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Dedicated to my teachers * * *

ABSTRACT

General Organization

This thesis contains a brief introduction to the area of β-lactam antibiotics and four other Chapters dealing with the syntheses of various 6-methoxy β-lactams. Due to the tremendous level of activity in this area the introductory literature material is presented in an illustrative approach rather than a comprehensive approach. Literature surveys were carried out using chemical abstracts from 1982 to February 1992. Experimental details are given at the end of each Chapter. Compounds in the schemes which did not lead to desired conclusion were not completely characterized; ^1H NMR and other spectral data whenever available are given in the Experimental section. IR was not recorded in most of these cases. Elemental analyses were not performed at all, since the data from such experiments do not always represent the purity of product.

CHAPTER 1

This section describes the development of various β-lactam antibiotics, major representative structures, mode of action and overall objectives of the research undertaken.

CHAPTER 2

7-Methoxy-7-ethyl and 7-methoxy-7-hydroxyethylisocephem analogs were prepared from 4-cinnamyl-3-methoxyazetidinone which was prepared in a multigram scale. This precursor can be purified simply by trituration with ether. The transformation of this monocyclic

starting material to the cyclization precursor involved introduction of an additional side-chain at C-3 *via.* generation of anion using lithium diisopropylamide and quenching of the anion with either ethyl iodide or acetaldehyde. In the case of the hydroxyethyl side-chain oxidation with pyridinium chlorochromate, reduction with L-Selectride and silylation with tert-butyldimethylsilyl triflate was required before carrying out further manipulations. The cinnamyl group was converted to a methylene bearing a leaving group and the p-methoxyphenyl moiety on nitrogen was cleaved and a suitable acetate side-chain was introduced. The anionic annulation with CS_2 gave the desired bicyclic compounds. An optically active isocephem having a thienamycin type side-chain at C-7 and and a racemic isocephem having a methoxy group at C-7 were prepared by similar method.

CHAPTER 3

7-Ethyl-7-methoxycarbacephem was prepared using a rhodium carbenoid reaction starting from 4-cinnamyl-3-methoxyazetidinone. A similar method was applied to prepare an advanced intermediate for 7-hydroxyethyl-7-methoxycarbacephem.

CHAPTER 4

6-Methoxy-PS 5 synthesis was attempted which was found to be unstable. The cyclization was carried out applying the rhodium carbenoid methodology. The cyclization precursor was obtained using nitroaldol condensation starting from an aldehyde which was prepared from 4-cinnamyl-3-methoxyazetidinone.

CHAPTER 5

Syntheses of 6-methoxy-1-methyl-PS 5 analogs were attempted starting from 3-ethyl-3-methoxy-4-methylcinnamylazetidinone. The introduction of 1-methyl group involved the reduction of a suitable α,β-unsaturated ester obtained *via*. palladium catalyzed carbonylation reaction.

ACKNOWLEDGEMENTS

I would like to thank all people who helped in completing this thesis.

First, I would like to express my sincere gratitude to my "guru", Professor T. Durst. It goes without saying that without his discerning vision this thesis would not be compiled. I really appreciated his confidence in my judgements, decisions and ideas relating to this piece of research which created ample opportunities to work independently. His continuous support and patience during rough days of this project helped me to continuously work toward the goal. Moreover, the relaxed and informal atmosphere helped me to learn both curricular and extra-curricular activities.

Dr. Madan K. Sharma is another key figure in this research. He had a great influence on me regarding chemistry in laboratory as well as my studies. He helped in laying the foundations of this project since most of the starting materials were prepared adapting his work. The many discussions I had during the two and half years of friendship were invaluable as it helped me to face criticism, think critically and plan actively.

I would like to thank all friends in my group who have directly or indirectly contributed in shaping this thesis: especially Rob Ben, who helped me by proof-reading this thesis; Livain Breau, who helped in conducting NMR experiments involving chiral shift reagents and Terry Connelly for general discussions in chemistry. Thanks are also due to two gifted summer colleagues: Majid Moghdam and Ramin Hamedani for their help in certain sections of this project. Mention should also be

given to Shawna MacKinnon who is a friend with exceptional PR skills and excels of organizing social activities.

Many thanks to Dr. Howard Alper and Dr. Davit Zargarin for their discussions on carbonylation reactions and letting me use the equipment related to these experiments.

Thanks to Dr. Heather Dettman, Dr. Tony Williams, Mr. Raj Capoor for NMR spectra; Dr. Corrine Bensimon for X-ray crystal structures; and Dr. Klem Kazakoff for mass spectra.

Dr. Harold Mastalerz, Bristol-Myers and Squibb, Candiac, Canada offered important support in this research through discussions regarding reverse-phase purifications and arrangement of *in vitro* antibacterial activity studies.

I would like to take this opportunity to thank Dr. Mohan B. Gewali (Tribhuvan University) for teaching me fundamentals of organic synthesis and guiding me in my pursuit of further studies; Dr. Krishna Ram Amatya (Royal Drug Research Laboratory) for providing an opportunity to learn experimental techniques of organic synthesis and guiding me in my pursuit of further studies; Mr. Nagendra M. Khadka (Tribhuvan University) for stimulating my interest in chemistry and Mr. Keshab L. Shrestha for excellent instruction in mathematics and science at my high school.

Finally, I would like to thank my parents for everything they have given and especially for their emphasis on the pursuit of excellence and adopting a pragmatic approach in every aspect of life, my grand-father for providing primary education in almost every subject and boosting my self-confidence, and my brother and sister for their affection.

TABLE OF CONTENTS

LISTS OF FIGURES

Numbers in parentheses represent the number of Chapter in which the compounds in bold numbers are described.

LIST OF TABLES

LIST OF ABBREVIATIONS

[α]----------specific rotation

Ac----------acetyl

AIBN----------azodiisobutyronitrile

anhyd----------anhydrous

APA----------aminopenicillanic acid

aq----------aqueous

Bn----------benzyl

BOC----------butyloxycarbonyl

calcd----------calculated

CAN----------ceric ammonium nitrate

CBz----------carbobenzyloxy

CDI----------carbonyldiimidazole

CI----------chemical ionization

DA----------diisopropylamine

DCC----------dicyclohexylcarbodiimide

DEPT----------distortionless enhancement by polarization transfer

DHP----------renal dehydropeptidase

DIPEA----------di-isopropylethylamine

DMAP----------dimethylaminopyridine

DMF----------dimethyl formamide

DMS----------dimethyl sulfide

DPPA----------diphenylphosphoryl azide

EPC----------enantiomerically pure compound

eq.----------equivalent

EWG----------electron withdrawing group

HLE----------human leukocyte elastase

HMDS----------hexamethyldisilazane

HMG Co A synthase----------2-hydroxy-3-methylglutaryl coenzyme A synthase

HRMS----------high resolution mass spectrum

imid. ----------imidazole

IR ----------infrared

LDA ----------lithium diisopropylamide

LHMDS ----------lithium hexamethyldisilazane

MCPBA ----------meta-chloroperbenzoic acid

MIC ----------minimum inhibitory concentration

MMPT----------magnesium monoperpthalate

MS ----------mass spectrum

Ms----------methanesulfonyl

NBS----------N-bromosuccinimide

NMR----------nuclear magnetic resonance

PCC----------pyridinium chlorochromate

PhtN----------pthalimido

PMP----------p-methoxyphenyl

PNB ----------p-nitrobenzyl

ppm----------parts per million

ppt.----------precipitate

TBAF----------tetrabutylammonium fluoride

TBDMS ----------t-Butyldimethylsilyl

TEA ----------triethylamine

Tf ----------trifluoromethanesulfonyl

THF----------tetrahydrofuran

tlc----------thin layer chromatography

TMEDA----------tetramethylethylenediamine

TMS----------trimethylsilyl

Tol----------toluene

Ts----------toluenesulfonyl

CHAPTER 1: INTRODUCTION

This chapter covers only highlights of the β-lactam antibiotic story since its beginning in 1929. Each subsequent chapter has its own more extensive introduction relevant to the specific topic discussed. The biosynthesis of these antibiotics will not be discussed in any detail for the sake of brevity.[1]

History

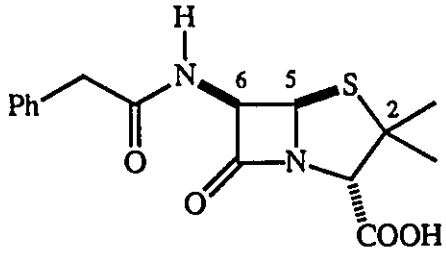
The inception of β-lactam antibiotic era commenced with the discovery of penicillin by Fleming in 1929 at St. Mary's Hospital, London, England. He reported the local antiseptic activity of *Penicillium notatum*, but did not pursue further studies in this area because of the difficulty in isolating it in large quantities. Florey's group was successful in isolating penicillins (such as 1) in sufficiently large quantities to conduct preliminary clinical studies in 1941.[2]

The chemistry of these compounds was extensively explored during the World War II due to the exceptional antibiotic properties of penicillin. The structure of penicillin remained a controversial issue until the three dimensional X-ray crystallographic study of benzylpenicillin was completed in 1945 by Dorothy Hodgkin and Barbara Low.[3]

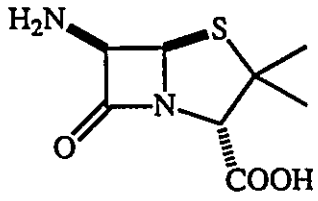
---

[1] Queener, S. W.; Neuss, N. In *Chemistry and Biology of β-Lactam Antibiotics*; R. B. Morin and M. Gorman, Ed.; Academic Press: New York, 1982; Vol. 3; p 1.
[2] Abraham, E. P. in *Chemistry and Biology of β-Lactam Antibiotics* ; R. B. Morin and M. Gorman, Ed.; Academic press: New York, 1982; p xii.
[3] Clarke, H. T.; Johnson, J. R.; Robinson, R. *The Chemistry of Penicillin*; Princeton University Press: Princeton, N.J., 1949.

Most of the early research on penicillins was aimed at introducing various amide side chains at C-6. Some variations in the amide side chain were accomplished biochemically by adding appropriate acids (largely derivatives of acetic acid) to the fermentation media. A major milestone in this area was achieved when 6-aminopenicillanic acid (6-APA) **2** was isolated by Batchelor and coworkers in 1959.[4] Soon after, it became available in large amounts. This opened the area of semisynthetic penicillins.



1 penicillin G



2 6-APA

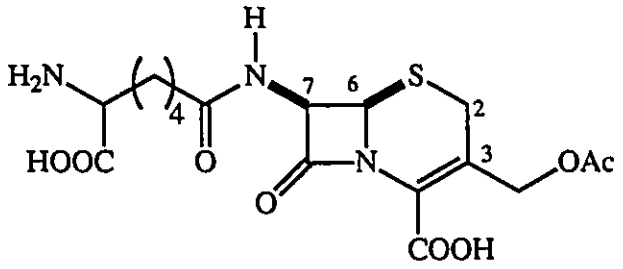
The first total synthesis of penicillin G was achieved by Sheehan in 1959.[5] Due to the efficiency of the fermentation process this and all other total syntheses of penicillins are mainly of academic interest.

In 1960s the discovery of cephalosporins[6] (*e.g.* **3**) added a new class of β-lactam antibiotics. The clinical importance of these antibiotics lies in the fact that they are effective against penicillin resistant bacteria. Further studies on new cephalosporins and analogs focused mainly on the variations in the substituents at C-3 and C-7. The bicyclic ring systems of the penicillins and cephalosporins including the *cis*

---

[4] Batchelor, F. R.; Doyle, F. P.; Nayler, J. H. C.; Rolinson, G. N. *Nature* **1959**, *183*, 257.
[5] Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 5838.
[6] Newall, C. E. In *Medicinal Chemistry: The role of Organic Chemistry in drug research*; S. M. Roberts and B. J. Price, Ed.; Academic Press: London (England), 1985; p 209.

arrangement of the amide side chain with respect to the sulfur containing ring are considered as the "classical" β-lactam antibiotics structures.



3 cephalosporin C

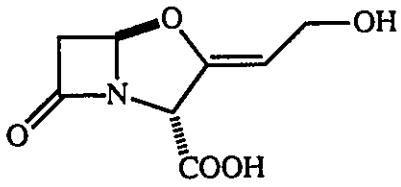
A new dimension was added when naturally occuring β-lactams having non-classical structures were discovered in 1976. One of these was clavulanic acid **4**.[7] This compound is itself not an antibiotic but is a potent β-lactamase inhibitor. This suggested the possibility of combination drugs made up of a broad spectrum but β-lactamase succeptible penicillin and a β-lactamase inhibitor to prevent the degradation of the antibiotic. A formulation of potassium clavulanate and amoxycillin trihydrate, called "Augmentin" which is effective against the β-lactamase producing or penicillin resistant bacteria, is marketed in several countries.[8] The discovery of clavulanic acid instigated considerable work in the development of other semisynthetic β-lactamase inhibitors such as **5**.[9]

---

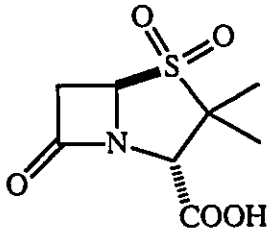
[7] Brown, A. G.; Butterworth, D.; Cole, M.; Hanscomb, G.; Hood, J. D.; Reading, C.; Rolinson, G. N. *J. Antibiotics* **1976**, *29*, 668.

[8] Brown, A. G. In *Medicinal Chemistry: The Role of Organic Chemistry in Drug Research*; S. M. Roberts and B. G. Price, Ed.; Academic press: London (England), **1985**; p 227.

[9] Foulds, C. D.; Kosmirac, M.; O'Sullivan, A. C.; Sammes, P. G. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; A. G. Brown and S. M. Roberts, Ed.; The Royal Society of Chemistry: London (England), **1985**; p 255.



4 clavulanic acid



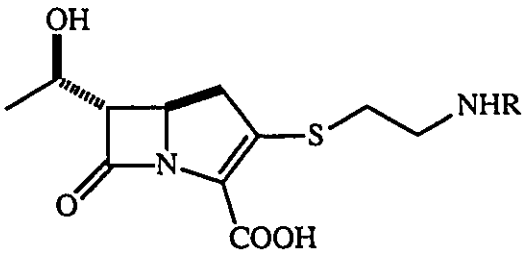
5

Another revolutionary event in the β-lactam saga was the discovery of thienamycin **6**,[10] a compound having both a broad spectrum of antibiotic activity and β-lactamase stability. However, thienamycin is chemically, thermally and metabolically unstable. A more stable analog, called imipenem **7**, has been developed and is being coadministered with cilastatin, an enzyme inhibitor.[11] Imipenem arguably represents one of the most complicated pharmaceuticals presently sold which is manufactured by total synthesis. The discovery of thienamycin and its outstanding biological properties was followed shortly by the isolation of many other non-classical carbapenems such as PS-5, carpetimycins and asparenomycins. The structures of these representative examples are given in Chapter 4.

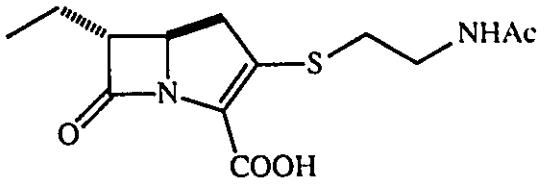
---

[10] (a) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B. In *Intersci. Conf. Antimicrob. Agents Chemotherap.* 16th; Chicago, Ill., **1976**; abstr. 227. (b) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiotics* **1979**, *32*, 1.

[11] Kahan, F. M.; Kropp, H.; Sundellof, J. S.; Brinbaum, J. *J. Antimicrob. Chemother.* **1983**, *12* (suppl. D), 1.

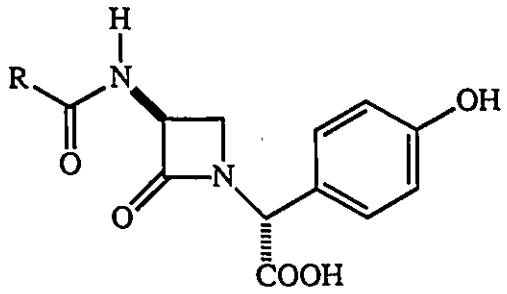


6 thienamycin, R = H
7 imipenem, R=–CH=NH

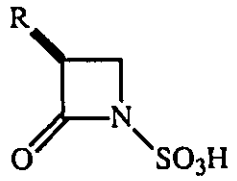


8 PS-5

The antibiotic activity of the norcardicins **9**[12] showed that the conventional bicyclic structure is not required and that monocyclic β-lactams can have antibiotic activity when suitable functional groups are present. Monobactams **10** are another class of monocyclic β-lactam antibiotics.[13]



9 norcardicins



10 monobactams

These findings ushered in an unprecedented level of research in this area. To date, a large number of β-lactam antibiotics with different structural variations have been prepared.[14] In order to illustrate the structural diversity among these antibiotics, a few generalized

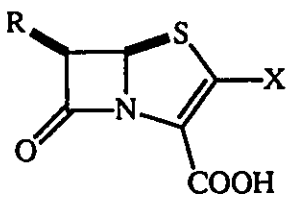
---

[12] Aoki, H.; Sakai, H.; Kohsaka, M.; Konomi, T.; Hosoda, J.; Kubochi, Y.; Iguchi, E.; Imanaka, H. *J. Antibiotics* **1976**, *29*, 492.

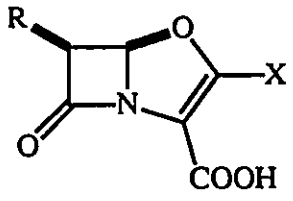
[13] (a) Imada, A.; Kitano, K.; Kintaka, K.; Muroi, M.; Asai, M. *Nature* **1981**, *289*, 590. (b) Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, D. M.; Georgopapdakou, N. H.; Koster, W. H.; Liu, W. C.; Parker, W. L.; Principe, P. A.; Rathnum, M. L.; Slusarchyk, W. A.; Trejo, W. H.; Wells, J. S. *Nature* **1981**, *291*, 489.

[14] (a) Flynn, E. H., Ed., *Cephalosporins and Penicillins*; Academic press: New York; **1972**. (b) R. B. Morin and M. Gorman, Ed., *Chemistry and Biology of β-Lactam Antibiotics*; Academic Press: New York; **1982**.

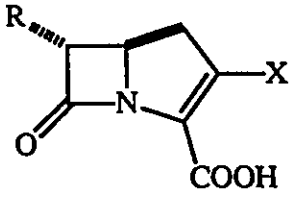
structures of several common classes of synthetic β-lactam antibiotics are given below.



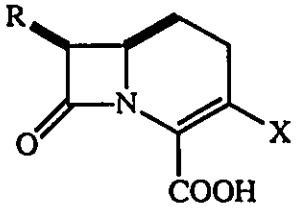
11 penems



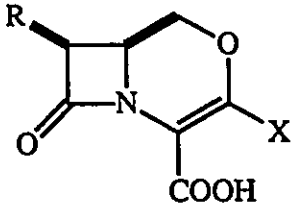
12 oxapenems



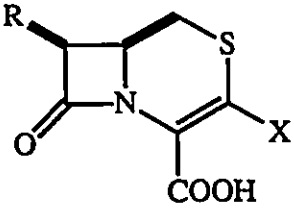
13 carbapenems



14 carbacephems



15 oxacephems



16 isocephems

Recently the last sacred requirement for the antibiotic activity in these compounds, the β-lactam ring itself, has been questioned. Replacement of the β-lactam carbonyl by a sulfone yielded a β-sultam analog **17** and replacement of the β-lactam nitrogen by a methine (CH) carbon giving a keto analog **18**. Both of these compounds were inactive. The expansion of β-lactam ring to larger rings gave inactive or weakly active compounds such as **19**.[15] The pyrazolidinones **20** were weakly active.[16] Lactivicidin **21** has β-lactam like antibiotic activity, but no β-

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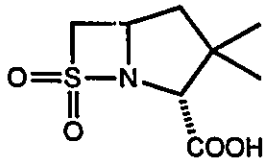
[15] Lowe, G.; Swain, S. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; A. G. Brown and S. M. Roberts, Ed.; The Royal Society of Chemistry: London (England), **1985**; p 209.

[16] Teransky, R. J.; Dranheim, S. E. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; P. H. Bently and R. Southgate, Ed.; The Royal Society of Chemistry: London (England), **1989**; p 139.

lactam ring.[17] Therefore, a β-lactam ring is not always necessary for β-lactam like antibacterial activity.



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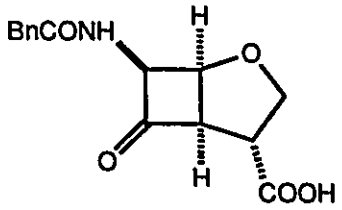

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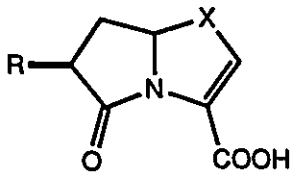

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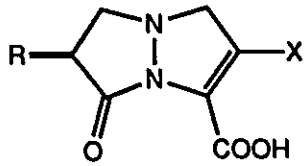

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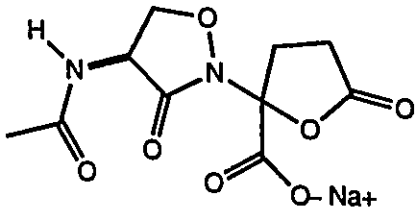

21

Mode of action and reaction

At this stage it is appropriate to consider briefly the mode of action of β-lactams. This is a very complex issue and detailed treatment of this aspect of β-lactam antibiotics will not be attempted.[18] The

---

[17] Nakao, Y. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; P. H. Bently and R. Southgate, Ed.; The Royal Society of Chemistry: London (England), 1989; p 119.

[18] (a) Page, M. I. *Acc. Chem. Res.* 1984, *17*, 144. (b) Waxman, D. J.; Strominger, J. L. In *Biology and Chemistry of β-lactam antibiotics*; R. B. Morin and M. Gorman, Ed.; Academic Press: New York, 1982; Vol. 3; p 209.

antibiotic must cross the external barrier of the bacterial cell *i.e.* the thick peptidoglycan layer of Gram-positive bacteria or the outer lipid layer and the peptidoglycan layer of Gram-negative bacteria in order to reach the binding sites of the β-lactam binding proteins in the bacterial cell wall. Over the years, several bacterial strains resistant to certain type of β-lactam antibiotics have been identified. The resistance is largely attributed to β-lactamases[19], peptides analogous to the β-lactam binding proteins in the cell wall. These β-lactamases effectively bind with the antibiotics and cleave the crucial β-lactam ring, making them ineffective before they reach their target proteins.

It has been shown that these antibiotics inhibit the bacterial cell wall synthesis by interfering with the peptidoglycan crosslinking. As a consequence, the cell wall becomes less rigid and fails to maintain osmotic balance. This leads to lysis or stasis of the bacterial population.

The antibiotics which reach the active site must have suitable stereoelectronic features in order to be recognized as a substrate. Attempts to correlate the antibiotic activities with structural parameters have been carried out by many chemists. One of the earliest ideas was the Tipper-Strominger hypothesis, which postulated that the antibacterial activity or the ability to inhibit the transpeptidation is best effected by compounds having a conformation close to that of the of D-ala-D-ala unit of transpeptidases.[20] Since many β-lactams with widely differing structures show high antibiotic activities, the significance of this is questionable. The β-lactam should

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[19] (a) Knowles, J. R. *Acc. Chem. Res.* **1985**, *18*, 97. (b) Brown, A. G. In *Medicinal Chemistry: The Role of Organic Chemistry in Drug Research*; S. M. Roberts and B. G. Price, Ed.; Academic press: London (England), **1985**; p 227.

[20] Tipper, D. J.; Strominger, J. L. *Proc. Natl. Acad. Sci. USA* **1965**, *54*, 1133.

be reactive enough to bind covalently with the serine moiety at the active site of β-lactam binding proteins.[21] The half life of the acylated enzymes should be long enough to stop peptidoglycan cross linking.

Several empirical parameters which represent the stereo-electronic factors or reactivity have been used as indices of antibacterial activities. One of them is the β-lactam carbonyl stretching frequency.[22] A higher frequency signifies a greater chemical reactivity. Very often, but by no means always, a higher frequency does correlate with the higher activity. The pyramidality of the β-lactam nitrogen is another factor. It is commonly described in terms of *h* value which represents the distance of the β-lactam nitrogen from the plane described by three atoms bonded to it.[23] Normally a higher *h* value indicates more reactive β-lactams. But this pyramidality is not a key factor when the electron withdrawing groups on the nitrogen increase the reactivity. The relative rate of hydrolysis of β-lactam is another commonly considered parameter.[24] A very reactive β-lactam may react with nucleophiles before it reaches the target binding site.

Based on the above discussion, the rational design of target molecules using stereochemical information derived from X-ray crystallography[25] and conformational evaluation of target molecules by

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21 Herzberg, O.; Moult, J. *Science* **1987**, *236*, 694.

22 Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1969**, *91*, 1401.

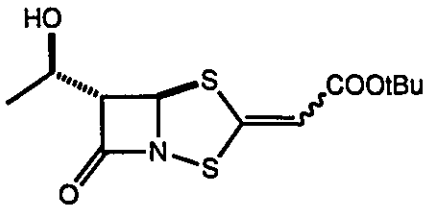
23 Sweet, R. M. In *Cephalosporins and Penicillins*; E. H. Flynn, Ed.; Academic Press: New York, 1972; p 281.

24 Indelicato, J. M.; Norvilas, T. T.; Pfeiffer, R. R.; Wheeler, W. J.; Wilham, W. L. *J. Med. Chem.* **1974**, *17*, 523.

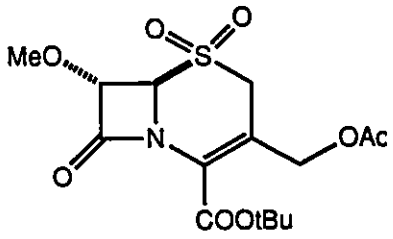
25 Bartolone, J. B.; Hite, G. J.; Kelly, J. A.; Knox, J. R. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; A. G. Brown and S. M. Roberts, Ed.; The Royal Society of Chemistry: London (England), 1984; p 318.

computational methods[26] could be a useful tool in the future, but at present the predictions from these methods are not very reliable. More-over, these methods do not address the various stages of the mechanism of the antibiotic activity mentioned above. Hence, the trial and error approach is still a worthwhile and commonly used approach in β-lactam antibiotic research.

Finally, it should be pointed out that work has begun investigating the inhibition of other enzymes by β-lactams. Azetidinones **22** and **23** are typical β-lactams which inhibit human leukocyte elastase[27] (HLE), an enzyme related to the pathogenesis of degenerative diseases such as emphysema, chronic bronchitis, cystic fibrosis, respiratory disease syndrome and rheumatoid arthritis.



22



23

The β-lactam **24** is found to inhibit 2-hydroxy-3-methylglutaryl-coenzyme A synthase[28] (HMG co A synthase) which is involved in cholesterol biosynthesis. The applications of β-lactams thus far confined to the field of antibiotics may be extended to other fields involving the

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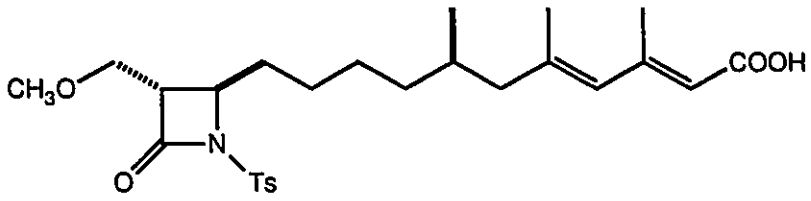
[26] Boyd, D. B. In *Chemistry and Biology of β-Lactam Antibiotics*; R. B. Morin and M. Gorman, Ed.; Academec Press: New York, **1982**; Vol. 1, p 437.

[27] (a) Jasys, V. J.; Kellog, M. S.; Volkmann, R. A. *Tetrahedron Lett.* **1991**, *32*, 3771. (b) Blacklock, T. J.; Butcher, J. W.; Soar, P.; Lamanec, T. *Chem. Abs.* **1991**, *114*, 163868a. Eur. Pat. Appl. EP 411,929. (c) Blacklock, T. J.; Butcher, J. W.; Sohar, P.; Lamanec, T. R.; Graboski, E. J. J. *J. Med. Chem.* **1989**, *54*, 3907.

[28] Thompson, K. L.; Chang, M. N.; Chiang, Y. P.; Yang, S. S.; Chabala, J. C.; Arison, B. H.; Greenspan, M. D.; Hanf, D. P.; Yudkovitz, J. *Tetrahedron Lett.* **1991**, *32*, 3337.

chemotherapy of diseases such as chronic bronchial maladies, cystic fibrosis etc.



2 4

Objectives and nature of studies

One key goal in the β-lactam research is the search for compounds more stable towards these β-lactamases thus making them useful antibiotics for the resistant bacteria.

The introduction of a methoxy group at the α to the β-lactam carbonyl group in penicillins and cephalosporins has been known to increase stability.[29] Compared to other substituents, the methoxy group was found to impart optimum effects in inhancing stability without significantly diminishing the biological activity. A similar increase in stability has been reported for 6-methoxy-epiPS-5.[30]

Based on these results, we undertook syntheses leading to α,α-disubstituted bicyclic β-lactams such as isocephems, carbacephems and carbapenems. Most of these compounds were prepared from a few common monocyclic precursors. This strategy of synthesizing various

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[29] Ponsford, R. J.; Basker, M. J.; Burton, G.; Guest, A. W.; Harrington, F. P.; Milner, P. H.; Pearson, M. J.; Smale, T. C.; Stachulski, A. V. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; A. G. Brown and S. M. Roberts, Ed.; The Royal Society of Chemistry: London (England), 1985; p 32.

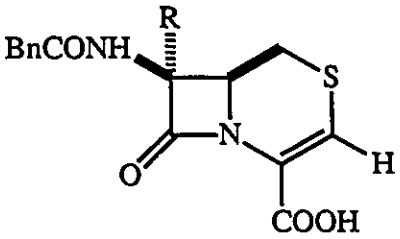
[30] (a) Yoshioka, T.; Watanabe, A.; Isshiki, K.; Fukagawa, Y. *Tetrahedron Lett.* **1986**, *26*, 4335. (b) Watanabe, A.; Fukagawa, Y.; Ishikura, T.; Yoshioka, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2091.

targets from a common precursor is particularly important in pharmaceutical research since it allows one to synthesize many examples quickly. Our interest in these compounds is based not only on the potential antibacterial activity but also on the fact that they offer a unique opportunity to develop and explore new synthetic methodologies.

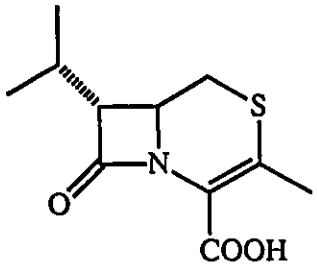
CHAPTER 2: ANIONIC 4+2 CYCLIZATION ROUTE TO 3-SULFUR SUBSTITUTED ISOCEPHEM ANALOGS

Structural diversity

Despite nearly twenty years of research, the synthesis of the nuclear analogs of cephems is still being actively pursued. Early interests in the isocephem area were largely synthetic, yielding isocephems with substituents such as phenylacetamido **1a** or a combination of phenylacetamido and methyl[1] **1b** or isopropyl[2] **2** or no substituents[3] **3** at C-7. These compounds were inactive.



1a R=H, **1b** R=Me



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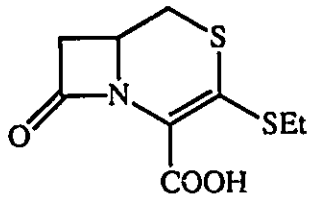


3

Gleason and colleagues synthesized isocephems **4-7** which carried the more typical amide side chain at C-7 and found that most of these compounds had good activity against *B. subtilis* and *Staphylococcus aureus*. Compound **4** is more active than the natural cephem analogs against Gram-negative bacteria but somewhat less active against *S.*

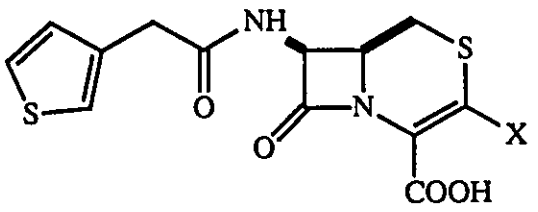
---

[1] Lowe, G.; Brunwin, D. M. *J. Chem. Soc. Perkin Trans. I* **1973**, 1321.

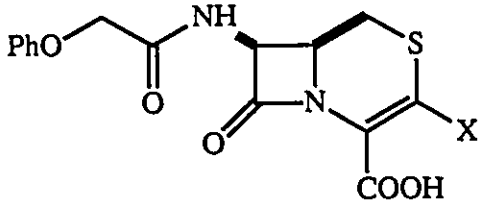
[2] Greff, Z.; Horvath, Z.; Nyitiai, J.; Katjar-Peredy, M.; Brlik, J. *J. Chem. Res.(S)* **1990**, 170.

[3] McCombie, S. W.; Metz, W. A.; Afonso, A. *Tetrahedron Lett.* **1986**, *27*, 305.

aureus and *S. faecalis*.[4] The isocephem analog bearing an additional 7-methoxy substituent in **6** was found to be inactive.[5]

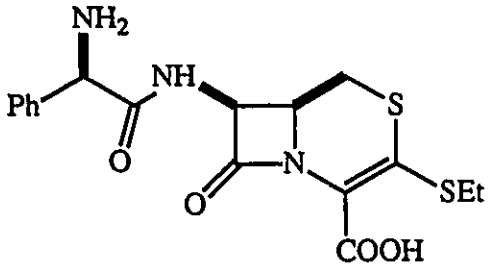


4 X=H, **5** X=Me



6 X=CH_3, **7** X=CH_2OAc

McCombie and collaborators reported several 7-N-amido-3-S-ethylisocephems. Compound **8** was found to have about half the antibacterial potency of D-phenylglycyldesacetoxyaminocephalosporanic acid (keflex), the cephem analog of **8**.[6] Since the product shown was a mixture of diastereomers the activity of the pure compound may be comparable to keflex. Most of the other derivatives reported were also more potent than their cephem counterparts.



8

Potentially useful isocephems were not discovered until the isocephem analog of ceftizoxime was prepared. This compound **9** was

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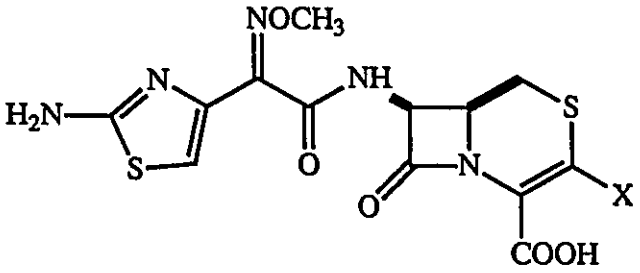
[4] Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353.

[5] Douglas, J. L.; Horning, D. E.; Conway, T. T. *Can. J. Chem.* **1978**, *56*, 2879.

[6] McCombie, S. W.; Metz, W. A.; Afonso, A. *Tetrahedron Lett.* **1986**, *27*, 305.

synthesized independently by chemists at the Sumitomo[7] and the Roussel Uclaf[8] companies. It was found to possess good activity against enterobacteriaceae and streptococci, which was comparable to ceftizoxime; but poor activity against staphylococci. Several 3-substituted analogs have been reported. The 3-sulfur substituted compounds **10** showed increased anti-staphylococcal activity but diminished Gram-negative activity. Compounds of type **11** were also found to have good antimicrobial activity; the pyridinium methyl (*i.e.* $Q=^{+}NC_5H_5$) derivative was found to have better Gram-positive and Gram-negative activity than cefotaxime.[9]



9 X=H; **10** X=SR; **11** X=CH_2Q, Q=quaternary ammonium nitrogen

Synthetic methods leading to isocephems

Not surprisingly, the pharmaceutical industry has been heavily involved in synthetic methodology development in this area. All general routes thus far described, with the exception of the diazo

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[7] Sumitomo Chemical Co. *Chem. Abs.* **1983**, *98*, 7100v. Japan Kokai Tokkyo Koho JP. 57,116 091.

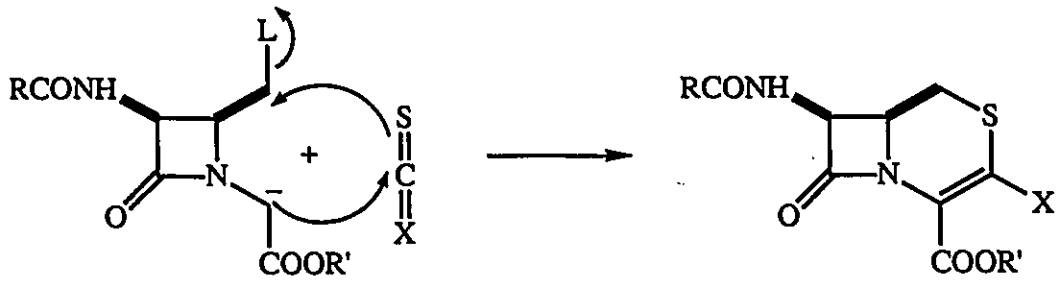
[8] Teutsch, J. G.; Bonnet, A.; Asjodi, J.; Costerousse, G. *Chem. Abs.* **1986**, *105*, 6351y. (Roussel-Uclaf) Eur. Pat. Appl. EP 153 229/1985.

[9] Aszodi, J.; Bonnet, A.; Chantot, J. F.; Costerrouse, G.; Teutsch, G. In *Recent Advances in the Chemistry of β-Lactam Antibiotics* The Royal Society of Chemistry: London (England), **1989**; p 350.

insertion route developed by Lowe, have had their origin in industry and are referred to by the company name in this section.

1) Roussel-Uclaf Method

This method involves generation of an enolate α to the β-lactam nitrogen and reaction with carbon disulfide or carbon oxysulfide.[10] The subsequent nucleophilic displacement of a suitably positioned leaving group by the resultant sulfur nucleophile gives the isocephem nucleus. This method is particularly useful for the preparation of isocephems having an oxygen or sulfur substituent at C-3. This route was reported after we had completed our preliminary results which are described in this chapter.



12 **13** **14** X=S or O
R'=$CH(Ph)_2$

2) Smith Kline and French (SKF) Method

An azetidinone bearing a 4-mercaptomethyl group is reacted with bromo or chloropyruvates in the presence of a base such as triethylamine. The alkylation of the thiolate is followed by aminal formation giving the bicyclic compound. Dehydration is conventionally carried out using thionyl chloride or trifluoroacetic anhydride,[11]

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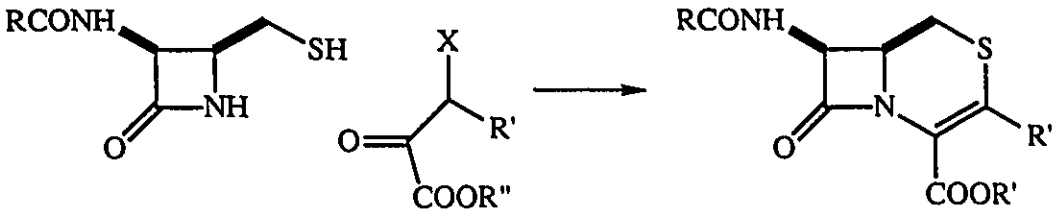
[10] Costerousse, G.; Cagniant, A.; Didierlaurent, S.; Proust, D.; Teusch, G. *Bull. Soc. Chim. Fr.* **1989**, 830.

[11] Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353.

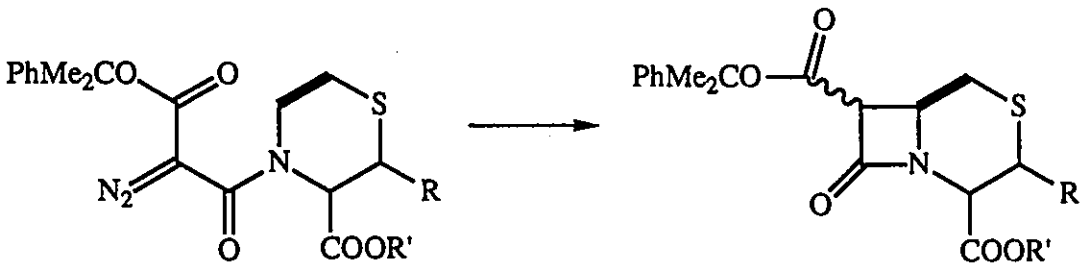
yielding structures such as **17** (R'=H). When Aszodi and collaborators applied this approach to the preparation of 3-sulfur substituted analogs **17** (R'=SR*), the dehydration method failed. However the use of diphosphorous tetraiodide gave modest yields of dehydration products.[12]



15 **16** **17**

3) Lowe's diazo insertion Method

Irradiation of the diazocompound **18** gave the bicyclic isocephem **19** *via*. C-H insertion of the resulting carbene.[13] The sulfur atom did not intercept the carbene. The C-7 ester function was exploited as a control group for introducing additional 7-methyl group or as a synthon for the introduction of 7-amido function.

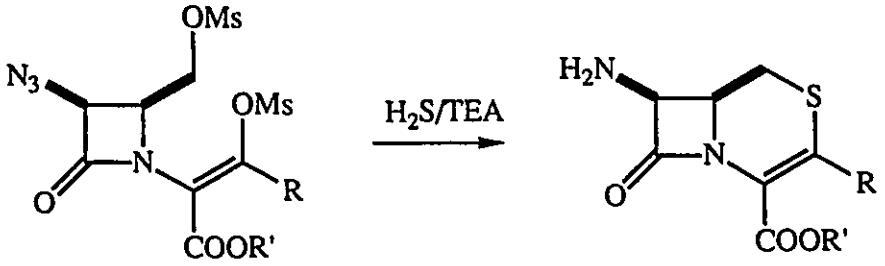


18 **19** R=H

3) Bristol Method

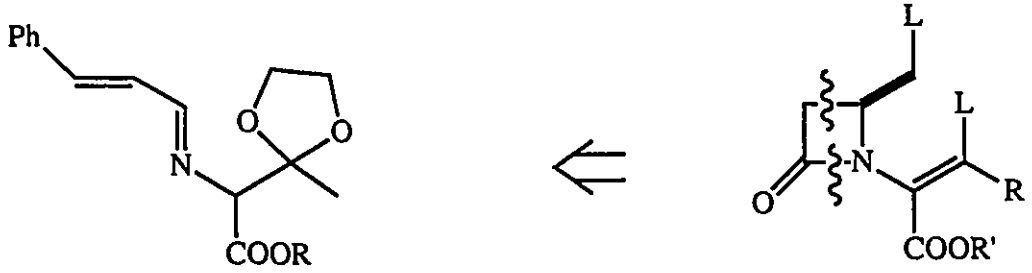
[12] Aszodi, J.; Chantot, J. F.; Teutsch, G.; Collard, J. *Heterocycles* **1989**, *28*, 1061.
[13] Lowe, G.; Brunwin, D. M. *J. Chem. Soc. Perkin Trans. 1* **1973**, 1321.

This method exploits the bivalency of sulfur and its soft nucleophilicity to obtain bicyclic isocephems starting with a suitable azetidinone such as **20**.[14] This annulation presumably involves a 1,4-addition-elimination sequence to generate an intermediate ene-thiolate and concomitant intramolecular nucleophilic displacement of the suitably located mesylate function by the thiolate intermediate. This method avoids the problematic dehydration of a tertiary alcohol required by the SKF method.



20 **21** R=H, R=Me

The preparation of cyclization precursor **20** involves the use of a suitably substituted imine in a 2+2 ketene imine cycloaddition and standard functional group transformations.

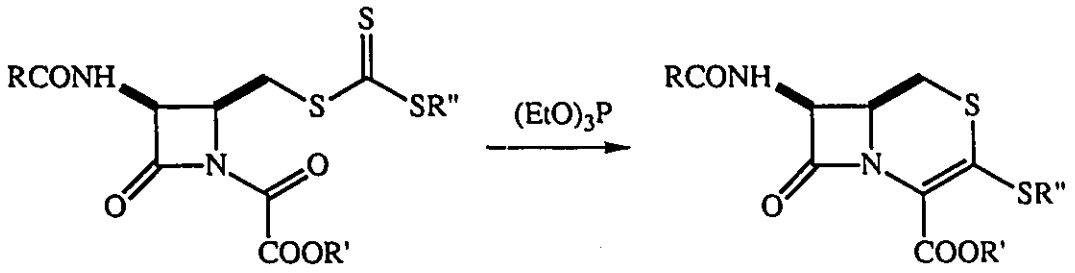


22 **20**

[14] (a) Doyle, T. W.; Douglas, J. L.; Belleau, B.; Meunier, J.; Luh, B. Y. *Can. J. Chem.* **1977**, *55*, 2873. (b) Doyle, T. W.; Douglas, J. L.; Belleau, B.; Conway, T. T.; Ferrari, C. F.; Horning, D. E.; Lim, G.; Luh, B. Y.; Martel, A.; Menard, M.; Morris, L. R. *Can. J. Chem.* **1980**, *58*, 2508.

4) Schering method

McCombie and colleagues reported good yields of 3-sulfur substituted isocephems when the oxalimide **23** derived from an azetidinone carrying a suitable trithiocarbonate at C-4 was heated with triethyl phosphite.[15] This reaction has been proposed to proceed through a carbene generated adjacent to the nitrogen. Attack of such a carbene on the thione group could lead to an episulfide which is subsequently desulfurized by the excess triethyl phosphite.[16]



23 **24**

Methodology development

The above discussion clearly indicates that the studies on 7,7-disubstituted isocephems are rare and only very few examples having a combination of either nitrogen and oxygen or nitrogen and methyl substituents at C-7 are known. As mentioned earlier, we have been attempting to synthesize 6,6-disubstituted carbapenems *via*. a 4+1 cyclization. Since the addition of the unstabilized carbanions to isocyanides and the alkylation of the resultant carbanion has been

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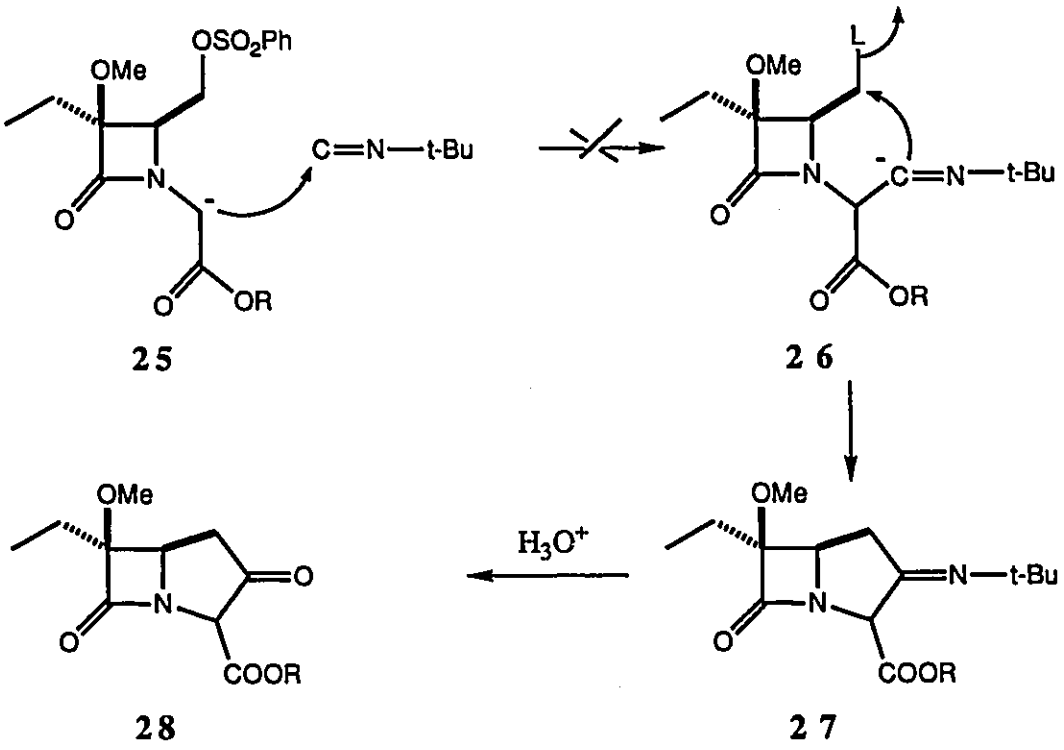
[15] McCombie, S. W.; Metz, W. A.; Afonso, A. *Tetrahehdon Lett.* **1986**, *27*, 305.
[16] for this type of mechanism proposition: Afonso, A.; Hon, F.; Weinstein, J.; Ganguly, A. K.; McPhail, A. T. *J. Am. Chem. Soc.* **1982**, *104*, 6138.

reported[17], we hoped a similar intramolecular version might be feasible with the stabilized carbanions. If the addition and intramolecular displacement proceeds as planned, it should lead to a convenient and novel method for preparing a key carbapenem intermediate. The bicyclic imine **27** or its tautomer enamine should be hydrolyzed readily to the ketone **28**. Bicyclic ketones with only one substituent at C-6 have already been shown to be important intermediates in carbapenem syntheses. When the substituent at C-6 is hydroxyethyl the bicyclic ketone intermediate is known as the "Merck ketone".



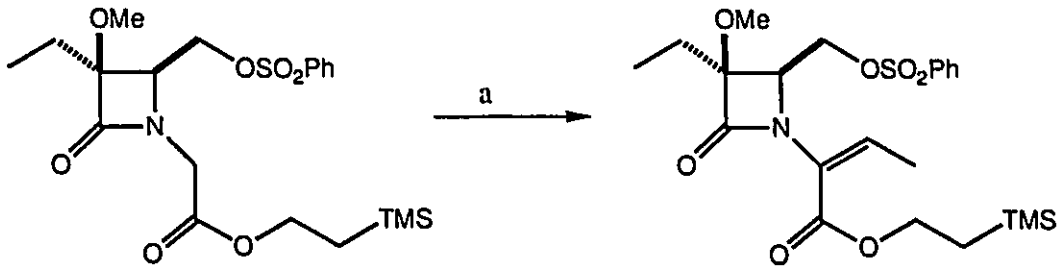
25 **26**

28 **27**

The question whether these reactions could be done without significant fragmentation of β-lactam ring due to the competing Grob type 1,4-elimination was examined. To probe this situation in our

[17] (a) Niznik, G. E.; Morrison, W. H., III; Walborsky, H. M. *J. Org. Chem.* **1974**, *39*, 600. (b) Marks, M. J.; Walborsky, H. M. *J. Org. Chem.* **1981**, *46*, 5405.

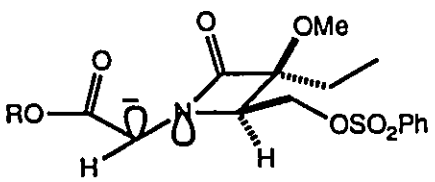
examples we decided to perform an experiment with acetaldehyde. When the anion **25**, obtained by treatment of **29** with LDA, was quenched with acetaldehyde at -78 °C and warmed to room tempera-



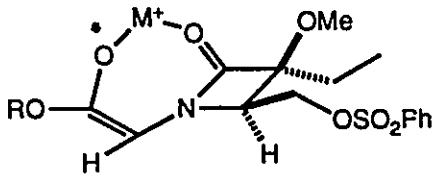
29 **30**

a) LDA, CH_3CHO, -78 °C to 25 °C, 18 h

ture the addition-elimination product **30** was isolated in 55% yield, thus removing the fear expressed above. The key peaks in the ^1H NMR spectrum at δ: 1.72 (3H, d, J=7.1 Hz, CH_3CH), 6.79 (1H, q, J=7.2 Hz, $CHCH_3$), 7.48-7.64 (3H, m, Ph), 7.81-7.85 (2H, m, Ph) and in mass spectrum (CI) at 456 (M^+-CO) are consistent with the structure shown. Perhaps, stereo-electronic factors play a key role in preventing the 1,4-elimination at low temperatures. One can expect the lone-pair on nitrogen and that on the carbanion to be *anti* to each other which makes the anion electron pair and the C-N bond orthogonal *e.g.* **25a**. Since elimination reactions are best effected when a *syn* or preferably an *anti* relationship exists between leaving group and anion 1,4-elimination in **25** is expected to be slow. In addition, the chelation of metal enolate with the oxygen atom of β-lactam carbonyl may lock the anion into a rigid and stable conformation **25b**, thus stabilizing the anion.



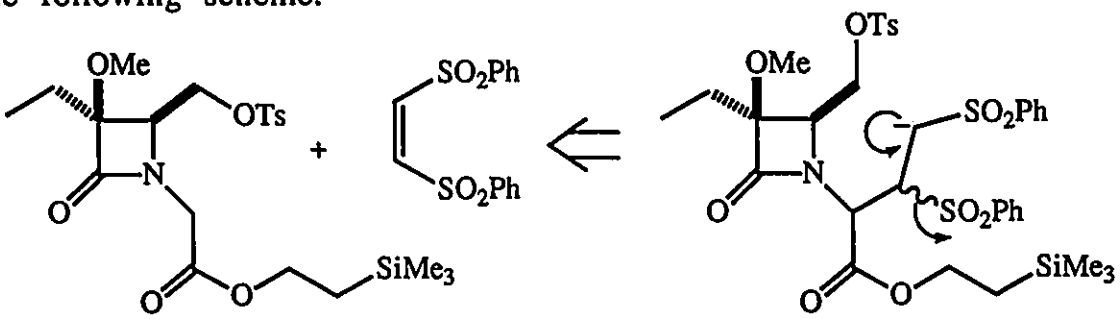
25a



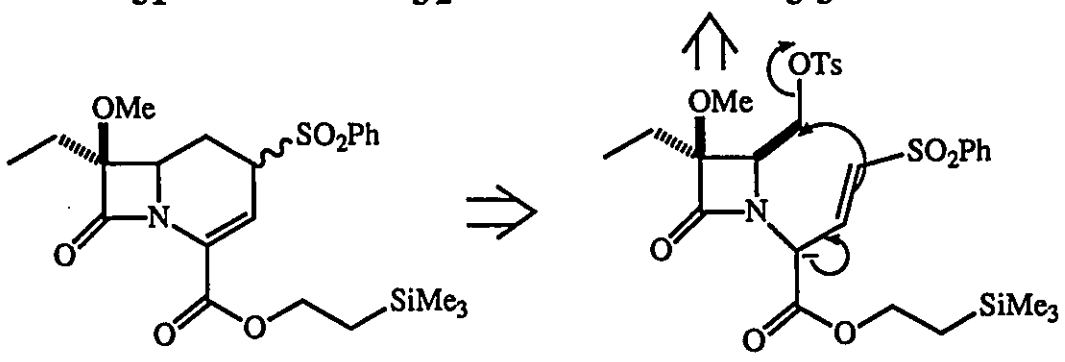
25b

When the anion **25** was generated by treatment of **29** in THF with 1.1 equivalent of LDA at -78 °C and exposed to the t-butyl isocyanide (-78 °C to 25 °C) condensation did not occur and only unreacted starting material was recovered. It appears that the anion **25** is not reactive enough towards t-butyl isocyanide.

We also attempted to apply the reaction of the anion **25** in a 4+2 cyclization involving an electrophilic C=C bond to prepare carbacephems. The receptor chosen was bisphenylsulfonylethene **32**. If such reaction were successful, the carbacephem **35** would be obtained as shown in the following scheme.

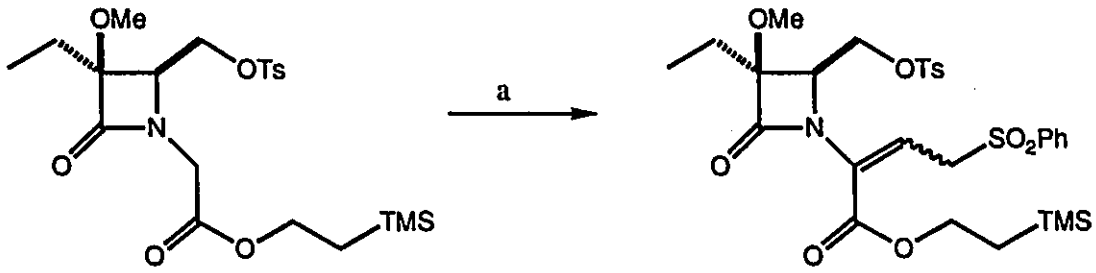


31 **32** **33**



35 **34**

When the anion, generated as described above, was reacted with a solution of bisphenylsulfonylethene **32** in THF (-78 °C to 25 °C), the initial addition of the carbanion derived from **31** to **32** did occur but the subsequent cyclization failed. The ^1H NMR spectrum of the major product obtained is consistent with the structure **34** [δ: 2.42 (3H, s, CH_3Ph), 3.88-4.27 (6H, m, CH_2O, CH_2OTs, CH_2SO_2Ph), 6.42 (1H, t, J=7.2 Hz, $CHCH_2SO_2Ph$), 7.32 (2H, d, J=8.0 Hz, Tol), 7.48-7.63 (3H, m, Ph), 7.71 (2H, d, J=8.4 Hz, Ph), 7.86 (2H, d, J=8.3 Hz, Tol)].

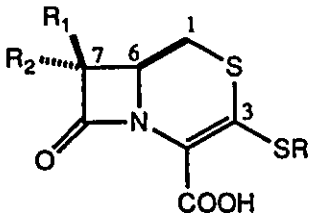


31 **34**

a) LDA, $PhSO_2CH{=}CHSO_2Ph$, THF, -78 °C to 25 °C

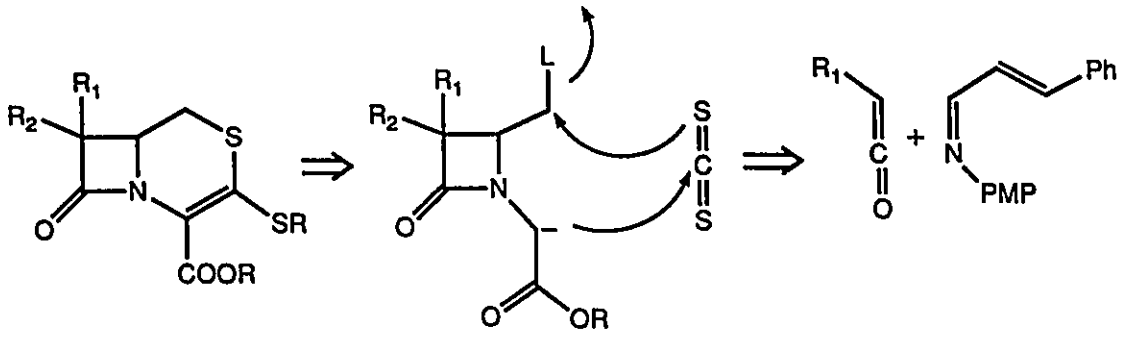
Target Isocephems

We decided to synthesize 3-sulfur substituted isocephems having substituents other than a conventional nitrogen at position 7 in order to capitalize on the precursors at hand. These precursors were prepared from the monocylic β-lactam which, in most cases, was obtained by a ketene-imine 2+2 cycloaddition. The following discussion deals with the successful completion of the total syntheses of 3-sulfur substituted isocephems **36-39**. Some of these isocephems such as **36** and **37** have either thienamycin (hydroxyethyl) or PS-5 (ethyl) type substituents at C-7 in addition to the methoxy group.



36: R_1=OMe, R_2=Et, R=Bn; **37**: R_1=OMe, R_2=(S)-hydroxyethyl, R=Bn; **38**: R_1=H, R_2=(R)-hydroxyethyl, R=Bn; **39**: R_1=OMe, R_2=H, R=Et

The overall strategy was to assemble the isocephem nucleus using an anionic 4+2 cyclization methodology as shown in the following retrosynthetic scheme.

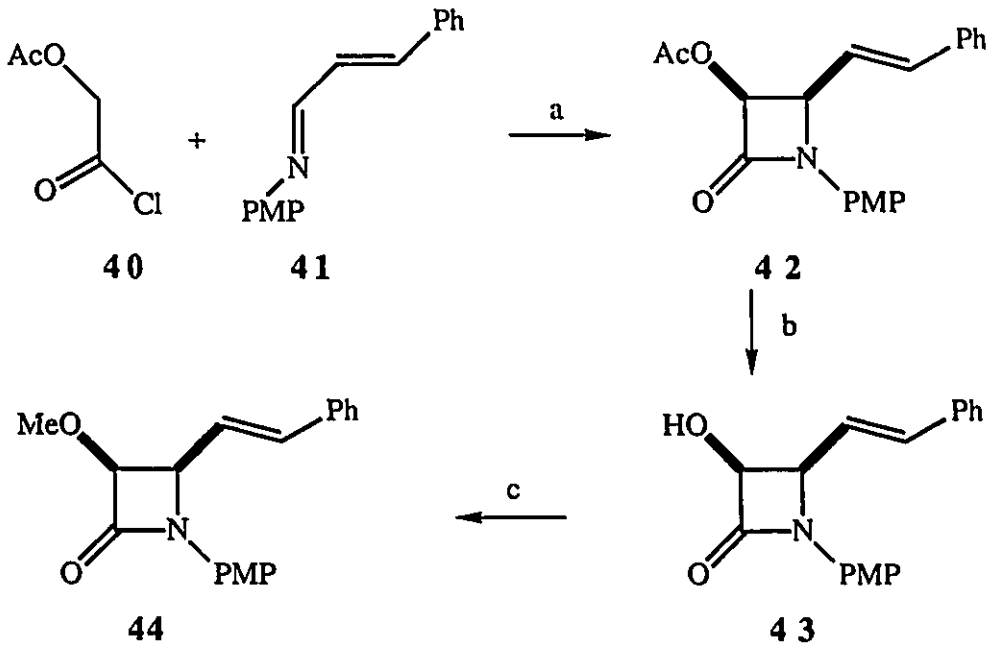


Retrosynthetic Scheme

Synthesis of Isocephems 36 and 37

The compounds **45** and **48** were chosen as starting materials for the synthesis of the target bicyclic compounds **36** and **37**, respectively. Considerable time was spent in scaling up the preparation of the azetidinone **44** to 84-147 millimolar scale. The precursor to these starting materials, 4-cinnamyl-3-methoxy-1-p-methoxyphenyl azetidinone **44**, can be prepared from methoxyacetyl chloride or its equivalent (*i.e.* methoxyacetic acid activated with DMF/oxalyl chloride)

or from acetoxyacetyl chloride. The later method is somewhat longer as it requires further deacetoxylation by the Zemplen method and methylation of the resultant hydroxy compound **43**.[18] However, this longer route is more reliable and reproducible on a large scale.



40 **41** **42** **43** **44**

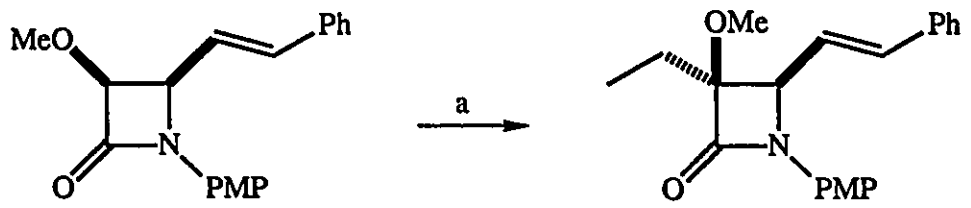
a) TEA, CH_2Cl_2, 0 °C to 25 °C; b) NaOMe, MeOH:THF (1:1), 25 °C; c) NaH, MeI, THF, 0 °C to 25 °C

The compounds, **45** and **48**, were initially prepared by Sharma on 2 and 0.33 millimolar scales by reaction of the anion derived from azetidinone **44** with excess iodoethane or acetaldehyde respectively.[19] Since multistep syntheses require large amounts of starting materials, these compounds were later prepared on 40-50 and 20-30 millimolar scales respectively. A surprising result was the formation of a minor isomer in LDA/acetaldehyde sequence which had *cis* relationship

[18] Sharma, M. K. *Ph. D. Thesis*, University of Ottawa, **1990**, p 149.

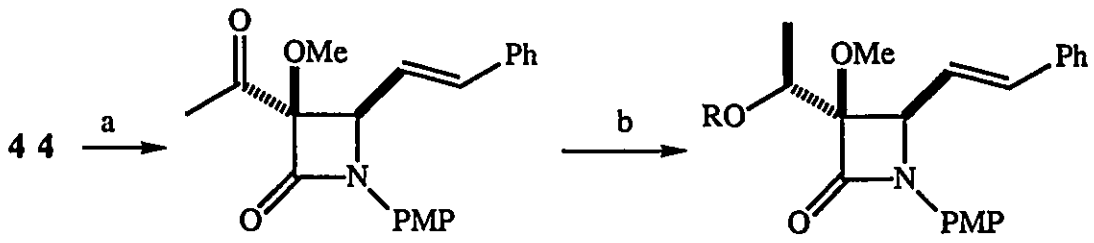
[19] (a) Durst, T.; Sharma, M. K.; Gabe, E. J.; Lee, F. L. *J. Org. Chem.* **1990**, *55*, 5525. (b) Sharma, M. K. *Ph. D. Thesis*, University of Ottawa, **1990**, p 91 (c) *ibid.* p 97.

between the hydroxyethyl group and the cinnamyl group. This compound was not observed in the small scale reactions. Although the amount of this material represented less than 5% of the total product, it caused significant separation problems. Finally, it was found this impurity could be removed by first converting the mixture to the TBDMS derivatives *via*. oxidation, reduction and silylation sequences and then carefully separating two diastereomers by column chromatography. It was also learnt that the anion reaction with acetaldehyde or iodoethane could be scaled only up to about 20 g scale, because beyond this the yields decreased significantly. This may be due to certain physical factors such as rate of mixing during stirring, localized heating in reaction vessels, etc.



44 **45**

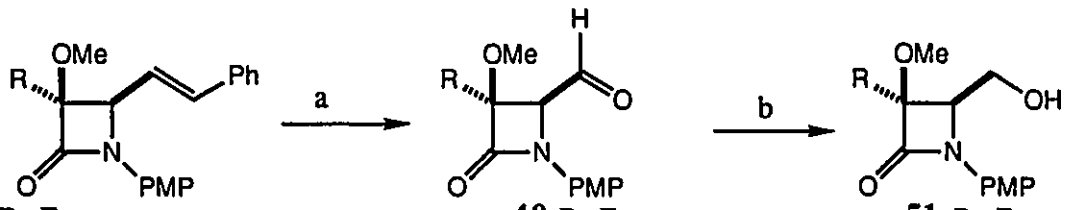
a) LDA, EtI, THF, -78 °C to -30 °C



46 **47** R=H, **48** R=TBDMS

a) LDA, CH_3CHO, THF, -78 °C; PCC, NaOAc, 4Å mol. sieves, CH_2Cl_2; b) L-Selectride, TMEDA, THF, -78 °C; **47** to **48**: TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C

The compounds **45** and **48** were ozonolyzed and reduced with sodium borohydride in a one pot sequence. Occasionally the separation of the alcohol **51** or **52** from benzyl alcohol, the byproduct, proved to be difficult. Ozonolysis when carried out in methylene chloride gave several products. However use of anhydrous dichloromethane and traces of methanol in the presence of 4Å mol. sieves gave a clean reaction. The product aldehydes were purified easily and isolated in excellent yields. The aldehydes **49** and **50** showed the expected low field proton peak at δ=9.70 ppm (d, J=3.3 Hz, CHO) and 9.79 ppm (d, J=2.2 Hz, CHO) respectively in ^{1}H NMR. They were further characterized by IR, ^{1}H NMR, MS and HRMS. These data are recorded in the Experimental section. These reasonably stable aldehydes were reduced with sodium borohydride to afford the alcohols **51** and **52** in 51% and 70% overall yield from **45** and **48**. These alcohols also gave spectral data consistent with the assigned structures.



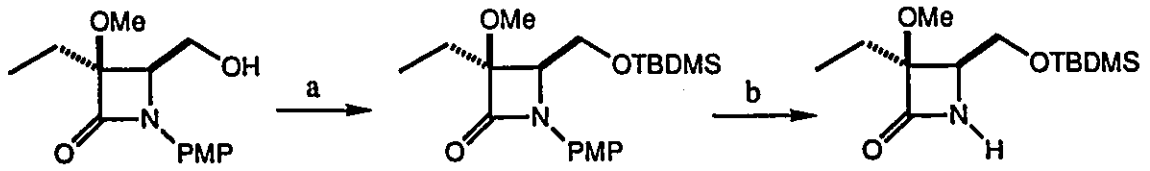
45 R=Et **49** R=Et **51** R=Et

48 R=(S)-CH(CH$_3$)OTBDMS **50** R=(S)-CH(CH$_3$)OTBDMS **52** R=(S)-CH(CH$_3$)OTBDMS

a) O_3, CH_2Cl_2, MeOH, -78 °C, DMS, -78 °C to 25 °C; b) $NaBH_4$, EtOH

The hydroxyl group of **51** was protected as a TBDMS ether, using TBDMSOTf and 2,6-lutidine, during the initial experiments designed to prepare the free NH azetidinones. Subsequent cleavage of the PMP group with CAN in acetonitrile at -5 °C to O °C occurred in poor yield. None of the fractions isolated by column chromatography of the crude

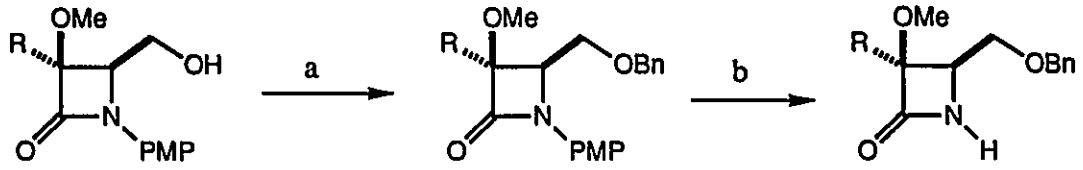
product obtained during the N-alkylation of **54** (NaH, DMF, ICH_2COOBn) gave a ^1H NMR spectrum corresponding to the desired product. Hence,



51 **53** **54**

a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; b) CAN, MeCN, H_2O, -5 °C to 0 °C

we chose a benzyl protective group. For this purpose, the hydroxyl group in **51** or **52** was converted to corresponding alkoxide using NaH and then quenched with benzyl bromide to give benzyl ethers **55** and **56**. Oxidative removal of the PMP group using CAN now occurred satisfactorily affording the NH compounds **57** and **58**.[20] The byproduct,



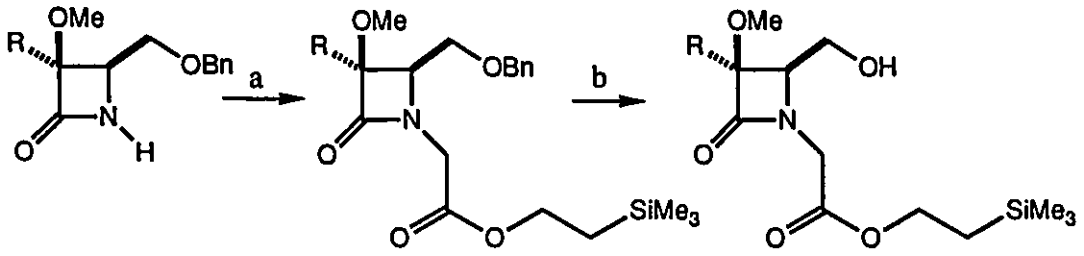
51 R=Et **55** R=Et **57** R=Et
52 R=(S)-CH(CH_3)OTBDMS **56** R=(S)-CH(CH_3)OTBDMS **58** R=(S)-CH(CH_3)OTBDMS

a) NaH, BnBr, DMF, 0 °C to 25 °C; b) CAN, MeCN, H_2O, -5 °C to 0 °C

benzoquinone, and residual starting material were removed by passing the crude reaction mixture through a silica gel column and the product, thus obtained, was reacted with β-trimethylsilylethyl bromoacetate and NaH in DMF at 0 °C to introduce the required acetate side chain at nitrogen. The ^1H NMR of **59** verified the introduction of the β-trimethylsilylethyl acetate unit (δ=0.00, s, 9H; 0.88-1.00, CH_2TMS; 4.12-

[20] Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

4.47, OCH_2), and the infrared showed that the β-lactam ring had been retained (IR 1754 cm^{-1}). Similar spectral evidence for the presence of β-trimethylsilylethyl moiety [^1H NMR (δ=0.01, 9H, s; 0.84-0.96, 2H, m; and 2 OCH_2 hydrogens overlapping with multiplet at 3.92-4.20)] and the intact β-lactam ring (IR 1756 cm^{-1}) was obtained in case of **60**. The β-trimethylsilylethyl protective group for the acid function rather than more commonly used PNB, was chosen since the benzyl group used to protect the alcohol can be selectively cleaved by hydrogenolysis without affecting the ester function. The debenzylation of the N-alkylated compounds **59** and **60** was achieved in near quantitative yield with hydrogen and 10% palladium on carbon. The ^1H NMR, IR (3441 cm^{-1}, broad, OH) and M^+-43 peak in MS of the alcohol **61** was as expected.



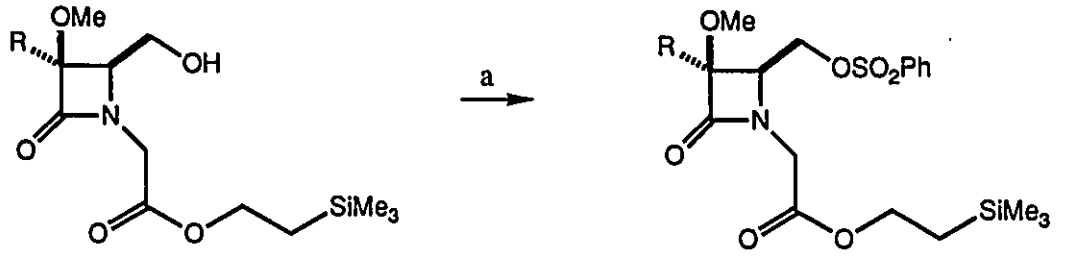
57 R=Et **59** R=Et **61** R=Et
58 R=(S)-$CH(CH_3)OTBDMS$ **60** R=(S)-$CH(CH_3)OTBDMS$ **62** R=(S)-$CH(CH_3)OTBDMS$

a) $BrCH_2COOCH_2CH_2SiMe_3$, NaH, DMF; b) H_2, Pd-C (10%), EtOH, 40 psi, 25 °C

The resultant free hydroxyl function in **61** and **62** was activated as its benzenesulfonate by adding a mixture of alcohol and benzenesulfonyl imidazole[21] in a dry DMF:THF mixture to a suspension of sodium hydride in DMF:THF (1:1). The usual method of preparing the

[21] Prepared by a similar method reported. Fraser-Reid, B.; Hicks, D. R. *Synthesis* 1974, 203.

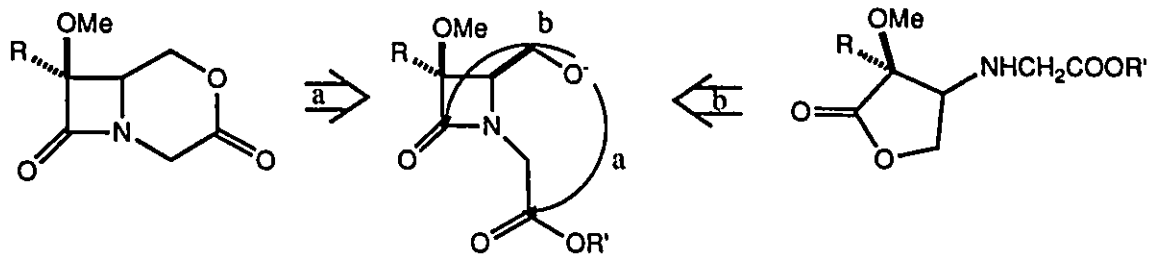
alkoxides by stirring the alcohol with NaH for several minutes and subsequent trapping with benzenesulfonyl imidazole was avoided, since the alkoxide **64** may react in an undesirable way to give lactones **65** or **66** if allowed to stir in the absence of an electrophile. Following this protocol, the compounds **29** and **63** were obtained in 80% and 63% yields respectively (Fig. 1 and 2). The compound **29** gave the expected peaks in IR at 1770 and 1740 (C=O), 1370, 1190 (SO_2) cm^{-1}; in its ^1H NMR at δ: 0.00 (9H, s, TMS), 0.87-1.02 (5H, m, CH_3, CH_2TMS), 3.72 (1H, d, J=18.1 Hz, NCH_AH_BCOOR), 4.15 (5H, m, 2 x OCH_2, NCH_AH_BCOOR), 7.51-7.66 (3H, m, Ph), 7.85-7.897 (2H, m, Ph) ppm and in MS at 414 (M^+-43, 2). Compound **63** also showed the key IR absorption at 1757 (C=O) cm^{-1}. ^1H NMR peaks were found at δ=0.01 (15H, s, TMS, $(CH_3)_2Si$), 0.93-0.99 (2H, m, CH_2Si), 3.85 (1H, d, J=17.9 Hz, NCH_AH_BCOOR), 4.00-4.31 (7H, m, HCO, H_2CO, HCN, NCH_AH_BCOOR), 7.49-7.89 (5H, m, Ph) ppm. The expected protonated molecular ion peak in chemical ionization mass spectrum was found at m/e=588.



61 R=Et
62 R=(S)-CH(CH_3)OTBDMS

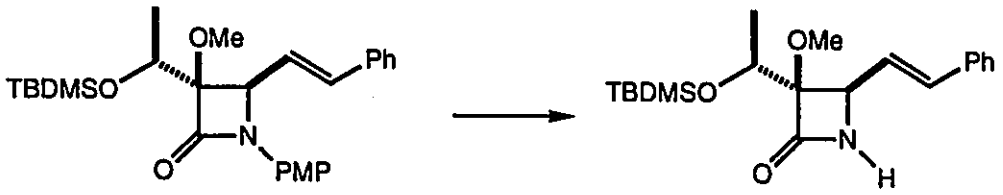
29 R=Et
63 R=(S)-CH(CH_3)OTBDMS

a) $PhSO_2$imid, NaH, THF:DMF (1:1), 0 °C to 25 °C



65 **64** **66**

At this stage we evaluated the preceding synthetic schemes involving the conversion of **45** and **48** to **29** and **63** respectively. Protection of alcohols **51** and **52** as their benzyl ethers and subsequent deprotection represent two extra steps. A shorter sequence could be realized either if the PMP group could be cleaved prior to the ozonolysis of the cinnamyl group (*e.g.* preparation of **67**) or if the alkylation of the azetidinone **69** could be achieved without disturbing the benzenesulfonate group. Unfortunately CAN cleavage of PMP group in the compound **48** failed.



48 **67**

In the second approach, the benzenesulfonate **69** was prepared in 55% yield by simply using the sequence of reactions shown below. When the alkylation was carried out by first treatment with NaH and subsequent addition of benzyl iodoacetate to the alkoxide at 0 ^{o}C, the reaction mixture contained numerous spots from which the desired alkylation product **70** could not be isolated. Thus we completed

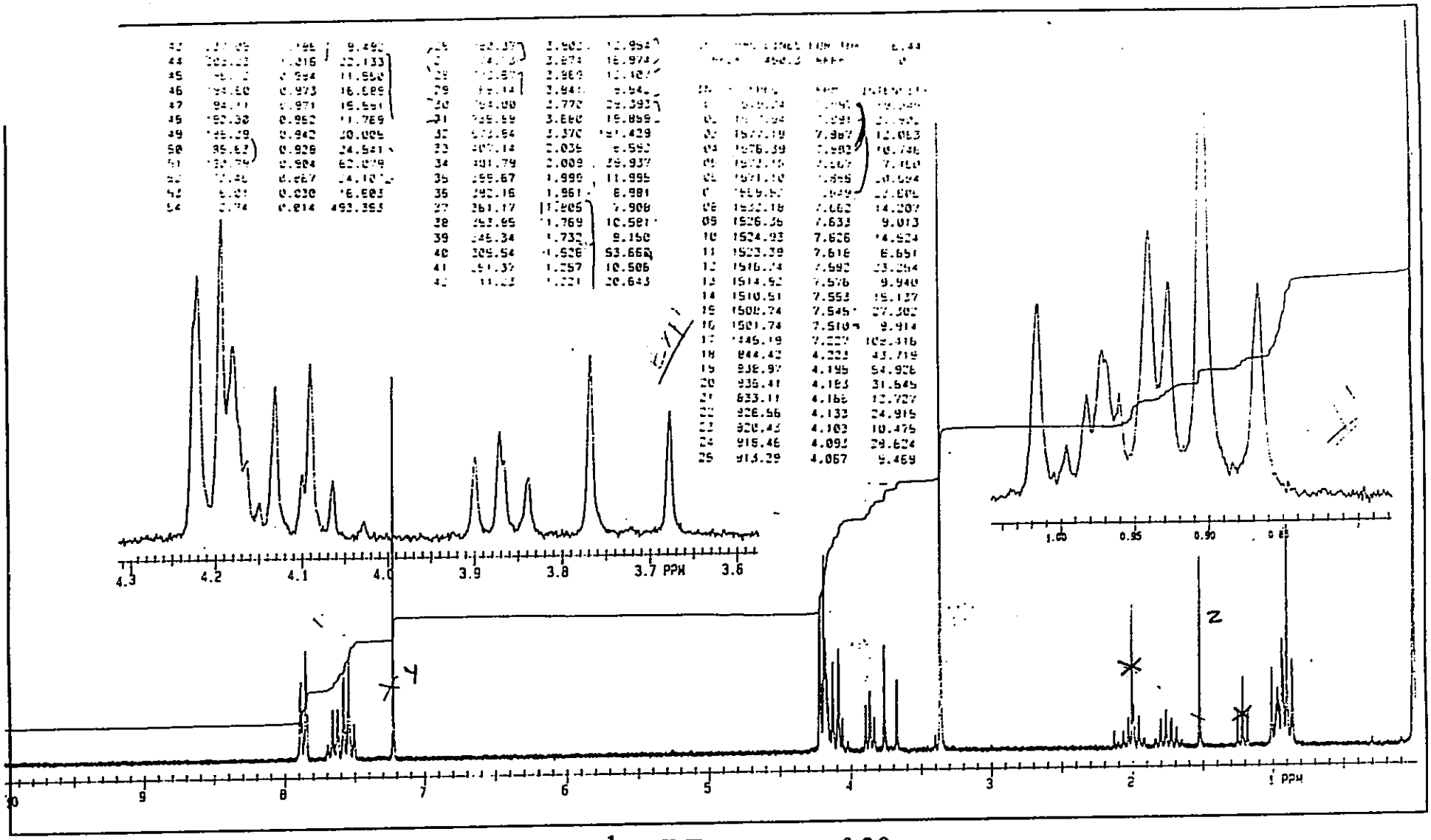


Fig. 1 ^{1}H NMR spectrum of 29

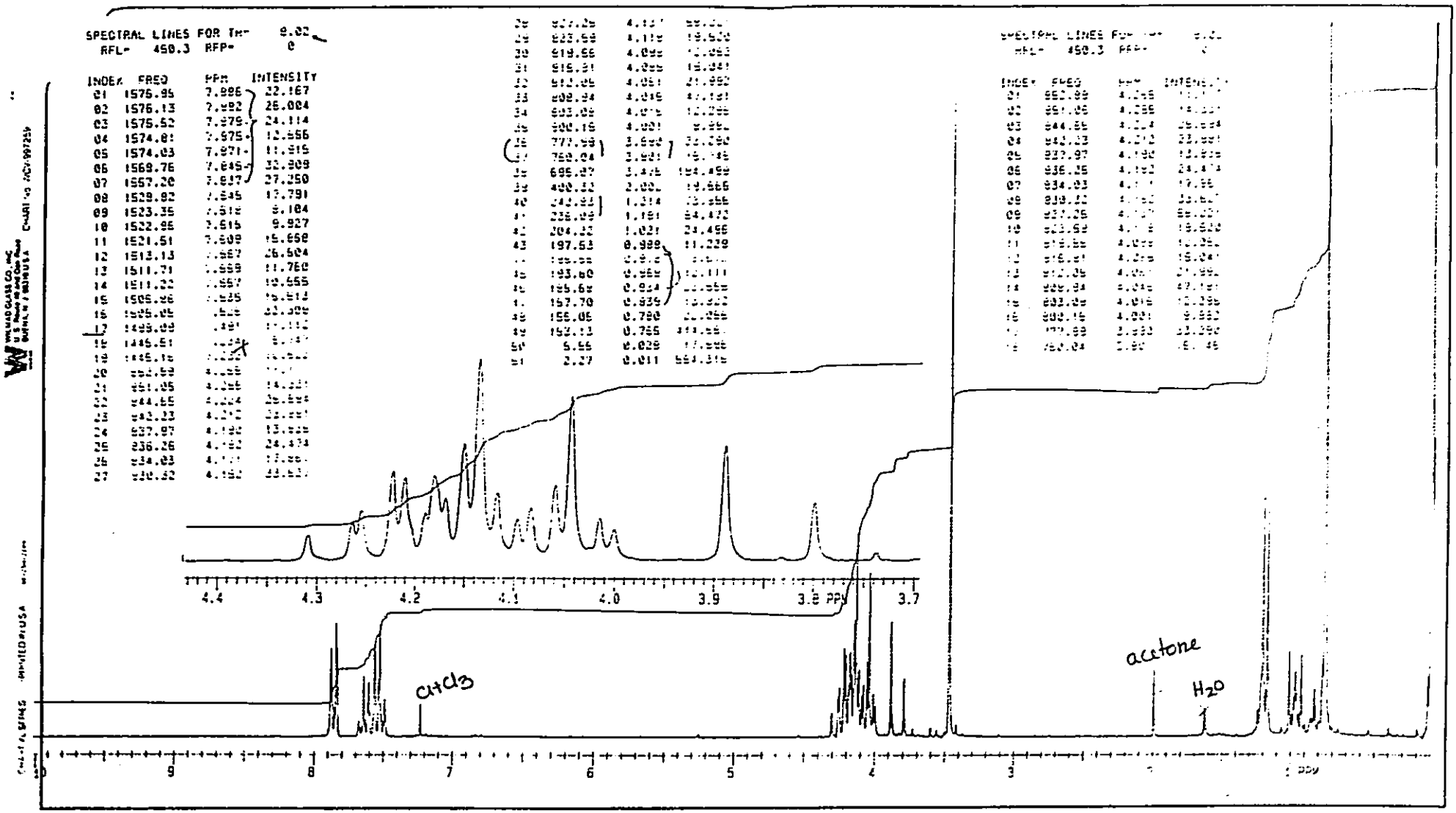
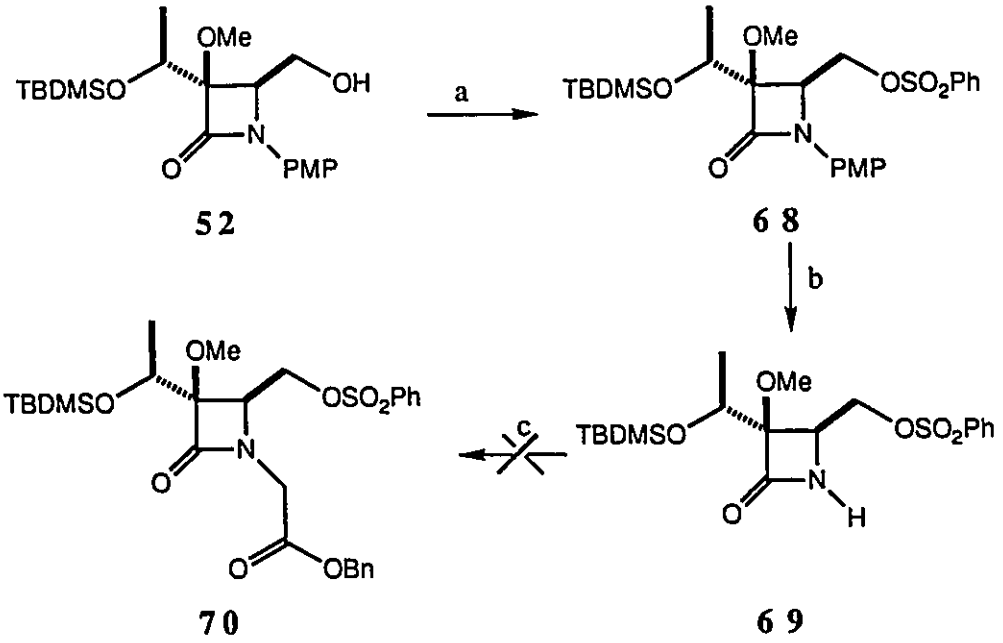


Fig. 2 ^{1}H NMR spectrum of **63**

synthesis of **29** and **63** *via*. the protection-deprotection sequences mentioned above.

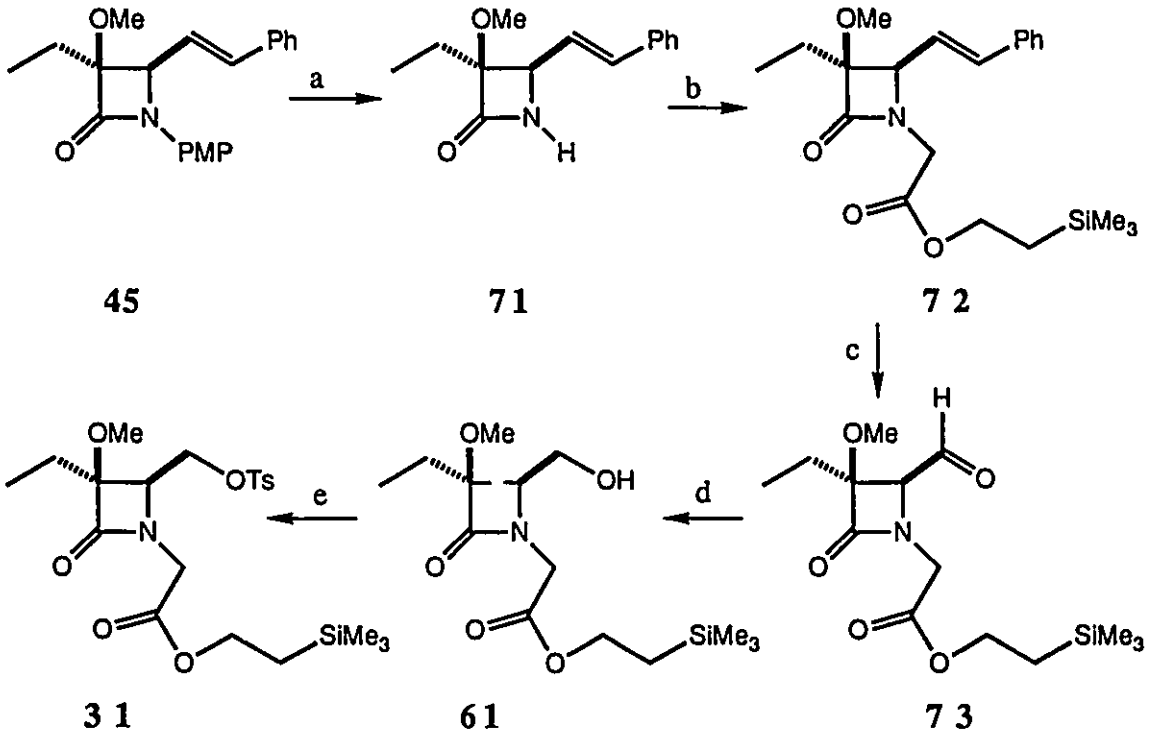


52 **68** **70** **69**

a) NaH, $PhSO_2$imid, DMF, 0 °C; b) CAN, McCN, H_2O, -5 °C to 0 °C; c) NaH, ICH_2COOBn, DMF, 0 °C

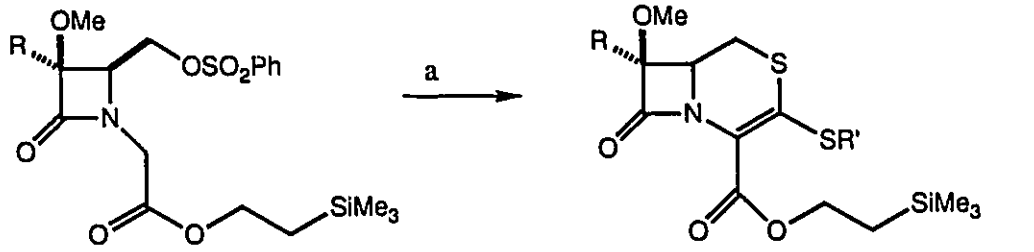
After the completion of the syntheses of isocephems **36** and **37**, we decided to re-examine the CAN reaction in the compound **45**. At the usually recommended temperature for this reaction *i.e.* -5 °C to 0 °C, the cleavage product was isolated only in low yield. The NH compound **71** was obtained in a much superior yield of 52% when the reaction temperature was lowered to -25 °C to -30 °C. Our initial experiment with **48** might have failed due to poor mixing techniques, temperature control and monitoring the completion of reaction. Since compounds such as **45** and **48** behaved poorly during this reaction, one may speculate concerning the participation of the cinnamyl group with the cleavage of the C-N bond of β-lactam.

The N-alkylation of **71** and ozonolysis of cinnamyl group of **72** was carried out using the methods described above. When the reduction of the aldehyde **73** was attempted first with sodium borohydride the yield was low. This could be due to the side reaction of the resultant alkoxide **64** suggested on page 31. Sodium cyanoborohydride reduction under acidic condition (pH 3-4) afforded the desired alcohol **61** in 15% overall yield from **45** (4 steps). This compares to the 14% yield obtained *via*. the sequences which involved the extra protection-deprotection steps (*i.e.* through intermediates **49-51-55-57-59**). The tosylation of **61** was carried out using toluenesulfonyl chloride in pyridine at 0 °C to give **31** in 72% yield.



a) CAN, MeCN, H_2O, -30 °C to -25 °C; b) NaH, $BrCH_2COOCH_2CH_2SiMe_3$, DMF, 0 °C; c) O_3, CH_2Cl_2, MeOH, -78 °C, DMS, -78 °C to 25 °C; d) $NaCNBH_3$, MeOH, pH 3-4, 25 °C; e) TsCl, pyridine, 0 °C

The big moment in this project arrived. Treatment of **29** with freshly prepared LDA solution in THF at -78 °C generated the ester enolate which was quenched *in situ* with carbon disulfide. The first experiment failed. Since the experiment involving the reaction of the anion **25** with acetaldehyde had shown that the generation and trapping of the anion with electrophiles was not a problem, a possible cause of failure might have been the quality of carbon disulfide. The experiment with carbon disulfide from new unopened bottle (supplied by BDH Chemicals, reagent grade) gave the desired bicyclic compound. (Carbon disulfide was carefully dried and distilled prior to use in both successful and unsuccessful cases). Purification of the product enethiol



29 R=Et
64 R=(S)-CH(CH$_3$)OTBDMS

74 R=Et, R'=H;
75 R=(S)-CH(CH$_3$)OTBDMS, R'=H

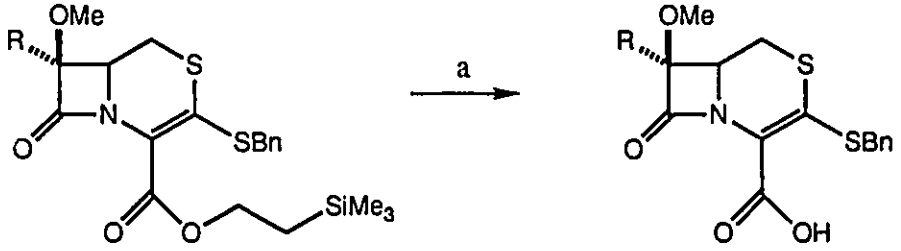
b

76 R=Et, R'=Bn
77 R=(S)-CH(CH$_3$)OTBDMS, R'=Bn

a) LDA, CS_2, THF, -78 °C to 25 °C; b) NaH, BnBr, THF, 0 °C

74 *via*. silica gel chromatography was difficult due to streaking. Therefore, the crude product was placed on a column, washed with 1:5 ethyl acetate:hexanes to remove the faster moving impurities; the desired compound was then desorbed by an ethyl acetate wash. S-Benzylation was accomplished in 95% yield by treatment with sodium

hydride and benzyl bromide. The product **75**, a yellowish solid, mp 82-84 °C, showed carbonyl peaks at 1760 and 1710 cm^{-1} (in IR) attributed to the β-lactam and the unsaturated ester moieties respectively. The key features in the ^1H NMR spectrum of **76** were the ABX pattern due to the N-CH-CH_2-S grouping at δ=2.88, 3.27 and 3.60 ppm (J_{AB} = 12.4 Hz, J_{AX}=9.8 Hz and J_{BX}=3.2 Hz), a singlet at δ=4.09 ppm for SCH_2Ph and the 9H singlet at δ=0.01 ppm due to the β-TMS group. Finally, the free acid **36**, mp 189-191 °C, was obtained in 74% yield by deprotection with 1.5 equivalent of tetrabutylammonium fluoride (TBAF)[22] in THF at room temperature for 17 h and acidification (Fig. 3). This compound was characterized by IR (3440, 1763 and 1654 cm^{-1}); ^1H NMR (300 MHz, acetone-d_6) δ=0.92 (3H, t, J=7.4 Hz, CH_3), 1.73-2.26 (2H, m, CH_2CH_3) acetone peak overlaps, 3.10-3.14 (2H, m, CH_2S), 3.34 (3H, s, OCH_3), 3.60-3.65 (1H, m, HCN), 4.04 (2H, d, J=3.4 Hz, SCH_2Ph), 7.17-7.30 (5H, m, Ph); ^{13}C NMR δ=7.8 (CH_3), 23.5 (CH_2), 28.8 (CH_2), 39.9 (CH_2), 55.2 (CH), 55.9 (CH_3O), 128.2 (CH), 129.3 (CH), 130.1 (CH), 137.6 (C); MS 365 (M^+, 20) and HRMS for $C_{16}H_{17}NO_4S_2$.



76 R=Et
77 R=(S)-CH(CH_3)OTBDMS

36 R=Et
37 R=(S)-CH(CH_3)OH

a) TBAF, THF, 25 °C

Compound **37** was obtained as a white solid in 75% yield (Fig. 4); mp 209-211 °C, IR: 3549 (broad, OH), 1736 (C=O), 1655 (COOH) cm^{-1}; ^1H

[22] Carpino, L. A.; Tsao, J. H. *J. Chem. Soc. , Chem. Commun.* **1978**, 358.

NMR (300 MHz, acetone-d_6 + 1 drop D_2O with HOD irradiation) δ:=1.24 (3H, d, J=6.5 Hz, CH_3), 3.17-3.21 (2H, m, H_2CS), 3.48 (3H, s, OCH_3), 3.88 (1H, dd, J=4.8, 8.3 Hz, HCN), 4.10 (2H, d, J=1.7 Hz, H_2CPh), 4.30 (1H, q, J=6.6 Hz, HCO), 7.21-7.33 (5H, m, Ph); ^{13}C NMR (THF-d_8) δ=18.0 (CH_3), 29.9 (CH_2), 40.6 (CH_2), 52.7 (CH), 54.6 (CH_3), 64.9 (HC), 96.1 (C), 124.5 (C=C), 125.2 (C=C), 128.0 (CH), 129.1 (CH), 130.1 (CH), 137.8 (C, Ph carbons), 162.4 (C=O), 163.9 (C=O); MS 381 (M^+, 2) and HRMS for $C_{16}H_{19}NO_3S_2$.

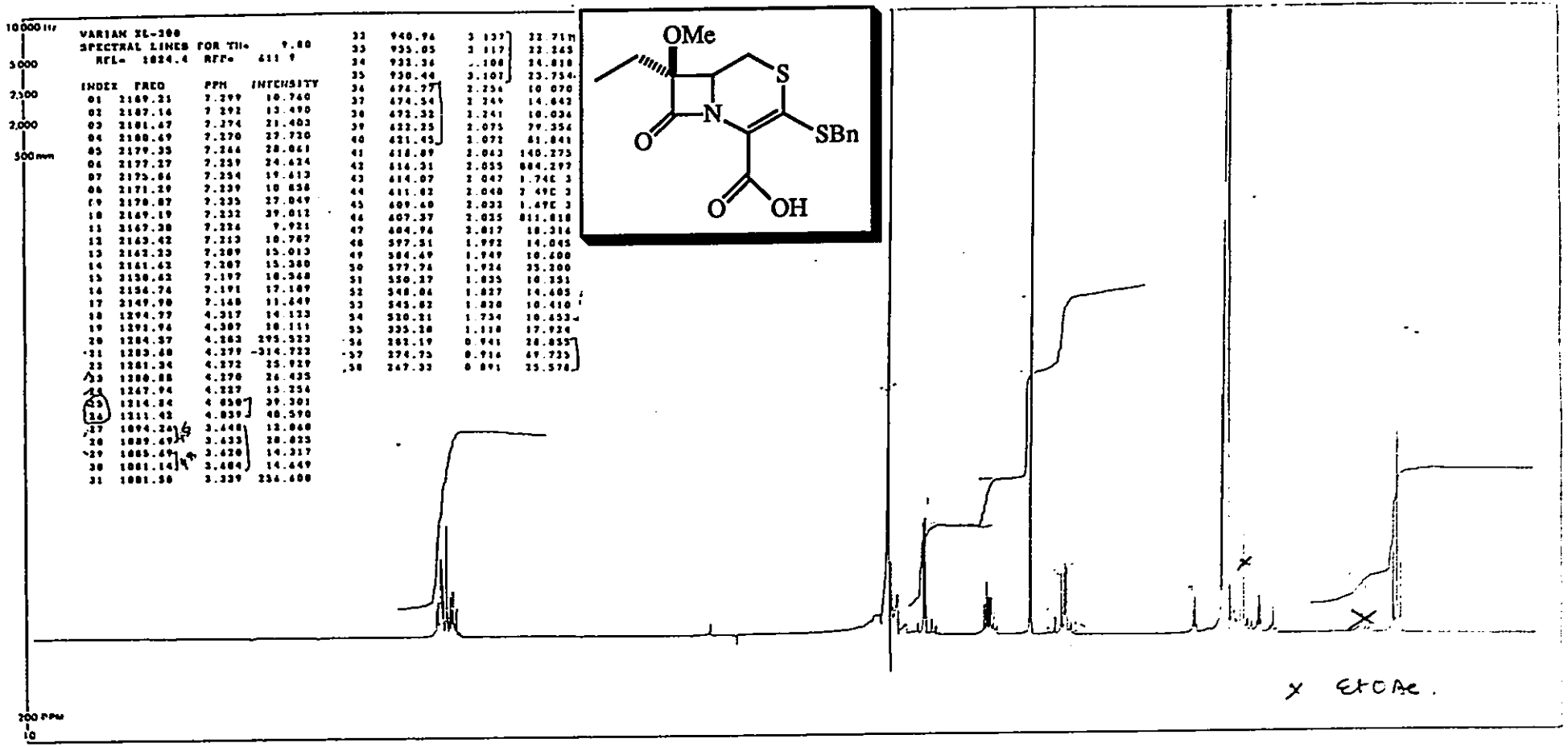


Fig. 3 ^{1}H NMR spectrum of **36**

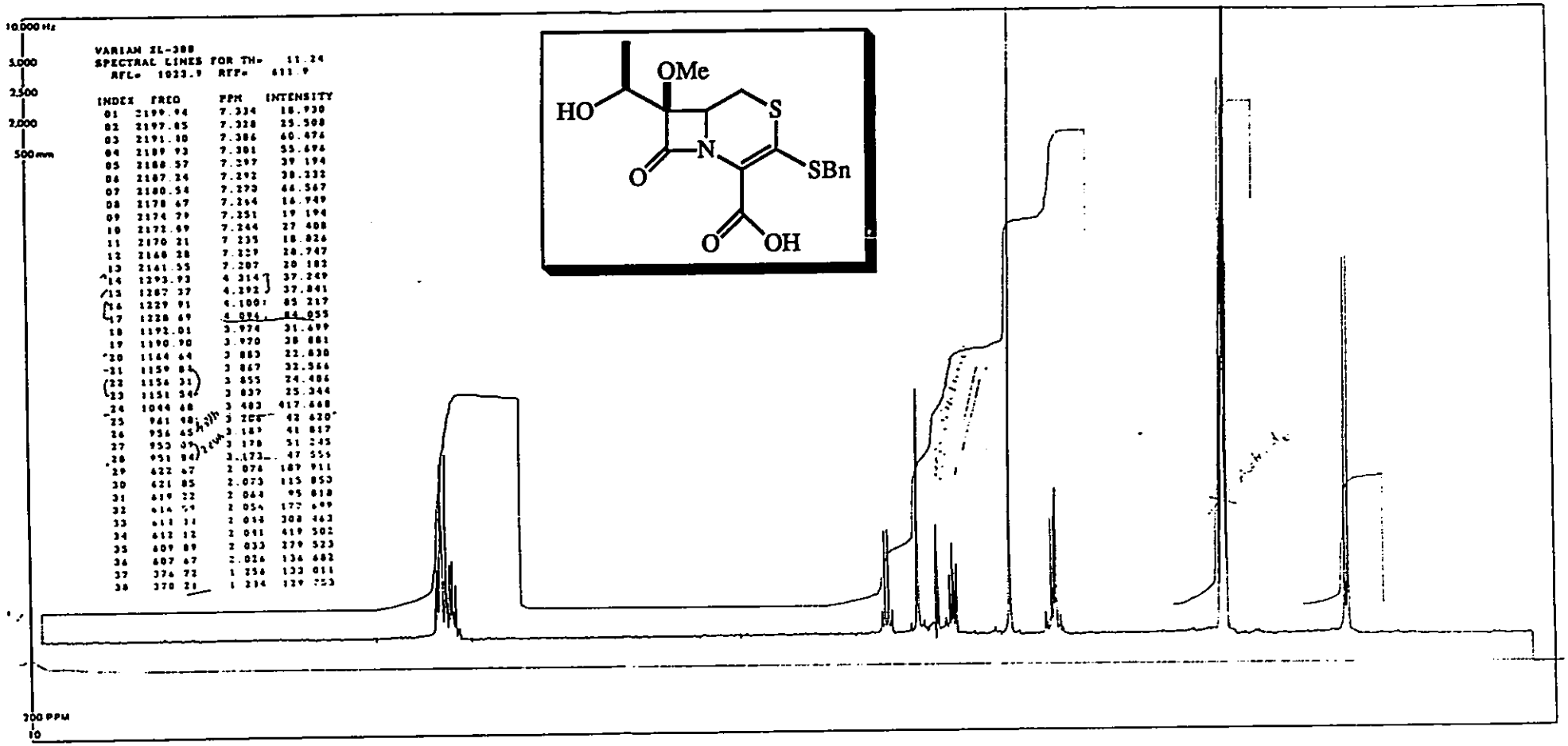
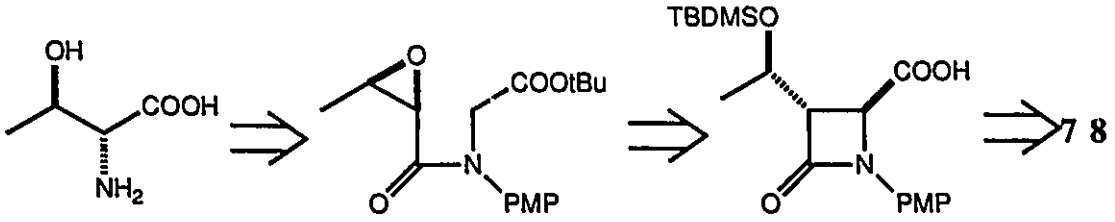


Fig. 4 ^{1}H NMR spectrum of 37

Synthesis of enantiomerically pure form of (+)-38

The use of enantiopure starting materials in the synthesis of enatiomerically pure compounds (EPC) is a common approach. Such building blocks or chirons are usually derived from natural compounds such as carbohydrates, amino acids, terpenes etc. Hiraoka and coworkers have prepared a variety of thienamycin precursors from L-threonine.[23] The key transformations in this sequence are shown below.



The key monocyclic 4-tosyloxymethyl azetidinone **78**, obtained following Hiraoka's procedure (ref. 24), was alkylated with β-trimethylsilylethyl bromoacetate by adding a mixture of tosylate **78** and the bromoacetate dropwise to a suspension of NaH in DMF to afford **79** (oil, IR 1760 cm^{-1}) in 70% isolated yield. The 4+2 cyclization of **79** as above with LDA and carbon disulfide afforded a 3-mercapto isocephem intermediate **80** (1763 cm^{-1}) which was immediately S-benzylated to give **81**, mp 99-101 °C, in 63% yield. The presence of the β-trimethylsilylethyl group in **81** was supported by the appearance of peaks at δ=0.02, 9H [these $SiMe_3$ signals overlaps with $Si(Me)_2$ signal of TBDMS group], 0.92-1.01, 2H, m, CH_2Si and 3.94-4.27 (OCH_2 signal overlapping with other OCH and OCH_2 signals). The loss of peaks from tosylate indicated the formation of the bicyclic ring. Deprotection of

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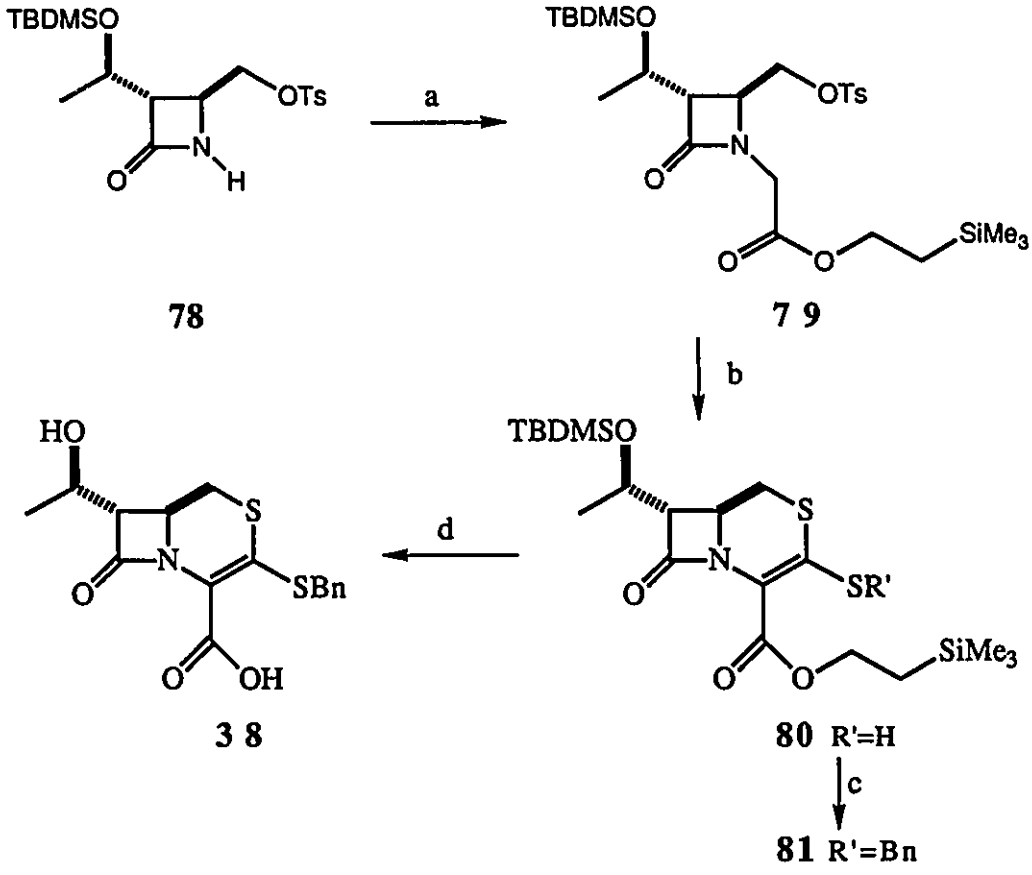
[23] Shiozaki, M.; Ishida, N.; Hiraoka, T.; Maruyama, H. *Tetrahedron* **1984**, *40*, 1795.

both the 6-hydroxyethyl and the acid function occurred upon overnight treatment with TBAF in THF to afford (+)-**38** in 21% yield as a yellowish white solid (Fig. 5), mp 155-156 °C (decomp), $[\alpha]_D^{22}$ = +21.2° (*C* 1.9, MeOH), IR: 3371 (OH, broad), 1758 cm^{-1} (C=O); ^1H NMR (300 MHz, acetone-d_6) δ=1.27 (3H, d, J=6.3 Hz, CH_3), 3.06 (1H, dd, J=2.4, 6.4 Hz, CHCO), 3.15 (1H, dd, J=12.4, 10.1 Hz, CH_2S), 3.41 (1H, dd, J=3.3, 12.4 Hz, CH_2S), 3.79-3.84 (1H, m, HCN), 4.12 (2H, s, CH_2Ph), 4.16 (1H, q, J=6.5 Hz, CH_3CHO), 7.24-7.38 (5H, m, Ph); ^{13}C NMR δ=22.3 (CH_3), 32.7 (CH_2), 40.3 (CH_2), 49.5 (CH), 65.3 (CH), 65.9 (CH), 128.2 (CH), 129.3 (CH), 130.1 (CH) and 137.8 (C) (Ph carbons), 162.5 (C=O), 165.4 (C=O) and MS 352 (M+1, 25).



a) NaH, $BrCH_2COOCH_2CH_2SiMe_3$, DMF, 0 °C; b) LDA, CS_2, THF, -78 °C to 25 °C; c) NaH, BnBr, THF, 0 °C; d) TBAF, THF

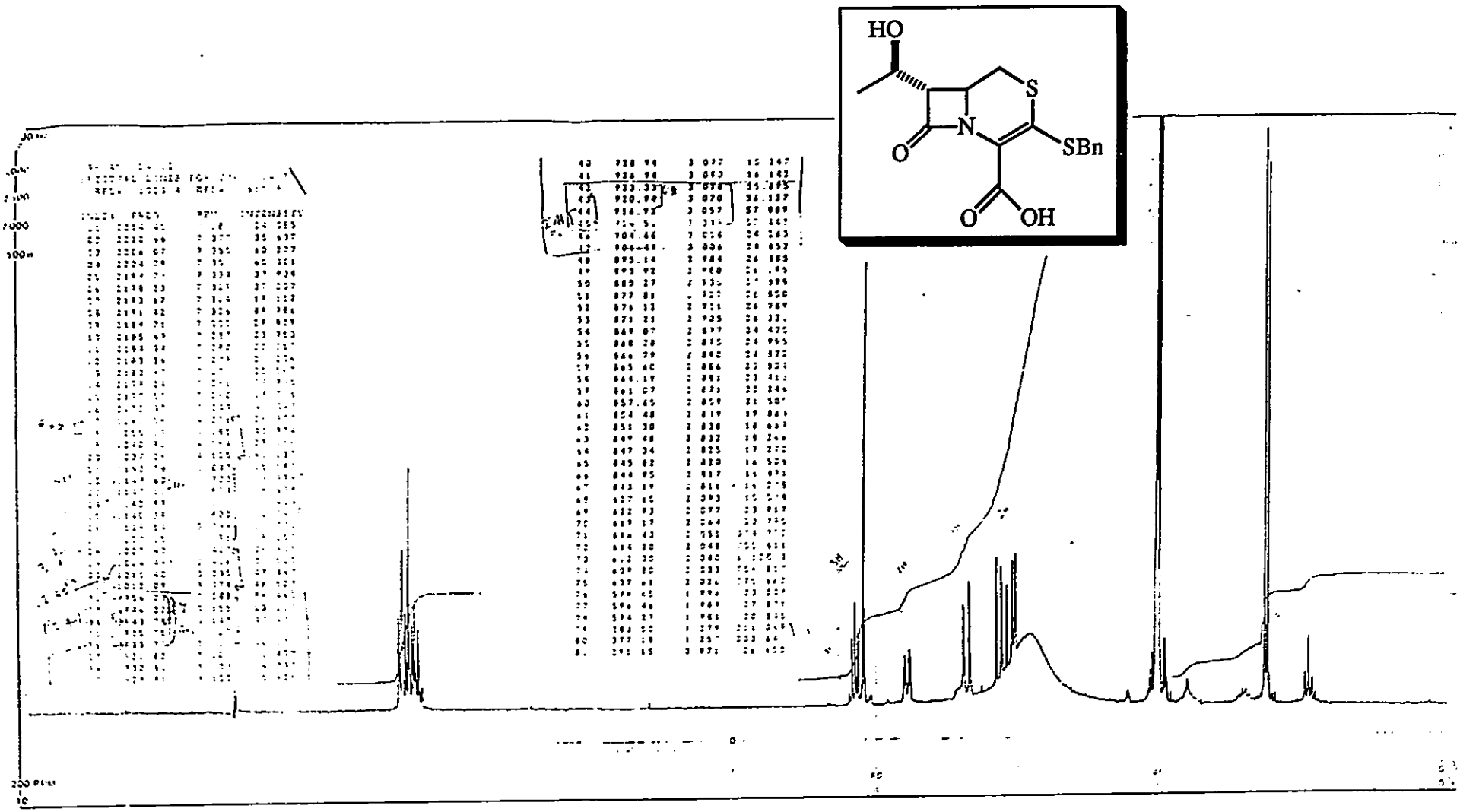
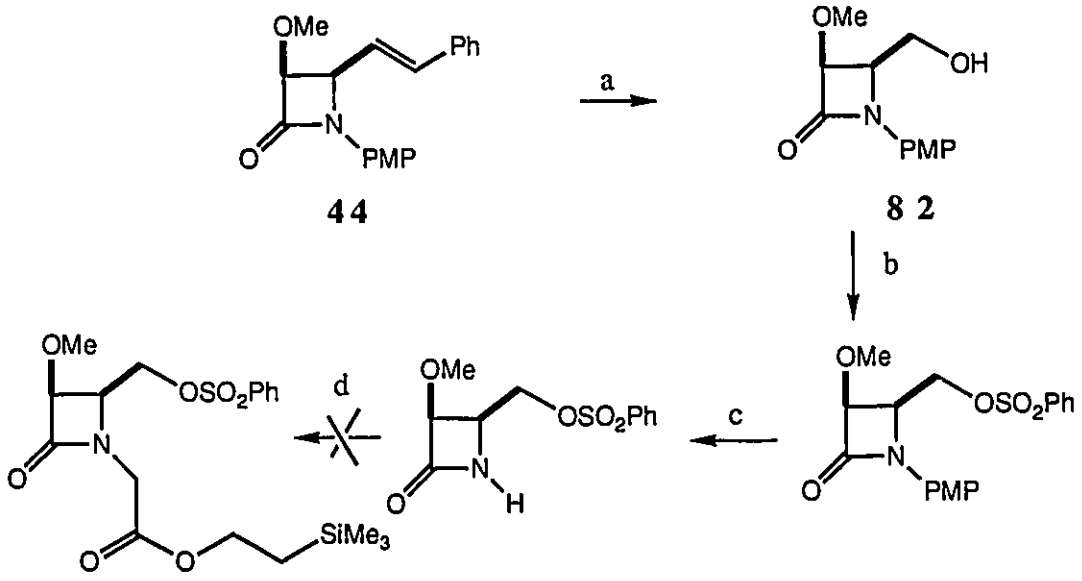


Fig. 5 ^{1}H NMR spectrum of **38**

Synthesis of the 7-methoxy isocephem 39

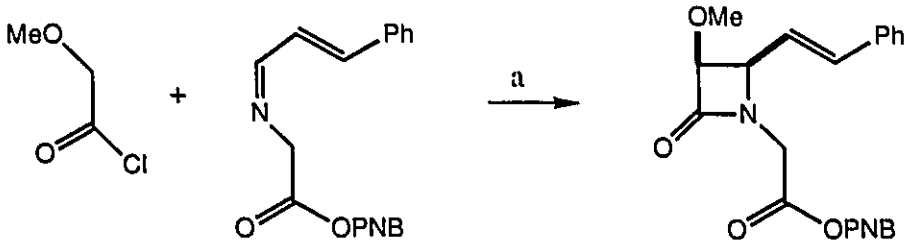
The isocephem **39** was synthesized in order to establish the generality of the anionic 4+2 annulation methodology using carbon disulfide. The initial effort was directed to utilize the readily available azetidinone **44**. The conversion of **44** to **84** was carried out by applying the usual sequence of reactions: reductive ozonolysis, benzenesulfonylation and CAN oxidation. When the azetidinone **84** was subjected to the N-alkylation condition (addition of both **84** and the bromoacetate to NaH in DMF, the condition which worked well for the alkylation of **78** the reaction was found to yield many products and the desired product **85** could not be isolated from the reaction mixture. Therefore, this approach was abandoned and an equivalent of **85**, the PNB ester **92** was prepared as described below.



44 **82** **85** **84** **83**

a) O_3, CH_2Cl_2, MeOH, -78 °C, $NaBH_4$, EtOH, -78 °C to 25 °C; b) NaH, $PhSO_2$imid, DMF, 0 °C; c) CAN, MeCN, H_2O, -5 °C to 0 °C; d) NaH, $BrCH_2COOCH_2CH_2SiMe_3$, DMF, 0 °C to 25 °C

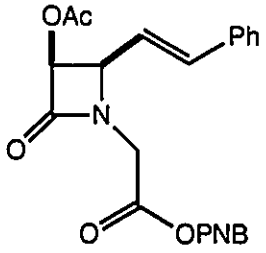
The required monocyclic precursor **88** was eventually obtained by a very short route. Cycloaddition of the imine **87** derived from the p-nitrobenzyl ester of glycine and *trans*-cinnamaldehyde with *in situ* generated methoxyketene afforded **88**, albeit in only 18% yield.



86 **87** **88**

a) TEA, CH_2Cl_2, 0 °C to 25 °C

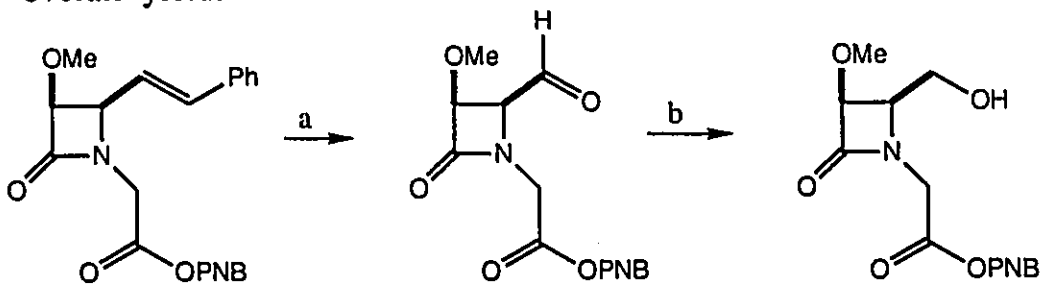
The precursor to the 4+2 cyclization, **92**, could be obtained in only four steps from readily available precursors. Thus it was crucial to improve the yield of the azetidinone **88**. Since the conversion of **87** to **88** gave only low yield, we looked for an alternate approach. The earlier experiment showed that the 2+2 cycloaddition of acetoxyacetyl chloride with imine **41**, dervived from cinnamaldehyde and p-anisidine, gave better yield than did methoxyacetyl chloride.[24] Encouraged by this result, we carried out the cycloaddition of the ketene derived from acetoxyacetyl chloride and imine **87**. Surprisingly, the impure (by ^1H NMR) azetidinone **89** was isolated in lower yield than that for **88**.



89

[24] see p 25.

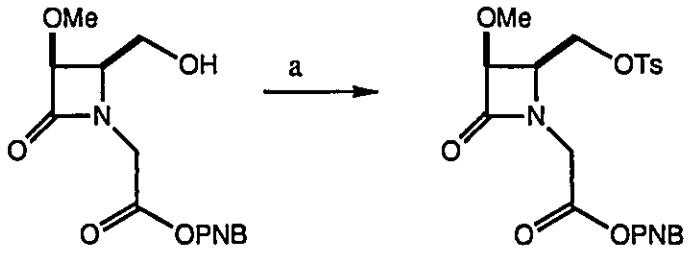
Ozonolysis of the compound **88** followed by reduction of the aldehyde **90** with sodium cyanoborohydride[25] gave the alcohol **91** in 59% overall yield.



88 **90** **91**

a) O_3, CH_2Cl_2, MeOH, -78 °C, DMS, -78 °C to 25 °C; b) $NaCNBH_3$, MeOH, pH 3-4, 25 °C

Tosylation of **91** with toluenesulfonyl chloride and pyridine as a solvent afforded **92** (in 69% yield) which was suitable for a 4+2 cyclization. This compound gave satisfactory spectral data consistent with its structure; IR (film): 1762 (C=O), 1522 and 1353 (NO_2) cm^{-1}; ^1H NMR δ: 2.43 (3H, s, CH_3Ph), 3.45 (3H, s, OCH_3), 3.97 (1H, d, J=18.1 Hz, NCH_AH_BCOOR), 4.20-4.21 (4H, m, H_2CO, HCN, NCH*H*COOR), 4.59 (1H, d, J=5.6 Hz, HC-C=O), 7.33 (2H, d, J=8.3 Hz, Tol.), 7.50 (2H, d, J=8.9 Hz, PNB), 7.72 (2H, d, J=8.2 Hz, Tol.), 8.21 (2H, d, J=8.9 Hz, PNB) and MS (CI): 479 (M^++1, 0.6).



91 **92**

a) TsCl, pyridine, 0 °C to -5 °C

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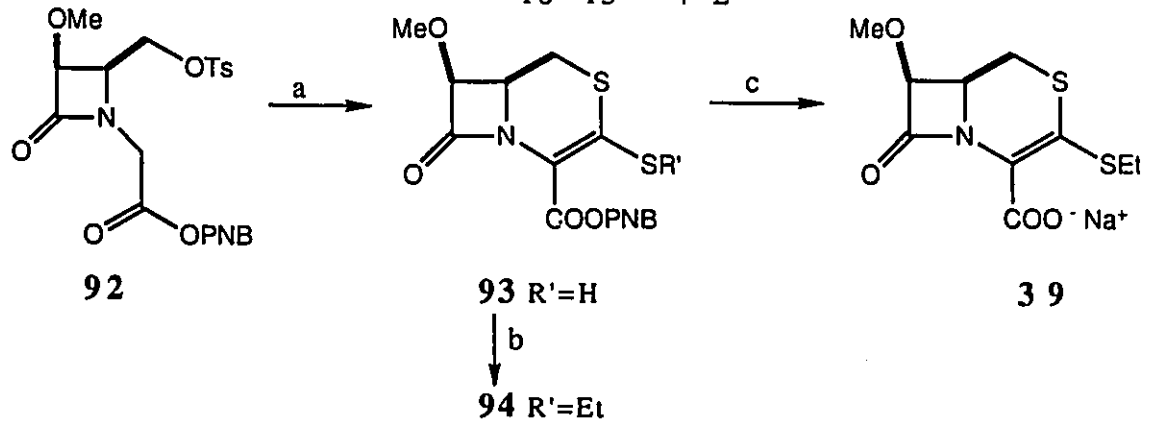
[25] Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Amer. Chem. Soc.* **1971**, *93*, 2897.

Reaction of **92** with freshly prepared LHMDS solution followed by carbon disulfide addition gave the desired bicyclic intermediate **93** which was alkylated with iodoethane to give isocephem **94**. The overall yield of **94** (oil, IR: 1767, 1699, 1517, 1342 cm^{-1}) from **88** *via*. this five step sequence was 37%. The other spectroscopic properties were also in agreement with the structure assignment. The sodium salt, **39**, was obtained in 56% yield as a white powder, mp 190-191 °C, IR 1752 and 1610 cm^{-1} after hydrogenolysis of **94** with 10% palladium on carbon, treatment of the resultant mixture with equimolar amount of sodium bicarbonate and purification *via*. reverse phase flash column chromatography (Fig. 6). Other spectral evidences for this compound are as follows: ^1H NMR (300 MHz, D_2O) δ: 1.26 (3H, t, J=7.4 Hz, CH_3), 2.86-2.94 (2H, overlapping q, J=7.3 Hz, SCH_2CH_3), 3.20 (1H, dd, J=12.5, 9.6 Hz, CH_2S), 3.29 (1H, dd, J=12.5, 3.7 Hz, CH_2S), 3.50 (3H, s, OCH_3), 4.05 (1H, ddd, J=3.6, 4.5, 9.6 Hz, HCN), 4.98 (1H, d, J=4.5 Hz, HC-C=O); ^{13}C NMR (300 MHz, D_2O) δ: 13.6 (CH_3), 27.5 (CH_2S), 28.3 (CH_2S), 51.8 (CH_3O), 58.8 (HCN), 85.0 (*HC*-C=O), 115.8 (C=C), 165.O (C=O), 167.9 (C=O); MS (for free acid) 275 (M^+, 1) and HRMS for $C_{10}H_{13}NO_4S_2$.



a) LHMDS, CS_2, THF, -78 °C to 25 °C; b) NaH, EtI, THF, 0 °C to 25 °C; c) H_2, Pd-C (10%), EtOH:THF

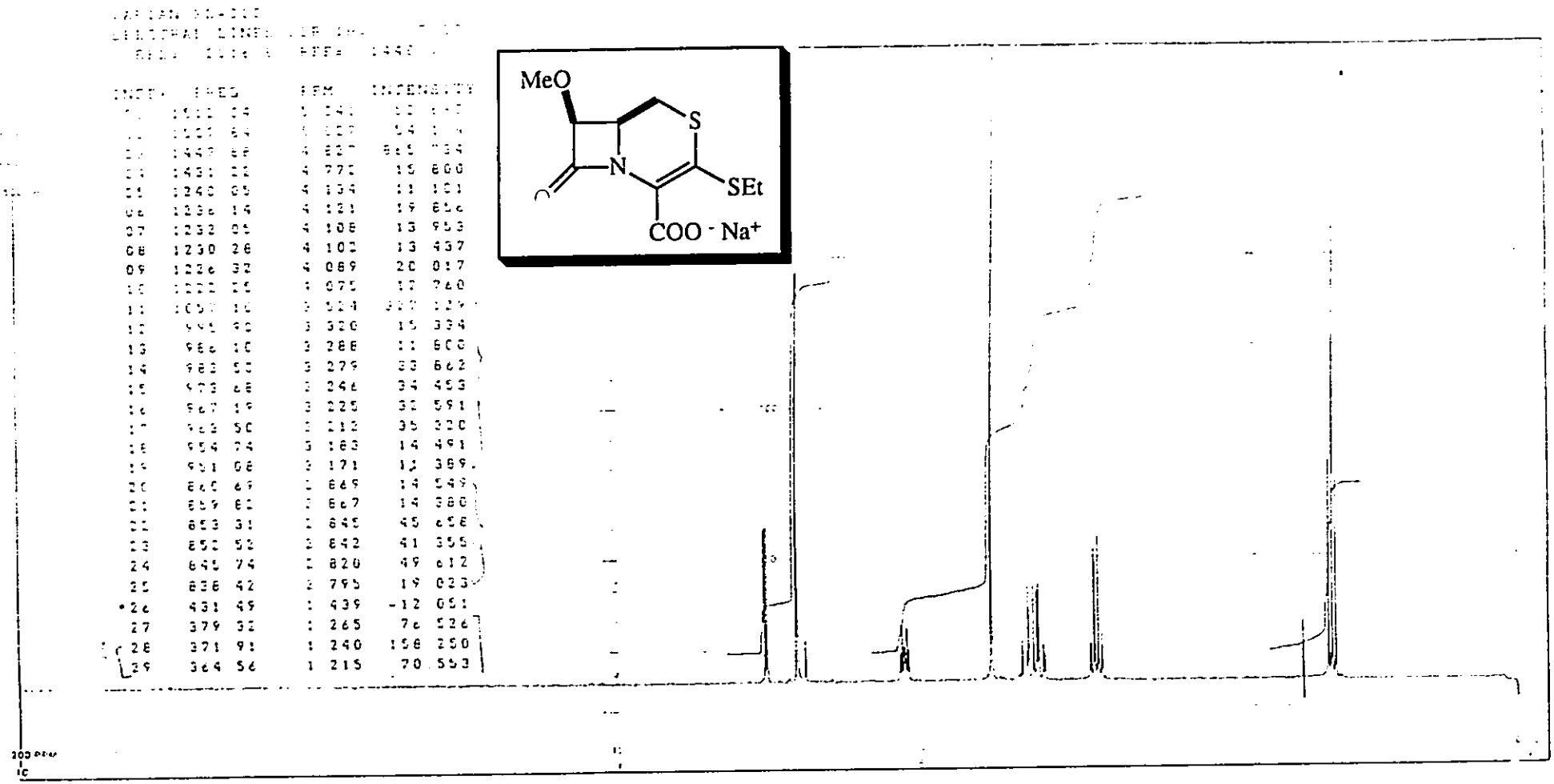


Fig. 6 ^{1}H NMR spectrum of 39

Interestingly, amongst the four bicyclic acids **36-39**, the isocephem carboxylic acid **37**, bearing both the methoxy and hydroxyethyl groups at C-7 , has a surprisingly low β-lactam carbonyl stretching frequency, 1736 cm^{-1}, compared to 1752-1763 cm^{-1} for other derivatives **36**, **38** and **39**. This unusually low carbonyl frequency brings into the question whether the structural assignment for **37** is correct. Careful comparison of other spectroscopic properties of **37** and the remaining members of this group, *e.g.* the vicinal coupling constants between the methylene group at C-1 and the C-6 hydrogen (J_{AB}=12.5, J_{AX}=4.8, J_{BX}=8.3 vs. J_{AB}=12.0-12.5, J_{AX}=3.3-4.6, J_{BX}= 8.6-10.1 Hz for the analogs), the chemical shifts of the remaining hydrogen on C-6 (3.88 ppm vs. 3.60-4.05 ppm) revealed no anomalies. The mass spectrum of **37** excluded the possibility of a simple β-lactam ring opening by an external nucleophile. Finally, the internal esterification of the side-chain hydroxy group with concomitant β-lactam ring opening to form a 4.3.1 bicyclic system having amino, carboxylic acid and a 7-membered lactone functionalities, would account for the 1736 cm^{-1} carbonyl band. This is excluded by the observation that the chemical shift of the secondary hydrogen on the hydroxyethyl group does not undergo the expected 0.5 ppm deshielding upon esterification. We therefore conclude that the structure assignment of **37** is correct.

At this stage the biological activity question was examined. Homothienamycin had been shown to be inactive.[26] During the course

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[26] Salzmann, T.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193.

Table 1 Antibacterial data for compounds 36, 37, 38 & 39: MIC (μg/mL)

		Compounds				
Organism	A No.	36	37	38	39	imipenem
1. S. pneumoniae/Todd Hewitt	A9585	8	>64	>64	>64	0.001
2. S. pyogenes/Todd Hewitt	A9604	8	>64	>64	64	0.001
3. E. faecalis	A20688	>128	>128	>128	>128	0.5
4. E. faecium	A24885	>128	>128	>128	>128	2
5. S. aureus/Pen.	A9537	128	>128	>128	128	0.007
6. S. aureus/50% human serum	A9537S	-	-	-	-	-
7. S. aureus/ NCCLS strain	A24227	>128	>128	>128	>128	0.015
8. S. aureus/ Pen. +	A9606	>128	>128	>128	>128	0.015
9. S. aureus/ Pen. +	A15090	>128	>128	>128	>128	0.015
10. S. aureus/MR28degC+NaCl	A20699	>128	>128	>128	>128	32
11. S. aureus/ Homo MR 30 Deg. C	A27222	>128	>128	>128	>128	16
12. S. epidermidis	A24548	>128	>128	>128	>128	0.015
13. S. epidermidis/Homo MR28degC+NaCl	A25783	>128	>128	>128	>128	0.015
14. S. haemolyticus	A21638	>128	>128	>128	>128	0.125
15. E. coli	A15119	>128	>128	>128	>128	0.06
16. E. coli/NCCLS strain	A20697	>128	>128	>128	>128	0.06
17. K. pneumoniae	A9664	>128	>128	>128	>128	0.06
18. E. cloacae	A9659	>128	>128	>128	>128	1
19. P. mirabilis	A9900	>128	>128	>128	>128	1
20. P. vulgaris	A21559	>128	>128	>128	>128	1
21. N. morganii	A15153	>128	>128	>128	>128	1
22. P. rettgeri	A22424	>128	>128	>128	>128	1
23. P. stuartii	A20615	>128	>128	>128	>128	0.5
24. S. marcescens	A20019	>128	>128	>128	>128	0.5
25. P. aeuriginosa	A9843	>128	>128	>128	>128	1
26. P. aeruginosa/NCCLS strain	A21508	>128	>128	>128	>128	1
27. P. aeruginosa	A15195	>128	>128	>128	>128	1
28. P. aeruginosa/Imipenem MIC=8	A26830	>128	>128	>128	>128	8
29. P. aeruginosa/Imipenem MIC=32	A26833	>128	>128	>128	>128	32
30. P. cepacia	A20820	>128	>128	>128	>128	2
31. X. maltophilia	A24258	>128	>128	>128	>128	>128
32. H. influenzae/P- W/1%sup. C	A9729	>64	>64	>64	>64	0.125
33. H. influenzae/P+ W/1%sup. C	A21515	>64	>64	>64	>64	0.125

In vitro Antibacterial activity. Conventional microtiter dilution process were used for determination of minimum inhibitory concentrations (MICS). Organisms were grown overnight in Mueller-Hinton Broth (Difco) at 37 °C. Twofold dilutions of the stock solution of each compound (125 μg/mL) were made in Mueller-Hinton Broth (Difco) to obtain a test concentration range from 0.005 to 125 μg/mL. The wells were then inoculated with approximately 10^4 organisms. The microtiter plates were incubated at 37 °C for 18 h. The MIC was the lowest concentration of the test compound that yielded no visible growth.

of our experiments reports on oxacephems[27] and cephems[28] having a thienamycin type (hydroxyethyl) substituent at the 7-position showed that such compounds possess low antibacterial activity; some of them showed β-lactamase inhibition. Biological screening studies of the compounds prepared in this study **36-39** showed no useful antibiotic activity (Table 1); possible β-lactamase activity was not investigated.

Related synthetic attempts

In order to facilitate the study of the potential of 4+1 and 4+2 cycloaddition reactions as suggested in the conversions of **25** to **28** and **31** to **35** (see page 20 and 22 respectively) with different electrophiles, we decided to prepare several simpler β-lactams in order to test model reactions.

The β-lactam **95** is readily available by chlorosulfonyl isocyanate (CSI) addition to iodo-2-methyl-1-propene and sodium sulfite reduction.[29] When **95** and β-trimethylsilylethyl bromoacetate was treated with the suspension of the NaH in DMF, the usual N-alkylation condition used earlier in case of **78**, the reaction mixture gave a quite complex ^{1}H NMR spectrum. The desired alkylated product could not be isolated from this mixture.

Hrystak had reported that the diazo derivatives obtained from β-ketoester inserted into the NH bond of the β-lactams not only

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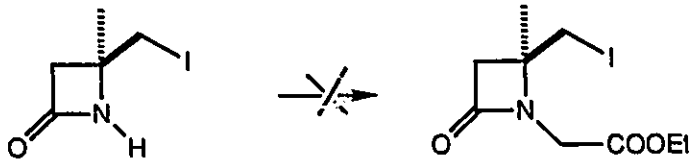
[27] (a) Murakami, M.; Aoki, T.; Nagata, W. *Heterocycles* **1990**, *30* (1, Spec. Issue), 567. (b) Nishimura, S.; Sasako, H.; Yasuda, N.; Matsumoto, Y.; Kamimura, T.; Sakane, K.; Takaya, J. *J. Antibiot.* **1989**, *42*, 1124.

[28] Nishimura, S.; Yasuda, N.; Sasaki, H.; Matsumoto, Y.; Kamimura, T.; Sakane, K.; Takaya, T. *J. Antibiotics* **1989**, *42*, 159.

[29] Durst, T.; O'Sullivan, M. J. *J. Org. Chem.* **1970**, *35*, 2043.

intramolecularly but also intermolecularly.[30] An attempt to obtain **96** by reacting **95** with 1.4 eq. of ethyl diazoacetate in toluene or with 6 eq. of ethyl diazoacetate in refluxing benzene in presence catalytic rhodium acetate, resulted in the recovery of a large amount of **95**, dimer of diazo compound and a small amount of a second product which could not be identified by ^{1}H NMR spectral analysis.



95 **96**

The second model cyclization precursor **99** was prepared by a standard sequence of reactions involving ozonolysis with reductive workup using $NaBH_4$ and conversion of the intermediate alcohol to its benzenesulfonate from readily available precursor **97**.[31] The compound **99** was a yellowish oil; ^{1}H NMR δ=1.42 (9H, s, t-Bu), 2.66 (1H, dd, J=1.6, 14.2 Hz, H_AC-3), 3.06 (1H, dd, J=5.1, 14.8 Hz, H_BC-3), 3.63 (1H, d, J=18.1 Hz, C*H*$_A$H$_B$COOR), 4.01 (1H, d, J=18.1 Hz, C*H*$_B$H$_A$COOR), 4.04-4.31 (3H, m, HC-4, CH_2O), 7.52-7.68 (3H, m, Ph), 7.86-7.90 (2H, m, Ph) and MS(CI): 356 (M^++1, 5).

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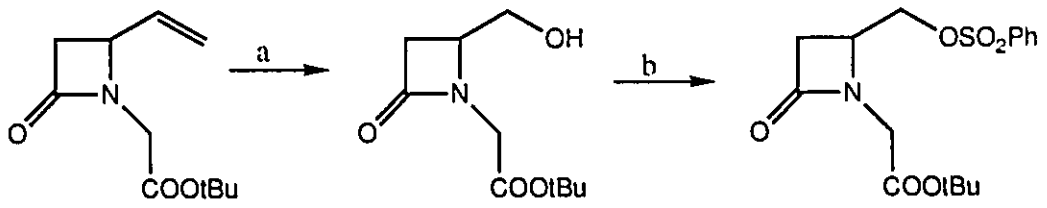
30 Hrystak, M. D. *Ph. D. Thesis*, University of Ottawa, **1988**, p 27.

31 Durst, T.; Van Den Elzen, R.; LeBelle, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 9261.

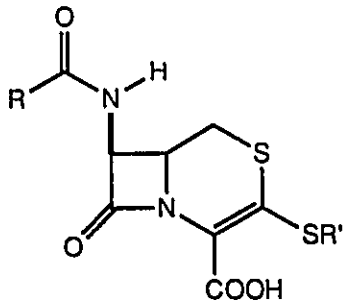


97 98 99

a) O_3, CH_2Cl_2:MeOH (8:1), -78 °C, $NaBH_4$, EtOH, -78 °C to 25 °C; b) $PhSO_2$imid, NaH, DMF, 0 °C

Reaction of **99** with 1.1 equivalent of LDA in THF followed by quenching with carbon disulfide at -78 °C and warming to 25 °C gave a crude product which was fractionated by column chromatography. No evidence of the formation of the desired bicyclic compound was observed upon examination of ^1H NMR spectrum of various compounds. The anion of **99** was also quenched with 1.1 equivalent of phenyl vinyl sulfone in THF at -78 °C and warmed to 25 °C over 18 h. The reaction mixture upon column chromatography gave two impure fractions whose ^1H NMR indicated the presence of two phenyl sulfonyl groups. Based on this observation one may infer that the initial Michael type addition occurred but the resultant anion did not undergo subsequent cyclization. Reaction of **99** with dimethyl methoxymethylidene-malonate under similar conditions gave several products one of which appeared to be an impure Michael adduct based on the complex ^1H NMR spectrum. Perhaps, the bulk and low nucleophilcities of the resultant carbanions obtained upon Michael addition were not favorable for the cyclization in both phenyl vinyl sulfone and dimethyl methoxymethylidenemalonate reactions. Similar result was also observed during the reaction of **31** with bisphenylsulfonylethylene **32** as described in page 23.

Since most of the biologically active isocephems have a nitrogen substituent at C-7, we studied approaches to isocephems having only nitrogen (**100**), hydroxyethyl and nitrogen (**101**) and ethyl and nitrogen (**102**) substituent at C-7. The compounds, **101** and **102**, are hybrids bearing a substituent typical of thienamycin and PS-5, respectively.



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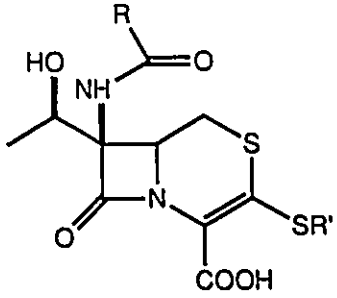

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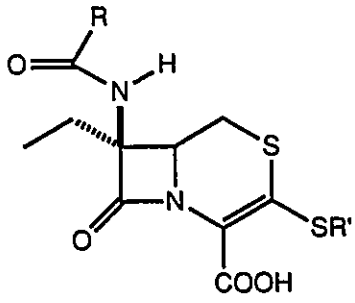
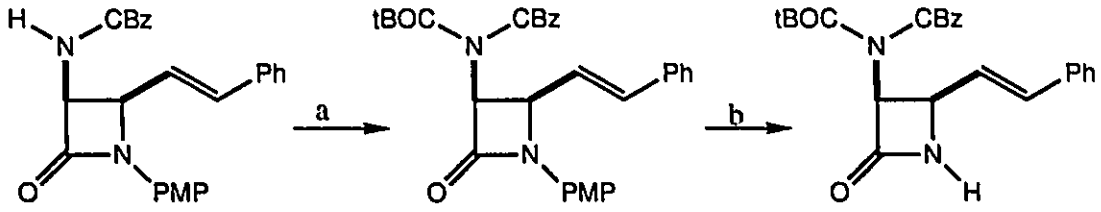


102

The azetidinone **103** was prepared by 2+2 ketene imine cycloaddition using carbobenzyloxyglycine activated with DMF/oxalyl chloride and imine **41** as described by Sharma.[32] The N-H bond at C-3 of **103** was protected with an additional tBOC group so that this group could not interfere with the required anion formation. CAN cleavage of the PMP group of **104** gave the compound **105**. The ^{1}H NMR and MS(CI) data for this compound is in agreement with the structure assignment (see the Experimental section). The N-alkylation was attempted by adding a mixture of **105** and 1.5 equivalent of trimethylsilylethyl bromoacetate in DMF to the suspension of 1.1 equivalent of sodium hydride in DMF at 0 ^{o}C and stirring the resultant

[32] Sharma, M. K. *Ph. D. Thesis*, University of Ottawa, **1990**, p 216.

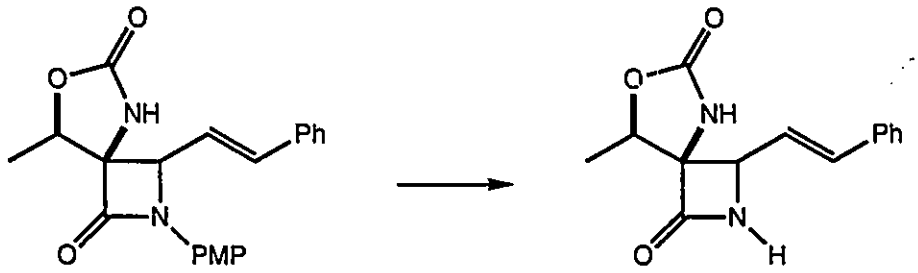
reaction mixture (at 0 °C to 25 °C) for 18 h. The expected N-alkylation product could not be isolated from the reaction mixture.



103 **104** **105**

a) $(tBOC)_2O$, DMAP, TEA, DMF; b) CAN, $McCN:H_2O$, -30 °C to -25 °C

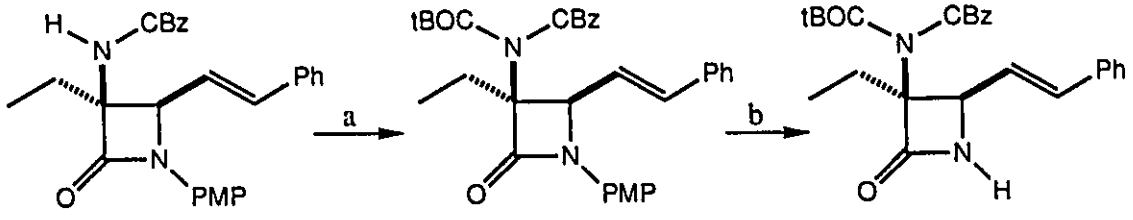
Compound **107**, obtained from **103** *via*. **106**[33] was subjected to similar N-alkylation conditions ($NaH/BrCH_2COOCH_2CH_2SiMe_3/DMF$, $NaH/ICH_2COOtBu/THF$ and $KOH/ BrCH_2COOtBu/CH_2Cl_2$ at 0 °C to 25 °C for 18 h). Again none of the desired product was obtained.



106 **107**

The azetidinone **110** having an ethyl group and a nitrogen substituent were prepared from **103** as shown in the following scheme using standard methods.

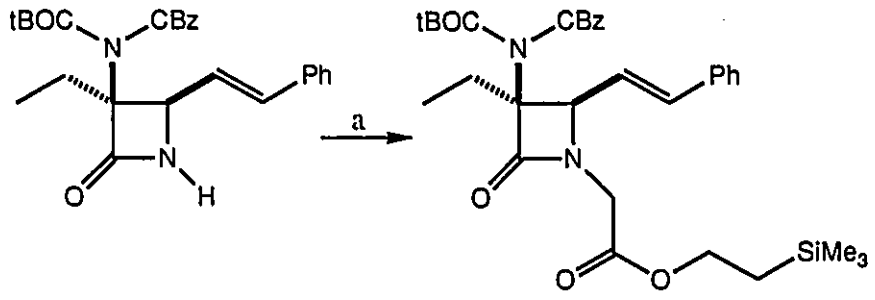
[33] Prepared by a method described: Sharma, M. K. *Ph. D. Thesis*, University of Ottawa, **1990**, p 120.



108 **109** **110**

a) $(tBOC)_2O$, DMAP, TEA, DMF; b) CAN, McCN:H_2O, -30 °C to -25 °C

In this case, the N-alkylation ($BrCH_2COOCH_2CH_2SiMe_3$, NaH, DMF, 0 °C to 25 °C, 18 h) proceeded in a desired manner and gave 40-55% of **111** which gave all expected peaks in ^1H NMR at δ=0.00 (9H, s, TMS), 0.92-1.01 (2H, m, CH_2Si), 1.11 (3H, t, J=7.5 Hz, CH_3CH_2), 1.28 (9H, s, t-Bu), 2.14-2.32 (1H, m, CH_2CH_3), 2.49-2.68 (1H, m, CH_2CH_3), 3.50 (1H, d, J=18.0 Hz, CH_AH_BCOOR), 4.12-4.26 (2H, m, CH_2O), 4.34 (1H, d, J=18.0 Hz, CH_BH_ACOOR), 4.37 (1H, d, J=7.9 Hz, HCN), 5.03 (2H, apparent d, J=2.2 Hz?, CH_2Ph), 6.12 (1H, dd, J=7.6, 16.2 Hz, HC=CHPh), 6.62 (1H, d, J=16.2 Hz, HC=CHPh), 7.17-7.36 (5H, m, Ph) and MS (CI) at 581 (M^++1-28, 8).

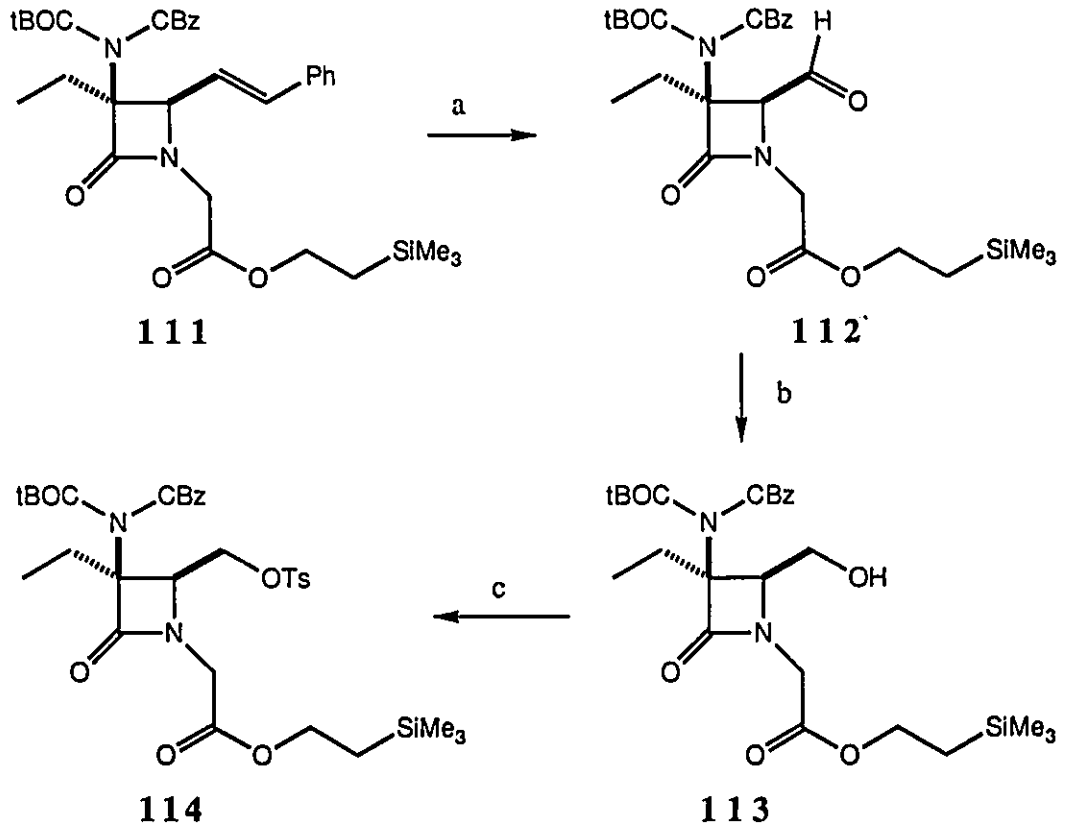


110 **111**

a) $BrCH_2COOCH_2CH_2SiMe_3$, NaH, DMF, 0 °C to 25 °C

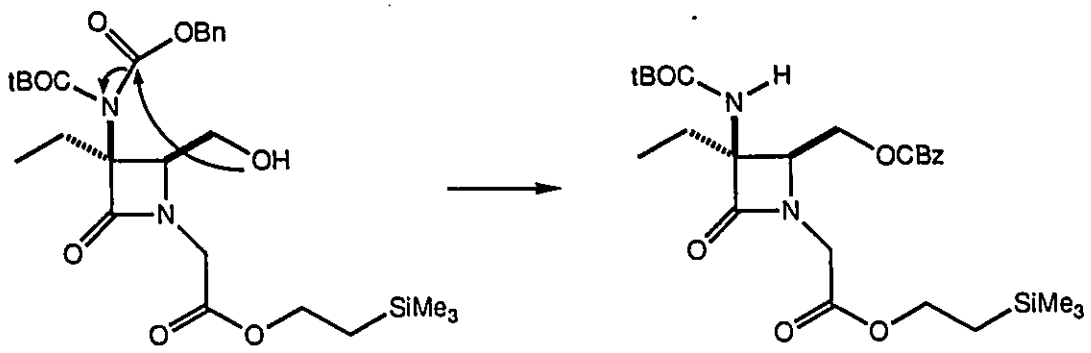
The cyclization precursor **114** was obtained from **111** by the usual sequence of reactions: ozonolysis, sodium cyanoborohydride reduction and tosylation. It gave the following analytical data consistent with the proposed structure; IR: 1780, 1750, and 1720 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ=0.01 (9H, s, TMS), 0.97-1.05 (5H, m, CH_2Si,

CH_3CH_2), 1.34 (9H, s, t-Bu), 2.05-2.17 (1H, m, CH_2CH_3), 2.37-2.45 (4H, m, overlapping with s at 2.41, CH_2CH_3, CH_3Ph), 3.68 (1H, d, J=18.2 Hz, CH_AH_BCOOR), 3.96 (1H, dd, J=3.1, 9.2 Hz, CH_AH_BO), 4.13-4.26 (4H, m, CH_BH_AO, CH_BH_ACOOR, OCH_2), 4.34 (1H, dd, J=3.2, 10.2 Hz, HCN), 5.14 (2H, d apparent, J=2.3 Hz, CH_2Ph), 7.27-7.35 (7H, m, Ph, Tol), 7.68 (2H, d, J=8.4 Hz, Tol) and MS(CI): 663 (M^++1-28, 1). The tosylation of **113** was found to proceed in low yield. A side product was isolated and tentatively assigned the structure **115** based on its ^1H NMR spectral analysis of **115** and the product **116** obtained by hydrogenolysis. This product, **115**, may have resulted from the transfer of the carbobenzyloxy group from nitrogen to the hydroxyl group.

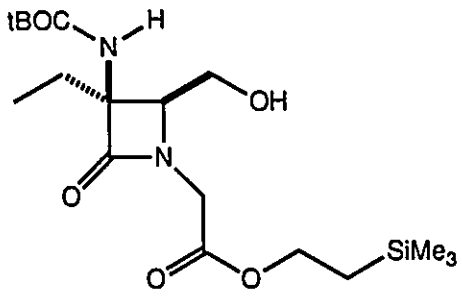


a) O_3, CH_2Cl_2, MeOH, -78 °C, DMS, -78 °C to 25 °C ; b) $NaCNBH_3$, MeOH, 25 °C; c) TsCl, pyridine, 0 °C to 5 °C

The anion of **114**, generated using 1.1 equivalent of LDA was quenched with carbon disulfide, as described in the earlier successful examples. The desired bicyclic isocephem could not be isolated and about 80% of starting material was recovered. This failure could also be due to the fact that carbon disulfide was used from a bottle which had been opened and stored for two months. Due to the limited supply of the compound **114** further experiments were not repeated.



113 **115**



116

As mentioned several times in the earlier parts of this chapter, the studies dealing with the anionic 4+2 cyclization involving carbon disulfide were greatly complicated by the "source" of the carbon disulfide. Successful results were often obtained when the carbon disulfide used was distilled from P_2O_5 immediately after opening a new

bottle. Amazingly, inferior results were obtained when the carbon disulfide, from the same bottle which has been opened and immediately resealed, was distilled and used. This variance caused one to question whether some of the unsuccessful experiments might have been successful with a new source of carbon disulfide. It was considered impractical to purchase a new supply (1 L bottle) use less than 1 mL and discard the rest. We also used anhydrous carbon disulfide supplied by Aldrich Chemical Co. in 100 mL sure seal bottle in one of the final experiment. We did not need to study the behavior of this supply on storage because we stopped the experiment. Thus this problem remains to be solved.

EXPERIMENTAL SECTION

General Techniques

Melting points were determined by use of a Gallenkamp melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded as films on sodium chloride plates for oils, and potassium bromide (KBr) pellets for solids using either a Perkin Elmer 783 or a Bomem MB100 spectrometer. IR spectra were not taken for those compounds which either were difficult to handle or did not lead to the desired conclusion. Mass spectra were obtained by means of a AEIMS 9025 or a Kratos Concept 2H instrument. Possible fragmentation and relative intensity in percentage were reported in parentheses while quoting the mass spectral data. High resolution mass spectra were recorded whenever applicable. Elemental analyses would not be reported.

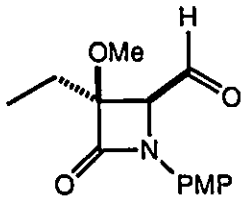
Nuclear magnetic resonance (NMR) spectral analyses were performed on a Gemini (for 200 MHz) or a Varian XL-300 (300 MHz) spectometer. Samples were normally prepared as solutions in $CDCl_3$; deviations from these samples were indicated whenever applicable. The peak patterns were noted as singlet (s), doublet (d), triplet (t), quartet (q), doublets of doublets (dd), or multiplet (m). In ^{13}C spectra, the number of attached protons were determined by DEPT or ADEPT experiments. These data were used as a guideline for assignment of carbons to their peaks and thus were not reported separately. Chemical shifts (δ) were reported in ppm downfield to tetramethylsilane.

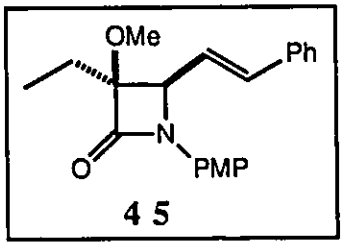
Flash Column Chromatogiaphy were carried out in most of the experiments using Terrochem 230-400 mesh silica gel as the adsorbent. The term column chromatography, used in the experimental details refers to the flash column technique. Thin layer chromatography (tlc) was performed on Kieselgel 60 F_{254} precoated silica plates of 0.25 mm thickness. The spots were visualized by variety of methods such as uv, iodine, or molybdate-heat. Reverse phase column chromatography was performed using Bondpak C-18 silica gel.

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen atmosphere. Diisopropylamine (DA), hexamethyldisilazide (HMDS) and dimethylformamide (DMF) were distilled under a nitrogen atmoshere, from calcium hydride and stored over 4Å molecular sieves. Dichloromethane was distilled from phosphorous pentoxide (P_2O_5) and stored over 4Å molecular sieves. Butyllithium was purchased from Aldrich and used after titration with diphenylacetic acid in THF at 0 °C. Sodium hydride was obtained as 60% dispersion in mineral oil and used as such. Benzyl bromide, methyl iodide and ethyl iodide were purchased from Aldrich were used as such. Toluenesulfonyl chloride was recrystallized from THF. Acetoxyacetyl chloride was prepared from glycolic acid and methoxyacetyl chloride from methoxyacetic acid (Aldrich). Carbon disulfide was purchased from BDH and distilled from P_2O_5 and stored over 4Å molecular sieves under inert atmosphere. In one final experiment anhydrous carbon disulfide from Aldrich (sure seal bottle 100 mL) was used as such. β-Trimethylsilylethyl bromoacetate was prepared by acylation of β-trimethylsilylethanol with bromoacetyl chloride or bromide.

Solvents were removed by Buchi rotary evaporator connected to a water aspirator. Usual work up, frequently referred in following experimental descriptions, consists of washing with 10% HCl, 5% $NaHCO_3$, and saturated brine after dilution with appropriate solvents, drying of combined organic layer with anhydrous magnesium sulfate and filtration. Unless otherwise noted all reactions were conducted under inert atmosphere (nitrogen).

3-Ethyl-4-formyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (49)





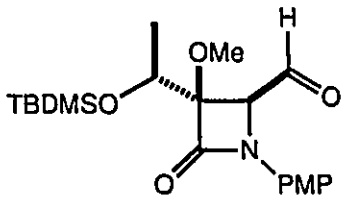
45

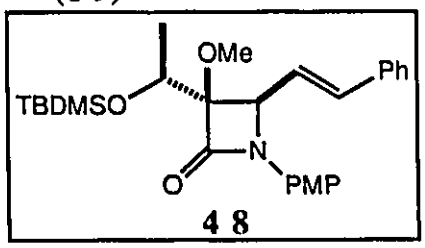
Azetidinone **45**[34] (8.0 g, 24 mmol) was dissolved in 300 mL of dry CH_2Cl_2 and 3 mL of CH_3OH containing about 1 g of crushed 4Å mol. sieves. The reaction mixture was cooled to -78 °C under N_2 and ozone was passed through the solution until the bluish color of excess ozone appeared. Dimethyl sulfide (5-10 mL, excess) was added after the removal of excess ozone and the resulting mixture was warmed to 25 °C over a period of 18 h. The reaction mixture was filtered and the filtrate was concentrated in vacuum. Flash column chromatography of the crude product (1:10 EtOAc:hexanes) gave 4.0 g (64%) of **49** as a yellowish oil; IR: 1744 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 1.05 (3H, t,

[34] Sharma, M. K. *Ph. D. Thesis*, University of Ottawa, **1990**, p 91.

J=7.4 Hz, CH_3), 1.77-1.95 (1H, m, CH_2CH_3), 2.05-2.23 (1H, m, CH_2CH_3), 3.48 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.22 (1H, d, J=3.3 Hz, CHN), 6. 84 (2H, dd, J=2.3, 6.9 Hz, PMP), 7.23 (2H, dd, J=2.3, 6.9 Hz, PMP), 9.70 (1H, d, J=3.3 Hz, CHO); MS: 263 (M^+, 38), 235 (M^+-28, 5), 206 (M^+-28-29, 46), 204 (M^+-28-31, 12); HRMS for $C_{14}H_{17}NO_4$ calcd 263.1156, found 263.1139.

3-t-Butyldimethylsilyloxyethyl-4-formyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (50)



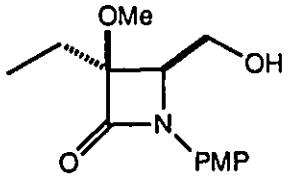


48

The aldehyde **50** was obtained in 60-80% yield as a colorless oil after column chromatography (1:10 EtOAc:hexanes) of the crude product obtained by ozonolysis of the azetidinone **48**[35] as described above; IR: 1749 (C=O) cm^{-1}; ^1H NMR (300 MHz) δ: 0.07 (3H, s, CH_3Si), 0.07 (3H, s, CH_3Si), 0.78 (9H, s, t-BuSi), 1.30 (3H, d, J=6.4 Hz, CH_3), 3.54 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.24 (1H, d, J=6.4 Hz, CH_3CHO), 4.57 (1H, d, J=2.2 Hz, HCN), 6.84 (2H, dd, J=2.2, 6.9 Hz, PMP), 7.26 (2H, dd, J=2.2, 6.9 Hz, PMP), 9.79 (1H, d, J=2.2 Hz, CHO); MS: 393 (M^+, 6), 336 (M^+-57, 50), 308 (M^+-57-28, 12), 292 (M^+-101, 18), 230 (M^+-163, 1).

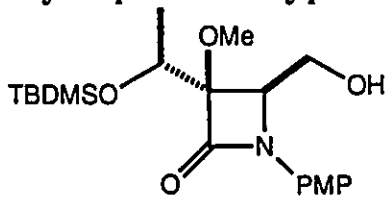
[35]Sharma, M. K. *Ph. D. Thesis*, University of Ottawa, **1990**, p 97.

3-Ethyl-4-hydroxymethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (51)



The aldehyde **49** (4.0 g, 15.2 mmol) was dissolved in 50 mL of EtOH at 25 °C. $NaBH_4$ (0.164 g, 4.56 mmol) was added in one portion and the mixture was stirred for 30 min. The excess $NaBH_4$ was destroyed by stirring with Amberlite (1-2 g) for 10 min. The mixture was filtered, the solvent was evaporated and the crude product was purified by column chromatography (1:3 EtOAc:hexanes) to afford 3.2 g (80%) of **51** as a colorless oil; IR: 3300 (OH), 1735 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.99 (3H, t, J=7.4 Hz, CH_3), 1.62-1.82 (1H, m, CH_2CH_3), 2.06-2.24 (1H, m, CH_2CH_3), 2.55 (1H, broad, OH), 3.60 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.94-3.96 (3H, broad m, CHN, CH_2O), 6.83 (2H, dd, J=2.4, 6.8 Hz, PMP), 7.32 (2H, dd, J=2.4, 6.8 Hz, PMP); MS: 265 (M^+, 26), 206 (M^+-59, 39), 192 (M^+-73, 8), 164 (imine$^+$-1, 4), 149 (M^+-116, 80), 116 (M^+-149, 19); HRMS for $C_{14}H_{19}NO_4$ calcd 265.1311, found 265.1321.

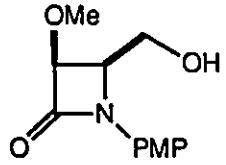
3-t-Butyldimethylsilyloxyethyl-4-hydroxymethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (52)



The reduction of the aldehyde **50** was carried out as described above to yield 88% of **52** as a colorless oil after purification by column chromatography (1:4 EtOAc:hexanes); IR: 1740 (C=O) cm^{-1}; ^1H NMR (300 MHz) δ: 0.07 (6H, s, CH_3SiCH_3), 0.84 (9H, s, t-BuSi), 1.23 (3H, d, J=6.5 Hz,

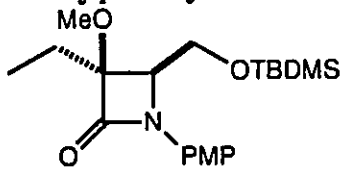
CH_3), 3.72 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.78-4.00 (2H, m, H_2CO), 4.13 (1H, dd, J=3.6, 6.3 Hz, HCN), 4.28 (1H, q, J=6.5 Hz, CH_3CHO), 6.85 (2H, dd, J=2.3, 6.9 Hz, PMP), 7.36 (2H, dd, J=2.2, 6.9 Hz, PMP); MS: 395 (M^+, 9), 380 (M^+-15, 1), 338 (M^+-57, 76), 246 (M^+-149, 1), 215 (230^+-15, 0.3).

4-Hydroxymethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (82)



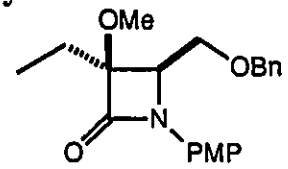
A solution of the azetidinone **44** (1.50 g, 4.85 mmol) in 80 mL of dry CH_2Cl_2 and 2 mL of MeOH was cooled to -78 °C. Ozone was passed through the solution until the bluish color appeared. $NaBH_4$ (0.2 g, 5.55 mmol) was added and the reaction mixture was stirred for 18 h while letting it to warm to room temperature. The reaction mixture was washed with 10% HCl, 5% $NaHCO_3$ and brine consecutively. Trituration of the crude product with 20% ether in hexanes gave 700 mg (61%) of **82** as a white solid; mp 99-100 °C; ^1H NMR (300 MHz) δ: 2.33 (1H, dd, J=5.9, 7.7 Hz, OH), 3.68 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.01-4.06 (2H, m, CH_2O), 4.23-4.28 (1H, m, HCN), 4.66 (1H, d, J=5.2 Hz, HC-3), 6.86 (2H, d, J=9.2 Hz, PMP), 7.36 (2H, d, J=9.2 Hz, PMP); MS: 237 (M^+, 18), 209 (M^+-28, 1), 192 (M^+-28-17, 3), 165 (M^+-72, 8), 149 (M^+-88, 100).

4-t-Butyldimethylsilyloxymethyl-3-ethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (53)



Alcohol **51** (1.22 g, 4.60 mmol) in 20 mL of dry CH_2Cl_2 was treated with TBDMSOTf (2.1 mL, 6.90 mmol) and 2,6-lutidine (1.0 mL, 9.2 mmol) at 0 °C for 1 h. The reaction mixture was diluted with an additional 20 mL of CH_2Cl_2 and washed successively with 1% ice-cold HCl, 5% $NaHCO_3$ and saturated brine. Purification of the crude product by column chromatography (1:8 EtOAc:hexanes) afforded 1.50 g (86%) of **53** as an oil; ^1H NMR (200 MHz) δ: 0.01 (6H, s, CH_3SiCH_3), 0.87 (9H, s, t-BuSi), 0.98 (3H, t, J=7.5 Hz, CH_3), 1.67-1.77 (1H, m, CH_2CH_3), 2.02-2.09 (1H, m, CH_2CH_3), 3.52 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.83-3.96 (3H, m, H_2CO, CHN), 6.81 (2H, d, J=9.1 Hz, PMP), 7.53 (2H, d, J=9.1 Hz, PMP); MS: 379 (M^+, 18), 351 (M^+-28, 5), 322 (M^+-57, 9), 294 (322^+-28, 23), 149 (M^+-230, 25); HRMS calcd for $C_{20}H_{33}O_4NSi$ 379.2177, found 379.2148.

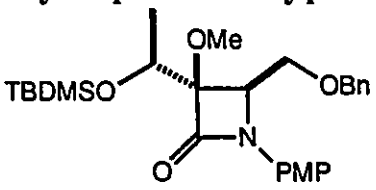
4-Benzyloxymethyl-3-ethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (55)



NaH (0.64 g, 0.013 mol) was added to 3.2 g (0.012 mol) of alcohol **51** dissolved in 50 mL of dry DMF at 0 °C under N_2. This suspension was stirred for 10 min. Benzyl bromide (1.43 mL, 0.012 mol) was added and the reaction mixture was stirred without further cooling for 18 h. Usual workup gave a brownish oil which was purified by column

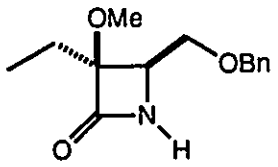
chromatography (1:8 EtOAc:hexanes) to yield 3.4 g (80%) of benzyl ether **55** as an oil; IR: 1744 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.96 (3H, t, J=7.4 Hz, CH_3), 1.62-1.82, (1H, m, CH_2CH_3), 2.06-2.24, (1H, m, CH_2CH_3), 3.53 (3H, s, OCH_3), 3.76 (4H, s with overlapping dd, OCH_3, CH_2O), 3.87 (1H, dd, J=3.7, 10.8 Hz, CH_2O), 4.06 (1H, dd, J=3.7, 6.5 Hz, CHN), 4.52-4.53 (2H, broad s, CH_2Ph), 6.83 (2H, dd, J=2.2, 6.8 Hz, PMP), 7.23-7.37 (5H, m, Ph), 7.55 (2H, dd, J=2.2, 6.8 Hz, PMP); MS: 355 (M^+, 16), 327 (M^+-28, 6), 297 (M^+-28-30, 2), 206 (M^+-149, 54), 149 (M^+-206, 38).

3-t-Butyldimethylsilyloxyethyl-4-benzyloxymethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (56)



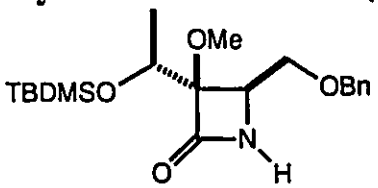
The alcohol **52** was benzylated as above to yield 87% of **56** as a yellow oil after purification by column chromatography (1:10 EtOAc:hexanes); IR: 1748 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.04 (3H, s, CH_3Si), 0.04 (3H, s, CH_3Si), 0.79 (9H, s, t-BuSi), 1.25 (3H, d, J=6.4 Hz, CH_3), 3.59 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.60-3.90 (2H, m overlaps with OMe, H_2CO), 4.17 (1H, q, J=6.4 Hz, CH_3CHO), 4.29 (1H, dd, J=3.0, 6.8 Hz, HCN), 4.53 (2H, s, CH_2Ph), 6.83 (2H, dd, J=2.3, 6.3 Hz, PMP), 7.28-7.32 (5H, broad s, Ph), 7.59 (2H, dd, J=2.3, 6.9 Hz, PMP); MS: 485 (M^+, 8), 428 (M^+-57, 33), 396 (M^+-57-32, 2), 336 (M^+-149, 4), 306 (336^+-30, 2); HRMS calcd for $C_{27}H_{39}NO_5Si$ 485.2595, found 485.2612.

4-Benzyloxymethyl-3-ethyl-3-methoxy-2-azetidinone (57)



Compound **55** (3.2 g, 9.01 mmol) was dissolved in 50 mL of CH_3CN and cooled in ice salt bath (-5 °C to 0 °C). CAN (14.82 g, 27.03 mmol) in 25 mL of ice-cold water was added dropwise over 15 min. Brown color appeared and disappeared during the early stages of addition; no noticeable color change was observed at the end of addition. The solution was stirred for further 10 min. [The progress of reaction must be followed carefully by tlc.]. Typical workup and chromatography (1:2 EtOAc:hexanes) gave 1.32 g (59%) of a brownish oil which was not characterized since it was not pure and taken to the next step without further purification.

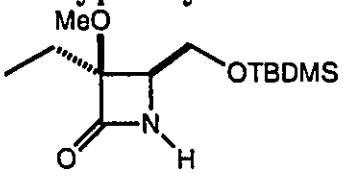
3-t-Butyldimethylsilyloxyethyl-4-benzyloxymethyl-3-methoxy-2-azetidinone (58)



The PMP group in the azetidinone **56** was cleaved as described above to obtain **58** as an oil in 87% yield after purification by column chromatography (1:3 EtOAc:hexanes); IR: 3300 (broad, NH), 1758 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.02 (3H, s, CH_3Si), 0.04 (3H, s, CH_3Si), 0.83 (9H, s, t-BuSi), 1.22 (3H, d, J=6.4 Hz, CH_3), 3.53 (3H, s, OCH_3), 3.50-3.60 (1H, m overlaps with OMe, CH_AH_BO), 3.66 (1H, dd, J=3.3, 10.1 Hz, CH_BH_AO), 3.84 (1H, dd, J=3.4, 11.8 Hz, HCN), 4.12 (1H, q, J=6.4 Hz,

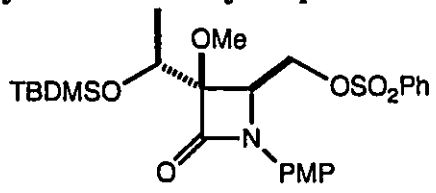
CH_3CHO), 4.51 (2H, s, CH_2Ph), 6.17 (1H, broad s, NH), 7.26-7.34 (5H, broad s, Ph); MS: 379 (M^+, 1), 336 (M^+-43, 4), 322 (M^+-57, 100), 279 (M^+-100, 99), 231 (322^+-91, 5).

3-Ethyl-4-t-butyldimethylsilyloxymethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (54)



The cleavage of PMP group of **53** (1.50 g, 3.96 mmol) was carried out as described above to yield 200 mg (18%) of **54** as a brown oil after purification by column chromatography (1:4 EtOAc:hexanes); ^1H NMR (200 MHz) δ: 0.03 (6H, s, CH_3SiCH_3), 0.85 (9H, s, t-BuSi), 0.95 (3H, t, J=6.5 Hz, CH_3), 1.63-1.74 (1H, m, CH_2CH_3), 1.93-2.08 (1H, m, CH_2CH_3), 3.44 (3H, s, OCH_3), 3.51 (1H, dd, J= 7.6, 4.8 Hz, HCN), 3.67 (1H, dd, J=8.0, 10.6 Hz, CH_AH_BO), 3.81 (1H, dd, J=4.4, 10.5 Hz, CH_BH_AO), 6.08 (1H, broad s, NH); MS: 258 (M^+-15, 2), 230 (M^+-43, 3), 216 (M^+-57, 21), 188 (M^+-85, 26), 173 (188^+-15, 49).

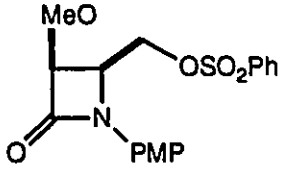
3-t-Butyldimethylsilyloxyethyl-4-benzenesulfonyloxymethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (68)



NaH (60%) dispersion (56 mg, 1.40 mmol) was added to the solution of the alcohol **52** (500 mg, 1.27 mmol) in 20 mL of DMF at 0 °C. Benzenesulfonyl imidazole (529.5 mg, 2.54 mmol) in 5 mL of DMF was added slowly by cannula. The reaction mixture was stirred for 18 h while allowing it to warm to ambient temperature. Purification of the

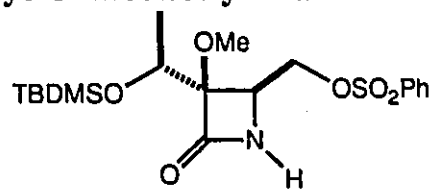
crude product obtained, after the usual workup and removal of the solvent, was carried out by column chromatography (1:10 EtOAc:hexanes) to give 344 mg (77%) of **68** as a colorless oil; ^{1}H NMR (200 MHz) δ: 0.02 (6H, s, CH_3SiCH_3), 0.75 (9H, s, t-BuSi), 1.20 (3H, d, J=6.4 Hz, CH_3), 3.52 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.07- 4.38 (4H, m, CH_3CHO, H_2CO, HCN), 6.81 (2H, d, J=9.2 Hz, PMP), 7.34 (2H, d, J=9.2 Hz, PMP), 7.47-7.61 (3H, m, Ph), 7.77-7.82 (2H, M, Ph); MS: 535 (M^+, 7), 478 (M^+-57, 70), 450 (M^+-57-28, 4), 329 (478^+-149, 24), 305 (M^+-230, 2); HRMS calcd for $C_{26}H_{37}NO_7SSi$ 535.2056, found 535.2066.

4-Benzenesulfonyloxymethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (83)



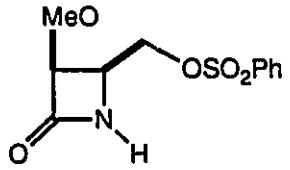
A solution of the alcohol **82** (1.00 g, 4.22 mmol) and $PhSO_2$imid (1.32 g, 5.57 mmol) in 15 mL of DMF was added to a suspension of NaH (223 mg, 5.58 mmol) in 20 mL of DMF and stirred 1.5 h. The reaction mixture was worked up in usual manner using ether as a solvent and purified by column chromatography (1:1 EtOAc:hexanes) to give 930 mg (58%) of **83** as an oil; ^{1}H NMR (200 MHz) δ: 3.48 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.20-4.37 (2H, m, H_2CO), 4.37-4.62 (1H, m, CHN), 4.61 (1H, d, J=4.9 Hz, HC-3), 6.81 (2H, d, J=9.1 Hz, PMP), 7.30 (2H, d, J=9.1 Hz, PMP), 7.48-7.65 (3H, m, Ph), 7.79 (2H, d, J=9.7 Hz, Ph); MS: 377 (M^+, 6), 304 (M^+-73, 1), 220 (M^+-157, 1), 192 (220^+-28, 17), 149 (M^+-228, 75).

3-t-Butyldimethylsilyloxyethyl-4-benzenesulfonyloxymethyl-3-methoxy-2-azetidinone (69)



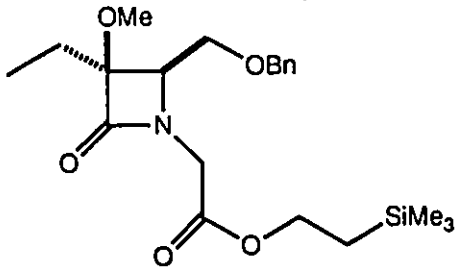
Azetidinone **68** (334 mg, 0.624 mmol) was reacted with CAN (as described for **57**) to yield 198 mg (71%) of **69** as a yellowish oil after purification by column chromatography (1:3 EtOAc:hexanes); ^{1}H NMR (200 MHz) δ: 0.02 (6H, s, CH_3SiCH_3), 0.79 (9H, s, t-BuSi), 1.18 (3H, d, J=6.4 Hz, CH_3), 3.48 (3H, s, OCH_3), 3.88 (1H, dd, J=5.4, 6.3 Hz, HCN), 4.07-4.15 (3H, m, CH_2O, CH_3CHO), 6.15 (1H, broad s, NH), 7.52-7.67 (3H, m, Ph), 7.86-7.92 (2H, m, Ph); MS(CI): 430 (M^++1, 20), 415 (M^++1-15, 13), 402 (M^++1-28, 100), 386 (M^+-43, 2), 372 (M^+-57, 29).

4-Benzenesulfonyloxymethyl-3-methoxy-2-azetidinone (84)



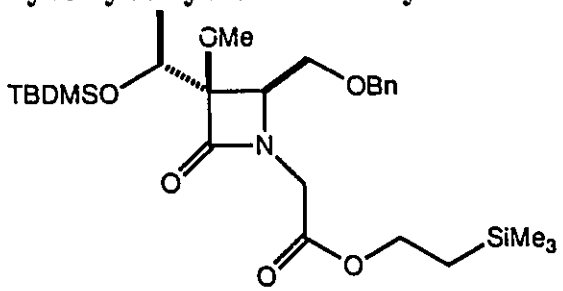
Azetidinone **83** (930 mg, 2.47 mmol) was treated with CAN (4.05 g, 7.39 mmol) as described above. The crude product was placed on a silica gel column. The less polar impurities were removed by elution with 1:3 EtOAc:hexanes. Elution with EtOAc gave 482 mg (72%) of **84** as a brown oil; ^{1}H NMR (200 MHz) δ: 3.45 (3H, s, OCH_3), 3.97-4.17 (2H, m, CHN, CH_AH_BO), 4.26 (1H, dd, J=6.5, 9.6 Hz, CH_AH_BO), 4.55 (1H, dd, J=3.7, 4.7 Hz, CH-3), 6.20 (1H, broad s, NH), 7.51-7.67 (3H, m, Ph), 7.89 (2H, d, J=6.9 Hz, Ph); MS(CI): 272 (M^++1, 2), 244 (M^++1-29, 100), 172 (M^+-100, 0.5), 114 (M^+-157, 8).

β-Trimethylsilylethyl (4-benzyloxymethyl-3-ethyl-3-methoxy-2-azetidinon-1-yl)acetate (59)



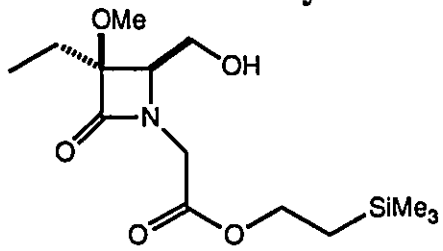
NaH (0.26 g, 5.47 mmol) was suspended in 25 mL of dry DMF and cooled to 0 °C under N_2. A mixture of the compound **57** (1.24 g, 4.97 mmol) and β-trimethylsilylethyl bromoacetate (1.30 g, 5.47 mmol) in 10 mL of dry DMF was added by cannula and stirred overnight at 25 °C. The reaction mixture was diluted with 35 mL of ether, subjected to the usual workup procedure and purified by column chromatography (1:8 EtOAc:hexanes) to yield 1.4 g (70%) of **59** as a yellow oil; IR: 1754 (C=O, broad, 2 overlapping peaks) cm^{-1}; ^1H NMR (200 MHz) δ: 0.00 (9H, s, TMS), 0.88-1.00 (5H, m overlapping t, CH_3, CH_2TMS), 1.69-2.11 (2H, m, CH_2CH_3), 3.45 (3H, s, OCH_3), 3.68 (1H, dd, J=7.3, 3.7 Hz, CHN), 3.75-3.91 (3H, m, CH_2OBn, NCH_AH_BCOOR), 4.12-4.47 (3H, m, OCH_2CH_2TMS, NCH_AH_BCOOR), 7.23-7.33 (5H, m, Ph); MS(CI): 408 (M^++1, 4), 380 (M^++1-28, 100), 352 (M^++1-56, 71), 244 (M^++1-164, 15), 149 (M^++1-269, O=C-$NCH_2COOCH_2CH_2TMS^+$, 76).

β-Trimethylsilylethyl 4-benzyloxymethyl-3-t-butyldimethylsilyloxyethyl-3-methoxy-2-azetidinon-1-ylacetate (60)



The reaction of **58** with β-trimethylsilylethyl bromoacetate was performed as described above to give **60** as a yellow oil in 68% yield. Chromatography solvent (1:8 EtOAc:hexanes); IR: 1756 (broad, C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (9H, s, TMS), 0.013 (3H, s, CH_3Si), 0.03 (3H, s, CH_3Si), 0.83 (9H, s, t-BuSi), 0.84-0.96 (2H, m, CH_2Si), 1.25 (3H, d, J=6.4 Hz, CH_3), 3.56 (3H, s, OCH_3), 3.65-3.76 (2H, m, CH_2O), 3.92-4.20 (6H, m, CHN, CHO, NCH_2COO, CH_2O), 4.46 (2H, s, CH_2Ph), 7.23-7.30 (5H, m, Ph); MS(CI): 538 (M^++1, 6), 523 (M^++1-15, 0.3), 510 (M^++1-28, 71), 495 (510^+-15, 3), 482 (M^++1-56, 17).

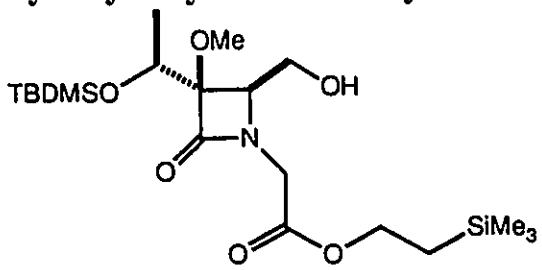
β-Trimethylsilylethyl 4-hydroxymethyl-3-ethyl-3-methoxy-2-azetidinon-1-ylacetate (61)



Benzyl ether **59** (1.32 g, 3.23 mmol) was dissolved in 20 mL of EtOH and 200 mg Pd-C (10%) was added and hydrogenated at 40 psi and 25 °C for 18 h. After removal of the catalyst, the solution was concentrated in vacuum. The crude product was purified by passing through a small silica gel plug (EtOAc) to yield 0.82 g (80%) of a

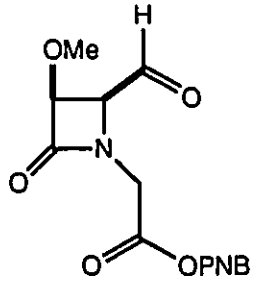
colorless oil **61**; IR: 3441 (broad, OH), 1746 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.00 (9H, s, TMS), 0.93-1.00 (5H, m, CH_3, CH_2TMS), 1.60-1.82 (1H, m, CH_2CH_3), 2.01-2.20 (1H, m, CH_2CH_3), 2.59 (1H, dd, J=5.6, 5.9 Hz, OH), 3.51 (3H, s, OCH_3), 3.53-3.72 (1H, m) , 3.83 (2H, m), 4.20 (4H, m) these multiplets could not be assigned completely (HCN, $2XCH_2O$, NCH_2COOR); MS: 274 (M^+-43, 3), 246 (M^+-43-28, 1), 216 (imine$^+$-1, 0.7), 173 (M^+-116-28, 1), 116 (M^+-201, 36).

β-Trimethylsilylethyl 4-hydroxymethyl-3-t-butyldimethylsilyloxyethyl-3-methoxy-2-azetidinon-1-ylacetate (62)



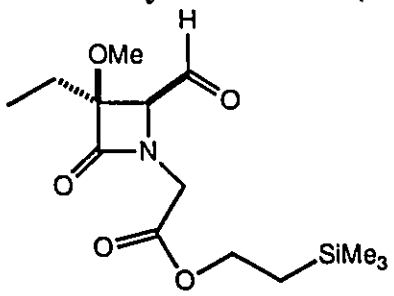
This compound **62** was obtained in 95% yield as described above and taken to the next step without further characterization.

p-Nitrobenzyl 4-formyl-3-methoxy-2-azetidinon-1-ylacetate (90)



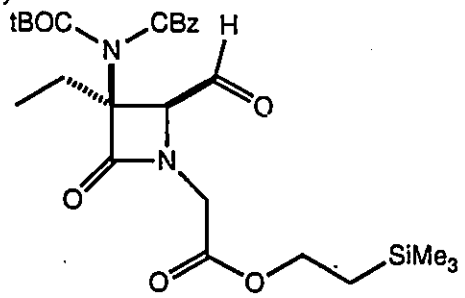
The ozonolysis of **88** (2.5 g, 6.31 mmol) was done as in case of compound **49**. The aldehyde **90** (2.0 g, 98% yield) was obtained after purification by column chromatography (2:1 EtOAc:hexanes). Due to its tendency to oxidize in air, it was reduced directly as described on page 76.

β-Trimethylsilylethyl 4-formyl-3-ethyl-3-methoxy-2-azetidinon-1-ylacetate (67)



Azetidinone **66** (360 mg, 0.925 mmol) was ozonolyzed in the usual manner and the crude product purified by column chromatography (1:4 EtOAc:hexanes) to give 220 mg (75%) of **67** as a colorless oil; IR: 1740-1780 (broad, C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.00 (9H, s, TMS), 0.92-1.00 (2H, m, CH_2Si), 1.07 (3H, t, J=7.4 Hz, CH_3CH_2), 1.80-2.20 (2H, m, CH_2CH_3), 3.41 (3H, s, OCH_3), 3.93 (1H, d, J=18.3 Hz, CH_AH_BCOOR), 4.13-4.21 (2H, m, CH_2O), 4.25 (1H, d, J=1.3 Hz, CHN), 4.34 (1H, d, J=18.3 Hz, CH_BH_ACOOR), 9.65 (1H, d, J=1.4 Hz, CHO); MS: 315 (M^+, 3), 287 (M^+-28, 1), 272 (M^+-43, 6), 244 (272^+-28, 8), 214 (M^+-101, 1).

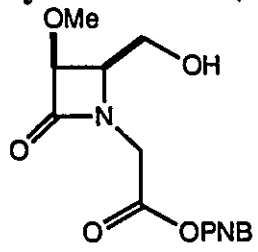
β-Trimethylsilylethyl 4-formyl-3-ethyl-3-(N-t-butyloxy-carbonyl, N-carbobenzyloxy)amino-2-azetidinon-1-ylacetate (112)



The azetidinone **111** (1.00 g, 1.65 mmol) was ozonolyzed as described above to yield 600 mg (68%) of **112** as a yellowish oil which

is unstable and reduced immediately; chromatography solvent (1:6 EtOAc:hexanes); ^{1}H NMR (200 MHz) δ: 0.00 (9H, s, TMS), 0.92-1.00 (2H, m, CH_2Si), 1.07 (3H, t, J=7.5 Hz, CH_3CH_2), 1.53 (9H, s, t-Bu), 2.14-2.25 (1H, m, CH_2CH_3), 2.43-2.54 (1H, m, CH_2CH_3), 3.80 (1H, d, J=18.1 Hz, NCH_BH_ACOOR), 4.13-4.22 (2H, m, OH_2C), 4.35 (1H, d, J=18.0 Hz, NCH_AH_BCOOR), 4.35 (1H, d, J=1.6 Hz, HCN), 5.15 (2H, apparent broad d, J=na, CH_2Ph), 7.33 (5H, s, Ph), 9.67 (1H, d, J=1.7 Hz, CHO); MS(CI): 465 (M^++1-28-42, 1), 451 (M^++1-28-56, 4), 435 (M^++1-100, 3), 407 (M^++1-128, 59), 363 (407^+-44, 16).

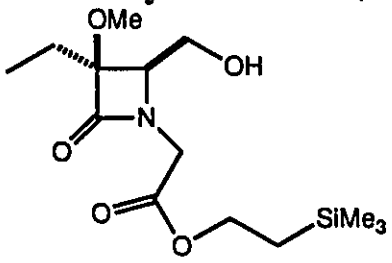
p-Nitrobenzyl 3-methoxy-4-hydroxymethyl-2-azetidinon-1-ylacetate (91)



The aldehyde **90** was dissolved in 20 mL of THF and 20 mL of EtOH. Two drops of bromocresol green and 2 drops of 10% HCl were added followed by sodium cyanoborohydride (0.78 g, 12.41 mmol). The reaction mixture turned blue. The yellowish color was maintained by adding HCl. After 3.5 h the reaction mixture was diluted with 40 mL of water and extracted with 3X30 mL of CH_2Cl_2. The crude product was purified column chromatography (1.5:1 EtOAc:hexanes) to give 1.2 g (60%) of oil; IR: 3342 (broad, OH), 1750 (C=O), 1522 and 1348 (NO_2) cm^{-1}; ^{1}H NMR (200 MHz) δ: 3.53 (3H, s, OCH_3), 3.84 (2H, d, J=4.2 Hz, CH_2OH), 3.98 (1H, d, J=18.1 Hz, NCH_AH_BCOOR), 3.98 (1H, m overlaps with other peak at 3.98, HCN), 4.26 (1H, d, J=18.1 Hz, NCH_AH_BCOOR), 4.58 (1H, d, J=4.9 Hz, HC-C=O), 5.21 (2H, s, OCH_2PNB), 7.46 (2H, d, J=8.8 Hz, PNB),

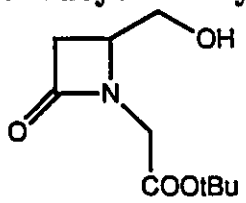
8.16 (2H, d, J=8.8 Hz, PNB); MS(CI): 325 (M^++1, 2), 297 (M^++1-28, 1), 279 (M^+-46, 3), 247 (279^+-32, 12), 228 (M^++1-97, 93).

β-Trimethylsilylethyl 3-ethyl-4-formyl-3-methoxy-2-azetidinon-1-ylacetate (61)



The aldehyde **67** (160 mg, 0.58 mmol) in 2 mL of EtOH was treated with $NaCNBH_3$ (126 mg, 1.32 mmol) as described for compound **91** to yield 119 mg (74%) of alcohol **61** after purification by column chromatography (1:2 EtOAc:hexanes). The ^1H NMR was identical to that obtained by earlier method (p 73).

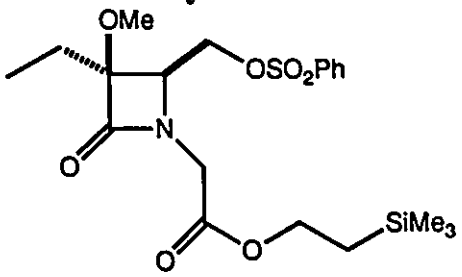
t-Butyl 4-hydroxymethyl-2-azetidinon-1-ylacetate (98)



Azetidinone **97** (992 mg, 3.95 mmol) dissolved in 40 mL of dry CH_2Cl_2 and 5 mL of MeOH was ozonolyzed at -78 °C. $NaBH_4$ (84.5 mg, 2.35 mmol) in 5 mL of EtOH was added and the reaction mixture was stirred for 18 h (-78 °C to 25 °C). The reaction mixture was brought to pH 5 by stirring with Amberlite, filtered and concentrated to yield 1.07 g (99%) of **98** as an oil. The product was taken to the next step without further purification; ^1H NMR (200 MHz) δ: 1.38 (9H, s, t-Bu), 2.79-2.89 (2H, m, H_2C-3), 3.28-3.69 (4H, m, HCN, CH_2O, CH_AH_BCOOR), 4.18 (1H, d,

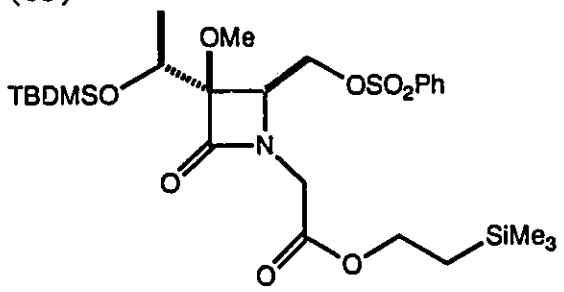
J=18.3 Hz, CH_AH_BCOOR); MS(CI): 216 (M^++1, 34), 188 (M^++1-28, 9), 172 (M^++1-44, 20), 160 (216^+-56, 100), 118 (160^+-42, 43).

β-Trimethylsilylethyl 4-benzenesulfonyloxymethyl-3-ethyl-3-methoxy-2-azetidinon-1-ylacetate (29)



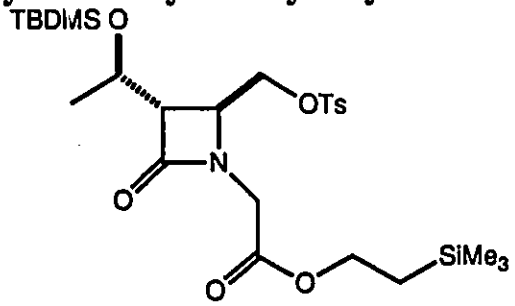
To a solution of the alcohol **61** (0.8 g, 2.52 mmol) in 20 mL of THF was added 1.03 g (5.1 mmol) of benzenesulfonyl imidazole in 20 mL of dry DMF (soln A). NaH (0.11 g, 2.77 mmol) was suspended in 20 mL of a mixture of THF and DMF (1:1) and cooled to 0 °C under N_2. Soln A was added slowly by cannula and the mixture was stirred without further cooling for 18 h. The reaction mixture was diluted with 40 mL of ether and washed with 10% HCl, 5% $NaHCO_3$ and brine (30 mL each) respectively. Column chromatography (1:9 EtOAc:hexanes) gave 0.92 g (80%) of **29** as a colorless oil; IR: 1770 and 1740 (C=O), 1370 and 1190 (SO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.00 (9H, s, TMS), 0.87-1.02 (5H, m, CH_3, CH_2TMS), 1.73-1.81 (1H, m, CH_2CH_3), 1.96-2.01 (1H, m, CH_2CH_3), 3.37 (3H, s, OCH_3), 3.72 (1H, d, J=18.1 Hz, NCH_AH_BCOOR), 3.87 (1H, dd, J=5.5, 6.6 Hz, CHN), 4.15 (5H, m, 2 x OCH_2, NCH_AH_BCOOR), 7.51-7.66 (3H, m, Ph), 7.85-7.90 (2H, m, Ph); MS: 414 (M^+-43, 2), 386 (M^+-71, 2), 256 (M^+-201, 12), 242 (256^+-14, 2).

β-Trimethylsilylethyl 4-benzenesulfonyloxymethyl-3-t-butyldimethylsilyloxyethyl-3-methoxy-2-azetidinon-1-ylacetate (63)



The compound **63** was prepared from **62** as described above in 63% yield as a colorless oil after purification by chromatography (1:7 EtOAc:hexanes); IR: 1757 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (15H, s, TMS, CH_3SiCH_3), 0.77 (9H, s, t-BuSi), 0.93-0.99 (2H, m, CH_2Si), 1.20 (3H, d, J=6.7 Hz, CH_3CH), 3.48 (3H, s, OCH_3), 3.85 (1H, d, J=17.9 Hz, NCH_AH_BCOOR), 4.00-4.31 (7H, m, HCO, $2XH_2CO$, HCN, NCH_AH_BCOOR), 7.49-7.89 (5H, m, Ph); MS(CI): 588 (M^++1, 2), 573 (M^++1-15, 0.4), 560 (M^++1-28, 98), 530 (M^++1-57, 12), 502 (530^+-28, 6).

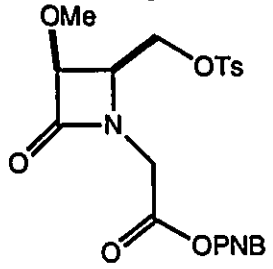
β-Trimethylsilylethyl 4-toluenesulfonyloxymethyl-3-(R)-t-butyldimethylsiloxyethyl-2-azetidinon-1-ylacetate (79)



NaH (0.052 g, 1.176 mmol) was suspended in 5 mL of DMF and cooled to 0 °C under N_2. The solution of tosylate **78** (0.364 g, 0.98 mmol) and β-trimethylsilylethyl bromoacetate (0.28 g, 1.17 mmol) in 10 mL of dry DMF was then added to the NaH suspension by cannula (color

becomes reddish) and stirred overnight at 25 °C. The crude product obtained upon usual workup was purified by column chromatography (1:5 EtOAc:hexanes) to give 0.391 g (70%) of **79** as a yellow oil; IR: 1760 (broad, C=O), 1367 and 1182 (SO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.02 (15H, s, TMS, $(CH_3)_2Si$), 0.78 (9H, s, t-BuSi), 0.92-1.01 (2H, m, CH_2Si), 1.16 (3H, d, J=5.2 Hz, CH_3CH), 2.43 (3H, s, CH_3Ph), 2.80 (1H, dd, J=2.2, 6.0 Hz, HC-C=O), 3.80 (1H, d, J=17.9 Hz, NCH_AH_BCOOR), 3.95 (1H, d, J=17.9 Hz, NCH_AH_BCOOR), 3.94-4.27 (6H, m, HCO, H_2CO), 7.32 (2H, d, J=8.1 Hz, Tol), 7.75 (2H, d, J=8.5 Hz, Tol); MS(CI): 572 (M^++1, 5), 557 (M^++1-15, 0.6), 544 (M^++1-28, 100), 515 (M^++1-57, 7), 272 (M^++1-200, 2).

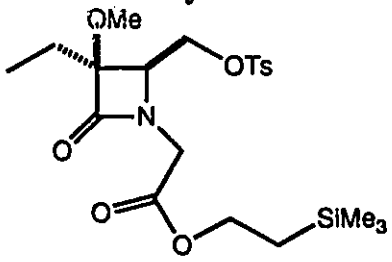
p-Nitrobenzyl 3-methoxy-4-toluenesulfonyloxymethyl-2-azetidinon-1-ylacetate (92)



Tosyl chloride (0.49 g, 2.57 mmol) was dissolved in 4 mL of pyridine and added to the alcohol **91** (0.564 g, 1.7 mmol) at room temperature under N_2. It was stored at -5 to 0 °C for 18 h. Purification of the crude product by column chromatography (1:3 EtOAc:hexanes) yielded 0.579 g (69%) of **92** as a colorless oil; IR: 1762 (C=O), 1522 and 1353 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 2.43 (3H, s, CH_3Ph), 3.45 (3H, s, OCH_3), 3.97 (1H, d, J=18.1 Hz, NCH_AH_BCOOR), 4.20-4.21 (4H, m, H_2CO, HCN, NCH_AH_BCOOR), 4.59 (1H, d, J=5.6 Hz, HC-C=O), 7.33 (2H, d, J=8.3 Hz, Tol), 7.50 (2H, d, J=8.9 Hz, PNB), 7.72 (2H, d, J=8.2 Hz, Tol), 8.21 (2H, d,

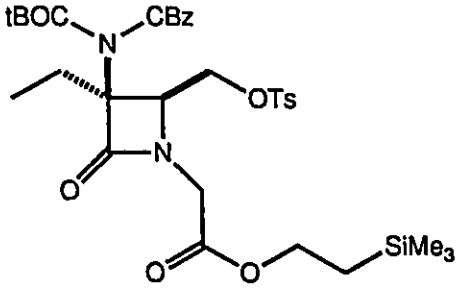
J=8.9 Hz, PNB); MS(CI): 479 (M^++1, 0.6), 451 (M^++1-28, 0.6), 371 (M^++1-108, 14), 343 (M^++1-143, 0.6).

β-Trimethylsilylethyl 4-toluenesulfonyloxymethyl-3-ethyl-3-methoxy-2-azetidinon-1-ylacetate (31)



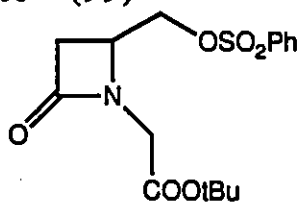
Alcohol **61** (118 mg, 0.37 mmol) and toluenesulfonyl chloride (107 mg, 0.56 mmol) were dissolved in 1 mL of pyridine and stored at -5 °C to 0 °C for 24 h. Usual work up and purification by column chromatography (1:3 EtOAc:hexanes) gave 126 mg (72%) of **31** as a colorless oil; ^{1}H NMR (200 MHz) δ: 0.03 (9H, s, TMS), 0.92 (3H, t, J=7.4 Hz, C*H*$_3$CH$_2$), 0.96-1.02 (2H, m, CH$_2$Si), 1.74-1.81 (1H, m, C*H*$_2$CH$_3$), 1.94-2.01 (1H, m, C*H*$_2$CH$_3$), 2.45 (3H, s, CH$_3$Ph), 3.39 (3H, s, OCH$_3$), 3.74 (1H, d, J=18.0 Hz, C*H*$_A$H$_B$COOR), 3.88 (1H, t, J=6.1 Hz, HCN), 4.12-4.23 (5H, m, CH$_2$O, C*H*$_A$H$_B$COOR, CH$_2$OTs), 7.34 (2H, d, J=8.6 Hz, Tol), 7.76 (2H, d, J=8.2 Hz, Tol); MS(CI): 472 (M^++1, 6), 444 (M^++1-28, 100), 416 (M^++1-56, 67), 372 (M^++1-101, 6), 317 (M^++1-155, 4).

β-Trimethylsilylethyl [3-ethyl-4-tosyloxymethyl-3-(N-t-butyloxycarbonyl, N-carbobenzyloxy)amino-2-azetidinon-1-yl]acetate (114).



The tosylation of this compound was achieved in 14% yield after purification by column chromatography (1:10 EtOAc:hexanes) following the procedure described for the compound **31**. IR: 1780, 1750 and 1720 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (9H, s, TMS), 0.97-1.05 (5H, m, CH_2Si, CH_3CH_2), 1.34 (9H, s, t-Bu), 2.05-2.17 (1H, m, CH_2CH_3), 2.37-2.45 (4H, m, overlapping with s at 2.41, CH_2CH_3, CH_3Ph), 3.68 (1H, d, J=18.2 Hz, CH_AH_BCOOR), 3.96 (1H, dd, J=3.1, 9.2 Hz, CH_AH_BO), 4.13-4.26 (4H, m, CH_BH_AO, CH_BH_ACOOR, OCH_2), 4.34 (1H, dd, J=3.2, 10.2 Hz, HCN), 5.14 (2H, d apparent, J=2.3 Hz, CH_2Ph), 7.27-7.35 (7H, m, Ph, Tol), 7.68 (2H, d, J=8.4 Hz, Tol); MS(CI): 663 (M^++1-28, 1), 635 (M^++1-56, 2), 601 (M^++1-90, 2), 591 (M^++1-100, 5), 563 (591^+-28, 17).

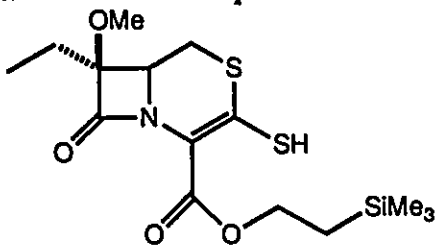
t-Butyl 4-benzenesulfonyloxymethyl-2-azetidinon-1-yl-acetate (99)



The alcohol **98** (1.00 g, 4.65 mmol) and benzenesulfonyl imidazole (1.23 g, 5.91 mmol) in 10 mL of DMF:THF (1:1) was added to the suspension of NaH (0.20 g, 5.0 mmol) in 15 mL of DMF at 0 °C. After

stirring for 18 h at 0 °C to 25 °C, the reaction mixture was worked up using EtOAc as a solvent. Purification of the crude product by column chromatography (1:6 EtOAc:hexanes) afforded 385 mg (23%) of **99** as a yellowish oil; ^{1}H NMR (200 MHz) δ: 1.42 (9H, s, t-Bu), 2.66 (1H, dd, J=1.6, 14.2 Hz, H_AC-3), 3.06 (1H, dd, J=5.1, 14.8 Hz, H_BC-3), 3.63 (1H, d, J=18.1 Hz, C$H_A$$H_B$COOR), 4.01 (1H, d, J=18.1 Hz, C$H_B$$H_A$COOR), 4.04-4.31 (3H, m, HCN, CH_2O), 7.52-7.68 (3H, m, Ph), 7.86-7.90 (2H, m, Ph); MS(CI): 356 (M^++1, 5), 328 (M^++1-28, 1), 300 (M^++1-56, 100), 258 (300^+-42, 31), 254 (M^++1-102, 5).

β-Trimethylsilylethyl 3-mercapto-7-methoxy-7-ethyl-1-dethia-2-thia-3-cephemcarboxylate (74)

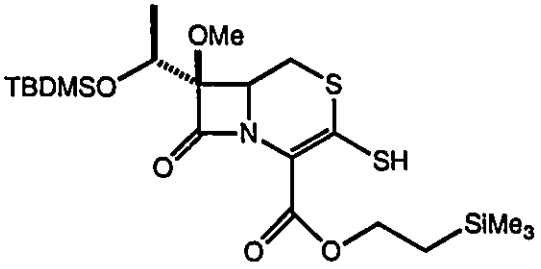


A solution of compound **29** (0.389 g, 0.851 mmol) in 10 mL of dry THF was cooled to -78 °C under N_2 and added to an LDA solution (1.1 eq) in 5 mL of THF at -78 °C *via.* cannula. The yellow solution was stirred for 15 min and excess CS_2[36] was added by cannula (pinkish tinge appeared). The reaction mixture was allowed to warm slowly to room temperature over a period of 18 h. The solvent was removed. The faster moving impurities in the crude product were removed by eluting with 1:4 EtOAc:hexanes and the desired compound was obtained by an EtOAc flush. The yellowish oil (0.22 g, 71%), reasonably pure by NMR, was carried through the next step without further purification; IR:

[36] Carbon disulfide from old bottles gave poor results even after distillation and thus only new bottles were used.

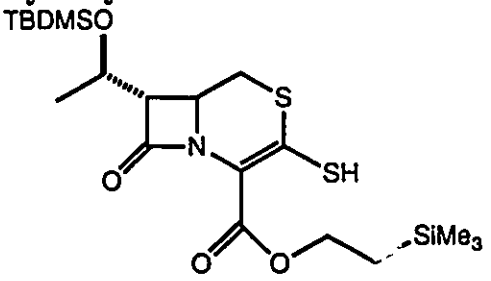
1770 and 1690 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.00 (9H, s, TMS), 1.00 (3H, t, J=7.4 Hz, CH_3), 1.07-1.10 (2H, m, CH_2TMS overlapping with CH_3), 1.85-2.14 (2H, m, CH_2CH_3), 2.85 (1H, dd, J=3.0, 12.2 Hz, CH_2S), 3.46 (4H, s overlapping with dd, J=9.7, 12.2 Hz, OCH_3, CH_2S), 3.61 (1H, dd, J=3.0, 9.7 Hz, HCN), 4.02 (1H, broad, SH), 4.23-4.36 (2H, m, OCH_2); MS(CI): 376 (M^++1, 6), 361 (M^++1-15, 2), 348 (M^++1-28, 29), 332 (M^++1-44, 22), 320 (M^++1-56, 100).

β–Trimethylsilylethyl 3-mercapto-7-methoxy-7-t-butyldimethylsilyloxyethyl-1-detia-2-thia-3-cephemcarboxylate (75)



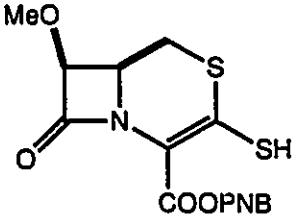
The cyclization reaction was carried out as described above yielding 88% of **75** as a yellow oil; chromatography solvent (1:1 EtOAc:hexanes to remove faster moving impurities and EtOAc elution for the product **75**); IR: 1747 (broad, C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (9H, s, TMS), 0.04 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si), 0.84 (9H, s, t-Bu), 1.01-1.11 (2H, m, CH_2Si), 1.26 (3H, d, J=6.4 Hz, CH_3), 1.70 (1H, broad s, SH), 2.80 (1H, dd, J=3.5, 12.6 Hz, CH_AH_BS), 3.44 (1H, dd, J=9.7, 12.6 Hz, CH_AH_BS), 3.58 (3H, s, OCH_3), 3.73 (1H, dd, J=3.5, 9.7 Hz, CHN), 4.25 (3H, m, HCO, H_2CO); MS(CI): 506 (M^++1, 3), 505 (M^+, 1), 490 (M^+-15, 3), 478 (M^+-28, 31), 449 (M^+-57, 2).

β–Trimethylsilylethyl 3-mercapto-7-(R)-t-butyldimethyl-silyloxyethyl-1-dethia-2-thia-3-cephemcarboxylate (80)



This compound was obtained in 82% yield as a yellow oil by applying the annulation method described above; IR: 1763 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (12H, s, TMS, CH_3Si), 0.06 (3H, s, CH_3Si), 0.85 (9H, s, t-Bu), 1.10 (2H, t, J=8.9 Hz, CH_2Si), 1.23 (3H, d, J=6.2 Hz, CH_3), 2.77 (1H, dd, J=2.2, 5.4 Hz, HCC=O), 3.09 (2H, dd, 1.5, 7.5 Hz, CH_2S), 3.70 (1H, m, HCN), 3.80 (1H, s, SH), 4.20-4.40 (3H, m, HCO, CH_2O); MS: 447 (M^+-28, 2), 432 (447-15$^+$, 5), 418 (447-29$^+$, 5), 390 (447-57$^+$, 12), 346 (447-101, 16).

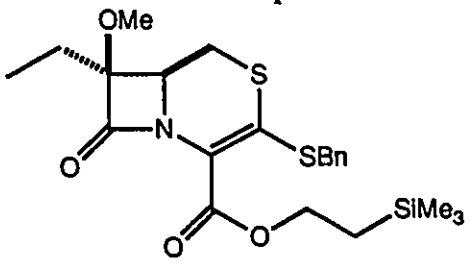
p-Nitrobenzyl 3-mercapto-7-methoxy-1-dethia-2-thia-3-cephemcarboxylate (93)



This compound was obtained as a yellow solid in 57% yield; mp 161-163 °C; chromatography solvent (2:1 EtOAc:hexanes followed by EtOAc elution); IR (KBr): 3378 (SH), 1749 and 1716 (C=O) cm^{-1}; ^1H NMR (300 MHz) δ: 3.22-3.23 (1H, m, CH_AH_BS), 3.31-3.38 (1H, m, CH_AH_BS), 3.49 (3H, s, OCH_3), 4.03-4.08 (1H, m, HCN), 4.50 (1H, broad s, SH), 4.94-4.54 (1H, d, J=4.4 Hz, HC-3), 5.30 (1H, d, J=13.9 Hz, CH_AH_BPNB), 5.44 (1H,

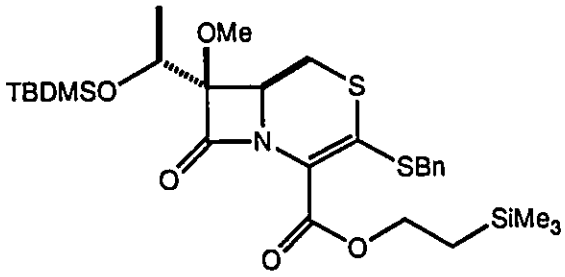
d, J=13.9 Hz, CH_AH_BPNB), 7.80 (2H, d, J=8.9 Hz, PNB), 8.20-8.24 (2H, d, J=9.0 Hz, PNB).

β-Trimethylsilylethyl 3-benzylthio-7-methoxy-7-ethyl-1-dethia-2-thia-3-cephemcarboxylate (76)



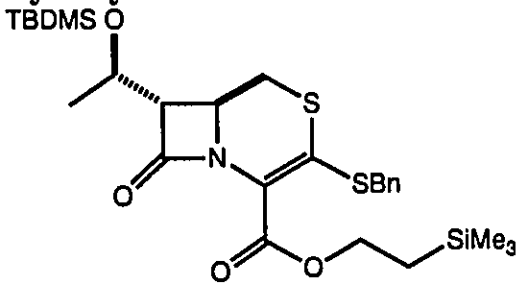
NaH dispersion (0.025 g, 0.63 mmol) was added to a solution of the enethiol **74** (0.215 g, 0.573 mmol) in 5 mL of dry THF at 0 °C. When the effervescence subsided, benzyl bromide (0.7 mL, 0.573 mmol) was added by syringe (white ppt. appeared). The cooling bath was removed and the reaction mixture was stirred for 30 min, diluted with 5 mL of EtOAc and washed with brine. Further workup and purification by column chromatography (1:8 EtOAc:hexanes) yielded 0.254 g (95%) of a yellowish solid **76**; mp 80-82 °C; IR: 1760 and 1710 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (9H, s, TMS), 0.96-1.08 (5H, m, CH_3, CH_2TMS), 1.87-2.12 (2H, m, CH_2CH_3), 2.88 (1H, dd, J=3.2, 12.4 Hz, CH_2S), 3.27 (1H, dd, J=9.8, 12.3 Hz, CH_2S), 3.45 (3H, s, OCH_3), 3.58 (1H, dd, J=3.2, 9.8 Hz, HCN), 4.09 (2H, s, SCH_2Ph), 4.23-4.32 (2H, m, OCH_2), 7.22-7.32 (5H, m, Ph); MS: 465 (M^+, 8), 437 (M^+-28, 7), 422 (M^+-28-15, 7), 378 (M^+-56-31, 6), 346 (M^+-91-28, 0.5), HRMS for $C_{22}H_{33}NO_4S_2Si$ calcd 465.1461, found 465.1448.

β-Trimethylsilylethyl 3-benzylthio-7-methoxy-7-t-butyldimethylsilyoxyethyl-1-dethia-2-thia-3-cephemcarboxylate (77)



Compound **77** was obtained as a yellowish solid in 65% yield as described above; mp 111-112 °C; chromatography solvent (1:15 EtOAc: hexanes); IR: 1748 (C=O), 1692 (COOR) cm^{-1}; ^1H NMR (200 MHz) δ: 0.00 (9H, s, TMS), 0.05 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si), 0.85 (9H, s, t-BuSi), 0.99-1.07 (2H, m, CH_2TMS), 1.26 (3H, d, J=6.4 Hz, CH_3CH), 2.85 (1H, dd, J=3.3, 12.6 Hz, CH_2S), 3.25 (1H, dd, J=9.8, 12.6 Hz, CH_2S), 3.56 (3H, s, OCH_3), 3.71 (1H, dd, J=3.3, 9.7 Hz, HCN), 4.10 (2H, s, SCH_2Ph), 4.19-4.30 (3H, m, HCO, H_2CO), 7.24-7.30 (5H, m, Ph); MS: 595 (M^+, 31), 580 (M^+-15, 0.7), 567 (M^+-28, 14), 552 (M^+-43, 26), 538 (M^+-57, 11).

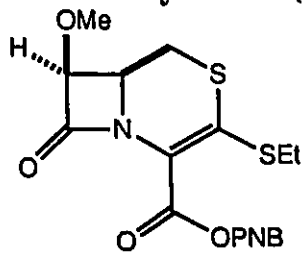
β-Trimethylsilylethyl 3-benzylthio-7-(R)-t-butyldimethylsiloxyethyl-1-dethia-2-thia-3-cephemcarboxylate (81)



Compound **81** was obtained as a yellow solid in 63% yield, mp 99-101 °C, $[\alpha]_D^{22}$ -4.7° (*C* 0.7, $CHCl_3$); chromatography solvent (1:5 EtOAc: hexanes), IR: 1766 (C=O), 1719 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.02 (9H, s, TMS), 0.06 (6H, s, CH_3SiCH_3), 0.86 (9H, s, t-BuSi), 1.03-1.20 (2H,

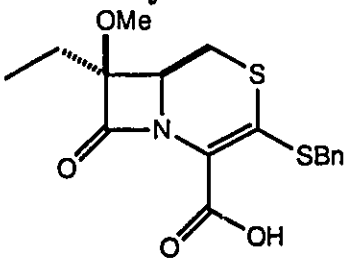
m, H_2CSi), 1.22 (3H, d, J=6.2 Hz, CH_3CH), 2.86 (1H, dd, J=3.6, 5.1 Hz, HC-C=O), 2.88 (1H, d, J=10.1 Hz, H_2CS), 3.81 (1H, dd, J=3.4, 12.4 Hz, H_2CS), 3.68-3.74 (1H, m, HCN), 4.04 (2H, s, SCH_2Ph), 4.22-4.34 (3H, m, HCO, H_2CO), 7.22-7.40 (5H, m, Ph); MS: 565 (M^+, 3), 537 (M^+-28, 2), 522 (M^+-43, 2), 508 (M^+-57, 0.8), 480 (508^+-28, 4).

p-Nitrobenzyl 3-ethylthio-7-methoxy-1-dethia-2-thia-3-cephemcarboxylate (94)



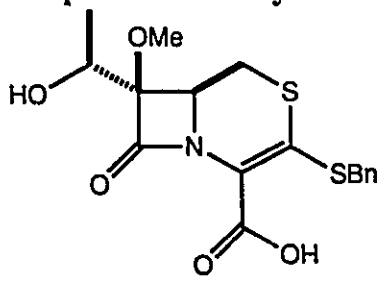
Compound **94** was obtained as a yellow solid in 39% yield; mp 149-150 °C; IR: 1767 (C=O), 1699 (COOR), 1517 and 1342 (NO_2) cm^{-1}; ^1H NMR (300 MHz) δ: 1.29 (3H, t, J=7.4 Hz, CH_3CH), 2.89-2.98 (2H, overlapping q, H_2CCH_3), 3.03 (1H, dd, J=12.6, 3.4 Hz, CH_2S), 3.32 (1H, dd, J=9.9, 12.7 Hz, CH_2S), 3.54 (3H, s, OCH_3), 3.91-3.97 (1H, m, HCN), 4.82 (1H, d, J=4.6 Hz, HCC=O), 5.27 (1H, d, J=13.4 Hz, CH_2PNB), 5.37 (1H, d, J=13.4 Hz, CH_2PNB), 7.61 (2H, d, J=8.9 Hz, PNB), 8.20 (2H, d, J=8.7 Hz, PNB); ^{13}C NMR (200 MHz) δ: 14.2 (CH_3), 27.6 (CH_2S), 28.6 (CH_2S), 50.3 (OCH_3), 59.2 (CHN), 65.8 (CH_2PNB), 85.3 (HCC=O), 104.7 (C=C), 123.6 and 128.7 (CH of PNB), 142.8 and 147.6 (C of PNB), 160.6 (C=O), 164.1 (C=O); MS: 411 (M^++1, 1), 410 (M^+, 7), 382 (M^+-28, 12), 351 (382^+-31, 14), 337 (M^+-84, 1); HRMS for $C_{17}H_{18}N_2O_6S_2$ calcd 410.0623, found 410.0621.

3-Benzylthio-7-ethyl-7-methoxy-1-dethia-2-thia-3-cephemcarboxylic acid (36)



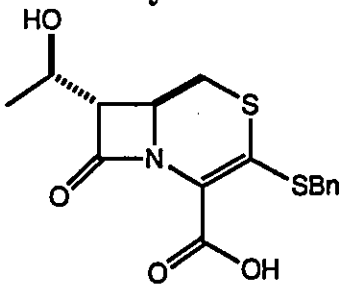
TBAF (0.28 mL, 0.27 mmol, 1M solution in THF) was added to a solution of the compound **76** (86 mg, 0.185 mmol) in 1 mL of THF at 25 °C. It was then stirred overnight (17 h) under N_2. EtOAc (5 mL) and 0.3 N HCl (1 mL) was added to the reaction mixture (pH=1). The aqueous layer was separated and extracted with EtOAc twice (5 mL each). The combined organic layer (containing some white crystalline particles) was concentrated without drying and the crude product was recrystallised from ether-acetone (1:1) mixture containing traces of water (1-2 drops.) to give 50 mg (74%) of **36** as a white solid; mp 189-191 °C (decomp); IR: 3437 (broad, OH), 1763 and 1654 (C=O) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ: 0.92 (3H, t, J=7.4 Hz, CH_3), 1.73-2.26 (2H, m, CH_2CH_3) acetone peak overlaps, 3.10-3.14 (2H, overlapping 2 sets of dd, J=12.0, 4.6, 8.6 Hz, CH_2S), 3.34 (3H, s, OCH_3), 3.60-3.65 (1H, m, HCN), 4.04 (2H, d, J=3.4 Hz, SCH_2Ph), 7.17-7.30 (5H, m, Ph); ^{13}C NMR (300 MHz) δ: 7.8 (CH_3), 23.5 (CH_2), 28.8 (CH_2), 39.9 (CH_2), 55.2 (CH), 55.9 (CH_3O), 128.2 (CH), 129.3 (CH), 130.1 (CH), 137.6 (C); MS: 365 (M^+, 20), 337 (M^+-28, 38), 321 (M^+-44, 22), 293 (M^+-44-28, 47), 262 (M^+-100, 4); HRMS for $C_{17}H_{19}NO_4S_2$ calcd 365.0745, found 365.0750.

3-Benzylthio-7-hydroxyethyl-7-methoxy-1-dethia-2-thia-3-cephemcarboxylic acid (37)



TBAF deprotection of **77** gave **37** as a white solid in 75% yield; mp 209-211 °C; crystallization in aq CH_3OH, IR: 3549 (broad, OH), 1736 (C=O), 1655 (COOH) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6 + 1 drop D_2O with HOD irradiation) δ: 1.24 (3H, d, J=6.5 Hz, CH_3), 3.17-3.21 (2H, overlapping 2 sets of dd, J=12.5, 4.8, 8.3 Hz, H_2CS), 3.48 (3H, s, OCH_3), 3.88 (1H, dd, J=4.8, 8.3 Hz, HCN), 4.10 (2H, d, J=1.7 Hz, H_2CPh), 4.30 (1H, q, J=6.6 Hz, HCO), 7.21-7.33 (5H, m, Ph); ^{13}C NMR (300 MHz, THF-d_8) δ: 18.0 (CH_3), 29.9 (CH_2), 40.6 (CH_2), 52.7 (CH), 54.6 (CH_3), 64.9 (HC), 96.1 (C), 124.5 (C=C), 125.2 (C=C), 128.0 (CH), 129.1 (CH), 130.1 (CH), 137-8 (C, Ph carbons), 162.4 (C=O), 163.9 (C=O); MS: 381 (M^+, 2), 353 (M^+-28, 3), 337 (M^+-44, 5), 309 (M^+-72, 8), 293 (M^+-88, 1); HRMS for $C_{16}H_{19}NO_3S_2$ (M^+-44) calcd 337.0805, found 337.0784.

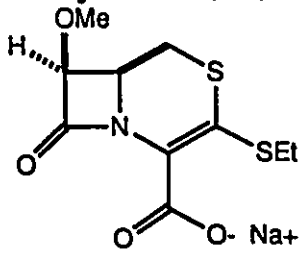
(+)-3-Benzylthio-7-(R)-hydroxyethyl-1-dethia-2-thia-3-cephemcarboxylic acid (38)



This compound was obtained from **81** as a yellowish white solid in 21% yield; mp 155-156 °C (decomp), $[\alpha]_D^{22}$ +21.2° (*C* 1.9, MeOH),

recrystallization from aq MeOH (2-3 drops of water per mL); IR: 3371 (OH, broad), 1758 (C=O) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ: 1.27 (3H, d, J=6.3 Hz, CH_3), 3.06 (1H, dd, J=2.4, 6.4 Hz, CHCO), 3.15 (1H, dd, J=12.4, 10.1 Hz, CH_2S), 3.41 (1H, dd, J=3.3, 12.4 Hz, CH_2S), 3.79-3.84 (1H, m, HCN), 4.12 (2H, s, CH_2Ph), 4.16 (1H, q, J=6.5 Hz, CH_3CHO), 7.24-7.38 (5H, m, Ph); ^{13}C NMR (300 MHz) δ: 22.3 (CH_3), 32.7 (CH_2), 40.3 (CH_2), 49.5 (CH), 65.3 (CH), 65.9 (CH), 128.2 (CH), 129.3 (CH), 130.1 (CH) and 137.8 (C) (Ph carbons), 162.5 (C=O), 165.4 (C=O); MS: 352 (M^++1, 25), 337 (M^++1-15, 0.5), 324 (M^++1-28, 0.6), 308 (M^++1-44, 89), 293 (308^+-15, 1).

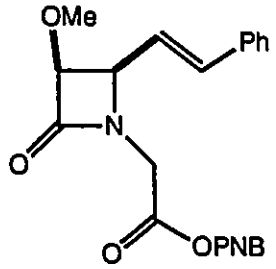
Sodium 3-ethylthio-7-methoxy-1-dethia-2-thia-3-cephemcarboxylate (39)



The compound **94** (0.12 g, 0.292 mmol) was dissolved in 30 mL of THF and 30 mL of EtOH and hydrogenated in presence of 50 mg of Pd-C (10%) at 14 psi. Tlc after 10 h showed the presence of starting material. An additional 20 mL of EtOH and 150 mg of catalyst were added and hydrogenation was continued at 30 psi for 3 h. The mixture was filtered through a celite pad and concentrated in vacuum. The yellowish foam was treated with 1 eq of $NaHCO_3$ (based on starting material) in 10 mL of water. The aq layer was washed twice with EtOAc (10 mL each) and lyophilized to give a crude sodium salt. Purification by reverse phase flash column chromatography (10% CH_3CN in H_2O) gave 45 mg (56%) of **39** as a white powder; mp 190-191 °C (decomp);

IR: 1752 (C=O), 1610 (COO^-) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ: 1.26 (3H, t, J=7.4 Hz, CH_3), 2.86-2.94 (2H, overlapping q, J=7.3 Hz, SCH_2CH_3), 3.20 (1H, dd, J=12.5, 9.6 Hz, CH_2S), 3.29 (1H, dd, J=12.5, 3.7 Hz, CH_2S), 3.50 (3H, s, OCH_3), 4.05 (1H, ddd, J=3.6, 4.5, 9.6 Hz, HCN), 4.98 (1H, d, J=4.5 Hz, HCC=O); ^{13}C NMR (300 MHz, D_2O) δ: 13.6 (CH_3), 27.5 (CH_2S), 28.3 (CH_2S), 51.8 (CH_3O), 58.8 (HCN), 85.0 (HCC=O), 115.8 (C=C), 165.0 (C=O), 167.9 (C=O); MS (for free acid): 275 (M^+, 1), 247 (M^+-28, 4), 231 (M^+-44, 16), 203 (M^+-72, 22); HRMS for $C_{10}H_{13}NO_4S_2$ calcd 275.0305, found 275.0296.

p-Nitrobenzyl 3-methoxy-4-cinnamyl-2-azetidinon-1-yl-acetate (88)

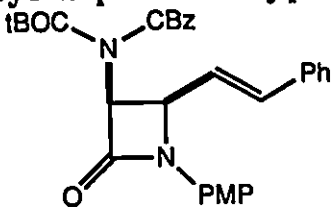


p-Nitrobenzyl glycine (7.5 g., 0.036 mol) and cinnamaldehyde (5.1 g, 0.039 mol) in 200 mL of CH_2Cl_2 was stirred with excess of anhyd $MgSO_4$ for 1 h. [Longer reaction time yielded a poor quality imine.] The imine[37] solution was quickly filtered into a dry flask containing 1.5 g of 4Å mol. sieves and cooled to -78 °C under N_2. Et_3N (6.5 mL, 0.047 mol) was added by syringe and an additional 50 mL of CH_2Cl_2 was introduced to dissolve imine. Methoxyacetyl chloride (3.5 mL, 0.037 mol) in 20 mL of CH_2Cl_2 was added dropwise over 15 min and the solution was allowed to slowly warm to 25 °C. After 5 h, 100 mL of 10% HCl was added and resulting layers separated. The crude product,

[37] Costerousse, G.; Cagniant, A.; Didierlaurent, S.; Proust, D.; Teusch, G. *Bull. Soc. Chim. Fr.* **1989**, 830.

obtained *via* standard workup procedure, was purified by repeated column chromatography (1:2 EtOAc:hexanes) to give 3.0 g (18%) of **88** as a yellow oil which solidified after a week; mp 102-103 °C; IR: 1750-1770 (broad, C=O), 1520 and 1350 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 3.44 (3H, s, OCH_3), 3.79 (1H, d, J=18.2 Hz, NCH_AH_BCOOR), 4.25 (1H, d, J=18.4 Hz, NCH_BH_ACOOR), 4.49 (1H, dd, J=9.2, 4.4 Hz, HCN), 4.70 (1H, d, J=4.4 Hz, HC-C=O), 5.20 (2H, s, CH_2PNB), 6.20 (1H, dd, J=15.9, 9.2 Hz, HC=C), 6.66 (1H, d, J=15.9 Hz, C=CHPh), 7.24-7.46 (7H, m, Ph and PNB), 8.13 (2H, d, J=18.3 Hz, PNB); MS: 396 (M^+, 3), 366 (M^+-30, 5), 325 ($imine^+$+1, 26), 235 (M^+-161, 1), 160 (M^+-236, 89); HRMS for $C_{21}H_{20}N_2O_6$ calcd 396.1318, found 396.1320.

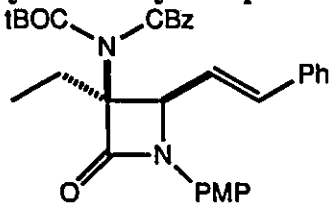
(3-N-carbobenzyloxy, N-t-butyloxycarbonyl)amino-4-cinnamyl-1-p-methoxyphenyl-2-azetidinone (104)



$(tBOC)_2O$ (5.66 g, 26.0 mmol) was added dropwise to the solution of azetidinone **103** (7.40 g, 17.3 mmol), 200 mg of DMAP and TEA (4.81 mL, 34.6 mmol) in 30 mL of DMF at 25 °C. The reaction mixture was stirred for 18 h. Usual work up using EtOAc as a solvent and purification by column chromatography (1:2 EtOAc:hexanes) gave 830 g (91%) of **104** as a yellowish oil; ^1H NMR (200 MHz) δ: 1.38 (9H, s, t-Bu), 3.74 (3H, s, OCH_3), 4.84 (1H, dd, J=7.9, 5.7 Hz, HCN), 5.53 (1H, d, J=5.6 Hz, HC-3), 5.18 (2H, s, CH_2Ph), 6.25 (1H, dd, J=8.0, 6.2 Hz, *H*C=CHPh), 6.67 (1H, d, J=16.2 Hz, HC=C*H*Ph), 6.81 (2H, d, J=9.1 Hz, PMP), 7.20-7.30 (5H, broad s, Ph), 7.37 (2H, d, J=9.1 Hz, PMP); MS(CI): 529 (M^++1, 7), 473

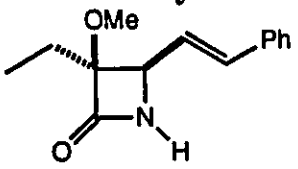
(M^++1-56, 2), 429 (M^++1-56-44, 100), 385 (429$^+$-44, 16), 324 (473$^+$-149, 10).

(3-N-carbobenzyloxy, N-t-butyloxycarbonyl)amino-4-cinnamyl-3-ethyl-1-p-methoxyphenyl-2-azetidinone (109)



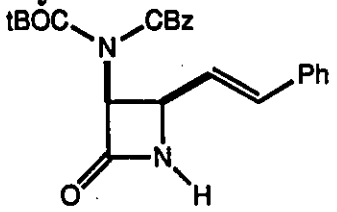
A solution of $(tBOC)_2O$ (6.00 g, 26.1 mmol) in 40 mL of THF was added dropwise to the mixture of azetidinone **108** (8.0 g, 17.5 mmol), 1 g of 4 Å mol. sieves, 20 mL of dry DMF and 4.90 mL (35 mmol) of TEA. The reaction misture was refluxed for 3 h. [The method described for **104** can be applied but unreacted starting material was recovered sometimes under those conditions.] Purification by column chromatography (1:6 EtOAc: hexanes) yielded 5.1 g (52%) of **109** as a yellowish oil; ^{1}H NMR (200 MHz) δ: 1.09 (3H, t, J=7.5 Hz, CH_3CH_2), 1.27 (9H, s, t-Bu), 2.01-2.22 (1H, m, CH_2CH_3), 2.50-2.65 (1H, m, CH_2CH_3), 3.74 (3H, s, OCH_3), 4.51 (1H, d, J=7.0 Hz, HCN), 5.01 (2H, apparent d, J could not be calculated, CH_2Ph), 6.25 (1H, dd, J=16.1, 7.0 Hz, *H*C=CHPh), 6.70 (1H, d, J=16.2 Hz, HC=C*H*Ph), 6.80 (2H, d, J=8.8 Hz, PMP), 7.11-7.27 (10H, m, Ph), 7.38 (2H, d, J=8.8 Hz, PMP); MS: 457 (M^++1-100, 7), 413 (457$^+$-44, 1), 349 (M^++1-100-108, 64), 238 (imine$^+$+1, 2), 149 (M^+-408, 100).

4-Cinnamyl-3-ethyl-3-methoxy-2-azetidinone (71)



A solution of azetidinone **45** (6.50 g, 19.3 mmol) in 250 mL of MeCN was cooled to -25 °C to -30 °C. [Some material precipitated out after 10 min but the procedure was continued without further addition of the solvent.] CAN (32 g, 58.4 mmol) in 60 mL of ice-cold water was added dropwise over 20 min. The initial greenish black color turned yellow and at the end of the reaction time, the homogeneous solution was brown. Usual workup using ethyl acetate for extraction gave a yellow solid which on trituration with ether gave the β-lactam, **71**, as a white solid (2.30 g, 52%); mp 102-103 °C; IR: 1760 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 1.03 (3H, t, J=7.4 Hz, CH_3CH_2), 1.84-2.05 (2H, m, CH_2CH_3), 3.46 (3H, s, OCH_3), 4.10 (1H, d, J=7.0 Hz, HCN), 6.25 (1H, broad s, NH), 6.29 (1H, dd, J=8.6, 16.0 Hz, *H*C=CHPh), 6.54 (1H, d, J=15.9 Hz, HC=C*H*Ph),), 7.23-7.41 (5H, m, Ph); MS: 231 (M^+, 13), 216 (M^+-15, 36), 188 (M^+-43, 7), 132 (imine$^+$+1, 66).

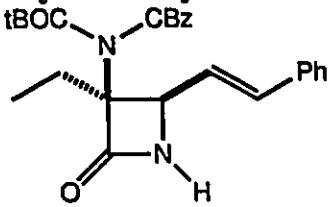
3-(N-carbobenzyloxy, N-t-butyloxycarbonyl)-amino-4-cinnamyl-2-azetidinone (105)



The azetidinone **104** (5.00 g, 9.47 mmol) was treated with CAN (15.60 g, 28.5 mmol) as described above. Purification of the crude product by column chromatography (1:2 EtOAc:hexanes) yielded 2.30 g (59%) of **105** as a brown oil; ^1H NMR (200 MHz) δ: 1.37 (9H, s, t-Bu),

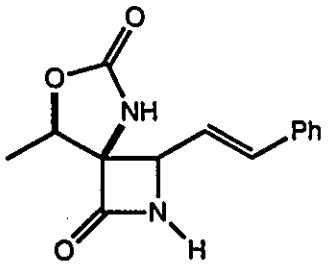
4.52 (1H, m, HCN), 5.16 (2H, s, CH_2Ph), 5.43 (1H, dd, J=1.1, 5.5 Hz, HC-3), 6.11 (1H, broad s, NH), 6.14-6.26 (1H, dd, overlapping with NH, *H*C=CHPh), 6.51 (1H, d, J=16.1 Hz, HC=C*H*Ph), 7.21-7.28 (10H, broad s, and over-lapping m, Ph); MS(CI): 379 (M^++1-44, 1), 369 (M^++1-56, 2), 323 (M^++1-100, 96), 279 (323^+-44, 47), 215 (315^+-108, 39).

3-(N-carbobenzyloxy, N-t-butyloxycarbonyl)-amino-4-cinnamyl-3-ethyl-2-azetidinone (110)



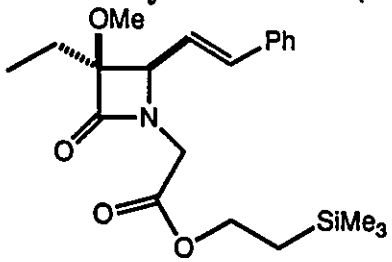
Azetidinone **109** (4.00 g, 7.33 mmol) was treated with CAN (7.60 g, 13.9 mmol) as described above to afford 1.94 g (60%) of **110** as a yellowish oil; chromatography solvent (1:3 EtOAc:hexanes); ^1H NMR (200 MHz) δ: 1.09 (3H, t, J=7.5 Hz, CH_3CH_2), 1.26 (9H, s, t-Bu), 2.00-2.18 (1H, m, CH_2CH_3), 2.44-2.59 (1H, m, CH_2CH_3), 4.20 (1H, d, J=6.7 Hz, HCN), 4.97 (1H, d, J=12.1 Hz, CH_AH_BPh), 5.05 (1H, d, J=11.8 Hz, CH_BH_APh), 5.93 (1H, broad s, NH), 6.23 (1H, dd, J=7.7, 16.1 Hz, *H*C=CHPh), 6.64 (1H, d, J=16.1 Hz, HC=C*H*Ph), 7.13-7.29 (10H, broad m, Ph); MS(CI): 451 (M^++1, 2), 423 (M^++1-28, 0.2), 409 (M^++1-42, 1), 407 (M^++1-44, 1), 395 (M^++1-57, 3).

4-Cinnamyl-3,3-spiro-[(4'-methyl-5,5-oxazolidinone)]-2-azetidinone (107)



Azetidinone **106** (800 mg, 2.20 mmol) in 50 mL of MeCN was reacted with CAN (1.2 g, 2.19 mmol) in 25 mL of H_2O as described above at 0 °C. Purification of the crude product by column chromatography afforded 216 mg (38%) of **107** as a colorless oil; ^1H NMR (200 MHz) δ: 1.57 (3H, d, J=6.6 Hz, CH_3CH), 4.25 (1H, d, J=6.8 Hz, HCN), 4.93 (1H, q, J=6.6 Hz, CHO), 6.13 (1H, dd, J=6.9, 15.9 Hz, *H*C=CHPh), 6.30 (1H, broad s, NH), 6.35 (1H, broad s, NH), 6.62 (1H, d, J=15.9 Hz, HC=C*H*Ph), 7.27-7.40 (5H, broad m, Ph); MS: 258 (M^+, 5), 215 (M^+-43, 4), 199 (M^+-59, 2), 170 (215^+-45, 2), 132 (M^+-126, 100); HRMS calcd for $C_{14}H_{14}O_3N_2$ 258.1001, found 258.0976.

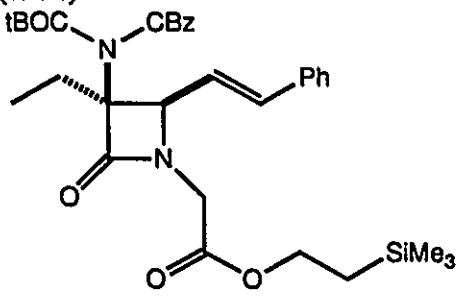
β-Trimethylsilylethyl 4-cinnamyl-3-ethyl-3-methoxy-2-azetidinon-1-ylacetate (66)



Compound **65** (507 mg, 2.19 mmol) and β-trimethylsilylethyl bromide (575 mg, 2.41 mmol) in 5 mL of DMF were added to the suspension of NaH (96 mg, 2.41 mmol) in 10 mL of DMF at 0 °C. The reaction mixture was stirred for 4 h. The reaction mixture was worked

up with EtOAc as a solvent and purified by column chromatography (1:9 EtOAc:hexanes) to yield 386 mg (45%) of the product **66** as a yellowish oil; ^{1}H NMR (200 MHz) δ: 0.00 (9H, s, TMS), 0.91-1.00 (2H, m, CH_2Si), 1.03 (3H, t, J=7.4 Hz, CH_3CH_2), 1.80-2.15 (2H, m, CH_2CH_3), 3.47 (3H, s, OCH_3), 3.58 (1H, d, J=18.0 Hz, CH_AH_BCOOR), 4.14-4.27 (4H, m, CHN, CH_BH_ACOOR, CH_2O), 6.24 (1H, dd, J=8.9, 16.0 Hz, *H*C=CHPh), 6.62 (1H, d, J=15.9 Hz, HC=C*H*Ph), 7.26-7.42 (5H, m, Ph); MS: 389 (M^+, 2), 361 (M^+-28, 1), 346 (M^+-43, 3), 331 (346$^+$-15, 5), 288 (M^+-101, 13).

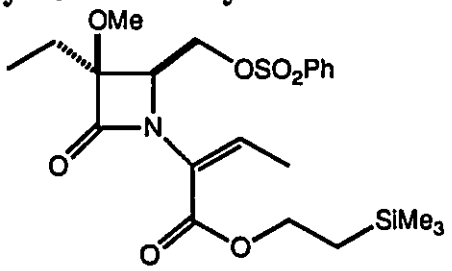
β-Trimethylsilylethyl [4-cinnamyl-3-ethyl-3-(N-t-butyloxycarbonyl, N-carbobenzyloxy)amino-2-azetidinon-1-yl]acetate (111)



Azetidinone **110** (930 mg, 2.07 mmol) was treated with β-trimethylsilylethyl bromide (540 mg, 2.26 mmol) as described above to yield 1.00 g (80%) of **111** as a yellow oil after purification by column chromatography (1:5 EtOAc:hexanes); ^{1}H NMR (200 MHz) δ: 0.00 (9H, s, TMS), 0.92-1.01 (2H, m, CH_2Si), 1.11 (3H, t, J=7.5 Hz, CH_3CH_2), 1.28 (9H, s, t-Bu), 2.14-2.32 (1H, m, CH_2CH_3), 2.49-2.68 (1H, m, CH_2CH_3), 3.50 (1H, d, J=18.0 Hz, CH_AH_BCOOR), 4.12-4.26 (2H, m, CH_2O), 4.34 (1H, d, J=18.0 Hz, CH_BH_ACOOR), 4.37 (1H, d, J=7.9 Hz, HCN), 5.03 (2H, apparent d, J=2.2 Hz, CH_2Ph), 6.12 (1H, dd, J=7.6, 16.2 Hz, *H*C=CHPh), 6.62 (1H, d, J=16.2 Hz, HC=C*H*Ph), 7.17-7.36 (5H, m, Ph); MS(CI): 581 (M^++1-28, 8),

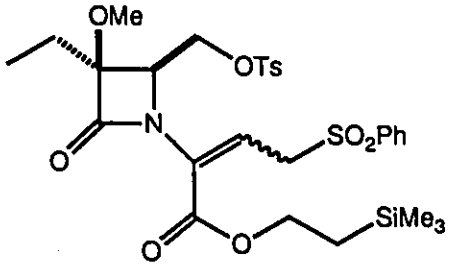
553 (M^++1-56, 21), 509 (M^++1-100, 44), 481 (509$^+$-28, 66), 465 (481$^+$-15, 5).

β-Trimethylsilylethyl [2'-(4-benzenesulfonyloxymethyl-3-ethyl-3-methoxy-2-azetidinon-1-yl)]but-2'-enoate (30)



Compound **29** (82 mg, 0.18 mmol) was treated with 1.1 eq. of LDA. The resultant anion was quenched with excess acetaldehyde. The reaction mixture was stirred for 18 h (-78 °C to 25 °C). Usual work up and purification of the crude product by small column chromatography (1:10 EtOAc:hexanes) afforded 48 mg (55%) of **30**; ^{1}H NMR (200 MHz) δ: 0.02 (9H, s, TMS), 0.86-1.03 (5H, m, CH_3, CH_2Si), 1.72 (3H, d, J=7.1 Hz, CH_3CH), 1.70-1.84 (1H, m, CH_2CH_3), 1.97-2.05 (1H, m, CH_2CH_3), 3.39 (3H, s, OCH_3), 4.05-4.28 (5H, m, OCH_2, OCH_2, CHN), 6.79 (1H, q, J=7.2 Hz, $CHCH_3$), 7.48-7.64 (3H, m, Ph), 7.81-7.85 (2H, m, Ph); MS(CI): 456 (M^++1-28, 27), 428 (M^++1-56, 5), 328 (428$^+$-100, 7), 270 (428$^+$-158, 100), 226 (270$^+$-44, 64).

β-Trimethylsilylethyl 2'-(4-benzenesulfonyloxymethyl-3-ethyl-3-methoxy-2-azetidinon-1-yl)-4'-benzenesulofnylbut-2'-enoate (34).

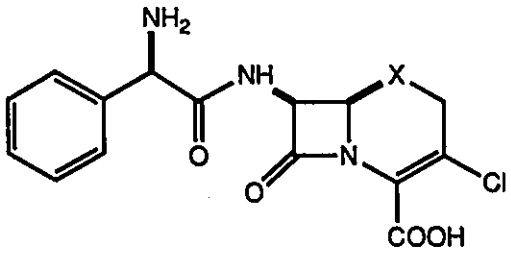


The anion of compound **31** was prepared as described above and quenched with a solution of sulfone at -78 °C. The reaction mixture was stirred while allowing it to warm to room temperature. Usual work up and purification of the crude product by column chromatography (1:6 EtOAc:hexanes) yielded 80 mg (51%) of **34**; ^{1}H NMR (200 MHz, crude sample) δ: 0.02 (9H, s, TMS), 0.96-1.05 (2H, m, CH_2Si), 1.65-1.72 (1H, m, CH_2CH_3), 1.73-2.02 (1H, m, CH_2CH_3), 2.42 (3H, s, CH_3Ph), 3.36 (3H, s, OCH_3), 3.88-4.27 (6H, m, CH_2O, CH_2OTs, CH_2SO_2Ph), 4.37 (1H, dd, J=4.4, 7.7 Hz, CHN), 6.42 (1H, t, J=7.2 Hz, $CHCH_2SO_2Ph$), 7.32 (2H, d, J=8.0 Hz, Tol), 7.48-7.63 (3H, m, Ph), 7.71 (2H, d, J=8.4 Hz, Ph), 7.86 (2H, d, J=8.3 Hz, Tol).

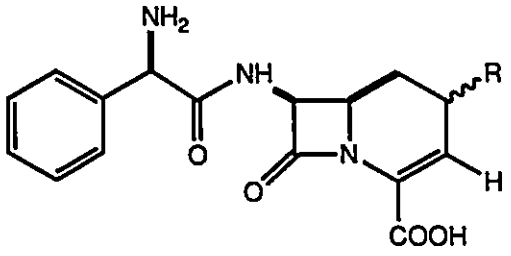
CHAPTER 3: CARBACEPHEMS

Structure activity studies

Christensen and collaborators were the first to synthesize carbacephems (complete cephalosporin mimics) and found that the replacement of sulfur in cephems by a methylene group did not lead to a significant loss in antibiotic activity.[1] Subsequent work led to carbacefachlor **2**, also known as loracarbef[2] (LY163892 or KT3777), which is a potential clinical candidate as it possesses a broad spectrum of activity against microbial pathogens. This compound also has good chemical stability because no decomposition products were observed when it was incubated at 37 °C for 22 h at physiological pH.



1 X=S, cefachlor and
2 X=CH_2, loracarbef



3 R=H

Hirata discovered that a conventional C-3 substituent, present in most of cephems, is not neccessary for useful biological activity in carbacephems. Interestingly, he found that enantiopure compound **3** has better activity than its racemate by a surprisingly large factor of 4 or greater.

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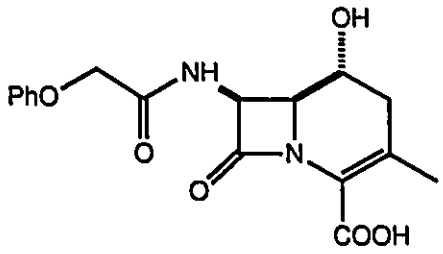
[1] (a) Guthikonda, R. N.; Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7584. (b) Firestone, R. A.; Fahey, J. L.; Maciejewicz, N. S.; Patel, G. S.; Christensen, B. G. *J. Med. Chem.* **1977**, *20*, 551.

[2] Matsukuma, I.; Yoshiiye, S.; Mochida, K.; Hashimoto, Y.; Sato, K.; Okachi, R.; Hirata, T. *Chem. Pharm. Bull.* **1989**, *37*, 1239. and references therein.

Colvin *et. al.* prepared the 1-α-hydroxy analog **4** which has a high infrared frequency for its β-lactam carbonyl peak and an *h* value 0.204 Å; nevertheless it was found to be inactive.[3] This result indicated that the IR and *h* values are not reliable indices of antibiotic activity (see chapter 1 for discussion of these terms in relation to the activity of the β-lactams).



4

Hirata and colleagues also prepared several carbacephems having substituents such as methyl, azido, hydroxy etc. at C-2. The 2-α–methyl isomer **5** had higher activity (comparable to **3**) than 2-β-methyl analog **6**.[4] The 2-azido-carbacephem **7** had a minimum inhibitory concentration (MIC) of 1.56 μg/mL against *Staphylococcus aureus* 269-P.[5] The 2-hydroxy carbacephem **10** having an amino-4-thiazolyl-2-(Z)-methoxyiminoacetamido side chain at the C-7 position, showed broad spectrum of Gram-negative antibiotic activity including the inhibition of *Pseudomonas aeruginosa*.[6] This activity was lacking in **9**.

---

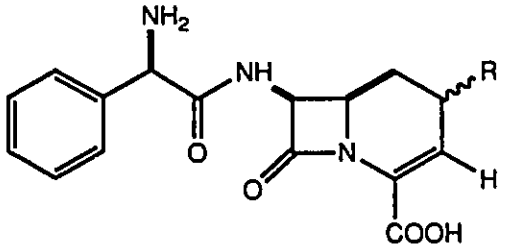
[3] Bremner, J. A. S.; Colvin, E. W.; Gallacher, G.; MacLeod, A. *Tetrahedron Lett.* **1983**, *24*, 3783.

[4] Ogasa, T.; Saito, H.; Hashimoto, Y.; Sato, K.; Hirata, T. *Chem. Pharm. Bull.* **1989**, *37*, 315.

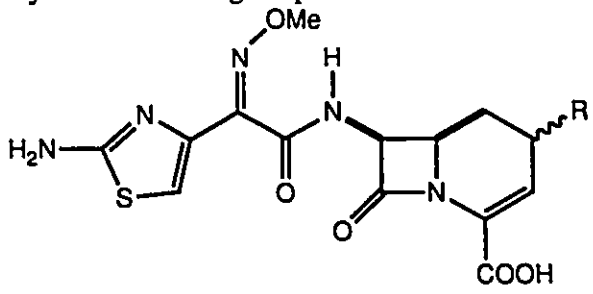
[5] Hirata, T.; Sato, A.; Kobayashi, S. *Chem. Abs.* **1983**, *99*, 158124x. Eur. Pat. appl. EP 82, 501.

[6] Hirata, T.; ogasa, T.; Saito, S.; Kobayashi, S.; Sato, A.; Ono, Y.; Hashimoto, Y.; Takasawa, S.; Sato, K.; Mineura, K. In *21st Intersci. Conf. On Antimicrob. Agents Chemother.*; **1981**; Abst. No. 557.

Gram-negative activity was reduced when the methoxyimino group of the side chain of **9** was substituted by an amino group.[7]

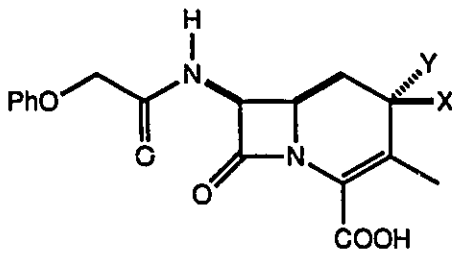


5 R=α-CH_3; **6** R=β-CH_3
7 R=N_3; **8** R=OH

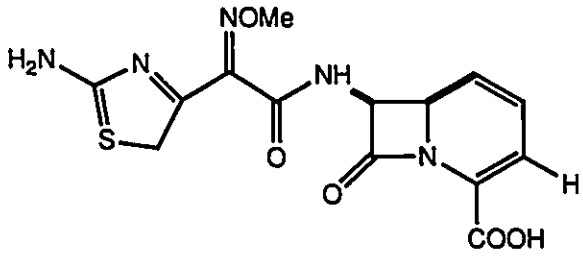


9 R=H, KT 3767
10 R=OH, KT 3937

The results obtained by Doyle's group indicated that an electron withdrawing group at C-2 such as an oxo function **11**, maintained the activity relative to the cephem counterpart but when this group was reduced and converted to functional groups such as acetoxy in **12**, the antibacterial activity was reduced.[8]



11 X+Y=O, **12** X=OAc, Y=H



13

Structural modifications at both C-1 and C-2 have also been reported. Hirata *et. al.* synthesized the 1,2-dehydrocarbacephem **13** expecting that the added strain would result in a more reactive β-lactam carbonyl group. Although infrared frequencies were comparable

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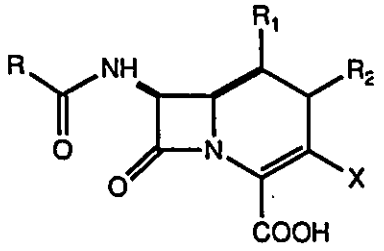
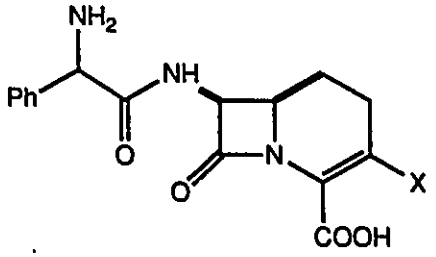
[7] Ikota, N.; Shibata, H.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 3299.

[8] Doyle, T. W.; Martel, A.; Douglas, J. L.; Belleau, B.; Conway, T. T.; Ferrari, C. F.; Harning, D. E.; Lim, G.; Menard, M.; Morris, L. R.; Luh, B. *Can. J. Chem.* **1980**, *58*, 2508.

or higher than the corresponding carbacephems, the antibacterial activity of **13** was poor. Hence they inferred that the planarity of the six membered ring caused by the additional double bond is not favorable for antibiotic activity.[9] The 1,2-substituted analogs such as 1,2-dihydroxy **14**, 1,2-chlorohydrin **15** or 1,2-bromohydrin **16** derivatives were less active than the parent 1,2-unsubstituted compound.[10]





14 R_1=OH, R_2=OH, **15** R_1=Cl, R_2=OH, **16** R_1=Br, R_2=OH

17 X=STetrazolyl, **18** X=OCH_3
19 X=H, **20** X=CH_2STetrazolyl

The introduction of 3-sulfur substituents containing a heterocyclic ring such as 4-pyridyl or N-methyltetrazolyl group resulted in an improvement in antibiotic activity compared to 3-H or 3-Cl compounds. An increase in the chemical stability of **17** compared to the corresponding cephems was also noted.[11] Other substituents at this position have also been reported. Compound **18** had lower activity than **19** whereas, the compound **20** had biological activity comparable to **19**. The methyl group in compound **22** lowered the activity compared to **21**

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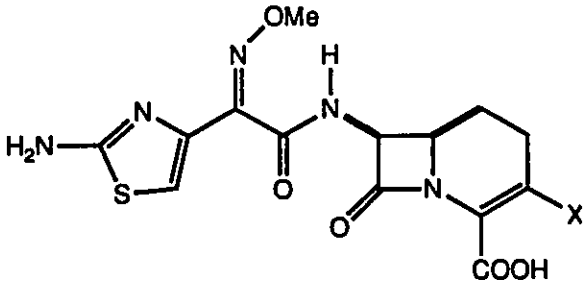
[9] Saito, H.; Matsushima, H.; Shiraki, C.; Hirata, T. *Chem. Pharm. Bull.* **1989**, *37*, 275.
[10] Saito, H.; Suzuki, F.; Hirata, T. *Chem. Pharm. Bull.* **1989**, *37*, 2298.
[11] Mochida, K.; Ogasa, T.; Shimada, J.; Hirata, T.; Sato, K.; Okachi, R. *J. Antibiotics* **1989**, *XLII*, 283.

while the tetrazolylthiomethyl group retained the activity in **23**.[12]



21 X=H, **22** X=CH_3, **23** X=CH_2STetrazolyl, **24** X=SO_2R

The introduction a 3-sulfonyl group as in compound **24** reduced the Gram-negative activity and the chemical stability.[13] In contrast, a quaternary nitrogen group at this carbon gave compound **25** which possesed good biological activity and β-lactamase stability.[14] The 3-cyclopropyl derivative **26** was less stable compared to the thia congener.[15] The introduction of various alkyl groups and carboxyalkyl groups at C-3 position as in case of **27** has been reported.[16] They did not report biological activities in this paper. The 3-carboxyalkyl-1-carbacephems were chemically and biologically more stable and had potent antimicrobial activity.[17]

---

[12] Uyeo, S.; Ono, H. *Chem. Pharm. Bull.* **1980**, *28*, 1563.

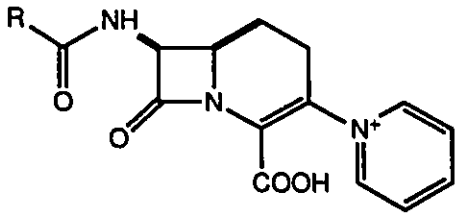
[13] Crowell, T. A.; Halliday, B. D.; McDonald, J. H., III; Indelicato, J. M.; Pasini, C. E.; Wu, E. C. Y. *J. Med. Chem.* **1989**, *32*, 2436.

[14] Cook, G. K.; McDonald J. H., I.; Alborn, W., JR.; Boyd, D. B.; Eudaly, J. A.; Indelicato, J. M.; Johnson, R.; Kasher, J. S.; Pasini, C. E.; Preston, D. A.; Wu, E. C. Y. *J. Med. Chem.* **1989**, *32*, 2442.

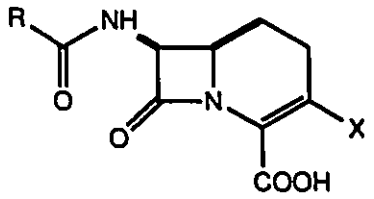
[15] Spry, D. O.; Snyder, N. J.; Kasher, J. S. *J. Antibiotics* **1989**, *XLII*, 1653.

[16] Cook, G. K.; Hornback, W. J.; Jordan, C. L.; McDonald III, J. H.; Munroe, J. E. *J. Org. Chem.* **1989**, *54*, 5828.

[17] Eudaly, J. A.; Hornback, W. J.; Johnson, R. L.; Jordan, C. L.; Munroe, J. E.; Wright, W. E.; Wu, C. Y. E. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; P. H. Bently and R. Southgate, Ed.; The Royal Society of Chemistry: London (England), **1989**; p 333.

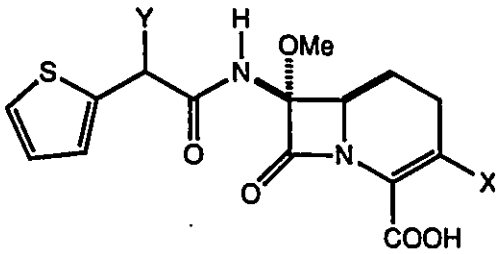


25

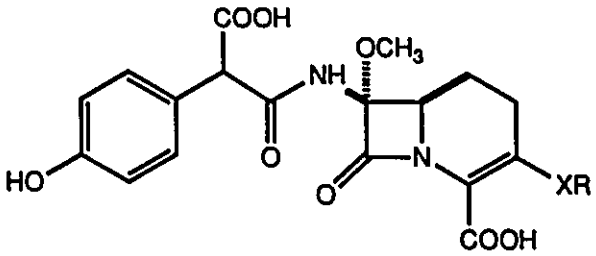


26 X= cyclopropyl
27 X=alkyl or COOR

Some 7,7-disubstituted carbacephems have been described by Firestone[18] (**28-29**) and by Ueyo[19] (**30-31**). These compounds typically have a 7-methoxy function in additon to a normal amide nitrogen substituent. The difference in biological activity between these carbacephems and 7-demethoxy analogs was not reported by these authors.



28 X=CH_3, Y=H
29 X=CH_2OCONH_2, Y=H
30 X=CH_2OCONH_2,, Y=COOH



31 XR=CH_2STetrazolyl, Y=H

Synthetic strategies

An amazing variety of strategies for fusing the pre-existing β-lactam ring in order to generate carbacephems have been reported. These will be briefly discussed below. In many instances many

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[18] Firestone, R. A.; Fahey, J. L.; Maciejewicz, N. S.; Patel, G. S.; Christensen, B. G. *J. Med. Chem.* **1977**, *20*, 551.
[19] Uyeo, S.; Ono, H. *Chem. Pharm. Bull.* **1980**, *28*, 1563.

examples exist using a particular strategy, but only the key reaction is described. The structures of the compounds are generalized to simplify presentation. Methods which gave carbacephe(a)ms without a 4-carboxyl function are not discussed.[20]

1) Rhodium carbenoid insertion

This method, developed by Merck chemists, is by far the best method of preparing carbacephems. The ease of reaction (both in terms of cyclization yields and purification of the product) and high catalytic turnover are the appealing features of this procedure. A variety of methods leading to the cyclization precursors has been reported. The reaction is presumed to proceed through a rhodium carbenoid species which undergoes the insertion reaction into the NH bond resulting in bicyclic compounds.[21] [Cyclizations using this methodology which lead to carbapenems will be described in next chapter.]

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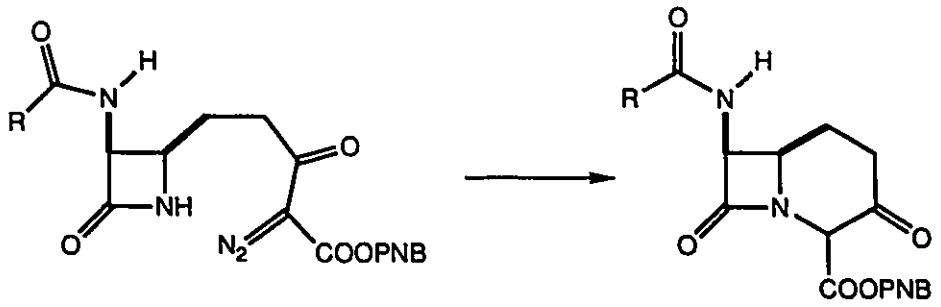
[20] (a) Mori, M.; Higuchi, Y.; Kagechika, K.; Shibasaki, M. *Heterocycles* **1989**, *29*, 853. (b) Izawa, K.; Nishi, S. *Chem. Abs.* **1986**, *104*, 109353j. (c) Mori, M.; Kanda, N.; Ban, Y. *J. Chem. Soc. Chem. Commun.* **1986**, 1375. (d) Joyeau, R.; Kobaiter, R.; Sadet, J.; Wakselman, M. *Tetrahedron Lett.* **1989**, *30*, 337. (e) Joyeau, R.; Yadav, L. D. S.; Wakselman, M. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1899. (f) KeshavaMurthy, K. S.; Hassner, A. *Tetrahedron Lett.* **1987**, *28*, 97. (g) Sakamoto, M.; Watanabe, S.; Fujita, T.; Tohnishi, M.; Aoyama, H.; Omote, Y. *J. Chem. Soc. Perkin Trans. 1* **1988**, 2203. (h) Miyake, M.; Tokutalee, N.; Kishisawe, M. *Synth. Commun.* **1984**, *14*, 353. (i) Burgemeister, T.; Dannhart, G.; Mach-Bindl, M. *Chem. Abs.* **1989**, *110*, 23596.

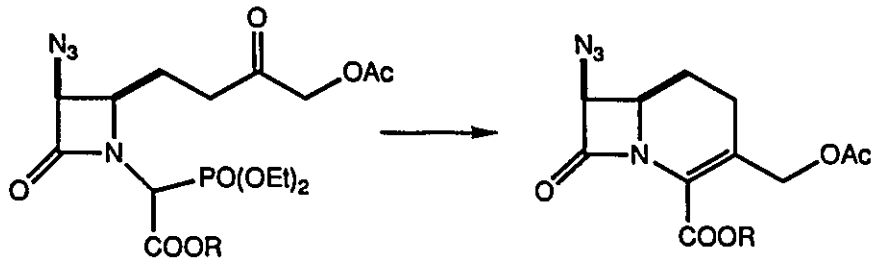
[21] Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193.



32 33

2) Intramolecular Wittig reaction

The annulation *via*. intramolecular Wittig type reactions was also developed by Merck chemists in their synthesis of carbacephems.[22] In most of the cases the yields of bicyclic compounds obtained in this type of cylization are modest.



34 35

The cyclization precursor **34** was prepared in 30% yield by 2+2 ketene imine cycloaddition using the imine **36** and azidoacetyl chloride. The complete carbon skeleton and all functional groups required for the cyclization of the second ring were incorporated into the imine. However this cycloadditon reaction leading to the β-lactam ring is difficult for several reasons: (1) the imine is not conjugated with other double bonds thus making it unstable and difficult to handle and (2) the

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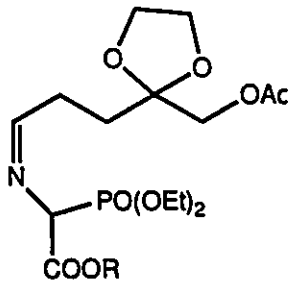
22 (a) Guthikonda, R. N.; Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7584. (b) Firestone, R. A.; Fahey, J. L.; Maciejewicz, N. S.; Patel, G. S.; Christensen, B. G. *J. Med. Chem.* **1977**, *20*, 551. (c) Finkelstein, J.; Holden, K. G.; Prechonock, C. D. *Tetrahedron Lett.* **1978**, *19*, 1629.

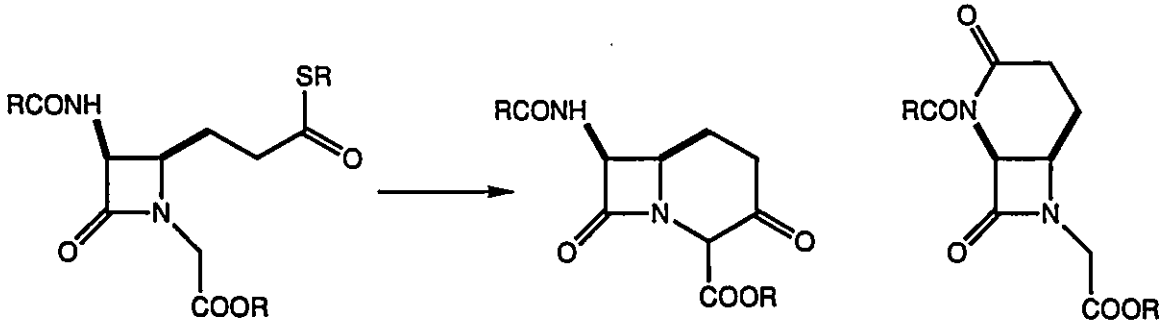
imine has enolizable protons, one of which could be lost and lead to the formation of an open chain enamide.



36

3) Enolate condensation reactions

Hatanaka utilized Dieckmann cyclization reactions in which thioesters are used as electrophilic carbonyl components to obtain carbacephems.[23] When one equivalent of LHMDS was used, cyclization occurred through the amide nitrogen to give **38a**. However use of 3 equivalents of LHMDS gave the desired bicyclic ketone **38** which has been elaborated to carbacephems. Jackson's and Wiegel's groups also carried out similar studies.[24]



37 **38** **38a**

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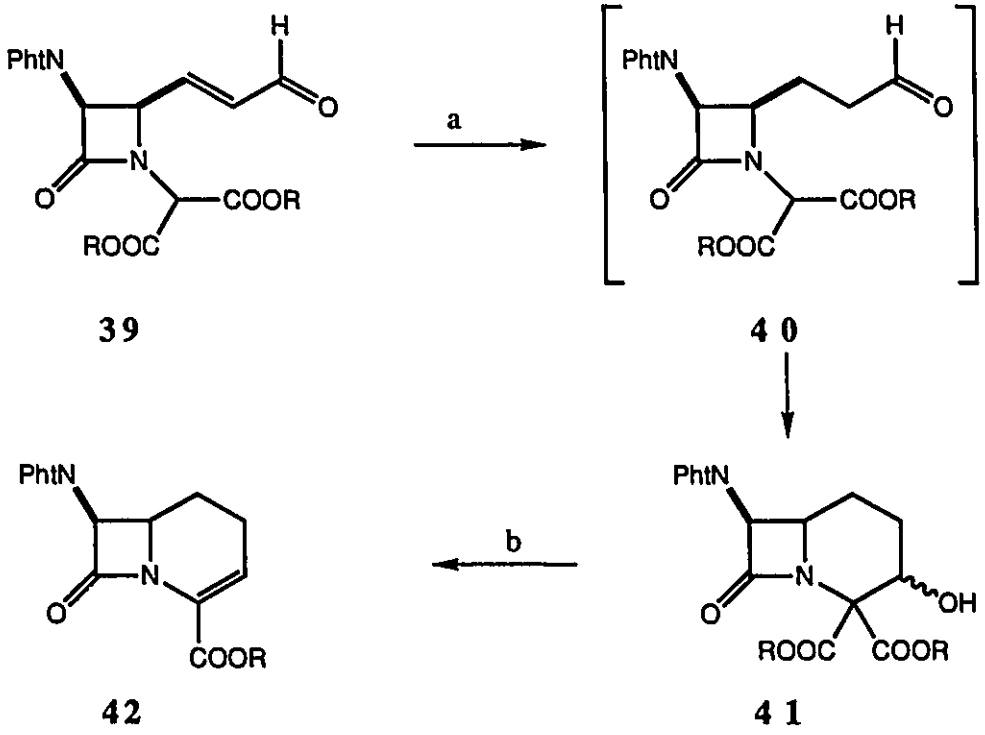
[23] Hatanaka, M.; Ichimaru, T. *Tetrahedron Lett.* **1983**, *24*, 4837.

[24] (a) Jackson, B. G.; Gardner, J. P.; Heath, P. C. *Tetrahedron Lett.* **1990**, *31*, 6317. (b) Frazier, J. W.; Staszak, M. A.; Wiegel, L. O. *Tetrahedron Lett.* **1992**, *33*, 857. (c) see also `Neyer, G.; Achat, J.; Danzer, B.; Ugi, I. *Heterocycles* **1990**, *30*, 863.

Hirata and Mochida generated the carbacephem ring system *via.* an intramolecular malonate condensation. The aldehyde **39**, upon reduction of the α,β-unsaturated double bond with H_2/Pd cyclized spontaneously to give **41**, which on decarboxylation-elimination reaction yielded the carbacephem intermediate **42**.[25]



a) H_2, Pd-C; b) MsCl, Pyridine, LiI

4) Radical Cyclization

Radical cyclizations have been extensively studied during past decade. It is therefore not surprising that such approaches have been applied to the syntheses of bicyclic β-lactams.[26] Due to the availability

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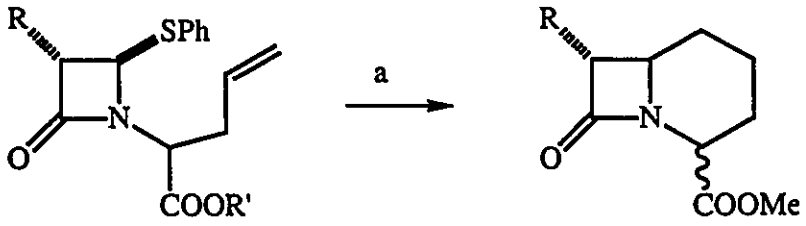
[25] Mochida, K.; Hirata, T. *Chem. Pharm. Bull.* **1988**, *36*, 3642.

[26] Kametani, T.; Chu, S. D.; Itoh, A.; Maeda, S.; Honda, T. *J. Org. Chem.* **1988**, *53*, 2683. see also: (a) Beckwith, A. L. J.; Boate, D. R. *Tetrahedron Lett.* **1985**, *26*, 1761. (b) Just, G.; Sacripante, G. *Can. J. Chem.* **1987**, *65*, 104. (a) Knight, J.; Parsons, P. J.; Southgate, R. *J. Chem. Soc. Chem. Commun.* **1986**, 78. (b) Knight, J.; Parsons, P. J. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1237.

of the 4-thiophenyl β-lactams and thus the possibility of generating a radical at that carbon these studies have focused on the generation of the key C1-C6 carbon-carbon bond in carbacephems. Carbacephams having 7-ethyl or 7-hydroxyethyl substituents have been prepared by this method in about 50% yield. Kametani and coworkers have noted that cyclization of **43** occurs preferentially *via.* the 6-endo route and not the more frequently encountered 5-exo pathway which would have resulted in 1-methylcarbapenams. These authors claimed that no carbapenams were formed during this reaction and rationalized this observation by acknowledging the severe strain in carbapenams compared to carbacephams. This reaction, when applied to the azetidinone having an acetylenic bond as a radical receptor, gave Δ^1-carbacephem in about 10% yield.

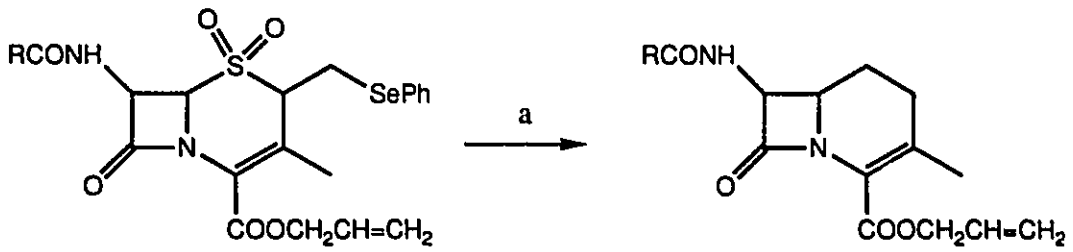


43 **44**

a) Bu_3SnH, AIBN

An unusual synthesis of the 3-methylcarbacephem **46** had been reported by Blaszczak.[27] The synthesis commenced with the treatment of the selenium compound **45** derived from a cephalosporin sulfone, wtih Bu_3SnH/AIBN at 100 °C.

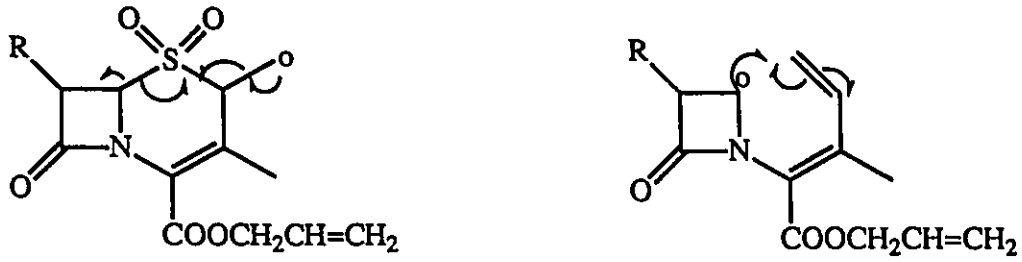
[27] Blaszczak, L. C. *Chem. Abs.* **1990**, *113*, 131868p. Eur. Pat. Appl. EP 359,540



45 46

a) Bu_3SnH, AIBN, 100 °C, diglyme

Presumably, this reaction condition generated the radical intermediate **47**, which after extrusion of sulfur dioxide, gave **48**. Subsequent 6-endo cyclization afforded the carbacephem **46**.



47 48

5) Wasserman tricarbonyl cyclization

The conversion of the tricarbonyl system **49** was treated with fluoride ion which led to desilylation and spontaneous cyclization to the bicyclic carbacephem nucleus which upon dehydroxylation with TMSI gave **50**.[28] The examples of failure during the rhodium carbenoid cyclization such as in penem synthesis has been shown in Chapter 2. Since a tricarbonyl compound can be obtained from a suitable β-ketoester which is also a key precursor to diazo compound, this method could be an alternative in those cases.

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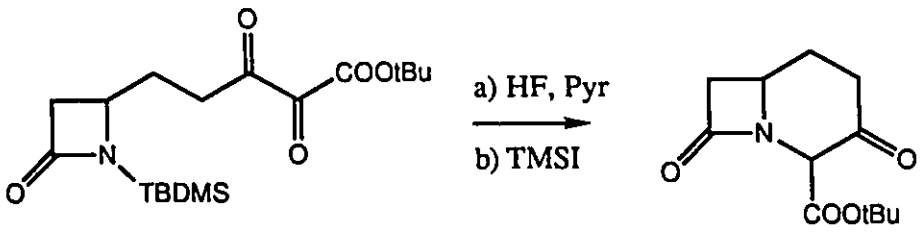
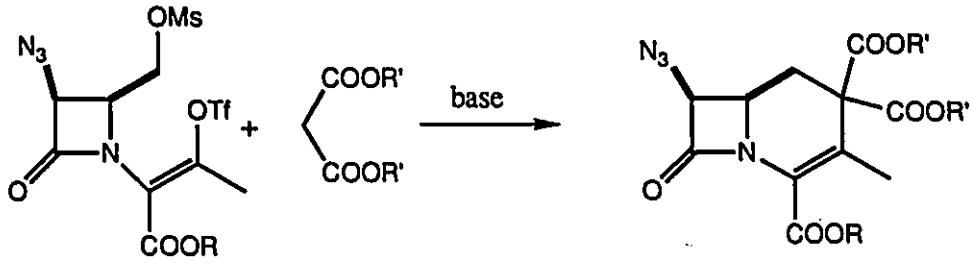
[28] Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3743.



49 **50**

6) 5+1 Cyclization

This method utilizes a malonate as a lynch pin to tie together the two carbons bearing good leaving groups in compound **51**. The complete sequence: Michael addition, elimination and intramolecular alkylation occurs in one pot.[29]



51 **52** **53**

The cyclization precursor **51** was prepared from **54** by a 2+2 cycloaddition reaction with the ketene derived from azidoacetyl chloride and subsequent transformation of the ketal to an enol triflate under standard conditions.

Doyle and coworkers have converted **53** to the Δ^2-carbacephem **55** by decarboxylative hydrolysis of ester groups. This conversion involves double decarboxylation to yield an allylic carbanion which preferentially protonates at the carbon α to the carboxyl group.

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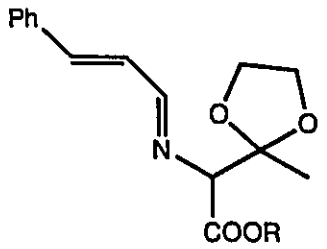
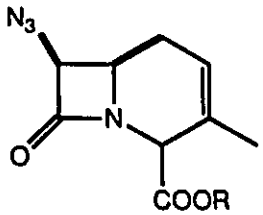
[29] (a) Doyle, T. W.; Conway, T. T.; Casey, M.; Lim, G. Can. J. Chem. 1979, *57*, 222. (b) Doyle, T. W.; Conway, T. T.; Lim, G.; Luh, B. *Can. J. Chem.* **1979**, *57*, 227. (c) Doyle, T. W.; Martel, A.; Luh, B. *Can. J. Chem.* **1979**, *57*, 614. (d) Doyle, T. W.; Martel, A.; Douglas, J. L.; Belleau, B.; Conway, T. T.; Ferrari, C. F.; Harning, D. E.; Lim, G.; Menard, M.; Morris, L. R.; Luh, B. *Can. J. Chem.* **1980**, *58*, 2508.

Compound **55** has been utilized in the preparation of C-2 functionalized carbacephems.



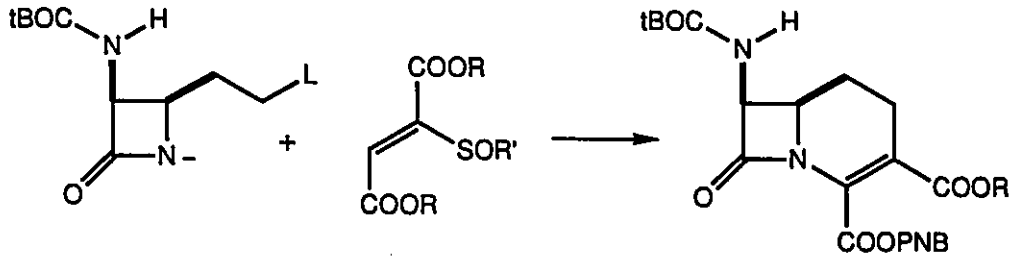
54



55

7) 4+2 Cyclization

Tandem Michael addition to the suitable receptor **56** and intramolecular alkylation of the resulting anion has been exploited by Munroe and collaborators.[30] During their studies only low yield of the bicyclic product **58** was obtained.



56 **57** **58**

They isolated a byproduct **60** which might have caused the reduction in yield. The formation of **60** can be rationalized by invoking the elimination of the sulfinate *via.* equilibration to the less stable anion **59.**

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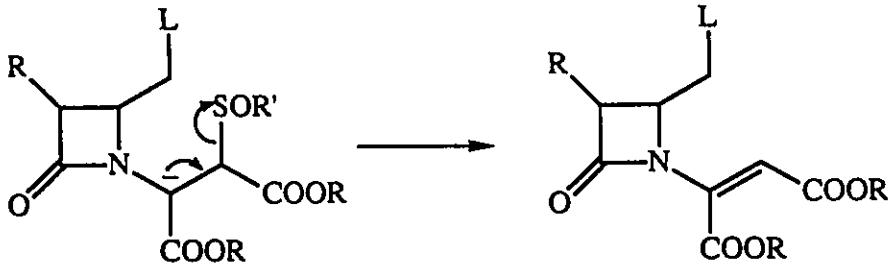
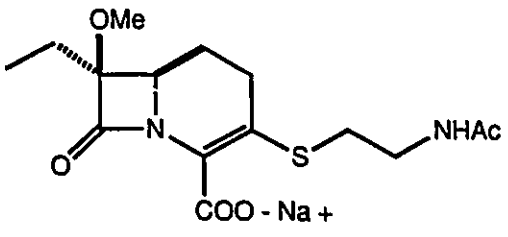
30 Eudaly, J. A.; Hornback, W. J.; Johnson, R. L.; Jordan, C. L.; Munroe, J. E.; Wright, W. E.; Wu, C. Y. E. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; P. H. Bently and R. Southgate, Ed.; The Royal Society of Chemistry: London (England), 1989; p 333.



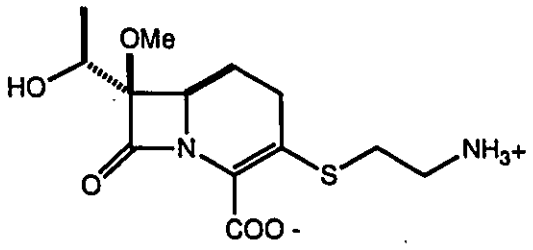
5 9 **6 0**

Carbacephem analogs 61 and 62

The preparation of the carbacephem analogs **61** and **62** which carry a 7-β-methoxy group in addition to either an ethyl or hydroxyethyl group typical of PS-5 or thienamycin antibiotics[31] respectively will be discussed in the following section. As mentioned in the introduction to this chapter the most important methodology[32] for the construction of the bicylic ring system of both carbapenems and carbacephems is the rhodium carbenoid insertion route developed by Cama and collaborators[33] during the preparation of oxapenams and extended to carbapenems by Ratcliffe[34] and coworkers at Merck.



61



62

Surprisingly, this cyclization procedure has not been applied to examples which carry a methoxy group at the carbon α to the β-lactam carbonyl in the final product.[35] Success in such cases is by no means

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[31] Ratcliffe, R. W.; Albers-Schonberg, G. In *Chemistry and Biology of β-Lactam Antibiotics*; R.W. Morin and M. Gorman, Ed.; Academic press: New York, **1982**; Vol. 2; p 227.

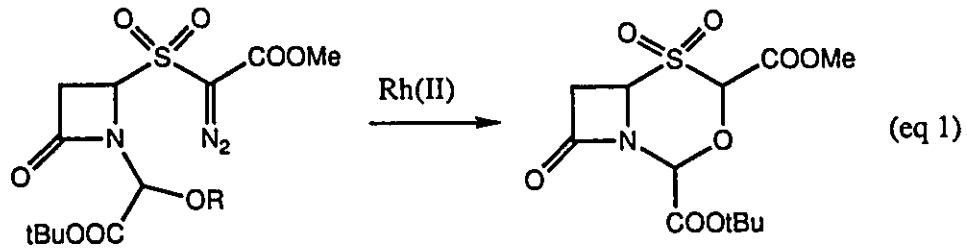
[32] see Chapter 2 page 23 for unsuccessful anionic 4+2 cyclization approach to carbacephems.

[33] Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1978**, *19*, 4233.

[34] Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.

[35] (a) Chu, D. T. W.; Hengeveld, J. E.; Lester, D. *Tetrahedron Lett.* **1983**, *24*, 139. (b) Foxton, P. M. W.; Mearman, R. C.; Newall, C. E.; Ward, P. *Tetrahedron Lett.* **1981**, *22*, 2497. (c) Watanabe, A.; Fukagawa, Y.; Ishikura, T.; Yoshioka, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2091. (d) Yoshioka, T.; Watanabe, A.; Isshiki, K.; Fukagawa, Y. *Tetrahedron Lett.* **1986**, *26*, 4335.

assured since intramolecular trapping of carbenoids by ether oxygen (eq 1) has been often observed and studied in considerable detail.[36]



(eq 1)

63 64

Successful rhodium carbenoid cyclizations have been reported in the synthesis of 1-methoxycarbapenem[37], 1-oxapena(e)m[38] and 1-oxacepham[39] nuclei. In these examples the ethereal oxygen is one or two carbons removed from the carbenoid centre. These results do not undermine the importance of the present study since the distance and stereochemical relationship of methoxy groups to the carbenoid center is quite different in the problem at hand. Nitrogen substituents, when present at these positions, have been shown to give mixed results. For example, the azido group interferes in the cyclization process as shown in the equation 2.[40]

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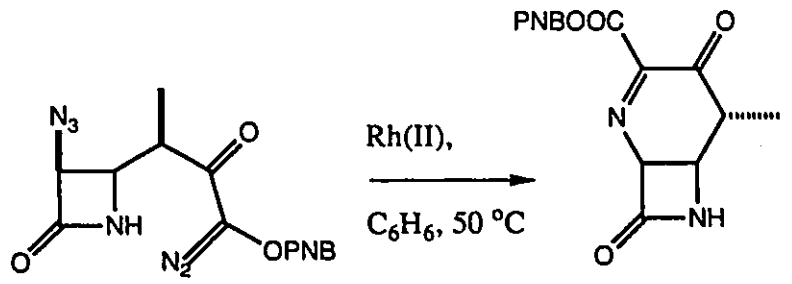
[36] (a) Taylor, K. G. *Tetrahedron* **1982**, *38*, 2751. (b) Burke, S. D.; Grieco, P. A. In *Organic Reactions* John Wiley and sons: New York, **1979**; Vol. 26; p 361. (c) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348. (d) Wenkert, E.; Alonso, M. E.; Buckwaler, B. L.; Sanchez, E. L. *J. Am. Chem. Soc.* **1983**, *105*, 2021. (e) Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 301. (f) Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 251. (g) Crackett, P. H.; Sayer, P.; Stoodley, R. J.; Greengrass, C. W. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1235.

[37] Nagao, Y.; Abe, T.; Shimizu, H.; Kumagai, T.; Inoue, Y. *J. Chem. Soc. Chem. Commun.* **1989**, 821.

[38] (a) Cama, L. D.; Firestone, R. A.; Christensen, B. G. In *Abstracts of the tenth middle Atlantic regional meeting of ACS*; ACS: Philadelphia, Pa., **1976**, Feb. 23-26; abstract J-16. (b) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1978**, *19*, 4233.

[39] (a) Haebich, D.; Hartwig, W. *Tetrahedron* **1984**, *40*, 3667. (b) Yamamoto, S.; Itani, H.; Takahashi, H.; Tsuji, T.; Nagata, W. *Tetrahedron Lett.* **1984**, *25*, 4545.

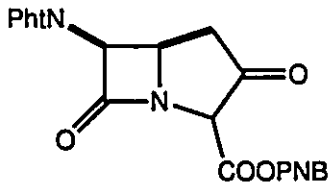
[40] Salzmann, T. N.; DiNinno, F. P.; Greenlee, M. L.; Guthikonda, R. N.; Quesada, M. L.; Schmitt, S. M.; Herrmann, J. J.; Woods, M. F. In *Recent Advances in the Chemistry*



(eq 2)

65 **66**

Successful annulations have been reported in the case of carbacephem[41] and carbapenem **67**[42] with α-nitrogen substituent. It appears that the nature of the substituent and its stereochemical relationship with the carbenoid govern the product obtained. Yamamoto and collaborators reported small amounts of product derived from the insertion of the carbenoid into the NH bond at C-7 (**68**) during a cyclization study leading to an oxacephem having a 7-nitrogen group.[43]



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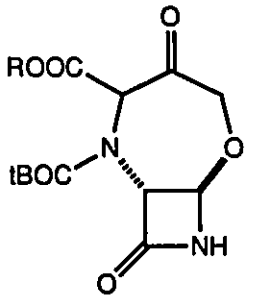

68

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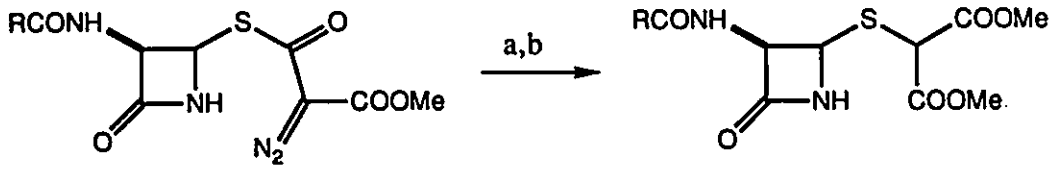
of β-Lactam Antibiotics; A. G. Brown and S. M. Roberts, Ed.; The Royal Society of Chemistry: London (England), **1985**; p 171.

[41] Evans, D. A.; Sjorgen, E. B. *Tetrahedron Lett.* **1985**, *27*, 3787.

[42] Yamamoto, K.; Nishio, M.; Kato, Y. *Tetrahedron Lett.* **1982**, *23*, 5339.

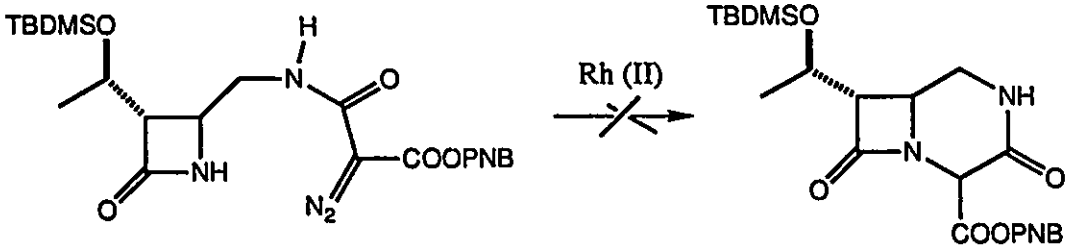
[43] Yamamoto, S.; Itani, H.; Takahashi, H.; Tsuji, T.; Nagata, W. *Tetrahedron Lett.* **1984**, *25*, 4545.

Failure of the carbenoid methodology during attempted cyclizations to penems[44] and 2-dethia-2-azaisocephems[45] has also been reported.



69 **70**

a) Rh(II), b) MeOH



71 **72**

The combination of ring size and the 7,7-disubstitution pattern of **61** and **62** call for addressing the issue of structure-activity relationships. As mentioned earlier, carbacephems having a typical amide substituent at C-7 are chemically more stable than the analogous cephalosporins, and tend to have comparable biological activity. The replacement of the amide nitrogen by an ester oxygen at the carbon α to the β-lactam carbonyl in penicillin and cephalosporin was found to diminish the activity.[46] Homothienamycin is more stable than

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[44] Marchand-Brynaert, J.; Ghosez, L.; Cossement, E. *Tetrahedron Lett.* **1980**, *21*, 3081.

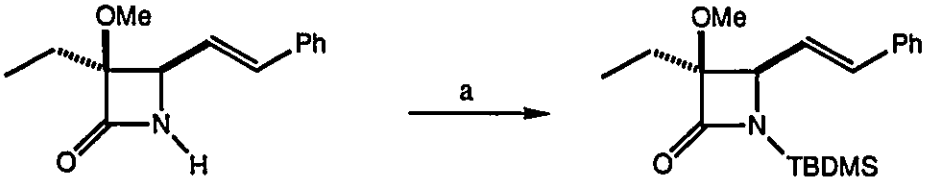
[45] Shiozaki, M.; Ishida, N.; Maruyama, H. *Chem. Abs.* **1987**, *107*, 58697b.

[46] (a) Sheehan, J. C.; Lo, Y. S. *J. Am. Chem. Soc.* **1972**, *94*, 8253. (b) Sheehan, J. C. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; J. Elks, Ed.; The Chemical Society: London (England), **1977**; p 20.

thienamycin but inactive.[47] Some activity has been reported in oxacephems bearing a hydroxyethyl substituent.[48] A cephem having a 7-hydroxyethyl was found to have low activity but good β-lactamase inhibition property.[49] These results indicate that the compounds may not have the high antimicrobial activity displayed by thienamycin. Thus the compounds **61** and **62** were considered worthwhile targets from methodology point of view as model compounds.

Preparation of the β-ketoesters 81 and 85

The 3,3-disubstituted azetidinone **73** was available in multigram quantity as described in Chapter 2.[50] N-Silylation was achieved by using t-butyldimethylsilyltriflate[51] (TBDMSOTf) and 2,6-lutidine at 0 °C to 25 °C.



73 **74**

a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to 25 °C

Ozonolysis of the N-TBDMS derivative **74** was carried out in dichloromethane with traces of methanol and molecular sieves to yield

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[47] Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193.

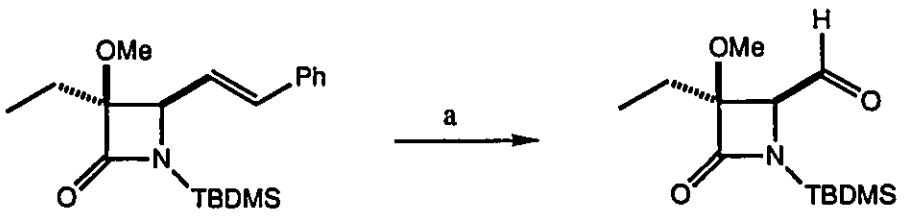
[48](a) Murakami, M.; Aoki, T.; Nagata, W. *Heterocycles* **1990**, *30*, 567. (b) Nishimura, S.; Sasako, H.; Yasuda, N.; Matsumoto, Y.; Kamimura, T.; Sakane, K.; Takaya, J. *J. Antibiotics* **1989**, *42*, 1124.

[49] Nishimura, S.; Yasuda, N.; Sasaki, H.; Matsumoto, Y.; Kamimura, T.; Sakane, K.; Takaya, T. *J. Antibiotics* **1989**, *42*, 159.

[50] see Chapter 2 page 95 for details of preparation of this compound.

[51] Corey, E. J.; Cho, H.; Rucker, C.; Hua., D. H. *Tetrahedron Lett.* **1981**, 22, 3455.

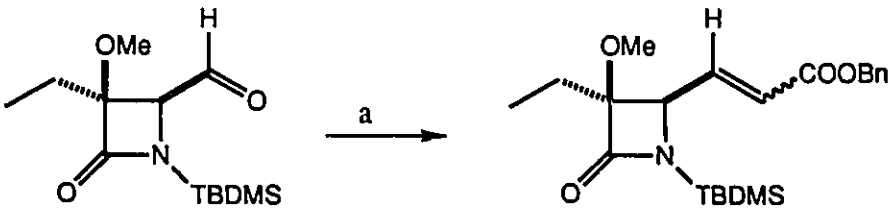
75 (IR: 1755 and 1740 cm^{-1}; ^1H NMR δ: 9.61 ppm) in 81% overall yield from **73**.



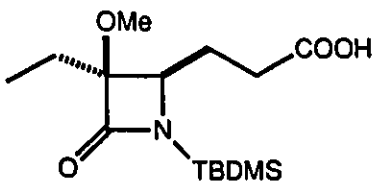
74 **75**

a) O_3, CH_2Cl_2, MeOH, -78 °C, DMS, -78 °C to 25 °C

The two carbon homologation of **75** to **77** was achieved in excellent yield and in a practical manner on a multigram scale in two steps. Wittig reaction using benzyl(triphenylphosphoranylidene)acetate afforded the corresponding α, β-unsaturated ester **76**. During the Wittig reaction a mixture of *cis-trans* isomers were obtained in about 1:4 ratio, as determined from the comparision of the integrals of olefinic signals in the ^1H NMR. However, this was of little consequence since both isomers can readily be reduced to the carboxylic acid, **77**. Both reduction of the double bond and the debenzylation occurred upon hydrogenation with 10% Pd on C.



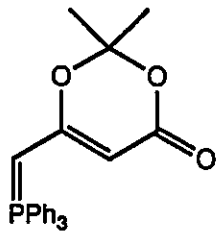
75 76



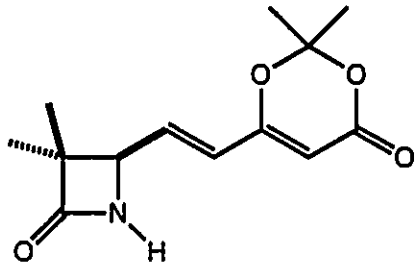
77

a) Ph_3P=CHCOOBn, toluene, reflux; b) H_2, Pd-C, EtOH, 25 °C

Wittig reaction resulting in four carbon homologations using (triphenylphosphoranylidene)-2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **78** has been reported.[52] This suggested an alternate route from **75** to **81**. However, in our hands this reagent proved to be difficult to prepare and purify, especially on a multigram scale. Furthermore, one double bond has to be selectively reduced and as the disubstitution pattern in our azetidinones increases the steric hindrance at C-5, this reduction may not be facile.



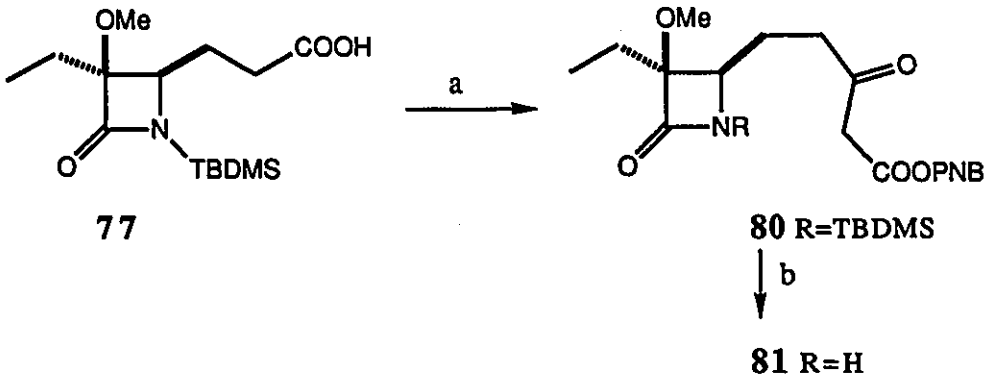
78



79

52 Bodurow, C.; Carr, M. A. *Tetrahedron Lett.* **1989**, *30*, 4081.

The further elaboration of **77** to β-ketoester **80** was achieved by activation with carbonyldiimidazole and subsequent reaction with the magnesium salt of the mono-p-nitrobenzyl ester of malonic acid following the Masamune protocol.[53] Methanolic HCl treatment of the N-silyl β-ketoester **80** gave the key desilylated compound **81**. This compound showed peaks at 3292 (NH), 1522 and 1348 (NO_2) cm^{-1} in IR and δ=5.24 ppm for two benzylic protons, two sets of doublets at δ=7.50 and 8.21 ppm (J=8.9 Hz) for the aromatic protons of p-nitrobenzyl group and δ=5.90 ppm for NH in ^1H NMR.



77

80 R=TBDMS

b

81 R=H

a) CDI, THF, $Mg(OOCCH_2COOPNB)_2$, THF, 25 °C; b) 10% HCl, MeOH, 25 °C.

A similar sequence was used to obtain the intermediate **85** having both the 7-methoxy and epithienamycin type side chains at C-3. The preparation of the aldehyde **82** has already been described in Chapter 2.[54] Removal of the p-methoxyphenyl group with CAN afforded the expected aldehyde which was rather unstable and difficult to handle compared to the N-silylated aldehyde **75**. Therefore, the aldehyde was quickly purified by column chromatography to a usable

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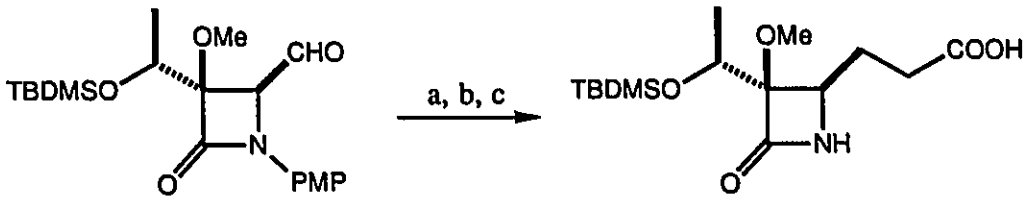
[53] Masamune, S.; Brooks, D. W.; Lu, L. D. L. *Angew. Chem. Int. Ed. Engl.* **1978**, *18*, 72.
[54] See Chapter 2 page 63 for experimental details.

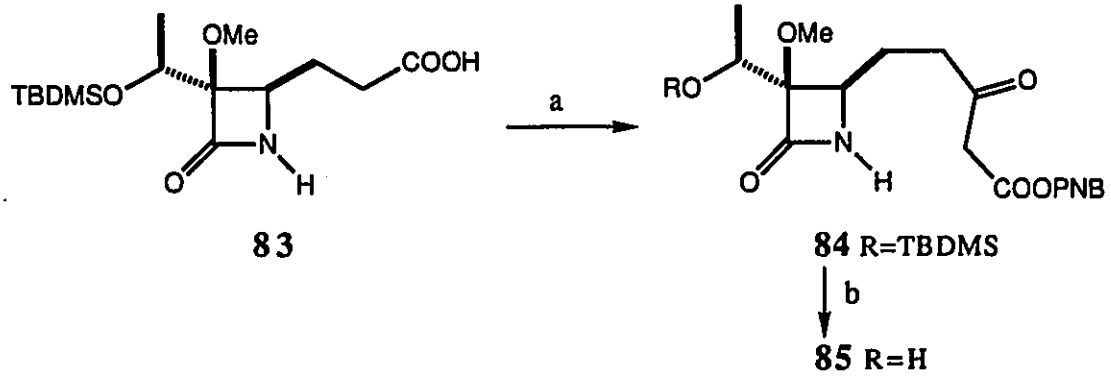
state and subjected to the Wittig homologation sequence described above. The carboxylic acid **83** was obtained in 36% overall yield from **82**. This compound was characterized by IR, ^{1}H NMR and MS including HRMS.



82 **8 3**

a) CAN, MeCN, H_2O, -10 °C; b) Ph_3P=CHCOOBn, toluene, reflux; c) H_2, Pd-C, EtOH, 25 °C.

The homologation of **83** to the β-keto ester **85** was again achieved using Masamune's method and desilylation with methanolic HCl. Compound **85** was obtained as a yellow oil. The presence of the key functional groups is supported by IR (CH_2Cl_2): 3327 (NH), 1740 (broad C=O), 1523 and 1348 (NO_2) cm^{-1}. The introduction of the p-nitrobenzyl acetate group was indicated by ^{1}H NMR peaks at δ: 3.56-3.65 (6H, m with overlapping s due to OCH_3, CHN, CH_2), 5.23 (2H, s, CH_2PNB), 7.49 (2H, d, J=8.2 Hz, PNB) and 8.20 (2H, d, J=8.8 Hz, PNB) ppm.



83

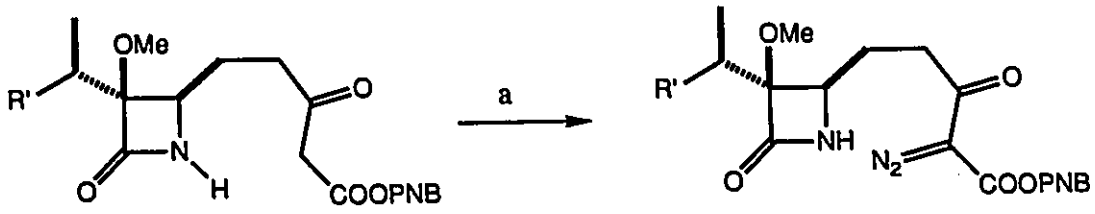
84 R=TBDMS

85 R=H

a) CDI, THF, $Mg(OOCCH_2COOPNB)_2$, THF, 25 °C; b) 6N HCl, MeOH, 25 °C.

Annulation

Diazo transfer between **81** or **85** and 4-carboxybenzenesulfonazide was achieved in the presence of excess triethylamine.[55] Both diazo compounds showed typical IR peaks at 2120 cm^{-1}.



81 R'=H
85 R'=OH

86 R'=H
87 R'=OH

a) 4-HOOCPhSO_2N_3, Et_3N, MeCN, 0 °C

The resulting diazo compounds, **86** and **87**, were refluxed in benzene with about 0.3 mol% of $Rh_2(OAc)_4$ to give **88** (60% from **81**) and **89** (32% from **85**), respectively. No other major products were evident by tlc which indicated that interference by the methoxy group in the carbenoid cyclization was not a major concern. The formation of the second ring in both products is evident from the ^1H NMR and IR spectrum. The appearance of an AB pattern for the benzylic protons (δ: 5.25 ppm, 1H, d, J=13.9 Hz and 5.47 ppm, 1H, d, J=13.4 Hz) and shift of the β-lactam carbonyl peak in IR from 1740 (monocyclic precursor) to 1752 cm^{-1} (bicyclic ketoester) are expected changes in going from **81** to **88**. The conversion of **85** to **89** shows similar changes. The benzylic protons in **85** (δ: 5.23 ppm, s) became a AB quartet in **89** (δ: 5.24 ppm, 1H, d, J=13.7 Hz and 5.45 ppm, d, J=13.4 Hz). A concomitant shift of the IR peak for the β-lactam carbonyl from 1740 to 1750 cm^{-1} was also

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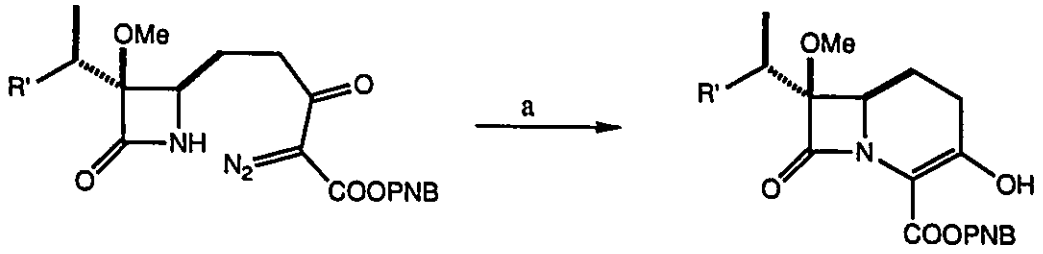
55 Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.

observed.

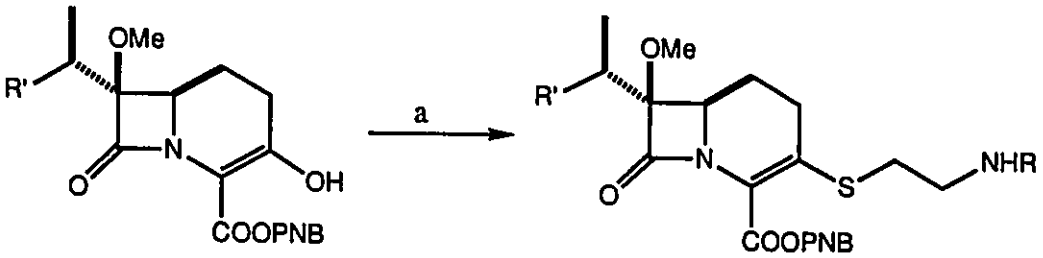


86 R'=H
87 R'=OH

88 R'=H
89 R'=OH

a) $Rh_2(OAc)_4$, C_6H_6, reflux

The conversion of **88** to **90** involved the activation of enol group with diphenylchlorophosphate followed by addition of N-acetylaminoethanethiol[56] in the presence of diisopropylethylamine (DIPEA). The intermediate of epi-homothienamycin analog **91** was obtained in similar manner using carbo-p-nitrobenzyloxyamino-ethanethiol.



88 R'=H
89 R'=OH

90 R'=H, R=Ac
91 R'=OH, R=COOPNB

a) $(PhO)_2POCl$, DIPEA, MeCN, 0 °C, $HSCH_2CH_2NHR$ (R=Ac or COOPNB), DIPEA, 0 °C

Removal of the p-nitrobenzyl groups from **90** and **91** *via.* catalytic hydrogenation afforded the crude carboxylic acids. Purification by reverse phase column chromatography and lyophilization of the resultant aqueous solution gave compound **61** as a white powder; mp:

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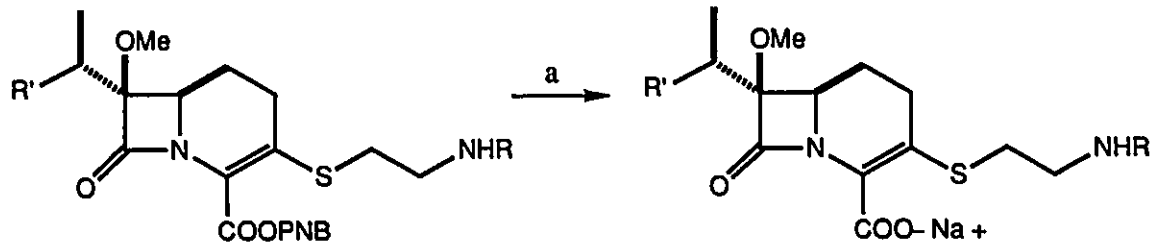
[56] Shinkai, I.; Liu, T.; Reamer, R.; Sletzinger, M. *Synthesis* **1980**, 924.

becomes translucent at 177-178 °C and chars at or above 217 °C; IR (KBr): 1742, β-lactam C=O. ^{1}H NMR (Fig. 7), ^{13}C NMR (Table 2) and MS including HRMS were in agreement with the structure of the compound **61**.

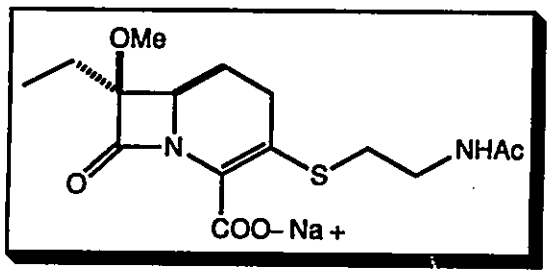


90 R'=H, R=Ac **61** R'=H, R=Ac

a) H_2, Pd-C, THF:H_2O.

Table 2 ^{13}C NMR data for the compound **61**.

Chemical Shift, (ppm) δ	type of carbon
9.6	CH_3
24.1	CH_2
24.6	CH_3
25.4	CH_2
28.8	CH_2
32.5	CH_2
42.1	CH_2
55.5	CH_3O
60.6	CH
94.2	C-7
120.4	C=C
134.7	C=C
169.7	C=O
172.8	C=O
177.2	C=O



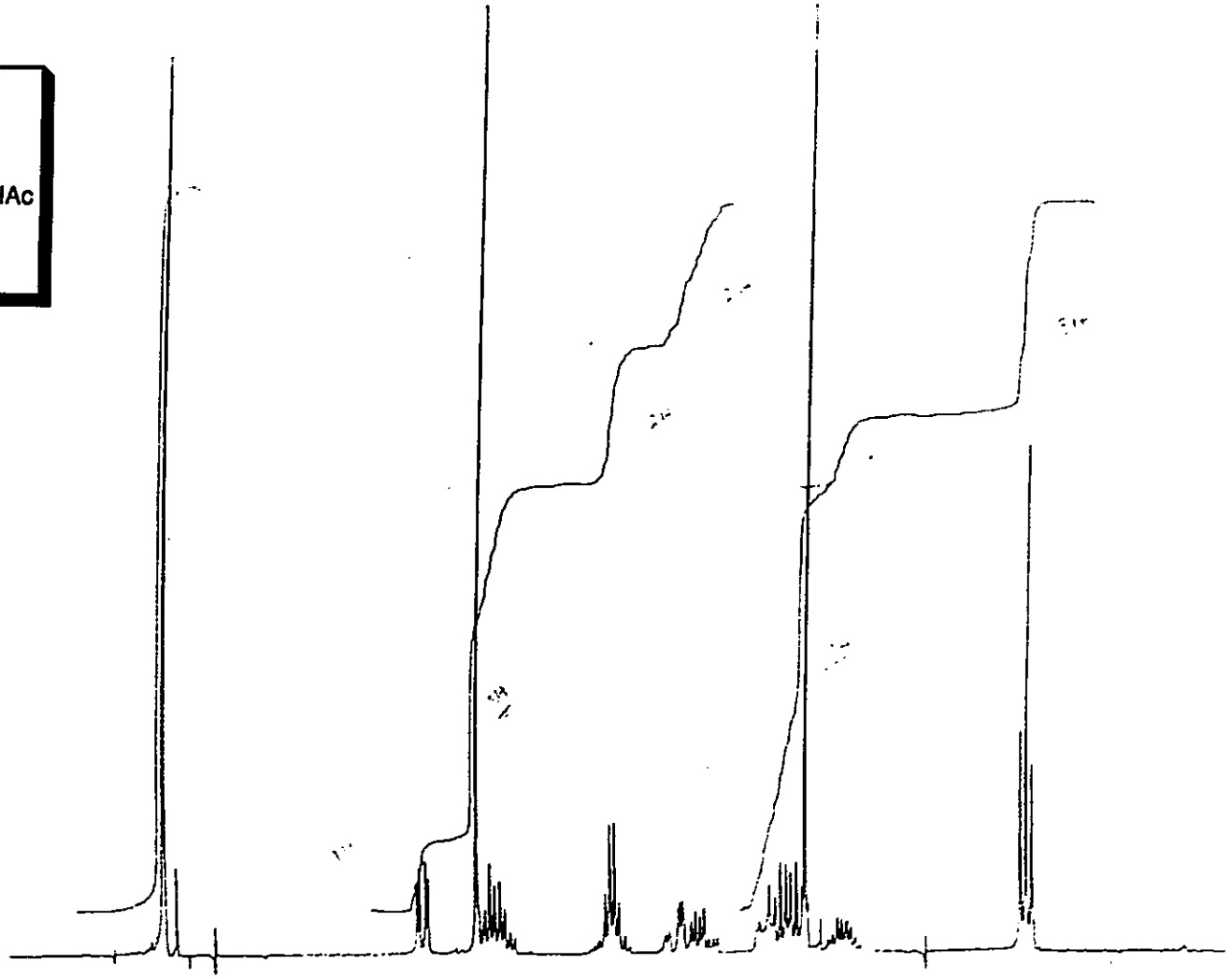


Fig. 7 ^{1}H NMR spectrum of **61**

In vitro antibacterial activity of **61** was determined by conventional microtiter dilution procedures. The MICs were higher than 64 μg/mL for organisms such as *S. pneumoniae, S. pyogenes, H. influenzae* and 128 μg/mL *E. faecalis, E. faecium, S. aureus, S. epidermidis, S. haemolyticus, E. coli, K. pneumoniae, E. cloacae, P. mirabilis, P. vulgaris, N. morganii, P. rettgeri, S. marcescens, P. aeruginosa, P. cepacia and X. maltophilia.*

Purification of the carboxylic acid **62** derived from **91** was unsuccessful on the first attempt. Due to a lack of material and the discouraging results observed in the studies of antibacterial activity of **61**, purification of this compound was not repeated.

Conclusion

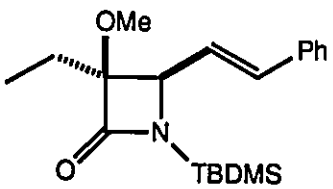
7-Methoxyhomo-PS-5 **61** was found to be inactive as an antibacterial compound. From a methodology point of view, this study did indicate that the rhodium carbenoid annulation can be applied in β-lactams having a methoxy group α to the lactam carbonyl. Application of this methodology to the preparation of several 6-methoxy carbapenems including 6-methoxy-PS 5 will be discussed in the following chapters. None of these examples display intervention by the α-methoxy group.

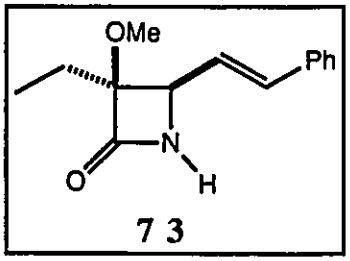
EXPERIMENTAL SECTION

General techniques

The spectrometers used in the analysis of the compounds, general work up and purification methods have already been described in the Experimental section of Chapter 2. Toluene and benzene were distilled from sodium benzophenone ketyl and stored over 4Å molecular sieves. Analytical grade MeOH and 99% ethanol were used without further purification. The magnesium salt of the mono p-nitrobenzyl ester of malonic acid was purchased from Kasei Chemical Co. Acetonitrile was distilled from calcium hydride and stored over 4Å molecular sieves. Reverse phase column chromatography was performed using Waters C-18 Bondpak silica gel in a manner similar to the flash column chromatography. Lyophilization was carried out by freezing the aqueous solution in dry-ice acetone bath and drying under high vacuum.

1-t-Butyldimethylsilyl-4-cinnamyl-3-ethyl-3-methoxy-2-azetidinone (74)



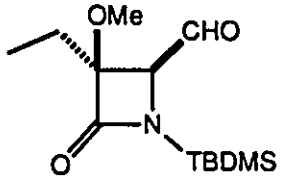


73

2,6-Lutidine (2.32 mL, 19.9 mmol) and TBDMSOTf (3.43 mL, 14.9 mmol) were sequentially added *via.* syringe to a solution of **73** in 50

mL of dry CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and 1.5 h at room temperature. Usual workup and purification by column chromatography (1:15 EtOAc:hexanes) gave 3.40 g (99%) of a pale yellowish oil **74**; IR: 1744 (β-lactam C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.15 (3H, s, CH_3Si), 0.21 (3H, s, CH_3Si), 0.93 (9H, s, t-BuSi), 0.97 (3H, t, J=7.3 Hz, CH_3CH_2), 1.79-2.01 (2H, m, CH_2CH_3), 3.43 (3H, s, OCH_3), 3.98 (1H, d, J=8.7 Hz, CHN), 6.22 (1H, dd, J=16.0, 8.9 Hz, CH=CHPh), 6.54 (1H, d, J=16.0 Hz, CH=CHPh), 7.10-7.30 (5H, m, Ph); MS: 345 (M^+, 11), 330 (M^+-15, 18), 302 (M^+-15-28, 4), 288 (M^+-57, 3), 188 (M^+-157, 100); HRMS calcd for $C_{20}H_{31}NO_2Si$ 345.2112, found 345.2118.

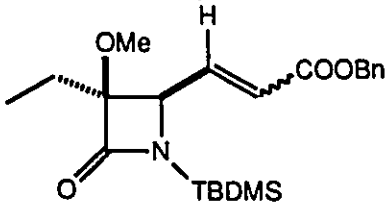
1-t-Butyldimethylsilyl-3-ethyl-4-formyl-3-methoxy-2-azetidinone (75)



Ozone was passed through a solution of **74** (3.40 g, 9.85 mmol) in 50 mL of dry CH_2Cl_2 and 5 mL of MeOH containing about 0.50 g of 4Å molecular sieves at -78 °C till the solution was bluish. Excess ozone was removed by bubbling dry nitrogen through the reaction mixture and 3 mL of dimethyl sulfide was added. The resulting reaction mixture was warmed slowly to 25 °C and stirred for 18 h. After removal of the solvent, the crude product was purified by flash column chromatography (1:10 EtOAc:hexanes) to yield 2.20 g (82%) of aldehyde **75** as a colorless oil; IR: 1740 (CHO), 1755 (β-lactam C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.10 (3H, s, CH_3Si), 0.29 (3H, s, CH_3Si), 0.94 (9H, s, t-Bu), 1.01 (3H, t, J=7.3 Hz, CH_3CH_2), 1.68-1.88 (1H, m, CH_2CH_3), 1.94-2.12 (1H, m, CH_2CH_3), 3.40 (3H, s, OCH_3), 3.81 (1H, d, J=3.1 Hz, CHN), 9.61 (1H, d,

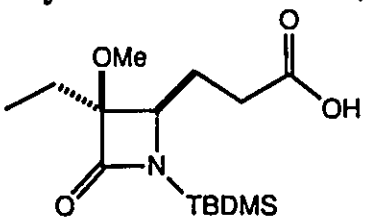
J=3.0 Hz, CHO); MS: 272 (M^++1, 3), 244 (M^++1-28, 3), 214 (M^+-57, 29), 187 (M^++1-28-57, 87); 171 (M^+-100, 3).

1-t-Butyldimethylsilyl-4-(2'-carbobenzyloxyethenyl)-3-ethyl-3-methoxy-2-azetidinone (76)



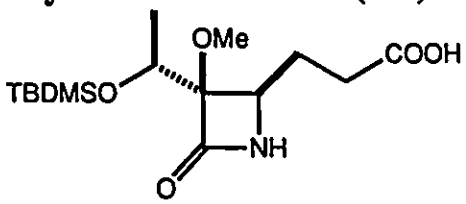
The solution of benzyl(triphenylphosphoranylidene)acetate (3.99 g, 9.73 mmol) in 100 mL of toluene was stirred with aldehyde **75** (2.20 g, 8.12 mmol) at 50-60 °C for 18 h. Toluene was removed and the residue was triturated with 100 mL of hexanes. Triphenylphosphine oxide was removed by filteration. The filtrate was concentrated to a yellow oil which on purification by column chromatography (1:10 EtOAc:hexanes) gave 3.10 g (95%) of a *cis-trans* (1:4, judged by comparing integrals in ^{1}H NMR as well as weight after separation by column chromatography) mixture of the corresponding α,β unsaturated ester **76** as a colorless oil; IR: 1750 and 1728 (C=O) cm^{-1}; ^{1}H NMR (200 MHz, for pure trans isomer) δ: 0.12 (3H, s, CH_3Si), 0.21 (3H, s, CH_3Si), 0.87-1.00 (12H, t, J=7.4 Hz, overlapping with s of t-Bu, CH_3CH_2), 1.69-2.08 (2H, m, CH_2CH_3), 3.41 (3H, s, OCH_3), 3.92 (1H, dd, J=0.7, 9.0 Hz, CHN), 5.13 (1H, d, J=12.5 Hz, CH_AH_BPh), 5.26 (1H, d, J=12.5 Hz, CH_AH_BPh), 5.99 (1H, dd, J=15.8, 0.7 Hz, CH=CHCOOR), 6.95 (1H, dd, J=8.9, 15.8 Hz, CH=CHCOOR), 7.34 (5H, s, Ph); MS: 403 (M^+, 0.6), 388 (M^+-15, 3), 346 (M^+-57, 16), 312 (M^+-91, 2), 304 (M^+-99, 4); HRMS calcd for $C_{22}H_{33}NO_4Si$ 403.2179, found 403.2179.

1-t-Butyldimethylsilyl-4-(2'-carboxyethyl)-3-ethyl-3-methoxy-2-azetidinone (77)



The ester **76** (3.10 g, 7.69 mmol) was dissolved in 10 mL of EtOH and hydrogenated in the presence of 2 g of Pd-C (10%) at 20 psi for 18 h. Removal of the catalyst and the solvent gave 2.40 g (99%) of the acid **77** as a colorless oil; IR: 3127 (COOH), 1741 (C=O), 1676 (COOH) cm^{-1}; ^1H NMR (200 MHz) δ: 0.18 (3H, s, CH_3Si), 0.21 (3H, s, CH_3Si), 0.87-0.94 (12H, t with overlapping s, CH_3CH_2, t-Bu), 1.48-1.68 (1H, m, CH_2CH_3), 1.90-2.12 (3H, m, CH_2CH_3, CH_2), 2.21-2.61 (2H, m, CH_2CO), 3.37 (1H, dd, J=4.8, 9.2 Hz, CHN), 3.47 (3H, s, OCH_3); MS: 315 (M^+, 5), 300 (M^+-15, 14), 272 (M^+-15-28, 5), 258 (M^+-57, 12), 243 (258^+-15, 1); HRMS calcd for $C_{15}H_{29}NO_4Si$ 315.1868, found 315.1867.

3-t-Butyldimethylsilyloxyethyl-4-(2'-carboxyethyl)-3-methoxy-2-azetidinone (83)

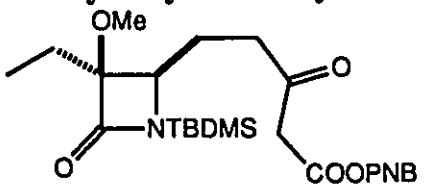


The aldehyde **82** (7.10 g, 18 mmol) was reacted with CAN (29.59 g, 54 mmol) at -10 °C to yield 3.50 g (66%) of N-deprotected aldehyde as a brown oil after column chromatography (1:4 EtOAc:hexanes). This compound showed the aldehyde proton at 9.61 ppm and was judged to be about 60% pure by ^1H NMR. It was used as such.

Reaction of the aldehyde (3.50 g, 12 mmol) with benzyl triphenylphosphoranylideneacetate (7.35 g, 17.9 mmol) gave 2.70 g (51%) of a brownish oil after column chromatography (1:4 EtOAc: hexanes); ^{1}H NMR (200 MHz, for mixture of *cis-trans* isomers) δ: 0.04 + 0.06 + 0.08 (6H, $SiCH_3$), 0.84 (9H, s, t-Bu), 1.28 + 1.30 (3H, 2 sets of d, J=6.4 Hz, CH_3), 3.47 + 3.48 (3H, 2s, OCH_3), 4.05 + 4.20 (1H, q, J=6.4 Hz, CHO), 4.36 (dd, J=5.8, other coupling constants could not be calculated from the spectrum) + 5.06 (dd, J= 2.0, 6.1 Hz) - both of these proton signals are for 1H, CHN, 5.12 (d, J=2.38 Hz) + 5.13 (s) - both of these signals are for 2H, CH_2Ph, 5.97-6.03 (dd, J=1.9, 11.6 Hz) + 6.00-6.08 (dd, J=1.5, 15.8 Hz) - 1H, $CH_A{=}CH_BPh$, 6.38-6.47 (less than 2H, broad d overlapping with dd, J=6.1, 11.6 Hz, NH, $CH_A{=}CH_BPh$) + 7.00-7.08 (less than 1H, dd, J=15.8, 5.8 Hz, $CH_A{=}CH_BPh$ from *trans* isomer), 7.33 (5H, s, Ph).

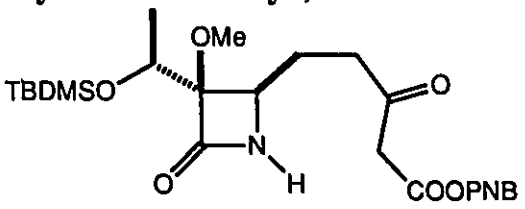
The resultant oil was hydrogenated to yield 2.10 g (99%) of **83** as a brown oil; IR: 3362 (COOH), 1740 (C=O) cm^{-1}; ^{1}H NMR (200 MHz) δ: 0.02 (3H, s, CH_3Si), 0.04 (3H, s, CH_3Si), 0.84 (9H, s, t-Bu), 1.21 (3H, d, J=6.4 Hz, CH_3CH_2), 1.80-1.93 (2H, m, CH_2COO), 2.20-2.55 (2H, m, CH_2CH_2COO), 3.58 (3H, s, OCH_3), 3.59-3.72 (1H, m, overlaps with 3.58 of OCH_3, CHN), 4.10 (1H, q, J=6.4 Hz, CHO), 6.73 (1H, broad s, NH); MS: 316 (M^+-15, 2), 302 (M^+-29, 1), 287 (M^+-44, 3), 274 (M^+-57, 26), 230 (M^+-101, 21), HRMS calcd for $C_{14}H_{26}NO_5Si$ (M^+-15) 316.1576, found 316.1578.

1-t-Butyldimethylsilyl-3-ethyl-3-methoxy-4-(4'-p-nitrobenzyloxycarbonyl-3'-oxobutyl)-2-azetidinone (80)



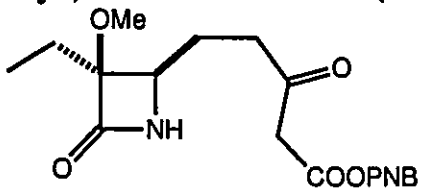
Carbonyldiimidazole (CDI, 1.50 g, 9.52 mmol) was added to a solution of the acid **77** (2.00 g, 6.35 mmol) in 10 mL of THF and the mixture was stirred at 25 °C for 3.75 h. The suspension of the magnesium salt of the mono-p-nitrobenzyl ester of malonic acid (3.20 g, 6.39 mmol) was added by cannula and stirred vigorously for 16 h. The reaction mixture was diluted with EtOAc and washed with saturated NaCl solution. Column chromatography (1:4 EtOAc:hexanes) of the resulting crude product afforded 0.70 g (22%) of **80** as a colorless oil; IR: 1735 (C=O), 1524 and 1332 (NO_2) cm^{-1}; ^1H NMR (300 MHz) δ: 0.19 (3H, s, CH_3Si), 0.23 (3H, s, CH_3Si), 0.88 (3H, t, J=7.4 Hz, CH_3CH_2), 0.93 (9H, s, t-Bu), 1.52-1.60 (1H, m, CH_3CH_2), 1.82-2.03 (3H, m, CH_3CH_2), 2.46-2.63 (2H, m, CH_2CO), 3.35 (1H, dd, J=11.0, 3.2 Hz, CHN), 3.47 (3H, s, OCH_3), 3.5i (1H, d, J=7.5 Hz, $COCH_2COOR$), 3.54 (1H, d, J=7.5 Hz, $COCH_2COOR$), 5.25 (2H, s, CH_2PNB), 7.52 (2H, d, J=8.9 Hz, PNB), 8.21 (2H, d, J=8.9 Hz, PNB); MS: 492 (M^+, 2), 477 (M^+-15, 1), 435 (M^+-57, 2), 335 (M^+-157, 54), 303 (335^+-32, 10).

3-Hydroxyethyl-3-methoxy-4-(4'-p-nitrobenzyloxy-carbonyl-3'-oxobutyl)-2-azetidinone (84)



The carboxylic acid **83** (2.13 g, 6.43 mmol) gave 1.2 g (37%) of β-ketoester **84** as a yellow oil using the above homologation procedure; chromatography solvent 1:2 (EtOAc:hexanes); IR: 3160-3400 (broad NH), 1720-1770 (broad C=O), 1520 and 1350 (NO_2) cm^{-1}; ^1H NMR (300 MHz) δ: 0.4 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si), 0.86 (9H, s, t-Bu), 1.21 (3H, d, J=6.4 Hz, CH_3CH_2), 1.88-1.94 (2H, m, CH_2CO), 2.38-2.76 (2H, m, CH_2CH_2CO), 3.52 (1H, d, J=1.7 Hz, $COCH_AH_BCOOR$), 3.59 (3H, s, OCH_3), 3.61 (1H, s, $COCH_AH_BCOOR$), 3.64-3.68 (1H, m, CHN), 4.11 (1H, q, J=6.4 Hz, CHO), 5.20 (2H, s, CH_2PNB), 6.02 (1H, s, NH), 7.51 (2H, dd, J=2.0, 6.9 Hz, PNB), 8.22 (2H, dd, J=2.0, 6.8 Hz, PNB); MS: 451 (M^+-57, 2), 377 (M^+-131, 2), 298 (M^+-195-15, 8), 256 (298^+-42, 4), 231 (M^+-277, 11).

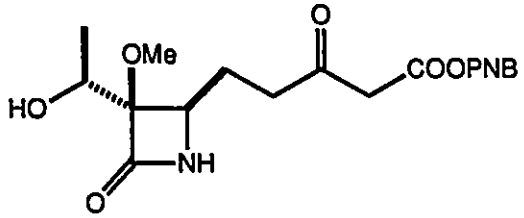
3-Ethyl-3-methoxy-4-(4'-p-nitrobenzyloxycarbonyl-3'-oxobutyl)-2-azetidinone (81)



The β–ketoester **80** (0.70 g, 1.42 mmol) in 10 mL of MeOH was stirred overnight with 1 mL of 10% aq HCl. The excess acid was neutralized by adding solid $NaHCO_3$. The crude product obtained after work up using EtOAc as a solvent for extraction was purified by column chromatography (6:4 hexanes:EtOAc) to yield 0.39 g (73%) of **81** as a

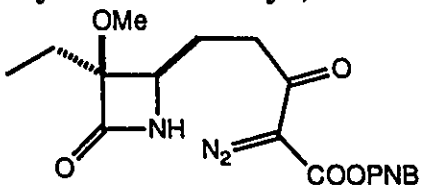
pale yellowish oil; IR: 3292 (NH), 1740 (C=O), 1720 (COOR), 1522 and 1348 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.91 (3H, t, J=7.4 Hz, CH_3CH_2); 1.62-1.69 (1H, m, CH_2CH_3), 1.86-2.03 (3H, m, CH_2CH_3, CH_2), 2.54-2.69 (2H, m, CH_2CO), 3.41-3.52 (6H, m, overlapping with s at 3.48, OCH_3, $COCH_2COOR$, CHN), 5.24 (2H, s, CH_2PNB), 5.90 (1H, broad, NH), 7.50 (2H, d, J=8.9 Hz, PNB), 8.21 (2H, d, J=8.9 Hz, PNB); MS(CI): 379 (M^++1, 9), 351 (M^++1-28, 50), 333 (M^++1-28-18, 12), 319 (M^++1-60, 33), 301 (319^+-18, 1).

3-Hydroxyethyl-3-methoxy-4-(4'-p-nitrobenzyloxy-carbonyl-3'-oxobutyl)-2-azetidinone (85)



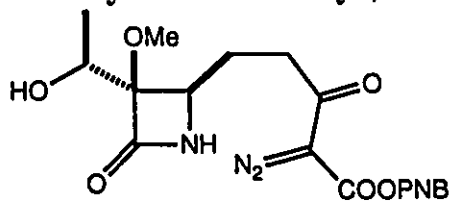
O-Desilylation of the β-ketoester **84**, obtained above, was effected by treating the methanolic solution of this ester (1.2 g, 2.36 mmol) with 2 mL of 6N HCl dropwise at 0 °C to 25 °C for 18 h. The crude product was passed through a short silica gel column using EtOAc to afford 630 mg (68%) of **85** as a yellow oil; IR (CH_2Cl_2): 3327 (NH), 1740 (broad C=O), 1523 and 1348 (NO_2) cm^{-1}; ^1H NMR (300 MHz) δ: 1.20 (3H, overlapping with EtOAc, CH_3CH_2), 1.80-2.10 (2H. m, CH_2), 2.30-2.70 (2H, m, CH_2), 3.56-3.65 (6H, m with overlapping s due to OCH_3, CHN, CH_2), 4.12 (1H, overlapping with EtOAc, 5.23 (2H, s, CH_2PNB), 6.20 (1H, s, broad, NH), 7.49 (2H, d, J=8.2 Hz, PNB), 8.20 (2H, d, J=8.8 Hz, PNB); MS(CI): 353 (M^++1-42, 2), 279 (M^++1-116, 2), 274 (M^++1-120, 20), 259 (M^++1-136, 1), 215 (M^++1-180, 6). This compound was purified after conversion to the corresponding diazo compound.

3-Ethyl-3-methoxy-4-(4'-diazo-4'-p-nitrobenzyloxy-carbonyl-3'-oxobutyl)-2-azetidinone (86)



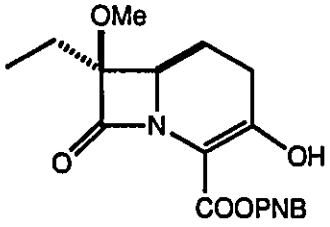
4-Carboxybenzenesulfonazide (0.37 g, 1.63 mmol) was added to a solution of the compound **81** (0.38 g, 1.00 mmol) in 25 mL of dry MeCN at 0 °C. The resulting suspension turned to a clear solution after the addition of TEA (0.56 mL, 4.02 mmol) and was stirred for 6 h. During this time the reaction mixture continued to turn cloudy. The reaction mixture was diluted with EtOAc and washed successively with 5% $NaHCO_3$ and saturated NH_4Cl. Purification of the crude product by column chromatography (2:5 EtOAc:hexanes) gave 0.35 g (85%) of the desired diazo compound **86** as a colorless oil; IR (CH_2Cl_2): 3292 (NH), 2143 (N_2), 1756 and 1727 (C=O), 1523 and 1348 (NO_2) cm^{-1}; ^1H NMR (300 MHz) δ: 0.93 (3H, t, J=7.4 Hz, CH_3CH_2), 1.62-1.70 (1H, m, CH_2CH_3), 1.90-2.06 (3H, m, CH_2CH_3, CH_2CO), 2.79-2.95 (2H, m, CH_2CO), 3.46 (1H, t, J=6.7 Hz, CHN), 3.49 (3H, s, OCH_3), 5.34 (2H, s, CH_2PNB), 5.95 (1H, broad t, NH), 7.52 (2H, d, J=8.8 Hz, PNB), 8.24 (2H, d, J=8.8 Hz, PNB); MS(CI): 377 (M^++1-28, 2), 349 (M^++1-28-28, 5), 305 (M^++1-100, 0.5), 214 (349-135^+, 0.1), 198 (349-151^+, 5).

3-Hydroxyethyl-3-methoxy-4-(4'diazo-4'-p-nitrobenzyl-oxycarbonyl-3'-oxobutyl)-2-azetidinone (87)



Compound **85** (610 mg, 1.55 mmol), when subjected to the diazo transfer reaction, yielded 520 mg (80%) of **87** as a yellowish semisolid after usual workup and column chromatography (1:2 acetone:hexanes); IR: 3200-3600 (broad OH), 2120 (N_2), 1700-1780 (broad C=O), 1520 and 1350 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 1.23 (3H, d, J=6.5 Hz, CH_3CH), 1.80 (1H, broad s, OH), 1.83-1.98 (2H, m, CH_2CH_2), 2.86-2.98 (2H, m, $COCH_2CH_2$), 3.63 (4H, m with overlapping s, OCH_3, CHN), 4.15 (1H, q, J=6.6 Hz, CHO), 5.31 (2H, s, CH_2PNB), 6.12 (1H, broad s, NH), 7.50 (2H, d, J=8.9 Hz, PNB), 8.23 (2H, d, J=8.9 Hz, PNB); MS: 277 (M^+-114-29, 2), 198 (M^+-194-28, 1), 170 (M^+-250, 62), 188 (M^+-278, 0.6).

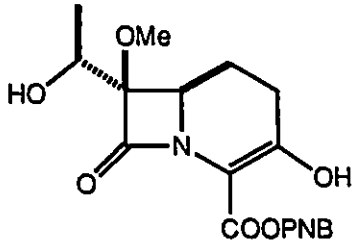
p-Nitrobenzyl 7-ethyl-7-methoxy-3-hydroxyl-1-carba-1-dethia-3-cephemcarboxylate (88)



The diazo compound **86** (0.35 g, 0.86 mmol) was dissolved in 30 mL of dry benzene and 15 mL of solvent was distilled off. After cooling to 25 °C under N_2, about 1 mg of $Rh_2(OAc)_4$ was added and the solution was refluxed overnight. Purification of the crude product by column chromatography (2:5 EtOAc:hexanes) furnished 0.23 g (70%) of the product **88** as a white solid; mp: 125-126 °C; IR (KBr): 3435 (broad OH),

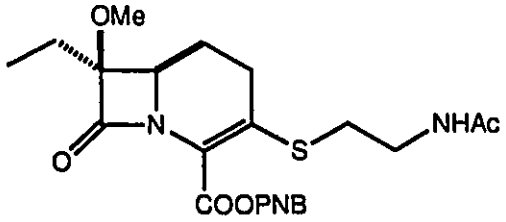
1752 (C=O), 1518 and 1344 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 1.00 (3H, t, J=7.4 Hz, CH_3CH_2), 1.55 (1H, broad s, OH), 1.79-2.21 (4H, m, CH_2CH_3, CH_2), 2.47-2.54 (2H, m, CH_2CO), 3.40-3.48 (4H, dd, J=10.3, 4.4 Hz, overlapping with s, CHN, OCH_3), 5.25 (1H, d, J=13.9 Hz, CH_AH_BPNB), 5.47 (1H, d, J=13.4 Hz, CH_BH_APNB), 7.66 (2H, d, J=8.9 Hz, PNB), 8.21 (2H, d, J=8.9 Hz, PNB); MS: 376 (M^+, 2), 348 (M^+-28, 5), 318 (M^+-28-30, 2), 302 (318^+-16, 0.3), 240 (M^+-136, 2); HRMS calcd for $C_{18}H_{20}N_2O_7$ 376.1268, found 376.1256.

p-Nitrobenzyl [3-hydroxy-7-(1'-hydroxyethyl)-7-methoxy]-1-carba-1-dethia-3-cephemcarboxylate (89)



After a rhodium carbenoid insertion reaction of the diazo compound **87** (400 mg, 0.950 mmol) and purification by column chromatography (2:3 acetone:hexanes), 370 mg (40%) of **89** was isolated as a yellowish oil; IR: 1710-1780 (broad peak centered at 1750 C=O), 1520 and 1350 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 1.26 (3H, d, J=6.5 Hz, CH_3CH_2), 1.97-2.14 (2H, m, CH_2CO), 2.48-2.60 (2H, m, CH_2CH_2CO), 3.64 (4H, 2s due to OCH_3 overlapping with CHN), 3.83 (1H, s, COCHCOO), 4.38 (1H, q, J=6.7 Hz, CHO), 5.24 (1H, d, J=13.7 Hz, CH_AH_BPNB), 5.45 (1H, d, J=13.4 Hz, CH_BH_APNB), 7.63 (2H, d, J=8.3 Hz, PNB), 8.20 (2H, d, J=9.8 Hz, PNB) The ^1H NMR looked like a mixture of ketoenol tautomers based on the complexity of the spectrum and the 2 methoxy peaks; MS: 391 (M^+-1, 0.4), 277 (M^+-115, 100), 271 (M^+-121, 15), 256 (M^+-136, 2), 211 (M^+-180, 11).

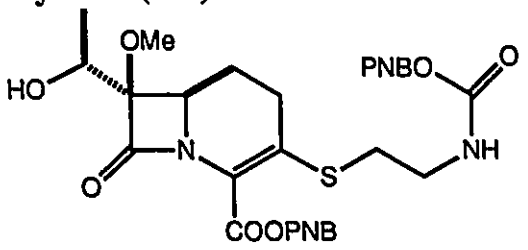
p-Nitrobenzyl 7-ethyl-7-methoxy-3-N-acetylaminoethanethio-1-carba-1-dethia-3-cephemcarboxylate (90)



Compound **88** (0.20 g, 0.53 mmol) in 5 mL of dry MeCN was cooled to 0 °C under N_2. Addition of DIPEA (0.12 mL, 0.69 mmol) gave a yellow colored solution. The color disappeared when the reaction mixture was stirred for 1 h after the addition of diphenylchlorophosphate (0.13 mL, 0.63 mmol). A solution of N-acetylaminoethanethiol (0.12 g, 1.01 mmol) in 2 mL of dry MeCN and DIPEA (0.12 mL, 0.69 mmol) was added and the reaction mixture was stirred for 1 h. After usual workup using EtOAc as a solvent, column chromatography of the crude product was carried out using a gradient of solvents. 1:2 EtOAc:hexanes gave starting compound **88**, 3:1 EtOAc:hexanes N-acetylaminoethanethiol and 20:40:40 hexanes:EtOAc:MeCN 0.20 g (81%) of the desired product **90** as a yellowish oil; IR ($CHCl_3$): 3329 (broad, NH), 1755 (β-lactam C=O), 1713 (COOR), 1660 (CONH), 1530 and 1361 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.98 (3H, t, J=7.4 Hz, CH_3CH_2), 1.75-2.10 (7H, m with overlapping s at 1.90 due to CH_3CO, CH_2, CH_2CH_3), 2.43-2.76 (2H, m, CH_2), 2.79 (2H, t, J=5.8 Hz, CH_2S), 3.25-3.46 (6H, m, with overlapping s at 3.35 due to OCH_3, CH_2N, CHN), 5.20 (1H, d, J=13.6 Hz, CH_AH_BPNB), 5.30 (1H, d, J=13.7 Hz, CH_BH_APNB), 6.76 (1H, broad t, NH), 7.52 (2H, d, J=8.9 Hz, PNB), 8.09 (2H, d, J=8.9 Hz, PNB); ^{13}C NMR (200 MHz) δ: 7.3 (CH_3), 21.3 (CH_2), 22.7 (CH_3), 22.8 (CH_2), 26.6 (CH_2), 30.1 (CH_2), 38.9 (CH_2), 52.7 (CH_3O), 56.7

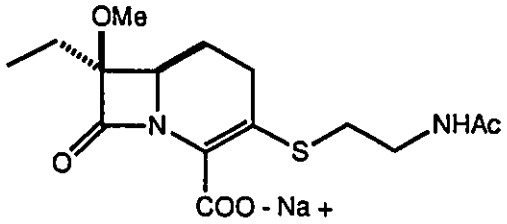
(CH), 65.7 (CH_2PNB), 90.7 (C-7), 122.6 (C=C), 123.6 (CH of PNB), 128.4 (CH of PNB),133.2 (C=C), 142.9 (C of PNB), 147.6 (C of PNB), 162.1 (C=O), 166.3 (C=O), 170.7 (C=O); MS: no M^+ ion in EI or CI, 356 (M^+-121,1), 328 (356-28, 4).

p-Nitrobenzyl 7-hydroxyethyl-7-methoxy-3-N-carbo-p-nitronezyloxyaminoethanethio-1-carba-1-dethia-3-cephem-carboxylate (91)



The reaction of **89** with carbo-p-nitronezyloxyaminoethanethiol was carried out as described above and the crude product purified by column chromatography (20:20:80 EtOAc:hexanes:MeCN) to afford a yellow oil in 68% yield; IR: 3400 (broad, OH), 1700-1770 (broad, C=O), 1520 and 1350 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 1.26 (3H, d, J=6.4 Hz, CH_3CH_2), 1.80-2.60 (4H, m, CH_2CH_2), 2.88-2.94 (2H, m, CH_2N), 3.34-3.59 (2H, m, CH_2S), 3.60 (3H, s, CH_3O), 3.63-3.68 (1H, m, CHN), 4.38 (1H, q, J=6.5 Hz, CHO), 5.16 (2H, s, CH_2PNB), 5.27 (1H, d, J=13.5 Hz, CH_AH_BPNB), 5.39 (1H, d, J=13.4 Hz, CH_BH_APNB), 5.59 (1H, broad s, NH), 7.48 (2H, d, J=8.8 Hz, PNB), 7.58 (2H, d, J=9.0 Hz, PNB), 8.19 (4H, d, J=8.8 Hz, PNB); MS :highest peak is 238 (MW=630).

Sodium 7-ethyl-7-methoxy-3-N-acetylaminoethanethio-1-carba-1-dethia-3-cephemcarboxylate (61)



The PNB ester **90** (0.20 g, 0.42 mmol) in 20 mL of THF:H_2O (1:1) was hydrogenated in presence of 0.12 g of Pd-C (10%) at 40 Psi and 25 °C for 7 h. After removal of the catalyst and THF, the suspension was treated with 36 mg of $NaHCO_3$. The resulting mixture was washed with EtOAc and the aq. layer was lyophilized to give 0.14 g of crude product. Reverse phase column chromatography (10% MeCN in H_2O) yielded 0.13 g (77%) of **61** as a white solid; mp: becomes translucent at 177-178 °C and chars at or above 217 °C; IR (KBr): 3396 (broad, NH), 1742 (β-lactam C=O), 1661 (CONH), 1610 (COO^-) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ: 0.99 (3H, t, J=7.4 Hz, CH_3CH_2), 1.79-1.91 (1H, m, CH_2CH_3), 1.98 (3H, s, CH_3CO), 2.00-2.17 (3H, m, CH_2CH_3, CH_2), 2.42-2.54 (2H, m, CH_2), 2.80-2.86 (2H, m, CH_2S), 3.31-3.42 (2H, m, CH_2N), 3.44 (3H, s, OCH_3), 3.68 (1H, dd, J=11.7, 3.4 Hz, CHN); ^{13}C NMR (200 MHz, D_2O) δ: 9.6 (CH_3), 24.1 (CH_2), 24.6 (CH_3), 25.4 (CH_2), 28.8 (CH_2), 32.5 (CH_2), 42.1 (CH_2), 55.5 (CH_3O), 60.6 (CH), 94.2 (C-7), 120.4 (C=C), 134.7 (C=C), 169.7 (C=O), 172.8 (C=O), 177.2 (C=O); MS of free acid: 342 (M^+, 0.4), 341 (M^+-1, 2), 314 (M^+-28, 8), 270 (M^+-72, 5), 242 (M^+-100, 2); HRMS calcd for $C_{15}H_{22}N_2O_5S$ (free acid) 342.1235, found 342.1242.

CHAPTER 4: SYNTHESIS OF 6-METHOXY-PS-5 AND ATTEMPTED APPROACHES TO RELATED CARBAPENEMS

Thienamycin and related natural carbapenems

Thienamycin **1** was first isolated from the fermentation broth of *S. cattleya* in 1976. Thienamycin is tremendously appealing to both synthetic chemists and pharmacologists since it is highly potent against a broad range of bacterial infections and also possesses structural features which are quite different from other classical β-lactam antibiotics such as penicillins and cephalosporins. The bicyclic ring system of thienamycin has a methylene group instead of sulfur atom of penicillins and a double bond in the five membered ring, hence all compounds having this structure are categorized as *carbapenems*.[1] The presence of an aminoethanethio side-chain at C-2 and a 1-hydroxyethyl group at C-6 is unusual among the classical β-lactams. The *trans* relationship between the hydroxyethyl side-chain and the five membered ring is also unusual. The *cis* epimer of thienamycin has been isolated but these compounds are more reactive towards β-lactamases than thienamycin. The absolute stereochemistry of thienamycin is 5R, 6S and 8R. Its epimers having 6R and 8S configurations have already been described.

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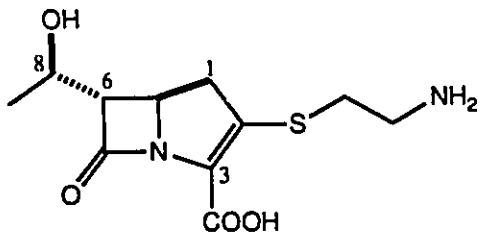
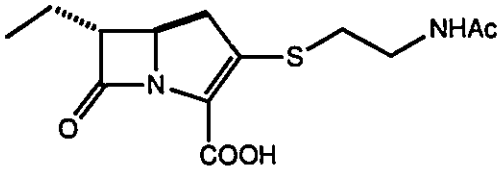
[1] Reviews on carbapenems: (a) Ratcliffe, R. W.; Albers-Schonberg, G. In *Chemistry and Biology of β-Lactam Antibiotics*; R. B. Morin and M. Gorman, Ed.; Academic Press: New York, **1982**, p 227. (b) Southgate, R.; Elson, S. In *Progress in the Chemistry of Natural Products*; W. Herz, H. Griesback, G. W. Kirby and C. Tamm Ed.; Springer: New York, **1985**, Vol. 47, p 1.



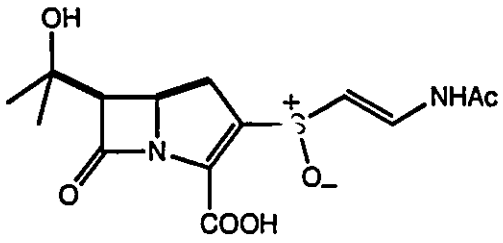
1 thienamycin



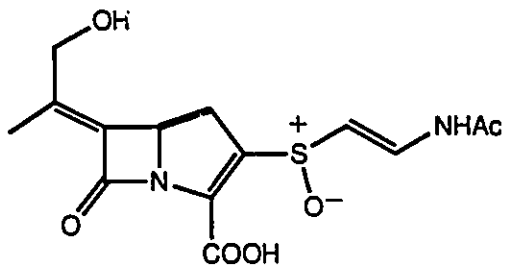
2 PS-5

Since the discovery of thienamycin more than forty natural carbapenems have been isolated. A related carbapenem, PS-5 **2** has significant inhibitory properties against a variety of Gram-positive and Gram-negative bacteria and shows β-lactamase stability.

The carpetimycins **3** and asparenomycins **4** have 6-(2-hydroxy)-propyl and 6-(1-hydroxy)propylidene groups respectively. Ohno and coworkers found R configuration at the sulfoxide by comparison of synthetic material with natural carpetimycin A.[2] Asparenomycin A was found to have 5R and also R configuration at the sulfur of sulfoxide. The epimer of asparenomycin A with S configuration at sulfoxide is less active than its R isomer.[3]



3 carpetimycin A



4 asparenomycin A

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[2] Iimori, T.; Takahashi, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 1659.

[3] Ueyo, S. In *Recent Advances in the Chemistry of β-Lactam Antibiotics;* A. G. Brown and S. M. Roberts, Ed.; The Royal Society of Chemistry: London (England), **1985**; p 131.

Structural modifications of carbapenems

Due to the chemical instability of thienamycin, a lot of effort has been directed to obtain more stable analogs. Modification or introduction of substituents at various positions has been reported.

One of these attempts involve the modification of side-chain at C-2. (The C-1 substituted analogs will be discussed in Chapter 5.) Numerous analogs having a variety of 2-sulfur side-chains derived from complex mercaptans have been synthesized.[4] RS-533 **5** is a typical example which is more active and chemically more stable than thienamycin.[5] The replacement of aminoethanethio side-chain by 2-aminoethyl group (C-2 carbon) led to dethiathienamycin **6** which showed diminished antibacterial activity (about half that of thienamycin).[6] Other examples bearing carbon substituents at C-2 have been reported.[7] One interesting 2-carbon substituent is the nitromethyl group as in **7**. Both thienamycin and PS-5 analogs bearing this side-chain has been found to be active as antibiotics.[8] Replacement of a

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[4] (a) Yamamoto, K.; Yoshioka, T.; Kato, Y.; Isshiki, K.; Nishiro, M.; Nakamura, F.; Shimauchi, Y.; Ishikura, T. *J. Antibiotics* **1983**, *36*, 407. (b) Yoshioka, T.; Kojima, I.; Isshiki, K.; Watanabe, A.; Shimauchi, Y.; Okabe, M.; Fukagawa, Y.; Ishikura, T. *J. Antibiotics* **1983**, *36*, 1473. (c) Ueda, Y.; Vinet, V. *Can. J. Chem.* **1989**, *67*, 2184.

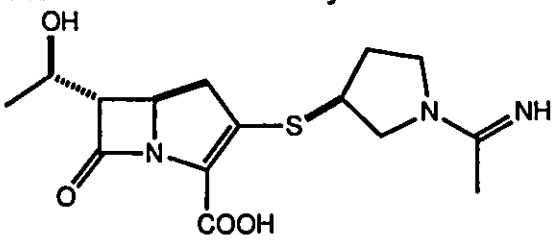
[5] Shibata, T.; Iino, K. *Heterocycles* **1986**, *24*, 1331.

[6] Fujimoto, K.; Iwano, Y.; Hirai, K. *Tetrahedron Lett.* **1985**, *26*, 89.

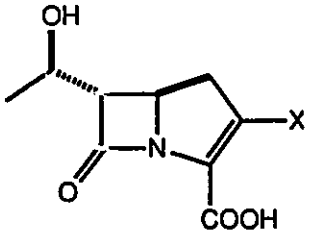
[7] (a) Rano, T. A.; Greenlee, M. L.; DiNinno, F. P. *Tetrahedron Lett.* **1990**, *31*, 2853. (b) Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *Pure Appl. Chem.* **1987**, *59*, 455. (c) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 2013. (d) Cama, L. D.; Wildonger, K.; Guthikonda, R. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron* **1983**, *39*, 2531. (e) Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *J. Med. Chem.* **1987**, *30*, 871. (f) Shiozaki, M.; Ishida, N.; Maruyama, H.; Hiraoka, T.; Sugawara, S. *J. Antibiotics* **1984**, *37*, 57. (g) Ona, H.; Uyeo, S.; Fukao, T.; Doi, M.; Yoshida, T. *Chem. Pharm. Bull.* **1985**, *33*, 4382. (h) Schmitt, S. M.; Salzmann, T. N.; Shih, D. H.; Christensen, B. G. *J. Antibiotics* **1988**, *41*, 780. (i) Ueda, Y.; Maynard, S. C. *Tetrahedron Lett.* **1988**, *29*, 5197.

[8] Yoshioka, T.; Yamamoto, K.; Shimauchi, Y.; Fukagawa, K.; Ishikura, T. *J. Chem. Soc. Chem. Commun.* **1984**, 1513.

sulfur side-chain by a nitrogen substituent at C-2 gave carbapenem **8** with less antibiotic activity than thienamycin.[9]

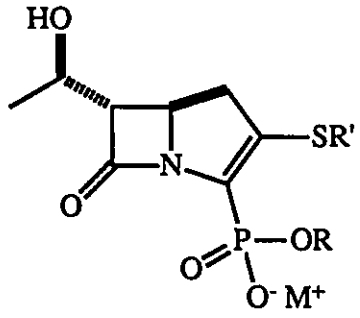


5 RS 533

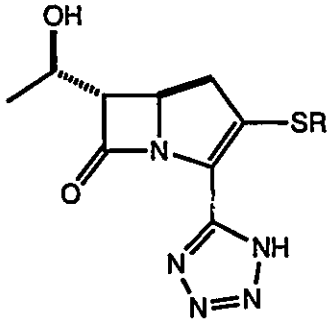


6 X=$CH_2CH_2NH_2$
7 X=CH_2NO_2
8 X=NHR

Interestingly, increased DHP (renal dehydropeptidase, an enzyme found in mammalian kidney which is responsible for the metabolic cleavage of thienamycin and related carbapenems) stability was observed in the case of 3-phosphonyl carbapenems **9** compared to 3-carboxyl and 3-tetrazolyl carbapenems.[10] The phosphonic acid or ester derivatives of carbapenems having a methoxy group instead of sulfur at C-2 were inactive or weakly active.[11] A thienamycin analog with a 3-tetrazolyl group **10** has been claimed as a useful antibiotic.[12]



9



10

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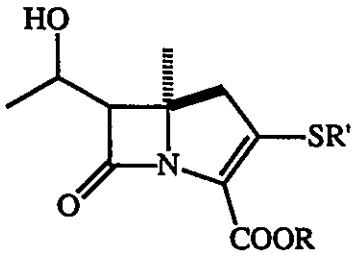
[9] (a) Chabala, J. C.; Christensen, B. G.; Ratcliffe, R. W.; Woods, M. F. *Tetrahedron Lett.* **1985**, *26*, 5407. (b) Higashi, K.; Takemura, M.; Sato, M.; Furukawa, M. *J. Org. Chem.* **1985**, *50*, 1996.

[10] Andrus, A.; Christensen, B. G.; Heck, J. A. *Tetrahedron Lett.* **1984**, *25*, 595.

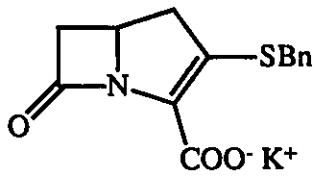
[11] Mak, C. P.; Mayerl, C.; Fliri, H. *Tetrahedron Lett.* **1983**, *24*, 347.

[12] Andrus, A.; Christensen, B. G.; Heck, J. A. *Chem. Abs.* **1986**, *105*, 78749f. U. S. US 4,544,557.

Onoue and Narukawa[13] prepared several thienamycin derivatives such as **11** with a C-5 methyl group. They reasoned that the methyl group should induce greater electron density at the β-lactam carbonyl carbon due to its electron donating effect. Hence the chemical reactivity of these carbapenems should decrease due to the decrease in electrophilicity of carbonyl group. These compounds showed an activity somewhat lower than that of N-acetylthienamycin. Compared to 5-un-substituted compounds, these 5-methyl analogs were more stable in mouse kidney homogenase.



11



12

The C-6 unsubstituted analogs such as **12** are unstable.[14] The replacement of the 6-(1-hydroxyethyl) substituent with functional groups attached by a nitrogen[15] or oxygen[16] atom at C-6 position has

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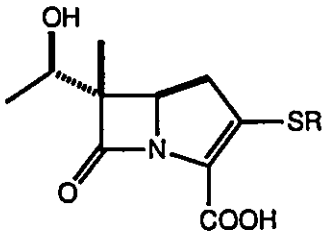
13 Onoue, H.; Narukawa, Y. *J. Antibiotics* **1989**, *XLII*, 1100. *For example without hydroxyethyl at C-6*: Ponsford, R. J.; Roberts, P. M.; Southgate, R. *J. Chem. Soc. Chem. Commun.* **1979**, 847.

14 (a) Cama, L.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 2013. (b) Basker, M. J.; Bateson, J. H.; Baxter, A. J. G.; Ponsford, R. J.; Roberts, P. M.; Southgate, R.; Smale, T. C.; Smith, J. *J. Antibiotics* **1981**, *34*, 1224. (c) Oida, S.; Yashida, A.; Ohki, E. *Chem. Pharm. Bull.* **1980**, *28*, 3494. (d) Ponsford, R. J.; Roberts, P. M.; Southgate, R. *J. Chem. Soc. Chem. Commun.* **1979**, 847. (e) Shibasaki, M.; Nishida, A.; Ikegami, S. *Tetrahedron Lett.* **1982**, *23*, 2875. (f) Takano, S.; Kasahara, C.; Ogawasara, K. *Chem. Lett.* **1982**, 631. (g) Ueda, Y.; Damas, C. E.; Belleau, B. *Can. J. Chem.* **1983**, *61*, 1996.

15 (a) Koller, W.; Linkies, L.; Pietsch, H.; Rehling, H.; Reuschling, D. *Tetrahedron Lett.* **1982**, *23*, 1545. (b) Hakimelahi, G. H. *Helv. Chim. Acta* **1982**, *65*, 1378.

16 Foxton, P. M. W.; Mearman, R. C.; Newall, C. E.; Ward, P. *Tetrahedron Lett.* **1981**, 22, 2497.

been reported. Satoh and Tsuji prepared the 6-methylthienamycin analog **13**.[17]



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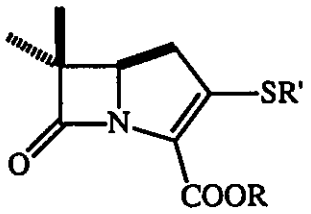
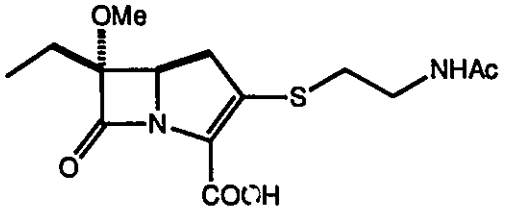


14

6,6-Dimethylcarbapenem **14** has also been synthesized.[18] Similarly introduction of 6-methoxy group in 6-epiPS-5 **15** resulted in increased chemical stability compared to PS-5.[19] Bateson and coworkers synthesized the *cis* carbapenem **16** having chloro and hydroxyethyl groups at C-6.[20]



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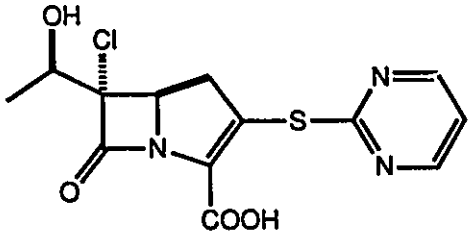

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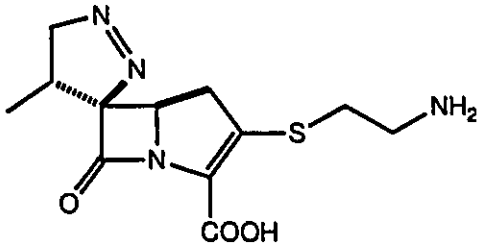
[17] Satoh, H.; Tsuji, T. *Heterocycles* **1988**, *27*, 2803.

[18] (a) Ohtani, M.; Watanabe, F.; Narisada, M. *J. Antibiotics* **1985**, *38*, 610. (b) Ohtani, M.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1984**, *49*, 5271. see also (c) Christensen, B. G.; Ratcliffe, R. W. *Chem. Abs.* **1986**, 104, 109348m, U.S. US 4,530,841. (no data).

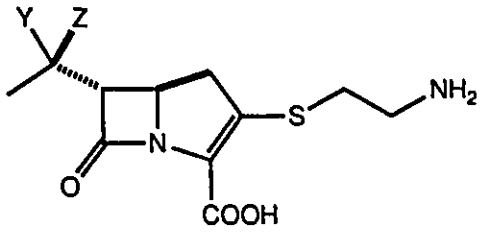
[19] (a) Watanabe, A.; Fukagawa, Y.; Ishikura, T.; Yoshioka, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2091. (b) Yoshioka, T.; Watanabe, A.; Isshiki, K.; Fukagawa, Y. *Tetrahedron Lett.* **1986**, *26*, 4335.

[20] Bateson, J. H.; Robins, A. M.; Southgate, R. *J. Chem. Soc. Perkin Trans. 1* **1991**, 29.

Corbett prepared 6,6-disubstituted spirocyclic compounds **17** *via.* dipolar cycloaddition reactions using suitable 6,7-unsaturated carbapenems.[21]



17



18 Y=H, Z=F
19 Y=H, Z=tetrazolyl
20 Y, Z=-$(CH_2)_3SO_2$-
21 Y, Z=-$O(CH_2)_2O$-

DeVries and colleagues prepared a series of carbapenems such as **18** in which the hydroxy function of thienamycin side-chain was replaced by fluorine. These compounds were found to have little or no antibacterial activity.[22] Coulton replaced the hydroxy group with a tetrazolyl group to give **19**.[23] Another unusual structural modification at this center is the introduction of the cyclic sulfone **20**.[24] The MIC of this compound against *S. aureus* FDA 209P was reported to be 3.12 μg/mL. A ketal function has also been introduced at this position to yield **21**.[25]

The addition of a methoxy group at C-8 of thienamycin resulted in a carbapenem **22** with diminished antibacterial activity relative to

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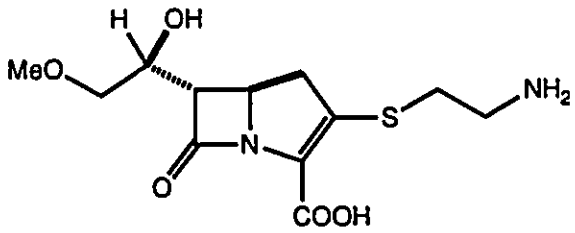
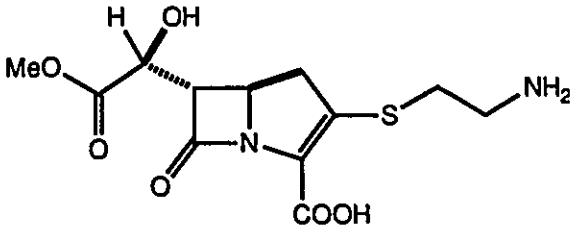
21 Corbett, D. F. *J. Chem. Soc. Perkin Trans. 1* **1986**, 421.
22 (a) DeVries, J. G. *Tetrahedron Lett.* **1984**, *25*, 5989. (b) DeVries, J. G. *Heterocycles* **1985**, *23*, 1081. (c) DeVries, J. G.; Sigmund, G.; Vorisek, G. *Heterocycles* **1985**, *23*, 1915.
23 Coulton, S. *Chem. Abs.* **1982**, *98*, 89057t. Eur. Pat. Appl. EP 59,554.
24 Yoshioka, K.; Tamura, N.; Natsugari, H. *Chem. Abs.* **1985**, *103*, 178113x.
25 Fetter, J.; Lempert, K.; Kajtar, M. P.; Bujtas, G.; Simig, G. *J. Chem. Res.(S)* **1987**, 28.

thienamycin.[26] Haebich and Hartwig replaced the methyl group at C-8 by a carboxymethyl group to yield **23**.[27]



22



23

Annulation methodologies

Although the synthesis of carbapenems has been extensively reviewed,[28] a brief discussion of the key methodologies is presented below. Methods leading to bicyclic molecules without a suitable carboxyl group at C-3 are given minimum space and/or not discussed at all.

1) Rhodium carbenoid insertion

Perhaps the best method developed so far is the rhodium carbenoid cyclization developed by Merck chemists.[29] This method has been widely applied in many carbapenems. This reaction has very high catalytic turn over (1:1000 catalyst:substrate). However this methodology fails in case of unusually strained carbapenems (Chapter 5) and penems having soft heteroatoms (see Chapter 3, page 119).

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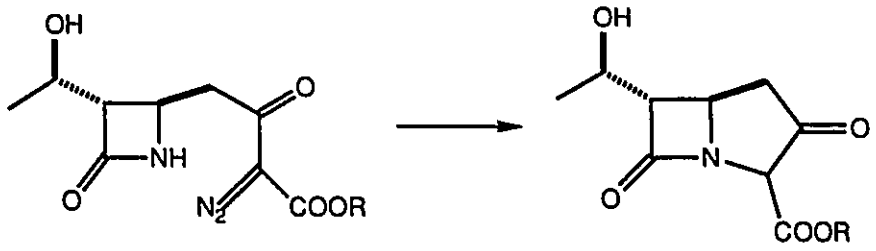
26 Ohtami, M.; Watanabe, F.; Narrisada, M. *J. Antibiotics* **1985**, *38*, 610.

27 Haebich, D.; Hartwig, W. *Tetrahedron Lett.* **1987**, *28*, 781.

28 (a) Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 463. (b) Kametani, T.; Nagahara, T. *Heterocycles* **1987**, *25*, 729.

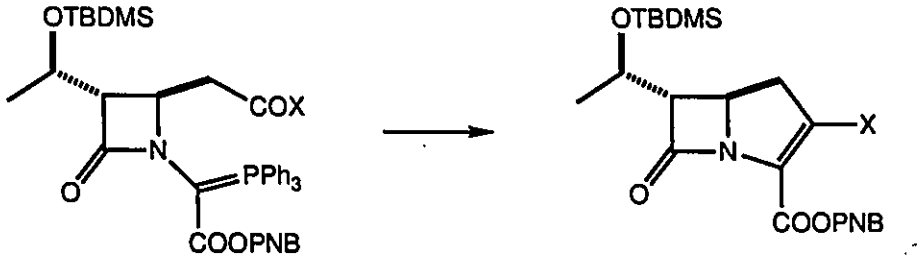
29 (a) Mellillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783. (b) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.



24 25

2) Wittig reaction

Intramolecular Wittig reaction reaction has been applied to aldehydes, ketones and thioesters. This is one of the most commonly used methods after Merck method.[30]

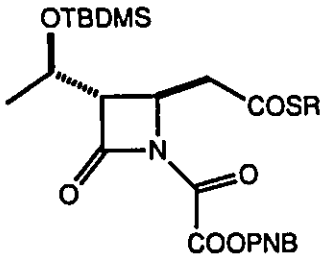


26 27

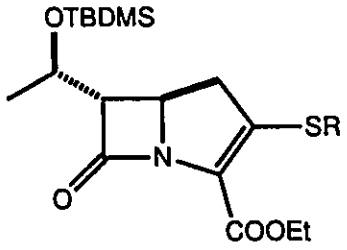
3) Phosphite coupling

This method developed by chemists at Schering[31] is an alternative to the Intramolecular Wittig approach. This cyclization has been proposed to proceed *via.* a carbene (oxalimide carbon, α to the nitrogen) type intermediate.

30 Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 8006.
31 Yoshida, A.; Tajima, Y.; Takeda, N.; Oida, S. *Tetrahedron Lett.* **1984**, *25*, 2793.



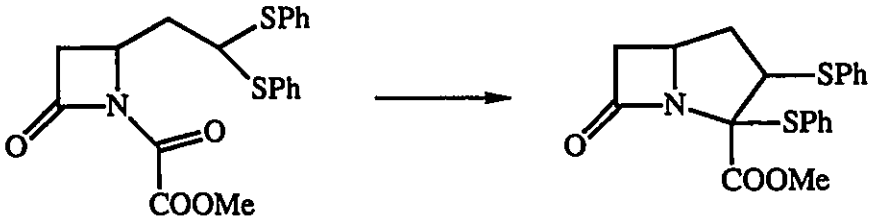
28



29

4) Kametani's methodology

This method[32] is somewhat related to the phosphite coupling method developed by Schering chemists. Reaction of the oxalimide group with triethyl phosphite generates a carbene species which presumably gives a sulphur ylide by reaction with the sulfur atom of the thioacetal. Subsequent rearrangement of the ylide yields the bicyclic product **31**.



30 31

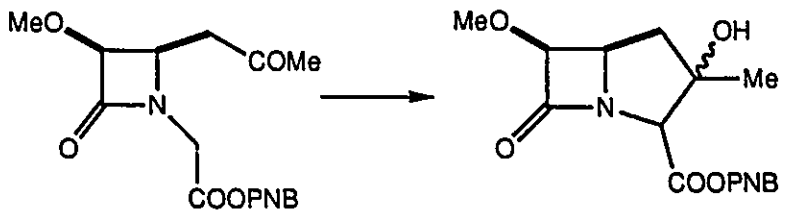
4) Aldol and Dieckmann condensation

Foxton[33] applied an aldol condensation methodology to prepare carbapenems. The selective generation of a carbanion at the carbon α to the nitrogen without competing deprotonation of other acidic protons in **32a** is interesting. The bicyclic compound **33** was obtained in 33% yield.

---

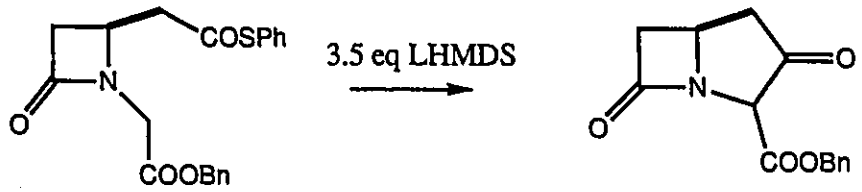
[32] Kametani, T.; Chu, S. D.; Itoh, T. C.; Wang, A.; Nakayama, T.; Honda, T. *J. Chem. Soc. Chem. Commun.* **1988**, 544.

[33] Foxton, P. M. W.; Mearman, R. C.; Newall, C. E.; Ward, P. *Tetrahedron Lett.* **1981**, 22, 2497.



32a **33**

The use of thioester as an electrophilic carbonyl allowed to extend this methodology to the cases where enolizable hydrogens are present at C-5 yielding the desired bicyclic ketoester **34**.[34] The yield of this annulation is better than that involving aldehydes or ketones.



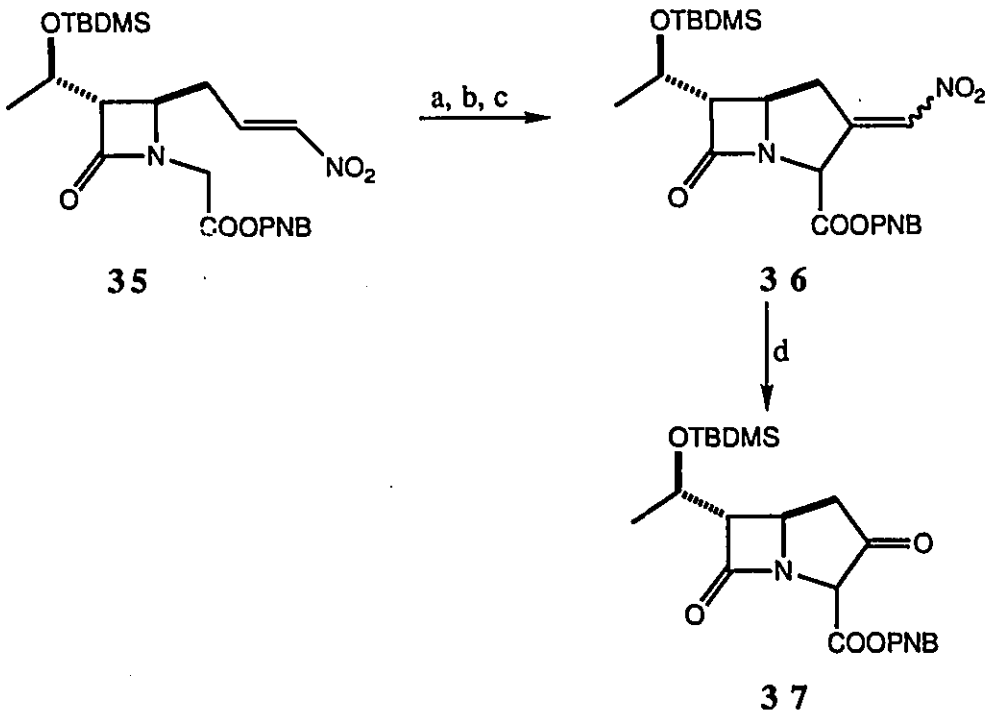
32b **34** (79%)

6) Michael addition

Hanessian applied intramolecular addition of an enolate to a nitro-olefin.[34a] Normally, this addition is a high risk strategy because by comparing the acidity of enolizable protons one would expect deprotonation at homoallylic position. The resultant anion can undergo ring cleavage reaction. However, when the reaction was performed at -100 °C the desired bicyclic product was obtained.

---

[34] *For condensation with thioesters*: Hatanaka, M.; Yamamoto, Y.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1981**, *22*, 3883.
34a Hanessian, S.; Desilets, D.; Bennani, Y. L. *J. Org. Chem.* **1990**, *55*, 3098.



a) LHMDS, THF, -100 °C; b) PhScCl; c) H_2O_2; d) O_3

7) Tandem (3+2) Michael addition and cyclization

Hirai and coworkers[35] prepared the bicyclic ketoester precursor of thienamycin *via.* 3+2 cyclization involving Michael addition of the β-lactam nitrogen to a suitable receptor and subsequent cyclization. The yield in this cyclization is low presumably due to the elimination of SCH_3 *via.* 1,2 proton shift. Mastalerz also studied similar cyclization strategy using allenes.[36] Although the yield was reasonable in cyclization step the subsequent reaction leading to a carbapenem intermediate 41 was unsuccessful. (During our studies in this type of cyclization methodology we also encountered similar problems.)

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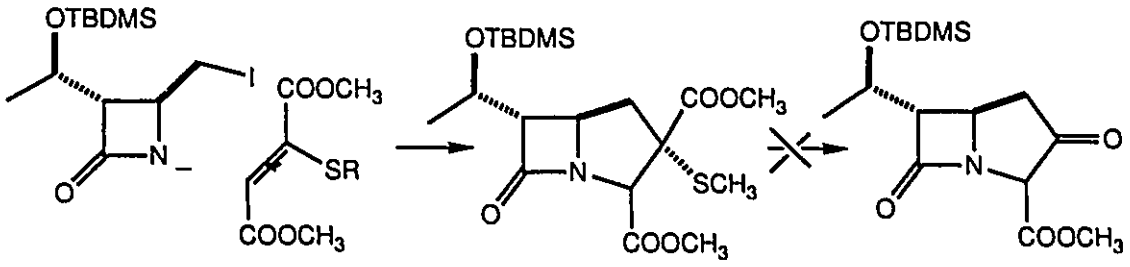
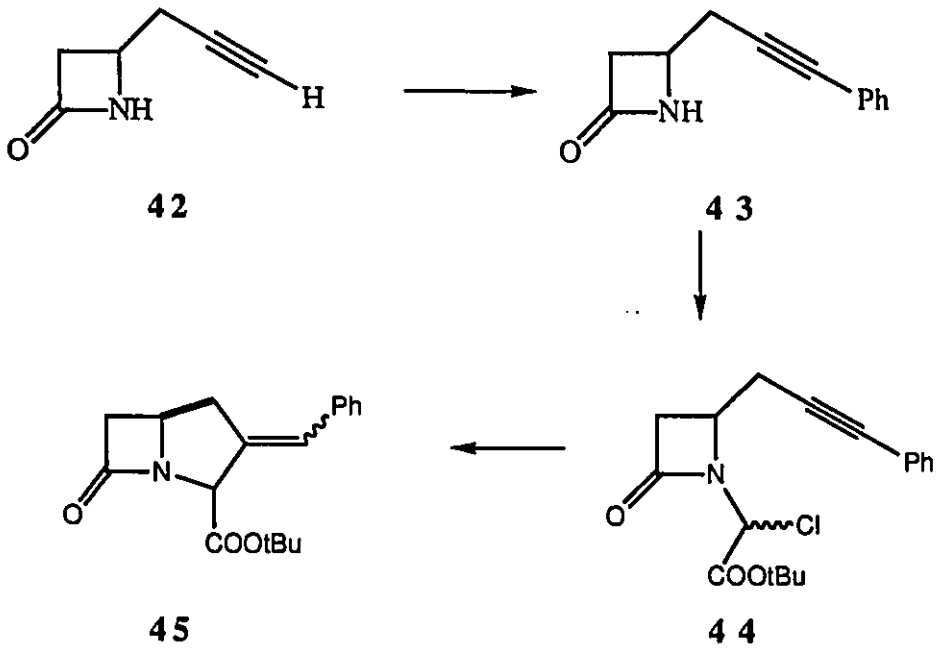
35 Fujimoto, K.; Iwano, Y.; Hirai, K. *Tetrahedron Lett.* **1984**, *25*, 1151.
36 Mastalerz, H.; Vinet, V. *Tetrahedron Lett.* **1985**, *26*, 4315.



38 39 40 41

8) Radical cyclization

Bachi and coworkers[37] prepared a carbapenam using a radical cyclization. The cyclization worked well when a phenylacetylene moiety was used but failed when a terminal double bond or triple bond was used.



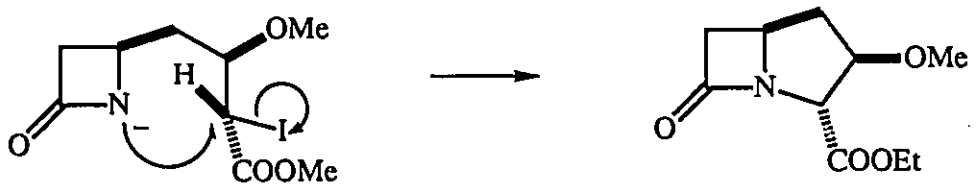
42 43 45 44

9) S_N2 cyclization

The cyclization *via.* nucleophilic substitution leading to N-C bond formation is highly dependent on the stereochemical features of the

[37] Bachi, M. D.; Mesmaeker, A. D.; Mesmaeker, N. S. *Tetrahedron Lett.* **1987**, *28*, 2887.

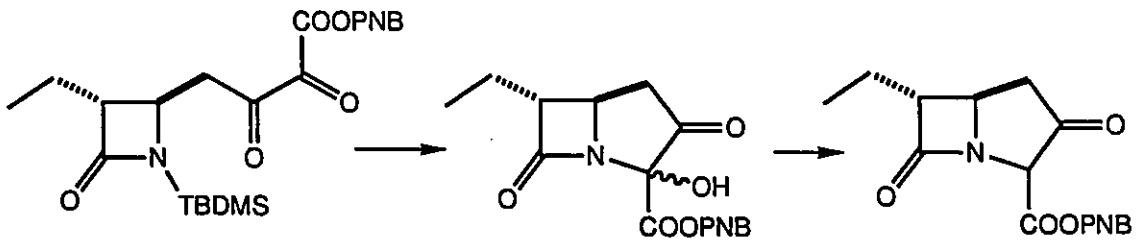
substrate. The example shown below **46** cyclizes to give 80% yield of carbapenam **47**, but its epimer polymerized under similar conditions.[38]



46 **47**

10) Wasserman's methodology

Wasserman prepared PS-5 intermediate **50** by cyclization of tricarbonyl system **48**.[39] The cyclization proceeds with excellent yield. However the deoxygenation step gives poor yield (30% when carboxylic protective group is p-nitrobenzyl and 42% for t-butyl group).



93% 30%

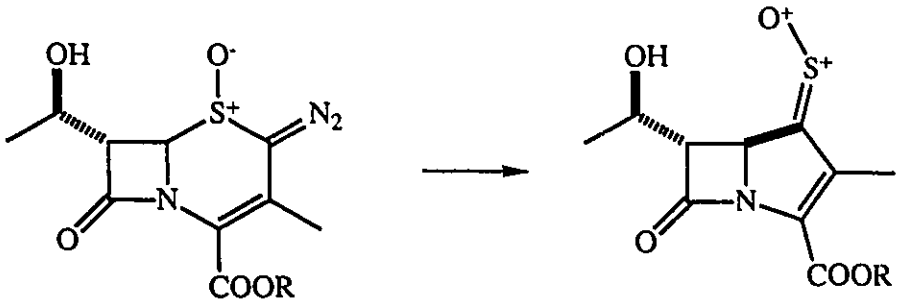
48 **49** **50**

11) Ring contraction reactions

Rosati and collaborators used a photochemical Wolff-type rearrangement reaction to prepare carbapenems.[40] The compound **52** was used as a precursor to carbapenems having C-1 oxo or hydroxy function.

---

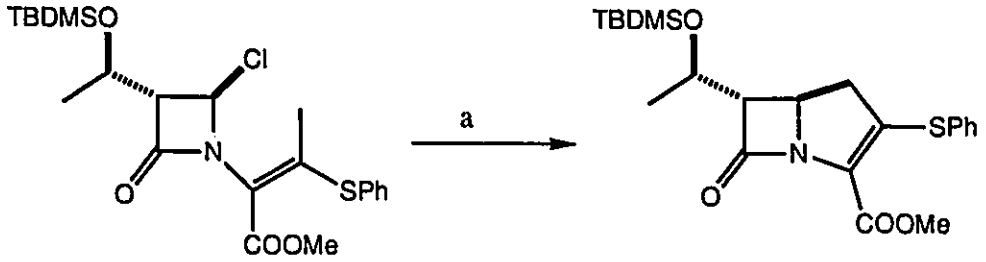
[38] Dumas, F.; d'Angelo, J. *Tetrahedron Lett.* **1986**, *27*, 3725.
[39] Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3747.
[40] Rosati, R. L.; Kapili, L. V.; Morrissey, P.; Retsema, J. A. *J. Med. Chem.* **1990**, *33*, 291.



51 52

12) Bristol method

Dextraze reported the cyclization to a carbapenem by carbon-carbon bond formation at C-1 and C-5 position.[41] The yield of **54** in this synthesis is low (17%).



53 54

a) LHDMS, $AgBF_4$

13) Methods in which β-lactam ring is formed at a later stage

Yoshioka and coworkers prepared the 6-hydroxy carbapenam **56** by DCC mediated cyclization of an amino acid.[42] Although the yield in this reaction is very good, the number of steps involved in conversion of this compound to 6-methoxy-epi-PS-5 is high making it an unattractive approach. Bachi and Rosenblum used a similar strategy.

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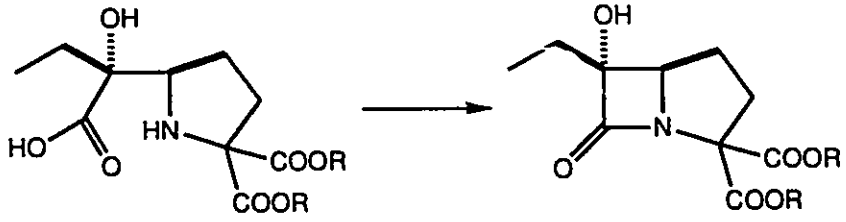
41 Dextraze, P. *Chem. Abs.* **1989**, *110*, 172997m, U.S. US 4,769,451.

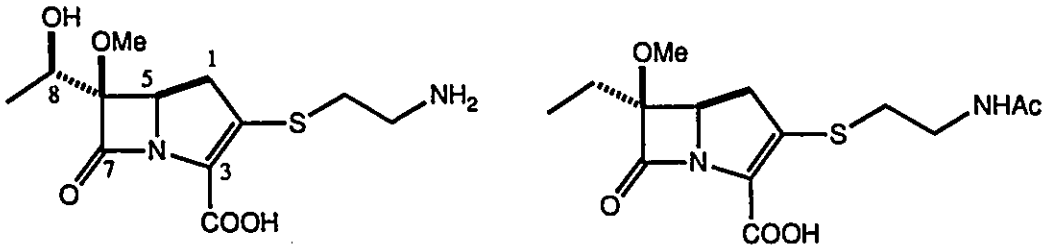
42 (a) Yoshioka, T.; Watanabe, A.; Isshiki, K.; Fukagawa, Y. *Tetrahedron Lett.* **1986**, *26*, 4335. (b) Bachi, M. D.; Breiman, R.; Meshulam, H. *J. Org. Chem.* **1983**, *48*, 1439.



55 56

Attempted approaches to 6-methoxycarbapenems

As mentioned in Chapter 1, 6-methoxycarbapenems having thienamycin **57** or PS-5 **58** type side-chains at C-6 may be more stable than thienamycin or PS-5. Hence we attempted to synthesize these carbapenems.



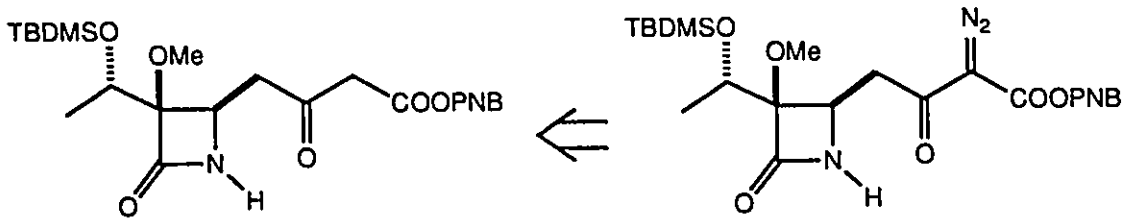
57 58

The following sections describe in brief, a number of synthetic pathways which were investigated prior to finding one that allowed us to complete the synthesis of a 6-methoxycarbapenem. These approaches are presented in more or less the same chronological order as they were carried out. All approaches seemed reasonable based on literature precedent. However in the specific situations, many of the sequences did not lead to desired targets, as certain reactions failed or gave poor yields or gave poor stereochemical control. Thus these appr-

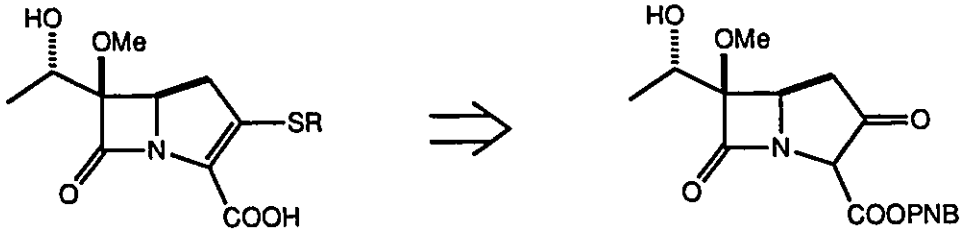
oaches were abandoned. It seems that the additional methoxy group at C-3 in the monocyclic β-lactam exerted a more pronounced stereochemical influence than expected. Thus the approaches, which were based on the literature models without this methoxy group, proved to be overly optimistic. Although these experiments did not lead to desired conclusions it was felt necessary to include them in order to present a realistic account of events which led to the development of a successful approach.

The spectroscopic data concerning establishment of structures of products will not be described in the following sections. Most of these reactions were followed by ^1H NMR. Mass spectra were recorded whenever feasible. Infrared spectra were not obtained. These data are presented in the Experimental section of this Chapter. We feel confident that the available data are consistent with the structures given in the following discussion.

Since the Merck method is the best method available for the synthesis of carbapenems, we decided to prepare 6-methoxy-7-epithienamycin **62** as shown in the following retrosynthetic scheme which involved the preparation of β-ketoester **59**, rhodium carbenoid cyclization of the corresponding diazo compound **60** followed by introduction of a sulfur side-chain at C-2 of **61**. The introduction of the various nucleophiles into the bicyclic thienamycin intermediate *i.e.* demethoxy analog of **61**, at C-2 has been well developed.

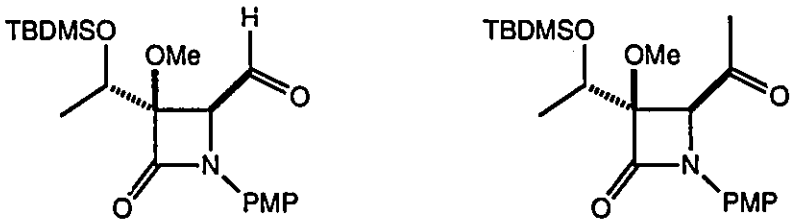


59 **60**



62 **61**

Initial studies involved the use of compounds **63** and **64** for the preparation of **59** or **60**. The preparation of compound **63** has already been described in Chapter 2. The compound **64** was prepared from the corresponding methylcinnamylazetidinone **68** by ozonolysis.[43]

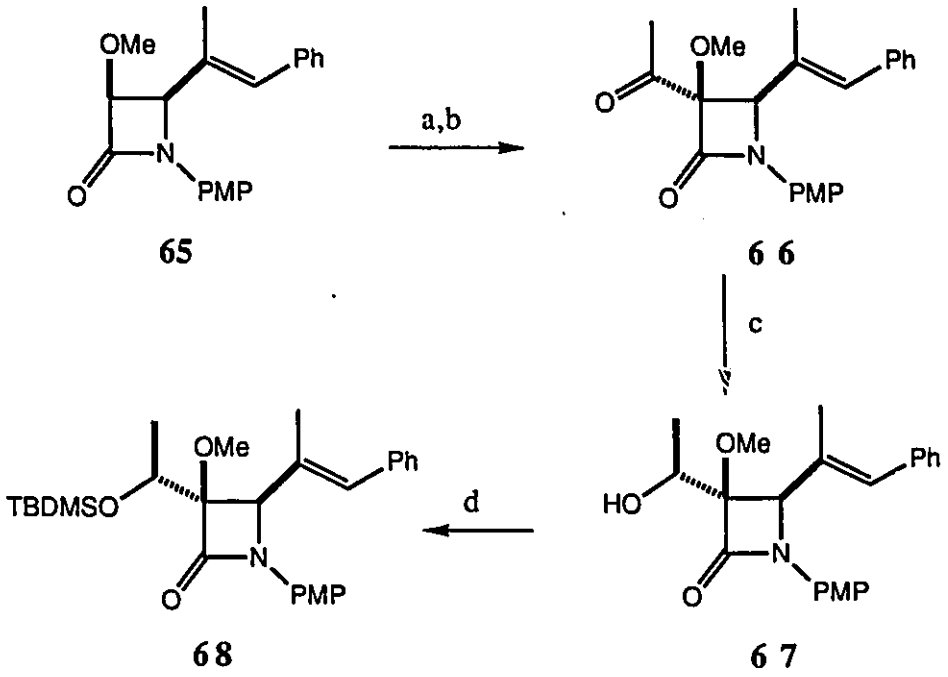


63 **64**

The monocyclic azetidinone **65** was prepared using a 2+2 ketene imine cycloaddition reaction of an imine (derived from p-anisidine and 1-methylcinnamaldehyde) with methoxyacetic acid activated with

[43] Preparation: Sharma, M. K. *Ph.D. Thesis*, University of Ottawa, **1990**, p 176.

DMF/oxalyl chloride in the presence of TEA.[44] The cycloaddition was carried out on a 175 mmol scale of imine in 76-80% yield. The anion derived from **65** was quenched with acetaldehyde to yield 3-hydroxyethyl azetidinone as a mixture of epimers. Oxidation with PCC and subsequent reduction of **66** using L-Selectride/TMEDA afforded one pure diastereomer **67** and the hydroxyl group was protected as its TBDMS ether.



a) LDA, CH_3CHO, THF, -78 °C; b) PCC, CH_2Cl_2, NaOAc, 4Å mol. sieves; c) L-Selectride, TMEDA, THF, -78 °C; d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C

The relative configuration at the hydroxyethyl side-chain in **68** was established by conversion of **69** to **64** *via.* a sequence of reactions involving ozonolysis of the cinnamyl group and addition of methyllithium to the resultant aldehyde followed by oxidation with PCC.

[44] Sharma, M. K. *Ph. D. thesis*, University of Ottawa, **1990**, p 211 and 216 details of similar conversions has already been described by him (note the difference in scale).

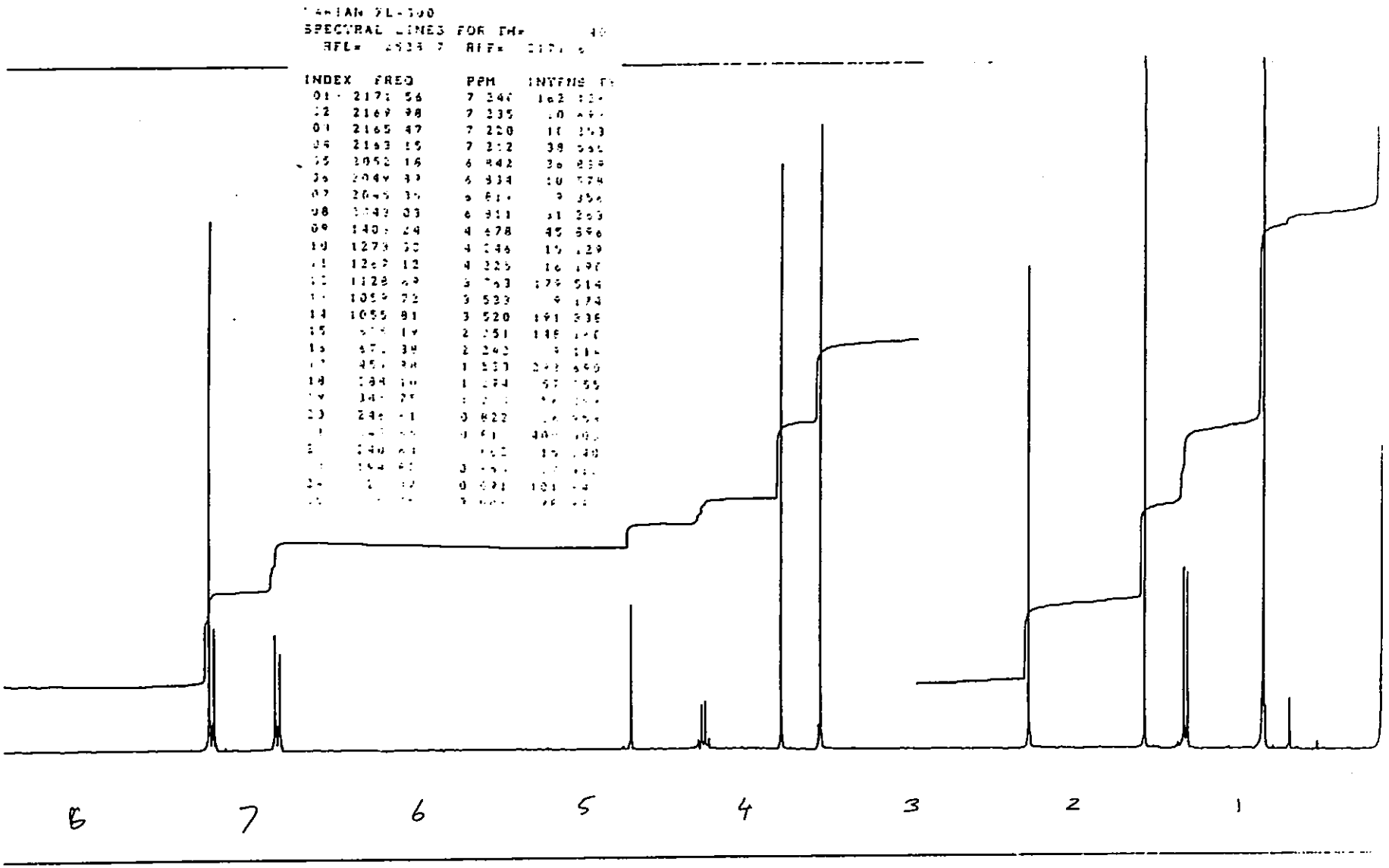


Fig. 8 ^{1}H NMR spectrum of 64 from 68

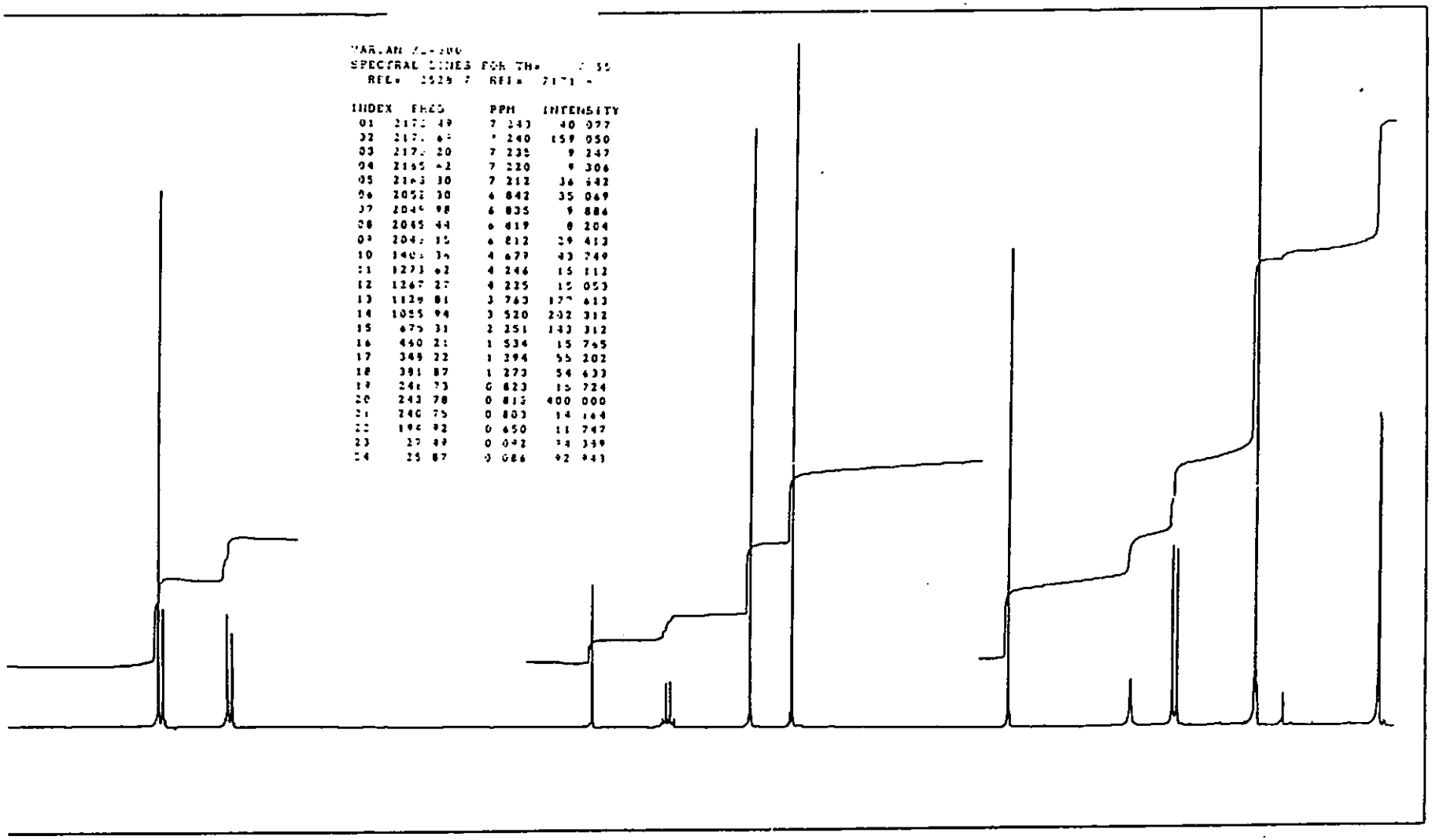
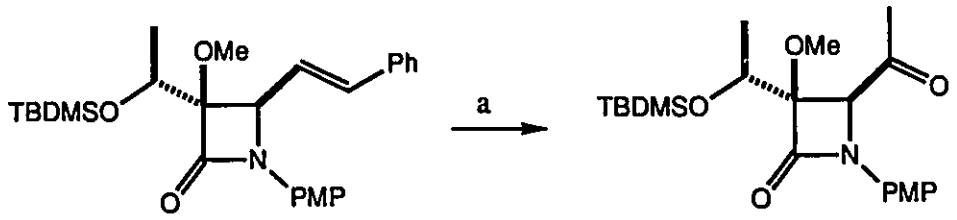


Fig. 9 ^{1}H NMR spectrum of 64 from 69

Since the sample of the acetyl compound **64** obtained from **69** is identical in ^1H NMR (Fig. 8 and 9) to that from **68**, the configuration at this center of both **68** and **69** is the same.



69 **64**

a) O_3, CH_2Cl_2, MeOH, DMS, -78 °C to 25 °C; b) MeLi, THF, -78 °C; c) PCC, CH_2Cl_2, 4Å mol. sieves, NaOAc.

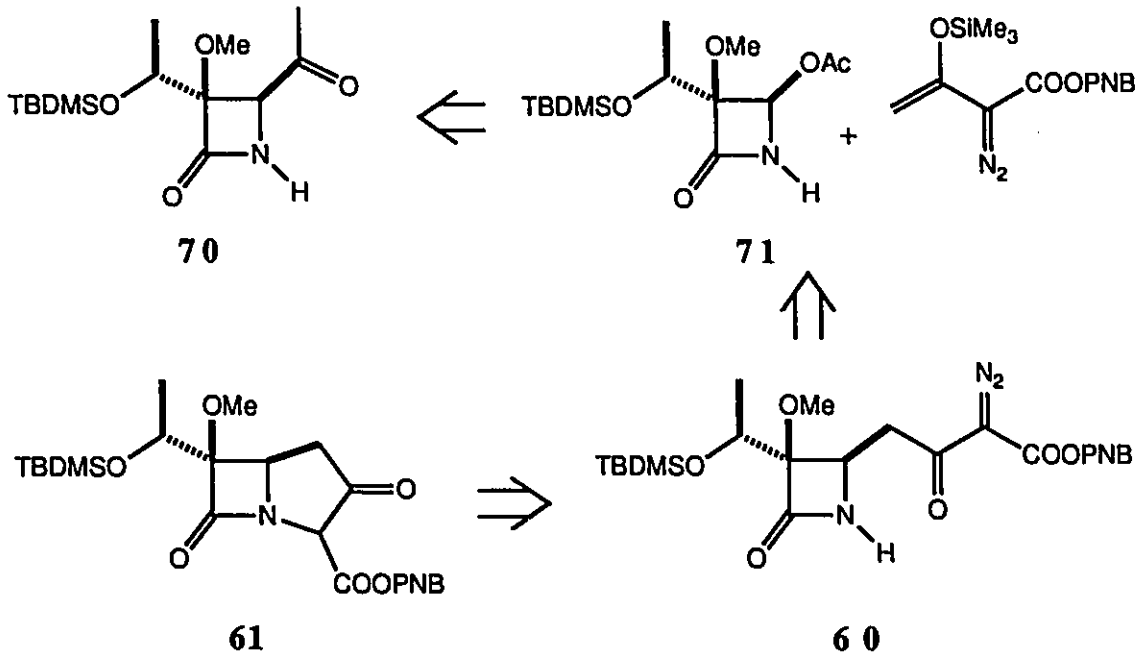
When the project was initiated we had felt confident and most certainly hopeful that both **63** and **64** had all the required stereochemical features of thienamycin. The configuration of **69** has been determined by X-ray crystallography.[45] Unfortunately the X-ray structure of **69** showed that the configuration at the hydroxyethyl side-chain is that of epithienamycin. Hence **64** should also have an epithienamycin type configuration at the hydroxyethyl side-chain. Nevertheless, we decided to investigate the possibility of using **63** or **64** in order to prepare the 6,6-disubstituted analogs such as **62**.

1) Synthetic approach involving C-C bond formation at C-4

At this point, the synthetic problem appeared to have been reduced to the development of a simple and effective methodology for the production of **59** from either **63** or **64**. Since **60** should be

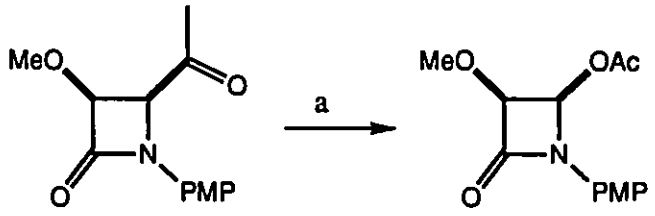
[45] Sharma, M. K. *Ph.D. Thesis*, University of Ottawa, 1990, p 80.

accessible *via.* a convergent route starting from the ketone **70** initial studies were directed towards effecting transformations shown below.[46]



70 **71** **61** **60**

When compound **72**, obtained by ozonolysis of **65**, was treated with MCPBA in refluxing dichloroethane for 24 hours the acetate **73** (*cis*, based on the J=3.6 Hz for proton signal at C-3) was obtained in 34% yield.



72 **73**

a) MCPBA, $C_2H_4Cl_2$

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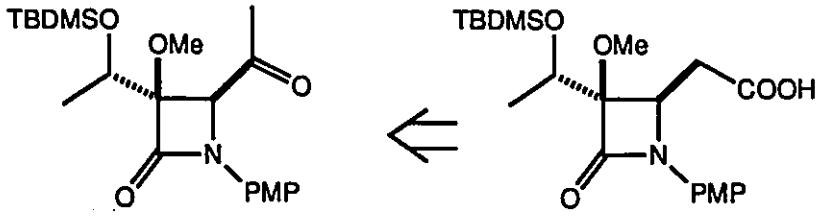
[46] (a) Karady, S.; Amato, J. S.; Reamer, R. A.; Wienstock, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 6765. (b) Takano, S.; Kasahara, C.; Ogasawara, K. *Chem. Lett.* **1982**, 631. (c) Reider, P. J.; Grabowski, E. J. *Tetrahedron Lett.* **1982**, *23*, 2293 and references therein.

The Baeyer Villiger reaction of **64** and **70** was unsuccessful under a variety of conditions (such as MCPBA/$NaHCO_3$, MCPBA/H^+, MCPBA only, at 0 °C to refluxing dichloroethane; MMPT[47], H_2O_2/acetic acid, peracetic acid, CAN[48]/MeCN/60 °C). In case of MCPBA and MMPT reactions, starting ketones were recovered. The starting material was destroyed in other experiments. The failure of the Baeyer Villiger reaction could presumably be due to the additional steric hindrance conferred by the t-butyldimethylsiloxyethyl group since the ketone **72** without this substituent gave the rearranged product **73**.

2) Approaches involving 1,2-carbonyl transposition in **64**

An alternate approach to the β-ketoester **59**, which would allow us to take advantage of the *cis* relationship between the methoxy group and the C-4 acetyl substituent, requires the conversion of **64** to the carboxylic acid **74** followed by two carbon homologation to **59**. Such a sequence requires a 1,2-transposition of the carbonyl[49] on the acetyl side-chain of **64**.



64 **74**

A possible solution to this is to introduce hetero-atom substituents at the α-carbon of the acetyl moiety, reduce the carbonyl group,

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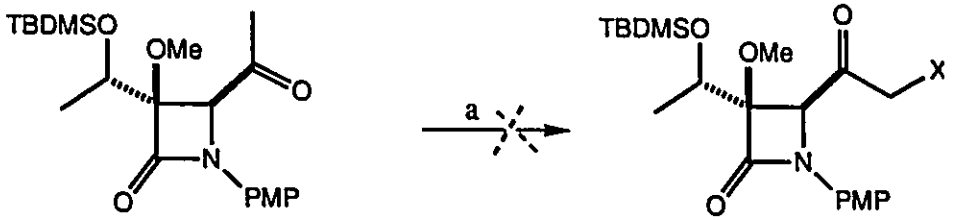
[47] Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015.

[48] (a) Trahanovsky, W. S.; Young, L. B. *J. Org. Chem.* **1966**, *31*, 2033. (b) Mehta, G.; Pandey, P. N.; Ho, T. L. *J. Org. Chem.* **1976**, *41*, 953.

[49] Kane, V. V.; Singh, V.; Martin, A.; Doyle, D. L. *Tetrahedron* **1983**, *39*, 345.

activate the resultant hydroxyl group as a mesylate and eliminate it to yield a vinyl thioether or vinyl ether. Attempts to introduce sulfur (LDA/PhSSPh[50], LDA/$MeSSO_2Me$[51]) or oxygen (LDA,TMSCl/MCPBA[52]) substituents at the methyl group α to the carbonyl could not be developed on preparatively useful scales. In most of these reactions the crude products gave complex ^1H NMR spectra indicating many products and pure products could not be isolated.



64 **75** X=SMe, **76** X=SPh, or **77** X=OH

a) LDA, PhSSPh or LDA, $MeSSO_2Me$ or LDA, TMSCl; MCPBA

The enolsilyl ether derived from **64** was treated with bromine at -78 °C for 45 minutes to yield α-bromo product **78**. This bromide was converted to the 4-vinyl azetidinone **79** *via*. reduction of carbonyl group, activation of hydroxy group as a mesylate and elimination using zinc. We intended to transform this 4-vinyl azetidinone **79** to 4-(2-hyroxyethyl)azetidinone **80**,[53] by hydroboration. The reaction of **79** with borane/THF[54] at 0 °C to 25 °C for 3 h gave abysmal yield of mixture of regioisomeric alcohols (12% of **80** and 9% of its regioisomer),

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50 Trost, B. M.; Hiroi, K.; Kurozumi, S. *J. Am. Chem. Soc.* **1975**, *97*, 438.

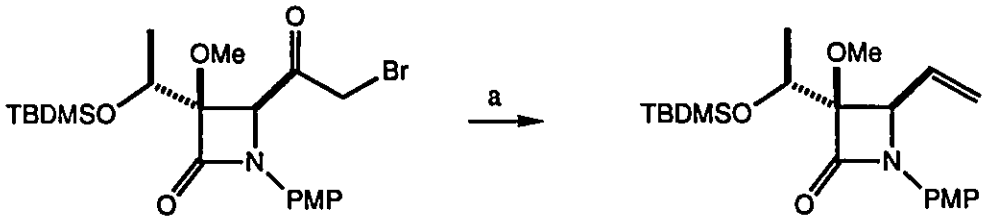
51 (a) Greene, A. E.; LeDrian, C.; Crabbe, P. *J. Org. Chem.* **1980**, *45*, 2713. (b) Backer, H. J. *Bull. Chim. Soc. Belg.* **1953**, *62*, 3. *Chem. Abs.* **1954**, *48*, 5075c.

52 Rubottom, G. M.; Gruber, J. M.; Juve, Jr., H. D.; Charleson, D. A. *Org. Synth.* **1985**, *64*, 118.

53 Ikota, N.; Yoshino, O.; Koga, K. *Chem. Pharm. Bull.* **1982**, *30*, 1929.

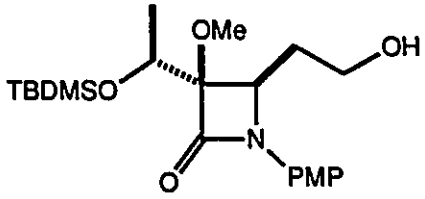
54 Brown, H. C.; Zwiefel, G. *J. Am. Chem. Soc.* **1960**, *82*, 4708.

while no reaction occurred with 9-BBN at 25 °C for 24 h and at 67 °C for 3 h.[55]



78 79

a) $NaBH_4$, EtOH; MsCl, TEA, CH_2Cl_2; Zn, NaI, acetone:DMF

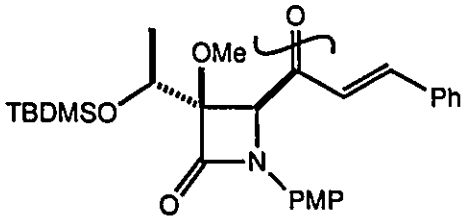


80

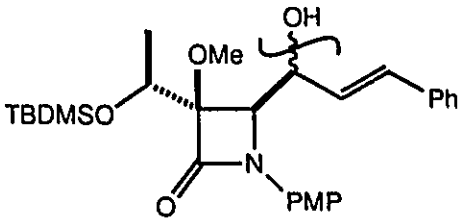
Since the above sequences for a 1,2-carbonyl transposition were unsatisfactory, the following scheme was probed. The anion of the ketone **64** was quenched with benzaldehyde at -78 °C and the resultant aldol was converted to α,β-unsaturated ketone **81** by refluxing in benzene in the presence of toluenesulfonic acid. This ketone upon deoxygenation and ozonolysis of the double bond was expected to result in the desired 1,2-carbonyl transposition product. Deoxygenation by converting the ketone to a dithiane derivative and subsequent desulfurization with Raney Nickel could not be completed since the attempted preparation of dithiane derivative with propanedithiol and $BF_3.OEt_2$ at 25 °C for 24 hours resulted in destruction of starting material. Reduction of **81** with sodium borohydride and cerium

[55] Scouten, C. G.; Brown, H. C. *J. Org. Chem.* **1973**, *38*, 4093.

trichloride gave the allylic alcohol **82**. Deoxygenation of this alcohol **82** *via*. a free radical[56] (NaH, CS_2, MeI and Bu_3SnH) or carbocation[57] (ZnI_2, $NaCNBH_3$) intermediates was unsuccessful.



81



82

3) Approaches involving S_N2 reactions at C-5

These sequences involve the use of aldehyde **63** obtained from 4-cinnamylazetidinone. Sodium borohydride reduction of **63** and mesylation of the resultant alcohol gave the mesylate **83** in excellent yield (90%). [The crude mesylate obtained was used in subsequent reaction without further purification.] Reaction of **83** with sodium iodide in refluxing acetone for 18 hours gave 79% of iodide **86**. The mesylate **83** upon reaction with CAN under the usual conditions gave 55% yield of the N-unsubstituted compound **84** which was converted to iodide **88** by applying a procedure similar to that for **86**. In this case the displacement reaction could not be pushed to completion since the prolonged heating resulted in the buildup of a non β-lactam product. (The structure of this compound could not be determined unambiguously; it is thought to be an isomeric γ-lactam). The NH compounds **84** and **87** obtained from mesylates **83** and **84** were

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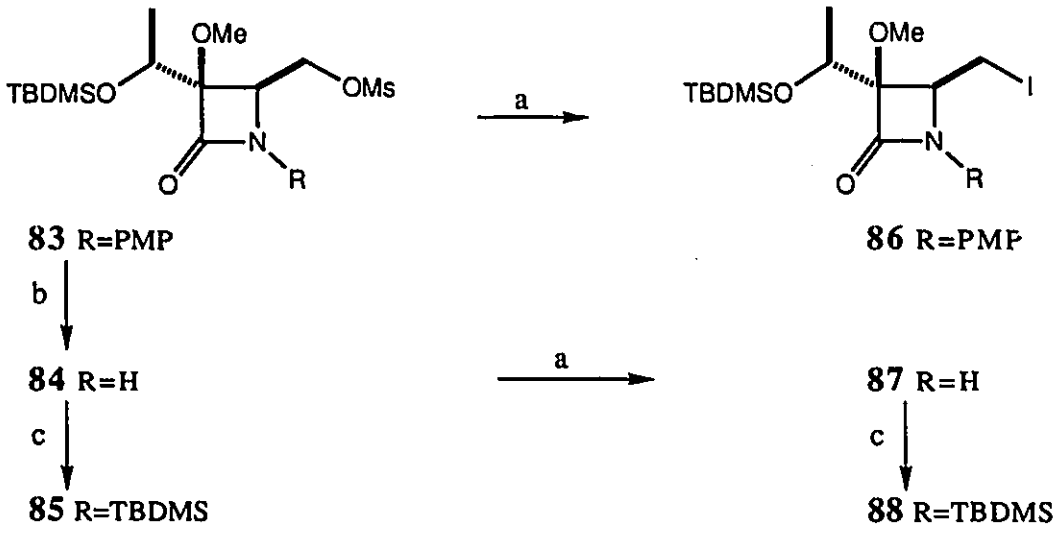
56 Tacono, S.; Ramussen, J. R. *Org. Synth.* **1985**, *64*, 57.

57 (a) Kim, S.; Oh, C. H.; Ko, J. S.; Ann, K. H.; Kim, Y. J. *J. Org. Chem.* **1985**, *50*, 1927. (b) Lau, C. K.; Dufresne, C.; Belenger, P. C.; Pic'tre, S.; Scheigetz, J. *J. Org. Chem.* **1986**, *51*, 3038.

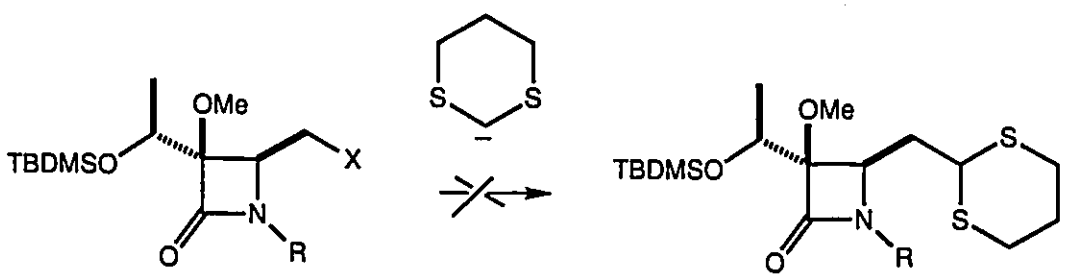
silylated with TBDMSOTf and 2,6-lutidine in dichloromethane at 0 °C to afford **85** and **88** in more than 90% yield respectively.



83 R=PMP
84 R=H
85 R=TBDMS
86 R=PMP
87 R=H
88 R=TBDMS

a) NaI, acetone, reflux; b) CAN, MeCN:H_2O, -5 °C to 0 °C; c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to 25 °C

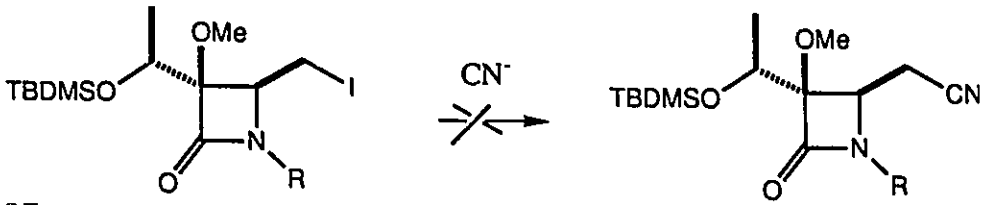
2-Lithio-1,3-dithiane, generated by treatment of dithiane with 1.1 equivalent of n-BuLi for 1 hour at -20 °C failed to give conclusive results when reacted with either the N-silylated iodide **88**, the N-silylated mesylate **85** or the iodide **87** (2 equivalents of reagent was used in this example) for 18 hours at -20 °C to 25 °C.



85 R=TBDMS, X=OMs
87 R=H, X=I
88 R=TBDMS, X=I

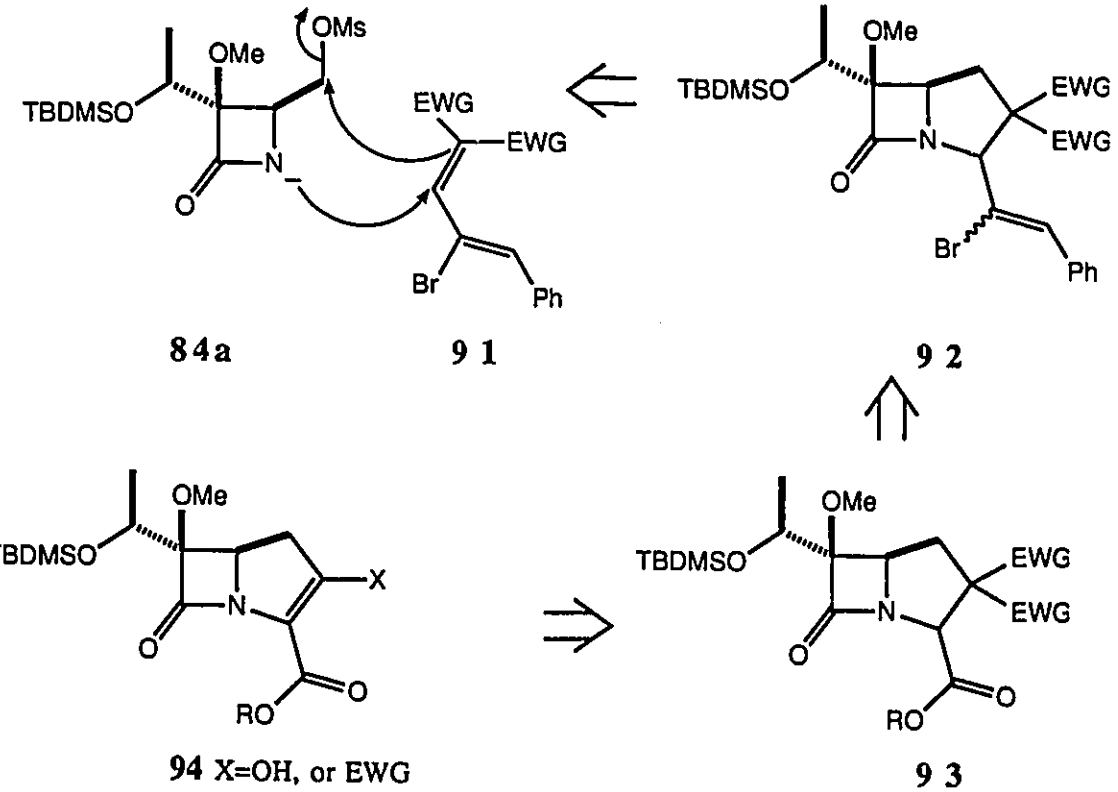
89

The iodide **87** when reacted with sodium cyanide in refluxing DMF for 18 hours gave a complex reaction mixture which was not further investigated.



87 R=H **90**

The mesylate **84** or iodide **87** appear to be valuable intermediates for a 3+2 type Michael induced cyclization reaction which has been a part of continuing study in our laboratory. The overall plan is shown in the following retrosynthetic scheme.

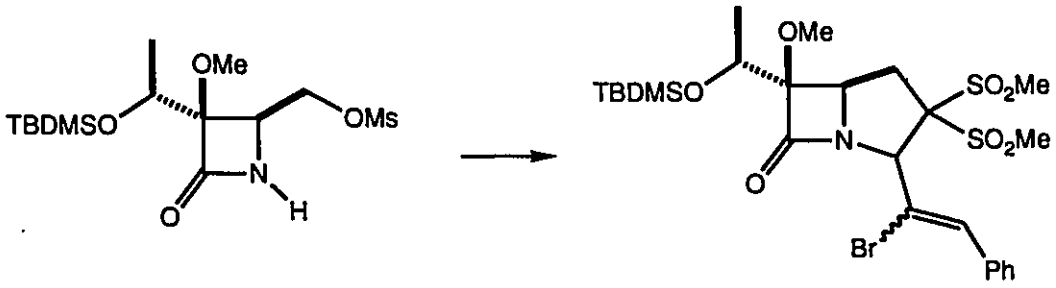


84a **91** **92**

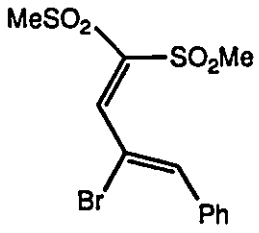
94 X=OH, or EWG **93**

Reaction of the mesylate **84** with Michael acceptor **95** in the presence of powdered KOH in THF at 25 °C for 3 hours gave the 3+2

cyclocondensation product **96** in 42% yield. The yield of this product increased to 65% when the reaction time was extended to 18 hours. Although this reaction is quite efficient in assembling the carbapenem ring system the attempts to convert the bromocinnamyl group to an ester group by ozonolysis followed by trapping of resultant acyl bromide with benzyl alcohol or methanol failed. When benzyl alcohol was used in this reaction ozonolysis of **96** was carried out at -78 °C and stirred with excess DMS for 18 hours. Benzyl alcohol (1.1 eq) and TEA (2.2 eq) was added at 0 °C to the reaction mixture which was stirred for further 2 hours. Only benzyl alcohol was isolated from the reaction mixture after usual workup. In another experiment the compound **96** was dissolved in 20 ml of CH_2Cl_2:MeOH (1:1) and ozonolyzed at -20 °C. The resultant mixture was stirred with excess DMS for 18 hours. Usual workup afforded only intractable crude product.

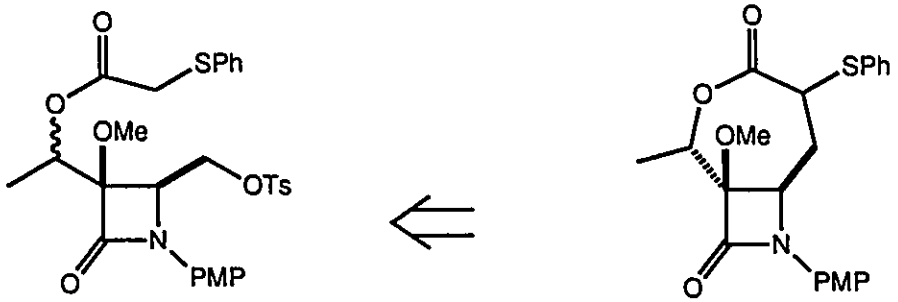


84 **96**

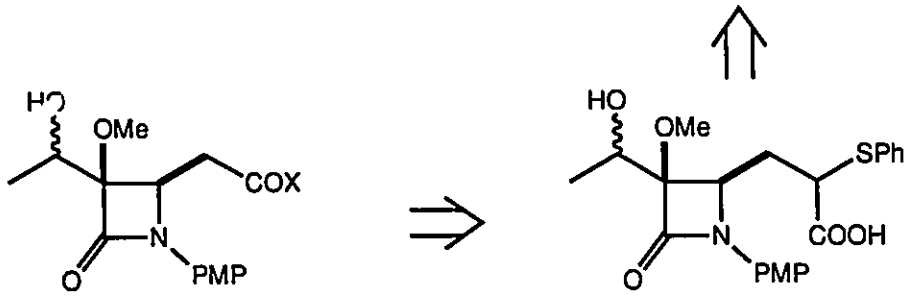


95

The above experiment clearly indicated that intramolecular displacement at this carbon is facile compared to the intermolecular S_N2 version. Therefore we also attempted to homologate the carbon chain from a different direction. A thioacetate moiety attached at the hydroxyethyl side-chain was chosen as a masked carboxyl(nyl) synthon. The anion of **97** upon intramolecular reaction was expected to give the seven membered lactone **98**. Examination of the molecular models indicated that the formation of **98** was feasible.



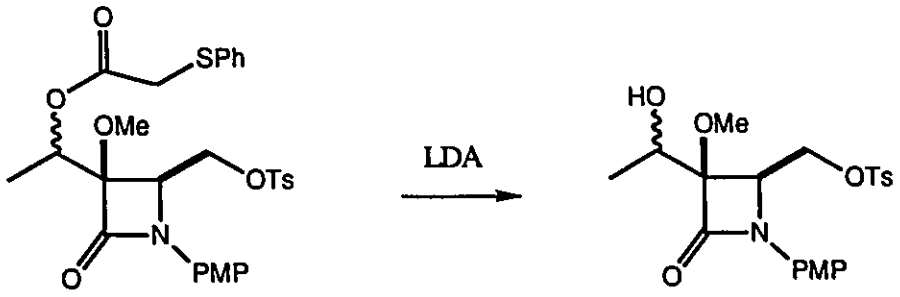
97 **98**



100 **99**

A solution of tosylate **97** in THF was added to a solution of LDA (1.1 eq) in THF at -78 °C and warmed to 25 °C over a period of 18 hours and the crude product was purified by column chromatography. Only the hydroxyethyl compound **101** was isolated from the reaction mixture (25% from **97**). The structure of **101** was established by

comparison with the known ^1H NMR spectrum. The formation of this product can be explained in terms of an elimination reaction to give a phenylthioketene and **101**.



97 **101**

4) Approaches involving the homologation of **63**

At this point it seemed that the homologation of aldehyde **63** might be a better course of action, since the addition at a sp^2 carbon has different steric requirements compared to the S_N2 reaction at a sp^3 carbon. Surprisingly, anions derived from methyl thiomethyl-methanesulfoxide[58] (n-BuLi, THF, -20 °C to 25 °C, 18 h) and methoxymethylsilane[59] (s-BuLi, TMEDA, THF, -78 °C to 25 °C, 20 h) did not add cleanly to **63**. The ^1H NMR spectra of crude products showed mostly unreacted starting material. In contrast, the anion of chloro-methyltrimethylsilane[60] (s-BuLi, TMEDA, THF, -78 °C to 25 °C, 20 h) gave a reasonable yield of epoxysilane **102** as a mixture of diastereomers. Attempted conversion of **102** to the aldehyde **103** by treatment with acids under various conditions resulted in either a recovery (1 eq of CF_3COOH, 10% aq. THF) or destruction ($BF_3.OEt_2$, -20

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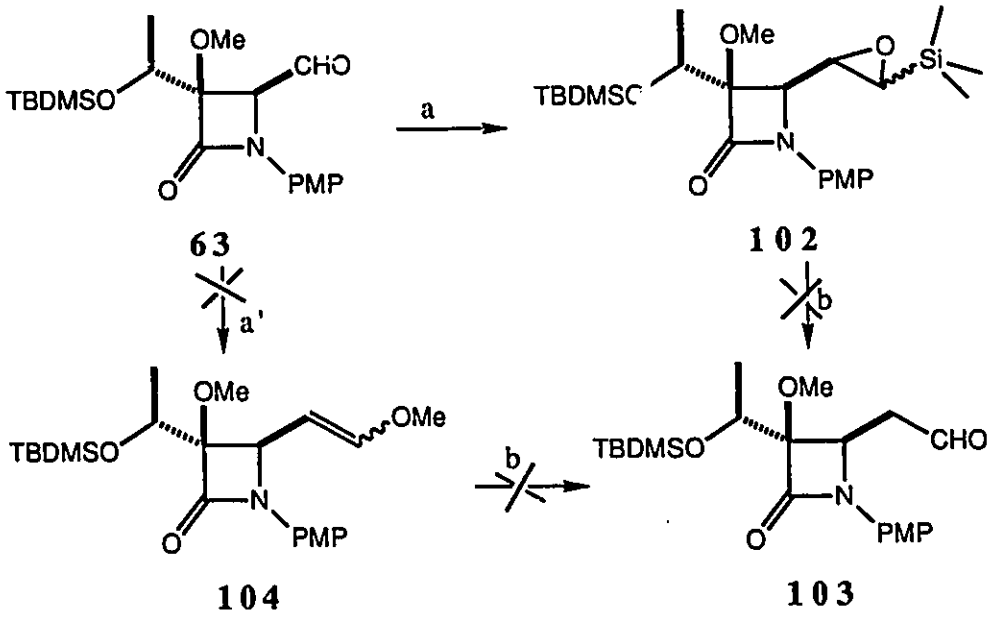
[58] Ogura, K.; Yamashita, M.; Suzuki, M.; Tsuchuhashi, G. *Tetrahedron Lett.* **1974**, *22*, 3653.
[59] Magnus, P.; Roy, G. *J. Chem. Soc. Chem. Commun.* **1979**, 822.
[60] Stork, G.; Colvin, E. *J. Am. Chem. Soc.* **1970**, *93*, 2080.

°C to 25 °C, 24 h or CF_3COOH, refluxing $C_2H_4Cl_2$, 18 h) of the starting material **102**.



a) $ClCH_2SiMe_3$, s-BuLi; a') $MeOCH_2SiMe_3$ or $Ph_3P{=}CHOMe$; b) H^+

The conversion of the aldehyde **63** to **103** *via.* a homologous enol ether **104** appeared to be another reasonable approach. The reaction of triphenylphosphoranylidenemethoxymethane[61] was carried out under two different conditions: (a) sodium hydride was added to a mixture of aldehyde and requisite phosphonium salt (1.1 eq) and the reaction mixture was stirred at 25 °C for 2 hours and 67 °C for 18 h, and (b) ylide was prepared by treatment with n-BuLi at 0 °C for 30 minutes, a solution of aldehyde **63** was added to it and the reaction mixture stirred at 0 °C to 25 °C. In both cases only unreacted starting material was seen in ^1H NMR spectra of crude products.

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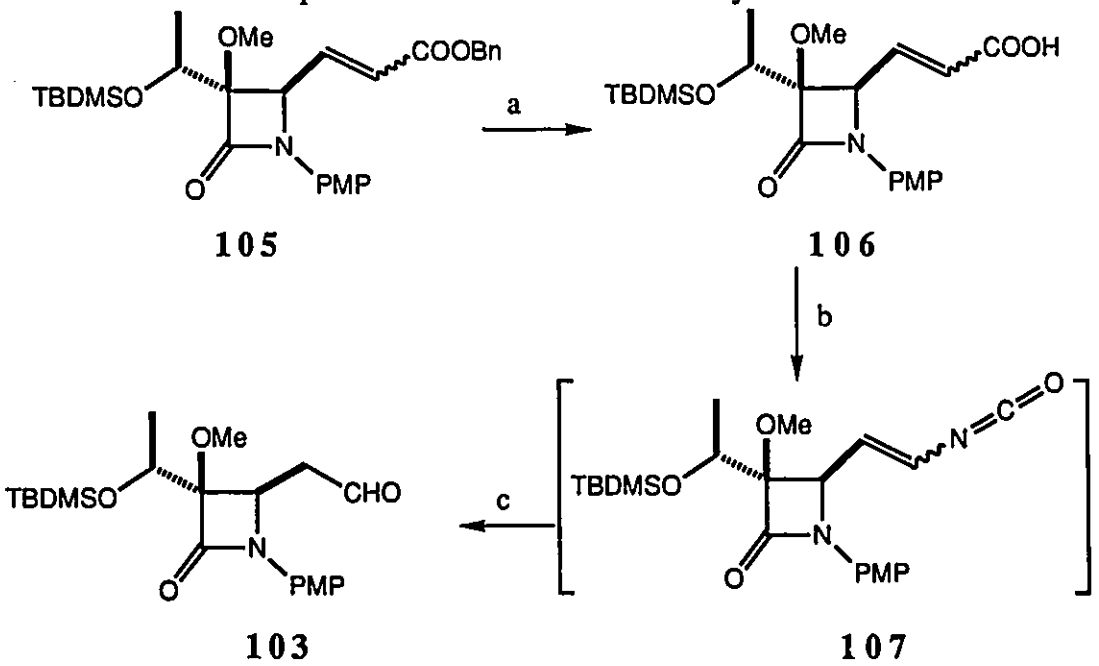
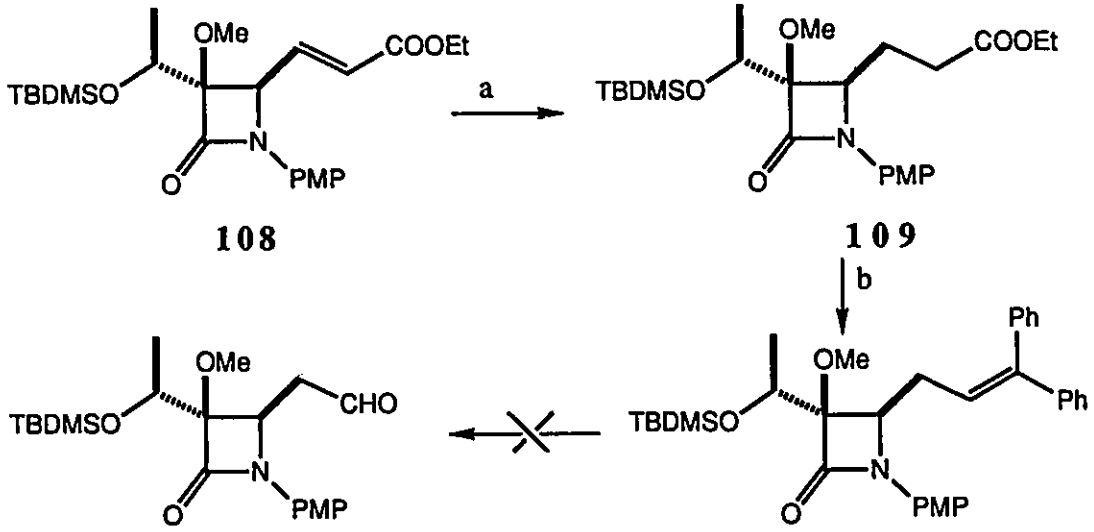
[61] for use of this reagent: (a) Rousseau, G.; LePerchec, P.; Conia, J. M. *Synthesis* **1977**, 67. and references therein.

Thus, it was quite surprising to find that the α,β-unsaturated ester **105** was obtained from **63** in 84% yield after heating with stabilized ylide such as benzyl triphenylphosphoranylideneacetate (THF or $C_2H_4Cl_2$ or toluene, reflux, 24 h). The conversion of **105** to the homologated aldehyde **103** was accomplished by the following sequence. Selective deprotection under transfer hydrogenation conditions (Pd-C, cyclohexene, EtOH, ultrasound) afforded α,β-unsaturated acid **106** in 72% yield. The acid **106** was treated with 1.1 equivalent of diphenylphosphoryl azide (DPPA) in the presence of TEA in refluxing toluene for 18 h to effect Curtius rearrangement. The reaction mixture from this rearrangement reaction containing crude **107** was stirred with 10% HCl for about 15 minutes to yield **103**. The overall yield in the conversion of **106** to **103**, 26% (0.68 g of **106**), was reduced to 16% (1.3 g of **106**). This sequence was abandoned since it could not be scaled up without a drastic loss of yield.



a) Pd-C(10%), C_6H_{10}, EtOH; b) DPPA, TEA, toluene, reflux; c) H^+

The ester **108** was obtained in 91% yield by reaction of the aldehyde **63** with ethyl triphenylphosphoranylidineacetate in refluxing THF for 20 hours. Hydrogenation of **108** in EtOH at 40 psi for 6 hours afforded **109** in 99% yield. Attempts to cleave one extra carbon in the ester **109** by conversion to **110** and subsequent ozonolysis in dichloromethane in the presence of traces of methanol gave several intractable products whereas the catalytic ruthenium tetroxide reaction[62] ($RuCl_3$, $NaIO_4$, 0 °C to 25 °C) resulted in a complex reaction mixture from which the desired product could not be isolated. The ozonolysis of the enol silylether derived from **109** at -78 °C gave very low (<10%) yield of the homologated aldehyde **103**.



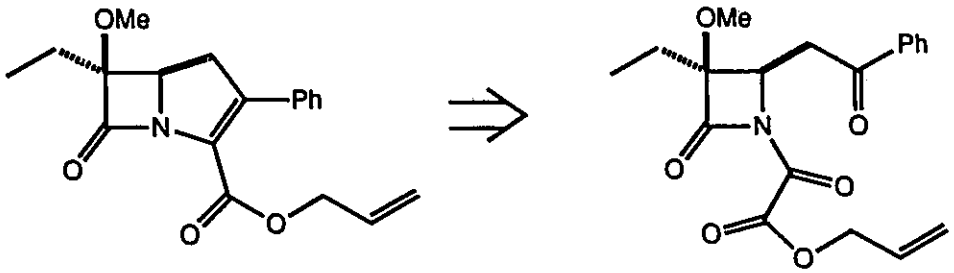
a) H_2, Pd-C(10%), EtOH, 40 psi; b) PhLi, THF, -78 °C to 25 °C; TsOH, toluene, reflux

5) Attempted synthesis of a 2-phenylcarbapenem

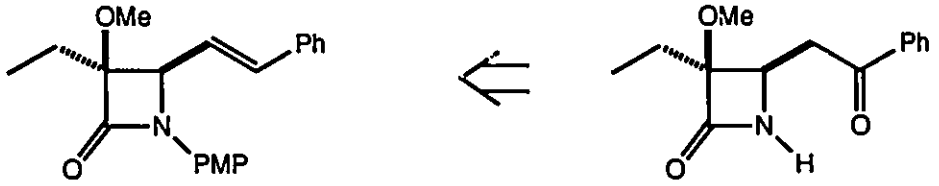
Since most of the reactions described above which involved the cleavage of cinnamyl group and homologation of carbon side-chain at C-

62 Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

4, did not lead to desired targets, we thought of using a different approach in which all carbons present in the cinnmayl group would be incorporated into the product. This would be possible if the transformations shown in the following retrosynthetic scheme were accomplished. It was planned to construct the bicyclic ring in **111** from oxalimide **112** by applying the triethyl phosphite coupling reaction (see p 152). This required transformation of **114** to **112**.



111 **112**

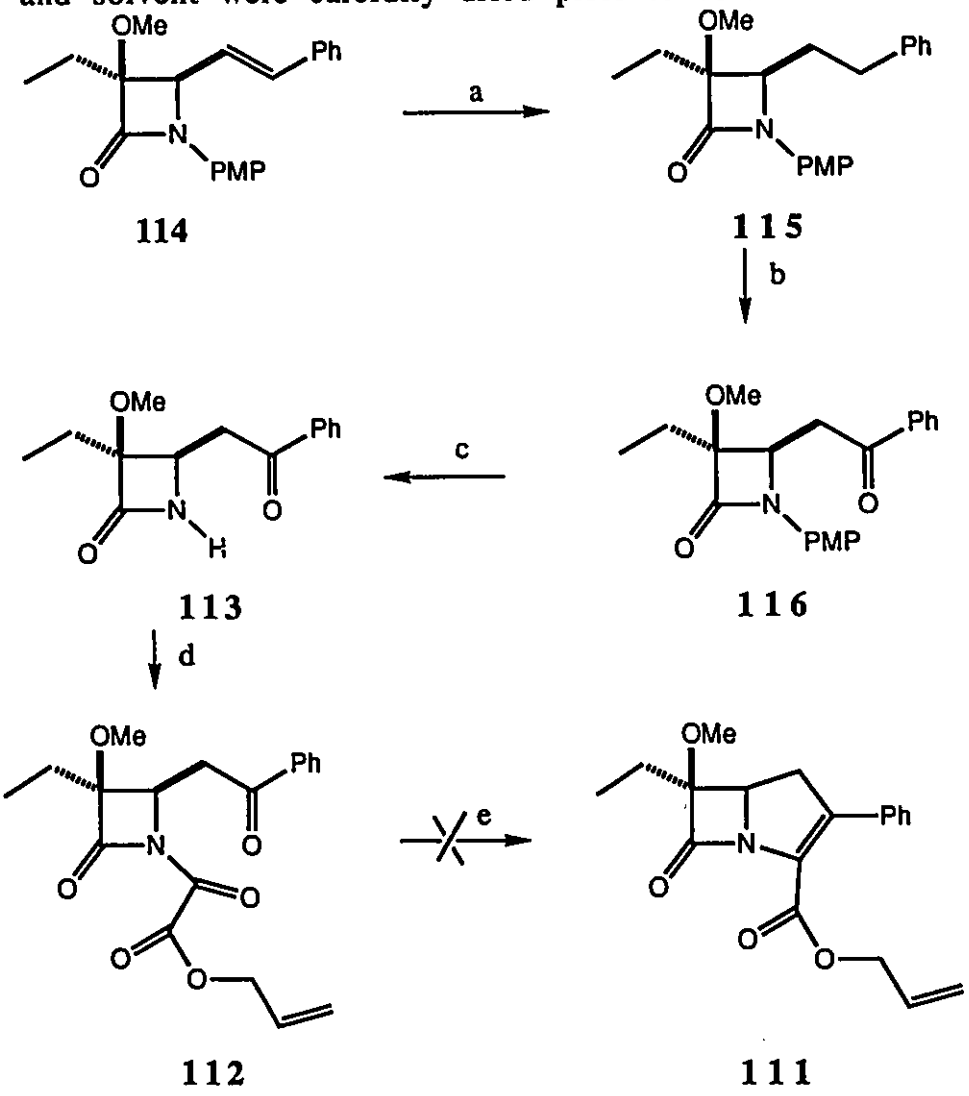


114 **113**

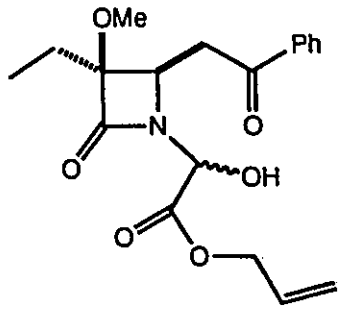
The azetidinone **114**[63] was hydrogenated at 40 psi in ethanol using Pd-C(10%) for 18 hours to afford the saturated compound **115**. Oxidation at the benzylic carbon of **115** by bromination (NBS, AIBN, CCl_4, hυ, reflux, 8 h), hydroxylation (aq $AgNO_3$, acetone, 3-5 h) and oxidation (PCC, CH_2Cl_2, 18 h) afforded ketone **116** in 23% overall yield form **115**. The cleavage of the PMP group under usual conditions gave

[63] Sharma, M. K. *Ph. D. Thesis*, University of Ottawa, **1990**, p 91.

a 65% yield of **113** which was treated with allyloxalyl chloride in the presence of DIPEA to yield the oxalimide **112** in 79% yield. When the cyclization was attempted with two equivalents of triethyl phosphite in refluxing toluene for 3 hours, only a small amount of reduced material **117** was obtained. This could be due to the trapping of a carbene intermediate with water. This result is quite surprising since both reagent and solvent were carefully dried prior to use.



a) H_2, Pd-C(10%), EtOH, 40 psi; b) NBS, AIBN, CCl_4, reflux, hυ; $AgNO_3$, aq acetone; PCC, CH_2Cl_2; c) CAN, MeCN, H_2O, -5 °C to 0 °C; d) $ClCOCOOCH_2CH{=}CH_2$, DIPEA, CH_2Cl_2, 0 °C to 25 °C



117

Nitromethane as one carbon synthon

Initial attempts to use nitromethane as a synthon for a one carbon homologation were unsatisfactory due to the difficulties in product purification largely because of incomplete reactions or retro nitro-aldol condensation. In these early studies, condensation with aldehyde **63**, activation of the hydroxy group as an acetate or a mesylate of the adduct and the elimination to form a nitro-olefin were carried out using equimolar quantities of reagents. Subsequent to these experiments Palomo and coworkers published nitromethane condensations with analogous β-lactam aldehydes.[64] In their procedure the condensation was carried out in excess nitromethane as a solvent in the presence of a catalytic amount of TEA as a base. Excess unreacted nitromethane can readily be removed in a rotary evaporator. A solution of crude adduct in dichloromethane was added to excess methanesulfonyl chloride and TEA at -78 °C to achieve activation of the hydroxy group. After stirring for 45 minutes, excess TEA was added at -50 °C and the reaction mixture was warmed slowly to -10 °C to complete elimination

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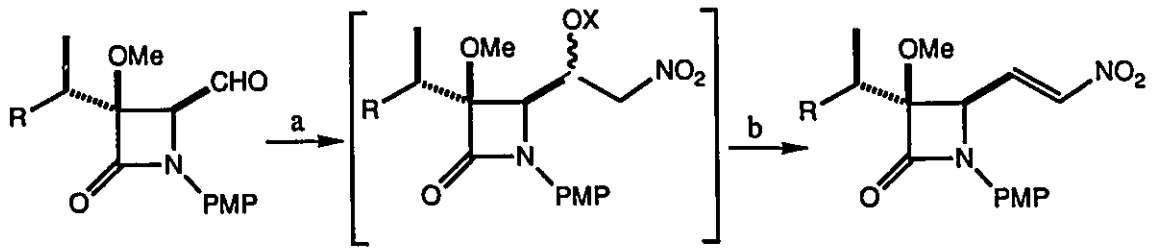
[64] Palomo, C.; Aizpurua, J. M.; Cossio, F. P.; Garcia, J. M.; Lopez, M. C.; Oiarbide, M. *J. Org. Chem.* **1990**, *55*, 2070.

(Miyashita dehydration).[65] Nitro-olefins **122** and **121** were isolated in 65% overall yields from **118** and **63** respectively. Evidence for the formation of these nitro-olefins was available from IR, ^{1}H NMR and MS including HRMS. These data are recorded in the Experimental section.



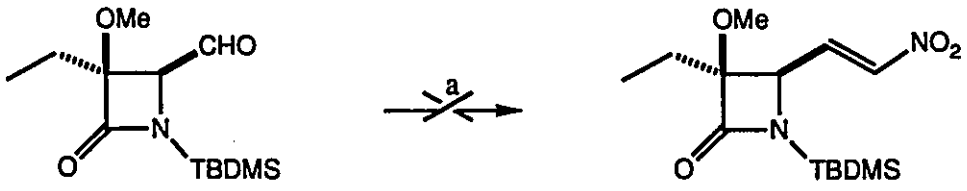
63 R=OTBDMS
118 R=H

119 R=OTBDMS, X=Ms
120 R=H, X=Ms

121 R=OTBDMS
122 R=H

a) CH_3NO_2, TEA; TEA, MsCl, CH_2Cl_2, -78 °C to -50 °C; b) TEA, -50 °C to -10 °C

The cleavage of the PMP group might complicate the utility of this sequence. [This was found to be the case in subsequent cleavage reactions of products derived from nitro compound **122**.] Hence the nitromethane reaction was attempted with the aldehyde **123**. Unfortunately, the crude product gave quite complex ^{1}H NMR which indicated the loss of TBDMS group. Hence this reaction was not further investigated.



123 **124**

a) CH_3NO_2, TEA; TEA, MsCl, CH_2Cl_2, -78 °C to -50 °C; TEA, -50 °C to -10 °C

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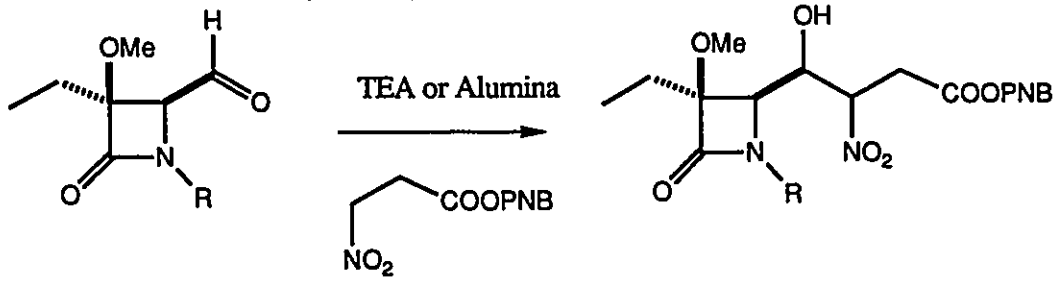
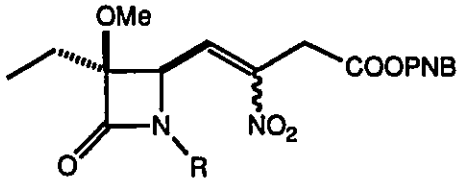
[65] Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 2945.

The feasibility of using a three carbon homologating reagent, benzyl 3-nitropropionate **125** was also explored. Condensation of **125** with aldehyde **118** (TEA, MeCN, 18 h, 25 ^{o}C) gave 49% of a mixture of **126** and an α,β-unsaturated ester due to the elimination of the nitro group. Examination of ^{1}H NMR of crude adduct showed olefinic signals at δ: 6.08 ppm (1H, ddd, J=0.6, 2.0 and 15.7 Hz) and 7.03 (1H, dd, J=4.2, 15.7 Hz) consistent with the elimination of nitro group from **126** to form an α,β-unsaturated ester. Subsequent dehydration under Miyashita conditions afforded only 11% of the desired elimination product **127** (5% overall yield from **118**). Use of alumina as a solid reaction medium for the condensation of **125** with **118** gave 37% of **126**. The olefinic signals were not observed in ^{1}H NMR indicating that the elimination of the nitro group is not a problem under these conditions. This adduct gave 30% of **127** when subjected to Miyashita conditions. Although the overall yield of **127** from **118** increased to 11%, this conversion is still inadequate for multistep synthesis. Therefore, this convergent approach was abandoned.



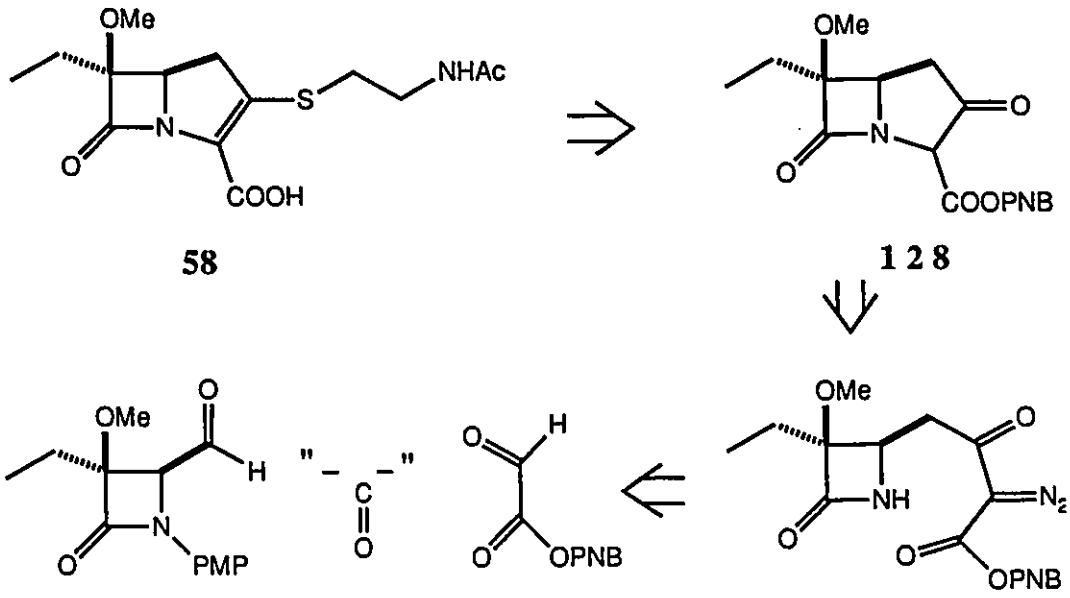
118 R=PMP **125** **126** R=PMP



127 R=PMP

Synthesis of 6-methoxy-PS-5

At this stage, we decided to exploit the nitro-oloefin **122** in the synthesis of 6-methoxy-PS-5 **58** as shown in the following retrosynthetic scheme. It was planned to prepare of **58** *via.* **128** from **129** by applying the Merck cyclization method. This required the transformation of the aldehyde **118** to **129**. Since the nitromethane condensation on **118** to yield nitro-olefin **122** has been accomplished, it should be possible to build the required carbon skeleton of **129** by using nitromethane as a formyl dianion synthon **131**.



58 **128**

118 **131** **130** **129**

Nitro-olefin **122** was readily reduced to **132** in 46-50% yield by treatment with sodium borohydride in 1:1 mixture of ethanol and dioxane at room temperature.[66] The formation of **132** is supported by the following spectral data: IR: 1744 (C=O), 1386 and 1513 (NO_2) cm^{-1};

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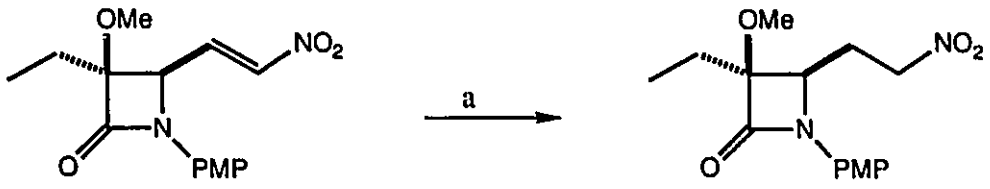
66 Bhattacharya, A.; Mukhopadhyay, R.; Pakrashi, S. C. *Synthesis* **1985**, 886.

the following spectral data: IR: 1744 (C=O), 1386 and 1513 (NO_2) cm^{-1}; ^1H NMR δ: 2.02-2.39 (2H, m, CH_2CH_3, $CH_2CH_2NO_2$), 2.62-2.80 (1H, m, $CH_2CH_2NO_2$), 4.44-4.51 (2H, m, CH_2NO_2); MS: 308 (M^+) and HRMS for $C_{15}H_{20}N_2O_5$.



122 **132**

a) $NaBH_4$, EtOH:dioxane (1:1)

Further extension of the carbon skeleton by two carbons was achieved by condensation of compound **132** with p-nitrobenzyl glyoxylate[67] using 4Å molecular sieves and a catalytic amount of TEA in THF at 25 °C for 24 hours. Since **130** exists as its hydrate, molecular sieves were used to liberate **130** which underwent *in situ* condensation to afford a corresponding adduct in 60% yield. Miyashita dehydration sequence was applied to afford nitro-olefin **133** in 57% yield. This elimination sequence is complicated by a ring opening reaction *via*. a retro-Michael addition shown in eq. 1 especially when longer reaction time and/or excess TEA was used. The compound **133** was identified by ^1H NMR of crude product and converted to a β-ketoester **135** without further purification and characterization.

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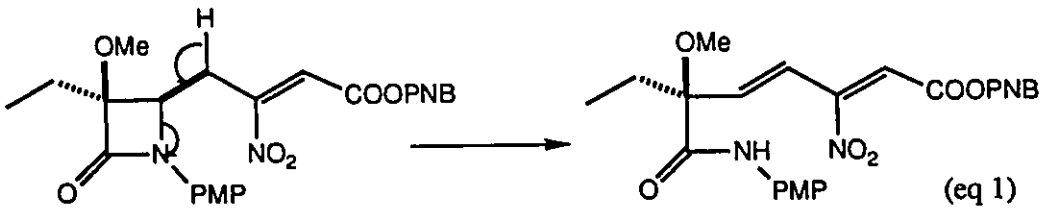
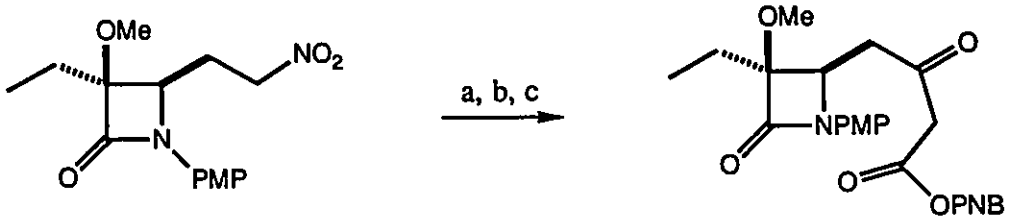
[67] Woodward, R. B.; Pfaendler, H. R.; Ernest, I.; Gosteli, J.; Greengrass, C. W.; Holoick, W.; Jackman, D. E. *J. Am. Chem. Soc.* **1978**, *100*, 8214.



133 **134**

The impure olefin **133** was treated with tributyltin hydride in dry dichloromethane for 3 hours at room temperature and the resultant tin-nitronate was ozonolyzed *in situ* to afford ketone **135** in 35% yield. This compound gave all the key spectral data: IR: 1740 (C=O), 1515 and 1351 (NO_2) cm^{-1}; ^1H NMR δ: 3.57 (2H, s, $COCH_2COOR$); MS: 470 (M^+) and HRMS for $C_{24}H_{26}N_2O_8$. Thus the overall conversion of **132** to **135**, shown below, was achieved in 12% overall yield.

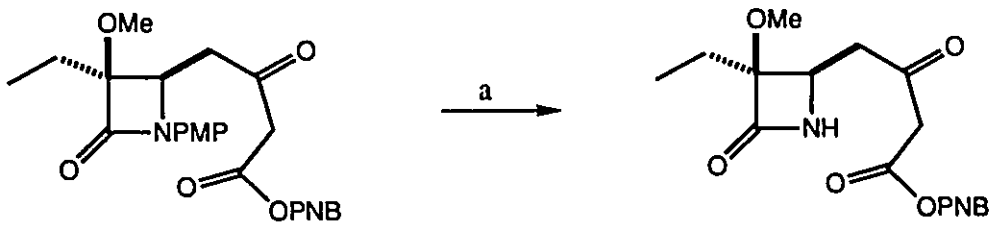


132 **135**

a) $(HO)_2CHCOOPNB$, TEA, 4Å molecular sieves, THF, 0 °C to 25 °C; b) MsCl, TEA, CH_2Cl_2, -78 °C, TEA, -50 °C to 25 °C; c) Bu_3SnH, CH_2Cl_2; O_3, DMS, -78 °C to 25 °C

The p-methoxyphenyl (PMP) group of **135** was cleaved using ceric ammonium nitrate (CAN) to yield the NH compound **136** in 24-30% yield.[68]

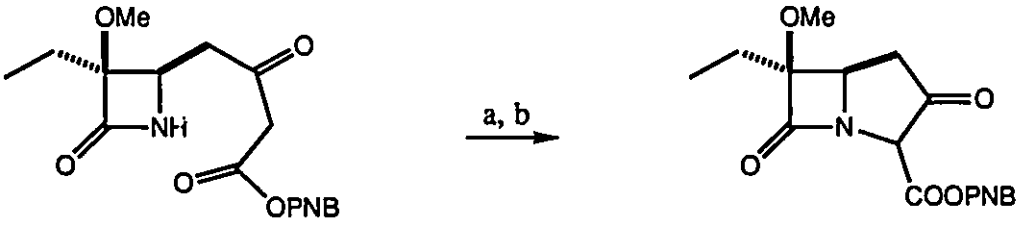
[68] Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.



135 **136**

a) CAN, MeCN:H_2O, -20 °C to -30 °C

The conversion of **136** to bicyclic compound **128** was accomplished by using rhodium carbenoid insertion reported by Merck chemists.[69] Diazo transfer reaction of **136** with 4-carboxybenzenesulfonazide[70] and TEA afforded corresponding diazo compound in 72% yield (IR: 2142 cm^{-1}). A rhodium carbenoid insertion (using cat. rhodium octanoate in benzene) of the resultant diazo compound afforded the bicyclic compound **128** in 60% yield. The formation of a second ring is characterized by the splitting of benzylic proton signal into AB patterned doublets in ^1H NMR at 5.22 and 5.32 ppm (J=13.4 Hz) and shift of β-lactam carbonyl absorption in IR to 1770 cm^{-1}. This compound gave all required spectral data including HRMS.



136 **128**

a) 4-$HOOCC_6H_4SO_2N_3$, TEA, MeCN, 0 °C to 25 °C; b) $Rh_2(OOCC_7H_{15})_4$, C_6H_6, reflux

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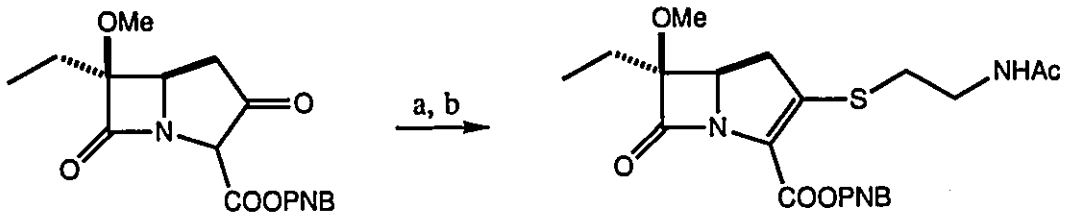
69 Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.

70 Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.

Compound **128** was activated by treatment with diphenylchlorophosphate and diisopropylethylamine (DIPEA). The *in situ* reaction of the resultant enolphosphate with N-acetylaminoethanethiol[71] and DIPEA gave **137** in 36% yield. (Fig. 10). Compound **137** was obtained as a yellowish foam and gave all required spectral data to support its structure; IR: 3334 (broad, NH), 1773 (C=O, β-lactam), 1702 (COOR), 1660 (CONH), 1520 and 1340 (NO_2) cm^{-1}; ^1H NMR δ: 0.97 (3H, t, J=7.4 Hz, CH_3CH_2), 1.81-2.21 (5H, m overlapping with s, CH_2CH_3, CH_3CO), 2.85-3.15 (3H, m, CH_2S, $CH_ACH_BCH_XN$), 3.30-3.60 (6H, m with overlapping s, CH_3O, CH_2N, $CH_ACH_BCH_XN$), 4.03 (1H, t, J=9.3 Hz, CHN), 5.18 (1H, d, J=14.0 Hz, CH_ACH_BPNB), 5.46 (1H, d, J=13.9 Hz, CH_ACH_BPNB), 7.60 (2H, d, J=8.9 Hz, PNB), 8.17 (2H, d, J=8.8 Hz, PNB); ^{13}C NMR δ: 7.4 (CH_3), 22.9 (CH_2), 23.2 (CH_3CO), 31.9 (CH_2), 35.1 (CH_2), 39.8 (CH_2), 52.5 (CH_3O), 60.4 (CHN), 65.0 (CH_2), 80.3 (C), 123.5 (C=C), 123.7 (CH, PNB), 128.0 (CH, PNB), 143.2 (C, PNB), 147.5 (C=C), 150.4 (C), 160.8 (C=O), 170.6 (C=O), 176.8 (C=O); MS(CI): 464 (M^++1, 1); HRMS for $C_{20}H_{25}O_6N_3S$ (M^+-CO).



128 **137**

a) $(PhO)_2POCl$, DIPEA, McCN, 0 °C; b) $HSCH_2CH_2NHCOCH_3$, DIPEA; 0 °C to 25 °C

Final deprotection of PNB group of **137** was carried out by hydrogenation using Pd-C(10%) in aqueous THF. Conversion to the

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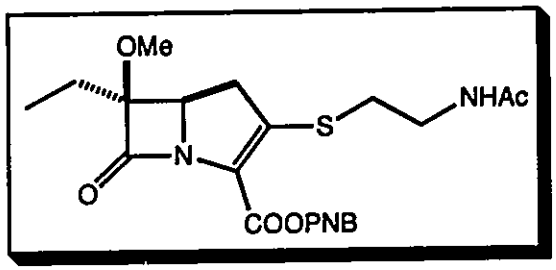
[71] Shinkai, I.; Liu, T.; Reamer, R.; Sletzinger, M. *Synthesis* **1980**, 924.



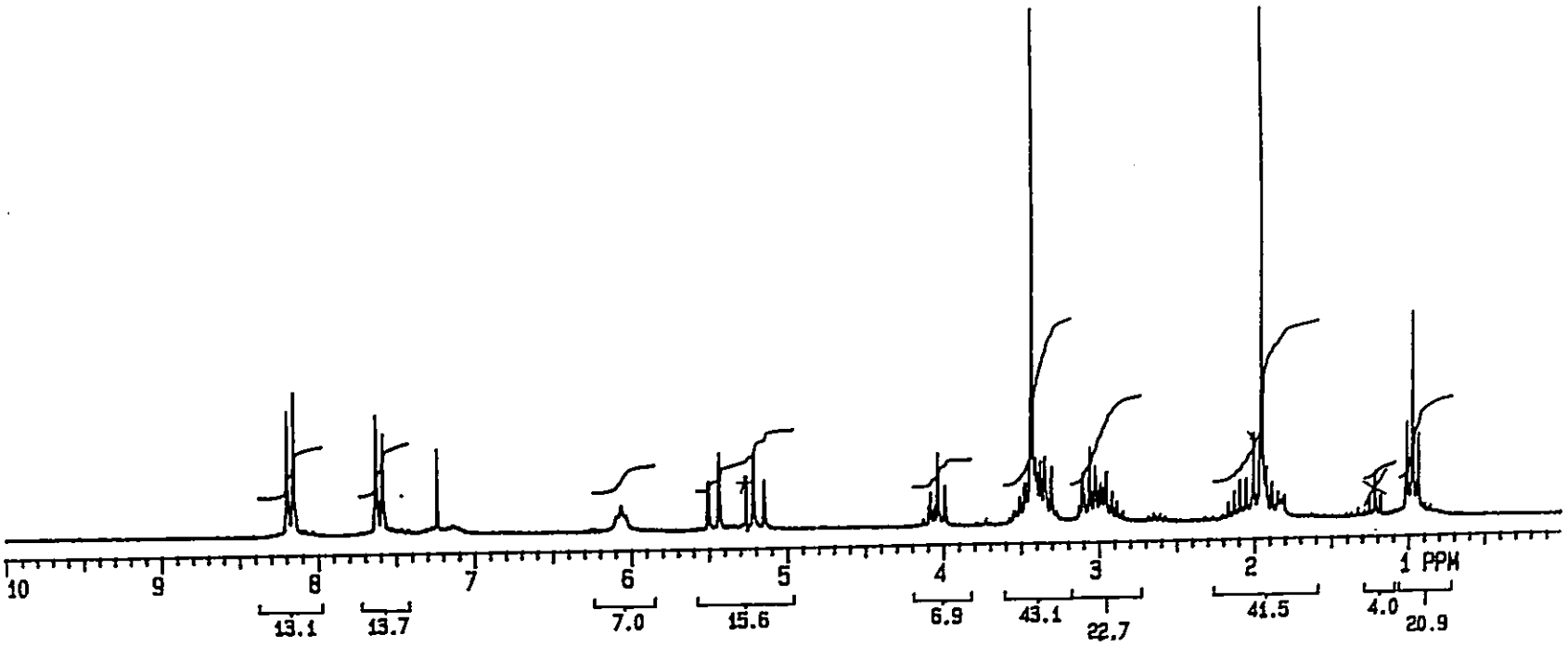
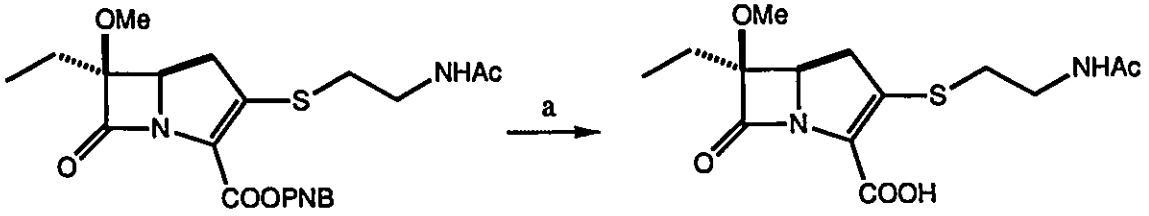


Fig. 10 ^{1}H NMR spectrum of 137

sodium salt of **58** and lyophilization gave a brownish grey solid. The ^1H NMR spectrum indicated the presence of **58**; ^1H NMR (300 MHz, D_2O) δ: 0.98 (3H, t, J=7.4 Hz, CH_3CH_2), 1.87-2.11 (5H, m with overlapping s at 1.96, CH_2CH_3, CH_3CO), 2.94-3.02 (2H, m, CHHS, CHH), 3.22-3.44 (5H, m with overlapping s at 3.34, CH_2N, CH_3O), 4.09 (1H, t, J=9.2 Hz, CHN). However, attempted purification by reverse phase column chromatography failed since the product decomposed indicating 6-methoxy PS-5 **58** is unstable compared to its epimer at C-6 and PS-5 **2** itself. This indicated that a methoxy group at concave face of bicyclic carbapenems exerts destabilizing effect in PS-5 type compounds.



137 **58**

a) H_2, Pd-C (10%), THF:H_2O (1:1)

Nitro-olefin 121 as an intermediate for 1-substituted carbapenems

As many examples of hetero-atom directed addition of nucleophiles to Michael acceptors are known,[72] it appeared that the nitro-olefins such as **121** could be valuable intermediates for the preparation of the 1-substituted carbapenems. Hence the addition of methylmagnesium cuprate and vinylmagnesium cuprate were carried out.

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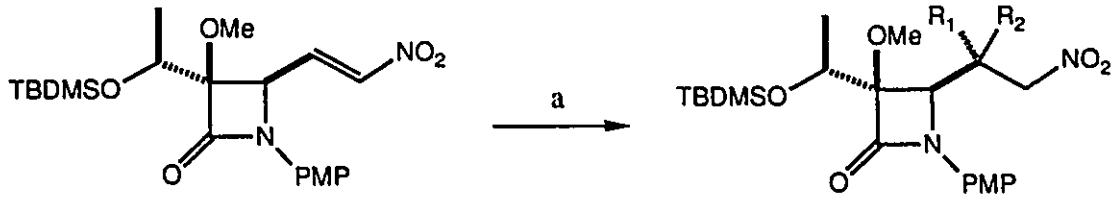
[72] Roush, W. R.; Leuser, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231.

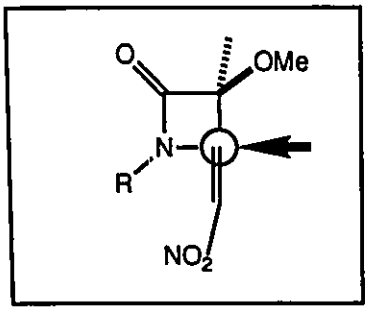


121

138a R_1=Me, R_2=H
138b R_1=H, R_2=Me
139 R_1=CH=CH_2, R_2=H

a) McMgBr, CuI, THF, -78 °C or CH_2=CHMgBr, CuI, THF, -78 °C

The addition of a methyl group gave a mixture (1:1) of diastereomers **138a** and **138b**. However, the addition of vinyl cuprate afforded only one isomer of **139**. The relative configuration of **139** was established by X-ray crystallography experiment (Fig. 11, ORTEP diagram). This compound gave all the expected spectral data which are listed in the Experimental section. The observed stereoselectivity can be rationalized by invoking a Felkin Ahn type model shown below.[73]



[73] (a) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, *20*, 3465. (b) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1980**, *21*, 4727. (c) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981**, *22*, 3997. (d) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

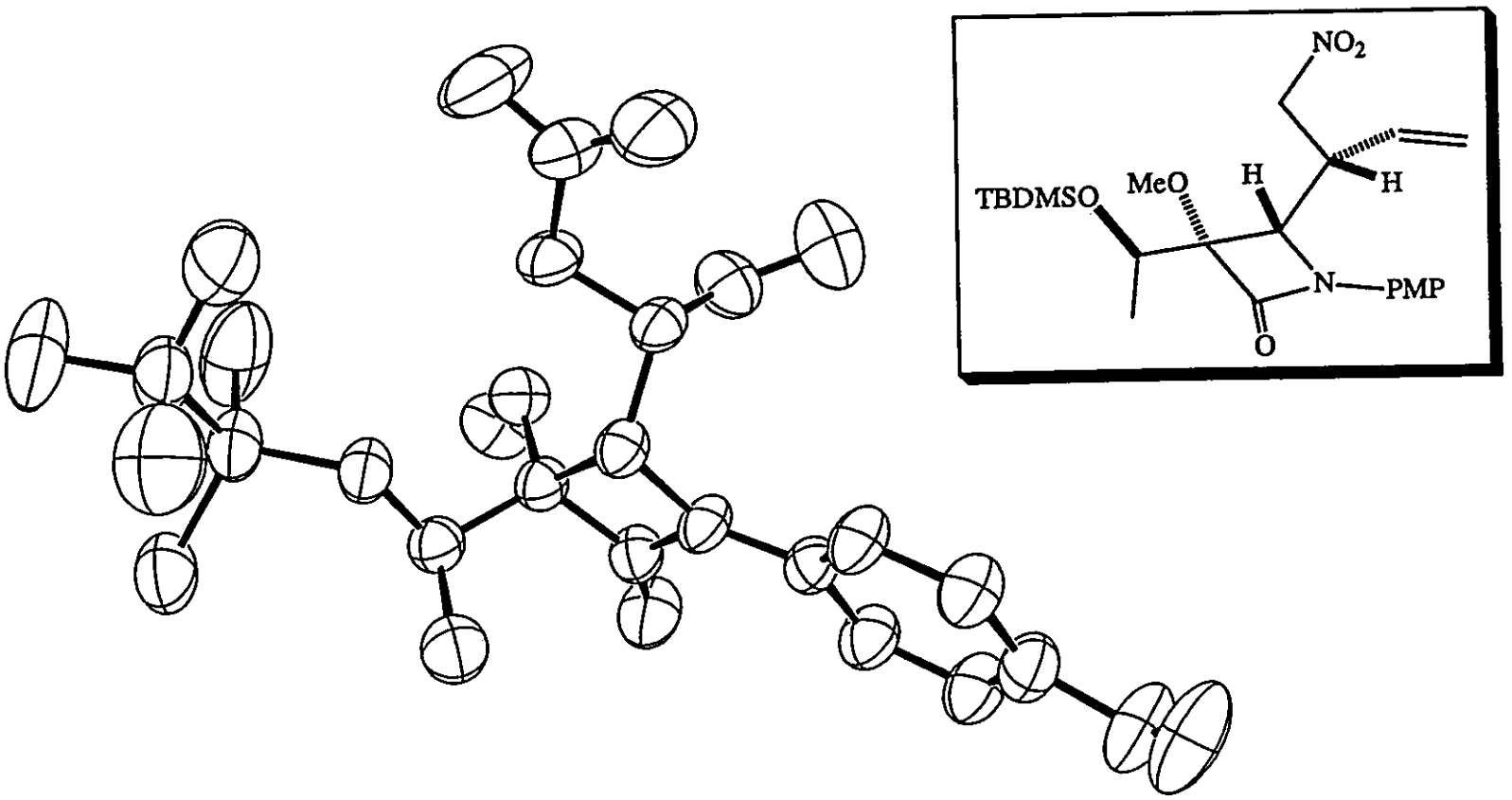
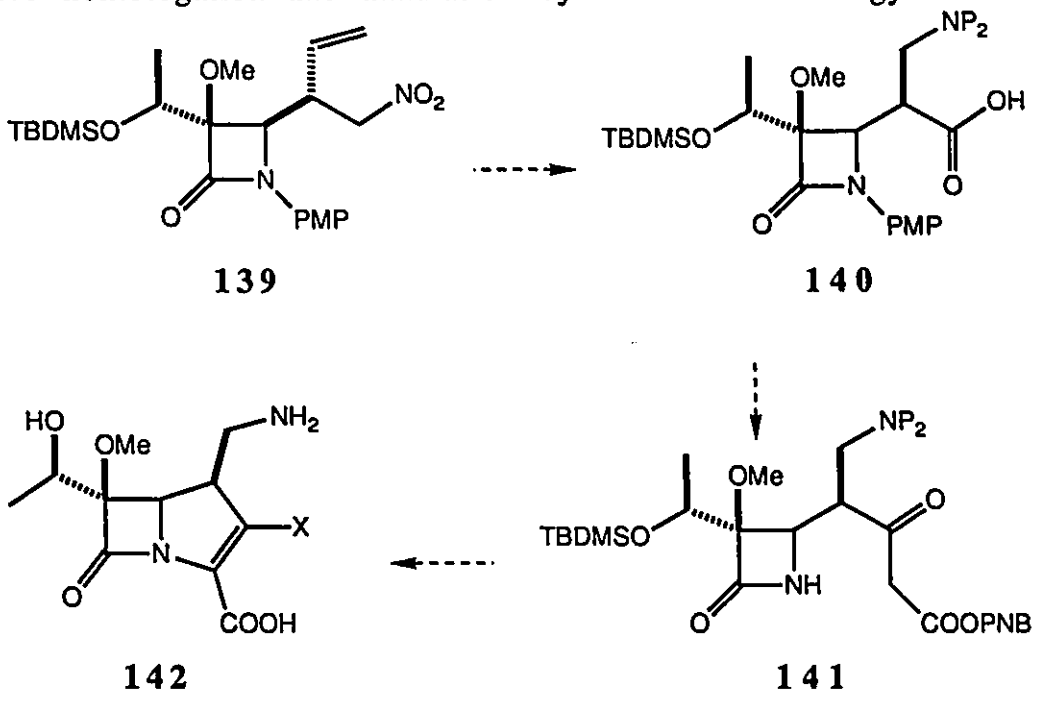


Fig. 11 ORTEP diagram of **139**

Compound **139** could be a valuable precursor to 1-β-aminomethyl carbapenems such as **142**. Similar 1-β-aminoalkyl compounds have been reported in a series of communication by Bristol Chemists.[74] This would require the conversion of the vinyl group to a carboxylic group and the reduction of nitro function to an amino group. Protection of the amino group should furnish **140**. The conversion of **140** to **142** would involve homologation and annulation by Merck methodology.



139 **140**

142 **141**

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[74] (a) Bachand, C.; Banville, J.; Bouthillier, G.; Corbeil, J.; Daris, J. P.; Desiderio, J.; Fung-Tomc, J.; Lapointe, P.; Martel, A.; Mastalerz, H.; Remillard, R.; Tsai, Y.; Menard, M.; Kessler, R. E.; Partyka, R. A. In *75 th Canadian Chemical Conference and Exhibition*; Chemical Institute of Canada: Edmonton, **1992**; Abstract 457 ME B2P. (b) Martel, A.; Banville, J.; Bachand, C.; Bouthillier, G.; Corbeil, J.; Fung-Tomc, J.; Lapointe, P.; Mastalerz, H.; Rao, V. S.; Remillard, R.; Turmel, B.; Menard, M.; Kessler, R. E.; Partyka, R. A. In *75 th Canadian Chemical Conference and Exhibition*; Chemical Institute of Canada: Edmonton, **1992**; Abstract 458 ME B2P. (c) Martel, A.; Banville, J.; Bachand, C.; Bouthillier, G.; Corbeil, J.; Desiderio, J.; Fung-Tomc, J.; Lapointe, P.; Rao, V. S.; Remillard, R.; Turmel, B.; Menard, M.; Kessler, R. E.; Partyka, R. A. In *75 th Canadian Chemical Conference and Exhibition*; Chemical Institute of Canada: Edmonton, 1992; Abstract 459 ME B2P. (d) Rao, V. S.; Bachand, C.; Banville, J.; Bouthillier, G.; Desiderio, J.; Fung-Tomc, J.; Lapointe, P.; Martel, A.; Mastalerz, H.; Remillard, R.; Michel, A.; Menard, M.; Kessler, R. E.; Partyka, R. A. In *75 th Canadian Chemical Conference and Exhibition*; Chemical Institute of Canada: Edmonton, **1992**; Abstract 456 ME B2P.

Conclusion

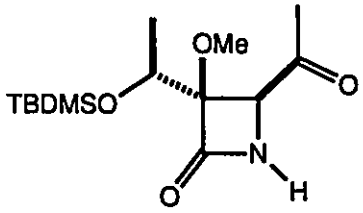
Despite the considerable difficulties rendered by the methoxy group in these studies, the overall conversion of **118** to **58** was effected in ten steps. The yield in this conversion is low mainly due to the poor yield in the CAN reaction of β-ketoester **135**. The preparation of **121** indicates similar cyclization to 6-methoxy-7-epithienamycin should be possible. This would require further optimization experiments or transposing the difficult steps in the synthetic sequence. An interesting feature of the above sequence is that the intermediate **136** was obtained with retention of the *cis* relationship of the C-4 substituent with C-3 methoxy group observed in the 2+2 cycloaddition reaction. It also allowed us to establish the potential utility of nitromethane as a formyl dianion synthon in the preparation of carbapenem intermediates. Surprisingly, the 6-methoxy PS-5 **58** is unstable compared to its epimer and PS-5 **2** itself. As a result the antibacterial activity of **58** could not be evaluated.

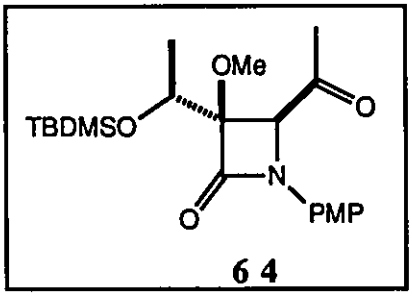
EXPERIMENTAL SECTION

General techniques

The general techniques described in Chapter 2 and 3 also apply in the following description. Trimethylsilyl chloride was distilled from CaH_2 under nitrogen just before use. Benzaldehyde and methanesulfonyl chloride were distilled before use. DIPEA and 2,6-lutidine were distilled from CaH_2 and stored over 4Å molecular sieves. Benzyl and ethyl triphenylphosphoranylidineacetates were prepared from corresponding bromoacetates and triphenylphosphine. NBS was purified by recrystallization from water. Triethyl phosphite was dried using sodium, distilled and used immediately. Benzyl nitropropionate was prepared from a suitable acid chloride and benzyl alcohol in the absence of bases such as TEA.

4-Acetyl-3-t-butyldimethylsilyloxyethyl-3-methoxy-2-azetidinone (70)





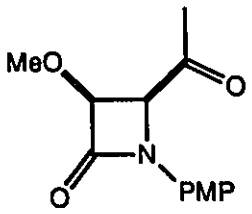
64

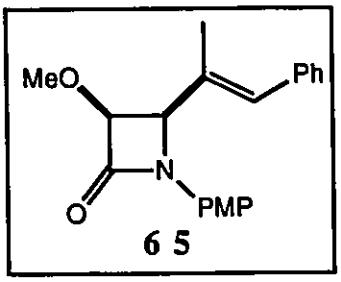
CAN (1.30 g, 2.37 mmol) in 12 mL of H_2O was added dropwise to a solution of azetidinone **64**[75] (301 mg, 0.74 mmol) in 20 mL of MeCN at -2 °C to 0 °C. After 30 min, the reaction mixture was diluted with EtOAc

[75] Sharma, M. K. *Ph.D. Thesis*, University of Ottawa, **1990**, p 176.

and worked up in a usual manner. Purification of the crude product by column chromatography (1:4 EtOAc:hexanes) afforded 166 mg (75%) of **70** as a yellow oil; ^{1}H NMR (300 MHz) δ: 0.10 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.89 (9H, s, t-Bu), 1.29 (3H, d, J=6.4 Hz, CH_3CH), 2.18 (3H, s, CH_3CO), 3.45 (3H, s, OCH_3), 4.19 (1H, q, J=6.4 Hz, $OCHCH_3$), 4.32 (1H, s, CHN), 6.20 (1H, broad s, NH); MS(CI): 302 (M^++1, 7), 274 (M^++1-28, 7), 270 (M^++1-32, 100), 258 (M^+-43, 6), 244 (M^+-57, 20).

4-Acetyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (72)





About 1 g of 4Å molecular sieves was added to a solution of 4-(1-methyl-cinnamyl)-3-methoxy-1-p-methoxyphenyl-2-azetidinone **65**[76] (6.46 g, 20.2 mmol) in 250 mL of CH_2Cl_2 and 50 ml of MeOH. Ozone was passed through this solution at -78 °C until a bluish color appeared. DMS (ca. 5 mL) was added to the reaction mixture which was stirred overnight (-78 °C to 25 °C). After removal of the solvent the crude product was triturated with ether to yield 3.80 g (76%) of **72** as a solid; mp 124-125 °C; ^{1}H NMR (300 MHz) δ: 2.20 (3H, s, CH_3CO), 3.53 (3H, s, CH_3O), 3.77 (3H, s, CH_3O), 4.58 (1H, d, J=5.4 Hz, CHN), 4.82 (1H, d, J=5.4 Hz, CHO), 6.86 (2H, d, J=9.1 Hz, PMP), 7.23 (2H, d, J=9.2 Hz, PMP); MS: 249 (M^+, 26), 221 (M^+-28, 1), 205 (M^+-44, 1), 190 (205-15$^+$, 7), 178 (M^+-71, 24); HRMS calcd for $C_{13}H_{15}NO_4$ 249.0986, found 249.0993.

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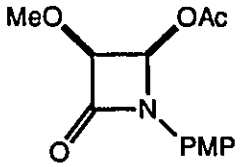
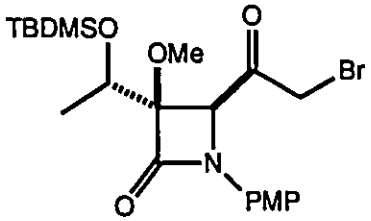
[76] Sharma, M. K. *Ph.D. Thesis*, University of Ottawa, **1990**, p 149.

4-Acetoxy-3-methoxy-1-p-methoxyphenyl-2-azetidinone (73)



Azetidinone **72** (6.00 g, 24.1 mmol) in 20 mL of $C_2H_4Cl_2$ was refluxed with 4 eq of MCPBA (16.6 g, 9.62 mmol) and a crystal of 2,6-di-t-butylphenol for 24 h. The reaction mixture was diluted with 40 mL of CH_2Cl_2 and washed consecutively with 5% $NaHSO_3$, 5% $NaHCO_3$ and brine. Purification of the crude product by column chromatography (1:4 EtOAc:hexanes) afforded 2.20 g (34%) of **73** as a white solid; mp 80-84 °C; ^1H NMR (300 MHz) δ: 2.20 (3H, s, CH_3CO), 3.58 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 4.73 (1H, d, J=3.5 Hz, CHN), 6.53 (1H, d, J=3.5 Hz, CHO), 6.88 (2H, d, J=9.1 Hz, PMP), 7.37 (2H, d, J=9.2 Hz, PMP); MS: 249 (M^+, 26), 221 (M^+-28, 1), 205 (M^+-44, 1), 190 (205-15$^+$, 7), 178 (M^+-71, 24); HRMS calcd for $C_{13}H_{15}NO_4$ 265.0948, found 265.0946.

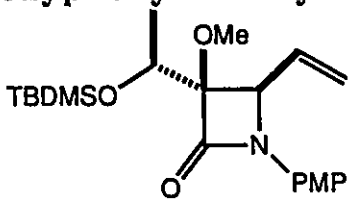
4-Bromoacetyl-3-t-butyldimethylsilyloxyethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (78)



TMSCl (6 mL, 47.3 mmol) followed by a solution of **64** (1.60 g, 3.93 mmol) in 20 mL of THF was added to 0.84 mmol of LDA in 20 mL of THF at -78 °C over 15 min. The reaction mixture was stirred for an additional 1 h. 10% Bromine in THF was added dropwise over 45 min till a slight yellowish color persisted. After 10 min, the reaction mixture

was worked up in the usual manner using EtOAc as a solvent. Purification of the crude product by column chromatography (1:10 EtOAc:hexanes) gave 356 mg (19%) of **78** as a white solid (Yield was 25% on a 400 mg scale bromination); ^{1}H NMR (300 MHz) δ: 0.10 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.84 (9H, s, t-Bu), 1.28 (3H, d, J=6.4 Hz, CH_3CH), 3.52 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.87 (1H, d, J=11.7 Hz, CH_AH_BCO), 4.12 (1H, d, J=11.7 Hz, CH_AH_BCO), 4.28 (1H, q, J=6.4 Hz, $OCHCH_3$), 5.15 (1H, s, CHN), 6.84 (2H, d, J=9.1 Hz, PMP), 7.24 (2H, d, J=9.1 Hz, PMP); MS: 487 (M^++2, 4), 485 (M^+, 4), 428 (M^+-57, 38), 400 (M^+-28-57, 3), 336 (M^+-149, 7).

3-t-Butyldimethylsilyloxyethyl-3-methoxy-1-p-methoxyphenyl-4-vinyl-2-azetidinone (79)



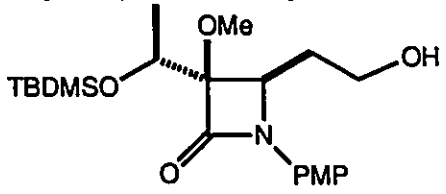
$NaBH_4$ (16 mg, 0.44 mmol) was added to a solution of bromo compound **78** (113 mg, 0.23 mmol) in 2 mL of CH_2Cl_2 and 8 mL of EtOH. After stirring for 1.25 h, the reaction mixture was acidified to pH 3 by adding 10% HCl and extracted with 10 mL of CH_2Cl_2 twice. The combined organic layer was washed with 5% $NaHCO_3$ and brine respectively. The crude product, obtained in quantitative yield after removal of the solvent, was used as such in the next step without further purification.

MsCl (0.02 mL, 0.258 mmol) and TEA (0.04 mL, 0.287 mmol) were sequentially added to a solution of crude bromohydrin obtained as described above (103 mg, 0.211 mmol) in 10 mL of CH_2Cl_2 and the

reaction mixture was stirred for 1.5 h. Usual workup gave 103 mg (86%) of a bromomesylate.

The bromomesylate obtained (93 mg, 0.165 mmol), NaI (0.375 g, 2.50 mmol) and Zn (165 mg, 2.52 mmol) was mixed with 15 mL of acetone:DMF (1:1) and the mixture was refluxed for 10 h. Purification of the crude compound by column chromatography (1:10 EtOAc: hexanes) gave 41 mg (45% overall yield from **78**) of **79**; ^{1}H NMR (300 MHz) δ: 0.04 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.76 (9H, s, t-Bu), 1.30 (3H, d, J=6.4 Hz, CH_3CH), 3.60 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.14 (1H, q, J=6.3 Hz, $OCHCH_3$), 4.55 (1H, d, J=7.5 Hz, CHN), 5.39-5.46 (2H, m, CH_2=CH), 5.98 (1H, ddd, J=7.4, 10.3 and 17.4 Hz, CH_2=CH), 6.82 (2H, d, J=9.1 Hz, PMP), 7.36 (2H, d, J=9.2 Hz, PMP); MS: 391 (M^+, 5), 359 (M^+-32, 0.5), 334 (M^+-57, 27), 185 (M^+-57-149, 52), 161 (M^+-230, 68).

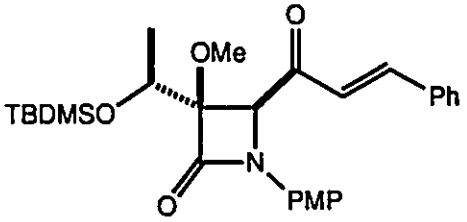
3-t-Butyldimethylsilylethyl-4-(2'-hydroxy)ethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (80)



Olefin **79** (158 mg, 0.404 mmol) in 10 mL of THF was cooled to 0 °C and BH_3.THF (1M, 0.2 mL, 0.2 mmol) was added by syringe. The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 1 h. A few drops of water, 0.5 mL of 3M NaOH and 0.1 mL of 30% H_2O_2 were added to the reaction mixture at 0 °C and heated in a water bath for 6 h. The purification of products by column chromatography (1:1 CH_2Cl_2:hexanes) afforded 80 mg (51%) of unreacted olefin, 15 mg (9%) of a regioisomeric alcohol and 20 mg (12%) of product **80**; ^{1}H NMR (300 MHz) δ: 0.08 (6H, s, CH_3SiCH_3), 0.84 (9H, s, t-Bu), 1.25 (3H, d, J=6.4

Hz, C*H*$_3$CH), 1.86-2.02 (1H, m, CH_2), 2.16-2.32 (1H, m, CH_2), 2.34-2.40 (1H, broad t, OH), 3.62-3.82 (8H, m, with overlapping 2s at 3.72 and 3.77, OCH_3, OCH_3, OCH_2), 4.21-4.26 (2H, m, CHO, CHN), 6.86 (2H, d, J=9.0 Hz, PMP), 7.33 (2H, d, J=9.1 Hz, PMP); MS: 409 (M^+, 9), 394 (M^+-15, 1), 352 (M^+-57, 99), 320 (352-32$^+$, 24), 260 (M^+-149, 2).

3-t-Butyldimethylsilyloxyethyl-3-methoxy-4(1'-oxo-3'-phenyl-2'-propene)-1-p-methoxyphenyl-2-azetidinone (81)

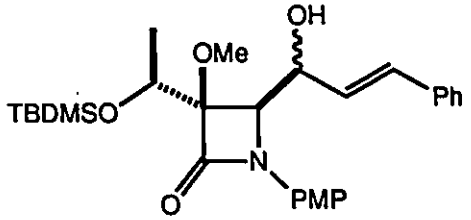


1.1 Eq of LDA (prepared from 1.1 mL of DA and 2.7 mL of n-BuLi, 2.48 M) was added by cannula to a solution of **64** (2.50 g, 6.15 mmol) in 50 mL of THF at -78 °C. After 10 min, benzaldehyde (0.65 mL, 6.40 mmol) was added to the reaction mixture which was stirred for 20 min and quenched with satd NH_4Cl at -78 °C. Extraction of the product with EtOAc and purification of the resultant impure product by column chromatography (1:4 EtOAc:hexanes) gave 2.65 g (83%) of an adduct.

The aldol, obtained above, was refluxed in benzene in the presence of a catalytic amount of toluene sulfonic acid for 20 h to yield 2.45 g (96%) of **81** as an oil; ^{1}H NMR (300 MHz) δ: 0.10 (3H, s, CH_3Si), 0.11 (3H, s, CH_3Si), 0.80 (9H, s, t-Bu), 1.35 (3H, d, J=6.3 Hz, C*H*$_3$CH), 3.50 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.26 (1H, q, J=6.3 Hz, OC*H*CH$_3$), 4.94 (1H, s, CHN), 6.83 (2H, d, J=9.1 Hz, PMP), 6.93 (1H, d, J=16.1 Hz, C*H*=CHPh), 7.28 (2H, d, J=9.1 Hz, PMP), 7.34-7.41 (3H, m, Ph), 7.54-7.57 (2H, m, Ph), 7.73 (1H, d, J=16.1 Hz, CH=C*H*Ph); MS: 495 (M^+, 10), 480

(M^+-15, 0.7), 438 (M^+-57, 55), 410 (M^+-57-28, 3), 266 (M^+-229, 10); HRMS calcd for $C_{28}H_{37}O_5NSi$ 495.2448, found 495.2460.

3-t-Butyldimethylsilyoxyethyl-4-(1'-hydroxy-3'-phenyl-2'-propen-1'-yl)-1-p-methoxyphenyl-2-azetidinone (82)



A solution of the α,β-unsaturated ketone **81** (2.45 g, 4.95 mmol) in 50 mL of EtOH was treated with 1.5 eq of $NaBH_4$ in the presence of a catalytic amount of $CeCl_3$[77] (0 °C to 25 °C, 20 h). Then the reaction mixture was neutralized by adding about 2 g of Amberlite and filtered. The residue obtained after concentration of the filtrate was dissolved in EtOAc and washed with H_2O twice. Purification of the crude product by column chromatography (1:2 EtOAc:hexanes) afforded 2.30 g (93%) of **82**; ^1H NMR (300 MHz) δ: 0.07+0.08 (6H, 2s, CH_3SiCH_3), 0.85+0.90 (9H, 2S, t-Bu), 1.22+1.26 (3H, 2d, J=6.4 Hz, CH_3CH), 3.74+3.76 (3H, 2s, OCH_3), 3.75+3.80 (3H, 2s, OCH_3), 4.22-4.29 (2H, m, CHO, CHN), 4.69-4.34 (1H, s+broad s, CHO), 6.23 (1H, dd, J=6.3, 16.0 Hz, C*H*=CHPh), 6.56 (1H, dd, J=1.4, 16.1 Hz, CH=C*H*Ph), 6.79-6.85 (2H, m, PMP), 7.21-7.44 (7H, m, Ph, PMP); MS: 497 (M^+, 11), 482 (M^+-15, 1), 440 (M^+-57, 18), 408 (M^+-57-32, 6), 336 (M^+-161, 100); HRMS calcd for $C_{28}H_{39}O_5NSi$ 497.2596, found 497.2591.

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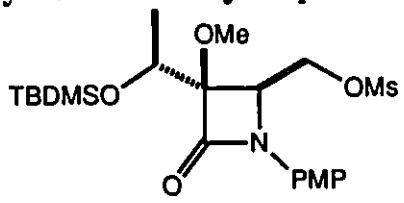
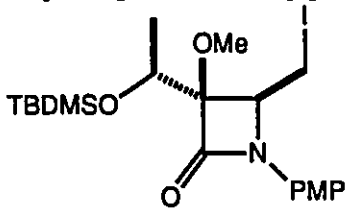
[77] Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

3-t-Butyldimethylsilyloxyethyl-4-methanesulfonyloxy-methyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (83)



Aldehyde **63** was reduced with $NaBH_4$ to give an alcohol.[78] The alcohol, thus obtained, (3.50 g, 8.86 mmol) was dissolved in 50 mL of THF. MsCl (0.75 mL, 9.69 mmol) and TEA (1.5 mL, 10.8 mmol) were sequentially added to the solution of alcohol at 0 °C. After stirring for 30 min, the reaction mixture was worked up in a usual manner using CH_2Cl_2 as a solvent. Purification of the crude product by column chromatography (1:4 EtOAc:hexanes) gave 3.80 g (91%) of mesylate **83** as an oil; ^1H NMR (300 MHz) δ: 0.06 (6H, s, CH_3SiCH_3), 0.81 (9H, s, t-Bu), 1.25 (3H, d, J=6.4 Hz, CH_3CH), 2.93 (3H, s, OSO_2CH_3), 3.66 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.12 (1H, q, J=6.4 Hz, $OCHCH_3$), 4.35-4.45 (2H, m, CH_2O), 4.56 (1H, dd, J=3.4, 10.6 Hz, CHN), 6.86 (2H, d, J=9.2 Hz, PMP), 7.41 (2H, d, J=9.2 Hz, PMP); MS: 473 (M^+, 6), 458 (M^+-15, 1), 416 (M^+-57, 80), 388 (416-28$^+$, 4), 267 (416-149$^+$, 34).

3-t-Butyldimethylsilyloxyethyl-4-iodomethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (86)



The mesylate **83** (2.80 g, 6.08 mmol) was treated with NaI (2.73 g, 18.2 mmol) in 25 mL of refluxing acetone for 18 h. The reaction

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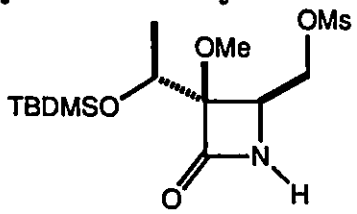
[78] see Chapter 2, p 64.

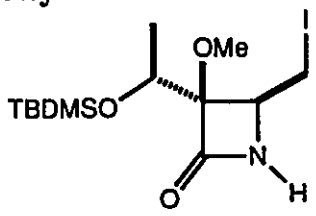
mixture was diluted with 50 mL of CH_2Cl_2, the precipitate was removed by filtration and the filtrate was evaporated in vacuum. The residue was dissolved in 25 mL of CH_2Cl_2 and successively washed with 5% $NaHSO_3$, 5% $NaHCO_3$ and water. The crude product thus obtained, was purified by column chromatography (1:5 EtOAc:hexanes) to afford 2.30 g (79%) of **86**; ^1H NMR (60 MHz) δ: 0.00 (6H, s, CH_3SiCH_3), 0.70 (9H, s, t-Bu), 1.30 (3H, d, J=6.0 Hz, CH_3CH), 2.85-3.50 (2H, m, CH_2I), 3.70 (6H, s, OCH_3), 3.90-4.50 (2H, m, CHO, CHN), 6.75 (2H, d, J=10 Hz, PMP), 7.30 (2H, d, J=10 Hz, PMP).

3-t-Butyldimethylsilyloxyethyl-4-methanesulfonyloxymethyl-3-methoxy-2-azetidinone (84)



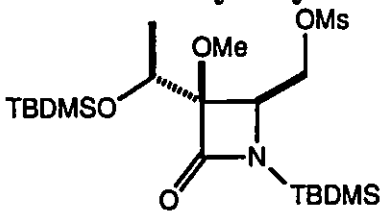
The mesylate **83** (538 mg, 1.14 mmol) was cleaved with CAN following a procedure as described for the preparation of **70** to yield 232 mg (55%) of **84** as an oil; ^1H NMR (60 MHz, contains EtOAc) δ: 0.00 (6H, s, CH_3SiCH_3), 0.85 (9H, s, t-Bu), 1.20 (3H, d, J=6.0 Hz, CH_3CH, overlapping with H_2O), 3.00 (3H, s, OSO_2CH_3), 3.55 (3H, s, OCH_3), 3.80-4.40 (4H, m, CHN, CHO, CH_2O), 6.60 (1H, broad s, NH).

3-t-Butyldimethylsilyloxyethyl-4-iodomethyl-3-methoxy-2-azetidinone (87)



Mesylate **84** (232 mg, 0.632 mmol) was treated with NaI (317 mg, 2.1 mmol) in 8 mL of acetone at reflux temperature for four days. Removal of the solvent from the reaction mixture afforded a crude product which was purified by column chromatography (1:4 EtOAc:hexanes) to afford 133 mg (53%, yield in this reaction is inconsistent due to the formation of a non β-lactam product) of iodide **87** as an oil; ^{1}H NMR (300 MHz) δ: 0.05 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si), 0.86 (9H, s, t-Bu), 1.24 (3H, d, J=6.4 Hz, CH_3CH), 3.20-3.23 (2H, m, CH_2I), 3.60 (3H, s, OCH_3), 3.98 (1H, dd, J=5.2, 9.0 Hz, CHN), 4.11 (1H, q, J=6.4 Hz, CHO), 6.13 (1H, broad s, NH); MS(CI): 400 (M^++1, 6), 384 (M^+-15, 15), 372 (M^++1-28, 94), 342 (M^+-57, 12), 231 (M^++1-169, 2).

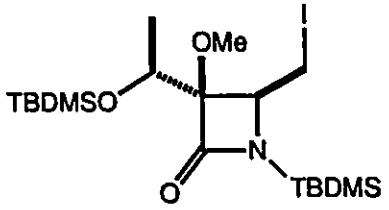
1-t-Butyldimethylsilyl-3-t-butyldimethylsilyloxyethyl-4-methanesulfonyloxymethyl-3-methoxy-2-azetidinone (85)



The crude mesylate **84** (230 mg, 0.478 mmol) in 10 mL of CH_2Cl_2 was treated with 2,6-lutidine (0.11 mL, 0.94 mmol) and TBDMSOTf (0.17 mL, 0.74 mmol) at 0 °C. The reaction mixture was worked up in a usual manner to give a crude product which was purified by column chromatography (1:4 EtOAc:hexanes) to afford 185 mg (61%) of **85** as an

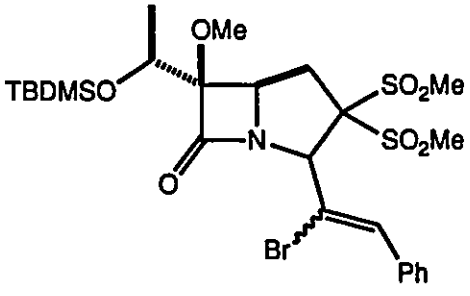
oil; ^{1}H NMR (300 MHz) δ: 0.05 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si), 0.24 (3H, s, CH_3Si), 0.25 (3H, s, CH_3Si), 0.87 (9H, s, t-Bu), 0.96 (9H, s, t-Bu), 1.21 (3H, d, J=6.5 Hz, CH_3CH), 2.99 (3H, s, OSO_2CH_3), 3.58 (3H, s, OCH_3), 3.76-3.82 (1H, m, CHN), 4.08-4.24 (2H, m, CHO, CH_2O), 4.36-4.42 (1H, m, CH_2O); MS(CI): 482 (M^++1, 74), 467 (M^++1-15, 1), 454 (M^++1-28, 3), 424 (M^+-57, 14), 350 (M^+-131, 70).

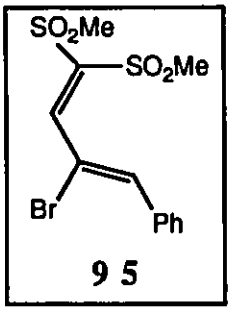
1-t-Butyldimethylsilyl-3-t-butyldimethylsilyloxyethyl-4-iodomethyl-3-methoxy-2-azetidinone (88)



The iodide **87** (190 mg, 0.476 mmol) was N-silylated as described above to yield 236 mg (92%) of **88** as a brownish oil; ^{1}H NMR (60 MHz) δ: 0.15 (6H, s, CH_3Si), 0.25 (3H, s, CH_3Si), 0.30 (3H, s, CH_3Si), 0.95 (9H, s, t-Bu), 1.00 (9H, s, t-Bu), 1.35 (3H, d, J=6.0 Hz, CH_3CH), 3.10-3.30 (2H, m, CH_2I), 3.60 (3H, s, OCH_3), 3.80-4.15 (2H, m, CHN, CHO).

3-Bromocinnamyl-6-(1'-t-butyldimethylsilyloxy)ethyl-6-meethoxy-2,2-*bis*methylsulfonyl-2-oxo-4-azabicyclo[2.3]-heptane (96)



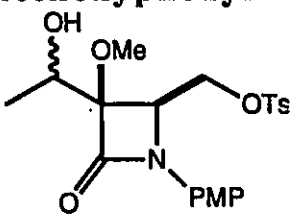


95

The sulfone **95** (183 mg, 0.50 mmol) was added to the solution of mesylate **84** (168 mg, 0.45 mmol) in 10 mL of THF. Powdered KOH

(28.5 mg, 0.51 mmol) was also added and the mixture was stirred for 3 h. The reaction mixture was washed with satd NH_4Cl and the organic layer was extracted with EtOAc. Purification of the crude product by column chromatography (1:4 EtOAc:hexanes) afforded 122 mg (42%) of **96** [When the reaction was carried out for the longer reaction time (18 h) the yield of bicyclic β-lactam **96** was 66% and about 18% of uncyclized Michael adduct was also isolated.]; ^1H NMR (300 MHz) δ: 0.07 (3H, s, CH_3Si), 0.08 (3H, s, CH_3Si), 0.88 (9H, s, t-Bu), 1.29 (3H, d, J=6.4 Hz, CH_3CH), 2.86 (1H, dd, J=9.0, 14.2 Hz, CH_AH_B), 3.06 (1H, dd, J=5.2, 14.7 Hz, CH_AH_B), 3.30 (3H, s, CH_3SO_2), 3.34 (3H, s, CH_3SO_2), 3.62 (3H, s, OCH_3), 4.28-4.34 (2H, m, CHN, $OCHCH_3$), 4.35-4.45 (2H, m, CH_2O), 5.77 (1H, s, NCH-3), 7.33-7.41 (3H, m, Ph), 7.47 (1H, s, C=CHPh), 7.60-7.63 (2H, m, Ph); MS: 638 (M^++1, 0.5), 610 (M^++1-28, 21), 580 (M^+-57, 1), 558 (M^+-80, 0.3), 530 (558-28, 3).

3-Hydroxyethyl-3-methoxy-4-toluenesulfonyloxymethyl-1-p-methoxyphenyl-2-azetidinone (101)



The tosylate **101** was obtained in 96% (900 mg) yield by treatment of corresponding TBDMS derivative[79] (1.19 g, 2.16 mmol) with 1 mL of 6N HCl in 25 mL of MeOH at 25 °C for 19 h; white solid; mp 110-112 °C; ^1H NMR (300 MHz) δ: 1.23 (3H, overlapping dd, J=6.6,

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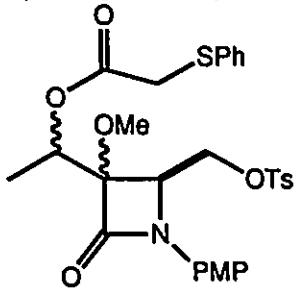
[79] This compound is a mixture of diastereomers at C-3 and hydroxyethyl carbon. This compound was prepared from **65** *via.* a sequence of reactions involving LDA/acetaldehyde, TBDMSOTf/2,6-lutidine/ 0 °C to 25 °C, O_3/$NaBH_4$/-78 °C to 25 °C, and TsCl/pyridine/0 °C.

6.4 Hz, CH_3CH), 1.80+2.08 (1H, 2d, J=5.6, 3.0 Hz, OH), 2.42 (3H, s, CH_3Ph), 3.54+3.60 (3H, 2s, OCH_3), 3.78+3.79 (3H, 2s, OCH_3), 4.21-4.40 (4H, m, CHO, CHN, CH_2O), 6.82-6.85 (2H, m, PMP), 7.26-7.34 (4H, m, PMP, tol), 7.68-7.71 (2H, m, tol); MS: 435 (M^+, 13), 407 (M^+-28, 2), 319 (M^+-116, 2), 263 (M^+-265, 0.4), 255 (M^+-149-31, 9); HRMS calcd for $C_{21}H_{25}NO_7S$ 435.1349, found 435.1357.

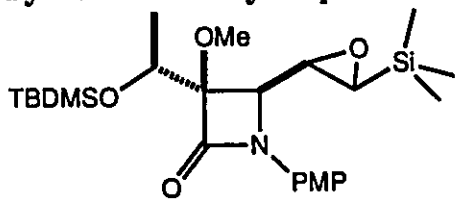
3-(1-S-Phenylthioacetoxy)ethyl-3-methoxy-4-toluene-sulfonyloxymethyl-1-p-methoxyphenyl-2-azetidinone (97)



A solution of oxalyl chloride (0.34 mL, 3.90 mmol) in about 2 mL of CH_2Cl_2 was added dropwise to a solution of DMF (0.28 mL, 3.56 mmol) in 2 mL of CH_2Cl_2 was cooled to 0 °C. [CAUTION: CO is formed in this step.] After 10 min, a solution of phenylthioacetic acid (544 mg, 3.24 mmol) in 10 mL of CH_2Cl_2 was added to the DMF/oxalyl chloride adduct obtained above. The reaction mixture thus obtained, was added to a mixture of **101** (900 mg, 2.16 mmol) and TEA (0.6 mL, 4.31 mmol) in 50 mL of CH_2Cl_2 at 0 °C. [CAUTION: Extra outlets in reaction vessel were added to avoid undesirable consequences due to the development of pressure.] The reaction mixture was worked up in a usual manner to give a crude product which was purified by column chromatography (1:8 EtOAc:hexanes) to afford 312 mg (26%) of **97**; ^1H NMR (300 MHz) δ: 1.86-1.35 (3H, 2 sets of d, J=6.6 Hz, 2 sets of d, J=6.4 Hz, CH_3CH), 2.41 (3H, 2s, CH_3Ph), 3.45-3.65 (5H, m, $COCH_2S$, OCH_3), 4.21-4.31 (3H, m,

CHN, CH_2OTs), 5.32-5.58 (1H, 3 sets of q, one q has J=6.6 Hz, CHO), 6.81-6.86 (2H, m, PMP), 7.19-7.37 (10H, m, Ph, Tol), 7.66-7.71 (2H, m, PMP); MS: 586 (M^++1, 26), 570 (M^+-15, 0.5), 476 (M^+-109, 6), 463 (M^++1-123, 14), 418 (M^+-168, 74);

3-t-Butyldimethylsilyloxyethyl-4-(2'-trimethylsilyl)-glycidyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (102)

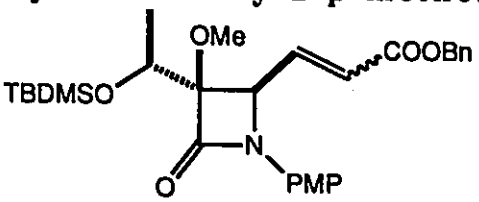


s-BuLi (0.85 mL, 1.21 mmol) was added by syringe to a solution of chloromethyltrimethylsilane (0.095 mL, 1.10 mmol) in 10 mL of THF at -78 °C. After 10 min, TMEDA (0.18 mL, 1.21 mmol) was added and the reaction mixture was stirred for an additional 1.5 h. A solution of aldehyde **63** (393 mg, 1.0 mmol) in 5 mL of THF was added by cannula. The reaction mixture was stirred for 18 h while warming it slowly to 25 °C. Usual work up of the reaction mixture gave 0.529 g of a crude product which was purified by means of a chromatotron (1:10 EtOAc:hexanes) to afford 65 mg (14%) of **102a**, 103 mg (22%) of **102b** and 60 mg (15%) of unreacted aldehyde **63**.

Isomer A **102a**: ^1H NMR (300 MHz) δ: 0.04 (3H, s, CH_3Si), 0.05 (3H, s, CH_3Si), 0.07 (9H, s, TMS), 0.81 (9H, s, t-Bu), 1.19 (3H, d, J=6.3 Hz, CH_3CH), 2.20 (1H, d, J=3.7 Hz, OCHSi), 3.22 (1H, dd, J=3.7, 7.2 Hz, calcd using a ruler, CHO), 3.57 (1H, d, J=7.2 Hz, CHN), 3.63 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.20 (1H, q, J=6.3 Hz, $OCHCH_3$), 6.88 (2H, d, J=9.2 Hz, PMP), 7.57 (2H, d, J=9.2 Hz, PMP); MS: 479 (M^+, 6), 464 (M^+-15, 1), 422 (M^+-57 31), 330 (M^+-149, 1), 249 (M^+-230, 5).

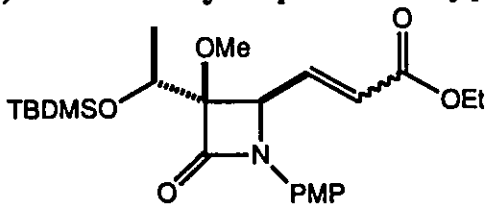
Isomer B **102b**: ^{1}H NMR (300 MHz) δ: -0.02 (3H, s, CH_3Si), 0.03 (3H, s, CH_3Si), 0.20 (9H, s, TMS), 0.61 (9H, s, t-Bu), 1.43 (3H, d, J=6.3 Hz, CH_3CH), 2.43 (1H, d, J=5.4 Hz, OCHSi), 3.39 (1H, dd, J=5.3, 8.6 Hz, CHO), 3.66 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.82 (1H, d, J=8.6 Hz, CHN), 4.07 (1H, q, J=6.3 Hz, $OCHCH_3$), 6.86 (2H, d, J=9.2 Hz, PMP), 7.58 (2H, d, J=9.1 Hz, PMP); MS: 479 (M^+, 6), 464 (M^+-15, 1), 422 (M^+-57, 23), 330 (M^+-149, 1), 249 (M^+-230, 5).

4-(2'-Benzyloxycarbonylvinyl)-3-t-butyldimethylsilyloxyethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (105)



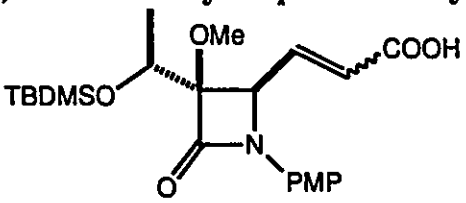
Aldehyde **63** (1.60 g, 4.07 mmol) and benzyl triphenylphosphoranylidineacetate (2.90 g, 6.10 mmol) was refluxed in 50 mL of $C_2H_4Cl_2$ for 24 h. Usual work up of the reaction mixture afforded a crude product which was purified by column chromatography (1:10 EtOAc:hexanes) to give 2.00 g (84%) of **105** as a colorless oil; ^{1}H NMR (300 MHz, *trans* isomer) δ: 0.03 (3H, s, CH_3Si), 0.04 (3H, s, CH_3Si), 0.74 (9H, s, t-Bu), 1.30 (3H, d, J=6.4 Hz, CH_3CH), 3.55 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.12 (1H, q, J=6.3 Hz, CHO), 4.71 (1H, dd, J=1.2, 6.5 Hz, CHN), 5.17 (2H, apparent d, J=1.6 Hz, CH_2Ph), 6.12 (1H, dd, J=1.3, 15.8 Hz, CH=C*H*COOR), 6.82 (2H, d, J=9.2 Hz, PMP), 7.08 (1H, dd, J=6.5, 15.9 Hz, C*H*=CHCOOR), 7.28 (2H, d, J=9.2 Hz, PMP), 7.32-7.36 (5H, m, Ph); MS: 525 (M^+, 2), 494 (M^+-31, 1), 468 (M^+-57, 23), 436 (468-32$^+$, 3), 295 (M^+-230, 12).

3-t-Butyldimethylsilyloxyethyl-4-(2'-ethyloxycarbonyl-vinyl)-3-methoxy-1-p-methoxyphenyl-2-azetidinone (108)



Aldehyde **63** (1.40 g, 3.56 mmol) was treated with ethyl triphenylphosphoranylideneacetate (1.86 g, 5.34 mmol) in refluxing THF for 20 h to yield 1.50 g (91%) of **108** as an oil; ^{1}H NMR (300 MHz, trans isomer) δ: 0.04 (3H, s, CH_3Si), 0.05 (3H, s, CH_3Si), 0.75 (9H, s, t-Bu), 1.25-1.32 (6H, m, CH_3CH_2, CH_3CH), 3.56 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.13 (1H, q, J=6.4 Hz, $CHCH_3$), 4.19 (2H, q, J=7.1 Hz, CH_2O), 4.71 (1H, dd, J=1.2, 6.5 Hz, CHN), 6.06 (1H, dd, J=1.3, 15.8 Hz, CH=CHCOOR), 6.84 (2H, d, J=9.2 Hz, PMP), 7.04 (1H, dd, J=6.5, 15.8 Hz, CH=CHCOOR), 7.30 (2H, d, J=9.1 Hz, PMP); MS: 463 (M^+, 4), 432 (M^+-31, 2), 406 (M^+-57, 56), 374 (406-32$^+$, 7), 257 (406-149$^+$, 61).

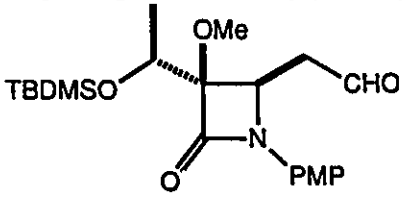
3-t-Butyldimethylsilyloxyethyl-4-(2'-hydroxycarbonyl-vinyl)-3-methoxy-1-p-methoxyphenyl-2-azetidinone (106)



Compound **105** (2.00 g, 3.81 mmol) in 50 mL of EtOH and 10 mL of cyclohexene was mixed with 1.8 g of Pd-C (10%) and sonicated in an ultrasound bath for 3 h. The reaction mixture was filtered through a celite pad and the filtrate was concentrated in vacuum to give 1.20 g (72%) of **106**; ^{1}H NMR (300 MHz) δ: 0.04 (3H, s, CH_3Si), 0.05 (3H, s, CH_3Si), 0.75 (9H, s, t-Bu), 1.30 (3H, d, J=6.4 Hz, CH_3CH), 3.55 (3H, s,

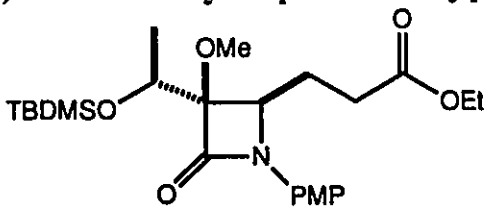
OCH_3), 3.77 (3H, s, OCH_3), 4.14 (1H, q, J=6.4 Hz, CH_3CHO), 4.73 (1H, dd, J=1.1, 6.6 Hz, CHN), 6.07 (1H, d, J=15.7 Hz, HC=CHCOO), 6.84 (2H, d, J=9.1 Hz, PMP), 7.11 (1H, dd, J=7.5, 15.9 Hz, HC=CHCOO), 7.29 (2H, d, J=9.1 Hz, PMP); MS: 435 (M^+, 6), 420 (M^+-15, 1), 407 (M^+-28, 1), 378 (M^+-57, 55), 229 (M^+-57-149, 61); HRMS calcd for $C_{22}H_{33}O_6NSi$ 435.3521, found 435.2103.

3-t-Butyldimethylsilyloxyethyl-4-(2'-oxoethyl)-3-methoxy-1-p-methoxyphenyl-2-azetidinone (103)



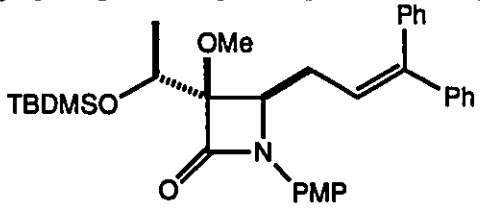
The carboxylic acid **106** (0.55 g, 1.26 mmol), DPPA (0.273 mL, 1.27 mmol) and TEA (0.176 mL, 1.26 mmol) were mixed in 20 mL of THF which was refluxed for 18 h. The reaction mixture was cooled to 25 °C and stirred with 10 mL of 10% HCl for 15 min. Extraction using EtOAc as a solvent and usual work up of the reaction mixture gave a crude product which was purified by column chromatography (1:9 EtOAc:hexanes) to give 120 mg (23%) of aldehyde **103**; ^1H NMR (300 MHz) δ: 0.06 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si), 0.79 (9H, s, t-Bu), 1.28 (3H, d, J=6.4 Hz, CH_3CH), 2.90-2.93 (2H, m, CH_2CO), 3.63 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.18 (1H, q, J=6.4 Hz, CH_3CHO), 4.60 (1H, dd, J=3.5, 6.7 Hz, CHN), 6.85 (2H, d, J=9.1 Hz, PMP), 7.28 (2H, d, J=9.1 Hz, PMP), 9.80 (1H, broad s, CHO); MS: 407 (M^+, 3), 392 (M^+-15, 0.4), 350 (M^+-57, 56), 230 (M^+-177, 2), 201 (350-149$^+$, 20).

3-t-Butyldimethylsilyloxyethyl-4-(2'-ethoxycarbonyl-ethyl)-3-methoxy-1-p-methoxyphenyl-2-azetidinone (109)



The α,β-unsaturated ester **108** (386 mg, 0.83 mmol) was dissolved in about 20 mL of 99% EtOH and 45 mg of Pd-C (10%) was added. This mixture was hydrogenated at 40 psi for 6 h. After removal of the catalyst and the solvent, the crude product was purified by passing through a short column (1:10 EtOAc: hexanes) to give 384 mg (99%) of **109** as a colorless oil; ^{1}H NMR (300 MHz) δ: 0.06 (6H, s, CH_3SiCH_3), 0.82 (9H, s, t-Bu), 1.19 (3H, d, J=6.4 Hz, CH_3CH), 1.25 (3H, t, J=7.1 Hz, CH_3CH_2), 1.82-1.98 (1H, m, CH_2), 2.22-2,52 (3H, m, CH_2CH_2CO), 3.67 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.07-4.20 (4H, m, CHO, CH_2O, CHN), 6.87 (2H, d, J=9.1 Hz, PMP), 7.40 (2H, d, J=9.1 Hz, PMP); MS: 465 (M^+, 9), 450 (M^+-15, 2), 408 (M^+-57, 100), 316 (M^+-149, 2), 235 (M^+-230, 11); HRMS calcd for $C_{24}H_{39}O_6NSi$ 465.3999, found 465.2534.

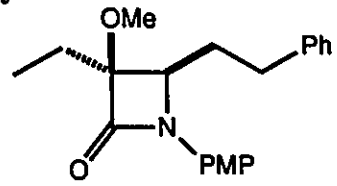
3-t-Butyldimethylsilyloxyethyl-3-methoxy-4-(3',3'-*bis*-phenylprop-2-enyl-1-p-methoxyphenyl-2-azetidinone (110)



Phenyllithium (1.8 M, 1.4 mL, 2.52 mmol) was added to a solution of ester **109** (472 mg, 1.02 mmol) in 20 mL of THF at -78 °C by a syringe. The reaction mixture was stirred for 20 h while allowing it to warm to 25 °C. Purification of the crude product by column chroma-

tography (1:4 EtOAc:hexanes) gave 262 mg (45%) of the corresponding diphenylalcohol derivative which was dehydrated by treatment with a catalytic amount of toluenesulfonic acid (ca. 10 mg) in refluxing toluene for 18 h to give **110** in 226 mg (40 % overall yield from **109**); ^{1}H NMR (200 MHz) δ: 0.01 (3H, s, CH_3Si), 0.02 (3H, s, CH_3Si), 0.73 (9H, s, t-Bu), 1.26 (3H, d, J=6.4 Hz, CH_3CH), 2.41-2.53 (1H, m, CH_AH_B), 2.64-2.71 (1H, m, CH_AH_B), 3.67 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.00 (1H, dd, J=4.9, 9.1 Hz, CHN), 4.13 (1H, q, J=6.4 Hz, $OCHCH_3$), 6.14 (1H, dd, J=6.6, 8.8 Hz, $CH=CPh_2$), 6.72 (2H, d, J=9.2 Hz, PMP), 7.07 (2H, d, J=9.2 Hz, PMP), 7.12-7.43 (10H, m, Ph); MS: 557 (M^+, 22), 542 (M^+-15, 2), 500 (M^+-57, 100), 472 (M^+-57-28, 3), 408 (M^+-149, 4); HRMS calcd for $C_{34}H_{43}O_4NSi$ 557.2959, found 557.2950.

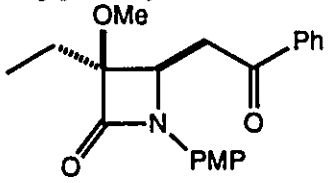
3-Ethyl-3-methoxy-4-(2-phenyl)ethyl-1-p-methoxyphenyl-2-azetidinone (115)



Azetidinone **114** (4.64 g, 13.8 mmol) was hydrogenated in 30 mL of EtOH in the presence of 400 mg of Pd-C(10%) at 40 psi for 18 h. Removal of the catalyst and the solvent from the reaction mixture afforded a crude product which was purified by column chromatography (1:4 EtOAc:hexanes) to yield 4.02 (87%) of **115** as an oil; ^{1}H NMR (200 MHz) δ: 0.99 (3H, t, J=7.5 Hz, CH_3CH_2), 1.60-1.79 (1H, m, CH_2CH_3), 2.01-2.19 (3H, m, CH_2CH_3, CH_2CH_2Ph), 2.46-2.62 (1H, m, CH_2CH_2Ph), 2.72-2.86 (1H, m, CH_2CH_2Ph), 3.62 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.83 (1H, dd, J=3.8, 8.7 Hz, CHN), 6.82 (2H, d, J=9.2 Hz, PMP), 7.16-7.31 (7H, m, Ph, PMP); MS: 339 (M^+, 7), 311 (M^+-28, 0.4), 239 (M^+-100, 5), 190

(M^+-149, 2), 162 (311-149^+, 1); HRMS calcd for $C_{21}H_{25}O_3N$ 339.1833, found 339.1849.

3-Ethyl-3-methoxy-4-(2-oxo-2-phenyl)ethyl-1-p-methoxyphenyl-2-azetidinone (116)



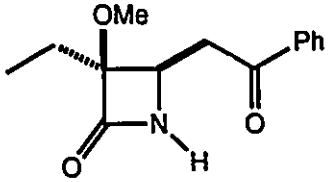
Azetidinone **115** (4.0 g, 11.8 mmol) and NBS (2.2 g, 17.7 mmol) and a catalytic amount of AIBN was dissolved in 120 mL of dry CCl_4. The reaction mixture was refluxed for 8 h and simultaneously irradiated by means of a lamp. The reaction mixture was diluted with dichloromethane and washed with 50 mL of water. The aq layer was extracted twice with 30 mL of EtOAc. Removal of the solvent from combined organic layer afforded a crude product which was purified by column chromatography (1:9 EtOAc:hexanes) to give 3.45 g (70%) of the bromo derivative of **115**. Complete purification at this stage was difficult.

The benzylic bromide, obtained as described above, (3.43 g, 8.22 mmol) was treated with aq $AgNO_3$ (1.58 g, 9.87 mmol) in acetone for 3 to 5 h in the dark. The crude product, obtained after removal of solvent and inorganic compounds, was purified by column chromatography (1:2 EtOAc:hexanes) to give 1.60 g (55%) of the corresponding alcohol.

The alcohol, prepared as described above, (1.60 g, 4.51 mmol) was oxidized with PCC (2.91 g, 13.53 mmol) in dry CH_2Cl_2 for 18 h. Removal of chromium residues and the solvent from the reaction mixture gave a crude product which was purified by column chromatography (1:4 EtOAc:hexanes) to afford 955 mg (60%) of **116** as a yellow oil; ^1H NMR

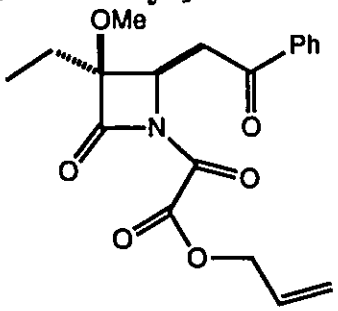
(200 MHz) δ: 1.02 (3H, t, J=7.5 Hz, CH_3CH_2), 1.80-1.95 (1H, m, CH_2CH_3), 2.01-2.20 (1H, m, CH_2CH_3), 3.26 (1H, dd, J=3.6, 8.0 Hz, CH_ACH_BCO), 3.50 (3H, s, OCH_3), 3.57 (1H, dd, J=8.3, 18.1 Hz, CH_ACH_BCO), 3.75 (3H, s, OCH_3), 4.68 (1H, dd, J=3.6, 8.4 Hz, CHN), 6.85 (2H, d, J=9.1 Hz, PMP), 7.32 (2H, d, J=9.2 Hz, PMP), 7.39 (3H, m, Ph), 7.91-7.96 (2H, broad d, J=9.7 Hz, Ph); MS: 353 (M^+, 9), 325 (M^+-28, 4), 310 (325-15^+, 2), 253 (M^+-100, 4), 204 (M^+-149, 1).

3-Ethyl-3-methoxy-4-(2-oxo-2-phenyl)ethyl-2-azetidinone (113)



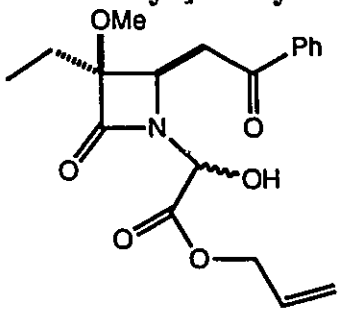
The PMP moiety of ketone **116** (950 mg, 2.69 mmol) was cleaved using CAN as described in the preparation of **70**. Purification of the crude product by column chromatography (1:2 EtOAc:hexanes) afforded 432 mg (65%) of **113** as a brown oil; ^1H NMR (200 MHz) δ: 0.97 (3H, t, J=7.5 Hz, CH_3CH_2), 1.70-1.85 (1H, m, CH_2CH_3), 2.01-2.14 (1H, m, CH_2CH_3), 3.28-3.33 (2H, m, CH_2CO), 3.52 (3H, s, OCH_3), 3.99 (1H, dd, J=5.0, 8.1 Hz, CHN), 6.18 (1H, broad s, NH), 7.41-7.57 (3H, m, Ph), 7.92-7.97 (2H, broad d, J=8.6 Hz, Ph); MS: 360 (M^+-32, 8), 344 (M^+-15, 7), 332 (M^++1-32, 100), 318 (M^+-41, 4), 302 (M^+-57, 6).

Allyl [3-ethyl-3-methoxy-4-(2-oxo-2-phenyl)ethyl-2-azetidinon-1-yl]-2-oxoethanoate (112)



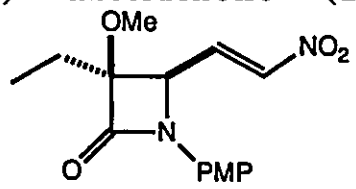
DIPEA (0.45 mL, 2.58 mmol) was added dropwise to a solution of ketone **113** (320 mg, 1.29 mmol) in 15 mL of CH_2Cl_2 at 0 °C. Allyloxalyl chloride (0.30 g, 2.03 mmol) in 2 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 30 min and worked up in a usual manner. Purification of the crude product by column chromatography (1:6 EtOAc:hexanes) afforded 0.367 g (79%) of **112** as an oil; ^1H NMR (200 MHz) δ: 1.06 (3H, t, J=7.5 Hz, CH_3CH_2), 1.90-2.20 (2H, m, CH_2CH_3), 3.41 (3H, s, OCH_3), 3.55-3.70 (2H, m, CH_2CO), 4.07-4.82 (3H, m, CHN, CH_2O), 5.85-6.10 (1H, m, $HC=CH_2$), 5.30-5.46 (2H, m, $HC=CH_2$), 7.40-7.60 (3H, m, Ph), 7.90-7.95 (2H, broad d, J=7.5 Hz calcd by ruler, Ph); MS: 215 (M^+-32, 2), 204 (M^+-43, 7), 175 (204-29$^+$, 2), 142 (M^+-105, 0.3), 127 (142-15$^+$, 6).

Allyl [3-ethyl-3-methoxy-4-(2-oxo-2-phenyl)ethyl-2-azetidinon-1-yl]-2-hydroxyethanoate (117)



This compound **117** was obtained by refluxing **112** with triethyl phosphite in toluene for 3 h after purification of the crude product by column chromatography (1:3 EtOAc:hexanes); ^{1}H NMR (200 MHz) δ: 0.94 (3H, t, J=7.5 Hz, CH_3CH_2), 1.70-2.10 (2H, m, CH_2CH_3), 3.33-3.46 (2H, m, CH_2CO), 3.46+3.49 (3H, 2s, OCH_3), 4.12-4.45 (2H, m, CHN, HO), 4.68-4.80 (2H, m, CH_2O), 5.05-5.38 (2H, m, $HC=CH_2$), 5.48-5.92 (2H, m, CHO, $HC=CH_2$), 7.37-7.58 (3H, m, Ph), 7.90-7.94 (2H, m, Ph).

3-Ethyl-3-methoxy-1-p-methoxyphenyl-4-(2-nitro-vinyl)-2-azetidinone (122)



TEA (0.88 mL, 6.32 mmol) was added to a solution of aldehyde **118**[80] (11.20 g, 42.4 mmol) in 65 mL of nitromethane and the reaction mixture was stirred at 25 °C for 6 h. Removal of solvent yielded a crude nitro-aldol adduct (dark red oil) which was taken to the next step without further purification.

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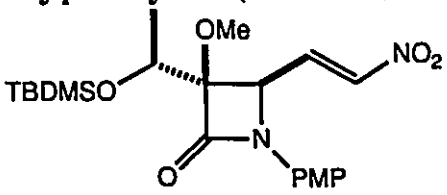
80 see Chapter 2 p 62.

In another flask, freshly distilled methanesulfonylchloride (9.8 mL, 127 mmol) in 20 mL of dry CH_2Cl_2 was added dropwise to a solution of TEA (17.7 mL, 127 mmol) in 80 mL of dry CH_2Cl_2 at -78 °C. The crude nitro-aldol adduct was dissolved in 120 mL of dry CH_2Cl_2 (some 4Å molecular sieves were added to ensure moisture free conditions) and added dropwise to the methanesulfonylchloride and TEA mixture and stirred for 2 h (Yellow color appeared). After 10 min, the bath was removed and the reaction mixture was stirred for 35 min. The reaction mixture was recooled to -50 °C. TEA (17.7 mL, 127 mmol) was added and stirred for 1 h at -50 °C. The reaction mixture was warmed slowly to -10 °C over 7.5 h. Usual aqueous workup and purification of the crude product by column chromatography (1:4 EtOAc:hexanes) yielded 8.50 g (65%) of **122** as a yellow oil; IR: 1740-1770 (broad C=O), 1510-1540 and 1360 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 1.03 (3H, t, J=7.5 Hz, CH_3CH_2), 1.78-1.96 (1H, m, CH_2CH_3), 2.04-2.18 (1H, m, CH_2CH_3), 3.49 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.65 (1H, d, J= 6.5 Hz, CHN), 6.85 (2H, d, J=8.9 Hz, PMP), 7.08 (1H, dd, J=0.9, 13.9 Hz, $HC=CHNO_2$), 7.22-7.35 (3H, m, $HC=CHNO_2$, PMP); MS: 306 (M^+, 15), 260 (M^+-46, 18), 232 (M^+-46-28, 17), 206 (M^+-100, 30), 149 (M^+-157, 100%); HRMS calcd for $C_{15}H_{18}N_2O_5$ 306.1213, found 306.1197.

3-t-Butyldimethylsilyloxyethyl-3-methoxy-1-p-methoxyphenyl-4-(2-nitro)vinyl-2-azetidinone (121)



The aldehyde **63**[81] (0.193 g, 0.491 mmol) was dissolved in 5 mL of nitromethane and 1 drop of TEA. The mixture was stirred for 9 h. The conversion to nitro-olefin was carried out in as described above. The reaction mixture was washed with saturated NH_4Cl and aq layer was extracted with EtOAc twice. The crude product was purified by column chromatography (1:10 EtOAc:hexanes) to yield 0.140 g (65%) of nitro-olefin **121** as a yellowish solid; mp: 109-110 °C; IR (KBr): 1743 (C=O), 1520 and 1349 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.04 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si), 0.76 (9H, s, t-Bu), 1.28 (3H, d, J=6.4 Hz, CH_3CH), 3.56 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.18 (1H, q, J=6.5 Hz, $CHCH_3$), 4.79 (1H, dd, J=1.1, 6.1 Hz, CHN), 6.85 (2H, d, J=9.0 Hz), 7.16 (1H, dd, J=1.1, 13.6 Hz, $CH=CHNO_2$), 7.25-7.38 (3H, dd, J=13.5, 5.8 Hz of $CH=CHNO_2$, overlapping with PMP); MS: 436 (M^+, 8), 421 (M^+-15, 81), 390 (M^+-46, 2), 379 (M^+-57, 90), 362 (M^+-46-28, 12); HRMS calcd for $C_{21}H_{32}O_6N_2Si$ 436.1994, found 436.2012.

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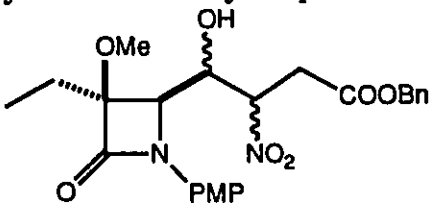
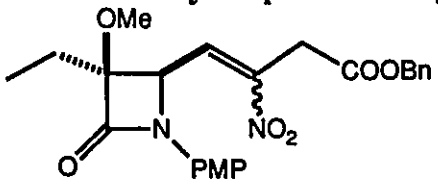
[81] see Chapter 2, p 64.

4-(3'-Benzyloxycarbonyl-2'-nitro-1'-hydroxyprop-1'-yl)-3-ethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (126)



TEA (0.18 mL, 1.32 mmol) was added to a mixture of aldehyde **118** (0.317 g, 1.20 mmol) and benzyl nitropropionate (0.504 g, 2.41 mmol) in 10 mL of MeCN at 25 °C. The reaction mixture was stirred for 18 h, then diluted with 10 mL of EtOAc and washed with 10% HCl followed by satd NaCl. The crude product, obtained, was purified by column chromatography (1:4 to 1:2 EtOAc: hexanes) to afford 280 mg (49%) of impure **126**. Examination of ^{1}H NMR spectrum showed an α,β-unsaturated ester derived from **126** as a major impurity. Impure **126** was used in next step without further purification.

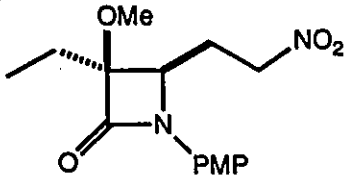
4-(3'-Benzyloxycarbonyl-2'-nitroprop-1'-en-1'-yl)-3-ethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (127)



Adduct **126** (275 mg, 0.58 mmol) in 10 mL of dichloromethane was added dropwise to a mixture of methanesulfonyl chloride (0.14 mL, 1.74 mmol) and TEA (0.25 mL, 1.79 mmol) at -78 °C. The reaction mixture was stirred and gradually warmed over a period of 1 h. TEA (0.25 mL, 1.79 mmol) was added to the reaction mixture which was stirred for 18 h at 0 °C to 25 °C. The crude product was purified by column chromatography (3:17:5 EtOAc:hexanes:CH_2Cl_2) to yield 30 mg

(11%) of **127** as a yellowish oil; IR: 1780 (C=O), 1560 and 1360 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.95-1.05 (3H, m, CH_3CH_2), 1.80-2.20 (2H, m, CH_2CH_3), 3.45+3.49 (3H, 2s, OCH_3), 3.74 (5H, broad s, OCH_3, CH_2CO), 4.45 (1H, d, J=8.6 Hz, CHN), 5.10-5.17 (2H, m with overlapping s, CH_2Ph), 6.81-6.87 (2H, m, PMP), 7.22-7.44 (8H, m, PMP, Ph, $CH=CNO_2$); MS (expanded CI): 455 (M^++1, 100), 439 (M^+-15, 17), 427 (M^+-28, 30), 364 (M^++1-91, 10), 355 (M^++1-100, 2).

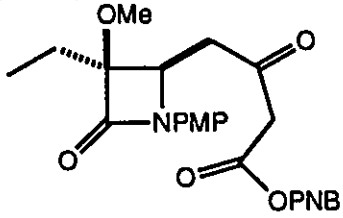
3-Ethyl-3-methoxy-1-p-methoxyphenyl-4-(2-nitro-ethyl)-2-azetidinone (132)



Nitro-olefin **122** (8.50 g, 27.8 mmol) was dissolved in 200 mL of 1,4-dioxane:EtOH (1:1) and cooled to 0 °C. Sodium borohydride (0.28 g, 7.8 mmol) was added in one portion. Vigorous effervescence ensued and yellow color faded. The reaction was complete after stirring for 1.5 h at 0 °C to 25 °C. Excess borohydride was quenched by adding 3-4 g of Amberlite. Amberlite was filtered off and the filtrate (pH 6) was concentrated in vacuum. Purification of the crude product by column chromatography (1:5 EtOAc: hexanes) gave 6.10 g (71%) of **132** as a yellow oil; IR: 1744 (C=O), 1513 and 1386 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.95 (3H, t, J=7.5 Hz, CH_3CH_2), 1.59-1.79 (1H, m, CH_2CH_3), 2.02-2.39 (2H, m, CH_2CH_3, $CH_2CH_2NO_2$), 2.62-2.80 (1H, m, $CH_2CH_2NO_2$), 3.58 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.97 (1H, dd, J=2.9, 10.1 Hz, CHN), 4.44-4.51 (2H, m, CH_2NO_2), 7.25 (2H, d, J=9.3 Hz, PMP), 7.31(2H, d, J=10.0 Hz, PMP); MS: 308 (M^+, 16), 280 (M^+-28, 3), 206 (M^+-102, 15), 193 (M^+-

115, 21), 149 (M^+-159, 100); HRMS calcd for $C_{15}H_{20}N_2O_5$ 308.1354, found 308.1363.

3-Ethyl-3-methoxy-1-p-methoxyphenyl-4-(3'-p-nitrobenzyloxycarbonyl-2'-oxopropyl)-2-azetidinone (135)



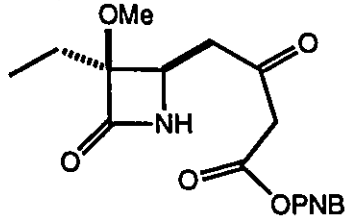
p-Nitrobenzylglyoxylate (4.20 g, 18.5 mmol) in 50 mL of dry THF was added to the solution of **132** (6.10 g, 19.8 mmol) in 200 mL of THF in the presence of 20 g of 4Å molecular sieves and TEA (0.27 mL, 1.94 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h, filtered, concentrated and purified by column chromatography (1:2 EtOAc:hexanes) to yield 6.60 g (60%) of the corresponding adduct.

Methanesulfonylchloride (2.96 mL, 38.2 mmol) in 20 mL of CH_2Cl_2 was added dropwise to a solution of TEA (5.33 mL, 38.2 mmol) in 80 mL of CH_2Cl_2 at -78 °C, followed by a solution of the nitro-aldol adduct obtained above (6.60 g, 12.8 mmol) in 75 mL of CH_2Cl_2. When the bath temperature reached -50 °C, TEA (1.80 mL, 12.9 mmol) was added by syringe and slowly warmed to 25 °C over 3 h. Usual workup and purification (1:3 EtOAc:hexanes) gave 3.63 g (57%) of **133** as an orange solid.

97% Tributyltin hydride (3.1 mL, 11.2 mmol) was added to a solution of nitro-olefin **133** (3.63 g, 7.27 mmol) in 50 mL of CH_2Cl_2. After stirring at 25 °C for 18 h, one more eq of tributyltin hydride was added and the mixture was stirred for 3 h. Ozonolysis of the resulting tin nitronate with reductive work up with dimethylsulfide (DMS) and

removal solvent followed by tin impurities by partitioning between acetonitrile and hexanes gave crude **135**. Purification of this crude product by column chromatography (1:3 EtOAc:hexanes) yielded 1.20 g (35%) of **135** as a yellowish oil (still contaminated with traces of tin residue); IR: 1740 (C=O), 1515 and 1351 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.94 (3H, t, J=7.4 Hz, CH_3CH_2), 1.70-1.90 (1H, m, CH_2CH_3), 2.00-2.20 (1H, m, CH_2CH_3), 2.98-3.03 (2H, m, CH_2CHN), 3.53 (3H, s, OCH_3), 3.57 (2H, s, $COCH_2COOR$), 3.75 (3H, s, OCH_3), 4.42 (1H, dd, J=8.8, 5.0 Hz, CHN), 5.23 (2H, s, CH_2PNB), 6.84 (2H, d, J=9.1 Hz, PMP), 7.24 (2H, d, J=9.1 Hz, PMP), 7.49 (2H, d, J=8.9 Hz, PNB), 8.19 (2H, d, J=8.9 Hz, PNB); MS: 470 (M^+, 7), 455 (M^+-15, 2), 443 (M^+-27, 2), 431 (M^+-39, 2), 321 (M^+-149, 3); HRMS calcd for $C_{24}H_{26}N_2O_8$ 470.1691, found 470.1690.

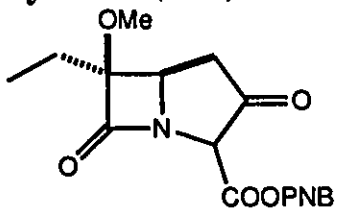
3-Ethyl-3-methoxy-4-(3'-p-nitrobenzyloxycarbonyl-2'-oxopropyl)-2-azetidinone (136)



CAN (3.08 g, 5.62 mmol) in 15 mL of ice-cold water was added dropwise to a solution of compound **135** (1.20 g, 2.55 mmol) in 25 ml of MeCN at -20 °C to -30 °C over 30 min. Usual workup (avoid $NaHCO_3$ wash) of the reaction mixture with EtOAc and purification of the crude product by column chromatography (1:1 EtOAc: hexanes) 226 mg (24%) of **136** as an oil; IR: 3302 (broad, NH), 1748 (broad, C=O), 1522 and 1347 (NO_2) cm-1; ^1H NMR (200 MHz) δ: 0.91 (3H, t, J=7.4 Hz, CH_3CH_2), 1.63-1.81 (1H, m, CH_2CH_3), 1.93-2.11 (1H, m, CH_2CH_3), 2.88 (2H, dd, J=6.8, 6.1 Hz, CH_2CO), 3.47 (3H, s, OCH_3), 3.56 (2H, s, $COCH_2CO$), 3.85 (1H,

dd, J=6.1, 7.1 Hz, CHN), 5.25 (2H, s, CH_2PNB), 6.01 (1H, broad s, NH), 7.50 (2H, d, J=8.9 Hz, PMP), 8.21 (2H, d, J=8.8 Hz, PMP); MS(CI): 365 (M^++1, 22), 337 (M^++1-28, 66), 212 (M^+-152, 11), 184 (212-28$^+$, 98).

p-Nitrobenzyl (6-ethyl-6-methoxy-2-oxocarbapenam)-3-carboxylate (128)

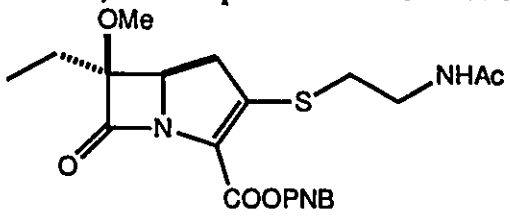


4-Carboxybenzenesulfonazide (307 mg, 1.35 mmol) was added to a solution of β-ketoester **136** obtained above (470 mg, 1.29 mmol) in 4 mL of MeCN and cooled to 0 °C. TEA (0.35 mL, 2.51 mmol) was added. The reaction mixture was stirred for 5 h, worked up in a usual manner and purified by column chromatography (1:1 EtOAc:hexanes) to yield 360 mg (72%) of diazo compound (IR: 3305 NH, 2142 N_2 and 1760 C=O cm^{-1}).

The diazo compound (360 mg, 0.923 mmol) was dissolved in 50 mL of benzene and 30 mL of which was distilled off. The solution left was cooled to 25 °C under nitrogen. A catalytic amount of rhodium octanoate (about 1 mg) was added to the reaction mixture which was refluxed for 2.5 h. Removal of the solvent and the catalyst [by passing through a small silica gel plug (1:1 EtOAc:hexanes)] gave 200 mg (60%) of **128** as a reddish oil; IR: 1770 (C=O), 1750 (C=O), 1523 and 1348 (NO_2) cm^{-1}; ^{1}H NMR (200 MHZ) δ: 1.02 (3H, t, J=7.4 Hz, CH_3CH_2), 1.99-2.18 (2H, m, CH_2CH_3), 2.58 (1H, dd, J=18.9, 7.0 Hz, $CH_AH_BCH_XN$), 2.85 (1H, dd, J=18.9, 7.9 Hz, $CH_AH_BCH_XN$), 3.44 (3H, s, OCH_3), 4.06 (1H, dd, J=7.0, 7.8 Hz, CH_XN), 4.64 (1H, s, CH), 5.22 (1H, d, J=13.4 Hz,

CH_ACH_BPNB), 5.32 (1H, d, J=13.4 Hz, CH_BCH_APNB), 7.51 (2H, d, J=8.9 Hz, PNB), 8.21 (2H, d, J=8.8 Hz, PNB); MS: 362 (M^+, 2), 226 (M^+-136, 3), 182 (M^+-180, 9), 154 (182-28$^+$, 2), 136 (M^+-226, 4); HRMS calcd for $C_{17}H_{18}N_2O_7$ 362.1162, found 362.1138.

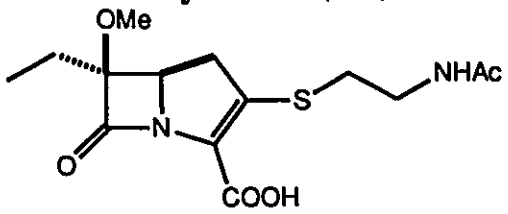
p-Nitrobenzyl 6-ethyl-6-methoxy-2-(2'-N-acetylamino-ethanethio)carbapen-2-em-3-carboxylate (137)



DIPEA (0.20 mL, 1.15 mmol) and diphenylchlorophosphate (0.21 mL, 1.01 mmol) was sequentially added to a solution of the bicyclic ketoester **128** (200 mg, 0.554 mmol) in 3 mL of MeCN by syringe. The reaction mixture was stirred for 1 h at 25 °C. Then, N-acetylamino-ethanethiol (125 mg, 1.06 mmol) in 5 mL of MeCN was added by cannula. DIPEA 0.20 mL, 1.15 mmol) was added immediately to the reaction mixture which was stirred for 1 h. Usual workup of the reaction mixture using EtOAc as a solvent and purification of the crude product by column chromatography (1:10 EtOAc:hexanes) gave 156 mg (36%) of **137** as a yellowish foam; IR: 3334 (broad, NH), 1773 (C=O, β-lactam), 1702 (COOR), 1660 (CONH), 1520 and 1340 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.97 (3H, t, J=7.4 Hz, CH_3CH_2), 1.81-2.21 (5H, m overlapping with s, CH_2CH_3, CH_3CO), 2.85-3.15 (3H, m, CH_2S, $CH_ACH_BCH_XN$), 3.30-3.60 (6H, m with overlapping s, CH_3O, CH_2N, $CH_ACH_BCH_XN$), 4.03 (1H, t, J=9.3 Hz, CHN), 5.18 (1H, d, J=14.0 Hz, CH_ACH_BPNB), 5.46 (1H, d, J=13.9 Hz, CH_ACH_BPNB), 6.06 (1H, broad s, NH), 7.60 (2H, d, J=8.9 Hz, PNB), 8.17 (2H, d, J=8.8 Hz, PNB); ^{13}C NMR

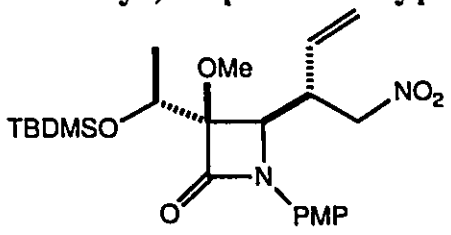
(300 MHz) δ: 7.4 (CH_3), 22.9 (CH_2), 23.2 (CH_3CO), 31.9 (CH_2), 35.1 (CH_2), 39.8 (CH_2), 52.5 (CH_3O), 60.4 (CHN), 65.0 (CH_2), 80.3 (C), 123.5 (C=C), 123.7 (CH, PNB), 128.0 (CH, PNB), 143.2 (C, PNB), 147.5 (C=C), 150.4 (C), 160.8 (C=O), 170.6 (C=O), 176.8 (C=O); MS(CI): 464 (M^++1, 1), 436 M^++1-28, 33), 404 (436-32, 7), 364 (M^++1-100, 2), 317 (364-47, 1); HRMS calcd for $C_{20}H_{25}O_6N_3S$ (M^+-28) 435.1404, found 453.1434.

6-Methoxy-PS-5 (58)



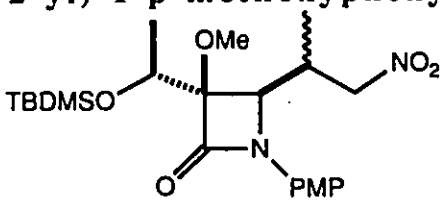
The compound **137** was dissolved in 10 mL of THF:H_2O (1:1) and hydrogenated in the presence of 22 mg of Pd-C (10%) at 1 atm and 25 °C for 4 h. After removal of the catalyst by filtration, 8 mg of $NaHCO_3$ was added to the filtrate. The aq layer was washed with EtOAc (ca. 5 mL) and lyophilized to give 20 mg of a brown solid. The ^1H NMR spectrum of this compound indicated **58** to be impure. These impurities may be derived from the decomposition products of **58** since purification led to the decomposition of the product. The signals which suggest the presence of **58** are listed below: ^1H NMR (300 MHz, D_2O) δ: 0.98 (3H, t, J=7.4 Hz, CH_3CH_2), 1.87-2.11 (5H, m with overlapping s at 1.96, CH_2CH_3, CH_3CO), 2.94-3.02 (2H, m, CH_AH_BS, CH_AH_B), 3.22-3.44 (5H, m with overlapping s at 3.34, CH_2N, CH_3O), 4.09 (1H, t, J=9.2 Hz, CHN).

3-t-Butyldimethylsilyloxyethyl-3-methoxy-4-(1-nitro-but-3-en-2-yl)-1-p-methoxyphenyl-2-azetidinone (139)



Nitro-olefin **121** (74 mg, 0.17 mmol) and CuI (20 mg, 0.105 mmol) were mixed with 5 mL of dry THF. A solution of vinylmagnesium bromide (1M, 0.34 mL, 0.34 mmol) in THF was added by syringe at -78 °C. The reaction mixture was warmed slowly to 25 °C over a period of 18 h, quenched with satd NH_4Cl and extracted with 10 mL of EtOAc thrice. The crude product obtained after removal of the solvent from the organic layer was purified by column chromatography (1:15 EtOAc:hex-anes) to yield 36 mg (46%) of **139** as a white solid; mp: 112-114 °C; IR (KBr): 1742 (C=O), 1513 and 1378 (NO_2) cm^{-1}; ^1H NMR (300 MHz) δ: 0.08 (6H, s, CH_3SiCH_3), 0.86 (9H, s, t-Bu), 1.16 (3H, d, J=6.5 Hz, CH_3CH), 3.66 (3H, s, OCH_3 + 1H, m, $CHCH_2NO_2$), 3.78 (3H, s, OCH_3), 4.25 (2H, d, J=4.8 Hz, with overlapping q, J=6.7 Hz, CHN, CHO), 4.51 (1H, dd, J=4.9, 13.3 Hz, $CH_AH_BNO_2$), 4.60 (1H, dd, J=8.8, 13.3 Hz, $CH_AH_BNO_2$), 4.89 (1H, dd, J=1.0, 17.2 Hz, CH_AH_B=CH), 5.18 (1H, d, J=10.6 Hz, CH_AH_B=CH), 5.84 (1H, ddd, J=17.2, 10.4, 9.0 Hz, CH_AH_B=CH), 6.88 (2H, d, J=9.1 Hz, PMP), 7.30 (2H, d, J=9.1 Hz); ^{13}C NMR (300 MHz) δ: -4.8 (CH_3Si), -4.5 (CH_3Si), 18.0 (CSi), 18.8 (CH_3), 25.7 (CH_3 of t-Bu), 42.0 (CH), 54.4 (OCH_3), 55.5 (OCH_3), 58.3 (CH), 66.0 (CH), 76.1 (CH_2), 92.4 (C-3), 114.6 (CH of PMP), 118.9 (CH of PMP), 121.0 (CH_2=CH), 129.7 (C of PMP), 132.5 (CH_2=CH), 156.7 (C of PMP), 163.4 (C=O); HRMS calcd for $C_{23}H_{36}O_6N_2Si$ 464.2312, found 464.2332.

3-t-Butyldimethylsilyloxyethyl-3-methoxy-4-(1-nitro-prop-2-yl)-1-p-methoxyphenyl-2-azetidinone (138)

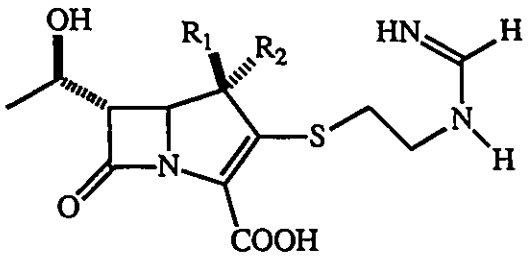


An equal mixture of diastereomers (**138a** and **138b**) were obtained in 73% (27 mg) yield by adding MeMgBr (3M, 0.06 mL, 1.80 mmol) to nitro-olefin **121** (35.5 mg, 0.81 mmol) in the presence of CuI (10 mg, 0.052 mmol) at -78 °C as described above; ^{1}H NMR (200 MHz, crude product) δ: 0.07 (6H, s, CH_3SiCH_3), 0.84 (9H, s, t-Bu), 1.06-1.11 (3H, 2dd, J=6.9 Hz, C*H*$_3$CH), 1.16 (3H, d, J=6.4 Hz, C*H*$_3$CH), 2.90-3.15 (1H, m, C*H*CH$_3$), 3.66-3.77 (3H, s, OCH_3), 3.77 (3H, 2s, OCH_3), 4.18-4.47 (4H, overlapping m, CHO, CHN, CH_2NO_2), 6.83-6.90 (2H, m, PMP), 7.25-7.32 (2H, m, PMP).

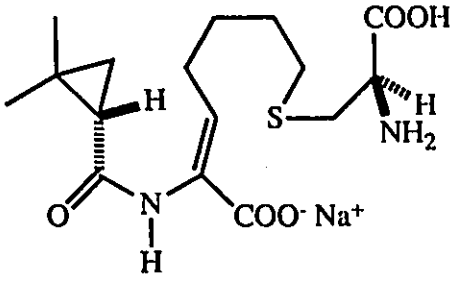
CHAPTER FIVE: 1-METHYL-6,6-DISUBSTITUTED CARBAPENEMS

1-Substituted carbapenems

The chemical instability and the susceptibility to renal dehydropeptidase, DHP-I, of thienamycin and related compounds posed a major problem concerning its clinical use.[1] The development of imipenem[2] **1**, the N-formimidoyl derivative of thienamycin, solved the problem of the chemical stability. In order to overcome its hydrolysis by DHP-I in mammalian kidney, an enzyme inhibitor such as cilastatin **2** is added to pharmaceutical formulations of imipenem.



1 R_1=H=R_2, imipenem



2

Later, Merck chemists demonstrated that the introduction of a 1-β-methyl group imparts the beneficial effect of improving the DHP-I stability while maintaining the desirable, broad spectrum antibiotic activity.[3] As a consequence of this discovery a large number of 1-β-

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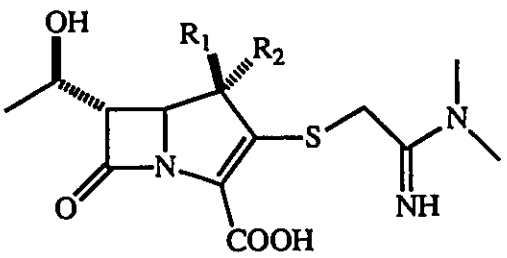
[1] (a) Kropp, H.; Sundelof, J. G.; Hadju, R.; Kahan, F. M.; *Antimirob. Agents Chemother.* **1982**, *22*, 62. (b) Leanza, W.J.; Wildonger, K. J.; Miller, T.W.; Christensen, B. G. *J. Med. Chem.*, **1979**, *22*,1435.

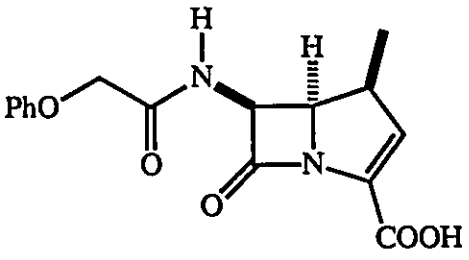
[2] Leanza, W.J.; Wildonger, K. J.; Miller, T.W.; Christensen, B. G. *J. Med. Chem.*, **1979**, 22,1435.

[3] (a) Shih, D.H.; Baker, F.; Cama,L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29. (b) Shih, D.H.; Fayter, J. A.; Cama, L. D.; Christensen, B. G.; Hirschfield, J. *Tetrahedron lett.*,**1985**, 26, 583. (c) Shih, D. H.; Cama, L.; Christensen, B. G. *Tetrahedron lett.* **1985**, *26*, 587.

methyl carbapenems **3** have been reported. Most of these compounds have a typical thienamycin type *i.e.* hydroxyethyl substituent at C-6 position but vary considerably with respect to the nature of the substituent at the C-2 carbon.[4]



3 R_1=Me, R_2=H



4

Aside from this series, few carbapenems having a substituent other than a hydroxyethyl at C-6 have been reported. The substitution by an acyl amino group (bonded to C-3 through nitrogen) at this position did not lead to significant enhancement of chemical or enzymatic stability.[5] The antibacterial activity of carbapenem **4** bearing a penicillin V type substituent is considerably reduced.

Chemists at Bristol-Myers Squibb Co. have reported the preparation of 1-β-methyl carbapenems having an asparenomycin type[6] **5-6**, northienamycin type[7] **7** substituents, carbonyl (amide)[8] **8**

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[4] (a) for synthesis of 1-methyl-2-aryl carbapenems: Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *J. Med. Chem.*, **1987**, *30*, 871.

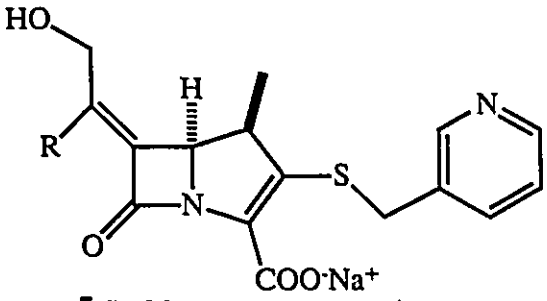
[5] (a) Salzmann, T. N.; DiNinno, F. P.; Greenlee, M. L.; Guthikonda, R. N.; Quesada, M. L.; Schmitt, S. M.; Herrmann, J. J.; Woods, M. F. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; A. G. Brown and S. M. Roberts, Ed.; The Royal Society of Chemistry: London (England), **1985**; p 171. (b) for 6-N amido carbapenam: Salzmann, T. N.; DiNinno, F. P.; Greenlee, M. L. *Chem. Abstr.***1991**, *114*, 81409N, Eur. Pat. Appl. EP. 381532.

[6] Bouthillier, G.; Mastalerz, H.; Menard, M. *Tetrahedron lett.* **1991**, *32*, 1023.

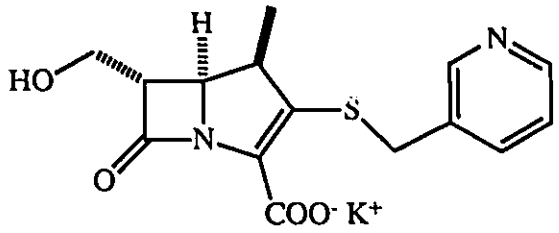
[7] Ruediger, E. H.; Solomon, C. *J. Org. Chem.* **1991**, *56*, 3183.

[8] Mastalerz, H.; Menard, M. *Heterocycles* **1991**, *32*, 93.

and aminoethyl[9] **9-10** substituents at C-6. The biological activity of first two type of compounds **5-7** was not reported. The carbapenem **8** with an amido substituent, was found to be moderately active against the Gram-positive bacteria. Its half life is 1.3 h at 37 °C and pH 7.4.



5 R=Me, asparenomycins
6 R=H, asparenomycin analogs



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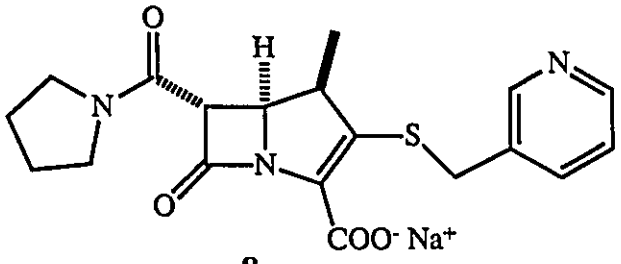
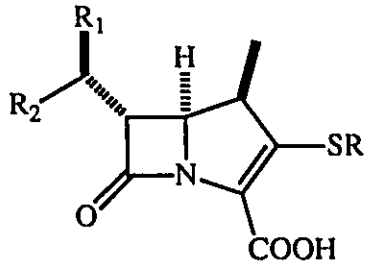


8



9 R_1=NH_2, R_2=Me
10 R_1=Me, R_2=NH_2
11 R_1=H, R_2=NH_2

The aminoethyl group in **9-10** imparts interesting biological activity. Unlike the hydroxyethyl carbapenems, the activity of both R and S isomers of aminoethyl carbapenems is identical. The parent 6-(1-aminoethyl)carbapenems have low Gram-positive but good Gram-negative activity including activity against *Pseudomonas*. The DHP stability of R isomer is greater than that of R hydroxyethyl compound. The stability of these compounds in the acidic range (pH 2) is increased

[9] Private communication. see also Banville, J. *Chem. Abs.* **1991**, *114*, 61831r. Eur. Pat. Appl. EP 372,582.

but decreased near the neutral range (pH 7.4). Acylation with amino acids or dipeptides decreases the antibacterial activity as does N-methylation. The 6-aminomethyl carbapenem **11** showed higher *in vitro* activity but it is less stable and *in vivo* activity is markedly reduced.

Related studies dealt with the synthesis of a variety of carbapenems having a substituent other than a methyl group at C-1 position. Cama and Shah reasoned that substituents having a steric bulk intermediate between hydrogen and methyl such as fluoro group should increase the DHP-I stability and maintain antibacterial activity.[10] However, the 1,1-difluoro-2-phenyl carbapenem **12** did not survive the lyophilization. Substitution by a β-ethyl, β-hydroxyethyl or β-methoxy group retained the DHP-I stability but reduced the biological activity significantly.[11] Nagao and coworkers also synthesized 1-β-methoxy carbapenem **13**[12], but did not report its biological activity. Rosati's group also introduced a hydroxy or oxo group at this position.[13] They reported that the 1-hydroxy carbapenem has a broad range of antibacterial activity.

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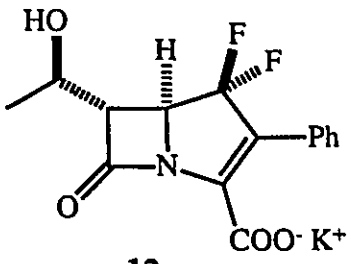
[10] Shah, N. V.; Cama, L. D. *Heterocycles* **1987**, *25*, 221.

[11] Andrus,A.; Baker, F.; Bouffard, F. A.; Cama, L. D.; Christensen, B. G.; Guthikonda, R. N.; Heck. J. V.; Johnston, D. B. R.; Leanza, W. J.; Ratcliffe, R. W.; Salzmann, T. N.; Schmitt, S. M.; Shih, D. H.; Shah, N. V.; Wildonger, K. J.; Wilkening, R. R. In *The Recent Advances in the Chemistry of β- Lactam Antibiotics*. Brown, A. G.; Roberts, S. M., Ed.; The Royal Society of Chemistry, London (Eng), **1984**, p 86.

[12] Nagao, Y.; Abe, T.; Shimizu, H.; Kumagai, T.; Inoue, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 821.

[13] (a) Rosati, R. L.; Kapili, L. V.; Morrissey, P.; Bordner, J.; Subramanian, E. *J. Amer. Chem. Soc.* **1982**, *104*, 4262. (for 1-oxo compound.) (b) Rosati, R. L.; Kapili, L. V.; Morrissey, P.; Retsema, J. A. *J. Med. Chem.* **1990**, *33*, 291.



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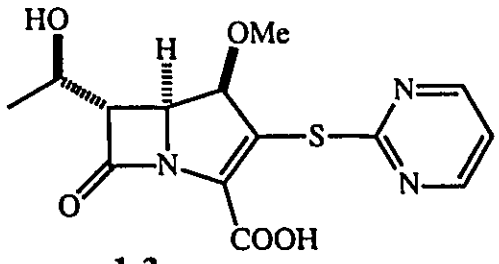
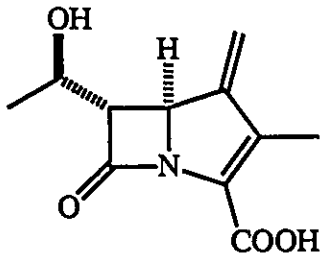
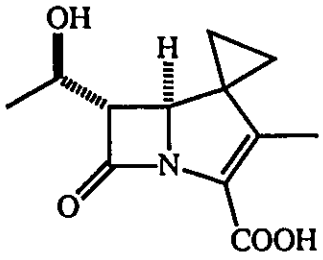


13

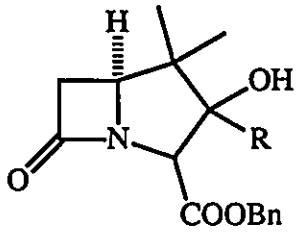
Kim and coworkers have described 1-methylene **14** and 1-spiro cyclopropyl **15** carbapenems.[14] They found that the 1-methylene compound **14** was chemically very unstable whereas the 1-spirocyclopropyl **15** was 100 times less stable to DHP than 1-β-methyl carbapenem. 1,1-Dimethyl carbapenems **16-18** which lack appropriate substituents at C-6 carbon and hence antibacterial activity, have been synthesized.[15]



14



15



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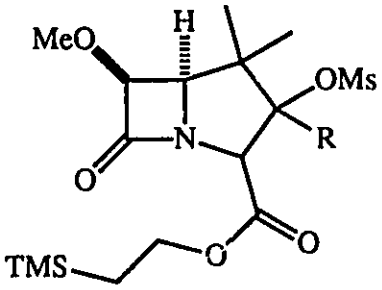

17

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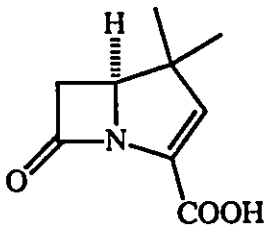
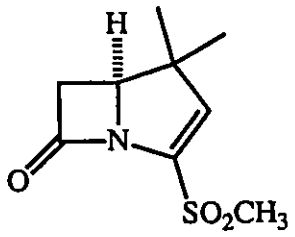
[14] Kim, C. U.; Misco, P. F.; Luh, B. Y. *Heterocycles* **1987**, *26*, 1193.

[15] (a) Shibuya, M.; Kubota, S. *Tetrahedron lett.* **1980**, *21*, 4009. (b) Shibuya, M.; Kubota, S. *Tetrahedron lett.* **1981**, 22, 3611. (c) Chu, D. T. W.; Hengeveld, J. E.; Lester, D. *ibid.* **1983**, *24*, 139.

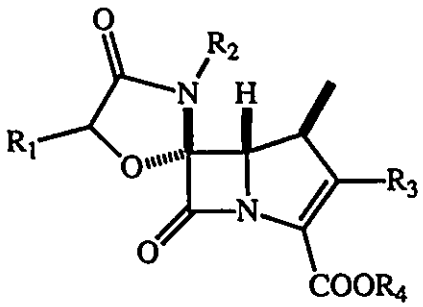


18a



18b

A series of 1-methylcarbapenems having two substituents at C-6 such as **19** has been reported by Merck chemists.[16]

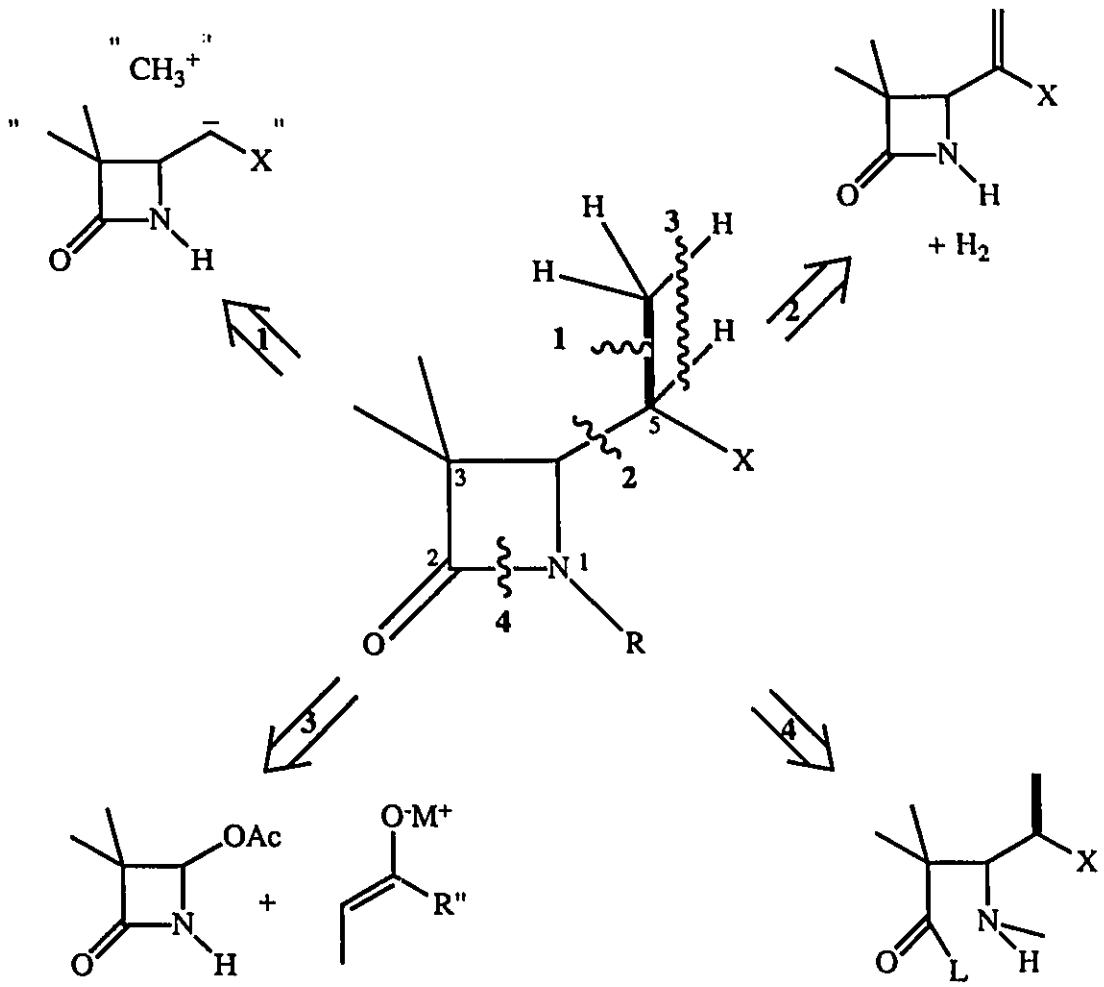


19

Methods for stereoselective introduction of 1-β-methyl group

The survey of existing methods reveals that there are four different approaches for introduction of a methyl group at this position.

[16] Greenlee, M. L.; DiNinno, F. P.; Salzmann, T. N. *Chem. Abs.* **1991**, *114*, 42389m, Eur. Pat. Appl. EP 381,534.



Various approaches towards 1-methyl carbapenems

(1) Reaction of C-5 carbanions with methyl electrophiles:

The "C-5" carbanions of azetidinones such as **20** give very poor yields because of the competing retro-Michael addition resulting in the rupture of β-lactam ring (eq 1). However, the dianion of azetidinone **22**, when treated with methyl iodide at low temperature gave **23** with good yield.[17] The stereoselectivity observed in these reactions favor the α isomers which makes this approach unattractive as a method to prepare β-methyl carbapenem precursors.

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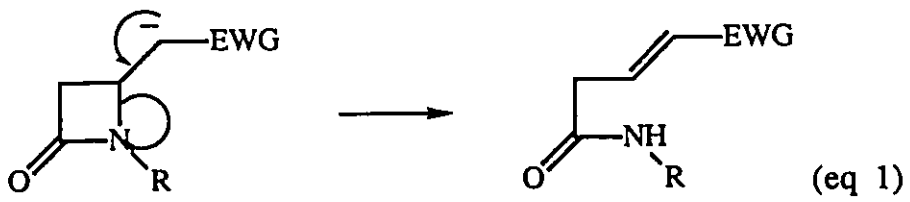
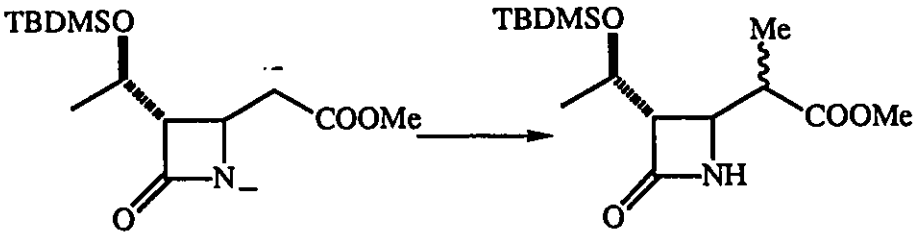
[17] Shih, D.H.; Baker, F.; Cama,L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.

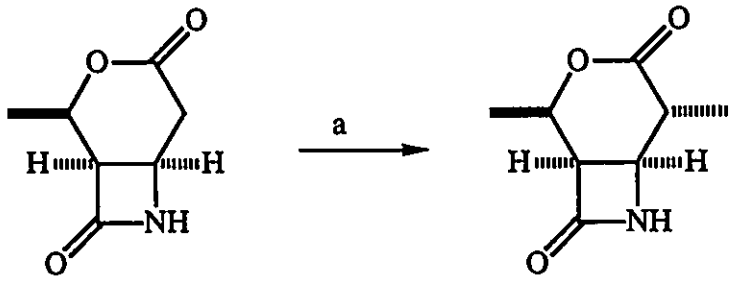


20 21 (eq 1)



22 23 (eq 2)

Ohno rationalized the introduction of a methyl group might be more selective in the alkylation of the dianion derived from the bicyclic azetidinone **24**. This alkylation indeed has been shown to yield exclusively the isomer **25** which when unravelled possesses the desired β-methyl stereochemistry.[18]



24 **25**

a) 2.2 LDA, MeI, THF, -78 °C.

(2) Stereoselective addition of nucleophiles at C-4 of azetidinones:

The addition of simple ester enolates at C-4 carbon is again fraught with the problem of ring cleavage *via.* retro-Michael addition (eq 3).

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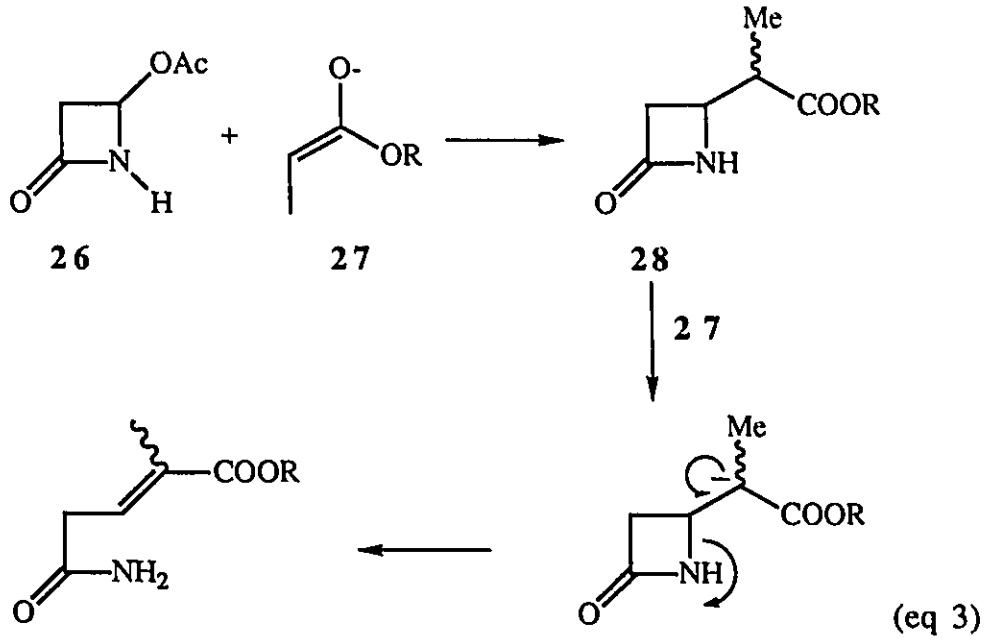
[18] Ohno, M.; Kaga, H.; Kobayashi, S. *Tetrahedron Lett.* **1989**, *30*, 113.



Barrett and Quayle described the reaction of enolsilyl ethers and 4-acetoxy azetidinone **26** in the presence of a catalytic amount of TMSOTf (0.1 eq.).[19] This result showed the possibility of constructing this critical C-C bond under non-basic conditions. To date, numerous variations of this type of methodology has been published often with good to excellent stereoselectivity. Menard and coworkers reported excellent diastereoselectivities in the reaction of **30** with enolsilyl ethers from thioesters in the presence of zinc chloride.[20] The diastereo-

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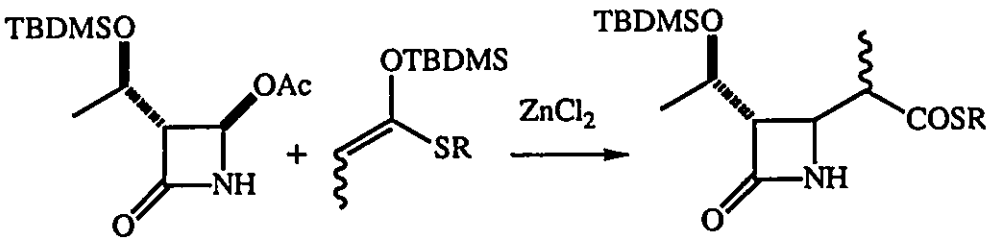
19 Barrett, A. G.M.; Quayle, P. *J. Chem. Soc., Chem. Commun.* **1981**, 1076. *For other studies with enolsilyl ethers*: (a) Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. lett.* **1985**, 1343. (b) Shibata, T.; Lino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugiyama, Y. *Tetrahedron lett.* **1985**, *26*, 4739. *For use of nucleophiles having only one enolizable hydrogen*: (c) Greengrass, C. W.; Hoople, D. W. T. *Tetrahedron lett.* **1981**, *22*, 1161. (d) Kim, C. U.; Luh, B.; Partyka, R. A. *Tetrahedron lett.* **1987**, *28*, 507.

20 Martel, A.; Daris, J. P.; Bachand, C.; Corbeil, J.; Menard, M. *Can. J. Chem.* **1988**, *66*, 1537.

selectivities are dependent on the nature of the substituent on sulfur of the enolates such as **31** and **32**.



30 **31 & 32** **33 & 34**

e. g. **31 & 33** R=t-Bu, α:β=92:8 (74%) and
32 & 34 R=3-methylpyrid-2-yl. α,β=-:>98 (85-90%)

The stereoselectivity of this addition is also found to depend on the nature of metal used in the enolates. Kim *et. al.* reported enolate from thioester **35** added in excellent yield showing α selectivity in the presence of TMSCl and in good yield with β selectivity in the presence of dicyclopropyl zirconium dichloride and TMSOTf.[21] Excellent stereoselective additions have been accomplished using zinc[22], boron[23], or tin[24] enolates bearing a suitable oxazolidinone, thiazolidinone or thiazolidinethione auxiliaries (Table 3). The boron enolate having Evan's chiral auxillary has been found to give a product with >99% enantiomeric purity.

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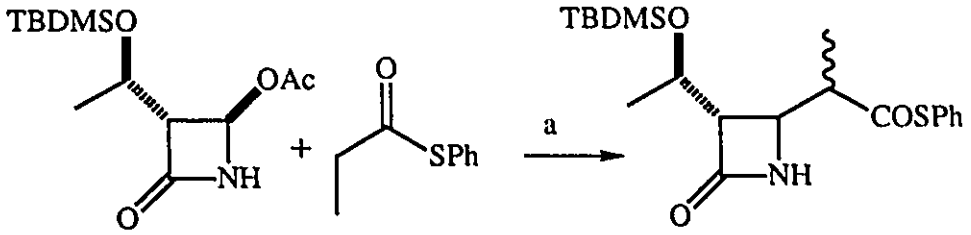
21 Kim, C. U.; Luh, B.; Partyka, R. A. *Tetrahedron lett.* **1987**, *28*, 507.

22 (a) Ito, Y.; Terashima, S. *Tetrahedron lett.* **1987**, *28*, 6625. (b) Ito, Y.; Sasaki, A.; Tamato, K.; Sunagawa, M.; Terashima, S. *Tetrahedron* **1991**, *47*, 2801. (c) Ito, Y.; Terashima, S.; Kobayashi, Y. *Tetrahedron lett.* **1989**, *30*, 5631.

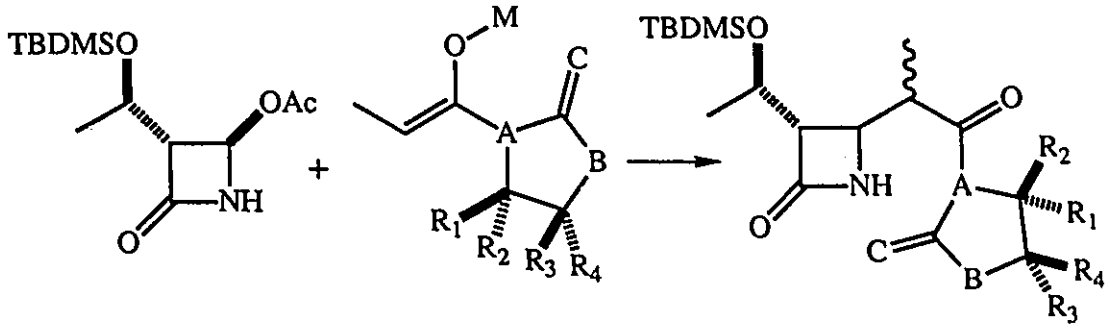
23 Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Amer. Chem. Soc.* **1986**, *108*, 4675.

24 (a) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Amer. Chem. Soc.* **1986**, *108*, 4673. (b) De'ziel, R.; Favreau, D. *Tetrahedron lett.* **1986**, *27*, 5687. (c) De'ziel, R.; Favreau, D. *Tetrahedron lett.* **1989**, *30*, 1345. (d) Nagao, Y.; Kumagai, T.; Abe, T.; Toga, T.; Ochiai, M.; Inoue, Y.;Machida, K. *J. Chem. Soc., Chem. Commun.***1987**, 602. (e) Nagao, Y.; Kumagai, T.; Hagiwara, Y.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391. (f) Shirai, F.; Nakai, T. *J. Org. Chem.* **1987**, *52*, 5492.



30 **35** **36**

a) LDA, TMSCl, α:β=95:5 (87%) or LDA, $Zr(Cp)_2Cl_2$, α:β=3:97 (52%)



30 **37** **38**

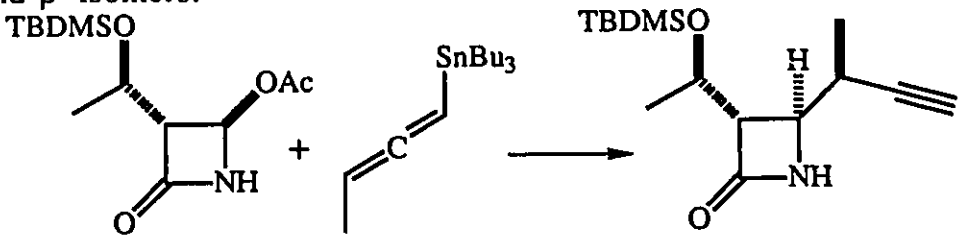
Table 1 Stereoselective addition of enolates to 30

M	A	B	C	R_1	R_2	R_3	R_4	Yield	α:β	Ref.
Zn	N	O	O	Me	Me	H	H	94%	5.6:1	22
Zn	N	O	O	nBu	nBu	-(CH_2)-		97%	20:1	22
Zn	N	O	O	H	iPr	H	H	99%	91:9	22
Zn	N	O	O	H	Bn	H	H	91%	90:10	22
B	N	O	O	H	iPr	H	H	95%	**>99:1**	23
Si	N	O	O	H	iPr	H	H	78-93%	40-60%	23
Sn	N	S	S	H	Et	H	H	80%	90:10	24
Sn	N	S	S	H	iPr	H	H	74%	91:9	24
Sn	N	O	S	Me	Me	H	H	79%	24:1	24

Similar reactions of this type include Lewis acid catalyzed addition of suitably functionalized allenic tin compound **39**.[25] The nature of the Lewis acid appears to govern the diastereoselectivity of this reaction. Trimethylsilyl triflate (TMSOTf) gave 98% of a 1:1 mixture of α and β

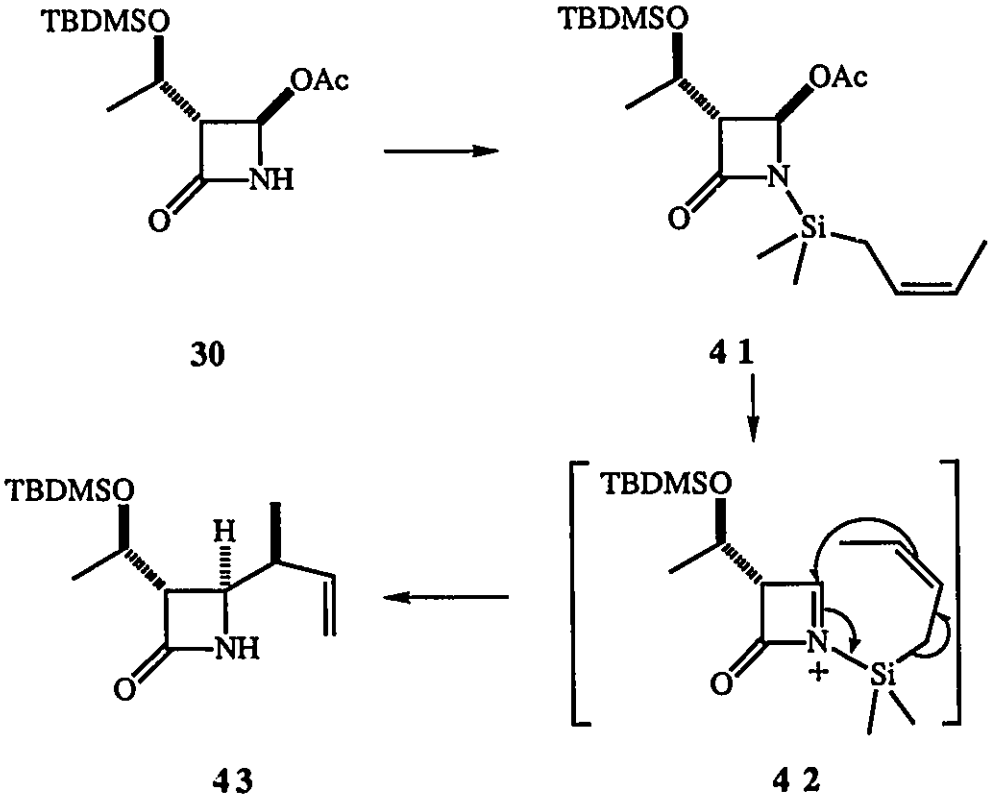
[25] Haruta, J.; Nishi, K.; Kikuchi, K.; Matsuda, S.; Tamura, Y.; Kita, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2338.

isomers, whereas boron trifluoride etherate gave 89% of a 4:1 mixture of α and β isomers.



30 39 40

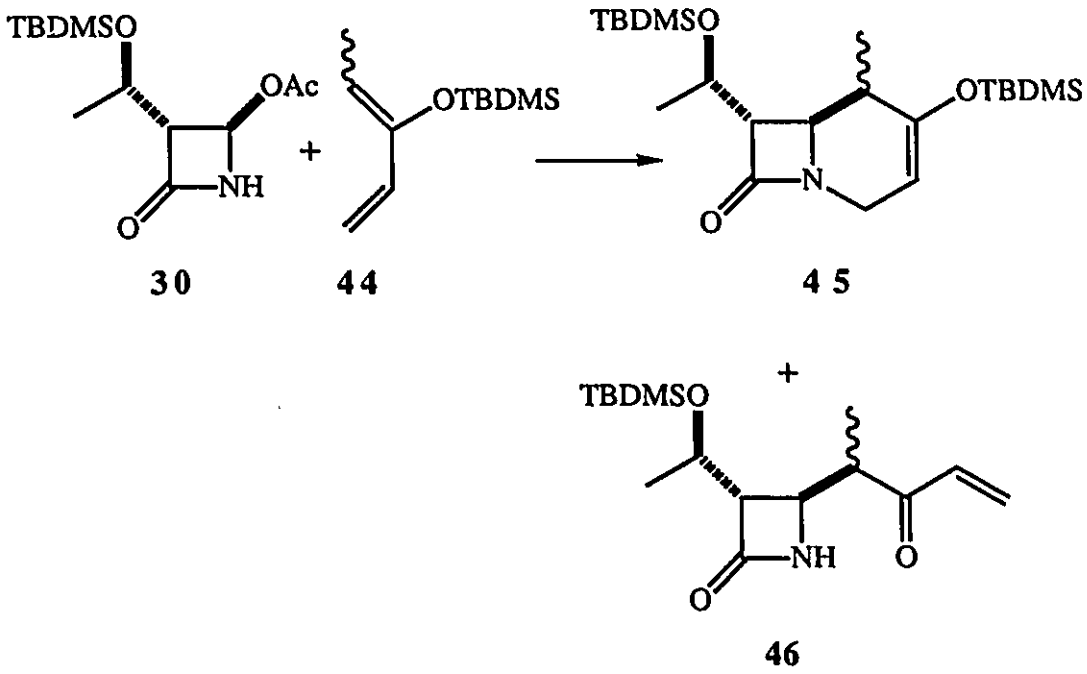
Uyeo and Itani carried out a 3,3' sigmatropic rearrangement reaction to introduce a β-methyl group.[26] This reaction can also be visualized as an intramolecular crotylsilylation. The yield of **43** is good (84%) and the observed diastereoselectivity (97:3) is excellent. The selectivity is influenced dramatically by the nature of Lewis acid employed.



30 41 43 42

[26] Uyeo, S.; Itani, H. *Tetrahedron lett.* **1991**, *32*, 2143.

Meyers prepared 1-methyl carbapenems *via.* 2+4 cycloaddition.[27] The compound **45** was obtained in 65% yield with 80:20 diastereomeric ratio.



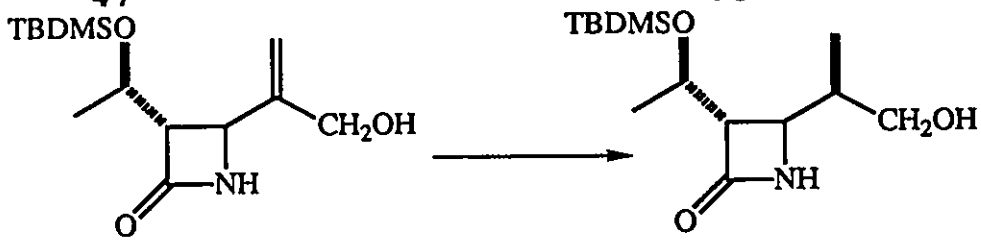
(3) Reduction of a methylene group at C-5:

The reduction of α,β-unsaturated ester **47** with hydrogen and catalyst gave poor diastereoselectivity.[28] Shibasaki and coworkers found L-Selectride reduction of **47** in the presence of 2-butanol gave good diastereoselectivity (α:β=1:8).[29] Noyori's group reported excellent selectivity (α:β=0.1:99.9) in the reduction of allylic alcohol **49** using BINAP-Ru(II) catalyst.[30]

---

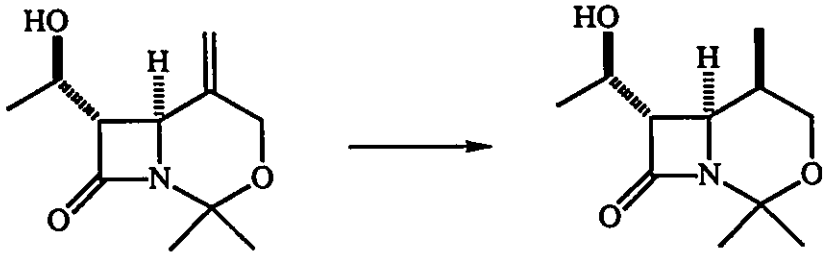
[27] Meyers, A. I.; Sowin, T. J. *J. Org. Chem.* **1988**, *53*, 4156.
[28] Kim, C. U.; Luh, B.; Partyka, R. A. *Tetrahedron lett.* **1987**, *28*, 507.
[29] Shibasaki, M.; Iimori, T. *Tetrahedron lett.* **1986**, *27*, 2149.
[30] Noyori, R.; Nagao, K.; Hsiao, Y.; Kitomura, M. *Tetrahedron lett.* **1990**, *31*, 549.

47 48



49 50

The reduction of bicyclic acetonide **51** is quite unpredictable.[31] The selectivity is dependent on the nature of catalyst and solvent.



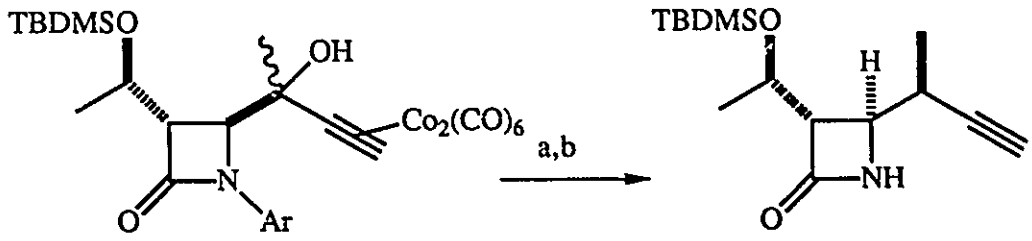
51 **52**

Liebeskind and Prasad reported reduction of propargyl cation stabilized by hexacarbonyldicobalt derived from **53**.[32] They rationalized the stereochemical outcome in terms of a Felkin Ahn type model.

---

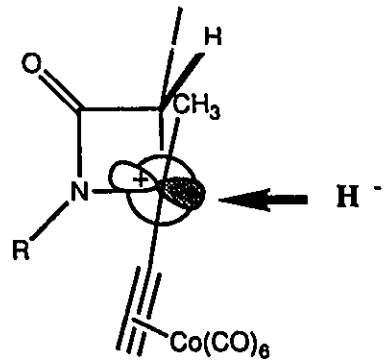
[31] Fuentes, L. M.; Shinkai, I.; King, A.; Purick, R.; Reamer, R. A.; Schmitt, S. M.; Cama, L. ; Christensen, B. G. *J. Org. Chem.* **1987**, *52*, 2563.

[32] Liebeskind, L. S.; Prasad, J. S. *Tetrahedron lett.* **1987**, *28*, 1857.



53 **40**

a) TFA, BH_3:DMS; b) CAN



54 model proposed by Liebeskind

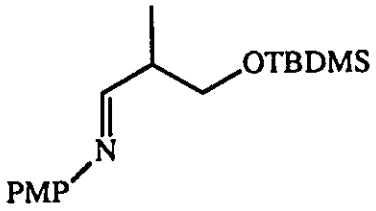
(4) Syntheses starting with a methylated fragment or its equivalent:

This approach includes syntheses in which the β-lactam ring is prepared after incorporation of the methyl group. Salzmann's group prepared 1-methylcarbapenems starting from imines (**55** and **56**) with a suitable methyl group using well known 2+2 cycloaddition.[33] (S)-Methyl 3-hydroxy-2-methylpropionate was used by Terashima to prepare enantiopure imine **55** which was reacted with diketene to yield an azetidinone intermediate, bearing a thienamycin type side-chain at C-3. They observed highest diastereoselectivities (11-15:1 with 49-52% combined yield) when methylimidazole was used as a catalyst.[34]

---

[33] Salzmann, T. N.; DiNinno, F. P.; Greenlee, M. L.; Guthikonda, R. N.; Quesada, M. L.; Schmitt, S. M.; Herrmann, J. J.; Woods, M. F. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; A. G. Brown and S. M. Roberts, Ed.; The Royal Society of Chemistry: London (England), **1985**; p 171.

[34] (a) Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron Lett.* **1986**, *27*, 6241. (b) Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S. *Tetrahedron* **1988**, *44*, 2149.



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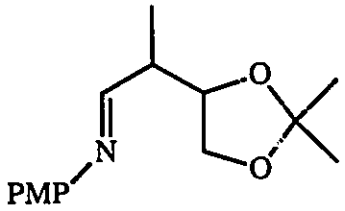
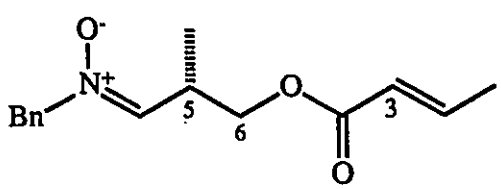


56

Kametani used the nitrone cycloaddition method to prepare intermediate **60**.[35] Intermolecular cycloaddition gave equal amounts of all four diastereomers. When the intramolecular reaction was carried out a single isomer of adduct **58** was obtained in 51% yield. The conversion of **58** to **60** was carried out in five steps in 77% overall yield. In addition to the good yield, the induction of three chiral centers in one step is quite appealing.



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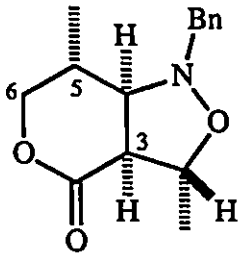

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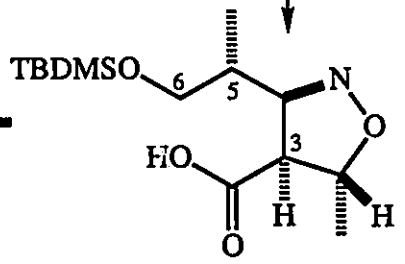

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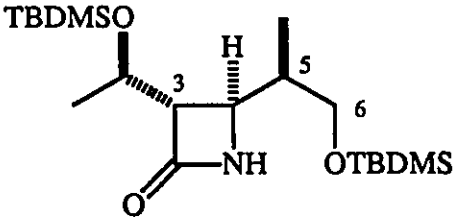
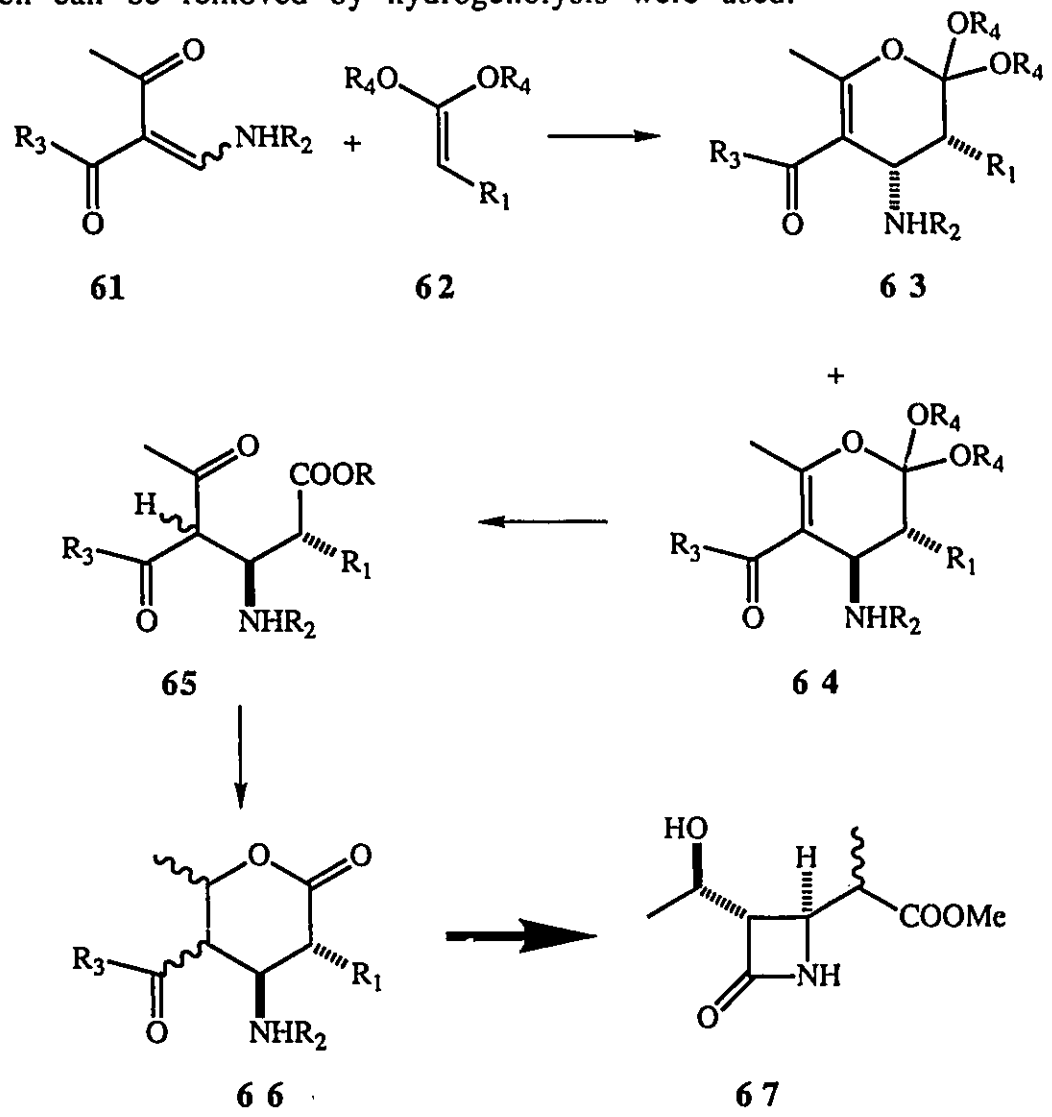


60

35 Kametani, T.; Ihara, M.; Takahashi, M.; Fukumoto, K. *J. Chem. Soc., Perkin. Trans 1* **1989**, 2215.

Turner prepared lactone **66** by exploiting hetero Diels Alder methodology.[36] The cycloaddition step proceeded with diastereo-selectivities ranging from 1:1 to 1:20 and the yields are greater than 75%. In subsequent transformations, epimerization at the carbon bearing methyl group occurred in most of the cases, to give mixtures of α and β isomers. This problem was eliminated when protective groups which can be removed by hydrogenolysis were used.



61 **62** **63**

65 **64**

66 **67**

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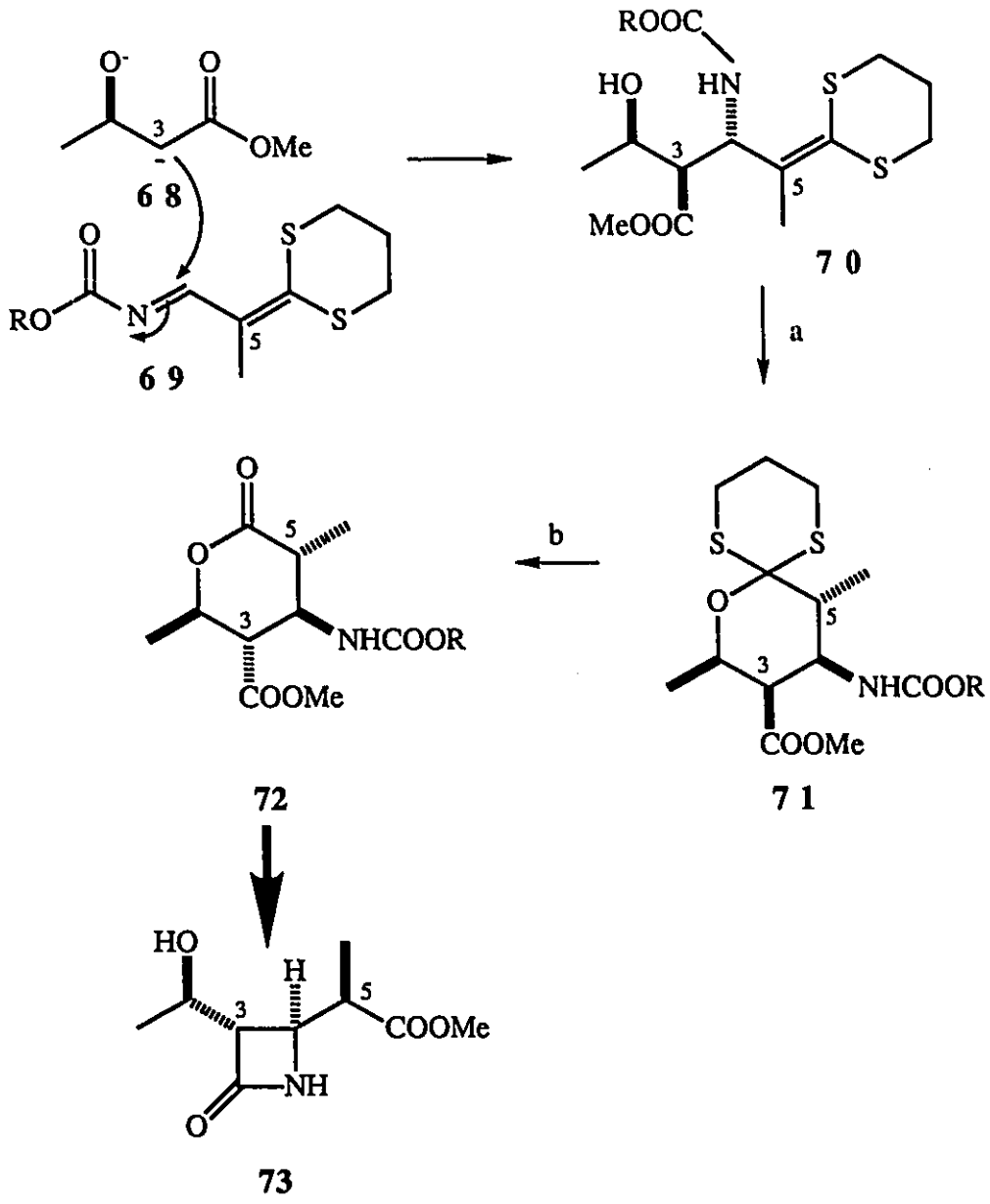
[36] Bayles, R.; Flynn, A. P.; Galt, R. H. B.; Kirby, S.; Turner, R. W. *Tetrahedron lett.* **1988**, *29*, 6345.

Hatanaka approached this problem by using the addition of the dianion **68** to imine **69** to create two new chiral centers. The diastereoselectivity in this condensation step is low. The best selectivity (*syn:anti*=1:4) was observed in the reaction of the anion derived from t-butyl hydroxybutyrate (which, he reported, was difficult to prepare in good yields). The *syn:anti* ratio in this step dropped to 1:2 when **68** was used. The fourth chiral center was created during the formation of pyranoside **71** under acidic conditions.[37] This cyclization proceeded stereospecifically to give **71** exclusively. The synthesis of imine **69** required six steps. Further six steps (43% overall yield) were required to convert **70** to the carbapenem intermediate **73**.

[37] Hatanaka, M. *Tetrahedron lett.* **1987**, *28*, 83.

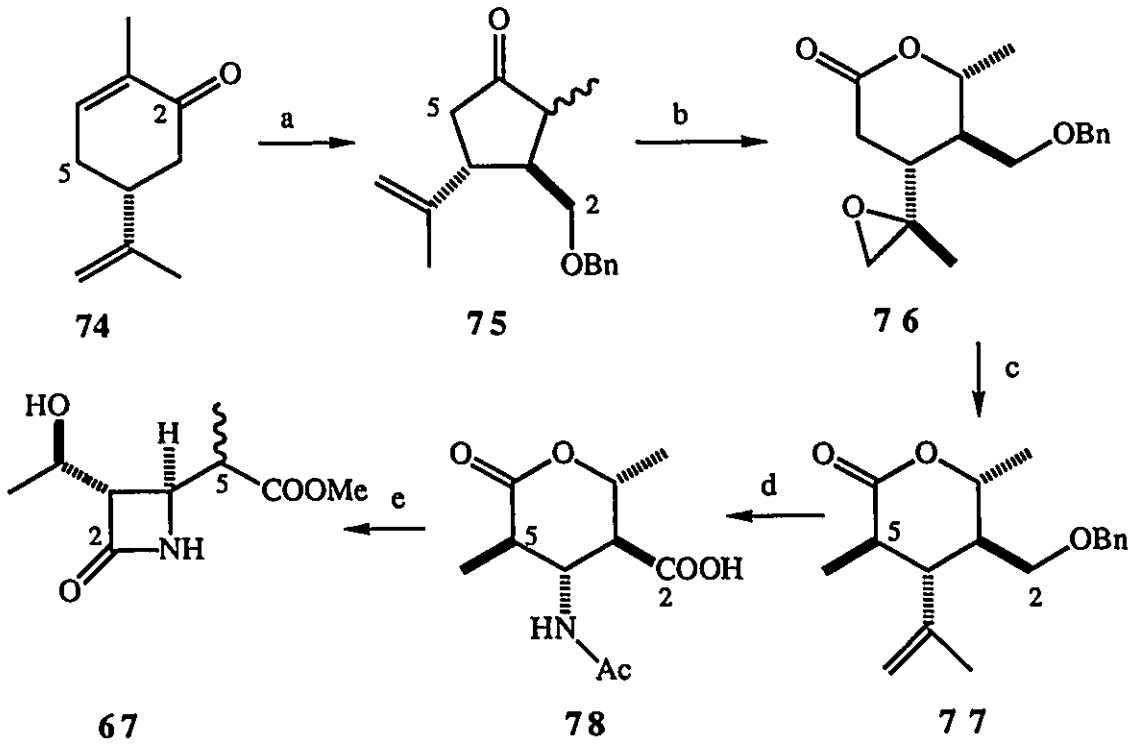


a) HCl, CH_2Cl_2; b) NaOMe, MeOH; $CuCl_2$, CuO

Honda's group used (-)-carvone **74** as a chiron to prepare a closely related lactone **78**.[38] The introduction of the nitrogen of the β-lactam by using Beckmann rearrangement is an interesting step. Ketone **75** was prepared from **74** in six steps. This approach is quite imaginative but requires many steps. During the final steps, equal

[38] Honda, T.; Ishizone, H.; Naito, K.; Suzuki, Y. *Heterocycles* **1990**, *31*, 1225.

amount of epimers (at C-5) of **67** were formed.

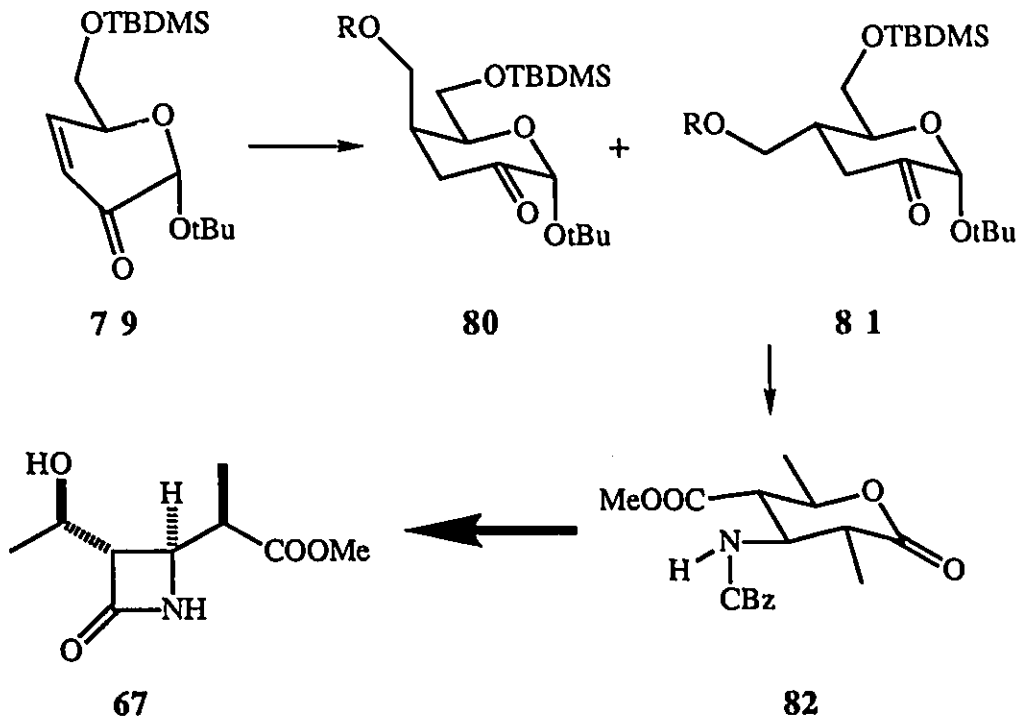


74 **75** **76** **77** **78** **67**

a) i. H_2O_2, NaOH; ii. NaOMe; iii. $HOCH_2CH_2OH$, H^+; iv. $LiAlH_4$; v. BnBr, NaH, DMF; vi. H^+; b) MCPBA; c) Zn, NaI, NaOAc, AcOH; d) i. OsO_4, $NaIO_4$, ii. $H_3N^+OH\ Cl^-$; iii. $POCl_3$, pyridine; iv. H_2, Pd-C; v. PDC, DMF; e) i. 10N HCl, reflux; ii. MeOH; iii. DCC, propylene oxide, MeOH

Fraser-Reid used carbohydrate precursors to prepare a similar intermediate.[39] His synthesis includes some interesting reactions such as photochemical addition of methanol to enone **79** with stereochemical induction opposite to that observed during the addition of cuprates. But this strategy is not practical for the synthesis of 1-methylcarbapenems because of the large number of steps involved and low overall yield.

[39] Fraser-Reid, B.; Udodong, U. E. *J. Org. Chem.* **1988**, *53*, 2131.



79 80 81

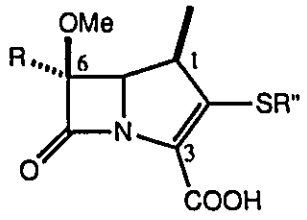
67 82

1-Methyl-6-methoxycarbapenems

Although a large number of 1-methylcarbapenems have been reported, only a limited attention has been directed to C-6 disubstituted 1-methylcarbapenems.[40] If the two substituents at the C-1 and C-6 position exert a cumulative stabilizing effect without a reduction in antibacterial activity, such carbapenems may prove to be clinically valuable candidates. Based on an earlier discussion in Chapter 4, the 6-methoxy group has a stabilizing effect on the β-lactams. The 1-β-methyl group also stabilizes carbapenems as mentioned earlier. Therefore, we began to explore the synthetic sequences leading to 1-β-methyl-6-β-methoxycarbapenems **83**. It should be pointed out that

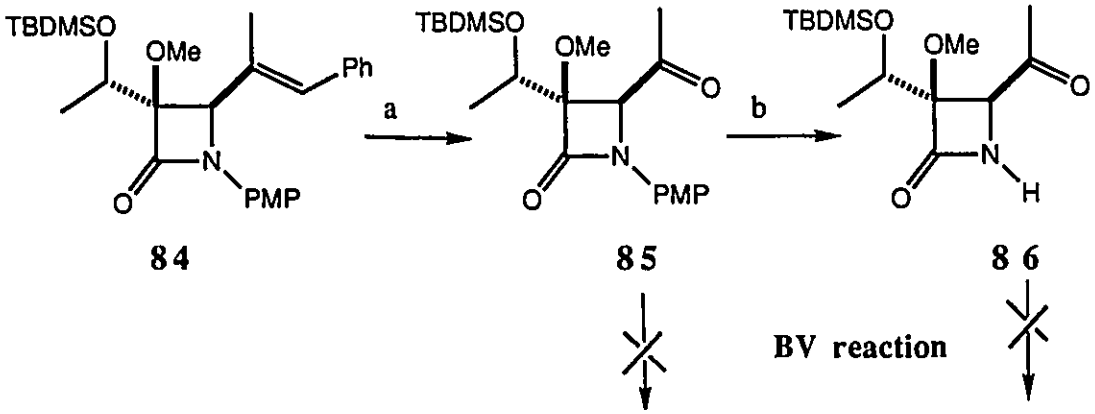
[40] Greenlee, M. L.; DiNinno, F. P.; Salzmann, T. N. *Chem. Abs.* **1991**, *114*, 42389m, Eur. Pat. Appl. EP 381,534.

these compounds have both methyl and methoxy groups on the concave face of the V-shaped bicyclic ring system. One can expect increased risk in synthesis of these compounds due to this unfavorable steric hindrance. However, the examination of a molecular model did not reveal it to be an impossible situation.



8 3

Four basic methods of incorporating the 1-β-methyl group were described in the introduction to this Chapter. Method 1 is quite unsatisfactory due to the poor selectivity. Method 2 has extensively been studied in thienamycin type molecules, but during our studies towards 6-methoxy thienamycin intermediates, the Baeyer Villiger reaction of **85** and **86** leading to the C-4 acetoxyazetidinones failed.

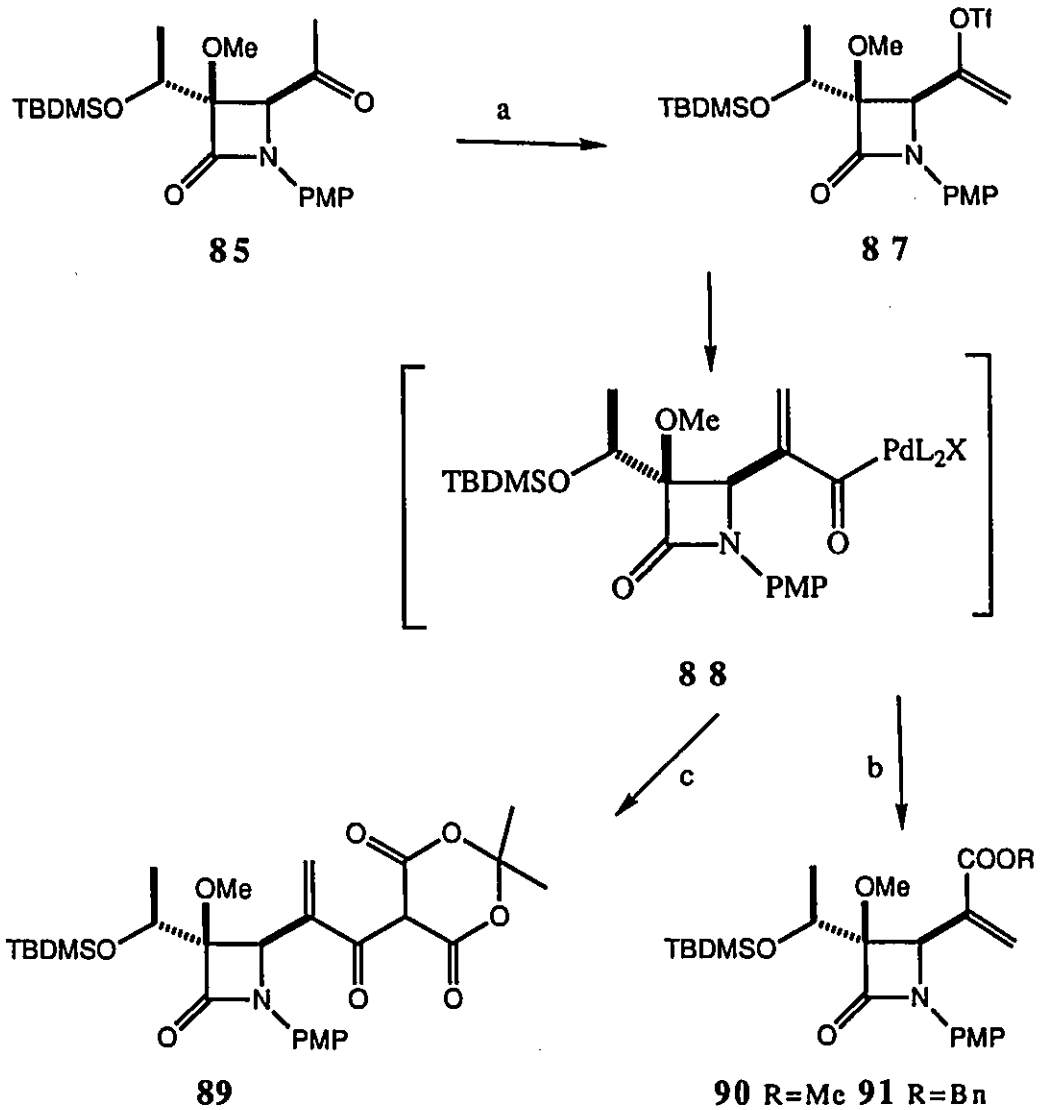


84 **85** **86**

a) O_3, CH_2Cl_2, DMS, -78 °C to 25 °C; b) CAN, MeCN, -2 °C to 0 °C

Carbonylations

We chose the reduction approach over method 4 because the methodology to prepare ketone **85** has already been established. The elaboration of the compound **85** into intermediates **91**, which is suitable for the synthesis of bicyclic 1-methylcarbapenems by rhodium carbenoid insertion, is outlined below.



85 **87** **88** **89** **90** R=Me **91** R=Bn

a) LDA, $PhN(Tf)_2$, THF, -78 °C to 25 °C; b) $Pd(OAc)_2$, PPh_3, TEA, THF, MeOH or BnOH, CO, 25 °C; c) $Pd(OAc)_2$, PPh_3, TEA, THF, Meldrum's acid, CO, 25 °C

The conversion of C-4 acetyl compound **85** to its enol triflate **87** was achieved by using LDA and N-phenyl trifluoromethanesulfonimide.[41] The enol triflate showed characteristic olefinic peaks in its ^1H NMR spectrum at δ=5.20 (1H, dd, J=0.9, 4.2 Hz) and 5.45 (1H, d, J=4.2 Hz). The carbonylation[42] reaction was carried out using palladium acetate and triphenylphosphine as a catalyst. It is presumed to proceed by insertion of the metal into the carbon-oxygen bond of the enol triflate. This metal species can exchange ligands with carbon monoxide. The resultant intermediate, after reductive elimination, yields an acyl palladium species. When methanol and benzyl alcohol were used as nucleophiles to trap the acyl palladium intermediate, the corresponding esters (**90** and **91**) were isolated in good yields. The methyl ester **90**, white solid, mp 89-90 °C, showed three singlets for methoxy groups at δ=3.50, 3.76 and 3.81 ppm in the ^1H NMR. The benzyl ester **91** is pale-yellowish solid with surprisingly, the same melting point as the methyl ester. This ester contains two diastereotopic benzylic protons which appeared as AB doublets at δ=5.18 and 5.29 ppm with a coupling constant of 12.5 Hz. These products require an additional de-esterification step. An attempt to obtain the carboxylic acid directly from the acyl palladium intermediate by using water instead of the above alcohols was unsuccessful. The use of Meldrum's acid as a nucleophile afforded **89** in poor yield (15%). This approach is appealing since the adduct **89** can, in principle, be converted to β-ketoesters[43] by reaction with various alcohols thereby eliminating the activation and

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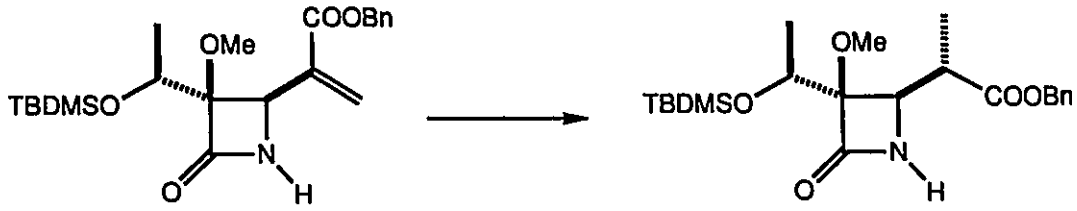
[41] McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
[42] Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
[43] Oikawa, Y.; Yoshioka, T.; Sugano, K.; Yonemitsu, O. *Org. Synth.* **1984**, *63*, 198.

homologation sequence. Due to the low yield, this approach was not pursued. Overall, the enol triflate carbonylation reaction is regiospecific compared to carbonylation of similar acetylenic compound in which case the product from the double carbonylation was isolated as a minor product.[44]

Reductions

The reduction of azetidinone **92** (a yellowish solid: mp 73-74 °C, obtained by CAN cleavage of PMP group of **91** at -5 °C to 0 °C) with L-Selectride[45] in 1:1 mixture of THF and sec. butyl alcohol at -78 °C gave only one isomer of **93**. The yield in this reduction is modest (40%).



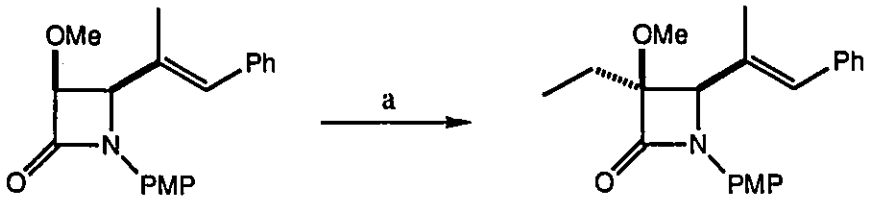
92 **93**

a) L-Selectride, THF:2-butanol (1:1), -78 °C, 1 h.

At this stage the relative configuration at this new chiral center is unknown. The configuration shown in **93** is based on the results of the reduction of a related azetidinone having an 3-ethyl group **100** instead of 3-t-butyldimethylsilyloxyethyl substituent (see discussions at page 259). Catalytic hydrogenations of **90** and **92** in EtOH and CH_2Cl_2, respectively using palladium on carbon gave mixtures of diastereomers in almost equal amounts as indicated by the integrals for the doublets of newly created methyl group.

Having established a method to prepare a pure diastereomer of 1-

methylcarbapenem intermediate, we decided to perform annulation experiments leading to bicyclic compounds. At this stage (while waiting for the results on X-ray studies aimed to establish the configuration) we turned our attention to the synthesis of 1-methyl-6-methoxy-PS-5, since it requires fewer steps compared to thienamycin derivative. The preparation of α,β-unsaturated ester **98** is shown below. The 3,3-disubstituted azetidinone **95** was prepared in 92% yield by treatment of anion derived from **94** (53 mmol) with iodoethane in THF at -78 °C to -30 °C.

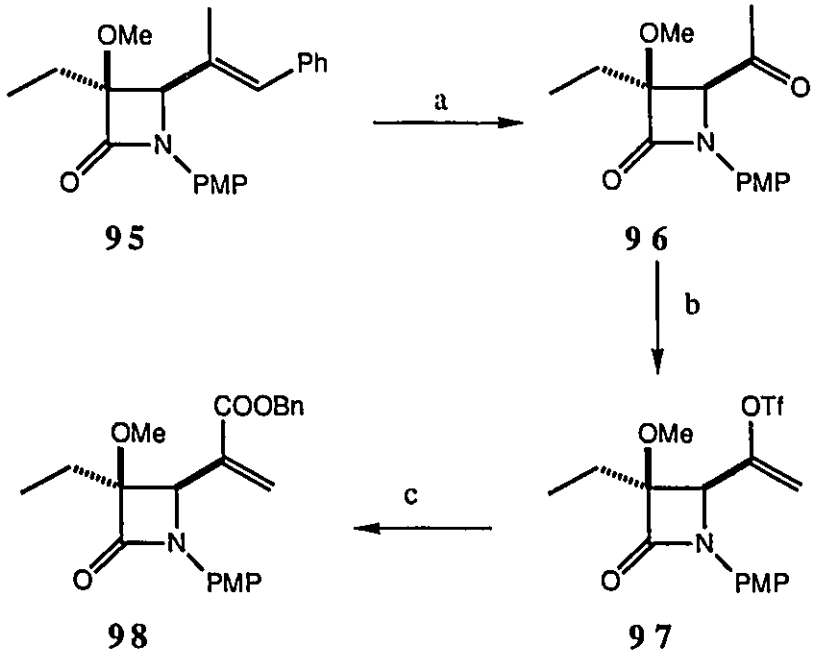


94 **95**

a) LDA, EtI, THF, -78 °C to -30 °C

Ozonolysis was carried out in a similar manner as in the case of **85**. The formation of **96** is again well evidenced by the loss of signals for the phenyl group in the ^{1}H NMR. The enol triflate **97** [vinylic protons: δ=5.15 (J=5.0 Hz) and 5.44 ppm (J=4.2 Hz) respectively] was prepared by a method similar to **87** again using McMurry's reagent. Careful examination of tlc and integrals in ^{1}H NMR spectrum revealed that **97** is contaminated, in some preparations with a byproduct (presumably PhNHTf) of McMurry's reagent. The traces of this impurity did not interfere with subsequent carbonylation. The benzyl ester group in **98** was chosen since it can be cleaved under relatively mild hydrogenation conditions thus preventing epimerization, which is likely

to occur during the basic hydrolysis of an ester. This ester **98** compared to **91** did not give an AB splitting pattern for benzylic protons in ^1H NMR (δ=5.24 ppm, s).



95 **96** **97** **98**

a) O_3, CH_2Cl_2, MeOH, -78 °C; DMS, -78 °C to 25 °C; b) LDA, $PhN(Tf)_2$, THF, -78 °C to 25 °C; c) $Pd(OAc)_2$, PPh_3, TEA, THF, BnOH, CO, 25 °C

The PMP group of **98** was cleaved with CAN in the usual manner to yield **99** which was reduced with L-Selectride in THF: sec.-butyl alcohol (1:1) to give a reduced ester with a diastereomeric ratio of 1:7 (β:α). The diasteromeric ratio was determined by careful separation of two compounds by column chromatography and comparison of the mass of each isolated diastereomer (Fig. 12 and 13). The major isomer was isolated in 53% yield as a yellowish oil (IR: 3302 NH, 1761 C=O, 1731 C=O cm^{-1}). Notable features in the ^1H NMR spectrum of **100** are peaks at δ=1.16 ppm (d, J=7.1 Hz, CH_3CH) and 5.11 ppm (s, CH_2Ph). About 10-20% of a non β-lactam (retro-Michael addition) product was isolated from the baseline impurity.

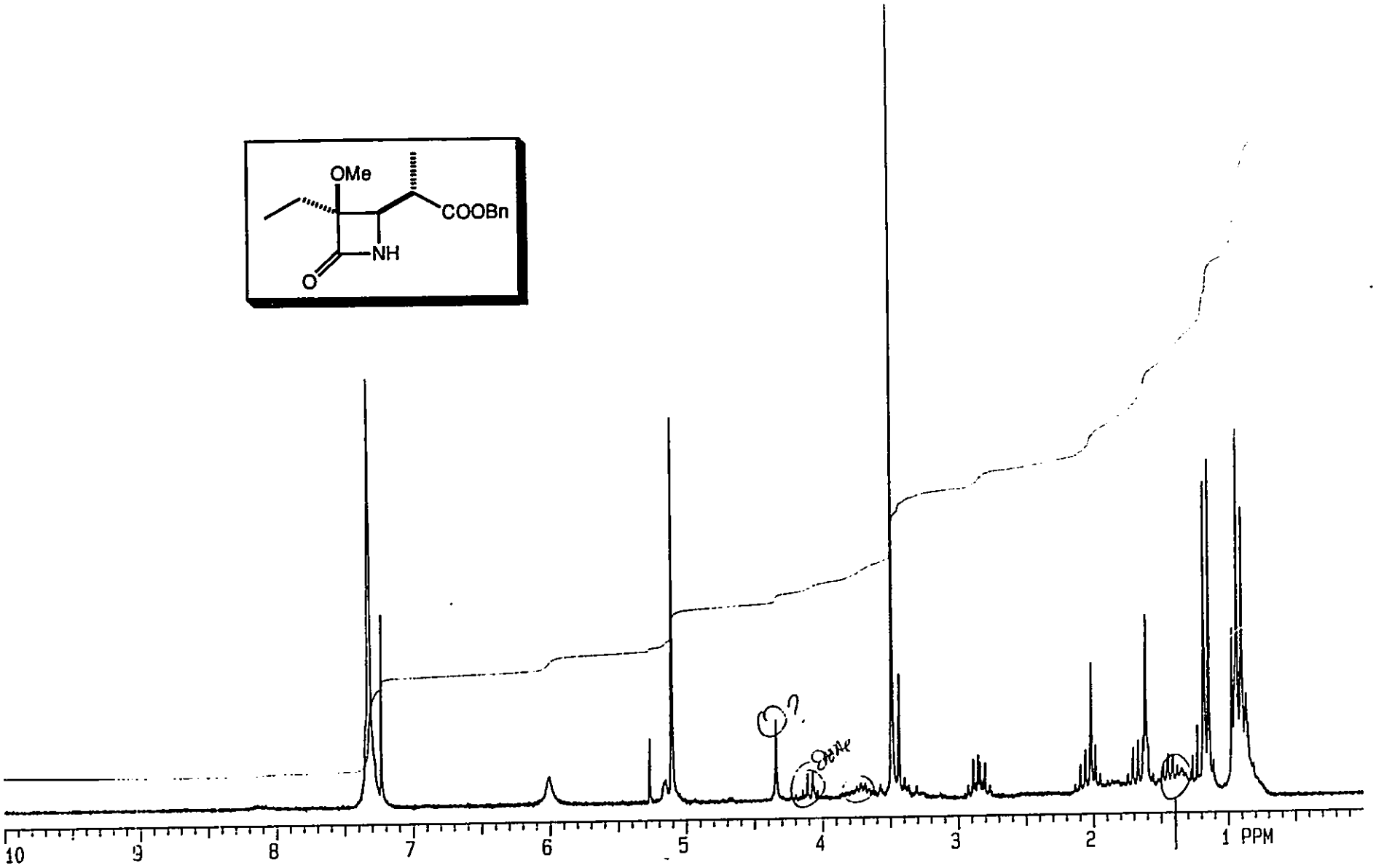


Fig. 12 ^{1}H NMR spectrum of **100**

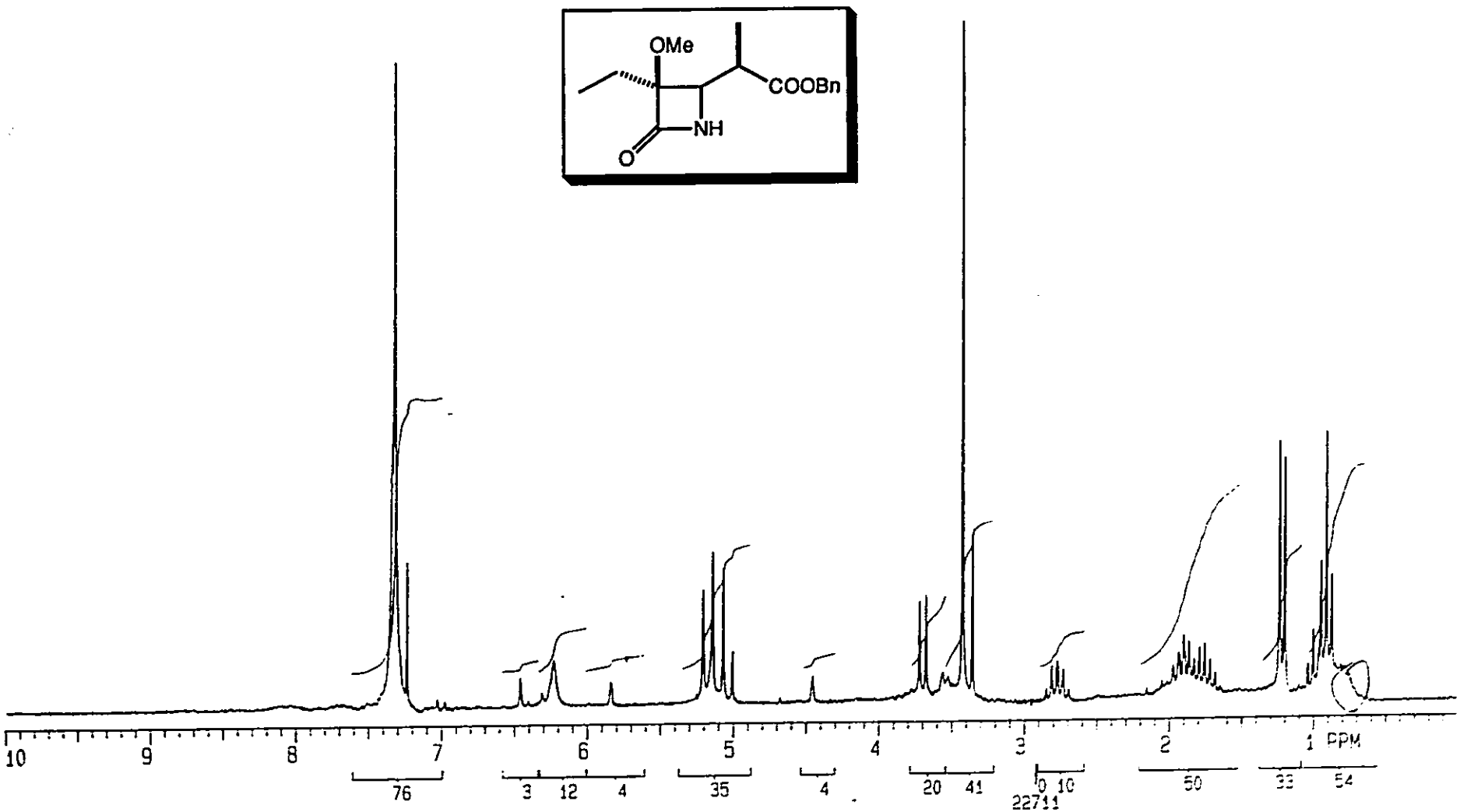
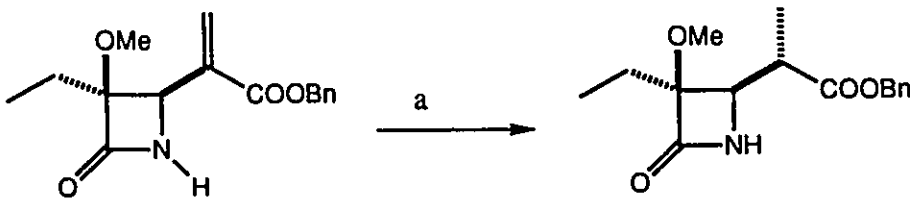


Fig. 13 ^{1}H NMR spectrum of **104** obtained as a minor diastereomer during L-Selectride reduction



99 **100**

a) L-Selectride, THF:2-butanol (1:1), -78 °C

The major product **100** was found to be an α-isomer by X-ray crystallography of the carboxylic acid **101** obtained by catalytic hydrogenation in the presence of 10% Pd-C in ethanol (Fig. 14, ORTEP diagram). The ^1H NMR of the crude sample contains some impurities that could not be identfied. In contrast, hydrogenation of **100** proceeds cleanly when methylene chloride was used as a solvent. The acid **101** is a white solid (mp: 139-141 °C) well characterized by MS, IR, ^1H NMR, ^{13}C NMR and HRMS. The important ^1H NMR peaks for this compound are doublets at 1.16 ppm for 5-methyl and 3.46 ppm for C-4 protons. The β-lactam ring of acid **101** was found to be hydrolyzed by atmospheric moisture at room temperature. The acid **101** is soluble in CH_2Cl_2 but the hydrolysis product is not. This methylene chloride insoluble residue when examined by MS gave molecular ion peak corresponding to the diacid **102** (*i.e.* M+18 where M is molecular mass of **101**) which probably exists as zwitterionic species hence is insoluble in dichloromethane. Inert atmosphere was therefore necessary for growing crystals. (Similar hydrolysis, evidenced by the loss of the β-lactam carbonyl absorption in the IR, 1720 cm^{-1}, was observed in the preparation of the acid derived from **93**).

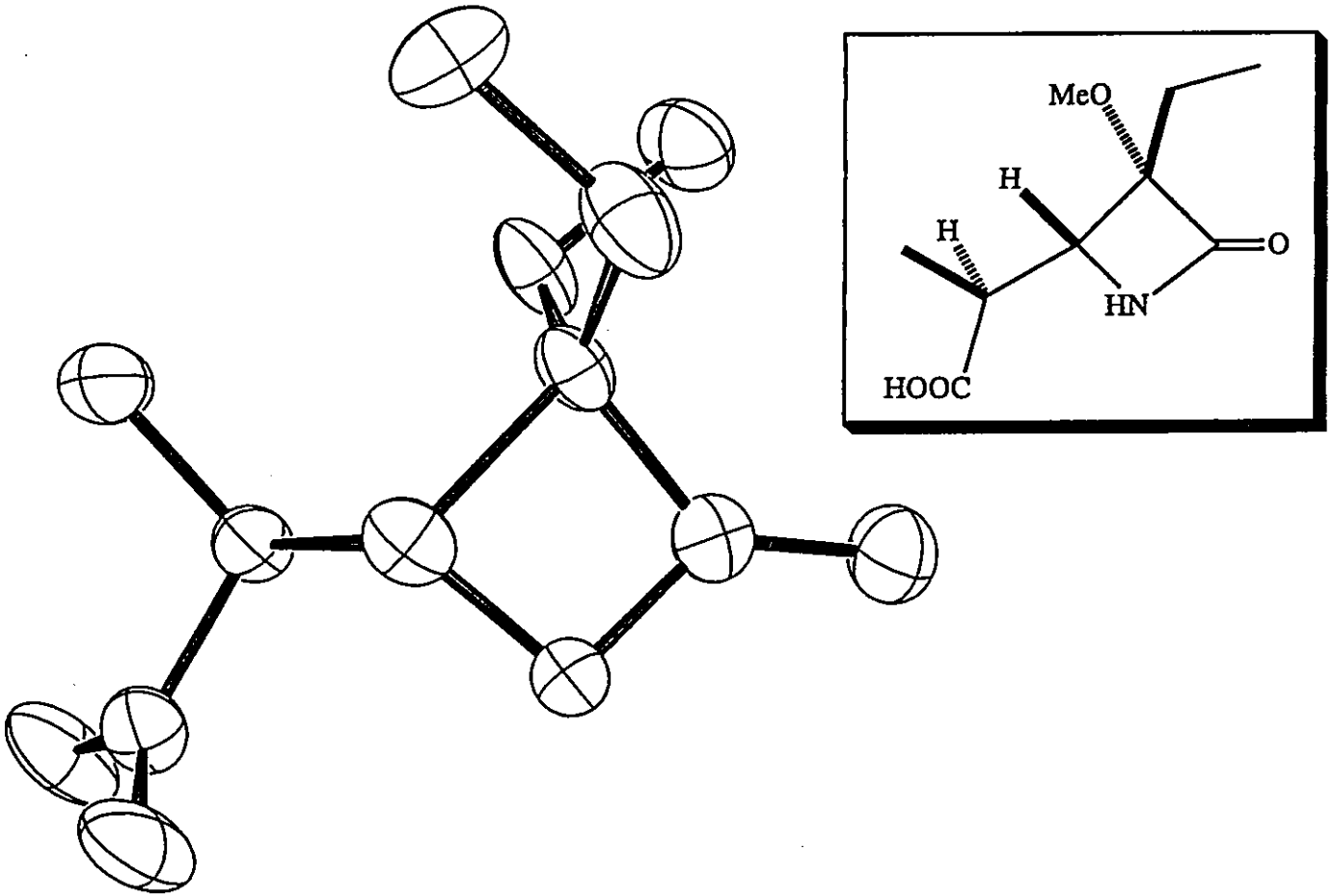
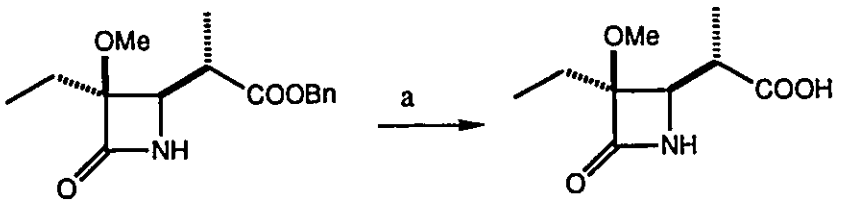
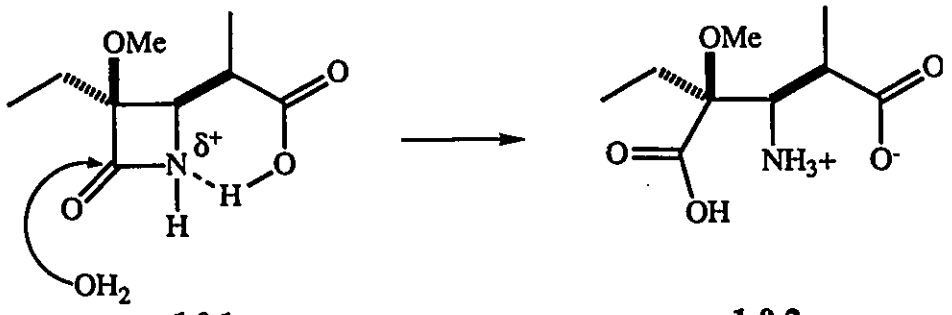


Fig. 14 ORTEP diagram of **101**



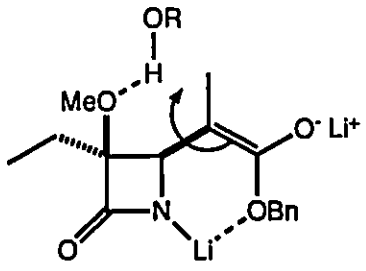
100 **101**

a) H_2 (1 atm), Pd-C (10%), EtOH or CH_2Cl_2



101 **102**

The observed stereoselectivity of the reduction is surprising and dissapointing. We had expected that the protonation of the intermediate chelated dianion **103** should occur preferentially from the less hindered convex side, giving the isomer which would lead to 1-β-methyl derivatives. The fact that **101** is obtained, may be explained by invoking the protonation from the hindered face perhaps through the hydrogen bonding of alcohol proton with the 3-methoxy group.



103

After the relative configuration at this newly created chiral center had been established, efforts were directed towards obtaining the

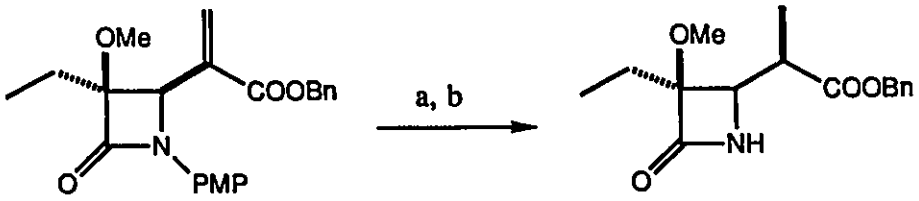
desired epimer at this center. The reduction of the α,β-unsaturated ester **98** having a PMP group at the β-lactam nitrogen with L-Selectride gave the reduced ester which was treated with CAN to produce ester **104** as a major product. Comparison by tlc showed that this material **104** is identical to the minor product obtained in the reduction of **99**. This experiment led to the conclusion that changing the nature of the substituent on the β-lactam nitrogen could reverse the diastereoselectivity of the reduction. However the yield in this reduction was rather low (29%) and the purification of the product was difficult.

When the reduction of **98** was carried out under catalytic hydrogenation conditions using 5% rhodium on carbon both reduction and debenzylation occurred. The concomitant debenzylation was somewhat surprising since rhodium on carbon had been used in reductions without hydrogenolysis of oxygen substituents at the benzylic position. The ^{1}H NMR of the crude product revealed that this reduction is not diastereoselective. More than 90% of the starting material was recovered upon attempted reduction of **98** with either sodium cyanoborohydride/HCl or hydrogen/Wilkinson's catalyst. The reduction of the same α,β-unsaturated ester **98** with sodium borohydride in the presence of nickel chloride[46] gave a mixture of diastereomers which is not separable by column chromatography. However, this mixture, after CAN cleavage of the PMP group, gave corresponding NH compounds including **108**. The diastereomeric ratio (5:1) can be determined both by ^{1}H NMR and by actual separation of

---

[46] Kido, F.; Tsutsumi, K.; Maruta, R.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1979**, *101*, 6420.

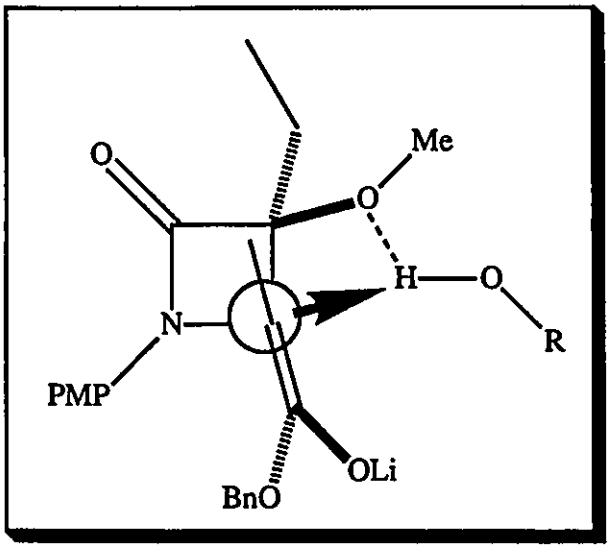
two diastereomers by column chromatography. Tlc and ^1H NMR indicated that the major product **104** in above reaction is identical to the minor product (β epimer) in L-Selectride reduction of α,β-unsaturated ester **99** (Fig. 15). The ester **104** is a yellowish solid (mp 70-72 °C) which gave a doublet at δ=1.21 ppm (J=7.2 Hz) for new methyl group (1.16 ppm, J=7.1 Hz for other epimer) and AB patterned doublets at δ=5.03 and 5.17 ppm with J=12.4 Hz for benzylic protons (5.11 ppm, s for other epimer).



98 **104**

a) $NaBH_4$, $NiCl_2$, EtOH, -78 °C to 0 °C, 1h; b) CAN, MeCN, -5 °C, 0.5 h

This change in diastereoselectivity of the reduction might be explained by assuming the non-chelated conformer of enolate **105** protonated from the less hindered face.



105

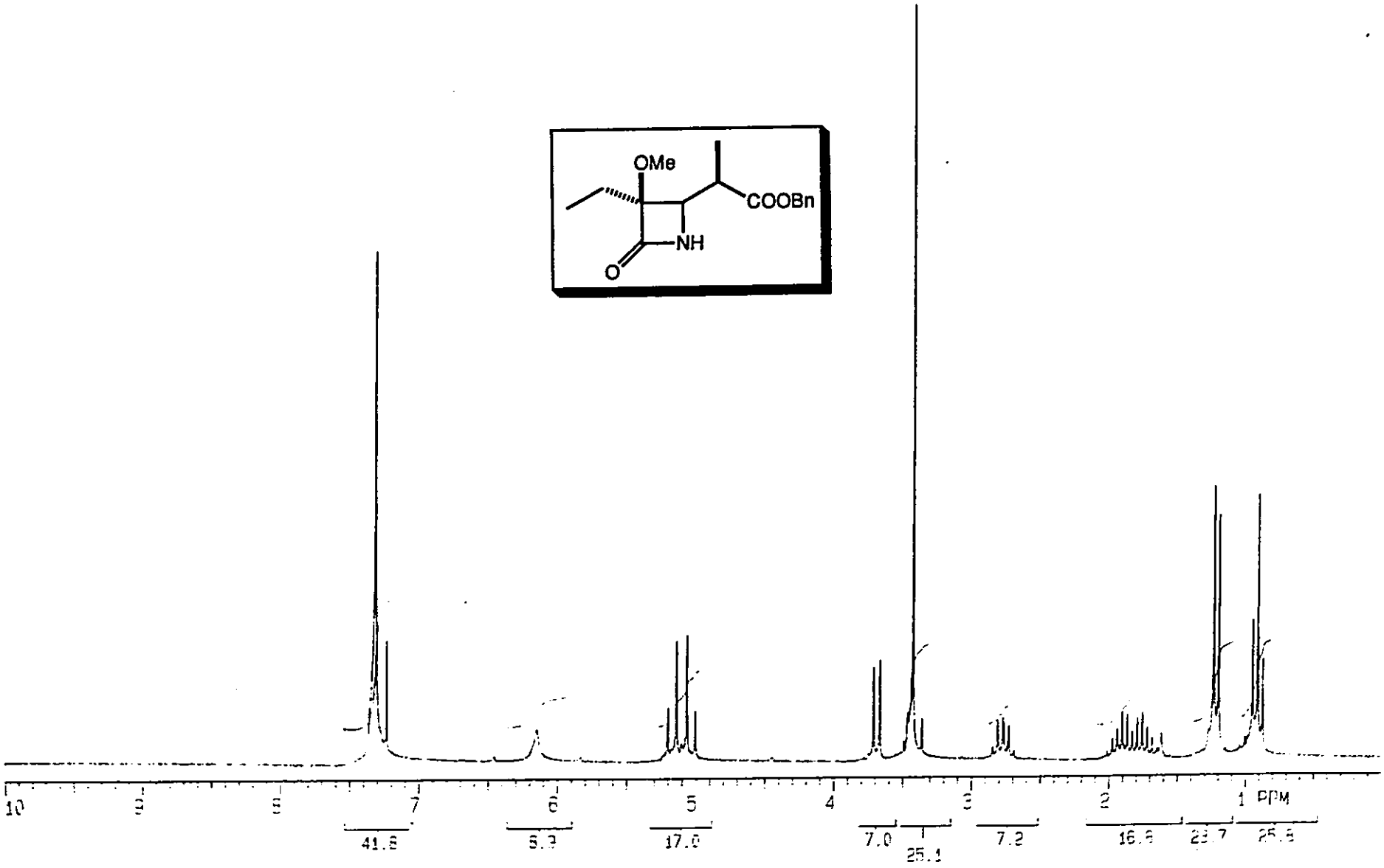


Fig. 15 ^{1}H NMR spectrum of **104**

Annulation

The homologation of acid **101** to β-ketoester **106** was carried out using Masamune's method.[47] As in the examples described in Chapter 3, the yields of the homologation involving acids derived from 3-methoxyazetidinones is low; in this case the yield is 20%. The conversion of β-ketoester **106** to diazo compound **107** was carried out by using a reported method.[48] The diazo compound **107** showed a typical signal at 2146 (N_2) cm^{-1} in IR spectrum. This compound gave M+1 peak in MS(CI) and showed the disappearance of the methylene signal (δ=3.61 ppm) of starting compound **106**. Rhodium(II) octanoate mediated diazo insertion reaction gave a mixture of products.[49] The ^1H NMR spectrum of crude product showed an AB pattern for the benzylic protons of PNB ester (δ=5.23 and 5.32 ppm, J=13.4 Hz) which indicated the formation of bicyclic ketoester **108**. The IR of crude product has a peak at 1770 cm^{-1} for β-lactam carbonyl indicating a strained bicyclic ring. Attempted purification of **108** by silica gel column chromatography was unsuccessful and the isolated fractions could not be characterized. The activation of **108** by diphenyl chlorophosphate and addition of N-acetyl aminoethanethiol in the presence of excess DIPEA failed to yield the desired product **109**.

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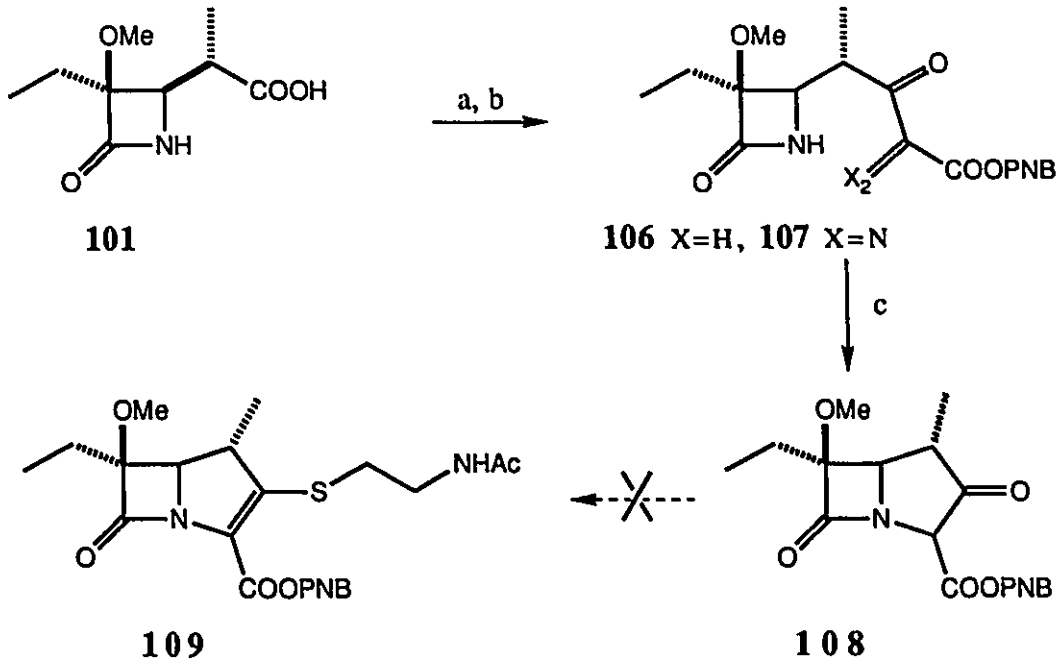
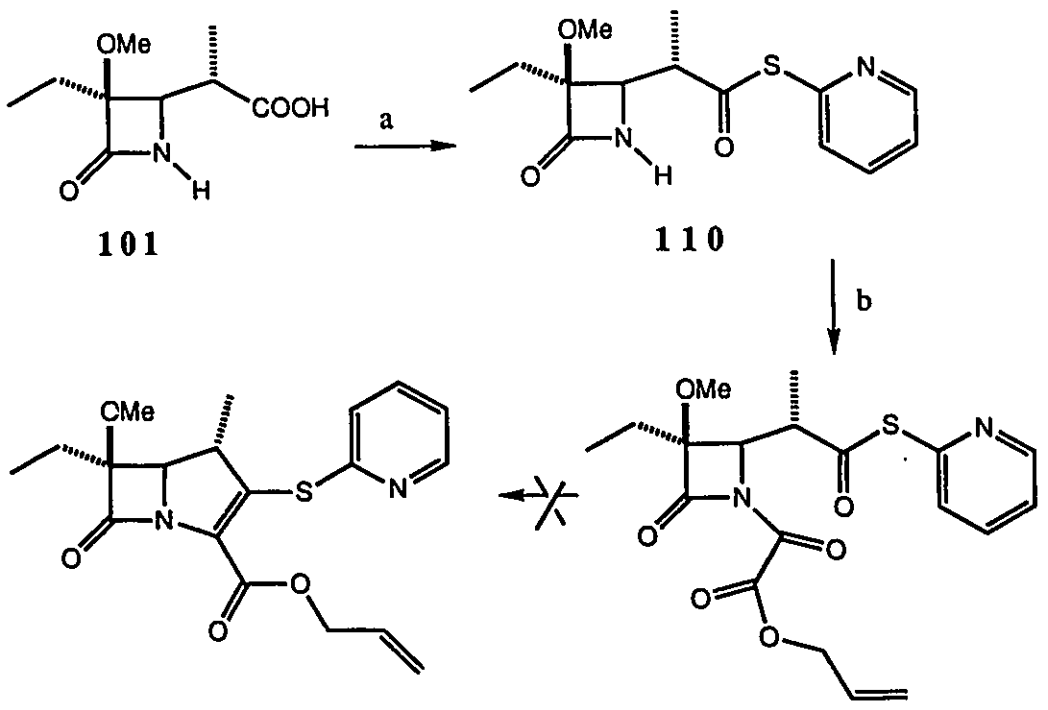
[47] Masamune, S.; Brooks, D. W.; Lu, L. D. L. *Angew. Chem. Int. Ed. Engl.* **1978**, *18*, 72.
[48] Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.
[49] for Rhodium cyclizations in 1-methylcarbapenems having a hetero atom at C-6: Salzmann, T. N.; DiNinno, F. P.; Greenlee, M. L.; Guthikonda, R. N.; Quesada, M. L.; Schmitt, S. M.; Herrmann, J. J.; Woods, M. F. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; A. G. Brown and S. M. Roberts, Ed.; The Royal Society of Chemistry: London (England), **1985**; p 171.



a) CDI, MeCN; $Mg(OOCCH_2COOPNB)_2$, MeCN, 60 °C; b) 4-$HOOCPhSO_2N_3$, TEA, MeCN, 0 °C; c) $Rh_2(OAc)_4$, C_6H_6, reflux, 2 h.

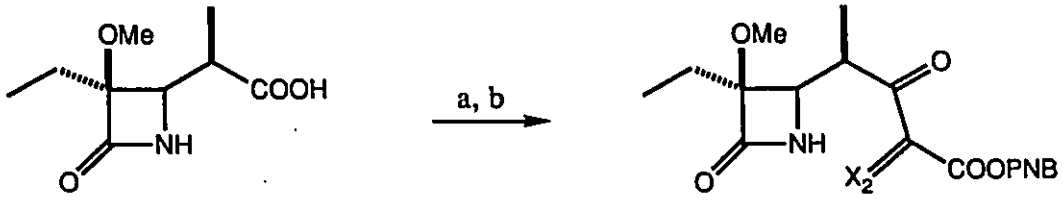
An alternate approach for obtaining 1-α-methyl carbapenem **112** is shown below. This involved the conversion of **101** to the thioester **110** using 2-mercaptopyridine and DCC. The ester **110** was then converted to oxalimide derivative **111** by reaction with allyloxalyl chloride. Due to the instability of **111** the planned phosphite cyclization could not be attempted.



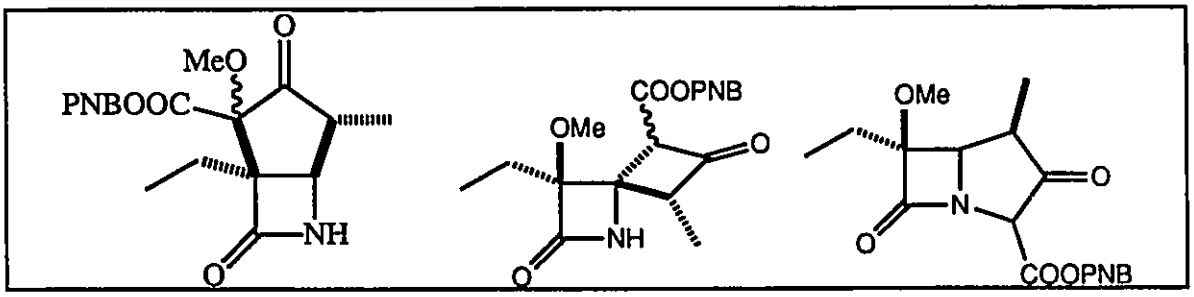
a) 2-mercaptopyridine, DCC, THF, 25 °C; b) $ClOCCOOCH_2CH{=}CH_2$, DIPEA, CH_2Cl_2,

The rhodium cylization method was attempted next in the β-methyl series. The acid **113** (1740 cm^{-1} absorption in IR and doublets at δ=1.24 and 3.66 ppm for 5-methyl and C-4 protons in ^1H NMR) was obtained by hydrogenation of **104** using methylene chloride as a solvent. The necessary two carbon homologation was accomplished as in the case of **106**; the yield of **114** was again low (15%). The diazo compound **115** was prepared again using 4-carboxybenzenesulfonazide and TEA. It showed an IR peak at 2142 cm^{-1} (N_2) and showed the disappearance of the methylene protons of **114** in the ^1H NMR. The diazo-insertion reaction was performed in dry benzene at ambient temperature. The examination of partially purified product by ^1H NMR, ^{13}C NMR, IR, and MS showed this product was not the desired carbapenem **116** since it showed a NH band at 3304 cm^{-1} in the IR spectrum. The presence of the NH function was further confirmed by

the appearance of a broad band at δ=6.17 ppm in the ^1H NMR. The available data is most consistent with the spirocyclic β-lactam **117** which resulted from the insertion of the rhodium carbenoid into the C-H bond at C-4 position. As mentioned earlier in this chapter, the steric congestion in **116** poses a big challenge in this cyclization reaction. The formation of **117** instead of **116** could be due to this factor. An alternate structure for this product could be **118** which results from the insertion of carbenoid to C-O bond. The lack of coupling between CH protons next to nitrogen and methyl respectively even in high resolution 300 MHz ^1H NMR made us to believe that the product is indeed **117**.



113 **114** X=H, **115** X=N

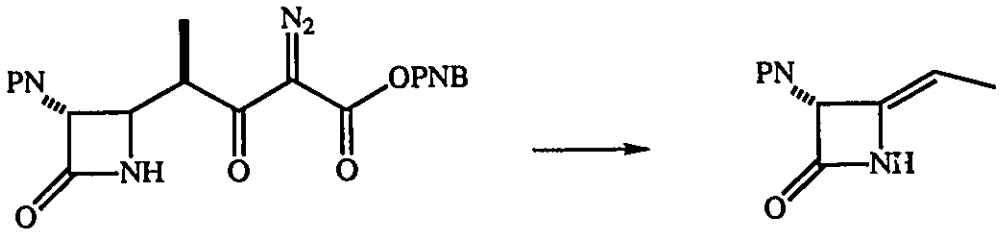


118 **117** **116**

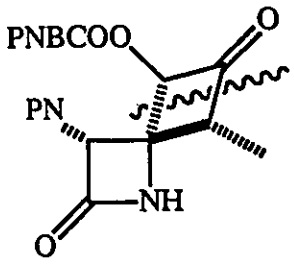
a) CDI, MeCN; $Mg(OOCCH_2COOPNB)_2$, MeCN, 60 °C; b) $4\text{-}HOOCPhSO_2N_3$, TEA, MeCN, 0 °C; c) $Rh_2(OOct)_4$, C_6H_6.

It has been reported that **120** is a major product during a rhodium carbenoid reaction. The formation of compound **120** from

119 presumably involved insertion carbene into C-H bond at C-4 to give 121 which underwent an elimination of a ketene.

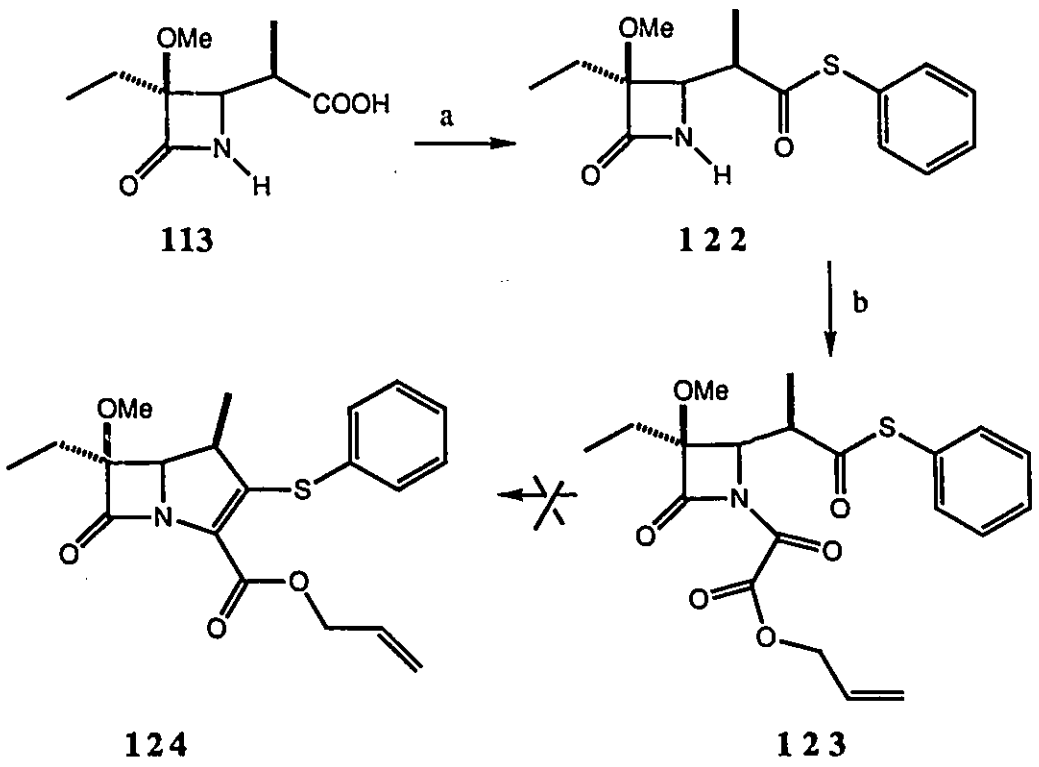


119 120



121

The phosphite coupling method in this series was attempted. The conversion of the carboxylic acid **113** to the cyclization precursor *i.e.* the oxalimide **123**, involved the DCC coupling reaction with thiophenol and subsequent reaction with allyloxalyl chloride in the presence of DIPEA. The compound **122** gave IR peaks at 1760 and 1701 cm^{-1} for β-lactam carbonyl and thioester group respectively. The cyclization reaction was carried out using a dilute solution of substrate and slow addition of a dilute solution of triethyl phosphite by means of a syringe pump. This experiment did not give the desired bicyclic compound **124**.



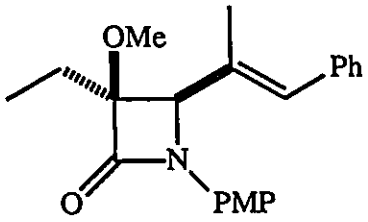
a) 2-Pyridylthiol, DCC, THF, 25 ^{o}C; b) $ClOCCOOCH_2CH{=}CH_2$, DIPEA, CH_2Cl_2, 30 min

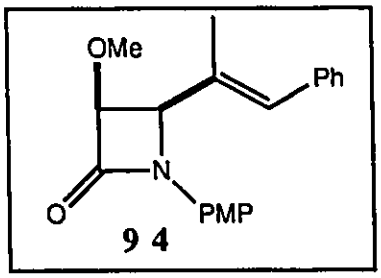
EXPERIMENTAL SECTION

General techniques

Details concerning spectrometers, solvent purification and chromatography have been described in earlier chapters. McMurry's reagent ($PhNTf_2$) was purchased from Aldrich Chemical Co. and used as received.

3-Ethyl-3-methoxy-1-p-methoxyphenyl-4-(1'-methyl-cinnamyl)-2-azetidinone (95)

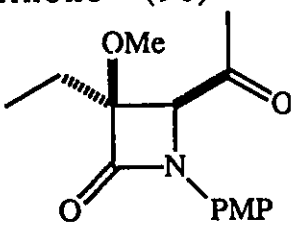




3-Methoxy azetidinone **94** (17.0 g, 52.63 mmol) was dissolved in 500 mL of dry THF and cooled to -78 °C. LDA solution (1.1 eq prepared from 30.5 mL of 1.9 M n-BuLi and 8.9 mL (63.62 mmol) of diisopropyl amine) was added by cannula and the reaction mixture was stirred for 30 min. The solution developed a brown color. Iodoethane (16.8 mL, 210.5 mmol) was added and stirred. The temperature was allowed to rise slowly to -30 °C. Usual workup of the reaction mixture using ethyl acetate as a solvent and purification of the crude product by column chromatography (1:8 EtOAc:hexanes) afforded 17.0 g (92%) of **95** as a white solid; mp 88-89 °C; IR (CH_2Cl_2 film): 1743 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 1.08 (3H, t, H=7.4 Hz, CH_3CH_2), 1.81-2.19 (5H, m with overlapping s at 1.95, CH_2, CH_3), 3.53 (3H, s, OCH_3), 4.36 (1H, s, CHN),

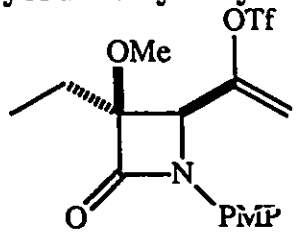
6.52 (1H, s, PhHC=C), 6.84 (2H, d, J=9.2 Hz, PMP), 7.23-7.42 (7H, m, Ph, PMP); MS: 351 (M^+, 16), 336 (M^+-15, 1), 321 (M^+-30, 1), 294 (M^+-57, 2), 250 (M^+-101, 100); HRMS calcd for $C_{22}H_{25}NO_3$ 351.1834, found 351.1833.

4-Acetyl-3-ethyl-3-methoxy-1-p-methoxyphenyl-2-azetidinone (96)



3-Ethyl-3-methoxyazetidinone **95** (11.20 g, 31.9 mmol) was dissolved in 250 mL of dry CH_2Cl_2, 4 Å molecular sieves (1.0 g) and 10 mL of MeOH was also added. The reaction mixture was cooled to -78 °C and ozone was passed till the reaction mixture was bluish and tlc indicated complete reaction. The excess ozone was removed by passing a stream of nitrogen through the reaction mixture. Excess DMS (5 mL) was added. The reaction mixture was stirred overnight and allowed to warm slowly to 25 °C over 18 h. After removal of the solid residue and solvents, the crude oil was purified by column chromatography (1:6 EtOAc:hexanes) to yield 6.80 g (77%) of **96** as a white solid; mp 85-86 °C; IR (CH_2Cl_2 film): 1745 [with a shoulder at 1730] (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 1.08 (3H, t, J=7.4 Hz, CH_3CH_2), 1.79-1.97 (1H, m, CH_2CH_3), 2.05-2.25 (4H, m overlapping with s at 2.21, CH_2CH_3, $COCH_3$), 3.48 (3H, s, OCH_3), 3.76 (3H, s, OCH_3),4.35 (1H, s, CHN), 6.84 (2H, d, J=9.16 Hz, PMP), 7.22 (2H, d, J=9.16, PMP); MS: 277 (M^+, 43), 248 (M^+-28, 3), 220 (M^+-28-29, 3), 206 (M^+-28-43, 100), 192 (220-28, 15); HRMS calcd for $C_{15}H_{19}NO_4$ 277.1300, found 277.1307.

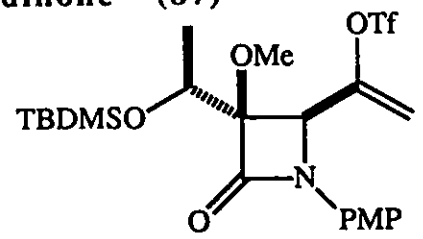
3-Ethyl-3-methoxy-1-p-methoxyphenyl-4-(1'-trifluoro-methylsulfonyloxyvinyl)-2-azetidinone (97)



A solution of C-4 acetyl azetidinone **96** (10.26 g, 37.04 mmol) in 200 mL of dry THF was cooled to -78 °C and 1.1 eq of freshly prepared LDA solution in THF was added by cannula. The reaction mixture was stirred for about 15 min and a solution of 15.9 g (44.5 mmol) of N-phenyltrifluoromethylsulfonimide[50] in 25 mL of THF was added by cannula. The reaction mixture was stirred overnight and allowed to warm to room temperature. After removal of the solvent, the crude product was purified by column chromatography (1:6 EtOAc:hexanes) to yield 13.80 g (91%) of **97** as a yellowish oil; IR: 1750 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 1.05 (3H, t, J=7.4 Hz, CH_3CH_2), 1.74-1.92 (1H, m, CH_2CH_3), 1.95-2.23 (1H, m, CH_2CH_3), 3.55 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.39 (1H, s, CHN), 5.15 (1H, d, J=5.0 Hz, H_2C=C), 5.44 (1H, d, J=4.3 Hz, H_2C=C), 6.87 (2H, d, J=9.0 Hz, PMP), 7.29 (2H, d, J=9.0 Hz, PMP); MS: 409 (M^+, 3), 381 (M^+-28, 1), 309 (M^+-100, 46), 295 (309-14, 1), 260 (M^+-149, 5); HRMS calcd for $C_{16}H_{18}NO_6SF_3$ 409.0781, found 409.0794.

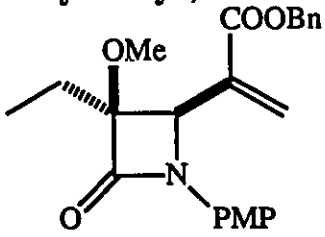
[50] purchased from Aldrich Chem. Co.

3-t-Butyldimethylsilyloxy-3-methoxy-1-p-methoxyphenyl-4-(1'-trifluoromethananesulfonyloxyvinyl)-2-azetidinone (87)



Compound **87** was prepared in 80% yield by a method similar to that of **97** as a white crystalline solid; mp 55-56 °C; IR: 1762 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.35 (6H, s, CH_3SiCH_3), 0.68 (9H, s, t-BuSi), 1.36 (3H, d, J=6.3 Hz, CH_3CH), 3.64 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.11 (1H, q, J=6.2 Hz, CHN), 4.64 (1H, d, J=0.7 Hz, CHN), 5.20 (1H, dd, J=0.9, 4.2 Hz, H_2C=C), 5.45 (1H, d, J=4.5 Hz, H_2C=C), 6.86 (2H, d, J=9.2 Hz, PMP), 7.34 (2H, d, J=9.2 Hz, PMP); MS: 539 (M^+, 6), 524 (M^+-15, 1), 482 (M^+-57, 83), 454 (M^+-57-28, 1), 333 (M^+-57-149, 79); HRMS calcd for $C_{22}H_{32}NO_7SF_3Si$ 539.1679, found 539.1650.

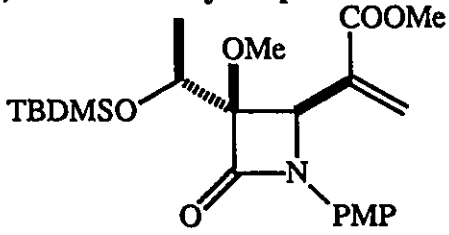
3-Ethyl-3-methoxy-1-p-methoxyphenyl-4-(1'-carboxybenzylvinyl)-2-azetidinone (98)



The vinyl triflate **97** (5.70 g, 14.07 mmol) was dissolved in 100 mL of THF. TEA (5.82 mL, 41.7 mmol), benzyl alcohol (4 mL, 38.6 mmol), palladium acetate (0.156 g, 0.695 mmol) and triphenylphosphine (0.365 g, 1.36 mmol) was added. Carbon monoxide gas was passed through the reaction mixture at room temperature for 6 h. After

removal of the solvent, the excess benzyl alcohol was removed in vacuum at 100 °C for several hours. The black crude oil was purified by column chromatography (1:6 EtOAc:hexanes) to yield 4.85 g (87%) of **98** as a yellowish oil; IR: 1752 (C=O), 1723 (COOR) cm^{-1}; ^1H NMR (200 MHz) δ: 1.00 (3H, t, J=7.5 Hz, CH_3CH_2), 1.91-2.02 (2H, q, J=7.6 Hz, CH_2CH_3), 3.42 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.83 (1H, d, J=0.6 Hz, CHN), 5.24 (2H, d, J=0.8 Hz, CH_2Ph), 5.66 (1H, d. J=0.8 Hz, $H_2C=C$), 6.47 (1H, s, $H_2C=C$), 6.82 (2H, d, J=8.1 Hz, PMP), 7.24-7.39 (7H, m, Ph, PMP); MS: 395 (M^+, 10), 367 (M^+-28, 20), 352 (M^+-28-15, 3), 295 (M^+-100, 11), 276 (M^+-28-91, 7); HRMS calcd for $C_{23}H_{25}NO_5$ 395.1755, found 395.1744.

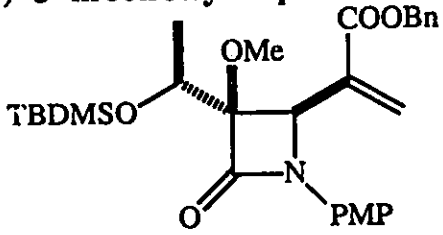
3-t-Butyldimethylsilyoxyethyl-4-(1'-carboxymethyl-vinyl)-3-methoxy-1-p-methoxyphenyl-2-azetidinone (90)



A method similar to that for **98**, except that benzyl alcohol was replaced by methanol, was used to obtain compound **90** in 69% yield as a yellowish oil which solidified slowly to a yellowish white solid; mp 89-90 °C; IR(CH_2Cl_2 film): 1752 cm^{-1}; ^1H NMR (200 MHz) δ: 0.04 (3H, s, CH_3Si), 0.05 (3H, s, CH_3Si), 0.64 (9H, s, t-BuSi),1.38 (3H, d, J=6.2 Hz, CH_3CH), 3.50 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.11 (1H, q, J=6.4 Hz, CHO), 5.00 (1H, d, J=1.3 Hz, CHN), 5.68 (1H, d, J=0.6 Hz, $H_2C=C$), 6.43 (1H, d, J=0.9 Hz, $H_2C=C$), 6.81 (2H, d, J=9.2 Hz, PMP), 7.30 (2H, d, J=9.2 Hz, PMP); MS: 449 (M^+, 3), 392 (M^+-57, 32), 360 (M^+-57-

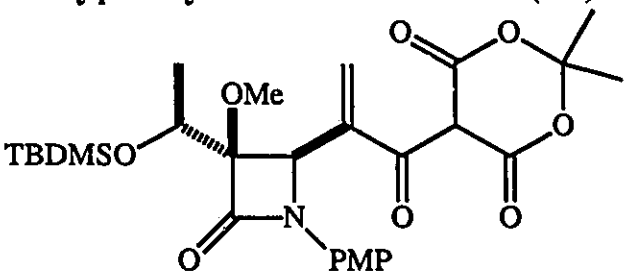
32, 3), 348 (M^+-57-44, 3), 243 (M^+-57-149, 20); HRMS calcd for $C_{23}H_{35}NO_6Si$ 449.2215, found 449.2224.

3-t-Butyldimethylsilyoxyethyl-4-(1'-carboxybenzyl-vinyl)-3-methoxy-1-p-methoxyphenyl-2-azetidinone (91)



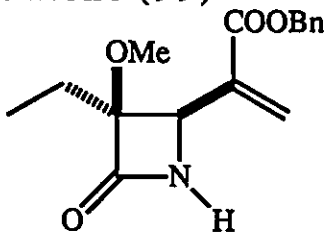
The carbonylation reaction was carried out by a method similar to that for **98**, to yield 62% of compound **91** as a pale yellow solid; mp 89-90 °C; IR (CH_2Cl_2): 1752, 1732 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: -0.11 (3H, s, CH_3Si), -0.07 (3H, s, CH_3Si), 0.58 (9H, s, t-BuSi), 1.32 (3H, d, J=7.3 Hz, CH_3CH), 3.50 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.99 (1H, q, J=6.2 Hz, CHO), 4.95 (1H, s, CHN), 5.18 (1H, d, J=12.5 Hz, CH_AH_BPh), 5.29 (1H, d, J=12.5 Hz, CH_AH_BPh), 5.68 (1H, dd, J=0.7, 1.6 Hz, $H_2C=C$), 6.48 (1H, d, J=0.4 Hz, $H_2C=C$), 6.79 (2H, d, J=9.2 Hz, PMP), 7.29 (2H, d, J=9.2 Hz, PMP), 7.36 (5H, s, Ph); MS: 525 (M^+, 2), 468 (M^+-57, 23), 436 (M^+-57-32, 2), 424 (M^+-57-44, 2), 319 (M^+-57-149, 3); HRMS calcd for $C_{29}H_{39}NO_6Si$ 525.2585, found 525.2566.

3-t-Butyldimethylsilyoxyethyl-4-[1'-carboxy(2",2"-dimethyl-1",3"-dioxane-4",6"-dion-5"-yl)vinyl]-3-methoxy-1-p-methoxyphenyl-2-azetidinone (89)



The enol triflate **87** (0.076 g, 0.141 mmol) was carbonylated in the presence of Meldrum's acid (0.02 g, 0.139 mmol) as described in the case of **98**, to yield **89** in 15% yield as a yellowish oil which slowly solidified to give a yellowish solid; mp 152-153 °C; ^{1}H NMR (200 MHz) δ: 0.04 (6H, s, CH_3SiCH_3), 0.65 (9H, s, t-Bu), 1.38 (3H, d, J=6.3 Hz, CH_3CH), 1.76 (6H, s, $2XCH_3$), 3.54 (3H, s, OCH_3), 3.56 (1H, s, CH), 3.59 (3H, 2s, OCH_3), 4.14 (1H, q, J=6.2 Hz, $CHCH_3$), 5.01 (1H, s, CHN), 5.80 (1H, s, H_2C=C), 6.56 (1H, s, H_2C=C), 6.83 (2H, d, J=9.2, PMP), 7.40 (2H, d, J=9.1 Hz, PMP).

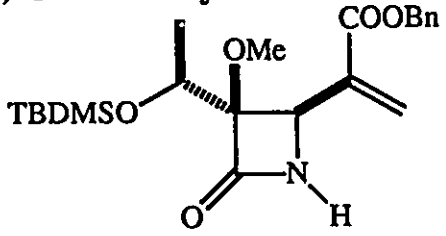
4-(1'-carboxymethylvinyl)-3-ethyl-3-methoxy-2-azetidinone (99)



The α,β-unsaturated ester **98** (7.50 g, 19.0 mmol) in 200 mL of MeCN was cooled to -15 °C to -30 °C. CAN (31.22 g, 57.0 mmol) in 50 mL of ice-cold water was added dropwise over 30 min and stirred for further 15 min. Usual workup and purification by column chromatography (1:3 EtOAc:hexanes) yielded 2.80 g (51%) of compound

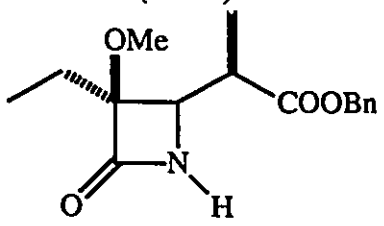
99 as a colorless oil; IR: 1761 (C=O), 1725 (COOBn) cm^{-1}; ^1H NMR (200 MHz) δ: 1.01 (3H, t, J=7.5 Hz, CH_3CH_2), 1.86-1.97 (2H, q, J=7.3 Hz, CH_2CH_3), 3.36 (3H, s, OCH_3), 4.46 (1H, t broad, J=1.6 Hz, CHN), 5.21 (2H, s, CH_2Ph), 5.83 (1H, t, J= Hz, H_2C=C), 5.99 (1H, broad s, NH), 6.46 (1H, t, J= Hz, H_2C=C), 7.34 (5H, s, Ph); MS (EI 10X expanded): 289 (M^+, 7), 274 (M^+-15, 6), 261 (M^+-28, 2), 258 (M^+-31, 2), 246 (M^+-44, 8).

3-t-Butyldimethylsilyoxyethyl-4-(1'-carboxybenzyl-vinyl)-3-methoxy-2-azetidinone (92)



The cleavage of the PMP group was achieved by a method described for **99** at -5 °C to 0 °C to yield 40% of **92** as a yellowish solid; mp 73-74 °C; IR: 3271 (NH), 1761 (C=O), 1725 (COOR) cm^{-1}; ^1H NMR (200 MHz) δ: -0.06 (3H, s, CH_3Si), -0.01 (3H, s, CH_3Si), 0.082 (9H, s, t-Bu), 1.29 (3H, d, J=6.2 Hz, CH_3CH), 3.36 (3H, s, OCH_3), 3.93 (1H, q, J=6.2 Hz, CHO), 4.60 (1H, d broad, J=1.5 Hz, CHN), 5.15 (2H, d, J=12.7 Hz, CH_AH_BPh), 5.25 (1H, d, J=12.3 Hz, CH_BH_APh), 5.84 (1H, dd, J=0.8, 1.6 Hz, H_2C=C), 6.00 (1H, broad s, NH), 6.46 (1H, overlapping dd, J=0.9, 1.4 Hz, H_2C=C), 7.34 (5H, s, Ph); MS (EI expanded): 419 (M^+, 4), 376 (M^+-43, 11), 362 (M^+-57, 100), 334 (M^+-57-28, 10), 318 (M^+-57-44, 20); HRMS calcd for $C_{18}H_{24}NO_5Si$ (M^+-57) 362.1436, found 362.1430.

3-Ethyl-3-methoxy-4-(1'-carboxybenzylethyl)-2-azetidinone (104)

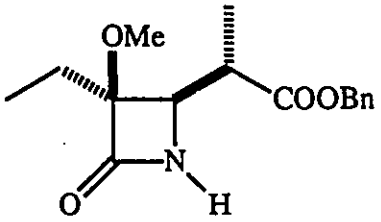


The α,β-unsaturated ester **98** (2.34 g, 5.92 mmol) was dissolved in 125 mL of MeOH and cooled to -78 °C. $NiCl_2.6H_2O$ (0.28 g, 1.18 mmol) and $NaBH_4$ (0.853 g, 23.7 mmol) were added. The reaction was found to be incomplete after stirring for 2 h, therefore the reaction mixture was then warmed to -60 °C and a yellowish brown color appeared at this stage. The reaction was still incomplete and hence warmed to -20 °C. An additional 0.2 g (5.55 mmol) of $NaBH_4$ was added and the color changed to brown. The reaction mixture was further warmed to 0 °C and 0.2 g more of $NaBH_4$ was added, at which point a black precipitate appeared. [It appears this reaction is complete within 1 h at -78 °C when 31 mg of α,β-unsaturated ester but took 2 h for 5.92 mmol scale]. The excess $NaBH_4$ was destroyed by adding 10% HCl and most of MeOH was removed under vacuum. The product was extracted with CH_2Cl_2 and purified by column chromatography (1:8 EtOAc:hexanes) to yield 1.20 g (51%) of **104** as an oil; IR: 1740 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.94 (3H, t, J=7.3 Hz, CH_3CH_2), 1.19 (3H, d, J=7.3 Hz, CH_3CH), 1.70-1.80 (1H, m, CH_2CH_3), 1.97-2.08 (1H, m, CH_2CH_3), 2.96-3.03 (1H, m, CH_3CH), 3.49 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.33 (1H, d, J=6.6 Hz, CHN), 5.12 (1H, d, J= 12.3 Hz, CH_ACH_BPh), 5.23 (1H, d, J=12.3 Hz, CH_ACH_BPh), 6.78 (2H, d, J=9.2 Hz, PMP), 7.22 (2H, d, J=8.3 Hz, 7.32 (5H, s, Ph); MS: 397 (M^+, 9), 369 (M^+-28, 2), 297 (M^+-100, 20), 248 (M^+-149, 8), 234 (M^+-

28-135, 4), HRMS calcd for $C_{23}H_{27}NO_5$ 397.1904, found 397.1897. This product contained a mixture of epimers at the newly created chiral center. The separation of these two epimers at this step was not possible and it was taken to the next step.

The ester, obtained as a mixture of isomers as described above, (1.05 g, 2.64 mmol) was dissolved in 30 mL of MeCN and cooled to -5 °C. CAN (4.35 g, 7.94 mmol) in 15 mL of ice-cold water was added dropwise over 20 min. After stirring for an additional 10 min, the reaction mixture was worked up using EtOAc in the usual manner. Purification of the crude product by column chromatography (1:3 EtOAc:hexanes) yielded 0.54 g (70%) of **104** as a yellowish solid; mp 70-72 °C; IR: 3264 (NH), 1758 and 1737 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.91 (3H, t, J=7.4 Hz, CH_3CH_2), 1.21 (3H, d, J=7.2 Hz, CH_3CH), 1.61-2.00 (2H, m, CH_2CH_3), 2.73-2.81 (1H, m, CH_3CH), 3.43 (3H, s, OCH_3), 3.69 (1H, d, J=9.0 Hz, CHN), 5.03 (1H, d, J=12.4 Hz, CH_ACH_BPh), 5.17 (1H, d, J=12.4 Hz, CH_ACH_BPh), 6.15 (1H, broad s, NH), 7.32 (5H, s, Ph); MS: 291 (M^+, 2), 248 (M^+-43, 35), 200 (M^+-91, 1), 191 (M^+-107, 1), 184 (M^+-107, 0.5); HRMS calcd for $C_{15}H_{20}O_3$ (M^+-43) 238.1435, 238.1415.

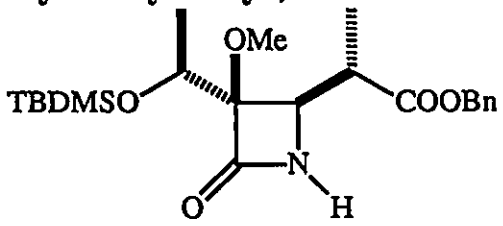
3-Ethyl-3-methoxy-4-(1'-carboxybenzylethyl)-2-azetidinone (100)



Compound **99** (2.80 g, 9.69 mmol) was dissolved in 50 mL of THF and 25 mL of 2-butanol and cooled to -78 °C. L-Selectride (24.2 mL, 0.0242 mmol) was added slowly by a syringe over a period of 20 min.

After stirring for 30 min the reaction was quenched with 10 % HCl at -78 °C and usual work up of the reaction mixture using EtOAc as a solvent and purification of the crude product by column chromatography (1:3 EtOAc:hexanses) afforded 1.50 g (53%) of reduced ester **100** as a yellowish oil; IR: 3302 (NH), 1761 (C=O), 1731 (COOR) cm^{-1}; ^1H NMR (200 MHz) δ: 0.94 (3H, t, J=7.4 Hz, CH_3CH_2), 1.16 (3H, d, J=7.1 Hz, CH_3CH), 1.55-1.71 (1H, m, CH_2CH_3), 1.98-2.09 (1H, m, CH_2CH_3), 2.80-2.89 (1H, m, $CHCH_3$), 3.99 (4H, s, with overlapping d, J=10.4 Hz, CHN, OCH_3), 5.11 (2H, s, CH_2Ph), 6.00 (1H, s broad, NH), 7.32 (5H, broad s, Ph); MS (expanded EI): 291 (M^+, 4), 263 (M^+-28, 0.4), 248 (M^+-43, 65), 200 (M^+-91, 3), 191 (M^+-100, 2). The configuration of major isomer was determined by an X-Ray structure of the carboxylic acid obtained after debenzylation and found to be as shown. The minor isomer in this reduction was also isolated and the diastereomeric ratio of this reduction was found to be 7:1 (α:β).

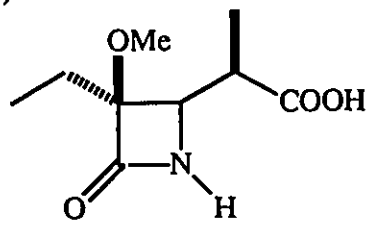
3-t-Butyldimethylsilyloxyethyl-3-methoxy-4-(1'-carboxybenzylethyl)-2-azetidinone (93)



L-Selectride reduction was performed as in the case of **100** to obtain **93** in 52% yield as a paleyellowish oil, IR ($CDCl_3$ film): 3275 (NH), 1745 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.04 (3H, s, CH_3Si), 0.06 (3H, s, CH_3Si), 0.85 (9H, s, t-Bu), 1.17 (3H, d, J=7.1 Hz, CH_3CH), 1.23 (3H, d, J=6.4 Hz, CH_3CHO), 2.43 (1H, dq, J=7.1, 10.6 Hz, $CHCH_3$), 3.60 (3H, s, OCH_3), 3.68 (1H, d, J=10.4 Hz, CHN), 4.14 (1H, q, J=6.4 Hz, CHO), 5.12 (2H, s,

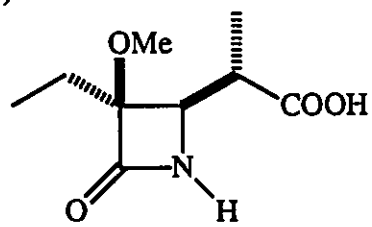
CH_2Ph), 6.02 (1H, d, J=2.2 Hz, NH), 7.35-7.38 (5H, broad s, Ph); MS (CI): 422 (M^++1, 11), 394 (M^++1-28, 75), 377 (M^++1-45, 2), 364 (M^++1-58, 8), 321 (M^++1-58-43, 8).

3-Ethyl-3-methoxy-4-(1'-carboxyethyl)-2-azetidinone (113)



The ester **104** (0.23 g, 0.79 mmol) was dissolved in 4 mL of CH_2Cl_2 and hydrogenated at 1 atm and 25 °C using 44 mg of Pd-C (10%) for 8 h. After removal of the catalyst by passing through a small Celite plug, the solvent was removed in vacuum to yield 0.149 g (94%) of acid **113** as a white solid; mp 135-136 °C, IR: 3360 (OH, NH), 1740 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.96 (3H, t, J=7.5 Hz, CH_3CH_2), 1.24 (3H, d, J=7.3 Hz, CH_3CH), 1.73-2.05 (2H, m, CH_2CH_3), 2.71-2.79 (1H, m, $CHCH_3$), 3.51 (3H, s, OCH_3), 3.66 (1H, d, J=8.8 Hz, CHN), 6.36 (1H, broad s, NH); MS(CI): 202 (M^++1, 35), 184 (M^++1-18, 1), 174 (M^++1-28, 88), 159 (M^++1-43, 4), 158 (M^++1-44, 3), 184 (M^++1-18, 1).

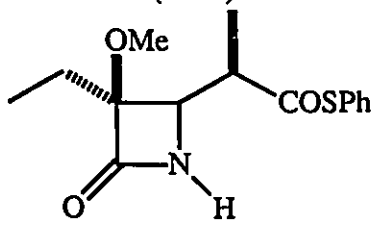
3-Ethyl-3-methoxy-4-(1'-carboxyethyl)-2-azetidinone (101)



The benzyl ester **100** (507 mg, 1.74 mmol) was dissolved in 20 mL of EtOH and hydrogenated in the presence of 100 mg of Pd-C (10%) at 1 atm and 25 °C for 6 h. A brownish solid was obtained after

removal of the solvent. The crude product was purified by treatment with $NaHCO_3$ solution (146 mg in 12 mL of water), washing with ether and acidification with concentrated HCl to yield 280 mg (80%) of **101** as an oil (which is unstable in moist air and can be crystallized under argon atmosphere to give colorless crystals; mp 139-141 °C, which became a foamy liquid at this temperature); IR ($CHCl_3$ film): 3287 (COOH), 1741 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.93 (3H, t, J=7.3 Hz, CH_3CH_2), 1.16 (3H, d, J=7.0 Hz, CH_3CH), 1.60-1.71 (1H, m, CH_2CH_3), 1.95-2.10 (1H, m, CH_2CH_3), 2.73-2.82 (1H, m, CH_3CH), 3.46 (1H, d, J=12.0 Hz, CHN), 3.49 (3H, s ovrlapping with d at 3.49, OCH_3), 6.97 (1H, broad s, NH), 7.71-7.75 (1H, broad s, COOH); MS: 201 (M^+, 2), 182 (M^+-18, 1), 158 (M^+-43, 16), 143 (M^+-43-15, 2.5), 113 (M^+-43-45, 100); HRMS calcd for $C_9H_{15}NO_4$ 201.1001, found 201.1001.

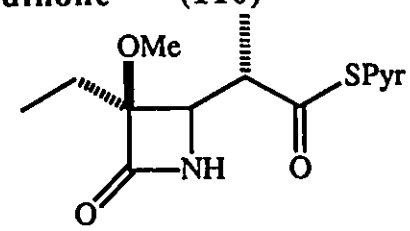
3-Ethyl-3-methoxy-4-(1'-carbothiophenylethyl)-2-azetidinone (122)



The carboxylic acid **113** (0.10 g, 0.496 mmol) and DCC (0.20 g, 0.969 mmol) were dissolved in 10 mL of THF at 25 °C. Thiophenol (0.07 mL, 0.682 mmol, freshly distilled under N_2) was added and the reaction mixture was stirred for 48 h. The solvent was removed by passing a stream of N_2 in a fumehood and the residue was purified by column chromatography (1:2 EtOAc:hexanes) to yield 0.132 g (90%) of **122** as a white solid; mp 108-109 °C; IR ($CDCl_3$ film): 3268 (NH), 1758 (C=O), 1700 (COS) cm^{-1}; ^1H NMR (200 MHz) δ: 0.93 (3H, t, J=7.4 Hz, CH_3CH_2),

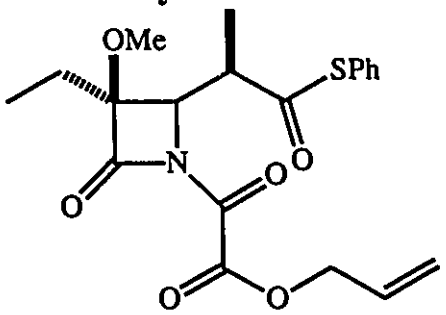
1.30 (3H, d, J=7.0 Hz, CH_3CH), 1.67-1.78 (1H, m, CH_2CH_3), 1.94-2.05 (1H, m, CH_2CH_3), 3.04-3.12 (1H, m, $CHCH_3$), 3.53 (3H, s, OCH_3), 3.76 (1H, d, J=7.9 Hz, CHN), 5.87 (1H, broad s, NH), 7.38 (5H, s, Ph); MS (CI): 294 (M^++1, 25), 292 (M^++1-2, 14), 266 (M^++1-28, 93), 251 (M^++1-43, 2), 184 (M^++1-100, 32); HRMS calcd for $C_{14}H_{15}O_2NS$ (M-32) 261.0815, found 261.0819.

3-Ethyl-3-methoxy-4-(1'-carbothiopyridylylethyl)-2-azetidinone (110)



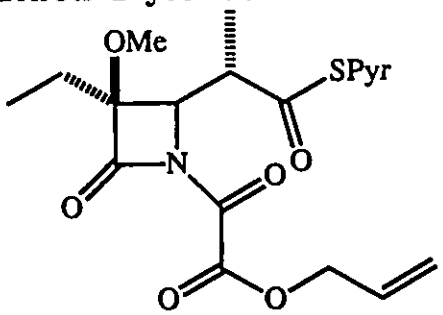
DCC coupling reaction was accomplished as above to give **110** in 69% yield as a yellow oil; chromatography solvent (1:1 EtOAc:hexanes); IR: 1753 (C=O), 1701 (O=C-S) cm^{-1}; ^1H NMR (200 MHz) δ: 0.94 (3H, t, J=7.5 Hz, CH_3CH_2), 1.28 (3H, d, J=7.0 Hz, CH_3CH), 1.61-2.07 (2H, m, CH_2CH_3), 3.46-3.56 (4H, m with overlapping s at 3.52, OCH_3, CHN), 6.40 (1H, broad s, NH), 7.25-7.40 (2H, m, SPyr), 7.68-7.73 (1H, m, SPyr), 8.62 (1H, m, SPyr); MS(CI): 295 (M^++1, 91), 267 (M^++1-28, 3), 224 (M^++1-28-43, 1), 186 (M^++1-109, 2), 158 (M^++1-109-28, 18).

Allyl 3-ethyl-3-methoxy-4-(1'-carbothiophenylethyl)-2-azetidinon-1-yloxoethanoate (123)



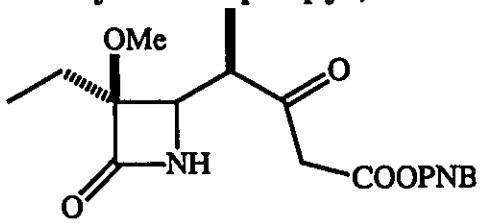
The thioester **122** (132 mg, 0.45 mmol) was dissolved in 4 mL of dry CH_2Cl_2 and cooled to 0 °C and DIPEA (0.093 mL, 0.534 mmol) was added by syringe. Allyloxalyl chloride (0.073 g, 0.492 mmol) in 1 mL of CH_2Cl_2 was added by cannula and the reaction mixture was stirred for 30 min, neutralized by 10% HCl and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with saturated NaCl. The crude product was quickly passed through a small silicagel plug (1:5 EtOAc:hexanes) to yield 150 mg (82%) of **123** as a yellowish oil; IR: 1804, 1754, 1705 and 1655 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.94 (3H, t, J=7.4 Hz, CH_3CH_2), 1.45 (3H, t, J=7.1 Hz, CH_3CH), 1.74-2.06 (2H, m, CH_2CH_3), 3.23-3.27 (1H, m, $CHCH_3$), 3.53 (3H, s, OCH_3), 4.79 (2H, d, J=6.0 Hz, CH_2O), 5.28-5.44 (2H, m, CH_2=CH), 5.88-6.02 (1H, m, CH=CH_2), 7.38 (5H, s, Ph) this compound contains some impurity derived from allyloxalyl chloride and DIPEA; MS (expanded EI): 405 (M^+, 1), 378 (M^+-27, 4), 373 (M^+-32, 8), 364 (M^+-41, 2), 296 (M^+-109, 5).

Allyl 3-ethyl-3-methoxy-4-(1'-carbothiopyridylethyl)-2-azetidinon-1-yloxoethanoate (111)



Compound **111** was obtained as a crude product and when the purification by column chromatography was attempted only decomposition products were isolated; ^{1}H NMR (200 MHz, crude sample contains excess allyloxalyl chloride and DIPEA) δ: 0.92-1.02 (3H, m, CH_3CH_2), 1.25-1.35 (3H, 2d, J=ca 7.0 Hz, calcd using a ruler, CH_3CH), 1.60-2.10 (2H, m, CH_2CH_3), 3.00-3.15 (1H, m, $CHCH_3$), 3.26+3.53 (3H, 2s, OCH_3), 3.55-3.70 (1H, m, CHN), 4.65-4.85 (2H, m, OCH_2), 5.20-5.50 (2H, m, CH_2=CH), 5.80-6.05 (1H, m, CH_2=CH), 7.25-7.37 (1H, m, Pyr), 7.60 (1H, d, J=ca 5.0 Hz, Pyr), 7.70-7.80 (1H, m, Pyr), 8.55-8.65 (1H, m, Pyr); MS (CI): 407 (M^++1, 2), 380 (M^++1-27, 2), 368 (M^++1-39, 0.2), 352 (M^++1-55, 0.4), 254 (M^++1-153, 1).

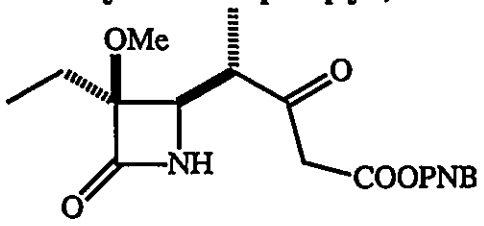
3-Ethyl-3-methoxy-4-(1'-methyl-3-p-nitrobenzyl-oxycarbonyl-2-oxopropyl)-2-azetidinone (114)



The carboxylic acid **113** (62 mg, 0.31 mmol) in 8 mL of dry MeCN was added to carbonyl diimidazole (CDI) (60 mg, 0.37 mmol) and stirred for 2 h. The magnesium salt of mono p-nitrobenzyl ester of malonic

acid (92 mg, 0.184 mmol) and a crystal of DMAP was added. The reaction mixture was maintained at 60 °C for 2 days. After removal of the solvent the product was purified by preparative thin layer chromatography (2:1 EtOAc:hexanes) yield 18 mg (15%) of **114** as a solid; mp 99-101 °C; IR: 3300 (NH), 1746 (C=O), 1523 and 1347 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.86 (3H, t, J=7.4 Hz, CH_3CH_2), 1.14 (3H, t, J=7.1 Hz, CH_3CH), 1.58-1.82 (1H, m, CH_2CH_3), 1.84-2.02 (1H, m, CH_2CH_3), 2.87-3.02 (1H, m, $CHCH_3$), 3.46 (3H, s, OCH_3), 3.64 (2H, d, J=2.1 Hz, $COCH_2COOR$), 3.68 (1H, J=9.4 Hz, CHN), 5.20 (1H, d, J=13.4 Hz, CH_ACH_BPh), 5.29 (1H, d, J=13.4 Hz, CH_ACH_BPh), 6.08 (1H, d, broad s, NH), 7.50 (2H, d, J=8.9 Hz, PNB), 8.20 (2H, d, J=8.8 Hz, PNB); MS(CI): 279 (M^++1-100, 1), 277 (M^++1-102, 1), 276 (M^++1-103, 1), 248 (M^++1-103-28, 1), 198 (M^++1-181, 0.2).

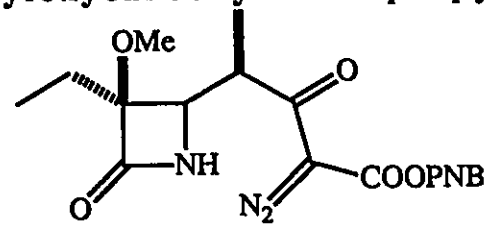
3-Ethyl-3-methoxy-4-(1'-methyl-3-p-nitrobenzyl-oxycarbonyl-2-oxopropyl)-2-azetidinone (106)



The acid **101** (75 mg, 0.37 mmol) was dissolved in 16 mL of MeCN and mixed with 90% pure CDI (81 mg, 0.44 mmol) in 2 mL of MeCN. After stirring for 3 h, this solution was added to the magnesium salt of mono p-nitrobenzyl ester of malonic acid (180 mg, 0.36 mmol) suspension in 10 mL of MeCN. The resulting reaction mixture was stirred at 60 °C for 18 h. The solvent was removed and the crude product was purified by column chromatography (1:2 EtOAc:hexanes) to yield 28 mg (20 %) of **106** as a white solid; ^1H NMR (200 MHz) δ: 0.92

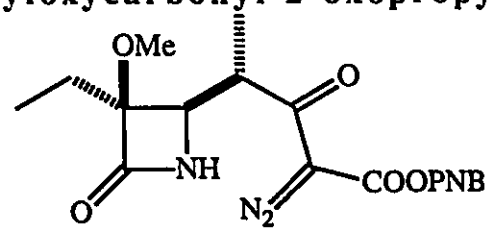
(3H, t, J=7.4 Hz, CH_3CH_2), 1.14 (3H, d, J=7.2 Hz, CH_3CH), 1.60-1.71 (1H, m, CH_2CH_3), 1.99-2.10 (1H, m, CH_2CH_3), 2.94-3.03 (1H, m, $CHCH_3$), 3.42-3.52 (4H, m with overlapping s at 3.48, CHN, OCH_3), 3.61 (2H, d, J=1.1 Hz, $COCH_2COOR$), 5.24 (2H, s, CH_2PNB), 6.05 (1H, broad s, NH), 7.49 (2H, d, J=8.8 Hz, PNB), 8.20 (2H, d, J=8.8 Hz, PNB); MS (CI): 379 (M^++1, 22), 351 (M^++1-28, 100), 336 (M^++1-43, 2), 333 (M^++1-46, 1), 279 (M^++1-100, 1).

3-Ethyl-3-methoxy-4-(1'-methyl-3'diazo-3'-p-nitrobenzyloxycarbonyl-2-oxopropyl)-2-azetidinone (115)



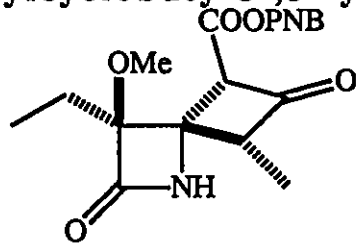
The β-ketoester **114** (16 mg, $4.23X10^{-2}$ mmol) in 2 mL of MeCN was added to 4-carboxybenzenesulfonazide (13 mg, $5.72\ x10^{-2}$ mmol) at 0 °C. TEA (0.024 mL, 0.172 mmol) was added by syringe. The solvent was removed after 1.5 h and the residue was purified by preparative thin layer chromatography (2:1 EtOAc:hexanes) to yield 14 mg (82%) of diazo compound **115** as an oil; IR: 3306 (NH), 2142 (N_2), 1755 and 1720 (C=O), 1523 and 1347 (NO_2); ^1H NMR (200 MHz) δ: 0.92 (3H, t, J=7.4 Hz, CH_3CH_2), 1.16 (3H, d, J=6.6 Hz, CH_3CH), 1.68-1.94 (2H, m, CH_2CH_3), 3.42 (3H, s, OCH_3), 3.70-3.86 (2H, m overlapping, CHN, $CHCH_3$), 5.35 (2H, s, CH_2PNB), 5.90 (1H, broad s, NH), 7.52 (2H, d, J=8.5 Hz, PNB), 8.23 (2H, d, J=8.8 Hz, PNB); MS (CI): 377 (M^++1-28, 0.2), 318 (M^++1-43-16, 0.2), 274 (M^++1-131, 6), 230 (M^++1-131-44, 2), 199 (M^++1-206, 1).

3-Ethyl-3-methoxy-4-(1'-methyl-3'-diazo-3'-p-nitrobenzyloxycarbonyl-2-oxopropyl)-2-azetidinone (107)



The diazo compound was prepared from β-ketoester **106** (28 mg, $7.4X10^{-5}$ mmol) in 80% yield after purification by column chromatography (1:2 EtOAc:hexanes) as described above; IR: 2146 (N_2), 1758 and 1721 (C=O), 1523 and 1347 (NO_2) cm^{-1}; ^1H NMR (200 MHz) δ: 0.95 (3H, t, J=7.4 Hz, CH_3CH_2), 1.11 (3H, d, J=6.8 Hz, CH_3CH), 1.61-1.76 (1H, m, CH_2CH_3), 2.10-2.12 (1H, m, CH_2CH_3), 3.51 (3H, s, OCH_3), 3.63 (1H, d, J=10.0 Hz, CHN), 3.71-3.86 (1H, dq, J=6.6, 10.0 Hz, $CHCH_3$), 5.35 (2H, s, CH_2PNB), 5.88 (1H, broad s, NH), 7.53 (2H, d, J=8.8 Hz, PNB), 8.24 (2H, d, J=8.8 Hz, PNB); MS (CI): 405 (M^++1, 1), 377 (M^++1-28, 29), 349 (M^++1-56, 77), 334 (M^++1-28-43, 1), 331 (M^++1-28-46, 1).

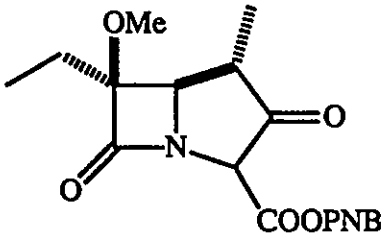
3-Ethyl-4,4-spiro(2'-p-nitrobenzyloxycarbonyl-1-oxo-4-methylcyclobuty-3',3'-yl)-2-azetidinone (117)



Benzene (2.5 mL) was distilled from a solution of the diazo compound **115** (14 mg, $3.46X10^{-5}$ mol) in about 5 mL of benzene. The remaining solution was cooled under nitrogen. About 0.1 mg of rhodium octanoate was added and the mixture was stirred at 25 °C for 18 h. Purification of the product by preparative thin layer

chromatography (2:1 EtOAc:hexanes) yielded 8 mg (61%) of spirocylic compound **117** as a foam; IR: 3304 (NH), 1768 (C=O), 1522 and 1346 (NO_2) cm^{-1}; ^1H NMR (300 MHz) δ: 1.12 (3H, t, J=7.5 Hz, CH_3CH_2), 1.21 (3H, d, J=7.5 Hz, CH_3CH), 2.09 (2H, q, J=7.5 Hz, CH_2CH_3), 3.33 (1H, q, J=7.4 Hz, overlapping with s from impurity, $CHCH_3$), 3.65 (3H, s, OCH_3), 3.72 (1H, s, COCHCOOR), 5.29 (1H, d, J=14.2 Hz, CH_AH_BPNB), 5.41 (1H, d, J=14.2 Hz, CH_BH_APNB), 6.07 (1H, broad s, NH), 7.60 (2H, d, J=8.9 Hz, PNB), 8.22 (2H, d, J=8.9 Hz, PNB); ^{13}C NMR (300 MHz) δ: 8.4 (CH_3), 17.0 (CH_3), 22.7 (CH_2), 41.1 (CH), 60.3 (CH), 64.6 (OCH_3), 76.2 (CH_2PNB), 104.1 (C-3), 123.7 (CH PNB), 127.7 (CH PNB), 143.6 (C), 147.5 (C), 162.7 (C=O), 166.5 (C=O), 166.8 (C=O) [one of these carbonyls should be from impurity and two quaternary carbons (C-4 and C=O) were not observed]; MS(CI): 377 (M^++1, 4), 347 (M^++1-30, 1), 316 (M^++1-30-31, 26), 288 (M^++1-30-31-28, 1), 241 (M^++1-136, 1).

p-Nitrobenzyl 3-ethyl-1-methyl-1-methoxy-2-oxocarbapenamcarboxylate (108)



The desired product **108** was obtained in 67% pure form (determined by NMR) by the reaction of 107 with rhodium ocanoate in refluxing benzene for 2h. The compound was found to decompose on silica gel and could not be completely characterised; IR: 1770, 1746 (C=O) cm^{-1}; ^1H NMR (300 MHz crude) δ: 1.03 (3H, t, J=7.4 Hz, CH_3CH_2), 1.20 (3H, t, J=7.0 Hz, CH_3CH), 1.77-2.24 (2H, m, CH_2CH_3), 2.76-2.88 (1H, apparent p, J=7.1 Hz, $CHCH_3$), 3.48 (3H, s, OCH_3), 3.60 (1H, d, J=7.2 Hz,

CHN), 4.20 (1H, s, COCHCOOR), 5.23 (1H, d, J=13.4 Hz, CH_AH_BPNB), 5.32 (1H, d, J=13.4 Hz, CH_AH_BPNB), 7.52 (2H, d, J=8.8 Hz, PNB), 8.22 (2H, d, J=8.8 Hz, PNB). [These NMR signals were obtained from a spectrum of crude sample using cosy experiment.]

CLAIMS TO ORIGINAL RESEARCH

1. Four novel isocephem analogs (2)**36**, (2)**37**, (2)**38** and (2)**39** were synthesized *via*. anionic 4+2 cyclization reaction using CS_2. The antibacterial activities of these compounds have been studied. The MIC values indicated that these compounds are inactive as antibiotics.

2. Two carboxylic acids (3)**77** and (3)**83** suitable for preparation of carbacephem intermediates, were obtained by Wittig reaction involving benzyl triphenylphosphoranylideneacetate and hydrogenation resulting in reduction of the double bond as well as debenzylation.

3. 7-Ethyl-7-methoxycarbacephem analog (3)**61** was prepared by applying rhodium carbenoid insertion. This compound was also inactive as an antibiotic.

4. Nitromethane was utilized as a formyl dianion synthon to prepare the β-ketoester (4)**135** which served as a key intermediate for carbapenems.

5. p-Nitrobenzyl ester of 6-methoxy-PS-5 (4)**137** was prepared by rhodium carbenoid insertion. Deprotection by hydrogenolysis appeared to afford an unstable carbapenem which could not be purified.

6. 6-Methoxy-1-α-methylcarbapenem intermediate (5)**100** and its 1-β-methyl epimer (5)**104** were prepared *via*. a stereodivergent approach involving chelation controlled and non-chelation controlled reduction of azetidinone (5)**98**.

7. The rhodium carbenoid cyclization of (5)**115** gave a rather unusual product (5)**117**. The formation of this product indicate that C-H insertion reaction occurs in preference to N-H insertion when a severe steric congestion disfavors the latter process.

PUBLICATIONS FROM THIS THESIS

*Durst, T.; Shakya, S. **Anionic 4+2 cyclization route to 3-sulfur substituted isocephem analogs.** *Heterocycles* **1992**, *34*, 67.

*Durst, T.; Shakya, S. R. **Studies on novel carbacephems: Synthesis of 7-methoxyhomo-PS-5 and 7-methoxy-8-epihomo-thienamycin.**

(manuscript accepted for publication in Can. J. Chem.)