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APPROACHES TO β-LACTAM SYNTHESIS

1. Δ-1 CARBAPENEMS
2. 1-(DIALKYLAMINOMETHYL)-AZETIDIN-2-ONES
3. Δ-3 CARBACEPHEMS

by

Arvad Bevin Hamlet

Thesis submitted to the School of Graduate Studies in partial fulfillment for the requirements for the degree of M.Sc. in Chemistry

University of Ottawa

Ottawa, Ontario

To Joan, Tanya, and Tracy

ABSTRACTS

1. Δ-1 Carbapenems

A model study directed towards the synthesis of the Δ-2 carbapenem ring system of thienamycin, via the Δ-1 isomer, was investigated.

Michael adducts were formed by reacting the N-lithio salt of 4-vinylazetidin-2-one with vinyl phosphonates bearing a phenyl group and an oxidised sulfur substituent. Ozonolysis of these adducts in CH_2Cl_2 at - 78°, followed by treatment with 1 equivalent of NaH in THF, gave Δ-1 carbapenems. The sulfur and phenyl substituents, respectively, occupied the C_2 and C_3 positions of the thienamycin nucleus.

Attempts of Michael addition onto vinyl phosphonates, bearing a carboxylate function, as present at the C_3 position of thienamycin, were not successful.

2. 1-(Dialkylaminomethyl)-Azetidin-2-ones

The use of dialkylaminomethyl derivatives as a new β-lactam N-H protecting group was investigated. The group was found to be stable to basic reagents but easily removed with dilute aqueous acids. 1-Dialkylaminomethyl derivatives bearing a 4-substituent were converted in good yield and in high stereoselectivity into trans-3,4-disubstituted derivatives via reaction with LDA and subsequent addition of electrophiles. The products of several of these sequences are of interest as intermediates to thienamycin related substances.

3. Δ-3 Carbacephems

The 4-(3'-butenyl)-azetidin-2-one was used to synthesise the Δ-3-carbacephem- and the trans-7-hydroxyethyl-Δ-3-carbacephem-4-carboxylic acids. The trans hydroxyethyl side chain was introduced stereoselectively via the reaction of the 3-lithio salt of the key intermediate 1-pyrrolidinomethyl-4-(3'-butenyl)-azetidin-2-one, either with acetaldehyde or with ethyl acetate followed by K-Selectride or $NaBH_4$ reduction.

Opposite stereochemical preferences were observed in the K-Selectride and $NaBH_4$ reductions. K-Selectride reduction produced approximately a 9:1 ratio of trans (R) vs trans (S) isomers in the hydroxyethyl side chain, whereas a 1:2 ratio [trans (R) vs trans (S)] was observed for $NaBH_4$.

ACKNOWLEDGEMENTS

I am especially indebted to the following:

Professor T. Durst for his guidance, patience, advice, encouragement and zeal throughout my studies;

Other members of staff of the Chemistry Department;

Margie Glinski for her constructive comments and helpful suggestions;

My wife Joan for her understanding, encouragement and support throughout the course of this work.

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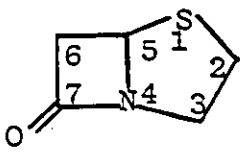

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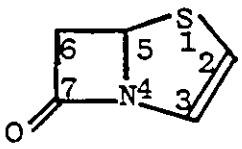

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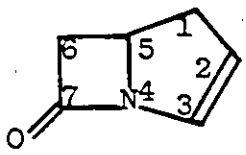
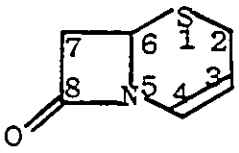


Δ-2-carbapenem



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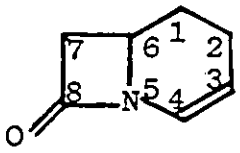


Δ-3-carbacephem

ABBREVIATIONS

IR - infrared

NMR - ^{1}H nuclear magnetic resonance

TLC - thin layer chromatography

THF - tetrahydrofuran

MCPBA - m-chloroperbenzoic acid

M.S. - mass spectrum

M^{+} - parent molecular ion

$NaBH_4$ - sodium borohydride

LDA - lithium diisopropyl amide

DMS - dimethyl sulfide

DMAP - 4-(dimethylamino)pyridine

NaH - sodium hydride

$SOCl_2$ - thionyl chloride

PPh_3 - triphenyl phosphine

nBuLi - n-butyllithium

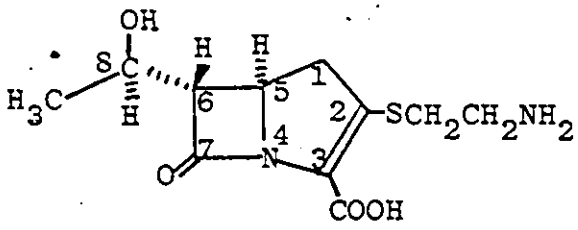
DBN - 1,5-diazobicyclo-4,3,0-non-5-ene

^{13}C NMR - ^{13}C nuclear magnetic resonance

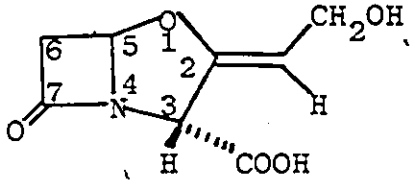
PNB - p-nitrobenzyl

1 INTRODUCTION

The synthesis of β-lactam antibiotics has long been an extensive area of research. However, interest has intensified over the last six years, since the discovery of thienamycin 1 and clavulanic acid 2. Thienamycin 1, isolated from Streptomyces cattleya (1), is a rather unusual bicyclic β-lactam antibiotic. On the other hand, clavulanic acid 2, isolated from Streptomyces clavuligerus (2), acts as a β-lactamase inhibitor.



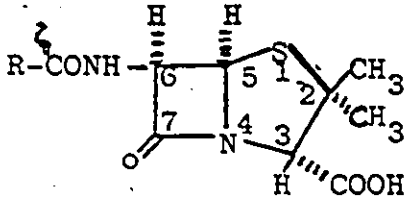
1



2

Thienamycin 1, has three structural features not found in the well-known penam and cephem antibiotics, the penicillins 3 and cephalosporins 4, respectively: (1) an α-hydroxyethyl side chain instead of a β-amido side chain at C-6; (2) a cysteamine side chain at position 2; and (3) a highly strained nucleus consisting of an unsaturated five membered ring fused to a β-lactam, in which a methylene group

replaces the sulphur, found in conventional ß-lactam antibiotics, at position 1 (3).



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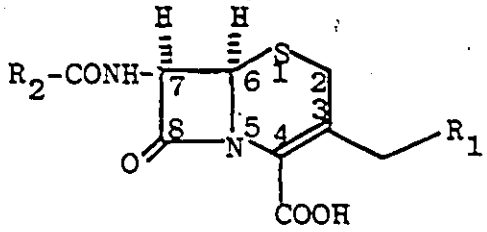


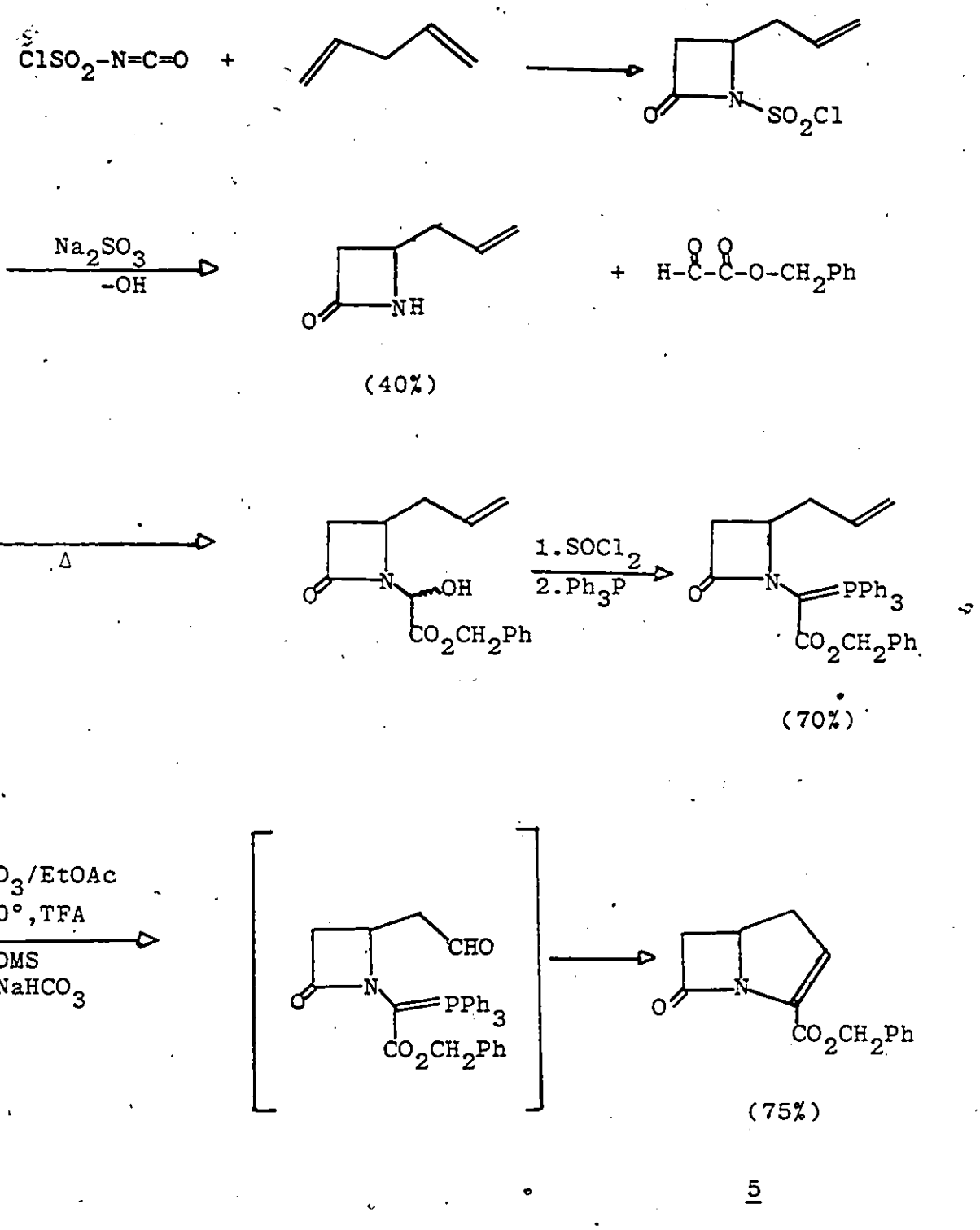
4

R= $-CH_2O-Ph$	Penicillin V	R_1= $-OCOCH_3$	Cephalosporin C
R= $-CH_2Ph$	Penicillin G	R_2= $-(CH_2)_3CHNH_2$ COOH	
R= $-CH_2CH=CHCH_2CH_3$	Penicillin F		
R= $-n-C_7H_{15}$	Penicillin K	R_1= -H	Cephalexin
		R_2= $-CH(NH_2)Ph$	

More interestingly, thienamycin 1 also displays unusually broad spectrum antibacterial activity. It is highly potent against both gram-positive and gram-negative bacteria, and is resistant to bacterial ß-lactamases (1).

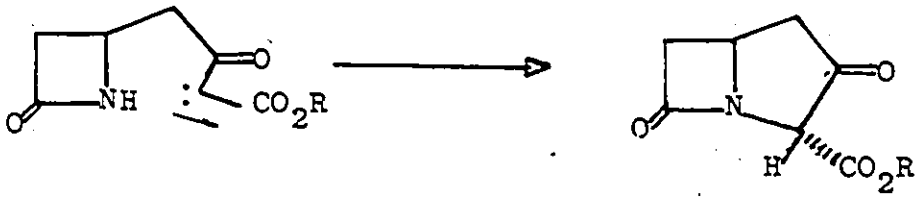
Over the past four years, several routes have been described for the synthesis of the carbapenem ring system of thienamycin. For example, Southgate and coworkers (4) reported the synthesis of this system, using an intramolecular Wittig reaction to form the Δ-2 double bond. (Scheme 1)

Scheme 1


ClSO2-N=C=O +
SO2Cl
Na2SO3
-OH
NH
+ H-C-C-O-CH2Ph
(40%)
Δ
OH
CO2CH2Ph
1.SOCl2
2.Ph3P
PPh3
CO2CH2Ph
(70%)
1.O3/EtOAc
-70°,TFA
2.DMS
3.NaHCO3
CHO
PPh3
CO2CH2Ph
CO2CH2Ph
(75%)

5

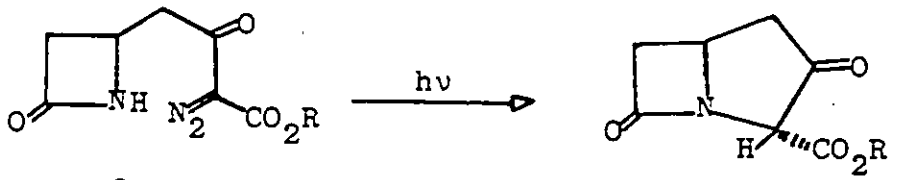
Christensen et al (5) have developed a novel synthesis for this carbapenem ring system, using a highly efficient carbene insertion reaction. The bicyclic nucleus was produced via the formation of the N-C_3 bond, as outlined in equation 1.



(1)

6 7

The generation of the carbene was effected through the decomposition of the α-diazo-ß-ketoester 8. Photochemical decomposition gave a 1:9 mixture of the desired product 7 and the relatively unstable imide isomer 9. Metal (rhodium (II) acetate) catalyzed decomposition, however, produced 7 as a single isomer in near quantitative yield.



8 7

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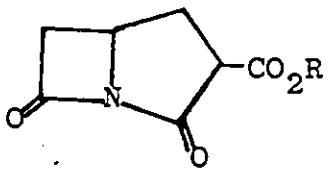

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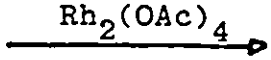
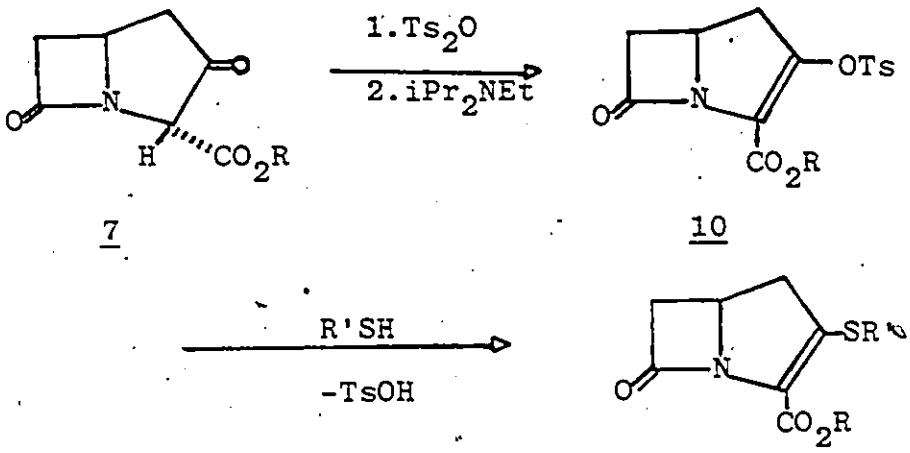
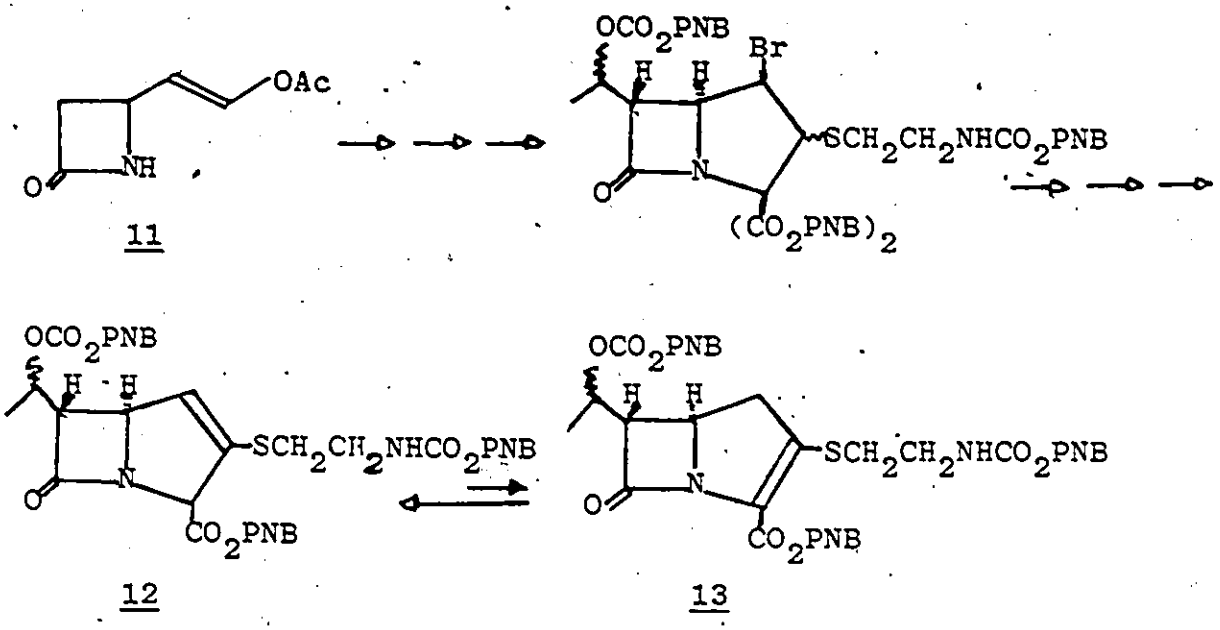


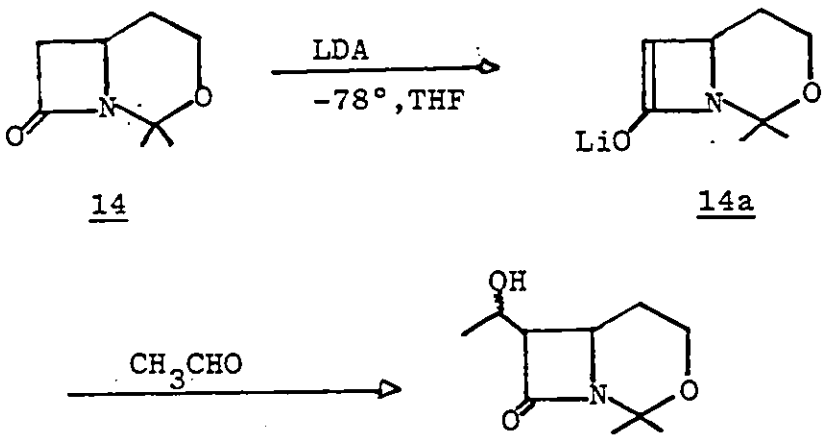
Tosylation of the bicylic ketoester 7 provided the carbapenem ring system as the vinyl tosylate 10. Thienamycin derivatives could be prepared from 10 by treatment with various mercaptans, the transformation occurring via an addition-elimination process.



Several groups have described an approach to the Δ-2 carbapenem system via isomerization of the Δ-1 system. For instance, Johnston and coworkers (6) prepared the Δ-1 carbapenem 12, as an intermediate, in the first thienamycin synthesis. The derivative 12 was prepared starting from 11 via a lengthy series of reactions comprising of at least eighteen steps. (Some aspects of this synthesis are discussed on page 6). Partial isomerization of 12 with diisopropylamine in DMSO gave a 4:1 mixture of 12 and the thienamycin derivative 13.

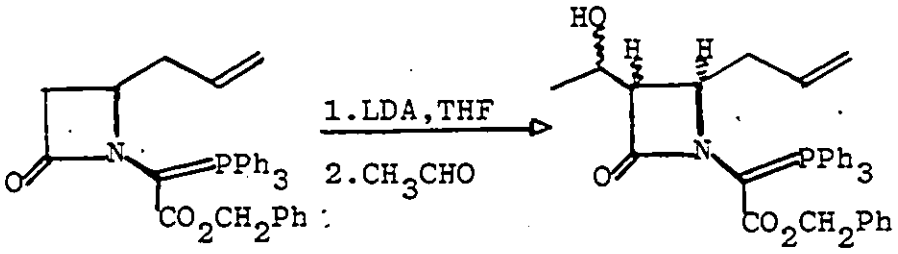


In their synthesis of thienamycin, Johnston et al (6) introduced the hydroxyethyl side chain by a condensation reaction between the lithio derivative 14a and acetaldehyde.



The introduction occurred with considerable trans:cis stereoselectivity but with almost no control over the side chain stereochemistry. The various isomers were separated and the appropriate one converted to thienamycin.

Southgate et al (4) were able to introduce the hydroxyethyl side chain by hydroxyalkylating the phosphorane 15 at -78°. Again, the introduction occurred with limited selectivity. Cyclization of the intermediate 16 (obtained in 65% yield) gave, after silica gel chromatography, 9% cis 17 and 29% of trans 18 isomers.



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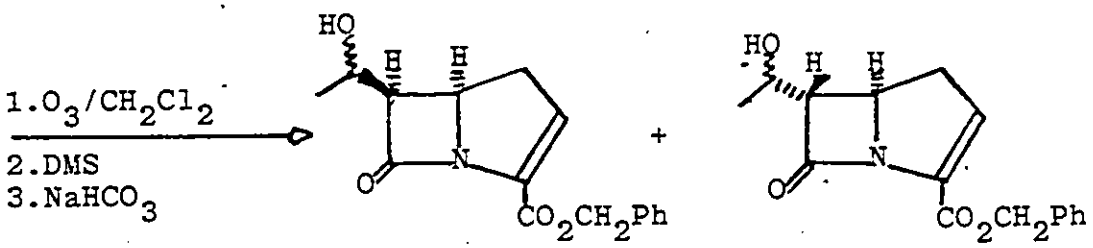
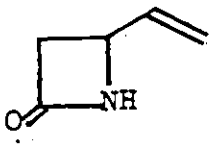


17 18

At the time this work was begun *, a stereoselective introduction of the hydroxyethyl side chain had not been developed. It was therefore decided to investigate this aspect. In addition, the use of the monocyclic ß-lactams 19 and 20 as potential starting materials for carbapenem and carbacephem ring systems, respectively, was planned.



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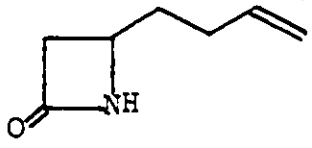

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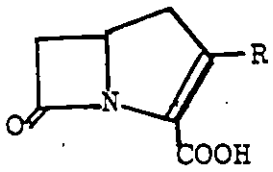
* In the two year time interval between the completion of the experimental work and the writing of this thesis, a number of important developments have been reported pertaining to the thienamycin problem. These will be described wherever appropriate in the subsequent chapters of this thesis.

2 SYNTHESIS OF Δ-1 CARBAPENEMS

Introduction

It has been established that antibiotic activity in carbapenems resides essentially only in the isomers 21 bearing the double bond in the Δ-2 position (7). The Δ-1 isomers 22 prepared to date (6,8,9) do not show significant biological activity.



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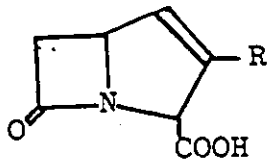
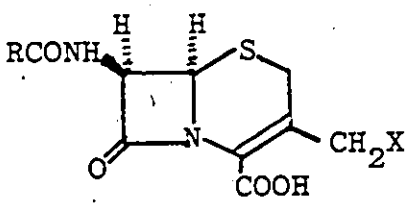
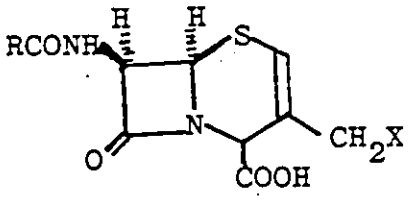


21 22

A parallel situation exists in the cephalosporins where the Δ-3 isomers 23 are active but the Δ-2 isomers 24 are not (10). The difference in biological activity has been explained in terms of the increasing acylating power of the isomers in which the nitrogen lone pair is conjugated with the double bond; thereby resulting in less overlap with the carbonyl group and hence a weaker OC-N bond (11).

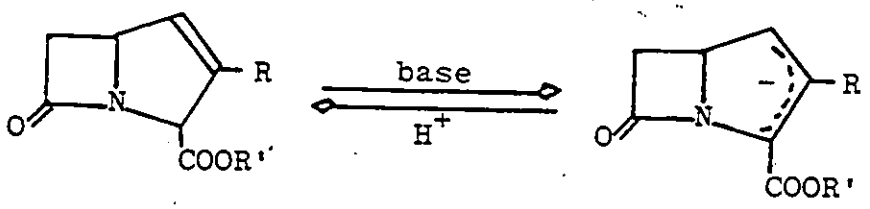


vs



23 24

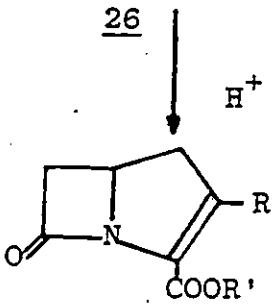
Thus, Δ-1 isomers of thienamycin and derivatives thereof, have not been primary synthetic targets. However, in the first reported thienamycin synthesis, Christensen and coworkers (6) prepared the protected Δ-1 isomer 12, which was isomerized to the desired Δ-2 derivative 13 upon heating with diisopropylamine in DMSO. The equilibration favoured the Δ-1 over Δ-2 isomer by a ratio of 4:1 and thus the yield of the desired material was quite low. Other authors (8,9) have also found that the Δ-1 ⟶ Δ-2 carbapenem isomerization is unfavourable via a base catalyzed process involving the allylic anion 26.



25

a[8] R = CO_2Et
R' = tBu

b[9] R = CH_2OCOPh
R' = PNB

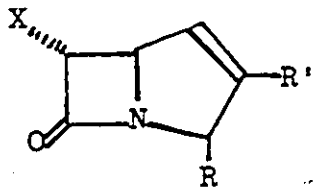


Despite the lack of activity in the Δ-1 derivatives and the difficulty experienced in converting these compounds to the active Δ-2 isomers, we nevertheless felt that an efficient synthesis of Δ-1 carbapenems would be of considerable value. The enhanced stability of the Δ-1 over the Δ-2 isomers would allow for chemical manipulation and thereby facilitate investigation into the reactivity of the carbapenems. Furthermore, a viable Δ-1 carbapenem synthesis presumably could provide the impetus for development of methods of isomerization.

Results and Discussion

Retrosynthetic analysis of the Δ-1 carbapenems shown in Scheme 2 suggested that the double bond and the five-membered ring might best be introduced via an intramolecular Wittig or Horner-Wittig reaction. The aldehydic intermediate 30 should readily be generated by ozonolysis of the C=C in 29. It was anticipated that 29 might be assembled in a one step Michael addition reaction involving the readily available N-lithio- or N-sodio β-lactam 28 and a suitably substituted vinyl phosphonate 27.

Consideration of this scheme indicated that it should be suitable for the preparation of Δ-1 carbapenems bearing a variety of groups in the C_2 position depending on the structure of the vinyl phosphonate used in the Michael addition reaction. Furthermore, a variety of substituents can readily be introduced into the 3 position (position 6 in the carbapenem) of the other starting material, 4-vinyl-azetidin-2-one 19, with considerable stereochemical control (See Chapter 3) and thus a successful development of the above scheme would yield a carbapenem of the general type 31.



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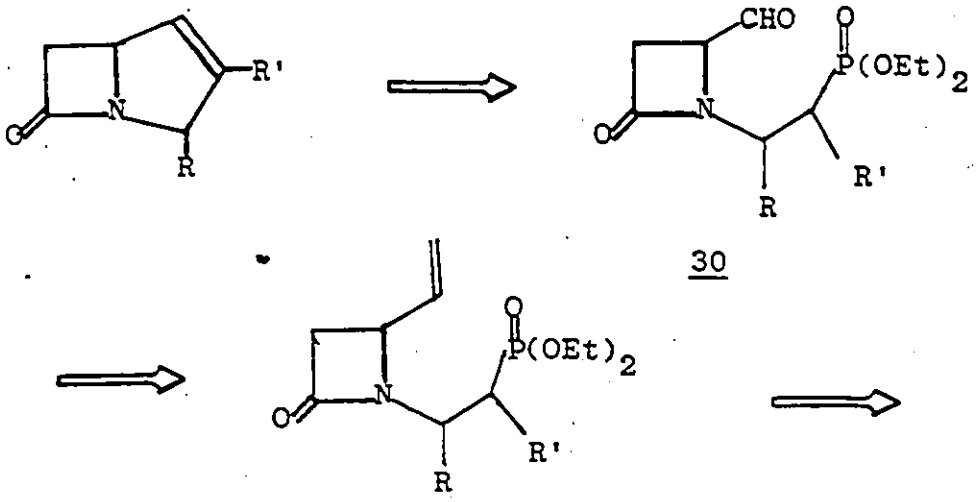
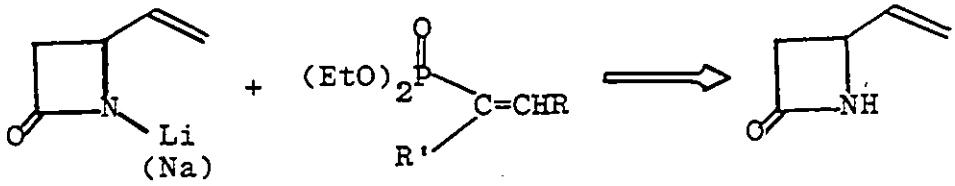
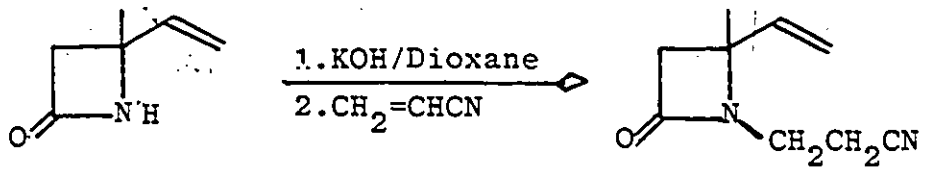
Scheme 2



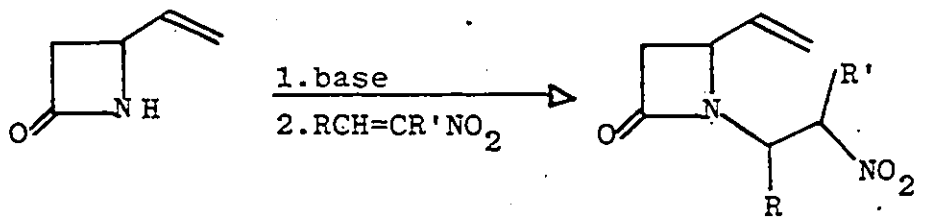


28 27 19

Several examples of Michael addition reactions involving 4-vinylazetidin-2-one have been demonstrated in this laboratory. For example, Lebelle obtained 33 in 92% yield, when 32 was reacted with acrylonitrile and potassium hydroxide in dioxane (12). Hyrtsak also found that 19 added to a variety of nitro-olefins to afford 34 in good yields (13).



32 33

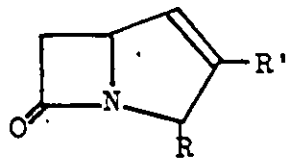


19 34

R = Ph R' = H

R = CH_3 R' = CH_3

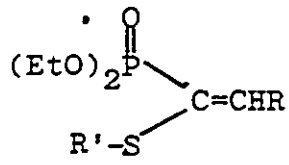
At the time this work was begun, Venugopalan and Durst (14) has already demonstrated the viability of Scheme 3. They found that Michael addition of the N-lithio salt of 19 to vinyl phosphonates gave adducts, which upon ozonolysis and base treatment provided the Δ-1 carbapenems 35.



35

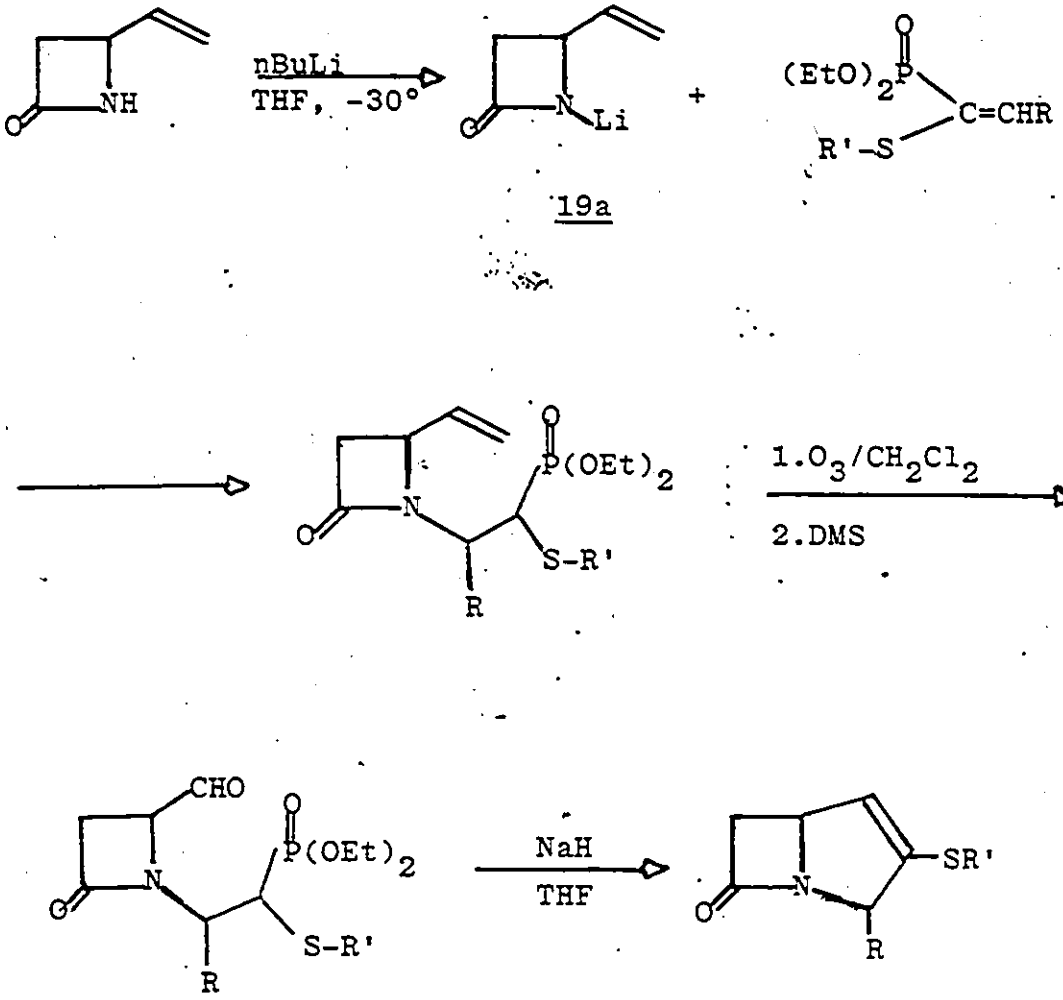
a	R = H	R'	= CO_2Et
b	R = H	R'	= CO_2tBu
c	R = Ph	R'	= CO_2Et
d	R = CO_2tBu	R'	= CO_2Et

It was therefore felt that through sulfur stabilized carbanions, addition could be achieved onto vinyl phosphonates of type 36. Cyclisation would afford the carbapenems with a C_2 sulfur bearing substituent, which would serve as a precursor for the cysteamine side chain present in thienamycin.



36

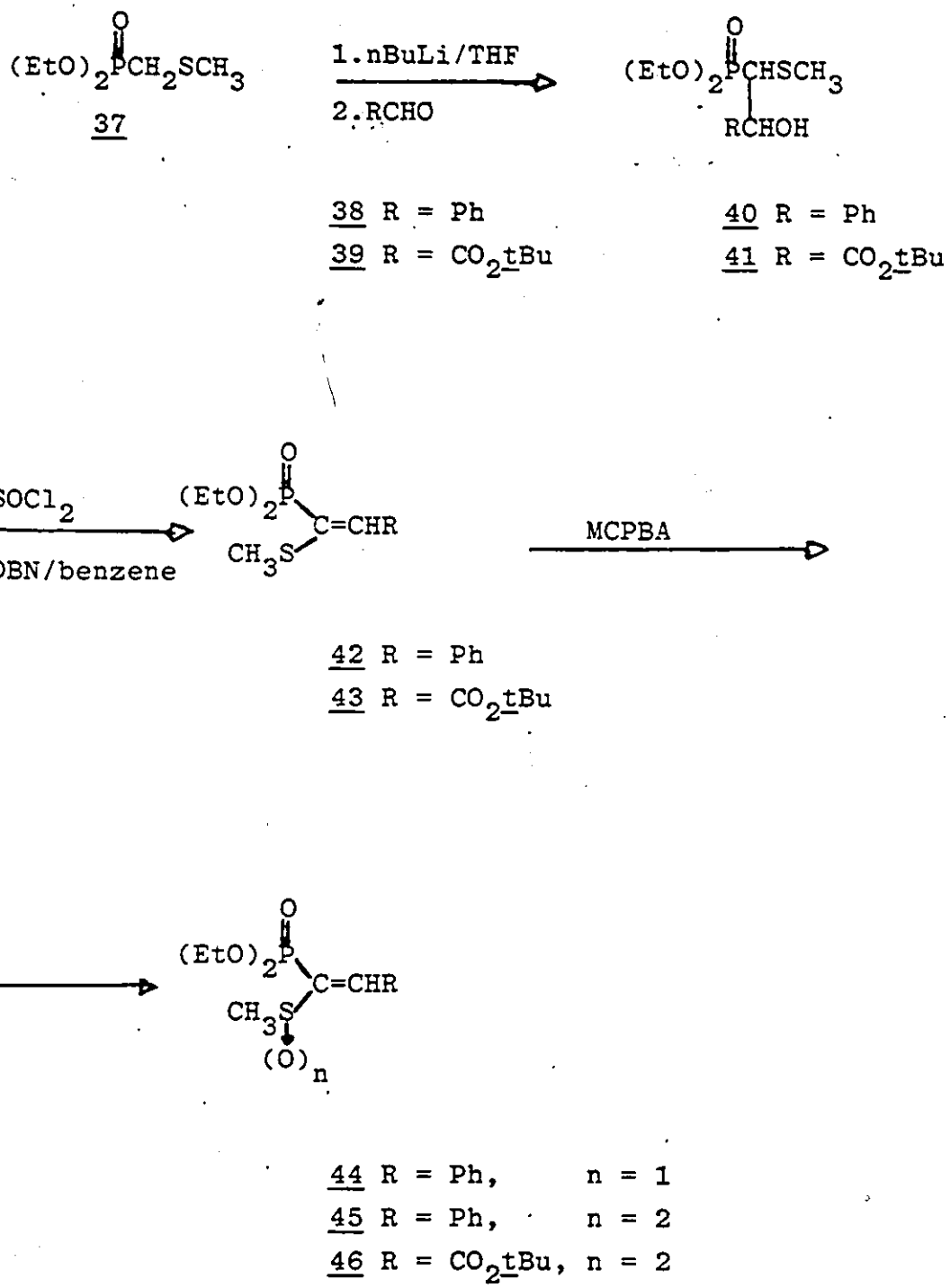
Scheme 3


nBuLi
THF, -30°
NH
N
Li
(EtO)2P
C=CHR
R'-S
19a
P(OEt)2
S-R'
R
1.O3/CH2Cl2
2.DMS
CHO
P(OEt)2
S-R'
R
NaH
THF
SR'
N
R

Preparation of vinyl phosphonates

Scheme 4 outlines the preparation of the different vinyl phosphonates used in this study.

Scheme 4



38 R = Ph
39 R = CO_2tBu

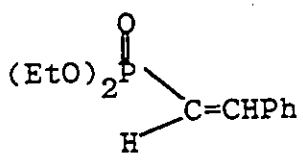
40 R = Ph
41 R = CO_2tBu

42 R = Ph
43 R = CO_2tBu

44 R = Ph, n = 1
45 R = Ph, n = 2
46 R = CO_2tBu, n = 2

The key starting compound 37, NMR: δ = 3.5 (t,J=7Hz,6H), 2.3 (s,3H), 2.7 (d,J=13Hz,2H), 4.2 (p,J=7Hz,4H), was obtained in 58% yield by refluxing $(EtO)_3P$ and CH_3SCH_2Cl at 150° for 5 hours (15). Reaction of 37 with nBuli in THF at -78°, followed by condensation with benzaldehyde gave the hydroxy adduct 40 as an isomeric mixture in 97% yield. Compound 40 was chlorinated with thionyl chloride, then treated with DBN (16) in benzene to afford the olefin 42, NMR: δ = 1.4 (t,J=7Hz,6H), 2.45 (s,3H), 4.22 (p,J=7Hz,4H), 7.3-7.9 (m.6H), as a single isomer (17), in 44% overall yield.

The chloro compound was relatively stable and could be purified by column chromatography. However, when the reaction sequence was completed without purification of the chloride, a minor olefinic product, NMR: δ = 1.34 (t,J=7Hz,6H), 4.1 (p,J=7Hz,4H), 6.17 (t,J=18Hz,1H), 7.47 (t,J=18Hz,1H), 7.2-7.4 (m,5H), was isolated. This exhibited a molecular ion peak at m/e = 240 on its mass spectrum and was assigned the structure 47.



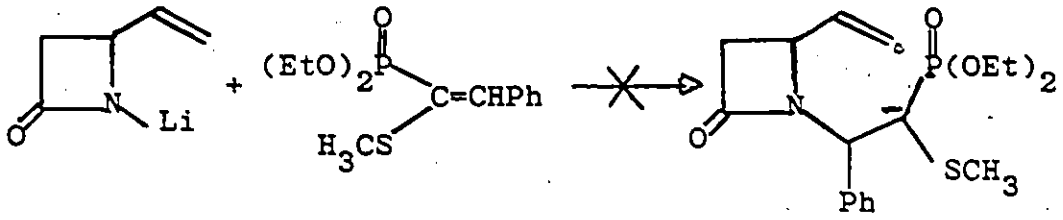
47

Oxidation of the sulfide 42 with two equivalents MCPBA furnished the sulfone 45, NMR: δ = 1.16 (t,J=7Hz,6H), 3.33 (s,3H), 4.13 (p,J=7Hz,4H), 7.3-7.8 (m,5H), 8.23 (d,J=23Hz,1H), in 73% yield after chromatography. Similarly, with one equivalent MCPBA, the sulfide 42 yielded 72% of the sulfoxide 44. NMR: δ = 1.5 (t,J=7Hz,6H), 3.1 (s,3H), 4.15-4.55 (m,4H), 7.5 (s,5H), 8.05 (d,J=21Hz,1H).

Michael Addition and Cyclisation reactions

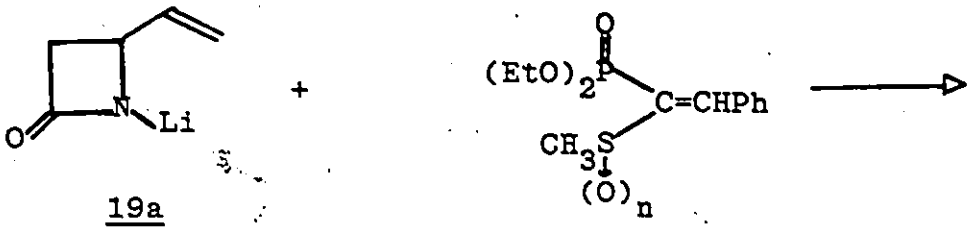
The Michael addition reactions were carried out by adding the phosphonate to a solution of 19a, prepared from 4-vinylazetidin-2-one and one equivalent of nBuLi in THF, at -30°. The reaction mixture was stirred for 30 minutes, quenched with aqueous ammonium chloride, and the crude product purified by column or preparative thin layer chromatography (p.t.l.c.).

In this manner, when 19a was reacted with 42, no Michael adduct was formed. This was indicated by the NMR spectrum, which showed the presence of both starting materials. It seemed evident that the SCH_3 and phosphonate groups were not effective enough in stabilizing the anion 48, therefore the addition of 19a to phosphonates bearing an oxidized sulfur substituent was investigated.

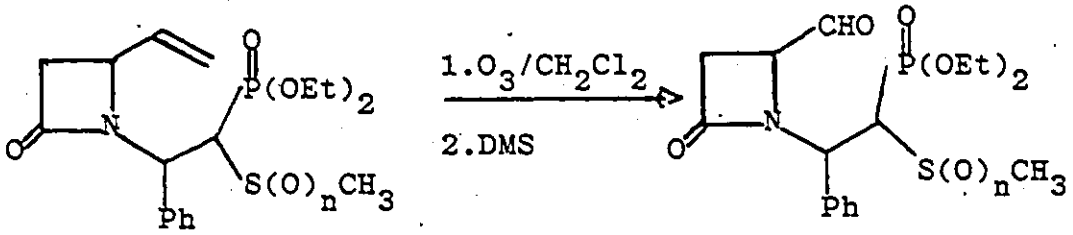


19a 42 48

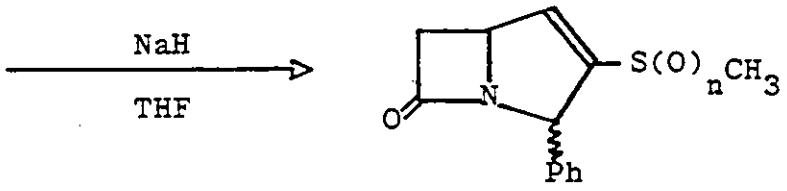
Thus, compound 50 was obtained on reaction of the sulfone 45 with 19a, in 61% yield. The NMR spectrum of 50 was very complex and the infrared spectrum showed a strong β-lactam absorption at 1750 cm^{-1} and bands at 1150 and 1330 cm^{-1}, indicative of the sulfone function. Ozonolysis and cyclisation of 50 using sodium hydride in THF for 7 hours gave the carbapenem 52, as a 2:1 mixture of isomers, in 50% yield. The isomers were separated by thin layer chromatography. Both the major, m.p. 115-120°, and minor isomer m.p. 144-146°, showed strong infrared absorption at 1780, 1310 and 1150 cm^{-1}. The major isomer had NMR resonances at δ = 2.36 (s,3H), 3.1-3.6 (m,2H), 4.5-4.7 (m,1H), 5.38 (q,J=2Hz,1H), and 7.2-7.5 (m,6H). NMR peaks for the minor isomer occurred at δ = 2.36 (s,3H), 3.10 (dd,J=16,3Hz,1H), 3.56 (dd,J=16,6Hz,1H), 4.8-4.9 (m,1H), 5.90 (q,J=2Hz,1H).



19a



49 n = 1
50 n = 2



51 n = 1
52 n = 2

Similarly, 49 was obtained in 80% yield by the reaction of 19a with the sulfoxide 44. Again, the NMR spectrum was very complex but strong infrared absorption was observed at 1060 and 1750 cm^{-1}. Ozonolysis and subsequent NaH treatment of 48, afforded the carbapenem 51 in 31% yield,

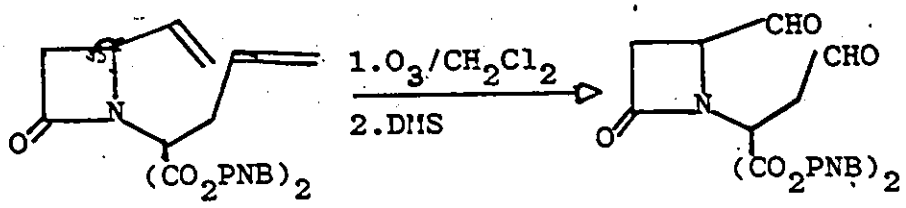
accompanied by 9% of the sulfone 52, due to inadvertent oxidation of the sulfoxide during the ozonolysis reaction. The NMR spectrum of 51 indicated a mixture of isomers. No attempt was made to separate these isomers. However, oxidation of 51 with one equivalent of MCPBA clearly gave the sulfone 52, again as a 2:1 mixture of isomers. The exo vs endo phenyl group stereochemistry of these isomers has not yet been assigned.

An attempt was then made to extend the above model study into a synthesis of a thienamycin derivative. In this regard, it was envisaged that the vinyl phosphonate 43, through its t-butyl ester function, would be a feasible precursor for the carboxylate found at C_3 in thienamycin.

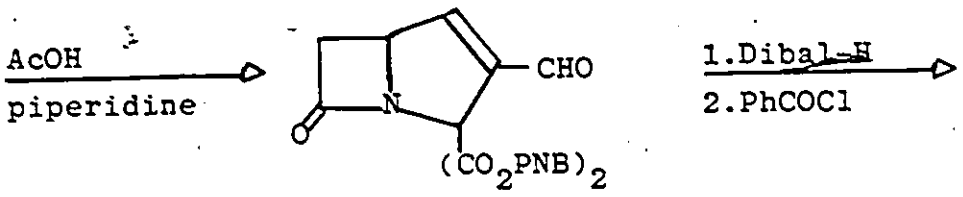
The t-butyl glyoxylate required for the formation of 43 was not available commercially and therefore was prepared in the following manner. Fumaryl chloride was esterified with t-butyl alcohol (18), to give di-t-butyl fumarate, NMR: δ = 1.5 (s,18H), 6.6 (s,2H), which upon ozonolysis afforded 50% of t-butyl glyoxylate 39. Condensation with 37 provided the hydroxy compound 41, which was chlorinated and dehydrohalogenated to afford 43. NMR: δ = 1.4 (t,J=7Hz,6H), 1.5 (s,9H), 2.6 (s,3H), 4.2 (p,4H), 6.8 (d,J=21Hz,1H). Oxidation of 43 to the sulfone 46, NMR: δ = 1.4 (t,J=7Hz,6H), 1.5 (s,9H), 3.1 (s,3H), 4.1-4.6 (m,4H), 6.8 (d,J=21Hz,1H), was effected in 76% yield, with two equivalents MCPBA.

In the manner described above, Michael addition reactions were then attempted. When 19a was reacted with 43 however, no adduct was formed; instead, both starting materials were isolated. Similarly, reaction between 19a and the sulfone 46 was also unsuccessful. Examination of the crude product by NMR indicated that most of the SO_2CH_3 group had been lost. The crude product was separated by preparative thin layer chromatography and furnished some recovered 4-vinylazetidin-2-one together with a small amount of material which could not be identified. This product was not further characterized. The failure of 46 to undergo a Michael addition reaction with 19a was a great disappointment; the reason is not obvious especially since it was anticipated that 46 should be a better Michael acceptor than the model compounds 44 and 45. Because of its reactivity, the possible polymerization of 46 is probably responsible for its absence in the recovered material.

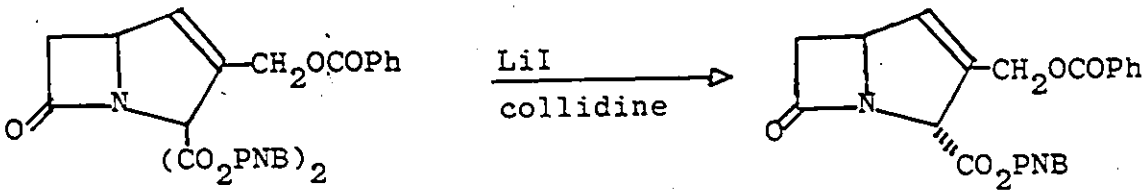
Since this work has been completed, a number of authors have reported approaches towards the thienamycin synthesis via the Δ-1 isomer. For example, Hirai et al (9) formed the Δ-1 carbapenem by an aldol condensation reaction between the C_1 and C_2 positions. The dialdehydic compound 54, formed by ozonolysis and DMS treatment of 53, was reacted with piperidine and acetic acid to give Δ-1 carbapenem derivative 55 in 25% yield.



53 54



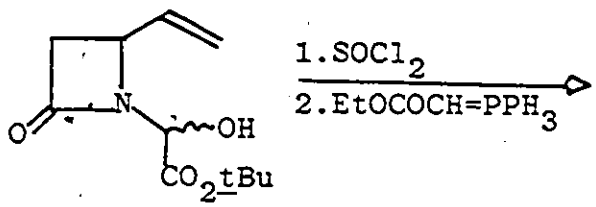
55



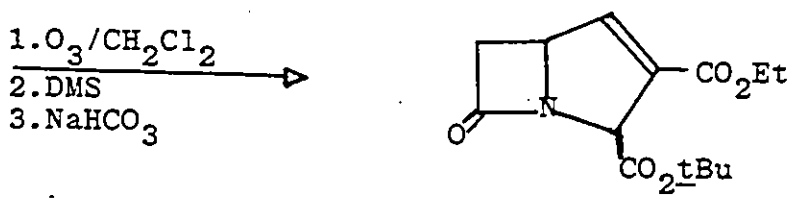
56 57

Careful reduction of the aldehyde 55 to the allylic alcohol, followed by treatment with benzoyl chloride gave the benzoyl derivative 56. Decarboalkoxylation of 56 with LiI in collidine yielded the Δ-1 penem 3-carboxylate 57 (52%). However, attempts at isomerization of the double bond to the Δ-2 position were not successful.

More recently, Stoodley and Sharma (8) utilised an intramolecular Wittig reaction to construct the Δ-1 carbapenem system. The carbinol 58, was obtained from reaction of 4-vinylazetidin-2-one and t-butyl glyoxylate, in 80% yield. Treatment with thionyl chloride converted 58 to the chloride, which was immediately reacted with ethoxycarbonyltriphenyl phosphorane, to provide the phosphorane 59 (44%). Ozonolysis of 59 followed by treatment with DMS and sodium bicarbonate, afforded the Δ-1 carbapenem 60. Again, attempts at conversion to the Δ-2 isomer via base catalysis were not fruitful.



58 59



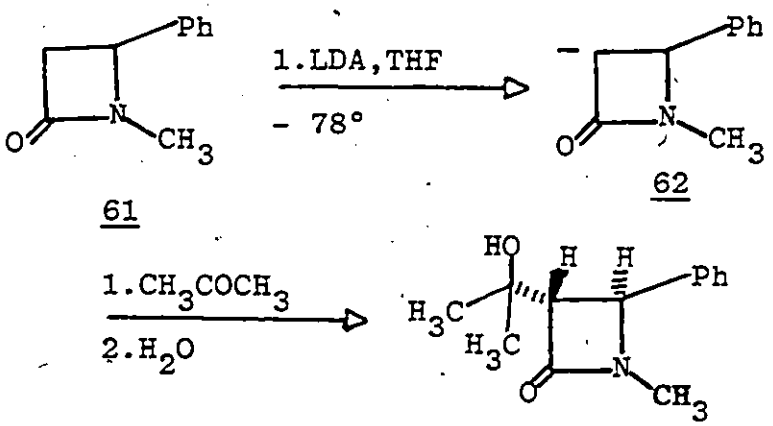
60

3 THE DIALKYLAMINOMETHYL FUNCTION AS A BASE STABLE, β-LACTAM NITROGEN PROTECTING GROUP

Introduction

Any approach towards thienamycin's synthesis necessitates stereoselectivity in the introduction of the α-hydroxyethyl side chain and control of the stereochemistry at C_8. Attempts to resolve this problem have been directed towards the use of a suitable β-lactam N-blocking group, thereby allowing generation of the monoanion at C_6 and subsequent C-C bond formation.

Several years ago in this laboratory, Durst *et al* (19) demonstrated the utility and reactivity of β-lactam enolates. For example, it was shown that N-substituted β-lactams such as 61 gave, via monoanion 62, almost exclusively N-alkylated *trans* 3,4-disubstituted products.

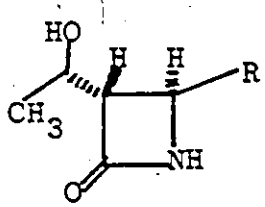


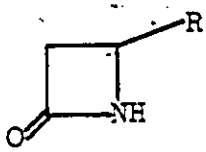
These results suggested that the use of an appropriate N-blocking group would allow considerable stereoselectivity in the introduction of the α-hydroxyethyl side chain present in thienamycin. Such a group would have to be base stable and easily removable under mild acidic conditions to provide the free N-H, thereby enabling the pursuit of the bicyclic nucleus.

Accordingly, Christensen and coworkers (6) employed the acetonide 14 as the N-blocking group in the first total synthesis of thienamycin. The hydroxyethyl side chain was introduced via a condensation with acetaldehyde and the enolate 14a, with a significant amount of the desired trans stereochemistry, but without control over the side chain stereochemistry. Other reports (4,20) have also indicated that very little stereocontrol is exerted at C_8 when hydroxyethylation is effected through condensation of the monoanion with acetaldehyde.

Of particular interest as potential starting points to thienamycin or derivatives thereof, are trans-3-(1'-hydroxyethyl)-4-vinylazetidin-2-one 63, and trans-3-(1'-hydroxyethyl)-4-(3'-butenyl)azetidin-2-one 64, since the corresponding 3-unsubsituted derivative 19, has been used to prepare thienamycin itself (6), and the Δ-1 carbapenem (8,9,14) ring system, and 20 has been used to prepare carbacephems and carbapenams (21). In this chapter methods

which are suitable either for the preparation of 63 and 64 both as a 1:1 mixture of side chain isomers, and highly enriched in the desirable thienamycin stereochemistry are described. These methods are based, in part, on the use of the dialkylaminomethyl function as a base-stable, β-lactam nitrogen protecting group.

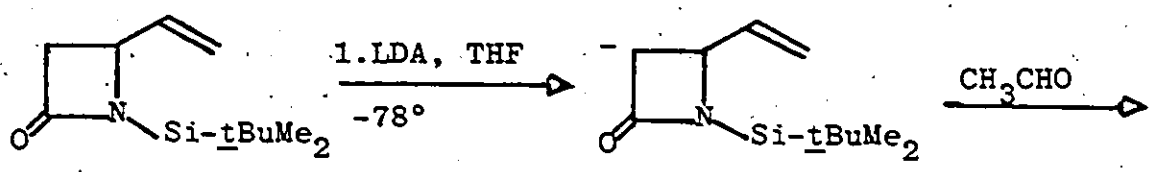




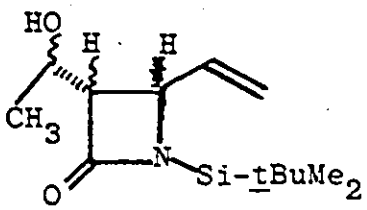
63	R = $CH{=}CH_2$	19	R = $CH{=}CH_2$
64	R = $CH_2CH_2CH{=}CH_2$	20	R = $CH_2CH_2CH{=}CH_2$

Results and Discussion

The tert-butyldimethylsilyl group has previously been used as an N-protecting group in β-lactams (5). This group is stable to alkyl lithiums and allows the generation of the monoanion 65a through which a variety of substituents can be introduced at position 3 (position 6 in thienamycin) of the β-lactam ring. Most recently, Bouffard and Christensen (22) completed a careful study of introduction of the thienamycin side chain onto the 1-tert-butyldimethylsilyl-4-vinylazetidin-2-one 65. These authors reported that under a variety of conditions the monoanion 65a reacted with acetaldehyde to give an 84:16 mixture of trans:cis isomers. The trans isomer was obtained as an approximate 1:1 mixture of (R) and (S) side chain isomers. Considerably higher ratios of the desirable trans R-isomer (thienamycin isomer) could be obtained by first acylating and then reducing the 3-acyl derivative 66 with K-Selectride.



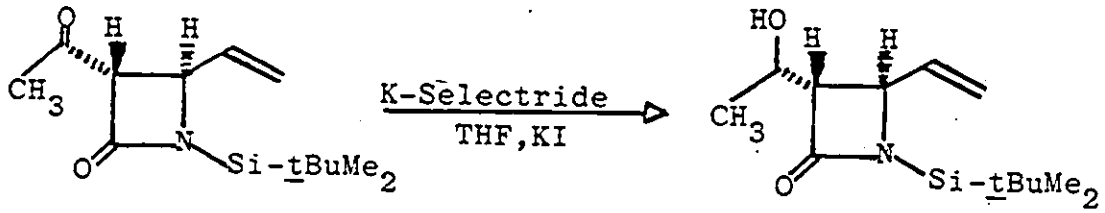
65 65a



65b

trans (R)	trans (S)	cis (R)	cis (S)
46	38	14	2

(Ref. 22)



66 67

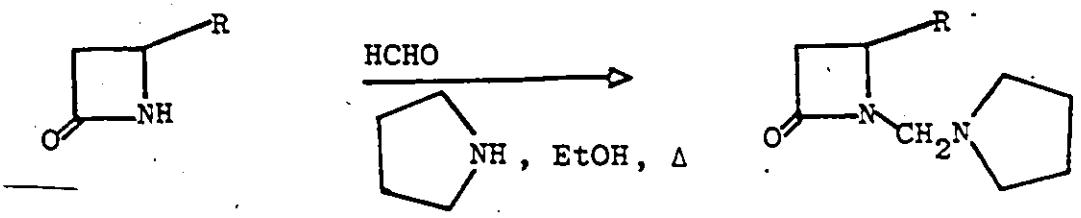
$$\frac{\text{trans (R)}}{\text{trans (S)}} = \frac{88}{12}$$

The feasibility of using the dialkylaminomethyl function as a potential N-blocking group was suggested by the work of Testa et al (23). They reported that β-lactams

reacted readily with secondary amines such as pyrrolidine and morpholine in the presence of 37% formaldehyde solution to afford the 1-dialkylaminomethyl derivative. We felt that the dialkylaminomethyl group might serve as a useful and inexpensive base-stable protecting group, thus enabling introduction of substituents into the 3-position with the desirable trans stereochemistry. The protecting group was expected to be acid labile.

Thus, when compound 19 was refluxed with formaldehyde and pyrrolidine in ethanol for 3 hours 93% of 68 was obtained as a clear oil, b.p 109-112°/.3mm Hg. The NMR peaks were observed at δ = 1.7-1.84 (m,4H), 2.54-2.70 (m,4H), 2.68 (dd,J=16,2Hz,1H), 3.23 (dd,J=16,5Hz,1H), 3.76 (J_{AB}=13.5Hz,1H), 4.14 (J_{AB}=13.5Hz,1H), 4.11 (m,1H), 5.22-5.98 (m,3H). The IR spectrum showed strong carbonyl absorption at 1750 cm^{-1}, indicating retention of the β-lactam ring.

Similarly, 20 was converted to 69, a clear oil, b.p 140-143°/.7mm Hg, in 92% yield. Again the IR spectrum indicated the strong β-lactam carbonyl absorption at 1750 cm^{-1}. Peaks on the NMR spectrum occurred at δ = 1.54-2.22 (m,8H), 2.38-2.72 (m,5H), 3.05 (dd,J=16,5Hz,1H), 3.86 (J_{AB}=13.5Hz,1H), 4.12 (J_{AB}=13.5Hz,1H), 3.68 (m,1H), 4.88-6.17 (m,3H).



19 R = $CH=CH_2$

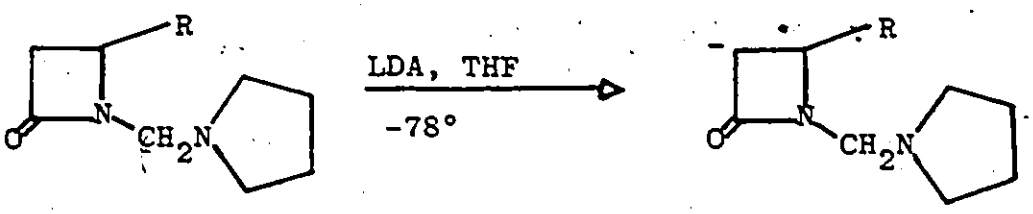
20 R = $CH_2CH_2CH=CH_2$

68 R = $CH=CH_2$

69 R = $CH_2CH_2CH=CH_2$

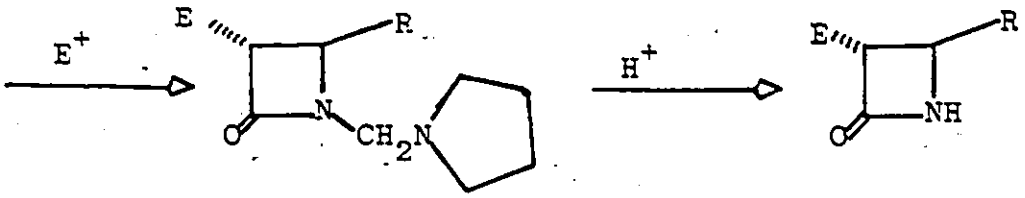
Facile removal of the group could be achieved by refluxing in methanolic HCl or a mixture of THF-1%HCl (aq) The lactams 19 and 20 could be recovered from 68 and 69 in good yields.

Carbanion formation from 68 and 69 was carried out by the addition of the N-protected azetidin-2-one (ß-lactam) to one equivalent of LDA in THF at -78°. The appropriate electrophile was then added and the reaction mixture was stirred for an additional 5 minutes, quenched at low temperature with saturated NH_4Cl and worked up to give crude products. These were purified by column chromatography or hydrolysed immediately to give 3,4-di-substituted derivatives, bearing the free N-H.



68a R = $CH{=}CH_2$

69a R = $CH_2CH_2CH{=}CH_2$



In this manner, the 1-pyrrolidinomethyl-4-(3'butenyl) azetidin-2-one 69 was converted to the deprotected acetone derivative 72, in 79% yield. The removal of the pyrrolidinomethyl group was achieved by refluxing in THF-1%HCl (aq)

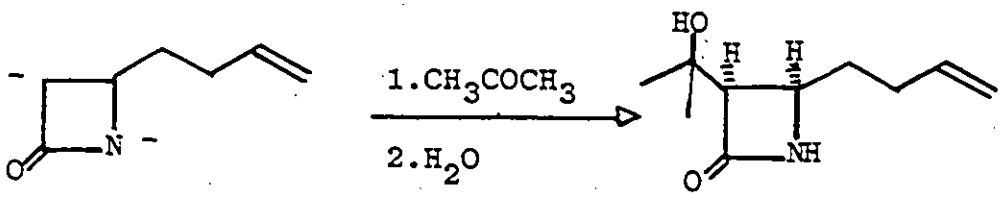
The characteristically strong β-lactam absorption was observed at 1755 cm^{-1} on the IR spectrum. The NMR resonances occurred at δ = 1.24 and 1.4 (two singlets corresponding to the two diastereotopic CH_3 groups); 1.6-2.2 (a multiplet, due to the four methylene side chain hydrogens); 2.76 (a doublet, J=2Hz, assignable to the C_3 hydrogen); 3.6 (a triplet of doublets due to the C_4 hydrogen); 5-6.3 (a multiplet assignable to the three vinylic hydrogens).

The assignment of the relative stereochemistry at C_3 and C_4 was based on the size of J_{H_3,H_4}. Kagan et al (24) and others (25,26) have observed that a coupling constant of 6Hz between H_3 and H_4 is indicative of cis stereochemistry, whereas J_{trans} is about 2Hz. Thus, based on the observed 2Hz coupling constant between H_3 and H_4, compound 72 was determined to be the trans isomer. No cis isomer was detected or isolated. (See below)

The pure cis isomer 71 was accessible through reaction of the dianion 70 (27) with acetone. Interestingly, the reaction of 70 with acetone gave, in 75% yield, a 1:1 mixture of cis 71 [white crystals, m.p 118-120°, NMR: δ = 1.35 and 1.46 (2s, due to the disatereotopic CH_3 groups), 1.86-2.3 (m,two CH_2 groups in the butenyl side chain), 3.25 (d,J=6Hz, corresponding to resonance of C_3 hydrogen), 3.60-3.87 (m, assignable to C_4 hydrogen), 4.95-6.0 (m, due to the three vinylic hydrogens)] and trans 72. The isomers were readily separated by silica gel chromatography. Thus, using NMR spectroscopy and keying in on the H_3 resonances, which are distinctly different for both isomers, it was possible to place the upper limit of the cis isomer in the reaction of the monoanion of 69 and acetone at less than 3%.

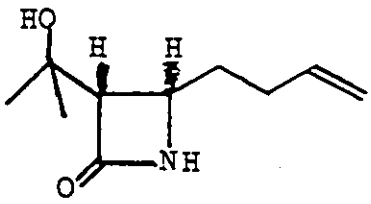
The 1,3-dianion 70 route appears to give greater amounts of the cis-3,4-disubstituted products than any of

the monanion reactions (4,20,28) and may therefore be of value in the preparation of carpetimycins 73 (29) and derivatives. Generally, the reactions of 70 show less selectivity than those of the monoanions of 68 and 69, presumably due to the much higher reactivity of the dianions compared to the monoanions.

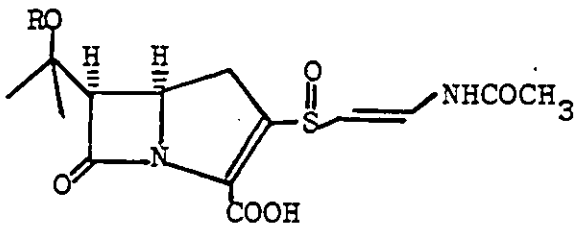


70 71

+



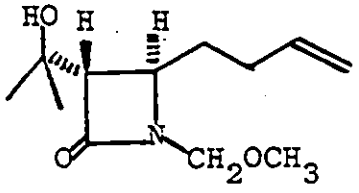
72



73 Carpetimycin A, R = H

Carpetimycin B, R = SO_3H

The removal of the protecting group from the acetone derivative of 69 in methanolic HCl furnished only 45% of compound 72. This poor yield was partly due to the formation of the side product 74 (15%) during the hydrolysis reaction. The structure was assigned on the basis of its spectroscopic data. The NMR spectrum displayed peaks at δ = 1.3 and 1.4 (2s,6H) 1.6-2.5 (m,4H) 2.5 (OH exchangeable with D_2O), 2.86 (d,J=2Hz,1H), 3.3 (s,3H), 3.6-3.8 (m,1H), 4.54 (b.s,2H), 4.9-6.1 (m,3H). The β-lactam absorption occurred at 1750 cm^{-1} on the IR spectrum and the mass spectrum had a molecular ion peak at m/e = 227.

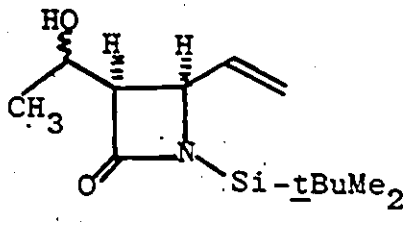


74

This alternate method of hydrolysis was developed first and used throughout the remainder of this chapter. Although not repeated, it can safely be assumed that better yields could have been realised under the improved THF-aqueous HCl reaction conditions. (See below)

The 1-pyrrolidinomethyl-4-vinylazetidin-2-one 68 was also used to study the stereoselectivity of the carbanion reactions. Thus, the deprotected acetone adduct 75, was obtained from 68 in 52% yield as a colorless oil, after chromatography. The NMR signals at δ = 1.23 and 1.4 (2s,6H), 2.9 (J=2Hz,1H), 3.4 (OH exchangeable with D_2O), 4-4.4 (m,1H), 5.06-6.2 (m,3H), 6.7 (N-H, exchangeable with D_2O) supported the structure. The small coupling constant (J_{H_3,H_4}) was the basis for the assignment of the trans β-lactam stereochemistry. Again, no trace of cis isomer was detected.

Compound 68 was also converted to the acetaldehyde derivative 80, as a 1:1 diastereomeric mixture, in 58% yield. The absence of significant amount of cis product accompanying the trans isomer 80 was ascertained by NMR using the reported chemical shift value of H_3 (3.33 and 3.41 in cis (R) and cis (S) respectively) in cis 77 (22) as a model. No trace of a peak in this area was visible in the spectrum of crude 80. Peaks on the NMR spectrum of 80 occurred at δ = 1.26 and 1.32 (two doublets, J=6Hz, corresponding to the two CH_3 groups); 2.91 (doublet of doublets, J=6Hz and 2Hz due to the H_3 resonance); 3.59 (OH), 3.96-4.26 (multiplet, assignable to H_4 and H_8 (thienamycin numbering), 5.13-6.14 (multiplet, due to the three vinylic hydrogens) and 6.91 (N-H).



77

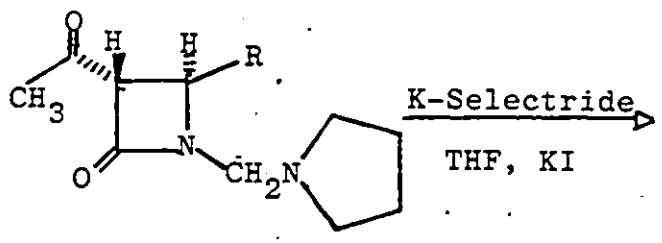
Condensation of the monoanion 68a with ethyl acetate furnished the acetylazetidinone 78 in 63% yield. Compound 78, a pale green oil, was relatively labile and purification was accomplished by HPLC*. The IR spectrum showed carbonyl absorptions at 1715 and 1760 cm^{-1}, corresponding to the ketone and β-lactam, respectively. The NMR peaks displayed at δ = 1.69-2.06 (m,4H), 2.32 (s,H) 2.54-2.73 (m,4H), 3.84 (J_{AB}=14Hz,1H), 4.22 (J_{AB}=14Hz,1H), 4.54 (dd,J=7,2Hz,1H), 5.24-5.93 (m,3H) and the small coupling constant (J_{H_3,H_4}) for the remaining C_3 hydrogen at δ = 3.97 were again consistent with the assigned trans β-lactam stereochemistry. The accessibility of 78 via direct acylation with ethyl acetate on 68a seemed a

---

* The use of HPLC was crucial. Simple column chromatography resulted in considerable decomposition of 78. The difference between the two procedures is mainly in terms of column contact time: less than 10 mins for HPLC, and more than 2 hours for ordinary chromatography.

much better reaction compared to that of Bouffard and Christensen (22), who obtained only 10-30% yield of 66, using acetyl chloride as the acylating agent.

Highly stereoselective reduction of 78 was obtained using the K-Selectride reduction procedure of the above authors (22). Thus, the reduced compound 79, NMR: δ = 1.26 and 1.35 (2d,J=6Hz,3H), 1.7-1.9 (m,4H), 2.56-2.8 (m,4H), 2.93 (dd,J=7,2Hz,1H assigned to H_3), 3.84 (J_{AB}=13Hz,1H), 4.2 (J_{AB}=13Hz,1H), 4.06-4.26 (m,1H corresponding to H_4), 5.16-6.1 (m,3H), was obtained in 60% yield. Hydrolysis provided the isomer 80, in which the desired relative stereochemistry of thienamycin (3) predominated in the ratio of 4:1. $NaBH_4$ reduction of 78 gave a 1:2 ratio of 79 and the trans (S) diastereomer in 72% yield. Bouffard and Christensen also noted that $NaBH_4$ and K-Selectride gave opposite stereochemical preferences.

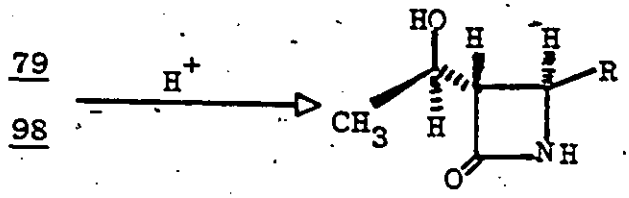


78 R = $CH{=}CH_2$

81 R = $CH_2CH_2CH{=}CH_2$

79 R = $CH{=}CH_2$

98 R = $CH_2CH_2CH{=}CH_2$



79
98

80 R = $CH{=}CH_2$

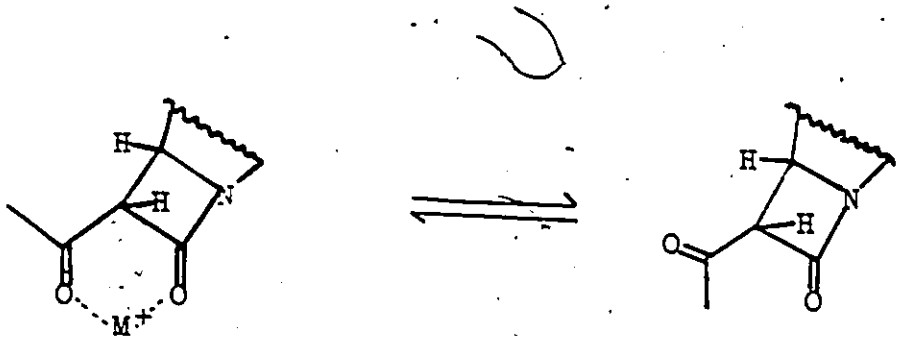
82 R = $CH_2CH_2CH{=}CH_2$

The experimental evidence of these authors (22) suggests that the predisposition for the desired 8 (R) epimer is probably due to a directed hydride attack on a syn-chelated reaction immediate as represented by I in Scheme 5 (30,31,32,33). Preferred attack of the borohydride anion on the ß-face of the ketone carbonyl of I generates the desired 8 (R) carbinol. This mechanism is further supported by experiments in which ionizing additives (crown ethers, HMPA) were shown to alter the product ratio, consistently producing relatively more of the 8 (S) carbinol. It is believed that these additives probably effect displacement of the conformational equilibrium I⟶II toward the latter, in which ß-face attack of the borohydride anion on the ketone carbonyl of anti conformer II, generates the 8 (S) carbinol. The type of Selectride counter ion plays a similarly striking role in affecting product ratio. For example, comparison of L-Selectride (34) with K-Selectride (35) reductions showed a reversal in the

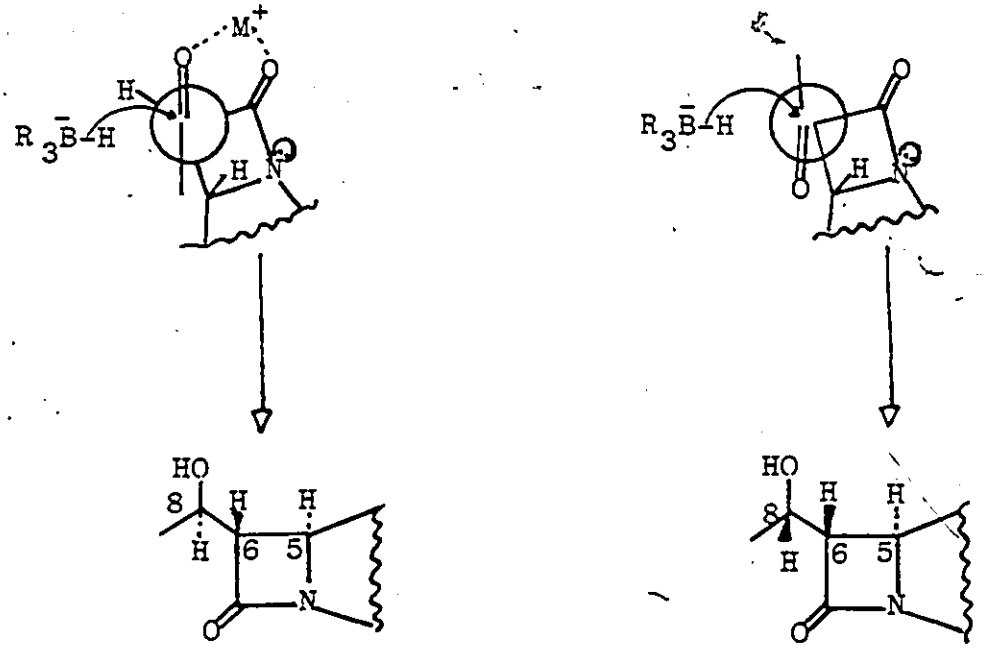
product ratio favoring, in the latter case, the desired 8 (R) isomer (29:71 vs 73:27).

The preferred β-face attack of the bulky (sec-Bu)$_3$ BH_4^- is probably a result of both steric and electrostatic interactions. Attack on the face of the ketone carbonyl opposite to that indicated by the Newman projections of I and II is disfavored in both instances by steric interference due to H_5, and electrostatic repulsion between the negatively charged borohydride anion and the lone pair electrons of the lactam nitrogen.

Scheme 5



I II

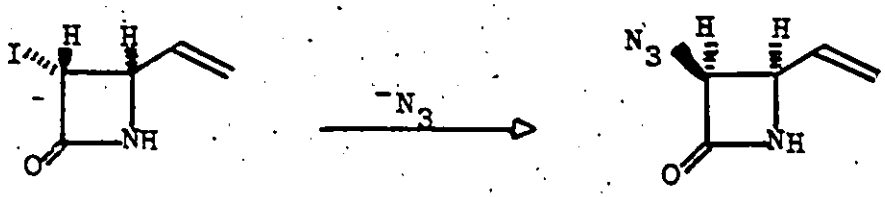


8R 8S

Similar results were recorded from the 3-acyl derivative 81, prepared from 69, in 68% yield. Detailed discussion will be presented in chapter 4, where the elaboration of 69 to a carbacephem nucleus is described. The acetaldehyde adduct 82, obtained in 74% yield from 69, will also be discussed at that time.

The benzophenone derivative 83, m.p 121-124°, was prepared from 68 in 83% yield. Hydrolysis of 83 gave 65% of 84, m.p 118-120°. Also, the benzaldehyde derivative 86, m.p 93-98°, was, in like manner, obtained as a 2:1 side chain isomeric mixture, in 85% yield. The structural identification of 84 and 86 was based on the spectroscopic data shown in Table 1.

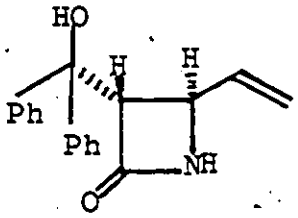
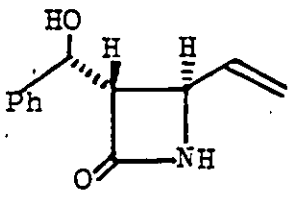
Our interest in the iodo compound 87 stemmed from its potential as a precursor towards cis-3,4-disubstituted β-lactams. For example, azide displacement of the iodide could afford 88, bearing cis β-lactam stereochemistry characteristic of penicillins and cephalosporins (36). Consequently, 87 was acquired in 63% yield from 68. Resonances at δ = 4.33 (dd, J = 7,2Hz,1H), 4.62 (m,1H), 5.28-6.12 (m,3H), 6.84 (N-H) constituted its NMR spectrum and the small coupling constant J_{H_3,H_4} at δ = 4.33 supported the assigned trans β-lactam stereochemistry.



87 88

Table 1

Spectroscopic data of compounds 84 and 86

	NMR (δ)	IR (cm^{-1})
 84	2.96 (s, OH exchangeable with D_2O), 3.98 (m,2H), 4.78-5.76 (m,3H), 6.05 (N-H), 7.14-7.56 (m,10H).	1760 3450
 86	3.2 and 3.3 (two dd,J=6, 2Hz,1H), 3.85-3.98 and 4.25-4.34 (m,1H), 4.9-5.9 (m,4H) and 7.2-7.4 (m,5H).	1755 3480

The results of the condensation of the anions 68a and 69a with various electrophiles and the removal of the N-H protecting group are summarised in Table 2.

Table 2

Derivatives of 4-vinyl- and 4-(3'-butenyl)-azetidin-2-one

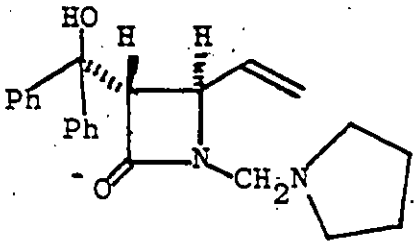
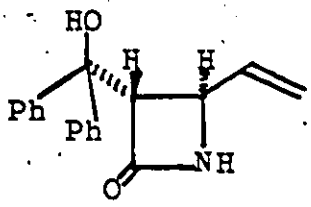
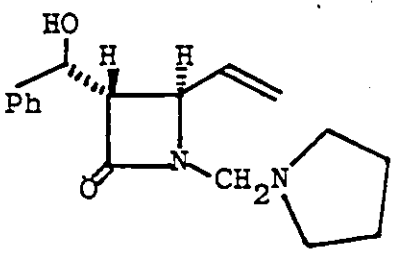
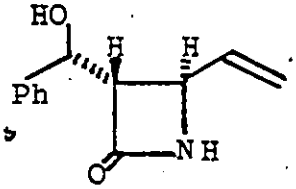
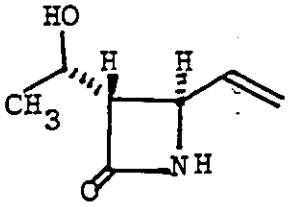
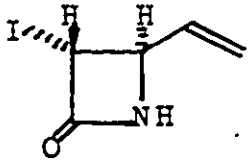
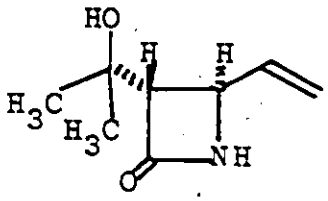
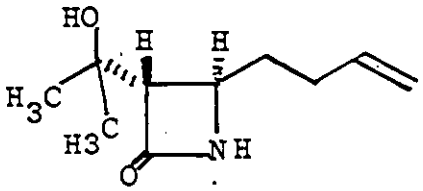
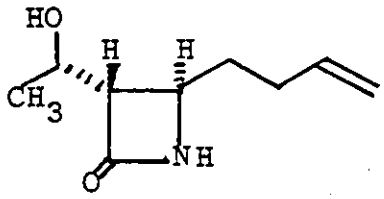
	Yield		Yield
	83%		65% [a]
83		84	
	84%		85% [a]
85		86	
			58% [b]
		80	
			63% [b]
		87	

Table 2 (continued)

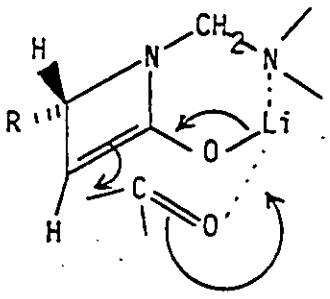
	Yield
 75	52% [b]
 72	79% [b,c]
 82	74% [b]

[a] deprotection step only

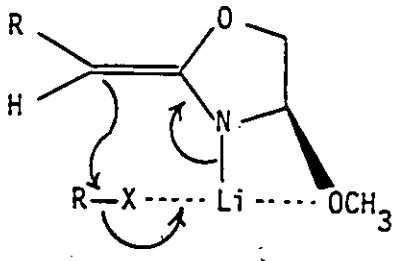
[b] overall yield

[c] deprotection THF/1%HCl

The role of the dialkylaminomethyl function in determining exclusively, the trans stereochemistry in the carbanion reactions of 68a and 69a is not quite clear. This high trans selectivity is possibly related to an internal chelation involving the pyrrolidine nitrogen, as illustrated in 89 below. Such a chelation, which should help deliver the electrophile from the same side as the chelating group is similar to that proposed by Meyers et al (43) as an explanation of the asymmetric induction observed in the alkylation of the carbanions obtained from optically active 2-alkyl-4-methoxy-1,3-oxazolines, 90.



89

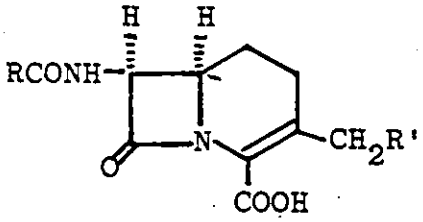


90

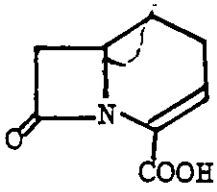
4 SYNTHESIS OF Δ-3-CARBACEPHEM-4-CARBOXYLIC ACID AND TRANS-7-HYDROXYETHYL-Δ-3-CARBACEPHEM-4-CARBOXYLIC ACID

Introduction

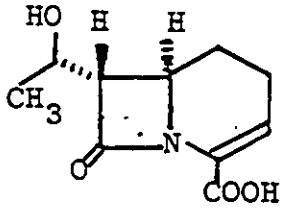
The antibacterial activity of the Δ-3 carbacephalosporins (37,38) suggested that activity might be vested in the Δ-3 carbacephem derivatives bearing either no side chain or the thienamycin side chain at C_7. Nitrogen lone pair conjugation with the Δ-3 double bond, serves to increase the acylating power and consequently antibiotic activity in these types of molecules.



91



92



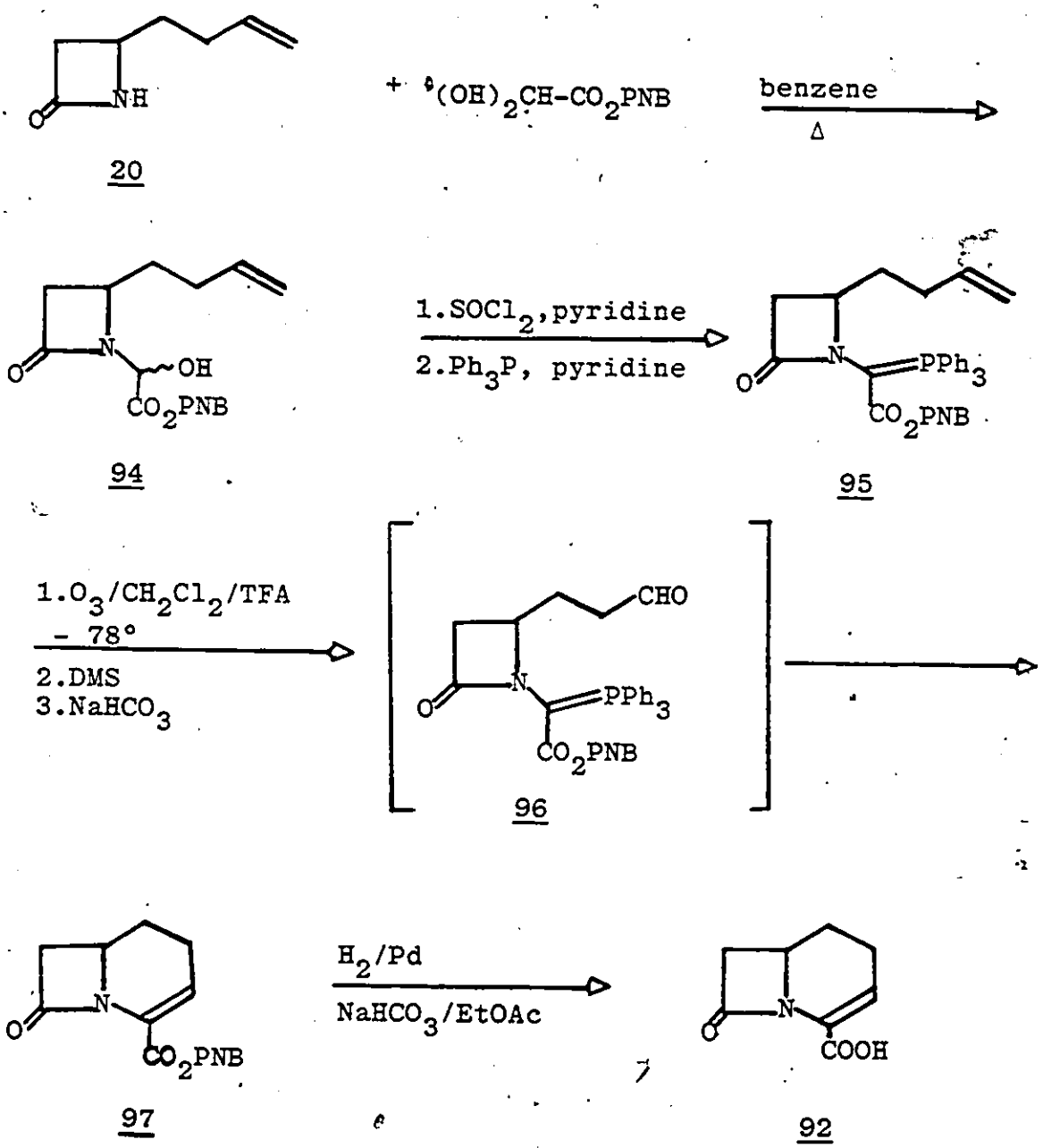
93

In contrast to the carbapenems, the carbacephem ring system is less strained. Thus, carbacephems predictably, would be less active but possibly more selective in their mode of action. In this chapter, the synthesis of the carbacephems 92, Δ-3-carbacephem-4-carboxylic acid and 93, trans-7-hydroxyethyl-Δ-3-carbacephem-4-carboxylic acid, is described.

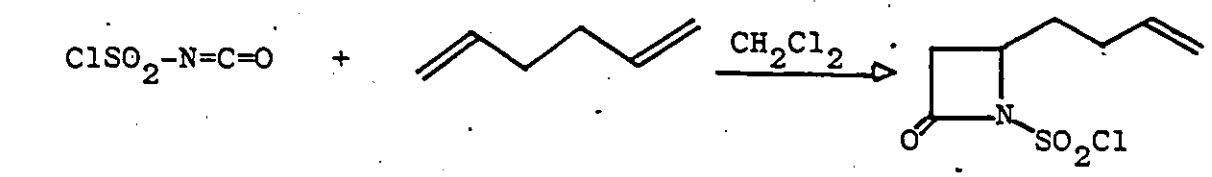
Results and Discussion

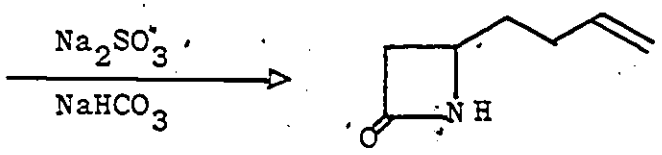
Our synthetic strategy for formation of the carbacephem nucleus is outlined in Scheme 6. This employed compound 20 as the key starting material and the sequence originated by Woodward et al (39) was followed to provide the phosphorane 95. An intramolecular Wittig reaction was then used for ring closure. This ensured the position of the double bond at the required 3-position.

Scheme 6



Compound 20 was easily prepared in 61% yield, by reaction of chlorosulfonyl isocyanate and 1,5-hexadiene, in CH_2Cl_2 followed by reduction with sodium sulfite (40).





20

Reaction of the hydroxy compound 94, prepared in 98% yield by refluxing 20 and hydrated p-nitrobenzyl glyoxylate in benzene, with thionyl chloride in pyridine and THF provided the chloride, which was immediately treated with triphenyl phosphine. The resulting phosphorane 95 was obtained as a foam, in 61% yield after silica gel chromatography. Its structure followed from its spectroscopic data and method of synthesis. (Experimental section)

A solution of 95 in triflouroacetic acid (41) and methylene chloride was ozonised at -78° until excess ozone was present (blue color). Addition of dimethyl sulfide

followed by treatment with saturated sodium bicarbonate regenerated phosphorane 96, which immediately cyclised to yield the ester 97. Purification on silica gel chromatography afforded 97 as white crystals, m.p 134-136°, in 65% yield. Peaks on the NMR spectrum occurred at δ = 1.3-1.7 (m,1H), 2.1-2.5 (m,3H), 2.7 (dd,J=16,2Hz,1H), 3.35 (dd,J=16,6Hz,1H) 3.5-3.7 (m,1H), 5.3 (J_{AB}=12Hz,1H), 5.45 (J_{AB}=12Hz,1H), 6.45 (dd,J=2Hz,1H), 7.65 (d,J=9Hz,2H), 8.2 (d,J=9Hz,2H) and the IR spectrum showed β-lactam and ester absorptions at 1765 and 1730 cm^{-1}, respectively.

Palladium catalysed hydrogenolysis of the ester 97 provided the acid 92, as a white solid, m.p 154-156°. Strong carbonyl absorption at 1765 cm^{-1} indicated that the β-lactam ring was intact. NMR resonances were observed at δ = 1.25-1.85 (m,1H), 2.15-2.60 (m,3H), 2.87 (dd,J=16, 2Hz,1H), 3.38 (dd,J=16,5Hz,1H), 3.6-3.8 (m,1H), 6.45-6.55 (m,1H), 8.9 (COOH, exchangeable with D_2O).

However when 92 was subjected to biological testing, only marginal antibacterial activity was observed.(Table 3)

Table 3

Antibacterial Activity of New Beta-Lactam 92

Organism		MIC (μg/ml)	
		92	Ampicillin
S. pneumoniae	A-9585	16	0.004
S. pyogenes	A-9604	16	0.008
S. aureus	A-9537	63	0.03
S. aureus+50% serum	A-9537	63	0.06
S. aureus Pen-Res.	A-9606	>125	>125
S. aureus Meth-Res.	A15097	>125	>125
S. faecalis	A20688	>125	0.25
E. coli	A15119	>125	1
E. coli	A20341-1	>125	>125
K. pneumoniae	A15130	>125	>125
K. pneumoniae	A20468	>125	>125
P. mirabilis	A-9900	>125	0.06
P. vulgaris	A21559	>125	63
P. morganii	A15153	>125	63
S. marcescens	A20019	>125	16
E. cloacae	A-9659	>125	32
E. cloacae	A-9656	>125	>125
P. aeruginosa	A-9843A	>125	>125
P. aeruginosa	A21213	>125	>125

Table 3 (continued)

Ability of New Beta-Lactam to Inhibit Hydrolysis of an indicator Cephalosporin (BL-S 604) by β-Lactamases from Two Bacterial cultures

Compound	M P C (µg/ml)*	
	K. pneumoniae A20634 (TEM enzyme)	S.aureus A9606
92	100	100
Clavulanic Acid	0.05	0.4

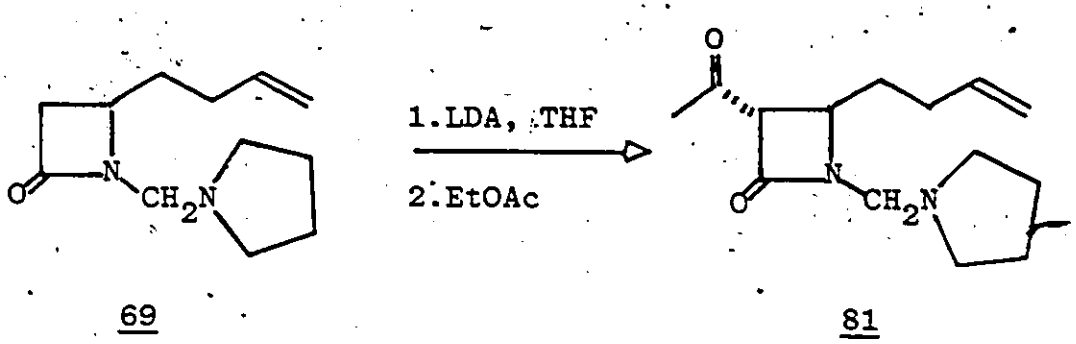
* Minimum Protective Concentration: Lowest concentration of compound that protects BL-S 604 from hydrolysis by β-lactamases within 30 minutes of exposure under standard test conditions (Method EI-1).

Using the methodology developed for 92 and the dialkylaminomethyl function as the N-H protecting group (Chapter 3), we also prepared compound 93. The hydroxyethyl side chain was introduced onto 20 either via direct hydroxyethylation of the anion 69a with acetaldehyde or by the acylation - reduction route.

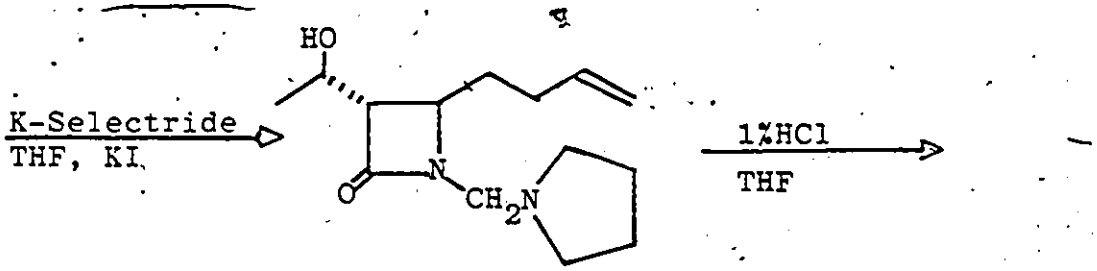
In the former, the trans adduct 82 was obtained as a 1:1 diastereomeric mixture in 74% yield. Compound 82, an oil, showed IR β-lactam and hydroxyl absorptions at 1755 and 3450 cm^{-1}, respectively. Estimation of the 1:1 ratio from the NMR spectrum was based on the two CH_3 doublets at δ = 1.27 and 1.32; the trans β-lactam stereochemistry was assigned on the basis of the small coupling constant (J_{H_3,H_4}=2Hz) observed for the H_3 resonance at δ = 2.81 (See experimental section for other NMR data).

When 82 was prepared by the acylation - K-Selectride reduction procedure, the trans isomer with the desired side chain stereochemistry dominated in a 9:1 ratio, as indicated by the lone CH_3 doublet at δ = 1.27. This isomer was converted to the carbonate 99, in 77% yield, by treatment with p-nitrobenzylchloroformate and 4-(dimethylamino)pyridine in CH_2Cl_2. The choice of 4-(dimethylamino)pyridine as base was crucial for the formation of the carbonate in good yield (42), since the reaction proceeded poorly (10-30%) when other bases (e.g pyridine, triethylamine) were tried.

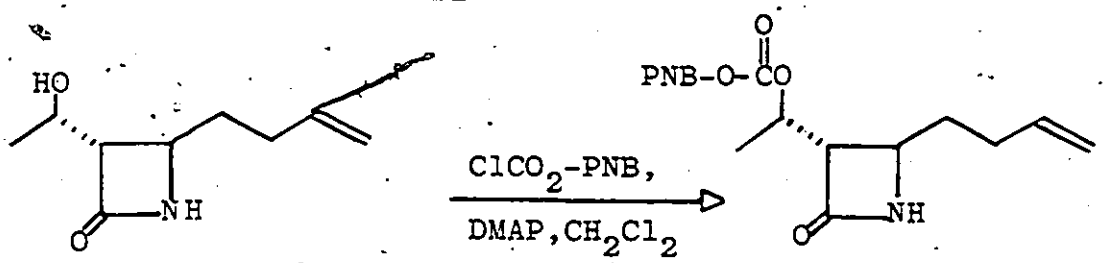
Scheme 7



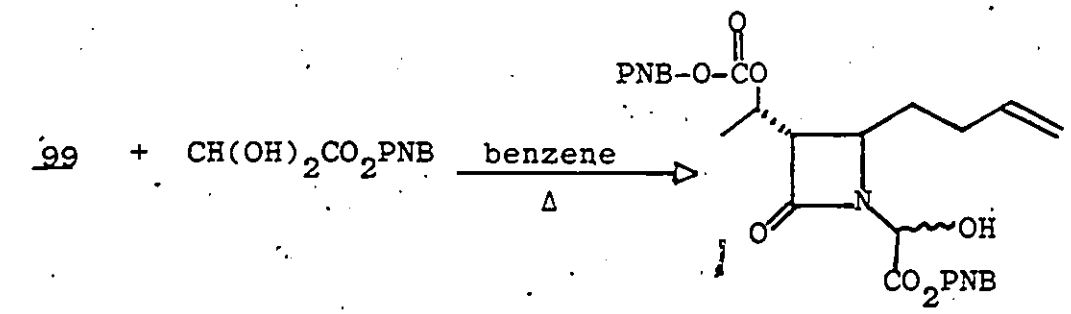
69 81



98

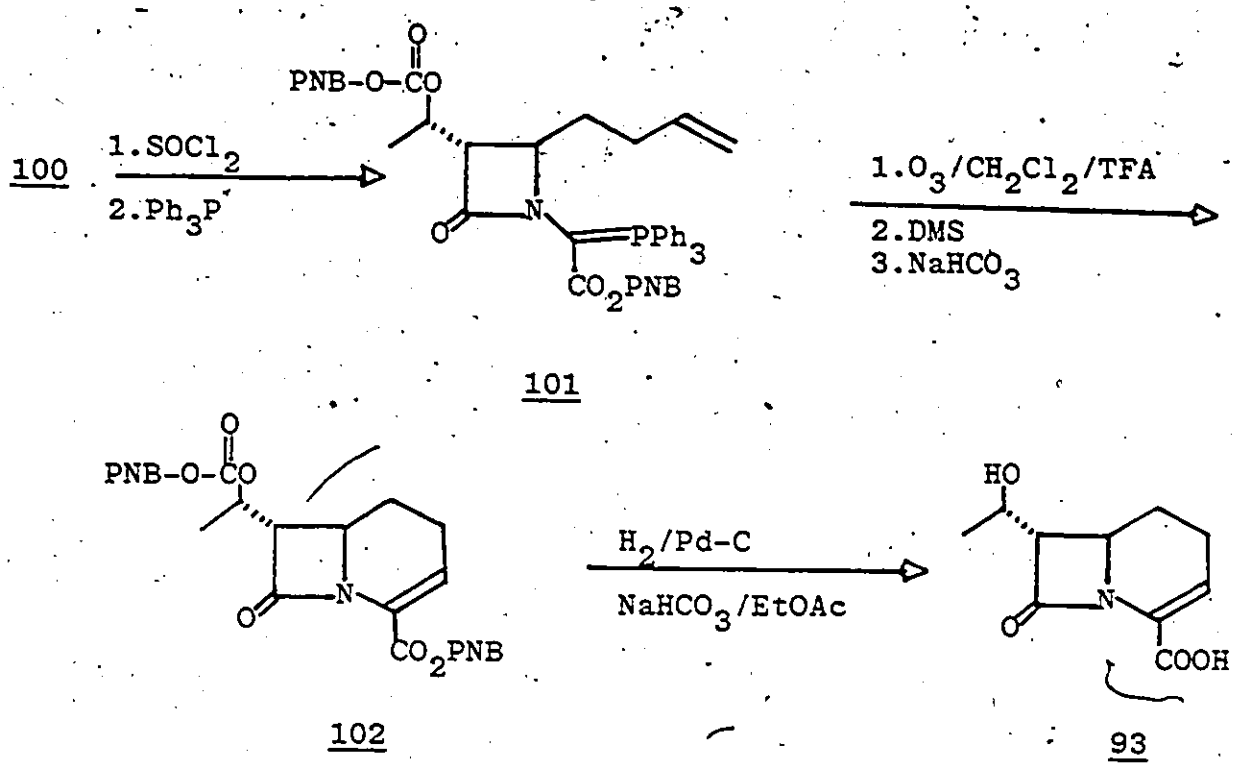


82 99



100

Scheme 7 (continued)



Using the sequence of reactions employed for the formation of 92, compound 99 was carried on to the synthesis of 93. (Scheme 7) The protected carbacephem derivative 102, white crystals, m.p 162-165°, was obtained from the phosphorane in 47% yield. NMR peaks at δ = 1.5 (d,J=6Hz,3H), 2.12-2.54 (m,4H), 3.08 (dd,J=8,2Hz,1H), 3.45-3.66 (m,1H), 5.23 (s,2H), 5.08-5.50 (m,3H), 6.34-6.46 (m,1H), 7.45-7.63 (m,4H), 8.16 (d,J=8Hz,4H) confirmed its structure and the lone CH_3 doublet indicated the presence of a single diastereomer.

Hydrogenolysis of 102, in the presence of 10% palladium

on charcoal, gave the Δ-3-carbacephem hydroxy acid 93, white crystals, m.p 93-95°, in 40% yield.*

After this work was completed, Salzmann and his coworkers (20) used the highly efficient carbene insertion reaction to synthesize the carbacephem nucleus of homothienamycin, a ring expanded analog of thienamycin. The dianion of tert-butylacetoacetate 104 was regiospecifically alkylated with the iodoazetidin-2-one 103, to give the keto ester 105. Conversion of 105 to the diazo derivative 106 was accomplished by reaction with p-carboxybenzenesulfonyl azide, and the crucial ring closure effected by heating 106 in benzene with a catalytic amount of rhodium acetate. The enolic bicyclic product 107 was tosylated to yield 70% of 108.

Treatment of 108 with LDA and quenching the enolate with acetaldehyde provided the hydroxyethyl side chain as a mixture of isomers. The desired trans (R) isomer was separated chromatographically and substitution of the tosyl group with cysteamine, followed by hydrolysis of the tert-butyl ester gave homethienamycin 110. However, the biological activity of 110 was very low.

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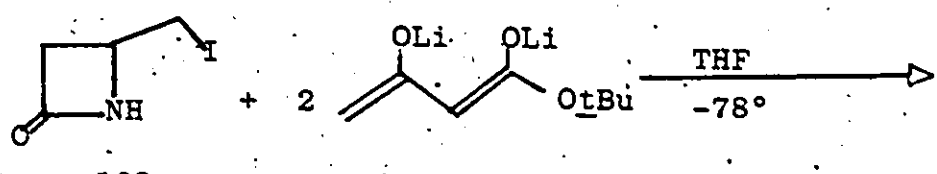
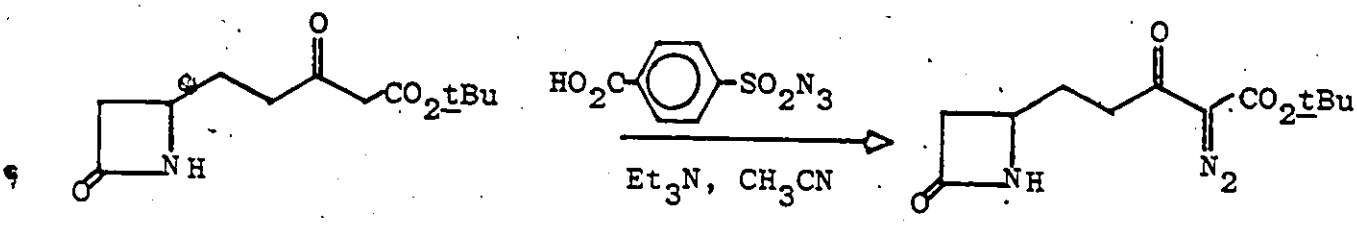
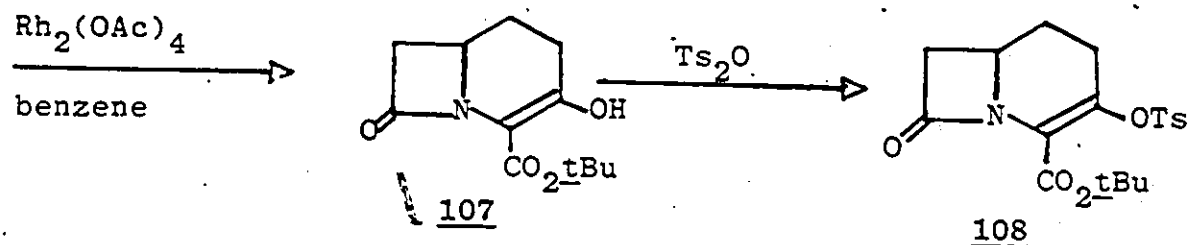
* Only 18 mg of 93 was obtained. A minimum of 25 mg is needed for a comprehensive antibacterial assay. Consequently, the activity of 93 could not be adequately determined.



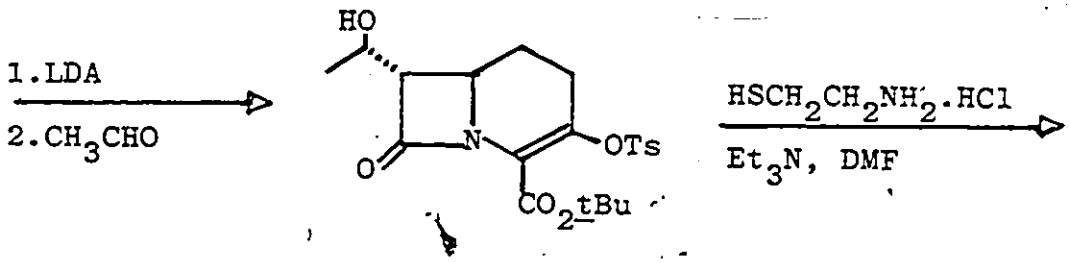
103 + 2 104



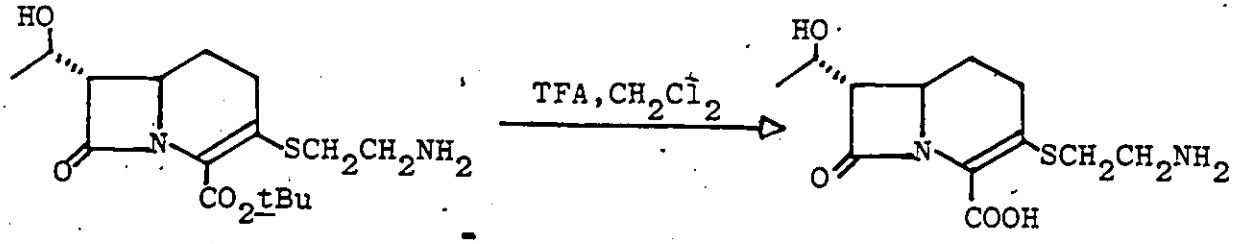
105 106



107 108



109



110

5 EXPERIMENTAL

Infrared spectra were recorded as films for liquids and in $CHCl_3$ solution for solids on a Unicam SP-1100 spectrophotometer. Proton nuclear magnetic resonance (NMR) spectra were obtained on Varian Associates Model HA-100 and Model T-60A with deuterochloroform as solvent (unless otherwise indicated), and tetramethylsilane (TMS) as internal standard. Peak positions are given in δ units as parts per million (ppm) from TMS. The following designations are used in characterising NMR signals: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), broad singlet (b.s), doublet of doublets (dd), multiplet (m), and broad(ened). ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were obtained on a Varian Associates FT-80 NMR Spectrometer. Peak positions are reported in δ units as parts per million (ppm) from TMS. The following designations are used in describing the signals from the off-resonance partially coupled spectra: doublet (d), triplet (t), quartet (q), and quaternary. Melting points (m.p) were taken on a Gallenkamp apparatus and are uncorrected: boiling points (b.p) are also not corrected. Combustion analyses were carried out by Canadian Microanalytical Service Ltd., Vancouver, British Columbia. Mass spectra were recorded by Dr. John Krause of this department. Thin-layer (TLC)

chromatography was carried out on Merck 60 F-254 precoated plates of 0.25mm thickness. The adsorbant used for column chromatography was 60-200 mesh Baker Silica Gel. All reactions involving alkyl lithiums were done in freshly distilled anhydrous tetrahydrofuran (THF) and under N_2. Usual work-up refers to quenching the reaction with excess H_2O or aqueous NH_4Cl, extraction with CH_2Cl_2, drying the organic extracts over $MgSO_4$, and evaporation of the solvents under reduced pressure. The eluting solvents ethyl acetate and hexane were distilled before using.

Unless otherwise stated, all compounds which are described were obtained as clear viscous oils after purification by column chromatography. Their structure follows from their method of synthesis, spectral properties and further conversion into compounds which were fully characterized. All solids, unless otherwise described, were obtained as white granular solids.

(1) Δ-1 Carbapenems

4-vinylazetidin-2-one 19

Chlorosulfonyl isocyanate (CSI, 100g; 0.7 mole) was added to 54g (1 mole) 1,3-butadiene in 250 ml benzene, and the reaction mixture was left at 0° for one week. At the end of this period, the mixture was added slowly to a solution of 380g (3 moles) Na_2SO_3 and 173g $NaHCO_3$ in 750 ml water - 250 ml CH_2Cl_2 and kept at 0° during the reaction. The layers were separated and the aqueous layer extracted with 3X100 ml CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and after removal of the solvent, acetone was added to coagulate the polymer. The mixture was then filtered and chromatographed on a short silica column, with acetone as eluant. The acetone was evaporated and the crude product distilled at 75-78°/.25mm Hg to give 44g (65%) of the vinyl β-lactam 19.

NMR: δ 2.5-2.9 (m,1H), 3.0-3.4 (m,1H), 4.0-4.3 (m,1H) 5.0-5.4 (m,2H), 5.7-6.2 (m,1H), 6.6 (b.s., N-H)

Phosphonate 37

In a 200 ml round bottom flask, fitted with a reflux condenser and drying tube was added 51.9 ml (.247 mole)

triethylphosphite and 18.9 ml (.225 mole) methyl chloromethyl sulfide. The reaction mixture was refluxed in an oil bath at 150° for 5 hours. After this time the solution was distilled and the product 37 collected at 102°/.8mm Hg. Yield: 26g (58%), clear liquid.

NMR: δ 3.5 (t,J=7Hz,6H), 2.3 (s,3H), 2.7 (d,J=13Hz,2H), 4.2 (p,J=7Hz,4H)

Hydroxy phosphonate sulfide 40

To 2g (10.1 mmoles) of 37 in 20 ml dry THF at -78°, was added 1.1 equivalents of nbutyl lithium (11.1 mmoles). After stirring for 45 minutes, freshly distilled benzaldehyde was added and stirring continued for an additional 20 minutes. The reaction was quenched with aqueous ammonium chloride solution and extracted with 1X30 ml ether and 2X30 ml CH_2Cl_2. The organic extracts were combined, dried and the solvent removed on a rotary evaporator. Chromatography (1:2 ethyl acetate/hexane) of the crude product afforded 2.95g (97%) of 40.

NMR: δ (d_2O) 1.3 and 1.4 (2t,6H), 1.76 and 2.0 (2s,3H), 2.8 (dd,J_{PH}=17Hz,J_{HH}=9Hz,1H), 4.1 and 4.2 (2p,4H), 4.9 (dd,J_{PH}=12Hz,J_{HH}=9Hz,1H), 7.3-7.6 (m,5H)

IR: OH, 3440 (broad)

Vinyl phosphonate sulfide 42

Thionyl chloride (.94 ml; 13.16 mmoles) was added dropwise to a solution of the alcohol 40 (2g; 6.58 mmoles) and pyridine (13.16 mmoles; 1.06 ml) in 50 ml 1:1 dioxane/-THF at -10°. The reaction was allowed to warm to room temperature then stirred for 4 hours. The mixture was then filtered, the solvent evaporated and the residual oil taken up in 40 ml methylene chloride and washed with 30 ml 5% HCl. The aqueous layer was washed with 2X20 ml CH_2Cl_2 and combined organic layers dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude chloro compound, which was added to a solution of DBN (13.16 mmoles; 1.63 ml) in 60 ml benzene, and the reaction refluxed for 24 hours. At the end of this period 40 ml ether were added. The mixture was washed once with 50 ml 5% HCl and 50 ml water. The organic layer was dried and the solvent evaporated to afford 824 mg of phosphonate 42 (44% based on 40), after chromatography. An amount of 180 mg (11%) of side product 47 was also isolated.

NMR: δ 1.4 (t,J=7Hz,6H), 2.45 (s,3H), 4.22 (p,J=7Hz,4H)
7.3-7.9 (m,6H)

NMR: 47 δ 1.34 (t,J=7Hz,6H), 4.1 (p,J=7Hz,4H), 6.17 (t,J=18Hz,1H), 7.47 (t,J=18Hz,1H) 7.2-7.4 (m,5H)

M.S m/e, M^+=240

Vinyl phosphonate sulfone 45

Two equivalents of MCPBA (5.62 mmoles; 1.14g) in CH_2Cl_2 were added dropwise to a solution of the sulfide 42 (2.81 mmoles; 804 mg) in 15 ml methylene chloride at 0°. The reaction was stirred at room temperature for one hour then washed with 1X30 ml saturated sodium sulfite, followed by 2X20 ml 5% NaOH solution. The organic extract was dried and the solvent removed. Chromatography of the resultant oil on 40g silica gel (1:3 ethyl acetate/hexane) provided 656 mg (73%) of 45 as a clear oil.

NMR: δ 1.16 (t,J=7Hz,6H), 3.33 (s,3H), 4.13 (p,J=7Hz,4H) 7.3-7.8 (m,5H), 8.23 (d,J=23Hz,1H)

IR: SO_2, 1150 (s) and 1320 (s)

Vinyl phosphonate sulfoxide 44.

The sulfide 42 (603 mg; 2.11 mmoles) was dissolved in 15 ml dry methylene chloride and the solution cooled in an ice bath. MCPBA (1.1 equivalents; 400 mg) in CH_2Cl_2 was added dropwise and the reaction mixture was stirred at room temperature for one hour. The solution was then washed with 20 ml saturated sodium sulfite, 20 ml 5% sodium hydroxide solution and the organic extract dried over $MgSO_4$. Evaporation of the solvent gave a solid material that was crystallised in ether - petroleum ether. Yield: 457 mg (72%), white crystals, m.p 71-73°.

NMR: δ 1.5 (t,J=7Hz,6H), 3.1 (s,3H), 4.15-4.55 (m,4H), 7.5 (s,5H), 8.05 (d,J=21Hz,1H)

IR: S=O, 1050 (s)

M.S.

Fragment m/e	Rel. Abundance	Assignment
302	10	M^+
183	100	$[M-SOCH_3-2(C_2H_4)]^+$
239	53	$[M-SOCH_3]^+$
77	42	Ph^+
197	28	$[M-Ph-C_2H_4]^+$

Preparation of t-butyl glyoxylate 39

A 250 ml three-necked flask was fitted with a thermometer, a reflux condenser protected with a calcium chloride guard tube, and a pressure equalised dropping funnel. A mixture of 31 ml t-butyl alcohol and 25 ml N-N-dimethyl aniline was placed in the flask, and a solution of 10g fumaryl chloride in about 20 ml $CHCl_3$ was added slowly from the dropping funnel while the reaction flask was cooled in an ice bath. The rate of dropping was regulated so that the temperature did not exceed 30°. After addition was complete, the dark red mixture was heated under reflux for 3 hours. The mixture was then cooled, 50 ml of cold 6N H_2SO_4 was added with stirring, and the product was extracted with 3X75 ml portions of ether. The combined ether extracts were washed once with 6N H_2SO_4, twice with water, twice with 10% Na_2CO_3, once with saturated NaCl and finally dried over anyhydrous $MgSO_4$. Removal of the ether under reduced pressure afforded 7.02g (48%) of di-t-butyl fumarate as off-white crystals.

NMR: δ 1.6 (s,18H), 6.6 (s,2H)

IR: C=O, 1740 (s)

The above fumarate (19.5 mmoles; 4.5g) was dissolved in 60 ml methylene chloride and the solution ozonised at -78° until excess ozone was detected. (blue color) Nitrogen was bubbled through the reaction mixture to remove excess ozone, then 7 ml dimethyl sulfide added to reduce the ozonide. After the solvent was evaporated, distillation under reduced pressure provided 2.52g (50%) of t-butyl glyoxylate 39, a clear oil, b.p 30-32°/.4mm Hg.

NMR: δ 1.6 (s,9H), 9.5 (CHO)

Hydroxy phosphonate sulfide 41

Using the preceding procedure, the phosphonate 37 (5.05 mmoles; 1g) was converted to its carbanion (5.56 mmoles; 1.1 equivalents nBuLi), then treated with t-butyl glyoxylate 39 (5.56 mmoles; 722 mg). Work up as above followed by chromatography furnished 698 mg (42%) of 41 and 310 mg of recovered starting material 37.

NMR: δ 1.3 (t,J=7Hz,3H), 1.5 (s,9H), 2.3 (s,3H), 3.2 (dd,J_{PH}=17Hz,J_{HH}=4Hz,1H), 3.8 (dd,J_{PH}=20Hz, J_{HH}=6Hz,1H)

IR: C=O, 1740 (s); OH, 3360 (broad)

Vinyl phosphonate sulfide 43

To a solution of 41 (7.80 mmoles; 2.56g) in pyridine (9.36 mmoles; .754 ml) and 50 ml 1:1 dioxane/THF at -10° was added dropwise .67 ml of thionyl chloride. The reaction was allowed to warm to room temperature, stirred for additional 4 hours, then worked up as above to provide 755 mg of the chloro compound. This was refluxed with DBN (3.27 mmoles; .41 ml) in 30 ml benzene for 4 hours, and following work up, 428 mg (71%) of the phosphonate sulfide 43 was isolated, after preparative thin layer chromatography.

NMR: δ 1.4 (t,J=7Hz,6H), 1.5 (s,9H), 2.6 (s,3H), 4.2 (p,4H), 6.8 (d,J=21Hz,1H)

Vinyl phosphonate sulfone 46

The sulfide 43 (1.55 mmoles; .481 mg) was similarly oxidised with 2 equivalents (630 mg) MCPBA. Work up and chromatography afforded the sulfone 46, an oil, in 76% yield.

NMR: δ 1.4 (t,J=7Hz,6H), 1.5 (s,9H), 3.1 (s,3H), 4.1-4.6 (m,4H), 6.8 (d,J=21Hz,1H)

IR: SO_2, 1330 (s) and 1150 (s); C=O, 1730 (s)

Michael Addition Reactions

General Procedure:

About 200 mg of the β-lactam 4-vinylazetidin-2-one 19 was dissolved in 10 ml THF and reacted with one equivalent of nBuLi, under a nitrogen atmosphere at -30°. To the resultant cloudy solution was added the vinyl phosphonate, and the now clear reaction mixture was stirred for 30 minutes. Work up was complished by quenching with 10 ml aqueous NH_4Cl, extracting with 1X20 ml ether followed by 2X30 ml CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude Michael adduct was purified by column chromatography, using ethyl acetate/hexane as eluant.

Michael Adduct 50

To a solution of 19a, prepared from 200 mg (2.06 mmoles) of 4-vinylazetidin-2-one and nBuLi (2.06 mmoles) in 10 ml THF at -30°, was added 656 mg (2.06 mmoles) 45. The reaction was stirred for 30 minutes then quenched with 10 ml aqueous NH_4Cl. After work up, the crude product was chromatographed (1:2 ethyl acetate/hexane) on 45g silica gel to yield 61% of 50, as a clear viscous oil.

NMR: The NMR spectrum was very complex but in general agreement with the expected product.

IR: C=O, 1750 (s); SO_2 1150 (s) and 1330 (s)

Michael Adduct 49

The 4-vinylazetidin-2-one 19 (2.12 mmoles; 205 mg) was reacted with nBuLi (2.12 mmoles), then treated with the phosphonate 44 (2.12 mmoles; 641 mg). After stirring for 30 minutes, the reaction was quenched with 10 ml aqueous NH_4Cl. Usual work up followed by chromatography (2:1 ethyl acetate/hexane) on 40g silica gel afforded 676 mg (80%) of 49.

NMR: The NMR spectrum was very complex but in general agreement with the expected product.

IR: C=O, 1750 (s); S=O, 1060 (s)

Attempted Michael Addition of 19a onto 42

nBuLi (2.06 mmoles) was added to a solution of 4-vinylazetidin-2-one (2.06 mmoles; 200 mg) in 10 ml THF, at -30°. The resultant cloudy solution was treated with the phosphonate 42, stirred for 30 minutes, then

quenched with 10 ml aqueous NH_4Cl. Work up in the usual manner provided a material which by NMR was identical to a mixture of the starting components.

An attempt to perform the above reaction with potassium hydroxide in dioxane led to polymerisation of 19.

Attempted Michael Addition of 19a onto 43

A solution of 19a was prepared from 19 (.645 mmole; 62 mg) and nBuLi (.645 mmole) in 7 ml THF at -30°. This was treated with the phosphonate 43 (.645 mmole; 200 mg) and the reaction mixture stirred for 30 minutes. Aqueous NH_4Cl (10 ml) was added and work up gave a material which was indicated by NMR to be both starting compounds.

Attempted Michael Addition of 19a onto 46

The N-lithio salt 19a was formed by reacting nBuLi (1.03 mmole) with 19 (1.03 mmole; 100 mg) in 10 ml THF at -30°. To the resultant solution was added the phosphonate 46 (1.03 mmole; 352 mg). The reaction mixture was stirred for 30 minutes, quenched with 10 ml aqueous NH_4Cl and worked up in the usual manner. Purification

by preparative thin layer chromatography furnished recovered starting β-lactam 19 together with small amounts of material which could not be identified. When the above reaction was repeated at lower temperatures (-60°), similar results were recorded.

Conversion of 50 to Carbapenem 52

The adduct 50 (1.13 mmole; 470 mg) was dissolved in 20 ml CH_2Cl_2 and ozonised at -78° until excess ozone was detected. (blue color) After bubbling nitrogen to remove the excess ozone, the solution was treated with 2 ml dimethyl sulfide. The solvent was evaporated and the crude product, a viscous oil, was dissolved in 20 ml THF, cooled to -30° and stirred with 1.13 mmole NaH for 30 minutes, then at room temperature for a further 7 hours. The reaction mixture was then quenched with aqueous NH_4Cl and extracted with 1X10 ml ether and 3X15 ml CH_2Cl_2. The crude product (303 mg) was purified on preparative silica gel plates to yield 147 mg (50%) of 52, as a 2:1 mixture of isomers. Both the major, m.p 115-120° and minor isomer, m.p 144-146°, were obtained as white solids. The exo vs endo phenyl group structure was not assigned.

NMR: (major isomer) δ 2.36 (s,3H), 3.1-3.6 (m,2H), 4.5-4.7 (m,1H), 5.38 (q,J=2Hz,1H), 7.2-7.5 (m,6H)

(minor isomer) δ 2.36 (s,3H), 3.10 (dd,J=16, 3Hz,1H), 3.56 (dd,J=16,6Hz,1H), 4.8-4.9 (m,1H), 5.90 (q,J=2Hz,1H)

IR: C=O, 1780 (s); 1310 (s) and 1150 (s)

M.S.

Fragment m/e	Rel. Abundance	Assignment
263	10	M^+
183	83	$[M-HOSOCH_3]^+$
115	100	$[Ph-C_3H_2]^+$
77	31	Ph^+

^{13}C NMR: (minor isomer) δ 43.53 (q), 44.17 (t), 59.24 (d), 67.73 (d), 137.27 (s), 141.16 (d), 151.29 (s), 176.36 (s)

Aromatics 127.26, 129.13, 129.29

Anal. Calcd. for $C_{13}H_{13}O_3NS$: C, 59.30; H, 4.97; N, 5.32

Found C, 59.08; H, 4.84; N, 5.29

Conversion of 49 to Carbapenem 51

A solution of 49 (.706 mmole; 282 mg) in 20 ml CH_2Cl_2 was ozonised at -78° until a slight blue color was detected. Nitrogen was passed through the solution to remove excess ozone and dimethyl sulfide (1 ml) added to reduce the ozonide. Evaporation of the solvent provided the crude product, which was dissolved in 20 ml THF, treated with .71 mmole NaH and stirred at -30° for 30 minutes. The reaction mixture was stirred for an additional 6 hours at room temperature, then quenched with NH_4Cl (aqueous) solution. Work up as above followed by preparative thin layer chromatography afforded 54 mg (31%) of 51 and 15 mg (9%) of 52, formed during the ozonolysis reaction due to inadvertent oxidation of the sulfoxide.

NMR: δ 2.5 and 2.63 (2s,3H), 2.95-3.4 (m,2H), 4.4-4.7 (m,1H), 5.2 and 5.7 (2q, 1H), 6.8-7.0 (m,1H), 7.3-7.5 (m,5H)

IR: C=O, 1775 (s), S=O, 1055 (s)

The above sulfoxide 51 (.219 mmole; 54 mg) was oxidised with one equivalent of MCPBA in 5 ml CH_2Cl_2. The sulfone 52 (42 mg;74%) was clearly obtained again as a 2:1 mixture of isomers.

(2) 1-(Dialkylaminomethyl)-Azetidin-2-ones

4-(3'-butenyl)-azetidin-2-one 20

Chlorosulfonyl isocyanate (.353 mole; 50g) was added dropwise to a solution of 1,5-hexadiene (.549 mole; 45g) in 200 ml dry CH_2Cl_2 at 0°. After addition of 3g of anhydrous K_2CO_3, the reaction mixture was allowed to stand for 2 weeks at room temperature under a dry atmosphere. The sulfonyl chloride was then reduced in the following manner. To a solution of 300 ml ether and 600 ml saturated sodium sulfite, the reaction mixture was added dropwise and the pH (approx. 9) controlled by simultaneous addition of 10% potassium hydroxide solution. The organic layer was separated and the aqueous extracted with 3X150 ml CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to yield 33.7g of crude product as a pale yellow oil. The last traces of solvent were removed under reduced pressure, and distillation afforded 27g (61%) of clear oil b.p 120°-123°/.5mm Hg.

NMR: δ 1.5-2.3 (m,4H), 2.3-2.8 (m,1H), 2.9-3.3 (m,1H), 3.4-3.8 (m,1H), 4.8-5.2 (m,2H), 5.4-6.1 (m,1H), 6.8 (b.s., NH)

IR: C=O, 1765 (s); NH, 3450 (broad)

1-(pyrrolidinomethyl)-4-(3'-butenyl)-azetidin-2-one 69

3g (24 mmoles) 4-(3'-butenyl)-azetidin-2-one 20 and 2.4 ml formaldehyde were heated to reflux in 40 ml ethanol and treated with dropwise addition of 2.01 ml pyrrolidine. Continued refluxing for 2 hours, followed by evaporation of the solvent under reduced pressure afforded a pale brown oil, which was distilled at .7mm Hg/b.p 140°-143°. Yield: 4.58g (92%).

NMR: δ 1.54-2.22 (m,8H), 2.38-2.72 (m,5H), 3.05 (dd,J=16,5Hz,1H), 3.86 (J_{AB}=13.5Hz,1H), 4.12 (J_{AB}=13.5Hz,1H), 3.68 (m,1H), 4.88-6.17 (m,3H)

IR: C=O, 1750 (s)

Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45
Found C, 69.59; H, 9.42; N, 12.85

1-(pyrrolidinomethyl)-4-vinylazetidin-2-one 68

The 4-vinylazetidin-2-one 19 (41.24 mmoles; 4g) and 4.1 ml formaldehyde (38% solution) in 45 ml ethanol were heated to reflux, then treated with dropwise addition of 3.44 ml pyrrolidine. After refluxing for 2 hours, evaporation of the ethanol in vacuo gave a pale yellow

oil. Distillation at .3mm Hg/b.p 109°-112°, afforded 6.87g (93%) of product 68, as a clear oil.

NMR: δ 1.70-1.84 (m,4H), 2.54-2.70 (m,4H), 2.68 (dd,J=16,2Hz,1H), 3.23 (dd,J=16,5Hz,1H), 3.76 (J_{AB}=13.5Hz,1H), 4.14 (J_{AB}=13.5Hz,1H), 4.11 (m,1H), 5.22-5.98 (m,3H)

IR: C=O, 1750 (s)

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54
Found C, 66.08; H, 9.25; N, 15.82

Formation of the Monolithio salts with LDA

General Procedure:

The lithium diisopropyl amide (LDA) was formed by reacting 1.2 equivalents of nBuLi (2.4M or 2.6M in hexane) with 1.2 equivalents of diisopropyl amine in 10 ml THF, at -78°. Addition of the appropriate azetidin-2-one (1g) gave an orange colored anion. After stirring for 2-5 minutes, the appropriate electrophile was added, and the reaction mixture stirred for an additional 10-20 minutes. The usual work gave the crude products which were purified by recrystallization or silica gel column

chromatography. Hydrolysis of the 1-pyrrolidinomethyl group was achieved by refluxing in methanolic HCl or THF-1%HCl (1:6) for 3 hours. The hydrolysed product was isolated by extractions with CH_2Cl_2 and dried over $MgSO_4$. Purification was accomplished by recrystallisation or column chromatography. Yields refer to purified materials.

Reactions of Monolithio anion 68a

Benzophenone derivative 84

To the LDA solution, which was prepared by reacting 1.28 ml of nBuLi (2.6M in hexane) with .467 ml diisopropylamine in 8 ml THF, was added 500 mg (2.78 mmoles) of compound 68. Benzophenone (1.2 equivalents; 607 mg) was then added to the orange colored anion. The work up afforded 1.05g of crude product, which was recrystallised in ether-Hexane to yield 830 mg (83%) of 83, a white powder, m.p 121°-124°.

The 1-pyrrolidinomethyl group was removed as follows: 400 mg (1.10 mmoles) of the white powder was dissolved in 3 ml methanol, followed by addition of 18 ml 1% HCl. The reaction mixture was refluxed for 3 hours. Work up by 5X20 ml extractions with CH_2Cl_2 gave 280 mg of crude

product, which was recrystallised in ether-petroleum ether to afford 200 mg (65%) of the trans isomer 84, as fine white crystals, m.p 118°-120°.

NMR: δ 2.96 (s, OH exchangeable with D_2O), 3.98 (m,2H), 4.78-5.76 (m,3H), 6.05 (N-H, exchangeable with D_2O), 7.14-7.56 (m,10H)

IR: C=O, 1760 (s); OH, 3450 (broad)

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01
Found C, 77.37; H, 6.12; N, 4.68

Benzaldehyde derivative 86

Compound 68 (2.78 mmoles; 500 mg) was reacted with 3.34 mmoles (1.2 equivalents) LDA in 8 ml dry THF for 5 minutes, then condensed with 354 mg (1.2 equivalents) of freshly distilled benzaldehyde The crude reaction product was chromatographed on 35g silica gel. Elution with ethyl acetate-hexane (2:1) gave 667 mg (84%) of 85, a very viscous oil. Hydrolysis of this oil (611 mg) in 4 ml methanol and 20 ml 1% HCl afforded a 2:1 isomeric mixture (368 mg; 85%) of the trans product 86, as an off white solid. Recrystallisation in CH_2Cl_2-hexane gave pale yellow crystals, m.p 93°-98°.

NMR: δ 3.2 and 3.3 (2dd, J=6,2Hz,1H), 3.85-3.98 and 4.25-4.34 (m,1H), 4.9-5.9 (m,4H), 7.2-7.4 (m,5H)

IR: C=O, 1755 (s); OH, 3480 (broad)

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89
Found C, 69.75; H, 6.53; N, 6.87

Iodide derivative 87

To a solution of 2.78 mmoles of the lithio salt of 68, prepared from 500 mg (2.78 mmoles) and 1.2 equivalents (3.34 mmoles) LDA was added 846 mg (3.34 mmoles; 1.2 equivalents) of iodine. The reaction mixture was stirred at -78° for 15 minutes. Work up gave 930 mg crude which was immediately hydrolysed by dissolving in 5 ml methanol - 25 ml 1% HCl then refluxing for 3 hours. The usual work up followed by column chromatography purification (4:1 hexane-ethyl acetate), provided 387 mg (63%) of the iodide 87.

NMR: δ 4.33 (dd,J=7,2Hz,1H), 4.62 (m,1H), 5.28-6.12 (m,3H), 6.84 (N-H, exchangeable with D_2O)

IR: C=O, 1757 (s); N-H, 3300 (broad)

Acetaldehyde derivative 80.

Compound 68 (11.1 mmoles; 2g) was reacted with 1.2 equivalents (13.3 mmoles) of LDA in 15 ml dry THF for 10 mins, at -78°. Excess acetaldehyde (2.5 ml) was then added to the orange colored reaction mixture and stirring continued for an additional 10 minutes. The crude material obtained from the work up was hydrolysed in 5 ml methanol - 30 ml 1% HCl solution. The usual isolation procedure afforded 1.2g of crude product, which was purified by column chromatography on 50g silica gel. Elution with 1:2 ethyl acetate - hexane gave 911 mg (58%) of the acetaldehyde derivative 80.

NMR: δ 1.26 and 1.32 (2d,J=6Hz,3H), 2.91 (dd,J=6,2Hz,1H)
3.59 (s,OH,1H), 3.96-4.26 (m,2H), 5.13-6.14 (m,3H)
6.91 (N-H,1H)

IR: C=O, 1750 (s); OH, 3450 (broad)

M.S. m/e, $M-H_2O$ = 123

Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.56; H, 7.86; N, 9.92
Found C, 59.54; H, 8.24; N, 10.18

Acetone derivative 75

Excess acetone (1 ml) was added to a solution of the monoanion 68a, prepared from 400 mg (2.22 mmoles) 68 and 1.2 equivalents (2.66 mmoles) LDA in 5 ml THF, at -78°. Work up gave the crude product, which was hydrolysed by refluxing in 5 ml THF - 25 ml 1% HCl for 3 hours. The deprotected trans acetone adduct 75 was thus obtained in 52% yield. (179 mg)

NMR: δ 1.23 and 1.4 (2s,6H), 2.9 (d,J=2Hz,1H), 3.4 (OH, exchangeable with D_2O), 4-4.44 (m,1H) 5.06-6.2 (m,3H), 6.7 (N-H, exchangeable with D_2O)

IR; C=O, 1760 (s); OH, 3480 (broad)

Ethyl Acetate derivative 78

To the anion generated from 4g (22.22 mmoles) of compound 68 and 1.2 equivalents (26.66 mmoles) LDA in 35 ml THF, was added 2.6 ml of ethyl acetate. The reaction mixture was stirred for 20 minutes, then worked up in the usual manner. Purification of the crude product by high pressure liquid chromatography (HPLC) with 4:1 ethyl acetate - hexane as eluent yielded 3.10g (63%) of the acetyl derivative 78. This compound was

very labile and was subsequently reduced.

NMR: δ 1.69-2.06 (m,4H), 2.32 (s,3H), 2.54-2.73 (m,4H), 3.84 (J_{AB}=14Hz,1H), 4.22 (J_{AB}=14Hz,1H), 3.97 (d,J=2Hz,1H), 4.54 (dd,J=7,2Hz,1H), 5.24-5.93 (m,3H)

IR: C=O, 1715 (ketone); C=O, 1760 (β-lactam)

Reduction of 1-(pyrrolidinomethyl)-trans-3-acetyl-4-vinyl-azetidin-2-one 78

Sodium Borohydride reduction

Compound 78 (3.60 mmoles; 800 mg) was dissolved in 25 ml ethanol and the reaction mixture cooled to -30° in an acetone - dry ice bath. Sodium borohydride (1.30 mmoles; 68 mg) was then added. After stirring for 2 hours, the mixture was partitioned between saturated ammonium chloride (20 ml) - ether (25 ml), and the organic layer extracted. The aqueous layer was extracted with 4X25 ml CH_2Cl_2, the combined organic layers dried over $MgSO_4$ and the solvents evaporated. The crude product was chromatographed with 3:1 ethyl acetate - hexane as eluent, to yield 577 mg (72%) of 79.

NMR: δ 1.26 and 1.35 (2d,J=6Hz,3H), 1.7-1.9 (m,4H), 2.56-2.8 (m,4H), 2.93 (dd,J=7,2Hz,1H), 3.84 (J_{AB}=13Hz, 1H), 4.2 (J_{AB}=13Hz,1H), 4.06-4.26 (m,1H), 5.16-6.1 (m,3H)

The pyrrolidinomethyl group of 79 was removed in the usual way to provide compound 80, in 60% yield.

NMR: δ 1.26 and 1.32 (2d,[1:2],J=6Hz,3H); other data identical to that above.

K-Selectride reduction

To a solution of 459g (2.07 mmoles) of compound 78 and 344 mg KI in 7 ml ether at 25°, was added 12.4 ml of K-Selectride (.5M in THF; 3 equivalents). The reaction was stirred for 3 hours then worked up as above. Purification by column chromatography (2:1 ethyl acetate - hexane) gave 276 mg (60%) of the hydroxyethyl compound 79. Hydrolysis of 79 was carried out to give 80, as above.

NMR: δ 1.26 and 1.32 (2d,[9:1],J=6Hz,3H); other data identical to that above.

Reactions of the Monolithio anion 69a

Acetaldehyde derivative 82

The lithio salt of compound 69 (8.93 mmoles; 1.86g), was reacted with 2.5 ml acetaldehyde at -78° for 10 minutes. Work up provided 3.14g of crude product which was immediately hydrolysed. Isolation in the usual manner, followed by column chromatography purification (1:2 ethyl acetate - hexane) gave 1.12g (74%) hydroxyethyl compound 82.

NMR: δ 1.27 and 1.32 (2d,J=7Hz,3H), 1.64-1.85 (m,2H), 2.02-2.24 (m,2H), 2.81 (dd,J=6.5,2Hz,1H), 3.18 (OH) 3.42-3.83 (m,1H), 3.95-4.25 (m,1H), 4.97-6.04 (m,3H) 6.72 (N-H)

IR: C=O, 1755 (s); OH, 3450 (broad)

M.S. m/e, $M-H_2O$ = 151

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28
Found C, 63.63; H, 9.34; N, 7.92

Acetone derivative 72

Excess acetone (2.5 ml) was added to a THF solution (10 ml) of the monoanion 69a, prepared from 1g (4.81 mmoles)

69 and 1.2 equivalents (5.77 mmoles) LDA, at -78°. The reaction mixture was stirred for 5 minutes, then worked up. The crude product was hydrolysed in refluxing THF - 1% HCl (1:6) to give cleanly 694 mg (79%) of the acetone derivative 72.

NMR: δ 1.24 and 1.4 (2s,6H), 1.6-2.2 (m,4H), 2.76 (d,J=2Hz,1H), 3.6 (t of d,1H), 5-6.3 (m,3H)

IR: C=O, 1755 (s); OH, 3450 (s)

Only 45% of 72 was obtained when hydrolysis was carried out in methanolic HCl. This was partly due to the formation of the side product 74, in 15% yield.

NMR: 74 δ 1.3 and 1.4 (2s,6H), 1.6-2.5 (m,4H) 2.5 (OH, exchangeable with D_2O), 2.86 (d,J=2Hz,1H), 3.3 (s,3H), 3.6-3.8 (m,1H), 4.54 (b.s.,2H), 4.9-6.1 (m,3H)

IR: C=O, 1750 (s); OH, 3450 (broad)

M.S. m/e, M^+ = 227

Ethyl Acetate derivative 81

To the anion generated from 5g (24.04 mmoles) of compound 69 and 1.2 equivalents (28.84 mmoles) LDA in 25 ml THF, was added 2.84 ml ethyl acetate. The reaction mixture was stirred for 10 minutes, then worked up in the usual way. The crude product was purified by high pressure liquid chromatography (HPLC) with 4:1 ethyl ethyl acetate - hexane as eluent. Yield of the acetyl derivative 81: 4.37g (73%).

NMR: δ 1.67-2.22 (m,8H), 2.33 (s,3H), 2.48-2.74 (m,4H) 3.83 (d,J=2Hz,1H), 3.77 (J_{AB}=13.5Hz,1H), 4.27 (J_{AB}=13.5Hz, 1H), 4.13 (m,1H), 4.88-6.17 (m,3H)

IR: C=O, 1714 (s) (ketone); C=O, 1760 (s) (β-lactam)

Reduction of 1-(pyrrolidinomethyl)-3-acetyl-4-(3'-butenyl)-azetidin-2-one 81

Sodium Borohydride reduction

To a solution of 750 mg (3 mmoles) of 81 in 25 ml ethanol at -30° was added 57 mg (1.5 mmole) of sodium borohydride. The solution was stirred for 2 hours, then taken up in ether (20 ml) and washed with saturated NH_4Cl. (25 ml)

The organic layer was separated and the aqueous layer extracted with 4X25 ml CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and evaporated to give crude 98, which was chromatographed on 40g silica gel. Elution with 3:1 ethyl acetate - hexane afforded 530 mg (71%) of the hydroxyethyl product 98. Hydrolysis of the pyrrolidinomethyl group in methanolic HCl (1%) afforded 82, in 68% yield.

NMR: δ 1.27 and 1.32 (2d,[1:2],J=7Hz,3H); other data identical to that above

K-Selectride reduction

A 0.5M solution of K-Selectride in THF (3 equivalents; 110.4 ml) was added to 4.6g (18.4 mmoles) of the β-keto lactam 81, in 30 ml anhydrous ether under a N_2 atmosphere. The resulting solution was stirred for 3 hours, then worked up as above. The crude was purified by column chromatography (2:1 ethyl acetate - hexane) to yield 3g (65%) of 98.

NMR: 98 δ 1.27 (d,J=7Hz,3H), 1.6-2.33 (m,8H), 2.76 (dd,J=7,2Hz,1H), 3.0 (O-H), 3.76 (J_{AB}=13Hz,1H), 4.1 (J_{AB}=13Hz,1H), 3.6-4.2 (m,2H), 4.8-6.1 (m,3H)

Hydrolysis of 98 by refluxing in methanol - HCl (1%) provided 82, as above.

NMR: δ 1.27 (single d,J=7Hz,3H); other data identical to that above

Reaction of the Dilithio anion 70 with Acetone

To 4-(3'-butenyl)-azetidin-2-one (8mmoles; 1g) dissolved in 45 ml THF at 0° was added 2 equivalents (16 mmoles) of nBuLi. The reaction mixture was stirred for 30 minutes during which time the solution darkened considerably. Excess acetone (2.5 ml) was added and the solution allowed to stir for a further 15 minutes. The crude product obtained upon usual work up was chromatographed (1:2 ethyl acetate - hexane) to provide 1.09g (75%) of a 1:1 mixture of trans:cis isomers. The isomers were readily separated by silica gel chromatography. The cis isomer was obtained as white crystals, m.p 118°-120°.

NMR: cis isomer δ 1.35 and 1.46 (2s,6H), 1.86-2.3 (m,4H), 3.25 (d,J=6Hz,1H), 3.6-3.87 (m,1H), 4.95-6.0 (m,3H)

trans isomer δ 1.24 and 1.4 (2s,6H), 1.6-2.22 (m,4H) 2.76 (d,J=2Hz,1H), 3.6 (t of d,1H), 5-6.3 (m,3H)

IR: C=O, 1755 (s); OH, 3450 (broad)

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64
Found C, 65.43; H, 9.40 N, 7.59

(3) Δ-3 Carbacephems

Alcohol 94

A solution of the 4-(3'-butenyl)-azetidin-2-one 20 (24 mmoles; 3g) and hydrated p-nitrobenzyl glyoxylate (1:1 equivalents; 5.99g) in 80 ml benzene was refluxed under a Dean-Stark apparatus for 17 hours. The solvent was evaporated and the crude product chromatographed (1:2 ethyl acetate - hexane) on 240g silica gel to yield 7.91g (98%) of 94, a very viscous oil.

NMR: δ 1.6-2.3 (m,4H), 2.6 (dd,J=2Hz,1H), 3.1 (dd,J=5Hz,1H), 3.8 (O-H), 4.2 (m,1H), 5.4 (s,2H), 4.8-6.0 (m,4H), 7.6 (d,J=9Hz,2H), 8.2 (d,J=9Hz,2H)

IR: C=O, 1730 (s) (ester); C=O, 1760 (s) (β-lactam); OH, 3450 (broad)

Phosphorane 95

To a mixture of the alcohol 94 (16 mmoles; 5.38g) and pyridine (2.05 equivalents; 2.64 ml) in 100 ml

THF/dioxane (1:1) was added $SOCl_2$ (2 equivalents; 2.28 ml) dropwise, under N_2 at -10°. The reaction was stirred at -10° for .5 hour, allowed to warm to room temperature and stirred for an additional 1½ hours. Evaporation of the solvent gave the crude chloro compound, which was unstable on silica gel. Triphenylphosphine was added to a solution of the crude chloro compound in THF/dioxane (100 ml; 1:1). Pyridine (1:2 equivalents; 1.54 ml) was added at room temperature, and the reaction mixture heated overnight at 50°. Evaporation of the solvent followed by chromatography (short column) with increasing concentration of ethyl acetate (1:4 ethyl acetate - hexane; 1:1 ethyl acetate - hexane) provided 5.62g (61%) of phosphorane 95, as a foam.

NMR: The spectrum was difficult to analyse, but nonetheless, was in general agreement with the expected product.

Δ-3 Carbacephem p-nitrobenzyl ester 97

The phosphorane 95 (3.11 mmoles; 1.80g) was dissolved in 40 ml dry CH_2Cl_2 and trifluoroacetic acid (1.6 ml) added. Ozone was passed through the solution at -78° until excess was detected. (blue color) Nitrogen was then bubbled through the solution to remove excess ozone, dimethyl sulfide (2.4 ml) added and the mixture stirred and let reach 0°. Ice cold CH_2Cl_2 (30 ml) and saturated

$NaHCO_3$ (60 ml) were added and the resulting mixture was shaken thoroughly. The organic layer was washed again with cold $NaHCO_3$ solution (20 ml). The aqueous layer was extracted with 2X30 ml CH_2Cl_2, the combined organic layers dried over $MgSO_4$ and the solvents removed in vacuo. Cyclisation occurred immediately, and the ester 97, m.p 134°-136°, was obtained in 65% yield (610 mg) after silica gel chromatography (1:3 ethyl acetate - hexane).

NMR: δ 1.3-1.7 (m,1H), 2.1-2.5 (m,3H), 2.7 (dd,J=16, 2Hz,1H), 3.35 (dd,J=16,6Hz,1H), 3.5-3.7 (m,1H) 5.3 (J_{AB}=12Hz,1H), 5.45 (J_{AB}=12Hz,1H), 6.45 (dd,J=2Hz, 1H), 7.65 (d,J=9Hz,2H), 8.2 (d,J=9Hz,2H)

IR: C=O, 1730 (s) (ester); C=O, 1765 (s) (β-lactam)

M.S. m/e, M^+ = 302

Anal. Calcd. for $C_{15}H_{14}N_2O_5$ C, 59.60; H, 4.63; N, 9.27
Found C, 59.64; H, 4.56; N, 9.02

Δ-3 Carbacephem carboxylic acid 92

A solution of 850 mg (2.66 mmoles) of ester 97 in 50 ml ethyl acetate was vigorously stirred at room temperature in a H_2 atmosphere with 550 mg of a 10%

palladium on charcoal as catalyst in the presence of 22 ml of a .2M aqueous solution of $NaHCO_3$. After 10 minutes, the catalyst was filtered off and washed with 10 ml of .2M aqueous $NaHCO_3$ and lots of ethyl acetate. The aqueous layer was separated and acidified with 35 ml 5% oxalic acid. Repeated extractions with 5X30 ml CH_2Cl_2 afforded 202 mg (46%) of acid 92, white crystals, m.p 154°-156°, after preparative thin layer chromatography.

NMR: δ 1.25-1.85 (m,1H), 2.15-2.6 (m,3H), 2.87 (dd, J=16,2Hz,1H), 3.38 (dd,J=16,5Hz,1H), 3.6-3.8 (m,1H), 6.45-6.55 (m,1H), 8.9 (COOH, exchangeable with D_2O)

IR: C=O, 1765 (s); COOH, 3480 (broad)

^{13}C NMR: 22.55 (t), 25.03 (t), 43.07 (t), 47.66 (d), 124.32 (d), 128.10 (s), 161.74 (s), 167.42 (s)

Anal Calcd.for $C_8H_9NO_3$: C, 57.48; H, 5.39; N, 8.38
Found C, 56.70; H, 5.39; N, 8.13

Carbonate 99

DMAP (1.2 equivalents; 1.25g) in 1 ml CH_2Cl_2 was added to a solution of 82 (8.52 mmoles; 1.44g) and p-nitrobenzyl-

chloroformate (10.22 mmoles; 2.20g) in 4 ml CH_2Cl_2 and cooled to 0°, under a N_2 atmosphere. A white precipitate appeared immediately. The cooling bath was removed, and stirring continued for 2.5 hours. The reaction mixture became homogenous within 50 minutes. Prior to work up the reaction mixture was doubled in volume by adding CH_2Cl_2. Work up (5% HCl, H_2O (3X), NaCl) gave the crude product as an oil which was purified by silica gel (70g) chromatography to provide the carbonate 99, in 77% (2.27g) yield.

NMR: δ 1.43 (d,J=6Hz,3H), 1.6-2.2 (m,4H), 2.93 (dd, J=8,2Hz,1H), 3.45-3.7 (m,1H), 5.2 (s,2H), 4.8-5-8 (m,4H), 6.1 (N-H), 7.46 (d,J=9Hz,2H), 8.16 (d,J=9Hz,1H)

IR: C=O, 1760 (s) (β-lactam)

Alcohol 100

Compound 99 (2.10 mmoles; 730 mg) and hydrated p-nitrobenzyl glyoxylate (1.1 equivalents; 524 mg) in 30 ml benzene, were refluxed under a Dean-Stork apparatus for 17 hours. The solvent was evaporated and the crude product chromatographed (1:2 ethyl acetate - hexane) on 50g silica gel, to provide 100, as a foam

in 71% yield (830 mg) yield.

NMR: δ 1.43 (d,J=6Hz,1H), 1.65-2.2 (m,4H), 3.0 (dd,J=8,2Hz,1H), 3.5-3.8 (m,1H), 5.23 (s,2H), 5.33 (s,2H), 4.8-5.6 (m,5H), 7.5 (d,J=9Hz,4H), 8.2 (d,J=9Hz,4H)

IR: C=O, 1760 (s); OH, 3460 (broad)

Phosphorane 101

To a mixture of the alcohol 100 (1.44 mmoles; 800 mg) and pyridine (2.05 equivalents; .24 ml) in 30 ml THF/dioxane (1:1), was added $SOCl_2$ (2 equivalents; .20 ml) dropwise, under N_2 atmosphere at -10°. The reaction was stirred for .5 hour at -10°, allowed to warm to room temperature and stirred for an additional 1.5 hours. The solvent was evaporated to give the crude chloro compound which was redissolved in 40 ml dioxane/THF (1:1), and treated with triphenylphosphine (1.2 equivalents; 453 mg). Pyridine (1.2 equivalents; .14 ml) was added at room temperature and the reaction mixture heated overnight at 50°. The solvent was evaporated to give the crude phosphorane 101, which was chromatographed (25g silica gel; short column) with increasing concentration of ethyl acetate.

(1:4 ethyl acetate - hexane followed by 1:1 ethyl acetate - hexane) Yield: 536 mg (50%, based on 100).

NMR: The spectrum was not readily analysable, but nonetheless, in agreement with the expected product.

Protected hydroxyester, Δ-3 Carbacephem 102

To a solution of the phosphorane 101 (.654 mmole; 524g) in 20 ml CH_2Cl_2 was added .5 ml trifluoroacetic acid. The mixture was cooled to -78° and ozonised until excess ozone was detected. (blue color) Nitrogen was passed through the solution to remove excess ozone then DMS (1 ml) added. After allowing the reaction mixture to warm to 0°, ice cold CH_2Cl_2 (15 ml) and saturated $NaHCO_3$ (30 ml) were added and the resulting mixture was shaken thoroughly. Cyclisation occurred immediately. The organic layer was washed again with cold saturated $NaHCO_3$ (20 ml) and the aqueous layer extracted with 2X20 ml CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent removed on the rotary evaporator. The protected hydroxy ester 102, white solid, m.p 162°-165°, was obtained in 47% (160 mg) yield, after preparative thin layer chromatography.

NMR: δ 1.5 (d,J=6Hz,3H). 2.12-2.54 (m,4H), 3.08 (dd,J=8,2Hz,1H), 3.45-3.66 (m,1H), 5.23 (s,2H), 5.08-5.5 (m,3H), 6.34-6.46 (m,1H), 7.45-7.63 (m,4H), 8.16 (d,J=8Hz,4H)

IR: C=O, 1760 (s)

Anal. Calcd. for $C_{25}H_{23}N_3O_{10}$: C, 57.14; H, 4.41; N, 8.0
Found C, 56.60; H, 4.35; N, 7.70

Hydroxyethyl carboxylic acid, Δ-3 Carbacephem 93

A solution of 100 mg (.190 mmole) of the protected hydroxy ester 102 in 7 ml ethyl acetate was vigorously stirred at room temperature under a H_2 atmosphere with 74 mg 10% palladium on charcoal as catalyst in the presence of 3.1 ml of a .2M aqueous solution of $NaHCO_3$. After 5 minutes, the catalyst was filtered off and washed with 1.5 ml of .2M aqueous $NaHCO_3$ and lots of ethyl acetate. The aqueous layer was separated and acidified with 10 ml 5% oxalic acid. Repeated extractions with 5X15 ml portions CH_2Cl_2, followed by drying and evaporation of the combined organic extracts provided 18 mg (40%) of the hydroxy acid 93, white crystals, m.p 93-95°.

NMR: δ 1.30 (d,J=6Hz,3H), 1.25-1.70 (m,1H), 2.0-2.5 (m,3H), 3.02 (dd,J=6,2Hz,1H), 3.60-3.8 (m,1H) 4.50 (OH and COOH, exchangeable with D_2O), 4.0-4.4 (m,1H), 6.35-6.45 (m,1H)

IR: C=O, 1765 (s); OH and COOH, 3500 (broad)

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CLAIMS TO ORIGINAL RESEARCH

1. The Δ-1 carbapenems bearing either the $-SOCH_3$ or the $-SO_2CH_3$ substituents at C_2, and phenyl group at C_3 were prepared.

2. Attempted Michael addition reactions of N-lithio 4-vinylazetidin-2-one and vinyl phosphonates, bearing t-butyl carboxylate and oxidised sulfur functionalities produced no Michael adducts.

3. The 1-pyrrolidinomethyl-4-vinylazetidin-2-one and -4-(3'-butenyl)-azetidin-2-one were employed as intermediates in highly stereoselective preparation of several trans-3,4-disubstituted azetidin-2-ones.

4. The 1-pyrrolidinomethyl function, an effective N-H blocking group, was stable to basic reagents and readily removed under mild acidic conditions.

5. The Δ-3-carbacephem-4-carboxylic acid was prepared from 4-(3'-butenyl)-azetidin-2-one.

6. The trans-7-hydroxyethyl-Δ-3-carbacephem-4-carboxylic acid was also prepared from 4-(3'-butenyl)-azetidin-2-one. The trans-7-hydroxyethyl substituent was introduced stereoselectively via the 1-pyrrolidinomethyl-4-(3'-butenyl)-azetidin-2-one intermediate.