84** could also be obtained quantitatively using Ac_2O and DMAP, providing exclusive acylation at the β-C1-OH.

Subsequent removal of the C12-OH in **84** using Et_3SiH and 12 equiv of TFA gave **85** in 89% yield.[60] The reductive cleavage was selective for the more reactive allylic C-12 hydroxyl group. Such chemoselectivity is also likely due to the assistance from the pyranyl oxygen atom, for the C-12 hydroxyl group is essentially situated in the gamma position of an enol-ether. Deacylation of **85** gave the desired triol **86** in 90% yield.

SCHEME 20



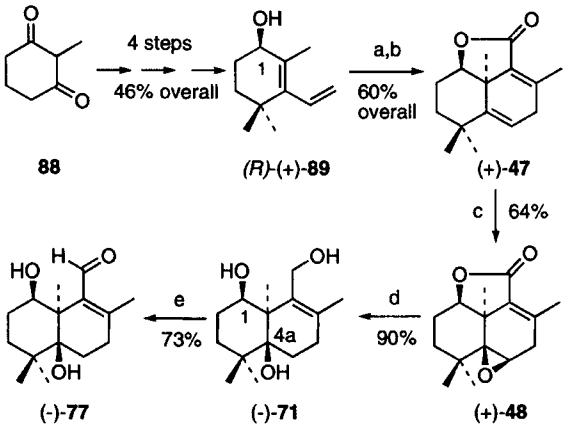
Ley's TPAP oxidation of triol **86** led to the pentacycle **87** in 90% yield [Scheme 20]. To circumvent the *retro-aldol-aldol* that was observed earlier for **75** under kinetic conditions [Scheme 17], protocols using DDQ and IBX[65] were examined to install the double bond in the A-ring but were not successful. Schlosser's base, prepared by deprotonating diisopropylamine with *n*-BuLi in the presence of KO*t*-Bu, proved to be effective in the selenation using PhSeBr. This outcome is presumably due to some countercation effect since LDA or KHMDS did not work well. Subsequent oxidative elimination of the selenide intermediate using H_2O_2 led to (±)-arisugacin A [**1**] in 67% yield for the two steps.[66,67]

The synthetic sample matched spectroscopically [co-spectra of ^{1}H NMR in pyridine-d_5] and analytically [TLC: in 2:1 EtOAc : hexane; 2:1 ether : hexane; 1:9 acetone : $CHCl_3$] with the natural (+)-arisugacin A.

IX. An Enantioselective Synthesis of (-)-Arisugacin A

To achieve synthesis of (-)-arisugacin A [**1**], *(R)*-**89** was obtained readily from 2-methyl-1,3-cyclohexanedione **88** in 4 steps with an overall yield of 46%, featuring vinylogous ester formation, Stork-Danheiser double alpha methylation,[52,68,69] vinyl Grignard addition followed by acidic work-up,[68] and an asymmetric CBS reduction [Scheme 21].[70,71]

SCHEME 21

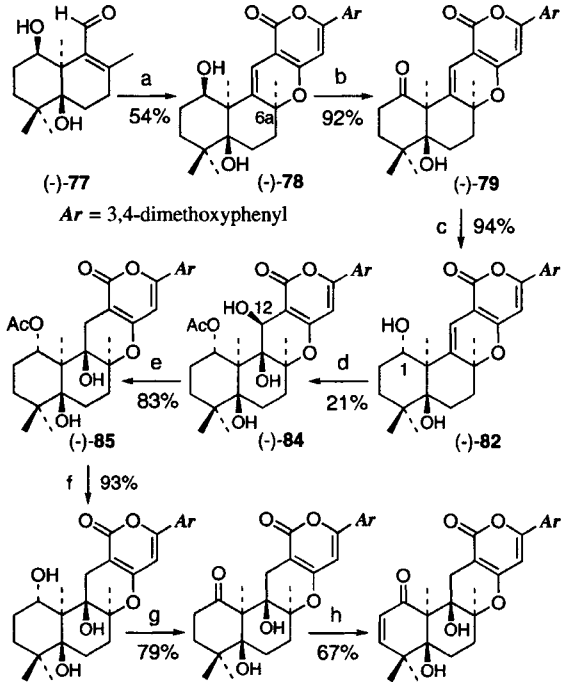


The level of enantiomeric excess [*ee*] for *(R)*-**89** was found to be in the range of 85-95% using ^{1}H NMR ratios of corresponding diastereomeric naproxen esters. By comparing with optical rotation of the known *(S)*-**89** [$[\alpha]^{23}_D$ = - 53.0° (c 1.0, $CHCl_3$)] with an *ee* >90% [confirmed by Mosher's esters],[71a] optical rotation of *(R)*-**89** [$[\alpha]^{23}_D$ = + 53.2 ° (c 1.0, $CHCl_3$)] also confirms its level of *ee* and absolute configuration at C1.

DCC/DMAP mediated esterification of 2-butynoic acid using (+)-*(R)*-**89** followed by intramolecular Diels-Alder cycloaddition of the resulting ester in refluxing *n*-decane [conc. 0.07 *M*] provided the tricyclic lactone (+)-**47** in 60% overall yield [Scheme 21]. Epoxidation of (+)-**47** using *m*-CPBA led to β-epoxy lactone (+)-**48** in 64% yield. The β-epoxy lactone (+)-**48** is highly crystalline, unlike the racemic form.

Subsequent recrystallization using 1:1 mixture of EtOAc and hexane provided (+)-**48** with >97% *ee*. A successful one-pot reduction of (+)-**48** using AlH_3 carefully generated *in situ*[72] gave triol (-)-**71** in 90% yield. Ley's TPAP oxidation of triol (-)-**71**, without protecting either the C1- or C4a-hydroxyl group, afforded enal (-)-**77** in 73% yield, although some lactolization of (-)-**77** was observed at higher temperatures or in acidic media.

SCHEME 22



a) 0.5 equiv *L*-proline, THF, 65 °C, 1.5 equiv of **12**.
b) 5 mol% TPAP, 1.4 equiv NMO, CH_2Cl_2, 3 h.
c) $NMe_4BH(OAc)_3$, AcOH, rt, 30 min.
d) 20 equiv CH_3CO_3H, pH 7 buffer, CH_2Cl_2, rt.
e) Et_3SiH, TFA , CH_2Cl_2, rt, 4h.
f) K_2CO_3, MeOH, rt, 2 h.
g) 5 mol% TPAP, 1.4 equiv NMO, CH_2Cl_2, 3 h.
h) i. LDA, KO*t*-Bu, HMPA, THF, -78 °C, PhSeBr; ii. 10 equiv H_2O_2, AcOH, THF, 0 °C to rt, 1.5 h.

The key formal [3 + 3] cycloaddition reaction of enal (-)-**77** with the pyrone **12** under the standard conditions[20,35-38] using *L*-proline as the initiator for the formation of the iminium salt led to the desired pentacycle (-)-**78** in 54% yield a single diastereomer [Scheme 22]. To render *L*-proline useful in the iminium formation, solubility was an issue,[53] and thus, THF was used in place of EtOAc, the solvent most frequently used in our previous studies.[37] Subsequent TPAP oxidation of (-)-**78** led to keto pentacycle (-)-**79** in 92% yield, and a directed reduction of (-)-**79** using $NMe_4BH(OAc)_3$ in AcOH gave exclusively the diol pentacycle (-)-**82** in 94% yield with β-C1-OH.

Dihydroxylation[60] of (-)-**82** in pyridine, a protocol used for our racemic synthesis was found to be difficult here mainly due to problems in the isolation of the tetraol product. We elected to go with the epoxidation protocol[60] using various peroxy acetic acids, and the best result gave (-)-**84** in 21% yield in addition to a hexacycle in 28% yield.[63,64]

Subsequent removal of the C12 hydroxyl group in (-)-**84** using Et_3SiH and TFA[60] gave diol acetate pentacycle (-)-**85** in 83% yield. Deacylation of (-)-**85** followed by TPAP oxidation of triol (-)-**86** gave pentacycle (-)-**87** in 73% overall yield. Schlosser's base was again effective in the selenation, and subsequent oxidative elimination of the selenide using H_2O_2 afforded in 67% overall yield (-)-arisugacin A [**1**] that matched spectroscopically with natural and racemic samples.[73]

The optical rotation of synthetic (-)-arisugacin A [**1**] $[[\alpha]^{23}_D = -79.0^\circ$ (c 0.1, $CHCl_3)]$ confirms the originally assigned absolute configuration for the natural (+)-arisugacin A $[[\alpha]^{23}_D = +72.0^\circ$ (c 0.1, $CHCl_3)]$.

X. Conclusions

We have described here our struggle and success in achieving a 20-step total synthesis of (±)-arisugacin A with an overall yield of 2.1%, and a slightly modified 17-step total synthesis of (-)-arisugacin A with an overall yield of 4.3%. This synthesis features a formal [3 + 3] cycloaddition reaction of α,β-unsaturated iminium salts with 6-aryl-4-hydroxy-2-pyrones that involves a highly stereoselective 6π–electron electrocyclic ring-closure of 1-oxatriene. This methodology proves to be useful in syntheses of other natural products.

A strategic dihydroxylation-deoxygenation protocol leading to the desired angular C12a-OH was developed to serve as a critical step in the final total synthesis of arisugacin A. Our synthetic endeavor also led to an interesting observation of an unexpected retro-aldol-aldol sequence in the AB-ring. The enantioselective synthesis features a CBS asymmetric reduction and confirms the absolute configuration of the natural (+)-arisugacin A.

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References and Footnotes

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1. a) Õmura, S., Kuno, F., Otoguro, K., Sunazuka, T., Shiomi, K., Masuma, R., Iwai, Y., *J. Antibiotics* **1995**, *48*, 745. b) Kuno, F., Otoguro, K., Shiomi, K., Iwai, Y., Õmura, S., *J. Antibiotics* **1996**, *49*, 742. c) Otoguro, K., Kuno, F., Õmura, S., *Pharmacol. Ther.***1997**, *76*, 45. e) Otoguro, K., Shiomi, K., Yamaguchi, Y., Arai, N., Sunazuka, T., Masuma, R., Iwai, Y., Õmura, S., *J. Antibiotics* **2000**, *53*, 50.
2. John, V.; Lieberburg, I.; Thorsett, E. D. in *Annual Rep. Med. Chem.* Academic Press, INC.: Orlando, **1993**, *Vol. 28*, 197.
3. Alzheimer, A., *Gesamte Psychiatrie* **1907**, *64*, 1264.
4. a) Ling, K. H., Yang, C.-K., Peng, F.-T., *Appl. Environ. Micobiol.* **1979**, *37*, 355. b) Hseu, T. H., Yang, C.-K., Ling, K. H., Wang, C. J., Tang, C. P., *Cryst. Struct. Commun.* **1982**, *11*, 199.
5. a) Tomoda, H., Tabata, N., Yang, D. J., Namatame, I., Tanaka, H., Õmura, S., Kaneko, T., *J. Antibiotics* **1996**, *49*, 292. b) Nagamitsu, T., Sunazuka, T., Obata, R., Tomoda, H., Tanaka, H., Harigaya, Y., Õmura, S., Smith, A. B. III, *J. Org. Chem.* **1995**, *60*, 8126. c) Parker, K. A., Resnick, L., *J. Org. Chem.* **1995**, *60*, 5726.
6. For a review article on therapeutic treatment of Alzheimer's Disease see: Giacobini, E.; Becker, R. "*Alzheimer's Disease: From Molecular Biology to Therapy.*" Birkhauser: Boston, **1997**.
7. For a lead reference on Cholinergic Hypothesis see: Perry, E. K., *Brit. Med. Bullet.* **1986**, *42*, 63.
8. For ***tacrine***, see: Summers, W. K., Majovski, L. V., Marsh, G. M., Tachiki, K., Kling, A., *N. Engl. J. Med.* **1986**, *315*, 1241.
9. For ***aricept***, see: Inoue, A., Kawai, T., Wakita, M., Iimura, Y., Sugimoto, H., Kawakami, Y., *J. Med. Chem.* **1996**, *39*, 4460.
10. For total syntheses of ***huperzine A*** see: a) Kozikowski, A. P., Campiani, G., Nacci, V., Sega, A., Saxena, A., Doctor, B. P., *J. Chem. Soc., Perkin Trans. I***1996**, 1287. b) Xia, Y., Kozikowski, A. P., *J. Am. Chem. Soc.* **1989**, *111*, 4116. c) Qian, L., Ji, R., *Tetrahedron Lett.* **1989**, *30*, 2089.
11. For ***physostigmine***, see: Davis, K. L., Mohs, R. C., Tinklenberg, J. R., *N. Engl. J. Med.* **1979**, *301*, 946.

12. For ***galanthamine***, see: Fulton, B., Benfield, P., *Drugs and Aging* **1996**, 60.
13. Summers, W. K., Koehler, A. L., Marsh, G. M., Tachiki, K., Kling, A., *Lancet* **1989**, 729.
14. For leading references on ***forsklin***, see: a) Corey, E. J., Jardine, P. D. S., Rohloff, J. C., *J. Am. Chem. Soc.* **1988**, *110*, 3672. b) Jenkins, P. R., Menear, K. A., Barraclough, P., Nobbs, M. S., *J. Chem. Soc. Chem. Comm* **1984**, 1423. c) Nicolaou, K. C., Li, W. S., *J. Chem. Soc., Chem. Comm.* **1985**, 421. d) Ziegler, F. E., Jaynes, B. H., Saindane, M. T., *J. Am. Chem. Soc.* **1987**, *109*, 8115.
15. For a recent review, see: Ghosh, C. K., Ghosh, C., *Indian J. Chem.* **1997**, 968.
16. a) Cremins, P. J., Saengchantara, S. T., Wallace, T. W., *Tetrahedron* **1987**, *13*, 3075. 3-Mentholoxycarbonylchromone was successful in some asymmetric [4 + 2] cycloadditions, see: b) Ohkata, K., Kubo, T., Miyamoto, K., Ono, M., Yamamoto, J., Akiba, K. *Heterocycles* **1994**, *38*, 1483. For an example of 3-acylchromone functioning as a dienophile in a dimerization process, see: c) Ghosh, C. K., Bhattacharyya, A., Bandyopadhyay, C., *J. Chem. Soc., Chem. Comm.* **1984**, 1319.
17. Groundwater, P. W., Hibbs, D. E., Hursthouse, M. B., Nyerges, M., *J. Chem. Soc., Perkin Trans. I* **1997**, 163, and see reference 3 cited within.
18. Sain, B., Prajapati, D., Mahajan, A. R., Sandhu, J. S., *Bull. Soc. Chim. Fr.***1994**, *131*, 313.
19. a) White, J. D., Kim, N.-S., Hill, D. E., Thomas, J. A., *Synthesis* **1998**, 619. b) Chen, D., Wang, J., Totah, N. I., *J. Org. Chem.* **1999**, *64*, 1776. c) Seth, P. P., Totah, N. I., *J. Org. Chem.* **1999**, *64*, 8750. d) Seth, P. P., Totah, N. I., *Org. Lett.* **1999**, *1*, 1411.
20. For a review in this area, see, Hsung, R. P., Wei, L.-L., Sklenicka, H. M., Shen, H. C., McLaughlin, M. J., Zehnder, L. R., in *Trends in Heterocyclic Chemistry.* **2001**, *7*, p1-24.
21. a) Ikawa, M., Stahmann, M. A., Link, K. P., *J. Am. Chem. Soc.* **1944**, *66*, 902. b) Seidman, M., Robertson, D. N., Link, K. P., *J. Am. Chem. Soc.* **1950**, *72*, 5193. c) Seidman, M., Link, K. P., *J. Am. Chem. Soc.* **1952**, *74*, 1885.
22. a) de March, P., Moreno-Mañas, M., Casado, J., Pleixats, R., Roca, J. L., Trius, A., *J. Heterocycl. Chem* **1984**, *21*, 1369. b) de March, P., Moreno-Mañas, M., Casado, J., Pleixats, R., Roca, J. L., *J. Heterocycl. Chem.* **1984**, *21*, 85.
23. For leading references on electrocyclic ring-closures involving 1-oxatrienes see: a) Kametani, T., Kajiwara, M., Fukumoto, K., *Tetrahedron* **1974**, *30*, 1053. b) Shishido, K., Ito, M., Shimada, S.-I., Fukumoto, K., Kametani, T., *Chem. Lett.* **1984**,1943. c) Shishido, K., Shitara, E., Fukumoto, K., *J. Am. Chem. Soc.* **1985**, *107*, 5810. d) Shishido, K., Hiroya, K., Fukumoto, K., Kametani, T., *Tetrahedron Lett.* **1986**, *27*, 971.
24. For recent reviews on step-wise [3 + 3] formal cycloadditions leading to bridged carbocycles, pyridines or pyridones using enamines, enaminones, enol ethers, or β-

ketoesters see: a) Filippini, M.-H., Rodriguez, J., *Chem. Rev.* **1999**, *99*, 27. b) Rappoport, Z. "*The Chemistry of Enamines in The Chemistry of Functional Groups.*" John Wiley and Sons, New York, **1994**. c) Filippini, M.-H., Faure, R., Rodriguez, J., *J. Org. Chem.* **1995**, *60*, 6872, and see references 21-33 cited therein.

25. a) Seebach, D., Missbach, M., Calderari, G., Eberle, M., *J. Am. Chem. Soc.* **1990**, *112*, 7625. b) Landesman, H. K., Stork, G., *J. Am. Chem. Soc.* **1956**, *78*, 5129. c) Hendrickson, J. B., Boeckman, R. K. Jr., *J. Am. Chem. Soc.* **1971**, *93*, 1307. d) Alexakis, A., Chapdelaine, M. J., Posner, G. H., *Tetrahedron Lett.***1978**, *19*, 4209.
26. a) Tietze, L. F., Beifuss, U., *Angew. Chem., Int. Ed. Engl.***1993**, *32*, 131. b) Tietze, L. F., *J. Heterocycl. Chem.* **1990**, *27*, 47.
27. For **phomactin A**, see: a) Sugano, M., Sato, A., Iijima, Y., Oshima, T., Furuya, K., Kuwano, H., Hata, T., Hanzawa, H., *J. Am. Chem. Soc.* **1991**, *113*, 5463. b) Sugano, M., Sato, A., Iijima, Y., Furuya, K., Haruyama, H., Yoda, K., Hata, T., *J. Org. Chem.* **1994**, *59*, 564. c) Sugano, M., Sato, A., Iijima, Y., Furuya, K., Kuwano, H., Hata, T., *J. Antibiot.* **1995**, *48*, 1188.
28. a) Miyaoka, H., Saka, Y., Miura, S., Yamada, Y., *Tetrahedron Lett.* **1996**, *37*, 7107. b) Foote, K. M., Hayes, C. J., Pattenden, G., *Tetrahedron Lett.* **1996**, *37*, 275. c) Foote, K. M., John, M., Pattenden, G., *Synlett.* **2001**, 365. d) Kallan, N. C., Halcomb, R. L., *Org. Lett.* **2000**, *2*, 2687. e) Mogr, P. J., Halcomb, R. L., *Org. Lett.* **2002**, *4*, 2413. f) Seth, P. P., Totah, N. I., *Org. Lett.* **2000**, *2*, 2507. g) Mi, B., Maleczka, R. E., Jr. *Org. Lett.* **2001**, *3*, 1491. h) Chemler, S. R., Iserloh, U., Daneshefsky, S. J., *Org. Lett.* **2001**, *3*, 2949. i) Houghton, T. J., Choi, S., Rawal, V. H., *Org. Lett.* **2001**, *3*, 3615. j) Balnaves, A. S., McGowan, G., Shapland, P. D. P., Thomas, E. J., *Tetrahedron Lett.* **2003**, *44*, 2713.
29. For total syntheses of phomactin A, see: a) Goldring, W. P. D., Pattenden, G., *Chem. Commun* **2002**, 1736. b) Mohr, P. J., Halcomb, R. L., *J. Am. Chem. Soc.* **2003**, *125*, 1712.
30. For isolations of **penostatins**, see: a) Takahashi, C., Numata, A., Yamada, T., Minoura, K., Enmoto, K., Nakai, M., Matsuda, C., Nomoto. K., *Tetrahedron Lett.* **1996**, *37*, 655. For synthesis, see: b) Snider, B. B., Liu, T., *J. Org. Chem.* **2000**, *65*, 8490.
31. For isolation of **rhododaurichromanic acids**: Kashiwada, Y., Yamzaki, K., Ikeshiro, Y., Yamagishi, T., Fujioko, T., Mihashi, K., Mizuki, K., Cosentino, L. M., Fowke, K., Morris-Natschke, S. L., Lee, K.-H., *Tetrahedron* **2001**, *57*, 1559.
32. a) Shu, Y.-Z., Ye, Q., Li, H., Kadow, K. F., Hussain, R. A., Huang, S., Gustavson, D. R., Lowe, S. E., Chang, L. P., Pirnik, D. M., Kodukula, K., *Bioorg. Med. Chem. Lett.* **1997**, *17*, 2295. b) Organ, M. G., Bratovanov, S., *Tetrahedron Lett.* **2000**, *41*, 6945. c) Organ, M. G., Bilokin, Y. V., Bratovanov, S., *J. Org. Chem.* **2002**, *67*, 5176.

33. Jonassohn, M., Sterner, O., Anke, H., *Tetrahedron* **1996**, *52*, 1473.
34. Hua, D. H., Chen, Y., Sin, H.-S., Maroto, M. J., Robinson, P. D., Newell, S. W.,; Perchellet, E. M., Ladesich, J. B., Freeman, J. A., Perchellet, J.-P., Chiang, P. K., *J. Org. Chem.* **1997**, *62*, 6888.
35. For our preliminary communications on the formal [3 + 3] cycloaddition approach to arisugacin A, see: a) Shen, H. C., Degen, S. J., Mulder, J. A., Hsung, R. P., Douglas C. J., Golding, G. M., Johnson, E. W., Mathias, D. S., Morgan, C. D., Mueller, K. L., Shih, R. A., Abstract No. ORGN-664, 216th ACS National Meeting, Boston, MA, Fall, **1998**. b) Hsung, R. P., Shen, H. C., Douglas, C. J., Morgan, C. D., Degen, S. J., Yao, L. J., *J. Org. Chem.* **1999**, *64*, 690.
36. McLaughlin, M. J., Shen, H. C., Hsung, R. P., *Tetrahedron Lett* **2001**, *42*, 609.
37. Shen, H. C., Wang, J., Cole, K. P., McLaughlin, M. J., Morgan, C. D., Douglas, C. J., Hsung, R. P., Coverdale, H. A., Gerasyuto, A. I., Hahn, J. M., Liu, J., Wei, L.-L., Sklenicka, H. M., Zehnder, L. R., Zificsak, C. A., *J. Org. Chem.* **2003**. *68*,1729.
38. For our first natural product synthesis employing this methodology, see: McLaughlin, M. J., Hsung, R. P., *J. Org. Chem.* **2001**, *66*, 1049.
39. Cravotto, G., Nano, G. M., Tagliapietra, S., *Synthesis*, **2001**, 49.
40. For aza-[3 + 3] cycloaddition reaction using vinylogous amides, see: Hsung, R. P., Wei, L.-L., Sklenicka, H. M., Douglas, C. J., McLaughlin, M. J., Mulder, J. A., Yao, L. J., *Org. Lett.* **1999**, *1*, 509.
41. For stereoselective aza-[3 + 3] cycloaddition, see: a) Sklenicka, H. M., Hsung, R. P., McLaughlin, M. J., Wei, L.-L., Gerasyuto, A. I., Brennessel, W. W., *J. Am. Chem. Soc.* **2002**, *124*, 10435. b) Sklenicka, H. M., Hsung, R. P., Wei, L.-L., McLaughlin, M. J., Gerasyuto, A. I., Degen, S. J., Mulder, J. A., *Org. Lett.* **2000**, *2*, 1161.
42. For intramolecular formal aza-[3 + 3] cyclcoaddition, see: Wei, L.-L., Sklenicka, H. M., Gerasyuto, A. I., Hsung, R. P., *Angew. Chem. Int. Ed.* **2001**, *40*, 1516.
43. For natural product synthesis, see: McLaughlin, M. J., Hsung, R. P., Cole, K. C., Hahn, J. M., Wang, J., *Org. Lett.* **2002**, *4*, 2017.
44. For other efforts in this area, see: a) Hedley, S. J., Moran, W. J., Price, D. A., Harrity, J. P. A., *J. Org. Chem.* **2003**, *68*, 4286. b) Chang, M.-Y., Lin, J. Y.-C., Chen, S. T., Chang, N.-C., *J. Chin. Chem. Soc.* **2002**, *49*, 1079. c) Hedley, S. J., Moran, W. J., Prenzel, A. H. G. P., Price, D. A., Harrity, J. P. A., *Synlett* **2001**, 1596. d) Jabin, I., Revial, G., Monnier-Benoit, N., Netchitailo, P., *J. Org. Chem.* **2001**, *66*, 256. e) Hua, D. H., Chen, Y., Sin, H.-S., Robinson, P. D., Meyers, C. Y., Perchellet, E. M., Perchellet, J.-P., Chiang, P. K., Biellmann, J.-P., *Acta Cryst.* **1999**,*C55*,1698. f) Benovsky, P., Stephenson, G. A., Stille, J. R., *J. Am. Chem. Soc.* **1998**, *120*, 2493. g) Heber, D., Berghaus, Th., *J. Heterocycl. Chem.***1994**,*31*,1353.

45. For leading references on electrocyclic ring-closures involving 1-azatrienes, see: a) Maynard, D. F., Okamura, W. H., *J. Org. Chem* **1995**, *60*, 1763. b) de Lera, A. R., Reischl, W., Okamura, W. H., *J. Am. Chem. Soc.* **1989**, *111*, 4501. For an earlier account, see: c) Oppolzer, V. W., *Angew. Chem.* **1972**, 22, 1108.

46. For a recent account similar to Okamura's work, see: a) Tanaka, K., Mori, H., Yamamoto, M., Katsumura, S., *J. Org. Chem.* **2001**, *66*, 3099. For their account on stereoselective ring closure, see: b) Tanaka, K., Katsumura, S., *J. Am. Chem. Soc.* **2002**, *124*, 9660.

47. a) Hsung, R. P., *J. Org. Chem.* **1997**, *62*, 7904. b) Hsung, R. P., *Heterocycles* **1998**, *48*, 421.

48. Degen, S. J., Mueller, K. L., Shen, H. C., Mulder, J. A., Golding, G. M., Wei, L.-L., Zificsak, C. A., Neeno-Eckwall, A., Hsung, R. P., *Bioorg. Med. Chem. Lett.* **1999**, 973.

49. Granum, K. A., Merkel, G., Mulder, J. A., Debbins, S. A., Hsung, R. P., *Tetrahedron Lett.***1998**, *39*, 9597.

50. Hsung R. P., Zificsak, C. A., Wei, L.-L., Zehnder, L. R., Park, F., Kim, M., Tran, T. T.-T., *J. Org. Chem.* **1999**, *64*, 8736.

51. 3-Acylchromones can undergo efficient inverse demand [4+2] cycloadditions with electron rich olefins. For a leading reference see: Wallace, T. W., Wardell, I., Li, K.-D., Leeming, P., Redhouse, A. D., Chanlland, S. R., *J. Chem. Soc., Perkin Trans. I* **1995**, 2293, and references cited within.

52. Delpech, B., Calvo, D., Lett, R., *Tetrahedron Lett.* **1996**, *37*, 1015.

53. These reactions are best carried out in toluene and/or EtOAc using piperidine/Ac_2O, or piperidinium salts as well as other amine salts. Hydrochloride salts tend to be even more reactive. *L*-Proline does not work well for this reaction contrary to other literature accounts, especially in EtOAc.

54. a) Overman, L. E., Rabinowitz, M. H., *J. Org. Chem.* **1993**, *58*, 3235. b) Overman, L. E., Rabinowitz, M. H., Renhowe, P. A., *J. Am. Chem. Soc.* **1995**, *117*, 2657.

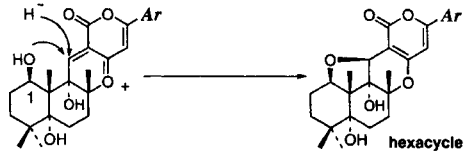
55. For our formal [3 + 3] cycloaddition approach to arisugacin A, see: Zehnder, L. R., Hsung, R. P., Wang, J.-S., Golding, G. M., *Angew. Chem. Int. Ed.* **2000**, *39*, 3876.

56. For Ōmura's independently reported epoxy diol approach, see: Handa, M., Sunazuka, T., Nagai, K., Kimura, R., Shirahata, T., Tian, Z. M., Otoguro, K., Harigaya, Y., Ōmura, S., *J. Antibiotics* **2001**, *54*, 382.

57. Douglas C. J., Sklenicka, H. M., Shen, H. C., Golding, G. M., Mathias, D. S., Degen, S. J., Morgan, C. D., Shih, R. A., Mueller, K. L., Seurer, L. M., Johnson, E. W., Hsung, R. P., *Tetrahedron* **1999**, *55*, 13683.

58. Zehnder, L. R., Dahl, J. W., Hsung, R. P., *Tetrahedron Lett.* **2000**, *41*, 1901.

59. For a preliminary communication on this problem and our solution, see: Zehnder, L. R., Hsung, R. P., Wang, J., Abstract No. ORGN-51, 220th ACS Nationa Meeting, Washington D.C., Spring, **2000**.
60. Zehnder, L. R., Wei, L.-L., Hsung, R. P., Cole, K. P., McLaughlin, M. J., Shen, H. C., Sklenicka, H. M., Wang, J., Zificsak, C. A., *Org. Lett.* **2001**, *3*, 2141.
61. For a preliminary communication on these results, see: Cole, K. P., Zehnder, L. T., Wei, L.-L., Wang, J., Hsung, R. P., Abstract No. ORGN-178, 222nd ACS National Meeting, Chicago, IL, Fall, **2001**.
62. Wang, J., Cole, K. P., Wei, L. L., Zehnder, L. R., Hsung, R. P., *Tetrahedron Lett.* **2002**, *43*, 3337.
63. When using various peroxyacids, the best result gave the tentatively assigned hexacycle [Reference 28] as the major product in 28% yield with the desired product in only 21% yield.
64. The hexacycle was likely a result of intramolecular trapping of the incipient oxocarbenium intermediate by the C1-OH.



65. Nicolaou, K. C., Zhong, Y.-L., Baran, P. S., *J. Am. Chem. Soc.* **2000**, *122*, 7596
66. Cole, K. P., Hsung, R. P., Yang, X.-F., *Tetrahedron Lett.* **2002**, *43*, 3341.
67. For Õmura's eventual total synthesis of (±)-arisugacin A, see: Sunazuka, T., Handa, M., Nagai, K., Shirahata, T., Harigaya, Y., Otoguro, K., Kuwajima, I., Õmura, S., *Org. Lett.* **2002**, *4*, 367.
68. Stork, G., Danheiser, R. L., *J. Org. Chem.* **1973**, *38*, 1775.
69. Calvo, D., Port, M., Delpech, B., Lett, R., *Tetrahedron Lett.* **1996**, *37*, 1023.
70. a) Corey, E. J., Bakshi, R. K., Shibata, S., *J. Am. Chem. Soc.* **1987**, *109*, 5551. b) Corey, E. J., Bakshi, R. K., Shibata, S., *J. Am. Chem. Soc.* **1987**, *109*, 7925. c) Corey, E. J., Shibata, S., Bakshi, R. K., *J. Org. Chem.* **1988**, *53*, 2861.
71. a) Corey, E. J., Jardine, P. D. S., T. Mohri., *Tetrahedron Lett.* **1988**, *29*, 6409. b) Corey, E. J., Jardine, P. D. S., *Tetrahedron Lett.* **1989**, *30*, 7297. c) Corey, E. J., Bakshi, R. K., *Tetrahedron Lett.* **1990**, *31*, 611. d) Corey, E. J., Link, J. O., *Tetrahedron Lett.* **1992**, *33*, 4141.
72. Andrejevic, V., Bjelakovic, M., Mihailovic, M. M., Mihailovic, M. L., *Helv. Chim. Acta.*, **1985**, *68*, 2030.
73. Cole, K. P.; Hsung, R. P. *Tetrahedron Lett.* **2002**, *43*, 8791.

STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 4

TOTAL SYNTHESIS OF KAINOIDS BY DEAROMATIZING ANIONIC CYCLIZATION

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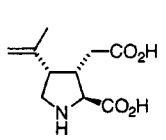
I. Introduction: the discovery of the dearomatising cyclisation

Our work on the kainoids (Scheme 1) was prompted not by their interesting biological activity and structure,[1] nor primarily by the fact that as synthetic challenges for a starting academic they appear to be an achievable target, but by a combination of two chance observations during 1994-5, my first year as a lecturer in Manchester. The first was made by my first undergraduate project student, who was trying some ortholithiation chemistry with the chiral amide **4**, hoping for some atroposelectivity.[2] In the event, the conditions we chose gave only 20% of 1:1 mixture of **5a** and **5b**. The major product from the reaction was the remarkable tricyclic lactam **6** (Scheme 2).[3]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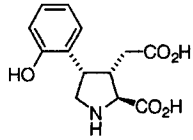
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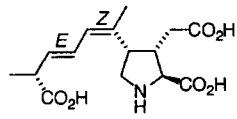
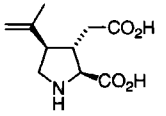
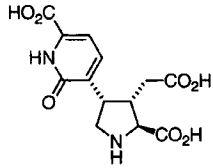

(–)-domoic acid **3**


(+)-α-allokainic acid **1a**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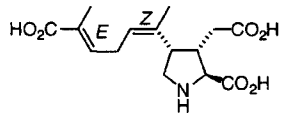
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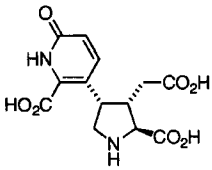
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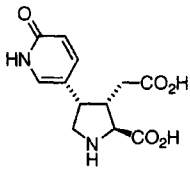
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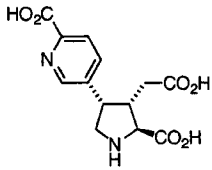
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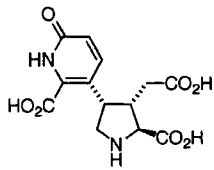
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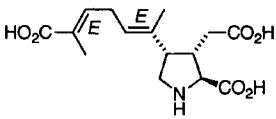
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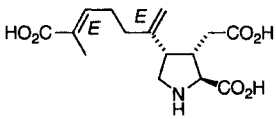
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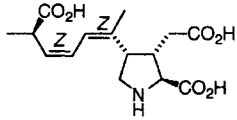
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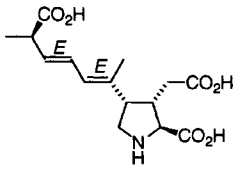
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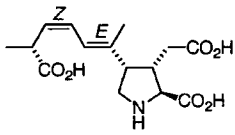
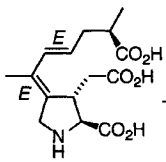
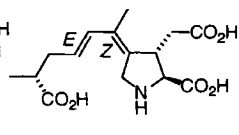
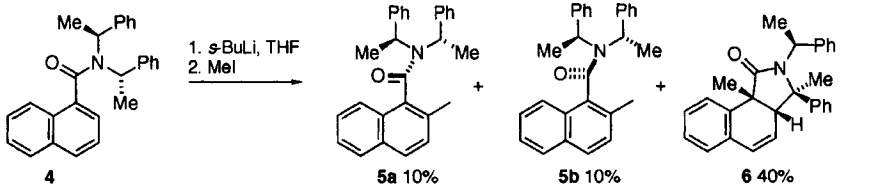

isodomoic acid F **3f**


isodomoic acid G **3g**

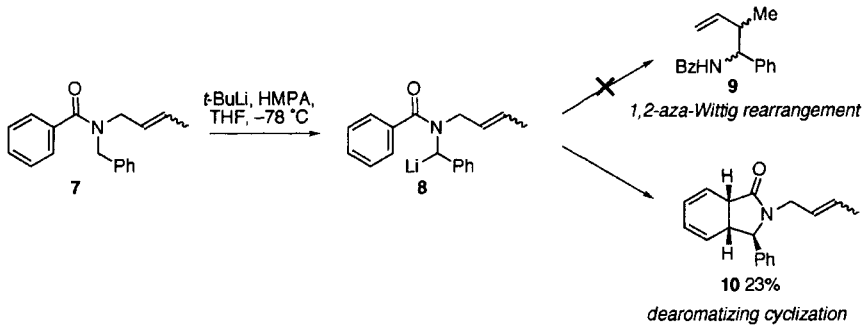

isodomoic acid H **3h**

SCHEME 1



SCHEME 2

The second observation was made by a graduate student with another research group in the Department of Chemistry at Manchester, who had been developing a [2,3]-aza-Wittig rearrangement, and whose PhD thesis gave me my first experience of the role of an examiner. She had tried to rearrange the lithiated amide **8** to **9** by treating amide **7** with *t*-BuLi in the presence of HMPA at –78 °C, and had isolated, in 23% yield, a by-product which had clearly lost aromaticity in the aromatic ring and which turned out to be **10** (Scheme 3).[4]



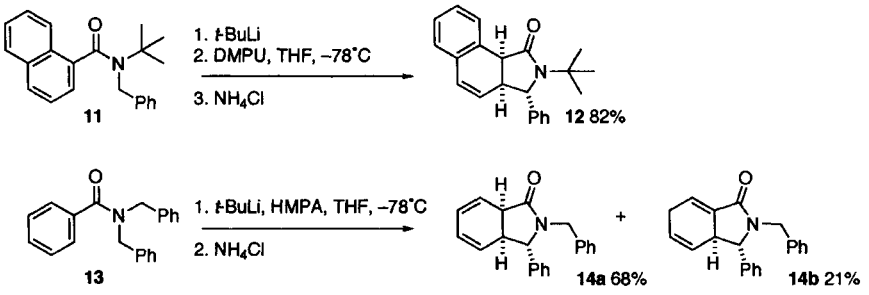
SCHEME 3

It soon became clear that both observations were the same reaction in different guises, the naphthamide giving a better yield but the benzamide remarkably yielding a fully dearomatised product. Given that for two decades chemists[5-16] had been functionalising tertiary amides using alkyllithiums, I was fully expecting to find that these "dearomatizing anionic cyclizations" were already known. But they were not: the nearest example was a report by Schaumann[17] of the dearomatising anionic cyclisation of a lithiated aziridine, along with a scattered two or three examples of rather less similar cyclisations of organolithiums onto aromatic rings.[18-20] (More recently other dearomatising anionic cyclisations have come to light,[21-23] most notably of phosphonamides[24-28]).

II. Establishing the cyclisation as a viable synthetic reaction

I managed to convince chemists at Merck Sharp and Dohme in Harlow that this new reaction was worth investigating further, and in collaboration with them I appointed my second PhD student, Anjum Ahmed, to work on this project. We quickly established that the cyclisation is a general reaction of *N*-benzyl amides,[29,30] along with some allyl-substituted amides.[31] Naphthamides[29] such as **11** were easier to

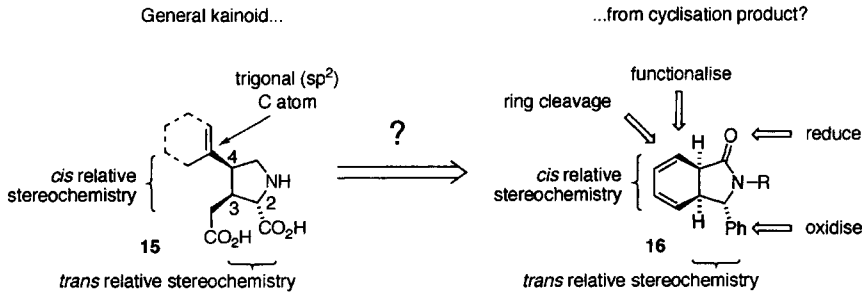
cyclise than benzamides, requiring simply lithiation with *s*-BuLi at –78 °C with subsequent addition of DMPU increasing the cyclisation rate and improving yields. With benzamides such as **13** the *t*-BuLi – HMPA conditions chanced upon in the reaction in Scheme 3 gave among the best yields possible (Scheme 4). Some X-ray crystal structures established the relative stereochemistry around the newly formed lactam ring, and it was at this stage that we were struck by the possibility of using the cyclisation in the synthesis of members of the kainoid family.



SCHEME 4

III. The strategy: conversion of cyclisation products to kainoids

The kainoids, principal examples of which are shown in Scheme 1, are all pyrrolidine-dicarboxylic acids with the general structure **15**.[1] The parent member of the family is kainic acid, and biologically active kainoids all share the features highlighted in Scheme 5. One of their most important features, and one which has made them more of a synthetic challenge than they would otherwise have been, is the *cis* relative stereochemistry of the two substituents at the C3 and C4 positions. Our cyclisation products **16**, when mapped onto the kainoids, also exhibit *cis* stereochemistry at these positions because of their 6,5-fused bicyclic structure, and indeed several previous syntheses of kainoids incorporate this *cis* stereochemistry by tying the two groups into a ring during the synthesis.[32] It seemed reasonable to propose a synthetic route from **16** to molecules of type **15** which would require some functional group transformations, including the challenging oxidation of the aryl ring at C2 to a carboxylate substituent,[33-36] and an appropriate late-stage ring cleavage reaction of the six membered ring joining the C3 and C4 substituents.



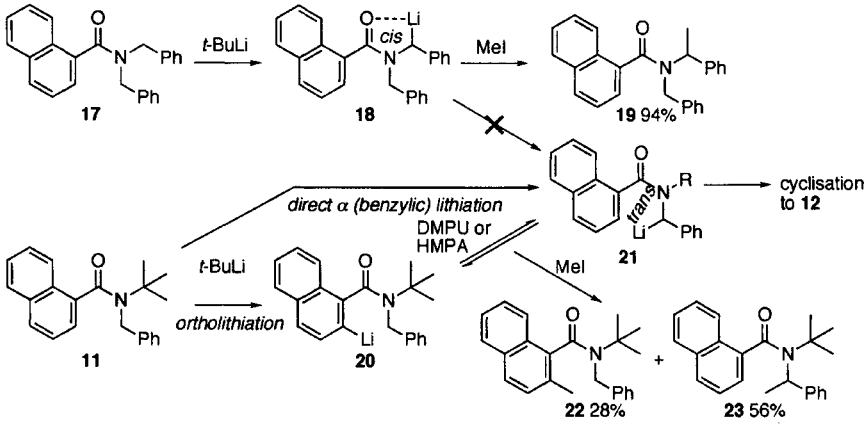
SCHEME 5

IV. Structural and mechanistic features of the cyclisation

In order to approach the kainoids as targets, and put this synthetic strategy into action, we needed to make a number of methodological improvements on the "raw" cyclisation results. The early work of Anjum Ahmed had concentrated principally on the naphthamide cyclisations,[29] partly because they gave single regioisomers of the dearomatised products and also because it turned out that they could be carried out without the need for HMPA. She had established a few key features of compounds which gave good results, some of which we could link to mechanistic features of the cyclisation. One of the first things we noted was that consistently good yields could be obtained only when one of the groups carried by the nitrogen atom was bulky. For example, although *N,N*-dibenzylbenzamide **13** could be cyclised in acceptable yield in the presence of HMPA, *N,N*-dibenzylnaphthamide **17** was lithiated α to nitrogen to give **18** (and could be alkylated to give **19**) but failed to cyclise. Dibenzyl amides are typically lithiated *syn* to oxygen,[9,37,38] where the lithium atom benefits from O–Li coordination. But for the benzyllithium **16** to adopt a conformation **22** in which the anion can attack the ring, an unfavourable loss of O–Li complexation has to occur. By contrast, *N-t*-butyl-*N*-benzylamides such as **11** adopt a conformation which places the single benzyl group permanently within reach of the ring, and the benzylic organolithium **21** is able to cyclise without the need for further bond rotations.

Using deuterium labelling, we found that we could follow the detailed choreography of the deprotonation (Scheme 6).[39] While some of the amide **11** was clearly deprotonated directly in the α (benzylic) position to give **21**, a significant amount was ortholithiated first, to give **20** and the

anion thus formed subsequently "translocated" to the benzylic position of the amide. Trapping experiments (MeI gave a 2:1 mixture of ortho-functionalised **22** and α-functionalised **23**) suggested that **20** and **21** are in equilibrium, and that DMPU or HMPA biases the equilibrium in favour of **21**.



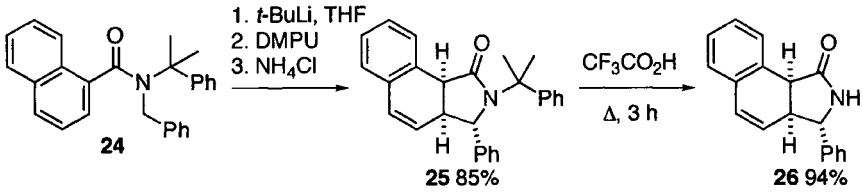
SCHEME 6

This may provide an explanation for the surprisingly good yields obtained from cyclisation of **11**, and also for the general observation that best yields were obtained from benzamides when the organolithium was formed under the conditions which promote cyclisation, since then the anion formed *trans* to oxygen by translocation from the *ortho* position cyclises before it has an opportunity to translocate a second time to the position *syn* to oxygen. Unfortunately, we still could not cyclise dibenzyl naphthamides because lithiating naphthamides in the presence of HMPA or DMPU resulted in direct nucleophilic addition of the lithiating reagent to the naphthamide ring itself.

V. Cumyl as a protecting group

The *t*-butyl group provided us with some useful "work-horses" for developing the scope of the cyclisation, since *N*-t-butylbenzylamine is cheap and readily available. However, we found it was almost impossible to remove from the products, even on extended treatment with acid. Replacing one of the methyl groups of the *t*-butyl with a phenyl group, however, stabilised the positive charge formed during E1 elimination and allowed us to deprotect the products to yield *N*-unsubstituted

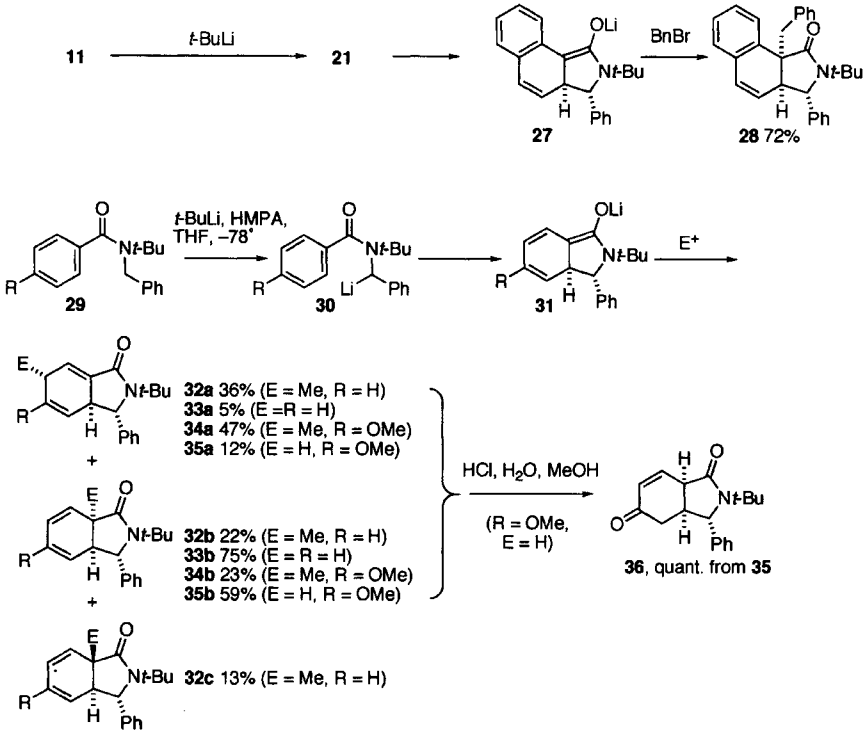
pyrrolidinones.[40] Thus cyclisation of **24** gives **25** and hence **26**. This "cumyl" protecting group, more or less simultaneously published by Snieckus[41,42] is not a true protecting group in the sense that it has to be introduced at the start of the sequence by using cumylamine as a staring material. (Cumylamine **84** is rather expensive commercially, but is reportedly[41] simple to make[43]).



SCHEME 7

VI. Functionalised benzamides: enones as products

The final step of the cyclisation mechanism also required some tinkering work before it was suitable for application to a total synthesis. The initial product of the cyclisation reaction is in fact an extended enolate, **27** from the naphthamides and **31** from the benzamides (Scheme 8). Enolate **27** can be alkylated or protonated both regio- and stereoselectively, giving a 6,5-cis-fused product and avoiding dearomatising the second aromatic ring of the naphthalene system. On the other hand, **31** was generally alkylated or protonated non-regioselectively, and indeed alkylation was non-stereoselective too,[30,44] forming difficult-to-separate mixtures of dienes. We had some limited success in controlling the regioselectivity of the protonation with this compound, but we realised that if the dienes were functionalised with methoxy groups they would both be enol ethers **35** and therefore hydrolysable to give enones, with the regiochemistry of the double bonds in the hydrolysed products being under thermodynamic control – an opportunity for stereocontrol reminiscent of that available in the Birch reduction of anisoles.[45] And indeed, cyclisation of **29** (R = OMe) gave the enone **36** in 71-73% overall yield, even without isolation of the intermediate enol ethers **35**.[44]

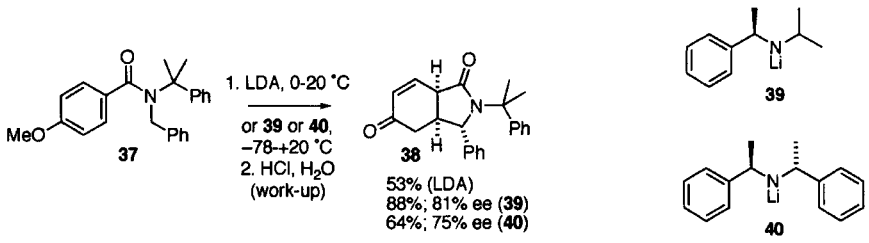


SCHEME 8

VII. Avoiding HMPA: LDA as a cyclisation promoter

There remained two obstacles to the general use of the cyclisation in synthesis: the fact that the cyclisation gives racemic products, and the requirement for the use of pyrophoric *t*-BuLi and carcinogenic HMPA in order to give good yields. In the event we managed to overcome both of these problems by building on a single observation. Our first attempts to develop an asymmetric cyclisation made use of (–)-sparteine in place of the HMPA, but with little success, partly due to the insolubility of the starting amide in solvents which typically give good enantioselectivities with (–)-sparteine.[46] The other group of broadly successful chiral bases are the chiral lithium amides, such as **39** or **40**, though in almost all of the cases in which these compounds react selectively they have been used to deprotonate at one of two enantiotopic reaction sites rather than to remove one of two enantiotopic protons from a single carbon atom.[47]

In preparation for an attempted asymmetric cyclisation using **40**, we managed to establish that LDA was sufficiently basic – just – to deprotonate the benzylic position of an N-benzylbenzamide, but only at temperatures above about –30 °C. Raising the temperature still further – to around 0 °C – promoted the cyclisation, and temperature control turned out to be an effective alternative to the use of HMPA in the cyclisation reaction.[40] Avoiding *t*-BuLi afforded not only the practical benefits of not having to use such a pyrophoric reagent, but also allowed greater versatility of starting material, since LDA promoted cyclisation of even halogenated benzamides and 2-naphthamides, both of which gave extensive side reactions with *t*-BuLi. At this stage we were satisfied that we had hit on practical, optimum conditions for the racemic cyclisation of benzamides, and we published our findings.[40]



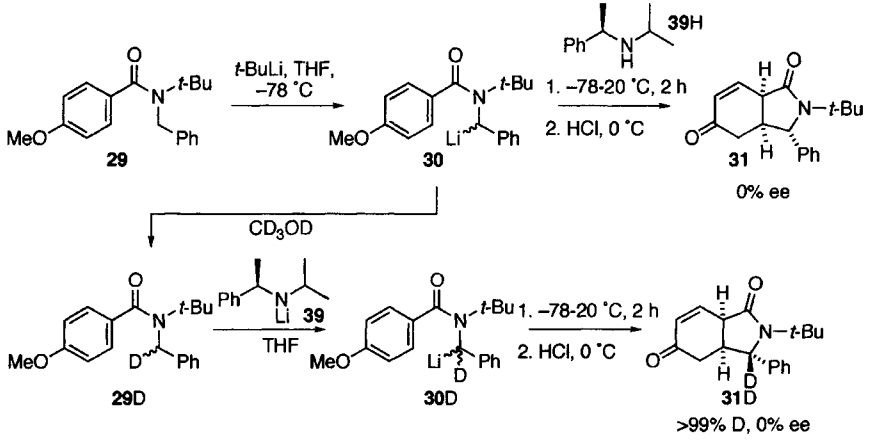
SCHEME 9

VIII. Asymmetric cyclisation with chiral lithium amides

Meanwhile, however, we were keen to convert the LDA-promoted cyclisation into an asymmetric cyclisation by replacing LDA with **39** or **40**. It was a very pleasant surprise when we discovered that even an unoptimised reaction using **40** gave cyclised product in good ee. Tweaking of the reaction conditions (**40** is more basic than LDA and will allow deprotonation at a lower temperature) increased the enantioselectivity to 75% ee (Scheme 9).[48] Initially, yields were low, because we had problems separating the amine (**40**H) from the product. However, changing the base from **40** to the even simpler **39** solved this problem, because the hydrochloride salt of **39** seems much less soluble in organic solvents than that of **40**. Base **39** gave a maximum of 88% yield and 81% ee in the cyclisation (Scheme 9).[48]

How does the asymmetric cyclisation work? Two steps are involved – the lithiation step and the cyclisation step – and there are two limiting

possibilities for the source of the asymmetry in the reaction. Either the cyclisation step itself is stereoselective, with the stereochemistry induced by the presence of the chiral amine **39H**, perhaps acting as a chiral ligand for the organolithium during the cyclisation, or the lithiation step is stereoselective and the stereochemistry of **38** is a consequence of stereospecific cyclisation of an intermediate chiral organolithium which has configurational stability on the timescale of its cyclisation. Although similar considerations have informed the investigation of the stereochemistry of (–)-sparteine-promoted reactions of benzyllithiums,[49] neither possibility has any direct precedent, because rarely have chiral lithium amides been used to substitute enantioselectively one of two enantiotopic protons at a prochiral methylene group, nor have they been used as chiral ligands for organolithiums less basic than LDA.[47]

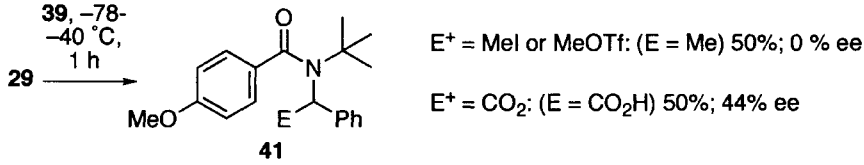


SCHEME 10

We investigated the possibility that **39H** acts as a ligand, introducing enantioselectivity in the cyclisation step of the sequence, by making the intermediate **30** as a racemate and cyclising it in the presence of **39H** (Scheme 10). Racemic product was formed, indicating that enantioselectivity is introduced in the first, lithiation step. This implies that the intermediate organolithium is configurationally stable, at least on the timescale of its cyclisation. Configurational stability is known in similar *N*-Boc benzylamines,[49] so this hypothesis did not seem unreasonable. A second experiment confirmed that the stereochemistry of the organolithium intermediate is responsible for the stereochemistry of the final cyclisation product: cyclisation of the racemic deuterated

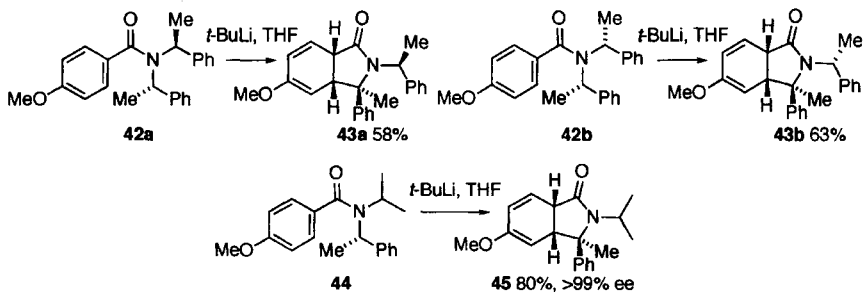
compound **29**D, even using the chiral base **39**, gave racemic but deuterated material **31**D: the kinetic isotope effect has overridden the enantioselectivity of the base, generating a racemic intermediate organolithium **30**D and therefore racemic product.

Given that this was apparently the first time an enantiomerically enriched benzyllithium had been made using a chiral lithium amide base, we tried trapping it with an external electrophile. Only by carbonation did we manage to obtain any enantioselectivity in the product **41** (Scheme 11): slower electrophilic quenches (such as, evidently, methyl iodide) presumably allow time for organolithium to racemise.[48]



SCHEME 11

IX. Stereospecific cyclisation of chiral benzamides



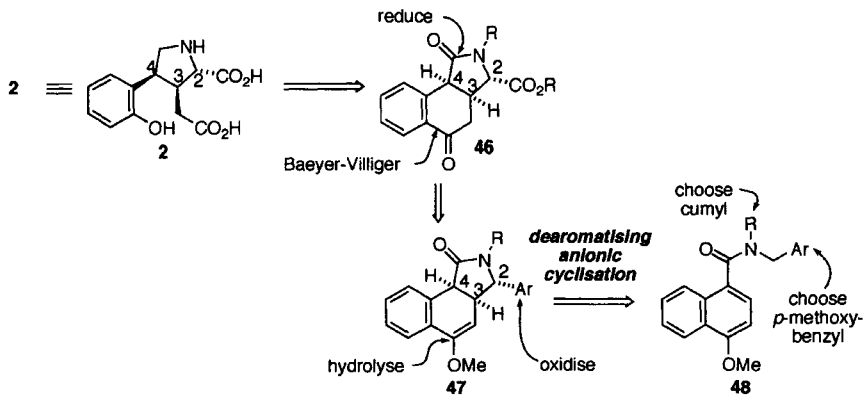
SCHEME 12

Lithiated tertiary *N*-Boc-benzylamines are considerably more configurationally stable than their secondary analogues,[38] so we proposed that lithiating and cyclising amides such as **44** might preserve stereochemistry of the starting material through into the product. We expected tertiary centres to cyclise without difficulty because the first cyclisation we had ever observed was of 1-naphthamide **4** bearing a chiral substituent. Unlike *N,N*-dibenzyl naphthamides, *N,N*-bis-(α-methylbenzyl)naphthamides generally cyclise successfully even without

an additive (DMPU or HMPA).[50] We verified first of all that the cyclisations of **42a** and **42b** were stereospecific: each starting diastereoisomer gave a different diastereoisomer of the product **43** (Scheme 12), so both lithiation and cyclisation must be stereospecific, proceeding via a configurationally stable tertiary benzyllithium intermediate.[51,52] When we cyclised **44**, and a series of related examples,[52] the product **45** was formed in high ee – the product stereochemistry depends solely on the absolute stereochemistry of the centre in the starting amide **44**. These results account for the stereoselectivity evident in the cyclisation of **4**,[50] though it also became evident that stereospecificity in the naphthamide cyclisations was complicated by the presence of a stereogenic Ar–CO axis at low temperature.[53] An alternative asymmetric cyclisation of naphthamides is discussed below.

X. Synthesis of the acromelic analogue 2

A. STRATEGY



SCHEME 13

Our early work on kainoid synthesis was conducted in the racemic series while we were still establishing a reliable method for carrying out the asymmetric cyclisation, and we made both **2** and kainic acid **1** in racemic form first, later developing an asymmetric version of the entire synthesis of **1** and of the synthesis of a key intermediate for **2**.

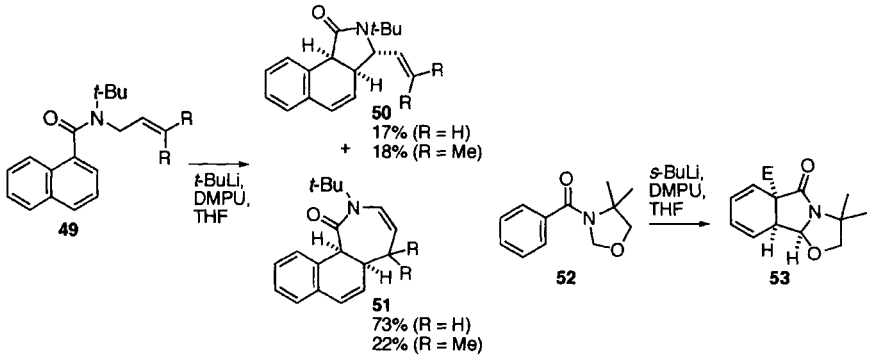
There were several reasons for setting our sights on arylkainoid **2**[54] as our first target. Firstly, being both highly active as a neurotransmitter analogue but also an unnatural product, it is a particularly desirable

candidate for chemical synthesis. Three previous approaches,[55-57] and one complete synthesis,[54] existed in the literature. Our plan both for this compound and for all the other kainoids we aimed to synthesise made use of a feature common to two of these approaches: the important *cis* relationship between the C3-and C4-substituents would be controlled by deriving both from a ring system, in this case **46** (Scheme 13). The precursor ring system **47** would itself be available by cyclisation of **48**, in which the methoxy group acts as the precursor to the carbonyl group we shall need for the ring cleavage step.

Key steps in the synthesis would then include 1. the deprotection and probably reprotection at *N*; 2. the oxidation of the phenyl substituent which is generated at C2 to give a carboxylic acid derivative; 3. the cleavage of the ring of **46** (we expected this to be achieved by Baeyer-Villiger oxidation,[54] though other reactions are possibilities); and 4. functional group interconversions and final deprotections to yield the target **2**. Of these stages, we saw the oxidation step to cleave the phenyl ring as the most problematic, and we put in a considerable amount of effort to trying to cyclise amides bearing groups other than benzyl, reasoning that if, say, an allyl group would cyclise, the resulting vinyl-substituted tricycle would be easier to oxidise to a carboxylic acid derivative under mild conditions.

B. MORE READILY OXIDISABLE SUBSTITUENTS?

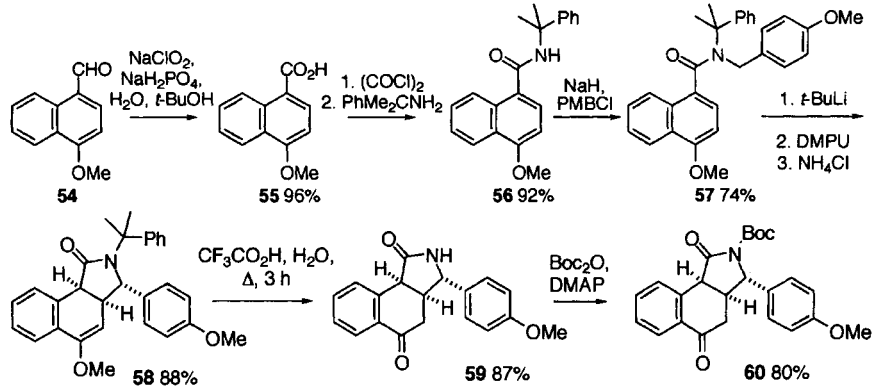
Our challenge was to find a subset of substituents for which the cyclising organolithium is (a) stable enough to form but (b) not so stable that it would not cyclise. In fact, apart from benzyl and a few simple substituted benzyl groups, we found very few substituents which fell into this class. Our original hope, that allyl substituents might result in vinyl-substituted five-membered rings, was only partially fulfilled since the main products of cyclisation of **49** were the seven-membered ring compounds **51**, with rather little **50** (Scheme 14).[31] More recently, we have discovered that the oxazolidines **52** can also be cyclised to the tricycles **53**,[58] and these compounds are discussed further below. This discovery unfortunately came too late for us to incorporate it into the syntheses described here, though it may form the key reaction in planned future work on the domoic/isodomoic acid series.



SCHEME 14

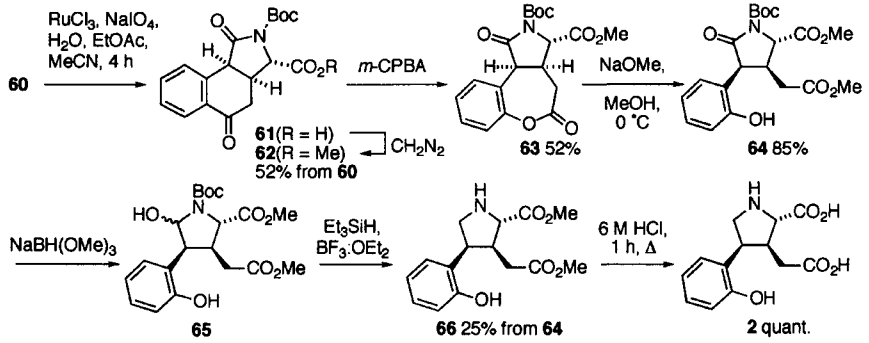
C. THE SYNTHESIS OF RACEMIC **2**.[59]

Our synthesis of **2** therefore started with the amide **56**, which we made from cumylamine and the available aldehyde **54** (Scheme 15). Anticipating that the oxidation of the phenyl ring would be assisted by greater electron density,[35,36] we decided to incorporate into the ring a *para* methoxy substituent: alkylation with *p*-methoxybenzyl chloride gave **57**. Our early work on this target was carried out before we discovered that cyclisation is optimal with LDA, and we used *t*-BuLi and DMPU to cyclise **57** to **58**, which we found was easily deprotected to yield **59**. The acid needed to deprotect the cumyl group also hydrolysed the methyl enol ether functionality of **58** to the keto group of **59**.



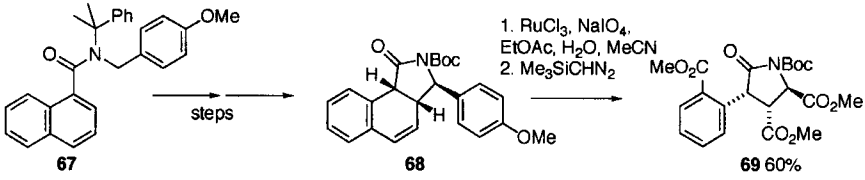
SCHEME 15

We tried oxidations of aryl groups in compounds such as **59** with free N–H positions, but found that they invariably gave messy product mixtures, so we chose to reprotect **59** with a Boc group, one of the few protecting groups capable of withstanding the Ru(VIII) oxidising agent planned for the next step. Here we met problems arising from the unusual acidity of the proton α to the amide carbonyl group: **59** is an arylogous acetoacetamide derivative. The main by-product from the protection was a doubly *N,*O-Boc-protected product, which was remarkably difficult to deprotect and recycle. Of the conditions we tried, by far the best were Boc_2O in the presence of a catalytic quantity of DMAP in acetonitrile which gave principally the desired **60**, plus 15% recyclable **59**.



SCHEME 16

Oxidative degradation of the *p*-methoxyphenyl ring of **60** to the acid **61**,[33-36] which was isolated as its ester **62**, was surprisingly clean, though yields never rose above about 55% for this transformation (60% appears to represent the limit in yield for almost any Ar → CO_2R oxidation process using Ru(VIII)). A super-excess of periodate is required in the reaction, though success can be achieved with either the original Sharpless MeCN–CCl_4–H_2O system[33] or by replacing CCl_4 with EtOAc. The selectivity of the oxidation towards electron-rich aromatic systems means that the carbonyl-substituted ring remains intact. In a parallel sequence, we also showed that the cyclisation product **68** from **67** could be oxidised selectively to yield **69**, with presumably an initial oxidation of the alkene providing a carboxylic acid substituent which protects the adjacent ring from further degradation (Scheme 17).[60]

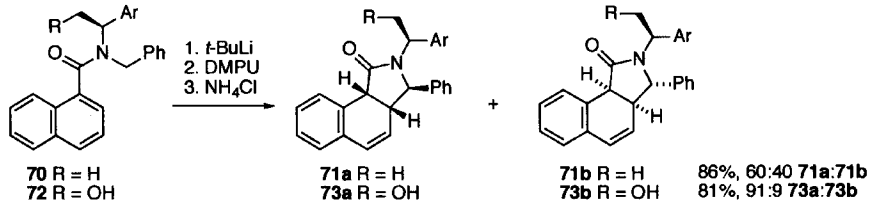


SCHEME 17

Now for the cleavage of the cyclohexanone ring. There is no question in this sequence (unlike the ones which follow) that the cleavage of the six-membered ring of **62** to generate the 3,4-*cis* stereochemistry of **2** should be carried out by Baeyer-Villiger oxidation. In the event, *m*-CPBA generated the lactone **63** cleanly from **62**, with the bonus that not only has the 6-membered ring been cleaved, but also we have installed the required 2-hydroxy substituent on the aryl substituent. Ring opening of **63** is simply a methanolysis of the lactone, but the conditions required for this transformation have to be mild in order to avoid the epimerisation of the stereogenic centre adjacent to the amide carbonyl group of **64** to give *trans* stereochemistry.

The final steps of the sequence are all downhill: the unfortunately low-yielding two-stage reduction of the pyrrolidinone to a pyrrolidine, and deprotection to yield **2** in racemic form.

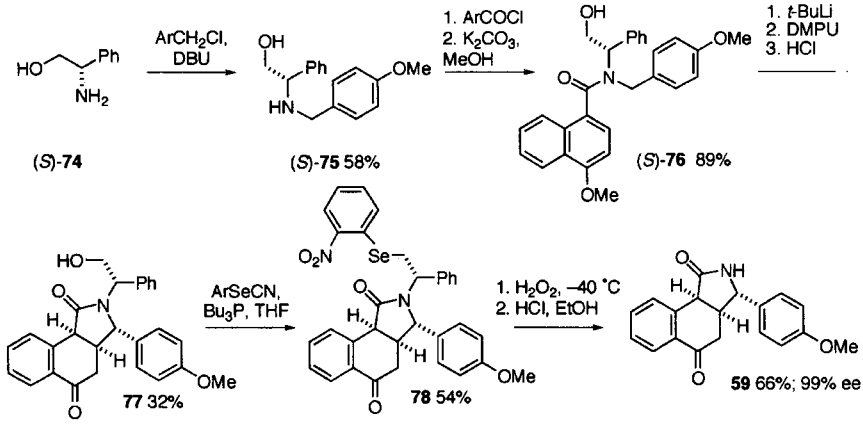
D. Application of a chiral auxiliary to the asymmetric synthesis of **2**.[60]



SCHEME 18

Attempts to induce asymmetry in the cyclisation of **57** using the chiral lithium amides, which had worked well with simple benzamides, were frustrated by the inherent chirality, at low temperature, of the naphthamide itself. This feature is common to all 2-substituted tertiary aromatic amides, which may become atropisomeric at low temperature due to slow rotation about the Ar–CO bond.[48] We therefore sought to

develop an alternative method based on the use of a chiral auxiliary (Scheme 18). Early attempts with **70** failed due to lack of diastereoselectivity, but when the auxiliary was modified to the phenylglycinol-based group of **72**, incorporating a second point of coordination for Li, good selectivity for the formation of **73a** was obtained.[60]



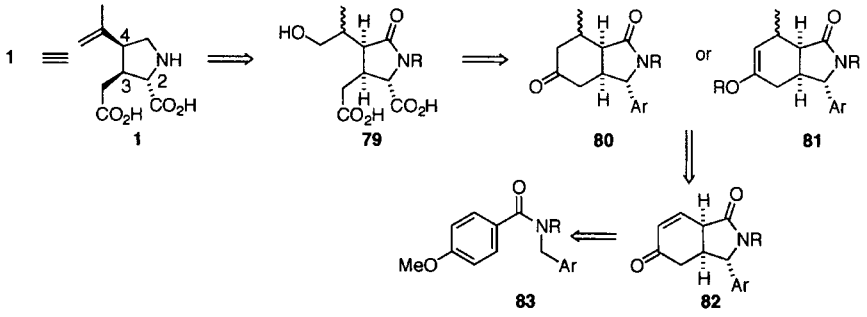
SCHEME 19

When this diastereoselective cyclisation was incorporated into the synthesis of **2**, several drawbacks became apparent (Scheme 19). A number of additional steps were required to incorporate the auxiliary into the cyclisation starting material **76**, and to remove it from the product, and purification of the only 2:1 mixture of diastereoisomers of **77** obtained from the cyclisation meant that overall yields were poor. So although we were able to make **59** in enantiomerically pure form and therefore complete a "formal" asymmetric synthesis of **2**, chiral auxiliary methods never appeared again in our cyclisation work.

Most of the work on the target **2** was carried out by Anjum Ahmed, who made the intermediate (±)-**59**, and Ryan Bragg, who took this intermediate through to the end of the sequence and developed the asymmetric route to **59**. However, it was only in the closing stages of his postgraduate studies that we realised that the final product he had made was not **2** but a diastereoisomer, arising from epimerisation during the lactone-opening step. Kirill Tchabanenko therefore took over the task of carrying **63** through the sensitive lactone-opening step to yield (±)-**2**.

XI. Synthesis of kainic acid 1.[61,62]

A. STRATEGY



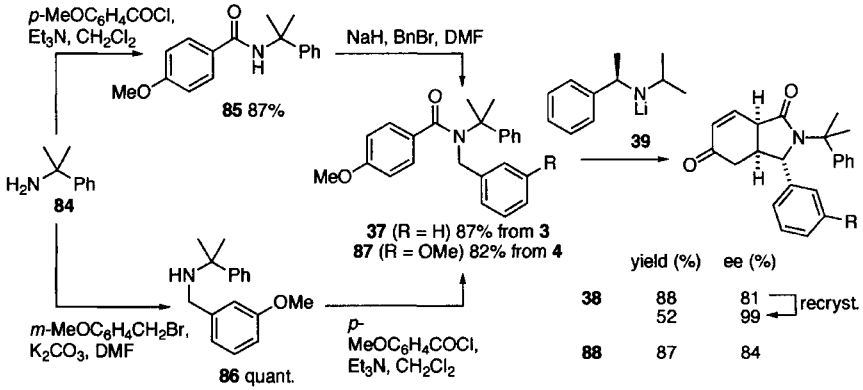
SCHEME 20

Most of Kirill Tchabenenko's time working with me, however, was spent on the synthesis of kainic acid **1** itself. Kainic acid has a few features that make the strategy for its synthesis differ somewhat from that for the synthesis of **2**. The principal one is the presence of an alkene in the target, which of course cannot be present during the ruthenium-promoted ring-degradation step. In principle, if we imagine this alkene arising from elimination of water from an alcohol **79** (Scheme 20) the rest of the route could nonetheless follow closely the strategy used for **2**. However an important point stands out clearly: while ring cleavage using **62** was always going to be unequivocal in its regioselectivity, the same could not be said for ketone **80**, which bears two very similar α-unsubstituted carbon atoms, and would probably oxidise non-regioselectively. In addition, we envisaged adding the carbon atom not present in **83** as a cuprate to the enone **82**. This strategy would have the added bonus of providing us with an intermediate **81** whose oxidation (by ozonolysis or similar) would allow an alternative method for cleavage of the ring with greater certainty about regioselectivity.

B. THE SYNTHESIS

This was our initial plan, and we set about making the starting materials **37** or **87**. We used the cumyl group as a readily removable bulky protecting substituent, but we found that while the amide **85** could be readily, if slowly, benzylated, it was surprisingly much harder to alkylate with a *p*-methoxy substituted benzyl halide than its naphthamide

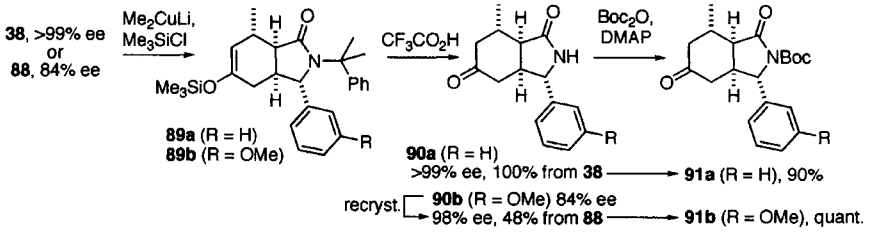
equivalent had been. Reasoning that the rate of Ru(VIII)-promoted ring degradation should not depend significantly on the position of the electron donating substituent, we opted to alkylate instead with the more stable and less reactive *m*-methoxybenzyl bromide, and first to alkylate cumylamine to give **86** and then **4**. Early racemic cyclisations used *t*-BuLi to lithiate **37** and HMPA to promote the cyclisation, and these conditions were published in our racemic synthesis,[61] but we know now that LDA works as well and gives similar yields. In the asymmetric cyclisation, both **37** and **87** performed adequately, but product **38** offered the advantage of being crystalline and therefore allowed the ee of the product to be improved to 99% at this stage. Nonetheless, we carried both compounds through the next steps expecting **88** to regain the advantage in the ring degradation step.



SCHEME 21

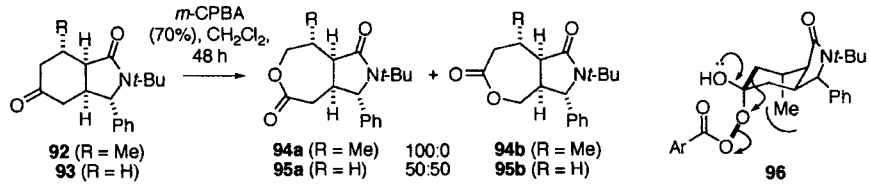
The cyclisation products could be isolated in several different guises depending on the nature of the reaction work up. An enol ether is the initial product of a neutral or basic quench, but even the mild acid wash required to remove the amine base from the mixture turned out to be sufficient to hydrolyse the enol ether to the enone **38** or **88**. More vigorous acidic conditions (warming in TFA or, as we have recently found, formic acid) removed the cumyl group. At this stage, however, we were willing to leave the cumyl group in place while we used the enone as an acceptor for the conjugate addition of methyl cuprate in the presence of trimethylsilyl chloride, giving **89**. A single diastereoisomer was formed, with the methyl group on the *exo* face of the bicyclic system,

though this is unimportant to the final target which lacks this stereogenic centre.



SCHEME 22

As indicated above, our initial plan was to cleave in an oxidative manner the silyl enol ether of **89** as a means of opening the ring and forming the *cis* C3-C4 stereochemistry. However, several problems beset this plan, including control of the oxidation state of the ozonolysis products and potential chemoselectivity problems in subsequent oxidation of the aryl ring. Although these problems were probably surmountable, they slowed our progress considerably. During this time, we decided to try Baeyer-Villiger cleavage of the ring on the off chance that we could obtain at least some useful material for further steps in the synthesis. Our first attempt, using the model compound **92**, yielded the remarkable result that the oxidation was fully regioselective, in the desired sense (Scheme 23)! The origin of this remarkable, and extremely useful, selectivity is still not fully clear, but experiments with the analogue **93** suggested that the methyl group is essential. Our working hypothesis is that this group, which is pseudoaxial on the bicyclic structure, forces the intermediate perester **96** to adopt a conformation in which the bond marked in bold in **96** is more antiperiplanar to the breaking O–O bond than the alternative.

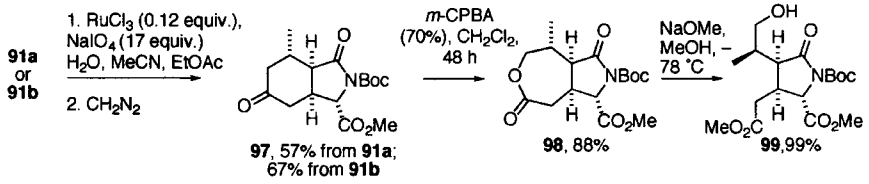


SCHEME 23

We were eager to apply this reaction to the real synthesis, but since the lactone product of the Baeyer-Villiger reaction, and each intermediate

from then on, contains sites of potential competing oxidation by Ru(VIII), we decided first to oxidise the aryl ring to an ester substituent. The cumyl group does not withstand ruthenium oxidation, so we removed both the cumyl and silyl groups of **89** with trifluoroacetic acid to give crystalline ketones **90**. Compound **90b** was fortunately crystalline: recrystallisation returned material of 99% ee (Scheme 22). The lack of conjugation between the amide and the carbonyl now meant that Boc protection of both enantiomerically pure compounds **90** was straightforward.

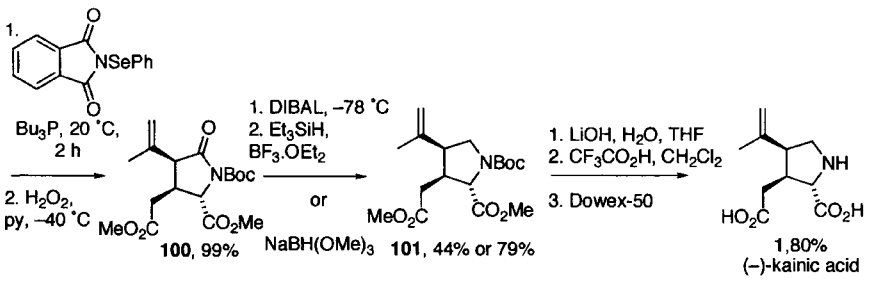
Oxidation of **91** with Ru(VIII)[33-36] was faster and slightly higher yielding for **91b**, but both performed acceptably, giving the ester **97** (Scheme 24) As we had hoped, when we treated **97** with *m*-CPBA we generated a single regioisomer of the lactone **98** in 88% yield – not a trace of the alternative lactone was present.



SCHEME 24

As before, ring opening of the lactone **98** required careful control to prevent epimerisation, and indeed migration of Boc to the primary hydroxyl group of **99**, but NaOMe in methanol at –78 °C gave the alcohol **99** essentially quantitatively.

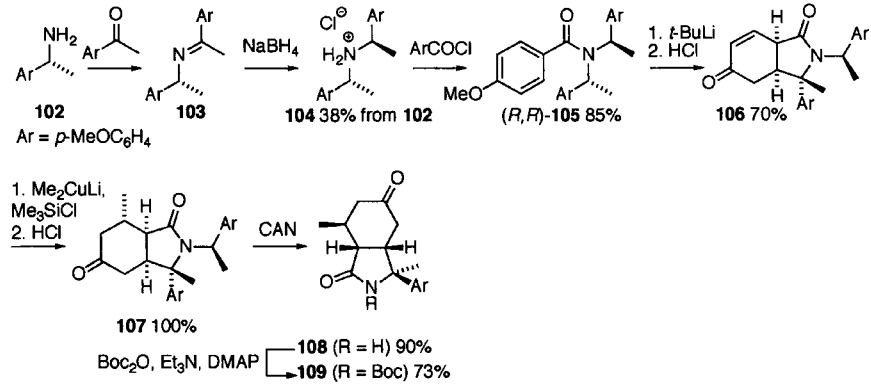
The final steps of the synthesis require functional group interconversions of alcohol to alkene, amide to amine, and deprotection. Elimination of water from **99** could not be achieved with $MsCl/Et_3N$, but conversion first to the selenide with N-phenylselenenophthalimide (this method we found to be less capricious than the method using *o*-nitrophenylselenenyl cyanide which we used in the synthesis of **2** and which we used in our published racemic synthesis of **1**), then selenoxide elimination, gave **100** (Scheme 25). Amide **100** has four carbonyl groups; reduction of just one of them could be achieved either in one step with $NaBH(OMe)_3$ or in two steps with DIBAL and Et_3SiH and $BF_3{:}OEt_2$ (the latter being lower yielding but apparently more consistently reliable). Final deprotection yielded a sample of (–)-kainic acid identical by NMR and optical rotation with the natural material.



SCHEME 25

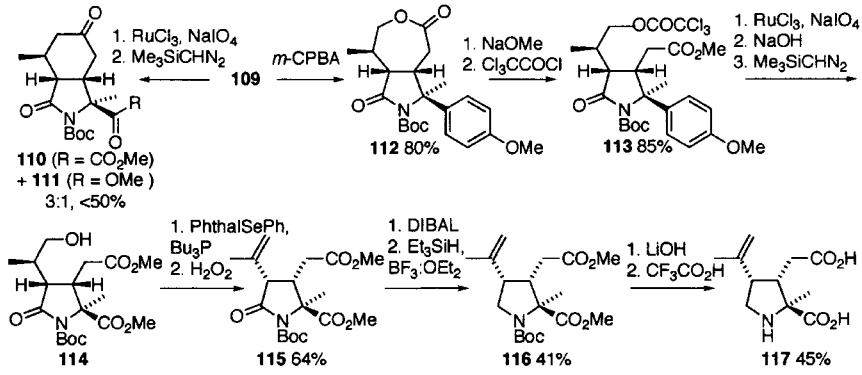
XII. Synthesis of a novel methylkainoid.[51]

The synthesis of these two known kainoids demonstrated clearly that this strategy, of employing the cyclisation to set up functionality and stereochemistry for manipulation into a kainoid structure, was feasible and competitive with other routes to the kainoids. We wanted next to demonstrate its versatility. Simple changes in starting materials, or especially at the conjugate addition step, should make it possible to carry through a number of features to the final kainoid target. As an example, Schemes 26 and 27 shows the synthesis of the novel methyl-substituted kainoid **117**, which can be made in enantiomerically pure form by exploiting the stereospecific cyclisation of chiral **105**, the methoxy-substituted analogue of **42a**, in which each of the three methoxy groups has a different role to play



SCHEME 26

105 was made from amine **102** by stereoselective reduction of the imine **103** and acylation. It cyclises stereospecifically, just like **42a**, and the first methoxy group ensures that acid hydrolysis converts the initial enol ether product to an enone **106**. The second methoxy group means that the exocyclic α-methyl-*p*-methoxybenzyl group is susceptible to oxidative cleavage with ceric ammonium nitrate. Conjugate addition of Me_2CuLi to **106** gave the ketone **107** quantitatively, and treatment with ceric ammonium nitrate followed by Boc_2O gave the carbamate **109**.



SCHEME 27

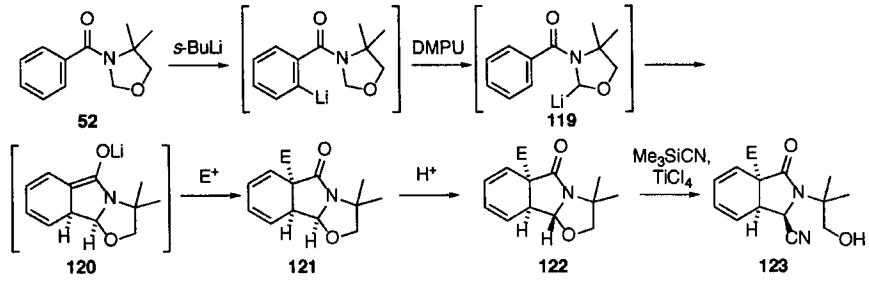
Conversion of **109** to a kainoid analogue is assisted by the third MeO group, which facilitates the introduction of the CO_2R substituent. However, oxidative removal of the methoxyphenyl ring of **109** with Ru(VIII) was only partially successful – steric hindrance from the methyl group largely derailed the degradation of the ring one stop before the target carboxylic acid derivative, giving (after methylation) mainly **110** and little **111** (Scheme 27) We returned to the carbamate **109** and subjected it to Baeyer-Villiger oxidation with *m*-CPBA, regioselectively rupturing the cyclohexanone ring to give lactone **112**. Careful methanolysis (NaOMe, –78 °C) of the lactone avoided epimerisation α to the amide carbonyl group, giving an alcohol which was protected as its trichloroacetate **113**. Oxidative degradation of the methoxyphenyl ring at this stage in the synthesis still stopped short of completion, but basic hydrogen peroxide was sufficient to further oxidise any α-ketoacid to the carboxylic acid. Hydrolysis of the trichloroacetate ester took place concurrently, and the product was isolated after methylation with trimethylsilyldiazomethane as the ester **114**. The kainoid isopropenyl group of **115** was revealed by elimination of water from **114** via a

selenoxide; reduction of the lactam carbonyl group with DIBAL and Et_3SiH gave **116** and deprotection yielded **117**, an α-methylated analogue of kainic acid. Alkyl substituted kainoids have been made before and their properties investigated,[63] but this is the first synthesis of **117**.

XIII. Future prospects: the domoic/isodomoic acid family

The next challenge facing us is to apply the strategy to the largely unsynthesised[64,1] domoic and isodomoic family **3**. Our aim here is to introduce their diene side chains by nucleophilic-electrophilic functionalisation of the enone **82**. There is, however, one major problem: the unsaturation in the domoic sidechains makes chemoselectivity problems arising from the aryl ring degradation almost impossible to overcome. Again the need arises for a version of the cyclisation which does not depend on benzylic lithiation.

Recently, we may have discovered the solution, and I will finish with an outline of what might be achieved by cyclisation of benzoyloxazolidines (Scheme 28). The compounds **52** is ortholithiated by *s*-BuLi, but like its *N*-benzyl analogue, treatment with DMPU promotes anion translocation and cyclisation to give **121**.[58] The products have an unusually hindered *syn* tricyclic structure, and are rapidly epimerised to the *trans* tricyclic **122** on treatment with Lewis or Brønsted acid. Importantly, the presence of the "aminal" centre means that a carboxylate substituent can be introduced here as a nucleophile: treatment with Me_3SiCN for example gives **123**, presumably by S_N2-like substitution with inversion. Future work on the kainoids may well use this reaction as a starting point, though we still have to develop an asymmetric version and a means of deprotecting the resulting hydroxy-*tert*-butyl group.



SCHEME 28

Acknowledgements

I am grateful to all the talented co-workers who have pushed forward our work on these cyclisation reactions to this point, namely Anjum Ahmed, Ryan Bragg, Samreen Yasin, Kirill Tchabanenko, Christel Menet, Savroop Purewal and Katherine Hebditch.

References and Footnotes

1. Parsons, A. F., *Tetrahedron* **1996,** *52*, 4149.
2. Clayden, J., *Synlett* **1998**, 810.
3. Jaeger, S. PhD thesis, University of Manchester, 1996.
4. Beech, C. Final year undergraduate project report, University of Manchester, 1995.
5. Fraser, R. R.; Boussard, G., Potescu, I. D., Whiting, J. J., Wigfield, Y. Y., *Can. J. Chem.* **1973,** *51*, 1109.
6. Beak, P., Brubaker, G. R., Farney, R. F., *J. Am. Chem. Soc.* **1976,** *98*, 3621.
7. Beak, P., Brown, R. A., *J. Org. Chem.* **1977,** *42*, 1823.
8. Beak, P., McKinnie, B. G., Reitz, D. B., *Tetrahedron Lett.* **1977**, 1839.
9. Beak, P., Reitz, D. B., *Chem. Rev.* **1978,** *78*, 275.
10. Reitz, D. B., Beak, P., Tse, A., *J. Org. Chem.* **1981,** *46*, 4316.
11. Beak, P., Snieckus, V., *Acc. Chem. Res.* **1982,** *15*, 306.
12. Beak, P., Brown, R. A., *J. Org. Chem.* **1982,** *47*, 34.
13. Beak, P., Tse, A., Hawkins, J., Chen, C. W., Mills, S., *Tetrahedron* **1983,** *39*, 1983.
14. Beak, P., Meyers, A. I., *Acc. Chem. Res.* **1986,** *19*, 356.
15. Beak, P., Lee, W.-K., *Tetrahedron Lett.* **1989,** *30*, 1197.
16. Snieckus, V., *Chem. Rev.* **1990,** *90*, 879.
17. Breternitz, H.-J., Schaumann, E., Adiwidjaja, G., *Tetrahedron Lett.* **1991,** *32*, 1299.
18. Hoell, D., Lex, J., Müllen, K., *J. Am. Chem. Soc.* **1986,** *108*, 5983.
19. Padwa, A., Filipkowski, M. A., Kline, D. N., Murphree, S. S., Yeske, P. E., *J. Org. Chem.* **1993,** *58*, 2061.
20. Crandall, J. K., Ayers, T. A., *J. Org. Chem.* **1992,** *57*, 2993.
21. Aggarwal, V. K., Ferrara, M., *Org. Lett.* **2000,** *2*, 4107.
22. Aggarwal, V. K., Alonso, E., Ferrara, M., Spey, S. E., *J. Org. Chem.* **2002,** *67*, 2335.
23. Nishiwaki, K., Ogawa, T., Matsuo, K., *Angew. Chem. Int. Ed.* **2002,** *41*, 484.
24. Fernández, I., Ortiz, F. L., Tejerina, B., Granda, S. G., *Org. Lett.* **2001,** *3*, 1339.
25. Gómez, G. R., Ortiz, F. L., *Synlett* **2002**, 781.
26. Sanchez, C. M. A., Iglesias, M. J., Ortiz, F. L., *Tetrahedron Lett.* **2002,** *43*, 2565.
27. Fernández, I., Ortiz, F. L., Velazquez, A. M., Granda, S. G., *J. Org. Chem.* **2002,** *67*, 3852.
28. Fernández, I., Acebal, A. F., Granda, S. G., Ortiz, F. L., *J. Org. Chem.* **2003,** *68*, 4472.
29. Ahmed, A., Clayden, J., Rowley, M., *Chem. Commun.* **1998**, 297.
30. Ahmed, A., Clayden, J., Yasin, S. A., *Chem. Commun.* **1999**, 231.
31. Ahmed, A., Clayden, J., Rowley, M., *Synlett* **1999**, 1954.
32. For more detailed discussion of previous syntheses, see references 1, 61 and 62.
33. Carlsen, P. H., Katsuki, T., Martín, V. S., Sharpless, K. B., *J. Org. Chem.* **1981,** *46*, 3936.

34. Nuñez, M. T., Martín, V. S., *J. Org. Chem.* **1990,** *55*, 1928.
35. Shioiri, T., Matsuura, F., Hamada, Y., *Pure Appl. Chem.* **1994,** *66*, 2151.
36. Matsuura, F., Hamada, Y., Shioiri, T., *Tetrahedron* **1994,** *50*, 265.
37. Schlecker, R., Seebach, D., Lubosch, W., *Helv. Chim. Acta* **1978,** *61*, 512.
38. Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002.
39. Ahmed, A., Clayden, J., Rowley, M., *Tetrahedron Lett.* **1998,** *39*, 6103.
40. Clayden, J., Menet, C. J., Mansfield, D. J., *Org. Lett.* **2000,** *2*, 4229.
41. Metallinos, C., Nerdinger, S., Snieckus, V., *Org. Lett.* **1999,** *1*, 1183.
42. Metallinos, C., *Synlett* **2002,** 1556.
43. Balderman, D., Kalir, A., *Synthesis* **1978,** 24.
44. Clayden, J., Tchabanenko, K., Yasin, S. A., Turnbull, M. D., *Synlett* **2001**, 302.
45. Rabideau, P. W., Marcinow, Z., *Organic Reactions* **1992,** *42*, 1.
46. Hoppe, D., Hense, T., *Angew. Chem. Int. Ed.* **1997,** *36*, 2282.
47. O'Brien, P., *J. Chem. Soc. Perkin Trans. 1* **1998**, 1439.
48. Clayden, J., Menet, C. J., Mansfield, D. J., *Chem. Commun.* **2002**, 38.
49. Beak, P., Basu, A., Gallagher, D. J., Park, Y. S., Thayumanavan, S., *Acc. Chem. Res.* **1996,** *29*, 552.
50. Bragg, R. A., Clayden, J., *Tetrahedron Lett.* **1999,** *40*, 8323.
51. Clayden, J., Knowles, F. E., Menet, C. J., *Tetrahedron Lett.* **2003,** *44*, 3397.
52. Clayden, J., Knowles, F. E., Menet, C. J., *Synlett* **in press.**
53. Bragg, R. A., Clayden, J., *Tetrahedron Lett.* **1999,** *40*, 8327.
54. Hashimoto, K., Horikawa, M., Shirahama, H., *Tetrahedron Lett.* **1990,** *31*, 7047.
55. Hashimoto, K., Shirahama, H., *Tetrahedron Lett.* **1991,** *32*, 2625.
56. Maeda, H., Kraus, G. A., *J. Org. Chem.* **1997,** *62*, 2314.
57. Maeda, H., Selvakumar, N., Kraus, G. A., *Tetrahedron* **1999,** *55*, 943.
58. Clayden, J., Purewal, S., Helliwell, M., Mantell, S. J., *Angew. Chem. Int. Ed.* **2002,** *41*, 1091.
59. Ahmed, A., Bragg, R. A., Clayden, J., Tchabanenko, K., *Tetrahedron Lett.* **2001,** *42*, 3407.
60. Bragg, R. A., Clayden, J., Bladon, M., Ichihara, O., *Tetrahedron Lett.* **2001,** *42*, 3411.
61. Clayden, J., Tchabanenko, K., *Chem. Commun.* **2000**, 317.
62. Clayden, J., Menet, C. J., Tchabanenko, K., *Tetrahedron* **2002,** *58*, 4727.
63. Collado, I., Ezquerra, J., Mateo, A. I., Rubio, A., *J. Org. Chem.* **1998,** *63*, 1995.
64. Ohfune, Y., Tomita, M., *J. Am. Chem. Soc.* **1982,** *104*, 3511.

STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 5

TOTAL SYNTHESIS OF JATROPHATRIONE, AN UNPRECEDENTED [5.9.5] TRICYCLIC ANTILEUKEMIC DITERPENE

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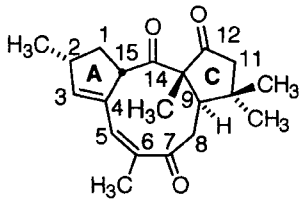
I. Introduction

The discovery that the architecturally unusual tricyclic diterpene jatrophatrione (**1**) is produced by the roots of *Jatropha macrorhiza* Benth was announced by Torrance, et al in 1976.[1] In conjunction with the unveiling of **1** came recognition of its very respectable inhibitory activity against P-388 lymphocytic leukemia. Although the structural assignment to jatrophatrione was reliably based upon an X-ray crystallographic study, this detailed investigation did not lead to a rigorous determination of absolute stereochemistry. Rather, the configurations of the several stereogenic centers in **1** were inferred by comparison to the somewhat related jatrophone (**2**), which had been isolated six years earlier by Kupchan and his co-



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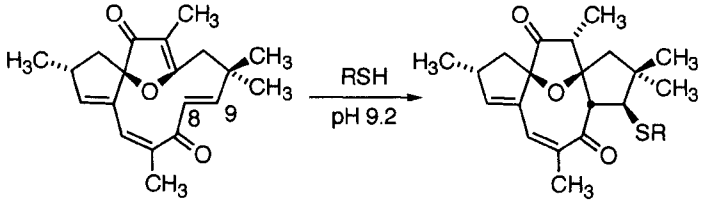
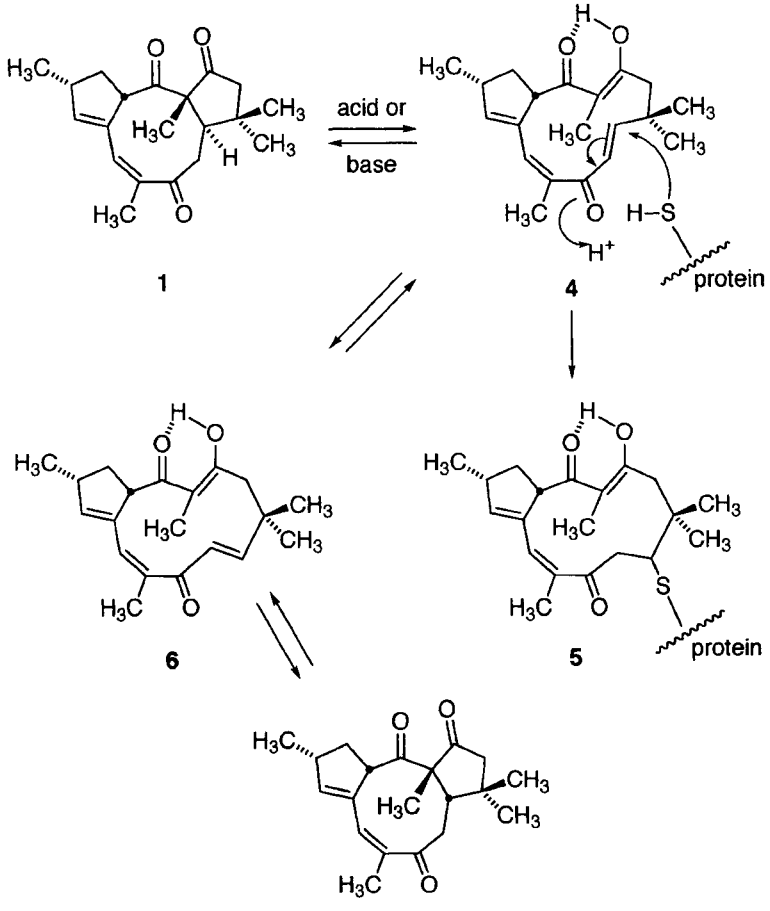


2 3

workers from the botanically related *J. gossypiifolia.*[2] Other structurally related compounds include kanserinine A and B,[3] euphoscopin A and B,[4] euphorinin,[5] characiol A-H,[6] and particularly citlalitrione.[7] Many of these natural products likewise exhibit appreciable biological activity. For example, **2** attracted early synthetic interest because of its strong inhibitory action against several carcinomas.[2,8]

When subjected to the action of propanethiol under basic conditions (pH 9.2), jatrophone (**2**) undergoes a Michael reaction across its C8-C9 double bond, followed by facile transannular cyclization to give the tetracyclic diketone **3**.[2,9] The susceptibility of this enone part structure to conjugate addition has been proposed to constitute the event responsible for the pronounced biological activity of **2**.[9]

To account for the fact that jatrophatrione (**1**) is biologically effective despite its lack of unsaturation at C8-C9, Torrance postulated that **1** may first be subject to a retrograde Michael process with a 1,3-dicarbonyl unit as the leaving group to generate **4** (Scheme 1).[1] In turn, **4** could be captured in a manner paralleling the **2** → **3** conversion. However, in a probe experiment jatrophatrione proved to be inert to butanethiol under comparable conditions. It is perhaps equally important to recognize that covalent attachment of the mercaptan also did not occur at C3 or C5, presumably due to the extensive structural deformation in that sector of the diterpene. This



SCHEME 1

architecturally enforced structural deformation prevents conjugative overlap between the associated double bonds and neighboring carbonyl group. Attention is called specifically to the crystallographically defined torsion angle of only 61.0° for C5-C6-C7-O3. Molecular mechanics calculations closely reproduce this topology for the conformation of lowest energy.

Among the other noteworthy structural features of **1** are its central nine-membered B ring that is home to three of the four stereogenic centers. The 1,5 relationship of two carbonyls such as those positioned at C7 and C14 has traditionally fostered transannular cyclizations in medium-sized rings. Accordingly, this

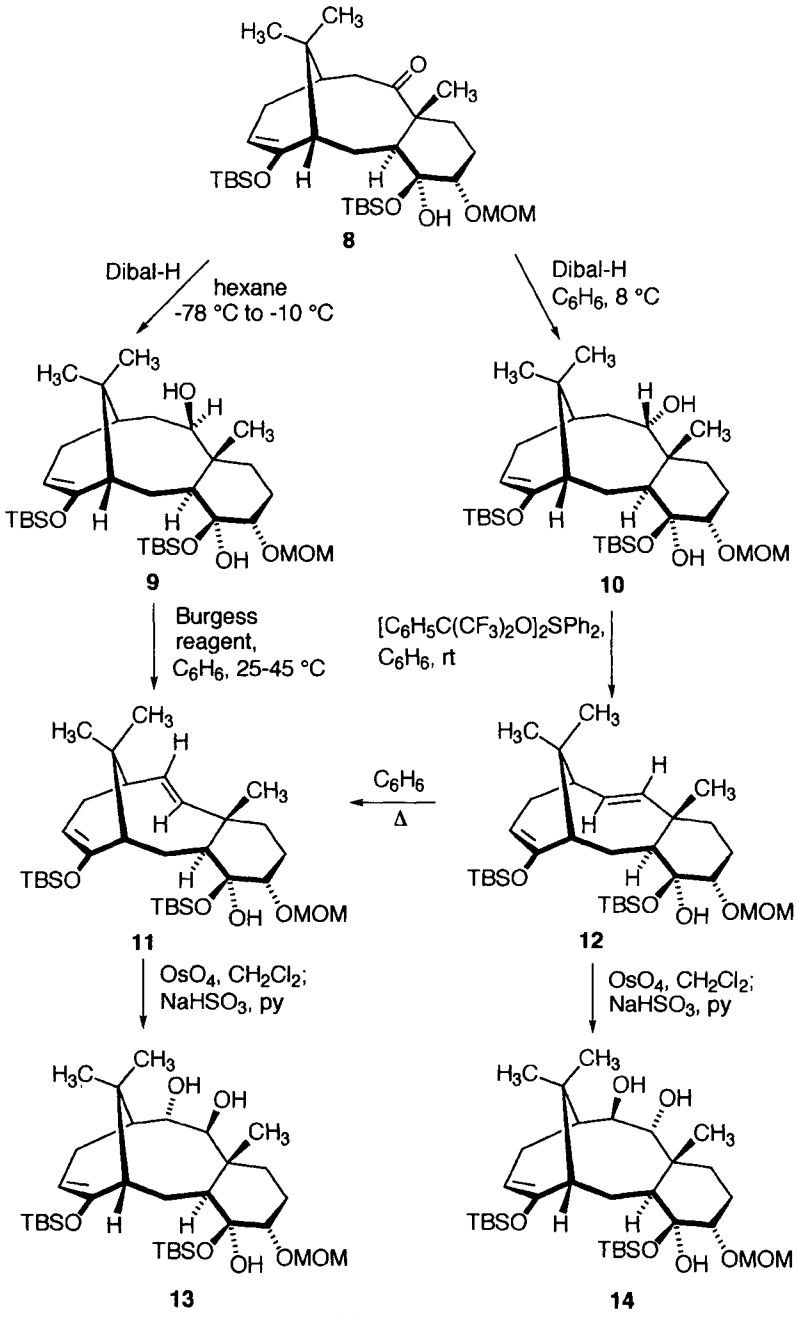
proclivity will need to be either curtailed or perhaps more realistically utilized to synthetic advantage.

II. Retrosynthetic Analysis

In the last couple of months of his postdoctoral stint in our group, Tom Zydowsky volunteered to undertake some preliminary studies aimed at a possible synthesis of jatrophatrione. In our collective view, it was considered premature to discard the otherwise attractive mechanism of action concept advanced above. Of particular fascination to us was the possibility of facilitating the reverse Michael step by beginning with the C9 epimer **7**. As judged by the results of MM2 calculations, this single configurational change causes **7** to be more strained than **1** by approximately 6.5 kcal/mol. Thus, we would hope to equilibrate **7** to the thermodynamically more favored jatrophatrione. However, this goal is not without potential complications. One of the more readily perceived possible problems stems from the fact that the *E*-configured C8-C9 double bond in first-formed **6** must be capable of internal rotation about the adjacent single bonds prior to reclosure with delivery of **1**. Indications derived from molecular mechanics calculations were that **4** is only 1.3 kcal/mol less stable than **6**.[10]

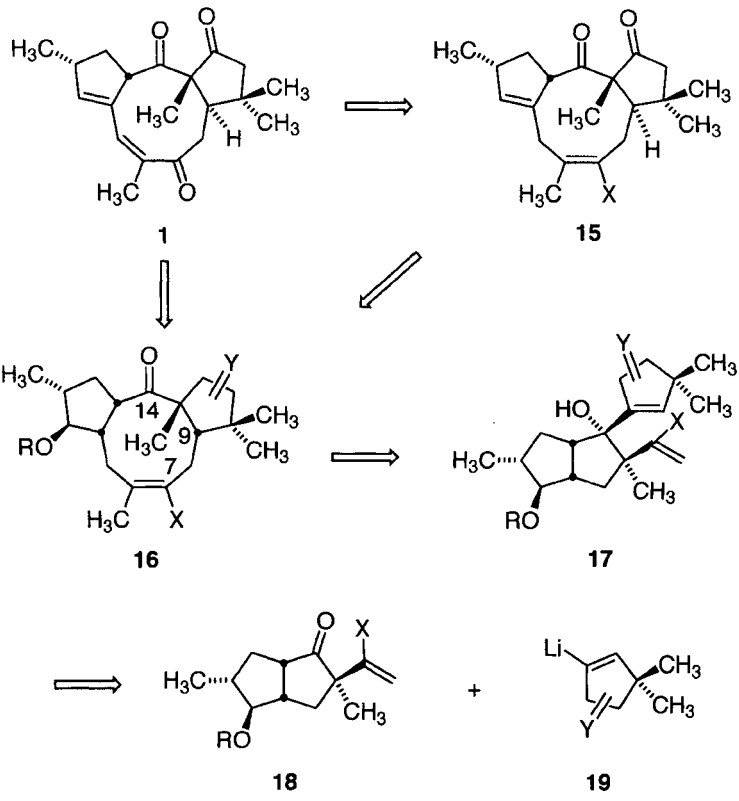
Encouragement regarding the feasibility of attaining stereochemical control in this manner came from an unexpected source. During Mangzhu Zhao's quest of taxusin, the discovery was made that ketone **8** could be reduced cleanly to either the β-alcohol **9** or its α-epimer **10** (Scheme 2).[11] In both cases, the reagent was diisobutylaluminum hydride, with complete stereochemical reversal attainable uniquely by means of a solvent change from hexane to benzene. These alcohols were separately dehydrated to the *trans*-cycloalkenes **11** and **12**. In line with the modestly greater stability of **11** (~3.0 kcal/mol), heating **12** in C_6H_6 resulted in its unidirectional conversion to **11**. Both **11** and **12** underwent osmylation to give the diastereomeric trans diols **13** and **14**, respectively, with attack occurring from the only available open direction external to the ring.

Notwithstanding the analogy offered by Scheme 2, these considerations were nevertheless regarded as being risky. The capacity to invert configuration at C9 by a more reliable chemical means was incorporated into our retrosynthetic analysis for this



SCHEME 2

reason. In crude outline form, arrival at **1** was envisioned to involve the formation of **16** from **17** via anionic oxy-Cope rearrangement[12]



SCHEME 3

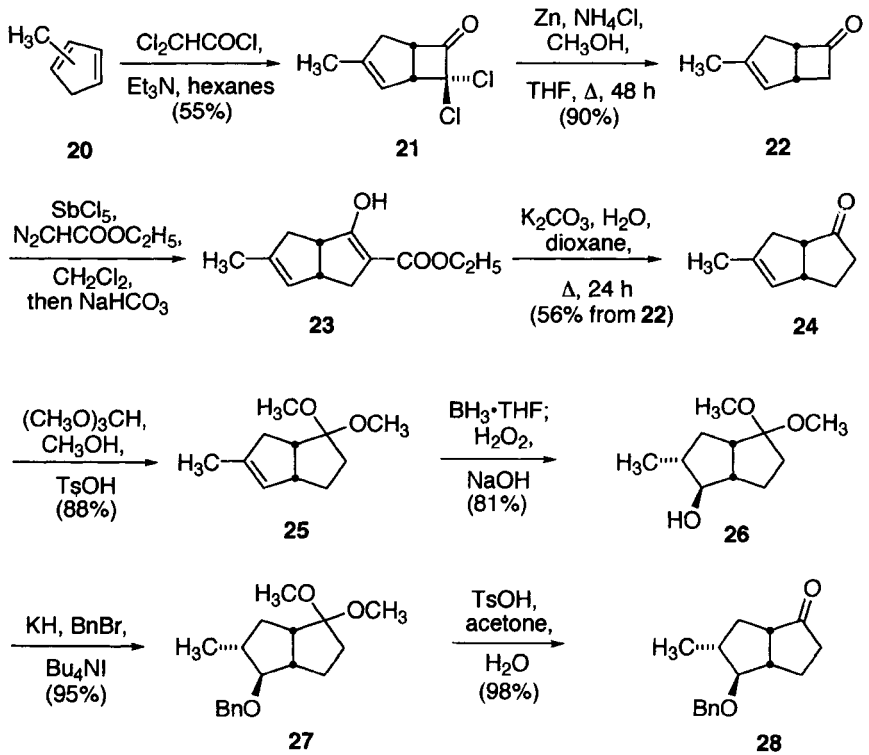
with in situ methylation of the enolate anion generated as the end-product of this [3.3] sigmatropic shift. Were the substituent X to be hydrogen, these intermediates would probably be underfunctionalized. In contrast, if X were a methoxy group, its role in **16** would be that of an enol ether and a more immediate precursor to the carbonyl group in **1**. Also, the oxygenated substituents at C7 and C14 in **16** will have earlier been chemically differentiated.

Variability is also possible for Y. In the simplest disconnection, it can be envisioned to be part of a β-dicarbonyl subunit, precisely as is present in the target molecule. However, these circumstances would run the risk of undesirable *O*-methylation en route to **16** if steric crowding were to emerge as a competitive side reaction. Alternatively, we expected a simple double bond within the five-membered ring to serve our purposes adequately.

It will be recognized that the topologies of **16** and **17** differ significantly. The former is a hemispherical structure as a direct consequence of the all-cis relationship of its four ring juncture sites. The crossing from **16** to **15**, if it became necessary to make this passage, would necessitate that the readily accessible H9 be reattached from the more crowded interior of the bowl-like framework. Such an epimerization is made workable only if the process is mediated by suitable neighboring group involvement.

III. Preparation of the Diquinane Building Block

Our point of departure toward **18** was methylcyclopentadiene (**20**), which had previously been shown by Brady and Hieble to undergo [2 + 2] cycloaddition in the presence of dichoroketene to give predominantly the bicyclic adduct **21**[13] (Scheme 4). The most efficient means to generate ketone **22** was to effect dechlorination with zinc and ammonium chloride in a combined solvent system



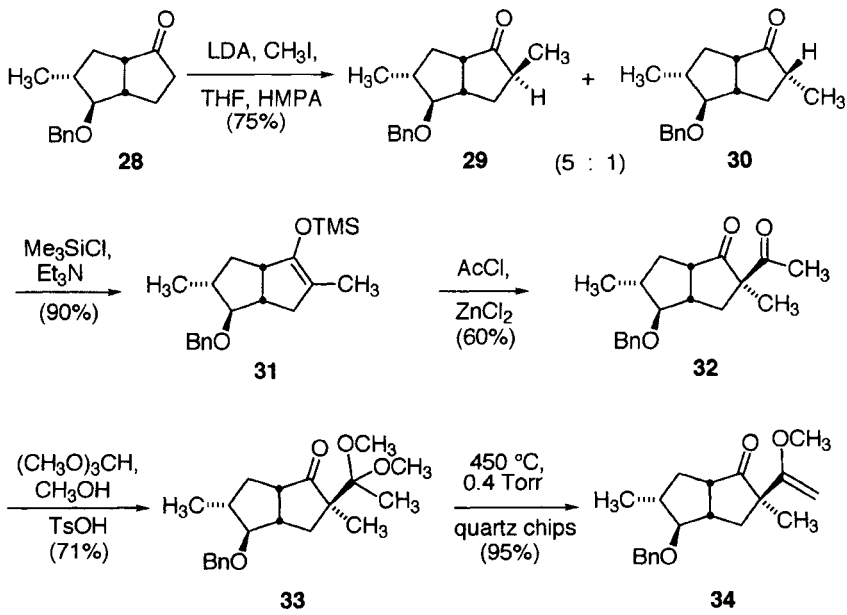
SCHEME 4

consisting of THF and methanol.[14] The desired homologation of **22** to **23** requires that the lesser substituted α carbon participate in the ring expansion step involving ethyl diazoacetate. This regioelectivity had previously been recognized to mandate the presence of a Lewis acid.[15] Following some preliminary screening studies, antimony pentachloride emerged as our reagent of choice. Since the product was a ester-enol mixture (see **23**), decarboxylation to deliver the keto diquinane **24** was performed in advance of chromatographic purification.

The carbonyl group in **24** could be temporarily protected as the dioxolane,[16] or somewhat more efficiently as the dimethyl acetal **25**.[17] Subsequent conventional hydroboration led stereoselectively to the β alcohol **26**. Although our earliest considerations called for ultimate base-promoted elimination of the OR substituent in intermediates more advanced than **16**, we later came to recognize that a methoxy derivative was not going to fulfill this role to our satisfaction. Alternatively, the tactic of forming the benzyl ether at this point ultimately proved well suited to the eventual return to an unmasked hydroxyl at this site.[17,18]

At this point, consideration was next accorded to proper introduction of the pair of substituents as in **34**. As expected, the regiocontrolled introduction of a methyl group proved not to be problematic, and lithium diisopropylamide came to be favored as the base. The β isomer **29** predominted by a factor of 5:1 over the α isomer for the usual steric reasons (Scheme 5). To reach silyl enol ether **31**, it was most efficient and practical to react the **29/30** mixture with chlorotrimethylsilane under thermodynamic conditions. This step proved to be critical, as it allowed for implementation of the Lewis acid-catalyzed acetylation of **31** under conditions where the benzyloxy substituent was inert. Equally convenient was the option to transform the modest levels of enol acetate produced competitively back to starting ketone by saponification with methanolic potassium hydroxide.

Fortunately, the reactivity levels of the two ketone carbonyls in **32** were sufficiently disparate to permit selective ketalization of that located on the pendant chain. The conversion to **33** was achieved in good yield by means of trimethyl orthoformate in excess methanol with *p*-toluenesulfonic acid as catalyst. Subsequent exposure of this

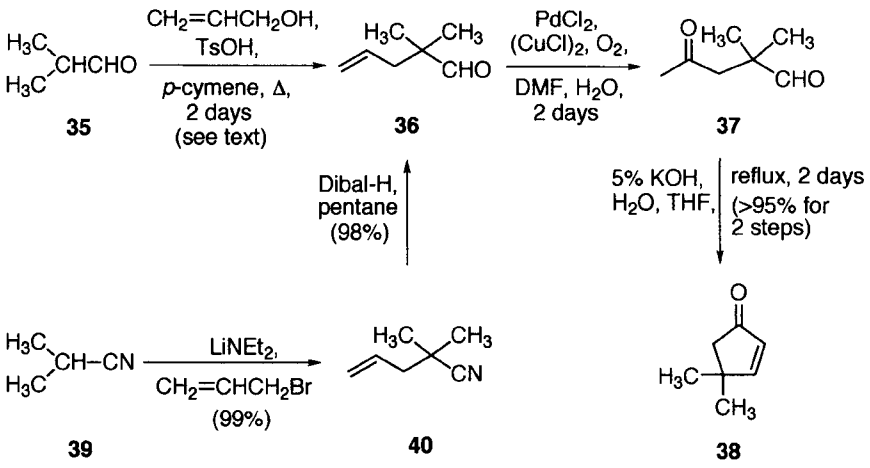


SCHEME 5

intermediate to flash vacuum pyrolysis conditions at 450 °C and 0.4 Torr over quartz chips provided the desired **34**. The high efficiency of this particular transformation (95%) is particularly noteworthy. Scott Edmondson's inventive aptitude was relied upon to make this step workable on a preparative scale.[16]

IV. Acquisition of the Brominated Cyclopentadiene

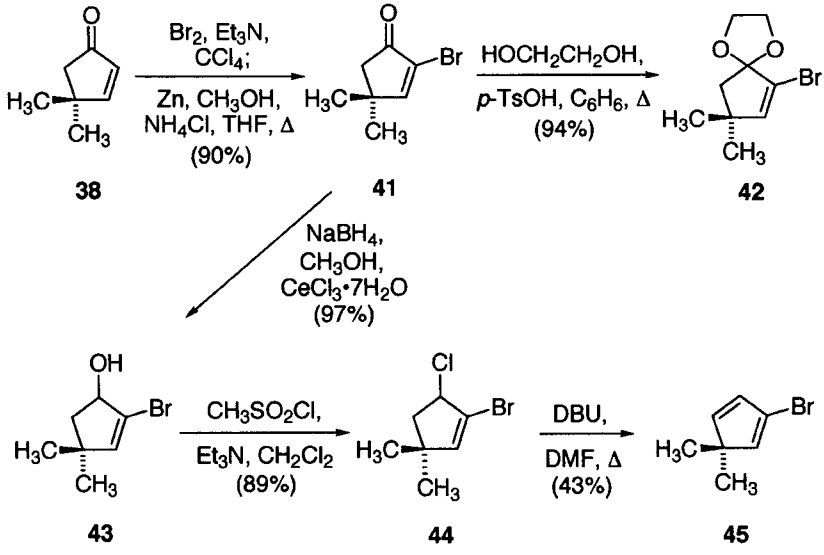
Although a clear route to **19** was identified as requiring 4,4-dimethylcyclopentenone (**38**) as starting material, the only known route to this cyclic ketone at this time (Scheme 6)[19] soon gained the reputation in our laboratories of being simultaneously capricious, inefficient, labor intensive, and time consuming. The crux of the problem was the first step involving the in situ ketalization/Claisen rearrangement of isobutyraldehyde (**35**) with allyl alcohol. For these reasons, Oliver Long designed an alternative approach based on isobutyronitrile (**39**) as the starting point.[17] This significant improvement is not scale-limited and offers excellent throughput. Thus, the correct number of carbon atoms is set at the outset by *C*-allylation of **39**, with lithium diethylamide serving as the base.[20] The diisobutylaluminum hydride reduction that immediately follows[21]



SCHEME 6

provided aldehyde **36**, which proved to be an excellent substrate for Wacker oxidation as earlier recognized.[19]

Careful examination of our retrosynthetic options suggested that bromocyclopentenone acetal **42** and bromocyclopentadiene **45** might serve our needs. To this end, we advanced to bromo enone **41** as a common link (Scheme 7).[16] Despite the steric bulk offered by the



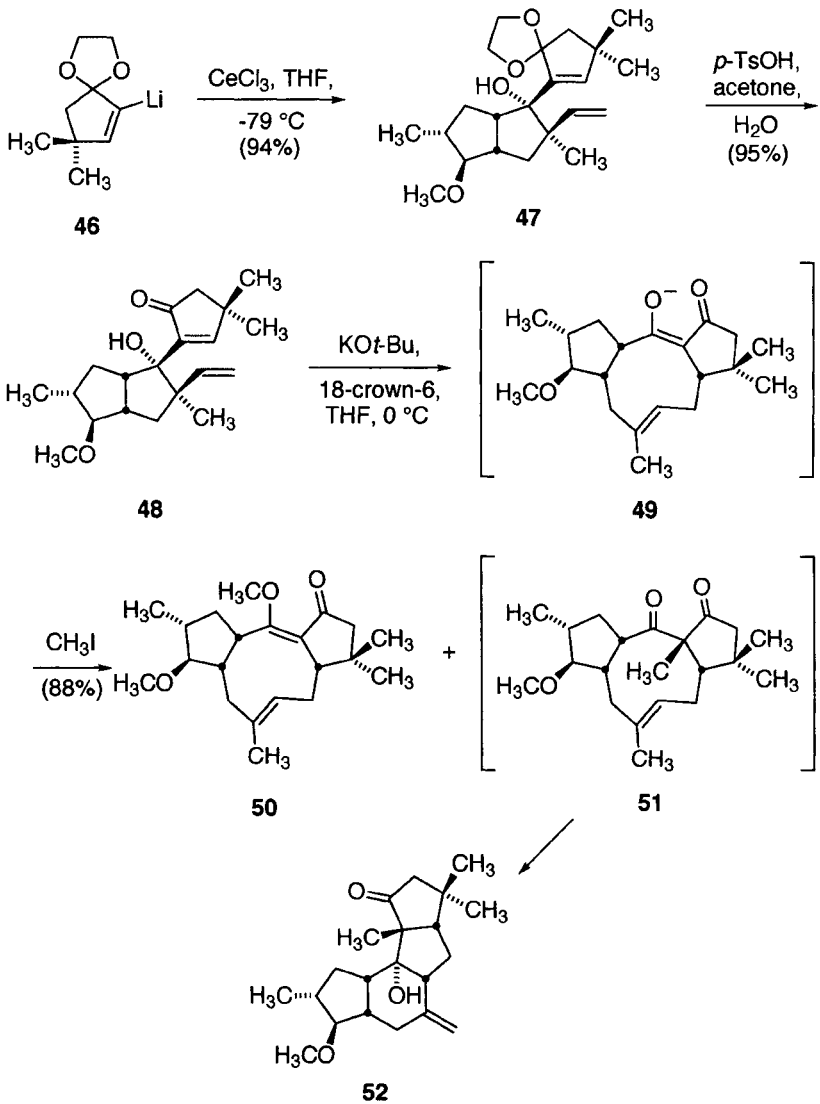
SCHEME 7

flanking bromine atom in **41**, acetal **42** and carbinol **43** were both formed readily without indication of serious kinetic retardation. The dehydration of **43** proved rather troublesome at first. However, Renato Skerlj soon recognized that chloride **44** could be obtained by exposing the allylic alcohol to the action of methanesulfonyl chloride and triethylamine. Shogo Nakatani taught us how to scale up this key transformation and to bring about the critical elimination step. While the conversion to **45** can be brought about with sodium iodide in acetone, greater reproducibility was achieved with DBU in warm dimethylformamide. A further advance was made when it was recognized that the volatile bromocyclopentadiene could be routinely utilized as a solution in pentane, thereby bypassing the need to handle it in a pure state for the upcoming coupling steps.

V. Defining the Nonserviceability of Bromo Acetal 42

Two assumptions are intrinsic to the **17** → **16** transformation integral to our retrosynthetic plan. The first concerns the adoption of a chairlike transition-state arrangement during the electronic reorganization that was to operate within **17**. Considerable precedent in favor of this option is available from prior reports describing the behavior of simpler structural analogues.[22,23] It was also anticipated that entry of the angular methyl group would occur on the more sterically accessible β surface of the enolate anion. Beyond this, we anticipated that transannular ring closures would operate whenever mechanistically feasible. On the positive side, we were hopeful that such events could be used to our advantage.

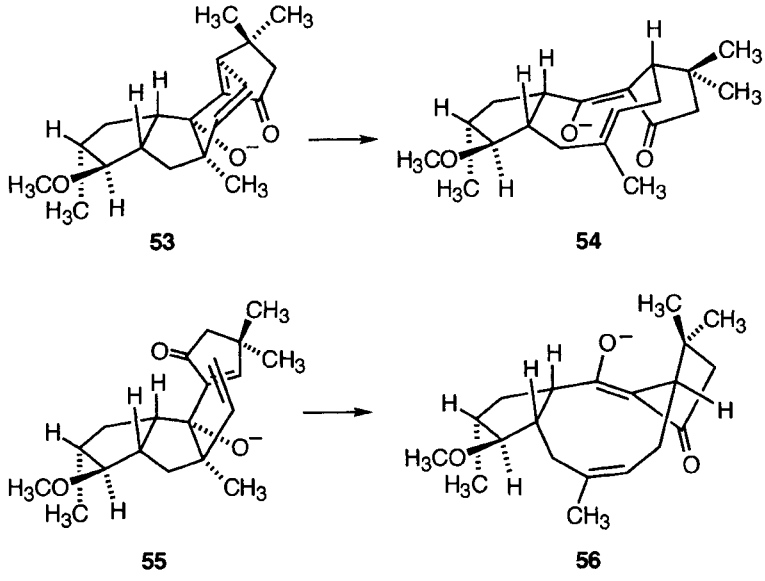
In early studies, the coupling of cyclopentenyllithium **46** to the vinylated methoxy congener of ketone **34** in the presence of anhydrous cerium trichloride[24] gave **47** in 94% yield without evidence of competing enolization (Scheme 8).[16] The highly stereocontrolled course of this 1,2-addition was a most welcomed development that set the stage admirably for examination of the projected ring expansion. Prior to this event, the ketone carbonyl was unmasked by acidic hydrolysis to make **48** available. The cis juxtapositioning of the two double bonds in **48** appeared to us on the basis of analogy[12,25] to be particularly well constructed for [3,3] sigmatropic rearrangement via chairlike transition state **53** (Scheme 9). Use of this reaction trajectory would result in the proper merger of chirality, with the three angular hydrogens assuming an all-cis



SCHEME 8

relationship as in **54**. In contrast, the boatlike alternative **55** is more congested and not conducive to proper matching of the stereogenic centers (see **56**). The differing nature of the double bond geometries in **54** and **56** is also of interest.

At the experimental level, the treatment of **48** with potassium *tert*-butoxide and 18-crown-6 in THF at 0 °C for 1 h with subsequent introduction of excess methyl iodide gave rise to a 1:1.7 mixture of



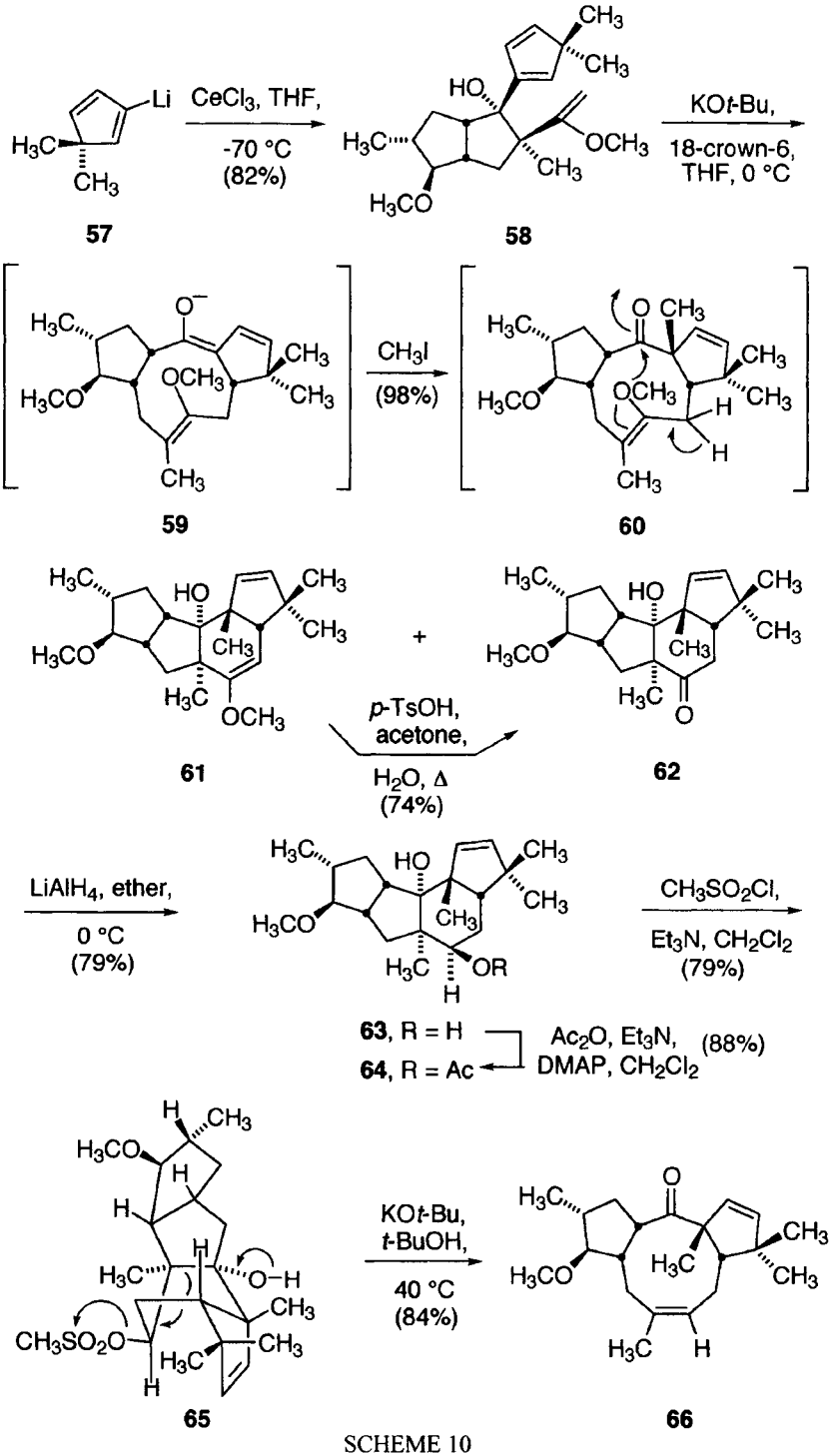
Scheme 9

50 and **52**. The relative stereochemistry of tricyclic ketone **50** was ascertained by NOE studies. Recourse to X-ray crystallography rigorously established the structural features of **52**. Of special significance is its transoid B/C ring fusion, which in turn requires that the cyclononene double bond common to **49-51** be *E* as drawn.[26-30]

Although the anionic oxy-Cope rearrangement of **47** served admirably as a means for accessing **50** and **52**, the utility of the major tetracyclic product was not viewed with optimism. We identified a variety of options for central bond cleavage therein, but the steps needed to accomplish this chemistry were certain to result in appreciable lengthening of the synthetic undertaking. For these reasons, we turned our attention instead to the deployment of **45** as the precursor to the nucleophile of choice.

VI. Arrival at the Carbotricyclic Network

When Li-Qiang Sun joined the group to initiate his postdoctoral studies, he elected to examine the consequences of adding **57** to the *O*-methyl analogue of **34** (Scheme 10). While the formation of **58** proved uneventful in the presence of $CeCl_3$, caution had to be exercised while performing the rearrangement/methylation step. We


Li
CeCl3, THF,
-70 °C
(82%)
KOt-Bu,
18-crown-6,
THF, 0 °C
57
58
CH3I
(98%)
59
60
p-TsOH,
acetone,
H2O, Δ
(74%)
61
62
LiAlH4, ether,
0 °C
(79%)
CH3SO2Cl,
Et3N, CH2Cl2
(79%)
63, R = H
64, R = Ac
Ac2O, Et3N,
DMAP, CH2Cl2
(88%)
KOt-Bu,
t-BuOH,
40 °C
(84%)
65
66

SCHEME 10

had uncovered a short time earlier that the complexation of potassium ions with the crown ether leaves enolate anion **59** in an unsolvated, highly reactive state where it is prone to capture by molecular oxygen.[31] Once proper precautions were exercised, the combined yield of **61** (64%) and **62** (34%) realized in this step was very gratifying. To reach these tetracyclic products, **59** had to experience methylation from the β direction, thereby generating ketone **60**. Its central ring is evidently highly reactive, with transannular ene cyclization now occurring along a trajectory totally different from that exhibited by **51**. In this earlier example, proton abstraction took place at the extra-annular methyl substituent. In contrast, the additional methoxy group in **60** directs the ene reaction to operate along that intra-annular pathway involving the allylic ring methylene adjacent to the OCH_3 substituent as shown. Ultimately, mild acid hydrolysis of **61** transformed the entire reaction mixture into the lone product **62**, a molecule that was initially difficult to characterize because of its dynamic conformational properties on the NMR time scale at room temperature. A first-order spectrum was, however, recordable at 77 °C.

The β-hydroxy ketone nature of **62** suggested to us that it might well be a substrate ideally suited to Grob fragmentation.[32,33] In this way, the central C-C bond could be cleaved under conditions of stereochemical control. Since olefin geometry in the impending Grob product is directly linked to the relative orientation of the leaving group,[34] it became important to effect reduction to **63**. The use of lithium aluminum hydride in ether generated a carbinol mixture with 10:1 selectivity in favor of the β isomer. The ^1H NMR spectrum of this major product was unfortunately too poorly resolved to permit unequivocal assignment. When Nat Monck prepared its acetate **64**, he quickly recognized that the puzzle could now be solved through the application of HETCOR and long-range C-H correlation techniques, in tandem with diagnostic NOE enhancements. These studies confirmed that axial hydride delivery had indeed occurred to orient the secondary hydroxyl equatorially as desired.

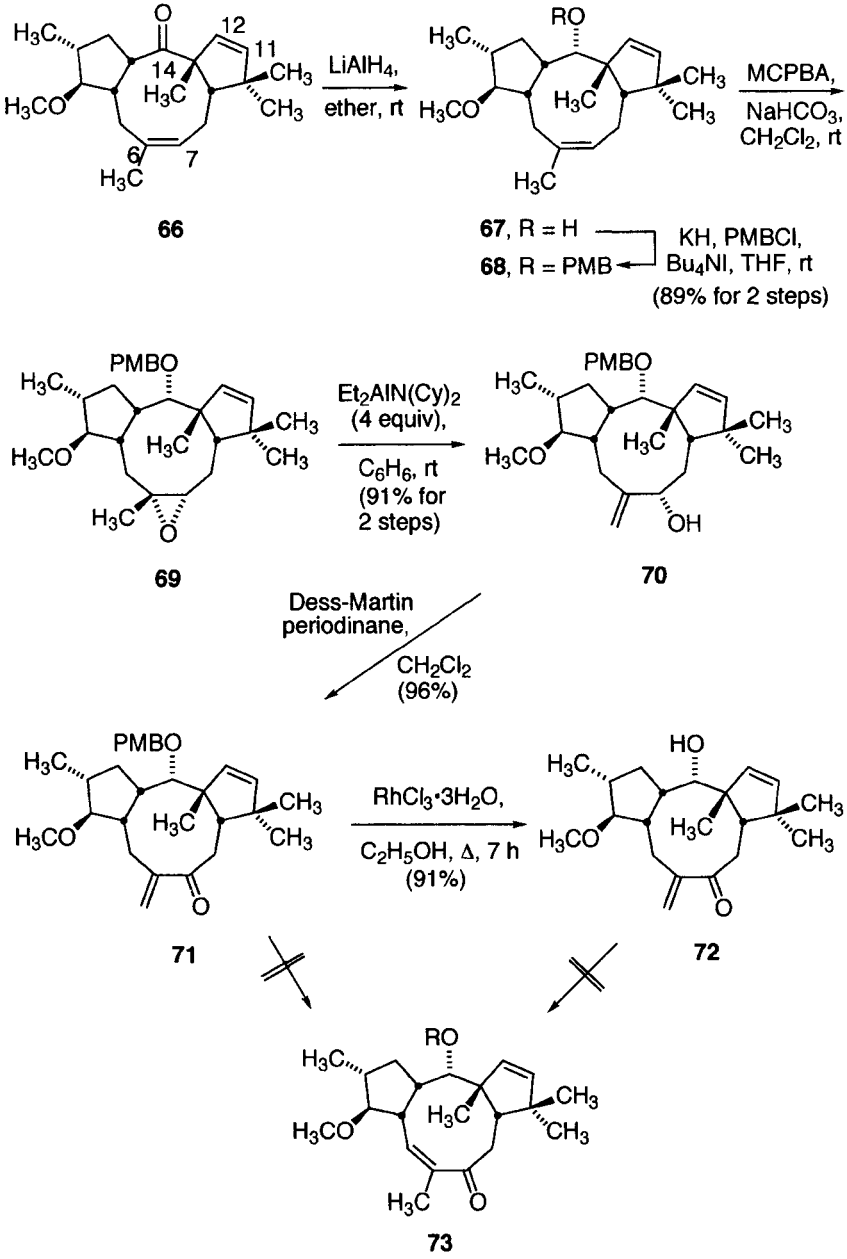
Treatment of the derived mesylate with potassium *tert*-butoxide in *tert*-butyl alcohol resulted in smooth and efficient conversion to

the [5.9.5] tricyclic ketone **66**, the *Z*-olefin geometry illustrated in **65**, such that the leaving group is oriented antiperiplanar to the σ bond experiencing scission.

VII. More Advanced Functionalization of Potential 9-Epi Precursors

With the development of a concise route to **66**, which is notably well tailored to cis orientation of the four ring juncture positions, came the need to develop the chemistry of this intermediate for the purpose of generating 9-epijatrophatrione (**7**). With Scott Edmondson poised to assume these responsibilities, the project was in good hands. The first issue that he chose to explore involved the regioselective functionalization of the C6-C7 olefinic center. Since **66** was available in quantity, we continued to advance in the methoxy series. In line with the ground state conformation of **66**, its reduction with lithium aluminum hydride in ether was met with exclusive attack from the convex face of the ketone carbonyl (Scheme 11). After formation of *p*-methoxylbenzyl ether **68**, its epoxidation was likewise found to proceed stereopecifically. The structural assignment to **69** is based on that made to a diol generated subsequently in which dihydroxylation from the α face was corroborated by crystallographic methods.[35] Isomerization of **69** to allylic alcohol **70** was accomplished with diethylaluminum dicyclohexylamide at room temperature. Under these conditions, proton abstraction occurred smoothly at the methyl group to introduce an exocyclic double bond.[36] Once oxidation with the Dess-Martin periodinane[37] had been completed, the option to remove the PMB protecting group from **71** was exercised to provide **72**.

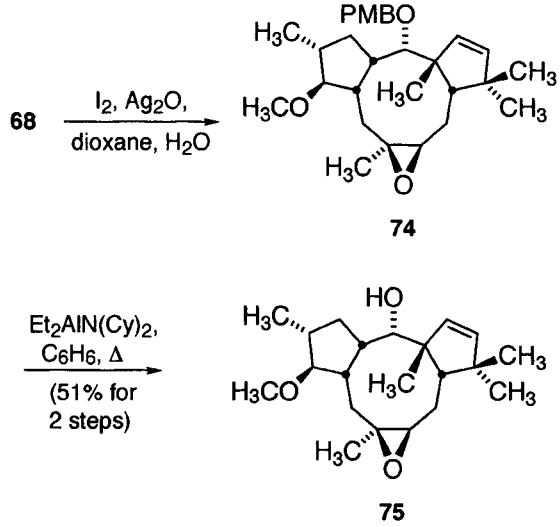
This series of successful events now caused us to direct attention to the feasibility of exocyclic to endocyclic olefin isomerization. Precedent is lacking with regard to this phenomenon in medium-sized rings. In our hands, reagents such as palladium on carbon[38] and rhodium trichloride[39] proved to be totally ineffective in bringing about the desired positional shift. This inertness prompted Scott to alter the conformation of the tricyclic substrate by preparing the isomeric epoxide **75** (Scheme 12). This transformation was accomplished with a combination of iodine and silver(I) oxide in aqueous dioxane.[40] However, neither **74** nor **75** proved reactive to a cadre of bases, presumably because the methyl group is not now



66 **67**, R = H **68**, R = PMB **69** **70** **71** **72** **73**

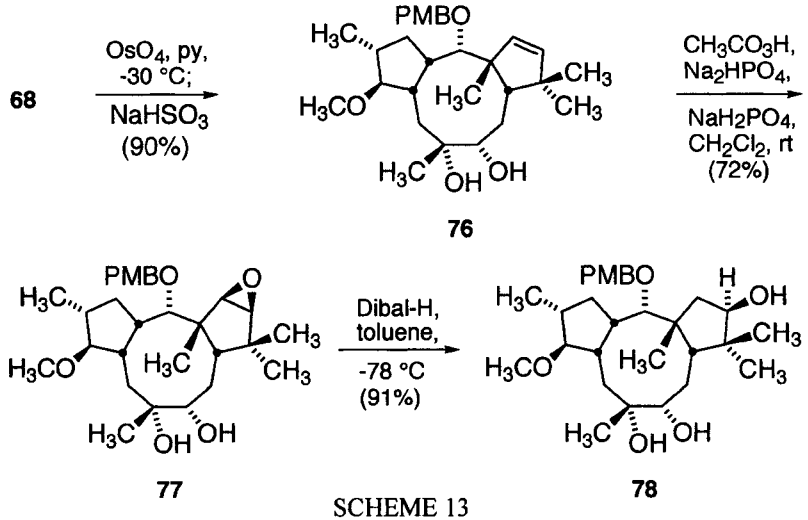
SCHEME 11

sterically accessible. At this point, it was apparent that an alternative approach had to be devised for installing the C7-C8 double bond.



SCHEME 12

For the sake of maximizing efficiency, the decision was made to prove the preceding question concurrently with the further functionalization of ring C. As reflected in our earlier studies involving **68**, the appreciably hindered C11-C12 double bond located in the five-membered ring was not expected to be more reactive than its counterpart in ring B in other settings. Indeed, dihydroxylation with osmium tetraoxide furnished **76**, epoxidation of which led in a



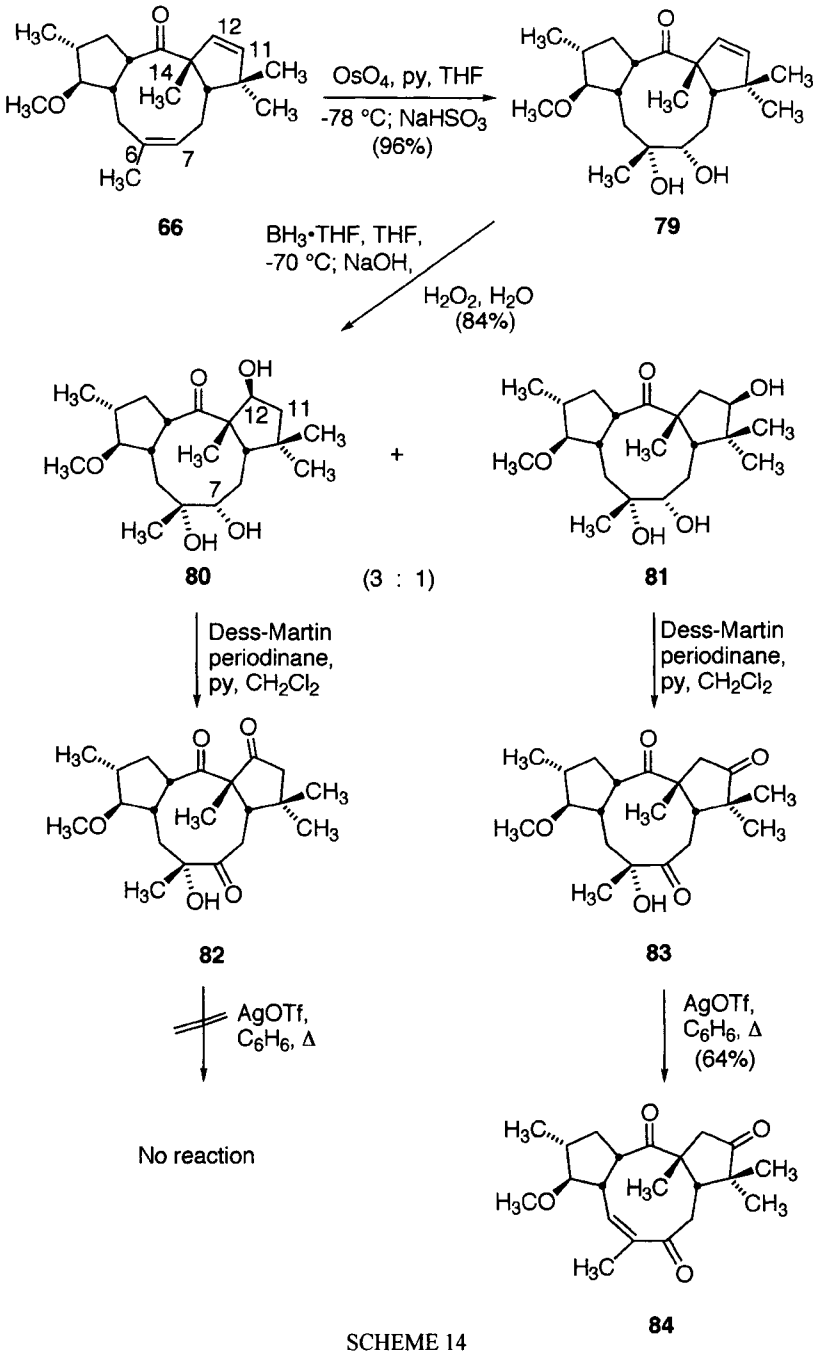
SCHEME 13

very slow reaction to **77** (Scheme 13). The high crystallinity of

76 provided the opportunity to unequivocally ascertain its stereochemistry by X-ray crystallographic methods.[35] Both C-O bonds of the oxirane ring in **77** are seen to be neopentyl in nature, with different sets of carbon atoms flanking the three-membered ring. The high level of steric shielding was reflected in the inertness of **77** toward reduction with diisobutylaluminum hydride. However, ring cleavage does occur at -78 °C in the presence of the less solvated Dibal-H in toluene reagent system. The process was entirely regioselective, giving rise to **78** in 91% isolated yield. The preferential oxygenation of C11 rather than C12 was unacceptable and caused us to explore execution of the osmylation step at an earlier stage of the synthesis.

The reactivity of **66** proved to be encouragingly high at -78 °C, being transformed almost quantitatively into **79** (Scheme 14). Further, the hydroboration-oxidation of **79** was uneventful and afforded a 3:1 mixture of alcohols rich in the desired isomer **80**. Clearcut distinction between this pair of regioisomers relied on the application of 2D NMR methods for the assignment of all the proton and carbon signals. On the basis of these data, it was made quite apparent that the carbinol proton residing at C12 in **80** is positioned within the shielding cone of the nearby carbonyl and is consequently shifted downfield to 4.90 ppm. This is not possible for the corresponding proton in **81**, which is located at 3.80 ppm. For the subsequent oxidation of these intermediates, it was necessary to avoid chromium reagents because of anticipated cleavage of the glycol to the corresponding keto aldehyde. Quite unexpectedly, the Dess-Martin periodinane reagent triggered this undesirable transformation to a modest level. At this point, we took note of the fact that others had seen fit to moderate the reactivity of this reagent through the co-addition of pyridine.[41] This simple modification of the experimental conditions served very well to produce triketones **82** and **83** independently. Single crystal X-ray analysis of **82** confirmed the regioselectivity of the hydroboration as well as the stereoselectivity of the osmylation.

The next challenge in our pursuit of 9-epijatrophatrione (**7**) was the proper elimination of the elements of water from **82**. However, **82** proved to be remarkably recalcitrant to dehydration under a wide variety of conditions.[42] Companion studies involving **83** turned up one exciting lead. When heated with silver triflate or silver



SCHEME 14

perchlorate in benzene,[43] smooth conversion to **84** was observed. Following our demonstration of the inertness of **82** to silver(I) salts,

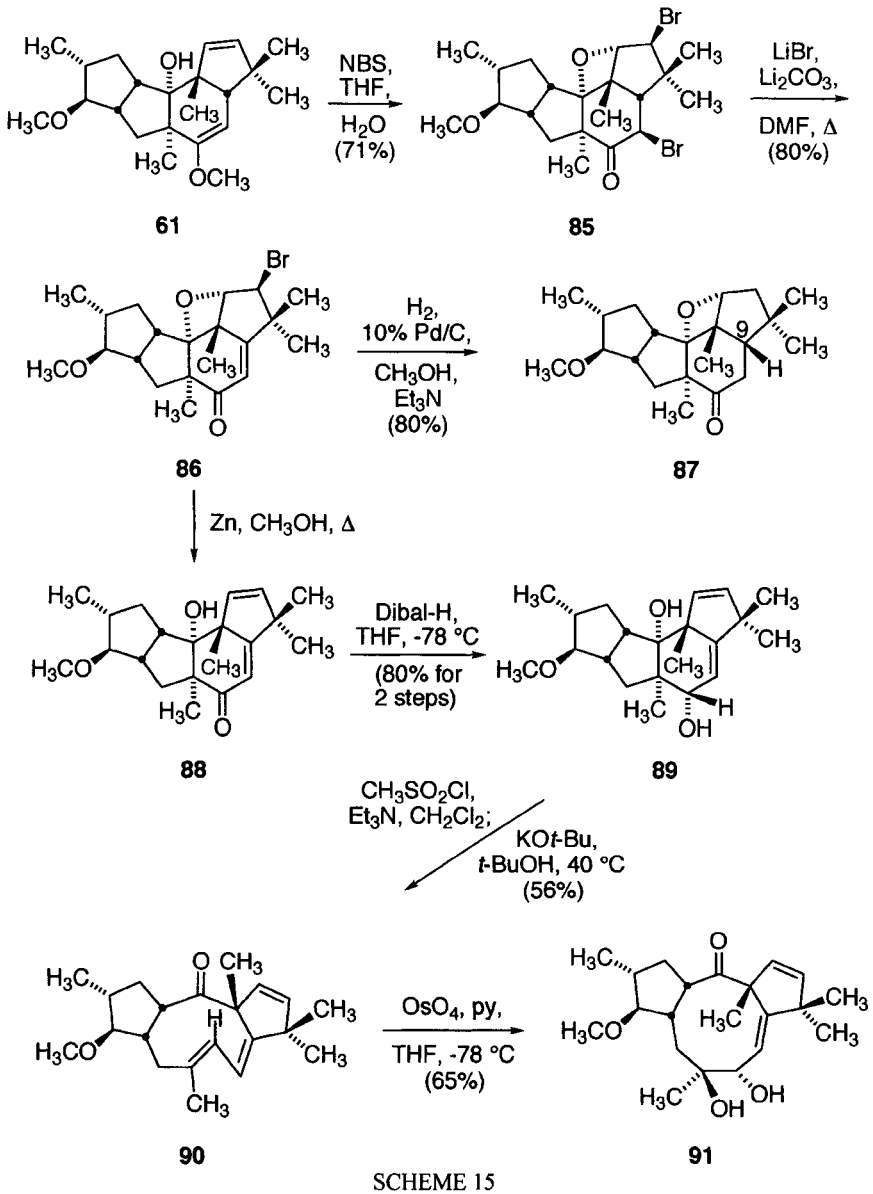
this triketone came to be regarded as an intermediate unsuited to completion of the synthesis.

For a variety of reasons, many of which are not detailed herein, the wisdom of installing the β-dicarbonyl array too soon was brought into question. Were this step relegated to the final stages of the synthesis, the built-in sensitivity arising from the potential for β-elimination would be skirted. In this connection, the demise of **82** prompted the consideration of unsaturated precursors to **1** and **7** as viable synthetic candidates.

VIII. Elaboration of 8,9-Dehydro Precursors

The positioning of a double bond across C8/C9 would presumably allow for definition of the stereochemistry of C9 at a later stage, and make possible in principle the acquisition of both **1** and **7** from a common intermediate. With these goals in mind, **61** was reacted with *N*-bromosuccinimide in aqueous tetrahydrofuran.[35] Our expectation was that bromination of the enol ether and generation of a bromooxetane would materialize concurrently (Scheme 15). That **85** had indeed been isolated in 71% yield was initially supported by NMR spectroscopy and later corroborated by crystallographic analysis. Subsequent recourse to a mixture of lithium bromide and lithium carbonate in hot dimethylformamide[44] resulted in the elimination of one equivalent of HBr and formation of the α,β-unsaturated ketone **86**. Of some significance is the realization that this step planarizes C9 without perturbing the stereogenicity of the remaining nine chiral centers.

Fully as expected from the inspection of molecular models, the generation of the oxetane ring has the effect of heightening the structural curvature in compounds such as **85** and **86**. Reagent approach from the exterior should materialize under kinetically controlled conditions. These features are reflected in the catalytic hydrogenation of **86**, which results in saturation of the double bond from the β surface along with reductive debromination to furnish **87**. The lesson learned here is that the oxetane ring should be released or not formed at all if an opportunity to approach C9 from the α direction has any chance to take place.



61 85 86 87 88 89 90 91

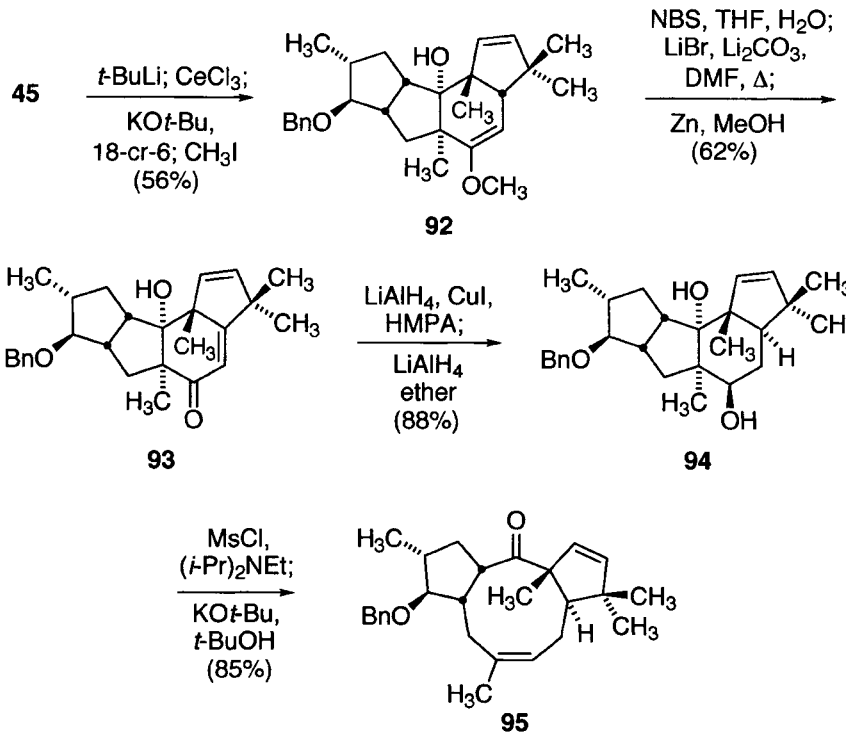
SCHEME 15

This line of thinking prompted the treatment of **86** with zinc in refluxing methanol for the purpose of generating **88**. When this ketone was reduced with diisobutylaluminum hydride in tetrahydrofuran at low temperature, the cis diol **89** was produced with a stereoelectivity in excess of 10:1. Monomesylation of the

major isomer was easily realized in a fully regioselective manner, thereby permitting access to tricyclic ketone **90**. These discoveries, alongside the dihydroxylation of **90** to generate **91**, served as an encouraging backdrop and provided reasonable assurances that we now comprehended for the most part the rather rigorous timing of the chemical events that would culminate in a successful approach to jatrophatrione (**1**).

IX. Setting the Natural Configuration at C9

The undertaking described above alerted us to a number of tactical issues necessarily associated with synthetic operations involving a functionalized [5.9.5] tricyclic framework. The three most prominent were: (a) facile transannular bonding; (b) limited kinetic stability following introduction of the 1,3-dicarbonyl unit at C12 and C14; and (c) an exceptionally high proclivity for reagent attack on the most sterically accessible convex surface, most particularly in the case of the all-cis stereoisomer. Chiefly because of the last criterion, pursuit of the 9-epi isomer **7** was curtailed in favor of natural jatrophatrione. This decision mandated that a means be found for the convenient α-positioning of H9 as in **1**. To this end, **93** was synthesized as readily as its methoxy analog **88** (Scheme 16).[17,18] The opportunity to screen a large variety of protocols involving hydroxyl-directed hydrogenation[45] then presented itself. In brief, the considerable amount of time spent to saturate the double bond in the desired manner was to no avail. To further enrich the number of substrates, the D-ring α-epoxide of **93** was prepared and likewise scrutinized. When no useful findings materialized, an examination of the conjugate reduction of **93** began. Just as the continuous string of failed experiments was beginning to frustrate Jiong Yang, he was attracted to a notably brief report by Saegusa[46] in which the ability of CuI to promote the efficient 1,4-reduction of enones by lithium aluminum hydride in the presence of HMPA was touted. These conditions, which may constitute an especially simple means for preparing copper hydride, proved to be extremely useful. The major product (77%) was the dihydro ketone in which hydride delivery had occurred predominantly syn to the hydroxyl (stereoeslectivity greater than 14:1). Diol **94** was also produced (12%). Once this outcome was recognized, the initially formed mixture was routinely reduced directly with additional $LiAlH_4$ to generate **94** predominantly (88% isolated). For comparison



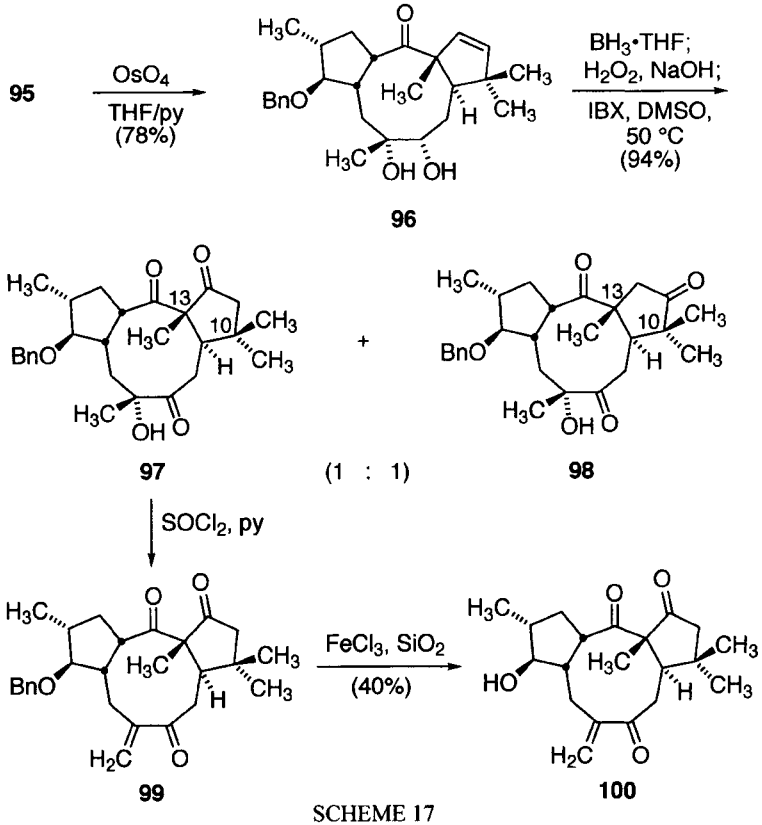
SCHEME 16

purposes, **93** was also reduced with $LiAlH_4$ in the absence of CuI and HMPA. Under these circumstances, diol **94** was produced in only 11% yield. The structural features of **94** were deduced by 2D NMR methods and by direct comparison with the 9β epimer that was already available to us.

Once **94** was in hand, it proved an easy matter to bring about its transformation regioselectively into the monomesylate and to bring about subsequent Grob fragmentation. These two steps delivered **95** with a level of efficiency (85% overall) higher than that previously encountered in the all-cis series, *viz.* **63** → **66**.

X. Responding to a Siren Call

Our first experiments involving **95** were concerned with establishing the dienone functionality along the leading edge of the target structure (C3-C7). The divergent behavior of **82** and **83** was singled out as an important observation and prompted our curiosity to



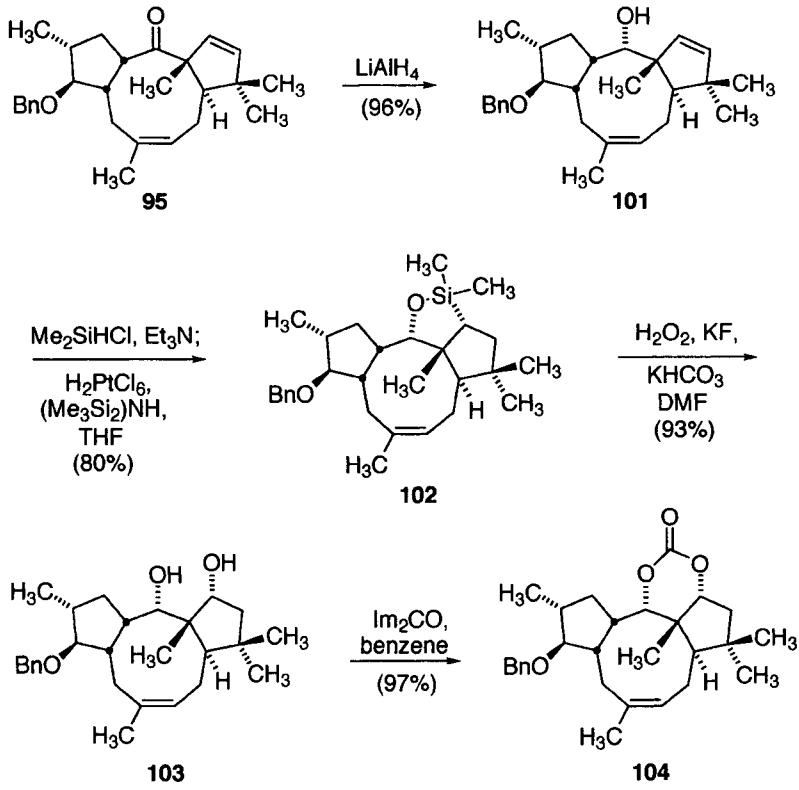
SCHEME 17

determine the impact of a change to trans B/C ring fusion on the ease of comparable dehydration. Accordingly, **95** was dihydroxylated with osmium tetraoxide. A slow reaction ensued to generate **96**, which fortunately exhibited no obvious tendency to undergo transannular hemiketalization (Scheme 17). As a result, **97** and **98** could be generated by sequential hydroboration and oxidation with *o*-iodoxybenzoic acid.[47] Following the chromatographic separation of these regioisomers, the dehydration of **97** was probed. After a series of experiments showed this transformation to be quite erratic, we settled on the use of thionyl chloride in pyridine for this purpose. Only the exocyclic olefin **99** could be characterized (40%). Once again, the sensitivity customarily seen following introduction of the β-dicarbonyl unit made its appearance. We had not yet learned our lesson well! As before, we were also not able to generate the endocyclic enone isomer. Our hopes that ferric chloride adsorbed on silica gel[48] would serve as a mild way to introduce the entire dienone segment by inducing as well the elimination of benzyl alcohol were

dashed when it was determined that unprecedented debenzylation occurred to form **100**. The possibility of generating the xanthate of **100** was not feasible as a direct result of the general sensitivity of this class of triketones to basic reagents.

XI. Preferred Means for Functionalizing the Northern Rim

Following the identification of these additional problematic steps, we pursued the reduction of ketone **95** to alcohol **101** for the purpose of exploring intramolecular hydrosilylation[49,50] as an ultimate means of oxygenating C12 exclusively (Scheme 18). To our delight, conversion of the dimethylsilyl ether to **102** proceeded smoothly in the presence of a catalytic amount of H_2PtCl_6. No evidence was found for competitive operation of a process other than internal capture of the silyl hydride functionality to form the five-membered siloxane. Originally, we intended to maintain the C-Si bond in place until the later stages of the synthesis. However, the reaction conditions required to make the proper advances proved sufficiently

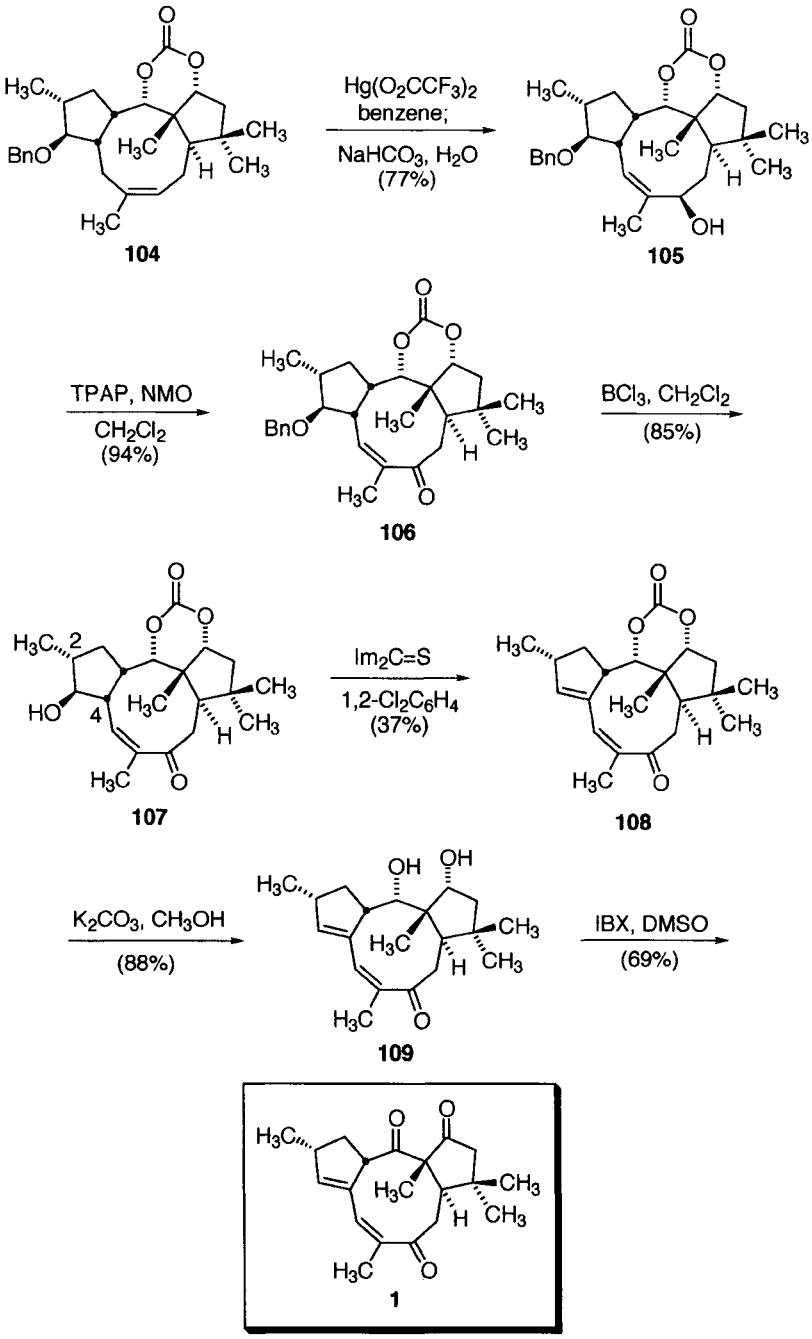


SCHEME 18

vigorous to preclude this option. Consequently, **102** was subjected to Tamao oxidation only to find that conventional conditions involving hydrogen peroxide and potassium fluoride in a mixture of methanol and tetrahydrofuran containing potassium bicarbonate afforded **103** in low yield, even after long reaction times.[50] In his own inimitable way, Jiong Yang followed suit by evaluating a number of alternative solvent systems. The outcome of this activity was the discovery that a change to dimethylformamide[51] shortened the reaction time to 8 h while consistently delivering the diol in yields well above the 90% level. Protection as the cyclic carbonate **104** followed,[52] this intermediate ultimately serving as the key intermediate in the successful route to jatrophatrione.

XII. Relevance of the Treibs Reaction to the End Game

With completed construction of the northern rim of our target, the proper introduction of functionality in the southern C3-C7 sector now had to be devised. Initially, we placed our hopes in regiodirected epoxide ring cleavages and conventional allylic oxidation protocols. However, none of these attempts proved fruitful, thus forcing us to resolve our needs in a different manner. In his reasonably desperate search for alternative indications regarding more obscure ways to proceed, Jiong came across a quite brief 1948 single author report that described the feasibility of inducing the allylic oxidation of olefins upon heating with mercuric acetate in acetic acid.[53] This process, dubbed by us as the Treibs reaction, was upon further tracking noted to have been deployed only very infrequently since that time.[54-56] The influence one draws from reading these published reports is that the conditions were viewed as somewhat forcing. Indeed, the C-Si bond in **102** proved sensitive to the action of mercuric acetate in refluxing benzene. This was not the situation with **104**, which underwent conversion to **105** in 77% yield (Scheme 19). The highly desirable transposition of the double bond seen to operate in the course of this reaction has been rationalized mechanistically by us in terms of initial attack at the pi bond by the mercury reagent to generate a mercurinium ion. Rather unique perhaps is the ring opening of the mercurinium ion to an allylic mercurial, thereby setting the stage for the solvolytic formation of Hg(O) and one or both allylic acetates.[54,57]



SCHEME 19

This model served as the rationale for considering the possibility that subsequent stirring of the reaction mixture with $NaHCO_3$ in

water might lead stereoselectively to **105** in a simple one-pot operation. The remarkably good regioselectivity associated with this transformation is attributed to the unsymmetrical nature of the putative mercurinium ion, whose biased "open character" places modest positive charge on the methyl-substituted carbon (C6), thereby inducing more facile deprotonation at C5 as allyl mercurial character develops.

In this connection, our finding that the allylic mercury intermediate represents the only isolated product following reaction in THF, CH_2Cl_2, or HMPA is pertinent. The generation of this species appears to be rapid in all media. The ensuing step in which Hg(II) is reduced to Hg(O) likely serves as the rate-determining step. If so, the role of nonpolar benzene may be to stabilize the transition state and accelerate the overall rate. No allylic alcohol having an exocyclic double bond was formed, a feature that hints to the possible operation of thermodynamic control.

On reaching **105**, oxidation to give **106** was accomplished with tetra-*n*-propylammonium perruthenate.[58] Debenzylation was subsequently achieved by taking advantage of the chemoselectivity exhibited by boron trichloride in dichloromethane.[59] At this juncture, syn elimination of the C3 hydroxyl group in **107** was mandated. It will be recognized that two regiochemical options are available. Of these, a strong kinetic preference for dehydration toward H2 with avoidance of the site of ring fusion (H4) was exhibited during pilot studies carried out on less advanced analogues of **107**. However, these model systems lacked the C5-C6 double bond. Therefore, we took the position that the presence of the enone segment in this tricyclic system could induce a higher level of acidification at H4 despite the nonplanarity of the chromophore.

First to be explored was xanthate formation. However, this thrust was doomed to failure because of the sensitivity of **107** to base, a likely result of its vinylogous aldol character. Subsequently, it was determined that the desired dehydration could be accomplished simply by heating **107** with thiocarbonyldiimidazole in 1,2-dichlorobenzene.[60] This process gave rise to the desired **108** (37% isolated) along with the $\Delta^{2,3}$ isomer (10%), from which it could be readily separated chromatographically. Hydrolytic removal of the cyclic carbonate in **108** required 3 h to proceed to completion when

performed with K_2CO_3 in methanol at room temperature. This reaction time is significantly longer than that required for **105**, where quantitative conversion to the triol was complete in only 5 min.[61] This kinetic inequality may be a reflection of greater ring strain in the latter example. The final twofold oxidation, accomplished with IBX in DMSO,[47] gave **1** in 69% yield.

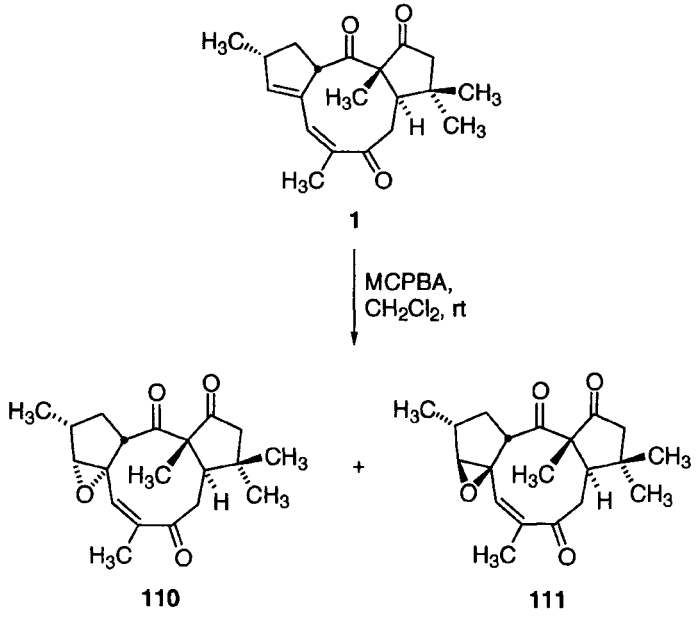
As we neared completion of this endeavor, contact was made with Professor Robert Bates, a long standing friend dating back to my graduate days at M.I.T. Bob had been involved with the original isolation and characterization of jatrophatrione. Unfortunately, he was not in a position to honor our request for a copy of the ^{1}H NMR spectrum and/or a small authentic sample. The relevance of these reference materials increased with time. Our synthetic jatrophatrione exhibited a 500 MHz NMR spectrum entirely congruent with that of the natural product recorded at lower field strength. However, the ^{13}C NMR data originally reported differed from our measurements recorded systematically at 100 and 125 MHz. How could this be? Certainly, we could not claim that comparative analysis had been successfully achieved.

Little time passed before we consulted with Dr. Charles Cottrell, our resident NMR guru. Chuck recalled that he had encountered similar phenomena on two prior occasions during his 30+ year career, both associated with the instrument type employed by the Arizona researchers. In both prior cases, the discrepancy was caused by an error in the dwell clock divider chain of the Fourier transform spectrometer. The dwell time, which is generated by the dwell clock located in the digitizer, sets the frequency width of the spectrum. The relationship between them is SW = 1/(2*DW) where SW is the sweep width in Hertz and DW is the dwell time. Importantly, the shift differences between the peaks seen in our spectrum and those of the literature increase the further we go from TMS. Therefore, the discrepancy is not due to a simple referencing problem which would give a constant difference between the peaks of the two spectra. Nor could a temperature or concentration difference account for these observations. Our conclusion that we were dealing instead with a systematic error was supported by a plot of the increasing difference versus chemical shift where high linear correlation ($\rho = 0.998$) was obvious.

XIII. The Ultimate Characterization of Jatrophatrione

Although the spectroscopic dilemma described above may be classified as minor by some, our perfectionist tendencies prompted us to seek a companion source of structural confirmation. Our search for natural products closely related in structure to **1** was rewarded by the discovery of a report that appeared in 1988 concerning the identification of constituents obtained by extraction of the roots of "tlapelex patli". This plant is native to northeastern Mexico and the name is Aztec for *Jatropha dioica*.[7] The natives of this region appear to have recognized for some time its beneficial effects in the treatment of skin cancer. The Texas A+M University team headed by Ian Scott determined by spectroscopic means and X-ray crystal structure analysis that the major active constituent of *J. dioica* is citlalitrione (**111**). In essence, **111** constitutes a monoepoxide of jatrophatrione.

We seized the opportunity to subject **1** to the action of *m*-chloroperbenzoic acid in dichloromethane at room temperature (Scheme 20). To our delight, citlalitrione was indeed produced, although the α-epoxide **110** was formed more predominantly. The



1 **110** **111**

SCHEME 20

^1H and ^{13}C NMR spectra of synthetic **110** were identical to those registered by Dr. Howard Williams and made available to us by him.

XIV. Conclusion

The successful *de novo* generation of jatrophatrione (**1**) and citlalitrione (**111**) constitutes the first successful syntheses of any [5.9.5] tricyclic diterpenoid. The length of the linear sequence from the point of convergency (Scheme 16) is 20 steps. The highlights of this venture include an anionic oxy-Cope rearrangement that conveniently sets in place a tetracyclic structural framework (*viz.* **92**) amenable to further chemical modification. Following arrival at dienone **93** seven steps later, use was made of intramolecular hydrosilylation to guarantee the cis relationship of the two hydroxy groups at C12 and C14 and to protect this functionality as a cyclic carbonate. A notably productive step involved application of the Treibs reaction to **104**, the resulting allylic alcohol serving as a pivotal platform for regiocontrolled dehydration as defined by **107** → **108**. The ultimate oxidation to the 1,3-diketone level established this sensitive fragment as late as possible. The conversion of **1** to citlalitrione (**111**) confirmed that the total synthesis of jatrophatrione had indeed been realized.

Acknowledgments

The successful synthesis of jatrophatrione described in this chapter was made possible because of the talents and research prowess of a devoted group of co-workers. Particular thanks and appreciation go to Drs. Scott Edmondson, Yun Oliver Long, Nat Monck, Shogo Nakatani, Renato Skerlj, Li-Qiang Sun, Jiong Yang, and Tom Zydowsky for their individual contributions to the project. In addition, I would Like to thank Prof. Robin Rogers (University of Alabama) for the X-ray crystallographic analysis, Prof. Ian Scott and Dr. Howard Williams (Texas A+M University) for copies of the spectra of citlalitrione, and Dr. Charles Cottrell (Ohio State University) for an insightful discussion regarding technicalities involved in the recording of ^{13}C NMR shifts.

References and Footnotes

1. Torrance, S. J., Wiedhopf, R. M., Cole, J. R., Arora, S. K., Bates R. B., Beavers, W. A., Cutler, R. S., *J. Org. Chem.* **1976**, *41*, 1855.
2. (a) Kupchan, S. M., Sigel, C. W., Matz, M. J., Saenz Renauld, J. A., Haltiwanger, R. C., Bryan, R. F., *J. Am. Chem. Soc.* **1970**, *92*, 4476. (b) Haltiwanger, R. C., Bryan, R. F., *J. Chem. Soc., B* **1971**, 1598. (c) Kupchan,

S. M., Sigel, C. W., Matz, M. J., Gilmore, C. J., Bryan, R. F., *J. Am. Chem. Soc.* **1976**, *98*, 2295.
3. (a) Uemura, D., Hirata, Y., Chen, Y.-P., Hsu, H.-Y., *Tetrahedron Lett.* **1975**, *21*, 1697. (b) Uemura, D., Katayama, C., Uno, E., Sasaki, K., Hirata, Y., Chen, Y.-P., Hsu, H.-Y., *Tetrahedron Lett.* **1975**, *21*, 1703.
4. Yamamura, S., Kosemura, S., Ohba, S., Ito, M., Satio, Y., *Tetrahedron Lett.* **1981**, *22*, 5315.
5. Sahai, R., Rastogi, R. P., Jakupovic, J., Bohlmann, F., *Phytochemistry* **1981**, *20*, 1665.
6. Seip, E., Hecker, E., *Phytochemistry* **1984**, *23*, 1689.
7. Villarreal, A. M., Dominguez, X. A., Williams, H. J., Scott, A. I., Reibenspies. J., *J. Nat. Prod.* **1988**, *51*, 749.
8. (a) Taylor, M. D., Smith, A. B., III, Furst, G. T., Gunasekara, S. P., Bevelle, C. A.; Cordell, G. A., Farnsworth, N. R., Kupchan, S. M., Uchida, H., Branfman, A. R., Dailey, R. G., Jr., Sneden, A. T., *J. Am. Chem. Soc.* **1983**, *105*, 3177. (b) Lillehaug, J. R., Kleppe, K., Sigel, C. W., Kupchan, W. M., *Biochim. Biophys. Acta* **1973**, *327*, 92.
9. Taylor, M. D., Smith, A. B., III, Malamas, M. S., *J. Org. Chem.* **1983**, *48*, 4257.
10. Hofferberth, J. E. unpublished work from this laboratory.
11. Paquette, L. A., Zhao, M., *J. Am. Chem. Soc.* **1993**, *115*, 354.
12. Paquette, L. A., *Tetrahedron* **1997**, *53*, 13971.
13. Brady, W. T., Hieble, J. P., *J. Am. Chem. Soc.* **1972**, *94*, 4278.
14. Grieco, P. A., *J. Org. Chem* **1972**, *37*, 2363.
15. Sugihara, Y., Sugimura, T., Murata, I., *J. Am. Chem. Soc.* **1981**, *103*, 6738.
16. Paquette, L. A., Nakatani, S., Zydowski, T. M., Edmondson, S. D., Sun, L.-Q., Skerlj, R., *J. Org. Chem.* **1999**, *64*, 3244.
17. Yang, J., Long, Y. O., Paquette, L. A., *J. Am. Chem. Soc.* **2003**, *125*, 1567.
18. Paquette, L. A., Yang, J., Long, Y. O., *J. Am. Chem. Soc.* **2002**, *124*, 6542.
19. Magnus, P. D., Nobbs, M. S., *Synth. Commun.* **1980**, *10*, 273.
20. Julia, S., Julia, M., Linstrumelle, G., *Bull. Soc. Chim. Fr.* **1966**, 3499.
21. Marshall, J. A., Andesen, N. H., Schlicher, J. W., *J. Org. Chem.* **1970**, *35*, 858.
22. Kato, T., Kondo, H., Nishino, M., Tanaka, M., Hata, G., Miyake, A., *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2958.
23. (a) Marvell, E. N., Whalley, W., *Tetrahedron Lett.* **1970**, 509. (b) Fan, W., White, J. B., *Tetrahedron Lett.* **1993**, *34*, 957.
24. Paquette, L. A. *"Encyclopedia Of Reagents for Organic Synthesis,"* Paquette, L. A., Editor-in-Chief, John Wiley and Sons: Chichester, 1995, p 1031.
25. Paquette, L. A., *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.
26. Terada, Y., Yamamura, S., *Tetrahedron Lett.*, **1979**, *18*, 1623.
27. Wender, P. A., Hubbs, J. C., *J. Org. Chem.* **1980**, *45*, 365.
28. Williams, J. R., Callahan, J. F., *J. Org. Chem.* **1980**, *45*, 4475.
29. (a) Srinivasan, R., Rajagopalan, K., *Tetrahedron Lett.* **1998**, *39*, 4133. (b) Janardhanam, S., Devan, B., Rajagopalan, K., *Tetrahdron Lett.* **1993**, *34*, 6761. (b) Balakumar, A., Jamardjamam, S., Rajagopalan, K., *J. Org. Chem.* **1993**, *58*, 5482.
30. (a) Shanmugam, P., Rajagopalan, K., *Tetrahedron* **1996**, *52* 7737. (b) Shanmugam, P., Devan, B., Srinivasan, R., Rajagoplan, K., *Tetrahedron* **1997**, *53*, 12637.

31. Paquette, L. A., DeRussy, D. T., Pegg, N. A., Taylor, R. T., Zydowsky, T. M., *J. Org. Chem.* **1989**, *54*, 4576.
32. (a) Corey, E. J., Mitra, R. B., Uda, H., *J. Am. Chem. Soc.* **1963**, *85*, 362. (b) Corey, E. J., Mitra, R. B., Uda, H., *J. Am. Chem. Soc.* **1964**, *86*, 485.
33. Tanabe, M., Crowe, D. F. *Tetrahedron Lett.* **1964**, 1955.
34. Becker, K. B., Grob, C. A., *Chem. Double-Bonded Functional Groups* **1977**, *2*, 653-723.
35. Paquette, L. A., Edmondson, S. D., Monck, N., Rogers, R. D., *J. Org. Chem.* **1999**, *64*, 3255.
36. Crandall, J. K., Apparu, M., *Org. React.* **1983**, *29*, 345.
37. (a) Dess, D. B., Martin, J. C., *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. M., Martin, J. C., *J. Am. Chem. Soc.* **1991**, *113*, 7277.
38. Burn, D., Kirk, D. N., Petrow, V., *Tetrahedron* **1965**, *21*, 1619.
39. (a) Andrieux, J., Barton, D. H. R., Patin, H., *J. Chem. Soc., Perkin Trans. 1* **1977**, 359. (b) Grieco, P. A., Nishizawa, M., Marinovic, N., Ehmann, W. J., *J. Am. Chem. Soc.* **1976**, *98*, 7102. (c) Genet, J. P., Ficini, J., *Tetrahedron Lett.* **1979**, 1499.
40. (a) Parrilli, M., Barone, G., Adinolfi, M., Mangoni, L., *Tetrahedron Lett.* **1976**, 207. (b) Polniaszek, R. P., Stevens, R. V., *J. Org. Chem.* **1986**, *51*, 3023. (a) Paquette, L. A., Wang, T.-Z., Philippo, C. M. G., Wang, S., *J. Am. Chem. Soc.* **1994**, *116*, 3367.
41. (a) Chen, S.-H., Horvath, R. F., Joglar, J., Fisher, M. J., Danishefsky, S. J., *J. Org. Chem.* **1991**, *56*, 5834. (b) Vloon, W. J., van den Bos, J. C., Koomen, G.-J., Pandit, U. K., *Tetrahedron* **1992**, *48*, 8317.
42. For relevant examples of the β-elimination of alcohols to generate cyclic dienones, see (a) Baettig, K., Dallaire, C., Pitteloud, R., Deslongchamps, P., *Tetrahedron Lett.* **1987**, *28*, 5249. (b) Marinier, A., Baettig, K., Dallaire, C.; Pitteloud, R., Deslongchamps, P., *Can. J. Chem.* **1989**, *67*, 1609. (c) Liu, H.-J., Dieck-Abularach, T., *Heterocycles* **1987**, *25*, 245.
43. For a lead reference, see: Mukaiyama, T., Kuwahara, M., Izawa, T., Ueki, M., *Chem. Lett.* **1972**, 287.
44. For lead references, see: Wang, X., Paquette, L. A., *Tetrahedron Lett.* **1993**, *34*, 4579.
45. (a) Thompson, H. W., McPherson, E., *J. Am. Chem. Soc.* **1974**, *96*, 6232. (b) Brown, J. M., Naik, R. G., *J. Chem. Soc., Chem. Commun.* **1982**, 348. (c) Stork, G., Kahne, D. E., *J. Am. Chem. Soc.* **1983**, *105*, 1072. (d) Crabtree, R. H., Davis, M. W., *J. Org. Chem.* **1986**, *51*, 2655. (e) Paquette, L. A., Peng, X., Bondar, D., *Org. Lett.* **2002**, *4*, 937.
46. Tsuda, T., Fujii, T., Kawasaki, K., Saegusa, T., *J. Chem. Soc. Chem. Commun.* **1980**, 1013.
47. Frigerio, M., Santagostino, M., *Tetrahedron Lett.* **1994**, *35*, 8019.
48. Keinan, E., Mazur, Y., *J. Org. Chem.* **1978**, *43*, 1020.
49. (a) Tamao, K., Nakajima, T., Sumiya, R., Arai, H., Higuchi, N., Ito, Y., *J. Am. Chem. Soc.* **1986**, *108*, 6090. (b) Tamao, K., Tanaka, T., Nakajima, T., Sumiya, R., Arai, H., Ito, Y., *Tetrahedron Lett.* **1986**, *27*, 3377.
50. Review: Jones, G. R., Landais, Y., *Tetrahedron* **1996**, *52*, 7599.
51. Tamao, K., Ishida, N., Kumada, M., *J. Org. Chem.* **1983**, *48*, 2120.
52. Kutney, J. P, Ratcliffe, A. H., *Synth. Commun.* **1975**, *5*, 47.
53. Treibs, W., *Naturwissenschaften* **1948**, *35*, 125.

54. Arzoumanian, H., Metzger, J., *Synthesis* **1971**, 527.
55. Massiot, G., Husson, H.-P., Potier, P., *Synthesis* **1974**, 722.
56. Reischl, W., Kalchhauser, H., *Tetrahedron Lett.* **1992**, *33*, 2451.
57. Wiberg, K. B., Nielsen, S. D., *J. Org. Chem.* **1964**, *29*, 3353.
58. (a) Griffith, W. B., Ley, S. V., *Aldrichimica Acta* **1990**, *23*, 13. (b) Ley, S. V., Norman, J., Griffith, W. P., Marsden, S. P., *Synthesis* **1994**, 639.
59. Williams, D. R., Brown, D. C., Benbow, J. W., *J. Am. Chem. Soc.* **1989**, *111*, 1923.
60. Williams, D. R., Coleman, P. J., Henry, S. S., *J. Am. Chem. Soc.* **1993**, *115*, 11654.
61. Yang, J. unpublished observations in this laboratory.

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STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 6

ALKYNYLIODONIUM SALTS IN ORGANIC SYNTHESIS

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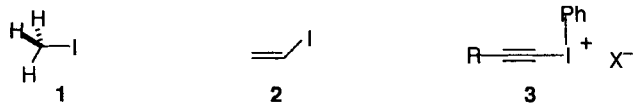
I. Introduction to Alkynyliodonium Salts and Alkylidenecarbene Chemistry

Organic iodides have long played key roles in the construction of complex carbon skeleta. The (almost) unique combination of nucleofugacity and polarizability of the iodide atom has made alkyl (sp^3) iodides, e.g., **1**, particularly vulnerable to displacement by (polarizable) carbon nucleophiles.[1] That these properties have been exploited in innumerable carbon-carbon bond-forming transformations over the history of organic synthesis needs no further mention. More recently, these same favorable carbon-iodide bond characteristics have been parleyed into a range of transition metal-mediated carbon-carbon bond forming processes utilizing alkenyl- or aryl (sp^2) iodides **2**.[2] But, what about the prospects for alkynyl (sp) iodides in carbon-carbon bond forming reactions? A few scattered reports of the use of R-C≡C-I substrates in metal-catalyzed additions reminiscent of the alkenyl iodide chemistry have appeared,[3] but it was the introduction of the much more electrophilic alkynyliodonium salts **3** that triggered an upsurge in interest in carbon-carbon bond-forming transformations via the (sp)-carbon–I

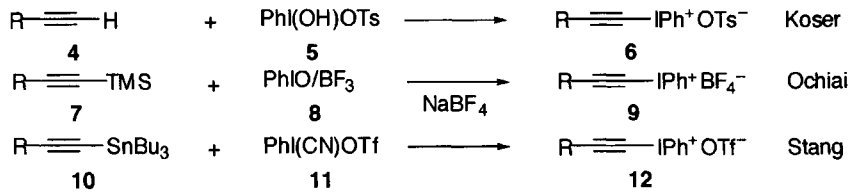
bond.[4] These organoiodine species participate in nucleophilic addition reactions only through an indirect mechanism that bears little resemblance to the more familiar chemistry of (sp^3) C-I and (sp^2) C-I compounds. The unconventional mechanistic course of alkynyliodonium/nucleophile chemistry, however, introduces new and exciting opportunities for accessing a wide range of functionally complex products that otherwise might be difficult to prepare. It is just these opportunities that motivated our efforts in the alkynyliodonium salt area, and the development of new cyclization reactions featuring this chemistry, especially within the context of natural products synthesis, has been the focus of a sustained effort at Penn State over the past 8 years.[5]



1 2 3

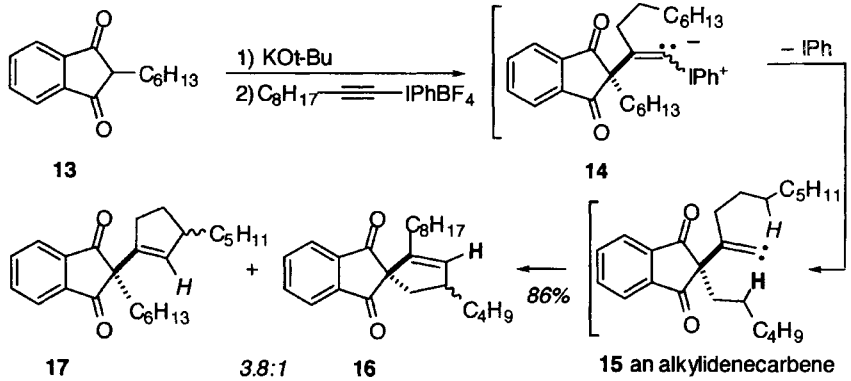
FIGURE 1. Organic iodides used in synthesis.

Two major breakthroughs in alkynyliodonium salt chemistry preceded our entry into this area, and, in fact, provided the necessary foundation to launch our program. One of these contributions was from the laboratory of Peter Stang, where he and Victor Zhdankin showed in 1991 that the iodonium transfer reagent PhI(CN)OTf (**11**) could convert alkynylstannanes into alkynyliodonium salts with exquisite selectivity (Scheme 1).[6a] Prior to this disclosure, existing methods of alkynyliodonium salt synthesis used reagent combinations like PhI(OH)OTs/RC≡CH (Koser)[6b] or $PhIO/BF_3$/RC≡C–TMS (Ochiai)[6c] that were acidic enough to raise concerns about chemoselectivity and compatibility in the multifunctional and sensitive substrates that typically attend a project in complex molecule synthesis. In contrast, the Stang reagent **11** has proven to be completely selective for electrophilic addition at the ≡C–Sn bond even in molecules that contain several other potentially nucleophilic and/or electron rich sites (*vide infra*). This level of selectivity is an absolute requirement for downstream success in the synthesis work.



SCHEME 1. Representative methods for alkynyliodonium salt preparation.

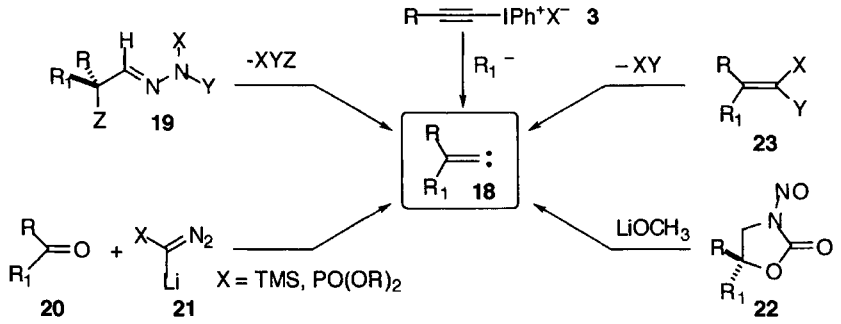
The second critical advance in the area of alkynyliodonium salt chemistry can be attributed to Ochiai,[7] who made the fundamental discovery that cyclopentene products are formed upon combination of alkynylphenyliodonium tetrafluoroborates with polarizable enolates (Scheme 2). The mechanistic course of the transformation was framed in terms of alkylidenecarbene chemistry, and it represented a novel and efficient means to access this reactive intermediate. Many subsequent studies buttressed these provisional conclusions about the intermediacy of alkylidenecarbenes in alkynyliodonium salt chemistry.[8] Further exploration of the scope of this reaction led to the encouraging observation that soft, polarizable nucleophiles like azide, sulfinate, phenoxide, various thiolates, phosphine, and carboxylates all engaged in productive additions with alkynyliodonium salts.[9] Thus, the range of acceptable nucleophiles encompassed atoms populating much of the "organic" periodic table. However, the requirements of polarizability, or "softness", in the nucleophile were brought to light by the failure of alkyl metals, unstabilized enolates, alkoxides, or amines to perform in a similar manner. Rather, in the few cases where characterizable products could be identified, the reaction course of an alkynyliodonium salt with one of these charge-localized nucleophiles was dominated by attack at the iodine atom with discharge of an alkyne fragment.[10] Ultimately, these limitations may have contributed to the fact that this chemistry seemed to pass under the radar of the organic synthesis community for over a decade.



SCHEME 2. Ochiai's original observation of alkynyliodonium/nucleophile reactivity.

Our own interest in exploring alkynyliodonium salt chemistry was born of a simple idea: if we could identify amine substituents that brought the nitrogen's nucleophilicity within the acceptable range for alkynyliodonium salt addition, then we might be in a position to develop

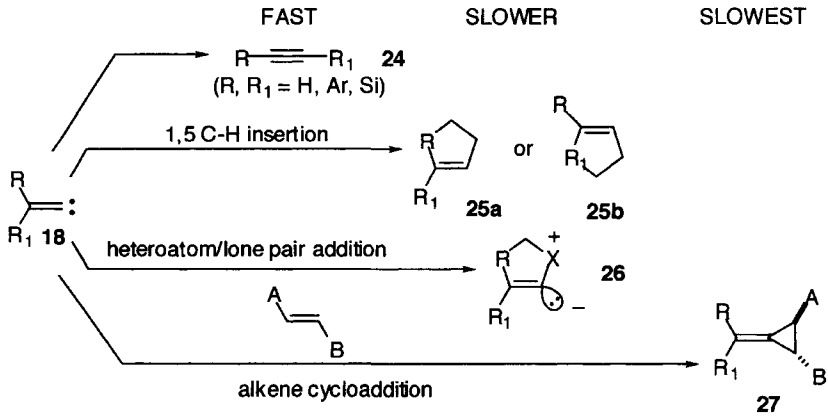
new strategy-level transformations that could be applied to alkaloid synthesis. One implicit benefit of such a strategy is convergency, as only the alkynyliodonium salt approach to reactive alkylidenecarbene intermediates permits introduction of the carbene's substituents from different sources. All other methods of alkylidenecarbene generation require the pre-assembly of fully substituted precursors at some non-trivial expense of labor (Scheme 3). To the extent that convergency scales with overall efficiency in a synthesis plan, this advantage made alkynyliodonium salt chemistry seem worthy of pursuit.



SCHEME 3. Methods for alkylidenecarbene generation.

This line of reasoning led us to view alkynyliodonium salts as stable and accessible precursors to functionalized alkylidenecarbenes. Through judicious design of appropriately substituted alkynyliodonium salts, the rich and varied chemistry of alkylidenecarbenes might be harnessed for specific synthesis objectives. Much prior work has delineated the structural and chemical characteristics of this very reactive intermediate (Scheme 4).[11] Alkylidenecarbenes can be best described structurally as alkene-like with an sp-hybridized carbon bearing an empty p orbital and a filled sp orbital at the terminus. Spectroscopic studies on $(CH_3)_2C{=}C$: frozen in an Ar matrix confirmed the singlet nature of the carbene's ground state as well as delineating some reactivity parameters,[11i] and a remarkable low-temperature X-ray structure of an alkylidenecarbenoid allowed further refinement of structural models.[11f] A combination of high resolution stimulated emission pumping spectroscopy and computations has led to a heat of formation estimate for the parent species $H_2C{=}C$: of ΔH_f = 100 kcal/mol,[11h] making this carbene one of the most energetic organic fragments known (compare singlet methylene, H_2C: $\Delta H_f \sim 95$ kcal/mol)[12]. This energy can be discharged through a variety of pathways depending upon the substituents attached. When either R or R_1 (cf. **18**) is a proton, aryl ring, or silicon atom, an extremely rapid 1,2-shift ensues to

reform the alkyne, a process familiar to most organic chemists within the context of the Corey-Fuchs acetylene synthesis.[13] From the standpoint of our synthesis objectives, this 1,2-shift represents an undesirable event and underscores a serious inherent limitation of any methodology that might emerge from this chemistry: we will be constrained to passing through alkylidenecarbene intermediates bearing only alkyl or heteroatom substituents. Under those circumstances, the carbene is long-lived enough to participate in productive bond-forming processes like the 1,5 C-H insertion (**18** → **25a/b**) first reported by Ochiai. Competitive with this C-H insertion chemistry is a heteroatom-lone pair formal insertion (**18** → **26**) in substrates featuring a 1,5 disposition between carbene terminus and heteroatom. Surprisingly, a delicate balance exists between these two options when both are presented to the carbene, and subtle steric and/or electronic effects can steer the competition towards one manifold or the other. If all of these reactivity options are absent, a slower concerted cycloaddition with added alkene can be observed, **18** → **27**. Methylenecyclopropane products are formed with complete retention of stereochemical information. Hammett-type studies with substituted alkenes lend credence to the view that alkylidenecarbenes are only slightly electrophilic ($\rho \approx -0.5$).[11e]



SCHEME 4. Reactivity options for alkylidenecarbenes.

The wealth of productive bond-forming processes that radiate from this one intermediate can make planning a synthesis route around alkynyliodonium/alkylidenecarbene chemistry a daunting prospect. The key to steering the alkylidenecarbene down a desired pathway involves exploiting proximity effects to juxtapose an appropriately reactive trap near the carbene terminus. These constraints in carbene reactivity

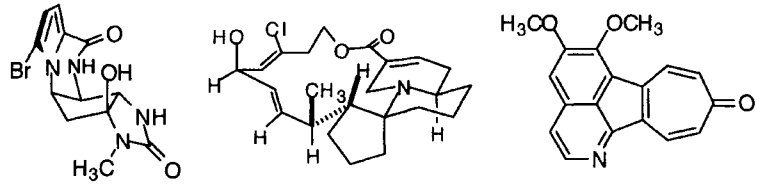
translate into challenges in alkynyliodonium salt synthesis, where the goal will be to prepare suitably configured bifunctional species that contain both the iodonium salt precursor and the carbene trap. The reduction of this approach to practice will be evident within the context of the natural product synthesis projects detailed next.

II. The Synthesis Targets: Scope of the Problem

Choosing target molecules to showcase the alkynyliodonium salt-based methodology requires a careful cost-benefit analysis. Selecting targets that are hopelessly complex runs the risk of burying the key iodonium salt transform amongst a seemingly endless parade of functional group manipulations, thereby diluting its impact on the synthesis. At the other extreme, focusing on simple targets that would otherwise be readily accessible through application of standard reaction sequences might marginalize the chemistry. Rather, we sought targets of medium size and complexity that possessed unconventional structural elements cognate with some of the reaction products depicted in Scheme 4. In particular, molecules that offered stereochemical challenges which were well suited to the stereospecific C-H insertion processes of alkylidenecarbenes might highlight the advantages of alkynyliodonium salt-based strategies in synthesis. The target search was aided by formulating a list of specific attributes of this chemistry that might add value to the synthesis: (1) Otherwise unactivated C-H bonds can be engaged in C-C bond-forming reactions with predictable control of regiochemistry. (2) The C-H insertion reaction proceeds with strict retention of stereochemical information. (3) Alkenes combine with alkylidenecarbenes to form strained methylenecyclopropane products, which themselves may be capable of further productive reactions.

A desire to exploit the C-H insertion chemistry in a remote functionalization sequence (attribute #1) prompted a search for a functionally rich cyclopentanoid target that could be traced back to a simple acyclic acetylenic precursor. Agelastatin A (**28**) appeared to meet this requirement in that it featured a core cyclopentane ring adorned with no less than four nitrogen substituents on stereogenic carbons.[14] Since cyclopentylamines conceivably could arise through nitrogen (nucleophilic) addition to an alkynyliodonium salt as per **3** → **18** → **25a** with R_1 = "N:", it appeared that the cyclopentyltetramine core of agelastatin A might offer several distinct opportunities for realizing this approach. As it turned out, this possible redundancy of routes was welcome and necessary, as it took three generations of alkynyliodonium

salt/alkylidenecarbene-based plans to finally identify a successful approach, as described in the following section.



28 agelastatin A **29** halichlorine **30** pareitropone

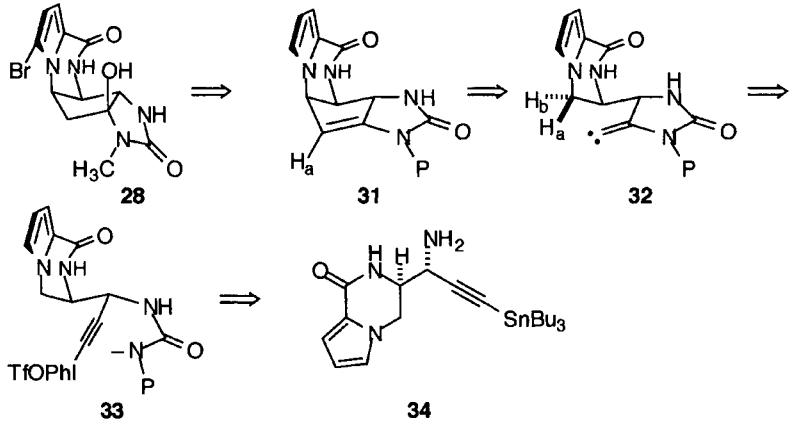
FIGURE 2. Synthesis targets for alkynyliodonium salt chemistry.

In a second thrust, highlighting the value of stereospecificity in alkylidenecarbene C-H insertions (attribute # 2) called for a target that featured a demanding cyclopentyl stereogenic center. The rather more complex marine alkaloid halichlorine (**29**) came into focus in this regard, as its core tricyclic skeleton was framed about a pivotal quaternary stereogenic center at the juncture of the cyclopentyl and piperidine rings.[15] Work toward this target is still ongoing, but enough progress has been made in preparing the tricyclic core through alkynyliodonium salt chemistry to illustrate the role that this chemistry plays in accessing the structure.

Finally, the recognition that high-energy alkylidenecarbenes plausibly could give rise to high-energy methylenecyclopropanes (attribute #3) forms the basis of ongoing studies in the development of cascade reaction sequences. The key to realizing these objectives lies in designing substrates with built-in kinetically accessible decomposition pathways for the methylenecyclopropanes so they can be steered predictably to a final product of desired structure. One particular manifestation of this overall strategy utilizes an aryl ring as the carbene trap, with subsequent rearrangement of the methylenecyclopropane to yield a cycloheptatriene product via norcaradiene-type electrocyclic reorganization. The coalescence of these thoughts sent us on a search for related cycloheptatriene-derived targets, and the tropoloisoquinoline alkaloid pareitropone (**30**) appeared quite suitable.[16] Thus, three disparate target molecules, whose syntheses could each benefit from different aspects of alkynyliodonium salt-based chemistry, were in hand. The trials, tribulations, frustrations, and occasional successes that defined their synthesis efforts will be detailed in the next sections.

III. Early Studies on the Synthesis of Agelastatin A

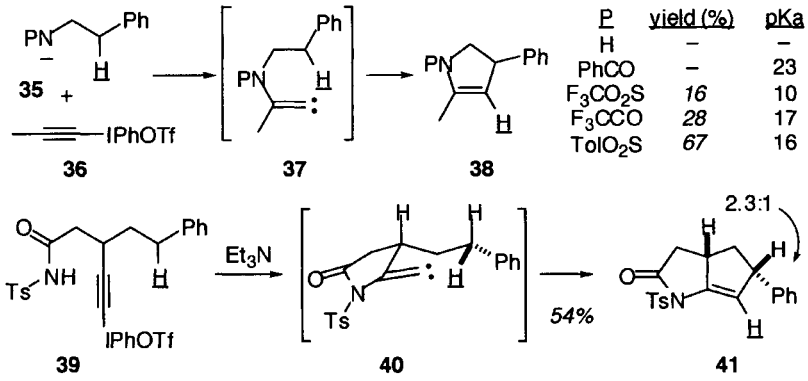
The initial conceptualization of the agelastatin A problem took on the form shown below (Scheme 5).[17] The key transform in this sequence features intramolecular addition of an amide-derived anion to a tethered alkynyliodonium salt within **33**. The alkylidenecarbene generated from this nucleophilic addition, **32**, then has a choice of two diastereotopic C–H bonds (H_a or H_b) for 1,5 insertion. Reaction with H_a would provide an advanced intermediate **31** en route to the target **28**. Successful execution of this plan would extend alkynyliodonium salt chemistry in three new directions: (1) use of an amine derivative as a nucleophile, (2) intramolecularity in the nucleophile addition step, and (3) diastereoselectivity upon alkylidenecarbene C-H insertion. At the initiation of this project, a lack of precedent on any of these topics suggested that focused scouting experiments to assess feasibility would be prudent before beginning work towards the natural product itself.



SCHEME 5. A first generation approach to the agelastatin A skeleton through alkynyliodonium salt chemistry.

Only the azide anion amongst the multitude of possible nitrogen nucleophiles had reported utility in alkynyliodonium salt addition chemistry at the inception of this project. Therefore, extension of this chemistry to amines and amide derivatives occupied our attention at the outset. The requirement for a soft, polarizable nucleophile limited our options, and screening a primary amine as well as some common amide derivatives in the prototype transformation **35** + **36** → **38** led to the first sense that this goal was achievable (Scheme 6).[5a-c] In fact, the common amine protecting group tosyl proved to be the most effective modulator of amine nucleophilicity in this assay. Interestingly, amide pKa does not

scale with yield in this transformation, revealing the first of what was to be many nuances within the chemistry of alkynyliodonium salts uncovered in this work. The use of the simple amide PhCONH– did not lead to any formation of dihydropyrrole product in our hands, but in subsequent work, Witulski did discover a set of experimental conditions favorable for the use of this nucleophile.[18]

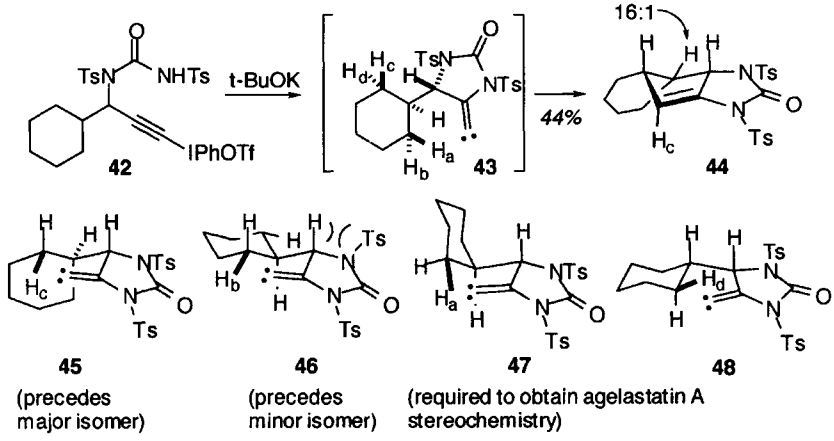


SCHEME 6. Preliminary results in support of the agelastatin A project.

Intramolecularity was the next issue to be probed within the context of alkynyliodonium salt/nucleophile addition reactions.[5a,c] No prior history was available to guide us, and so the prospects for success remained uncertain. Of primary concern was the potential for iodonium salt/base destructive interactions in competition with the desired N–H deprotonation reaction. A substrate that bore some resemblance to key portions of the agelastatin precursor **33** was prepared (Scheme 6), compound **39**. This species duplicated the alkynyliodonium/"amide" pairing of the real system, but it lacked the complex piperazine carbene trap of **33**. The tosylimide (pre)nucleophile was proposed as a compromise between what we really wanted (an N-methyl amide) and what would likely work (a tosylamide). Simple treatment of **39** with mild base effected the desired bicyclization to afford the tosylimide product **41** in decent yield. A transition state model **40** for C–H insertion that features an equatorial phenyl unit might rationalize the observed sense of diastereoselectivity. So, at least for **39**, no evidence for possible interference by iodonium/base reactions was detected.

These encouraging results prompted us to study the bicyclization chemistry of a more realistic model system in order to probe stereochemical issues relevant to the planned **32** → **31** conversion. Once again, we had no precedents to guide our expectations at this formative

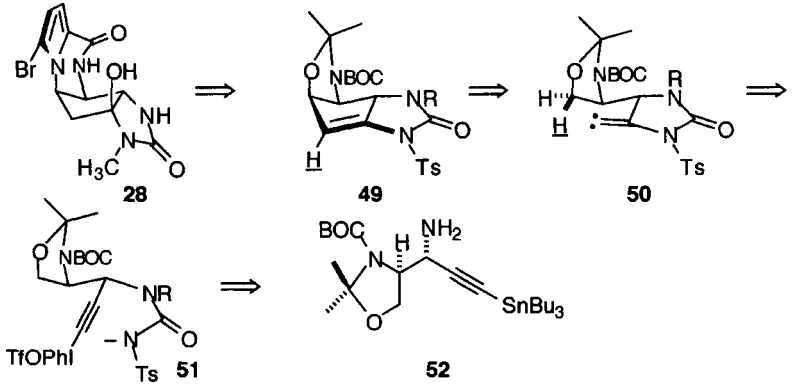
stage of the project, although transition state models for alkylidenecarbene 1,5 C–H insertion developed by Gilbert might serve as a foundation for understanding our results.[19] The bicyclic precursor **42** was assembled with the expectation that it would illuminate this issue (Scheme 7). Treatment of this tosylimide/alkynyliodonium salt with base triggered formation of an intermediate alkylidenecarbene **43** that had four diastereotopic C–H bonds 1,5 disposed to the carbene terminus. Each C–H insertion was defined by a unique transition state model, **45** – **48**. *A priori*, the influences of the different steric and (subtle) electronic environments of each C–H bond on the energetics of carbene insertion were difficult to evaluate, and so a prediction in advance of performing the experiment was ill-advised. In actuality, the C–H insertion reaction proceeded with high diastereoselectivity, and a 16:1 preference for isomer **44** was observed. This product can be traced to transition state model **45**, and the minor isomer is derived from the related species **46**. No products that might have passed through transition state models **47** or **48** could be detected. It appeared that chair-like transition states (**45** and **46**) were strongly favored over their boat-like alternatives (**47** and **48**). Within the chair-like manifold, it is possible to identify an untoward steric interaction between the tosyl group and a cyclohexyl methylene [shown as) ( ] in transition state model **46** that is absent in **45**. This interaction might be the defining energetic feature that steered the reaction so persuasively toward **44**. Unfortunately, the isomer that would emerge from transition state model **47** maps onto the desired agelastatin A stereochemistry, and that product was not seen.



SCHEME 7. Preliminary results which do not support the agelastatin A project.

The conclusion that this synthesis plan was no longer tenable, seemed inescapable. And so, wiser but no further along, we decided to salvage what we could from this exercise and export that information into a second-generation approach to agelastatin A that was designed to avoid this stereochemical pitfall.

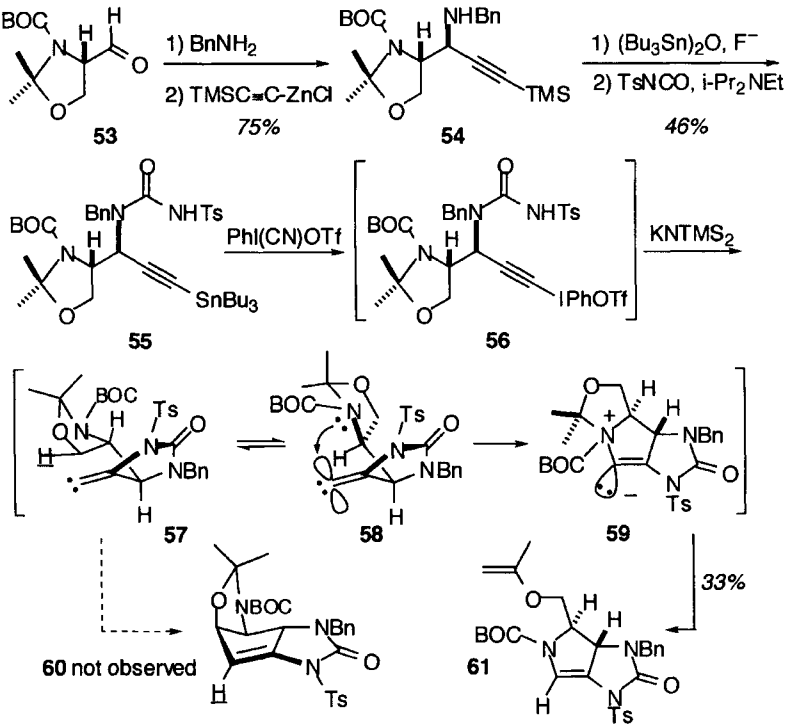
A second strategy for agelastatin A synthesis evolved from consideration of a conservative approach toward setting cyclopentane ring stereochemistry (Scheme 8). The approach relies on entering the key alkynyliodonium salt/alkylidenecarbene sequence **51** → **49** with two of the cyclopentyl stereogenic centers already in place and providing the appropriate steric bias to set the third center correctly. The piperazinone ring then would be annelated onto the cyclopentane ring at the end of the synthesis. The carbene **50** can be backtracked through the alkynyliodonium salt intermediate **51** to a simple (–)-serine derivative **52**.



SCHEME 8. A second generation approach to the agelastatin A skeleton through alkynyliodonium salt chemistry.

The second-generation synthesis effort commenced with commercially available (+)-serine-derived Garner's aldehyde (**53**) (Scheme 9).[20] This choice would lead to the antipode of agelastatin A in the event of a successful synthesis outcome, but this subtlety did not concern us at this point. Fujisawa's method of diastereoselective propargylamine synthesis was employed for the conversion of **53** into **54**.[21] This chiral species, which possesses the correct relative stereochemistry at two of the four stereogenic centers of the cyclopentyl core of agelastatin A, was processed on to alkynylstannane **55** by routine transformations. Sequential treatment of this iodonium salt precursor with Stang's reagent and then a strong base led to isolation of a single identifiable product. The clear presence of an enecarbamate proton in the ^{1}H NMR spectrum of

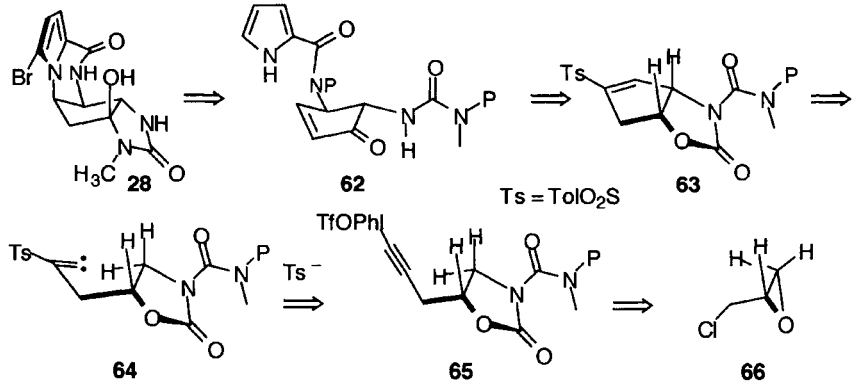
this isolate was received with much enthusiasm. Unfortunately, this enthusiasm was quickly dampened upon more thorough examination of the ^{1}H and ^{13}C NMR data. In fact, the complete spectral data were consistent only with the dihydropyrrole structure **61**. No evidence for the desired cyclopentane species **60** was observed. A mechanistic rationale for the formation of **61** is provided by the series of intermediates **57-59**.[5g] Apparently, the N–BOC's lone pair provides a more reactive source of electron density than the desired C–H bond, and the carbene engages this nucleophile in zwitterion formation to the exclusion of any other reaction course. This zwitterion **59** decomposes through proton loss/proton gain to furnish the observed product **61**. In retrospect, perhaps this result might have been anticipated, but a lack of precedent for this type of transformation within the alkylidenecarbene literature left us unprepared on this point. Once again, a promising (?) route to agelastatin A had been thwarted by unanticipated reactivity of the alkylidenecarbene. This effort was terminated, and the information learned from this painful lesson was folded into the next (and last!) generation approach to agelastatin A.



SCHEME 9. Another failed attempt to access the agelastatin A skeleton via alkynyliodonium salt chemistry.

IV. Completion of the Syntheses of (–)-Agelastatin A and (–)-Agelastatin B

The final incarnation of the agelastatin A synthesis project abandoned the notion of internal nucleophile delivery to the alkynyliodonium salt in order to test the thesis that a less constrained framework might be better able to access the transition state for C–H insertion (Scheme 10).[51,m] Of course, this plan does not, in and of itself, ensure that any competition between C–H insertion and heteroatom-lone pair addition will favor the former option. Just such a competition inevitably will exist, given the connectivity of the target, but this new approach can better accommodate modifications in the heteroatom's substituents. Variation in these substituents might, in turn, modulate the reactivity of the heteroatom's lone pairs. Thus, the target **28** is envisioned to be accessible from the cyclopentenone **62**, a species bearing the crucial *trans* disposition between the two amide units. This enone should be available via the tosylcyclopentene **63** through appropriate manipulation of existing functionality. The cyclopentene ring of **63** can be identified as a cue for synthesis via application of an alkynyliodonium salt/alkylidenecarbene cascade starting from the simple alkyne **65**. In this plan, the key sequence will be triggered by addition of exogenous nucleophile (sulfinate), in contrast to the earlier intramolecular attempts. Work in the correct chiral series is assured by the choice of (*R*)-epichlorohydrin as the starting point of the route.

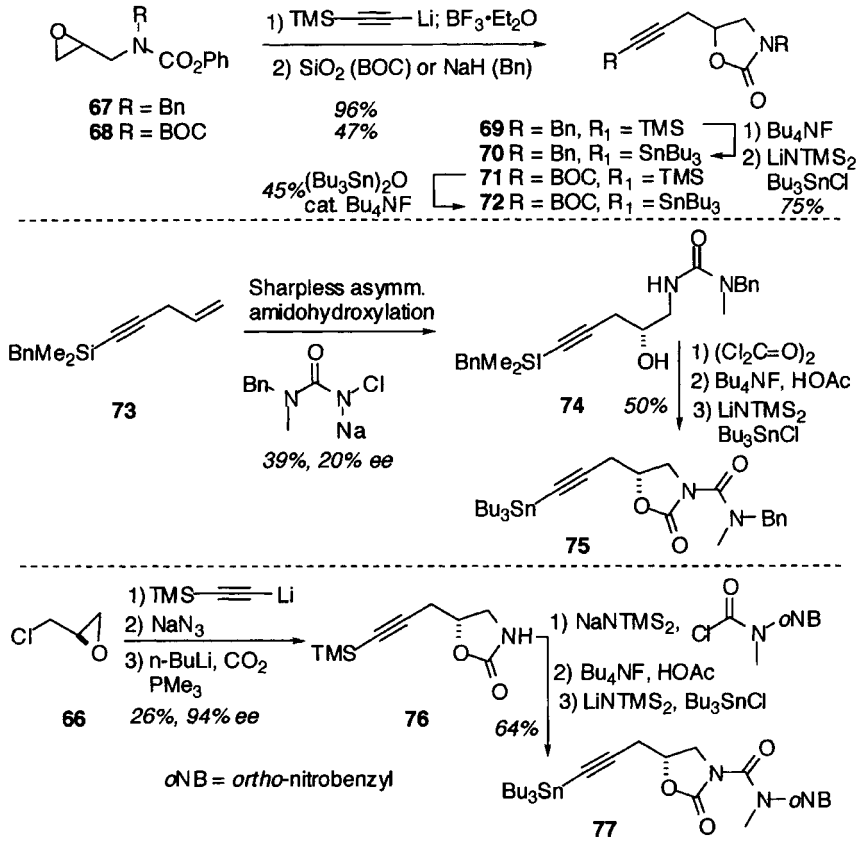


SCHEME 10. The third (and final) approach to agelastatin A through alkynyliodonium salt chemistry.

The unexpected heteroatom lone pair reactivity exposed during the failed 2nd approach to agelastatin A mandated that sufficient attention be directed to the cyclization options of **64**. As with carbene intermediate

57/58 (Scheme 9), the alkylidenecarbene **64** has the opportunity for either C–H insertion (→ **63**) or addition to the oxazolidinone oxygen's lone pair. In this circumstance, a prudent first goal would seem to involve exploration of this competition as a function of the one variable that we can control, the oxazolidinone substituent(s). This objective was reduced to practice through synthesis of a series of substituted propargyl oxazolidinone substrates for the iodonium salt chemistry (Scheme 11). The epoxides **67** and **68** were serviceable starting points for preparation of the corresponding *N*-benzyl and *N*-BOC oxazolidinones **70** and **72**, respectively. In both cases, BF_3-mediated alkynyl anion addition to the oxiranes went smoothly, but only in the benzyl series could we identify experimental conditions that led to high-yielding closure of the oxazolidinone ring. The Buchwald tin-for-silicon exchange reaction[22] could be applied only to the BOC-substituted compound **71**, and we had to resort to a two-step "classical" approach to stannylate **69**. A desire to introduce chirality into this synthesis work led to the examination of the Sharpless asymmetric amidohydroxylation procedure with enyne **73**.[23] This transformation probed three unknowns in the Sharpless lore: (1) the regioselectivity of nitrogen and oxygen addition to a propargyl-substituted alkene, (2) the level of ee attainable with this type of substrate, and (3) the use of a halourea derivative as the nitrogen component. After much optimization, the experiment could be described as only modestly successful. Low yields and poor ee's dampened any enthusiasm for incorporating this chemistry in the agelastatin A route, but the use of a urea function in the transformation was established, and the ligand control of regioselectivity was excellent. Closure of the oxazolidinone ring with diphosgene and standard alkynylstannane introduction led to the substrate **75**. The final oxazolidinone of interest, **77**, differed from **75** only by incorporation of an ortho nitro benzyl group (*o*-NB) on the urea's nitrogen atom. That this remote substituent might exert any influence on the chemistry of the alkylidenecarbene seemed a bit of a stretch at this point, but we were soon to learn about yet another subtlety in the chemistry of this reactive intermediate. Rather, at this early stage of development, this seemingly innocuous substitution was inspired only by a desire to consolidate downstream deprotection steps. The synthesis of **77** began with a chiral starting material and a known reaction, the addition of TMSC≡C-Li to **66** with formation of an alkynyloxirane product.[24] Azide-mediated opening of the oxirane ring within this species followed by oxazolidinone closure using Vilarrasa's procedure[25] delivered **76** in high ee, reflecting the enantiomeric enrichment of the epichlorohydrin starting material. Attachment of the nitrobenzyl urea fragment via the oxazolidinone anion proceeded cleanly on nitrogen, and swapping tin-for-

silicon at the alkyne terminus followed the usual sequence to furnish chiral substrate **77**.



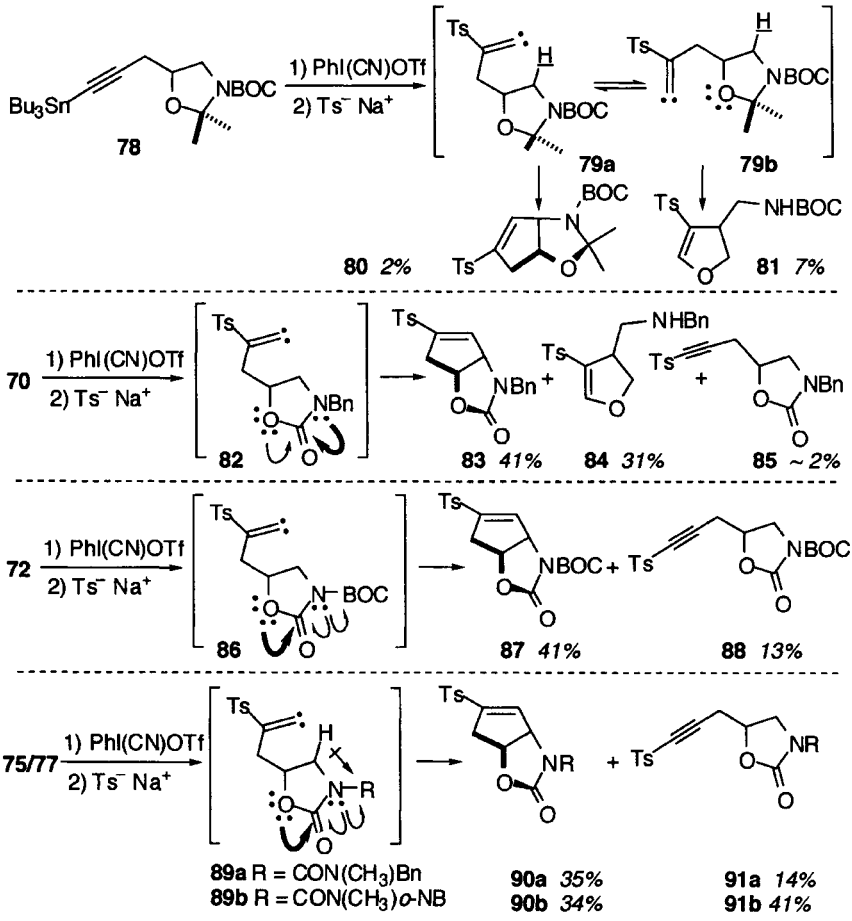
SCHEME 11. Synthesis of oxazolidinone alkynylstannanes related to **65**.

Each of the oxazolidinones **70**, **72**, **75**, and **77**, as well as the related acetonide species **78**, were subjected to identical alkylidenecarbene generating sequences in order to examine the role of substituents on the all-important C–H insertion:oxygen-lone pair addition ratio (Scheme 12). The acetonide substrate **78** was allowed to react with Stang's reagent and then sulfinate in sequence to give a complex mixture of products from which only minor quantities of characterizable material could be extracted following extensive chromatography. The isolated products **80** and **81** appeared to originate from C–H insertion and oxygen-lone pair addition, respectively. The low yields caution against overinterpretation of these results, but it is interesting to note that reaction at oxygen

apparently was favored over C–H insertion with this substrate. A conspicuous improvement in yield and selectivity attend the use of the oxazolidinone-based substrates. With the *N*-benzyl species **70**, approximately 75% of the starting material can be accounted for in the product distribution, and there was a slight advantage for C–H insertion over oxygen addition. Interestingly, a trace of the rearranged alkyne product **85** was seen. This species presumably arose from a 1,2-shift within carbene **82**. We have no evidence which directly speaks to the identity of the carbene ligand that shifts, but earlier labeling studies conducted by Ochiai on related alkyl, sulfonyl alkylidenecarbenes provided unequivocal evidence that it is the sulfone that migrates.[26] The formation of even minor amounts of **85** was surprising, and perhaps it should have alerted us to coming events, but at this juncture, this observation did not hold undue significance. The three imide-type oxazolidinone substrates **72**, **75**, and **77** all behaved similarly upon alkylidenecarbene generation, affording differing amounts of the C–H insertion products **87**, **90a**, and **90b**, and the 1,2-shift products **88**, **91a**, and **91b**, respectively. Importantly, no carbene-oxygen reaction products were detected in any of these transformations. Thus, incorporation of an imide function in the substrate shut down the undesired oxygen-lone pair addition option, but at the expense of a burgeoning competition from the 1,2-sulfone shift.

What features drive these reactivity trends? Much can be explained by considering the variation in electron demand at both of the two reactive sites. The data obtained are consistent with the hypothesis that alkylidenecarbene reaction rates at each of the two loci scale with the electron density at those sites. Furthermore, if the electron density is sufficiently depleted at both sites, then the normally slower 1,2-sulfone shift can become prominent. Thus, the acetonide function of **79a/b** imposes no significant electron demand on the attached oxygen, and not surprisingly, the reaction is biased towards this site. The carbonyls of **70**, **72**, **75**, and **77** all present a very different picture of electron demand, varying from least with **70** to most with **77** (see arrows in **82**, **86**, and **89a/b**, Scheme 12). With these substrates, only the *N*-benzyl species **70** retains enough electron density on oxygen to engage the carbene productively in reaction. Once the nitrogen's lone pair is tied up in resonance with the exocyclic carbonyls in **72**, **75**, and **77**, the "ester resonance" of the ring oxygen should be ramped up, leading to a depletion of electron density at this site. However, this advantageous adjustment of electron density within the molecule comes at a price. As the exocyclic carbonyl becomes more electropositive, it necessarily must increase its claim to electron density through the sigma framework of the

oxazolidinone ring. This drain of electron density in turn should translate to a depletion of same in the C–H bond destined for insertion. The *o*-nitrobenzyl group of **89b** should exact a heavier toll in this regard than the benzyl analogue **89a**, an expectation consistent with the observation that the default option (1,2-sulfone shift) is more prevalent from the former than the latter carbene. The results of these studies make it clear that the trade-offs inherent in this alkylidenecarbene system render it difficult to simultaneously optimize the desired C–H insertion path while minimizing both of the competing reaction channels. Nevertheless, the brevity of the route to **90b**, even if the overall yield only approaches mediocre, fuels the hope that enough material can be carried on to continue the agelastatin A synthesis.

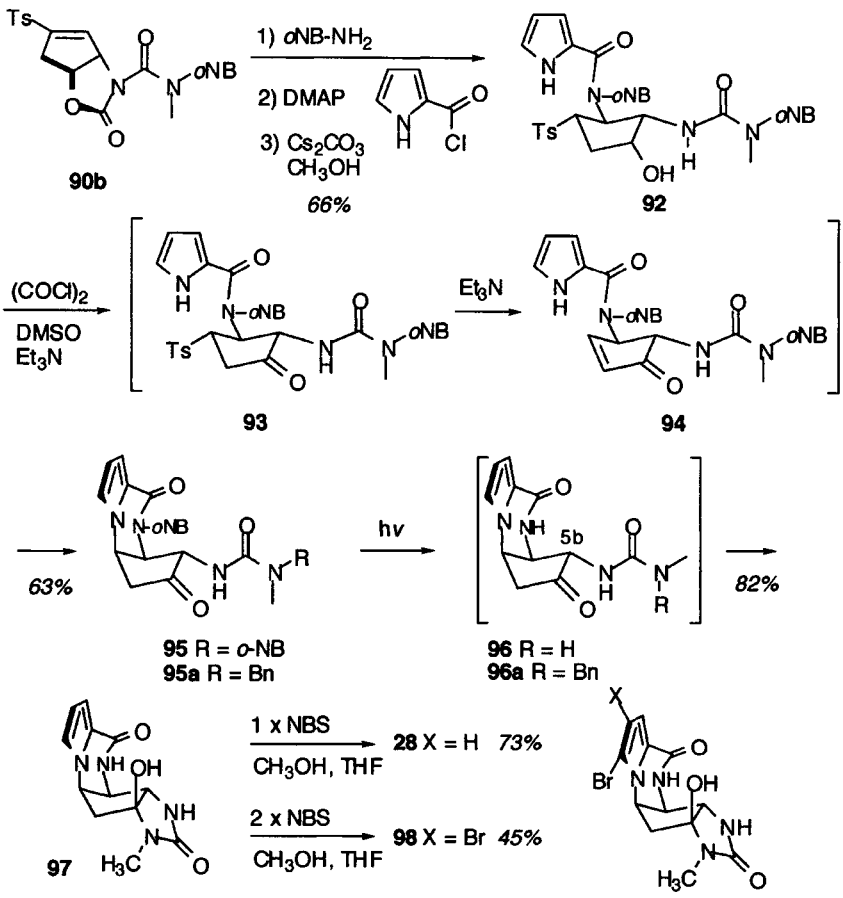


SCHEME 12. Alkynyliodonium salt cyclizations: An examination of C–H vs. O-lone pair reactivity.

The next phase of the synthesis focused on attaching two more nitrogens to the cyclopentane framework in a stereochemically controlled manner (Scheme 13). The sulfone moiety, which already had played a key role in triggering the cyclopentene-forming reaction sequence, also will occupy a central position in both of these C-N bond-forming processes. Initially, the electron-withdrawing character of this function was exploited in activating the alkene of **90b** for conjugate addition of an ammonia equivalent packaged as the *o*-nitrobenzylamine. Interestingly, ammonia itself attacked the oxazolidinone carbonyl and not the unsaturated sulfone unit of **90b.** Diastereoselectivity in this addition was complete, presumably in response to the pronounced steric bias of the bicyclo[3.3.0]octane framework. The secondary amine within this conjugate addition product was acylated only sluggishly with 2-pyrrolecarbonyl chloride. Finally, the oxazolidinone carbonyl was excised by treatment of this acylated pyrrole intermediate with Cs_2CO_3 in methanol. If it is true that every successful synthesis required one lucky step, then this seemingly trivial hydrolysis is it for this project. Many frustrating attempts at this transformation with an extensive range of bases, solvents, concentrations, temperatures, etc, were necessary before we honed in on the singularly successful conditions indicated. All other combinations of reaction parameters led to either conversion of the intermediate oxazolidinone into a plethora of uncharacterized materials, or to elimination of the pyrrole carboxamide fragment with regeneration of the unsaturated sulfone **90b**. Once this hurdle was crossed, we were positioned to explore the second cascade cyclization sequence of the route. This process commenced upon treatment of the cyclopentanol **92** with the standard Swern oxidation recipe. Rapid conversion of the secondary alcohol in **92** into a ketone followed, and the excess base now present mediated the elimination of the elements of *p*-toluenesulfinic acid to provide an intermediate and undetected cyclopentenone **94**. An *N*-Bn version of this enone could be identified in earlier scouting experiments using non-basic Dess-Martin oxidation conditions with an *N*-Bn analogue of **92**. In the basic media of the Swern workup, however, a rapid intramolecular cyclization of the nucleophilic pyrrole nitrogen furnished tricycle **95** as the only detectable product. So, in its final role in this synthesis, the sulfone was sacrificed as a leaving group. The stereochemical outcome of this cyclization can be rationalized by invoking either kinetic (axial attack) or thermodynamic (most stable isomer) control. Fortunately, both control elements converge on the same isomer.

The acquisition of tricycle **95** sets the stage for the final drive towards agelastatin A. Photochemical cleavage of both *o*-NB protecting groups cleanly delivered the tetracyclic debromoagelastatin product **97**. This reaction possibly proceeded through the transient urea **96** before cyclizing to **97**, depending upon the precise sequence of the two deprotection steps. The fact that **96** only had a fleeting existence, if it was formed at all, was crucial to maintaining the stereochemical integrity of the product. Prior studies with substrate **95a** led to a completely different outcome upon photochemical scission of the pyrrole carboxamide's *o*-NB group. In that series, facile epimerization at C(5b) provided **96a** as an isolable mixture of diastereomers. In this case, it is plausible to speculate that replacement of the bulky pyrrole carboxamide *o*-NB group with a proton removed a steric impediment to C(5b) planarization, and facile enolization/epimerization then occurred. In contrast, **96** (if it existed at all) apparently didn't persist long enough to suffer epimerization in competition with cyclization. Once cyclized to **97**, epimerization at C(5b) was not possible.

The final operation of the agelastatin work, monobromination of the pyrrole ring, was not without its risks. If this step fails, the entire synthesis fails. The anticipated sensitivity of the bromopyrrole moiety to decomposition under a variety of experimental conditions led us to postpone bromide introduction until the end, and now it was time to see if we had blundered. Initial screening experiments on limited material were not encouraging. The isolation of small amounts of monobrominated product admixed with the dibromide in abundance (agelastatin B, (**98**)) as well as other uncharacterized material left us concerned. However, observations of the reaction solution made during these initial studies provided some insight on how to steer the bromination to **28**. It appeared that the starting compound **97** was only scarcely soluble in the $CHCl_3$ reaction medium, but material was dragged into solution as the bromination progressed due to the greater solubility of the monobromide **28**. Once soluble, **28** then was susceptible to further bromination, leading to the dibromide **98**. This problem was solved by the simple expedient of running the bromination of **97** under ionic conditions in a much more polar reaction medium. In a mixture of THF and methanol, **97** was completely soluble, and it smoothly underwent monobromination with one equivalent of brominating agent to afford the natural product (–)-agelastatin A (**28**) contaminated by less than 4% of the dibromide **98**. In a deliberate attempt to synthesis this dibromide, also a natural product, treatment of pyrrole **97** with an excess of brominating agent provided the desired product in modest yield.



SCHEME 13. Completion of the synthesis of (–)-agelastatin A and (–)-agelastatin B.

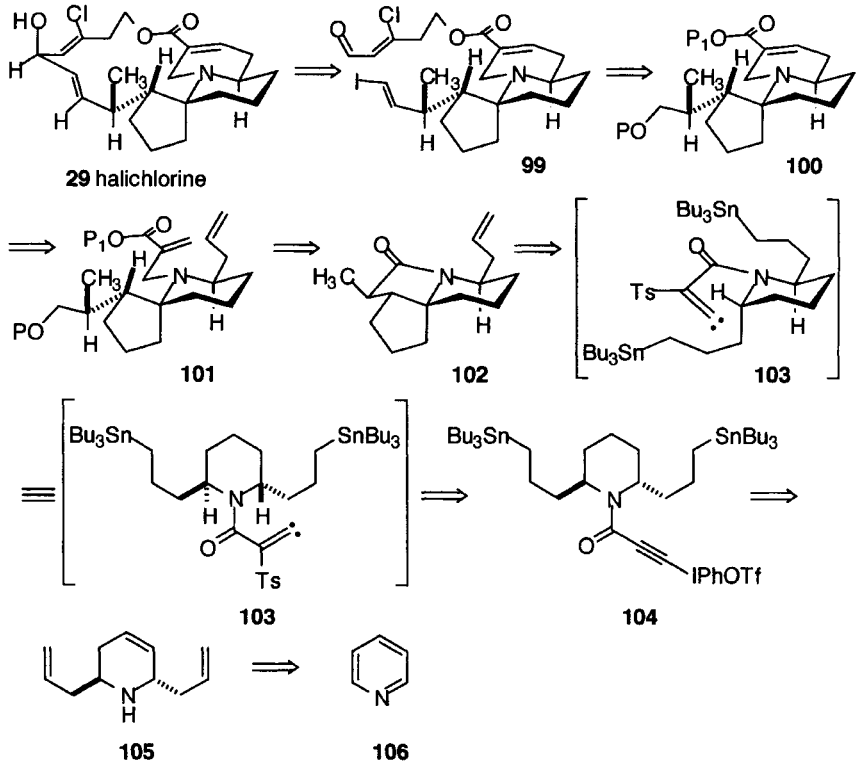
The successful syntheses of (–)-agelastatin A and (–)-agelastatin B demonstrated for the first time that alkynyliodonium salts and their derived alkylidenecarbenes could be productively utilized in complex natural products synthesis. The fact that the final iteration of the synthesis plan looks strikingly different from either the original or the 2nd generation version is a pointed reminder that multifunctional substrates can often complicate simple reaction processes. Nevertheless, encouraged by this success, we decided to apply this chemistry in other, potentially more demanding contexts in synthesis studies directed toward halichlorine and pareitropone, as detailed next.

V. Synthesis Studies on Halichlorine

Halichlorine (**29**) presents a much more challenging target for alkynyliodonium salt chemistry by virtue of its tricyclic core, embedded quaternary center, and a functionally and stereochemically complex macrolactone belt that spans the equator of the molecule. The sheer size of halichlorine compared to the more compact agelastatin framework tends to minimize the significance of any one individual step in its synthesis, and so we recognized that other interesting chemistry in addition to the alkynyliodonium salt-based transformation must be included in order to justify this effort. The alkynyliodonium salt → alkylidenecarbene → 1,5 C–H insertion sequence at the fulcrum of the synthesis plan will test the limits of this chemistry for introduction of sterically hindered quaternary centers. In addition, versatile but little-used pyridine addition chemistry developed by Bubnov[28] occupies a key role in alkyne substrate synthesis, whereas post-cyclization formation of the macrolactone bridge is scheduled to proceed via a demanding version of the Hiyama-Nozaki-Kishi (H-N-K) reaction.[29] A retrosynthetic analysis for the preparation of **29** is shown below (Scheme 14).

As advertised, an intramolecular, stereoselective H-N-K reaction is planned to close the macrolactone ring as the final transformation of the route. The iodoalkene unit of **99** should be available via an aldehyde derived from the CH_2OP function within precursor **100**. The core tetrahydropyridine ring is envisioned to arise from ring-closing olefin metathesis of the diene shown in **101**. The methacrylate segment of **101** can be traced back to an alkylation of the piperidine nitrogen of **102** after liberation via amide reductive ring opening. The synthesis of **102** will feature a MacDonald-type[30] internal alkylation of an eneamide precursor to **102** with one of the two pendant propyl tin residues. The cyclopentane-type ring of **102** provides the cue for alkynyliodonium salt chemistry via intermediates **103** and **104**. The C2 symmetric alkylidenecarbene **103** (amide rotomers excepted) has two equivalent tertiary C–H bonds at optimum insertion distance from the carbene's terminus. The symmetry features of **104** allow an economy of effort in the synthesis of precursors, provided that eventual differentiation of the termini can be achieved. The C–H insertion reaction of alkylidenecarbene **103** relies on rigorous retention of stereochemistry upon bond formation in order to deliver the quaternary center of **102** with an appropriate relationship to the resident stereogenic center. In this way, the alkynyliodonium salt chemistry facilitates the entire synthesis plan by delivering a core structure bearing useful functionality at key structural positions optimally located for assembly of the remainder of the

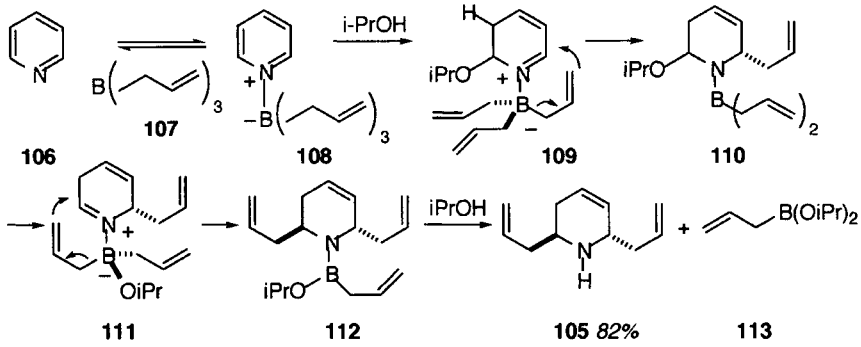
halichlorine framework in a concise and efficient manner. The trans 2,6-disubstituted tetrahydropyridine ring of **105** can be accessed in a single operation from pyridine, the ultimate starting material of this synthesis.



SCHEME 14. Retrosynthetic analysis for halichlorine.

The halichlorine project starts with simple pyridine, whose humble status as a commodity chemical is elevated remarkably by application of Bubnov's allylation chemistry[28] (Scheme 15). This bis allylation reaction, when under kinetic control, leads strictly to the trans 2,6-diallyl product **105**. Higher reaction temperatures promote trans-to-cis equilibration. The mechanism suggested by Bubnov, which encompasses the intermediates **108** through **112**, is supported by labeling studies and the observation that complex **108**, in the absence of alcohol, does not participate in any addition chemistry. A transient role for the ether **109** is not demanded by any experimental evidence, and so this aspect of the Bubnov mechanism remains speculative. Bubnov has shown that this transformation tolerates some additional functionality on both the allyl fragment and the pyridine ring, but for our purposes, the stripped down

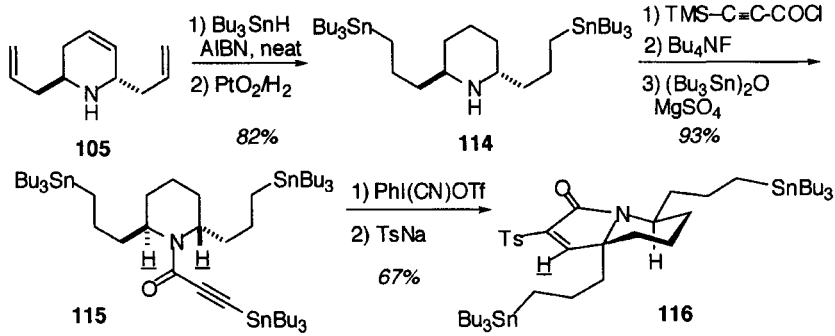
version shown suffices. This reaction is completely scalable, and yields do not suffer upon increasing the scope of the reaction from 100's of milligrams to ten grams of pyridine.



SCHEME 15. The Bubnov synthesis of 2,6-diallyltetrahydropyridine.

The acquisition of **105** establishes the desired C2 symmetry of the system save for the ring's alkene. Therefore, the next task involved removing this superfluous function without concomitant destruction of the terminal alkenes (Scheme 16). Such selectivity is not normally within the purview of hydrogenation reactions, and so an indirect approach was indicated. An anticipated need for functional handles at the termini of the propyl chains guided our thinking, and the known propensity of radical addends to preferentially attack terminal alkenes over internal alkenes suggested several solutions.[31] Among these possibilities, tin radical was judged to have the most favorable blend of reactivity and downstream functionalization options, but one concern remained. Addition of tin radical to the terminal alkene would generate a secondary alkyl radical intermediate poised for addition to the ring alkene in a normally quite rapid 1,5-hexenyl-type radical cyclization. Could we identify experimental conditions that favored the desired secondary radical trapping by Sn–H over cyclization? The one experimental variable at our disposal was reagent concentration, and by screening several different concentration regimes, limiting reactivity in either direction was observed. From the standpoint of advancing the halichlorine project, it became expedient to simply heat **105** and Bu_3SnH/AIBN in the absence of solvent, a protocol that led to very high yields of the terminal tin adducts to the exclusion of cyclization products. Hydrogenation of the remaining alkene then delivered **114**. Acylation of this hindered secondary amine with the sensitive acid chloride TMSC≡CCOCl required much optimization, starting with the preparation of the acid chloride

itself. Following literature reports on the synthesis of this species with oxalyl chloride did not provide a product of sufficient purity to acylate **114** in good yield,[32a] and so recourse was made to the method of Ghosez using $(CH_3)_2C{=}C(Cl)N(CH_3)_2$ as a neutral chloride transfer reagent.[32b] In this way, reproducibly high yields of the propynoyl chloride free of acidic impurities could be realized. Since the propynyl tin compound was actually desired, some effort was expended in ultimately futile attempts to prepare $Bu_3SnC{\equiv}CCOCl$. The stannylalkyne **115** could be prepared, however, through the two-step sequence of desilylation and then terminal alkyne stannylation. With the key cyclization precursor **115** in hand, attention was directed to the alkynyliodonium salt → alkylidenecarbene → 1,5 C–H insertion process detailed earlier (Scheme 14). *In situ* generation of an alkynyliodonium salt from **115** proceeded smoothly as expected, and rapid cannulation of a cold DME solution of this sensitive intermediate into a refluxing suspension of TsNa in DME led to isolation of a single major reaction product. Spectroscopic characterization of this material provided data only consistent with the desired structure **116**. The relatively high yield of this transformation was gratifying, given the less-than-auspicious performance of the iodonium salt derived from alkynyltin substrate **77** in the agelastatin work. Some initial concerns about the regiochemistry of addition to the alkynyl unit of **104** (Scheme 14) were addressed by earlier work from Stang's laboratory,[33] where the Utah group showed that iodoniumpropynylamide derivatives favored nucleophilic addition at the carbon β to the apparently more activating iodonium group and not β to the carbonyl. No trace of the 1,2-shift-derived alkynylsulfone product was detected, a result which speaks to the perhaps more prominent role of electronic effects (cf. the agelastatin system, Scheme 12) rather than steric effects in governing the facility of alkylidenecarbene 1,5 C–H insertion reactions.



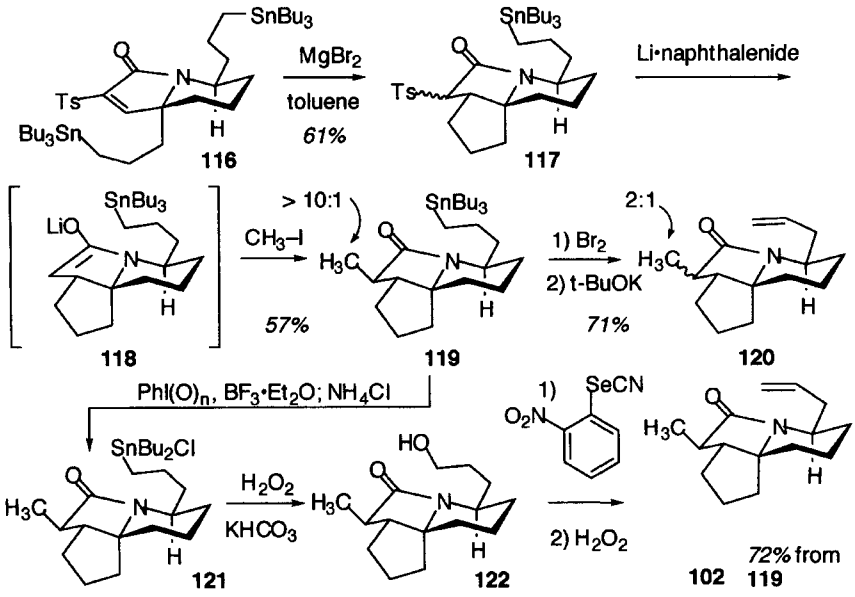
SCHEME 16. Synthesis and iodonium salt cyclization chemistry of the alkynylstannane **115**.

The choice of the bisstannane **116** as a synthesis subgoal was predicated on the expectation that the now distinct tin groups could be manipulated selectively (Scheme 17). To accomplish this task, we planned to exploit the enforced proximity of one of the two tin groups with the β carbon of the enone system. MacDonald has demonstrated that favorably positioned alkyl tin bonds can serve as competent nucleophiles with Lewis acid-activated α, β-unsaturated ketones,[30] and it is just this reactivity pattern that provides the means to differentiate between the two tin atoms. Treatment of the eneamide **116** with a range of Lewis acids did indeed promote the desired carbon-carbon bond formation, but to differing extents. The Lewis acids preferred by MacDonald in the original work ($TiCl_4$, $SnCl_4$) delivered the desired product **117** in modest yields (35 – 45%), values equaled by various lanthanide triflates as well. Magnesium bromide in toluene was the most successful reagent, and reproducible yields in the 55 – 61% range were routinely obtained at different reaction scales.

Two further operations were necessary to secure the next milestone, tricycle **102**. The tosyl group had to be replaced with a β-face methyl unit, and the original secondary allyl unit had to be regenerated from the remaining tin group. The acidity of the proton between the Ts and CO functions suggested that pursuing the former task first would minimize functional group incompatibilities. Two related sequences could be envisioned for the tosyl-to-methyl conversion: methylation first and then reductive detosylation, or reductive detosylation followed by methylation. The deciding factor in this choice turned out to be the level of diastereoselectivity attained in both cases. Methylation of **117** (NaH, CH_3I) followed by reductive detosylation provided the requisite secondary methyl amide as a 1:1 mixture of epimers (76%). In contrast, the inverse sequence shown as **117** → **118** → **119** furnished the desired product as essentially a single β-face methyl stereoisomer.[34] Presumably, methylation of an intermediate enolate **118** is responsive to the concave/convex nature of the carbon framework, and carbon-carbon bond formation is confined to the more exposed face. On the other hand, protonation of the methylated version of enolate **118** does not appear to be as biased, an observation possibly rationalized by the much smaller size of the electrophile.

The second operation en route to tricycle **102**, retrieval of the terminal alkene function first installed through the Bubnov reaction, commenced with a survey of electrophilic reagents that might plausibly cleave (oxidize) the propyl-tin bond within **119**. The problem inherent in this

seemingly simple goal arises from the similarity between all four tin ligands. Any oxidizing reagent would have to be used in large excess, a situation that could give rise to overreaction and/or difficulties in isolating product from spent reagent. Initial attempts with known hydride abstracting agents (DDQ, trityl cation, tropylium cation) led to either complex mixtures or recovered starting material. Clearly, we had not yet identified the correct blend of reactivity and selectivity in our choices of oxidants. Halogenation proved to be a better prospect, as **119** could be converted cleanly into the corresponding propyl bromide (not shown) upon exposure to excess Br_2 in CH_2Cl_2. Unfortunately, this promising beginning had to be abandoned when treatment of this bromide with bases strong enough to effect dehydrobromination also epimerized the secondary methyl center. Typical of these efforts is the conversion of **119** into **120** in good overall yield, but as an unacceptable mixture of diastereomers.



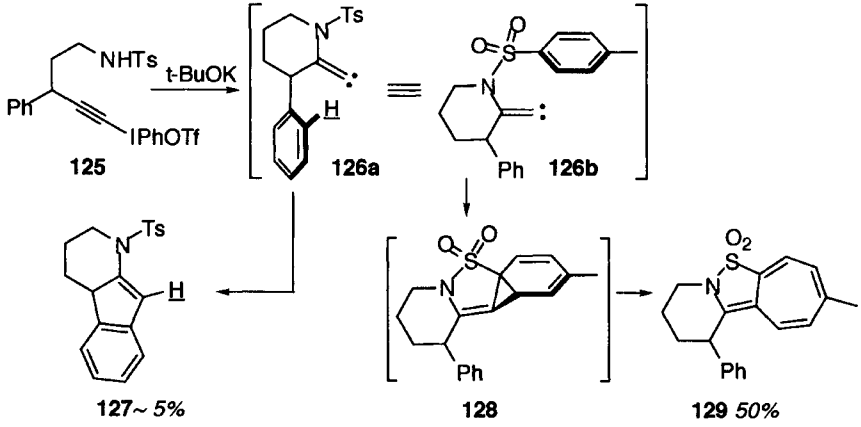
SCHEME 17. Formation of the tricyclic amide **102**.

This result dictated that any alkene-generating elimination process has to proceed via conditions not basic enough to enolize the tertiary amide. Using a procedure developed by Ochiai,[35] the tetraalkylstannane unit of **119** was converted into the chlorotrialkylstannane of **121** in excellent yield. The formation of a halotin species enabled the use of the Tamao-Fleming oxidation[36] for formation of the primary alcohol within **122**.

This alcohol emerged from the oxidation sequence pure enough for direct entry into a selenoxide-mediated elimination procedure (**122** → **102**) originally introduced by Grieco.[37] The selenation/oxidative elimination transform proceeded under essentially neutral conditions, which preserved the stereochemical integrity of the secondary methyl center. The yield for this four-step sequence (**119** → **102**) compares favorably with the more direct two-step approach (**119** → **120**), and it has the obvious benefit that the stereogenic center is not disturbed. Overall, the tricyclic **102**, bearing four of the stereogenic centers of the target halichlorine, can be prepared from pyridine in 12 steps. The continuation of the synthesis plan currently is under active investigation.

VI. Synthesis of Pareitropone

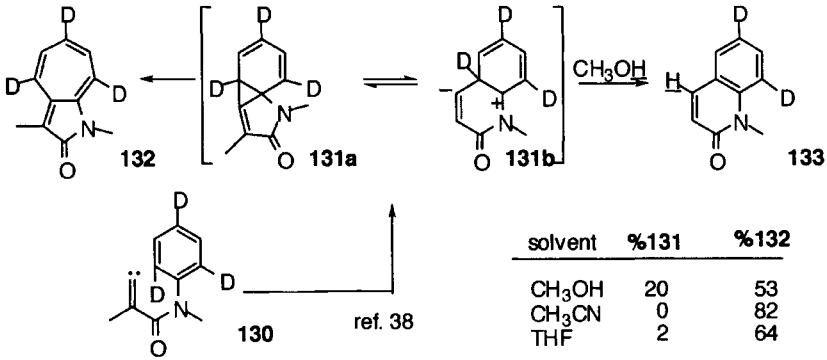
The pareitropone project began quite by accident after an unexpected observation expanded our thinking about potentially accessible targets for alkynyliodonium salt/alkylidenecarbene chemistry (Scheme 18). Treatment of the tosylamide iodonium salt **125** with base under standard conditions was designed to provide no more than routine confirmation of the aryl C–H insertion capabilities, which were first exposed in indole-forming reactions using tosylanilide anion nucleophiles and propynyl(phenyl)iodonium triflate,[5b] of the intermediate carbene **126**. However, this substrate did not perform as expected, since only trace amounts of the 1,5 C–H insertion product **127** was detected. One major product was formed, and analysis of its spectral data provided yet another surprising lesson in alkynyliodonium salt chemistry for us. The data was only consistent with the unusual cycloheptatriene structure **129**.



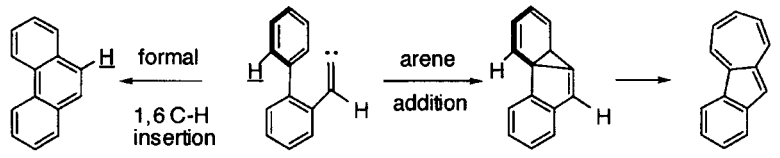
SCHEME 18. Unexpected arene addition chemistry of alkylidenecarbenes.

Backtracking from reaction product **129**, speculation about the origin of this species led to the initially uncomfortable hypothesis that carbene **126** must have participated in a cycloaddition process with the tosyl unit's aryl ring in preference to C–H insertion. This curious result may be the outcome of a situation where proximity trumps electronics, as the mismatch between the electrophilic carbene and the electron deficient aryl ring would seem, *a priori*, to dissuade cycloaddition.

We have no evidence that allows differentiation between reaction through a highly strained methylenecyclopropane **128** and its zwitterionic ring-opened isomer (cf. **131b**, Scheme 19). The closed-shell form **128** is shown for simplicity only. The real surprise in this reaction was not aryl ring addition per se, but rather the fact that such addition was favored over 1,5 C–H insertion. Earlier studies by Gilbert (Scheme 19) documented the feasibility of aryl ring addition for alkylidenecarbenes generated through diazoalkene chemistry.[38] In the Gilbert series, permissive evidence accrued from solvent variation and solvent labeling studies support the case for a zwitterionic intermediate **131b**, perhaps in equilibrium with the strained norcaradiene system **131a**. Delving a little deeper into the literature on this topic reveals even earlier work by Harrington et al. (Scheme 20), who demonstrated that under the extreme conditions of flash vacuum pyrolysis, the alkylidenecarbene **134** partitions between 1,6 C–H insertion (→**135**) and arene cycloaddition (→**137**).[39] With caveats about the relevance of gas-phase chemistry noted, the formation of **137** was as encouraging as the production of **135** was discouraging with respect to our emerging plans for pareitropone synthesis.



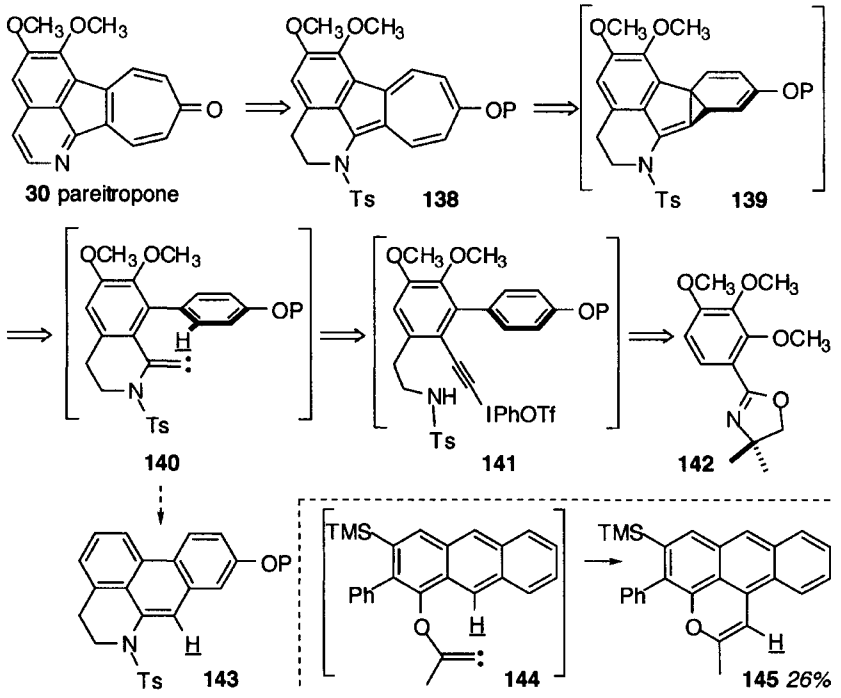
SCHEME 19. Gilbert's precedent for alkylidenecarbene/aryl ring additions.



135 *72 %* **134** formed at 700 °C, FVP **136** ref. 39 **137** *28 %*

SCHEME 20. Harrington's precedent for alkylidenecarbene/aryl ring additions.

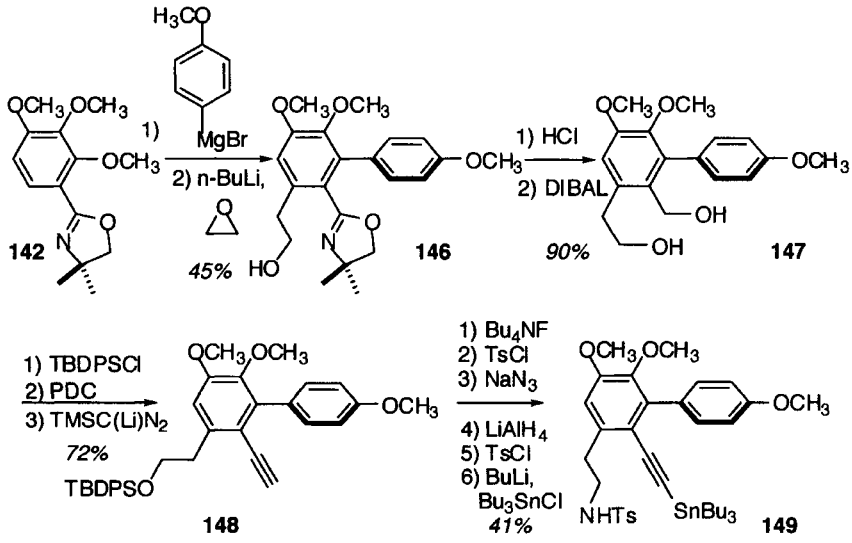
The cyclopentannelated cycloheptatriene ring system of pareitropone (**30**) provided the structural cue for application of this nascent development in aryl ring addition chemistry (Scheme 21).[40] The fully aromatic tetracyclic framework of pareitropone was viewed as a thermodynamic sink that inexorably would be formed from any number of variants of the azulenyl precursor **138**, a molecule that sits precariously on the verge of aromaticity itself. Of course, such naïve thinking became the downfall of the initial attempt at this target, but, at the planning stages, optimism triumphed over rational analysis. The benzannelated azulene penultimate intermediate **138** is just a strain-driven electrocyclization removed from a familiar methylenecyclopropane precursor **139**, the product of intramolecular alkylidenecarbene/aryl ring cycloaddition. This carbene, in turn, has a β-nitrogen substituent, the perfect target for intramolecular alkynyliodonium salt addition chemistry with **141**. In this instance, the normally facile 1,2-aryl shift of arene-substituted alkylidenecarbenes would lead to a cycloheptyne product, a process hopefully more energetically penalizing than the desired addition to the peri-positioned aryl ring. Of more immediate concern was the prospect for 1,6 C–H insertion within **140** to furnish a stable phenanthrene product **143**. Just such reactivity is suggested by Harrington (**134** → **135**, Scheme 20) and confirmed in our own studies with **144**, which participated in 1,6 C–H insertion to the exclusion of the desired aryl addition.[5k] To the extent that proximity dictates reactivity with these highly energetic carbene intermediates, density functional calculations (Becke-Perdew model with the DN* basis set) of a stripped down version of **140** revealed that the carbene terminus-to-ipso position of the aryl ring was approximately 2/3 Å shorter than the distance to H. Nevertheless, the issues surrounding potential reactivity manifolds for alkylidenecarbene **141** can only be settled through experiment. The preparation of the alkynyliodonium salt **141** is really an exercise in penta-substituted arene ring construction, and a better approach than the versatile and robust chemistry developed by Dr. Albert Meyers at Colorado State could not be imagined.[41]



SCHEME 21. Retrosynthesis of pareitropone (**30**).

The first pass at pareitropone synthesis commenced with an oxazoline-promoted nucleophilic aromatic substitution reaction between **142** and *p*-methoxyphenyl Grignard (Scheme 22). The choice of the *p*-methoxyphenyl Grignard was based on expediency (this Grignard is commercially available), but it will turn out that if more attention was paid to the phenoxy protecting group at this early stage, we might have saved some grief at a later stage of the plan. However, a desire to test quickly the key bicyclization step overwhelmed any concerns about protecting group details. Continued exploitation of the oxazoline ring's valuable activation capabilities led to facile ortho metalation and subsequent hydroxyethylation with ethylene oxide to provide **146**. The synthesis plan actually called for installation of a β-*N*-tosylethyl fragment at this ortho position, a unit that indeed could be attached in good yield by simply substituting tosyl aziridine for ethylene oxide in the aryl anion quench.[42] Unfortunately, this nitrogen-containing intermediate proved to be a dead end, as subsequent transformations failed with the *N*-tosylethyl group present. The β-hydroxyethyl group, in fact, played a crucial role in the oxazoline's hydrolysis to form a lactone.[43] Without this internal

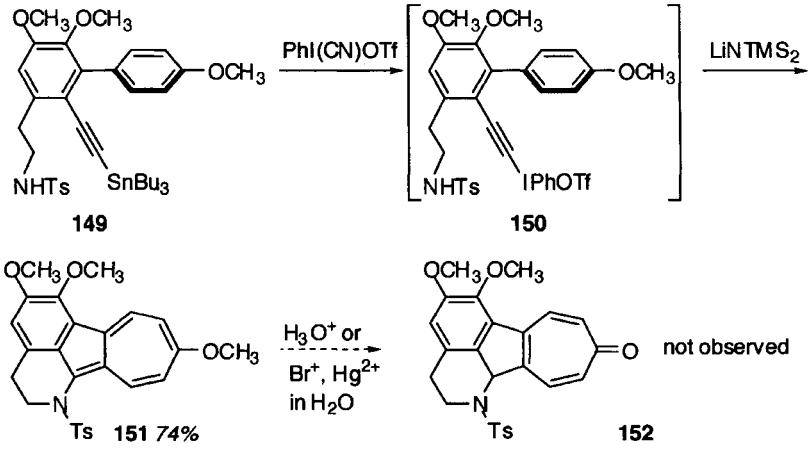
assistance (i.e., an NH-Ts or $OSiR_3$ analogue), experimental conditions that hydrolyzed the hindered oxazoline could not be found. Reduction of this lactone provided diol **147**, which was selectively protected at the primary alcohol in preparation for alkyne formation. The use of lithiotrimethylsilyldiazomethane in this alkyne-forming process illustrates the curious fact that an alkylidenecarbene is generated in the precise position as that desired for arene addition later in the synthesis. In this instance, however, the hydrogen attached to the carbene ensures that 1,2-shift to regenerate the alkyne, and not arene addition, prevails. Standard but somewhat lengthy functional group transformations on the alkynyl silyl ether **148** delivered the desired *N*-tosyl stannylalkyne **149** in preparation for the key cascade reaction sequence.



SCHEME 22. Synthesis of the pentasubstituted aryl core of pareitropone - first iteration.

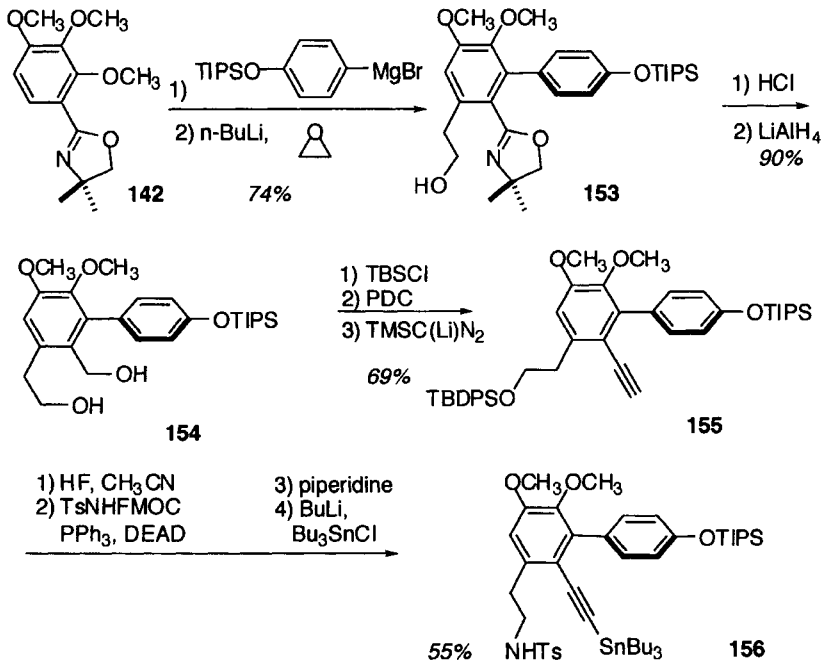
Conversion of the alkynylstannane within **149** into the corresponding alkynyliodonium salt **150** proceeded as expected, and this fragile intermediate was treated immediately with base at low temperature (Scheme 23). TLC analysis of the crude reaction mixture indicated only a single off-baseline product, quite visible as a bright purple spot. Isolation of this compound by chromatography and characterization by standard spectral techniques led to the realization that the desired cycloheptatrienylidene product **151** had been formed in good yield. Careful examination of the crude reaction mixture's ^1H NMR spectrum did not provide any indication that a 1,6 C–H insertion-derived

phenanthrene product was formed. The optimism spawned by this first-trial success quickly diminished as repeated attempts to hydrolyze the enol ether portion of **151** failed. All manner of electrophile was enjoined in the attempt to unmask the tropone ring, but in the end only small amounts of fluorene-type materials could be identified in the complex reaction mixtures. Apparently, the tosylenamide in **151** was a more willing participant than the enol ether in electrophile addition experiments. Perhaps the angle strain engendered by placing this functionality at the juncture of three rings contributed to its heightened reactivity. Whatever the reason, the solution to this problem was obvious: replace the refractory methyl ether with a more labile version of same.



SCHEME 23. First attempt at the tropoloisoquinoline-forming cascade sequence.

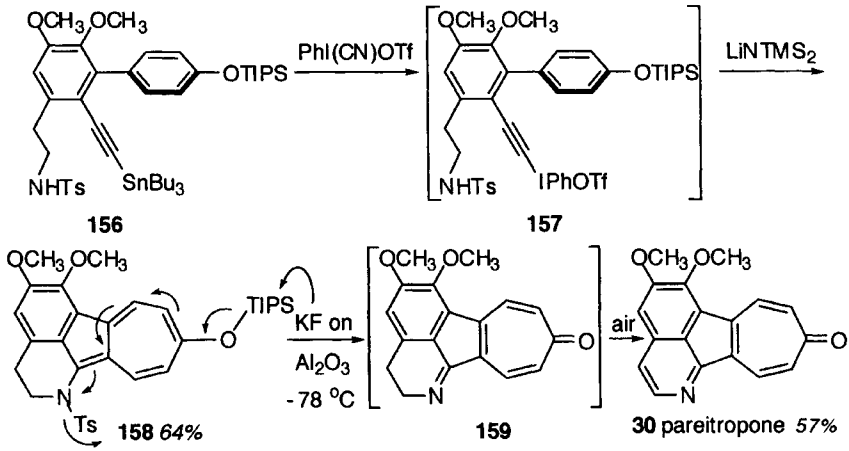
The TIPS ether analogue of the initial Grignard reagent would lead to a cycloheptatrienylidene product that might meet this requirement (Scheme 24). And so, we began again with the same oxazoline **142** and a little better appreciation of the importance of our protecting group choice on the pendant aryl ring. The chemistry proceeded similarly to the original route up to alkyne intermediate **155**. Conversion of this species to the requisite *N*-tosyl alkynylstannane **156** followed a briefer new sequence of functional group manipulations highlighted by nitrogen introduction via Mitsunobu chemistry.[44]



SCHEME 24. Synthesis of the pentasubstituted aryl core of pareitropone - second iteration.

The enhanced electron density of the TIPSO-substituted aryl ring in **156** compared to its H_3CO- version raised concerns about the selectivity of iodonium transfer, but Stang's reagent performed as hoped and only the alkynyliodonium salt product was formed (Scheme 25). Immediate treatment of this crude material with base at low temperature led to a green solution from which a blue-green solid could be isolated following workup and chromatography. Spectral analysis confirmed that the desired cycloheptatrienylidene **158** was formed from the OTIPS-substituted substrate as well. As with the previous series, no evidence for phenanthrene production was forthcoming. With **158** in hand, it was time to reap the benefits of our TIPS-inspired adjustments to the route. Certainly any whiff of fluoride would inevitably propel this species toward pareitropone, or so we thought. Six months later, we had no pareitropone, but we did have a much greater appreciation for the subtleties of **158**'s chemistry. Exposure of **158** to any fluoride source, whether acidic or basic in character, under a range of temperature and solvent regimes, led time-after-time to complete destruction of the starting material without formation of any identifiable products. What was going wrong with this "simple" process? A major clue was revealed

when, by chance, we tried KF-impregnated alumina as the fluoride source.[45] In this single unique trial, a discrete, isolable product was formed. The spectral data initially were puzzling, as no aliphatic (-CH_2-CH_2-) protons were evident in the ^{1}H NMR spectrum. However, consternation quickly turned to elation when a check of pareitropone's literature spectral data indicated identity. We had finally made pareitropone, although perhaps by an unexpected finale. Subsequent runs with this fluoride source occasionally afforded crude product mixtures that contain variable amounts of a (-CH_2-CH_2-)-bearing species (^{1}H NMR) along with pareitropone. The signals for this saturated compound disappeared upon exposure to air, suggesting that dihydropareitropone **159** is a first-formed product of the desilylation, but that aerobic oxidation quickly consumes it. Control experiments designed to probe the role that this singular reagent combination plays in allowing isolation of pareitropone indicated that (1) pareitropone (and presumably dihydropareitropone as well) is attacked rapidly by fluoride to furnish crude reaction mixtures reminiscent of those produced originally by **158**/F^- reaction, (2) KF by itself destroyed **158**, and (3) exposure to Al_2O_3 did not affect **158** in any way. Taken together, these observations suggest that the alumina is responsible for salvaging this transformation, perhaps by sequestering any pareitropone (or dihydropareitropone) as it is formed. In this way, it is removed from solution and therefore avoids the destructive effects of reaction with fluoride.



SCHEME 25. Second attempt at the tropoloisoquinoline-forming cascade sequence. Preparation of pareitropone.

VII. Conclusions

The syntheses of agelastatin and pareitropone, and the work completed towards halichlorine, demonstrate just some of the possibilities that this alkynyliodonium salt-based methodology offers for efficient polycycle assembly from relatively simple precursors. The key is designing a substrate with appropriately positioned nucleophilic atom, alkyne, and, most importantly, a carbene trap, in order to steer the various reactive intermediates toward a desired goal. This strategic requirement is both the strength and the weakness of the methodology, as care must be taken to ensure that overall efficiency is not sacrificed in overly complicated substrate design. On the other hand, for those systems where clean, concise routes to a properly designed substrate can be identified, the alkynyliodonium salt→ alkylidenecarbene→ C–H insertion/alkene(arene) addition cascade can be a very efficient means to increase molecular complexity en route to targeted structures.

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References

1. Patai, S. "*The Chemistry of the Carbon-Carbon Bond*," J. Wiley & Sons: New York, 1973.
2. Diederich, F., Stang, P. J., "*Metal Catalyzed Cross-Coupling Reactions*," Wiley-VCH; New York, 1998.
3. (a) For an example of a Hiyami-Nozaki-Kishi reaction using an alkynyliodide substrate, see Dhimane, A.-L., Aissa, C., Malacria, M., *Angew. Chem. Int. Ed.* **2002**, *41*, 3284. (b) For an example of Stille coupling using an alkynyliodide substrate, see Timbart, L., Cintrat, J.-C., *Chem-Eur J.* **2002**, *8*, 1637.
4. (a) Varvoglis, A. "*Hypervalent Iodine in Organic Synthesis*," Academic Press: San Diego, 1996. (b) Stang, P. J., *J. Org. Chem.* **2003**, *68*, 2997.
5. (a) Schildknegt, K., Bohnstedt, A. C., Feldman, K. S., Sambandam, A., *J. Am. Chem. Soc.* **1995**, *117*, 7544. (b) Feldman, K. S., Bruendl, M. M., Schildknegt, K., *J. Org. Chem.* **1995**, *60*, 7722. (c) Feldman, K. S., Bruendl, M. M., Schildknegt, K., Bohnstedt, A. C., *J. Org. Chem.* **1996**, *61*, 5440. (d) Feldman, K. S., Bruendl, M. M., *Tetrahedron Lett.* **1998**, *39*, 2911. (e) Feldman, K. S., Mareska, D. A., *J. Am. Chem. Soc.* **1998**, *120*, 4027. (f) Feldman, K. S., Mareska, D. A., *Tetrahedron Lett.* **1998**, *39*, 4781. (g) Feldman, K. S., Mingo, P. A., Hawkins, P. C. D., *Heterocycles* **1999**, *51*, 1283. (h) Feldman, K. S., Mareska, D. A., *J. Org. Chem.* **1999**, *64*, 5650. (i) Feldman, K. S., Wrobleski, M.

L., *Org. Lett.* **2000**, *2*, 2603. (j) Feldman, K. S., Wrobleski, M. L., *J. Org. Chem.* **2000**, *65*, 865. (k) Feldman, K. S., Perkins, A. L., *Tetrahedron Lett.* **2001**, *42*, 6031. (l) Feldman, K. S., Saunders, J. C., *J. Am. Chem. Soc.* **2002**, *124*, 9060. (m) Feldman, K. S., Saunders, J. C., Wrobleski, M. L., *J. Org. Chem.* **2002**, *67*, 7096. (n) Feldman, K. S., Cutarelli, T. D., *J. Am. Chem. Soc.* **2002**, *124*, 11600. (o) Feldman, K. S., Cutarelli, T. D., Di Florio, R., *J. Org. Chem.* **2002**, *67*, 8528.

6. (a) Stang, P. J., Zhdankin, V. V., *J. Am. Chem. Soc.* **1991**, *113*, 4571. (b) Koser, G. F., Rebrovic, L., Wettach, R. H., *J. Org. Chem.* **1981**, *46*, 4324. (c) Ochiai, M., Kunishima, M., Sumi, K., Nagao, Y., Fujita, E., Arimoto, M., Yamaguchi, H., *Tetrahedron Lett.* **1985**, *26*, 4501.
7. Ochiai, M., Kunishima, M., Nagao, Y., Fuji, K., Shiro, M., Fujita, E., *J. Am. Chem. Soc.* **1986**, *108*, 8281.
8. (a) Stang, P. J., Zhdankin, V. V., *Tetrahedron* **1998**, *54*, 10927. (b) Varvoglis, A., *Tetrahedron* **1997**, *53*, 1179.
9. a) Stang, P. J., *Angew. Chem. Int. Ed.* **1992**, *31*, 285 and references cited therein. b) Fischer, D. R., Williamson, B. L., Stang, P. J., *Synlett.* **1992**, 535. c) Bachi, M. D., Bar-Ner, N., Crittell, C. M., Stang, P. J., Williamson, B. L., *J. Org. Chem.* **1991**, *56*, 3912. d) Stang, P. J., *Russ. Chem. Bull.* **1993**, *42*, 12. e) Williamson, B. L., Tykwinski, R. R., Stang, P. J., *J. Am. Chem. Soc.* **1994**, *116*, 93. f) March, P., Williamson, B. L., Stang, P. J., *Synthesis* **1994**, 1255. g) Tykwinski, R. R., Whiteford, J. A., Stang, P. J., *J. Chem. Soc., Chem. Commun.* **1993**, 1800. h) Ochiai, M., in *Reviews on Heteroatom Chemistry, Volume 2*, Oae, S., Ed. MYU, Tokyo, 1989, pg. 92. i) Ochiai, M., Ito, T., Takaoka, Y., Kunishima, M., Tani, S., Nagao, Y., *J. Chem. Soc., Chem. Commun.*, **1990**, 118. j) Ochiai, M., Kunishima, M., Tani, S., Nagao, Y., *J. Am. Chem. Soc.* **1991**, *113*, 3135. k) Ochiai, M., Kunishima, M., Fuji, K., Nagao, Y., *J. Org. Chem.* **1988**, *53*, 6144. l) Ochiai, M., Takaoka, Y., Nagao, Y., *J. Am. Chem. Soc.* **1988**, *110*, 6565. m) Margida, A., Koser, G. F., *J. Org. Chem.* **1984**, *49*, 4703. n) Kitamura, T., Stang, P. J., *Tetrahedron Lett.* **1988**, *29*, 1887. o) Tykwinski, R. R., Stang, P. J., Peisky, N. E., *Tetrahedron Lett.* **1994**, *35*, 23. p) Stang, P. J., *Acc. Chem. Res.* **1991**, *24*, 304. q) Stang, P. J., Zhdankin, V. V., *J. Am. Chem. Soc.* **1991**, *113*, 4571. r) Zhdankin, V. V., Scheuller, M. C., Stang, P. J., *Tetrahedron Lett.* **1993**, *34*, 6853.
10. For example, see Margida, A. J., Koser, G. F., *J. Org. Chem.* **1984**, *49*, 4703.
11. (a) Stang, P. J., *Chem. Rev.* **1978**, *78*, 383, and references cited therein. (b) Ervin, K. M., Ho, J., Lineberger, W. C., *J. Chem. Phys.* **1989**, *91*, 5974. (c) Bodor, N., Dewar, M. J. S.; Wasson, J. S. *J. Am. Chem. Soc.* **1972**, *94*, 9095. (d) Gallo, M. M., Hamilton, J. P., Schaeffer, H. F. III, *J. Am. Chem. Soc.* **1990**, *112*, 8714. (e) Gilbert, J. C., Giamalva, D. H., *J. Org. Chem.* **1992**, *57*, 4185. (f) Maercker, A., *Angew. Chem. Int. Ed.* **1993**, *32*, 1023. (g) Johnson, R. P.; Daoust, K. J. *J. Am. Chem. Soc.* **1995**, *117*, 362 (h) Hayes, R. L., Fattal, E., Govind, N., Carter, E. A., *J. Am. Chem. Soc.* **2001**, *123*, 641. (i) Reed, S. C., Capitosti, G. J., Zhu, Z., Modarelli, D. A., *J. Org. Chem.* **2001**, *66*, 287.
12. Bodor, N., Dewar, M. J. S., Wasson, J. S., *J. Am. Chem. Soc.* **1972**, *94*, 9095.
13. Corey, E. J., Fuchs, P. L., *Tetrahedron Lett.* **1972**, 3769.
14. (a) D'Ambrosio, M., Guerriero, A., Debitus, C., Ribes, O., Pusset, J., Leroy, S., Pietra, F., *J. Chem. Soc., Chem. Commun.* **1993**,1305. (b) Hong, T. M., Jímenez, D. R., Molinski, T. F., *J. Nat. Prod.* **1998**, *61*, 158. (c) D'Ambrosio, M., Guerriero, A., Chiasera, G., Pietra, F., *Helv. Chim. Acta.* **1994**, *77*, 1895. (d) D'Ambrosio, M., Guerriero, A., Ripamonti, M., Debitus, C., Waikedre, J., Pietra,

F., *Helv. Chim. Acta* **1996**, *79*, 727. (e) Mourabit, A. A., Potier, P., *Eur. J. Org. Chem. 2001*, 237.

15. (a) Kuramoto, M., Tong, C., Yamada, K., Chiba, T., Hayashi, Y., Uemura, D., *Tetrahedron Lett.* **1996**, *37*, 3867. (b) Arimoto, H., Hayakawa, I., Kuramoto, M., Uemura, D., *Tetrahedron Lett.* **1998**, *39*, 861.
16. Morita, H., Takeya, K., Itokawa, H., *Bioorg. Med. Chem. Lett.* **1995**, *5*, 597.
17. Other approaches to the synthesis of agelastatin A can be found in: (a) Stein, D., Anderson, G. T., Chase, C. E., Koh, Y.-h., Weinreb, S. M., *J. Am. Chem. Soc.* **1999**, *121*, 9574. (b) Baron, E., O'Brien, P., Towers, T. D., *Tetrahedron Lett.* **2002**, *43*, 723.
18. Witulski, B., Stenfel, T., *Angew. Chem. Int. Ed.* **1998**, *37*, 489.
19. Gilbert, J. C., Giamalva, D. H., Baze, M. E., *J. Org. Chem.* **1985**, *50*, 2557.
20. Garner, P., Park, J.M., *Org. Synth.* **1991**, *70*, 18.
21. T. Fujisawa, T., Nagai, M., Koike, Y., Shimizu, M., *J. Org. Chem.*, **1994**, *59*, 5865.
22. Warner, P. B., Buchwald, S. L., *J. Org. Chem.*, **1994**, *59*, 5822.
23. (a) Reddy, K. L., Sharpless, K. B., *J. Am. Chem. Soc.* **1998**, *120*, 1207. (b) Bruncko, M., Schlingloff, G., Sharpless, K. B., *Angew. Chem. Int. Ed.* **1997**, *36*, 1483. (c) Rudolph, J., Sennhenn, P. C., Vlaar, C. P., Sharpless, K. B., *Angew. Chem. Int. Ed.* **1996**, *25*, 2810.
24. Takano, S., Kamikubo, T., Sugihara, T., Ogasawara, K., *Tetrahedron: Asymmetry* **1992**, *3*, 853.
25. Ariza, X., Pineda, O., Urpí, F., Vilarrasa, J., *Tetrahedron Lett.* **2001**, *42*, 4995.
26. Ochiai, M., Kunishima, M., Tani, S., Nagao, Y., *J. Am. Chem. Soc.* **1991**, *113*, 3135.
27. The total synthesis of halichlorine has been achieved: (a) Trauner, D., Schwartz, J. B., Danishefsky, S. J., *Angew. Chem. Int. Ed.* **1999**, *38*, 3542. Other approaches to the halichlorine structure can be found in: (b) Arimoto, H., Asano, S., Uemura, D., *Tetrahedron Lett.* **1999**, *40*, 3583. c) Lee, S., Zhao, Z., *Org. Lett.* **1999**, *1*, 681. (d) Ciblat, S., Canet, J.-L., Troin, Y., *Tetrahedron Lett.* **2001**, *42*, 4815. (e) Shindo, M., Fukuda, Y.-i., Shishido, K., *Tetrahedron Lett.* **2000**, *41*, 929. (f) Clive, D. L. J., Yeh, V. S. C., *Tetrahedron Lett.* **1999**, *40*, 8503. (g) Koviach, J., Forsyth, C. J., *Tetrahedron Lett.* **1999**, *40*, 8529. (h) Fenster, M. D. B., Patrick, B. O., Dake, G. R., *Org. Lett.* **2001**, *3*, 2109. (i) Lee, S., Zhao, Z., *Tetrahedron Lett.* **1999**, *40*, 7921. (j) Wright, D. L., Schulte, J. P. II, Page, M. A., *Org. Lett.* **2000**, *2*, 1847. (k) Yokota, W., Shindo, M., Shishido, K., *Heterocycles* **2001**, *54*, 871. (l) Ito, T., Yamazaki, N., Kibayashi, C., *Synlett.* **2001**, 1506.
28. (a) Bubnov, Y. N., Shagova, E. A., Evchenko, S. V., Ignatenko, A. V., *Russ. Chem.* Bull. **1994**, *43*, 645. (b) Bubnov, Y. N., *Pure & Appl. Chem.* **1994**, *66*, 235. (c) Bubnov, Y. N., *Royal Soc. Chem.* **1997**, *201*, 123. (d) Bubnov, Y. N., Demina, E. E., Dekaprilevich, M. O., Struchkov, Y. T., *Russ. Chem.* Bull. **1997**, *46*, 1356. (e) Bubnov, Y. N., Klimkina, E. V., Ignatenko, A. V., *Russ. Chem.* Bull. **1998**, *47*, 941. (f) Bubnov, Y. N., Demina, E. E., Ignatenko, A. V., *Russ. Chem.* Bull. **1997**, *46*, 1306. (g) Bubnov, Y. N., Demina, E. E., Ignatenko, A. V., *Russ. Chem.* Bull. **1997**, *46*, 606. (h) Bubnov, Y. N., Klimkina, E. V., Ignatenko, A. V., *Russ. Chem.* Bull. **1998**, *47*, 451. (i) Bubnov, Y. N., Klimkina, E. V., Ignatenko, A. V., *Russ. Chem. Bull.* **1998**, *47*, 1175. (j) Gurskii, M. E., Potapova, T. V., Bubnov, Y. N., *Russ. Chem. Bull.* **1998**, *47*, 1410. (k) Bubnov, Y. N., Demina, E. E., Bel'sky, V. K., Zatonsky, G. V., Ignatenko, A. V., *Russ. Chem. Bull.* **1998**, *47*, 2249. (l) Bubnov, Y. N., Klimkina, E. V., Lavrinovich, L. I.,

Zykov, A. Y., Ignatenko, A. V., *Russ. Chem. Bull.* **1999**, *48*, 1696. (m) Bubnov, Y. N., Klimkina, E. V., Zhun, I. V., Pastukhov, F. V., Yampolski, I. V., *Royal Soc. Chem.* **2000**, *253*, 446. (n) Bubnov, Y. N., Pastukhov, F. V., Starikova, Z. A., Ignatenko, A. V., *Russ. Chem. Bull., Int. Ed.* **2001**, *50*, 2172. (o) Bespalova, N. B., Shuvalova, O. V., Zaikin, V. G., Borisov, R. S., Pastukhov, F. V., Bubnov, Y. N., *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 645.

29. (a) Takai, K., Tagashira, M., Kuroda, T., Oshima, K., Utimoto, K., Nozaki, H., *J. Am. Chem. Soc.* **1986**, *108*, 6048. (b) Schreiber, S. L., Meyers, H. V., *J. Am. Chem. Soc.* **1988**, *110*, 5198. (c) Cintas, P., *Synthesis*, **1992**, 248. (d) Muller, B., Ferezou, J.-P., Lallemand, J.-Y., Pancrazi, A., Prunet, J., Prange, T., *Tetrahedron Lett.* **1998**, *39*, 279. (e) Maguire, R. J., Mulzer, J., Bats, J. W., *Tetrahedron Lett.* **1996**, *37*, 5487. (e) Pilli, R. A., Victor, M. M., *Tetrahedron Lett.* **2002**, *43*, 2815.
30. MacDonald, T. L., Mahalingam, S., *J. Am. Chem. Soc.* **1980**, *102*, 2113.
31. (a) Curran, D. P., Porter, N. A.; Giese, B. "*Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*," VCH: New York, 1996. (b) Giese, B. "*Radicals in Organic Synthesis*," Pergamon Press: New York, 1986.
32. (a) Hamada, T., Suzuki, D.; Urabe, H., Sato, F., *J. Am. Chem. Soc.* **1999**, *121*, 7342. (b) Devos, A.; Remion, J., Frisque-Hesbain, A.-M.; Colens, A., Ghosez, L., *J. Chem .Soc., Chem. Commun.* **1979**, 1180.
33. Williamson, B. L.; Tykwinski, R. R., Stang, P. J., *J. Am. Chem. Soc.* **1994**, *116*, 93.
34. (a) Kurth, M. J., O'Brien, M. J., *J. Org. Chem.* **1985**, *50*, 3846. (b) Coltart, D. M., Danishefsky, S. J., *Org. Lett.* **2003**, *5*, 1289,
35. Ochiai, M., Iwaki, S., Ukita, T., Matsuura, Y., Shiro, M., Nagao, Y., *J. Am. Chem. Soc.* **1988**, *110*, 4606.
36. Jones, G. R., Landis, Y., *Tetrahedron* **1996**, *52*, 7599.
37. Grieco, P. A., Gilman, S., Nishizawa, M., *J. Org. Chem.* **1976**, *41*, 1485.
38. (a) Gilbert, J. C., Blackburn, B. K., *J. Org. Chem.* **1986**, *51*, 4087. (b) Gilbert, J. C., Blackburn, B. K., *Tetrahedron Lett.* **1990**, *31*, 4727.
39. Brown, R. F. C., Eastwood, F. W., Harrington, K. J., McMullen, G. L., *Aust. J. Chem.* **1974**, *27*, 2393.
40. (a) Banwell, M. G., Hamel, E., Ireland, N. K., Mackay, M. F., *Heterocycles* **1994**, *39*, 205. (b) Banwell, M. G., Bonadio, A., Turner, K. A., Ireland, N. K., Mackay, M. F., *Aust. J. Chem.* **1993**, *46*, 325. (c) Banwell, M. G., Hamel, E., Ireland, N. K., Mackay, M. F., Serelis, A. K., *J. Chem. Soc., Perkin Trans. 1* **1993**, 1905. (d) Banwell, M. G., *Pure Appl. Chem.* **1996**, *68*, 539. (e) Evans, D. A., Hart, D. J., Koelsch, P. M., Cain, P. A., *Pure Appl. Chem.* **1979**, *51*, 1285. (f) Molina, P., Garcia-Zafra, S., Fresneda, P. M., *Synlett* **1995**, 43. (g) Boger, D. L., Takahashi, K., *J. Am. Chem. Soc.* **1995**, *117*, 12452. (h) Lee, J. C., Cha, J. K., *J. Am. Chem. Soc.* **2001**, *123*, 3243.
41. (a) Meyers, A. I., Gant, T. G., *Tetrahedron* **1994**, *50*, 2297. (b) Reuman, M., Meyers, A. I., *Tetrahedron* **1985**, *41*, 837.
42. Hoye, T. R., Chen, M., Hoang, B., Mi, L., Priest, O. P., *J. Org. Chem.* **1999**, *64*, 7184.
43. Patel, H. A., MacLean, D. B., *Can. J. Chem.* **1983**, *61*, 7.
44. Bach, T., Kather, K., *J. Org. Chem.* **1996**, *61*, 7642.
45. Blass, B. E., *Tetrahedron* **2002**, *58*, 9301.

STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 7

HOW TO THREAD A STRING THROUGH THE EYE OF A MOLECULAR NEEDLE: TEMPLATE SYNTHESIS OF INTERLOCKED MOLECULES

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I. Mechanically Interlocked Molecules: A Historical Perspective

Chemists know that covalent bonds usually define the term "molecule" in that all atoms within a molecule are connected with each other by covalent bonds. Beyond the molecule, weaker, non-covalent bonds govern the regime of supramolecular chemistry[1], which deals with the forces and interactions *between* individual molecules. This classification is based on the strength of the binding forces. Covalent bonds are in the range of several hundreds of kJ/mol, while the individual non-covalent interaction usually is much weaker ranging: from 1 kJ/mol for weak Van-der-Waals interactions up to about 200 kJ/mol for weak ligand-metal coordination. In particular, the coordination of ligands to a metal center is a good example to illustrate that it is not always easy to distinguish a

molecule from a supramolecule, since there is a continuum ranging from weak ligand-metal interactions to strong covalent ligand-metal donor bonds. However, there is a third type of bonding, which in principle does not even require attractive interactions for its existence. It is the mechanical bond.[2] Just imagine two ring-like molecules threaded into each other like the members of a chain. Such an architecture is called a catenane, a name which is derived from the Latin word "catena" for chain. Even if there is no attraction between the two rings, they cannot be separated without opening one of them. Admittedly, in most cases of such molecules, non-covalent interactions are operative, but in principle this is not a prerequisite, since one ring is locked within the other.

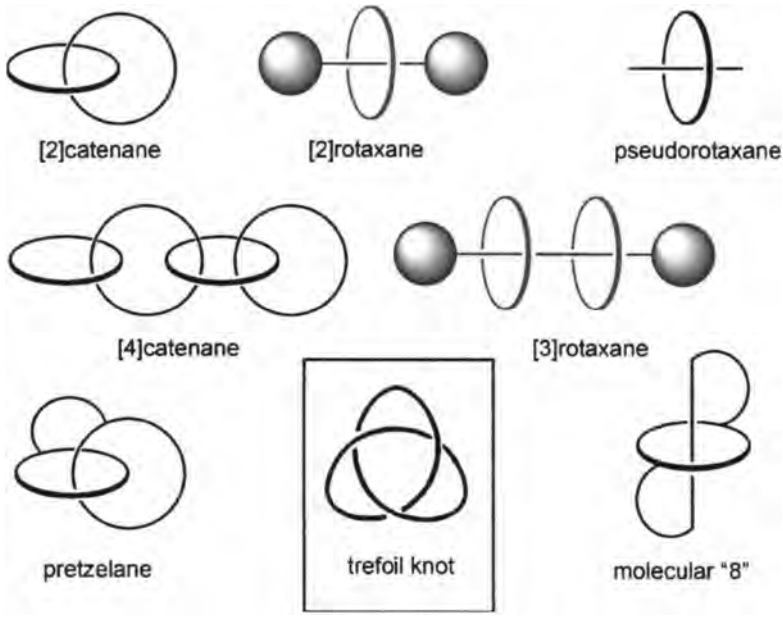


FIGURE 1: DIFFERENT MECHANICALLY INTERLOCKED MOLECULES AND THEIR NAMES. FIGURES IN BRACKETS COUNT THE NUMBER OF SEPARATE, MECHANICALLY BOUND SUBUNITS.

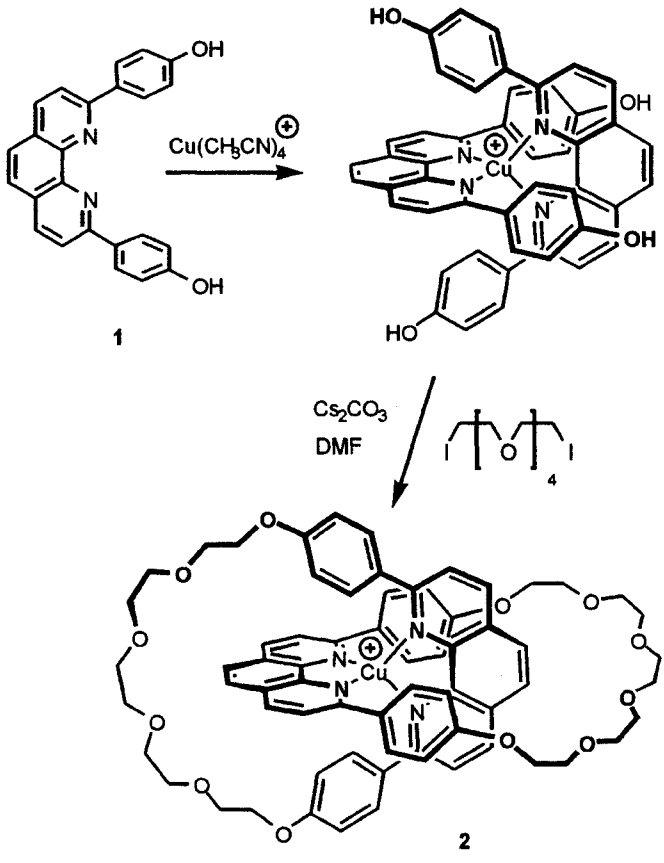
In this chapter, we will deal with ways to synthesize these catenanes and other types of mechanically interlocked molecules. They have some extraordinary features which we will highlight in passing in the following chapters, but the focus will be on their synthesis. However, before starting with this discussion, we should briefly introduce the players in our game (Figure 1). Instead of intertwining two macrocyclic rings, one could

thread a string-like molecule through a macrocycle. The resulting pseudorotaxane will only be stable, if the axle is held inside the wheel by at least some weak attractive forces. It can however be stabilized by adding bulky stopper groups to the ends of the axle yielding a rotaxane. This building principle may lead to higher catenanes and rotaxanes just by adding more components. Many other similar architectures have been synthesized. By bridging the two wheels of a catenane, a pretzel-shaped molecule[3] is formed, and connecting the axle of a rotaxane with its wheel by two bridges leads to a figure-eight-type molecule.[4] It is important to note that the latter two molecules as well as the trefoil knot each represent a single molecule that bears an intramolecular mechanical bond.

The first attempts to chemically synthesize such molecules were carried out in the early 1960s. Basically, two almost equally inefficient procedures were developed: the statistical synthesis[5] and a directed protocol[6] in which both wheels of a catenane were connected by suitable covalent bonds that were cleaved after closing both rings. The statistical approach lead to yields lower than 1% for the first catenane.[5a] The yield of a rotaxane prepared this way could be increased to 6% by connecting the wheel to a solid phase and treatment with an excess of axle components in 70 repetitive steps.[5b] On the other hand, the directed synthesis has been applied to both rotaxanes and catenanes and is a multi-step sequence of organic transformations with a low overall yield not at all justifying the required synthetic effort. The extremely difficult accessibility of catenanes and rotaxanes for a long time hampered the investigation of their properties. Consequently, mechanically interlocked molecules remained esoteric species that did not attract much attention among chemists. From these considerations, it should become clear that new synthetic strategies had to be found in order to make these species well accessible.

The situation changed dramatically, when in the mid-80's *Sauvage* and his co-workers[7] reported the synthesis of a catenane based on a copper template (Scheme 1). Two suitably functionalized phenanthroline ligands **1** are coordinated tetrahedrally to a central Cu(I) ion. Two macrocyclization steps complete the catenate **2** (i.e. the metal complex of a catenane), which can be converted to the metal-free catenane through demetallation with cyanide. The discovery of the enormous utility of non-covalent templates[8] for the synthesis of catenanes, rotaxanes, and knots gave the field fresh impetus and triggered its quick growth towards more and more complicated intertwined structures, towards different synthetic schemes, and towards functional species, so-called molecular machines. One consequence of these considerations is that in this chapter we will

not deal with complicated synthetic schemes or sophisticated preparative methods. Instead, the true challenge is the design of well-suited non-covalent interactions permitting control over the reactivity of the components to yield the desired products. The task is to program the reactants during their synthesis so that intermolecular forces yield suitably organized complexes.



SCHEME 1: SYNTHESIS OF A CATENATE BASED ON A CU(I)-MEDIATED TEMPLATE EFFECT. THE CATENANE CAN BE LIBERATED BY DEMETALLATION WITH CYANIDE.

II. A Primer to Templated Organic Synthesis

A template must serve different purposes: (i) It organizes reaction partners in such a way that a desired product is formed that would not form as easily in the absence of the template or would be formed as a minor component in a mixture of several competing products. Thus, its first task is to control reactivity. (ii) In order to achieve this, the template needs to bind to the reaction partners. Molecular recognition is consequently a prerequisite for templated synthesis. Thus, the binding sites of the components must be complementary to each other. (iii) The control of reactivity and the recognition of the reaction partners imply that information is stored in the template and transferred to the product of the reaction. The third important aspect is thus information transfer.

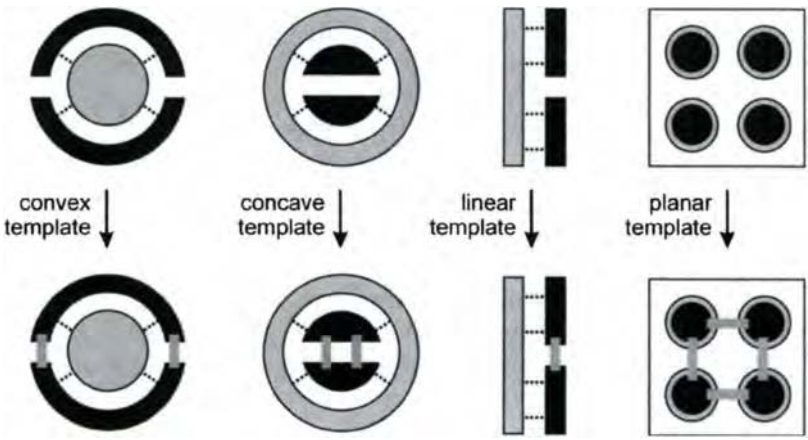


FIGURE 2: SCHEMATIC CLASSIFICATION OF TEMPLATES ACCORDING TO THEIR TOPOLOGY. THE TEMPLATE IS SHOWN IN GREY, THE REACTION PARTNERS IN BLACK. DOTTED LINES REPRESENT NON-COVALENT BONDS, GREY STICKS ARE NEW COVALENT BONDS BETWEEN THE REACTION PARTNERS.

There are different ways to categorize templates. One could for example try to distinguish template effects according to the non-covalent interactions involved. This classification has the major disadvantage that it becomes ambiguous for templates which operate *via* several different types of intermolecular forces. The template effect could involve hydrogen bonds and π-donor/π-acceptor interactions at the same time and it would immediately be unclear to which category it belongs. A better way is to classify the template according to its topology (Figure 2). The

early template syntheses of crown ethers utilized a central metal ion around which a macrocycle formed with a certain size selectivity.[9] Such templates could be called convex, because of their convex surface. The copper ion template shown in Scheme 1 is another example of such a convex template. In contrast, a receptor which binds two reaction partners inside a cavity and brings them to reaction is concave. This is true for many templates leading to mechanically interlocked species. One of the most prominent natural templates, DNA, could be called linear according to this classification. A surface may act as a planar template. A beautiful example of a planar template is a recently reported electropolymerization using a liquid crystalline phase as the template.[10]

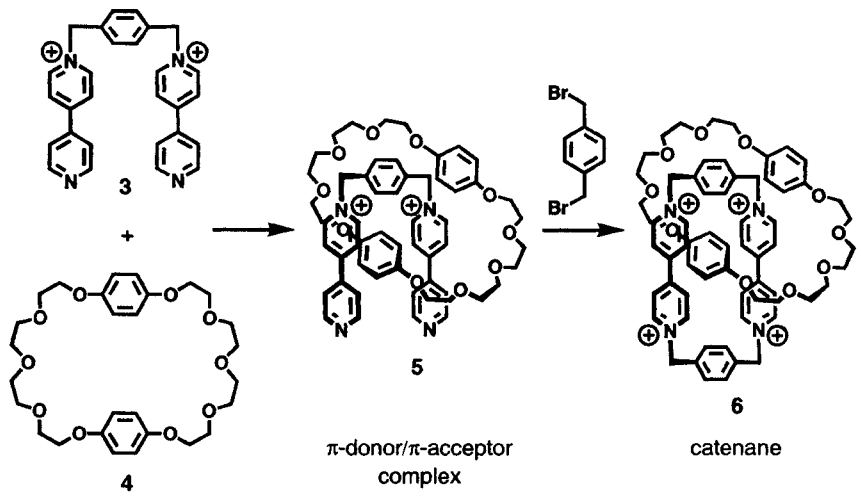
Another important point is to distinguish between a template and a catalyst. On one hand there are templates which do not promote catalytic reactions. They have to be removed from the product by separation techniques and need to be used in stoichiometric amounts. On the other hand, there are catalysts which do not organize the reactants in space but rather change their intrinsic reactivity. Thus, they cannot be regarded as templates. However, there are also mixed forms, where a template at the same time increases reactivity catalytically or where a catalyst organizes the reactants with respect to their geometry. All definitions of "template" suffer somewhat from this continuous transition from templates to catalysts and we should keep in mind that a distinction between these categories is not always straightforward.

Similarly, there is a difference between a reactant and a template. A strict definition would imply that the template must be removable after successfully mediating a certain reaction. Instead, a reactant becomes part of the product in one or another form. However, we will see that definitions become blurred again, when discussing the syntheses of rotaxanes, catenanes, and knots. The Cu(I)-mediated template effect for catenane formation is in accord with a strict definition, because the copper ion can be removed after macrocyclization of the second ring. Many of the other methods for the preparation of interlocked molecules are based on macrocycles which bind part of the other component in a pseudorotaxane fashion. This part is then reacted so that the desired species, e.g. a catenane or a rotaxane, is formed. The macrocyclic template thus finally becomes part of the product and might consequently be considered as a reactant rather than a template. Nevertheless, these methods are widely accepted as template syntheses in the chemical literature. We therefore suggest a more abstract definition of a template which is based on its ability to organize the reactants appropriately through covalent or non-covalent bonding interactions.

Finally, we should discuss the thermodynamics and kinetics of a template.[11] A thermodynamic template shifts an equilibrium to one side and thus has an effect on the free enthalpy of reaction. In a subsequent chemical reaction, this may lead to a product different from that formed in the non-templated reaction, because here another molecule is the major component in the equilibrium. This kind of template is related to dynamic combinatorial chemistry.[12] An equilibrium between many different species exists. At least in principle, a large variety of structures is possible, even if not all species are present as detectable components in the mixture. Addition of a template shifts the equilibrium to one side. A non-reversible reaction will then freeze out the preferred structure from which the template can usually be removed in a final purification step. Consequently, thermodynamic templates have an effect on ΔH and ΔS. In contrast, kinetic templates act on the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. They lower the activation enthalpy by stabilizing the transition structure and enhancing its reactivity, and they also produce a more favorable activation entropy by bringing the reactants together into close proximity and organizing them into a geometric arrangement favoring their reaction with each other. Consequently, one out of several reaction pathways is favored by lowering its barrier and the desired product is obtained at a higher reaction rate as compared to others that would be formed as the major products in the absence of the template.

III. Template Effects for the Syntheses of Rotaxanes, Catenanes, and Knots

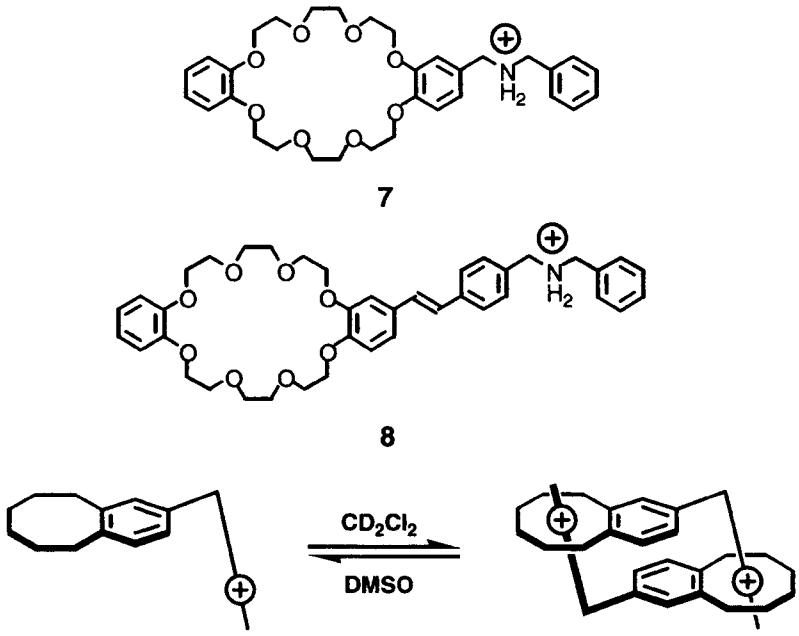
With the discovery that non-covalent forces can be utilized for the template-directed synthesis of mechanically interlocked molecules, this field entered a phase of quick growth. First, most groups concentrated on the design and realization of different topologies. For quite some time, the beauty of intertwined structures formed the focus and the motivation for many researchers. Many new template effects were discovered and designed that make use of different types of weak interactions between the components. Besides the Cu(I) template described above, template syntheses of rotaxanes, catenanes, and other interlinked molecules have been based on π-donor π-acceptor interactions,[13] hydrogen bonding,[14] hydrophobic effects,[15,16] and even chelation of a Grignard reagent by a crown ether.[17] Before we discuss in greater detail the rotaxane and catenane chemistry at Bonn, some of these template effects should be highlighted to give an impression of how multifaceted the structures of mechanically interlocked molecules have become meanwhile.



SCHEME 2: A CATENANE SYNTHESIS BASED ON π -DONOR/π-ACCEPTOR INTERACTIONS. INSTEAD, THE FORMATION OF A ROTAXANE IS POSSIBLE BY ATTACHING STOPPERS TO THE TWO FREE PYRIDINES IN THE DONOR/ACCEPTOR COMPLEX.

Stoddart and his group[13] utilized π-donor π-acceptor interactions between electron-poor paraquat (4,4'-bipyridinium) and electron-rich hydroquinone or naphtoquinone moieties (**3** and **4**) in order to preorganize a pseudorotaxane **5** which can then be converted to the catenane **6** (Scheme 2) by macrocyclization of the second wheel. Alternatively, functionalization of **5** with appropriate stopper groups yields a rotaxane. Besides π-donor/π-acceptor interactions, C-H•••O hydrogen bonds[18] between the CH_2 groups next to the charged nitrogen atoms and the crown ether oxygen atoms help to stabilize these complexes. Usually, such π-donor/π-acceptor complexes are nicely colored due to a charge transfer transition from the electron-rich to the electron-poor component. An almost infinite number of synthetic variations using this strategy is available: For example, a hydroquinone axle centerpiece can be threaded into a macrocycle bearing two paraquat moieties and addition of two stoppers yields rotaxanes with paraquat wheels. A paraquat centerpiece also binds inside a bis-hydroquinone wheel and thus leads to "inverse" rotaxanes bearing the paraquat unit in their axles. Instead of preforming the macrocycle and threading an axle through its cavity, a complete axle equipped with two stopper groups can be converted into a rotaxane by clipping an open analogue of the macrocycle around its centerpiece. The rotaxane is then formed by a macrocyclization step.[19]

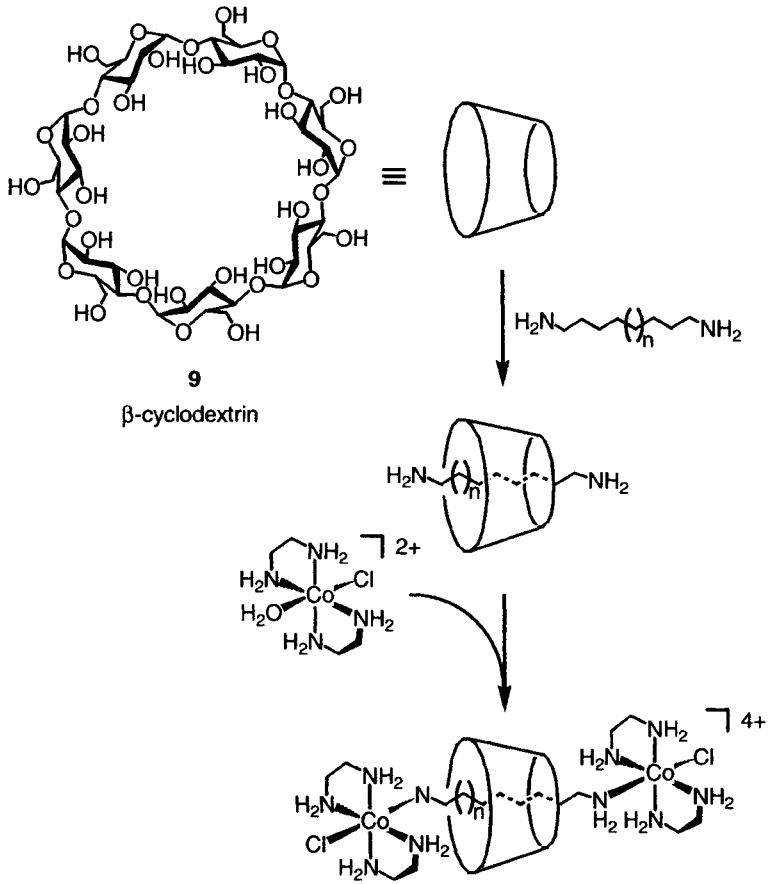
Of course, hydrogen bonding is an excellent candidate for non-covalent templating, in particular because hydrogen bonds are directional in nature and thus help to exactly position two building blocks for a rotaxane appropriately relative to each other. Secondary ammonium ions can be inserted into crown ethers by hydrogen bonds and stoppered to yield a rotaxane.[14] Two recent examples for "daisy-chain" pseudorotaxanes assembling through these interactions are depicted in Scheme 3.[20] Upon photoexcitation, dimers are formed from monomer **8** in a [2+2] cycloaddition which is controlled by supramolecular forces.



SCHEME 3: DAISY-CHAIN PSEUDOROTAXANES SELF-ASSEMBLING IN DICHLOROMETHANE THROUGH HYDROGEN BONDS BETWEEN AMMONIUM IONS AND CROWN ETHERS. THE STRUCTURES OF THE MONOMERS **7** AND **8** ARE SHOWN ABOVE A CARTOON ILLUSTRATING THE DIMERIZATION OF TWO MONOMERS.

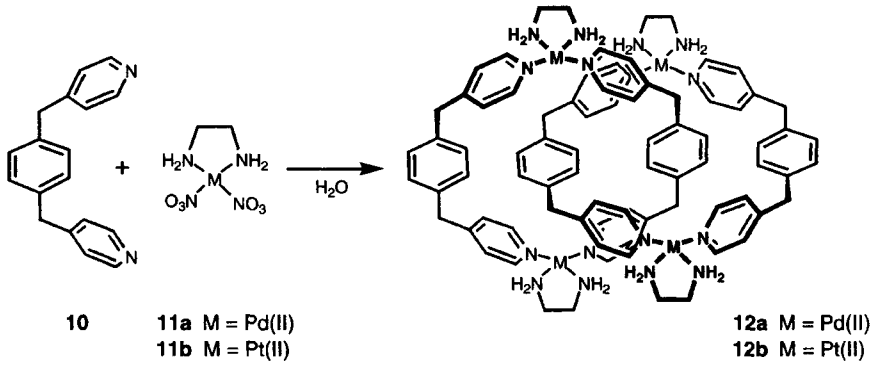
However, directionality of individual non-covalent interactions is not always needed and even non-directional forces such as the hydrophobic effect can be utilized for the preparation of interlocked structures. Cyclodextrins may serve as a first example. They are macrocycles built from α-glycosidic D-glucose subunits. While their hydrophilic, OH group-decorated surface makes them water soluble, they bear a lipophilic

cavity inside that is capable of binding non-polar guests in polar solvents such as water. The binding interaction is the so-called hydrophobic effect, which is predominantly based on favorable interactions between water molecules in the surrounding solvent rather than truly attractive forces between host and guest. Water-water interactions are very favorable if they remain undisturbed by unpolar surfaces and thus any unpolar system tends to minimize its surface in water[21]. This effect can be used to synthesize rotaxanes by threading an unpolar diamine axle centerpiece through the cavity of a cyclodextrin and then capping the ends of the axle with bulky stopper groups [22](Scheme 4).



SCHEME 4: A ROTAXANE SYNTHESIS BASED ON HYDROPHOBIC EFFECTS WHICH LEAD TO INCLUSION OF AN UNPOLAR AXLE CENTERPIECE INTO THE CAVITY OF β-CYCLODEXTRIN **9**. THE BIS-(ETHYLENE DIAMINE) CHLORO COBALT(II) STOPPERS ARE SUFFICIENTLY LARGE AND POLAR TO PREVENT DESLIPPING OF THE AXLE.

A completely different type of catenane is also formed through the action of hydrophobic forces by self-assembly of building blocks bearing metal ions (M = Pd, Pt) and ditopic pyridine ligands (Scheme 5).[16] When the two components are mixed in water, the catenane forms spontaneously, again minimizing the hydrophobic surfaces by inclusion of unpolar ligands of one macrocycle in the cavity of the other and *vice versa.* An interesting feature of these compounds is the reversibility of catenane formation, if the metal is palladium. Even at room temperature, the Pd complexes equilibrate, while the platinum complexes require higher temperatures or high salt concentrations in order to make the coordinative bonds sufficiently labile for an exchange of the ligands.

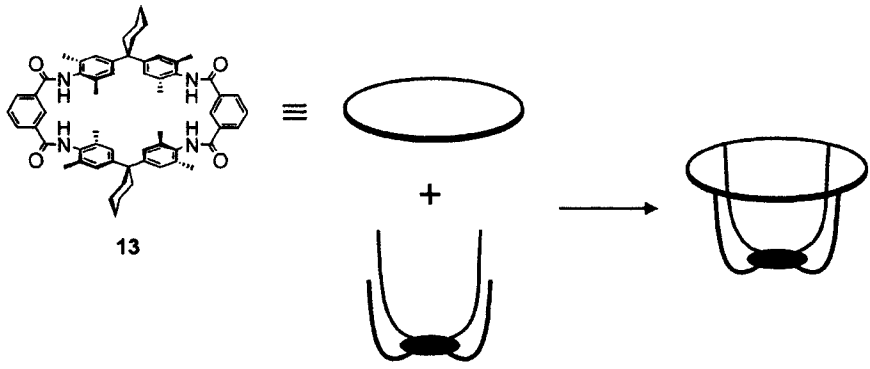


SCHEME 5: CATENANES **12a,b** SELF-ASSEMBLE IN WATER THROUGH HYDROPHOBIC INTERACTIONS FROM A DITOPIC LIGAND (**10**) AND PALLADIUM OR PLATINUM COMPLEXES **11a,b**. THE COORDINATION GEOMETRY AT THE METAL CENTERS AND THE RIGIDITY OF THE LIGANDS DETERMINE THE FINAL STRUCTURE.

This brief summary on template effects for the syntheses of interlocked molecules not only shows that a broad variety of different non-covalent interactions mediate the threading step in their preparations, it also intends to demonstrate how many different structural types of such molecules exist, each of which has its own properties and special characteristics. However, regardless of the different structures and varying features of these molecules, the common motif among all of them is the presence of a mechanical bond.

IV. A Surprising Formation of Catenanes through a Network of Hydrogen Bonds

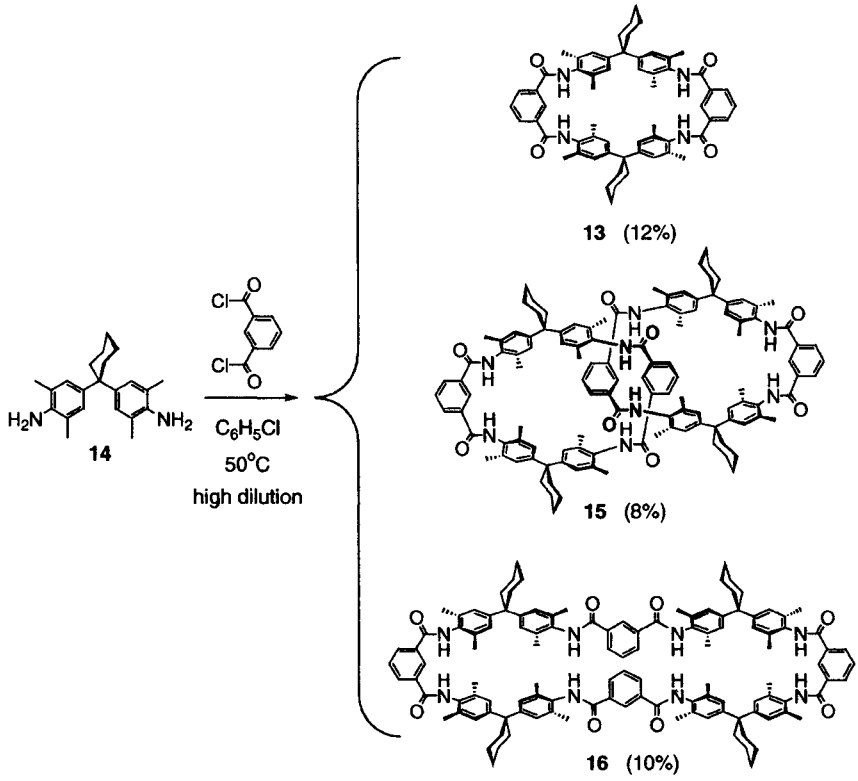
Often scientific progress emerges from the luck to find surprising and completely novel results. However, luck alone without the ability to recognize it will have no effect, while a researcher who is open-minded enough to follow a surprising finding to where it may finally lead, will sometimes open the window into a new, fascinating area of research. The present article will deal with such events more than once and the time has come to present the first one here.



SCHEME 6: SCHEMATIC REPRESENTATION OF THE SYNTHETIC APPROACH TO BASKET-SHAPED MOLECULES WITH AN INTERNAL CAVITY WHICH MIGHT BE USEFUL FOR MOLECULAR RECOGNITION OF GUEST MOLECULES.

In the 1980's, *Vögtle* and his co-workers studied cyclophanes, cryptophanes, and macrobicyclic cage compounds and aimed for the syntheses of basket-shaped molecular cavities.[23] A tetralactam macrocycle such as **13** was intended to form the starting point of the synthesis of such basket-shaped molecules (Scheme 6). The basic idea was that appropriate functionalization of the four amide bonds with a suitable tetrapodal reactant would provide facile access. In order to avoid the formation of oligomers or polymers, the synthesis of macrocycle **13** was performed under high dilution conditions. High dilution favors *intramolecular* over *intermolecular* reactions and thus should give a higher yield of macrocyclization products rather than polymerization. Surprisingly, the reaction in Scheme 7 afforded three defined products besides oligo- or polymeric material:[24] Two macrocycles of different sizes, one being the desired tetralactam ring **13**, the other one (**16**) being twice as large, and catenane **15** which was formed in this one step

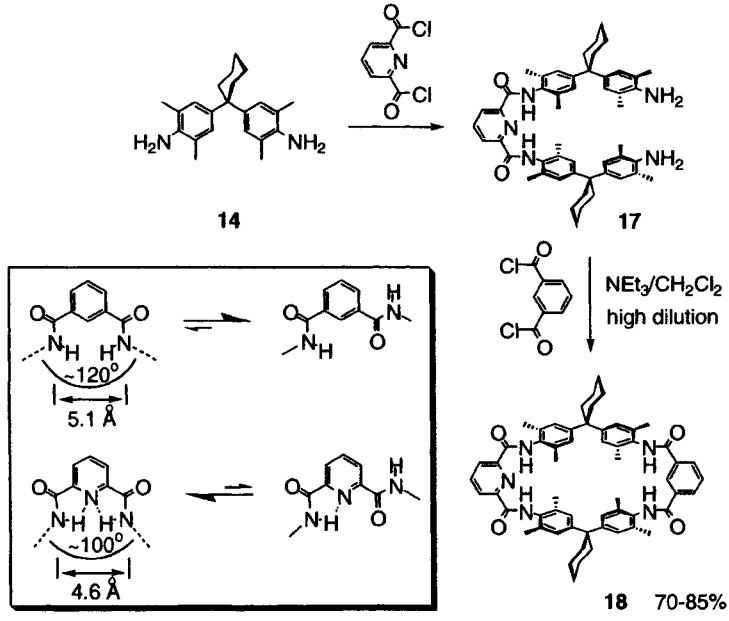
synthesis in 8% yield and has the same elemental composition and molecular weight as the octalactam macrocycle **16**. The same finding was made almost simultaneously by *Hunter* so that an independent confirmation for the surprising catenane formation was available.[25]



SCHEME 7: THE MACROCYCLIZATION OF PRECURSOR **14** WITH ISOPHTHALIC ACID DICHLORIDE UNDER HIGH DILUTION CONDITIONS YIELDS A TETRALACTAM MACROCYCLE **13**, THE CATENANE **15**, AND A LARGER OCTALACTAM MACROCYCLE **16**.

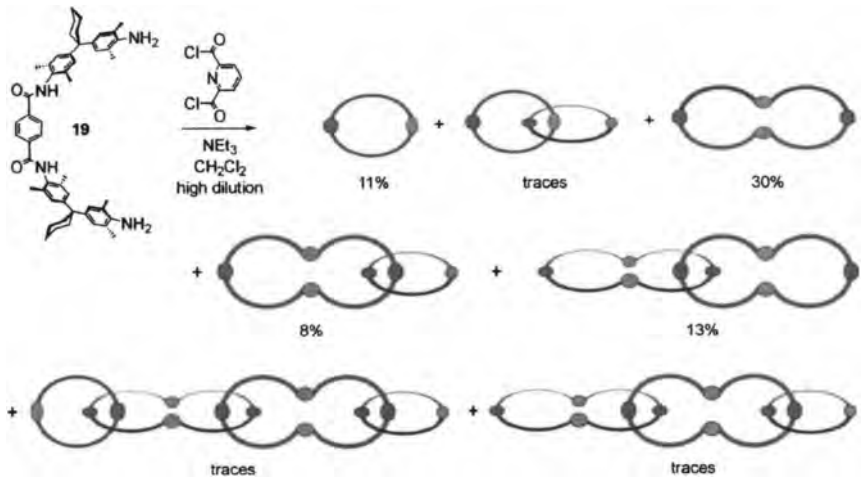
One question of course was, what the scope and limitations of the new catenane synthesis were and how the yields of the catenane could be increased. The first step towards greater variability of this synthesis was the stepwise sequence shown in Scheme 8. It permits the generation of macrocycles which are desymmetrized with respect to their two dicarboxylic amide building blocks. Many catenanes with such wheels can be synthesized by this strategy.[26] It turned out that the product

distribution and the yields of the macrocycles and catenanes are quite sensitive to structural variations. If one, for example uses 2,6-pyridine dicarboxylic acid dichloride instead of isophthalic acid dichloride in the same reaction, the yield of macrocycle **18** (Scheme 8) increases significantly, while the catenane could not be isolated.[27] This finding can be traced back to a typical feature[28] of the pyridine dicarboxylic amide building block **17**: The pyridine nitrogen atom is capable of forming rather strong intramolecular hydrogen bonds to the vicinal amide NH hydrogens. In intermediate **17**, these hydrogen bonds preorganize the precursor into a geometry favorable for macrocyclization. However, it also leads to a narrower cavity in macrocycle **18** which hampers threading of a second wheel to form a catenane. The strength of these hydrogen bonds is calculated at the AM1 level of theory to be on the order of almost 5 kcal/mol, which is in good agreement with recent experiments.[29] Another result of the calculations is that the distance between the two amide nitrogen atoms vicinal to the pyridine ring is shorter by almost 10% as compared to the isophthalic acid amide analogue.[29]



SCHEME 8: A STEPWISE ROUTE TO UNSYMMETRICAL MACROCYCLES. WITH 2,6-PYRIDINE DICARBOXYLIC ACID DICHLORIDE BUILDING BLOCK **17** IS FORMED WHICH IS PREORGANIZED FOR MACROCYCLIZATION AND THUS GIVES HIGHER YIELDS OF MACROCYCLE **18** AS COMPARED TO **13**. THE INSET SHOWS THE HYDROGEN BONDING PATTERN IN THE PYRIDINE BUILDING BLOCKS AND THE EFFECTS IT HAS ON CONFORMATIONAL EQUILIBRIA AND GEOMETRIC PARAMETERS.

Another very interesting example for the structure dependent shift in product distribution is the use of terephthalic instead of isophthalic acid subunits. The *para*-substitution shifts the product distribution towards octalactam macrocycles analogous to **16**. The curvature introduced by these building blocks is not sufficient for an efficient synthesis of small macrocycles. In combination with the pyridine dicarboxylic acid building block octalactam macrocycles are preferred. These larger wheels bear two binding sites for recognition of suitable guests[30] and thus it is no surprise that catenanes can be formed from them setting the stage for higher catenanes such as those shown in Scheme 9.[31] Again, the hydrogen bonding within the pyridine dicarboxylic amide plays a pivotal role since it preorganizes the binding sites with both NH groups pointing inwards.



SCHEME 9: THE USE OF TEREPHTHALIC ACID BUILDING BLOCK **19** LEADS TO PRONOUNCED FORMATION OF OCTALACTAM MACROCYCLES WHICH REPRESENT DITOPIC RECEPTORS AND THUS ARE CAPABLE OF DOUBLE INTERLOCKING AND OF FORMING HIGHER OLIGOCATENANES.

Exploring the structural variety of possible catenanes and macrocycles is one thing, understanding the template effect operative in catenane formation is more challenging because it requires the large arsenal of methods available to supramolecular chemistry. For a detailed picture, the binding of the components of the catenanes during macrocyclization needs to be uncovered and understood as completely as possible including in particular the weak intermolecular bonds, which are usually reversibly formed and more difficult to analyze due to quick dynamic processes.

For the amide catenanes, it seems reasonable to speculate that hydrogen bonding is most important. Molecular modeling suggests that three hydrogen bonds can be formed between a secondary amide of the guest (the open wheel of the catenane before cyclization) and three amides of the host (the already closed tetralactam macrocycle). According to this model, two of the NH hydrogen atoms of the same isophthalic acid amide form a bifurcated hydrogen bond to the carbonyl group of the guest, while the NH group of the guest donates its hydrogen atom towards a carbonyl group of the other isophthalic acid building block of the host. This picture is strongly supported by single crystal X-ray structures of catenanes,[32] where this pattern even appears twice (Figure 3), and by binding studies with various carbonyl compounds.[33] A comparison of secondary amide guests with those bearing ester, tertiary amide, or ketone functionalities reveals a remarkable difference in binding energies. While the latter group of carbonyl compounds binds with binding constants lower than 20 M^{-1}, the secondary amides have a more than tenfold higher binding constant (250 – 300 M^{-1}). This strongly points to the importance of the third hydrogen bond besides the bifurcated one for the template effect.

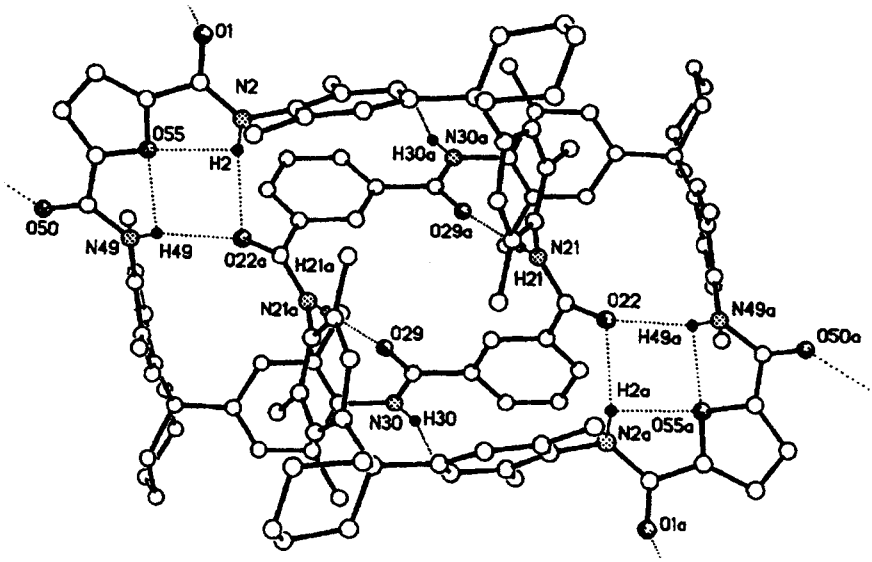
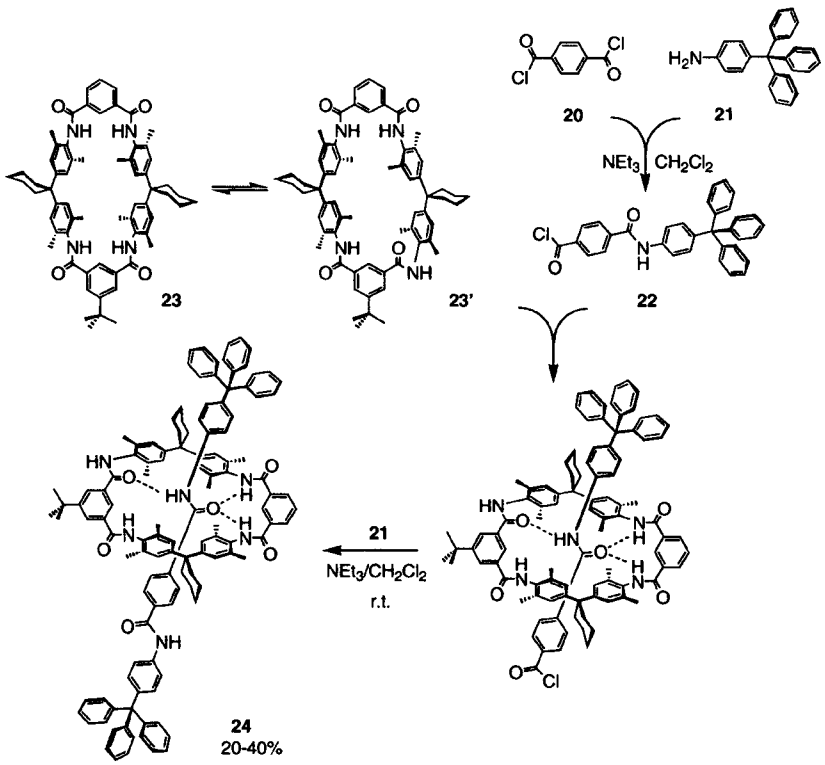


FIGURE 3: SINGLE CRYSTAL X-RAY STRUCTURE OF A CATENANE SHOWING THE HYDROGEN BONDING PATTERN WHICH IS POSTULATED TO MEDIATE THE TEMPLATE EFFECT BEFORE RING CLOSURE OF THE SECOND WHEEL. THE CATENANE SHOWN BEARS ONE FURANE DICARBOXYLIC ACID BUILDING BLOCK INSTEAD OF THE ISOPHTHALIC ACID ANALOGUE. SIMILAR TO PYRIDINE, THE FURANE FORMS INTRAMOLECULAR HYDROGEN BONDS WITH THE ADJACENT AMIDE NH PROTONS.

V. Extending the Amide-Based Template Synthesis to Rotaxanes

Once the amide template was understood, it was possible to transfer it to the synthesis of other interlocked molecules. The strategic idea behind this is that cutting open one of the rings of a catenane and addition of a bulky stopper to the ends of the resulting string would again provide access to a stable, mechanically interlocked species. Consequently, the formation of rotaxanes was attempted with success (Scheme 10). The centerpiece of the axle usually is a carboxylic acid dichloride such as terephthalic acid dichloride **20** and the stopper, e.g. tritylaniline **21**, bears an amino group. In the first step, one stopper reacts with the centerpiece to yield semi-axle **22**. While the binding energy of acid chlorides to the wheel is low, the secondary amide bond of the semi-axle is capable of mediating the threading of the axle into the wheel. Again, the formation of three hydrogen bonds can be assumed, which is in line with AM1 calculations (Figure 4) and X-ray crystal structures of rotaxanes.[3]



SCHEME 10: SYNTHESIS OF AMIDE ROTAXANES BY A TEMPLATE EFFECT BASED ON THE FORMATION OF HYDROGEN BONDS BETWEEN SEMI-AXLE AND WHEEL.

One point should be mentioned: Tetralactam macrocycles such as **13** or **23** appear to be rather rigid structures due to the aromatic rings and the amide groups connecting them. Nevertheless, there is sufficient conformational flexibility to allow the macrocycle to exist in various conformations with respect to the in/out-positions of the amide groups. The NH protons may be directed into the macrocycle cavity (as in **23**) or they can be located in an outward direction (as in **23'**). According to molecular modeling and AM1 calculations,[34] these conformations all exist within an energy range of ca. 1 kcal/mol so that one can assume that they are equilibrating with each other.

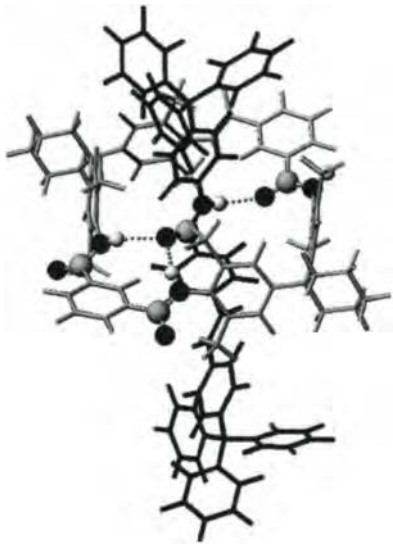
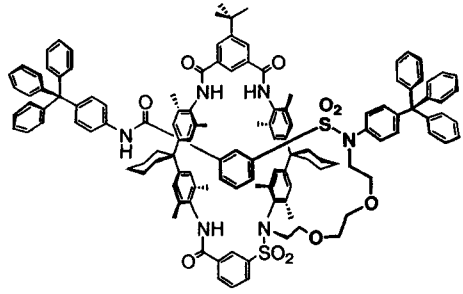


FIGURE 4: AM1-OPTIMIZED STRUCTURE OF AN AMIDE ROTAXANE SHOWING THE HYDROGEN BONDING PATTERN WHICH IS THOUGHT TO MEDIATE THE TEMPLATE EFFECT THREADING THE AXLE INTO THE MACROCYCLE. THE WHEEL IS SHOWN IN GREY, THE AXLE IN BLACK. THE AMIDE GROUPS INVOLVED IN THE HYDROGEN BONDING PATTERN ARE DEPICTED AS BALL-AND-STICK MODEL.

A large number of structurally different rotaxanes have been prepared, including several examples where one of the amide groups is replaced by a sulfonamide group in both the wheel and the axle. Since a sulfonamide is more acidic than a carboxamide, it can easily be deprotonated and alkylated with primary alkyl or benzylic bromides. This reaction can be used to connect axle and wheel by a flexible bridge providing access to new classes of mechanically interlocked species such as the [1]rotaxane shown in Scheme 11 or a figure-8-shaped molecule[4] which is shown in a cartoon representation in Figure 1.



SCHEME 11: A [1]ROTAXANE WITH A FLEXIBLE TETHER BETWEEN THE TWO SULFONAMIDE GROUPS INCORPORATED IN THE WHEEL AND THE AXLE.

VI. Molecular Topology and Topological Chirality

Topology is a mathematical discipline dealing with certain well-defined geometrical transformations. While Euclidean geometry (the "everyday geometry" we all normally use) answers questions such as "How large is an object?", or "What is its three-dimensional shape?" the actual size or the details of the shape of an object do not matter in topology. All transformations which can be performed continuously *and* which can be reversed continuously are topologically allowed. This leads to the conclusion that the two representations of a cup shown in Figure 5 are topologically equivalent. Just imagine that we use a piece of clay with the shape of the disk on the right. We could easily make a cup out of it as depicted on the left just by stretching and condensing the appropriate parts of the disk without removing or adding a piece or breaking the disk anywhere. In contrast to Euclidean geometry, typical questions in topology are of a qualitative nature: "Does the object contain a hole?" or "Can one take apart the object or are all parts connected to each other?"

FIGURE 5: TWO TOPOLOGICALLY EQUIVALENT REPRESENTATIONS OF A CUP. NOTE THAT CLOSING THE HOLE IS NOT A TOPOLOGICALLY ALLOWED TRANSFORMATION, BECAUSE OPENING A HOLE IN THE RESULTING DISC REQUIRES A NON-CONTINUOUS TRANSFORMATION (REPRODUCED FROM REF. 35 WITH KIND PERMISSION BY WILEY-VCH, WEINHEIM).

These considerations can be applied to molecules. First we have to define a molecular graph – which can most easily be done by following the molecular backbone of each of the interlocked components. A catenane can be represented as two intertwined rings, a rotaxane as a straight line penetrating a wheel, and finally a knot as three entangled loops which all belong to the same ring – just like the schematic drawings in Figure 6. Topologically speaking, a catenane is not equivalent to two separated rings. Similarly, a knot is topologically not the same as a non-intertwined ring, because in both cases, no continuous transition between the two topological isomers is possible. The molecular graph needs to be cut in order to transfer one of the isomers into the other one. This situation is different for rotaxanes. In reality, the stopper groups are large enough to prevent deslipping of the axle, but in terms of topology the size of the stoppers is irrelevant. Consequently, the stoppers can be condensed to a point with no spatial extension resulting in the pseudorotaxane-like structure in the center of Figure 6. We can even go further and take apart the axle and wheel and separate them without breaking the rules of topology.

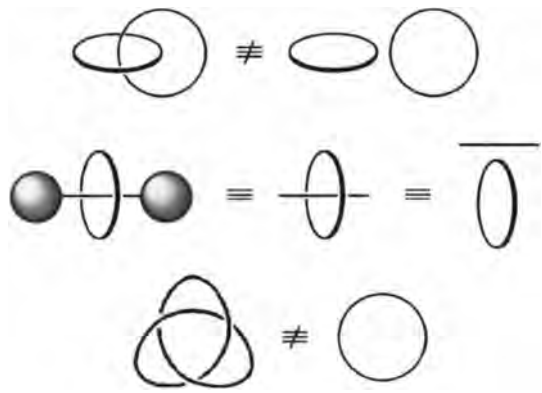


FIGURE 6: TOPOLOGICALLY EQUIVALENT AND NON-EQUIVALENT TRANSFORMATIONS OF A CATENANE (TOP), A ROTAXANE (MIDDLE), AND A KNOT (BOTTOM).

Why do we discuss the issue of topology here in such detail? It is important to understand the topological properties of intertwined structures, because this allows us to easily understand a highly interesting chemical feature: topological chirality.[36] Without any chiral center involved, these species can be made chiral. Just imagine that we introduce

a directionality in each of the subunits of the catenane and rotaxane in Figure 7, for example by using a certain atom sequence which is not symmetrical. Then, each subunit is achiral, but the combination of two rings or a ring with an appropriate axle makes the catenane or rotaxane different from its mirror image thus generating two enantiomers. The reader is invited to test his or her imagination and to try to exactly match the architectures shown on the left in Figure 7 with those on the right just by rotating them. While this is easily possible with the catenane and rotaxane in Figure 6, it is impossible with the species depicted in Figure 7. The knot is even inherently chiral without any modification concerning directionality.[37]

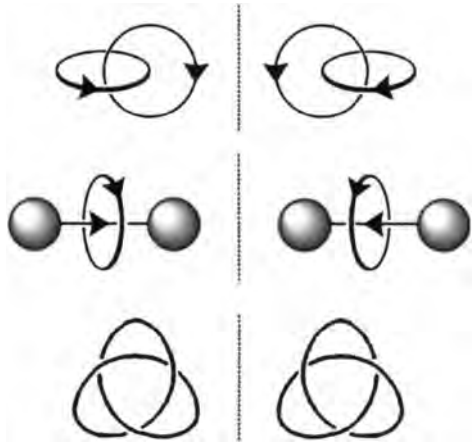


FIGURE 7: TOPOLOGICALLY CHIRAL CATENANE (TOP), ROTAXANE (MIDDLE), AND KNOT (BOTTOM). THE ARROWS INDICATE AN ATOM SEQUENCE INTRODUCING A DIRECTIONALITY INTO THE COMPONENTS OF THE CATENANE AND ROTAXANE. THE KNOT IS INHERENTLY CHIRAL AND DOES NOT NEED ANY SUCH ELEMENT OF DIRECTIONALITY.

Topological chirality thus is a very special form of chirality and one might well ask what consequences it has for the separability of the enantiomers and their chiroptical properties. In the beginning, there was not too much hope that a separation of the enantiomers of large and flexible molecules like rotaxanes or catenanes would be feasible, if they didn't contain chiral centers and thus differed only by marginal structural differences. However, HPLC on a chiral stationary phase indeed allowed the separation of the enantiomers surprisingly well. One example is shown in Figure 8.[3,38] The rotaxanes shown bear a sulfonamide group in

the wheel and another one in the axle. Both sulfonamides provide the directionality required for topological chirality. If one for example defines a path from the SO_2 group to the NH (the other way is of course possible, but it is important not to mix these definitions), one can draw arrows such as those shown in Figure 7. The two enantiomers of this rotaxane can be separated after derivatization with a bridge connecting the two sulfonamides. CD spectroscopy of the two enantiomers yields two CD spectra that are more or less mirror images of each other and thus provides evidence for non-racemic material with opposing optical rotational dispersions.

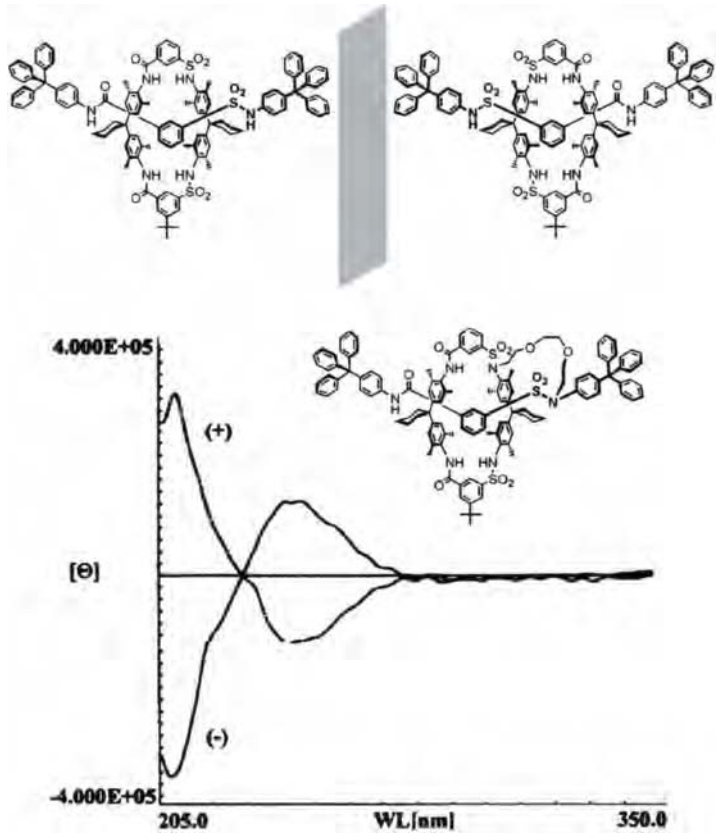
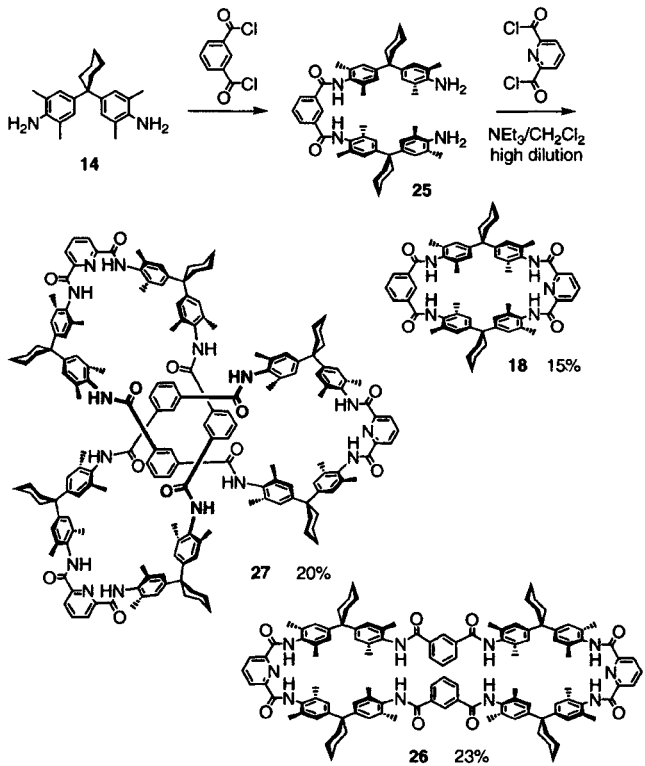


FIGURE 8: TOP: TOPOLOGICALLY CHIRAL ROTAXANE AND ITS MIRROR IMAGE. NOTE THAT ONLY THE SULFONAMIDES INCORPORATED IN WHEEL AND AXLE PROVIDE THE DIRECTIONALITY REQUIRED TO GENERATE TOPOLOGICAL CHIRALITY. BOTTOM: IN FORM OF ITS DERIVATIVE WHICH BEARS A BRIDGE BETWEEN THE TWO SULFONAMIDES THE ENANTIOMERS CAN BE SEPARATED AND CD SPECTRA OBTAINED FROM EACH OF THEM.

VII. A Trefoil Knot

It is a formidable challenge to design a template effect for the synthesis of a trefoil knot (Figure 1, bottom).[39] Exactly three crossing points need to be fixed during the synthesis by non-covalent bonds in order to generate a knot rather than a large non-intertwined macrocycle which would result from a precursor with only one crossing. Two crossings would give rise to a catenane after ring closure of the macrocycles. Similar, more than three crossings would lead to different interlocked species. In view of these difficulties, it was a great surprise that a knot was formed as a byproduct, when the reaction sequence shown in Scheme 8 was reversed (Scheme 12).[27] In this reaction three distinct reaction products were isolated: the expected tetralactam macrocycle **18**, its larger brother **26**, and the knot **27**.



SCHEME 12: A TREFOIL KNOT **27** FORMS AS A BYPRODUCT TOGETHER WITH THE EXPECTED MACROCYCLE **18** AND ITS LARGER OCTALACTAM ANALOGUE **26**, WHEN THE REACTION SEQUENCE SHOWN IN SCHEME 8 IS REVERSED AND EXTENDED DIAMINE **25** IS REACTED WITH 2,6-PYRIDINE DICARBOXYLIC ACID DICHLORIDE.

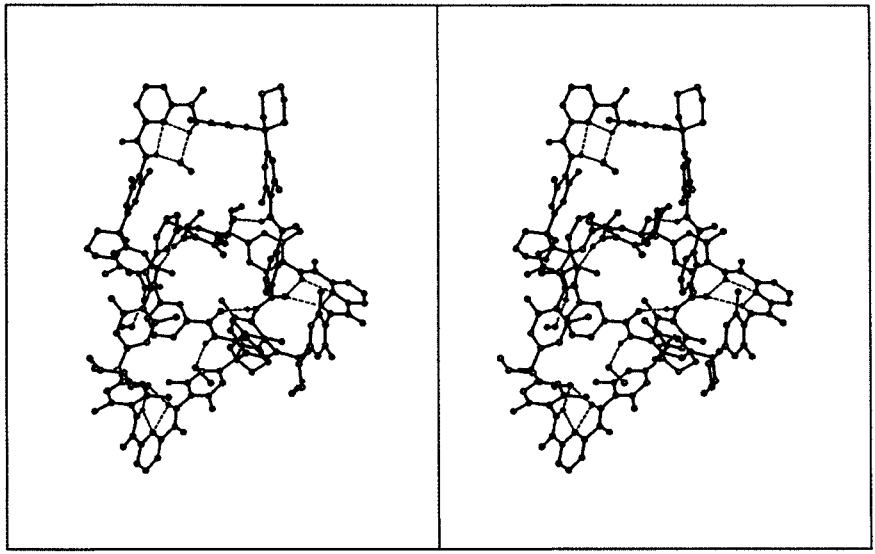


FIGURE 9: SINGLE CRYSTAL X-RAY STRUCTURE OF THE TREFOIL AMIDE KNOT AS A STEREOIMAGE FOR 3D-VIEWING.

The characterization of the knotted structure is a non-trivial problem. The ^{1}H and ^{13}C NMR spectra are too complex to permit a conclusive interpretation. Finally, after the single crystal X-ray structure showed that the molecule was indeed a knot, it became clear that the complexity of the NMR spectra is due to a slow dynamic process.[40] Two of the loops are different from the third one due to internal hydrogen bonding. The interconversion of the two types of loops is slow on the NMR timescale and thus leads to a more complex signal pattern than expected. Initially however, it was not clear whether molecule **27** had the knot structure shown, or whether it was one of two other isomers with the same number of subunits and the same elemental composition. A catenane built from one tetra- and one octalactam wheel or a non-intertwined macrocycle bearing six diamines **14**, three isophthalic acid, and three pyridine dicarboxylic acid subunits would also account for the molecular mass obtained from a MALDI-TOF mass spectrum. In order to solve the problem of characterization, three methods were applied to distinguish and unambiguously identify the knot among other structures. The first one is X-ray crystallography, for which suitable crystals could be obtained and the structure of the knot in the solid state is shown in Figure 9. The second method relies on the fact that the knot is inherently chiral due to

its topology, while the corresponding catenane and simple macrocycles are not when generated from the same building blocks. Of course, the knot is formed as a racemate. Consequently, the separation of the enantiomers is a prerequisite for obtaining CD spectra which then provide evidence for the knotted structure. These experiments were carried out[41] and the UV and CD chromatograms of a representative HPLC run are depicted in Figure 10 and show that a baseline separation of both knot enantiomers is possible. The two enantiomers give rise to signals in the CD spectra with opposite signs. Even the determination of the absolute configuration was possible by comparison of the experimental CD spectra with those obtained from a theoretical calculation.

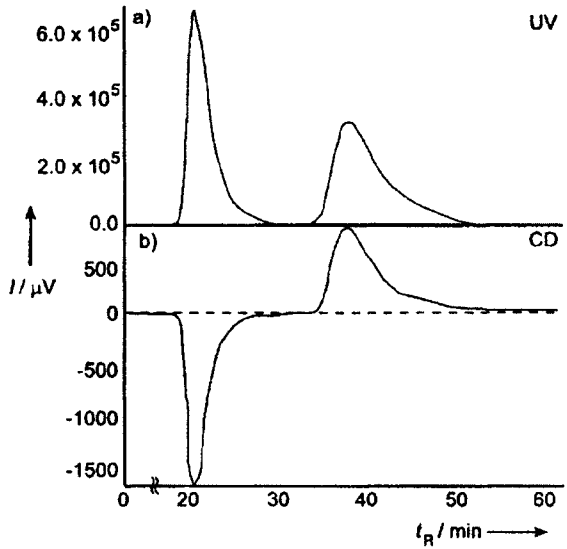
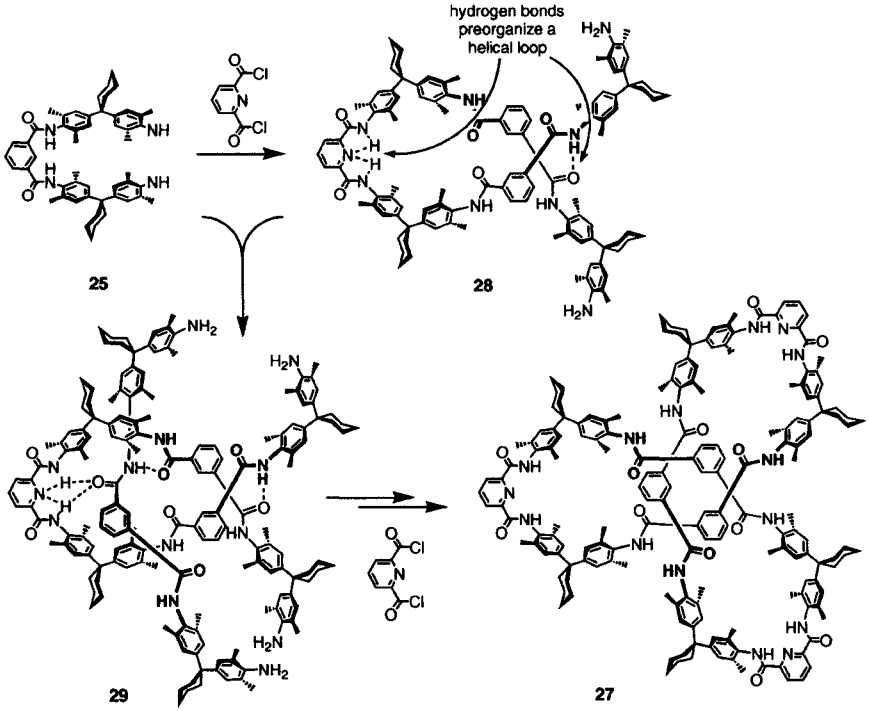


FIGURE 10: UV CHROMATOGRAM (TOP TRACE) AND CD CHROMATOGRAM (BOTTOM TRACE) OF THE TRFOIL AMIDE KNOT. SINCE THE KNOT IS THE ONLY CHIRAL PRODUCT, THE CD TRACE, WHICH SHOWS TWO BANDS OF EQUAL INTEGRATIONS WITH OPPOSITE SIGNS OF THE CD SIGNAL, PROVIDES EVIDENCE FOR THE FORMATION AND SUCCESSFUL SEPARATION OF BOTH ENANTIOMERS BY CHIRAL HPLC.

The third method which provides evidence for a knotted structure is mass spectrometry.[42] With electrospray ionization (ESI) it is possible to ionize the knot and other similar molecules by protonation and to transfer them into the highly diluted gas phase of a mass spectrometer. In a so-called tandem-MS experiment, the parent ion, i.e. the protonated knot, is isolated and subjected to collisions with a stationary gas inside the

collision cell of the mass spectrometer. The collisions induce fragmentation reactions which are often indicative of an ion's structure. Typically, mono-macrocyclic compounds fragment by water losses originating from the protonated amide bond. A catenane, however, undergoes cleavage of one of the wheels followed by deslipping of the other. Consequently, the water loss is only marginal, while the major fragment corresponds to one of the two macrocycles. If the knot is subjected to this experiment, an intense water loss is observed ruling out any catenated structures. The differentiation of a knotted from a non-knotted macrocycle is more challenging and requires more sophisticated ion mobility experiments which measure the collisional cross section, that means the ion size. Since the knotted structure is more compact as compared to a non-intertwined macrocycle, this experiment suggests the smaller size of the knot.



SCHEME 13: TENTATIVE TEMPLATE MECHANISM LEADING TO THE FORMATION OF A TREFOIL KNOT. AFTER COUPLING TWO EXTENDED DIAMINES **25** WITH A PYRIDINE DICARBOXYLIC ACID DICHLORIDE BUILDING BLOCK, A HELICAL LOOP IS FORMED WHICH IS STABILIZED BY INTRAMOLECULAR HYDROGEN BONDING AND MAY SERVE AS THE HOST FOR THE THIRD SUBUNIT **25**. BINDING OF **25** IN **28** IS AGAIN MEDIATED BY HYDROGEN BONDING IN A SIMILAR FASHION AS COMPARED TO THE ROTAXANE AND CATENANE SYNTHESES OUTLINED ABOVE. TWO SUBSEQUENT REACTIONS WITH PYRIDINE DICARBOXYLIC ACID DICHLORIDES FINALIZE THE KNOT SYNTHESIS.

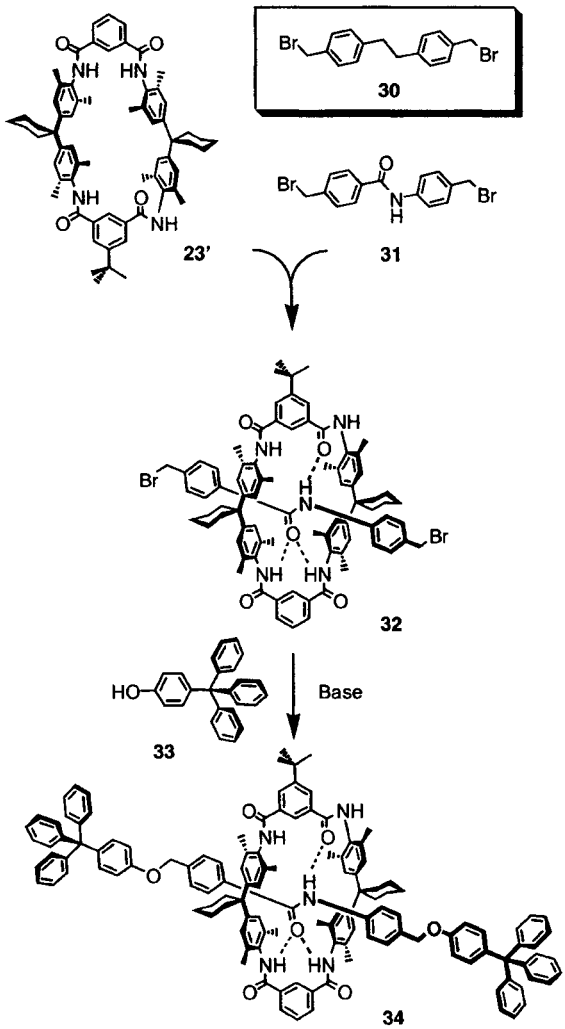
Experiments[27] and calculations[34] point to the template mechanism for knot formation as depicted in Scheme 13. One of the loops of the knot is generated by reaction of extended diamine **25** with 2,6-pyridine dicarboxylic acid dichloride. The pyridine nitrogen preorganizes both arms by intramolecular hydrogen bonding and an additional hydrogen bond holding the two branches together remote from the pyridine. Consequently, a helical loop is formed which resembles very much the small macrocycle **18** with respect to the positions of the amide bonds. A third extended diamine **25** can then be threaded into loop **28** and may form a similar set of three hydrogen bonds as described above for the syntheses of catenanes and rotaxanes. In complex **29**, the curvature of the diamine subunits brings the correct ends in close proximity which then just need to be connected in order to obtain the knotted structure.

This mechanism is in line with the experimental finding that a *t*-butyl substituted isophthalic acid unit does not yield detectable amounts of the knot, while the pyridine dicarboxylic acid building block can easily be substituted without drastic effects on the knot yield. This strongly points to intermediates in knot formation, in which the isophthalic acid units are buried inside a structure which does not permit large steric changes, while the pyridines are located at the periphery of that complex. The loop-diamine complex **29** well accounts for that. Further support for the proposed mechanism comes from the fact that the reversed reaction sequence shown in Scheme 8 does not give rise to detectable amounts of the knot, although basically the same building blocks are used. In this sequence, however, a loop analogous to **28** cannot be preorganized well, because the central pyridine in **28** is replaced by an isophthalic acid which is not capable of forming the intramolecular hydrogen bonds. Thus, the wrong curvature is realized and a hydrogen bonding pattern as in **29** is not favorable so that no knot is formed. This result points to the importance of the intramolecular hydrogen bonding within the pyridine dicarboxamide unit.

VIII. The Next Surprise: Rotaxane Synthesis Mediated by a Template Based on Hydrogen-Bonded Anions

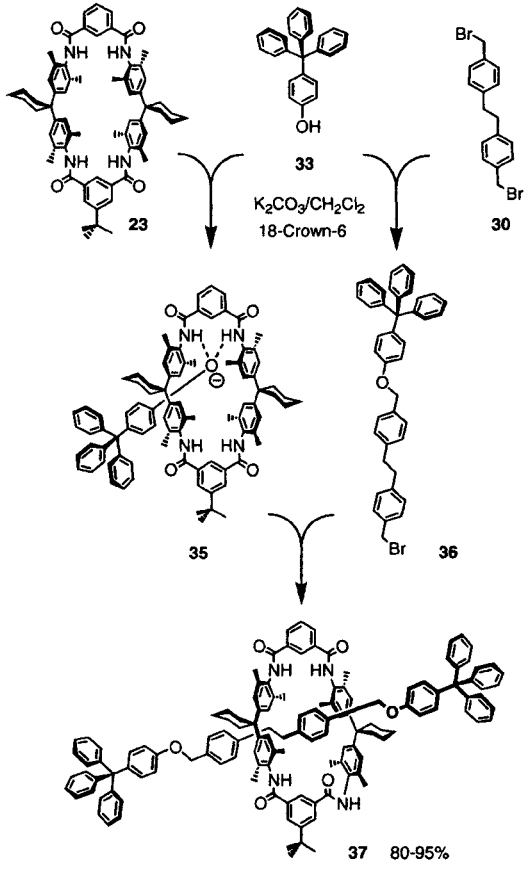
Another approach to test a template mechanism is to use appropriate control compounds that can be expected to fail to yield the rotaxanes or catenanes, if the tentative mechanism is indeed operative. In order to gain further support for the template mechanism of amide rotaxane formation (Scheme 10), it is desirable to have additional evidence for the

importance of the binding of an axle amide group inside the wheel cavity. For this purpose, axle centerpieces that were used as control compounds do not bear the acid chloride group in the presence of an amide or that bear no carbonyl group at all. The stopper attachment was intended to proceed by a nucleophilic substitution of benzylic bromides by phenolate stoppers (Scheme 14).



SCHEME 14: AXLE CENTERPIECES **30** AND **31** THAT WERE USED AS CONTROL COMPOUNDS FOR A MORE DETAILED INVESTIGATION OF THE MECHANISM OF AMIDE ROTAXANE FORMATION.

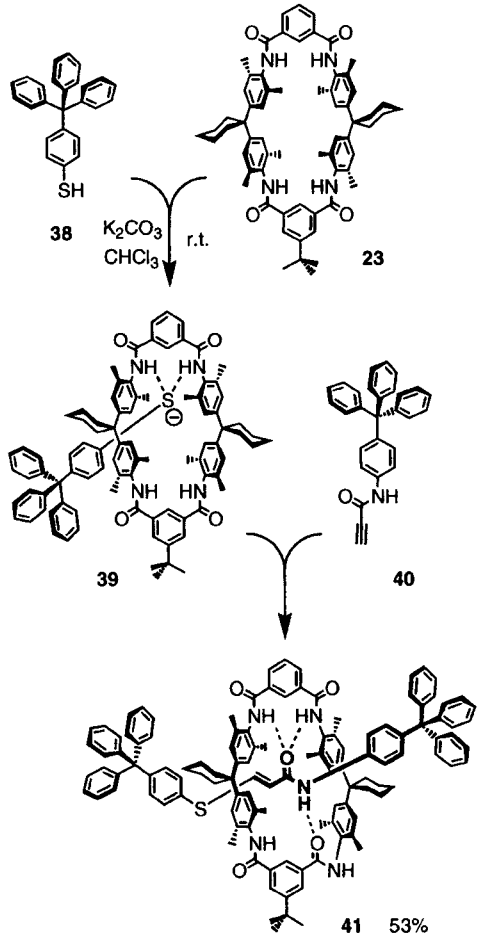
If hydrogen bonding to the amide group in the axle centerpiece is indeed important for rotaxane formation, one would expect that centerpiece **30** would not give rise to any rotaxane, while **31** should give rotaxane **34** through intermediate **32** with similar yields as found for other amide rotaxanes. However, the result was completely unexpected and very surprising: Centerpiece **30**, although not appropriately functionalized, was almost completely consumed in rotaxane **37** (Scheme 15), which was formed with 80% to 95% yield.[43]



SCHEME 15: A NEW ANION TEMPLATE EFFECT FOR THE SYNTHESES OF ETHER ROTAXANES.

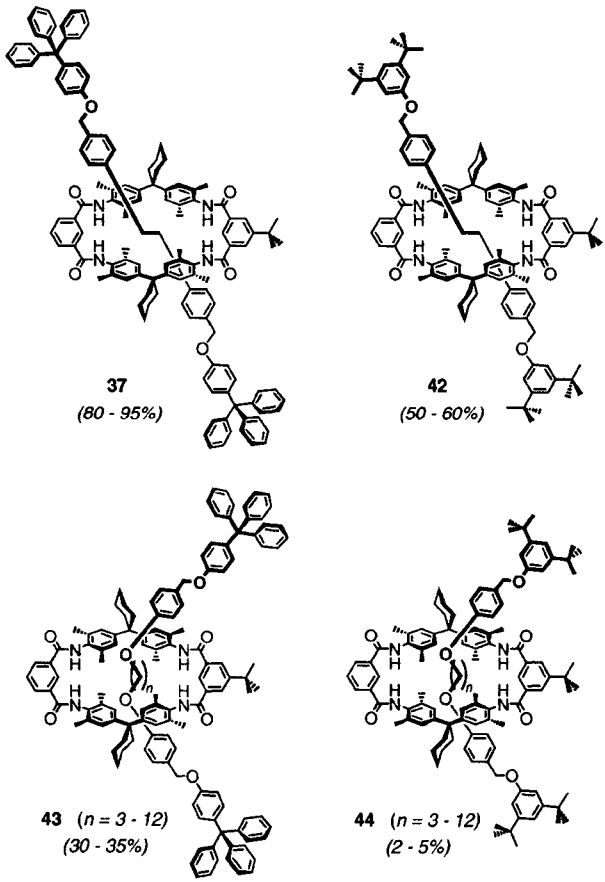
Since axle centerpiece **30** does not contain any functional group which is capable of forming strong interactions with the wheel, it seems

convincing to assume that a new template effect is operative in the synthesis of rotaxane **37**. Indeed, ^{1}H NMR titrations of the wheel with the deprotonated stopper phenolate convincingly shows the phenolate to be strongly hydrogen bonded to two of the amide hydrogens. The binding constant in dichloromethane, a non-competitive solvent, is much larger than 10^5 M^{-1} indicating that the equilibrium is almost completely on the side of the stopper/wheel complex. Thus, it was postulated that the stopper wheel complex **35** reacts as a supramolecular nucleophile with semi-axle **36** which is formed *in situ*.[44] After attachment of the second stopper, the wheel is trapped on the axle yielding a stable rotaxane.



SCHEME 16: ANION-TEMPLATED ROTAXANE SYNTHESIS VIA A MICHAEL ADDITION REACTION.

With this anion template effect,[45] several different types of rotaxanes besides those with ether groups connecting the stoppers and the axle centerpiece have been synthesized, among them analogues containing acetal and ester groups instead of the ethers.[46] Even Michael addition reactions (Scheme 16) with a stopper/wheel complex have been successfully used to connect the axle centerpiece to it and trap the wheel on the axle.[47] The best results were obtained, when the greater nucleophilicity of a thiophenolate stopper **38** was utilized together with the acetylene carboxamide **40** as the Michael receptor. The reaction is again assumed to proceed *via* the stopper/wheel complex **39** and yields rotaxane **41** with 53% yield.



SCHEME 17: THE YIELDS OF ROTAXANES SYNTHESIZED *VIA* THE ANION TEMPLATE STRATEGY DEPEND MUCH ON THE PARTICULAR STRUCTURE OF THE STOPPERS AND AXLE CENTERPIECES.

IX. Problems and Solutions: A Synthetic Approach to Rotaxanes with Functional Groups in the Axle Centerpiece

The first problems with the new anion-templated rotaxane synthesis were encountered when the preparation of rotaxanes with smaller 3,5-di-*t*-butyl phenol stoppers was attempted (Scheme 17). These rotaxanes were intended for the investigation of their deslipping behavior[29,48] which should provide insight into the size complementarity of the stopper and the wheel cavity. For this purpose, smaller stoppers are needed and a yield of 2% to 5%, which was obtained for **44** independent of the length of the axle centerpiece, was thus quite disappointing.

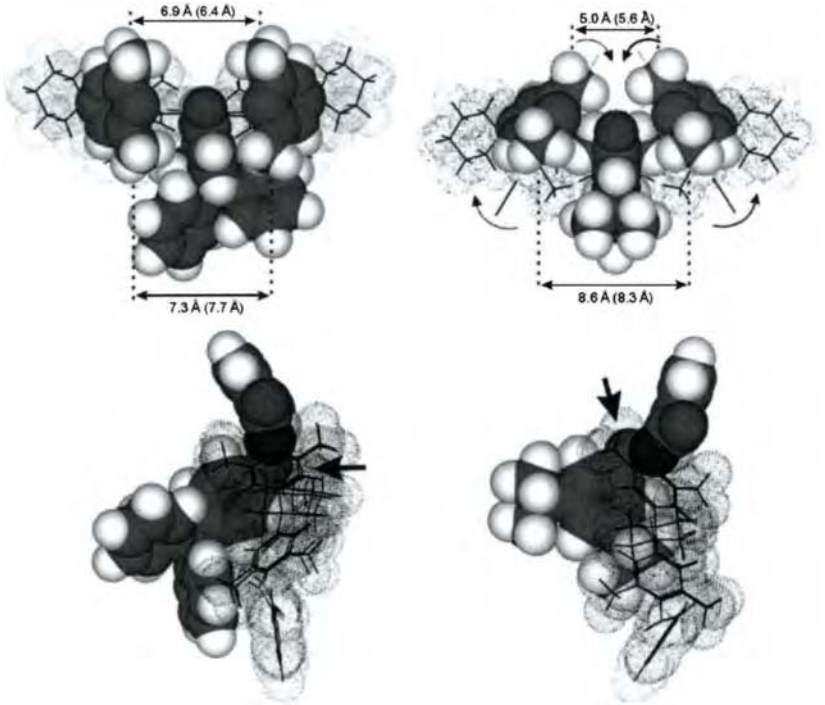
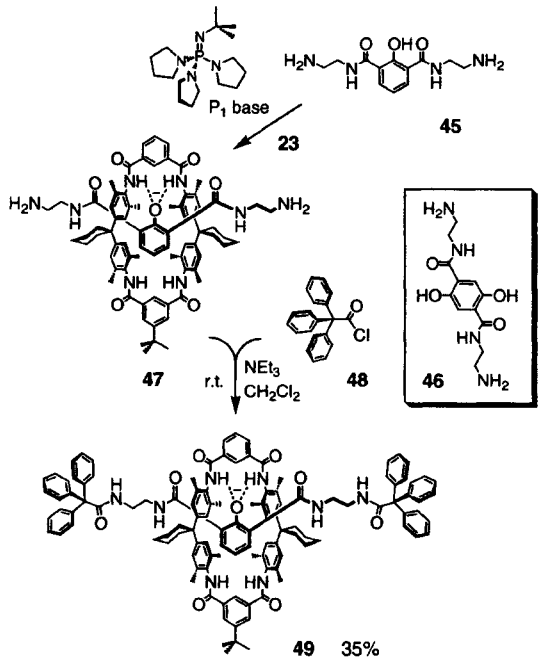


FIGURE 11: MINIMAL ENERGY CONFORMATIONS OF STOPPER WHEEL COMPLEXES WITH TRITYLPHENOLATE (LEFT) AND 3,5-DI-*T*-BUTYLPHENOLATE (RIGHT) AS OBTAINED FROM A 3000 STEP MONTE CARLO CONFORMATIONAL SEARCH WITH THE AMBER* FORCE FIELD. TOP ROW: VIEW INTO THE WHEEL CAVITY WHICH SHOWS THE OPEN ATTACK PATH FOR THE SEMI-AXLE ELECTROPHILE ON THE LEFT AND THE CLOSED PATH ON THE RIGHT. DISTANCES BETWEEN EACH PAIR OF TWO OPPOSITE METHYL GROUPS OF THE WHEEL ARE GIVEN (AVERAGE FOR A FAMILY OF FAVORABLE CONFORMATIONS IN PARENTHESIS). BOTTOM ROW: THE DIFFERENT CONFORMATIONS OF THE STOPPER WHEEL COMPLEXES PRESENT THE REACTIVE PHENOLATE OXYGEN TOWARDS THE SIDE INDICATED BY THE LARGE ARROWS. IN THE CASE OF THE 3,5-DI-*T*-BUTYL PHENOLATE, THE ELECTROPHILE APPROACHES FROM THE WRONG SIDE PREVENTING ROTAXANE FORMATION.

An analysis of the different stopper/wheel complexes by molecular modeling provided insight into the reasons why the yield decreases so much depending on the details of the stopper structure (Figure 11). A 3000 step conformational search using the Monte Carlo algorithm yields different families of favorable conformations for the two complexes.[49] With the trityl phenolate stopper, the complex is open for the attack of the electrophile from the side of the wheel opposite to the stopper. The reactive free electron pair of the phenolate (which is not involved in hydrogen bonding) is presented to that side so that a reaction with the incoming electrophile will yield the rotaxane. In contrast, the smaller 3,5-di-*t*-butyl phenolate stopper inserts itself deeper into the cavity of the wheel which leads to a conformation closed for attack from the opposite side. Instead, the electrophile can more favorably attack from the same side so that initially a weakly hydrogen bonded wheel/axle complex is formed. Since the axle and wheel are not bound to each other by a mechanical bond, the complex easily dissociates into free axle and free wheel and the rotaxane yields are drastically reduced.



SCHEME 18: A NOVEL TEMPLATE EFFECT FOR THE SYNTHESES OF ROTAXANES WITH FUNCTIONALIZED CENTERPIECES. THE STOPPERS ARE ATTACHED AT A POSITION REMOTE FROM THE WHEEL CAVITY SO THAT STERIC PROBLEMS CAN BE AVOIDED.

A potential solution to this problem is to separate the functional groups used for stopper attachment from that mediating the template effect. This approach is realized in a rotaxane synthesis[50] which is based on axle centerpieces **45** or **46** (Scheme 18). They bear phenolic OH groups which after deprotonation form hydrogen bonds with two of the amide protons of tetralactam macrocycle **23**. The triphenyl acetic acid stoppers **48** can now be attached to the amino groups at the ends of the ethylene diamine spacers which are positioned remote from the wheel in wheel/centerpiece complex **47**. Consequently, steric problems can be avoided during the preparation of the rotaxane. Two points deserve to be mentioned here: For the deprotonation of the centerpieces the P1 phosphazene base was used. This base is very strong with a pK_a value around 40.[51] However, its basicity is not the major issue here. More important is that it solubilizes the axle centerpiece anions even in solvents such as dichloromethane and thus permits a straightforward reaction yielding the rotaxane. This is particularly interesting when taking into account that the protonated centerpieces **45** and even more so **46** are not soluble, while their P1-salts are. The second point is that the wheel acts as an efficient protecting group for the phenolate. The hydrogen bonds connecting axle and wheel are strong for the deprotonated phenolate and the wheel is positioned so that these hydrogen bonds can effectively be formed. All attempts to methylate the phenolate oxygen with as small reagents as methyl iodide failed. This reaction is easy to perform for a phenolate outside the wheel. Besides the mass spectral and NMR spectrometric characterization, it is particularly this finding which provides evidence for the interlocked structure.

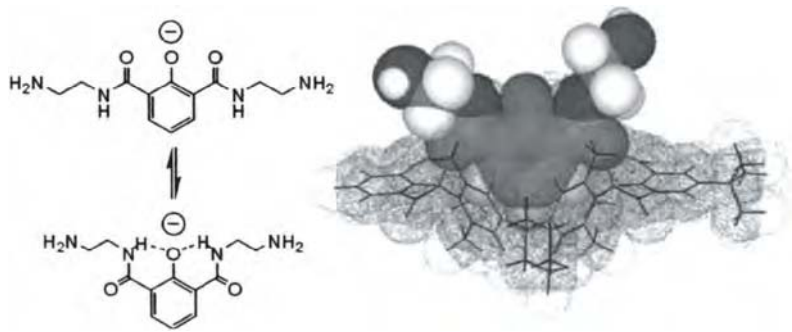


FIGURE 12: LEFT: INTRAMOLECULAR HYDROGEN BONDING WITHIN THE DEPROTONATED AXLE CENTERPIECE. RIGHT: AN ENERGETICALLY FAVORABLE CONFORMATION OF **47**, WHICH DOES NOT LEAD TO ROTAXANE FORMATION AND THUS MAY RATIONALIZE THE LOW ROTAXANE YIELDS OF 20% TO 30 %.

However, at 35%, the yield for rotaxane **49** shown in Scheme 18 is still not satisfactory. When trying to understand, why the yield is so low despite of a considerably high binding constant for the centerpiece/wheel complex, molecular modelling is often very helpful. One potential reason for a low yield of ca. 35% is shown in Figure 12. Upon deprotonation of the phenolate, intramolecular hydrogen bonds can be formed with the amide groups in the axle centerpiece. This automatically organizes the two amide carbonyl groups into a position favorable for the formation of a total of four hydrogen bonds with the wheel. In this conformation, both amino groups to which the stoppers are finally attached, point to the same side of the wheel and thus no mechanically bound structure is formed from this complex. Indeed, force field and semi-empirical calculations predict that this structure is very similar, but slightly more favorable in energy as compared to the threaded analogue so that the slight preference for the formation of a non threaded complex which dissociates to finally yield the free axle. Currently, attempts are made which intend to avoid the presence of amide groups in close proximity to the phenolate in order to further improve the synthesis of rotaxanes bearing functional groups in their centerpieces.

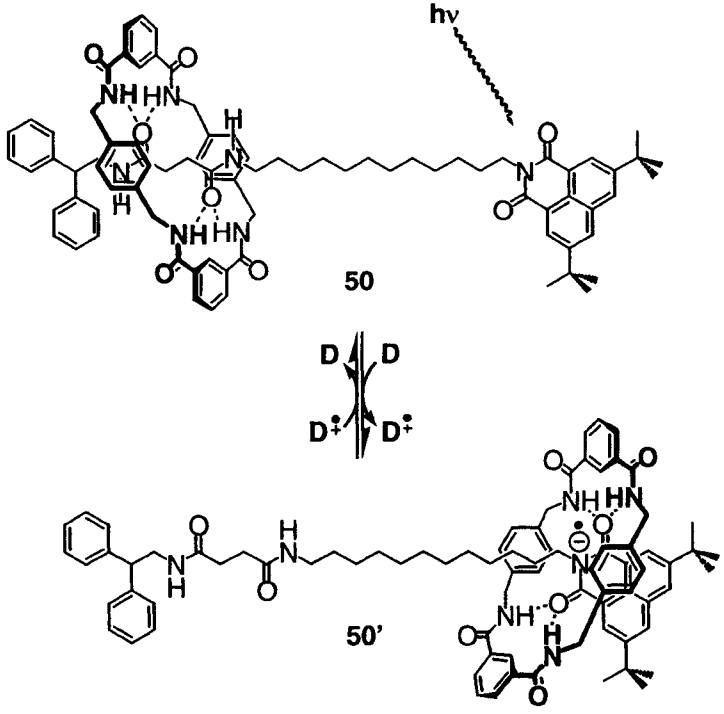
X. Conclusions and Future Perspectives

With these results we arrived at the end of our story on the development of efficient template strategies for rotaxanes, catenanes, and knots. It hopefully became clear that the rational design of template effects for the synthesis of interlocked molecules is still a challenge. Although the vast number of articles on host-guest chemistry and template syntheses for such compounds suggests that this chemistry is well understood, most of the template effects used today have been found by coincidence rather than design. Many surprising findings have led to the state-of-the-art of the field and it is by no means trivial to find, develop, and optimize new template effects. A profound understanding of the non-covalent interactions mediating the template synthesis will help much in the design efforts and is thus of utmost importance for the whole field of catenane, rotaxane, and knot chemistry.

This is particularly true, since rotaxanes and catenanes have entered a stage in their development, in which they have undergone the transition from beautiful structures with ever-new topologies to those which possess function. Many so-called molecular devices have been synthesized and studied with respect to a controlled motion of the two components relative

to each other.[52] The external stimulus inducing a defined motion can be a chemical reaction (e.g. protonation/deprotonation sequences), irradiation with light, or redox reactions.

At the end of this chapter let us – as an outlook into future perspectives – thus present only one of these functional molecules that utilize the mechanical bond in order to allow and control large-amplitude motions within a rotaxane (Scheme 19). In its resting state, rotaxane **50** exists with a smaller analogue of tetralactam wheel **23** hydrogen bonded to the amide carbonyl groups on the left.[53] Irradiation with light of the appropriate wavelength excites the stopper at the opposite end of the axle and induces an electron transfer from an electron donor (e.g. DABCO = diaza bicyclo[2.2.2]octane) to that stopper. The so-formed anion radical provides a better hydrogen bond acceptor and the wheel moves to the other end of the axle. Reduction of the anion radical reverses the process and the wheel moves back to the left side in Scheme 19.



SCHEME 19: A LIGHT-DRIVEN MOLECULAR SHUTTLE WITH WHICH MOLECULAR MOTIONS CAN BE INDUCED BY AN EXTERNAL STIMULUS.

Such controlled motion might become even more important, if one realizes that a bistable, controllable rotaxane might be useful as a nanoscale electronic device. One state would then be the "0", the other would represent the "1" state of one bit of a computer memory. Even if we have a long way to go before using these molecules as reliable functional units in electrical circuits minimized to nanometer dimensions, it seems to be of great promise and such promise demands the intense study of ways to synthesize these molecules and the detailed examination of their properties.

Acknowledgments

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References and Footnotes

1. a) Vögtle, F. *"Supramolekulare Chemie"*, Teubner: Stuttgart, 1992. b) Lehn, J.-M. *"Supramolecular Chemistry"*, Verlag Chemie: Weinheim 1995. c) Schneider, H.-J., Yatsimirsky, A. *"Principles and Methods in Supramolecular Chemistry"*, Wiley: New York, 2000. c) Steed, J. W., Atwood, J. L. *"Supramolecular Chemistry"*, Wiley: New York, 2000.
2. a) Schill, G. *"Catenanes, Rotaxanes and Knots"*, Academic Press: New York, 1971. b) *"Molecular Catenanes, Rotaxanes and Knots"*, Eds. Sauvage, J.-P., Dietrich-Buchecker, C. Wiley-VCH: Weinheim, 1999.
3. a) Reuter, C., Seel, C., Nieger, M., Vögtle, F. *Helv. Chim. Acta* **2000**, *83*, 630. b) Reuter, C., Mohry, A., Sobanski, A., Vögtle, F. *Chem. Eur. J.* **2000**, *6*, 1674.
4. Reuter, C., Wienand, W., Schmuck, C., Vögtle, F. *Chem. Eur. J.* **2001**, *7*, 1728.
5. a) Wasserman, E. *J. Am. Chem. Soc.* **1960**, *82*, 4433. b) Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1967**, *89*, 5723.
6. a) Schill, G., Lüttringhaus, A. *Angew. Chem.* **1974**, *76*, 567; *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 564. b) Schill, G., Zollenkopf, H. *Liebigs Ann.* **1969**, *721*, 53.
7. For reviews, see: a) Dietrich-Buchecker, C. O., Sauvage, J.-P. *Chem. Rev.* **1987**, *87*, 795. b) Sauvage, J.-P. *Acc. Chem. Res.* **1990**, *23*, 319. Recently, a catenane synthesis based on a ruthenium template has been reported: P. Mobian, J.-M. Kern, J.-P. Sauvage, *J. Am. Chem. Soc.* **2003**, *125*, 2016.
8. a) Busch, D. H., Stephensen, N. A. *Coord. Chem. Rev.* **1990**, *100*, 119. b) Cacciapaglia, R., Mandolini, L. *Chem. Soc. Rev.* **1993**, *22*, 221. c) Gerbeleu, N. V., Arion, V. B., Burgess, J. *"Template Synthesis of Macrocyclic Compounds"*, Wiley-VCH: Weinheim, 1999. d) *"Templated Organic Synthesis"*, Eds. Diederich, F., Stang,

P. J. Wiley-VCH: Weinheim, 2000. e) Hubin, T. J., Busch, D. H. *Coord. Chem. Rev.* **2000**, *200-202*, 5.

9. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7019.
10. a) Hulvat, J. F., Stupp, S. I. *Angew. Chem.* **2003**, *115*, 802; *Angew. Chem. Int. Ed.* **2003**, *42*, 778. Also, see the recent review: van Bommel, K. J. C., Friggeri, A., Shinkai, S. *Angew. Chem.* **2003**, *115*, 1010; *Angew. Chem. Int. Ed.* **2003**, *42*, 980.
11. Anderson, S., Anderson, H. L. *Templates in Organic Synthesis: Definitions and Roles* in ref. 8d, p. 1.
12. a) Eliseev, A. V., Lehn, J.-M. *Curr. Top. Microbiol.* **1999**, *243*, 159. b) Otto, S., Furlan, R. L. E., Sanders, J. K. M. *Drug Discov. Today* **2002**, *7*, 117.
13. Raymo, F. M., Stoddart, J. F. *Organic Template-Directed Syntheses of Catenanes, Rotaxanes, and Knots* in ref. 2b., p. 143.
14. a) Kolchinski, A. G., Busch, D. H., Alcock, N. W. *J. Chem. Soc., Chem. Commun.* **1995**, 1289. b) Ashton, P. R., Campell, P. J., Chrystal, E. J. T., Glink, P. T., Menzer, S., Philp, D., Spencer, N., Stoddart, J. F., Tasker, P. A., Williams, D. J. *Angew. Chem.* **1995**, *107*, 1997; *Angew. Chem. Int. Ed.* **1995**, *34*, 1865. c) Ashton, P. R., Chrystal, E. J. T., Glink, P. T., Menzer, S., Schiavo, C., Stoddart, J. F., Tasker, P. A., Williams, D. J. *Angew. Chem.* **1995**, *107*, 2001; *Angew. Chem. Int. Ed.* **1995**, *34*, 1869. d) Glink, P. T., Schiavo, C., Stoddart, J. F., Williams, D. J., *J. Chem. Soc., Chem. Commun.* **1996**, 1483. e) Ashton, P. R., Collins, A. N., Fyfe, M. C. T., Menzer, S., Stoddart, J. F., Williams, D. J. *Angew. Chem.*, **1997**, *109*, 760; *Angew. Chem. Int. Ed.* **1997**, *36*, 760.
15. a) Harada, A., Li, J., Kamachi, M. *Nature* **1992**, *356*, 325. b) Ogino, H. *New. J. Chem.* **1993**, *17*, 683. c) Isnin, R., Kaifer, A. E. *Pure Appl. Chem.* **1993**, *65*, 495. d) G. Wenz, *Angew. Chem.* **1994**, *106*, 851; *Angew. Chem. Int. Ed.* **1994**, *33*, 803. e) Armspach, D., Ashton, P. R., Ballardini, R., Balzani, V., Godi, A., Moore, C. P., Prodi, L., Spencer, N., Stoddart, J. F., Tolley, M. S., Wear, T. J., Williams, D. J. *Chem. Eur. J.*, **1995**, *1*, 33. f) Born, M. Ritter, H. *Angew. Chem.*, **1995**, *107*, 342; *Angew. Chem. Int. Ed.* **1995**, *34*, 309.
16. a) Fujita, M., Oguro, D., Miyazawa, M., Oka, H., Yamaguchi, K., Ogura, K. *Nature*, **1995**, *378*, 469. b) Fujita, M. *Acc. Chem. Res.* **1999**, *32*, 53.
17. Markies, P. R., Akkerman, O. S., Bickelhaupt, F. *Organometallics* **1994**, *13*, 2616.
18. a) Jorgensen, W. L., Severance, D. L., *J. Am. Chem. Soc.* **1990**, *112*, 4768. b) Amabilino, D. B., Anelli, P.-L., Ashton, P. R., Brown, G. R., Córdova, E., Godínez, L. A., Hayes, W., Kaifer, A. E., Philp, D., Slawin, A. M. Z., Spencer, N., Stoddart, J. F., Tolley, M. S., Williams, D. J., *J. Am. Chem. Soc.* **1995**, *117*, 11142. c) Ashton, P. R., Baldoni, V., Balzani, V., Credi, A., Hoffmann, H. D. A., Martínez-Díaz, M.-V., Raymo, F. M., Stoddart, J. F., Venturi, M., *Chem. Eur. J.* **2001**, *7*, 3482.
19. Ashton, P. R., Goodnow, T. T., Kaifer, A. E., Reddington, M. V., Slawin, A. M. Z., Spencer, N., Stoddart, J. F., Vicent, C., Williams, D. J., *Angew. Chem.* **1989**, *101*, 1404; *Angew. Chem. Int. Ed.* **1989**, *28*, 1396.
20. Amirsakis, D. G., Elizarov, A. M., Garcia-Garibay, M. A., Glink, P. T., Stoddart, J. F., White, A. J. P., Williams, D. J. *Angew. Chem.* **2003**, *115*, 1158; *Angew. Chem. Int. Ed.* **2003**, *42*, 1126.
21. Saenger, W. *Angew. Chem.* **1980**, *92*, 343; *Angew. Chem. Int. Ed.* **1980**, *19*, 344.
22. Ogino, H. *J. Amer. Chem. Soc.* **1981**, *103*, 1303.
23. Seel, C., Vögtle, F., *Angew. Chem.* **1992**, *104*, 542; *Angew. Chem. Int. Ed.* **1992**, *31*, 528.

24. Vögtle, F., Hoss, R., Meier, S. *Angew. Chem.* **1992**, *104*, 1628; *Angew. Chem. Int. Ed.* **1992**, *31*, 1619.
25. a) Hunter, C. A. *J. Chem. Soc., Chem. Commun.* **1991**, 749. b) Hunter, C. A. *J. Am. Chem. Soc.* **1992**, *114*, 5303.
26. For a review, see: a) Jäger, R., Vögtle, F., *Angew. Chem.* **1997**, *109*, 966; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 930. Similar amide type catenanes with smaller wheels have also been synthesized. See, for example: b) Kidd, T. J., Leigh, D. A., Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599. c) Bermudez, V., Capron, N., Gase, T., Gatti, F. G., Kajzar, F., Leigh, D. A., Zerbetto F., Zhang, S., *Nature* **2000**, *406*, 608.
27. Safarowsky, O., Nieger, M., Fröhlich, R., Vögtle, F. *Angew. Chem.* **2000**, *112* 1699; *Angew. Chem. Int. Ed.* **2000**, *39*, 1616.
28. a) Johnston, A. G., Leigh, D. A., Nehzat, L., Smart, J. P., Deegan, M. D. *Angew. Chem.* **1995**, *107*, 1327; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1202. b) Hamuro, Y., Geib, S. J., Hamilton, A. D. *Angew. Chem.* **1994**, *106*, 465; *Angew. Chem. Int. Ed.* **1994**, *33*, 446; b) Hunter, C. A., Sarson, L. D. *Angew. Chem.* **1994**, *106*, 2424; *Angew. Chem. Int. Ed.* **1994**, *33*, 2313.
29. Affeld, A., Hübner, G. M., Seel, C., Schalley, C. A. *Eur J. Org. Chem.* **2001**, 2877.
30. a) Hunter, C. A., D. H. Purvis, *Angew. Chem.* **1992**, *104*, 779; *Angew. Chem. Int. Ed.* **1992**, *31*, 792. Also, see: b) Carver, F. J., Hunter, C. A., Shannon, R. J., *J. Chem. Soc., Chem. Commun.* **1994**, 1277. c) Adams, H., Carver, F. J., Hunter, C. A., Osborne, N. J., *Chem. Commun.* **1996**, 2529. d) Allott, C., Adams, H., Bernad, Jr., P. L., Hunter, C. A., Rotger, C., Thomas, J. A., *Chem. Commun.* **1998**, 2449.
31. Schwanke, F., Safarowsky, O., Heim, C., Silva, G., Vögtle, F. *Helv. Chim. Acta* **2000**, *83*, 3279. Also, see the olympiadane: Amabilino, D. B., Ashton, P. R., Boyd, S. E., Lee, J. Y., Menzer, S., Stoddart, J. F., Williams, D. J., *Angew. Chem.* **1997**, *109*, 2160; *Angew. Chem. Int. Ed.* **1997**, *36*, 2070.
32. Mohry, A., Vögtle, F., Nieger, M., Hupfer, H. *Chirality* **2000**, *12*, 76.
33. Seel, C., Parham, A. H., Safarowsky, O., Hübner, G. M., Vögtle, F. *J. Org. Chem.* **1999**, *64*, 7236.
34. Schalley, C. A., Reckien, W., Müller, S., Brüggemann, J., Peyerimhoff, S., Vögtle, F., unpublished results.
35. Sobanski, A.; Schmieder, R.; Vögtle, F. *Chem. unserer Zeit* **2000**, *34*, 160.
36. a) Chambron, J.-C.; Dietrich-Buchecker, C.; Sauvage, J.-P. *Top. Curr. Chem.* **1993**, *165*, 131. b) Mislow, K. *Top. Stereochem.* **1999**, 1. c) Reuter, C.; Schmieder, R.; Vögtle, F. *Pure Appl. Chem.* **2000**, *72*, 2233.
37. Meskers, S. C. J.; Dekkers, H. P. J. M.; Rapenne, G.; Sauvage, J.-P. *Chem. Eur. J.* **2000**, *6*, 2129.
38. For examples of topologically chiral catenanes, see: c) Ashton, P. R.; Heiss, A. M.; Pasini, D.; Raymo, F. M.; Shipway, A. N.; Stoddart, J. F.; Spencer, N. *Eur. J. Org. Chem.* **1999**, 995.
39. a) Rapenne, G.; Dietrich-Buchecker, C.; Sauvage, J.-P., *J. Am. Chem. Soc.* **1999**, *121*, 994. Ashton, P. R., Matthews, O. A., Menzer, S., Raymo, F. M., Spenzer, N., Stoddart, J. F., Williams, D. J., *Liebigs Ann./Recueil* **1997**, 2485. (c) Adams, H., Ashworth, E., Breault, G. A., Guo, J., Hunter, C. A., Mayers, P. C., *Nature* **2001**, *411*, 763.
40. Lukin, O., Vögtle, F., personal communication.
41. Vögtle, F., Hünten, A., Vogel, E., Buschbeck, S., Safarowsky, O., Recker, J., Parham, A., Knott, M., Müller, W. M., Müller, U., Okamoto, Y., Kubota, T.,

Lindner, W., Francotte, E., Grimme, S., *Angew. Chem.* **2001**, *113*, 2534; *Angew. Chem. Int. Ed.* **2001**, *40*, 2468.
42. Schalley, C. A., Hoernschemeyer, J., Li, X.-y., Silva, G., Weis, P. *Int. J. Mass Spectrom.*, in press.
43. Hübner, G. M., Gläser, J., Seel, C., Vögtle, F. *Angew. Chem.* **1999**, *111*, 395; *Angew. Chem. Int. Ed.* **1999**, *38*, 383.
44. Seel, C., Vögtle, F. *Chem. Eur. J.* **2000**, *6*, 21.
45. A similar anion template effect has been developed, which additionally makes use of attractive interactions between the anion and its counterion for threading the center piece into the wheel: a) Wisner, J. A., Beer, P. D., Berry, N. G., Tomapatanaget, B., *Proc. Natl. Acad. Sci. (USA)* **2002**, *99*, 4983; b) Wisner, J. A., Beer, P. D., Drew, M. G. B., Sambrook, M. R., *J. Am. Chem. Soc.* **2002**, *124*, 12469.
46. a) Reuter, C., Wienand, W., Hübner, G. M., Seel, C., Vögtle, F., *Chem. Eur. J.* **1999**, *5*, 2692. b) Li, X.-y., Illigen, J., Nieger, M., Michel, S., Schalley, C. A., *Chem. Eur. J.*, **2003**, *9*, 1332.
47. Reuter, C., Vögtle, F., *Org. Lett.* **2000**, *2*, 593.
48. a) Felder, T., Schalley, C. A., *Angew. Chem.* **2003**, *115*, 2360; *Angew. Chem. Int. Ed.* **2003**, *42*, 2258. b) Linnartz, P., Bitter, S., Schalley, C. A., *Chem. Eur. J.*, submitted.
49. Schalley, C. A., Silva, G., Nising, C.-F., Linnartz, P. *Helv. Chim. Acta* **2002**, *85*, 1578.
50. Ghosh, P., Mermagen, O., Schalley, C. A., *Chem. Commun.* **2002**, 2628.
51. Schwesinger, R., Hasenfratz, C., Schlemper, H., Walz, L., Peters, E.-M., Peters, K., von Schnering, H. G., *Angew. Chem.* **1993**, *105*, 1420; *Angew. Chem. Int. Ed.* **1993**, *32*, 1361.
52. For selected reviews on molecular machines, see: a) Drexler, K. E., *Annu. Rev. Biophys. Biomol. Struct.*, **1994**, *23*, 377. b) Balzani, V., Gómez-López, M., Stoddart, J. F., *Acc. Chem. Res.*, **1998**, *31*, 405. c) Sauvage, J.-P., *Acc. Chem. Res.*, **1998**, *31*, 611. d) Collin, J.-P., Gaviña, P., Heitz, V., Sauvage, J.-P., *Eur. J. Inorg. Chem.*, **1998**, 1. e) Asfari, Z., Vicens, J., *J. Incl. Phenom. Macrocyc. Chem.* **2000**, *36*, 103. f) Balzani, V., Credi, A., Raymo, F. M., Stoddart, J. F., *Angew. Chem.* **2000**, *112*, 3484; *Angew. Chem. Int. Ed.* **2000**, *39*, 3348. g) Schalley, C. A., Beizai, K., Vögtle, F., *Acc. Chem. Res.* **2001**, *34*, 465. h) Collin, J.-P., Dietrich-Buchecker, C., Gaviña, P., Jimenez-Molero, M. C., Sauvage, J.-P., *Acc. Chem. Res.* **2001**, *34*, 477. i) Shipway, A. W., Willner, I., *Acc. Chem. Res.* **2001**, 34, 421. j) Pease, A. R., Jeppesen, J. O., Stoddart, J. F., Luo, Y., Collier, C. P., Heath, J. R., *Acc. Chem. Res.* **2001**, 34, 433. k) Ballardini, R., Balzani, V., Credi, A., Gandolfi, M. T., Venturi, M., *Acc. Chem. Res.* **2001**, 34, 445. l) Schalley, C.A., *Angew. Chem.* **2002**, *114*, 1583; *Angew. Chem. Int. Ed.* **2002**, *41*, 1513. m) Felder, T., Schalley, C. A., *Artificial Rotary Motors Based on Rotaxanes* in: *Highlights in Bioorganic Chemistry*, Wennemers, H., Schmuck, C. (Eds.), Wiley-VCH, Weinheim, in press..
53. Brouwer, A. M., Frochot, C., Gatti, F. G., Leigh, D. A., Mottier, L., Paolucci, F., Roffia, S., Wurpel, G. W. H., *Science* **2001**, *291*, 2124.

STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 8

TOTAL SYNTHESIS OF SPONGISTATIN 1 (ALTOHYRTIN A): A TALE OF TEN ALDOLS

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I. Introduction

The opening of Charles Dickens' classic novel, *A Tale of Two Cities* – "It was the best of times, it was the worst of times" – will sound familiar to those who work on the total synthesis of complex natural products. Many emotional highs and lows are experienced during ambitious total synthesis projects. There can be periods when it seems that nature is contriving against the bench chemist, cruelly preventing all attempts to achieve the desired transformation, while at other times a string of successes may leave one feeling they have the Midas touch.

This chapter attempts to recount some of the highs and lows encountered during the Paterson group's total synthesis of spongistatin 1/altohyrtin A, an extremely rare marine macrolide with a seductively complex structure in combination with displaying promising anticancer properties. We provide the reader with an emotional roller coaster ride through a project that spanned some 7 years, with early studies aimed at

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developing the methodology needed to tackle this "hot target", leading on to the tense final stages, involving intricate coupling reactions of densely functionalised subunits, and the final push to solve the many problems encountered and complete the total synthesis. The perspective taken is one of a PhD student (MJC) involved in the later phases of the synthetic effort, leading right up to the exhilarating final stages. As such, and due to the need for brevity, a great deal of the initial pioneering work by the first "spongi" students and postdocs is not covered in equal detail. We emphasise that the eventual success of this challenging project was due to the hard work, enthusiasm and determination of all in the "spongi team", who are listed in the acknowledgements.

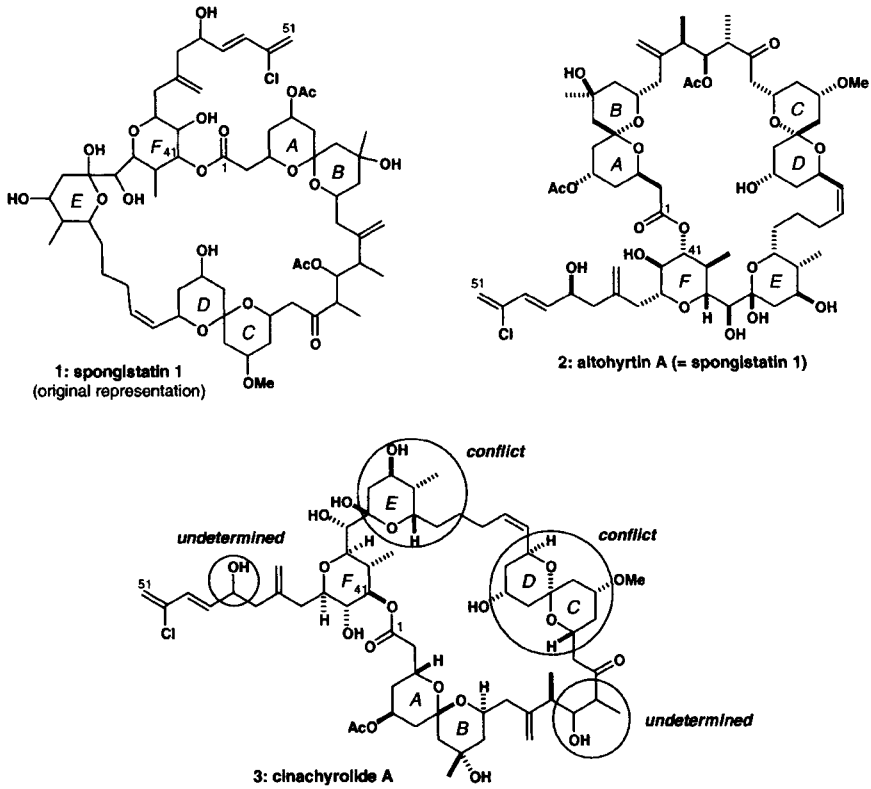


FIGURE 1. ORIGINALLY PROPOSED STRUCTURES FOR SPONGISTATIN 1 (**1**), ALTOHYRTIN A (**2**) AND CINACHYROLIDE A (**3**), SHOWING THAT NO STEREOCHEMISTRY WAS DETAILED IN THE ORIGINAL REPRESENTATION OF **1**, THE PARTIAL STEREOCHEMISTRY PROPOSED FOR **3** CONFLICTED WITH THAT FOR **2** AND LATER REPRESENTATIONS OF **1** BY PETTIT.

In 1993, Pettit *et al.* reported the isolation and gross structure of spongistatin 1 (**1**, original representation), the first of an unprecedented family of extremely potent antimitotic macrolides of sponge origin (Figure 1).[1] Also in 1993, Kobayashi/Kitagawa and the group of Fusetani reported the isolation from different sponge sources of the altohyrtins (as in **2**)[2] and cinachyrolide A (**3**),[3] respectively, having the same gross structures as those reported for the spongistatins. Initially, there were some notable discrepancies apparent in the relative stereochemical relationships attributed to these unprecedented 42-membered macrolides, where the Kitagawa/Kobayashi group was the only one to propose the full relative and absolute configuration, as shown in structure **2** for altohyrtin A.[2d] Thus, initiating our total synthesis programme required a best guess at the target's stereostructure and the design of a flexible approach to allow later corrections if required. As it turned out, the Evans and Kishi groups were the first past the post in the "spongi race", reporting their completed total syntheses of altohyrtin C and altohyrtin A in late 1997 and early 1998, respectively.[4,5] This served to confirm the full stereostructure in **2** and established that the spongistatins indeed had identical structures to the altohyrtins.

The spongipyran family[6] of marine macrolides are among the most potent cancer cell growth inhibitory antimitotic agents tested by the National Cancer Institute (NCI), with spongistatin 1/altohyrtin A (**2**) being one of the most active members of the class. The exceptional level of cytotoxicity displayed by this compound in the NCI 60 human carcinoma cell line screen (mean panel GI_{50} 1.3 x 10^{-10} M) is complemented by potency against a subset of highly chemoresistant tumour types (GI_{50} 2.5-3.5 x 10^{-11} M) and promising preliminary *in vivo* results in xenograft experiments. However, despite this enticing biological profile, further testing has been severely hampered by the paltry supply from the natural sponge source (*e.g.* 13.8 mg from 400 kg wet sponge in the original collection by Pettit).

Due to the promising anticancer properties exhibited by the spongistatins, the lack of material available from the sponge sources, the uncertain stereochemical assignment (when we started out in 1994) and the unprecedented molecular architecture, these intriguing compounds represent compelling targets for total synthesis. Within our group, we aimed to establish a highly flexible synthetic route, allowing access to significant quantities of spongistatin 1/altohyrtin A (**2**) (the most potent congener), along with novel structural analogues, to enable preclinical development to resume. We were regularly spurred on in our quest by the constant encouragement of Prof. Pettit. In addition, we had a great deal of

company from many other synthetic groups around the world that were also attracted to the spongistatin problem.[7,8] We now start our adventure.....

II. Retrosynthetic Analysis

The spongipyran natural products present a bewildering array of functionality for the organic chemist to ponder. In the case of spongistatin 1/altohyrtin A (**2**), there are 24 stereogenic centres to be dealt with; a 42-membered macrolactone (longest carbon chain); two spiroacetals, only one of which benefits from two stabilising anomeric effects; a *bis*-tetrahydropyran segment and a highly sensitive chlorotrienol side-chain. Our retrosynthetic analysis for spongistatin 1/altohyrtin A (**2**) involved the disconnection of the molecule into three portions of roughly similar complexity (Figure 2).

The principal fragment couplings envisaged were an aldol reaction to unite the AB- and CD-spiroacetal subunits (**4** and **5**) *via* formation of the C_{15}-C_{16} bond and the accompanying stereocentres, a Wittig coupling between an ABCD aldehyde subunit and EF phosphonium salt **6**, followed by a regioselective macrolactonisation at the C_{41} hydroxyl. The dissection of the target into three fragments to be assembled in late-stage coupling reactions allows for a high degree of convergency, with no major functional group manipulations required following the fragment coupling steps.

Ten key aldol disconnections were identified as part of our overall strategy for assembling this highly oxygenated polyketide. As shown in Figure 2, three of these are present in the AB-spiroacetal subunit, two in the CD-spiroacetal subunit, one to join these two fragments together and four aldol disconnections are apparent in the C_{29}-C_{51}, EF-containing subunit. The mixture of acetate- and propionate-derived portions in the various subunits **4**-**6** would require the development of efficient and highly stereoselective aldol reactions of methyl and ethyl ketones, respectively, with appropriate aldehyde partners. Altogether, the total synthesis of spongistatin 1 provided an unparalleled opportunity to showcase the versatility and practicality of asymmetric aldol methodology based on the use of ketone-derived boron enolates, as developed extensively in our group. For a comprehensive literature survey, experimental details, and transition state models, rationalising the stereoinduction for these synthetically important C–C bond forming reactions, the reader is directed to two recent reviews.[9a,b] Additionally,

such a complex and demanding natural product provided the exciting challenge of developing new synthetic methodologies, both with regard to asymmetric aldol reactions and in other areas, as well as (hopefully) solving the many unanticipated chemical and logistical problems that would inevitably be encountered along the route.

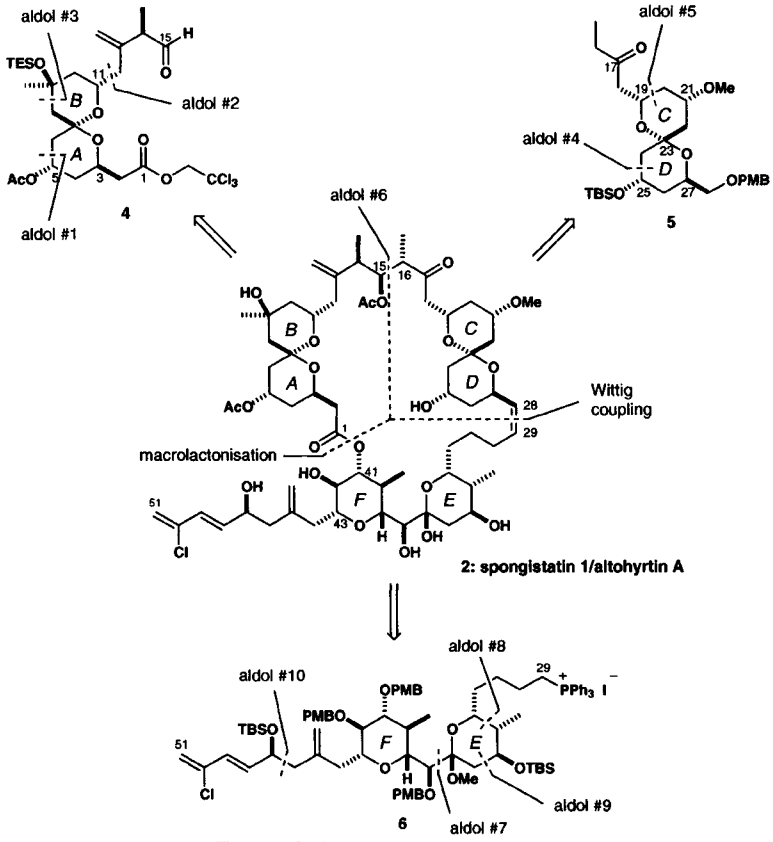


FIGURE 2. RETROSYNTHETIC ANALYSIS.

III. The AB-Spiroacetal Subunit

The C_1-C_{15} fragment of spongistatin 1, comprising the AB-spiroacetal **4**,[10] exhibits an "axial-axial" disposition of the two acetal oxygen atoms at C_7 and hence benefits from two stabilising anomeric effects (Figure 3). Based on this, it was expected that the correct spiroacetal would be

provided under thermodynamic conditions, such as acid-catalysed acetal formation from a linear precursor.

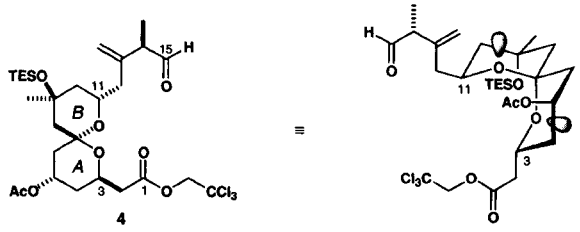
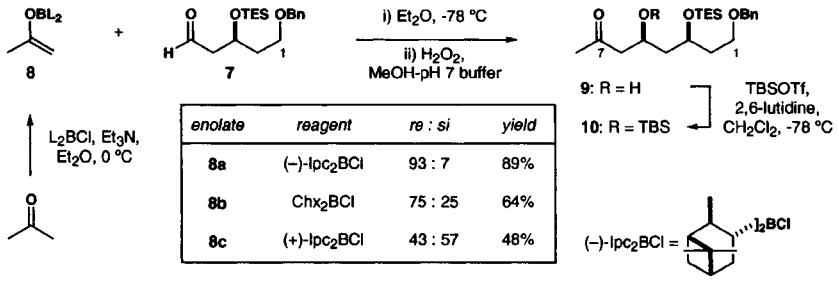


FIGURE 3. THE AB-SPIROACETAL SUBUNIT.

A. ALDOL #1

The first instance of an asymmetric aldol reaction in our spongistatin synthesis involved the reaction of aldehyde **7**, readily available in excellent enantiopurity (97% ee) *via* Brown's allylation methodology,[11] with the enol borinate **8a**, generated *in situ* from the reaction of acetone with (–)-Ipc_2BCl (Et_3N, Et_2O, 0 °C).[10a,b] Following an oxidative workup, this matched reaction gave predominantly the desired 1,3-*syn* isomer **9** (93:7 ds) in 89% yield (Scheme 1). By comparison, the dicyclohexylboron enolate **8b** delivered **9** with reduced selectivity (75:25 ds), while using enolate **8c**, prepared from (+)-Ipc_2BCl, overturned the inherent 1,3-*syn* induction from the aldehyde to give a modest preference for the 1,3-*anti* diastereomer. Subjection of **9** to TBSOTf and 2,6-lutidine provided the corresponding TBS ether **10**.



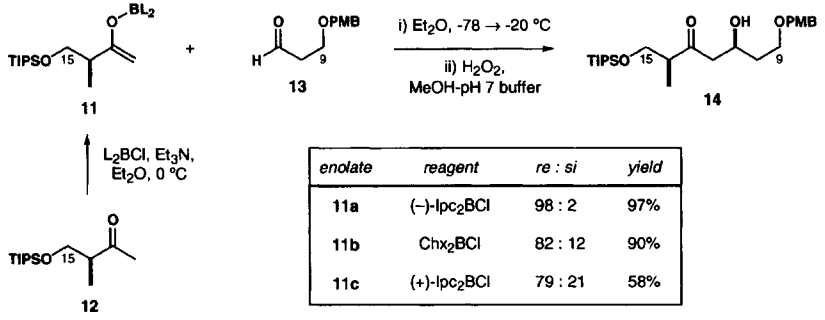
enolate	*reagent*	*re : si*	*yield*
8a	(–)-Ipc_2BCl	93 : 7	89%
8b	Chx_2BCl	75 : 25	64%
8c	(+)-Ipc_2BCl	43 : 57	48%

SCHEME 1

B. ALDOL #2

Previous work by our group had demonstrated that high levels of 1,4-*syn* diastereoselection were possible in boron-mediated aldol reactions of

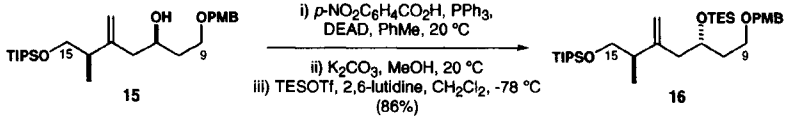
certain α-chiral methyl ketones, and could be enhanced by appropriate choice of Ipc ligand chirality.[12] In the present case, the 1,4-*anti* relationship between the C_{11} and C_{14} stereocentres was best realised by combining a highly 1,4-*syn* selective, matched aldol reaction with a subsequent Mitsunobu inversion at C_{11}.[10c] Enol borinate **11a**, derived from methyl ketone **12** by reaction with (–)-Ipc_2BCl and Et_3N, underwent the desired aldol addition with aldehyde **13** to provide a 97% yield of the 1,4-*syn* product **14** (98:2 ds). Once again, use of Chx_2BCl (enolate **11b**) or the mismatched (+)-Ipc_2BCl (enolate **11c**) led to lower levels of 1,4-*syn* selectivity, 82:18 ds and 79:21 ds, respectively (Scheme 2).



enolate	*reagent*	*re : si*	*yield*
11a	(–)-Ipc_2BCl	98 : 2	97%
11b	Chx_2BCl	82 : 12	90%
11c	(+)-Ipc_2BCl	79 : 21	58%

SCHEME 2

Not surprisingly, an attempt at direct Mitsunobu inversion of β-hydroxyketone **14** led only to elimination, yielding the corresponding α,β-unsaturated ketone. To circumvent this problem, **14** was converted to homoallylic alcohol **15** by Petasis methylenation *via* the corresponding TES ether. Attempts to methylenate β-hydroxyketone **14** directly under Petasis conditions led to substantial decomposition via elimination and retro-aldol pathways. Alcohol **15** underwent smooth Mitsunobu inversion to give, following methanolysis and TES ether formation, the desired 1,4-*anti* compound **16** (Scheme 3). This was then converted in three straightforward steps to aldehyde **17**, ready for the proposed aldol union with ketone **10**.

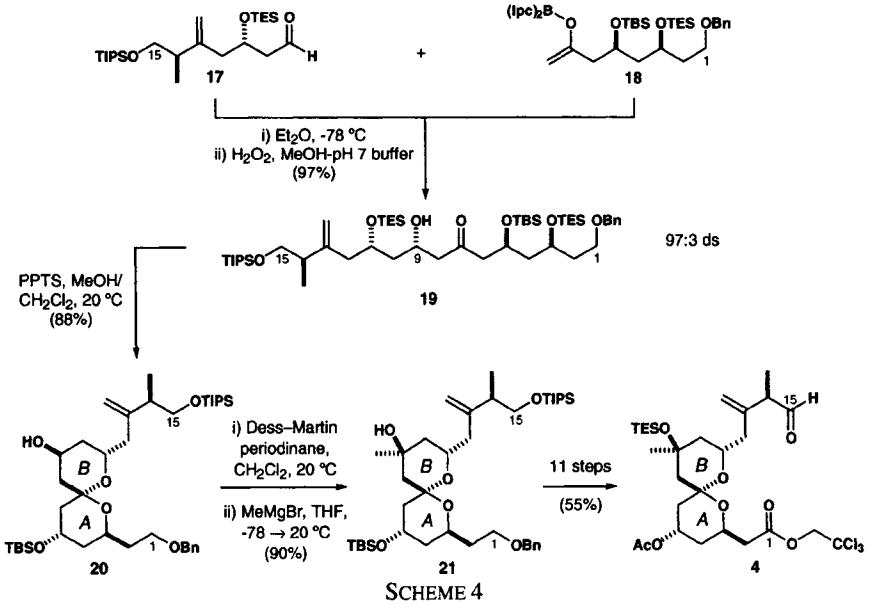


SCHEME 3

C. ALDOL #3

The third and final aldol reaction utilised in our synthesis of the AB-spiroacetal subunit exploited triple asymmetric induction, wherein the influence of all three chiral components (aldehyde, ketone and boron reagent) were matched (Scheme 4). As such, the reaction of aldehyde **17** with enolate **18**, prepared using (–)-Ipc_2BCl, provided the desired aldol adduct **19** in 81% yield (97:3 ds). The 1,3-*syn* preference of aldehyde **17**, the 1,5-*anti* preference of ketone **10** (see following section) and the stereodirecting influence of the boron reagent act in a synergistic fashion, facilitating the excellent level of stereocontrol observed.

Selective desilylation of **19** was accompanied by spiroacetal formation to provide the thermodynamically favoured AB-spiroacetal **20**. At this stage, stereoselective introduction of the C_9 methyl substituent was achieved by oxidation of the secondary alcohol moiety to the corresponding ketone, followed by equatorial addition of MeMgBr to provide spiroacetal **21**, bearing all of the necessary stereogenic centres contained in the C_1-C_{15} portion of the spongistatins. From this point, a series of functional group interconversions were all that was needed to arrive at the fully elaborated AB-spiroacetal aldehyde **4**, ready for the challenging aldol coupling with the CD-spiroacetal ketone **5**.[10d]



SCHEME 4

IV. The CD-Spiroacetal Subunit

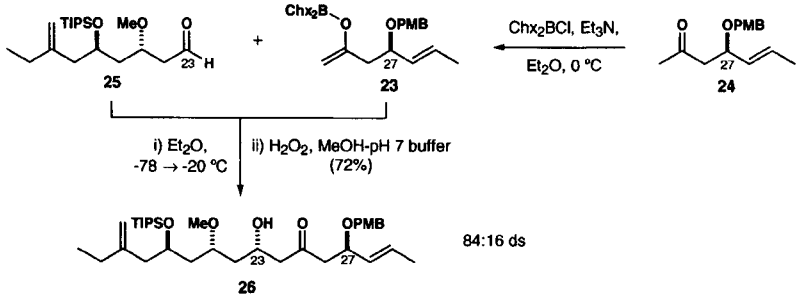
The C_{16}-C_{28} fragment of spongistatin 1, comprising the CD-spiroacetal **5**, exhibits an "axial-equatorial" disposition of the two acetal oxygen atoms and hence, unlike the AB-spiroacetal system, benefits from only one stabilising anomeric effect (Figure 4).

FIGURE 4. THE CD-SPIROACETAL SUBUNIT.

At the outset of our work on this section of the spongistatin structure,[13] it was not known whether an internal acetalisation procedure, analogous to that employed for the AB subunit, would lead to the desired spiroacetal **22a** rather than the potentially more stable **22b**. However, the axial C_{25} hydroxyl may hydrogen bond to an acetal oxygen, providing structure **22a** additional stability not available to **22b**, and this might be exploited in our synthetic endeavours.

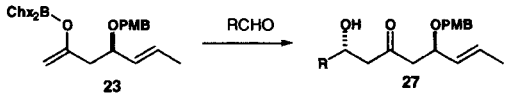
A. A SURPRISING RESULT: REMOTE 1,5-*ANTI* STEREOINDUCTION

Initially, two distinct approaches to this portion of the spongistatins were pursued. The first relied on *bis*-desilylation of a linear precursor and concomitant spiroacetal formation. A complementary strategy was based on the stepwise construction of the C- and D-rings. This latter route (Scheme 5) utilised the boron-mediated aldol reaction between enolate **23**, derived from ketone **24**, and aldehyde **25**, yielding **26** in 72% yield with a high degree of 1,5-*anti* selectivity (84:16 ds). Considering that the stereocentre created in this step (C_{23}) is subsequently destroyed in the next by oxidation to the corresponding ketone, it is to the credit of Karl Gibson that the stereoselectivity of this reaction was paid such close attention.



SCHEME 5

This work resulted in the discovery of high levels of substrate-based, 1,5-*anti* stereoinduction in the boron-mediated aldol reactions of a variety of chiral β-alkoxy methyl ketones with prochiral aldehydes.[14] A typical example is shown in the reaction of methyl ketone enolate **23** with simple aldehydes, leading to the 1,5-*anti* adducts **27** with remarkably high levels (>95:5) of long-range acyclic stereoinduction (Scheme 6). While the mechanistic basis of this remarkable effect must lie in a subtle balance of electronic and steric effects operating in the highly ordered cyclic transition state, the finer details still need to be determined.[9b] This new method for remote stereocontrol has been applied not only in several aspects of our spongistatin total synthesis, but also in other 1,3-polyol syntheses,[15] and a similar effect has been independently observed by the Evans group.[14b]

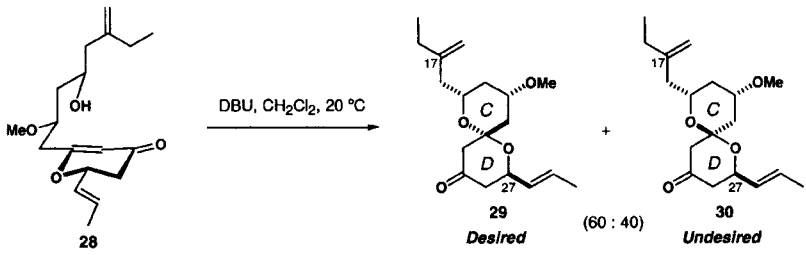


compound	*R*	*anti : syn*	*yield*
27a	*i*-Pr	97 : 3	79%
27b	C(Me)=CH$_2$	97 : 3	82%
27c	CH=CHMe	98 : 2	80%

SCHEME 6

The kinetic control approach to constructing the CD-spiroacetal segment envisaged a hetero-Michael cyclisation of the dihydropyrone **28** (derived from **26** by sequential oxidation to the β-diketone, PMB removal and cyclisation to provide the D-ring), where axial attack might be favoured (Scheme 7). In practice, treatment of **28** with DBU led to installation of the C-ring *via* hetero-Michael reaction, with a small preference (60:40) for formation of the desired spiroacetal **29** over **30**. Despite the modest selectivity observed in this mode of spiroacetal formation, the endeavour highlighted an important new means for

achieving remote acyclic stereoinduction in a 1,5-*anti* sense, which would prove invaluable to our ongoing spongistatin work.



SCHEME 7

B. ALDOL #4

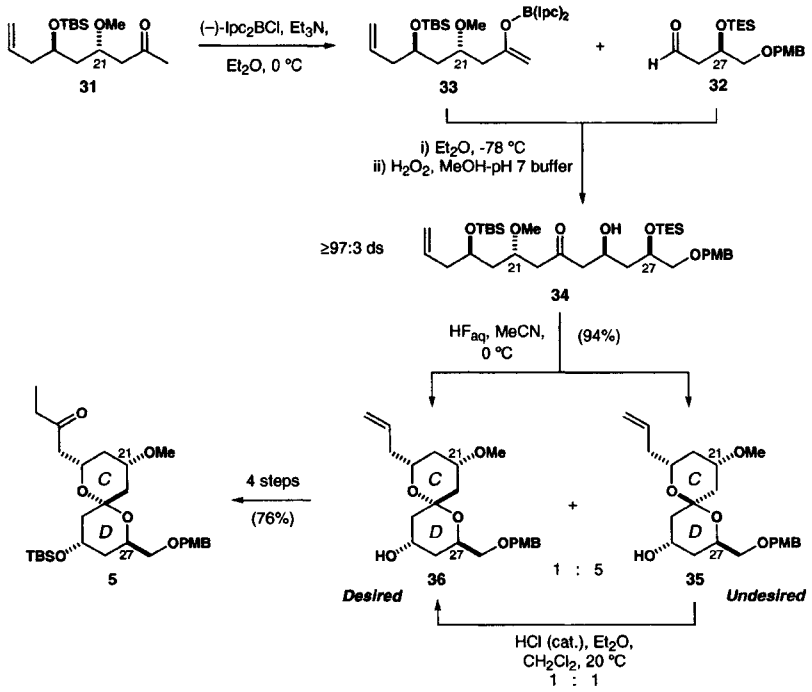
The alternative thermodynamic approach to establishing the CD-spiroacetal subunit relied on the aldol union of ketone **31** with aldehyde **32**, both available in high enantiomeric purity *via* Brown allylation methodology. Enolisation of ketone **31** with (–)-Ipc_2BCl/Et_3N in Et_2O led to regioselective formation of enol borinate **33**, which underwent smooth aldol reaction with aldehyde **32** to provide the adduct **34** in 85% yield, with excellent selectivity for the desired diastereomer (≥97:3 ds). Notably, once again, this boron-mediated aldol reaction exploits triple asymmetric induction, *i.e.* the influence of all three chiral components (aldehyde, ketone and boron reagent) are matched (Scheme 8).

Treatment of **34** with aqueous HF in MeCN solution led to desilylation with concomitant acetal formation favouring the undesired spiroacetal **35** over **36** (*ca.* 5:1). This was not a welcome result! At this juncture, we surveyed some equilibration conditions to yield more favourable quantities of the desired spiroacetal isomer **36**. Bearing in mind the possibility of an intramolecular hydrogen bond between the axial C_{25} hydroxyl and an acetal oxygen in **36**, which is not possible in **35**, we rapidly established that acid catalysed (HCl) equilibration in an aprotic solvent ($CDCl_3$, CH_2Cl_2, Et_2O) provided *ca.* 1:1 mixtures of **35** and **36**.

Separation of these spiroacetal isomers was initially achieved using normal phase semi-preparative HPLC, which allowed re-equilibration of the undesired spiroacetal **35** and thereby a method to convert essentially all of the material to the desired isomer **36** after several cycles. The scale-up of this procedure was greatly facilitated by the determination of a simple method for separating the spiroacetal isomers by flash column

chromatography. Thus, a few hours spent running TLCs in a number of eluent mixtures saved a great deal of labour later on.

The desired spiroacetal **36** was converted to the TBS ether and the terminal alkene moiety was elaborated to the corresponding ethyl ketone in four steps, to provide the fully-functionalised CD-spiroacetal ketone **5**, now ready for aldol union with the AB-spiroacetal aldehyde **4**. This route was found to be highly scalable, enabling production of multi-gram quantities of the desired C_{16}-C_{28} fragment **5** with little need to repeat the synthetic sequence.



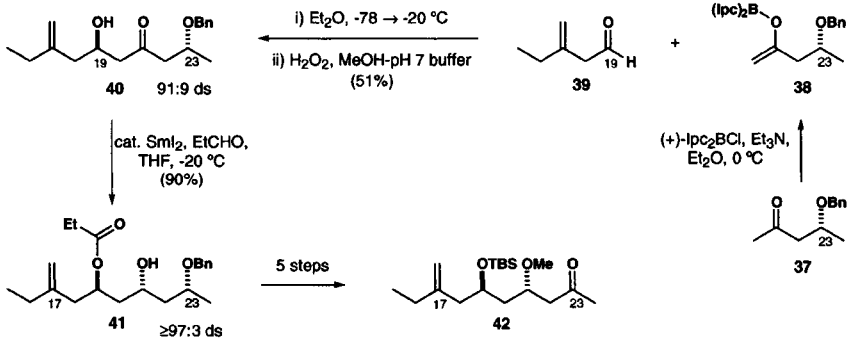
SCHEME 8

C. ALDOL #5

Whereas the thermodynamic route described above relied on reagent control to establish the spongistatin C_{19} and C_{21} stereocentres, the discovery of highly stereoselective 1,5-*anti* aldol reactions of methyl ketones enabled us to examine an alternative,[16] substrate-based stereocontrol route to **5**. Regioselective enolisation of enantiomerically pure ketone **37**, derived from a readily available biopolymer, gave enol

borinate **38** *in situ* (Scheme 9). Reaction of this species with the volatile and readily isomerisable aldehyde **39** provided aldol adduct **40** (91:9 ds) in an unoptimised yield of 51%. The high stereoselectivity of this reaction was the result of the matched 1,5-*anti* preference of ketone **37** and appropriate choice of Ipc ligands on the boron atom. That the acid- and base-sensitive aldehyde **39** undergoes this reaction without any sign of double bond migration is testimony to the mild nature of the boron-mediated aldol reaction.

With the required configuration established at C_{19}, a 1,3-*anti* selective reduction was pursued. The Evans-Tishchenko reduction, utilising catalytic SmI_2 and an aldehyde (in this case EtCHO), was found to be ideal in this instance, providing the mono-acylated diol **41** with complete 1,3-*anti* selectivity (≥97:3 ds). The C_{23} stereocentre, having served its purpose in the remote stereocontrol at C_{19}, is no longer necessary. Thus, after some manipulation of protecting groups, the C23 position was converted to the corresponding carbonyl function providing **42** and thereby enabling the aldol union with aldehyde **32**. From this point, the synthesis proceeded without incident in an analogous manner to that described above.



SCHEME 9

The CD-spiroacetal subunit of the spongistatins proved to be of an appropriate level of complexity that several different synthetic strategies were evaluated. Access to the desired spiroacetal **5** was readily achieved by acid catalysed equilibration of the mixture of spiroacetals in aprotic solvents, followed by separation and recycling of the undesired isomer. Furthermore, the 1,5-*anti* aldol reaction of methyl ketones proved invaluable for construction of certain portions of the target molecule.

V. The Northern Hemisphere

The spiroacetal subunits **4** and **5** were two of the most complex partners to be used in an aldol coupling by our group. Model studies[10b] had confirmed our belief that α-methyl-β-methylene aldehydes of type **4** would undergo aldol reaction with (*E*)-enolates to deliver the *anti*- aldol adducts with high levels of Felkin-Anh induction, corresponding to the desired spongistatin (15*S*,16*S*)-configuration. Furthermore, these model studies had shown that the potentially precarious (14*R*)-stereocentre survived unscathed from this chemistry.

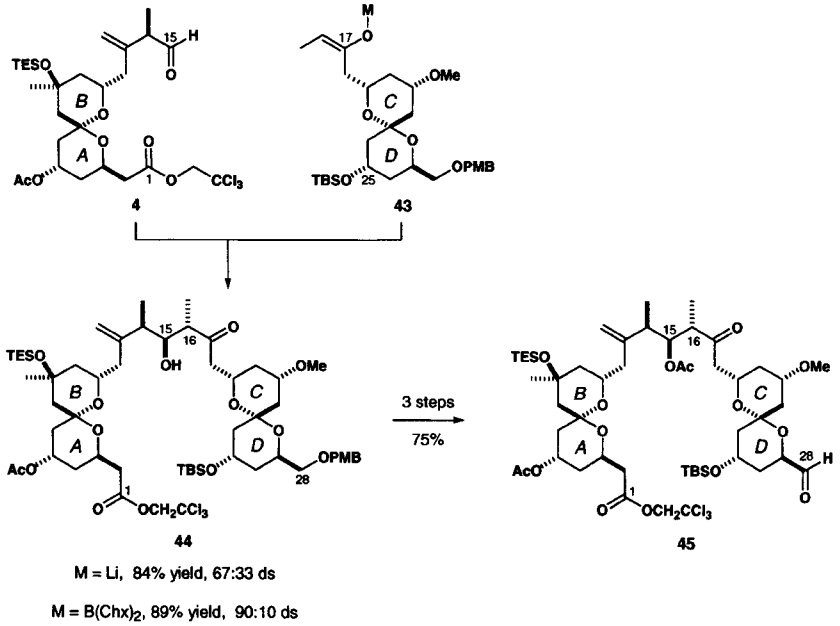
A. ALDOL #6

The first attempts to accomplish aldol coupling of the AB- and CD-spiroacetal subunits involved selective enolisation (Chx_2BCl) of **5** followed by exposure to aldehyde **4**. Following oxidative workup, only trace quantities of the desired aldol adduct were obtained, and furthermore none of the valuable starting materials were recovered! As with most total synthesis endeavours, this key coupling step was first investigated on a very small scale. After establishing successful routes to the two spiroacetal subunits, and fully characterising all relevant compounds, the frontline material was now available to scout out the exciting next steps in the total synthesis. Often it is the case that the first methods investigated are not wholly successful and so valuable advanced material is lost to exploring different ideas and optimising conditions. When the first few trials of the boron-mediated aldol coupling of **4** and **5** had failed to deliver the desired product in synthetically useful quantities and had destroyed valuable materials, attention was quickly turned to the lithium-mediated variant.

Formation of the lithium (*E*)-enolate **43** (2 equiv.) from ketone **5** was readily achieved using LiTMP•LiBr (Scheme 10). Reaction with aldehyde **4** was rapid (< 2 min) at –78 °C, providing the aldol adduct **44** as the major diastereomer (84%, 67:33 ds).[10c] Additionally, the excess ketone could be recovered quantitatively. This fragment coupling reaction was found to be fairly robust, providing sufficient quantities of **44** to enable further investigation of our proposed synthetic route. However, the possibility of using the boron-mediated variant remained in our minds, and around this time the Evans group reported on a similar coupling step.[4c] If this pivotal coupling reaction were coerced to proceed, the diastereoselectivity was expected to be superior relative to the lithium aldol reaction and a stoichiometry close to 1:1 seemed more feasible in

the case of boron, particularly upon scaling up to larger quantities. For these reasons, the boron-mediated aldol coupling of **4** and **5** was re-investigated intermittently amongst the work being done to carry through material *via* the lithium aldol reaction. It was also around this time that we received a highly encouraging letter from Prof. Pettit, expressing his admiration for the synthetic work which had been carried out thus far within our group, and re-iterating just how exciting the biological properties of the spongistatins were. This was a timely morale boost for us, and a greatly appreciated gesture of support.

Our persistence with the boron-mediated aldol reaction of **4** and **5** was rewarded when the reaction was conducted without recourse to the usual oxidative workup. Other work conducted by our group had shown that oxidative cleavage of certain aldol borinates under standard conditions (H_2O_2, pH 7 buffer, H_2O/MeOH) led to poor yields of the aldol products. In the case of **44,** the oxidative step was omitted and the reaction mixture was placed directly on silica gel and then eluted to afford aldol adduct **44** in excellent yield (89%) and with improved diastereoselectivity (90:10 ds) relative to the corresponding lithium conditions.[17]



SCHEME 10

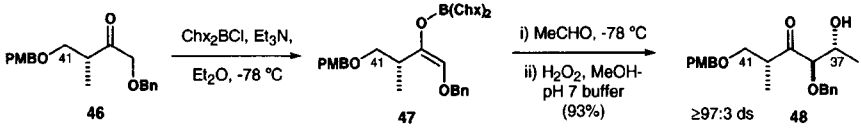
This coupling procedure proved highly efficient upon scaling up and also operationally straightforward, requiring simply that the reaction mixture be placed at the top of a silica gel flash column to break down the intermediate boron aldolate for *ca.* 20 min prior to elution. The remaining three steps required to convert **44** into the fully-functionalised northern hemisphere aldehyde **45** were readily achieved, providing material for Wittig coupling with the southern hemisphere ylide. While we first prepared the ABCD aldehyde **45** in early 1997, we were sadly lacking the southern hemisphere to go forward to complete the total synthesis. This logistical problem required a sustained effort by the "spongi team" to tackle the problems posed by the highly challenging C_{29}-C_{51} fragment.

VI. The Southern Hemisphere

The C_{29}-C_{51} fragment **6** of spongistatin 1 incorporates two tetrahydropyran moieties, the E- and F-rings, along with an array of 11 stereogenic centres. Owing largely to the dense oxygenation of the C_{35}-C_{43} segment and the sensitive nature of the chlorotrienol side-chain, construction of subunit **6** represents one of the more challenging aspects of the spongistatin venture, particularly with regard to choice of appropriate protecting groups. The target fragment **6**, which we selected for our synthetic efforts, is a triphenylphosphonium salt, as required for a (*Z*)-selective Wittig coupling with the northern hemisphere aldehyde **45**. Protection of the hydroxyl groups at C_{38}, C_{41} and C_{42} as the corresponding PMB ethers would allow for late-stage selective deprotection, prior to a regioselective macrolactonisation engaging the C_{41} hydroxyl. The hydroxyl groups at C_{35} and C_{47} would be protected as TBS ethers and the hemiacetal hydroxyl at C_{37} would be masked as the corresponding methyl acetal. It was planned that these silicon protecting groups and the methyl acetal would be removed under mild conditions in the final step of the synthesis.

A. ALDOL #7

Early work on this region of the spongistatins had established a concise route to the C_{36}-C_{46} segment, incorporating the F-ring tetrahydropyran.[18] The synthesis began in earnest with enolisation of enantiopure glycolate ketone **46**, to afford (*E*)-enolate **47** *in situ*, followed by a highly diastereoselective aldol reaction with MeCHO to provide **48** in 93% yield as the sole adduct (≥97:3 ds) by ^{1}H NMR analysis (Scheme 11).



SCHEME 11

This aldol reaction is believed to proceed *via* a chair-like transition state ***TS*-1**, in which the α-hydrogen of the boron enolate eclipses the double bond, in order to minimise A(1,3) strain (Figure 5).[19] The choice then is whether the methyl (***TS*-2**) or the *p*-methoxybenzyloxymethyl (PMBOCH$_2$-) group (***TS*-1**) is directed into the transition state, towards the aldehyde component. On steric grounds, the methyl group may be considered the more likely candidate. However, the stereochemical outcome of this aldol reaction, and many related cases, suggests that it is the PMBOCH$_2$- group which faces inwards. This contra-steric preference has been rationalised on electronic grounds, *i.e.* the disfavoured transition state ***TS*-2** may experience an unfavourable repulsion between the oxygen lone pairs of the boron enolate and the PMB ether. This unfavourable interaction would not be present in the transition state ***TS*-1** leading to the observed product **48**. More recently, Corey and co-workers have proposed the involvement of formyl hydrogen bonds to rationalise the observed stereoselectivity of processes utilising boron and non-boron Lewis acids.[20] Following these suggestions, an intramolecular hydrogen bond between the MeCHO formyl hydrogen and the β-oxygen atom of the enolate, thereby stabilising transition state ***TS*-1**, may then be invoked to rationalise the observed selectivity in the present aldol reaction.

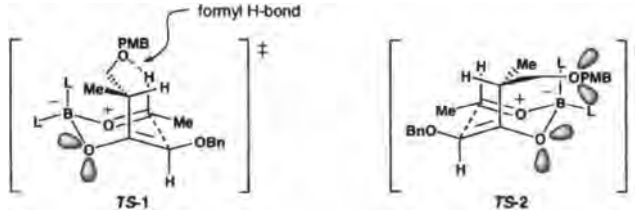


FIGURE 5. DIASTEREOMERIC TRANSITION STATES FOR GLYCOLATE ALDOL REACTION.

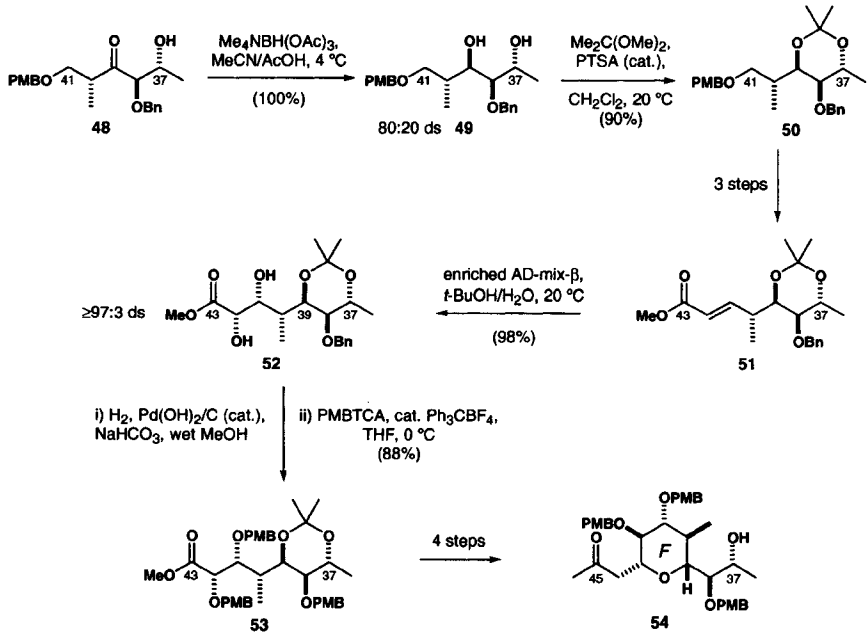
A stereoselective reduction of **48** with Me$_4$NBH(OAc)$_3$ provided the corresponding 1,3-*anti* diol **49** (80:20 ds), which was then converted to acetonide **50** (Scheme 12). Although these compounds were separable, this was more conveniently achieved at a later stage. Attempts to utilise the samarium promoted Evans-Tishchenko reduction on **48** failed to

provide useful quantities of product, presumably due to unproductive sequestration of the catalytic samarium species *via* chelation between the C_{37} alcohol and C_{38} benzyl ether moieties. Conversion of **50** to α,β-unsaturated ester **51** was achieved in three steps, involving DDQ-mediated removal of the PMB ether, oxidation with the Dess–Martin periodinane and Horner–Wadsworth–Emmons (HWE) olefination. Through synthetic manipulations on compounds in this sequence, the acid-lability of the 1,3-*trans* acetonide became apparent. Hence, transformations performed on compounds bearing this functionality had to be performed using conditions as close to neutral as possible, especially in the presence of protic solvents. Thus, removal of the PMB group from **50** was best achieved in the presence of pH 7 buffer at 0 °C and oxidation of the resultant alcohol under Swern conditions was found to be unreliable (destroying valuable material on several occasions).

B. ELABORATION TO THE F-RING

The Sharpless asymmetric dihydroxylation protocol, using enriched AD-mix-β, gave solely the desired (41*R*,42*S*)-diol **52** in 98% yield. The importance of the choice of benzyl protecting group at C_{38} is illustrated by the fact that the analogous TBS ether underwent dihydroxylation under the same conditions with markedly reduced facial selectivity (*ca.* 67:33 ds). However, the benzyl ether was an unsuitable protecting group to be carried through to the final stages of the synthesis and hence a protecting group swap was undertaken. Our synthetic strategy called for a regioselective macrolactonisation engaging the C_{41} hydroxyl of a triol *seco*-acid as the penultimate step. This allowed for a relatively simple protecting group plan, involving the use of one mode of protection for the C_{38}, C_{41} and C_{42} oxygens and the application of silyl protecting groups in other regions to be removed in the final step by global deprotection. The implementation of PMB ethers at C_{38}, C_{41} and C_{42} had a number of advantages, including their stability to acid and base used in subsequent steps and orthogonality to the silyl ethers employed elsewhere in the molecule. It was envisaged that the three-fold removal of the PMB groups would be readily effected by treatment with DDQ at a late stage, shortly prior to macrolactonisation. Potential problems we foresaw with this strategy were (i) oxidation of the silyl protected allylic alcohol moiety of the side-chain and (ii) acid-catalysed epimerisation of the sensitive CD-spiroacetal during prolonged exposure to the DDQ conditions. However, we had confidence that suitable conditions could be developed which avoided these prospective pitfalls.

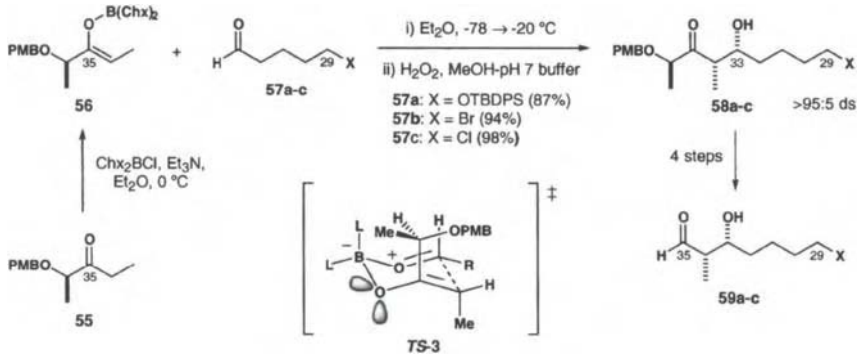
Removal of the C_{38} benzyl ether of **52** was best achieved by hydrogenolysis ($Pd(OH)_2/C$, H_2) in wet MeOH in the presence of $NaHCO_3$.[17] This added mild base was found to be necessary to avoid removal of the acetonide moiety to deliver a highly polar and useless pentaol. In one disastrous early experiment, we sacrificed a substantial amount of advanced material by premature cleavage of the acetonide due to traces of acid – this was a black day for the project indeed! Three-fold PMB protection of the resultant triol was achieved by treatment with *p*-(methoxybenzyl)-trichloroacetimidate (PMBTCA) under mild catalysis with Ph_3CBF_4, providing the *tris*-PMB ether **53** in 88% yield for the two steps. From this point, reduction to the corresponding aldehyde and HWE chain extension with dimethyl (2-oxopropyl)-phosphonate were followed by treatment with acetic acid in aqueous THF and equilibration with KOH in MeOH to yield solely the desired F-ring tetrahydropyran **54**, having all five substituents equatorially arranged.



SCHEME 12

C. ALDOL #8

At this juncture, the C_{36}-C_{46} segment **54** could, in principle, be elaborated to append the C_{47}-C_{51} side-chain or the C_{29}-C_{35} E-ring fragment, in either order. Indeed, both of these options were explored, however, due to the labile nature of the C_{47}-C_{51} side-chain, the most successful strategy involved first appending the F-ring segment then the sensitive chlorodienol side-chain. The C_{29}-C_{35} segment was rapidly constructed by utilising some suitable *syn*-aldol chemistry developed by our group (Scheme 13).[21] Treatment of lactate-derived, PMB-protected, α-hydroxy ketone **55** with Chx_2BCl/Et_3N led to selective formation of the (*Z*)-enol borinate **56**, in contrast to the (*E*)-selective enolisation obtained with the analogous benzoyl protected ketone. Reaction of **56** with aldehyde **57**, followed by oxidative workup, provided the *syn*-aldol adduct **58** in good yield (>95:5 ds). This reaction is believed to proceed *via* transition state ***TS*-3**, where the PMB ether and enolate oxygens are directed away from each other and the methyl group is outside. Four further steps were then required to arrive at the desired aldehyde **59**, ready for aldol coupling with the F-ring subunit.



SCHEME 13

Initial work involved the functionalisation of C_{29} as a TBDPS ether (as in **59a**). However, this proved to be incompatible with our overall approach. An alternative, and somewhat more direct strategy involved the incorporation of a halogen at C_{29} from the outset. This was expected to be entirely compatible with subsequent steps, conveniently undergoing transformation into the corresponding triphenylphosphonium salt at a later stage. Initially, the bromide **59b** was chosen and indeed was found to be admirably compatible with the ensuing chemistry. However, during

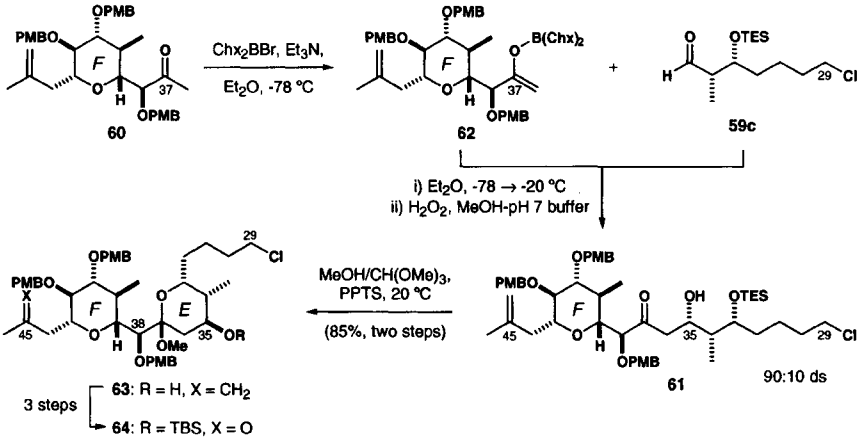
prolonged exposure of a subsequent intermediate to conditions involving TBSCl and imidazole in DMF, significant halide exchange was observed to yield inseparable Br/Cl mixtures. Although this was not a terminal problem for the synthesis plan, it did unnecessarily complicate the interpretation of characterisation data. Utilisation of the corresponding chloride **59c** from the beginning, removed these complications and was readily converted into the desired phosphonium salt, *via* the iodide, at a later stage.

D. ALDOL #9

The aldol reaction to unite ketone **60**, available from **54** by Petasis olefination and oxidation at C_{37}, with aldehyde **59c** proved a highly challenging task (Scheme 14). Earlier model studies of the Mukaiyama aldol reaction of aldehyde **59c** with simple lactate-derived silyl enol ethers had demonstrated a strong preference for Felkin-Anh induction from the aldehyde. This preference was also exhibited to varying extents in the reaction of aldehyde **59c** with boron, tin and lithium enolates. The application of these methods to the coupling of the highly oxygenated ketone **60** and aldehyde **59c** failed to deliver any of the desired compound **61**. The lithium-mediated aldol reaction was the only variant to deliver any aldol adduct, and this was found to be the undesired diastereomer, in the opposite sense to Felkin-Anh attack on aldehyde **59c**. Given the numerous successes of boron enolates in the coupling of complex fragments, we were disappointed by the failure of Chx_2BCl/Et_3N conditions to provide any desired aldol adduct, resulting solely in recovery of starting materials. Several attempts were made to effect the desired transformation using Chx_2BCl under a variety of conditions, none of which led to the formation of the desired aldol adduct. However, when recourse was made to the use of the more reactive Chx_2BBr in this procedure, success was had at last!

Treatment of ketone **60** with Chx_2BBr/Et_3N in Et_2O at –78 °C led to smooth enolisation to give **62**, which was followed by reaction with aldehyde **59c** to provide aldol adduct **61** as the major diastereomer (90:10 ds). Provided that recently prepared (<2 weeks old), high quality Chx_2BBr was used, this procedure reproducibly delivered the desired aldol adduct at a variety of scales. Acid-promoted desilylation (PPTS, MeOH, $(MeO)_3CH$) was accompanied by formation of the E-ring as a methyl acetal **63**, and at this stage separation of the small amount of C_{35} epimeric compound was readily achieved. Three straightforward steps then provided the C_{29}-C_{46} methyl ketone **64**, ready for introduction of the

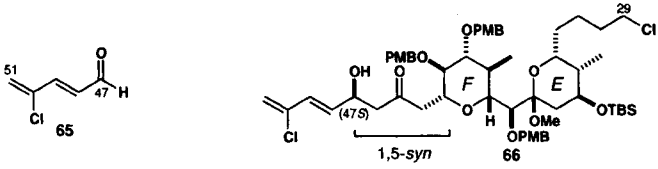
remaining elements of the side-chain. It took considerable time, effort and persistence to achieve the synthesis of the C_{29}-C_{46} subunit **64**, but once a path had been cleared, the chemistry was found to be robust and readily allowed for the production of significant quantities of advanced material for the southern hemisphere.



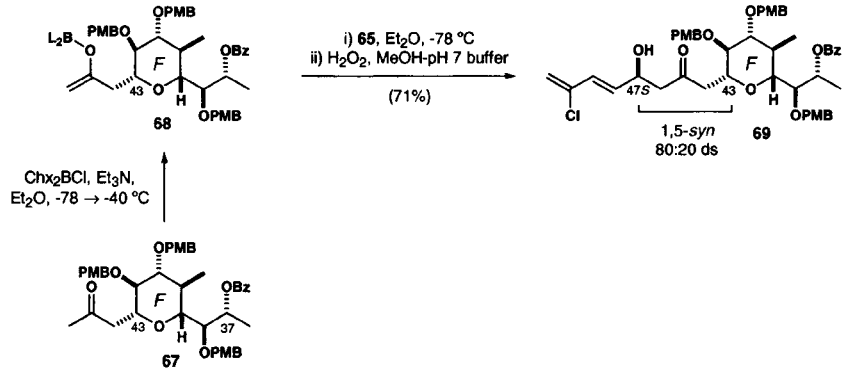
SCHEME 14

E. ALDOL #10

The final aldol reaction used in our synthesis of spongistatin 1 was one of the more remarkable reactions of this type our group has witnessed over the years. The aldol union of ketone **64** with (*E*)-4-chloro-2,4-pentadienal **65** required the creation of the (47*S*) stereochemistry in the resultant alcohol **66**. Formally, this would require 1,5-*syn* induction from the ketone **64**, which is opposite to that observed previously for boron aldol reactions with simple β-alkoxy methyl ketones. However, ketone **64** is densely packed with stereocentres, and predicting the influence of these remote centres on the reaction outcome was not possible with any degree of certainty. It was hoped that should **64** display undesirable 1,5-*anti* bias, this may be overturned by appropriate choice of Ipc ligands on boron.



Model studies related to this aldol coupling involved the reaction of F-ring ketone **67** with aldehyde **65**. Enolisation with Chx_2BCl to produce **68**, and aldol reaction with **65** provided adduct **69** in 71% yield, following oxidative workup, as the major diastereomer (80:20 ds) by ^1H NMR analysis (Scheme 15). Furthermore, this substrate-based stereocontrol could be reinforced by the use of (+)-Ipc_2BCl to increase the reaction diastereoselectivity to 91:9 ds. These results were very encouraging, not only were we able to effect aldol reaction with the sensitive aldehyde **65**, but we appeared to have a good chance for inducing the desired configuration at C_{47} for the spongistatin side-chain. Once the full C_{29}-C_{46} fragment **64** became available, it was time to move away from model studies and onto the "real thing!"

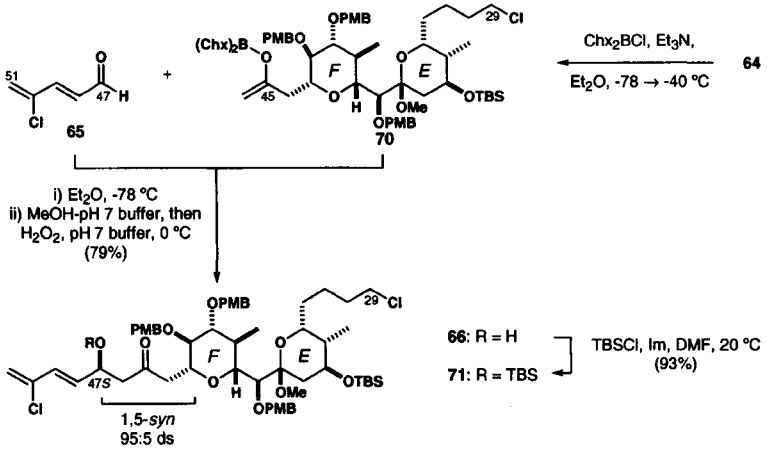


SCHEME 15

The lithium aldol reaction between ketone **64** and aldehyde **65** was successful at providing moderate quantities of a *ca.* 1:1 mixture of **66** and its undesired C_{47} epimer, which were readily separable by TLC and flash chromatography. With TLC samples of these two aldol adducts at hand, ketone **64** was subjected to Chx_2BCl/Et_3N resulting in clean formation of enol borinate **70** which was exposed to an excess of **65** (Scheme 16). Analysis of the reaction mixture by TLC clearly showed the disappearance of ketone **64** accompanied by appearance of aldol adduct **66** and minute amounts of undesired C_{47} epimer. Such a clearly efficient and selective reaction caused great excitement! However, elation turned to despair when, after a standard oxidative workup, none of the desired aldol adduct could be isolated. Clearly the oxidative workup was at fault once again and was to be avoided. The reaction between **64** and **65** was repeated, this time placing the reaction mixture directly on a silica column. In this instance, the aldol adduct **66** was isolated in 73% yield

with excellent selectivity (95:5 ds) for the 1,5-*syn* product. The level and direction of stereocontrol observed in this reaction was a very welcome surprise, and could not have been planned beforehand, and reflects how great an influence remote stereocentres can have in boron-mediated aldol reactions.

The material provided by this initial reaction was sufficient to explore some further chemistry, but soon there was a need for more. Repetition of the procedure resulted in highly variable results. In some cases, the aldol adduct was afforded in significant yield, while in several other cases little or none of **66** was isolated. On one of these anguishing occasions, the column fractions seen to contain **66** were noticed to visibly darken and become cloudy as solvent was removed *in vacuo*. Analysis of these samples by ^{1}H NMR showed broad signals related to regions of **66** but no sign of the desired product itself. In another instance, an evaporated column fraction thought to contain **66** was seen to slightly fume when bench-grade CH_2Cl_2 was added to it! In despairing of ever persuading this key reaction to reproducibly yield **66**, it was tempting to dismiss these observations as illusory, conjured up by a weary mind. However, it seemed most likely that the silica workup of the reaction was proving insufficient at breaking down the intermediate boron aldolate and/or boronic acid related impurities were co-eluting with the desired product and then destroying it upon concentration.



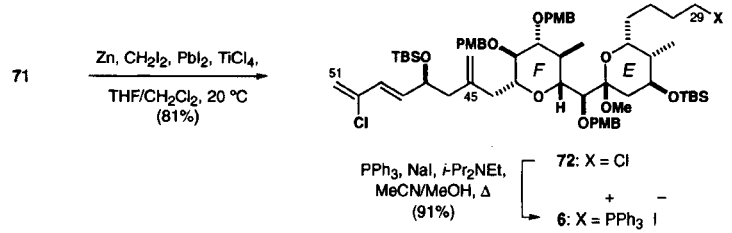
SCHEME 16

A re-evaluation of the oxidative workup procedure was warranted in the current instance. Although this method had failed previously, it was reasoned that a carefully controlled oxidative workup may result in a

more robust and reliable procedure. Gratifyingly, a protocol was rapidly developed that provided a consistently high yield of the desired aldol adduct **66**. This involved very careful control of the quantity of H_2O_2 used, and the way in which it was introduced to the reaction mixture. Utilising this procedure, it was possible to reproducibly obtain the desired aldol adduct in good yield (79%), and maintaining excellent 1,5-*syn* selectivity (95:5 ds). Protection of allylic alcohol **66** as the corresponding TBS ether was best performed by brief exposure to TBSCl and imidazole in DMF, providing **71**, which was much more stable towards storage than **66**.

F. EF-SUBUNIT: THE FINAL STEPS

Methylenation of the carbonyl function within **71** was required and model studies on related compounds had suggested that the Petasis olefination was unsuitable in this case. The modified methylenation procedure of Takai[22] was found to be more productive. However, once again we encountered problems of reproducibility. In this case, the quality of the zinc metal used was found to be absolutely crucial to the success of the reaction. Zinc powder which had been purified according to standard procedures was found to be unsatisfactory. The most reliable method for activating the zinc, prior to formation of the Takai methylenating reagent was treatment of a suspension of the zinc in THF with an aliquot of TMSCl, followed by removal of the THF solution and successive washes of the zinc with fresh THF. When this procedure was adhered to the desired methylenation product **72** was obtained in reproducibly high yields (81%). The final step, in preparation for the Wittig coupling with the northern hemisphere aldehyde **45**, involved the direct conversion of **72** into phosphonium salt **6** by heating with PPh_3 in the presence of NaI (Scheme 17).[17]



SCHEME 17

VII. Wittig Coupling of the Northern and Southern Hemispheres

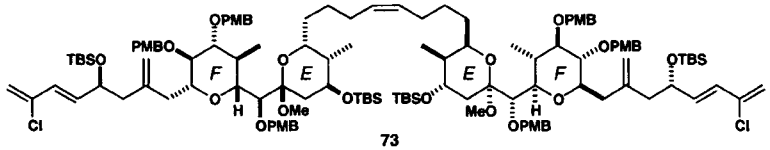
Significant effort was expended on model studies of the crucial ABCD + EF Wittig coupling step. This work not only provided a means for testing this strategy with regard to effectiveness and level of (*Z*)- double bond selectivity, but equally important was the development of practical methods for conducting this step. Initial model studies involving the Wittig coupling of E-ring phosphonium salts with simple aldehydes failed to give synthetically viable quantities of the desired alkene products under standard conditions (LHMDS, THF). The weak colourations observed in the ylide formation step suggested that adventitious water was having a deleterious effect on the reaction, despite best efforts to avoid any traces of moisture in the system. This may have been largely due to the hygroscopic nature of the phosphonium salt, but was likely exacerbated by the extremely small scale at which these reactions were being performed. Two possible desiccants were examined as *in situ* scavengers of water. Perhaps unsurprisingly, 4Å molecular sieves were ineffective in this role, whereas powdered calcium hydride was found to be uniquely effective. A model Wittig coupling between an E-ring phosphonium salt and EtCHO which proved unproductive under standard conditions, provided the desired alkene in 80% yield when CaH_2 was incorporated into the reaction medium. From this point, our confidence in completing the total synthesis grew steadily.

A. DELAYED DEPARTURE

Having spent a productive three year period of laboratory work associated with this project, it was nearing time for MJC to write-up his PhD thesis and move on to other things. It was proposed that the major component of this thesis writing should be performed in Australia, and so a non-refundable, no date changes, airline ticket had been purchased for the trip well ahead of time, it being a difficult thing to procure flights of this type at an affordable student price. However, there was such momentum with the work with recent breakthroughs, that at this point all parties agreed that more time was needed to crack the last few problems. So as the original airline ticket passed its date and became void, another one was secured for a later date and the toughest leg of the spongistatin journey was undertaken.

Extension of the *in situ* CaH_2 method to the Wittig reaction of more complex model compounds, on ever smaller quantities of material, led progressively to the formation of C_{16}-C_{39} (CDE), C_1-C_{39} (ABCDE) and

C_1-C_{46} (ABCDEF) spongistatin substructures, all accompanied by excellent selectivity (>95:5) for the required (*Z*)-alkene. Despite the psychological boost afforded by producing these large structures, the yields obtained in these more complex situations were lower than desired (14-32%). Nevertheless, with great anticipation the Wittig coupling of the fully-functionalised, C_{29}-C_{51} phosphonium salt **6** with aldehyde **45** was attempted. To our great disappointment, utilisation of the above Wittig coupling procedure, with *in situ* CaH_2, failed to provide any of the desired product. Indeed, a significant quantity (24%) of an undesired by-product **73** was obtained. Ylides which do not contain stabilising α-substituents are well known to react rapidly with molecular oxygen, to afford symmetrical alkenes by autoxidative self-condensation, presumably *via* the intermediacy of the corresponding aldehyde. Hence, the presence of adventitious oxygen appeared to be the latest evil to be combated.

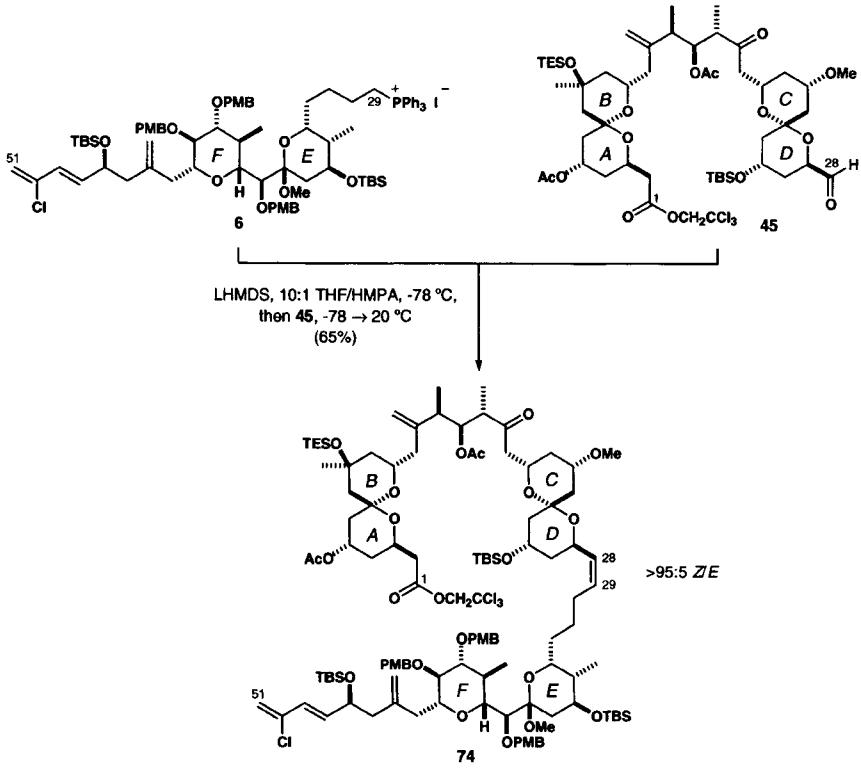


73

In order to conserve precious quantities of the full C_{29}-C_{51} phosphonium salt **6**, a model E-ring compound was once again utilised. A freeze-pump-thaw protocol was utilised in an effort to degas the phosphonium salt solution and aldehyde **45** prior to their attempted union. Under these conditions, exasperatingly, the corresponding E-ring alkene dimer, resulting from oxygen-induced autoxidative dimerisation, was produced in near quantitative yield!

At this point, so much effort had been expended on exploring the use of this Wittig coupling methodology that supplies of the model phosphonium salts had been exhausted. In a brave (or perhaps foolish) move, a modification to the previous Wittig procedure was attempted on the fully-functionalised components, phosphonium salt **6** and aldehyde **45** (Scheme 18). Firstly, an elaborate attempt was made to prevent the introduction of oxygen into the reaction medium. A second modification to the Wittig procedure was the use of HMPA as a co-solvent for the reaction. The decision to use HMPA was based upon the success of Nicolaou and co-workers in their coupling of two complex fragments, *via* Wittig reaction with HMPA as co-solvent, in their synthesis of brevetoxin B.[23] Despite the risks associated with changing two variables at the same time and performing the reaction on valuable "front-end" material, we

were confident we had a much greater understanding of the important factors in this crucial Wittig coupling step.



SCHEME 18

Encouragingly, under these new conditions (LHMDS, THF/HMPA), phosphonium salt **6** yielded an intensely orange-coloured ylide solution. After introduction of aldehyde **45**, the resultant mixture was warmed to 0 °C whereupon it turned blood red in hue. These heartening signs were first observed on a wintry Friday evening in Cambridge and were soon reinforced by promising TLC evidence. After a rapid workup and a column conducted with bated breath and barely contained excitement, a quick trip to the NMR spectrometer uncovered those two joyous, greatly anticipated alkene signals at *ca.* 5.5-5.8 ppm, along with all the other complexities associated with the ABCD and EF portions of the molecule brought into intimate association. As was customary for the Paterson group on a Friday night, most of them, including the leader, were relaxing in the local pub (The Panton Arms). So the single page A3 printout of the

^{1}H NMR spectrum for **74** was proudly taken directly to the Panton, resulting in a spontaneous celebration. Although somewhat stained by its use as a beer mat that night, this long sought-after NMR spectrum is still preserved as a memento of that important breakthrough. It may not yet have been the natural product, but **74**, which represented the fully protected *seco*-acid of spongistatin 1, could now be reliably produced in 60-65% yield (>95:5 *Z*/*E*). Given the efforts we had made to ensure a concise endgame we were now truly on the home stretch.

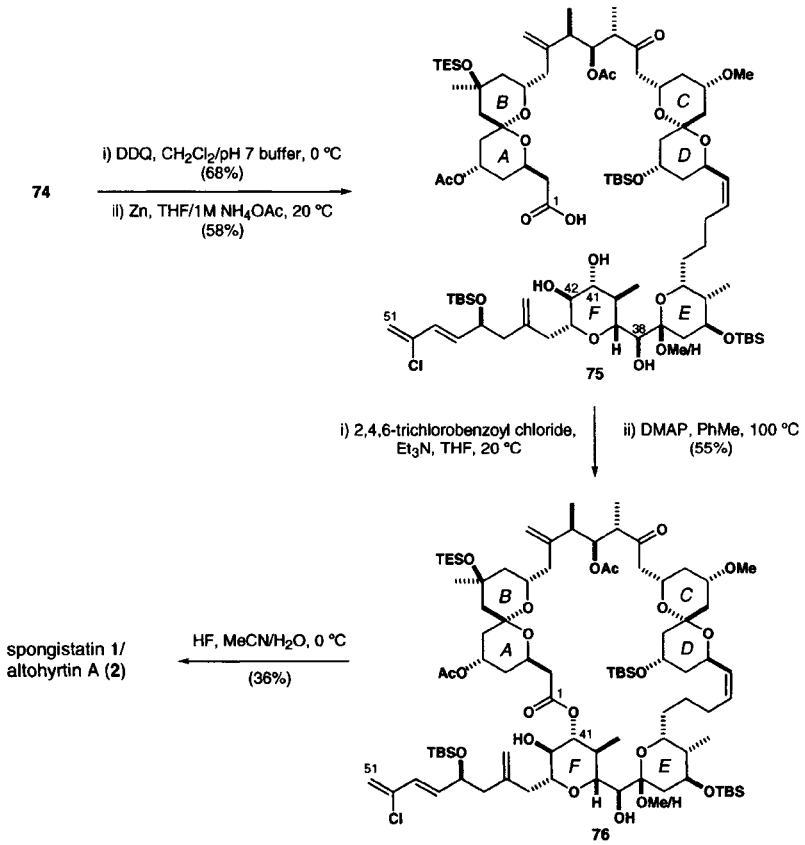
VIII. Final Steps

With the fully protected *seco*-acid **74** of spongistatin 1 in hand, all that remained to complete the total synthesis was removal of the PMB ether and trichloroethyl ester protecting groups, regioselective macrolactonisation and global deprotection. The DDQ-mediated removal of the three PMB groups in **74** turned out to be relatively trouble-free, involving brief exposure to an excess of DDQ in the presence of pH 7 buffer (Scheme 19). This accomplished the smooth removal of all three PMB groups without effecting the sensitive chlorodienol side-chain or CD-spiroacetal subunits. Partial hydrolysis of the E-ring methyl acetal to the corresponding hemiacetal was unavoidable, but of little consequence as the mixture was able to be taken through the remaining steps of the synthesis. Exposing the C_1 carboxylic acid was achieved by treatment with zinc powder in THF/1M NH_4OAc to yield the *seco*-acid **75**.

A. THE FINAL COUNTDOWN

With the clock ticking down to a flight from Heathrow (in time for MJC to celebrate Christmas 2000 in Australia) and very little material available (<1 mg), the macrolactonisation step was pursued. Due to the extremely small scale involved, monitoring the reaction progress by TLC was found to be impossible. After a slow (7 hour) addition of the anhydride to the refluxing DMAP solution (in C_6H_6), TLC analysis of the concentrated mixture was not encouraging. Attempts to purify the crude mixture by micro-scale flash chromatography were made difficult due to the large excess of 2,4,6-trichlorobenzoyl chloride related by-products. Exhaustive analysis of column fractions by ^{1}H NMR (500 MHz, C_6D_6) revealed a component which appeared to correspond with the desired macrocycle **76**. Further purification of this heavily contaminated macrocyclic component by HPLC was found to be difficult. The

compound did not appreciably absorb at 254 nm, the typical wavelength used for HPLC analysis. Presumably the UV spectral characteristics of **76** are similar to that of spongistatin 1, λ_{max} (MeOH) = 216 nm. Detection at these shorter wavelengths prohibits the use of EtOAc mixtures as eluent. In the event, purification of the crude macrocyclic component by HPLC (10:90 *i*-PrOH/hexanes, detection at 220 nm) was not successful. Regardless, the mixture was subjected to global deprotection conditions in the hope that a small sample of spongistatin 1 could be obtained.



SCHEME 19

Exposure of **76** to HF in H_2O/MeCN for 20 hours was followed by a short microscale flash column. Analysis by ^1H NMR spectroscopy (500 MHz, CD_3CN, 16 hours) of the global deprotection product showed it to be a complex mixture, however there were some encouraging signals. Purification of this mixture was attempted by HPLC-MS (25:75

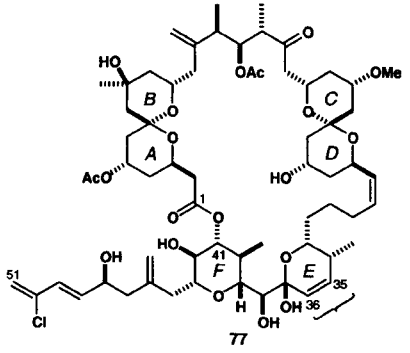
H_2O/MeOH). It was with great excitement that a peak was observed (R_t 13 minutes) with strong ions at m/z 1245.6 ($[M + Na]^+$, 100) and 1240.1 ($[M + NH_4]^+$, 23). This component was collected and analysed by high field ^1H NMR, once again requiring >16 hours of acquisition to observe the important signals, heavily swamped by impurities. Unfortunately, the HPLC had not been overly successful, probably due to overloading of the analytical scale column, but some characteristic signals were evident. Although not conclusive at the time, this close match of partial data from ^1H NMR spectra provided tantalising evidence that the preceding steps resulted in the formation of a small quantity (50 micrograms at best) of our first crop of synthetic spongistatin 1 (**2**).

At this point, the revised departure date for MJC had arrived, and although it was tempting for him to remain longer and resolutely tie down the total synthesis, it was time to move on, and write up his thesis. The well-poised project passed into the capable hands of David Chen, as the final member of the "spongi team". A typically impressive solo effort from David at this late stage resulted in many improvements in the final steps of the synthesis, accomplished over the first few months of 2001. Together with the prior development of robust, highly scaleable routes to the individual subunits, this now allowed the generation of significant quantities (ca. 15 mg) of spongistatin 1, allowing its complete characterisation (including a stunning 800 MHz NMR spectrum, as well as the first pristine ^{13}C NMR to be obtained on synthetic material), and enabling the biological testing of this much sought after anticancer agent to be resumed. Indeed, some of our synthetic spongistatin was provided to Prof. Pettit at the Cancer Research Institute in Arizona to allow further preclinical evaluation. However, this was not quite the end of the "spongi" tale of ten aldols.

B. SYNTHETIC SPONGISTATIN ANALOGUES - "SPONGILOGUES"

An important advantage afforded by the synthesis of natural products is the access this provides to structurally diverse analogues, enabling the establishment of structure-activity relationships (SAR). Little is known about the spongistatins in this regard. Our synthesis rapidly provided access to two novel "spongilogues" which have proven valuable as SAR probes.[24] The E-ring dehydrated compound **77** was afforded as a minor (and, at the time, unwanted) by-product of the final aqueous HF induced deprotection step. The side-chain truncated compound **78** was obtained from Wittig coupling of a C_{29}-C_{46} phosphonium salt with northern hemisphere aldehyde **45**, followed by deprotection, macrolactonisation

and global deprotection steps. Illustrated in Table 1 are the results of growth inhibition experiments for paclitaxel/Taxol (**79**), synthetic spongistatin 1 (**2**), E-ring dehydrated analogue **77** and side-chain truncated analogue **78**.



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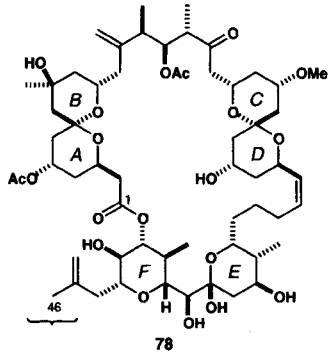

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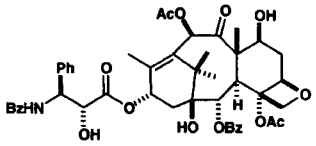

79: paclitaxel/Taxol

In all cases, **2** was found to be substantially more active (6- to 2000-fold) than paclitaxel (**79**), and was particularly effective against the MIP101 cell line, indicating that it is a poor substrate for the P-glycoprotein (Pgp) drug efflux pump. Given the already exceptional cytotoxicity displayed by **2**, we were surprised and delighted to observe that the E-ring dehydrated analogue **77** was generally (2- to 4-fold) more potent than the parent natural product. Analogue **77** had low picomolar IC_{50} values, in the range 0.007-0.08 nM, against this set of cancer cell lines. This indicates that the C35 hydroxyl of **2** is unnecessary for biological activity, and that its removal leads to an increase in potency. In contrast, the dramatic attenuation of cytotoxicity for analogue **78**, against all cell lines employed in these assays (*e.g.* 0.587 and 0.407 μM against the MIP101 and HCT116 colon carcinoma cell lines), reveals that the C_{47}-C_{51} chlorodiene allylic alcohol moiety is an essential structural feature. These results suggest that the full C_{44}–C_{51} triene side-chain is a crucial part of the spongipyran pharmacophore.

TABLE I
GROWTH INHIBITION AGAINST HUMAN CANCER CELL LINES

IC_{50} values (nM)	**79**	**2**	**77**	**78**
MIP101 colon (Pgp-1 overexpressing)	200	0.1	0.08	587
HCT116 colon	0.3	0.05	0.02	407
1A9PTX22 ovarian (mutation in β-tubulin)	47	0.03	0.007	> 632
1A9 ovarian (parental)	1	0.03	0.007	> 632
A549 non-small cell lung	6	0.07	0.04	> 632

IX. Conclusions

This total synthesis adventure advanced our knowledge of factors influencing the stereochemical outcome of complex aldol coupling steps and other reactions, and also resulted in better understanding of the criteria for selecting appropriate tactics and strategies for complex natural product synthesis. Overall, our synthetic route to **2** proceeds in 33 steps and 1.0% yield for the longest linear sequence. With respect to material output, valuable quantities of synthetic spongistatin 1/altohyrtin A were obtained (approximating to the 2.4 tons of the initial sponge collection required for isolating the natural product), enabling further biological evaluation of these remarkable anti-cancer compounds. Additionally, by using the developed methodology, two novel spongistatin analogues were synthesised and tested for growth inhibition against human tumour cell lines, providing invaluable SAR data to help define the pharmacophore.

The "spongi" journey was at times a bumpy and frustrating one, but nevertheless wholly rewarding to all involved. Once more, Charles Dickens' *A Tale of Two Cities* has a poignant passage in this regard:

"Unsettled weather, a long journey, uncertain means of travelling, a disorganised country, a city that may not be even safe for you."

"My dear Charles," said Mr. Lorry, with cheerful confidence, "you touch some of the reasons for my going: not for my staying away."

Acknowledgements

The work described in this chapter would not have been possible without the tireless efforts and experimental skill of the following people (the "spongi" team): José Luis Aceña, Jordi Bach, David Chen, Karl Gibson, Andrew Hodgson, Linda Keown, Roger Norcross, Renata Oballa, Thomas Trieselmann, Debra Wallace.

References and Footnotes

1. a) Pettit, G. R., Chicacz, Z. A., Gao, F., Herald, C. L., Boyd, M. R., Schmidt, J. M., Hooper, J. N. A., *J. Org. Chem.* **1993**, *58*, 1302; b) Pettit, G. R., Cichacz, Z. A.,

Gao, F., Herald, C. L., Boyd, M. R., *J. Chem. Soc., Chem. Commun.* **1993**, 1166; c) Pettit, G. R., Herald, C. L., Cichacz, Z. A., Gao, F., Schmidt, J. M., Boyd, M. R., Christie, N. D., Boettner, F. E., *J. Chem. Soc., Chem. Commun.* **1993**, 1805; d) Pettit, G. R., Herald, C. L., Cichacz, Z. A., Gao, F., Boyd, M. R., Christie, N. D., Schmidt, J. M., *Nat. Prod. Lett.* **1993**, *3*, 239; e) Pettit, G. R., Cichacz, Z. A., Herald, C. L., Gao, F., Boyd, M. R., Schmidt, J. M., Hamel, E., Bai, R., *J. Chem. Soc., Chem. Commun.* **1994**, 1605; f) Bai, R., Chicacz, Z. A., Herald, C. L., Pettit, G. R., Hamel, E., *Mol. Pharmacol.* **1993**, *44*, 757; g) Pettit, R. K., McAllister, S. C., Pettit, G. R., Herald, C. L., Johnson, J. M., Chicacz, Z. A., *Int. J. Antimicrob. Agents* **1998**, *9*, 147; h) Bai, R., Taylor, G. F., Chicacz, Z. A., Herald, C. L., Kepler, J. A., Pettit, G. R., Hamel, E., *Biochemistry* **1995**, *34*, 9714.

2. a) Kobayashi, M., Aoki, S., Sakai, H., Kawazoe, K., Kihara, N., Sasaki, T., Kitagawa, I., *Tetrahedron Lett.* **1993**, *34*, 2795; b) Kobayashi, M., Aoki, S., Kitagawa, I., *Tetrahedron Lett.* **1994**, *35*, 1243; c) Kobayashi, M., Aoki, S., Sakai, H., Kihara, N., Sasaki, T., Kitagawa, I., *Chem. Pharm. Bull.* **1993**, *41*, 989; d) Kobayashi, M., Aoki, S., Gato, K., Kitagawa, I., *Chem. Pharm. Bull.* **1996**, *44*, 2142.
3. Fusetani, N., Shinoda, K., Matsunaga, S., *J. Am. Chem. Soc.* **1993**, *115*, 3977.
4. a) Evans, D. A., Coleman, P. J., Dias, L. C., *Angew. Chem. Int. Ed.* **1997**, *36*, 2738; b) Evans, D. A., Trotter, B. W., Cote, B., Coleman, P. J., *Angew. Chem. Int. Ed.* **1997**, *36*, 2741; c) Evans, D. A., Trotter, B. W., Cote, B., Coleman, P. J., Dias, L. C., Tyler, A. N., *Angew. Chem. Int. Ed.* **1997**, *36*, 2744.
5. a) Guo, J., Duffy, K. J., Stevens, K. L., Dalko, P. I., Roth, R. M., Hayward, M. M., Kishi, Y., *Angew. Chem. Int. Ed.* **1998**, *37*, 187; b) Hayward, M. M., Roth, R. M., Duffy, K. J., Dalko, P. I., Stevens, K. L., Guo, J., Kishi, Y., *Angew. Chem. Int. Ed.* **1998**, *37*, 192.
6. For a review, see: Pietruszka, J., *Angew. Chem. Int. Ed.* **1998**, *37*, 2629.
7. Three other groups have completed spongistatin/altohyrtin total syntheses: a) Smith, A. B., III, Zhu, W., Shirakami, S., Sfouggatakis, C., Doughty, V. A., Bennett, C. S., Sakamoto, Y., *Org. Lett.* **2003**, *5*, 761 and references therein; b) Crimmins, M. T., Katz, J. D., Washburn, D. G., Allwein, S. P., McAtee, L. F., *J. Am. Chem. Soc.* **2002**, *124*, 5661; c) Prof. C. H. Heathcock, personal communication.
8. Synthetic studies towards the spongistatins have been reported by the following groups: Anderson, Barrett, Boyes, Hoffmann, Ley, Mead, Nakata, Paquette, Roberts, Roush, Samadi and Vogel.
9. a) For a review of asymmetric aldol reactions using boron enolates, see: Cowden, C. J., Paterson, I., *Org. React.* **1997**, *51*, 1; b) For a theoretical treatment of the mechanistic basis of stereoinduction in the aldol reactions of chiral boron enolates with aldehydes using transition state computer modelling, see: Bernardi, A., Gennari, C., Goodman, J. M., Paterson, I., *Tetrahedron: Asymmetry* **1995**, *6*, 2613 and references cited therein.
10. a) For full details on the asymmetric aldol reactions of enol diisopinocampheylborinates, see: Paterson, I., Goodman, J. M., Lister, M. A., Schumann, R. C., McClure, C. K., Norcross, R. D., *Tetrahedron* **1990**, *46*, 4663; b) Paterson, I., Oballa, R. M., Norcross, R. D., *Tetrahedron Lett.* **1996**, *37*, 8581; c) Paterson, I., Oballa, R. M., *Tetrahedron Lett.* **1997**, *38*, 8241; d) Paterson, I., Wallace, D. J., Oballa, R. M., *Tetrahedron Lett.* **1998**, *39*, 8545.

11. a) Jadhav, P. K., Bhat, K. S., Perumal, P. T., Brown, H. C., *J. Org. Chem.* **1986**, *51*, 432; b) Brown, H. C., Randad, R. S., Bhat, K. S., Zaidlewicz, M., Racherla, U. S., *J. Am. Chem. Soc.* **1990**, *112*, 2389.
12. Paterson, I., Goodman, J. M., Isaka, M., *Tetrahedron Lett.* **1989**, *30*, 7121.
13. Paterson, I., Wallace, D. J., Gibson, K. R., *Tetrahedron Lett.* **1997**, *38*, 8911.
14. a) Paterson, I., Gibson, K. R., Oballa, R. M., *Tetrahedron Lett.* **1996**, *37*, 8585; b) Evans, D. A., Coleman, P. J., Côté, B., *J. Org. Chem.* **1997**, *62*, 788.
15. Paterson, I., Collett, L. A., *Tetrahedron Lett.* **2001**, *42*, 1187.
16. Paterson, I., Coster, M. J., *Tetrahedron Lett.* **2002**, *43*, 3285.
17. Paterson, I., Chen, D. Y.-K., Coster, M. J., Aceña, J. L., Bach, J., Gibson, K. R., Keown, L. E., Oballa, R. M., Trieselmann, T., Wallace, D. J., Hodgson, A. P., Norcross, R. D., *Angew. Chem. Int. Ed.* **2001**, *40*, 4055.
18. Paterson, I., Keown, L. E., *Tetrahedron Lett.* **1997**, *38*, 5727.
19. Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
20. Corey, E. J., Barnes-Seeman, D., Lee, T. W., *Tetrahedron Lett.* **1997**, *38*, 4351 and references therein.
21. a) Paterson, I., Wallace, D. J., Velazquez, S. M., *Tetrahedron Lett.* **1994**, *35*, 9083; b) Paterson, I., Wallace, D. J., *Tetrahedron Lett.* **1994**, *35*, 9087; c) Paterson, I., Wallace, D. J., *Tetrahedron Lett.* **1994**, *35*, 9477; d) Paterson, I., Wallace, D. J., Cowden, C. J., *Synthesis* **1998**, 639.
22. Takai, K., Kakiuchi, T., Kataoka, Y., Utimoto, K., *J. Org. Chem.* **1994**, *59*, 2668.
23. Nicolaou, K. C., Rutjes, F. P. J. T., Theodorakis, E. A., Tiebes, J., Sato, M., Untersteller, E., *J. Am. Chem. Soc.* **1995**, *117*, 10252.
24. Paterson, I., Aceña, J. L., Bach, J., Chen, D. Y.-K., Coster, M. J., *Chem. Commun.* **2003**, 462.

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STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 9

THE RING-CLOSING METATHESIS APPROACH TO FUMAGILLOL

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I. Introduction

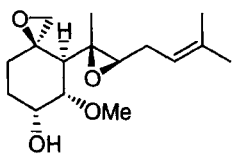
Although olefin metathesis has been used for many years in the polymer industry, the lack of defined catalytic species and harsh conditions of the reaction had long prevented its use in total synthesis. With the advent of very active and chemoselective, well-defined catalysts derived from ruthenium or molybdenum, things have changed dramatically and, in the last years, the Ring-Closing Metathesis reaction (RCM) has become widely accepted as one of the major tools available to the synthetic organic chemist. Rarely has a new reaction had such a deep impact on the design of synthetic routes. The modern Ru- and Mo-based catalysts will only react with olefinic double bonds or with carbon-carbon triple bonds and are inert toward many functions normally considered to be highly reactive. For example, successful RCMs are possible with substrates containing carbonyl groups (including aldehydes), hydroxyls, or even carboxylic acids. On the other hand, if several double or triple bonds are present in the substrate molecule, side reactions may be a problem and the synthesis has to be planned accordingly. Another striking difference with other major synthetic methods is the rapidity with which

metathesis was adopted in total synthesis, despite the fact that, at the present time, mechanistic aspects of the reaction remain imperfectly known. It can even be said that, at least in part, the current knowledge about RCM has been gained "the hard way ", i.e. through failed synthetic approaches based on this reaction. In our laboratory, we became interested in the RCM reaction as a useful means for preparing several classes of biologically active molecules. One of the most successful applications of RCM in our laboratory has been the synthesis of fumagillol and fumagillin analogs.

II. The synthesis of fumagillol.

A. Introduction

Esters of fumagillol (**1**), a complex sesquiterpenic alcohol, exhibit a broad range of biological activities. The naturally-occurring fumagillin (**2**) which was discovered in 1951[1] and synthesized in the racemic form by Corey et al. in 1972,[2] has long been known for its antibiotic and antiparasitic properties. Unfortunately, toxic side effects have limited its use to veterinary medicine and, until a few years ago, it might have seemed strange to devote important research efforts to the synthesis of fumagillin analogs.



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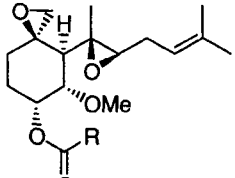

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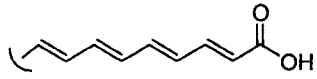

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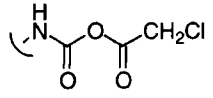


Things changed in the 90's, after Folkman et al. showed fumagillin to be a potent inhibitor of angiogenesis,[3] suggesting potential benefits in the

antitumor and antiinflammation areas. From the ensuing studies, aimed at identifying more active and safer analogs of fumagillin, TNP-470 (**3**) emerged as a promising candidate for the treatment of cancer. This potential is currently being examined both in preclinical and clinical studies.

Until recently, however, essentially all fumagillin analogs were obtained by semisynthesis involving hydrolysis of fumagillin to fumagillol and modification of the 6-hydroxyl group (esterification by various carboxylic acids,[4] conversion to amines and derivatives[5]) or modification of the spiroepoxide.[6] (Figure 1).

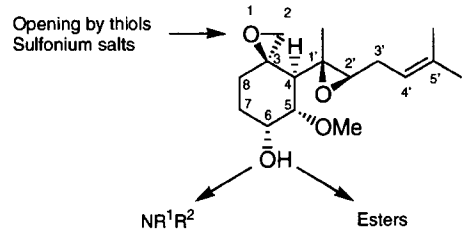
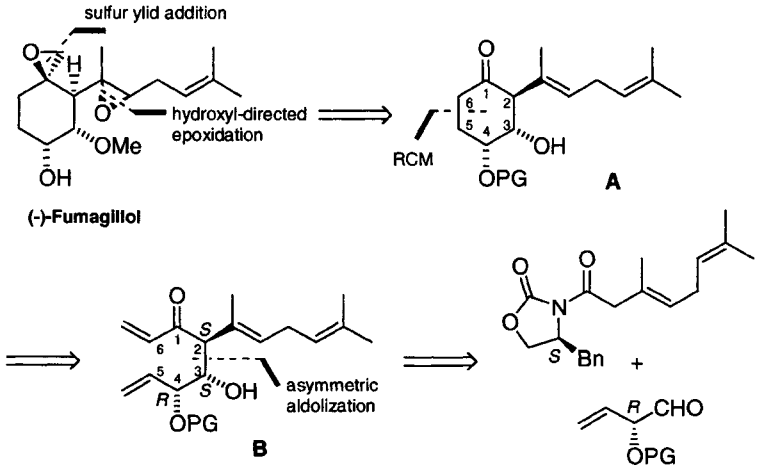


FIG. 1

The mode of action of fumagillin began to be clarified in 1997 when two groups independently reported this molecule's covalent binding to, and irreversible inhibition of, methionine aminopeptidase II (MetAP-2). Following this finding, comparison of enzyme inhibition and effects on angiogenesis was done. Using a limited number of analogs, a good correlation between the degree of inhibition of MetAP-2 and antiangiogenic activity was observed.[7,8] Shortly afterwards, the X-ray structure of the human MetAP-2 / fumagillin complex was reported, providing important information about the nature of the interaction between fumagillin and the enzyme. In particular, the irreversible inhibition was shown to be the result of an attack of His 321 in MetAP-2 on the spiroepoxide of fumagillin with formation of a covalent bond.[9] Knowledge of the biological target of fumagillin led to a renewal of interest from medicinal chemists. When we initiated our research in October 1998 and apart from Corey's work in 1972, only one synthesis of (–)-fumagillin had been reported,[10] to be compared with four syntheses during the following three years.[11-14]

B. RETROSYNTHESIS

While our first aim was to develop a new synthesis of fumagillol, we also wanted the synthesis to be usable for accessing certain new fumagillin analogs. We specifically targeted the C7-C8 part of the molecule (see Figure 1) which, upon inspection of the published X-ray structure of the human MetAP-2 / fumagillin complex, seemed to be important for the protein/ligand interaction. This "left part" of the molecule bears no functional group and is not accessible through semisynthesis. As a result, no fumagillin analogs modified at C7 or C8 were known.



SCHEME 1

For some time, we had been successfully using the ring-closing metathesis (RCM) reaction for accessing highly functionalized molecules and this was the starting point of our retrosynthetic analysis shown in Scheme 1. Inspection of the literature suggested that the conversion of a synthetic intermediate like **A** to fumagillol would not pose major problems. A key disconnection in **A** between carbon atoms C5 and C6 (corresponding to C7 and C8 in fumagillol) led to the dienic ketone **B**. We also recognized that absolute and relative stereochemistries at carbon atoms C2, C3 and C4 in **B** could in principle be readily obtained through

the well precedented Evans asymmetric aldolization, using boron enolates and protected 2-hydroxy-but-3-enal. The product of the RCM would be an α,β–unsaturated ketone which could be converted to a wide variety of fumagillol / fumagillin analogs.

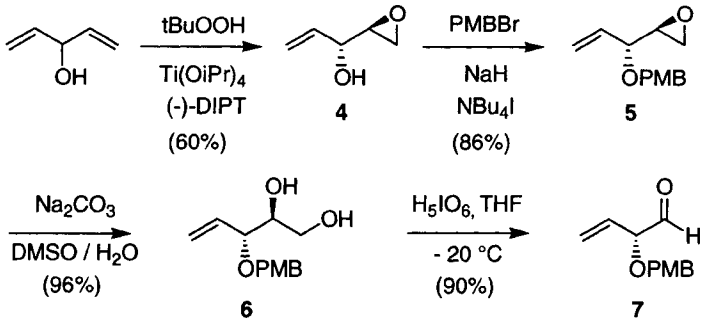
C. SYNTHESIS

With the general strategy of the synthesis being established, we turned our attention to its practical implementation and we felt that certain elements deserved a particular attention:

* The starting aldehyde was expected to be particularly sensitive and prone to conjugation as reported for racemic 2-(*tert*-butyl-dimethyl-silanyloxy)-but-3-enal.[15] In our case, racemization was an additional problem.
* No asymmetric synthesis of 2-hydroxy-but-3-enal or derivatives was known.
* The Evans reaction, involving β,γ-unsaturated oxazolidinones and β,γ-unsaturated aldehydes was unprecedented (but, according to the literature, Evans aldolizations of α-alkoxyaldehydes worked well).[16]
* There was only one reported example of successful RCM involving an α,β-unsaturated ketone.[17] RCM of α,β-unsaturated esters was known to be difficult unless special conditions, possibly not applicable to ketones (the addition of Lewis-acids), were used.[18-20]

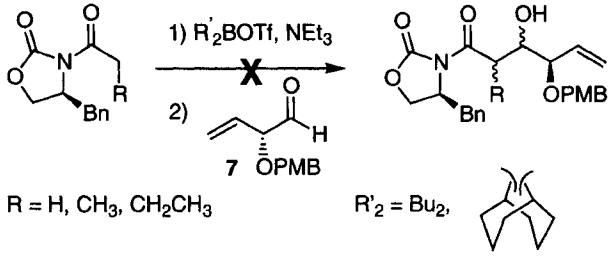
The required aldehyde was prepared in four steps from divinylcarbinol as shown in Scheme 2.

While the known desymmetrization of divinylcarbinol[21,22] by asymmetric Sharpless epoxidation worked well, introduction of the PMB group (which was chosen for its mild removal conditions) required the use of the unstable, non-commercially available PMB bromide (using the commercially available but less reactive PMB chloride, in presence of NaH, led to Payne rearrangement).



SCHEME 2

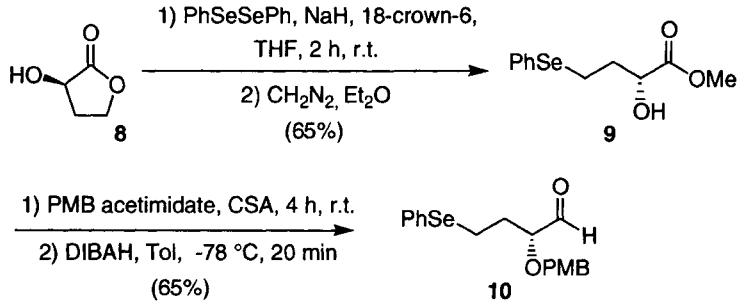
Epoxide opening proceeded uneventfully but the fourth step proved to be tricky. After some experimentation we found that cleavage of the diol by periodic acid proceeds well at low temperature but, unfortunately, and as expected, the resulting aldehyde proved to be extremely sensitive: chromatography over silica gel consistently led to partial migration of the olefinic double bond. The same happened upon removal of solvents if bath temperature was allowed to exceed 40 °C. We managed, however to obtain the desired aldehyde (7) reasonably pure, on a 100 mg scale, by working at low temperature and limiting purification to a rapid filtration through a silica gel pad. It was obvious at that point that the method would be very difficult to apply to larger scale syntheses. Nevertheless, keeping this in mind, we turned our attention to the Evans reaction. In order not to accumulate difficulties, we decided to start our studies with simple models. To our disappointment, all attempts to couple aldehyde **7** with the boron enolates of simple 3-acyl-4-benzyl-oxazolidin-2-ones failed completely (Equation 1).[23]



(1)

Although we did not try to analyze the reason for these failures, the fact that the starting oxazolidinones were recovered unchanged in each case suggests that the sensitive aldehyde cannot tolerate the reaction conditions and gets destroyed before it has a chance to react in the desired way.

We attributed the failure of the reaction to the presence of an unstable deconjugated system and thought that, perhaps, protection of the double bond during the Evans aldolization might help solving the problem. It appeared to us that aldehyde **10** perfectly fulfilled our requirements: it should withstand the Evans aldolization conditions yet the phenylselenenyl group should be easy to remove afterwards. This aldehyde was synthesized as shown in Scheme 3.



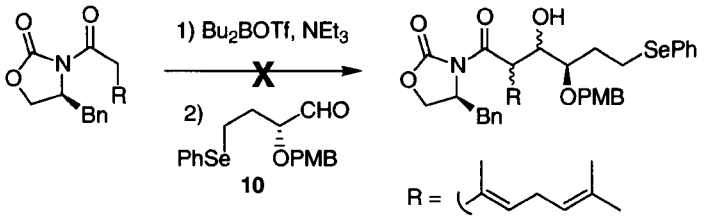
SCHEME 3

In our initial attempts, opening of (*R*)-(+)-α-hydroxybutyrolactone was effected using the system PhSeSePh / $NaBH_4$, in DMF at high temperature.[24] Under these conditions, however, reproducibility was a problem and much better and consistent results were obtained using non-complexed sodium PhSeNa (prepared from PhSeSePh and NaH), in THF, at room temperature. Treatment with CH_2N_2 cleanly afforded the stable ester **9** whose reduction again posed problems: while the reaction proceeded in high yield as judged by TLC and NMR, we obtained erratic results when measuring the optical rotation of the compound. The reaction was carefully monitored and the culprit was identified: usual workup conditions for DIBAL reductions recommend the controlled hydrolysis of aluminium-containing intermediates to a gel which can be filtered. We found aldehyde **10** to be extremely sensitive to these work up conditions, undergoing time-dependent racemization with measured α_D's

ranging from + 30° to + 6°! Reverting to a more classical work up (low temperature addition of MeOH, then addition of brine and extraction with cyclohexane) allowed us to keep racemization at an acceptable level. Using these conditions, the aldehyde was reproducibly obtained in good yield, with an acceptable 77 % ee (as measured by ^{1}H-NMR using the chiral shift reagent Eu(hfc)$_3$), the corresponding α_D being + 50°.

In view of the well-documented successful Evans aldolization of α-alkoxyaldehydes, we were very surprised and disappointed by the negative results observed when attempting to couple **10** with an oxazolidinone as shown in Equation 2.

In contrast to what we observed in our experiments using **7**, the starting oxazolidinone was not recovered. The products of the reaction were not identified, but did not correspond to the expected adducts. It is likely that the oxidative work up, necessary for cleaving B-O and B-C bonds is not compatible with the selenide function. However, we could not find evidence of the (desired) olefinic elimination products that could have been expected.



(2)

At this point, the experience gained from the first part of our work was summarized.

* We knew that α-alkoxy-β,γ-unsaturated aldehydes were not suitable for Evans condensations
* We could prepare α-alkoxy-γ-phenylselenenyl aldehydes as "stable" equivalents of α-alkoxy-β,γ-unsaturated aldehydes but their reaction with boron enolates did not lead to the expected condensation products, probably due to inadequate work up conditions.

It became clear that we had reached a dead end and that our strategy needed to be modified. Considering the time and amount of work invested up to now, however, we were reluctant to drastically change our original approach and looked for alternatives which would allow us to capitalize on our results.

It is known that, besides the boron enolates most commonly used because they lead to excellent yields and ee's, several other types of enolates can be used in Evans type condensations. Among these, lithium enolates looked particularly attractive: they are easily prepared and they react with aldehydes in good yield and with good enantioselectivity. Furthermore, they do not require an oxidative work up which, in our case appeared to be a key advantage.

Evans type aldolizations using boron or lithium enolates are mechanistically different. Although both reactions lead predominantly to 2,3-*syn*-aldols, the enantioselectivities are inverted i.e. whereas in our original strategy (*S*)-oxazolidinones lead to the desired 2(*S*), 3(*S*) aldols, the same result via lithium enolates requires switching to (*R*)-oxazolidinones. This change of selectivity has been explained by differing complexation patterns in boron and lithium enolates as shown in Figure 2.[25,26]

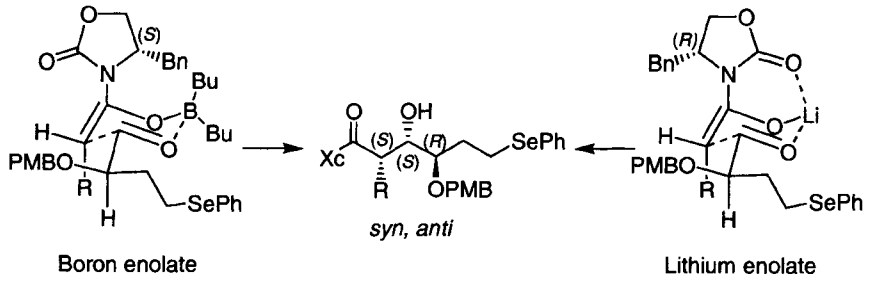
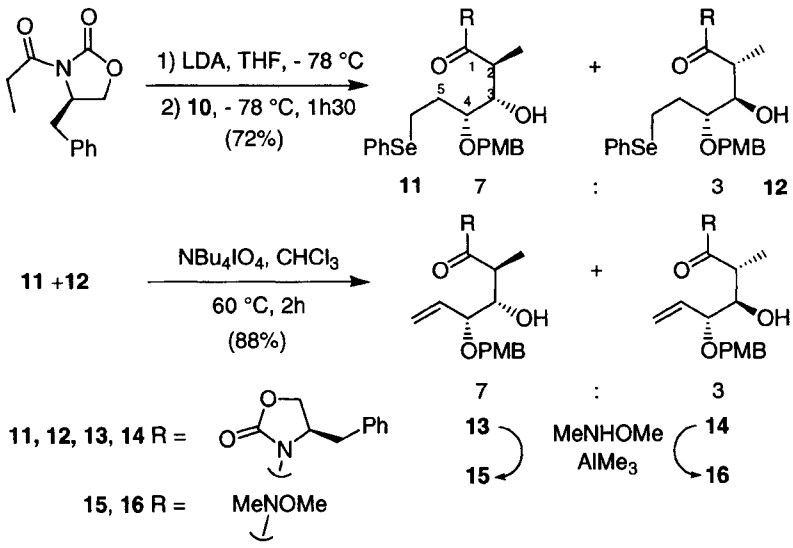


FIG. 2

Once again the first experiments were performed on a simple model using lithiated (*S*)-3-propionyl-4-benzyl-oxazolidin-2-one and aldehyde **10**. To our delight, the reaction afforded in good yield a 7 : 3 mixture containing two adducts which could not be separated at this stage. Although the selectivity of the reaction was rather poor, the most

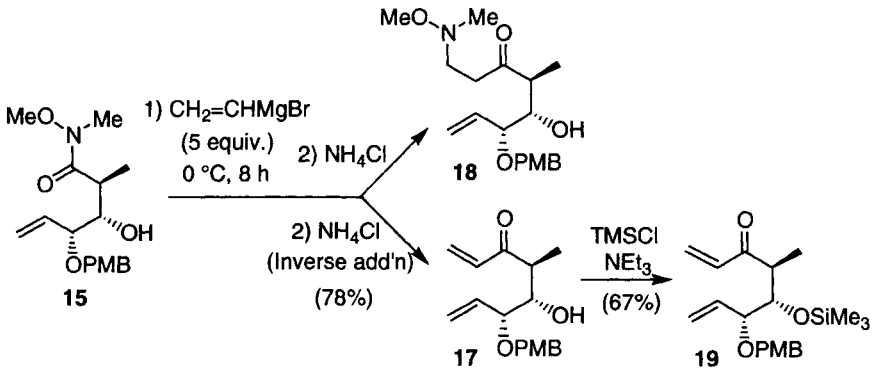
important thing was to firmly establish the relative and absolute stereochemistries at C2 and C3 in the adducts and to confirm that the major adduct indeed had the (2*S*, 3*S*, 4*R*) desired configuration. To this effect, we decided not to try to optimize the model reaction as this would not necessarily be transposable to the preparation of fumagillol itself and we decided to proceed directly to the next steps of the synthesis (Scheme 4). After some experimentation, we found that clean oxidative elimination of phenylselenenic acid occurred upon treatment with NBu_4IO_4 under anhydrous conditions. In contrast, using H_2O_2 as oxidizing agent led to several poorly identified products, with one of them clearly resulting from opening of the oxazolidinone ring. These results may in part explain our failure when using boron enolate chemistry with **10**. The two oxazolidinones **13** and **14** could then easily be separated and treated with *N,O*-dimethyl-hydroxylamine / $AlMe_3$ to afford the corresponding Weinreb amides.



SCHEME 4

Inspection of the NMR spectra of amides **15** and **16** revealed coupling constants $J_{H2,\ H3}$ = 4.2 and 5.2 Hz, respectively, indicative of a *syn* relationship between H2 and H3.[27] At this point we made the (reasonable)

bet that **13** was the right isomer and this compound was selected for the rest of our model studies. Cleavage of the Weinreb amide **15** proceeded well provided that two conditions were respected. Fresh solutions of vinylmagnesium bromide had to be used (otherwise significant amounts of aldehyde, resulting from reduction of the Weinreb amide were obtained) and quenching had to be done by inverse addition of the reaction mixture to a saturated NH_4Cl solution (otherwise the β-aminoketone **18** was obtained quantitatively) (Scheme 5).



SCHEME 5

With **17** now readily available, we proceeded to the key RCM reaction. Our first results, using Grubbs's catalyst **[Ru]-b** (see Scheme 6) were not encouraging as cyclization products were obtained in only 11 % yield along with unidentified material. Addition of $Ti(OiPr)_4$ (to disrupt the potential stable ruthenium chelate) (Figure 3) did not improve the yield and led to the formation of decomposition products.

The solution to the problem was found when the free alcohol **17** was converted to the corresponding trimethylsilylether **19** (Scheme 5), prior to RCM. The cyclization then proceeded smoothly, in the presence of $Ti(OiPr)_4$ (30 mol%) to afford cyclohexenone **23** in good yield. The reaction was repeated using the methyl ether **21** with similar results. Finally, catalytic hydrogenation of cyclohexenone **24** afforded model compound **25**. Inspection of the NMR data indicated a large (J = 11 Hz) coupling between H2 and H3, and a small (J = 2.4 Hz) coupling between

H3 and H4, respectively, characteristic of *trans*-diaxial and *cis*-relationships, thus confirming the assumed structure of **13**.

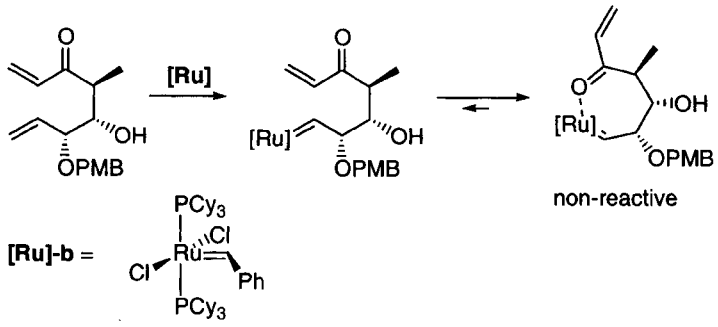
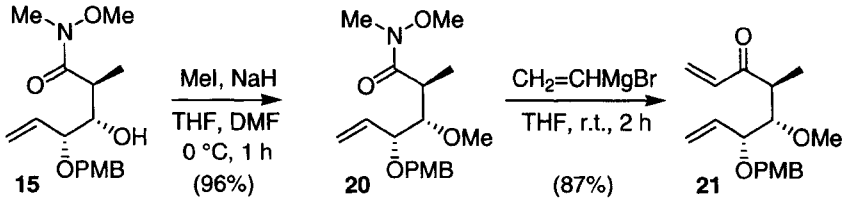
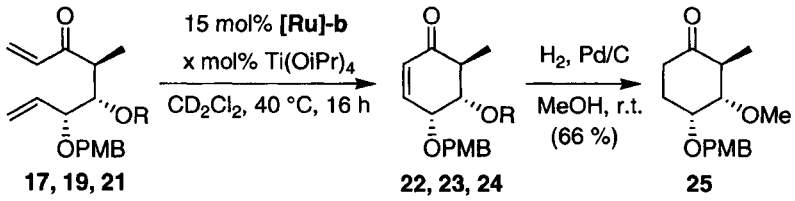


FIG. 3

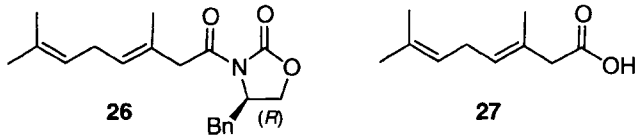




Cpd #	17, 22	17, 22	19, 23	21, 24
R	H	H	$SiMe_3$	Me
x mol% $Ti(OiPr)_4$	0	30	30	30
Yield (%)	11	11	77	59

SCHEME 6

The remaining steps for conversion to the fully functionalized cyclohexane found in fumagillol would consist in the precedented stereoselective formation of the spiroepoxide and the removal of the PMB group. Considering these steps as trivial, we turned our attention to the synthesis of fumagillol itself. Our synthetic plan now required the synthesis of the (*R*)-oxazolidinone **26** and its precursor *trans*-isogeranic acid **27** (Figure 4).

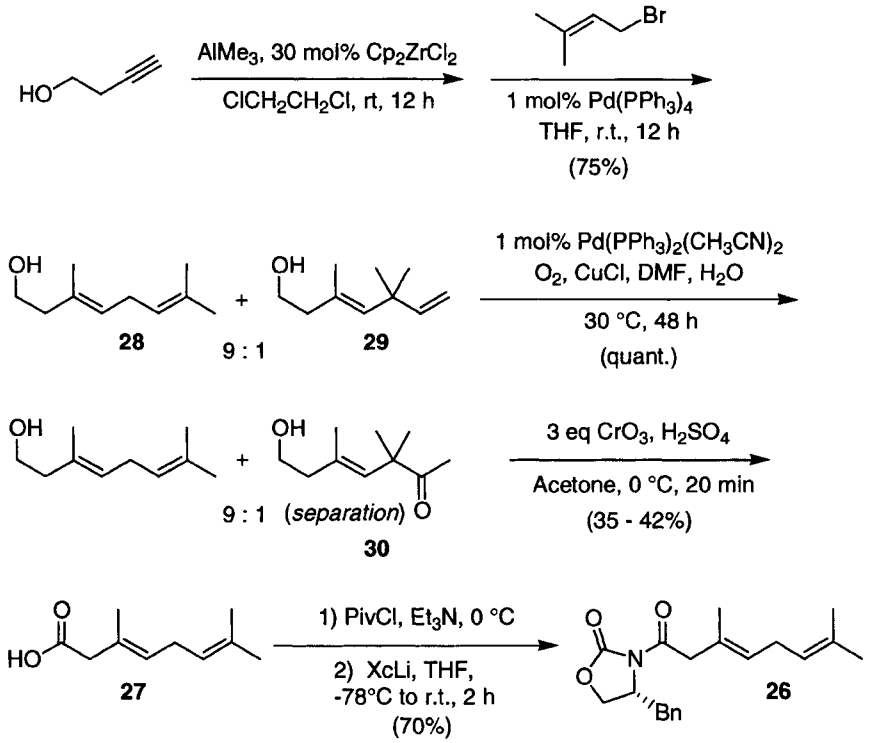


26 **27**

FIG. 4

Curiously, although *E*:*Z* mixtures of isogeranic acid had been prepared long ago,[28] no synthesis of pure *trans*-isogeranic acid had been published prior to our work. In addition, inspection of the literature revealed that isogeraniol, a logical synthetic precusor of isogeranic acid had been rarely prepared and only by complex, non-specific routes. This required us to develop our own synthesis of *trans*-isogeranic acid shown in Scheme 7.

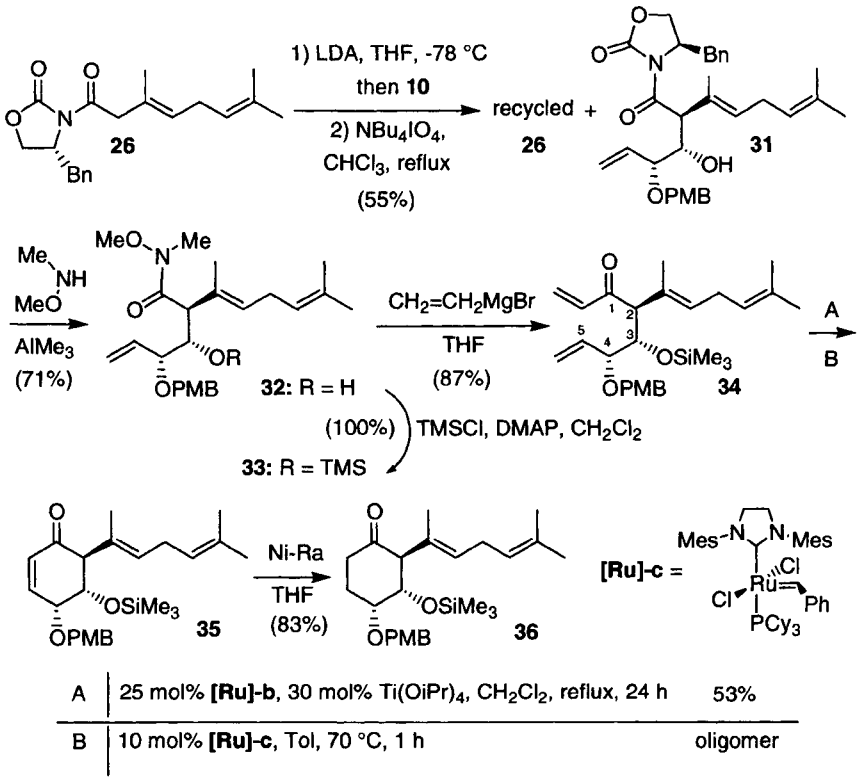
The synthesis deserves a few comments. The first step of the sequence is a Negishi coupling between homopropargylic alcohol and 1-bromo-3-methyl-but-2-ene. The reaction works well, and the amount of palladium complex required for the coupling can be decreased to as low as 1 mol%, thus allowing the reaction to be applicable to the synthesis of multigram quantities of isogeraniol. However, in addition to isogeraniol **28**, we always observe the formation of ca. 10 % of the unwanted isomer **29**. This was a major problem as **28** and **29** could not be separated from each other, using a variety of methods. The solution was finally found by exploiting the sensitivity of the Wacker reaction to steric effects: it is known that the reaction will readily convert terminal olefines to methyl ketones while internal olefinic double bonds react much more sluggishly if at all. Accordingly, the mixture **28** + **29** was treated under Wacker conditions. **29** was quantitatively converted to the ketone **30** which could be easily separated from unchanged **28**.



SCHEME 7

The best temperature for the reaction was found inadvertently: 3 months after we successfully prepared our first batch of isogeraniol, more compound was needed but, to our dismay, we were unable to repeat our earlier experiments. After much unsuccessful experimentation, the PhD student involved in the project realized that the first preparation had been done in summer, when room temperature easily reaches 30 °C in the laboratory as opposed to November, when it does not exceed 20 °C. He then carried out the reaction at 30 °C and we were delighted to see the reaction progressing smoothly as before and in a reproducible way. Why the reaction does not proceed at all at lower temperatures remains unclear. Finally, the oxidative step needed to be carefully controlled but afforded the desired (smelly) isogeranic acid in good overall yield. Using the above, simple method, *trans*-isogeraniol could be prepared in 40 g batches, which were converted to *trans*-isogeranic acid **27**, then

oxazolidinone **26** as needed. Our next task was to prepare appreciable quantities of the key intermediate substituted cyclohexanone **36** (Scheme 8).



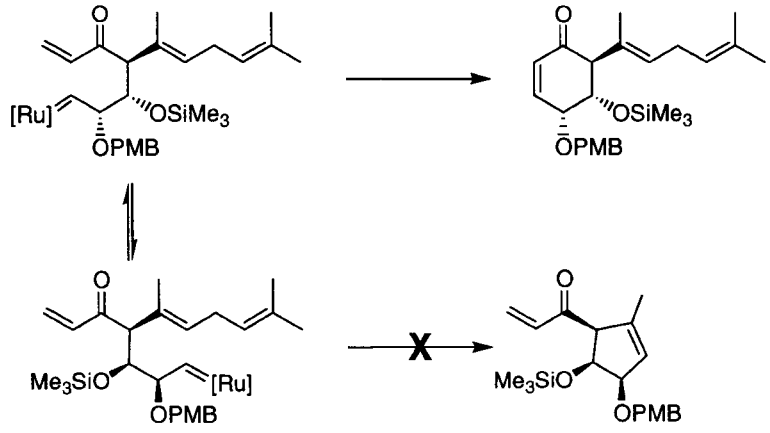
SCHEME 8

In the first step, leading directly to the deselenylated aldol product **31**, Evans aldolization was followed by treatment of the reaction mixture with NBu_4IO_4 to effect the oxidative removal of the phenylselenenyl group. Significant differences between this sequence and our previous model studies were observed.

Despite numerous attempts, only partial conversion of the oxazolidinone to the aldol product occurred and the yield of aldol products could not be raised above 55 %. A welcome difference was the isolation of only one aldol isomer as compared to the 7:3 ratio obtained in

the model study (of course, we assumed that this aldol was indeed the desired isomer)! Another positive point is the possibility of partially recovering and recycling the unreacted valuable oxazolidinone **26**. Conversion of **31** to the Weinreb amide **32** proceeded cleanly using the conditions established earlier (see Scheme 4).

We knew from our model studies that the metathesis step only worked well when the 3-hydroxy group in the ketone precursor was protected. Accordingly, the Weinreb amide **32** was first converted quantitatively to the corresponding trimethylsilyl ether **33**. Formation of the methyl ether found in fumagillol at this point was discarded because, at some point, a free OH group would be needed for directed epoxidation of the 1', 2' olefinic double bond (see Figure 1 and Scheme 1). Treatment of **33** with vinyl magnesium bromide afforded the α,β-unsaturated ketone **34** in excellent yield, which was submitted to RCM conditions. Using the "1st generation" Grubbs's catalyst **[Ru]-b** in the presence of $Ti(OiPr)_4$, an optimized yield of 53% of cyclohexenone **35** was obtained. Although this yield is not excellent, the reaction is clean and, very importantly, we were relieved to see that one of our points of concern proved to be unjustified. In the triolefin **34** there are two options for the initial ruthenium carbene (presumably formed on the electron rich but less hindered olefinic double bond) to react (Scheme 9) and there was no literature precedent which would have allowed us to predict with certainty which, of the electron-poor, non hindered, vs. electron rich, trisubstituted double bonds would react preferentially.

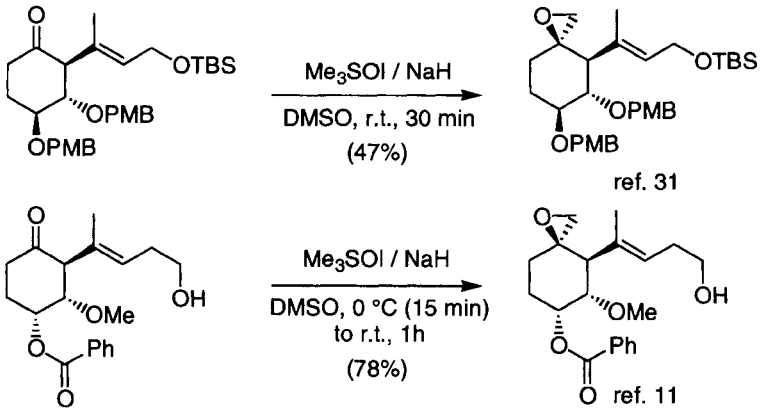


SCHEME 9

In an effort to improve the yield of the RCM, we tried using the "2nd generation" Grubbs's catalyst **[Ru]-c**, which had just become commercially available. We found that the catalyst was not compatible with $Ti(OiPr)_4$. When the Lewis acid was omitted we observed a rapid disappearance of the starting material with formation of unidentified polymeric material.

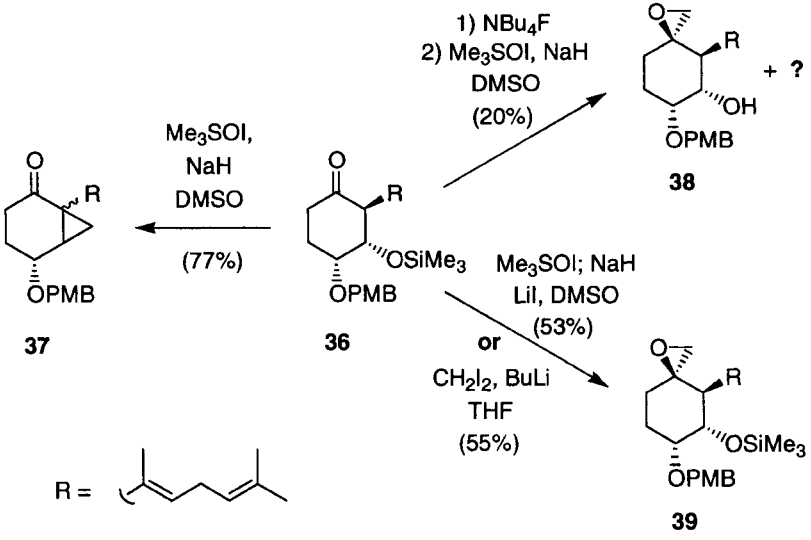
Finally, the conjugated double bond in cyclohexenone **35** was cleanly reduced by Raney nickel to provide cyclohexanone **36** in excellent yield.[29]

Our next task was the introduction of the spiroepoxide function. Epoxides are classically prepared from ketones by action of sulfonium or sulfoxonium ylides.[30] More specifically, in our case, dimethylsulfoxonium methylide, known to transfer methylene in an equatorial fashion, was the reagent to use.[31] However, considering the presence of a β-leaving group (the TMSO group) in substrate **36**, we were initially concerned by the basic character of sulfoxonium ylides. At this stage of the work, a new report of fumagillin synthesis[11] and the first synthesis of FR65814,[32] a compound closely related to fumagillin had appeared. In both cases the epoxide was installed without problems using dimethylsulfoxonium methylide (Scheme 10). This led us to be fairly confident in the feasibility of our approach.



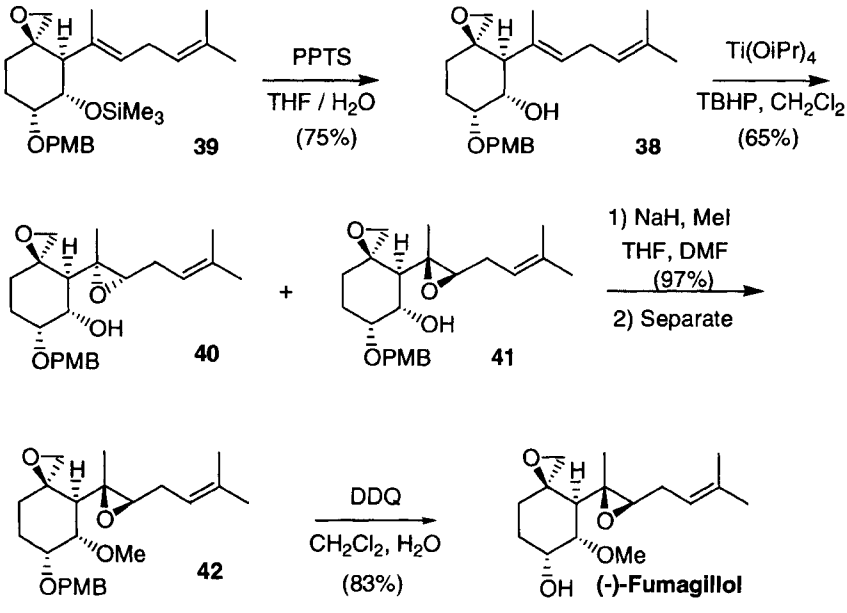
SCHEME 10

In fact, in our first experiments, just what we feared happened: treatment of ketone **36** by dimethylsulfoxonium methylide provided in good yield cyclopropylketone **37** obviously resulting from β-elimination of the TMSO- group and cyclopropanation of the resulting α,β-unsaturated ketone by excess ylide. Similar observations were independently made by Simpkins et al. during their synthesis of fumagillin.[14] In an effort to minimize β-elimination, the TMSO- group was converted back to the corresponding alcohol. No cyclopropylketone was formed but the desired epoxide **38** was only obtained in an unacceptable (20 %) yield, along with unidentified impurities. We then examined the effect of adding metal salts in the medium. In particular, we were pleased to find that addition of LiI allowed the epoxidation yield to be raised to 53 %. We have no firm rationale to propose that would explain this effect: could Li^+ form a complex with the naked sulfoxonium ylide, thus reducing its basicity? In retrospect, we think that luck played an important role, but whatever the reason, the yield of the spiroepoxide became comparable to those reported in similar cases.[11, 31] Epoxidation could also be carried out using the CH_2I_2 / BuLi system ("ICH_2Li").[33] The yields were similar to those obtained by the sulfoxonium ylide / LiI method. These experiments are summarized in Scheme 11.



SCHEME 11

Everything was now set for the final stages of our fumagillol synthesis which are shown in Scheme 12. Following the cleavage of the trimethylsilylether in **39** to the corresponding alcohol **38**, which was best effected under acidic conditions,[34] we proceeded to the directed epoxidation of the 1', 2' double bond. There were literature precedents describing the regio- and stereoselective epoxidation of the 1,4-dienic side chain by catalytic $VO(acac)_2$ / tBuOOH,[35] in similar – but not identical – fumagillol precursors.[12, 32] In our case, however, while the reaction proceeded with complete regioselectivity, there was a total lack of stereoselectivity, leading to a 1:1 mixture of (1'*R*, 2'*R*) and (1'*S*, 2'*S*) isomers with a conversion that did not exceed 50 %. The best conditions for this epoxidation turned out to be the use of stoechiometric $Ti(OiPr)_4$ / tBuOOH.[35] This led to complete, 100 % regioselective but still non-stereoselective conversion of **38** to an inseparable mixture of (1'*R*, 2'*R*) (**40**) and (1'*S*, 2'*S*) (**41**) isomers obtained in 65 % yield. The two last steps, methylation of the free hydroxyl group (the two methyl ethers became easily separable by chromatography) and removal of the PMB group, proceeded without further problem, to afford fumagillol and definitely confirming the – until that stage only assumed – configuration of aldol **31**.



SCHEME 12

D. CONCLUSION

When we initiated our work at the end of 1998, the X-ray structure of the human MetAP-2 / fumagillin complex had just been published. This had triggered the interest of several research groups, besides ours, and one might have assumed that the field would be very competitive. It was, indeed, if one considers only the "declared" aim: the synthesis of fumagillol (or fumagillin). As a result, several excellent syntheses of fumagillol / fumagillin have been published in the last five years. On the other hand, despite its relatively small size, the fumagillol molecule is heavily functionalized and can be retrosynthetically analyzed in many different ways leading to as many potential synthetic approaches each with its own advantages. Our synthesis was designed to target a specific part (the C7-C8 area) of the fumagillin structure for modification and, in this respect, proved to be extremely useful.[36] Finally, despite the many adaptations that needed to be done as the synthesis proceeded, the original retrosynthetic analysis, which had to confront itself with "real" bench chemistry, survived, not undamaged but still alive.

Acknowledgments

This work would not have been possible without the involvement of two exceptional graduate students: Dr. Jean-Guy Boiteau and Vincent Rodeschini. We are very grateful to them for their high degree of expertise, their motivation and commitment. We are sure that the few periods of doubt have been rapidly forgotten in view of the final, very positive outcome of their work. We also thank our colleagues, Drs. Didier Lenouen and Stéphane Bourg for their competent help with difficult NMR problems. Finally, we are very grateful to the French Centre National de la Recherche Scientifique (CNRS) and Galderma R&D, for cosponsoring of this project and for fellowships to J-G. B and V. R.

References and Footnotes

1. Elbe, T. E., Hanson, F. R. *Antibiot. Chemother.* **1951**, *1*, 54.
2. Corey, E. J., Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.
3. Ingber, D., Fujita, T., Kishimoto, S., Sudo, K., Kanamaru, T., Brem, H., Folkman, J. *Nature* **1990**, *348*, 555.
4. Marui, S., Itoh, F., Kozai, Y., Sudo, K., Kishimoto, S. *Chem. Pharm. Bull.* **1992**, *40*, 96.
5. Marui, S., Kishimoto, S. *Chem. Pharm. Bull.* **1992**, *40*, 575.
6. Marui, S., Yamamoto, T., Sudo, K., Akimoto, H., Kishimoto, S. *Chem. Pharm. Bull.* **1995**, *43*, 588.

7. Sin, N., Meng, L., Wang, M. Q. W., Wen, J. J., Bornmann, W. G., Crews, C. M. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 6099.
8. Griffith, E.C., Su, Z., Turk, B. E., Chen, S., Chang, Y.-W., Wu, Z., Bieman, K., Liu, J.O. *Chem. Biol.* **1997**, *4*, 461.
9. Liu, S., Widom, J., Kemp, C. W., Crews, C. M., Clardy, J. *Science* **1998**, *282*, 1324.
10. Kim, D., Ahn, S. K., Bae, H., Choi, W. J., Kim, H. S. *Tetrahedron Lett.* **1997**, *38*, 4437.
11. Taber, D. F., Christos, T. E., Rheingold, A. L., Guzei, I. A. *J. Am. Chem. Soc.* **1999**, *121*, 5589.
12. Vosburg, D. A., Veiler, S., Sorensen, E. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 971.
13. Boiteau, J.-G., Van de Weghe, P., Eustache, J. *Org. Lett.* **2001**, *3*, 2737.
14. Hutchings, M., Moffat, D., Simpkins, N. S. *Synlett* **2001**, 661.
15. Hayashi, M., Yoshiga, T., Nakatani, K., Ono, K., Oguni, N. *Tetrahedron* **1994**, *50*, 2821.
16. Sibi, M. P., Lu, J., Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848.
17. Krykstolaitytè, S., Hammer, K., Undheim, K. *Tetrahedron Lett.* **1998**, *39*, 7595.
18. Nicolaou, K. C., Rodriguez, R. M., Mitchell, H. J., Van Delft, F. L. *Angew. Chem. Int. Ed.* **1998**, *37*, 1874.
19. Ghosh, A. K., Capiello, J., Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651.
20. Fürstner, A., Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.
21. Schreiber, S. L., Schreiber, T. S., Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525.
22. Smith, D.B., Wang, Z., Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793.
23. We tried the boron enolates of 3-acetyl-, 3-propionyl-, and 3-butyryl-4-benzyl-oxazolidin-2-one prepared either from BBN-triflate or freshly prepared Bu_2OTf under usual reaction conditions.
24. Liotta, D., Santiesteban, H. *Tetrahedron Lett.* **1977**, *50*, 4369.
25. Abdel-Magid, A., Pridgen, L. N., Eggleston, D. S., Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595.
26. Bonner, M. P., Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299.
27. Heathcock, C. H. "Asymmetric Synthesis", Ed. Morrison, J. D. Academic Press: New York, 1984, Vol. 3, p. 111-112.
28. Hurst, J. J., Whitham, G. H. *J. Chem. Soc.* **1960**, 2864
29. Barrero, A. F., Alvarez-Manzaneda, E. J., Chahboun, R., Menese, R. *Synlett* **1999**, 1663.
30. (a) Corey, E. J. ; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782. (b) Corey, E. J., Chaykovsky, M. *J. Am. Chem. Soc.* **1962**; *84*, 867.
31. Corey, E. J., Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
32. Amano, S., Ogawa, N., Ohtsuka, M., Childa, N. *Tetrahedron* **1999**, *55*, 2205-2224
33. Konosu, T., Takeda, N., Tajima, Y., Yasuda, H., Oida, S. *Chem. Pharm. Bull.* **1990**, *38*, 1258.
34. Cunat, A. C., Diez-Martin, D., Ley, S.V., Montgomery, F. J. *J. Chem. Soc. Perkin Trans. 1* **1996**, 611.
35. Sharpless, K.B., Verhoeven, T.R. *Aldrichimica Acta* **1979**, *12*, 63.
36. From intermediate **32**, a palette of fumagillin analogs could be prepared: Eustache, J., Boiteau, J.-G., Tarnus, C., Rodeschini, V., Van de Weghe, P. WO 03040119, 2003.

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STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 10

DEVISING AN ESPECIALLY EFFICIENT ROUTE TO THE 'MIRACLE' NUTRIENT COENZYME Q_{10}

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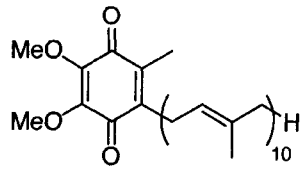
I. What's "CoQ_{10}"?

I had no clue; ... CoQ what? Having zero biochemistry to my credit, I thought coenzymes were biomolecules I had successfully avoided in graduate school and would never have to worry about. Man, was I wrong. And to think that now I routinely give talks on this topic, ...most of which is on the biochemistry of this crucial compound.[1] Of course, my opening question for the audience is, "How many of you have ever heard of "coenzyme Q_{10}"? (Figure 1) Usually, everyone just sits there; no hands go up. I know what they're all thinking: so what? Hey, if no one else knows about this stuff, how important could it be, right? Having seen these looks many times before, I know all-too-well that within minutes the tide will rapidly change as the importance of this little-known and unappreciated compound is seen to impact the health and well-being of every person on the planet. Everyone. No exceptions. As the hour passes, I have done my



CoQ_{10} (ubiquinone)

FIGURE 1. Structure of CoQ_{10}

best to pass along much of what took years for me to learn about this subject. I've gone over the 3D structure, with its highly lypophilic 50-carbon side-chain, shown samples of raw CoQ as well as the various forms in which it is sold over-the-counter (Figure 2), and even swallowed a 50 mg softgel midway through the talk just for impact. But after concluding my presentation, thinking that "I'm done", few leave. Questions fly; most are general, but many are personal. I slip in some additional information, show another transparency or two, but ultimately I am forced to remind listeners that my training is in chemistry, not medicine. Nonetheless, for this group at least, CoQ is no longer a stranger.

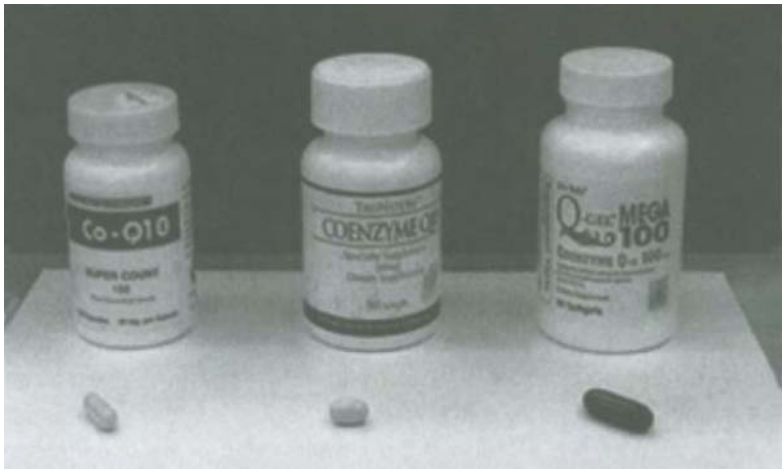
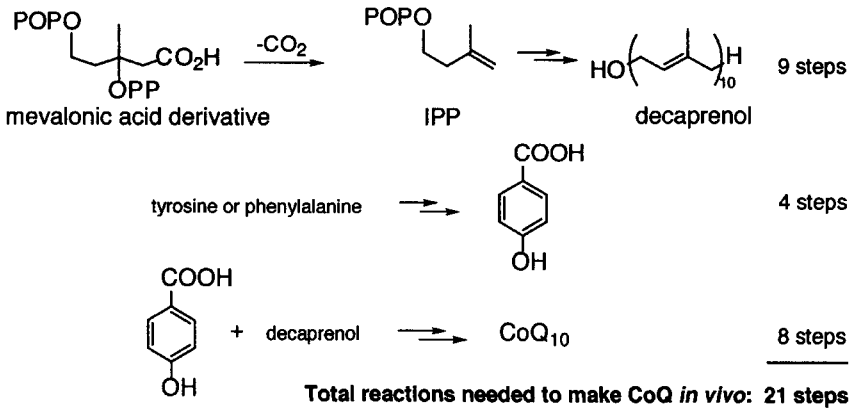


FIGURE 2. Various forms of commercial CoQ_{10}: caplets, softgels, and G-Gel.

The story I tell on CoQ, which is based on strictly factual information, is taken in large measure from basic textbooks on biochemistry.[2] These data are quite compelling, even somewhat

overwhelming. The fact alone that CoQ is also known as 'ubiquinone', which derives from the presence of this coenzyme in every human cell (*i.e.,* it is ubiquitous), makes one wonder why evolution chose this particular compound to be so prevalent in the human body. Few realize that is localized mainly in the organs that work the hardest for the life of the body, such as the liver, pancreas, kidneys and brain.[3] By far, however, most of the about 1.5 grams total CoQ in each of us is in heart tissue. This is not coincidence, as it is this natural product which mediates electron transfer in our mitochondria,[4] a phenomenon directly tied to energy transport which goes into the making of cellular ATP.[2] Thus, given the fact that CoQ mediates respiration, a net 4-electron reduction of oxygen to water, so do we derive from this process the currency of life: energy.[2]

Again the question arises, if CoQ is such a fundamental biomolecule, how could it be that so few among us know anything about it? The answer seems to be associated with the relative concentration of CoQ_{10} in our cells over time, which is presumably monitored through standard blood tests. That is, a coenzyme functions much like a vitamin; however, it is its origin that distinguishes one from the other. Thus, while we understand the necessity of vitamin intake through our diet, CoQ_{10} is not considered an "essential" vitamin, since it is made in our cells. Thus, notwithstanding the fact that 21 steps are required to biosynthesize CoQ_{10} in each cell (Scheme 1),[4] most people produce enough CoQ



SCHEME 1. Biosynthesis of CoQ_{10}

early in life to maintain a healthy state. The problem is that we age. And as we age, our levels of CoQ_{10}, which peak in our prime around age 20, drop precipitously as the efficiency of our biosynthetic machinery continues to drop (Figure 3; Table I).[5] Even if we assumed that each of the steps involved remained 95% yielding, what percentage relative to our peak levels would be left after 21 steps? As chemists, we fully understand the implications. The biosynthetic scheme may be convergent at step 10, but does it really matter, yield-wise? Thus, the bottom line here is clear: our lives begin with cellular levels of CoQ_{10} on the increase; it is a "non-essential" compound we all make *in vivo*, and while it would be wise to take supplemental amounts while young for its prophylactic

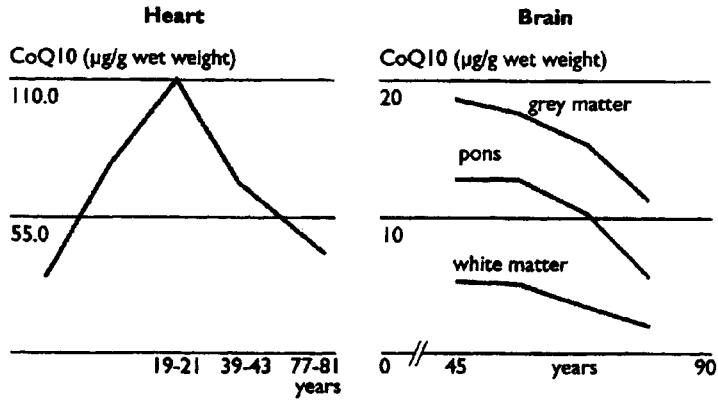


FIGURE 3. CoQ_{10} levels in the heart and brain as a function of age.

TABLE I

Age-Related Changes in the Ubiquinone Content of Human Organs (in µg/g wet weight tissue)

	Age Group				
Organ	**1–3 days**	**0.7–2 years**	**19–21 years**	**39–41 years**	**77–81 years**
Heart	36.7	78.5	110.0	75.0	47.2
Kidney	17.4	53.4	98.0	71.1	64.0
Liver	12.9	45.1	61.2	58.3	50.8
Pancreas	9.2	38.2	21.0	19.3	6.5
Spleen	20.7	30.2	32.8	28.6	13.1
Lung	2.2	6.4	6.0	6.5	3.1
Adrenal	17.5	57.9	16.1	12.2	8.5

effects, we pay little attention to it. In time, however, CoQ levels drop in our cells, and thus one should think of it as an essential vitamin, just as we think about taking supplemental vitamin C.

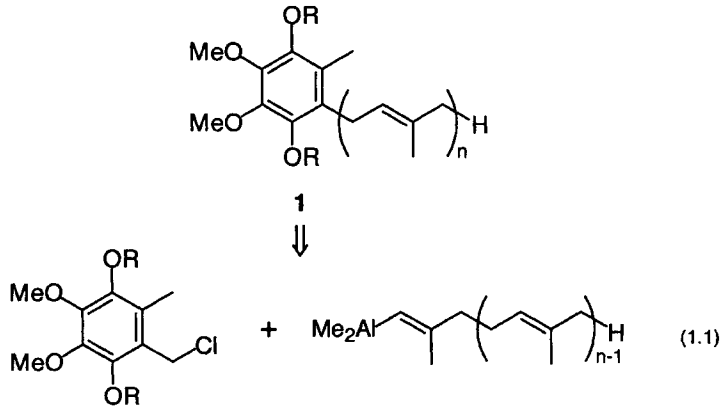
II. Why Bother to Synthesize CoQ_{10}?

Since there are many successful approaches to this compound,[6] this question seems quite reasonable. Certainly we were not looking to accomplish "just another synthesis of CoQ_{10}." The impetus grew out of our multi-year investment in making lower homologues, such as $CoQ_{3\text{-}8}$.[7] The incentives for these were obvious; one look at the price for CoQ_6 in a Sigma catalog reveals that it retails for over $20,000/gram, while CoQ_9 commands in excess of $40,000/gram! I was sure that we could compete with these prices. The explanation for these seemingly inflated numbers probably is due to a lack of an efficient fermentation process, and perhaps a limited market for research quantities of these compounds. On the other hand, CoQ_{10} is produced almost exclusively *via* fermentation,[8] with the world's supply coming out of three companies in Japan.[9] The purple non-sulfur bacteria that produce CoQ_{10},[8] to the tune of *ca.* 120 metric tons/year, however, are not perfect. That is, small amounts (*ca.* 0.3%) of the *'cis'* isomer (*i.e.,* the double bond isomer at the olefin closest to the quinone), and/or CoQ_9 ($\leq$0.3%) may be present in commercial material. Although these 'impurities' are harmless, they are non-trivial to remove and thus limit the purity of product that can be offered. Synthesis, though facing totally different issues, has the potential to provide material of the highest quality.

Thus, in addition to the challenge of engineering a short and hopefully efficient route to CoQ_{10}, there were additional incentives in the form of both purity of product, and potentially the economy of scale. The latter notion was to take on added significance in light of recent findings by an NIH study on CoQ_{10}, which documented its beneficial impact on the progression of Parkinson's disease.[10] Given the over one million Americans alone afflicted with this neurological disorder, and the levels at which CoQ_{10} was administered and found most effective (1.2 g/day), the demand on this nutraceutical could increase significantly. Perhaps synthetic material might some day help to meet the anticipated demand.

III. Putting Good Ideas to Use

In our early efforts aimed at preparing allylated (protected) hydroquinone precursors to CoQ (*e.g.*, **1**) wherein the geometry of the olefin was fully controlled,[11] we anticipated that Pd(0) would mediate a coupling between a benzylic chloride and an *E*-vinyl alane (Eq. 1.1). Although precedent in the form of work from Negishi's lab suggested this approach would be successful,[12] more highly functionalized, electron-rich aromatics in our hands led to modest yields of allylated aromatic products. The postdoc looking into this methodology, Gerd Bulow (from Aachen), after many attempts to improve on the Pd-catalyzed approach, came into my office one day and boldly suggested that nickel might do a better job. Although this sounded like a good idea, I had no experience in this area. Fortunately, however, Gerd did, and so began our program in organonickel chemistry.

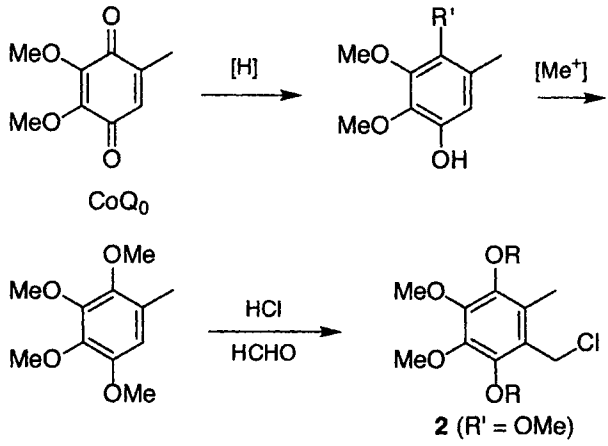


To help work out conditions for the key Ni-catalyzed coupling, I convinced Kirk Stevens, a relatively new graduate student from Pat McDougal's labs at Reed College, to join in the effort. This seemed at the time a bit of a gamble, since I was 'mixing' a highly trained, formal German postdoc with a very 'lassaire faire' sort of guy with tied-back long red hair and shades. Nonetheless, the combo cliqued and we were able to finely tune the key coupling of the protected hydroquinone portion of CoQ with model system vinyl alanes derived from Negishi's carboalumination of simpler terminal alkynes.[13] The critical observation

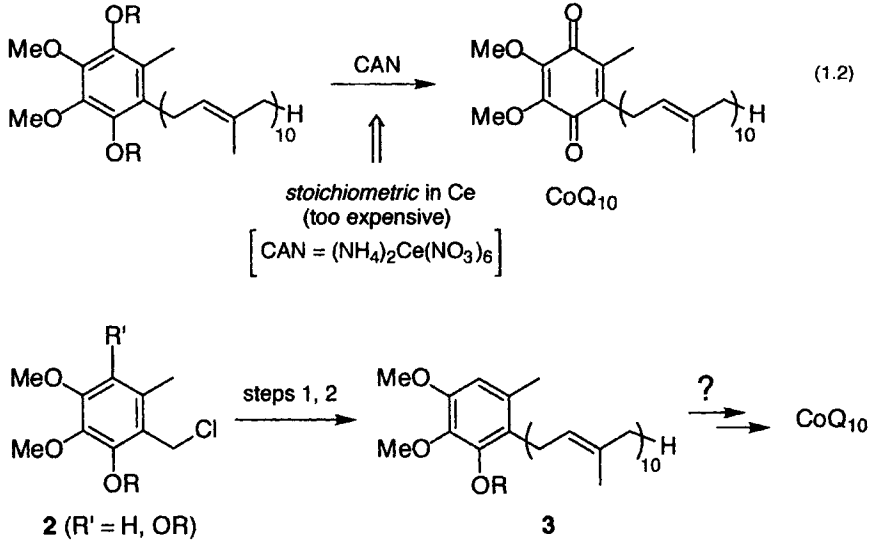
was that the zirconium salts present, introduced in 'catalytic' amounts as part of the Negishi protocol, are detrimental to these Ni(0)-catalyzed couplings and need to be precipitated out from the reaction medium. This was certainly not at first an obvious call. Initially, yields for these couplings were only modest, and we had no idea why. We knew the salts could impact a group 10 transition metal, but it was only by trial and error that we found that removing them from the reaction mixture led to high yields of desired allylated aromatics. Once the nuances had been determined, including the switch from CH_2Cl_2 to 1,2-dichloroethane,[14] the coupling reaction that would eventually install the 49-carbon fragment of the 50 carbon CoQ_{10} side-chain was ready to be applied.

Unfortunately, we knew that the protected hydroquinone portion **1** (*cf.* Equation 1.1), the precursor to the *p*-quinone in the target, would not allow for an acceptable coupling partner in this form for practical reasons. Firstly, it would have to be made from CoQ_0, which itself is expensive. To arrive at protetcted hydroquinone **2** from CoQ_0 required its reduction, protection (usually as the methyl ether (R = Me in **2**) using Me_2SO_4), and then chloromethylation to arrive at benzylic chloride **2** (Scheme 2).[7] Lastly, we knew there was no chance that ceric ammonium nitrate (CAN) could be relied upon to induce the final oxidation from a protected hydroquinone to the CoQ *p*-quinone; it is too expensive as a stoichiometric oxidant, and presented overwhelming waste disposal issues (Eq. 1.2) Thus, desperately needed was a good idea as to what to use in place of **2** both as a coupling partner and *p*-quinone equivalent, and which is both readily available and inexpensive. A few years earlier, an old friend from Yale, Dr. Sam Kumar, had given me the unpublished scheme used in India to prepare CoQ_0. The earlier intermediates in this 4-step sequence, all of which ultimately derive from gallic acid, are inexpensive on the multi-kilo scale. The question we faced was, are any of these appropriate for conversion to a benzylic chloride such as **2**, or a related aromatic, that could eventually be readily oxidized via intermediate **3** to the CoQ nucleus (Scheme 3)? This single question occupied much of our thinking for months...perhaps it was years, while we worked on the syntheses of the lower homologues ($CoQ_{3\text{-}8}$).[7] This scheme to CoQ_0 was distributed to everyone in the group even remotely associated with the CoQ project. I quizzed postdocs in the hallway, prodded graduate

students from other groups, and occasionally challenged visiting seminar speakers and my own colleagues (although I left the P-chemists out on



SCHEME 2. Conversion of CoQ_0 to benzylic chloride **2**.

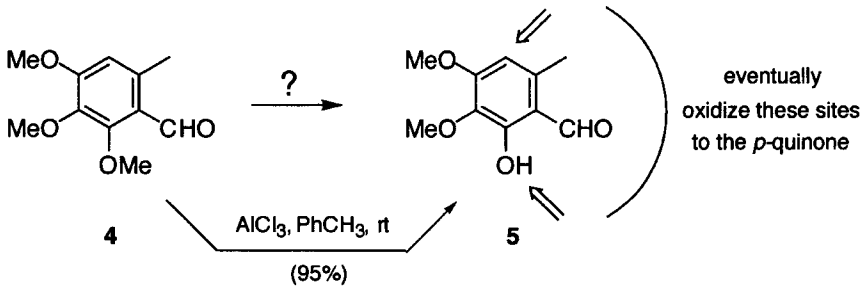


Step 1. Ni(0)-catalyzed coupling
Step 2. loss of protecting group 'R'

SCHEME 3. Conditions that the phenol protecting group R must withstand

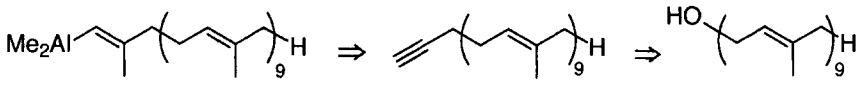
this one) to suggest an inroad to a useful derivative. Finally, after staring yet again at these simple molecules, I realized that trimethoxybenzaldehyde **4**, by virtue of a selective demethylation, provided the differentiation needed for subsequent autoxidation to the *p*-quinone bearing the CoQ substitution pattern (Scheme 4). So I asked a seasoned group member, Paul Mollard, to put in a couple of hours in the library rather than three weeks in the lab to see what was known about the proposed regioselective removal of methyl ethers in such cases. We were shocked to learn that this reaction on the *identical* substrate had been accomplished long ago and in high yield by the action of $AlCl_3$![15] Sure enough, when Paul exposed aldehyde **4** to a slight excess of this Lewis acid, regiospecific demethylation took place to give phenol **5** in *ca.* 95% yield.

Once we knew how to differentiate methoxy groups in **4**, all the pieces fell into place, at least on paper. Major decisions still had to be made, however. For example, protecting group chemistry: the newly generated phenol **5**, an acid, would not be tolerated during the eventual



SCHEME 4. Selective demethylation of readily available aldehyde **4**

coupling of the moisture-sensitive vinyl alane side-chain. The protecting group selected would have to meet several criteria: (1) withstand a hydride reducing agent and subsequent chlorination with HCl, a sequence needed to transform the aldehyde in **5** to the corresponding phenol-protected benzylic chloride **2**; (2) be unaffected by the Ni(0)-catalyzed coupling in the presence of a vinyl alane **6** (Scheme 5); (3) undergo both the 'on' and 'off' steps in high yields, using inexpensive reagents. Secondly, assuming



6 **7** (solanesol)

SCHEME 5. Retrosynthesis of coupling partner vinyl alane **6**.

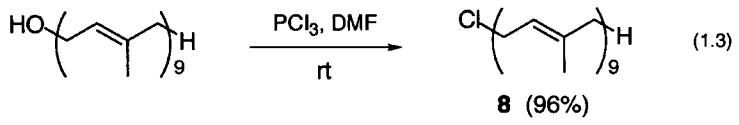
these requirements are met, which inexpensive reagent could achieve the final oxidation from the newly freed phenol **3** (R = H) directly to CoQ_{10}?

As Paul and I considered available options, trying our best to think from the process chemists' perspective, we realized the limited array of protecting groups that had been used in previous syntheses of CoQ: benzoates[6j,k] and ethers.[6d,e,i] Neither type of derivative of **2** looked attractive for our route; the former introduced electrophilic and Lewis basic centers, while he latter might be tough to remove. Ultimately, we were intrigued by the notion of a sulfonate derivative, which we speculated would not interfere with either of the two steps (*cf.* Scheme 3) *en route* to the CoQ_{10} precursor phenol **3** (R = H). Although the mesylate was an obvious candidate its acidic α-protons might complicate removal. Therefore, we settled on the tosylate. If this choice allowed us to get through the sequence to the penultimate species **3** (R = H), we simply had to believe that a way would be found to do the oxidation to the quinone. After all, if life depends so heavily on the facility with which CoQ_{10} shuttles between the oxidized and reduced (*i.e.,* hydroquinone) forms, any compound that is structurally close to the CoQ nucleus for which a mechanistic pathway exists, would hopefully respond favorably when given the opportunity to be oxidized. Put another way: we figured that 3.5 billion years of evolution was on our side.

IV. The Synthesis: Few Steps, High Yields, ...and No Excuses!

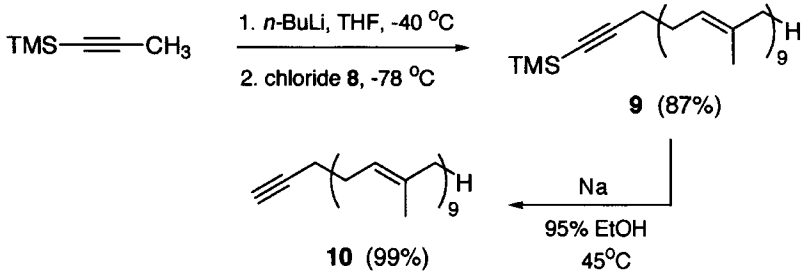
Although the choice of polar head group for the route in the form of benzylic chloride **2** (R = Ts) had been settled, access to the remaining 49 carbons in the side chain in the form of vinyl alane **6** had to be addressed. We knew that 45 of these would have to come in the form of the nonaprenoidal (*i.e.,* a nine x 5-carbon isoprene-derived) alcohol solanesol **7** (*cf.* Scheme 5), a component of tobacco waste. By attaching a 3-carbon fragment in the form of propyne, our tandem carboalumination/Ni-catalyzed coupling[7] was not likely to disappoint us

as a means to completing assemblage of the required 50 carbon side-chain. Thus, starting with commercially obtained solanesol of high purity, Paul looked for the best method to prepare the corresponding chloride **8**, bearing in mind that there would be no option for a chromatographic clean-up of this allylic system. After screening dozens of reagent/solvent combinations, we were thrilled to find that PCl_3 in DMF at room temperature cleanly afforded the desired product after aqueous workup in over 96% yield as a low melting solid (Eq. 1.3). A great start, but it's only one step down, five to go. Now for the alkylation...



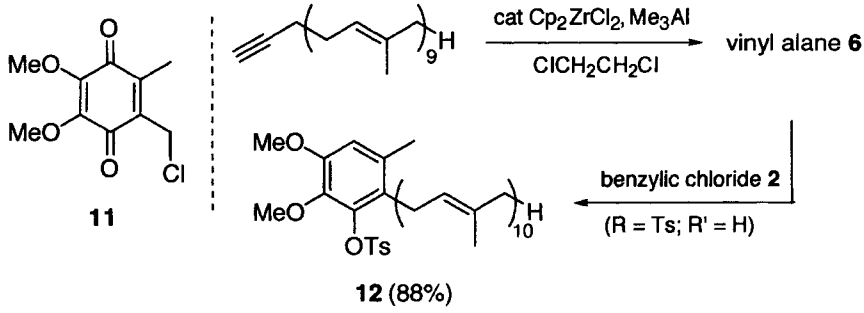
8 (96%) (1.3)

Our chances were pretty good. Metalating TMS-propyne with *n*-BuLi was straightforward; we had alkylated this three-carbon unit previously in our march toward $CoQ_{6\text{-}8}$, but not using such a lipophylic (45 carbon) alkylating agent. Nonetheless, with solanesyl chloride **8** being an allylic electrophile, the desired C-C bond could readily be made, even at –78°C (Scheme 6). Unfortunately, although the isolated yield was good (*ca.* 87%), the remaining mass was distributed among by-products mainly due to competitive E2 elimination and to a lesser degree, from S_N2' addition. Since these side-processes led to innocuous hydrocarbons once the TMS group had been removed, there was no reason to purify further the initial TMS-alkyne **9**. Desilylation with sodium in warm 95% EtOH lead quantitatively to the 48 carbon hydrocarbon terminal alkyne **10**.



SCHEME 6. Alkylation/desilylation using TMS-propyne.

At the time, the next step was viewed as the BIG hurdle. Sure, we had worked out this anticipated Ni(0)-catalyzed coupling on simpler systems and were quite confident that it would 'deliver'. But as just about every target-oriented synthetic organic chemist knows, oftentimes unfortunately from experience, "the model is the model, and the 'real' is the 'real'." Furthermore, in our route to $CoQ_{3\text{-}8}$, we had relied on the far more reactive chloromethylated quinone **11** as coupling partner,[7] *not* benzylic chloride **2** (R = Ts). The actual coupling was dependent upon a successful carbometalation, which again had never been done (at least by us) on such a 'greasy' substrate. Although it took some time, Paul was able to get this first step in the sequence to go very cleanly and completely, so long as good quality Me_3Al (in hexanes) was employed (Scheme 7). The switch in solvent from CH_2Cl_2 to dry 1,2-dichloroethane, which increased the polarity of the medium (albeit slightly, from ε 8.93 to 10.36),[17] also made a big difference. Once the vinyl alane was formed *in situ* and the zirconium salts had been precipitated with hexanes, the coupling to product **12** was uneventful (Scheme 7).

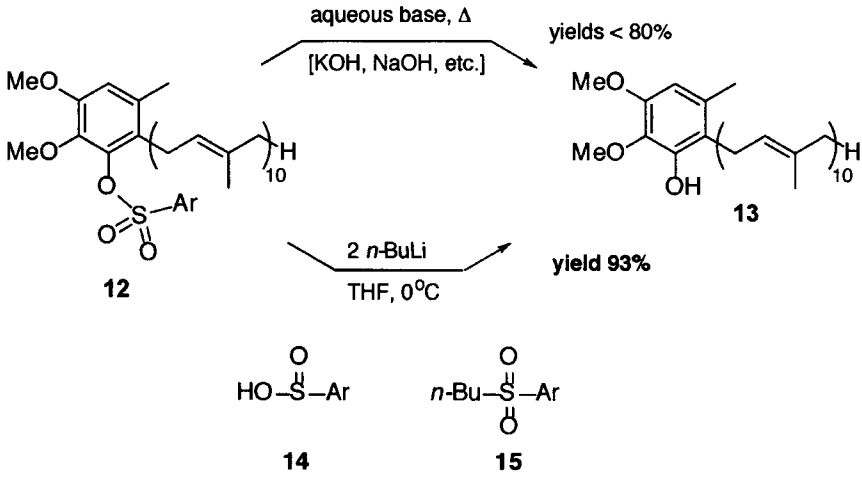


SCHEME 7. Installation of the CoQ_{10} side-chain

With only two steps left, one of which was a protecting group removal, we were beginning to think that this synthesis is going to work out every bit as well as we had hoped. I should have known better, for it's thoughts such as these that seem to continuously come back to haunt me. I figured, looking at Paul's oily product that otherwise is composed of just an aromatic ring and isolated olefins, what could possibly go wrong taking off a tosylate? The obvious, least expensive method was to simply

treat the tosylate with (hot) aqueous alkali (Scheme 8). This, in fact, did remove the tosyl group to afford phenol **13**, but (due to solubility problems?) the reactions were always slow independent of conditions (KOH, NaOH; co-solvents, etc.) Thus, somehow, the isolated yields never even made it to 80%. Don't ask me why. I don't know.

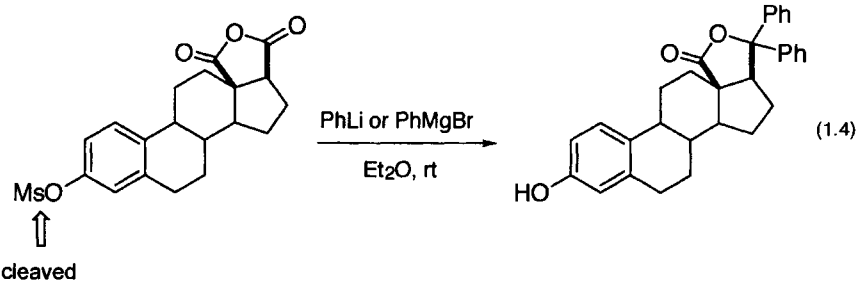
Plan B. What reagent is hot, cheap, and likely to react quickly at sulfur in a tosylate? *n*-BuLi came immediately to mind, and fortunately, this was actually the ticket to success for this seemingly 'trivial' step. Exposure of tosylate **12** dissolved in THF at 0°C to a standard, commercial source of this base/nucleophile/electron donor in hexanes led to a very clean unmasking to the free phenol **13** upon mild acid workup (Scheme 8). That two equivalents of *n*-BuLi are required for full consumption of educt (47% yield with only stoichiometric use), is good evidence that an SET process is the likely mechanism, as opposed to



SCHEME 8. Deprotection of tosylate **12** to free phenol **13**

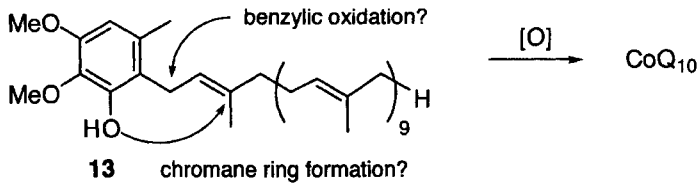
direct nucleophilic attack at sulfur. This was a lucky break, since the by-product of detosylation, therefore, is likely to be water-soluble sulfinic acid **14**, rather than the corresponding organic soluble aryl butyl sulfone **15**. Few literature precedents for cleavage of an aryl sulfonate with an organolithium could be found, although such a reaction dated back to work by Barton in 1968.[18] Exposure of an aryl mesylate in a steroidal framework to phenyl Grignard or phenyllithium unmasked the phenol

(Eq. 1.4). Obviously, this was far from a textbook case of an alcohol deprotection, and from what additional listings can be found in Green and Wuts' monograph for such deprotections,[19] we probably should go back and develop this chemistry further.



(1.4)

Fortunately, the isolated yield for this detosylation was high (93%), but perhaps the really good news was that the resulting penultimate intermediate phenol **13** is a stable, white crystalline solid (mp 49.0 – 50.5°C). Although delighted by this finding, Paul and I were far from extending 'high 5's' to each other. The final step, the oxidation, was looking much more threatening: getting an oxygen at the vacant site on the aromatic ring, and then a second oxidation to the quinone without competing benzylic oxidation or ring closure to the chromane skeleton (Scheme 9)...well, my best advice to Paul at this point to deal with the impending stress was to double his daily intake of CoQ_{10}!



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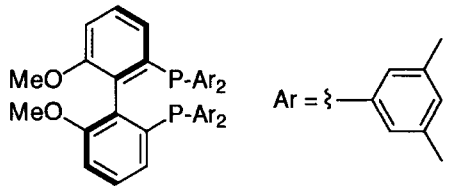
SCHEME 9. Potential complications upon oxidation of phenol **13**.

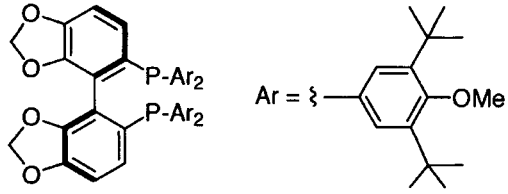
V. The Final Oxidation...It's All About the Ligand

Although I have been in this business for decades, it wasn't until recently that a full appreciation for the extent to which the lives of organic chemists are controlled by ligands really struck me. Even with years of

cuprate chemistry behind me; through all the controversy over higher order, lower order, ...whatever order cuprates, which or course focused on cyanide as a ligand on copper (or not!),[20] it still did not have the same impact on me until we entered the realm of asymmetric catalysis. Here we saw such dramatic swings in reactivity and stereodifferentiation by nonracemic bidentate phosphine ligands, such as Roche's BIPHEP **16**[21] and Takasago's SEGPHOS **17**[22] (Figure 4), on the chemistry of coppery hydride (CuH)[23] that it was impossible not to conclude that while the metal counts, the ligands rule! And so, in hindsight, we approached the oxidation of phenol **13** rather naively, hoping that a time-honored oxidizing agent such as $K_3Fe(CN)_6$,[24] potassium thiosulfate ($K_2S_2O_8$),[25] or H_2O_2/HOAc[26] would work. Not a chance. We tried them all, but they just laughed at us and sent us home for the day.



16 (Roche's *(R)*-3,5-xyl-MeO-BIPHEP)

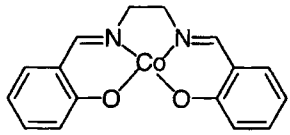


17 (Takasago's *(R)*-DTBM-SEGPHOS)

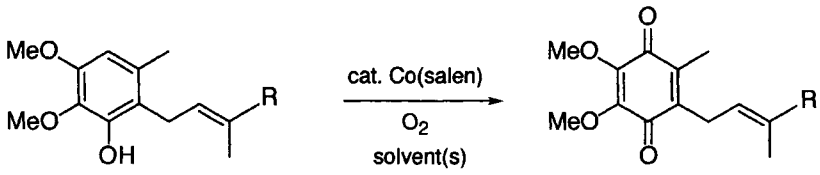
FIGURE 4. Nonracemic biaryl lignads for asymmetric catalysis.

Further digging in the literature led us to focus on the simplest, ethylenediamine-derived Co(salen), **18**, which used catalytically in the presence of oxygen appeared to offer great promise in that phenols could be oxidized all the way to *para*-quinones with little, if any, accompanying *ortho*-oxidation (Scheme 10).[27] Initial studies on *model* system **19** indicated that while 10% Co(salen) in THF gave a low 19% yield of

quinone **20**, switching to CH_3CN afforded 25% product after 24 hours, and in DMF, 28% was realized. Addition of two equivalents of pyridine, presumably as a stabilizing ligand on the metal, dramatically raised the yield to 79%, although the reaction time increased to 49 hours. Less pyridine lowered the extent of product formation (1 equiv: 74%; 0.1 equiv.: 69%, but messy), and 2,6-lutidine sent the yields south in a hurry (*ca.* 25%).



18 [Co(salen)]



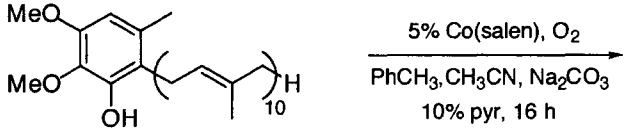
19 (R = C_6H_{13}-*n*)

	20
THF	19%
CH_3CN	25%
DMF	28%
CH_3CN + 1 pyr	74%
CH_3CN + 2 pyr	79%

SCHEME 10. Model study on catalytic Co(III) oxidations of phenol **19**

Applying our 'best' conditions from this model to the 'real', we still could not get respectable numbers, and it was clear that the 10% cobalt catalyst being used was far too much metal for this catalytic process, especially as the final step in the synthesis. More trials and more tribulations later, eventually issues such as reagent and substrate solubilities, importance of added pyridine as well as solid Na_2CO_3 got us to a procedure based on 5% Co(salen) which produced CoQ_{10} in 68% isolated yield (Eq. 1.5). The quality of the CoQ obtained was excellent; none of the *'cis'* isomer, as expected, was present. Nonetheless, there was also no doubt that starting material had not been fully consumed, suggesting that the catalyst was dying over time.

As so often happens in academia, students get the point in their graduate school careers when it's 'time to go', and although Paul and I sensed that work on this final oxidation was far from over, experimental work on CoQ was put on hold while Paul's Ph.D. thesis was written. His



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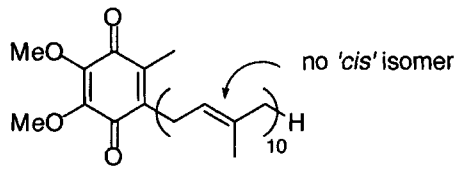


(1.5)

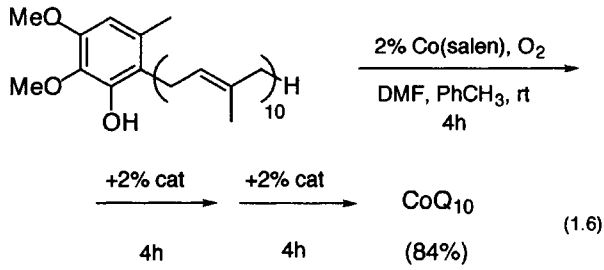
CoQ_{10} (68%) + recovered phenol

seminal contributions to this synthesis had been made, and while our short 6-step sequence to CoQ_{10} proceded in 45% overall yield, publication was not about to happen until the last step had received more attention. But who in the group was 'ripe' to step in and quickly address the one reaction parameter Paul had not varied: yeah, ...the ligand.

So I looked over my scorecard, as would any team manager, and picked a 'player' I knew would deliver: Steve Pfeiffer. As one of the most senior group members, he had all the experience necessary to get into this CoQ project quickly. As incentive for him to accept this yet additional project along with the five others he had ongoing, was the prospect of co-authorship on what I envisioned would be a nice *JACS* communication. Living up to expectations, Steve *immediately* agreed to tackle this key reaction. As luck would have it, I had just returned from the 6th Brazilian Meeting on Organic Synthesis (BMOS) held in Curitiba, thanks to an invitation by Prof. Fabio Simonelli at the Universidade Federal do Parana (UFPR). During a poster session I noticed some recent quinone work being presented by the PI from Tim Brocksom's group (at the Universidade Federal de Sao Carlos; UFSCAr/Brazil).[28] Out of a conversation with Tim and his wife Ursula, I began to appreciate the importance of both the solvent and the manner in which such an oxidation is performed. That is, DMF seemed to be used frequently, and perhaps most importantly, oxygen was continuously bubbled through the medium.

Thirdly, they encouraged me to add fresh catalyst over time, rather than the total being introduced at the beginning of the reaction. Needless to say, I was taking notes feverishly, and these experimental modifications to Paul's oxidation would be at the top of our list for Steve to try. In Steve's first experiment, using DMF and continuous bubbling, the isolated yield increased to 74%. While the DMF was important for solubilizing the cobalt catalyst, the substrate on the other hand, was non-polar and thus, relatively insoluble in this solvent. By altering the medium to 1:1 DMF : toluene, the yield increased again to 81%. We were on a roll!

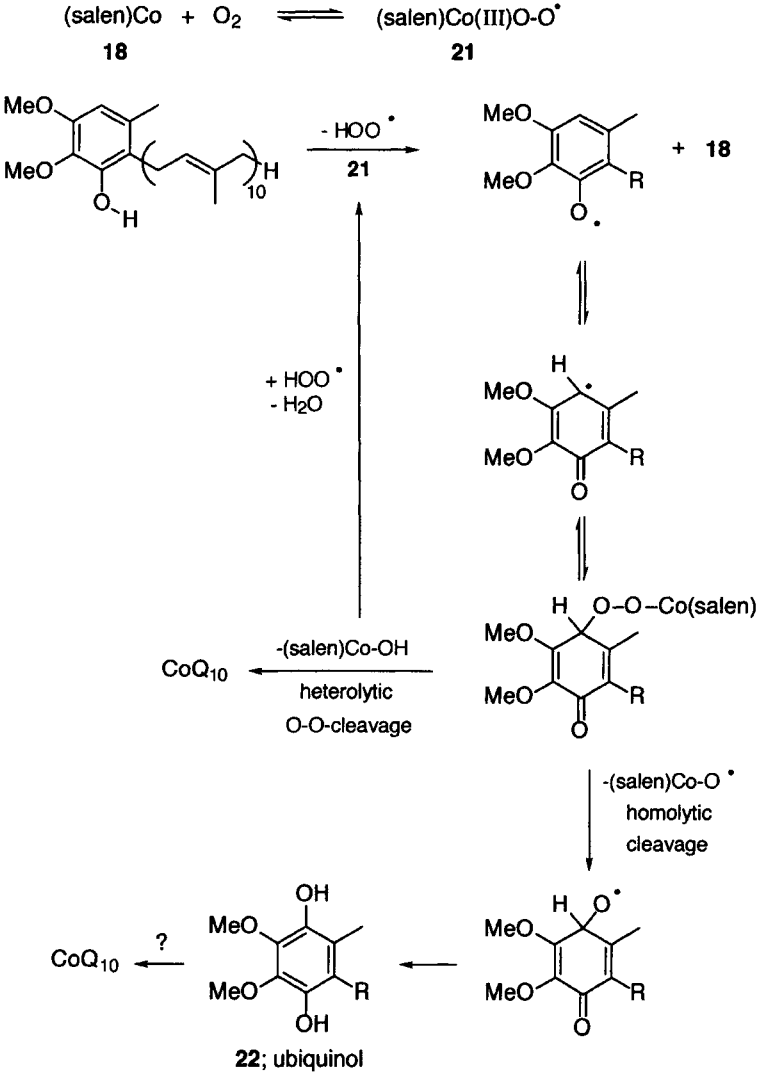
After extending congratulations to Steve, the residual mentor in me just had to ask: "By the way, Steve, any idea where the rest of the mass goes"? He quickly responded that the "by-product" is the initial product of oxidation: the hydroquinone (*i.e.*, the reduced form of CoQ_{10}). In other words, it seemed that the Co(salen) did not have enough "umph" to go the distance. It did the first oxidation on 100% of the phenolic educt, but at first glance seemed to die by the time about 80% of this newly formed material had been subsequently converted to the quinone. By spreading the 6% Co(salen) to be used over three 2% portions being added every four hours, the yield went up yet again, now standing at 84% (Eq. 1.6). Not bad, but given it's the last step, we still had to chase that remaining 16% of the leftover hydroquinone.



(1.6)

The only option left to us at this point seemed to be...what else? ... the ligand. A mechanistic analysis according to a proposed sequence by Beckett (Scheme 11)[29] suggested that Co(III) species **21** involving the simple salen ligand **18** may be susceptible to either homo- or heterolytic cleavage. The former presumably leads to only partially oxidized hydroquinone **22** (ubiquinol), while the desired β-elimination proceeds on to CoQ.

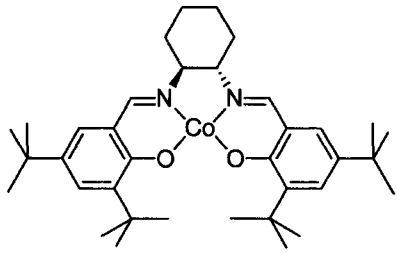
The obvious choice (at least from the standpoint of availability) to test the role of the salen ligand chelating Co(II) was to buy Jacobsen's cobalt catalyst, **23**[30] (Scheme 12). This species would introduce several new structural and stereoelectronic factors at the same time (relative to the



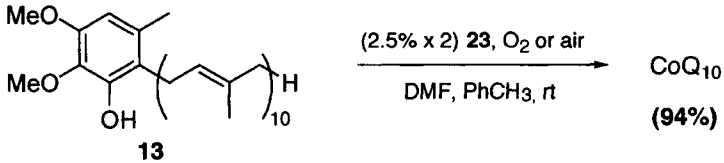
SCHEME 11. Mechanistic possibilities to account for formation of both CoQ_{10} and ubiquinol.

simplest salen ligand having been used thus far), but it was too easy not to try. On Steve's first attempt, all other parameters being equal, CoQ_{10} was isolated in 94% yield. The same result was obtained using air in place of oxygen as re-oxidant. The reaction was almost 'spot-to-spot'; no starting material remained, although trace amounts of hydroquinone could still be detected by TLC.

The product (being lypophilic and thus insoluble in DMF), however, precipitated in large measure from the reaction mixture. This was one of those all-too-infrequent moments that every mentor relishes. When the



23; Jacobsen's Co catalyst



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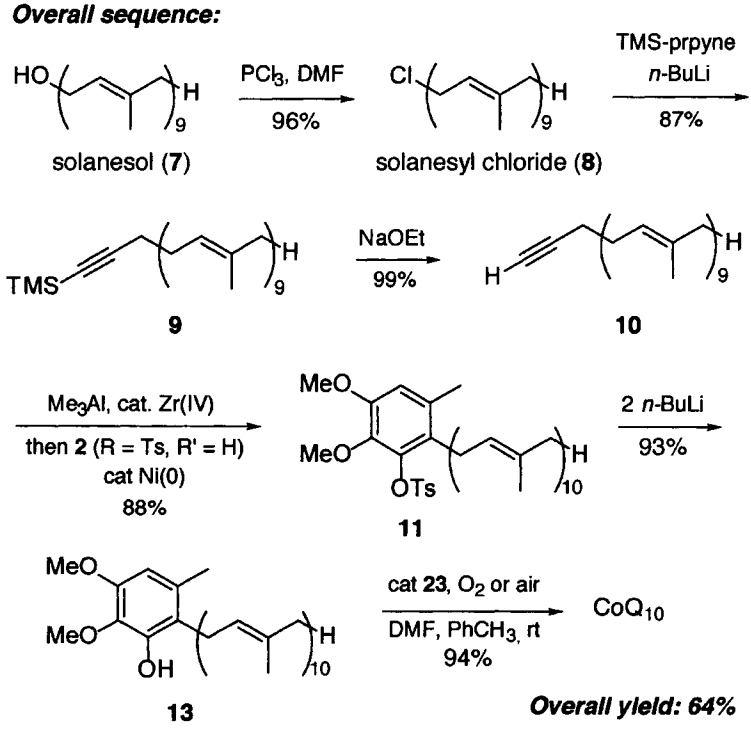
SCHEME 12. Oxidation of phenol **13** to CoQ_{10}

numbers had been crunched, the overall isolated yield for these six steps stood above 64% (Scheme 13).

VI. Final Thoughts

In looking over the sequence, I wonder if there is still room for improvement. Surely some effort on the alkylation of lithiated TMS-propyne might raise the efficiency of this lowest yielding step. Quite likely the Ni(0)-catalyzed coupling, which stands conservatively at 88%, can be increased perhaps substantially, as virtually all of the model systems on which it is based proceed in yields > 90%. But this is not for us to do; rather, should our academic route be pursued by industrial

partners as an entry point to the lucrative CoQ_{10} market, so then would experienced process chemists be given the opportunity to enhance these individual steps, converting our academic route on the gram scale into a robust industrial process for making CoQ at the kilo level or beyond. With the yields as they now stand, for every 1.2 kilograms of solanesol invested, a kilogram of CoQ_{10} is to be expected. However, we as academicians take considerable pride in having identified this route which, through hard work and determination on the part of those who first



SCHEME 13. Summary of overall route to CoQ_{10}

developed the required methodology, and then by those who put the pieces together, emerged a very good synthesis of CoQ_{10}. Collaboration; it's a beautiful thing.

Acknowledgements

The students, who made exceptional experimental and intellectual contributions as discussed in this account, are most deserving of the credit for our groups work in the CoQ area. Financial support by the NSF, the UCSB Committee on Research, Boehringer-Ingelheim (fellowship to S. Pfeiffer), and the DAAD (fellowship to G. Bulow) is warmly acknowledged with thanks. We are most appreciative of the efforts by Dr. Sam Kumar of Sarchem Labs (Navesink, NJ) for providing several of the key raw materials used in this work. Highly valued and timely contributions by both Will Chrisman and Bryan Frieman during the course of these studies must also be acknowledged.

References

1. Bliznakov, E. G., Hunt, G. L. *The Miracle Nutrient Coenzyme Q_{10}*; Elsevier/North-Holland Biomedical Press: New York, 1986. *Coenzyme Q: biochemistry, bioenergetics, and clinical applications of ubiquinone*; Lenaz, G., Ed.; Wiley: New York, 1985. *Coenzyme Q: molecular mechanisms in health and disease*; Kagan, V. E., Quinn, P. J., Eds.; CRC Press: Boca Raton, 2001.
2. Garrett, R. H. Grisham, C. M. *Biochemistry*; Saunders College Publishing: Orlando, 1999. Stryer, L. *Biochemistry*; W.H. Freeman and Company: New York, 1995. Nelson, D. L., Cox, M. M. *Lehninger Principles of Biochemistry*; Worth Publishers: New York, 2000.
3. Sinatra, S. T. *The Coenzyme Q_{10} Phenomenon*; Keats Publishing, Inc.: New Canaan, 1998.
4. Mitochonrial Ubiquinone; Ebadi, M., Marwah, J., Chopra, R., Eds.; Prominent Press: Scottsdale, AZ, 2001, volumes 1,2.
5. Littarru G.P. *Energy and Defense*, Casa Editrice Scientifica Internazionale, Rome, 1995. Miller, B., *Coenzyme Q_{10}*; Oak Enterprise, Selangor Darul Ehsan, Malaysia, 2000.
6. (a) Negishi, E-i., Liou, S-Y., Xu, C., Huo, S., *Org. Lett.* **2002**, *4*, 261. (b) Van Liemt, W. B. S., Steggerda, W. F., Esmeijer, R., Lugtenburg, J., *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 153. (c) Duralski, A. A., Watts, A., *Tetrahedron Lett.* **1992**, *33*, 4983. (d) Yanagisawa, A., Nomura, N., Nobuyoshi, N., Noritake, Y., Yamamoto, H., *Synthesis* **1991**, *12*, 1130. (e) Eren, D., Keinan, E., *J. Am. Chem. Soc.* **1988**, *110*, 4356. (f) Eto, H., Eguchi, C., *Chem. Lett.* **1988**, 1597. (g) Mohri, M., Kinoshita, H., Inomata, K., Kotake, H., Takagaki,

H.; Yamazaki, K., *Chem. Lett.* **1986**, 1177. (h) Sato, K., Miyamoto, O., Inoue, S., Yamamoto, T., Hirasawa, Y., *J. Chem. Soc., Chem. Commun.* **1982**, *3*, 153. (i) Naruta, Y., *J. Org. Chem.* **1980**, *45*, 4097. (j) Terao, S., Kato, K., Shiraishi, M., Morimoto, H., *J. Org. Chem.* **1979**, *44*, 868. (k) Terao, S., Kato, K., Shiraishi, M., Morimoto, H., *J. Chem. Soc., Perkin Trans. 1* **1978**, *10*, 1101. (l) Inoue, S., Yamaguchi, R., Saito, K., Sato, K., *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3098.

7. Lipshutz, B. H., Bulow, G., Fernandez-Lazaro, F., Kim, S-K., Lowe, R., Mollard, P., Stevens, K. L., *J. Am. Chem. Soc.* **1999**, *121*, 11664.
8. Sasikala, C., Ramana, C. V., *Adv. Appl. Microbio.* **1995**, *41*, 173.
9. Nisshin Flour, Mitsubishi, and Kyowa Hako Kogyo.
10. http://www.msnbc.com/news/821158.asp?0si=-. See also the NIH "Fact Sheet" on CoQ_{10} at http://ods.od.nih.gov/showpage.aspx?pageid=90
11. Lipshutz, B. H., Bulow, G., Lowe, R. F., Stevens, K. L., *J. Am. Chem. Soc.* **1996**, *118*, 5512.
12. Negishi, E.I.; Matsushita, H.; Okukado, N. *Tetrahedron Lett.*, **1981**, *22*, 2715.
13. Negishi, E., *Acc. Chem. Res.* **1987**, *20*, 65. Negishi, E., Van Horn, E. E., Yoshida, T., *J. Am Chem. Soc.* **1985**, *107*, 6639. Negishi, E., *Pure Appl. Chem.* **1981**, *53*, 2333.
14. Van Horn, D. E.; Negishi, E. *J. Am Chem. Soc.* **1978**, *100*, 2252.
15. Paul, E. G., Wang, P. S-C., *J. Org. Chem.* **1979**, *44*, 2307. Aquila, v. H., *Liebigs Ann. Chem.* **1969**, *721*, 220.
16. Kanazawa, M., Takahashi, T. In *Biochemical and Clinical Aspects of Coenzyme Q_{10}*; Yamamura, Y., Folkers, K., Ito, Y., Eds.; Elsevier: Amsterdam, 1981; Vol III, p 31. Rowland, R. L., Latimer, P. H., Giles, J. A., *J. Am. Chem. Soc.* **1956**, *78*, 4680.
17. Landolt, H. H. "Zahlenwerte und Functionen", 6th ed.; Springer: Berlin, 1959; Vol. II/6.
18. Baldwin, J. E., Barton, D. H. R., Dainis, I., Pereira, J. L. C., *J. Chem. Soc. C* **1968**, 2283. See also Koga, Y., Kusama, H., Narasaka, K., *Bull. Chem. Soc. Jp.* **1998**, *71*, 475.
19. Greene, T. W., Wuts, P. G. M. *Protective Groups in Organic Synthesis*, Wiley, N.Y., 1991, 2nd Ed. See also, as examples, Sidhar, M., Kumar, B. A., Narender, R., *Tetrahedron Lett.* **1998**, *39*, 2847; Koga, Y., Kusama, H., Narasaka, K., *Bull. Soc. Chem. Jp.* **1998**, *71*, 78.
20. Krause, N., *Angew. Chem. Intl. Ed.* **1999**, *38*, 79.

21. Schmid, R., Broger, E. A., Cereghetti, M., Crameri, Y., Foricher, J., Lalonde, M., Muller, R. K., Scalone, M., Schoettel, G., Zutter, U., *Pure. Appl. Chem.* **1996**, *68*, 131. Schmid, R., Foricher, J., Cereghetti, M., Schonholzer, P., *Helv. Chim. Acta* **1991**, *74*, 370.
22. Saito, T., Yokozawa, T., Ishizaki, T., Moroi, T., Sayo, N., Miura, T., Kumobayashi, H., *Adv. Synth. Catal.* **2001**, *343*, 264.
23. Lipshutz, B. H., Noson, K., Chrisman, W., Lower, A., *J. Am. Chem. Soc.* **2003**, *125*, 8779. Lipshutz, B. H., Noson, K., Chrisman, W., *J. Am. Chem. Soc.* **2001**, *123*, 12917.
24. Matsumoto, M., Kobayashi, H., *J. Org. Chem.* **1985**, *50*, 1766.
25. Behrman, E. J., *Organic Reactions* **1988**, *35*, 421.
26. Shimazu, M., Orita, H., Hayakawa, T., Takehira, K., *Tetrahedron Lett.* **1989**, *30*, 471.
27. See, as examples, Kraus, G. A., Choudhury, P. K., *Tetrahedron Lett.* **2001**, *42*, 6649; Bloomer, J. L., Stagliano, K. W., *Tetrahedron Lett.* **1993**, *34*, 757.
28. Dockal, E. R., Cass, Q. B., Brocksom, T. J., Brocksom, U., Correa, A. G., *Synth. Commun.* **1985**, *15*, 1033.
29. Beckett, M. A., *Inorg. Chim. Acta* **1989**, *157*, 171.
30. Schaus, S. E., Brandes, B. D., Larrow, J. F., Tokunaga, M., Hansen, K. B., Gould, A. E., Furrow, M. E., Jacobsen, E. N., *J. Am. Chem. Soc.* **2002**, *124*, 1307.

STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 11

TOTAL SYNTHESIS OF LIPID I AND LIPID II: LATE-STAGE INTERMEDIATES UTILIZED IN BACTERIAL CELL WALL BIOSYNTHESIS

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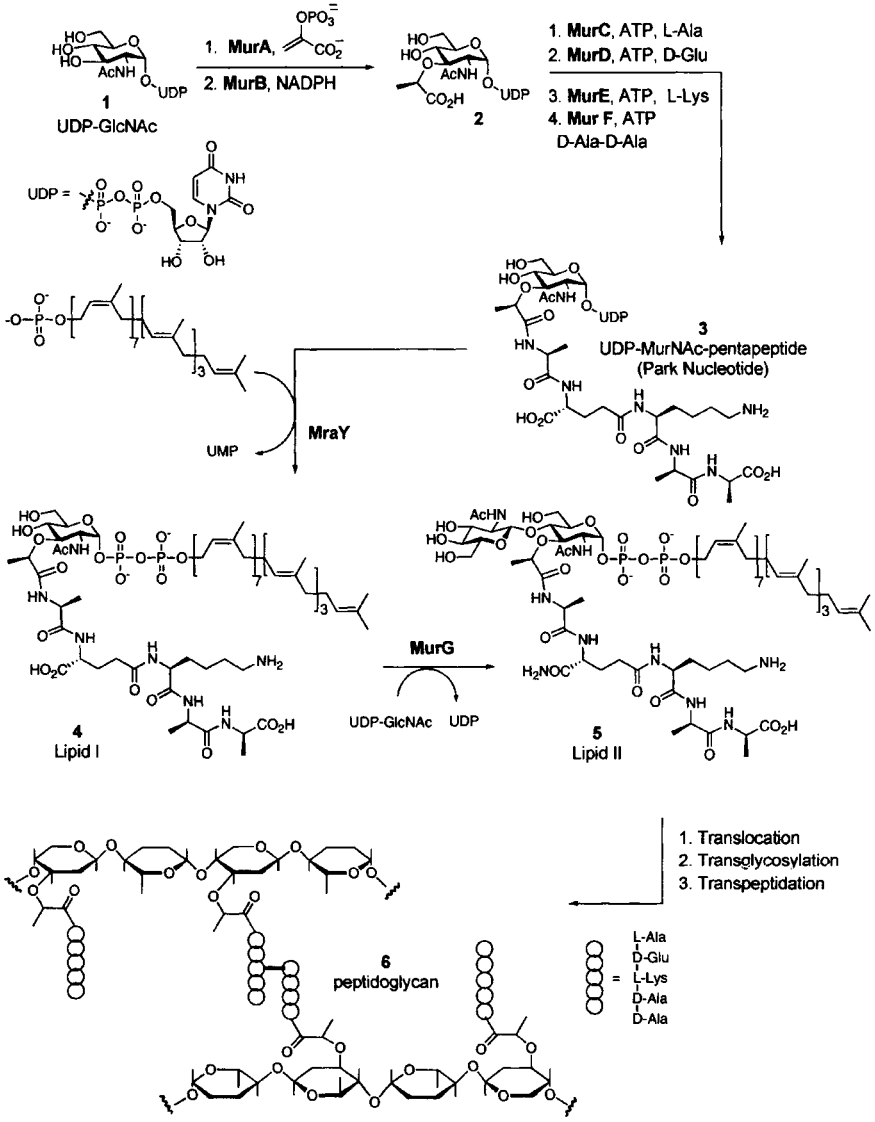
I. Introduction to Bacterial Cell Wall Biosynthesis

This account of our strategy for the synthesis of late stage intermediates utilized in the cell wall biosynthetic cascade was initiated in 1997 as part of research program whose principal aim was to identify new antibacterial agents with novel modes of action. Cell wall biosynthesis inhibitors have historically dominated treatment regimens for the management of bacterial infections.[1] Two of the most widely used classes of antibiotics, namely β-lactams and glycopeptides (e.g., vancomycin), derive their antibacterial activity through inhibition of key steps in the bacterial cell wall biosynthesis cascade. The emergence of bacterial resistance to these agents has begun to erode their once dependable clinical efficacy and has heightened the urgency for the identification and development of novel chemotherapeutic agents.[2]

In an effort to better understand emerging antimicrobial resistance mechanisms at the molecular level, and to enable identification of new agents, a renewed emphasis has been placed on the study of the enzymes involved in bacterial cell wall (peptidoglycan) biosynthesis. Structural and mechanistic information gained from these studies could be an invaluable asset to be used for the identification and/or design of new antibacterial agents with novel modes of action. Recent advances in biochemistry and bacterial genomics have facilitated the isolation and purification of the enzymes utilized in peptidoglycan biosynthesis. Isolation of the cell wall precursors from natural sources, however, has proven difficult and is impractical for securing quantities necessary to enable detailed mechanistic study. To address this difficulty, we initiated a program directed toward the synthesis of lipid I and lipid II; late-stage intermediates utilized in peptidoglycan biosynthesis.

Bacterial peptidoglycan consists of a network of β-[1,4]-linked carbohydrate polymers that are cross-linked through pendant pentapeptide chains.[3,4] The biosynthetic cascade is believed to occur in three distinct stages [Scheme 1]; the first stage taking place within the bacterial cytoplasm and resulting in the conversion of UDP-N-acetylglucosamine (UDP-GlcNAc, **1**) into UDP-N-acetylmuramic acid pentapeptide (Park Nucleotide, **3**). The initial step in this conversion is mediated by the MurA enzyme, which facilitates the transfer of an enolpyruvyl group onto the C(3) hydroxyl group of the UDP-GlcNAc precursor. Subsequent reduction mediated by MurB, an NADPH-dependent enolpyruvyl reductase, provides UDP-N-acetylmuramic acid (UDP-MurNAc, **2**) bearing a lactate handle used as the anchor for incorporation of the pentapeptide side chain. A series of ATP-dependent ligases (MurC-F) facilitate elaboration of the pentapeptide side chain. The ligases introduce, in succession, L-Ala, D-Glu, L-Lys,[5] and D-Ala-D-Ala to provide the fully elaborated UDP-MurNAc-pentapeptide **3**, also known as the Park Nucleotide.[6]

The second stage of this cascade takes place at the cytoplasmic surface of the bacterial cell membrane. In the first reaction, MraY catalyzes a pyrophosphate exchange reaction wherein the UDP-MurNAc-pentapeptide precursor is coupled to a membrane-anchored C_{55} lipid carrier with ejection of UMP to provide undecaprenylpyrophosphoryl-MurNAc-pentapeptide **4**, also know as lipid I. In the second reaction, the MurG enzyme catalyzes the transfer of GlcNAc from a UDP-GlcNAc precursor to the C(4)-hydroxyl group of the lipid-linked MurNAc-pentapeptide. The product of this enzymatic reaction, lipid II **5**, is the



SCHEME 1

final momomeric intermediate utilized in the bacterial cell wall biosynthetic cascade.[7]

In some Gram-positive bacteria, lipid II may be further modified by attachment of 1-5 amino acid residues to the ε-amino group of the lysine (or meso-DAP) residue. Frequently, these additional residues are

glycines, although organisms incorporating L-serine, L-threonine, and other amino acids are known.[3,4,8]

Subsequent to its formation by MurG, lipid II is translocated to the extracellular surface of the bacterial cell membrane where the membrane-anchored disaccharyl-pentapeptide is polymerized into β-[1,4]-linked glycan strands through the action of the membrane-bound bacterial transglycosylases. The undecaprenyl carrier lipid released during the glycosylation reaction is subsequently translocated across the cytoplasmic membrane to be recycled. In reactions mediated by the bacterial transpeptidases, the glycan polymers are then cross-linked via amide bond formation between the terminal amino group of the lysine residue, or the amino terminus of an attached peptide chain (vide supra), and the penultimate D-Ala residue of a neighboring glycan strand. The amide bond is established with concomitant loss of the terminal D-Ala residue. Mature peptidoglycan is a single macromolecule, which contains multiple layers of cross-linked glycan strands, and precisely defines the size and shape of the bacterial cell.

Our studies of the bacterial enzymes utilized in peptidoglycan biosynthesis required an ample supply of both lipid I and lipid II. Isolation of these precursors from bacterial sources presented significant challenges. First, each of these intermediates is present in very low copy numbers. For example, in *E. coli*, the copy numbers for lipid I and lipid II are estimated to be approximately 700 and 1000-2000 molecules per cell, respectively.[9] Second, separation of miniscule amounts of the cell wall precursors from the comparatively large amounts of cellular lipid and membrane components is technically challenging and further compromises the ability to isolate sufficient quantities of the enzyme substrates to enable detailed mechanistic studies.[10]

In recognition of the difficulty in obtaining the lipid intermediates in quantities to facilitate detailed mechanistic study of the peptidoglycan biosynthetic enzymes, we initiated an effort directed toward a chemical synthesis of both lipid I and lipid II. As was the case with the fermentation/isolation protocols, we anticipated several technical challenges that would need to be addressed in order to reach the target compounds. These challenges, and their solutions, will be discussed in the sections that follow.

II. Retrosynthetic Analysis for Lipid I.

The diversity of structural elements present in lipid I mandated a synthetic plan that would efficiently manage variables such as structural

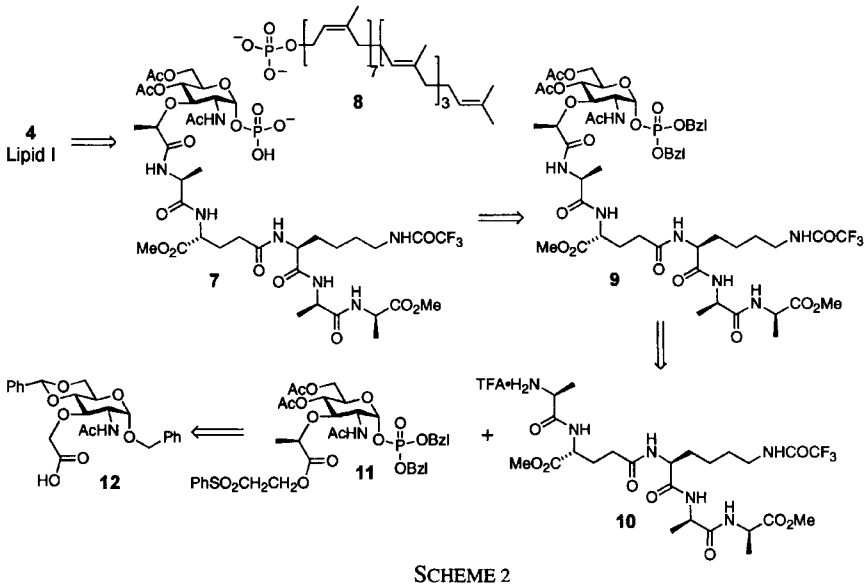
complexity, chemical stability, and protective group strategies. In our first analysis of the lipid I structure, we became acutely aware of the potential issues regarding the timing for installation of the lipid diphosphate. Foremost among our concerns was the anticipated acid sensitivity of the diphosphate linkage since it is both allylic and glycosidic. This concern, in turn, impacted our synthetic strategy on several levels. First, any synthetic transformations that would take place subsequent to introduction of the lipid diphosphate could not utilize acidic reaction or work-up conditions. This consideration also mandated that base cleavable protective groups be utilized for the carbohydrate core and peptide side chain if these were to be removed in a late-stage global deprotection. Second, we were also concerned about the possibility that insolubility or micelle formation could interfere with chemical transformations subsequent to introduction of the lipid side chain. Thus, we wanted to minimize the number of chemical transformations that would be required after introduction of the lipid side chain.

Our retrosynthetic analysis for lipid I is presented below [Scheme 2]. Our protected version of lipid I employed acetate protective groups for the carbohydrate hydroxyls, methyl esters for each of the carboxyl groups in the pentapeptide side chain, and trifluoroacetate for the terminal amino group of the lysine residue. These base-cleavable protective groups could be removed in a single operation in the final step of our synthesis and would not subject the sensitive diphosphate linkage to acidic reagents or reaction conditions.

Our first disconnection revealed glycosyl monophosphate **7** and undecaprenyl monophosphate **8**.[11] This disconnection was chosen because previous work, directed toward the synthesis of the Park Nucleotide **3**, had shown it possible to introduce an anomeric phosphate with anomeric selectivity in favor of the desired α-anomer. A second reason for choosing this disconnection was that undecaprenyl monophosphate was available for purchase from a commercial source. Thus, if we could identify a mild method for joining these two fragments, only a global deprotection step would be required to arrive at lipid I.

A second consideration in the design of carbohydrate-derived coupling partner **7** was the choice of protective group for the anomeric phosphodiester precursor. This group must be orthogonal to protective groups utilized in the carbohydrate subunit, as well as those employed in the peptide side chain, so as to ensure selective unmasking of the phosphodiester prior to the diphosphate coupling reaction. For this purpose we chose benzyl protective groups that would be, fortuitously, incorporated during the phosphitylation/oxidation sequence utilized to

install the anomeric phosphate. Thus monosaccharyl pentapeptide **9** was revealed as our next target in the retrosynthetic direction.



SCHEME 2

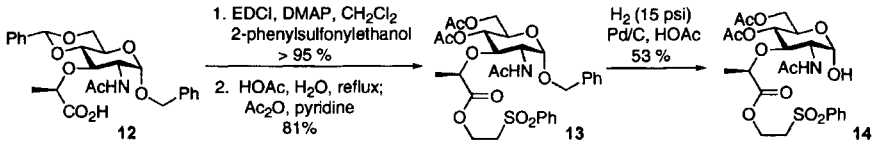
The pentapeptide side chain **10** would be prepared in protected form using standard peptide chemistry methods and would be introduced via coupling with an activated ester intermediate deriving from muramic acid derivative **11**. Phenylsulfonylethyl protection of the lactate carboxyl group would provide complete protective group orthogonality and would allow the lactate carboxyl group to be unmasked for peptide coupling under mild reaction conditions. Phenylsulfonylethyl ester **11** would, in turn be prepared from a differentially protected muramic acid derivative **12**, the key starting material for our synthesis of lipid I.

III. Synthesis of Phosphomuramyl Pentapeptide

The initial target for our chemical synthesis of lipid I was phosphomuramyl pentapeptide **9**. At the outset, we were confident in our ability to prepare the monosaccharyl pentapeptide core structure, but were unsure of our ability to install the anomeric phosphate with the desired α-stereochemistry. We were also concerned about the timing for introduction of the anomeric phosphate since solubility and anomeric selectivity could be strongly influenced by the presence or absence of the peptapeptide side chain. In addition, we had not settled on a method for

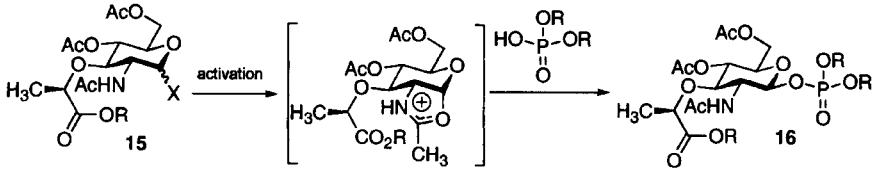
installation of the lipid diphosphate linkage although we were guided somewhat by our premise that the reaction conditions needed to be mild and non-acidic.

Our synthesis began [Scheme 3] with conversion of our protected muramic acid analog **12** to the corresponding phenylsulfonylethyl ester **13**. Our selection of phenylsulfonylethyl protection for the lactate carboxyl group was driven by the notion that this group must be orthogonal to all other protective groups and, if we were to remove it after installation of the anomeric phosphate, it must be efficiently removed under mildly basic reaction conditions. Hydrolysis of the 4,6-*O*-benzylidene acetal followed by acylation of the liberated hydroxyl groups provided diacetate **13**. Hydrogenolytic cleavage of the anomeric benzyl protective group provided lactol **14** and set the stage for our attempts at introduction of the anomeric phosphate group.



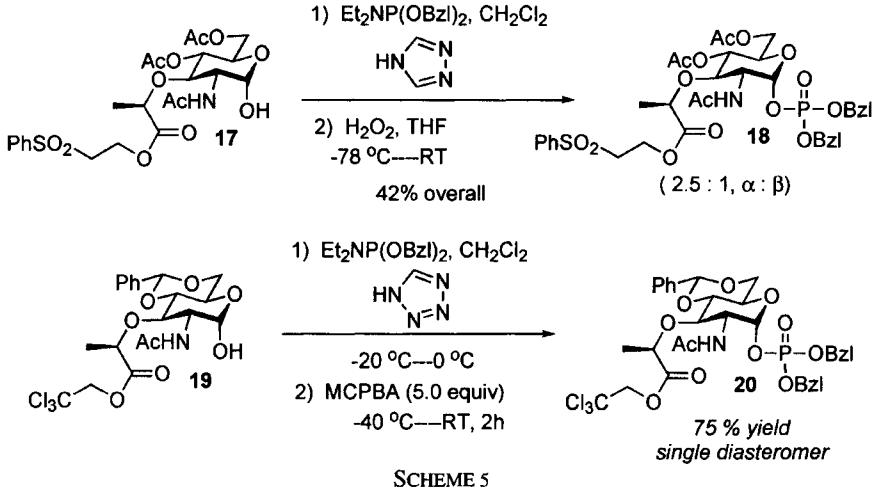
SCHEME 3

We were faced with some modest constraints with respect to the method we chose for introduction of the anomeric phosphate. Since our carbohydrate contained a C(2) acetamido group capable of neighboring group participation, reactions wherein the carbohydrate functions as the electrophilic component generally favor formation of 1,2-*trans* linked glycosyl phosphates [Scheme 4]. This would not provide a glycosyl phosphate with the stereochemistry required for a lipid I (or lipid II) total synthesis.[12] Although there were reports of carbohydrate-derived oxazolines having provided α-linked phosphates,[13] we chose instead to focus on methods that utilized a nucleophilic carbohydrate component.



SCHEME 4

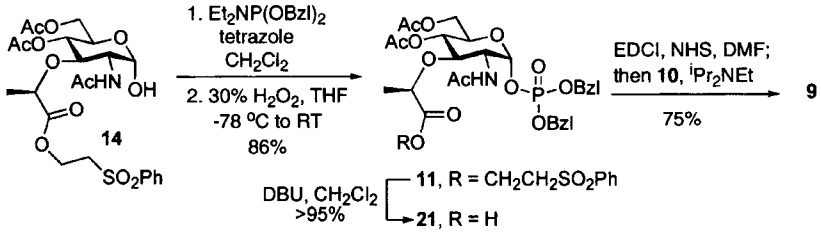
Our premise for the selection of a phosphitylation/oxidation sequence derived from its successful application during the course of the Park nucleotide synthesis.[14] Hitchcock reported the phosphitylation/oxidation of lactol **17**, existing predominantly as the α-anomer, provided the desired α-phosphate, albeit with a modest 2.5 : 1 preference.[15] In related work, the Walker group reported a similar phosphitylation/oxidation sequence applied to lactol **19** provided α-phosphate **20** as the exclusive product in very good chemical yield.[16]



SCHEME 5

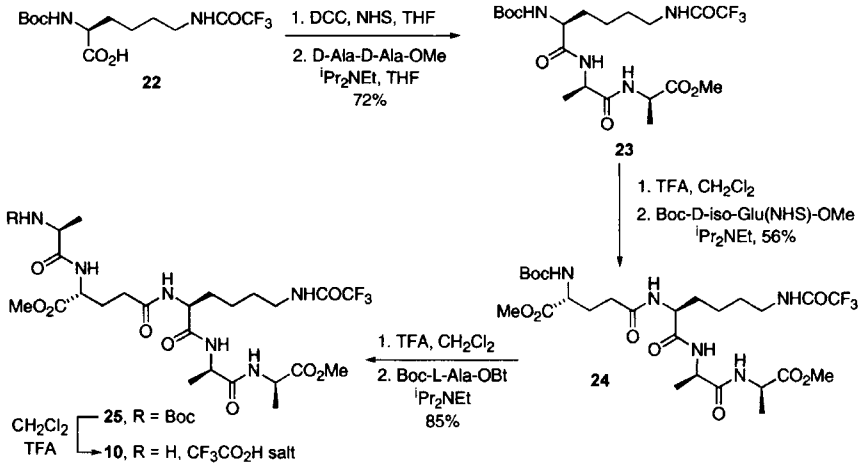
We were concerned about the apparent lack of anomeric selectivity in the Hitchcock example while at the same time encouraged with the results reported by Walker. Apart from the differing protecting group schemes used in each example, we felt the enhanced preference for production of the α-anomer observed in the latter example may have been due to the choice of acid catalyst. The Hitchcock precedent suggested that anomerization was competitive with capture of the activated phosphoramidite reagent by the anomeric hydroxyl group. Although we could not discount the possibility that the observed preference for the α-anomer in the Walker example could be, at least in part, due to a torsional effect exerted by the 4,6-*O*-benzylidene acetal,[17] we felt that the more likely explanation was that the more acidic catalyst (tetrazole, pKa = 4.9 versus triazole, pKa = 10.0) provided a greater equilibrium concentration of the activated phosphoramidite reagent, such that capture by the α-hydroxyl group occurred much faster than anomerization and capture by the more nucleophilic β–anomer.[18]

Thus, as shown below [Scheme 6], exposure of lactol **14** to dibenzyl-*N,N*-diethylphosphoramidite and 1*H*-tetrazole in dichloromethane followed by oxidation of the intermediate phosphite with 30% hydrogen peroxide provided the desired α-phosphate **11** ($^3J_{H1H2}$ = 3.4 Hz) in 86% yield as a single diastereomer. The stage was now set for introduction of the pentapeptide side chain.



SCHEME 6

The lactyl carboxyl group was unmasked by exposure of the phenylsulfonylethyl ester to DBU. Carboxyl group activation of muramic acid derivative **21** was achieved by conversion to the corresponding NHS ester (N-hydroxysuccinimide, EDCI, DMF). The pentapeptide fragment **10** was readily prepared in quantity using standard peptide synthesis protocols [Scheme 7]. Addition of a DMF solution of pentapeptide **10** to a solution of ^{i}PrNEt$_2$ and the NHS ester deriving from **21** provided the protected muramyl pentapeptide **9** in excellent overall yield.



SCHEME 7

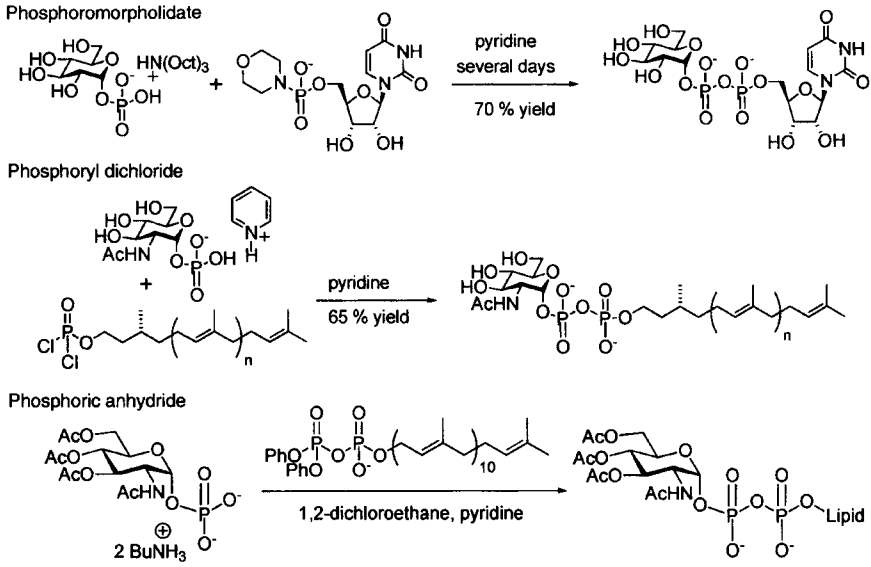
At this point, we had achieved access to an orthogonally protected phosphomuramyl pentapeptide derivative poised to enable completion of our lipid I total synthesis. The technical hurdles that remained to be addressed were: 1) identification of a mild method for installation of the lipid diphosphate linkage, 2) global deprotection, and 3) final purification of our synthetic lipid I. Our solutions to these problems are addressed in the following section.

IV. Lipid I Endgame

Having now reached a precursor that would enable our final approach to the lipid I target, our first task was to identify a mild method for installation of the chemically sensitive allylic diphosphate linkage. Initially, we considered the methods shown below and illustrated with representative examples [Scheme 8].

Phosphoromorpholidate intermediates, initially developed by Khorana and Moffatt,[19] have been widely used for the construction of nucleoside diphosphates. The construction of the diphosphate linkage typically involves exposure of a carbohydrate-derived phosphate nucleophile to phosphoromorpholidate electrophile in pyridine solvent. This protocol was attractive from the point of view that it can be executed on completely deprotected precursors. This method suffers, however, from the lengthy reaction times required for reasonable conversion, although a tetrazole modification, introduced by Wong,[20] had been shown to shorten reaction times considerably. The major drawback of this method, for our own purposes, is that it would require construction of either a carbohydrate-derived phosphoromorpholidate or the preparation of a phosphoromorpholidate intermediate deriving from our rather expensive undecaprenyl monophosphate precursor.

A second method that we considered involved condensation of a carbohydrate-derived phosphate salt with an in situ-generated phosphoryl dichloride.[21] The requisite phosphoryl dichlorides are prepared via exposure of a lipid phosphate to a Vilsmeier-type reagent. This protocol has been used successfully for the preparation of lipid diphosphate linkages in the dolichol series (i.e., lipids lacking an allylic double bond proximal to the diphosphate linkage). However, we were once again, hesitant to expose our undecaprenyl phosphate precursor to activation conditions that produce HCl as a by-product.

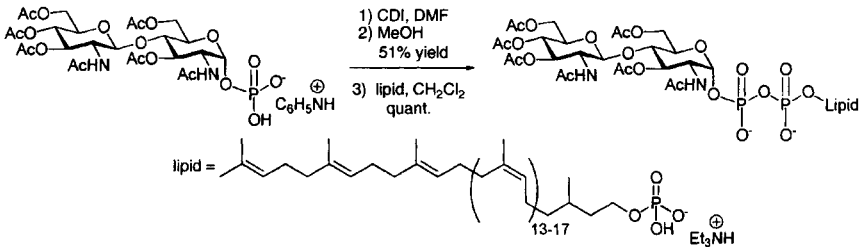


SCHEME 8

Similar concerns regarding the stability of our activated lipid intermediate led us to reject a method that involves the *in situ* preparation of lipid-derived phosphoric anhydrides.[22] The common theme for each of the methods illustrated above is that each involves activation of the lipid intermediate for the diphosphate coupling reaction. Given the expense of the undecaprenyl monophosphate precursor, we sought a method that would entail activation of the carbohydrate fragment for capture by an undecaprenyl monophosphate nucleophile. This, in principle, would also allow the opportunity for the coupling reaction to take place under basic reaction conditions and enable us to preserve the chemical integrity of our expensive lipid precursor.

Ultimately, we settled on a protocol that relied on in situ generation of a carbohydrate-derived phosphorimidazolidate for coupling with a lipid monophosphate [Scheme 9].[23,24] The procedure involved activation of an anomeric phosphate by exposure to carbonyldiimidazole (CDI) followed by quenching of the CDI with methanol. The activated intermediate is then exposed to a lipid phosphate salt and was reported to provide the lipid diphosphate in quantitative yield for the coupling step. Coward has successfully applied this protocol toward the construction of dolichyl-linked lipid diphosphates (see below),[23] but the basic reaction conditions

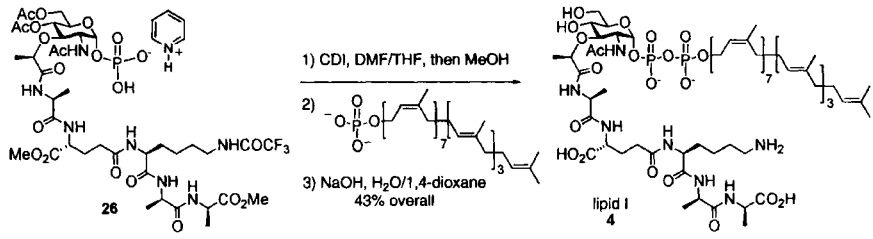
appeared better suited to address our lingering fears regarding the acid-lability of the diphosphate linkage present in lipid I.



SCHEME 9

In model reactions employing a glucosamine-derived anomeric phosphate, we found that we were able to monitor the appearance of the phosphoroimidazolidate intermediate by mass spectrometry. Similarly, we were able to monitor its disappearance upon slow addition of a farnesyl monophosphate salt added via syringe.

It now remained for us to apply the Coward protocol to our system and complete the synthesis of lipid I. Thus, phosphate **26** [Scheme 10], prepared by reductive cleavage of the phosphodiester protective groups of **9** (H_2, Pd/C in MeOH, followed by pyridine, 91% yield), was converted to the corresponding phosphoroimidazolidate, whose formation was readily monitored via mass spectrometry. Excess carbonyldiimidazole was quenched via addition of methanol. The lipid phosphate salt was then added in portions via syringe until complete consumption of the phosphoroimidazolidate intermediate was observed. Mass spectrometry also allowed us to monitor the appearance of the desired lipid-linked diphosphate product. When the reaction was judged to be complete, the reaction solution was carefully concentrated and the crude product was treated with sodium hydroxide in aqueous dioxane in order to achieve global deprotection. The crude product was purified by reverse-phase



SCHEME 10

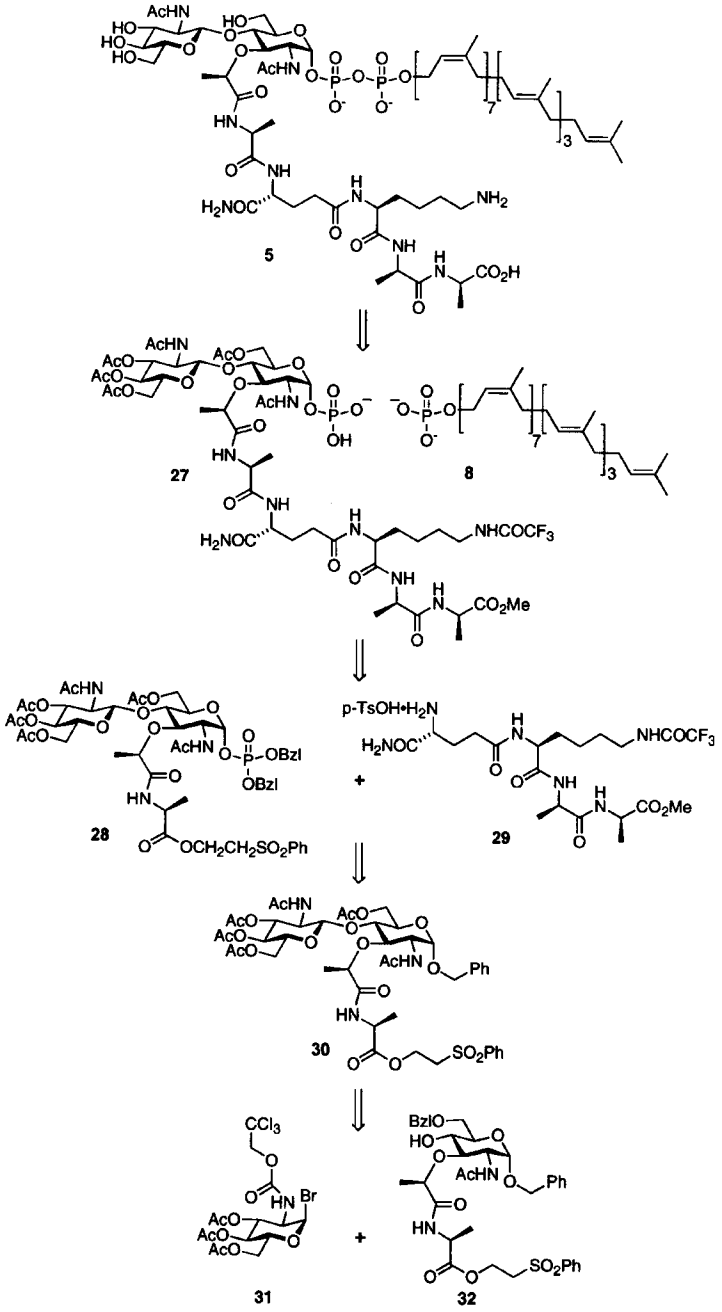
HPLC (C_8) using an aqueous ammonium bicarbonate/methanol solvent system. Upon lyophilization, lipid I was isolated as a white solid in 43% overall yield from **4**.[25]

In summary, we were able to develop a chemically robust synthetic route to lipid I, the penultimate intermediate utilized in bacterial cell wall biosynthesis. The identification of a method for stereoselective introduction of the anomeric phosphate and a protocol to enable diphosphate coupling were pivotal to our success and ultimately provided the precedent for our chemical synthesis of lipid II detailed in the sections that follow.

V. Retrosynthetic Analysis for Lipid II.

Our retrosynthetic analysis for lipid II built upon the precedent established during the course of our lipid I synthesis. The principal difference between these structures is the presence of the second sugar residue (*N*-acetylglucosamine, NAG) engaged in a β-[1,4]-linkage to the adjoining N-acetylmuramic acid (NAM) residue. Ultimately, the presence of this second sugar residue mandated some significant alterations of our original retrosynthetic strategy. The strategy illustrated below is that which was used for the assembly of lipid II. The rationale for this strategy will be further clarified in the following sections.

Following the lipid I analogy, we would introduce the lipid diphosphate at a late stage in the synthesis that would leave only a global deprotection as a final step.[26] Disconnecting the diphosphate linkage provided the first retrosynthetic intermediates, disaccharyl pentapeptide **27** and the commercially available undecaprenyl monophosphate **8**. Precursor **27** would be prepared by coupling of disaccharyl monopeptide **28** with tetrapeptide **29**. This disconnection was a risky one in that it presented the possibility for epimerization of the L-Ala α-stereocenter during a peptide coupling reaction employing an activated ester intermediate. Our original synthetic plan was to incorporate the entire pentapeptide in a single synthetic step. The rationale for this strategic departure will be discussed in the following section. Disaccharyl monopeptide **28** can be derived from **30** via cleavage of the phosphodiester protective groups and application of the phosphitylation/oxidation sequence utilized for lipid I. It is again important to note here that our protective group scheme must be triply orthogonal in order to allow selective unmasking of the anomeric hydroxyl and lactate carboxyl groups in the presence of other protected functionality. In turn, disaccharide **30** could be obtained from a Königs-



SCHEME 11

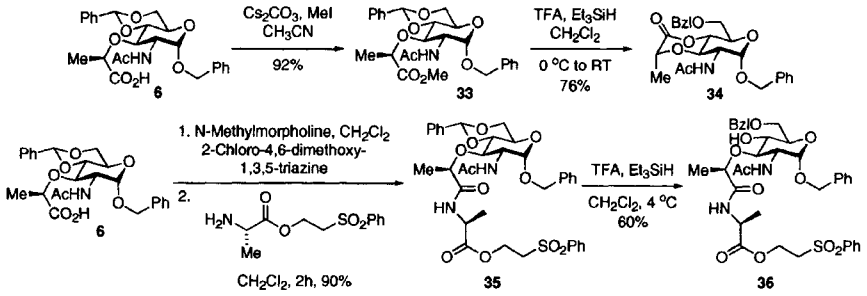
Knorr glycosidation reaction between glycosyl donor **31** and acceptor **32**. A carbamate protective group was chosen for the C(2) amino substituent of glycosyl donor **31** on the basis of its propensity toward neighboring group stabilization of the oxonium ion intermediate and thus favoring selective production of the desired β-glycosidic linkage. The assembly of disaccharide **30** is detailed in the following section.

VI. Assembly of an Orthogonally Protected NAG-NAM Disaccharide

A. PREPARATION OF GLYCOSYL ACCEPTOR **36**

Our synthetic efforts directed toward the synthesis of an orthogonally protected version of the NAG-NAM disaccharide[27] began with a study to assess the reductive opening of the 4,6-*O*-benzylidene acetal of our muramic acid starting material. Literature precedent reinforced by our own experience suggested that an ether protective group would be required at C(6) of our glycosyl acceptor for activation in the glycosidation reaction. Thus, reductive opening of an ester derivative of **6** was envisaged to unmask the C(4) hydroxyl group for the glycosidation reaction while preserving benzyl protection at the C(6) hydroxyl. In addition, carrying out the ring-opening reaction on an ester derivative would facilitate incorporation of the entire pentapeptide side chain via a coupling reaction involving an activated lactate ester intermediate.

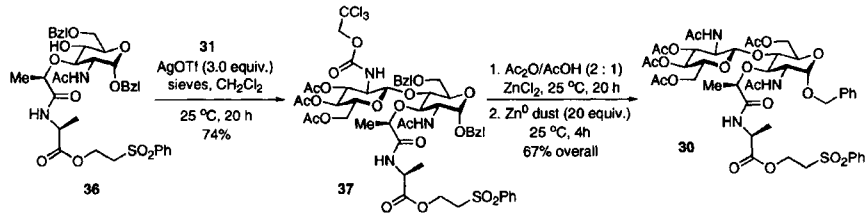
To test this strategy, we prepared methyl ester **33** from our bulk starting material, muramic acid derivative **6**. When **33** was treated with trifluoroacetic acid and triethylsilane under the reported reaction conditions,[28] lactone **34** was obtained in good yield [Scheme 12]. Apparently, acid catalyzed lactonization of the ring-opened intermediate proceeded at a rate competitive with ring opening itself.[29] We found that installation of the first amino acid residue (L-Ala) of the pentapeptide side chain completely suppressed acid-catalyzed cyclization of the reduction product. At the same time, however, we introduced the possibility of partial epimerization of the L-Ala α-stereocenter during the peptide coupling reaction that will elaborate the remainder of the pentapeptide side chain. With a reliable route to multiple gram quantities of our glycosyl acceptor in hand, our attention turned to construction of the β-[1,4]-glycosidic linkage.



SCHEME 12

B. THE NAG-NAM GLYCOSIDATION REACTION

As mentioned above, we wanted to employ a glycosyl donor with C(2) protection that would enable neighboring group stabilization of the oxonium ion intermediate. This should then favor the formation of a β-[1,4] glycosidic linkage upon capture of the oxonium ion by acceptor **36**. Wong and co-workers had measured the relative rates of glycosidic bond formation using various 2-amino-2-deoxyglucopyranose donors and noted a 40-fold relative reactivity increase with donors employing trichloroethoxycarbonyl (Troc) protection for the C(2) amino group when compared to those employing phthaloyl protection.[30] Thus, our efforts focused on glycosyl donor **31**, which was readily available in three steps from glucosamine. When glycosyl donor **31** and acceptor **36** were combined under rigorously anhydrous Königs-Knorr conditions, the desired β-linked disaccharide **37** was obtained in 74% yield after chromatographic purification.



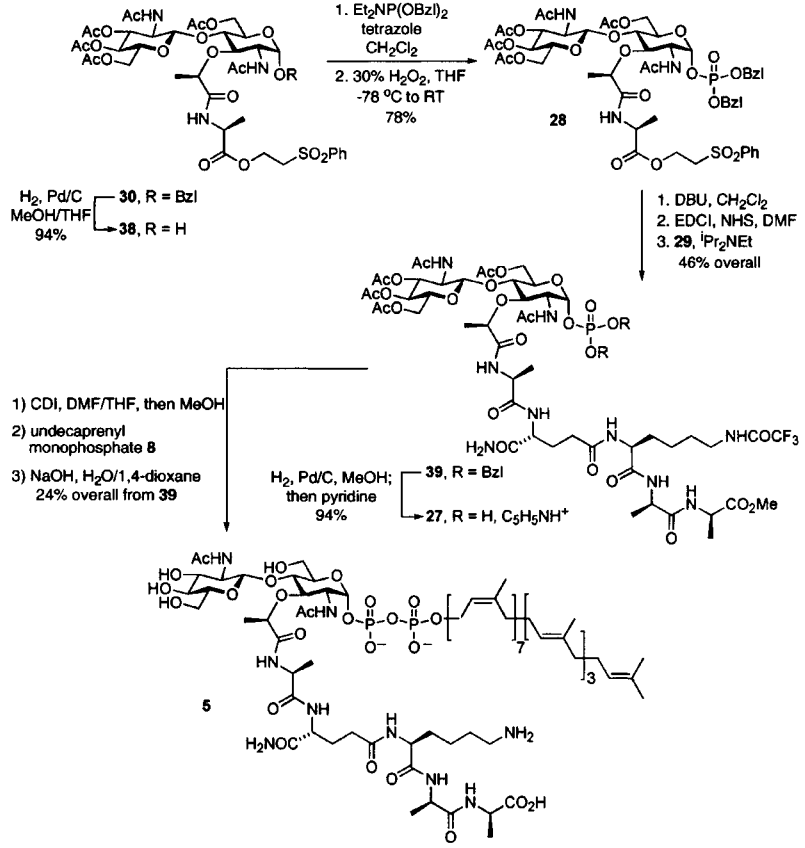
SCHEME 13

Finally, it remained for us to convert the protective group scheme required for glycosidation to a protection scheme for the lipid II endgame. To achieve this, four protective group interchange reactions were carried out in a single operation. Disaccharide **37** was dissolved in acetic

anhydride/acetic acid and treated with anhydrous $ZnCl_2$, which cleaved the muramyl C(6) benzyl ether, revealing the free hydroxyl group that acetylated in situ. Zinc dust was then added to the same reaction mixture to remove the Troc group and revealed the glucosamine amino group, which also acetylated in situ [Scheme 13].[31] Disaccharide **30** was obtained in 67% overall yield after flash chromatography and crystallization.[29]

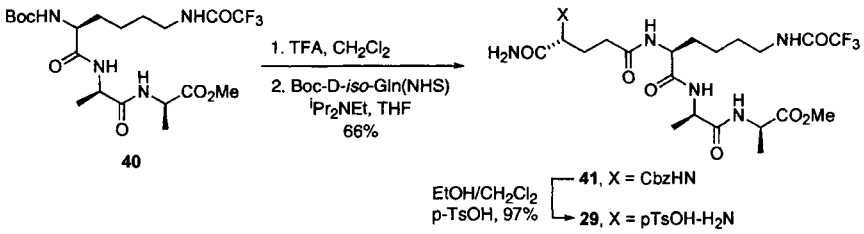
VII. Total Synthesis of Lipid II

With a reliable and reproducible route to multiple gram quantities of the key disaccharide intermediate **30** and the precedent established by our



SCHEME 14

lipid I synthesis, we were now in position quickly reach our final target compound, lipid II. Toward this end, our sequence began with hydrogenolysis of benzyl ether **30** to provide lactol **38** in 94% yield [Scheme 14]. The stage was now set for introduction of the anomeric phosphate. Once again we employed the phosphitylation protocol with 1*H*-tetrazole catalysis followed by oxidation of the intermediate phosphite with 30% H_2O_2.[15,16] This transformation caused some concern for us since, given the structural differences in the carbohydrate components, we could not be completely confident that this reaction would favor selective production of the desired α-phosphate. Nonetheless, we were elated when we obtained a 78% yield of phosphate **28** as the sole isolated product having the desired α-configuration as judged by proton coupling constant analysis ($^3J_{H1H2}$ = 3.0 Hz). Our next step set the stage for elaboration of the pentapeptide side chain. Thus, unmasking of the lactate carboxyl group was achieved by treatment of **28** with DBU. The carboxylic acid intermediate was activated by conversion to the corresponding NHS ester. Addition of a DMF solution of tetrapeptide **29** [Scheme 15] to a solution of the activated ester and $^iPr_2NEt$ in DMF provided disaccharyl pentapeptide **39** in 46% overall yield from **28**. Hydrogenolytic cleavage of the phosphodiester protective groups followed by evaporation of the crude product from pyridine provided the



SCHEME 15

monopyridyl salt **27** and set the stage for the final diphosphate coupling reaction. Activation of anomeric phosphate as its phosphoroimidazolidate, followed by exposure to undecaprenyl monophosphate **8** in DMF/THF over 4 days cleanly afforded the coupled product.[23] Global deprotection was achieved through exposure of the crude diphosphate to sodium hydroxide in aqueous dioxane and provided lipid II **5** in 24% overall yield (from **27**) after reverse-phase HPLC purification.[32,33]

VIII. Concluding Remarks

The emergence of bacterial resistance antimicrobial agents that inhibit bacterial cell wall biosynthesis has hastened the search for novel, yet to be exploited, targets for chemotherapeutic intervention. Advances in molecular biology and biochemistry have now made it possible to isolate and study the enzymes involved in the peptidoglycan biosynthesis pathway. Yet, despite the ready availability of these enzymes, detailed study of resistance mechanisms has lagged due to the limited availability of the natural substrates. Our goal at the outset of this work was to demonstrate that organic synthesis could provide a very powerful solution to problem of substrate availability. It is our anticipation that the chemical synthesis of lipid I and lipid II will provide valuable biochemical tools to advance the understanding of the enzyme mechanisms implicated in the peptidoglycan biosynthesis pathway and, hopefully, lead to the identification of new chemotherapeutic agents with novel modes of action.

Acknowledgements

The successful synthetic efforts described in this chapter would not have been possible without the combined efforts of a truly exceptional group of co-workers. They are, in alphabetical order: James A. Aikins, William J. Hornback, Scott C. Maudlin, Shankar S. Saha, Brian E. Winger, and Mohammad Zia-Ebrahimi. I would like to extend my sincere appreciation to everyone involved in the biochemical and spectroscopic characterization of the synthetic versions of lipid I and lipid II: William Alborn, Robert Boyer, Melissa Clague, James Gilliam, and David Peake. I also wish to thank Eli Lilly and Company for their support of this work. Finally, I would like to thank Larry Blaszczak for his insights, persistence, and continuous support throughout the completion of this project.

References and Footnotes

1. Gale, E. F., Cundliffe, E., Reynolds, P. E., Richmond, M. H., Waring, M. J. *The Molecular Basis of Antibiotic Action*; 2nd ed.; Wiley-Interscience: New York, 1981.
2. Chu, D. T. W., Plattner, J. J., Katz, L. *J. Med. Chem.* **1996**, *39*, 3853.
3. Holtje, J.-V. *Microbiol. Mol. Biol. Rev.* **1998**, *62*, 181.
4. Bugg, T. D. H., Walsh, C. T. *Nat. Prod. Rep.* **1992**, 199.
5. In Gram-negative bacteria, as well as some Gram-positive strains, meso-diaminopimelic acid (meso-DAP) is incorporated in place of L-Lys.
6. Park, J. T. *J. Biol. Chem.* **1952**, *194*, 877.
7. In Scheme 1, lipid II is shown with a glutamine residue replacing the glutamate residue shown in the lipid I precursor. In some bacterial strains, for example, Streptococcus pneumoniae, a glutamine residue is present in lipid II. Experiments

have shown lipid I and lipid II (D-Glu) are substrates for an ATP-dependent amidation reaction. See: Siewert, G., Strominger, J. L. *J. Biol. Chem.* **1968**, *243*, 783.
8. Schleiffer, K. H., Kandler, O. *Bacteriol. Rev.* **1972**, *36*, 407.
9. van Heijenoort, Y., Gomez, M., Derrien, M., Ayala, J., van Heijenoort, J. *J. Bacteriol.* **1992**, *174*, 3549.
10. See, for example: (a) Umbreit, J. N., Strominger, J. L. *J. Bacteriol.* **1972**, *112*, 1306; (b) Nakagawa, J., Tamaki, S., Tomioka, S., Matsuhashi, M. *J. Biol. Chem.* **1984**, *259*, 13937; (c) Brötz, H., Bierbaum, G., Leopold, K., Reynolds, P. E., Sahl, H.-J. *Antimicrob. Agents Chemother.* **1998**, *42*, 154.
11. Undecaprenyl monophosphate bis-ammonium salt may be purchased from: Institute of Biochemistry and Biophysics, Polish Academy of Sciences, ul. Pawinskiego 5A, 02-106 Warszawa, Poland.
12. For leading references, see: (a) Boons, G.-J., Burton, A., Wyatt, P. *Synlett* **1996**, 310; (b) Schmidt, R. R., Braun, H., Jung, K.-H. *Tetrahedron Lett.* **1992**, *33*, 1585; (c) Sabesan, S., Neira, S. *Carbohydr. Res.* **1992**, *223*, 169; (d) Schmidt, R. R., Wegmann, B., Jung, K.-H. *Liebigs Ann. Chem.* **1991**, 121; (e) P. Pale, P., Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 4547; (f) Veeneman, G. H., Broxterman, H. J. G., Van der Marel, G. A., Van Boom, J. H. *Tetrahedron Lett.* **1991**, *32*, 6175; (g) Bannwarth, W., Trzeciak, A. *Helv. Chim. Acta* **1987**, *70*, 175.
13. (a) Khorlin, A. Y., Zurabyan, S. E., Antonenko, T. S. *Tetrahedron Lett.* **1970**, 4803; (b) Warren, C. D., Herscovics, A., Jeanloz, R. W. *Carbohydr. Res.* **1978**, *61*, 181; (c) Inage, M., Chaki, H., Kusumoto, S., Shiba, T. *Tetrahedron Lett.* **1981**, *22*, 2281.
14. Hitchcock, S. A., Eid, C. N., Aikins, J. A., Zia-Ebrahimi, M., Blaszczak, L. C. *J. Am. Chem. Soc.* **1998**, *120*, 1916.
15. Sim, M. M., Kondo, H., Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 2260.
16. Men, H., Park, P., Ge, M., Walker, S. *J. Am. Chem. Soc.* **1998**, *120*, 2484.
17. Fraser-Reid, B., Wu, Z., Andrews, C. W., Skowronski, E., Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1434.
18. For mechanistic studies on the role of 1*H*-tetrazole in phosphoramidite coupling reactions, see: (a) Dahl, B. H., Nielsen, J., Dahl, O. *Nucleic Acids Res.* **1987**, *15*, 1729; (b) Berner, S., Muehlegger, K., Seliger, H. *Nucleic Acids Res.* **1989**, *17*, 853.
19. Roseman, S., Distler, J. J., Moffatt, J. G., Khorana, H. G. *J. Am. Chem. Soc.* **1961**, *83*, 659.
20. Wittman, V., Wong, C.-H. *J. Org. Chem.* **1997**, *62*, 2144.
21. Imperiali, B., Zimmerman, J. W. *Tetrahedron Lett.* **1990**, *31*, 6485.
22. Warren, C. D., Jeanloz, R. W. *Biochemistry* **1972**, *11*, 2565.
23. Fang, X., Gibbs, B. S., Coward, J. K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2701-2706.
24. Danilov, L. L., Maltsev, S. D., Shibaev, V. N., Kochetkov, N. K. *Carbohydr. Res.* **1981**, *88*, 203.
25. For the first reported synthesis of lipid I, see: Ye, X.-Y., Lo, M. C., Brunner, L., Walker, D., Kahne, D., Walker, S. *J. Am. Chem. Soc.* **2001**, *123*, 3155.
26. Care would have to be exercised when exposing the pentapeptide to hydroxide ion-mediated deprotection conditions since the base-catalyzed rearrangement of iso-glutamine to glutamate in peptidoglycan-related structures has been observed.

(a) Keglevic, D., Derome, A. E. *Carbohydrate Res.* **1989**, *186*, 63; (b) Keglevic, D., Kidric, J. J. *Carbohydrate Res.* **1992**, *11*, 119.

27. For other reported syntheses of the NAG-NAM disaccharide, see: (a) Mercer, C., Sinaÿ, P. *Tetrahedron Lett.* **1973**, *13*, 1029; (b) Durette, P. L., Meitzner, E. P., Shen, T. Y. *Carbohydr. Res.* **1979**, *77*, C1; (c) Kusumoto, S., Yamamoto, K., Imoto, M., Inage, M., Tsujimoto, M., Kotani, S., Shiba, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1411; (d) Kusimoto, S., Imoto, M., Ogiku, G., Shiba, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1419; (e) Farkas, J., Ledvina, M., Brokes, J., Jezek, J., Zajicek, J., Zaoral, M. *Carbohydr. Res.* **1987**, *163*, 63; (f) Kinzy, W., Schmidt, R. R. *Liebigs Ann. Chem.* **1987**, 407; (g) Termin, A., Schmidt, R. R. *Liebigs Ann. Chem.* **1989**, 789; (h) Ledvina, M., Farkas, J., Zajicek, J., Jezek, J., Zaoral, M. *Collect. Czech. Chem. Commun.* **1989**, *54*, 2784; (i) Termin, A., Schmidt, R. R. *Liebigs Ann. Chem.* **1992**, 527.
28. DeNinno, M. P., Etienne, J. B., Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669.
29. Saha, S. L., VanNieuwenhze, M. S., Hornback, W. J., Aikins, J. A., Blaszczak, L. C. *Org. Lett.* **2001**, *3*, 3575.
30. Zhang, Z., Ollmann, I., Ye, X.-S., Wischnat, R., Baasov, T., Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *120*, 1916.
31. Yang, G., Ding, X., Kong, F. *Tetrahedron Lett.* **1997**, *38*, 6725.
32. A small amount (<5%) of a second product is routinely observed during the coupling reaction. Isolation and preliminary spectroscopic characterization suggests this product may be a diastereomer that could, presumably, arise from epimerization of the L-Ala α-stereocenter during the peptide-coupling event.
33). Scientists at DuPont Pharmaceuticals have also published a synthesis of lipid II. Schwartz, B., Markwalder, J. A., Wang, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11638.

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STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 12

RING REARRANGEMENT METATHESIS (RRM) – A NEW CONCEPT IN PIPERIDINE AND PYRROLIDINE SYNTHESIS

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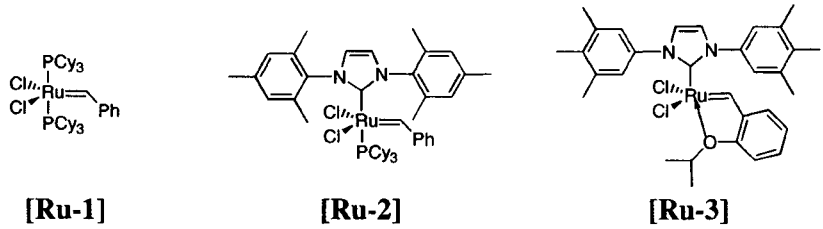
I Introduction

Nitrogen based heterocycles are present in an array natural products, thousands of which have been mentioned in clinical or preclinical studies.[1] Thus, the synthesis of piperidine-[2] and pyrrolidine-[3] derivatives have attracted much attention from the modern day organic chemists. Of particular interest are strategies that lead to chiral heterocyclic derivatives.[4]

This chapter deals with applying ruthenium catalysed olefin metathesis to the synthesis of piperidine and pyrrolidine containing compounds.

II. Olefin Metathesis

Olefin metathesis has proved to be a powerful synthetic tool in organic synthesis.[5] The advent of well-defined metal carbene complexes with remarkable functional group tolerance has rendered metathesis as an efficient route to the synthesis of new C-C bonds. Examples of widely used ruthenium metathesis catalysts include **[Ru-1]**,[6] **[Ru-2]**[7] and **[Ru-3]** [8] (Figure 1).



[Ru-1] **[Ru-2]** **[Ru-3]**

FIGURE 1: Ruthenium metathesis catalysts

Aside from polymerisation reactions, olefin metathesis can be classified into three categories, ring closing metathesis (RCM), ring opening metathesis (ROM) and cross metathesis (CM) (Figure 2).

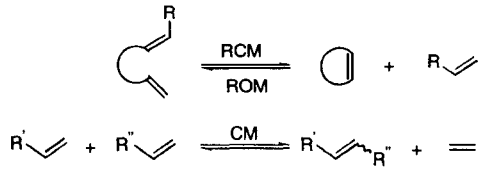


FIGURE 2: Ring closing metathesis (RCM), ring opening metathesis (ROM) and cross metathesis (CM)

III. Domino Reactions – Ring Rearrangement Metathesis (RRM)

In classical organic synthesis, the individual bonds in the target molecule are usually formed step by step. Starting from relatively simple starting compounds, the structural complexity in the molecule slowly increases in the course of the synthesis. Domino, or tandem, reactions are

processes that involve at least two transformations in one step, in which the subsequent reaction always occurs at the functionality formed in the previous step. These transformations can be either bond formation or bond cleavage. For example, linking several metathesis reactions (e.g. ROM-RCM, RCM-ROM-RCM or ROM-RCM-CM) allows for the rapid construction of complex structures from simple precursors in only one pot. Domino metathesis reactions of this type can be referred to as ring rearrangement metathesis (RRM). This concept will be illustrated by discussing heterocyclic systems, hence introducing the construction of piperidines and pyrrolidines.

IV. Heterocyclic Systems

RRM has been implemented in the synthesis of fused carbocycles[9] as well as a number of polycyclic ethers.[10] This has been extended to the synthesis of piperidines and pyrrolidines *via* ROM-RCM or RCM-ROM-RCM combinations (Figure 3).

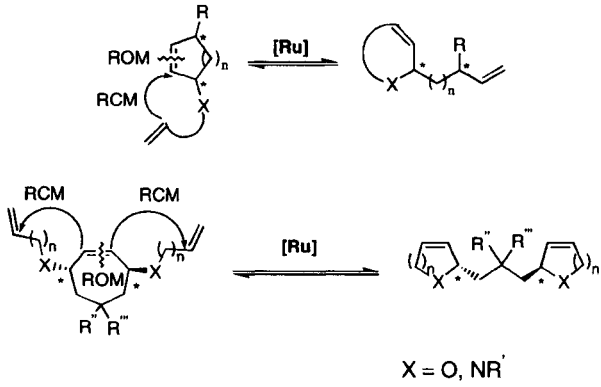


FIGURE 3: ROM-RCM (upper); RCM-ROM-RCM (lower)

These reactions are driven by a combination of factors, including a loss of ring strain or the release of a volatile olefin such as ethylene. They can also be kinetically controlled by the formation of a less reactive carbene complex. An important feature of RRM is the catalytic transfer of stereocentres from the corresponding substituted carbocycles, *i.e.* the chirality embedded in the carbocyclic starting material is completely transferred to the product side chain. This allows chirality to be introduced by means of side chains at the carbocycle. Synthetically, this

is a very attractive feature as side chains can be readily introduced from easily accessible or commercially available compounds. Strategically, this method is extremely flexible and allows the synthesis of a myriad of chiral heterocycles. Such discoveries drive the imagination of synthetic organic chemists to find applications which fully utilise the route.

We have synthesised a number of natural products containing piperidine or pyrrolidine units using the RRM strategy (Figure 4).

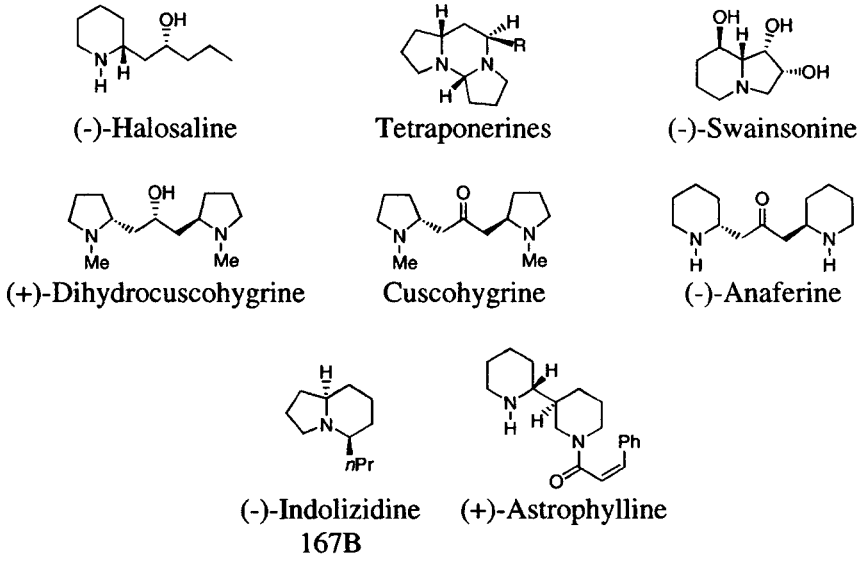


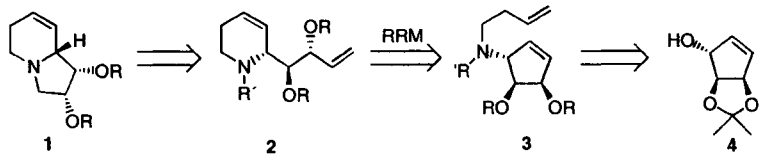
FIGURE 4: Natural products synthesised *via* a ring rearrangement strategy

Each of these natural alkaloids will be discussed individually, not only to illustrate the power of RRM, but also to provide an insight into the thought process that is required to apply basic chemical research to a practical end.

V. ROM-RCM

A. 1,2,3,8a-HEXAHYDROINDOLIZINE

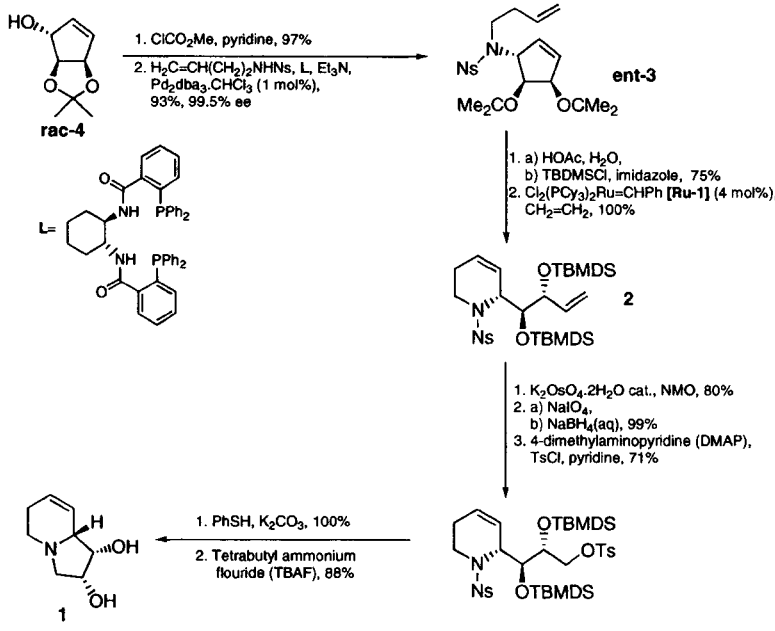
Studies have been carried out to illustrate the general applicability of a ROM-RCM sequence.[11,12] One example of these studies is the synthesis of 1,2,3,5,6,8a-hexahydroindolizine **1**.[11] An insight into the design of the synthesis can be gained from examining the retrosynthetic analysis (Scheme 1).



SCHEME 1

The target compound **1** can be obtained from the functionalised tetrahydropyridine **2**, which in turn can be obtained from the cyclopentenylamine **3** *via* ruthenium catalysed RRM. The racemic alcohol **4** is readily accessible from cyclopentadiene,[13] which was converted to the enantiomerically pure ring rearrangement precursor **3** in one step. This highly efficient palladium (0) catalysed allylic amination step was achieved with the aid of the chiral diphosphine ligand **L**,[14] yielding **3** in a 93% yield and a 99.5% ee. The RRM was carried out in a quantitative yield using **[Ru-1]**. This rearrangement, like all the ROM-RCM discussed in this chapter, was carried out in the presence of ethylene. Ethylene acts as a final CM partner to release the ruthenium. It also generates the active ruthenium methylidene catalyst and suppresses dimerisation. Subsequent steps were carried out with retention of stereochemistry to give the target compound **1** (Scheme 2).

This example outlines how RRM can be harnessed for the synthesis of novel alkaloids. It also illustrates the various factors that need to be considered when designing a synthesis to harness a particular strategy *i.e.* the enantiomeric synthesis of the RRM precursor.



SCHEME 2

B. (-)-SWAINSONINE

This method was adapted towards the synthesis of the natural product swainsonine which closely resembles 1,2,3,5,6,8a-hexahydroindolizine (**1**).

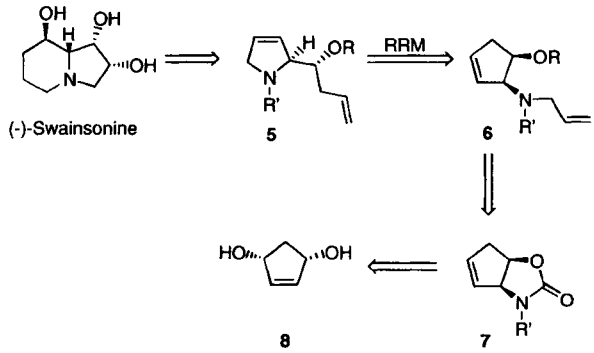
1 (-)-Swainsonine

FIGURE 5: 1,2,3,5,6,8a-hexahydroindolizine (**1**) and (-)-swainsonine

Swainsonine was first isolated from the fungus *Rhizoctonia leguminicolain*[15] in 1973 and has since attracted a great deal of biological and synthetic attention.[16] It is found to be an effective inhibitor of α-D-mannosidases including the glycoprotein-processing enzyme mannidase II.[17] It also exhibits important antimetastatic, antitumor-proliferative, anticancer and immunoregulating activity.[17] Swainsonine was the first

inhibitor to be selected for testing as an anticancer drug, reaching phase I clinical trials. Due to its promising biological profile, much effort has been devoted to the development of efficient syntheses of these azasugar analogue.[18]

Despite the similarity between compound **1** and (-)-swainsonine, a different retrosynthetic strategy was devised for the synthesis of (-)-swainsonine (Scheme 3).[19] The ring rearrangement yielded the hydropyrrolidine **5**, which was prepared from the precursor **6**. The enantiometrically pure oxazolidine derivative **7** was a suitable chiral starting material, as it was efficiently synthesised from the diol **8**. As with the synthesis of **1**, a palladium (0) catalysed allylic amination was carried out in the presence of ligand **L** (Scheme 2)[14] to give **7** with an ee of 97%, which was increased to >99% on recrystallisation with dichloromethane/hexane.

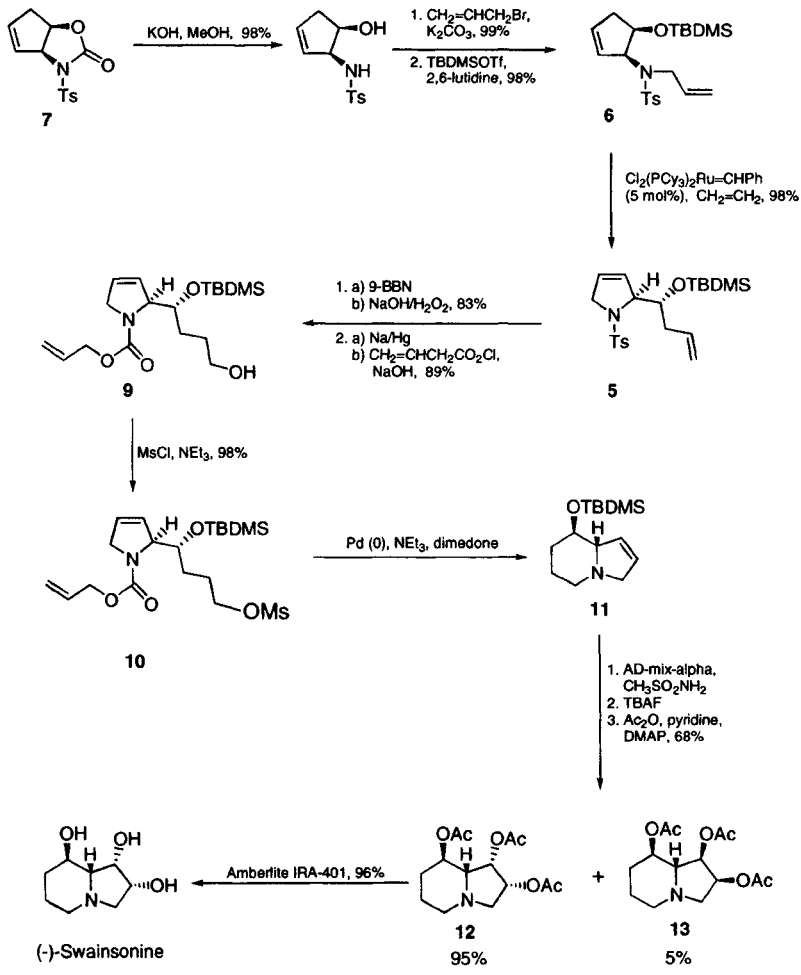


SCHEME 3

The enantiomerically pure oxazolidinone derivative **7** (Scheme 4),[14,20] was converted into the metathesis precursor **6** by a sequence of carbamate hydrolysis, amide alkylation and protection of the secondary alcohol as the TBDMS ether in a 95% overall yield. Subsequent **[Ru-1]** catalysed ROM-RCM converted **6** into the desired dihydropyrrole **5**.

The key element of the synthesis is the use of the sterically demanding TBDMS ether, which shifts the equilibrium completely towards the product. Attempts to carry out the RRM with the benzyl ether analogue of **6** afforded a starting material/product ratio of 18:1. The sterically demanding TBDMS ether was far superior to the benzyl ether as the increased interaction between substituents facilitates ring opening. In

addition, dimerisation of products is suppressed by the introduction of this large substituent at the hydroxy group. Again, it is important to note that with all RRM reactions, the stereochemical integrity of the two chiral centers is completely preserved in the rearrangement.



SCHEME 4

The six membered ring was formed by first functionalising the terminal double bond *via* selective hydroboration using 9-BBN, followed by oxidative work-up to yield the terminal alcohol. To ensure successful hydroboration, lead tetraacetate was added to **5**. This removed all traces

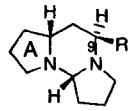
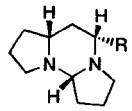
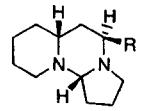
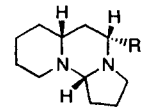
of ruthenium that interfered with the hydroboration. Subsequent deprotection of the tosyl group was achieved by freshly prepared sodium amalgam in methanolic phosphate buffer solution, but attempts to induce cyclisation by *in situ* activation of the terminal alcohol were unsuccessful. Therefore, protection with allyl chloroformate was carried out to yield **9** and the primary alcohol was mesylated to provide the cyclisation precursor **10**. At this point deprotection of the allyl oxycarbonyl group using polymer bound $Pd(PPh_3)_4$ was carried out and nucleophilic substitution of the mesylate by the freed amino group established the six-membered ring, hence the indolizidine derivative **11**.

The final step to achieve (-)-swansonine from the indolizidine **11** required oxidation of the alkene, which proved to be surprisingly non-trivial. A procedure to carry out this transformation using OsO_4, NMO, acetone and water at room temperature has been reported to give good selectivity (88:12)[21] in favour of the desired configuration. In the case of the oxidation of **11**, after desilylation and triacetate protection almost no diastereoselectivity was observed (**12-13** = 50:50-42:58). An alternative method was implemented which required AD-mix-alpha,[22] which improved the diastereoselectivity of **12:13** to (20:1). Final hydrolysis of **12** using Amberlite resin yielded the desired product.

The syntheses of 1,2,3,5,6,8a-hexahydroindolizine (**1**) and (-)-swainsonine were successfully carried out *via* a ROM-RCM strategy, and final CM with ethylene to free the ruthenium. Two different synthetic routes were implemented to achieve a similar compound. In the case of 1,2,3,5,6,8a-hexahydroindolizine **1**, the six-membered ring was established first using RRM and in the case of (-)-swainsonine, the five-membered ring was established first. In both cases, the ring rearrangement precursors were enantiomerically pure five-membered carbocycles, which can be synthesised efficiently from racemic starting materials.

C. TETRAPONERINES

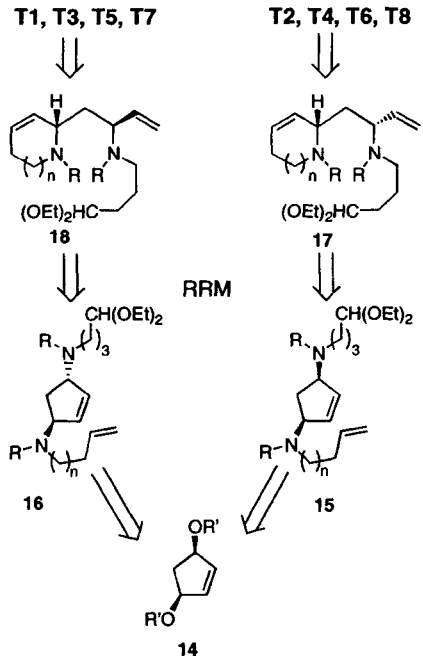
Another example of a natural product that we synthesised using a ROM-RCM sequence are tetraponerines.[23] Tetraponerines (**T1-T8**) (Figure 6) were isolated from the venom of the New Guinean ant *Tetraponera sp.*[24] These alkaloids represent the major constituents of the contact poison and contaminated enemies immediately show symptoms of nerve poisoning.

T1 R=C_3H_7 **T2** R=C_3H_7 **T3** R=C_3H_7 **T4** R=C_3H_7
T5 R=C_5H_{11} **T6** R=C_5H_{11} **T7** R=C_5H_{11} **T8** R=C_5H_{11}

FIGURE 6: Tetraponerines **T1-T8**

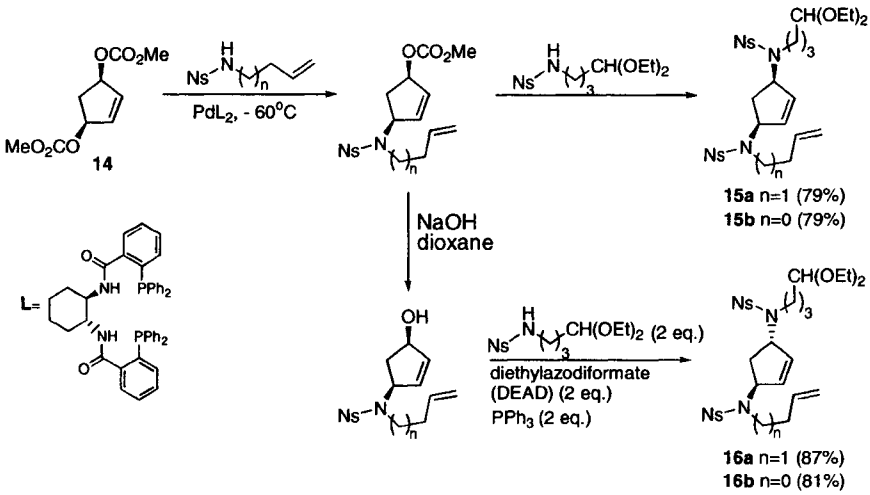
Tetraponerines (**T1-T8**) each contain three stereocentres and differ from one another in the side chain and stereochemistry at C-9, and the size of ring A. Due to these features, a general procedure for the synthesis of these unusual alkaloids is challenging. A general strategy utilising RRM to synthesise tetraponerines **T1-T8** was developed and can be seen in the retrosynthetic analysis (Scheme 5).



SCHEME 5

Dicarbonate **14** was used as the starting material to achieve both *cis*- and *trans*- ring rearrangement precursors **15** and **16**. ROM-RCM of the five-membered carbocycles **15** and **16** leads to **17** and **18**. These compounds contain a terminal double bond at position 9, which can be easily functionalised and are set up to form the tricyclic tetraponerines.

The key step is the synthesis of the metathesis precursor, which was required in both the *cis*- and *trans*- configurations. The *cis*-configuration was obtained *via* enantioselective domino allylic alkylations (Scheme 6, **15a** and **15b**). For the *trans*-configuation, an allylic alkylation was used to introduce the first amine, but the second amine was introduced *via* the Mitsunobu reaction[25] to achieve an inversion of the stereocentre (Scheme 6, **16a** and **16b**).



SCHEME 6

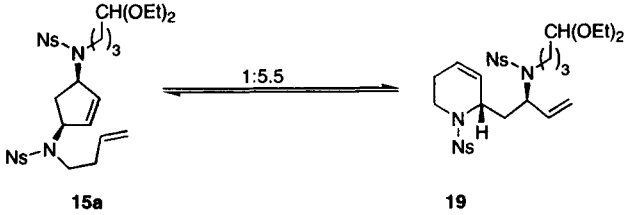
Once all the metathesis precursors were available, the synthesis was continued by detailed investigations of the RRM. The metatheses were carried out in CH_2Cl_2 with 5 mol % of **[Ru-1]**. To reiterate, the reaction was carried out in the presence of ethylene in order to accelerate the metathesis and to avoid the formation of side products. The first RRM was carried out with the *cis*- precursor **15a** at room temperature and showed slow conversion to the dihydropyridine **19** (Scheme 7). The conversion was accelerated by performing the reaction at 35 °C, yielding **19** (79%) after 2 days. A mixture of **15a** and **19** in a 1:5.5 ratio was

determined by ^{1}H NMR and no other products were detected. When running the reaction with the *trans*- precursor **16a**, under the same conditions, the ratio of **16a**:**20** was only 1:2. To improve this ratio, the influence of *N*-protecting groups on the equilibrium was investigated. Nosyl (Ns) was replaced by benzyloxycarbonyl (Cbz) and the effect on the rate and the yield of the reaction was dramatic. Compound **21** was converted to **22** in 12 h at room temperature with complete consumption of the starting material. A possible explanation for this observation is that internal complexation of the carbonyl to the ruthenium occurs yielding the less reactive carbene complex, thus making the reaction irreversible.

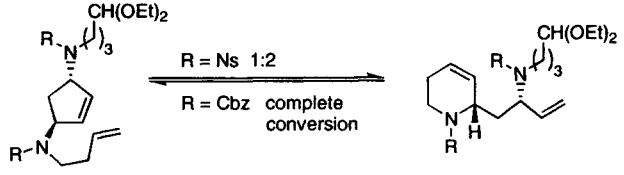
In a similar manner, the dihydropyrrole derivatives were investigated. The Ns protected *cis*- precursor **15b** underwent ring rearrangement to give **23** in an 89% yield in a ratio of **15b**:**23** of 1:10. However, only a ratio of 2.5:1 was observed in the metathesis of the *trans*-precursor **16b**. The Ns protection group was replaced with CBz to give **25**. The subsequent RRM to yield **26** proceeded with complete conversion.

In the case of both the Ns protected five- and six-membered heteocycles, the *cis*-configurated precursors were obtained more efficiently than the *trans*-configurated precursor. However, the introduction of the Cbz protecting group in the *trans*-derivatives resulted in quantitative conversion to the desired products.

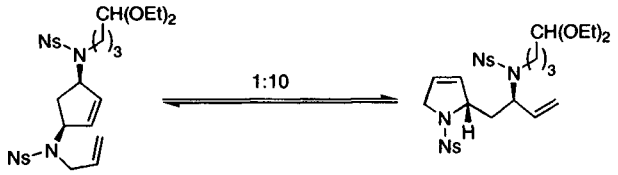
After successful completion of all rearrangement reactions, the incorporation of the different side chains of the tetraponerines was attempted by employing a cross metathesis reaction. However, the cross metathesis of **19** and **22** with allyltrimethylsilane in the presence of 10% **[Ru-1]** was unsuccessful due to the formation of a carbene with low reactivity. The use of Schrock's molybdenum catalyst[26] **[Mo]** (Figure 7) also failed to show any conversion. The terminal double bonds of **19** and **22** were assumed to be too hindered for cross metathesis. An alternative route to incorporate the different alkyl chains of the tetraponerines was necessary (Scheme 8).



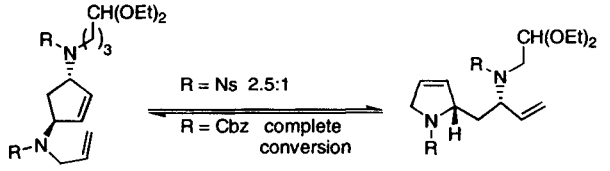
15a **19**



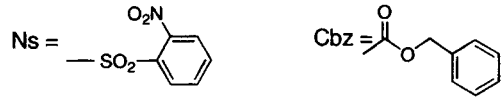
16a R=Ns **20** R=Ns
21 R=Cbz **22** R=Cbz



15b **23**



16b R=Ns **24** R=Ns
25 R=Cbz **26** R=Cbz



SCHEME 7

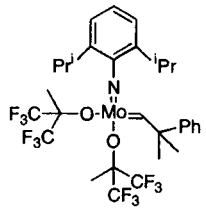
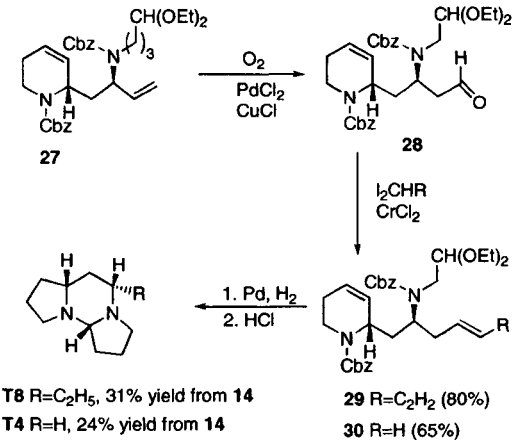


FIGURE 7 : Molybdenum metathesis catalyst **[Mo]**

We found that under the conditions of the Wacker oxidation,[27] the terminal double bonds of the metathesis products were cleanly transformed to the corresponding aldehydes. While the regioselective oxidation of protected allylic alcohols has been reported,[28] the selective Wacker oxidation of an allylic amine derivative to the aldehyde is unprecedented. The Ns protected precursor **19** produced only the starting amine ($NsN(H)CH_2CH_2CH_2CH(OEt)_2$). Consequently, the Ns protecting groups were exchanged with Cbz (**27**) which successfully led to the desired aldehyde **28**.

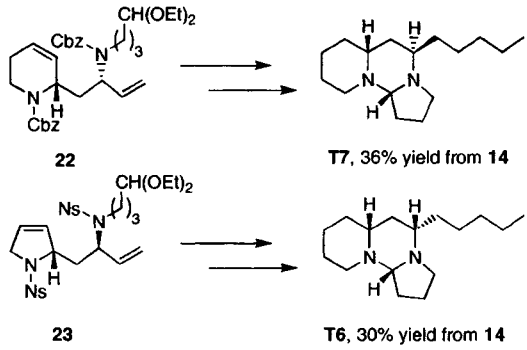


SCHEME 8

This aldehyde intermediate was then olefinated using the Takai olefination.[29] This step was also attempted using the Wittig olefination, but the basic conditions lead to *retro*-Michael side reactions, hence resulting in low yields. The Takai olefination avoids the use of basic conditions and produced **29** and **30** in good yields.

The synthesis was continued with the cleavage of the protecting groups with concomitant hydrogenation of the double bonds employing Pd/C in EtOH. The diethyloxy acetal was cleaved under acidic conditions (5% HCl), followed by selective cyclisation, to give **T4** and **T8** in 31 and 24% overall yields, respectively (Scheme 8).

Other enantiopure tetraponerines that were synthesised by this route are **T7** and **T6** (Scheme 9). The synthesis of these representative tetraponerines demonstrates the high efficiency and flexibility of the metathesis rearrangement.

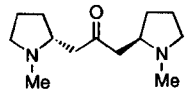


SCHEME 9

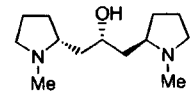
VI. RCM-ROM-RCM – establishing alkaloids containing two rings

A. CUSCOHYGRINE AND (+)-DICUSCOHYGRINE

Cuscohygrine was isolated in 1889 from the leaves of *Erythroxylon coca* and the structure established by Liebermann.[30] Later, it was reported to be a minor component of many other *Solanaceae* alkaloids.[31] Like related alkaloids, cuscohygrine epimerizes readily so that it has never been obtained as an optically active material. In contrast, naturally occurring dihydrocuscohygrine isolated by Turner in 1981[32] occurs in different *Solanaceae* species as the (-)-enantiomer.



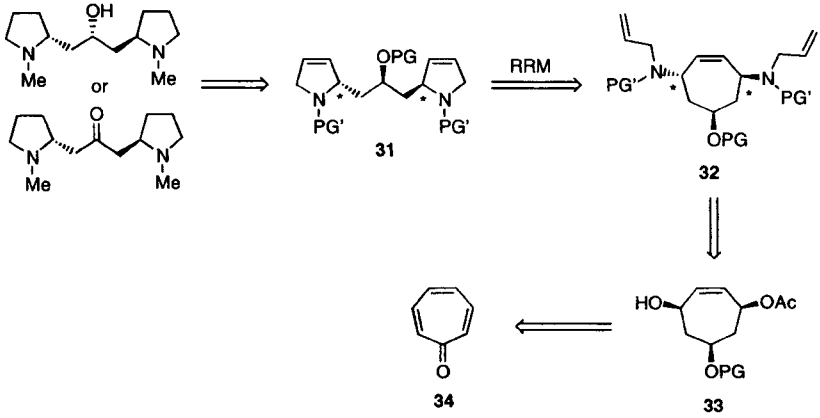
cuscohygrine



(+)-dihydrocuscohygrine

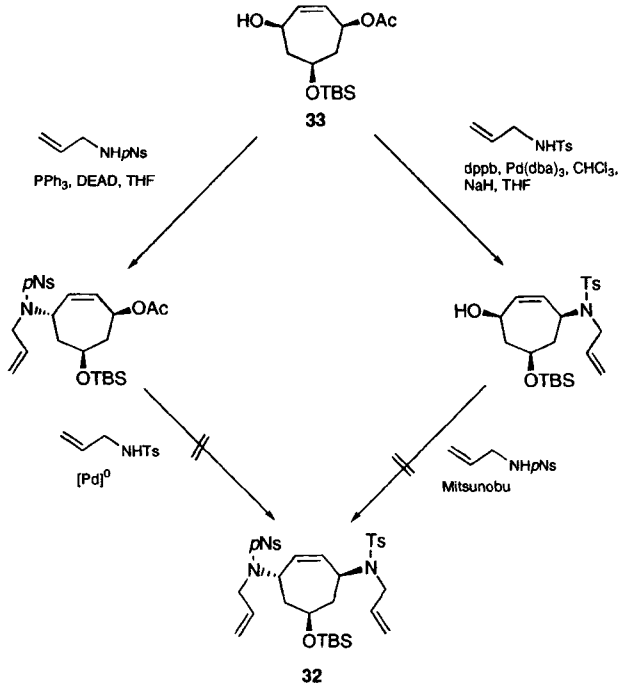
FIGURE 8: Cuscohygrine and (+)-dicuscohygrine

A RCM-ROM-RCM strategy was employed as the key step to the synthesis of these alkaloids (Scheme 10).[33] Both alkaloids can be derived from the protected bis-hydropyrrole **31** which is the ring rearranged product from the seven-membered carbocycle **32**. Compound **32** can be obtained from the enantiomerically pure triol derivative **33**, which in turn can be obtained from commercially available tropone **34**.[34]



SCHEME 10

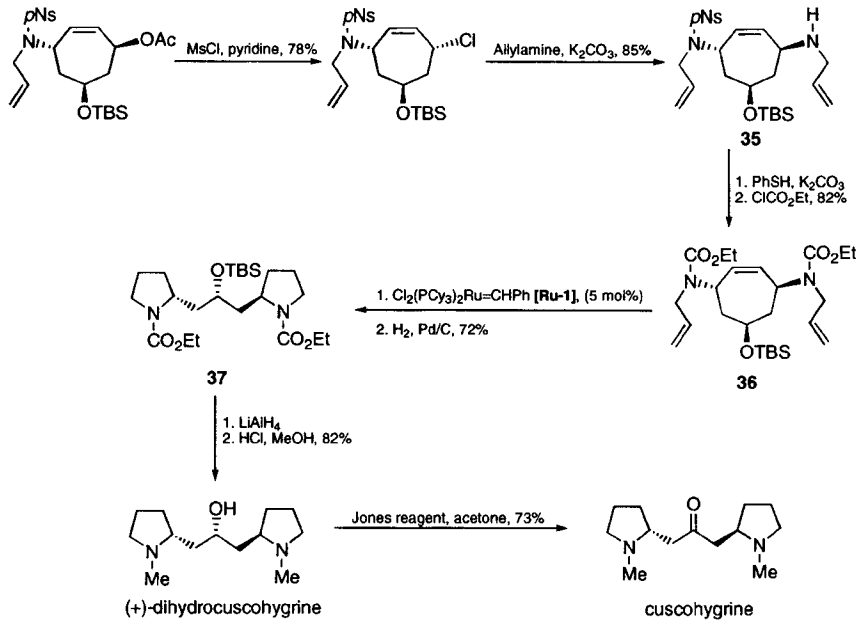
The RRM precursor was synthesised in a multistep procedure from alcohol **33**. The first allyl amino side chain was introduced by a Mitsunobu reaction with Ns protected allylamine with inversion of configuration. Attempts to introduce the second N-protected allylamine *via* an η^3-allyl Pd(0)-substitution failed. Changing the order of the substitution was also unsuccessful (Scheme 11).



SCHEME 11

An alternative route was implemented which involved replacement of the acetate with chlorine with inversion of configuration and subsequent introduction of allyl amine to give **35**. Carbamates have proven to be better than Ns as protecting groups in olefin metathesis reactions,[9] which led to the preparation of the carbamate protected precursor **36**. The RRM of **36** was carried out with 5 mol% **[Ru-1]** in boiling CH_2Cl_2 for 36h, followed by hydrogenation to give **37** (Scheme 12).

Subsequent reduction of the carbamate with $LiAlH_4$ and *O*-deprotection with concentrated HCl in ethanol gave (+)-dihydrocuscohygrine in >98% purity (GC) and a 30% overall yield from **33**.

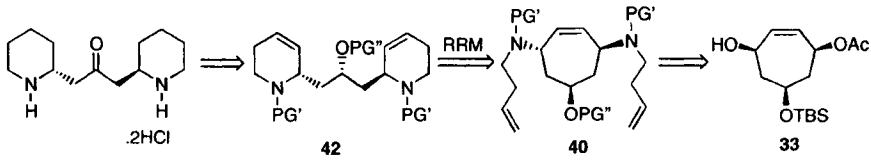


SCHEME 12

The oxidation of this enantiomerically pure compound to give cuscohygrine was attempted. It was found that the use of the Jones reagent in acetone was the most efficient, yielding cuscohygrine in a 73% yield, as a diastereomeric mixture of the *meso-* and *d,l*-cuscohygrine. Attempts to control the oxidation of (+)-dihydrocuscohygrine to give enantiomerically pure cuscohygrine were made, but were unsuccessful.

B. (-)-ANAFERINE

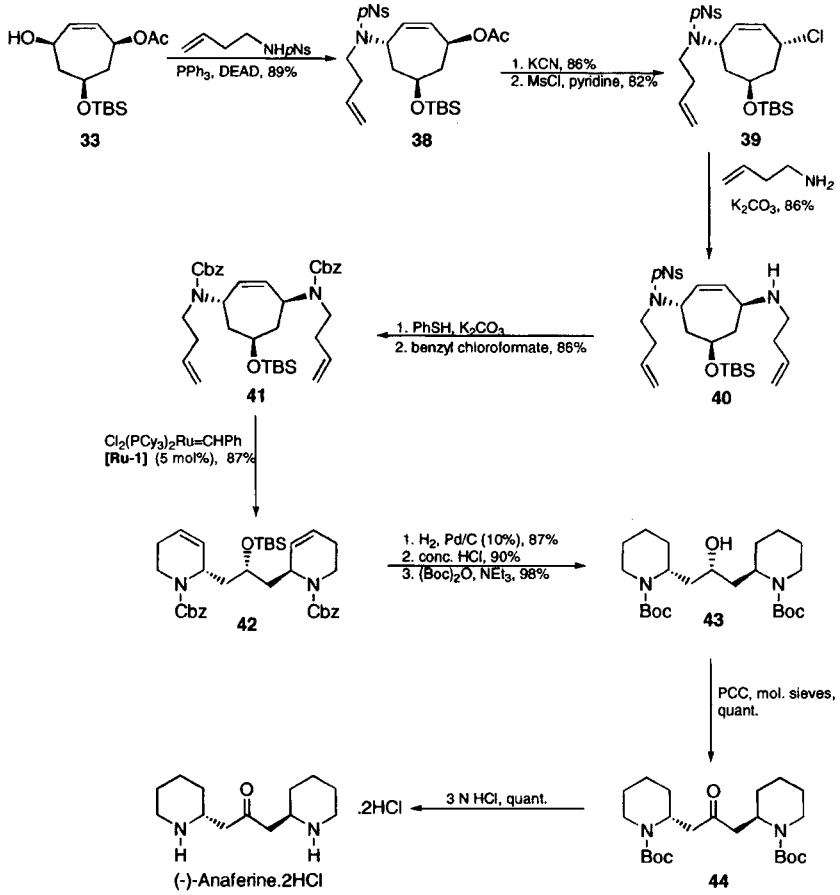
(-)-Anaferine was first isolated in 1962 by Schwarting *et al.*[35] from *Withania somnifera* Dunal as a mixture of diastereomers. The pure compound is rather labile in neutral or basic media, due to easy epimerisation *via* a retro- Michael-Michael reaction sequence. Acid solutions and salts, such as dihydrochlorides of (-)-anaferine are configurationally stable. The first enantioselective synthesis of (-)-anaferine dihydrochloride was accomplished using RRM as shown in the retrosynthetic analysis (Scheme 13).[36]



SCHEME 13

This approach is similar to the synthesis of (+)-dihydrocuscohygrine and cuscohygrine with respect to the way the RRM precursor is established. The first amino side chain was introduced to **33** by the Mitsunobu reaction using *N*-but-3-enyl-*N*-nosylamine with inversion of configuration to give amine **38** in 89% yield. The next step involved the introduction of another but-3-enylamino side chain, which was attempted directly *via* η^3-allylpalladium substitution and a suitable *N*-nucleophile. Several attempts with different nucleophiles (e.g. but-3-enylamine, sodium azide, *N*-but-3-enyl-n-nosylamine) and catalyst systems (e.g. $Pd(PPh_3)_4$, $Pd_2(dba)_3.CHCl_3$, complex/PPh_3, or dppb, $Pd(OAc)_2/PPh_3$ or dppb) were unsuccessful. As with (+)-dihydrocuscohygrine and cuscohygrine a double inversion strategy was implemented. The acetate was replaced by chlorine to give **39**, followed by introduction of the second but-3-enylamino side chain to give **40**, with net retention of configuration (Scheme 14).

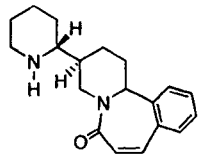
Further exchange of protecting groups from Ns to Cbz gave the RRM precursor **41**. RRM was carried out with **[Ru-1]** in refluxing CH_2Cl_2 to give **42** in an 87% yield. Hydrogenation was successfully carried out with retention of the stereochemistry, followed by alcohol deprotection and exchange of the *N*-protecting groups to give **43**. Subsequent oxidation with pyridinium chlorochromate (PCC) gave **44** quantitively. Final deprotection of **44** with dilute hydrochloric acid afforded the desired product, (-)-anaferine.2HCl.



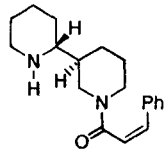
SCHEME 14

C. (+)-ASTROPHYLLINE

Several new alkaloids were isolated at the end of the sixties from *Astrocasia phyllanthoides*, a shrub belonging to the *Euphorbiaceae* family and native to Central America.[37,38] Astrocasine was proposed as the structure for the predominant alkaloid, based largely on spectral data (IR, UV, NMR, MS) and partial degradation studies. Later, (+)-astrophylline was isolated from the same plant, which is the first natural *cis*-cinnamoyl alkaloid to be reported.[37]



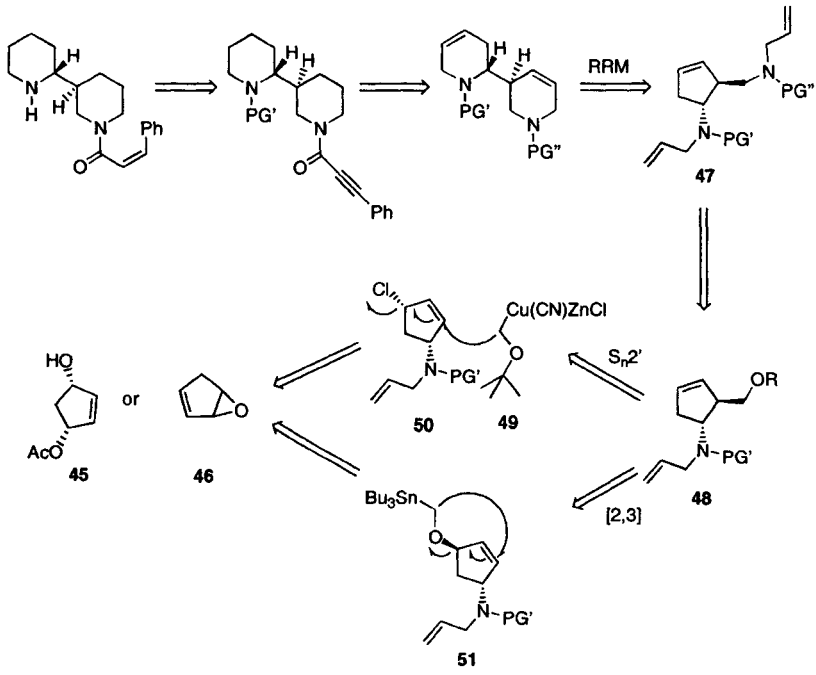
(+)-astrocasine



(+)-astrophylline

FIGURE 9: (+)-Astrocasine and (+)-astrophylline

The retrosynthesis of (+)-astrophylline can be accomplished by the use of a simple starting material (**45** or **46**) (Scheme 15).[39]



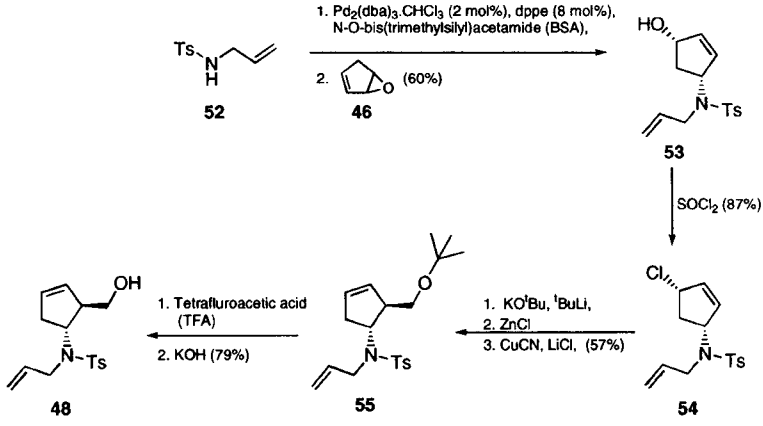
SCHEME 15

The key ring rearrangement precursor **47** was to be obtained from **48**. Two routes to the synthesis of **48** were proposed; one *via* S_N2'-*anti* addition of zinc cyanocuprate **49** to *cis*-1,4-disubstituted chloride **50**,[40] and the other *via* a [2,3]-Wittig-Still[41] rearrangement of stannane **51**.[42] Both intermediates **50** and **51** can be obtained from either epoxide **46**[43] or

enantiopure acetate **45**,[44,45] both of which are trivial to prepare in multigram quantities.

Protecting groups play a big role in this synthesis. The successful application of both S_N2' and [2,3]-Wittig-Still rearrangement was highly dependent on the choice of protecting group (discussed below). It was also fundamental to the synthesis to have orthogonal *N*- protecting groups which could be cleaved separately.

Pd(0)-catalysed allylic amination of the racemic epoxide **46** was carried out with tosyl protected allylamine **52** to give the alcohol **53** in a reasonable yield (Scheme 20). Tosyl protected allylamine was chosen as other standard protecting groups (Ns, Cbz, Boc) were found to be problematic in later steps. Subsequent chlorination of the hydroxy functionality with thionyl chloride afforded **54** in a 5:1 (cis:trans) diastereomeric mixture, which was separated by column chromatography. The halogen leaving group was essential as the corresponding triflates and mesylates were too unstable to be conveniently handled and the acetate was found to be unreactive in the organometallic addition step. Ether **55** was obtained in >98% de by treating **54** with the cyanocuprate **49** (which was prepared *in situ* from MTBE). Subsequent hydrolysis gave the desired alcohol in a 45% yield (Scheme 16).

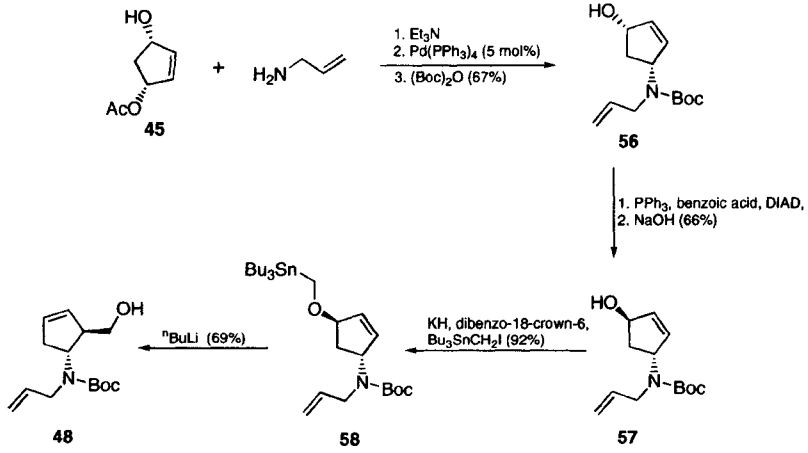


SCHEME 16

The use of a [2,3] Wittig-Still sigmatropic arrangement for the synthesis of **48** was also investigated. The advantage of this reaction is

that it can tolerate a greater range of protecting groups compared with the S_N2' process. Carbamate-protecting groups such as *tert*-butyloxycarbonyl (Boc), are inert under the basic rearrangement conditions, but are incompatible with the S_N2' reaction. Initial studies showed the Boc-moiety to be compatible, in terms of cleavage conditions, with the functionality present in later stages of the synthesis.

The Boc-protected amine **56** was synthesised from **45**, allylamine and catalytic amounts of $Pd(PPh_3)_4$, followed by the addition of Boc_2O (Scheme 17). The stereochemistry at C4 was then inverted *via* a Mitsunobu reaction with benzoic acid to give the *trans*-1,4-disubstituted alcohol **57**. Treatment of **57** with tributyl-iodomethylstannane yielded **58** in a high yield. Finally, the [2,3]-sigmatropic rearrangement was carried out in the presence of *n*-BuLi at –78 °C to give **48** in good yields.

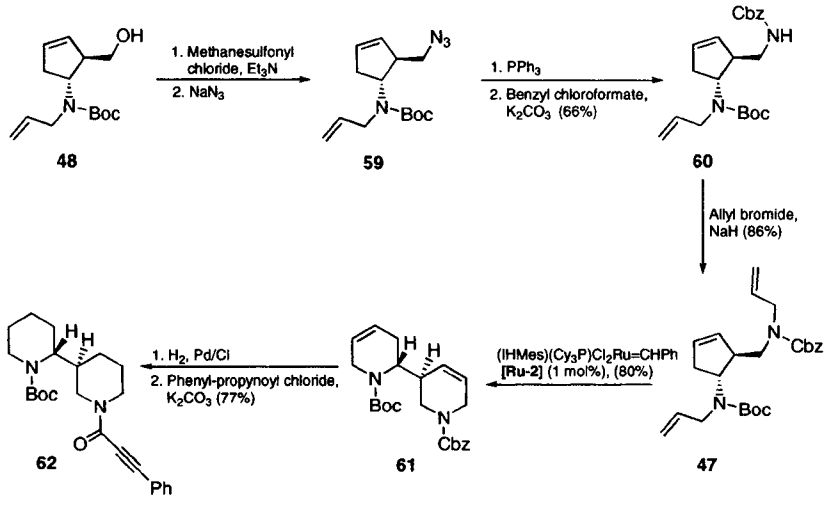


SCHEME 17

Both the organocuprate (Scheme 16) and the Wittig-Still (Scheme 17) route to the synthesis of enantiopure **48** were successfully achieved. The Wittig-Still route was favoured as it is a stereoselective synthesis that is compatible with large scale operations and it allows the use of the desirable Boc-protecting group.

As Boc was chosen as the first protecting group, a Cbz protected amine was introduced. This difference in protecting groups allowed them to be differentiated, which was crucial in the synthesis of (+)-astrophylline.

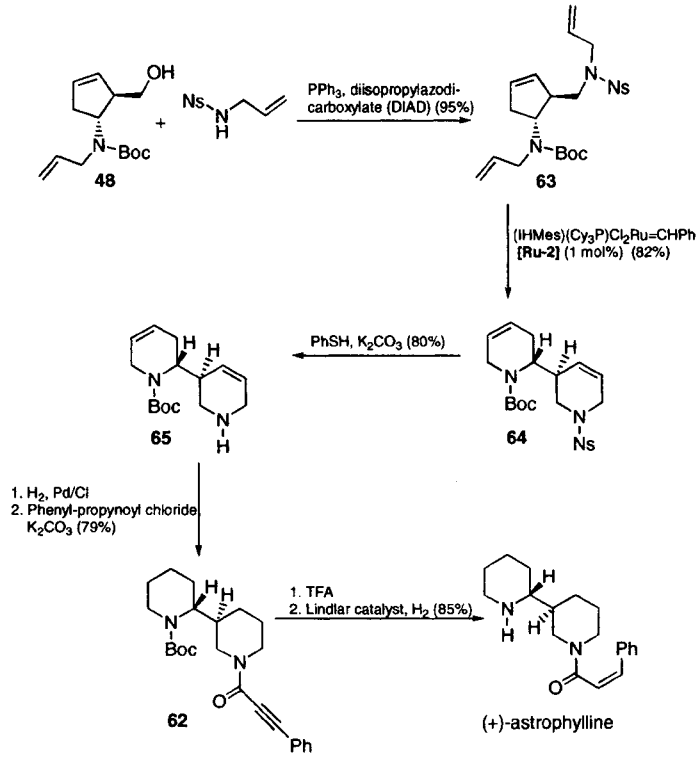
Conversion of compound **48** to the corresponding mesylate followed by substitution with sodium azide gave **59**. The Staudinger reaction[46] was performed under standard conditions to give the amine, which was protected with Cbz to give compound **60**. *N*-alkylation yielded the RRM precursor **47**. The RRM was carried out using **[Ru-2]** in refluxing CH_2Cl_2, to give **61** with complete transfer of stereochemical information. Compound **61** was then selectively Cbz-deprotected under hydrogenation conditions in the presence of catalytic Pd/C and phenylpropynoyl chloride was added to give **62** (Scheme 18).



SCHEME 18

Although the synthesis of **62** was successful, it was only obtained in a 35% yield from **48**. It was postulated that the direct transformation of **48** to the Ns-protected **63** would be a higher yielding route than the route *via* the azide **59** (Scheme 19).

Transformation of **48** to **63** was accomplished in a 95% yield. RRM was carried out using the same conditions as for **47** (Scheme 18), to give **64** in an 82% yield. Deprotection of the Ns-group with thiophenol led to the amine **65**, and a subsequent hydrogenation-acylation sequence provided intermediate **62**.



SCHEME 19

Overall, this route from **48** to **62** is three steps shorter than the original synthetic pathway and gives an improved yield of 49%. Final steps entailed the cleavage of the Boc-group and subsequent *cis* selective Lindlar hydrogenation of the triple bond to complete the total synthesis of (+)-astrophylline.

VII. RCM-ROM-RCM – strategic formation of cyclic silylethers

A. (-)-HALOSALINE

The first natural product to be synthesised with the use of the RCM-ROM-RCM sequence was the piperidine alkaloid (-)-halosaline (Figure 10).[47]

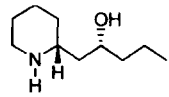
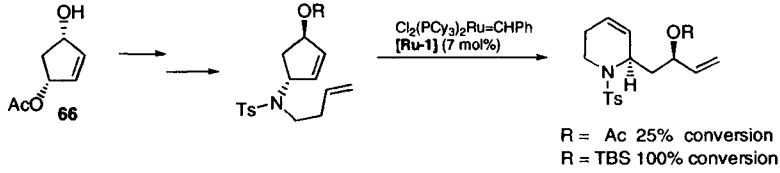


FIGURE 10: (-)-Halosaline

(-)-Halosaline was isolated from *Haloxylon Salicornicum*[48] and is representative of a group of natural piperidine alkaloids that differ in the relative and absolute configuration at C2 and C8, as well as the length of the alkyl moiety at C8.

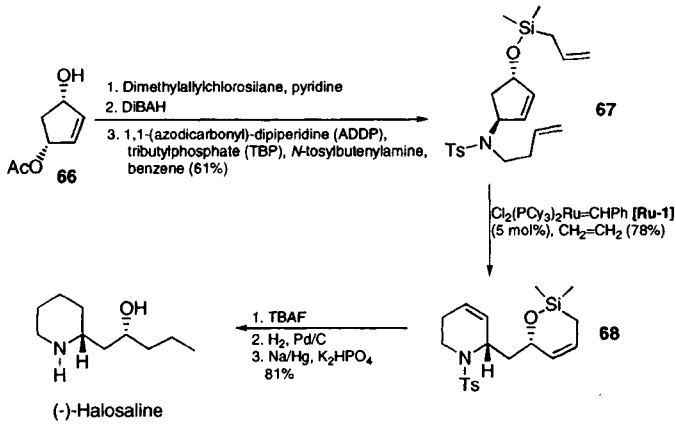
Acetate **66** was used as the starting material as it is readily prepared in high enantiomeric purity (> 99% ee) by enzymatic hydrolysis of the meso diacetate.[45] Firstly, the alcohol was protected and the choice of protecting group proved to be crucial to the success of this synthesis. The ring rearrangement carried out with the acetate protected precursor, resulted in low conversions (Scheme 20). In contrast, implementation of the precursor protected with the sterically demanding TBS group resulted in complete conversion (Scheme 20).



SCHEME 20

In the final synthesis a silicon tethered olefin was used as a protecting group that facilitates a RCM-ROM-RCM sequence. An alternative strategy was to carry out ROM-RCM with TBS protected alcohol (Scheme 20) and subsequent CM, but this strategy was low yielding.

On addition of the dimethylallylsilane, the acetate of compound **66** was hydrolysed. The Mitsunobu reaction was carried out with the resulting hydroxyl group to introduce *N*-tosylbutenylamine yielding the ring rearrangement precursor **67** in a 61% yield.



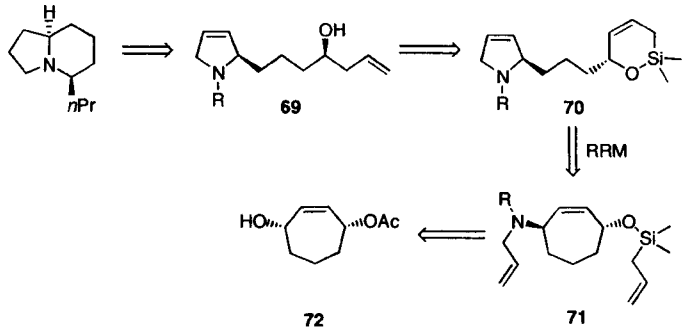
SCHEME 21

The RRM with **[Ru-1]** gave compound **68**, which has the same configuration at C2 and C8 as (-)-halosaline. Desilylation, hydrogenation and cleavage of the tosyl group gave (-)-halosaline in a 40% yield from acetate **66** (Scheme 21).

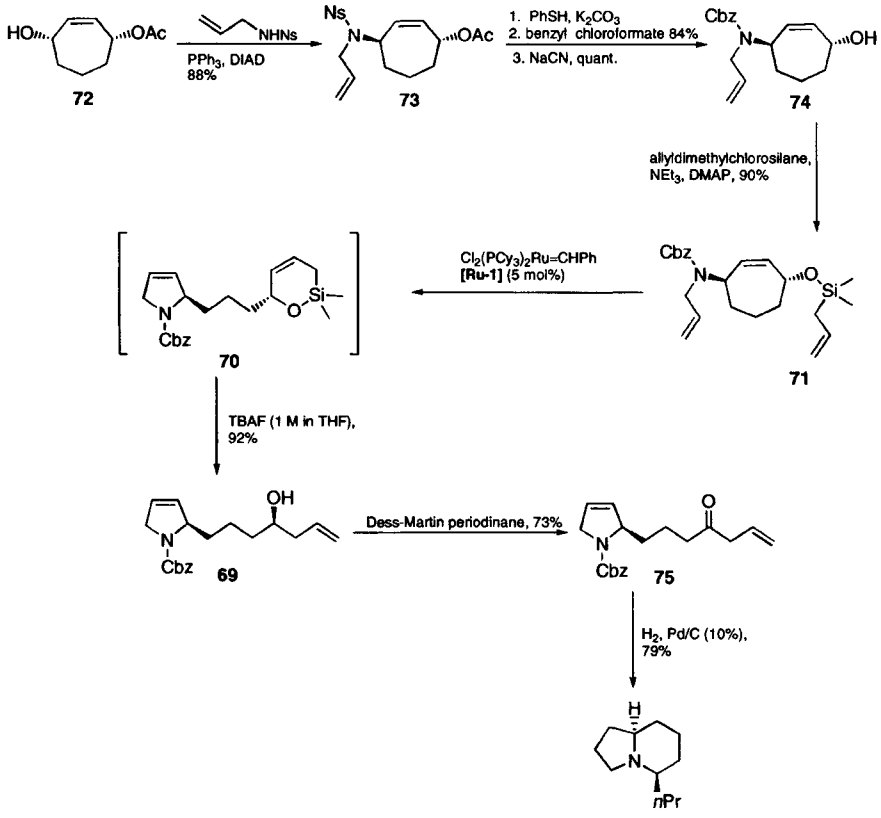
B. (-)-INDOLIZIDINE 167B

Indolizidine 167B is one of the simple representatives of the series of indolizidine alkaloids isolated as trace components from the skin of a neotropical frog caught on the Isla de Colon, Panama.[49] Skin secretions of such frogs have been recognised to be a rich source of biologically active substances.[50] Among them, indolizidine alkaloids have been identified as non-competitive blockers of neuromuscular transmission useful for pharmaceutical applications. This has led to the investigation of short and efficient syntheses of substituted indolizidines.

As with the synthesis of (-)-halosaline, the proposed retrosynthetic strategy of (-)-indolizidine 167B includes use of the dimethylallylsilyl protecting group in the RCM-ROM-RCM sequence (Scheme 22).[51]



SCHEME 22



SCHEME 23

Enantiopure **72** was converted to **73** by performing the Mitsunobu reaction. An exchange of protecting groups was then carried out (for reasons outlined in previous sections) and the free alcohol **74** generated. Subsequent *O*-silylation formed the RRM precursor **71** in a 90% yield. The metathesis and the subsequent silyl ether cleavage were performed in a one pot procedure to give **69** (Scheme 23).

The final ring closure was attempted *via* several methods (O-activation, N-deprotection and intramolecular nucleophilic replacement, O-mesylation and subsequent hydrogenation, intramolecular Mitsunobu reaction), but all attempts were unsuccessful. The method implemented involved an intramolecular reductive amination. Compound **69** was oxidised with Dess-Martin periodinane to afford ketone **75**, which was then hydrogenated in the presence of Pd/C, to give the desired ring-closed product (-)-indolizidine 167B.

VIII. Conclusions

RRM is an efficient and powerful tool in the modern day organic chemistry. This chapter has outlined its use in establishing heterocyclic rings, especially its application in the synthesis of nitrogen containing heterocycles in natural products. The elegance of this domino reaction is underpinned by the transfer of stereochemical information from the ring rearrangement precursors to the desired cyclic structures. The beauty of this strategy is the ability to synthesise complex chiral products from simple starting materials. Interest in this method is growing due to the significant advantages it presents.

Acknowledgements

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References

1. Watson, P. S., Jiang, B., Scott, B. *Org. Lett.* **2000**, *2*, 3679.

2. For examples of piperidine synthesis see: a) Doernyei, G., Incze, M., Moldvai, I., Szantay, C. *Synthetic Commun.* **2003**, *33*, 2329, b) Holsworth, D. D., Bakir, F., Uyeda, R. T., Ge, Y., Lau, J., Hansen, T. K., Andersen, H. S. *Synth. Commun.* **2003**, *33*, 1789, c) Hedley, S. J., Moran, W. J., Price, D. A., Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286.
3. For examples of pyrrolidine synthesis see: a) Dhavale, D. D., Matin, M. M., Sharma, T., Sabharwal, S. G. *Bioorg. Med. Chem.* **2003**, *11*, 3295, b) Kumar, A. R., Reddy, J. S., Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 5687, c) Lee, J., Reynolds, C., Jetter, M. C., Youngman, M. A., Hlasta, D. J., Dax, S. L., Stone, D. J., Zhang, S.-P., Codd, E. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1879.
4. a) Bailey, P. D., Millwood, P. A., Smith, P. D. *J.C.S. Chem. Commun.* **1998**, 633, b) Laschat, S., Dickner, T. *Synthesis* **2000**, 1781.
5. For reviews on olefin metathesis see: a) Connon Stephen, J., Blechert, S. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 1900, b) Fürstner, A. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3012, c) Roy, R., Das, S. K. *Chem. Commun.* **2000**, 519, d) Philips, A. J., Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75, e) Armstrong, S. K. *J.C.S.Perkin Trans. 1* **1998**, 371, f) Grubbs, R. H., Chang, S. *Tetrahedron* **1998**, *54*, 4413, Ivin, K. J. *J. Mol. Catal. A* **1998**, *133*, 1, g) *Alkene Metathesis in Organic Synthesis*, Springer: Berlin, 1998, Randall, M. L., Snapper, M. L. *J. Mol. Catal. A* **1998**, *133*, 29, h) Schuster, M., Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2037.
6. a) Nguyen, S. T., Grubbs, R. H., Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858, b) Schwab, P., France, M. B., Ziller, J. W., Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039, c) Schwab, P., Grubbs, R. H., Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
7. Scholl, M., Trnka, T. M., Morgan, J. P., Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.
8. a) Garber, S. B., Kingsbury, J. S., Gray, B. L., Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168, b) Gessler, S., Randl, S., Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973.
9. Stragies, R., Blechert, S. *Synlett* **1998**, 169.
10. a) Zuercher, W. J., Hashimoto, M., Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634, b) Harrity, J. P. A., Visser, M. S., Gleason, J. D., Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488, c) Burke, S. D., Quinn, K. J., Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626.
11. Ovaa, H., van der Marel, G. A., van Boom, J. H., Stragies, R., Blechert, S. *Chem. Commun.* **2000**, 1501.
12. a) Ovaa, H., Stapper, C., van der Marel, G. A., Overkleeft, H. S., van Boom, J. H., Blechert, S. *Tetrahedron* **2002**, *58*, 7503, b) Voigtmann, U., Blechert, S. *Synthesis* **2000**, 893.
13. Wolczunowicz, G., Cocu, F. G., Posternak, T. *Helv. Chim. Acta* **1970**, *53*, 2275.
14. Trost, B. M., Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
15. Guengerich, F. P., DiMari, S. J., Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055.
16. Nishimura, Y. *Studies in Natural Products Chemistry, Atta-ur-Rahman, Ed.,Elsevier: Amsterdam, 1992; Vol. 10, pp 495-583.*
17. El Nemr, A. *Tetrahedron* **2000**, *56*, 8579.

18. a) Zhao, H., Hans, S., Cheng, X., Mootoo, D. R. *J. Org. Chem.* **2001**, *6*, 1761, b) Trost, B. M., Patterson, D. E. *Chem. Eur. J.* **1999**, *5*, 3279, de Vincente, J., c) Arrayas, R. G., Canada, J., Carretero, J. C. *Synlett* **2000**, 53.
19. Buschmann, N., Rueckert, A., Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325.
20. a) Trost, B. M., Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339, b) Van Vranken, D. L., Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
21. Mukai, C., Sugimoto, Y., Miyazawa, K., Yamaguchi, S., Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281.
22. Kolb, H. C., van Niewenhze, M. S., Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
23. Stragies, R., Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584.
24. Brakman, J. C., Daloze, D., Pasteels, J. M., Van Hecke, P., Declercq, J. M., Stinwell, V., Francke, W. *Z. Naturforsch* **1987**, *42c*, 627.
25. Mitsunobu, O. *Synthesis* **1981**, 1.
26. Schrock, R. R., Murdzek, J. S., Bazan, G. C., Robbins, J., DiMare, M., O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
27. Tsuji, J. *Synthesis* **1984**, 369.
28. Kang, S.-K., Jung, K.-Y., Chung, J.-U., Namkoong, E.-Y., Kim, T.-H. *J. Org. Chem.* **1995**, *60*, 4678.
29. Okazoe, T., Takai, K., Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951.
30. a) Liebermann, C. *Ber.* **1889**, *22*, 675, b) Liebermann, C., Cybulski, G. *Ber.* **1895**, *28*, 578.
31. Leete, E. *Phytochemistry* **1983**, *22*, 699.
32. Turner, C. E., Elsohly, M. A., Hanus, L., Elsohly, H. N. *Phytochemistry* **1981**, *20*, 1403.
33. Stapper, C., Blechert, S. *J. Org. Chem.* **2002**, *67*, 6456.
34. a) Johnson, C. R., Golebiowski, A., Steensma, D. H., Scialdone, M. A. *J. Org. Chem.* **1993**, *53*, 7185, b) Johnson, C. R., Golebiowski, A., Steensma, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 9414.
35. a) Rother, A., Bobbitt, J. M., Schwarting, A. E. *Chem. Ind.* **1962**, 654, b) Schwarting, A. E., Bobbitt, J. M., Rother, A., Atal, C. K., Khanna, K. L., Leary, J. D., Walter, W. G. *Lloydia* **1963**, *26*, 258.
36. Blechert, S., Stapper, C. *Eur. J. Org. Chem.* **2002**, 2855.
37. Lloyd, H. A. *Tetrahedron Lett.* **1965**, *50*, 4537.
38. Lloyd, H. A. *Tetrahedron Lett.* **1965**, *22*, 1761.
39. Schaudt, M., Blechert, S. *J. Org. Chem.* **2003**, *68*, 2913.
40. a) Corey, E. J., Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3165, b) Singer, R. D., Knochel, R. *Chem. Rev.* **1993**, *93*, 2117, c) Ernst, M., Helmchen, G. *Synthesis* **2002**, *14*, 1953.
41. Still, W. C., Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.
42. a) Ovaa, H., Lastdrager, H. B., Codee, J. D. C., van der Marel, G. A., Overkleeft, H. S., van Boom, J. H. *J.C.S.Perkin Trans. 1* **2002**, *21*, 2370, b) Riether, D., Mulzer, J. *Org. Lett.* **2000**, *2*, 3139.
43. Gerdil, R., Liu, H., Bernardineli, G. *Helv. Chim. Acta* **1999**, 418.
44. Liu, W., Ghosh, A. K. *J. Org. Chem.* **1997**, *62*, 7908.
45. Johnson, C. R., Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287.
46. Staudinger, H., Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
47. Stragies, R., Blechert, S. *Tetrahedron* **1999**, *55*, 8179.

48. Michel, K. H., Sandberg, F., Haglid, F., Norin, T. *Acta Pharm. Suecica* **1967**, *4*, 97.
49. Daly, J. W., Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*, Pelletier, S. W., Ed., Wiley: New York, 1986, Vol. 4, p 1.
50. Michael, J. P. In *Alkaloids*, Cordell, G. A., Ed., Academic Press: London, 2001, Vol. 55, p 92, Daly, J. W., Garraffo, H. M., Spande, T. F. In *Alkaloids*, Cordell, G. A., Ed., Academic Press: London, 1993, Vol. 43, p 186.
51. Zaminer, J., Stapper, C., Blechert, S. *Tetrahedron Lett.* **2002**, *43*, 6739.

STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 13

CATALYTIC ASYMMETRIC TOTAL SYNTHESIS OF (–)-STRYCHNINE AND FOSTRIECIN

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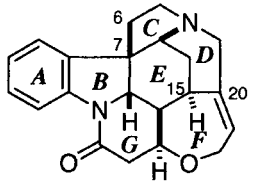
I. Introduction

The development of highly efficient asymmetric catalysts is one of the most intensively investigated research fields today.[1] Catalytic asymmetric reactions are extremely powerful in terms of the practicality and atom economy.[2] The power of asymmetric catalysis is rapidly growing, so as to be applicable to syntheses of natural products with complex structures. We call total syntheses using catalytic asymmetric reactions in key steps "catalytic asymmetric total syntheses". In this chapter, we describe our recent success in catalytic asymmetric total syntheses of (–)-strychnine and fostriecin. Both of the total syntheses involve catalytic asymmetric carbon–carbon bond forming reactions using bifunctional catalysts developed in our group[3] as key steps.

II. Catalytic Asymmetric Total Synthesis of (–)-Strychnine

Strychnine (1) is the flagship compound of the family of *Strychnos* alkaloids and, considering its molecular weight, is one of the most complex natural products.[4] Only twenty-four skeletal atoms are



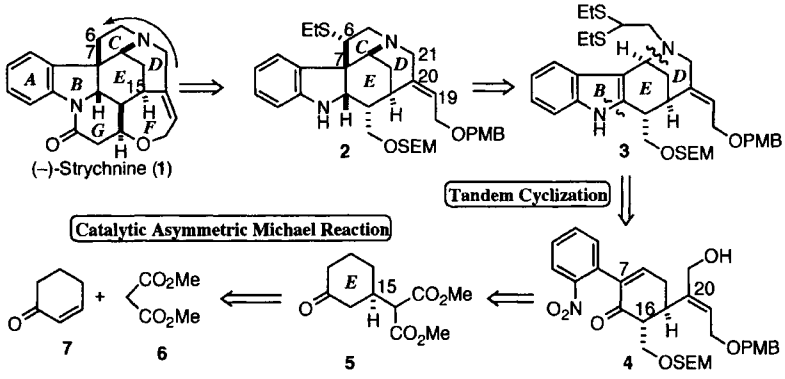
(–)-Strychnine (**1**)
FIGURE 1

assembled in seven rings and its structure contains six contiguous asymmetric carbon atoms, of which five are included within one saturated six-memberd ring (E-ring).[5] Strychnine was first isolated in 1818 from the Southeast Asian *Strychnos nux-vomica* and *Strychnos ignatti*.[6] Extensive degradative and structural studies culminated in the elucidation of strychnine's structure in 1946.[7] Later the relative[8a-d] and absolute[8e,f] configurations were confirmed by X-ray crystal analyses. Strychnine toxicity arises from the blocking of postsynaptic inhibition in the spinal cord and lower brain stem where it acts as a competitive ligand at the neuronal receptor for glycine.[9] This property has made strychnine very useful as a tool in experimental pharmacology.

A. RETROSYNTHETIC ANALYSIS

The structural complexity of strychnine coupled with its biological activity has served as the impetus for numerous synthetic investigations. The first total synthesis, one of the most significant achievements in the history of organic synthesis, was reported by Woodward in 1954.[10a] Nearly forty years after Woodward's pioneering work, a number of groups have reported the total synthesis[10] and four of them have culminated in enantioselective synthesis of the natural enantiomer.[10c,e,g,j] As summarized in Bonjoch's excellent review,[4a] the major stumbling blocks in the synthesis are the generation of the spirocenter at C7 and the assembling of the bridged framework (CDE core ring). In the previous strategies, the C6–C7 bond was generated in the early stage of synthesis, probably due to the difficulty of the generation of the C7 quaternary center; thus, in many cases, the CDE ring system was assembled in the direction of C-ring to D-ring. Although an intramolecular alkylation strategy was applied for the construction of the C-ring in the synthesis of structurally simpler indole alkaloids,[11b,12] this strategy has not been utilized for the synthesis of strychnine. The reason might be that intramolecular alkylation of dithioacetal is the only method to afford a cyclic product. Thus, desulfurization in the presence of exocyclic olefin is inevitable. We previously developed the highly practical catalytic asymmetric Michael reaction and it makes it possible to prepare optically pure Michael product

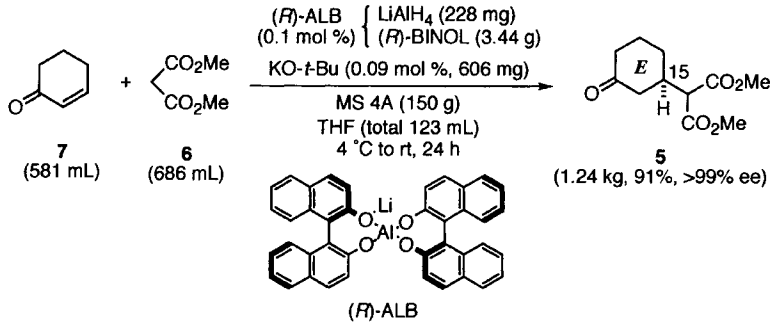
5 in more than kilogram scale.[11c] In order to utilize the Michael product **5** effectively in our synthesis, we planned to assemble the CDE ring system from the D-ring to the C-ring and constructed the C7 spirocenter in the last stage by intramolecular alkylation (Scheme 1).



SCHEME 1

B. HIGHLY PRACTICAL CATALYTIC ASYMMETRIC MICHAEL REACTION

The use of catalytic asymmetric reactions for the synthesis of highly enantiomerically enriched chiral compounds is of growing importance in organic chemistry and in industrial production in terms of atom economy. A number of asymmetric catalyses have been reported, some of which have industrial applications. Most catalytic asymmetric carbon–carbon bond formations, however, often are difficult to produce on a manufacturing scale in terms of catalyst efficiency, enantioselectivity, or chemical yield. To address this issue, we attempted to improve the AlLibis(binaphthoxide) (ALB) catalyzed Michael reaction, which we previously developed.[11a,b] We examined the additive effect, solvent effect, and ligand tuning, and eventually discovered that under highly concentrated (almost neat) conditions even 0.1 mol % of the catalyst completed the reaction in 24 h at ambient temperature without lowering chemical yield or the high enantiomeric excess (Scheme 2).[11c] After the reaction completed, simple filtration, washing, and crystallization afforded more than a kilogram of the chemically and optically pure Michael product **5** in 91% yield.

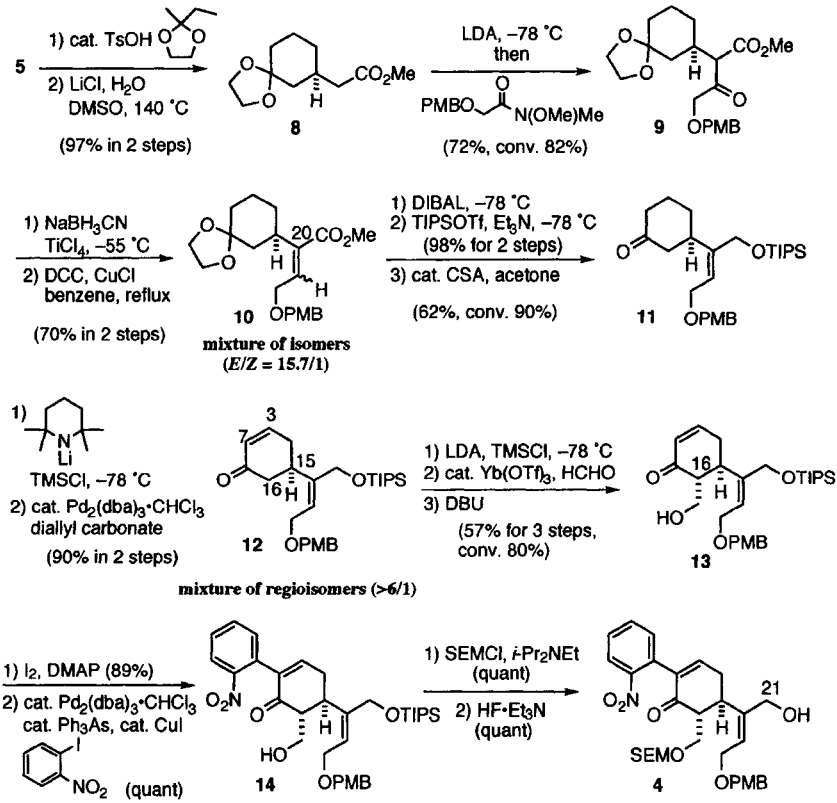


SCHEME 2

C. PREPARATION OF THE KEY INTERMEDIATE: ELABORATION OF THE HYDROXYLETHYLIDENE SIDE CHAIN AND FUNCTIONALIZATION OF THE E-RING

Having the optically pure Michael product **5** in large quantities, we then focused on the transformation of **5** to the key intermediate **4** (Scheme 3). Our first challenging step was the elaboration of the hydroxylidene side chain at C20 (*E*)-selectively. After attempting several strategies, the best result was achieved by *anti*-selective reduction of β-keto ester **9** by $NaBH_3CN$ with $TiCl_4$ at *–55 °C* following *syn*-elimination by DCC-CuCl (Overman's method; 72% for 2 steps, *E*:*Z* = 15.7:1).[10c] DIBAL reduction of **10** (*E*, *Z* mixture), followed by silylation of the primary alcohol with TIPSOTf, and conversion of the ketal to ketone afforded, after silica gel chromatography, pure (*E*)-**11**. Regioselective enol silyl ether formation was facilitated by the action of the sterically hindered base lithium 2,2,6,6-tetramethylpiperidide to form the corresponding enol silyl ether regioselectively (C7:C16 = >6:1). Following the Saegusa-Ito reaction using $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %) in the absence of phosphine ligand provided **12** in 90% yield.[13] Next, to introduce one carbon unit at C16 prior to the indole formation, we examined direct methoxycarbonylation and hydroxymethylation using **12** or more advanced products. Unfortunately, in most cases, there was aromatization of the corresponding cyclic β-keto ester or elimination of the corresponding β-hydroxyketone to the enone, respectively. Instead, mild aldol reaction of enol silyl ether in aqueous formaldehyde, which was developed by Kobayashi,[14] was effective for the formation of **13** (C16α:C16β = ca. 3:1). Both diastereomers were expected to be applicable to the synthesis

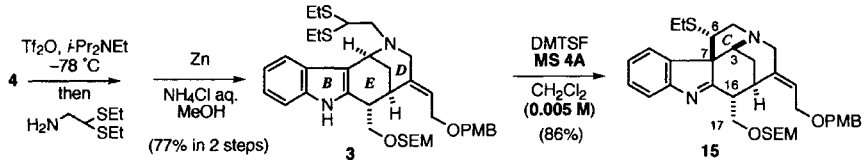
because the C16 stereocenter can be epimerized during the last stage. Unexpected aromatization, however, proceeded in the next iodination step when **13β** was used. Thus, **13β** was converted to the thermodynamically more stable **13α** by treatment with DBU prior to iodination. Subsequent iodination with DMAP and a Stille coupling reaction in the presence of CuI produced **14** efficiently, in contrast to the poor result (<5%) that occurred in the absence of CuI. Finally, protection of the primary alcohol with SEMCl and removal of the TIPS group provided the key intermediate **4** in excellent yield.



SCHEME 3

D. ASSEMBLING THE BRIDGED BCDE RING: TANDEM CYCLIZATION AND INTRAMOLECULAR ALKYLATION OF A DITHIOACETAL

We then focused on the construction of the BCDE-ring system. Initially, we examined 1,4-addition of the secondary amine to the enone after introduction of the amine moiety at C21 of **4**. However, it was found to be difficult due to the rapid retro reaction.[15] Numerous attempts finally led us to examine a tandem cyclization (Scheme 4). After introduction of the amine moiety, the crude mixture was simply treated with Zn in MeOH–aq. NH_4Cl to provide **3** in 77% yield. This tandem cyclization might proceed by the following sequence: (1) reduction of nitro group to amine by Zn, (2) formation of iminium cation intermediate, and (3) 1,4-addition of the secondary amine. Our next goal was to construct the C-ring. We examined the intramolecular electrophilic attack of a thionium ion to generate the C7 spirocenter. The reported procedure using DMTSF (dimethylmethylthiosulfonium fluoroborate),[11b,12a,16] unfortunately, provided unsatisfactory results (<20% yield) due to generation of aldehyde, formation of an unknown dimer, and over-reaction of **15** with DMTSF. The described conditions successfully suppressed such side reactions and highly improved the yield (86%).

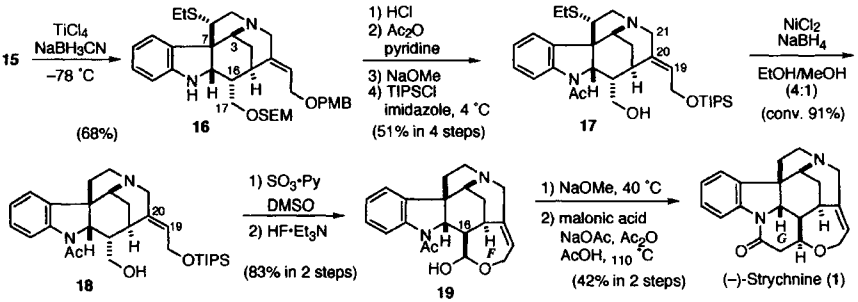


SCHEME 4

E. COMPLETION OF THE TOTAL SYNTHESIS: REDUCTION OF IMINE AND DESULFURIZATION

Reductions of imines in similar indole alkaloids under neutral conditions often result in the cleavage of C3–C7 bond and acidic conditions solved this problem. On the other hand, reduction of **15** under acidic conditions proceeded by elimination of the "OSEM" moiety to give C16–C17 exocyclic olefin. After testing numerous neutral or acidic conditions, we determined that treatment with 5 equiv of $TiCl_4$ at –78 °C before the addition of $NaBH_3CN$ effectively prevented the ring opening

reaction and accelerated reduction. As a result, **16** was obtained in 68% yield. The last major hurdle involved chemoselective reduction of the thioether (desulfurization)[17] in the presence of exocyclic olefin. The Raney Ni (W-2) reduction was the first choice for this purpose. Even deactivated Raney Ni in acetone, however, promoted considerable migration of exocyclic olefin (C19–C20) to endocyclic olefin (C20–C21).[18] Eventually, Ni boride[19] emerged as a promising candidate. Although a conventional protocol caused over-reduction instead of migration, by changing the solvent (EtOH:MeOH = 4:1) and addition order, **18** was obtained in 91% yield based on consumed starting material with high selectivity (>10:1). Consecutive SO_3•Py oxidation of the primary alcohol and deprotection of the TIPS group afforded (+)-diaboline (**19**)[20] through epimerization of the C16 stereocenter. Finally, removal of the acetyl group provided the crude Wieland-Gumlich aldehyde, which was converted to (–)-strychnine (**1**) by the established method.[10,21]



SCHEME 5

III. Catalytic Asymmetric Total Synthesis of Fostriecin

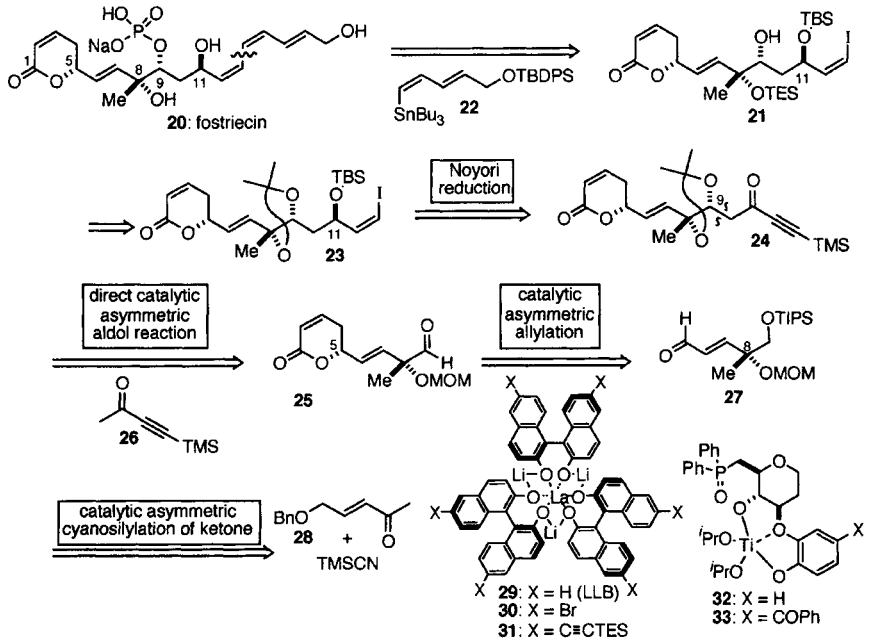
Fostriecin (**20**, CI-920) is a novel metabolite of *Streptomyces pulveraceus* that was first isolated in 1983 by a research group at Warner Lambert-Parke Davis.[22] It displays antitumor activity against a broad range of cancerous cell lines in vitro. This activity is suggested to be intimately related to the potent and highly selective inhibitory activity against serine/threonine phosphatase PP2A.[23] In fact, fostriecin is the most selective protein phosphatase inhibitor reported to date, and it

displays 10^4 times greater affinity for PP2A and PP4 versus PP1. Detailed studies on structure-activity relationship of fostriecin might lead to a new insight into the selective roles of phosphatase subtypes. Therefore, fostriecin is a novel lead compound for anticancer drugs, as well as an important biological tool.

In 1997, Boger's group determined the relative and absolute configuration of fostriecin based on synthetic and degradation studies.[24] They later reported the first total synthesis.[25] Since then, six total syntheses,[26] including ours,[27] have been reported, reflecting the highly focused interest in this compound. Our synthetic route is characterized by the fact that all the stereocenters of **20** are constructed through catalytic asymmetric reactions promoted by external chiral asymmetric catalysts. This route might be advantageous for rapid synthesis of stereoisomers of **20**.

A. RETROSYNTHETIC PLAN

Our retrosynthesis is shown in Scheme 6. Efforts to synthesize **20** should focus mainly on the following three points: (1) construction of the four chiral stereocenters, (2) construction of the configurationally labile *cis–cis–trans*-conjugated triene, and (3) selective phosphate ester construction at the C-9 secondary alcohol. To access point (2), we chose a cross-coupling reaction between *cis* vinyl iodide **21** and *cis* vinyltin **22** at a late stage. During the course of our studies, Imanishi reported that **21**, containing the proper protection pattern to access point (3), can be synthesized from **23**.[26c,d] Thus, we employed **23**, which contains all the chiral stereocenters of fostriecin, as a key intermediate for our synthesis. The chiral secondary alcohol at C-11 should be constructed using a Noyori reduction[28] of the corresponding acetylenic ketone **24**. The chiral secondary alcohol at C-9 of **24** should be constructed through a catalytic asymmetric aldol reaction of aldehyde **25** and ketone **26** promoted by a Lewis acid–Brönsted base two-center asymmetric catalyst, which was developed in our group.[29] α,β-Unsaturated lactone **25** should be synthesized through catalytic asymmetric allylation of aldehyde **27**, followed by ring-closing olefin metathesis (RCM) using Grubbs' catalyst. Finally, the tetrasubstituted chiral center at C-8 should be constructed using the catalytic asymmetric cyanosilylation of ketones promoted by the



SCHEME 6

Lewis acid–Lewis base two-center asymmetric catalyst (**32** or **33**) developed in our group.[30]

B. APPLICATION OF THE CATALYTIC ASYMMETRIC CYANOSILYLATION OF KETONE

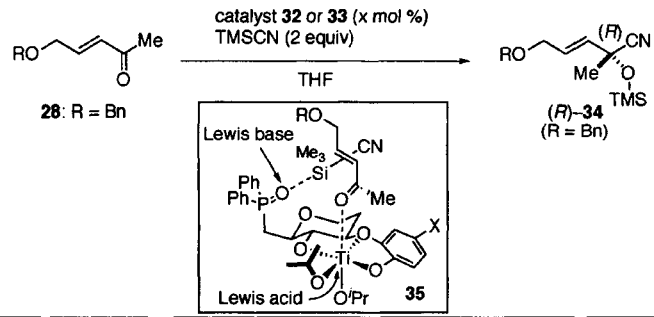
We began our synthesis by finding the optimum reaction conditions for the catalytic asymmetric cyanosilylation of ketone **28** (Table 1). Based on previous studies,[30] the titanium complex of a D–glucose derived ligand (catalyst **32** or **33**) generally gives (*R*)–ketone cyanohydrins, which is required for a synthesis of natural fostriecin.

First observed was a significant protecting-group effect of the substrate allylic alcohol on the reactivity and enantioselectivity (Table 1, entries 1–4). Among the ketones studied, benzyl-protected **28** gave the most promising results and cyanohydrin **34** with 86% ee was obtained in 58% yield using **32** as the catalyst (10 mol %, entry 4). To improve the yield with a lower catalyst loading, the reaction was performed at a higher temperature, however the enantioselectivity decreased significantly (entry

5). Next, we employed the tuned catalyst **33** containing a benzoyl group at the catechol moiety[30b] under high concentration (>12 M to THF), and the product was obtained in synthetically acceptable reaction time, yield, and enantioselectivity (entry 6). The reaction was performed on a 50–g scale without any difficulty (entry 7). The chiral ligand was recovered in 95% yield after silica gel column chromatography, and could be used at least several times without any loss of catalyst activity.

Our proposed transition state model for this catalytic enantioselective cyanosilylation of ketone is shown as **35**.[30a] The titanium acts as a Lewis acid to activate the substrate ketone, while the phosphine oxide acts as a Lewis base to activate TMSCN. The intramolecular transfer of the activated cyanide to the activated ketone should give the (*R*)-cyanohydrin in high selectivity. The successful results described above clearly demonstrate the practicality of our asymmetric catalyst for cyanosilylation of ketones.

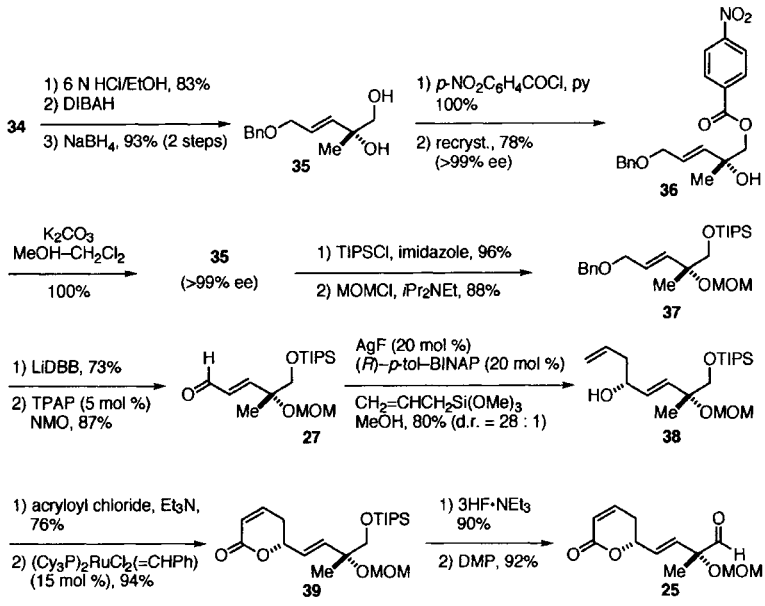
Table 1. Catalytic Enantioselective Cyanosilylation



entry	substrate (R)	catalyst (mol %)	temp (°C)	time (h)	yield (%)	ee (%)
1	TBS	**32** (10)	–40	168	75	65
2	MOM	**32** (10)	–40	240	32	87
3	Ac	**32** (10)	–40	240	82	85
4	Bn (**28**)	**32** (10)	–40	120	58	86
5	Bn (**28**)	**32** (5)	–20	36	94	71
6	Bn (**28**)	**33** (5)	–20	48	93	85
7[a]	Bn (**28**)	**33** (5)	–25	48	93	85

[a] Scale of reaction = 50 g.

The next task was to enrich the enantiomeric excess and to construct the C-5 chiral carbon through allylation of aldehyde **27** (Scheme 7). Ethanolysis of **34** followed by a two–step reduction gave diol **35**.



SCHEME 7

Enantiomerically pure compound was obtained by recrystallization of the corresponding *p*-nitrobenzoyl ester **36** in 78% yield. After hydrolysis, selective protection of the diol, reductive debenzylation using lithium di-*t*-butyl biphenylide (LiDBB), and TPAP–catalyzed oxidation gave aldehyde **27**.

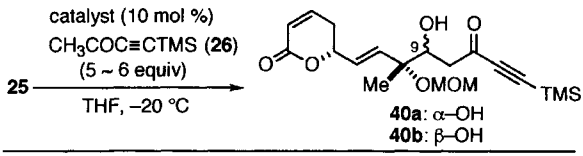
We confirmed that the stereocenter at C-8 does not control the stereoselectivity of addition to the aldehyde, based on the fact that the reaction of **27** with allyl Grignard reagent gave a 1:1 mixture of diastereomers. Thus, for the synthesis of **38**, we first tried Keck allylation[31] using 20 mol % of catalyst prepared from $Ti(O^iPr)_4$ and (*R*)–BINOL and allyltributyltin (2 equiv). The reaction, however, did not proceed well and the product was obtained in only 39% yield with a diastereomeric ratio (d.r.) of 7 : 1. Based on the hypothesis that the low catalyst activity is due to the coordination of the MOM oxygen to the Lewis acid, Yamamoto's silver–catalyzed asymmetric allylation was tried next.[32] The use of a soft metal should minimize adverse effect of the oxygen coordination to the catalyst. As expected, using 20 mol % of AgF–(*R*)-*p*-tol-BINAP complex, the reaction proceeded smoothly at –20 °C and the desired isomer **38** was obtained in 80% isolated yield after

separation of the diastereomer (d.r. = 28 : 1). Esterification with acryloyl chloride and RCM using Grubbs' catalyst gave lactone **39**, which was desilylated and oxidized by Dess–Martin periodinane (DMP) to give aldehyde **25**, the substrate for the catalytic asymmetric aldol reaction.

C. DIRECT CATALYTIC ASYMMETRIC ALDOL REACTION OF AN ACETYLENE KETONE

Despite the versatility of acetylenes, there has been no previous use of an acetylenic ketone as a donor in direct catalytic enantioselective aldol reactions. The aldol reaction using **26** as a donor proved to be difficult,

Table 2. Direct Catalytic Asymmetric Aldol Reaction

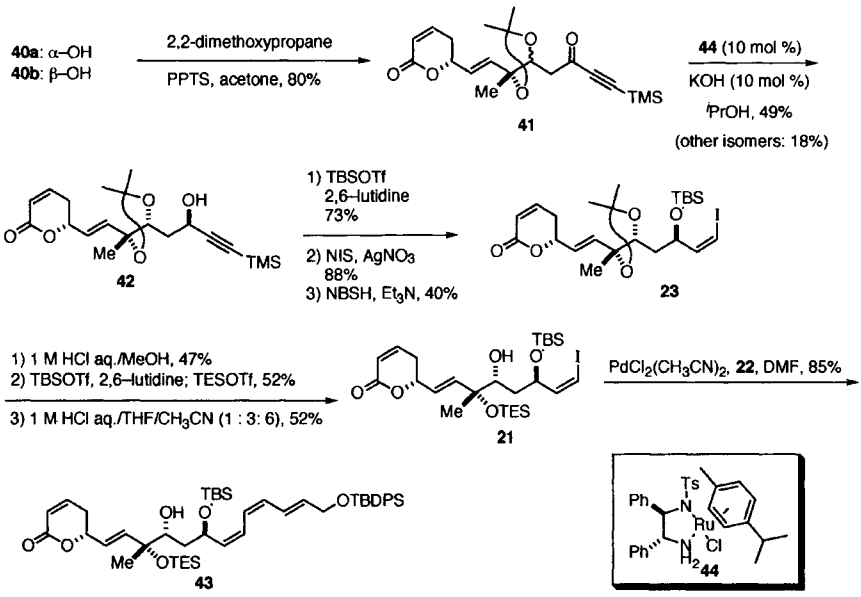


entry	catalyst	additives	time (h)	yield (%)	d.r.
1	**29**	–	16	65	3.6:1
2	**29**	KOH–H_2O	4	50	2.0:1
3	**30**	–	11	79	2.0:1
4	**31**	–	11	80	1.5:1

possibly due to a fast retro-aldol reaction, and reactions with the lithium enolate and the zinc enolate derived from **26** did not proceed efficiently. (*S*)-LLB (**29**: 10 mol %), however, promoted the reaction smoothly at –20 °C, and the desired aldol product was obtained in 65% yield with a 3.6:1 diastereoselectivity (Table 2, entry 1). Using the LLB-KOH-H_2O complex[29b] or decreasing the basicity of the bimetallic complex using the substitution effect of BINOL (catalysts **30** and **31**) did not produce any beneficial results. Although the selectivity was not satisfactory even in the optimized case, the effect of the chiral heterobimetallic complex is significant considering that the reaction did not proceed with 10 mol % of La(O^{i}Pr)$_3$. Considering the versatility of acetylenes and unique reactivity of acetylenic ketones, we are currently optimizing the generality of this direct catalytic enantioselective aldol reaction.

D. COMPLETION OF THE FORMAL TOTAL SYNTHESIS

The mixture of **40a** and **40b** was directly converted to the corresponding acetonide **41** (Scheme 8). Then, the asymmetric transfer hydrogenation was performed following Noyori's procedure.[28] The

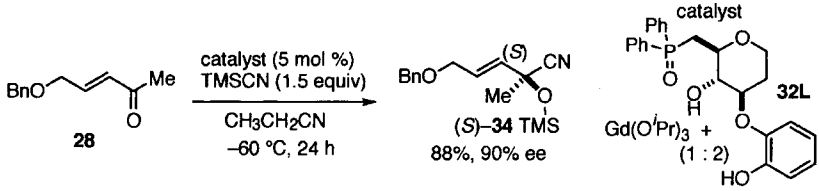


SCHEME 8

stereoselectivity from the desired isomer was extremely high (>97:3) and stereochemically pure **42** was obtained in 49% isolated yield after silica gel column chromatography. Protection of the propargylic alcohol, iododesilylation of the acetylene,[33] and diimide reduction using *o*–nitrobenzenesulfonylhydrazide (NBSH)[34] gave *cis* vinyl iodide **23**. Vinyl iodide **21** containing the appropriate protection pattern was synthesized from **23**, using a modified version of Imanishi's procedure.[26c] Stille coupling between **21** and **22**[35] under ligand–free conditions gave **43**, which is the common intermediate reported by Jacobsen, Imanishi, and Hatakeyama. Thus, we achieved the formal catalytic asymmetric total synthesis of fostriecin.

E. ATTEMPT AT SYNTHESIS OF A STEREOISOMER OF FOSTRIECIN

To demonstrate the uniqueness of our synthetic strategy, we are currently attempting to synthesize other stereoisomers of fostriecin. Initial results are promising as shown in Scheme 9. Thus, using the (*S*)–selective gadolinium catalyst for ketone cyanosilylation,[36] a product with the unnatural configuration was obtained in 90% ee. Synthesis of other stereoisomers and evaluation of the biologic activity is now ongoing.



SCHEME 9

IV. Closing Remarks

We describe herein our recent achievement of total syntheses of (–)-strychnine and fostriecin. The key stereocenters were constructed using catalytic asymmetric reactions developed in our group. Catalytic asymmetric reactions that can produce versatile chiral building blocks with high practicality should ensure further efficient total synthesis of complex molecules in future.

Acknowledgments

The research described in this paper was possible through the dedication of co-workers, whose names are acknowledged on the publications from our laboratory cited here.

References and Footnotes

1. (a) Jacobsen E. N., Pfaltz A., Yamamoto H. "*Comprehensive Asymmetric Catalysis*," Springer, 1999. (b) Ojima, I. "*Catalytic Asymmetric Synthesis*," VCH; New York, 2000.
2. (a) Trost B. M., *Science* **1991**, *254*, 1471. (b) Trost B. M., *Angew. Chem., Int. Ed.*

Engl. **1995**, *34*, 259.

3. For recent reviews, see: (a) Shibasaki, M. Kanai, M., *Chem. Pharm. Bull.* **2001**, *49*, 511. (b) Shibasaki, M., Kanai, M., Funabashi, K., *Chem. Commun.* **2002**, 1989.
4. For a representative review, see: (a) Bonjoch, J., Solé, D., *Chem. Rev.* **2000**, *100*, 3455. (b) Nicolaou, K.C., Sorensen, E.J. "*Strychnine*" in "*Classics in Total Synthesis*," VCH: New York, 1996, p. 21.
5. The numbering system and ring labeling based on the biogenetic interrelationship of indole alkaloids is used throughout this paper, see: Le Men, J., Taylor, W.I., *Experientia* **1965**, *21*, 508.
6. (a) Pelletier, P.J., Caventou, J.B., *Ann. Chim. Phys.* **1818**, *8*, 323. (b) Pelletier, P.J., Caventou, J.B., *Ann. Chim. Phys.* **1819**, *10*, 142.
7. (a) Briggs, L.H., Openshaw, H.T., Robinson, R., *J. Chem. Soc.* **1946**, 903. (b) Holmes, H.L., Openshaw, H.T., Robinson, R., *J. Chem. Soc.* **1946**, 910.
8. (a) Robertson, J.H., Beevers, C.A., *Nature* **1950**, *165*, 690. (b) Robertson, J.H., Beevers, C.A., *Acta Crystallogr.* **1951**, *4*, 270. (c) Bokhoven, C., Schoone, J.C., Bijvoet, J.M., *Acta Crystallogr.* **1951**, *4*, 275. (d) Mostad, A., *Acta Chem. Scand.* **1985**, *39B*, 705. (e) Peerdeman, A.F., *Acta Crystallogr.* **1956**, *9*, 824. (f) Nagarajan, K., Weissmann, Ch., Schmid, H., Karrer, P., *Helv. Chim. Acta* **1963**, *46*, 1212-1231.
9. Aprison, M.H. in "*Glycine Neurotransmision*," Eds. Otterson, O.P., Storm-Mathisen, J. Wiley: New York, 1990, p. 1-23.
10. (a) Woodward, R.B., Cava, M.P., Ollis, W.D., Hunger, A., Daeniker, H.U., Schenker, K., *J. Am. Chem. Soc.* **1954**, *76*, 4749; Woodward, R.B., Cava, M.P., Ollis, W.D., Hunger, A., Daeniker, H.U., Schenker, K., *Tetrahedron* **1963**, *19*, 247. (b) Magnus, P., Giles, M., Bonnert, R., Kim, C.S., McQuire, L., Merritt, A., Vicker, N., *J. Am. Chem. Soc.* **1992**, *114*, 4403; Magnus, P., Giles, M., Bonnert, R., Johnson, G., McQuire, L., Deluca, M., Merritt, A., Kim, C.S., Vicker, N., *J. Am. Chem. Soc.* **1993**, *115*, 8116. (c) Knight, S.D., Overman, L.E., Pairaudeau, G., *J. Am. Chem. Soc.* **1993**, *115*, 9293; Knight, S.D., Overman, L.E., Pairaudeau, G., *J. Am. Chem. Soc.* **1995**, *117*, 5776. (d) Stork, G. Disclosed at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, September 21, 1992. (e) Kuehne, M.E., Xu, F., *J. Org. Chem.* **1993**, *58*, 7490; Kuehne, M.E., Xu, F., *J. Org. Chem.* **1998**, *63*, 9427. (f) Rawal, V.H., Iwasa, S., *J. Org. Chem.* **1994**, *59*, 2685. (g) Solé, D., Bonjoch, J., García-Rubio, S., Peidró, E., Bosch, J., *Angew. Chem., Int. Ed.* **1999**, *38*, 395; Solé, D., Bonjoch, J., García-Rubio, S., Peidró, E., Bosch, J., *Chem. Eur. J.* **2000**, *6*, 655. (h) Eichberg, M.J., Dorta, R.L., Lamottke, K., Vollhardt, K.P.C., *Org. Lett.* **2000**, *2*, 2479; Eichberg, M.J., Dorta, R.L., Grotjahn, D.B., Lamottke, K., Schmidt, M., Vollhardt, K.P.C., *J. Am. Chem. Soc.* **2001**, *123*, 9324.

(i) Ito, M., Clark, C.W., Mortimore, M., Goh, J.B., Martin, S.F., *J. Am. Chem. Soc.* **2001**, *123*, 8003. (j) Nakanishi, M., Mori, M., *Angew. Chem., Int. Ed.* **2002**, *41*, 1934. (k) Bodwell, G.J., Li, J., *Angew. Chem., Int. Ed.* **2002**, *41*, 3261.

11. (a) Shibasaki, M., Sasai, H., Arai, T., *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236. (b) Shimizu, S., Ohori, K., Arai, T., Sasai, H., Shibasaki, M., *J. Org. Chem.* **1998**, *63*, 7547. (c) Xu, Y., Ohori, K., Ohshima, T., Shibasaki, M., *Tetrahedron* **2002**, *58*, 2585.
12. (a) Amat, M., Linares, A., Bosch, J., *J. Org. Chem.* **1990**, *55*, 6299. (b) Shin, K., Moriya, M., Ogasawara, K., *Tetrahedron. Lett.* **1998**, *39*, 3765 and references therein.
13. Minami, I., Takahashi, K., Shimizu, I., Kimura, T., Tsuji, J., *Tetrahedron* **1986**, *42*, 2971 and references therein.
14. (a) Kobayashi, S., *Chem. Lett.* **1991**, 2087. (b) Kobayashi, S., Hachiya, I., *J. Org. Chem.* **1994**, *59*, 3590.
15. Easy retro-1,4-additions of 8-*aryl*-2-azabicyclo[3,3,1]nonan-7-ones were reported, see: Bonjoch, J., Quirante, J., Solé, D., Castells, J., Galceran, M., Bosch, J., *Tetrahedron*, **1991**, *47*, 4417.
16. Trost, B. M., Murayama, E., *J. Am. Chem. Soc.* **1981**, *103*, 6529.
17. For a general review, see: Caubère, P., Coutrot, P. in "*Comprehensive Organic Synthesis*;" Eds. Trost, B.M., Fleming, I. Pergamon: Oxford, 1991, vol. 8, p. 835.
18. The transformation of strychnine to neostrychnine by normal Raney Ni in EtOH was reported, see: Beddoes, R.L., Gorman, A.A., Prescott, A.L., *Acta Cryst.* **1994**, *C50*, 447 and references therein.
19. Boar, R.B., Hawkins, D.W., McGhie, J.M., *J. Chem. Soc. Perkin Trans. 1* **1973**, 654.
20. Nicoletti, M., Goulart, M.O.F., De Lima, R., Goulart, A.E., Delle Monache, F., Marini, B.G.B., *J. Nat. Pro.* **1984**, *47*, 953. (b) Wenkert, E., Cheung, H.T.A., Gottlieb, H.E., *J. Org. Chem.* **1978**, *43*, 1099 and references therein.
21. Ohshima, T., Xu, Y., Takita, R., Shimizu, S., Zhong, D., Shibasaki, M., *J. Am. Chem. Soc.* **2002**, *124*, 14546; **2003**, *125*, 2014 (correction).
22. (a) Tunac, J. B., Graham, B. D., Dobson, W. E., *J. Antibiot.* **1983**, *36*, 1595. (b) Stampwala, S. S., Bunge, R. H., Hurley, T. R., Willmwe, N. E., Brankiewicz, A. J., Steinman, C. E., Smitka, T. A., French, J. C., *J. Antibiot.* **1983**, *36*, 1601.
23. For a review, see: Lewy, D. S., Gauss, C. M., Soenen, D. R., Boger, D. L., *Curr. Med. Chem.* **2002**, *9*, 2005.
24. Boger, D. L., Hikota, M., Lewis, B. M., *J. Org. Chem.* **1997**, *62*, 1748.
25. Boger, D. L., Ichikawa, S., Zhong, W., *J. Am. Chem. Soc.* **2001**, *123*, 4161.
26. (a) Chavez, D. E., Jacobsen, E. N., *Angew. Chem. Int. Ed.* **2001**, *40*, 3667. (b)

Reddy, Y. K.; Falck, J. R., *Org. Lett.* **2002**, *4*, 969. (c) Miyashita, K., Ikejiri, M., Kawasaki, H., Maemura, S., Imanishi, T., *Chem. Commun.* **2002**, 742. (d) Miyashita, K., Ikejiri, M., Kawasaki, H., Maemura, S., Imanishi, T., *J. Am. Chem. Soc.* **2003**, *125*, 8238. (e) Wang, Y.-G., Kobayashi, Y., *Org. Lett.* **2002**, *4*, 4615. (f) Esumi, T., Okamoto, N., Hatakeyama, S., *Chem. Commun.* **2002**, 3042.

27. Fujii, K., Maki, K., Kanai, M., Shibasaki, M., *Org. Lett.* **2003**, *5*, 733.
28. Matsumura, K., Hashiguchi, S., Ikariya, T., Noyori, R., *J. Am. Chem. Soc.* **1997**, *119*, 8738.
29. (a) Yamada, Y. M. A., Yoshikawa, N., Sasai, H., Shibasaki, M., *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yoshikawa, N., Yamada, Y. M. A., Das, J., Sasai, H., Shibasaki, M., *J. Am. Chem. Soc.* **1999**, *121*, 4168.
30. (a) Hamashima, Y., Kanai, M., Shibasaki, M., *J. Am. Chem. Soc.* **2000**, 7412. (b) Hamashima, Y., Kanai, M., Shibasaki, M., *Tetrahedron Lett.* **2001**, *42*, 691.
31. Keck, G. E., Krishnamurthy, D., Grier, M. C., *J. Org. Chem.* **1993**, *58*, 6543.
32. Yanagisawa, A., Kageyama, H., Nakatsuka, Y., Asakawa, K., Matsumoto, Y., Yamamoto, H., *Angew. Chem. Int. Ed.* **1999**, *38*, 3701.
33. Nishikawa, T., Shibuya, S., Hosokawa, S., Isobe, M., *Synlett* **1994**, 485.
34. Myers, A. G., Zheng, B., Movassaghi, M., *J. Org. Chem.* **1997**, *62*, 7507.
35. Mapp, A. K., Heathcock, C. H., *J. Org. Chem.* **1999**, *64*, 23.
36. Yabu, K., Masumoto, S., Yamasaki, S., Hamashima, Y., Kanai, M. Du, W., Curran, D. P., Shibasaki, M., *J. Am. Chem. Soc.* **2001**, *123*, 9908.

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STRATEGIES AND TACTICS IN ORGANIC SYNTHESIS, VOL. 4

Chapter 14

THE SYNTHESIS OF (±)-STRYCHNINE VIA A COBALT-MEDIATED [2 + 2 + 2]CYCLOADDITION

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I. Introduction - The Objectives of Organic Synthesis

A thorough discussion of strategy and tactics in a chemical synthesis requires an explanation of the objectives of such an endeavor. The development of an overall or near-goal strategy, say a retrosynthetic analysis, and the employment of tactics, such as individual unique or precedented transformations, requires some definable goals. After all, a general can hardly prepare for battle without some well-defined objective for victory. In science, the notion of progress is often alluded to as a goal.

Yet, how exactly do we define and achieve progress? In total organic synthesis, the answer seems obvious. The objective is to synthesize the target molecule. Indeed, remarkably complex compounds, dragged from the depths of the ocean or coaxed from some obscure bit of soil, often encourage the development of brilliant strategies and tactics. However, this cannot be the only goal. What sense is there in synthesizing the same target or class of targets repeatedly? Why marshal resources to produce a molecule with no medicinal value or in impractically minute quantities? In fact, chemists have objectives beyond the achievement of a nominal synthesis. These may include assembling the molecule in as few steps as possible or maximizing overall yield by enhancing the efficiency of bond construction. Some seek to elevate a synthesis to an aesthetic level, achieving a certain admirable elegance, beauty, or cleverness. Many point to the importance of synthesis as a driver of innovation in synthetic methodology, a "contest with nature" that leads to removal of once confounding synthetic roadblocks. Collectively, these objectives help define the parameters of progress in organic synthesis.

Yet, such commonly cited objectives do not encompass all of the goals pursued through modern synthetic organic chemistry. Atom economy, energy efficiency, or the use of environmentally benign reagents, characterized by the term "green chemistry,"[1] are goals that can dramatically affect the strategy and tactics of a synthesis. These considerations can have a very practical purpose. Manufacturing facilities and research laboratories are subject to pressures for waste and/or energy minimization that may preclude the use of certain reagents, solvents, or reaction conditions. Other fundamentally economic considerations can modify the objectives of a synthesis. In industry, chemists may need to produce the target molecule as rapidly as possible and have no time to even consider synthetic efficiency, versatility, or elegance. Clearly, progress in synthesis can have different meanings when one considers social, economic, and individual constraints.

It has become increasingly important to carefully evaluate the rationale for an organic synthesis. Chemists face increasing pressure to balance a number of different, often conflicting, objectives in the course of their work. In academia, practitioners are more sensitive than ever to the commercial potential of research innovations. Even those chemists uninterested in commercialization may be unable to avoid the demand for more explicit accounting of the goals of their research, and their contribution to "progress." Today, budget managers in government are bringing unprecedented pressure on publicly funded scientific institutions

to derive quantifiable measurements for the benefits resulting from the taxpayers' investment in basic research.

Thus, to better define progress in organic synthesis, one needs insight into how the myriad of possible objectives actually affect the strategies and tactics employed in the day-to-day of synthetic projects. It is the purpose of this account, then, to reflect what objectives influenced choices in the lab and, in turn, drove the development of our successful approach to the infamous alkaloid strychnine. We hope the reader will gain not only an appreciation of the excitement and intricacies of this particular synthesis, but also insight into his or her own motivations and goals in pursuing one of the most persistently vibrant and vigorous fields of science.

II. Target Strychnine

"Strychnine!" With this exclamation and an air of excitement, Robert Woodward began the 1963 account of his group's landmark synthesis of this alkaloid.[2] When he began his efforts in 1948, the total synthesis of strychnine was by far the most ambitious undertaking in natural product synthesis. However, it was only the latest in a series of historic scientific achievements featuring this infamous molecule. The alkaloid is present in abundance, up to 2% by weight, in certain plants of the *Strychnos* genus, originally catalogued by Linneaus in 1753. Early in the 19th century, strychnine became one of the first natural products extracted and purified in quantity and served to demonstrate the then novel notion that acid fixing substances are produced by plants, a discovery that is now expressed in the definition of an alkaloid as a naturally-occurring nitrogenous base.

Strychnine went on to play a starring role in a celebrated chapter of classical structure elucidation chemistry. This effort, taking place before the advent of modern spectroscopic techniques, took more than 40 years of painstaking, methodical analysis. The heroes of this era were the groups of Woodward, Leuchs, and Robinson,[3] the latter two researchers independently suggesting the structure as **1** in the late 1940's.[4] While this feat became the crowning achievement of classical structure elucidation, it also served as its finale. Only four years later, confirmation of the structure of strychnine was obtained by X-ray crystallography, and the end of chemical degradative analysis was at hand.[5]

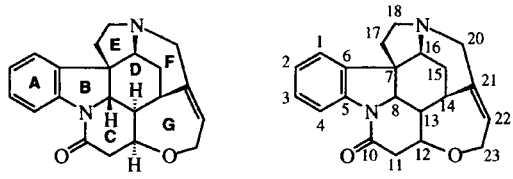


FIGURE 1
THE STRYCHNINE (1) STRUCTURE WITH NUMBERING AND RING LABELING USED THROUGHOUT THIS ACCOUNT.

While a variety of medical uses for the alkaloid have been practiced over the years, these have largely proven to be unjustified. The primary commercial utility of strychnine is as a rodent poison and animal stimulant. The toxicity of strychnine stems from its highly selective and extremely potent (5-10 nM) antagonism of the glycine receptor, a ligand-gated ion channel regulating transmission between neurons and moderated by the amino acid glycine acting as a neurotransmitter.[6] As such, strychnine remains an important tool in biochemical studies of this receptor.

Remarkably, Woodward's synthetic achievement, first reported in 1954, stood unmatched for nearly 40 years. However, the challenge posed by the molecule, with its seven rings and six stereocenters displayed across the framework of only 24 atoms, combined with its historical significance, motivated many synthetic chemists, including our group, to pursue its resynthesis. Though the target had little medicinal value and is readily available in nature, its assembly was pursued primarily as a means for the design and development of novel synthetic methods. Beginning in 1992, several successful new approaches have been published.[7,8] Importantly, by using the metrics of enantioselectivity, overall yield, and total number of synthetic steps, these syntheses can be viewed as a kind of indicator of progress in synthetic organic chemistry (Table 1). Indeed, the goal of measuring up favorably to these standards certainly influenced the strategy and tactics employed in the work described here.[9]

III. The Cobalt Way to Strychnine

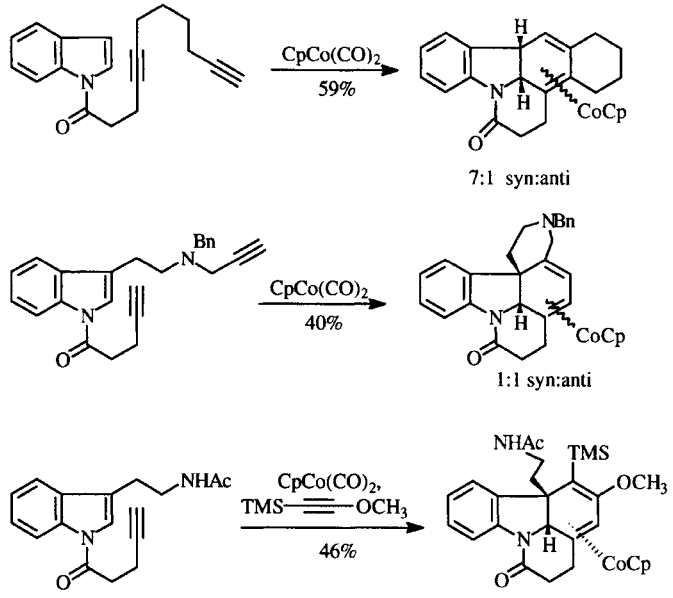
More important than the actual synthesis itself, the central goal of this project required the employment of the cobalt-mediated [2 + 2 + 2] cycloaddition during the synthetic sequence. Pioneered by our group and

TABLE I
COMPARISON OF STRYCHNINE SYNTHESES

Principal Author	Year	Form/Source	# of Linear Steps	Overall Yield
Woodward	1954	(±)	27	0.00006%
Magnus	1992	(-)/relay	27	0.03%
Stork	1992	(±)	15	[a]
Kuehne	1993	(±)	22	1%
Overman	1993	(+) & (-)/enzymatic	28	3%
Rawal	1994	(±)	15	10%
Martin	1996	(±)	19	3%
Kuehne	1998	(-)/chiral pool	22	4%
Bonjosch	1999	(-)/chiral pool	15	0.2%
Martin	2001	(±)	18	0.007%
Mori	2002	(-)/chiral catalysis	24	0.0005%
Shibasaki	2002	(-)/chiral catalysis	33	0.007%
Bodwell	2002	(±)	12	3%

[a] Yields not available

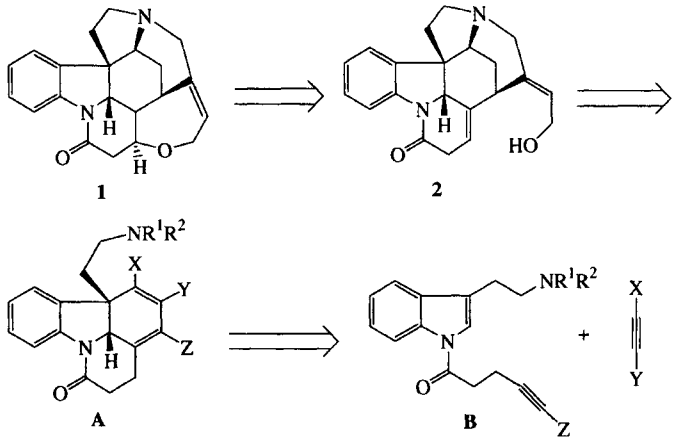
extensively developed over the last 30 years, this reaction has proven to be a powerful tool for the construction of complex, polycyclic molecules. The ability of cyclopentadienylcobalt to effect the cyclization of three unsaturated functionalities with a high degree of chemo-, regio-, and stereoselectivity has resulted in the synthesis of several complex natural[10] and unnatural[11] products. Among the wide variety of unsaturated functionalities that participate in this reaction are a number of aromatic heterocyclic double bonds, such as those in pyrrole,[12] imidazole,[13] thiophene, furan,[14] and benzofuran.[15] It was the capacity of the indole nucleus to serve as a substrate in this reaction that served as the original inspiration for our group's synthetic endeavor. While examining the reactivity of enamines in the cobalt-mediated [2 + 2 + 2]cycloaddition, graduate student Doug Grotjahn discovered the ability of N-acylated, alkyne-tethered indoles to cyclize to multi-ring products (Scheme 1), initially as cobalt complexes, readily demetalated by mild oxidation.[16] The reactions proved to have a number of characteristics amenable to a total synthesis of strychnine. With the starting indole incorporating the A and B rings of the target, the reaction formed the C and D rings, as well as the C7 spirocenter, in one step. Functionalized alkynes could participate in the reaction, often with a high degree of regioselectivity, allowing flexibility that might be needed to successfully form the E and F rings.



SCHEME 1

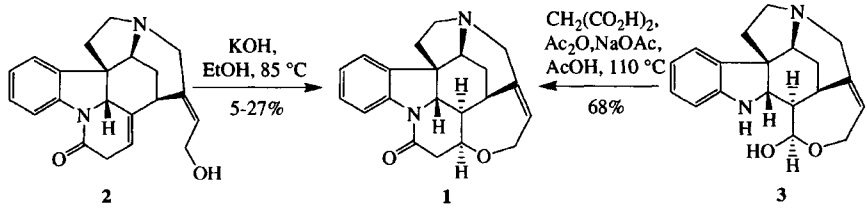
Finally, the cyclizations give the cis orientation of the H and R substituents at the 2 and 3 position of the indole. With such an opportunity to demonstrate synthetic utility of the method on such a celebrated and challenging molecule, Grotjahn immediately embarked upon a total synthesis of **1**.

The general approach envisioned at the time presented the partly intermolecular cyclization of *N*-(4-pentynolyl)indole derivatives **B** to furnish a dihydrocarbazole system **A** constituting the A,B,C, and D frame of **1** (Scheme 2). From these ABCD intermediates, formation of the next three rings would proceed in a stepwise fashion. By using readily available tryptamine derivatives in the [2 + 2 + 2]cyclization, construction of the E ring was envisaged to occur by nucleophilic attack of the distal nitrogen on the D ring diene unit. Ring F might then be accessible by a transition metal catalyzed coupling of an appropriately functionalized *N*-alkenyl appendage, thus providing the strychnine derivative isostrychnine (**2**). Closure of the final ring would then be accomplished through the well-known isostrychnine-strychnine isomerization (Scheme 3).[17] At the time, the notoriously poor yield of this transformation did not daunt the synthetic planners. After all, at the outset of this work in the mid-1980s, Woodward's synthesis remained unmatched and his route also included



SCHEME 2

the same ultimate step. Many subsequent syntheses of strychnine have avoided this poor conversion by employing a final C ring closing through the Wieland-Gumlich aldehyde **3**.[18] Thus, the looming "hit" of the final low yielding conversion was implicit throughout the project.



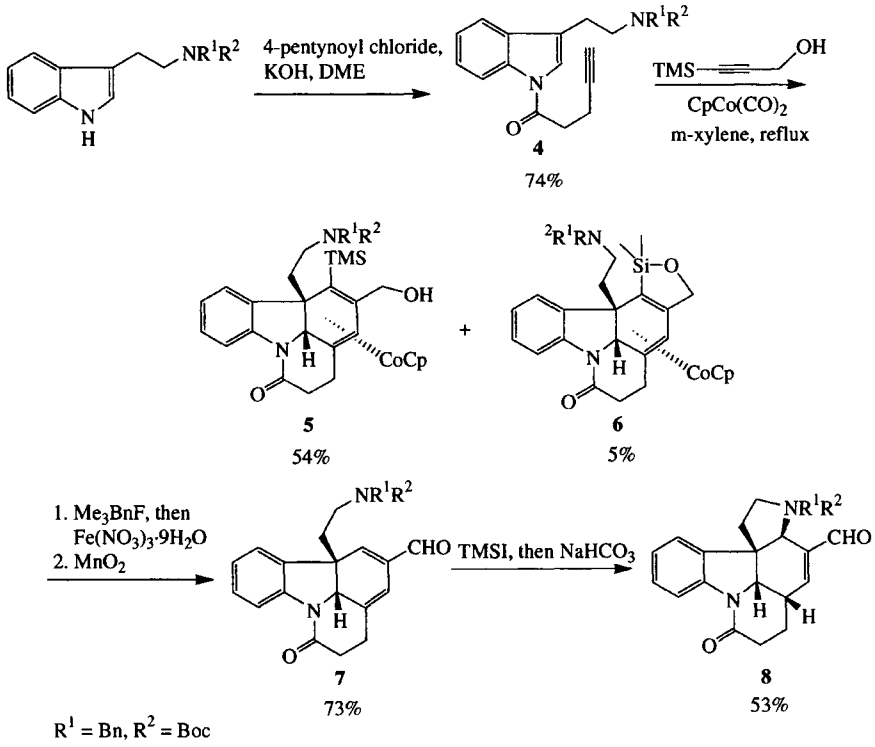
SCHEME 3

IV. Unsuccessful Approaches to Strychnine From ABCD Intermediates

The critical final ring-forming reactions would prove the most troublesome, but also the most interesting aspects of our strychnine synthesis, prompting the exploration of numerous different strategies and methods to effect these key steps. The first problem was the generation of the pyrrolidine E ring. While it could be solved in several ways, it will be seen that further elaboration towards the target molecule became an overriding challenge.

A. FORMATION OF THE E RING VIA INTRAMOLECULAR CONJUGATE ADDITION

The presence of a double bond at C15-C16 in the cycloaddition product suggested the exploration of an intramolecular conjugate addition of the exocyclic nitrogen. To activate the receptor, aldehyde **7** was made, ultimately derived from the [2 + 2+ 2]cyclization of *N*-4-pentynoyl tryptamine **4** and a propargyl alcohol (Scheme 4). This reaction proceeded with excellent regioselectivity, if only in moderate yield, producing cobalt complex **5** and a small amount of silyl ether **6**. Both of these could be deprotected and demetalated, affording, after oxidation, the target aldehyde. Unmasking the nucleophilicity of the amino function readily furnished the desired pyrrolidine ring in the shape of pentacycle **8**. However, spectral evidence clearly indicated that reprotonation of the substrate had occurred from the wrong side (from our point of view!) of the macrocycle, creating a cis relationship between the C8 and C13

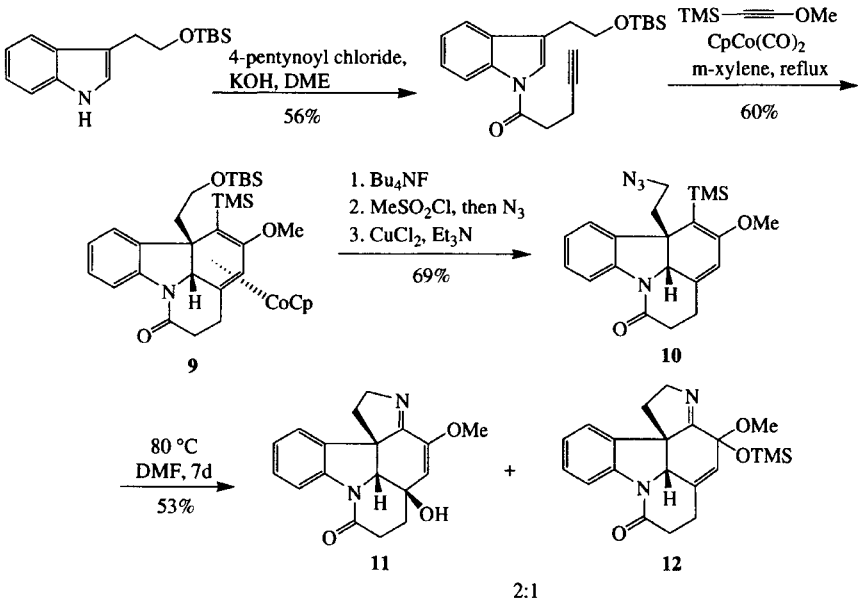


SCHEME 4

methine hydrogens. Attempts at base-catalyzed isomerization failed, suggesting that the system had found its thermodynamic minimum. Thus, Grotjahn was forced to abandon this approach. Yet, the utility of an intramolecular conjugate addition for E ring formation was not forgotten, and the concept would later prove its worth.

B. FORMATION OF THE E RING VIA INTRAMOLECULAR DIPOLAR CYCLOADDITION

Another attractive method for E ring formation featured an intramolecular [2+3]cycloaddition of an azide moiety, emanating from the indole 3-position via a two-carbon linker, to, now, an electron-rich version of the C15-C16 double bond.[19] The cycloaddition precursor **10** was made via **9**, in turn assembled by regioselective cocylization of protected methoxyacetylene (Scheme 5). In a puzzling turn of events, thermolysis of the azide product in toluene at moderate temperature (to minimize nitrene formation) and in low concentration (to suppress intermolecular reactions) produced the two oxidized pentacyclic products **11** and **12** in a 2:1 ratio. Performing the reaction in a more polar solvent (DMF, 80 °C, 7 d) altered the ratio to 5:1.[20]

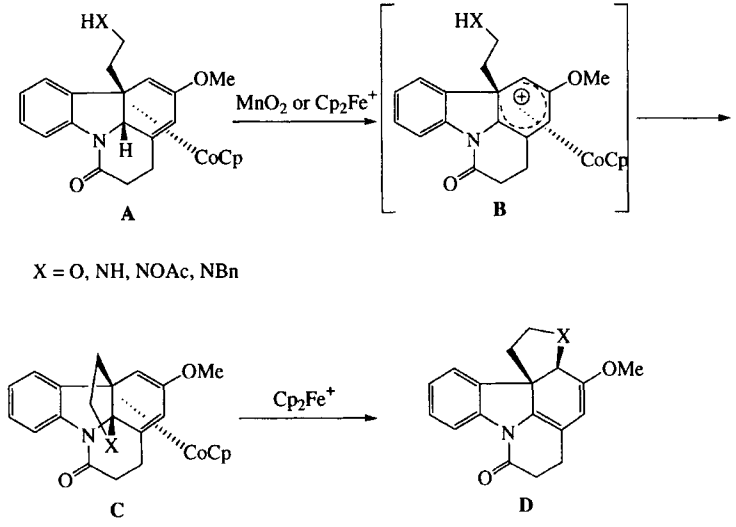


SCHEME 5

Although this strategy had solved the problem of pyrrolidine ring formation, the unexpected incorporation of the oxygen functions in both products presented a new one. Strenuous measures to eliminate air from the reaction mixture failed to avoid this complication, suggesting that the reaction intermediates (which may be either zwitterionic or radical in nature) were remarkably efficient scavengers of O_2. Thus, faced with additional steps required to manipulate these groups in a productive way and the already poor yield of the dipolar cycloaddition, this approach was abandoned.

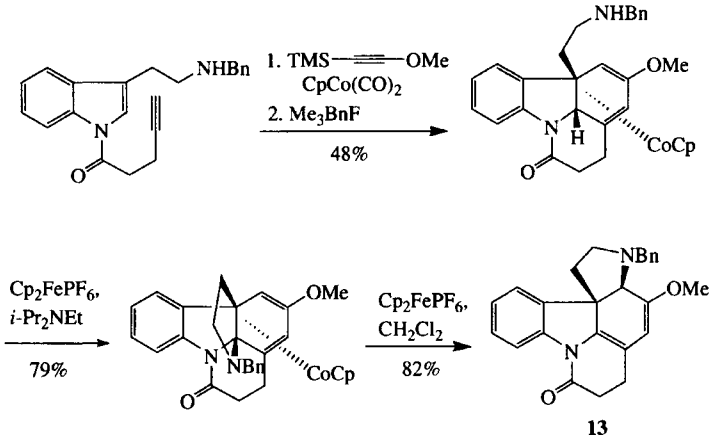
C. FORMATION OF THE E RING VIA OXIDATIVE CYCLIZATION AND REARRANGEMENT

A third and more "organometallic" plan for E ring construction utilized the complexed metal-diene unit to activate the D ring towards nitrogen addition. Grotjahn discovered that upon attempted oxidative demetallation with MnO_2 or ferrocenium cation, cobalt complexes **A** instead underwent unexpected oxidative ring closure to pyrrolidine propellanes **C** (Scheme 6). This transformation was theorized to involve the intermediacy of CpCo-stabilized cations of the type **B**. Even more surprisingly, when the cobalt was finally removed by renewed oxidation of **C**, the conditions could be manipulated to give either the free ligand as such or in its desired isomeric form **D.**



SCHEME 6

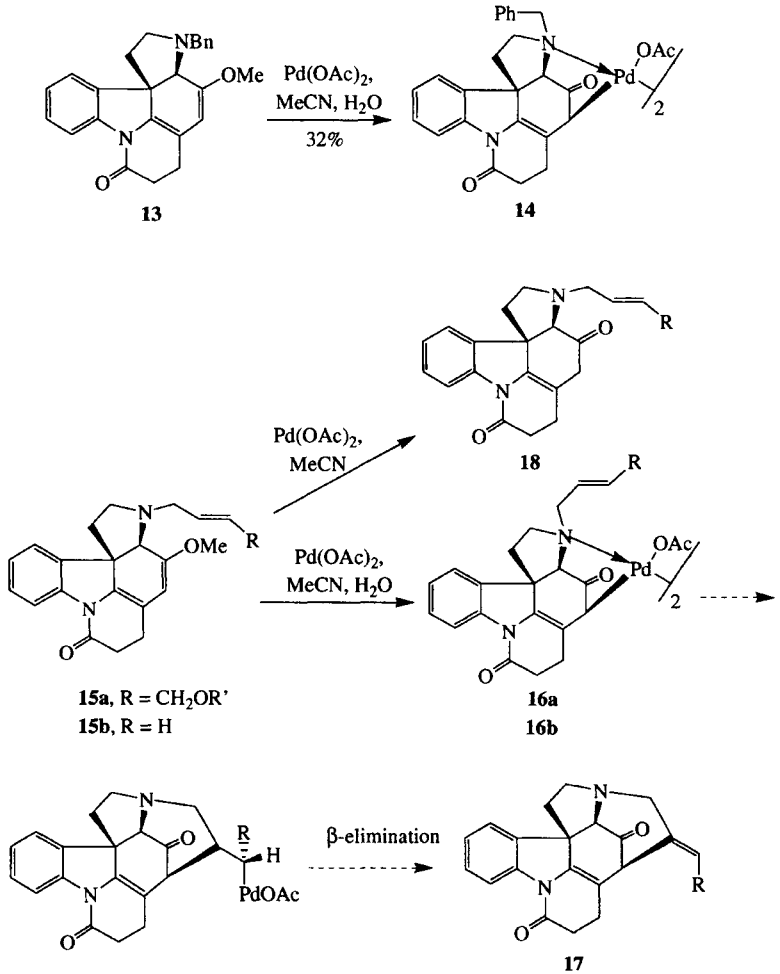
Access to molecules of the type **D** presented the opportunity to employ the methoxydiene unit in the assembly of the F ring and, in the process, restore the required cis juncture between the C and D rings, lost in **C**. In the event, the double rearrangement sequence was optimized for **13** (Scheme 7). Unfortunately, attempts to hydrolyze the dienol ether system with acid were unsuccessful. Presumably, this difficulty had its origin in the protonation of the tertiary nitrogen and associated dipolar repulsion slowing the rate of hydrolysis. Attempts to obviate this problem by replacing the *N*-benzyl moiety with an electron withdrawing substituent were thwarted by the resistance of **13** to catalytic hydrogenolysis.



SCHEME 7

Next, we considered the activation of **13** towards hydrolysis by π-complexation of a cationic metal unit to the electron-rich diene system. On the basis of the well-known palladium-mediated addition of nucleophiles to alkenamines, it was anticipated that the enol ether function in **13** would add H_2O in the presence of Pd(II).[21] Interestingly, exposure of **13** to a slight excess of $Pd(OAc)_2$ led to the isolation of **14** (Scheme 8). This material suggested the exploitation of the existing Pd-C linkage for carbon-carbon bond formation with an appropriate *N*-side chain. In particular, the intramolecular syn insertion of the allylic double bond in the *trans*-butenyl substituent in **15b** and subsequent syn β-hydride elimination would give the desired E-alkene **17**. This proposal was examined using alkene **15a** as a model system, synthesized in a manner similar to **13**. Upon exposure to $Pd(OAc)_2$ under the conditions

used for **13**, only a low yield (ca. 25%) of impure complex **16a** was obtained, perhaps due to competing Wacker-type oxidation of the alkene function. Reaction of **15a** in the absence of water gave **18**.



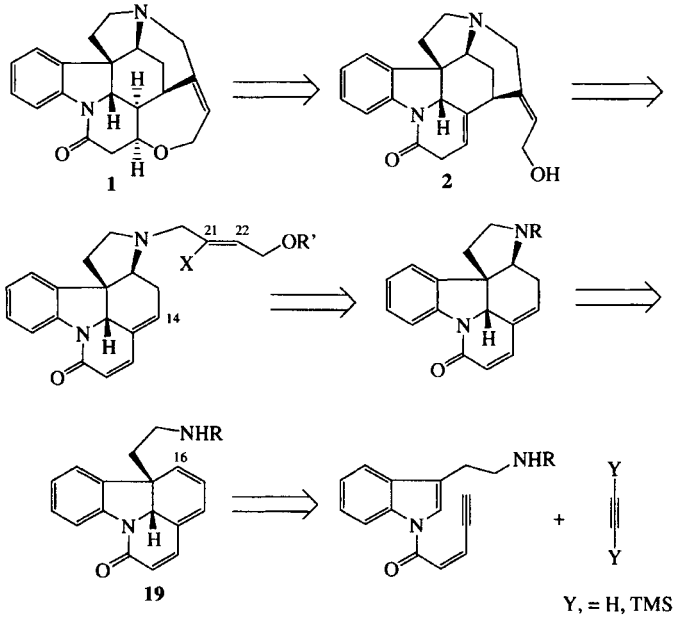
SCHEME 8

Thus, even though this strategy toward the E ring was attractive, not the least because of its originality, difficulties in elaborating the D ring methoxydiene unit compromised its viability in a strychnine synthesis. Grotjahn decided it was time to move on, leaving the completion of the strychnine project to future researchers.

V. Successful Approach to Strychnine: Part 1 - A "Simpler" Plan Hits Snags

A. A "SIMPLER" PLAN

Grotjahn's struggle with functionality on the D ring, which had been incorporated originally to facilitate the necessary C-N and C-C bond forming reactions, suggested that the approach to the E and F rings should be redesigned. The successful intramolecular conjugate additions that led to the pyrrolidine ring described above encouraged us to return to this C-N bond forming strategy, but, this time, the C15-C16 linkage would be activated by a π-system extending all the way to the amide carbonyl, as in **19** (Scheme 9). Should Michael addition be successful, the product would be usable again in this manner, offering a variety of approaches to the construction of the piperidine F ring from a properly

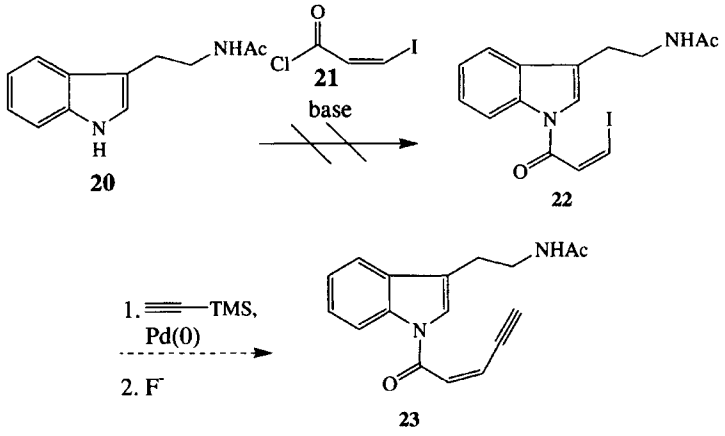


SCHEME 9

functionalized *Z*-4-hydroxy-2-butenyl unit. This sequence would eliminate the need for a regioselective [2 + 2 + 2]cycloaddition and appeared simple. However, as is often the case in synthesis, nature had roadblocks in store that impeded any smooth advance.

B. FIRST SYNTHESIS OF THE ENYNOYLINDOLE [2 + 2 + 2]CYCLOADDITION PRECURSOR

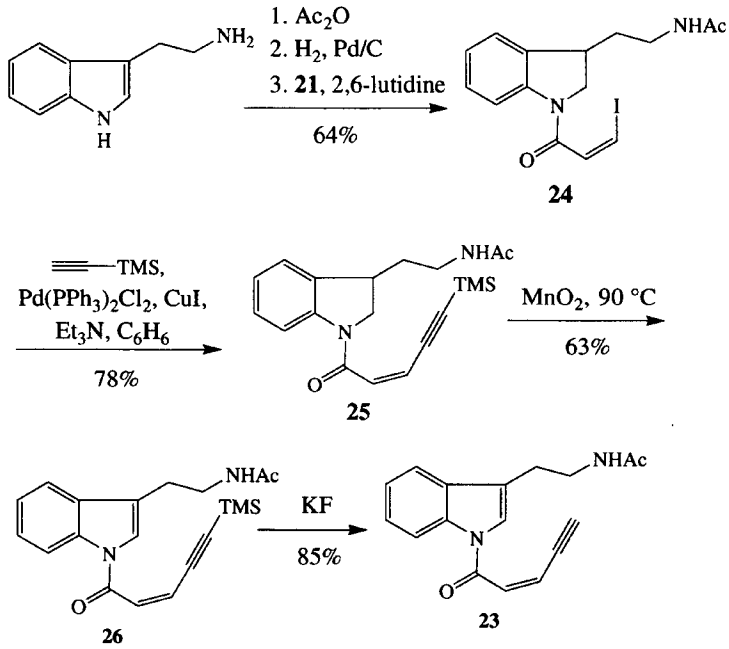
Indeed, the next coworker on this project, postdoctoral fellow Leila Dorta, almost immediately encountered difficulties with the preparation of the [2 + 2 + 2]cycloaddition substrate **23** (Scheme 10). Formation of the enyne moiety was envisioned to proceed smoothly from the *cis*-3-iodoacryloyl(acetyl)tryptamine **22** via palladium-mediated coupling chemistry very familiar to our group. However, the properly acylated indole system proved surprisingly difficult to generate. Conditions that had worked well for the acylation of the indole nitrogen with unsaturated acid chlorides failed to yield any of the desired unsaturated amide upon exposure to iodoacryloyl chloride **21**.[22] Deprotonation with hydroxide bases (KOH in DME),[23] alkyllithiums (BuLi),[24] and weak amines (Et_3N, 2,4-lutidine)[22b] all destroyed the acid chloride and returned the starting indole **20**. Attempted acylation employing Illi's phase-transfer method (NaOH, Bu_4NSO_4) proved similarly disappointing.[25] The reason for these failures remains obscure, but seems to originate from the unsaturation of the acid chloride and not the tryptamine. For example, deprotonation of the amide hydrogen (pK_a = 17,[26] in comparison to pK_a = 16.6 for 3-methylindole[27]), a possible confounding side reaction, did not



SCHEME 10

seem detrimental, since indole itself also failed to acylate under these conditions.

To facilitate amide formation, the nucleophilicity of the heterocyclic nitrogen center was increased by the reduction of the aromatic indole system to an indoline (Scheme 11).[28] Acylation now proceeded smoothly, as did the subsequent coupling step.[29] However, rearomatization, a step necessary to employ the [2 + 2 + 2]cycloaddition, proved troublesome. Wilkinson's catalyst[30] destroyed the system, while oxidation with DDQ[31] resulted in poor yields (31%) of **26**. Desilylation rendered cycloaddition precursor **23**. Another researcher on the project, Diplomstudent Kai Lamottke, working to complete the equivalent of a master's degree, doubled the efficiency of the oxidation step with freshly prepared MnO_2.[23,32] The stage seemed set for the cobalt-mediated cyclization.



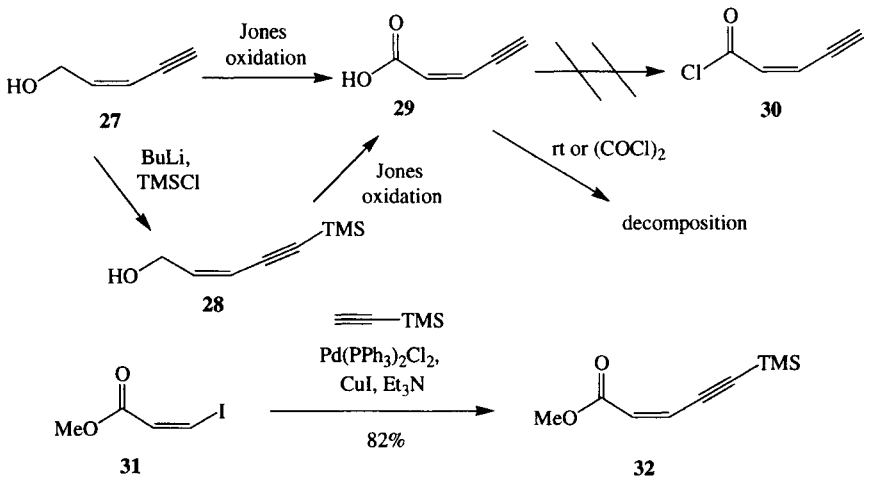
SCHEME 11

VI. Successful Approach to Strychnine: Part 2 - An Unprecedented [2 + 2 + 2]Cyclization

A. AN IMPROVED SYNTHESIS OF THE ENYNOYLINDOLE CYCLOADDITION PRECURSOR

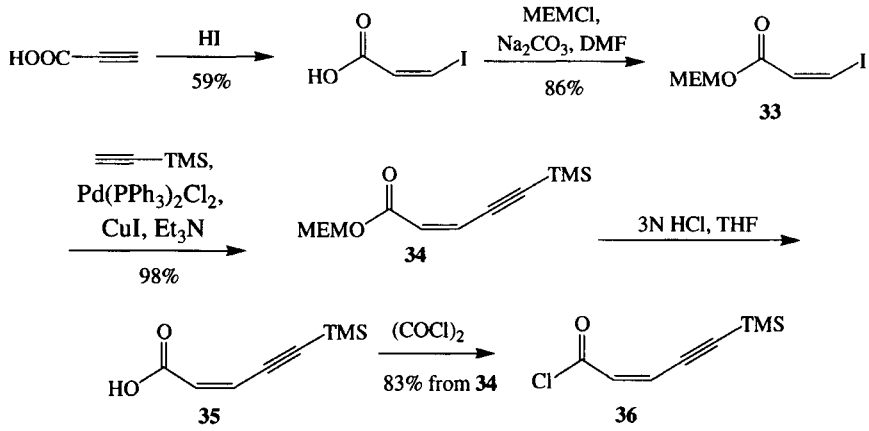
It was then that one of the coauthors of this article, Michael Eichberg, joined the project. Remarkably rapid total syntheses of strychnine had appeared in the literature, notably by Stork[7k,8a] and Rawal.[7h] Thus, the somewhat inelegant reduction-acylation-rearomatization sequence seemed simply too cumbersome for the desired succinct synthesis of **1**, as well as too time-consuming to make the quantities of material needed for further synthetic studies. Furthermore, despite the difficulties encountered previously, the acylation of indole with α,β-unsaturated acid chlorides seemed a soluble problem. However, ascertaining the futility of previous attempts, various other promising methods failed. These included heterocyclic acyl transfer agents (DMAP, DMF or benzene),[33] NaH, and even a boric acid mediated coupling.[34]

Consequently, a more convergent plan was executed that was also thought to utilize a potentially more stable acryloyl building block than **21**, namely **30**. Dorta had obtained some preliminary results previously. She found that oxidation of propargyl alcohol **27** with Jones reagent could afford the desired acid **29** (Scheme 12). However, this compound polymerized to a black solid upon standing or upon attempted acid chloride generation.[35] Trimethylsilyl protection of the triple bond did not help much, as oxidation of stable **28** resulted in deprotection to unstable acid **29**. An alternative way to introduce the alkyne unit would be the coupling of *cis*-iodoacrylic acid with TMSA. However, this reaction failed, both under the conditions used for the coupling of **24** (Scheme 11), as well as those employing zinc.[36] However, this coupling worked in the case of the methyl ester **31** to provide **32**. The success of this last transformation led to the execution of Scheme 13, exploiting the readily cleaved methoxyethylmethyl protecting group. This strategy allowed **33** to undergo smooth coupling to form enyne **34**. Hydrolysis gave the stable (!) pentenynoic acid **35** and, finally, the acid chloride **36**. This compound was stable to cis/trans isomerization for at least 24 hours at 0 °C. Moreover, the reaction sequence was scaled up with little effort to afford multi-gram quantities, a critical feature for an early stage intermediate in a multi-step synthesis.

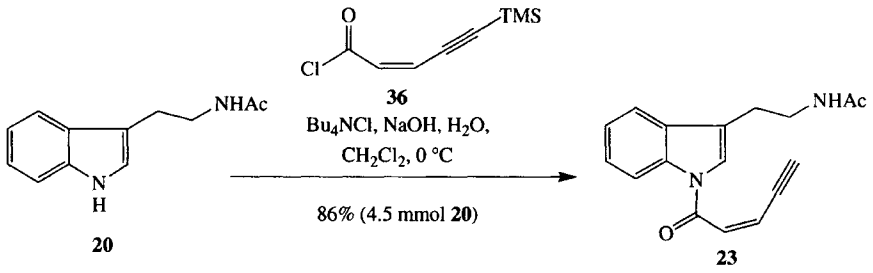


SCHEME 12

With this new acid chloride in hand, the acylation of the indole nitrogen under various conditions was attempted yet again, eventually turning to phase transfer techniques.[37] While Illi's method,[25] which featured Bu_4NHSO_4 as the catalyst, failed, use of Bu_4NBr gave the target enynoylindole **23**, optimized on a respectable scale (0.9 g, 4.5 mmol of **20**) to afford **23** in 82% yield using Bu_4NCl as the phase-transfer agent (Scheme 14). This outcome required modulation of the temperature,



SCHEME 13

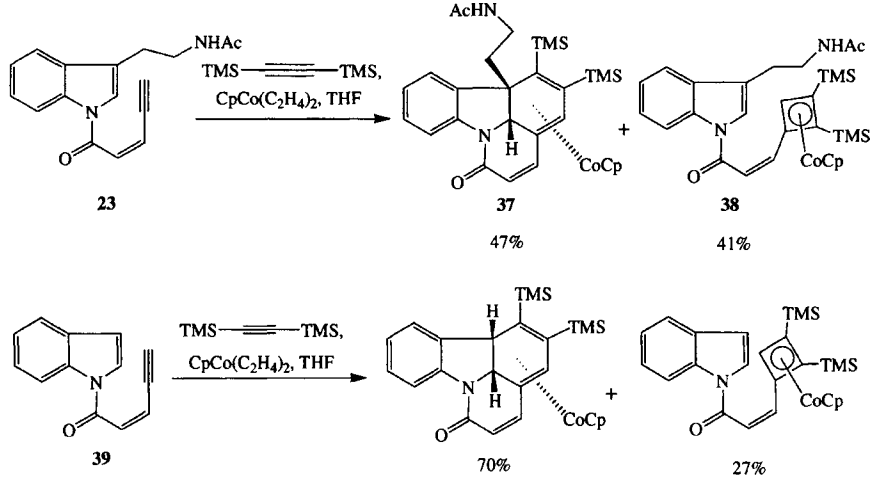


SCHEME 14

stirring rate, quantity of Bu_4NCl catalyst, rate of addition of the acid chloride, and the addition of discrete quantities of water to the CH_2Cl_2 solvent mixture.[38]

B. THE KEY [2 + 2 + 2] CYCLOADDITION STEP

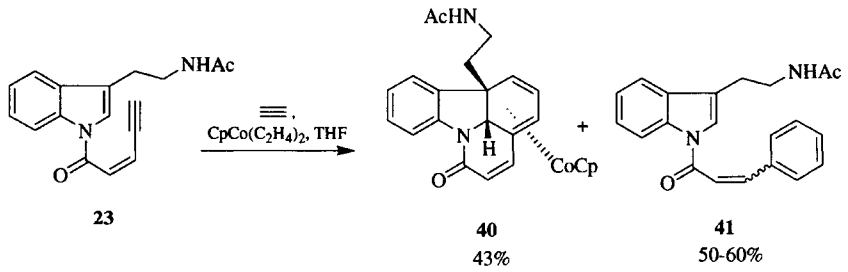
Efficient access to **23** finally allowed the examination of the pivotal cobalt-mediated [2 + 2 + 2]cycloaddition. Initial experiments employed bis(trimethylsilyl)acetylene (BTMSA) as a cocylization partner (Scheme 15). This alkyne had been used previously with great success, because it does not autocyclize and is relatively volatile and, hence, can be used as a solvent. However, while successful, the reaction generated a significant



SCHEME 15

quantity of cyclobutadiene **38** at the expense of the desired dihydrocarbazole **37**, a deviation attributed to the relative bulk of the trimethylsilyl groups. Indeed, this problem is apparent even in the case of the less hindered indole derivative **39.** In addition, strategically, these trimethylsilyl groups were unnecessary and needed to be removed, a task that proved troublesome. Attention was therefore turned to acetylene itself as a cocyclization partner, an as yet untried variant in this chemistry.

Lamottke was the first to execute this variant. He found that a solution of **23,** saturated with acetylene gas and exposed to an excess of $CpCo(C_2H_4)_2$, formed the desired target **40** in 43% yield (Scheme 16). This promising result was the starting point for the experimental efforts of one of the authors. While the process was reproducible, attempts to scale it up beyond sub-millimolar quantities, necessary for a fairly early and critically important synthetic step, led to significant decreases in yield (17-24%). The difficulty appeared to be formation of cinnamic amide **41**, isolated in 50-60% yields as a mixture of cis and trans isomers.[39] Minimization of this unwanted product required consideration of the [2 + 2 +2]cycloaddition mechanism.

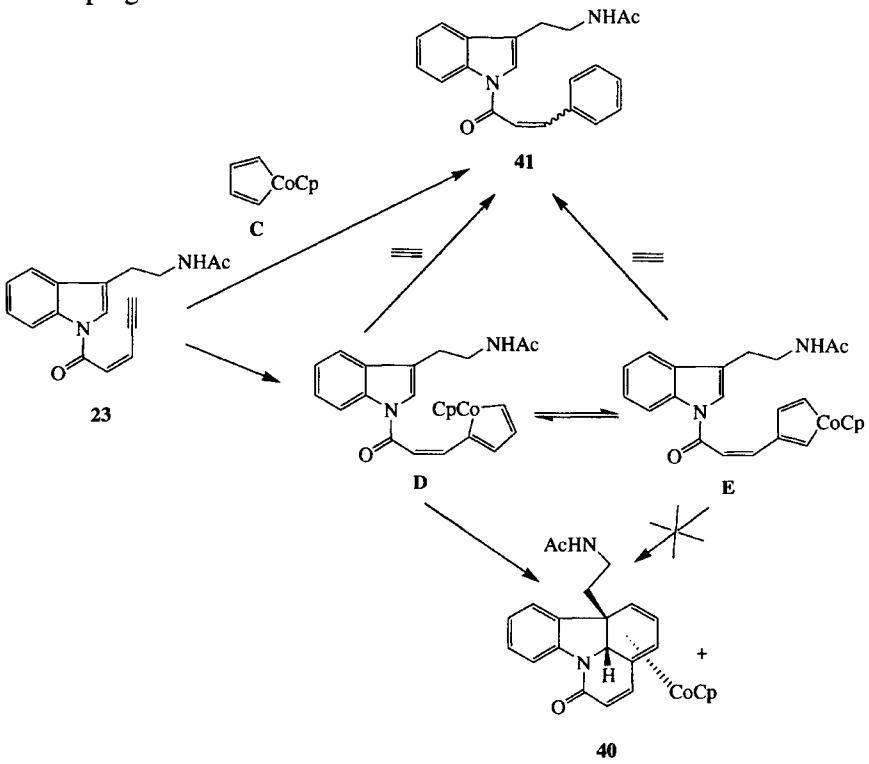


23 **40** 43% **41** 50-60%

SCHEME 16

The offending amide **41** was thought to be the terminus of two general pathways, either the reaction of **23** with **C**, derived by oxidative coupling of two molecules of acetylene, or of either (or both) of the metallacyclopentadiene intermediates **D** or **E** with acetylene (Scheme 17).[40] This picture suggested that yields of **40** might be improved by reducing the steady state acetylene concentration in the reaction mixture. Such a modification would retard the formation of **C** and the trapping of (the presumably equilibrating)[40c] **B** and **C** by acetylene. Thus, at 5mM concentrations of **23**, moderating the rate of acetylene addition and concomitantly purging the reaction mixture with a stream of nitrogen or argon led to yields (46%) of **40** on a 1-3 mmol scale. Manipulation of

various other variables such as solvent, rate or order of addition of the nongaseous reagents, various additives, and different CpCo sources were inconsequential or led to reductions in yield. Thus, despite a great deal of effort, little improvement in the efficiency of the cyclization was achieved eventually beyond that originally observed by Dorta or Lamottke. Nevertheless, the ability to perform the reaction on moderate scales (1 g, 3.5 mmol) with consistent results was gratifying, as it made further progress much less tedious.

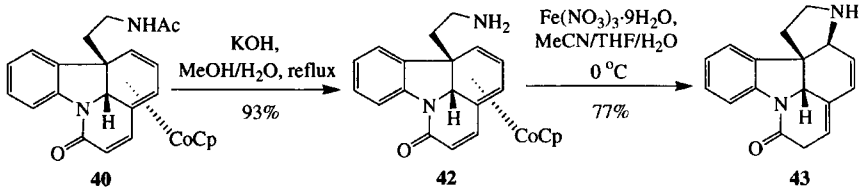


SCHEME 17

VII. Successful Approach to Strychnine: Part 3 - Formation of the E Ring by Oxidative Demetallation/Intramolecular Conjugate Addition

In preparation for E ring closure, the appended nitrogen center required deacylation for sufficient nucleophilicity. Of concern were the

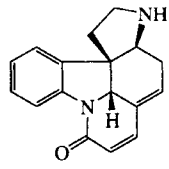
strongly basic conditions required to hydrolyze acetamides, which could have been deleterious to ring C in **40**. Fortunately, the target amine **42** could be produced in excellent yields (90-95%) despite the rather harsh conditions employed [KOH (165 equiv), MeOH/H_2O (1:1), reflux, 6h] (Scheme 18). It is possible that the electron-donating and somewhat bulky CpCo moiety protects the adjacent functionality. Good fortune persisted, as exposure of the complexed diene to a variety of oxidative demetalation reagents commonly used in our group readily afforded the desired pentacycle **43** containing the pyrrolidine E ring. Best yields (77%) were obtained with an iron(III) system, $Fe(NO_3)_3 \cdot 9H_2O$.[16a] Although a formal 1,8-conjugate addition, the E ring closure occurred under conditions similar to those used in the rearrangements forming **13** (Scheme 7) and may proceed through a radical cation cobalt species.



40 **42** **43**

SCHEME 18

Surprisingly, **43** was consistently isolated as the C12-C15 diene, as opposed to a system in conjugation with the amide carbonyl. That this was in fact the kinetic product was revealed by isomerization of **43** to **44** upon exposure to sodium methoxide. However, **44** was unstable and difficult to purify, not surprising, considering its functionality. If this problem could be resolved later, secondary amine **43** would represent a



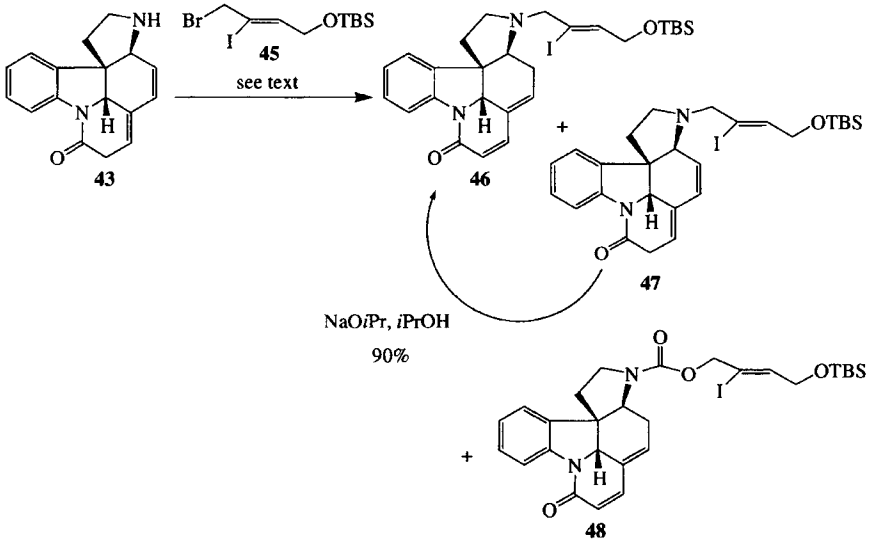
44

useful synthetic intermediate for further attempts to construct the piperidine F ring, since it would allow the attachment of whatever functionalized side chain proved necessary for the critical C14-C21 bond forming reaction.

VIII. Successful Approach to Strychnine Part 2 – The Battle for the F Ring

A. SETTING THE STAGE – CLEAN ISOMERIZATION AND ATTACHMENT OF A FUNCTIONALIZED SIDE CHAIN

A well known problem of strychnine synthesis is the stereoselective introduction of the allylic ether in **1**. One popular solution to this challenge is the provision of this stereochemistry through a small synthon in a partially convergent fashion. For example, in their respective strategies, Stork,[7k,8a] Rawal,[7h] and Bonjosch[7e] all employed a functionalized butenyl ether group at a similar stage. We pursued the same approach, alkylating **43** with known iodoalkene **45** (Scheme 19), a compound that featured not only a readily activated sp^2-carbon-iodine center amenable to a variety of carbon-carbon bond forming reactions, but



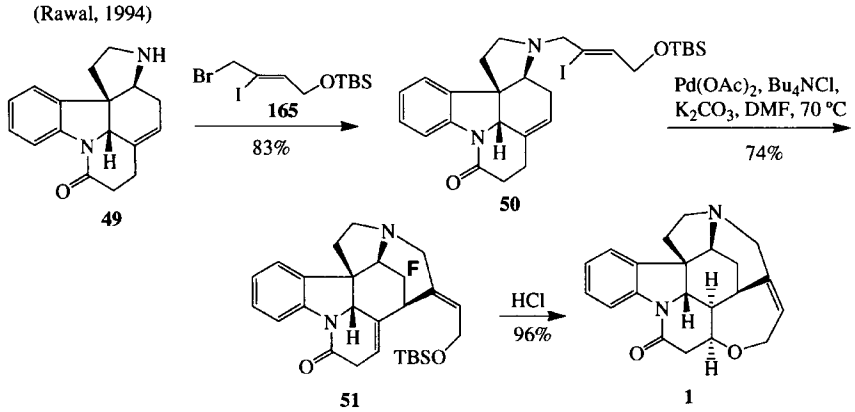
SCHEME 19

also the desired stereochemistry. In the hope of minimizing the number of overall discrete synthetic steps, a one-pot alkylation-isomerization sequence of **43** to **46** was examined extensively. However, use of a variety of carbonate and phosphate bases, as well as a hindered amine (DBU), in several different polar, aprotic solvents, proved frustrating. These attempts either failed to lead to double bond isomerization, producing **47**, or, in the case of carbonate bases, were complicated by

formation of the carbamate **48**.[41] Ultimately, we were forced to adopt a discrete two step protocol. The optimal system for the alkylation proved to be Li_2CO_3 in DMF, delivering **47** in 74% yield. Meanwhile, the somewhat hindered isopropoxide base provided the best yields for isomerization. Thus, **46** was generated in 66% yield in these two steps, setting the stage for F ring closure.

B. A QUICK OUT? ATTEMPTED FORMAL SYNTHESIS OF STRYCHNINE VIA A DOUBLE BOND REDUCTION TO RAWAL'S INTERMEDIATE

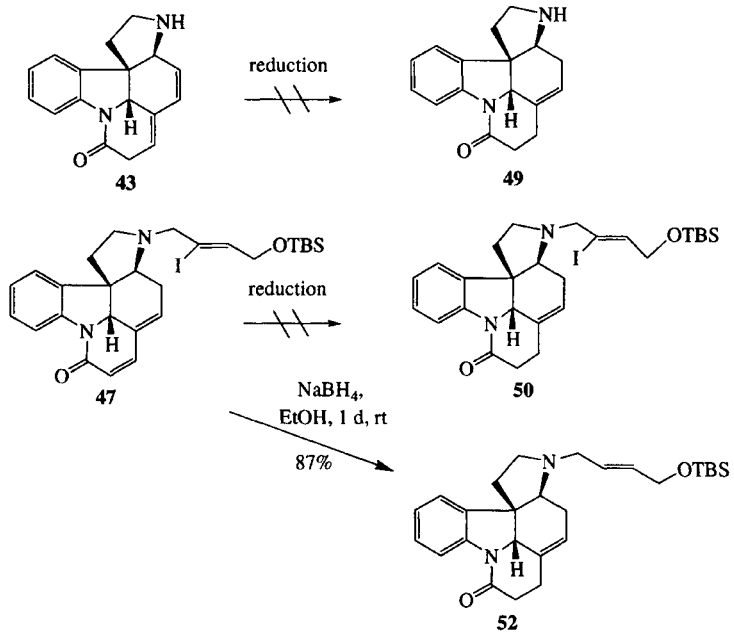
The amines **43**, **46**, and **47** constituted dehydro analogs of two intermediates in Rawal's strychnine synthesis, **49** and **50** (Scheme 20).[7h] This suggested that a simple reduction of the C ring double-bond, while conserving a C14-C15 unsaturation, would access synthetic relay points only two (via a Heck cylization of **50**) or three (via alkylation of **49** with side chain **45**, then Heck reaction) steps from **1**, and allow the claim of a formal synthesis.



SCHEME 20

The issue became one of selective reduction of the 1,3 diene moiety, and various conditions for 1,4 hydrogen addition were examined. Unfortunately, all of these failed. For **43**, complex, difficult to purify mixtures of various reduction products were generated under various hydrogenation and dissolving metal conditions (Scheme 21).[42] The amines **46** and **47** had the additional problem of the readily reducible alkenyl iodide segment. Indeed, exposure to hydride reagents led to quite facile hydrodehalogenation, with products such as **52**. Thus, it became

clear that, while tantalizingly close, selective reduction and a formal synthesis was likely to remain elusive. In any case, it seemed somewhat unsporting to pursue this course, as **46** had all the functionality necessary to forge a unique approach to F ring closure.



SCHEME 21

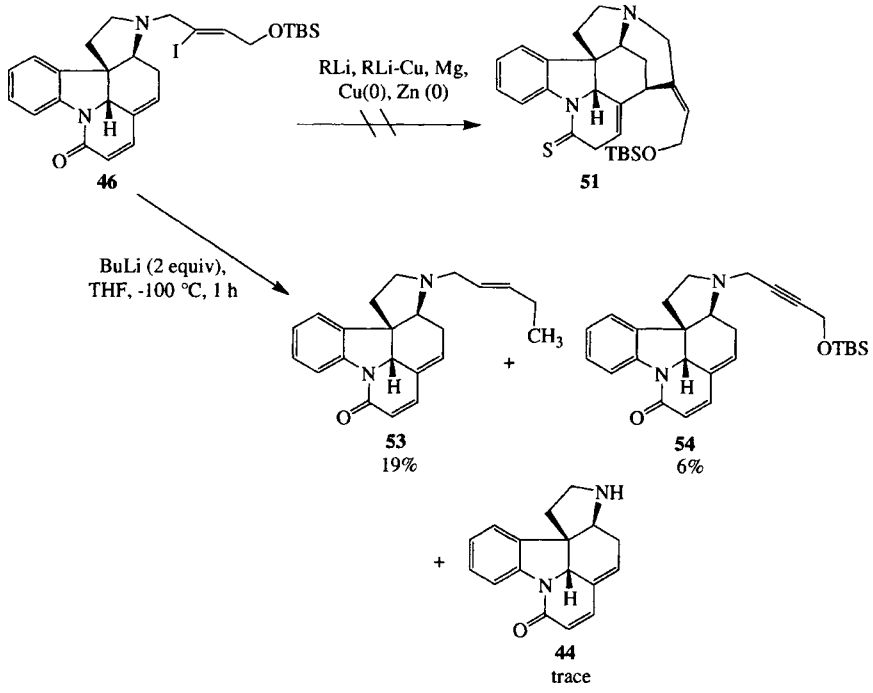
C. SO CLOSE, YET SO FAR – ATTEMPTED CLOSURE OF RING F VIA AN INTRAMOLECULAR CONJUGATE ADDITION

Following the strategy depicted in Scheme 9, **46** offered a conjugated amide unit activating C14 to nucleophilic attack and an iodine substituent at C21 which we envisioned to be readily activated homo- or heterolytically by a variety of inorganic and organometallic reagents, while maintaining the C21-C22 stereochemistry. Therefore, the conversion of C21 to a nucleophilic carbanion, followed by an intramolecular 1,6-conjugate addition appeared to be the simplest path to forming the piperidine F ring. The product, hexacycle **51** (see Scheme 20), would be only two precedented steps away from strychnine.

1. *Formation of Nucleophilic C21 via Metal-Halogen Exchange*

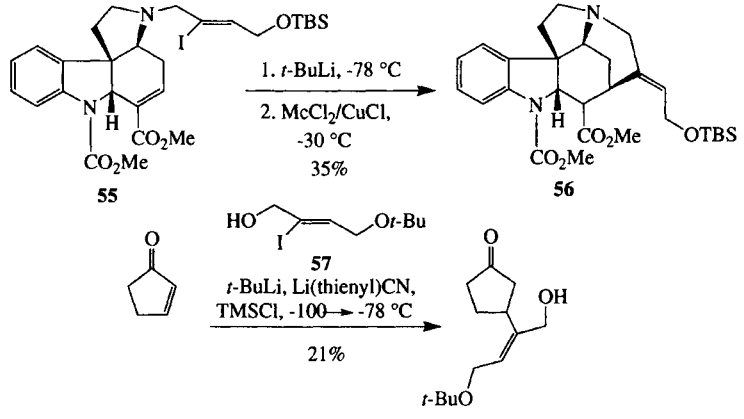
The most direct means for initiating the desired transformation would be an iodine-metal exchange via Grignard formation or employing alkyllithium reagents, followed by transmetalation to an organocuprate intermediate. At first, hopes were high that these well-known reactions, with so many procedural variations available, would provide the desired product. As these studies wore on, however, experiment after experiment would end in failure and hopes for a successful conversion dimmed. With Mg reagents, reactions either returned starting material (Mg, MeI, Et_2O, 40 °C, 4 d) or led to a complex mixture of products (Mg, TMSCl, 1,2-dibromoethane, THF, 65 °C, 1 d).[43] Attempts at iodide-magnesium exchange with *i*-Pr_2Mg,[44] both with and without added Cu(I), caused extensive decomposition of the starting material. Alkyllithium reagents followed a similar pattern. Adding BuLi (1 equiv) or *t*-BuLi to a THF solution of **46** at –76 °C, followed by the usually excellent transmetalation reagent LiCu(thienyl)CN[45] or $MnCl_2/CuCl$[46] gave a mixture from which only starting material could be recovered. Greater amounts of lithium reagents invariably furnished complex mixtures. Addition of trimethysilyl chloride, intended to activate the enone system, also failed. Activated copper and zinc systems were examined similarly. However, both "Rieke" copper, generated from CuCN-2LiBr and naphthalene anion at –100 °C,[47] and "Rieke" zinc, derived from $ZnCl_2$,[48] while consuming starting material, did not furnish identifiable products.

As substantial quantities of advanced intermediate **46** were lost to such fruitless chemistry, we felt compelled to find some explanation. Careful examination of the complex product mixtures provided some useful insights. For example, reaction of **46** with BuLi (1.8 equiv) at –100 °C resulted in both deiodinated alkene **53** and alkyne **54** (Scheme 22). In addition, analysis by GC/MS indicated the presence of a trace of the secondary amine **44**. Reactions with other alkyllithium reagents also tended to show at least some traces of one or more of these products, and, in some cases, returned products indicating addition of the alkyl group to **46**. Clearly the starting material was susceptible to a number of side reactions, including hydrogen iodide elimination, loss of the butenyl side chain, direct addition of the lithium alkyl, and deprotonation at C15 to either reform **46** or possibly generate **53** by intramolecular proton transfer. Finally, it is also feasible that some of the reagents effected direct electron transfer to the dienamide segment, the resulting radical anion suffering an unknown fate.



SCHEME 22

Other researchers had encountered related problems in attempting to link C14 to C21 via carbanion-mediated conjugate additions. Stork and co-workers reported a successful transformation of iodide **55** to ABDEF



SCHEME 23

intermediate **56**, utilizing *t*-BuLi mediated iodine-lithium exchange, followed by transmetalation using a $MnCl_2$/CuCl system (Scheme 23).[7k,8a] However, this reaction proceeded in poor yields (35%) and was difficult to reproduce.[49] Overman and co-workers observed consistently low yields of the conjugate addition of allylic alcohol **57** to cyclopentenone to form an early intermediate on route to **1**.[7g] They attributed this problem to the destruction of the electrophile via allene intermediates, a rationale that could also explain observation of amine **44**.

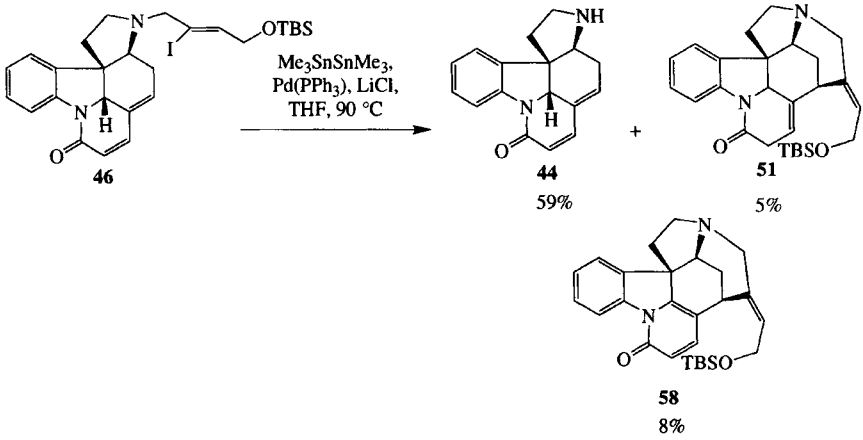
2. *Application of Organochromium Reagents to Induce Conjugate Addition*

The sensitivity of **46** suggested a milder method for the activation of the pertinent carbon center. Organochromium reagents seemed excellent candidates, as they exhibit tolerance of functionality in the course of 1,2-additions to carbonyls and require only mild conditions.[50] In addition, alkenyl halides have been shown to insert Cr(II) readily.[51] However, stirring **46** with $CrCl_2$ (3.5 eq) doped with 5% $NiCl_2$[52] for 2 days in DMF returned the starting iodide (36%) and the dehalogenated alkene **53** (12%). Use of DMSO as solvent gave similar results. Isolation of **53** suggested possible activation of C21, but a sluggish addition to C14. Addition of CuI to the reaction mixture apparently failed to generate a more reactive organocuprate and gave, after 3 days, a 1:1 mixture of **53** and unreacted starting material (80% recovery). Adding TMSCl to the mixture, in an effort to activate the enone, gave desilylated **46** within one hour in 73% yield, and the reaction was not investigated further. Further attempts in pure DMSO with a large excess of $CuCl_2$/$NiCl_2$,[53] or reaction at elevated temperature (100 °C), led to complex mixtures. Thus, this approach was abandoned.

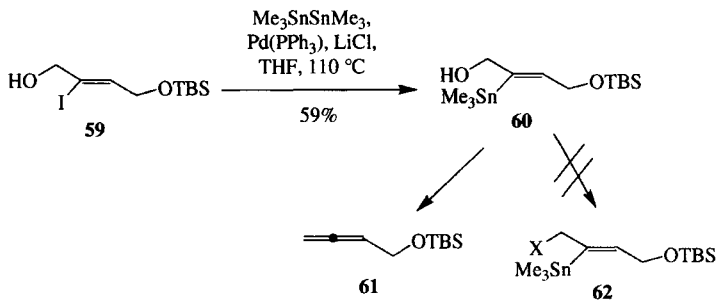
3. *Application of Alkenyl Stannanes to Induce Conjugate Addition*

Another mild approach to carbanion formation and conjugate addition could be through organotin reagents. Alkenyl stannanes are readily transmetalated by organocuprates[54] or Cu(I) salts (CuCl, CuCN).[55] Direct generation of the required stannane from **46** led to some interesting observations. Treatment with $Me_3SnSnMe_3$ and $Pd(PPh_3)_4$ in THF[56] in a sealed flask heated to 90 °C resulted in a mixture dominated by amine **43** (59%), but also containing hexacyclic pyridone **58**, as well as silylated isostrychnine (**51**) (Scheme 24) in 8% and 5% isolated yields, respectively. As other studies would later show, **51** and **58** originate from

the Pd-mediated addition of C21 to the C12-C13 double bond and either the intermolecular reduction of the Pd-C carbon bond or β-elimination of the C8 hydrogen (vide infra). Attempted installation of the trimethyltin moiety on the butenyl side chain prior to alkylation of **43** was successful with iodo alcohol **59** (Scheme 25) providing the alkenyltin species **60**. However, several efforts to convert the hydroxy substituent into a leaving group under a variety of conditions, including bromination and sulfonate ester formation, resulted in rapid β-elimination to form allene **61**,[57] even at -78 °C. Notably, tin derivatives such as **62** do not appear in the literature, while systems with a homoallylic leaving group or a tin atom situated at the 3- rather than the 2-position of the alkene (with respect to the leaving group) are known.[58] This result constituted further evidence of the tendency of the alkenyl side chain to eliminate when activated.



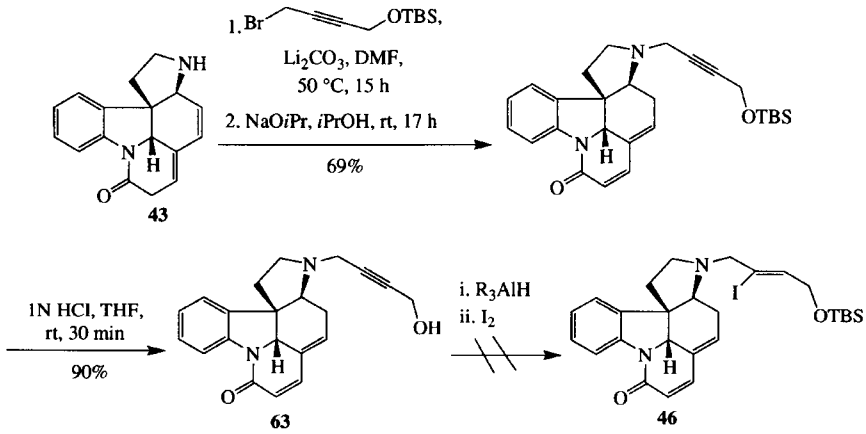
SCHEME 24



SCHEME 25

4. *Formation of Nucleophilic C21 via a Directed Reduction of a Propargyl Alcohol*

Another attempt at establishing the C21-C24 linkage was based on an alternative side chain. The ability of aluminum hydride reagents to selectively reduce propargyl alcohols was thought to be usable to direct the reduction of alkyne **63** and induce the subsequent closure of the F ring. Thus, **63** was synthesized by alkylation of **43** with 1-bromo-4-*t*-butyl(dimethyl)siloxybut-2-yne,[59] followed by isomerization and deprotection in 62% overall yield (Scheme 26). To examine the stability of the pentacyclic core of the molecule to these hydride reagents, the reactions of **63** were quenched with I_2, and the product mixtures were examined for signs of iodo alcohol **46**. Unfortunately, exposure of **62** to Red-Al[60] resulted only in recovered starting material (1-2 equiv Red-Al) or decomposition (>2 equiv). Use of diisobutylaluminum hydride (DIBAL)[61] also failed to effect alkyne reduction.

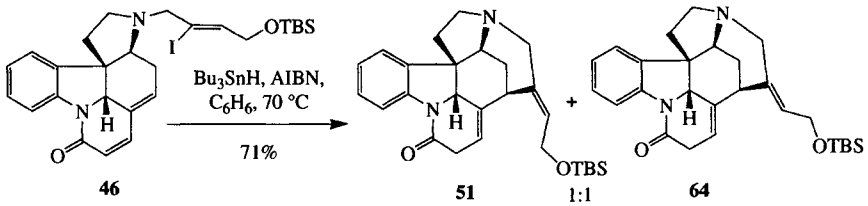


SCHEME 26

D. SUCCESS AT LAST: FORMATION OF THE F RING VIA RADICAL MEDIATED CLOSURE

The sensitivity of **46** to conjugate addition reaction conditions indicated to us the need for a mechanistically distinct approach to formation of the penultimate ring of strychnine. The fact that the weak carbon-iodide bond (~57 kcal/mol) is readily cleaved heterolytically suggested the potential for a radical-mediated ring piperidine closure.[62] Indeed, reaction of **46** with Bu_3SnH and Et_3B in toluene[63] at room

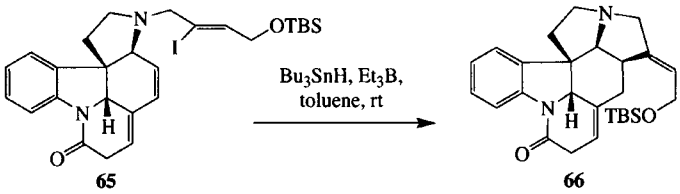
temperature for one day gave primarily the deiodinated alkene **53** as a mixture of cis and trans isomers (3:7), the desired hexacyclic silyl ether **51** and its Z-isomer **64** (1:1), and recovered **46** (Scheme 27). Switching to benzene as solvent essentially reversed the above outcome, giving predominately **51** and **64** (1:1), with smaller amounts of a cis/trans **53** mixture and recovered **46** (6%). The isolation of the uncyclized, reduced **53** suggested a somewhat sluggish 6-*exo*-trig closure, giving opportunity for either an intermolecular reduction of the radical by Bu_3SnH, or an intramolecular 1,5-hydrogen shift[64] from the C15 methylene. The solution to this problem would require heating the reaction. Indeed, formation of the uncyclized system could be minimized by reaction of **46** and Bu_3SnH in refluxing benzene, with AIBN as initiator, to give **51** and **64**, again as a 1:1 mixture, in 71% yield.



SCHEME 27

Unfortunately, the efficiency of cyclization was marred by the loss of C21-C22 stereochemistry. While the facile isomerization of the intermediate alkenyl radical, with an estimated barrier of 2 kcal/mole,[65] cannot be avoided, it was hoped that variation of the reaction conditions would affect the relative rates of ring closure of the two isomeric reactive species. However, reaction of the desilylated alcohol failed to improve the ratio of isomers and ruled out any steric effect of the bulky *t*-butyl(dimethyl)silyl ether. Employment of TMS_3SiH as a radical source[66] gave an improved isomer ratio (2:1, **51/64**), but in lower yield (40%). Similar results were obtained with Ph_3SnH, which gave 24% of **51** and 17% of **64**, as well as 24% of the dehalogenated **53**. Low temperature conditions might also slow the isomerization or the ring closure rate of the undesired isomer. However, we encountered difficulty in activating the starting material under such conditions. At –78 °C, using $BF_3{\cdot}OEt_2/Et_3B$[67] or Et_2Zn[68] as initiators, **46** was left untouched, or, with an excess of the alkyl zinc reagent, decomposition occurred. Exposure of **46** and Bu_3SnH to irradiation by a Hanovia lamp at –20 °C in toluene, with 2.2-dimethoxy-2-phenylacetophenone[69] as a photoinitiator, ended in

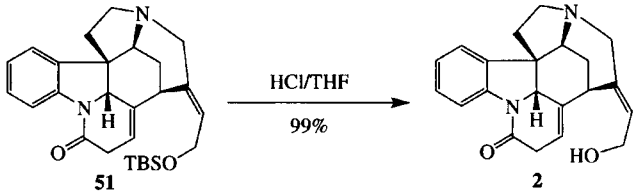
a mixture of starting material and dehalogenated alkene **53**. Reaction with SmI_2, which has shown some selectivity in vinyl radical cyclizations,[70] resulted in extensive decomposition of the starting material. Interestingly, tin hydride reduction of diene isomer **65** did not cause 6-*endo* closure, but rather led to a mixture containing 5-*exo*-trig product **66** (Scheme 28).



65 **66**

SCHEME 28

As in Rawal's synthesis (Scheme 20), deprotection of the silyl ether **51** under acidic conditions provided isostrychnine (**2**) in almost quantitative yield (Scheme 29). The synthetic material was identical with the natural compound in its ^1H and ^{13}C NMR spectra and by TLC.



51 **2**

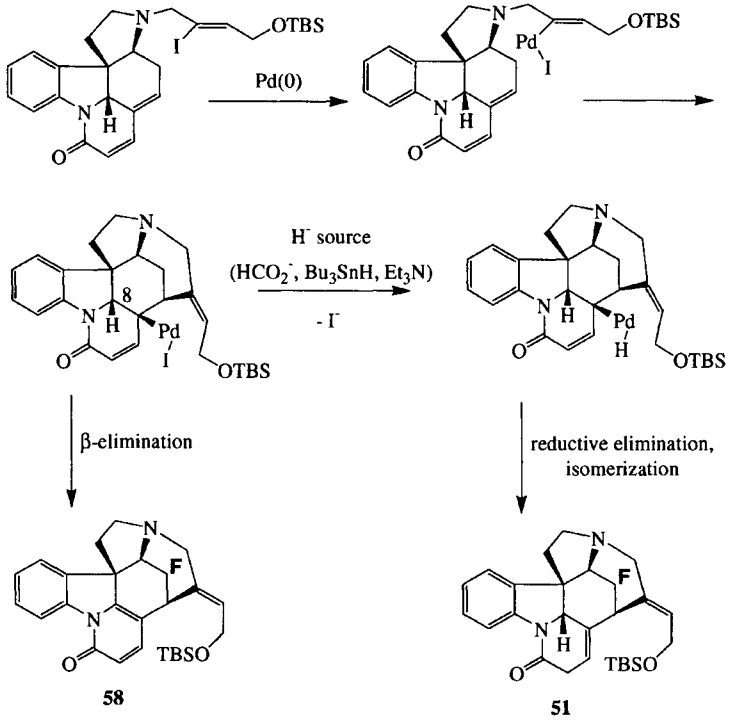
SCHEME 29

E. TRANSITION-METAL MEDIATED CLOSURE OF THE F RING: MORE SUCCESS, SORT OF

1. *Palladium-Mediated Ring Closure: A Well-Trodden Path With a New Destination*

Another method for activating the versatile alkenyl halide moiety was the oxidative addition of a late transition metal species, which would then facilitate insertion of the C13-C14 double bond. The Rawal,[7h] Bonjosch,[7e] and Mori[7b] syntheses of 1 all employed a Pd-mediated intramolecular Heck reaction to build the F ring of the molecule.[71] Our system, in as much as it contained additional unsaturation, was somewhat different from those in the literature and thus had the potential for displaying new chemistry. For example, in Rawal's approach (Scheme

20), Pd-mediated coupling of **50** could, in principle, terminate via β-elimination of either the C8 or C12 hydrogens. However, only the latter was observed. In our case, pentacycle **46** has only the C8 hydrogen available, and the normal course of the Heck reaction would be expected to produce pyridone **58** (Scheme 30). If β-elimination proved slow, an added hydride source might "capture" the palladium σ-complex and provide the desired formal conjugate addition product **51**.

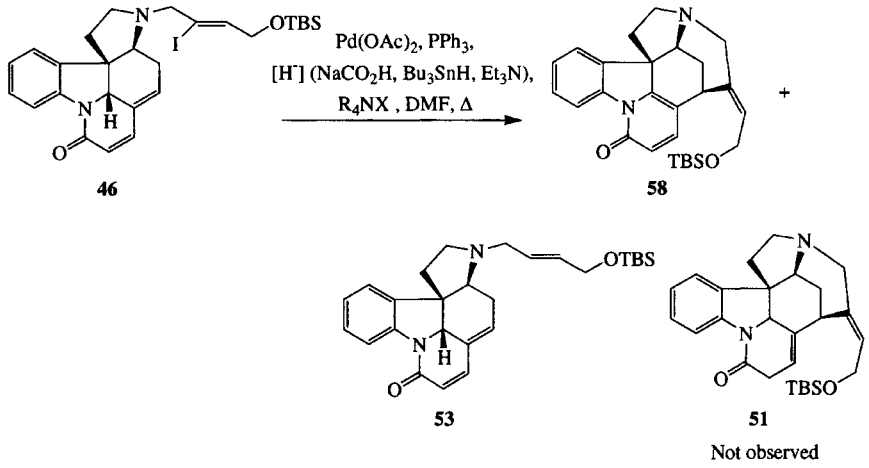


58 **51**

SCHEME 30

Predictably, exposure of **46** to Rawal's conditions [$Pd(OAc)_2$, Bu_4NCl, K_2CO_3, DMF, 70 °C] generated **58**. Unfortunately, upon stirring **56** with catalytic $Pd(OAc)_2/PPh_3$ in the presence of two equivalents of sodium formate and Et_3NCl as a phase transfer catalyst, again only **58** was obtained (Scheme 31).[72] Flooding the system with a ten-fold excess of formate salt produced only **53**, indicating that formate addition to the palladium σ-complex and reductive elimination had occurred before intramolecular cyclization. Use of intermediate stoichiometry gave

mixtures of **53** and **58**. Clearly, β-elimination was too fast in both instances. Nevertheless, **58** contained the desired new ring and, although an extra reduction step would be required, strychnine was again within reach.



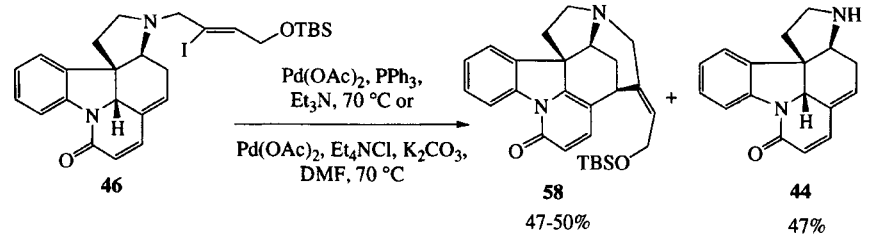
46 **58** **53** **51**

Not observed

SCHEME 31

2. *Optimization of the Intramolecular Heck Reaction and a New "Old" Reduction*

The preparation of **58** was optimized, leading to $Pd(OAc)_2$ and PPh_3 in Et_3N or $Pd(OAc)_2$, Bu_4NCl, and K_2CO_3[73] as the preferred conditions (Scheme 32). Although the yield remained consistently between 47-50%, the latter reagents gave the pyridone relatively quickly (2-4 h), while the former, although sluggish (18-22 h), also liberated **44**, a useful synthetic material that could be recycled to produce **53**.

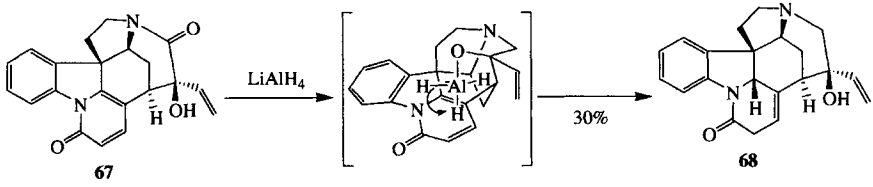


46 **58** 47-50% **44** 47%

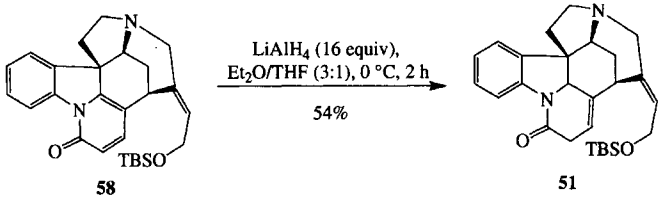
SCHEME 32

In addition to being a synthetically useful by-product, the isolation of **44** suggested that the moderate yields of the Heck coupling were due to β-elimination of the butenyl side chain, perhaps via an intermediate palladium amide complex. While the reason for the readiness of this E-butenyl geometry to undergo elimination is unclear, it is clearly a facile process, having been observed several times previously (as noted).

With reasonable quantities of **58** in hand, the focus became the reintroduction of the C8 methine hydrogen via a stereo- and regioselective hydride addition to the aromatic pyridone ring. Such reductions have featured in a number of approaches to **1**. Most analogous to ours was Woodward's conversion of pyridone **67** to **68**, a transformation he suggested to proceed through the directing effect of the appended hydroxy substituent (Scheme 33).[2] While our system lacked such a group, examination of structural or AM1 calculated models of **58** did not seem to show significantly greater steric bias for either the *re* or *si* faces of **58** or the enolate intermediate. Happily, reaction of **58** with $LiAlH_4$[2b,74] led to the isolation of **51** in 39 % yield (Scheme 34). cutting the reaction time or quantity of reducing agent failed to improve the efficiency, but running the reaction at 0 °C did increase the yield to a more acceptable 54%.



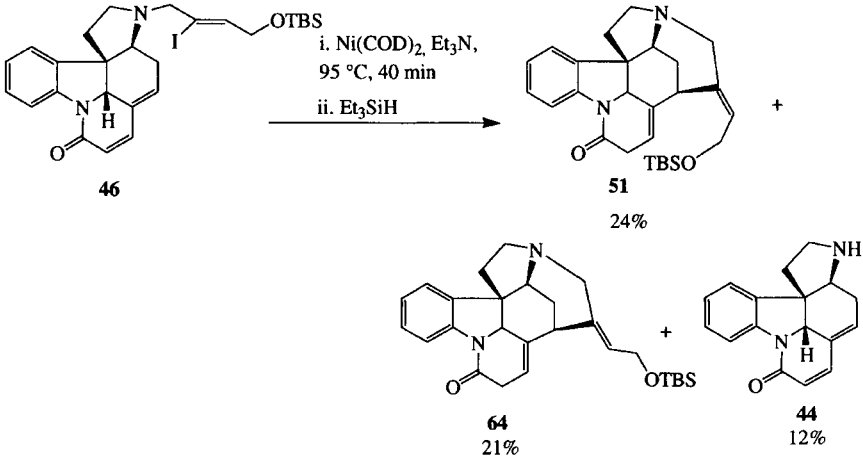
SCHEME 33



SCHEME 34

3. *Nickel-Mediated Ring Closure*

Like palladium, nickel promotes tandem cyclization-capture sequences via oxidative addition and alkene insertion. This procedure has found successful application in the formation of piperidine and pyrrolidine rings,[75] including those in Curan alkaloid systems analogous to ours.[76] Here, Ni-H β-elimination is slowed by the presence of a distal amino group in the substrate, which serves to coordinate with the metal in the transient alkenyl- or alkylnickel species. This effect allows trapping with a hydride source. Indeed, reaction of **43** with $Ni(COD)_2$ in the presence of Et_3N in dry MeCN, followed by the addition of Et_3SiH, gave a mixture of the desired isostrychnine ether **51**, its Z-isomer **64**, and amine **44** (Scheme 35). Traces of both the cis and trans isomers of the reduced, uncyclized alkene **53** were also observed. When, instead of Et_3SiH, an aqueous acid quench (NH_4Cl) was administered, the same mixture was obtained, albeit in a somewhat altered ratio (**51**, 21%; **53**, 11%; **44**, 18%).



46 **51** 24% **64** 21% **44** 12%

SCHEME 35

Thus, while cyclization occurred to the tune of overall 45%, almost half of it proceeded with loss of C21-C22 stereochemistry. A radical process through homolytic cleavage of the carbon-iodine bond and subsequent isomerization of the vinyl radical could be responsible (vide supra), possibly initiated by electron transfer from Ni(I) in the mixture.[77,78] Nevertheless, a third approach to strychnine had been developed. Having accomplished such and one author's graduate career

coming to an end, it was decided to proceed no further and to deem the cobalt way to strychnine a success.

IX. Conclusions

It is now essential to review this "cobalt-way" to strychnine in terms of the objectives that influenced the strategies and tactics we employed along the way. The reader will note how these objectives evolved with time. At first, the desire was simply to find a viable way to construct strychnine via the ABCD intermediates available through the cobalt-mediated [2+2 +2]cycloaddition of alkynes and indoles. Difficulties with initial approaches drove us eventually to explore new routes and some untried cyclization conditions, including the use of acetylene. However, by this time the growing list of successful strychnine syntheses by other groups also spurred our competitive spirit. The goal then became to strive for the shortest, highest yielding, and most "elegant" synthesis possible. This encouraged us to streamline the preparation of enynoylindole **23**, maximize the efficiency of the cobalt-mediated cycloaddition, and work to simultaneously alkylate and isomerize amine **43**. The last crucial step, the formation of the F ring, became an "epic" battle for similar reasons. The stubborn desire to produce the best synthesis possible led to an exhaustive examination of intramolecular carbon-carbon bond forming options. Eventually, extensive studies of conjugate addition chemistry, the search for alternatives to the loss of C21-C22 alkene stereochemistry in the radical and nickel-mediated closures, and the desire to avoid the poor yields and extra step necessitated by an intramolecular Heck reaction left us exhausted of options and time.

But the final results were far from disappointing. As the reader can see, despite several false starts and various barriers to progress, a quite rapid and modestly efficient synthesis of racemic strychnine was achieved ultimately. The synthesis reaches **1** in 10 or 11 steps from tryptamine, or, in the longest linear sequence, 14 or 15 steps from propiolic acid. It proceeds in 0.28%, 0.19%, and 0.19% for the tin, nickel, and palladium-mediated pathways, respectively. Thus, in comparison to others, the cobalt-mediated approach to racemic strychnine did, for a time, become the shortest. This distinction was short-lived, however, as, in 2002, Bodwell described a new sequence that affords strychnine in only 12 steps.[7a] But then, such is exactly the manner in which organic synthesis should progress. The sophistication and power of synthetic methodology grows as challenges to the ingenuity of the chemist are met.

The various approaches to strychnine described in this chapter attest to the robust nature of the cobalt-mediated [2 + 2 + 2]cycloaddition of alkynes to indoles It is this reaction we wished to highlight with our work. It provided the extensive change in molecular flexibility that made it possible to envisage a short strategy. In addition, it allowed the stereo- and regioselective incorporation of a variety of functions into the so-assembled dihydrocarbazole nucleus and thus entry into the rich carbon-carbon and carbon-nitrogen bond forming chemistry of the metal-complexed and decomplexed cyclohexadiene products. Finally, the story is also a more general tribute to the power of transition metals in organic synthesis, as every critical ring forming step was performed with the help of organometallic reagents.

Acknowledgements

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References and Footnotes

1. (a) Anastas, P. T., Kirchoff, M. M., *Acc. Chem. Res.* **2002**, *35*, 686; (b) Fahrenkamp-Uppenbrink, J., *Science* **2002**, *297*, 798.
2. (a) Woodward, R. B., Cava, M. P., Ollis, W. D., Hunger, A., Daeniker, H. U., Schenker, K. J., *J. Am. Chem. Soc.* **1954**, *76*, 4749. (b) Woodward, R. B., Cava, M. P., Ollis, W. D., Hunger, A., Daeniker, H. U., Schenker, K. J., *Tetrahedron* **1963**, *19*, 247.
3. For a review of these efforts, see: Smith, G. F. In "*The Alkaloids*," Ed. Manske, R. H. F. Academic Press: New York 1965, vol. 8, p. 591-671.
4. (a) Briggs, L. H., Openshaw, H. T., Robinson, R. J., *J. Chem. Soc.* **1946**, 903. (b) Woodward, R. B., Brehm, W. J., Nelson, A. L., *J. Am. Chem. Soc.* **1947**, *69*, 2250. (c) Woodward, R. B., Brehm, W. J., *J. Am. Chem. Soc.* **1948**, *70*, 2107.
5. Robertson, J. H., Beevers, C. A., *Acta Crystallogr.* **1951**, *4*, 270. (b) Bokhoven , C., Schoone, J. C., Bijovet, J. M., *Acta Crystallogr.* **1951**, *4*, 275. (c) Peerdemann, A. F., *Acta Crystallogr.* **1956**, *9*, 824.
6. (a) Rajendra, S., Lynch, J. W., Schofield, P. R., *Pharmacol. Ther.* **1997**, *73*, 121. (b) Béchade, C., Sur, C., Triller, A., *Bioessays* **1994**, *16*, 735.
7. (a) Bodwell, G. J., Li, J., *Angew. Chem. Int. Ed.* **2002**, *41*, 3261. (b) Nakanishi, M., Mori, M., *Angew. Chem. Int. Ed.* **2002**, *41*, 1934. (c) Ohshima, T., Xu, Y., Takita, R., Shimizu, S., Zhong, D., Shibasaki, M., *J. Am. Chem. Soc.* **2002**, *124*, 14546. (d) Ito, M., Cameron, C. W., Mortimore, M., Goh, J. B., Martin, S. F., *J. Am. Chem. Soc.* **2001**, *123*, 8003. (e) Solé, D., Bonjoch, J., García-Rubio, S., Peidró, E., Bosch,

J., *Chem. Eur. J.* **2000**, *6*, 655. (f) Kuehne, M. E., Xu, F., *J. Org. Chem.* **1998**, *63*, 9427. (g) Knight, S. D., Overman, L. E., Pairaudeau, G., *J. Am. Chem. Soc.* **1995**, *117*, 5776. (h) Rawal, V. H., Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685. (i) Kuehne, M. E., Xu, F., *J. Org. Chem.* **1993**, *58*, 7490. (j) Magnus, P., Giles, M., Bonnert, R., Johnson, G., McQuire, L., Deluca, M., Merritt, A., Kim, C. S., Vicker, N., *J. Am. Chem. Soc.* **1993**, *115*, 8116. (k) Stork, G., Reported at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, September 21, 1992.

8. For reviews, see: (a) Bonjoch, J., Sole, D., *Chem. Rev.* **2000**, *100*, 3455. (b) Beifuss, U., *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1144.
9. For other accounts of this synthesis, see: (a) Eichberg, M. J., Dorta, R. L., Grotjahn, D. B., Lamottke, K., Schmidt, M., Vollhardt, K. P. C., *J. Am. Chem. Soc.* **2001**, *123*, 9324. (b) Eichberg, M. J., Dorta, R. L., Lamottke, K., Vollhardt, K. P. C., *Org. Lett.* **2000**, *2*, 2479.
10. Saa, C., Crotts, D. D., Hsu, G., Vollhardt, K. P. C., *Synlett* **1994**, 487 and references therein.
11. (a) Vollhardt, K. P. C., Mohler, D. L. In "*Advances in Strain in Organic Chemistry*," JAI Press: Greenwich 1996, vol. 5, p. 121-160. (b) Bruns, D., Miura, H., Vollhardt, K. P. C., Stanger, A., *Org. Lett.* **2003**, *4*, 549 and references therein.
12. Sheppard, G. S., Vollhardt, K. P. C., *J. Org. Chem.* **1986**, *51*, 5496.
13. Boese, R., Knölker, H. J., Vollhardt, K. P. C., *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1035.
14. Boese, R., Harvey, D. F., Malaska, M. J., Vollhardt, K. P. C., *J. Am. Chem. Soc.* **1994**, *116*, 11153.
15. (a) Pérez, D., Siesel, B. A., Malaska, M. J., David, E., Vollhardt, K. P. C., *Synlett* **2000**, 366. (b) Pelissier, H., Rodriguez, J., Vollhardt, K. P. C., *Chem. Eur. J.* **1999**, *5*, 3549.
16. (a) Grotjahn, D. B., Vollhardt, K. P. C., *J. Am. Chem. Soc.* **1986**, *108*, 2091. (b) Boese, R., Van Sickle, A. P., Vollhardt, K. P. C., *Synthesis* **1994**, 1374.
17. Prelog, V., Battegay, J., Taylor, W. I., *Helv. Chim. Acta.* **1948**, *31*, 2244.
18. Anet, F. A. L., Robinson, R., *Chem. Ind.* **1953**, 245.
19. Uhle, F. C., *J. Org. Chem.* **1967**, *32*, 1596.
20. Kadaba, P. K., *Synthesis* **1973**, 71.
22. (a) Tsuji, J. "*Palladium Reagents and Catalysis*," Wiley: New York 1995, p. 21-50. (b) Holton, R. A., Kjonaas, R. A., *J. Am. Chem. Soc.* **1977**, *99*, 4177. (c) Alyea, E. C., Dias, S. A., Feurgeson, G., McAlees, A. J., McCrindle, R., Roberts, P. J., *J. Am. Chem. Soc.* **1977**, *99*, 4985. (d) McCrindle, R., Fergueson, G., Khan, M. A., McAlees, A. J., Ruhl, B. L., *J. Chem. Soc., Dalton Trans.* **1981**, 986.
22. (a) Moss, R. A., Wilk, B., Krogh-Jespersen, K., Westbrook, J. D., *J. Am. Chem. Soc.* **1989**, *111*, 6729. (b) Wilson, R. M., Commons, T. J., *J. Org. Chem.* **1975**, *50*, 4467.
23. Fatiadi, A., *Synthesis* **1976**, 65.
24. De Silva, S. O., Snieckus, V., *Can. J. Chem.* **1978**, *56*, 1621.
25. Illi, V. O., *Synthesis* **1979**, 387.
26. Homer, R. B., Johnson, C. D. In "*The Chemistry of Amides*," Ed. Zabicky, J. Wiley: New York 1970, p. 188-197.
27. Remers, W. A. In "*Indoles*," Part one, Ed. Houlihan, W. J. Wiley: New York 1972, p. 14.

28. Daly, J. W., Mauger, A. B., Yonemitsu, O., Antonov, V. K., Takase, K., Witkop, B., *Biochemistry* **1967**, *6*, 648.
29. (a) Sonogashira, K. In "*Comprehensive Organic Synthesis*," Eds. Trost, B. M., Fleming, I. Pergamon Press: Oxford 1990, vol. 3, p. 521-561. (b) Takahashi, S., Kuroyama, Y., Sonogashira, K., Hagihara, N., *Synthesis* **1980**, 627. (c) Sonogashira, K., Tohda, Y., Hagihara, N., *Tetrahedron Lett.* **1975**, *15*, 4467.
30. Nishiguchi, T., Tachi, K., Fukuzumi, K., *J. Org. Chem.* **1975**, *40*, 237.
31. (a) Feng, H., Foxman, B. M., Snider, B. B., *J. Am. Chem. Soc.* **1998**, *120*, 6417. (b) Satoshi, O., Yamafuji, T., Chaki, H., Morita, H., Todo, Y., *Chem. Pharm. Bull.* **1995**, *43*, 1492. (c) Fu, P. P., Harvey, R. G., *Chem. Rev.* **1978**, *78*, 317.
32. Fatiadi, A. J., *Synthesis* **1976**, 113.
33. (a) Chaudhary, S. K., Hernandez, O., *Tetrahedron Lett.* **1979**, *20*, 99. (b) Höfle, G., Steglich, W., Vorbrüggen, H., *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
34. Terashima, M., Fujioka, M., *Heterocycles* **1982**, *19*, 91.
35. Heilbron, I., Jones, E. R. H., Sondheimer, F., *J. Chem. Soc.* **1947**, 1583.
36. (a) Kotora, M., Negishi, E., *Synthesis* **1997**, 121. (b) Abarbri, M., Parrain, J.-L., Cintrat, J.-C., Duchêne, A., *Synthesis* **1996**, 82.
37. Oldroyd, D. L., Weedon, A. C., *J. Org. Chem.* **1994**, *59*, 1333.
38. For a discussion of phase-transfer catalysis, see: (a) Sasson, Y., Rothenberg, G. In "*Handbook of Green Chemistry and Technology,*" Eds. Clark, J., Macquarrie, D. Blackwell: Oxford 2002, p. 206-257. (b) Dehmlow, E. V., Dehmlow S. S. "*Phase Transfer Catalysis*," VCH: Weinheim 1980.
39. Loss of cis stereochemistry seems to be associated with a catalytic action of the cobalt center. Stirring of *cis-N*-acetyl-1-(1-oxo-3-phenyl-prop-2-enyl)indol-3-ethanamine with substoichiometric amounts of $CpCo(C_2H_4)_2$ at room temperature led to complete conversion to *trans-N*-acetyl-1-(1-oxo-3-phenyl-prop-2-enyl)indol-3-ethanamine within 2 hours.
40. (a) Hardesty, J. H., Koerner, J. B., Albright, T. A., Lee, G-Y., *J. Am. Chem. Soc.* **1999**, *121*, 6055. (b) Diercks, R., Eaton, B. E., Gürtzgen, S., Jalisatgi, S., Matzger, A. J., Radde, R. H., Vollhardt, K. P. C., *J. Am. Chem. Soc.* **1998**, *120*, 8247.
41. Gómez-Parra, V., Sánchez, F., Torres, T., *Synthesis* **1984**, 282.
42. (a) Kuo, C. H., Patchett, A. A., Wendler, N. L., *J. Org. Chem.* **1983**, *48*, 1991. (b) Carruthers, W. "*Some Modern Methods of Organic Synthesis*," Cambridge University Press: Cambridge 1987, p. 440-441. (c) Hudlicky, T., Sinai-Zingde, G., Natchus, M. G., *Tetrahedron Lett.* **1987**, *28*, 5287. (d) Kadin, S. B., *J. Org. Chem.* **1966**, *31*, 620.
43. (a) Piers, E., Friesen. R. W., *Can. J. Chem.* **1992**, 70, 1204. (b) Touet, J., Baudouin, S., Brown, E., *Tetrahedron: Asymmetry* **1992**, *3*, 587. (c) Hackett, M., Whitesides, G. M., *J. Am. Chem. Soc.* **1988**, *110*, 1449.
44. Rottländer, M., Boymond, L., Cahiez, G., Knochel, P., *J. Org. Chem.* **1999**, *64*, 1080.
45. (a) Angle, S. R., Fevig, J. M. Knight, S. D., Marquis, R. W., Jr., Overman, L. E., *J. Am. Chem. Soc.* **1993**, *115*, 3966. (b) Lipshutz, B. H., Koerner, M., Parker, D. A., *Tetrahedron Lett.* **1987**, *28*, 945.
46. Alami, M., Marquais, S., Cahiez, G., *Org. Synth.* **1995**, *72*, 135.

47. (a) Rieke, R. D., Stack, D. E., Dawson, B. T., Wu, T-C., *J. Org. Chem.* **1993**, *58*, 2492. (b) Rieke, R. D., Stack, D. E., Dawson, B. T., Wu, T-C., *J. Org. Chem.* **1993**, *58*, 2483. (c) Ebert, G. W., Rieke, R. D., *J. Org. Chem.* **1988**, *53*, 4482.
48. (a) Hanson, M. V., Rieke, R. D., *J. Am. Chem. Soc.* **1995**, *117*, 10775. (b) Zhu, L., Wehmeyer, R. M., Rieke, R. D., *J. Org. Chem.* **1991**, *56*, 1445. (c) Rieke, R. D., *Acc. Chem. Res.* **1977**, *10*, 301.
49. Stork, G. Personal Communication, **1999**.
50. For a comprehensive review of carbon-carbon bond formation with organochromium reagents, see: (a) Fürstner, A., *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A., Scheid, G., *Synthesis* **1999**, 1.
51. Kress, M. H., Ruel, R., Miller, W. H., Kishi, Y., *Tetrahedron Lett.* **1993**, *34*, 6003.
52. Jin, H., Uenishi, J., Christ, W. J., Kishi, Y., *J. Am. Chem. Soc.* **1986**, *108*, 5644.
53. Roe, M. B., Whittaker, M., Proctor, G., *Tetrahedron Lett.* **1995**, *36*, 8103.
54. Behling, J. R., Babiak, K. A., Ng, J. S., Campbell, A. L., Moretti, R., Koerner, M., Lipshutz, B. H., *J. Am. Chem. Soc.* **1988**, *110*, 2641.
55. (a) Piers, E., McEachern, E. J., Burns, P. A., *Tetrahedron* **2000**, *56*, 2753. (b) Piers, E., Skupinska, K. A., Wallace, D. J., *Synlett* **1999**, 1867. (c) Piers, E., McEachern, E. J., Burns, P. A., *J. Org. Chem.* **1995**, *60*, 2322.
56. (a) Wulff, W. D., Peterson, G. A., Bauta, W. E., Chan, K.-S., Faron, K. L., Gilbertson, S. R., Kaesler, R. W., Yang, D. C., Murray, C. K., *J. Org. Chem.* **1986**, *51*, 277. (b) Knight, S. D., Overman, L. E., Pairaudeau, G., *J. Am. Chem. Soc.* **1995**, *117*, 5776.
57. (a) Crandall, J. K., Batal, D. J., Lin, F., Reix, T., Nadol, G. S., Ng, R. A., *Tetrahedron* **1992**, *48*, 1427. (b) Aumann, R., Trentmann, B., *Chem. Ber.* **1989**, *122*, 1977.
58. (a) Piers, E., Cook, K. L., *J. Chem. Soc., Chem. Commun.* **1996**, 1879. (b) Piers, E., Romero, M. A., *J. Am. Chem. Soc.* **1996**, *118*, 1215. (c) Piers, E., Friesen, R. W., Keay, B. A., *J. Chem. Soc., Chem. Commun.* **1985**, 809.
59. Najdi, S. D., Olmstead, M. M., Schore, N. E., *J. Organomet. Chem.* **1992**, *431*, 335.
60. Marshall, J. A., Shearer, B. G., Crooks, S. L., *J. Org. Chem.* **1987**, *52*, 1236.
61. Corey, E. J., Krist, H. A., Katzenellenbogen, J. A., *J. Am. Chem. Soc.* **1970**, *92*, 6314.
62. Jasperse, C. P., Curran, D. P., Fevig, T. L., *Chem. Rev.* **1991**, *91*, 1237.
63. Takayama, H., Watanabe, F., Kitajima, M., Aimi, N., *Tetrahedron Lett.* **1997**, *38*, 5307.
64. Beckwith, A. L. H., Ingold, K. U. In "*Rearrangements in Ground and Excited States*," Ed. de Mayo, P. Academic Press: New York 1980, vol. 1, p. 161-310.
65. (a) Jiao, X.-Y., Bentrude, W. G., *J. Am. Chem. Soc.* **1999**, *121*, 6088 and references therein. (b) Stork, G., Baine, N. H., *J. Am. Chem. Soc.* **1982**, *104*, 2321.
66. Chatgilialoglu, C., *Acc. Chem. Res.* **1992**, *25*, 188.
67. Ooi, T., Hokke, Y., Maruoka, K., *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1181.
68. Ryu, I., Araki, F., Minakata, S., Komatsu, M., *Tetrahedron Lett.* **1998**, *39*, 6335.
69. Sander, M. R., Osborn, C. L., *Tetrahedron Lett.* **1974**, *15*, 415.
70. Capella, L., Montevecchi, P. C., Navacchia, M. L., *J. Org. Chem.* **1995**, *60*, 7424.
71. For recent reviews of the intramolecular Heck reaction see: (a) Link, J. T., *Org. React.* **2002**, *60*, 157. (b) Braese, S., de Meijere, A. In "*Handbook of*

Organopalladium Chemistry for Organic Synthesis," Ed. Negishi, E. Wiley: Hoboken 2002, vol. 1, p. 1223-1254.

72. Burns, B., Grigg, R., Santhakumar, V., Sridharan, V., Stevenson, P., Worakum, T., *Tetrahedron* **1992**, *48*, 7297.
73. Jeffery, T., *Tetrahedron Lett.* **1985**, *26*, 2667.
74. Gallagher, T., Magnus, P., Huffman, J. C., *J. Am. Chem. Soc.* **1983**, *105*, 4750.
75. (a) Solé, D., Cancho, Y., Llebaria, A., Moretó, J. M., Delgado, A., *J. Am. Chem. Soc.* **1994**, *116*, 12133. (b) Solé, D., Cancho, Y., Llebaria, A., Moretó, J. M., Delgado, A., *J. Org. Chem.* **1996**, *61*, 5895. (c) Cancho, Y., Martín, J. M., Martinez, M., Llebaria, A., Moretó, J. M., Delgado, A., *Tetrahedron* **1998**, *54*, 1221.
76. Bonjosch, J., Solé, D., Garcia-Rubio, S., Bosch, J., *J. Am. Chem. Soc.* **1997**, *119*, 7231.
77. Readman, S. K., Marsden, S. P., Hodgson, A., *Synlett* **2000**, 1628 and references therein.
78. For a closely related example of stereochemical scrambling reported in the synthesis of the *Strychnos* alkaloid mossambine, see: Kuehne, M. E., Wang, T. S., Seraphin, D., *J. Org. Chem.* **1996**, *61*, 7873.

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