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UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

For Louise

# Abstract

Part A:

The synthesis of tabtoxinine-β-lactam was attempted using several routes. Hydroxylation of several 3-alkylideneaxetidin-2-ones with MoOPh lead to the formation of 3-hydroxyalkenylazetidin-2-ones in fair to good yields. The prerequisite 3-alkylideneazetidin-2-ones were formed from 3-trimethylsilylazetidin-2-ones and aldehydes via a Peterson olefin synthesis. Attempts to complete a synthesis of tabtoxinine-β-lactam using this methodology were not sucessful. Two routes to tabtoxinine in which the β-lactam moiety is constructed late in the synthesis were also investigated, neither one being fruitful.

Part B:

Several chiral thiolanes were designed and built for possible conversion into sulfonium salts. The derived sulfur ylides were expected to react with carbonyl compounds to give optically active epoxides. Syntheses from D-mannitol did not produce a successful candidate, but the S-benzyl ylide obtained from an L-tartrate derived thiolane did successfully transfer it's benzylidene group to produce *trans* stillbene oxide with 19 % enanteomeric excess. This represents the first example of successfull transfer of asymmetry in the reaction of an optically active sulfonium ylide with a carbonyl compound.

# Acknowledgements

I would like to express my thanks and appreciation to all who in various capacities contributed to the completion of this work.

First and foremost, Tony Durst whose guidance, advice, criticism, prodding, encouragement and friendship are warmly appreciated. Tony possesses a mixture of qualities which make him an ideal supervisor.

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Thanks to Raj Capoor and Dr. Clem Kazakoff for the fine nmr and mass spectral service throughout. Dr. Heather Dettman is responsible for much of the "special effects" nmr in this thesis. Thanks to Dr. John Krause for assistance of all kinds and for sports pool financing.

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Finally, I would like to express my appreciation to Louise Charron, for keeping me going and for making it all worthwhile and for whom this thesis is dedicated.

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# List of Abbreviations

$(AcO)_2O$ ..... Acetic anhydride

2-APB ..... 2-Amino-4-phosphonobutyric acid

Ac ..... Acetyl

AcCl ..... Acetyl chloride

Ad ..... 1-Adamantyl

ADEPT ..... Auto DEPT

ADP ..... Adenosine diphosphate

AIBN ..... Azobisisobutylnitrile

ATP ..... Adenosine triphosphate

Bn ..... Benzyl

BOC ..... *t*-Butyloxycarbonyl

Bz ..... Benzoyl

CBZ ..... Benzyloxycarbonyl

cy ..... Cyclohexyl

$\Delta$ ..... Heat (reflux)

DBN ..... 1,5-Diazabicyclo-[4.3.0]-non-5-ene

DCC ..... Dicyclohexylcarbodiimide

DEAD ..... Diethyl azidodicarboxylate

DEPT ..... Distortionless enhanced polarization transfer

DMF ..... N,N-Dimethylformamide

DMS ..... Dimethylsulfide

DMSO ..... Dimethylsulfoxide

E ..... Electrophile or electrophilic

ee ..... Enantiomeric excess

EtOAc ..... Ethyl acetate

FGI ..... Functional group interconversion

Gln ..... Glutamine

Glu ..... Glutamic acid

HETCOR ..... Heteronuclear correlation nmr spectroscopy

HMDS ..... Hexamethyldisylazane

HOAc ..... Acetic acid

HOMCOR ..... Homonuclear correlation nmr spectroscopy

hrms ..... High resolution mass spectrometry

$H_z$ ..... Hertz

*i*Pr ..... Isopropyl

ir ..... Infrared

L ..... Leaving group

LAH ..... Lithium aluminum hydride

LDA ..... Lithium diisopropylamide

LiHMDS ..... Lithium hexamethyldisilazide

*m*CPBA ..... *m*-Chloroperoxybenzoic acid

Me ..... Methyl

MeOH ..... Methanol

MeOTf ..... Methyl trifluorosulfonate

Ms ..... Mesylate

NBS ..... N-Bromosuccinimide

*n*BuLi ..... *n*-Butyllithium

nmr ..... Nuclear magnetic resonance

NOE ..... Nuclear Overhauser effect

Nu ..... Nucleophile or nucleophilic

PG ..... Protecting group

Ph ..... Phenyl

Pi ..... Phosphate

PMP ..... *p*-Methoxyphenyl

$PPh_3$ ..... Triphenylphosphine

ppm ..... Parts per million

Pt ..... Phthaloyl

PTC ..... Phase transfer catalysis

PTS ..... *p*-Toluenesulfonic acid

py ..... Pyridine

TBAB ..... Tetrabutylammonium bromide

TBAC ..... Tetrabutylammonium chloride

TBAF ..... Tetrabutylammonium fluoride

TBAI ..... Tetrabutylammonium iodide

TBS ..... *t*-Butyldimethylsilyl

TBS-Cl ..... *t*-Butyldimethylsilyl chloride

TBSOTf ..... *t*-Butyldimethylsilyl trifluorosulfonate

*t*BuSH ..... *t*-Butylthiol

TEA ..... Triethylamine

Tf ..... Triflate

TFA ..... Trifluoroacetic acid

THF ..... Tetrahydrofuran

Thr ..... Threonine

TLC ..... Thin layer Chromatography

TMEDA ..... N,N,N',N'-Tetramethylethylenediamine

TMS ..... Trimethylsilyl

TMS-Cl ..... Chlorotrimethylsilane

$TMS\text{-}N_3$ ..... Azidotrimethylsilane

Ts ..... Tosylate

# PART A: STUDIES DIRECTED TOWARDS THE SYNTHESIS OF TABTOXININE-β-LACTAM

## Introduction

### History of tabtoxin and tabtoxinine

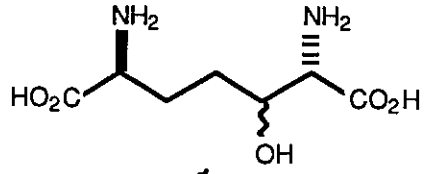
In 1917 a leafspot disease of tobacco plants in North Carolina was described.[1] The affliction was called wildfire because of its rapid spread and was considered the most destructive tobacco disease at that time.[2] The disease is characterized by the appearance of yellow lesions on the leaves of infected plants. The bacterium responsible for the condition was identified as *Pseudomonas tabaci*.. Symptoms were also shown to be caused by culture filtrates of this bacterium, indicating that the bacteria produced an exotoxin which was responsible for the observed chlorosis (loss of chlorophyll) in infected plants.[3]

In 1952 Woolley developed an assay for the toxin and also devised a means of purification.[4] Throughout the study he noted that the toxin was very unstable. It was deactivated in a few minutes in alkaline solution, although more slowly in acid. Exposure to methanol also increased the decomposition rate. He also observed that the material was deliquescent. Mild basic hydrolysis gave two amino acid products, one of which could be further hydrolyzed with 6 N HCl

---

[1] F. A. Wolf, A. C. Foster. *Science*, **46**, 361 (1917).
[2] F. A. Wolf. *North Carolina Exp. Sta. Bull.* , **246**, 1 (1922).
[3] A. C. Braun. *Proc. Nat. Acad. Sci.*, **36**, 423 (1950).
[4] D. W. Woolley, R. B. Pringle, A. C. Braun. *J. Biol. Chem.*, **197**, 409 (1952).

to give a new product which was ninhydrin active. This product and its precursor derived from the toxin were both unknown amino acids. Woolley christened the new amino acid (derived from the toxin) tabtoxinine.[5] Woolley also at this time proposed a structure for the new amino acid **1**, and tentatively assigned stereochemistry to the amino groups.



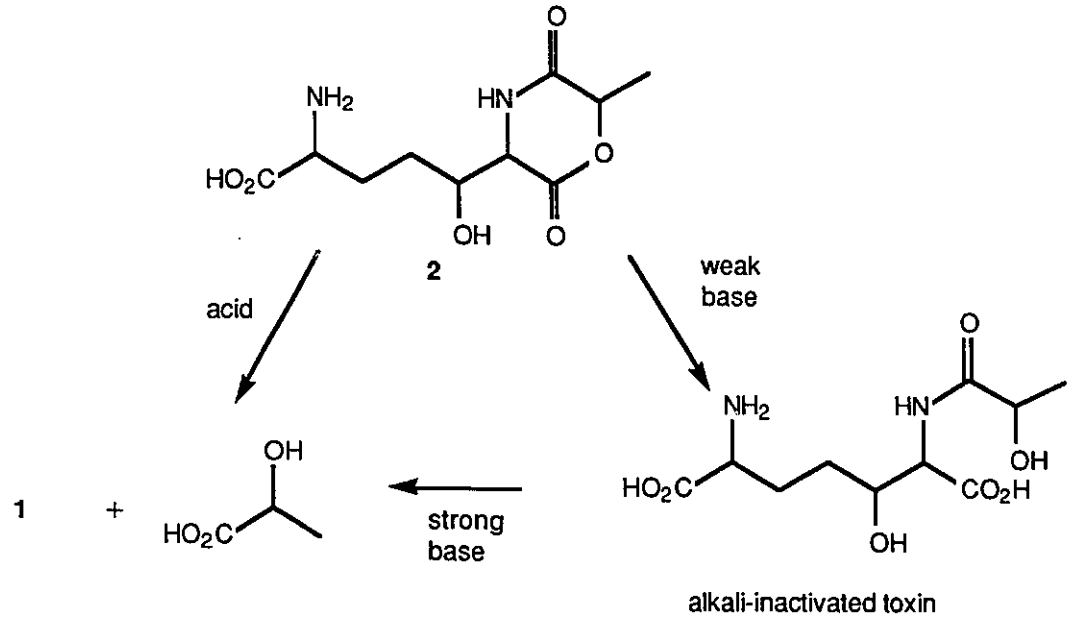

**1**

Reaction of Woolley's tabtoxinine with ninhydrin gave 2 moles of $CO_2$ per mole of tabtoxinine, indicating that two α-amino acid moieties were present. Periodate degradation gave glutamic acid, indicating the position of the hydroxyl group. Woolley also showed that tabtoxinine was not affected by rat kidney D-amino acid oxidase which led him to suggest L configurations for the amino acid moieties.

Later, Woolley[6] proposed a structure for the toxin itself, incorporating his tabtoxinine **1** and lactic acid, which he found in hydrolysates of the toxin using strong acid or base. Mild basic treatment gave a ninhydrin positive substance which he called alkali - inactivated toxin. This substance could be cleaved with strong alkali to lactic acid and tabtoxinine. Also noted was the fact that alkali - inactivated toxin and the toxin were not affected by periodate suggesting that the α-amino group of the tabtoxinine residue was blocked in both cases. The ease of alkaline cleavage and the fact that an acid was formed led Woolley to suggest the structure **2** for the toxin.

---

[5] D. W. Woolley, G. Schaffner, A. C. Braun. *J. Biol. Chem.*, **198**, 807 (1952).
[6] D. W. Woolley, G. Schaffner, A. C. Braun. *J. Biol. Chem*, **215**, 485 (1955).




Subsequent to this, Woolley and Stewart[7] showed that the proposed structure for tabtoxinine was in error. They synthesized all four diastereomers of α,ε-diamino-β-hydroxypimelic acid (**1**), and by comparing physical characteristics of the compounds, as well as physical characteristics of derivatives with authentic samples of tabtoxinine showed that although some characteristics matched, that **1** could not be the true structure of tabtoxinine.

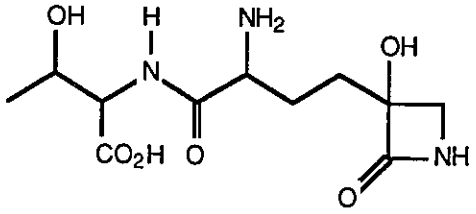
Following this work, Sinden and Durbin[8] examined hydrolysates of the *P. tabaci* toxin. Using ion exchange chromatography, they isolated in addition to tabtoxinine only threonine and small amounts of serine. No lactic acid was observed. The failure to observe lactic acid was thought to be due to an impurity in Woolley's isolates.

---

[7] a) J. M. Stewart, D. W. Woolley. *J. Am. Chem. Soc.*, **78**, 5336, (1956); b) J. M. Stewart. *J. Am. Chem. Soc.*, **83**, 435 (1961).

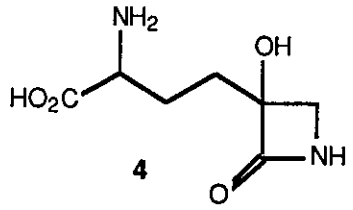
[8] S. L. Linden, R. D. Durbin. *Phytopathology*, **60**, 360(1970).

The structure of tabtoxinine was finally elucidated in 1971.[9] Analysis of the toxin by spectroscopic means led to the proposal of the accepted structure **3**, for wildfire toxin.




**3**

Hydrolysis of the toxin gave tabtoxinine and threonine as the only products. Tabtoxinine was not isolated with an intact β-lactam, but as the open chain isomer. A structure for tabtoxinine containing a β-lactam moiety (**4**) was assumed however, the lactam being destroyed upon hydrolysis.




**4**

Stewart also noticed that the toxin decayed rapidly in solution (as did Woolley) and was able to determine that a δ-lactam **5** was formed in this way.

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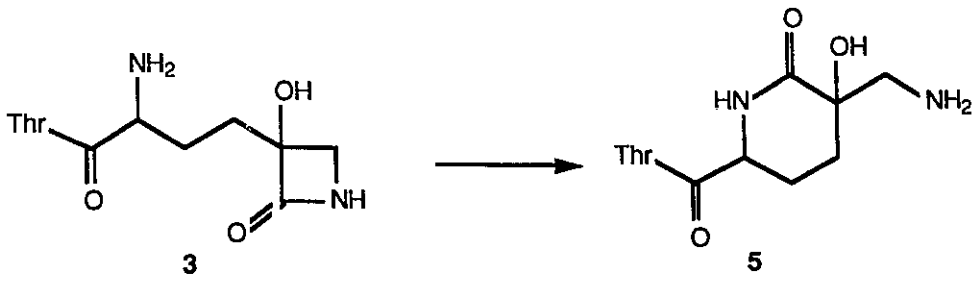
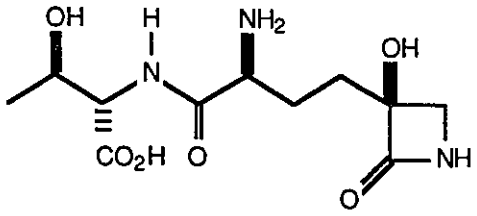
[9] W. W. Stewart. *Nature*, **229**, 174 (1971).




Stewart named this inactive form of the toxin isotabtoxin. Shortly after this, a report was published[10] detailing the isolation and characterization of wildfire toxin from other *Pseudomonas* species. The authors of this study succeeded in isolating tabtoxinine-δ-lactam and proposed the trivial name tabtoxin for the wildfire toxin. Later tabtoxinine-β-lactam was successfully isolated and characterized.[11] In a separate study, the stereochemical configuration of tabtoxinine-β-lactam was elucidated by x-ray crystalography[12] and found to be as shown below.



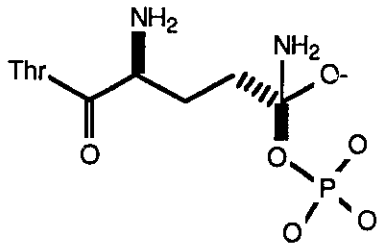

3

[10] P. A. Taylor, H. K. Schnoes, R. D. Durbin. *Biochem. Biophys. Acta.*, **286**, 107 (1974).
[11] R. D. Durbin, T. F. Uchytil, J. A., Steele, R. de L. D. Ribeiro. *Phytochemistry*, **17**, 147 (1978).
[12] J. P. Scannell, D. L. Pruess, J. F. Blount, H. A. Ax, M. Kellett, F. Weiss, T. C. Demny. T. H. Williams, A. Stempel. *J. Antibiot.*, **28**, 1 (1975).

**Mode of action of tabtoxin**

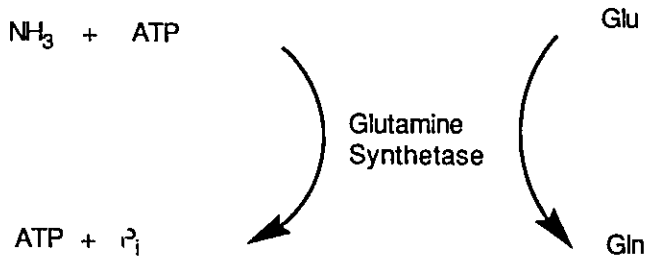
Tabtoxin was originally thought to interfere in the metabolism of methionine since it produced lesions similar to those produced by methionine sulfoximine.[4] This was reasonable at the time since methionine sulfoximine was thought to be an antagonist of methionine[13] in the alga *Chlorella vulgaris.* Later work demonstrated that the addition of L-methionine directly into colonies of infected algae reversed the effects of tabtoxin in the algae but was not successful in counteracting chlorosis in plants.[14] In animals, tabtoxin produced convulsions[15] and was found to inhibit cerebral glutamine synthetase.[16] On the basis of these findings, it was supposed that tabtoxin manifested its toxic effects by glutamine synthetase inhibition. Injection of L-glutamine into tobacco leaves insulted with tabtoxinine prevented the chlorosis.[14] Incubation of pea glutamine synthetase with tabtoxin resulted in loss of transferase activity which was reduced upon inclusion of L-glutamine.[1] This strongly suggests that glutamine synthetase is in fact the enzyme inhibited by tabtoxin.

Stewart[4] speculated on a possible intermediate in the inhibition, a phosphorylated derivative of the toxin.




[13] A. C. Braun. *Phytopathology,* **45**, 659 (1955).
[14] S. L. Sinden, R. D. Durbin. *Nature*, **219**, 379 (1968).
[15] S. L. Sinden, R. D. Durbin, T. F. Uchytil, C. Lamar. *Toxicol. Appl. Pharmacy*, (1968).
[16] O. Z. Sellinger, P. Weiler. *Biochem. Pharm.* ,**12**, 989 (1963)

It was later demonstrated that tabtoxin was inactive on purified glutamine synthetase, and toxic effects were realized only upon hydrolysis of tabtoxin, releasing tabtoxinine-β-lactam.[17] It is now thought that chlorosis in plants is caused by the accumulation of ammonia.[18] Ammonia is normally handled by the glutamine synthetase system which converts glutamic acid to glutamine, consuming a mole of $NH_3$ in the process.




The production of glutamine is also essential for normal metabolism since glutamine is the source of nitrogen in amino acid biosynthesis. Glutamine also supplies nitrogen in the urea cycle and is used in pyrimidine biosynthesis.[19]

Tabtoxinine-β-lactam is currently an important phytotoxin in that it is useful in elucidating the mode of action of glutamine synthetase.[20] It is currently available only by isolation from bacterial broths. Although efficient procedures for it's isolation have been recently developed,[21] these techniques provide only

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[17] T. F. Uchtil, R. D. Durbin. *Experimentia*, **36**, 301 (1980).

[18] a) T. A. Frantz, P. M. Peterson, R. D. Durbin. *Plant Physiol.*, **69**, 345 (1982); b) J. G. Turner, J. M. Debbage. *Physiol. Plant Pathol*, **20**, 223 (1982).

[19] a) B. J. Miflin, P.J. Lea. *Ann. Rev. Plant Physiol.*, **28**, 299 (1977); b) A. Meister in *The Enzymes*, P.D. Boyer, Ed. Academic: New York, p.699.

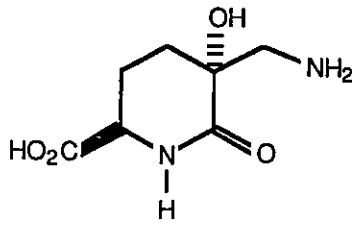
[20] P. J. Langston-Unkefer, A. C. Robinson, T. J. Knight, R. D. Durbin. *J. Biol. Chem*, **262**, 1608 (1981).

[21] M. D. Thomas, P. J. Langston-Unkefer, T. F. Uchytil, R. D. Durbin. *Plant Physiol.* , **21**, 912 (1983).

small amounts of material ( 28-37 mg $l^{-1}$ of bacterial broth). Therefore a convenient synthesis of this material would be useful.

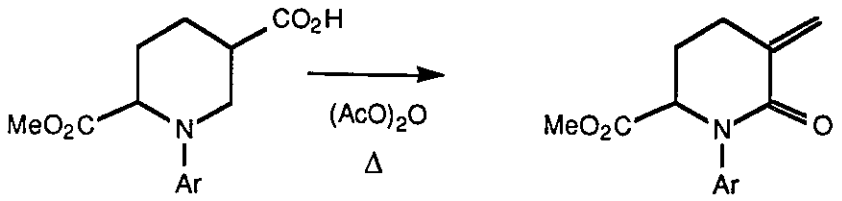
## Synthetic studies of tabtoxinine

Possibly because of it's small size and difficult functionality, tabtoxinine has not been a popular synthetic target. Shortly after the structure of tabtoxinine was elucidated, Rapoport[22] described a synthesis of tabtoxinine in it's δ form **6**.




**6**

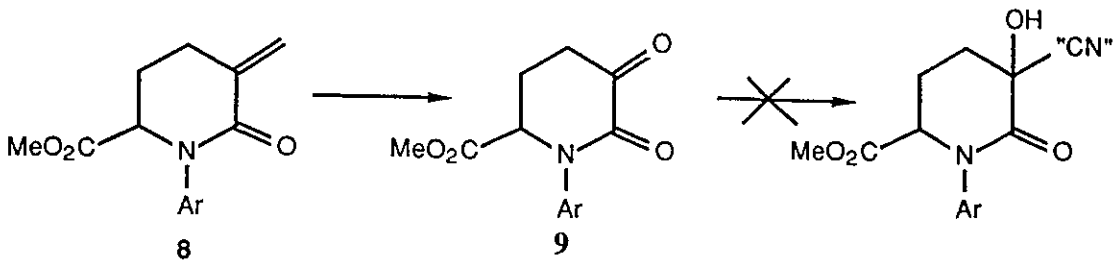
Rapoport's synthesis begins with the piperidine derivative **7** which contains the carbon skeleton of tabtoxinine and requires only functional group manipulation to realize the target. Exposure of **7** to refluxing acetic anhydride gave lactam **8** via an α-methylenelactam rearrangement.[23]




**7** **8**

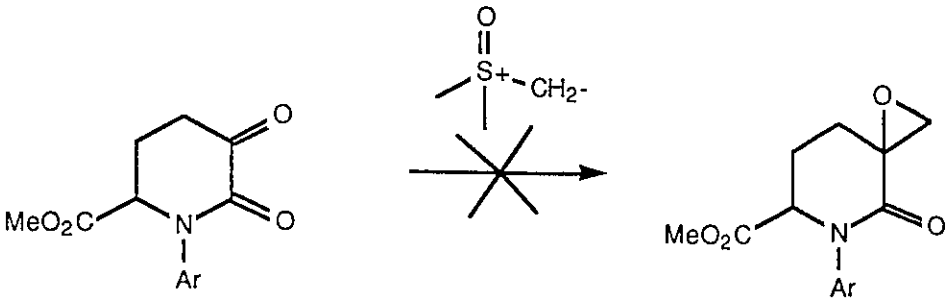
[22] D. L. Lee, H. Rapoport. *J. Org. Chem.*, **40**, 3491 (1975).
[23] D. L. Lee, C. J. Morrow, H. Rapoport. *J. Org. Chem*, **39**, 893 (1974).

Initial attempts to add "C-N" type nucleophiles to ketolactam **9** derived from **8** were unsuccessful.



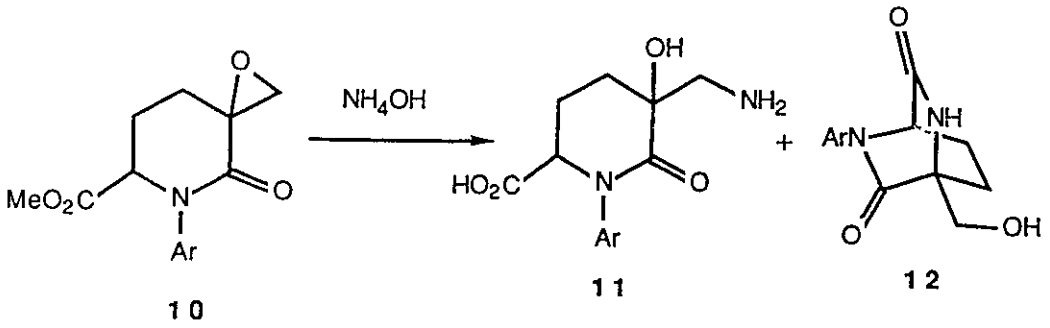

**8** **9**

Rapoport was also unable to effect a clean reaction with **9** and dimethyloxosulfonium methylide to give epoxylactam **10**.




**10**

Compound **10** could be obtained however by epoxidation of methylenelactam **8** with *m*CPBA. Reaction of **10** with ammonium hydroxide gave the desired adduct **11** along with smaller amounts of diketopiperazine **12.**




10 11 12

Removal of the *p*-methoxybenzyl moiety with TFA gave tabtoxinine-δ-lactam. This synthesis was not stereospecific but Rapoport was able to produce the correct diastereomer by separating the diastereomeric epoxides **10**.

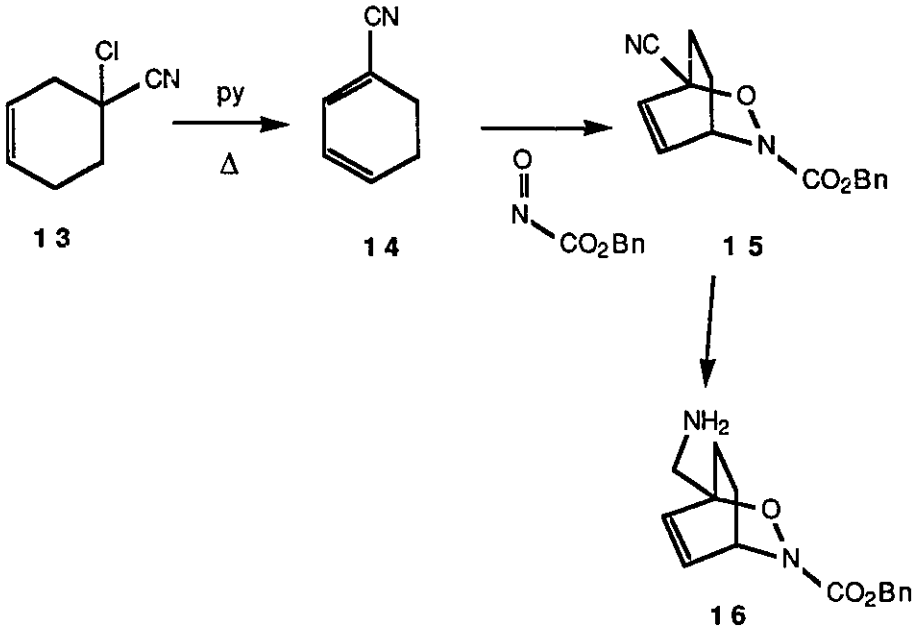
Recently, Baldwin has reported stereospecific syntheses of tabtoxin[24] and tabtoxinine-β-lactam.[25] Both syntheses use the same approach, with minor functional group differences. Baldwin's initial synthesis was of tabtoxin but he stated that tabtoxinine-β-lactam could not be prepared by the same sequence.[24a] In fact, both sequences are very similar and only one need be described.

Cyclohexene **13**, prepared by a Diels-Alder reaction of 2-chloroacetonitrile and butadiene, was converted to diene **14** by refluxing in pyridine. Treatment of **14** with benzyl nitrosoformate gave cycloadduct **15**.

---

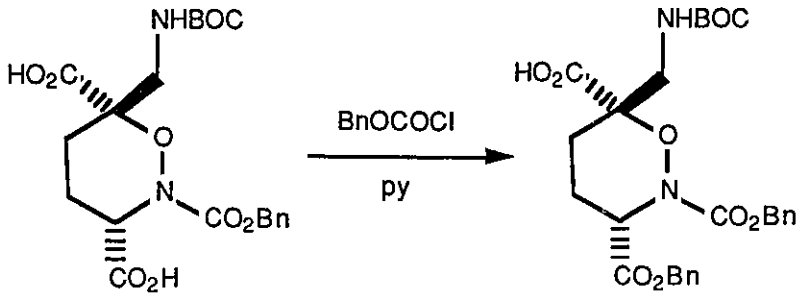
[24] a) J. E. Baldwin, P. D. Bailey, G. Gallacher, K. A. Singleton, P. M. Wallace. *J. Chem. Soc.,Chem. Commun.*, 1049 (1983); b) J. E. Baldwin, P. D. Bailey, G. Gallacher, M. Otsuka, K. A. Singleton, P. M. Wallace. *Tetrahedron*, **40**, 3695 (1984).

[25] a) J. E. Baldwin, M. Otsuka, P. M. Wallace. *J. Chem Soc. ,Chem. Commun.*, 1549 (1985); b) J. E. Baldwin, M. Otsuka, P. M. Wallace. *Tetrahedron*, **42**, 3110 (1986).




13 14 15 16

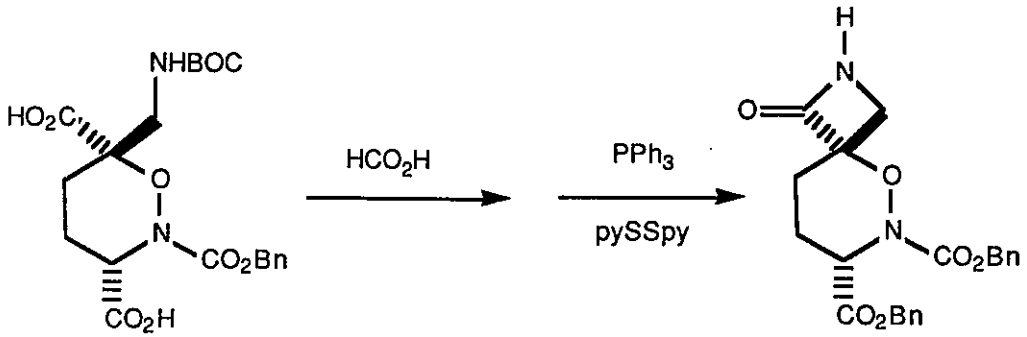
Reduction of **15** to amine **16** was achieved with $NaBH_3(OCOCF_3)$. This compound (**16**) is a common intermediate in both of Baldwin's constructions. The amine in compound **16** was then protected as a *t*-BOC derivative. Oxidative cleavage of the olefin in **16** revealed the carboxylate functions of tabtoxinine giving diacid **17**.




17 18

The acid functions were successfully differentiated by decarboxylative esterification with benzyloxycarbonyl chloride giving **18** in moderate yield.

Cyclization to give spiro-β-lactam **19** was achieved after deblocking the amine function by treatment with formic acid.




**18** **19**

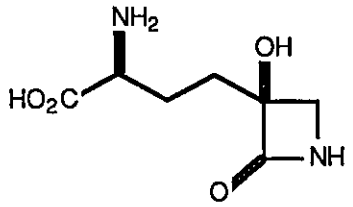
The synthesis of tabtoxinine-β-lactam was completed by employing catalytic hydrogenation, which gave debenzylation together with reductive cleavage of the N-O bond.

Although Baldwin has described an imaginative and highly stereoselective synthesis of tabtoxinine-β-lactam, it is somewhat lengthy. In addition, the synthetic protocol calls for a difficult differentiation of esters. Therefore, room exists for additional, possibly more practical syntheses of this interesting molecule.

# Chapter 1
# Early Explorations in Tabtoxinine-β-Lactam Synthesis

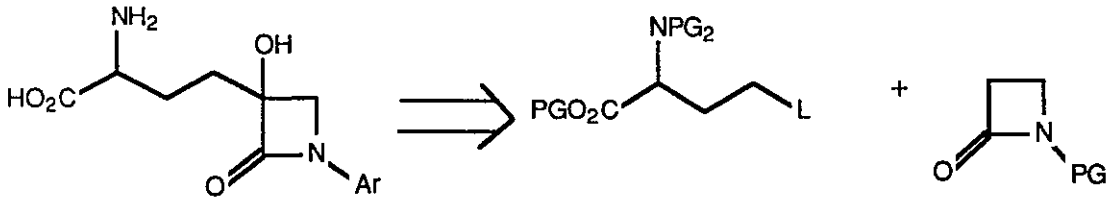
## Retrosynthetic analysis

Tabtoxinine-β-lactam **4** is a small molecule containing various functionalities which present difficulties.




**4**

The amino acid moiety may present problems during the synthesis. The amino group in this molecule is known to react with the β-lactam producing the unwanted δ-lactam isomer. Therefore this group should be blocked as long as possible during the synthesis. Amino acids are also known to epimerize to some extent during certain peptide syntheses, and so if a stereospecific synthesis is desired, reaction conditions must be chosen so as to minimize this risk. To construct the carbon backbone, the following disconnection was envisaged.




4

The left hand fragment should be derivable from homoserine, a readily available amino acid. The right hand fragment would also be prepared via existing β-lactam methodology.

The tertiary alcohol is the fly in the ointment. Syntheses of β-lactams with 3-hydroxy or 3-alkoxy substituents are uncommon. Such molecules have been produced by photolysis of α-oxo amides,[26] photolytic reaction of benzoylformate in the presence of imines[27] and by the [2 +2] cycloaddition of imines with ketenes derived from α-hydroxyactetic acid derivatives.[28] The reaction of 3-oxo-β-lactam derivatives with nucleophiles such as hydride,[29] cyanide,[29] or Wittig reagents[30] is also reported to give 3-hydroxy-β-lactams. However this requires a reversal of the electrophilic (E) and nucleophilic (Nu) components. This may be difficult since intramolecular reaction may occur on the left hand

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[26] a) H. Aoyama, T. Hasegawa, M. Watabe, H. Shiraisi, Y. Omote. *J. Org. Chem.*, **43**, 419 (1978); b) H. Aoyama, K. Miyazaki, M. Sakomoto, Y. Omote. *J. Chem. Soc., Chem. Commun.*, 333 (1983); c) H. Aoyama, M. Sakamoto, K. Kuwabara, K. Yoshida, Y. Omote. *J. Am. Chem. Soc.*, **105**, 1958 (1983).

[27] H. Aoyama, M. Sakamoto, K. Yoshida, Y. Omote. *J. Heterocyclic. Chem.*, **20**, 1099 (1983).

[28] a) M. S. Manhas, S. G. Amin, R. D. Glazer. *J. Heterocyclic. Chem.*, **16**, 283 (1979); b) F. P. Cossio, C. Palomo. *Tetrahedron Lett.*, 4239 (1985); c) J. M. Aizpurua, M. Oiarbide, C. Palomo. *Tetrahedron Lett.*, 5365 (1987); d) A. Arrieta, B. Lecea, F. P. Cossio, C. Palomo. *J. Org. Chem.*, **53**, 3784 (1988).

[29] Y. S. Lo, J. C. Sheehan. *J. Am. Chem. Soc.*, **94**, 8253 (1972).

[30] a) J. C. Sheehan, A. Buku, E. Chacko, T. J. Commone, Y. S. Lo, S. Young, D. R. Ponzi, W. C. Schwarzel. *J. Org. Chem.*, **42**, 4045 (1971); b) J. C. Sheehen, Y. S. Lo, J. Löliger, C. C. Podewell. *J. Org. Chem.*, **39**, 1444 (1974).

fragment between the carbanionic centre and the ester protecting group of the amino acid moiety.

The first three methods listed tend to require special substrates for the reaction to be successful. Of these, the [2 + 2] cyclization is the most forgiving in terms of substituent variety, but 4-unsubstituted β-lactams are only produced upon subsequent manipulation.† Therefore, new methodology was required for the introduction of the 3-hydroxyl function. As a first approach, it was decided to attempt a direct oxidation of an enolate generated from a suitably protected 3-alkyl-β-lactam. This approach, if successful would allow for a rapid synthesis of the target. Also, β-lactam enolates are known to add electrophiles *trans* [31] to any substituent at position 4, and this could possibly provide a means of achieving an asymmetric synthesis.

## Studies on the hydroxylation of enolates of 3-alkyl-β-lactams

The well known 4-phenyl-2-azetidinone[32] **20** was prepared and blocked with a 1-(dialkylaminomethyl) protecting group.[33]

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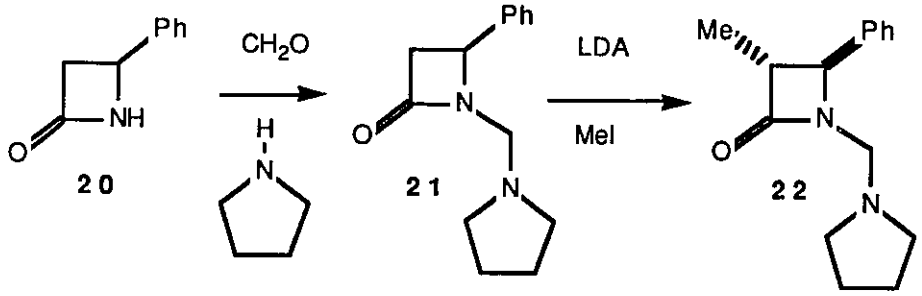
† 3-phthalyl-4-unsubstituted-β-lactams can be produced by direct [2 + 2] cyclization. 3-Oxy analogs are not reported. See T. Kamiya, T. Oku, O. Nakaguchi, H. Takeno, M. Hashimoto. *Tetrahedron Lett.*, 5119 (1978).

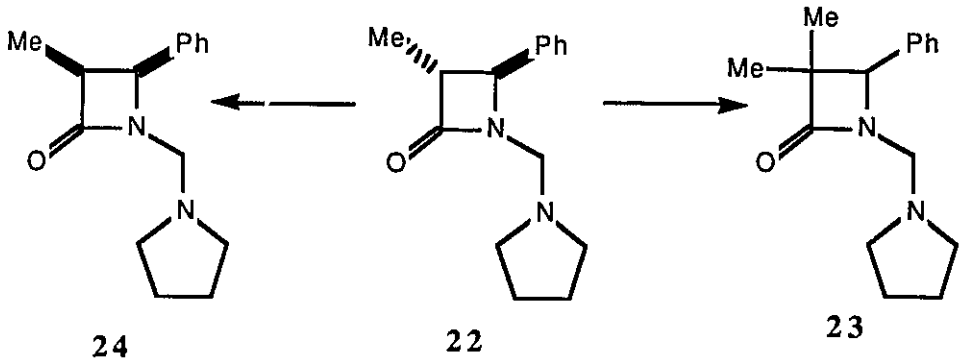
[31] A. B. Hamlet, T. Durst. *Can. J. Chem.*, **61**, 411 (1983).

[32] R. Graf. *Liebigs Ann. Chem.*, **661**, 111 (1963).

[33] C. Cignarelli, G, E. Christiani, E. Testa. *LiebigsAnn. Chem.*, **661**, 181 (1963).




Alkylation with methyl iodide proceeded smoothly to give *trans* 3-methyl-4-phenylazetidinone **22**. The *trans* relationship was established by the observance of an nmr coupling constant of 2.2 Hz for the lactam ring protons. Although enolization of **21** was easy, generation of the enolate of **22** with LDA could not be detected by attempted deuteration, silylation or alkylation with $D_2O$, TMS-Cl or MeI respectively. Anion formation was observed however, by the inclusion of 1 equivalent of TMEDA[34] in the reaction medium.




Quenching of this enolate with $CH_3I$ gave a mixture of 3,3-dimethyl product **23** (36 %) as well as smaller amounts of **22** and **24**. The product **23**

[34] a) G. G. Eberhardt, W. A. Butte. *J. Org. Chem.*, **29**, 2928 (1964); b) E. J. Corey, D. Seebach. *J. Org. Chem.*, **31**, 4097 (1966).

was characterized by the appearance of two methyl signals at δ1.49 and δ0.77 in the proton nmr. The signal for the 3-methyl group in the *cis* isomer **24** was located 0.63 ppm upfield of the 3-methyl signal in **22**. Correspondingly, the signal for the α-hydrogen in **24** was 0.52 ppm downfield from the 3-hydrogen in **22**. These differences are explained by the anisotropic effect of the phenyl ring on the *cis* methyl group of **24** and on the *cis* H of **22**. In addition, the coupling constant for H-3 and H-4 of **24** was much larger (5.0 Hz) than the respective coupling in **22** (2.2 Hz), verifying that **24** had the *cis* 3,4 stereochemistry. This geometry was expected since **24** would arise by protonation of the enolate of **22** which would preferentially occur *trans* to the 4-phenyl group. The presence of TMEDA is thought to exert an accelerating influence on the formation of enolates, and does not enhance acidity.[35]

Having demonstrated that 3-alkyl-4-phenylazetidin-2-ones could be successfully alkylated, the introduction of a hydroxyl moiety was then examined. Attempted oxidation of the **22** enolate with 2-sulfonyloxaziridine[36] or with molecular oxygen failed to give oxidation products and resulted only in the recovery of a mixture of **22** and the *cis* isomer **24**. The fact that **24** was observed confirmed that an enolate had in fact been generated, but would not react with the oxygen delivering electrophiles employed.

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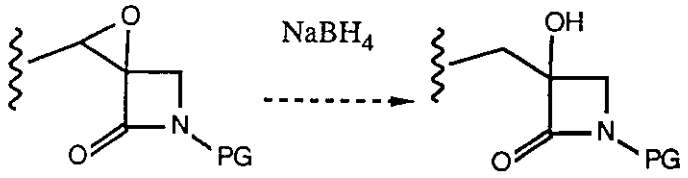
[35] a) S. Raucher, G. A. Koolpe. *J. Org. Chem.*, **43**, 3794 (1978); b) R. R. Fraser, T. S. Mansour. *Tetrahedron Lett.*, 331 (1986).

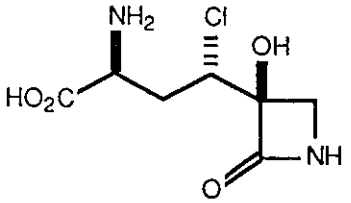
[36] F. A. Davis, L. C. Vishwakarma, J. M. Billmers, J. Finn. *J. Org. Chem.*, **49**, 3243 (1984).

**Studies on the synthesis of spiro(3,4)-oxirane-β-lactam systems**

Since oxidation of a 3-alkyl substituted β-lactam enolate did not give satisfactory results, an alternate approach was devised in which an oxaazaspiro compound is opened with hydride giving the desired 3-hydroxy species.




This sequence would not only be useful in a tabtoxinine synthesis, but could be easily modified to give the chlorinated analog **20**,[12] which is isolated from fermentation broths of an unidentified *Streptomyces* bacterium.




**20**

Such oxaspirolactams are known, having been produced by the action of CsF on suitable precursors.[37] More highly functionalized analogs have recently been produced in these laboratories.[38]

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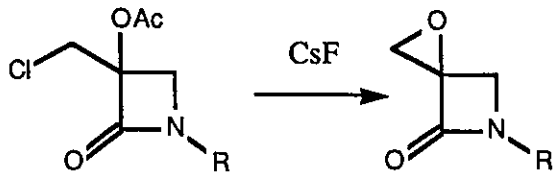
[37] S. Sebti, A. Foucaud. *Tetrahedron*, **40**, 3223 (1984).
[38] M. K. Sharma, T. Durst. Unpublished results.




Reaction of the enolate of **21** with acetaldehyde gave 3-(2-hydroxyethyl)-4-phenylazetidinone **25** as a mixture of diastereomers in moderate yield. The diastereomers were produced in a 1:1 ratio and were both shown to have *trans* relationships in the 3,4 positions of the β-lactam by the virtue of the small (2.0 Hz) coupling constant. Compound(s) **25** was(were) mesylated using standard conditions, giving **26** also as an inseparable mixture of diastereomers. The mesylate(s) **26** was(were) then treated directly with $NaHCO_3$ in MeOH[39] giving 3-alkenyl-4-phenyl-β-lactams **27** and **28** in low yield. These products were separable by flash chromatography[40] and were readily distinguished by $^1H$ nmr. The vinyl hydrogen of **27** appeared at δ5.46, upfield of the vinyl hydrogen of **28** at δ6.11. Additionally the vinylic methyl group of **27** was downfield of the analogous $CH_3$ group in **28**. The $CH_3$ of **27** appearing at δ1.96 while the $CH_3$ of **28** was located at δ1.50. The assignment of stereochemistry was based on observations noted previously.[39]

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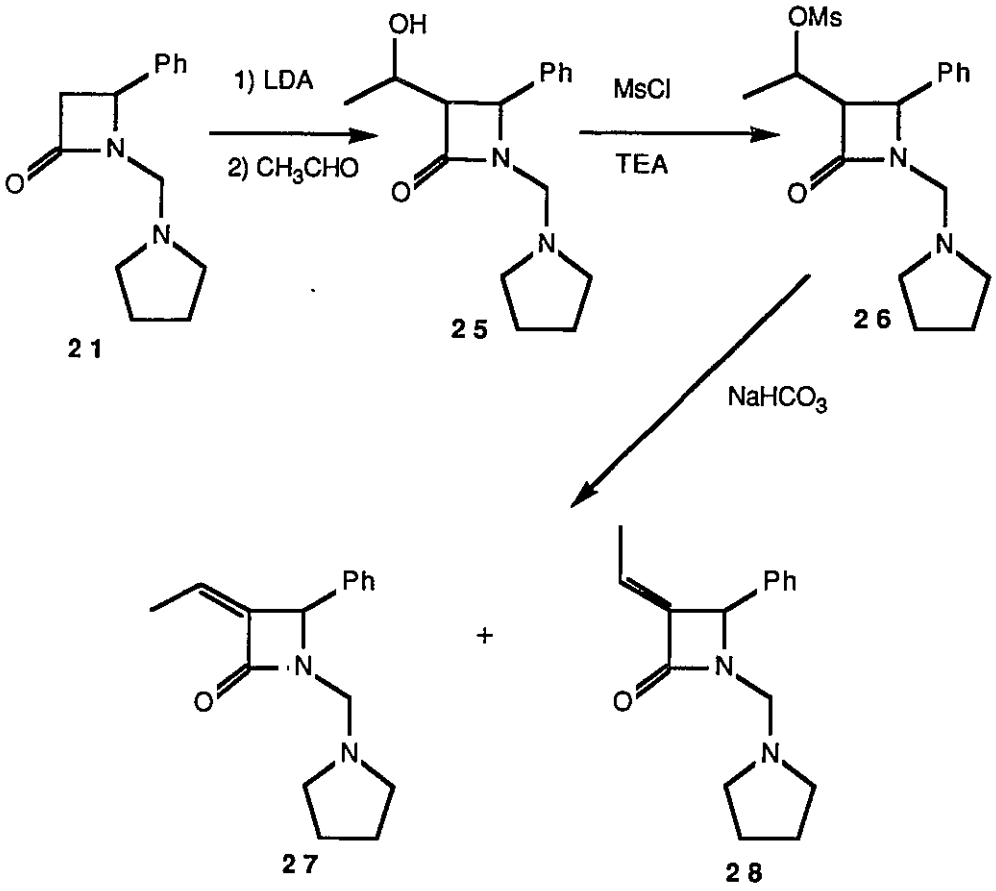
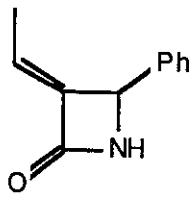
[39] F. A. Bouffard, D. B. R. Johnston, B. G. Christensen. *J. Org. Chem.*, **45**, 1130 (1980).
[40] W. C. Still, M. Kahn, A. Mitra. *J. Org. Chem.*, **43**, 2923 (1978).



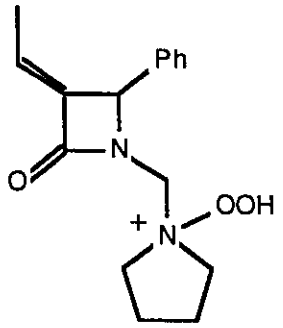

21 25 26 27 28

Attempted epoxidation of **27** or **28** with *m*CPBA was unsuccessful. A reaction of **28** with excess $H_2O_2$ at reflux resulted no in epoxidation but in removal of the pyrrolidinomethyl protecting group giving 3-alkylidene lactam **29**.




29

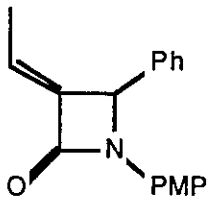
This deprotection presumably proceeds via oxidized intermediate **30** and proceeded in high yield.




**30**

This procedure is a nice alternative to the conditions described previously for the removal of the pyrrolidinomethyl group.[31] Typically, acid hydrolysis is used to effect deprotection, however in the presence of acid sensitive functionalities, oxidative removal could be a useful option.

The short supply of **27** and **28** due to poor yields and difficult purification meant that the number of epoxidation attempts was limited. A similar compound **31**, was therefore prepared by a [2 + 2] cycloaddition of crotonyl chloride and the imine derived from *p*-anisidine and benzaldehyde,[41] followed by rearrangement of the double bond using DBN.

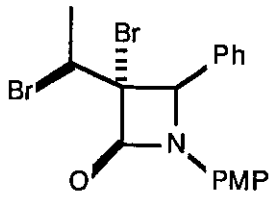



**31**

[41] M. S. Manhas. Personal communication.

This compound also proved to be resistant to *m*CPBA in refluxing dichloroethane (2,6 di-*t*-butylphenol present as a radical inhibitor) and $H_2O_2$ (basic[42] and neutral conditions). Attempted bromohydrin formation with NBS in wet DMSO[43] also returned the starting material intact.

It was expected that the epoxidation would be difficult since the double bond in compound **31** is conjugated to an amide carbonyl, nevertheless compound **31** did react with bromine. A reaction with bromine was performed in order to determine if the double bond was reactive towards strong electrophiles. Dibromo derivative **32** was obtained in high yield as a single isomer. Presumably, the bromonium ion will form with the bromine *trans* to the phenyl ring. Opening of this bromonium species at the 2-position of the side chain should result in the following relative stereochemistry.




**32**

Since an epoxide could not be obtained from an α,β-unsaturated β-lactam, it was decided to employ a modified Darzens reaction. In this reaction, an α-hydroxy sulfide would be converted to an epoxide via the appropriate sulfonium salt.

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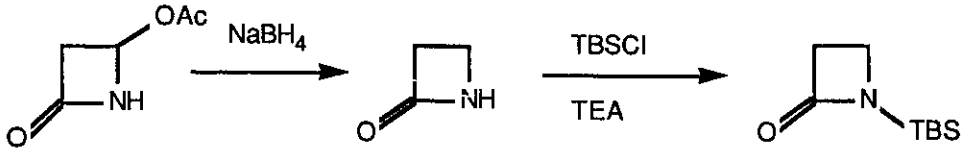
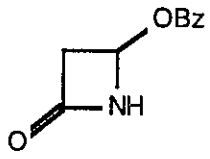
[42] a) G. B. Payne, P. H. Williams. *J. Org. Chem.*, **24**, 54 (1959); b) B. Zwaneburg, J. ter Wiel. *Tetrahedron Lett.*, 935 (1973).

[43] a) D. R. Dalton, J. B. Hendrickson, D. Jones. *J. Chem. Soc., Chem. Commun.*, **591** (1966); b) D. R. Dalton, V. P. Dutta. *J. Chem. Soc. (B)*, **85** (1971); c) A. J. Sisti. *J. Org. Chem.*, **35**, 2670 (1970).

The 4-unsubstituted β-lactam **35** was obtained from the readily available 4-acetoxyazetidin-2-one **34**.[44] Pfaendler and Hoppe[45] had reported that treatment of **34** with $KBH_4$ in $H_2O$ gave **35** in 69% yield, but provided few experimental details. It was found that $NaBH_4$ in ethanol gave **35** in 84% yield from a non-aqueous workup. Compound **35** is now a moderately expensive ($21.00/g U.S.) product available from Aldrich. Apparently it is produced from 4-benzoyloxyazetidin-2-one **36** since employees complained that **35** produced allergic reactions in some workers.[46] Compound **35** was readily protected as **37** with *t*-butyldimethylsilyl chloride in DMF in 61% yield after distillation. Compound **37** was frequently contaminated with the lower boiling *t*-butyldimethylsilyl ether which could be removed *in vacuo*.




**34** **35** **37**




**36**

The enolate of **35** was generated with LDA in THF and quenched with methyl disulfide. Flash chromatography gave sulfide **38** along with bissulfide **39** in 59% overall yield. These products were obtained in a 1:1.2 ratio. The use

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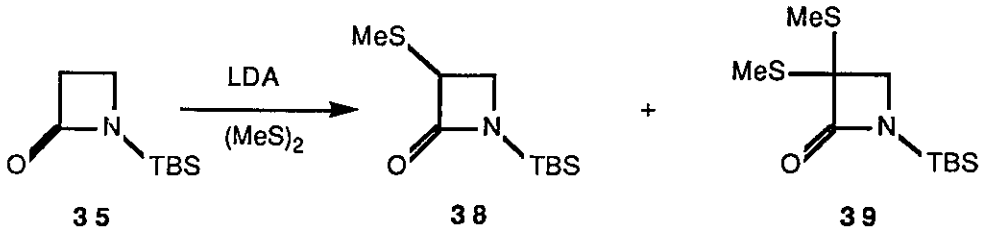
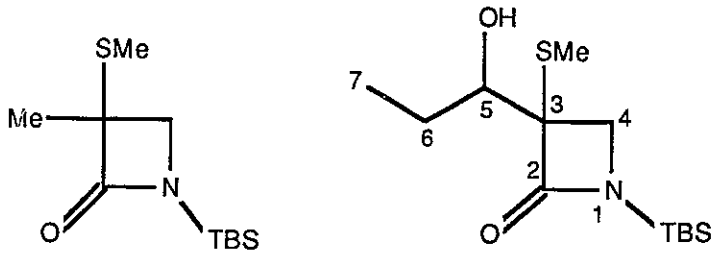
[44] a) K. Clauβ, D. Grimm, G. Prossel. *Liebigs Ann. Chem.*, 539 (1974); b) S. J. Mickel, C. N. Hsiao, M. J. Miller. *Org. Syn.*, **64**, 135 (1987).
[45] H. R. Pfaendler, Hoppe. *Heterocycles*, **23**, 265 (1985).
[46] A. Bader. Personal communication.

of inverse addition gave **38** and **39** in a 1:1 ratio, but in higher overall yield (73%).




**35** **38** **39**

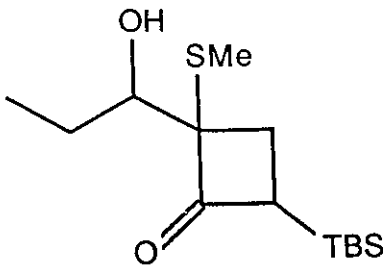
An anion of **38** could be easily produced and was readily alkylated with MeI or propionaldehyde to give **40** and **41** in 75 and 79% yield respectively.

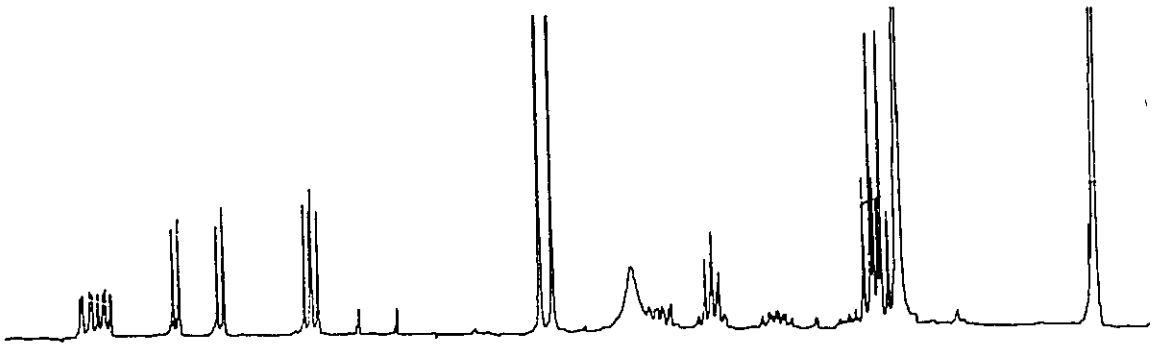


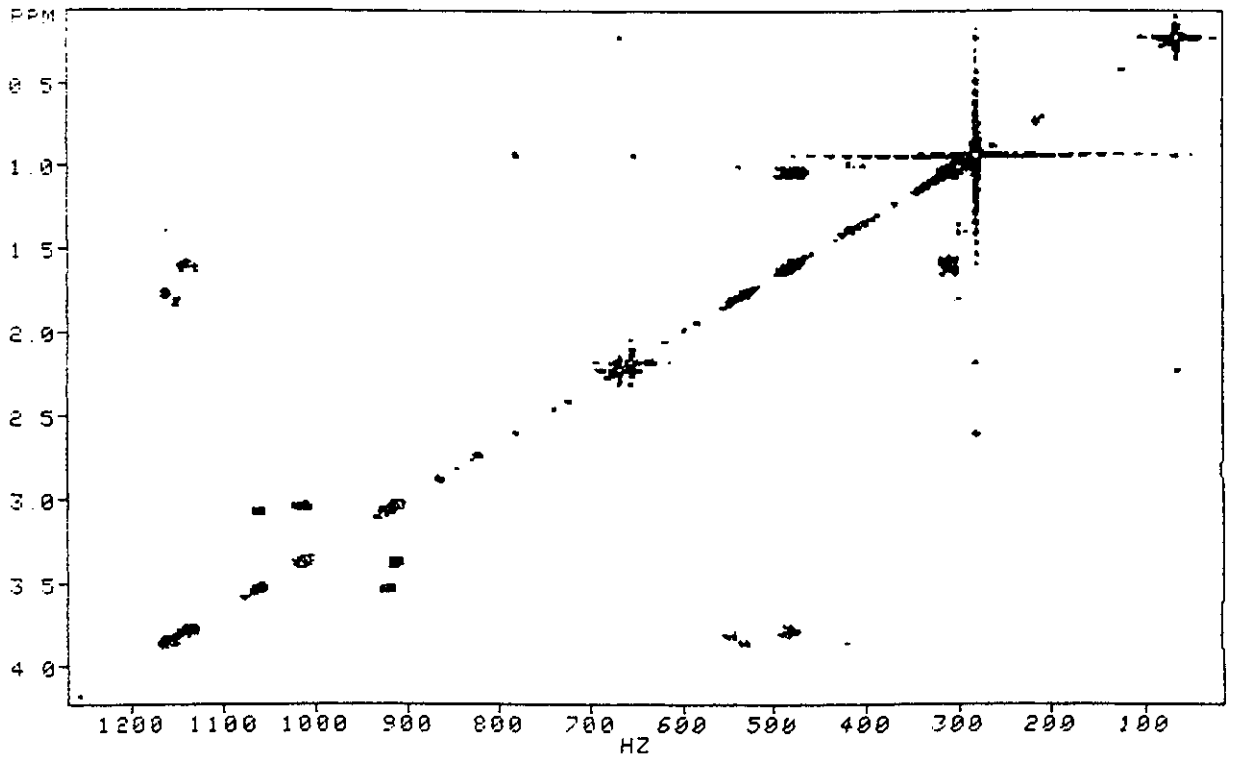

**40** **41**

Compound **41** was isolated as a 1:1 mixture of inseparable diastereomers. The 300 MHz nmr spectrum of this mixture clearly showed that two diastereomers were present. The protons at C-4 of the azetidinone appeared as two overlapping AB patterns with similar coupling constants. The C-5 proton of each diastereomer overlapped at approximately δ3.8, both diastereomers producing doublets of doublets. One isomer showed C-6 proton absorbances of multiplets at δ1.75 and δ1.38, with a C-7 signal at δ1.00. The other isomer produced C-6 resonances at δ1.60 and δ1.10 and a C-7 triplet at δ1.04. The assignment of signals to one isomer or the other is based on interactions observed in a standard HOMCOR experiment (figure 1). Unfortunately, it is impossible at this time to assign a *threo* or *erythro*

**Figure 1**: HOMCOR spectrum of **41** (Mixture of diastereomers)





configuration to either set. Attempts at producing a sulfonium salt and subsequently a spiro epoxide through the action of methyl iodide, either neat or with $AgClO_4$ were unsuccessful.

Although an epoxide could not be generated from any of the approaches described in this chapter, it was felt that the experience gained with 3-alkenylazetidinones could be put to use in later approaches.

# Chapter 2
# Oxidation of 3-Alkylidene-β-Lactams

## A radical approach

3-Ethylidene-4-phenylazetidin-2-one **31** possesses an allylic system, which provides a means of introducing functionality onto the 3-position of the β-lactam. Using the related compound **42**,[39] several attempts were made using radical conditions ($Pb(OAc)_4$; NBS, AIBN) to introduce a function which could be later converted to the desired 3-hydroxy-β-lactam. The use of $Pb(OAc)_4$ resulted in decomposition, while NBS in refluxing $CCl_4$ returned intact compound **42**.


42 43

The realization that an unsaturated carbanion of the type **43** might be more readily oxygenated than the corresponding alkyl derivatives was the first real breakthrough of this study. Allyl systems are known to enhance the acidity of positions α to a carbonyl group. In addition, since allyl anions were known to preferentially add hard electrophiles in the α–position rather than at the γ-

carbon[47] it was felt that the control of regiochemistry in the oxygenation reaction would not be a problem.

## A carbanionic approach

As a verification of this hypothesis, the reaction of the lithium enolate of **42**, generated by treatment with LDA, was treated with methyl iodide and after flash chromatography, 3-methyl-3-vinyl β-lactam **44** was isolated in 60 % yield. The formation of 3-methyl-3-vinyl-β-lactam **44**, via the reaction of the enolate of **42** with MeI showed that the above statement was valid in the β-lactam series. Encouraged by this result, the enolate of **42** was reacted with dry $O_2$; this reaction provided 3-hydroxy-β-lactam **45** in 30 % yield. Compound **45** exhibited an infrared absorption at 1750 $cm^{-1}$ indicating the retention of a β-lactam. The nmr spectrum showed a clear ABX pattern at δ5.59 ($H_A$), δ5.47 ($H_B$) and δ5.18 ($H_X$) as expected for the terminal vinyl group. The *trans* coupling constants were somewhat large ($J_{AB}$ = 17.34 $H_Z$ for example) which made the analysis of the system easy. Presumably the hydroxyl group and phenyl group are *trans*, since alkylations of β-lactam enolates at position 3 are known to proceed *anti* to any large group at position 4.[31] Unfortunately, this conclusion could not be corroborated spectroscopically since the proton at C-4 showed no NOE interactions. The use of oxodiperoxymolybdenum(pyridine)hexamethyl-phosphoramide (MoOPH)[48] not only gave an improved yield (67 %) of **45**, but workup was also relatively easy since the organometallic complex was readily

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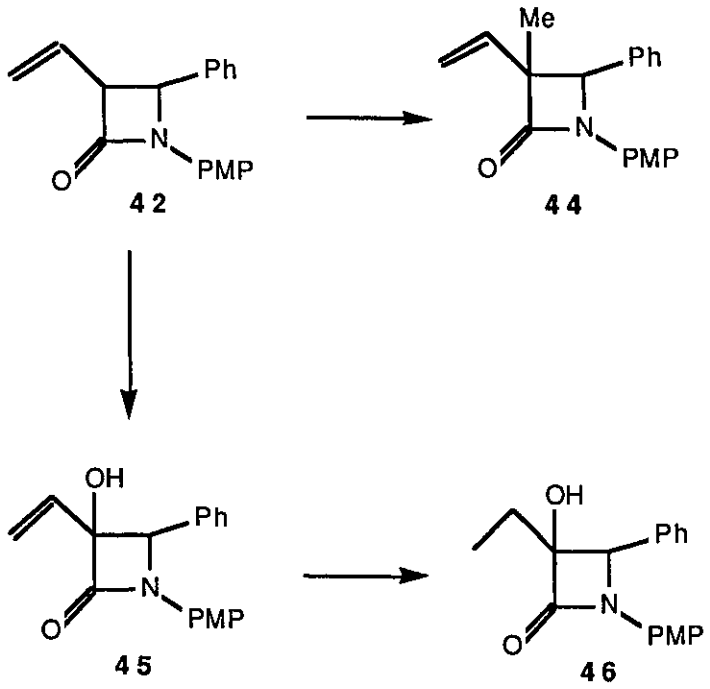
[47] For Leading References see: M. Majewski, G. B. Mpango, M. T. Thomas, A. Wu, V. Snieckus. *J. Org. Chem.*, **46**, 2029 (1981).

[48] a) E. Vedejs, D. A. Engler, J. E. Telschow. *J. Org. Chem.*, **43**, 188 (1978); b) M. Mimoun, L. Seree de Roch, L. Sajus. *Bull. Soc. Chim. Fr.* 1471, (1969); c) E. Vedejs, S. Larson. *Org. Syn.*, **64**, 127 (1986).

removed by aqueous extraction. In contrast, 2-sulfonyloxaziridine[49] gave very complex mixtures. This result is somewhat disappointing since Davis has recently disclosed results indicating that such hydroxylations can be done in excellent yields and also asymmetrically using sulfonyl oxaziridines derived form camphor.[50]




Compound **45** was smoothly hydrogenated over $PtO_2$ to give a highly crystalline solid, mp 129-130 °C, which was identified as **46**. The methylene hydrogens of **46** showed surprisingly large nonequivalence. The possibility of isomers was ruled out however by the appearance of only the required 14 resonances in the $^{13}C$ spectrum.

Now that compounds such as **46** were accessible via the route described above, a method for constructing the prerequisite 3-

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[49] F. A. Davis, L. C. Vishwakarma, J. M. Billmers, J. Finn. *J. Org. Chem.*,**49**, 3243 (1984).

[50] a) F. A. Davis, T. G. Ulatowski, M. S. Haque. *J. Org. Chem.*,**52**, 5288 (1987); b) F. A. Davis, M. S. Haque, T. G. Ulatowski, J. C. Towson. *J. Org. Chem.*,**51**, 2402 (1986); F. A. Davis, M. S. Haque. *J. Org. Chem.*,**51**, 4083 (1986).

alkylideneazetidinones was required. The elimination reaction of mesylates such as **26** was a possible choice, but presented purification problems (Chapter 1). A promising alternative involved the use of a Peterson olefination.[51] The preparation of 3-alkenylazetidin-2-ones from 3-(trimethylsilyl)-azetidin-2-ones and ketones has been described,[52] and presumably aldehydes could also be employed.

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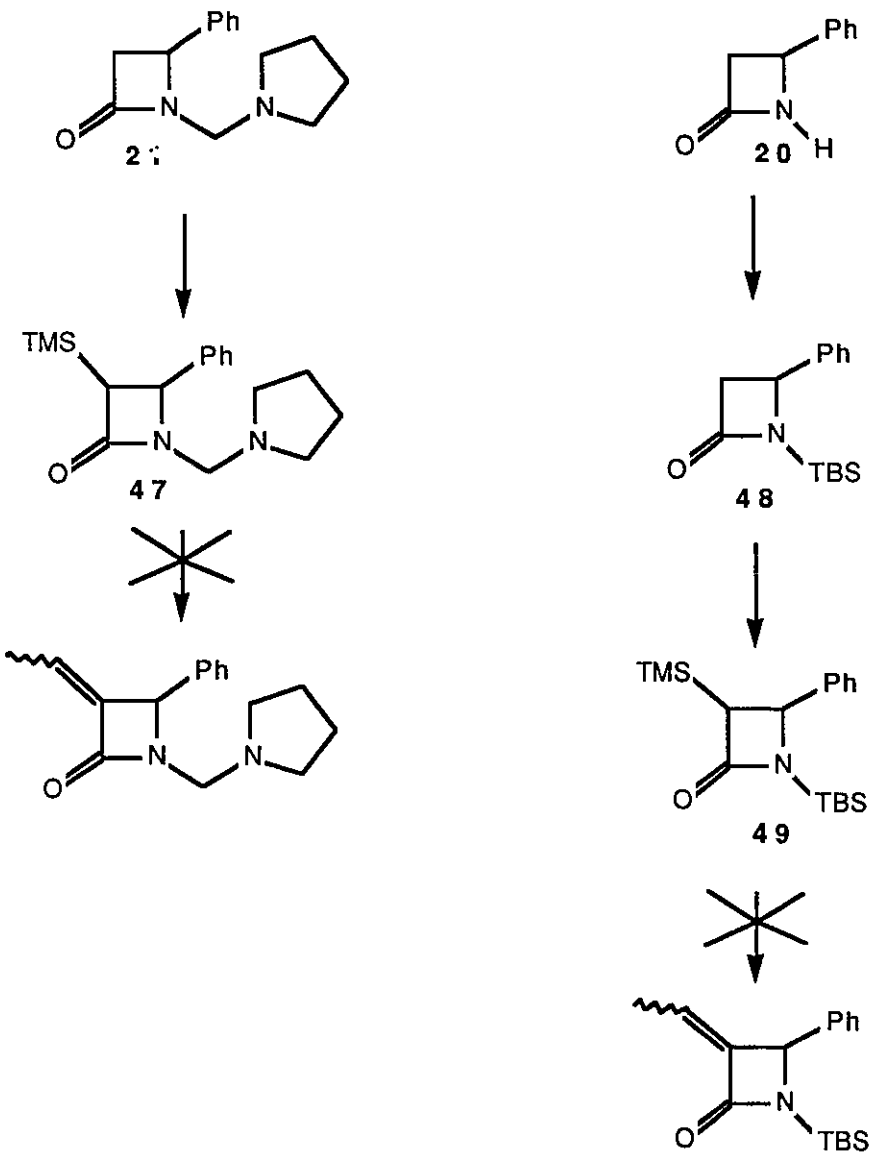
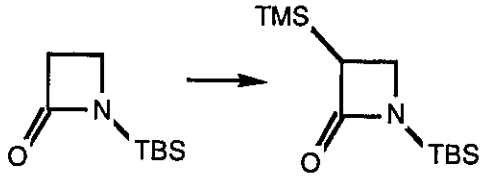
[51] P. J. Peterson. *J. Org. Chem.*, **33**, 780 (1968).
[52] S. Kano, T. Ebata, K. Funaki, S. Shibuya. *Synthesis*, 746 (1978).




The enolate of **21** was condensed with freshly distilled trimethylsilyl chloride giving the required material **47** in 65 % yield. Several attempts to condense this substance with propionaldehyde and acetaldehyde were not successful. It was thought that part of the difficulty rested with the separation of the reaction mixture due to the high polarity of the pyrrolidinomethyl protecting group on silica gel. Therefore it was decided to turn to the *t*-butyldimethylsilyl

group as a more workable protecting group. Lactam **20** was readily condensed with TBS-Cl in DMF giving the known[53] derivative **48** in good yield. Addition of a trimethylsilyl group proceeded without incident to provide 3-trimethylsilyl derivative **49** as a highly crystalline solid (mp 72°C). As before, condensation attempts were unsuccessful, even in the presence of TMEDA. Since the Peterson sequence was previously reported to be successful with 4-unsubstituted β-lactams, it was reasoned that the bulky 4-phenyl moiety was preventing deprotonation by steric interference. At this point it made sense to employ a 4-unsubstituted substrate since this would be required eventually in the synthesis of tabtoxinine and furthermore it would avoid the perceived crowding problem. β-Lactam **35** was smoothly converted into the 3-trimethylsilyl product **50** by treatment with LDA followed by addition of TMS-Cl. Compound **50** was obtained in quantitative yield and was used without further purification.

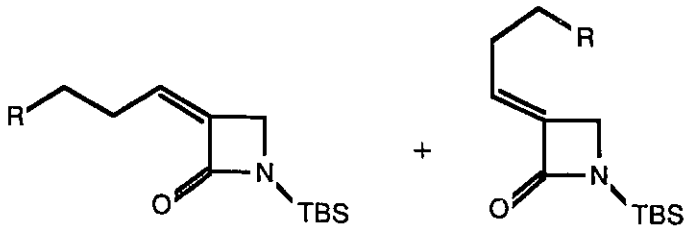



**35** **50**

The lithium enolate of **50**, prepared by exposure to LDA at -78 °C, was reacted with propionaldehyde to give a mixture of **51** and **52** in 60 % overall yield. These isomers could be easily separated by flash chromatography and were readily distinguished by $^1$H nmr. The assignment of stereochemistry is

[53] H. J. Bergmann, R. Mayrnhofer, H. H. Otto. *Arch. Pharm.*, **319**, 203 (1986).

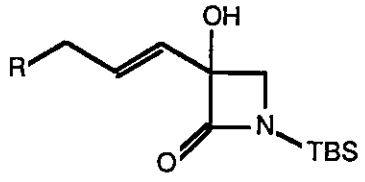
based on observations noted above (Chapter 1). Propionaldehyde was chosen as an initial case since a 3 carbon aldehyde would give a derivative from which the regiochemistry of the subsequent hydroxylation could be easily evaluated. Reaction of **50** with hydrocinnamaldehyde gave **53** and **54** in 58 % overall yield. As with **51** and **52**, the Z-isomer **53** was easily distinguished from the E-isomer **54** by the chemical shift differences in the olefinic hydrogens of each isomer.




R = H, **51**
R = Ph, **53**

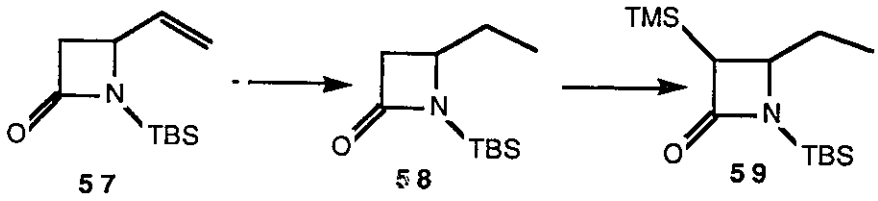
R = H, **52**
R = Ph, **54**

Generation of the allylic enolate of **51** with LDA followed by addition of solid MoOPH at - 78 °C and subsequent warming until the solution had cleared gave a crude product which was purified by flash chromatography to give the desired 3-hydroxy-3-alkenyl-β-lactam **55** in 41 % yield. The hydroxyl was delivered α to the amide as expected and not in the γ position. This was clearly evident by the integration of two olefinic protons in the nmr spectrum. The regenerated alkene moiety was shown to have an E-configuration as indicated by the large (15.50 $H_z$) coupling of the vinylic protons. In a similar manner, product **53** gave hydroxylated material **56** in 31 % yield. The regio- and stereochemistry of this substance was found to be analogous to that of **55**.



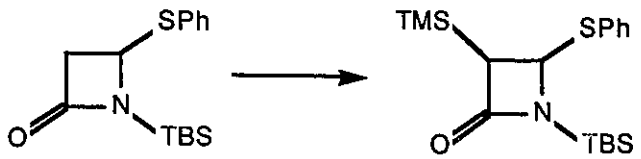

R = H, **55**
R = Ph, **56**

At this time, other products, substituted at position 4 of the β-lactam were prepared in order to see if the hydroxylation would behave and deliver the electrophile *trans* to these substituents. Hydrogenation of 4-vinyl-1-*t*-butyl-dimethylsilylazetidin-2-one[54] **57** proceeded to give 4-ethylazetidin-2-one **58** in a clean reaction. This compound reacted readily with TMS-Cl as before affording 3-trimethylsilyl product **59**. In a similar manner, the thiophenyl derivative **60**, prepared from 4-thiophenylazetidin-2-one,[55] was also easily condensed with TMS-Cl after LDA treatment giving **61**. A 4-thiophenyl compound was chosen since 4-thiophenylazetedin-2-one was available in optically active form[56] and could possibly be used in a subsequent asymmetric synthesis.




**57** **58** **59**

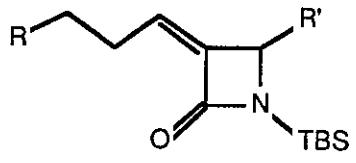
[54] F. A. Bouffard, D. B. R. Johnston, B. G. Christensen. *J. Org. Chem.*,**45**, 1130 (1980).
[55] A. Yoshida, T. Hayashi, N. Takeda, S. Oida, E. Ohki. *Chem. Pharm. Bull.* **29**, 1854 (1981).
[56] M. Shibasaki, A.. Nishida, S. Ikegami. *J. Chem. Soc. Chem. Commun.*, 1324 (1982).



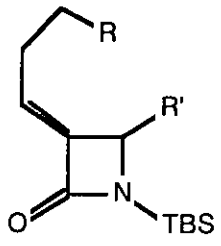

**60** **61**

Compounds **59** and **61** were obtained in pure form by flash chromatography. As expected, the relative stereochemistry at positions 3 and 4 of the β-lactams was found to be *trans*, as evidenced by the magnitude of the coupling constants of the ring protons.

3-Trimethylsilyl product **59** was readily deprotonated with LDA and proceeded to react with propionaldehyde giving **62** and **63** in yields similar to those obtained by the reaction of **50** with propionaldehyde. Reaction of the anion of **59** with hydrocinnamaldehyde gave a good yield of **64** and **65**. In all cases, the Z-ene-lactams **51, 53, 62** and **64** were eluted before the corresponding E-isomers **52, 54, 63** and **65** upon flash chromatography, and were obtained in slightly higher proportions.

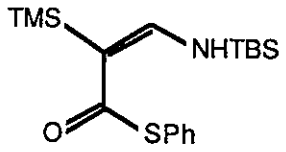



R = H, R' = Me **62**
R = Ph, R' = Me **64**
R = H, R' = SPh **66**
R = Ph, R' = SPh **70**



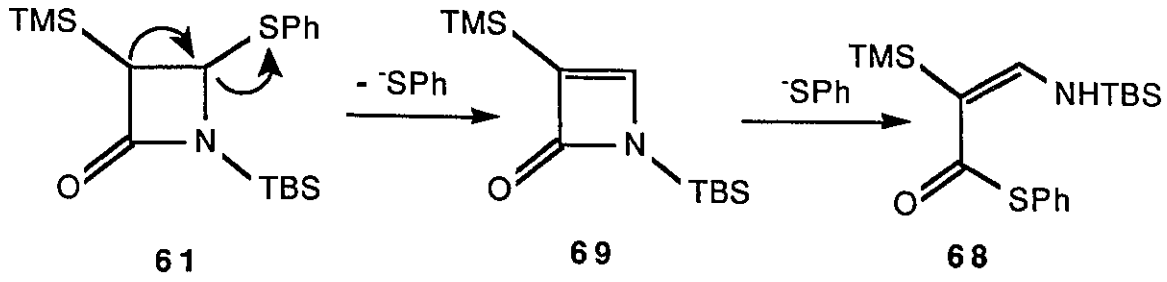

R = H, R' = Me **63**
R = Ph, R' = Me **65**
R = H, R' = SPh **67**
R = Ph, R' = SPh **71**

The reaction of the enolate of **61** with propionaldehyde at -78 °C gave a disappointing yield of **66** and **67**. The reaction mixture smelled strongly of thiophenol and the major product isolated, in 30 % yield, was a crystalline material assigned structure **68** on the basis of spectroscopic data. An infrared spectrum showed signals at 1605 $cm^{-1}$ and 1551 $cm^{-1}$ only, indicating that the β-lactam was no longer intact. Aside from signals for thiophenoxy, trimethylsilyl, and *t*-butyldimethysilyl groups, compound **68** showed only a doublet at δ6.67 (J = 15.25 $H_Z$) and a broad singlet at δ9.0. A HOMCOR spectrum of this material indicated that the signals at δ6.67 and δ9.0 were strongly coupled as expected for a structure such as **68**. This compound could arise by elimination of thiophenoxide to give the unsaturated β-lactam **69** followed by attack at the carbonyl group by thiophenoxide to afford thioester **68**.



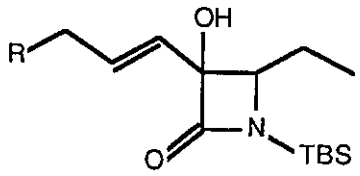

**68**

The yield of desired products **66** and **67** could be increased to 37 and 28 % yield respectively by allowing only one minute for the formation of the enolate of **61**. The reaction of the enolate of **61** with hydrocinnamaldehyde using the normal reaction time gave **68** as the major product, with **70** and **71** being formed in smaller amounts. Using the short enolate formation time, **70** and **71** were obtained in 35 and 26 % yield respectively.




**61** **69** **68**

Generation of the 4-ethyl-3-allylic enolates of **62** and **64** with LDA followed by treatment with MoOPh as described above for 4-unsubstituted allylic enolates **51** and **53**, gave the expected products **72** and **73** after flash chromatography. As before, hydroxylation occurred in the position α to the amide with the alkene formed having an E-configuration as was found for product **55**. The relative stereochemistry on the lactam ring was not determinable, however it is presumed that the hydroxyl group enters *trans* to the substituent at position 4.




R = H, **72**
R = Ph, **73**

Attempted oxidation of the 3-alkenyl-4-thiophenoxyazetin-2-ones **66** and **70** was unsuccessful, even using the attenuated reaction time. The crude reaction mixture smelled strongly of thiophenol.

## Attempted synthesis of tabtoxinine-β-lactam

Having established that a hydroxyl group could be introduced at position 3 of a substituted azetidinone, it was decided that a total synthesis of tabtoxinine-β-lactam could now be undertaken. For the synthesis to be successful, an amino acid fragment would have to be prepared which contained an aldehyde functionality as required for the Peterson coupling, and protecting groups which could withstand the organolithium conditions employed. A review of the literature produced a preparation of the required free amino acid aspartic β-semialdehyde by ozone cleavage of the double bond of the allylglycine.[57] Following on this the aldehyde function of aspartic β-semialdehyde could be "protected" as an olefin until required blocking of the amino and carboxylate functions was completed.

Initially it was decided that both of the protons of the amine should be occupied, so that extra base would not be required in the subsequent coupling.

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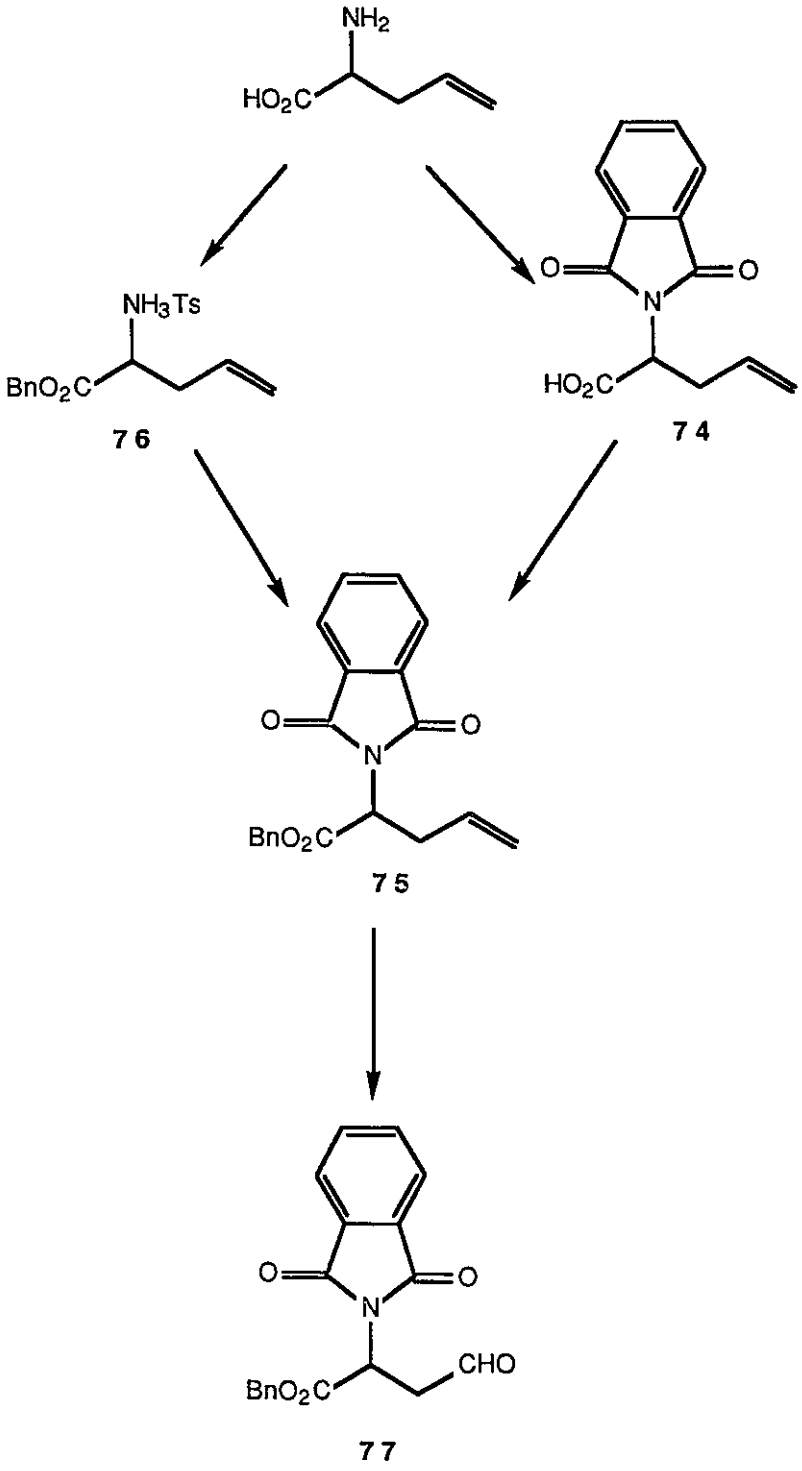
[57] S. Black, N. G. Wright. *J. Biol. Chem.*, **213**, 39 (1955).




76 74 75 77

The amine moiety of D,L-allylglycine (2-aminopent-4-enoic acid) was blocked as a phthalamide derivative by refluxing a mixture of amino acid, phthalic anhydride and triethylamine in benzene.[58] In order to facilitate the reaction, water was removed by azeotropic distillation in a modified Dean-Stark apparatus. Despite this, the reaction required 36 h to run to completion, but proceeded in near quantitative (98 %) yield, giving the crystalline derivative **74** (mp 109-110 °C). This compound was successfully esterified with benzyl alcohol giving **75**, but the yield in this reaction was a disappointing 40 %. The overall yield of **75** was improved by simply reversing the order of protection. Thus, esterification of allylglycine was carried out with excess benzyl alcohol and 1.05 equivalents of *p*-toluenesulfonic acid[59] and using azeotropic distillation to drive the reaction. As before, the reaction was sluggish, but persistence was rewarded by the isolation of the highly crystalline (mp 102-103°C) amino acid ester hydrotosylate **76** in 90 % yield.

Compound **76** was suspended in a solution of 1.6 equivalents of phthalic anhydride in benzene, and was converted to the free base by the addition of an equivalent of TEA. Azeotropic distillation using a modified Soxlet loaded with 4 Å molecular sieves gave the required product **75** in 92 % yield after flash chromatography.

The aldehyde function was then revealed by ozonolysis in $CH_2Cl_2$ at -78 °C. This reaction proceeded rapidly and cleanly giving the desired aldehyde **77** as a single product after treatment with DMS. Flash chromatography was performed to remove DMSO giving aldehyde **77** in 75 % yield. This compound displayed the required aldehyde resonance in the $^1H$ nmr at δ9.77. This signal

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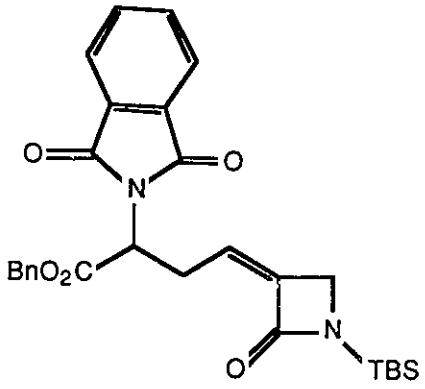
[58] a) E. Hoffman, H. Schiff-Shennau. *J. Org. Chem.*,**27**, 4686 (1962); b) T. Sasaki, K. Minamoyo, H. Iton. *J. Org. Chem.*, **43**, 2320 (1978).

[59] H. K. Miller, H. Waelsch. *J. Am. Chem. Soc.*, **74**, 1092 (1952).

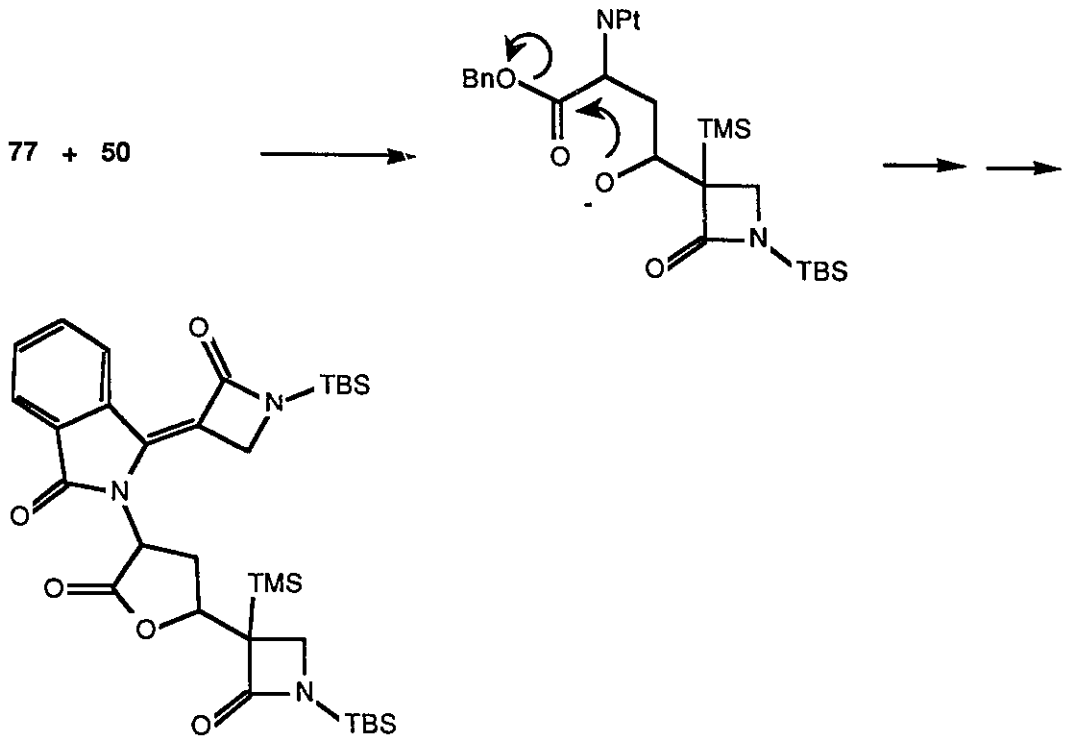
was split into a triplet (J = 0.84 Hz) by the neighboring methylene group, the protons of which appeared as the AB part of an ABX pattern, with an additional coupling to the aldehyde hydrogen (J = 0.89 Hz).

Aldehyde **77** was condensed with TMS lactam **50** using standard conditions (LDA, THF, -78°C). Extractive workup gave a clear colorless oil which was shown by TLC to contain 3 major zones. These were isolated by flash chromatography and analyzed by mass spectrometry and 60 $MH_Z$ nmr. The zone with the slowest mobility was found to be recovered aldehyde **77**. The fastest moving zone proved to be **50**, contaminated with small amounts of another unidentified product(s). The zone of intermediate mobility displayed a molecular ion at the correct m/z ratio, as well as coarse nmr features which could be consistent with a Peterson product. This material was further purified by preparative layer chromatography which provided two substances, the slower of which proved to be the desired product **78**, isolated in < 5 % yield. Although only one isomer could be detected, it could confidently be assigned a Z-configuration based on the position (δ5.56 ppm) of the olefin proton resonance. Attempts at increasing the amount of **78** recovered by employing a short reaction time or lower temperatures were not successful.




**78**

The substance with higher mobility was a solid material with a molecular weight, as indicated by mass spectrometry, of 654. The nmr spectrum of this material was very unusual (figure 2). The nmr displayed the expected resonances for the 4 aromatic hydrogens of the phthalamide, however the position of one hydrogen was unexpectedly far downfield at 9.06 ppm. This doublet (J=7.8 Hz) was shown by means of a HOMCOR spectrum (figure 3) to be coupled to an aromatic proton at δ7.62, and was therefore not the result of an aldehyde residue. In addition to the unusual aromatic resonances, two distinct AB patterns appeared in the 4.1-3.1 region of the spectrum. Only <u>one</u> AB pattern, due to the β-lactam C-4 protons had been expected. The remaining signals at δ5.00 (1H), δ4.42 (1H) and a multiplet at δ2.62-2.36 (2H) were shown by HOMCOR to be interacting. Analysis of the coupling by HOMCOR suggest that the δ5.00 and δ4.42 signals result from hydrogens on carbons which are separated by a methylene (2.62-2.36 multiplet). To account for this, a 2-furanone structure is proposed, with the phthalamide at position 3 and the β-lactam Peterson adduct at position 5 as in structure **79**. Such a structure could arise if the Peterson intermediate closes at the benzyl ester instead of displacing the adjacent trimethylsilyl moiety.




79

The extra β-lactam suggested by the extraneous AB pattern and extra TBS signal is thought to be bonded to the phthalamide. This could explain the anomalous aromatic signal at δ9.06 as being the result of anisotropy induced by the nearby carbonyl. A Wittig type reaction on esters and amides is an uncommon but not unknown occurrence. A similar reaction involving thioesters was employed by Woodward in penem syntheses.[60]

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[60] a) I. E. J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, R. B. Woodward. *J. Am. Chem. Soc.*, **100**, 8214 (1978); b) H. R. Pfaendler, I. E. G. Gosteli, R. B. Woodward. *J. Am. Chem. Soc.*, **102**, 2039 (1980).

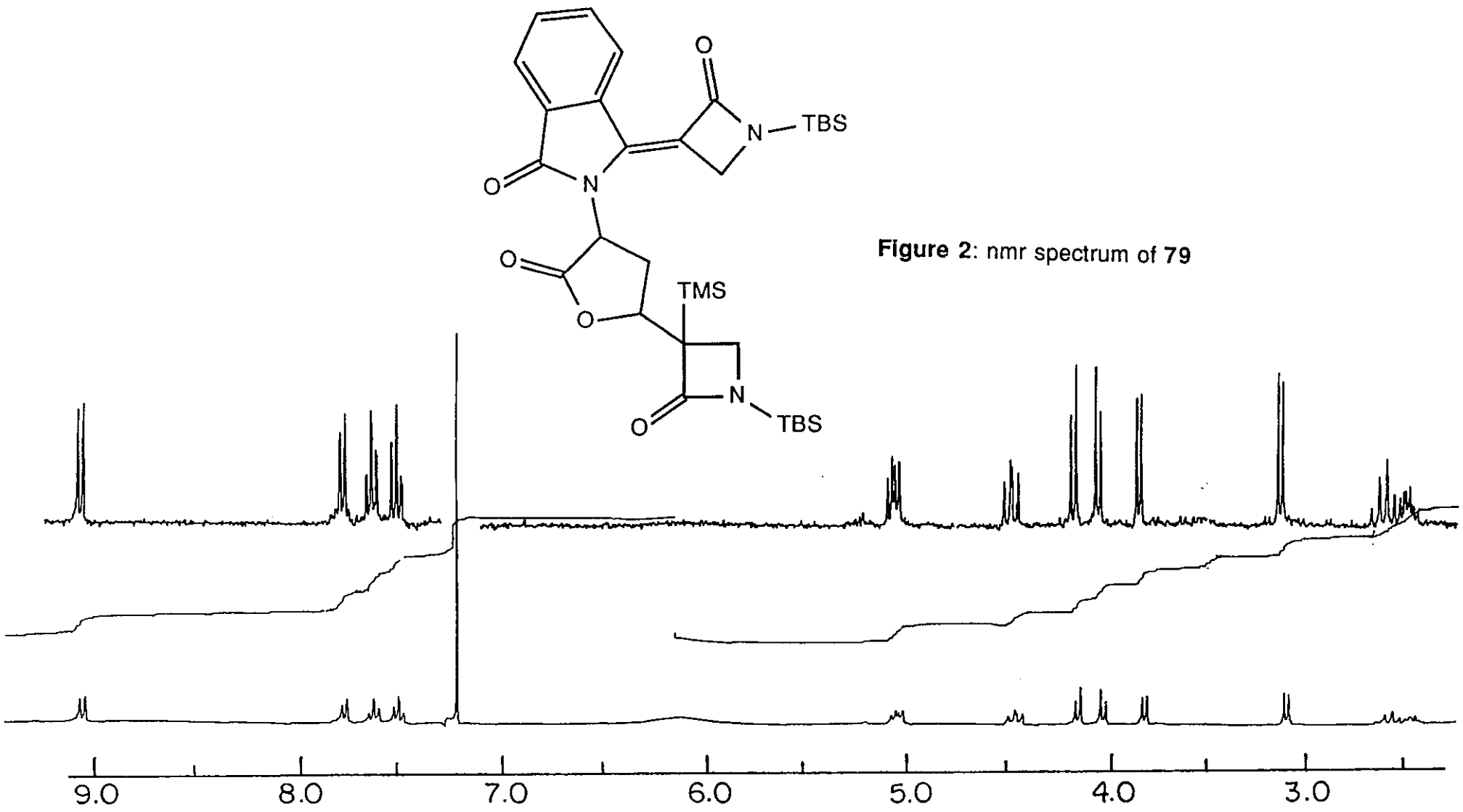
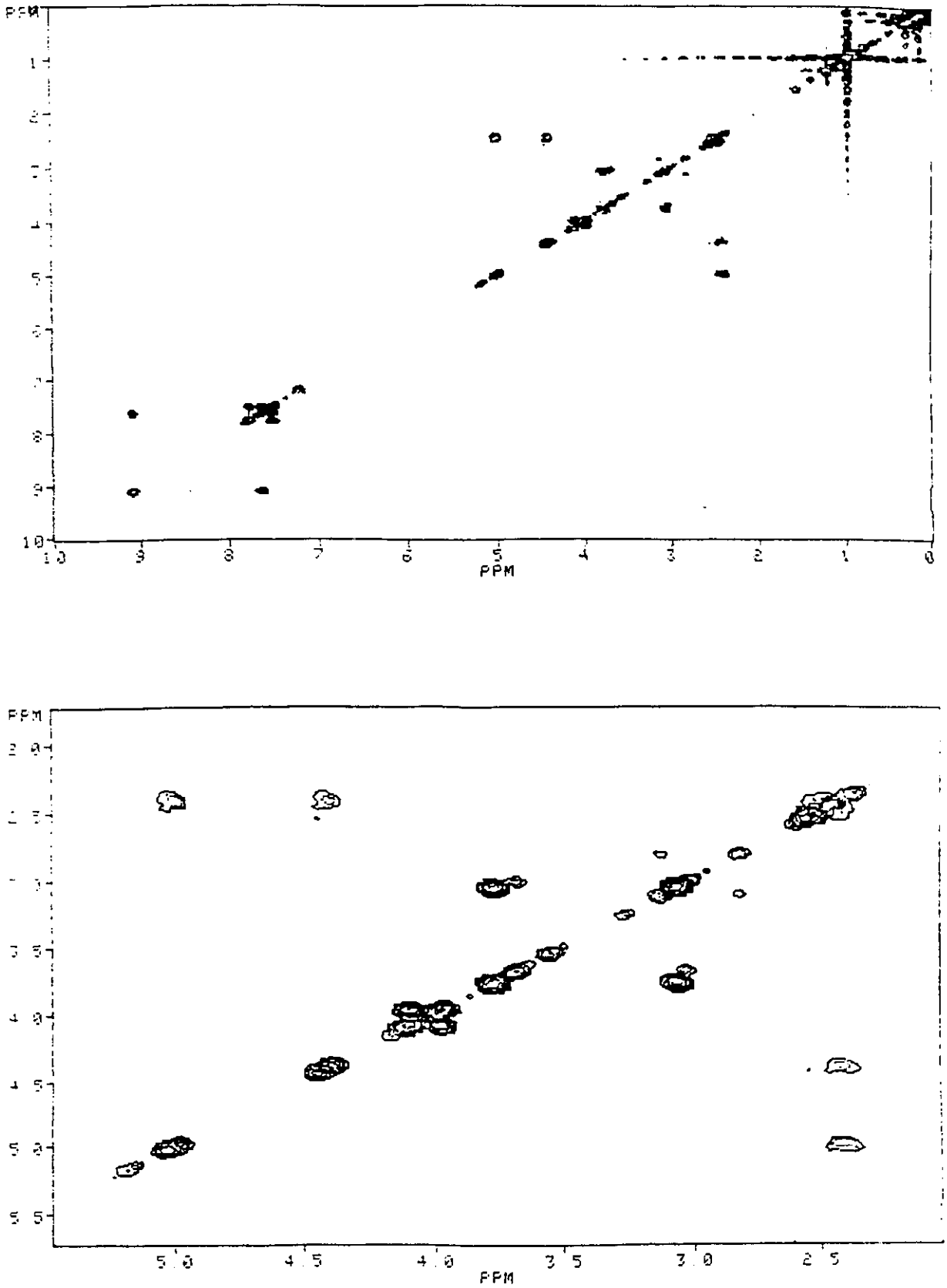


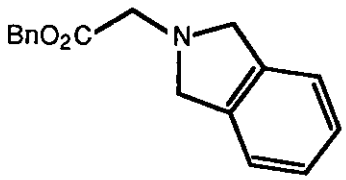

**Figure 2**: nmr spectrum of **79**

**Figure 3**: HOMCOR spectrum of 79



Since compound **78** was isolated in such abysmal yield, and the ester moiety was also affected by the reaction conditions, the synthesis using these blocking groups was not further pursued.

An approach using an isoindenyl as the blocking group for the amino function of the amino acid was then tried. Glycine benzyl ester was refluxed in $CH_3CN$ with $\alpha,\alpha'$ dichloro-o-xylene and diisopropylethylamine to give product **80** in 38 % yield. This material however readily decomposed upon exposure to air. Because of this instability the isoindolyl group was not further pursued in spite of it's ease of introduction and spectral simplicity.

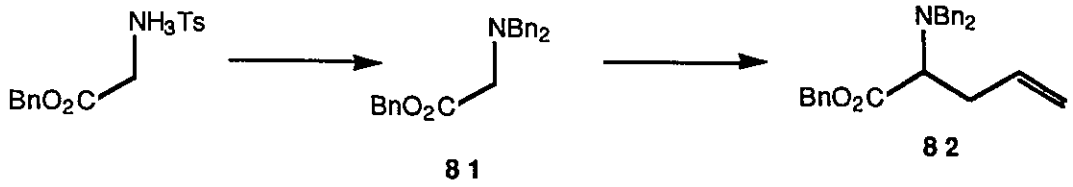



**80**

The reaction of glycine benzyl ester with benzyl bromide under conditions similar to those described above for compound **80** gave derivative **81** in quantitative yield. Alkylation using LDA and allyl iodide produced protected allyl glycine **82** in 59% yield. Product **82** could also be produced in approximately 50 % yield by the action of benzyl bromide on allyl glycine under basic conditions,[61] but material produced in this way was contaminated with benzylethylether, a by-product of the reaction of the solvent and benzyl bromide. This ether displayed an $R_f$ value identical to that of **82**. This, and the low volatility of benzylethylether made it difficult to prepare pure samples of **82**

[61] L. Velluz, G. Amiaro, R. Heymès. *Bull. Chim. Soc. Fr.*, 201 (1955).

in this manner. Hence, for preparative purposes, **82** was prepared from glycine as previously described.




**81** **82**

Unfortunately, it proved to be impossible to isolate an aldehyde from the ozonolysis reaction of **82**. Ozonolyses were performed in dry $CH_2Cl_2$ at - 78 °C, using both DMS and $PPh_3$ to decompose the ozonide formed. Although a 60 $MH_Z$ nmr spectrum of the crude reaction mixture showed the presence of an aldehyde, no such product could be isolated by flash chromatography of the rapidly discoloring mixture. Several attempts were also made using an excess of trifluoroacetic acid to protect the tertiary amine against oxidation, but these attempts were also fruitless. Reactions were also tried in which the ozonolysis products were worked up cold and then added directly without further purification to a solution of the enolate of **50**. These reactions not only produced no Peterson products, but dibenzylamine was isolated in relatively large amounts. The reasons for the failure of this reaction are not understood.

One final attempt was made, this time employing the well known benzylcarbamate (CBZ) group. Allylglycine was readily converted into it's CBZ derivative **83** using standard conditions[62] in excellent yield. Conversion to the benzyl ester[63] proceeded rapidly to give ester **84**. This product was easily

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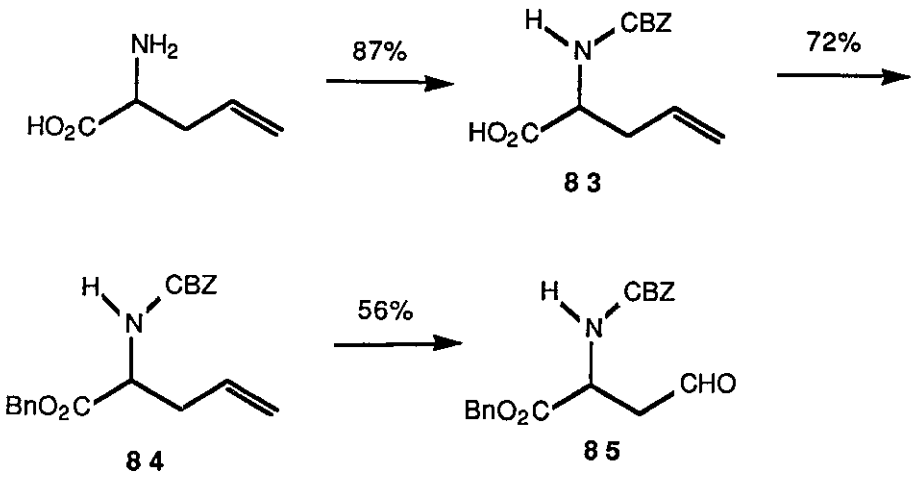
[62] H. E. Carter, R. L. Frank, H. W. Johnston. *Org. Syn. Coll. Vol. 3,* 167, (1955)
[63] D. Ben-Ishai, A. Berger. *J. Org. Chem.*, **17**, 1564 (1952).

purified by flash chromatography and obtained as a colorless oil. Ozonolysis of this product using standard conditions gave aldehyde **85** as a single product after flash chromatography.



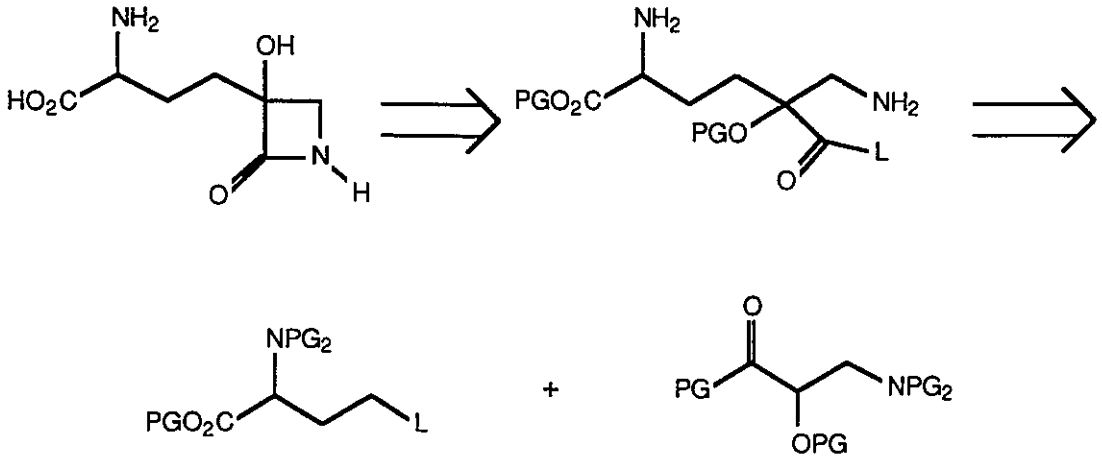

**83** **84** **85**

Once again however, it proved to be impossible to obtain a Peterson adduct with **50**, even though the expected deprotonation of the amine should inhibit elimination. These reactions were carried out by using either two equivalents of LDA or by pre-treating **85** with sodium hydride. No recognizable products could be found in the complex reaction mixtures.

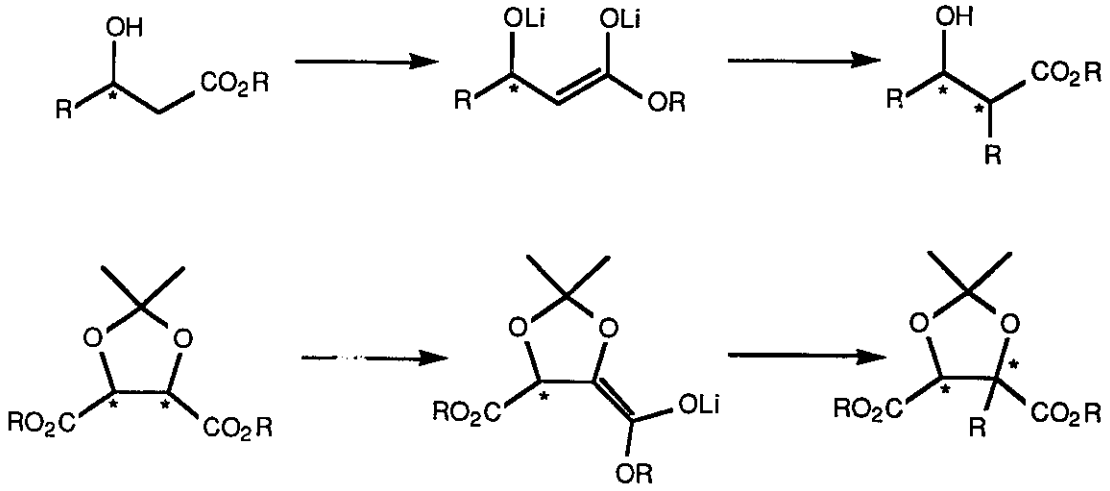
# Chapter 3
# Synthetic Approaches Using a Latent β-Lactam

## Synthesis based on Miller technology

With the problems encountered in the previous attempts at the synthesis of tabtoxinine-β-lactam, it was felt that a synthesis in which the azetidinone ring is constructed late in the process might be more successful. This sequence could also be made to be more efficient if a way could be found to introduce the troublesome 3-hydroxyl group early in the scheme. More importantly, such a synthesis could be asymmetric by using a method which establishes the configuration at the C-3 carbon, possibly by use of a chiral protecting group or groups. This is shown in retrosynthetic form below.



Technology which could possibly be useful to the tabtoxinine problem has been slowly evolving in the laboratories of Professor Seebach.[64] Early work involved the use of existing chiral centres to influence the configuration at the newly formed site. Examples using 3-hydroxy butyrate and isoproylidene tartrates are shown below.




Diastereoselectivity was good but Seebach and others[65] noted that alkylation was not always efficient especially with the tartrate enolates. Seebach then developed the idea of using a chiral protecting group. The novelty of this concept was that the protecting group reagent itself need not be chiral. The existing asymmetry in the substrate was employed to generate asymmetry in the auxiliary through a diastereoselection process. Chiral information was then transferred back to the substrate during alkylation. Even in

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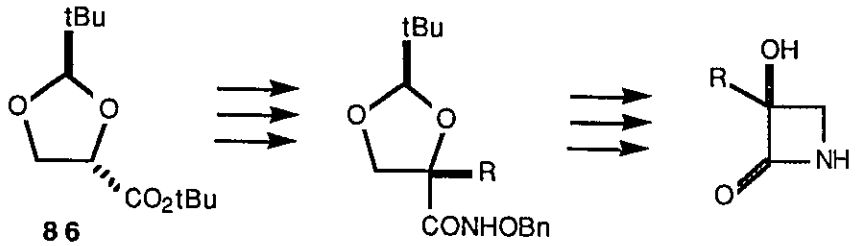
[64] a) M. Züger, T. Weller, D. Seebach. *Helv. Chim. Acta.*, **63**, 2005 (1980); b) D. Seebach, D. Wasmuth. *Helv. Chim. Acta.*, **63**, 197 (1980); c) D. Seebach, R. Naef. *Angew. Chem. Int. Ed. Engl.*, **20**, 1030 (1981).

[65] a) W. Ladner. *Angew. Chem. Int. Ed. Engl.*, **21**, 449 (1982); b) W. Ladner. *Chem. Ber.*, **116**, 3413 (1983); c) R. W. Hoffmann, W. Ladner. *Chem. Ber.*, **116**, 2704 (1983).

early experiments, this idea was very effective.[66] This reaction sequence gave tertiary α-hydroxy esters as products, and therefore seemed ideal for the required task.

The initial choice was glyceric acid derivative **86**.[67] This compound was reported to give excellent results in asymmetric alkylations, and was readily prepared from serine. It has the required carbon atoms to build the β-lactam moiety and is functionalized for later lactam formation by conversion of the *t*-butyl ester into a hydroxamic acid ester.




**86**

Before work proceeded however, lactam formation from this type of substrate needed to be tested. The required model was prepared from methacrylate in the following manner.

Methyl methacrylate was epoxidized using *m*CPBA in refluxing dichloroethane containing 2,6-di-*t*-butylphenol as a radical scavenger. This procedure gave the known[68] epoxide **87** in c.a. 60% yield after distillation. Conversion to the required acetal **88** was achieved by exposure to acetone at low temperature in the presence of $SnCl_4$.[69]

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[66] D. Seebach, R. Naef. *Helv. Chim. Acta.*, **64**, 2704 (1981).
[67] D. Seebach, M. Coquoz. *Chimia*, **39**, 20 (1985).
[68] D. L. MacPeek, D. S. Starcher, B. Phillips. *J. Am. Chem. Soc.*, **81**, 680 (1959).
[69] a) G. Willfang. *Ber. Dtsch. Chem. Ges.*, **74**, 145 (1941); b) G. T. Pearce, W. E. Gore, R. M. Silverstein. *J. Org. Chem.*, **41**, 2797 (1976); c) P. A. Bartlett, J. Myerson. *J. Org. Chem.*, **44**, 1625 (1979); d) J. N. Blackett, J. M. Coxon, M. P. Hartshorn, A. J. Lewis, G. R. Little, G. L. Wright. *Tetrahedron*, **26**, 1311 (1970).

Saponification of **88** proceeded rapidly and without incident giving acid **89** in good yield. This material was treated with thionyl chloride[70] giving the acid chloride **90** in low yield (47%). Attempts to condense this product with methoxylamine were unsuccessful. The hydroxamic acid ester was desired since the plan was to employ the so-called Miller cyclization[71] to close the lactam ring. In this technique, a suitably substituted hydroxamate is treated with DEAD/$PPh_3$ or $PPH_3/CCl_4$ and is reported to be a good method for β-lactam construction. The next attempt was made using dicyclohexylcarbodiimide (DCC). Reaction of **89** and methoxylamine in THF in the presence of DCC using the procedure described by Miller gave none of the desired product. Instead, O-acylurea **91** was extracted from the reaction mixture. The identity of this product was inferred by the nmr spectrum which showed a large multiplet (22 H) resulting from the cyclohexyl residues. The infrared spectrum, in addition to an ester absorption at 1705 $cm^{-1}$, displayed a moderate absorption at 1650 $cm^{-1}$ which indicated the presence of an acyl urea. This product unfortunately would not condense with methoxylamine and was therefore not a useful intermediate. After carbonyldiimidazole also failed to effect the desired amide formation, a mixed anhydride prepared from **89** and ethyl chloroformate was tried. The reaction was performed in $CH_2Cl_2$ using TEA as a catalyst. This was a very convenient reaction since the intermediate anhydride did not have to be isolated. Instead, direct addition of methoxylamine gave the desired product **92**. Compound **92** showed infrared absorptions at 3400 $cm^{-1}$ and 1680 $cm^{-1}$ indicative of the presence of the hydroxamate moiety. In addition to signals for the protons at C-5 of the dioxolane (AB pattern at δ4.27 and δ3.78), and singlets

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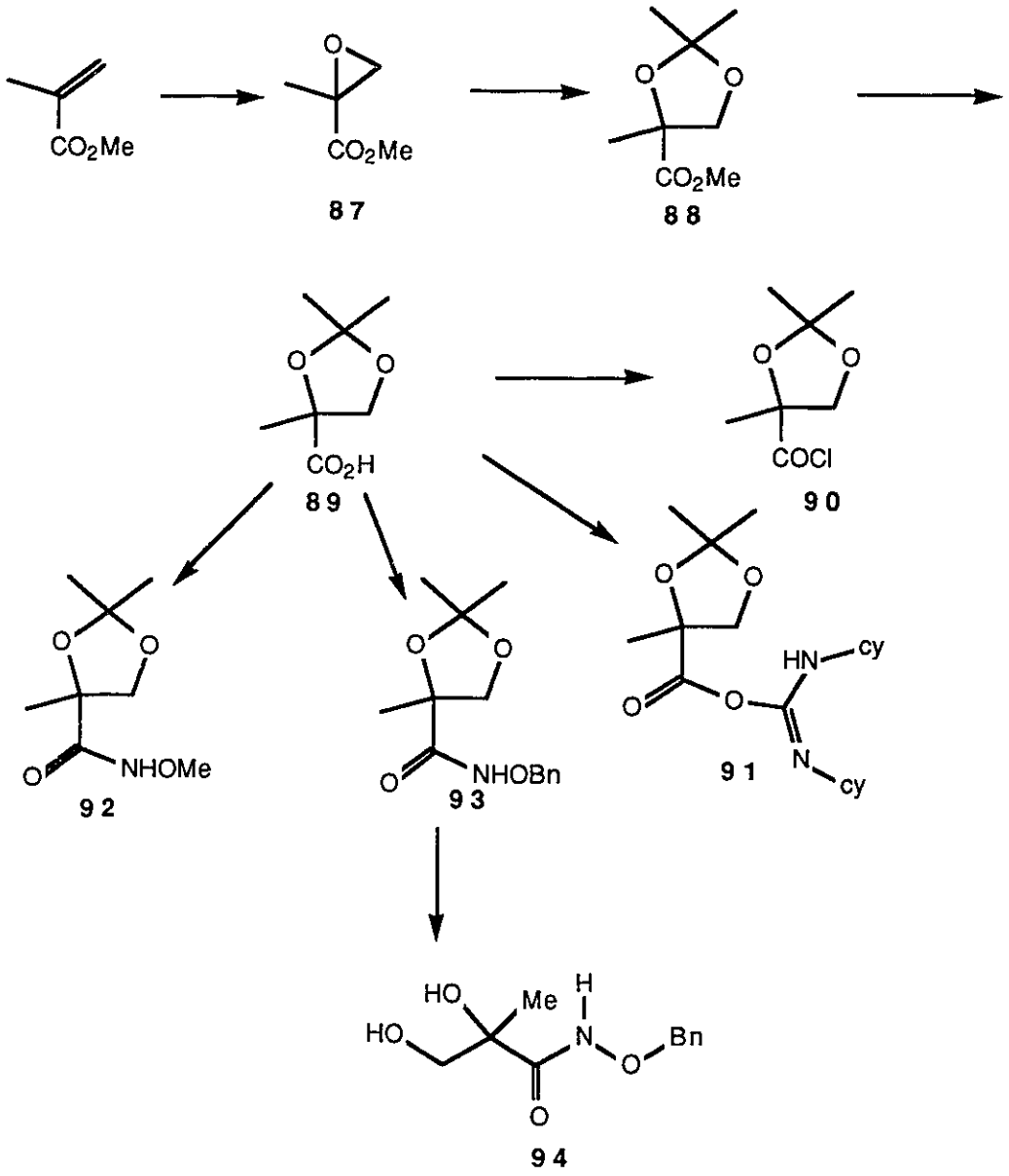
[70] M. Viscontini, W. F. Frei. *Helv. Chim. Acta.*, **55**, 574 (1972).
[71] M. J. Miller, P. G. Mattingly, M. A. Morrison, J. F. Kerwin Jr. *J. Am. Chem. Soc.*, **102**, 7076 (1980).

for the three methyl groups of the dioxolane system (at δ1.53, δ1.48 and δ1.46); a methoxyl singlet at δ3.76 and broad signal at δ9.01 (NH) were noted.

Having established conditions for conversion of **88** into hydroxamic acid esters such as **92**, the O-benzyl hydroxamate **93** was prepared. This compound displayed dioxolane nmr signals similar to those noted for hydroxamate **92**, along with standard O-benzyl resonances (5 aromatic protons, AB pattern at δ4.97 and 4.95 ppm). The O-benzyl group is recommended by Miller since it is easily removed after β-lactam construction is completed.


CO2Me
87
88
CO2H
89
COCl
90
NHOMe
92
NHOBn
93
HN
cy
N
cy
91
HO
Me
H
HO
N
O
Bn
O
94

Removal of the isopropylidine protecting group of **93** using standard conditions[72] gave diol **94** in 86% yield after flash chromatography. Attempts to prepare an azetidinone from **94** using the Miller conditions ($PPh_3/CCl_4$; $PPh_3$/DEAD) gave complex mixtures whose ir spectra did not show the presence of a β-lactam (1740-1780 $cm^{-1}$). It is possible that the tertiary alcohol rather than the NH displaces the activated primary hydroxyl function thereby resulting in oxirane rather than β-lactam formation (structure (i)), This intermediate is not convertible into a β-lactam since this process would require a 4-*endo-tet* opening of the epoxide, a process which has not been reported in the literature.[73] Blocking the tertiary alcohol would require initial protection of the adjacent primary function, thus lengthening a subsequent synthesis. Also, the hydroxamic acid ester is somewhat nucleophilic and may interfere. For these reasons it was felt that an approach of this type was undesirable and was therefore abandoned.


(i)

## Synthesis based on Ohno technology

In contrast to the Miller procedure in which a nucleophilic amide component is used to effect β-lactam closure, the Ohno[74] method involves a

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[72] M. L. Lewbart, J. J. Schneider. *J. Org. Chem.*, **34**, 3505 (1969).
[73] a) B. Corbel, T. Durst. *J. Org. Chem.*, **41**, 3648 (1976); b) G. Stork, L. D. Camma, R. D. Coulson. *J. Am. Chem. Soc.*, **96**, 5268 (1974); c) G. Stork, J. F. Cohen. *J. Am. Chem. Soc.*, **96**, 5270 (1974).
[74] S. Kobayashi, T. Iimori, T. Izawa, M. Ohno. *J. Am. Chem. Soc.*, **103**, 2406 (1981).

classical amide formation from an acid and an amide. The starting material is a β-amino acid, which upon the action of dipyridyl disulfide and triphenylphosphine cyclizes to the azetidinone. The reaction is not a new one as other activators such as AcCl, $PCl_3$, $SOCl_2$,[75] Grignards,[76] and DCC[77] have been employed to achieve closure. Each of these methods tend to be substrate specific and reaction conditions are often critical. The recently devised Ohno method appears to be the most general.

The proposed synthetic protocol is outlined in scheme 1. Oxazoline derivative **95**[78] is readily made from aspartic acid. The oxazoline protecting group was chosen since it was easily removed and protected both protons of the amide. As well, the carbamate moiety reduces the nucleophilicity of the nitrogen. The group is also useful since the β-acid group of aspartic acid can be selectively functionalized.

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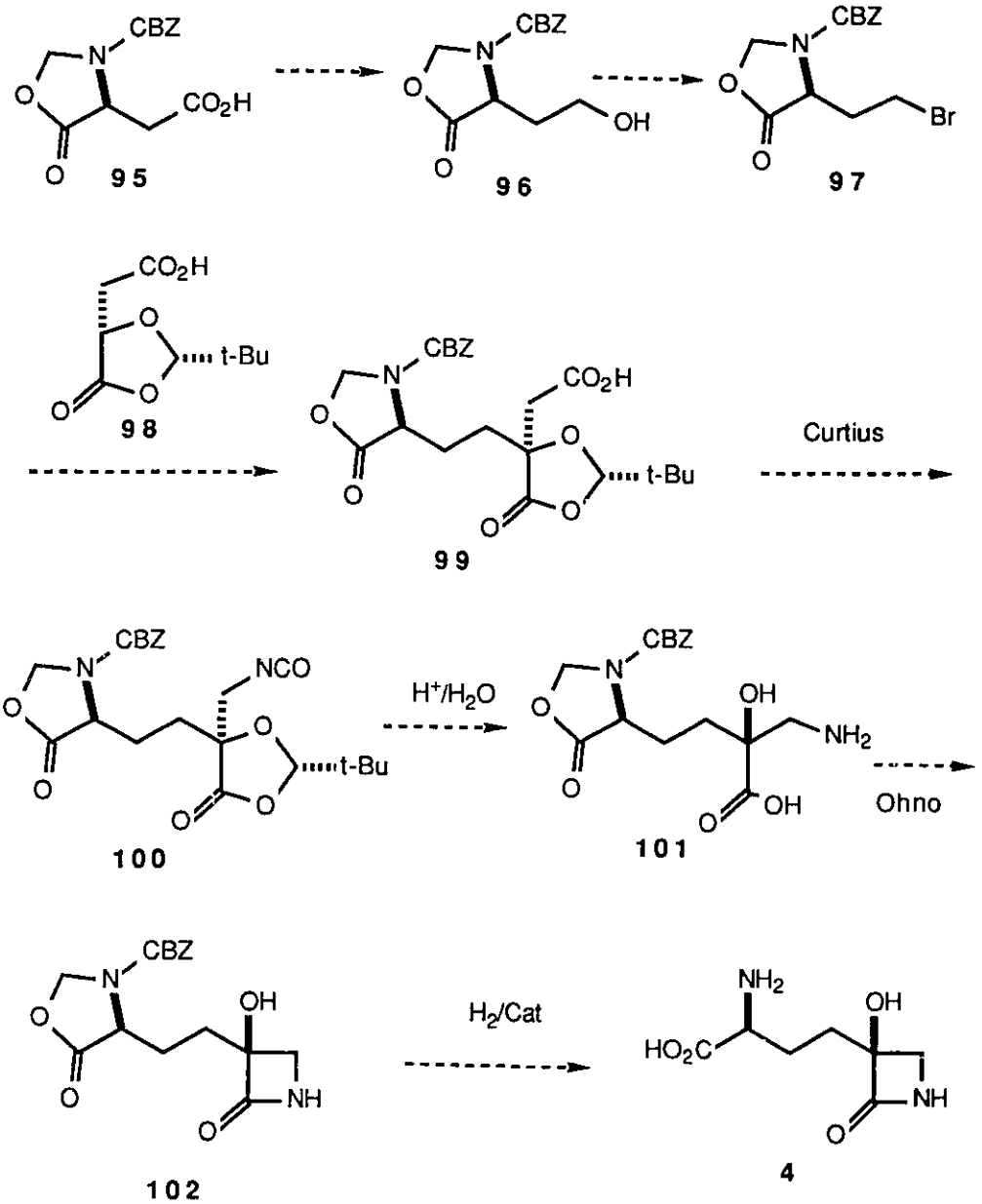
[75] a) J. C. Sheehan, E. J. Corey. *Org. React.*, **9**, 388 (1957); b) N. Ikota, H. Shibata, K. Koga. *Heterocycles*, **14**, 1077 (1980); c) R. Busson, H. Vanderhaghe. *J. Org. Chem.*, **43** ,4438 (1978).

[76] a) A. Breckpot. *Bull. Soc. Chim. Belg.*, **32**, 412 (1923); b) E. Testa. *Liebigs Ann. Chem.*, **639**, 157 (1961); c) L. Birkofer, J. Schramm. *Liebigs Ann. Chem.*, 2195 (1975).

[77] a) J. C. Sheehan, G. D. Lauback. *J. Am. Chem. Soc.*, **73**, 4376 (1951); b) D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, M. Sletzinger. *Tetrahedron Lett.*, 2783 (1980); c) T. Kametani, S. Huang, S. Yokohama, Y. Suziki, M. Ihara. *J. Am. Chem. Soc.*, **102**, 2060 (1980).

[78] M. Itoh. *Chem. Pharm. Bull.*, **17**, 1679 (1969).

Scheme 1


CBZ
N
O
CO2H
95
OH
96
Br
97
t-Bu
98
99
Curtius
NCO
100
H+/H2O
NH2
101
Ohno
NH
102
H2/Cat
HO2C
4

Reduction to **96** was expected to be easy, as well as the subsequent conversion to the known compound **97**.[79] The fragment which would eventually become the β-lactam would then be introduced. Compound **98** has been described by Seebach,[80] and is known to add electrophiles in a highly diastereoselective manner. With all the carbon atoms attached, a series of functional group interconversions were envisaged which would result in the production of the desired product. Key features in this sequence include the Curtius rearrangement of **99**, removing a carbon and introducing nitrogen, as well as the Ohno cyclization of **101**.

It was decided to assemble the left hand fragment i.e. **97** as the initial subgoal. Thus **95** was treated with $BH_3$·DMS in THF containing an excess of $(MeO)_3B$.[81] After nmr analysis showed that reduction was complete, the reaction was worked up by repeated rotary evaporation with methanol followed by flash chromatography. The reaction gave a good yield of not the desired product **96**, but of N-CBZ-α-aminobutyrolactone **103**. The nmr spectrum of this material displayed a methylene signal at δ4.45-4.18 (multiplet overlaid with a multiplet resulting from the proton α to the ester) which showed that this carbon was attached to an ester oxygen. The ir spectrum contained an absorption at 1780 $cm^{-1}$ indicative of a 5-membered lactone. Conspicuous in it's absence was any nmr signal near δ5.5-5.3 for the protons normally present in the oxazoline ring. Reaction at low temperature of **95** with $BH_3$·THF also gave the same result. This product could arise by simple transesterification with the newly formed alcohol of intermediate **96**.

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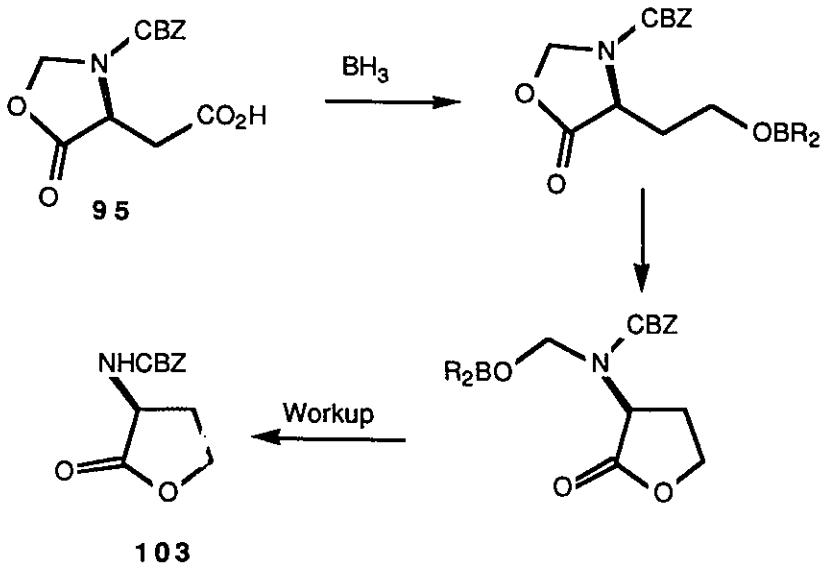
[79] D. H. R. Barton, Y. Hervé, P. Potier, J. Thierry. *J. Chem. Soc., Chem. Commun.*, 1298 (1984).
[80] D. Seebach, R. Naef, G. Calderari. *Tetrahedron*, **40**, 1313 (1984).
[81] C. F. Lane, H. L. Hyatt, J. Daniels, H. B. Hopps. *J. Org. Chem.*, **39**, 3052 (1974).

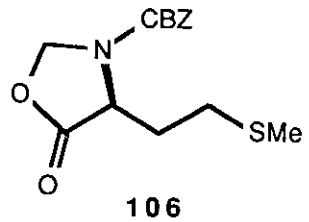



Since the straightforward reduction of **95** to **96** could not be controlled, a new approach was required.

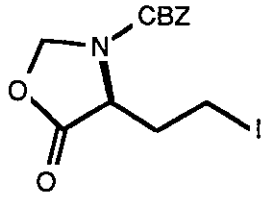
A closer look at the literature at this point gave the solution. Homoserine derivatives are typically prepared by the hydrolysis of the sulfonium salt of methionine.[82] Instead of hydrolysis, substitution with a halide should give the desired product. Normally the homoserine formation is preformed on the free amino acid, however the same interconversion should be feasible with a protected methionine derivative. Such a product, **106**, was readily prepared from N-CBZ-methionine by the acid catalyzed condensation with paraformaldehyde. Blocked methionine **106**, displayed a pair of AB patterns in the proton nmr which were assigned to the benzyl and oxazoline hydrogens (δ5.21, 5.16 and δ5.51, 5.25 respectively). A pair of multiplets in the δ2.5-2.2 region of the spectrum were observed as a result of the pair of methylenes on the side chain at position 4 of the oxazoline. The ir spectrum contained two

[82] a) R. D. G. Cooper, F. J. L. McShane, G. A. Koppel. *Tetrahedron Lett.*, 2243 (1978); b) J. E. Baldwin, A. Flinn. *Tetrahedron Lett.*, 3605 (1987).

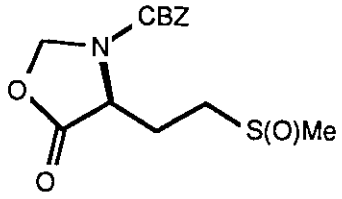
carbonyl absorptions at 1800 $cm^{-1}$ and at 1715 $cm^{-1}$ which indicated the presence of an ester in a five membered ring and of a carbamate. Reaction of **106** with MeI and NaI in DMF[83] for 24h at 60°C gave a mixture of **106** and iodide **107**. The presence of **107** was confirmed by $^{13}C$ nmr, in which the carbon bearing the iodine is shifted far upfield (δ -2.59), but compounds **106** and **107** proved to be chromatographically inseparable. The mixture was a syrup, and since a previous attempt to distill **106** resulted in decomposition, a chemical means of removing unreacted **106** was required. Thus the mixture was treated with *m*CPBA which oxidized the sulfide in **106** to the sulfoxide **108** and left **107** untouched. Compounds **107** and **108** have very different $R_f$ values and could be easily separated. This extra step was later shown to be unnecessary however, since extended reaction times gave iodide **107** which was free of starting material.




**106**




**107**




**108**

Iodide **107** exhibited two superimposed AB patterns in the $^1H$ nmr, attributed to the benzylic hydrogens and to the protons at C-2 of the oxazoline.

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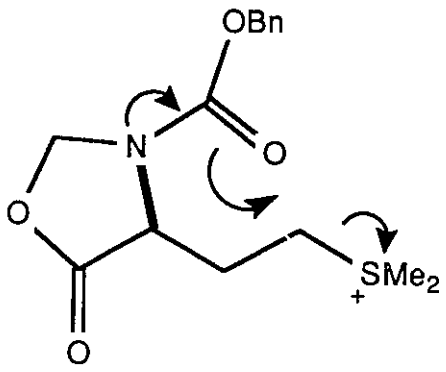
[83] E. J. Corey, M. Jautelat. *Tetrahedron Lett.*, 5787 (1968).

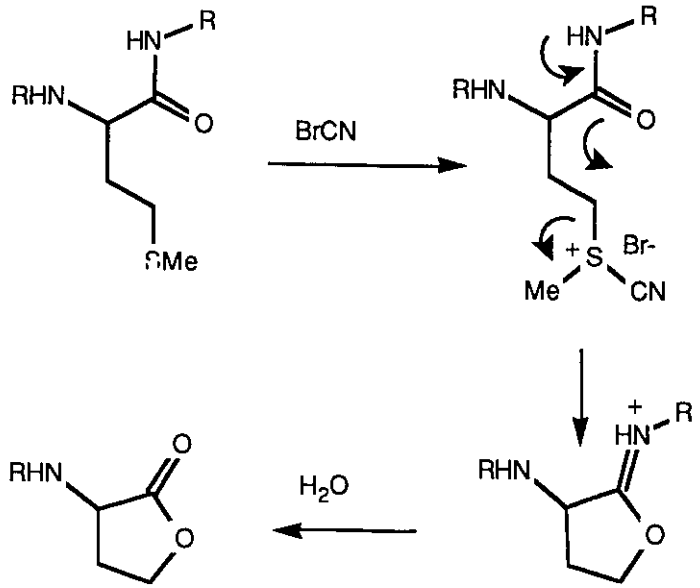
A triplett appeared at δ4.34 which was assigned to the amino acid methine proton. In addition a triplett at δ3.21 attributable to the halogenated carbon's hydrogens and a multiplet (δ2.5) resulting from the remaining methylene were observed. In order to achieve reasonable resolution, the spectrum was accumulated at 55°C, since the room temperature spectrum did not give useful information. In fact, all derivatives containing the benzyloxycarbonyl blocked oxazoline blocking group required that nmr work be done at elevated temperatures because of the restricted rotation about the N-C bond of the carbamate. This restriction is so severe that several products were not fully resolved, even at 55°C.

In the preparation of iodide **107**, a drop of mercury was included in the reaction mixture as recommended by Corey to prevent iodine formation. Under these conditions, yields were in the range of 50 - 55 %. However some preparations gave a product which was very unpleasant to work with. The crude iodide **107** in these reactions appeared normal on TLC and nmr, but even brief exposure to the compound produced a very unpleasant taste in the mouths of workers in the lab. The contaminant could not be removed by chromatography or by repeated recrystallization. Because of the unpleasantness of this trace contaminant which is as yet unidentified, iodide **107** was subsequently prepared without mercury. Reaction mixtures had to be washed with a sodium sulfite solution upon workup though, to remove $I_2$.

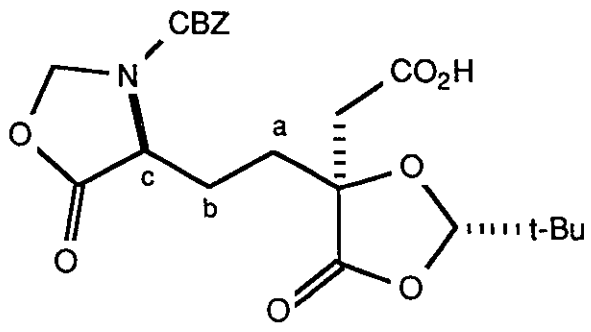
The formation of **107** was found to be sometimes troublesome. Although returns in the 50 % range could be obtained, yields in the 20 - 30 % range were the norm. The reason for this may be the result of nucleophilic attack of the carbamate carbonyl on the sulfonium salt which begins to unravel the oxazoline protecting group.




This reaction would be similar to that involved in the cleavage of peptides with cyanogen bromide. This reagent is used to cleave peptides specifically at methionine residues as shown below.




The dianion of malic acid derivative **98** was generated with LiHMDS and quenched with 1 equivalent of iodide **107**. From this reaction mixture was isolated in moderate yield, a product which was tentatively identified as the desired adduct **99** shown below.




**99**

This compound displayed strong absorptions in the infrared at 1800 $cm^{-1}$,consistent with the retention of both 5-membered rings, a band at 1720 $cm^{-1}$ due to the carbamate and a broad absorption from 3300-2500 $cm^{-1}$ due to the H-bonded OH of the carboxylic acid.

The nmr spectrum of this adduct is shown in figure 4. The nmr spectrum contained two AB absorbances in the range δ5.27 to δ4.97 which were attributed to the benzylic and oxazoline C-2 protons as described for compound **107**. An additional AB pattern appeared at δ3.00 and δ2.81 which originated with the protons α to the acid. The acetal proton was visible as a singlet at δ5.27. These signals were consistent with a structure such as **99**. What was troubling however was the appearance of the remaining resonances. A pair of multiplets at δ2.30 - 2.20 and at δ2.15 -2.04 were assigned to the protons at position b. These protons were shown by a HOMCOR spectrum (figure 5) to be coupled

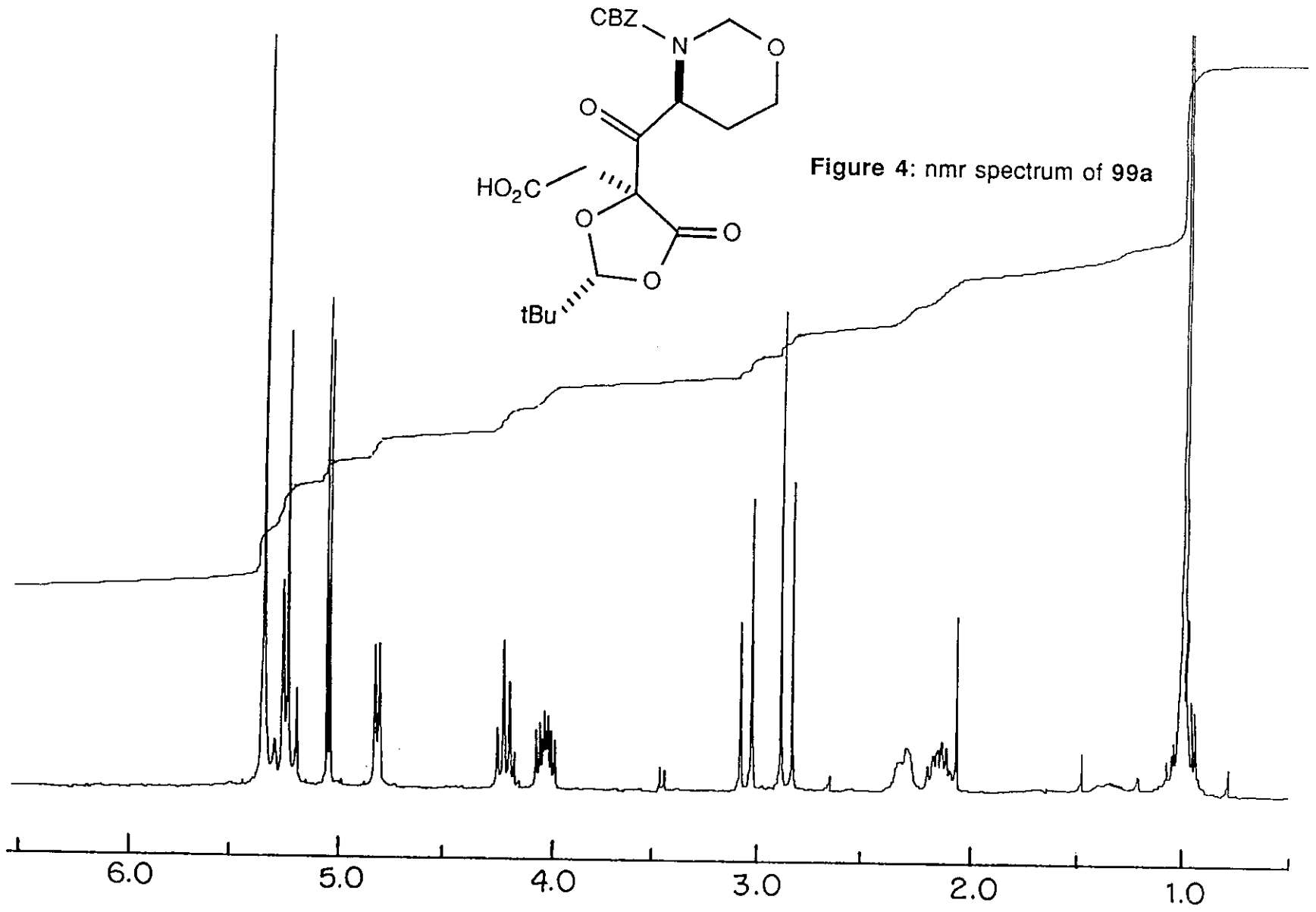
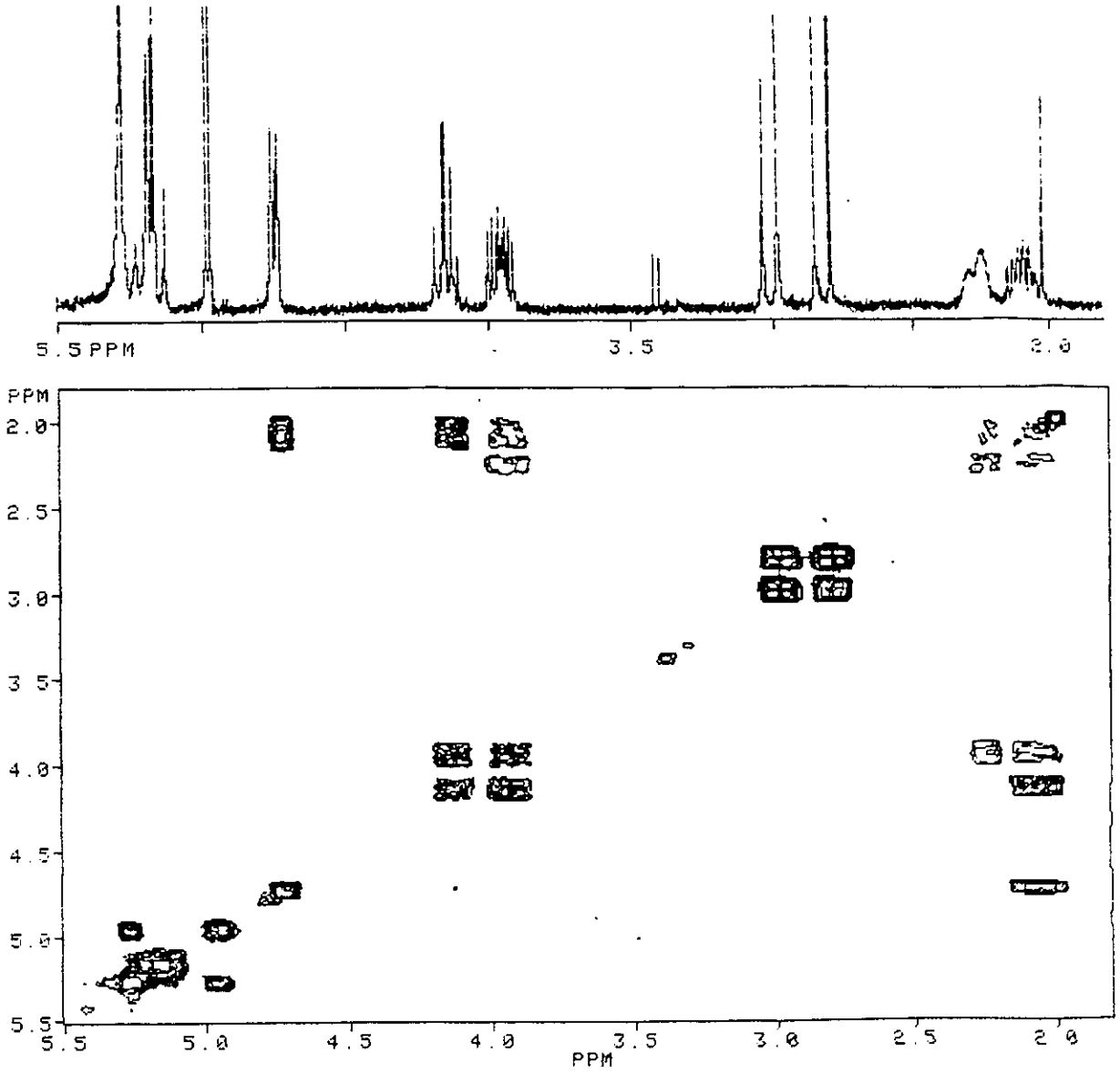
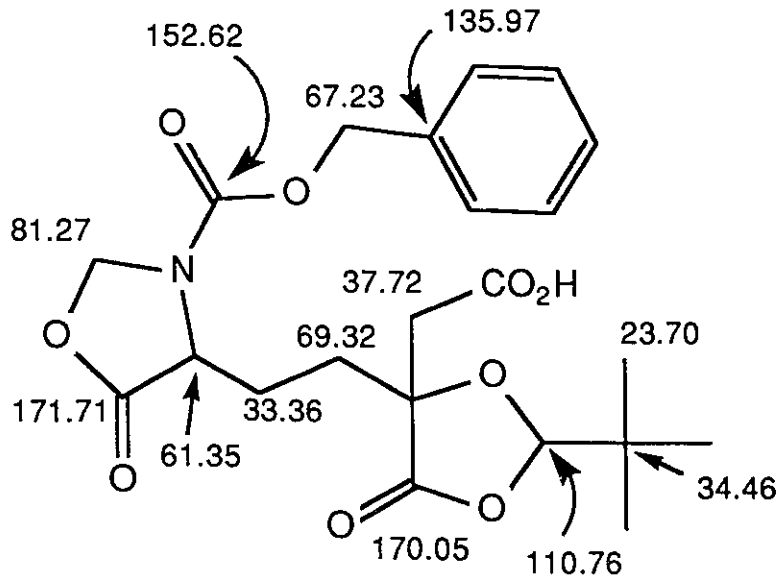



**Figure 4**: nmr spectrum of **99a**

**Figure 5:** HOMCOR spectrum of **99a**



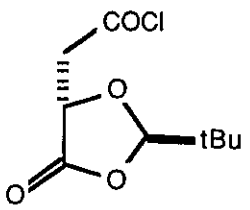
to a pair of signals at δ4.09 - 3.90 (multiplet) and δ4.15 (triplet), which were assigned to the a hydrogens. The b hydrogen at δ2.15 - 2.04 was also coupled to a signal at δ4.74 which appeared as a doublet and was assigned to position c. The fact that this signal (δ4.74) was coupled to only one H on the adjacent methylene was highly unusual and was thought to arise from a rigid conformation of the molecule, but this conformation was not readily apparent upon the study of models. The position of the signals for carbon a was also disturbing as was the fact that the HOMCOR recorded no interaction between the δ4.15 triplet and the multiplet at δ2.30 - 2.20. At this time, no explanation was forthcoming concerning these anomalities. Since protons on adjacent carbons did not couple, a carbon spectrum was acquired in order to further clarify matters. This spectrum, with the exception of one resonance was consistent with structure **39**. The inconsistency was a methylene absorption at δ69.32. The assignment of this signal was derived through a process of elimination: all other resonances were assigned, and then the remaining signal (δ69.32) was assigned to position a, the remaining carbon. These assignments are summarized below.



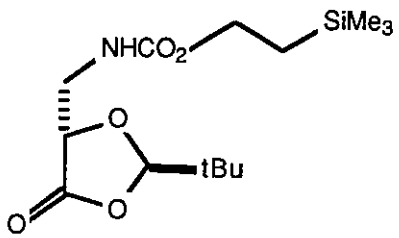

The possibility was considered that the anomalous signal was due to the stabilization of a conformation in which the carbon in question is strongly deshielded, due to intramolecular hydrogen bonding between the acid and one of the carbonyl groups. Therefore the methyl ester was produced by titration of **99** with $CH_2N_2$ and examined spectroscopically. This material, ester **109** displayed $^1H$ and $^{13}C$ resonances which were nearly identical to those of the supposed acid **99**, indicating that hydrogen bonding was not responsible for the anomalous nmr signals.

While the structures of **99** and **109** were being investigated, work progressed on the Curtius reaction for the next step. The plan at this step was to prepare a carbamate, rather than to try to isolate the isocyanate. Thus, **98** was converted to the acid chloride **110** by treatment with oxalyl chloride in dry $CH_2Cl_2$. The initial reaction was sluggish and required catalysis by the addition of a drop of DMF. Acid chloride **110** was not isolated, but was treated

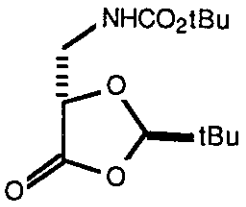
directly with azidotrimethylsilane (TMS-$N_3$) in benzene.[84] After refluxing the mixture for 90 min, two equivalents of 2-trimethylsilylethanol were introduced and reflux continued for an additional 2 h. This process gave β-trimethylsilylethyl carbamate **111** in 81 % overall yield. The β-trimethylsilylethyl group was selected since it offered two means of deprotection, fluoride treatment[85] or hydrolysis in trifluoracetic acid.[86] Both methods are mild and do not affect the CBZ group.[87] Carbamate **111** was also available by the action of diphenylphosphorylazide[88] on **98** in refluxing dry benzene containing 1 equivalent of triethylamine and β-trimethylsilylethyl ethanol.




**110**




**111**




**112**

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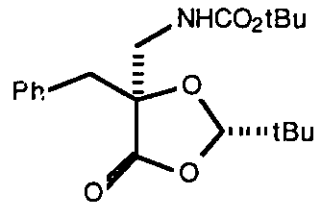
[84] J. H. MacMillan, S. S. Wasburne. *J. Org. Chem.*, **38**, 2883 (1973).
[85] L. A. Carpino, A. C. Sau. *J. Chem. Soc., Chem. Commun.*, 514 (1979).
[86] L. A. Carpino, J. H. Tsao, H. Ringsdorf, E. Fell, G. Hettrich. *J. Chem. Soc., Chem. Commun.*,358 (1978).
[87] A.R. Mitchell, R. B. Merrifield. *J. Org. Chem.*,**41**, 2015 (1976).
[88] a) T. Shioriri, K. Ninomiya, S. Yamada. *J. Am. Chem. Soc.*, **94**, 6203 (1972); b) T. Shiori, S. Yamada. *Org. Syn.* **62**, 187 (1984).

Malic acid derivative **98** could also readily converted into the *t*-butyl carbamate **112** which would yield the deprotected amine as it's ammonium salt simply by exposure to TFA. This substance was obtained in 85 % yield using the oxalyl chloride/TMS-$N_3$ method, although a long reaction time was required. Periodic monitoring of the reaction by nmr integration indicated that the reaction had a half-life of approximately five hours. Surprisingly low yields of **112** (30 %) were obtained by using the $(PhO)_2P(O)N_3$ method.

At this point the synthetic plan was altered slightly. Originally the Curtius rearrangement was slated to be carried out after the condensation of **98** and **107** had been secured (scheme 1). This proposal had been weakened by the inability to satisfactorily characterize **99** and **109**. With carbamates **111** and **112** in hand, it seemed reasonable that dianions of these materials could be condensed properly with iodide **107**. As an added bonus, by performing the Curtius reaction first, the synthesis would be made more convergent.

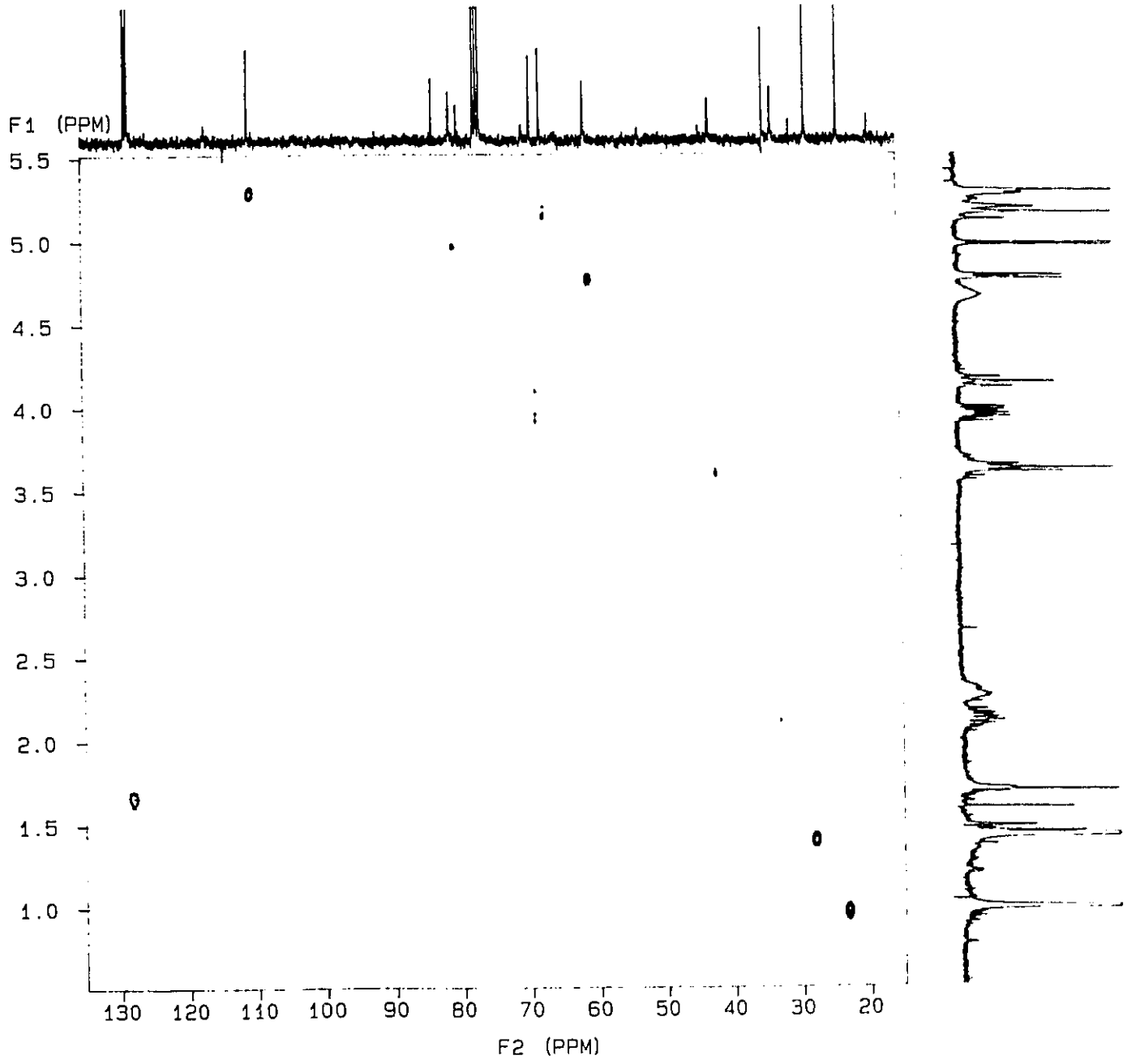
Tertiary butyl carbamate **112** was therefore treated with two equivalents of LiHMDS and subsequently one equivalent of benzyl bromide was added. Standard extractive workup followed by flash chromatography gave benzyl derivative **113** in 41 % yield. Although the stereochemistry of the addition was indeterminate, a single isomer was obtained as evidenced by the clean $^1H$ and $^{13}C$ nmr spectra. The spectral data for this compound is presented in the experimental section. This isomer is assumed to be that resulting from addition of the benzyl bromide *trans* to the *t*-butyl group.



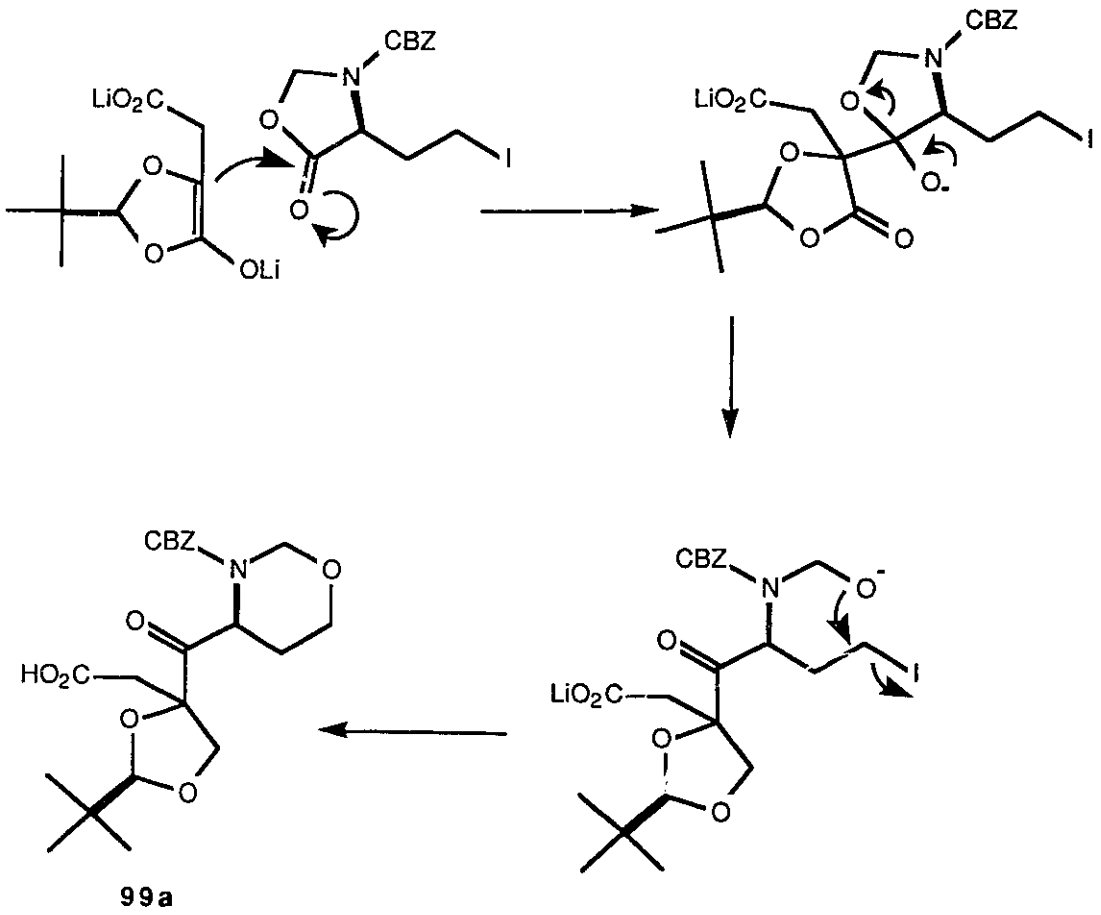

**113**

Having confirmed that **112** could be successfully alkylated, an attempt was made to condense tne enolate of **112** with iodide **107**. This reaction gave a product (**114**) with spectral characteristics very similar to that of compounds **99** and **109**. Since the spectroscopic data for **99** and **109** were somewhat ambiguous and did not allow us to assign these structures with complete confidence the data, including the HETCOR spectrum of **114** (figure 6) was carefully analyzed. Essentially no new information was forthcoming from this experiment other than establishing that the anomalous signal at δ69.13 corresponded to the multiplet and triplet at δ4.62 and δ4.12. Something was obviously wrong with the assignments of the products from the reaction of the dianion of acid **98** and carbamate **113** with iodide **107**, but no alternate structure was obvious at that time. The problem was that all structural features appeared to be intact, with only the nmr signals for one methylene being shifted too far downfield. Mass spectral analysis displayed the correct molecular ions. We had expected and hoped to obtain **99**, **109** and **114** and had tried to fit the data to these compounds. When finally faced with the conclusion that these structures could not be correct we considered carefully all other possible reaction pathways between the acid **98** and urethane **112** and the iodide **107**. The iodide **107** has, in addition to the alkyl iodide a second electrophilic site, the oxazoline carbonyl group. Since the oxazoline ring is reported to be reasonably stable to basic conditions[78] we initially ignored this centre. However

**Figure 6**: Partial HETCOR of **114**



attack of the enolate on this function should yield a tetrahedral intermediate which produces an alkoxide upon collapse to a carbonyl group. The alkoxide thus generated can displace the iodide intramolecularly to generate a 1,3-oxazine structure **99a**.

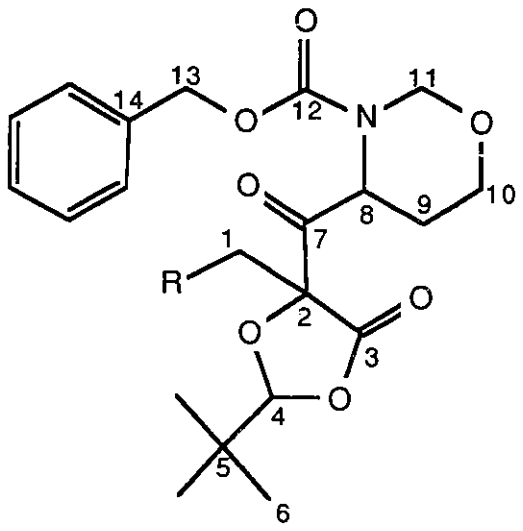



**99a**

As shown in table 1, the 1,3-oxazine structure fits comfortably all of the available data. The protons at carbon 11 would be expected to produce an AB pattern in the same region of the spectrum (δ5.3-5.0) in which the analogous oxazoline hydrogens resonated. The protons at carbon 10 should produce a

signal in the 4 ppm range which is in fact observed. No ketonic signals in the 200 ppm region of the $^{13}C$ spectrum could be discerned, but this may be a consequence of the low number of transients secured. The full assignment for **99a** is shown below. The carbonyl frequency in the infrared at 1800 $cm^{-1}$ is due to the dioxolane carbonyl and that at 1720 assigned to both the ketone and carbamate functions.

**Table 1**: Table showing key $^{13}C$ assignments for compounds **99a**, **109a**, and **114a**.

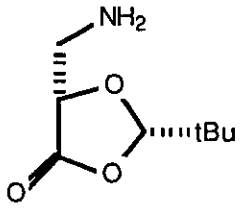



| Carbon | Chemical Shift in ppm Adduct **99a** R=$CO^2H$ | Adduct **109a** R=$CO_2Me$ | Adduct **114a** R=$NHCO_2tBu$ |
|---|---|---|---|
| 1 | 37.72 | 38.08 | 42.77 |
| 2 | 81.83 | 81.32 | 83.55 |
| 3 | 170.05 | 170.08 | 169.90 |
| 4 | 110.76 | 110.63 | 110.56 |
| 5 | 34.46 | 34.37 | 34.65 |
| 6 | 23.70 | 23.67 | 23.63 |
| 7 | NO[a] | NO | NO |
| 8 | 61.35 | 61.34 | 61.23 |
| 9 | 33.36 | 33.43 | 33.41 |
| 10 | 69.32 | 69.24 | 69.13 |
| 11 | 81.27 | 81.99 | 81.01 |
| 12 | 152.62 | 152.52 | 152.28 |
| 13 | 67.23 | 67.70 | 67.74 |
| 14 | 135.97 | 136.06 | 135.92 |

[a]Not observed

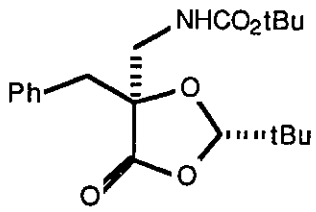
While the structure of these compounds was being investigated, experiments were performed on the assumption that the correct products had

been obtained. If a correct product such as **114** could be secured, then eventual deprotection to the Ohno precursor **101** would be required. The acetal and carbamate had been selected so that mild acid hydrolysis would remove both groups in a single process. Hydrolysis of **98** confirmed this. Dissolution of **98** in 80 or 90 % trifluoroacetic acid (TFA) for one hour gave a quantitative crude yield of malic acid (recrystalized in 77 % yield). This reaction proved to be the exception however. Exposure of **112** to identical conditions resulted in removal of the carbamate, but the acetal stayed fast so that amine **115** was produced as indicated by an nmr of the crude material.

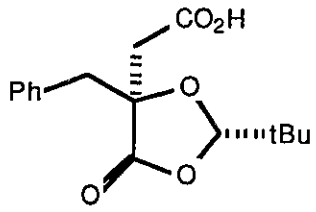



**115**

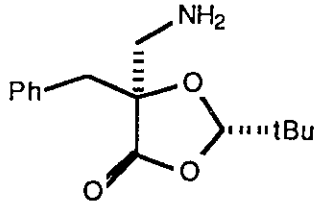
Even after extended treatment with TFA, amine **115** was the only observable product. β-Trimethylsilylethyl derivative **110** also gave amine **115** after dissolution in TFA solution. Substituted products **113** (carbamate) and **116** (acid)[80] were also subjected to deprotection conditions.




**113**




**116**




**117**

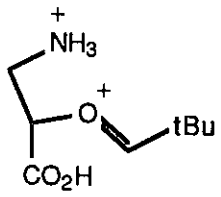
Acid **116** was completely untouched by TFA at room temperature but is reported by Seebach to be cleaved by refluxing in *p*-toluenesulfonic acid solution for three hours. Carbamnate **113** gave amine **117** relatively easily but removal of the acetal required extremely vigorous conditions (table 2). These conditions were harsh enough to remove the oxazoline protecting group of **95** and return aspartic acid.

**Table 2**: Table showing the various conditions tried for the hydrolysis of substituted carbamate **113**.

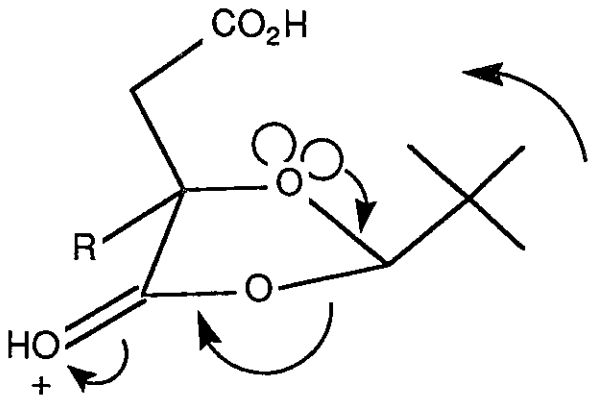
| Solvent | Time(h) | Temperature(°C) | Result[a] |
|---|---|---|---|
| 98 % TFA | 2 | RT[b] | **117** |
| 90 % TFA | 1 | RT | **117** |
| 80 % HOAc | 1/2 | 60 | NR[c] |
| 90 % TFA | 1 | 60 | **117** |
| 6 N HCl | 2 | 80 | NR |
| 10 % NaOH | 1/2 | RT | NR |
| 6 N HCl/THF[d] | 2 | 70 | **117** |
| 90 % TFA | 3 | 80 | Complete Hydrolysis |
| 90 % TFA | 1 1/2 | 80 | 60 % Hydrolysis + 40 % **117** |
| TFA/$(CF_3CO)_2O$ | 2 | RT | **117** |

[a] As determined by nmr
[b] Room temperature
[c] No reaction
[d] Homogeneous solution

The difficulty in removing the pivalic acetal is thought to be a result of two influences. The difficulty in deprotecting the carbamates may be due to the proximity of an ammonium cation to the oxonium ion in the acidic solution.



The sluggishness of deprotection of **116** may be a result of rigidity imposed on the dioxolane by the presence of a bulky benzyl group at position 5. Examination of models suggests that a slight puckering of the five membered ring is required for correct alignment of orbitals in the acetal system.




In order for the oxygen orbital to be anti-periplanar to the departing C-O bond, the *t*-butyl group must squeeze inwards slightly thus rotating the acetal into proper orientation. If R is a hydrogen, steric interactions are small enough to permit this folding motion. If R is larger than H then non-bonding interactions between the carboxylate side chain and the *t*-butyl group become significant. Rotation is inhibited and proper stereoelectronic alignment is prevented. Therefore, even if a proper adduct were obtained, the conditions required to remove this acetal would completely deprotect the molecule.

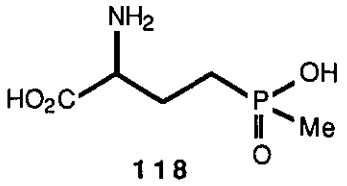
This study has investigated several methods for preparing tabtoxinine-β-lactam. Initial attempts at introducing a hydroxyl moiety into position 3 of the β-lactam were not successful with 3-alkyl lactams, but 3-alkenyl lactams were

shown to be readily hydroxylated. Unfortunately, this method could not be extended into a synthesis.

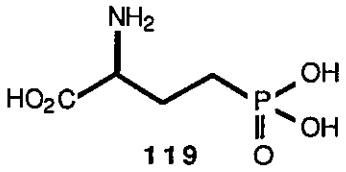
Possible future investigations could examine more carefully the formation of spiro epoxy β-lactams (Chapter 1) and their subsequent reductions to 3-hydroxyazetidinones. The 3-alkenyl lactam hydroxylation technology developed could bear fruit in a synthesis if the proper arrangement of protecting groups could be discovered. Perhaps the Miller strategy outlined above would be a winner if a way could be found to effect ring closure.

## Attempted synthesis of phosphinothricine and 2-APB

We had iodide **107** available early in the previous study and wondered if it could be used to prepare other unusual amino acids. Therefore a search was conducted to find products which could possibly be made from it. Two such molecules are phosphinothricine **118** and 2-amino-4-phosphonobutyric acid (2-APB) **119**.




**118**




**119**

Phosphinothricine **118**, like tabtoxinine-β-lactam **4**, has been shown to be a potent glutamine synthetase inhibitor,[89] and shows strong antifungal and

[89] a) J. A. Colanduoni, J. J. Villatranca. *J. Biorg. Chem.*, **19**, 163 (1986); b) S. M. Ridley, S. F. McNally. *Plant Sci.*, **39**, 31 (1985); c) E. Bayer, K. H. Gugel, K. Hägel, H. Hagenmeier, S. Jessipow, W. A. König, H. Zähner. *Helv. Chim. Acta.*, **55**, 224 (1972).

herbicidal[90] activity. It is isolated form culture broths of *Streptomyces viridochromegenes* and *Streptomyces hygroscopicus.*[91] 2-APB **119** also exhibits glutamine synthetase activity[92] and shows an inhibitory effect in nerve cell synapses.[93] 2-APB has also been reported to poses antiviral characteristics.[89c] Both 2-APB and phosphinothricine have been synthesized,[94] but efficient asymmetric preparations are unknown. With the chiral butyric acid derivative **107** in hand, the preparation of **118** and **119** would require only a successful Arbusov reaction and deprotection. This sequence was thought to be reasonable since in the formation of **107**, iodide ion selectively displaces the sulfonium salt rather than interacting with the oxazoline ester. The highly nucleophilic phosphorus was expected to show a similar preference for the alkyl halide affording the desired alkyl phosphite. Before the study was undertaken however, the optical purity of iodide **107** was established by independent synthesis. A closer examination of the crude nmr spectra of the reduction product of **95** showed that lactonization had occurred in only some reactions, or upon later chromatography. Therefore the reduction of **95** was repeated with the intention of using the crude alcohol **96** directly. This reaction proved to be a matter of luck since unlactonized alcohol **96** was observed on

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[90] K. Weissermel, H. J. Kleiner, M. Finke, U. H. Felcht. *Angew. Chem. Int. Ed. Engl.*, **20**, 223 (1981).

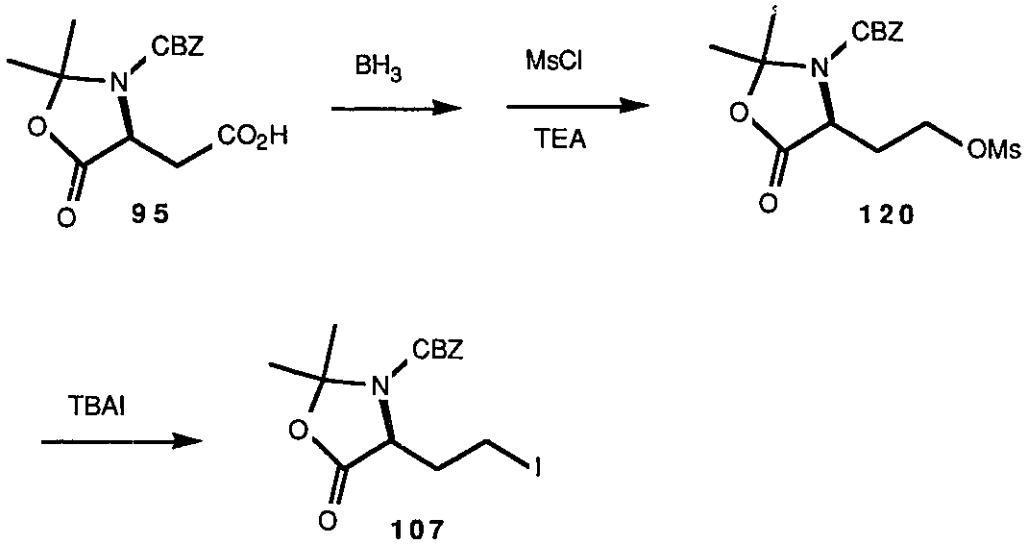
[91] Y. Kondo, T. Shomura, Y. Ogawa, T. Tsuruoka, H. Watanabe, K. Tetsukawa, T. Suzuki, C. Moriyama, J. Yoshida, S. Inoue, T. Niida. *Meiji Seika. Kenkyo Nempo.*, 34 (1973), CA **81**:89705 (1974).

[92] a) B. Lejczak, H. Starzemska, P. Mastalerz. *Experimentia,* **37**, 461 (1981); b) S. G. Cull-Candy, J. F. Donnellan, R. W. James, G. G. Lunt. *Nature*, **262**, 408 (1976); c) W. Chung. *Can. J. Biochem.*, **55**, 332 (1977).

[93] J. F. Koerner, C. W. Cottman. *Brain Research,* **216** 192 (1981).

[94] a) D. Mastalerz. *Acta. Biochim. Polon.*, **4**, 19 (1957); b) J. R. Chambers, A. F. Isbell. *J. Org. Chem.*, **29**, 832 (1964); c) C. Wasielewski, K. Antczak. *Synthesis*, 540 (1981); d) H. Zeiss. *Tetrahedron Lett.*, 1255 (1987); e) E. Gruszecka, P. Mastalerz, M. Soroka. *Roczn. Chem.*, **49**, 2127 (1975); f) H. Gross, T. Cinauk, *J. Prakt. Chem.*, **318**, 157 (1976); g) N. Minowa, S. Fakatsu, T. Niida, M. Takada, S. Sato. *Tetrahedron Lett.*, 2391 (1981); h) E. W. Logusch. *Tetrahedron Lett.*, 5935 (1986); i) N. Minowa, M. Hirayama, S. Fukatsu. *Tetrahedron Lett.*, 1147 (1984); j) J. M. Varlet, G. Fabre, F. Sauveur, N. Collignon. *Tetrahedron*, **37**, 1377 (1981).

average about one time in three. Crude products with promising nmr spectra were treated immediately with methanesulfonyl chloride and triethylamine, and mesylate **120** was prepared in a maximum yield of 35 %. Conversion of this product to iodide **107** was accomplished with tetrabutylammonium iodide in THF[95] resulting in a 36 % yield of **107** which was not optimized. The optical rotation of this product agreed with that of the previously prepared iodide within 1%, thus indicating that the compound was a single enantiomer.




Attempts to effect an Arbusov reaction with **107** and $(BnO)_2P(O)CH_3$, $(EtO)_2$ $P(O)CH_3$[96] or $(MeO)_3P$ were unsuccessful as flash chromatography of the crude materials returned only **107**. These reactions were carried out at 80 °C under a stream of dry nitrogen to remove alkyl iodides. A Michaelis-Becker

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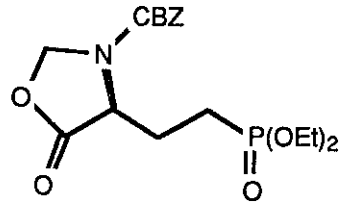
[95] C. H. Heathcock, B. L. Finkelstein, E. T. Jarui, P. A. Radel, C. R. Hadley. *J. Org. Chem.*, **53**, 1922 (1988).

[96] M. M. Campbell, N. I. Carruthers, S. J. Mickel. *Tetrahedron*, **38**, 2513 (1982).

reaction of **107** with sodium diethyl phosphite[97] gave what appeared to be the desired adduct **121** in 47 % yield.




R=Et **121**
R=Bn **122**

This compound displayed resonances in the $^1H$ nmr at δ5.27 and δ5.14 (AB pattern) which were attributed to the benzylic protons. Two multiplets at δ5.27 - 5.25 and δ5.00 - 4.98 were assigned to the oxazoline (C-2) hydrogens, the proton at the α position of the amino acid appeared as a multiplet at δ4.77 - 4.75. The methylene β to the amino acid resonated as a multiplet at δ2.21 - 2.18 with signals for the remaining methylene as multiplets at δ4.27 - 4.09 and δ4.04 - 3.98. The infrared spectrum of this compound was troubling in that no absorbance in the 1800 $cm^{-1}$ region could be seen. This meant that the oxazoline ester could not be intact. A $^{13}C$ spectrum showed several inconsistencies. The C-2 oxazoline carbon, which normally appears at δ68-69 resonated at δ80.76. The methylene carbon which should have been bonded to the phosphorus appeared at δ69.67. Carbons directly bonded to phosphorus normally resonate at δ32 and show an extremely strong carbon phosphorus coupling. For example, the $J_{CP}$ coupling constant for $(EtO)_2P(O)CH_3$ is 144 $H_Z$. The resonance at δ69.67 did show phosphorus coupling, but the coupling constant was small (9.8 $H_Z$). The fact that the α carbon of the amino acid

[97] G. Sturtz. *Bull. Soc. Chim. Fr.* ,2340 (1964).

displayed a strong (13.4 $H_Z$) coupling was strange. Also puzzling was the observance that the intervening methylene (δ32.75) did not couple to phosphorus at all. As anticipated, no resonance at δ170 could be discerned for the oxazoline carbonyl. In fact no resonance could be found for this carbon at all.

Iodide **107** was also found to react with sodium dibenzyl phosphite to give a compound which was analogous to diethyl derivative **121**. This compound, **122**, was initially assumed to posses the structure pictured above for **121**. Compound **122** however was investigated much more thoroughly than **121**. A HOMCOR spectrum showed that the amino acid α proton at δ4.72-4.68 was coupled to a multiplet at δ2.13-2.03, which in turn interacted with a complex signal at δ4.06-3.96. A HETCOR confirmed the earlier analysis that the γ carbon of the amino acid moiety in fact resonated near 70 ppm, but no other useful information was forthcoming. A special $^{13}C$ spectrum was also run using a relaxation delay of one second between transients and a 3μs (28°) pulse in order to enhance signals of carbons possessing long relaxation times. This technique brought out two signals appearing at δ113.55 and δ110.47. Either these are two signals or one resonance with an incredibly large (232 Hz) C-P coupling constant. In any case the position of this signal(s) is in the range of resonances for orthoester or acetal type carbons.

A $^{31}P$ spectrum of this compound (**122**) showed a resonance at δ13.53. The position of this resonance shows conclusively that the structure contains an alkyl phosphite moiety. The observed location of the $^{31}P$ resonance suggests a four co-ordinate phosphorus.[98] On the basis of this, the following structure is proposed for compounds **121a** and **122a**.

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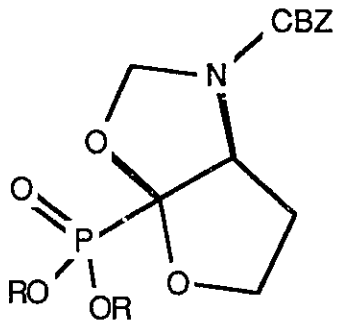
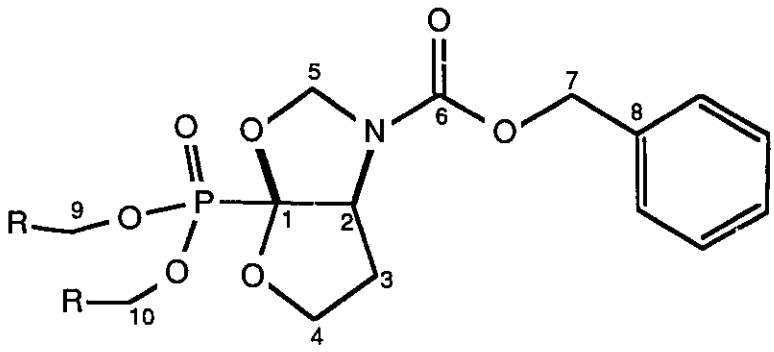
[98] E. Fluck, G. Heckmann, in "Phosphorus - 31 nmr Spectroscopy in Stereochemical Analysis", J. G. Verkade, L. D. Quin ed., VCH Publishers, 1987, pp 61 - 108.




R = Et, **121a**
R = Bn, **122a**

This structure contains the four co-ordinate phosphorus indicated by the $^{31}P$ nmr of **122a** (analog **121a** also shows a similar resonance). As well this structure explains the position of the $^{13}C$ resonance of the former ester carbon (112.01 ppm) and also the large C-P coupling noted for this carbon. Also nicely accounted for is the position of the amino acid $\gamma$ carbon resonance and the C-P coupling observed for the $\alpha$ carbon of the amino acid. A congested structure such as this could also explain why the R groups of the phosphono group are distinguishable by nmr spectroscopy. The $^{13}C$ resonance assignments of **121a** and **122a** are summarized in table 3.

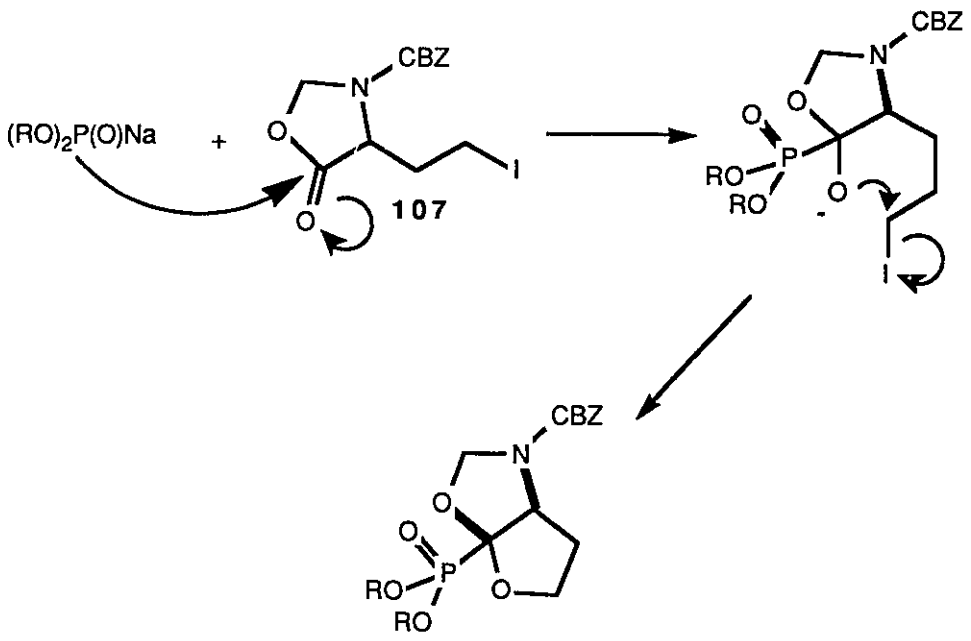
**Table 3**: Table showing the $^{13}C$ resonance assignments for phosphites **121a** and **122a**.




| Carbon | **121a** Resonance | **122a** Resonance |
|---|---|---|
| 1 | NO[a] | 112.01[b] (232)[c] |
| 2 | 63.15 (13.4) | 63.20 (13.3) |
| 3 | 32.75 | 32.73 |
| 4 | 69.67 (9.8) | 69.81 (10.0) |
| 5 | 80.76 | 80.80 |
| 6 | 152.54 | 152.38 |
| 7 | 67.52 | 67.51 |
| 8 | 135.93 | 135.89 |
| 9 | 63.65 (6.7) | 69.06 (6.7) |
| 10 | 63.75 (8.7) | 69.15 (6.9) |

[a] Not Observed
[b] In ppm
[c] $J_{CP}$ in Hz

The formation of these compounds (**121a** and **122a**) would be initiated by nucleophilic reaction of the phosphonate anions with the oxazoline ester in a manner analogous to the process noted previously for **99a**, **109a** and **114a**. However the phosphorus moiety stabilizes the tetrahedral intermediate sufficiently so that collapse to a ketone does not occur. This intermediate must exist long enough for the alkoxide to displace the iodide intramolecularly resulting in the bicyclic products **121a** and **122a**.




Obviously the oxazoline group is much more susceptible to nucleophilic attack than we had expected on the basis of the literature. It survived only the I- treatment of the sulfonium salt in the formation of **107**. Thus the iodide can only be displaced if the amino acid is protected in another manner.

# EXPERIMENTAL

## General Remarks

Melting points were determined by use of a Gallenkamp digital melting point apparatus and are uncorrected. Infrared (ir) spectra were run as films on sodium chloride plates for oils, and in chloroform ($CHCl_3$) or as potassium bromide (KBr) pellets for solids using a Perkin Elmer 783 spectrophotometer. Frequencies are reported in $cm^{-1}$. Mass spectra (ms) were recorded on an AEIMS 9025 instrument. The peak intensities are given as a % of the base peak (100%) intensity.

Proton nmr spectra were taken in deuterochloroform ($CDCl_3$), unless otherwise noted, using a Varian XL-300 300 MHz spectrometer. Spectra run at 60 MHz were obtained on a Varian EM-360 instrument. The chemical shifts are reported in ppm downfield relative to the standard tetramethylsilane ($\delta$ scale). The coupling patterns are noted as singlets (s), doublets (d), triplets (t), quartets (q), doublets of doublets (dd), broad (br) or multiplet (m). In $^{13}C$ spectra, the number of protons attatched to each carbon was determined by DEPT or ADEPT spectra. For convenience this data is reported in terms of the off-resonance decoupled multiplicities one would have observed.

Column chromatography was accomplished using Baker or Terochem 60-200 mesh silica as the adsorbent. Flash chromatography was done using Merck type 9385 silica gel (Terochem). Thin layer chromatography (TLC) was performed on Merck 60 $F_{254}$ and Kieselgel 60 $F_{254}$ precoated silica plates of 0.25 mm thickness and visualized by means of U.V., $I_2$ or by charring.

Purifications by Chromatotron were performed on a Harrison Research Chromatotron model 7924 using silica gel coated rotors (1mm, 2mm, and 4mm thickness). High pressure liquid chromatography (HPLC) was performed on a Waters Prep LC/System 500A. Preparative layer chromatography was done on PSC-Fertigplatten Kieselgel 60 $F_{254}$ plates (25 cm X 25cm X 1 mm ) (Merck 13895).

Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl under a nitrogen atmosphere prior to use. Diisopropylamine, hexamethyldisilazine (HMDS), triethylamine (TEA), hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were distilled from calcium hydride under a nitrogen atmosphere. Dry benzene, ether, hexane and cyclohexane were all prepared by distillation over sodium benzophenone ketyl. Methylene chloride was dried by distillation from phosphorus pentoxide. N-Bromosuccinimide (NBS) was recrystallized from water. Dimethyl sulfoxide (DMSO) was dried by distillation at atmospheric pressure discarding a forerun of c.a. 20 %, followed by sequential storeage over molecular sieves.[99] Butyllithium was used as received from Aldrich after titration with diphenylacetic acid. LDA was prepared by adding the appropriate amount of *n*-butyllithium in hexanes solution to a slight excess of diisopropylamine in THF at -78 °C. Sodium hydride was obtained as a 58 % dispersion and was washed with hexanes prior to use. All other solvents or reagents were distilled or were of reagent grade quality.

Solutions in organic solvents were stripped of solvent with a Buchi evaporator connected to a water aspirator. Unless otherwise indicated all reactions were conducted under an atmosphere of nitrogen.

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[99] D. R. Burfield, R. H. Smithers, *J. Org. Chem.*, **43**, 3966 (1978).

## Chapter 1:

### 4-Phenyl-2-pyrrolidinomethylazetidin-2-one (21)

4-Phenylazetidin-2-one (8.16 g, 55.5 mmol) was refluxed in 45 mL of ethanol containing 6.4 mL of formalin and 5.5 mL of pyrrolidine for 7h. The solvent was then removed under reduced pressure and the residue distilled (155°C/0.8mm) to give 9.6 g (75%) of 4-phenyl-2-pyrrolidinomethylazetidin-2-one **21** as a pale yellow liquid . $^1$H nmr: 7.40-7.36 (m, 5H), 4.72-4.69 (br, 1H), 4.25 (d, $J_{AB}$= 13.12, 1H), 3.59 (d, $J_{AB}$= 13.12, 1H), 3.41 (dd, J=5.25, 14.85, 1H), 2.85 (dd, J=2.40, 15.00, 1H), 2.62-2.55 (m, 4H), 1.76-1.72 (m, 4H); ir ($CHCl_3$): 1748; ms: 230 ($M^+$), 70 (BP) ($M^+$-160).

### *trans*-3-Methyl-4-phenyl-2-pyrrolidinomethylazetidin-2-one (22)

To a solution of 1.2 equivalents of LDA in THF at -78°C was added 3.0 g (13.0 mmol) of 4-phenyl-2-pyrrolidinomethylazetidin-2-one **21** in THF. The resulting deep orange solution was stirred at -78°C for 10 minutes and then 2 mL of MeI was added all at once. This solution was stirred at -78°C for an additional 10 minutes and then quenched with saturated $NH_4Cl$ solution. The mixture extracted with $CH_2Cl_2$, washed with water and dried over $MgSO_4$. Removal of solvent followed by flash chromatography (3 % MeOH in EtOAc) gave 2.2 g of **22** as a pale yellow oil (69%). $^1$H nmr : 7.25 (s, 5H), 4.21 (d, $J_{AB}$=12.90, 1H), 3.55 (d, $J_{AB}$=12.90, 1H), 4.22 (d, J=2.2, 1H), 2.98 (dq, $J_q$=7.4, $J_d$=2.2, 1H), 2.70-2.41 (m, 4H), 1.90=1.52 (m, 4H), 1.41 (d, J=7.4, 3H); ir (thin film): 1750; ms: 244 ($M^+$).

**_cis_-3-Methyl-4-phenyl-2-pyrrolidinomethylazetidin-2-one (24)**

To a solution of 1 equivalent of LDA and 1 equivalent of TMEDA in THF at -78°C was added 117 mg ( 0.48 mmol) of **22** in THF. The solution was stirred for 10 minutes and 0.2 mL of freshly distilled trimethylsilyl chloride was added. Stirring was continued at -78°C for a further 20 minutes. The reaction mixture was quenched with saturated $NH_4Cl$, extracted with ether, washed with water and dried over $MgSO_4$. Flash chromatography (acetone:hexanes, 1:2) gave 38 mg of **24** as a pale yellow oil (33%). $^1H$ nmr : 7.18 (m, 5H), 4.84 (d, J=5.0, 1H), 4.28 (d, $J_{AB}$=13.30, 1H), 3.50 (dq, $J_q$=7.8, $J_d$=5.0, 1H), 3.65 (d, $J_{AB}$= 13.30, 1H), 2.7-2.4 (m, 4H), 1.9-1.6 (m, 4H), 0.78 (d, J=8.0, 3H); ir (thin film): 1745; ms: 244 ($M^+$).

**3,3-Dimethyl-4-phenyl-1-pyrrolidinomethylazetidin-2-one (23)**

Azetidin-2-one **22** (106 mg, 0.43 mmol) in 2 mL of THF was added to a solution of 1 equivalent of LDA in 5 mL THF containing 1 equivalent of TMEDA at -78°C. The reaction mixture was stirred for 20 minutes, 0.2 ml of MeI was added and the resulting solution stirred for a further 20 minutes at -78°C. The reaction mixture was then quenched with saturated $NH_4Cl$, extracted with ether, washed with water and dried over $MgSO_4$. Removal of solvent and flash chromatography (acetone:hexanes, 1:2) gave 40 mg of **23** as a pale yellow oil (36%). $^1H$ nmr : 7.4-7.1 (m, 5H), 4.5 (s, 1H), 4.32 (d, $J_{AB}$= 12.25, 1H), 3.70 (d, $J_{AB}$= 12.25, 1H), 2.7-2.4 (m, 4H), 1.9-1.6 (m, 4H), 1.49 (s, 3H), 0.77 (s, 3H); ir ( thin film):1750; ms: 258 ($M^+$).

**_trans_-3-(1'-Hydroxyethyl)-4-phenyl-2-pyrrolidinomethylazetidin-2-one (25)**

To a solution of 1.2 equivalents of LDA in THF at -78°C was added 3.5 g (15.2 mmol) of 4-phenyl-2-pyrrolidinomethylazetidin-2-one **25** in THF. After stirring at -78°C for 20 minutes, an excess of freshly distilled acetaldehyde was introduced via syringe. The light green solution was stirred at -78°C for an additional 10 minutes and then the reaction was stopped by the addition of saturated $NH_4Cl$ solution. Extraction with $CH_2Cl_2$ followed by drying over $MgSO_4$ gave a yellow syrup after solvent removal. This material was purified by flash chromatography (EtOAc) to give 2.2 g (53%) of **25** as a yellow syrup. $^1H$ nmr: (mixture of two isomers) 7.4-7.3 (m, 10H), 4.8 (d, J=2, 1H), 4.5 (d, J=2, 1H), 4.3-4.1 (m, 4H), 3.65-3.55 (m, 2H), 3.1-3.0 (M, 2H), 2.7-2.5 (m, 8H), 1.8-1.7 (m, 8H), 1.4 (d, J=7, 3H), 1.3 (d, J=7, 3H).

**3-(1'-Methylsulfonylethyl)-4-phenyl-2-pyrrolidinomethylazetidin-2-one (26)**

To a solution of 2.2 g (8.03 mmol) of 3-(1'-hydroxyethyl) derivative **25** in dry $CH_2Cl_2$ at 0°C was added 1.4 mL (9.6 mmol) of TEA followed by 0.62 mL (8.1 mmol) of $CH_3SO_2Cl$. After stirring for 30 minutes, the reaction was washed with water and dried over $MgSO_4$. Removal of the solvent gave 2.44 g (86%) of a yellow foam which was used without further purification. An analytical sample (30 mg) was abtained by flash chromatography (EtOAc) of 80 mg of the crude material. $^1H$ nmr : (mixture of two isomers) 7.4-7.3 (m, 10H), 5.2-5.05 (m, 2H), 4.75 (d, J=2, 1H), 4.7 (d, J=2, 1H), 4.4 (d, $J_{AB}$= 12, 1H), 4.3 (d, $J_{AB}$=12, 1H), 3.21 (d, $J_{AB}$=12, 1H), 3.19 (d, $J_{AB}$=12, 1H), 3.25-3.15 (m, 2H), 3.05 (s, 3H), 3.00 (s,

3H), 2.7-2.5 (m, 8H), 1.8-1.7 (m, 8H), 1.6 (d, J=7, 3H), 1.5 (d, J=7, 3H); ms (Chemical Ionization (CI)) : 353 (22.3) ($M^+$ +1).

**3-Ethylideneazetidin-2-ones (27 and 28)**

A solution of crude mesylate **26** (2.36g, 6.7 mmol) was refluxed in 20 mL of methanol with 1.2 g (13.5 mmol) of $NaHCO_3$ for one hour. The solution was cooled, filtered and stripped of methanol with a rotary evaporator. The residue was take up in $CH_2Cl_2$ and washed with water. After drying over $MgSO_4$ and solvent removal, the remaining material was purified by HPLC (EtOAc:hexanes, 2:1), giving 168 mg (10%) of Z-ene lactam **27** and 150 mg (9%) of E-ene lactam **28**. For **27**: $^1H$ nmr : 7.34-7.21 (m, 5H), 5.46 (dq, $J_d$=1.83, $J_q$=7.25, 1H), 4.93 (s, 1H), 4.32 (d, $J_{AB}$=13.19, 1H), 3.70 (d, $J_{AB}$=13.19, 1H), 2.57-2.49 (m, 4H), 1.96 (d, J=7.44, 3H), 1.7-1.6 (m, 4H); ir (thin film) 1740; ms: 256 (0.8) ($M^+$). For **28**: $^1H$ nmr: 7.37-7.29 (m, 5H) 6.2 (dq, $J_d$=1.52, $J_q$=7.38, 1H), 5.10 (s, 1H), 4.27 (d, $J_{AB}$= 13.59, 1H), 3.70 (d, $J_{AB}$=13.59, 1H), 2.6-2.5 (m, 4H), 1.75-1.70 (m, 4H), 1.50 (d, J=7.27, 3H); ir (thin film) 1740.

**E-3-Ethylidene-4-phenylazetidin-2-one (29)**

A homogeneous mixture of 2 mL of 30% $H_2O_2$ and 10 mL of THF containing 50 mg (0.2 mmol) of **28** was refluxed for one hour. The mixture was then extracted with $CH_2Cl_2$ and dried over $MgSO_4$. Removal of the solvent gave a crude product which was purified by flash chromatography (EtOAC:hexanes, 1:1) affording 30 mg of **29** as a white solid (89 %). $^1H$ nmr : 7.38-7.27 (m, 5H), 6.30 (br, 1H), 6.20 (dq, $J_d$=1.00, $J_q$=7.50, 1H), 5.08 (s, 1H), 2.48 (d, J=7.45, 3H); ir (KBr) 1740; ms : 173 (30.2) ($M^+$).

**3-Vinyl-4-phenyl-1-*p*-methoxyphenylazetidin-2-one (42)**

This material was prepared according to the method of Manhas.[41] Thus 7.0 g of the imine derived from benzaldehyde and *p*-anisidine was refluxed in dry TEA. To this refluxing solution was added 2.7 mL of crotonyl chloride in dry benzene. After refluxing for 7 hours, the solution was cooled and diluted with $CH_2Cl_2$. The resulting suspension was washed with water, dried over $MgSO_4$ and the solvent removed leaving 9.2 g of a black solid. Ether washing gave 2.2 g of **42** as a brown powder. $^1H$ nmr: 7.4-7.2 (m, 8H), 6.8-6.75 (m, 2H), 6.1-6.0 (m, 1H), 5.4-5.3 (m, 2H), 4.75 (d, J=2, 1H), 3.72 (s, 3H), 3.7 (d, J=2, 1H); ir (KBr): 1750; ms : 279 (19) ($M^+$).

**3-Ethylidene-4-phenyl-*p*-methoxyphenylazetidin-2-one (31)**

This product was prepared as described by Manhas.[41] Thus 2.07 g (7.42 mmol) of **42** was stirred in dry $CH_2Cl_2$ at room temperature with 1.0 mL of DBN until TLC (EtOAc:hexanes, 2:1) indicated that no starting material remained (27 h). The solution was then washed with 10% HCl and water and dried. Evaporation of the solvent gave 1.98 g of a tan solid which was recrystallized from ethyl acetate giving a white solid mp 130°C (1.32g, 64%). 50 mg of this material was further purified by flash chromatography (EtOAc:hexanes, 2:1) giving 45.4 mg of the slower eluting Z-3-ethylidene-4-phenyl-1-*p*-methoxyphenylazetidin-2-one **31** mp 154°C and 1.4 mg of the E isomer. For the E isomer: $^1H$ nmr : 7.3-7.2 (m, 8H), 6.8 (d, J=9, 2H), 5.6 (q, J=8, 1H), 5.25 (s, 1H), 3.75 (s, 3H), 2.05 (d, J=8, 3H); ir (KBr) : 1760; ms : 279 (BP) ($M^+$). For the Z

isomer: $^1$H nmr : 7.4-7.2 (m, 8H), 6.75 (d, J=9, 2H), 6.2 (q, J=8, 1H), 5.35 (s, 1H), 3.7 (s, 3H), 1.5 (d, J=8, 3H); ir (KBr): 1760; ms: 279 (69) ($M^+$).

**3-Bromo-3-(1'bromoethyl)-4-phenyl-1-*p*-methoxyphenylazetidin-2-one (32)**

50 mg (0.18 mmol) Of **31** was dissolved in 5 mL of $CH_2CL_2$ and 0.1 mL of a 10% solution of $Br_2$ in $CH_2Cl_2$ was introduced. After stirring at room temperature for 5 hours, TLC indicated that the reaction could be complete. The material was then stripped of solvent and purified by PLC (EtOAc:hexanes, 1:9) to give 64 mg (80%) of **32** as a yellow oil. $^1$H nmr : 7.40-7.25 (m, 9H), 5.22 (s, 1H), 4.56 (q, J=9.5, 1H), 3.75 (s, 3H), 1.90 (d, J=9.5, 3H); ir (thin film) 1740; ms (CI): 439.9 (35.9) ($M^+$ +1).

**Azetidin-2-one (35)**

To an ethanolic solution of 3.44 g of **34** at 0°C was added 1.01 g of $NaBH_4$ and the resulting solution stirred for one hour at 0°C until the evolution of hydrogen had ceased. An excess of acidic Amberlite resin was then added at once and this suspension stirred for 1/2 hour at 0°C. The resin was then filtered off and the ethanol removed under reduced pressure. The resulting white solid was washed with ethyl acetate to remove boron compounds, filtered and the ethyl acetate removed under reduced pressure. This process was repeated with $CH_2Cl_2$ to give 1.60 g (84%) of **35** as white crystals mp 72 °C (lit. mp 73-74°C). [100]

[100] R. W. Holley, A. D. Holley, *J. Am. Chem. Soc.*, **71**, 2129 (1949).

**1-*t*-Butyldimethylsilylazetidin-2-one (37)**

A solution of 1.60 g of **35**, 3.72 g of *t*-butyldimethylsilyl chloride and 3.76 mL of triethylamine in 20 mL DMF was stirred at 0°C for 1/2 hour. The amine hydrochloride was filtered off and 40 mL of water added to the filtrate. This solution was extracted with ether (4 X 50 ml) and the combined ether fractions washed with water. Drying over $MgSO_4$ followed by removal of solvent under reduced pressure gave a pale yellow oil which was distilled (75-77°C/1mm) to give 2.54 g (61%) of **37** as a colorless liquid . $^1H$ nmr : 3.22 (t, J=4.90, 2H), 3.00 (t, J=4.90, 2H), 0.93 (s, 9H), 0.21 (s, 6H); ir (thin film): 1745; ms: 185 ($M^+$), 128 (BP) ($M^+$-57); *Anal.* calcd. for $C_9H_{19}NOSi$: C 58.38, H 10.27, N 7.57; found: C 58.02, H 10.24, N 7.33.

**3-Methylsulfenyl-1-*t*-butyldimethylsilylazetidin-2-one (38)**

**Method A:**

To a solution of 1.2 equivalents of LDA in THF at -78°C was added a solution of 1.5 g (8.11 mmol) of 1-*t*-Butyldimethylsilylazetidin-2-one **37** in THF. After stirring at -78°C for 20 minutes, 0.73 mL (1 equivalent) of methyl disulfide was introduced via syringe. This mixture was stirred at -78°C for 20 minutes and then saturated $NH_4Cl$ was added. The mixture was extracted with ether and washed with water. The 1.8 g of crude product was purified by flash chromatography (EtOAc:hexanes, 1:9) giving 718 mg of disulfide **39** (32 %) eluting with a TLC $R_f$ of 0.50 and 678 mg (27 %) of monosulfide **38** with an $R_f$ of 0.25. For **38**: $^1H$ nmr : 4.15 (dd, J=2.65, 2.99, 1H), 3.51 (t, J=5.74, 1H), 3.10 (dd,

J=3.09, 6.46, 1H), 2.15 (s, 3H), 0.93 (s, 9H), 0.24 (s, 3H), 0.21 (s, 3H); ir (thin film): 1745; ms (CI): 232 (89.5) ($M^+$ +1), 174 (15.2) ($M^+$ -57). For **39** : $^1$H nmr : 3.35 (s, 2H), 2.23 (s, 6H), 0.94 (s, 9H), 0.22 (s, 6H); ir (thin film) : 1745; ms (CI) : 278 (77.8) ($M^+$ +1).

**Method B:**

A solution of the enolate of **37** (764 mg, 4.13 mmol) was prepared as described above. This solution was then transferred via cannula into a THF solution of methyl disulfide which had been precooled to -78°C. Workup as described above gave 424 mg of disulfide **39** (37%) and 349 (36 %) of sulfide **38**.

**3-Methyl-3-methylsulfenyl-1-*t*-butyldimethylsilylazetidin-2-one (40)**

A solution of the enolate of sulfide **38** was prepared by the addition of a THF solution of **38** ( 108 mg, 0.47 mmol) to solution of 1.2 equivalents of LDA in THF at -78°C and 0.05 mL of methyl iodide was added. The reaction was quenched with saturated NH4Cl, extracted with ether and washed with water. Flash chromatography (EtOAc:hexanes, 1:9) of the resulting yellow oil gave 86.2 mg of **40** (75 %) as a clear colorless oil along with 23 mg of recovered **38** (21 %). $^1$H nmr : 3.24 (d, $J_{AB}$=7.20, 1H), 3.18 (d, $J_{AB}$=7.20, 1H), 1.56 (s, 3H), 1.54 (s, 3H), 0.92 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H); ir (thin film) : 1745; ms (CI) : 246 ($M^+$ +1).

**3-(1'-Hydroxypropyl)-3-methylsulfenyl-1-*t*-butyldimethylsilylazetidin-2-one (41)**

A solution of the enolate of **38** (546 mg, 2.36 mmol) was prepared as described above and exposed to 0.24 mL (1.4 equivalents) of freshly distilled propionaldehyde. After stirring for 20 minutes at -78°C, the mixture was quenched with saturated $NH_4Cl$, extracted with ether and washed with water. Flash chromatography (EtOAc:hexanes, 1:5) of the material remaining after drying over $MgSO_4$ and solvent removal gave 648 mg (79%) of **41** as a clear colorless oil (solidifes in refridgerator). $^1H$ nmr : (mixture of isomers) 3.86 (dd, J=2.30, 9.89, 1H), 3.80 (dd, J=5.35, 7.51, 1H), 3.54 (d, $J_{AB}$=6.28, 1H), 3.38 (d, $J_{AB}$=6.84, 1H), 3.07 (d, $J_{AB}$=6.28, 1H), 3.04 (d, $J_{AB}$=6.84, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 1.75 (m, 2H), 1.61 (quintet, J=7.27, 2H), 1.04 (t, J=7.32, 3H), 1.00 (t, J=7.30, 3H), 0.94 (s, 9H), 0.22 (s, 6H); ir (thin film) : 3450, 1725; ms 290 (BP) ($M^+$ +1).

## Chapter 2:

### 4-Ethyl-1-*t*-butyldimethylsilylazetidin-2-one (58)

4-Vinylazetidin-2-one **57** (2.87 g, 13.47 mmol ) was stirred in methanol with 100 mg of 10% Pd/C under $H_2$ at atmospheric pressure until 333 mL of $H_2$ had been consumed ( 2 h). The solution was then filtered and the methanol removed under reduced pressure. The pale yellow oil containing residual catalyst was purified by column chromatography (EtOAc:hexanes, 1:3) to give 91% of **58** as a clear, colorless liquid. $^1$H nmr : 3.5 (m, 1H), 3.07 (dd, J=5.37, 15.22, 1H), 2.56 (dd, J=2.74, 15.22, 1H), 1.86 - 1.83 (m, 1H), 1.44 - 1.40 (m, 1H), 0.94 (s, 9H), 0.87 (t, J=7.44, 1H), 2.01 (s, 3H), 1.99 (s, 3H); ir (thin film): 1750; ms: 213 ($M^+$), 156 (BP) ($M^+$-57); *Anal.* calcd. for $C_{11}H_{23}NOSi$: C 61.97, H 10.80, N 6.57; found C 62.07, H 10.66, N 6.44.

### 3-Methyl-3-vinyl-4-phenyl-1-*p*-methoxyphenylazetidin-2-one (44)

A solution of 3-vinyl-β-lactam **42** (100 mg, 0.36 mmol) in THF was added to a solution of 1.2 equivalents of LDA in THF at -78°C. To the resulting solution was added an axcess of methyl iodide. After stirring at -78°C for 20 minutes, saturated $NH_4Cl$ was added and the solution extracted with ether. After drying over $MgSO_4$ and solvent removal, column chromatography (EtOAc:hexanes, 1:7) gave 63 mg (75%) of a yellow oil identified as **44**. $^1$H nmr : 7.39-7.19 (m, 5H), 7.56 (d, $J_{AB}$=9.87, 2H), 6.56 (d, $J_{AB}$=9.87, 2H), 5.42-5.25 (m, 2H), 5.02 (dd, J=2.64, 9.58, 1H), 4.85 (s, 1H), 3.76 (s, 3H), 1.65 (s, 3H); ms : 293 (19.7) ($M^+$).

**General procedure for the preparation of 3-trimethylsilyl-1-*t*-butyldimethylsilylazetidin-2-ones: 50, 59, 61.**

A solution of *t*-butyldimethylsilylazetidin-2-one (**35, 58, 60**) in THF was added to 1.2 equivalents of LDA generated in situ from diisopropylamine and *n*-butyllithium (ca. 2.5N in hexane) in THF at -78°C. After 10 minutes, 1.2 equivalents of freshly distilled trimethylsilyl chloride was introduced and the mixture stirred at -78°C for an additional 10 to 20 minutes. The solution was then quenched with saturated $NH_4Cl$ and extracted twice with ether. The combined extracts were washed with $H_2O$ and dried over $MgSO_4$ before the solvent was removed under reduced pressure.

**3-Trimethylsilyl-1-*t*-butyldimethylsilylazetidin-2-one (50)**

1.07 g (5.82 mmol) of **35** was treated as described above to give 1.49 g (96%) of **50** as a clear colorless oil . This material was used without further purification. $^1$H nmr : 3.26 (t, J=5.93, 1H), 2.94-2.86 (m, 2H), 0.92 (s, 9H) 0.19 (s, 3H), 0.18 (s, 3H), 0.09 (s, 9H); ir (thin film ): 1730; ms: 257 ($M^+$), 242 ($M^+$-15), 200 ($M^+$-57).

**3-Trimethylsilyl-4-ethyl-1-*t*-butyldimethylsilylazetidin-2-one (59)**

Compound **58** (525 mg, 2.46 mmol) gave 585 mg (83%) of **59** after flash chromatography (EtOAc:hexanes, 1:7). $^1$H nmr : 3.21-3.18 (m, 1H), 2.42 (d, J=2.63, 1H), 1.90-1.80 (m, 1H), 1.40-1.30 (m, 1H), 0.93 (s, 9H), 0.85 (t, J= 7.44, 3H), 0.18 (s,3H), 0.17 (s, 3H), 0.09 (s, 9H); ir (thin film): 1730; ms (CI): 286 (BP)

($M^+$+1); *Anal.* calcd. for $C_{14}H_{31}NOSi$: C 58.95, H 10.88, N 4.91; found: C 59.23, H 10.69, N 4.63.

**3-Trimethylsilyl-4-thiophenyl-1-*t*-butyldimethylsilyl-azetidin-2-one (61)**

Azetidin-2-one **60** (1.04 g, 3.65 mmol) gave 980 mg (75%) of **61** after flash chromatography (EtOAc:hexanes, 1:25) (75%). $^1H$ nmr : 7.46-7.43 (m, 2H), 7.34-7.30 (m, 3H), 4.64 (d, J=2.38, 1H), 2.89 (d, J=2.39, 1H), 0.98 (s, 9H), 0.25 (s, 3H), 0.23 (s, 3H), -0.03 (s, 9H); ir (thin film ): 1740, 1580; ms (CI): 366 (BP) ($M^+$ +1), 256 (72) ($M^+$ -110); hrms calcd. for $C_{12}H_{26}NOSi$: 256.1552; found 256.1532 ($M^+$-109).

**3-Trimethylsilyl-4-phenyl-1-pyrrolidinomethylazetidin-2-one (47)**

Azetidin-2-one **21** (510 mg, 2.22 mmol) gave 669 mg of **47** as yellow waxy crystals (65 %). Recrystallization gave a white powder. $^1H$ nmr : 7.4 -7.2 (m, 5H), 4.3 (d, J=2, 1H), 4.2-4.15 (m, 4H), 2.8 (d, J=2, 1H), 2.7-2.6 (m, 4H), 1.9-1.7 (m, 4H), 0.2 (s, 9H); ms : 302 (0.2) ($M^+$).

**3-Trimethylsilyl-4-phenyl-1-*t*-butyldimethylsilylazetidin-2-one (49)**

Compound **48** ( 110 mg, 0.42 mmol) gave silyl derivative **49** in 62 % yield (87.5 mg) after column chromatography (EtOAc:hexanes, 1:15) as a white solid. Recrystallization from MeOH/$H_2O$ gave a solid melting at 72°C. $^1H$ nmr : 7.33-7.31 (m, 5H), 4.26 (d, J=2.63, 1H), 2.79 (d, J=2.81, 1H), 0.88 (s, 9H), 0.14 (s, 12H), -0.16 (s, 3H); ir (KBr) : 1750; ms (CI) : 334 (BP) ($M^+$ +1), 276 (28.4) ($M^+$-

57); *Anal.* calcd. for $C_{18}H_{31}NOSi_2$: C 64.86, H 9.31, N 4.20; found : C 64.53, H 9.56, N 4.08.

**General procedure for the preparation of 3-alkylideneazetidine-2-ones (51-54, 62-67, 70, 71).**

To a solution of 1.2 equivalents of LDA in THF (prepared as above) was added a solution of 3-trimethylsilyl-1-*t*-butyldimethylsilylazetidin-2-one (**50**, **59**, **61**) in THF at -78°C. After stirring for 10 minutes, 1.5 equivalents of aldehyde was added to the golden yellow solution via syringe. The resulting mixture was stirred for 10 to 20 minutes and then quenched with saturated $NH_4Cl$, extracted twice with ether, washed with water and dried over $MgSO_4$. Removal of solvent under reduced pressure gave a syrup which was purified by flash chromatography. In all cases, the Z- isomers **51**, **53**, **62**, **64**, **66**, **70** were eluted before the E-isomers **52**, **54**, **63**, **65**, **67**, **71**.

From 664 mg of **50** and 50% excess propionaldehyde was obtained 203 mg (33%) of **51** and 181 mg (31%) of **52** as clear colorless oils. For **51:** $^1H$ nmr : 5.52 (t, J=8.4, 1H), 3.60 (s, 2H), 2.48 (quint, J= 8.5, 2H), 1.02 (t, J=8.4, 3H), 0.92 (s, 9H), 0.20 (s, 6H); ir (thin film): 1730; ms: 225.1 ($M^+$), 168 (BP) ($M^+$-57); *Anal.* calcd. for $C_{12}H_{25}NOSi$: C 64.00, H 10.22, N 6.22; found C 64.12, H 10.08, H 6.19. For **52**: $^1H$ nmr : 6.11 (t, J=7.5, 1H), 3.75 (s, 2H), 2.10 (quint, J=7.5, 2H), 1.05 (t, J=7.5, 3H), 0.95 (s, 9H), 0.24 (s, 6H); ir (thin film): 1740; ms: 225.1 ($M^+$), 168 (BP) ($M^+$-57); *Anal.* calcd. for $C_{12}H_{23}NOSi$: C 64.00, H 10.22, N 6.22; found C 64.09, H 10.29, N 6.07.

From 164 mg of **50** and 50% excess hydrocinnamaldehyde was obtained 57.2 mg (35%) of **53** and 38.6 mg (23%) of **54**, both as clear

colorless oils. For **53**: $^1$H nmr : 7.29-7.16 (m, 5H), 5.54 (t, J=8.5, 1H), 3.59 (s, 2H), 2.84-2.75 (m, 4H), 0.93 (s, 9H), 0.22 (s, 6H); ir ($CH_2Cl_2$) 1720; ms: 301 ($M^+$), 244 (89.2) ($M^+$-57); hrms calcd. for $C_{18}H_{27}NOSi$: 301.1860; found 301.1870. For **54**: $^1$H nmr : 7.24-7.09 (m, 5H), 6.08 (t, J=8.3, 1H), 3.44 (s, 2H), 2.71 (t, J=8.4, 2H), 2.31 (q, J=8.4, 2H), 0.87 (s, 9H), 0.16 (s, 6H); ir ($CH_2Cl_2$): 1730; ms: 301 ($M^+$), 244 (BP) ($M^+$-57); *Anal.* calcd. for $C_{18}H_{27}NOSi$: C 71.76, H 8.97, N 4.65; found C 71.89, H 9.11, N 4.93.

From 547mg of **59** and 50% excess propionaldehyde was obtained 180 mg (37%) of **62** and 145 mg (30%) of **63**, both as clear colorless oils. For **62**: $^1$H nmr : 5.53 (dt, J=1.08. 7.70, 1H), 3.91 (dd, J= 2.39, 8.30, 1H), 2.48 (quint, J= 7.65, 2H), 1.80-1.77 (m, 1H), 1.60-1.53 (m, 1H), 1.03 (t, J=7.52, 3H), 0.95 (s, 9H), 0.93 (t, J=7.46, 3H), 0.24 (s, 3H), 0.19 (s, 3H); ir (thin film): 1735; ms: 253 ($M^+$), 196.1 (BP) ($M^+$-57); *Anal.* calcd. for $C_{14}H_{27}NOSi$: C 66.40, H 10.67, N 5.53; found C 62.66, H 11.01, N 5.56. For **63**: $^1$H nmr : 6.03 (dt, J=1.50, 7.66, 1H), 4.25 (b, 1H), 2.06 (quint, J=7.56, 2H), 1.82-1.74 (m, 2H), 1.03 (t, J=7.52, 3H), 0.948 (s, 9H), 0.90 (t, J=7.37, 3H), 0.27 (s, 3H), 0.18 (s, 3H), ir (thin film): 1740; ms: 253 ($M^+$), 196 (BP) ($M^+$-57); hrms calcd. for $C_{14}H_{27}NOSi$: 253.1860; found 253.1850.

From 214 mg of **59** and 50% excess hydrocinnamaldehyde was obtained 114 mg (46%) of **64** and 73 mg (29%) of **65**, both as clear colorless oils. For **64**: $^1$H nmr : 7.27 (m, 5H), 5.22 (t, J=7.2, 1H), 3.84 (m, 1H), 2.81-2.75 (m, 4H), 1.75-1.70 (m, 1H), 1.45-1.40 (m, 1H), 0.94 (s, 9H), 0.869 (t, J=7.4, 3H), 0.23 (s, 3H), 0.19 (s, 3H); ir (thin film): 1730; ms: 329 ($M^+$), 272 (16) ($M^+$-57); *Anal.* calcd. for $C_{20}H_{31}NOSi$: C 72.95, H 9.42, N 4.26; found C 72.25, H 9.56, N 4.35. For **65**: $^1$Hnmr : 7.29-7.20 (m, 5H), 6.06 (t, J=7.8, 1H), 4.02 (s, 1H), 2.76-2.69 (m, 2H), 2.37-2.33 (m, 2H), 0.93 (s, 9H), 0.811 (t, J=7.41, 3H), 0.24 (s, 3H),

0.16 (s, 3H); ir (thin film): 1740; ms: 329 ($M^+$), 272 (BP) ($M^+$-57); hrms calcd. for $C_{16}H_{22}NOSi$: 272.1469; found 272.1492 ($M^+$-57).

From 340 mg of **61** and 50% excess propionaldehyde was obtained 45 mg (15%) of **66** and 43 mg (14%) of **67**, both as clear colorless oils. Eluting in the fastest fractions was 102 mg (30%) of **68**, which was recrystalized from methanol, mp 102°C. For **66**: $^1H$ nmr : 7.43-7.27 (m, 5H), 5.52 (t, J=9.3, 1H), 5.30 (s,1H), 2.34 (quint, J=9.0, 2H), 0.97 (s, 9H), 0.91 (t, J=7.51, 3H), 0.30 (s, 3H), .025 (s, 3H); ir (thin film): 1740; ms (CI): 334 ($M^+$+1), 224 (60) ($M^+$-109); *Anal.* calcd. for $C_{18}H_{27}NOSSi$: C 64.86, H 8.11, N 4.20; found C 64.69, H 8.35, N 4.20. For **67**: $^1H$ nmr : 7.43-7.38 (m, 2H), 7.29-7.27 (m, 3H), 5.98 (t, J=8.0, 1H), 5.40 (s, 1H), 2.17 (quint, J=8.03, 2H), 0.99 (t, J=7.45, 3H), 0.96 (s, 9H), 0.30 (s, 3H), 0.25 (s, 3H); ir (thin film): 1750; ms (CI): 334 ($M^+$+1), 224 (63) ($M^+$-109); hrms calcd. for $C_{12}H_{22}NOSi$ 224.1469; found 224.1493 ($M^+$-109). For **68**: 1H nmr : 9.0 (br, 1H), 7.45-7.36 (m, 5H), 6.77 (d, J= 15.25, 1H), 0.86 (s, 9H), 0.30 (s, 9H), 0.14 (s, 3H); ir ($CHCl_3$): 3600, 1605, 1551; ms (CI): 366 $M^+$+1; hrms calcd. for $C_{12}H_{26}NOSi_2$ 356.1552; found 256.1532 ($M^+$-109).

From 468 mg of **61** and 50% excess hydrocinnamaldehyde was obtained 81 mg (15%) of **70** and 61 mg (12%) of **71** both as clear colorless oils. 127 mg of **68** (27%) was also obtained in the fastest fractions. For **70**: $^1H$ nmr : 7.42-7.36 (m, 5H), 7.28-7.20 (m, 5H), 5.54 (t, J=7.8, 1H), 5.24 (s, 1H), 2.83-2.73 (m, 4H), 0.96 (s, 9H), 0.29 (s, 3H), 0.245 (s, 3H); ir (thin film): 1740; ms (CI): 410 ($M^+$+1), 300 (BP) ($M^+$-109); hrms calcd. for $C_{18}H_{26}NOSi$ 300.1782; found 300.1760 ($M^+$-109). For **71**: $^1H$ nmr : 7.42-7.36 (m, 10H), 6.00 (t, J=8.1, 1H), 4.98 (s, 1H), 2.80-2.45 (m, 4H), 0.93 (s, 9H), 0.26 (s,3H) 0.22 (s, 3H); ir (thin film): 1750; ms (CI): 410 ($M^+$+1), 300 (BP) ($M^+$-109); hrms calcd. for $C_{18}H_{26}NOSi$ 300.1782; found 300.1775 ($M^+$-109).

**General procedure for MoOPH hydroxylations**

To a solution of LDA (1.2 equivalents) in THF at -78°C was added a solution of 3-alkylidene-1-*t*-butyldimethylsilylazetidin-2-one **42, 51, 53, 62, 64** in THF. After stirring for 10 minutes, 1.5 equivalents of MoOPH was added at once. The solutions immediately turned orange or blue. Following MoOPH addition, the acetone bath was removed and the solution stirred until clear (10-15 min). Once MoOPH dissolution was complete, the solution was quenched with a 10% $Na_2SO_3$, extracted twice with ether, washed with 10% HCl, dried over $MgSO_4$ and the solvent removed under reduced pressure. Products were purified by flash chromatography.

**45** : From 100 mg of **42** was obtained 71 mg (67%) of **45** as a white solid which was recrystallized from ethyl acetate mp = 145°C. $^1$H nmr : 7.33-7.17 (m, 5H), 7.24 (d, $J_{AB}$=9.07, 2H), 6.78 (d, $J_{AB}$=9.07, 2H), 5.59 (dd, $J_{AB}$=17.34, $J_{AX}$=11.10, 1H), 5.47 (dd, $J_{AB}$= 17.34, $J_{BX}$=0.92, 1H), 5.18 (dd, $J_{AX}$=11.10, $J_{BX}$=0.92, 1H), 5.10 (s,1H), 3.74 (s, 3H); ir (thin film): 3600, 1750; ms: 295 (M+); hrms calcd. for $C_{18}H_{17}NO_3$: 295.1207; found 295.1244.

**55**: From 95 mg of **51** was obtained 41.2 mg (41%) of **55** as a clear colorless oil. $^1$H nmr : 5.96 (dq, $J_q$= 6.47, $J_d$=15.50, 1H), 5.67 (dd, J=1.74, 15.50, 1H), 3.33 (d, $J_{AB}$=6.05, 1H), 3.28 (d, $J_{AB}$=6.05, 1H), 1.73 (dd, J=1.59, 6.47, 3H), 0.93 (s, 9H), 0.24 (s, 3H), 0.21 (s, 3H); ir ($CH_2Cl_2$): 3550, 1642; ms (CI): 242 (BP) ($M^+$+1); *Anal.* calcd. for $C_{12}H_{23}NO_2Si$: C 59.75, H 9.54, N 5.81; found C 59.86, H 9.56, N 6.00.

**56**: From 161.5 mg of **53** was obtained 52 mg (31%) of **56** as a clear colorless oil. $^1$H nmr : 7.29-7.14 (m, 5H), 6.12 (dt, $J_d$=15.57, $J_t$=6.75, 1H), 5.72 (dt, $J_d$= 15.54, $J_t$=1.54, 1H), 3.41 (dd, J=6.05, 2H), 3.34 (d, $J_{AB}$=6..11, 1H), 3.30

(d, $J_{AB}$=6.11, 1H), 2.78 (s, 1H), 0.91 (s, 9H), 0.24 (s, 3H), 0.21 (s, 3H); ir ($CHCl_3$): 3500, 1740; ms (CI): 318 ($M^+$); *Anal.* calcd. for $C_{18}H_{27}NO_2Si$: C 68.14, H 8.52, N 4.42; found C 67.99, H 8.93, N 4.38.

**72**: From 159 mg of **62** was obtained 90 mg (53%) of **72** as a white solid mp = 99°C. Recrystallization from hexanes did not change the melting point. $^1H$ nmr : 5.95 (dq, $J_d$=15.62, $J_q$=6.53, 1H), 5.59 (dd, J=1.65, 15.62, 1H), 3.45 (dd, J=3.17, 11.45, 1H), 2.64 (s, 1H), 1.77 (dd, J=1.60, 6.51, 3H), 1.7-1.6 (m, 1H), 1.5-1.4 (m,1H), 0.94 (s, 9H), 0.88 (t, J=7.35, 3H), 0.25 (s, 3H), 0.22 (s, 3H); ir ($CHCl_3$): 3500, 1740; ms: 269 ($M^+$), 212 (9.3) ($M^+$-57); *Anal.* calcd. for $C_{14}H_{27}NO_2Si$: C 62.45, H 10.04, N 5.20; found C 62.65, H 10.22, N 5.20.

**73**: From 290 mg of **64** was obtained 100 mg (33%) of **73** as a white solid which was recrystallized from hexane mp = 101°C. $^1H$ nmr : 7.30-7.21 (m, 5H), 6.11 (dt, $J_d$=15.56, $J_t$=6.62, 1H), 5.61 (dt, $J_d$=15.61, $J_t$=1.55, 1H), 3.48-3.42 (m, 3H), 2.60 (s, 1H), 1.7-1.6 (m, 1H), 1.4-1.3 (m, 1H), 0.92 (s, 9H), 0.86 (t, J=7.41, 3H), 0.24 (s, 3H), 0.21 (s, 3H); ir ($CHCl_3$): 3300, 1730; ms: 345 ($M^+$), 288 (10) ($M^+$-57); *Anal.* calcd. for $C_{20}H_{31}NO_2Si$: C 69.56, H 8.98, N 4.06; found C 69.30, H 8.98, N 3.92.

### 3-Ethyl-3-hydroxy-4-phenyl-1-(4-methoxyphenyl)-azetidin-2-one (46)

71 mg of **45** in THF was stirred with 21 mg of 10% $PtO_2$ under an atmosphere of $H_2$ at atmospheric pressure for 1 hour. The solution was then filtered through a pad of celite and the solvent removed under reduced pressure to give 73mg (100%) of **46** as a white solid melting at 130°C. Recrystallization from ethyl acetate did not change the melting point. $^1H$ nmr : 7.33-7.23 (m, 5H), 7.21 (d, $J_{AB}$= 9.04, 2H), 6.77 (d, $J_{AB}$=9.04, 2H), 4.99 (s, 1H), 3.73 (s, 3H), 1.57

(sextet, J=7.45, 1H), 1.37 (sextet, J=7.27, 1H), 0.84 (t, J=7.45, 3H); $^{13}C$ nmr : 168.68 (s), 156.20 (s), 134.27 (s), 130.45 (s), 128.67 (d), 128.25 (d), 126.98 (d), 119.15 (d), 114.19 (d), 87.93 (s), 69.50 (d), 55.33 (q), 25.08 (t), 6.84 (q); ir (KBr): 3400, 1720; hrms calcd. for $C_{18}H_{19}NO_3$: 297.1363; found 297.1367.

**N-Phthalimidoallylglycine (74)**

A mixture of 100 mg ( 0.87 mmol) of d,l-allylglycine, 148 mg phthalic anhydride and 0.14 mL triethylamine was refluxed in benzene. Water was removed using a Soxlith loaded with activated molecular sieves. After refluxing for 36 h, the solvent was replaced by EtOAc, and the solution washed with 10 % HCl, dried over $MgSO_4$ and stripped of solvent giving 215 mg of white crystals. Hexanes washing gave 208 mg (98 %) of **74** as white crystals mp 109-110°C. $^1H$ nmr : 7.86-7.69 (m, 4H), 5.77-5.64 (m, 1H), 5.10-4.96 (m, 3H), 3.94-3.84 (m, 2H); ir ($CH_2Cl_2$) : 1722, 1778; ms : 245 (6.4) ($M^+$).

**Allylglycine benzyl ester hydrotosylate (76)**

A suspension of 486 mg (4.23 mmol) of allylglycine and 817 mg (4.40 mmol) *p*-toluenesulfonic acid monohydrate was refluxed in benzene containing 2 mL of benzyl alcohol using a Soxlith loaded with molecular sieves to remove water. After 48 h the suspension had cleared indicating that the reaction was complete. Benzene was then removed and the resulting syrup washed 3 times with 15 mL portions of a hexanes:dry ether, 14:1 mixture to remove excess benzyl alcohol. The residue was diluted with $CH_2Cl_2$ and hexanes added until the mixture was cloudy. Cooling to 0°C gave cream colored crystals which were washed with anhydrous ether affording 1.32 g (90 %) of ester **76** as

white powder mp 102-103 °C. $^1$H nmr : 8.24 (s, 1H), 7.70 (d, $J_{AB}$=9.0, 2H), 7.29-7.22 (m, 5H), 7.08 (d, $J_{AB}$=9.0, 2H), 5.59-5.48 (m, 1H), 5.11 (d, $J_{AB}$=11.7, 1H), 5.00 (d, $J_{AB}$=11.7, 1H), 5.08-4.96 (m, 2H), 4.10-4.00 (m, 1H), 2.57 (t, J=2.0, 2H), 2.28 (s, 3H).

**N-Phthaloyl allylglycine benzyl ester (75)**

**Method A:**

N-Phthalimidoallylglycine **74** (204 mg, 0.83 mmol) and 1/2 mL of benzyl alcohol were refluxed in benzene with a catalytic amount of PTS using a Dean-Stark to remove water. After 18 h, the reaction mixture was stripped of solvent and purified by flash chromatography (EtOAc:hexanes, 1:4) which delivered 114 mg (41 %) of **75** as a clear colorless oil. $^1$H nmr : 7.83-7.69 (m, 4H) 7.30-7.24 (m, 5H), 5.78-5.63 (m, 1H), 5.20 (d, J=12.3, 1H), 5.16 (d, J=12.3, 1H), 5.08-4.96 (m, 2H), 3.05-2.96 (m, 2H); ir ($CH_2Cl_2$) : 1720, 1778; ms (CI) : 336 (BP) ($M^+$ +1).

**Method B:**

A mixture of 150 mg (0.40 mmol) of **76**, 100 mg phthalic anhydride (0.64 mmol) and 0.60 mL triethylamine was refluxed in benzene with azeotropic water removal. After 24 h the solution was cooled, stripped of solvent and purified by flash chromatography affording 122 mg of **75** (92 %).

**Benzyl N-phthaloyl-4-oxo-butanoate (77)**

A solution of **75** (119 mg, 0.36 mmol) in $CH_2Cl_2$ was prepared and cooled to -78°C. This solution was then treated with $O_3$ until saturated (blue color). Excess ozone was removed by the passage of nitrogen and the ozonide decomposed by the addition of 1 mL of dimethyl sulfide. The solution was then warmed to room temperature, the solvent removed and the resulting yellow syrup purified by flash chromatography (EtOAc:hexanes, 1:3) to give 89 mg (75 %) of **77** as a clear colorless oil. $^1$H nmr : 9.77 (t, J=0.84, 1H), 7.86-7.71 (m, 4H), 7.30-7.21 (m, 5H), 5.52 (dd, $J_{AX}$=7.87, $J_{BX}$=5.94, 1H), 5.17 (m, 2H), 3.52 (ddd, $J_{AB}$=18.44, $J_{AX}$=7.87, J=0.89, 1H), 3.30 (ddd, $J_{AB}$=18.44, $J_{BX}$=5.94, J=0.89, 1H); ir (thin film) : 1720, 1745, 1775; ms (CI) : 338 (BP) ($M^+$).

**Peterson coupling of (77) and β-lactam (50)**

A solution of the enolate of **50** (127 mg, 0.49 mmol) was prepared as described above and 151 mg (0.49 mmol) of aldehyde **77** was added. Workup as described above gave 46 mg of a mixture of **78** and **79** after flash chromatography (EtOAc:hexanes, 1:3). This mixture was further purified by PLC giving 11 mg of **79** (3 %) eluting first and 12 mg (4 %) of **78**. For **78** : $^1$H nmr : 7.86-7.80 (m, 2H), 7.72-7.68 (m, 2H), 7.28 (s, 5H), 5.56 (t, J=8.1, 1H), 5.23 (d, $J_{AB}$=12.6, 1H), 5.15 (d, $J_{AB}$=12.6, 1H), 4.99 (dd, J=9.6, 3.0, 1H), 3.55 (d, $J_{AB}$=8.4, 1H), 3.51 (d, $J_{AB}$=8.4, 1H), 3.4-3.3 (m, 2H), 0.80 (s, 9H), 0.12 (s, 6H); ms (CI) : 505 (49) ($M^+$ +1). For **79** : $^1$H nmr : 9.06 (d, J=7.8, 1H), 7.78 (d, J=9.0, 1H), 7.62 (t, J=8.7, 1H), 7.50 (t, J=8.4, 1H), 5.00 (dd, J=12.0, 6.0, 1H), 4.42 (dd, J=12.0, 9.6, 1H), 4.11 (d, $J_{AB}$=7.8, 1H), 3.98 (d, $J_{AB}$=7.8, 1H), 3.78 (d, $J_{AB}$=6.3, 1H), 3.07

(d, $J_{AB}$=6.3, 1H), 2.62-2.36 (m, 2H), 0.95 (s, 9H), 0.93 (s, 9H), 0.37-0.12 (m, 21H); ms (CI) : 655 ($M^+$ +2).

**N-Isoindonylglycine (8)**

200 mg (0.59 mmol) Of glycine benzyl ester hydrotosylate was refluxed in $CH_3CN$ with 104 mg of α,α'-dichloro-o-xylene (0.60 mmol) and 0.33 mL ($i$-Pr)$_2$NEt (1.30 mmol) for 90 minutes. The solution was then stripped of solvent and the residue taken up in $CH_2Cl_2$, washed with water, dried over $MgSO_4$ and $CH_2Cl_2$ removed. Purification by chromatotron (EtOAc:hexanes, 1:7) gave **80** as a colorless oil (60 mg, 38 %). $^1$H nmr : 7.36-7.32 (m, 5H), 7.17 (2, 4H), 5.18 (s, 2H), 4.12 (s, 4H), 3.65 (s, 2H); ms : 276 (2.5) ($M^+$), 176 (26.5) ($M^+$ - 91).

**Benzyl N,N-dibenzylglycine (81)**

4.0 g Of glycine benzyl ester hydrotosylate (11.9 mmol) was suspended in $CH_3CN$ with 450 mg benzyl bromide (24.9 mmol) and 500 mg ($i$-Pr)$_2$NEt (40 mmol). This mixture was refluxed for one hour and then $CH_3CN$ removed . The residue was taken up in $CH_2Cl_2$, washed with water, dried over $MgSO_4$ and the solvent removed giving 4.10g (100 %) of **81** as a colorless oil. An analytical sample was obtained by chromatotron chromatography (EtOAc:hexanes, 3:97). $^1$H nmr : 7.35-7.19 (m, 15H), 5.11 (s, 2H), 3.80 (s, 4H), 3.32 (s, 2H); $^{13}$C nmr : 170.90 (s), 138.68 (s), 135.66 (s), 128.67 (d), 128.32 (d), 128.17 (d), 128.06 (d), 127.55 (d), 126.98 (d), 65.86 (t), 57.63 (t), 56.36 (t); ms : 345 (3.2) ($M^+$), 254 (27) ($M^+$ - 91).

**Benzyl N, N-dibenzyl-2-amino-4-pentenoate (82)**

A solution of benzyl N,N-dibenzylglycine **81** (4.0 g, 11.6 mmol) in THF was added to 1.2 equivalents of LDA in THF at -78°C. After 15 minutes, 2.0 g (one equivalent) of allyl iodide was added in one portion. The mixture was stirred at -78°C for an additional 20 minutes, then saturated $NH_4Cl$ was added. Extraction with ether gave a crude product which was purified by flash chromatography (EtOAc:hexanes, 2:98) giving 2.63 g (59 %) of **82** as a colorless oil. $^1H$ nmr : 7.41-7.16 (m, 15H), 5.74-5.63 (m, 1H), 5.22 (d, $J_{AB}$=12.26, 1H), 5.13 (d, $J_{AB}$=12.26, 1H), 5.04-4.98 (m, 2H), 3.88 (d, $J_{AB}$=13.89, 2H), 3.50 (d, $J_{AB}$=13.89, 2H), 3.46 (t, J=7.95, 1H), 2.54-2.48 (m, 2H); $^{13}C$ nmr : 172.07 (s), 139.39 (s), 135.98 (s), 134.86 (d), 128.77 (d), 128.52 (d), 128.41 (d), 128.31 (d), 128.13 (d), 126.92 (d), 116.95 (t), 72.76 (t), 66.06 (t), 60.83 (d), 34.07 (t); ir (thin film) : 1730; ms (CI) : 386 (BP) ($M^+$ +1).

**Benzyl N-(benzyloxycarbonyl)-2-amino-4-pentenoate (84)**

A solution of N-benzyloxycarbonyl-allylglycine (3.77 g, 15.14 mmol) (prepared from d,l-allylglycine in 87 % yield), 2.5 g benzyl alcohol (23 mmol) and 200 mg PTS was refluxed in benzene using a Dean-Stark apparatus to remove water. After 4h, no more water was being collected and so the reaction was cooled, washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Removal of solvent gave 5.4 g of a colorless liquid which was purified by flash chromatography giving 3.7 g (72 %) of **84** as a colorless oil. $^1H$ nmr : 7.33 (s, 10H), 5.66-5.54 (m, 1H), 5.29-5.02(m, 8H), 4.50-4.45 (m, 1H), 2.57-2.49 (m, 2H); $^{13}C$ nmr : 171.40 (s), 155.60 (s), 136.14 (s), 135.17 (s), 131.79 (d), 128.54 (d),

128.46 (d), 128.28 (d), 128.11 (d), 128.03 (d), 119.43 (t), 67.24 (t), 67.04 (t), 53.40 (d), 37.78 (t); ir (thin film) : 3350, 1730, 1720; ms (CI) : 340 (96) ($M^+$ +1).

**Benzyl N-(benzyloxycarbonyl)-2-amino-4-oxo-butanoate (85)**

300 mg (0.88 mmol) of **84** was dissolved in $CH_2Cl_2$ and cooled to -78°C. $O_3$ was passed through the solution until it was saturated (blue color). Excess ozone was removed by $N_2$ flushing and then 1/2 mL of DMS was added. After stirring at -78°C for 1/2 h the solution was warmed to room temperature and the solvent removed. Flash chromatography (EtOAc:hexanes, 1:3) gave 154 mg (51 %) of **85** as a colorless oil. $^1H$ nmr : 9.69 (s, 1H), 7.36-7.26 (m, 10H), 5.70-5.65 (m, 1H), 5.19-5.08 (m, 4H), 4.68-4.60 (m, 1H), 3.15-3.06 (m, 2H); $^{13}C$ nmr : 198.87 (d), 170.35 (s), 155.60 (s), 135.94 (s), 134.93 (s), 128.56 (d), 128.47 (d), 128.33 (d), 128.22 (d), 128.18 (d), 128.02 (d), 67.73 (t), 67.22 (t), 49.24 (d), 45.86 (t); ir (thin film): 3350, 1740, 1700; ms (CI) : 342 (74.2) ($M^+$ +1).

## Chapter 3:

### Methyl methacrylic oxide (87)

Freshly distilled methyl methacrylate (10.0 g, 0.1 mmol) was refluxed in dichloroethane with 20 g (0.1 mmol) of *m*CPBA and 200 mg 2,6-di-*t*-butylphenol until no peroxide remained (starch-iodide test negative, 4 h reaction time). The solution was cooled to room temperature and 3-chlorobenzoic acid removed by filtration. The filtrate was washed with 10% $NaSO_3$, 10% $NaHCO_3$ and brine, then dried over $MgSO_4$ and the dichlorethane removed. Distillation (61 °C at 30mm; lit bp : 66°C at 30mm[68]) gave 7.10g (61%) of **87** as a colorless liquid. $^1H$ nmr (60 MHz) : 3.68 (s, 3H), 3.05 (d, $J_{AB}$=7, 1H), 2.70 (d, $J_{AB}$=7, 1H), 1.53 (s, 3H); ms : 117 (2.2) ($M^+$+1), 116 (0.2) ($M^+$), 101 (34), ($M^+$-15).

### 2,2-Dimethyl-4-methylcarboxylate-4-methyl-1,3-dioxolane (88)

1.6 mL (60 mmol) of freshly distilled $SnCl_4$ was added carefully via a dropping funnel to a mixture of 6.86g (60 mmol) of epoxide **87** and 4.5 mL of dry acetone in 50 mL $CCl_4$ at -40°C. The solution was held at -40°C for 1/2 h and then allowed to warm slowly to room temperature at which time 20 mL of saturated $Na_2CO_3$ solution was added. After stirring for 10 minutes, the layers were separated and the organic phase washed twice with water. Following $MgSO_4$ treatment and solvent removal, distillation (85-87°C at 30 mm) gave 8.42g (82%) of **88** as a colorless liquid. $^1H$ nmr (60MHz) : 4.27 (d, $J_{AB}$=9, 1H), 4.03 (s, 3H), 4.01 (d, $J_{AB}$=9, 1H), 1.44 (s, 6H), 1.50 (s, 3H); ir (thin film) : 1750; ms : 159 (95) ($M^+$-15).

**2,2-Dimethyl-4-methyl-1,3-dioxolane-4-carboxylic acid (89)**

A mixture of 10 mL of 20% NaOH and 40 mL of THF containing 3.0 g of **88** was vigorously stirred at room temperature until TLC indicated that no starting material remained (20h). The solution was diluted with water and ether and the organic phase drawn off and discarded. The aqueous layer was acidified with concentrated HCl and extracted with ether (4X). The combined ether extracts were dried over $MgSO_4$. Removal of the ether gave 2.39 g of **89** as a clear colorless oil which was used without further purification. Storeage in a refrigerator resulted in solidification and a small sample was recrystallized from hexanes (70 % recovery) giving **89** as white crystals melting at 67-68°C. $^1H$ nmr (60 MHz) : 9.59 (br, 1H), 4.34 (d, $J_{AB}$=9, 1H), 3.77 (d, $J_{AB}$=9, 1H), 1.57 (s, 3H), 1.5 (s, 6H); ir ($CH_2Cl_2$) : 3400, 1725; ms (CI) : 161 (BP) ($M^+$ +1).

**2,2-Dimethyl-4-methyl-1, 3-dioxolane-4-carboxylic acid chloride (90)**

**Method A:**

A thionyl chloride solution of acid **89** (1.31g, 8.19 mmol) was refluxed for one hour. The excess $SOCl_2$ was then removed using an aspirator and the residue distilled (95°C at 15 mm) giving 694 mg of **90** as a yellow liquid (47%). $^1H$ nmr (60 MHz) : 4.41 (d, $J_{AB}$=8.5, 1H), 3.73 (d, $J_{AB}$=8.5, 1H), 1.58 (s, 3H), 1.50 (s, 3H), 1.43 (s, 3H); ir (thin film): 1780; ms : 179 (0.2) ($M^+$ +1).

**Method B:**

To a solution of 294 mg ( 1.84 mmol) of acid **89** in $CH_2Cl_2$ at room temperature was added 0.20 mL of oxalyl chloride (1.1 equivalents). When no reaction occurred, one drop of DMF was introduced. After the evolution of gas had ceased (1 h), the solution was concentrated *in vacuo* giving 330 mg of acid chloride **90** (100 %) as a colorless syrup.

**Attempted condensation of acid (89) and $MeONH_2$ using DCC**

Methoxylamine hydrochloride (80 mg, 0.94 mmol) was suspended in THF at room temperature and dissolved by the addition of 0.13 mL (0.94 mmol) of TEA. 100 mg (0.63 mmol) of acid **89** was then added followed by 132 mg (0.63 mmol) of DCC. After stirring overnight at room temperature the solution was filtered. Recrystallization of the residue (209 mg) from ethyl acetate gave 108 mg of urea **91** as white crystals mp=157-158°C. $^1H$ nmr: 4.43 (d, $J_{AB}$=8.9, 1H), 3.85 (d, $J_{AB}$=8.9, 1H), 2.04-1.04 (m, 31H); ir ($CH_2Cl_2$) : 3450, 1705, 1650; ms (CI): 367 (85) ($M^+$ +1).

**2,2-Dimethyl-4-methyl-1,3-dioxolane-4-methyl hydroxamate (92)**

210 mg (1.31 mmol) of acid **89** was stirred at 0°C in dry $CH_2Cl_2$ containing 0.37 mL (2.65 mmol) of triethylamine. To this solution was added 0.12 mL (1.31 mmol) of freshly distilled ethyl chloroformate followed 30 minutes later by 109 mg of methoxylamine hydrochloride. After stirring at room temperature for 1 h, the solution was filtered. The residue was then washed with

anhydrous ether and the supranate concentrated giving 240 mg of a colorless syrup. Flash chromatography (EtOAc:hexanes, 1:1) gave 54 mg (22%) of **92** as transparent needles mp 53°C. $^1$H nmr : 9.01 (br, 1H), 4.27 (d, $J_{AB}$=9.0, 1H), 3.78 (d, $J_{AB}$=9.0, 1H), 3.76 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H), 1.46 (s, 3H); ir ($CH_2Cl_2$) : 3400, 1680; ms (CI) : 190 (BP) ($M^+$ +1).

**2,2-Dimethyl-4-methyl-1,3-dioxolane-4-benzyl hydroxamate (93)**

Using a proceedure similar to that described for compound **92**, 109 mg (0.68 mmol) of acid **89** was converted into benzyl hydroxamate **93** in 62% yield (112 mg) after flash chromatography (EtOAc:hexanes, 1:2). This material was obtained as white crystals melting at 63-64°C after recrystallization from anhydrous ether/hexanes. $^1$H nmr : 8.90 (s, 1H), 7.44-7.37 (m, 5H), 4.98 (d, $J_{AB}$=11.1, 1H), 4.95 (d, $J_{AB}$=11.1, 1H), 4.32 (d, $J_{AB}$=9.03, 1H), 3.85 (d, $J_{AB}$=9.03, 1H), 1.50 (s, 3H), 1.37 (s, 3H), 1.24 (s, 3H); ir ($CH_2Cl_2$) : 3420, 1690; ms (CI) : 266 (49) ($M^+$ +1).

**Hydrolysis of 2,2-Dimethyl-4-methyl-1,3-dioxolane-4-benzyl hydroxamate (93)**

Benzyl hydroxamate **93** (704 mg, 2.66 mmol) was refluxed in 5 mL of 80% acetic acid until TLC indicated that no starting material remained (2 1/2 h). The mixture was then concentrated and subjected to flash chromatography (EtOAc) which yielded 516 mg of **93** as a colorless syrup (86%). $^1$H nmr : 7.40-7.35 (m, 5H), 4.89 (s, 2H), 3.98 (d, $J_{AB}$=11.3, 1H), 3.73 (d, $J_{AB}$=11.3, 1H), 1.30 (s, 3H); ir ($CH_2Cl_2$) : 3600, 3400, 1680; ms (CI) : 226 (BP) ($M^+$ +1).

**N-(Benzyloxycarbonyl)-2-amino butyrolactone (103)**

A solution of 141 mg of acid **96** (0.51 mmol) in THF containing $(MeO)_3B$ (5:1 ratio) was treated with 0.1 mL of $BH_3$·DMS at 0°C. After stirring at 0°C for 1/2 h, the mixture was stirred at room temperature overnight. Methanol was then added and the solution concentrated. Rotary evaporation was performed an additional two times with methanol and the residue was flash chromatographed (EtOAc:hexanes, 5:1) giving 100 mg of **103** as a clear colorless oil (84%). $^1$H nmr : 7.35-7.27 (m, 5H), 5.21-5.13 (m, 3H), 2.82-2.73 (m, 1H), 2.26-2.11 (m, 1H); if ($CHCl_3$) : 1780, 1715; ms (CI) : 236 (75) ($M^+$ +1).

**3-Benzyloxycarbonyl-5-oxo-4-oxazolidine-(2'-methylthioethane) (106)**

A mixture of (S)-N-CBZ-methionine (2.0g, 7.07 mmol), 600 mg paraformaldehyde and 50 mg PTS in benzene was refluxed for 18h, the water being removed by means of a Dean-Stark apparatus. The resulting solution was washed with 5% $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of the solvent gave 2.1 g of a clear colorless liquid which gave 2.02 (99%) of **106** after column chromatography (EtOAc:hexanes, 1:3). $^1$H nmr (55°C) : 7.35 (s, 5H), 5.51 (d, $J_{AB}$=4.37, 1H), 5.25 (d, $J_{AB}$=4.37, 1H), 5.20 (d, $J_{AB}$=12.32, 1H), 5.16 (d, $J_{AB}$=12.32, 1H), 4.38 (t, J=4.72, 1H), 2.59-2.49 (m, 2H), 2.29-2.18 (m, 2H), 2.02 (s, 3H); $^{13}$C nmr (55°C) : 171.84 (s), 152.90 (s), 135.49 (s), 128.67 (d), 128.57 (d), 128.23 (d), 77.81 (t), 68.01 (t), 53.75 (d), 29.50 (t), 29.07 (t), 14.93 (q); ir (thin film) : 1800, 1715; ms (CI) : 296 (BP) ($M^+$ +1); *Anal.* calcd. for $C_{14}H_{17}NO_4S$ : C 56.95, H 5.76, N 4.75; found : C 57.28, H 5.90, N 4.67; $[\alpha]_D$ (c= 1.72, $CHCl_3$) : +127.32°.

**3-Benzyloxycarbonyl-5-oxo-4-oxazolidine-(2'-methyethylsulfoxide) (108)**

157 mg of **106** (0.53 mmol) was stirred in $CHCl_3$ at 0°C with 114 mg of *m*CPBA for 2 h at which time TLC indicated that no starting material remained. The solution was then washed with 10 % $Na_2SO_3$, 5% $NaHCO_3$ and dried over $MgSO_4$. Flash chromatography (EtOAc) gave 63 mg (38%) of sulfixide **108** as a colorless oil. $^1H$ nmr : 7.25 (s, 5H), 5.5 (br, 1H), 5.25-5.05 (m, 3H), 4.20 (br, 1H), 2.8 (br, 2H), 2.5 (s, 3H), 2.4 (br, 2H); ir ( $CH_2Cl_2$) : 1800, 1720, 1055; ms (CI) : 312 (BP) ($M^+$+1). *Anal.* calcd. for $C_{14}H_{17}NO_5S$ : C 54.02, H 5.46, N 4.50; found : C 53.60, H 5.16, N 4.20.

**(S)-3-Benzyloxycarbonyl-5-oxo-4-oxazolidine-(2'iodoethane) (107)**

A DMF solution (20 mL) of 1.10 g (3.73 mmol) of **106**, 10 mL of methyl iodide and 800 mg of NaI was stirred at 60°C with two drops of mercury for 48h. The solution was cooled and excess MeI removed by rotary evaporation. 70 mL of water was then added and the solution extracted with ether (4X). The etherial extracts were combined and washed with water* and dried over $MgSO_4$. After solvent removal, the resulting yellow oil was chromatographed (EtOAc:hexanes, 1:3) giving 720 mg of **107** as a colorless oil. This material later solidified and melted at 83-84°C after EtOAc recrystallization. $^1H$ nmr (55°C) : 7.35 (s, 5H), 5.52 (d, $J_{AB}$=5.1, 1H), 5.24 (d, $J_{AB}$=5.1, 1H), 5.21 (d, $J_{AB}$=12.26, 1H), 5.18, (d, $J_{AB}$=12.26, 1H), 4.33 (t, J=5.86, 1H), 3.21 (t, J=8.2, 2H), 2.45 (m, 2H); $^{13}C$ nmr

* If mercury was not included in the reaction. the ether phase was washed with 10% $Na_2SO_3$ and then with water.

(55°C) : 171.16 (s), 152.93 (s), 135.09 (s), 128.74 (d), 128.49 (d), 128.32 (d), 77.98 (t), 68.25 (t), 55.31 (d), 34.72 (t), -2.59 (t); ir ($CH_2Cl_2$) : 1800, 1720; ms (CI) : 376 (12.9) ($M^+$+1); *Anal.* calcd. for $C_{13}H_{14}NO_4I$ : C 41.60, H 3.73, N 3.73; found : C 41.79, H 3.64, N 3.40; $[\alpha]_D$(c = 1.81, $CHCl_3$) : +80.0°.

**N-(β-Trimethylsilylethylcarbonyl)-(S)-2-*t*-butyl-5-oxo-1,3-dioxolane-(S)-4-methylamine (111)**

**Method A:**

To a $CH_2Cl_2$ solution of 500 mg (2.48 mmol) of acid **98** and 0.26 mL oxalyl chloride (3.00 mmol) was added one drop of DMF. After the evolution of gas had ceased (1 h) the solvent was removed by rotary evaporation giving a yellow solid. This material was immediately suspended in dry benzene and 0.39 mL of TMS-$N_3$ was added which caused the suspension to clear. The solution was then refluxed for 1/2 h after which time 0.78 mL (5.45 mmol) of β-trimethylsilylethanol was introduced. Reflux was continued for an additional 2 h and then the solvent removed. Flash chromatography (EtOAc:hexanes, 1:3) of the residue gave 636 mg (81 %) of **111** as white crystals melting at 65 °C after recrystallization from anhydrous ether/hexanes. $^1H$ nmr : 5.15 (d, J=1.63, 1H), 4.9 (br, 1H), 4.35 (t, J=5.38, 1H), 4.14 (t, J=8.2, 2H), 3.68-3.58 (m, 2H), 0.96 (s, 11H), 0.01 (s, 9H); $^{13}C$ nmr : 171.76 (s), 156.45 (s), 109.72 (d), 74.17 (d), 63.45 (t), 40.72 (t), 34.28 (s), 23.35 (q), 17.68 (t), -1.53 (q); ir (KBr) : 3400, 1790, 1720; ms (CI) : 318 (1.5) ($M^+$ +1); *Anal.* calcd for $C_{14}H_{27}NO_5Si$ : C 52.99, H 8.52, N 4.42; found : C 52.70, H 8.68, N 4.36.

**Method B:**

A solution of 99 mg (0.49 mmol) of acid **98** and 0.07 mL of triethylamine (0.49 mmol) in dry benzene was prepared and 135 mg of $(PhO)_2P(O)N_3$ (0.49 mmol) was added. After refluxing for 1 h, the mixture was cooled to room temperature and injected with 0.14 mL (1.0 mmol) of β-trimethylsilylethanol and then reflux was continued for an additional 2 h. The solution was then allowed to cool and the solvent replaced by ether. After washing with 10 % NaOH, drying over $MgSO_4$ and solvent removal, 117 mg (75 %) of **111** was obtained as a colorless oil.

**N-(*t*-butylcarbonyl)-(S)-2-*t*-butyl-5-oxo-1,3-dioxolane-(S)-4-methylamine (112)**

From 674 mg ( 2.47 mmol) of acid **98** was obtained 772 mg (85 %) of carbamate **112** as a clear colorless oil using a proceedure similar to method A described above for carbamate **111**. The reaction used *t*-butanol in place of β-trimethylsilylethanol and was monitored by nmr (25 h reaction time). Workup was as described above. $^1$H nmr : 5.15 (d, J=1.22, 1H), 4.9 (br, 1H), 3.66-3.62 (m, 1H), 3.52-3.46 (m, 1H), 1.42 (s, 9H), 0.96 (s, 9H); $^{13}$C nmr : 171.74 (s), 155.30 (s), 109.67 (d), 79.85 (s), 74.36 (d), 40.41 (t), 34.37 (s), 28.37 (q), 23.46 (q); ir ($CHCl_3$) : 3450, 1790, 1715; ms : 273 (1.8 ) ($M^+$); *Anal.* calcd. for $C_{13}H_{23}NO_5$: C 57.14, H 8.42, N 5.13; found : C 56.66, H 8.38, N 4.91.

**N-(*t*-butylcarbonyl)-(S)-2-*t*-butyl-5-oxo-1,3-dioxolane-4-benzyl-4-methylamine (113)**

To a solution of the dianion of carbamate **112** (786 mg, 2.88 mmol) (generated with LDA) in THF at -78°C was added 0.40 mL of freshly distilled benzyl bromide. After stirring at -78°C for 1/2 h, saturated $NH_4Cl$ solution was added and the mixture extracted with ether. After washing with water and $MgSO_4$ treatment, removal of solvent and flash chromatography (EtOAc:hexanes, 1:5) of the residue gave 434 mg (41%) of **113** as a colorless oil. $^1H$ nmr : 7.29-7.22 (m, 5H), 4.82 (br, 1H), 4.24 (s, 1H), 3.52-3.47 (m, 2H), 3.12 (d, $J_{AB}$=13.98, 1H), 2.95 (d, $J_{AB}$=13.98, 1H), 1.41 (s, 9H), 0.82 (s, 9H); $^{13}C$ nmr : 173.50 (s), 155.46 (s), 133.97 (s), 130.10 (d), 128.55 (d), 127.44 (d), 109.29 (d), 83.54 (s), 79.79 (s), 45.42 (t), 39.38 (t), 34.38 (s), 28.38 (q), 23.39 (q); ms : 363 (2.6) ($M^+$); *Anal.* calcd. for $C_{20}H_{29}NO_5$ : C 66.12, H 7.99, N 3.86; found : 65.30, H 7.81, N 4.05.

**General proceedure for the alkylation of iodide (107) with 1,3-dioxolane dianions of (98)and (112)**

A solution of LiHMDS was prepared by the addition of the appropriate amount (2.2 equivalents) of *n*-butyllithium in hexanes to a slight excess of HMDS in THF at -78°C. To this solution was added the appropriate 1,3-dioxolane derivative in THF. After allowing 20 minutes for anion formation, a solution of iodide **107** in THF was added via cannula. The mixture was stirred at -78°C for an additional 20 minutes, and then saturated $NH_4Cl$ solution

introduced. Extraction with ether, $MgSO_4$ treatment and solvent removal gave crude products which were purified chromatographically.

From 205 mg (1.0 mmol) of acid **98** and 380 mg of iodide **107** was obtained 228 mg (50 %) of **99a** as a colorless oil (flash chromatography solvent : EtOAc:hexanes, 1:1). $^1H$ nmr (55°C) : 7.35 (s, 5H), 5.27 (d, $J_{AB}$=4.4, 1H), 5.27 (s, 1H), 5.19 (d, $J_{AB}$=12.1, 1H), 5.15 (d, $J_{AB}$=12.1, 1H), 4.97 (d, $J_{AB}$=4.4, 1H), 4.74 (d, J=8.43, 1H), 4.15 (t, J=8.43, 1H), 4.10-3.90 (m, 1H), 3.00 (d, $J_{AB}$=16.0, 1H), 2.82 (d, $J_{AB}$=16.0, 1H), 2.30-2.22 (m, 1H), 2.15-2.04 (m, 1H), 0.94 (s, 9H); $^{13}C$ nmr (55°C) : 171.71 (s), 170.05 (s), 152.62 (s), 135.97 (s), 128.67 (d), 128.42 (d), 128.14 (d), 110.76 (d), 81.83 (s), 81.27 (t), 69.32 (t), 67.85 (t), 61.35 (d), 37.72 (t), 34.46 (s), 33.36 (t), 23.70 (q); ir ($CHCl_3$) : 3500, 1800, 1718; ms : 449 (0.7) ($M^+$).

From 91 mg of carbamate **112** (0.33 mmol) and 125 mg of iodide **107** was obtained 66 mg ( 47 %) of **114a** as a colorless wax (flash chromatography solvent : EtOAc:hexanes 1:3). $^1H$ nmr (55°C) : 7.34 (s, 5H), 5.30-5.25 (m, 3H), 5.15 (t, J=6.6, 2H), 4.96 (d, J=4.2, 1H), 4.76 (d, J=6.1, 1H), 4.62 (br, 1H), 4.12 (t, J=8.2, 1H), 3.97-3.90 (m, 1H), 3.63-3.58 (m, 2H), 2.3-2.2 (m, 1H), 2.2-2.0 (m, 1H), 1.40 (s, 9H), 0.97 (s, 9H); $^{13}C$ nmr (55°C) : 169.90 (s), 155.26 (s), 152.28 (s), 135.92 (s), 128.52 (d), 128.24 (d), 128.18 (d), 110.56 (s), 83.55 (s), 81.01 (t), 79.93 (s), 69.13 (t), 67.70 (t), 61.23 (d), 42.77 (t), 34.65 (s), 33.42 (t), 28.39 (q), 23.63 (q); ms : 520 (1.4) ($M^+$).

**Esterifictation of (99)**

Product **99a** (50 mg, 0.11 mmol) was dissolved in dry ether and treated with $CH_2N_2$ at 0°C until the solution was yellow. Glacial acetic acid was then added until the solution was decolorized and the mixture then concentrated. Preparative layer chromatography (EtOAc:hexanes, 1:2) gave 46 mg of ester **109** as a colorless oil. $^1H$ nmr (55°C) : 7.34 (s, 5H), 5.26 (d, $J_{AB}$=4.15, 1H), 5.26 (s, 1H), 5.20 (d, $J_{AB}$=12.53, 1H), 5.14 (d, $J_{AB}$=12.53, 1H), 4.98 (d, $J_{AB}$=4.15, 1H), 4.72 (d, J=6.1, 1H), 4.14 (t, J=8.84, 1H), 3.98-3.93 (m, 1H), 3.63 (s, 3H), 2.96 (d, $J_{AB}$=15.38, 1H), 2.80 (d, $J_{AB}$=15.38, 1H), 2.3-2.0 (m, 2H), 0.93 (s, 9H); $^{13}C$ nmr (55°C) : 170.08 (s), 167.93 (s), 152.52 (s), 136.06 (s), 128.65 (d), 128.38 (d), 128.12 (d), 110.63 (d), 81.98 (t), 91.32 (s), 69.24 (t), 67.75 (t), 61.34 (d), 51.91 (q), 38.08 (t), 34.37 (s), 33.43 (t), 23.67 (q); ir ($CHCl_3$) : 1800, 1740, 1720; ms : 463 (3.9) ($M^+$).

**N-(Benzyloxycarbonyl)-1-aza-3, 4-dioxobicyclo-[3.3.0]-octane-7-diethylphosphite (121a)**

A solution of sodium diethylphosphite was prepared by adding 0.19 mL of diethylphosphite to a suspension of NaH (71 mg, 1.2 equivalents) in DMF at room temperature. After stirring for 1h, 459 mg (1.22 mmol) of iodide **107** in DMF was added and the mixture stirred at room temperature overnight. Water was then added and the mixture extracted several times with ether. The combined etherial extracts were washed with water, dried over $MgSO_4$ and concentrated leaving 450 mg of a yellow oil which gave 220 mg (47%) of phosphite **121a** as a colorless oil after flash chromatography (EtOAc:hexanes,

2:1). $^{1}H$ nmr (55°C) : 7.35-7.31 (m, 5H), 5.27-5.25 (m, 1H), 5.17 (d, $J_{AB}$=12.45, 1H), 5.14 (d, $J_{AB}$=12.45, 1H), 5.00-4.98 (m, 1H), 4.77-4.75 (m, 1H), 4.27-4.09 (m, 5H), 4.04-3.98 (m, 1), 2.21-2.18 (m, 2H), 1.33 (t, J=7.08, 3H), 1.30 (t, J=7.08, 3H); $^{13}C$ nmr (55°C) : 152.54 (s), 135.93 (s), 128.42 (d), 128.14 (d), 127.88 (d), 80.76 (t), 69.67 (t) ($J_{CP}$=9.8), 67.53 (t), 63.75 (t) ($J_{CP}$=8.7), 63.65 (t) ($J_{CP}$=6.7), 63.15 (d) ($J_{CP}$=13.4), 32.75 (t), 16.39 (q), 16.32 (q); $^{31}P$ nmr (55°C) : 13.52; ir (thin film) : 1720, 1260, 1040; ms (CI) : 386 (BP) ($M^{+}$+1); *Anal.* calcd. for $C_{17}H_{24}NO_7P$ : C 52.99, H 6.24, N 3.64; found C 52.51, H 6.34, N 3.82; $[\alpha]_D$ (c = 0.234, $CHCl_3$) : +58.1°.

**N-(Benzyloxycarbonyl)-1-aza-3, 4-dioxobicyclo-[3.3.0]-octane-7-dibenzylphosphite (122)**

To a mixture of 551 mg ( 2.00 mmol) of iodide **107** and 0.53 mL (2.20 mmol) of dibenzyl phosphite in DMF at room temperature was added 115 mg of NaH (2.20 mmol) in three portions. After stirring at room temperature for 5 h, water was added and the mixture extracted with ether. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated. Flash chromatography (EtOAc:hexanes, 1:1) gave 474 mg (63%) of **122** as a colorless oil. $^{1}H$ nmr (55°C) : 7.36-7.25 (m, 15H), 5.16-5.04 (m, 7H), 4.97-4.95 (m, 1H), 4.72-4.68 (m, 1H), 4.06-3.96 (m, 2H), 2.13-2.03 (m, 2H); $^{13}C$ nmr (55°C) : 152.38 (s), 136.02 (s) ($J_{CP}$=5.8), 135.96 (s) ($J_{CP}$=5.5), 135.89 (s), 128.39 (d), 128.23 (d), 128.15 (d), 127.87 (d), 127.75 (d), 127.74 (d), 80.80 (t), 69.81 (t) ($J_{CP}$=10.0), 69.15 (t) ($J_{CP}$=6.9), 69.06 (t) ($J_{CP}$=6.7), 67.51 (t), 63.20 (d) ($J_{CP}$=13.3), 32.74 (t); $^{31}P$ nmr (55°C) : 13.53; ir (thin film) : 1720; ms (CI) : 510 (BP) ($M^{+}$+1); *Anal.* calcd. for $C_{27}H_{28}NO_7P$ : C 63.66, H 5.50, N 2.75; C 64.18, H 5.77, N 2.72; $[\alpha]_D$ (c = 5.45, $CHCl_3$) : +41.4°.

**(S)-3-Benzyloxycarbonyl-5-oxo-4-oxazolidine-(2'-methylsulfonylethane) (130)**

To a solution of 880 mg ( 5.06 mmol) of acid **95** in THF (5 mL) and $(MeO)_3B$ (1 mL) was added 0.40 mL of $BH_3$·DMS at room temperature. After stirring at room temperature for 3 h, methanol was added and the solution concentrated. The residue was rotary evaporated two additional times with methanol and then immediately dissolved in dry $CH_2Cl_2$ ( some precipitate forms which does not affect the subsequent reaction ). After cooling to 0°C, 0.32 mL of $CH_3SO_2Cl$ (1.3 equivalents ) is added followed by 0.57 mL (1.3 equivalents ) of TEA. This solution was stirred at 0°C for 1/2 h and then at room temperature for 1/2 h, washed with 10% HCl, saturated $NaHCO_3$, water and dried over $MgSO_4$. The syrup remaining after solvevt removal was flash chromatographed (EtOAc:hexanes, 1:1) giving 384 mg (35%) of mesylate **120** as a yellow oil. $^1H$ nmr (55°C) : 7.36-7.32 (m, 5H), 5.51 (d, $J_{AB}$=4.39, 1H), 5.31 (d, $J_{AB}$=4.39, 1H), 5.21 (d, $J_{AB}$=12.02, 1H), 5.17 (d, $J_{AB}$=12.02, 1H), 4.41-4.31 (m, 3H), 2.25 (s, 3H), 2.43-2.35 (m, 2H); $^{13}C$ nmr (55°C) : 152.00 (s), 135.08 (s), 128.70 (d), 128.59 (d), 128.31 (d), 77.99 (t), 68.28 (t), 63.89 (t), 51.86 (d), 37.58 (q), 31.63 (t); ir (thin film) : 1800, 1720; ms (CI) : 343 (0.5) ($M^+$).

**Conversion of mesylate (130) into iodide (107)**

A solution of 264 mg of mesylate **130** in THF containing 5 mg TBAI was stirred vigorously with 180 mg of NaI for 20 h. The solution was diluted with ether and washed with water. After $MgSO_4$ drying and solvent removal, flash

chromatography (EtOAc:hexanes, 1:3) gave 104 mg of **107** (36%). $[\alpha]_D$ (c = 0.962, $CHCl_3$) : +78.6°.

# PART B: DESIGN AND SYNTHESIS OF CHIRAL METHYLENE TRANSFER REAGENTS WITH $C_2$ SYMMETRY

## Introduction

The last decade has seen a tremendous surge of interest in asymmetric chemistry in which optical activity is used or induced. Modern synthetic organic chemists appear to be obsessed with the concept of asymmetric synthesis as evidenced by the wealth of recent literature on the subject. Many syntheses use pre-existing chirality in starting materials, and carry the asymmetric centre through the synthesis.[101] Other chemistry focuses on the development of reactions and reagents which induce the formation of chiral centres in molecules which were not previously optically active. Among the more important reactions for which asymmetric technology now exists include the aldol condensation,[102] Diels-Alder cycloaddition,[103] hydroboration,[104] and the epoxidation of allylic alcohols.[105] These processes are all very powerful

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[101] S. Hanessian. "Total Synthesis of Natural Products, The 'Chiron' approach". Pergamon, London, 1983.

[102] For reviews see: a) C.H. Heathcock in "Comprehensive Carbanion Chemistry Vol. II", T. Durst, E. Buncel Ed., Elsevier, Amsterdam, 1983; b) D. A. Evans, J. R. Nelson, T. R. Taber. *Topics in Stereochemistry*, **13**, 1 (1982); c) S. Masamune, W. Choy. *Aldrichimica Acta*, **15**, 47(1982).

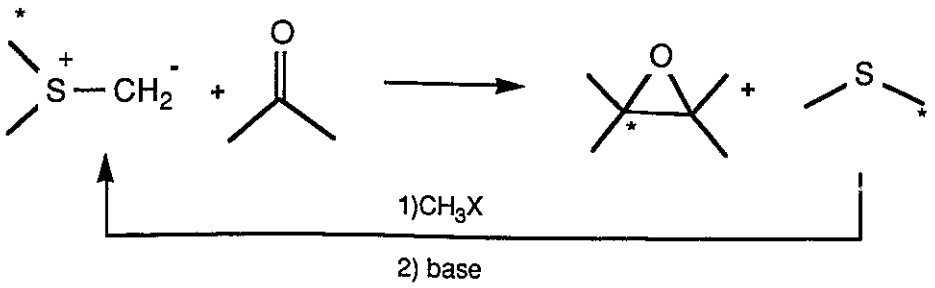
[103] For example: a) S. Masamune, W. Choy, J. S. Petersen, L. R. Sita. *Angew. Chem. Int. Ed. Engl.*, **24**, 1 (1985); b) D. A. Evans, K. T. Chapman, J. Bisaha. *J. Am. Chem. Soc.*, **110**, 1238 (1988).

[104] J. H. Brewster. *Aldrichimica Acta*, **20**, 3 (1987).

[105] Y. Gao, r. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless. *J. Am. Chem. Soc.*, **109**, 5765 (1987). and references therein.

transformations and can be used to construct a large variety of molecules, but plenty of room remains for the development of new strategies and reagents.

One such reagent which has been severely neglected with respect to asymmetric induction is the sulfur ylide. These versatile intermediates carry out several useful transformations such as epoxidation (shown below) and cylclopropanation as well as undergoing rearrangements.[106] Despite this, no asymmetric sulfur ylides which transfer chirality effectively have been reported. Such a reaction would, in principle, be an important addition to methodology since it would produce optically active epoxides whose value as synthetic intermediates is without dispute. More importantly, in contrast to other reactions which yield chiral epoxides, the reaction of sulfur ylides with carbonyl compounds involves carbon-carbon bond formation and can be used to construct more complex molecules from simpler ones. It should also be noted that the sulfide, the by-product of the epoxidation reaction can be reconverted to the key chiral ylide by an alkylation reaction followed by treatment with an appropriate base.




In 1973, Trost[107] reported that (+)-1-adamantylallylethylsulfonium salt **123**, which was obtained in optically pure form by a resolution, rearranged

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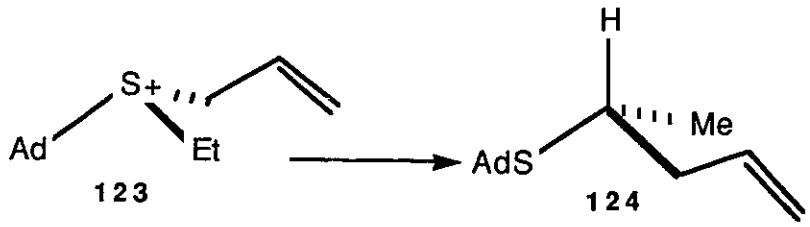
[106] a) A. C. Knipe in "The Chemistry of the Sulphonium Group", S. Patai ed, Interscience, New York (1981); b) B. M. Trost, L. S. Meluin Jr. "Sulfur Ylides, Emerging Synthetic intermediates", Academic Press, New York (1975).

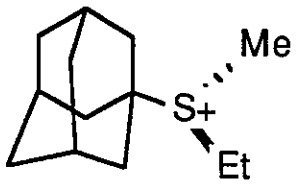
[107] B. M. Trost, R. F. Hammen. *J. Am. Chem. Soc.*, **95**, 962 (1973).

smoothly to give sulfide **124**. This reaction was shown to occur with 97 % retention of optical activity. Racemic sulfur ylides have also been rearranged in a similar manner using chiral bases and solvents giving products with low enantiomeric excess (ee).[108]




**123** **124**

Products not arising from rearrangements however, have not been prepared asymmetrically using sulfur ylides derived from sulfonium salts. The 1-adamantylethylmethylsulfonium salt **125** did successfully transfer a methylene to benzaldehyde forming styrene oxide, but the epoxide produced proved to be racemic. A cyclopropanation reaction using the same reagent also occurred without asymmetric induction.[107] A report of a successful methylene transfer using a chiral phase transfer catalyst[109] was later shown to be incorrect.[110]




**125**

The lack of published material concerning chiral sulfur ylides in asymmetric synthesis is surprising because of their synthetic utility. For this reason, we decided to embark upon a study whose goal would be to develop

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[108] B. M. Trost, W. G. Biddlecom. *J. Org. Chem.*, **38**, 3438 (1973).
[109] T. Hiyama, T. Mishima, H. Sawasa, H. Nozaki. *J. Am. Chem. Soc.*, **97**, 1626 (1975).
[110] T. Hiyama, T. Mishima, H. Saeada, H, Nozaki. *J. Am. Chem. Soc.*, **98**, 641 (1976).

such a compound. This project, if successful would not only provide a new asymmetric reagent but provide new insight concerning stereochemical aspects of the epoxidation reaction (see pages 139-144).

**Design of a chiral sulfur ylide**

To have the best chance of success, the design of a suitable reagent must be carefully considered. The compound to be prepared should be capable, at least on paper of inducing high enantioselectivity and should also be designed so that it is convenient to use. To accommodate these requirements, we reasoned that a suitable reagent would meet the following criteria.

1) The reagent should have $C_2$ symmetry since reagents which have similar symmetry properties have been used successfully as chiral auxiliaries.
2) The reagent should possess a cyclic structure to minimize conformational partitioning. A five membered ring (thiolane) would be preferred.
3) The reagent should have the chiral centres located as close as possible to the reaction centre to avoid attenuation of the chiral information.
4) The reagent should be easily prepared in as few synthetic steps as possible, using reactions and purifications amenable to large scale work.
5) The reagent should be produced from inexpensive reagents which are already chiral, thus avoiding the need for a resolution

6) The reagent should have low volatility to avoid the unpleasant odor usually associated with sulfides. The low volatility would also facilitate efficient recovery. Ideally the reagent would be a solid.

Many of the more successful reagents developed for asymmetric transformations possess $C_2$ symmetry. Notable examples include the Sharpless epoxidation;[105] *trans* 2,5-dimethylpyrrolidine **126**, which has been used in vinylogous urethanes[111] and in eneamine chemistry;[112] *trans* 2,5-dimethylborolane **127**, which has produced excellent enantioselectivity in hydroboration reactions[113] and in the addition of allyl boranes to aldehydes;[114] and the binaphthyl ruthenium catalytic hydrogenation reagents[115] such as **128** which have produced spectacular results in reducing ketones, β-ketoesters, allylic and homoallylic alcohols.

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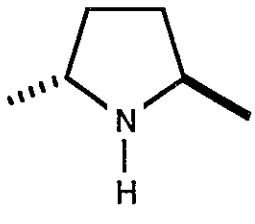
[111] a) A. D. Adams, R. H. Schlessinger, J. R. Tata, J. J. Vemit. *J. Org. Chem.*, **51**, 3070 (1986); b) R. H. Schlessinger, E. J. Iwanowicz, J. P. Springer. *J. Org. Chem.*, **51**, 3073 (1986); c) R. H. Schlessinger,J. R. Tata, J. P. Springer. *J. Org. Chem.*, **52**, 708 (1987) ; d) R. H. Schlessinger, E. J. Iwanowicz. *Tetrahedron Lett.*, 2083 (1987).

[112] J. K. Whitesell, S. W. Felman. *J. Org. Chem.*, **42**, 1663 (1977).

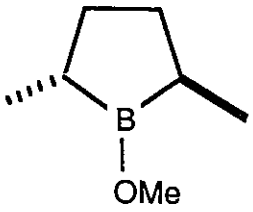
[113] S. Masamune, B. M. Kim, J. S. Petersen, T. Sato, S. J. Veenstra. *J. Am. Chem. Soc.*, **107**, 4549 (1985).

[114] J. Garcia, b. M. Kim, S. Masamune. *J. Org. Chem.*, **52**, 4831 (1987).

[115] a) H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara,R. Noyori. *J. Am. Chem. Soc.*, **109**, 1596 (1987); b) R. Noyori, T. Ohkuma, M. Kitamura, T. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa. *J. Am. Chem. Soc.*, **109**, 5856 (1987); c) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori. *J. Am. Chem. Soc.*, **110**, 629 (1988).




126

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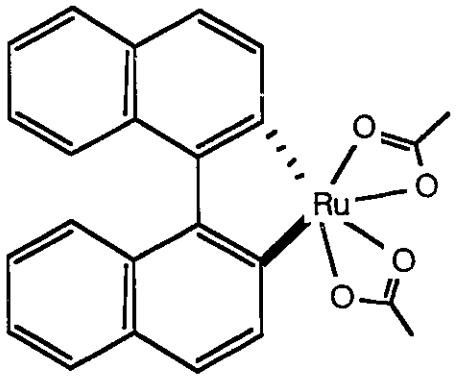
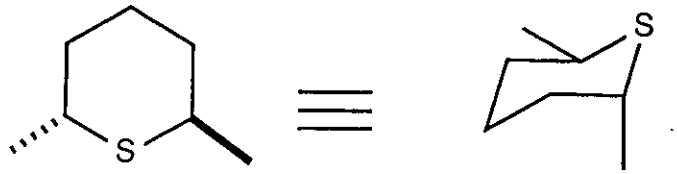



128

The $C_2$ symmetry in all of these molecules may be the major reason responsible for the high homochiralities[103a] observed in products obtained using these reagents. In a molecule with $C_2$ symmetry, the two chiral centres reinforce each other since the molecule can in effect present identical faces to the prochiral reactant no matter which way they approach each other. A $C_2$ reagent can react in two orientations with the substrate, but both sides of the $C_2$ reagent are identical so the reagent "sees" only one face. In addition to providing the best chance for success, the relative simplicity of a $C_2$ reagent should allow one to predict the outcome of a reaction, and would simplify mechanistic investigations and calculations.

A ring structure is also desired since this adds rigidity to the system and reduces the number of degrees of freedom in the transition state. A molecule which is acyclic will tend to be "floppy" and adopt conformations which minimize non-bonding interactions. In an asymmetric reagent, some non-bonding interactions are desirable between substrate and auxiliary since this will restrict the number of conformations in the transition state. As well, a ring structure will hold the chiral groups fixed, in a way such that they can reinforce each other's influence. Ideally, these effects will produce a transition state with only one

possible configuration and thus obtain complete stereoselectivity. An auxiliary which is incapable of altering it's shape has the best chance of achieving this. The ring of choice would be a 5-membered one (thiolane). This ring is large enough so that the molecule is not subject to a large amount of strain while larger rings are capable of adopting numerous conformations and therefore do not satisfy the rigidity requirements for the reagent. The relative flatness of the 5 membered ring is also important since this produces true $C_2$ symmetry. An analogous 6 membered ring for example holds one methyl group axially and the other equatorially and conformationally therefore is not $C_2$ symmetric.



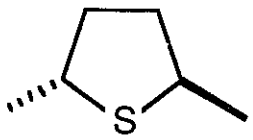

apparent $C_2$ not $C_2$

A large molecule with remote stereocentres would not be a wise choice for a useful auxiliary since the chiral information must travel a long distance to reach the substrate and this information could be lost through vibrational motion of the intervening atoms. Logically, a molecule with stereocentres located close to the reaction site has the best chance of producing an asymmetric reaction since the stereocentres will have a direct effect on transition state geometry. Therefore a high priority consideration must be to construct an auxiliary with chiral centres placed close at hand, adjacent to the sulfur.

The preparation of the auxiliary should be simple and rapid. Sequences which readily produce multigram quantities are also desirable. These practicalities would greatly contribute to a reagent's acceptance and

usefulness. A synthesis using inexpensive chiral starting materials is a laudable goal since a resolution is a tedious process. Beginning with molecules of known configuration also means that the configuration of the auxiliary will be known, without recourse to circular dichroism or X-ray techniques. A short synthesis would also minimize any loss of optical activity through accidental epimerization. The utility of a short preparation was recently summed up by H. C. Brown[116] who noted that although *trans* 2,5-dimethylborolane **127** produced excellent asymmetry, the preparation and resolution of the material was long and tedious whereas one could obtain ee's almost as high using boranes derived from the readily available α-pinene in one step. A tradeoff therefore exists between optical activity attained and the amount of effort required to achieve a given induction.

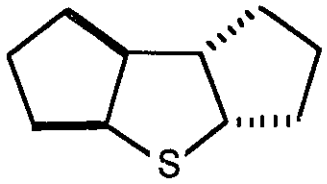
A final consideration in the design of a suitable molecule is the physical properties of the reagent. A non-hygroscopic solid would be convenient to use and to purify, but the physical properties of any given substance are difficult to predict. More reasonably, one would want a molecule with a high enough molecular weight so that the volatility is limited and the partition coefficients between organic solvents and water are large, thus giving an auxiliary which is easily recovered in high yield. As well, a compound which is fairly stable and which has a long shelf life is also desired for obvious reasons.




**129**

[116] H. C. Brown, Third Chemical Congress of North America, Toronto, June (1988).

A molecule which possess many of these attributes is *trans*-2,5-dimethylthiolane **129**. This molecule is cyclic and possesses the required $C_2$ symmetry. The chiral centres are located adjacent to the sulfur and are thus in close proximity to the reaction centre. (±) *Trans* 2,5-dimethylthiolane is readily synthesized[117] from *trans* 2,5-hexanediol which has been prepared in optically pure form by yeast reduction[118] and also by a resolution.[119] A more refined possibility is dicyclopentanothiolane **130**. This compound is larger than **129** and therefore is less likely to be troublesome due to high volatility. An added bonus is the fact that the *cis* fused bicyclo-[3.3.0]-octane framework prevents epimerization α to the sulfur, since the resulting *trans* fused 5,5 ring system is thermodynamically disallowed. A similar product containing a central pyrrolidine has recently been reported,[120] but in order to be prepared in enantiomerically pure form, it had to be resolved.




**130**

## Mechanistic considerations and feasibility

The mechanism of the reaction between a sulfonium ylide and a carbonyl group was proposed over 25 years ago by Johnson.[121] The sulfonium ylide

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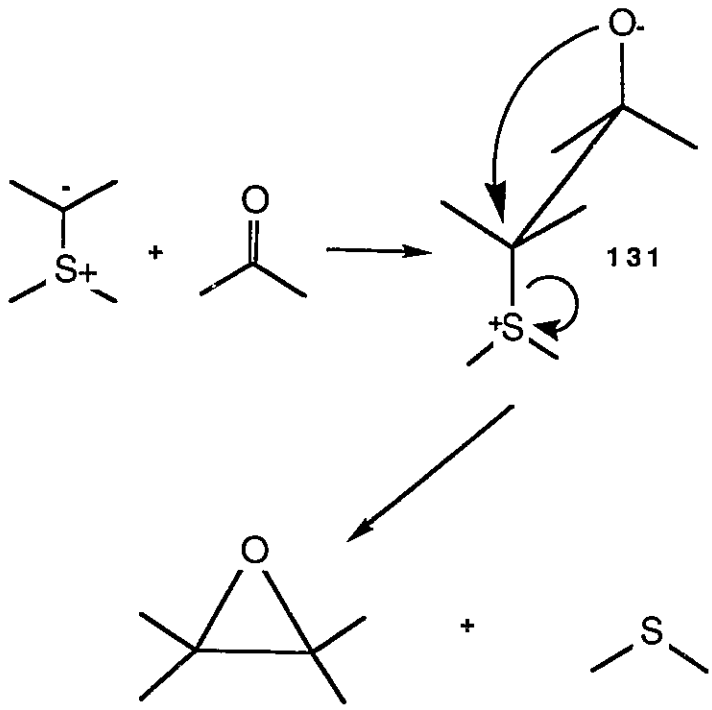
[117] E. L. Eliel, R. O. Hutchins, R. Mebane, R. L. Willer. *J. Org. Chem.*, **41**, 1052 (1976).
[118] J. K. Lieser. *Synth. commun.*, **13**, 765 (1983).
[119] J. K. Whitesell, D. Reynolds. *J. Org. Chem.*, **48**, 3548 (1983).
[120] J. K. Whitesell, M. A. Minton, K-M. Chan. *J. Org. Chem.*, **53**, 5383 (1988).
[121] A. W. Johnson, R. B. Iacount. *J. Am. Chem. Soc.*, **83**, 417 (1961).

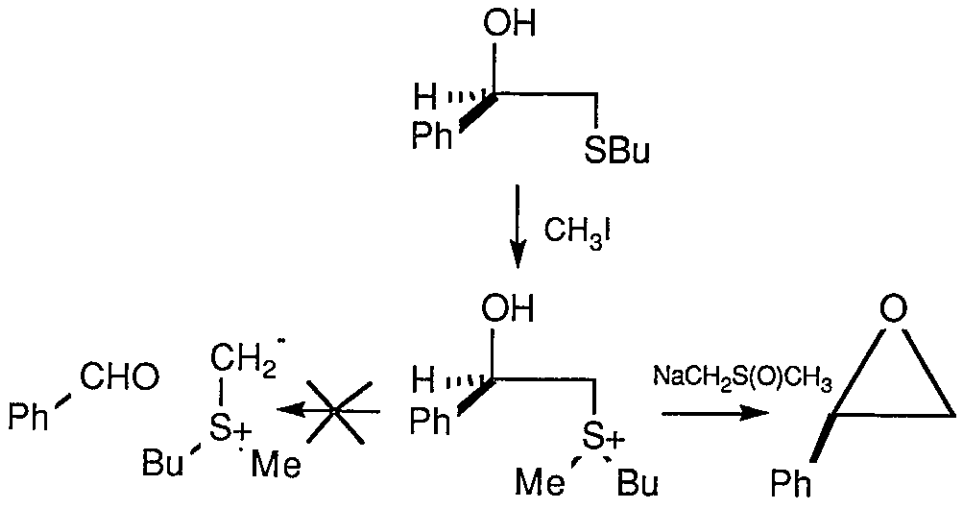
undergoes nucleophilic addition onto the carbonyl group to form a *trans*-betaine intermediate such as **131**. This betaine intermediate then evolves towards an oxirane via an intramolecular $S_N2$ displacement of the sulfonium group by the neighboring oxygen.

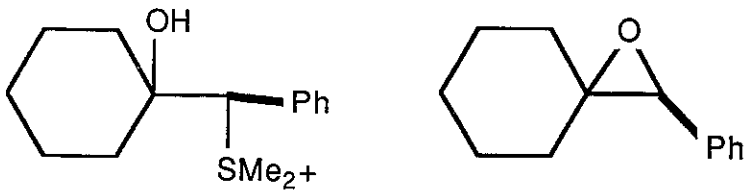



The formation of the *trans* betaine **131** was shown to be essentially irreversible by Johnson[122] who prepared an optically active β-hydroxyl sulfide which was methylated and exposed to dimsyl sodium in DMSO. The resulting reaction produced styrene oxide with an optical purity of 90 %, thus indicating that the collapse of the betaine to form an oxirane occurred much faster than the

[122] C. R. Johnson, C. W. Schroeck, J. R. Shanklin. *J. Am. Chem. Soc.*, **95**, 7424 (1973).

fragmentation of the betaine back to ylide and carbonyl component. Related results had been reported earlier by the Durst group[123] who observed similar behavior with optically active betaine **132.**




**132**

$[\alpha]_D$ = -78° (c = 0.7, EtOH) $[\alpha]_D$ = -26.5° (c = 2.5, pentane)

An experiment[124] involving the reaction of cyclododecene epoxides with mercaptans to form hydroxy sulfides such as **133**, subsequent sulfonium salt

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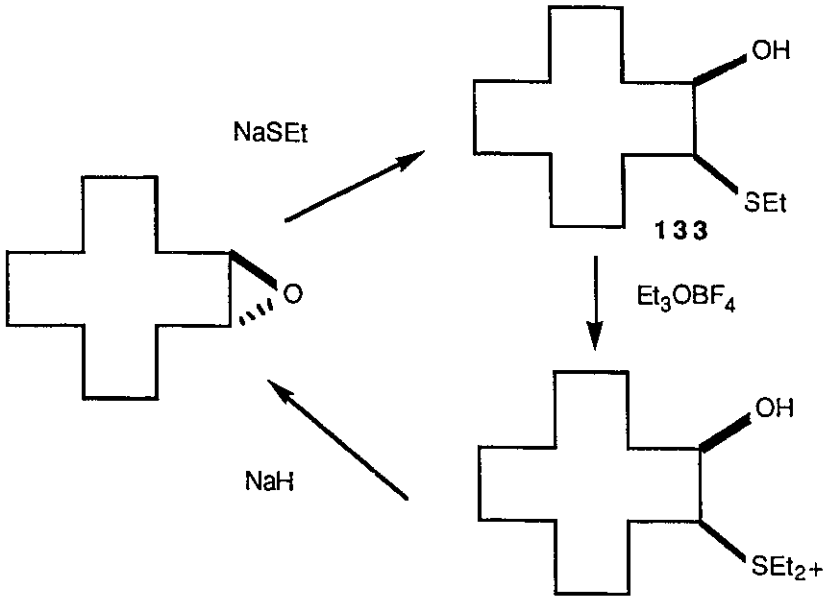
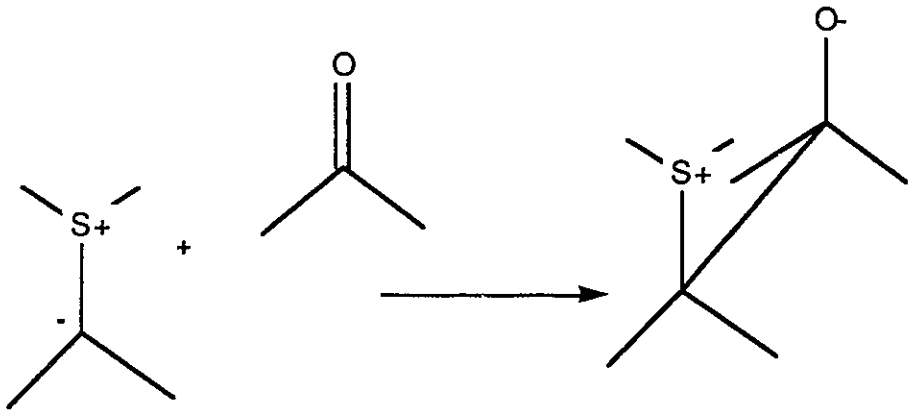
[123] T. Durst, R. Viau, R. Van Den Elzen, C. H. Nguyen. *J. Chem. Soc., Chem. Commun.*, 1334 (1971).

[124] J. M. Townsend, K. B. Sharpless. *Tetrahedron Lett.* 3313 (1972).

formation and base-catalyzed decomposition of the resulting betaines, returned essentially intact the starting *cis* or *trans* epoxide. This result showed that betaine formation was irreversible, since stereochemical information was retained throughout the reaction.




The important step in the reaction of sulfonium ylide and carbonyl from a stereochemical point of view is therefore the initial betaine formation, since any asymmetry in this intermediate should be transmitted to the oxirane with no loss of integrity. Two basic orientations are possible in the reaction of a sulfonium ylide and a carbonyl moiety. The first to be considered is the head-to-head interaction in which the sulfur and oxygen are oriented *syn* to each other in an encounter complex. This is depicted in simplified form below.




This type of approach was initially proposed on the basis of observations noted previously for phosphorus ylide reactions.[125] The head-to-head orientation should actually be an orthogonal 2a + 2s cycloaddition type intermediate in order to comply with the rules of orbital symmetry. The head-to-head type of reaction was employed to explain the preference for axial attack noted in the reaction of dimethylsulfonium methylide with substituted cyclohexanones.[126] During equatorial attack, dimethylsulfonium methylide would experience severe interactions with the axial hydrogens adjacent to the carbonyl, while an axial approach involves less severe interactions with more remote hydrogens.[106b]

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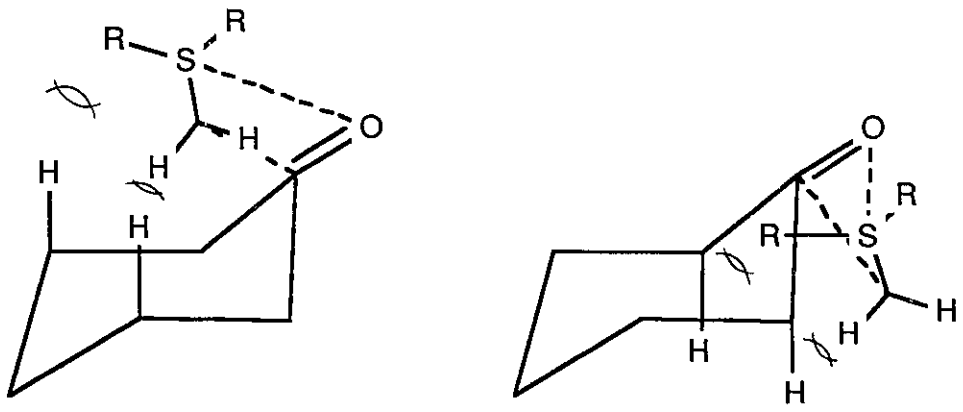
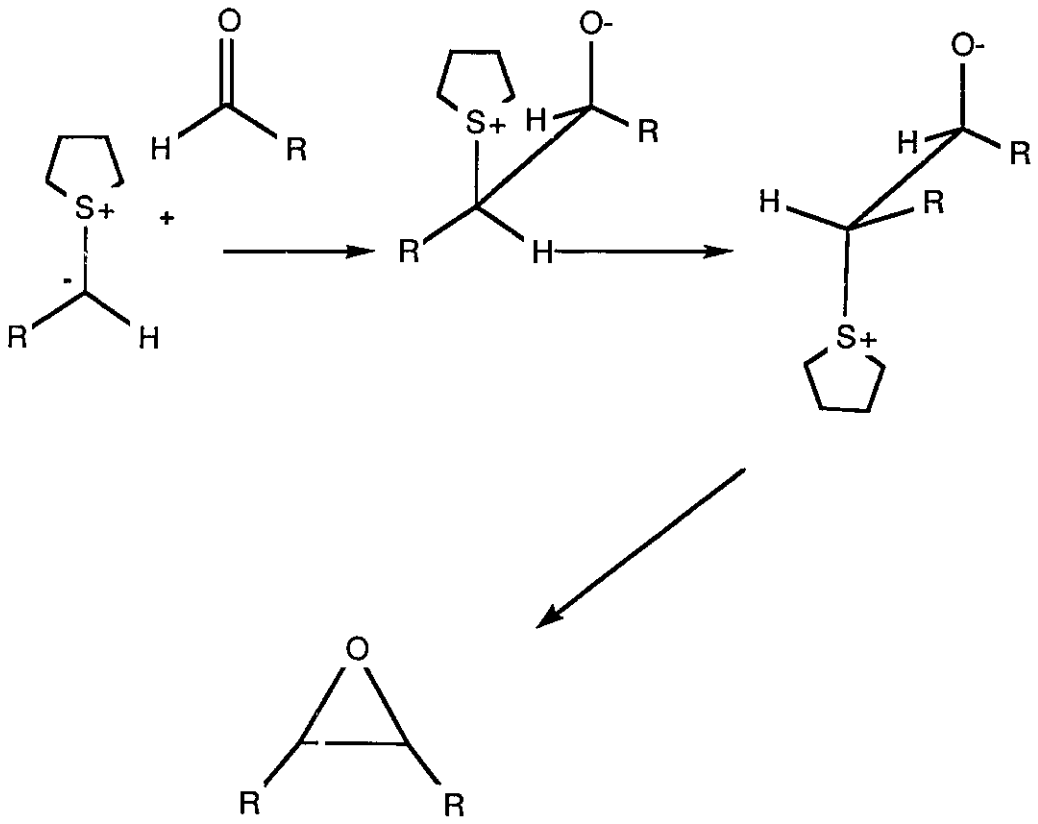
[125] E. Vedejs, K. A. J. Snoble. *J. Am. Chem. Soc.*, **95**, 5778 (1973).

[126] a) E. J. Corey, M. Chaykovsky. *J. Am. Chem. Soc.*, **87**, 1353 (1965); b) R. G. Carlson, N. S. Behn. *J. Org. Chem.*, **32**, 1363 (1967).

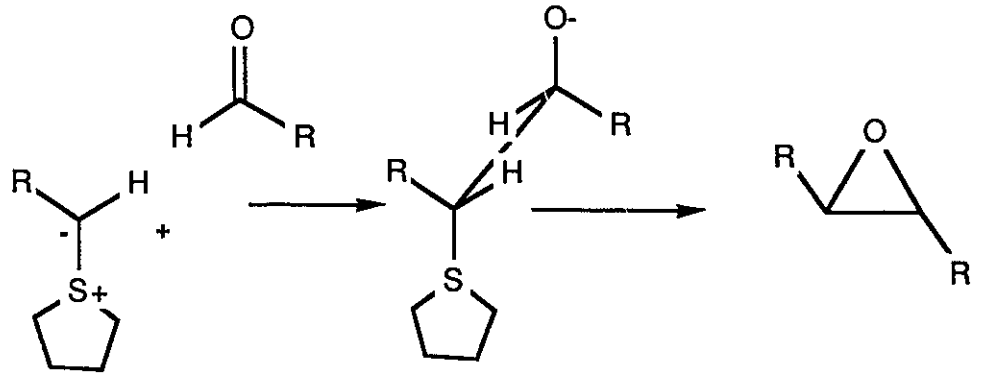



Head-to-head approach is not compatible however with other observations which have been noted. Substituted ylides react with an aldehyde to give preferentially a *trans* oxirane. For example, various tetramethylenesulfoniumbenzylides were shown to produce *trans* oxiranes exclusively upon condensation with a number of benzaldehydes.[127] The head-to-head reaction is illustrated in simplified form below. As shown, the initial adduct resulting from a head-to-head type of reaction leads to the unobserved *cis* oxirane, and so the existence of a head-to-head mechanism seems unlikely.

[127] M. Hetschko, J. Gosselck. *Chem. Ber.*, **106**, 996 (1973).




The alternative to a head-to-head approach is a head-to-tail reaction, in which the oxygen and sulfur orient themselves so that they are *anti*-periplanar to each other. The head-to-tail type of orientation would easily explain the formation of *trans* oxiranes with substituted ylides.



An orientation of this kind can also account for the preference of sulfonium salts for the axial approach to cyclohexanones, since the sulfur has to locate itself almost inside the six membered ring to approach equatorially. Recent theoretical calculations[128] have probed the mechanism of the epoxide forming reaction. A surprising conclusion, that a betaine was a transition state but not an intermediate, was made by these authors.

What are the consequences of a head-to-tail reaction with respect to asymmetric induction? Formation of a betaine using a head-to-tail reaction would appear to be the best possible mechanism for a stereoselective reaction. This alignment places the auxiliary *syn* to the substituents on the carbonyl function, and therefore the greatest preference for Si or Re selectivity would be generated. In a head-to-head approach, the chiral auxiliary can only interact with the lone pairs of the oxygen and could not possibly induce much facial selectivity. Therefore if a head-to-tail mechanism is operative, there is a good chance that enantioselectivity will be observed. Conversely, if homochirality is obtained, this would be strong evidence for the existence of this type of addition.

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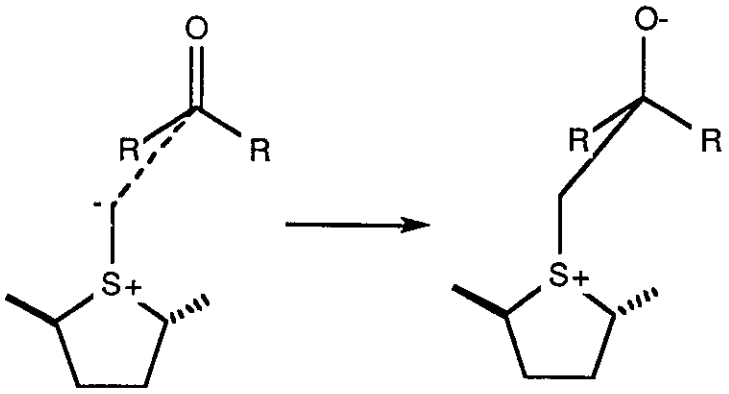
[128] F. Volatron, O. Eisenstein. *J. Am. Chem. Soc.*, **109**, 1 (1987).



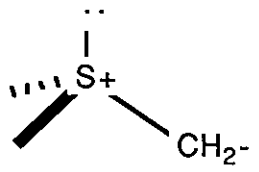

One facet of this project which we considered to be important was the problem of predicting and/or rationalizing any asymmetry which might be observed in epoxidation reactions. In examining this problem, we exclusively employed the head-to-tail type of reaction which appears to us to be the most logical mode of reaction. A serious difficulty exists however in that the structure of unstabilized sulfur ylides is not precisely known. Two possibilities are shown below.


A B

The structure B could arise by delocalization of the carbon electron density into low lying *d* orbitals of the sulfur.[107] Delocalization can also be accommodated by the *p* orbitals of the sulfur.[129] In any case, a double bonded resonance hybrid such as B could give either a planar structure or one in which the alkyl groups on sulfur are orthogonal to groups on carbon ( by $p_C$-$d_S$ overlap with orthogonal $d_S$ orbitals). An ylide structure with a C-S double bond in either

[129] R. Hoffmann, J. M. Howell, E. L. Muetterties. *J. Am. Chem. Soc.*, **94**, 3047 (1972).

case leads to a flat ylide with true $C_2$ symmetry and makes analysis somewhat simple. Conversely structure A gives a more complicated situation. The lone pair on sulfur causes the sulfur to adopt a pyramidal geometry and thus enforces a "bent" configuration on the ylide. This would produce an ylide with pseudo $C_2$ symmetry and complicate the analysis of stereochemistry.




The existence of this type of structure has been demonstrated in the case of stabilized ylides by both nmr an X-ray techniques. The nmr spectra of stabilized sulfur ylides which possess three different substituents on sulfur display AB patterns, thus indicating a pyramidal geometry about sulfur.[130] X-ray crystal structures of other ylides clearly demonstrate that sulfur is non-planar in these molecules.[131] Since these ylides are stabilized, the non-planar geometry at sulfur could be a consequence of delocalization of negative charge into the electron withdrawing group rather than into sulfur, so these results obtained with stabilized ylides therefore may not apply to unstabilized ones. Other evidence, gathered from studies with non-stabilized ylides seems to agree with the stabilized ylide observation that the sulfur is pyramidal. The fact that sulfonium salt **123** rearranges with no loss of chirality indicates that the intermediate ylide cannot be flat. An ylide produced from chiral sulfonium salt **125** was quenched with water to return intact **125** with no loss of optical

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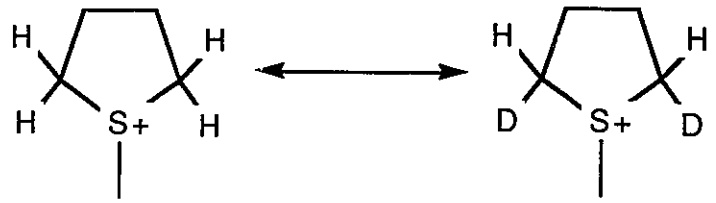
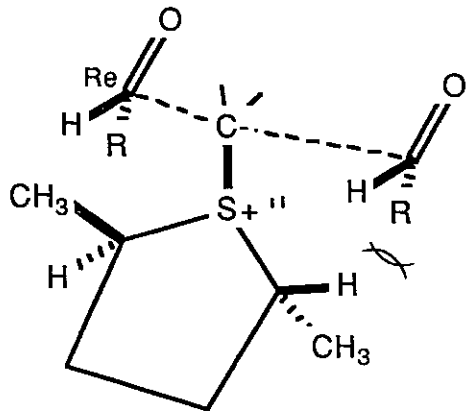
[130] a) K. W. Ratts. *Tetrahedron Lett.*, 4707 (1966); b) A. F. Cook, J. G. Moffatt. *J. Am. Chem. Soc.*, **90**, 740 (1968).
[131] J. P. Schaefer, L. L. Reed. *J. Am. Chem. Soc.*, **94**, 908 (1972).

activity.[107] An nmr study[132] involving H-D exchange on a thiolanium salt showed a large preference for exchanging hydrogens on one side of the ring only, also indicating that the sulfur is pyramidal.



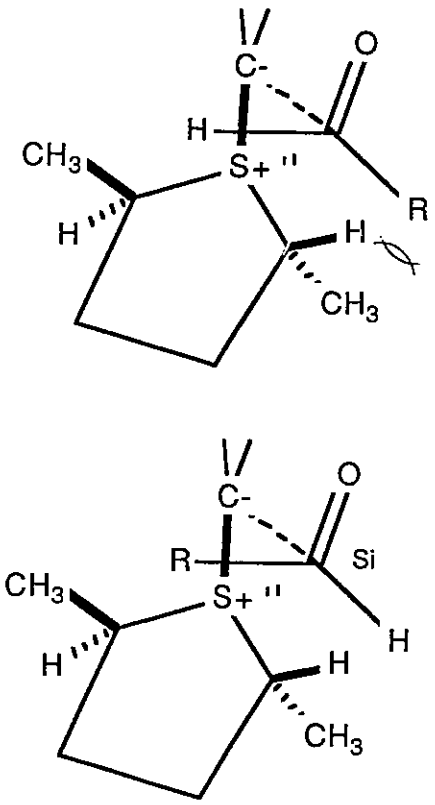

Two types of interaction are possible between a carbonyl compound and a pyramidal sulfur ylide, they are the top-or-bottom and side approaches. As is shown below, each type of reaction leads to a different predictions regarding the stereochemical outcome. A better understanding leading to future predictions may be possible after some preliminary results have been obtained. Theoretical studies show that an orthogonal ylide (side approach) is preferred.[128]

[132] a) C. Barbarella, A. Garbesi, A. Fava. *Helv. Chim. Acta.*, **54**, 341 (1971); b) C. Barbarella, A. Garbesi, A. Fava. *Helv. Chim. Acta.*, **54**, 253 (1971); c) C. Barbarella, A. Garbesi, A. Boicelli, A. Fava. *J. Am. Chem. Soc.*, **95**, 8051 (1973).




Side-to-side

In the side type of interaction, the carbonyl component approaches the ylide so that the large R group on the carbonyl is *syn* to the lone pair on sulfur. Approach with R anti to the lone pair results in severe interactions with the substituents α to the sulfur and on the concave side of the molecule. As shown above, this leads to a preference for reaction at the Re face of the aldehyde since presentation of the aldehyde Si face results in interaction with the underlying convex methyl group.




Top-to-bottom

In the top-or-bottom approach, the aldehyde must approach the ylide from the lone pair side only (convex side), because the other face of the ylide is somewhat concave and access is limited by the methyl and hydrogen on that side of the auxiliary. With this restriction, the aldehyde moves to the convex face presenting its' Si face, since R will experience non-bonded interactions with the methyl group during Re face approach (see above).

# Chapter 1
## Synthesis from mannitol

As stated above, the original choice for the sulfide auxiliary was *trans* 2,5-dimethylthiolane **129**. This product is less than ideal however. The resolution of the starting diol does not give large amounts of material ( 300 mg from 5 g of diol) and therefore is not a practical means of preparing **129** in optically active form. The alternative preparation of the required chiral diol is by a yeast reduction. In our hands, attempts to prepare chiral diol by the described yeast reduction procedure were unsuccessful and extremely time consuming. Subsequent discussions with Dr. D. Brooks of Ayerst Co. indicated that modifications to the procedure employed would produce better results, but experience with racemic **129** in the interim indicated that this would not be a good choice for an asymmetric auxiliary. Thiolane **129** has a very unpleasant odor and is somewhat volatile (b.p. 78 - 82°C at 90 mm, this corresponds to about 130°C at atmospheric pressure) making recovery difficult and inefficient. During the course of this study, we learned of an attempt to use chiral thiolane **129** in the epoxidation of benzaldehyde.[133] Although details were not supplied, an optically active salt of **129** was reported to be capable of forming an ylide which would add to benzaldehyde thus producing styrene oxide, but no enanteoselectivity could be detected. This result could be a consequence of epimerization at the positions α to the sulfur since the protons located at these

[133] Whitesell. 8TH IUPAC Conference, Nancy, France (1988).

centres are known to be slightly acidic.[132] Other possible explanations include loss of facial selectivity with an unsubstituted ylide or small chiral groups which cannot produce significant non-bonded interactions with the aldehyde pendant groups. In any case, it was decided to pursue a synthesis of a carbohydrate derived thiolane for reasons of convenience in reactions and also the established chirality would eliminate any need for resolutions or diastereoselectivity.

Mannitol is an inexpensive sugar alcohol which is readily available in large quantities. It possesses the required $C_2$ symmetry as well as having abundant functionality for the attachment of bulky groups, which may contribute to a product with agreeable physical and inductive characteristics. Therefore 1,3:4,6-di-O-benzylidene-D-mannitol[134] **135** was prepared and converted to the known dimesylate **136** using standard conditions ($CH_2Cl_2$, TEA, $CH_3SO_2Cl$, 0°C). The dimesylate **136** had been previously prepared in 83 % by Sinclair,[135] we managed to obtain the highly crystalline dimesylate **136** in quantitative yield by using triethylamine in place of pyridine. Attempts to convert dimesylate **136** into the corresponding thiolane were not successful. Refluxing **136** in a DMF/ethanol mixture with $Na_2S{\cdot}9H_2O$[117] gave no reaction, with dimesylate **136** being recovered quantitatively. Similar results were obtained using sodium thiolacetate, in THF or using PTC;[136] lithium *t*-butyl thiolate;[137] thiourea;[138] bis-(tributylin)sulfide;[139] or with $H_2S$, under a variety of conditions (solvents :

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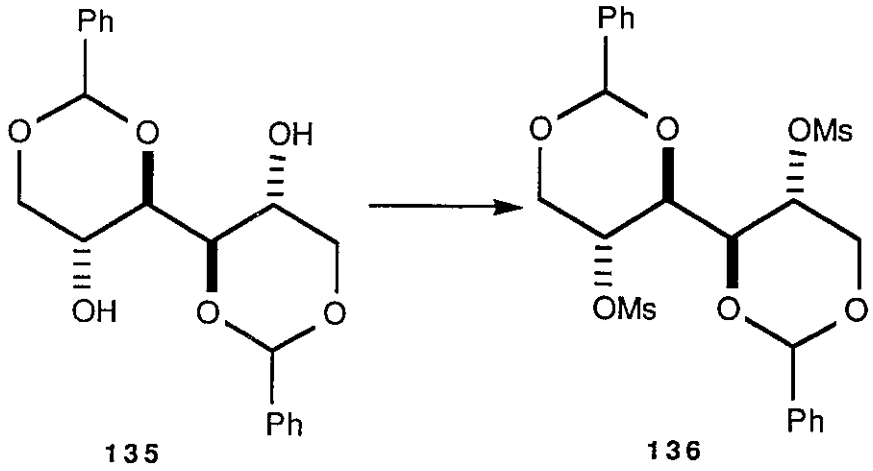
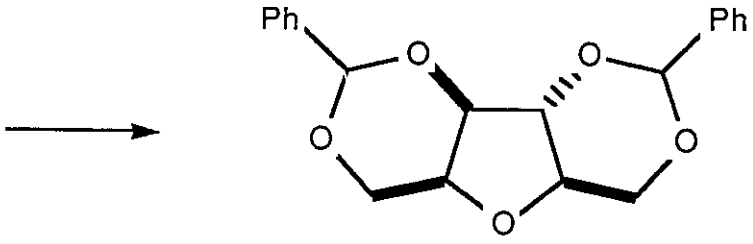
[134] N. Baggett, P. Stribblehill. *J. Chem. Soc., Perkin I*, 1123 (1977).
[135] H. B. Sinclair. *Carbohydr. Res.*, **12**, 150 (1970).
[136] a) W. A. Bonner. *J. Am. Chem. Soc.*, **73**, 2659 (1951); b) D. Horton, M. L. Wolfrom. *J. Org. Chem.*, **27**, 1794 (1962).
[137] C. Daigenais. Unpublished results
[138] G.G. Urquhart, J. W. Gates. Jr., R. Connor. *Org. Syn., Coll. Col. III*, 363 (1955).
[139] a) D. N. Harpp, M. Gingras, T. Aida, T. H. Chan. *Synthesis*, 1122 (1987); b) D. N. Harpp, M. Gingras. *Tetrahedron Lett.*, 4373 (1987); M. Gingras, D. N. Harpp. *Tetrahedron Lett.*, 4669 (1988).

$CH_2Cl_2$, DMF, $CH_3CN$; bases : TEA, NaOAc; temperatures : 20°C or at 60 to 80°C). Refluxing **136** in THF with 10 % NaOH (homogeneous solution) did not give any detectable reaction. A reaction was finally effected by refluxing a mixture of **136**, *t*-BuSH, pyridine and *n*BuLi in DMF for 18 h. Chromatotron chromatography of the crude material gave a 27 % yield of a solid product identified as tetrahydrofuran **137** along with some unreacted dimesylate. The nmr spectrum of **137** contained resonances for 10 different non-aromatic protons, indicating that the $C_2$ symmetry of the starting material had been compromised. Mass spectrometry showed a molecular ion fragment at m/z = 341 (chemical ionization : M + 1) which indicated that a tetrahydrofuran (molecular weight 340 ) had been obtained. This type of product presumably arises from oxygen-sulfur bond cleavage of one of the sulfonate esters, the revealed alkoxide easily undergoing ring closure by displacing the remaining mesylate group to give a 5 membered epoxide.

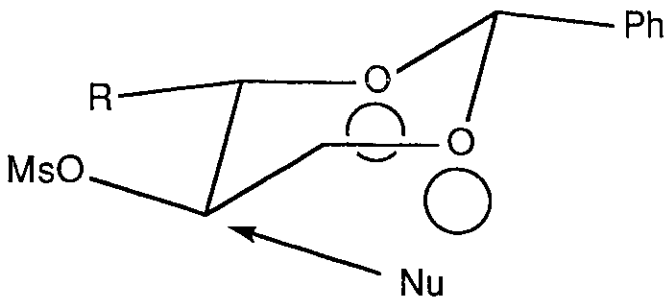



135 136




137

In order to displace a mesylate function from **136**, an incoming nucleophile must approach from under the dioxane chair as shown below. This trajectory could be inhibited by interaction of the nucleophile with the axial lone pairs of the oxygen and therefore displacement is effectively prevented. On the other hand, more efficient leaving groups may compensate for this effect by easing the energetic requirements of the displacement.




Several attempts to convert protected mannitol **135** into a dibromide using $PPh_3 \cdot Br_2$ or $PPh_3 \cdot CBr_4$[140] were not successful, and returned the diol intact. Since neither of these approaches was effective in producing a thiolane, mannitol derivative **135** was then converted to ditriflate **138**. This material, like dimesylate **136** had also been reported in the literature,[141] but the reported procedure (THF, py, $(CF_3SO_2)_2O$, -5°C) was unsatisfactory due to the high reactivity of THF for triflic anhydride. The use of $CH_2Cl_2$ at 0°C as the reaction medium proved to be more convenient, and gave high yields of the ditriflate. This material was a solid which could be recrystallized, but only with large losses of material. The recrystallized product (mp 75 °C) was spectroscopically identical to the crude material (300 MHz nmr), and so ditriflate **138** was subsequently prepared fresh and used immediately without further purification.

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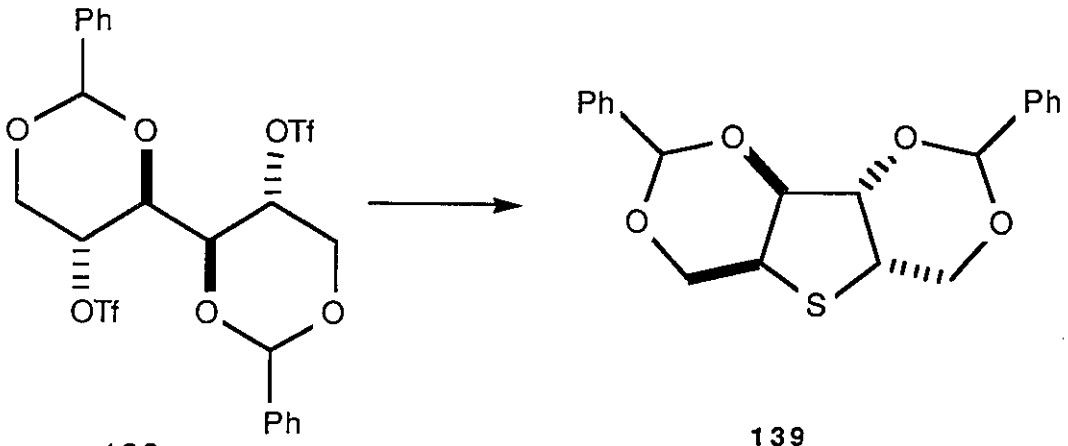
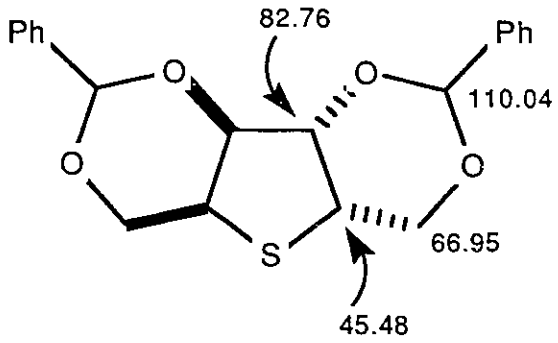
[140] a) P. J. Gargee, R. Johansson, B. Samulesson. *Synthesis*, 168 (`1984); b) R. G. Weiss, E. I. Synder. *J. Org. Chem.*, **36**, 403 (1971); c) L. Kaplan. J. Org. Chem., **31**, 3454 (1966); d) J. P. Schaefer, D. S. Weinberg. *J. Org. Chem.*, **30**, 2635 (1965).

[141] T. K. M. Shing. *J. Chem. Soc., Chem. Commun.*, 262 (1987).



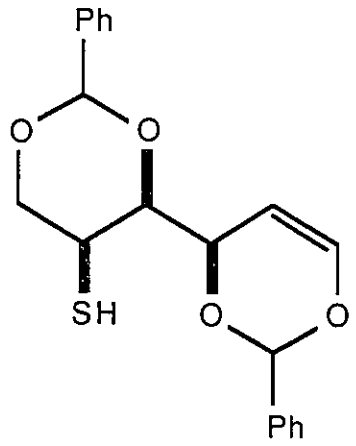

**138** **139**

Reaction of the ditriflate **138** with $Na_2S$ in warm DMF resulted in rapid disappearance of starting material, while treatment with NaH, *t*BuSH in $Et_2O$ and with $H_2S$/TEA in $CH_2Cl_2$, both at room temperature for 18 h, produced no reaction, and incredibly the ditriflate was recovered unharmed. The Harpp reagent ($(Bu_3Sn)_2S$) was also unsuccessful and extensive decomposition of the starting material resulted upon exposure of this reagent to the ditriflate. Addition of a solution of **138** in $CH_3CN$ to a dark blue solution of TEA/$H_2S$ in $CH_3CN$, gave an 18 % yield of the desired thiolane **139** after extensive chromatotron chromatography. This product retained $C_2$ symmetry as evidenced by both $^1H$ and $^{13}C$ nmr. The $^{13}C$ spectrum was most informative showing an acetal carbon resonance at δ100.04, a methylene at δ66.95 and two methines at δ82.76 and δ45.48 in addition to four aromatic signals. The chemical shift of the latter methine clearly shows attachment to a sulfur atom. The key $^{13}C$ spectral assignments for this compound are shown below.




**139**

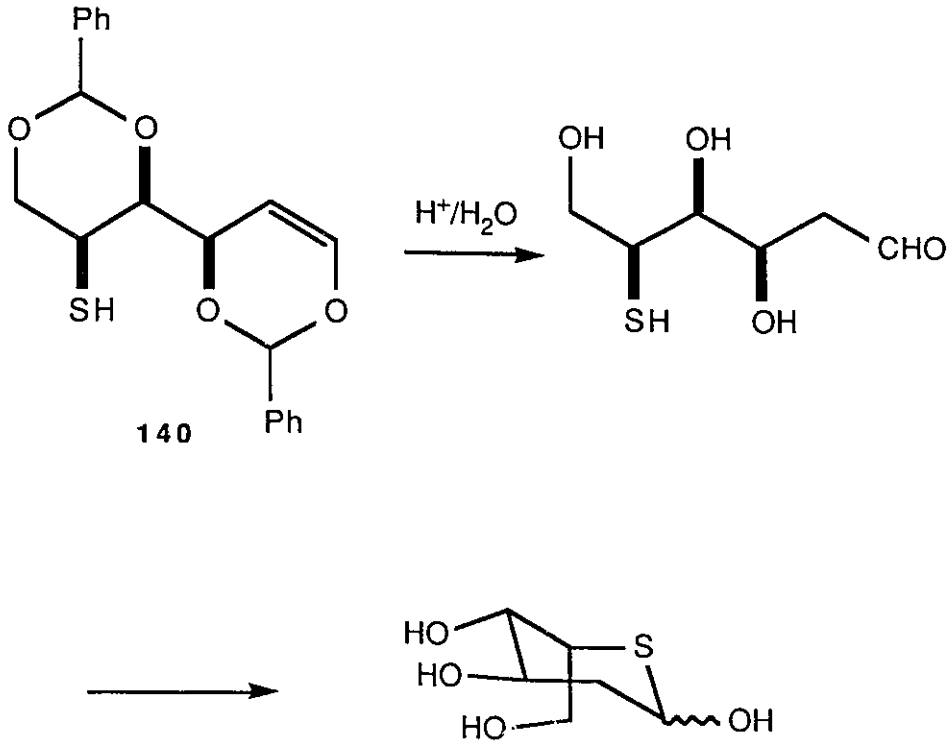
The yield of thiolane **139** obtained from ditriflate **138** was subsequently improved to 42 % by using DMF as the solvent. The use of pyridine as a base or reactions at higher temperatures were not successful. In preparations of **139** using DMF as solvent, a foul smelling by-product was observed which was identified as **140**. Unfortunately this material became the major product in preparative reactions.



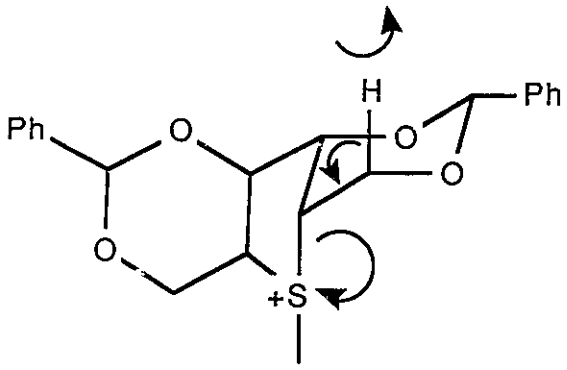

**140**

This material displayed resonances for olefinic protons at δ6.76 and δ5.01, both appearing as doublets of doublets. These chemical shifts are typical of hydrogens bonded to the α and β carbons of an enol ether. The carbon spectrum also showed the presence of unsaturation by the appearance of methine resonances at δ146.03 and δ98.18 (this latter assignment is tentative since the acetal carbons show similar chemical shift and intensity). Since ADEPT indicated that only one methylene was present in the molecule, this product was identified as isomer **140**.

The formation of **140** is possibly a consequence of the configuration of thiolane **139**. As stated above, nucleophilic displacement may be inhibited by non-bonded interactions of the oxygens' axial lone pairs with the approaching nucleophile. The extreme reactivity of the triflate function could easily bring about elimination if nucleophilic displacement is not rapid enough to compete with the alternate elimination pathway. Such an elimination should occur prior to ring closure but probably after sulfur introduction since no doubly eliminated products were observed. Product **140** could conceivably find use as an intermediate in the preparation of unusual thioglycosides by hydrolysis of the benzylidene acetal functions.




Unfortunately attempts to alkylate thiolane **139** and thus produce the desired chiral sulfonium salt (MeOTf, $CH_2Cl_2$,; BnBr, $CH_2Cl_2$; $Me_2SO_4$, $CH_2Cl_2$; MeI, $AgClO_4$, ether) resulted in rapid decomposition of the starting material. Such decomposition may be the result of a β-elimination similar to that depicted below since the sulfur is attached to the dioxane in an axial fashion and is therefore easily eliminated by removal of the axial hydrogen which is oriented *anti*-periplanar to the sulfur. Alternately cleavage of the acetal moiety by the strong alkylating agents used would also result in decomposition.




**139**

In October 1988 a report was published[142] detailing the accidental preparation of thiolane **139**. An attempt to deoxygenate dibenzylidene derivative **135** using the standard Barton radical deoxygenation conditions[143] resulted in the formation of a compound which the authors identified as being **139**. They proposed a possible mechanism in which a thiocarbonate is transferred onto the initial carbon radical centre, forming a dithiocarbonate type intermediate which then ring closes to form **139**.

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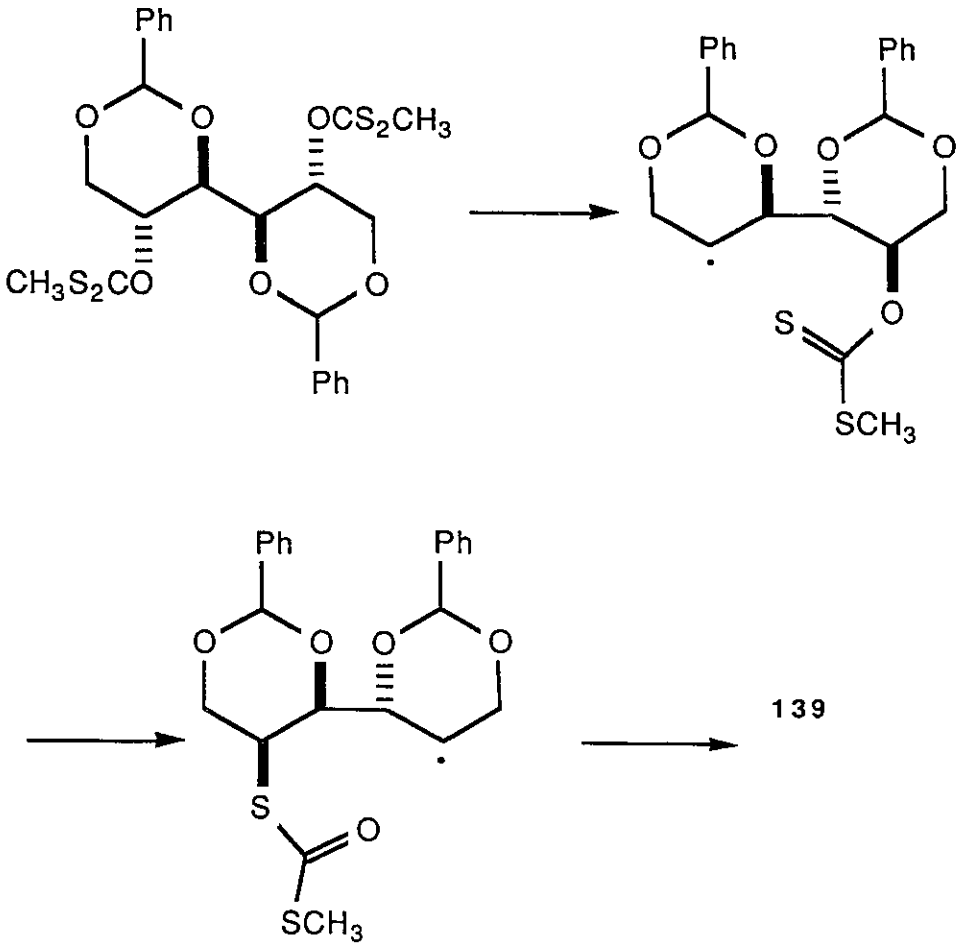
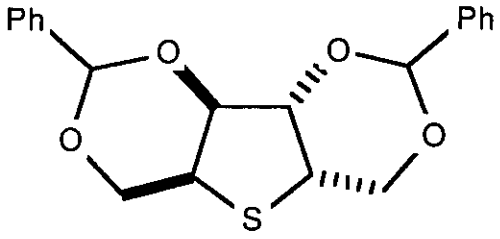
[142] A. V. R. Rao, K. A. Reddy, M. K. Gurjar, A. C. Kunwar. *J. Chem. Soc., Chem. Commun.*, 1273 (1988)

[143] D. H. R. Barton, W. B. Motherwell. *Pure. Appl. Chem.*, **53**, 15 (1981).

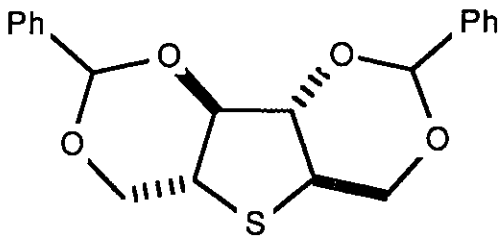



Our experience with thiolane **139** lead us to believe that this is not the product obtained. As was discussed above, **139** undergoes decomposition readily and it's cis fused 5, 6 ring structure make it an unstable isomer. Because a radical reaction would be expected to occur without retention of stereochemistry, we felt that the formation of the more stable trans fused product

**141** would be a more likely outcome. The original paper does not supply spectral data, so the described experiments were repeated. Surprisingly, the product so obtained was found to be the *syn-anti-syn* isomer **139** as the 300 MHz nmr of the material was indistinguishable from the spectrum of the previously prepared material. This result could be useful however, since the preparation of **139** from a bis-xanthate is much more efficient than the triflate route devised in the work and therefore larger amounts of material could be made available for further study.




**139**

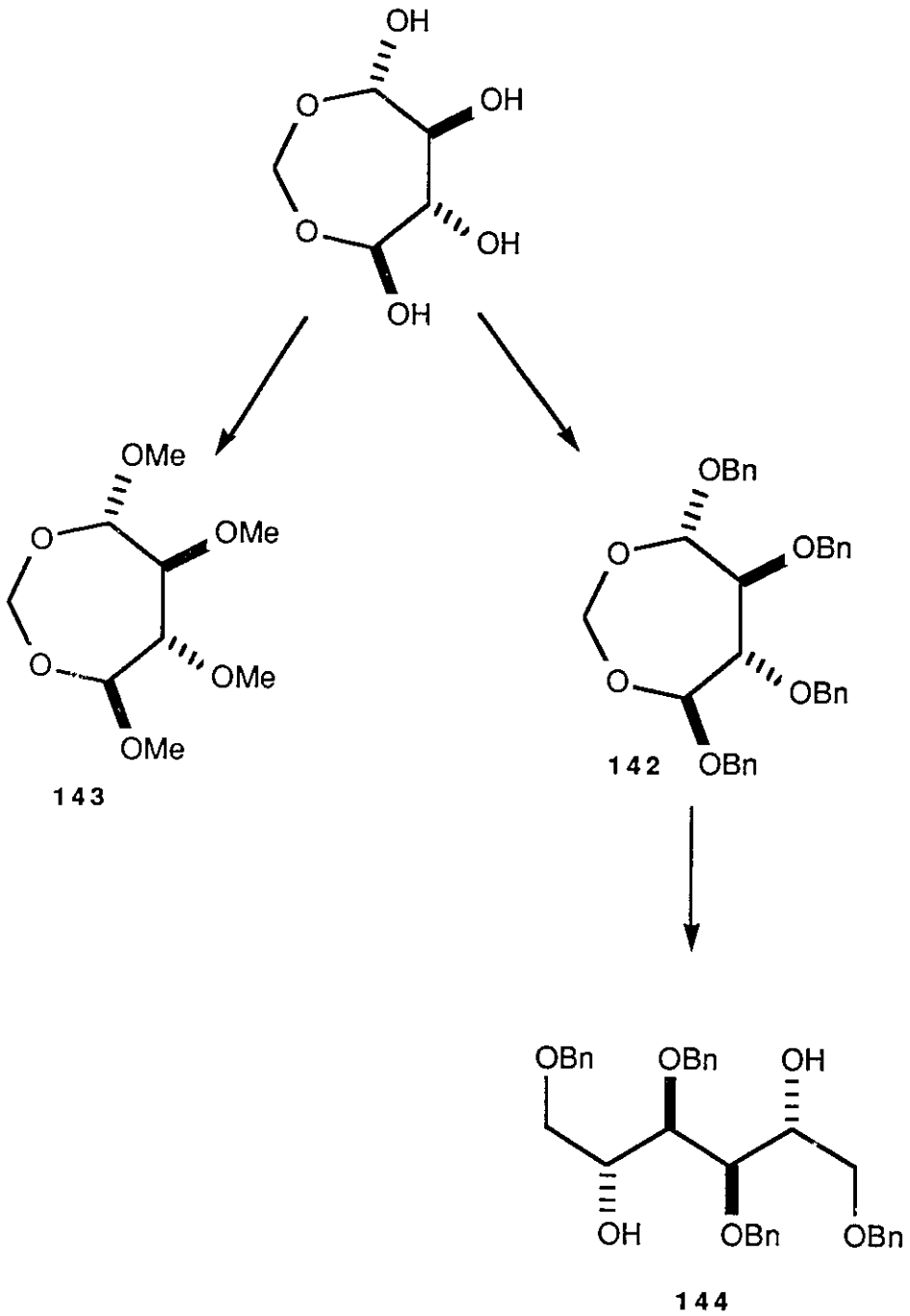



**141**

Since a tricyclic thiolane derivative such as **139** did not produce satisfactory results, it was decided to attempt to prepare a thiolane which did not contain any additional rings or acetals. Avoiding a tricyclic structure would eliminate the lone pair interference of the dioxane rings since the groups in an acyclic molecule could adopt conformations which minimize this type of interaction. Compounds which do not contain acetal functions would be less susceptible to undesired "random" alkylation at positions other than sulfur. Thus 2,5-di-O-methylene-D-mannitol was prepared according to the established

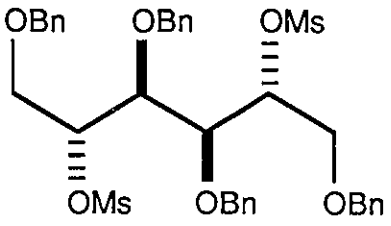
procedure[144] and perbenzylated under standard conditions (BnBr, NaH, DMF) affording tetrabenzyl derivative **142** in 86 % yield. Tetramethyl product **143** was also prepared using similar conditions, but was observed to be somewhat volatile and was not pursued. Hydrolysis of the methylene acetal with 15 % $H_2SO_4$ in refluxing methanol gave diol **144** in good yield. This compound displayed proton nmr resonances at δ4.0, δ3.48, δ3.63 and δ3.57 which were assigned to the various protons of the hexitol chain. The signals at δ3.63 and δ3.57 appeared as the AB part of an ABX system, while the signal at δ4.0 was a broad multiplet which was assigned to the methine bonded to the OH and resonated as the X part of the ABX pattern. The remaining doublet at δ3.84 was assigned to the internal methine proton.

[144] A. T. Ness, R. M. Hann, C. S. Hudson. *J. Am. Chem. Soc.*, **53**, 2215 (1943).

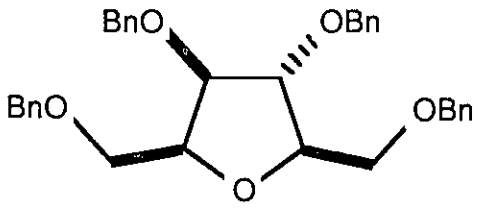



Diol **144** was smoothly converted into dimesylate **145** using standard conditions. The $^{1}H$ nmr of this product was very similar to that of diol **144**, but

the formation of a dimesylate was confirmed by the appearance of a methyl singlet at δ2.92 and by the downward shift of the methine signal for protons at C-2;C-5 from δ4.0 to δ4.9. Attempts to convert dimesylate **145** into a thiolane ( $(Bu_3Sn)_2S$, $CH_3CN$, TBAF; TEA, $H_2S$, DMF; $Na_2S$, DMF, Δ) returned intact the dimesylate. As with the benzylidene diol **135**, diol **144** was treated with triflic anhydride and pyridine in an attempt to prepare a bistriflate. This reaction resulted in the production of a product which was clearly not the desired ditriflate, but instead was identified as substituted tetrahydrofuran **146**. The $^1H$ nmr spectrum of this material was complex, but clearly indicated a loss of $C_2$ symmetry. Chemical ionization mass spectrometry displayed a molecular ion consistent with the assigned structure. Apparently the acyclic structure is unhindered enough to permit easy cyclization, even at low temperatures. A reaction of diol **144** and triflic anhydride was performed by beginning the reaction at -78°C and allowing it to slowly warm until TLC indicated that the starting material had been consumed. After workup, tetrahydrofuran **146** was isolated as the only product.




**145**




**146**

The next goal involved the preparation of a partially deoxygenated product since the less crowded penultimate product so produced would cyclize more easily without the need for triflates. The first route began with 1,2:5,6-di-O-isopropylidene-D-mannitol **147**[145] which was transformed into bisbenzyl ether **148** using phase transfer catalysis in 60 % yield. Stirring this material in 80 % acetic acid gave the tetrol **149** in quantitative yield. We had employed this route since several reports[146] had appeared which indicated that the primary hydroxyl moieties of tetrol derivatives similar to **149** could be successfully differentiated from the adjacent secondary function. Attempts to do this using procedures similar to those described resulted in the formation of complex mixtures. In addition to these methods (TsCl, py; MsCl, py; TsCl, py then $(AcO)_2O$; TsCl, py then AcCl ) N-tosylimidazole[147] also failed to effect a satisfactory reaction.

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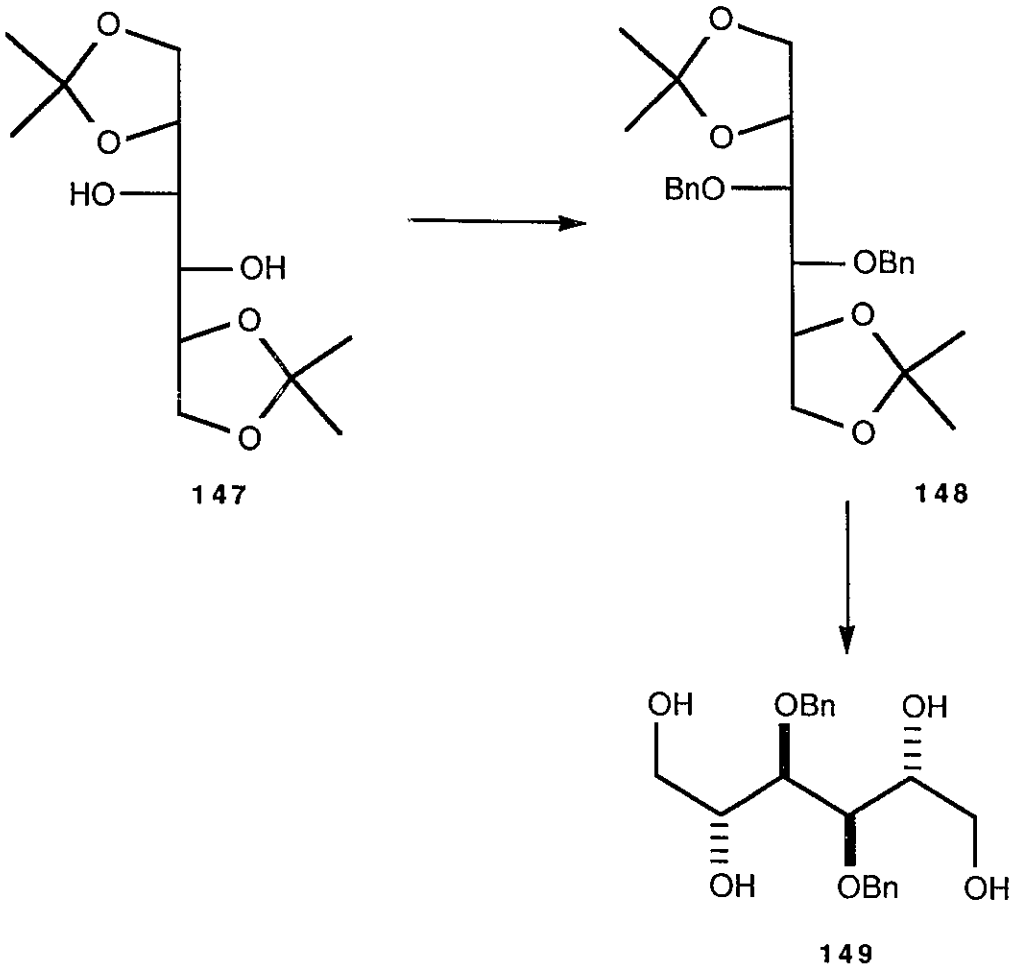
[145] a) E. Baer. *J. Am. Chem. Soc.*, **67**, 338 (1945); b) R. S. Tipson, A. Cohen. *Carbohydr. Res.*, **7**, 232 (1968); c) G. F. Chittenden. *Carbohydr. Res.*, **84**, 350 (1980); d) G. F. Chittenden. *Carbohydr. Res.*, **87**, 219 (1980); e) M. L. Wolfrom, A. B. Diwadkar, J. Gelas, D. Horton. *Carbohydr. Res.*, **35**, 87 (1974); f) J. L. Debost, J. Gelas, D. Horton. *J. Org. Chem.*, **48**, 1381 (1983). Each of these methods has been critically reviewed : J. Kuszmann, E. Tomori, I. Meerwald. *Carbohydr. Res.*, **128**, 87 (1984). These authors reccomend the original method of Baer.

[146] a) J. Kuszmann. *Carbohydr. Res.*, **71**, 1232 (1974); b) J. Kuszmann, P. Sohár. *Carbohydr. Res.*, **83**, 63 (1980).

[147] D. Hicks, B. Fraser-Reid. *Synthesis*, 203 (1974).

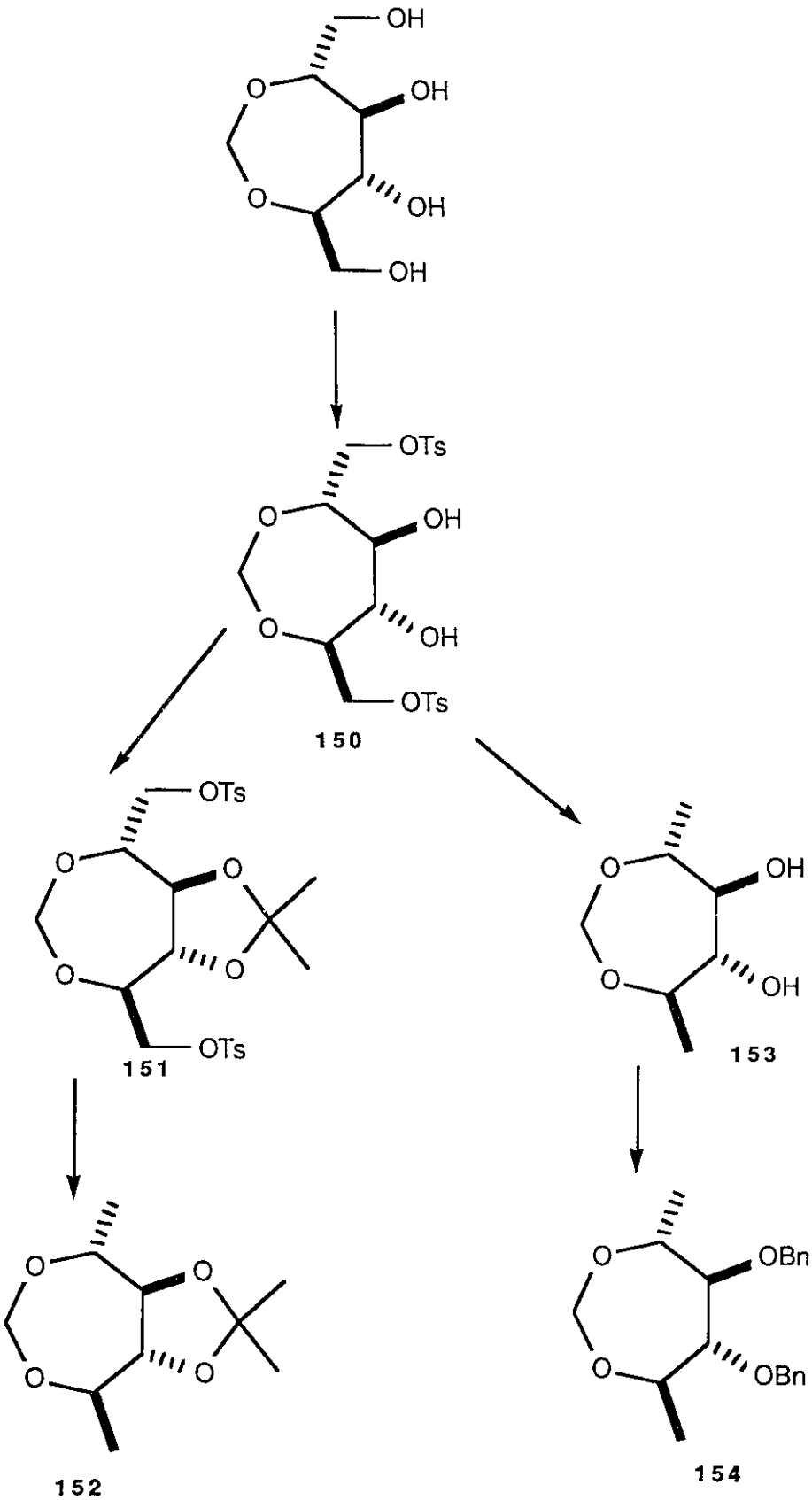



147 148 149

Because selectivity for a primary hydroxyl could not be achieved satisfactorily with a mannitol derivative blocked at the 3, 4 positions, we decided to use a starting material in which the 2, 5 positions were occupied. Moving the open secondary alcohol functions one position away from the primary moieties could result in increased selectivity since reagents would not be approaching similar functions which were side by side. The previously employed 2,5-di-O-

methylene-D-mannitol was transformed into the known[148] ditosylate **150** in 80% yield. Isopropylidene formation with $FeCl_3$ and acetone gave blocked derivative **151** in 50% yield. Removal of the tosylate ester with lithium aluminumhydride (LAH) proceeded without incident to give deoxygenated product **152** in a return of 60 %. Before the removal of the acetonide could be investigated, ditosylate **150** was successfully transformed into the desired product **153** by LAH reduction. This reaction involves initial protection of the hydroxyl groups as aluminate ethers followed by $S_N2$ displacement of the tosylate functions, and proved to be a convenient way of preparing **153**. Benzylation in THF using benzyl bromide, sodium hydride and catalytic tetrabutylammonium iodide[149] gave the expected product **154** in 72 % yield.

[148] S. B. Baker. *Can. J. Chem.*, **31**, 821 (1953).
[149] C. Czernecki, C. Georgoulis, C. Provelenghiou. *Tetrahedron Lett.*, 3535 (1976).


OH
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O
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O
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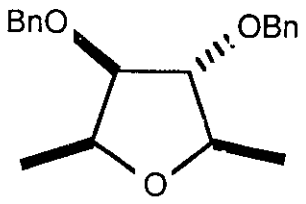
151
OTs
OH
OH
153
O
O
O
O
152
OBn
OBn
154

The removal of the methylene acetal of **154** proved to be extremely troublesome. Refluxing in 90% HOAc or 90% TFA resulted in no reaction. Hydrolysis in methanol containing $H_2SO_4$ (20 % solution) gave tetrahydrofuran product **155**, both at reflux and at room temperature. An attempt to trap any alcohols formed by performing the hydrolysis of **154** in an $(AcO)_2O$/HOAc mixture was ineffective. Addition of catalytic sulfuric acid resulted in the recovery of benzyl acetate in good yields. The use of boron trichloride[150] resulted in decomposition. No reaction could be observed in attempts to oxidize the methylene acetal with ozone,[151] or remove it with lead tetra-acetate.




**155**

Because the methylene acetal of **154** had been impossible to remove, an attempt was made to use a benzylidene acetal instead. Thus 1,3:2,5:4,6-tri-O-benzylidene-D-mannitol **156** was made[152] and refluxed in $CCl_4$ with two equivalents of NBS.[153] The product of this reaction, dibromide **157** produced a very interesting $^1H$ nmr spectrum. The symmetry of the molecule appeared to have been broken because of the large number of signals however compound

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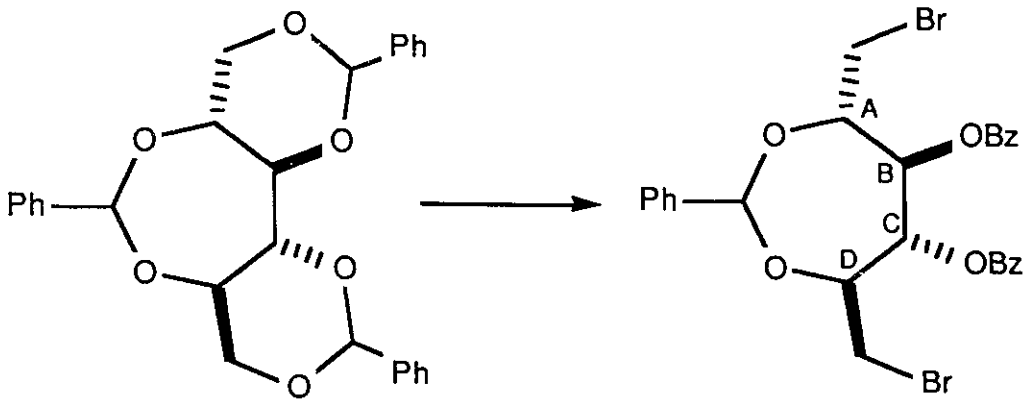
[150] a) J. G. Bonner. *Methods Carbohydr. Chem.*, **2**, 314 (1963); b) S. Teitel, J. O'Brien, A. Brossi. *J. Org. Chem.*, **31**, 3368 (1972).
[151] a) P. Deslongchamps, C. Moreau. *Can. J. Chem.*, **49**, 2465 (1971); b) R. J. Taillefer, S. E. Thomas, V. Nadeau, S. Flizár, H. Henry. *Can. J. Chem.*, **58**, 1138 (1980).
[152] T. S. Patterson, A. R. Todd. *J. Chem. Soc.*, 2876 (1929).
[153] S. Hanessian. *Methods Carbohydr. Chem.*, **6**, 183 (1972).

**157** possesses an additional chiral centre at the benzylidene acetal carbon. This places each of the hexitol hydrogens in different environments and produces a complex spectrum.




**156** **157**

The two bromomethylene moieties each appeared as the AB part of ABX patterns in the δ3.58 to δ3.33 region of the spectrum. The four interior protons however, appeared to form a complex pattern, which was designated as an XABY system. The protons at position A were assigned to a multiplet at δ4.52-4.45. This signal forms the X part of the XABY pattern, as well as coupling to the adjacent bromomethylene (X part of an ABX). The proton at position B was assigned to a resonance at δ5.60 (AB part of an XABY pattern) and proton C to and XABY signal at δ5.47. A remaining multiplet at δ4.26-4.20 was assigned to position D. The chemical shifts of these four protons and their interrelating coupling constants were originally determined by employing the standard ABX

formula[154], using the approximation that the A and D protons together formed the X part of the ABX. The values obtained in this manner are shown in table 4. The validity of this assumption was verified by performing a spin simulation experiment using the values in table 4 as the initial data set. The simulated spectrum (figure 7) was strikingly similar to the actual spectrum (figure 8) indicating that the initial analysis was valid. The simulated chemical shifts and coupling constants are reproduced in table 5.

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[154] R. J. Abraham, P. Loftus. "Proton and Carbon-13 NMR Spectroscopy", John Wiley & Sons, Toronto, 1383. pp 74-75.

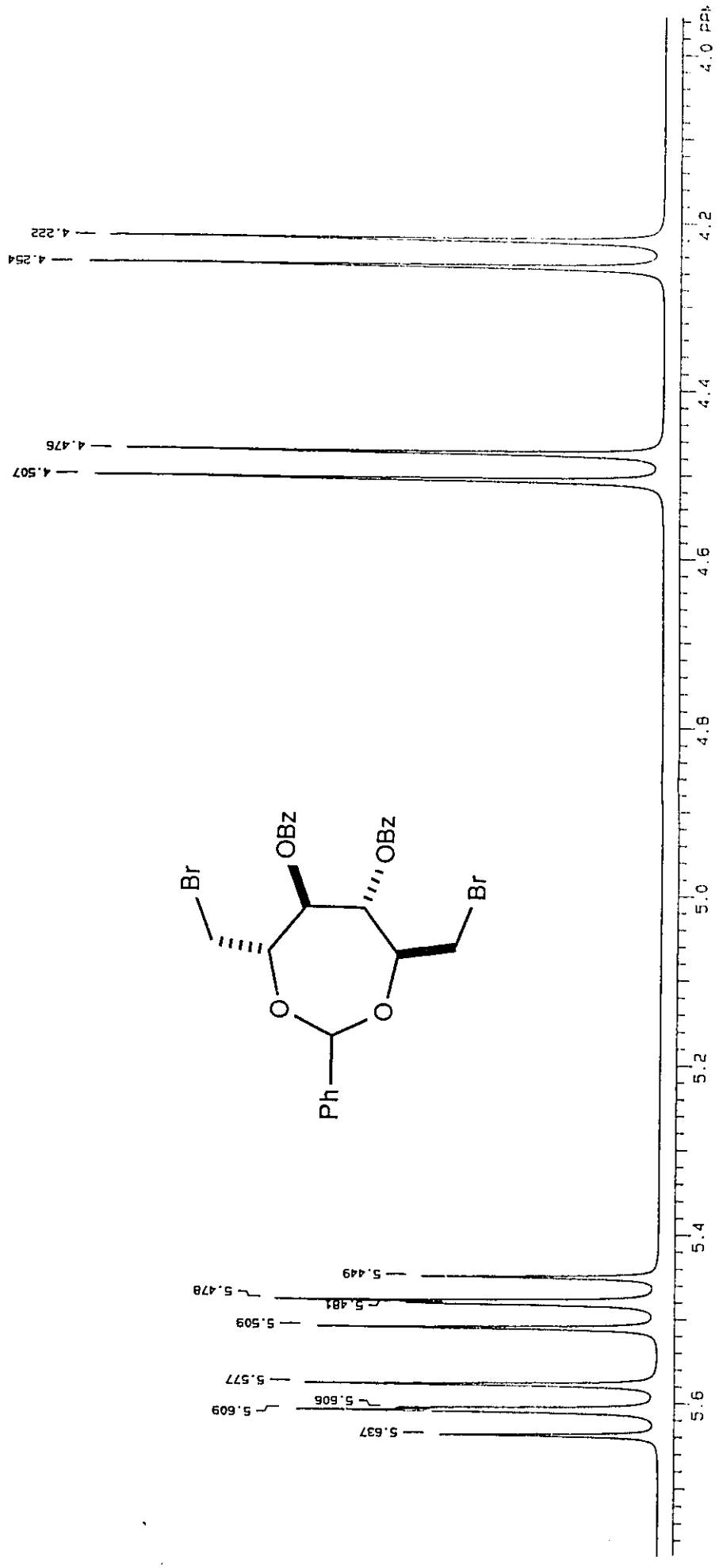



**Figure 7**: Spin simulation nmr spectrum of **157**

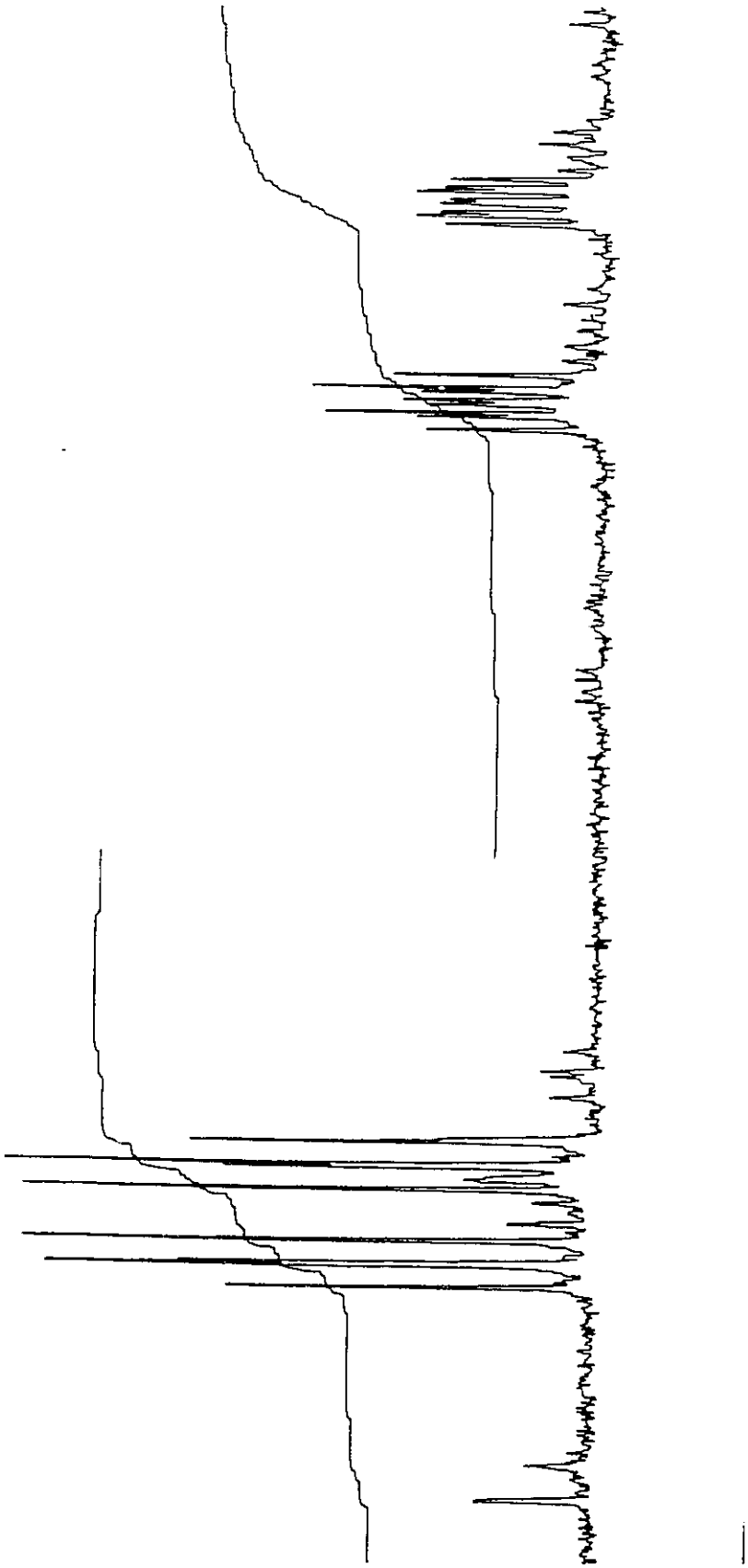
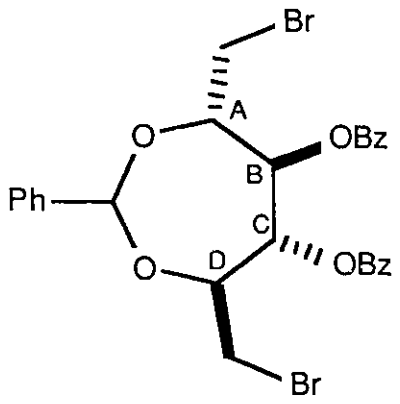


**Figure 8**: Expansion of nmr spectrum of **157**

**Table 4**: Chemical shifts and coupling constants calculated by hand for the XABY system of **157**. Values are given in Hertz.

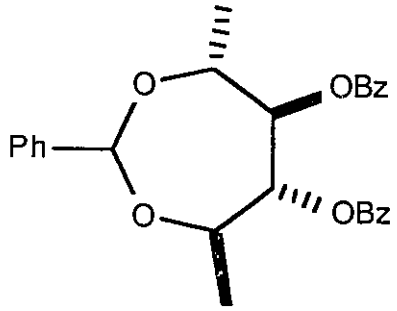



**157**

| | |
|---|---|
| $\nu_A$ = 1270 | $J_{AB}$=9.6 |
| $\nu_B$ = 1680.8 | $J_{AC}$=0.0 |
| $\nu_C$ = 1643.6 | $J_{AD}$=0.0 |
| $\nu_D$ = 1335 | $J_{BC}$=8.5 |
| | $J_{BD}$=0.0 |
| | $J_{CD}$=9.6 |

**Table 5**: Chemical shifts and coupling constants calculated by spin simulation for the XABY system of **157**. Values are given in Hertz.

| | |
|---|---|
| $\nu_A$ = 1270 | $J_{AB}$=9.49 |
| $\nu_B$ = 1681.7 | $J_{AC}$=0.0 |
| $\nu_C$ = 1644.3 | $J_{AD}$=0.0 |
| $\nu_D$ = 1347 | $J_{BC}$=8.5 |
| | $J_{BD}$=0.0 |
| | $J_{CD}$=9.41 |



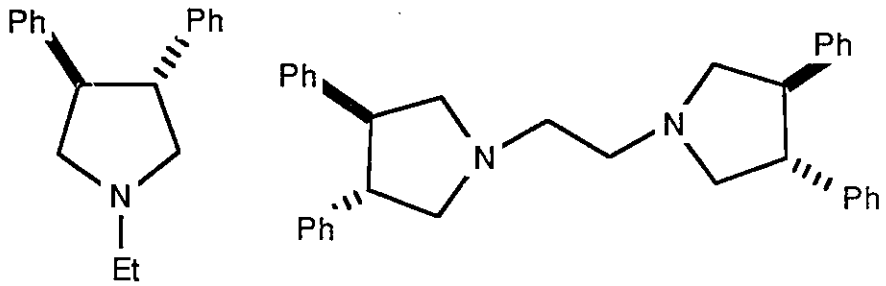

**158**

An attempted reduction of **157** with lithium aluminumhydride returned only benzyl alcohol, none of the desired product could be observed. A reaction with $NaBH_4$ in DMF[155] gave a poor yield of crude **158**, which could not be satisfactorily purified. Tributyltinhydride gave a complex mixture, while an additional $LiAlH_4$ reaction containing LiH to regenerate $LiAlH_4$ [156] also was unsuccessful. A reaction with superhydride afforded benzyl alcohol as the only recoverable product.

[155] M. E. Vol'din, M. Dvolaitzky, I. Levin. *Bull. Soc. Chim. Fr.*, 1526 (1970).
[156] J. E. Johnson, R. H. Blizzard, H. W. Carhart. *J. Am. Chem. Soc.*, **70**, 3664 (1948).

# Chapter 2
# Synthesis from Tartrate

Because of the various difficulties encountered in attempts to synthesize a suitable thiolane from mannitol, it was decided to employ a simpler carbohydrate starting material. The substance chosen was L-tartrate since it is readily available and is functionalized in such a way that thiolane formation was expected to be easy. The major drawback to a thiolane derived from tartrate is that the chiral centres would not be at the most favorable α position but at the more remote β sites. Some precedence does exist however demonstrating that substrates substituted in such a way can induce asymmetry. Roush has achieved moderate to good selectivity using diisopropyl tartrate modified (E)-crotonylboronates in aldol type condensations,[157] and the related tertiary amines have been successful in asymmetric osmylation reactions.[158]




[157] a) W. R. Roush, R. L. Halterman. *J. Am. Chem. Soc.*, **108**, 294 (1986); b) W. R. Roush, A. D. Palkowitz, M. A. J. Palmer. *J. Org. Chem.*, **52**, 316 (1987); W. R. Roush, A. E. Walts, L. K. Hoong. *J. Am. Chem. Soc.*, **107**, 8186 (1985).

[158] K. Tomioka, M. Nakajima, Y. Iitaka, K. Koga. *Tetrahedron Lett.*, 573 (1988).

Our synthesis began with the recently available ditosylate **159** which is easily prepared from diethyl or dimethyl-D-tartrate in three steps.[159] Removal of the isopropylidene function by refluxing in 80 % acetic acid proceeded smoothly giving diol **160** in quantitative yield. The $^1H$ nmr spectrum of this compound indicated the presence of tosylate functions by the appearance of a clear aromatic AB pattern at δ7.76 and δ7.34 along with a methyl singlet at δ2.44. The tetrol backbone protons resonated as multiplets at 4.16-4.04 ppm and at 3.90-3.86 ppm. In order to avoid tampering with the tosylate functions, a protecting group which could be applied using acidic conditions was chosen. Thus diol **160** was dissolved in dry $CH_2Cl_2$ with a slight excess of dihydropyran and catalytic amount of PTS was added.[160] These conditions gave the bis-(tetrahydropyran) derivative **161** in high yield. Cyclization using $Na_2S{\cdot}9H_2O$ gave the desired thiolane **162** in poor (26 %) yield. This product was obtained as a mixture of diastereomers since the acetal carbons represent additional chiral centres. No selectivity was observed with regard to these centres as the nmr spectrum of **162** showed the presence of three isomers in a 1:2:1 ratio (figure 9). Various attempts to alkylate **162** and produce a sulfomium salt resulted in decomposition; reagents tried included MeI, $AgClO_4$; $Me_3OBF_4$; MeOTf; MeI in ether; MeI neat; benzyl bromide, $H_2O$, Δ. The observed decomposition may be the result of β-eliminations, or more likely a consequence of interaction of the acetal function with the strong alkylating reagents employed.

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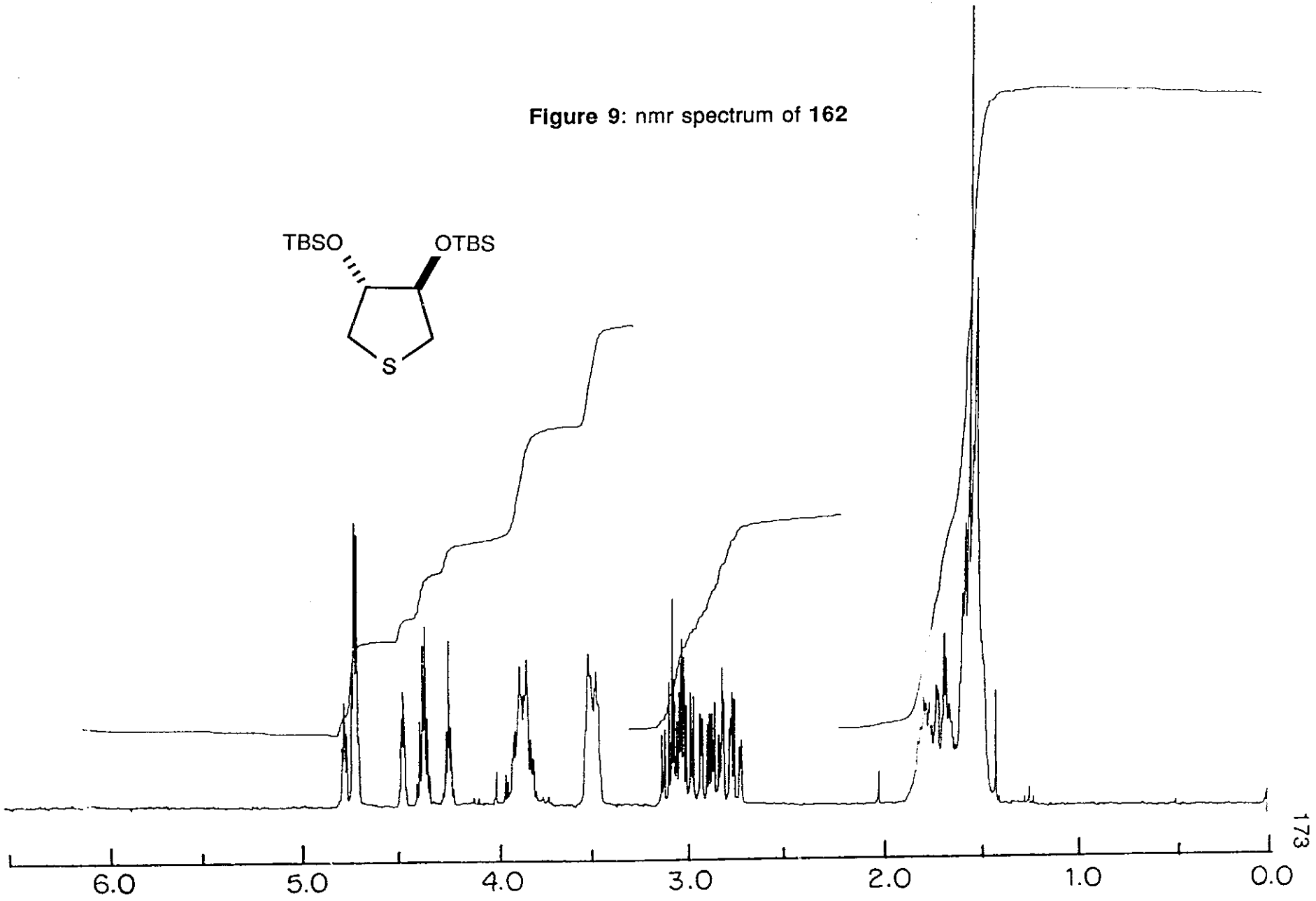
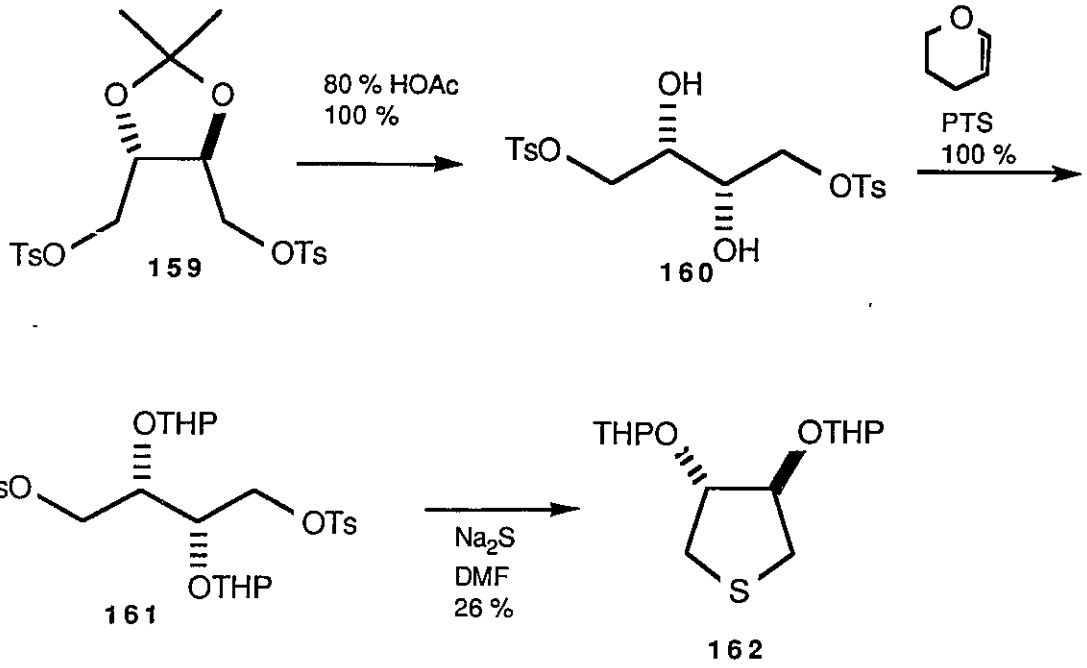
[159] B. A. Murrer, J. M. Brown, P. A. Parker. *Synthesis*, 350 (1979).
[160] K. F. Bernady, M. B. Floyd, J. F. Poletto, M. J. Weiss. *J. Org. Chem.*, **44**, 1438 (1979).

**Figure 9**: nmr spectrum of **162**

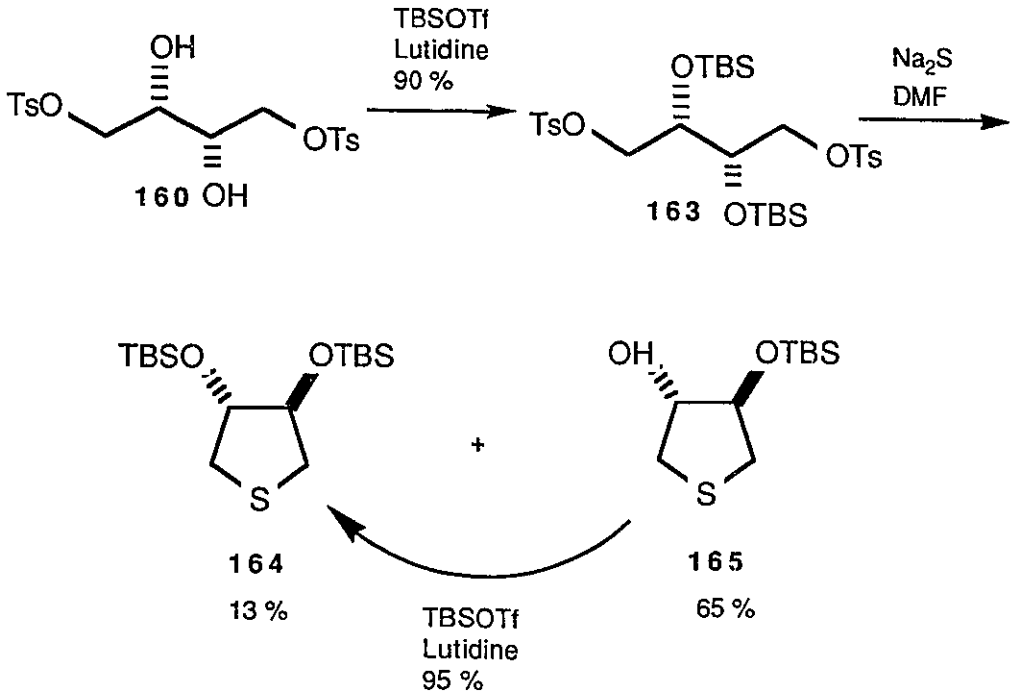





In order to avoid the problem of acetal decomposition, the easily introduced *t*-butyldimethylsilyl (TBS) ether was substituted for the tetrahydropyranyl group. Thus diol **160** was silylated using *t*-butyldimethylsilyl triflate[161] with 2,6-lutidine as base affording disilyl ether **163** in 90 % yield. Three large singlets at δ0.74 (18H), δ0.01 (6H) and at δ -0.03 (6H) in the $^1$H nmr confirmed the presence of two TBS functions. The retention of the tosylate groups was indicated by the appearance of standard tosylate resonances at δ7.72, δ7.31 (both forming an AB pattern) and at δ2.43 (singlet). The tetrol backbone protons appeared as multiplets at δ4.09 and δ3.78-3.75. Cyclization

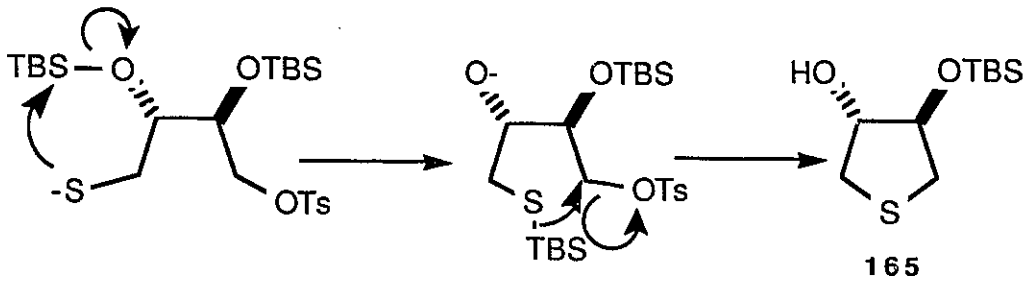
[161] R. F. Stewart, L. L. Miller. *J. Am. Chem. Soc.*, **102**, 4999 (1980).

of this material using $Na_2S$ gave a low yield (13 %) of the desired thiolane **164** along with a 65 % yield of desilylated derivative **165**.



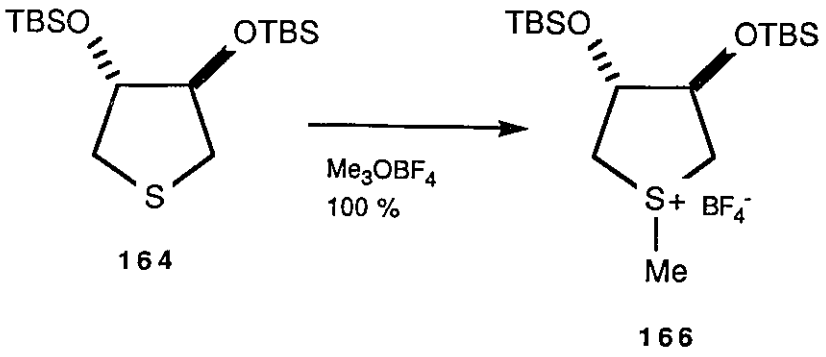

Product **165** displayed an nmr spectrum which showed the absence of one TBS group, along with a loss of $C_2$ symmetry. Mass spectrometry indicated that the product had a molecular weight consistent with structure **165**. This product may arise from a transfer of silicon from oxygen to sulfur in the pre-cyclization intermediate and thus a TBS group is then lost as cyclization occurs. Alcohol **165** was readily converted to the desired product **164** using TBSOTf in $CH_2Cl_2$ in 95 % yield, resulting in an overall yield of **164** from ditosylate **163** of 75 %. The $^{13}C$ nmr spectrum of **164** contained only the expected six resonances. The methylene carbons adjacent to the sulfur resonated at δ35.86 while the methine carbons bearing oxygen appeared at δ78.98. In addition to these signals, peaks resulting from the various carbons in the TBS group were

also noted. The *t*-butyl group produced large signals at δ25.82 ($CH_3$) and at δ18.05 (quaternary carbon). The two pairs of methyl groups bonded directly to silicon resonated at -4.54 and -4.62 ppm.

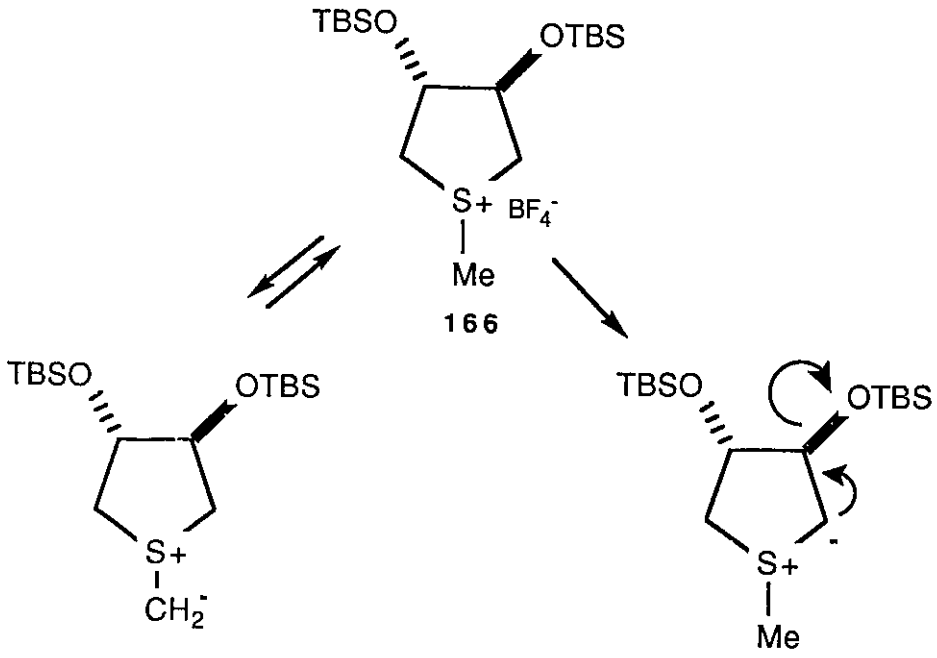



**165**

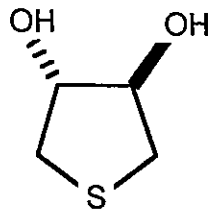
Alkylation of thiolane **164** with Meerwein's salt gave a quantitative yield of the desired sulfonium salt **166**. The formation of this compound was confirmed by $^1H$ and $^{13}C$ nmr experiments, which both showed downfield shifts for the resonances of the methylene groups located adjacent to the sulfur with respect to resonances observed for thiolane **164**. The magnitude of this shift was approximately 1 ppm for $^1H$ (δ2.50-3.15 moving to δ3.35-3.89) and 10 ppm for $^{13}C$ (δ35.86 ppm moving to δ48.60 and δ52.41 ppm). The $C_2$ symmetry of the compound was shown to have been compromised by the pyramidal geometry of the sulfur as evidenced by the doubling of resonances in the $^1H$ and $^{13}C$ spectra of **166**. The $^{13}C$ spectrum of **166** contained 11 resonances (10 for the thiolane and one S-methyl resonance at δ28.48) in contrast to only the minimum six observed for thiolane **164**.



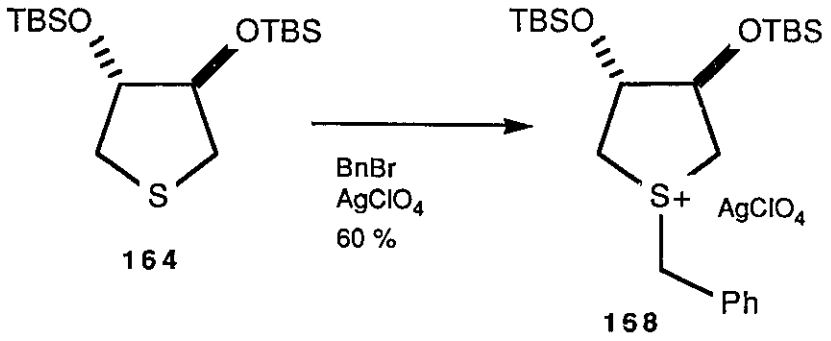

Attempts to generate an ylide from methylsulfonium salt **166** and condense it with benzaldehyde resulted in decomposition of the salt and recovery of benzaldehyde. The bases used were LDA; LDA, TMEDA; *n*BuLi; 50 % NaOH, PTC; $NaCH_2S(O)CH_3$. The observed decomposition may be a consequence of competitive deprotonation of one of the ring protons which can result in elimination.



In order to overcome this difficulty it was decided to to prepare a substituted sulfonium salt possessing a moderately activating group. Allyl iodide gave no reaction, even after several days. Refluxing **164** in ethanol with benzyl bromide[162] gave a good yield of the product (**167**) resulting from TBS removal instead of the expected benzylsulfonium salt formation.




**167**




**164** **168**

Addition of $AgClO_4$ to a solution of **164** and benzyl bromide in anhydrous ether gave a moderate yield of benzylsulfonium salt **168**. This material displayed poor solubility and moderate instability, but 60 MHz nmr indicated that a salt had been formed based on the downfield chemical shifts

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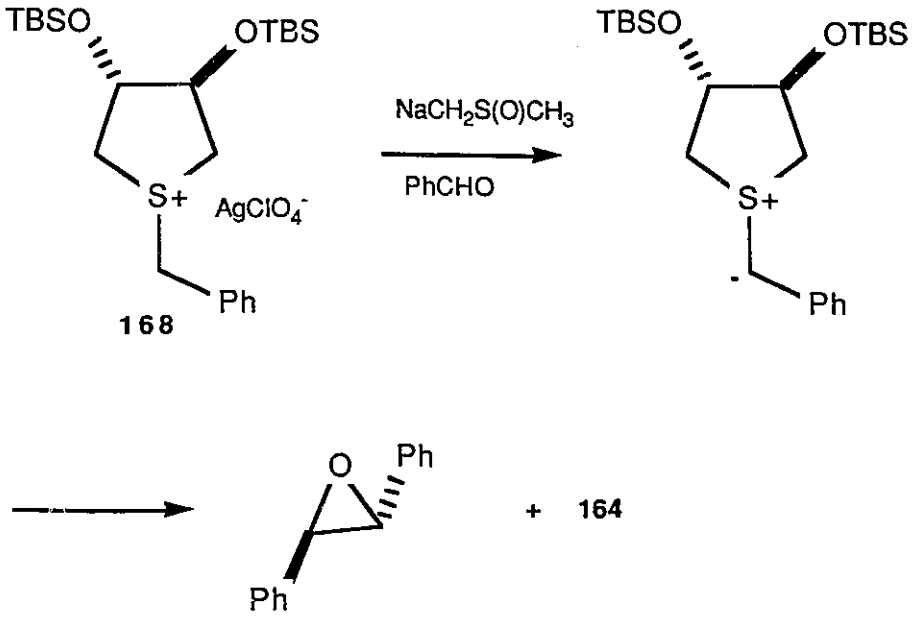
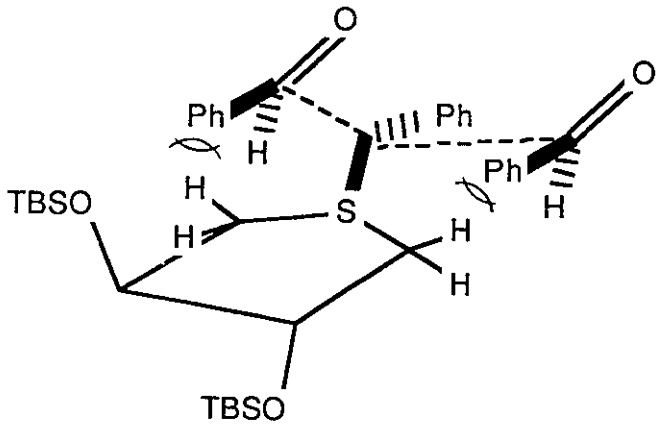
[162] M. J. Hatch. *J. Org. Chem.*, **34**, 2133 (1969).

similar to those noted previously for **166**. For example, the methylene resonances observed at δ2.03 and δ2.62 for **164** appeared as part of a multiplet at δ4.8-3.5, a shift of approximately 1 ppm. Reaction of **166** with dimsyl sodium at -10°C followed by addition of freshly distilled benzaldehyde gave *trans* stillbene oxide in 27 % yield, no *cis* epoxide was observed. Furthermore, the *trans* stillbene oxide was optically active with an $[\alpha]_D$ = 55.2° (c= 1.05, acetone). The predominant isomer was found to be the (R, R) isomer based on comparison with the literature value of 291° (c= 0.05, acetone).[163] Thus *trans* stillbene oxide was formed from the ylide derived from **168** and benzaldehyde with 19 % enanteomeric excess.

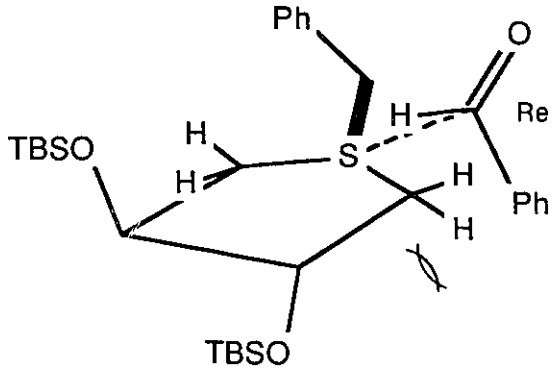
[163] a) M. Imuta, H. Ziffer. *J. Org. Chem.*, **44**, 2505 (1979); b) J. Read, I. G. M. Campbell. *J. Chem. Soc.*, 2377 (1930).

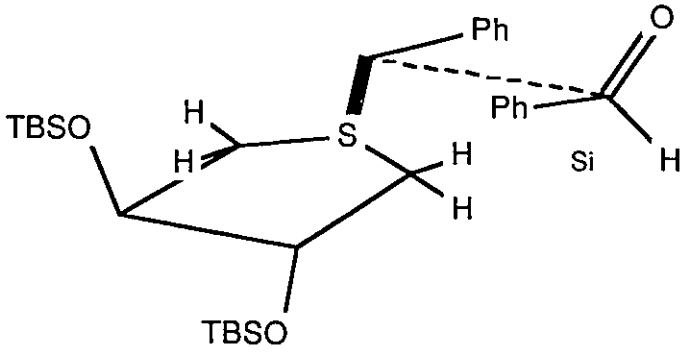



Examination of models provides a possible explanation for the observed (R, R) selectivity. It should be noted that the following explanation is extremely tentative since the detailed transition state(s) for epoxide formation are unknown. For a side approach to be occurring to the ylide of **168**, the large phenyl ring of the ylide must locate itself *syn* to the sulfur lone pair since a *trans* orientation would place it in a crowded position over the thiolane ring. With the phenyl group thus located in an *exo* position, approach of benzaldehyde to give a *trans* product is inhibited by interaction of the phenyl ring of benzaldehyde with the hydrogens α to sulfur. Therefore it would appear that the top-or-bottom reaction is operating since the side reaction is difficult.




In the top-or-bottom approach, the phenyl ring of the ylide will now be on either side of the thiolane ring as shown below. In both cases, the aldehyde approaches from the sulfur lone pair side (see pages 143-144) but presentation of the aldehyde's Re face (which would produce the (S, S) isomer) is inhibited by interaction with the TBS moiety which is *syn* to the sulfur lone pair. Thus the Si face is the most favorable site of attack and the (R, R) is the major isomer.



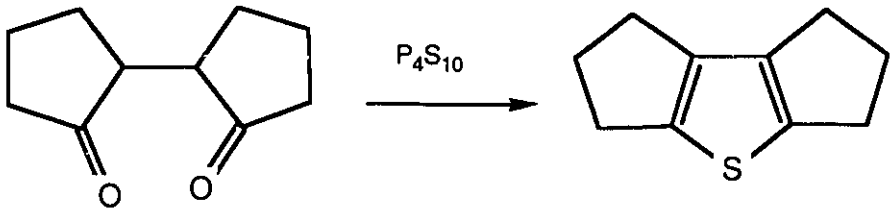




The observation of asymmetric induction in the reaction of a sulfur ylide with an aldehyde is significant, despite the rather low enanteomeric excess observed, since this is the first case recorded of asymmetric epoxidation using a sulfonium ylide. Most importantly, the above result suggests that the idea proposed in this part of the the present thesis is conceptually correct and that an appropriately constructed ylide may react with aldehydes to give epoxides with synthetically useful enanteomeric excess.

An attempt to prepare such a molecule is described in the appendix which follows. Though not successful, the results obtained should assist in the planning of other approaches and designs. The observation of a significant chiral induction observed in the reaction of the ylide from **168** and benzaldehyde justifies the renewed efforts.

# Appendix
## Attempts to Synthesize An "All-Carbon" $C_2$ Symmetric Thiolane

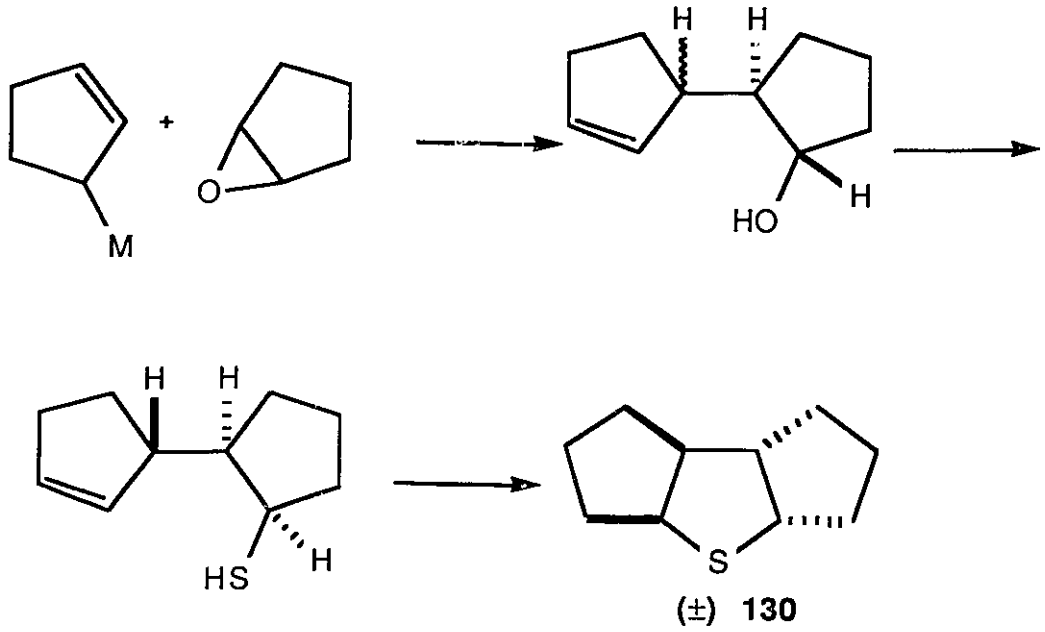
A chiral thiolane with an all-carbon backbone would be an ideal choice for an auxiliary since the lack of heteroatoms should eliminate the problems associated with sulfonium salt formation and the possibility of β-eliminations in the derived ylides. *Trans* 2,5-dimethylthiolane **129** is one possibile target, but as discussed previously (page 131-132) it is a less than ideal choice. Dicyclopentanothiolane **130** is much better for reasons discussed on page 132, but would require a resolution. The method used by Whitesell[120] to prepare a related amine involving a bicyclo ketone is unfortunately not applicable to a thiolane since introduction of sulfur is reported to lead to a thiophene derivative[164] which would be difficult if not impossible to reduce to the desired *trans* thiolane product.




Work has been carried out in this laboratory[165] to see if **130** could be prepared using a different and partially stereoselective route. The general

[164] H. Paul. *Chem. Ber.*, **93**, 2395 (1960).
[165] P-J. Corson, T. Durst. Unpublished results.

scheme depicted below involved opening an epoxide with an allylic anion, introducing sulfur and then obtain **130** by a radical mediated ring closure.




(±) **130**

The use of an epoxide would ensure that the proper *cis* geometry in the right hand ring would later exist for easy ring formation, however no adducts with cyclopentene- or cyclohexene-oxide could be obtained due to the difficulty of preparing the appropriately metallated cyclopentene. Therefore an analogous system was investigated, in which the five membered rings fused to the thiolane are derived from indene as shown below. This type of approach was thought to be easier to complete since indene is easily metallated and indene oxide readily opens at the benzylic position[166] to give the required hydroxyalkene. As an additional benefit the nmr spectra and TLC chromatograms in an indene sequence should be easier to evaluate.

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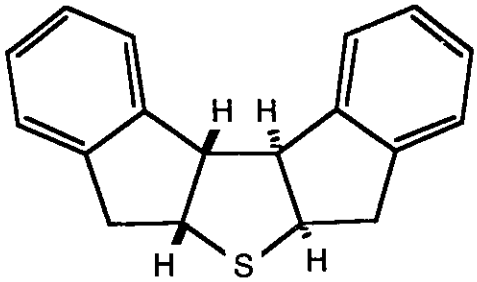
[166] D. G. Talekar, A. S. Rao. *Synthesis*, 595 (1983).




**169**

Indene oxide was prepared by the base catalyzed ring closure of 2-bromo-1-indanol using NaH in place of KOH as described in the literature.[167] The epoxidation of indene using *m*CPBA was found to be unsatisfactory due to the extreme acid sensitivity of indene oxide.[168] A procedure using *m*CPBA in a two-phase buffer system[169] was also unsatisfactory because of the large amounts of peracid required.

Reaction of the anion of indene, generated with *n*BuLi, and indene oxide in THF at -78°C followed by warming to room temperature gave a moderate yield of adduct **170**. The olefinic bond was shown to be in the position depicted by the observance of only one olefinic resonance in the proton nmr at δ6.13. The methylene protons adjacent to this double bond resonated as a tight doublet at δ3.36. The signals for the cyclopentene aliphatic hydrogens appeared at δ3.33, 2.97 (ABX pattern; methylene protons); at δ4.75-4.67 (ABX pattern; methine bearing OH) and at δ4.34 (doublet; remaining methine) These assignments were confirmed by decoupling the resonance at *ca.* δ4.7 which

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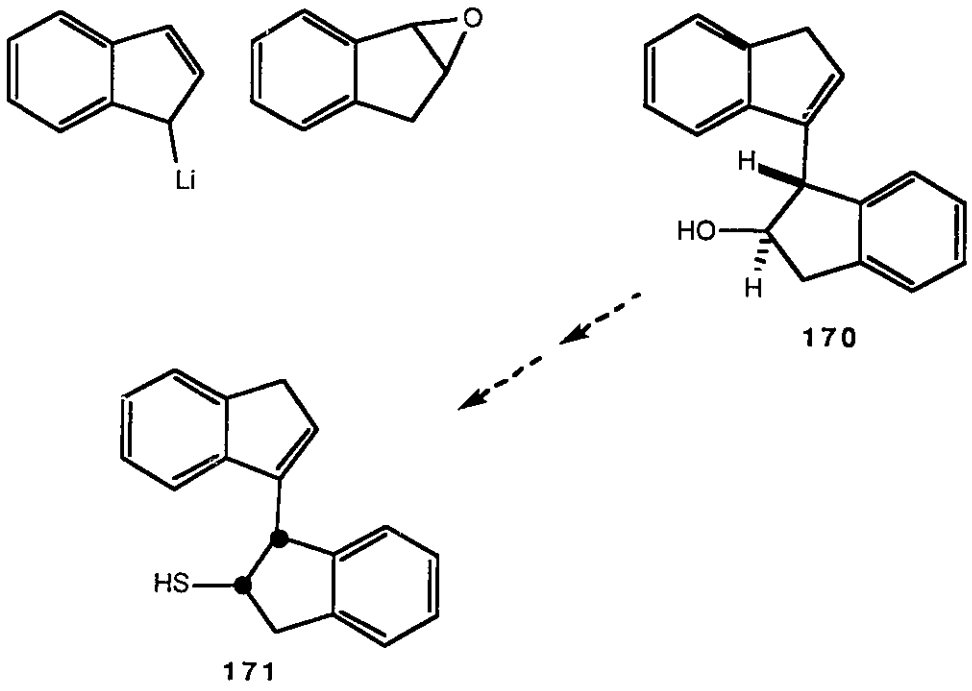
[167] A. Balsamo, G. Berti, P. Crotti, M. Ferretti, B. Macchia, F. Macchia. *J. Org. Chem.*, **39**, 2596 (1974)
[168] A. Gagis, A. Fusco, J. T. Benedict. *J. Org. Chem.*, **37**, 3181 (1972).
[169] M. Imuta, H. Ziffer. *J. Org. Chem.*, **44**, 1351 (1979).

caused the resonance at δ4.34 to collapse to a singlet and the ABX system to appear as a simple AB pattern.




**170**

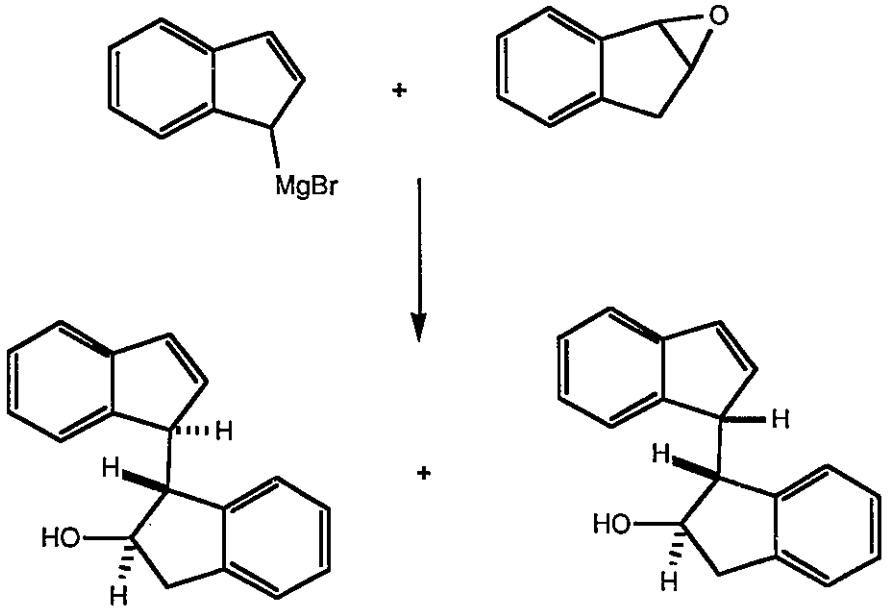
**171**

The formation of this isomer was disquieting since if carried through would eventually give a mercaptan such as **171**. Ring formation with this material to produce the desired thiolane **169** would require an unfavourable 5-*endo-trig* ring closure. The isomerization to **170** is thought to be a result of bond migrations via allylic anions catalyzed by the strongly basic conditions employed.

To avoid this problem the condensation was repeated using indenylmagnesium bromide[170] in place of the lithium species. This reaction

[170] K. D. Smith, J. L. Atwood. *Inorg. Syn.*, **16**, 137 (1975).

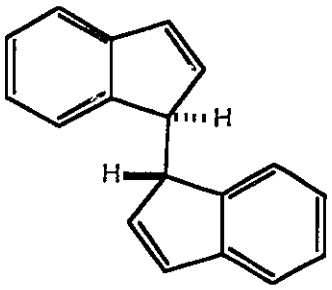
resulted in the formation of two isomeric alcohols **172a** and **172b** in 58 % overall yield.



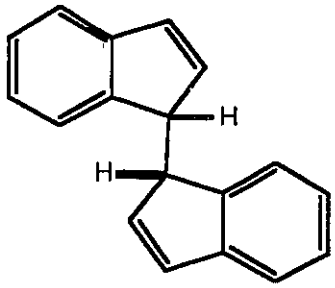

**172a** **172b**

The major isomer, **172a** was shown to possess an *anti-anti* configuration on the basis of the olefinic protons' chemical shifts. These hydrogens resonated at δ6.82 and δ6.06 while the corresponding protons of *anti-syn* isomer **172b** resonated at δ6.87 and δ6.57. The assignment of *anti-anti* configuration to isomer **172a** and *anti-syn* to **172b** is based on observations noted previously[171] in which the authors found that racemic **173** (*anti* isomer) displayed chemical shifts for the olefinic protons which were generally lower and more widely separated than the corresponding chemical shifts of meso **173** (*syn* isomer).

[171] N. E. Heimer, M. Hojjatie, C. A. Panetta. *J. Org. Chem.*, **47**, 2593 (1982).

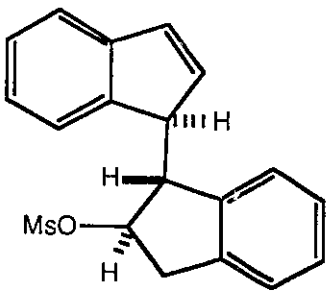



Racemic **173**

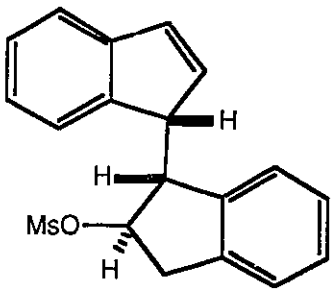



Meso **173**

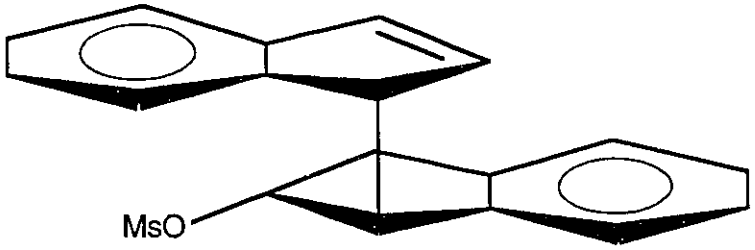
Compounds **172a** and **172b** were both converted to the corresponding mesylates **174a** and **174b**, in moderate yield using standard conditions ($CH_3SO_2Cl$, TEA, $CH_2Cl_2$). The $^1H$ nmr spectrum of *anti-anti* isomer **174a** was particularly interesting in that the chemical shift of the signal assigned to the mesylate methyl group was located 1 ppm upfield of the normal position for such a function. This anomaly is likely the result of the predominance of the rotamer of **174a** in which the mesylate function is held under the aromatic ring of the other indenyl group. The methyl group therefore experiences shielding brought about by anisotropy from the aromatic system.




**174a**

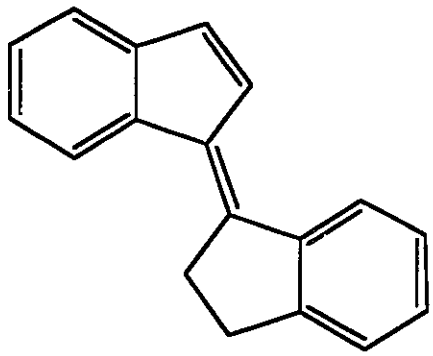



**174b**




**174a**

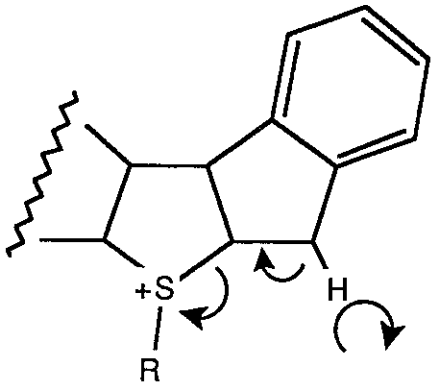
The type of conformation may be responsible for the inability to introduce sulfur into **174a** (thiourea; sodium thioacetate; $Na_2S$, DMSO) since the reagent would need to squeeze under the aromatic ring to displace the mesylate in an $S_N2$ fashion. These reactions gave as the major product, compound **175** as a result of an elimination followed by migration of the double bond. The proton nmr spectrum of **175** contained resonances for only two olefinic hydrogens at δ6.83 and δ5.72. Resonances for 4 aliphatic protons appeared in the 3.53-2.93 ppm range, all appearing as complex multiplets. Compound **174b** also gave this product when treated with $LiSCH_2Ph$ in THF.



**175**

The easy elimination reactions observed for the mesylate **174** lead us to question whether **169** would be the ideal thiolane since ylides produced from **169** may be prone to cleavage of the thiolane ring by a β-elimination as

shown below. This elimination is more likely to be a problem in **169** than in the ylides derived from the dimethyl- or dicyclopentanothiolanes **129** and **130** since the β hydrogens in question are benzylic in **169**.



# Experimental

## Chapter 1:

### 1,3:4,6-Di-O-benzylidene-D-mannitol-2,5-di-O-methanesulfonate (136)

To a suspension of 2.0 g (5.6 mmol) of 1,3:4,6-di-O-benzylidene-D-mannitol and 1.6 mL of triethylamine (12.3 mmol) in dry $CH_2Cl_2$ at 0°C was added dropwise a solution of 0.86 mL of $CH_3SO_2Cl$ (12.3 mmol) in $CH_2Cl_2$. After stirring at 0°C for one hour, the solution was washed with 10 % HCl, 5 % $NaHCO_3$ and water and then dried over $MgSO_4$. Following solvent removal, 2.86 g (99 %) of dimesylate **136** was obtained was a white foam which later solidified. This material was used without further purification. An analytical sample was recrystallized from acetone/water mp = 187°C (lit.[135] mp = 187-189°C ). $^1H$ nmr : 7.50-7.45 (m, 4H), 7.38-7.33 (m, 6H), 5.51 (s, 2H), 4.55 (dd, J=5.45,10.79, 2H), 4.13 (d, J=9.22, 2H), 3.85 (t, J=10.50, 2H), 3.02 (s, 6H).

### 1,3:4,6-Di-O-benzylidene-2,5-anydroglucitol (137)

A DMF solution of dimesylate **136** (520 mg, 1.0 mmol), *n*BuLi ( 1.0 mmol), *t*BuSH (0.11 mL, 1.0 mmol) and pyridine (0.10 mL, 1.0 mmol) was refluxed for 18h. The solution was then cooled, diluted with water and extracted with ether. The combined etherial extracts were diluted with $CH_2Cl_2$, washed with brine and dried over $MgSO_4$. Removing the solvent left 580 mg of a brown

oil. Repeated chromatotron chromatography (methanol on first pass, second run using EtOAc:hexanes, 1:2) gave 92 mg of **137** as a yellow solid (27 %) along with 140 mg (27%) of recovered **136**. $^1$H nmr : 7.53-7.24 (m, 10H), 5.67 (s, 1H), 4.74-4-4.49 (m, 1H), 4.54 (dd, J=4.52,9.77, 1H), 4.22-4.13 (m, 3H), 3.99-3.93 (m, 2H), 3.54 (dt, $J_d$=4.42, $J_t$=9.88, 1H); ir (KBr) : 1220, 1100; ms (CI) : 341 (BP) ($M^+$ +1).

**1,3:4,6-Di-O-benzylidene-D-mannitol-2,5-di-O-trifluoromethane-sulfonate (138)**

To a suspension of 500 mg ( 1.4 mmol) of **135** in dry $CH_2Cl_2$ at 0°C was added 0.25 mL of dry pyridine (2.9 mmol) followed by a $CH_2Cl_2$ solution of triflic anhydride (0.50 mL, 2.8 mmol). After stirring at 0°C for 20 minutes, the clear solution was washed with ice cold portions of $H_2O$, 10 % HCl, 5 % $NaHCO_3$, $H_2O$; dried over $MgSO_4$ and stripped of solvent leaving 850 mg of a pale yellow solid identified as **138** ( 95 %). This material was used immediately without further purification. A small sample was recrystallized in c.a. 50 % yield from ether/hexanes and melted at 75°C (lit.[141] mp = 74-75°C). $^1$H nmr : 7.47-7.35 (m, 10H), 5.53 (s, 2H), 5.33-5.25 (m, 2H), 4.57 (dd, J=5.38, 10.75, 2H), 4.16 (d, J=9.04, 2H), 3.95 (t, J =10.63, 2H); ms (CI) : 622 (18.9) ($M^+$).

**2',3:4,5'-Di-O-benzylidene-(2S, 5S)-bis-hydroxymethyl-(3R, 4R)-dihydroxy-thiolane (139)**

Gaseous hydrogen sulfide was passed through a solution of 0.50 mL of triethylamine in DMF at 0°C untill saturated. Additional triethylamine (1.0 mL) was then added followed by a solution of 400 mg (0.64 mmol) of ditrifiate **138** in

DMF. After 18 h at room temperature the solution was diluted with water and extracted with ether. The etherial extracts were washed with water, dried over $MgSO_4$ and freed of solvent giving 250 mg of white solid. Chromatotron chromatography ($CH_2Cl_2$ ) gave 96 mg (42 %) of **139** as a white solid mp = 205°C. Eluting in the early fractions was 87 mg (38 %) of thiol **140** obtained as a white foam. For **139** : $^1H$ nmr : 7.54-7.50 (m, 4H), 7.41-4.36 (m, 6H), 5.52 (s, 2H), 4.58 (d, J=2.41, 2H), 4.30-4.29 (m, 4H), 3.98-3.95 (m, 2H); $^{13}C$ nmr : 137.67 (s), 129.07 (d), 128.20 (d), 126.11 (d), 100.04 (d), 82.76 (d), 66.95 (t), 45.48 (d); ir (KBr) : 1150, 1200; ms : 356 (25.3) ($M^+$); hrms calcd. for $C_{20}H_{20}O_4S$ : 356.1080; found : 356.1043. For **140**: $^1H$ nmr : 7.54-7.49 (m, 4H), 7.40-7.31 (m, 6H), 6.76 (dd, J=1.04, 6.44, 1H), 5.92 (s, 1H), 5.57 (s, 1H), 5.01 (dd, J=1.58, 6.44, 1H), 4.95 (dt, $J_d$=7.82, $J_t$=1.46, 1H), 4.33 (dd, $J_{AB}$=11.66, $J_{AX}$=2.37, 1H), 4.24 (dd, $J_{AB}$=11.66, $J_{BX}$=1.52, 1H), 4.12 (dd, J=2.05, 7.79, 1H), 2.82 (dd, J=1.78, 11.48, 1H), 2.43 (d, J=11.38, 1H); $^{13}C$ nmr : 146.03 (d), 137.62 (s), 136.80 (s), 129.07 (d), 128.97 (d), 128.18 (d), 126.24 (d), 126.10 (d), 101 77 (d), 100.15 (d), 98.19 (d), 81.96 (d), 75.97 (d), 74.43 (t), 36.25 (d); ir (thin film) 1110; ms (CI) : 357 (1.2) ($M^+$ +1).

**2,5-O-Methylene-1,3,4,6-tetra-O-benzyl-D-mannitol (142)**

A solution of 2,5-methylene-D-mannitol (2.0 g, 10.3 mmol) in DMF was added to a suspension of 2.47 g (51.5 mmol) of NaH in DMF at 0°C. After stirring at 0°C for 15 min, 20 mg of TBAI was introduced followed by the dropwise addition of benzyl bromide (8.80 g, 4.2 mmol). After complete addtion the mixture was allowed to stir at room temperature overnight. The solution was then diluted with water and extracted with ether. The etherial extracts were washed with water and dried over $MgSO_4$. The yellow oil remaining after

solvent removal was chromatographed (EtOAc:hexanes, 1:7) giving 4.92 g (86 %) of **142** as colorless oil. $^1$H nmr : 7.33-7.13 (m, 20H), 4.84 (s, 2H), 4.77 (d, $J_{AB}$=10.99, 2H), 4.62 (d, $J_{AB}$=10.99, 2H), 4.57 (d, $J_{AB}$=12.12, 2H), 4.54 (d, $J_{AB}$=12.12, 2H), 3.80-3.68 (m, 8H); ir (thin film) 1640, 1150; ms (CI) : 555 (24.1) ($M^+$+1).

**2,5-O-Methylene-1,3,4,6-tetra-O-methyl-D-mannitol (143)**

A solution of 2,5-methylene-D-mannitol (300 mg, 1.55 mmol) in DMF containing 3.0 mL of methyl iodide (7.75 mmol) was stirred for 18 h at room temperature with 600 mg (8 mmol) of finely powdered KOH. Dilution with water, extraction with ether, washing with water and drying over $MgSO_4$ gave a colorless solution which was stripped of solvent. Flash chromatography ( EtOAc:hexanes, 2:1) of the residue gave 198 mg of **143** as a colorless liquid (51 %). $^1$H nmr: 4.77 (s, 2H), 3.58 (br, 6H), 3.53 (s, 6H), 3.39 (s, 6H), 3.26-3.23 (m, 2H); ir (thin film) : 1150; ms (CI) : 251 (75.4) ($M^+$ +1).

**1,3,4,6-Tetra-O-benzyl-D-mannitol (144)**

Methylene acetal **142** (980 mg, 1.77 mmol) was dissolved in 4 mL of methanol and 1 mL of concentrated $H_2SO_4$ carefully added. After refluxing this solution for 45 minutes, TLC indicated that no starting material remained. The hot solution was cast into 50 mL of water and the resulting slurry extracted with ethyl actetate. The combined organics were washed with 5 % $NaHCO_3$, and the $NaHCO_3$ washings extracted with EtOAc. The EtOAc solutions were combined and dried over $MgSO_4$ then stripped of solvent giving 821 mg (86 %) of diol **144** as a colorless syrup which was used without further perification. $^1$H nmr :

7.35-7.21 (m, 20), 4.63 (d, $J_{AB}$=11.28, 2H), 4.52 (d, $J_{AB}$=11.28, 2H), 4.49 (d, $J_{AB}$=11.99, 2H), 4.47 (d, $J_{AB}$=11.99, 2H), 4.05-3.95 (m, 2H), 3.84 (d, J=7.82, 2H), 3.63 (dd, $J_{AB}$=9.61, $J_{AX}$=5.27, 2H), 3.57 (dd, $J_{AB}$=9.61, $J_{BX}$=3.35, 2H); ir (thin film) : 3500, 1602, 1150; ms (CI) : 543 (64) ($M^+$ +1).

**2,5-Di-O-methanesulfonyl-1,3,4,6-tetra-O-benzyl-D-mannitol (145)**

A $CH_2Cl_2$ solution of diol **144** (821 mg, 1.51 mmol) was treated at 0°C with 0.22 mL of TEA (3.3 mmol) followed by 0.12 mL of $CH_3SO_2Cl$ (3.1 mmol). After stirring 1/2 h at 0°C and 1/2 h at room temperature, the solution was washed with 10 % HCl, 5 % $NaHCO_3$, water; dried over $MgSO_4$ and stripped of solvent giving a yellow oil which was purified by column chromatography (EtOAc:hexanes, 1:3), this procedure afforded 1.03 g (99 %) of dimesylate **145** as a colorless oil. $^1H$ nmr : 7.33-7.23 (m, 20H), 4.94-4.91 (m, 2H), 4.67 (d, $J_{AB}$=10.88, 2H), 4.62 (d, $J_{AB}$=10.88, 2H), 4.51 (d, $J_{AB}$=11.66, 2H), 4.47 (d, $J_{AB}$=11.66, 2H), 3.99 (dd, J=0.98, 3.25, 2H), 3.87 (dd, $J_{AB}$=11.26, $J_{AX}$=7.41, 2H), 3.78 (dd, $J_{AB}$=11.26, $J_{BX}$=3.51, 2H), 2.92 (s, 6H); ir (thin film) : 1600, 1350, 1180; ms (CI) : 603 (1.9) ($M^+$ +1).

**2,2-Anhydro-1,3,4,6-tetra-O-benzyl-D-glucitol (146)**

To a solution of 256 mg of diol **144** (0.47 mmol) and 0.09 mL of pyridine ( 1.03 mmol) in $CH_2Cl_2$ at -78°C was added 0.18 mL (1.03 mmol) of triflic anhydride. The solution was held at -78°C for 20 minutes and then allowed to slowly warm to 0°C. Once the solution had reached 0°C it was washed with ice cold portions of 5 % HCl, 5 % $NaHCO_3$ and water and dried over $MgSO_4$. Column chromatography of the residue remaining after solvent removal gave

244 mg (94 %) of **146** as a colorless oil. $^1H$ nmr : complex spectrum; ir (thin film) : 1600, 1240; ms (CI) : 525 (4.8) ($M^+$ +1).

**3,4-Di-O-benzyl-1,2:5,6-di-O-isopropylidene-D-mannitol (148)**

Ten grams of diisopropylidene-D-mannitol **147** (38 mmol) was dissolved in $CH_2Cl_2$ with 50 mg of $Bn(Et)_3N^+Cl^-$, 5 mg NaI and 16.3 g benzyl bromide (95 mmol). 6.2 g of finely powdered KOH was then added and the mixture vigorously stirred at room temperature untill TLC indicated that the reaction was complete (48 h). The solution was then washed with water, dried over $MgSO_4$ and stripped of solvent giving 19 g of a yellow syrup. Distillation (165-170 at 0.1 mm) of this material gave 10.2 g (60 %) of **148** as a yellow syrup. $^1H$ nmr 7.31-7.25 (m, 10H), 4.68 (s, 4H), 4.23-4.19 (m, 2H), 4.01-3.96 (m, 2H), 3.86-3.76 (m, 4H), 1.40 (s, 6H), 1.32 (s, 6H); $^{13}C$ nmr : 138.15 (s), 128.28 (d), 127.97 (d), 127.68 (d), 108.68 (s), 79.97 (d), 75.88 (d), 74.63 (t), 66.83 (t), 26.79 (q), 25.35 (q); ir (thin film) : 1200, 1070; ms (CI) : 443 (3.9) ($M^+$ +1).

**3,4-Di-O-benzyl-D-mannitol (149)**

3,4-Di-O-benzyl-1,2:5,6-di-O-isopropylidene-D-mannitol **148** (5.07 g, 11.5 mmol) was dissolved in 40 mL of 80 % acetic acid and let stand at room temperature untill TLC indicated that the reaction was complete (24 h). The solution was then stripped of solvent and excess acetic acic removed by rotary evaporation with water and then with ethanol, followed by azeotropic distillation with benzene to remove the last traces of water. Final solvent removal gave 4.17 g (100 %) of **149** as a yellow syrup which was used without further

purification. $^1H$ nmr : 7.38-7.27 (m, 10H), 4.59 (s, 4H), 3.98-3.93 (m, 2H), 3.81-3.65 (m, 6H); ir (thin film) : 3400; ms (CI) : 363 (83) ($M^+$ +1).

**1,6-Di-O-toluenesulfonyl-3,4-O-isopropylidene-2,5-O-methylene-D-mannitol (151)**

An acetone solution of 1.07 g (2.13 mmol) of ditosylate **150** was stirred at room temperature for 18 h with 170 mg (1 mmol) of $FeCl_3$ in the presence of 4Å molecular sieves. A 5 % $Na_2CO_3$ solution ( 2 mL) was then added and the mixture concentrated on a rotary evaporator. Water was introduced ( 10 mL) and the solution extracted with $CH_2Cl_2$. After $MgSO_4$ treatment and solvent removal, the remaining syrup was purified by column chromatography (EtOAc: hexanes, 1:1) which afforded 563 mg (49 %) of **151** as a colorless syrup along with 250 mg (25%) of recovered **150**. $^1H$ nmr : 7.77 (d, $J_{AB}$=8.08, 4H), 7.32 (d, $J_{AB}$=8.08, 4H), 4.71 (s, 2H), 4.26 (dd, $J_{AB}$=10.74, $J_{AX}$=4.87, 2H), 4.11 (dd, $J_{AB}$=10.74, $J_{BX}$=2.27, 2H), 3.89 (dd, J=2.41, 6.86, 2H), 2.43 (s, 6H), 1.30 (s, 6H); ir (thin film) : 1600, 1350; ms (CI) : 543 (3.0 ) ($M^+$ +1).

**1,6-Dideoxy-3,4-O-isopropylidene-2,5-O-methylene-D-mannitol (152)**

To a solution of 541 mg (1.0 mmol) of ditosylate **152** in THF was added excess Lithium aluminumhydride (250 mg) and the resulting mixture refluxed for 24 h. The solution was then cooled to room temperature and water (1/2 mL) added followed by 10% NaOH (1/2 mL) and then $MgSO_4$. The resulting white slurry was filtered through celite giving 112 mg of a colorless oil after removal of the solvent from the filtrate. Column chromatography (EtOAc:hexanes, 1:8) gave

98 mg (49 %) of **152** as a colorless oil. $^1$H nmr : 4.82 (s, 2H), 3.75-3.71 (m, 4H), 1.39 (s, 6H), 1.33 (d, J=5.9, 6H); ir (thin film) : 1390, 1240, 1080; ms (CI) 203 (5.0) ($M^+$ +1).

**1,6-Dideoxy-2,5-O-methylene-D-mannitol (153)**

A THF solution of ditosylate **150** (18.5 g, 36.8 mmol) was added to a suspension of 3 g of LAH in THF at such a rate so that a gentle reflux was maintained. After addition was complete the solution was refluxed overnight and then cooled to room temperature at which time 3 mL of water then 3 mL of 10 % NaOH was carefully added. After filtering, the residue was boiled in THF (5 minutes) then refiltered. The combined THF filtrates were concentrated giving 10 g of a red slush which was purified by flash chromatography (EtOAc:hexanes, 1:1) which returned 3.84 g of **153** as a yellow solid (60 %). An analytical sample was obtained by further flash chromatography giving **153** as a colorless solid. $^1$H nmr : 4.75 (s, 2H), 3.68-3.63 (m, 2H), 3.19-3.15 (m, 2H), 1.29 (d, J=6.4, 6H); ir (KBr) : 3400, 1220; ms (CI) : 175 (7.7) ($M^+$ +1).

**1,6-Dideoxy-3,4-di-O-benzyl-2,5-O-methylene-D-mannitol (154)**

A solution of 3.84 g (22 mmol) of diol **153** in DMF was prepared and added carefully to a suspension of 3 equivalents of NaH in DMF at 0°C. After 1/2 h, 9.8 g (2.1 equivalents) of benzyl bromide was slowly introduced and the resulting mixture stirred 18 h at room temperature. Dilution with water, extraction with ether and drying over $MgSO_4$ gave a yellow solid which was recrystallized from methanol giving 5.50 g of pure **154** (73 %) as white needles melting at 112-113°C. $^1$H nmr : 7.35-7.24 (m, 10), 4.83 (d, $J_{AB}$=10.75, 2H), 4.73 (s, 2H),

4.66 (d, $J_{AB}$=10.75, 2H), 3.77-3.72 (m, 2H), 1.31 (d, J=6.4, 6H); ir (KBr) : 1600, 1260; ms (CI) : 343 (BP) ($M^+$ +1); *Anal.* calcd. for $C_{21}H_{26}O_4$ : C 73.68, H 7.60; found : C 73.34, H 7.90.

**2,5-Anhydro-3,4-di-O-benzyl-1,6-dideoxy-D-glucitol (155)**

To a methanol solution (4 mL) of 107 mg of **154** was added carefully 1 mL of concentrated $H_2SO_4$. After standing at room temperature for 3 h, TLC indicated that no more starting material remained. The mixture was poured into water and extracted with EtOAc. The EtOAc extracts were washed with 5 % $NaHCO_3$, dried over $MgSO_4$ and stripped of solvent giving 92 mg of **155** (91 %) as a colorless oil after flash chromatography (EtOAc:hexanes, 1:5). $^1H$ nmr : 7.36-7.25 (m, 10H), 4.65 (d, $J_{AB}$=12.07, 1H), 4.49 (d, $J_{AB}$=12.10, 1H), 4.48 (d, $J_{AB}$=12.07, 1H), d, $J_{AB}$=12.10, 1H), 4.05 (dq, $J_d$=4.02, $J_q$=6.41, 1H), 3.85 (dq, $J_d$=4.47, $J_q$=6.40, 1H), 3.76 (dd, J=1.36, 4.05, 1H), 3.62 (dd, J=1.34, 4.48, 1H), 1.32 (d, J=6.4, 3H), 1.32 (d, J=6.37, 3H); ir (thin film) : 1200; ms (CI) : 313 (20.5) ($M^+$ +1).

**1,6-Dibromo-1,6-dideoxy-2,5-O-benzylidene-3,4-dibenzoyl-D-mannitol (157)**

A $CCl_4$ solution of 1,3:4,6:2,5-tri-O-benzylidene-D-mannitol (328 mg, 0.73 mmol) containing 261 mg of N-bromosuccinimide (1.46 mmol) was refluxed untill TLC indicated that no starting material remained (1 1/2 h). The solution was allowed to cool and succinimide removed by filtration. Chromatotron chromatography (EtOAc:hexanes, 1:7) of the filtrate residue gave 282 mg (63%) of **157** as a white foam. $^1H$ nmr : 7.93-7.24 (m, 15H), 6.03 (s, 1H),

5.68 (dd, $J_{AB}$=8.5, $J_{AX}$=9.6, 1H), 5.47 (dd, $J_{AB}$=8.5, $J_{BY}$=9.6, 1H), 4.52-4.45 (m, 1H), 4.26-4.20, (m, 1H), 3.58 (d, $J_{AB}$=11.0, $J_{AX}$=1.26, 1H), 3.54 (d, $J_{AB}$=11.0, $J_{BX}$=0.56, 1H), 3.37 (d, $J_{AB}$=11.23, $J_{AX}$=5.10, 1H), 3.33 (d, $J_{AB}$=11.23, $J_{BX}$=5.10, 1H); ir (thin film) : 1730, 1265, 1150; ms (CI) : 603 (2.1) ($M^+$ +1, $^{79}Br+^{79}Br$), 605 (1.6) ($M^+$ +1, $^{79}Br+^{81}Br$), 607 ($M^+$ +1, $^{81}Br+^{81}Br$).

## Chapter 2:

### 1,4-Di-O-toluenesulfonyl-L-threitol (160)

*Trans* 4,5-bis-(tosyloxymethyl)-2,2-dimethyl-1,3-dioxolan **159** (9.75 g, 20.7 mmol) was refluxed in 15 mL of 80 % acetic acid untill TLC indicated that no starting material remained (1/2 h). The solution was then cooled and acetic acid removed by rotary evaporation. The residue was taken up into ethyl acetate and washed with saturated $NaHCO_3$, the aqueous washings being further extracted with EtOAc. The organic phases were combined and dried over $MgSO_4$. Removal of EtOAc left 8.78 g (98 %) of ditosylate **160** as a white solid which was used without further purification. $^1H$ nmr : 7.76 (d, $J_{AB}$=8.14, 4H), 7.34 (d, $J_{AB}$=8.14, 4H), 4.16-4.04 (m, 2H), 3.90-3.86 (m, 4H), 2.44 (s, 6H); ir (KBr) : 3500, 1600, 1180; ms (CI) : 431 (19.5) ($M^+$ +1); $[\alpha]_D$ (c=1.07, EtOAc) = -0.56°.

### 2,3-Bis-O-(tetrahydropyranyl)-1,4-di-O-toluenesulfonyl-L-threitol (161)

To a $CH_2Cl_2$ solution of ditosylate **160** (9.65g, 22.4 mmol) containing 5.7 g of dihydropyran (3 equivalents) was added 50 mg of *p*-toluenesulfonic acid at room temperature. After stirring at room temperature for 1/2 h, TLC indicated that the reaction was complete. The mixture was washed with saturated $NaHCO_3$, dried over $MgSO_4$ and stripped of solvent giving a red syrup which was purified chromatographically (EtOAc:hexanes, 1:2) affording 13.5 g of pale orange syrup identified as **161** (100%). An analytical sample was obtained by

chromatotron chromatography. $^1H$ nmr (mixture of isomers) : 7.76-7.64 (m, 4H), 7.32-7.22 (m, 4H), 4.58-4.38 (m, 2H), 4.24-3.24 (m, 10H), 2.44 (s, 6H), 1.86-1.26 (m, 12H); ir (thin film) : 1600, 1380.

**(3R, 4R)-3,4-Bis-O-(tetrahydropyranyl)-thiolane (162)**

To a DMF solution (200 mL) of ditosylate **161** (13.5 g, 22.4 mmol) at room temperature was added 5.8 g (27 mmol) of freshly powdered $Na_2S{\cdot}9H_2O$. The resulting yellow mixture was stirred for 18 h at room temperature untill TLC indicated that the reaction was complete. At this time the green solution was diluted with water and extracted with ether. Washing with water, drying over $MgSO_4$ and removal of solvent gave 5.3 g of yellow syrup which was distilled (150-160°C at 0.1 mm) affording 1.70 g (26 %) of thiolane **162** as a mixture of isomers. $^1H$ nmr : 4.90-4.68 (m, 4H), 4.56-4.20 (m, 4H), 4.16-3.72 (m, 4H), 1.86-1.42 (m, 12H); ir (thin film) : 1200, 1120, 1020; ms (CI) : 289 (75) ($M^+$ +1).

**2,3-Bis-O-(*t*-butyldimethylsilyl)-1,4-Di-O-toluenesulfonyl-L-theitol (163)**

To a DMF solution of diol **160** (8.78g, 20.4 mmol) at 0°C was added 10.3 mL of *t*-butyldimethylsilyl triflate (42.8 mmol) followed by the dropwise addition of 5.2 mL (44.9 mmol) of 2,6-lutidine. This solution was then stirred at room temperature for 18 h after which time it was diluted with water and extracted with ether. The etherial extracts were washed with 10 % HCl, saturated $NaHCO_3$ and water and then dried over $MgSO_4$. Solvent removal followed by flash chromatography (EtOAc:hexnaes, 1:7) returned 12.1 g (90 %) of disilyl derivative **163** as a colorless syrup. $^1H$ nmr : 7.72 (d, $J_{AB}$= 8.15, 4H), 7.31 (d,

$J_{AB}$=8.15, 4H), 4.09 (d, J=7.76, 2H), 3.78-3.75 (m, 4H), 2.43 (s, 6H), 0.74 (s, 18H), 0.01 (s, 6H), -0.03 (s, 6H); ir (thin film ) : 1600, 1250; ms : 601 (3.8) (M+ -57); $[\alpha]_D$ (c=1.77, $CHCl_3$) = -22.3°.

**(3R, 4R)-3,4-Di-O-(*t*-butyldimethylsilyl)-thiolane (164)**

To a DMF solution of 12.1 g of silyl derivative **163** (18.4 mmol) was added 5.3 g of powdered $Na_2S{\cdot}9H_2O$ (22.1 mmol) in one portion. The resulting yellow solution was stirred at room temperature untill TLC indicated that no staring material remained (18 h) at which time the solution was green. The solution was diluted with water and extracted with ether. The etherial extracts were washed with water, dried by $MgSO_4$ treatment and stripped of solvent on a rotary evaporator. Flash chromatography of the remaining material (EtOAc:hexanes, 1:5) gave 800 mg (13 % ) of thiolane **164** as a colorless liquid along with 2.80 g (65 %) of desilylated product **165**. For **164**: $^1$H nmr : 4.11(dd, $J_{AX}$=3.39, $J_{BX}$=2.39, 2H), 3.03 (dd, $J_{AB}$=10.72, $J_{AX}$=3.39, 2H), 2.62 (dd, $J_{AB}$=10.72, $J_{BX}$=2.39, 2H), 0.86 (s, 18H), 0.06 (s, 12H); 13C nmr : 78.98 (d), 35.86 (t), 25.82 (q), 18.04 (s), -4.54 (q), -4.62 (q); ir (thin film) : 1255, 1070; ms : 291 (61) ($M^+$ -57); $[\alpha]_D$ (c=0.58, $CHCl_3$) = 26.9°, (c= 2.98, acetone) = 29.0°. For **165** : $^1$H nmr : 4.24-4.21 (m, 1H), 4.15-4.11 (m, 1H), 3.18-2.96 (m, 2H), 2.73-2.43 (m, 2H), 0.86 (s, 9H), 0.07 (s, 6H); ir (thin film) : 3400, 1250, 1160; ms : 177 (56) ($M^+$ -57); $[\alpha]_D$ (c=2.16, $CHCl_3$) = 41.5°.

**Re-silylation of 3-(R)-O-(*t*-butyldimethylsilyl)-4-(R)-hydroxythiolane (164)**

To a $CH_2Cl_2$ solution of **165** ( 2.8 g, 11.5 mmol) at 0°C containing 3.02 mL of *t*-butyldimethylsilyl triflate (12.6 mmol) was added dropwise 1.54 mL (13.4 mmol) of 2,6-lutidine. After stirring at 0°C for 2h, TLC indicated that the reaction was complete. The solution was washed with 10 % HCl, saturated $NaHCO_3$ and water then dried over $MgSO_4$. The pink slush so obtained was flash chromatographed (EtOAc:hexanes, 1:99) giving 3.65 g (91 %) of **164** as a clear colorless liquid.

**Methyl (3R, 4R)-3,4-bis-O-(*t*-butyldimethylsilyl)-thiolane tetrafluoroborate (166)**

To a solution of thiolane **164** (187 mg, 0.54 mmol) in dry $CH_2Cl_2$ was added 83 mg (0.59 mmol) of $Me_3OBF_4$. After stirring for 1h, TLC indicated that the reaction was complete and so excess $Me_3OBF_4$ was removed by filtration. Rotary evaporation of the filtrate left 242 mg (100%) of sulfonium salt **166** as a colorless gel. $^1H$ nmr : 4.53-4.48 (m, 2H), 3.89 (dd, $J_{AB}$=12.85, $J_{AX}$=3.08, 1H), 3.74 (dd, $J_{AB}$=14.02, $J_{AX}$=3.28, 1H), 3.49 (dd, $J_{AB}$=12.85, $J_{BX}$= 0.04, 1H), 3.35 (dd, $J_{AB}$=14.02, $J_{BX}$=0.07, 1H), 3.15 (s, 3H), 0.88, s, 9H), 0.84 (s, 9H), 0.14 (s, 6H), 0.11 (s, 3H), 0.10 (s, 3H); $^{13}C$ nmr : 79.33 (d), 79.18 (d), 52.41 (d), 48.60 (d), 28.48 (q), 25.87 (q), 25.71 (q), 17.91 (s), 17.87 (s), -4.86 (q), -4.89 (q).

**(3R, 4R)-3,4-Dihydroxythiolane (167)**

An ethanolic solution of thiolane **164** (309 mg, 0.89 mmol) containing 180 mg (0.89 mmol) of benzyl bromide was refluxed for 18 h at which time TLC indicated that the starting material had been consumed. The solution was concentrated by rotary evaporation and then column chromatographed (EtOAc) giving 60 mg (58 %) of **167** as a white powder. $^1$H nmr : 4.23-4.19 (m, 2H), 4.09 (d, J=3.66, 2H, exchanges), 3.05 (dd, $J_{AB}$=10.60, $J_{AX}$=3.74, 2H), 2.66 (d, $J_{AB}$=10.60, $J_{BX}$=1.85, 2H); ir (KBr) : 3500; ms : 120 (89) ($M^+$); hrms calcd. for $C_4H_8O_2S$ : 120.0244; found : 120.0230.

**Benzyl (3R, 4R)-3,4-bis-O-(*t*-butyldimethylsilyl)-thiolane perchlorate (168)**

To an ether solution of 800 mg of thiolane **164** (800 mg, 2.3 mmol) containing 390 mg of benzyl bromide (2.3 mmol) was added 480 mg (2.3 mmol) of solid $AgClO_4$.‡ After stirring at room temperature for 1 h, the solution was filtered. Evaporation of the filtrate left 430 mg of **168** as a yellow slush (30 %). Extraction of the filtration residue with $CH_2Cl_2$ returned an additional 440 mg of **168** as a white foam (30 %). $^1$H nmr (acetone -$d_6$, 60 MHz) : 7.2 (s, 5H), 4.8-3.5 (m, 8H), 0.9 (s, 18H), 0.0 (s, 12H).

‡ $AgClO_4$ was dried by azeotropic distillation with benzene. **CAUTION** ! $AgClO_4$ is reported to be **SHOCK SENSITIVE** when prepared in this manner and should be handled with extreme care! See : R. Brinkley. *J. Am. Chem. Soc.*, **62**, 3524 (1940).

**Reaction of sulfonium salt (168) with benzaldehyde**

A THF solution of sulfonium salt **168** (214 mg, 0.4 mmol) was added to a solution of one equivalent of dimsyl sodium[126a] at -10°C. The solution was stirred for 1 minute and then a THF solution of freshly distilled benzaldehyde was introduced. The mixture was left at -10°C for an additional 20 minutes then diluted with water and extracted with ether. Drying over $MgSO_4$, solvent removal and chromatotron chromatography (hexanes:ether, 40:1) gave 71 mg (51%) of recovered **164** followed by 21 mg of *trans* stillbene oxide (27 %). $[\alpha]_D$ (c=1.05, acetone) = 55.2°; (lit.[163b] $[\alpha]_D$ (c=0.056, acetone) 291°.

## Appendix:

### 1*H*-Indene-1-(1'-indan-2-ol) (170)

To a THF solution of 200 mg (1.72 mmol) of freshly distilled indene was added 1.1 equivalents of *n*BuLi in hexanes at -78°C. After allowing 20 minutes for temperature equilabration, 220 mg (1.72 mmol) of indene oxide was introduced. The mixture was allowed to slowly warm to room temperature and then saturated $NH_4Cl$ solution was poured in. The mixture was extracted with ether and the etherial extracts dried with $MgSO_4$ after washing with water. Evaporation of solvent gave a brown syrup which was flash chromatographed (EtOAc:hexanes, 1:5) giving 221 mg of **170** as yellow foam (53 %). $^1H$ nmr : 7.49-7.01 (m, 8H), 3.16 (t, J=1.0, 1H), 4.75-4.67 (m, 1H), 4.34 (d, J=5.43, 1H), 3.36 (d, J=1.0, 2H), 3.33 (dd, $J_{AB}$=16.08, $J_{AX}$=6.26, 1H), 2.97 (dd, $J_{AB}$=16.08, $J_{BX}$=5.10, 1H); ir (thin film) : 3400; ms : 248 (34) ($M^+$), 230 (27) ($M^+$-18); hrms calcd. for $C_{18}H_{16}O$ : 248.1200; found : 248.1205.

### 3*H*-Indene-1-(1'-indan-2-ol) (172)

A solution of indenylmagnesium bromide was prepared by refluxing 1.32 g (11.4 mmol) of freshly distilled indene in THF with 11.35 mL of a 1.0 M ethylmagnesium bromide solution for 6 hours. The red solution was then cooled to 0°C and 1.50 g of indene oxide added. The yellow solution was stirred at 0°C for 1 h and then saturated $NH_4Cl$ solution added and the mixture extracted with ether. The etherial extracts were washed with 10 % HCl and water then dried by $MgSO_4$ treatment. Solvent removal followed by multiple flash chromatography (EtOAc:hexanes, 1:5) gave 1.07 g (38 %) of **172a** as a yellow syrup eluting as

the faster component and 560 mg (20 %) of **172b** as a yellow solid. For **172a**: $^1$H nmr : 7.63-7.18 (m, 8H), 6.82 (dd, $J_{AB}$=5.61, J=1.99, 1H), 6.06 (dd, $J_{AB}$=5.61, J=1.78, 1H), 4.08-4.06 (m, 1H), 3.88 (t, J=4.7, 1H), 3.63-3.57 (m, 1H), 3.06 (dd, $J_{AB}$=16.26, $J_{AX}$=6.89, 1H), 2.76 (dd, $J_{AB}$=16.26, $J_{BX}$=5.15, 1H); ir (thin film) : 3400; ms : 248 (2.2) ($M^+$), 230 (10.3) ($M^+$-18); hrms calcd. for $C_{18}H_{14}$ : 230.1094; found : 230.1095. For **172b** : $^1$H nmr : 7.35-7.12 (m, 5H), 7.04-6.95 (m, 2H), 6.87 (dd, $J_{AB}$=5.57, J=1.33, 1H), 6.72 (d, J=7.49, 1H), 6.57 (dd, $J_{AB}$=5.57, J=1.39, 1H), 4.05-4.03 (m, 1H), 3.92-3.80 (m, 1H), 3.79-3.70 (m, 1H), 2.89 (dd, $J_{AB}$=16.48, $J_{AX}$=7.06, 1H), 2.73 (dd, $J_{AB}$=16.48, $J_{BX}$=5.20, 1H); ir (thin film) : 3400; ms : 248 (9.7) ($M^+$), 230 (18) ($M^+$ -18), hrms calcd. for $C_{18}H_{14}$ : 230.1094; found : 230.1099.

**3*H*-Indene-1-(1'-indan-2-O-methanesulfonate) (174)**

A solution of the appropriate alcohol in $CH_2Cl_2$ at 0°C was sequentially treated with 1.2 equivalents of TEA and 1.1 equivalents of $CH_3SO_2Cl$. After stirring at 0°C for 1/2 h, the solutions were washed with 10 % HCl, saturated $NaHCO_3$, water and dried over $MgSO_4$. Solvent removal and flash chromatography gave the pure mesylates **174a** and **174b**. *Anti-anti* isomer **174a** was obtained from **172a** in 46 % yield. $^1$H nmr : 7.64-7.61 (m, 1H), 7.48-7.19 (m, 7H), 6.87 (dd, $J_{AB}$=5.52, J=1.86, 1H), 5.99 (dd, $J_{AB}$=5.52, J=1.85, 1H), 4.21-4.18 (m, 1H), 4.12-4.04 (m, 2H), 3.33 (dd, $J_{AB}$=17.48, $J_{AX}$=4.50, 1H), 3.14 (dd, $J_{AB}$=17.48,$J_{BX}$=1.32, 1H), 2.11 (s, 3H); ir (thin film) : 1350, 1180; ms : 326 (2.2) ($M^+$), 230 (33) ($M^+$-96); hrms calcd. for $C_{18}H_{14}$ : 230.1094; found 230.1093. *Anti-syn* isomer **174b** was obtained from **172b** in 71% yield. $^1$H nmr : 7.34-7.15 (m, 7H), 6.96-6.89 (m, 2H), 6.58-6.56 (m, 1H), 6.40 (d, J=7.51, 1H), 4.52-4.48 (m, 1H), 4.15-4.09 (m, 1H), 3.97-3.93 (m, 1H); ir (thin film) : 1350, 1170; ms : 326

(3.4) ($M^+$), 230 (79) ($M^+$ -96); hrms calcd. for $C_{19}H_{18}O_3S$ : 326.0974; found 326.1004.

# Claims to Original Research

1. 3-Methyl-4-phenyl-azetidin-2-one **22** was prepared and sucessfully alkylated at position 3
2. Several 3-alkenyl-β-lactams prepared by either elimination (**27**, **28**) or by Peterson olefination (**51**, **52**, **53**, **54**, **62**, **63**, **64**, **65**, **66**, **67**, **70**, **71**) were hydroxylated using MoOPH to give 3-hydroxy-3-alkenyn-β-lactams **45**, **55**, **56**, **72** and **73**. Several new protected versions of aspartic-β-semialdehyde were made ( **77**, **82**, **85** ) but failed to undergo efficient Peterson olefination with **50**.
3. The cyclization of a 2, 3-dihydroxy-2-methyl-propanohydroxamate **94** was attempted using technology developed elsewhere.
4. A new protected 2-amino-4-iodo-butanoate **107** was made and condensed with various nucleophiles. The preferred mode of attack was found to be at the carboxylate function rather than at the alkyl halide.
5. A chiral thiolane **139**, derived from mannitol was prepared and treated with various alkylating agents failed to produce chiral sulfonium salts.
6. A thiolane was prepared from dimethyl-L-tartrate and converted into S-methyl and S-benzyl sulfonium salts. No methylene transfer was observed in the reaction of the S-methyl salt **166** with benzaldehyde in the presence of a variety of bases and only decomposition of the sulfonium salt was observed. In contrast reaction of the S-benzyl sulfonium salt with dimsyl sodium in THF followed by addition of benzaldehyde gave (R, R) *trans* stillbene oxide in 27 % chemical yield and 19 % enanteomeric excess.