INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

UNIVERSITY OF ALBERTA

Synthetic Studies of Biologically Active Alkaloids: Asymmetric Synthetic Approaches to Epibatidine and Halichlorine

by

Vince Yeh ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

Spring, 2001

UNIVERSITY OF ALBERTA

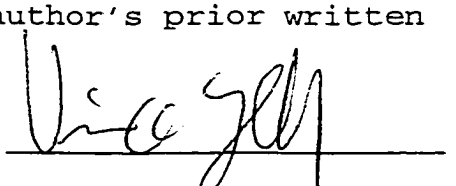
LIBRARY RELEASE FORM

NAME OF AUTHOR: Vince S. C. Yeh

TITLE OF THESIS: Synthetic Studies of Biologically Active Alkaloids: Asymmetric Synthetic Approaches to Epibatidine and Halichlorine

DEGREE: Doctor of Philosophy

YEAR THIS DEGREE GRANTED: 2001



7721 Sparbrook Crescent

Vancouver, B. C.

Canada

V5S-3K3

Date: 9th January 2001

UNIUNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Synthetic Studies of Biologically Active Alkaloids: Asymmetric Synthetic Approaches to Epibatidine and Halichlorine** submitted by **Vince Yeh** in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Dr. D. L. J. Clive

Dr. J. W. Lown

Dr. D. Hall

Dr. P. Sporns

Dr. G. Kotovych

Dr. R. Andersen

(External Examiner)

To my family

ABSTRACT

Chapter 1 describes the asymmetric synthesis of (-)-epibatidine. (*S*)-Pyroglutamic acid was converted into the (phenylthio)acetylene **27.1**, which undergoes radical cyclization to the 7-azabicyclo[2.2.1]heptane **14.2**. Ozonolysis then affords ketone **14.3**, a synthetic precursor of (-)-epibatidine.

Chapter 2 describes the asymmetric synthesis of the azaspiro core structure related to halichlorine and the pinnaic acids via two routes. Sulfone **20.4**, derived from (D)-glutamic acid, and aldehyde **14.2**, made by diastereoselective alkylation, were linked and elaborated into enamine sulfone **29.2**. This underwent 5-*exo* radical cyclization to **29.3**, which was desulfonylated to (-)-**32.1**, a compound that represents the spirobicyclic core of halichlorine. The second route involves elaboration of piperidine **66.1** into **79.1** by enantioselective alkylation and ring closing metathesis.

Chapter 3 describes the development of 4-fluorophenyl and 2-naphthyl sulfones for desulfonation studies.

ACKNOWLEDGMENTS

I would like to express my gratitude to Dr. D. L. J. Clive for his superb mentorship during the course of my Ph.D. program, and for his assistance during the preparation of this thesis.

I would also like to thank my labmates, past and present, for creating a stimulating scientific environment.

Thanks also go to a number of other people:

- the Staff of the IR, MS, NMR and elemental analysis labs. Particularly Glen, Angie, and Tom for their invaluable help and discussions.
- Elizabeth Nofziger for her friendship and support.

I acknowledge financial support provided by NSERC and AHFMR.

Finally, I would like to thank my family for their support and encouragement.

Table of Contents

LIST OF ABBREVIATIONS

AIBN.....2,2′-azobisisobutyronitrile

alloc.....allyloxycarbonyl

9-BBN.....9-borabicyclononane

Bn.....benzyl

t-Bu.....*tert*-butyl

COSY.....correlation spectroscopy

DCC.....dicylcohexylcarbodiimide

DIBAL-H.....diisobutylaluminum hydride

DMPU.....1,3-dimethyl-3,4,5,6-tetrahydro-2(1 *H*)-pyrimidinone

DMAP.....4-(dimethylamino)pyridine

DMF.....dimethylformamide

DMSO.....dimethyl sulfoxide

EDCI.....*N*-(3-dimethylamino)propyl-*N*-ethylcarbodiimide

G-COSY.....gradient correlation spectroscopy

HMPA.....hexamethylphosphoric triamide

HMBC.....^{1}H-detected multiple-bond heteronuclear multiple-quantum coherence

HMQC.....^{1}H-detected heteronuclear multiple-quantum coherence

KHMDS.....potassium hexamethyldisilazane

LDA.....lithium diisopropylamide

LHMDS.....lithium hexamethyldisilazane

MCPBA.....*m*-chloroperoxybenzoic acid

NMO.....4-methylmorpholine *N*-oxide

PCC.....pyridinium chlorochromate

Pg.....protecting group

Ph.....phenyl

PMB.....*p*-methoxybenzyl

Py.....pyridine

TBAF.....tetrabutylammonium fluoride

TBDPS.....*tert*-butyldiphenylsilyl

TMS.....trimethylsilyl

Tf.....trifluoromethanesulfonyl

TFA.....trifluoroacetic acid

THF.....tetrahydrofuran

TPAP.....tetra-*n*-propylammonium perruthenate

T-ROESY.....transmitter rotating frame nuclear overhauser and exchange spectroscopy

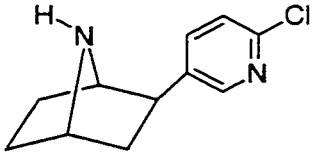
Ts.....*p*-toluenesulfonyl

TsOH.....*p*-toluenesulfonic acid

Epibatidine

Introduction

In 1992 Daly and coworkers at the NIH (Bethesda) reported the discovery and structural elucidation of (-)-epibatidine (**1**),[1] a new alkaloid isolated from the skin of



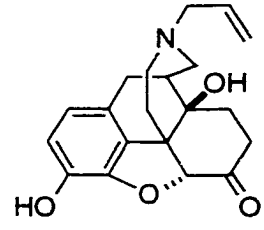
(-)-epibatidine **1**

the Ecuadorian poison frog, *Epipedobates tricolor*, of the family Dendrobatidae. The structure of **1** was unprecedented in nature; it features a strained nitrogen-bridged six-membered carbocycle – a 7-azabicyclo[2.2.1]heptane system – with an *exo*-oriented 5-(2-chloropyridyl) substituent. Since its discovery, epibatidine has received a great deal of attention from medicinal scientists and synthetic chemists.[2] There are numerous of publications in the literature related to **1**; here, I will briefly summarize the remarkable story of its discovery, structural elucidation and biological studies, as well as asymmetric syntheses.

The presence of toxins in the skin of colored frogs has been known for a long time by natives of Western Colombia, who to this day use the secretions from species of dendrobatid frogs to poison the tips of blow darts for hunting small game and birds. An extensive collaborative effort to study alkaloids isolated from dendrobatidae frogs, was undertaken by Charles W. Myers, a herpetologist, and John W. Daly. In an exploratory field trip to Western Ecuador in 1974 they collected a trace alkaloid with an analgesic potency that was 200-fold greater than that of morphine from the skin extracts of *Epipedobates tricolor*.[1] The amount of alkaloid **1** in the frog skin was dependent on the site of

collection, and only 60 mg of a complex mixture of alkaloids were isolated from 750 frogs.[3] It was later determined[4] that these frogs do not synthesize any of the alkaloids, but instead sequester them unchanged into skin glands from dietary sources. The alkaloids are used as chemical deterrents to predators.

After careful chromatographic separation, the initial 60-mg mixture yielded 500 μg of a novel chlorine-containing alkaloid with an empirical formula $C_{11}H_{13}ClN_2$. The material exhibited potent analgesic properties in mice. Furthermore, it was found that the opioid receptor antagonist naloxolone (**2**) did not block the analgesic action, and this observation



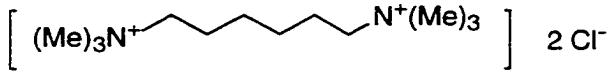
naloxone **2**

raised the suspicion that epibatidine does not act on opioid receptors. The sensitivity and power of NMR spectrometers in the 1970s was not sufficient to elucidate the structure of the new alkaloid. Further collections from field trips were not fruitful, and skin extracts of laboratory-raised frogs did not contain any **1**, a fact that reinforced the theory that the alkaloid was dietary in origin, and which also suggested that the natural source of **1** was not abundant.[5]

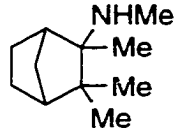
The sample of natural epibatidine was frozen until 1990. By that time the sensitivity and power of NMR spectroscopy had advanced sufficiently that the structure could be determined. The entire natural sample of epibatidine was acetylated to allow purification and structural determination. However, *N*-acetylepibatidine could not be de-acetylated, and all of the natural alkaloid was destroyed in these studies. The detailed biological evaluation of this

remarkable alkaloid could not be performed until synthetic samples became available. The first synthesis was reported by Corey's group in 1993.[6] In this work a synthetic intermediate was resolved, so as to provide both enantiomers of **1**.

Further biological evaluation of synthetic epibatidine proved that the target of activity was the nicotinic acetylcholine receptor (nAChR).[7] The analgesic activity was antagonized by the nAChR channel blocker mecamylamine (**4**), but was not affected by the nAChR antagonist hexamethonium (**3**).[8] Since hexamethonium has been shown to be incapable of crossing the blood brain barrier, it is believed that the primary mechanism of action of **1** is mediated through



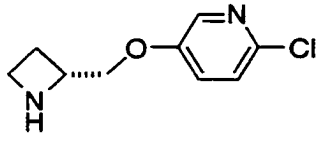
hexamethonium **3**



mecamylamine **4**

occupation of nAChR in the brain.[9] Both enantiomers of epibatidine can displace receptor-bound [^{3}H]nicotine from rat brain with similar concentrations (K_i = 55 pM), which makes epibatidine one of the most potent nAChR ligands known.[10] In vivo studies with mice show analgesic activity at a dose of 0.01 μmol kg^{-1}; however, at only slightly higher doses the compound caused death.[11]

Inspired by the structure and biological activity of epibatidine and the need to search for a non-opioid analgesic for pain control, scientists at the Abbott laboratories identified an azetidine analog [ABT-594] (**5**) that interacts with nAChR in a similar fashion to epibatidine but which is



ABT-594 5

much less toxic.[12] The Abbott researchers are currently conducting clinical trials to determine the safety profile of the compound.[13]

The saga of epibatidine is noteworthy from the perspective of the importance of natural product research and its transition to applied biomedical research that might lead to clinical drugs. Moreover, it demonstrates the power of chemical synthesis, for the research on epibatidine could not have continued without total synthesis of the natural product.

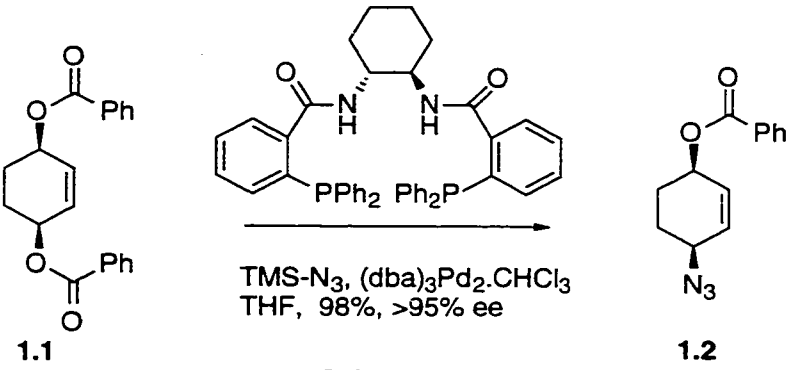
Asymmetric Synthesis of Epibatidine

Since its structural elucidation, epibatidine has attracted great interest from synthetic chemists around the world. There are almost fifty syntheses reported on epibatidine or its novel 7-azabicyclo[2.2.1]heptane substructure.[2] Many of the syntheses reported prior to 1997 have been extensively reviewed and, therefore, they will not be discussed in this thesis. I will focus on the asymmetric syntheses of epibatidine, and special attention will be given to the steps that introduce the asymmetry as well as to the main ring-forming reactions.

Trost's Synthesis

The first asymmetric synthesis of epibatidine was reported by Trost and Cook.[14] Their route began with a Pd(0)-catalyzed allylic substitution to desymmetrize the dibenzoate **1.1**, utilizing a chiral ligand and Me_3SiN_3 as a nucleophile. The azide **1.2** was obtained in high yield and ee (**Scheme 1**).

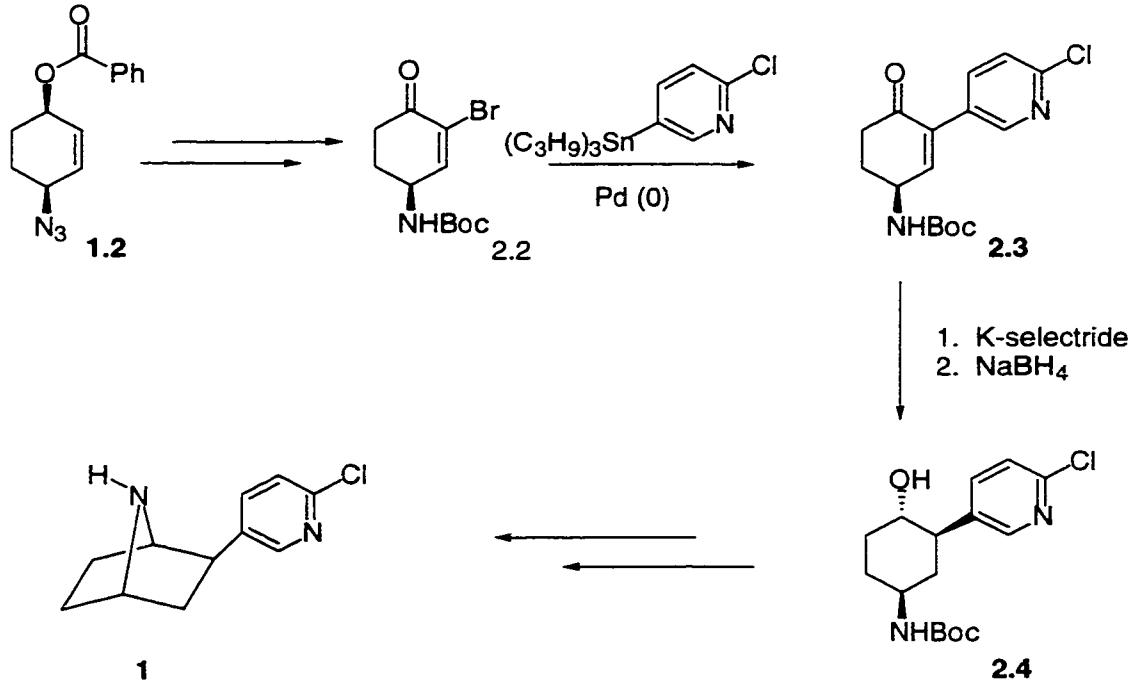
Azide **1.2** was then converted into vinyl bromide **2.2** so as to allow introduction of the pyridine ring by a Pd(0)-catalyzed cross coupling reaction (**2.2** → **2.3**). The remaining two stereogenic centers were established by chemo- and diastereoselective reduction of the double bond with K-Selectride, followed by diastereoselective reduction of the resulting ketone to give the *trans* amido alcohol **2.4**. The



1.1 1.2

Scheme 1

final ring closure utilized a transannular S_N2 cyclization to give epibatidine (**Scheme 2**).



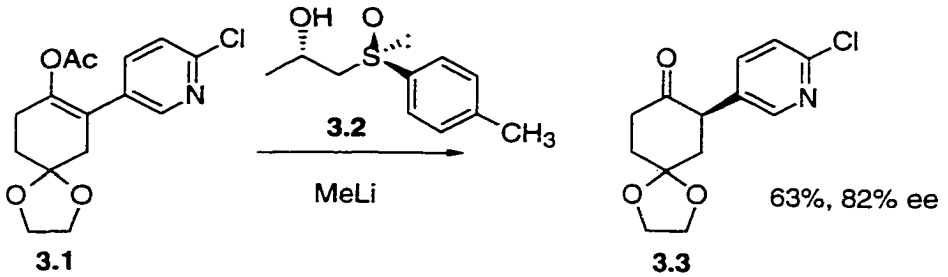
1.2 2.2 2.3

1 2.4

Scheme 2

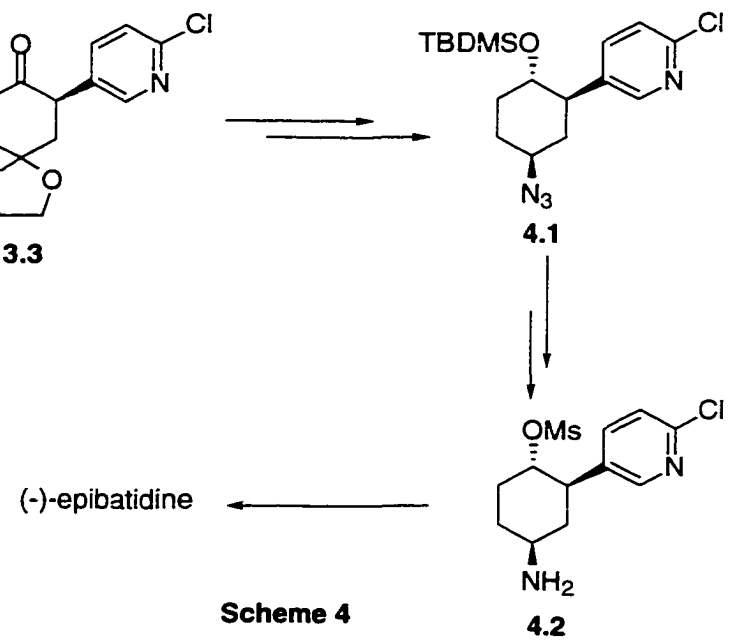
Kosugi's Synthesis

In Kosugi's synthesis[15] the source of chirality came from β-hydroxy sulfoxide **3.2**, which was used as a protonating reagent. The asymmetric protonation of the achiral lithium enolate of **3.1** gave cyclohexanone derivative **3.3** in 63% yield and 82% ee (**Scheme 3**).



Scheme 3

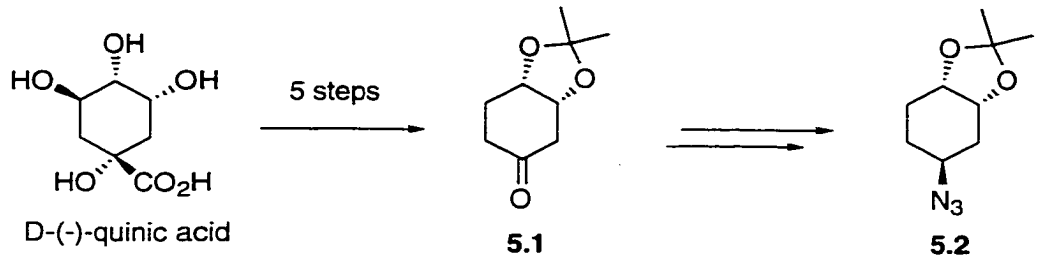
The remaining steps of the synthesis were similar to those used in Trost's route (**Scheme 4**).



Scheme 4

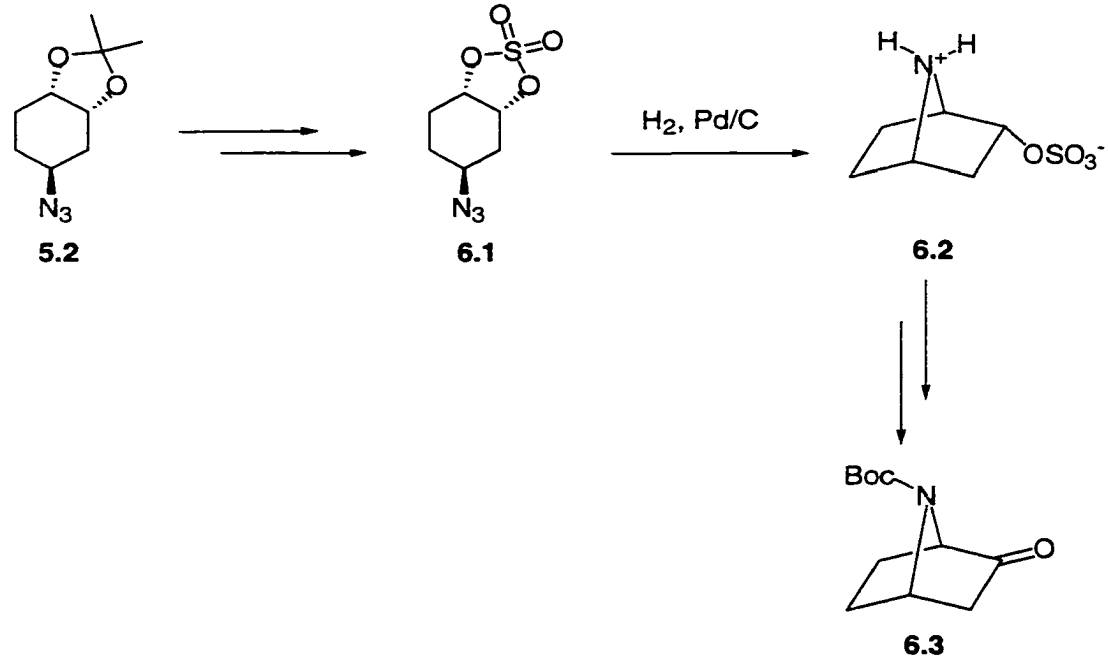
Albertini's Synthesis

Albertini *et al.*[16] based their synthesis on the enantiomerically pure cyclohexanone derivative **5.1**, which was derived in five steps from D-(-)-quinic acid. Compound **5.1** was then converted into azide **5.2** by diastereoselective reduction of the ketone functionality and subsequent S_N2 inversion of the stereogenic center by azide displacement of the derived mesylate (**5.1** → **5.2**, **Scheme 5**).



Scheme 5

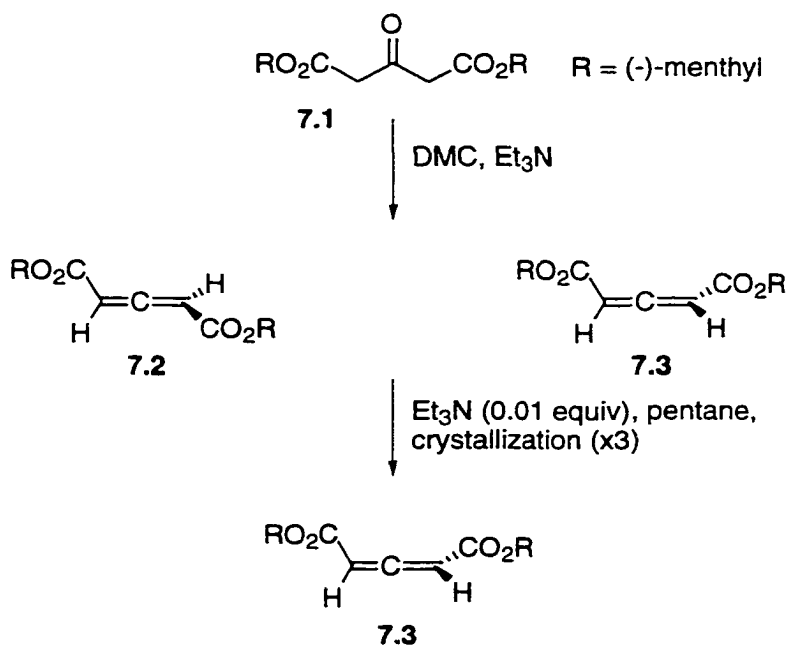
The acetonide was then converted into the corresponding cyclic sulfate **6.1** (**Scheme 6**). A concomitant intramolecular nucleophilic ring closure took place when **6.1** was submitted to hydrogenation, forming the azabicyclic core structure of epibatidine. After hydrolysis of the sulfate **6.2,** and the necessary functional group interconversions, ketone **6.3** was obtained (**Scheme 6**), a substance which had already been converted into epibatidine.



Scheme 6

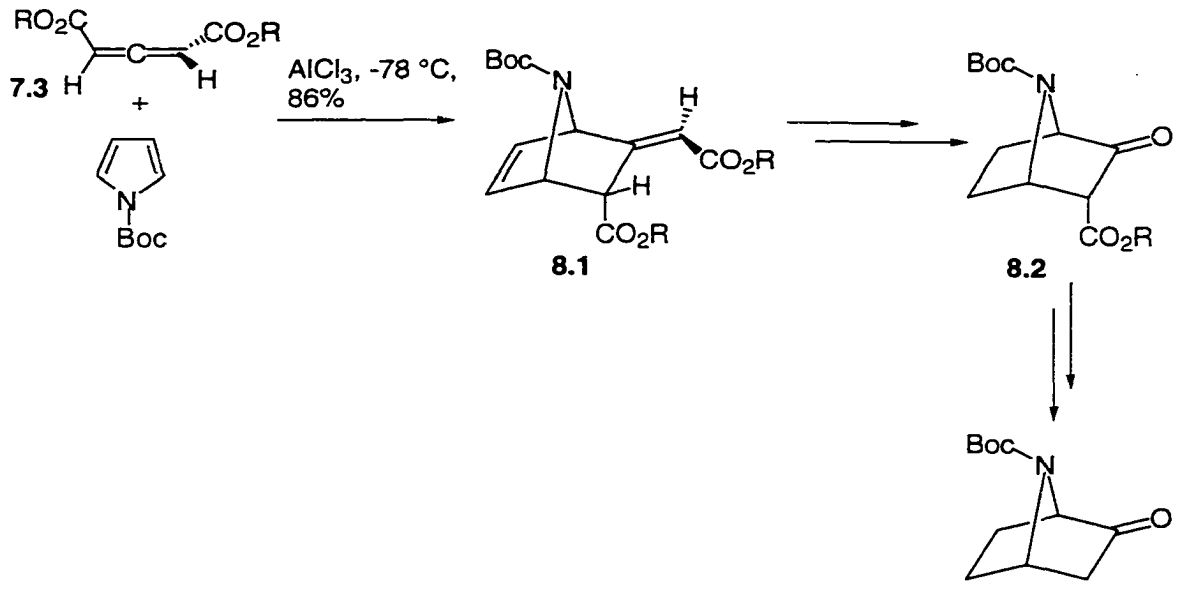
Node's Synthesis

The synthesis reported by Node[17] was based on a [4+2] cycloaddition of the enantiomerically pure allene **7.3** and *N*-Boc-pyrrole. The allene was derived from di-L-menthyl acetone-1,3-dicarboxylate (**7.1**) by treatment with 2-chloro-1,3-dimethylimidazolinium chloride (DMC) to give a 5:4 mixture of allenes, which were equilibrated with a catalytic amount of Et_3N and diastereomerically enriched by crystallization from pentane (**Scheme 7**).



Scheme 7

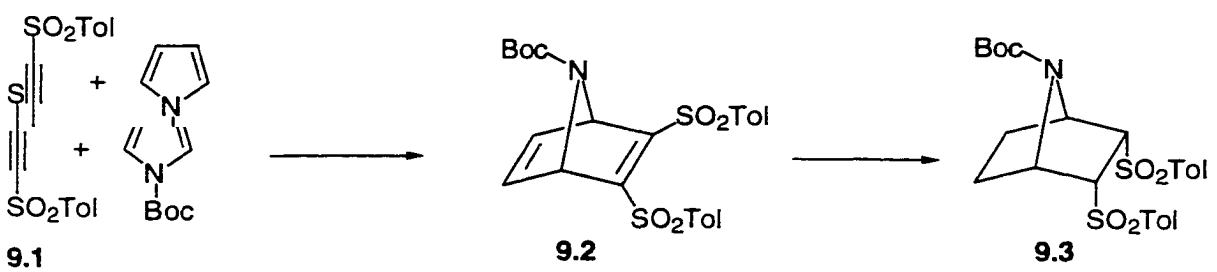
The key Diels-Alder reaction was carried out in the presence of the Lewis acid $AlCl_3$ and gave the *endo* cycloadduct **8.1** in 86% (**Scheme 8**). Compound **8.1** was subsequently converted into ketone **6.3**, a common synthetic intermediate for many of the epibatidine syntheses.



Scheme 8

Simpkins's Route

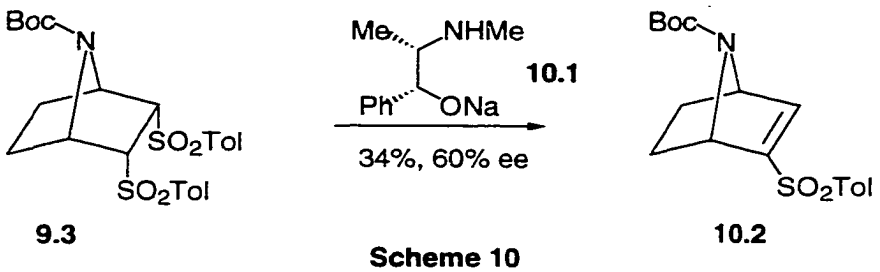
In Simpkins's synthesis,[18] a Diels-Alder reaction was also utilized to form the azabicyclic ring system. [4+2]-Cycloaddition between alkenyl *bis*-sulfone **9.1** and *N*-Boc-pyrrole gave adduct **9.2**, which was hydrogenated under high pressure to give bis-sulfone **9.3** (**Scheme 9**).



Scheme 9

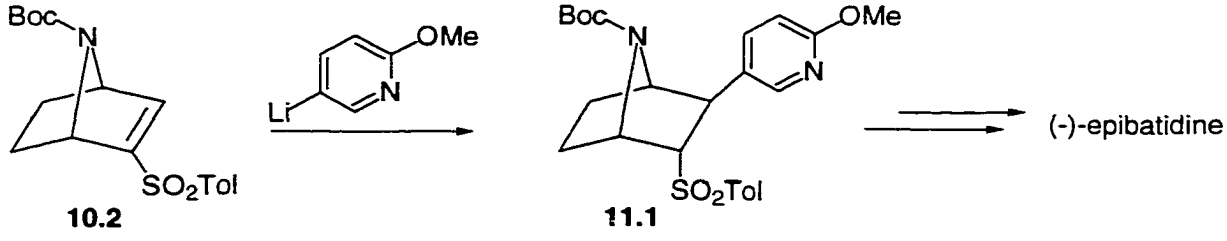
The asymmetry was created by a chiral base-induced sulfone metallation-sulfinate elimination. A wide variety of bases were examined and the best result was obtained from the sodium salt of ephedrine (**10.1**) to give the alkenyl sulfone **10.2** in 34% yield and 60% ee (**Scheme 10**).

The remainder of the synthesis included a Michael



Scheme 10

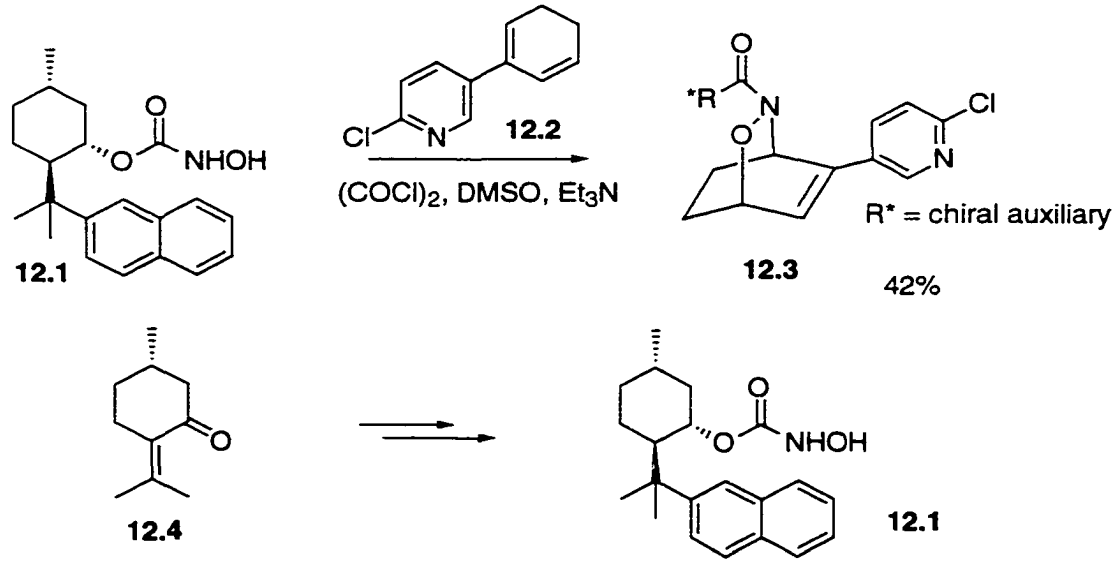
addition of the lithium salt of the pyridine heterocycle, and functional group manipulations (**Scheme 11**).



Scheme 11

Kibayashi's Route

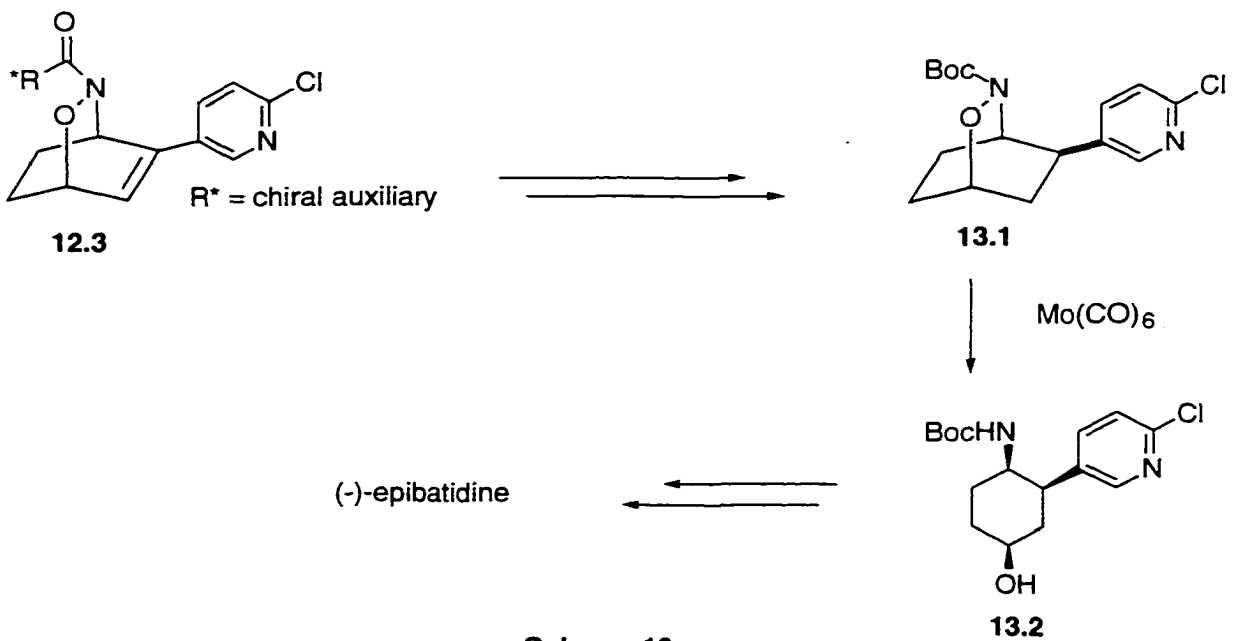
The asymmetric synthesis of epibatidine has been accomplished by Kibayashi *et al.*[19] by utilizing an asymmetric



Scheme 12

hetero Diels-Alder cycloaddition of an *N*-acylnitroso dienophile bearing the 8-naphthylmenthol unit as a chiral auxiliary. The reaction gave a major cycloadduct **12.3** (42% yield) plus two other isomers (**Scheme 12**).

The double bond was hydrogenated and the chiral auxiliary was reductively cleaved. Then the nitrogen was protected as a Boc-carbamate **13.1**. The N-O bond was cleaved with $Mo(CO)_6$ to give amino alcohol **13.2**. The final ring closure was achieved by a transannular S_N2 reaction (**Scheme 13**).

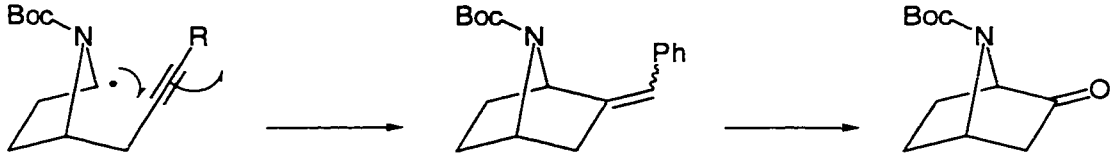


Scheme 13

Results and Discussion

Part 1 Synthetic Plan and Exploratory Studies

Our synthesis of epibatidine is based on the idea that ketone **14.3** (same as **6.3**), from which epibatidine is easily reached,[20] should be accessible by radical cyclization of an iminium radical species which contains an acetylenic side arm, such as **14.1**. Such a ring closure would form the core azabicyclic structure **14.2** of epibatidine with an exocyclic olefin, and this step would be followed by double bond cleavage as summarized in **Scheme 14**.



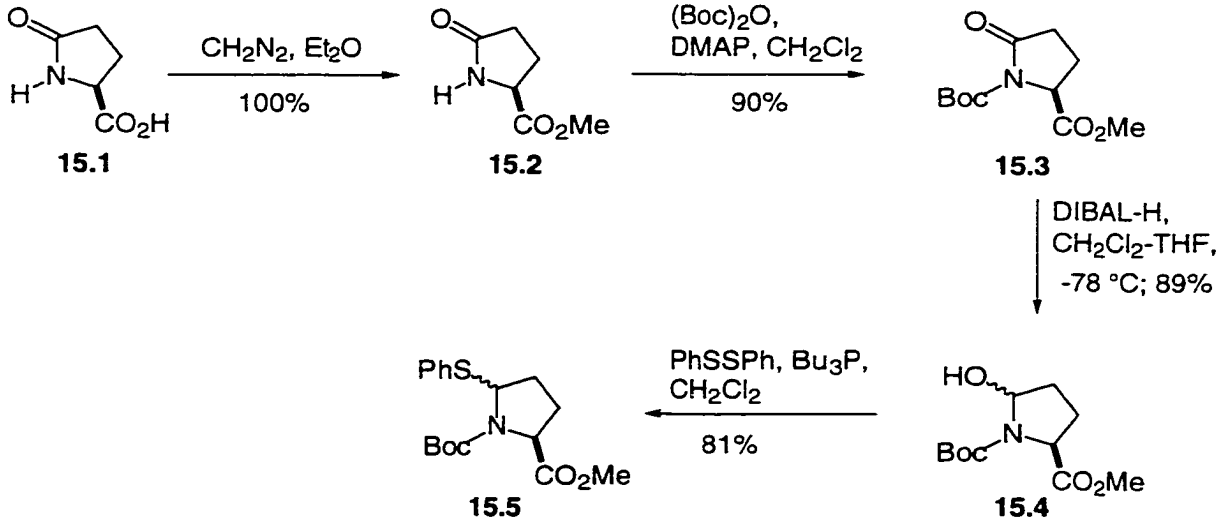
14.1 **14.2** **14.3**

Scheme 14

The acetylenic precursor to radical **14.1** can be derived from commercially available (*S*)-pyroglutamic acid. The stereogenic center that exists in the starting material will be used to establish the remaining two stereogenic centers in the natural product. Therefore it is crucial that the synthetic sequence contains no reactions that will epimerize this center.

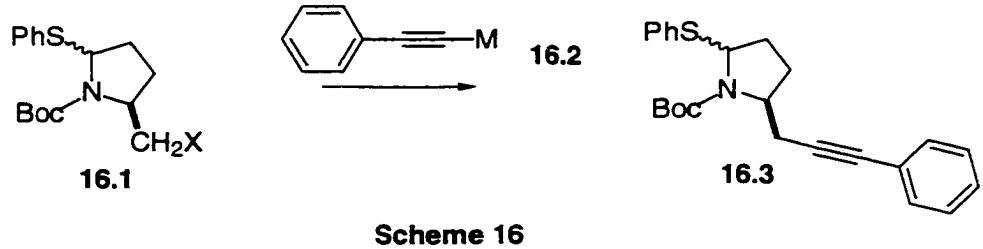
Our synthesis begins with esterification of (*S*)-pyroglutamic acid with diazomethane to give ester **15.2** (**Scheme 15**). The amino group was protected as its Boc carbamate by acylation with $(Boc)_2O$, using DMAP as a catalyst, to give the known ester **15.3**.[21] By taking advantage of the difference in reactivity of the three carbonyl groups in **15.3**, the imide carbonyl was selectively reduced with 1 equiv of DIBAL-H, thereby generating alcohol **15.4**.[22] The hydroxyl group was then replaced with a phenyl sulfide group by Mitsunobu reaction (PhSSPh, Bu_3P, DEAD) to

give **15.5**. Our intention was that the sulfide will serve to generate the radical later in the synthesis.



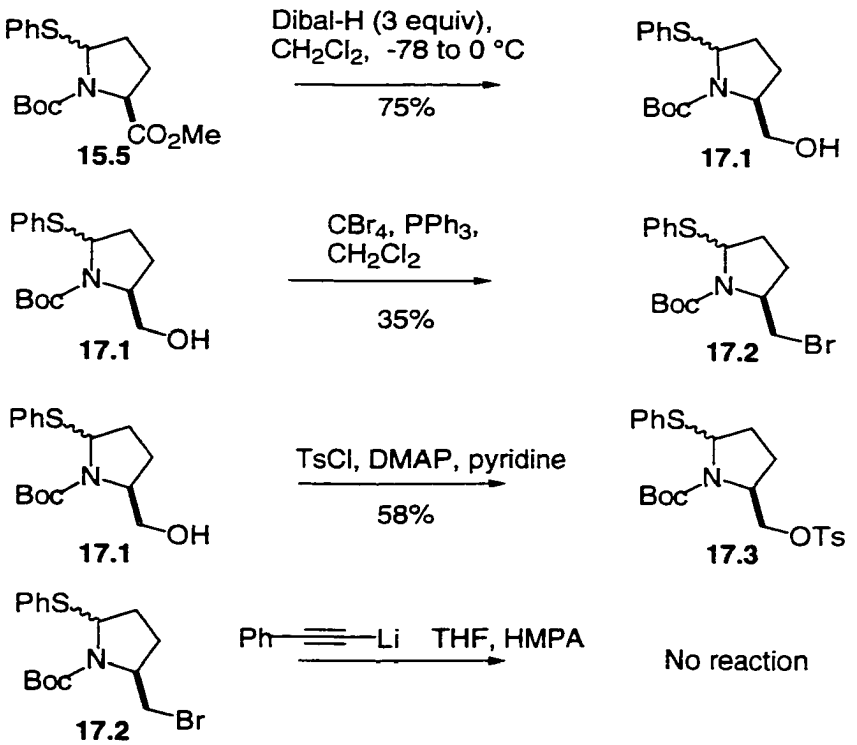
Scheme 15

With the phenyl sulfide unit in place, we turned our attention to installing the acetylene side arm. Our original plan was to introduce the acetylene by S_N2 displacement of a leaving group X by an acetylide ion (**Scheme 16**). Therefore,



Scheme 16

the methyl esters **15.5** were reduced to alcohols **17.1** with an excess of DIBAL-H. Our attempts to convert the alcohol into a leaving group gave low yields of bromides **17.2** or tosylates **17.3** (**Scheme 17**). This inefficiency may be due to the instability of the sulfide group under the reaction conditions. Moreover, the addition of lithium phenylacetylide to bromides **17.2** gave none of the desired

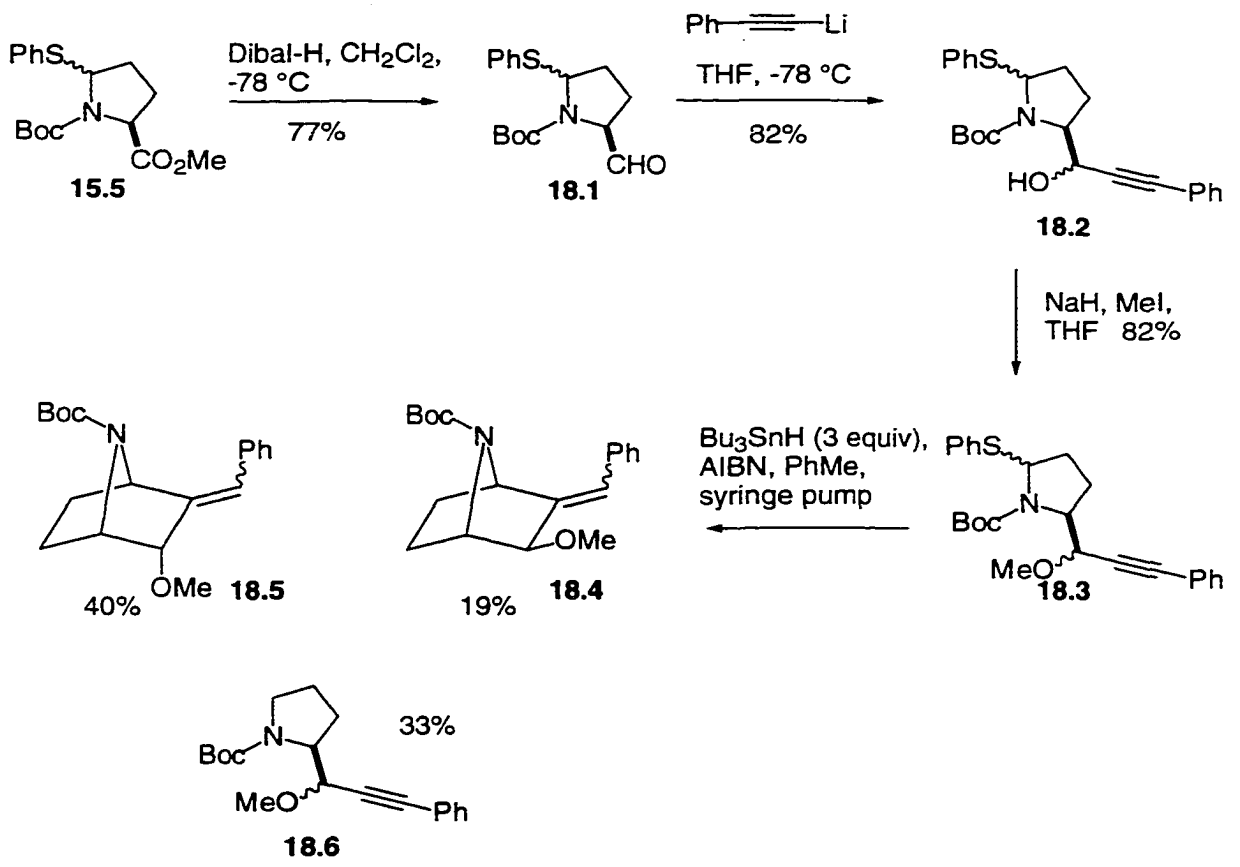


Scheme 17

displacement product.

Based on the above observations, we decided to introduce the acetylide via the aldehydes **18.1**. Hence, esters **15.5** was reduced with 1 equiv of DIBAL-H to give the corresponding aldehydes **18.1**. Addition of lithium phenylacetylide proceeded without incident to give a mixture of diastereomeric acetylenic alcohols **18.2**. The extraneous alcohol functionality was then protected as its methyl ether. We originally anticipated that the required deoxygenation could be dealt with at a later stage. Radical cyclization was carried out by slow (syringe pump) addition of a PhMe solution (0.1 M) of Bu_3SnH (3 equiv) and AIBN (0.1 equiv) to a heated (120 °C) solution of sulfide **18.3** in PhMe (**Scheme 18**).

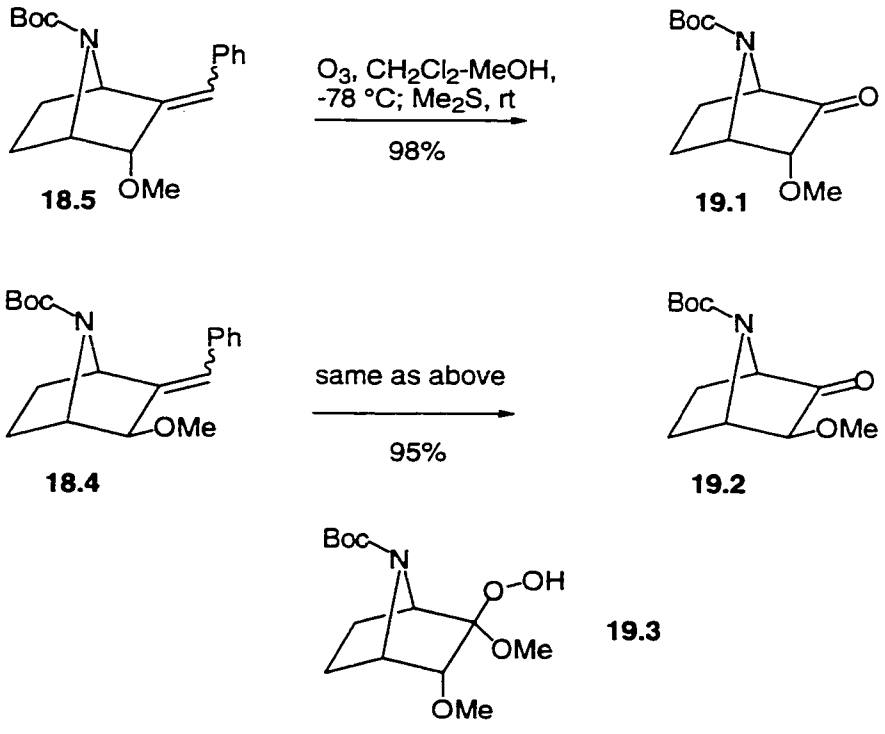
The cyclization step gave three products: the *endo* methoxy isomers **18.5** (40%), the *exo* methoxy isomers **18.4**



Scheme 18

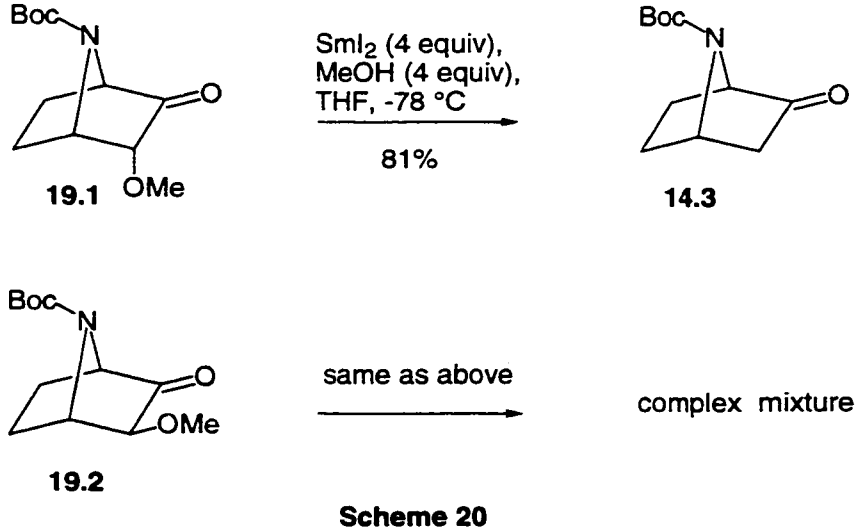
(19%), and the reduced products **18.6** (33%). It was found that at least 3 equivalents of Bu_3SnH were needed in order to complete the reaction. Pleased with this preliminary result for the key cyclization step, we continued with the synthesis by investigating the cleavage of the exocyclic double bond. The best conditions for such a task involved treating the olefins with O_3 at -78 °C, using 1:1 CH_2Cl_2-MeOH as solvent, followed by reductive work up with an excess of Me_2S. MeOH was needed in order to achieve a good yield for the ozonolysis step. The role of the MeOH is presumably to trap the highly reactive carbonyl oxide intermediate as a methanol adduct (**Scheme 19**).

All that remained to reach the desired key intermediate **14.3** was to remove the α-methoxy group from the respective



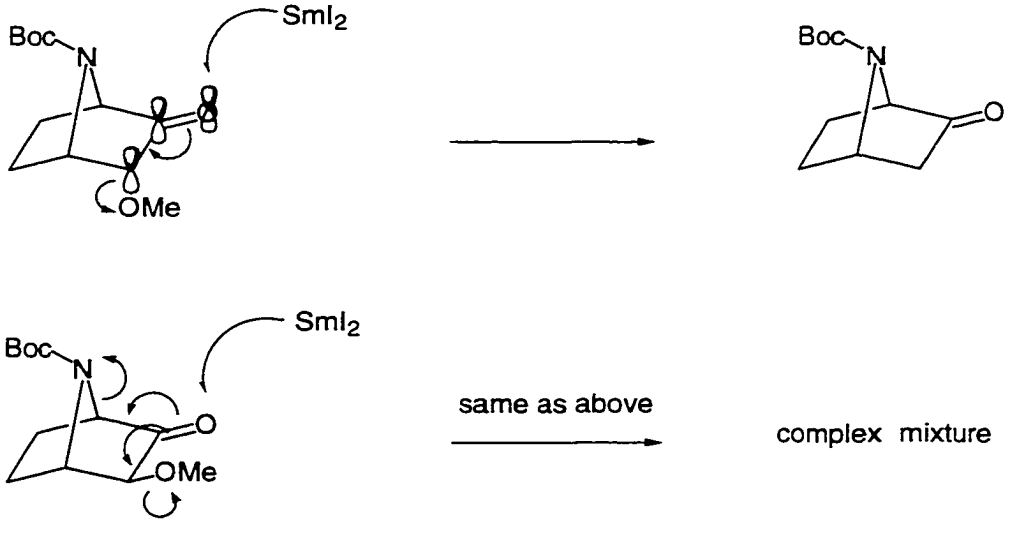
Scheme 19

ketones. SmI_2 was chosen to perform this task due to its mildness and the availability of precedent in successfully reducing α-oxygenated species.[23] Treatment of *endo*-methoxy ketone **19.1** with an excess (4 equiv) of a 0.1 M THF solution of SmI_2 at -78 °C gave the desired ketone **14.3** in 81%



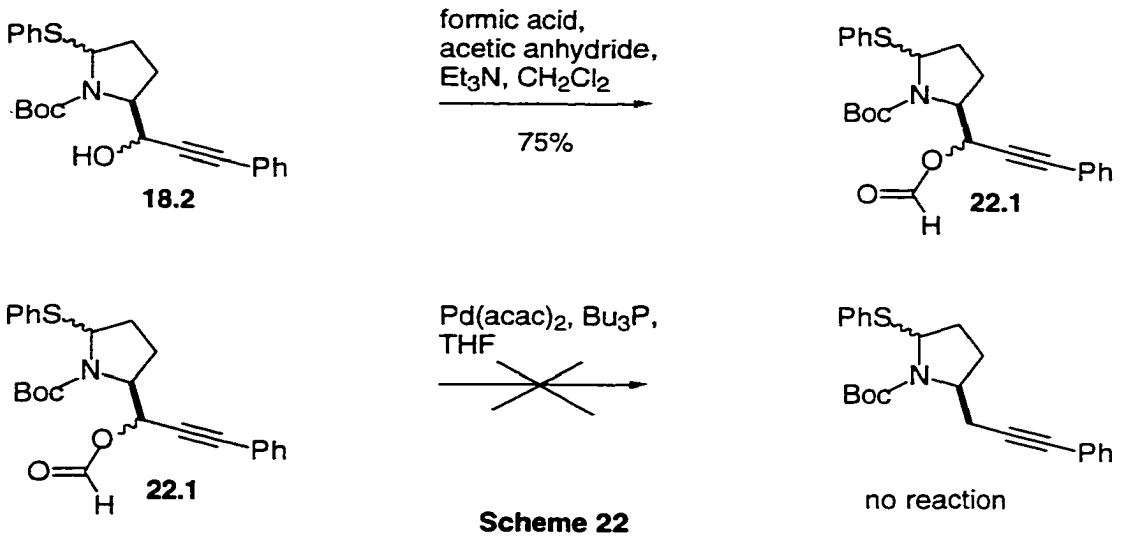
Scheme 20

(**Scheme 20**). On the other hand, under the same conditions the *exo*-methoxy ketone **19.2** gave a complex mixture. A possible explanation for this observation is that the orbital geometry of the *endo*-methoxy group is aligned for facile elimination of the leaving group (-OMe). However, the *exo* isomer does not possess such geometry, and therefore a competitive pathway might occur (**Scheme 21**).



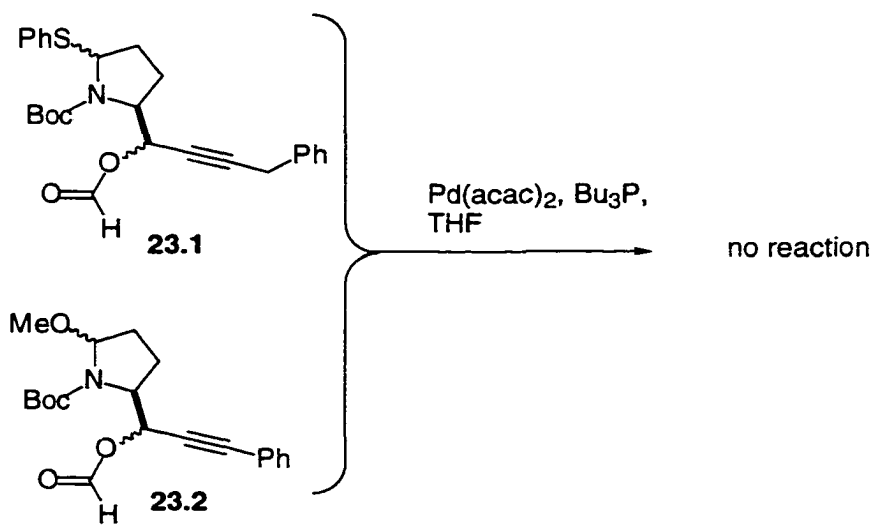
Scheme 21

Hampered by this result, we decided to go back a few steps in the synthetic scheme and solve the deoxygenation problem at an earlier stage. Realizing that there are literature examples[24] of deoxygenating acetylenic alcohols through the derived formate ester via Pd(0) catalysis, we decided to apply these conditions to our system. Alcohols **18.2** were acylated to the formate ester **22.1** through treatment with acetic-formic mixed anhydride. Treatment of **22.1** with $Pd(acac)_2$ and Bu_3P in THF showed no reaction, however, only starting material was recovered after a prolonged period of stirring (**Scheme 22**). We suspected that having a sulfide in the substrate might inhibit the metal catalyst, or changing the conjugated acetylene to an isolated acetylene might improve the reactivity. However, similar



Scheme 22

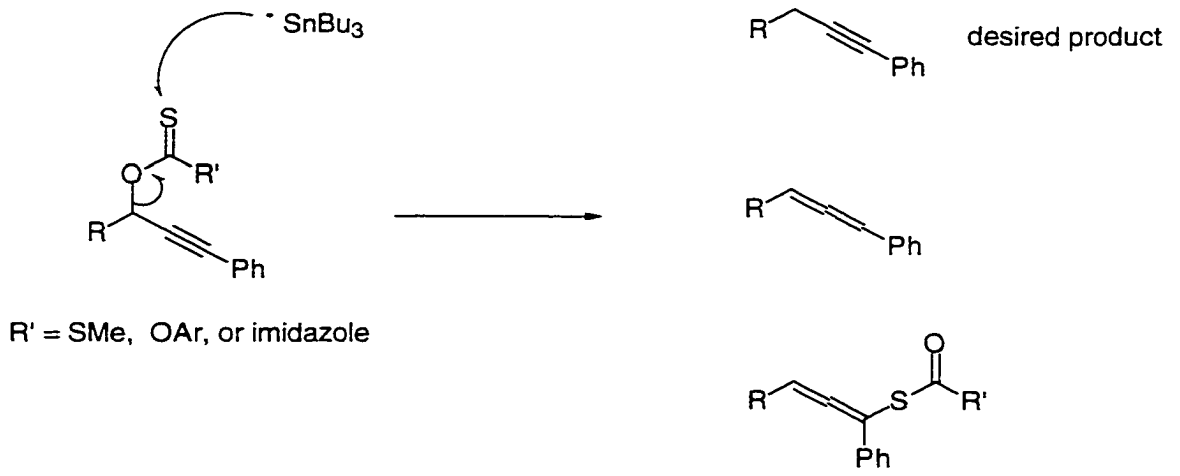
results were obtained when the substrates were altered (**Scheme 23**).



Scheme 23

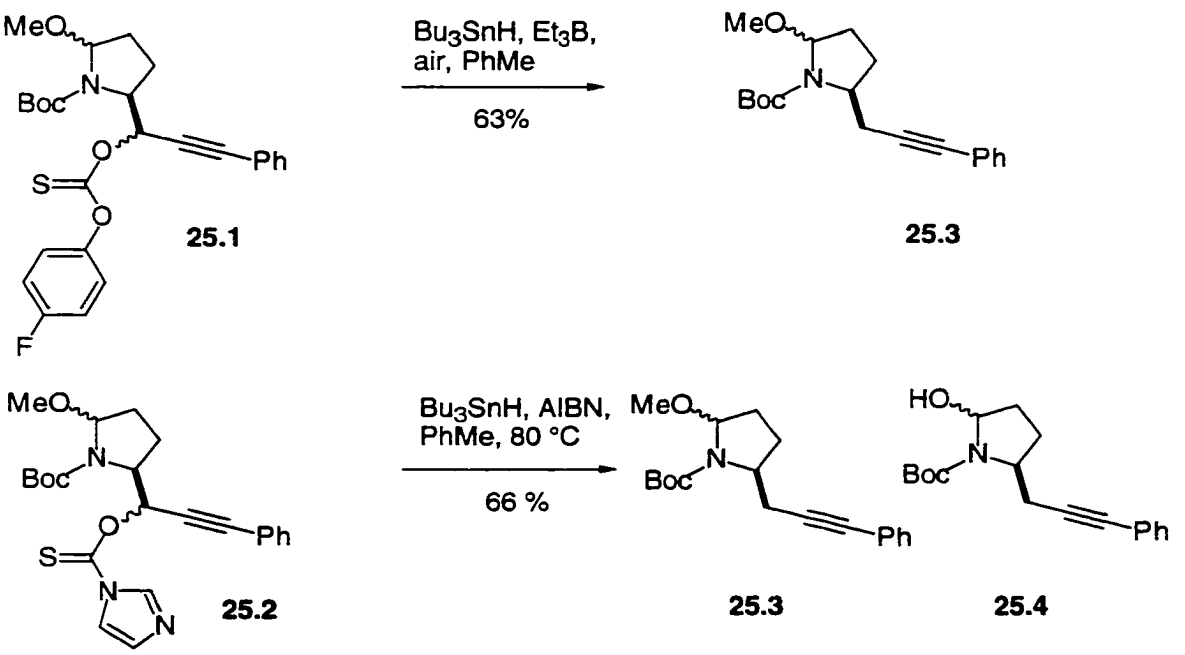
Guided by these results, we decided to attempt the deoxygenation by Barton and McCombie's method.[25] Barton and McCombie deoxygenation methodology has been very successful on various secondary alcohols; however, there are very few examples of its use for acetylenic alcohols. We were well aware of the risk of obtaining an allene product and of the

potential for the substrate to undergo a [3,3]-sigmatropic rearrangement (**Scheme 24**).[26]



Scheme 24

Gratifyingly, treatment of each of the thionoformates **25.1** and **25.2** with Bu_3SnH under the indicated conditions gave the desired acetylene product exclusively (**Scheme 25**).

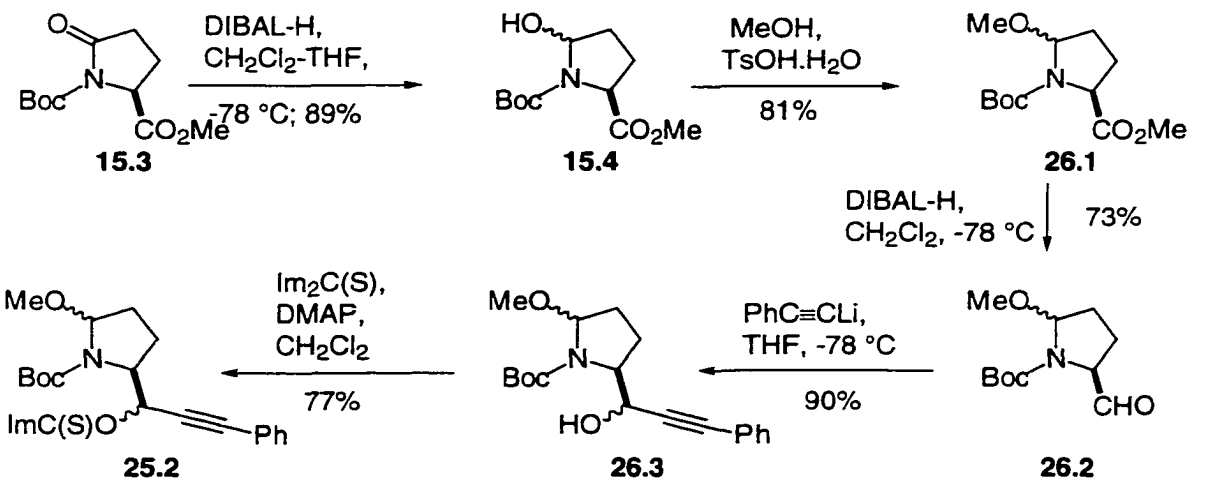


Scheme 25

At this point, we were at last in a position to complete a streamlined route that constitutes a formal synthesis of (-)-epibatidine, and this work is summarized in the following section.

Part 2 Formal Synthesis of (-)-epibatidine

Partial reduction of ester **15.3** with 1 equiv of DIBAL-H gave a diastereomeric mixture of hydroxy carbamates **15.4** (**Scheme 26**). We decided to delay the introduction of the phenylthio group until just before the radical cyclization; hence, replacement of the hydroxy group by a methoxy group

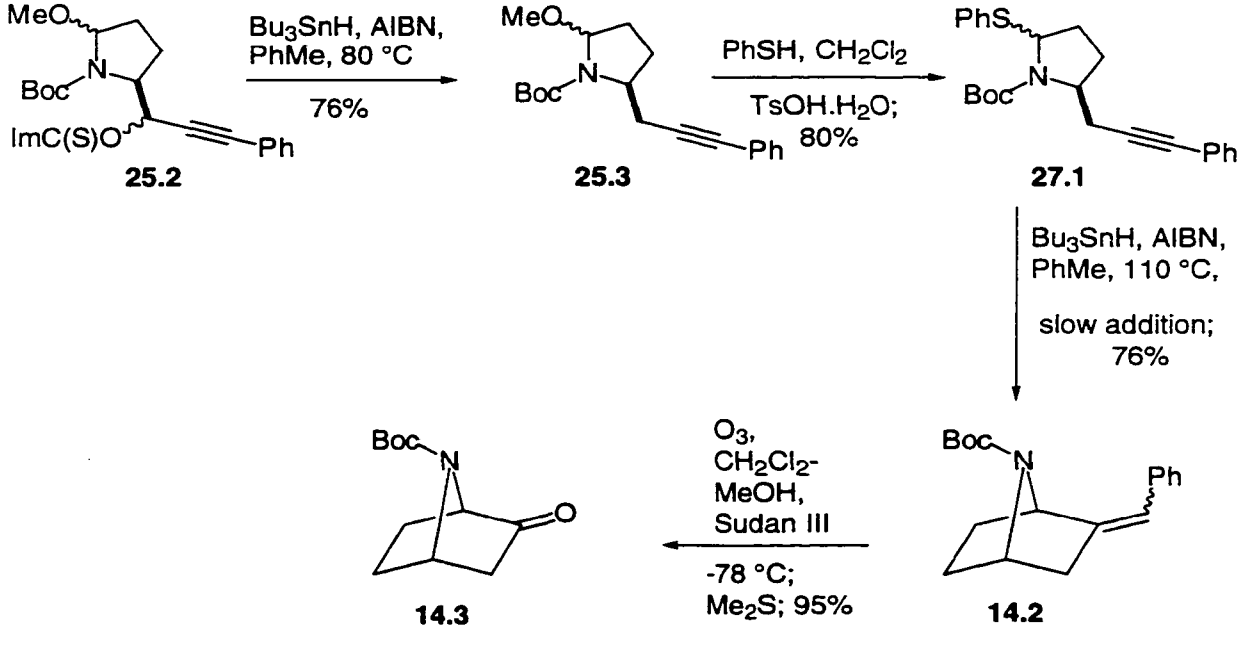


Scheme 26

was carried out in acidic (TsOH) methanol solution, to obtain a diastereomeric mixture of methoxy derivatives **26.1**. This structure allowed another partial reduction (1 equiv DIBAL-H), this time of the ester group, to obtain aldehydes **26.2**. With the aldehyde in hand, we were then ready to introduce an acetylenic side chain that would serve as the radical acceptor. Addition of lithium phenylacetylide gave a diastereomeric mixture of acetylenic alcohols **26.3**. As previously demonstrated, the extraneous hydroxy group was best deoxygenated by Barton and McCombie's method. Hence, alcohols **26.3** were acylated with $Im_2C=S$ and a catalytic

amount of DMAP to give a mixture of thionoimidazolides **25.2**, and these were treated with Bu_3SnH and a catalytic amount of AIBN in warm (80 °C) PhMe (**Scheme 27**). The desired deoxygenated acetylene was the only isolated product in this reaction (76%). One diastereomer of the deoxygenated carbamate **25.3** is very sensitive to acid hydrolysis (replacement of MeO by OH) but the hydrolysis is easily avoided by omitting the acid wash during workup. This two-step sequence represents a facile method of introducing an acetylene unit in a molecule for which a simple S_N2 reaction proved impossible. The method deserves to be explored for its generality and utility in synthesis of other natural products.

With **25.3** in hand, the methoxy group was replaced by a phenylthio group by treatment with PhSH and catalytic amount of TsOH in CH_2Cl_2 (**25.3** → **27.1**), and radical cyclization (**27.1** → **14.2**), effected by slow addition of Bu_3SnH (3 equiv) and AIBN in PhMe to a hot (110 °C) solution of **27.1**, gave the required azabicyclo[2.2.1]heptanes **14.2** (76%) as a mixture (ca 1:1) of two geometrical isomers (**Scheme 27**). It is



Scheme 27

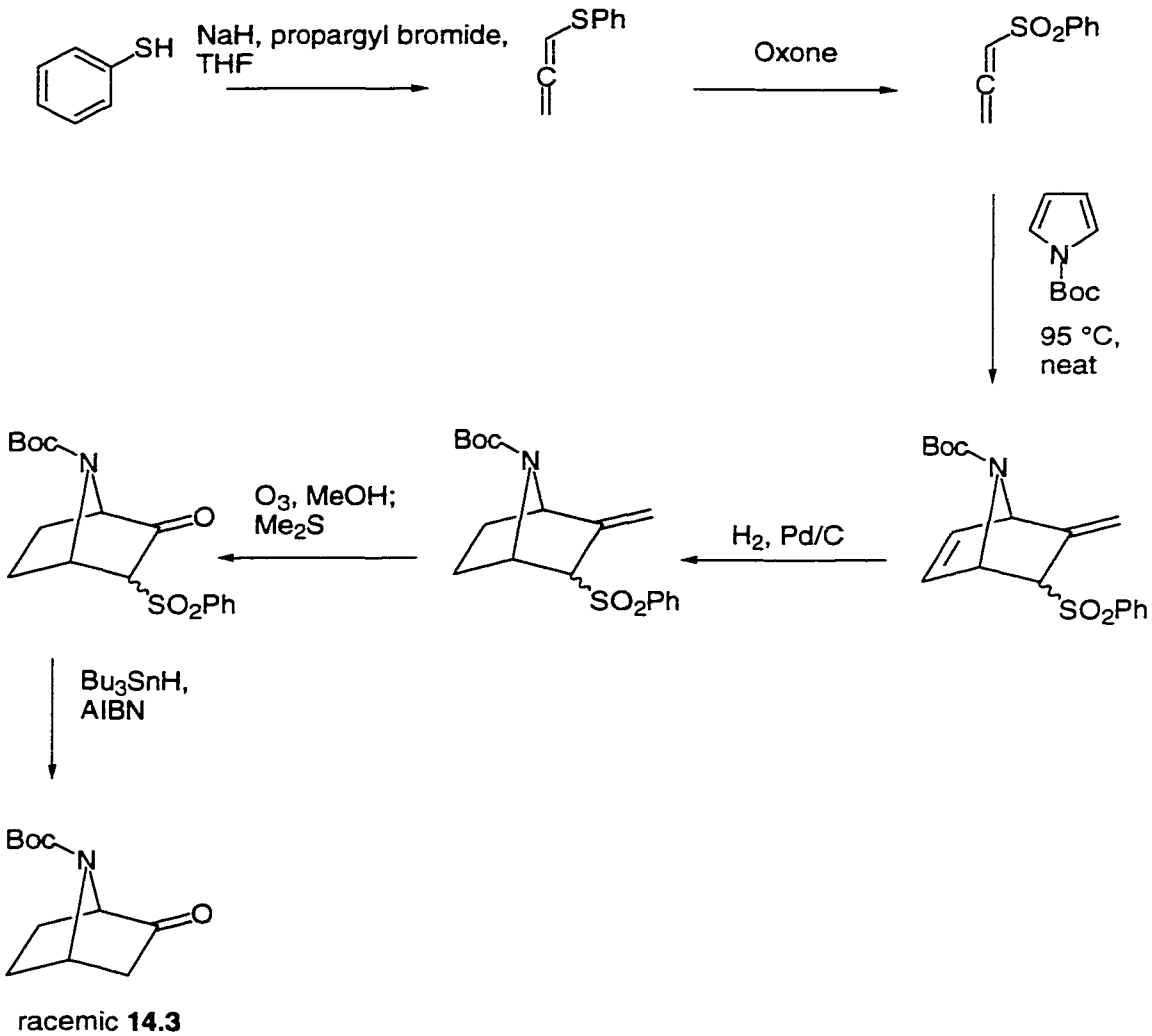
interesting to note that the yield of the cyclization step was higher than in the previous example where the acetylenic hydroxy group was still in place (cf. **Scheme 18**). It might be possible that the stereogenic center on the acetylenic side chain can influence the disposition of the chain during cyclization, therefore allowing one isomer to have a higher rate of cyclization.

Finally, ozonolysis, monitored by an internal indicator (Sudan III),[27] gave ketone **14.3** (95%), which was identified by comparison of its spectroscopic properties with the reported values. The compound had $[\alpha]^{26}_{D}$ -75.1 (*c* 1.56, $CHCl_3$).[20]

Ketone **14.3** is easily converted into (-)-epibatidine,[20] and so the synthesis of **14.3** constitutes a formal synthesis of the natural product. Application of the sequence to (*R*)-pyroglutamic acid [or to methyl (*R*)-1-(*tert*-butoxycarbonyl)-prolinate, by way of anodic oxidation[28]] would afford the enantiomer of epibatidine. The present approach involves very simple reactions from the readily accessible protected ester **15.3**.[29]

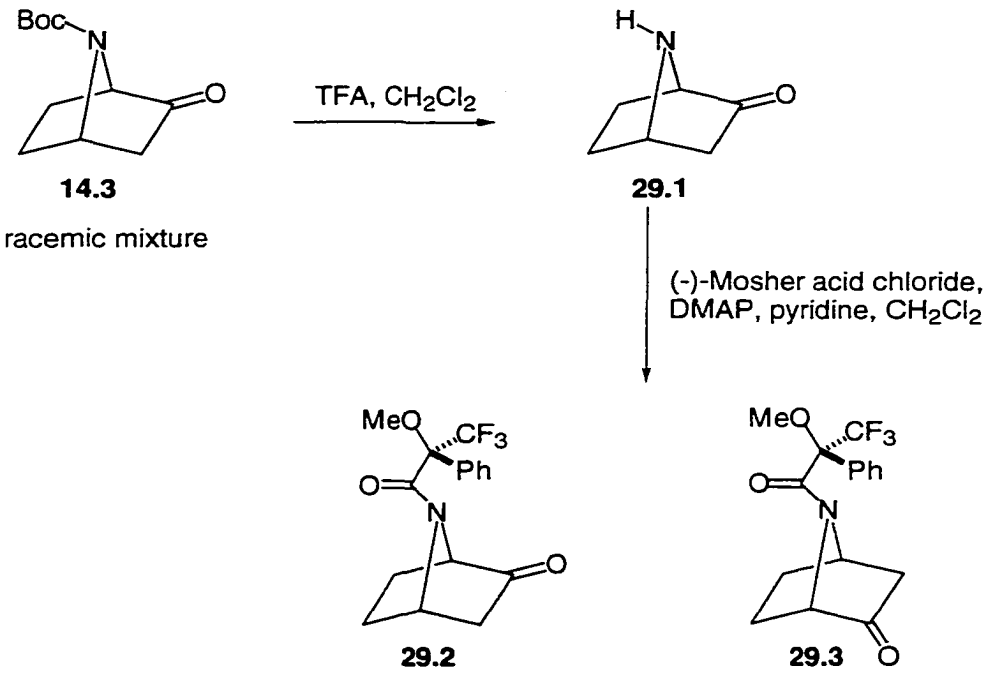
Part 3 Determination of Enantiomeric Excess

Although the value of the optical rotation obtained from our synthesis is very close to the reported value,[20] we wanted to confirm the enantiomeric excess by an NMR study of a Mosher amide (**29.2**). In order to compare the NMR data, a racemic mixture of ketone **14.3** was needed. There are several literature procedures for preparing racemic ketone **14.3**,[20] and we decided to use the one published by Trudell, because of its brevity.[20e] This route is summarized in **Scheme 28**, and was carried through without incident.



Scheme 28

With a sufficient amount of racemic ketone **14.3** in hand, the Boc group was removed by treatment with TFA, and the free amine was acylated with (-)-Mosher acid chloride to give amides **29.2** and **29.3** (***Scheme* 29**). The crude mixture from the acylation was examined by ^{19}F NMR. The best conditions for data acquisition involved heating the sample to 80 °C in order to remove the complexity caused by the presence of amide rotamers. The spectrum showed two distinct ^{19}F peaks at -70.0 and -70.2 ppm for the two diastereomers. Similarly, the ketone **14.3** derived from our own synthesis was converted



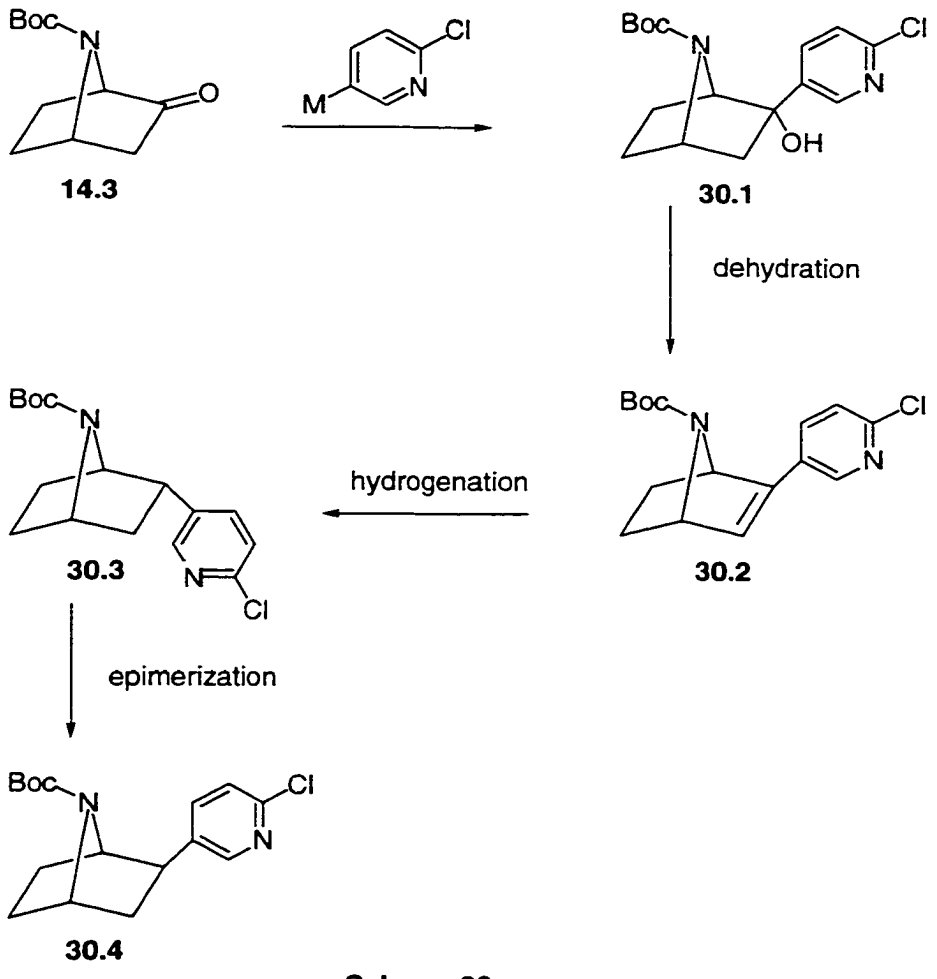
Scheme 29

into its Mosher amide. Gratifyingly, the ^{19}F NMR spectrum showed only one peak (-70.0 ppm), establishing that there was no epimerization in our synthetic sequence, and that our route was indeed enantiospecific.

Part 4 Studies Towards the Total Synthesis of Epibatidine

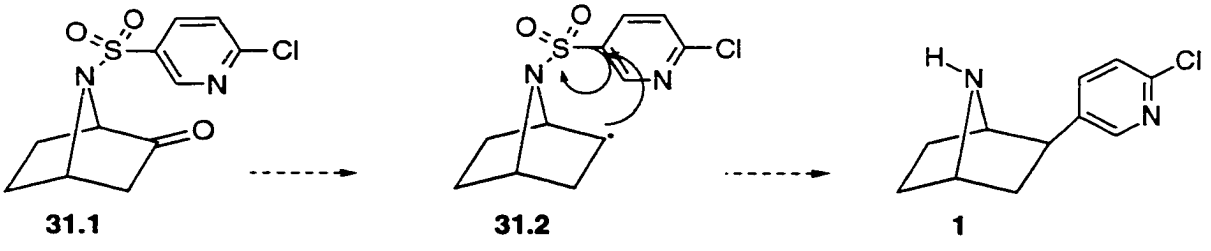
After the completion of our formal synthesis, we decided to look at ways of installing the chloropyridine ring. The existing methods reported in the literature often required a final epimerization of the *endo* pyridine isomer into the natural *exo* isomer (**Scheme 30**).[20d]

We were interested in a method of placing the pyridine ring stereospecifically on the *exo* face. Our idea was based on the attachment of the necessary pyridine heterocycle as a sulfonamide, such as **31.1**, followed by generation of a carbon radical at the ketonic carbon. This radical would then attack the pyridine ring at the *ipso* position so as to



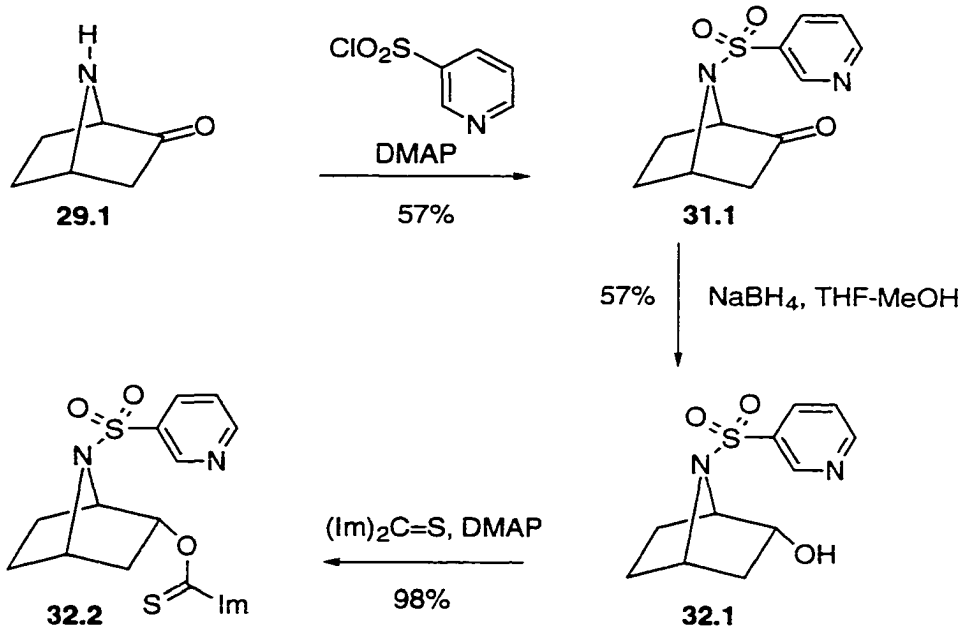
Scheme 30

deliver the heterocycle on the *exo* face, while extruding SO_2 (**Scheme 31**).[30]



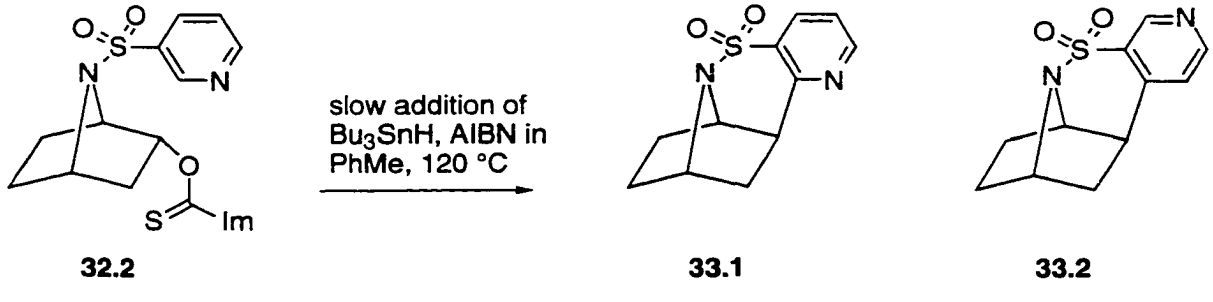
Scheme 31

The idea was tested in the following way. Ketone **29.1** was acylated with 3-pyridine sulfonyl chloride to give the corresponding sulfonamide **31.1** (**Scheme 32**). The ketone



Scheme 32

carbonyl was then reduced to the alcohol (**31.1** → **32.1**), the best reducing agent for this task being $NaBH_4$. An imidazole thionoformate group that had worked well for us in earlier radical deoxygenation experiments (see **Scheme 25**) was chosen to generate a carbon radical from alcohol **32.1**. Therefore, alcohol **32.1** was acylated with $Im_2C=S$ and a catalytic amount of DMAP to give thionimidazolide **32.2**. Radical generation effected by a slow addition of a PhMe solution of Bu_3SnH and AIBN to a hot (120 °C) PhMe solution of **32.2** gave radical adducts **33.1** and **33.2** as an inseparable mixture in a combined yield of 30% (**Scheme 33**).



Scheme 33

This experiment indicated the feasibility of using a radical transfer approach, but additional work is needed to control the regiochemistry of the transfer, and to improve the yield. A method for disengaging the SO_2-unit will also have to be found. We decided to leave these matters to someone else in the group, and turned our attention instead to the synthesis of halichlorine, a marine natural product with potentially significant biological properties.

Experimental Section

General procedures

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[31] and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Cannula transfers were done by supplying Ar under slight pressure to the flask containing the solution to be transferred.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid followed by charring with a heat gun, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF and Et_2O were distilled from sodium and benzophenone ketyl. MeCN, DMF, and pyridine were stirred overnight with crushed CaH_2, and then distilled (under water pump vacuum in the case of DMF), with protection from moisture.

FTIR measurements were made as casts from the specified solvent using potassium bromide plates.

The symbols s', d', t', and q' used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens,

respectively. In cases where the number of signals is less than expected, we assume this is due to coincident chemical shifts.

(*S*)-5-Oxo-1,2-pyrrolidinedicarboxylic Acid 1-(1,1-Dimethylethyl) 2-Methyl Ester (15.3).

15.2 **15.3**

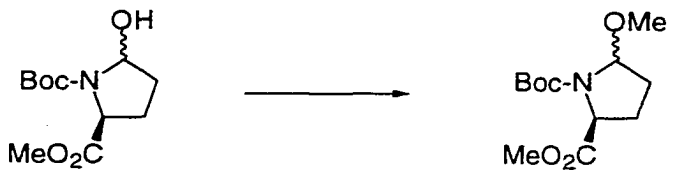
DMAP (0.652 g, 5.343 mmol) and $(Boc)_2O$ (5.831 g, 26.71 mmol) were added to a stirred solution of crude methyl pyroglutamate (2.55 g, 17.81 mmol) in dry CH_2Cl_2 (60 mL). Stirring was continued for 3 h, and the solvent was evaporated. Flash chromatography of the yellow residue over silica gel (5 x 20 cm), using 50:50 EtOAc-hexanes, gave methyl ester **15.3**[21] (3.89 g, 90%) as a colorless solid: mp 68-70 °C; FTIR (CH_2Cl_2 cast) 1792, 1749, 1715 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 1.45 (s, 9 H), 1.92-2.02 (m, 1 H), 2.21-2.60 (m, 3 H), 3.75 (s, 1 H), 4.56 (dd, J = 9.0, 3.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 21.7 (d'), 27.9 (q'), 31.4 (t'), 52.7 (q'), 59.2 (d'), 83.4 (s'), 149.5 (s'), 172.3 (s'), 173.2 (s'); exact mass (electrospray) *m/z* calcd for $C_{11}H_{17}NNaO_5$ (M + Na) 266.1004, found 266.1005. Anal. Calcd for $C_{11}H_{17}NO_5$: C 54.31, H 7.04, N 5.76. Found: C 54.04, H 7.04, N 5.66.

(2*S*)-5-Hydroxy-1,2-pyrrolidinedicarboxylic Acid 1-(1,1-Dimethylethyl) 2-Methyl Ester (15.4).

15.3 **15.4**

DIBAL-H (1 M in CH_2Cl_2, 5.62 mL, 5.62 mmol) was added to a stirred and cooled (-78 °C) solution of **15.3** (1.24 g, 5.11 mmol) in dry THF (17 mL). Stirring was continued for 15 min, the reaction was quenched by addition of $Na_2SO_4.10H_2O$ (1.69 g, 5.11 mmol), and the cold bath was removed. Stirring was continued for 1 h, and the mixture was filtered through a pad (3 x 5 cm) of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 25 cm), using 2:8 EtOAc-hexanes, gave **15.4** (1.00g, 80%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3456, 1757, 1741, 1699 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 2.99, 3.45, 3.57 (three br s, 9 H in all); 3.65, 3.76 (two s, 3 H in all), 4.29-4.38 (m, 1 H), 5.42-5.60 (m, 1 H), ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 27.2 (t'); 27.5 (t'), 28.2 (q'), 31.4 (t'), 32.7 (t'), 33.72 (t'), 52.4 (q'), 59.5 (d'),59.8 (d'), 80.9 (s'), 82.7 (d'), 153.5 (s'), 154.0 (s'), 173.3 (s'), 173.8 (s'); exact mass *m/z* calcd for $C_{11}H_{19}NO_5$ 245.1263, found 245.1268. Anal. Calcd for $C_{11}H_{19}NO_5$: C 53.86, H 7.80, N 5.71. Found: C 53.37, H 8.19, N 5.63.

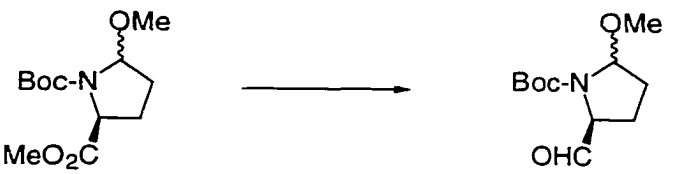
(2*S*)-5-Methoxy-1,2-pyrrolidinedicarboxylic Acid 1-(1,1-Dimethylethyl) 2-Methyl Ester (26.1).



15.4 **26.1**

A solution of *p*-TsOH.H_2O (0.18 g, 1.06 mmol) in anhydrous MeOH (20 mL) was added to α-hydroxycarbamate **15.4** (2.58 g, 10.61 mmol), and the mixture was stirred until reaction was complete (ca 1 h; tlc control, silica, 30% EtOAc-hexane). Saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 20% EtOAc-hexane, gave methoxycarbamates **26.1** (2.59 g, 100%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1751, 1710 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.37, 1.39, 1.45 (three s, 9 H in all); 1.68-2.12 (m, 3 H), 2.20-2.46 (m, 1 H), 3.30, 3.32, 3.35 (three s, 3 H in all), 3.66, 3.68, 3.70 (three s, 3 H in all), 4.20-4.30 (m, 1 H), 5.08-5.24 (m, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 27.4 (t'); 28.2 (q'), 28.4 (q'), 30.4 (t'), 31.4 (t'), 32.4 (t'), 33.1 (t'), 52.2 (q'), 55.4 (d'), 56.0 (d'), 59.2 (q'), 59.4 (q'), 59.6 (q'), 60.1 (q'), 80.6 (s'), 80.8 (s'), 88.9 (d'), 89.1 (d'), 89.5 (d'), 89.7 (d'), 154.2 (s'), 154.3 (s'), 173.3 (s'), 173.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{12}H_{21}NNaO_5$ (M + Na) 282.1317, found 282.1313. Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.77; H, 8.33; N, 5.30.

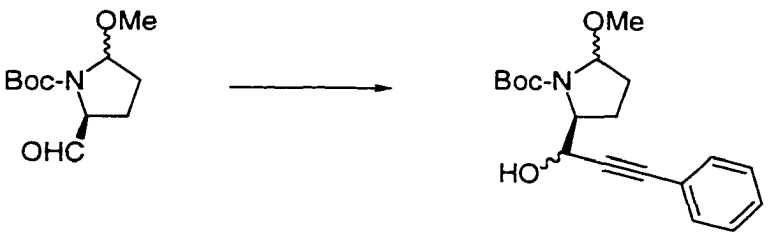
(2*S*)-2-Formyl-5-methoxy-1-pyrrolidinecarboxylic Acid 1,1-Dimethylethyl Ester (26.2).



26.1 **26.2**

DIBAL-H (1 M in CH_2Cl_2, 29 mL, 29 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ester **26.1** (3.76 g, 14.52 mmol) in CH_2Cl_2 (55 mL). After 15 min $Na_2SO_4.10H_2O$ (5 g) was added, and stirring was continued for 1 h. The resulting slurry was filtered through a pad (3 x 5 cm) of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (5 x 18 cm), using 20% EtOAc-hexane, gave aldehydes **26.2** (2.41 g, 73%) as a colorless oil, which was a mixture of diastereomers: FTIR (CH_2Cl_2 cast) 1737, 1710 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.39, 1.41, 1.47 (three s, 9 H in all); 1.57-2.00 (m, 3 H), 2.04-2.15 (m, 0.6 H), 2.21-2.43 (m, 0.4 H), 3.33, 3.34, 3.35 (three s, 3 H in all), 3.95-4.15 (m, 0.6 H), 4.18-4.25 (m, 0.4 H), 5.10-5.27 (m, 1 H), 9.37 (br s, 0.6 H), 9.48 (t, J = 2.0 Hz, 0.4 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 24.1 (t'), 24.8 (t'), 25.2 (t'), 25.8 (t'), 28.2 (q'), 28.4 (q'), 30.5 (t'), 31.5 (t'), 32.0 (t'), 32.9 (t'), 55.7 (d'), 56.2 (d'), 56.3 (d'), 64.8 (q'), 65.2 (q'), 65.5 (q'), 65.9 (q'), 81.2 (s'), 81.3 (s'), 89.5 (d'), 89.7 (d'), 154.2 (s'), 200.6 (s'), 200.7 (s'). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.48; H, 8.52; N, 6.03.

(2*S*)-2-(1-Hydroxy-3-phenyl-2-propynyl)-5-methoxy-1-pyrrolidinecarboxylic Acid 1,1-Dimethylethyl Ester (26.3).



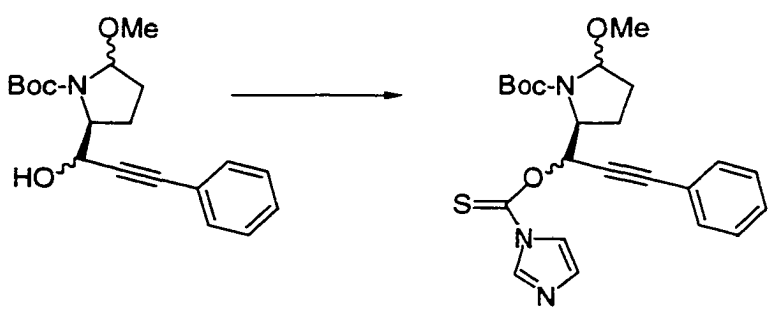
26.2 **26.3**

n-BuLi (2.5 M in hexane, 5.18 mL, 12.96 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of phenylacetylene (1.43 mL, 13.07 mmol) in THF (50 mL). After 20 min, a solution of aldehydes **26.2** (2.30 g, 10.05 mmol) in THF (6 mL plus 1 mL as a rinse) was added dropwise over ca 1 min. Stirring was continued for an additional 10 min at -78 °C, and the reaction was quenched with saturated aqueous NH_4Cl (4 mL). The mixture was extracted with Et_2O, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 20% EtOAc-hexanes, gave two separable fractions of alkynol **26.3** (3.15 g, 94%), each of which was a mixture of diastereoisomers and was a faintly yellow oil. The faster-running fraction, which contained trace impurities (^1H NMR, 300 MHz; ^{13}C NMR, 75.5 MHz), had: FTIR (CH_2Cl_2 cast) 3379, 3056, 2977, 2360, 2338, 1699, 1598 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.50 (s, 9 H), 1.65-2.02 (m, 2 H), 2.02-2.41 (m, 2 H), 3.29, 3.30, 3.32 (three s, 3 H in all), 4.08-4.27 (t, J = 8.5 Hz, 1 H), 4.47-4.95 (m, 1 H), 4.98-5.30 (m, 2 H), 7.27-7.35 (m, 3 H), 7.35-7.48 (m, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 25.4 (t'), 26.9 (t'), 27.2 (t'), 28.4 (q'), 28.5 (q'), 30.5 (t'), 32.0 (t'), 55.2 (q'), 55.8 (q'), 56.1 (q'), 63.6 (d'), 64.5 (d'), 65.5 (d'), 68.1 (d'), 81.5 (s'), 85.1 (s'), 88.3 (s'), 90.3 (d'), 91.5 (d'), 123.2 (s'), 128.6 (d'), 128.7 (d'), 131.9 (d'), 132.0 (d'); exact mass (electrospray) *m/z*

calcd for $C_{19}H_{25}NNaO_4$ (M + Na) 354.1681, found 354.1683.

The slower running fraction, which appeared to contain slight impurities (^{1}H NMR, 300 MHz; ^{13}C NMR, 75.5 MHz), had: FTIR (CH_2Cl_2 cast), 3419, 2977, 1699, 1682, 1598 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.50 (s, 9 H), 1.91-1.78 (m, 1 H), 1.95-2.30 (m, 3 H), 3.32 (s, 3 H), 4.13 (t, *J* = 8.0 Hz, 1 H), 4.41 (d, *J* = 2.0 Hz, 1 H), 4.75 (dd, *J* = 8.0 Hz, 4 Hz, 0.8 H), 4.92 (d, *J* = 4.0 Hz, 0.8 H), 4.99-5.09 (br s, 0.2 H), 5.10-5.17 (br s, 0.2 H), 7.28-7.36 (m, 3 H), 7.41-7.50 (m, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 25.3 (t'), 28.4 (q'), 30.4 (t'), 56.3 (q'), 62.4 (d'), 65.9 (d'), 81.3 (s'), 85.2 (s'), 89.3 (s'), 91.1 (d'), 123.2 (s'), 128.7 (d'), 128.8 (d'), 131.8 (d'), 132.0 (d'), 156.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{19}H_{25}NNaO_4$ 354.1681, found 354.1679. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.65; H, 7.60; N, 4.23, found C, 68.60; H, 7.79; N, 4.29.

(2*S*)-2-[1-(1*H*-imidazol-1-ylthiomethoxy)-3-phenyl-2-propynyl]-5-methoxy-1-pyrrolidinecarboxylic Acid 1,1-Dimethylethyl Ester (25.2).

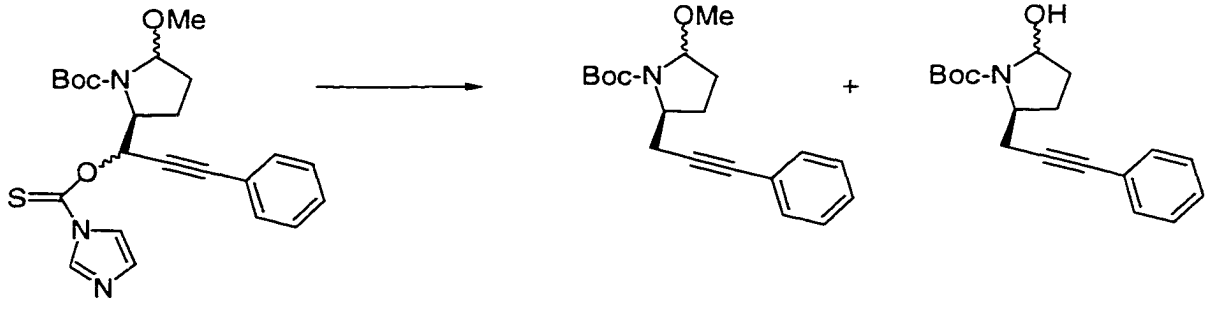


26.3 **25.2**

Thiocarbonyldiimidazole (0.288 g, 1.617 mmol) and DMAP (9 mg, 0.08 mmol) were added successively to a stirred solution of alkynols **26.3** (a mixture of slower- and faster-running isomers) (0.268 g, 0.808 mmol) in CH_2Cl_2 (5 mL). After 5 h the mixture was diluted with Et_2O (20 mL) and washed successively with 0.1 M hydrochloric acid, saturated

aqueous $NaHCO_3$, and brine. The organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% EtOAc-hexane, gave thionoimidazolide **25.2** (0.33 g, 92%) as a mixture of diastereomers, containing slight impurities (^1H NMR, 400 MHz): FTIR (CH_2Cl_2 cast) 3125, 2976, 2829, 2228, 1701, 1531, 1470, 1388 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.47, 1.52 (two s, 10 H in all), 1.89-2.05 (m, 2 H), 2.34-2.52 (m, 2 H), 3.30, 3.37 (two s, 6 H in all), 4.28-4.42 (m, 1 H), 4.94 (d, J = 3.0 Hz, 0.7 H), 5.10 (d, J = 3.0 Hz, 0.3 H), 6.96 (d, J = 4.0 Hz, 1 H), 7.05 (s, 1 H), 7.38 (d, J = 4.0 Hz, 2 H), 7.46 (d, J = 4.0 Hz, 2 H), 7.65 (d, J = 6.0 Hz, 1 H), 8.34 (d, J = 4.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 24.5 (t'), 25.7 (t'), 28.4 (q'), 30.8 (t'), 32.6 (t'), 56.2 (q'), 56.6 (q'), 60.4 (d'), 60.6 (d'), 74.6 (d'), 75.1 (d'), 80.9 (s'), 81.5 (s'), 82.9 (s'), 83.1 (s'), 88.8 (s'), 89.0 (s'), 90.6 (d'), 90.7 (d'), 116.5 (d'), 118.6 (d'), 121.7 (s'), 121.9 (s'), 126.7 (d'), 128.8 (d'), 129.0 (d'), 129.5 (d'), 129.7 (d'), 131.2 (d'), 131.4 (d'), 132.4 (d'), 153.6 (s'), 154.3 (s'), 183.7 (s'), 183.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{23}H_{27}N_3NaO_4$ (M + Na) 464.1619, found 464.1629.

(5*S*)-2-Methoxy-5-(3-phenyl-2-propynyl)-1-pyrrolidinecarboxylic Acid 1,1-Dimethylethyl Ester (25.3) and (5*S*)-2-Hydroxy-5-(3-phenyl-2-propynyl)-1-pyrrolidinecarboxylic Acid 1,1-Dimethylethyl Ester.

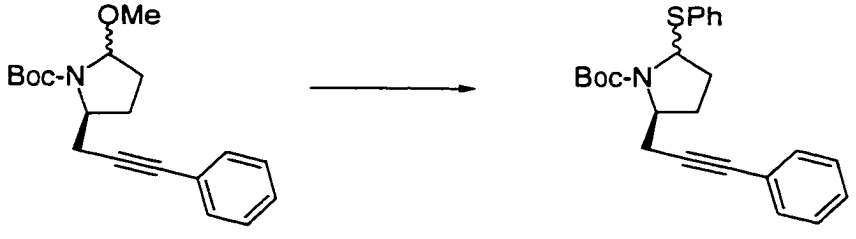


25.2 **25.3** **25.4**

AIBN (24 mg, 0.148 mmol) and Bu_3SnH (0.22 mL, 0.851 mmol) were added to a stirred solution of thionoimidazolide **25.2** (0.327 g, 0.740 mmol) in dry PhMe. The resulting mixture was stirred at 90 °C for 2 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 5% EtOAc-hexane, gave two separable compounds which were the methoxy and hydroxy aminals **25.3** and **25.4**(0.174 g, 74%, combined yield). The methoxy derivative (**25.3**) had: FTIR (CH_2Cl_2 cast) 2975, 2933, 1698, 1598 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.48 (s, 9 H), 1.78 (dddd, *J* = 8.0, 7.0, 6.0, 5.0 Hz, 1 H), 1.89 (dd, *J* = 14.0, 7.0 Hz, 1 H), 2.00-2.25 (m, 2 H), 2.62 (dd, *J* = 16.0, 8.0 Hz, 1 H), 2.98 (br d, *J* = 16.0 Hz, 1 H), 3.30 (s, 3 H), 3.95 (br s, 1 H), 5.10-5.23 (br s, 1 H), 7.22-7.34, and 7.34-7.45 (two m, 5 H in all); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 23.63 (t'), 24.73 (t'), 28.50 (q'), 28.63 (q'), 29.32 (t'), 30.31 (t'), 31.86 (t'), 32.37 (t'), 55.13 (q'), 56.25 (d'), 56.68 (d'), 57.50 (d'), 80.28 (s'), 82.10 (s'), 87.50 (s'), 87.98 (s'), 90.04 (d'), 90.28 (d'), 124.38 (s'), 127.99 (d'), 128.08 (d'), 128.58 (d'), 128.64 (d'), 131.86 (d'), 131.90 (d'); exact mass (electrospray) *m/z* calcd for $C_{19}H_{25}NNaO_3$ (M + Na) 338.1732, found 338.1736.

The hydroxy derivative **25.4** had: FTIR (CH_2Cl_2 cast) 2974, 1697, 1597 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.47 and 1.49 (two s, 11 H), 1.80-2.60 (m, 5 H), 2.40-2.62 (m, 1 H), 2.80 (td, *J* = 22.0, 3.0, 1.0 Hz, 1 H), 3.94-4.04 (m, 1 H), 5.36 (dddd, *J* = 15.0, 14.0, 12.0, 4.0 Hz, 1 H), 7.28-7.40 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 23.6 (t'), 24.8 (t'), 27.1 (t'), 27.5 (t'), 28.5 (q'), 31.4 (t'), 32.1 (t'), 56.5 (q'), 56.7 (d'), 57.0 (d'), 80.2 (s'), 82.1 (s'), 88.7 (s'), 89.5 (d'), 90.0 (d'), 124.4 (s'), 128.1 (d'), 128.6 (d'), 131.9 (d'); exact mass (electrospray) *m/z* calcd for $C_{18}H_{23}NNaO_3$ (M + Na) 324.1575, found 324.1573.

(2*S*)-2-(3-Phenyl-2-propynyl)-5-(phenylthio)-1-pyrrolidinecarboxylic Acid 1,1-Dimethylethyl Ester (27.1).



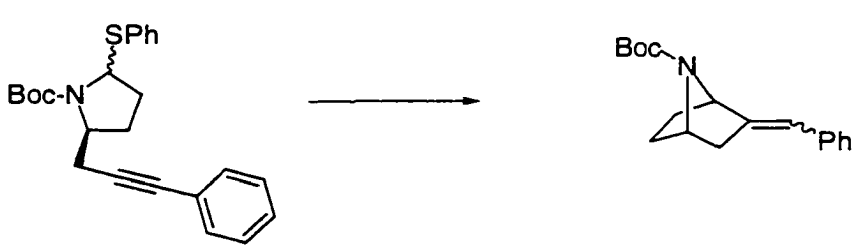
25.3 **27.1**

A mixture of methoxycarbamates **25.3** (0.174 g, 0.511 mmol), thiophenol (0.11 mL, 1.102 mmol), *p*-TsOH.H_2O (10 mg, 0.055 mmol), and powdered 4 Å molecular sieves (0.5 g) in dry CH_2Cl_2 (5 mL) was stirred for 3 h. The mixture was quenched by adding $NaHCO_3$ (0.2 g), and stirring was continued for 3 min. The mixture was filtered through a pad (2 x 5 cm) of Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate, and flash chromatography of the residue over silica gel (2 x 20 cm), using 2% EtOAc-hexane, gave **27.1** as two separable diastereomers (0.153 g, 71%). The faster-running diastereomer had: FTIR (CH_2Cl_2 cast) 3056, 2975, 1696, 1597 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.46, 1.52 (two s, 9 H in all), 1.93-2.30 (m, 3 H), 2.46 (octet, *J* = 6.0 Hz, 1 H), 2.60

(q, J = 9.0 Hz, 1 H), 2.81 (td, J = 17.0, 3.0 Hz, 1 H), 3.98 (dtd, J = 24.0, 8.0, 3.0 Hz, 1 H), 5.24 (dd, J = 21.0, 6.0 Hz, 1 H), 7.20-7.61 (m, 10); ^{13}C NMR (125.7 MHz, CD_2Cl_2) δ 23.8 (t'), 25.0 (t'), 27.6 (t'), 28.4 (q'), 28.5 (q'), 28.8 (t'), 32.0 (t'), 32.8 (t'), 57.0 (d'), 57.1 (d'), 68.76 (d'), 68.83 (d'), 80.7 (s'), 82.0 (s'), 82.4 (s'), 87.2 (s'), 87.6 (s'), 123.0 (d'), 123.9 (s'), 124.1 (s'), 127.95 (d'), 128.04 (d'), 128.1 (d'), 128.2 (d'), 128.6 (d'), 129.3 (d'), 131.8 (d'), 134.08 (d'), 134.13 (d'), 135.1 (s'), 153.0 (s'), 153.5 (s'); exact mass (electrospray) m/z calcd for $C_{24}H_{27}NNaO_2S$ 416.1660, found 416.1667. Anal. Calcd for $C_{24}H_{27}NO_2S$: C, 73.25; H, 6.92; N,; S, 8.15. Found: C, 72.98; H, 6.75; N, 3.50; S, 8.15.

The slower running diastereomer had: FTIR (CH_2Cl_2 cast) 3056, 2974, 1696, 1597, 1582 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.34, 1.45 (two s, 9 H in all), 1.99-2.33 (m, 4 H), 2.75 (br s, 1 H), 3.10 (br s, 1 H), 3.95 (br s, 1 H), 5.44 (br s, 1 H), 7.20-7.60 (m, 10 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 26.1 (t'), 28.4 (q'), 29.7 (t'), 33.0 (t'), 58.2 (d'), 68.8 (d'), 80.5 (s'), 82.5 (s'), 87.4 (s'), 124.3 (s'), 128.1 (d'), 128.6 (d'), 128.8 (d'), 129.2 (d'), 129.7 (d'), 132.0 (d'), 134.7 (d'), 135.0 (s'), 153.9 (s'); exact mass (electrospray) m/z calcd for $C_{24}H_{27}NNaO_2S$ 416.1660, found 416.1663.

(1*R*,4*S*)-2-(Phenylmethylene)-7-azabicyclo-[2.2.1]heptane-7-carboxylic Acid 1,1-Dimethylethyl Ester (14.2).



27.1 **14.2**

A solution of Bu_3SnH (0.295 mL, 1.097 mmol) and AIBN (12

mg, 0.073 mmol) in dry PhMe (10 mL) was added over 8 h (syringe pump) to a stirred and heated (110 °C) solution of sulfides **27.1** (0.144 g, 0.365 mmol) in dry PhMe (36 mL). Stirring and heating were continued for an additional 2 h, and the solvent was then evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 5% EtOAc-hexane, gave **14.2** (79 mg, 76%) as a mixture of isomers: FTIR (CH_2Cl_2 cast) 2975, 1701 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 1.40, 1.45 (two s, 9 H in all), 1.49-1.79 (m, 2 H), 1.80-2.12 (m, 2 H), 2.22 (dd, *J* = 16.0, 2.0 Hz, 0.5 H), 2.38 (dd, *J* = 16.0, 2.0 Hz, 0.5 H), 2.64 (dt, *J* = 17.0, 2.0 Hz, 0.5 H), 2.74 (dt, *J* = 17.0, 2.0 Hz, 0.5 H), 3.39 (t, *J* = 4.0 Hz, 0.5 H), 4.29 (t, *J* = 4.0 Hz, 0.5 H), 4.56 (d, *J* = 4.0 Hz, 0.5 H), 4.91 (d, *J* = 4.0 Hz, 0.5 H), 6.22 (s, 0.5 H), 6.38 (s, 0.5 H), 7.16-7.41 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 28.3 (q'), 28.4 (q'), 28.5 (t'), 28.9 (t'), 29.4 (t'), 30.2 (t'), 38.6 (t'), 40.0 (t'), 56.8 (d'), 57.8 (d'), 59.6 (d'), 64.6 (d'), 79.8 (s'), 119.5 (d'), 120.4 (d'), 125.7 (d'), 126.2 (d'), 126.7 (d'), 126.8 (d'), 127.5 (d'), 128.15 (d'), 128.23 (d'), 128.7 (d'), 128.8 (d'), 138.1 (s'), 143.8 (s'), 143.9 (s'), 155.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{18}H_{23}NNaO_2$ 308.1626, found 308.1625.

(1*R*,4*S*)-2-Oxo-7-azabicyclo[2.2.1]-heptane-7-carboxylic Acid 1,1-Dimethylethyl (Ester (14.3).

14.2 **14.3**

Pre-cooled ozonized oxygen (-78 °C) was passed into a stirred and cooled (-78 °C) solution of **14.2** (69 mg, 0.241 mmol) in dry CH_2Cl_2 (2 mL) and dry MeOH (2 mL), containing a crystal of Sudan III (Aldrich) (The ozone inlet tube extended

very close to the magnetic stirring bar). The ozone stream was turned off when total discoloration of the dye had occurred, and the mixture was flushed with O_2 for 15 min. Me_2S (2 mL) was added, the cold bath was removed, and stirring was continued for 2 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 10% EtOAc-hexane, gave ketone **14.3** (40 mg, 81%) as an oil: FTIR (CH_2Cl_2 cast) 2977, 2886, 1766, 1740 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.41 (s, 9 H), 1.56-1.65 (m, 2 H), 1.91-2.01 (m, 3 H), 2.42 (dd, J = 18.0, 5.0 Hz, 1 H), 4.17 (d, J = 5.0 Hz, 1 H), 4.51 (t, J = 4.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 24.7 (t'), 27.9 (t'), 28.3 (q'), 45.5 (t'), 56.6 (d'), 64.4 (d'), 80.8 (s'), 155.4 (s'), 209.7 (s'); exact mass (electrospray) *m/z* calcd for $C_{11}H_{17}NNaO_3$ 234.1106, found 234.1107.

(1*R*,4*S*)-7-(Pyridine-3-sulfonyl)-7-azabicyclo-[2.2.1]heptan-2-one (31.1).

29.1 **31.1**

3-Pyridyl sulfonyl chloride (0.51 g, 2.86 mmol) was added in one portion to a stirred solution of amine **29.1** (0.145 g, 1.304 mmol) and DMAP (0.40 g, 3.26 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 1 h and then diluted with saturated aqueous NH_4Cl (20 mL) and EtOAc (20 mL), and the phases were separated. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 30% EtOAc-hexane, gave **31.1** (0.334, 57%) as an oil: FTIR ($CHCl_3$ cast) 1761, 1694, 1164 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.68 (dd, J = 7.5, 1.5 Hz, 2 H), 2.00-2.15 (m, 3 H),

2.50 (dd, J = 18.5, 5.5 Hz, 1 H), 4.10 (d, J = 5.0, 1 H), 4.62 (dd, J = 6.5, 4.5 Hz, 1 H), 7.49 (ddd, J = 8.5, 5.5, 1.0 Hz, 1 H), 8.18 (ddd, J = 9.0, 3.0, 1.5 Hz, 1 H), 8.81 (dd, J = 5.0, 2.0 Hz, 1 H), 9.08 (d, J = 2.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 24.6 (t'), 28.8 (t'), 45.1 (t'), 59.5 (d'), 65.7 (d'), 124.2 (d'), 135.4 (d'), 136.6 (d'), 148.7 (d'), 154.3 (d'), 207.1 (s'); exact mass m/z calcd for $C_{11}H_{13}N_2O_3S$ 253.0646, found 253.0639.

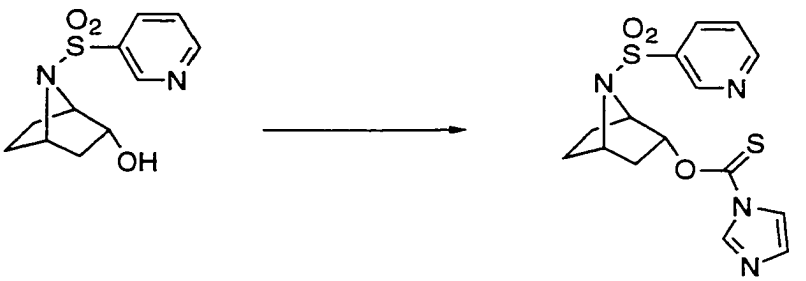
(1*R*,4*S*)-7-(Pyridine-3-sulfonyl)-7-azabicyclo-[2.2.1]heptan-2-ol (32.1).

31.1 **32.1**

$NaBH_4$ (38 mg, 1.00 mmol) was added in one portion to a stirred and cooled (0 °C) solution of ketone **31.1** (0.127 g, 0.503 mmol) in THF (5 mL) and MeOH (1 mL). After 10 min, the cooling bath was removed and stirring was continued for 5 h. EtOAc (20 mL) and water (10 mL) were added, and stirring was continued for 30 min. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 80% EtOAc-hexane, gave alcohol **32.1** (represented with an arbitrary stereochemistry for the OH) (73 mg, 57%) as an oil: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.09 (dd, J = 14.0, 4.0 Hz, 1 H), 1.48-1.60 (m, 2 H), 1.63-1.75 (m, 1 H), 2.16-2.30 (m, 2 H), 2.40-2.50 (br s, 1 H), 4.12 (ddd, J = 10.0, 5.0, 5.0 Hz, 2 H), 4.30-4.40 (m, 1 H), 7.47 (ddd, J = 8.0, 5.0, 1.0 Hz, 1 H), 8.16 (ddd, J = 8.5, 2.5, 1.5 Hz, 1 H), 8.77 (dd, J = 5.0, 2.5 Hz, 1 H), 9.04 (d, J = 3.0 Hz, 1 H), ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 21.2 (t'), 30.5

(t'), 40.2 (t'), 61.4 (d'), 63.3 (d'), 71.0 (d'), 124.1 (d'), 135.4 (d'), 137.9 (s'), 148.5 (d'), 153.5 (d').

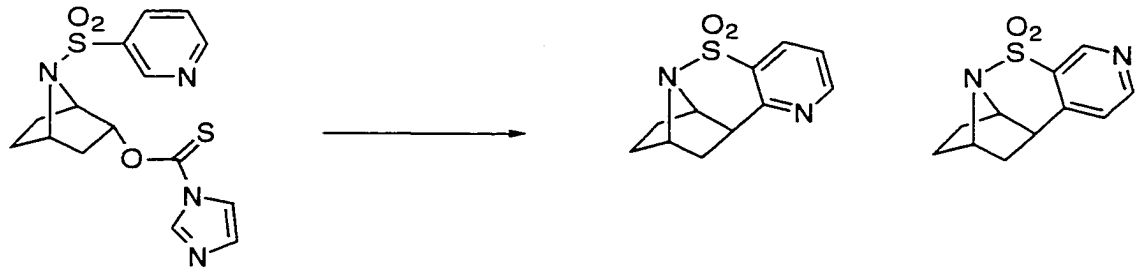
Imidazole-1-carbothioic Acid *O*-[(1*R*,4*S*)-7-(Pyridine-3-sulfonyl)-7-azabicyclo[2.2.1]heptan-2-yl] Ester (32.2).



32.1 **32.2**

$Im_2C=S$ (71 mg, 0.397 mmol) was added in one portion to a stirred solution of alcohol **32.1** (46 mg, 0.18 mmol) and DMAP (11 mg, 0.09 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 3 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (1 cm x 20 cm), using EtOAc, gave **32.2** (72 mg, 98%) as a yellow oil: ^1H NMR (400 MHz, CD_2Cl_2) δ 1.44 (dd, *J* = 14.5, 4.0 Hz, 1 H), 1.60-1.70 (m, 1 H), 1.70-2.05 (m, 3 H), 2.58 (ddd, *J* = 12.0, 5.5, 2.5 Hz, 1 H), 4.38 (t, *J* = 5.0 Hz, 1 H), 4.63 (t, *J* = 5.0 Hz, 1 H), 5.60 (dd, *J* = 5.5, 2.0 Hz, 1 H), 7.01 (s, 1 H), 7.51 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1 H), 7.60 (s, 1 H), 8.20 (ddd, *J* = 8.5, 2.5, 1.5 Hz, 1 H), 8.25 (s, 1 H), 8.80 (dd, *J* = 5.0, 2.5 Hz, 1 H), 9.13 (d, *J* = 3.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 23.2 (t'), 29.9 (t'), 37.8 (t'), 60.7 (d'), 60.9 (d'), 81.0 (d'), 118.3 (d'), 124.2 (d'), 131.4 (d'), 135.2 (d'), 137.4 (s'), 148.6 (d'), 154.0 (d'), 183.8 (s').

(2*S*)-8,14-Diaza-9-dioxo-9-thiatetracyclo-[8.4.0.0^{2,7}.0^{4,8}]tetradeca-1(10),11,13-triene (33.1) and (2*R*)-8,12-Diaza-9-dioxo-9-thiatetracyclo-[8.4.0.0^{2,7}.0^{4,8}]tetradeca-1(10),11,13-triene (33.2).



32.2 **33.1** **33.2**

A solution of Bu_3SnH (0.08 mL, 0.30 mmol) and AIBN (5 mg) in PhMe (3 mL) was added by syringe pump over 4 h to a stirred and heated (100 °C) solution of **32.2** (55 mg, 0.15 mmol) in PhMe (15 mL). Stirring was continued for 1 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 30% EtOAc-hexane, gave a 1.4:1 mixture of **33.1** and **33.2** (7 mg, 20%) as an inseparable mixture: FTIR (CH_2Cl_2 cast) 2956, 1577, 1330, 1170 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.55-1.70 (m, 2 H), 1.65-2.00 (m, 2 H), 2.05-2.20 (m, 2 H), 3.04 (dd, *J* = 8.0, 2.5 Hz, 0.41 H), 3.33 (dd, *J* = 8.0, 2.0 Hz, 0.59 H), 4.25-4.35 (m, 2 H), 7.14 (d, *J* = 5.0 Hz, 0.41 H), 7.36 (dd, *J* = 8.0, 5.0 Hz, 0.59 H), 8.06 (dd, *J* = 8.0, 2.0, 1.0 Hz, 0.41 H), 8.54-8.60 (m, 1 H), 8.80 (s, 0.45 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 28.0 (t'), 28.1 (t'), 30.9, 31.1 (t'), 37.8, 38.7 (t'), 44.1, 47.7 (d'), 60.8, 60.9 (d'), 66.2, 66.6 (d'), 121.1, 123.7 (d'), 134.0, 147.3 (d'), 151.6 (s'), 152.4, 152.8 (d'), 161.4 (s'); exact mass *m/z* calcd for $C_{11}H_{12}N_2O_2S$ 236.0619, found 236.0620.

References and Notes

1 Spande, T. H.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannel, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475.

2 Reviews on the total synthesis of epibatidine: (a) Szantay, C.; Kardos-Balogh, Z.; Szantay, C., Jr. *The Alkaloids;* Cordell, C. A., Ed,; Academic Press: San Diego, **1995**; Vol 46, p 95. (b) Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179. (c) Kibayashi, C.; Aoyagi, S. *Studies in Natural Products Chemistry;* Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1997; Vol. 19, p 66.

3 Badio, B.; Garraffo, H. M.; Spande, T. F.; Daly. J. W. *Med. Chem. Res.* **1994**, *4*, 440.

4 Daly, J. W.; Garraffo, H. M.; Myers, C. W. *Pharmaceut. News*, **1997**, *4*, 9.

5 Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162.

6 Corey, E. J.; Loh, T. P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600.

7 Badio, B.; Daly, J. W. *Mol. Pharmacol. 1994*, *45*, 563.

8 Qian, C.; Li, T.; Shen, T. Y. *Eur. J. Pharm.* **1993**, *150*, R13.

9 Damaj, M. I.; Creasy, K. R.; Grove, A. D.; Rosecrans, J. A.; Martin, B. R. *Brain Res.* **1994**, *664*, 34.

10 Dukat, M.; Damaj, M. I.; Glassco, W.; Dumas, D.; May, E. L.; Martin, B. R.; Glennon, R. A. *Med. Chem. Res.* **1994**, *4*, 131.

11 Bonhaus, D. W.; Bley, K. R.; Broka, C. A.; Fontana, D. J.; Leong, L.; Lewis, R.; Sheih, A.; Wong, E. H. F. *J. Pharmacol. Exp, Ther.* **1995**, *272*, 1199.

12 Bannon, A. W.; Decker, M. W.; Holladay, P.; Curzon, P.; Donnelly-Roberts, D. L.; Puttfarken, P.; Bitner, R. S.; Diaz, A.; Dickenson, A. H.; Posolt, R. D.; Williams, M.; Arneric, S. P. *Science*, **1998**, *289*, 77.

13 *Chemistry In Britain*, **1998**, *February*, 19.

14 Trost, B. M.; Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485.

15 Kosugi, H.; Abe, M.; Hatsude, R.; Uda, H.; Kato, M. *Chem. Commun.* **1997**, 1857.

16 Albertini, E.; Barco, A.; Benetti, S.; Risi, C.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1997**, *38*, 681.

17 Node, M.; Nishide, K.; Fujiwara, T.; Ichihashi, S. *Chem. Commun.* **1998**, 2363.

18 (a) Giblin, G, M.; Jones, C. D.; Simpkins, N. S. *Synlett* **1997**, 589. (b) Giblin, G, M.; Jones, C. D.; Simpkins, N. S. *Tetrahedron Lett.* **1998**, *39*, 1023.

19 Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397.

20 (a) Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 1771. (b) Hernández, A.; Marcos, M.; Rappoport, H. *J. Org. Chem.* **1995**, *60*, 2683. (c) Campbell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313. (d) Zhang, C.; Trudell, M. L. *J. Org. Chem.* **1996**, *61*, 7189. (e) Pavri, N. P.; Trudell, M. K. *Tetrahedron Lett.* **1997**, *38*, 7993.

21 (a) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6221. (b) Tourwe, D.; Betsbrugge, J. Van; Verheyden, P.; Hootelé, C. *Bull. Soc. Chim. Belg.* **1994**, *103*, 201.

22 The ethyl esters corresponding to **15.4** have been reported (Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180), and were prepared along the same lines; we used the methyl esters simply as a matter of convenience.

23 Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

24 Mandai, T.; Matsumoto, T.; Tsujiguchi, Y.; Matsuoka, S.; Tsuji, J. *J. Organomet. Chem.* **1994**, *474*, 343.

25 Hartwig, W. *Tetrahedron*, **1983**, *39*, 3609.

26 Cf. Harusawa, S.; Moriyama, H.; Kase, N.; Ohishi, H.; Yoneda, R.; Kurihara, T. *Tetrahedron* **1995**, *51*, 6475.

27 Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807-810.

28 Asada, S.; Kato, M.; Asai, K; Ineyama, T.; Nishi, S.; Izawa, K.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1989**, 486-488.

29 Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1998**, *39*, 4789.

30 Literature examples of aromatic ring transfer by *ipso* attack: (a) Kohler, J. J.; Speckamp, W. W. *Tetrahedron Lett.* **1977**, 631. (b) Tiecco, M. *Acc. Chem. Res.* **1980**, *13*, 51.

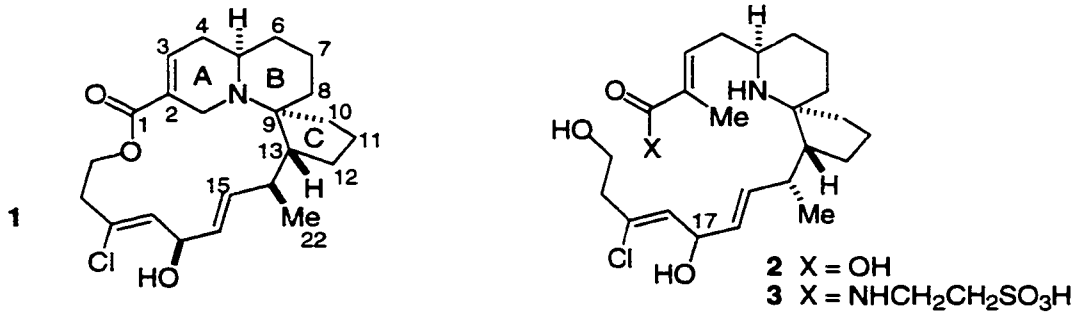
31 Supplied by Chemical Dynamics Corp., South Plainfield, N. J.

Halichlorine

Introduction

Marine organisms have been an inexhaustible source of natural products from the beginning of the systematic study of marine natural product chemistry about twenty years ago.[1] This area of research has yielded numerous compounds with novel structures that are not seen from terrestrial sources.[2] More importantly, many of the isolated compounds have shown important biological activities in mammalian systems. Although none of the discoveries has yet led to a pharmaceutical product, there is hope that one or more of the marine natural products will eventually do so.[3] Concurrent with the development of isolation techniques needed to obtain these natural products, structural elucidation techniques were also developed as a result of marine natural product studies. Moreover, synthetic chemists have been attracted to the challenge of developing new methods to attain the unusual and novel structures and to provide sufficient material for further biological studies.

In their search for biologically active compounds from marine organisms, Uemura and coworkers discovered[4] a substance which they called halichlorine (**1**) in extracts from the marine sponge *Halichondria okadai* Katoda. The compound was found to be a specific inhibitor of induced expression of vascular cell adhesion molecule-1 (VCAM-1) at IC_{50} 7 μg/mL.



Scheme 1

VCAM-1 is a member of the immunoglobulin superfamily.[5] It is expressed on the surface of endothelium cells to monitor and regulate leukocyte recruitment into inflamed tissue. Since leukocyte infiltration is involved in various allergic inflammatory disorders, as well as pathogenic processes such as asthma and arteriosclerosis, VCAM-1 has emerged as a potential target for drug discovery because, in principle, compounds that inhibit VCAM-1 expression could be useful in regulating leukocyte trafficking.

Interestingly, the structurally homologous compounds pinnaic acid (**2**) and tauropinnaic acid (**3**) were also isolated by Uemura and coworkers from a marine bivalve *Pinna muricata* – a completely different organism (**Scheme 1**).[6] The pinnaic acids were found to be specific inhibitors of phospholipase A_2 (PLA_2). Such inhibitors are considered to be potential drugs for the treatment of inflammation disease states, since PLA_2 is linked to the initial step in the cascade of enzymatic reactions which leads to the generation of inflammatory mediators.[7] For example, a cytosolic 85-kDa phospholipase A_2 exhibited specificity for the release of arachidonic acid – the precursor to thromboxanes and prostaglandins – from membrane phospholipids.

The fascinating structure of halichlorine is unprecedented in nature. It contains a quinolizidine nucleus with a five-membered ring spiro-attached to C(9). Appended to the five-membered ring is a divinyl carbinol side chain that is enclosed in a 15-membered macrolactone. The carbons C(9), C(13), and C(14) are contiguous stereogenic centers. Pinnaic acids, on the other hand, have the same carbon skeleton as halichlorine except for the tetrahydropyridine ring and the macrolactone. The absolute stereochemistry of halichlorine has been established by degradation studies.[8] However, the absolute stereochemistry of the pinnaic acids has not been confirmed, due to a lack of sufficient material for degradation studies. However, because of the similarities in structure, although differing sources, it is

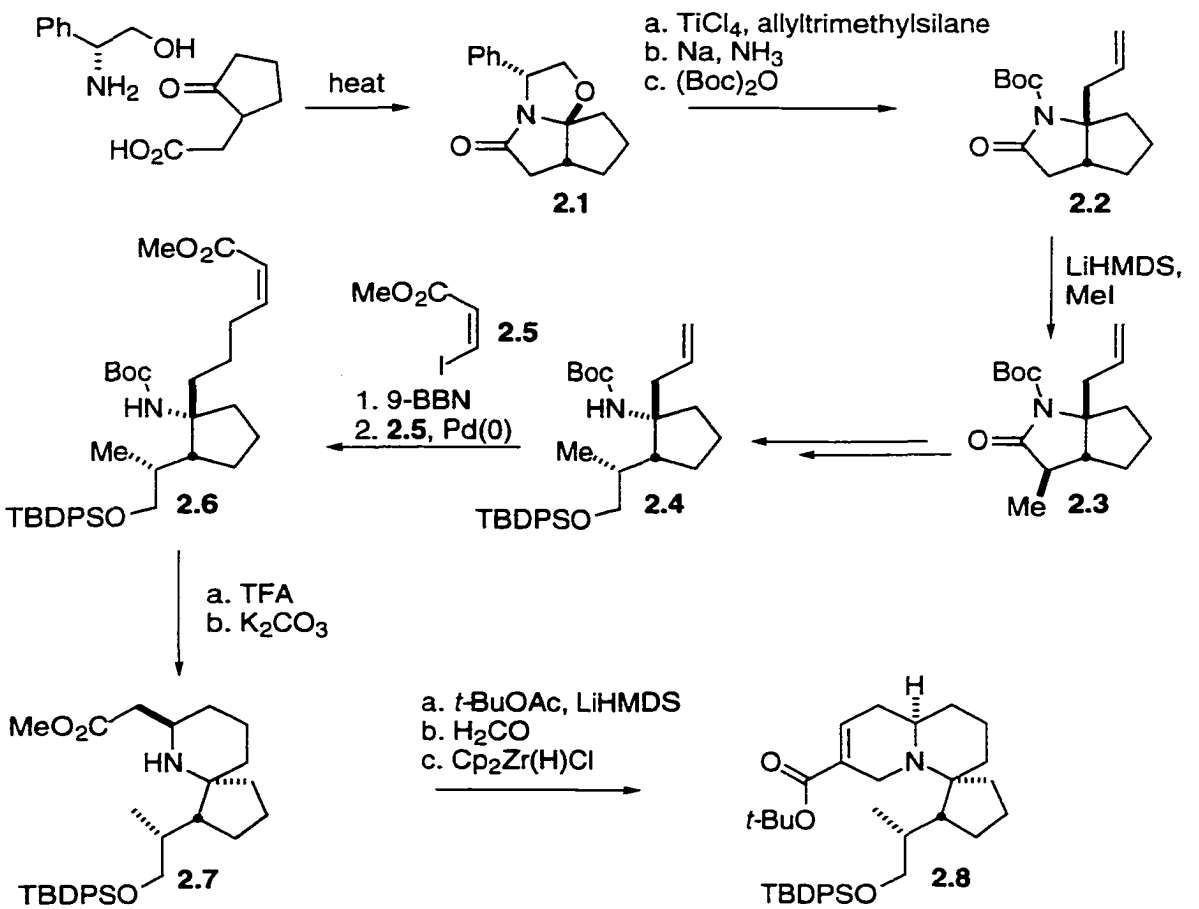
reasonable to postulate that the origin of these natural products might not be their respective organisms at all. Instead the compounds might come from a common symbiotic organism or from dietary sources.[9]

From a synthetic chemist's point of view, halichlorine is perceived as a challenging target due to the array of funtionalities and structural features. At the start of our own synthetic study, no synthetic work on halichlorine had been reported in the literature. However, several publications have appeared since 1999, including a total synthesis. These studies are summarized in the following section.

Synthetic Approaches to Halichlorine

Total Synthesis Of Halichlorine by Danishefsky

The first total synthesis of (+)-halichlorine was reported by Danishefsky *et al.* in 1999.[10] The synthesis began with a Lewis acid-catalyzed allylation of a Meyer's lactam so as to install the quaternary center with stereocontrol (**2.1** → **2.2**) (**Scheme 2**).



Scheme 2

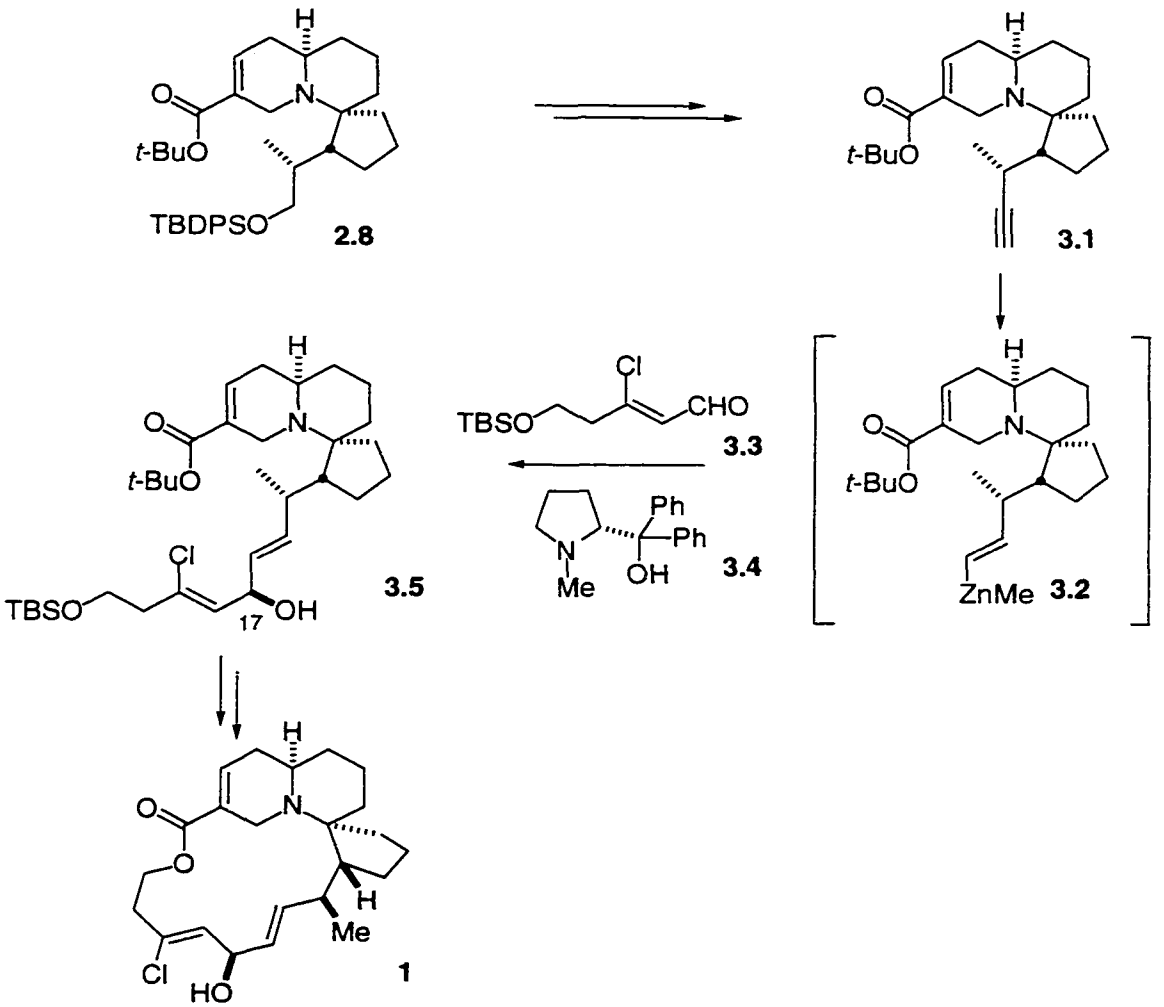
After reductive cleavage (Na, NH_3) of the chiral auxiliary and amide nitrogen protection, the lactam was alkylated with MeI. The cup-like structure of **2.2** causes the alkylation to take place from the convex face so as to correctly introduce the C(22) methyl group of the side chain.

The lactam was then hydrolyzed and the released carboxyl group was reduced and protected to give **2.4**.

At this point the stage is set for homologation of the allyl group using hydroborative Suzuki coupling with (*Z*)-iodoacrylate (**2.4** → **2.6**). Next, the amino protecting group was removed under acidic conditions and, after basification, the free amine underwent an *in situ* stereoselective Michael addition to the alkenoate, forming the fused piperidine ring system **2.7**.

The required tetrahydropyridine ring was then formed by a two-carbon chain extension of **2.7**, using a crossed Claisen condensation, followed by a Mannich reaction with formaldehyde to close the ring. The remaining β-carbonyl group was subsequently removed with $Cp_2Zr(H)Cl$ to give **2.8**. This tricyclic structure contains four of the five stereogenic centers of halichlorine.

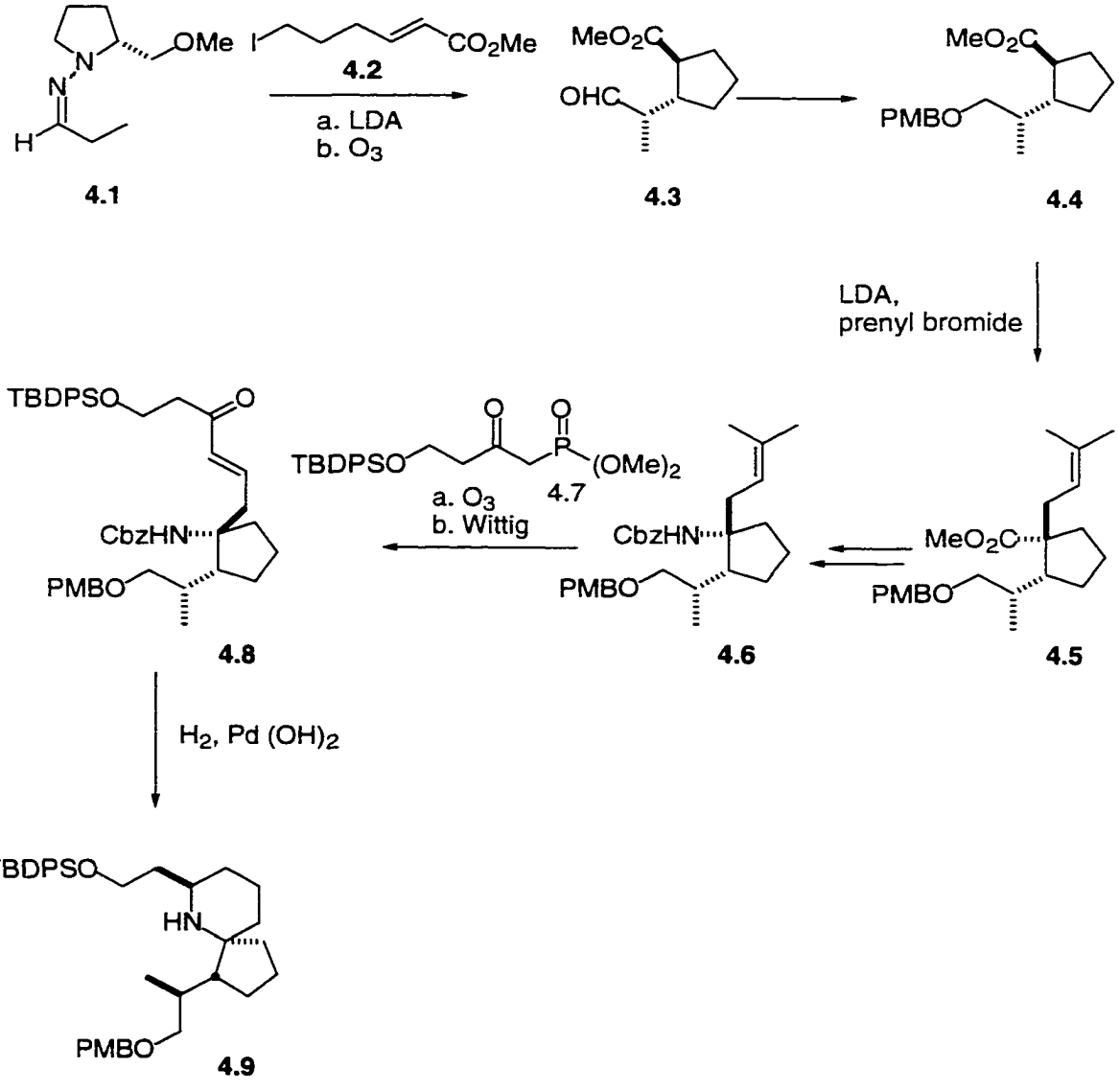
The remainder of the synthesis involved construction of the side chain and macrolactonization (**Scheme 3**). The silyl ether was cleaved and the resulting alcohol was homologated by one carbon to give acetylene **3.1,** via an intermediate aldehyde. This acetylene was converted into an organozinc species which, in the presence of an external chiral amino alcohol (**3.4**), added stereoselectively to aldehyde **3.3** to afford a 4:1 stereoisomeric mixture of the allylic alcohol **3.5** and its 17*S* isomer. After removing the protecting groups from the terminal alcohol and the carboxyl, the macrolactonization was carried out using Keck's conditions. This step was followed by a final deprotection of the divinylcarbinol on the side chain to complete the total synthesis of halichlorine.



Scheme 3

Arimoto's Asymmetric Synthesis of the Spirocyclic Core of Pinnaic Acid

Arimoto's group has reported an asymmetric synthesis of the spirocyclic core of pinnaic acid.[11] Their approach is based on an efficient asymmetric construction of the five-membered ring by a Michael addition-initiated ring closure of the SAMP enolate of **4.1** and iodide **4.2** (**Scheme 4**). After ozonolytic cleavage of the chiral auxiliary, the aldehyde was reduced and the resulting alcohol was protected as its *p*-methoxybenzyl ether **4.4**. A second stereoselective alkylation was carried out to install the quaternary center. After serving its purpose for the alkylation, the ester group was



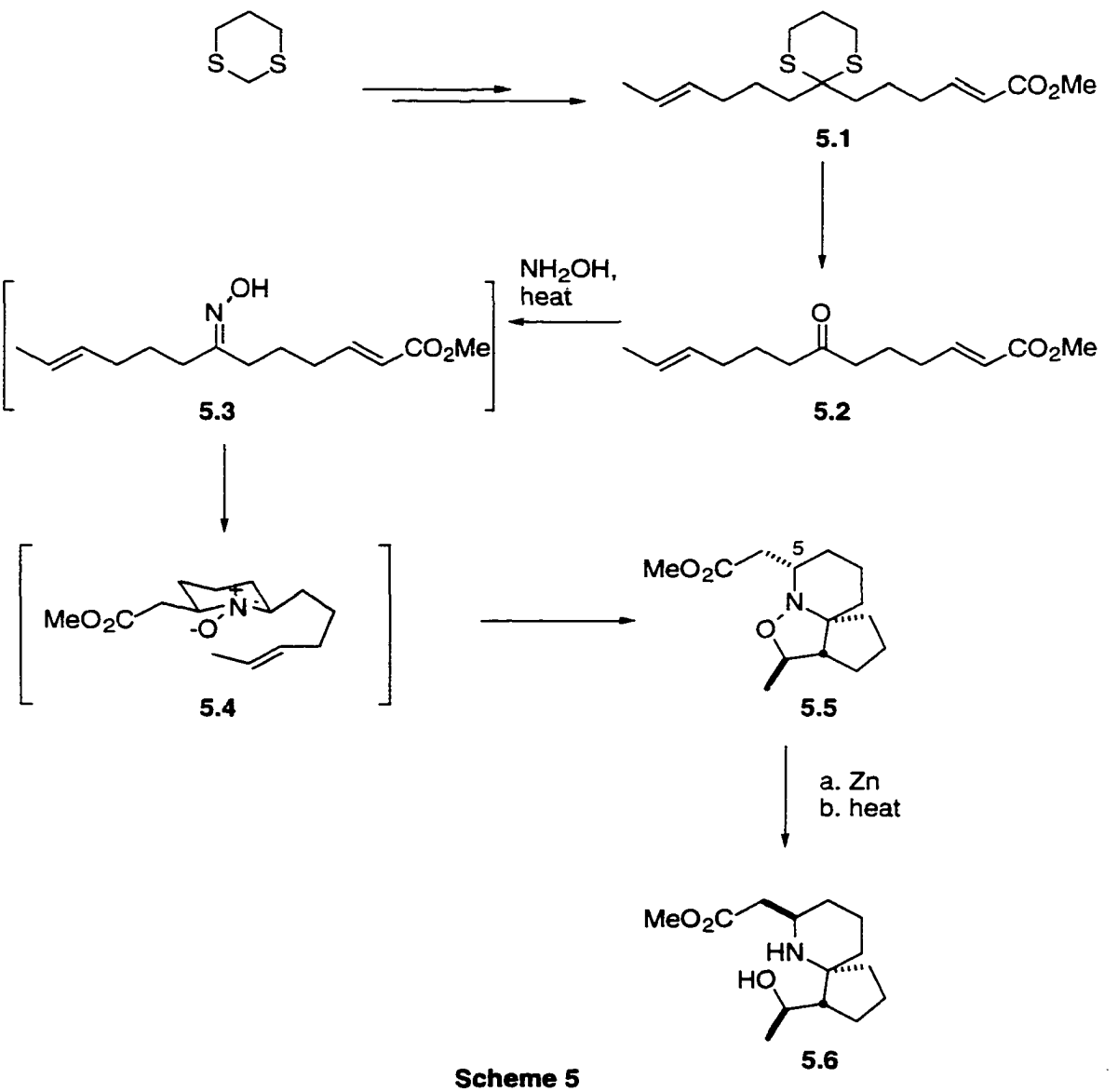
Scheme 4

converted into an amino group by way of a Curtius rearrangement, and the amino group was protected as its Cbz carbamate (**4.5** → **4.6**). The double bond was then cleaved by ozonolysis, and Horner-Emmons-Wadsworth coupling of with the top portion of the molecule gave **4.8**. Catalytic hydrogenation of **4.8** initiated a series of transformations in a single operation: saturation of the alkene, removal of the Cbz protecting group to release an amine, which condensed with the ketone to form a transient imine. This was also hydrogenated *in situ* to give the spirocyclic core of pinnaic

acid.

Zhao's Synthesis of the azaspirocyclic core

The synthetic studies reported[12] by Zhao *et al.* were based on sequential Michael addition and intramolecular [3+2] nitrone cycloaddition (**Scheme 5**). Enoate **5.1** was synthesized by dialkylation of 1,3-dithiane. The dithiane was then oxidatively cleaved to give ketone **5.2**. Heating the ketone in the presence of NH_2OH generated a transient oxime **5.3**, which underwent Michael addition of the nitrogen to the

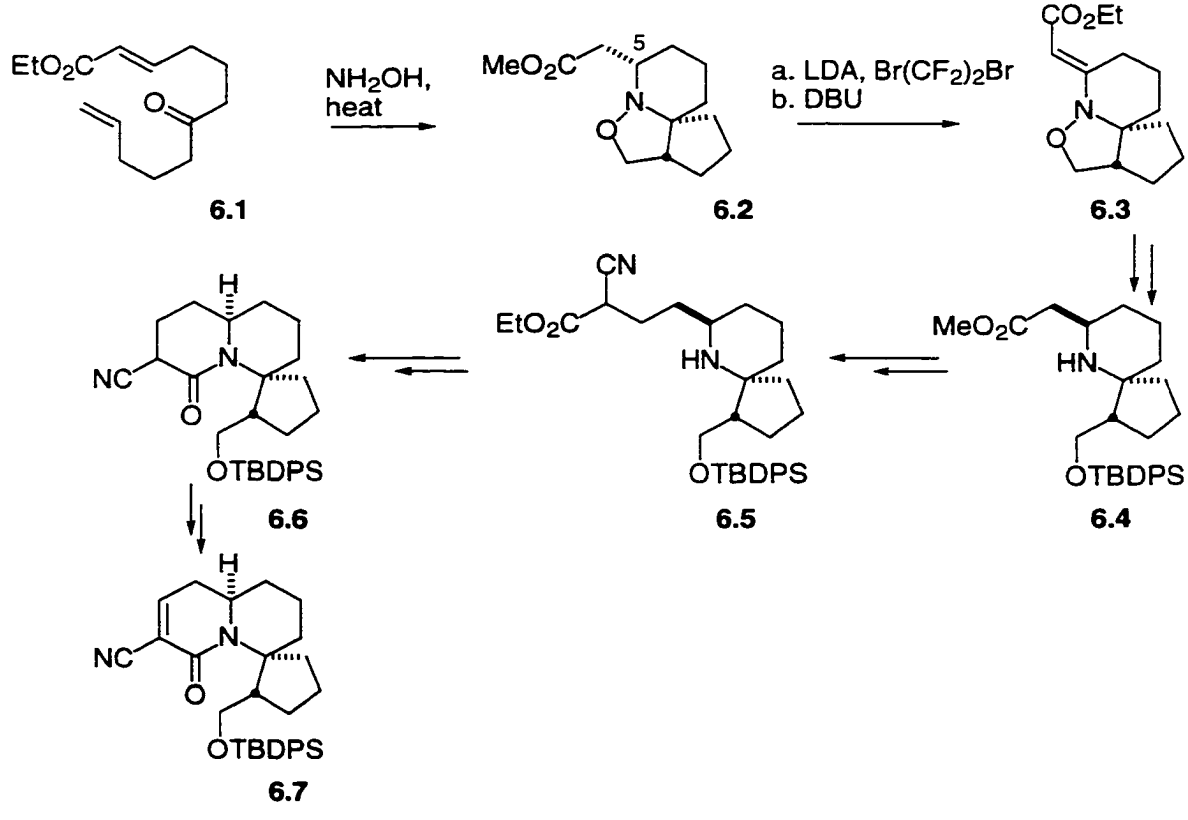


Scheme 5

enoate to form a nitrone which subsequently afforded cycloaddition adduct **5.5**. Compound **5.5** has all the required stereochemistry except at C(5). This center was epimerized thermodynamically through a retro-Michael–Michael reaction after the reductive cleavage of N-O bond, so as to give **5.6**, representing the core of halichlorine.

Shishido's synthesis of halichlorine core

Akin to Zhao's synthesis, Shishido reported[13] a route to the halichlorine core utilizing the same strategy of tandem Michael addition and nitrone [3+2] cycloaddition (**Scheme 6**). The C(5) center of **6.2** required epimerization. This was carried out by first creating the C(4)-C(5) double bond (**6.2** to **6.3**) and then hydrogenation. After reductive opening of the N-O bond and protection of the alcohol functionality, the ester **6.4** was homologated with cyanomalonate to give **6.5**.



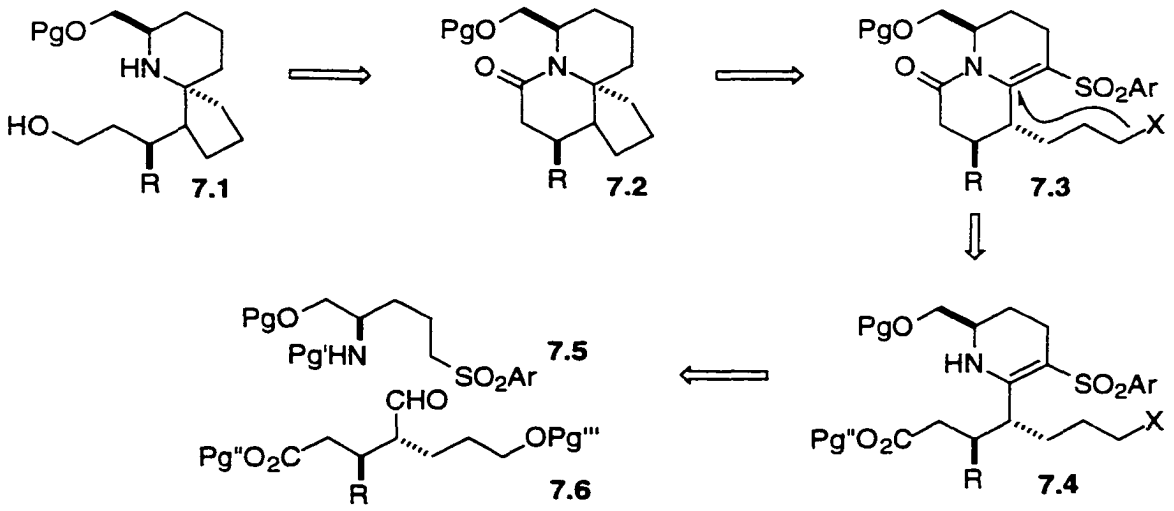
Scheme 6

The last ring was generated by an intramolecular acylation to give amide **6.6**. Introduction of the double bond was achieved by selenoxide elimination to afford tricyclic lactam **6.7** as the core of halichlorine.

Synthetic Studies on Halichlorine: Results and Discussion

Part 1. Synthetic Planning and Enantiospecific Synthesis of the Azaspirocyclic Core of Halichlorine

At the outset of our study we recognized that the main synthetic challenge of halichlorine resides in the densely functionalized azaspirocyclic core of the molecule. Therefore, our attention was focused on the efficient asymmetric synthesis of this core with the appropriate functionalities that would allow subsequent elaboration to the natural product. Retrosynthetically, the core structure **7.1** can be derived from reductive opening of the lactam ring of the tricyclic structure **7.2** (**Scheme 7**). Compound **7.2** can be derived by 5-*exo* radical cyclization of bicyclic lactam **7.3**, where X is a homolyzable group. We planned to utilize the rigidity of the bicyclic lactam to ensure the desired stereochemical outcome of formation of the five-membered ring. We felt that the bicyclic lactam **7.3** could be reached by intramolecular lactamization of piperidine **7.4**. Continuing our analysis, the piperidine ring was divided into



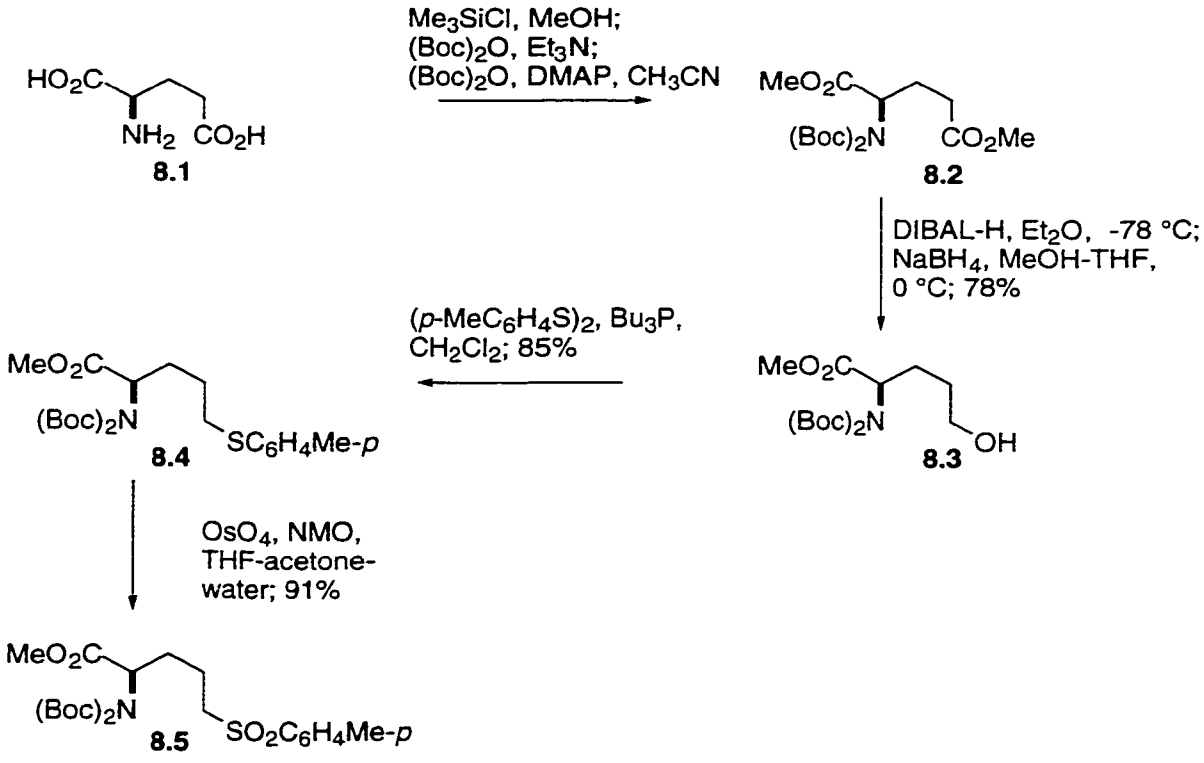
Pg, Pg', Pg", Pg''' = protecting groups, Ar = aryl, R = Me or H, X = homolyzable group.

Scheme 7

two fragments of similar complexity – the sulfone fragment **7.5** and the aldehyde fragment **7.6**, both being chiral.

Based on this plan, we embarked on the synthesis of the subunits. The sulfone fragment contains an amino alcohol functionality in which the stereogenic center is attached to the amino group; a readily available starting material would be (+)-glutamic acid. Following an existing literature procedure,[14] (+)-glutamic acid **8.1** was converted in three efficient steps into the di-Boc diester **8.2** (**Scheme 8**). Treatment with Me_3SiCl in dry MeOH generated HCl *in situ* and resulted in esterification of the diacid. After careful basification of the reaction mixture, the free amino group was acylated with *tert*-butyl dicarbonate. After aqueous work up, the second Boc group was introduced by stirring the crude diester in the presence of $(Boc)_2O$ and a catalytic amount of DMAP in MeCN to obtain **8.2** in >95% in each run. The second Boc group was needed for efficient reduction in the following step. The less sterically hindered ester group was regioselectively reduced with one equivalent of DIBAL-H in Et_2O at -78 °C to give the corresponding aldehyde (not shown), which was immediately reduced to alcohol **8.3** by 0.5 equivalent of $NaBH_4$ in 5:1 THF-MeOH. Attempted reduction of the ester directly to the alcohol, using 2 equivalents of DIBAL-H, gave a mixture of products. Therefore the reduction was carried out stepwise. Note that only 0.5 equivalent of $NaBH_4$ was used in the aldehyde reduction; if more than one equivalent was used, over reduction occurred at the Boc groups. The sulfide group was introduced under Mitsunobu conditions, in which tolyl disulfide was reacted in the presence of Bu_3P and alcohol **8.3** to give sulfide **8.4** in good yield. The sulfide was then oxidized by a catalytic amount of OsO_4 and NMO as the stoichiometric oxidant to give sulfone **8.5** in high yield.[15]

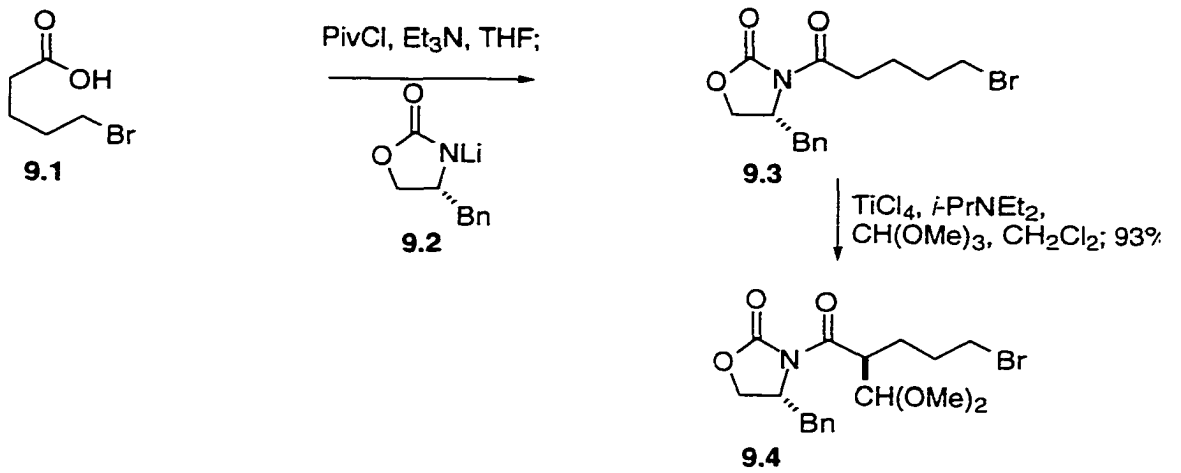
With sulfone **8.5** in hand, we turned our attention to the synthesis of the chiral aldehyde fragment. We decided to utilize methodology developed by Evans to introduce the



Scheme 8

necessary aldehyde functionality disguised temporarily as a dimethyl acetal.[16] Since a homolyzable group was needed later in the synthesis, we began by using 5-bromopentanoic acid to acylate the lithium salt of (*R*)-4-(phenylmethyl)-2-oxazolidinone **9.2**. (*R*)-4-(phenylmethyl)-2-oxazolidinone was easily obtained from an efficient three step synthesis starting from (*R*)-phenylalanine.[17] The acylation was accomplished via the mixed pivalic anhydride, in which the bromine functionality will serve to generate a primary radical (**Scheme 9**). Diastereoselective alkylation of imide **9.3** (through its titanium enolate) with $HC(OMe)_3$ gave the dimethyl acetal **9.4** in high yield and diastereoselectivity (>99%).[16]

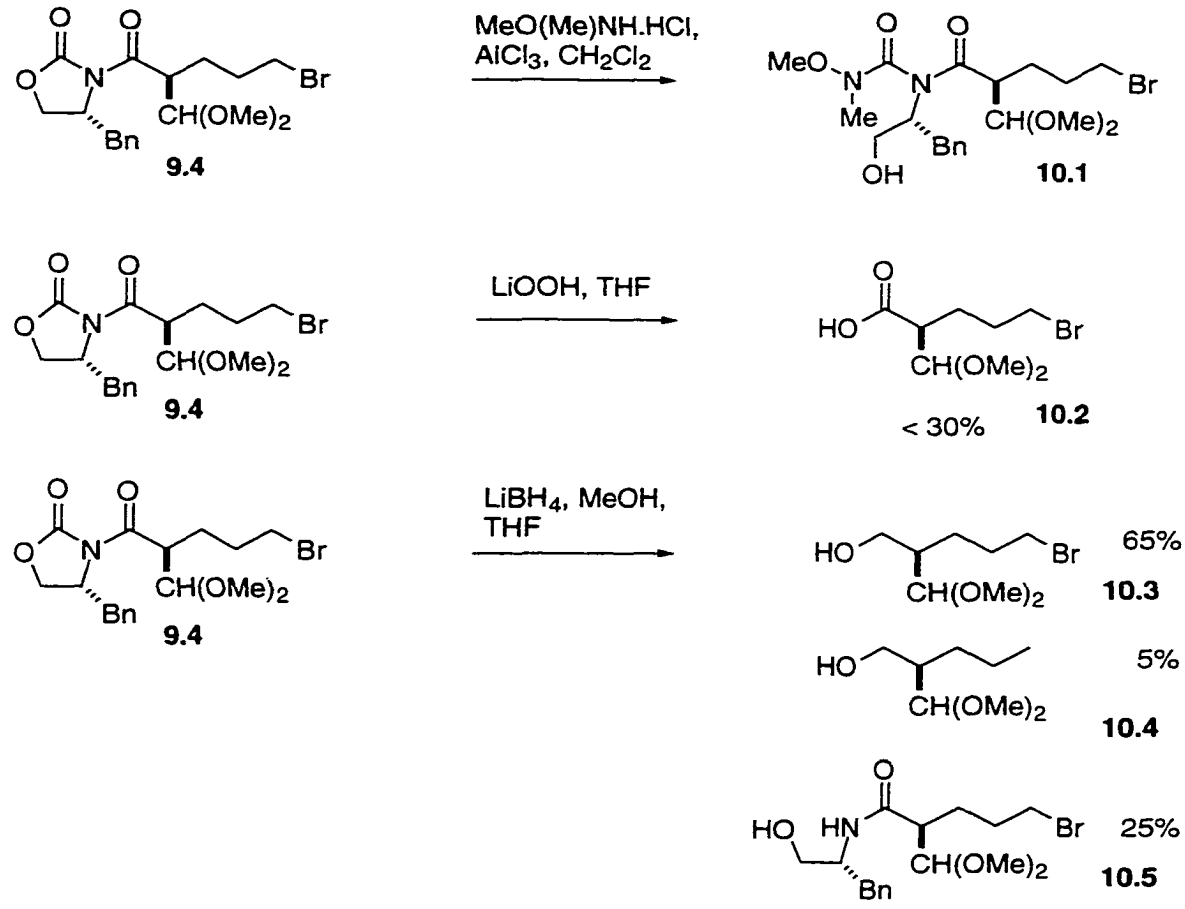
After serving its purpose of assisting alkylation, the chiral auxiliary needed to be removed. Surprisingly, this step turned out to be not trivial (**Scheme 10**). Transamination with MeO(Me)NH.HCl and Me_3Al[18] – a standard



Scheme 9

method for the formation of a Weinreb amide – gave only the ring-opened product **10.1**. After a careful examination of the literature examples, we recognized that most of the successful cases contain a free hydroxyl group at the β-position, which greatly assists the transamination process.[19] A mixture of transaminated product and ring-opened product is usually obtained in examples without a β-hydroxy functionality.[20] In our case, the bulky group at the α-position completely inhibited the desired transamination process. Hydrolysis of the imide using LiOOH in THF[21] gave a very low recovery of the desired acid **10.2**. Fortunately, reductive cleavage of the auxiliary could be achieved using 1.1 equivalents of $LiBH_4$ and 1.1 equivalents of MeOH,[22] and the desired alcohol **10.3** was isolated in 65% yield. The product mixture also contained the ring-opened product **10.5** in 25% and the debrominated alcohol **10.4** in 5% yield, respectively. Although the yield of **10.3** is not as high as we would like, we settled on this method of auxiliary cleavage. From these experiments we also learned that the primary bromine is quite labile, and we had to resort to using a protected alcohol in the starting material; the alcohol would be converted later in the synthesis into a homolyzable group.

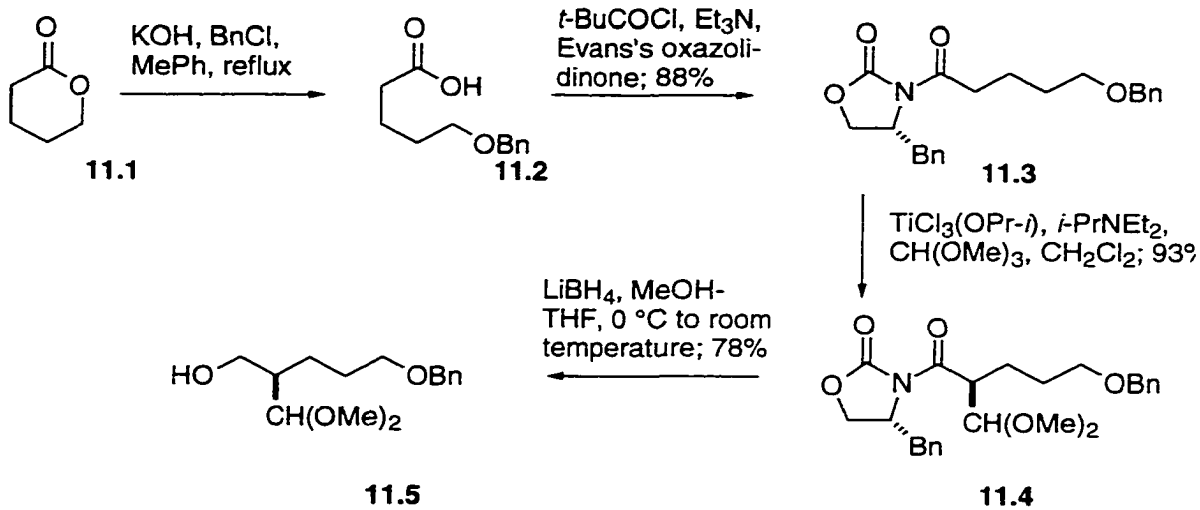
To this end, we began the synthesis again using δ-



Scheme 10

valerolactone. Following a procedure published by Weiler,[23] the lactone was hydrolyzed and protected as its benzyl ether, using KOH and BnCl in refluxing PhMe, so as to give acid **11.2** (**Scheme 11**). This acid was acylated with the lithium salt (**9.2**) of oxazolidinone via the mixed pivalic anhydride. Imide **11.3** was alkylated diastereoselectively via its titanium enolate, in the same way as shown above. A milder Lewis acid, $TiCl_3(OPr\text{-}i)$, was used instead of $TiCl_4$ in order to obtain a higher yield of the alkylation product **11.4**. Reductive cleavage of the oxazolidinone was best carried out using $LiBH_4$ (1.1 equivalents) and MeOH (1.6 equivalents) to give the desired alcohol in 78%, with the remaining material being the ring opened product (cf. **10.5**).

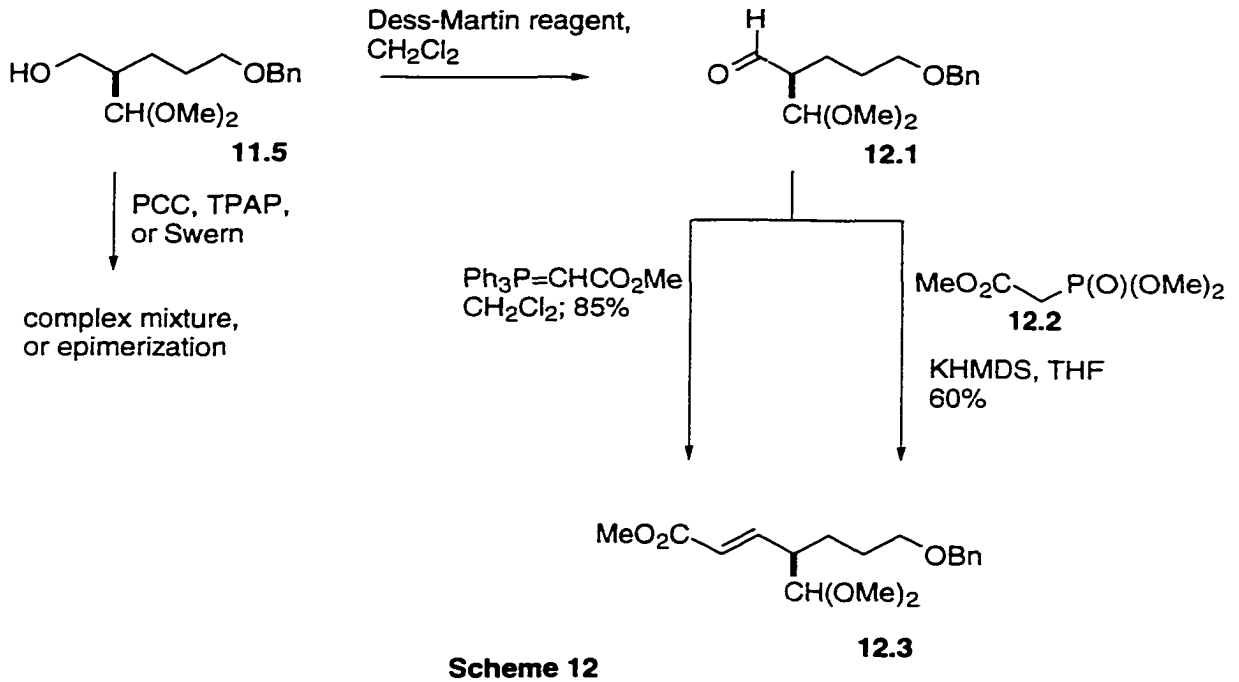
With alcohol **11.5** in hand, we examined methods for its homologation. After several experiments, we found that the



Scheme 11

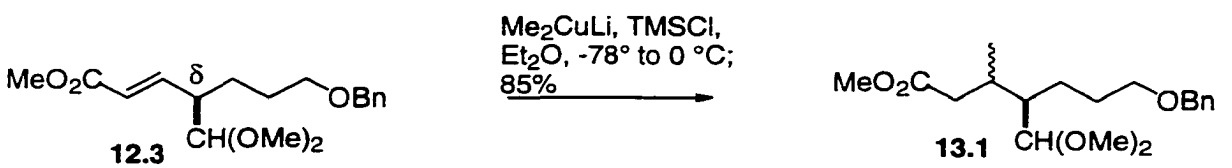
best reagent for oxidation of alcohol **11.5** to the very sensitive aldehyde **12.1** was the Dess-Martin periodinane.[24] Oxidation with TPAP/NMO[25] gave a low yield of the aldehyde, and PCC gave a complex mixture. Moreover, Swern oxidation afforded an epimerized product. Aldehyde **12.1** is sensitive to both acid and base, and it decomposes on silica or on standing in a concentrated solution. Therefore, it was usually used immediately after preparation, and as a crude isolate. A couple of methods were investigated for the Wittig olefination of aldehyde **12.1**. Use of the potassium salt of phosphonate **12.2** gave the alkenoate **12.3** in ca 60% yield. On the other hand, the stabilized ylide $Ph_3P{=}CHCO_2Me$ gave **12.3** in 85% from alcohol **11.5**.

With **12.3** in hand, we were now in a position to introduce the C(22) methyl group of the side chain. There are several literature examples of diastereoselective addition of organocuprate species to alkenoates with a δ stereogenic center, although most of the examples have a hydroxy substituent at the δ center.[26] We decided to try the conjugate addition with alkenoate **12.3**, hoping that the bulky dimethyl acetal unit would direct addition of methylcuprate diastereoselectively. Disappointingly, the addition of Me_2CuLi to **12.2** in the presence of Me_3SiCl[27] gave 1:1 mixture



Scheme 12

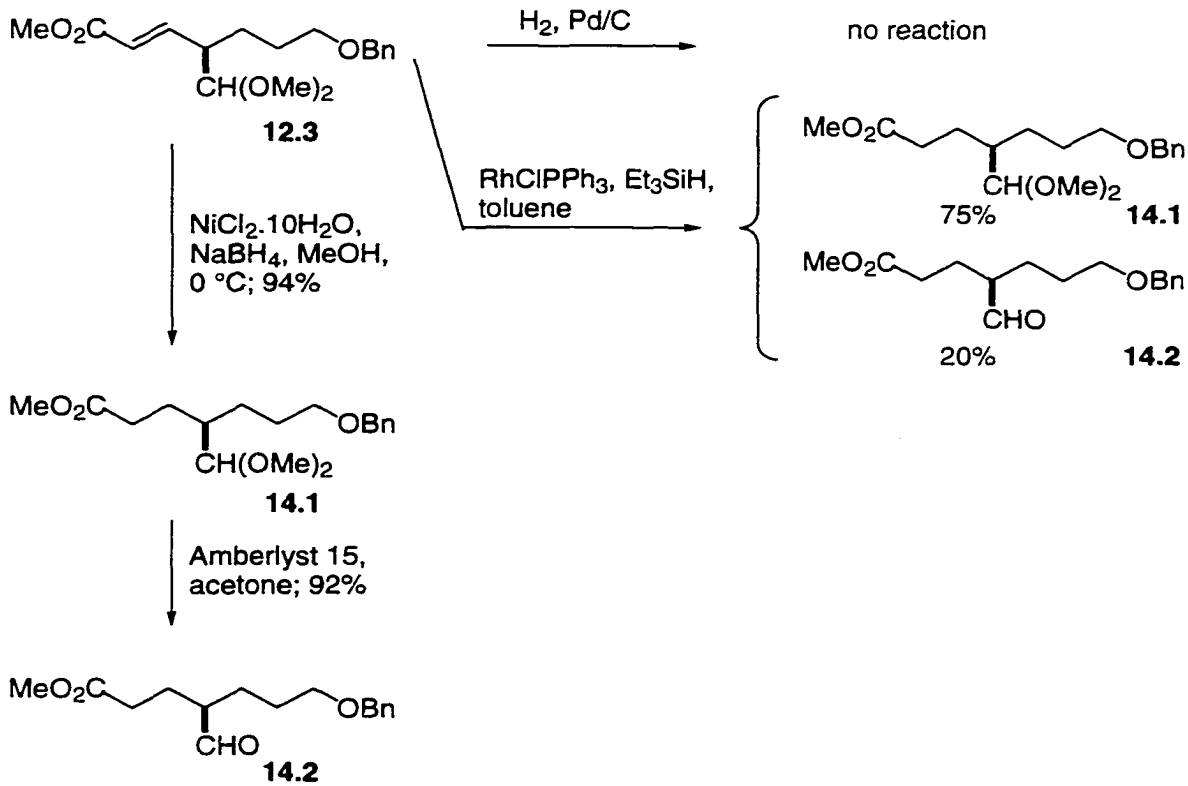
of the methyl adducts **13.1** (**Scheme 13**). Therefore, we decided to introduce the methyl group later in the synthesis, either at the tricyclic lactam stage (cf. **7.2**, **Scheme 7**) or at the present stage, but with the aid of a chiral auxiliary (*vide infra*).



Scheme 13

The double bond of **12.3** was reduced with nickel boride, generated in situ by reduction ($NaBH_4$) of a catalytic amount of $NiCl_2.6H_2O$ in cold MeOH, to give the saturated ester **14.1** in 94% (**Scheme 14**).[28] Other methods examined for this process included hydrogenation with H_2 and Pd/C, but under these conditions no reaction was observed. Under more forcing conditions, such as use of high pressure or high temperature, only decomposition mixtures were obtained. It

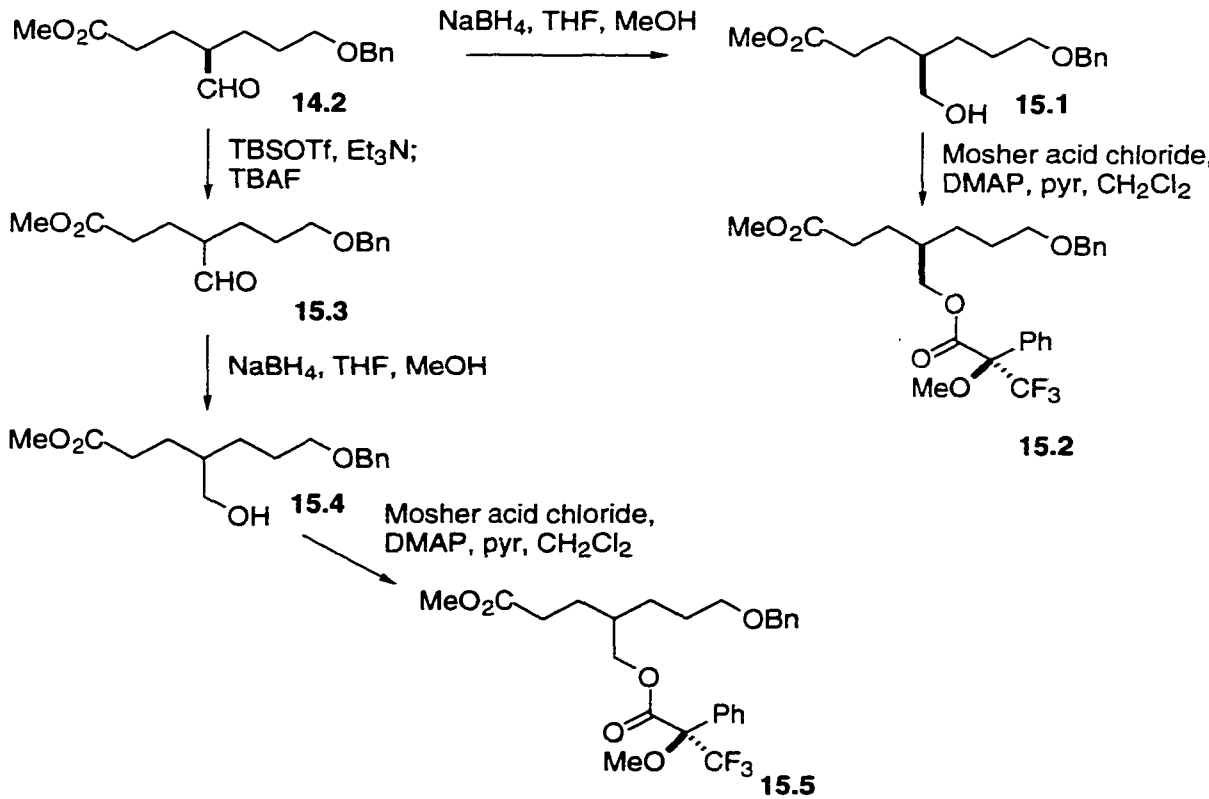
is reasonable to postulate that the bulky group next to the olefin prohibits efficient binding of the catalyst. Interestingly, use of Wilkinson's catalyst in a hydrosilation reaction,[29] gave the desired product **14.1** in 75% yield, accompanied by 20% of aldehyde **14.2**. The dimethyl acetal group in **14.1** is labile towards the Lewis acidic rhodium catalyst. Although this is inconsequential in the following step, the cleanness of the nickel boride reduction commended it as the reagent of choice for the olefin reduction. Finally, the dimethyl acetal was cleaved using Amberlyst-15



Scheme 14

in acetone[30] to give aldehyde **14.2** in 92% yield. This aldehyde was stable towards chromatography, but it was usually used crude. The optical purity of aldehyde **14.2** was determined by ^{19}F NMR on the Mosher ester derivative of the corresponding alcohol (**Scheme 15**). A single peak at δ -72.03 ppm with no signs of a shoulder was observed. For

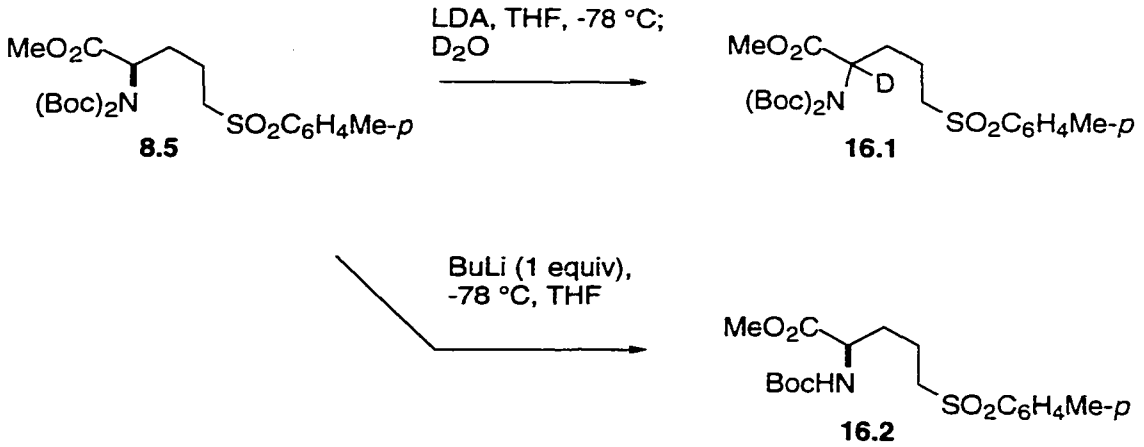
comparison, the racemic alcohol was synthesized by the epimerization of the aldehyde via the silyl enol ether, and then treatment with TBAF followed by reduction (**14.2** to **15.4**). The derived Mosher esters showed two peaks at δ -72.03 ppm and -72.01 ppm. This observation shows that there was no epimerization over the course of our synthetic sequence up to this point.



Scheme 15

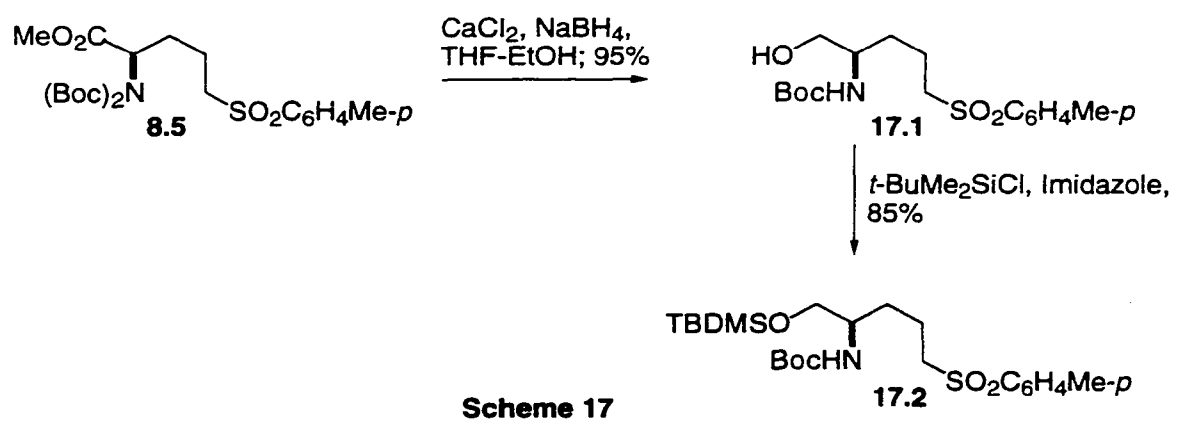
Before we committed aldehyde **14.2** to the crucial coupling step, we first examined the feasibility of using sulfone **8.5** to generate a nucleophilic anion. In a deprotonation study, using one equivalent of LDA, followed by quenching with D_2O, we found that deuterium was incorporated at the α-position next to the ester group (**Scheme 16**). In a similar experiment, using one equivalent of *n*-BuLi as base, we found that one of the Boc groups was cleaved. We concluded from these experiments that the ester group and the

di-Boc imide are too labile under conditions generally used for sulfone anion generation, and therefore these groups needed to be replaced.



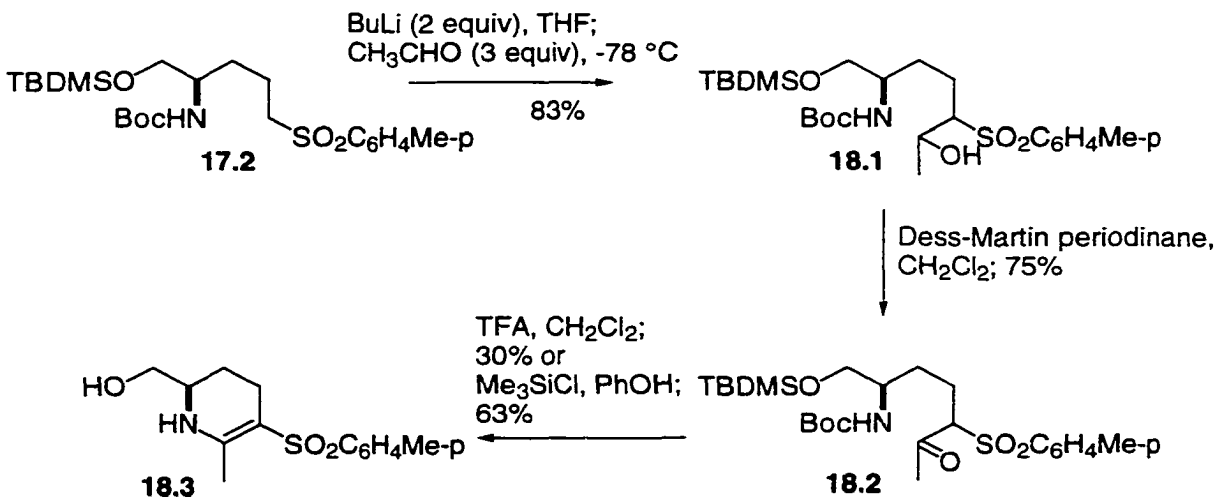
Scheme 16

Reduction of the ester group was achieved by treatment with $Ca(BH_4)_2$, generated *in situ* from the combination of anhydrous $CaCl_2$ and $NaBH_4$ in 1:1 THF-EtOH, to give alcohol **17.1** in high yield (95%) (**Scheme 17**). Under the above conditions one of the Boc groups was also cleaved, and hence we achieved two goals in one step. Interestingly, reduction of ester **8.5**, using an excess of DIBAL-H, gave a mixture of products consisting of alcohol **17.1** and the corresponding aldehyde. Alcohol **17.1** was then protected as its silyl ether **17.2** by reaction with *t*-$BuMe_2SiCl$ and imidazole.



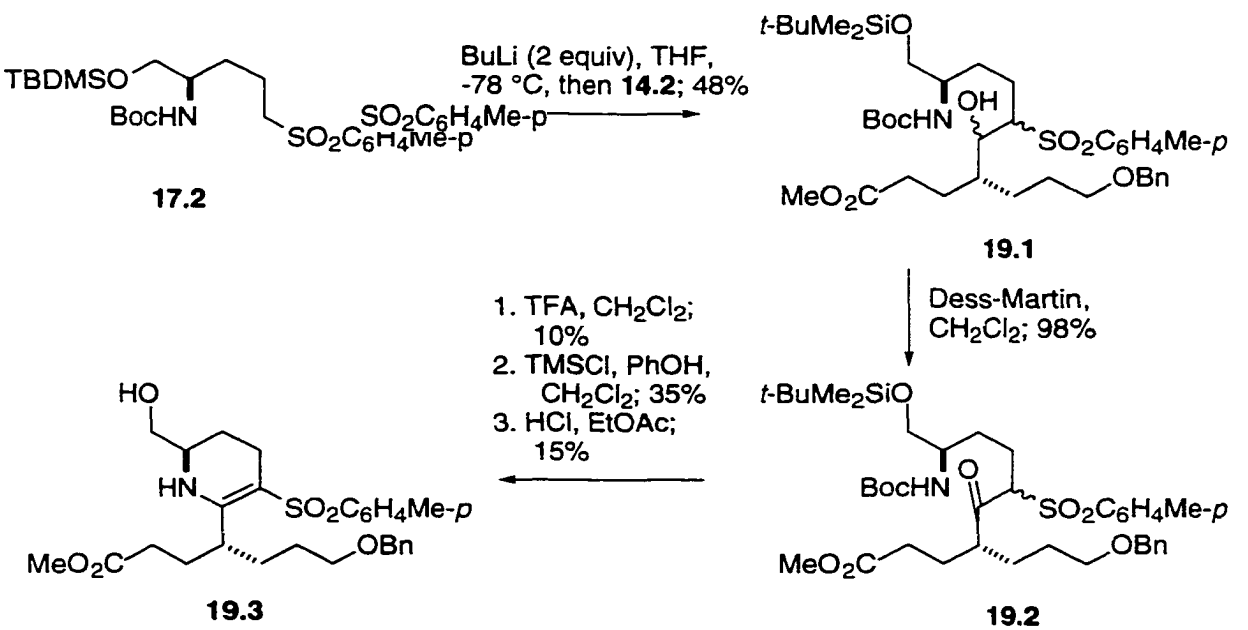
Scheme 17

Sulfone **17.2** was also subjected to a model study for the coupling reaction. The dianion of **17.2** was generated by treatment with 2 equivalents of *n*-BuLi in THF at -78 °C to give a bright yellow solution characteristic of sulfone anions. An excess of acetaldehyde was then slowly added to the dianion to quench the bright yellow color (**Scheme 18**). Hydroxy sulfone **18.1** was isolated from this reaction in 83% yield, as an inseparable mixture of diastereomers. Oxidation of the alcohol with the Dess-Martin periodinane gave ketone **18.2**. We anticipated that the liberated amino group would condense onto the ketone to form an enamine *in situ*. Therefore, removal of the Boc group under standard conditions (CF_3CO_2H in CH_2Cl_2) gave piperidine **18.3**, but in only 30% yield. Under different conditions (use of Me_3SiCl and PhOH[31] to generate HCl) **18.3** was obtained in 60% yield. In both cases, the silyl protecting group did not survive the strongly acidic conditions required for Boc cleavage, but we learned from these model studies that the desired piperidine ring could indeed be formed from ketone **18.2**, once the protecting group on the nitrogen had been removed.



Scheme 18

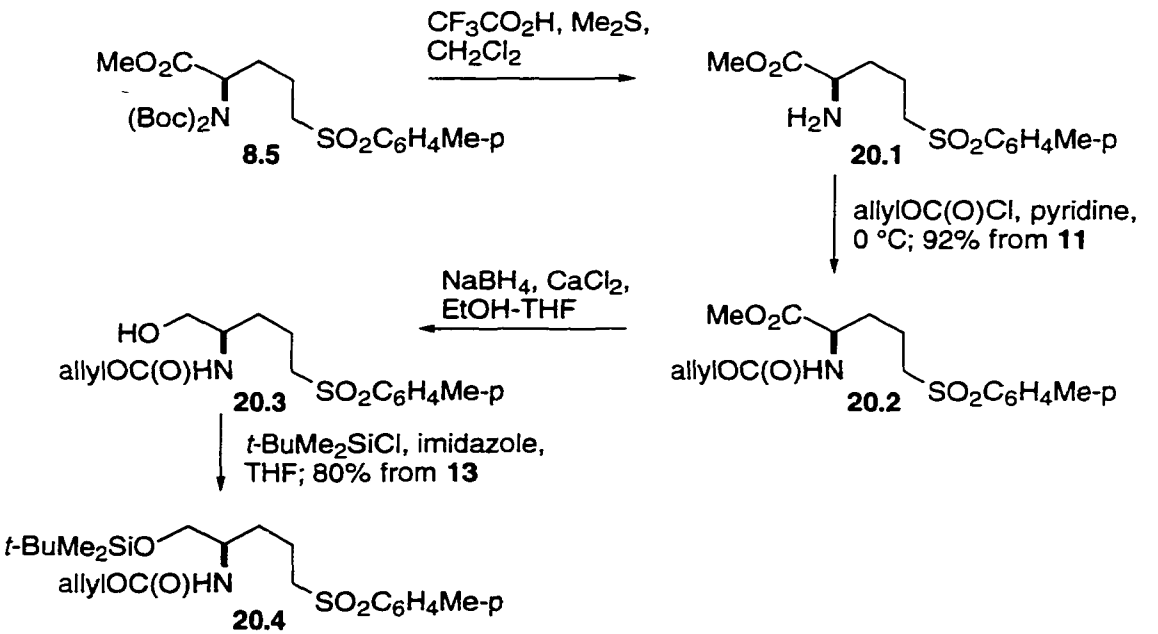
We felt confident that the same conditions used in our model study could also be applied to the coupling of sulfone **17.2** to aldehyde **14.2**. Hence, aldehyde **14.2** was added to a solution of the dianion of **17.2**, generated as described above. This procedure gave the desired hydroxy sulfones **19.1** in 48% yield. (**Scheme 19**). Although the yield is very modest, we decided to press on with our study. The hydroxy sulfones were oxidized by the Dess-Martin periodinane to give ketone **19.2**. To our dismay, formation of the piperidine ring was not as simple as in the model system. Under various conditions examined, **19.3** was obtained only in low yields. We conclude from these results that either the product **19.3** or the starting material could not withstand the strongly acidic conditions required for Boc cleavage. We decided, therefore, to use a different protecting group on nitrogen – one that could be removed under much milder conditions.



Scheme 19

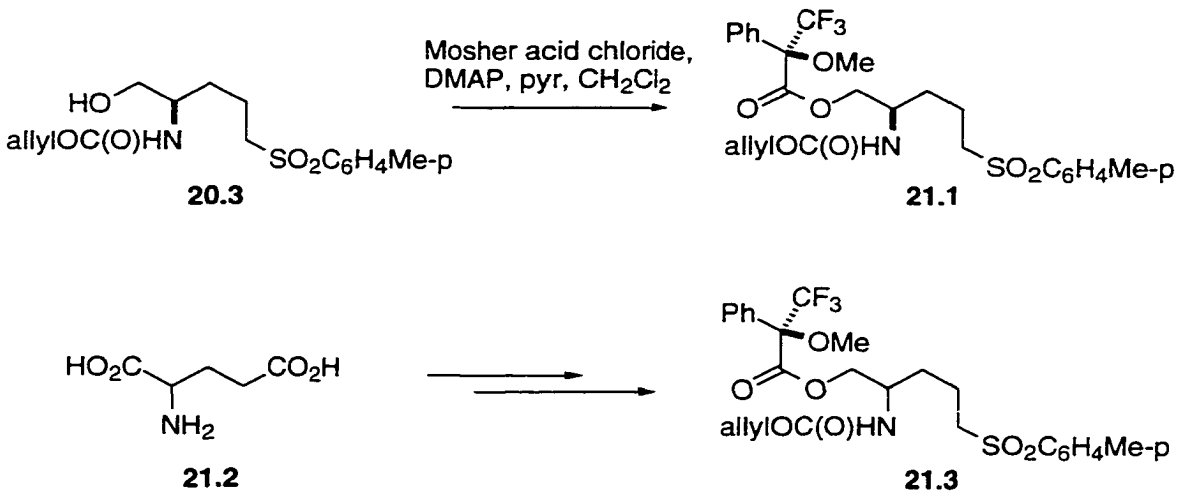
An alloc group (allyloxycarbonyl) was chosen for the task of nitrogen protection since it can be removed under very mild conditions, generally by catalysis with a form of Pd(0). The alloc group was introduced into the sulfone

fragment, starting from ester **8.5**. The Boc groups of **8.5** were removed by treatment with CF_3CO_2H in CH_2Cl_2 to give the amine **20.1** (**Scheme 20**). We found that the yield could be significantly improved if Me_2S was added to the reaction mixture to act as a trap for the highly reactive *t*-Bu^+ cation.[32] The amine, which was generally used without purification, was acylated with allyl chloroformate, using pyridine as a base, to give **20.2** in 92% yield from **8.5**. Once again, the ester was reduced with $CaCl_2/NaBH_4$ so as to give alcohol **20.3**, which was silylated without purification. In this way **20.4** was obtained in 80% yield after silica chromatography.



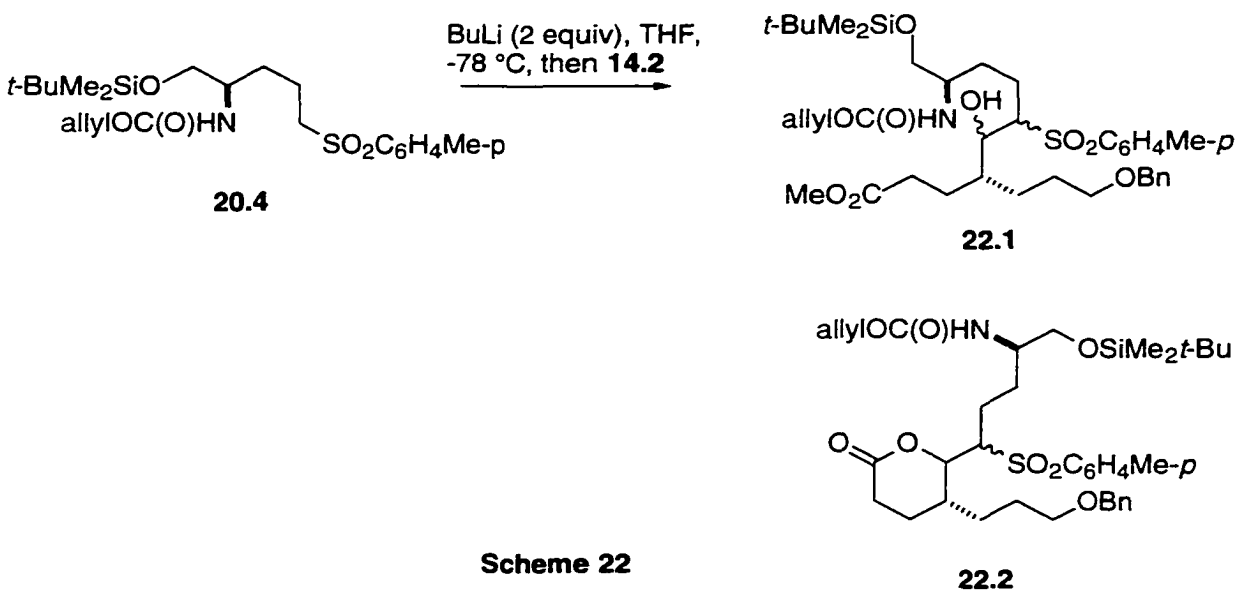
Scheme 20

The optical purity of the sulfone fragment was also examined by ^{19}F NMR of the Mosher ester **21.1** derived from alcohol **20.3** (**Scheme 21**). The spectrum showed a single peak at δ -71.96 ppm. For comparison, the racemic mixture of alcohols corresponding to **20.3** was synthesized from racemic glutamic acid (**21.2**); the derived Mosher esters **21.3** showed two distinct peaks at δ -71.98 ppm and -72.02 ppm.



Scheme 21

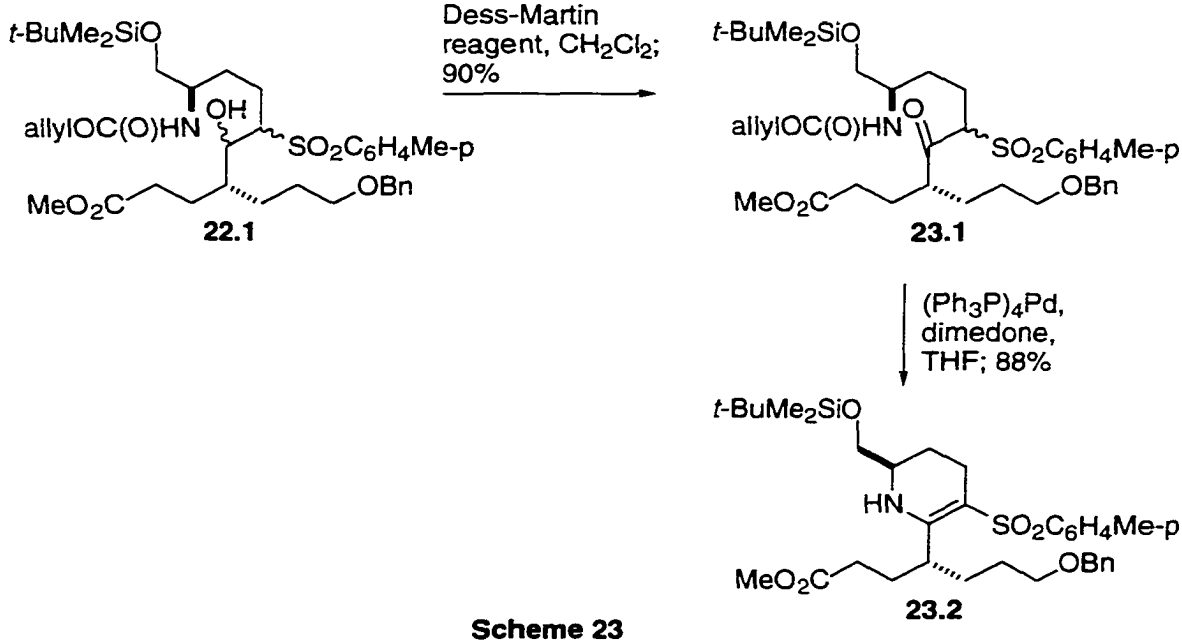
With sufficient sulfone **20.4** in hand, we decided to optimize the yield of the crucial coupling step. After



Scheme 22

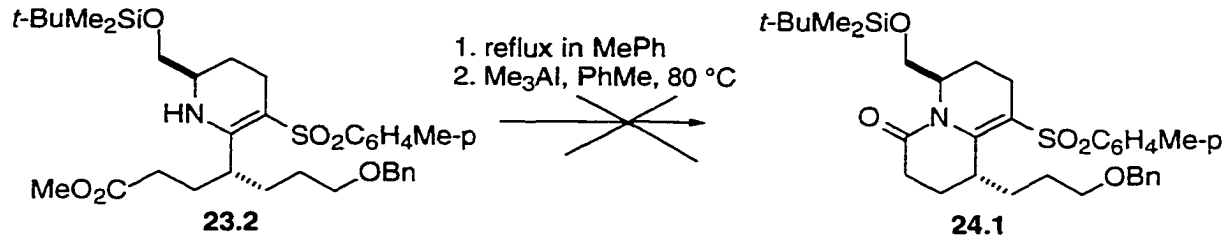
careful analysis of the product mixture from the coupling reaction we found lactone **22.2** as the major side product, which was usually isolated in 20 to 30% yield. In theory the lactone could be converted into **22.1** by hydrolysis and esterification, but we found that formation of lactone **22.2** could be suppressed if the aldehyde was added slowly via a syringe pump into the dianion solution. This procedure gave

the desired **22.1** in 77% yield. Oxidation of **22.1** with the Dess-Martin periodinane gave ketone **23.1** in 90% yield (**Scheme 23**). Treatment of ketone **23.1** with a catalytic amount of $(Ph_3P)_4Pd$, with dimedone as the allyl acceptor, then gave the desired **23.2** (88%), which was isolated as a single isomer. Having reached **23.2**, we felt we had made a key intermediate in our synthetic sequence.



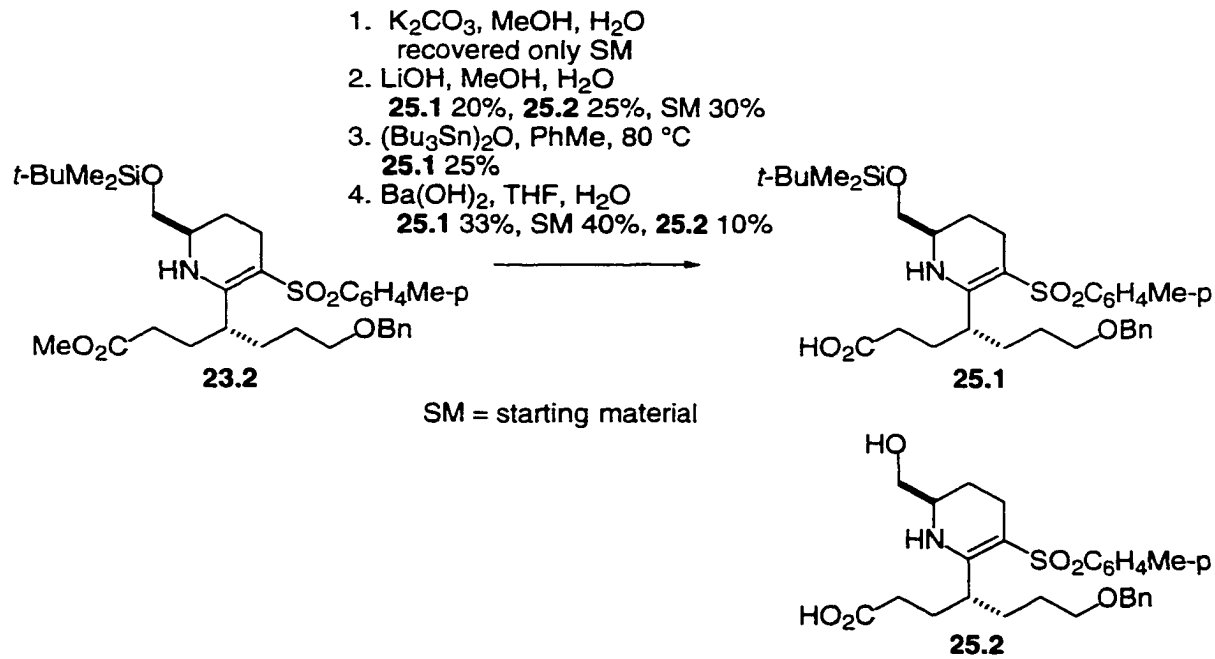
Scheme 23

Based on our original synthetic planning, we wished to use the ester functionality on the side arm to form a temporary intramolecular tether in the form of a six-membered lactam, in order to control the stereochemical outcome of the subsequent radical cyclization that generates the five-membered ring (*vide supra*). To implement this strategy we examined ways to form the lactam. In more direct approaches, such as heating **23.2** in PhMe at reflux, or using Me_3Al to activate the nitrogen nucleophile, none of the desired lactam **24.1** was formed and we recovered only the starting material (**Scheme 24**). More forcing conditions, such as longer reaction times or elevated temperatures, led to decomposition products. We then turned to the stepwise approach of



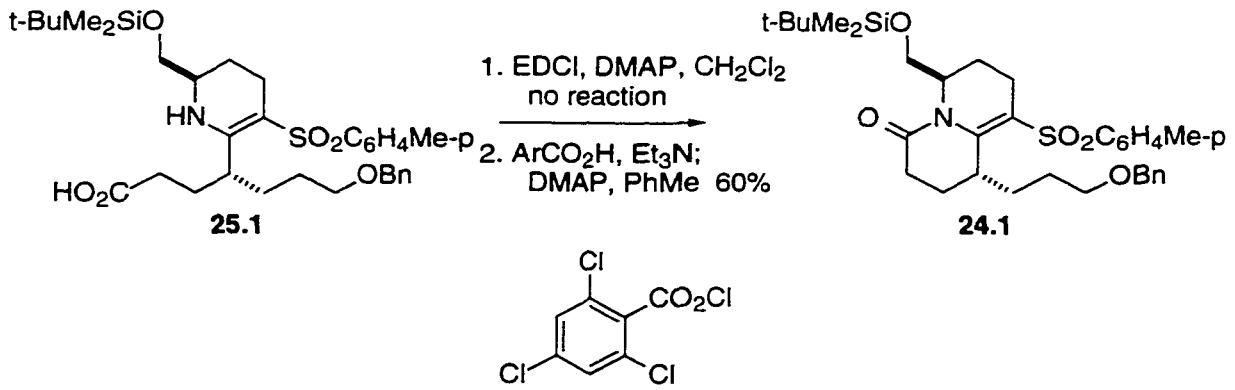
Scheme 24

hydrolyzing the ester to the corresponding acid, followed by intramolecular acylation. To our surprise, the methyl ester was unusually resistant to hydrolysis. Moreover, the silyl protecting group was found to be labile under the reaction conditions examined (**Scheme 25**). Hydrolysis using a base such as K_2CO_3, LiOH, or $Ba(OH)_2$ in $MeOH/H_2O$ or THF/H_2O gave only the starting material, or a mixture of products containing starting material and acids **25.1** and **25.2** in ratios given in Scheme 25. Similarly, a non-aqueous method, involving $(Bn_3Sn)_2O$[33] as a Lewis acid for cleavage of methyl esters, also gave predominantly the starting material with a small amount of the desired acid.



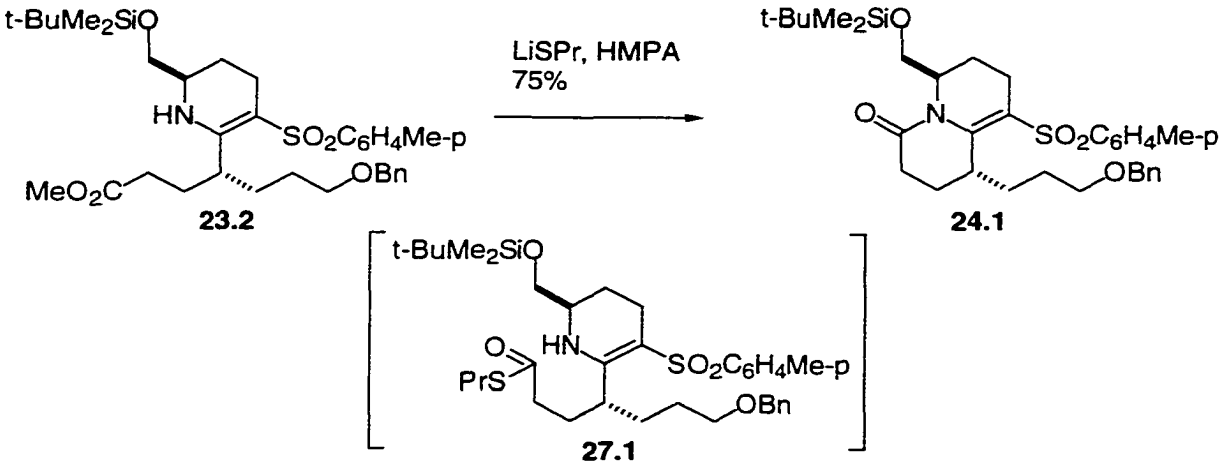
Scheme 25

Despite these difficulties, we were able to obtain enough acid **25.1** to investigate the intramolecular acylation. We found that the usual acylating reagents, such as EDCI, DCC or $Im_2C=O$, were not effective for ring formation. At this point we were convinced that the nitrogen is not particularly nucleophilic due to conjugation with the electron-withdrawing sulfone group, and therefore many of the reactions that work well for ordinary intramolecular acylations break down in our case. Fortunately, under Yamaguchi conditions – which involves activation of the acid as a mixed anhydride with 2,4,6-trichlorobenzoyl chloride[34] – we were able to obtain the desired lactam **24.1** in acceptable yields (**Scheme 26**).



Scheme 26

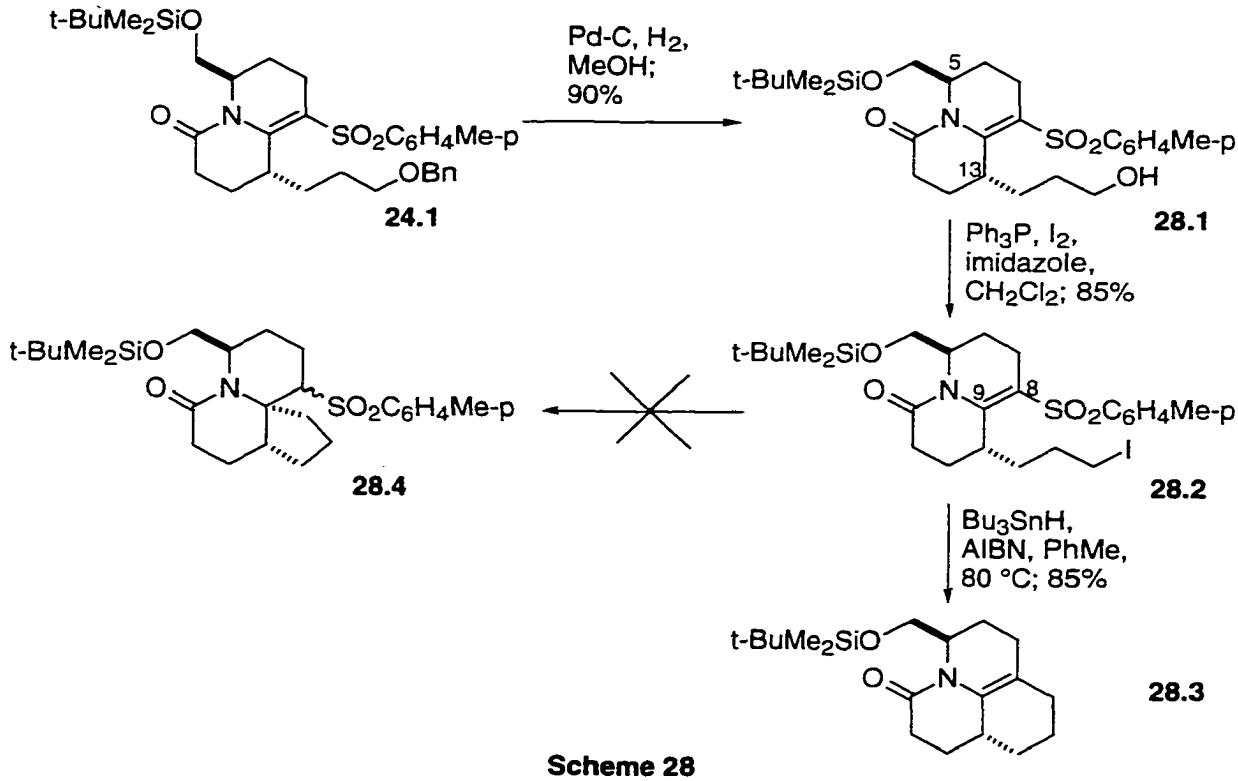
We realized that, in order for our synthetic plan to work, it was essential that we overcome the difficulty of ester hydrolysis. In search of a method that does not involve a basic aqueous reaction medium, we turned our attention to cleavage of esters by a nucleophilic mechanism. Treatment of ester **23.2** with PrSLi,[35] generated from *n*-BuLi and PrSH in HMPA, gave – to our surprise – the desire lactam **24.1** (75%), accompanied by 10% of acid **25.1**. A possible mechanistic explanation for this outcome might be that a thioester intermediate **27.1** was first generated by the attack of PrS^-, followed by capture of the nitrogen on this rather activated acyl group (**Scheme 27**). This fortuitous discovery



Scheme 27

should be further explored for use in intramolecular lactamizations and lactonizations, particularly in cases where conventional methods fail. Moreover, this procedure eliminates the ester hydrolysis step in our work.

With the crucial bicyclic lactam **24.1** now available, we progressed towards implementing the radical ring closure to generate the spirocyclic five-membered ring. The benzyl ether was cleaved under standard hydrogenation conditions to release alcohol **28.1** (**Scheme 28**). The compound was a solid and we were able to recrystallize it from CH_2Cl_2-hexane to obtain a crystal suitable for X-ray analysis. The structure (page 181) corroborated our assignment based on NMR measurements, and assured us that the stereochemistry of the two stereogenic centers at C(5) and C(13) was correct. Alcohol **28.1** was converted into iodide **28.2** by treatment with I_2, Ph_3P and imidazole. Radical cyclization was conducted by slow addition (syringe pump) of a PhMe solution of Bu_3SnH and a catalytic amount of AIBN to a warm (80 °C) solution of iodide **28.2** in the same solvent. Much to our surprise, cyclization occurred via the 6-*endo* pathway, to generate tricyclic compound **28.3** instead of the desired **28.4**. We were very perplexed with this result since 5-*exo* radical ring cyclization generally occurs at a much higher

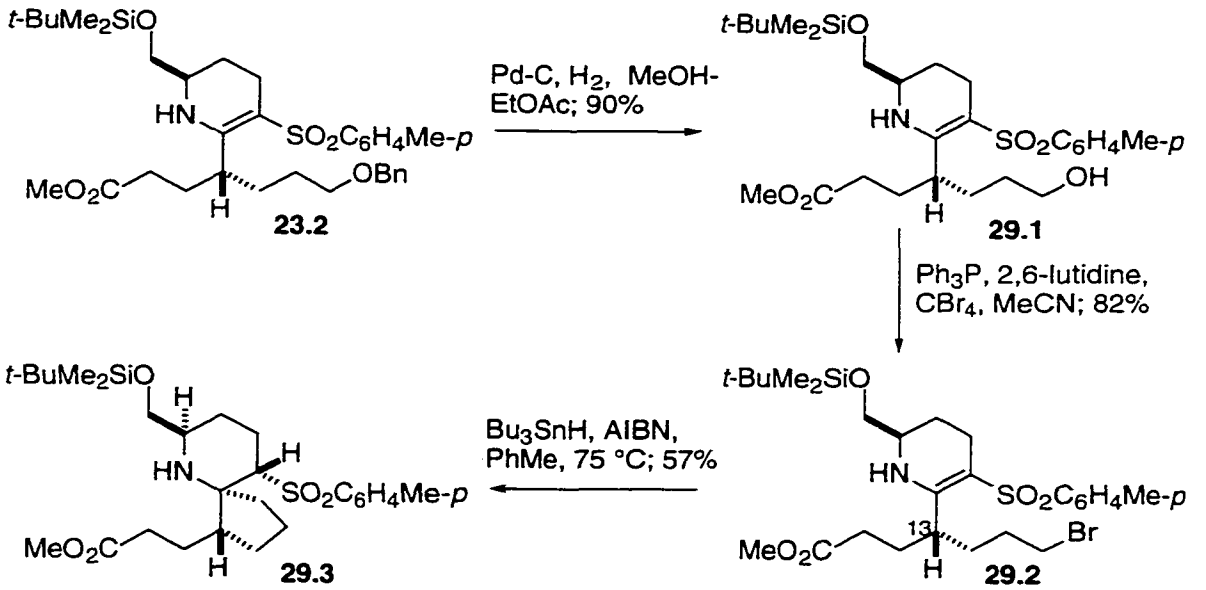


Scheme 28

rate than the 6-*endo* pathway (k_{5exo} = 2 x 10^5 sec^{-1} versus k_{6endo} = 4 x 10^3 sec^{-1}).[36] Moreover, in our example, the olefin is activated by an electron-withdrawing sulfone that we incorporated to aid the desired 5-*exo* cyclization. We attributed the observed abnormality to the constraints imposed by the rigid lactam ring, and we believe that the side chain involved in the cyclization was able to reach C(8) more easily than C(9), which is required for the 5-*exo* pathway to occur.

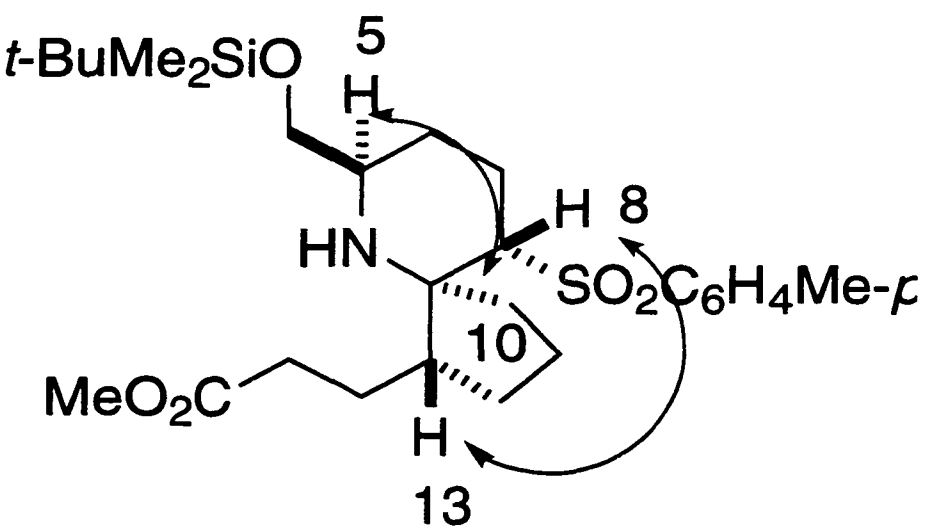
Hampered by this result, we decided to attempt the cyclization without the constraint of the lactam ring. To apply this change in strategy, the benzyl ether **23.2** was deprotected by hydrogenolysis to give alcohol **29.1**, which was converted into bromide **29.2** (CBr_4, PPh_3 and 2,6-lutidine, **Scheme 29**).

Radical cyclization was carried out by slow addition (syringe pump) of a PhMe solution of Bu_3SnH and a catalytic amount of AIBN to a warm (75 °C) and very dilute (0.02 M)



Scheme 29

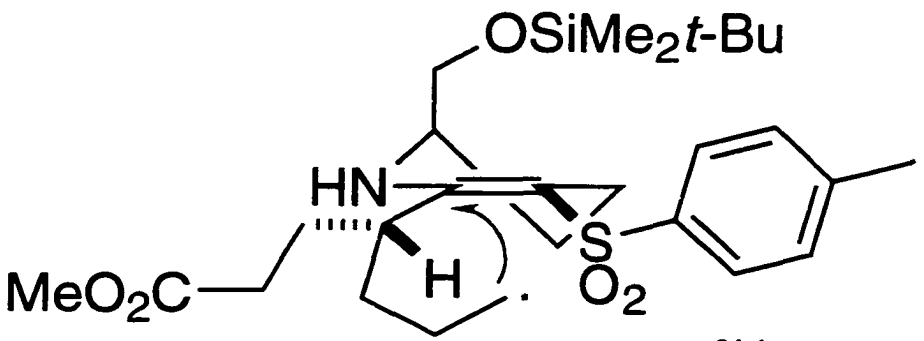
solution of bromide **29.2**, also in PhMe. Under these optimum conditions, the spirocyclic compound **29.3** was obtained in 57% yield as a single isomer, accompanied by the simple reduction product (replacement of Br by H, 30%). It was necessary to keep the temperature below 80 °C in order to suppress intramolecular S_N2 cyclization of the amino group onto the primary bromide. The structure of **29.3** was rigorously established by NMR experiments, which included G-COSY, HMQC,



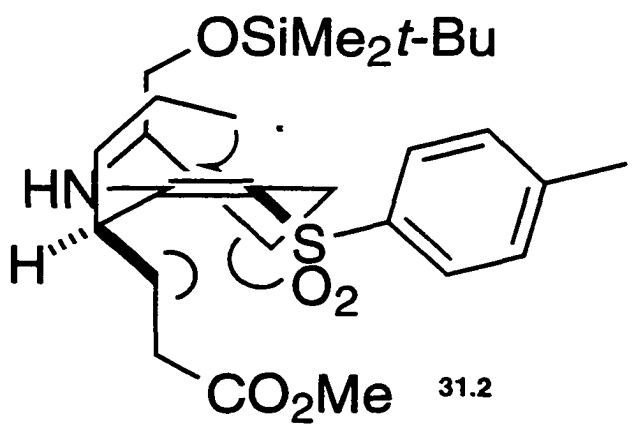
Scheme 30

HMBC, and T-ROESY measurements. Key T-ROESY cross-peaks were observed between H(5) and one of the H(10) hydrogens, and between H(13) and H(8) (**Scheme 30**).

The cyclization was regiospecific, and no 6-*endo* product was observed. We believe that the selectivity is controlled by the C(13) stereogenic center, which favors conformer **31.1** during the cyclization; consequently, the desired stereochemistry is generated at the quaternary center (**Scheme 31**). On the other hand, conformer **31.2**, which would lead to the wrong stereochemistry, has the ester group so disposed that it would suffer steric interactions with the sulfone group.



31.1

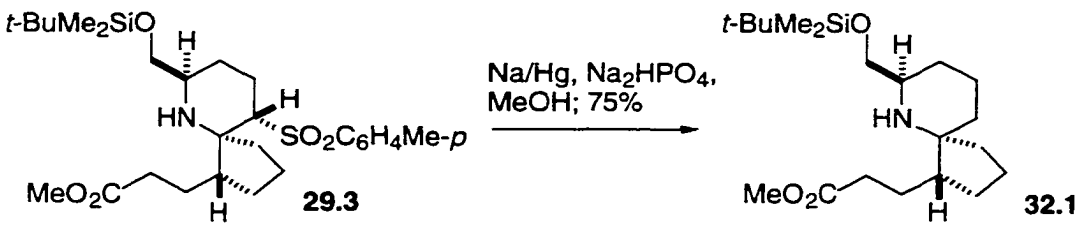


31.2

Scheme 31

With the spirocycle **29.3** in hand, we thought that the proposed key intermediate (**7.1**) in our halichlorine synthesis

was within our reach. Unexpectedly, the desulfonation was more difficult than we anticipated. Utilizing a procedure first published by Trost,[37] we treated the sulfone with the suggested amount of Na/Hg (1.5 g/mmol) in the presence of Na_2HPO_4 buffer in MeOH, but obtained only a small amount (ca 10%) of the desired product **32.1** (**Scheme 32**). Moreover, the product was very difficult to separate from the starting material by silica chromatography. Other methods examined for desulfonation included SmI_2/HMPA,[38] Li-napthalenide,[39] and Raney-Ni, but these gave either a complex mixture of decomposition products or produced no reaction. Optimization of the Na/Hg method by using a large excess (4.0 g/mmol of 10% Na/Hg) for a prolonged reaction time (10 h) gave 6-azaspiro[4.5]decane **32.1**, $[\alpha]_D$ -6.29 (c 0.27, CH_2Cl_2), representing the core of halichlorine and pinnaic acids, in 75%.[40]

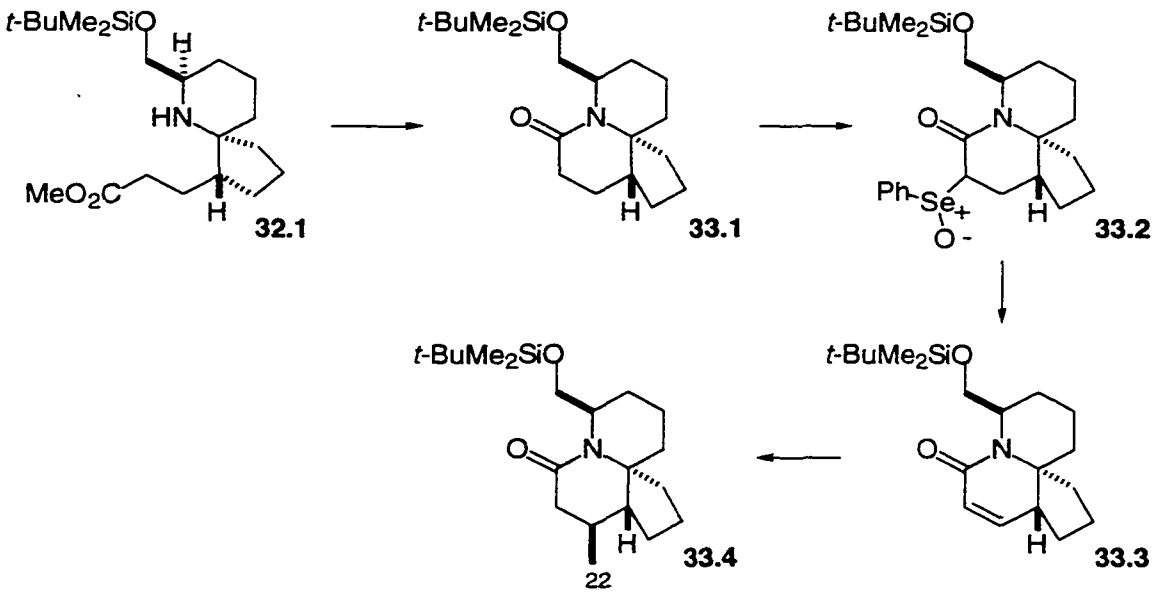


Scheme 32

The difficulty encountered in the above desulfonation prompted us to develop sulfone groups carrying electron-withdrawing functionalities to facilitate the desulfonation process, and the results of that project are summarized in the following chapter.

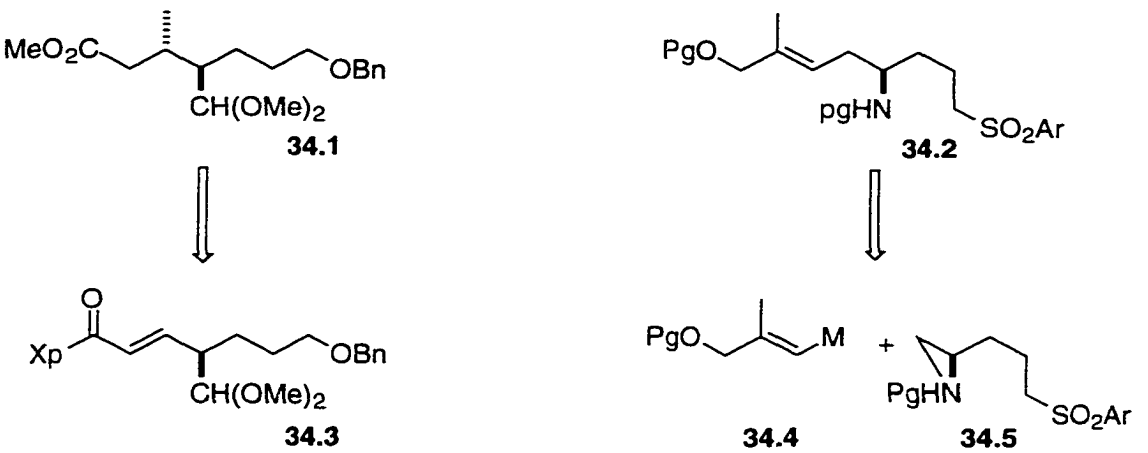
Part 2. The Elaboration of the Fragments

Having achieved our goal of forming the azaspirocyclic core by radical cyclization, we turned our attention towards installation of the C(22) methyl group on the side chain. In principle, it is possible to continue the synthesis from **32.1** by lactamization to generate a tricyclic structure such as **33.1**, followed by introduction of a double bond, perhaps by selenoxide elimination. It should then be possible to carry out a stereospecific Michael addition of a methylcuprate from the less hindered β-face of the molecule (**Scheme 33**).



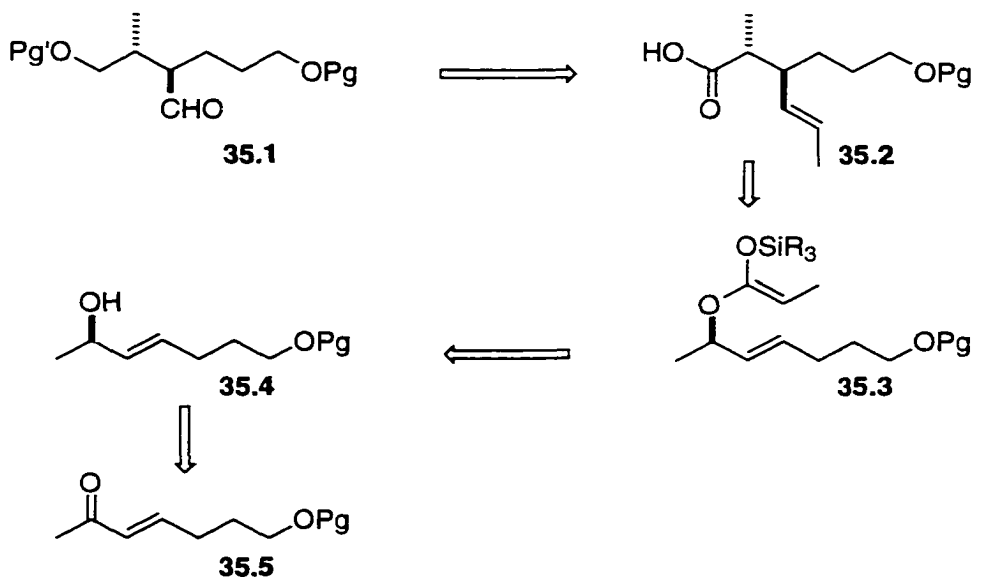
Scheme 33

However, we decided to take advantage of the convergency of our route and build more elaborate fragments that contain the C(22) methyl on the aldehyde fragment and the eventual C(1)-C(3) on the sulfone fragment (**Scheme 34**). We planned to introduce the C(22) methyl group diastereoselectively on **34.3** with the aid of an appropriate chiral auxiliary (Xp). We envisioned that introduction of the C(1)-C(3) carbons could be achieved by addition of an organometallic species to aziridine **34.5**.



Scheme 34

Before we embarked on the synthesis of the new aldehyde fragment, using the chiral auxiliary method, we investigated briefly the feasibility of synthesizing the fragment by a completely different route, based on the Ireland-Claisen rearrangement.

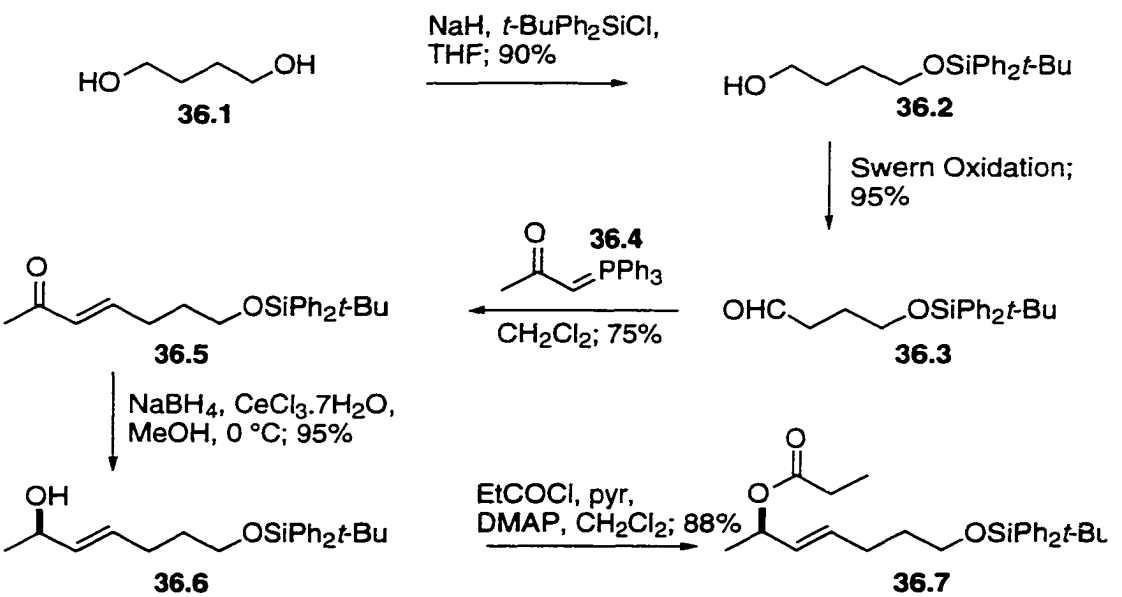


Scheme 35

The aldehyde fragment **35.1**, where the two alcohol funtionalities are differentially protected, was to be derived from the product of reduction and ozonolysis of acid

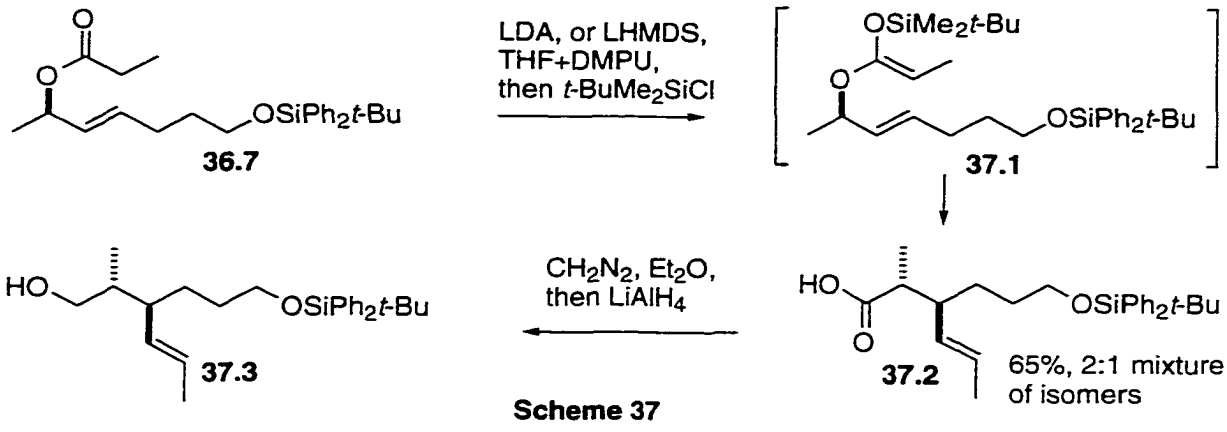
35.2 (**Scheme 35**). This acid is the product of Ireland-Claisen rearrangement[41] of *Z*-silyl enol ether **35.3** which, itself, would be derived from chiral allylic alcohol **35.4**.[42] We planned to carry out an enantioselective catalytic reduction of a ketone such as **35.5** to generate alcohol **35.4**. The merit of this new route is that it does not require a chiral auxiliary and so eliminates steps involving installation and removal of auxiliaries. The chirality is introduced in a single step catalytically; this makes the route more efficient and amenable to large scale synthesis of the aldehyde fragment.

This idea was put to the test by the following experiments. 1,4-Butanediol was monosilylated by a known procedure[43] to alcohol **36.2** (**Scheme 36**), and this was converted into ketone **36.5** by Swern oxidation followed by Wittig olefination, using stabilized ylide **36.4**. For the purpose of preliminary studies only the racemic alcohol was made. Hence, ketone **36.5** was reduced by $NaBH_4$-$CeCl_3.7H_2O$



Scheme 36

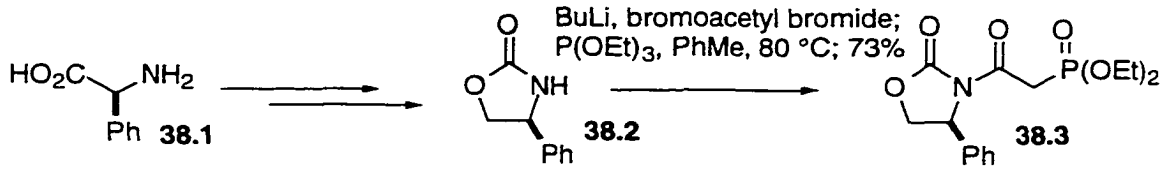
to give the racemic allylic alcohol **36.6**, which was then acylated with propionyl chloride to produce ester **36.7**.



Scheme 37

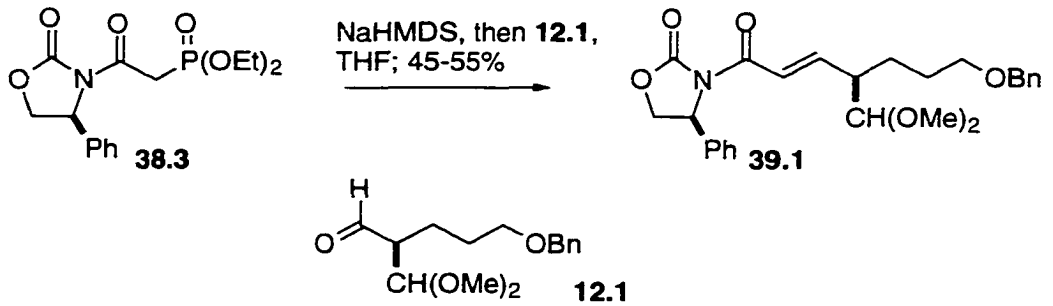
The stereogenic center carrying the methyl substituent on **37.2** was to be established by selective formation of a *Z*-silyl enol ether before the rearrangement. *Z*-Silyl enol ethers are generally formed with better than 90% selectivity by a bulky amide base in the presence of a polar non-protic solvent, such as DMPU or HMPA, followed by silylation.[44] On our substrate this task was more challenging than expected and, under the conditions we surveyed by varying the base [LDA or $(Me_3Si)_2NLi$] or the ratio of DMPU in THF we were unable to obtain more than a 2:1 diastereomeric ratio in the mixture of rearranged products (**37.2**). Moreover, the diastereomers were not separable by chromatography either at the stage of the acid **37.2** or the alcohol **37.3**. Due to these difficulties, the route based on an Ireland-Claisen rearrangement was abandoned, and we returned to our old method of using chiral auxiliaries.

Toward this end, phosphonate **38.3**, containing an (*S*)-4-phenyl-2-oxazolidinone subunit, was synthesized by a method based on literature procedures.[20] (*S*)-4-Phenyl-2-oxazolidinone **38.2**, which was derived from (*S*)-phenylglycine, was acylated with bromoacetyl bromide, and the product was then converted into phosphonate **38.3** by heating in the presence of $(EtO)_3P$ (**Scheme 38**). Phosphonate **38.3** was deprotonated with $(Me_3Si)_2NNa$ and reacted with the crude aldehyde **12.1** (**Scheme 39**). The desired imide **39.1** was isolated in at best 55% yield, after a protracted reaction



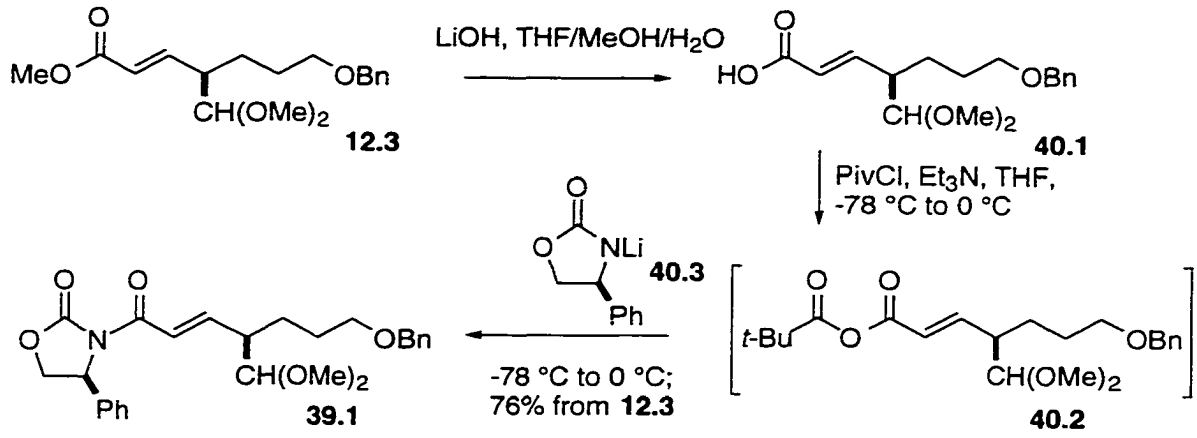
Scheme 38

time of 2 days. Under Masamune's conditions,[45] utilizing LiCl and *i*-Pr_2NEt in MeCN, only 33% of **39.1** was isolated. We attribute the unusual low yield to steric hindrance caused by the bulky dimethyl acetal group α to the aldehyde functionality and, since aldehyde **12.1**, is not stable at room temperature for a prolonged period, a significant amount of aldehyde presumably decomposed over the course of reaction.



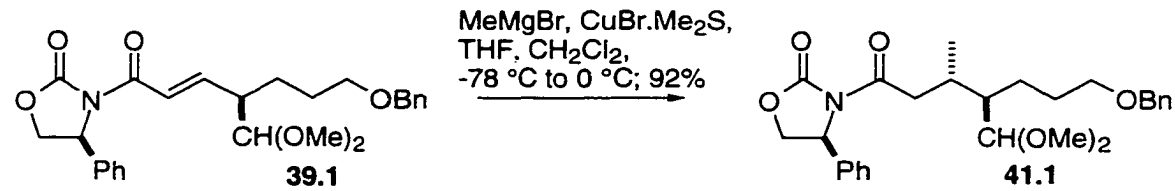
Scheme 39

In search of a more efficient method for introduction of the chiral auxiliary, we resorted to a stepwise but higher yielding sequence. Ester **12.3** was hydrolyzed under standard conditions (LiOH in THF/MeOH/H_2O). After careful acidification, using citric acid solution, to avoid hydrolysis of the dimethyl acetal, we obtained acid **40.1** in quantitative yield (**Scheme 40**). This acid was converted into the corresponding mixed pivalic anhydride (**40.2**) and treated with the lithium salt **40.3** to give imide **39.1** in 76%.



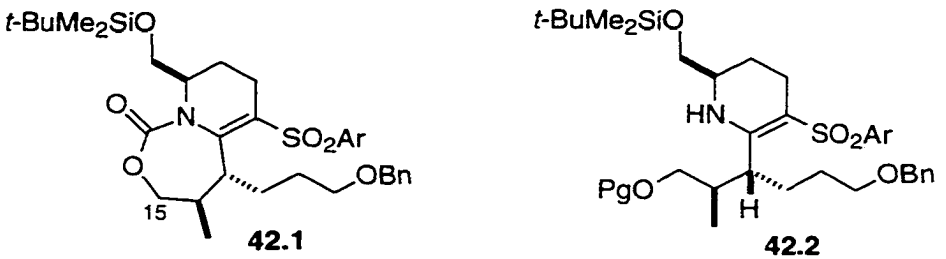
Scheme 40

With **39.1** in hand, we introduced the C(22) methyl group by a Cu(I)-catalyzed Grignard addition to the imide (**Scheme 41**).[46] Gratifyingly, the desired product was isolated as a single diastereomer in 92% yield, and no other stereoisomer was observed in the ^{1}H NMR spectrum of the crude mixture. The existing stereogenic center in **39.1** may have assisted in a double stereodifferentiation process.



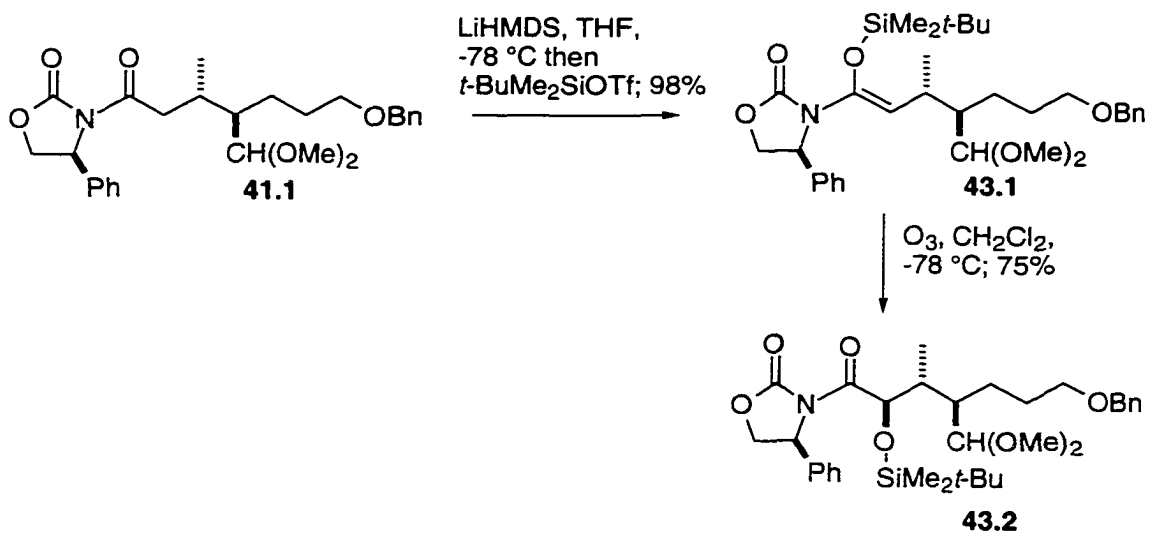
Scheme 41

With C(22) properly installed into the aldehyde fragment, we decided to aim for structures **42.1** and **42.2** as our immediate goals (**Scheme 42**). There were two reasons for choosing the seven-membered carbamate: first, we wished to examine if an expanded ring would direct the radical cyclization towards the desired 5-*exo* cyclization product, and secondly, the hydrolysis of the carbamate after the radical cyclization would give us an alcohol functionality at C(15) for extension of the side chain of halichlorine. With this goal in mind, we needed to remove the auxiliary from



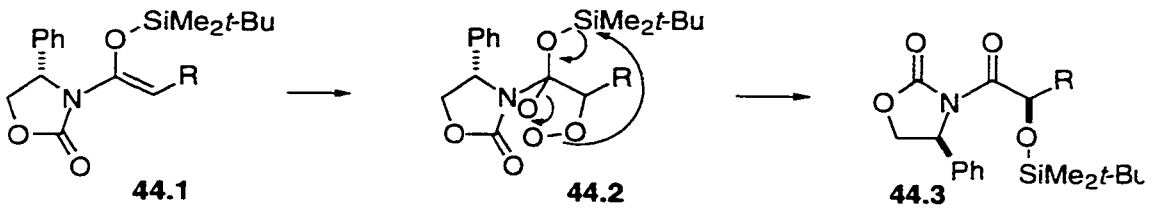
Scheme 42

41.1 and truncate the chain by one carbon. Imide **41.1** was treated with $(Me_3Si)_2NLi$ and *t*-$BuMe_2SiOTf$ to give the chromatographically stable silyl enol ether **43.1**. Attempted ozonolysis of the double bond gave **43.2** in 75% yield as a single isomer, instead of the desired aldehyde (**Scheme 43**). The stereochemistry of the newly-generated stereogenic center was not rigorously established, but we suspect that it is as shown. The geometry of the silyl enol ether is presumed to be *Z* based on analogy.[47] It is likely that the major



Scheme 43

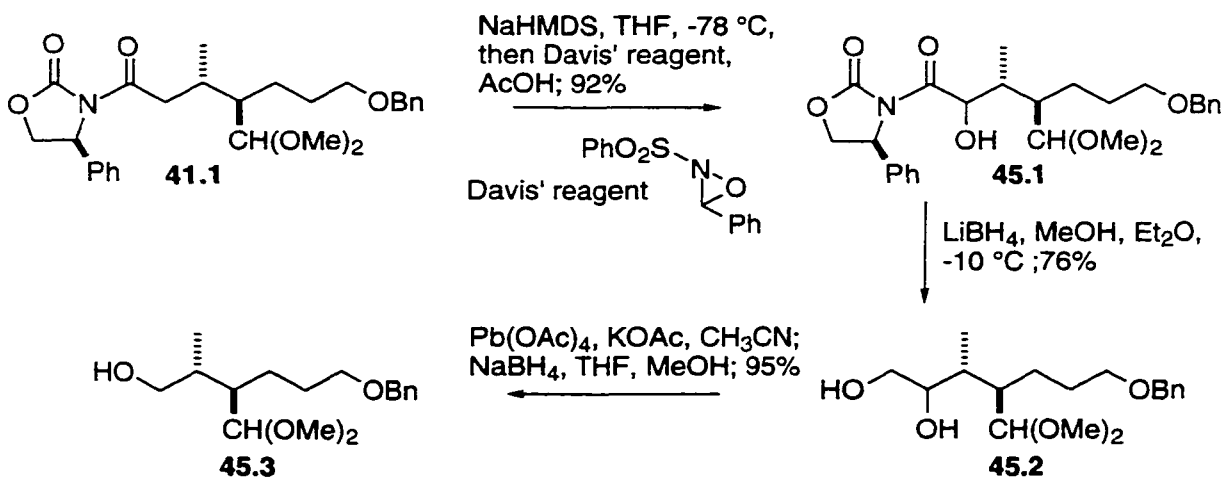
conformer of the silyl enol ethers is as shown in **44.1** due to dipole repulsion. Mechanistically, it is reasonable to rationalize that ozone attacks the top face of the double bond to form an intermediate ozonide **44.2**, which subsequently rearranges to give the silyl ether **44.3**, as shown in Scheme 44. Although ozonolysis did not accomplish the task of



Scheme 44

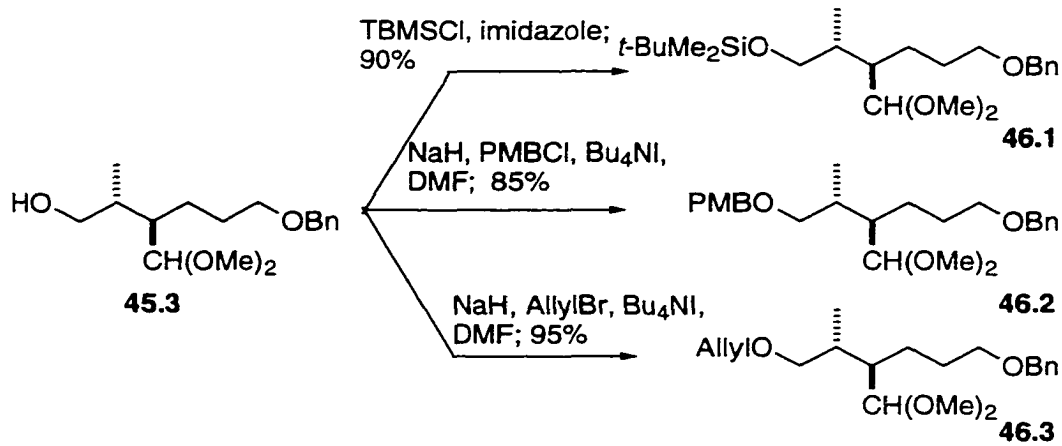
removing one carbon from our substrate, the experimental result showed that we might have in our hands a method of stereospecifically oxidizing the α position of a chiral imide with concurrent silyl protection. Due to our more pressing goal of synthesizing the natural product, the exploration of this discovery will be dealt with at a later time.

A stepwise approach was examined in order to accomplish the task of removing the auxiliary as well as one carbon from **41.1**. The α position of **41.1** was oxidized by Davis' oxaziridine, utilizing a method developed by Evans,[48] to give a 1:1 diastereomeric mixture of alcohols **45.1**. The stereochemistry is inconsequential since it will be destroyed during truncation. The auxiliary was reductively removed with $LiBH_4$ (1.1 equivalent) and MeOH (1.1 equivalent) in Et_2O to give a mixture of diols **45.2** (**Scheme 45**). The diols were then oxidatively cleaved, using $Pb(OAc)_4$ and AcOK as a buffer in MeCN, to give quantitatively an aldehyde that was



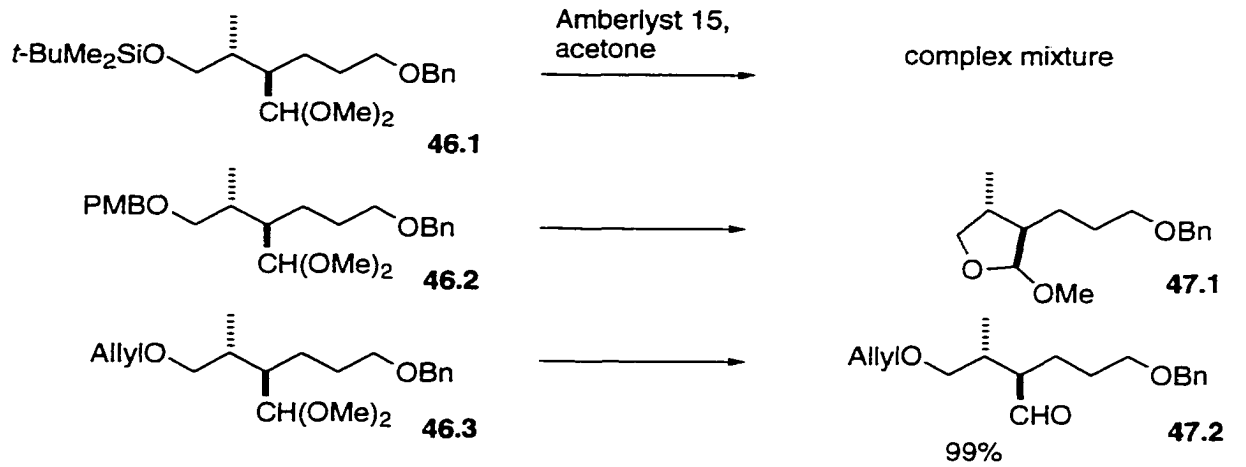
Scheme 45

immediately reduce with $NaBH_4$ to alcohol **45.3** in 93% over two steps. Alcohol **45.3** was isolated as a single isomer, a fact which meant that no epimerization had occurred over the two steps. Several protecting groups were examined for the alcohol and they were chosen due to their orthogonality with the other protecting groups that will subsequently be present in the advanced intermediate **42.2**, as well as their compatibility with the reaction conditions of the remaining synthetic steps. Therefore, alcohol **45.3** was converted into the corresponding silyl ether **46.1**, Pmb ether **46.2**, and allyl ether **46.3** (**Scheme 46**). The silyl and Pmb groups proved ineffective for alcohol protection since subsequent



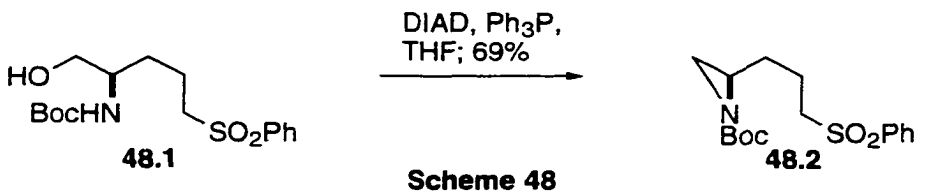
Scheme 46

cleavage of the dimethyl acetal led either to a complex mixture in the case of **46.1** or a cyclic acetal **47.1** whose stereochemistry was not assigned (**Scheme 47**). The allyl ether group in **46.3**, on the other hand, was stable under the same conditions. Treatment with Amberlyst-15 in acetone served to convert acetal **46.3** into aldehyde **47.2** quantitatively, without epimerization of stereogenic centers.



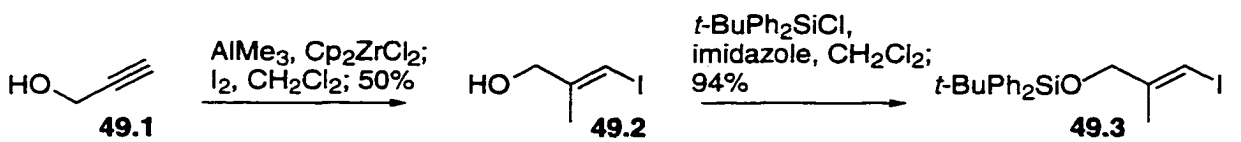
Scheme 47

Concurrently with our synthesis of the aldehyde fragment, we also investigated elaboration of the sulfone fragment. Alcohol **48.1** was synthesized analogously to **17.1**, and converted into the aziridine using Mitsunobu conditions (**Scheme 48**).[49]



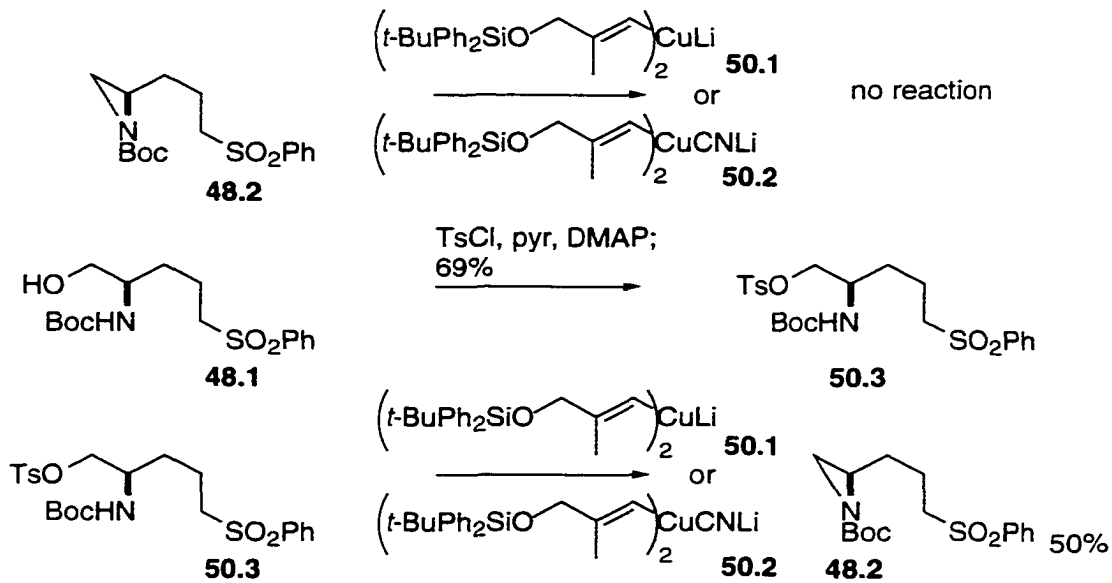
Scheme 48

The C(1)-C(3) fragment was synthesized from propargyl alcohol utilizing the Zr-assisted methylation developed by Negishi.[50] Treatment of propargyl alcohol with Me_3Al and a catalytic amount of Cp_2ZrCl_2 gave an intermediate aluminum alkene species that was quenched with I_2 to form iodo alcohol **49.2**. The alcohol was then protected as its silyl ether **49.3**, using *t*-$BuPh_2SiCl$ and imidazole (**Scheme 49**).



Scheme 49

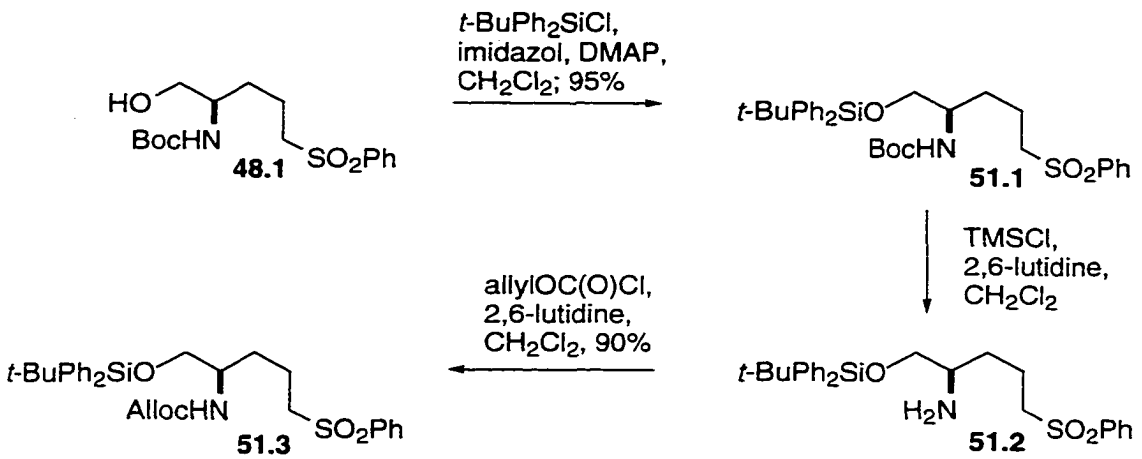
Having made iodide **49.3**, we then attempted to incorporate this four-carbon fragment by nucleophilic opening of the aziridine **48.2**. The iodide was first converted into an organolithium by treatment with 2 equivalents of *t*-BuLi, and then transmetallated with either CuI or CuCN to generate a cuprate (**50.1** and **50.2**). To our disappointment, neither of the cuprates was able to add as a nucleophile to aziridine **48.2** (**Scheme 50**). Under similar conditions, tosylate **50.3**, derived from alcohol **48.1** as shown, gave the aziridine **48.2** instead of the desired adduct.



Scheme 50

At this point we decided to delay the introduction of C(1)-C(3) until after we had arrived at the azaspirocylic core.

Alcohol **48.1** was protected as the corresponding silyl ether **51.1** (**Scheme 51**), *t*-$BuPh_2SiCl$ being used instead of the more labile *t*-$BuMe_2SiCl$ of our previous model in order to avoid unwanted protecting group cleavage. The Boc group of **51.1** was then removed under mild conditions (Me_3SiCl, 2,6-lutidine in CH_2Cl_2) to give amine **51.2** in quantitative yield.[51] The crude amine was acylated with allyl

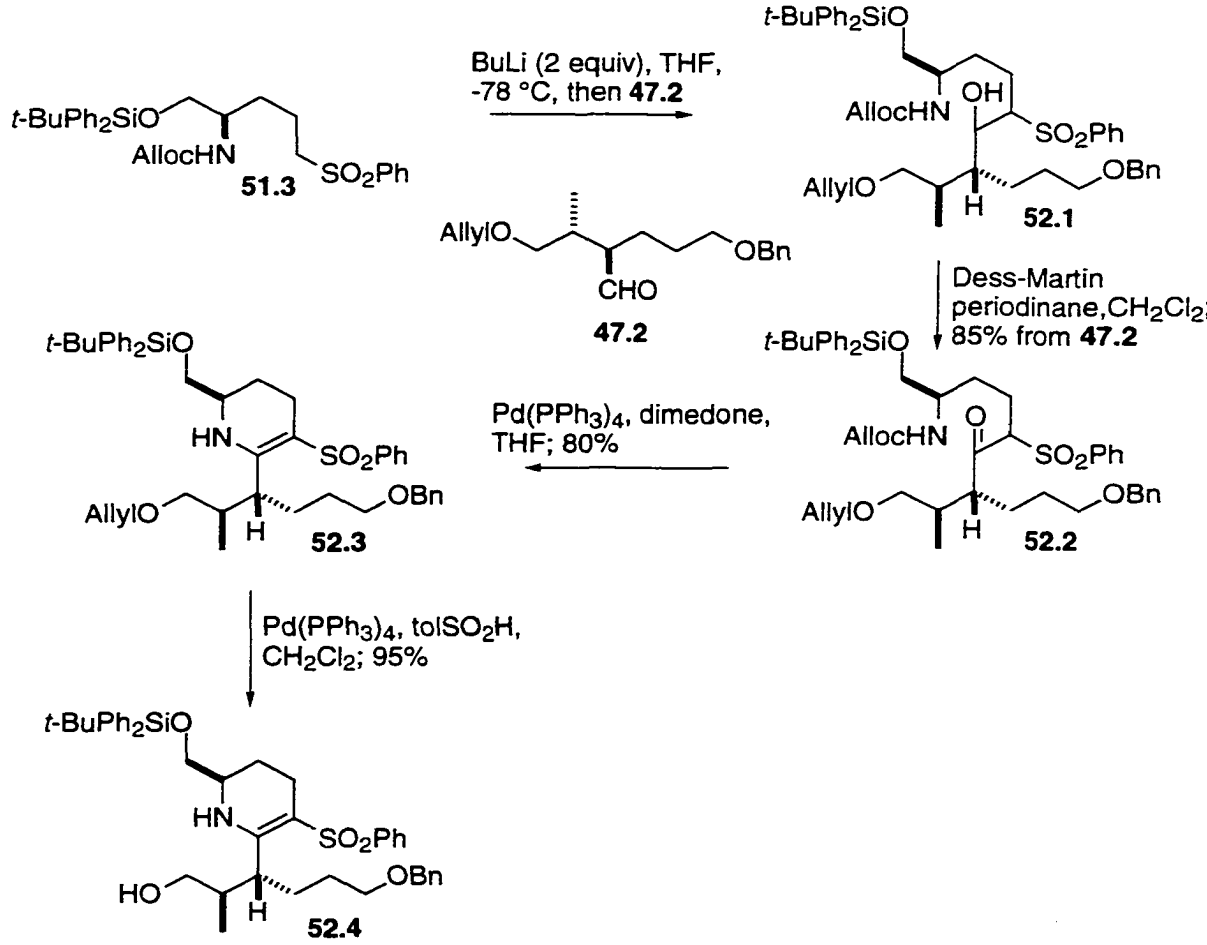


Scheme 51

chloroformate to give the alloc derivative **51.3** in 90% yield, after chromatographic purification.

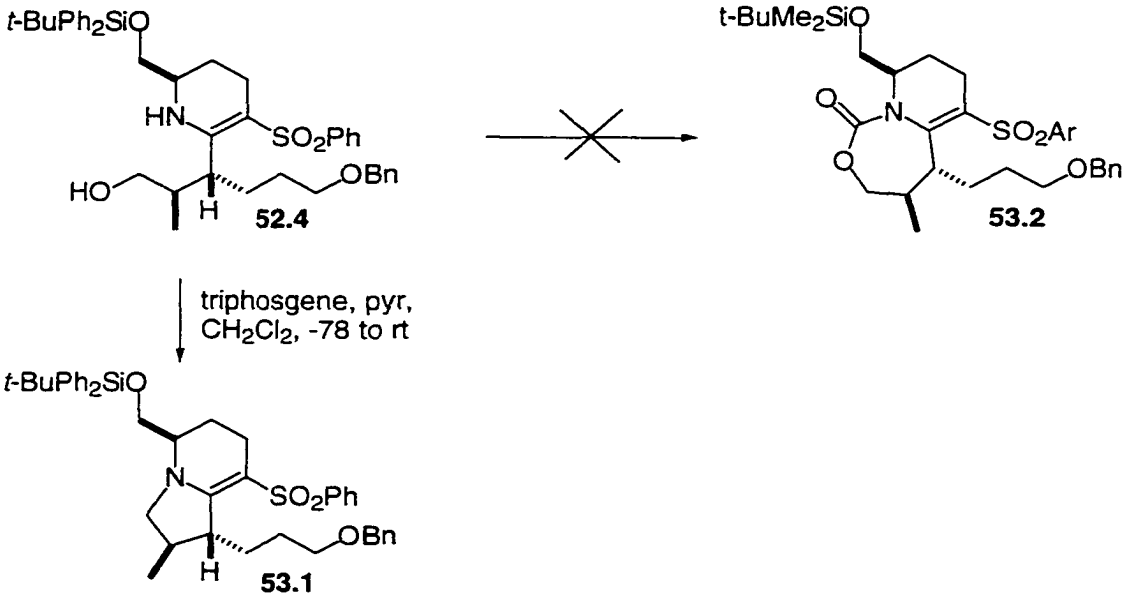
Coupling of the two fragments was now carried out under similar conditions to those developed in our earlier model. A slight excess of sulfone dianion derived from **51.3** was generated by the addition of two equivalents of *n*-BuLi. This step was followed by slow addition of a THF solution of aldehyde **47.2** to generate a diastereomeric mixture of hydroxy sulfones **52.1** (**Scheme 52**). The alcohol functionality was then oxidized by the Dess-Martin periodinane to give a diastereomeric mixture of ketones **52.2**. At this stage we were unsure if our previous conditions for removing the alloc group with concomitant formation of the piperidine ring would be suitable in this case, due to the presence of an allyl ether. Gratifyingly, treatment of **52.2** with a catalytic amount of $(Ph_3P)_4Pd$ and an excess of dimedone gave **52.3** as a single isomer. The allyl ether was untouched by the above conditions. With the piperidine ring in place, we turned our attention to removal of the allyl group from the allyl ether. After much experimentation, we found that the allyl ether could be cleaved easily, using a catalytic amount of $(Ph_3P)_4Pd$ and $TolSO_2H$ as the allyl acceptor.[52] Under these conditions, alcohol **52.4** was obtained in 95% yield. Intrigued with the idea of removing both the alloc and allyl groups with

concurrent formation of the piperidine ring, we treated ketone **52.2** with $(Ph_3P)_4Pd$ and $TolSO_2H$, but we were met with a much diminished yield of **52.4** (10-20%). With the application of these two methods of selective cleavage of allyl-type protecting groups, functional groups such as alcohols or, in our case, an amine and an alcohol can be protected orthogonally – a strategy that has not yet found wide application in synthesis.



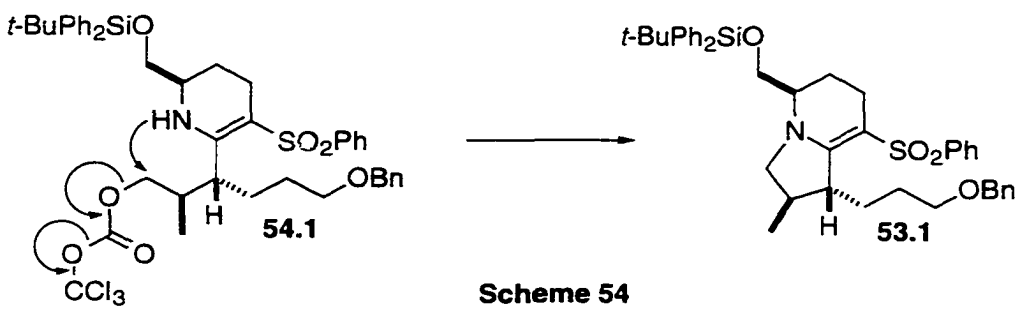
Scheme 52

Following our proposed idea of forming a seven-membered carbamate, we treated amino alcohol **52.4** with triphosgene and pyridine. Much to our surprise, the isolated product was the indolizidine **53.1** instead of the desired **53.2**. We surmise



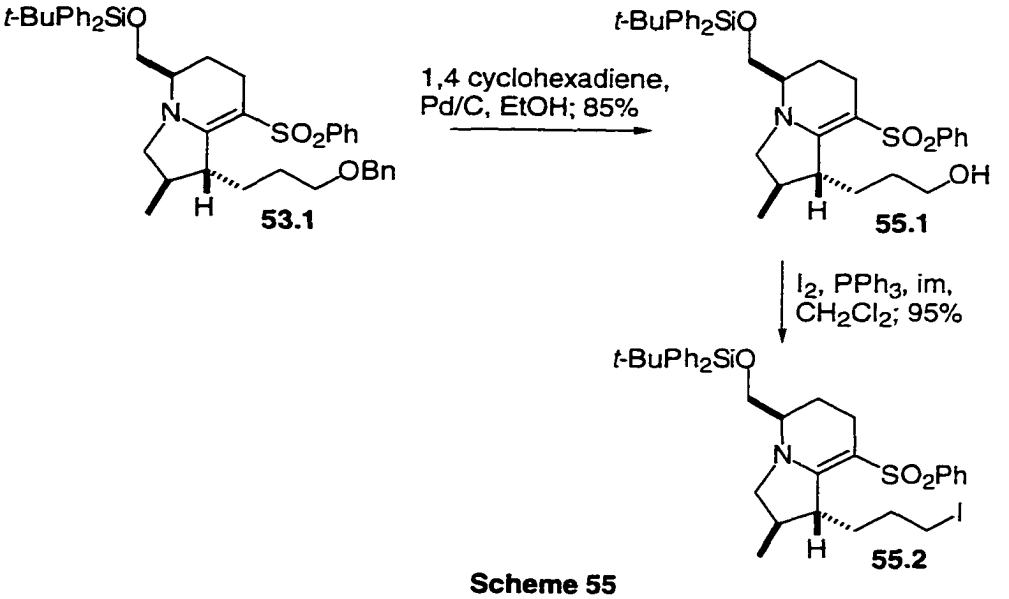
Scheme 53

that, due to the low nucleophilicity of the nitrogen as we have observed in a earlier model, the alcohol was first converted to an activated carbonate. Formation of the seven-membered ring was kinetically slower than formation of the five-membered ring, and the nitrogen attacked the highly activated C(15) to form a five-membered ring (**Scheme 54**).



Scheme 54

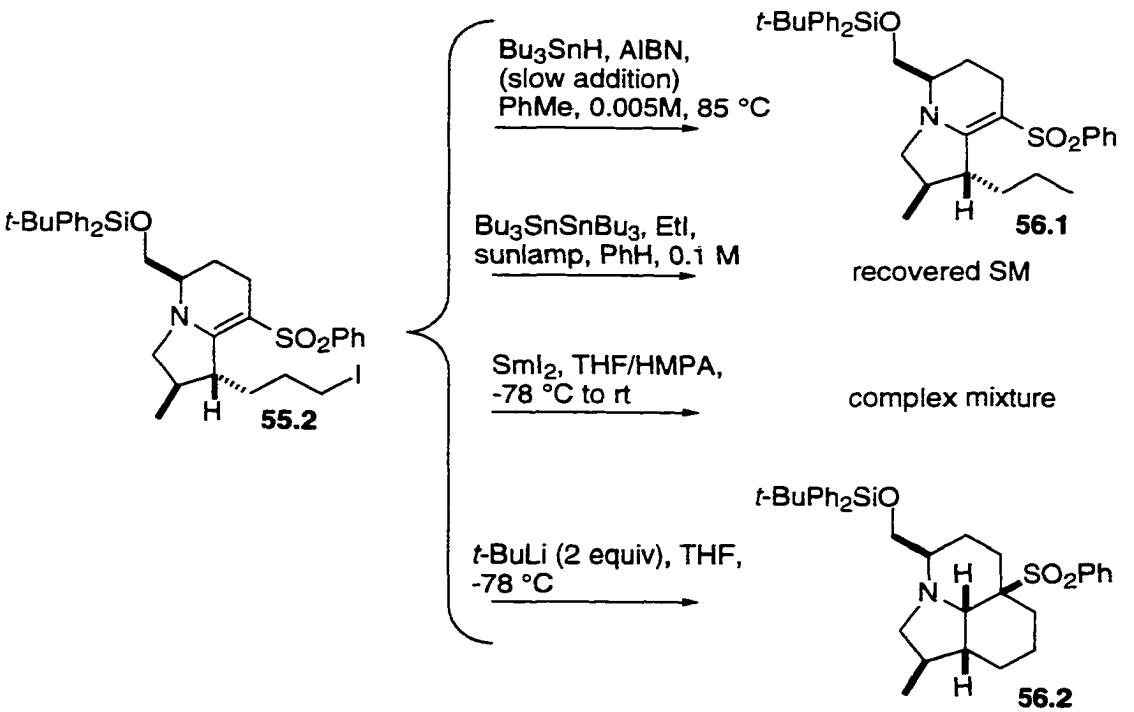
Despite this unfavorable result, we attempted the closure of the spirocyclic five-membered ring on indolizidine **53.1**. The benzyl ether was resistant to the standard hydrogenolysis utilizing H_2 with Pd/C. However, it was successfully removed under transfer hydrogenolysis conditions, using 1,4-cyclohexadiene as a hydrogen equivalent and Pd/C (**Scheme 55**). The resulting alcohol **55.1** was



Scheme 55

converted into iodide **55.2**, which serves as a radical cyclization precursor.

Disappointingly, under various conditions and reagents, none of the desired spirocyclization was observed. Under

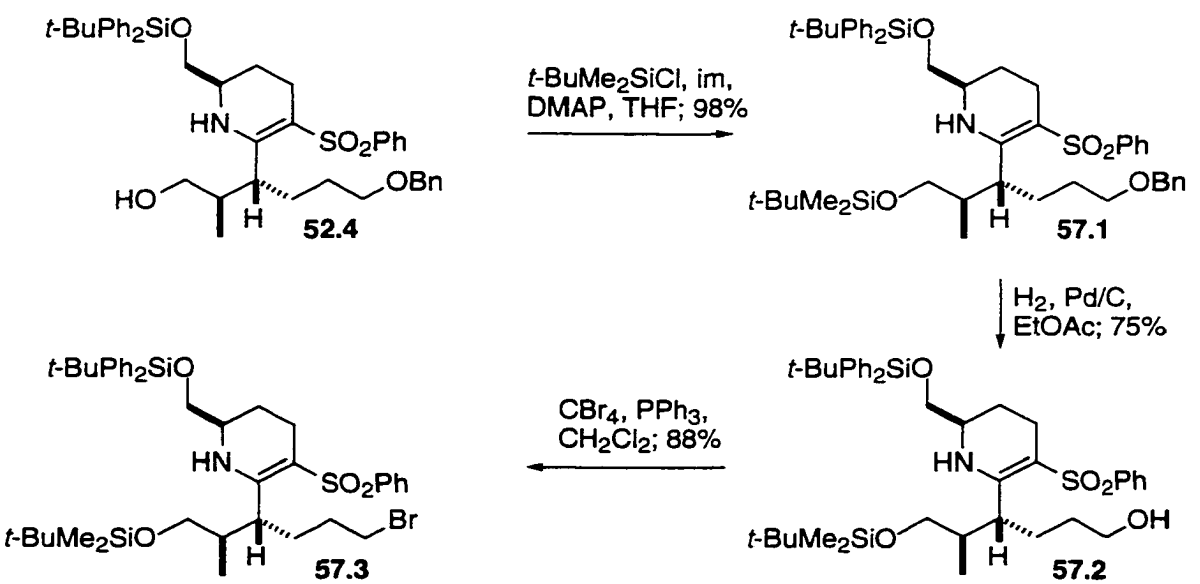


Scheme 56

standard tin hydride conditions of slow addition of Bu_3SnH and AIBN to a warm (85 °C) solution of the iodide in PhMe only the reduction product **56.1** (**Scheme 56**) was obtained. Using a UV-induced free radical conditions,[53] only the starting material was recovered. Treatment of iodide **55.2** with SmI_2 in THF/HMPA[54] produced a complex mixture. Finally, metallation of the iodide with *t*-BuLi (2 equivalents) gave the *6-endo* cyclized product **56.2** in 15% yield.

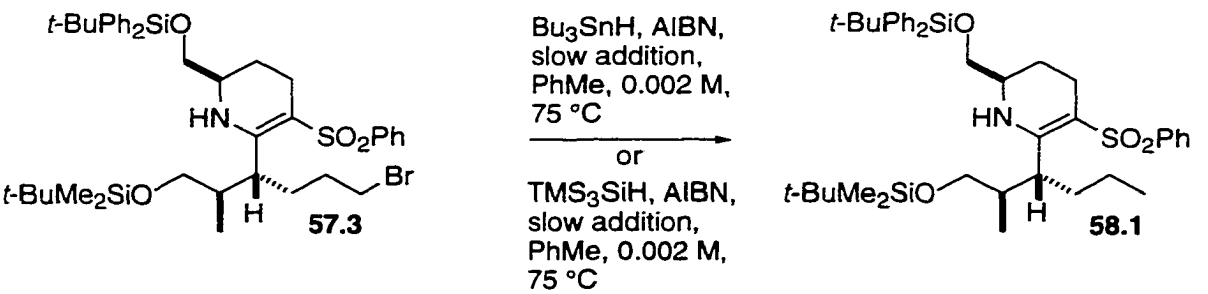
Although these results were disappointing, they were in agreement with what we have observed with the six-membered lactam **28.1** (see Scheme **28**). The bicyclic structure restricted movement of the side chain and hence the trajectory needed for the primary radical to reach C(9) for the desired 5-*exo* cyclization.

Attention was next turned towards cyclization of the five-membered ring without the bicyclic carbamate with the hope of achieving similar results as in our earlier model. Alcohol **52.4** was silylated with *t*-$BuMe_2SiCl$ to give **57.1**, which was subsequently debenzylated by hydrogenation (**Scheme 57**), and the resulting alcohol **57.2** was then converted into the corresponding bromide by treatment with CBr_4 and Ph_3P.



Scheme 57

We then attempted the radical cyclization using slow addition (syringe pump) of Bu_3SnH (1.3 equivalents) and AIBN (0.1 equivalents) to a dilute solution (0.02 M) of the bromide **57.3** in warm (75 °C) PhH. Disappointingly, only the reduced product **58.1** was isolated. We repeated the reaction using a 0.002 M solution of bromide, but to no avail. Even changing from Bu_3SnH to $(Me_3Si)_3SiH$,[55] a hydride reagent that has a lower rate of hydride donation, hence prolonging the lifetime of the primary radical, gave none of the desired cyclized product (**Scheme 58**). We are currently unsure why we observed no cyclization for substrate **57.3**.

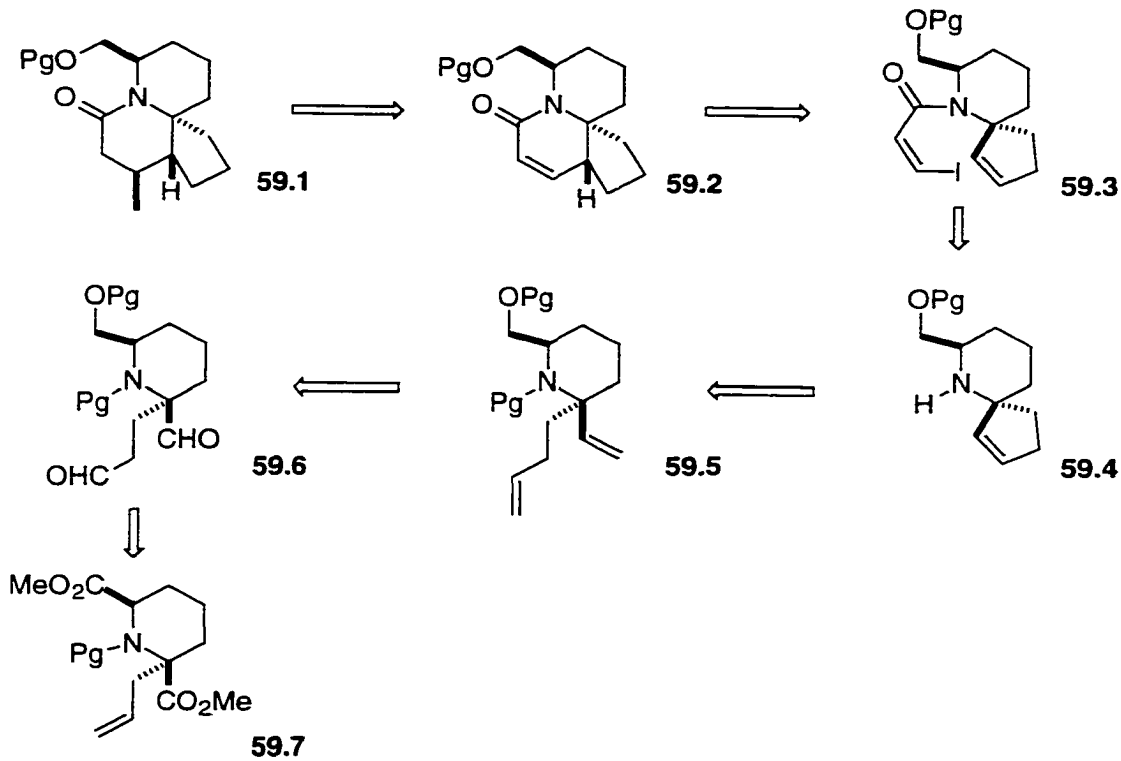


Scheme 58

Although we could return to our earlier model and continue our synthesis as outlined on Scheme 33, we decided to pursue a new and more efficient route to the azaspirocylic core of halichlorine.

Part 3. New Approach to Halichlorine

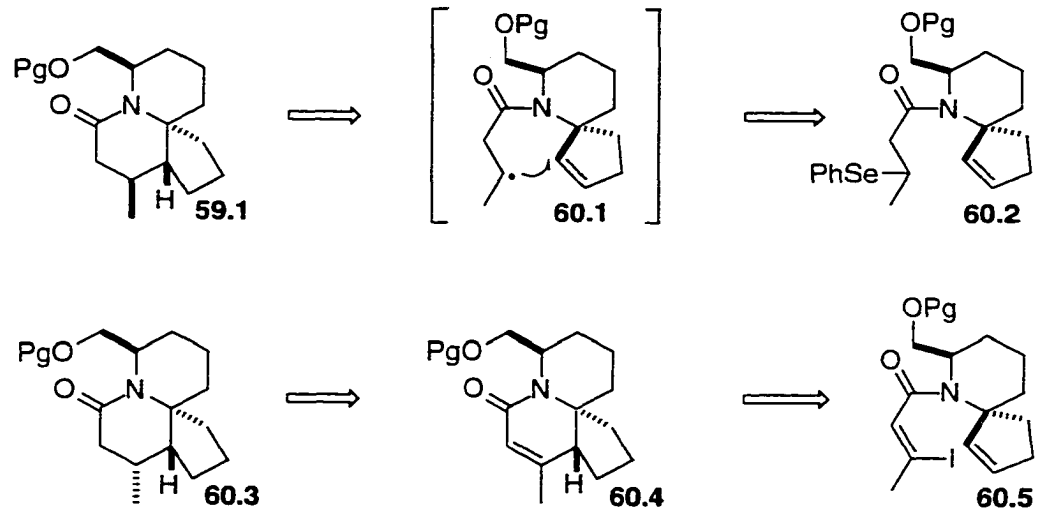
The main lesson that we learned from our previous studies is that formation of the spiro center in the halichlorine core was more challenging than expected, and there were stereochemical factors which were difficult to control that affected the efficiency of the key radical cyclization step. In our new design, we decided to address the stereospecific construction of the quaternary center as early as possible in the synthetic scheme. The retrosynthetic analysis is based on the following ideas



Scheme 59

(**Scheme 59**).

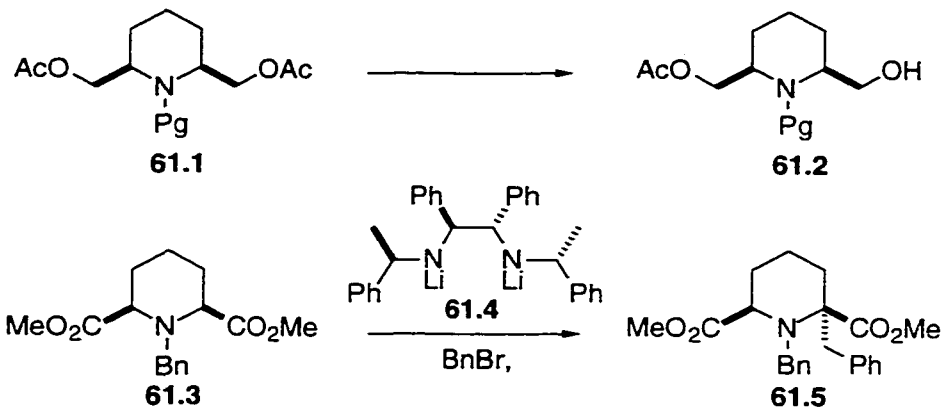
The tricyclic lactam **59.1**, as in our previous route, will be derived from a stereospecific methylcuprate addition to the unsaturated precursor **59.2**. Further bond disconnection between C(13) and C(14) gives rise to a spirocyclic lactam **59.3** where the nitrogen serves as a temporary linker for the side arm. Carbon-carbon bond formation between C(13) and C(14) will be achieved either via a 6-*exo* radical cyclization or an intramolecular Heck reaction under reductive conditions.[56] Similarly, the same cyclization can also be attempted using a homologated lactam with a pendant methyl group already incorporated in its structure, such as **60.2** or **60.5** (**Scheme 60**). Radical cyclization of selenide **60.2** might give the cyclized product with the correct stereochemistry. In contrast, Heck cyclization of iodide **60.5** will give rise to **60.4**, and selective conjugate hydride reduction from the less hindered α face should then afford the core of pinnaic acid (see **2**).



Scheme 60

Formation of the five-membered spirocyclic ring with an olefinic functionality will be accomplished by ring closing metathesis[57] of a diene such as **59.5**, which will be derived from dialdehyde **59.6** (**Scheme 59**). The dialdehyde can also serve as a precursor for formation of the five-membered ring by reductive coupling, using either a low-valent Ti reagent[58] or SmI_2,[59] followed by deoxygenation. The starting material will be the alkylation product of piperidine diester **59.7**. The merits of this new route are its conciseness and flexibility. Moreover, the challenge of the quaternary carbon formation is dealt with early in the synthesis.

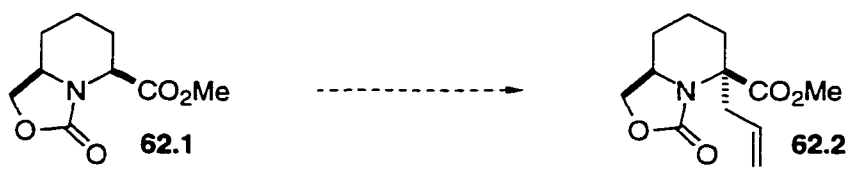
After surveying the literature for an appropriate starting material, we found two suitable candidates. The first, which was developed by Chenevert *et al.*[60] utilizes *Aspergillus niger* lipase to desymmetrize bisacetate **61.1** to give alcohol **61.2** with 98% ee. The second approach, found in a recent communication by Simpkins,[61] utilizes chiral diamide **61.4** to enantioselectively deprotonate one of the ester groups of **61.3**, and the resulting enolate then alkylates an electrophile on the α face of the piperidine ring to give **61.5** in >98% ee (**Scheme 61**). We decided to examine both



Scheme 61

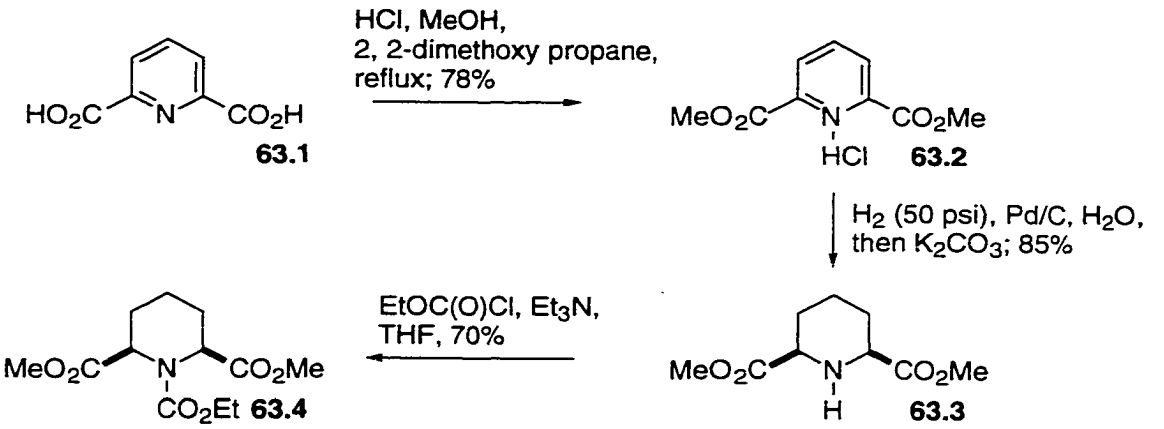
methods to see which would serve our purpose better.

Based on the first method, we selected ester **62.1**, which can be derived from alcohol **61.2**, as our immediate goal. We surmise that a diastereoselective alkylation of **62.1** will occur predominately on the convex (α) face to give **62.2**.



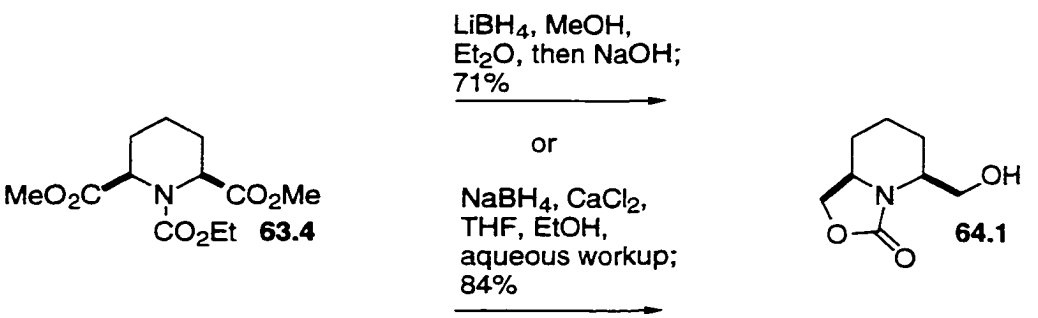
Scheme 62

We embarked on the synthesis with the cheap and readily available starting material 2,6-pyridinedicarboxylic acid **63.1**. The compound was esterified by treatment at reflux with HCl in MeOH containing 2,2-dimethoxypropane, to give the HCl salt of diester **63.2**.[60] The pyridine ring was then saturated by high pressure hydrogenation (50 psi) using 10% Pd/C as a catalyst to give the *cis*-diester **63.3** exclusively. The nitrogen was next acylated with EtOC(O)Cl to give carbamate **63.4**. For the purpose of preliminary studies, we decided to continue the synthesis using racemic material. Therefore, diester **63.4** was exhaustively reduced, using $LiBH_4$ in MeOH and Et_2O to a symmetrical diol (not shown) which was cyclized under basic conditions to racemic alcohol **64.1**



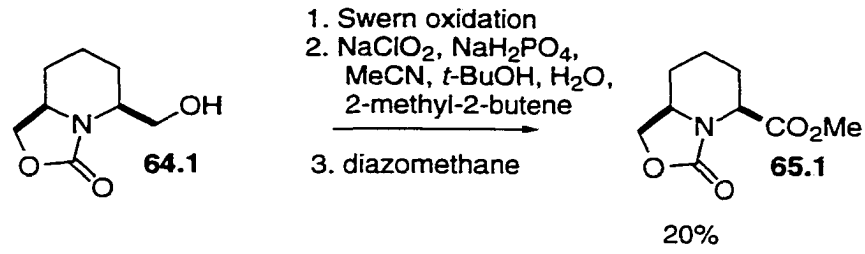
Scheme 63

(**Scheme 64**). The same transformation could also be carried out in a one-pot operation using $NaBH_4/CaCl_2$ as the reducing agent and, after aqueous work up, alcohol **64.1** was isolated in a higher (84% versus 71%) yield.



Scheme 64

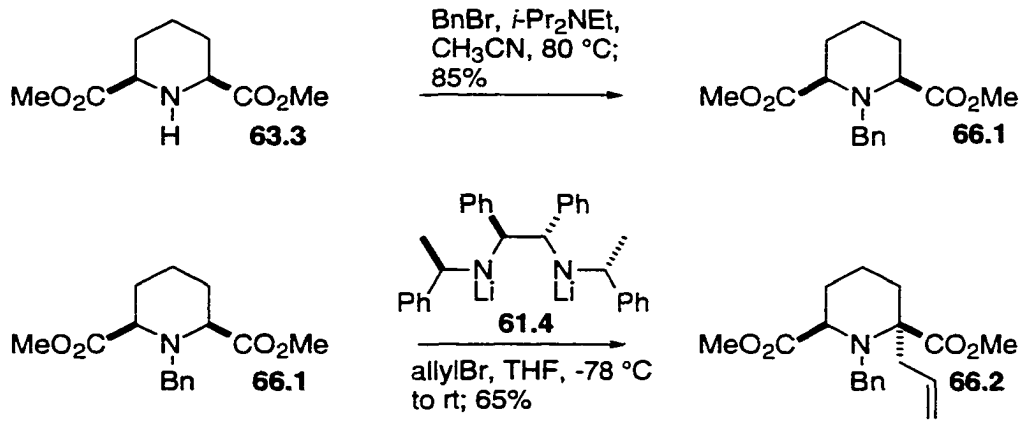
Alcohol **64.1** was then converted into ester **65.1** (same as **62.1**) by a three-step sequence. Oxidation of **64.1** under Swern conditions gave an intermediate aldehyde, which was immediately treated with $NaClO_2$ to produce the corresponding acid, and the ester **65.1** was then obtained in about 20% yield after esterification with diazomethane. We were unable to obtain a reasonable yield of ester **65.1**, although we made several attempts to do so. This is perhaps due to the high water solubility of the intermediate acid which caused a loss



Scheme 65

of material during aqueous work up. Hampered by this difficulty, we turned our attention to the second route, which turned out to be by far more efficient.

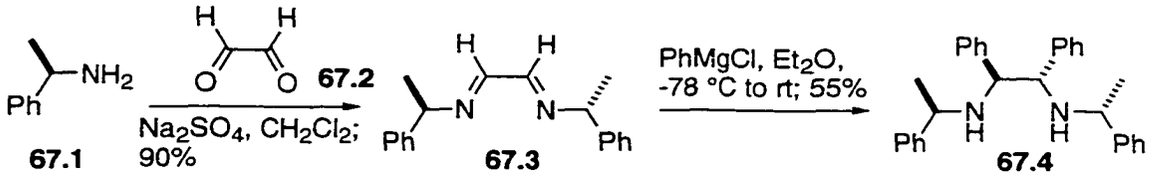
Amine **63.3** was benzylated with BnBr and *i*-Pr_2NEt in warm (80 °C) MeCN to give diester **66.1**. Following the procedure published by Simpkins,[61] **66.1** was alkylated using the chiral dilithium amide base **61.4** and allyl bromide to give **66.2** in 60-68% yield. Contrary to the original report, which claimed that the alkylated product is diastereomerically homogeneous, in our hands, the product is contaminated with 5-10% of a diastereomer which could not be separated by chromatography at this stage. We could, however, separate the diastereomer at a later stage in the synthesis (*vide infra*).



Scheme 66

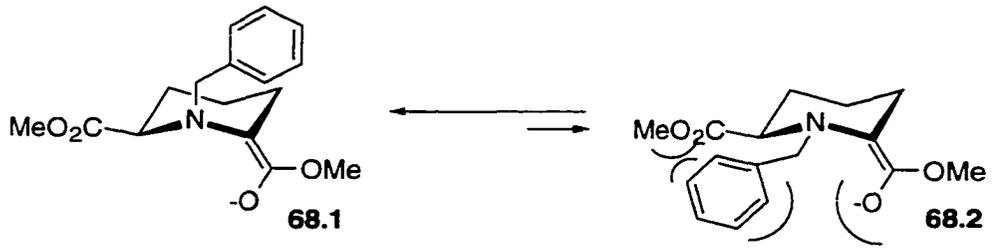
The chiral diamine was prepared by an efficient two step procedure, starting with commercially available (*R*)-(+)-α-methylphenylamine. Condensation of two equivalents of (*R*)-(+)-α-methylphenylamine and one equivalent of glyoxal, using

Na_2SO_4 as dehydrating agent, gave bisimine **67.3** in nearly quantitative yield.[62] Addition of PhMgCl to **67.3** took place diastereoselectively to produce the highly crystalline diamine **67.4**.[63] The diamine was recycled after each alkylation reaction by recrystallization.



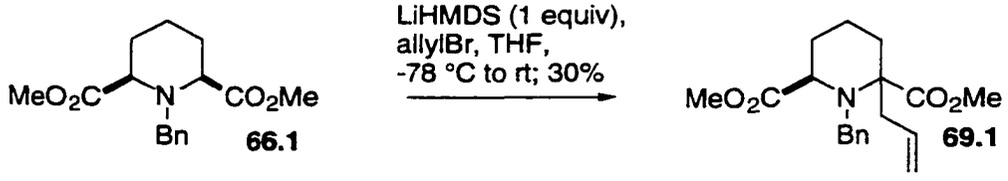
Scheme 67

The basis of the enantioselectivity in the alkylation reaction has not been proposed, but a reason for the diastereoselectivity has been suggested.[61] Species **68.1** was thought to be the major one in the alkylation; the benzyl group is likely to be disposed on the top face of the piperidine ring to alleviate $A^{1,3}$-strain, hence shielding the



Scheme 68

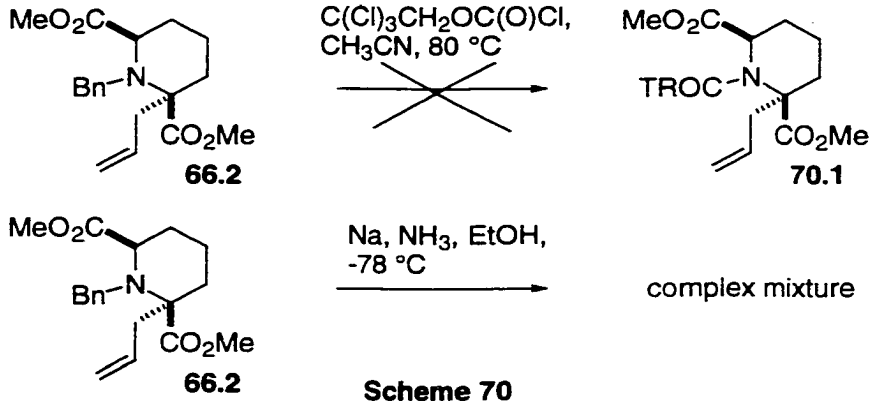
top face from the electrophile. Interestingly, we have used one equivalent of achiral amide base $(Me_3Si)_2NLi$ in the alkylation reaction and the product is a near 1:1 mixture of diastereomers in only 30% yield (**Scheme 69**). This



Scheme 69

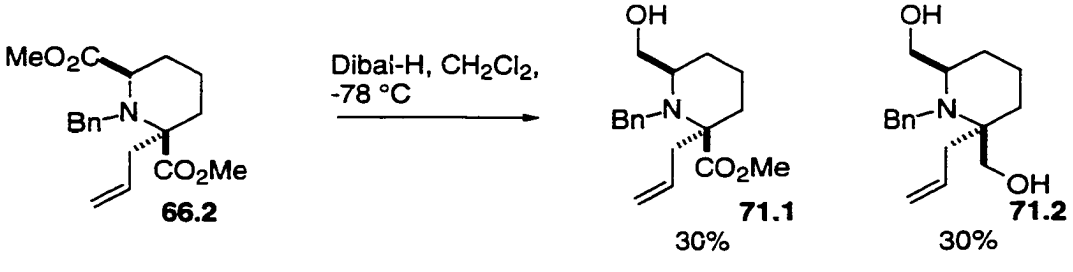
observation suggests that the real mechanism of this reaction may not be as simple as suggested in the literature. The active enolate may be in an aggregate with the chiral amide and this fact may be responsible for the high enantio- and diastereoselectivity.

With **66.2** in hand, we have achieved the construction of the crucial quaternary carbon center and established two stereogenic centers in a single step. After serving its purpose in directing the alkylation, we attempted to remove the benzyl group and exchange it for a carbamate protecting group on the nitrogen. Unfortunately, none of the conditions examined was fruitful. No desired carbamate was isolated using $Cl_3CCH_2OC(O)Cl$ to effect an alkylative debenzylation (**Scheme 70**). Under conditions of dissolving metal reduction, using Na in NH_3, a complex mixture was obtained.



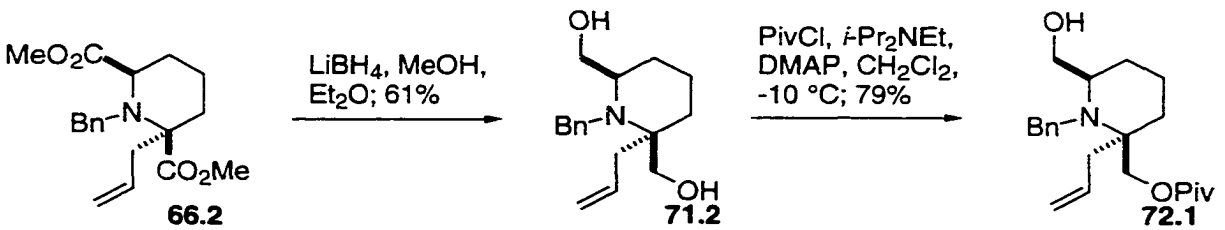
Scheme 70

We then attempted regioselective reduction of one of the ester groups. Slow addition of 2 equivalents of DIBAL-H gave



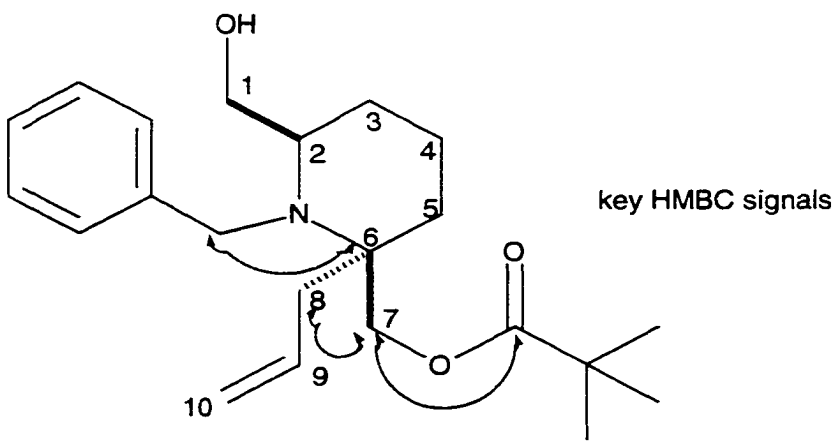
Scheme 71

30% yield of the desired mono-alcohol **71.1** and diol **71.2** in 30% (**Scheme 71**). We were unable to improve the yield of alcohol **71.1** by changing the amount of DIBAL-H or the solvent. Diester **66.2** was exhaustively reduced with an excess of $LiBH_4$ to give the pure diol **71.2** (**Scheme 72**). The diastereomer resulting from the alkylation step was separated at this stage. The diol could be selectively acylated with *t*-BuCOCl to give **72.1** in 79% yield along with 15% of the regioisomer (not shown) and 5% of doubly esterified product. Contrary to our expectations, acylation took place



Scheme 72

preferentially on the more sterically hindered alcohol. This fortuitous selectivity worked in our favor later in the synthesis (*vide infra*). The structure of **72.1** was assigned by extensive NMR experiments including G-COSY, HMBC, HMQC, and T-ROESY. The key HMBC signals are illustrated in Scheme 73, and they unambiguously established the location of the

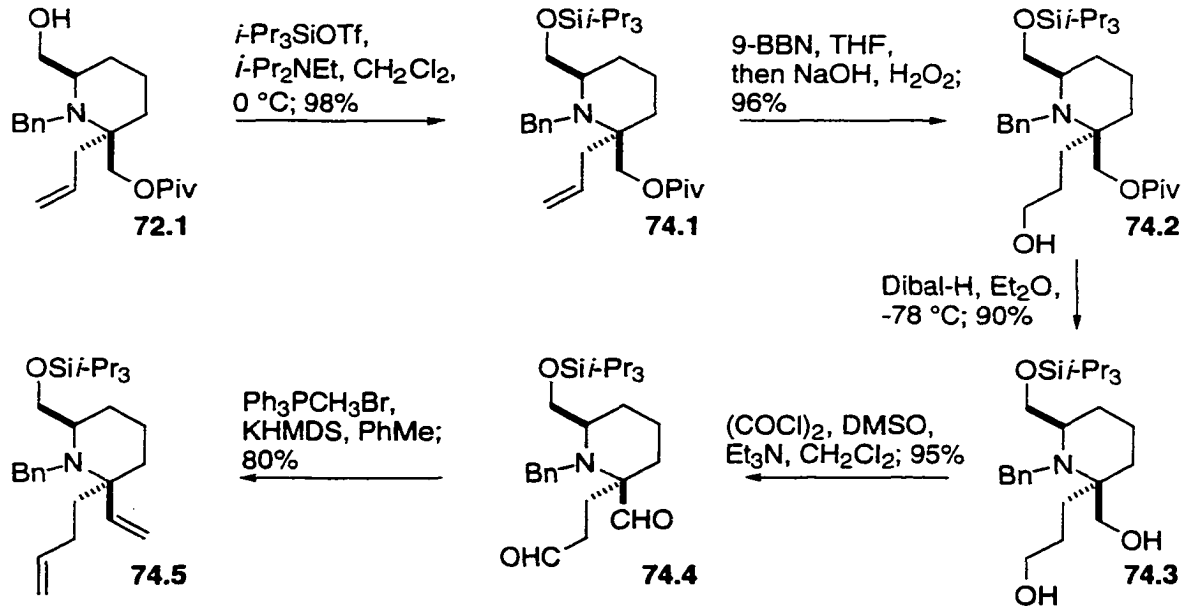


Scheme 73

t-BuCO group. Furthermore, strong T-ROESY cross peaks were observed between protons on C(8) and C(2), thus establishing the structure of **72.1** as shown (**Scheme 73**).

We now carried on the synthesis by converting the double bond of **72.1** into an alcohol by hydroboration. Treatment of **72.1** with 9-BBN showed no reaction after prolonged stirring. We suspected that the unprotected alcohol functionality was either quenching the borane reagent or was aiding complexation of the borane with the tertiary amine group, so rendering the reagent inactive. The alcohol was therefore protected as its triisopropyl silyl ether, using *i*-Pr_3SiOTf and *i*-Pr_2NEt (**Scheme 74**). Hydroboration of silyl ether **74.1** now proceeded smoothly to an intermediate alkylborane which was oxidized *in situ* with NaOH and H_2O_2 to afford alcohol **74.2** in over 90% yield.

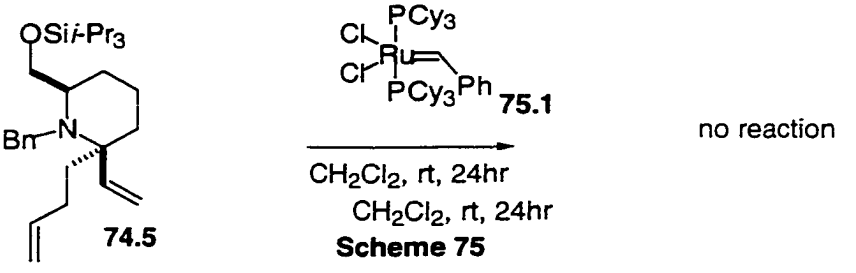
With the goal of reaching a diene such as **59.5** in mind, we proceeded to remove the *t*-BuCO group by reduction with DIBAL-H. This operation gave diol **74.3** without incident. After surveying the literature, we found a few examples of 1,5-diol oxidation under Swern conditions into the corresponding dialdehydes,[64] and we were confident that the



Scheme 74

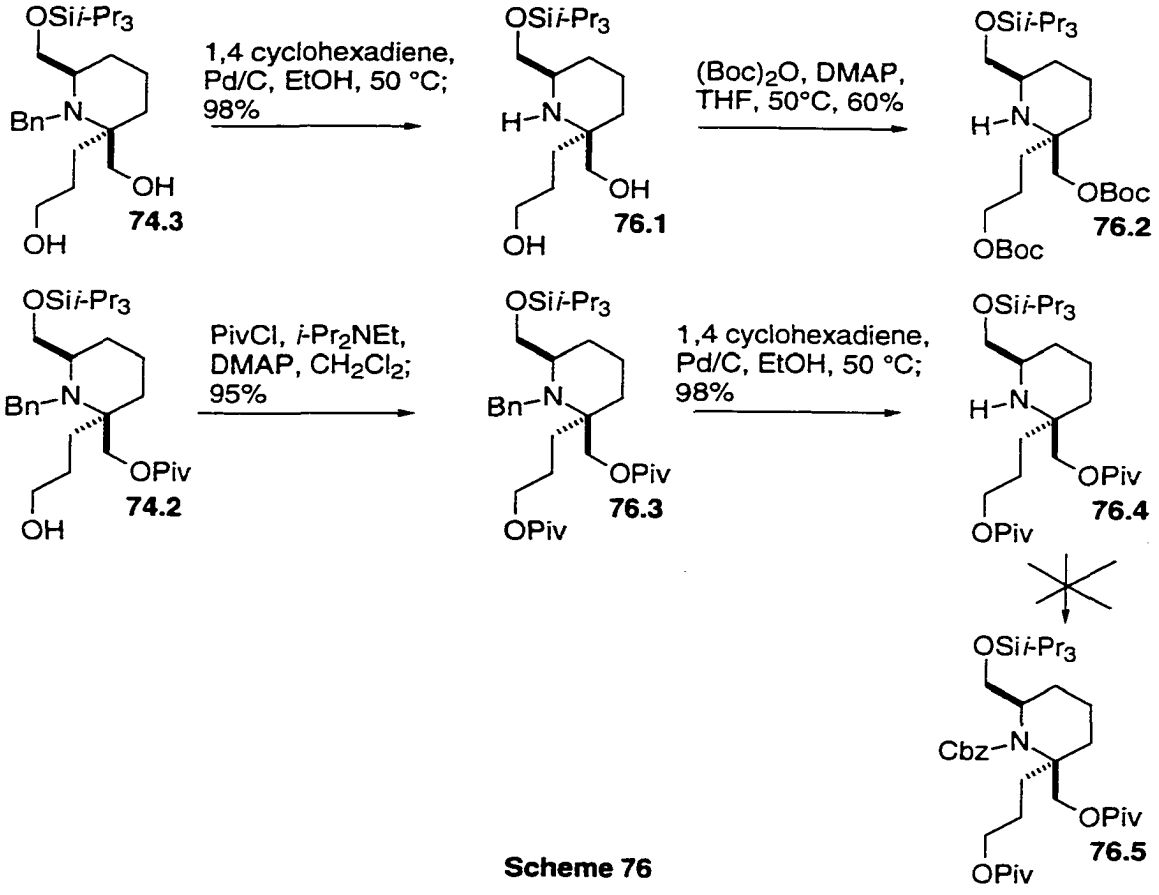
same procedure could be applied in our case. Gratifyingly, oxidation of diol **74.3** using standard Swern conditions with an excess of reagents gave dialdehyde **74.4** in near quantitative yield. The reaction mixture was precipitated with hexane and the crude dialdehyde was isolated by simple filtration and used in the following step without further purification.

The Wittig ylide ($Ph_3P=CH_2$) was generated under salt-free conditions using $(Me_3Si)_2NK$ as base, and it was allowed to react with dialdehyde **74.4** to give diene **74.5** in over 80% yield. The stage was now set for the crucial formation of the spirocyclic five-membered ring by ring closing metathesis. Treatment of diene **74.5** with Grubbs' catalyst **75.1**[65] in CH_2Cl_2 at room temperature for 24 h gave no trace of cyclized product, and the starting material was recovered quantitatively. After careful examination of the literature, we realized that there are very few examples of successful ring closing metathesis on amine substrates.[66] It is suspected that the amine nitrogen coordinates strongly to the Ru catalyst, hence poisoning its activity. Most of the successful ring closing metatheses on substrates that contain nitrogen have the nitrogen protected as a carbamate or sulfonamide.



Scheme 75

Guided by this information, we clearly needed to exchange the benzyl group in our substrate into an electron-withdrawing protecting group. The benzyl group was removed from diol **74.3** by transfer hydrogenolysis, using 1,4-cyclohexadiene as H_2 source and 10% Pd/C as catalyst, to give

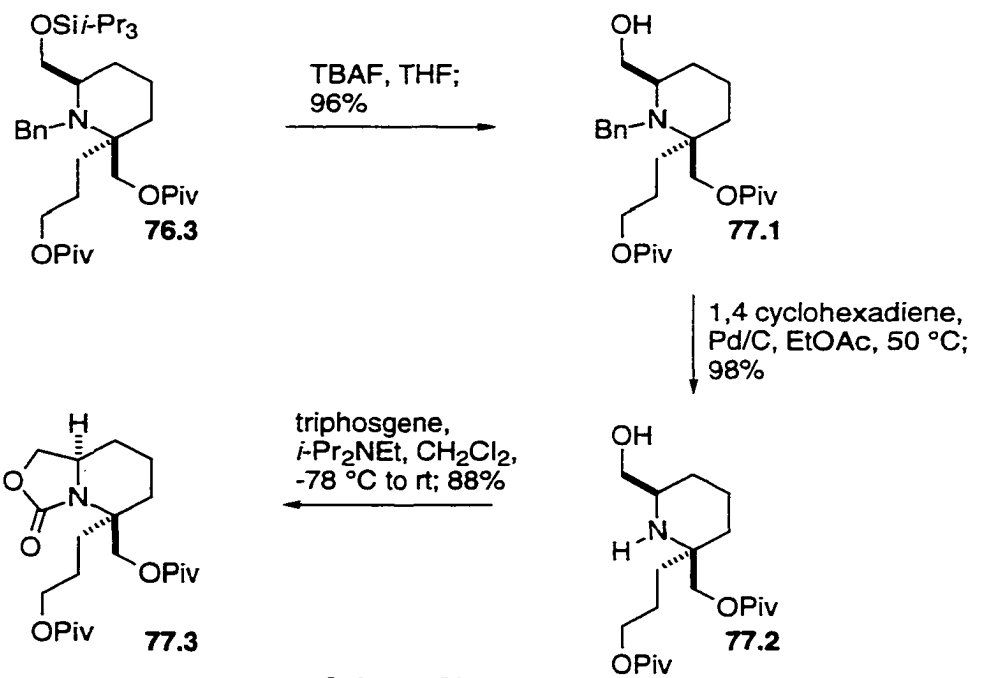


Scheme 76

76.1 in near quantitative yield. Attempted selective acylation of the nitrogen with $(Boc)_2O$ met with failure. The Boc group was installed on the primary alcohols instead and the reaction stopped at the stage of **76.2** even under forcing conditions (i.e., long reaction time and heating) (**Scheme 76**). Blocking the alcohol functionality as a pivaloyl ester **76.3**, and attempting the nitrogen protection using a more reactive acylating reagent such as CbzCl met with a similar fate. We concluded that the nitrogen in our substrate is simply too sterically hindered for intermolecular acylation reactions.

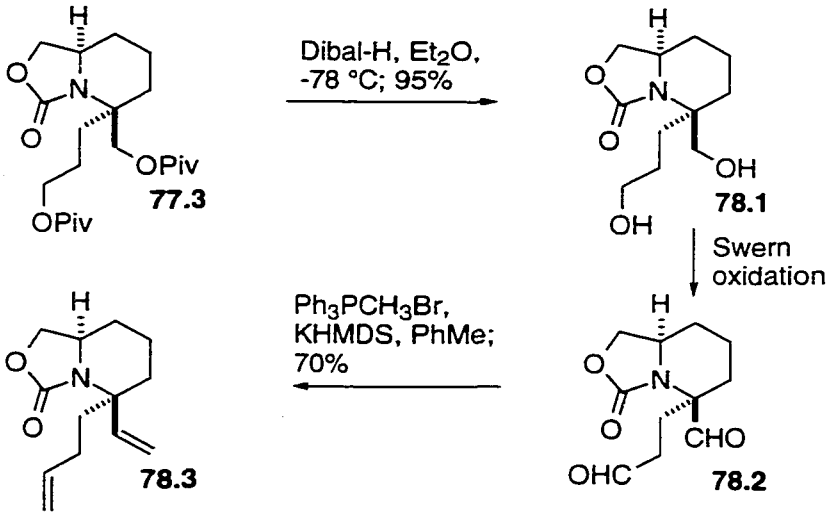
To overcome the problem of nitrogen protection, we decided to look for methods to introduce an acyl group intramolecularly. The most obvious choice would be a cyclic carbamate formed between the alcohol on C(1) and the nitrogen (see Scheme 73 for numbering). Such a carbamate protecting

group would serve not only to protect the alcohol and nitrogen functionalities, but could also be used as a handle for introduction of the side chain (*vide infra*). Towards this end, **76.3** was desilylated by treatment with TBAF to give alcohol **77.1** in near quantitative yield (**Scheme 77**). This step was followed by hydrogenolysis of the benzyl group using 1,4-hexadiene and 10% Pd/C. The reaction proceeded cleanly, and the desired amino alcohol **77.2** was isolated by simple filtration and evaporation of the solvent. The product **77.2** was then acylated with triphosgene to give carbamate **77.3** in high yield (88%).



Scheme 77

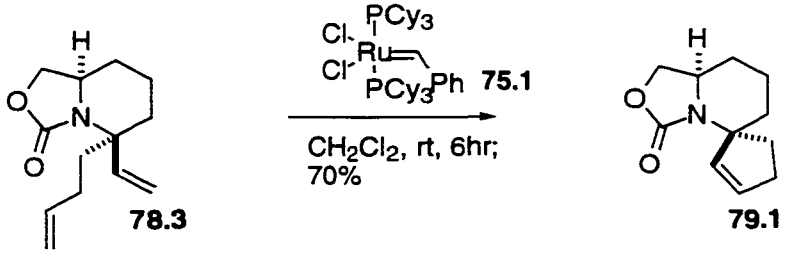
With **77.3** in hand, we proceeded to synthesize the desired diene. The *t*-BuCO groups on **77.3** were removed reductively by an excess of DIBAL-H to give diol **78.1** (95%) (**Scheme 78**). Swern oxidation of the diol gave the dialdehyde, which was isolated by simple filtration, as previously described for substrate **74.5**. The compound was used without further purification in the following Wittig olefination. Treatment of dialdehyde **78.2** with an excess of



Scheme 78

$Ph_3P{=}CH_2$ gave diene **78.3** in 70% yield from diol **78.1**.

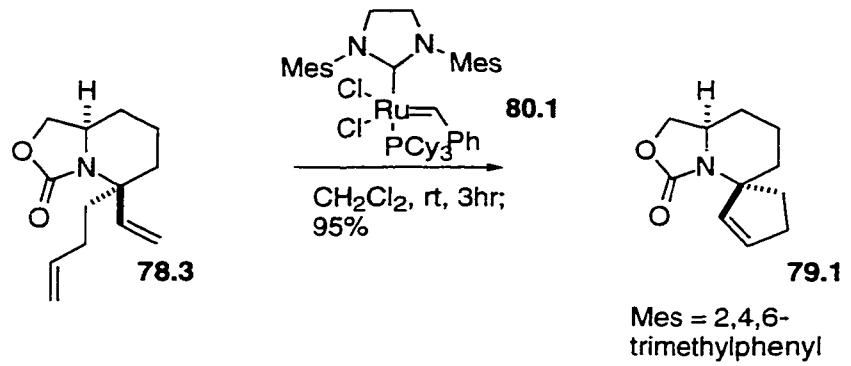
Ring closing metathesis of diene **78.3**, using alkylidene complex **75.1** gave the desired spirocyclic compound **79.1**. The reaction was carried out at room temperature for 6 h and **79.1** was isolated in 70% yield after chromatographic purification. In addition, the starting diene **78.3** was recovered (25%). The reaction seemed to have stopped, perhaps due to catalyst decomposition over the course of the reaction.[57] Nevertheless, we were gratified to reach the first milestone in our new approach towards the halichlorine core. Moreover, our example represents one of the most congested heterocyclic ring systems synthesized by ring closing metathesis.[66]



Scheme 79

The recent advent of superior *N*-heterocyclic carbene-

coordinated catalysts, such as ruthenium benzylidene **80.1**,[67] prompted us to test this catalyst on our substrate. Treatment of diene **78.3** with **80.1** gave the desired product **79.1** in nearly quantitative yield within 3 h. This result is consistent with the published reports of the superiority of **80.1** over the older catalyst, **75.1**.



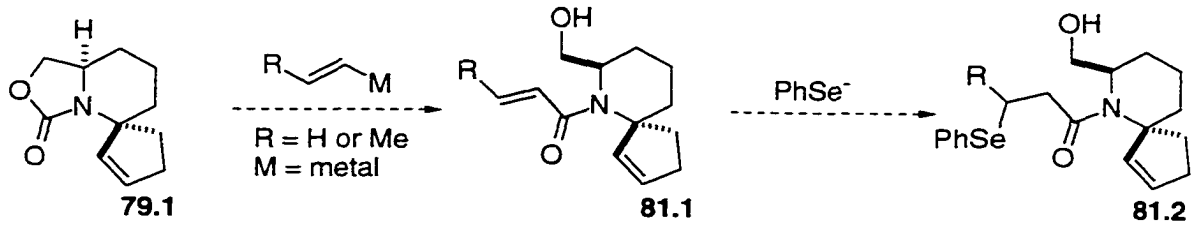
Scheme 80

The preparation of the spirocyclic olefin **79.1**, represents the point to which I have brought the synthesis. However, further work on this exciting project is continuing in our research group, and in the following section are some suggestions on how the synthesis might proceed from the spirocyclic intermediate **79.1**.

Proposals for completion of the halichlorine synthesis

Although compound **79.1** contains the azaspirocyclic ring system of halichlorine, there remain a number of formidable challenges in our total synthesis program. To carry on the synthesis from **79.1**, we envision that the side arm C(14)-C(16) can be introduced via the addition of an alkenyl organometallic species to open the internal carbamate so as to give unsaturated amide **81.1** (**Scheme 81**). There are very few examples of nucleophilic opening of carbamates reported in the literature.[68] However, this route is worth exploring due to its efficiency in utilizing a protecting group for the purpose of carbon-carbon bond formation. A homolyzable group

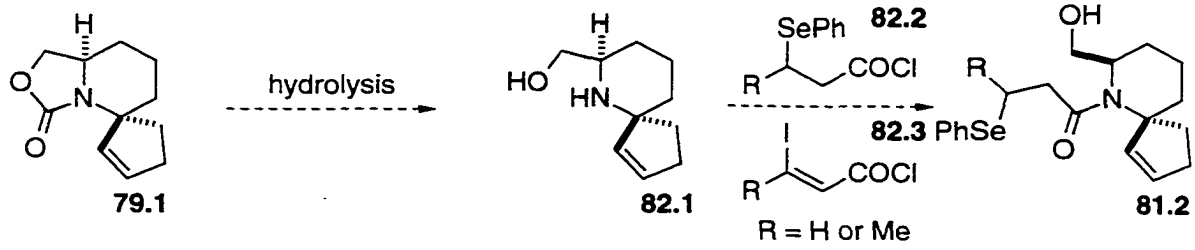
for the subsequent radical cyclization (see **Scheme 59**) will be introduced in the form of a Michael addition of $PhSe^-$ to unsaturated amide **81.1** to give cyclization precursor **81.2**.



79.1 **81.1** **81.2**

Scheme 81

Alternatively, the carbamate in compound **79.1** can be hydrolyzed under standard conditions, and the amino group selectively acylated with acid chloride **82.2** or **82.3** (**Scheme 82**). If the acylation occurs on both alcohol and amine, then the ester would be selectively hydrolyzed to give **81.2**.

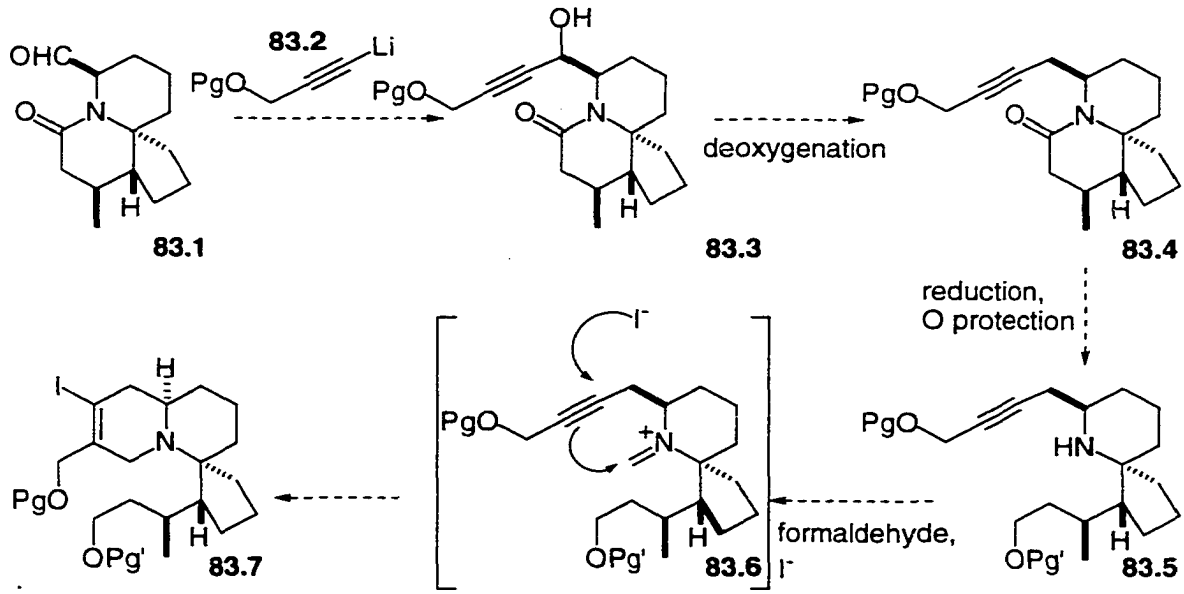


79.1 **82.1** **81.2**

Scheme 82

Following the synthetic plan outlined in Scheme 59, the tricyclic core **59.1** will serve as a starting point for the rest of the synthesis. Aldehyde **83.1**, available from **59.1** by deprotection and oxidation, will be homologated by acetylide **83.2** to alcohol **83.3** (**Scheme 83**). The extraneous alcohol functionality will be removed by the deoxygenation methodology developed during our synthesis of epibatidine (see Chapter 1). Reductive opening of lactam **83.4** by $LiNH_2BH_3$,[69] and protection of the resulting alcohol with a different protecting group (e.g. *t*-$BuMe_2Si$-) will give **83.5**. A Mannich type ring closing methodology developed by Overman,[70] involving formaldehyde and a halogen nucleophile

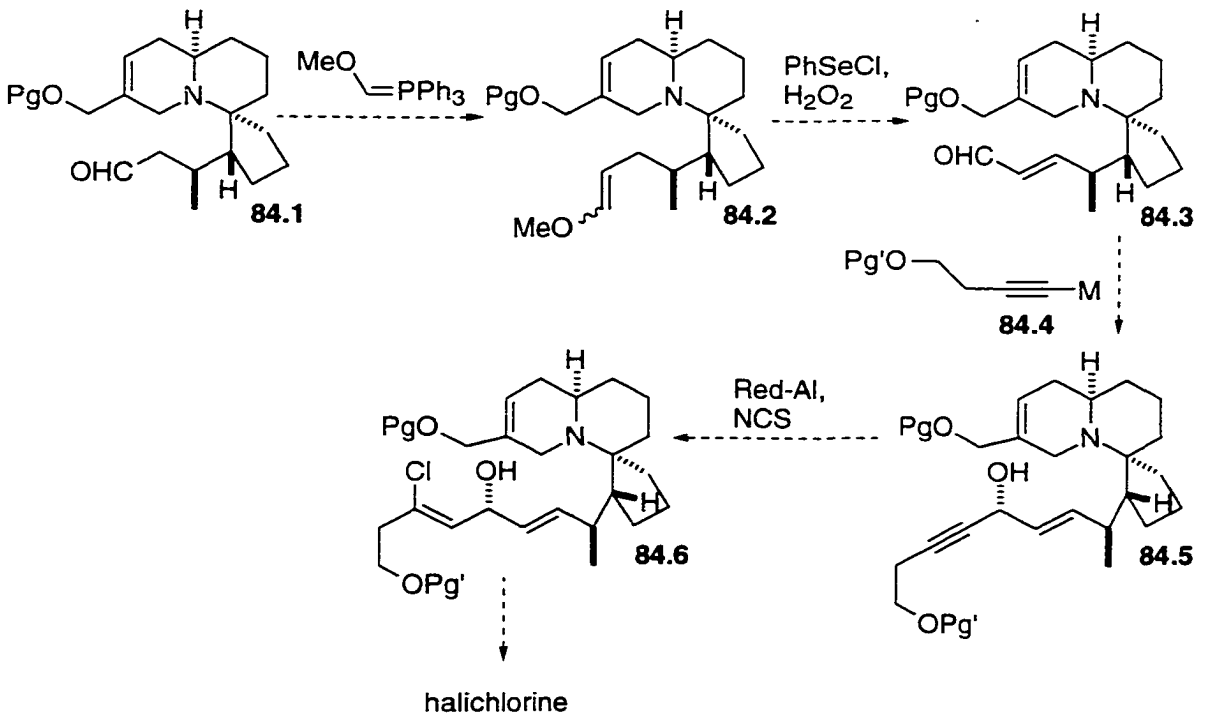
will then be applied in order to form the tetrahydropyridine ring of **83.7**. The halogen (I) will be removed by either *n*-BuLi or Bu_3SnH, and this step will be followed by selective deprotection of the C(16) alcohol and oxidation to aldehyde **84.1**.



Scheme 83

The aldehyde functionality will be used to attach the rest of the side arm. Unlike Danishefsky's synthesis, which suffered epimerization of the C(14) stereogenic center, aldehyde **84.1** is not epimerizable. Wittig homologation (**Scheme 84**) will extend the chain by one more carbon to give **84.2**, which is a masked form of aldehyde **84.3**. Unmasking the aldehyde with PhSeCl should give an intermediate selenide which, after oxidative elimination, will afford the more stable *E* unsaturated aldehyde **84.3**. The remainder of the side chain will be introduced as an acetylenic organometallic species **84.4** with the aid of a chiral ligand, such as the one developed by Carreira[71] to give alcohol **84.5** stereoselectively. If the hydroxyl-bearing stereogenic center cannot be controlled by acetylide addition, an

oxidation and reduction sequence will then be applied. There are a variety of known chiral hydride reducing agents for this task.[72]



Scheme 84

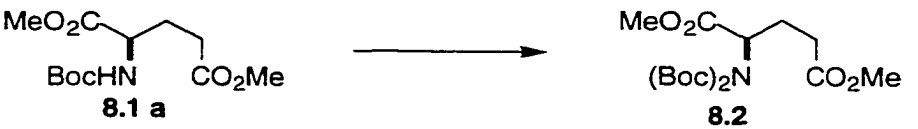
The *Z*-vinyl chloride will be installed by Red-Al reduction of the acetylene with the assistance of the alcohol, followed by an *N*-chlorosuccinimide quench to give **84.6**.[8] Selective deprotection of the C(1) alcohol, followed by oxidation to the corresponding acid, and protecting group adjustments will generate a compound that converges on Danishefsky's synthesis at a point where only two steps are required to reach halichlorine.

Experimental Section

N-[(1,1-Dimethylethoxy)carbonyl]-D-glutamic Acid Dimethyl Ester (8.1a).

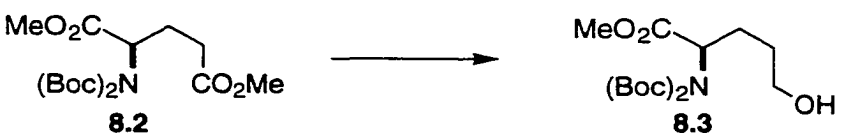
Me_3SiCl (31.0 mL, 224.6 mmol) was added to a stirred and cooled (0 °C) solution of (*R*)-glutamic acid (8.0 g, 54.37 mmol) in dry MeOH (120 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight. Et_3N (50 mL, 353.4 mmol) and $(Boc)_2O$ (13.0 g, 59.80 mmol) were then added and stirring was continued for 4 h. The solvent was evaporated, and the residue was triturated with water (100 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (10 x 30 cm), using 30% EtOAc-hexane, gave **8.1 a** (14.6 g, 98%) as a colorless oil: $[\alpha]^{25}_D$ -13.0 (*c* 1.00, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3372, 1741, 1716 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.40 (s, 9 H), 1.91 (m, 1 H), 2.13 (m 1 H), 2.39 (ddd, *J* = 7.5, 4.5 Hz, 4.5, 2 H), 3.65 (s, 6 H), 3.75 (s, 3 H), 4.28 (broad s, 1 H), 5.13 (broad s, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 28.0 (t'), 28.4 (q'), 30.3 (t'), 51.9 (q'), 52.6 (q'), 53.1 (d'), 80.1 (s'), 157.3 (s'), 173.0 (s'), 173.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{12}H_{21}NNaO_6$ 298.12665, found 298.12730. Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H 7.69, N, 5.09. Found: C, 52.19; H, 7.68; N, 4.99.

***N,N*-Bis[(1,1-dimethylethoxy)carbonyl]-D-glutamic Acid Dimethyl Ester (8.2).**



$(Boc)_2O$ (17.50 g, 80.02 mmol) was added to a stirred solution of **8.1 a** (14.69 g, 53.35 mmol) and DMAP (0.98 g, 8.0 mmol) in dry MeCN (89 mL). Stirring was continued overnight and the solvent was then evaporated. Flash chromatography of the residue over silica gel (15 cm x 30 cm), using 20% EtOAc-hexane, gave **8.2** (16.20g, 96%) as a colorless oil: $[\alpha]^{25}_D$ +41.5 (*c* 0.5, MeOH); FTIR (MeOH cast) 1795, 1744, 1701 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.42 (s, 18 H), 2.10-2.20 (m, 1 H), 2.32-2.48 (m, 3 H), 3.64 (s, 3 H), 3.69 (s, 3 H), 4.85-4.92 (m, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 25.5 (t'), 28.1 (q'), 30.8 (t'), 51.8 (q'), 52.4 (q'), 57.7 (d'), 83.5 (s'), 152.4 (s'), 171.2 (s'), 173.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{17}H_{29}NNaO_8$ 398.17908, found 398.17917. Anal. Calcd for $C_{17}H_{29}NO_8$: C, 54.39; H, 7.79; N, 3.73. Found: C, 54.50; H, 7.78; N, 3.74.

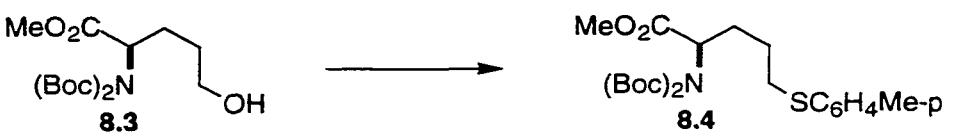
***N,N*-Bis[(1,1-dimethylethoxy)carbonyl]-5-hydroxy-D-norvaline Methyl Ester (8.3).**



DIBAL-H (1 M in hexane, 27 mL, 27 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **8.2** (7.71g, 24.47 mmol) in dry Et_2O (112 mL). The mixture was stirred for 5 min, and quenched with $Na_2SO_4.10H_2O$ (8 g). The cold bath was removed and stirring was continued until the mixture attained room temperature (ca 1 h). The resulting

thick white mixture was filtered through a pad (14 x 5 cm) of Celite, using Et_2O as a rinse. The solvent was evaporated and the resulting crude aldehyde was redissolved in THF (70 mL) and MeOH (14 mL), and cooled to 0 °C. $NaBH_4$ (0.92 g, 24.47 mmol) was added to the solution in one portion with stirring. After 5 min the mixture was quenched by dropwise addition of saturated NH_4Cl (10 mL) at 0 °C. The cold bath was removed, stirring was continued for 30 min, and the mixture was diluted with Et_2O (150 mL). The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (15 x 30 cm), using 30% EtOAc-hexane, gave **8.3** (6.0 g, 70%) as a colorless oil: $[\alpha]^{25}_D$ +33.68 (*c* 0.78, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3540, 1788, 1748, 1700 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.49 (s, 18 H), 1.50-1.61 (m, 3 H), 1.81-1.95 (m, 1 H), 2.11-2.22 (m, 1 H), 3.62 (q, J = 4.0 Hz, 2 H), 3.70 (s, 3 H), 4.84 (dd, J = 9.5, 5.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 26.7 (t'), 28.1 (q'), 29.8 9t'), 52.4 (q'), 58.3 (d'), 62.5 (t'), 83.4 (t'), 152.6 (s'), 171.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{16}H_{29}NNaO_7$ 370.18417, found 370.18430.

N,N-Bis[(1,1-dimethylethoxy)carbonyl]-5-[(4-methylphenyl)thio]-D-norvaline Methyl Ester (8.4).



Bu_3P (5.16 mL, 20.72 mmol) was added dropwise to a stirred solution of alcohol **8.3** (6.00 g, 17.27 mmol) and *p*-tolyl disulfide (5.53 g, 22.45 mmol) in CH_2Cl_2 (86 mL). Stirring was continued for 2 h and the solvent was evaporated. Flash chromatography of the residue over silica gel (13 cm x 30 cm), using 5% EtOAc-hexane, gave sulfide **8.4** (6.76 g, 86%) as a colorless oil: $[\alpha]^{25}_D$ +40.62 (*c* 6.25,

MeOH); FTIR (CH_2Cl_2 cast 1793, 1749, 1700 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.45 (s, 18 H), 1.55-1.70 (m, 2 H), 1.91-2.05 (m, 1 H), 2.12-2.25 (m, 1 H), 2.30 (s, 3 H), 2.89 (m, 2 H), 3.69 (s, 3 H), 4.81 (dd, *J* = 9.5, 5.0 Hz, 1 H), 7.08 (d, *J* = 8.5 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 21.0 (q'), 26.3 (t'), 28.1 (q'), 29.3 (t'), 34.3 (t'), 52.4, (q'), 58.1 (d'), 83.3 (s'), 130.0 (d'), 130.4 (d'), 133.4 (s'), 136.5 (s'), 152.5 (s'), 171.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{23}H_{35}NNaO_6S$ 476.20828, found 476.20790. Anal. Calcd for $C_{23}H_{35}NO_6S$: C, 60.90; H, 7.78; N, 3.09; S, 7.07. Found C, 60.67; H, 7.83; N, 3.06; S, 7.12.

N,N-Bis[(1,1-dimethylethoxy)carbonyl]-5-[(4-methylphenyl)sulfonyl]-D-norvaline Methyl Ester (8.5).

OsO_4 (2.5 wt% in *t*-BuOH, 3.90 mL, 0.30 mmol) was added to a stirred solution of sulfide **8.4** (6.76 g, 14.90 mmol) and *N*-methylmorpholine *N*-oxide (10.47 g, 89.40 mmol) in 5:5:1 THF-acetone-water (180 mL), affording a yellow solution. Stirring was continued for 20 h, the mixture was quenched by addition saturated aqueous $NaHSO_3$ (80 mL) with vigorous stirring. Stirring was continued for 30 min, and the mixture was partitioned between water (100 mL) and EtOAc (100 mL). The aqueous layer was washed with EtOAc (2 x 20 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 17 cm), using 20% EtOAc-hexane, gave sulfone **8.5** (6.97 g, 96%) as a colorless oil: $[\alpha]^{25}_D$ +31.58 (*c* 0.8, MeOH); FTIR (CH_2Cl_2 cast) 2980, 1792, 1748, 1700, 1597 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.45 (s, 18 H), 1.69 (dd, *J* = 7.0, 5.5 Hz, 1 H), 1.94 (ddd, *J* = 15.0, 7.50, 7.50 Hz, 1 H),

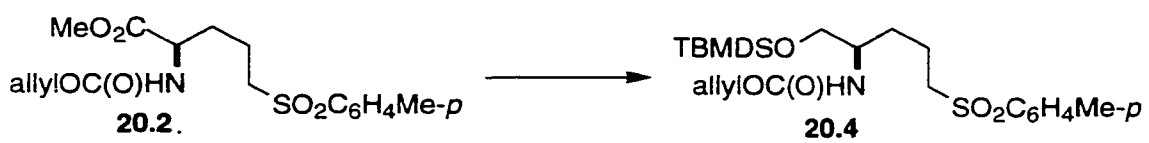
2.12 (ddd, J = 15.0, 7.50, 7.50 Hz, 1 H), 2.43 (s, 3 H), 3.09 (ddd, J = 16.0, 13.0, 7.5 Hz, 2 H), 3.65 (s, 3 H), 4.76 (dd, J = 10.0, 5.0 Hz, 1 H), 7.36 (d, J = 8.5 Hz, 2 H), 7.71 (d, J = 8.5, 2 H), ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 20.3 (t'), 21.7 (q'), 28.1 (q'), 28.9 (t'), 52.5 (q'), 56.1 (t'), 57.7 (d'), 83.6 (s'), 128.4 (d'), 130.3 (d'), 136.6 (s'), 145.2 (s'), 152.4 (s'), 171.0 (s'); exact mass (electrospray) m/z calcd for $C_{23}H_{35}NNaO_8S$ 508.19810, found 508.19680. Anal. Calcd for $C_{23}H_{35}NO_8S$: C, 56.89; H, 7.27; N, 2.88. Found: C, 56.63; H, 7.20; N, 2.77.

5-[(4-Methylphenyl)sulfonyl]-*N*-[(2-propenyloxy)-carbonyl]-D-norvaline Methyl Ester (20.2).

CF_3CO_2H (28 mL) was added dropwise to a stirred and cooled (0 °C) solution of **8.5** (11.76 g, 24.22 mmol) and Me_2S (3.55 mL, 48.43 mmol) in CH_2Cl_2 (60 mL). Stirring was continued for 20 min at 0 °C, the cold bath was removed, and stirring was continued for 3 h. The reaction was quenched by dropwise addition of saturated aqueous Na_2CO_3 (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The resulting crude amine was dissolved in freshly distilled CH_2Cl_2 (80 mL) and used without further purification. The solution was stirred and cooled (0 °C), and pyridine (4.31 mL, 53.28 mmol) and allyl chloroformate (4.62 mL, 43.59 mmol) were added successively. Stirring was continued for 3 h at 0 °C. The cold bath was removed, stirring was continued for 30 min, and the mixture was diluted with CH_2Cl_2 (100 mL), and washed with 10% hydrochloric acid (20 mL), saturated aqueous $NaHCO_3$ (2 x 20 mL) and brine, dried (Na_2SO_4), and evaporated. Flash

chromatography of the residue over silica gel (5 x 20 cm), using 20% EtOAc-hexane, gave **20.2** (8.34 g, 93%) as a colorless oil: $[a]^{25}_D$ +10.0 (c 0.7, MeOH); FTIR (MeOH cast) 3342, 2951, 1719, 1596 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 1.69-1.80 (m, 3 H), 1.89-1.93 (m, 1 H), 2.43 (s, 3 H), 3.01-3.13 (m, 2 H), 3.69 (s, 3 H), 4.26-4.30 (m, 1 H), 4.51 (d, *J* = 5.5 Hz, 2 H), 5.20 (dddd, *J* = 10.5, 4.0, 1.5, 1.5 Hz, 1 H), 5.24-5.34 (m, 2 H), 5.91 (ddd, *J* = 17.5, 12.0, 5.5 Hz, 1 H) 7.39 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 19.4 (t'), 21.7 (q'), 31.5 (t'), 52.8 (q'), 53.6 (d'), 55.8 (t'), 66.1 (t'), 117.7 (t'), 128.4 (d'), 130.3 (d'), 133.2 (d'), 136.5 (s'), 145.3 (s'), 156.0 (s'), 172.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{17}H_{23}NNaO_6S$ 392.11437, found 392.11420. Anal. Calcd for $C_{17}H_{23}NO_6S$: C, 55.27; H, 6.28; N, 3.79. Found: C, 55.23; H, 6.27; N, 3.67.

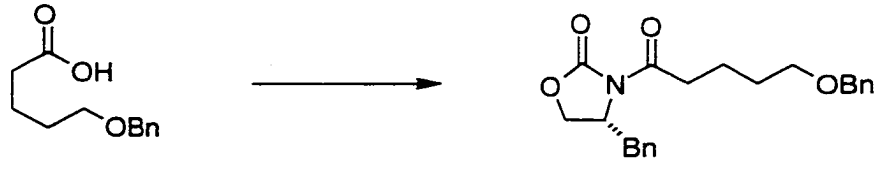
[(1R)-1-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-methyl]-4-[(4-methylphenyl)sulfonyl]butyl]carbamic Acid 2-Propenyl Ester (20.4).



Anhydrous $CaCl_2$ (3.87 g, 38.40 mmol) and $NaBH_4$ (2.90 g, 76.81 mmol) were added to a stirred and cooled (0 °C) solution of ester **20.2** (6.76 g, 18.29 mmol) in EtOH (45 mL) and THF (45 mL). The cold bath was left in place, but was not recharged, and the white suspension was stirred for 12 h. The mixture was quenched by dropwise addition of saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (100 mL). The aqueous layer was further extracted with EtOAc (2 x 100 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The resulting crude alcohol (**20.3**) was used without further purification.

Imidazole (3.72 g, 54.60 mmol) and *t*-$BuMe_2SiCl$ (6.06 g, 40.26 mmol) were added to a stirred solution of the crude alcohol **20.3** in dry THF (60 mL). Stirring was continued for 12 h, and the mixture was quenched with water (100 mL) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (7 x 30 cm), using 20% EtOAc-hexane, gave **20.4** (7.71 g, 92%) as a colorless oil: $[\alpha]^{25}_D$ +16.2 (*c* 1.30, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3352, 2953, 2928, 2857, 1721, 1648, 1528, 1301 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.89 (s, 9 H), 1.50-1.82 (m, 4 H), 2.46 (s, 3 H), 3.05 (ddd, *J* = 12.0, 9.0, 5.5 Hz, 1 H), 3.14 (m, 1 H), 3.56 (m, 3 H), 4.50 (d, *J* = 5 Hz, 1 H), 4.85 (broad d, *J* = 8 Hz, 1 H), 5.18 (dd, *J* = 10.4, 1.5 Hz, 1 H), 5.27 (ddd, *J* = 17.3, 3.5, 1.5, 1 H), 5.90 (ddd, *J* = 17.3, 10.4, 5.0 Hz, 1 H), 7.36 (d, *J* = 8.5 Hz, 1 H), 7.75 (d, *J* = 8.5, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ -5.5 (q'), 18.5 (s'), 20.0 (t'), 21.7 (q'), 26.0 (q'), 30.7 (t'), 52.1 (d'), 56.3 (t'), 65.1 (t'), 65.7 (t'), 117.4 (t'), 128.4 (d'), 130.2 (d'), 133.6 (d'), 136.7 (s'), 145.1 (s'), 156.1 (s'); exact mass (electrospray) *m/z* calcd for $C_{22}H_{37}NNaO_5SSi$ 478.20594, found 478.20551.

(4*R*)-3-[1-Oxo-5-(phenylmethoxy)pentyl]-4-(phenylmethyl)-2-oxazolidinone (11.3).



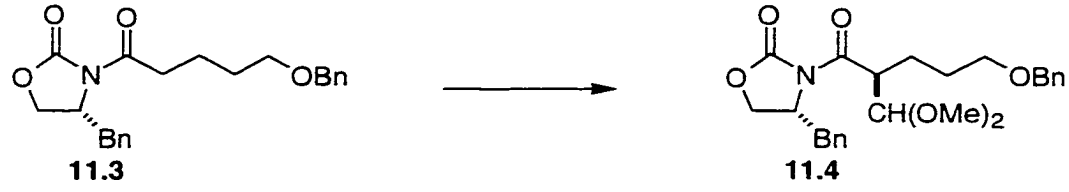
11.2 **11.3**

Et_3N (6.45 mL, 46.30 mmol) followed by *t*-BuCOCl (5.22 mL, 42.45 mmol) were added dropwise over ca 10 min to a stirred and cooled (-78 °C) solution of **11.2** (8.84 g, 42.45 mmol) in dry THF (130 mL). The reaction flask was

transferred to an ice bath, and the resulting thick white precipitate was stirred for 1 h at 0 °C, and then recooled to -78 °C.

In a separate flask, *n*-BuLi (2.5 M in hexane, 17.7 mL, 44.37 mmol) was added dropwise over ca 20 min to a stirred and cooled (-78 °C) solution of (4*R*)-4-benzyl-2-oxazolidinone (6.85 g, 38.59 mmol) in THF (100 mL). The resulting solution was transferred by cannula over ca 15 min to the flask containing the above mixed anhydride, and the mixture was stirred for 30 min at -78 °C. The cold bath was removed, and stirring was continued for 30 min, and the mixture was then quenched by addition of saturated aqueous NH_4Cl (200 mL). The mixture was extracted with Et_2O (2 x 100 mL), and the combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (30 x 15 cm), using 20% EtOAc-hexane, gave **11.3** (13.15 g, 93%) as a colorless oil: $[\alpha]^{25}_D$ -52.15 (*c* 1.39, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3062, 2921, 1781, 1699, 1495, 1386 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.64-1.83 (m, 4 H), 2.81 (dd, J = 19.3, 9.2 Hz, 1 H), 2.94 (dd, J = 15.3, 6.8 Hz, 2 H), 3.22 (dd, J = 18.5, 3.2 Hz, 1 H), 3.52 (t, J = 6 Hz, 2 H), 4.11-4.21 (m, 2 H), 4.50 (s, 2 H), 4.66 (ddd, J = 8.0, 8.0, 3.3 Hz, 1 H), 7.18-7.36 (m, 10 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 21.5 (t'), 29.5 (t'), 35.6 (t'), 38.1 (t'), 55.4 (d'), 66.6 (t'), 70.5 (t'), 73.2 (t'), 127.5 (d'), 127.7 (d'), 127.9 (d'), 128.6 (d'), 129.2 (d'), 129.6 (d'), 136.0 (s'), 139.4 (s'), 153.8 (s'), 173.3 (s'); Anal Calcd for $C_{22}H_{25}NO_4$: C, 69.5; H, 6.85. Found: C, 69.5; H, 6.80.

(4*R*)-3-[(2*S*)-2-(Dimethoxymethyl)-1-oxo-5-(phenylmethoxy)pentyl]-4-(phenylmethyl)-2-oxazolidinone (11.4).



11.3 **11.4**

$Ti(Oi\text{-}Pr)_4$ (2.05 mL, 6.89 mmol) and $TiCl_4$ (1 M in CH_2Cl_2, 20.94 mL, 20.94 mmol) were added to stirred and cooled (0 °C) CH_2Cl_2 (130 mL). After 10 min, **11.3** (9.74 g, 26.50 mmol) in CH_2Cl_2 (10 mL) was added by cannula and then $i\text{-}Pr_2NEt$ (5.19 mL, 29.15 mmol) was added dropwise. The resulting purple solution was stirred at 0 °C for 1 h, after which $HC(OMe)_3$ (3.47 mL, 31.8 mmol) was added dropwise by syringe. Stirring at 0 °C was continued for 1 h, during which time the solution gradually turned brown, and the reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (200 mL). The aqueous layer was extracted with CH_2Cl_2 (200 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (13 x 25 cm), using 20% EtOAc-hexane, gave **11.4** (10.91 g, 93%) as a viscous oil: $[a]^{25}_D$ -47.1 (*c* 3.98, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3028, 2935, 2861, 1778, 1694, 1115 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.52-1.65 (m, 2 H), 1.66-1.89 (m, 2 H), 2.79, (dd, *J* = 13.5, 9.0 Hz, 1 H), 3.19 (dd, *J* = 8.5, 3.3 Hz, 1 H), 3.36 (s, 3 H), 3.37 (s, 3 H), 3.46 (t, *J* = 6.0, 2 H), 4.11 (d, *J* = 5.5 Hz, 2 H), 4.40-4.50 (m, 1 H), 4.46 (s, 2 H), 4.60 (d, *J* = 8.2 Hz, 1 H), 4.66-4.74 (m, 1 H), 7.23-7.38 (m, 10 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 25.5 (t'), 27.5 (t'), 37.8 (t'), 45.6 (d'), 52.6 (d'), 55.5 (q'), 55.6 (q'), 66.0 (t'), 70.5 (t'), 73.1 (t'), 106.3 (d'), 127.5 (d'), 127.7 (d'), 127.9 (d'), 128.6 (d'), 129.2 (d'), 129.9 (d'), 136.0 (s'), 139.3 (s'), 153.6 (s'), 173.8 (s'); exact mass (electrospray) *m/z* calcd for $C_{25}H_{31}NNaO_6$ 464.2049, found 464.2056. Anal.

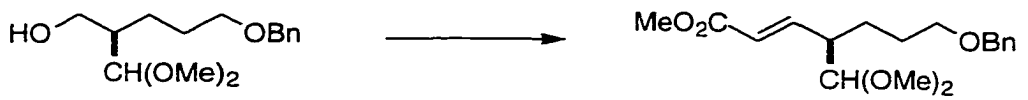
Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17. Found: C, 68.02; H, 7.05; N, 3.10.

(2*R*)-2-(Dimethoxymethyl)-5-(phenylmethoxy)-1-pentanol (11.5).

11.4 **11.5**

MeOH (1.72 mL, 42.3 mmol) and $LiBH_4$ (2 M in THF, 14.6 mL, 29.2 mmol) were added successively to a stirred and cooled (0 °C) solution of **11.4** (11.7 g, 26.5 mmol) in THF (88 mL). Stirring at 0 °C was continued for 2 h, the ice bath was removed, and stirring was continued for 5 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (100 mL) and diluted with EtOAc (200 mL). Stirring was continued for 30 min, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (7 x 35 cm), using 30% to 50% EtOAc-hexane, gave alcohol **11.5** (5.59 g, 78%) as a colorless oil: $[\alpha]^{25}_D$ +5.44 (*c* 1.01, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3457, 3029, 2934, 1603, 1453, 1100, 698 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.25-1.38 (m, 1 H), 1.42-1.55 (m, 1 H), 1.55-1.74 (m, 2 H), 1.74-1.84 (m, 1 H), 2.61 (dd, J = 7.2, 4.5 Hz, 1 H), 3.34 (s, 3 H), 3.40 (s, 3 H), 3.48 (t, J = 6.0 Hz, 2 H), 3.59 (ddd, J = 11.0, 11.0, 3.4 Hz, 2 H), 4.28 (d, J = 5.5 Hz, 1 H), 4.49 (s, 2 H), 7.23-7.37 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 23.7 (t'), 27.7 (t'), 43.2 (d'), 54.2 (q'), 56.0 (q'), 62.5 (t'), 70.9 (t'), 73.2 (t'), 109.1 (d'), 127.8 (d'), 128.0 (d'), 128.6 (d'), 139.3 (s'); exact mass (electrospray) *m/z* calcd for $C_{15}H_{24}NaO_4$ 291.1572, found 291.1565.

(2*E*,4*R*)-4-(Dimethoxymethyl)-7-(phenylmethoxy)-2-heptenoic Acid Methyl Ester (12.3).



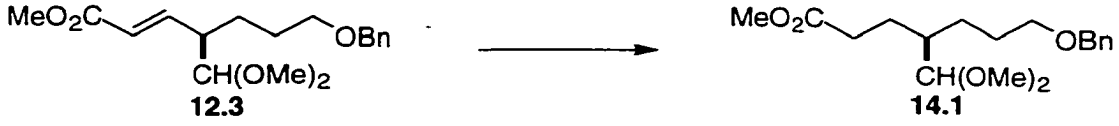
11.5 **12.3**

Dess-Martin periodinane (10.16 g, 23.95 mmol) was added in one portion to a stirred and cooled (0 °C) solution of alcohol **11.5** (5.59 g, 20.83 mmol) in CH_2Cl_2 (70 mL). After 10 min, the solution was warmed to room temperature and stirring was continued for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (100 mL) and aqueous $Na_2S_2O_3$ (1 M, 30 mL) and stirring was continued until the two phases were free of white precipitate. The aqueous layer was back-extracted with CH_2Cl_2 (2 x 70 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to afford the desired aldehyde as a pale yellow oil, which was used without further purification.

Methyl (triphenylphosphoranylidene)acetate (9.40 g, 28.12 mmol) was added in one portion to a stirred solution of the above aldehyde in freshly distilled CH_2Cl_2 (70 mL)and the resulting yellow solution was stirred for 12 h. The solvent was evaporated, and the resulting yellow precipitate was suspended in Et_2O (30 mL). The mixture was filtered through a pad (4 x 5 cm) of flash chromatography silica gel, using Et_2O as a rinse. Evaporation of the solvent, and flash chromatography of the residue over silica gel (4 x 30 cm), using 20% EtOAc-hexane, gave **12.3** (5.72 g, 85%) as a colorless oil: $[\alpha]^{25}_D$ -10.29 (*c* 0.34, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3029, 2948, 1858, 1723, 1659 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 1.32-1.75 (m, 4 H), 2.44-2.55 (m, 1 H), 3.31 (s, 3 H), 3.33 (s, 3 H), 3.44 (t, J = 6.2 Hz, 2 H), 3.72 (s, 3 H), 4.22 (d, J = 5.5 Hz, 1 H), 4.46 (s, 2 H), 5.83 (dd, J = 16.0, 1.0 Hz, 1 H), 6.75 (dd, J = 16.0, 9.6 Hz, 1 H), 7.22-7.43 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 26.4 (t'), 27.6 (t'), 46.1

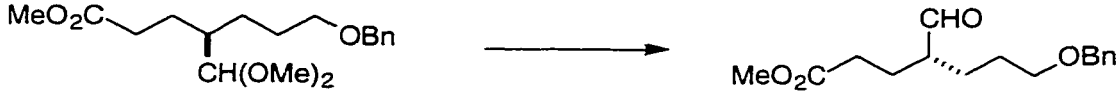
(d'), 51.6 (q'), 54.7 (q'), 70.5 (t'), 73.2 (t'), 107.0 (d'), 123.1 (d'), 127.8 (d'), 127.9 (d'), 128.6 (d'), 139.3 (s'), 148.3 (d'), 166.9 (s'). Anal Calcd for $C_{18}H_{26}O_6$: C, 67.06; H, 8.13. Found: C, 66.83; H, 8.20.

(4*R*)-4-(Dimethoxymethyl)-7-(phenylmethoxy)-heptanoic Acid Methyl Ester (14.1).



$NiCl_2.6H_2O$ (0.24 g, 1.01 mmol) and $NaBH_4$ (0.53 g, 13.92 mmol) were added successively to a stirred and cooled (0 °C) solution of **12.3** (4.08 g, 12.65 mmol) in MeOH (60 mL). After 5 min, water (150 mL) was added, and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 20% EtOAc-hexane, gave **14.1** (3.69 g, 97%) as a colorless oil: $[\alpha]^{25}_D$ +0.60 (*c* 0.50, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3029, 2947, 2860, 1737, 1257, 1200 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.24-1.36 (m, 1 H), 1.42-1.79 (m, 6 H), 2.34 (t, *J* = 7.6 Hz, 2 H), 3.31 (s, 3 H), 3.33 (s, 3 H), 3.45 (t, *J* = 6.3 Hz, 2 H), 3.63 (s, 3 H), 4.12 (d, *J* = 5.5 Hz, 1 H), 7.23-7.40 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 24.7 (t'), 26.0 (t'), 27.4 (t'), 32.0 (t'), 40.1 (d'), 51.6 (q'), 54.6 (q'), 55.0 (q'), 71.1 (t'), 73.1 (t'), 108.3 (d'), 127.7 (d'), 127.9 (d'), 128.6 (d'), 139.4 (s'), 174.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{18}H_{28}NaO$ 347.1834, found 347.1829. Anal Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.63; H, 8.88.

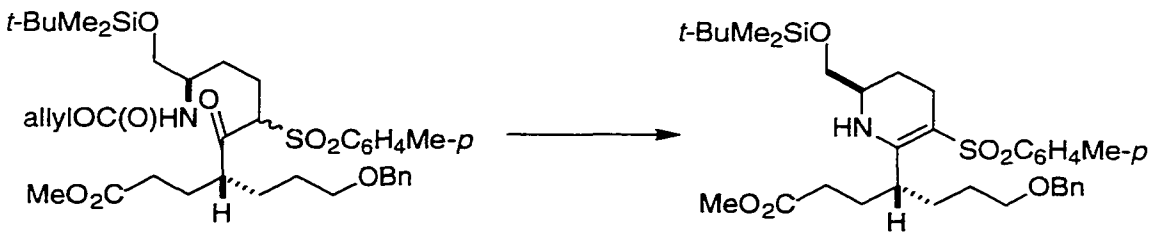
(4*R*)-4-Formyl-7-(phenylmethoxy)heptanoic Acid Methyl Ester (14.2).



14.1 **14.2**

Amberlyst-15 (0.6 g) was added to a stirred solution of acetal **14.1** (3.02 g, 9.3 mmol) in dry acetone (46 mL). Stirring was continued for 6 h, the resin was filtered off, and the solvent was evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 20% EtOAc-hexane, gave aldehyde **14.2** (2.51 g, 97%) as a clear oil: $[\alpha]^{25}_{D}$ +9.44 (*c* 1.62, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3029, 2948, 2858, 2716, 1736, 1495, 1102 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.50-1.66 (m, 3 H), 1.69-1.82 (m, 1 H), 1.94 (ddd, *J* = 21.2, 14.0, 8.2 Hz, 1 H), 2.22-2.40 (m, 3 H), 3.47 (t, *J* = 5.5 Hz, 2 H), 3.63 (s, 3 H), 4.45 (s, 2 H), 7.25-7.40 (m, 5 H), 9.57 (d, *J* = 2.4 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 24.0 (t'), 25.8 (t'), 27.4 (t'), 31.6 (t'), 51.1 (d'), 51.8 (q'), 70.3 (t'), 73.2 (t'), 127.8 (d'), 127.9 (d'), 128.6 (d'), 139.2 (s'), 173.6 (s'), 204.5 (d'); exact mass (electrospray) *m/z* calcd for $C_{16}H_{22}NaO$ 301.1415, found 301.1410.

(γ*R*,6*R*)-6-[[[(1,1-(Dimethylethyl)dimethylsilyl]-oxy]methyl]-1,4,5,6-tetrahydro-3-[(4-methylphenyl)-sulfonyl]-γ-[3-(phenylmethoxy)propyl]-2-pyridine-butanoic Acid Methyl Ester (23.2).

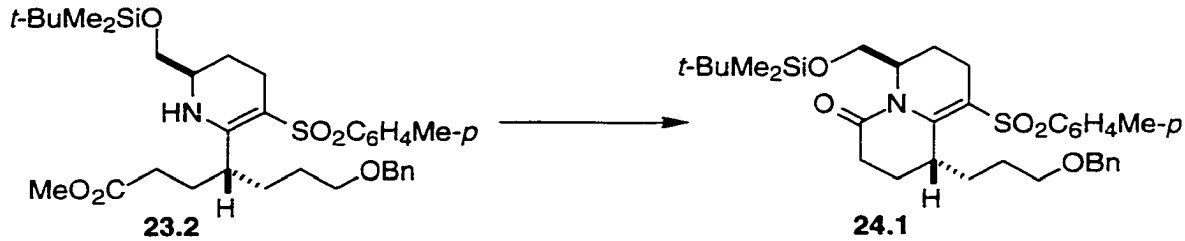


23.1 **23.2**

$Pd(PPh_3)_4$ (0.42 g, 0.36 mmol) was added to a stirred solution of **23.1** (2.66 g, 3.64 mmol) and dimedone (3.06 g, 21.84 mmol) in dry THF (36 mL) (protection from light). Stirring in the dark was continued for 3 h, at which point saturated aqueous $NaHCO_3$ (200 mL) was added to the mixture, which was then extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 20% EtOAc-hexane, gave **23.2** (2.01 g, 88%) as a faintly yellow oil: $[\alpha]^{25}_D$ -49.26 (*c* 4.88, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3433, 3378, 3061, 2950, 2856, 1737, 1585, 1517, 1494, 1278, 1083 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.06 (s, 6 H), 0.91 (s, 9 H), 1.20-1.60 (m, 6 H), 1.73-1.87 (m, 2 H), 2.18 (t, *J* = 8.2 Hz, 2 H), 2.32-2.43 (m, 1 H), 2.37 (s, 3 H), 2.61 (ddd, *J* = 16.0, 5.2, 5.2 Hz, 1 H), 3.21-3.32 (m, 1 H), 3.33-3.40 (m, 3 H), 3.62 (s, 3 H), 3.66 (dd, *J* = 9.5, 4.0 Hz, 1 H), 3.59-3.62 (m, 1 H), 3.71-3.82 (m, 1 H), 4.44 (s, 2 H), 4.70 (br s, 1 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.24-7.42 (m, 5 H), 7.78 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ -5.44 (q'), -5.36 (q'), 18.4 (s'), 21.5 (q'), 23.6 (t'), 24.0 (t'), 25.9 (q'), 27.7 (t'), 29.1 (t'), 30.9 (t'), 31.8 (t'), 37.7 (d'), 51.6 (d'), 52.6 (q'), 66.3 (t'), 70.6 (t'), 73.0 (t'), 101.7 (s'), 126.6 (d'), 127.7 (d'), 127.9 (d'), 128.6 (d'), 129.7 (d'), 139.3

(s'), 142.8 (s'), 149.6 (s'), 154.7 (s'), 173.8 (s'); exact mass (electrospray) *m/z* calcd for $C_{34}H_{52}NO_6SSi$ (M + H) 630.32846, found 630.32890.

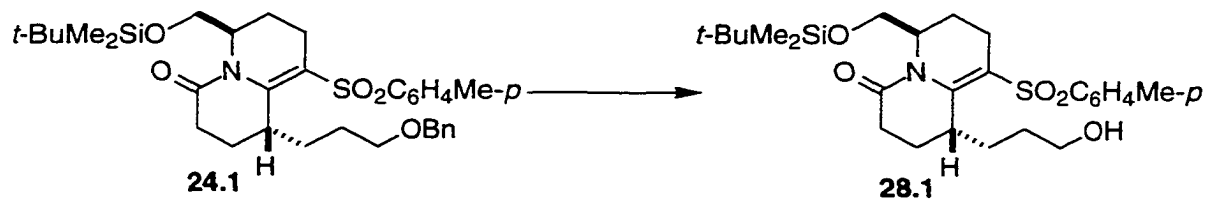
(1*R*,6*R*)-6-[[[(1,1-(Dimethylethyl)dimethylsilyl]-oxy]methyl]-1,2,3,6,7,8-hexahydro-9-[(4-methylphenyl)-sulfonyl]-1-[3-(phenylmethoxy)propyl]-4*H*-quinolizin-4-one (24.1).



n-BuLi (2.5 M in hexane, 0.88 mL, 2.19 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *n*-PrSH (0.20 g, 2.63 mmol) in dry HMPA (0.5 mL). Stirring was continued for 10 min, and the resulting white mixture was added by syringe to a stirred solution of **23.2** (0.27 g, 0.44 mmol) in HMPA (0.5 mL). Stirring was continued for 3 h, and the mixture was diluted with Et_2O (30 mL) and washed with water (2 x 10 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% EtOAc-hexane, gave **24.1** (0.19 g, 72%) as a colorless oil: $[\alpha]^{25}_D$ -48.9 (*c* 2.18 CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2952, 2928, 2856, 1734, 1685, 1587, 1360, 1257, 1181, 1088 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ -0.04 (s, 3 H), -0.01 (s, 3 H), 0.84 (s, 9 H), 1.35-1.50 (m, 3 H), 1.50-1.73 (m, 4 H), 1.79-1.89 (m, 1 H), 2.14-2.28 (m, 2 H), 2.38 (s, 3 H), 2.47-2.69 (m, 2 H), 3.26 (dd, *J* = 12.0, 9.5 Hz, 1 H), 3.32-3.50 (m, 3 H), 4.14-4.22 (m, 1 H), 4.45 (s, 2 H), 4.72-4.81 (m, 1 H), 7.28 (d, *J* = 8 Hz, 2 H), 7.30-7.35 (m, 5 H), 7.69 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ -5.4 (q'), 18.4 (s,), 19.8 (t'), 21.0 (t'), 21.6 (q'), 21.9 (t'), 25.9 (q'), 27.5 (t'), 28.5 (t'), 29.0 (t'), 32.6 (d'), 50.7 (d'),

60.7 (t'), 70.5 (t'), 73.2 (t'), 115.0 (s'), 127.0 (d'), 127.8 (d'), 127.9 (d'), 128.6 (d'), 130.1 (d'), 139.3 (s'), 140.4 (s'), 144.1 (s'), 151.4 (s'), 169.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{33}H_{47}NNaO_5SSi$ (M + Na) 620.28419; found 620.28389.

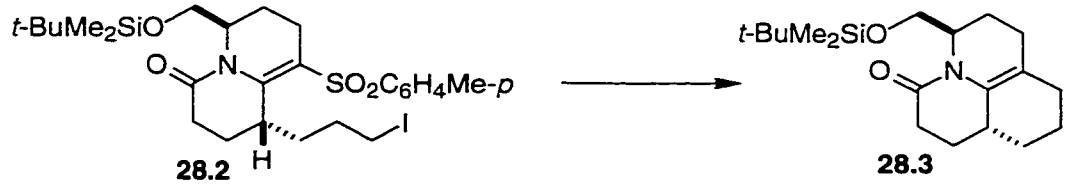
(1*R*,6*R*)-6-[[[(1,1-(Dimethylethyl)dimethylsilyl]-oxy]methyl]-1,2,3,6,7,8-hexahydro-1-[3-hydroxypropyl]-9-[(4-methylphenyl)sulfonyl]-4*H*-quinolizin-4-one (28.1).



Pd-C (10%, 35 mg) was added to a solution of **24.1** (0.157 g, 0.26 mmol) in MeOH (4 mL), and the mixture was stirred under H_2 (balloon) for 5 h, and then filtered through a pad (3 x 5 cm) of Celite, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 15 cm), using 50% EtOAc-hexane, gave alcohol **28.1** (0.124 g, 93%) as a white solid: $[\alpha]^{25}_D$ -47.51 (*c* 1.65, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3515, 2952, 2857, 1685, 1588, 1471, 1360, 1279, 1145, 1087, 838 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ -0.05 (s, 3 H), -0.09 (s, 3 H), 1.83 (s, 9 H), 1.40-1.71 (m, 6 H), 1.81 (ddd, *J* = 14.5, 5..5, 5.3 Hz, 1 H), 1.92 (br d, *J* = 4.0 Hz, 1 H), 2.10-2.28 (m, 2 H), 2.42 (s, 3 H), 2.47-2.70 (m, 3 H), 3.24 (dd, *J* = 9.8, 9.5 Hz, 1 H), 3.41 (dd, *J* = 9.5, 5.0 Hz, 1 H), 3.58 (dd, *J* = 11.4, 4.0 Hz, 2 H), 4.09-4.19 (m, 1 H), 4.75-4.84 (m, 1 H), 7.34 (d, *J* = 8.0 Hz), 7.70 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ -5.6 (q'), -5.4 (q'), 18.4 (s'), 19.5 (t'), 21.0 (t'), 21.6 (q'), 21.9 (t'), 25.9 (q'), 28.2 (t'), 28.4 (t'), 29.8 (t'), 32.0 (d'), 50.6 (d'), 60.8 (t'), 61.8 (t'), 114.6 (s'), 127.0 (d'), 130.2 (d'), 140.2 (s'), 144.3 (s'), 151.5 (s'), 169.5

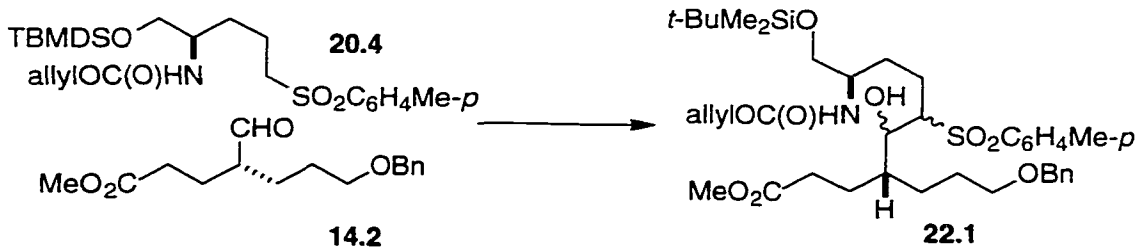
(s'); exact mass (electrospray) *m/z* calcd for $C_{26}H_{42}NO_5SSi$ (M + H) 508.25529, found 508.25530.

(3*R*,7a*R*)-3-[[[(1,1-(Dimethylethyl)dimethylsilyl]-oxy]methyl]-2,3,6,7,7a,8,9,10-octahydro-1*H*,5*H*-benzo[*i*,*j*]quinolizin-5-one (28.3).



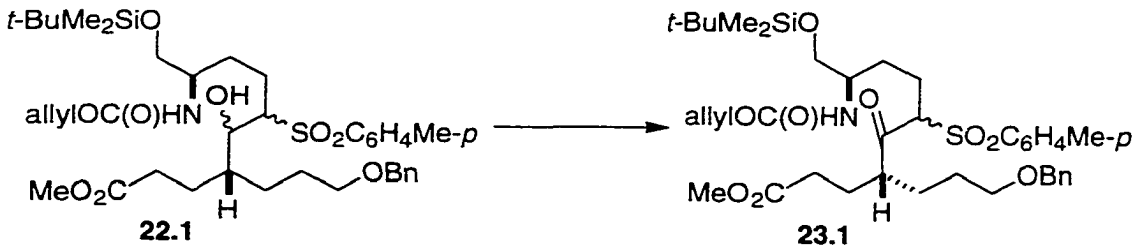
A solution of Bu_3SnH (85 mg, 0.29 mmol) and AIBN (6 mg, 0.04 mmol) in PhMe (3 mL) was added by syringe pump over 5 h to a stirred and heated (80 °C) solution of iodide **28.2** (0.12 g, 0.19 mmol) in PhMe (20 mL). Stirring was continued for 3 h after the addition. The mixture was then cooled and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% EtOAc-hexane, gave **28.3** (55 mg, 84%) as a yellow oil: $[\alpha]^{25}_D$ +113.6 (*c* 1.69, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2928, 2856, 1675, 1648, 1374, 1339, 1254, 837 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.42 (s, 3 H), 0.60 (s, 3 H), 0.89 (s, 9 H), 1.24 (ddd, *J* = 25.5, 11.6, 2.8 Hz, 1 H), 1.36-1.51 (m, 2 H), 1.58-1.69 (m, 1 H), 1.70-1.82 (m, 3 H), 1.85-2.18 (m, 6 H), 2.44 (dd, *J* = 12.4, 5.70 Hz, 1 H), 2.47 (dd, *J* = 5.5, 2.2 Hz, 1 H), 3.48 (dd, *J* = 20.0, 9.8 Hz, 1 H), 3.52 (dd, *J* = 10, 5.5 Hz, 1 H), 4.70-4.76 (m, 1 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ -5.4 (q'), -5.3 (q'), 18.4 (s'), 21.3 (t'), 22.3 (t'), 24.0 (t'), 26.0 (t'), 28.2 (t'), 30.2 (t'), 31.1 (t'), 33.1 (t'), 35.0 (d'), 49.0 (d'), 60.2 (t'), 112.0 (s'), 130.6 (s'), 167.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{19}H_{33}NNaOSi$ (M + Na) 358.21782, found 358.21777.

(4*R*,9*R*)-10-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-5-hydroxy-6-[(4-methylphenyl)sulfonyl]-4-[3-(phenylmethoxy)propyl]-9-[[(2-propenyloxy)carbonyl]-amino]decanoic Acid Methyl Ester (22.1).



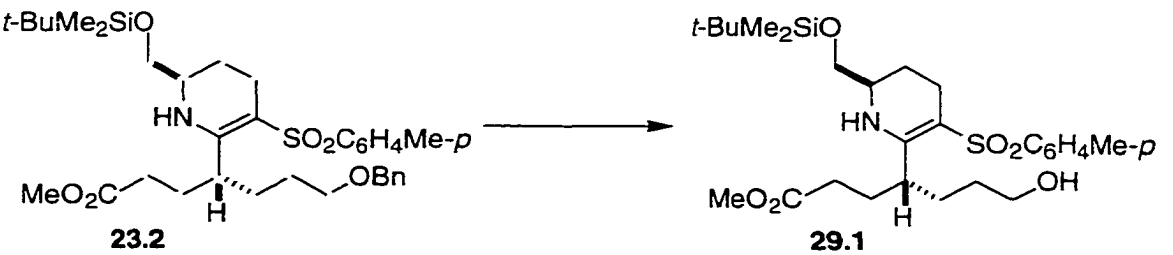
n-BuLi (7.1 mL, 2.5 M in hexane, 17.7 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of sulfone **20.4** (3.36 g, 7.38 mmol) in dry THF (35 mL). Stirring was continued for 1 h at -78 °C, and aldehyde **14.2** (1.17 g, 6.14 mmol) in THF (5 mL) was then added dropwise over 20 min at -78 °C. Stirring was continued for 30 min at -78 °C, and then saturated aqueous NH_4Cl (100 mL) was added. The mixture was extracted with Et_2O (2 x 100 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (6 x 30 cm), using 30% EtOAc-hexane, gave **22.1** (2.95 g, 66%) as a mixture of four diastereomers (^1H NMR): FTIR (CH_2Cl_2 cast) 3507, 3365, 3029, 2950, 2856, 1723, 1648, 1597, 1286, 1141, 1084, 778 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 0.03, 0.04, and 0.05 (three s, 6 H in all), 0.88, 0.89, 0.90 (three s, 9 H in all), 1.10-1.78 (m, 11 H), 1.82-2.03 (m, 2 H), 2.12-2.38 (m, 2 H), 2.42 and 2.46 (two s, 3 H in all), 2.94 (dd, J = 23.0, 2.4 Hz, 1 H), 3.08-3.14 (br s, 1 H), 3.22-3.34 (m, 2 H), 3.40-3.56 (m, 5 H), 3.61, 3.62, 3.63, 3.65 (four s, 3 H in all), 3.90 (dd, J = 20.0, 8.3 Hz, 1 H), 3.98-4.04 (m, 1 H), 4.44, 4.46, and 4.47 (three s, 2 H in all), 4.46-4.56 (m, 4 H), 4.74-5.0 (m, 1 H), 5.16-5.32 (m, 2 H), 5.88-5.96 (m, 1 H), 7.23-7.42 (m, 7 H), 7.75-7.82 (m, 2 H).

(4*R*,9*R*)-10-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-6-[(4-methylphenyl)sulfonyl]-5-oxo-4-[3-(phenyl-methoxy)propyl]-9-[[(2-propenyloxy)carbonyl]-amino]decanoic Acid Methyl Ester (23.1).



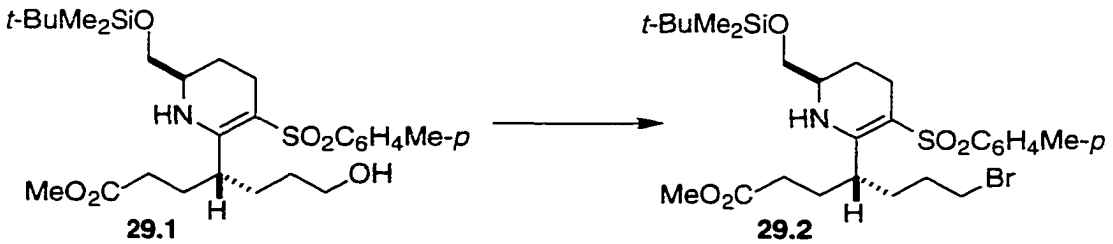
Dess-Martin periodinane (2.0 g, 4.66 mmol) was added in one portion to a stirred solution of **22.1** (2.95 g, 4.02 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 1 h, and then aqueous $Na_2S_2O_3$ (1 M, 5 mL) and saturated aqueous $NaHCO_3$ (30 mL) were added. Stirring was continued for 20 min, and the mixture was extracted with CH_2Cl_2 (20 mL x 2). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5 x 30 cm), using 20-30% EtOAc-hexane, gave ketone **23.1** (2.66 g, 90%) as a mixture of two diastereomers: FTIR (CH_2Cl_2 cast) 3372, 2951, 2856, 1719, 1648, 1597, 1317, 1304, 1252, 1148, 1085, 837 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ -0.02 and -0.01 (two s, 6 H in all), 0.84 and 0.85 (two s, 9 H in all), 1.20-1.65 (m, 7 H), 1.68-2.00 (m, 4 H), 2.25-2.40 (m, 1 H), 2.44 and 2.45 (two s, 3 H in all), 2.90-3.10 (m, 1 H), 3.34 (dd, J = 7.8, 2.0 Hz, 0.5 H), 3.40-3.56 (m, 4.5 H), 3.65 (s, 3 H), 4.47 and 4.49 (two s, 4 H in all), 4.78-4.90 (m, 1 H), 5.15-5.34 (m, 2 H), 5.84-5.98 (m, 1 H), 7.25-7.41 (m, 7 H), 7.60-7.72 (m, 2 H); exact mass (electrospray) *m/z* calcd for $C_{38}H_{57}NNaO_9SSi$ 754.3421, found 754.3414.

(γ*R*,6*R*)-6-[[[(1,1-(Dimethylethyl)dimethylsilyl]-oxy]methyl]-1,4,5,6-tetrahydro-γ-(3-hydroxypropyl)-3-[(4-methylphenyl)sulfonyl]-2-pyridinebutanoic Acid Methyl Ester (29.1).



10% Pd/C (0.5 g) was added to a solution of **23.2** (1.00 g, 1.58 mmol) in a mixture of EtOAc (5 mL) and MeOH (5 mL). The suspension was stirred under H_2 (balloon) for 5 h, and was then filtered through a pad (3 x 5 cm) of Celite, using EtOAc as a rinse. Evaporation of the solvent, and flash chromatography of the residue over silica gel (3 x 25 cm), using 50% EtOAc-hexane, gave alcohol **29.1** (0.77 g, 90%) as a colorless oil: $[\alpha]^{25}_D$ -52.96 (*c*, 1.08, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3433, 3378, 2950, 2928, 2856, 1737, 1584, 1519, 1494, 1384, 1384, 1259, 1081, 837 cm^{-1}; ^1H NMR (300 MHz, CH_2Cl_2) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.31-1.60 (m, 7 H), 1.74-1.87 (m, 2 H), 2.00-2.20 (m, 2 H), 2.34-2.46 (m, 1 H), 2.40 (s, 3 H), 2.60 (ddd, *J* = 15.5, 5.0, 5.0 Hz, 1 H), 3.22-3.33 (m, 1 H), 3.36 (t, *J* = 9.0 Hz, 1 H), 3.53 (dd, *J* = 11.3, 5.5 Hz, 2 H), 3.61 (s, 3 H), 3.68 (dd, *J* = 9.5, 4.0 Hz, 1 H), 3.20-3.80 (m, 1 H), 4.72 (br s, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ -5.5 (q'), -5.4 (q'), 15.5 (s'), 18.4 (t'), 21.5 (q'), 23.8 (t'), 24.0 (t'), 25.9 (q'), 28.6 (t'), 23.8 (t'), 24.0 (t'), 25.9 (q'), 28.6 (t'), 30.4 (t'), 31.8 (t'), 37.4 (d'), 51.7 (d'), 52.6 (q'), 62.5 (t'), 66.3 (t'), 101.5 (s'), 126.6 (d'), 129.8 (d'), 142.7 (s'), 143.0 (s'), 154.9 (s'), 173.7 (s').

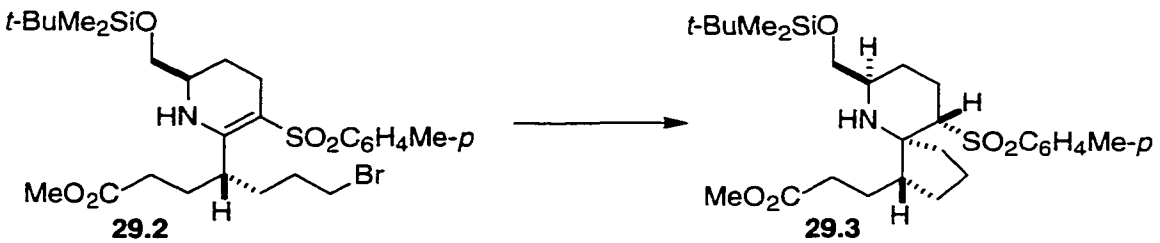
(γ*R*,6*R*)-γ-(3-Bromopropyl)-6-[[[(1,1-(dimethylethyl)dimethylsilyl]oxy]methyl]-1,4,5,6-tetrahydro-3-[(4-methylphenyl)sulfonyl]-2-pyridine-butanoic Acid Methyl Ester (29.2).



A solution of CBr_4 (0.21 g, 0.63 mmol) in dry MeCN (2 mL) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **29.1** (0.17 g, 0.32 mmol), PPh_3 (0.16 g, 0.64 mmol), and 2,6-lutidine (0.04 mL, 0.32 mmol) in MeCN (4 mL). After a further 20 min, the mixture was diluted with water (20 mL) and was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with aqueous $NaHSO_4$ (0.1 M, 2 x 3 mL), saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% EtOAc-hexane, gave bromide **29.2** (0.15 g, 80%) as a slightly yellow oil: $[\alpha]^{25}_D$ -34.0 (*c* 2.13, MeOH); FTIR (MeOH cast) 3373, 2951, 2928, 2857, 1735, 1582, 1492, 1253, 1171, 1143, 1083, 837 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ -0.06 (s, 3 H), -0.04 (s, 3 H), 0.90 (s, 9 H), 0.98-1.09 (m, 1 H), 1.20-1.28 (m, 1 H), 1.28 (dd, *J* = 15.0, 7.2 Hz, 2 H), 1.50-1.80 (m, 4 H), 1.95 (s, 3 H), 2.20-2.36 (m, 2 H), 2.41 (ddd, *J* = 15.5, 10.0, 5.0 Hz, 1 H), 2.71 (ddd, *J* = 15.5, 5.0, 5.0 Hz, 1 H), 2.82-3.05 (m, 4 H), 3.20 (dd, *J* = 9.0, 4.2 Hz, 1 H), 3.38 (s, 3 H), 4.12 (quintet, *J* = 8.0 Hz, 1 H), 4.52 (br s, 1 H), 6.90 (d, *J* = 8 Hz, 2 H), 7.90 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, C_6D_6) δ -5.5 (q'), -5.4 (q'), 18.2 (s'), 21.1 (q'), 23.6 (t'), 23.7 (t'), 25.9 (q'), 29.2 (t'), 30.5 (t'), 31.7 (t'), 32.6 (t'), 34.0 (t'), 36.8 (d'), 51.1 (d'), 52.1 (q'), 66.0 (t'), 103.4 (s'), 127.0 (d'), 129.5 (d'), 142.1 (s'), 143.2 (s'), 153.1 (s'), 173.1

(s'); exact mass (electrospray) *m/z* calcd for $C_{27}H_{45}BrNO_5SSi$ (M + H) 602.19711, found 602.19804.

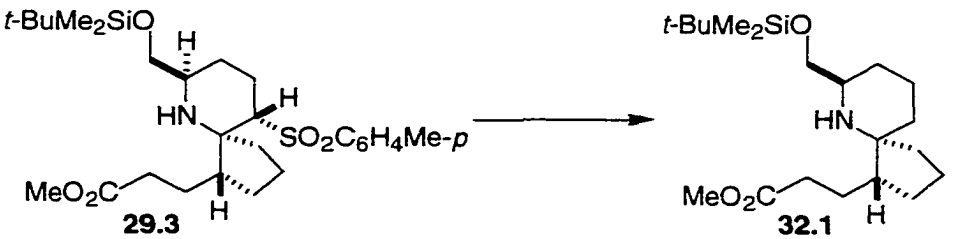
(1*R*,5*R*,7*R*,10*S*)-7-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-10-[(4-methylphenyl)sulfonyl]-6-azaspiro[4.5]decane-1-propanoic Acid Methyl Ester (29.3).



A solution of Bu_3SnH (0.15 mL, 0.58 mmol) and AIBN (20 mg, 0.11 mmol) in PhMe (6 mL) was added by syringe pump over 7 h to a stirred and heated (80 °C) solution of bromide **29.2** (0.23 g, 0.38 mmol) in PhMe (195 mL). Stirring was continued for 3 h after the addition, and the mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 10-20% EtOAc-hexane, gave **29.3** as an oil: $[\alpha]^{25}_D$ -16.03 (*c* 2.32, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3348, 2953, 2930, 2858, 1739, 1597, 1462, 1437, 1314, 1299, 1287, 1143, 1084, 1005, 837 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 0.95 (dddd, *J* = 25.0, 12.5, 5.0, 1.3 Hz, 1 H), 1.30-1.38 (m, 1 H), 1.46-1.54 (m, 2 H), 1.55 (ddd, *J* = 12.5, 7.0, 2.6 Hz, 1 H), 1.62-1.70 (m, 2 H), 1.73 (ddd, *J* = 13.5, 7.0, 3 Hz, 1 H), 1.79-1.87 (m, 2 H), 1.92 (ddd, *J* = 8.5, 8.4, 4.5 Hz, 1 H), 2.05-2.16 (m, 2 H), 2.22 (ddd, *J* = 15.5, 10.0, 6.4 Hz, 1 H), 2.36 (ddd, *J* = 15.5, 10.0, 6.4 Hz, 1 H), 2.74-2.81 (m, 2 H), 3.11 (dd, *J* = 12.5, 3.5 Hz, 1 H), 3.32 (dd, *J* = 9.5, 6.5 Hz, 1 H), 3.51 (dd, *J* = 9.5, 4.0 Hz, 1 H), 3.67 (s, 3 H), 7.38 (d, *J* = 8 Hz, 2 H), 7.76 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ -5.4 (q'), -5.3 (q'), 18.4 (s'), 20.4 (t'), 21.7 (q'), 24.2 (t'), 24.8 (t'), 26.0 (q'), 28.6 (t'), 28.9 (t'), 29.7 (t'), 33.5 (t'), 45.1 (d'),

51.1 (d'), 51.7 (q'), 65.1 (d'), 66.0 (s'), 67.3 (t'), 128.7 (d'), 130.0 (d'), 137.7 (s'), 144.8 (s'), 174.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{27}H_{46}NO_5SSi$ (M + H) 524.28659, found 524.28591.

(1*R*,5*S*,7*R*)-7-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-6-azaspiro[4.5]decane-1-propanoic Acid Methyl Ester (32.1).



Na(Hg) (10%, 0.23 g) and Na_2HPO_4 (44 mg) were added to a stirred solution of sulfone **29.3** (27 mg, 0.051 mmol) in dry MeOH (2 mL). The reaction was monitored by TLC (silica, 20% EtOAc-hexane), and after 3 h an additional portion of the amalgam (0.10 g) was added. Stirring was continued, and as soon as the starting material had been completely consumed (ca 5 h), the mixture was diluted with Et_2O (40 mL), washed with water (2 x 10 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 10% EtOAc-hexane, gave **32.1** (14 mg, 76%) as an oil: $[\alpha]^{25}_D$ -6.29 (*c* 0.27, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2929, 2858, 1741, 1471, 1438, 1360, 1256, 1086, 837, 777 cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.19-1.70 (m, 13 H), 1.78-1.90 (m, 2 H), 1.99 (ddd, *J* = 12.0, 8.0, 4.5 Hz, 1 H), 2.26 (ddd, *J* = 15.0, 9.5, 5.5 Hz, 1 H), 2.36 (ddd, *J* = 15.0, 9.5, 5.5 Hz, 1 H), 2.71-2.80 (m, 1 H), 3.34 (dd, *J* = 9.5, 7.5 Hz, 1 H), 3.52 (dd, *J* = 9.5 4.0 Hz, 1 H), 3.63 (s, 3 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ -5.3 (q'), -5.2 (q'), 18.5 (s'), 21.5 (t'), 22.7 (t'), 24.9 (t'), 26.0 (q'), 29.2 (t'), 29.9 (t'), 33.8 (t'), 34.4 (t'), 35.8 (t'), 50.2 (d'), 51.6 (d'), 53.2 (q'), 62.9 (s'), 68.5 (t'),

174.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{20}H_{40}NO_3Si$ 370.2777, found 370.2775.

(4*S*)-3-[(2*E*,4*R*)-4-(Dimethoxymethyl)-1-oxo-7-(phenylmethoxy)-2-heptenyl]-4-phenyl-2-oxazolidinone (39.1).

$LiOH.H_2O$ (3.15 g, 75.2 mmol) was added in one portion to a stirred solution of ester **12.3** (4.85 g, 15.0 mmol) in 2:2:1 THF-MeOH-water (150 mL) and the resulting yellow solution was stirred for 12 h (Ar atmosphere). The mixture was acidified to pH 2 with saturated aqueous citric acid and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with water (2 x 30 mL) and brine, dried ($MgSO_4$), and evaporated. The crude acid was used in the following step without further purification.

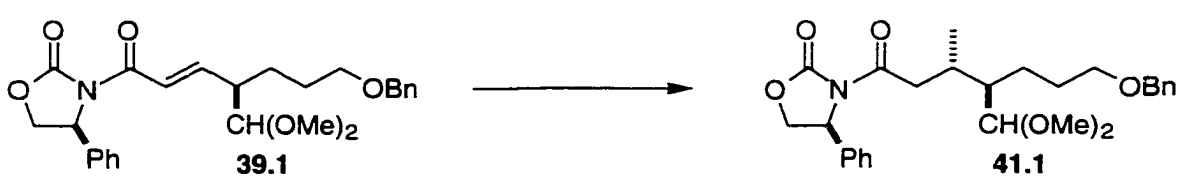
Et_3N (2.51 mL, 18.04 mmol), followed by pivaloyl chloride (2.22 mL, 18.04 mmol), were added to a stirred and cooled (-78 °C) solution of the above crude acid in freshly distilled THF (75 mL), and the resulting solution was stirred for 10 min at -78 °C and then for 1 h at 0 °C to obtain a thick white mixture.

Meanwhile, *n*-BuLi (2.5 M in hexanes, 12 mL, 29.00 mmol) was added over 10 min to a stirred and cooled (-78 °C) solution of 4-phenyl-2-oxazolidinone (4.45 g, 27.27 mmol) in THF (180 mL), and the resulting mixture was stirred for an additional 10 min at -78 °C.

The above lithium salt of the oxazolidinone was transferred via a cannula over ca 20 min to a stirred and cooled (-78 °C) solution of the above mixed anhydride, and stirring was continued for 1 h. Saturated aqueous NH_4Cl (100

mL) was added, the cold bath was removed, and the mixture was stirred for 30 min, and extracted with Et_2O (300 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (40 x 10 cm), using 30% EtOAc-hexane, gave imide **39.1** (5.25g, 77%) as a thick yellow oil, and recovered oxazolidinone (1.5 g). Imide **39.1** had: $[\alpha]^{25}_D$ +56.1 ° (*c* 0.52 in CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3031, 2935, 1777, 1687, 1636, 1454, 1383 cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ 1.32-1.64 (m, 3 H), 1.65-1.73 (m, 1 H), 2.60 (dddd, *J* = 10.3, 8.0, 6.0, 6.0 Hz, 1 H), 3.31 (s, 3 H), 3.32 (s, 3 H), 3.42 (t, *J* = 6 Hz, 2 H), 4.22 (d, *J* = 6.0 Hz, 1 H), 4.23 (dd, *J* = 9.0, 4.0, Hz, 1 H), 4.44 (s, 2 H), 4.69 (t, *J* = 8.9 Hz, 1 H), 5.44 (dd, *J* = 9.0, 4.0 Hz, 1 H), 6.87 (dd, *J* = 15.5, 9.5 Hz, 1 H), 7.25 (dd, *J* = 15.5, 0.5 Hz, 1 H), 7.22-7.41 (m, 10 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 26.4 (t'), 27.6 (t'), 46.4 (d'), 54.4 (q'), 54.6 (q'), 58.1 (d'), 70.5 (t'), 70.6 (t'), 73.1 (t'), 106.8 (d'), 122.4 (d'), 126.4 (d'), 127.7 (d'), 127.9 (d'), 128.6 (d'), 128.9 (d'), 129.4 (d'), 139.3 (s'), 139.8 (s'), 139.8 (s'), 150.3 (d'), 154.1 (s'), 164.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{26}H_{31}NNaO_6$ 476.2049; found 476.2043.

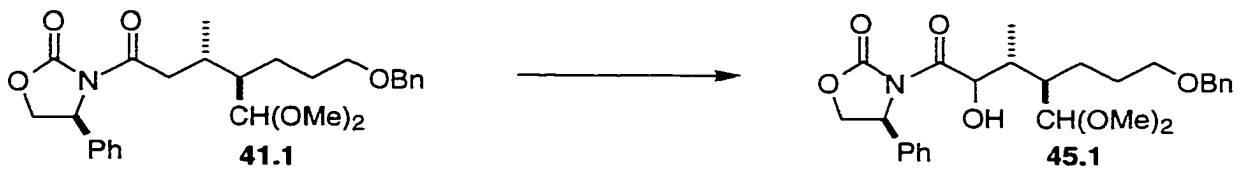
(4*S*)-3-[(3*S*,4*R*)-4-(Dimethoxymethyl)-3-methyl-1-oxo-7-(phenylmethoxy)heptyl]-4-phenyl-2-oxazolidinone (41.1).



MeMgBr (3 M in Et_2O, 7.72 mL, 23.16 mmol) was added dropwise to a stirred and cooled (-78 °C) and stirred suspension of CuBr.Me_2S (3.57 g, 17.37 mmol) in THF (23 mL) and Me_2S (13 mL). The resulting yellow suspension was

stirred for 15 min at -78 °C and the flask was then transferred to a cold bath at -10 °C, and stirring was continued for an additional 15 min. A solution of imide **39.1** (5.25 g, 11.58 mmol) in 2:1 THF-CH_2Cl_2 (50 mL) was transferred over ca 15 min via cannula into the stirred and cooled (-78 °C) cuprate solution. Stirring was continued for 30 min at -78 °C and the reaction flask was transferred to a cold bath at -10 °C. Stirring was continued for 1 h, and the reaction was quenched with saturated aqueous NH_4Cl (100 mL) and diluted with Et_2O (300 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (40 x 7 cm), using 10-30% EtOAc-hexane, gave imide **41.1** (4.70 g, 86%) as a viscous oil that solidified on standing: $[\alpha]^{25}_D$ +44.3 (*c* 0.83, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3010, 2935, 2875, 1781, 1781, 1704, 1603, 1454, 1384, 1100 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.84 (d, *J* = 7.0 Hz, 3 H), 1.28-1.42 (m, 2 H), 1.52-1.64 (m, 3 H), 1.64-1.74 (m, 1 H), 2.32 (dddd, *J* = 8.0, 7.5, 7.5, 4.5 Hz, 1 H), 2.88 (dddd, *J* = 16.0, 12.5, 12.5, 12.5 Hz, 1 H), 3.28 (s, 3 H), 3.30 (s, 3 H), 3.44 (t, *J* = 6.5 Hz, 2 H), 4.18 (d, *J* = 6.0 Hz, 1 H), 4.20 (dd, *J* = 9.0, 4.0 Hz, 1 H), 4.46 (s, 2 H), 4.64 (t, *J* = 9.0 Hz, 1 H), 5.38 (dd, *J* = 8.50, 3.50, Hz, 1 H), 7.20-7.39 (m, 10 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 16.3 (q'), 23.0 (t'), 29.3 (t'), 29.7 (d'), 40.5 (t'), 44.1 (d'), 54.2 (q'), 54.8 (q'), 58.0 9d'), 70.3 (t'), 71.2 ('t), 73.0 (t'), 107.9 (d'), 126.2 (d'), 127.7 (d'), 127.9 (d'), 128.6 (d'), 128.8 (d'), 129.4 (d'), 139.5 (s'), 140.0 (s'), 154.1 (s'), 172.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{27}H_{35}NNaO_6$ 492.2362, found 492.2367.

(4*S*)-3-[(3*S*,4*R*)-4-(Dimethoxymethyl)-2-hydroxy-3-methyl-1-oxo-7-(phenylmethoxy)heptyl]-4-phenyl-2-oxazolidinone (45.1).



$(Me_3Si)_2NNa$ (1 M in THF, 10.2 mL, 10.2 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of imide **41.1** (4.00 g, 8.53 mmol) in THF (40 mL). Stirring was continued for 45 min and a cooled (-78 °C) solution of Davis' reagent (3.12 g, 11.95 mmol) in THF (40 mL) was transferred over ca 15 min via cannula into the stirred enolate solution. After 15 min, the reaction was quenched at -78 °C with a solution of acetic acid (2.56 g, 42.6 mmol) in THF (40 mL). The cold bath was removed, stirring was continued for 30 min, and the mixture was diluted with Et_2O (300 mL). The ether layer was washed with saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue, which was a 1:1 diastereomeric mixture of hydroxy imides (^1H NMR), over silica gel (40 x 10 cm), using 10-30% EtOAc-hexane, gave one diastereomer (0.50 g) and a mixture of diastereomers of **45.1** (3.80 g) (the combined yield amounts to 92%). The single diastereomer had: FTIR (CH_2Cl_2 cast) 3499, 3063, 2937, 1782, 1709, 1200 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.82 (d, *J* = 7.0 Hz, 3 H), 1.38-1.50 (m, 1 H), 1.53-1.75 (m, 3 H), 1.80-1.89 (m, 1 H), 2.20 (dddd, *J* = 7.0, 7.0, 4.5, 4.5 Hz, 1 H), 3.23 (d, *J* = 7.5 Hz, 1 H), 3.32 (s, 3 H), 3.36 (s, 3 H), 3.44 (t, *J* = 6.0 Hz, 2 H), 4.30 (dd, *J* = 9.5, 3.0 Hz, 1 H), 4.31 (d, *J* = 5.0 Hz, 1 H), 4.47 (s, 2 H), 4.74 (t, *J* = 8.5 Hz, 1 H), 5.19 (dd, *J* = 8.0, 3.0 Hz, 1 H), 5.36 (dd, *J* = 8.5, 3.0 Hz, 1 H), 7.21-7.45 (m, 10 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 10.1 (q'), 23.2 (t'), 29.0 (t'), 35.7 (d'), 43.8 (d'), 54.5 (q'), 55.2 (q'), 58.5 (d'), 71.3 (t'), 73.0 (t'),

73.9 (d'), 107.9 (d'), 126.1 (d'), 126.4 (d'), 127.7 (d'), 127.9 (d'), 128.6 (d'), 129.5 (d'), 139.3 (s'), 139.5 (s'), 153.6 (s'), 174.7 (s'); exact mass (electrospray) *m/z* calcd for $C_{27}H_{35}NNaO_7$ 508.2311, found 508.2322.

(3*R*,4*R*)-4-(Dimethoxymethyl)-3-methyl-7-(phenylmethoxy)-1,2-heptanediol (45.2).

$LiBH_4$ (2 M in THF, 5.86 mL, 11.71 mmol) was added dropwise to a stirred and cooled (-10 °C) solution of hydroxyimide **45.1** (4.95 g, 10.19 mmol) in Et_2O (100 mL) and MeOH (0.47 mL, 11.71 mmol). Stirring was continued for 1 h at -10 °C and the mixture was then quenched with saturated aqueous $NaHCO_3$ (50 mL). The cold bath was removed, stirring was continued for 1 h, and the mixture was then extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (8 x 40 cm), using a gradient of 50% EtOAc-hexane, EtOAc and 10% MeOH-EtOAc, gave a single diastereomer (0.50 g) plus a mixture of diastereomers of **45.2** (2.07 g) (the combined yield amounts to 77%). The single diastereomer had: $[\alpha]^{25}_D$ -2.95 (*c* 0.44, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3416, 3062, 2933, 1453, 1102, 1071 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.92 (d, J = 8.0 Hz, 3 H), 1.40-1.50 (m, 1 H), 1.54-1.69 (m, 3 H), 1.70-1.80 (m, 1 H), 1.95 (dd, J = 8.0, 4.0 Hz, 1 H), 2.95 (d, J = 2.9 Hz, 1 H), 3.48 (s, 6 H), 3.46 (t, J = 6.0 Hz, 2 H), 3.42-3.56 (m, 3 H), 3.77 (sextet, J = 6 Hz, 1 H), 4.27 (d, J = 4.5 Hz, 1 H), 4.50 (s, 2 H), 7.20-7.38 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 11.8 (q'), 24.2 (t'), 28.8 (t'), 35.6 (d'), 44.2 (d'), 55.6 (q'), 55.8 (q'), 65.7 (t'), 70.9 (t'), 73.0 (d'), 73.2 (t'),

108.5 (d'), 127.8 (d'), 128.0 (d'), 128.6 (d'), 139.3 (s'); exact mass (electrospray) *m/z* calcd for $C_{18}H_{30}NaO$ 349.1991, found 349.1984.

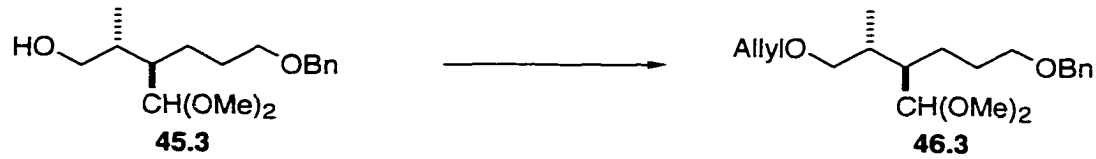
(2*R*,3*R*)-3-(Dimethoxymethyl)-2-methyl-6-(phenylmethoxy)-1-hexanol (45.3).

45.2 **45.3**

$Pb(OAc)_4$ (1.64 g, 3.71 mmol) was added in one portion to a stirred and cooled (0 °C) mixture of diol **45.2** (1.10 g, 3.38 mmol) and AcOK (1.86, 18.92 mmol) in dry MeCN (42 mL). After the diol was consumed (ca 5 min, tlc control, silica, 50 EtOAc-hexane), the mixture was diluted with Et_2O (300 mL) and filtered through a pad (5 x 10 cm) of Celite, using Et_2O as a rinse. The solvent was evaporated and the crude aldehyde was redissolved in 5:1 THF-MeOH (25 mL). $NaBH_4$ (0.38 g, 10.14 mmol) was added in portions to the stirred and cooled (0 °C) aldehyde solution. After 0.5 h, the ice bath was removed and stirring was continued for 3 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with Et_2O (100 mL). The organic extract was washed with water and brine, dried, ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 20% EtOAc-hexane, gave alcohol **45.3** as a clear oil (0.926 g, 84%): $[\alpha]^{25}_D$ +49.51 (*c* 1.66, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3474, 3029, 2931, 1495, 1453, 1099 cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ 0.89 (d, J = 7.5 Hz, 3 H), 1.35-1.42 (m, 2 H), 1.55-1.72 (m, 2 H), 1.75 (quintet, J = 6.5 Hz, 1 H), 1.81-1.91 (m, 1 H), 2.09 (br s, 1 H), 3.34 (s, 3 H), 3.36 (s, 3 H), 3.37-3.53 (m, 4 H), 4.24 (d, J = 5.0 Hz, 1 H), 4.48 (s, 2 H), 5.25-5.39 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.1 (q'), 23.5 (t'), 28.9 (t'), 35.9 (d'), 42.1 (d'), 54.9 (q'), 55.2 (q'), 66.3 (t'), 71.1

(t'), 73.1 (t'), 108.4 (d'), 127.8 (d'), 128.0 (d'), 128.6 (d'), 139.3 (s').

(6*R*,7*R*)-7-(Dimethoxymethyl)-6-methyl-4-oxa-10-(phenylmethoxy)-1-decene (46.3).



45.3 **46.3**

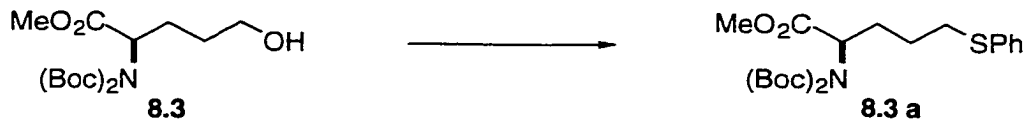
NaH (80% in oil, 0.81 g, 27.10 mmol) was added in one portion to a stirred and cooled (0 °C) solution of alcohol **45.3** (0.52 g, 5.41 mmol) in dry DMF (18 mL). After 5 min the ice bath was removed and stirring was continued for 1 h. Allyl bromide (0.59 mL, 6.77 mmol) was added dropwise at 0 °C and then Bu_4NI (0.60 g, 1.62 mmol) was added in one portion. The ice bath was left in place, but not recharged, and stirring was continued for 8 h. The mixture was then quenched by dropwise addition of MeOH (0 °C) and diluted with Et_2O (100 mL) and water (100 mL). The organic layer was washed with water (2 x 50 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 10 EtOAc-hexane, gave allyl ether **46.3** as a colorless oil (1.62 g, 90%): $[\alpha]^{25}_D$ -0.17 (*c* 0.58, CH_2Cl_2), FTIR (CH_2Cl_2 cast) 2932, 2855, 1475, 1101 cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ 0.85 (d, *J* = 7.5 Hz, 3 H), 1.31-1.40 (m, 2 H), 1.50-1.82 (m, 3 H), 2.01-2.09 (m, 1 H), 3.21 (dd, *J* = 12, 7.5 Hz, 1 H), 3.34 (s, 3 H), 3.35 (dd, *J* = 12, 7.5 Hz, 1 H), 3.36 (s, 3 H), 3.45 (t, *J* = 6 Hz, 2 H), 3.94 (dd, *J* = 5.5, 2.5 Hz, 2 H), 4.23 (d, *J* = 5.0 Hz, 1 H), 5.08-5.28 (m, 2 H), 5.86-5.98 (m, 1 H), 7.24-7.45 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 13.2 (q'), 22.5 (t'), 29.5 (t'), 33.2 (d'), 41.3 (d'), 54.2 (q'), 54.9 (q'), 71.2 (t'), 72.0 (t'), 73.0 (t'), 74.4 (t'), 108.1 (d'), 116.1 (t'), 127.7 (d'), 127.9 (d'), 128.6 (d'), 135.9 (d'), 139.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{20}H_{32}NaO_4$ 359.2198, found 359.2197.

(2*R*,3*R*)-3-Methyl-5-oxa-2-[3-(phenylmethoxy)-propyl]-7-octenal (47.2).

46.3 **47.2**

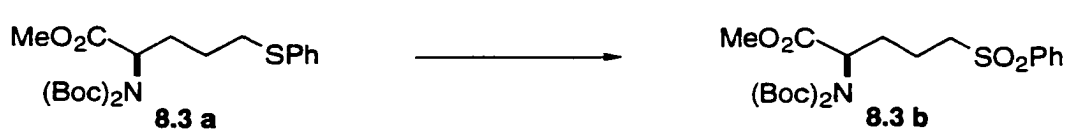
Amberlyst-15 (0.10 g) was added in one portion to a stirred solution of acetal **46.3** (0.459 g, 1.36 mmol) in dry acetone (7 mL). Stirring was continued for 1 h, the resin was filtered off, the solvent was evaporated, and the residue was dissolved in Et_2O (20 mL). The ether solution was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The crude aldehyde **47.2** (0.387 g, ca 99%) was obtained as a colorless oil and was used without further purification: $[\alpha]^{25}_D$ -9.59 (*c* 0.49, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2932, 2857, 1721, 1646, 1100 cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ 0.91 (d, J = 7.0 Hz, 3 H), 1.45-1.72 (m, 4 H), 2.19 (quintet, J = 6.5 Hz, 1 H), 2.26 (dddd, J = 10.5, 9.0, 9.0, 6.5 Hz, 1 H), 3.28 (dd, J = 10.0, 7.0 Hz, 1 H), 3.37 (dd, J = 10.0, 5.0 Hz, 1 H), 3.46 (t, J = 5.5 Hz, 2 H), 3.91 (d, J = 6.0 Hz, 2 H), 4.48 (s, 2 H), 5.13 (ddd, J = 10.5, 3.5, 1.5 Hz, 1 H), 5.23 (ddd, J = 16.5, 3.5, 1.5 Hz, 1 H), 5.88 (dddd, J = 16.5, 16.5, 6.5, 5.0 Hz, 1 H), 7.21-7.35 (m, 5 H), 9.60 (d, J = 3.5, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ, 14.3 (q'), 22.4 (t'), 28.2 (t'), 34.4 (d'), 54.9 (d'), 70.4 (t'), 72.2 (t'), 73.1 (t'), 73.5 (t'), 116.5 (t'), 127.8 (d'), 127.9 (d'), 128.6 (d'), 135.4 (d'), 139.3 (s'), 204.8 (d'); exact mass (electrospray) calcd for $C_{18}H_{26}NaO_3$ 313.1779, found 313.1778.

***N,N*-Bis[(1,1-dimethylethoxy)carbonyl]-5-(phenylthio)-D-norvaline Methyl Ester (8.3a).**



Bu_3P (24.0 mL, 95.99 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **8.3** (29.0 g, 83.49 mmol) and PhSSPh (20.9 g, 95.99 mmol) in CH_2Cl_2 (300 mL). The ice bath was removed and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (16 x 50 cm), using 10% EtOAc-hexane, gave sulfide **8.3a** (28.4 g, 77%) as a colorless oil: $[\alpha]^{25}_D$ +38.8 (*c* 0.71, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2979, 2934, 1794, 1748, 1701, 1584, 1367, 1135 cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ 1.43 (s, 18 H), 1.60-1.76 (m, 2 H), 2.01 (dddd, *J* = 11.5, 11.5, 5.5, 5.5 Hz, 1 H), 2.21 (dddd, *J* = 11.5, 11.5, 10.0, 6.5 Hz, 1 H), 2.93 (ddd, *J* = 11.5, 6.5, 6.5 Hz, 2 H), 3.68 (s, 3 H), 4.82 (dd, *J* = 9.5, 5.5 Hz, 1 H), 7.13-7.32 (m, 5 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 26.2 (t'), 28.1 (q'), 29.3 (t'), 33.5 (t'), 52.4 (d'), 28.0 (q'), 83.4 (s'), 126.2 (d'), 129.2 (d'), 129.4 (d'), 137.0 (s'), 152.5 (s'), 171.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{22}H_{33}NNaO_6S$ 462.1926, found 462.1921. Anal. Calcd for $C_{22}H_{33}NO_6S$: C, 60.11; H, 7.57; N, 3.19; S, 7.29. Found: C, 59.99; H, 7.53; N, 3.09; S, 7.30.

***N,N*-Bis[(1,1-dimethylethoxy)carbonyl]-5-(phenylsulfonyl)-D-norvaline Methyl Ester (8.3b).**



MCPBA (36.0 g, 75%, 155.11 mmol) was added in portions

to a stirred and cooled (0 °C) mixture of sulfide **8.3a** (28.4 g, 64.63 mmol) and $NaHCO_3$ (27.0 g, 323.0 mmol) in CH_2Cl_2 (350 mL). A thick white mixture formed after 1 h. Aqueous $Na_2S_2O_3$ (10%, 100 mL) and saturated aqueous $NaHCO_3$ (200 mL) were then added, the cold bath was removed, and stirring was continued for 30 min. The two phases were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (15 x 30 cm), using 30% EtOAc-hexane, gave sulfone **8.3b** (29.86 g, 98%) as a clear viscous oil: $[\alpha]^{25}_D$ +37.21 (*c* 1.04, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2980, 1791, 1747, 1699, 1585, 1447, 1368, 1306, 1277, 1147, 1134, 1087 cm^{-1}; ^1H NMR (300 MHz, CH_2Cl_2) δ 1.45 (s, 18 H), 1.70 (quintet, *J* = 8.0 Hz, 2 H), 1.95 (dddd, *J* = 11.5, 9.0, 8.0, 8.0 Hz, 1 H), 2.12 (dddd, *J* = 11.5, 9.0, 8.0, 5.0 Hz, 1 H), 3.11 (ddd, *J* = 15.0, 15.0, 9.0 Hz, 2 H), 3.68 (s, 3 H), 4.78 (dd, *J* = 9.5, 5.5 Hz, 1 H), 7.80-8.95 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 20.2 (t'), 28.1 (q'), 28.9 (t'), 52.5 (d'), 56.0 (t'), 57.7 (q'), 83.6 (s'), 128.4 (d'), 129.7 (d'), 134.0 (d'), 139.6 (s'), 152.4 (s'), 171.0 (s').

[(1*R*)-1-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-methyl]-4-(phenylsulfonyl)butyl]carbamic Acid 1,1-Dimethylethyl Ester (51.1).

$NaBH_4$ (4.51 g, 119.2 mmol) was added in one portion to a stirred and cooled (0 °C) mixture of $CaCl_2$ (6.61 g, 59.59 mmol) and sulfone **8.3b** (13.38 g, 28.38 mmol) in 1:1 THF-EtOH (150 mL). The ice bath was removed after 1 h and stirring was continued for 5 h. Saturated aqueous NH_4Cl (100 mL) was added dropwise to the resulting white slurry and the final thick slurry was diluted with EtOAc (100 mL) and water (100

mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated to leave a thick clear oil, which was redissolved in dry PhH (100 mL), and trace protic solvents were removed azeotropically under water-pump vacuum. The resulting alcohol **48.1** was used in the following step without further purification.

t-$BuPh_2SiCl$ (9.70 mL, 36.89 mmol) was added dropwise to a stirred solution of alcohol **48.1** (9.71 g, 28.38 mmol), imidazole (4.83 g, 70.95 mmol) and DMAP (0.70 g, 5.66 mmol) in CH_2Cl_2 (140 mL). Stirring was continued for 5 h and saturated aqueous NH_4Cl (100 mL) was then added. The organic layer was washed with water and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (8 x 30 cm), using 20% EtOAc-hexane, gave silyl ether **51.1** (14.38 g, 87%) as a clear, viscous oil: $[\alpha]^{25}_D$ +13.42 (*c* 2.60, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3373, 3070, 2958, 2857, 1709, 1587, 1305, 1169, 1148, 1112, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.42 (s, 9 H), 1.54-1.66 (m, 2 H), 1.66-1.85 (m, 2 H), 3.06 (ddd, *J* = 13.0, 10.0, 5.5 Hz, 1 H), 3.13-3.23 (m, 1 H), 3.54 (dd, *J* = 10.5, 4.0 Hz, 1 H), 3.56-3.64 (m, 1 H), 3.64 (dd, *J* = 10.0, 4.0 Hz, 1 H); 4.62 (d, *J* = 8.0 Hz, 1 H), 7.30-7.95 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.3 (s'), 19.5 (s'), 26.9 (q'), 28.4 (q'), 30.7 (t'), 51.1 (d'), 55.9 (t'), 65.8 (t'), 79.4 (s'), 127.8 (d'), 127.9 (d'), 128.1 (d'), 139.3 (d'), 129.9 (d'), 129.9 (d'), 133.1 (s'), 133.2 (s'), 133.6 (d'), 135.57 (d'), 135.59 (d'), 139.3 (s'), 155.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{32}H_{43}NNaOSSi$ 604.2528, found 604.2522.

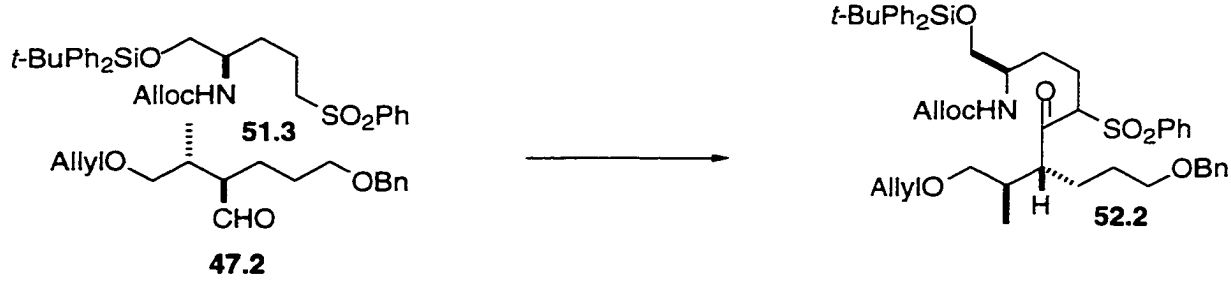
[(1*R*)-1-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-methyl]-4-(phenylsulfonyl)butyl]carbamic Acid 2-Propenyl Ester (51.3).

$Me_3SiOSO_2CF_3$ (10 mL, 54.36 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **51.1** (14.38 g, 24.71 mmol) and 2,6-lutidine (7.20 mL, 61.77 mmol) in CH_2Cl_2 (160 mL). The cold bath was left in place, but was not recharged, and stirring was continued for 4 h. MeOH (30 mL) was added to the solution, stirring was continued for 1 h, and water (100 mL) was added. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated.

The residual crude mixture of the desired amine and 2,6-lutidine was redissolved in freshly distilled CH_2Cl_2 (160 mL). Allyl chloroformate (4.80 mL, 44.47 mmol) was added dropwise to the stirred and cooled (0 °C) solution. Stirring was continued for 3 h and the solvent was evaporated. The residue was dissolved in Et_2O (300 mL) and washed with water (2 x 50 mL), 20% hydrochloric acid (4 x 50 mL), saturated aqueous $NaHCO_3$ (1 x 50 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (6 x 30 cm), using 30% EtOAc-hexane, gave **51.3** (13.16 g, 94%) as a clear viscous oil: $[\alpha]^{25}_D$ +10.32 (*c* 3.08, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3355, 3070, 2930, 2857, 1719, 1587, 1527, 1304, 1147, 1112, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.55-1.86 (m, 4 H), 3.00-3.22 (m, 2 H), 3.56 (br d, J = 7.5 Hz, 1 H), 3.59-3.68 (m, 1 H), 3.65 (br d, J = 7.5 Hz, 1 H), 4.51 (br d, J = 6.0 Hz, 2 H), 4.84 (d, J = 9.0 Hz, 1 H), 5.22 (br d, J = 10.0 Hz, 1 H), 5.29 (br d, J = 16.0 Hz, 1 H), 5.83-5.98 (m, 1 H), 7.30-7.95 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.3 (s'), 19.4 (t'), 26.9 (q'), 30.5 (t'), 51.7

(d'), 55.8 (t'), 65.6 (t'), 79.3 (t'), 117.7 (t'), 127.9 (d'), 128.1 (d'), 129.3 (d'), 129.9 (d'), 130.0 (d'), 132.9 (d'), 132.97 (s'), 133.02 (s'), 133.7 (d'), 135.6 (d'), 139.2 (s'), 155.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{31}H_{39}NNaO_5SSi$ 588.2215, found 588.2212.

[(1*R*,6*R*,7*R*)-1-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-7-methyl-5-oxo-6-[3-(phenylmethoxy)propyl]-4-(phenylsulfonyl)-9-oxa-11-dodecenyl]carbamic Acid 2-Propenyl Ester (52.2).

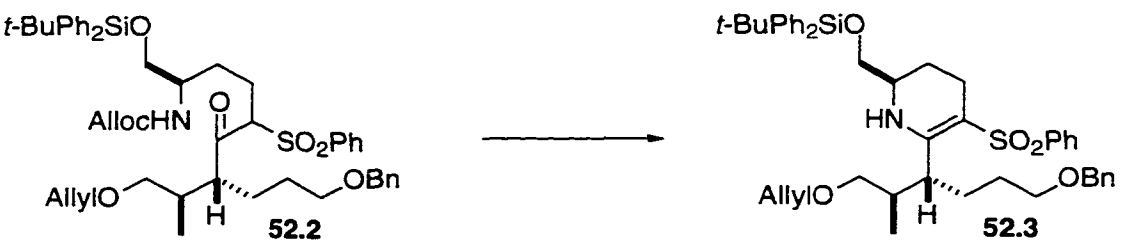


n-BuLi (2.5 M in hexane, 1.89 mL, 4.73 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of sulfone **51.3** (1.17 g, 2.06 mmol) in THF (20 mL). The resulting bright yellow solution characteristic of the sulfone dianion was stirred for an additional 30 min, and then a solution of aldehyde **47.2** (0.38 g, 1.33 mmol) in THF (3 mL) was added dropwise by syringe. Stirring at -78 °C was continued for another 30 min, and the mixture was quenched with saturated aqueous NH_4Cl (20 mL). The cold bath was removed, and stirring was continued for 30 min. The mixture was partitioned between Et_2O (100 mL) and water (50 mL), and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated.

The resulting crude hydroxy sulfone was dissolved in freshly distilled CH_2Cl_2 (15 mL) and solid $NaHCO_3$(0.84 g, 9.95 mmol) and Dess-Martin periodinane (0.85 g, 1.99 mmol) were added (stirring). Stirring was continued for 1 h. Aqueous $Na_2S_2O_3$ (20%, 20 mL) and saturated aqueous $NaHCO_3$ (50 mL) were

added and the mixture was stirred for 30 min. The mixture was extracted with CH_2Cl_2, and the organic extract was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 20% EtOAc-hexane, gave ketone **52.2** as a oil (0.99 g, 87%), which was a mixture (^1H NMR) of diastereomers: ^1H NMR δ 0.60 (d, J = 6.5, 2 H), 0.75 (d, J = 6.5 Hz, 1 H), 1.04 (s, 9 H), 1.30-1.55 (m, 5 H), 1.62-1.98 (m, 4 H), 2.08-2.15 (m, 2 H), 2.35-2.45 (m, 0.5 H), 2.85-2.95 (m, 0.5 H), 3.25-3.45 (m, 3 H), 4.45 (s, 2 H), 4.75-4.80 (br s, 1 H), 5.12-5.35 (m, 4 H), 5.85-6.0 (m, 2 H), 7.20-7.85 (m, 20 H).

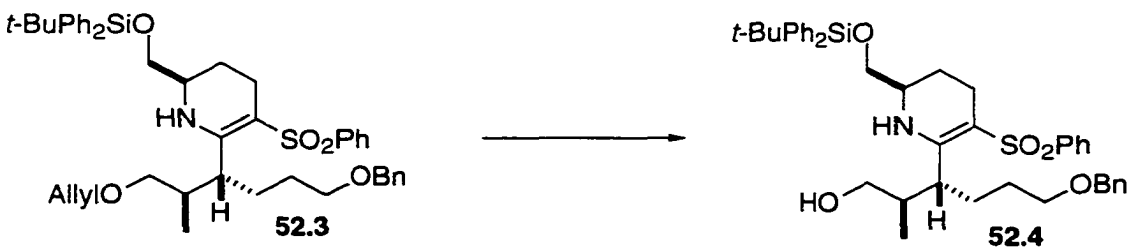
(6*R*)-6-[[[(1,1-(Dimethylethyl)diphenylsilyl]-oxy]methyl]-1,4,5,6-tetrahydro-3-(phenylsulfonyl)-2-[(1*R*,2*R*)-2-methyl-1-[3-(phenylmethoxy)propyl]-4-oxa-6-heptenyl]pyridine (52.3).



$Pd(PPh_3)_4$ (0.13 g, 0.116 mmol) was added in one portion to a stirred solution of ketone **52.2** (0.99 g, 1.16 mmol) and dimedone (0.82 g, 5.80 mmol) in THF (25 mL) (protection from light). Stirring in the dark was continued for 3 h, at which point saturated aqueous $NaHCO_3$ (50 mL) was added. The mixture was extracted with Et_2O (2 x 50 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$),and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 20% EtOAc-hexane, gave **52.3** (0.67 g, 77%) as a yellow oil: $[\alpha]^{25}_D$ -60.25 (*c* 0.78, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3435, 3376, 2929, 2856, 1578, 1494, 1282, 1112 cm^{-1}; ^1H NMR (400

MHz, CD_2Cl_2) δ 0.99 (d, *J* = 6.5 Hz, 3 H), 1.03 (s, 9 H), 1.24-1.50 (m, 4 H), 1.68-1.80 (m, 3 H), 2.38 (ddd, *J* = 16.5, 9.5, 5.5 Hz, 1 H), 2.56 (ddd, *J* = 16.5, 5.5, 5.5 Hz, 1 H), 2.86 (t, *J* = 9.0 Hz, 1 H), 3.24 (dd, *J* = 9.5, 5.5 Hz, 1 H), 3.30-3.38 (m, 1 H), 3.38 (t, *J* = 7.0 Hz, 2 H), 3.46 (dd, *J* = 12.0, 7.5 Hz, 1 H), 3.66 (ddd, *J* = 10.5, 10.5, 5.5, 1 H), 3.68 (dd, *J* = 11.0, 6.0 Hz, 1 H), 3.78 (ddd, *J* = 5.5, 4.0, 2.5 Hz, 2 H), 4.42 (s, 2 H), 5.03-5.10 (m, 1 H), 5.16 (ddd, *J* = 16.5, 3.5, 2.5 Hz, 1 H), 5.79 (dddd, *J* = 16.5, 11.0, 5.5, 5.5 Hz, 1 H), 7.24-7.52 (m, 15 H), 7.60-7.65 (m, 4 H), 7.81 (dd, *J* = 9.0, 1.5 Hz, 1 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 15.8 (q'), 19.4 (s'), 23.8 (t'), 23.9 (t'), 27.0 (q'), 27.5 (t'), 27.9 (t'), 37.5 (d'), 41.1 (d'), 52.7 (d'), 67.0 (t'), 70.8 (t'), 72.0 (t'), 73.0 (t'), 73.8 (t'), 101.4 (s'), 116.4 (t'), 126.8 (d'), 127.7 (d'), 127.9 (d'), 128.2 (d'), 128.6 (d'), 129.1 (d'), 130.26 (d'), 130.29 (d'), 132.0 (d'), 133.3 (s'), 135.8 (d'), 139.4 (s'), 145.7 (s'), 155.0 (s'); exact mass (electrospray) *m/z* calcd for $C_{45}H_{57}NNaO_5SSi$ 744.3624, found 744.3621.

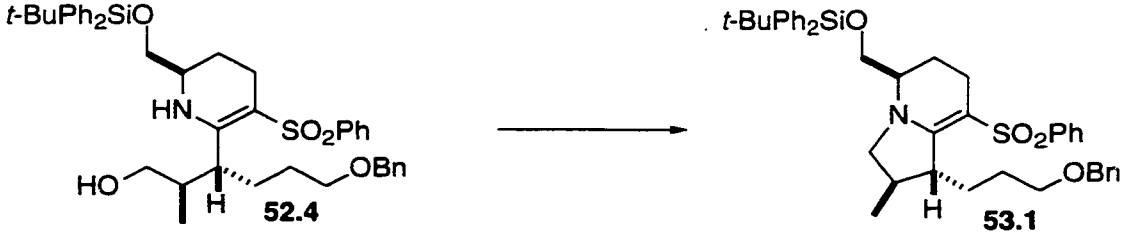
(6*R*)-6-[[[(1,1-(Dimethylethyl)diphenylsilyl]-oxy]methyl]-1,4,5,6-tetrahydro-3-(phenylsulfonyl)-2-[(1*R*,2*R*)-3-hydroxy-2-methyl-1-[3-(phenylmethoxy)-propyl]propyl]pyridine (52.4).



$Pd(PPh_3)_4$ (0.10g, 0.085 mmol) was added in one portion to a solution of **52.3** (0.643 g, 0.854 mmol) and toluenesulfinic acid (0.173 g, 1.11 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 2 h, and the mixture was then diluted with Et_2O (100 mL) and saturated aqueous $NaHCO_3$ (50

mL). The phases were separated and the organic phase was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% EtOAc-hexane, gave alcohol **52.4** as a yellow oil (0.512 g, 84%): $[\alpha]^{25}_D$ -63.5 (*c* 0.51, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3434, 3068, 2929, 2857, 1575, 1277, 1112, 1081 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.82-0.91 (m, 1 H), 1.01 (d, *J* = 5.5 Hz, 3 H), 1.03 (s, 9 H), 1.12-1.22 (m, 2 H), 1.40-1.70 (m, 3 H), 1.72-1.80 (m, 1 H), 2.34 (ddd, *J* = 10.0, 10.0, 5.0 Hz, 1 H), 2.72 (ddd, *J* = 16.0, 5.0, 5.0, Hz, 1 H), 2.85 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.23 (t, *J* = 6.0 Hz, 2 H), 3.26-4.0 (m, 2 H), 3.48 (dd, *J* = 11.0, 10.0 Hz, 1 H), 3.53-3.56 (m, 1 H), 3.58 (ddd, *J* = 11.5, 4.5, 4.5 Hz, 1 H), 3.74 (dd, *J* = 10.0, 4.0 Hz, 1 H), 4.38 (s, 2 H), 4.92 (br s, 1 H), 7.24-7.53 (m, 14 Hz, 7.58-7.63 (m, 4 H), 7.83 (dd, *J* = 9.0, 2.5 Hz, 2 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 14.9 (q'), 19.4 (t'), 23.7 (t'), 23.9 (t'), 27.0 (q'), 27.3 (t'), 27.8 (t'), 40.4 (d'), 40.7 (d'), 52.7 (d'), 65.4 (t'), 67.1 (t'), 70.6 (t'), 73.0 (t'), 101.6 (s'), 126.7 (d'), 127.8 (d'), 127.9 (d'), 128.2 (d'), 128.3 (d'), 128.6 (d'), 129.3 (d'), 130.3 (d'), 132.3 (d'), 133.3 (s'), 135.9 (d'), 139.3 (s'), 145.2 (s'), 155.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{42}H_{54}NO_5SSi$ 712.3492, found 712.3488.

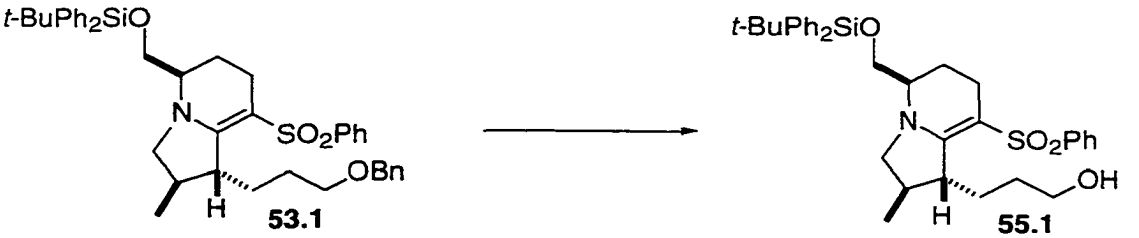
(1*R*,2*R*,5*R*)-5-[[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]methyl]-1,2,3,5,6,7-Hexahydro-2-methyl-8-(phenylsulfonyl)-1-[3-(phenylmethoxy)propyl]indolizine (53.1).



A solution of triphosgene (0.171 g, 0.575 mmol) in

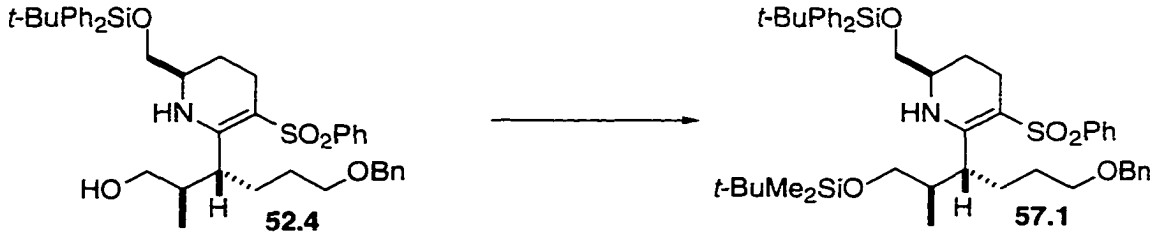
CH_2Cl_2 (3 mL) was added dropwise to a stirred and cooled (-78 °C) solution of **52.4** (0.205 g, 0.287 mmol) and pyridine (0.46 mL, 5.74 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 10 min at -78 °C. The cold bath was removed, stirring was continued for 1 h, and then water (40 mL) was added dropwise. The mixture was extracted with Et_2O (50 mL), and the organic extract was washed with saturated aqueous $CuSO_4$ (3 x 10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 20% EtOAc-hexane, gave **53.1** (0.179 g, 84%) as a yellow oil: $[\alpha]^{25}_D$ -29.44 (*c* 0.27 CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2956, 2856, 1592, 1444, 1359, 1113 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 0.91 (d, *J* = 7.0 Hz, 3 H), 1.02 (s, 9 H), 1.43-1.50 (m, 1 H), 1.54-1.60 (m, 2 h), 1.67-1.89 (m, 4 H), 1.98 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1 H), 2.10 (quintet, *J* = 6.5 Hz, 1 H), 2.32 (ddd, *J* = 15.0, 5.0, 5.0 Hz, 1 H), 3.06 (d, *J* = 10.0 Hz, 1 H), 3.30 (dd, *J* = 10.0 3.5 Hz, 1 H), 3.32-3.35 (m, 1 H), 3.41 (dd, *J* = 10.0, 6.5 Hz, 1 H), 4.45-4.54 (m, 3 H), 3.56 (dd, *J* = 10.5, 5.5 Hz, 1 H), 4.50 (s, 2 H), 7.26-7.62 (m, 20 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 29.3 (s'), 19.9 (t'), 20.8 (q'), 23.1 (t'), 27.0 (q'), 28.5 (t'), 31.4 (t'), 339.9 (d'), 51.3 (d'), 55.1 (d'), 56.6 (d'), 64.4 (t'), 70.8 (t'), 73.2 (t'), 92.4 (s'), 126.4 (d'), 127.7 (d'), 128.0 (d'), 128.1 (d'), 128.6 (d'), 129.0 (d'), 130.2 (d'), 131.5 (d'), 133.4 (s'), 133.5 (s'), 135.9 (d'), 139.4 (s'), 145.2 (s'), 159.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{42}H_{52}NO_4SSi$ 694.3386, found 694.3388.

[(1*R*,2*R*,5*R*)-5-[[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]methyl]-1,2,3,5,6,7-hexahydro-2-methyl-8-(phenylsulfonyl)indolizin-1-yl]propanol (55.1).



1,4-Cyclohexadiene (1.20 mL, 10.71 mmol) was added to a mixture of **53.1** (0.527 g, 0.712 mmol) and 10% Pd/C (0.263 g) in EtOH (7 mL), and the mixture was stirred at 50 °C for 8 h. The mixture was cooled to room temperature, diluted with EtOAc (10 mL), and filtered through a pad (2 x 3 cm) of Celite, using EtOAc as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 50% EtOAc-hexane, gave alcohol **55.1** (0.399 g, 86%) as a clear oil: $[\alpha]^{25}_{D}$ -80.26 (*c* 0.76, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3515, 2956, 2857, 1591, 1444, 1294, 1113 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.90 (d, *J* = 7.0 Hz, 3 H), 1.00 (s, 9 H), 1.36-1.48 (m, 1 H), 1.54-1.62 (m, 2 H), 1.66-2.02 (m, 4 H), 2.08 (quintet, *J* = 7.0 Hz, 1 H), 2.32 (ddd, *J* = 15.0, 5.0, 5.0 Hz, 1 H), 2.44 (dd, *J* = 8.5, 5.5 Hz, 1 H), 3.08 (d, *J* = 10.0 Hz, 1 H), 3.30 (dd, *J* = 12.0, 2.5 Hz, 1 H), 3.32-3.36 (m, 1 H), 3.42 (dd, *J* = 16.0, 10.5 Hz, 1 H), 3.48 (dd, *J* = 10.0, 6.0 Hz, 1 H), 3.55 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.58-3.64 (m, 1 H), 3.66-3.74 (m, 1 H), 7.32-7.75 (m, 15 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.3 (s'), 19.8 (t'), 20.7 (q'), 23.0 (t'), 27.0 (q'), 29.9 (t'), 30.6 (t'), 33.4 (d'), 49.9 (d'), 55.1 (d'), 56.5 (t'), 61.1 (t'), 64..4 (t'), 91.8 (s'), 126.3 (d'), 128.1 (d'), 129.1 (d'), 130.2 (d'), 131.7 (d'), 133.4 (s'), 133.5 (s'), 135.9 (d'), 144.9 (s'), 159.7 (s'); exact mass (electrospray) *m/z* calcd for $C_{35}H_{46}NO_4SSi$ 604.2916; found 604.2912.

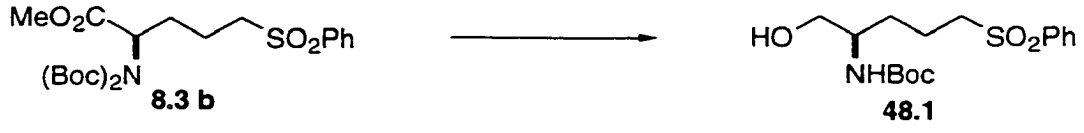
(6*R*)-6-[[[(1,1-(Dimethylethyl)diphenylsilyl]-oxy]methyl]-2-[(1*R*)-1-[(1*R*)-2-[[(1,1-(dimethylethyl)-dimethylsilyl]oxy]-1-methylethyl]-4-(phenylmethoxy)-butyl]-1,4,5,6-tetrahydro-3-(phenylsulfonyl)pyridine (57.1).



t-$BuMe_2SiCl$ (0.105 g, 0.694 mmol) was added in one portion to a stirred solution of **52.4** (0.330 g, 0.463 mmol), imidazole (0.095 g, 1.38 mmol), and DMAP (8.0 mg, 0.069 mmol) in THF (10 mL). Stirring was continued for 3 h and the mixture was diluted with Et_2O (30 mL) and saturated aqueous NH_4Cl (20 mL). The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 20% EtOAc-hexane, gave **57.1** (0.317g, 86%) as a colorless oil: $[\alpha]^{25}_D$ -45.75 (*c*, 1.39, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3435, 3374, 2953, 2856, 1588, 1471, 1360, 1082 cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ -0.92 (s, 3 H), -0.85 (s, 3 H), 0.84 (s, 9 H), 0.98 (d, J = 6.5 Hz, 3 H), 1.04 (s, 9 H), 1.25-1.51 (m, 4 H), 1.56-1.68 (m, 1 H), 1.70-1.82 (m, 2 H), 2.40 (ddd, J = 15.0, 10.0, 5.0 Hz, 1 H), 2.53 (ddd, J = 15.5, 5.0, 5.0 Hz, 1 H), 2.99 (t, J = 10.0 Hz, 2 H), 3.30-3.37 (m, 1 H), 3.39 (t, J = 6.5 Hz, 2 H), 3.47 (d, J = 10.0 Hz, 1 H), 3.48 (t, J = 10.0 Hz, 1 H), 3.59-3.66 (m, 1 H), 3.69 (dd, J = 10.0, 5.5 Hz, 1 H), 4.45 (s, 2 H), 5.06 (br s, 1 H), 7.25-8.85 (m, 20 H), ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ -5.1 (q'), 15.2 (q'), 18.4 (s'), 19.4 (s'), 23.8 (t'), 24.0 (t'), 26.1 (q'), 27.0 (q'), 27.5 (t'), 27.9 (t'), 40.2 (d'), 40.9 (d'), 52.6 (d'), 66.8 (t'), 67.0 (t'), 70.8 (t'), 73.1 (t'), 101.6 (s'), 126.7 (d'), 127.7

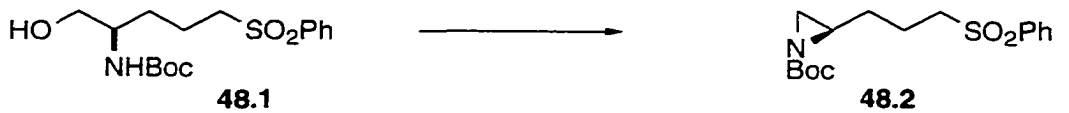
(d'), 127.9 9d'), 128.2 (d'), 128.6 (d'), 129.2 (d'), 130.3 (d'), 132.1 (d'), 133.4 (s'), 135.8 (d'), 139.4 (s'), 145.6 (s'), 155.1 (s'); exact mass (electrospray) *m/z* calcd for $C_{48}H_{68}NO_5SSi$ 826.4356, found 826.4350.

[(1*R*)-1-(Hydroxymethyl)-4-(phenylsulfonyl)butyl]-carbamic Acid 1,1-Dimethylethyl Ester (48.1).



$NaBH_4$ (0.353 g, 9.35 mmol) was added in one portion to a stirred and cooled (0 °C) mixture of ester **8.3b** (1.05 g, 2.22 mmol) and $CaCl_2$ (0.52 g, 4.67 mmol) in 1:1 THF-EtOH (12 mL). After 30 min, the cold bath was removed, and the white mixture was stirred for 5 h. Saturated aqueous NH_4Cl was then added dropwise, and the mixture was partitioned between EtOAc (30 mL) and water (30 mL). The aqueous phase was extracted with EtOAc (2 X 10 mL) and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 80% EtOAc-hexane, gave alcohol **48.1** (0.72 g, 94%) as a colorless oil: $[\alpha]^{25}_D$ +14.66 (*c*, 0.60, CH_2Cl_2), FTIR (CH_2Cl_2 cast) 3371, 2931, 2874, 1694, 1447, 1366, 1303, 1167, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9 H), 1.50-1.25 (m, 4 H), 3.04-3.23 (m, 2 H), 3.49-3.65 (m, 3 H), 4.62-4.70 (br s, 1 H), 7.53-7.70 (m, 3 H), 7.91 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.9 (t'), 28.4 (q'), 30.5 (t'), 52.2 (d'), 56.1 (t'), 65.5 (t'), 79.7 (s'), 128.3 (d'), 129.7 (d'), 134.0 (d'), 139.7 (s'), 156.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{16}H_{25}NNaO_3S$ 366.1351, found 366.1350.

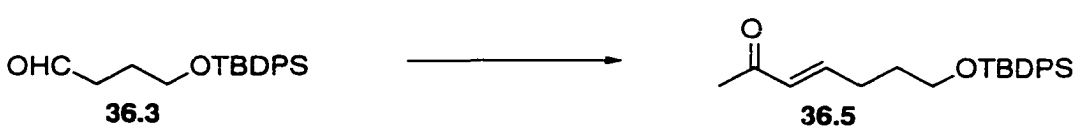
(2*R*)-2-[3-(Phenylsulfonyl)]propyl-1-aziridine-carboxylic Acid 1,1-Dimethylethyl Ester (48.2).



48.1 **48.2**

Di-isopropyl azodicarboxylate (0.70 mL, 3.56 mmol) was added dropwise to a stirred solution of **48.1** (1.06 g, 3.10 mmol) and Ph_3P (0.97 g, 3.72 mol) in THF (30 mL). Stirring was continued for 3 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (3.5 x 30 cm), using 30% EtOAc-hexane, gave aziridine **48.2** (0.693 g, 69%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (ddd, *J* = 15.0, 15.0, 8.0, 1 H), 1.44 (s, 9 H), 1.77 (dddd, *J* = 11.0, 7.0, 7.0, 4.0 Hz, 1 H), 1.87 (d, *J* = 3.5 Hz, 1 H), 1.94 (quintet, *J* = 7.5 Hz, 2 H), 2.24-2.32 (m, 3 H), 3.18 (ddd, *J* = 13.5, 9.0, 9.0, 1 H), 3.34 (ddd, *J* = 14.0, 8.5, 8.5 Hz, 1 H), 7.54-7.68 (m, 3 H), 7.92 (d, *J* = 9.5 Hz, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.6 (t'), 28.0 (q'), 30.8 (t'), 31.4 (t'), 37.0 (d'), 55.5 (t'), 81.4 (s'), 128.1 (d'), 129.3 (d'), 133.7 (d'), 139.2 (s'), 162.3 9s'); exact mass (electrospray) *m/z* calcd for $C_{16}H_{23}NNaO_4S$ 348.1245, found 348.1243.

(*E*)-7-[[(1,1-(Dimethylethyl)diphenylsilyl]-oxy]hept-3-en-2-one (36.5).



36.3 **36.5**

$CH_3C(O)C{=}PPh_3$ (5.54 g, 17.39 mmol) was added in one portion to a stirred solution of aldehyde **36.3** (4.37 g, 13.83 mmol) in CH_2Cl_2 (60 mL). Stirring was continued overnight and the solvent was then evaporated. The resulting yellow

precipitate was suspended in Et_2O (100 mL) and the mixture was filtered through a pad (5 x 5 cm) of flash chromatography silica gel. Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 30 cm), using 20% EtOAc-hexane, gave ketone **36.5** (3.77 g, 77%) as a clear oil: FTIR (CH_2Cl_2 cast) 3070, 2931, 1698, 1676, 1627, 1111 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.05 (s, 9 H), 1.74 (quintet, J = 7.0 Hz, 2 H), 2.18 (s, 3 H), 2.35 (ddd, J = 15.0, 7.0, 2.0 Hz, 2 H), 3.70 (t, J = 6.0 2 H), 6.04 (ddd, J = 16.0, 1.5, 1.5 Hz, 1 H), 6.78 (ddd, J = 16.0, 7.0 Hz, 1 H), 7.35-7.45 (m, 6 H), 7.65-7.70 (m, 4 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.4 (s'), 26.93 (q'), 26.99 (q'), 29.3 (t'), 31.4 (t'), 63.4 (t'), 128.0 (d'), 130.0 (d'), 131.8 (d'), 134.3 (s'), 135.9 9d'), 148.2 (d'), 198.5 (s').

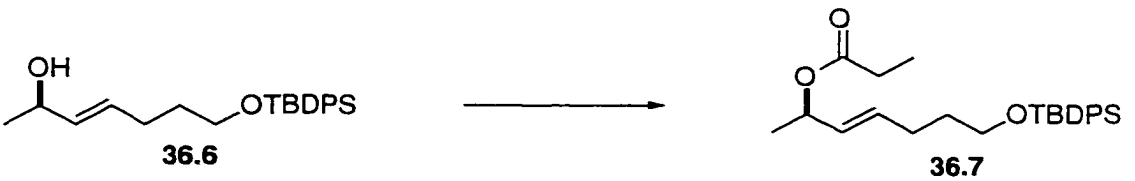
(*E*)-7-[[(1,1-(Dimethylethyl)diphenylsilyl]oxy]-hept-3-en-2-ol (36.6).

36.5 **36.6**

$NaBH_4$ (54 mg, 1.44 mmol) was added in portions to a stirred and cooled (0 °C) solution of ketone **36.5** (0.44 g, 1.20 mmol) and $CeCl_3.7H_2O$ (0.53 g, 1.44 mmol) in MeOH (10 mL). After 10 min, the cold bath was removed, and stirring was continued for 30 min. Water (20 mL) and Et_2O (40 mL) were added, and stirring was continued for 15 min. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% EtOAc-hexane, gave alcohol **36.6** (0.403 g, 91%) as a clear oil: FTIR (CH_2Cl_2 cast) 3346, 3048, 2960, 1589, 1427, 1111 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.04 (s, 9 H), 1.19 (d, J = 6.5 Hz, 3 H), 1.38 (br s, 1 H), 1.65 (quartet, J = 7.5, 2 H), 2.13 (quartet, J = 7.0 Hz, 2 H),

3.68 (t, J = 6.5 Hz, 2 H), 4.19 (quintet, J = 6.5 Hz, 1 H) 5.44-5.65 (m, 2 H), 7.35-7.45 (m, 6 H), 7.65-73 (m, 4 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.5 (s'0, 23.7 (q'), 27.0 (q'), 28.7 (t'), 32.5 (t'), 63.6 (t'), 69.0 (q'), 128.0 (d'), 129.9 (d'), 130.4 (d'), 134.5 (s'), 135.2 (d'), 135.9 (d').

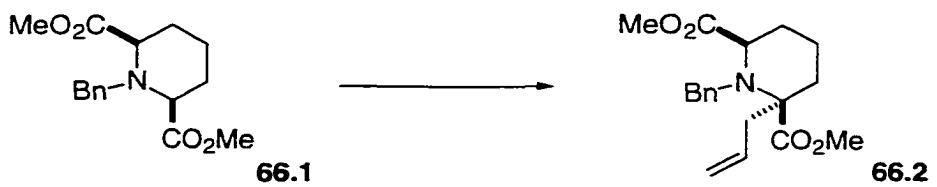
Propanoic Acid (*E*)-7-[[(1,1-(Dimethylethyl)-diphenylsilyl]oxy]hept-3-en-2-yl Ester (36.7).



36.6 **36.7**

CH_3CH_2COCl (0.13 mL, 1.46 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **36.6** (0.416 g, 1.128 mmol), pyridine (0.18 mL, 2.25 mmol), and DMAP (14 mg, 0.11 mmol) in CH_2Cl_2 (11 mL). The cold bath was removed, and stirring was continued for 3 h. The mixture was diluted with Et_2O (60 mL) and washed with 10% hydrochloric acid, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 10% EtOAc-hexane, gave ester **36.7** (0.41 g, 86%) as a clear oil: FTIR (CH_2Cl_2 cast) 3049, 2932, 1734, 1589, 111 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.03 (s, 9 H), 1.09 (t, J = 7.5 Hz, 3 H), 1.23 (d, J = 6.5 Hz, 3 H), 1.65 (quintet, J = 7.0 Hz, 2 H), 2.12 (quartet, J = 7.0 Hz, 2 H), 2.27 (quartet, J = 7.0 Hz, 2 H), 3.66 (t, J = 6.5 Hz, 2 H), 5.28 (dddd, J = 7.6, 7.6, 7.5, 7.5 Hz, 1 H), 5.47 (ddd, J = 15.5, 7.0, 1.5 Hz, 1 H), 5.68 (ddd, J = 15.5, 6.5, 0.5 Hz, 1 H), 7.35-7.45 (m, 6 H), 7.65-7.69 (m, 4 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 9.3 (q'), 18.5 (s'), 20.5 (q'), 27.0 (q'), 28.2 (t'), 28.8 (t'), 32.3 (t'), 63.6 (t'), 71.0 (d'), 128.0 (d'), 129.9 (d'), 130.5 (d'), 130.5 (d'), 132.6 (d'), 134.5 (s'), 135.9 (d').

(2*R*,6*R*)-1-(Phenylmethyl)-2-(2-propenyl)-2,6-piperidinedicarboxylic Acid Dimethyl Ester (66.2).

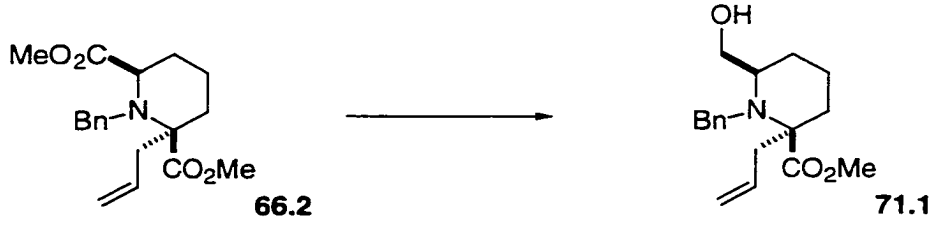


66.1 **66.2**

n-BuLi (2.5 M in hexanes, 18.4 mL, 45.96 mmol) was added dropwise over ca 30 min to a stirred and cooled (-78 °C) solution of chiral diamine **67.4** (9.66 g, 22.98 mmol) in dry THF (230 mL) to obtain a bright red solution. After 5 min, the dry-ice bath was removed and exchanged with a water bath, and stirring was continued for 30 min. The resulting dilithium amide solution was cooled (-78 °C) and a THF solution (50 mL) of diester **66.1** (5.77 g, 19.81 mmol) was added dropwise over 45 min. After 1 h, allyl bromide (2.10 mL, 23.77 mmol) was added dropwise over 2 min. Stirring at -78 °C was continued for 2 h, the cooling bath was removed, and stirring was continued for 12 h. Saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture was extracted with Et_2O (200 mL). The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (6 x 30 cm), using 10% Et_2O-hexane and 10% EtOAc-hexane, gave **66.2** (4.03 g, 61%) as a yellow oil: $[\alpha]^{25}_D$ +26.81 (*c* 1.1, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2949, 2874, 1729, 1639, 1451, 1166 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.45-1.70 (m, 3 H), 1.70-1.93 (m, 2 H), 2.25 (ddd, J = 14.0, 7.0, 3.0 Hz, 1 H), 2.48 (dd, J = 14.0, 7.5 Hz, 1 H), 2.72 (dd, J = 14.0, 7.0 Hz, 1 H), 3.50 (dd, J = 6.0, 2.5 Hz, 1 H), 3.61 (s, 3 H), 3.76 (s, 3 H), 3.80 (d, J = 15.5 Hz, 1 H), 4.57 (d, J = 15.5 Hz, 1 H), 5.07 (ddd, J = 9.0, 3.5, 1.5 Hz, 1 H), 5.11 (dd, J = 3.5, 1.5 Hz, 1 H), 5.78 (dddd, J = 16.0, 10.0, 10.0, 7.5 Hz, 1 H), 7.25-7.40 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.2 (t'), 28.3 (t'), 31.0 (d'), 33.1 (t'), 43.7

(t'), 51.1 (q'), 52.3 (t'), 57.6 (q'), 62.7 (s'), 118.6 (t'), 126.7 (d'), 127.9 (d'), 128.3 (d'), 132.8 (d'), 140.6 (s'), 174.0 (s'), 174.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{19}H_{26}NO_4$ 332.1856; found 332.1857.

(2*R*,6*R*)-6-(Hydroxymethyl)-1-(phenylmethyl)-2-(2-propenyl)-2-piperidinecarboxylic Acid Methyl Ester (71.1).



DIBAL-H (1 M in hexane, 0.94 mL, 0.94 mmol) was added dropwise over ca 5 min to a stirred and cooled (-78 °C) solution of diester **66.2** (0.136 g, 0.41 mmol) in CH_2Cl_2 (4 mL). After 20 min, $Na_2SO_4.10H_2O$ (1 g) was added and the ice bath was removed. Stirring was continued for 1 h, and the resulting thick white suspension was filtered through a pad (2 x 2 cm) of Celite. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 20 cm), using 20% EtOAc-hexane, gave alcohol **71.1** (37 mg, 30%) as a colorless oil along with diol **71.2** and starting material. Alcohol **71.1** had: $[\alpha]^{25}_D$ -14.73 (*c* 2.28, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3431, 3025, 2946, 1725, 1638, 1602, 1451, 1204 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.56-1.74 (m, 6 H), 2.04-2.15 (m, 1 H), 2.52 (dd, *J* = 14.0, 7.5 Hz, 1 H), 2.63 (dd, *J* = 14.0, 7.5 Hz, 1 H), 2.90 (quintet, *J* = 5.0 Hz, 1 H), 3.39 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1 H), 3.52 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1 H), 3.70 (s, 3 H), 3.99 (d, *J* = 16.0 Hz, 1 H), 4.08 (d, *J* = 16.0 1 H), 5.05 (dd, *J* = 3.5, 0.5 Hz, 1 H), 5.09 (d, *J* = 0.5 Hz, 1 H), 5.80 (dddd, *J* = 14.0, 7.5, 7.5, 0.5 Hz, 1 H), 7.22 (dd, *J* = 9.0, 8.0 Hz, 1 H), 7.32 (t, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ

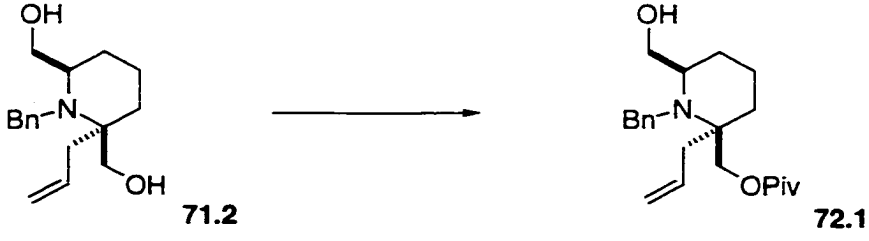
18.0 (t'), 25.7 (t'), 31.5 (t'), 39.6 (t'), 51.8 (d'), 52.9 (t'), 57.8 (q'), 61.7 (t'), 65.7 (s'), 118.2 (t'), 126.7 (d'), 127.2 (d'), 128.5 9d'), 133.5 (d'), 141.8 (s'), 177.2 (s'); exact mass (electrospray) *m/z* calcd for $C_{18}H_{26}NO_3$ 304.1907; found 304.1906.

(2*R*,6*R*)-1-(Phenylmethyl)-2-(2-propenyl)-2,6-piperidinedimethanol (71.2).

$LiBH_4$ (2 M in THF, 30.0 mL, 60.8 mmol) was added dropwise over ca 10 min to a stirred and cooled (0 °C) solution of diester **66.2** (4.03 g, 12.16 mmol) and MeOH (2.46 mL, 60.8 mmol) in Et_2O (122 mL). The ice bath was removed after the addition, and stirring was continued overnight. Saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture was stirred for 1 h. EtOAc (100 mL) was added, and the aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 30 to 50% EtOAc-hexane, gave diol **71.2** (2.05 g, 61%) as a colorless oil: $[\alpha]^{25}_D$ +6.04 (*c* 0.48, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3380, 3024, 2937, 1636, 1602, 1451, 1051 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.40-1.80 (m, 6 H), 2.28 (dd, *J* = 14.0, 7.0 Hz, 1 H), 2.61 (dd, *J* = 14.0, 7.0 Hz, 1 H), 2.70-2.83 (m, 1 H), 3.32 (dd, *J* = 12.0, 3.5 Hz, 1 H), 3.41 (d, *J* = 11.0 Hz, 1 H), 3.44 (d, *J* = 16.5 Hz, 1 H), 3.53 (dd, *J* = 12.0, 4.5 Hz, 1 H), 3.64 (d, *J* = 11.0 Hz, 1 H), 4.28 (d, *J* = 16.5 Hz, 1 H), 5.09 (dd, *J* = 9.0, 0.5 Hz, 1 H), 5.13 (dd, *J* = 16.0, 2.0 Hz, 1 H), 5.78 (dddd, *J* = 16.5, 9.5, 9.5, 7.0 Hz, 1 H), 7.22 (dd, *J* = 9.0, 8.0 Hz, 1

H), 7.32 (t, J = 8.0 Hz, 2 H), 7.42 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.8 (t'), 29.0 (t'), 30.0 (t'), 32.7 (t'), 52.4 (t'), 60.8 (d'), 61.5 (s'), 65.3 (t'), 67.5 (t'), 117.9 (t'), 126.8 (d'), 127.1 (d'), 129.1 (d'), 134.3 (d'), 142.5 (s'); exact mass (electrospray) m/z calcd for $C_{17}H_{26}NO_2$ 276.1958; found 276.1959.

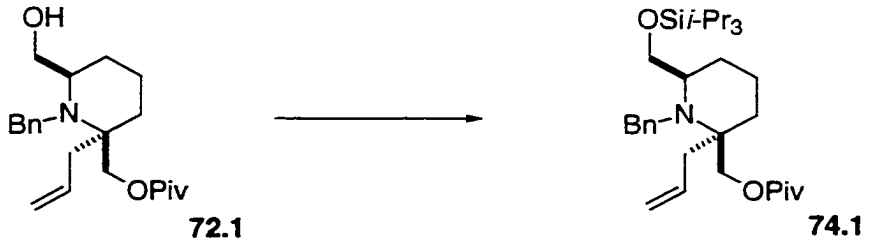
2,2-Dimethylpropanoic Acid (2*R*,6*R*)-6-(Hydroxymethyl)-1-(phenylmethyl)-2-(2-propenyl)-2-piperidinylmethyl Ester (72.1).



t-BuCOCl (0.40 mL, 3.27 mmol) was added dropwise over ca 10 min to a stirred and cooled (-10 °C) solution of diol **71.2** (0.858 g, 3.11 mmol), *i*-Pr_2NEt (1.11 mL, 6.23 mmol) and DMAP (0.01 g) in CH_2Cl_2 (40 mL). Stirring was continued for 2 h and saturated aqueous NH_4Cl (30 mL) and Et_2O (100 mL) were then added. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 20% EtOAc-hexane, gave alcohol **72.1** (0.88 g, 79%) as a colorless oil: $[\alpha]^{25}_D$ -2.93 (*c* 1.57, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3436, 2936, 2870, 1728, 1637, 1603, 1453, 1156 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.13 (s, 9 H), 1.20-1.79 (m, 6 H), 2.45 (dd, J = 14.0, 7.5 Hz, 1 H), 2.56 (dd, J = 14.0, 7.5 Hz, 1 H), 2.73-2.80 (m, 1 H), 3.25 (dd, J = 12.0, 2.5 Hz, 1 H), 3.51 (d, J = 16.5 Hz, 1 H), 3.53 (dd, J = 12.0, 4.0 Hz, 1 H), 4.05 (d, J = 16.5 Hz, 1 H), 5.13 (s, 1 H), 5.78 (dddd, J = 16.5, 10.5, 10.5, 0.5 Hz, 1 H), 7.20 (dd, J = 9.0, 8.0, 1 H), 7.33 (t, J = 8.0 Hz, 2 H), 7.41 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.5 (t'), 27.2 (q'), 28.3 (t'), 30.8 (t'), 32.7

70.4 (t'), 118.1 (t'), 126.4 (d'), 126.8 (d'), 128.8 (d'), 134.1 (d'), 142.8 (s'), 178.2 (s'); exact mass (electrospray) *m/z* calcd for $C_{22}H_{34}NO_3$ 360.2533; found 360.2530.

2,2-Dimethylpropanoic Acid (2*R*,6*R*)-1-(Phenylmethyl)-2-(2-propenyl)-6-[[[tris(1-methylethyl)silyl]oxy]methyl]-2-piperidinylmethyl Ester (74.1).

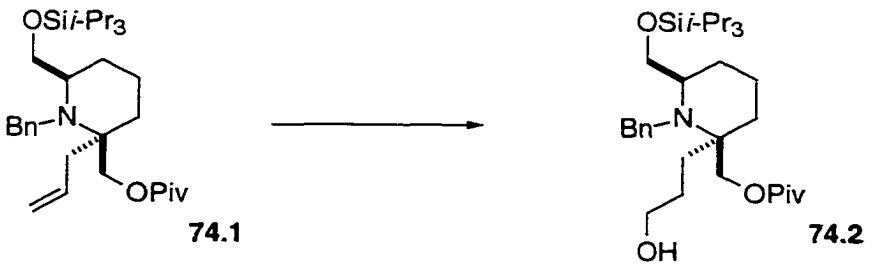


72.1 **74.1**

i-Pr_3SiOTf (2.48 mL, 9.22 mmol) was added dropwise over 3 min to a stirred and cooled (0 °C) solution of alcohol **72.1** (3.16 g, 8.79 mmol) and *i*-Pr_2NEt (3.13 mL, 17.58 mmol) in CH_2Cl_2 (40 mL). After 30 min, saturated aqueous NH_4Cl (40 mL) and Et_2O (100 mL) were added. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 5% EtOAc-hexane, gave **74.1** (4.53 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ +6.39 (*c* 0.72, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2942, 2865, 1731, 1637, 1603, 1461, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 21 H), 1.16 (s, 9 H), 1.35-1.68 (m, 5 H), 1.84-1.91 (m, 1 H), 2.42 (dd, *J* = 14.0, 7.5 Hz, 1 H), 2.55 (dd, *J* = 14.0, 7.5 Hz, 1 H), 2.82 (septet, *J* = 4.0 Hz, 1 H), 3.18 (dd, *J* = 9.5, 9.5, 1 H), 3.65 (dd, *J* = 9.5, 3.5 Hz, 1 H), 3.78 (d, *J* = 16.5 Hz, 1 H), 3.99 (s, 2 H), 4.18 (d, *J* = 16.5 Hz, 1 H), 5.07 (d, *J* = 16.5 Hz, 1 H), 5.08 (d, *J* = 6.0 Hz, 1 H), 5.80 (dddd, *J* = 16.5, 10.5, 10.5, 0.5 Hz, 1 H), 7.15 (dd, *J* = 9.0, 8.0 Hz, 1 H), 7.25 (t, *J* = 8.0 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.9 (d'), 18.0 (q'), 27.2 (q'), 28.8 (t'), 31.4 (t'), 34.9 (t'), 38.7 (s'), 52.1 (t'), 58.9 (s'), 59.7 (d'), 65.7 (t'), 70.2 (t'), 117.7 (t'), 126.1 (d'), 126.8 (d'), 128.0 (d'), 134.5

(d'), 142.9 (s'), 178.3 (s'); exact mass (electrospray) *m/z* calcd for $C_{31}H_{54}NO_3Si$ 516.3867; found 516.3865.

2,2-Dimethylpropanoic Acid (2*R*,6*R*)-2-(3-Hydroxypropyl)-1-(phenylmethyl)-6-[[[tris(1-methylethyl)silyl]oxy]methyl]-2-piperidinylmethyl Ester (74.2).

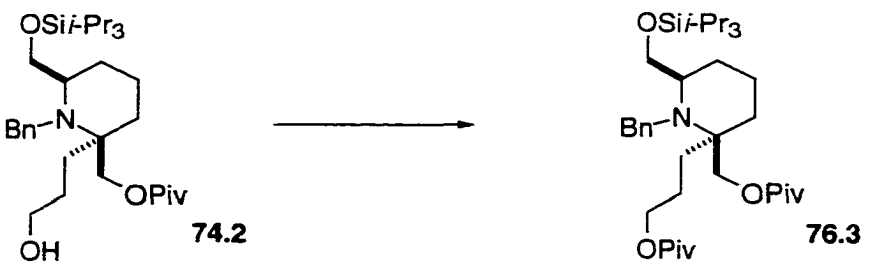


74.1 74.2

9-BBN (0.5 M in THF, 26.4 mL, 13.18 mmol) was added dropwise over ca 20 min to a stirred and cooled (0 °C) solution of **74.1** (4.53 g, 8.79 mmol) in THF (40 mL). The ice bath was removed after 10 min and stirring was continued overnight. The mixture was then recooled (0 °C) and MeOH (20 mL), NaOH (2 N, 50 mL), and water (30%, 6 mL) were added successively. After 10 min, the ice bath was removed and stirring was continued for 2 h. Et_2O (100 mL) and water (100 mL) were added. The aqueous phase was extracted with Et_2O (50 mL) and the combined organic phases were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 20% EtOAc-hexane, gave alcohol **74.2** (4.67 g, 96%) as a colorless oil: $[\alpha]^{25}_D$ +6.36 (*c* 1.10, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3387, 2942, 2865, 1730, 1603, 1462, 1067 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.93 (s, 21 H), 1.16 (s, 9 H), 1.35-1.75 (m, 8 H), 1.75-1.86 (m, 2 H), 2.87 (septet, *J* = 4.0 Hz, 1 H), 3.25 (dd, *J* = 9.0 Hz, 1 H), 3.63 (t, *J* = 6.0 Hz, 2 H), 3.67 (dd, *J* = 10.0, 4.5 Hz, 1 H), 3.79 (d, *J* = 16.5 Hz, 1 H), 3.95 (d, *J* = 12.0 Hz, 1 H), 4.03 (d, *J* = 12.0 Hz, 1 H), 4.12 (d, *J* = 16.5 Hz, 1 H), 7.13 (dd, *J* = 9.0, 9.0 Hz, 1 H), 9.22 (t, *J* = 9.0 Hz, 2 H), 7.35 (d, *J* = 9.0 Hz, 2 H); ^{13}C NMR (50.3 MHz,

$CDCl_3$) δ 11.8 (d'), 17.9 (q'), 18.1 (t'), 26.6 (t'), 27.1 (q'), 27.2 (t'), 28.0 (t'), 30.7 (t'), 38.8 (s'), 51.4 (t'), 58.6 (s'), 59.0 (d'), 63.5 (t'), 65.3 (t'), 70.1 (t'), 126.1 (d'), 126.8 (d'), 128.0 (d'), 142.7 (s'), 178.3 (s'); exact mass (electrospray) *m/z* calcd for $C_{31}H_{56}NO_4Si$ 534.3973; found 534.3971.

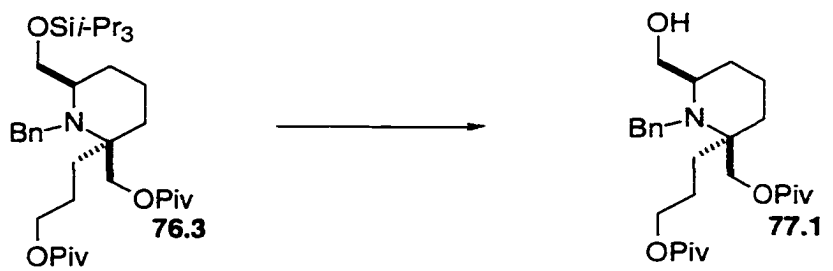
2,2-Dimethylpropanoic Acid (2*R*,6*R*)-2-[[(1,1-dimethylethyl)carbonyloxy]methyl]-1-(phenylmethyl)-6-[[[tris(1-methylethyl)silyl]oxy]methyl]-2-piperidinyl-propyl Ester (76.3).



t-BuCOCl (2.70 mL, 21.90 mmol) was added dropwise over ca 3 min to a stirred and cooled (0 °C) solution of alcohol **74.2** (4.67 g, 8.43 mmol), *i*-Pr_2NEt (6.0 mL, 33.66 mmol) and DMAP (0.20 g, 1.68 mmol) in CH_2Cl_2 (40 mL). After the addition, the ice bath was removed and stirring was continued for 3 h. Saturated aqueous NH_4Cl (40 mL) and Et_2O (100 mL) were added. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 5% EtOAc-hexane, gave **76.3** (4.98 g, 96%) as a colorless oil: $[\alpha]^{25}_D$ +2.85 (*c* 1.81, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2957, 2866, 1730, 1479, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 21 H), 1.16 (s, 9 H), 1.18 (s, 9 H), 1.40-1.86 (m, 10 H), 2.84 (septet, 4.0 Hz, 1 H), 3.26 (dd, *J* = 9.0, 9.0 Hz, 1 H), 3.68 (dd, *J* = 9.0, 4.0 Hz, 1 H), 3.80 (d, *J* = 16.5 Hz, 1 H), 3.96 (d, *J* = 11.0 Hz, 1 H), 4.01 (d, *J* = 11.0 Hz, 1 H), 4.04 (dd, *J* = 10.5, 6.0 Hz, 2 H), 4.08 (d, *J* = 16.5 Hz, 1 H), 7.16 (dd,

J = 8.0, 8.0 Hz, 1 H), 7.23 (t, J = 8.0 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.9 (d'), 17.95 (q'), 18.06 (t'), 23.2 (t'), 27.2 (q'), 27.3 (t'), 27.9 (t'), 30.7 (t'), 38.8 (s'), 38.9 (s'), 51.2 (t'), 58.4 (s'), 58.8 (d'), 64.8 (t'), 64.9 (t'), 70.1 (t'), 126.2 (d'), 126.8 (d'), 128.1 (d'), 142.5 (s'), 178.3 (s'), 178.6 (s'); exact mass (electrospray) m/z calcd for $C_{36}H_{64}NOSi$ 618.4553; found 618.4551.

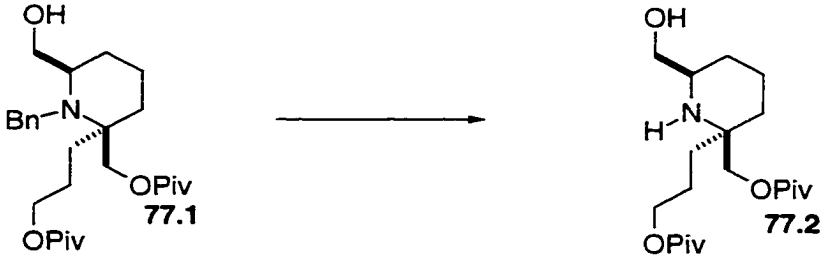
2,2-Dimethylpropanoic Acid (2*R*,6*R*)-2-[[(1,1-Dimethylethyl)carbonyloxy]methyl]-6-(hydroxymethyl)-1-(phenylmethyl)-2-piperidinylpropyl Ester (77.1).



Bu_4NF (1 M in THF, 20.1 mL, 20.1 mmol) was added to a stirred solution of **76.3** (4.98 g, 8.05 mL) in THF (40 mL). Stirring was continued for 2 h, and the solution was diluted with Et_2O (100 mL) and water (50 mL). The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 30% EtOAc-hexane, gave **77.1** (3.56 g, 96%) as a yellow oil: $[\alpha]^{25}_D$ +0.69 (c 0.72, CH_2Cl_2), FTIR (CH_2Cl_2 cast) 3534, 2969, 2871, 1727, 1602, 1284, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9 H), 1.20 (s, 9 H), 1.44-1.70 (m, 9 H), 1.78-1.88 (m, 1 H), 1.72-1.78 (m, 1 H), 3.28 (dd, J = 12.0, 3.5 Hz, 1 H), 3.50 (dd, J = 12.0, 4.0 Hz, 1 H), 3.54 (d, J = 17.0 Hz, 1 H), 4.00-4.14 (m, 4 H), 4.22 (d, J = 17.0 Hz, 1 H), 7.19 (dd, J = 8.0, 8.0 Hz, 1 H), 7.23 (t, J = 8.0 Hz, 2 H), 7.40 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.4 (t'), 23.4 (t'), 24.9 (t'), 27.1 (q'), 27.2

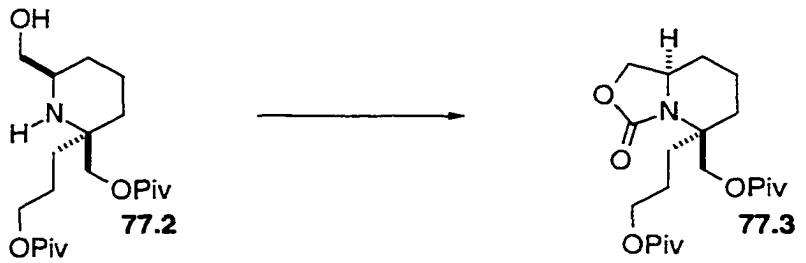
(q'), 27.7 (t'), 30.2 (t'), 38.8 (s'), 52.0 (t'), 59.0 (s'), 59.6 (t'), 63.7 (t'), 64.6 (t'), 70.3 (t'), 126.4 (d'), 126.7 (d'), 128.7 (d'), 142.5 (s'), 178.1 (s'), 178.5 (s'), exact mass (electrospray) *m/z* calcd for $C_{27}H_{44}NO_5$ 462.3219; found 462.3222.

2,2-Dimethylpropanoic Acid (2*R*,6*R*)-2-[[(1,1-Dimethylethyl)carbonyloxy]methyl]-6-(hydroxymethyl)-2-piperidinylpropyl Ester (77.2).



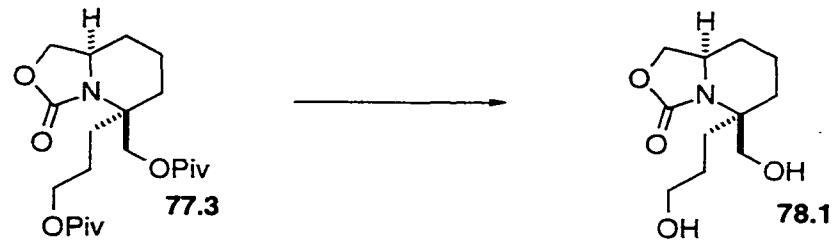
1,4-Cyclohexadiene (5.80 mL, 61.6 mmol) was added to a mixture of 10% Pd/C (1.20 g) and **77.1** (3.56 g, 7.72 mmol) in EtOAc (77 mL). The resulting mixture was warmed to 50 °C and stirred for 2 h. The mixture was allowed to cool to room temperature and was filtered through a pad (3 x 5 cm) of Celite. The solvent was evaporated and the residue was left under oil-pump vacuum for 1 h, to give **77.2** as a thick oil (2.83 g, 99%). The crude material, which was used in the following step without further purification, had: $[\alpha]^{25}_D$ -0.64 (*c* 1.56, CH_2Cl_2), FTIR (CH_2Cl_2 cast) 3328, 2958, 2871, 1729, 1480, 1284, 1157 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.21 (s, 9 H), 1.23 (s, 9 H), 1.42 (ddd, *J* = 15.0, 15.0, 5.0 Hz, 1 H), 1.53-1.80 (m, 9 H), 2.92-3.00 (m, 1 H), 3.48 (dd, *J* = 11.0, 8.0 Hz, 1 H), 3.64 (dd, *J* = 11.0, 4.0 Hz, 1 H), 3.94-4.10 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.2 (t'), 22.8 (t'), 27.2 (t'), 27.3 (q'), 27.5 (t'), 30.7 (t'), 38.8 (s'), 39.0 (s'), 52.0 (d'), 55.2 (s'), 64.5 (t'), 66.1 (t'), 70.0 (t'), 178.0 (s'), 178.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{20}H_{38}NO_5$ 372.2749; found 372.2752.

(4*R*,7a*R*)-4-[[(1,1-Dimethylethyl)carbonyloxy]-methyl]-4-[3-[(1,1-dimethylethyl)carbonyloxy]-propyl]hexahydrooxazolo[3,4-a]pyridin-3-one (77.3).



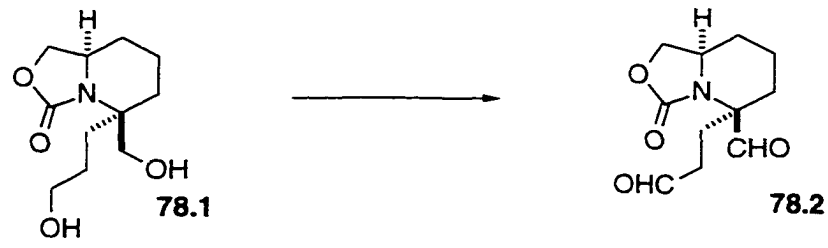
Triphosgene (0.83 g, 2.79 mmol) in CH_2Cl_2 (10 mL) was added dropwise over ca 5 min to a stirred and cooled (-78 °C) solution of **77.2** (0.691 g, 1.86 mmol) and *i*-Pr_2NEt (3.0 mL, 16.74 mmol) in CH_2Cl_2 (40 mL). The resulting mixture was stirred for 12 h, the ice bath being left in place but not recharged. The solvent was evaporated and the residue was redissolved in Et_2O (50 mL) and washed with saturated aqueous NH_4Cl (50 mL). The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 30 to 50% EtOAc-hexane, gave **77.3** (0.652 g, 88%) as a oil: $[\alpha]^{25}_D$ 0.0 (*c* 0.35, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2960, 2872, 1728, 1397, 1285, 1162 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.19 (s, 9 H), 1.21 (s, 9 H), 1.50-1.65 (m, 6 H), 1.75-1.95 (m, 4 H), 3.76 (ddd, *J* = 12.0, 6.0 Hz, 1 H), 4.05 (ddd, *J* = 6.0, 6.0, 2.5 Hz, 1 H), 4.40 (quintet, *J* = 7.0 Hz, 1 H), 4.44 (dd, *J* = 13.0, 11.0 Hz, 1 H), 4.82 (d, *J* = 11.0 Hz, 1 H), ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.8 (t'), 23.0 (t'), 27.2 (q'), 27.3 (q'), 28.3 (t'), 29.7 (t'), 31.6 (t'), 38.8 (s'), 38.9 (s'), 52.9 (d'), 57.7 (s'), 64.1 (t'), 66.0 (t'), 68.3 (t'), 156.4 (s'), 177.8 (s'), 178.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{21}H_{35}NNaO_6$ 420.2362; found 420.2363.

(4*R*,7a*R*)-Hexahydro-4-hydroxymethyl-4-(3-hydroxypropyl)oxazolo[3,4-a]pyridin-3-one (78.1).



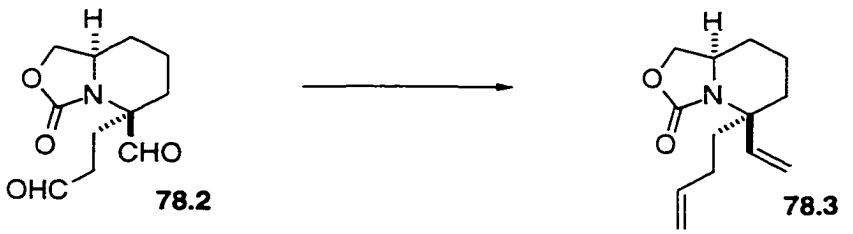
DIBAL-H (1 M in hexane, 3.81 mL, 3.81 mmol) was added dropwise over ca 3 min to a stirred and cooled (-78 °C) solution of diester **77.3** (0.303 g, 0.762 mmol) in Et_2O (8.0 mL). After the addition, stirring was continued for 10 min, and then $Na_2SO_4.10H_2O$ (3 g) was added and the ice bath was removed. Stirring was continued for 1 h. The resulting thick white mixture was filtered through a pad (1 x 2 cm) of Celite, using EtOAc (2 x 10 mL) as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 10 cm), using EtOAc to 10% MeOH-EtOAc, gave diol **78.1** (0.17 g, 95%) as an oil: $[\alpha]^{25}_D$ 0.0 (*c* 0.57, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3394, 2945, 2870, 1716, 1268 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.18-1.28 (m, 1 H), 1.34 (ddd, *J* = 13.5, 13.5, 4.5 Hz, 1 H), 1.50-1.72 (m, 5 H), 1.78 (dddd, *J* = 14.0, 4.0, 4.0, 4.0 Hz, 1 H), 1.85-1.99 (m, 2 H), 1.99-2.20 (br s, 1 H), 3.66 (t, *J* = 6.0 Hz, 2 H), 3.74 (dd, *J* = 14.0, 13.0 Hz, 2 H), 3.86 (dd, *J* = 7.0, 3.0 Hz, 1 H), 3.82-3.90 (m, 1 H), 4.45 (ddd, *J* = 7.0, 6.0, 6.0 Hz, 1 H), 4.70-5.50 (br s, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.7 (t'), 25.7 (t'), 26.7 (t'), 29.9 (t'), 30.0 (t'), 53.2 (d'), 60.7 (s'), 62.7 (t'), 67.4 (t'), 68.8 (t'), 158.2 (s'); exact mass (electrospray) *m/z* calcd for $C_{11}H_{19}NNaO_4$ 252.1711; found 252.1213.

(4*R*,7a*R*)-4-Formylhexahydro-4-(3-oxopropyl)-oxazolo[3,4-a]pyridin-3-one (78.2).



Dry DMSO (0.12 mL, 1.708 mmol) was added dropwise over ca 0.5 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.12 mL, 1.28 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 30 min, and then diol **78.1** (98 mg, 0.427 mmol) in CH_2Cl_2 (1 mL plus 1 mL as a rinse) was added dropwise over ca 0.5 min. Stirring was continued for 1 h, Et_3N (0.60 mL, 4.27 mmol) was added dropwise, and stirring was continued for 1 h. The dry-ice bath was removed and replaced with an ice bath. After the temperature has reached 0 °C after 10 min, hexane (20 mL) was added and the mixture was filtered through a pad (2 x 2 cm) of Celite. The solvent was evaporated to give dialdehyde **78.2** as a yellow oil, which was used in the following step without further purification. The crude material had: ^{1}H NMR (360 MHz, C_6D_6) δ 0.45 (ddd, *J* = 14.0, 14.0, 5.0 Hz, 1 H), 0.75-1.20 (m, 5 H), 1.83 (dddd, *J* = 7.0, 7.0, 7.0, 2.0 Hz, 1 H), 2.00 (dddd, *J* = 7.0, 7.0, 7.0, 2.0 Hz, 1 H), 2.43 (dddd, *J* = 12.0, 7.0, 7.0, 2.0 Hz, 1 H), 3.17 (dddd, *J* = 10.0, 8.0, 8.0, 3.5 Hz, 1 H), 3.25 (dd, *J* = 9.0, 9.0 Hz, 1 H), 3.85 (dd, *J* = 9.0, 8.0 Hz, 1 H), 9.37 (s, 1 H), 9.49 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 18.2 (t'), 21.1 (t'), 28.5 (t'0, 29.2 (t'), 39.1 (t'), 50.5 (d'), 63.8 (s'), 69.7 (t'), 157.5 (s'), 196.4 (d'), 200.8 (d').

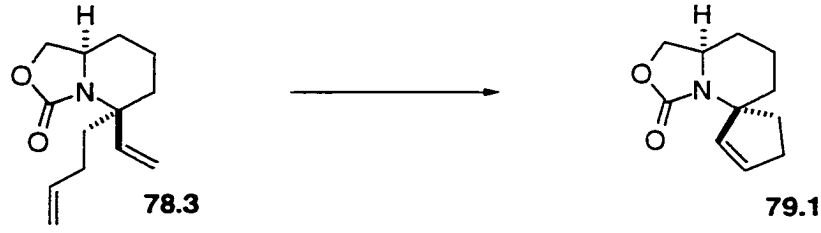
(4*R*,7a*R*)-4-(3-Butenyl)-4-ethenyloxazolo[3,4-*a*]-pyridin-3-one (78.3).



$(Me_3Si)_2NK$ (0.5 in PhMe, 4.10 mL, 2.05 mmol) was added dropwise over ca 0.5 min to a stirred and cooled (0 °C) suspension of Ph_3PCH_3Br (0.76 g, 2.13 mmol) in PhMe (5 mL). After the addition, the ice bath was removed and stirring was continued for 30 min. The yellow ylide mixture was recooled (0 °C) and a solution of all the above dialdehyde **78.2** (assumed to be 0.427 mmol) in PhMe (3 mL plus 1 mL as a rinse) was added dropwise over 2 min. The mixture was stirred for 10 h, the cold bath being left in place but not recharged. MeOH (3 mL) was added to quench the reaction, followed by EtOAc (50 mL) and water (50 mL). The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% EtOAc-hexane, gave diene **78.3** (66 mg, 70%) as a colorless oil: $[\alpha]^{25}_D$ +0.83 (*c* 0.36, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2942, 1747, 1639, 1392 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (ddd, *J* = 12.0, 12.0, 5.0 Hz, 1 H), 1.56-1.82 (m, 5 H), 1.85-2.05 (m, 3 H), 2.16-2.26 (m, 1 H), 3.75 (dd, *J* = 9.0, 2.0 Hz, 1 H), 3.74-3.84 (m, 1 H), 4.36 (dd, *J* = 7.0, 7.0 Hz, 1 H), 4.95 (ddd, *J* = 10.0, 3.0, 3.0 Hz, 1 H), 5.02 (ddd, *J* = 17.0, 3.0, 3.0 Hz, 1 H), 5.10 (d, *J* = 18.0 Hz, 1 H), 5.18 (d, *J* = 11.0 Hz, 1 H), 5.80 (dddd, *J* = 17.5, 10.0, 10.0, 5.0 Hz, 1 H), 6.44 (dd, *J* = 18.0, 11.0 Hz, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.9 (t'), 27.9 (t'), 29.5 (t'), 31.5 (t'), 35.0 (t'), 52.7 (d'), 59.5 (s'), 68.0 (t'), 112.0 (t'), 114.6 (t'), 138.1 (d'), 141.1 (d'), 156.8 (s'); exact mass

(electrospray) *m/z* calcd for $C_{13}H_{20}NO_2$ 222.1494; found 222.1496.

(4*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-4-Spiro[cyclo-pent-2-ene-1,4′-oxazolo[3,4-a]pyridin-3′-one] (79.1).



Diene **78.3** (63 mg, 0.284 mmol) in CH_2Cl_2 (3 mL plus 1 mL as a rinse) was added to a stirred solution of Grubb's catalyst (**80.1**) (24 mg, 0.028 mmol) in CH_2Cl_2 (3 mL). The resulting mixture was stirred at room temperature for 4 h. The solvent was evaporated and the residue was purified by flash chromatography over silica gel (1 x 20 cm), using 30-50% EtOAc-hexane, to give spiro compound **79.1** (52 mg, 95%) as an oil: $[\alpha]^{25}_D$ -11.18 (*c* 2.36, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3054, 2934, 2852, 1751, 1391, 1038 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.33 (ddd, *J* = 12.0, 12.0, 3.5 Hz, 1 H), 1.39-1.70 (m, 3 H), 1.75-1.89 (m, 3 H), 2.15 (ddd, *J* = 12.5, 8.0, 2.5 Hz, 1 H), 2.30 (dddd, *J* = 16.5, 8.0, 8.0, 2.0 Hz, 1 H), 2.50 (dddd, *J* = 16.5, 10.0, 4.0, 2.0 Hz, 1 H), 3.67 (dddd, *J* = 16.5, 8.0, 3.0, 3.0 Hz, 1 H), 3.77 (dd, *J* = 8.0, 8.0 Hz, 1 H), 4.32 (dd, *J* = 8.0, 8.0 Hz, 1 H), 5.80 (ddd, *J* = 6.0, 2.0, 2.0 Hz, 1 H), 6.01 (ddd, *J* = 6.0, 2.0, 2.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7 (t'), 29.7 (t'), 30.5 (t'), 32.7 (t'), 34.6 (t'), 54.5 (d'), 67.8 (t'), 68.4 (s'), 129.2 (d'), 135.8 (d'), 156.2 (s'); exact mass (electrospray) *m/z* calcd for $C_{11}H_{15}NNaO_2$ 216.1000; found 216.1000.

References and Notes

1 Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 1.

2 Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7, and previous reports in this series.

3 Kerr, R. G.; Kerr, S. S. *Expert Opin. Ther. Pat.* **1999**, *9*, 1207.

4 Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867.

5 (a) Springer, T. A. *Cell* **1994**, *76*, 301. (b) Carlos, T. M.; Harlan, J. K. *Blood* **1994**, *84*, 2068.

6 Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871.

7 (a) van den Bosch, H. *Biochim. Biophys. Acta* **1980**, *604*, 191. (b) Arita, H.; Nakano, T.; Hanasaki, K. *Prog. Lipid Res.* **1989**, *28*, 273.

8 Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861.

9 Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753.

10 Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3542.

11 Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583.

12 Zhao, Z.; Lee, S. *Tetrahedron, Lett.* **1999**, *40*, 7921.

13 Shindo, M.; Fukuda, Y.; Shishido, K. *Tetrahedron, Lett.* **2000**, *41*, 929.

14 Kokoots, G.; Padron, J. M.; Martin, T.; Gibbons, W. A.; Martin, V. S. *J. Org. Chem.* **1998**, *63*, 3741.

15 Cf. Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

16 Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

17 Lewis, N.; McKillop, A.; Taylor, R. J. K.; Watson, R. J. *Synth. Commun.* **1995**, *25*, 561.

18 Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1986**, *27*, 799.

19 Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica*

Acta **1997**, *30*, 3.

20 Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J, O. *J. Am. Chem. Soc.* **1998**, *120*, 12237.

21 Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

22 Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307.

23 Lermer, L.; Neeland, E. G.; Ounsworth, J. P.; Sims, R. J.; Tischler, S. A.; Weiler, L. *Can. J. Chem.* **1992**, *70*, 1427.

24 Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

25 Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

26 Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652.

27 Hanessian, S.; Sun, K. *Synthesis* **1991**, 1083.

28 Cf. Hanessian, S.; Grillo, T. A. *J. Org. Chem.* **1998**, *63*, 1049.

29 Liu, H. J.; Ramani, B. *Synth. Commun.* **1985**, *15*, 965.

30 Coppola, G. M. *Synthesis* **1984**, 1021.

31 Kaiser, E.; Tan, J. P.; Kubiak, T. M.; Merrifield, R. B. *Tetrahedron Lett.* **1988**, *29*, 303.

32 Masui, Y.; Chino, N.; Sakakibara, S. *Bull. Chem. Soc.* **1980**, *53*, 464.

33 Maseretti, O.; Furlan, R. *Aldrichimica Acta* **1997**, *30*, 55.

34 Inanagana, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

35 Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459. Cf. Hale, K. J.; Cai, J. *Tetrahedron Lett.* **1996**, *37*, 4233.

36 Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thomas, G.; Kulicke, K. J.; Trach, F. *Organic Reactions*, Paquette, L. A.; *et al.* Ed.; John Wiley and Sons, **1996**,

48, p 656.

37 Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

38 Kunzer, H.; Stahnke, M.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, *32*, 1949.

39 Beau, J-M.; Sinay, P. *Tetrahedron Lett.* **1985**, *26*, 6185.

40 Clive, D. L. J.; Yeh, V. *Tetrahedron Lett.* **1999**, *40*, 8503.

41 Wipf, P. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, **1991**; Vol. *5*, p 827.

42 Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

43 McDougol, P. G.; Rico, J. G.; Oh, Y.; Condon. B. D. *J. Org. Chem.* **1986**, *51*, 3388.

44 Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

45 Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

46 Qian, X. Q.; Russell, K. C.; Botiju, L. W.; Hruby, V. J. *Tetrahedron*, **1995**, *54*, 1033.

47 Thornton, E. R.; Bonner, M. P. *J. Am. Chem. Soc.* **1991**, *113*, 1299.

48 Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.

49 Baldwin, J. E.; Farthing, C. N.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett.* **1996**, *37*, 3761.

50 Rand, C. L.; van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093.

51 Sakaiyani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 820.

52 Honda, M.; Morita, H.; Najakara, I. *J. Org. Chem.* **1997**, *62*, 8932.

53 Curran, D. P.; Chen, M. H.; Spletzer, E.; Seong, C. M.; Chang, C. T. *J. Am. Chem. Soc.* **1989**, *111*, 8872.

54 Fukuzawa, S.; Tsuchimoto, T. *Synlett* **1993**, 803.

55 Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

56 Schmidt, B.; Hoffmann, H. M. R. *Tetrahedron* **1991**, *47*, 9357.

57 For a review on ring closing metathesis, see: Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 371.

58 Clive, D. L. J.; Murthy, K. S. K.; Wee, A.; Prasad. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018.

59 For a review on SmI_2 see: Molander, G. A.; Christina, R. H. *Chem. Rev.* **1996**, *96*, 307.

60 Chenevert, R.; Dickman, M. *J. Org. Chem.* **1996**, *61*, 3332.

61 Goldspink, N, J.; Simpkins, N. S.; Beckmann, M. *Synlett* **1999**, 1292.

62 Dieck, H.; Dietrich, J. *Chem. Ber.* **1984**, *177*, 694.

63 Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391.

64 Cf. (a) Tullis, J. S.; Vares, L.; Kann, W.; Norby, P.; Reins, T. *J. Org. Chem.* **1998**, *63*, 8284. (b) Heathcock, C. H.; Sterfford, J. A. *J. Org. Chem.* **1992**, *57*, 2566.

65 Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.

66 Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75.

67 Chatterjee, A. K.; Morgan, J, P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

68 Gompper *Chem. Ber.* **1957**, *90*, 374.

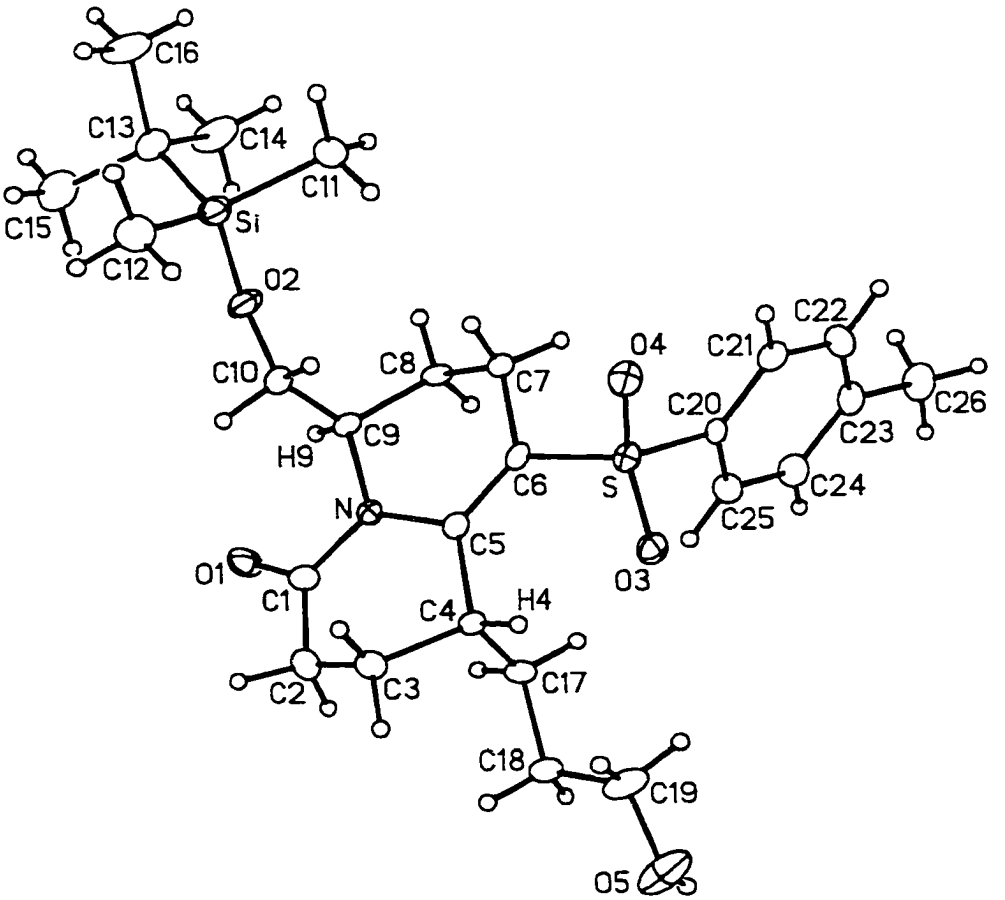
69 Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.

70 Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612 and 5934.

71 Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.

72 Seyden-Penne, J. *Reduction by the Alumino- and*

Borohydrides in Organic Synthesis; 2nd Edn.; Wily-VCH New York, 1997.

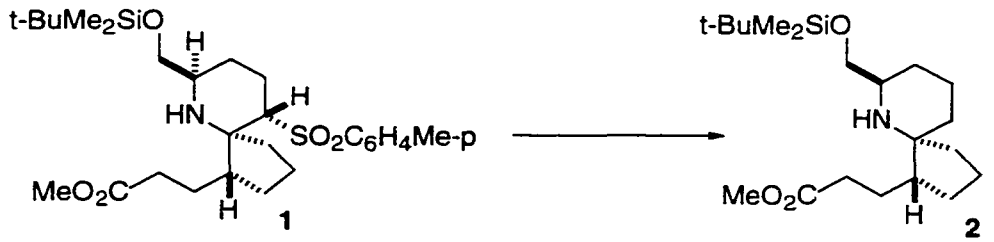


Crystal Structure of **28.1**

Desulfonation Studies

Introduction

During synthetic studies on halichlorine and the pinnaic acids,[1] it was necessary to remove the toluenesulfonyl group from the advanced intermediate **1** (Scheme 1). In preliminary experiments under standard conditions [10% Na(Hg) (1.5 g per



Scheme 1

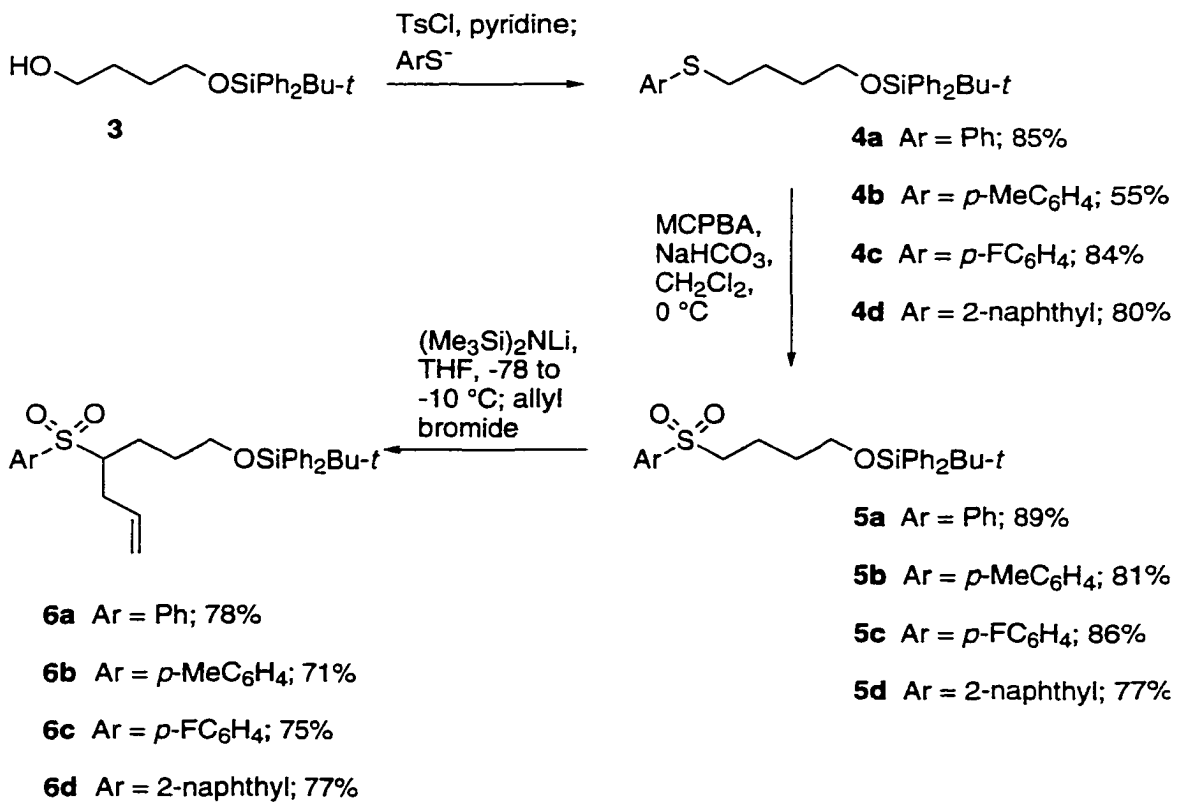
mmol sulfone), Na_2HPO_4, MeOH, -10 °C,],[2,3] we found that the reaction was very slow (24 h) and did not go to completion (30% conversion based on NMR examination of the reaction mixture). Eventually, optimization of the process led to the use of a large excess of reagent [6 g of 10% Na(Hg) per mmol of sulfone] at room temperature for 5 h, and under these conditions the yield was 75%.

Examination of the literature showed that the majority of comparable desulfonylations have been carried out with *phenyl* sulfones, and our experience with the reaction shown in Scheme 1 implies that electron-donating groups retard the process. While we appreciated that steric factors can play a role in the ease of desulfonylation, it was also clear that electronic factors, due to the nature or substitution pattern of the aromatic ring, might be important, and could offer a means of increasing the reactivity towards Na(Hg). With respect to our planned synthetic work on halichlorine, we felt it advisable to find a sulfone unit that could be more easily removed. A systematic study does not appear to have been made, and we have now compared desulfonylation of compounds containing 4-fluorophenyl-, *p*-toluene-, phenyl-,

and 2-naphthyl sulfones. We find, as expected, that electron-withdrawing groups attached to the benzene ring do indeed facilitate the reaction, and that the 2-naphthyl sulfone reacts at about the same speed as the 4-fluorophenyl sulfone.

Results and Discussion

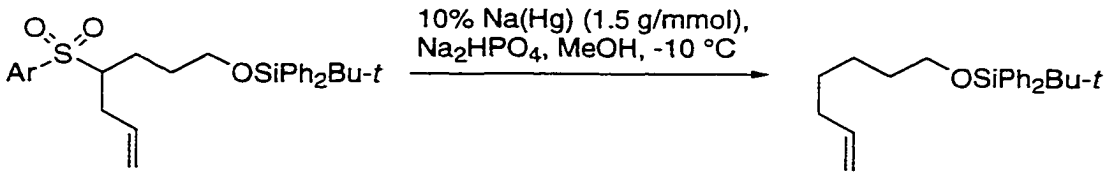
For this work, sulfones **5a-d** were prepared from protected alcohol **3**,[4] by the straightforward route summarized in Scheme 2. Alcohol **3** was first converted into an intermediate tosylate which was displaced by a sulfide anion, generated from $(Me_3Si)_2NLi$ and an aromatic thiol, to give the corresponding sulfides **4a-d**. The sulfides were then oxidized with two equivalents of MCPBA to sulfones **5a-d**, which were alkylated with allyl bromide to give the corresponding secondary sulfones **6a-d**.



Scheme 2

Each of the secondary sulfones **6a-d** was treated with 10% Na(Hg) in MeOH containing Na_2HPO_4, and the progress of the reaction was monitored by tlc at 10-min intervals. It was quickly established that the 4-fluorophenyl and 2-naphthyl sulfones are desulfonylated more rapidly than the others, and

that the reaction occurs at a very convenient rate at -10 °C, using only a modest excess of the amalgam. In both cases yields were very high and the reactions were complete within 30 min (**Scheme 3**).



6a Ar = Ph

6b Ar = *p*-MeC_6H_4

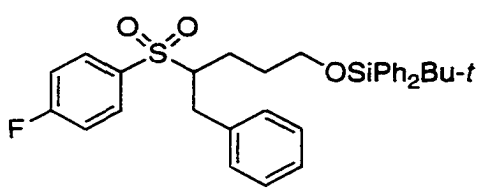
6c Ar = *p*-FC_6H_4

6d Ar = 2-naphthyl

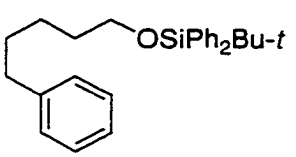
7: Ar = Ph; 1 h, 88%; Ar = *p*-MeC_6H_4; 1 h, 75% plus 15% **6b**; Ar = *p*-FC_6H_4; 30 min, 97%; Ar = 2-naphthyl; 30 min, 93%

Scheme 3

As the reaction is heterogeneous, we also carried out a control experiment in which a mixture of two sulfones was examined. For this purpose sulfone **6e** was prepared [by substituting benzyl bromide for allyl bromide in our normal alkylation (cf. **5a** → **6a**)]. An equimolar mixture of **6b** and **6e** was subjected to the standard conditions for



6e



8

desulfonylation, and the reaction was quenched by aqueous workup after 30 min. Examination of the total organic product by ^1H NMR and gc/ir showed that **6e** had been completely desulfonylated (to give **8**), while about ca 50% of **6b** remained unchanged.

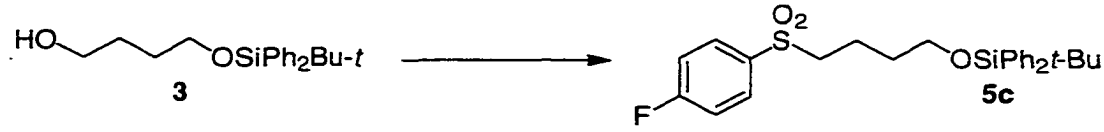
These experimental observations suggest that in the case

of delicate compounds where it is required to speed up desulfonylation, the use a fluoro-substituted or a 2-naphthyl sulfone may be advantageous.[5]

Experimental Section

General Procedures. Unless stated to the contrary, the general procedures used previously[6] were followed. The symbols s', d', t', and q' used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively.

(1,1-Dimethylethyl)[4-[(4-fluorophenyl)sulfonyl]-butoxy]diphenylsilane (4c).



TsCl (1.51 g, 7.92 mmol) was added in one portion to a stirred and cooled (0 °C) solution of alcohol **3**[4] (2.17 g, 6.60 mmol) in dry pyridine (8 mL). The cold bath was removed and stirring was continued for 10 h. The mixture was diluted with Et_2O (50 mL) and washed with saturated aqueous $CuSO_4$, saturated aqueous $NaHCO_3$, and brine. The combined organic extracts were dried ($MgSO_4$), and evaporated. The resulting crude sulfonate (2.89 g, 90%) was obtained as a yellow oil that was used directly in the next step.

$(Me_3Si)_2NLi$ (1 M in THF, 3 mL, 3 mmol) was added dropwise to a stirred and cooled (-10 °C) solution of 4-fluorobenzenethiol (0.38 g, 2.98 mmol) in THF (12 mL). Stirring was continued for 10 min, and a solution of the above crude sulfonate (1.20 g, 2.48 mmol) in THF (2 mL) was added dropwise. The cooling bath was removed and stirring was continued for 3 h. The mixture was diluted with Et_2O (30 mL), washed with aqueous NaOH (1 M) and brine, dried ($MgSO_4$), and evaporated. The resulting crude sulfide (0.96 g, 88%) was obtained as a yellow oil and used directly in the next step.

MCPBA (0.95 g, 5.50 mmol) was added in one portion to a stirred and cooled (0 °C) solution of the above crude sulfide

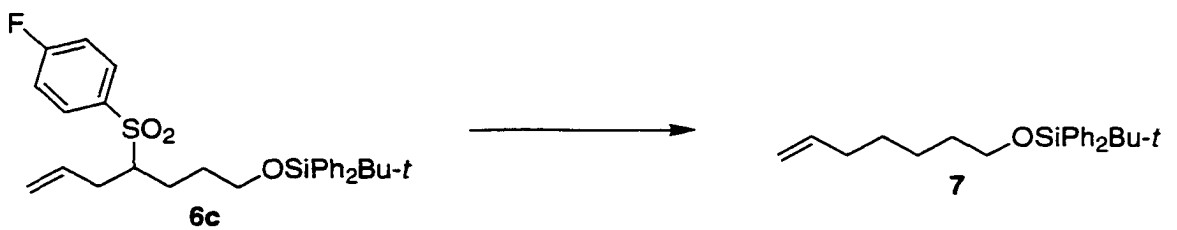
(0.96 g, 2.20 mmol) and $NaHCO_3$ (0.92 g, 11 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 20 min and saturated aqueous $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (20 mL) were then added, and the mixture was stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL), and the total combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 20% EtOAc-hexane, gave sulfone **4c** (0.82 g, 80%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3070, 2930, 1591, 1143, 1086 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.95 (s, 9 H), 1.61 (q, J = 6.0 Hz, 2 H), 1.75-1.83 (m, 2 H), 3.10 (t, J = 6.0 Hz, 2 H), 3.65 (t, J = 6.0 Hz, 2 H), 7.25 (t, J = 8.5 Hz, 2 H), 7.34-7.46 (m, 6 H), 7.60 (dd, J = 8.0, 1.5 Hz, 2 H), 7.89 (dd, J = 8.4, 5.0 Hz, 2 H); ^{13}C NMR (100.6 MHz, CD_2Cl_2) δ 19.4 (s'), 20.2 (t'), 26.9 (q'), 31.2 (t'), 56.5 (t'), 63.3 (t'), 116.7, 117.0 (d'), 128.0 (d'), 130.0 (d'), 131.3, 131.4 (d'), 134.0 (s'), 135.8 (d'), 164.9, 167.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{26}H_{31}FNaO_3SSi$ 493.16449, found 493.16462.

(1,1-Dimethylethyl)[4-[(4-fluorophenyl)sulfonyl]-6-heptenyloxy]diphenylsilane (6c).

$(Me_3Si)_2NLi$ (1 M in THF, 1.1 mL, 1.1 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of sulfone **5c** (0.46 g, 0.99 mmol) in THF (6 mL). The reaction flask was transferred to a cold bath set at -10 °C and stirring was continued for 0.5 h. Allyl bromide (0.13 mL, 1.48 mmol) was then added, and stirring was continued for 1 h at -10 °C. Saturated aqueous NH_4Cl (5 mL) and Et_2O (20 mL) were added,

the phases were separated and the organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 10-20% EtOAc-hexane, gave **6c** (0.35 g, 68%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3071, 2930, 2857, 1641, 1590, 1427, 1145 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.05 (s, 9 H), 1.55-1.80 (m, 3 H), 1.82-1.95 (m, 1 H), 2.35 (q, J = 7.5 Hz, 1 H), 2.55-2.65 (m, 1 H), 3.00-3.10 (m, 1 H), 3.61 (t, J = 5.5 Hz, 2 H), 5.05 (t, J = 0.5 Hz, 1 H), 5.10 (dd, J = 6.0, 1.5 Hz, 1 H), 6.65-5.82 (m, 1 H), 7.25 (t, J = 8.0 Hz, 2 H), 7.34-7.46 (m, 6 H), 7.60 (dd, J = 8.0, 1.5 Hz, 2 H), 7.89 (dd, J = 8.4, 5.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.4 (s'), 24.6 (t'), 27.0 (q'), 29.8 (t'), 32.7 (t'), 63.7 (d'), 64.3 (t'), 116.6, 116.9 (d'), 118.5 (t'), 128.0 (d'), 130.0 (d'), 132.0, 132.1 (d'), 133.9 (d'), 134.1 (s'), 135.9 (d'), 164.5, 167.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{29}H_{35}FNaO_3SSi$ 533.19579, found 533.19560.

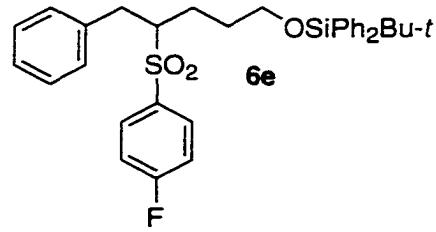
(1,1-Dimethylethyl)[6-heptenyloxy]diphenylsilane (7) from 6c.



10% Na(Hg) was added in one portion to a stirred and cooled (-10 °C) mixture of sulfone **6c** (0.105 g, 0.20 mmol) and Na_2HPO_4 (0.12 g, 0.82 mmol) in dry MeOH (4 mL). The progress of the reaction was monitored by tlc at 10-min intervals; complete disappearance of starting material being observed after 30 min. The mixture was then diluted with Et_2O (30 mL) and washed with water and brine, dried ($MgSO_4$), and evaporated to afford alkene **7** (70 mg, 97%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3062, 2939, 2871, 1642 cm^{-1}; ^1H NMR

(300 MHz, CD_2Cl_2) δ 1.04 (s, 9 H), 1.38 (q, J = 3.5 Hz, 2 H), 1.53-1.61 (m, 2 H), 2.03 (dd, J = 12.3, 6.0 Hz, 2 H), 3.67 (t, J = 6.25, 2 H), 4.89-5.02 (m, 2 H), 5.80 (ddd, J = 12.5, 12.5, 6.5 Hz, 2 H), 7.34-7.50 (m, 6 H), 7.60-7.72 (m, 4 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.5 (s'), 25.7 (t'), 27.0 (q'), 29.1 (t'), 32.8 (t'), 34.1 (t'), 64.4 (t'), 114.3 (t'), 128.0 (d'), 129.9 (d'), 134.6 (s'), 135.9 (d'), 139.5 (d'); mass (CI) *m/z* for $C_{23}H_{36}NOSi$ (M + NH_4) found 370.4.

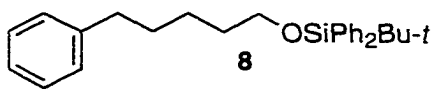
(1,1-Dimethylethyl)[4-[(4-fluorophenyl)sulfonyl]-[5-phenylpentyl]oxy]]diphenylsilane (6e).



6e

The procedure used to make **6c** was followed, using sulfone **5c** (0.36 g, 0.78 mmol), $(Me_3Si)_2NLi$ (1 M in THF, 0.88 mL), and BnBr (0.20g, 1.17 mL). Compound **6e** (0.31 g, 74%) was obtained as a colorless oil: FTIR (CD_2Cl_2 cast) 3069, 2957, 2857, 1590, 1427, 1236 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.95 (s, 9 H), 1.45-1.75 (m, 3 H), 1.81-1.94 (m, 1 H), 2.70 (dd, J = 15.0, 10.5 Hz, 1 H), 3.23-3.32 (m, 2 H), 3.48 (t, J = 6.0 Hz, 2 H), 7.05-7.08 (m, 2 H), 7.15-7.25 (m, 5 H), 7.30-7.45 (m, 6 H), 7.52-7.58 (m, 4 H), 7.89 (dd, J = 8.4, 5.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.4 (s'), 25.1 (t'), 27.0 (q'), 30.1 (t'), 34.9 (t'), 63.7 (t'), 66.4 (d'), 116.7, 117.0 (d'), 127.2 (d'), 128.0 (d'), 129.0 (d'), 129.4 (d'), 130.0 (d'), 132.0, 132.1 (d'), 134.1 (s'), 134.6 (s'), 135.9 (d'), 137.7 (s'), exact mass (electrospray) *m/z* calcd for $C_{33}H_{37}FNaO_3SSi$ 583.21144, found 583.21110.

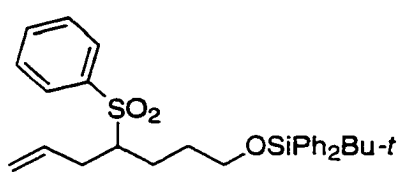
(1,1-Dimethylethyl)[(6-phenylheptyl)oxy]diphenylsilane (8).



8

The procedure used for the desulfonylation of **6c** was followed, using sulfone **6e** (0.125 g, 0.22 mmol), 10% Na(Hg) (0.34 g), and Na_2HPO_4 (0.129 g, 0.908 mmol). Compound **8** (83.3 mg, 94%) was obtained as a colorless oil: FTIR (CH_2Cl_2 cast) 3064, 2939, 2870, 1594, 1107 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.04 (s, 9 H), 1.35-1.46 (m, 2 H), 1.56-1.64 (m, 4 H), 2.59 (t, J = 7.5 Hz, 2 H), 3.67 (t', J = 6.5, 2 H), 7.08-7.30 (m, 5 H), 7.30-7.45 (m, 6 H), 7.62-7.70 (m, 4 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.4 (s'), 25.9 (t'), 27.0 (q'), 31.7 (t'), 32.8 (t'), 36.2 (t'), 64.3 (t'), 125.9 (d'), 127.9 (d'), 128.5 (d'), 128.8 (d'), 129.9 (d'), 131.3 (s'), 134.6 (s'), 135.9 (d'); mass (CI) m/z for $C_{27}H_{36}NOSi$ ($M + NH_4$) found 420.3.

(1,1-Dimethylethyl)diphenyl[4-(phenylsulfonyl)-6-heptenyloxy]silane (6a).

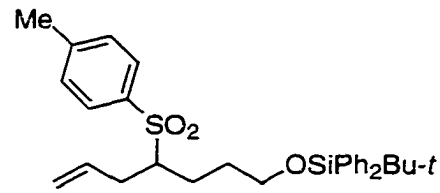


6a

The procedure used to make **6c** was followed, using sulfone **5a** (0.2 g, 0.44 mmol), $(Me_3Si)_2NLi$ (1 M in THF, 0.48 mL), and allyl bromide (79 mg, 0.66 mmol). Compound **6a** (0.16 g, 78%) was obtained as a colorless oil: FTIR (CH_2Cl_2 cast) 3070, 2957, 2857, 1640, 1588, 1304, 1146 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.05 (s, 9 H), 1.56-1.80 (m, 3 H), 1.84-1.96 (m, 1 H), 2.34 (ddd, J = 15.0, 8.0, 7.5 Hz, 1 H), 2.55-2.66

(m, 1 H), 3.05 (q, J = 6.5 Hz, 1 H), 3.60 (t, J = 6.0 Hz, 2 H), 5.05 (s, 1 H), 5.09 (d, J = 6.0 Hz, 1 H), 5.69-5.82 (m, 1 H), 7.35-7.49 (m, 6 H), 7.52-7.70 (m, 7 H), 7.82-7.90 (m, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 47.7 (s'), 52.6 (t'), 55.0 (q'), 57.9 (t'), 60.7 (t'), 91.8 (t'), 92.2 (t'), 146.4 (t'), 156.1 (d'), 157.2 (d'), 157.6 (d'), 158.0 (d'), 162.0 (d'), 162.2 (s'), 163.9 (d'), 166.5 (s'); exact mass (electrospray) m/z calcd for $C_{29}H_{36}FNaO_3SSi$ 515.20521, found 515.20549.

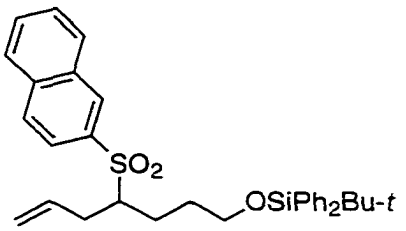
(1,1-Dimethylethyl)diphenyl[4-[4-methylphenyl)-sulfonyl]-6-heptenyloxy]silane (6b).



6b

The procedure used to make **6c** was followed, using sulfone **5b** (0.47 g, 1.01 mmol), $(Me_3Si)_2NLi$ (1 M in THF, 1.11 mL), and allyl bromide (0.18 g, 1.51 mmol). Compound **6b** (0.36 g, 71%) was obtained as a colorless oil: FTIR (CH_2Cl_2 cast) 3070, 2956, 2857, 1640, 1597, 1311, 1145 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.0 (s, 9 H), 1.55-1.78 (m, 3 H), 1.81-1.95 (m, 1 H), 2.35 (ddd, J = 15.5, 15.0, 6 Hz, 1 H), 2.55-2.65 (m, 1 H), 3.01 (q, J = 7 Hz, 1 H), 3.59 (t, J = 6.0 Hz, 2 H), 5.04 (s, 1 H), 5.09 (dd, J = 7.0, 1.5 Hz, 1 H), 5.69-5.82 (m, 1 H), 7.35-7.50 (m, 8 H), 7.55-7.65 (m, 4 H), 7.75 (d, J = 7.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.4 (s'), 21.7 (q'), 24.6 (t'), 27.0 (q'), 29.9 (t'), 32.7 (t'), 63.8 (t'), 64.1 (d'), 118.3 (t'), 128.0 (d'), 129.2 (d'), 130.0 (d'), 130.2 (d'), 134.2 (d'), 134.4 (s'), 135.5 (s'), 135.9 (d'), 145.1 (s'); exact mass (electrospray) m/z calcd for $C_{30}H_{38}NaO_3SSi$ 529.22086, found 529.22115.

(1,1-Dimethylethyl)[4-(2-naphthylsulfonyl)-6-heptenyloxy]diphenylsilane (6d).



6d

The procedure used to make **6c** was followed, using sulfone **5d** (0.44 g, 0.88 mmol), $(Me_3Si)_2NLi$ (1 M in THF, 1 mL), and allyl bromide (0.16 g, 1.32 mmol). Compound **6d** (0.37 g, 77%) was obtained as a colorless oil: FTIR (CH_2Cl_2 cast) 3070, 2930, 2856, 1640, 1625, 1589, 1304, 1111 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.98 (s, 9 H), 1.55-1.87 (m, 3 H), 1.90-2.01 (m, 1 H), 2.40 (q, J = 7.5 Hz, 1 H), 2.60-2.70 (m, 1 H), 3.11-3.21 (m, 1 H), 3.59 (t, J = 6.0 Hz, 2 H), 5.04 (s, 1 H), 5.08 (dd, J = 9.0, 1.5 Hz, 1 H), 5.70-5.85 (m, 1 H), 7.30-7.50 (m, 6 H), 7.55-7.72 (m, 6 H), 7.87 (dd, J = 7.0, 2.0 Hz, 1 H), 7.90-8.05 (m, 3 H), 8.50 (s, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.3 (s'), 24.6 (t'), 26.9 (q'), 29.9 (t'), 32.7 (t'), 63.8 (t'), 64.2 (d'), 118.4 (t'), 123.8 (d'), 128.0 (d'), 129.6 (d'), 129.8 (d'), 130.0 (s'), 131.0 (s'), 132.6 (s'), 134.1 (d'), 134.2 (s'), 135.5 (s'), 135.7 (s'), 135.9 (d'); exact mass (electrospray) *m/z* calcd for $C_{30}H_{38}NaO_3SSi$ 565.22086, found 565.22043.

References and footnotes

1 Clive, D. L. J.; Yeh, S. C. V. *Tetrahedron Lett.* **1999**, *40*, 8503.

2 Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

3 Review of the chemistry of sulfones: Simpkins, N. *Sulfones in Organic Synthesis*, Pergamon: London, 1993.

4 Barrett, A. G. M.; Flygare, J. A. *J. Org. Chem.* **1991**, *56*, 638..

5 Clive, D. L. J.; Yeh, V. S. C. *Synth. Commun.* **2000**, *30*, 3267.

6 Clive, D. L. J.; Wickens, P. L.; Sgarbi, P. W. M. *J. Org. Chem.* **1996**, *61*, 7426.