Synthesis of β-Lactams

A Thesis

by

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Synthesis of β-Lactams

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Abstract

The syntheses of the cephalosporin analogs cis-N-2'-carboxyphenyl-3-N-phenylacetamido-4-methoxymethyl-2-azetidinone and 7-β-phenylacetamido-3'-carboxybenzo[3,4]-0-2-isocephem are described. Both compounds possessed no significant antimicrobial activity toward a variety of bacteria.

The reaction of dimethylacryloyl chloride and crotonyl chloride with various Schiff bases afforded cis-β-lactams containing novel and potentially versatile side chains. Cis-N-2',4'-dimethoxybenzyl-3-ethyl-4-carboxymethyl-2-azetidinone, a key intermediate for the synthesis of cephalosporin and penicillin analogs containing an ethyl (PS-5) side chain, was synthesized.

A synthetic scheme for the synthesis of thienamycin analogs is described. Although the synthesis was not completed, the problems which remain to be solved are clearly described.

Synthèse de β-Lactames

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Résumé

La synthèse des analogues de céphalosporines, la cis-N-2'-carboxyphényle-3-N-phénylacétamido-4-méthoxyméthyle-2-azétidinone et le 7-β-phénylacétamido-3'-carboxylbenzo[3,4]-0-2-isocéphem, est décrite. Ces deux produits n'ont démontré aucune activité antimicrobienne contre diverses bactéries.

Les réactions des chlorures diméthylacryloyliques et crotonyliques avec diverses bases de Schiff fournissent des cis-β-lactames possédant des nouveaux groupements fonctionnels ayant un très grand potentiel. La cis-N-2'-4'-diméthoxybenzyle-3-éthyle-4-carboxyméthyle-2-azétidinone, un intermédiaire-clé à la synthèse de composés analogues aux céphalosporines et pénicillines ayant un groupement éthylique (PS-5), a été synthétisée.

On décrit également une séquence synthétique menant à des analogues à la thiénamycine. Les problèmes qui ont empêché le parachèvement de cette synthèse ont été clairement identifiés et décrits.

Acknowledgements

I would like to express my sincere gratitude to my research director, Dr. George Just, for his guidance and continuous encouragement throughout my stay in his laboratory.

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All my co-workers for their friendship and helpful discussions.

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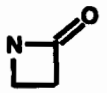
To my parents

Introduction

Preface

β-Lactams are 4-membered heterocyclic compounds of type 1. They were first synthesized by Staudinger in 1907[1]. Penicillin 2, the first of the modern antibiotics, discovered in the late 1920's[2], was found to contain this ring. In 1955, Abraham



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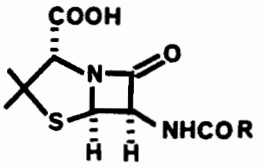

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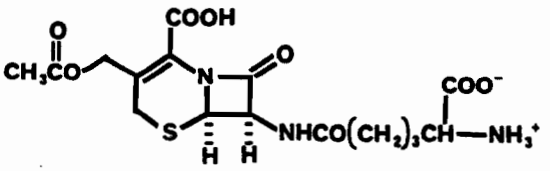
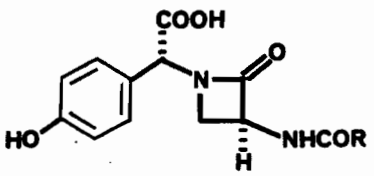
and Newton at Oxford University[3] isolated from a cephalosporium species of fungi a new β-lactam antibiotic substance Cephalosporin C(3). The structure was determined by the same workers in 1961[4] and confirmed by Hodgkin and Maslen[5] by means of single crystal X-ray diffraction studies.



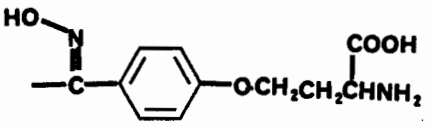
3

Since their discovery, the penicillins and the cephalosporins have been the drugs of choice for treating bacterial infections in man[6]. They have very low toxicity and the penicillins are easily obtained using fermentation techniques. Because of

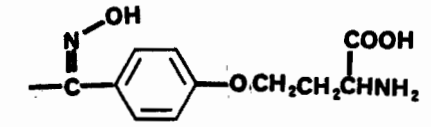
their importance, there has been an enormous amount of research on the biological and chemical properties of cephalosporins and penicillins. This effort has recently produced 3 new types of β-lactam antibiotics: Norcardicin A and B[7-10]; Thienamycin[11] and related compounds PS-5[12], MM4550(MC696-SY2-A), MM13902[13,14]; and Clavulanic[15] Acid. Norcardicin has interesting antimicrobial activity in vivo. Clavulanic Acid is a potent irreversible inhibitor of various β-lactamases. The thienamycins are not only effective against both Gram positive and Gram negative bacteria at low levels, but show also β-lactamase inhibitory activity.

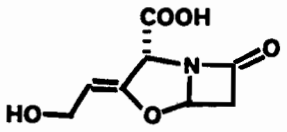


Norcardicin A

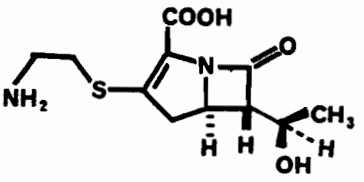


Norcardicin B

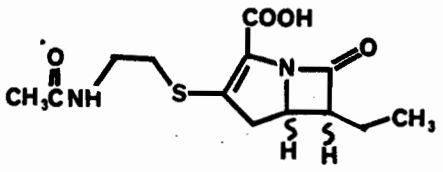




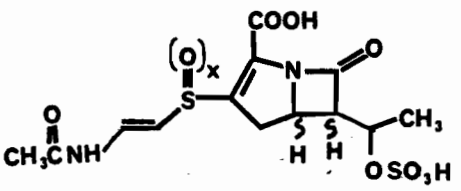
Clavulanic Acid



Thienamycin



PS-5



x=1 MM4550(MC696-SY2-A)

x=0 MM13902

Mode of action of the β-lactam antibiotics[16,17,18]

The low toxicity of the β-lactam antibiotics suggests that the drugs inhibit some bacterial structure which has no counterpart in higher animals. The β-lactam antibiotics are thought to inhibit bacterial cell wall synthesis. The bacterial cell wall, a characteristic bacterial structure entirely lacking in mammals, is a giant macromolecule which envelops the organism, supporting the bacterial cell membrane against lysis caused by the difference in osmolarity between the cell cytoplasm and the culture medium which is relatively hypotonic. A peptidoglycan is an important constituent of the cell wall. Its integrity is required for the maintenance of cell shape in bacteria. The backbone of the peptidoglycan consists of alternating residues of N-acetyl glucosamine and N-acetyl muramic acid. The N-acetyl muramic acid residues are substituted by peptide chains which are cross-linked to give a mesh like character to the peptidoglycan (Fig. 1, page 4). The synthesis of the peptidoglycan can be divided into three stages. The first two steps are the synthesis of the backbone and the attachment of the side chains. In the final stage, the side chains are cross-linked in a reaction catalyzed by a transpeptidase.

In 1965 Tipper and Strominger concluded, on the basis of different studies of the effects of penicillin on peptidoglycan synthesis on S.aureus that penicillin blocked the last cross-linking step in the peptidoglycan synthesis. They proposed that the transpeptidase reacted with the peptide bond between

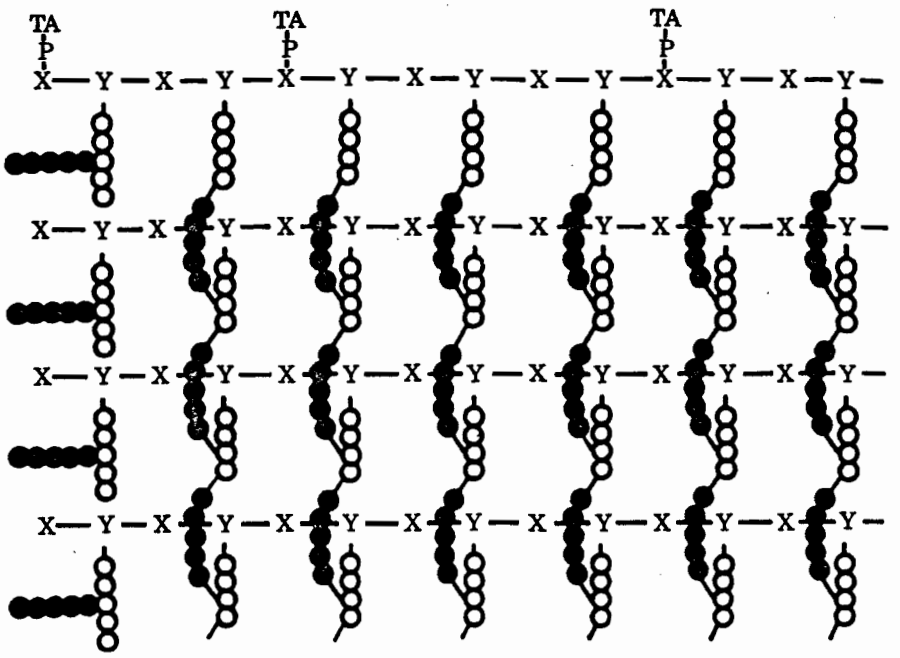


Fig. 1: Structure of the peptidoglycan of the cell wall of Staphylococcus aureus[18]. In this representation, X (acetylglucosamine) and Y (acetylmuramic acid) are the two sugars in the peptidoglycan. Open circles represent the four amino acids of tetrapeptide, L-alanyl-D-isoglutaminyl-L-lysyl-D-alanine. Closed circles are pentaglycine bridges which interconnect peptidoglycan strands. The nascent peptidoglycan units bearing open pentaglycine chains are shown at the left of each strand. TA-P is the teichoic acid antigen of the organism which is attached to the polysaccharide through a phosphodiester linkage.

the terminal D-alanines in the pentapeptide chain of uncross-linked peptidoglycan (Fig. 2). An acyl enzyme intermediate would be formed and the D-alanine released. The amino group from the prospective cross-bridge would next displace the enzyme from the acyl-enzyme intermediate regenerating the free enzyme and form a peptide cross-bridge. Penicillin was hypothesized to be an analogue of the terminal D-alanyl-D-alanine in the pentapeptide chain. The CO-N bond in the highly strained β-lactam ring would correspond to the peptide bond cleaved during transpeptidation, and penicillin might, in fact be an analogue of the transition state in peptide bond cleavage. The transpeptidase would react with the penicillin to open the β-lactam ring and form a penicilloyl enzyme intermediate.

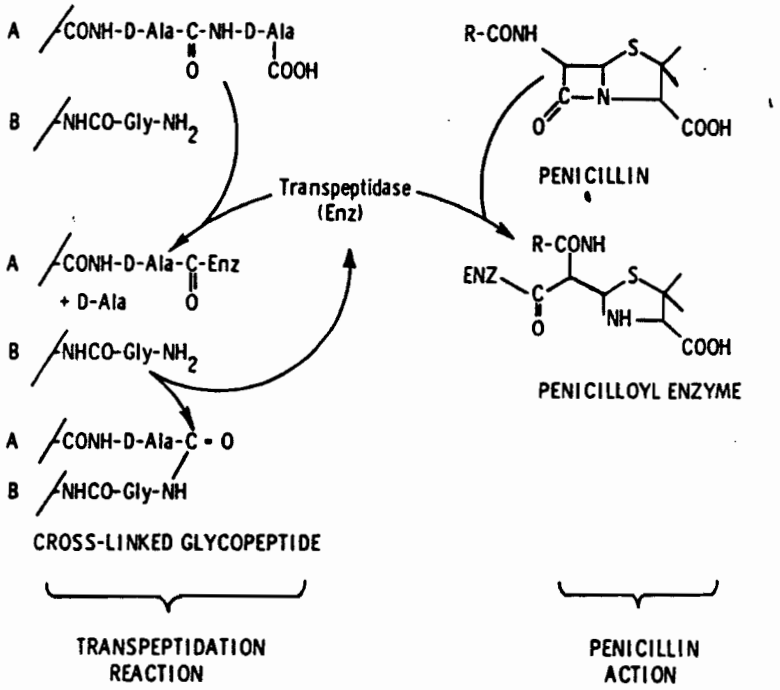


Fig. 2: Mechanism of action of penicillin proposed by Tipper and Strominger in 1965[16]. A represents the end of the main peptide chain of the glycan strand. B represents the end of the pentaglycine substituent from an adjacent

However, since the penicilloyl enzyme intermediate is stable, the transpeptidase would be inactivated, preventing any further incorporation of cross-linked peptidoglycan into the cell wall. Continuing growth of bacteria in the absence of the synthesis of rigid cross-linked peptidoglycan would then result in the rupture of the wall at the region of active cell wall growth and the release of the cell contents.

Recent studies have shown that the interaction of the β-lactam antibiotics with bacterial cells is very complex[20,21]. Bacteria do not contain a single penicillin sensitive transpeptidase which is the target for the β-lactam antibiotics but rather a large number of enzymes (transpeptidases, carboxypeptidases, endopeptidases) which are inhibited by the β-lactam antibiotics. The affinity of these enzymes to the β-lactam antibiotics varies. All of these enzymes are thought to have distinct functions in the biosynthesis of the peptidoglycan. Inactivation of these enzymes results in the characteristic effects that the antibiotics produce on the shape and dimension of bacteria. For example, all the morphological effects of β-lactams on E.coli can be explained by the inhibition of three penicillin binding proteins. Inhibition of any of these three penicillin binding proteins, which are most probably enzymes, will result in cell death. The way in which a particular β-lactam antibiotic kills bacteria depends on the affinity of each of the target enzymes for the antibiotic and the function of these enzymes in peptidoglycan synthesis. For example, in the presence of Mellicinam, which binds exclusively to protein

Table 1. Effects of β-lactam antibiotics on growth of *E. coli* predicted by their relative affinities for penicillin binding proteins[21]

Relative affinities of binding proteins 1B, 2 and 3 for a β-lactam antibiotic*	Morphological effects produced by three arbitrary concentrations of a β-lactam antibiotic			β-lactam showing this behaviour
	Low concentration	Medium concentration	High concentration	
1B > 2 or 3	Lysis	Lysis	Lysis	Cephalosporidine
2 > 1B > 3	Spherical cells	Lysis	Lysis	6-Aminopenicillanic acid
2 > 3 > 1B	Sperical cells	Filaments with bulges	Lysis	None known
2 ➤ 1B or 3	Spherical cells	Spherical cells	Spherical cells	Mecillinam
3 > 1B > 2	Filaments	Lysis	Lysis	Benzylpenicillin
3 > 2 > 1B	Filaments	Filaments with bulges	Lysis	Ampicillin

* 1B = cell elongation; 2 = cell shape; 3 = cell division.

2 (Table 1), E.coli bacteria grow into larger and larger spherical cells which finally lyse, while in the presence of Cephalexin, which binds preferentially to protein 3, E.coli cells cease dividing, and ultimately die. The pathways by which inhibition of these enzymes leads to cell death are unknown. Inhibition might trigger autolytic enzymes which destroy the cell[19].

Bacterial resistance to penicillins and cephalosporins[23]

The general trend over the years has been an increase of penicillin and cephalosporin resistant strains of some pathogens, though not all. Resistant strains of bacteria arise because no species of bacteria is homogeneous. During the treatment of an infection, the few mutants which are less sensitive to the particular β-lactam antibiotic used can survive. These mutants multiply and create a more resistant strain. The resistance of a species of bacteria can be due to the production of β-lactamases, a slight change of the target enzyme which lowers the affinity of a given β-lactam antibiotic or to decreased permeability of the cell. The greater resistance of Gram negative bacteria is largely due to the decreased permeability of their cell walls to the β-lactam antibiotics. Their cell walls are much more complex than those of the Gram positive bacteria.

β-Lactamases are large proteins produced by bacteria to destroy β-lactam antibiotics[22]. They hydrolyze the antibiotic before it reaches the target enzyme. Gram positive bacteria produce large amounts of β-lactamases in response to the presence of penicillins or cephalosporins and these β-lactamases are predominantly extra cellular. Gram negative bacteria produce much smaller amounts of β-lactamases and these are cell bound. The β-lactamases of Gram negative bacteria are very effective since they hydrolyze only the antibiotic that penetrates the cell wall. The structure of some β-lactamases has been deduced[24,25,26] and mechanisms for their mode of action

have been described[26] (Fig. 3).

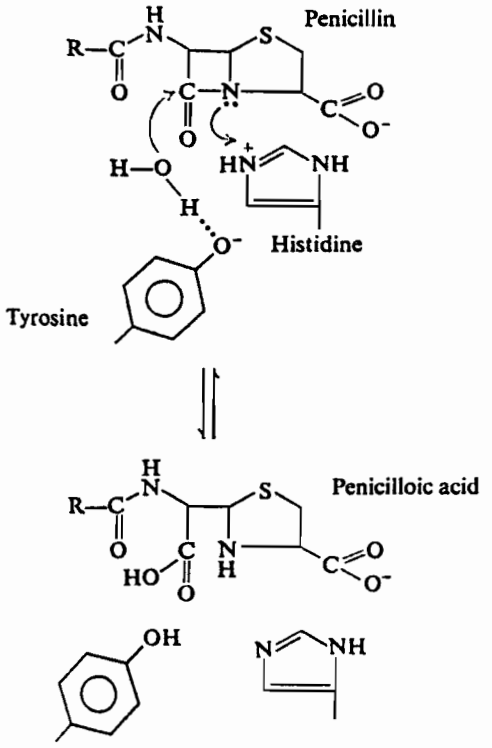


Fig. 3: Proposed mechanism for the mode of action of β-lactamase from E.coli[26]

Structure activity relationships

Since the discovery of penicillin and cephalosporin C, thousands of derivatives and analogues have been synthesized[27]. This has become necessary because of the increasing number of bacteria which are becoming resistant to the known β-lactam antibiotics. The structural features necessary for optimal activity were thought to be until recently[6,45]:

(a) a cis fused β-lactam ring

(b) an acylamino side chain which can be considerably varied or an $-N-\underset{\underset{H}{|}}{C}=N-$ side chain (amidino penicillins)

(c) an acidic function, the nature of which does not seem critical since it can be replaced by a tetrazole

(d) a 5 membered or 6 membered ring containing a double bond conjugated with the β-lactam ring nitrogen, conferring enough ring strain so as to raise the β-lactam i.r. frequency to > 1765 cm^{-1}.

Two recently isolated β-lactam antibiotics do not have all the above structural features. Thienamycin, although it has a trans-fused ring and a novel side chain, posseses high potency toward a large number of Gram positive and Gram negative bacteria. For some bacteria, Thienamycin is 10 to 100 times more potent than the traditional β-lactam antibiotics. It has been proposed[11] based on molecular models, that, although the side chain is trans, the hydroxyl group can occupy the same binding site as the nitrogen atom in the acyl amino side chain. This argument cannot be used for the deoxy derivative of Thienamycin, PS-5, which also has good antimicrobial activity. Although it has a very low β-lactam frequency (1720 cm^{-1}), Norcardicin A is active in vivo against a large number of very resistant bacteria. The discovery of these two types of β-lactam antibiotics indicates that the criteria listed above are too rigid. Compounds that do not fulfil all the criteria might still have significant antimicrobial activity.

Synthesis of β-lactam antibiotics

(a) Fermentation and semi-synthetic[6]

All of the cephalosporins and penicillins used for the treatment of bacterial infections are presently obtained either from fermentation of the appropriate fungi or through a semi-synthetic procedure. Pen G, Pen V and approximately one hundred others are obtained by adding the appropriate substituted acetic acid to the fermentation broth. All the others are obtained through acylation of 6-aminopenicillanic acid (6-APA). The cephalosporins are obtained either through

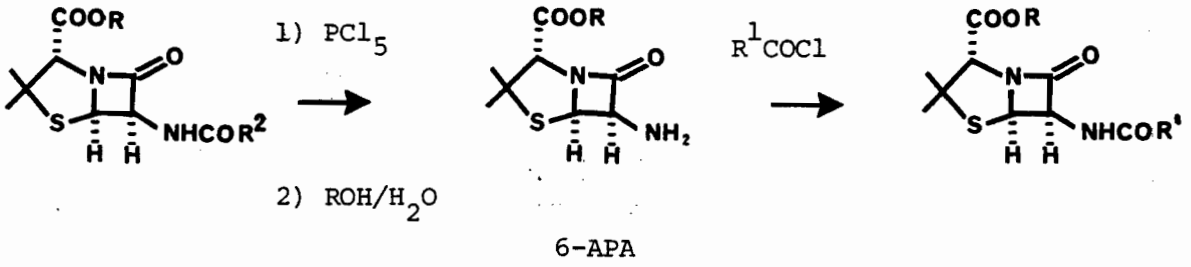


Fig. 4a Semi-synthetic procedure for the synthesis of penicillins

fermentation, from penicillins using the pen-cephem rearrangement[29], or through a semi-synthetic procedure similar to that used for penicillins.

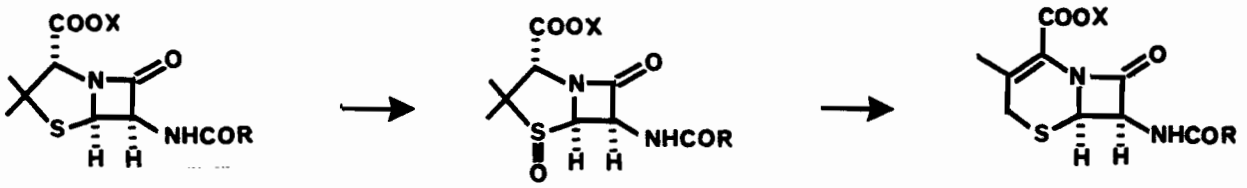


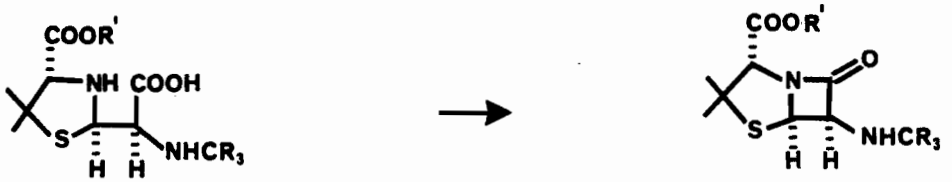
Fig. 4b Pen-cephem rearrangement[29,33].

(b) Total synthesis[34,35,33]

In the search for better β-lactam antibiotics, there has been considerable activity in the total synthesis of β-lactam antibiotics. Total synthesis allows the formation of many attractive structures not available by fermentation or semi-synthetic procedures.

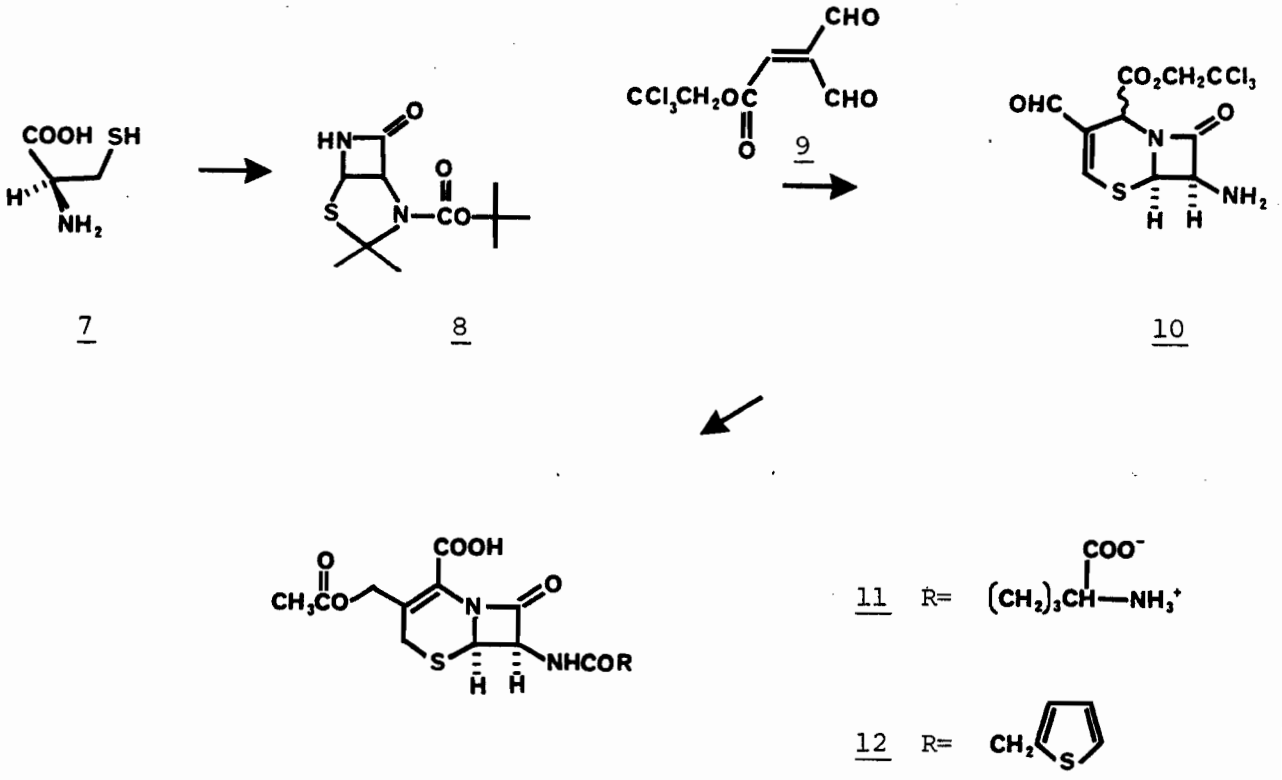
(i) Early developments

The first, synthesis of a penicillin was reported by Sheehan[30]. The key step was the cyclization of 5 to 6 using dicyclohexylcarbodiimide (DCC). A few years later in 1965, Woodward[31] announced in his Nobel Prize lecture the first



5 6

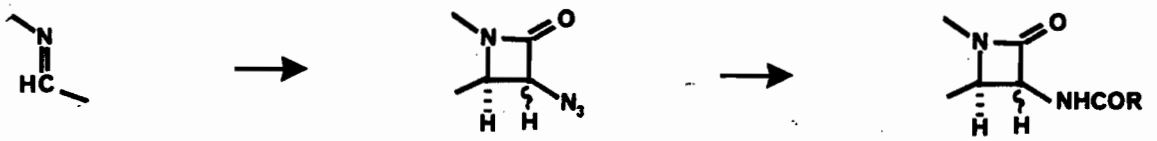
successful stereospecific synthesis of Cephalosporin C 11 and Cephalothin 12. By a series of ingenious and stereospecific transformations, L-cysteine 7 was converted to a key intermediate, the fused thiazolidine 8. Reaction of 8 with dialdehyde 9, followed by acid treatment, afforded 10. Subsequent manipulations gave 11 and 12. Using intermediate 8, Woodward and his co-workers have also synthesized nuclear analogues of cephalosporin[34,32]. Subsequently several other approaches to



the synthesis of cephalosporins and penicillins have been reported[28,34,35]. The most useful and versatile have been those using the reaction of imines with acid chlorides or the reaction of olefins with chlorosulphonyl isocyanate to form the β-lactam ring.

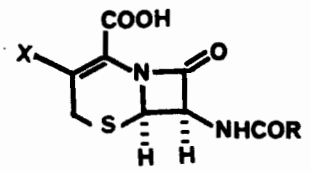
(ii) Acid chloride-imine approach

This route to bicyclic β-lactams is based on the well known cycloaddition of ketene precursors with imines[1]. It has been developed by Bose[36] and co-workers in a total synthesis of ± methyl epipenicillin. Bose found that treatment of imines with azidoacetyl chloride in the presence of triethylamine afforded azido β-lactams 13 which were easily transformed to the desired acylamino β-lactam 14. Reaction of 5 or 6 membered

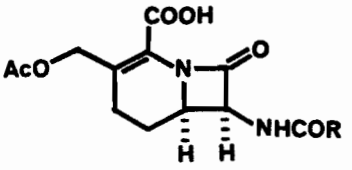


13 14

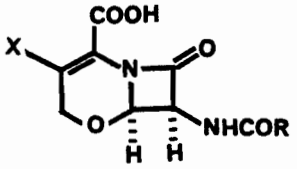
cyclic imines with azidoacetyl chloride afforded directly the bicyclic nucleus of penicillins and cephalosporins respectively. Unfortunately this direct approach gives the trans β-lactam which must be isomerized to the desired, but less stable, cis isomer. Although a procedure for this isomerization has been described in detail by Christensen[37], it has been little used by others[38]. A more successful approach has been to first form the β-lactam ring and then build the remaining ring. Both these approaches have been used by the Merck group to synthesize a large number of Cephalosporin C derivatives with structure A and also some nuclear analogues with structures B, C, and D[39-44]. Their approach is illustrated by the



A



B



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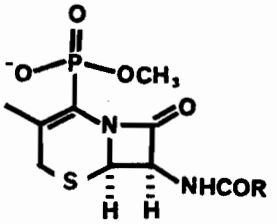
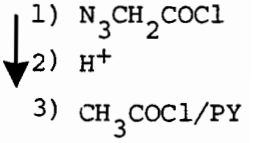
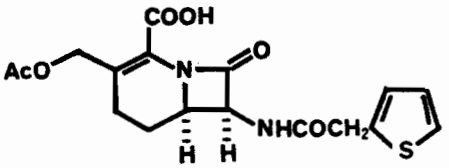


D

synthesis of 15. The antibacterial activity of compounds A, B and C was about the same. The phosphono derivative D was found to be less active than the corresponding cephalosporanic acid.





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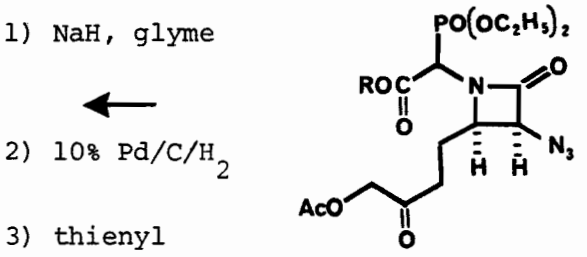
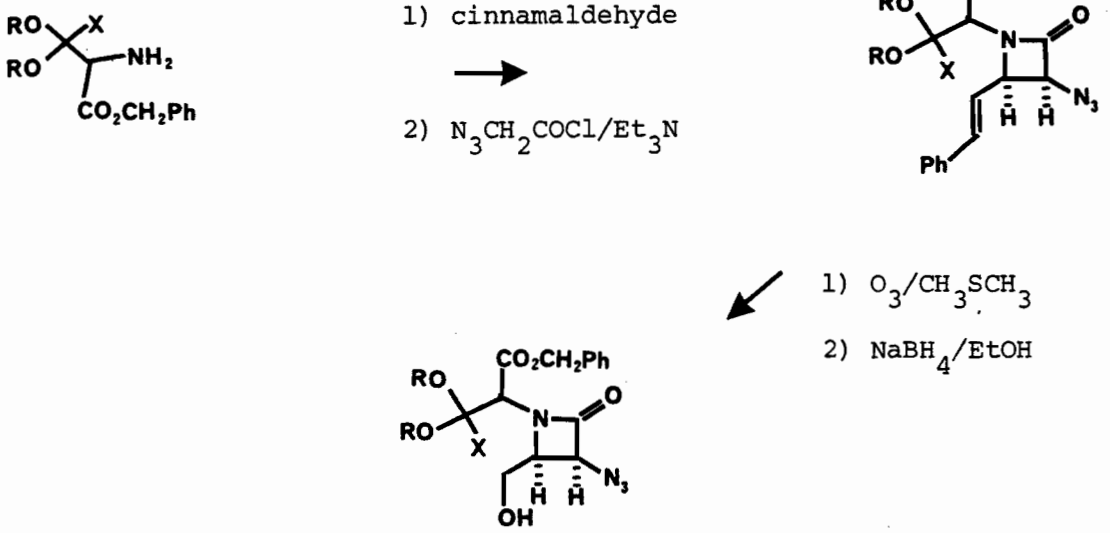


Recently chemists at Bristol Laboratories[45] and later at

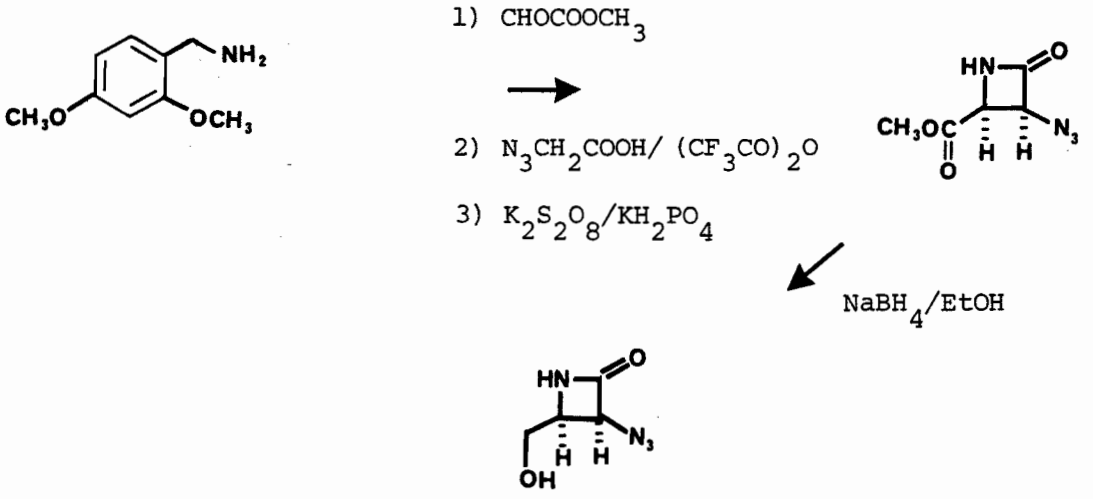
Smith, Kline and French Laboratories[52] reported new approaches toward nuclear analogues of penicillins and cephalosporins. Their key intermediates E and F are similar. An important

a) Bristol Approach



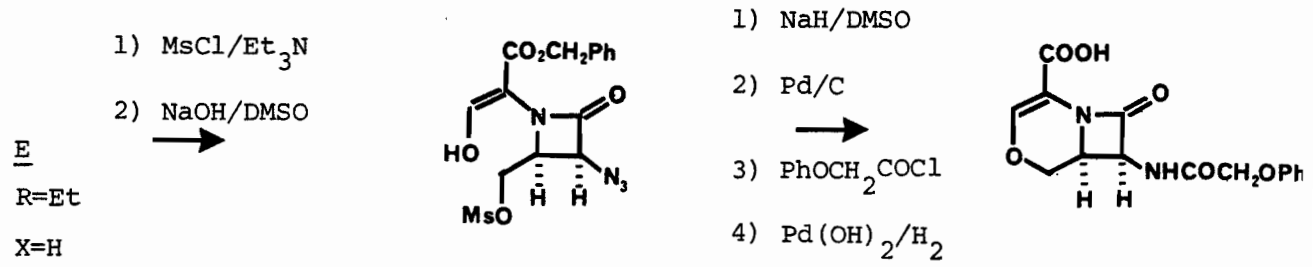
E

b) S.K.F. Approach



F

feature of both approaches is the exclusive formation in high yield of cis β-lactams. Each group was able to transform their key intermediate into a large number of nuclear analogs of penicillin and cephalosporins[45-51,52-55]. For example, 16 was synthesized from E and 17 from F.



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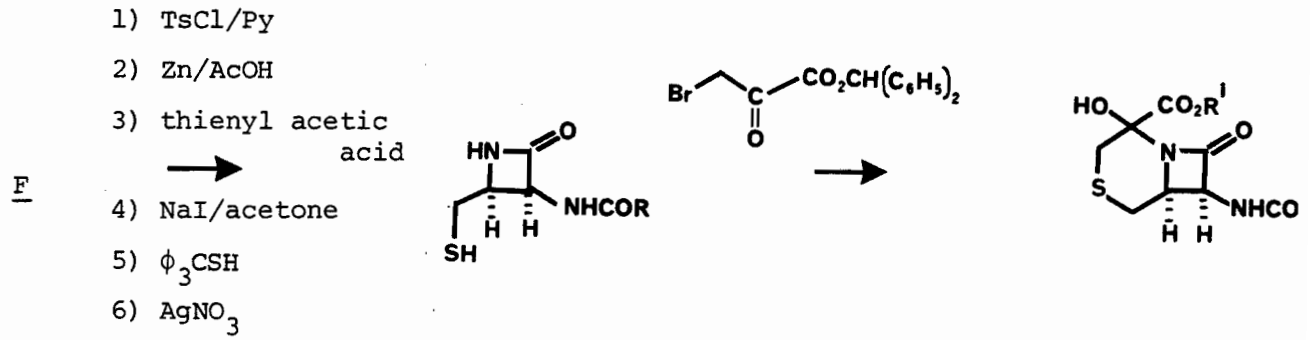
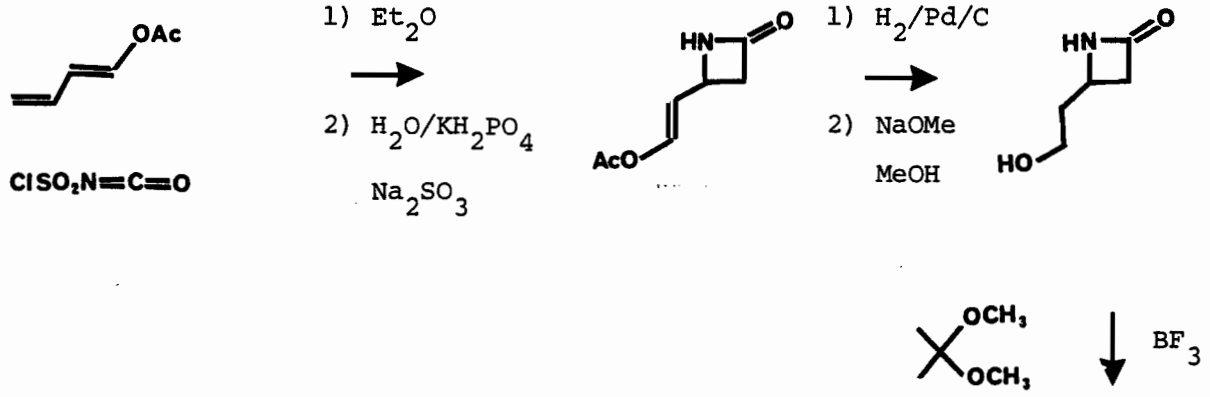


17

(iii) Chlorosulphonyl isocyanate-olefin route[57]

This approach is based on the known formation of β-lactams by cycloaddition of chlorosulphonyl isocyanate and olefins[56]. This reaction has been used to form the β-lactam ring in recent syntheses of thienamycin and clavulanic acid. The approach is illustrated by the Merck synthesis of thienamycin[11].



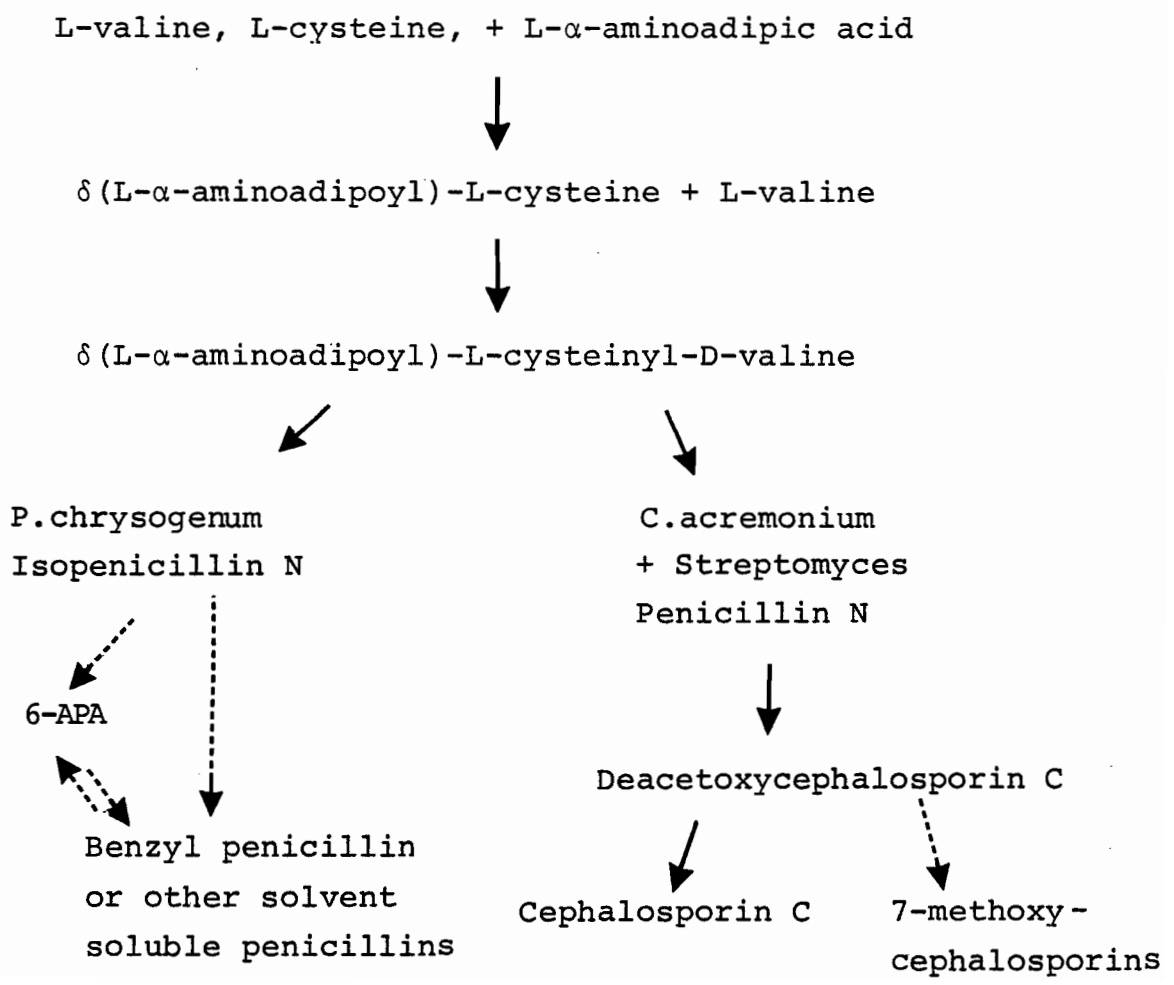
H

G

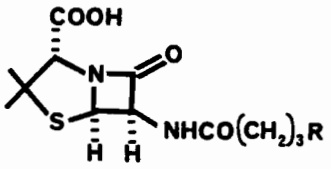
H was transformed in 13 steps to thienamycin. Intermediates G and H are very versatile and should allow the synthesis of many derivatives of thienamycin.

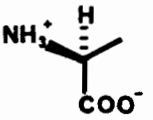
Biosynthesis of penicillins and cephalosporins[58,59]

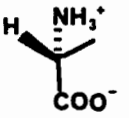
Only a few organisms synthesize β-lactam antibiotics. These compounds are secondary metabolites and their role is unknown. Various studies have shown that the formation of penicillins and cephalosporins by Penicillium chrysogenum, Cephalosporium acremonium and Streptomyces spp. is dependent on the presence of 3 amino acids, L-valine, L-cysteine and L-aminoadipic acid. Abraham[58] has proposed a pathway, consistent with recent studies on cell free systems, in which these amino acids are transformed to the penicillins and cephalosporins.



The process by which the tripeptide is transformed into isopenicillin N 18 and penicillin N 19 is unknown. No intermediates between the tripeptide and the fully formed rings have ever been isolated.

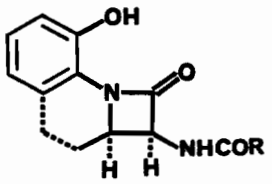


18 R= 

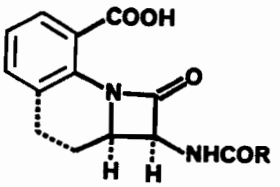
19 R= 

Brief description of project

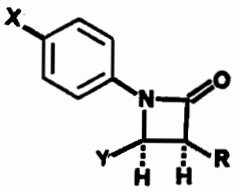
During the last few years we have been involved in the synthesis of penicillin and cephalosporin analogues with general structures I and J. These analogues have a cis fused β-lactam ring and an acylamino side chain like the cephalosporins but differ in that the acidic function is attached to an aromatic ring and that the strain of the β-lactam ring is generated by electron withdrawing groups attached to the benzene ring, and/or by fusing the aromatic and β-lactam rings by an additional ring as indicated. Compounds of general structure K have been synthesized by Bose[60] and some possess weak antimicrobial activity. We hoped that attachment of an acidic function and other modifications to increase the β-lactam frequency would increase their antimicrobial activity to useful levels.



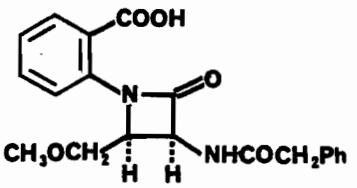
I



J

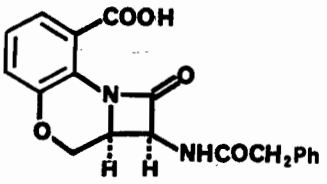


K



20

This thesis consists of two parts. The first two chapters describe the successful synthesis of 20 and 21. While this work was in progress Doyle published the synthesis of 22. The last chapter describes synthetic studies toward thienamycins.



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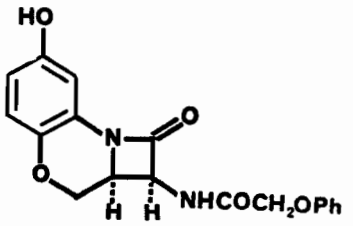
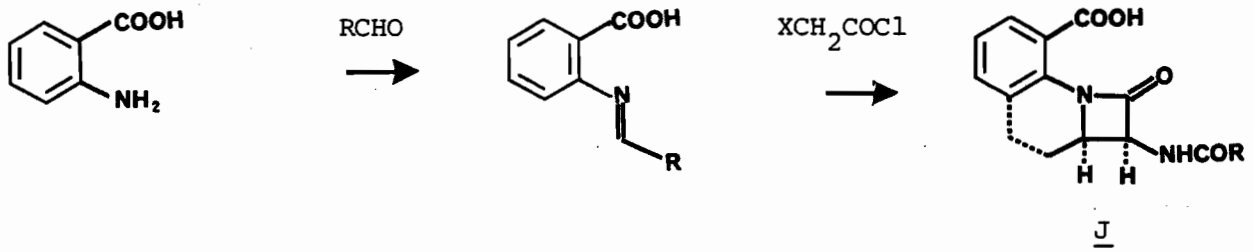


22

Chapter 1

Synthesis of cis-N-2'-carboxyphenyl-3-N-phenylacetamido-4-methoxymethyl-2-azetidinone

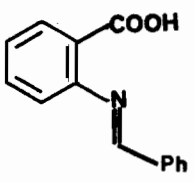
For the synthesis of compounds with the general structure J we decided to use the imine acid chloride approach. This approach allows the use of commercially available substituted anthranilic acids as starting materials (Fig. 5).



J

Fig. 5: General approach to the synthesis of compounds with general structure J

Although the reaction of Schiff bases of substituted anilines with several acid chlorides has been investigated by Bose[60,61,62] and others[63], ortho substituted anilines have been little studied[123]. As a model compound, the known benzylidene anthranilic[64] acid 23 was condensed with phthalimidoacetyl chloride[65]. Instead of the expected β-lactam 25, a crystalline compound, the spectral data of which was consistent with 24, was obtained. P.m.r. of 24 showed an AB quartet for the



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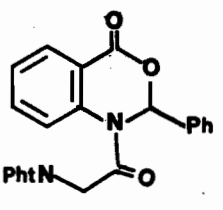

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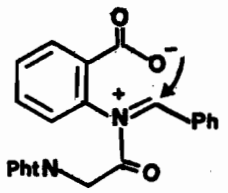
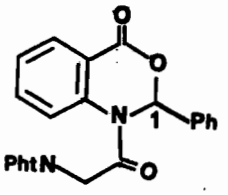
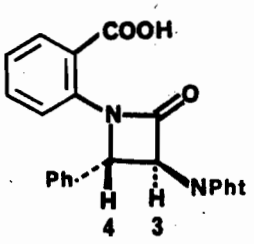




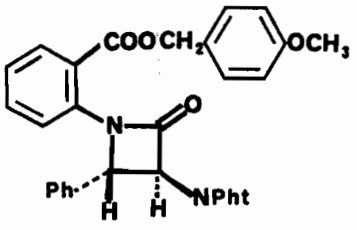
26 24

CH_2 group with J = 16 Hz. The two protons were not equivalent because of the asymmetric centre at C_1. Compound 24 was probably formed by trapping of the postulated intermediate 26 in the cycloaddition[70] by the carboxyl function as indicated. Bose[61] had also discovered that free carboxyl and hydroxyl functions interfered in the cycloaddition but he was unable to isolate any of the products. He[61] found that silylation of all interfering hydroxyl and carboxyl functions in the Schiff base followed by treatment with the appropriate acid chloride afforded good yields of β-lactams. When Schiff base 23 was silylated in situ before the addition of phthalimido acetyl chloride, the trans β-lactam 25 was obtained in 70% yield. Its structure followed from its spectral and analytical data and the stereochemistry of the ring junction from the fact that



25

$J_{3,4}$ = 2 Hz. In the p.m.r. spectra of cis β-lactams, $J_{3,4}$ varies from 4 to 6 Hz, while in trans β-lactams, it varies from 1.5 to 2.8 Hz[66,124]. The acid was characterized as its p-methoxybenzyl ester 27, $\nu_{C=O}$ (Nujol) 1780, 1720 cm^{-1}, obtained by reacting 25 with p-methoxybenzyl alcohol and 1.2 equivalent of di-neopentyl formamide acetal in acetonitrile[67]. The benzyl ester was converted to the free amine 28 by means of hydrazine in methylene chloride. In order to isomerize the trans β-lactam 28 to the desired cis isomer 30, we decided to use the Christensen[37] isomerization technique for amino β-lactams (page 25), which involves treatment of their p-nitrobenzaldehyde Schiff bases with phenyl lithium, followed by protonation under kinetically controlled conditions. Treatment of amine 28 with



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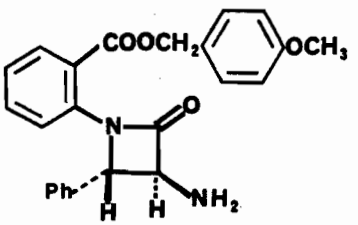

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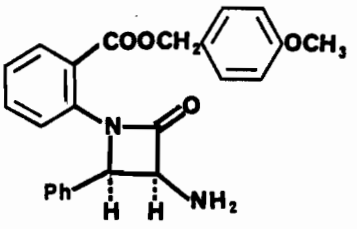
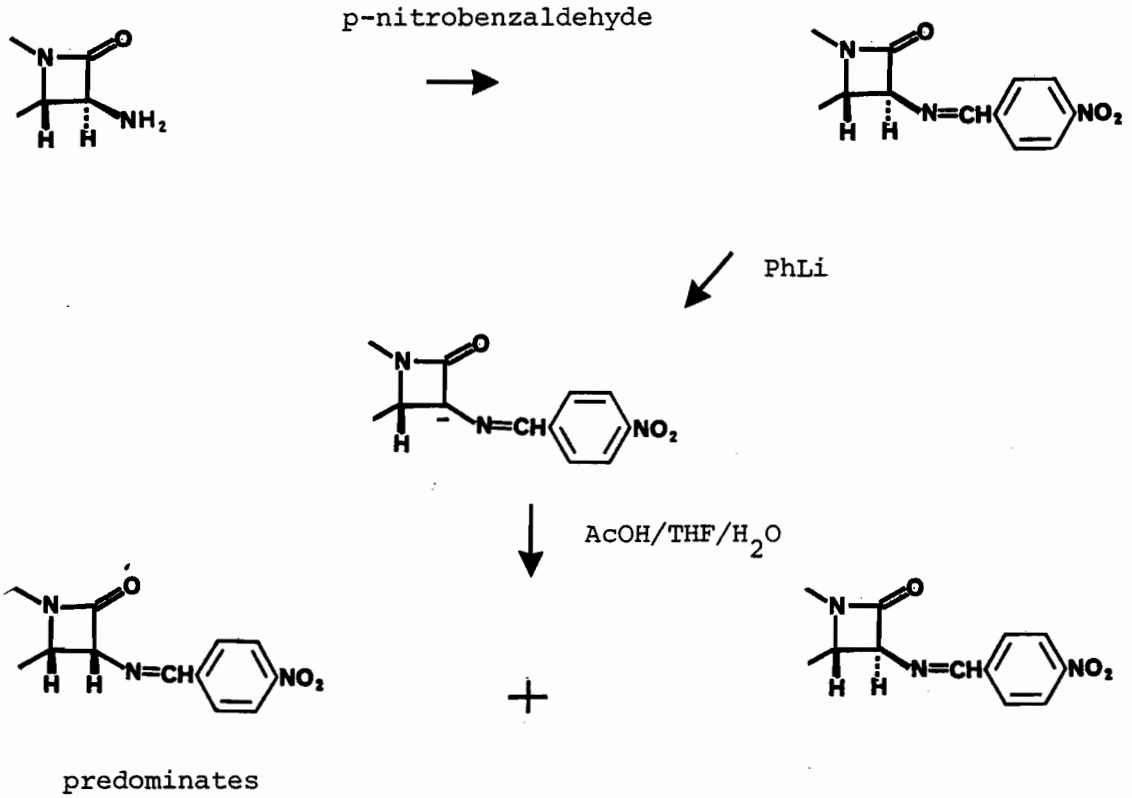
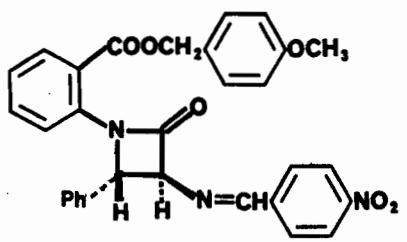


30

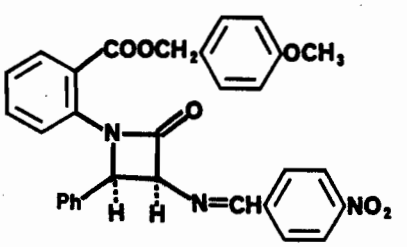
Fig. 6: Christensen's isomerization technique for amino β-lactams



1 equivalent of p-nitrobenzaldehyde in refluxing benzene afforded imine 29a i.r. ($CHCl_3$) γ_{max} 1775, 1730, 1620 cm^{-1}, in quantitative yield. The p.m.r. spectrum of 29a showed a characteristic singlet at 8.4 p.p.m. for the imine proton. Unfortunately, deprotonation of 29a with phenyl lithium at -78° followed by quenching with acetic acid/tetrahydrofuran/H_2O afforded a low yield of 29a, and no cis isomer 29b could be isolated

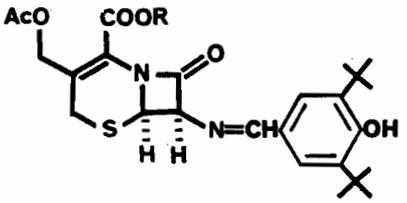


29a



29b

Nakao[68] et al have recently described a novel route to 7α-methoxy cephalosporins. They found that oxidation of imine 31 with lead dioxide afforded quinoidal compound 32. Quenching of 32 with methanol gave imine 33. Hydrolysis of 33 with Girard reagent T afforded 7α-methoxy amine 34 which was easily transformed to the desired 7α-methoxy cephalosporins. We reasoned



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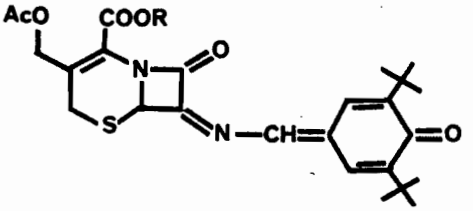

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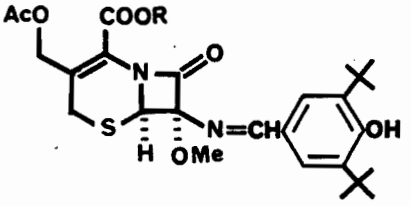

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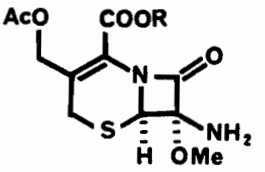
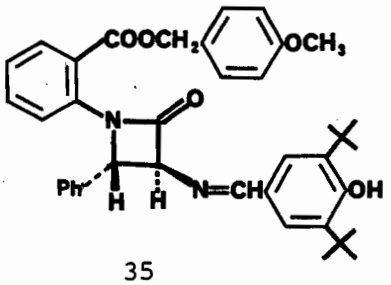


34

that treatment of 35 with PbO_2 followed by quenching with $ZnBH_4$ should give the desired cis β-lactam 36. Reaction of 28



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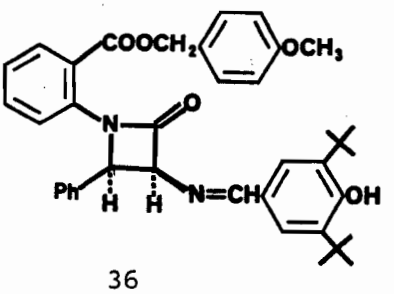
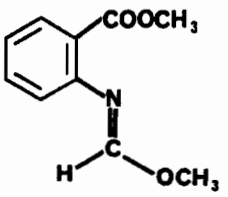


36

with 1 equivalent of 3,5-di-t-butyl-p-hydroxybenzaldehyde in refluxing benzene afforded 35 in quantitative yield. We were

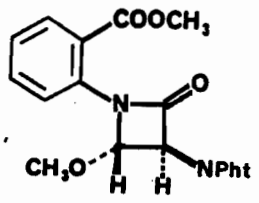
not able to achieve the transformation of 35 to 36.

We suspected that the difficulties in obtaining cis β-lactams may have been due to the relatively bulky phenyl group, and therefore performed a similar series of reactions using the imino ether 37. Heating a solution of methyl anthranilate and 2.2 equivalents of trimethyl orthoformate[69] under carefully controlled conditions afforded a 43% yield of 37, i.r. (neat) 1730, 1660 cm^{-1}. P.m.r. of 37 showed singlets at 3.7 and 3.8 p.p.m. for the two methyl groups. Addition of



37

phthalimidoacetyl chloride to imino ether 37 afforded a 35% yield of trans β-lactam, m.p. 175-176.5°, when the reaction was allowed to proceed for 24 hrs. In the p.m.r. spectrum of 38 each of the β-lactam protons appeared as a doublet with J = 2 Hz. When the reaction was stopped after 2 hrs, a 1:1 mixture of β-lactam 38 and methyl N-phthalimidoacetyl anthranilate 39 was obtained in 30% overall yield.



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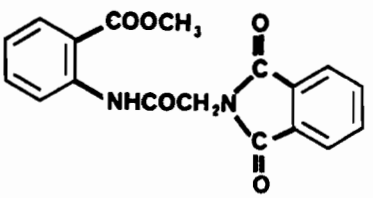
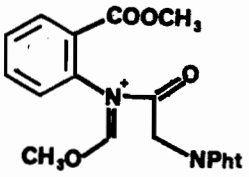


39

This suggested that the reaction did not proceed through a 2+2 addition of phthalimido ketene and imine 37, but in two stages, the first intermediate having structure 40[45] which is trapped presumably as the chloride 41. Quenching of 41 with



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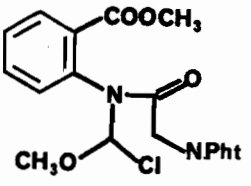
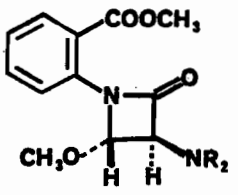
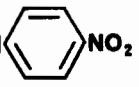


41

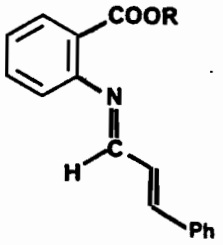
water during work-up would give methyl N-phthalimidoacetyl anthranilate 39, whereas a prolonged reaction time may lead to further formation of β-lactam 38. No β-lactam was obtained when imine 37 was treated with azidoacetyl chloride. Removal of the phthalimido protecting group with hydrazine in CH_2Cl_2 afforded amine 42 in low yield. Isomerization of trans β-lactam 42 via Schiff base 43 was also unsuccessful.

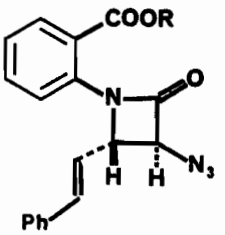


42 R, R=H

43 R, R =CH 

Not having been able to prepare a cis fused β-lactam using the approaches described, we investigated the method recently described by Doyle et al[45], which consisted in reacting azidoacetyl chloride with cinnamylidene Schiff bases, and which has been reported to give exclusively cis β-lactams. Treatment of anthranilic acid with redistilled cinnamaldehyde in refluxing benzene afforded a highly unstable Schiff base 44. Reaction of





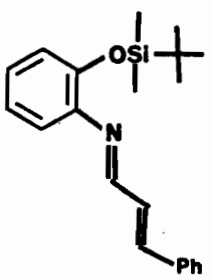
44 R=H

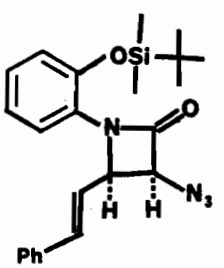
45 R=$(CH_3)_3Si$

46 R=H

47 R=CH_3

the silylated cinnamylidene Schiff base 45, prepared in situ from 44, with azidoacetyl chloride gave a low yield of trans β-lactam 46, which was characterized as its methyl ester 47. P.m.r. of the crude product only showed the presence of trans β-lactam. This was very surprising since the reaction of stable Schiff base 48 with azidoacetyl chloride afforded exclusively crystalline cis β-lactam 49[80] in good yield. Since the key dif-

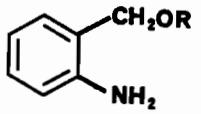




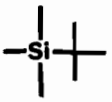
48

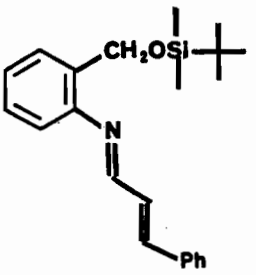
49

ference between 45 and 48 was that 48 contained an electron donating group on the aniline ring while 45 contained an electron withdrawing group, it was decided to repeat the sequence using the readily available o-aminobenzyl alcohol 50 as starting material and to oxidize the alcohol to the carboxylic acid at a later stage.



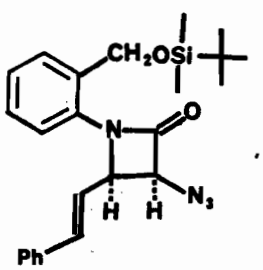
50 R=H

51 R= 



52

Silylation of 50 with tert-butyl dimethyl silyl chloride/imidazole[76] in dimethyl formamide afforded silyl ether 51 in quantitative yield. Amine ether 51 was converted to Schiff base 52 with 1 equivalent of cinnamaldehyde in refluxing benzene. Treatment of 52 with 1.2 equivalents of triethylamine followed by 1.15 equivalents of azidoacetyl chloride afforded β-lactam 53, m.p. 91-92, $\nu_{C=O}$(KBr) 1745 cm^{-1}, in excellent yield. In the p.m.r. spectrum of 53 (page 31), the β-lactam protons appeared as a multiplet at 5 p.p.m. Addition of $Eu(fod)_3$ did not separate



53

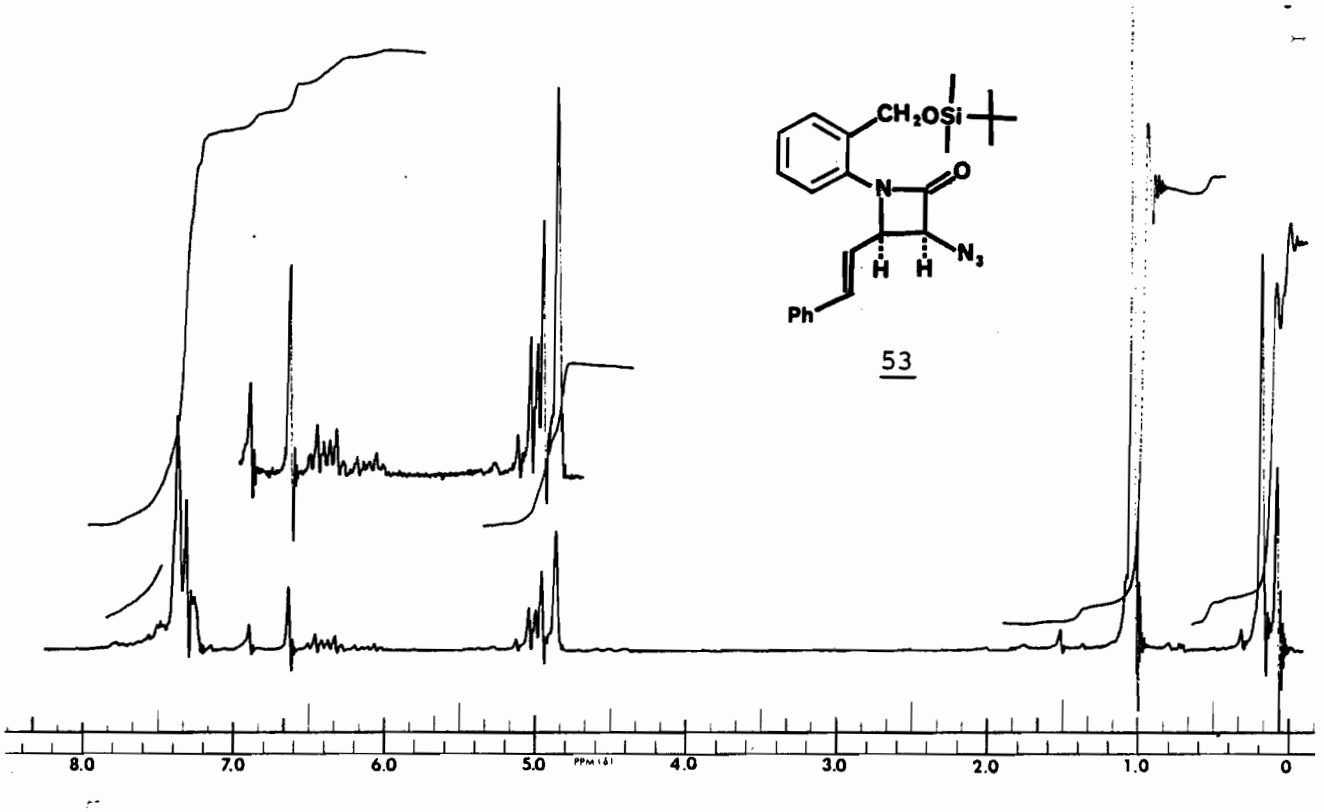


Fig. 7: The 60 MHz p.m.r. spectrum of azide 53

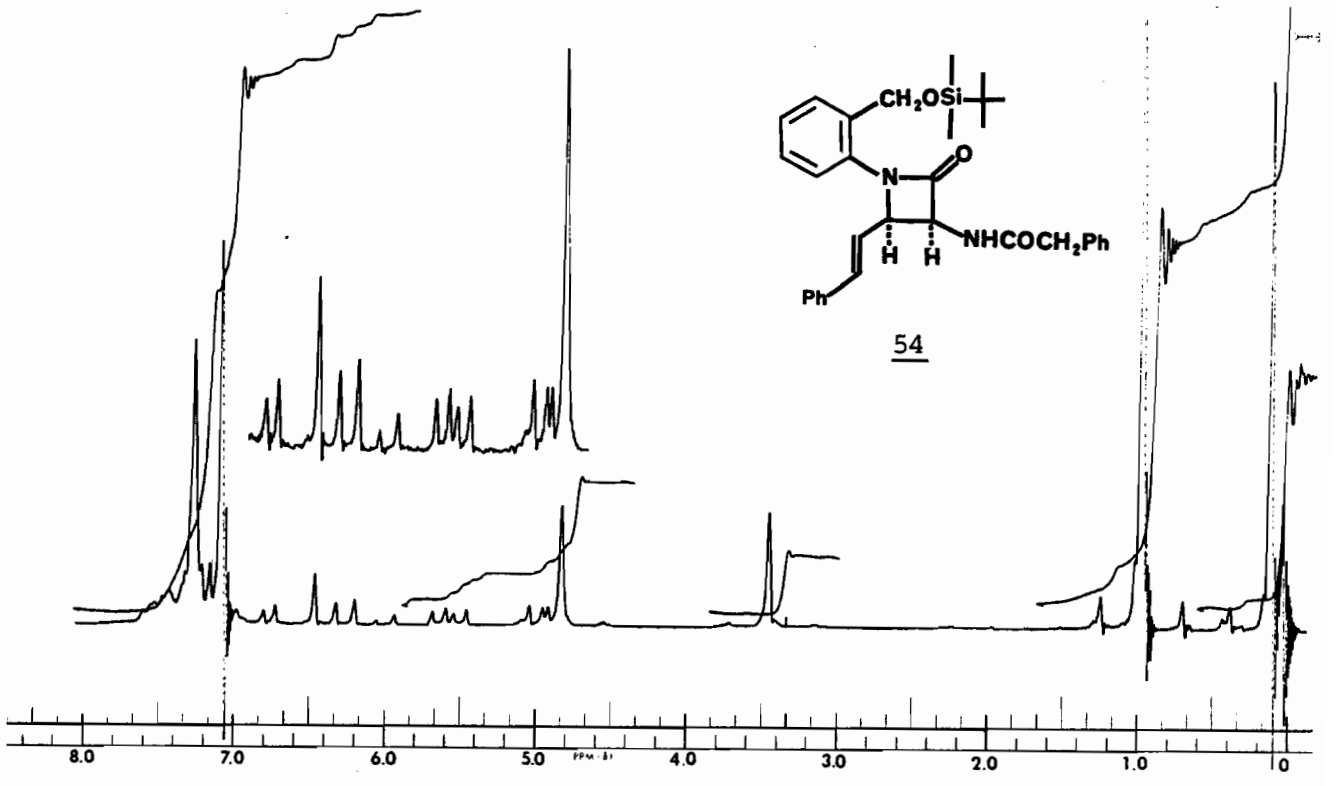
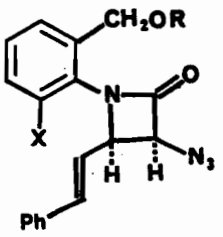


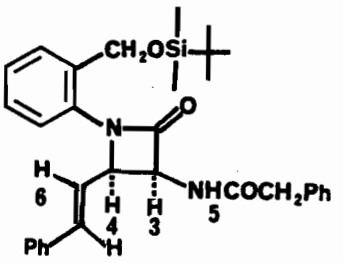
Fig. 8: The 60 MHz p.m.r. spectrum of amide 54

the signals for the two protons. In general, the stereochemistry of the cinnamyl azido β-lactams of type K could not be determined by p.m.r. at this stage because the β-lactam protons appeared as a multiplet which could not be separated. The stereochemistry could, however, be determined at later stages of the synthesis. The mass spectrum of 53 showed a molecular ion (M^+) at m/e 434, peaks for the loss of nitrogen and a t-butyl group from the molecular ion at m/e 406 and 377 respectively.

Reduction of 53 with hydrogen sulphide/triethylamine[45] followed by acylation with phenylacetyl chloride afforded amide 54, m.p. 108.5-109, $\nu_{C=O}$ 1750, 1680 cm^{-1}, in 60% yield based on 53. In the p.m.r. spectrum of 54 (page 31), H_3 appeared as a quartet ($J_{3,4}$ = 5 Hz, $J_{3,5}$ = 7 Hz), characteristic of cis acylamino β-lactams, at 5.6 p.p.m. H_4 also appeared as a quartet ($J_{3,4}$ = 5 Hz, $J_{4,6}$ = 7 Hz).



K

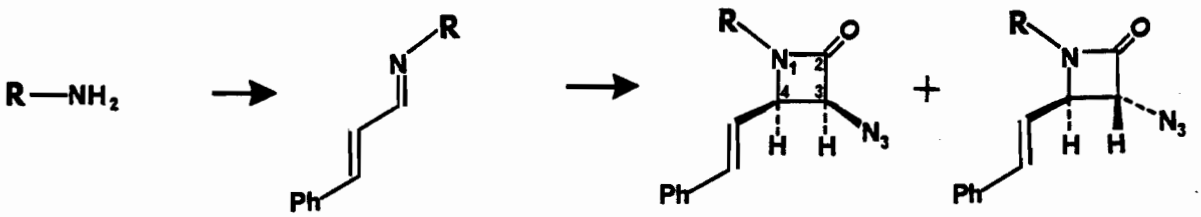


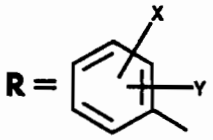
54

By changing the ortho substituent in 45 from an electron withdrawing ester to an electron donating ether group, the stereochemistry of the cycloaddition changed from trans to cis and the yield of the reaction went from 10-20% to 77%. We de-

cided to investigate this effect further and the sequence was repeated with other substituted anilines. The results are summarized in Table 2 (page 34). Substituted anilines with pKa's ≥ 2.4 seemed consistently to afford exclusively cis β-lactams. Anilines with pKa's less than 2.4 afforded either mixtures of cis and trans β-lactams or pure trans β-lactams. These results suggested that there were two distinct pathways for the reaction of cinnamylidene anilines with azidoacetyl chloride. In pathway 1 (page 35), the imine reacted with azidoacetyl chloride to give intermediate W. Deprotonation of W by triethylamine gave zwitterion Z. Electrostatic attraction between the negative charge density of the azido group and the positive charge density on the cinnamyl component stabilized the transition state leading to cis β-lactam[70] and therefore ring closure of Z afforded only cis β-lactam. In pathway 2, the imine reacted probably with azido ketene, formed from azidoacetyl chloride and triethylamine, and afforded trans β-lactam[77]. Imines derived from amines (a-h) with pKa's ≥2.4 reacted with azidoacetyl chloride exclusively by pathway 1 and afforded cis β-lactams. In amines with pKa's less than 2.4 (i,j,m,n), electron withdrawing substituents and ortho substituents on the aniline ring, which destabilize W, decreased the rate of pathway 1 sufficiently that pathway 2 became important and trans β-lactams were also formed. Imines derived from amines k and l reacted so slowly with azidoacetyl chloride that pathway 2 became the exclusive reaction pathway and only trans β-lactams were formed.

Table 2: The stereochemistry of the reaction of cinnamylidene Schiff bases of substituted anilines with azidoacetyl chloride





	pKa	yield cis isolated (NMR)	yield trans isolated (NMR)
(a) X=Y=H[a]	4.6[d]	50% (90%)	
(b) X=p-Cl, Y=H[a]	4.0[d]	40% (90%)	
(c) X=o-CH_2OTBDMS, Y=H	> 3[e]	70% (95%)	
(d) X=o-OTBDMS, Y=H[a]	> 3[e]	60% (90%)	
(e) X=o-CH_2OTBDMS, Y=o'-OTBDMS	> 3[e]	81% (90%)	
(f) X=Y=o-OTBDMS[a]	> 3[e]	40% (70%)	
(g) X=m-NO_2, Y=H[a]	2.46[d]	80%	
(h) X=o-OME, Y=p-COOMe[a]	2.4[f]	85%	
(i) X=p-Cl, Y=o-Cl[a]	2.05[d]	(60%)	(15%)
(j) X=o-COOH, Y=o'-OMe	2.0[c]	(15%)	(15%)
(k) X=o-COOH, Y=H	2.2[c]		(30%), (30%,THF)[b]
(l) X=o-OTBDMS, Y=p-NO_2[a]	< 1.5[e]		(2%), 50% (70%,THF)
(m) X=p-NO_2, Y=H[a]	1[d]	(50%)	(25%)
(n) X=p-NO_2, Y=o-CH_3[a]	∿1[e]	(5%)	(50%)

a = results obtained by A. Ugolini in our laboratories

b = cycloaddition performed in THF

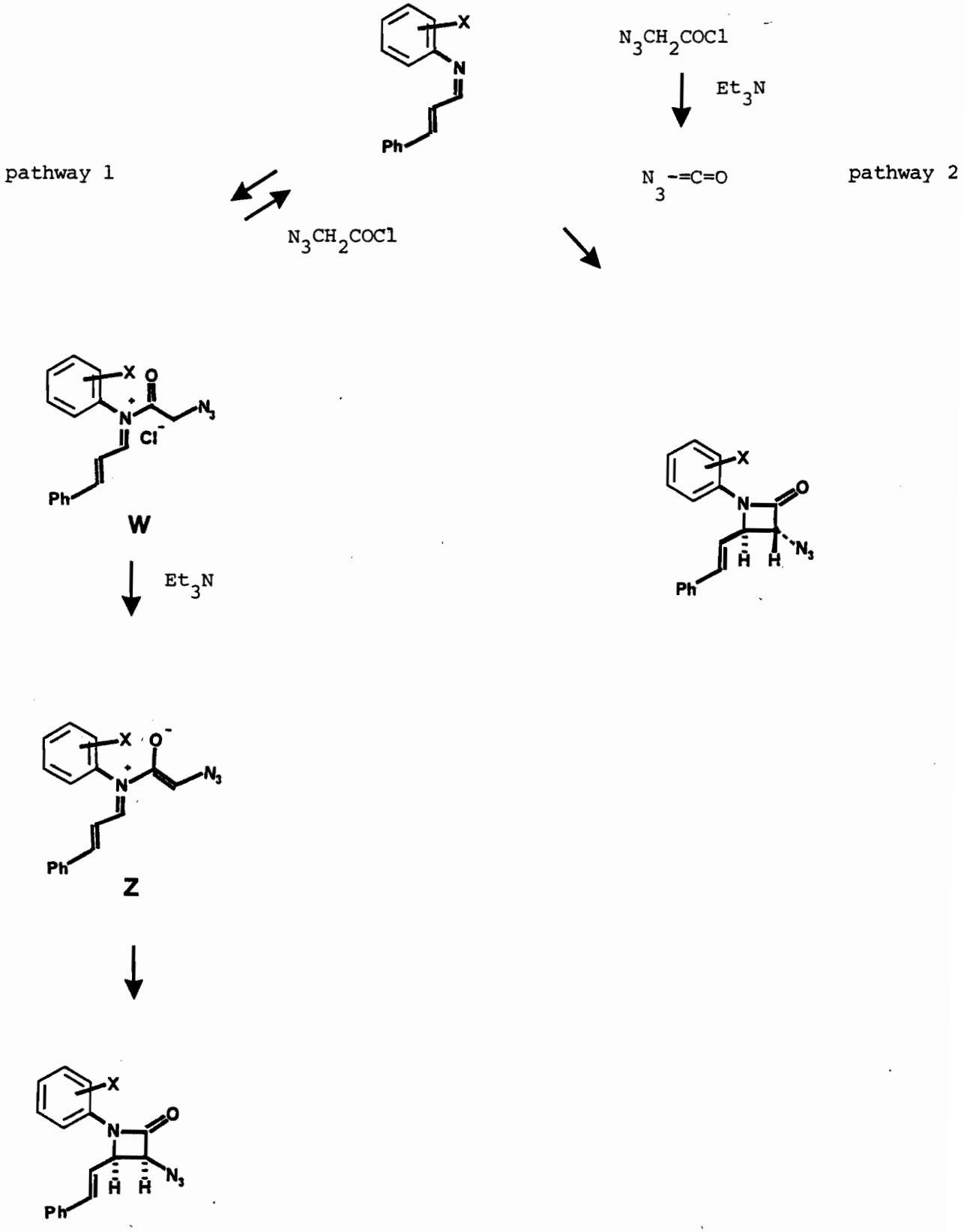
c = measured on corresponding methyl esters[73]

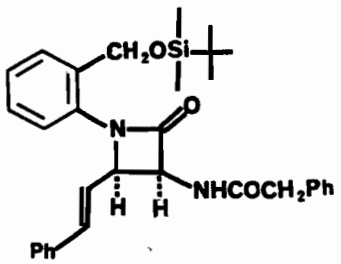
d = from literature[72]

e = estimated

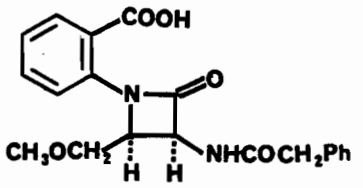
f = measured

Fig. 9: Mechanism for the cycloaddition of azidoacetyl chloride to cinnamylidene anilines



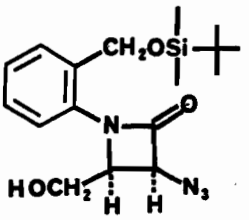


54

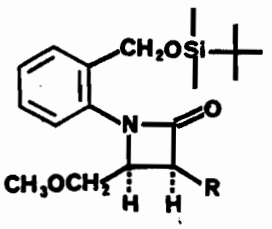


60

To transform 54 to the desired carboxylic acid 60 the cinnamylidene group had to be ozonolyzed and the silyl ether had to be oxidized to a carboxylic acid. Ozonolysis of 54 in ethanol, methanol, or methylene chloride gave a poorly defined mixture of oxidation products. Since we thought that the amide group interfered with the ozonolysis, the ozonolysis of the azide 53 was investigated. Ozonolysis of 53 in methanol, followed by sodium borohydride reduction[45], afforded an inseparable mixture of alcohol 55 and varying amounts of some other unidentified products. However, ozonolysis of azide 53 in redistilled isopropanol, followed by sodium borohydride reduction, gave, after work-up with pH 4.5 buffer, a reasonable yield of alcohol 55. Work-up with 1% HCl[45] instead of pH 4.5 buffer lead to hydrolysis of the silyl ether. Later we found that by using methylene chloride/ethanol 1:5 as solvent instead of isopropanol and purging with N_2[74], crystalline alcohol 55, m.p. 95-96°, could be obtained in 76% yield by simple crystallization of the crude product.



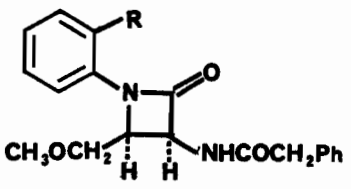
55



56 R=N_3

57 R=$NHCOCH_2Ph$

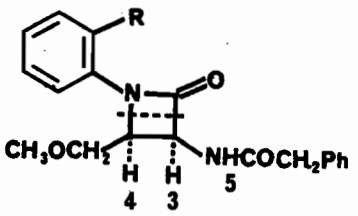
In order to differentiate the two alcohol functions, 55 was converted to its methyl ether 56 by means of excess diazomethane-boron trifluoride etherate[75] in 76% yield after chromatography. Reduction and acylation of the azide function gave amide 57, $\nu_{C=O}$ 1750, 1655 cm^{-1}. Removal of the silyl protecting group by treatment with aqueous trifluoroacetic acid in tetrahydrofuran gave alcohol 58 in good yield. Oxidation of 58 with pyridinium chlorochromate[78] afforded aldehyde 59 in 70% yield. Because of its mildness and selectivity we decided to first try Corey's method ($NaCN/Ag_2O_2$)[79] for the conversion of aldehyde 59 to the desired carboxylic acid 60. Unfortunately, oxidation of 59 with silver oxide/sodium cyanide opened the β-lactam ring. The aldehyde in 59 activated the



58 R=CH_2OH

59 R=CHO

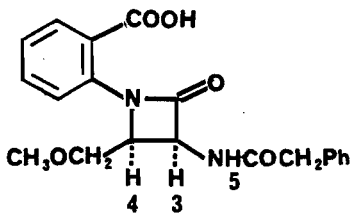
β-lactam ring towards ring opening by nucleophiles like CN^-. Attempts to oxidize either 58 or 59 with potassium permanganate[81] or with sodium periodate/ruthenium tetroxide[83] in aqueous acetone were also unsuccessful. In all these attempts the oxidation stopped at the aldehyde stage. Carboxylic acid 60, $\nu_{C=O}(CHCl_3)$ 1755, 1710, 1670 cm^{-1}, could be obtained in low yield from 58 using chromium trioxide in acetic acid/water[82]. T.l.c. showed that in the oxidation of alcohol 58, the conversion to aldehyde 59 was very rapid, whereas the oxidation of aldehyde 59 to carboxylic acid 60 was slow. P.m.r. of 60 (page 39) showed a quartet at 5.8 p.p.m. for H_3 ($J_{3,4}$ = 5 Hz, $J_{3,5}$ = 7 Hz) and a broad doublet for H_4 along with all other appropriate signals. Treatment of 60 with ethereal diazomethane afforded the corresponding methyl ether 61. The mass spectrum of 61 showed a molecular ion, a peak at M^+-31 which is consistent with a methyl ester and peaks at m/e 205 and 177 for the fragmentation shown on 61[71]. Carboxylic acid 60 showed no activity toward a variety of bacteria. This is not unexpected if we consider that $\nu_{C=O}$ of 60 is only 1755 cm^{-1}, while known active cephalosporins have $\nu_{C=O}$ of at least 1765 cm^{-1}.



59 R=CHO

60 R=COOH

61 R=$COOCH_3$



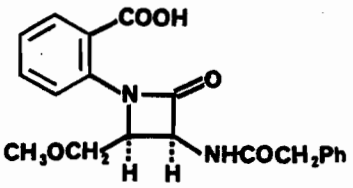
60

Fig. 10: The 90 MHz p.m.r. spectrum of carboxylic acid 60

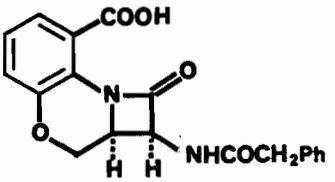
Chapter 2

Synthesis of 7β-phenylacetamido-3'-carboxy-benzo[3,4]-0-2-isocephem

In the previous chapter we described the synthesis of bicyclic anthranyl azetidinone 60, in which the β-lactam frequency was 1755 cm^{-1} and which, not surprisingly, showed no significant antimicrobial activity. It was decided to prepare the tricyclic anthranyl azetidinone 120 which we expected to absorb at considerably higher frequency and which should therefore be similar to classical β-lactams except for the position of the carboxylic acid.

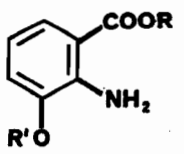


60

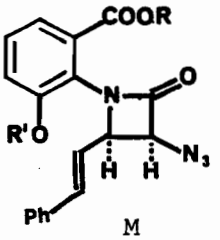


120

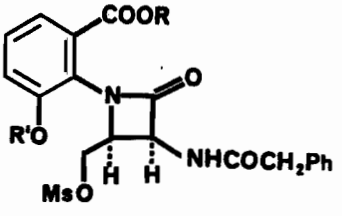
Our basic plan for the synthesis of 120 is illustrated below. We decided to start with a protected hydroxyl anthranilic acid L, form the β-lactam M as before, transform the styryl group to a mesylate N, deprotect the phenol, and cyclize the



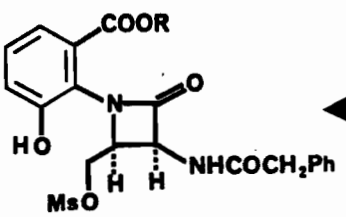
L



M



N

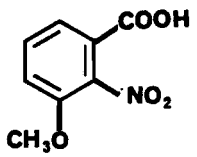


O

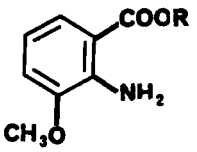
120

resulting compound O by treatment with base. Because of the electron-donating nature of the methoxy group, it was anticipated that some cis-fused compound may form.

The commercially available 3-methoxy-2-nitrobenzoic acid 62 was reduced to amine 63 with platinum oxide in ethanol and the resulting aminobenzoic acid 63 transformed to its methyl ester 64 with diazomethane.

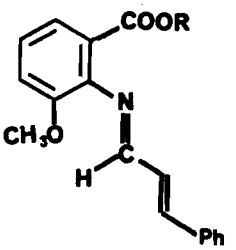


62



63 R=H

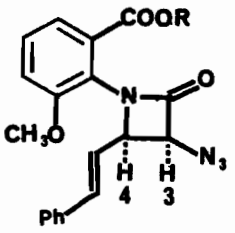
64 R=CH_3



65 R=CH_3

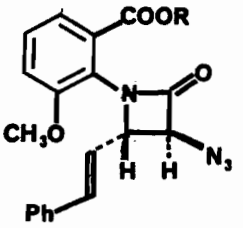
66 R=H

Attempts to convert 64 to its cinnamylidene Schiff base 65 failed. The free amino acid 63 was therefore directly converted to highly unstable Schiff base 66 by reaction with cinnamaldehyde in refluxing benzene using a Dean Stark apparatus. Reaction of crude 66 with trimethyl silyl chloride-triethylamine in methylene chloride followed by azidoacetyl chloride gave, after work-up, a mixture of β-lactams 67 and 69, amino acid 63 and some other unidentified products, presumably azidoacetyl chloride self-condensation products. Column chromatography afforded only partial separation. Methylation of the partially purified products and re-chromatography finally afforded an inseparable mixture of cis and trans β-lactams 68 and 70 in approximately 25% yield.



67 R=H

68 R=CH_3

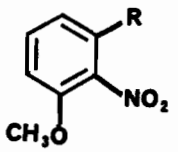


69 R=H

70 R=CH_3

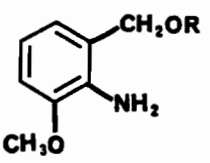
The p.m.r. spectrum in benzene d_6, after addition of $Eu(fod)_3$, clearly showed the presence of the cis isomer, $J_{3,4}$ = 5 Hz, and of the trans isomer, $J_{3,4}$ = 2 Hz. Since we could not separate the desired cis isomer from the trans isomer, it was decided to reduce the electron withdrawing carboxyl function, which was responsible for the low yield of the cycloaddition and the formation of the trans isomer, to an alcohol before carrying out the cycloaddition, and to eventually reoxidize the benzyl alcohol to the corresponding benzoic acid.

3-Methoxy-2-nitrobenzoic acid was reduced to the corresponding benzyl alcohol 71 with excess borane in tetrahydrofuran[84] in 65% yield. Treatment of 71 with excess methylal/phosphorus pentoxide afforded ether 72 in good yield. Catalytic hydrogenation (PtO_2) of the nitro group afforded amine 73 in excellent yield.

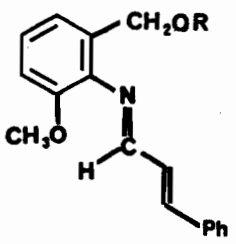


71 R=CH_2OH

72 R=$CH_2OCH_2OCH_3$



73 R=CH_2OCH_3



74 R=CH_2OCH_3

75 R=CH_2OCH_3

Aniline 73 was transformed to its cinnamylidene Schiff base 74 which, as expected, gave cis β-lactam 75 in good yield upon reaction with azidoacetyl chloride and triethylamine at -20°. The stereochemistry of the β-lactam in 75 could not be determined by p.m.r. The β-lactam protons showed up as a multiplet. Ozonolysis of 75 in isopropanol/methylene chloride followed by sodium borohydride reduction, afforded alcohol 76, i.r. ($CHCl_3$) 3300, 2100, 1760 cm^{-1}, in 56% yield. Treatment of 76 with methanesulfonyl chloride (MsCl)/triethylamine afforded mesylate 77. In the p.m.r. spectrum of 77, H_3 clearly appeared as a doublet with J = 5 Hz at 5.0 p.p.m. Therefore, 77, 76 and 75 were cis β-lactams. We had now reached the key steps in our synthesis, the removal of the protecting groups and the cyclization of the resulting diol mesylate 78.

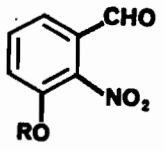
76 R=H

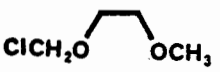
77 R=SO_2CH_3

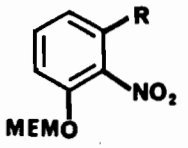
78

Unfortunately, treatment of either 77 or 75 with boron tribromide[85] or boron trichloride[86] led to destruction of the β-lactam ring. We therefore had to change the protecting groups on aniline 73.

Recently Corey reported a new alcohol protecting group, the β-methoxyethoxymethyl (MEM) group[87]. It was easily introduced and selectively removed in the presence of other alcohol protecting groups under mild conditions with zinc bromide or titanium tetrachloride. This group seemed ideal for our purposes. The required aniline was easily synthesized from 3-methoxy-2-nitrobenzaldehyde 79. Aldehyde 79 was quantitatively demethylated with excess boron tribromide in methylene chloride to phenol 80. Treatment of 80 with MEM chloride[87] 81 and diisopropylethylamine in methylene chloride afforded aldehyde 82. Reduction of 82 with sodium borohydride in ethanol afforded alcohol 83 in 90% yield. Protection of the alcohol with MEM chloride/diisopropylethylamine afforded the MEM ether 84 in 60% yield after column chromatography.







79 R=CH_3

80 R=H

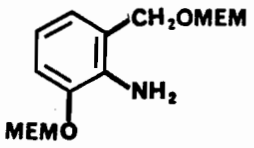
81

82 R=CHO

83 R=CH_2OH

84 R=CH_2OMEM

Catalytic hydrogenation of 84 afforded the desired amine 85. Treatment of the crude Schiff base, obtained by heating amine 85 for 8 hrs with cinnamaldehyde in refluxing benzene, with azidoacetyl chloride/triethylamine afforded the cis β-lactam 86 in good yield. Ozonolysis of 86 in isopropanol/methylene chloride, followed by reduction with sodium borohydride, afforded alcohol 87. Alcohol 87 was further characterized as the mesylate 88. To our surprise the MEM ether



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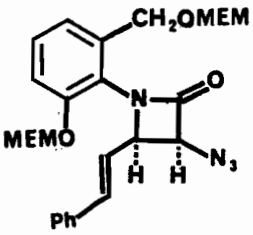

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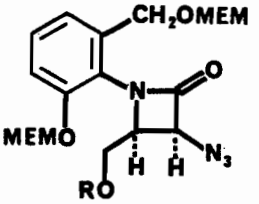
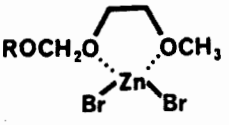


87 R=H

88 R=SO_2CH_3

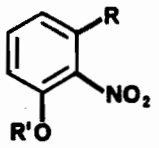
groups in either 88 or 86 could not be removed using the conditions described by Corey. When these compounds were added to a slurry of zinc bromide in methylene chloride, the zinc bromide clumped together and the reaction stopped. We later found out that nitrogen in the compounds probably interfered[88] with the formation of the complex 89, which is thought to be responsible for the cleavage of MEM ethers with Lewis acids like zinc

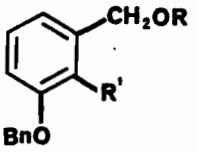


89

bromide. The MEM ethers in 86 and 88 were also very resistant to acid hydrolysis. They could not be removed without destruction of the β-lactam ring.

The sequence was repeated with amine 94 in which the alcohol functions were protected as benzyl and silyl ethers. Both these groups could be removed in the presence of the β-lactam ring. Amine 94 was synthesized in the following way from 3-hydroxy-2-nitrobenzaldehyde 80. Treatment of 80 with benzyl bromide/potassium carbonate in dimethyl sulfoxide afforded benzyl ether 90, m.p. 77-79°, in 50% yield. Sodium borohydride reduction gave alcohol 91 in quantitative yield.





90 R=CHO, R^1=CH_2Ph

91 R=CH_2OH, R^1=CH_2Ph

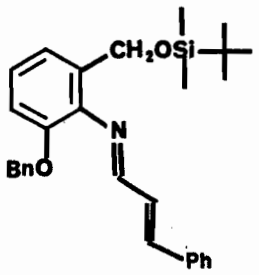
92 R=CH_2OH, R^1=H

93 R=H, R^1=NH_2

94 R=$(CH_3)_2SiBu^t$, R^1=NH_2

Catalytic hydrogenation of 91 in ethanol using platinum oxide as catalyst afforded amine 93 contaminated with approximately 10% of phenol 92. Washing with 5% sodium hydroxide removed the phenol and afforded pure 93. The success of the catalytic hydrogenation depended entirely on the activity of the platinum oxide used. Adams catalyst obtained from Matheson Coleman and Bell and from Anachemia (Montreal) gave excellent results while platinum oxide obtained from Ventron gave overreduction. The

platinum oxide from Ventron was too active and therefore not selective. It reduced the nitro group and cleaved the benzyl ether at about the same rate. Silylation with t-butyldimethylsilyl chloride afforded the desired amine 94 in 40% overall yield from 80. Treatment of amine 94 with cinnamaldehyde in refluxing benzene afforded Schiff base 95, approximately 85-90% pure by p.m.r. Reaction of the crude Schiff base 95 with azidoacetyl chloride/triethylamine at -20° afforded fairly pure cis β-lactam 96 after column chromatography. Ozonolysis of 96 in ethanol/methylene chloride at -78° followed by sodium borohydride reduction, afforded analytically pure alcohol 97, i.r. (film) 3400 (OH), 2100 (N_3), 1760 cm^{-1} (β-lactam), after column



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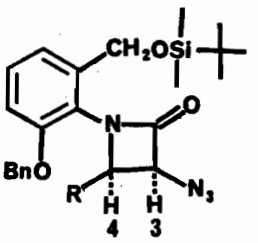


96 R= CH=CH-Ph

97 R= CH_2OH

chromatography. The ozonolysis was much cleaner (little polar by-products by t.l.c.) when N_2 was passed into the ozonolysis vessel at the same time as ozone in oxygen was bubbled through. In the p.m.r. spectrum of 97, H_3 appeared as a doublet, J = 5 Hz; 95, 96 and 97 were therefore cis β-lactams. Alcohol 97 was easily transformed to mesylate 98. Treatment of 98 with aqueous trifluoroacetic acid in tetrahydrofuran afforded

benzyl alcohol 99 in good yield. Oxidation of 99 with chromium trioxide in acetic acid/water gave carboxylic acid 100, m.p. 153-155°, in 42% yield. The i.r. spectrum of 100 in KBr was misleading and lead us to believe that the β-lactam had been hydrolyzed during the oxidation. It had only a broad band at 1740 cm^{-1} in the carbonyl region. However in solution there were two bands, one at 1720 cm^{-1} for the carboxylic acid and one at 1755 cm^{-1} for the β-lactam. In the solid state there must have been an intermolecular hydrogen bond which lowered the β-lactam frequency. Reaction of acid 100 with a slight excess of diphenyl diazomethane in acetonitrile afforded ester 101, $\nu_{C=O}$ ($CHCl_3$) 1780, 1730 cm^{-1}. Reduction with hydrogen sulphide/triethylamine and acylation with phenylacetyl chloride afforded amide 102, $\nu_{C=O}$ (KBr) 1770, 1720, 1660 cm^{-1}.

98 $R^1=(CH_3)_2SiBu^t$, $R=SO_2CH_3$

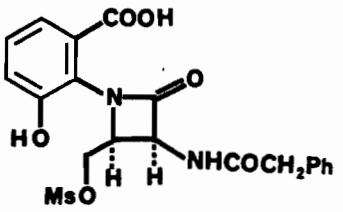
99 $R^1=H$, $R=SO_2CH_3$

100 $R=H$, $R^1=N_3$

101 $R=CH(Ph)_2$, $R^1=N_3$

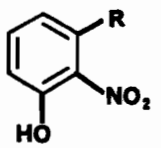
102 $R=CH(Ph)_2$, $R^1=NHCOCH_2Ph$

Attempts to remove the benzyl groups by catalytic hydrogenation and to cyclize the resulting phenol mesylate with DBU[50] or triethylamine in acetonitrile failed, as evidenced by p.m.r. which showed the presence of the mesylate group. The cyclization was not investigated further because we were successful in synthesizing the desired carboxylic acid by another route.



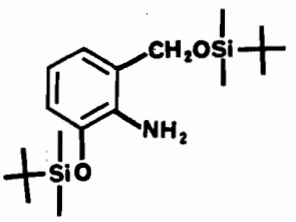
103

Since we had indications, based on model studies[80], that the desired cyclization proceeded well, when it was effected on a silyl mesylate of type 109, the sequence was repeated with a t-butyldimethylsilyl ether instead of a benzyl ether. Reduction of 80 with sodium borohydride in ethanol afforded alcohol 104. Catalytic hydrogenation of 104 afforded, after silylation with t-butyldimethylsilyl chloride, amine 105 in



80 R=CHO

104 R=CH_2OH



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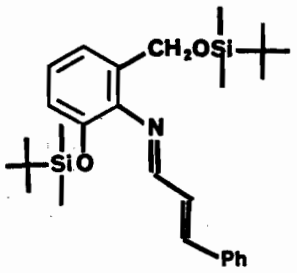

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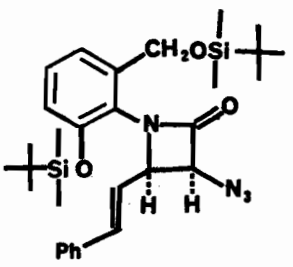
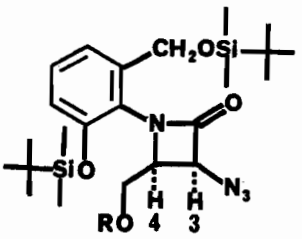


107

68% yield from 80. Aniline 105 was transformed to its cinnamylidene Schiff base 106, which upon treatment with azidoacetyl chloride/triethylamine afforded, after chromatography, fairly pure cis β-lactam 107 in 80% yield. Ozonolysis of 107 in ethanol/methylene chloride, followed by reduction with sodium borohydride afforded, after chromatography, pure alcohol 108, m.p. 112-112.5°, $\nu_{c=o}$ 1770 cm^{-1}, in 53% yield. It was transformed into its mesylate 109 in excellent yield. The p.m.r. spectrum of 109 showed a characteristic doublet at 5.0 p.p.m., J = 5 Hz, for H_3 and a three proton singlet at 2.75 p.p.m. for the mesylate, in addition to all other appropriate signals (page 51).



108 R=H

109 R=SO_2CH_3

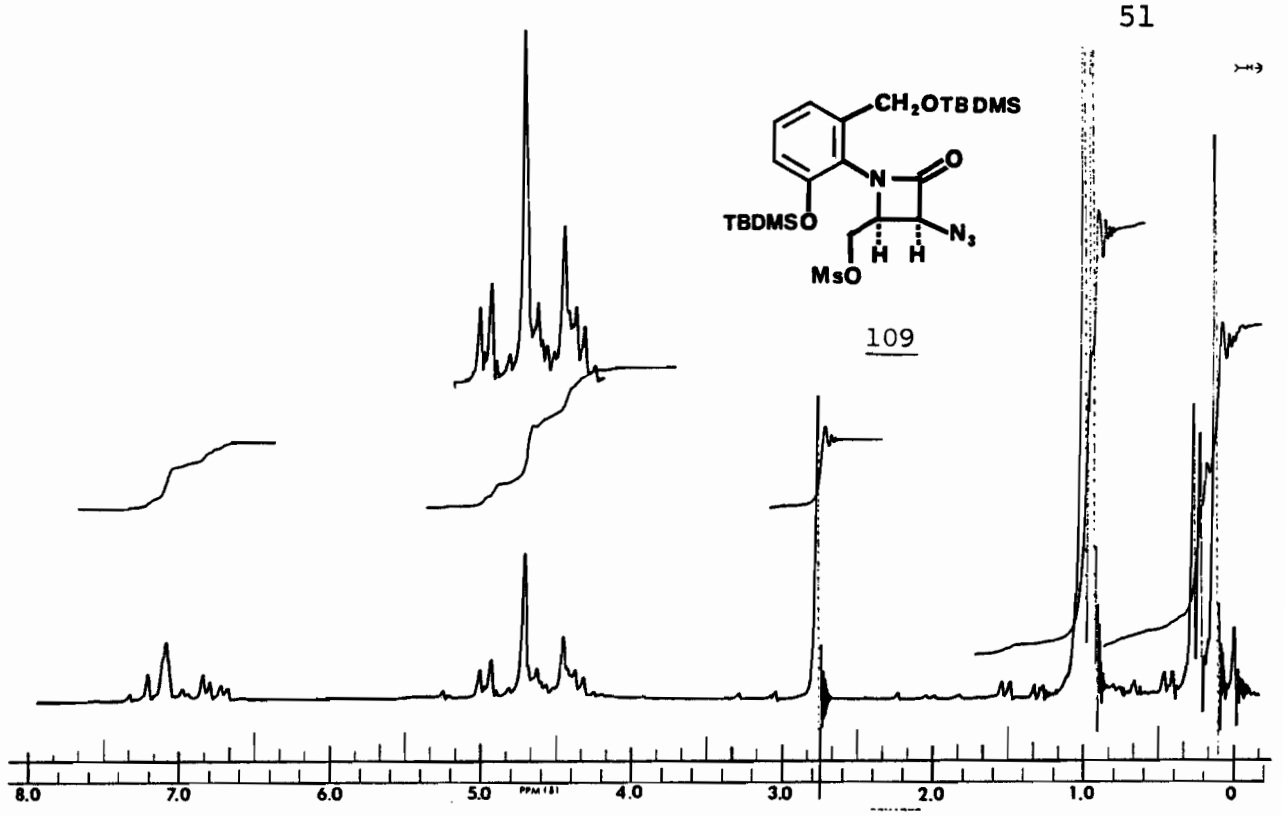
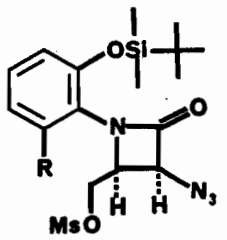


Fig. 11: The 60 MHz p.m.r. spectrum of mesylate 109



109 R=$CH_2OSi(CH_3)_2Bu^t$

110 R=H

111 R=H

112 R=$CH_2OSi(CH_3)_2Bu^t$

A. Ugolini in our laboratories found that treatment of 110 with 1 equivalent of tetra-n-butyl ammonium fluoride in tetrahydrofuran afforded tricyclic β-lactam 111 in good yield. We decided to try these conditions on our mesylate 109. Cyclization of 109 with 1 equivalent of tetra-n-butyl ammonium fluoride afforded 112 in good yield. Unfortunately, the yield was not very reproducible. The yield depended on the quality of the tetra-n-butyl ammonium fluoride used[89]. We therefore decided to investigate other fluoride salts. Treatment of 109 with excess caesium fluoride in tetrahydrofuran or acetonitrile did not give any cyclized product but treatment of 109 with 2 equivalents of potassium fluoride and .3 equivalents of 18-crown-6 in acetonitrile afforded consistently 112 in yields of greater than 90%. Unlike the cyclization with tetra-n-butyl ammonium fluoride, the amount of potassium fluoride used was not critical as long as 2 equivalents or more were used. Potassium fluoride/18-crown-6 only removed the phenolic silyl ether. The t.l.c. of the reaction mixture only showed the presence of 112 and the mesylate 109. The 60 MHz p.m.r. of 112 in benzene d_6

(page 54) clearly showed the presence of only one t-butyldimethylsilyl ether and no mesylate. Due to hindered rotation about the aryl-CH_2 bond, the hydrogens of the benzyl CH_2 were not equivalent and appeared as an AB quartet (J = 15 Hz) at 5.2 p.p.m. Analysis of the 100 MHz p.m.r. (page 54) allowed us to determine all the coupling constants between protons H_3, H_4, H_5 and H_6. H_3 was only coupled to H_4 (J = 5 Hz). H_4 was coupled to H_3 (J = 5 Hz), to H_5 (J = 4 Hz) and to H_6 (J = 10 Hz). H_5 was coupled to H_4 (J = 4 Hz) and to H_6 (J = 10 Hz). H_6 was coupled to H_4 (J = 10 Hz) and to H_5 (J = 10 Hz). Since $J_{3,4}$ was 5 Hz after the cyclization, the stereochemistry of the ring junction had been preserved and was still cis. The cyclization of 109 to 112, as expected, increased the β-lactam i.r. absorbtion frequency from 1770 cm^{-1} to 1780 cm^{-1}. Cyclization of 109, by decreasing the planarity of the β-lactam nitrogen, decreased the amide resonance in the β-lactam amide bond. This decrease in amide resonance reduced the double bond character of the β-lactam bond and therefore increased the i.r. absorbtion frequency of the β-lactam[90].

There were two possible routes from 112 to our desired carboxylic acid 120: the silyl ether could be first transformed to the carboxylic acid, and then the azido group reduced and acylated, or the sequence could be reversed. We chose to reduce and acylate the azido group first. This route eliminated the need to protect the carboxylic acid during acylation. Reduction (hydrogen sulphide/triethylamine) and acylation with phenylacetyl chloride of 112 afforded amide 113 in good yield.

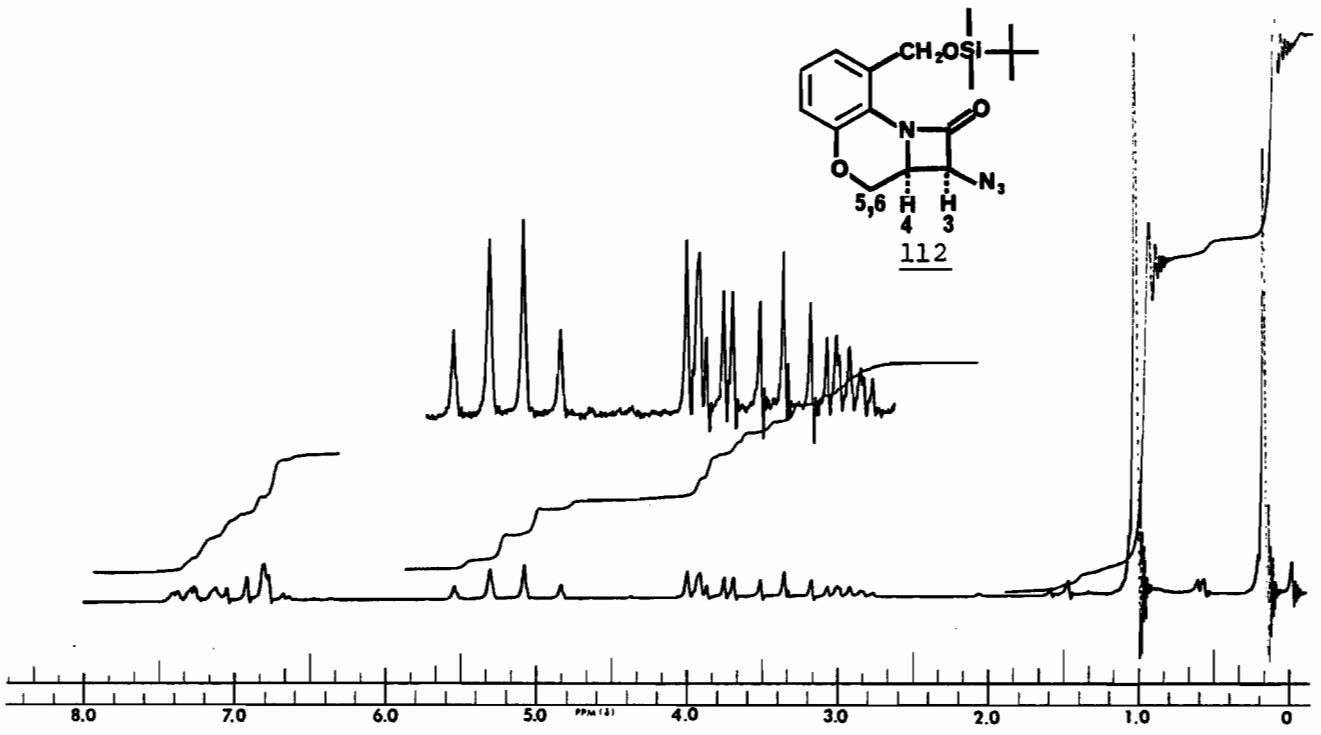


Fig. 12: The 60 MHz p.m.r. spectrum of β-lactam 112

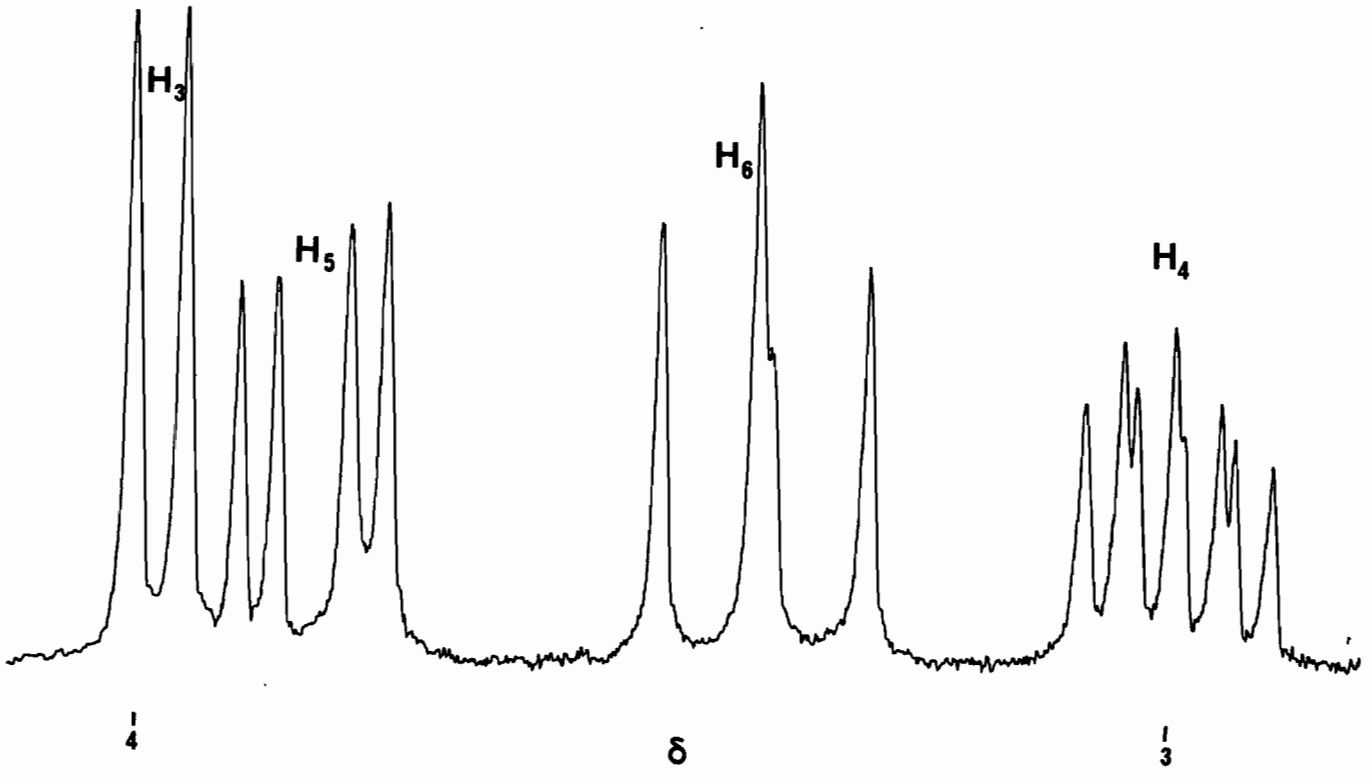
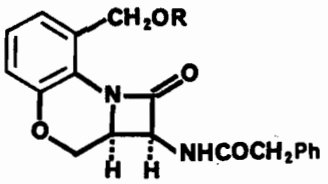
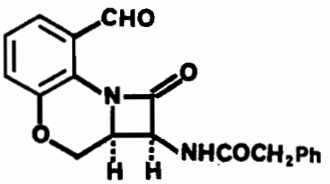


Fig. 13: The 100 MHz p.m.r. spectrum of β-lactam 112

Hydrolysis of the silyl ether with trifluoroacetic acid afforded alcohol 114a, m.p. 183-185°, $\nu_{C=O}$(KBr) 1775, 1660 cm^{-1}, in good yield. Attempts to oxidize alcohol 114a with chromium trioxide in acetic acid/water, potassium permanganate in pyridine[81], or sodium periodate/ruthenium tetroxide gave the corresponding aldehyde 114b (by t.l.c.) and no acid. Since the oxidation did not give the desired product we investigated the other route to carboxylic acid 120. Hydrolysis of 112 with



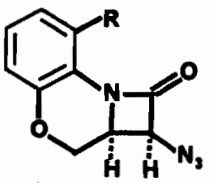


113 R=$Si(CH_3)_2Bu^t$

114a R=H

114b

trifluoroacetic acid afforded benzyl alcohol 115, m.p. 128-129°, m.s. m/e 246 (M^+), in 75% yield. After many unsuccessful attempts it was found that 115 could be oxidized to carboxylic acid 117 using chromium trioxide in acetic acetic/water. The oxidation took two days and afforded a mixture of the desired acid and aldehyde 116 in approximately 60% yield. Increasing



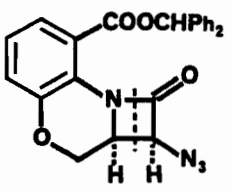
115 R=CH_2OH

116 R=CHO

117 R=COOH

the reaction time did not improve the yield of acid 117. Carboxylic acid 117 was not purified at this step. The crude reaction mixture was treated with a slight excess of diphenyldiazomethane in acetonitrile. Purification by preparative thick layer chromatography afforded 39% of ester 118, i.r. ($CHCl_3$) 1795, 1730 cm^{-1}, and 10% of aldehyde 116. In the 90 MHz p.m.r. spectrum of 118 (page 57), the peaks and coupling constants for protons H_3 to H_6 were very similar to those for the same protons in 112. Therefore, in oxidizing 112 to 117, the tricyclic cis-fused ring structure of 112 had not been altered. The mass spectrum of 118 showed a molecular ion, and peaks for the fragmentation shown on structure 118.

In summary, we were able to oxidize 115 to 117 but not 114a to 120. The amide group, presumably because of steric hindrance, interfered with the oxidation of aldehyde 114b to carboxylic acid 120. The rate of oxidation of alcohols to aldehydes with chromium trioxide and other oxidizing agents is known to be accelerated by steric hindrance, while the rate of oxidation of aldehydes to carboxylic acids is slowed down by steric hindrance[91]. Reduction (H_2S/Et_3N) and acylation



118

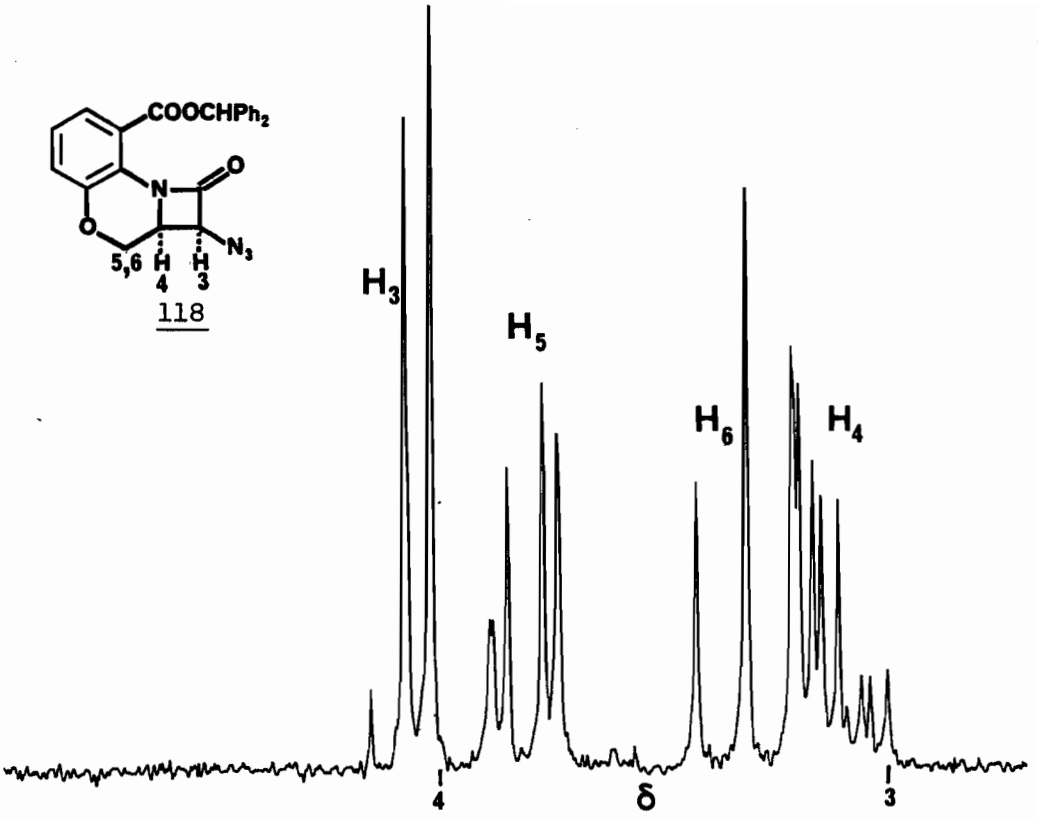


Fig. 14: The 90 MHz p.m.r. spectrum of 118

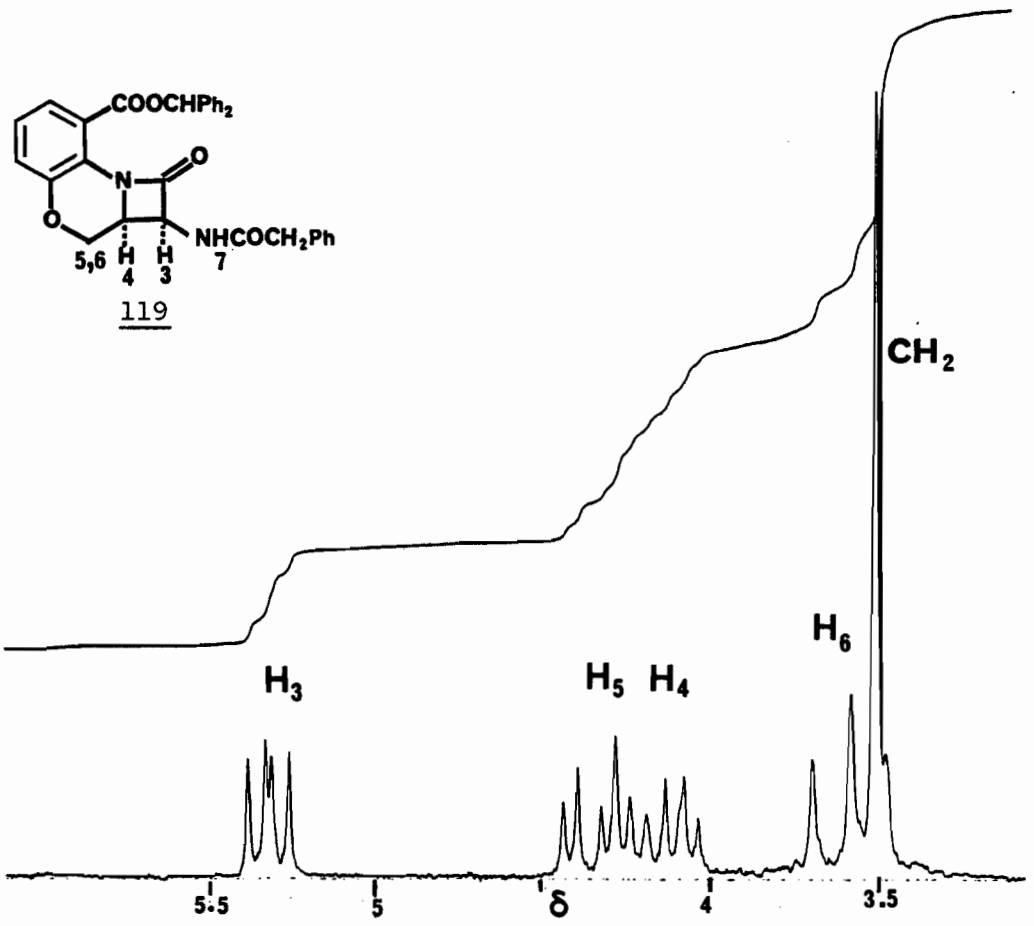
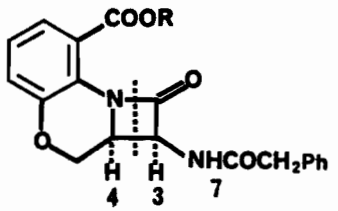


Fig. 15: The 90 MHz p.m.r. spectrum of 119

with phenylacetyl chloride of azide 118 afforded amide 119 in 72% yield. In the p.m.r. spectrum of 119 (page 57), H_3 appeared as a quartet ($J_{3,4}$ = 4.8 Hz, $J_{3,7}$ = 7 Hz), characteristic of cis-fused acylamino β-lactams, at 5.4 p.p.m. We had almost reached our goal and only the ester protecting group had to be removed. Attempts to remove the benzhydryl ester with trifluoroacetic acid/anisole failed and resulted in the decomposition of the β-lactam ester 119. However, catalytic hydrogenation, using palladium on charcoal in ethanol[92], gave the desired acid 120, $\nu_{C=O}$ (KBr) 1780, 1685, 1650 cm^{-1}, fully

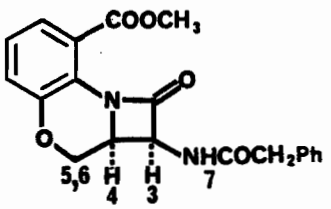


119 R=$CH(Ph)_2$

120 R=H

121 $R=CH_3$

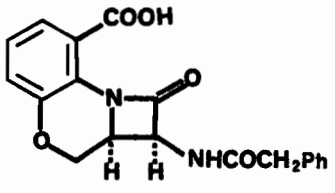
characterized as its methyl ester 121. In the p.m.r. spectrum of 121 (page 59), the peaks for H_3 to H_6 were identical to those for the same protons in 119. The mass spectrum of 121 showed a molecular ion, a peak at M^+-31 which is consistent with a methyl ester and peaks at 175 and 192 typical of the fragmen-



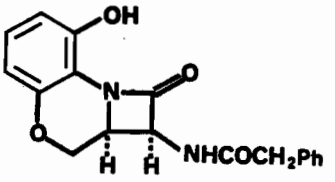
121

Fig. 16: The 90 MHz p.m.r. spectrum of 121

tation of β-lactams[71] as indicated in structure 121.

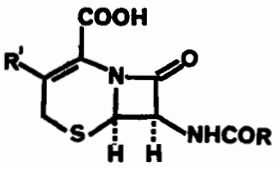


120



122

To our surprise carboxylic acid 120 showed no activity toward a variety of bacteria, while phenol 122[80], although it had a lower β-lactam i.r. absorption frequency (1760 cm^{-1}), displayed weak activity toward two bacteria. Phenol 122 has a hydroxyl group in the same place as the natural cephalosporins 123, while in carboxylic acid 120 the hydroxyl group is displaced by one carbon. It therefore seems probable that the position of the carboxyl function in cephalosporins is critical for antimicrobial activity.

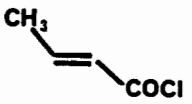


123

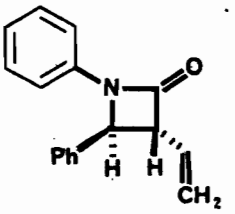
Chapter 3

Synthetic studies toward thienamycin analogues

Bose found that the reaction of crotonyl chloride 124 with benzylidene aniline afforded trans β-lactam 125 in 45% yield[93].

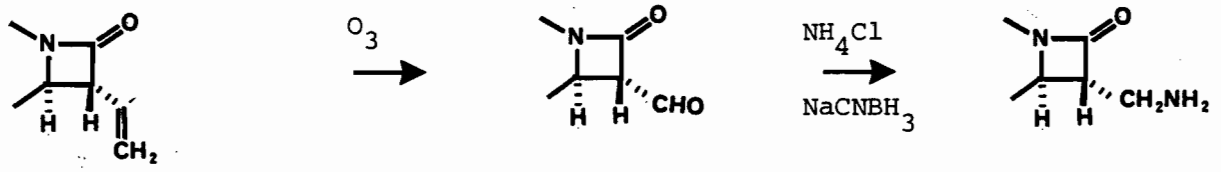


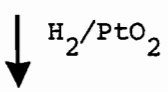
124

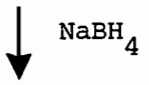


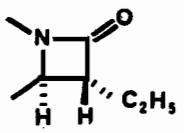
125

Since the double bond in 125 would allow the synthesis of many interesting analogues of thienamycin 126a, 126b and 126c, we decided to investigate this reaction further. We were especially

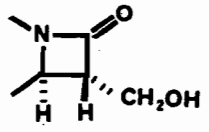




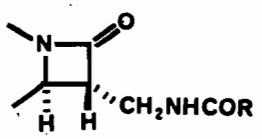




126a



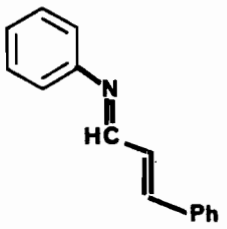
126b



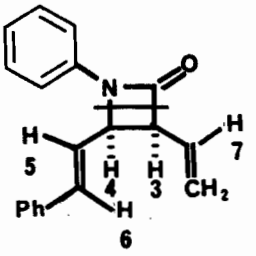
126c

interested in the reaction of 124 with cinnamylidene Schiff bases. The β-lactams that would be formed could be transformed into useful intermediates for the synthesis of cephalosporin and thienamycin analogues[45].

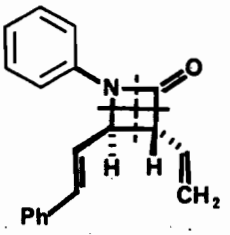
To our surprise, the reaction of cinnamylidene aniline 127, easily obtained by refluxing 1 equivalent of cinnamaldehyde and 1 equivalent of aniline in benzene, with crotonyl chloride/triethylamine afforded approximately a 5:1 mixture of cis β-lactam 128 and trans β-lactam 129 in 30% yield by p.m.r. Purification of the reaction mixture by flash chromatography[94] afforded a low yield of pure cis β-lactam 128. In the p.m.r. spectrum of 128 (page 63), H_4 appeared as a quartet ($J_{3,4}$ = 6 Hz, $J_{4,5}$ = 7 Hz) at 4.8 p.p.m., while H_3 appeared as a triplet ($J_{3,4}$ = 6 Hz, $J_{3,7}$ = 6 Hz)



127

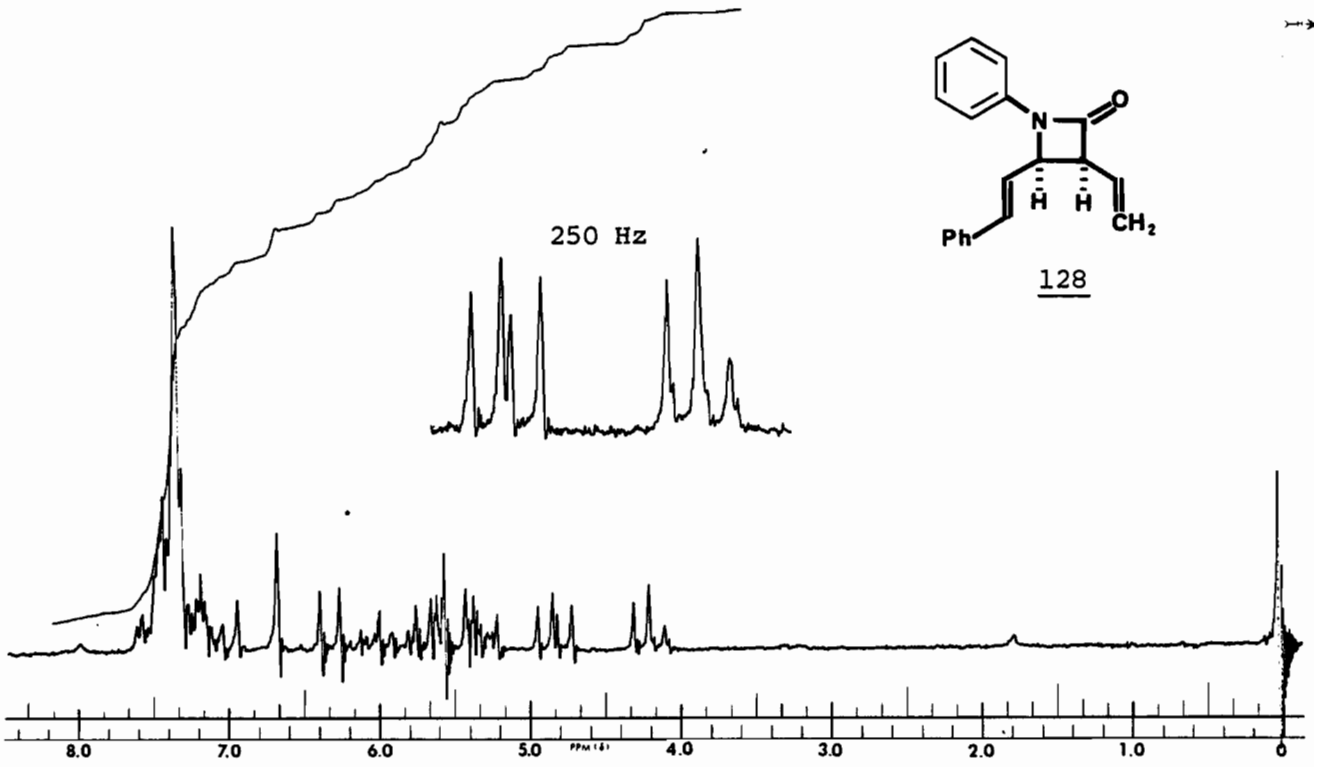


128



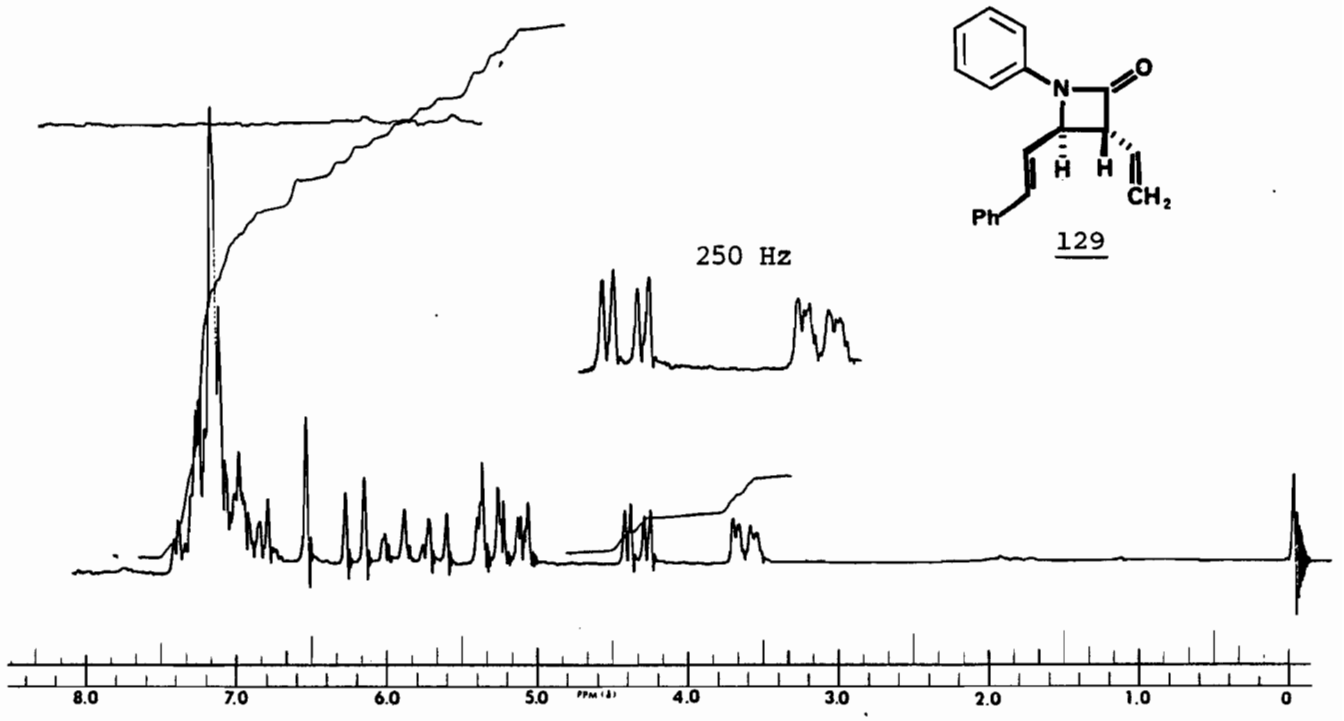
129

at 4.2 p.p.m. Since the p.m.r. spectrum of the crude reaction mixture showed that not all of the Schiff base had reacted at room temperature, the reaction was repeated at reflux. To our surprise an approximately 1:5 mixture of cis β-lactam 128 and trans β-lactam 129 was obtained in 40-45% yield (by p.m.r.). Purification by flash chromatography[94] afforded a small amount of pure trans β-lactam 129. In the p.m.r. spectrum of 129,



128

Fig. 17: The 60 MHz p.m.r. spectrum of β-lactam 128



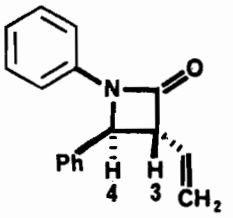
129

Fig. 18: The 60 MHz p.m.r. spectrum of β-lactam 129

(page 63), H_4 appeared as a quartet ($J_{3,4}$ = 2.5 Hz, $J_{4,5}$ = 7 Hz) at 4.4 p.p.m. and H_3 appeared as a broad doublet at 3.6 p.p.m.

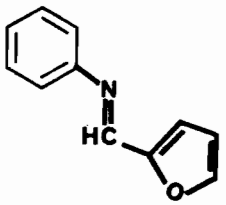
The i.r. spectrum of the two isomeric β-lactams 128 and 129 were identical while their mass spectra were similar. Both mass spectra showed strong molecular ions at m/e 275 and peaks at m/e 156 and 119. The two mass spectra only differed in the intensity of the peaks at m/e 206-208. The mass spectrum of the trans β-lactam showed intense peaks at m/e 207 (57.1%) and 208 (21.72%), while the mass spectrum of the cis β-lactam 128 had intense peaks at m/e 206 (100%) and m/e 207 (38.04%). The peaks at m/e 156 and 119 in both mass spectra were due to the fragmentation shown in 128 and 129 as a solid line. The peak at m/e 207 in the mass spectrum of 129 was probably due to the fragmentation shown in structure 129 as a dotted line. The origin of the intense peak at m/e 206 (M^+-69) in the mass spectrum of 128 is unknown.

These results made us doubt the result obtained by Bose for the cycloaddition of crotonyl chloride on benzylidene aniline. However, when we repeated the reaction in refluxing methylene chloride we also obtained exclusively trans β-lactam 125, m.p. 100-102°, in 40% yield after recrystallization. In the p.m.r. spectrum of 125, H_4 appeared as a doublet (J = 2.5 Hz) at 4.9 p.p.m.

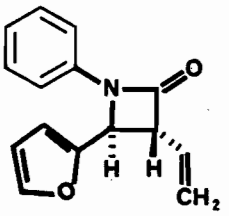


125

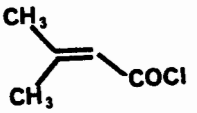
Since, like cinnamylidene β-lactams, furfurylidene β-lactams[48] can also be transformed into useful intermediates for the synthesis of cephalosporin derivatives, the cycloaddition was repeated with furfurylidene aniline 130. The Schiff base 130 was easily obtained in quantitative yield by refluxing for 4 hrs a solution of aniline in benzene with 1 equivalent of furfuraldehyde and removing the water formed with a Dean Stark trap. Treatment of 130 with crotonyl chloride/triethylamine in refluxing methylene chloride afforded a good yield of trans β-lactam 131. In the p.m.r. spectrum of 131, H_4 appeared as a doublet (J = 2.5 Hz) at 4.8 p.p.m.



130

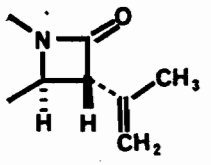


131



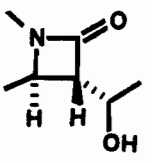
132

Since we were also interested in the synthesis of Thienamycin itself, we investigated the reaction of dimethylacryloyl chloride 132 with imines. Ozonolysis of the resulting β-lactam 133 followed by sodium borohydride reduction would afford

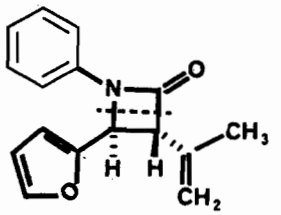


133

1) O_3
2) $NaBH_4$/EtOH



134

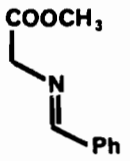


135

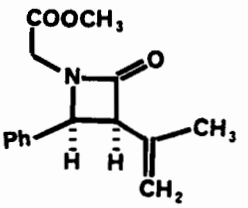
β-lactam 134 having the thienamycin side chain.

Treatment of 130 with acid chloride 132 and triethylamine afforded trans β-lactam 135, m.p. 84-86°, $\nu_{C=O}$ 1750 cm^{-1}. The mass spectra for 131 and 135 were very simple and showed peaks for the molecular ion and for the fragmentation shown in 135 as a dotted line.

To test the generality of these results, the reaction of crotonyl chloride 124 or dimethylacryloyl chloride 132 was investigated on a number of Schiff bases. Schiff bases 136, 138, 141 and 143 derived from amino esters and Schiff base 145 derived from an amino phosphonate were chosen because similar Schiff bases have been used in the synthesis of cephalosporin analogues (Bristol approach, p. 16, and Merck approach, p. 14), while Schiff base 147 derived from 2,4-dimethoxybenzylamine has been used to synthesize a key intermediate used for the synthesis of many cephalosporin and penicillin analogues (S.K.F. approach, p. 16). If dimethylacryloyl chloride and crotonyl chloride were to react with these Schiff bases, then these acid chlorides could be used instead of azidoacetyl chloride in preparing classical β-lactams with a thienamycin or PS-5 (ethyl) side chain.



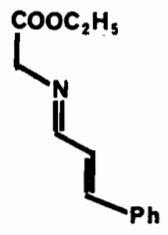
136



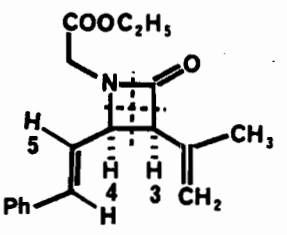
137

Reaction of 136 with dimethylacryloyl chloride/triethylamine afforded very little β-lactam 137 (by p.m.r. and i.r.) even when the cycloaddition was performed in refluxing dichloroethane.

The synthesis of Schiff base 138 proved to be difficult. Addition of 1 equivalent of cinnamaldehyde to ethyl glycinate in methylene chloride gave approximately a 1:1 mixture of the desired Schiff base 138 and some other unidentified products, presumably derived from 1,4 additon of ethyl glycinate. After much experimentation, we found that slow addition of 1 equivalent of cinnamaldehyde to ethyl glycinate[122] in methylene chloride containing magnesium sulphate at 0° afforded Schiff base 138 in approximately 85-90% yield (by p.m.r.). The reaction time was somewhat critical. Stirring for more than 2 hrs gave less Schiff base. Treatment of 138 with dimethylacryloyl chloride 132 and triethylamine afforded a good yield of cis β-lactam 139. In the p.m.r. spectrum of 139, H_4 appeared as a quartet



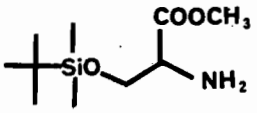
138



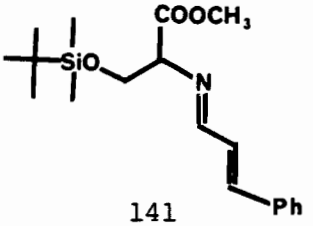
139

($J_{3,4}$ = 5 Hz, $J_{4,5}$ = 7 Hz) at 4.5 p.p.m. The mass spectrum showed a molecular ion at m/e 299 and peaks at m/e 82, 129, 170, 217 and 218 for the fragmentation shown in structure 139.

Treatment of Schiff base 141[95], easily obtained from amine 140 and 1 equivalent of cinnamaldehyde, with dimethylacryloyl chloride also gave a good yield of β-lactam 142. Like for the cycloaddition with azidoacetyl chloride[95], only one diastereomer was formed, as shown by p.m.r.

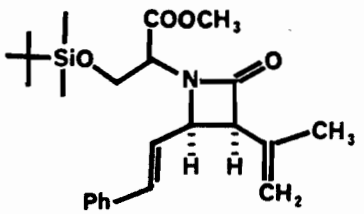


140

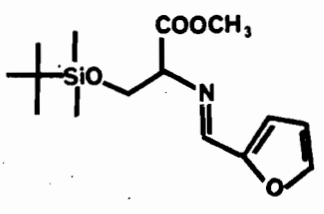


141

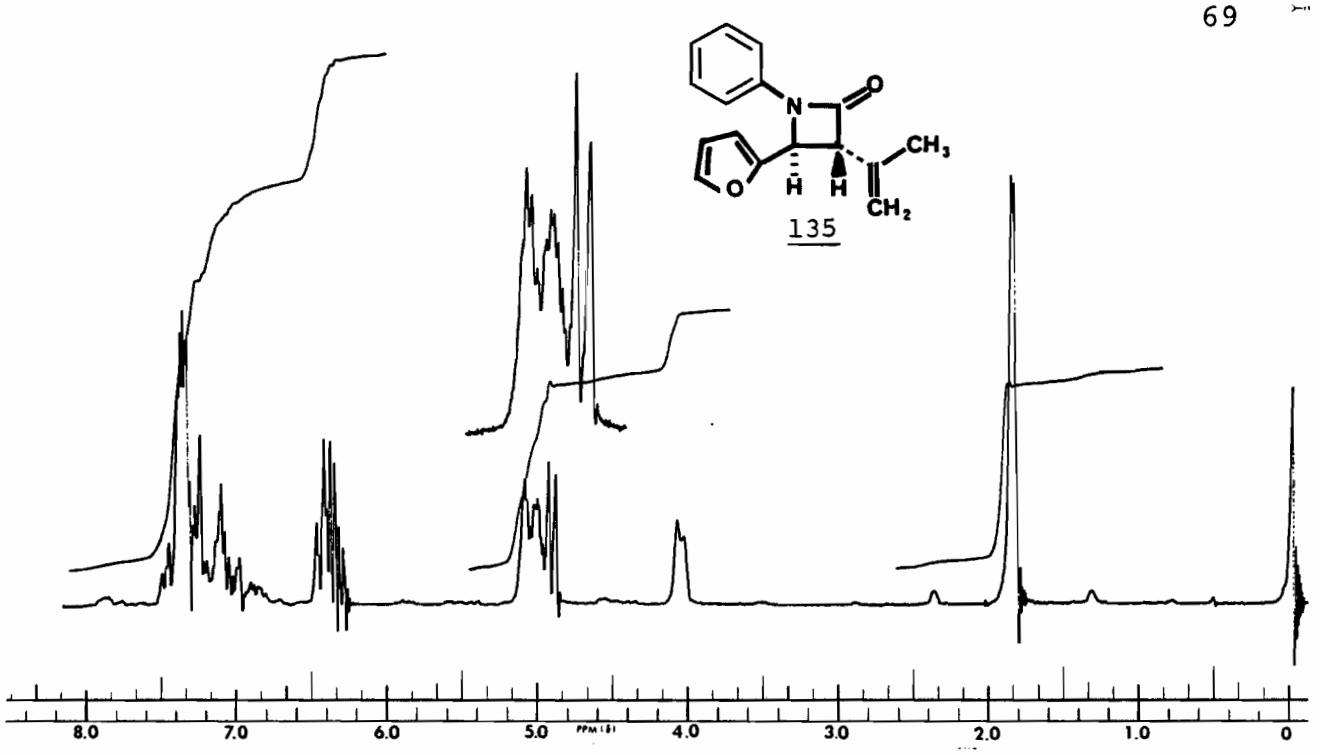
Reaction of amine 140 with 1 equivalent of furfuraldehyde in refluxing methylene chloride gave an excellent yield of Schiff base 143. To our surprise, reaction of Schiff base 143 with dimethylacryloyl chloride 132 in refluxing methylene chloride gave a low yield of cis β-lactam 144. There was no trace of the corresponding trans β-lactam, as shown by p.m.r. of the crude reaction mixture. In the p.m.r. spectrum of 144 (page 69), H_4 appeared as a doublet at 5.1 p.p.m. The chemical shift of the



142

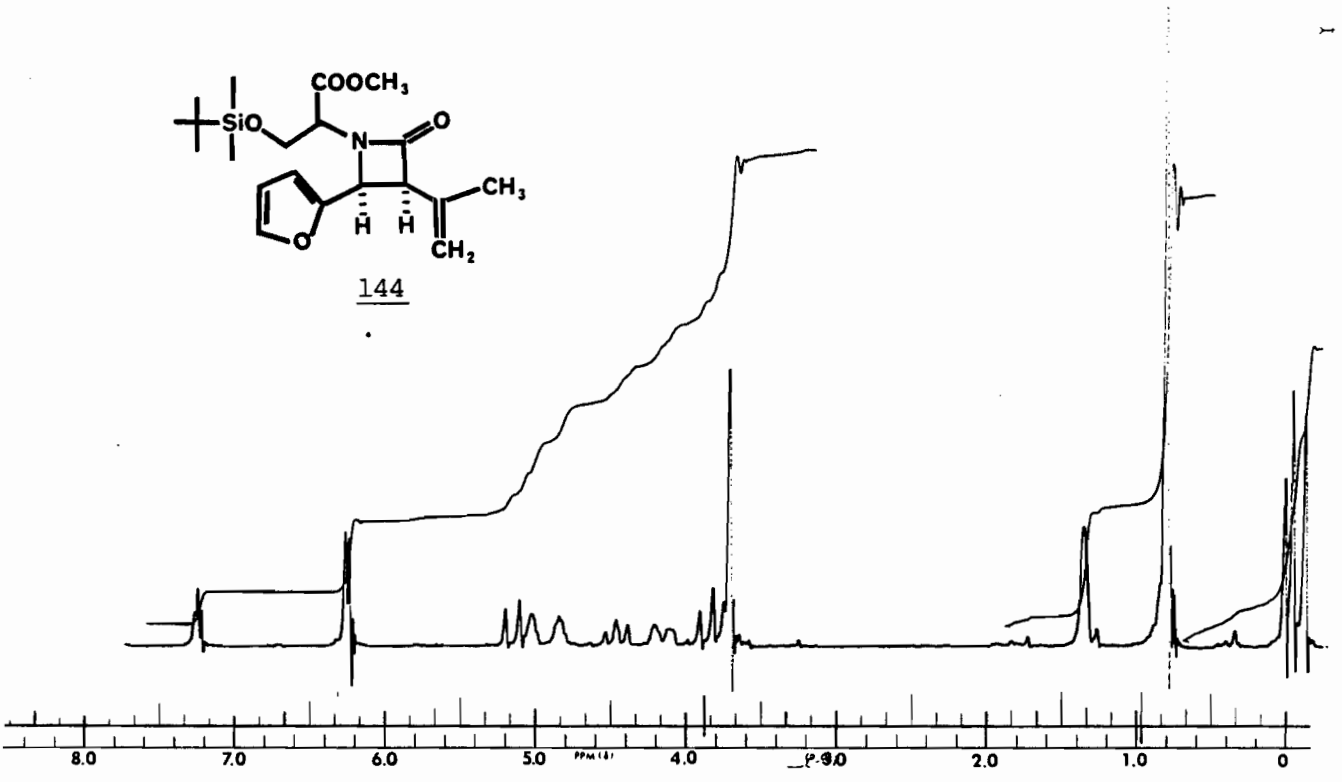


143



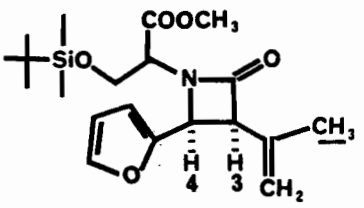
135

Fig. 19: The 60 MHz p.m.r. spectrum of β-lactam 135

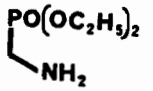


144

Fig. 20: The 60 MHz p.m.r. spectrum of β-lactam 144

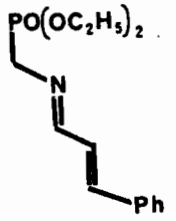


144

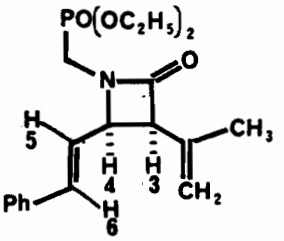


163

methyl group in the side chain was also consistent with the presence of a cis fused ring in 144. The methyl group in 144 (underlined) appeared at 1.5 p.p.m. which was .6 p.p.m. lower than it appeared in the p.m.r. of trans β-lactam 135. The shielding of the methyl group in 144 was probably due to the furan ring which was cis to the methyl group.

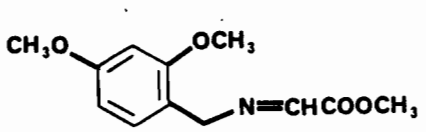


145

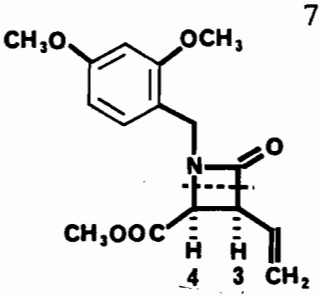


146

Unlike 138, Schiff base 145 was easily synthesized in quantitative yield by the addition of 1 equivalent of cinnamaldehyde to amino phosphonate 163[39] in methylene chloride containing magnesium sulphate. Addition of dimethylacryloyl chloride 132 to Schiff base 145 afforded cis β-lactam 146 in good yield. The p.m.r. spectrum of 146 was complicated by phosphorus coupling but could be interpreted by comparing it to that of 139. H_4 appeared as a doublet of quartets ($J_{4,P}$ = 1 Hz, $J_{3,4}$ = 5 Hz, $J_{4,5}$ = 7 Hz). Like the β-lactams derived from amino esters, the mass spectrum of 146 showed a very strong molecular ion at m/e 363 (99%) and peaks at 282 (100%), 170 (43%), and 82 (15%) for the usual β-lactam fragmentation.



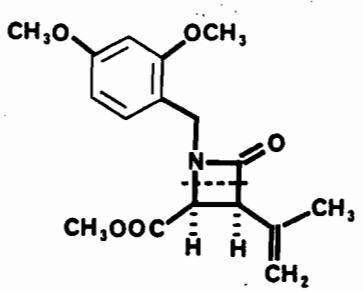
147



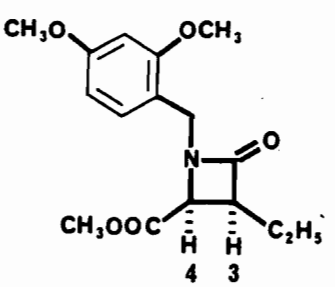
148

Treatment of Schiff base 147[52,96] with crotonyl chloride and triethylamine in refluxing methylene chloride afforded exclusively cis β-lactam 148, m.p. 68-69°, in 40% yield. In the p.m.r. spectrum of 148 (page 72), H_4 appeared as a doublet (J = 5 Hz) at 4.0 p.p.m. while H_3 appeared as a broad doublet (J = 5 Hz) at 3.7 p.p.m. Repeating the cycloaddition with dimethylacryloyl chloride also afforded cis β-lactam 149, m.p. 72-72.5° in fair yield. The p.m.r. spectrum of 149 was identical to that of 148 except for the signals due to the different side chains. The mass spectrum of each β-lactam showed a molecular ion and a peak at m/e 193 for the fragmentation shown in 148 and 149.

Catalytic hydrogenation (PtO_2) of 148 in ethanol at 30 psi afforded 150 in good yield. The p.m.r. spectrum of 150 (page 72) clearly showed a doublet (J = 5 Hz) for H_4 at 3.9 p.p.m. along with all other appropriate signals. β-Lactam 150 is perhaps the most useful of all the β-lactams synthesized up until now in this



149



150

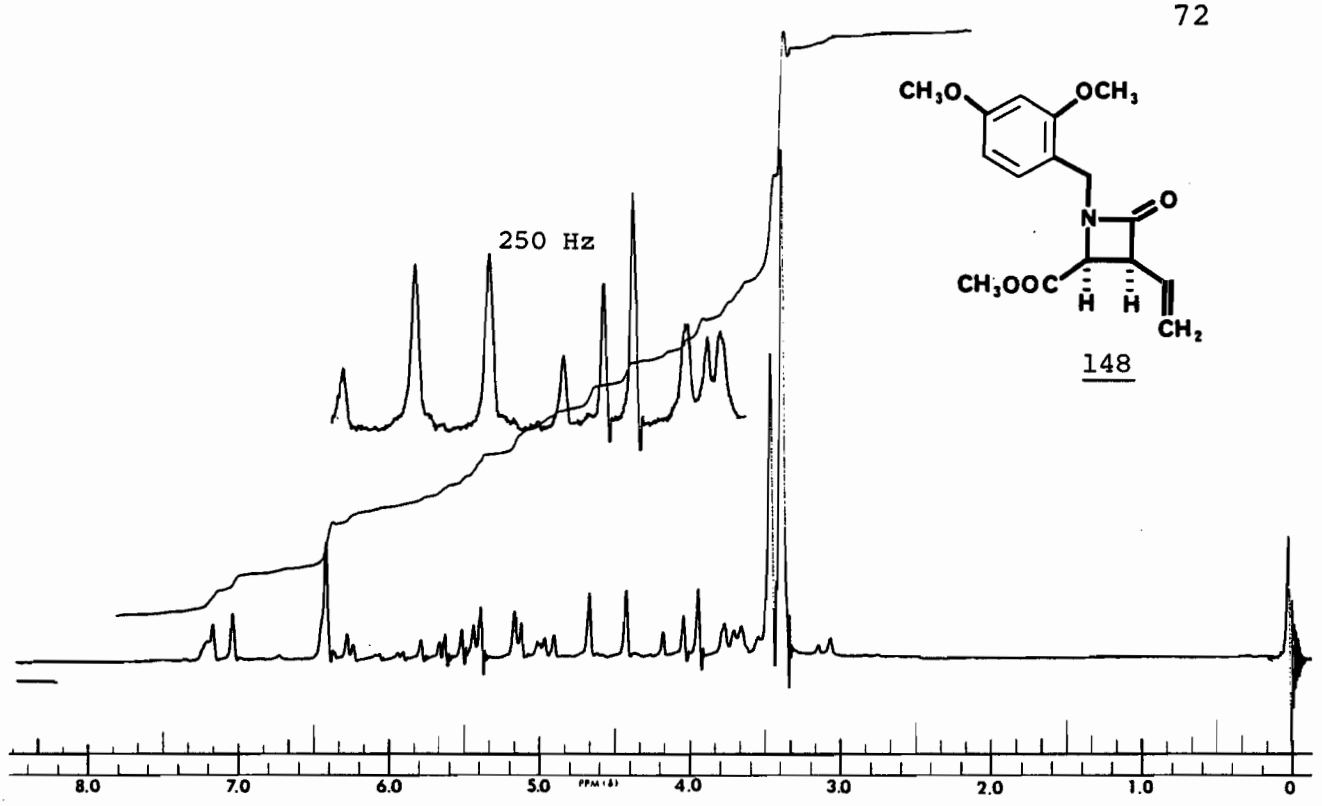


Fig. 21: The 60 MHz p.m.r. spectrum of β-lactam 148

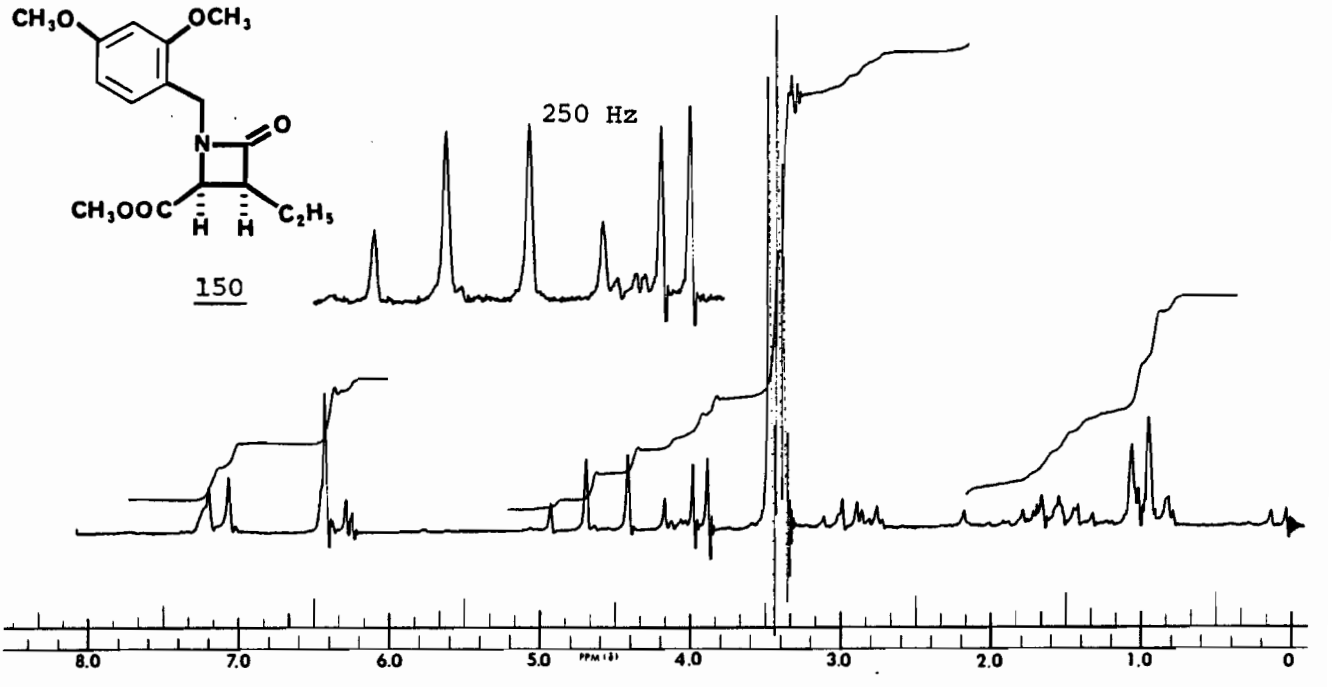
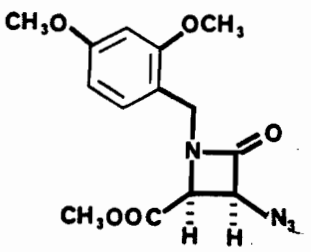


Fig. 22: The 60 MHz p.m.r. spectrum of β-lactam 150



151

chapter. Use of 150 instead of the corresponding azido β-lactam 151 in the Smith, Kline and French approach to cephalosporin and penicillin nuclear analogs (see p. 16) should allow the synthesis of analogs containing the ethyl (PS-5) side chain.

To summarize: unlike Schiff bases derived from anilines which gave either cis or trans β-lactams, Schiff bases derived from amino esters 138, 141, 143, amino phosphonate 145 and benzyl amine 147 afforded only cis β-lactams, when reacted with dimethylacryloyl chloride or crotonyl chloride which therefore behave like azidoacetyl chloride. The similarity of dimethylacryloyl chloride and crotonyl chloride to azidoacetyl chloride might be due to their ability to stabilize the transition state leading to cis β-lactams (see p. 74). While cinnamylidene Schiff bases react with azidoacetyl chloride at -20° or lower, the cycloaddition of these Schiff bases with dimethylacryloyl chloride or crotonyl chloride gave best results in refluxing methylene chloride. The higher reaction temperature necessary for completion of the cycloaddition was probably due to the decreased acylating ability of dimethylacryloyl chloride and crotonyl chloride or to a decreased acidity of the proton, which has to be abstracted for β-lactam formation.

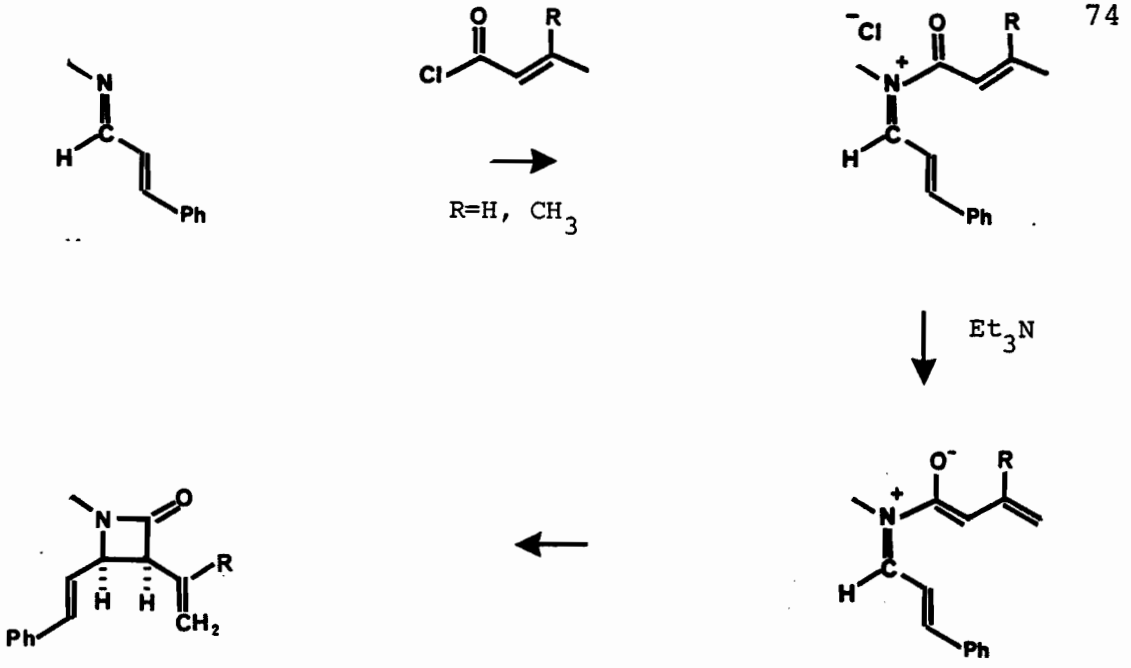
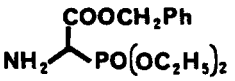
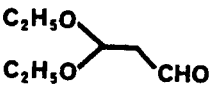


Fig. 23: Possible mechanism for the formation of cis β-lactams in the cycloaddition of acryloyl chlorides with cinnamylidene Schiff bases.

Having been successful in synthesizing β-lactams by reacting imines with acryloyl chlorides, we decided to use this reaction in the synthesis of thienamycin analogs. Our initial plan is shown on page 75. We planned to start from phosphonate 152 and form Schiff base 154 by reaction with aldehyde 153. Treatment of Schiff base 154 with dimethylacryloyl chloride should afford cis β-lactam 155. We felt that the transformation should occur because Christensen found that the reaction of a similar Schiff base 156[44] with azidoacetyl chloride afforded the corresponding β-lactam in fair yield. Ozonolysis of 155, sodium borohydride reduction, protection of the resulting alcohol, followed by hydrolysis of the acetal should afford aldehyde 157. Cyclization of the aldehyde with sodium hydride should afford protected thienamycin analog 158. Deprotection would afford thienamycin analog 159.

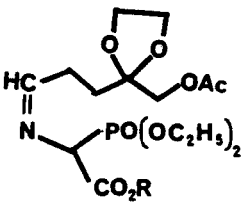


152

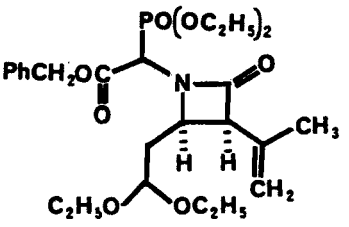


153

154



156



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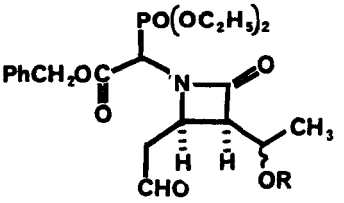

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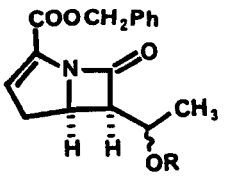

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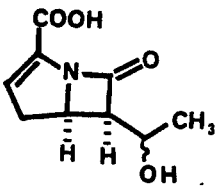
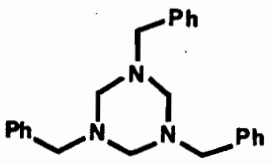


159

We first turned our attention to the synthesis of 152[39]. Treatment of triazine 160 with diethyl phosphite, followed by work-up with ethereal hydrogen chloride gave hydrochloride 161. Catalytic hydrogenation (Pd/C) of 161 gave hydrochloride 162. Neutralization of the hydrochloride with ammonia in chloroform gave amino phosphonate 163 in excellent yield. The p.m.r. and i.r. spectra of 163 were identical to those reported by Christensen. Stirring a solution of amine 163 and 1 equivalent of benzaldehyde in methylene chloride with magnesium sulphate afforded Schiff base 164 in excellent yield. Christensen reported[39] that treatment of 164 with 1 equivalent of phenyl lithium followed by addition of 1 equivalent of benzyl chloroformate gave a mixture of 164 and 165 which could be separated by chromatography on silica gel. Hydrolysis of 165 would then afford amino phosphonate 152. After much experimentation we found



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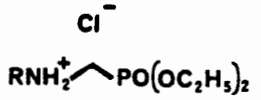
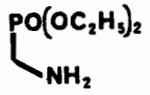
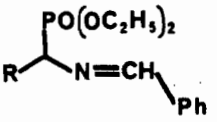


161 R=CH_2Ph

162 R=H



163

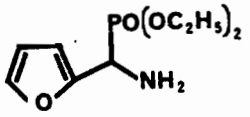


164 R=H

165 R=CO_2CH_2Ph

that, although treatment of 164 with phenyl lithium and quenching of the anion with benzyl chloroformate afforded a mixture of 164 and 165, chromatography on silica gel, even at 5°, afforded only a 5% yield of fairly pure 165. Most of the Schiff base probably hydrolyzed on the silica column.

Unable to synthesize 152 in a reasonable yield, we decided to synthesize a similar phosphonate 170. If we used 170 instead of 152 in our scheme (page 75), we would obtain β-lactam 166 instead of 155. Ozonolysis of 166 at room temperature, protection of the resulting carboxylic acid and sodium borohydride reduction of the methyl ketone would then afford 167. Protection of the alcohol, hydrolysis of the ketal and cyclization with sodium hydride would again give 158.



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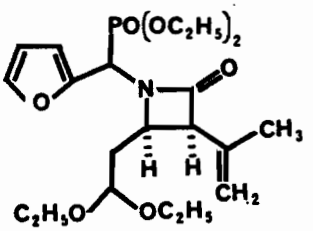
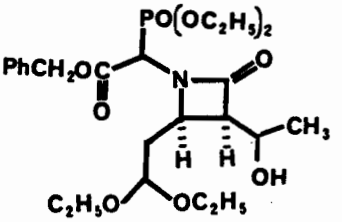
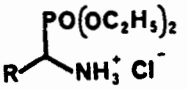


166

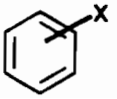


167

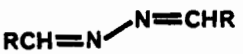
The traditional method for the synthesis of amino phosphonates with general structure M involves the treatment of the appropriate aldehyde with diethyl phosphite and ethanolic ammonia

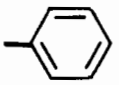


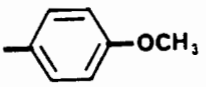
M

R =  , alkyl

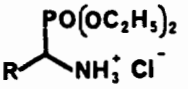
in a pressure bottle at approximately 100°[97]. We found that under these conditions furfuraldehyde did not afford any amino phosphonate. Recently Rachon and Wasielewski[98,99] have described a novel route to amino phosphonates 169 a and b. They found that heating a solution of the appropriate aromatic azine 168 a and b in neat diethyl phosphite containing .1 equivalent of sodium for 8 hrs and work-up with etheral hydrogen chloride gave amino phosphonates 169a, b. Using their conditions furfuraldehyde azine 168c[100] afforded the amino phosphonate hydro-

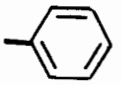


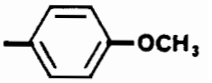
168 a) R= 

b) R= 

c) R= 

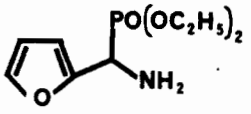


169 a) R= 

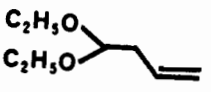
b) R= 

c) R= 

chloride 169c in fair yield. Neutralization of 169c with ammonia afforded the desired amino phosphonate 170. We next turned our attention to the synthesis of aldehyde 153. Self condensation of ethyl vinyl ether under the conditions described

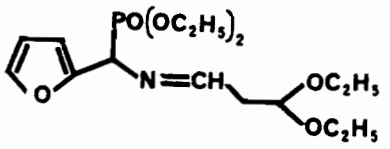


170

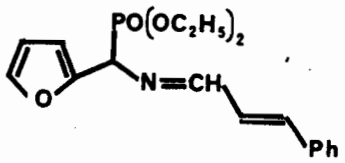


171

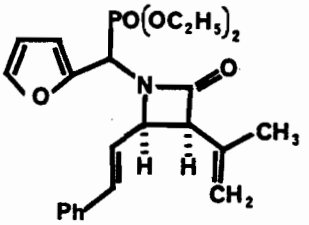
in a Japanese patent[101], afforded acetal 171 in 55% yield. Ozonolysis of 171[102] in ethyl acetate followed by hydrogenation of the ozonide in situ with palladium on calcium carbonate as catalyst afforded the desired aldehyde 153 in 45% yield. Condensation of 153 with amino phosphonate 170 afforded Schiff base 172a in quantitative yield. The p.m.r. spectrum of 172a showed a characteristic multiplet at 7.9 p.p.m. for the Schiff base proton. To our surprise treatment of 172a with dimethylacryloyl chloride or even with azidoacetyl chloride in refluxing methylene chloride, afforded very little β-lactam. The i.r. spectrum of the reaction mixture showed only weak absorption at 1770 cm^{-1} where we expected the β-lactam to absorb. Repeating the reaction in boiling dichloroethane with 2 or 3 equivalents of the acid chloride did not significantly increase the amount of β-lactam formed. The lack of reactivity of 172a could have been due to the phosphorane or due to the aldehyde component. When we repeated the cycloaddition on the corresponding cinnamylidene Schiff base 172b, a good yield of β-lactam 173 was obtained. The lack of reactivity of Schiff base 172a was therefore probably due to the aldehyde component.



172a

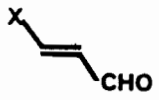


172b

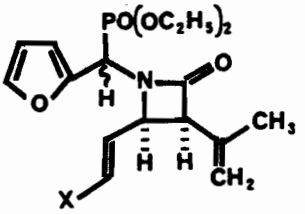


173

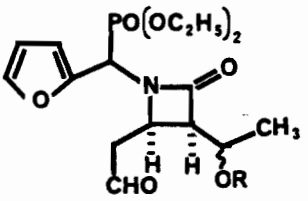
Since the key difference between the two aldehyde components was that Schiff base 172b was derived from an unsaturated aldehyde while 172a was not, it seemed likely that this double bond was necessary for the success of the cycloaddition. In our synthetic scheme the aldehyde component, therefore, had to have general structure N. Treatment of the corresponding Schiff base with dimethylacryloyl chloride would then afford β-lactam 174. We were therefore faced with the problem of finding an α,β-unsaturated aldehyde N such that 174, which is derived from it, could be transformed to 175.



N



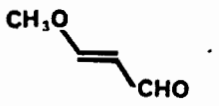
174



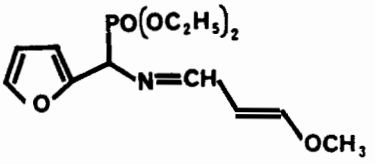
175

Since the aldehyde N in the synthesis had to have a double bond we were also faced with the problem of differentiating the two double bonds in 174. Our plan was to attack the two problems separately. We, therefore, decided to work out the transformation first with azidoacetyl chloride. The use of azidoacetyl chloride allowed us to concentrate on the problem of the transformation. Its use also simplified the p.m.r. spectra of the β-lactams formed. After solving the transformation problem we would return to the problem of differentiating the two double bonds in 174.

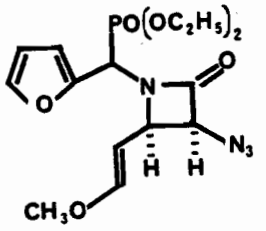
A solution might be to start with aldehyde 176[103]. However, even if we could synthesize the corresponding Schiff base 177, and from it the desired β-lactam 178, the conditions required to hydrolyze the vinyl ether in 178 to an aldehyde would almost certainly destroy β-lactam 178.



176

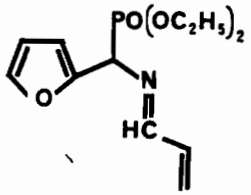


177



178

Another simple solution would be to start with acrolein and form Schiff base 179. Reaction with azidoacetyl chloride should afford β-lactam 180. Hydroboration of 180 followed by oxidation of the resulting alcohol would afford the desired aldehyde β-lactam 181. The synthesis of Schiff base 179 proved to be difficult. Addition of 1 equivalent of acrolein to a solution of amino phosphonate 170 in methylene chloride containing magnesium sulphate afforded only a 40% yield of Schiff base 179 contaminated with some other unidentified, presumably 1,4 addition, products. After many other unsuccessful attempts we found that addition of a large excess (greater than 10 equiva-



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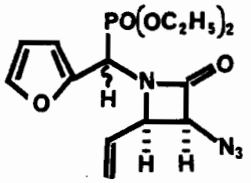
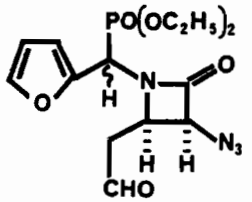


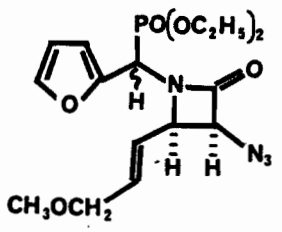
180



181

lents) of acrolein to amino phosphonate 170 in methylene chloride containing sodium sulphate afforded a good yield (greater than 90% by p.m.r.) of Schiff base 179. Treatment of 179 with azidoacetyl chloride/triethylamine at room temperature afforded a 40% yield of β-lactam 180, $\nu_{C=O}$ 1770 cm^{-1}. Because of the complexity of the p.m.r. spectrum of 180, the stereochemistry of the ring junction could not be determined but was most probably cis. The mass spectrum showed a very weak molecular ion and peaks at m/e 327 for the loss of the vinyl group from the molecular ion and at m/e 327 for the loss of nitrogen from the molecular ion. Unfortunately treatment of 180 with 3 equivalents of borane/tetrahydrofuran complex in tetrahydrofuran followed by oxidation with trimethyl amine N-oxide[104] in refluxing tetrahydrofuran afforded a complex mixture of products. The i.r. spectrum showed a weak absorption at 1770 cm^{-1}. The β-lactam had not survived the hydroboration conditions. The approach was abandoned. We had to try another substituent X in α,β-unsaturated aldehyde N.

We thought that if X were CH_2OCH_3, treatment of the resulting β-lactam 185 with palladium on charcoal[105] should isomerize the double bond to the corresponding vinyl ether 186. Ozonolysis of 186 would then afford the desired aldehyde 181. In order



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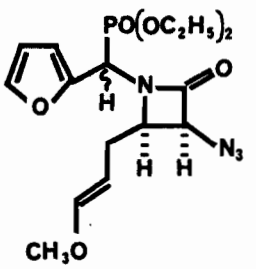
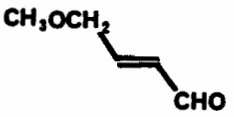


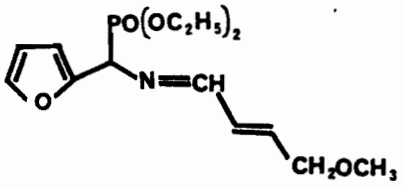
186

to synthesize β-lactam 185 we had to first synthesize the α,β-unsaturated aldehyde 183, which would be our starting material. Aldehyde 183 was synthesized from 2-butene-1,4 diol. Methylation with dimethyl sulphate/sodium hydroxide afforded the monomethyl ether 182[106] in low yield. Alcohol 182 has been oxidized to 183 using a modified Oppenhauer oxidation with cinnamaldehyde/$Al(i\text{-}OPr)_3$[106]. We were unable to oxidize 182 to 183 using these conditions but we found that alcohol 182 could be oxidized to aldehyde 183 using pyridinium chlorochromate[78]. Condensation of 183 with amine 170 afforded Schiff base 184 in approximately 90% yield by p.m.r. Treatment of Schiff base 184 with azidoacetyl chloride/triethylamine at room temperature afforded β-lactam 185, $\nu_{C=O}$ 1770 cm^{-1}, in 42% yield after column chromatography.

182



183



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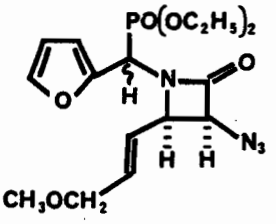
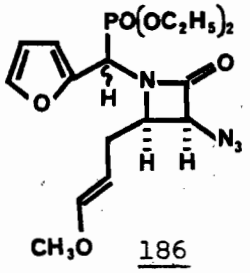


185

The p.m.r. spectrum of 185 was very complicated and the stereochemistry of the ring junction could not be determined by p.m.r. Since all the β-lactams formed from imines derived from α,β-unsaturated aldehydes and azidoacetyl chloride up until now were

cis, we could safely assign the cis stereochemistry to 185. The presence of two peaks for the methyl ether in the p.m.r. spectrum of 185 was, therefore, probably due to the presence of two diastereomers.

Unfortunately, treatment of 185 in refluxing ethanol with palladium on charcoal[105] or with tris-triphenylphosphine rhodium chloride using the conditions described by Corey[107] did not afford any of the expected rearranged product 186. Only starting material 185 was recovered. Steric hindrance in 185 probably prevented the isomerization. The isomerization of allyl ethers to vinyl ethers has been found to be sensitive to steric hindrance[108].



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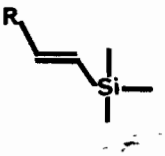

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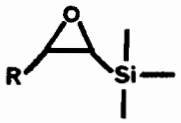


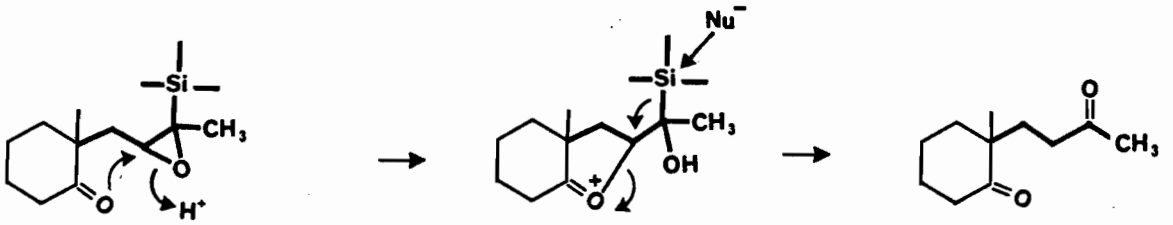
188

RCH2CHO

189

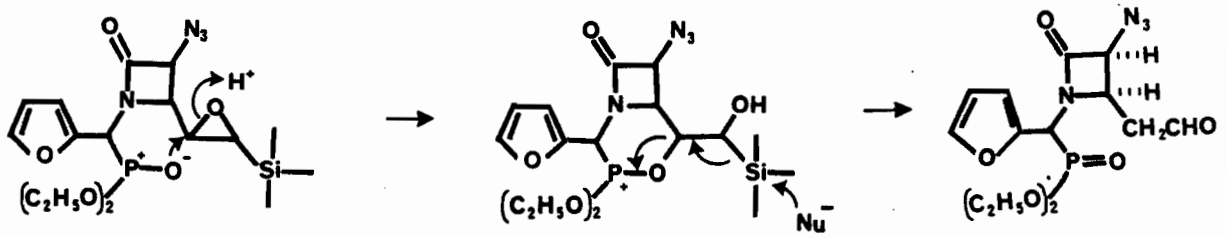
We next investigated the possibility of transforming the double bond to an aldehyde using the known transformation of vinyl silanes 187 to aldehydes 189. Stork found[109] that epoxidation of 187 to 188 with m-chloroperbenzoic acid, followed by treatment with acid, afforded good yields of aldehydes 189. He

also found[110] that the transformation of 190 to 191 occurred during epoxidation when an appropriate neighbouring group was present and that there was no need for the strong acid treatment for the rearrangement of the epoxy silane to the aldehyde. To explain these results Stork postulated that the carbonyl group participated in the rearrangement as shown. This observation made the use of this transformation even more at-



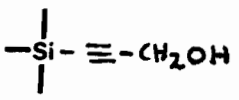
190 191

tractive. The phosphonate in the expected β-lactam 192 should also participate in the rearrangement of 192 to the desired aldehyde as shown.



192 193

The required α,β-unsaturated aldehyde 196 was easily synthesized from propargyl alcohol. Treatment of propargyl alcohol with 2 equivalents of n-butyl lithium followed by quenching with 2 equivalents of trimethylsilyl chloride gave, after work-up with aqueous acid, silyl alcohol 194[111,112]. Reduction of 194 with 2 equivalents of lithium aluminum hydride in refluxing tetrahydrofuran afforded fairly pure alcohol 195[113]. Oxidation of alcohol 195 with pyridinium chlorochromate[78] afforded trans aldehyde 196[114] in 45% yield based on 194. Condensation of aldehyde 196 with amino phosphonate 170 afforded Schiff base 197. In the p.m.r. spectrum of 197, the Schiff base proton appeared as a multiplet at 7.9 p.p.m. Treatment of 197 with azidoacetyl chloride afforded β-lactam 198, $\nu_{C=O}$ 1770 cm^{-1}, in 70% yield. The stereochemistry of the β-lactam could not be determined by p.m.r., but was most probably cis. We were unable to



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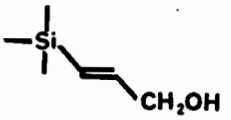

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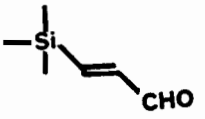

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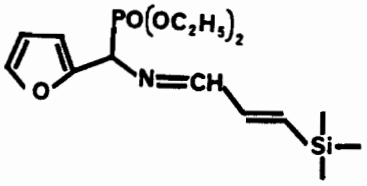

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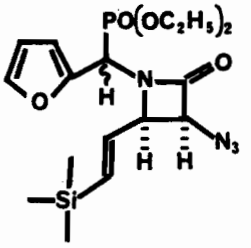


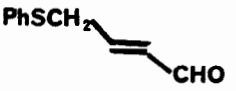
198

epoxidize 198 with m-chloroperbenzoic acid at room temperature[109] or in refluxing dichloroethane[115,116]. Attempts to epoxidize 198 with peracetic acid were equally unsuccessful. Steric hindrance in 198 probably prevented the epoxidation of the double bond.

Another way to achieve the desired transformation would be to start with aldehyde 201, and form β-lactam 203. Oxidation of 203 would give sulphone 204. Treatment of 204 with mild base should afford the α,β-unsaturated sulphone 205. Ozonolysis of 205 would give the desired aldehyde 181. Aldehyde 201 was synthesized from 2-butene-1,4 diol. Treatment of 2-butene-1,4 diol with thionyl chloride/pyridine afforded the monochloro derivative 199[117]. Heating 199 with thiophenol and sodium hydroxide[118] afforded alcohol 200 in 50% yield. Oxidation of 200 with pyridinium chlorochromate[78] gave fairly pure trans aldehyde 201. Attempts to purify aldehyde 201 by distillation lead to its decomposition while chromatography only afforded aldehyde 201 in

199

200



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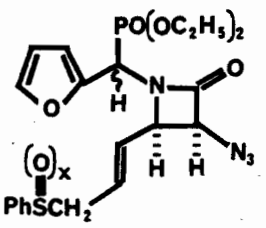
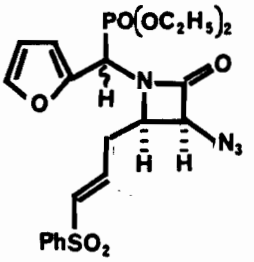


203 x=0

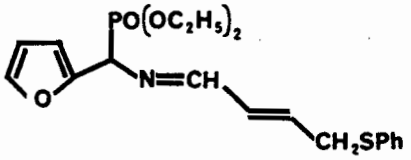
204 x=2



205

about 90% purity. Treatment of impure aldehyde 201 with amino phosphonate 170 gave Schiff base 202. Reaction of 202 with azidoacetyl chloride/triethylamine at room temperature gave a small amount of β-lactam (by p.m.r. and i.r.). Separation by column chromatography failed to give pure β-lactam. The failure of the reaction to give a reasonable yield of β-lactam was very surprizing. This might have been due to the reaction of the sulphur with the acid chloride.

An interesting way to achieve the desired transformation would be to start with aldehyde 206 and form the β-lactam 207. Treatment of 207 with p-toluenesulphonic acid would give the isomerized β-lactam 208[119]. Ozonolysis or treatment with osmium tetroxide/sodium periodate should then afford the desired aldehyde 181. Aldehyde 206 has not been described in the literature. We envisioned two possible routes to aldehyde 206.



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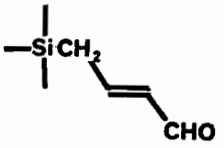

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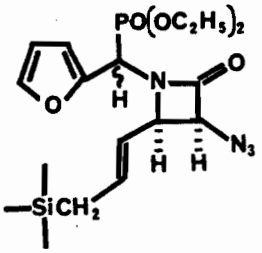

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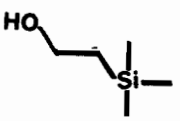

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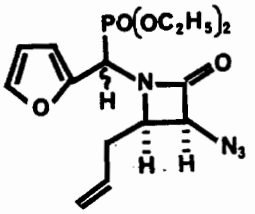

208

They are illustrated in Figure 24. The first route uses the new approach for the synthesis of substituted acroleins recently described by G. Tadema et al.[120] which involves reaction of propiolaldehyde diethyl acetal with Grignard reagents followed by acid hydrolysis of the resulting allene. The second is based on the route used for the synthesis of the new carboxylic acid protecting group 209[121]. Due to lack of time, these routes could, unfortunately, not be explored experimentally. This approach to achieve the desired transformation will be explored by A. Ugolini in Dr. Just's laboratory.

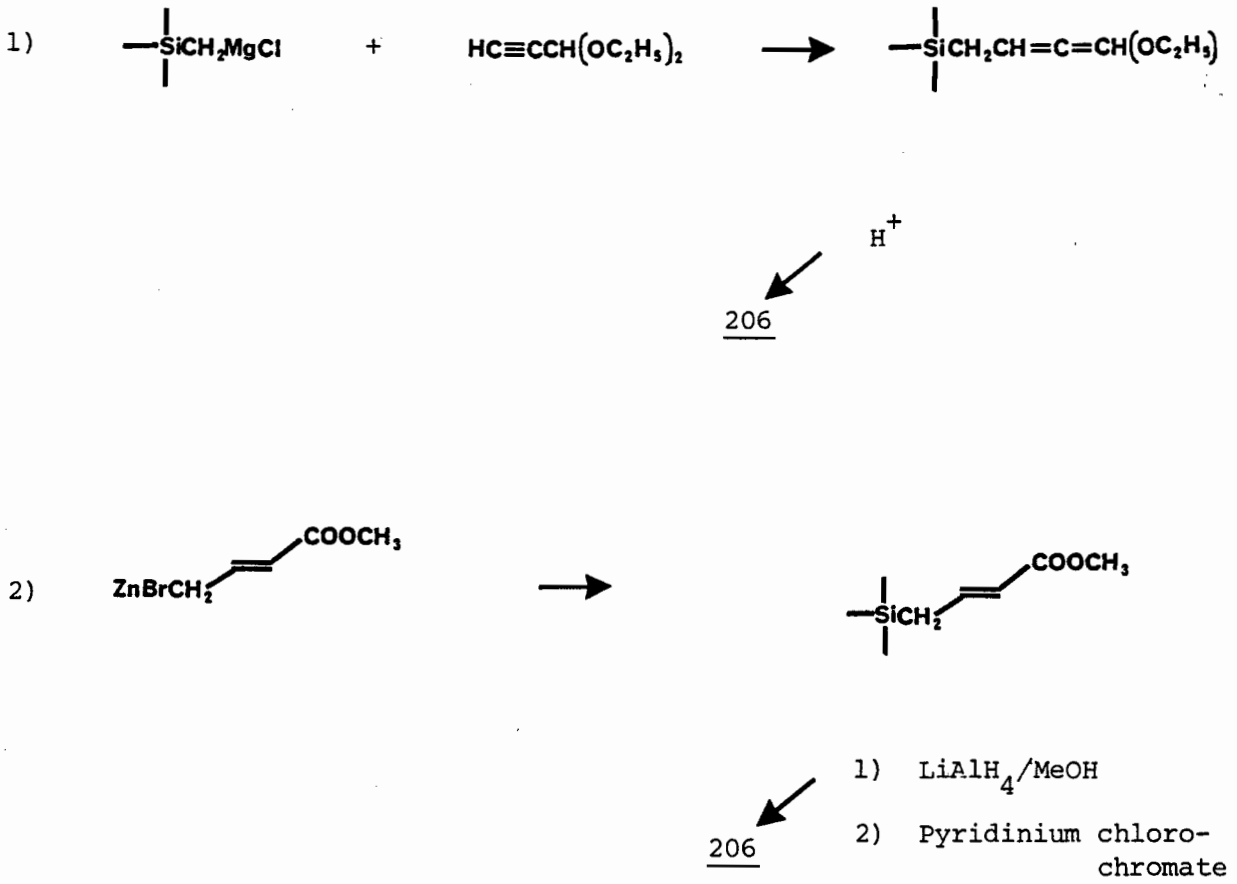

Fig. 24: Possible routes to aldehyde 206

Contributions to Knowledge

(1) The stereochemistry of the β-lactams formed by reacting azidoacetyl chloride with cinnamylidene Schiff bases derived from substituted anilines, was found to depend on the substituent. Schiff bases derived from electron rich anilines with pKa $\geq$ 2.4 afforded exclusively cis β-lactams.

(2) Cephalosporin analogs 60 and 120 were synthesized. The key step in the synthesis of 120 involved the novel cyclization of t-butyldimethylsilyl ether mesylate 109 with potassium fluoride/18-crown-6.

(3) The reaction of dimethylacryloyl chloride and crotonyl chloride with various Schiff bases afforded cis β-lactams in fair to good yields.

(4) β-Lactam 150, a key intermediate, for the synthesis of cephalosporin and penicillin analogs containing the PS-5 side chain was synthesized.

General Experimental

Melting points were determined on a Gallenkamp block and are uncorrected. Mass spectra (m.s.) were obtained on an AEl-MS-902 mass spectrometer or on an LKB-900 mass spectrometer at 70 eV using a direct insertion probe. Infrared (i.r.) spectra were obtained on Unicam SP1000, Perkin Elmer 257 and 297 spectrophotometers. Proton magnetic resonance (p.m.r.) spectra were recorded on Varian T-60, T-60A, HA-100 and on Brucker FT 90 spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in the δ scale in parts per million. Doublets ('d'), triplets ('t') and quartets ('q') were recorded at the center of the peaks, and multiplets ('m') as their range of absorption; other abbreviations used: singlet ('s') and broad ('b').

Analytical thin layer chromatography (t.l.c.) was performed on silica gel-coated plates (Machery Nagel Polygram G or Merck Silical Gel 60) and on a preparative scale on silica gel (Merck HF 254) coated glass plates (20 cm x 20 cm x 1 mm). Merck silica gel 60, Woelm alumina (neutral) and Camag alumina (supplied by Ventron) were used for normal chromatography. Silica Woelm 32-63 was used for flash chromatography.

Solvents were reagent grade unless otherwise specified. All evaporations were done under reduced pressure (water aspirator) with a bath temperature of 25-40° unless otherwise specified.

Elemental analyses were performed by Heterocyclic Chemical Corporation, Missouri and Midwest Microlab Ltd., Indianapolis, Indiana.

Experimental

Chapter 1

Lactone 24

To a solution of benzylidene anthranilic acid 23 (900 mg) in dry benzene (25 ml) containing triethylamine (.8 g) was added dropwise a solution of phthalimidoacetyl chloride (.9 g) in dry benzene (6 ml) over a period of 20 min. The reaction mixture was stirred for one more hour and the salt filtered off. The filtrate was washed with 1% HCl (2 x 10 ml), dried and evaporated. Chromatography of the filtrate on thick layer plates using $CHCl_3$/ether 3:1 as eluent afforded ∿ 100 mg of lactone 24, m.p. 185° (dec.); p.m.r. ($DCCl_3$): δ 4.9 (q, 2H, CH_2), 7.0-8.0 p.p.m. (m, 14H, aromatic + OC<u>H</u>Ph); i.r. ($HCCl_3$): γ_{max} 1780 (weak), 1740 cm^{-1}; m.s.: m/e 412 (M^+).

Phthalimido β-lactam 25

To Schiff base 23 (1.7 g, 7.6 mM) and triethylamine (1.8 g, 18 mM) in dry CH_2Cl_2 (50 ml) was added quickly trimethylchlorosilane (1.75 g, 16 mM) in CH_2Cl_2 (5 ml). The mixture was stirred for 5-10 min and then triethylamine (.8 g, 8 mM) was added. To the solution was added over 1½ hours a solution of phthalimidoacetyl chloride (1.7 g, 7.6 mM) in dry CH_2Cl_2 (100 ml). After the addition was complete the mixture was stirred for two more hours. After the addition of methanol (3 ml), the solution was washed with H_2O (50 ml), saturated NaCl solution (50 ml), dried ($MgSO_4$) and evaporated. The resulting solid was chromatographed on 60 g silica gel act III. Elution with CH_2Cl_2, and then ethyl ether-chloroform (1:1) afforded, after crystallization with $CHCl_3$-CCl_4, 1.7 g (55%) of β-lactam 25, m.p. 214-215°; p.m.r. ($DCCl_3$): δ 5.3 (d, 1H, CH, J = 2.5 Hz), 5.6 (d, 1H, CH, J = 2.5 Hz), 6.9-8.0 (m, 13H, C_6H_4 + C_6H_5), 11.2 p.p.m. (bs, 1H, COOH); i.r. (Nujol): γ_{max} 2300-3500 (COOH), 1770 (β-lactam), 1720 (phthalimide), 1690 cm^{-1} (COOH); m.s.: m/e 412 (M^+), 249, 225, 187, 163. Anal. Calcd for $C_{24}H_{16}N_2O_5$: C, 69.90; H, 3.91; N, 6.79. Found: C, 70.29; H, 4.09; N, 7.03.

Ester 27

To acid 25 (2.47 g, 6 mM) in dry acetonitrile (60 ml) was added p-methoxybenzyl alcohol (.91 g, 6.6 mM) and dineopentyl N,N-dimethyl formamide acetal (2.04 g, 8.7 mM). After sealing the flask under nitrogen, the solution was stirred at room temperature 24 hrs. Concentration down to 20 ml and filtration afforded 2.1 g (66%) of pure ester 27, m.p. 189-190°; p.m.r. ($DCCl_3$): δ 3.7 (s, 3H, OCH_3), 5.0 (d, 1H, CH, J = 2.5 Hz), 5.6 (d, 1H, CH, J = 2.5 Hz), 5.1 (bs, 2H, CH_2), 6.4-7.8 p.p.m. (m, 17H, aromatic); i.r. (Nujol): γ_{max} 1780 (β-lactam), 1720 cm^{-1} (ester and phthalimido).

Amine 28

To ester 27 (1.59 g, 3 mM) in CH_2Cl_2 (75 ml) was added hydrazine (120 µl, 3.8 mM). The solution was stirred 48 hrs at room temperature and the solid that formed was filtered off. Evaporation of the solvent afforded an oil which was chromatographed on silica gel act III using first $CHCl_3/CH_2Cl_2$ 1:1 as eluent. Elution with chloroform-ether (3:1) afforded .66 g (50%) of amine 28 as an oil. P.m.r. ($DCCl_3$): δ 1.9 (bs, 2H, NH_2), 3.9 (d, 1H, $\underline{CH}NH_2$, J = 2.5 Hz), 4.8 (d, 1H, $\underline{CH}Ph$, J = 2.5 Hz), 5.2 (s, 2H, CH_2), 6.6-7.7 p.p.m. (m, 13H, aromatic); i.r. ($CHCl_3$): γ_{max} 3400 (NH_2), 1770 (β-lactam), 1730 (ester), 1120 cm^{-1}.

Schiff base 29a

A solution of amine 28 (210 mg, .52 mM) and p-nitrobenzaldehyde (78 mg, .52 mM) in benzene (50 ml) was refluxed 1½ hrs using a Dean Stark trap. Removal of benzene afforded Schiff base 29a in quantitative yield; p.m.r. ($DCCl_3$): δ 3.8 (s, 3H, OCH_3), 4.7 (m, 1H, CH-N=C), 5.3 (bs, 2H, CH_2), 5.5 (s, 1H, CHPh, J = 2.5 Hz), 6.7-7.5 (m, 13H, C_6H_4 and C_6H_5), 8.0 (q, 4H, $NO_2C_6H_4$), 8.4 p.p.m. (s, 1H, HC=N); i.r. ($CHCl_3$): γ_{max} 1775 (β-lactam), 1730 (ester and phthalimido), 1620 cm^{-1} (C=N).

Schiff base 35

A solution of amine 28 (210 mg, .52 mM) and 3,5-di-tert-butyl-4-hydroxybenzaldehyde (128 mg, .55 mM) in benzene (50 ml) was refluxed 1½ hrs using a Dean Stark trap. Removal of benzene afforded Schiff base 35 in quantitative yield; p.m.r. ($CDCl_3$): δ 1.4 (s, 18H, Bu^t), 3.6 (s, 3H, OCH_3), 4.35 (bs, 1H, CH-N=C), 5.0-5.2 (m, 3H, CH_2, CHPh), 5.2-5.5 (m, 1H, OH), 6.6-7.6 (m, 15H, aromatic), 8.05 p.p.m. (s, 1H, CH=N); i.r. (film): γ_{max} 3650 (OH), 1770 (β-lactam), 1730 (ester), 1630 cm^{-1} (C=N).

Formimidate 37

Into methyl anthranilate (10 g, 66 mM) and trimethyl orthoformate (15 g, 141 mM) was bubbled HCl gas for a few seconds. The mixture was heated at 110° and the methanol formed distilled off. Near the end of the distillation a few crystals of TsOH were added. When 4 g of methanol was collected, the distillation was stopped and 2 g of anhydrous K_2CO_3 was added. Excess orthoformate was then distilled off at ∿ 60° (60 mm). Fractional distillation of the residue gave 5.5 g (43%) of almost colourless formimidate 37; p.m.r. ($DCCl_3$): δ 3.7 (s, 3H, OCH_3), 3.8 (s, 3H, OCH_3), 6.4-7.8 m (5H, C_6H_4 and HC=N); i.r. (film): γ_{max} 3000, 1730 (C=O), 1660 cm^{-1} (C=N); m.s.: m/e 193 (M^+).

β-Lactam ester 38

To formimidate 37 (9 g, 46 mM) in CH_2Cl_2 (150 ml) and triethylamine (5.0 g, 50 mM) under N_2 was added dropwise over 2 hrs phthalimidoacetyl chloride (12.25 g, 54 mM) in CH_2Cl_2 (100 ml). After 16 hrs, the solution was washed with H_2O (2 x 100 ml), dried ($MgSO_4$) and evaporated. Crystallization from $CHCl_3$/hexane, afforded 6 g (33%) of β-lactam 38, m.p. 175-176.5°; p.m.r. ($CDCl_3$): δ 3.3 (s, 3H, OCH_3), 3.81 (s, 3H, $COOCH_3$), 5.4 (d, 1H, CH, J = 2 Hz), 5.9 (d, 1H, CH, J = 2 Hz), 7.0-7.8 p.p.m. (m, 8H, C_6H_4); i.r. ($CHCl_3$): γ_{max} 1775 (β-lactam), 1730 (ester), 1400 cm^{-1}; m.s.: m/e 380 (M^+).

When the reaction was stopped after 2 hrs, a crystalline side product, methyl N-phthalimidoacetyl anthranilate 39, could be isolated by repeated chromatography on SiO_2 act III and recrystallization from $CHCl_3$-hexane, m.p. 188-190°; p.m.r. ($DCCl_3$): δ 3.8 (s, 3H, OCH_3), 4.7 (s, 2H, CH_2), 7.0-9.0 (m, 8H, C_6H_4), 11.5 p.p.m. (s, 1H, NH); i.r. ($CHCl_3$): γ_{max} 3300 (NH), 1780, 1725 (phthalimido, ester), 1690 cm^{-1} (amide).

Amine β-lactam 42

To β-lactam 38 (2.7 g, 7.1 mM) in CH_2Cl_2 (50 ml) was added hydrazine (.246 ml, 7.6 mM). After stirring at room temperature for 3 days, the orange solid was filtered off and washed with CH_2Cl_2. The filtrate was extracted with ice-cold 1% HCl (2 x 100 ml). After neutralization with 1N NaOH, the aqueous phase was extracted with chloroform (2 x 200 ml). Drying ($MgSO_4$), and evaporation afforded 500 mg (28%) of amine 42 as an orange gum. P.m.r. ($DCCl_3$): δ 1.8 (s, 2H, NH_2), 3.4 (s, 3H, OCH_3), 3.8 (s, 3H, $COOCH_3$), 4.1 (bs, 1H, $\underline{CH}NH_2$), 5.2 (bs, 1H, $\underline{CH}OMe$), 7.0-7.8 (m, 4H, C_6H_4); i.r. ($CHCl_3$): γ_{max} 3400 (NH), 1770 (β-lactam), 1730 cm^{-1} ($COOCH_3$); m.s.: m/e 250 (M^+), 192.

Schiff base 43

A solution of amine β-lactam 42 (125 mg, .5 mM) and p-nitrobenzaldehyde (76 mg, .5 mM) in benzene (30 ml) was heated at reflux for 2 hrs using a Dean Stark trap. Evaporation of benzene afforded Schiff base 43; p.m.r. ($DCCl_3$): δ 3.3 (s, 3H, OCH_3), 3.7 (s, 3H, CO_2CH_3), 4.8 (t, 1H, CHN=C), 5.5 (d, 1H, $\underline{CH}OCH_3$), 7.0-8.1 (m, 8H, C_6H_4), 8.3 p.p.m. (bs, 1H, N=CH); i.r. (neat): γ_{max} 1775 (β-lactam), 1730 (ester), 1620 cm^{-1} (C=N).

β-Lactams 46 and 47

Anthranilic acid (2.7 g, 20 mM) and cinnamaldehyde (2.64 g, 20 mM) was heated for 4 hrs using a Dean Stark trap, and the solvent evaporated. To the resulting Schiff base 44 was added triethylamine (6 g, 60 mM) in dry CH_2Cl_2 (200 ml) and then dropwise trimethylsilyl chloride (4 g, 37 mM) in CH_2Cl_2 (10 ml) at -5°. After stirring for 10 minutes a solution of azidoacetyl chloride (2.4 g, 20 mM) in CH_2Cl_2 (50 ml) was added at -5°. After stirring 30 more minutes at room temperature, methanol (5 ml) was added. The solution was washed with H_2O (2 x 100 ml), dried, and evaporated. Chromatography on SiO_2 (200 g) act III using first CH_2Cl_2 and then ether afforded 1 g of impure acid 46. An ethereal solution of 46 was treated with CH_2N_2. Chromatography on SiO_2 act III (20 g) using $CHCl_3$ as eluent gave 250 mg of ester 47 as a red oil. P.m.r. ($CDCl_3$): δ 3.8 (s, 3H, OCH_3), 4.5 (d, 1H, CHN_3, J = 2 Hz), 4.7 (q, 1H, CHCH=CHPh, J_1 = 2 Hz, J_2 = 7 Hz), 6.0 (q, 1H, J_1 = 7 Hz, J_2 = 18 Hz, CHCH=CHPh), 6.7 (d, 1H, HC=CHPh, J = 18 Hz), 6.9-7.5 p.p.m. (m, 9H, C_6H_5 and C_6H_4); i.r. ($CHCl_3$): γ_{max} 1760 (β-lactam), 1725 cm^{-1} (ester); m.s.: m/e 320 (M^+).

Silylether amine 51

To o-aminobenzyl alcohol 50 (1.23 g, 10 mM) in dry DMF (15 ml) was added imidazole (1.75 g, 25 mM) and tert-butyldimethylsilyl chloride (1.65 g, 11 mM). The solution was stirred at room temperature and partitioned between H_2O (50 ml) and ether (100 ml). The ether layer was washed with water (4 x 50 ml), dried and evaporated. A quantitative yield of silylether amine 51 was obtained. P.m.r. ($DCCl_3$): δ 0.05 (s, 6H, $Si(CH_3)_2$), 0.9 (s, 9H, $SiBu^t$), 4.0 (bs, 2H, NH_2), 4.6 (s, 2H, $\underline{CH_2}O$), 6.9-7.0 p.p.m. (m, 4H, C_6H_4); i.r (film): γ_{max} 3460, 3370, 2910, 1630, 1420, 1050 cm^{-1}.

Schiff base 52

A solution of amine 51 (4.72 g, 20 mM) and cinnamaldehyde (2.7 g, 20 mM) in benzene (50 ml) was heated at reflux for 8 hrs using a Dean Stark trap. Evaporation of benzene afforded a quantitative yield of Schiff base 52 as a yellow oil. P.m.r. ($DCCl_3$): δ 0.05 (s, 6H, $SiMe_2$), 0.9 (s, 9H, $SiBu^t$), 4.9 (s, 2H, $-CH_2O-$), 6.8-7.4 (m, 9H, aromatic), 7.9 p.p.m. (t, 1H, $\underline{HC}$=NPh); i.r. (film): γ_{max} 2910, 1640 (C=N) cm^{-1}.

β-Lactam azide 53

To a solution of Schiff base 52 (7.0 g) and triethylamine (2.4 g, 1.2 eq) in CH_2Cl_2 (200 ml) at -20° under nitrogen was added dropwise over 1 hr azidoacetyl chloride (2.8 g, 1.15 eq) in CH_2Cl_2 (100 ml). The solution was stirred for 1 hr at room temperature, washed with H_2O (2 x 100 ml), dried ($MgSO_4$) and evaporated. Treatment of the red oil with charcoal in ether gave, after crystallization from pentane, 6.0 g (74%) of β-lactam 53 as a white solid, m.p. 91-92°; p.m.r. ($DCCl_3$): δ 0.1 (s, 6H, $SiMe_2$), 0.95 (s, 9H, $SiBu^t$), 4.8 (s, 2H, CH_2O), 4.8-5.2 (m, 2H, $CH\text{-}CHN_3$), 6.0-6.9 (m, 2H, PhCH=CH-), 7.2-7.6 p.p.m. (m, 9H, aromatic); i.r. (KBr): γ_{max} 2900, 2100 (N_3), 1745 cm^{-1} (C=O); m.s.: m/e 434 (M^+), 406 (M^+-N_2), 377 (M^+-57). Anal. Calcd for $C_{24}H_{30}N_4O_2Si$: C, 66.40; H, 6.97; N, 12.92. Found: C, 66.31; H, 6.85; N, 12.91.

β-Lactam amide 54

Hydrogen sulphide was bubbled into a solution of azide 53 (450 mg, 1.1 mM) and triethylamine (150 mg, 1.5 mM) in CH_2Cl_2 (20 ml) at 0°. After 1 hr, the solution was purged with N_2, washed with H_2O (2 x 20 ml), dried and evaporated. To the crude product in CH_2Cl_2 (20 ml) and triethylamine (150 mg, 1.5 mM) was added dropwise phenylacetyl chloride (.237 g, 1.5 mM) in CH_2Cl_2 (1 ml). After stirring for 30 more minutes, the solution was washed with pH 4.5 buffer (20 ml), water (20 ml), dried ($MgSO_4$) and evaporated. The crude product was chromatographed on SiO_2 (20 g) act III using first CH_2Cl_2 as eluent. Elution with $CHCl_3$/ether 1:1 afforded after crystallization from pentane-chloroform 300 mg (60%) of amide 54 as a white solid, m.p. 108.5-109°; p.m.r. ($DCCl_3$): δ 0.1 (s, 6H, $SiMe_2$), 0.95 (s, 9H, Si-Bu^t), 3.4 (s, 2H, CH_2Ph), 4.8 (s, 2H, $\underline{CH_2}$—OTBDMS), 4.9 (q, 1H, $\underline{CH}CH{=}CHPh$, J_1 = 7 Hz, J_2 = 5 Hz), 5.6 (q, 1H, $\underline{CH}NH$, J_1 = 5 Hz, J_2 = 7 Hz), 6.2 (q, 1H, $\underline{CH}{=}CHPh$, J_1 = 7 Hz, J_2 = 16 Hz), 6.5 (d, $CH{=}\underline{CH}Ph$, 1H, J = 16 Hz), 7.0-7.5 p.p.m. (m, 10H, C_6H_5, C_6H_4 and NH); i.r. ($HCCl_3$): γ_{max} 3450 (NH), 2900 (N_3), 1750 (β-lactam), 1680 (amide), 1080 cm^{-1}; m.s.: m/e 524 (M^+), 467 (M^+-57).

Alcohol 55

Ozone was passed for 1½ hrs through a solution of azide 53 (4 g) in CH_2Cl_2 (80 ml) and ethanol (160 ml) at -78°. After purging with N_2, $NaBH_4$ (.8 g) was added and the solution allowed to warm up to room temperature (2 hrs). The reaction was quenched with pH 4.5 buffer (150 ml), evaporated and partitioned between $CHCl_3$ (200 ml) and H_2O (100 ml). Evaporation and drying ($MgSO_4$) afforded, after crystallization from hexane-CCl_4, 2.5 g of alcohol 55 (76%), m.p. 95-96°; p.m.r. ($DCCl_3$): δ 0.15 (s, 6H, $SiMe_2$), 0.9 (s, 9H, $SiBu^t$), 2.6 (bs, 1H, OH), 3.8 (bs, 2H, $\underline{CH_2}OH$), 4.3 (q, 1H, $\underline{CH}CH_2$), 4.7 (s, 2H, $\underline{CH_2}$OTBDMS), 4.8 (d, 1H, CHN_3, J = 5 Hz), 7.0-7.4 p.p.m. (m, 4H, C_6H_4); i.r. ($HCCl_3$): γ_{max} 3350 (OH), 2900, 2100 (N_3), 1755 (C=O), 1050 cm^{-1}.

Methyl ether 56

To a solution of alcohol 55 (450 mg) in dry CH_2Cl_2 (50 ml) at 0° was added 5 drops of a solution containing 0.5 ml $BF_3.Et_2O$ in ether (25 ml). To this pink solution was added excess (∿ 10 eq) of CH_2N_2 in ether over 30 min. After stirring for an additional hour, the suspension was filtered, washed with H_2O (25 ml), dried ($MgSO_4$) and evaporated. Chromatography of the residue on SiO_2 act III (20 g) using chloroform as eluent afforded 340 mg (74%) of methyl ether 56 as a clear colourless syrup. P.m.r. ($DCCl_3$): δ 0.1 (s, 6H, $SiMe_2$), .95 (s, 9H, Si-Bu^t), 3.2 (s, 3H, OCH_3), 3.3-3.7 (m, 2H, $\underline{CH_2}OCH_3$), 4.3 (q, 1H, $\underline{CH}CH_2OCH_3$), 4.5 (q, 2H, $\underline{CH_2}$OTBDMS), 4.6 (d, 1H, CHN_3, J = 5 Hz), 6.9-7.4 p.p.m. (m, 4H, C_6H_4; i.r. (neat): γ_{max} 2900, 2100 (N_3), 1760 (C=O) cm^{-1}.

Methoxy amide 57

Into a solution of methoxy azide 56 (340 mg, .9 mM) in CH_2Cl_2 (20 ml) and Et_3N (.25 ml, 2.5 mM) at 0°C was bubbled hydrogen sulfide for 5 min. The ice bath was removed and the solution let stand 1 hr, washed with H_2O (2 x 25 ml), dried (Na_2SO_4) and evaporated. To the crude product in CH_2Cl_2 (10 ml) was added pyridine (.5 ml, 6 mM) and then phenylacetyl chloride (.2 ml, 1.5 mM). After stirring at room temperature for 20 min, the solution was washed with pH 4.5 buffer (25 ml), dried ($MgSO_4$) and evaporated. The crude product after chromatography on SiO_2 act III using chloroform as eluent afforded 280 mg (65%) of amide 57 as a yellow syrup. P.m.r. ($DCCl_3$): δ 0.15 (6H, d, $SiMe_2$), 0.9 (s, 9H, $SiBu^t$), 2.9 (s, 3H, OMe), 3.2-3.6 (m, 2H, CH_2OCH_3), 4.2-4.4 (m, 1H, $\underline{CH}CH_2OMe$), 4.8 (q, 2H, $\underline{CH_2}OTBDMS$), 5.7 (q, 1H, $\underline{CH}NH$, J_1 = 5 Hz, J_2 = 7 Hz), 7.0-7.5 p.p.m. (m, 10H, C_6H_5, C_6H_4 + $CH\underline{NH}$); i.r. ($HCCl_3$): γ_{max} 3350, 2900, 1750 (β-lactam), 1665 (amide), 1100 cm^{-1}.

Benzyl alcohol 58

To a solution of amide 57 (280 mg) in THF (10 ml)/H_2O (2 ml) was added dropwise trifluoroacetic acid (2 ml). After stirring 10 minutes at room temperature the solution was poured onto 5% $NaHCO_3$ (50 ml) and extracted with ethyl acetate (2 x 50 ml). Drying ($MgSO_4$), evaporation and chromatography on thick layer plates (SiO_2, 20 x 20 cm) using ether/ethyl acetate (2:1) as eluent afforded 110 mg (52%) of alcohol 58 as a colourless syrup. P.m.r. ($DCCl_3$): δ 2.95 (s, 3H, OCH_3), 3.2-3.6 (m, 2H, $\underline{CH_2}OCH_3$), 3.7 (s, 2H, CH_2Ph), 3.8-4.2 (m, 1H, $CH_2\underline{OH}$), 4.3-4.5 (m, 1H, $\underline{CH}CH_2OCH_3$), 4.6 (s, 2H, $\underline{CH_2}OH$), 5.7 (q, 1H, $CH\underline{NH}$, J_1 = 5 Hz, J_2 = 7 Hz), 6.7-7.6 p.p.m. (m, 10H, NH, aromatic); i.r. ($CHCl_3$): γ_{max} 3350 (NH), 1745 (C=O), 1670 cm^{-1} (amide C=O).

Aldehyde 59

To a slurry of pyridinium chlorochromate (100 mg, .46 mM) and NaOAc (24 mg, .3 mM) in CH_2Cl_2 (2 ml) was added a solution of alcohol 58 (100 mg, .3 mM) in CH_2Cl_2 (1 ml). After stirring for 1 hr, the reaction mixture was poured into ether (50 ml). The solution was filtered (celite), washed with H_2O (2 x 50 ml) and dried (Na_2SO_4). Evaporation of ether gave 70 mg (70%) of aldehyde 59, m.p. 137-138°; p.m.r. ($CDCl_3$): 2.9 (s, 3H, OCH_3), 3.4 (m, 2H, $\underline{CH_2}OMe$), 3.7 (s, 2H, $\underline{CH_2}Ph$), 4.4-4.7 (m, 1H, $\underline{CH}CH_2OMe$), 5.8 (q, 1H, $\underline{CH}NH$, J_1 = 5 Hz, J_2 = 7 Hz), 6.7 (bd, 1H, NH, J = 7 Hz), 7.0-8.0 (m, 9H, aromatic), 10 p.p.m. (s, 1H, CHO); i.r. (KBr): γ_{max} 3300, 2880, 1755 (β-lactam), 1680 cm^{-1} (amide and aldehyde); m.s.: m/e 352 (M^+), 351 (M^+-1), 205, 146.

Carboxylic acid 60 and methyl ester 61

To a solution of alcohol 58 (85 mg) in acetic acid (4 ml) was added 1 ml of a solution of CrO_3 (800 mg) in AcOH (9 ml) and H_2O (1 ml). The solution was stirred overnight at room temperature, poured into H_2O (50 ml) and extracted with $HCCl_3$ (3 x 50 ml). The organic phase was washed with water (2 x 20 ml), and then extracted with $NaHCO_3$ (2 x 50 ml). Neutralization of the $NaHCO_3$ extracts with dilute HCl to pH 1 and extraction with chloroform (2 x 100 ml) afforded after drying ($MgSO_4$) and evaporation 25 mg of acid 60; p.m.r. ($DCCl_3$): δ 2.85 (s, 3H, OCH_3), 3.4 (bd, 2H, CH_2OCH_3), 3.7 (s, 2H, CH_2Ph), 4.6 (bd, 1H, $\underline{CH}CH_2OCH_3$), 5.8 (q, 1H, $\underline{CH}NH$, J_1 = 5 Hz, J_2 = 7 Hz), 6.8 (d, 1H, NH, J = 7 Hz), 6.8-7.8 (m, 9H, aromatic), 9.5 p.p.m. (bs, 1H, COOH); i.r. ($HCCl_3$): γ_{max} 2500-3500 (NH, OH), 1755 (β-lactam), 1710 (COOH), 1670 cm^{-1} (amide C=O). Treatment with diazomethane in ether gave methyl ester 61; m.s.: m/e 382 (M^+), 351 (M^+-31), 205 (base peak), 177.

Experimental

Chapter 2

β-Lactams 68 and 70

3-Methoxy anthranilic acid 63 (.8 g, 5 mM) and cinnamaldehyde (.66 g, 5 mM) in 50 ml benzene were heated at reflux for 24 hrs using a Dean Stark trap. After evaporation of the benzene, Me_3SiCl (.65 ml, 5.1 mM) in 10 ml CH_2Cl_2 was added dropwise to a solution of 66 in 50 ml CH_2Cl_2 containing Et_3N (1.4 g, 15 mM). The mixture was then cooled to -20° and azidoacetyl chloride (.6 g, 5 mM) in CH_2Cl_2 (10 ml) was added dropwise over 15 min. The reaction mixture was stirred for an additional 30 minutes and after the usual work-up, the crude product was chromatographed on SiO_2 act III (40 g). Elution with CH_2Cl_2, and then with $CHCl_3$-ether (1:1) afforded crude acid 67 and 69 as a mixture. An ethereal solution of the acid was methylated with CH_2N_2, washed with 5% HCl (4 x 50 ml) to remove anthranilic acid, and purified by thick layer plates (20 x 20 x 1 mm, SiO_2) using $CHCl_3$/ether (5:1). Yield 300 mg of 68 and 70; p.m.r. ($CHCl_3$): δ 3.8 (d, 6H, OCH_3), 4.2-5.0 (m, 2H, CH and CHN_3), 6.0-6.6 (m, 2H, PhCH=CH), 6.8-7.5 p.p.m. (m, 8H, C_6H_3 and C_6H_5); i.r. ($CHCl_3$): γ_{max} 1750, 1730 cm^{-1}; addition of $Eu(fod)_3$ separated the doublet at 3.8 into 4 singlets and multiplets at 4.2-5.0 to a doublet (1H) for CHN_3 of cis ($J_{3,4}$ = 5 Hz) and doublet (1H) for CHN_3 of trans ($J_{3,4}$ = 2 Hz).

3-Methoxy-2-nitrobenzyl alcohol 71

Borane (1 Molar) in tetrahydrofuran (28 ml) was added dropwise to a solution of 3-methoxy-2-nitrobenzoic acid (4 g, 22 mM) in tetrahydrofuran (75 ml). The solution was stirred overnight and methanol was added to destroy the borane. After several co-evaporations with methanol, the residue was dissolved in ethyl acetate (100 ml), washed with 10% $NaHCO_3$ (2 x 100 ml) and dried ($MgSO_4$). Evaporation afforded 2.4 g (65%) of 3-methoxy-2-nitrobenzyl alcohol; p.m.r. (acetone d_6: δ 3.8 (s, 3H, OCH_3), 4.5 (bs, 1H, $CH_2O\underline{H}$), 4.7 (s, 2H, $\underline{CH_2}OH$), 7.0-7.4 p.p.m. (m, 3H, C_6H_3).

Methoxymethyl ether 72

Alcohol 71 (2.4 g), phosphorus pentoxide (7 g) and methylal (10 ml) in methylene chloride (30 ml) were shaken 1 hr at room temperature. The solution was decanted from the solid residue. The solid residue was washed with methylene chloride (100 ml). The combined methylene chloride fractions were washed with 5% $NaHCO_3$ (100 ml), dried ($MgSO_4$) and evaporated. Chromatography of the residue on Al_2O_3 act III using methylene chloride as eluent afforded 2.25 g (76%) of methoxymethyl ether 72; p.m.r. ($CDCl_3$): δ 3.2 (s, 3H, $CH_2O\underline{CH_3}$), 3.7 (s, 3H, OCH_3), 4.5 (d, 4H, $\underline{CH_2}O\underline{CH_2}OCH_3$), 6.8-7.4 p.p.m. (m, 3H, C_6H_3); i.r. (film): γ_{max} 2940, 1610, 1530, 1140 cm^{-1}.

Amine 73

Alcohol 72 (2 g) in ethanol (50 ml) containing 50 mg of PtO_2 was hydrogenated at 40 psi in a Parr hydrogenator for 1 hr. Filtration and evaporation afforded a quantitative yield of amine 73; p.m.r. ($CDCl_3$): δ 3.4 (s, 3H, $CH_2O\underline{CH_3}$), 3.7 (s, 3H, OCH_3), 4.4 (bs, 2H, NH_2), 4.6 (d, 4H, $\underline{CH_2}O\underline{CH_2}OCH_3$), 6.6 (t, 3H, C_6H_5); i.r. (film): γ_{max} 3440, 3360 (NH_2), 1620, 1490, 1040 cm^{-1}.

β-Lactam 75

Amine 73 (3.8 g, 20 mM), cinnamaldehyde (2.64 g, 20 mM) and a crystal of p-toluene sulphonic acid in benzene (100 ml) were heated at reflux using a Dean Stark trap for 5 hrs. Evaporation of the benzene afforded Schiff base 74. To the Schiff base in methylene chloride (200 ml) and triethylamine (3 ml, 20 mM) at -20° was added dropwise over 1 hr a solution of azidoacetyl chloride (2.4 g) in methylene chloride (100 ml). After stirring for an additional 45 min the solution was washed with H_2O (2 x 100 ml), dried ($MgSO_4$) and evaporated. Chromatography of the residue on Al_2O_3 act III eluting with methylene chloride afforded 5.6 g (70%) of β-lactam 75; p.m.r. ($CDCl_3$): δ 3.2 (s, 3H, $CH_2O\underline{CH_3}$), 3.7 (s, 3H, OCH_3), 4.5 (d, 4H, $\underline{CH_2}O\underline{CH_2}OCH_3$), 4.7-5.0 (m, 2H, $\underline{CH}CH{=}CHPh$, CHN_3), 6.0-7.5 p.p.m. (m, 10H, C_6H_3, C_6H_5, $\underline{CH}{=}\underline{CH}$-Ph); i.r. (film): γ_{max} 2915, 2100 (N_3), 1760 (C=O), 1100 cm^{-1}.

β-Lactam alcohol 76

Azide 75 (1.2 g) was dissolved in methylene chloride (30 ml) and isopropanol (150 ml). The solution was cooled to -65° and ozone was bubbled through for 1 hr and 15 min. After purging excess ozone with nitrogen, sodium borohydride (150 mg) was added and the solution was allowed to warm up to room temperature. After the addition of pH 4.5 buffer (40 ml) the solution was evaporated. The residue was partitioned between $CHCl_3$ (100 ml) and water (50 ml). The organic phase was dried ($MgSO_4$) and evaporated. Chromatography of the residue on thick layer plates using $CHCl_3$/ether 3:1 afforded 550 mg (56%) of alcohol 76; p.m.r. ($CDCl_3$): δ 3.4 (s, 3H, $CH_2O\underline{CH_3}$), 3.8 (bs, 1H, $CH_2\underline{OH}$), 4.0 (d, 2H, $\underline{CH_2}OH$), 4.0 (s, 3H, OCH_3), 4.5-4.7 (m, 1H, $\underline{CH}CH_2OH$), 4.8 (q, 2H, $Ar\underline{CH_2}O$), 4.8 (s, 2H, OCH_2O), 5.0 (d, 1H, CHN_3, J=5 Hz), 7.0-7.5 p.p.m. (m, 3H, C_6H_3); i.r. ($CHCl_3$) 3300, 2100 (N_3), 1760 cm^{-1} (C=O).

Mesylate 77

Mesyl chloride (114 mg, 1 mM) in methylene chloride (5 ml) was added dropwise to a solution of alcohol 76 (330 mg, 1 mM) and triethylamine (100 mg, 1 mM) in methylene chloride (20 ml) at -78°. The solution was allowed to warm up to room temperature (1 hr) and washed with H_2O (2 x 20 ml). Drying ($MgSO_4$) and evaporation afforded mesylate 77 in quantitative yield. P.m.r. ($CDCl_3$): δ 2.8 (s, 3H, SO_2CH_3), 3.4 (s, 3H, $CH_2O\underline{CH_3}$), 3.8 (s, 3H, OCH_3), 4.2-4.4 (m, 1H, $\underline{CH}CH_2O$), 4.6 (q, 2H, $Ar\underline{CH_2}O$), 4.7 (s, 2H, $CH_2O\underline{CH_2}OCH_3$), 5.0 (d, 1H, CHN_3 J=5 Hz), 6.6-7.4 p.p.m. (m, 3H, C_6H_3).

3-Hydroxy-2-nitrobenzaldehyde 80

To a suspension of 3-methoxy-2-nitrobenzaldehyde (12 g, 66 mM) in CH_2Cl_2 (300 ml) at -78° was added dropwise over 1/2 hour a solution of BBr_3 (20 ml, 210 mM) in CH_2Cl_2 (200 ml). After the addition was complete, the dry ice acetone bath was removed and the red solution allowed to warm up to 20° (3 hrs). The red solution was poured into crushed ice (500 g) and extracted with ethyl acetate (1 ℓ). Drying ($MgSO_4$) and evaporation in vacuo afforded 11 g (94%) of crude 3-hydroxy-2-nitrobenzaldehyde 80, m.p. 140° (decomp); p.m.r. (DMSO d_6): δ 7.4-7.8 (m, 3H, C_6H_3), 10.4 (s, 1H, CHO), 11.4 p.p.m. (s, $C_6H_3\underline{OH}$); i.r. (CH_2Cl_2): γ_{max} 3300 (OH), 3000, 1710 (C=O), 1610 cm^{-1}.

Aldehyde 82

Diisopropylethylamine (2.1 g, 18 mM) and MEMCl (2.1 g, 18 mM) was added to a suspension of phenol 80 (2.1 g, 13 mM) in CH_2Cl_2 (50 ml). After stirring at room temperature for 3 hrs, the solution was washed with water (50 ml), dried ($MgSO_4$) and evaporated. Chromatography of the residue with $CHCl_3$ on Al_2O_3 act III afforded 1.6 g (53%) of aldehyde 82; p.m.r. ($CDCl_3$): δ 3.4 (s, 3H, OCH_3), 3.4-4.0 (m, 4H, $-OCH_2CH_2O-$), 5.5 (s, 2H, OCH_2O), 7.7 (m, 3H, C_6H_3), 10.3 p.p.m. (s, 1H, CHO); i.r. (KBr): γ_{max} 2900, 1710 cm^{-1} (CHO)

Alcohol 83

$NaBH_4$ (280 mg, 7.6 mM) was added to (1.6 g, 6.8 mM) of aldehyde 82 in EtOH (75 ml). After stirring 30 minutes at room temperature, 40 ml pH 4.5 buffer was added and the ethanol was removed on a rotary evaporator. The residue was extracted with ethyl acetate (2 x 50 ml). Drying ($MgSO_4$) and evaporation under vacuo afforded 1.4 g (88%) of alcohol 83; p.m.r. ($DCCl_3$): δ 3.4 (s, 3H, OCH_3) 3.4-4.0 (m, 5H, OCH_2CH_2O, OH), 4.6 (bs, 2H, $\underline{CH_2}OH$), 5.3 (2H, $-O\underline{CH_2}O$) 7.0-7.5 p.p.m. (m, 3H, C_6H_3); i.r. (film): γ_{max} 3100-3600 (OH), 2900, 1560 cm^{-1}.

MEM Ether 84

To 1.4 g (6.0 mM) of alcohol 83 in CH_2Cl_2 (40 ml) was added MEMCl (1 g, 8.3 mM) and diisopropylethylamine (1 g, 8.3 (mM). The reaction mixture was stirred 3 hrs, washed with H_2O (2 x 50 ml), dried ($NaSO_4$) and evaporated. Chromatography of the residue on Al_2O_3 act III using ether/CH_2Cl_2 1:10 afforded 1.15 g (60%) of the MEM ether 84; p.m.r. ($DCCl_3$), δ 3.4 (d, 6H, OCH_3), 3.4-4.0 (m, 8H, OCH_2CH_2O), 4.7 (s, 2H, $ArCH_2O$), 4.9 (s, 2H, OCH_2O), 5.4 (s, 2H, $ArOCH_2O$), 7.2-7.6 p.p.m. (m, 3H, C_6H_3).

Amine 85

Nitro MEM ether 84 (1 g) was hydrogenated 1½ hrs at 35 psi with 200 mg PtO_2 in a Parr hydrogenator. The reaction mixture was filtered through celite. Evaporation of the filtrate afforded 900 mg (100%) of amine 85; p.m.r. ($DCCl_3$): δ 3.4 (s, 6H, OCH_3), 3.4-4.0 (m, 8H, OCH_2CH_2O), 4.0-4.5 (bm, 2H, NH_2), 4.6 (s, 2H, $ArCH_2O$), 4.8 (s, 2H, OCH_2O), 5.3 (s, 2H, $ArOCH_2O$), 6.4-7.2 p.p.m. (3H, C_6H_3); i.r. (film): γ_{max} 3440, 3340 (NH_2), 2900, 1050 cm^{-1}.

β-Lactam 86

Amine 85 (2.95 g, 10 mM) was heated for 8 hrs with 1.32 g (10 mM) of cinnamaldehyde and a few crystals of p-toluenesulfonic acid in 50 ml of benzene using a Dean Stark trap. Evaporation of the benzene afforded crude Schiff base. To the crude Schiff base in 50 ml of dry CH_2Cl_2 and 1.0 g (10 mM) of Et_3N at -20° was added dropwise over 45 min 1.2 g (10 mM) of azidoacetyl chloride in 25 ml of CH_2Cl_2. After stirring for an additional hour at -20°, the reaction mixture was washed with H_2O (2 x 50 ml), dried ($MgSO_4$) and evaporated. Chromatography of the residue on Al_2O_3 act I using 10% Et_2O in CH_2Cl_2 afforded 3.0 g (60%) of β-lactam 86; p.m.r. ($CDCl_3$): δ 3.4 (d, 6H, OCH_3), 3.4-4.0 (m, 8H, OCH_2CH_2O), 4.7 (s, 2H, $ArCH_2O$), 4.8 (s, 2H, OCH_2O), 5.0 (m, 2H, CHN_3, $CHCH{=}CHPh$), 5.4 (s, 2H, $ArOCH_2O$), 6.4-7.7 (m, 2H, $CH{=}CHPh$), 7.0-7.6 p.p.m. (m, 8H, C_6H_3, C_6H_5); i.r. (film): γ_{max} 2900, 2100 (N_3) 1770 cm^{-1} (C=O).

Alcohol 87

O_3 (8 mM/hr) was bubbled into a solution of β-lactam 86 (500 mg, 1 mM) in CH_2Cl_2 (10 ml) and isopropanol (100 ml) cooled to -65° for 17 min. After purging excess ozone with nitrogen, $NaBH_4$ (40 mg) was added, and the solution allowed to warm up to room temperature (2 hrs). Buffer (pH 4.5) was added and the solution was almost evaporated to dryness. The residue was partitioned between water (20 ml) and $CHCl_3$ (50 ml). The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated. Chromatography of the residue on thick layer plates using U.S.P. ether afforded 200 mg (50%) of alcohol 87; p.m.r. ($CDCl_3$): δ 3.4 (d, 6H, OCH_3), 3.4-4.0 (m, 11H, OCH_2CH_2O, CH_2OH), 4.4-4.6 (m, 1H, $CHCH_2OH$), 4.6-5.1 (5H, CH_2OCH_2O, CHN_3), 5.4 (s, 2H, $ArOCH_2$) 7.0-7.5 p.p.m. (m, 3H, C_6H_3); i.r. (CH_2Cl_2): γ_{max} 3400 (OH), 2100 (N_3), 1760 cm^{-1} (C=O).

Mesylate 88

To alcohol 87 (100 mg, .23 mM) at -78° and 70 µl (.5 mM) of Et_3N in 10 ml of CH_2Cl_2 was added dropwise 35 µl (.4 mM) of MsCl in CH_2Cl_2 (2 ml). After 15 min, the cold bath was removed, the reaction mixture was allowed to warm up to room temperature (1 1/2 hrs) and washed with H_2O (2 x 10 ml). The CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated. Yield 110 mg (95%) of mesylate 88; p.m.r. ($CDCl_3$): δ 2.8 (s, 3H, SO_2CH_3), 3.4 (s, 6H, OCH_3), 3.4-4.0 (m, 8H, OCH_2CH_2O), 4.4-4.8 (m, 5H, $CHCH_2OMs$ $ArCH_2O$), 4.8 (s, 2H, OCH_2O), 5.2 (d, 1H, J = 5 Hz, CHN_3), 5.4 (s, 2H, $ArOCH_2O$), 7.0-7.4 p.p.m. (s, 3H, C_6H_3).

3-Benzyloxy-2-nitrobenzaldehyde 90

To 3-hydroxy-2-nitrobenzaldehyde (5 g, 29 mM) in DMSO (17 ml) was added benzyl bromide (5 g, 29 mM) and K_2CO_3 (5 g, 36 mM). The suspension was stirred overnight at room temperature. The reaction mixture was poured into water (500 ml) and extracted with ether (2 x 300 ml). The ether layer was washed with water (4 x 100 ml). Drying ($MgSO_4$) and evaporation afforded, 7 g of crude benzyl ether. Crystallization from chloroform-ether afforded 3.6 g (50%) of 90, m.p. 77-79°; p.m.r. ($CDCl_3$): δ 5.2 (s, 2H, CH_2O), 7.0-7.5 (m, 8H, C_6H_5 and C_6H_3), 9.8 p.p.m. (s, 1H, CHO); i.r. (KBr): γ_{max} 3000, 2900, 1705 cm^{-1} (CHO).

3-Benzyloxy-2-nitrobenzyl alcohol 91

To aldehyde 90 (8 g, 48 mM) suspended in EtOH (300 ml) and MeOH (50 ml) at 0° was added $NaBH_4$ (.4 g, 41 mM) in portions. After stirring for 1 hr, excess $NaBH_4$ was destroyed with acetic acid (2 ml). The residue, after evaporation of the solvent, was partitioned between 1% HCl (200 ml) and ethyl acetate (300 ml). Drying ($MgSO_4$) and evaporation afforded in quantitative yield alcohol 91; p.m.r. (acetone d_6): δ 2.8 (bs, 1H, $CH_2\underline{OH}$), 4.4 (s, 2H, $\underline{CH_2}OH$), 5.1 (s, 2H, $Ph\underline{CH_2}O$), 6.4-7.2 (m, 3H, C_6H_3), 7.3 p.p. (s, 5H, C_6H_5); i.r. (film): γ_{max} 3550, 3350 (OH), 2900 cm^{-1}.

Amine 93 and amine 94

A solution of alcohol 91 (5.2 g) and PtO_2 (400 mg) in ethanol (100 ml) was hydrogenated at 40 psi, using a Parr hydrogenator, for 2 hrs. The residue, after filtration of catalyst through celite and evaporation, was dissolved in ethyl acetate (200 ml) and washed with 5% NaOH (2 x 100 ml). Drying ($MgSO_4$) and evaporation of the ethyl acetate afforded 3.7 g (16 mM) of almost colourless amine 93 as a semi solid. The amine in DMF (75 ml) was immediately treated with tert-butyldimethylsilyl chloride (3.0 g, 20 mM), and imidazole (3.3 g, 48 mM). After stirring overnight at room temperature, the solution was partitioned between ether (200 ml) and water (500 ml). The ether layer was washed with water (4 x 100 ml), and dried ($MgSO_4$). Evaporation afforded a quantitative yield of silyl amine 94; p.m.r. ($CDCl_3$): δ 0.05 (s, 6H, $SiMe_2$), 0.90 (s, 9H, $Si\text{-}Bu^t$), 4.4 (bs, 2H, NH_2), 4.7 (s, 2H, $\underline{CH_2}$OTBDMS), 5.0 (s, 2H, $Ph\underline{CH_2}O$), 6.6-6.8 (m, 3H, C_6H_3), 7.4 p.p.m. (s, 5H, C_6H_5); i.r. (film): γ_{max} 3370, 3460 (NH_2), 2960, 2940 cm^{-1}.

Azide β-lactam 96

A solution of cinnamaldehyde (3.3 g, 25 mM), amine 94 (8.3 g, 24 mM) and a few crystals of TsOH in benzene (200 ml) was heated at reflux overnight using a Dean Stark trap. Evaporation of the solvent afforded Schiff base 95 as a light yellow oily solid. To the Schiff base dissolved in CH_2Cl_2 (200 ml) and triethylamine (3.3 g, 33 mM) at -20° under N_2 was added dropwise over 1 hr azidoacetyl chloride (3.6 g, 30 mM) in CH_2Cl_2 (100 ml). The red brown solution was stirred at -20° for one more hour. Washing with water (2 x 100 ml), drying ($MgSO_4$) and evaporation afforded after treatment with charcoal and filtration through Al_2O_3 (300 g) using CH_2Cl_2 as eluent, 11 g (84%) of fairly pure azido β-lactam 96, as an orange oil; i.r. (film): γ_{max} 2900, 2100 (N_3), 1770 cm^{-1} (C=O).

Alcohol 97

Ozone (8 mM/hr) was bubbled through a solution of crude β-lactam 96 (1.7 g) in EtOH (100 ml) and methylene chloride (20 ml) at -78° for 35 minutes. Excess ozone was removed with N_2 and $NaBH_4$ (850 mg) was added. After warming to room temperature (2 hrs), 100 ml of pH 4.5 buffer was added. Removal of solvent on a rotary evaporator and extraction with CH_2Cl_2 (2 x 300 ml) afforded, after drying ($MgSO_4$) and evaporation, crude alcohol (1.6 g). Careful column chromatography on SiO_2 act III (30 g) using chloroform as eluent afforded 850 mg (58%) of pure alcohol 97; p.m.r. ($DCCl_3$ + D_2O): δ 0.1 (s, 6H, s, $SiMe_2$), 0.95 (s, 9H, Si-Bu^t), 3.7 (d, 2H, $\underline{CH_2}OH$), 4.2-4.5 (m, 1H, $\underline{CH}CH_2OH$), 4.6 (d, 1H, CHN_3, J = 5 Hz), 4.71 (q, 2H, $\underline{CH_2}$OTBDMS), 5.0 (s, 2H, Ph$\underline{CH_2}$), 6.8-7.3 (m, 3H, C_6H_3), 7.4 p.p.m. (s, 5H, C_6H_5); i.r. (film): γ_{max} 3400 (OH), 2900, 2100 (N_3), 1760 (C=O), 1240, 1100 cm^{-1}; m.s.: m/e: 411 (M^+-57). Anal. Calcd for $C_{24}H_{32}N_4O_4Si$: C, 61.54; H, 6.84; N, 11.95. Found: C, 61.41; H, 7.12; N, 12.17.

Mesylate 98

To alcohol 97 (130 mg) in CH_2Cl_2 (10 ml) and triethylamine (80 µl) at -78° was added methane sulphonyl chloride (35 µl). After warming to 20°, usual work-up afforded a quantitative yield of mesylate 98; p.m.r. ($DCCl_3$): δ 0.15 (s, 6H, $SiMe_2$), 1.0 (s, 9H, SiBu^t), 2.6 (s, 3H, SO_2CH_3), 4.5 (d, 2H, $\underline{CH_2}OSO_2CH_3$), 4.8 (q, 1H, $\underline{CH}CH_2$), 4.8 (s, 2H, $\underline{CH_2}$OTBDMS), 4.9 (d, 1H, CHN_3, J = 5 Hz), 5.1 (s, 2H, $O\underline{CH_2}Ph$), 6.9-7.3 (m, 3H, C_6H_3), 7.4 p.p.m. (s, 5H, C_6H_5); i.r. ($CHCl_3$): γ_{max} 2900, 2100 (N_3), 1770 cm^{-1} (C=O).

Benzyl alcohol 99

To mesylate 98 (850 mg) in THF (25 ml) and H_2O (10 ml) was added dropwise trifluoroacetic acid (3 ml). The homogeneous solution was stirred at room temperature 20 min and poured into 5% $NaHCO_3$ (200 ml). Extraction with ethyl acetate (2 x 200 ml), drying ($MgSO_4$) and evaporation afforded crude mesylate benzyl alcohol 99. The crude benzyl alcohol was chromatographed on SiO_2, act III using first $CHCl_3$-ether (1:1) as eluent. Elution with ether afforded 470 mg (72%) of alcohol 99 as a colourless syrup; p.m.r. ($DCCl_3$): δ 2.7 (s, 3H, CH_3), 3.2 (bs, 1H, $CH_2\underline{OH}$), 4.4 (d, 2H, $\underline{CH_2}OMs$), 4.6 (s, 2H, $\underline{CH_2}OH$), 4.7 (q, 1H, $\underline{CH}-CH_2$), 4.9 (d, 1H, CHN_3, J = 5 Hz), 5.1 (s, 2H, $\underline{CH_2}Ph$), 6.8-7.4 (m, 3H, C_6H_3), 7.4 p.p.m. (s, 5H, C_6H_5); i.r. (film): γ_{max} 3450 (OH), 2900, 2100 (N_3), 1770 (C=O), 1350, 1180, 1100 cm^{-1}.

Carboxylic acid 100

Alcohol 99 (440 mg, 1 mM) was dissolved in acetic acid and 4.4 ml (2.6 mM) of a CrO_3 solution (600 mg CrO_3 in 9 ml AcOH ml H_2O) was added. After stirring overnight at room temperature, most of the acetic acid was evaporated. The residue was poured into pH 1.8 buffer (30 ml) and extracted with $CHCl_3$ (3 x 100 ml). Drying ($MgSO_4$), evaporation of $CHCl_3$ and trituration with ether, afforded 190 mg (42%) of acid 100 as a nearly white solid, m.p. 153-155°; p.m.r. ($DCCl_3$) δ: 2.7 (s, 3H, SO_2CH_3), 4.3-4.7 (m, 3H, $CHCH_2$), 4.9 (bd, 1H, CHN_3), 5.1 (s, 2H, $Ph\underline{CH_2}O$), 7-7.4 (m, 8H, C_6H_3 and C_6H_5), 10.8 p.p.m. (s, 1H, CO_2H); i.r. ($CHCl_3$): γ_{max} 2700-3200 (CO_2H), 2080 (N_3), 1775 (β-lactam), 1720 cm^{-1} (acid); i.r. (KBr): γ_{max} 1740 cm^{-1} (b, C=O).

Ester 101

Acid 100 (400 mg, .9 mM) was suspended in CH_3CN (20 ml) and treated with a 1 M solution of Ph_2CHN_2 in CH_3CN (1 ml). After stirring 1 hr at room temperature a few drops of acetic acid was added. Chromatography of the crude product on thick layer plates (20 x 20 cm) using $CHCl_3$-ether (5:1) as eluent afforded 420 mg (77%) of ester 101 as a white foam; p.m.r. ($CDCl_3$): δ 2.6 (s, 3H, SO_2CH_3), 4.2-4.6 (m, 4H, $CHCH_2$ and CHN_3), 5.1 (s, 2H, $O\underline{CH_2}Ph$), 7.2-7.6 p.p.m. (m, 19H, $CHPh_2$ + aromatic); i.r. ($CHCl_3$): γ_{max} 2100 (N_3), 1780 (β-lactam), 1730 cm^{-1} (ester).

Amide 102

H_2S was bubbled into a solution of 101 (390 mg, .6 mM) in 20 ml CH_2Cl_2 and Et_3N (.1 ml, .7 mM) at 0° for 5 min. After stirring 1 hr at 20°, the solution was purged with nitrogen (5 min). The reaction mixture was washed with H_2O (20 x 20 ml), dried and evaporated. To the crude product in CH_2Cl_2 (10 ml) and Et_3N (.1 ml, .7 mM) was added dropwise a solution of phenylacetyl chloride (108 mg, .7 mM) in CH_2Cl_2 (2 ml). After stirring for 1 hr at 0°, the solution was washed with H_2O (2 x 20 ml), dried and evaporated. Chromatography of the residue on SiO_2, act III (20 g) afforded after elution with ether, 275 mg (64%) of amide 102, m.p. 128-129° (dec.), n.m.r. ($CDCl_3$-DMSO-d_6): δ 2.90 (s, 3H, CH_3), 3.75 (s, 2H, $CO\underline{CH_2}Ph$), 4.7 (m, 3H, $CHCH_2$), 5.4 (s, 2H, $O\underline{CH_2}Ph$), 5.4 (m, 1H, $\underline{CH}NH$), 7.25 (s, 1H, $\underline{CH}Ph_2$), 7.25-8.0 p.p.m. (m, 19H, aromatic + NH); i.r. (KBr): γ_{max} 3300 (NH), 1770 (β-lactam), 1720 (ester), 1660 cm^{-1} (amide).

3-Hydroxy-2-nitrobenzyl alcohol 104

Crude phenol 80 (11 g, 65 mM) was dissolved in absolute ethanol (500 ml) and cooled to 0°. $NaBH_4$ (5g, 131 mM) was added in portions. The ice bath was removed and the red slurry stirred for 2 hrs at 20°. Acetic acid (5 ml) was added and the ethanol was removed on a rotary evaporator. The residue was dissolved in water (200 ml) and acidified with HCl to pH < 1. Extraction with ethyl acetate (2 x 300 ml), drying ($MgSO_4$) and evaporation afforded 10 g (90%) of 3-hydroxy-2-nitrobenzyl alcohol 104, m.p. 104-110° (dec.); p.m.r. (acetone-d_6): δ 4.6 (s, 2H, $\underline{CH_2}OH$), 4.5 (bs, 1H, $CH_2\underline{OH}$), 6.8-7.5 (m, 3H, C_6H_3), 10.4 p.p.m. (bs, 1H, $C_6H_3\underline{OH}$).

Amine 105

Alcohol 104 (10 g, 57 mM) was dissolved in ethanol (200 ml) and PtO_2 (.7 g) was added. The mixture was hydrogenated for 2 hrs in a Parr hydrogenator at 40 psi and filtered through celite. Evaporation of the filtrate afforded 8 g of the amine as a brown semi-crystalline solid. The amine was added to a solution of tert-butyldimethylsilyl chloride (21 g, 136 mM) and imidazole (23.5 g, 350 mM) in dry DMF (75 ml). The solution was stirred overnight at room temperature and partitioned between ether (300 ml) and water (750 ml). The ether layer was washed with water (4 x 200 ml), dried ($MgSO_4$) and evaporated. The crude product was chromatographed at SiO_2 act III (300 g). Elution with methylene chloride afforded 16 g (77%) of amine 105; p.m.r. ($CDCl_3$): δ .05 (s, 6H, $Si(CH_3)_2$), .25 (s, 6H, $Si(CH_3)_2$), .9 (s, 9H, $Si\text{-}Bu^t$), 1.0 (s, 9H, $Si\text{-}Bu^t$), 4.2 (bs, 2H, NH_2), 4.6 (s, 2H, CH_2O), 6.3-6.8 p.p.m. (m, 3H, C_6H_3); i.r. (film): γ_{max} 3500, 3400 (NH_2), 3000, 1630 cm^{-1}.

Azide β-lactam 107

Amine 105 (4.4 g, 11 mM) and cinnamaldehyde (1.6 g, 12 mM) and a few crystals of TsOH dissolved in dry benzene (150 ml) were refluxed overnight using a Dean Stark trap to remove the water formed. The crude product, after evaporation of benzene, was dissolved in CH_2Cl_2 (100 ml) and Et_3N (1.8 ml, 13 mM). To the solution under N_2 at -20° was added dropwise azidoacetyl chloride (1.5 g, 13 mM) in CH_2Cl_2 (80 ml) over 1 hr. The reaction mixture was stirred for 1 more hour and washed with H_2O (2 x 50 ml). Drying ($MgSO_4$) and evaporation afforded the crude product. Filtration through 100 g of Al_2O_3, act III, using CH_2Cl_2 as eluent afforded 5.5 g (81%) of β-lactam azide 107, suitable for the next reaction; i.r. (film): γ_{max} 2900, 2100 (N_3), 1770 cm^{-1} (C=O).

Alcohol 108

Into a solution of crude azide 107 (2.8 g) in ethanol (150 ml) and CH_2Cl_2 (30 ml) at -78° was passed ozone (8 mM/hr) for 45 minutes. After removing excess ozone with nitrogen (15 min), $NaBH_4$ (400 mg) was added. The solution was allowed to warm up to room temperature over a period of 2 hrs. To the slight yellow solution was added pH 4.5 buffer (150 ml). The ethanol was removed on a rotary evaporator and the residue extracted with $CHCl_3$ (2 x 100 ml). Drying ($MgSO_4$) and evaporation afforded 2.5 g of crude alcohol. Chromatography of the crude alcohol on SiO_2, act III (45 g), using $CHCl_3$ as eluent, afforded, after crystallization from pentane, 1.3 g (53%) of pure alcohol 108, m.p. 112-112.5°; p.m.r. ($CDCl_3$): δ 0.05 (d, 6H, $SiMe_2$), 0.25 (d, 6H, $SiMe_2$), 0.90 (s, 9H, Si-Bu^t), 1.0 (s, 9H, Si-Bu^t), 3.1 (bs, 1H, OH), 3.7 (bd, 2H, $\underline{CH_2}OH$), 4.2-4.4 (m, 1H, $\underline{CH}CH_2OH$), 4.7 (q, 2H, $\underline{CH_2}$OTBDMS), 4.7 (d, 1H, CHN_3, J = 5 Hz), 6.6-7.2 p.p.m. (m, 3H, C_6H_3); i.r. (KBr): 3450 (OH), 2900, 2150 (N_3), 1770 (C=O), 1600 cm^{-1} (C=C); m.s.: m/e 435 (M^+-57), 407 (M^+-57-28); Anal. Calcd for $C_{24}H_{40}N_4O_4Si$: C, 56.06; H, 8.18; N, 11.36. Found: C, 55.95; H, 8.03; N, 11.38.

Mesylate 109

To alcohol 108 (2 g, 4.1 mM) in CH_2Cl_2 (50 ml) and Et_3N (.8 ml, 5.6 mM) at -78° was added dropwise MsCl (.35 ml, 4.5 mM) in CH_2Cl_2 (5 ml). The solution was stirred for 30 minutes at -78° and allowed to warm up to room temperature (1 hr). The reaction mixture, after washing with water 2 x 50 ml), drying ($MgSO_4$) and evaporation under vacuo, afforded 2.2 g (95%) of mesylate 109 as an oily solid; p.m.r. ($CDCl_3$): δ 0.15 (d, 6H, $SiMe_2$), .25 (d, 6H, $SiMe_2$), .9 (s, 9H, Si-Bu^t), 1.0 (s, 9H, Si-Bu^t), 2.75 (s, 3H, CH_3), 4.4 (m, 2H, $\underline{CH_2}OSO_2CH_3$), 4.7 (m, 1H, $CH_2\underline{CH}$), 4.7 (s, 2H, $\underline{CH_2}$OTBDMS), 5.0 (d, 1H, CHN_3, J = 5 Hz), 6.7-7.4 p.p.m. (m, 3H, C_6H_3).

Azido β-lactam 112

To mesylate 109 (1 g, 1.7 mM) in CH_3CN (20 ml) was added KF (116 mg, 2 mM) and 18-crown-6 (75 mg, .3 mM). After stirring 5 hrs at room temperature, more KF (50 mg) and 18-crown-6 (75 mg) was added. After 4 more hours at room temperature, the reaction mixture was poured into water (200 ml) and extracted with CH_2Cl_2 (2 x 200 ml). Drying ($MgSO_4$) and evaporation afforded crude product contaminated with 18-crown-6. Chromatography on SiO_2, act III (20 g), using CH_2Cl_2 as eluent, afforded 580 mg (92%) of cyclized β-lactam 112 as a colourless oil; p.m.r. (benzene d_6): δ 0.2 (s, 6H, $SiMe_2$), 1.1 (s, 9H, Si-Bu^t), 2.8-4.0 (m, 3H, OCH_2CH), 4.0 (d, 1H, CHN_3, J = 5 Hz), 5.2 (q, 2H, $\underline{CH_2}$OTBDMS, J = 16 Hz); 6.6-7.6 (m, 3H, C_6H_3); i.r. ($CHCl_3$): γ_{max} 2900, 2100 (N_3), 1780 (C=O), 1600 cm^{-1} (C=C).

Amide 113

Into azide 112 (500 mg, 1.4 mM) dissolved in CH_2Cl_2 (20 ml) and Et_3N (.2 ml, 1.4 mM) at 0° was bubbled H_2S for 5 min. After stirring for 1 hr at room temperature, the solution was washed with H_2O (2 x 20 ml) dried ($MgSO_4$) and evaporated. To the crude product at 0° in CH_2Cl_2 (20 ml) and Et_3N (.2 ml, 1.3 mM) was added dropwise phenylacetyl chloride (.23 g, 1.5 mM) in CH_2Cl_2 (2 ml) over a period of 5 min. After stirring for 1 hr at room temperature, the solution was washed with pH 4.5 buffer (30 ml) and H_2O (30 ml), dried ($MgSO_4$) and evaporated. Chromatography of the residue on SiO_2 act II (20 g) using CH_2Cl_2up to CH_2Cl_2/ ether (1:1) afforded 530 mg (80%) of amide 113 as a colourless foam; p.m.r. ($DCCl_3$): δ 0.05 (s, 6H, Si-$(CH_3)_2$), .90 (s, 9H, Si-Bu^+), 4.3 (s, 2H, $\underline{CH_2}Ph$), 3.6-4.6 (3H, m, CH_2CH), 4.8 (q, 2H, CH_2O), 6.6-7.2 (m, 3H, C_6H_3), 7.3 p.p.m, (bs, 6H, C_6H_5 and $\underline{NH}$); i.r. ($CHCl_3$): γ_{max} 3400 (NH), 2900, 1765 (β-lactam C=O), 1680 cm^{-1} (amide C=O).

Alcohol amide 114a

To amide 113 (180 mg) in THF (5 ml) and H_2O (2 ml) was added dropwise trifluoroacetic acid (.8 ml). After stirring at room temperature 15 min, the solution was poured onto 10% $NaHCO_3$ and extracted with chloroform (2 x 50 ml). Drying ($MgSO_4$), evaporation and trituration with ether afforded 80 mg (60%) of alcohol amide 114a as white solid, m.p. 183-185°; p.m.r. (acetone d_6): δ 3.6 (s, 2H, $\underline{CH_2}Ph$), 4.0-4.6 (m, 3H, CH_2CH), 4.8 (bs, 3H, CH_2OH), 5.6 (q, 1H, $\underline{CH}NH$, J_1 = 4.5, J_2 = 7 Hz), 6.6-7.2 (m, 3H, C_6H_3), 7.2 p.p.m. (s, 5H, C_6H_5); i.r. (KBr): γ_{max} 3400 (OH), 3350 (NH), 1775 (β-lactam) C=O), 1660 cm^{-1} (amide C=O), m.s.: m/e 338 (M^+).

Benzyl alcohol 115

To azide 112 (580 mg) in THF (20 ml) and H_2O (6 ml) was added dropwise trifluoroacetic acid (3 ml). After stirring for 20 minutes at room temperature the reaction mixture was poured into 5% $NaHCO_3$ (200 ml) and extracted with CH_2Cl_2 (2 x 100 ml). The combined organic phases were dried ($MgSO_4$) and evaporated. Trituration of the oily residue with ether afforded 300 mg (75%) of alcohol 115, m.p. 128-129°; p.m.r. ($CDCl_3$-$DMSOd_6$, few drops D_2O): δ 3.8-4.4 (m, 3H, CH_2CH), 4.8 (q, 2H, $\underline{CH_2}OH$, J = 17 Hz), 5.6 (d, 1H, CHN_3, J = 5 Hz), 7.0 p.p.m. (m, 3H, C_6H_3); i.r. (KBr): δ_{max} 3380 (OH), 2900, 2100 (N_3), 1775 cm^{-1} (C=O); m.s.: m/e 246 (M^+), 218 (M^+-28), Anal. Calcd for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.76. Found: C, 53.57; H, 4.32; N, 22.44.

Ester 118

To alcohol 112 (420 mg, 1.7 mM) in AcOH (5 ml) was added 4.5 ml of CrO_3 solution (1 g CrO_3 in 1 ml H_2O and 9 ml AcOH). After stirring at 20° for 24 hrs, more CrO_3 solution (2.5 ml) was added. After a total time of 48 hrs the acetic acid was evaporated at 20°. The residue was partitioned between pH 1.8 buffer (20 ml) and chloroform (100 ml). The aqueous phase was extracted again with $CHCl_3$ (2 x 50 ml). The combined $CHCl_3$ extracts were washed with pH 1.8 buffer (2 x 20 ml), dried ($MgSO_4$), and evaporated. To the crude acid 117 (260 mg) dissolved in CH_3CN (20 ml) was added 9 ml (1.8 mM) of a solution of diphenyl diazomethane in CH_3CN (2 g Ph_2CN_2 in 100 ml CH_3CN). The red reaction mixture was stirred 1 hr at room temperature and quenched with acetic acid (3 drops). The crude product after evaporation of the solvent was chromatographed on thick layer plates (SiO_2) using $CHCl_3$/ether (9:1) as eluent. Extraction of band with r.f. ≃ .7 afforded 280 mg (39%) of ester 118 as a colourless foam; p.m.r. (C_6D_6 90 MHz): δ 3.0-3.4 (m, 1H, $CH_2\underline{CH}$), 3.3 (t, 1H, $CH\underline{H}CH$, $J_1 = J_2 = 10$ Hz), 3.8 (q, 1H, $C\underline{H}HCH$, $J_1 = 3$ Hz, $J_2 = 10$ Hz), 4.1 (d, 1H, CHN_3, $J = 5$ Hz), 6.4-7.6 p.p.m. (m, 14H, aromatic + $CHPh_2$); i.r. ($CHCl_3$): γ_{max} 2100 (N_3), 1795 (β-lactam), 1730 (ester); m.s.: m/e 426 (M^+), 397 (M^+-28), 343 (M^+-N_3CHCO), 215 (M^+-CO_2CHPh_2). Extraction of the band with r.f. ≃ .5 afforded 40 mg (10%) of aldehyde 116; p.m.r. ($CDCl_3$): δ 3.8-4.7 (m, 3H, CH_2CH), 5.2-5.4 (m, 1H, CHN_3), 7.0-7.6 (m, 3H, C_6H_3), 10.2 p.p.m. (s, 1H, CHO).

Amide 119

Hydrogen sulphide was bubbled into a solution of ester 118 (250 mg, .6 mM) and Et_3N (.1 ml, .7 mM) in CH_2Cl_2 at 0° for 5 min. The ice bath was removed and the orange solution stirred at room temperature. After 1 hr, excess H_2S was purged with nitrogen. The yellow solution was washed with H_2O (2 x 25 ml), dried ($MgSO_4$) and evaporated. To the resulting yellow gum dissolved in CH_2Cl_2 (20 ml) and Et_3N (.1 ml, .7 mM) was added at 0° phenylacetyl chloride (90 µl, .68 mM). After stirring for 1 hr at 0°, the solution was washed with pH 4.5 buffer (2 x 25 ml). Drying ($MgSO_4$), evaporation and chromatography on thick layer plates using $CHCl_3$-ether (10:1) afforded 235 mg (77%) of amide 119 as a slight yellow foam; p.m.r. ($CDCl_3$, 90 MHz): δ 3.5 (s, 2H, $\underline{CH_2}Ph$), 3.6 (t, 1H, $C\underline{H}HCH$, $J_1 = J_2 = 10$ Hz), 4.0-4.3 (m, 1H, $CH_2C\underline{H}$), 4.5 (q, 1H, $CH\underline{H}$, $J_1 = 3.5$ Hz, $J_2 = 10$ Hz), 5.3 (q, 1H, $C\underline{H}NH$, $J_1 = 4.5$ Hz, $J_2 = 7$ Hz), 6.8 (d, 1H, NH, J = 7 Hz), 7.0-7.6 p.p.m. (m, 19H, aromatic and $C\underline{H}Ph_2$); i.r. ($CHCl_3$): γ_{max} 3400 (NH), 2900, 1785 (β-lactam), 1730 (ester), 1690 cm^{-1} (amide).

Carboxylic acid 120 and ester 121

Ester 119 (250 mg) in EtOH (50 ml) containing 10% Pd/C (250 mg) was hydrogenated for 1 hr at 40 psi using a Parr hydrogenator. Filtration through celite and evaporation of the ethanol gave the crude acid. Trituration of the residue with ether afforded (65%) of acid 120 as a pale yellow solid, m.p. ∿ 140° (dec.); i.r. (KBr): γ_{max} 3350 (NH), 2500-3600 (OH), 1780 (β-lactam), 1685 (acid), 1650 (amide), 1380 cm^{-1}.

Treatment with ethereal CH_2N_2 and chromatography on thick layer plates using $CHCl_3$/ether (1:1) afforded after crystallization with benzene (70%) of ester 121 as a solid, m.p. 148-150°; p.m.r. ($CDCl_3$, 90 MHz): δ 3.6 (s, 2H, $\underline{CH_2}Ph$), 3.7 (t, 1H, C$\underline{H}$HCH, J = 10 Hz), 3.9 (s, 3H, OCH_3), 4.0-4.3 (m, 1H, $CH_2\underline{CH}$), 4.5 (q, 1H, CH$\underline{H}$CH, J_1 = 3.5 Hz, J_2 = 10 Hz), 5.5 (q, 1H, C$\underline{H}$NH, J_1 = 4.8 Hz, J_2 = 7 Hz), 6.8 (bd, 1H, NH, J = 7 Hz), 7.0-7.6 p.p.m. (m, 8H, C_6H_3 and C_6H_5); i.r. ($CHCl_3$): γ_{max} 3300, 1780 (β-lactam), 1730 (ester), 1680 cm^{-1} (amide); m.s.: m/e 366 (M^+), 355 (M^+-31), 192, 175, 160. Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.56; H, 4.95; N, 7.65. Found: C, 65.59; H. 5.45; N. 7.09.

Experimental

Chapter 3

Schiff base 127, 130

The aldehyde (20 mM) and aniline (1.86 g, 20 mM), in benzene (50 ml) were refluxed for 4 hrs using a Dean Stark trap to remove the water formed. Evaporation of the benzene afforded the Schiff base in quantitative yield.

Schiff base 127

P.m.r. ($CDCl_3$): δ 7-7.6 (m, 12H, C_6H_5 + CH=CH), 8.3 p.p.m. (t, 1H, CH=N); i.r. ($CDCl_3$): γ_{max} 1630 cm^{-1} (C=N).

Schiff base 130

P.m.r. ($CDCl_3$): δ 6.1 (m, 1H, furan), 6.6 (m, 1H, furan), 6.8-7.2 (m, 5H, C_6H_5), 7.3 (m, 1H, furan), 7.9 p.p.m. (s, 1H, CH=N); i.r. ($CDCl_3$): γ_{max} 1630 cm^{-1} (C=N).

Schiff base 138

Cinnamaldehyde (2.64 g, 20 mM) in CH_2Cl_2 (5 ml) was added dropwise to a solution of ethyl glycinate (1.8 g, 20 mM) in CH_2Cl_2 (40 ml) at 0° containing $MgSO_4$ (∿ 1-2 g). After stirring for 2 hrs at 0°, the solution was filtered through celite. Evaporation of the methylene chloride afforded Schiff base 138, approximately 85-90% pure by p.m.r; p.m.r. (CCl_4): δ 1.2 (t, 3H, CH_3), 4.0-4.5 (m, 4H, $O\underline{CH_2}CH_3$, CH_2), 7.0 (d, 2H, $\underline{CH}=\underline{CH}$-Ph), 7.2-7.6 (m, 5H, C_6H_5), 7.8-8.0 p.p.m. (m, 1H, $C\underline{H}$=N).

Schiff base 143

A solution of furfuraldehyde (.96 g, 10 mM) and amine 140 (2.33 g, 10 mM) in CH_2Cl_2 (50 ml) was refluxed overnight using a Dean Stark trap filled with 4A molecular sieves. Evaporation afforded Schiff base 143 in approximately 90% yield by p.m.r; p.m.r. (CCl_4): δ 0.05 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiBu^t$), 3.7 (s, 3H, OCH_3), 3.7-4.2 (m, 3H, $CHCH_2O$), 6.4 (s, 1H, furan), 6.8 (d, 1H, furan), 7.5 (m, 1H, furan), 8.0 p.p.m. (s, 1H, CH=N); i.r. (film): γ_{max} 2950, 1740 (ester), 1640 cm^{-1} (C=N).

β-Lactam 128

Crotonyl chloride (1.0 g, 10 mM) in methylene chloride (20 ml) was added dropwise over 30 min to a solution of Schiff base 127 (2 g, 10 mM) in methylene chloride at room temperature. After stirring for 1 more hour, the dark solution was washed with water (2 x 25 ml), dried ($MgSO_4$), and evaporated. P.m.r. showed that the product contained approximately 30% 128. Flash chromatography of the residue afforded 500 mg (15%) of pure cis β-lactam 128; p.m.r. (C_6D_6): δ 4.2 (t, 1H, $\underline{CH}CH=CH_2$, J = 6 Hz), 4.8 (q, 1H, $\underline{CH}CH=CHPh$, $J_{3,4}$ = 6 Hz, $J_{4,5}$ = 7 Hz), 5.2-6.0 (m, 3H, $-CH=CH_2$), 6.2 (q, 1H, $\underline{CH}=CHPh$, $J_{4,5}$ = 7 Hz, $J_{5,6}$ = 16 Hz), 6.8 (d, 1H, $CH=\underline{CH}Ph$, J = 16 Hz), 7.0-7.7 p.p.m. (m, 10H, C_6H_5); i.r. (film): γ_{max} 2950, 1750 (C=O), 1600 cm^{-1} (C=C); m.s.: m/e 275 (13.70%), 207 (38%), 206 (100%), 156 (92.9%).

Preparation of Schiff bases 145, 164, 172a, 172b, 184, 197 and 202

The aldehyde (10 mM) was added to a solution of the amino phosphonate (10 mM) in methylene chloride (25-30 ml) at room temperature, containing magnesium sulphate. The mixture was stirred at room temperature for 2 to 5 hrs, until the i.r. spectrum of the reaction mixture did not change. The solution was filtered. Evaporation of the filtrate afforded the Schiff base in 85-95% yield by p.m.r. All Schiff bases were used without further purification for the cycloaddition. The p.m.r. spectrum showed a multiplet at approximately 7.8 p.p.m. for the Schiff base proton, along with all other appropriate signals. The i.r. spectrum of the Schiff bases showed absorption at approximately 1650 cm^{-1} for the C=N bond.

Schiff base 179

Acrolein (2 ml) was added to a solution of amino phosphonate 170 (1.2 g, 5 mM) in methylene chloride at room temperature containing sodium sulphate (1 g). After stirring for 2 hrs the solution was filtered. Evaporation of the filtrate afforded Schiff base 179 in approximately 90% yield by p.m.r. P.m.r. ($CDCl_3$): δ 1.2 (d of t, 6H, $OCH_2\underline{CH_3}$), 3.6-4.2 (m, 4H, $O\underline{CH_2}CH_3$), 4.8 (d, 1H, $\underline{CH}PO(OEt)_2$, J = 20 Hz), 5.4-6.4 (m, 5H, furan, $CH=CH_2$), 7.3 (m, 1H, furan), 7.7 p.p.m. (q, 1H, CH=N); i.r. (film): γ_{max} 1620, 1650 (C=N) cm^{-1}.

Preparation of β-lactams 125, 129, 131, 135, 139, 142, 144, 146, 148, 149 and 173

To the appropriate Schiff base (10 mM) and triethylamine (1.0 g, 10 mM) in methylene chloride (50 ml) at reflux under nitrogen was added dropwise over 45 minutes a solution of the acid chloride (10 mM) in methylene chloride (25 ml). The reaction mixture was refluxed for 1 more hour and then washed with H_2O (2 x 50 ml). The methylene chloride layer was dried ($MgSO_4$) and evaporated. Recrystallization or chromatography of the residue afforded the β-lactam in the indicated yield.

β-Lactam 125

yield 40%, m.p. 100-102°; p.m.r. ($CHCl_3$): 4.2 (bd, 1H, CH-CH=CH_2), 4.9 (d, 1H, CH-Ph, J = 2.5 Hz), 5.2-6.5 (m, 3H, CH=CH_2), 7.2-7.5 p.p.m. (m, 10H, C_6H_5); i.r. ($CHCl_3$); γ_{max} 2950, 1750 (C=O), 1600 cm^{-1} (C=C).

β-Lactam 129

40% yield by p.m.r., isolated yield 20%; p.m.r. (C_6D_6): δ 3.6 (bq, 1H, CHCH=CH_2), 4.3 (q, 1H, CHCH=CHPh, $J_{3,4}$ = 2.5 Hz, $J_{4,5}$ = 7 Hz), 5.0-6.0 (m, 3H, CH=CH_2), 6.2 (q, 1H, CH=CHPh, $J_{5,6}$ = 16 Hz, $J_{4,5}$ = 7 Hz), 6.6 (d, 1H, CH=CHPh, J = 16 Hz), 6.8-7.4 p.p.m. (m, 10H, C_6H_5); i.r. (film): γ_{max} 2950, 1750 (C=O), 1600 cm^{-1} (C=C); m.s.: m/e 275 (12.2%), 208 (21.7%), 207 (57.11%), 156 (100%).

β-Lactam 131

50% yield, m.p. 98-99°; p.m.r. ($CDCl_3$): δ 4.05 (bq, 1H, $\underline{CH}CH=CH_2$, 4.8 (d, 1H, J = 2.5 Hz, $\underline{CH}$-furyl), 5.7-6.2 (m, 3H, $CH=CH_2$), 6.3-6.5 (m, 2H, furan), 7.0-7.5 p.p.m. (m, 6H, C_6H_5, furan); i.r. (CH_2Cl_2): γ_{max} 1750 (C=O), 1600 cm^{-1} (C=C), m.s.: m/e 239 (M^+), 120, 119.

β-Lactam 135

30% yield recrystallized, greater than 70% by p.m.r., m.p. 84-86°; p.m.r. ($CDCl_3$): δ 1.85 (s, 3H, $\underline{CH_3}$-C=CH_2), 4.1 (bd, 1H, $\underline{CH}$-C(CH_3)=CH_2), 4.9 (d, 1H, $\underline{CH}$-furyl, J = 2.5 Hz), 4.9-5.1 (m, 2H, C(CH_3)=$\underline{CH_2}$), 6.2-6.4 (m, 2H, furan), 6.8-7.4 p.p.m. (m, 6H, C_6H_5 and furan); i.r. (CH_2Cl_2): γ_{max} 1750 (C=O), 1600 cm^{-1} (C=C); m.s.: m/e 253 (M^+), 171, 134, 119.

β-Lactam 139

yield 50%; p.m.r. ($CDCl_3$): δ 1.3 (t, 3H, $OCH_2\underline{CH_3}$), 1.7 (s, 3H, CH_2=C-$\underline{CH_3}$), 4.2 (AB quartet, 2H, J = 18 Hz, $\underline{CH_2}CO_2Et$), 4.0-4.4 (m, 3H, $O\underline{CH_2}CH_3$ and $C\underline{H}C(CH_3)=CH_2$), 4.5 (q, 1H, $\underline{CH}CH=CHPh$, J_1 = 5 Hz, J_2 = 7 Hz), 5.1 (bd, 2H, C(CH_3)= $\underline{CH_2}$), 6.1 (q, 1H, $\underline{CH}$=CHPh, J_1 = 7 Hz, J_2 = 16 Hz, 6.7 (d, 1H, CH=$C\underline{H}$Ph, J = 16 Hz), 7.2-7.5 p.p.m. (m, 5H, C_6H_5); i.r. (film): γ_{max} 3000, 1755 cm^{-1} (C=O), m.s.: m/e 299 (M^+), 282, 170, 82.

β-Lactam 142

70% yield: p.m.r. ($CDCl_3$): δ 0.05 (d, 6H, $Bu^tSi(\underline{CH_3})_2$), .95 (s, 9H, $Bu^tSi(CH_3)_2$), 1.8 (s, 3H, $CHC(\underline{CH_3})=CH_2$), 3.5 (s, 3H, OCH_3), 3.8-4.0 (m, 3H, CH_2O, $\underline{CH}C(CH_3)=CH_2$), 4.3 (t, 1H, $\underline{CH}CH_2O$), 4.4 (q, 1H, $\underline{CH}CH=CHPh$, $J_{3,4} = 5$ Hz, $J_{4,5} = 7$ Hz), 4.8 (bd, 2H, $CHC(CH_3)=\underline{CH_2}$), 5.8 (q, 1H, $\underline{CH}=CHPh$, $J_{4,5} = 7$ Hz, $J_{5,6} = 16$ Hz), 6.4 (d, 1H, $CH=\underline{CH}Ph$, $J = 16$ Hz), 6.8-7.0 p.p.m. (m, 5H, C_6H_5); i.r. (film): γ_{max} 2900, 1760 (β-lactam), 1740 cm^{-1} (ester).

β-Lactam 144

30% yield by p.m.r., 10% recrystallized, m.p. 79-80°; p.m.r. ($CDCl_3$): δ -0.1 (d, 6H, $Bu^tSi\ (CH_3)_2$), .80 (s, 9H, $Bu^tSi(CH_3)_2$), 1.3 (bs, 3H, $C(\underline{CH_3})=CH_2$), 3.7 (s, 3H, OCH_3), 3.8 (t, 2H, CH_2O), 4.2 (bd, 1H, $\underline{CH}C(CH_3)=CH_2$), 4.4 (t, 1H, $\underline{CH}CH_2O$), 4.9 (bd, 2H, $C=\underline{CH_2}$), 5.1 (d, 1H, CH-furyl, $J = 2.5$ Hz), 6.2 (m, 2H, furyl), 7.2 p.p.m. (m, 1H, furyl); i.r. ($CHCl_3$) γ_{max} 2900, 1760 (β-lactam) 1740 cm^{-1} (ester); m.s.: m/e 336 (M^+-41).

β-Lactam 146

yield 60%; p.m.r. ($DCCl_3$): δ 1.4 (d of t, 6H, $OCH_2\underline{CH_3}$), 1.7 (s, 3H, $CH_2=C\underline{CH_3}$), 3.4 (d of AB quartet, 2H, $J_1 = 18$ Hz, $J_2 = 10$ Hz, $\underline{CH_2}PO(OEt)_2$), 4.2 (m, 5H, $O\underline{CH_2}CH_3$, $\underline{CH}C(CH_3)=CH_2$), 4.5 (d of q, 1H, $\underline{CH}CH=CHPh$, $J_1 = 1$ Hz, $J_2 = 5$ Hz, $J_3 = 7$ Hz), 5.1 (bd, 2H, $\underline{CH_2}=CCH_3$), 6.0 (q, 1H, $J_1 = 7$ Hz, $J_2 = 16$ Hz, $\underline{CH}=CHPh$), 6.8 (d, 1H, $CH=\underline{CH}Ph$, $J = 16$ Hz), 7.3 p.p.m. (m, 5H, C_6H_5); i.r. (film): γ_{max} 3000, 1760 (C=O), 1000 cm^{-1}; m.s.: m/e 305 (M^+), 193, 151.

β-Lactam 148

yield 40%, m.p. 68-69°; p.m.r. (C_6D_6): δ 3.4 (s, 6H, OCH_3), 3.5 (s, 3H, OCH_3), 3.7 (bd, 1H, $\underline{CH}CH=CH_2$), 4.0 (d, 1H, J = 5 Hz, $CHCO_2CH_3$), 4.5 (2H, AB quartet, CH_2), 4.9-6.0 (m, 3H, $CH=CH_2$), 6.2-7.2 p.p.m. (m, 3H, C_6H_3); i.r. (KBr): γ_{max} 2950, 1750 (C=O), 1610 cm^{-1}; m.s.: m/e 305 (M^+), 193, 151.

β-Lactam 149

yield 30%, m.p. 72-72.5°; p.m.r. (C_6D_6): δ 1.6 (s, 3H, $CH_2=C\underline{CH_3}$), 3.3 (s, 6H, OCH_3), 3.4 (s, 3H, OCH_3), 3.6 (bd, 1H, $\underline{CH}C(CH_3)=CH_2$), 3.9 (d, 1H, J = 5 Hz, $\underline{CH}CO_2CH_3$), 4.5 (AB quartet, 2H, CH_2), 5.0 (bd, 2H, $\underline{CH_2}=CCH_3$), 6.0-7.0 p.p.m. (m, 3H, C_6H_3); i.r. (KBr): γ_{max} 2950, 1750 (C=O), 1610 cm^{-1}; m.s.: m/e 319 (M^+), 193, 151.

β-Lactam 173

yield 60%; p.m.r. ($CDCl_3$): δ 1.2-1.6 (m, 6H, $OCH_2\underline{CH_3}$), 1.6 (bs, 3H, $C(\underline{CH_3})=CH_2$), 4.0-4.8 (m, 5H, $O\underline{CH_2}CH_3$, $\underline{CH}C(CH_3)=CH_2$), 4.9 (d of q, 1H, $\underline{CH}CH=CHPh$, J_1 = 2 Hz, J_2 = 5 Hz, J_3 = 7 Hz), 5.2 (bd, 2H, $\underline{CH_2}=CCH_3$), 5.3 (d, $\underline{CH}PO(OEt)_2$ of one diasteriomer, J = 20 Hz), 5.5 (d, $\underline{CH}PO(OEt)_2$ of other diasteriomer, J = 20 Hz), 5.4-7.6 p.p.m. (m, 10H, CH=CHPh, furan); i.r. ($CHCl_3$): γ_{max} 1760 cm^{-1} (C=O).

β-Lactam 150

A solution of 148 (200 mg) in ethanol (20 ml) was hydrogenated at 30 psi in a Parr hydrogenator using PtO_2 (20 mg) for 1 hr. The catalyst was filtered and the filtrate was evaporated. Flash chromatography of the residue afforded 140 mg (70%) of 150 as a colourless oil; p.m.r. (C_6D_6): δ .8-1.2 (m, 3H, $CH_2\underline{CH_3}$), 1.3-1.8 (m, 2H, $\underline{CH_2}CH_3$), 2.6-3.2 (m, 1H, $\underline{CH}CH_2CH_3$), 3.35 (s, 3H, OCH_3), 3.4 (s, 3H, OCH_3), 3.5 (s, 3H, OCH_3), 3.95 (d, 1H, $\underline{CH}CO_2CH_3$, J = 5 Hz), 4.5 (AB quartet, 2H, $\underline{CH_2}C_6H_3$), 6.2-7.2 p.p.m. (m, 3H, C_6H_3); i.r. (film): 2950, 1750 (C=O), 1610 cm^{-1}; m.s.: m/e 307 (M^+), 193, 151.

Amino phosphonate hydrochloride 161

A solution of diethylphosphite (8.28 g, 60 mM) and triazine 7.14 g, 20 mM) was heated for 5 hrs at 100°. The reaction mixture was dissolved in ether (500 ml) and ether saturated with HCl gas (300 ml) was added. The ether was decanted from the oil and the oil was dissolved in methylene chloride. Evaporation of the methylene chloride afforded an oily solid. Trituration with ether and filtration afforded 13 g (75%) of 161 as a white solid; p.m.r. (D_2O): δ 1.2 (t, 6H, $OCH_2\underline{CH_3}$), 3.3 (d, 1H, $\underline{CH}PO(OEt)_2$, J = 15 Hz), 4.0 (d of q, 4H, $O\underline{CH_2}CH_3$, J_1 = 8 Hz, J_2 = 2 Hz), 4.2 (s, 2H, $\underline{CH_2}Ph$), 7.4 p.p.m. (s, 5H, C_6H_5).

Amino phosphonate 163

Amino phosphonate hydrochloride 161 (5 g) in ethanol and 5% palladium on charcoal (1.7 g) was hydrogenated at 40 psi in a Parr hydrogenator overnight. The mixture was filtered through celite and evaporated. The residue was dissolved in chloroform (100 ml) and dry ammonia was bubbled in for 10-15 min. The resulting milky suspension was evaporated. Trituration with ether and filtration of the ammonium chloride afforded 2.6 g (90%) of amine 163 as a mobile oil; p.m.r. ($CDCl_3$): δ 1.3 (t, 6H, $OCH_2\underline{CH_3}$), 2.2 (bs, 2H, NH_2), 3.0 (bd, 2H, J = 12 Hz, $\underline{CH_2}NH_2$), 4.1 p.p.m. (d of q, 4H, J_1 = 8 Hz, J_2 = 1 Hz, $PO(O\underline{CH_2}CH_3)_2$).

Amino phosphonate hydrochloride 169c

Azine 168c (9.4 g) was added very slowly to a solution of sodium (400 mg) in redistilled diethyl phosphite (25 ml) under N_2. The reaction was instantaneous and very exothermic. The red-brown solution was heated 5 hrs at 85-90°. The solution was dissolved in ether (500 ml) and the resulting solid filtered. Ethereal HCl (300 ml) was then added to the filtrate at 0°. The ether was decanted from the red-brown oil and the oil was dissolved in CH_2Cl_2 (200 ml). Evaporation of the CH_2Cl_2 afforded a red-brown oil. Trituration with methylene chloride/ether afforded 11.8 g (44%) of the hydrochloride salt 169c as a tan to light orange solid; p.m.r. ($DCCl_3$): δ 1.2-1.6 (m, 6H, $OCH_2\underline{CH_3}$), 3.9-4.5 (m, 4H, $O\underline{CH_2}CH_3$), 5.2 (d, 1H, $\underline{CH}PO(OEt)_2$, J = 18 Hz), 6.3-6.5 (m, 1H, furan), 6.8-7.0 (m, 1H, furan), 7.4-7.6 (m, 1H, furan), 8.5-9.5 p.p.m. (bs, 3H, NH_3^+).

Amino phosphonate 170

Ammonia was bubbled through a cloudy solution of hydrochloride 169c in chloroform (150 ml) for 20-30 minutes. The resulting milky solution was evaporated, ether (200 ml) was added and the precipitate filtered off. Evaporation of the filtrate afforded 2 g (77%) of the amine as a light yellow oil; p.m.r. ($DCCl_3$): δ 1.2 (d of t, 6H, $OCH_2\underline{CH_3}$), 2.3 (bs, 2H, NH_2), 3.8-4.2 (m, 4H, $O\underline{CH_2}CH_3$), 4.2 (d, 1H, $-\underline{CH}PO(OEt)_2$, J = 18 Hz), 6.3-6.5 (m, 2H, furan), 7.3-7.5 p.p.m. (m, 1H, furan); i.r. (film): γ_{max} 3400, 3300 (NH_2), 3000, 1600, 1250, 1050 cm^{-1}.

Olefin acetal 171

To a mixture of acetone (29 g), HgO (1 g) and .2 to .3 ml $BF_3.Et_2O$ at 0° was added dropwise under nitrogen ethyl vinyl ether (108 g) keeping the temperature between 4-6° (6 hrs). The mixture was stirred 3 more hrs at 6-10°. Na_2CO_3 (1 g) was added, the mixture was stirred 20 min and filtered. Distillation of the residue afforded 6.0 g (55%) of 4,4-diethoxy-2-butene 171, b.p. 70°/50 mm, lit. b.p. 71.5°/60 mm. P.m.r. ($DCCl_3$): δ 1.0 (t, 6H, $OCH_2\underline{CH_3}$), 2.2 (t, 2H, $\underline{CH_2}CH=CH_2$), 3.0-3.6 (m, 4H, $O\underline{CH_2}CH_3$), 4.3 (t, 1H, CH), 4.8-5.1 (m, 2H, $\underline{CH_2}=CH$), 5.3-6.0 p.p.m. (m, 1H, $C\underline{H}=CH_2$).

3,3-Diethoxy propionaldehyde 153

Ozone was passed for 2 hrs into a solution of 171 (6.2 g) in ethyl acetate (100 ml). Excess ozone was removed by purging with nitrogen. After warming to room temperature, ethanol (100 ml) and $Pd/CaCO_3$ (1.5 g) was added. The mixture was hydrogenated at 40 psi in a Parr hydrogenator. The catalyst was removed by filtration through celite. Distillation of the filtrate afforded 2.8 g (45%) 3,3-diethoxy propionaldehyde 153, b.p. 70-72°/15 mm, lit. b.p. 74.5°/19 mm; p.m.r. ($CDCl_3$): δ 1.2 (t, 6H, $OCH_2\underline{CH_3}$), 2.5 (m, 2H, $\underline{CH_2}CHO$), 3.2-3.8 (m, 4H, $O\underline{CH_2}CH_3$), 4.8 (t, 1H, J = 5 Hz, $\underline{CH}CH_2CHO$), 9.2 (m, 1H, CHO).

Alcohol 182

Butenediol (40 g) was dissolved in an aqueous solution of sodium hydroxide (24 g in 100 cc of H_2O). Dimethylsulphate (31 g) was added dropwise with stirring at a temperature less than 70°. After stirring at 80° for a further 2 hrs, the reaction mixture was extracted continuously with ether for 24 hrs. The ether was dried ($MgSO_4$) and evaporated. Distillation of the residue afforded 13 g (29%) of alcohol 182; p.m.r. ($CDCl_3$ + few drops of D_2O): δ 3.3 (s, 3H, OCH_3), 3.9-4.3 (m, 4H, CH_2), 5.4-6.0 p.p.m. (m, 2H, CH=CH).

α,β-Unsaturated aldehyde 183

4-Methoxy-2-butenol 182 (8 g) in methylene chloride (20 ml) was added to a slurry of pyridinium chlorochromate (24 g) in methylene chloride (200 ml). After stirring for 2 hrs, ether (200 ml) was added. The mixture was filtered through celite and Florisil. Distillation of the filtrate afforded 3.0 g (37%) of 4-methoxy-2-butenal 183, b.p. 50-52°/12 mM, lit. b.p. 72-75°/26 mM; p.m.r. ($CDCl_3$): δ 3.4 (s, 3H, OCH_3), 4.1-4.3 (m, 2H, $\underline{CH_2}OCH_3$), 6-6.4 (m, 1H, CH=$\underline{CH}$-CHO), 6.6-7.0 (m, 1H, $\underline{CH}$=CH-CHO), 9.4 p.p.m. (d, 1H, CHO, J = 7 Hz); i.r. (film): γ_{max} 1690 cm^{-1} (C=O).

Silyl alcohol 194

n-Butyl lithium (150 ml of 1.6 M sol) was slowly added to tetrahydrofuran (150 ml) at -78°. To the stirred yellow solution was added dropwise a solution of propargyl alcohol (7 ml, 120 mM) in tetrahydrofuran (50 ml). Near the end of the addition, the stirring stopped (the solution formed a gel). The mixture was shaken manually for 10-15 min. After 1 hr at -78° trimethylsilyl chloride (30 ml, 240 mM) in tetrahydrofuran (30 ml) was added slowly over 45 minutes. The solution was allowed to warm up to room temperature (2 hrs) and 2% HCl (50 ml) was added slowly. After stirring for 15-20 min, the tetrahydrofuran layer was separated and the aqueous phase was reextracted with ether (100 ml). The combined organic phases were dried ($MgSO_4$). Vacuum distillation afforded 10.2 g (67%) of alcohol 194, b.p. 68-70°/7 mm, lit. 65°/10 mm; p.m.r. ($DCCl_3$ and few drops D_2O): δ (s, 9H, $Si(CH_3)_3$), 4.0 p.p.m. (s, 2H, $\underline{CH_2}OH$).

α,β-Unsaturated aldehyde 196

To a refluxing suspension of lithium aluminum hydride (.6 g) in tetrahydrofuran (100 ml) was added dropwise over 10 minutes a solution of the alcohol 194 (3.7 g) in tetrahydrofuran (25 ml). After refluxing for 2½ hrs saturated sodium chloride (10 ml) was added. The solution was decanted from the white sticky residue. The residue was thoroughly washed with tetrahydrofuran (3 x 50 ml). The combined tetrahydrofuran fractions were washed with satd. NaCl (20 ml), dried ($MgSO_4$) and evaporated. The residue was dissolved in methylene chloride and added to a slurry of pyridinium chlorochromate (6.5 g) and celite (6 g) in methylene chloride (100 ml). After stirring for 1½ hrs, ether (100 ml) was added. The mixture was filtered through a pad of Florisil and evaporated on a rotary evaporator (temperature < 20°). Vacuum distillation of the residue afforded 1.6 g (43%) of α,β-unsaturated aldehyde 196, b.p. 40-42°/8 mm; p.m.r. ($DCCl_3$): δ 0.1 (s, 9H, $(CH_3)_3Si$), 6.4 (q, 1H, J_1 = 7 Hz, J_2 = 18 Hz, CH=CH-$Si(CH_3)_2$), 7.0 (d, 1H, J = 18 Hz, CH=CH-$Si(CH_3)_2$), 9.4 p.p.m. (d, 1H, J = 7 Hz, CHO); i.r. (film): γ_{max} 2950, 1690 cm^{-1} (C=O).

Alcohol 200

Sodium hydroxide (4.2 g, 105 mM) was added slowly to a vigorously stirred mixture of chloride 199 (12.5 g, 90 mM) and thiophenol (10 ml, 100 mM) in water (40 ml) at 100°. The mixture was stirred for 5 hrs at 100°, extracted with ether (2 x 200 ml), dried ($MgSO_4$) and evaporated. Distillation of the residue afforded 12.5 g (50%) of alcohol 200, b.p. 115-120°/.2 mm, as a mixture of isomers (approximately 9:1 cis/trans); p.m.r. ($CDCl_3$ + few drops D_2O): δ 3.4-3.7 (m, 2H, $\underline{CH_2}OH$), 3.8-4.2 (m, 2H, $PhS\underline{CH_2}$), 5.0-6.0 (m, 2H, CH=CH), 7.0-7.5 p.p.m. (m, 5H, C_6H_5).

α,β-Unsaturated aldehyde 201

Alcohol 200 (3.6 g) in methylene chloride (10 ml) was added to a slurry of pyridinium chlorochromate (5.5 g, 1.4 eq) and 5 g of celite in methylene chloride (200 ml). After stirring 2 hrs at room temperature, ether (200 ml) was added. The mixture was filtered through a pad of celite and Florisil. Column chromatography of the residue on SiO_2 act II using methylene chloride afforded 2.2 g (60%) of fairly pure aldehyde; p.m.r. ($CDCl_3$): δ 3.6 (d, 2H, $\underline{CH_2}$-CH=CH, J = 7 Hz), 6.0 (q, 1H, CH=$\underline{CH}$CHO, J_1 = 16 Hz, J_2 = 7 Hz), 6.9 (d of t, 1H, $\underline{CH}$=CHCHO, J_1 = 16 Hz, J_2 = 7 Hz), 7.0-7.6 (m, 5H, C_6H_5), 9.8 p.p.m. (d, 1H, CH=CH-$\underline{CHO}$, J = 7 Hz); i.r. (film): γ_{max} 1690 cm^{-1} (C=O).

Synthesis of β-lactams 180, 185, and 198

Azidoacetyl chloride (1.2 g, 10 mM) in methylene chloride (25 ml) was added dropwise over 30 minutes to a solution of the Schiff base (10 mM) and triethylamine (1 g, 10 mM) in methylene chloride (50 ml). The brown to black solution was stirred 1 hr, washed with H_2O (2 x 50 ml), dried ($MgSO_4$) and evaporated. Chromatography of the residue on 80 g of SiO_2 act II using $CHCl_3$/1-2% MeOH as eluent afforded the β-lactam in the indicated yield as a mixture of diasteriomers.

β-Lactam 180

40% yield; p.m.r. ($CDCl_3$): δ 1.3 (bq, 6H, $OCH_2\underline{CH_3}$), 4.0-4.5 (m, 4H, $O\underline{CH_2}CH_3$), 4.5-5.6 (m, 6H, $\underline{CH}PO(OEt)_2$, CHN_3, $CHCH{=}CH_2$), 6.3-6.6 (m, 2H, furan), 7.4-7.5 p.p.m. (m, 1H, furan); i.r. (film): γ_{max} 3000, 2100 (N_3), 1770 cm^{-1} (C=O); m.s.: m/e 354 (M^+), 327 (M^+-27), 326 (M^+-28), 271.

β-Lactam 185

43% yield; p.m.r. ($CDCl_3$): δ 1.3 (bq, 6H, $OCH_2\underline{CH_3}$) 3.3 (d, 3H, OCH_3), 3.8 (bd, 2H, $\underline{CH_2}OCH_3$), 4.0-4.5 (m, 4H, $O\underline{CH_2}CH_3$), 4.8-6.0 (m, 5H, $\underline{CH}PO(OEt)_2$, CHN_3, $\underline{CH}CH=\underline{CH}Ph$), 6.3-6.6 (m, 2H, furan), 7.3-7.4 p.p.m. (m, 1H, furan); i.r. ($DCCl_3$): γ_{max} 2900, 2100 (N_3), 1770 cm^{-1} (C=O); m.s.: m/e 370 (M^+-28), 316, 315.

β-Lactam 198

yield 70%; p.m.r. ($CDCl_3$): δ -.1 (s, $Si(CH_3)_3$, of one diasteriomer); 0.0 (s, $Si(CH_3)_3$, of the other diasteriomer), 1.0-1.4 (m, 6H, $OCH_2\underline{CH_3}$), 3.8-4.3 (m, 4H, $O\underline{CH_2}CH_3$), 4.4-4.75 (m, 2H, CHN_3, $\underline{CH}CH=CH-Si(CH_3)_3$), 5.0 (d, $\underline{CH}PO(OEt)_2$ of one diasteriomer, J = 20 Hz), 5.3 (d, $\underline{CH}PO(OEt)_2$ of the other diasteriomer, J = 20 Hz), 5.5 (q, 1H, $\underline{CH}=CH-Si(CH_3)_3$, J_1 = 7 Hz, J_2 = 16 Hz), 5.8 (d, 1H, $CH=\underline{CH}-Si(CH_3)_3$, J = 16 Hz), 6.0-6.5 (m, 2H, furan), 7.2-7.4 (m, 1H, furan); i.r. (film): γ_{max} 2950, 2100 (N_3), 1770 cm^{-1} (broad, C=O); m.s.: m/e m/e 411 (M^+-15), 398 (M^+-28), 343.

Bibliography

1. H. Staudinger, Liebigs Ann. Chem., 356, 51 (1907).
2. T.H. Clark, J.R. Johnson and R. Robinson, "The Chemistry of Penicillin", Princeton University Press, Princeton, New York (1949).
3. G.G.F. Newton and E.P. Abraham, Nature (London), 175, 548 (1955); Biochem. J., 62, 651 (1955).
4. G.G.F. Newton and E.P. Abraham, Biochem. J., 79, 393 (1961).
5. D.C. Hodgkin and E.N. Maslen, Biochem. J., 79, 393 (1961).
6. E.H. Flynn, "Cephalosporins and Penicillins, Chemistry and Biology", Academic Press, New York, London (1972).
7. H. Aoki, H. Sakai, M. Kohsaka, T. Konomi, J. Hosada, T. Kubochi, E. Iguchi and H. Imanaka, J. Antibiotics, 29, 492 (1976).
8. M. Hashimoto, T. Komori and T. Kamiya, J. Amer. Chem. Soc., 98, 3023 (1976).
9. M. Hashimoto, T. Komori and T. Kamiya, J. Antibiotics, 29, 890 (1976).
10. Y. Mine, S. Nonoyama, H. Kojo, S. Fukada and M. Nishida, J. Antibiotics, 30, 932 (1977).
11. D.B.R. Johnston, S.M. Schmitt, F. Aileen Bouffard and B.G. Christensen, J. Amer. Chem. Soc., 100, 314 (1978).
12. K. Okamura, S. Hirata, Y. Okumura, Y. Fukagawa, Y. Shimauch, K. Kouno, T. Ishimura and J. Leun, J. Antibiotics, 31, 480 (1978).
13. A. Brown, D.F. Corbett, A.J. Eglington and T.T. Howarth, J. Chem. Soc. Chem. Comm., 523 (1977).

14. K. Maeda, S. Takahashi, M. Sezaki, K. Imuma, H. Naganawa, S. Kondo, M. Ohno and H. Umezawa, J. Antibiotics, 30, 770 (1977).

15. T.T. Howaith and A.G. Brown, J. Chem. Soc. Chem. Comm., 266 (1976).

16. P.M. Blumberg and J.L. Strominger, Bacteriol. Rev., 38, 291 (1974).

17. D.J. Tipper and J.L. Strominger, Proc. Nat. Acad. Sci. U.S.A., 54, 1133 (1965).

18. J.L. Strominger, P.M. Blumberg, H. Suginaka, J. Umbeit and G.G. Wickus, Proc. Roy. Soc. Ser. B, 179, 369 (1971).

19. A. Tomasz and S. Waks, Proc. Nat. Acad. Sci. U.S.A., 72, 4162 (1975).

20. D. Boyd, Proc. Nat. Acad. Sci. U.S.A., 74, 5239 (1977).

21. B.G. Spratt, Sci. Prog. Oxford, 65, 101 (1978).

22. M.H. Richmond and N.A.C. Curtis, Annuals of the N.Y. Academy of Sciences, 235, 553 (1974).

23. G.V. Rolinson, Proc. R. Soc. London B, 179, 403 (1971).

24. R.P. Ambler, Biochem. J., 151, 197 (1975).

25. R. Virden, A. Bristow and R.H. Pain, Biochem. J., 149 397 (1975).

26. G.K. Scott, Biochem. Soc. Trans., 1, 159 (1973).

27. "Progress in Medicinal Chemistry", edited by G.P. Ellis and G.B. West, Vol. 12, pp 395-477, American Elsevier Publishing Company Inc., New York, 1975.

28. P.G. Sammes, Chem. Rev., 133 (1976).

29. "Recent Advances in the Chemistry of β-Lactam Antibiotics", edited by J. Elks, special publication no. 28, the Chemical Society, Burlington House, London (1977).

30. J. Sheehan and Henry Logan, J. Amer. Chem. Soc., 84, 2983 (1962).

31. R.B. Woodward, K. Heusler, J. Gosten, P. Naegli, W. Opplizer, R. Ramage, S. Ranganathan and H. Vorburggen, J. Amer. Chem. Soc., 88, 852 (1966); Science 153, 487 (1966).

32. K. Heusler in ref. 6, pp 273-279.

33. P.G. Sammes, Chem. Rev., 76, 113 (1976).

34. B.G. Christensen, "Annual Reports in Medicinal Chemistry", edited by F.H. Clarke, p 271, Academic Press, New York, 1976.

35. M. Hashimoto and T. Kamiya, The Japanese Journal of Antibiotics, s-218, 1977.

36. A.K. Bose, G. Spiegelham and M.S. Manhas, J. Amer. Chem. Soc., 90, 4506 (1968).

37. R.A. Firestone, N.S. Maciejewicz, R.W. Ratcliffe and B.G. Christensen, J. Org. Chem., 39, 437 (1974).

38. Y. Yashman and J.A. Edwards, J. Org. Chem., 43, 1538 (1978).

39. R.W. Ratcliffe and B.G. Christensen, Tetrahedron Lett., 4645 (1973).

40. R.W. Ratcliffe and B.G. Christensen, Tetrahedron Lett., 4649 (1973).

41. R.W. Ratcliffe and B.G. Christensen, Tetrahedron Lett., 4653 (1973).

42. R.W. Ratcliffe and B.G. Christensen, Tetrahedron Lett., 3567 (1974).

43. L.D. Cama and B.G. Christensen, J. Amer. Chem. Soc., 96, 7582 (1974).

44. R. Firestone, J.L. Fahey, N.S. Maciejewicz, G. Patel and B.G. Christensen, J. Med. Chem., 551 (1977).

45. T.W. Doyle, B. Belleau, B.-Y. Luh, C.F. Ferrari, M. Menard, J.L. Douglas, D.T.-W. Chu, G. Linn, L.R. Morris, D. Rivest and M. Casey, Can. J. Chem., 55, 484 (1977).

46. T.W. Doyle, B. Belleau, B.-Y. Luh, T.T. Conway, M. Menard, J.L. Douglas, D.T.-W. Chu, G. Linn, L.R. Morris, P. Rivest and M. Casey, Can. J. Chem., 55, 484 (1977).

47. T.W. Doyle, B.-Y. Luh and A. Martel, Can. J. Chem., 55, 2700 (1977).

48. T.W. Doyle, A. Martel and B.-Y. Luh, Can. J. Chem., 55, 2708 (1977).

49. T.W. Doyle, B.-Y. Luh, D.T.-W. Chu and B. Belleau, Can. J. Chem., 55, 2719 (1977).

50. T.W. Doyle, Can. J. Chem., 55, 2714 (1977).

51. T.W. Doyle, J.L. Douglas, B. Belleau, J. Meunier and Bing-Yu Luh, 55, 2873 (1977).

52. W.F. Huffman, K.G. Holden, T.F. Buckley III, J.G. Gleason and L. Wu, J. Amer. Chem. Soc., 99, 2352 (1977).

53. D.B. Bryan, R.F. Hall, K.G. Holden, W.F. Huffman and J.G. Gleason, J. Amer. Chem. Soc., 99, 2353 (1977).

54. J. Finkelstein, K.G. Holden, R. Sneed and C.D. Perchonock, Tetrahedron Lett. 1855 (1977).

55. J. Finkelstein, K.G. Holden and C.F. Perchonock, Tetrahedron Lett., 1629 (1978).

56. J.K. Rasmussen and A. Hassner, Chem. Rev., 76, 389 (1976).

57. Ref. 29, p 46

58. Ref. 29, p 1

59. D.J. Aberhart, Tetrahedron, 33, 1545 (1977).

60. A.K. Bose, M.S. Manhas, J.C. Kapur, S.D. Sharma and S.G. Amin, J. Med. Chem., 17, 541 (1974).

61. A. K. Bose, S.D. Sharma, J.C. Kapur and M.S. Manhas, Synthesis, 216 (1973).

62. A.K. Bose, B. Anjaneyulu, S.K. Bhattacharya and M.S. Manhas, Tetrahedron, 23, 4769 (1967).

63. D.A. Nelson, J. Org. Chem., 37, 1448 (1972).

64. G. Stacy and R. Morath, J. Amer. Chem. Soc., 74, 3885 (1952).

65. J. Sheehan and V.S. Frank, J. Amer. Chem. Soc., 71, 1856 (1949).

66. H.B. Kagan, J.J. Basselier and J.L. Lucke, Tetrahedron Lett., 941 (1964).

67. H. Buchi, K. Steen and E. Eschenmoser, Helv. Chim. Acta, 48, 1746 (1965).

68. H. Yanagisawa, M. Fukushima, A. Ando and H. Nakaô, Tetrahedron Lett., 2705 (1975).

69. R.M. Roberts and P.S. Vogt, J. Amer. Chem. Soc., 78, 4778 (1956).

70. H. Moore, L. Hernandez Jr. and R. Chambers, J. Amer. Chem. Soc., 100, 2245 (1978).

71. M.S. Manhas and A.K. Bose, "Synthesis of Penicillin, Cephalosporins and Analogs", Marcel Decker, 1969, pp 23-26.

72. M. Kamlett and R. Minesinger, J. Org. Chem., 36, 610 (1971).

73. A.I. Biggs and R.A. Robinson, J. Chem. Soc., 388 (1961).

74. Developed by G. Hakimelahi in our laboratories.

75. E. Muller, R. Heischkeil and M. Bauer, Ann. Chem., 677, 55 (1964).

76. E.J. Corey and A. Venkateswarlu, J. Amer. Chem. Soc., 94, 6190 (1970).

77. J.L. Lucke and H.B. Kagan, Bull. Soc. Chim. (France), 2450 (1968).

78. E.J. Corey and J.W. Suggs, Tetrahedron Lett., 2647 (1975).

79. E.J. Corey, N.W. Gilman and B.E. Ganem, J. Amer. Chem. Soc., 90, 5616 (1968).

80. A. Ugolini and G. Just, unpublished results.

81. C.H. Robinson, L.E. Finckenor, R. Tiberi and E.P. Oliveto, Steroids, 3, 639 (1964).

82. L. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, p 144, John Wiley and Sons, N.Y., 1967.

83. J. Smejkal and L. Kalvoda, Coll. Czechoslov. Commun., 38, 1981 (1973).

84. L. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, p 200, John Wiley and Sons, N.Y., 1967.

85. J.F. McOmie, M.L. Watts and D.E. West, Tetrahedron, 24, 2289 (1968).

86. F.M. Dean, J. Goodchild, L.E. Houghton, J.A. Martin, R.B. Morton, B. Parton, A.W. Price and N. Somvichien, Tetrahedron Lett., 4153 (1966).

87. E.J. Corey, J.L. Gras and P. Ulrich, Tetrahedron Lett., 809 (1976).

88. Personal Communication, P. Ulrich, Harvard University.

89. Best results were obtained with $(nBu)_4NF$ prepared according to the procedure of J. Pless, J. Org. Chem, 39, 2644 (1974).

90. Ref. 6, p 302

91. "The Chemistry of the Carbonyl Group", edited by S. Patai, Vol. 1, pp 461-505, Interscience, New York, 1966.

92. R.E. Bowman and W.D. Fordham, J. Chem. Soc., 2758 (1951).

93. A.K. Bose, G. Spiegelman and M.S. Manhas, Tetrahedron Lett., 3167 (1971).

94. W. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978).

95. G. Just and T.J. Liak, Can. J. Chem., 56, 211 (1978).

96. J. Gleason, W.F. Huffman and K.G. Holden, U.S. patent 4,000,154, Dec. 28, 1976.

97. M.I. Kabachnik and T. Ya. Medved, Doklady Akad. Nauk. S.S.S.R., 83, 689 (1952).

98. J. Rachon and C. Wasielewski, Z. Chem., 254 (1973).

99. J. Rachon and C. Wasielewski, Tetrahedron Lett., 18, 1609 (1978).

100. N.I. Shuikin, M.V. Yushkeirch and G.S. Belikova, Sbornik Statei Obshchei Khim., 2, 1112 (1953); C.A., 49, 4616e (1955).

101. Saburo Hattori (to Mitsubishi Chemical Industries Ltd), Japanese patent 5069, July 17, 1957; C.A., 52, 10159d (1958).

102. Subori Hattori, Yûki Gôsei Kogaku Kyôkai Shi, 19, 453 (1961); C.A. 55, 20927c (1961).

103. A.P. Skoldinov, A.P. Arendaruk and T.M. Godzhello, J. Org. Chem. USSR, 6, 421 (1970).

104. G.W. Kabalka and H.C. Hedgecock, J. Org. Chem., 40, 1776 (1975).

105. R. Boss and R. Scheffold, Angew. Chem. Int. Ed., 15, 558 (1976).

106. I. Ichikizaki, C.C. Yao, Y. Fujita and Y. Hasebe, Bull. Chem. Soc., Japan, 28, 80 (1965).

107. E.J. Corey and W. Suggs, J. Org. Chem., 38, 3224 (1973).

108. P. Colborn and F. Scheinman, J. Chem. Soc. Perkin 1, 2870 (1973).

109. G. Stork and E. Colvin, J. Amer. Chem. Soc., 93, 2080 (1971).

110. G. Stork and M.E. Jung, J. Amer. Chem. Soc., 96, 3683 (1974).

111. E.J. Corey, G. Fleet and M. Kato, Tetrahedron Lett., 3963 (1973).

112. V.F. Mironov and N.G. Maksimova, Izv. Akad. Nauk. S.S.S.R. Otd. Khim. Nauk. 2059 (1960).

113. G. Stork, M.E. Jung, E. Colvin and Y. Noel, J. Amer. Chem. Soc., 96 3685 (1974).

114. R. Mantione and Y. Leroux, J. Organometallic Chem., 31, 5 (1971).

115. Y. Kishi, M. Aratani, H. Taninio, T. Fukayama, T. Goto, S. Inoue, S. Sugiura and H. Kakoi, Chem. Comm., 64 (1972).

116. Paul Donnini, Ph.D. thesis, page 72, McGill University, Montreal (1976).

117. J. Colonge and G. Porlane, Bull. Soc. Chim. France, 953 (1955).

118. Y. Besace and I. Marszak, Bull. Soc. Chim. France, 2275 (1971).

119. I. Fleming, personal communication, see also Chem. Comm., 679 (1976).

120. G. Tadema, P. Vermeer, J. Meyer and L. Brandsma, Rec. Trav. Chem. Pays Bas, 95, 66 (1976).

121. Peter Sieber, Helv. Chim. Acta, 60, 2711 (1977).

122. E.F. Rothgery and L.F. Hohnstedt, Inorg. Chem. 10, 181 (1971).

123. M.S. Manhas, S. Jeng and A.K. Bose, Tetrahedron, 24, 1237 (1968).

124. J.L. Luche, H.K. Kagan, R. Parthasarathy, G. Tsoucaris, C. de Rango and C. Zeliver, Tetrahedron, 24, 1275 (1968).