SYNTHESIS OF SOME NEW β-LACTAM ANTIBIOTICS

A Thesis

by

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Submitted to the Faculty of Graduate Studies and Research of McGill University in partial fulfillment of the requirements for the Degree of

Doctor of Philosophy

Department of Chemistry
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To my parents,.

To my wife.

Chemistry Ph.D.

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ABSTRACT

The syntheses of the cephalosporin analogs *cis*-N-(2'-hydroxyphenyl)-3-phenylacetamido-4-hydroxymethyl-2-azetidinone (37), *cis*-N-(2'-hydroxy-5'-nitrophenyl)-3-phenylacetamido-4-hydroxymethyl-2-azetidinone (59) and 7-β-phenylacetamido-3'-hydroxybenzo[3,4]-0,2-isocephem (77) are described. Compounds 37 and 59 were devoid of antibacterial activity, while β-lactam 77 showed weak activity against two microorganisms.

Two new ring systems, 2-phenylcarbapenams 146 and 157 have been prepared. These are key intermediates in the syntheses of phosphonic acid carbapenam 148 and the carboxylic acid derivative 158, respectively.

The one carbon homologation of β-trimethylsilyl-α,β-unsaturated esters with diazomethane was extended to the corresponding β-trimethylsilyl or β-t-butyldimethylsilyl aldehydes.

Chimie Ph.D.

SYNTHESE DE NOUVEAUX ANTIBIOTIQUES DE TYPE β-LACTAME

par

Antonio Ugolini

RESUME

On décrit la synthèse d'analogues de céphalosporines *cis*-N-(hydroxyphényl-2')phénylacétamido-3 hydroxyméthyl-4 azétidinone-2 (37), *cis*-N-(hydroxy-2' nitrophényl-5')phénylacétamido-3 hydroxyméthyl-4 azétidinone-2 (59) et phénylacétamido-7β hydroxybenzo[3,4]-3' isocéphem-0,2 (77). Les composés 37 et 59 étaient dépourvus d'activité antibactérienne, tandis que la β-lactame 77 avait une faible activité contre deux microorganismes.

Les deux nouveaux systèmes cycliques phényl-2 carbapénams 146 et 157 ont été préparés. Ces derniers constituent des intermédiaires clés pour la synthèse de l'acide phosphonique carbapénam 148 et de l'acide carboxylique correspondant 158.

L'homologation des esters β-triméthylsilylés α,β-insaturés d'un carbone à l'aide du diazométhane a été réalisée à partir des aldéhydes β-triméthylsilylés ou β-t-butyldiméthylsilylés correspondants.

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GLOSSARY OF ABBREVIATIONS

Ac	acetate
AcOH	acetic acid
app	apparent
b	broad
Bn	benzyl
Bu	butyl
18-c-6	18-crown-6
CI-ms	chemical ionization mass spectrometry
CSA	camphor sulfonic acid
d	doublet
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
g	gram
gc	gas chromatography
gc-ms	gas chromatography mass spectrometry
^{1}Hmr	proton magnetic resonance (spectrum)
ir	infrared (spectrum)
J	coupling constant (three bond)
^{2}J	coupling constant (two bond)
m	multiplet
m-CPBA	meta-chloroperbenzoic acid

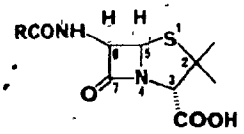
Me	methyl
MIC	minimum inhibitory concentration (μg/mL)
mL	milliliter
mmol	millimole
ms	mass spectrum
MsCl	mesyl chloride
nmr	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
p-TsOH	para-toluenesulfonic acid
ppm	parts per million
q	quartet
rt	room temperature
s	singlet
SM	starting material
t	triplet
TBDMS	tert-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilyl
tlc	thin layer chromatography
TMSCl	trimethylsilyl chloride

INTRODUCTION

PREFACE

The first β-lactam was synthesized by Staudinger[1] in 1907, but β-lactams as a class acquired importance only after it was established that penicillin contains a β-lactam unit 1, as an essential structural feature. Fleming's discovery[2] of penicillin 2, in 1929, was followed by the isolation[3] of cephalosporin C 3, in 1955, from a *Cephalosporium* species of fungi. The structure was confirmed by Hodgkin and Maslen[4], in 1961, by means of single crystal X-ray diffraction studies.

1



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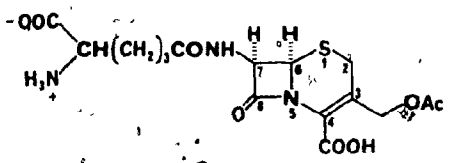

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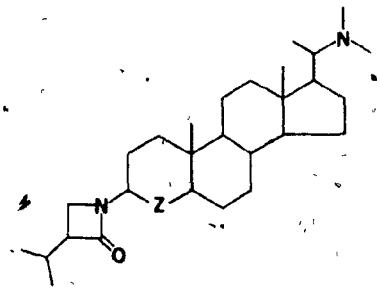
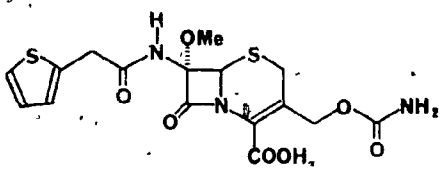
Penicillin was the first microbial metabolite to show sufficient separation between toxicity to the bacterial cell and toxicity to the mammalian host, to permit its use in the systemic treatment of bacterial infections in humans and animals. Aside from its low toxicity, it is

also easily obtained by fermentation, which is an important economic factor.

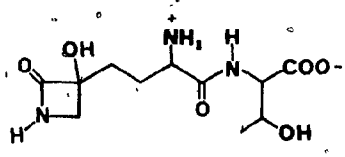
The great interest in β-lactam antibiotics has generated an enormous amount of research on the biological and chemical properties of cephalosporins and penicillins, as well as on the isolation of novel structures. The latter effort has recently produced new types of β-lactam antibiotics, such as: pachystermines[5] 4, cephamycins[6] (cefoxitin 5), clavulanic acid[7] 6, wildfire toxin[8] 7, bleomycin[9*] 8, nocardicin[10] 9, thienamycin[11] 10 and the related olivanic acids[12] 11.



Pachystermine 4. A Z = C=O; B Z = CH—OH



Cefoxitin 5



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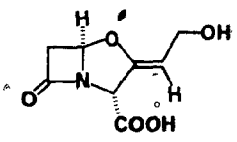

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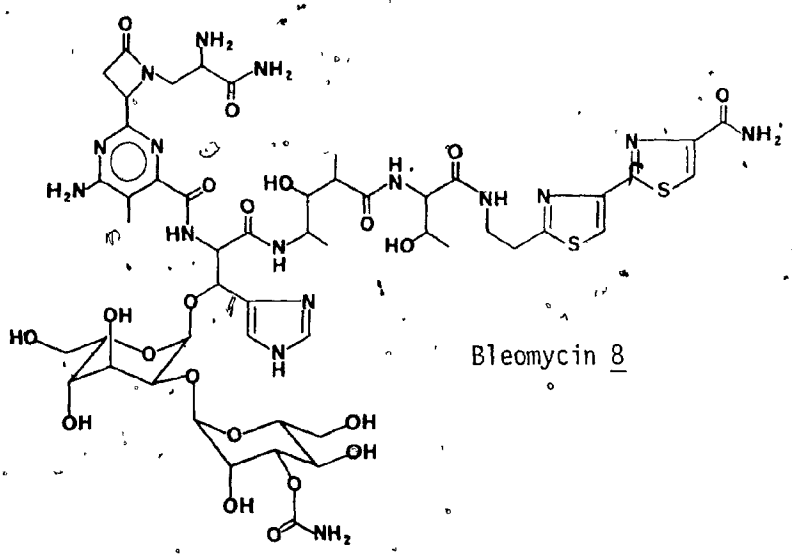
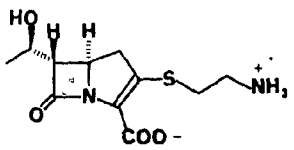
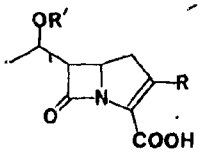
*Bleomycin A_2 was recently found to lack the β-lactam ring[127].



Bleomycin 8



Thienamycin 10



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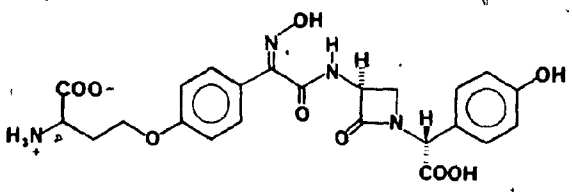

Nocardicin A 9

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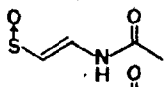
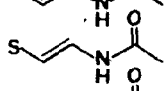
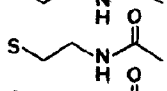
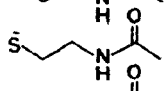
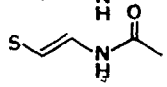
MM 4550		SO_3Na
MM 13902		SO_3Na
MM 7880		SO_3Na
MM 22380		H
MM 22382		H

Nocardicin A is active, *in vivo*, against a wide range of Gram-negative bacteria, e.g. *Pseudomonas*, *Proteus* and *E.coli*, but it has no activity against Gram-positive bacteria. It is also believed to stimulate

the host's immune response to the invading bacterium[13]. Thienamycins are not only effective against Gram-positive and Gram-negative bacteria at low levels, but also show β-lactamase inhibitory activity[14]. Olivanic acids possess good activity toward Gram-positive and Gram-negative organisms and are also powerful inhibitors of β-lactamases[15].

MODE OF ACTION OF β-LACTAM ANTIBIOTICS

Early observations of the effects of penicillin G on bacteria indicated a primary effect on cell wall integrity that was limited to growing cells, and that resulted in lysis unless the cells were protected by a medium of high osmolarity. Along with the relatively low toxicity of β-lactam antibiotics, this suggested that bacterial cell wall synthesis was inhibited. Mammalian cells lack this structural feature.

Bacterial cells are usually covered by a cell wall, which is located outside the cytoplasmic membrane (Fig. 1, p. 5). In Gram-positive bacteria, the wall is a thick, diffuse, structureless layer. It consists mainly of murein (peptidoglycan). In contrast, the thinner Gram-negative wall is composed of at least two layers, an outer membrane and an inner, structureless layer that corresponds to the murein, which is mainly responsible for the mechanical strength of the wall[16]. Its integrity is required for the maintenance of cell shape and for supporting the high osmotic pressure within the cell, about 20 atmospheres in Gram-positive organisms and about 5 atmospheres in the thinner walled Gram-negative type. The essential features of the

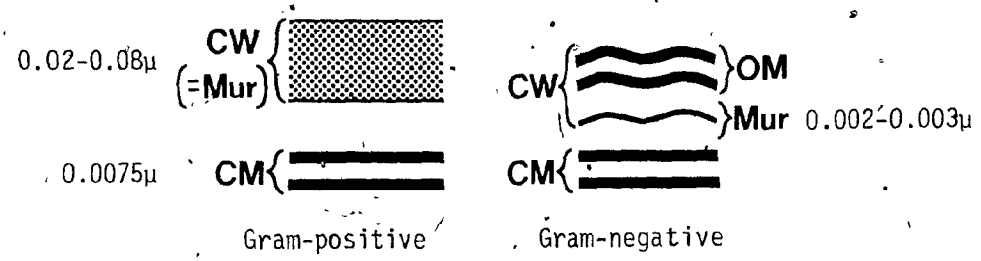


Fig. 1. Appearance of the surface layers of bacteria in thin sections. CW, cell wall; CM, cytoplasmic membrane; OM, outer membrane; Mur, murein (= peptidoglycan). Both Gram-positive and Gram-negative cells may contain extra layers of cell wall in addition to those shown here. Bacteria are about 1μ in diameter.

murein, found in virtually all bacteria, are a backbone of alternating N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc) residues having a β-1,4-linkage, a tetrapeptide substituent with alternating L and D residues, and a pentapeptide bridge from the terminal carboxyl of one tetrapeptide to an available amino group of a neighboring tetrapeptide (Fig. 2, p. 6)[16].

In vitro investigations, principally by Strominger and his colleagues, demonstrated that murein biosynthesis involves (1) cytoplasmic enzymes for formation of the nucleotide precursor, UDP-MurNAc-pentapeptide; (2) a membrane-bound enzyme for transfer of the phospho-MurNAc-pentapeptide from UMP to bactoprenol phosphate, the membrane-bound carrier lipid; and (3) further membrane-bound enzymes for addition of GlcNAc and the other components of the repeating unit of the mature peptidoglycan.

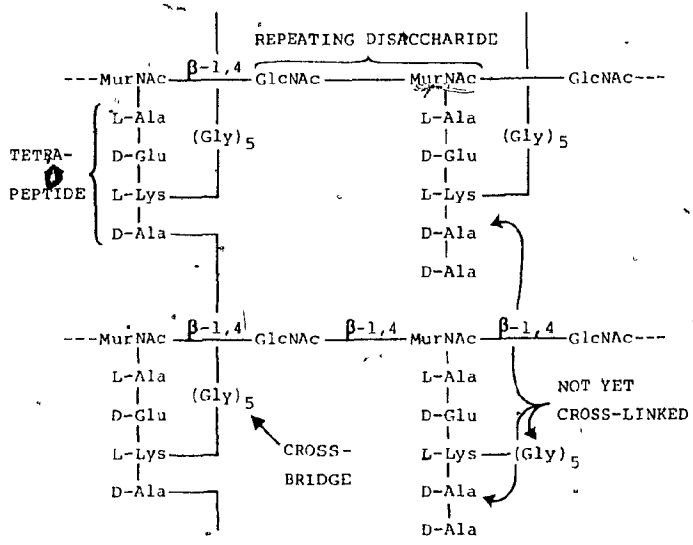


Fig. 2. Structure of peptidoglycan of *S.aureus*. The polysaccharide chains (backbone) are β-1,4-linked polymers of alternating residues of N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc = 3-O-D-lactyl ether of GlcNAc). The COOH of the lactic acid group is attached to a tetrapeptide, which in turn is linked by a pentaglycine bridge to a tetrapeptide on a nearby polysaccharide chain either above, below or in the depicted plane. Teichoic acid chains are attached to occasional MurNAc residues through a phosphodiester linkage.

Then, transport of the lipid intermediate through the membrane is followed by polymerization on its outer surface. The synthesis of the complete UDP-MurNAc-pentapeptide precursor, alone, requires 15 enzymes, present in the cytoplasm.

None of the above activities were found to be affected by penicillin *in vivo*, suggesting that the sensitive step was formation of peptide cross-links by transpeptidation. Inhibition of peptidoglycan cross-linkage by penicillin G was demonstrated in *S.aureus* cells *in vivo* by Wise and Park[17] and by Tipper and Strominger[18]. It was hypothesized that transpeptidation is a two-stage reaction in which the terminal D-alanines, in the pentapeptide of uncross-linked peptidoglycan, are cleaved releasing the C-terminal D-alanine and forming an acyl-D-alanyl enzyme intermediate. Transfer of the acyl-D-alanyl chain to an acceptor peptide, with concomitant liberation of the enzyme, completes the transpeptidation (Fig. 3, p. 8). It was further hypothesized[18] that penicillins and cephalosporins, which are both formed from L-cysteinyl-D-valine, are analogs of the particular conformation of the donor substrate. The amide bond in the highly strained β-lactam ring would correspond to the D-alanyl-D-alanine peptide bond cleaved during transpeptidation. β-Lactams may then be viewed better as transition state analogs than as analogs of the substrate in its normal state. Boyd[19] compared the three-dimensional structures of various penicillins and cephalosporins to the spatial characteristics of glycylglycine and the tetrahedral adducts formed when a nucleophile attaches to the amide carbonyl of this dipeptide (model for D-alanyl-D-alanine). Least-squares fitting showed that the tetrahedral adducts matched the β-lactam better than the parent dipeptide, one of the enantiomers being closer than the other. Once formed, the more stable penicilloyl enzyme intermediate effectively inactivates the transpeptidase. Continued bacterial

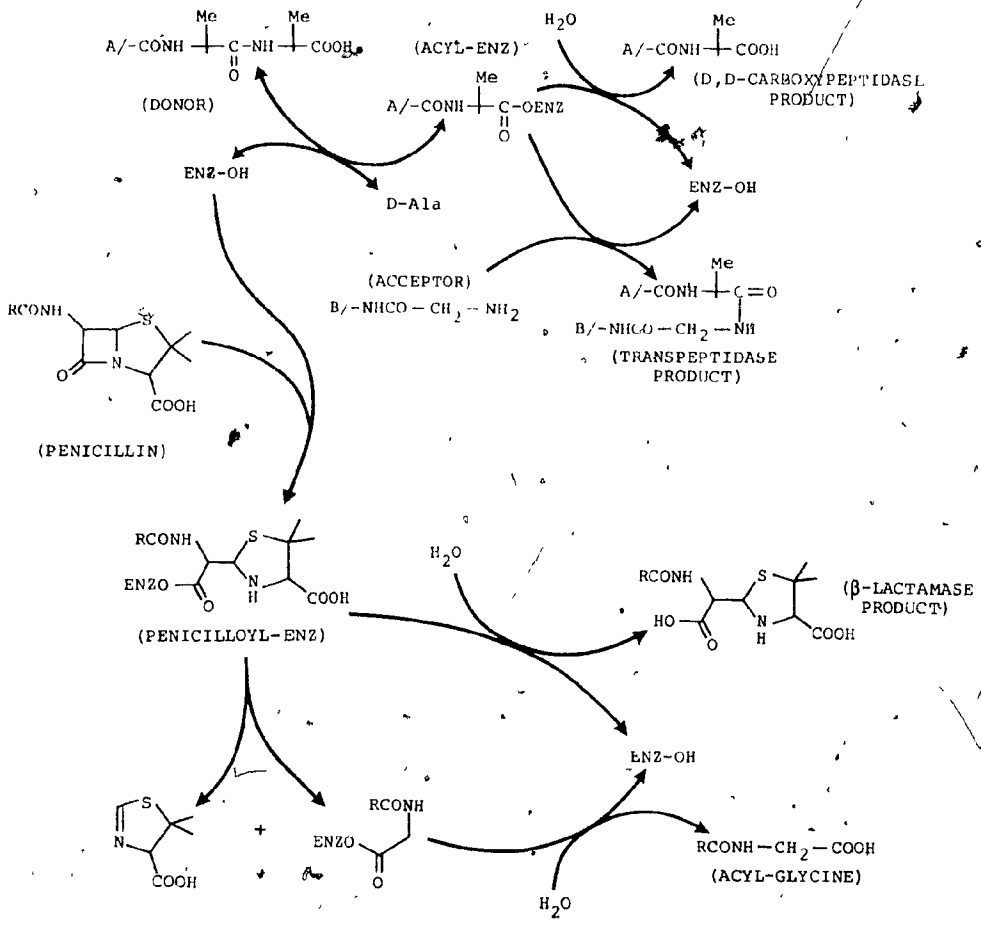


Fig. 3. Formation of acyl-enzyme intermediates in D,D-carboxypeptidase, D,D-transpeptidase, and β-lactamase action. "A" represents the end of the main peptide chain of the glycan strand. "B" represents the end of the pentaglycine substituent from an adjacent strand. Reactivation may result in formation of penicilloate or of thiazoline and acyl-glycine derivatives (Table 2, p. 13).

growth, in the absence of rigid cross-linked peptidoglycan, would result in rupture of the wall, in the region of active murein synthesis, and release of the cell contents. (Fig. 4).

Fig. 4 "Time"
April 21, 1980

Staphylococcus bacterium exploding
The wall ruptures at its weakest point

However, bacteria do not contain a unique penicillin-sensitive transpeptidase which is the target for the β-lactams, but rather a large number of enzymes, transpeptidases, carboxypeptidases and endopeptidases, which are inhibited by these antibiotics[20,21]. Also, affinities of these penicillin-binding proteins (PBP) for β-lactams are extremely variable (Table 1, p. 10). The PBP activities are not distinct, so that a specific enzyme may perform transpeptidase and endopeptidase functions to varying degrees[21]. Early studies on the binding of penicillin G to Gram-positive bacteria revealed the presence of a few thousand high

Table 1. Summary of available data on penicillin-binding proteins (PBP) of *Escherichia coli* K12

PBP	Mol wt	Molecules per cell	Relative affinity for Pen G	Mec	Kex	Lori	Cefox	Proposed function
1A	95	230	+	0	+	++	++	Peripheral cell wall extension,
1Bs	90	230	+	0	+	++	+	transpeptidase
2	66	200	+	+	0	0	0	Rod shape maintenance
3	60	50	+	0	++	+	+	Septum formation
4	44	110	+	0	+	...	...	D,D-carboxypeptidase 1B (membrane bound), 1C (soluble)
5	42	1800	++	0	0	...	...	D,D-carboxypeptidase 1A (membrane
6	40	570	++	0	0	...	...	bound)

NOTE. Molecular weights, inferred from mobility on polyacrylamide gel electrophoresis in sodium dodecyl sulfate buffers, are given in kilodaltons. Antibiotics listed are penicillin G (Pen G), mecillinam (Mec), cephalexin (Kex), cephaloridine (Lori), and cefoxitin (Cefox).

affinity sites per cell, as primary targets. A multiplicity of PBPs has been found in all organisms studied, including four in *S.aureus*, five in *B.subtilis* and between seven and nine in *E.coli*. It is also possible that other proteins whose interaction with penicillin is rapidly reversible would not be detected. An excess of unbound penicillin appears to play an essential role in the killing of some species. Bacteria, briefly exposed to lethal concentrations of penicillin, can be rescued if unbound penicillin is rapidly removed by the addition of β-lactamase.

The PBPs of *E.coli* have been investigated intensively by Spratt.[22] *E.coli* has a total of only about 2,000 PBP molecules per cell, about 10% of the number found in Gram-positive organisms (Table 1). A mutant lacking all three D,D-carboxypeptidase activities, 1A, 1B and 1C,

grows normally, suggesting that none of these enzymes are essential for growth[23]. PBP-2 has some function in the maintenance or production of the rod shape of *E.coli* cells[24]. The actual substrate and the activity of PBP-2 are not known, but the very high specificity for binding mecillinam 12 has been shown to produce enlarged, round cells that lyse slowly. PBP-3 preferentially binds furazlocillin, which at its minimum inhibitory concentration (MIC) prevents septal murein synthesis during cell division, causing the production of long filaments[25]. PBP-1A and the three PBP-1Bs preferentially bind cephaloridine, the primary effect of which, at its MIC, is to cause lysis. These PBPs are thought to be the major transpeptidases involved in elongation of the cell wall during cell division. Thus PBP-1A and PBP-1B appear to have redundant functions and both must be inactivated for cell death to occur[21].

In 1965 Tipper and Strominger[18] predicted that penicillin acylates the catalytically-active amino acid residues in the enzymes involved in peptidoglycan cross-linking. Recent studies proved this prediction to be correct for the D-alanine-carboxypeptidases from *Bacillus stearothermophilus* and *Bacillus subtilis*[26]. It was found that one molecule of penicillin or of peptide substrate binds per molecule of carboxypeptidase. Furthermore, both penicillin and substrate bind covalently to a single site, serine 36, on these enzymes.

Recently, Ghuysen[27] proposed that the functioning of the active site is mediated *via* distinctive subsites. First, the carboxyl group of the terminal D-alanyl-D-alanine or of the β-lactam antibiotics is

involved in somewhat inefficient binding to site A. Second, the lateral chain of the L-residue preceding D-alanyl-D-alanine, or the 6(7)-β substituent of penicillins and cephalosporins, reacts with some specific binding site B, causing conformational changes specifically devised to operate on the amide linkages of D-alanyl-D-alanine or the β-lactam ring. The second step is the driving force which governs the efficacy and specificity of enzyme action. The final step is the transfer of the activated D-alanyl or penicilloyl moiety, from the acyl-enzyme intermediate, to an exogenous nucleophile. With peptide substrates the process has a high turnover, whereas, with β-lactams, the process is slow. This latter property has been attributed to interaction between the monocyclic thiazolidine ring and a third binding site, which confers on the complex a conformation not suitable for nucleophilic attack. Enzymes slowly overcome this stabilization effect through C-5 - C-6 cleavage of the bound penicilloyl moiety. Other enzymes slowly release the bound metabolite in the form of penicilloate, behaving as low efficiency β-lactamases (Fig. 3, p. 8 ; Table 2, p. 13).

Finally, there is accumulating evidence implicating endogenous peptidoglycan hydrolases, autolysins, as mediators of cell death after exposure to β-lactam antibiotics and other inhibitors of murein synthesis[21,28]. Organisms defective in autolysin function remain sensitive to such drugs but survive in their presence, a phenomenon called tolerance. The optimal pH for killing cells of a variety of Gram-positive bacteria corresponds to the pH optimum of their major autolysin. In the

Table 2. Products formed during reactivation of enzymes inhibited by penicillin G

Products, enzymes	Source
Benzyl penicilloic acid (β-lactamase action)	
D,D-carboxypeptidase 1A (PBPs 5 and 6)	*Escherichia coli*
D,D-carboxypeptidase (at low ionic strength, activity not recovered)	*Actinomadura* R39
Particulate transpeptidase	*Streptomyces* R61
Penicillin-binding protein 4 (46K)	*Staphylococcus aureus*
Phenylacetyl glycine plus thiazoline fragment	
D,D-carboxypeptidase (reactivated at high ionic strength)	*Actinomadura* R39
D,D-carboxypeptidase (exocellular)	*Streptomyces* R61
D,D-carboxypeptidase (PBP 5)	*Bacillus subtilis*
D,D-carboxypeptidase	*Bacillus stearothermophilus*

NOTE. The *Actinomadura* R39 and *Streptomyces* R61 D,D-carboxypeptidases are soluble exocellular enzymes. All of the other enzymes are membrane-bound, and most have been identified with specific penicillin-binding proteins.

case of *S.pneumoniae*, the only recognized autolysin is an N-acetyl-muramyl-L-alanine amidase, and its inhibitor appears to be the Forssman antigen.

It seems that the bactericidal effects of inhibitors of murein synthesis are consequences of the secondary disturbance they cause in control of autolysins. It is not clear how this disturbance, excretion of inhibitor, is related to the different primary biochemical effects of these antibiotics.

BACTERIAL RESISTANCE TO β-LACTAM ANTIBIOTICS

Intrinsic

Resistant strains of bacteria arise because of the inhomogeneous nature of each single species. The survival of the more resistant mutants, during treatment with antibiotics, may lead to the growth of a more resistant strain. Gram-negative bacteria are inherently more resistant to classical antibiotics than Gram-positive ones, reflecting a greater complexity of the cell wall (Fig. 1, p. 5)[29]. Studies have shown that resistance is, in part, due to the lack of permeability of the membrane to these drugs[30]. Investigations with the aid of mutants revealed the existance of at least two general pathways for diffusion of small molecules across the outer membrane: a hydrophobic and a hydrophilic pathway. In the wild-type enteric bacteria, the hydrophobic pathway cannot be used owing to the absence of regions with phospholipid bilayers. Small hydrophilic molecules, however, penetrate the membrane through water-filled pores, produced by proteins called porins (Fig. 5, p. 15). In addition, there seems to be an exclusion limit for substrates with molecular weights above about 600.

Enzymatic

One of the most effective ways of resisting lethal exposure to β-lactam antibiotics is the production of β-lactamases, which rapidly hydrolyze the β-lactam to a β-amino acid. These extremely efficient

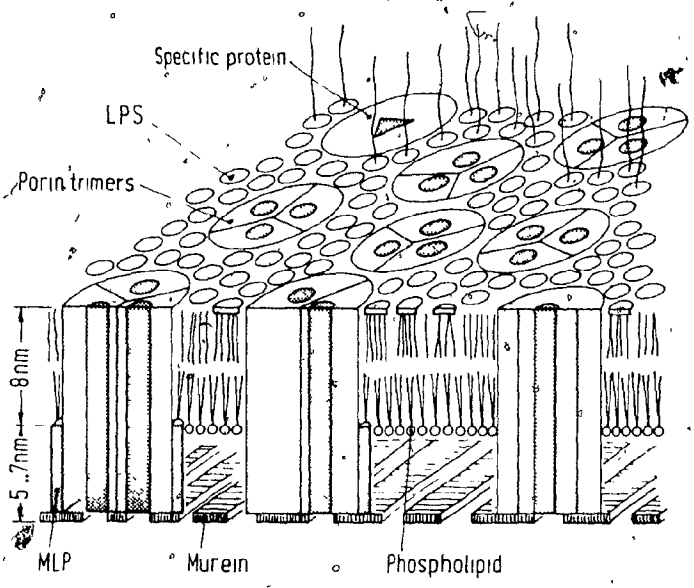


Fig 5 Speculative model of the *E coli* and *S typhimurium* cell wall Some features in this figure are highly speculative and have not been established experimentally these include the assumptions that each porin molecule produces a channel, that murein lipoprotein is joined to the membrane only via its hydrocarbon chains, and that murein lipoprotein associates with porin Spec protein protein which facilitates the diffusion of specific compounds LPS lipopolysaccharide MLP murein-lipoprotein

catalysts may be constitutive or inducible, they can be coded for chromosomally or by readily transferable plasmids, and they may be largely intracellular, largely extracellular, or, for Gram-negative bacteria, predominantly periplasmic[31,32]. Sequence homology was found between two carboxypeptidases and four β-lactamases, suggesting some evolutionary relationship[26]. Recently, an active site β-lactamase inhibitor, 6β-bromopenicillanic acid, was shown to bind covalently to serine 44 of

β-lactamase I from *B.cereus*[33,34]. In contrast, β-lactamase II from the same organism has not shown any sequence similarity and is exceptional in requiring divalent zinc for activity[35]. In Gram-negative organisms permeability compounds the β-lactamase problem. It has been shown that a plasmid β-lactamase in *E.coli* protects the bacterium from penicillin G but not from cephaloridine, even though the enzyme hydrolyzes the latter 50% faster[31].

STRUCTURE-ACTIVITY RELATIONSHIPS

Since the discovery of penicillins and cephalosporins, the thousands of semi-synthetic analogs which have been prepared are almost exclusively the C-6(7)* amide type[15]. The only other common variants are those produced at the C-3 methylene of cephalosporins by displacement of the acetoxy function.

Until recently, the structural features necessary for optimal activity were thought to be[20,36,37]: (a) a *cis*-fused β-lactam ring, (b) an acylamino side chain at C-6(7), (c) an acidic function at C-3(4) and (d) a penam or cephem skeleton, having enough ring strain to raise the β-lactam ir frequency above 1765 cm^{-1}. However, many novel β-lactam antibiotics, lacking one or more of the above requirements, have appeared recently[15].

S-1 Substituents: In contrast to penicillin sulfoxides and the cephalosporin S-sulfoxide, R-sulfoxides of various cephalosporins show

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*The number in parentheses refers to the cephalosporin numbering, when referring to both penicillins and cephalosporins.

variable and in some cases higher activity than the parent[38]. Also, some sulfones have been reported to be potent β-lactamase inhibitors[39,40].

Carboxyl Variations: Replacement of the carboxyl function with a phosphonic acid results in decreased activity relative to the parent cephalosporin. However, a phosphonic acid was used successfully in L-alanyl-L-1-aminoethylphosphonic acid, as a dipeptide alanylalanine mimetic[42]. A 3-tetrazolyl penam was found to be more potent than some conventional penicillins against a variety of organisms[41]. The concept of "bioisosterism" was discussed by Thornber[43].

C-5(6) Substituents: The few examples investigated of substitutions at the bridgehead position have shown drastic reductions in activity.

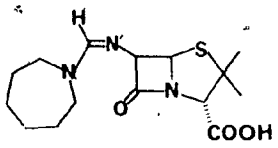
C-6(7) Substituents: The discovery that the naturally-occurring 7α-methoxycephalosporins, cephamycins, have enhanced stability to β-lactamases, has stimulated research in this area. Substitution at C-7 in the cephalosporin series uniformly increases stability to these enzymes. The 7α-methoxy group seems to be unique in this respect since bulkier groups also reduce the antibacterial activity. Unlike the cephalosporins, the activity of penicillins is not enhanced by the 6α-methoxy group.

C-6(7) Non-Classical Side Chains: The isosteric[56] 1-hydroxyethyl side chain on the C-6α position of the potent naturally-occurring thienamycin 10 is of interest. On penicillins and cephalosporins at the C-6(7) α and β positions it produced derivatives with lower activities than with the amide side chain. The β-amidino penicillins, of which

mecillinam 12 is used clinically, show remarkable activity. The 6α-chloropenicillanic acid sulfone[44] 13, 6β-bromopenicillanic acid[33] and clavulanic acid 6, which has no side chain, show anti β-lactamase activity.

Substitution of the β-Lactam Carbonyl Oxygen: Compounds in which the β-lactam carbonyl oxygen is replaced by a sulfur show from 1/20 to 1/1000 the activity of the parent compounds[15].

Nuclear Analogs: Cephalosporins with the S-1 atom replaced by an oxygen or a methylene group were found to retain the activity of the



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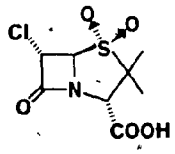

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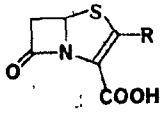

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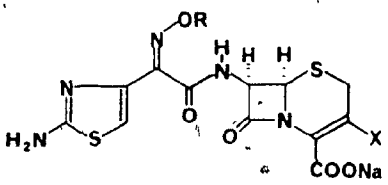
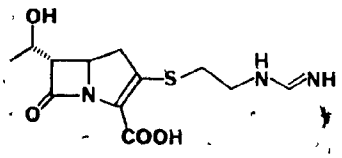


	R	X
15	$-CH_3$	$-H$
16	$-CH_3$	$-CH_2OCOCH_3$
17	$-C(CH_3)_2COOH$	$-CH_2-Py^+$



18

parent. Doyle and co-workers have reported the synthesis of N-2 and of O-2-isocephems[37,45]. The latter have comparable or better activity than the parent cephalosporins. Woodward and co-workers have reported the synthesis of penems 14[46], which are biologically very active. Nocardicins 9, which do not have a bicyclic structure, possess remarkable *in vivo* activity.

Compounds which have recently generated great interest are anti-pseudomonal cephalosporins 15, 16 and 17 with broad activity and resistance to β-lactamases, and the stable N-formimidoyl derivative[59] 18 of thienamycin, which was found to retain the spectrum of its parent with increased potency against *Pseudomonas*.

SYNTHESIS OF β-LACTAM ANTIBIOTICS

Fermentation and Semi-Synthetic

The simple and inexpensive nature of these procedures is the reason for their being the most convenient source of most antibiotics marketed. Penicillin G and V are obtained by adding the appropriately substituted acetic acid to the fermentation broth. From these penicillins others can be made by acylation of the easily obtained 6-aminopenicillanic acid (6-APA) (Fig. 6, p. 20). The cephalosporins are obtained by fermentation and semi-synthetic procedures and also through the penam-cephem rearrangement (Fig. 7, p. 20).

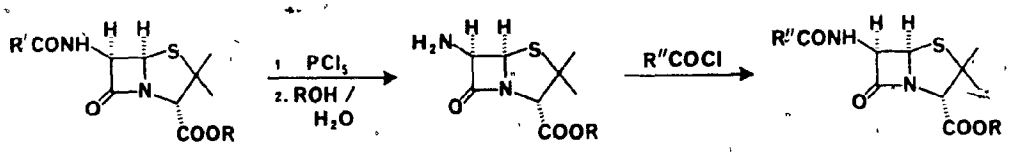


Fig. 6. Semi-synthetic route to penicillins.

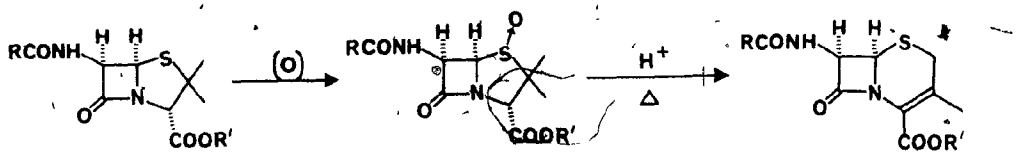


Fig. 7. Penam-cephem rearrangement.

Total Synthesis

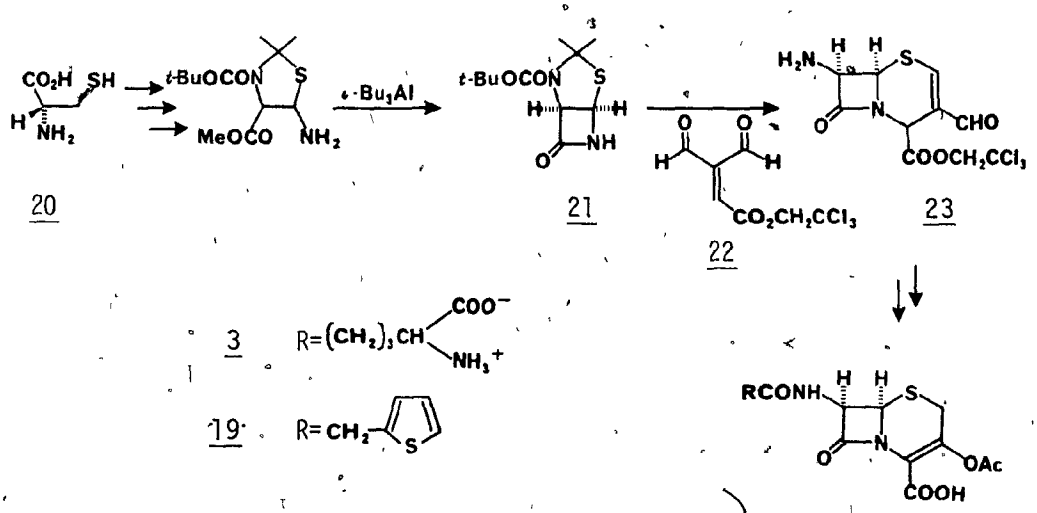
As a result of vigorous research, a vast amount of literature has accumulated over the years, in the field of total synthesis. The numerous synthetic approaches have been reviewed[47].

(i) Early syntheses

Sheehan was the first to report the synthesis of a penicillin[48] in 1962. The critical step was the formation of the β-lactam ring from the substituted β-amino acid using dicyclohexylcarbodiimide (DCC). Shortly after, in 1965, Woodward announced the first stereospecific total synthesis of cephalosporin C 3 and cephalothin 19, in his Nobel prize lecture[49].

Through a series of stereospecific transformations, L-cysteine (20)

was converted to the key intermediate 21, which was treated with dialdehyde 22 giving the C-7β amino β-lactam 23, after deprotection with

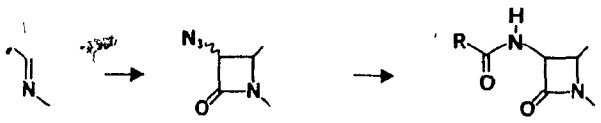


acid. Coupling of the side chains and elaboration of the C-3 substituent gave 3 and 19. Since then a multitude of approaches to the synthesis of various β-lactam antibiotics has been reported[47]. Of the numerous methods known for the formation of the β-lactam ring, the reaction of imines with acid chlorides and the reaction of olefins with chlorosulfonyl isocyanate (CSI) are the most useful and versatile.

(ii) Acid chloride-imine approach

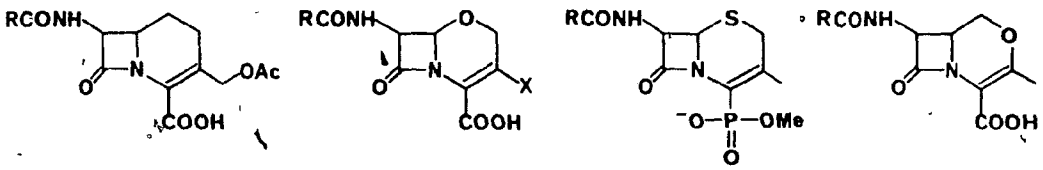
The first β-lactam was prepared by a ketene-imine interaction[1]. A variation of this reaction is the addition of activated substituted acetic acid derivatives to imines in the presence of a tertiary amine.

Thus, many acid chlorides, anhydrides and mixed anhydrides give β-lactams when added to suitable imines[50]. Bose found that treatment of imines with azidoacetyl chloride in the presence of triethylamine produced azido β-lactams 24, which could be easily transformed to the desired acylamino β-lactams 25. Reactions of this type have been used on 5- or 6-membered



24 25

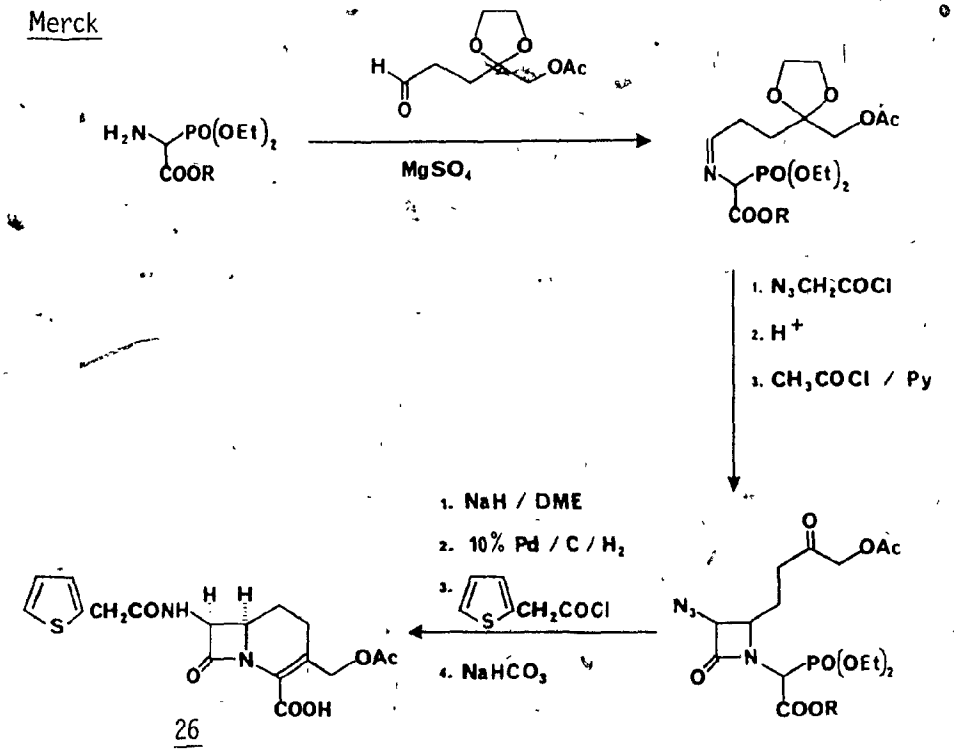
cyclic imines to produce the bicyclic nucleus of penicillins and cephalosporins directly[47]. However, this method gives the *trans* β-lactam which can then be isomerized[51] to the *cis* isomer. The most widely used approach has been to first form the β-lactam ring and then construct the remaining ring. The Merck and Bristol pharmaceutical companies have been intensely involved in the synthesis of β-lactam antibiotics. The Merck group has synthesized many nuclear analogs with structures of type A, B and C[52-54]. The Bristol group and also the Smith, Kline and French group have been involved in the synthesis of O-2-isocephems D.



A B C D

The antibacterial activity of A and B is retained, whereas in C it is reduced and D shows good activity. The Merck approach can be seen in the synthesis of 26.

Merck



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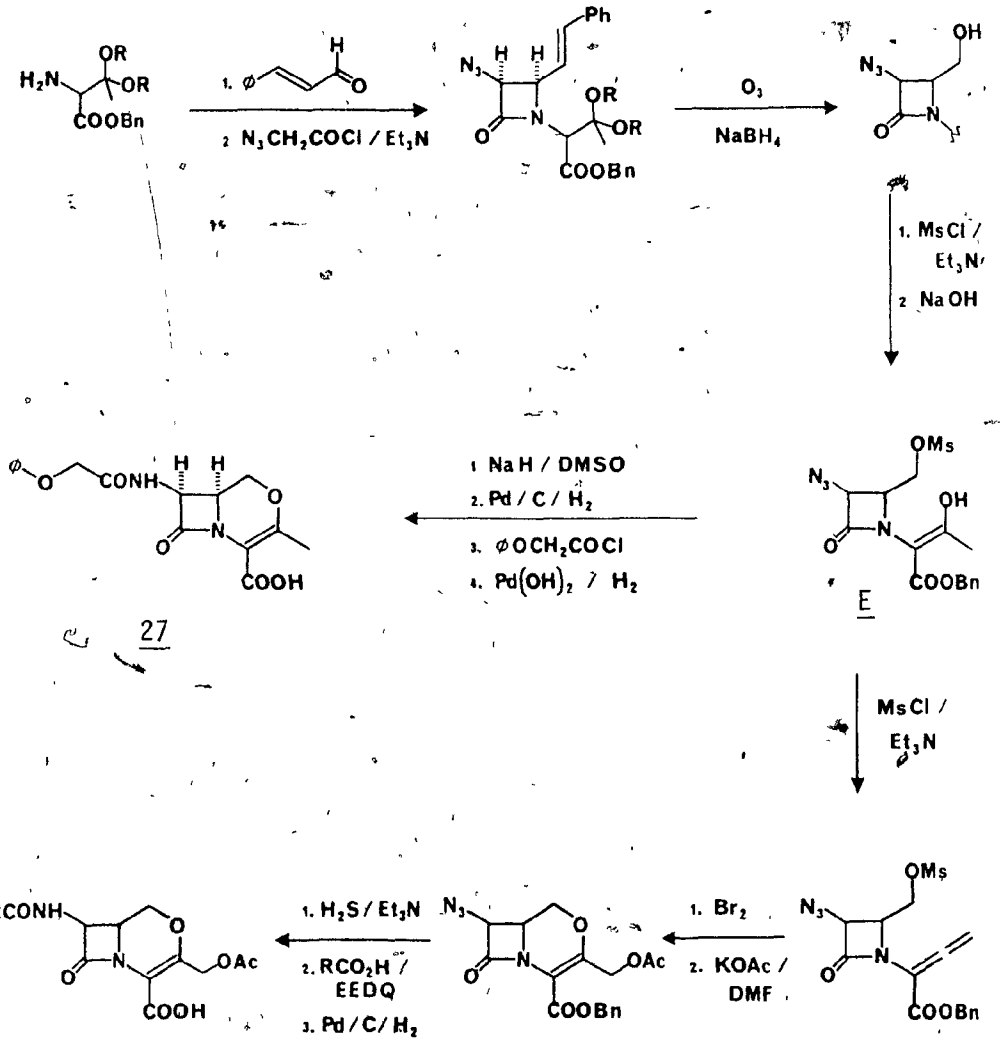
Recently, the Bristol group reported that the treatment of a cinnamylidene Schiff base with azidoacetyl chloride gave exclusively *cis* β-lactams[37]. This approach was used in the synthesis of 27. More recently their intermediate E was used to obtain a large number of derivatives of the type 28[55].

Bristol



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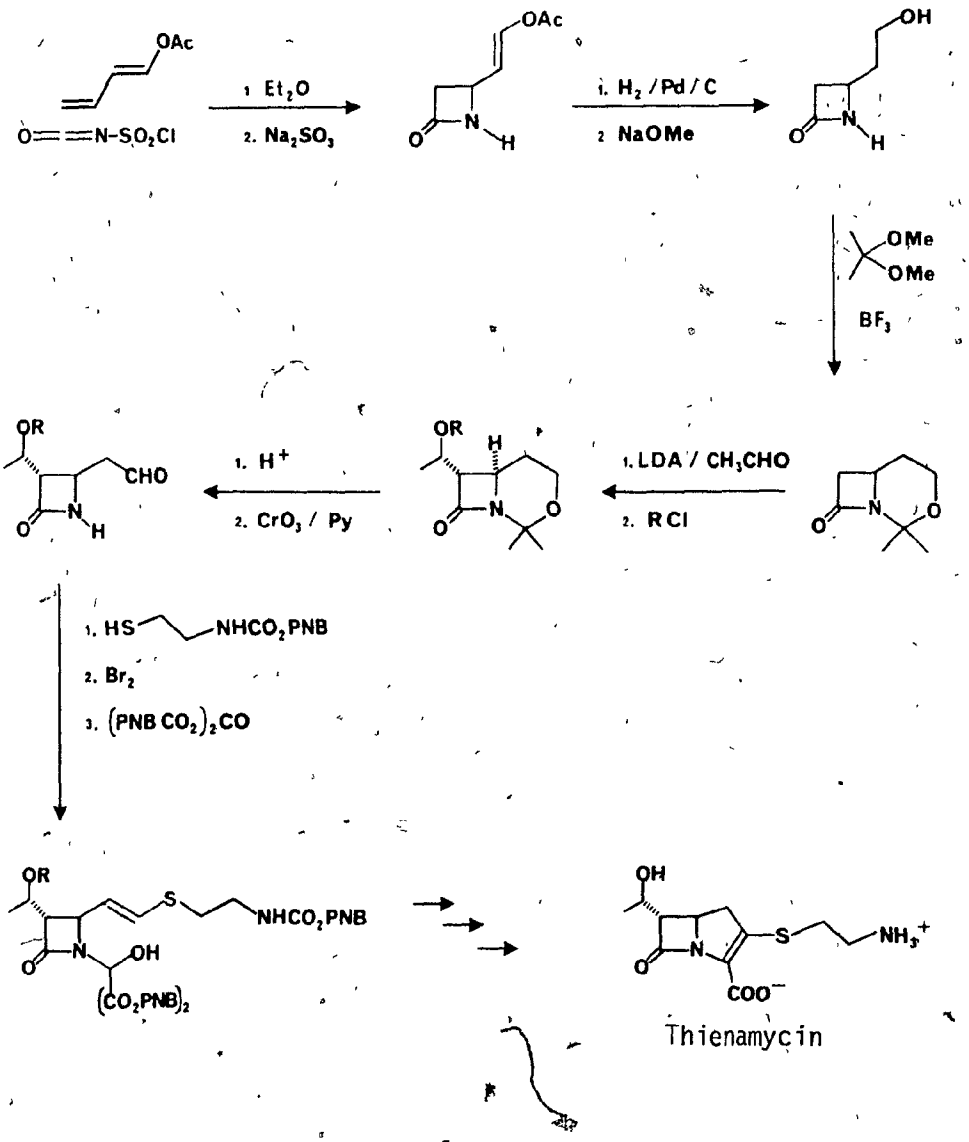
E

28

(iii) Chlorosulfonyl isocyanate-olefin route

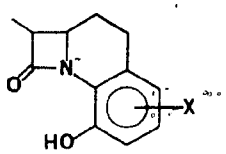
The β-lactams formed by the reaction of chlorosulfonyl isocyanate

and olefins are very versatile precursors to antibiotics. These precursors have been used in the syntheses of thienamycin[56] and clavulanic acid[57]. The Merck synthesis of thienamycin using the chlorosulfonyl isocyanate route is described below. However, a more recent stereocontrolled synthesis by the same group does not employ this method[58].

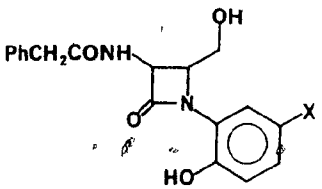


DESCRIPTION OF PROJECT

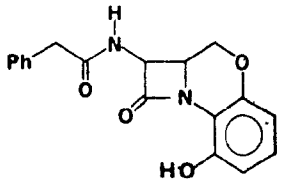
Our involvement in the synthesis of β-lactam antibiotics stemmed from an interest in structure F. Using a phenolic function to mimic the carboxylic acid of naturally-occurring antibiotics, introduction of an



F



37 X = H
59 X = NO_2



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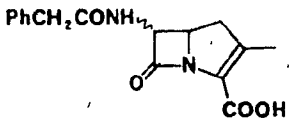


G

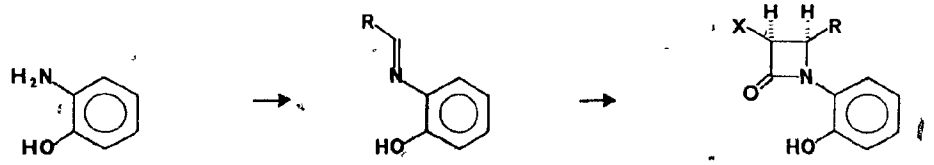
electron-withdrawing group on the aromatic ring would allow either enhancement of the acidity of the phenol or an increase in the reactivity (acylating ability) of the β-lactam ring. In the first chapter, the successful syntheses of the unfused model compounds 37 and 59 are discussed. The second chapter is an account of the successful synthesis of the tricyclic O-2-isocephem 77. Finally, the last chapter describes synthetic studies toward thienamycin analogs G, and the successful synthesis of two new carbapenam ring systems.

Although only one enantiomeric form is depicted throughout this work, all compounds prepared are racemic.

CHAPTER I

SYNTHESIS OF CIS-N-(2'-HYDROXYPHENYL)-3-PHENYLACETAMIDO-4-HYDROXYMETHYL-2-AZETIDINONE (37)

In the first part of this work, we were concerned with the synthesis of model compounds having the general structure H. We decided to use the imine-acid chloride approach, extensively used by Bose[60].

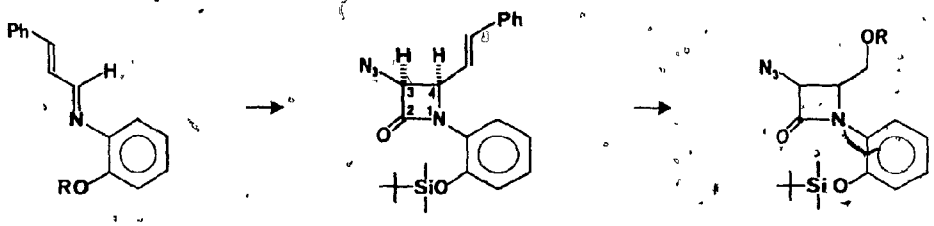


29 H

Our initial[61,62] condensations, using benzylidene anilines and either phthalimidoacetyl chloride[63] or azidoacetyl chloride, gave unsatisfactory results, yielding in most cases *trans* β-lactams or at best mixtures of *cis* and *trans* azetidinones. While this work was in progress, Doyle *et al.*[37,64] reported a versatile and reliable method for generating *cis* β-lactams, which consisted in addition of azidoacetyl chloride to a solution of a cinnamylidene Schiff base and triethylamine.

Using the procedure of Doyle *et al.*, o-aminophenol (29) was treated with cinnamaldehyde in refluxing benzene to give stable Schiff base 30. The pmr spectrum of 30 showed a resonance at 8.2 ppm

characteristic of the imine proton, and the ir spectrum displayed an imine stretching absorption at 1630 cm^{-1}. Silylation[65] of phenol 30



30 R = H
31 R = TBDMS

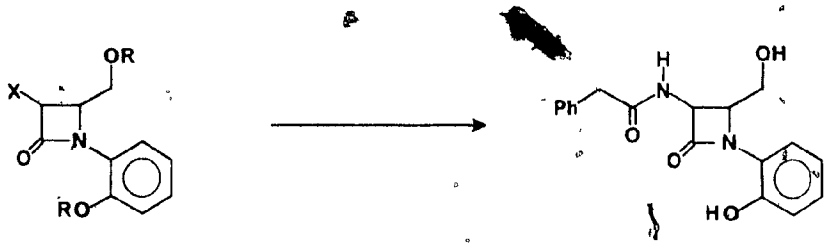
32

33 R = H
34 R = TBDMS

using t-butyldimethylsilyl chloride afforded silyl ether 31. Alternately, 31 could be obtained by first monosilylating o-aminophenol followed by condensation with cinnamaldehyde. Schiff base 31 was then treated with azidoacetyl chloride in the presence of triethylamine, at -20°, to give β-lactam 32, in 63% yield. The spectral data of 32 were consistent with its structure. An absorption at 1760 cm^{-1} was observed in the ir, for the β-lactam carbonyl, and the *cis* relationship of H-3 and H-4 was established from their coupling constant of 5 Hz. The pmr spectra of *cis* β-lactams are characterized by a $J_{3,4}$ of 4 to 6 Hz, whereas for *trans* β-lactams, it varies from 1.5 to 2.8 Hz[66]. No trace of the *trans* isomer was detected in the crude product, by pmr.

Ozonolysis of 32 in methanol at -78°, followed by *in situ* reduction

with sodium borohydride[37], afforded alcohol 33 in 88% yield. Silylation of 33 with t-butyldimethylsilyl chloride gave the *bis* silyl ether 34 in very good yield. The pmr spectrum of 34 confirmed the presence of two silyl ether groups. In the case of the alkyl silyl ether, the methyls appeared upfield from TMS at -0.10 and -0.15 ppm, and the t-butyl substituent appeared at 0.75 ppm.



35 R = TBDMS X = NH_2 37

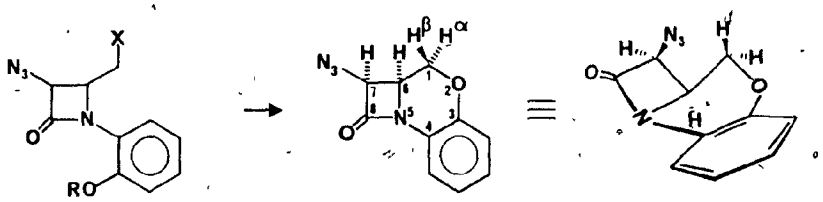
36 R = TBDMS X = $NHCOCH_2Ph$

Reduction of the azide function of compound 34 with hydrogen sulfide-triethylamine[37] in methylene chloride gave amino β-lactam 35, which was directly acylated with phenylacetyl chloride affording acylamino β-lactam 36. The chemical shifts of the methyl and t-butyl substituents on the alkyl silyl ether, in the series 34 to 36, appeared consistently upfield to those of the phenolic silyl ether. This effect may be attributed to the juxtaposition of the alkyl silyl ether within the shielding cone of the aminophenol moiety.

Treatment of *bis* silyl ether 36 with tetra-n-butylammonium

fluoride (TBAF) in dry tetrahydrofuran (THF) gave cis-N-(2'-hydroxyphenyl)-3-phenylacetamido-4-hydroxymethyl-2-azetidinone (37), in very good yield. The pmr characteristics of 37 were consistent with its structure. Its behaviour in the infrared, however, was peculiar. The ir spectrum of 37, as a potassium bromide pellet, revealed the presence of β-lactam and amide absorptions at 1695 and 1650 cm^{-1}, respectively. When a solution spectrum was taken, using acetonitrile as solvent, these bands appeared at 1720 and 1680 cm^{-1}, and when using dimethylsulfoxide as solvent, the β-lactam band was found at 1750 cm^{-1}. Tandem gas chromatography-mass spectrometry of the fully trimethylsilylated derivative, showed the presence of two components, a disilylated and a trisilylated derivative, with parent peaks at m/e 470 and 542 respectively. Formation of these derivatives was consistent with the structure of precursor 37. Compound 37 was found totally devoid of antibacterial activity, at 128 μg/mL, against a variety of organisms.

An intermediate in the above synthesis, namely 33, seemed to be well suited for model studies toward the generation of tricyclic structures of the type 40, in which the additional ring would, hopefully, confer extra steric strain to the β-lactam. Thus, hydroxymethyl β-lactam 33 was converted into the corresponding chloride 38, by means of thionyl chloride-pyridine in boiling benzene. Also, mesylate 39 was prepared from 33, by treatment with methanesulfonyl chloride-triethylamine, at -78°. Then, treatment of a tetrahydrofuran solution of either chloride 38 or mesylate 39 with 1.1 equivalents of TBAF gave instantaneously



38 R = TBDMS X = Cl

39 R = TBDMS X = OMs

40

tricyclic β-lactam 40, in high yield. Best results were obtained when relatively fresh solutions of TBAF were used*,67.

The pmr spectrum of tricyclic azido β-lactam 40, at 100 MHz, in

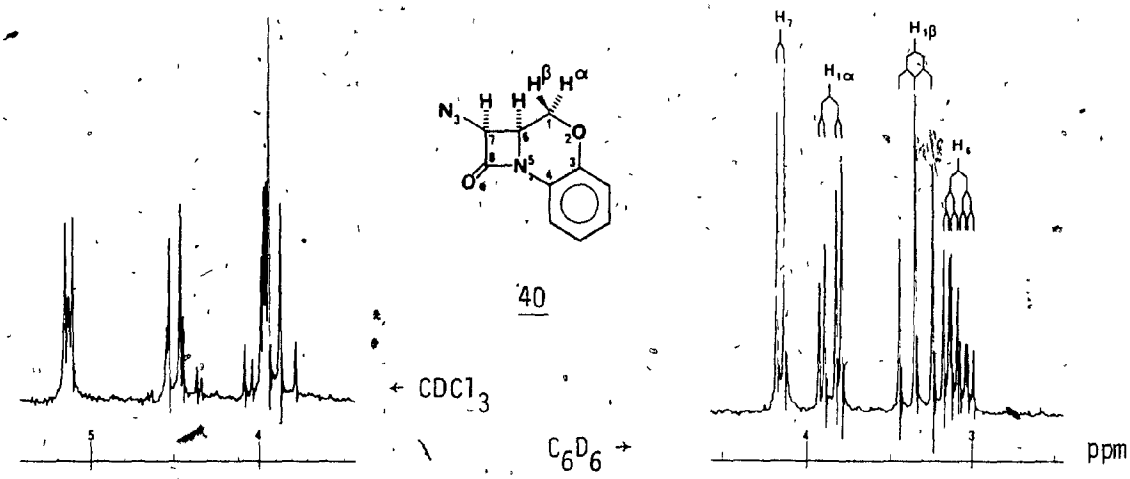


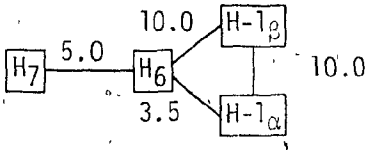
Fig. 8. Aliphatic proton signals of 40, at 100 MHz.

*See Experimental section, p. 101.

deuterochloroform, was uninterpretable due to the presence of substantial virtual coupling. In deuterobenzene, though, 40 exhibited a clean, nearly first order spectrum for the aliphatic protons (Fig. 8, p. 32). The chemical shifts and coupling constants (Table 3) were consistent with the conformation of 40 depicted earlier (p. 32), where H-1β adopts

Table 3. Pmr data on the aliphatic protons in β-lactam 40.

	H-7	H-1α	H-1β	H-6	^3J values (Hz)
$\delta(CDCl_3)$	5.13	4.5	3.9	4.0	
$\delta(C_6D_6)$	4.18	3.87	3.36	3.10	
ASIS=$\delta(CDCl_3)-\delta(C_6D_6)$	+0.95	+0.63	+0.54	+0.90	



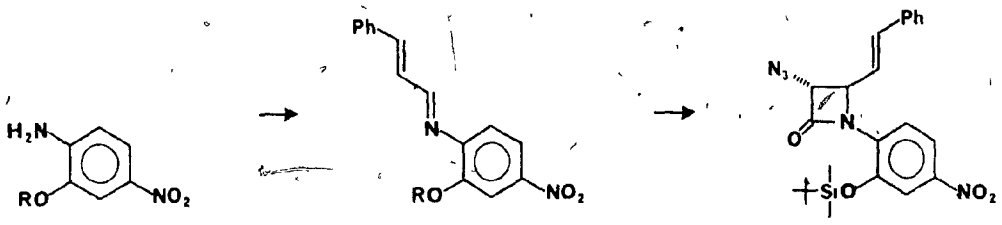
the axial and H-1α the equatorial orientation. The aromatic solvent-induced shifts observed correlate well with those obtained on analogous 7-β-azido-Δ^3-O-2-isocephem-4-carboxylates by Doyle and co-workers[64], who found that protons on the convex side of the molecule displayed the largest shifts.

The cyclization of 38 or 39 to 40, as expected, increased the β-lactam infrared absorption to 1780 from 1765 and 1770 cm^{-1}, respectively. The decreased planarity of the β-lactam nitrogen, resulting from formation of the tricyclic system, caused a decrease in amide resonance, which in turn, raised the infrared absorption frequency of the β-lactam carbonyl[36,68].

NITRO SUBSTITUENTS AND STEREOCHEMICAL STUDIES

Having found an efficient route to tricyclic structures of the type 40, we decided to investigate the possibility of introducing electronic strain into the β-lactam nucleus, *via* an electron withdrawing substituent on the aryl ring, para to the β-lactam nitrogen. It was hoped that the decreased electron density on the β-lactam nitrogen would further reduce the degree of amide resonance, thereby increasing the reactivity of the amide bond.

We chose the readily available 2-amino-5-nitrophenol (41) as starting material for this series of model studies. Protection of phenol 41 with t-butyldimethylsilyl chloride afforded silyl ether 42. Anilines 41 and 42 were separately treated with cinnamaldehyde, in boiling benzene, in a Dean-Stark apparatus, to give the Schiff bases 43 and 44, respectively.



41 R = H

42 R = TBDMS

43 R = H

44 R = TBDMS

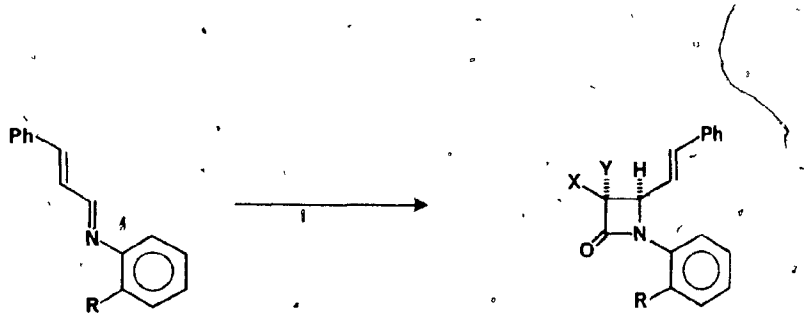
45

Schiff base 44 was considerably slower in forming than 43, due to the added bulkiness of the silyl protecting group. Compound 44 could also be obtained by silylation of phenol 43. Treatment of Schiff base 44 with azidoacetyl chloride-triethylamine afforded β-lactam 45, in very poor yield when methylene chloride was used as solvent, but in good yield when the reaction was carried out in tetrahydrofuran.

The β-lactam ir absorption appeared at 1770 cm^{-1}, 10 cm^{-1} higher than that of compound 32, indicating a slight increase in strain of the amide bond in 45. Disappointingly, however, inspection of the coupling constant of the β-lactam ring protons, 2 Hz, revealed a *trans* relationship for the substituents at C-3 and C-4. Since, at the time, a *cis*-substituted azetidinone was deemed a prerequisite for biological activity, and since studies in our laboratory[69] showed that the methods reported for isomerization of *trans* into *cis* β-lactams were not very efficient, we decided to abandon this approach.

We were still curious, however, about the reason for the change from *cis* to *trans* stereochemistry in the β-lactam formation, brought about by the addition of an electron-withdrawing substituent, on the aryl ring. Similar results were obtained by Dr. Zamboni, in our laboratory[69], when Schiff bases 46 and 47 were treated with azidoacetyl chloride. Schiff base 46 gave *cis* β-lactam 48, whereas 47, containing an electron-attracting ester, yielded *trans* β-lactam 49. Other substituted anilines were investigated and the results are summarized in Table 4 (p. 37). Schiff bases derived from anilines the pK_a values* of which were greater than

*To be precise, it is the pK_a of the conjugate acid of the aniline derivative that is being referred to.



46 R = $CH_2OTBDMS$

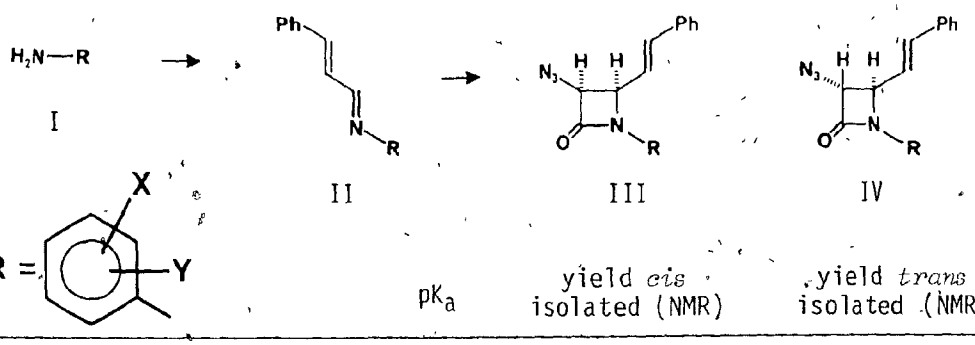
47 R = CO_2TMS

48 R = $CH_2OTBDMS$ X = N_3 Y = H

49 R = CO_2TMS X = H Y = N_3

or equal to 2.4 consistently produced *cis* β-lactams, whereas those with values less than 2.4 afforded either mixtures of *cis* and *trans* or pure *trans* β-lactams. These results suggested the involvement of at least two distinct reaction pathways in the β-lactam ring formation (Fig. 9, p. 38). In path "A" the imine may have reacted with azidoacetyl chloride to give the intermediate k. Deprotonation of k with triethylamine may have produced the zwitterion ℓ. Zwitterion ℓ may also have been generated through the interaction of the imine and azidoketene. The electrostatic attraction[37], produced by the negative charge density on the azido group and the partial positive charge on the cinnamyl appendage, may have stabilized the transition state leading to the *cis* β-lactam. Similar zwitterionic intermediates are involved in the formation of 3-cyano-2-azetidinones[70]. An alternate path, "B", cycloaddition of the imine

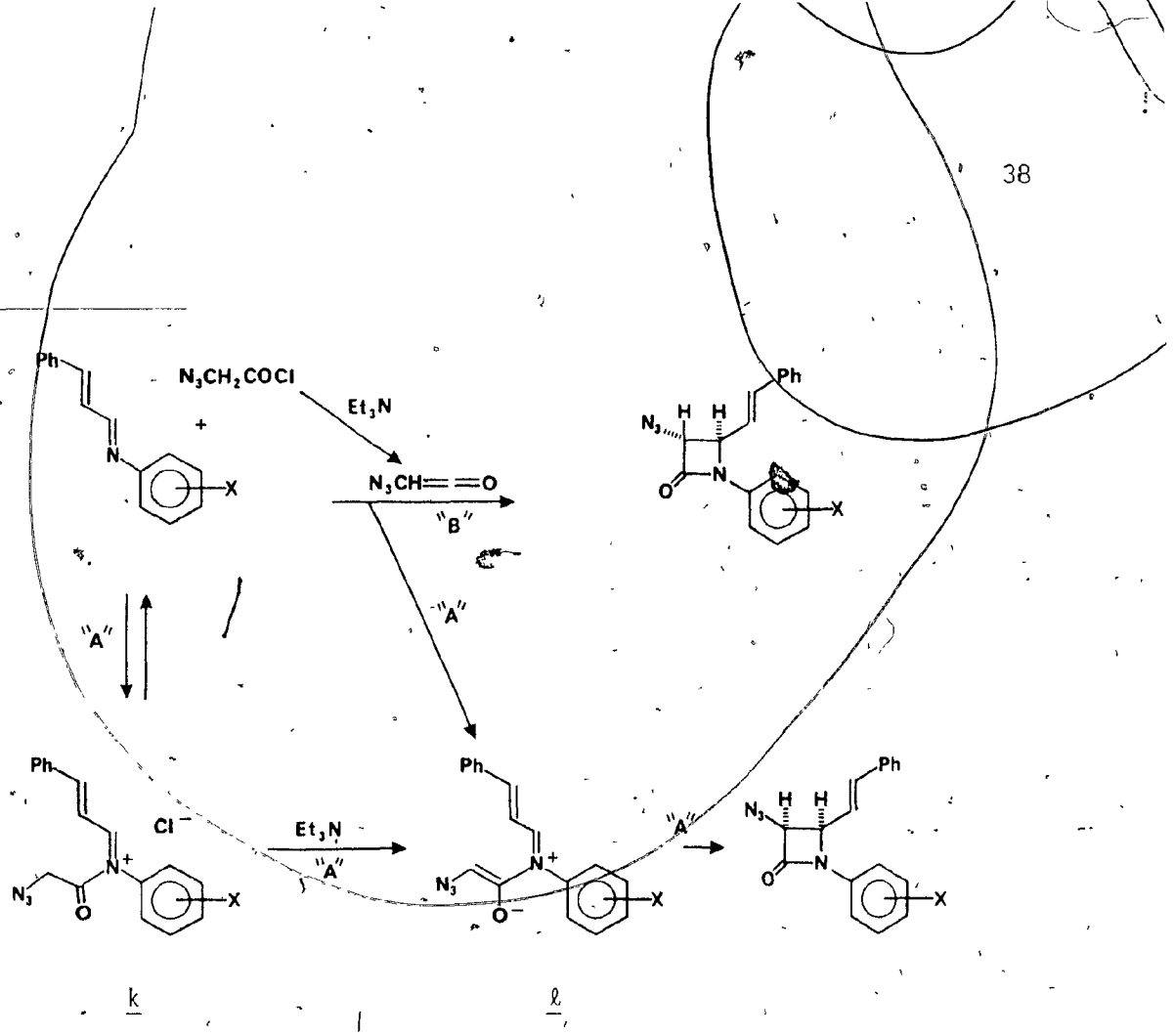
Table 4. Stereochemical results of the reaction of cinnamylidene Schiff bases of substituted anilines with azidoacetyl chloride.



	pK_a	yield *cis* isolated (NMR)	yield *trans* isolated (NMR)
(a) X=Y=H	4.6[d]	50% (90%), mp 123-125°	
(b) X=p-Cl, Y=H	4.0[d]	40% (90%), mp 121-121.5°	
(c) X=o-CH_2OTBDMS, Y=H[a]	> 3[e]	70% (95%), mp 85.5-86°	
(d) X=o-OTBDMS, Y=H	> 3[e]	63% (90%), mp 84-85°	
(e) X=o-CH_2OTBDMS, Y=o'-OTBDMS[a]	> 3[e]	81% (90%)	
(f) X=Y=o-OTBDMS	> 3[e]	59% (70%), mp 95-96°	
(g) X=m-NO_2, Y=H	2.46[d]	80%	
(h) X=o-OMe, Y=p-COOMe	2.4[f]	85%	
(i) X=p-Cl, Y=o-Cl	2.05[d]	(60%)	(15%)
(j) X=o-COOH, Y=o'-OMe[a]	2.0[c]	(15%)	(15%)
(k) X=o-COOH, Y=H[a]	2.2[c]		(30%); (30%,THF)[b]
(l) X=o-OTBDMS, Y=p-NO_2	<1.5[e]		(2%); 50% (70%,THF)[b]
(m) X=p-NO_2, Y=H	1[d]	50%	25%
(n) X=p-NO_2, Y=o-CH_3	1[e]	(5%)	(50%)

a = results obtained by Dr. R. Zamboni in our laboratory; b = cycloaddition performed in THF; c = measured on corresponding methyl ester; d = from literature[75]; e = estimated; f = measured[76].

with azidoketene, may have produced the *trans* β-lactam. Luche and Kagan have shown that with aldoketenes only *trans* β-lactams are formed[71]. Thus, it seemed that imines with parent anilines having pK_a's greater than or equal to 2.4, preferred to react through path "A", whereas those derived from anilines with pK_a's below 2.4 reacted through both path "A"



k ℓ

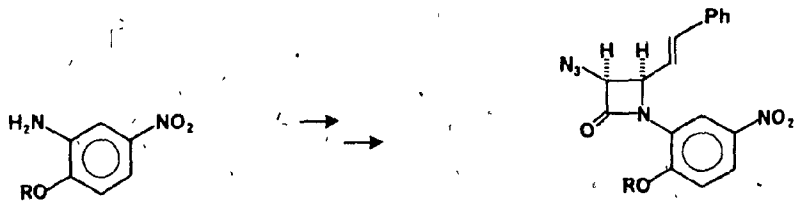
Fig. 9.

and "B" or "B" alone. Electron-withdrawing groups and ortho substituents produced similar effects in anilines with low pK_a's. Perhaps they destabilized intermediate ℓ enough to allow path "B" to contribute significantly, and in some cases solely, to β-lactam formation.

SYNTHESIS OF CIS-N-(2'-HYDROXY-5'-NITROPHENYL)-3-PHENYLACETAMIDO-4-HYDROXYMETHYL-2-AZETIDINONE (59)

At this point, we decided to modify the pK_a of the phenolic function. The aim was to increase its acidity in order for it to better mimic the carboxylic acid of classical antibiotics. We chose to use a

para-nitrophenol to accomplish this. Thus, the readily available 2-amino-



50 R = H

51 R = TBDMS

52 R = TBDPS

53 R = TBDMS

54 R = TBDPS

55 R = TBDPS $N_3 = NH_2$

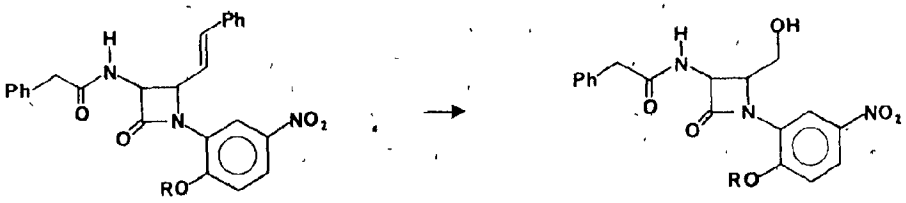
4-nitrophenol (50) was protected using t-butyldimethylsilyl chloride, in the usual manner, to give crystalline 51 from the crude mixture. Silyl ether 51 was treated with cinnamaldehyde to give the corresponding Schiff base. The crude Schiff base was then treated with azidoacetyl chloride-triethylamine to afford β-lactam 53, in 53% yield. Examination, of the coupling constant of the β-lactam ring protons, revealed they bore a *cis* configuration, exclusively. Reduction of the azide with hydrogen sulfide-triethylamine, followed immediately by acylation with phenylacetyl chloride afforded β-lactam 56. Unfortunately, it was found that the t-butyldimethylsilyl protecting group was partially removed during the reduction. This problem was temporarily resolved, by resilylation of the phenol immediately prior to acylation.

Ozonolysis of cinnamyl β-lactam 56 in ethanol-methylene chloride followed by treatment with sodium borohydride produced a deeply orange colored solution, during the reduction. Work-up with pH 4.5 buffer removed the color, and the product was found to be diol 59. The silyl protecting group was apparently removed during the reduction, by small amounts of ethoxide generated from the slow reaction of sodium borohydride with ethanol.

The β-lactam absorption of 59 was found at 1720 cm^{-1}. The pmr and the chemical ionization mass spectral data were also consistent with structure 59. The sodium salt 60 was prepared by treatment of 59 with sodium isopropoxide. In the sodium salt 60, the β-lactam absorption was shifted to 1745 cm^{-1}. Both 59 and sodium salt 60 showed no antibacterial activity toward a variety of bacteria. This was not totally unexpected since active cephalosporins have β-lactam absorptions of at least 1765 cm^{-1}.

Since the t-butyldimethylsilyl ether was labile to the azide reduction and to the ozonolysis-reduction conditions, we decided to investigate the use of the similar but more stable t-butyldiphenylsilyl (TBDPS) protecting group. This study would be useful in later experiments with structures of the type I, where the R groups would have to be stable to the ozonolysis-reduction conditions.

Thus, 2-amino-4-nitrophenol (50) was protected as the t-butyldiphenylsilyl ether 52. The Schiff base was formed in the usual manner and reacted, as mentioned previously, to give *cis* β-lactam 54 in good



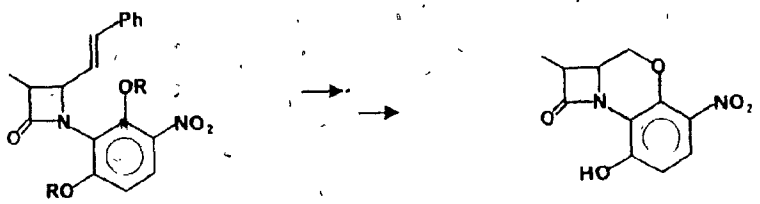
56 R = TBDMS

57 R = TBDPS

58 R = TBDPS

59 R = H

60 R = Na



I

yield. Unfortunately, when 54 was subjected to the azide reduction conditions, hydrogen sulfide-triethylamine, some of the silyl ether was cleaved. This was inconsequential, since the phenol could be easily reprotected, at this stage, in the same reaction vessel, affording amine 55. This amine was then acylated with phenylacetyl chloride to give β-lactam 57. The critical test of the adequacy of the t-butyldiphenylsilyl protecting group was the ozonolysis-reduction reaction. Were it to be cleaved at this point, it would not be a trivial task to differentiate the two alcohols generated, a phenol and a hydroxymethyl at C-4. Ozonolysis-sodium borohydride reduction of styryl β-lactam 57 afforded alcohol 58, in 71% yield. The t-butyldiphenylsilyl ether had survived the sodium borohydride-ethanol treatment.

Some of the intermediates in the above sequences were also screened for antibacterial activity (Table 5, p. 43). Compounds 55 and 57 were more potent than ampicillin and piperacillin against *E. cloacae* only, and compounds 53 and 54 were mildly active against some other bacteria. It is interesting to note that the above compounds all possessed silyl protecting groups. When the silyl group was removed as in 55a and 56a, the compounds lost all activity.

Table 5. *In vitro* testing results* for some β-lactam intermediates.

Organisms	MINIMAL INHIBITORY CONCENTRATION (MIC μg/mL)									
	53	54	55	55a	56	56a	57	59	Amp.	Pip.
E.cloacae MA75-1	>	>	64	>>	>	>>	64	>>	>	>
E.coli ESS 22-31	16	16	32	128	>	256	32	-	-	≤.06
Staph.aureus Q74-1	8	8	64	>>	>	>>	64	>>	≤.06	.25
Staph.aureus Q74-5	8	8	-	-	>	-	-	-	-	.25
Staph.aureus Q74-6	-	-	64	>>	-	>>	64	-	-	.25
Enterococcus SM77-15	32	32	128	>>	>	>>	128	>>	-	2
E.coli OSU75-1	32	32	-	-	>	-	-	>>	4	2
S.lutea PCI 1001	8	8	-	-	>	-	-	>>	≤.06	≤.06

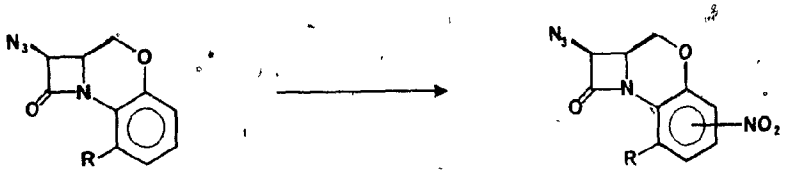
Note: 55a and 56a are the same as 55 and 56 except that the silyl group has been removed. > and >> represent >128 and >256, respectively. Amp. and Pip. are ampicillin and piperacillin, respectively.

NITRATION STUDIES

Since the presence of a nitro substituent on the aniline moiety presented some problems, in the initial steps of the syntheses, such as, formation of a *trans* β-lactam in the case of 45 and increased lability of the silyl ethers in the case of 53 and 54, we chose to investigate the feasibility of introducing the nitro function at a later stage, by nitration of the tricyclic intermediate 40.

* Antibacterial testing was performed by Ms. Kuck, Lederle Laboratories of the American Cyanamid Company.

Olah has shown that nitronium tetrafluoroborate easily and efficiently nitrates a variety of aromatic compounds, in non-acidic solvents[72]. Transfer nitration using N-nitropyridinium salts was also



40 R = H

74 R = OTBDMS

61 R = H

62 R = OTBDMS

found very useful on aromatic substrates[73]. Thus, tricyclic azide 40 was treated with nitronium tetrafluoroborate-collidine to afford an isomeric mixture of β-lactams 61. The mixture showed a β-lactam absorption at 1785 cm^{-1} and a considerable spreading of the aromatic signals in the pmr spectrum. No attempt was made to separate the isomers since we were not interested in compounds without a phenolic function. Instead, the nitration was repeated on β-lactam 74* and all three possible isomeric products 62 were detected, in approximately equal proportions, in the pmr of the crude material. However, attempted chromatography of this mixture resulted in destruction of the meta** nitro isomer, on contact with silica gel, an indication of the strong activation of the β-lactam

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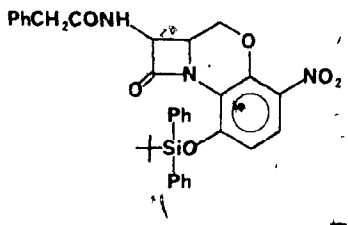
*Synthesis of 74 will be discussed in Chapter II.

**Ortho, meta and para positions are taken to be relative to the silyl ether.

bond. The mixture of ortho and para nitro compounds showed a β-lactam absorption at 1790 cm^{-1} in the infrared, and a characteristic AB quartet for the aromatic protons of each isomer, in the pmr spectrum. Efforts along these lines were continued by Y. Tsantrizos[74] in our laboratory, who was successful in obtaining β-lactam 63. Unfortunately, 63, having a β-lactam band at 1790 cm^{-1}, proved to be too unstable for testing and further manipulation.

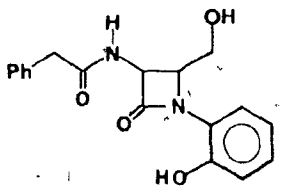


63

CHAPTER II

SYNTHESIS OF 7-β-PHENYLACETAMIDO-3'-HYDROXY-BENZO[3,4]-0-2-ISOCEPHEM

The preceding chapter described the efficient generation of tricyclic β-lactam 40 and the synthesis of model β-lactam 37, the β-lactam infrared frequency of which was rather low. The methodology explored in those studies was then applied to the synthesis of 77, which was



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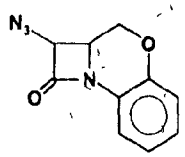

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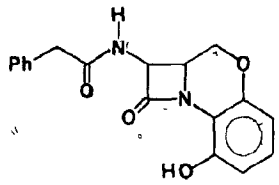
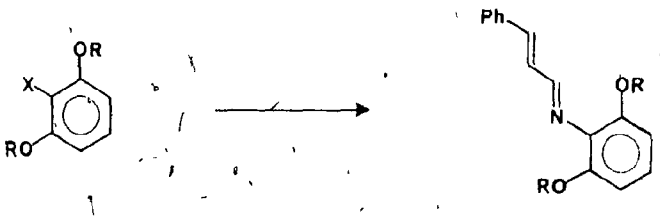


77

expected to exhibit an increased β-lactam infrared frequency as compared to that of 37. It was hoped that the additional ring would confer enough steric strain to the β-lactam to raise its infrared frequency to within the same range as active cephalosporins, at least 1765 cm^{-1}.

Our choice of starting material was 2-nitroresorcinol (64), readily obtained by nitration[77] of resorcinol. The nitro group was easily reduced, using platinum oxide-hydrogen, affording 2-aminoresorcinol (65). To our surprise, condensation with cinnamaldehyde, following the



64 R = H X = NO_2

65 R = H X = NH_2

66 R = CH_2Ph X = NO_2

67 R = TBDMS X = NH_2

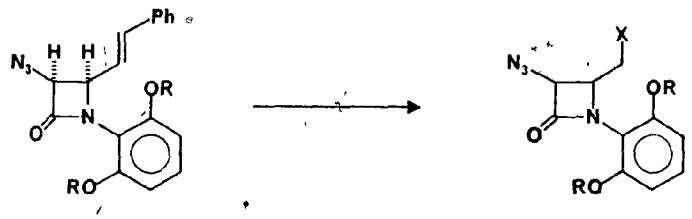
68 R = H

69 R = TBDMS

usual procedure, failed to produce any Schiff base 68. Instead, an unidentifiable tar was obtained. We decided to prepare the Schiff base of 2,6-dibenzyloxyaniline, for fear that the *bis* t-butyldimethylsilyl derivative may have been too hindered to react with cinnamaldehyde. Thus, 2-nitroresorcinol was dibenzylated using benzyl bromide-potassium carbonate in dimethylsulfoxide to give 66 in very good yield. Unfortunately, treatment with either platinum oxide-hydrogen or iron-hydrochloric acid[78] was unsuccessful in effecting the reduction of the nitro group in 66. At this point it was clear that reduction of the nitro group had to precede protection of the phenolic function. We decided to use the silyl protecting group, employed successfully in the previous chapter.

Thus, 2-aminoresorcinol was transformed into its *bis* t-butyldimethylsilyl ether 67, in the usual manner. When amine 67 was boiled

in benzene with cinnamaldehyde, Schiff base 69 was obtained in high yield. The pmr spectrum of 69 displayed a doublet of doublets, J = 3,5 Hz, at 8.3 ppm characteristic of the Schiff base hydrogen, and an imine absorption was found at 1640 cm^{-1} in the infrared. Without purification, Schiff base 69 was subjected to treatment with azidoacetyl chloride-triethylamine affording *cis* β-lactam 70, in good yield. That the β-lactam ring hydrogens were indeed *cis* became evident only in subsequent compounds



70 R = TBDMS

71 X = OH

72 X = OMs R = TBDMS

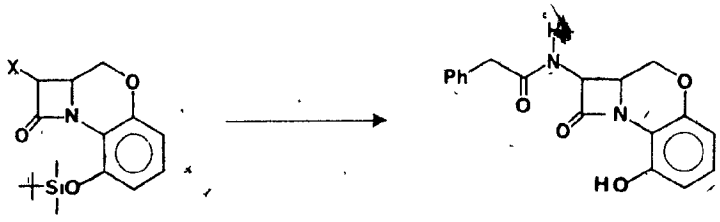
73 X = Cl

in this series, where the proton resonances did not overlap. The presence of the β-lactam, in 70, manifested itself as a band at 1770 cm^{-1} in the infrared.

Ozonolysis of 70 in methanol, as was described for 32, followed by sodium borohydride reduction, afforded unidentifiable products, in this instance. On the other hand, when the ozonolysis-reduction of 70 was carried out in ethanol-methylene chloride (4:1), alcohol 71 was

obtained in good yield. The proton on the azide-bearing carbon appeared as a doublet of 5 Hz, indicative of a *cis*-substituted β-lactam. In the infrared, the hydroxyl absorption was evident at 3500, the azide at 2100, and the β-lactam at 1765 cm^{-1}.

Alcohol 71 was smoothly converted into its mesylate 72, by the action of methanesulfonyl chloride-triethylamine at -78°. Facile and virtually instantaneous cyclization of 72 to tricyclic β-lactam 74 was accomplished using 1.05 equivalents of TBAF in tetrahydrofuran at 0°. On account of the high speed of this reaction, the concentration of the fluoride salt had to be known quite accurately, and since the activity of TBAF solutions was found to change with time*, we decided to investigate another fluoride salt[69,79]. Thus, the same transformation of 72 to 74 was achieved in equally high yield using potassium fluoride



74 X = N_3

75 X = NH_2

76 X = $NHCOCH_2Ph$

77

*See Experimental section, p. 101.

and one-third equivalent of 18-crown-6 in acetonitrile. Unlike cyclizations with TBAF, excess potassium fluoride could be used, since the reaction was complete only after 6 to 8 hours, thus allowing for very effective monitoring.

Subsequently, azide 74 was reduced to amino azetidinone 75 in the customary manner. The structure of this easily crystallized amine 75 was in accordance with all spectral and analytical data. The pmr spectrum (p. 51) of 75 was nearly first order at 200 MHz, and the parent ion was discernible in the mass spectrum (p. 52). Acylation of 75 with phenylacetyl chloride afforded amide 76 in high yield. Infrared analysis of 76 revealed β-lactam and amide bands at 1780 and 1670 cm^{-1}, respectively, and its high field pmr spectrum (p. 53) was easily interpretable.

Ultimately, β-lactam 76 was deprotected using TBAF in cold tetrahydrofuran, affording phenol 77 in 52% yield. The β-lactam absorption of 77, in acetonitrile, was recorded at 1760 cm^{-1}. This was considerably higher than 1720 cm^{-1}, found for bicyclic β-lactam 37, also in acetonitrile. Thus, the third ring had indeed conferred additional strain to the β-lactam nucleus, as expected. Phenol and amide bands were also present in the infrared of 77 at 3280 and 1655 cm^{-1}, respectively. The familiar pattern of proton resonances was observed in the pmr spectrum (p. 54), and a significantly strong parent ion was detected in its mass spectrum (p. 55).

Having synthesized β-lactam 77, we selected to investigate a slightly different approach (72 or 73 → 78 or 79 → 77) to its synthesis, in the event that an additional substituent on the aniline ring would

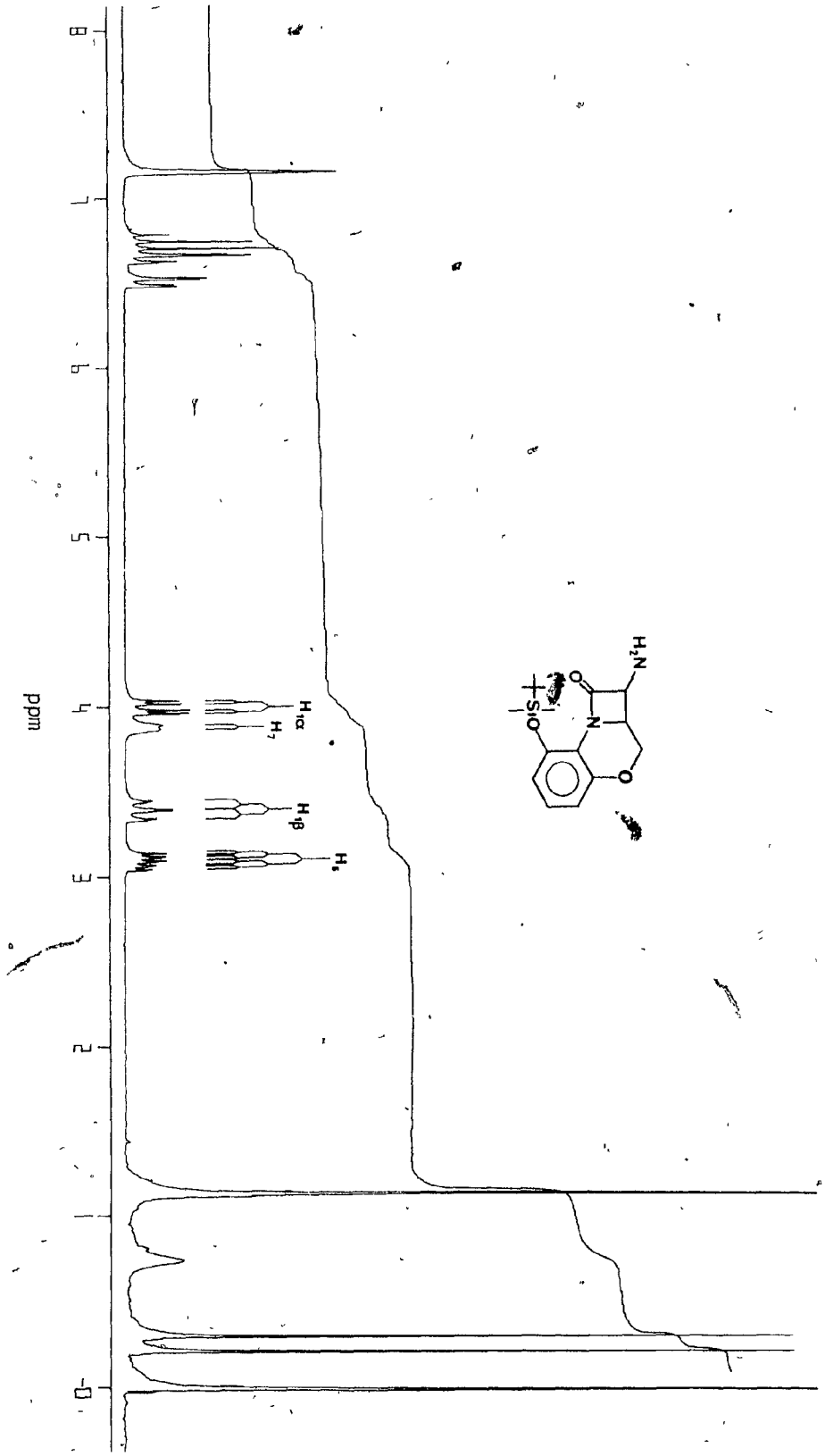


Fig. 10. 200 MHz pmr spectrum of 75, in C_6D_6.

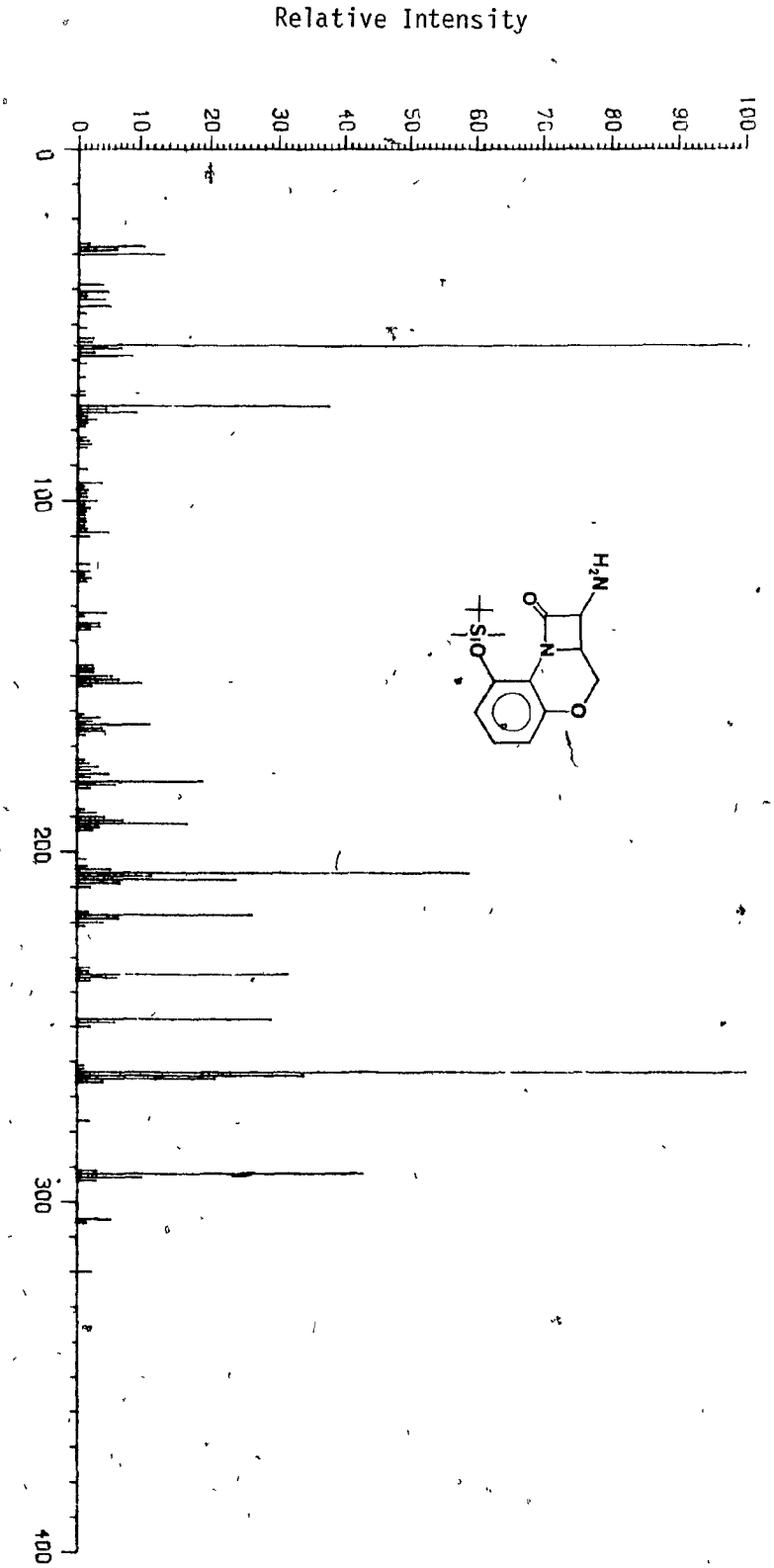


Fig. 11. Mass spectrum of 75.

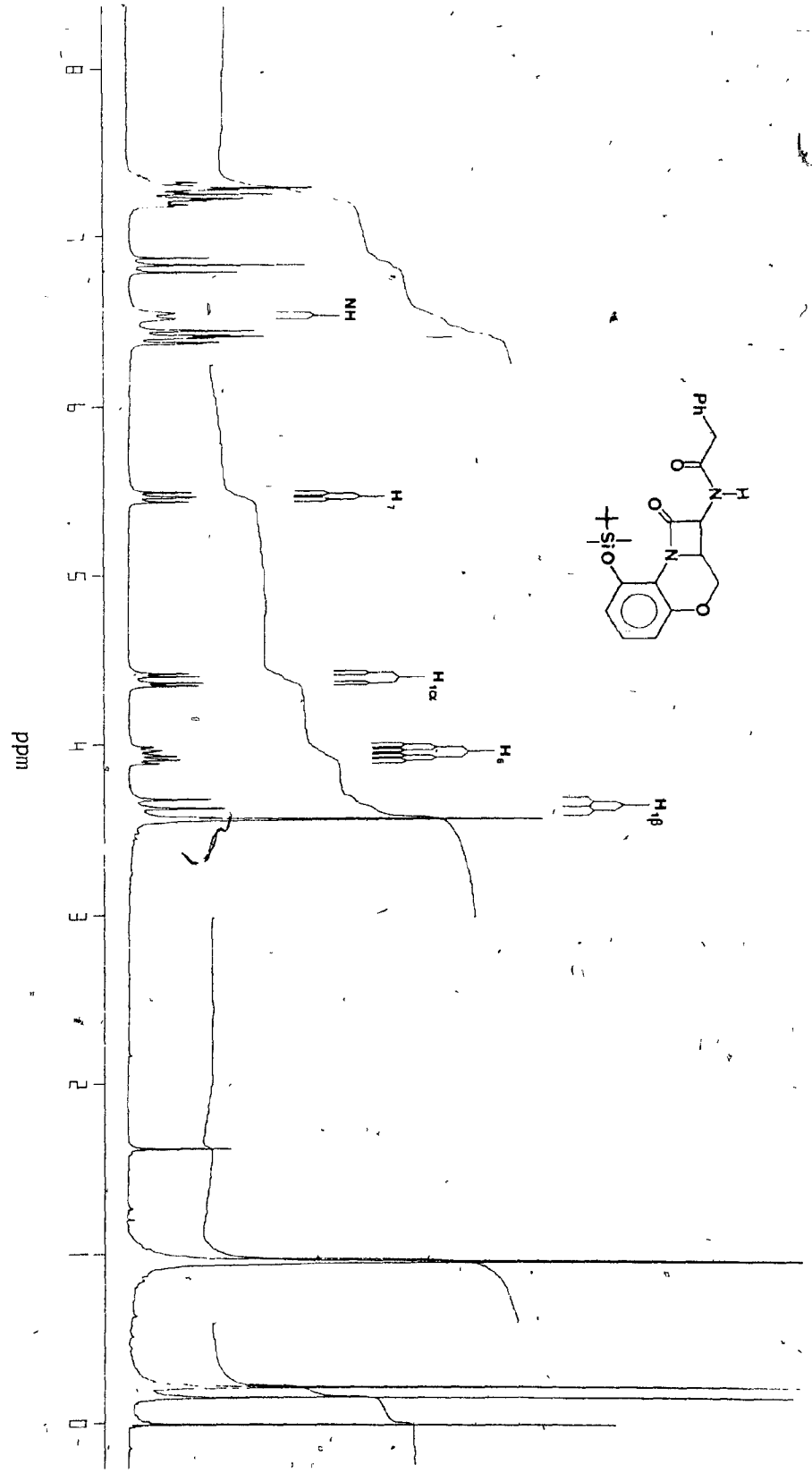


Fig. 12. 200 MHz pmr spectrum of 76, in $CDCl_3$.

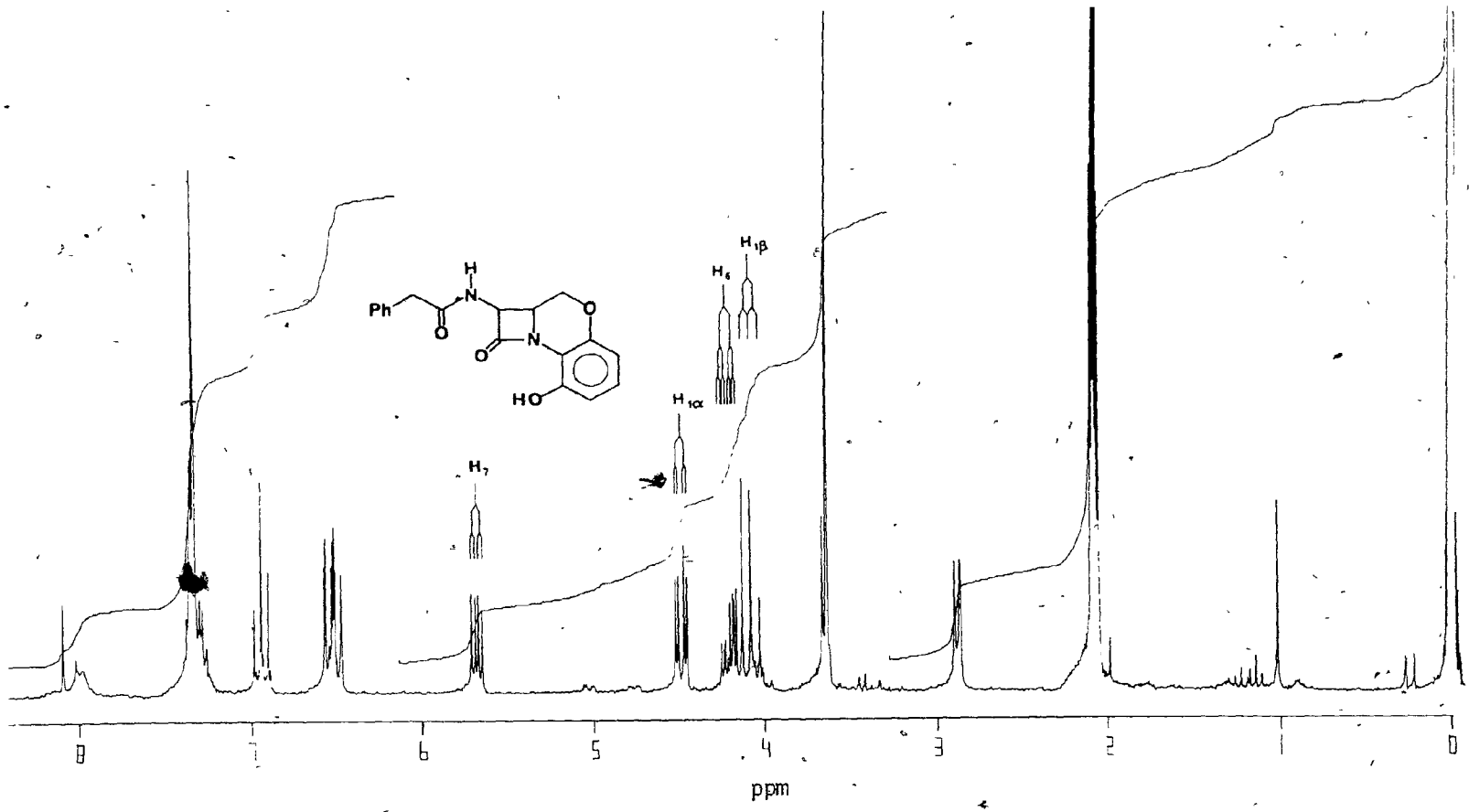


Fig. 13. 200 MHz pmr spectrum of 77, in acetone d_6.

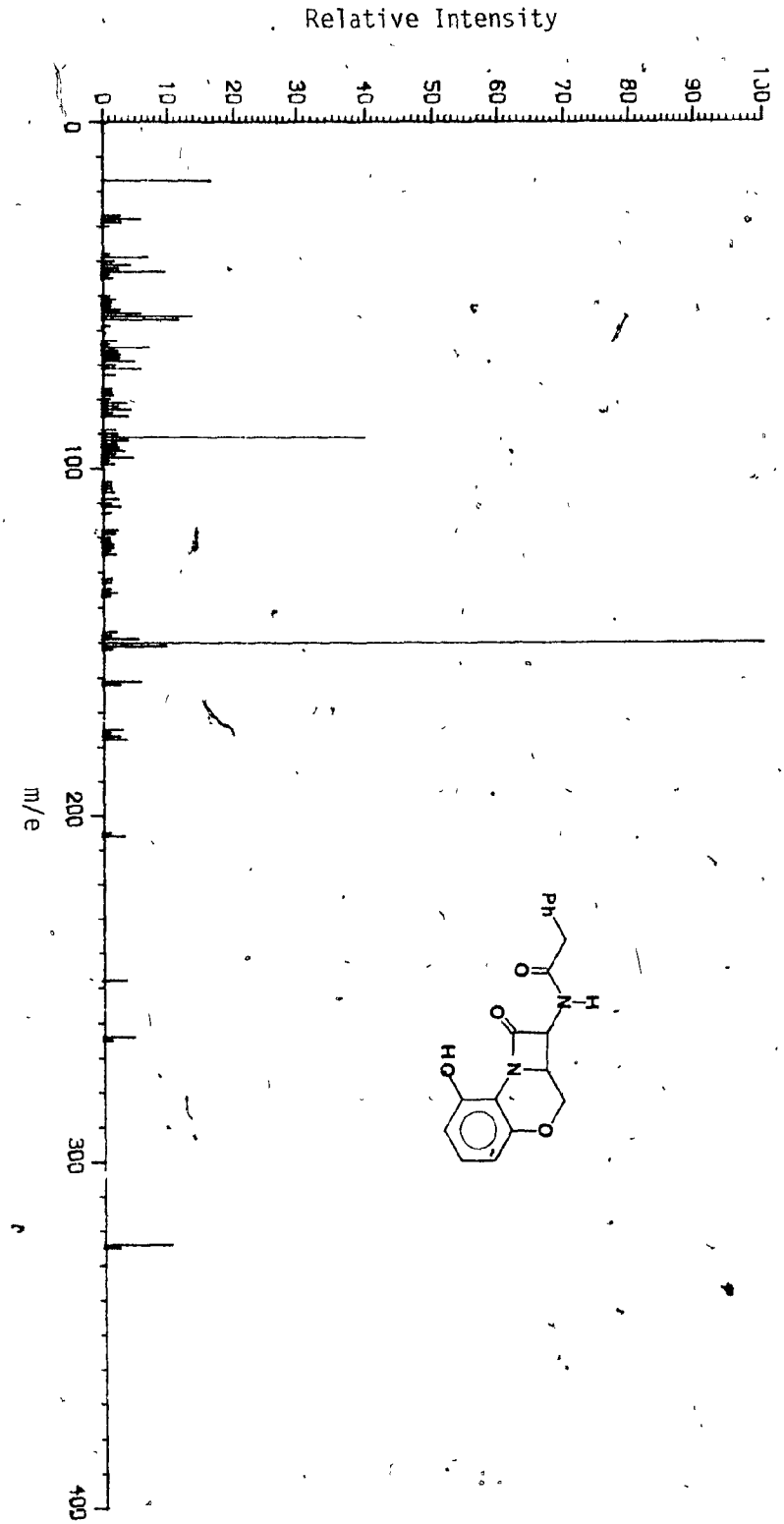
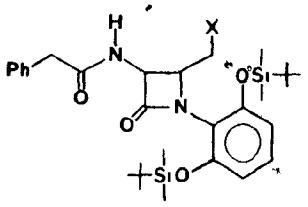


Fig. 14. Mass spectrum of 77.

require formation of the strained tricyclic structure at the latest possible stage. A nitro substituted aniline would require such a synthetic route, being on its own quite destabilizing to the system (Chapter I). In addition, it may also be possible to form the tricyclic framework and deprotect the remaining phenol in one operation.

To this end, we chose to attach the acylamino side-chain to β-lactam 71 prior to the construction of the final ring. Since the hydroxymethyl group on 71 would have had to be protected and since the corresponding chloride and mesylate had been previously prepared, we attempted the reduction-acylation on 72 and 73 (p. 48).

Therefore, mesylate 72 was treated with hydrogen sulfide-triethylamine and directly acylated, in the usual manner, affording amide mesylate 78 in good yield. Similarly, chloride 73 was easily



72 → 78 X = OMs

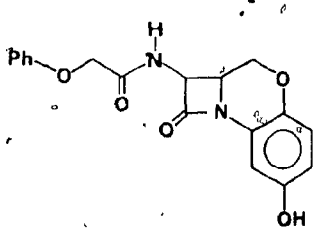
73 → 79 X = Cl

→ 77

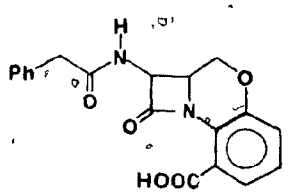
transformed into amide 79. When mesylate 78 was treated with potassium fluoride and a catalytic amount of 18-crown-6 in acetonitrile, only a

small quantity of β-lactam 76 was isolated from a mixture of unidentifiable products. Reaction of chloride 79 under similar conditions also afforded unidentifiable products, as did treatment of 79 with cesium fluoride in acetonitrile. On the other hand, when mesylate 78 or chloride 79 were reacted with TBAF in cold tetrahydrofuran, tricyclic β-lactam 77 was obtained in 55 and 48% yield respectively. It seemed therefore that the reaction conditions, when using cesium or potassium fluoride, unlike TBAF, were incompatible with the secondary amide function in 78 or 79, under the conditions described.

Phenol 77 showed weak activity only against two sensitive microorganisms. *Staphylococcus aureus* Q74-1 and *S. lutea* PCI-1001, both Gram-positive species, were inhibited at concentrations of 128 and 64 μg/mL of 77, respectively. Whilst this work was in progress, Doyle[80] reported the synthesis of weakly active 80a, which had a β-lactam band at 1780 cm^{-1}. Dr. Zamboni found[69,79] that the related carboxylic acid 80b, which also showed a β-lactam band at 1780 cm^{-1}, was totally devoid of activity toward a variety of bacteria. These results indicated that perhaps our initial hypothesis, on the spatial arrangement of the acidic function, was valid. It was unfortunate that the nitro derivative 63 (p. 45) proved to be too unstable for testing or further manipulation. Perhaps the replacement of the nitro function in 63 by a less electron-withdrawing group would produce an interesting compound.



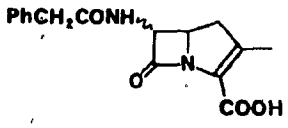
80a



80b

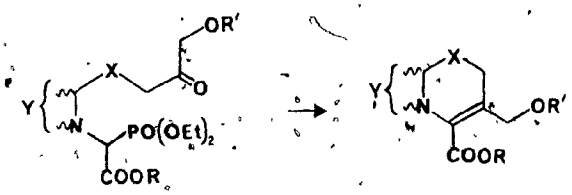
CHAPTER III

This chapter will deal with studies toward the synthesis of thienamycin analogs of the type G. This work was initiated by a colleague, Dr. R. Zamboni[69]. It was based on a cyclization scheme utilized by Christensen in the synthesis of cephalosporin-type antibiotics (Scheme 1, see also Introduction, p. 23)[52b,53,54,81]. This



G

type of intramolecular condensation, producing the carbapenem framework in G, would be the key step in our approach (Scheme 2, p. 59). The



X = CH_2 Y = β-lactam

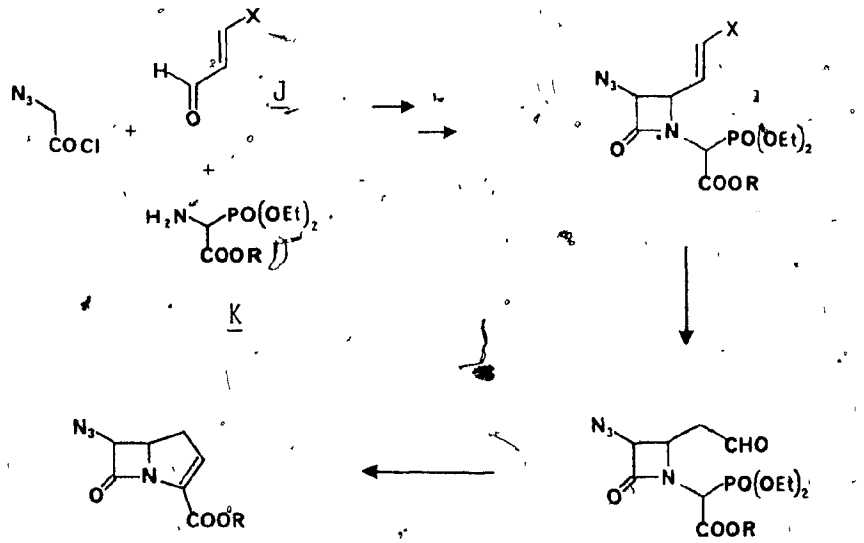
X = O Y = β-lactam

X = S Y = Schiff base

Scheme 1

synthesis of the key intermediate L was designed from three distinct fragments. The β-lactam ring would be constructed using the familiar

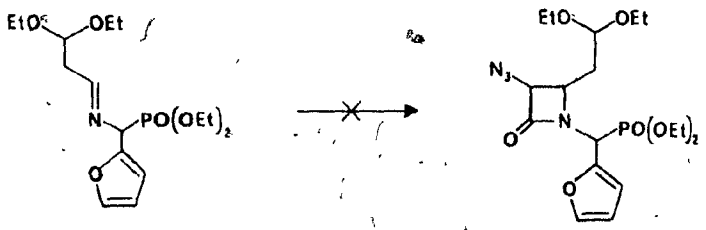
reaction of azidoacetyl chloride with a Schiff base. The imine, in turn, would be formed through condensation of an α-amino α-phosphonoester K



Scheme 2

with a substituted acrolein J, which would later be unraveled to the carbonyl function just prior to cyclization. A convenient preparation of α-amino α-phosphonoesters was developed by Dr. Hakimelahi[82] in our laboratory. It consisted in the addition of a dialkyl phosphite to the Schiff base formed from a glyoxylate and benzylamine, followed by deprotection of the amine. Our aim was to develop a β-substituted acrolein, which after β-lactam formation and rearrangement would yield a carbonyl function one methylene removed from the ring, as in L. An acrolein residue seemed necessary, since an analog lacking the double

bond failed to produce significant amounts of β-lactam, when the corresponding Schiff base 81 was treated with azidoacetyl chloride, whereas the cinnamylidene imine afforded a good yield of β-lactam[69].

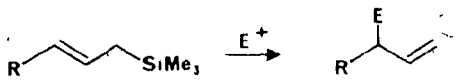


81

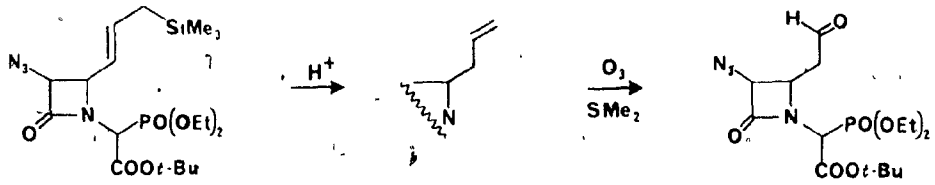
SILICON IN β-LACTAM SYNTHESIS

Recently, Fleming[83] reported that treatment of allylsilanes with electrophiles gave substitution products M, with loss of the silyl function and shift of the double bond. We envisaged that such a transformation might be useful in our synthesis. Conversion of N to O by treatment with acid followed by ozonolysis-dimethyl sulfide reduction should give the desired aldehyde P. Thus, our primary goal was the synthesis of aldehyde 83.

Reports[84-86] of transformations of various allenic ethers to α,β-unsaturated aldehydes prompted us to investigate this approach. Hence, 1,1-diethoxy-2-propyne[87] was reacted with trimethylsilylmethylmagnesium chloride[88] in the presence of copper(I) bromide to afford allenic ether 82 in good yield. This allene was found to be quite unstable, even when stored at -20°. Treatment of 82 with p-toluenesulfonic acid

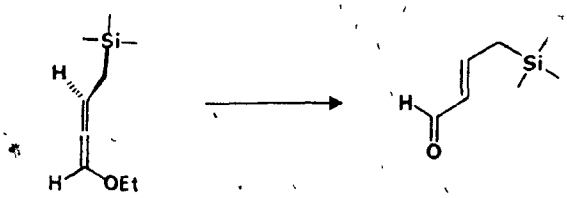


M



N O P

(p-TsOH) in moist ether or with hydrochloric acid in THF-water gave unidentifiable products. Attempted cleavage of the ethyl ether function

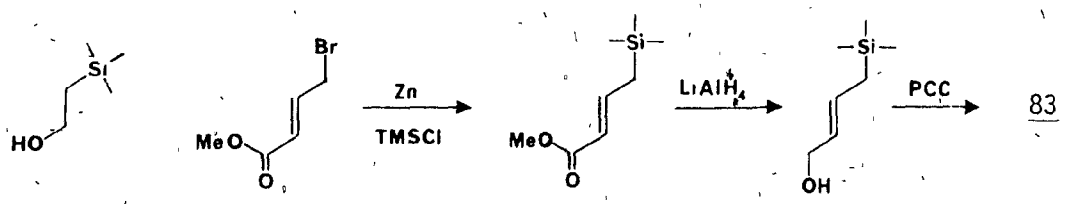


82 83

with trimethylsilyl iodide yielded similar results. Consequently, we opted to follow a different approach.

Based on the preparation of the carboxylic acid protecting group 84[89], we engaged in the synthesis of the vinylogous analog 86,

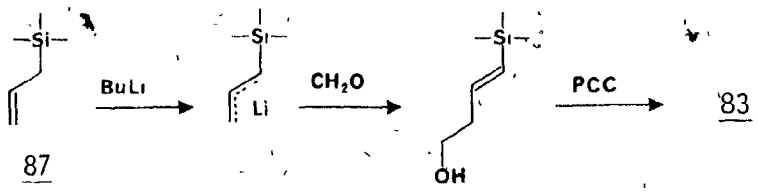
which should be easily oxidized with pyridinium chlorochromate (PCC) to α,β-unsaturated aldehyde 83. Unfortunately, attempts to trap the



84 85 86

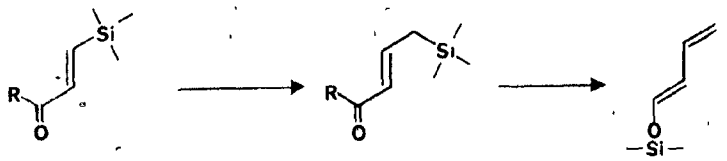
known Reformatsky reagent[90], prepared from methyl 4-bromocrotonate and zinc, with Me_3SiCl afforded several products inseparable by distillation. The desired compound 85 was not detected in the pmr spectrum of the crude material, as evidenced by the lack of a methylene signal at about 2 ppm. Consequently, this scheme was abandoned.

Allyltrimethylsilane (87) is easily metallated by butyllithium and the resulting species is known to react from the γ position exclusively, with carbonyl electrophiles[91,92]. We planned to use formaldehyde as the electrophile to obtain alcohol 88, which upon treatment with PCC should undergo both oxidation to the aldehyde and double-bond migration giving 83. However, when gaseous formaldehyde, obtained from the pyrolysis of paraformaldehyde[93], was bubbled through a solution of lithiated allyltrimethylsilane, only polymeric and unidentifiable products were recovered.



87 88 83

We then became interested in an observation made by Cunico *et al.*, who found that β-trimethylsilyl-α,β-unsaturated ester 89 reacted with diazomethane resulting in the stereospecific formation of homolog 91[94]. We chose to perform this homologation on the aldehyde counterpart of 89, namely compound 90. Thus, treatment of aldehyde 90[69] with ethereal diazomethane produced a practically instantaneous reaction (according to gc monitoring) and a vigorous evolution of nitrogen was observed. The



89 R = OMe 91 R = OMe 92

90 R = H 83 R = H

pmr spectrum of the crude reaction mixture was consistent with the structure of desired aldehyde 83. Bands at 1680 and 1630 cm^{-1} in the infrared also indicated the presence of an α,β-unsaturated aldehyde. When purification by distillation was attempted, no 83 was detected in the distillate. Instead, 83 was found to rearrange thermally to 1-trimethylsilyloxy-1,3-butadiene (92). Preliminary attempts to condense crude 83 and benzylamine, with magnesium sulfate in methylene chloride, indicated that the Schiff base was formed, according to infrared analysis. The band at 1680 cm^{-1} disappeared as an imine band at 1650 cm^{-1} appeared. Treatment of this crude Schiff base with azidoacetyl chloride afforded unidentifiable and inseparable products. Nonetheless, the presence of a β-lactam could be inferred by a weak absorption at 1750 cm^{-1}.

At this point, we decided to prepare the, hopefully, more stable t-butyldimethylsilyl derivative of 83. Thus, the readily available tetrahydropyranyl (THP) propargyl ether 93 was easily converted into silyl alkyne 94 and the THP function smoothly removed to give 95. Reduction of the triple bond using $LiAlH_4$, followed by oxidation of the allylic alcohol thus generated, gave α,β-unsaturated aldehyde 96. Homologation of 96 using ethereal diazomethane gave a virtually instantaneous reaction, as with 90, accompanied by evolution of nitrogen. Fortunately, aldehyde 97 was distillable, without thermal rearrangement to a silyloxybutadiene, and it could also be purified by flash chromatography*.

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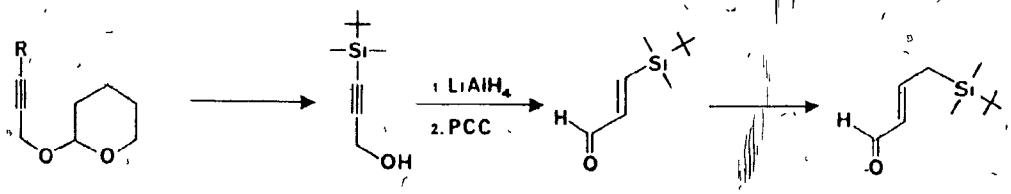
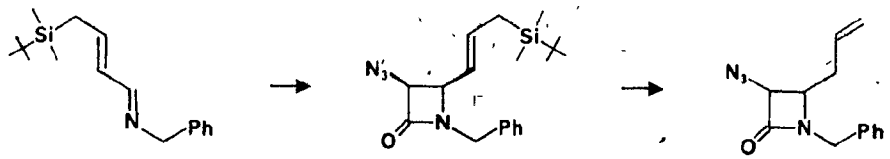
*See General Experimental, p. 99.



93 R = H

94 R = TBDMS

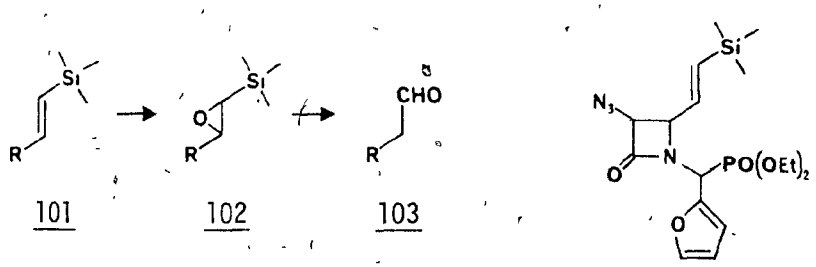
95 96 97



98 99 100

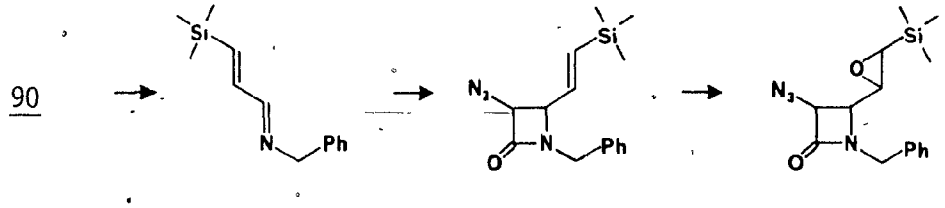
As a model, we chose to construct the simple N-benzyl β-lactam 99. Therefore, 97 was condensed with benzylamine to give Schiff base 98, which, when treated with azidoacetyl chloride-triethylamine at room temperature afforded *cis* β-lactam 99 exclusively. β-Lactam 99 was found to resist overnight treatment with either two equivalents of HBr or excess HF in aqueous THF. It was also recovered unchanged after stirring for one hour in aqueous THF containing HI. The yellow color formed during this reaction was found to occur from the interaction of HI and THF. β-Lactam 99 also withstood overnight reflux in benzene with an equivalent of pyridinium p-toluenesulfonate. When 99 was exposed to hydrogen bromide in methylene chloride or benzene for 10 minutes, a decrease in the β-lactam ir absorption relative to the azide band was noticed. One equivalent of trifluoroacetic acid (TFA) in carbon tetrachloride did not affect 99. When five equivalents were used, the disappearance of starting material required overnight reaction and the resulting mixture lacked the silyl group and a β-lactam band, but showed an amide absorption at 1670 cm^{-1}. It thus seemed that, protonation of 99 occurred preferentially on the β-lactam (amide) rather than the allylsilane.

We then decided to reinvestigate an alternate approach, initiated by Dr. Zamboni, for the generation of aldehyde P. The basis for this scheme was the known transformation of epoxysilanes 102 to aldehydes 103. Stork found[95] that epoxidation of vinylsilanes 101 to 102 with m-CPBA, followed by treatment with acid afforded good yields of



101 102 103 104

aldehydes 103. Attempts to epoxidize 104 under various conditions had failed to yield any epoxysilane[69]. Steric hindrance of the double bond was thought to be responsible for the inertness of 104. Initially, we chose to use a slightly less crowded model as substrate for our epoxidation attempts. Thus, previously-prepared aldehyde 90 was condensed with

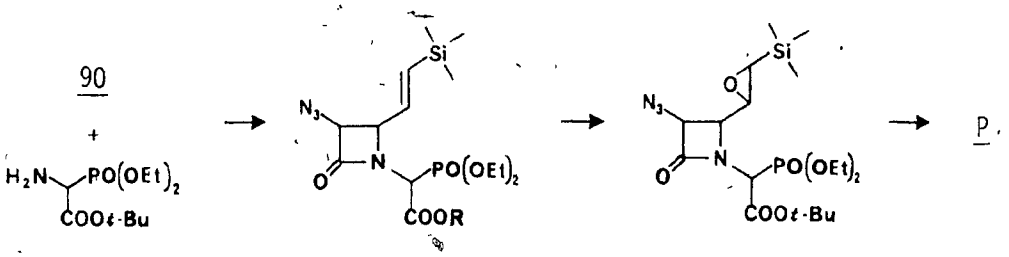


105 106 107

benzylamine and the resulting Schiff base 105 was treated with azidoacetyl chloride-triethylamine affording β-lactam 106, in good yield. The β-lactam absorption of 106 was found at 1765 cm^{-1} and the stereochemistry

of the ring proved to be *cis*, as determined by a coupling constant of 5 Hz. The stereochemistry of β-lactam 104 had not been determined, but was most likely *cis* by analogy with 106. Epoxidation of 106 with m-CPBA in methylene chloride or refluxing chloroform[96] failed to produce any epoxysilane 107. Similar reactions using ethyl ether, in which m-CPBA is considerably more soluble, were ineffectual in causing the desired transformation.

Unable to obtain epoxysilane 107 using model 106, we chose to pursue our original goal (Scheme 2, p. 59), where deprotection of the carboxyl function in 109 would permit the use of the free acid in 110 for



108 109 R = t-Bu 111

110 R = H

the intramolecular epoxidation of the vinylsilane using peracid. Thus, amine 108, prepared according to the modified procedure of Dr. Hakimelahi[82], was reacted with aldehyde 90, in the usual way, affording a good yield of β-lactam 109. The azide, β-lactam and ester functions

were readily identified in the ir spectrum of 109, at 2100, 1775 and 1740 cm^{-1}, respectively. The stereochemistry of the β-lactam ring could not be determined at this stage due to the overlap of signals in the pmr spectrum of 109.

Treatment of 109 with a large excess of m-CPBA in ether for three days failed to epoxidize the vinylsilane. Reaction of 109 and 3,5-dinitroperoxybenzoic acid[97] in methylene chloride produced a complex mixture of products*. We then moved to similar studies on the free carboxylic acid 110. Thus, cleavage of the t-butyl ester in 109 was found to proceed very smoothly using 30% trifluoroacetic acid in methylene chloride for three hours. The resulting acid 110 was found to be unstable to m-CPBA in ether and to 90% hydrogen peroxide-trifluoroacetic anhydride[98] in methylene chloride. In both cases, evolution of gas was observed, perhaps from the decarboxylation of 110.

Fortuitous inspection of a refrigerated sample of 106, which had been treated with m-CPBA, then evaporated and stored, revealed the major product to be epoxysilane 107. The pmr spectrum (p. 70) showed a nearly equal presence of two diastereomers 107, having *cis*-substituted β-lactam rings. A base peak at m/e 317 in the CI-ms was consistent with the structure of 107, and the presence of a β-lactam was indicated by a band at 1765 cm^{-1} in the ir. This observation suggested to us that, the concentration of the solution during the epoxidation was very important, and should be as high as possible.

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*However, signals at about 2 ppm, characteristic of epoxysilane protons, were visible in the pmr of the crude material.

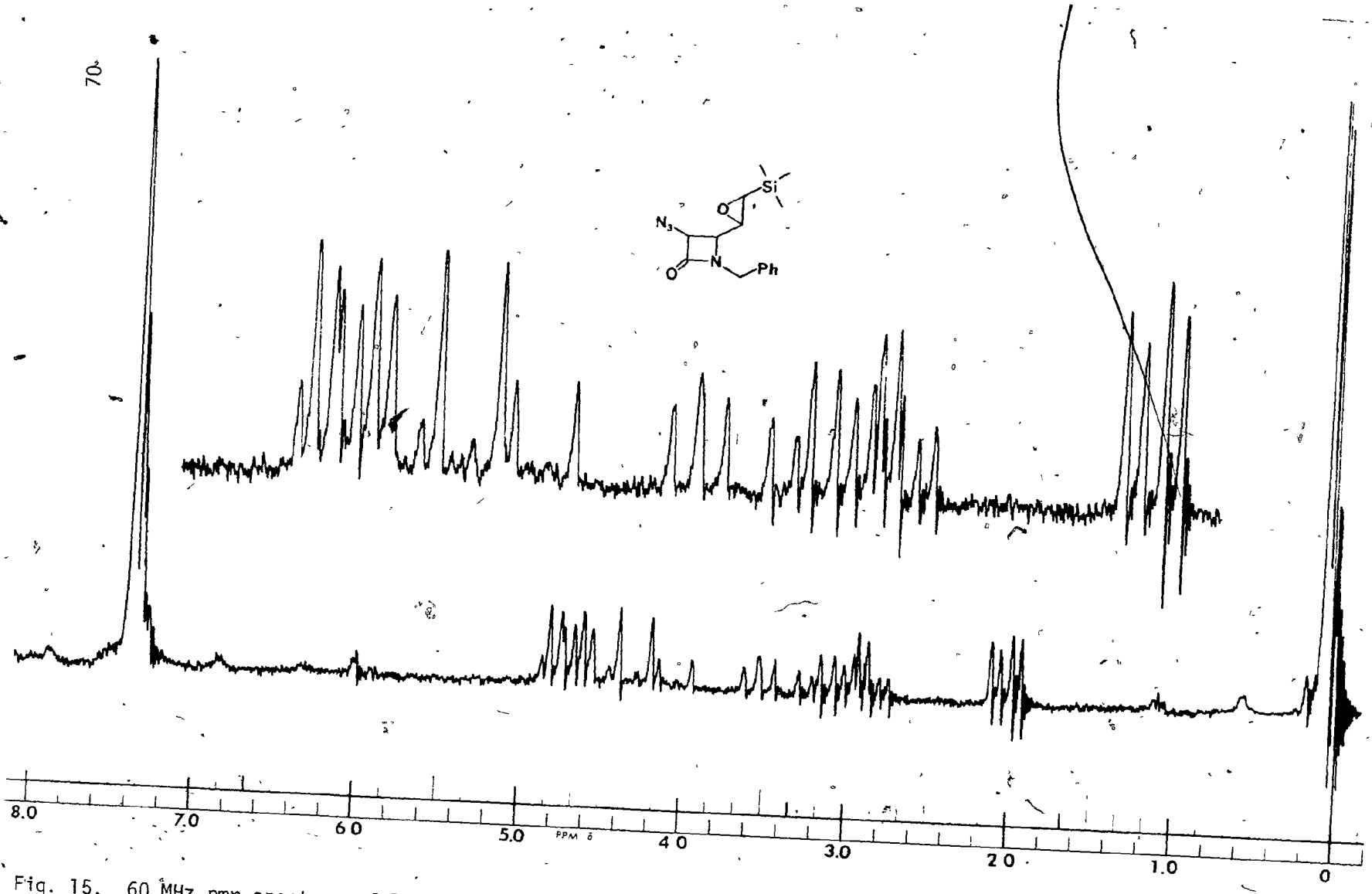


Fig. 15. 60 MHz pmr spectrum of 107, in $CDCl_3$.

Accordingly, an ethereal solution of 110 and m-CPBA was concentrated until viscous and reacted at 40° overnight to afford a 90% yield of epoxysilane 111. Although 111 could be separated into two fractions of very similar polarity by flash chromatography, each fraction was found to be composed of two diastereomers, as established by pmr.

Several attempts were made to rearrange epoxysilane 111 to aldehyde P, directly or through some intermediate species, such as an enol acetate or acetal (Fig. 16). Under weakly acidic conditions (acetic

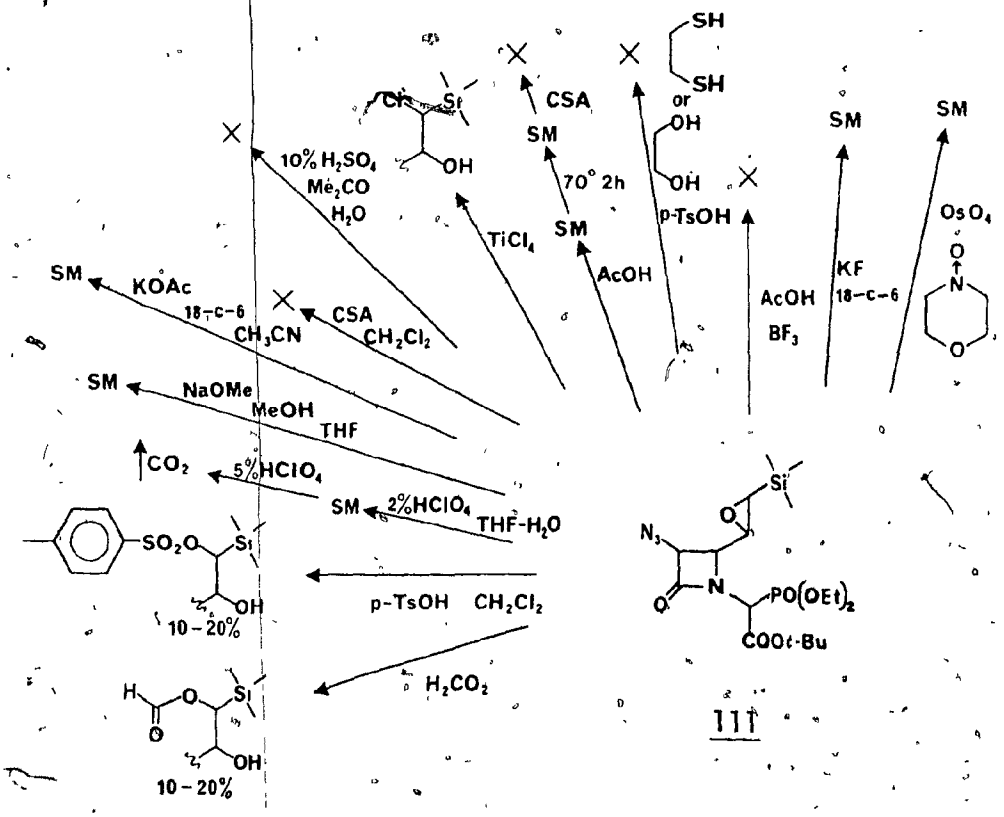
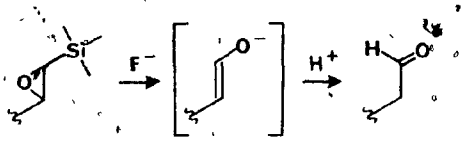


Fig. 16. Reactions carried out on epoxysilane 111. SM = starting material.

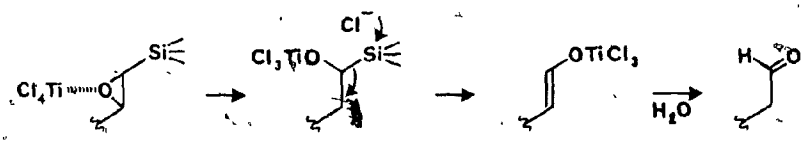
acid or 2% $HClO_4$ in THF-H_2O) 111 was recovered unreacted. When more acidic conditions (AcOH-BF_3, camphorsulfonic acid, or 5% $HClO_4$) were used, unidentifiable products were obtained. Two exceptions to these observations were found. Both formic and p-toluenesulfonic acids added to 111, in low yield reactions, to give the hydroxy esters shown in Fig. 16 (p. 71).

The treatment with KF - 18-crown-6 was based on the premiss that epoxysilanes rearrange to the aldehyde through an intermediate enolate[95,99]. However, Chan *et al.*[96] found that fluoride ion does not

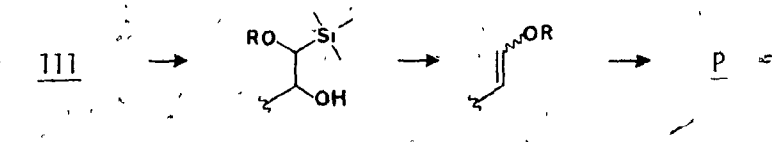


convert epoxysilanes into enolates but rather into epoxy anions. In any event, we were unable to obtain any reaction with KF - 18-crown-6.

The use of the strong Lewis acid $TiCl_4$ to cleave epoxysilanes is founded on the well-known stability of cations β to silicon[100]. We expected that such a cation, formed with $TiCl_4$, would react with chloride ion, as shown, to give the enolate. Instead, a low yield of the corresponding α-chloro-β-hydroxysilane was obtained. Recently, it was shown that epoxysilanes undergo regio- and stereospecific α-opening by a variety of nucleophiles, under acidic or basic conditions[101,102].



We then attempted to open epoxysilane 111 with KOAc - 18-crown-6 or NaOMe, hoping to obtain the respective α-acetoxysilane 112 or

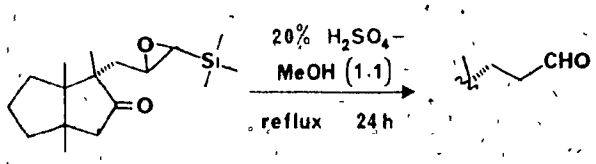


112 R = Ac 114 R = Ac

113 R = Me 115 R = Me

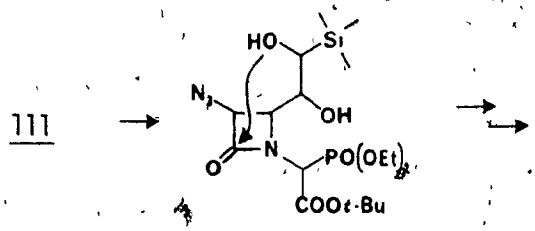
α-methoxysilane 113. Elimination of these β-hydroxysilanes under acidic or basic conditions[102] should then give the corresponding enol acetate 114 or enol ether 115, both of which may be hydrolyzed to the desired aldehyde P. Unfortunately, 111 resisted treatment with either KOAc - 18-crown-6 or NaOMe.

A rather unreactive epoxysilane 116 was recently reported by Paquette[103]. Transformation of 116 to the corresponding aldehyde was achieved using vigorous conditions. α,β-Dihydroxysilanes were found to



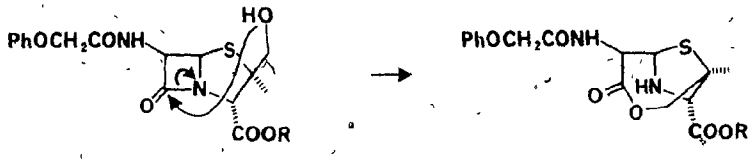
116

be intermediates in the conversion of epoxysilanes to aldehydes[101e,f]. Perhaps when sufficiently acidic conditions were used, 111 was indeed transformed to diol 117, but under such circumstances, continued to react

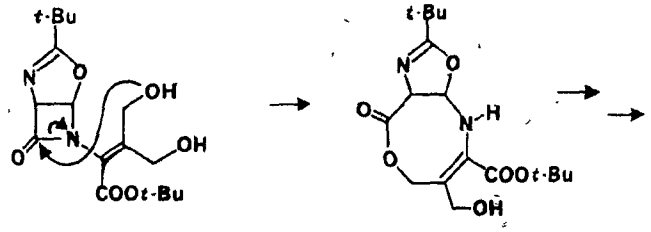


117

through an undesirable pathway. Such incidents are not uncommon. β-Lactam 118, for instance, was found unstable to silica gel chromatography, giving lactone 119[104]. Diol 120 was shown to undergo rearrangement to lactone 121 followed by further reaction[105].



118 119

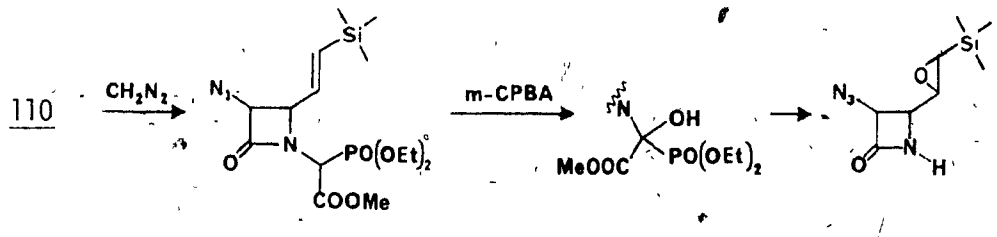


120 121

We next attempted to prepare diol 117 through the reaction of vinylsilane 109 (p. 68) with OsO_4 - N-methylmorpholine-N-oxide[106]. Diol 117, prepared under such non-acidic conditions, could, in principle, be acetylated then eliminated with fluoride ion to obtain enol acetate 114, which we thought should be easily hydrolyzed to aldehyde P. Vinylsilane 109 was, however, totally unreactive to the hydroxylation

with OsO_4 mentioned above.

In a final attempt to prepare the desired aldehyde through an epoxysilane, methyl ester 122 was synthesized from the free acid 110, by treatment with diazomethane. The methyl ester should be less hindering



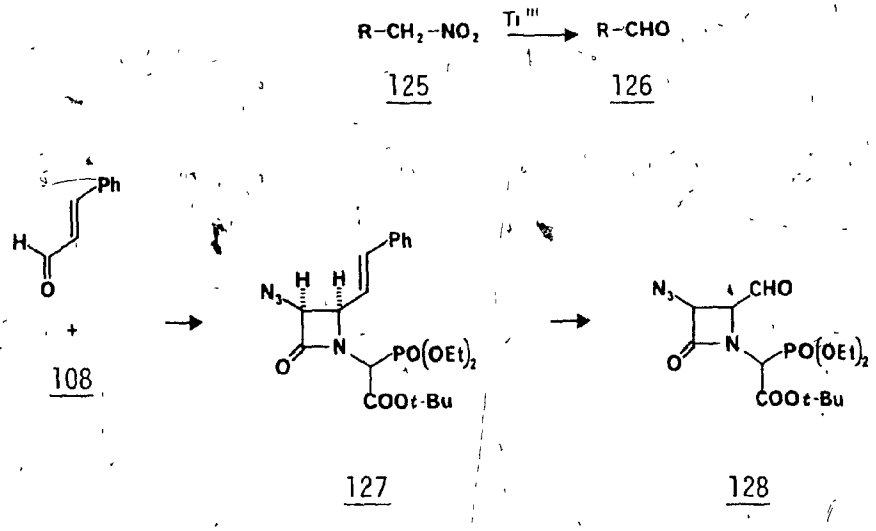
122 123 124

than the t-butyl group and should therefore facilitate hydrolysis of the epoxysilane. Treatment of vinylsilane 122 with m-CPBA, in the usual way, afforded a 47% yield of β-lactam 124. Presumably, 124 was formed through intermediate 123, which may have been formed during the epoxidation of 122. Whether the epoxidation or the hydroxylation occurred first was not determined and the reaction was not pursued.

ALDEHYDE FROM NITROALKANE

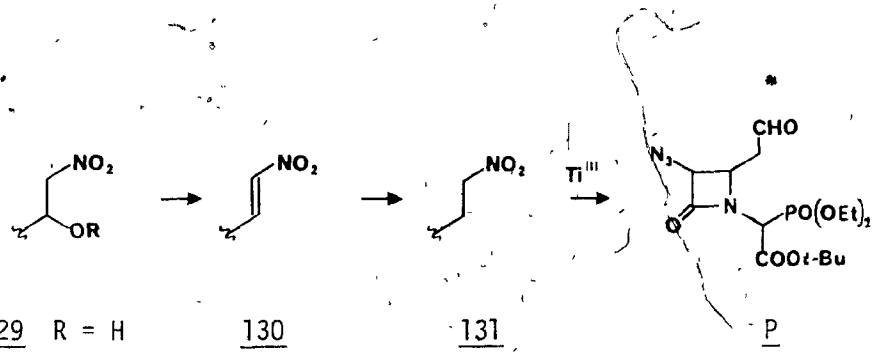
The numerous examples of mild conversions of aliphatic nitro compounds 125 to their corresponding carbonyl containing substances 126, using trivalent titanium[107,108], prompted us to investigate an approach to our desired aldehyde P (p. 61) in which such a transformation would be

applicable. The classical Nef[109] reaction usually employed for this type of conversion was not considered because the β-lactam ring would probably not survive its harshness.



The synthetic plan was to use compound 128, in which the missing carbon unit would be supplied by the addition of nitromethane to the aldehyde, followed by elaboration of the β-hydroxynitroalkane 129 thus generated.

The Schiff base formed by condensation of amine 108 and cinnamaldehyde was treated with azidoacetyl chloride, in the usual way, affording *cis* β-lactam 127, in 78% yield. Ozonolysis of 127 at -78° followed by dimethyl sulfide reduction produced the very easily hydrated



129 R = H 130 131 P

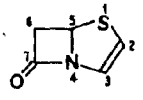
129a R = Ac

aldehyde 128. Dehydration was easily achieved by boiling in benzene using a Dean-Stark trap, after which the aldehyde proton could be easily identified as a clean doublet at 9.38 ppm. Wollenberg and Miller[110] reported a very efficient method for the preparation of saturated nitro compounds from aldehydes by the addition of nitromethane, catalyzed with fluoride ion as base. Using their procedure, nitromethane was condensed with aldehyde 128 in the presence of catalytic amounts of KF - 18-crown-6 forming β-hydroxynitroalkane 129. Acetylation of 129 with acetic anhydride-pyridine and 4-dimethylaminopyridine, as catalyst, afforded nitroolefin 130 contaminated with approximately 5% of the corresponding nitroacetate 129a, contrary to the results of Wollenberg and Miller who isolated only the nitroacetates. Finally, reduction of 130 and the intermediate nitroacetate 129a with methanolic sodium borohydride occurred smoothly affording nitroalkane 131, in 48% yield from 129, after chromatography. Treatment of the sodium salt of 131, prepared using

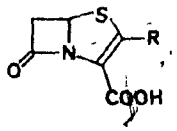
sodium methoxide, with a buffered (pH 5) solution of titanium trichloride[108] produced a multicomponent reaction mixture. The presence of aldehyde P or the corresponding hydrate in the complex mixture could not be determined unequivocally. Consequently, this scheme was abandoned.

2-PHENYLCARBAPENEMS AND PENAMS

In a series of recent publications, Woodward[111] described the synthesis of a new class of β-lactam antibiotics containing the novel penem skeleton Q. We were particularly interested in the biological



Q



S

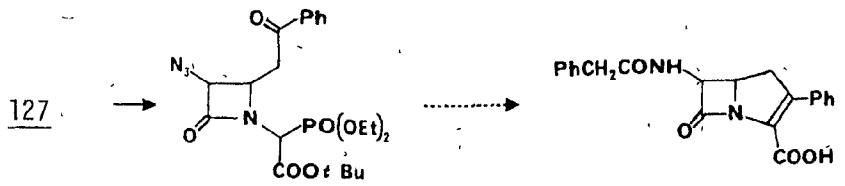
132 R = Ph

Table 6. Minimum Inhibitory Concentrations (MIC) (μg/ml)

	Gram-positive strains					Gram-negative strains				
S	*Staphylococcus aureus* (Smith) 14	*Staphylococcus aureus* 2999 (resistant)	*Streptococcus pyogenes* Aronson/K 1129	*Streptococcus pneumoniae*/111/84	*Neisseria meningitidis*/K 1316	*Haemophilus influenzae* NCIC 4560	*E. coli* 205	*Salmonella typhimurium* 277	*Proteus vulgaris*/K 856	*Pseudomonas aeruginosa*, K 1118
R = CH_3	1	1	0.5	0.5	0.1	4	8	4	8	8
R = phenyl	1	4	0.05	0.1	0.1	4	8	8	4	*b*
R = *n*-pentyl	0.2	2	0.05	0.05	0.05	2	32	16	32	64
cephalexin	1	8	1	1	0.5	32	8	4	128	*a*
penicillin V	0.05	64	0.05	0.05	0.5	4	128	64	*a*	*a*

[a] No inhibition at 128 μg/ml [b] Not measured

activity of compound 132 (Table 6, p. 79). We decided to attempt the synthesis of an analogous compound 134, lacking the sulfur atom and having the usual acylamino side-chain. We thought it might be possible

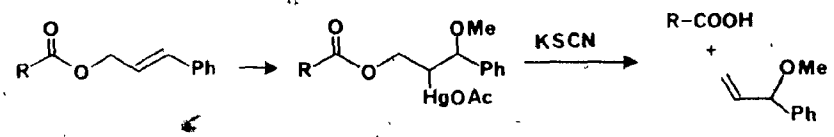


133 134

to achieve this through the base induced cyclization of 133. Although aryl ketones are less reactive than their alkyl counterparts, we hoped the fact that we would be attempting an intramolecular cyclization to form a five-membered ring would counter their diminished reactivity.

The immediate problem was the hydration of the double bond in 127. Brown[112] reported an extremely facile oxymercuration-demercuration of styrene to give 1-phenylethanol in high yield, using mercuric acetate followed by sodium borohydride. Application of this method to 127 should yield the corresponding benzyl alcohol which would then be oxidized to 133. When 127 was added to mercuric acetate in THF-water, the reaction was found to be considerably slower than in the cases reported by Brown; the disappearance of 127 (by tlc) requiring overnight treatment. To our surprise, *in situ* demercuration using alkaline sodium

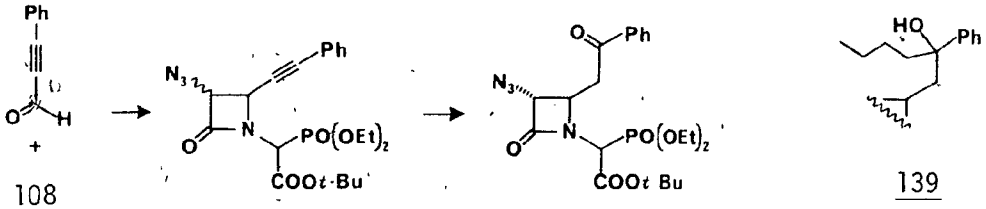
borohydride regenerated almost quantitatively styryl β-lactam 127. Similar results were obtained at 60°. Apparently, a complex was formed but oxymercuration did not occur. The more electrophilic mercuric trifluoroacetate[113] also gave similar results. Corey[114] reported the



135

easy cleavage of cinnamyl esters 135 by oxymercuration with mercuric acetate in methanol containing 0.1 equivalent nitric acid followed by demercuration with KSCN. Oxymercuration of 127 under these conditions followed by treatment with sodium borohydride afforded unreacted 127 and degradation products.

Since the cinnamyl residue in 127 appeared to be quite insensitive to the action of mercuric salts, we proceeded to synthesize the hopefully-more-reactive acetylenic counterpart 136. Consequently, the Schiff base prepared from 108 and readily available phenylpropargyl aldehyde was reacted in the usual manner to afford a one to two mixture of *cis* and *trans* β-lactams 136 and 137, respectively. W.Y. Liu[115] has also successfully prepared several acetylenic β-lactams from Schiff bases of substituted anilines and phenylpropargyl aldehyde. When *cis* β-lactam 136 was treated with mercuric acetate in ethyl acetate according to the procedure of Kagan *et al.*[116], no reaction was observed. When the



108

136 *cis*

137 *trans*

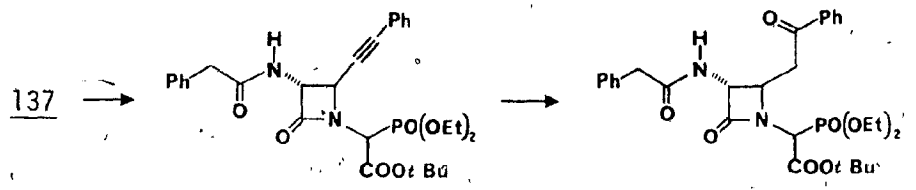
138

139

more electrophilic mercuric trifluoroacetate was used unidentifiable products were obtained, even in the presence of yellow mercuric oxide as acid scavenger. Infrared analysis showed the disappearance of azide and β-lactam bands. On the other hand, treatment of *trans* β-lactam 137 with two equivalents each of mercuric trifluoroacetate and mercuric oxide in wet ethyl acetate followed by exposure to gaseous hydrogen sulfide afforded ketone 138 in good yield. Attempted cyclization of 138 using triethylamine, DBU or sodium hydride produced unidentifiable mixtures, the ir spectra of which showed drastically reduced azide and β-lactam bands. Potassium t-butoxide did not cause any reaction of 138 at -78°, but polar materials were formed on warming to room temperature. Reaction of 138 with n-butyllithium at -78° gave the addition product 139 in 20% yield along with unreacted starting material.

We thought the azide function was perhaps interfering with the

cyclization of 138 and decided to attempt similar reactions on acylamino β-lactam 140. Thus, reduction of azide 137 with hydrogen sulfide-



140 141

triethylamine followed by direct acylation with phenylacetyl chloride gave amide 140. The phenylacetylene residue was smoothly hydrated as before to give phenylketone 141. Attempted cyclization of 141 with potassium t-butoxide at -20° in THF failed to produce the corresponding t-butyl ester of bicyclic β-lactam 134, but gave a rearranged product. The reaction which had occurred, proceeded in two distinct stages. First, a slightly less polar product appeared (by tlc) within 20 minutes, which was then converted to a much less polar material after an additional 20 minutes. Triethylamine also effected the same reaction, although requiring a considerably longer reaction time. One such reaction was quenched midway, with aqueous ammonium chloride. The initially formed product appeared to be 142, according to the spectral evidence. The second and final substance generated under these conditions seemed to be 143, based on pmr (p. 84), ir and mass spectral data.

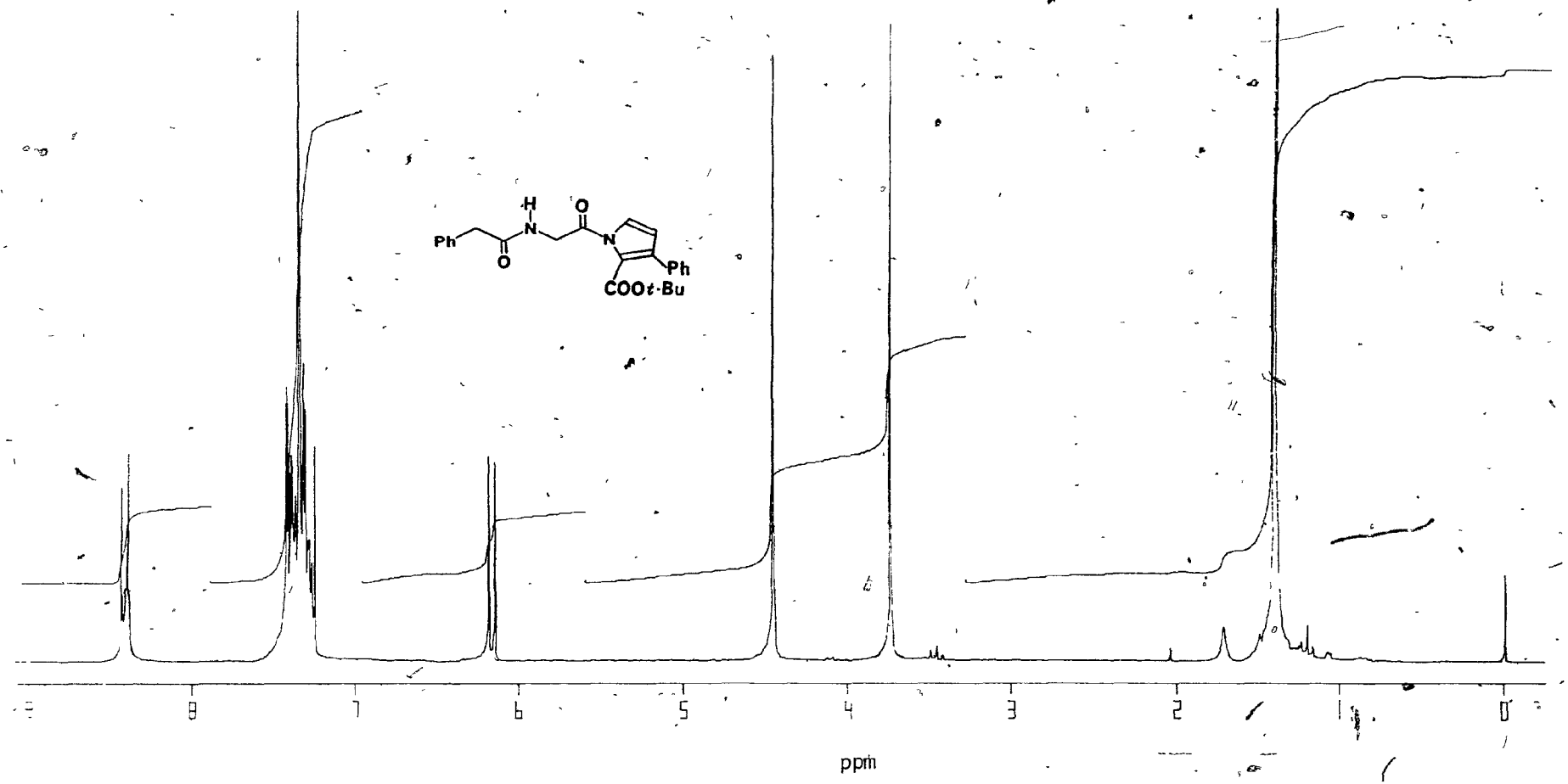
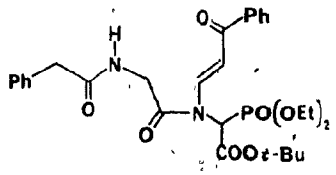
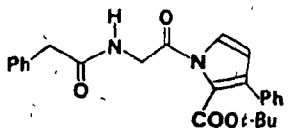


Fig. 17. 200 MHz pmr spectrum of 143, in $CDCl_3$.



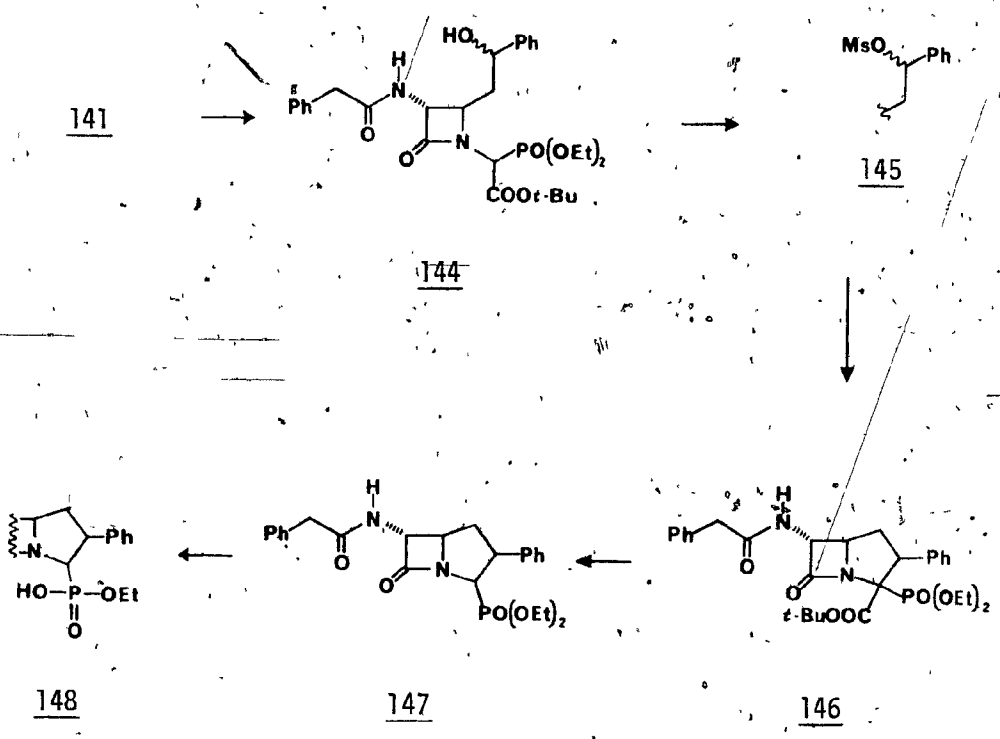
142

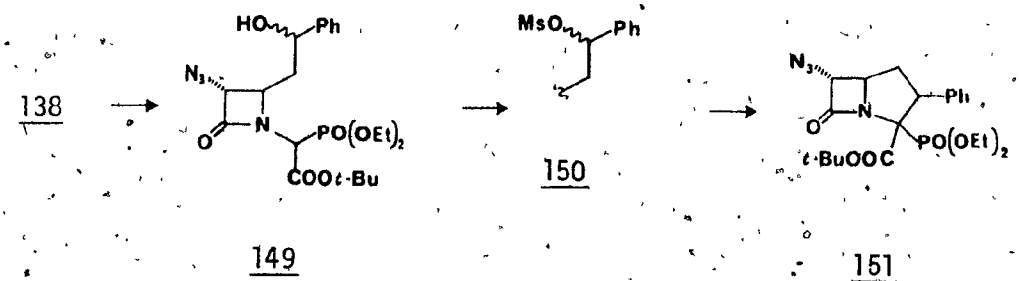


143

It therefore seemed that the facile elimination to 142 would preclude formation of the desired bicyclic system in 134. Thus, we decided to investigate the synthesis of the saturated analog 148, which we thought should not pose similar problems.

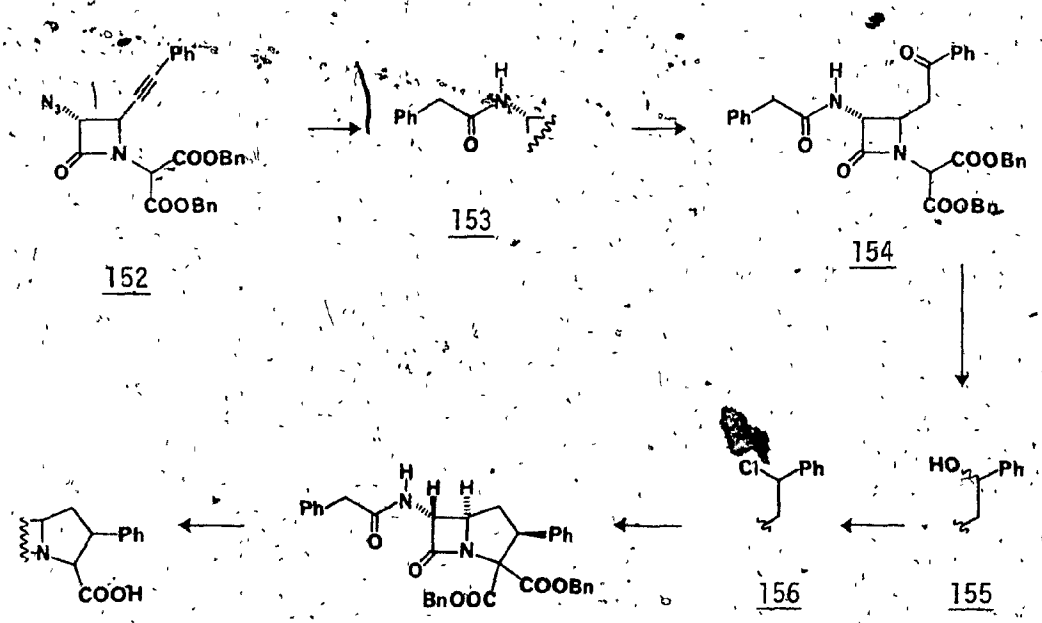
Hydrogenation of 141 at 40 psi using PtO_2 failed to effect reduction of the ketone. Treatment with sodium borohydride supported on alumina[117] gave a multicomponent mixture. Finally, reaction of 141 with sodium borohydride in ethanol afforded 144 in good yield. Mesylation of 144 in the usual way gave mesylate 145 although, prolonged reaction produced the corresponding benzylic chloride. Exposure of mesylate 145 to triethylamine in acetonitrile or to potassium acetate in DMF afforded bicyclic β-lactam 146. The β-lactam ir frequency was found to shift from 1765 to 1780 cm^{-1} upon cyclization of 145 to 146. A similar phenomenon was observed in the azido series upon cyclization of 150 to 151.


141
144
145
146
147
148


138
149
150
151

Unfortunately, preliminary attempts to cleave the t-butyl ester in 146 with 20% trifluoroacetic acid in CH_2Cl_2 also brought about the rupture of the β-lactam ring.

Whilst this work was in progress, Dr. Hakimelahi generously provided us with the very laboriously prepared dibenzyl malonate β-lactam 152[118]. Although only the *trans* compound was used for subsequent transformations, the actual β-lactam formation yielded a roughly one to two mixture of *cis* and *trans* β-lactams. Using 152, we were hoping to



achieve the synthesis of the carboxylic acid analog of 148, namely compound 158. Thus, amide formation in the usual manner afford β-lactam

153. The pmr spectra in the malonate series (p. 89 to 93) were considerably easier to interpret than in the previous phosphonate esters due to the absence of the diethyl phosphonate resonances and the occurrence of fewer diastereomers. Hydration of acetylene 153 followed by reduction of the ketone 154 thus formed gave alcohol 155, as a 4 to 1 mixture of diastereomers. Subsequent transformations were performed on the major, less-polar isomer.

According to results obtained by Dr. Hakimelahi, mesylation of a malonate ester related to 155 with methanesulfonyl chloride-triethylamine gave C-sulfonation, exclusively. However, using pyridine as base he was able to mesylate the alcohol selectively. Consequently, 155 was treated with methanesulfonyl chloride-pyridine. The mesylate corresponding to alcohol 155 was never isolated, since it was transformed to chloride 156, under the reaction conditions. Exposure of 156 to triethylamine in acetonitrile for two days generated bicyclic β-lactam 157. The β-lactam ir frequency of 157 was 1785 cm^{-1}. The pmr spectrum of 157 (p. 93) showed the presence of a single diastereomer, the structure of which was consistent with that depicted.

Decoupling experiments, which permitted assignment of the coupling constants indicated on p. 147, made structure 157 the most likely. For phosphonate 146, which had served to work out the reaction sequence used for the synthesis of 157, this type of assignment had unfortunately not been possible because of the complexity of the signals observed. It may be noted at this point that many of the assignments

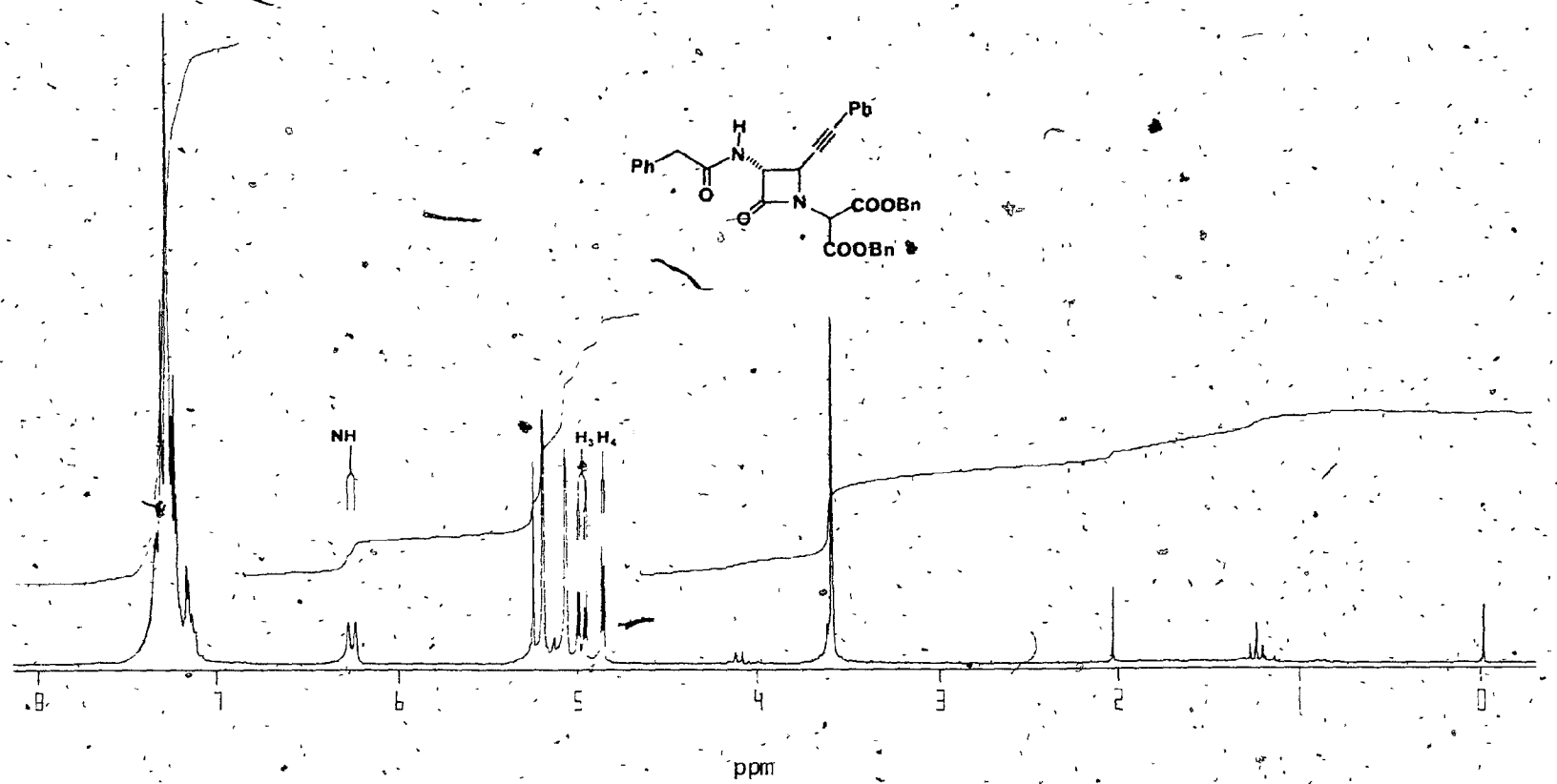


Fig. 18. 200 MHz pmr spectrum of 153, in $CDCl_3$.

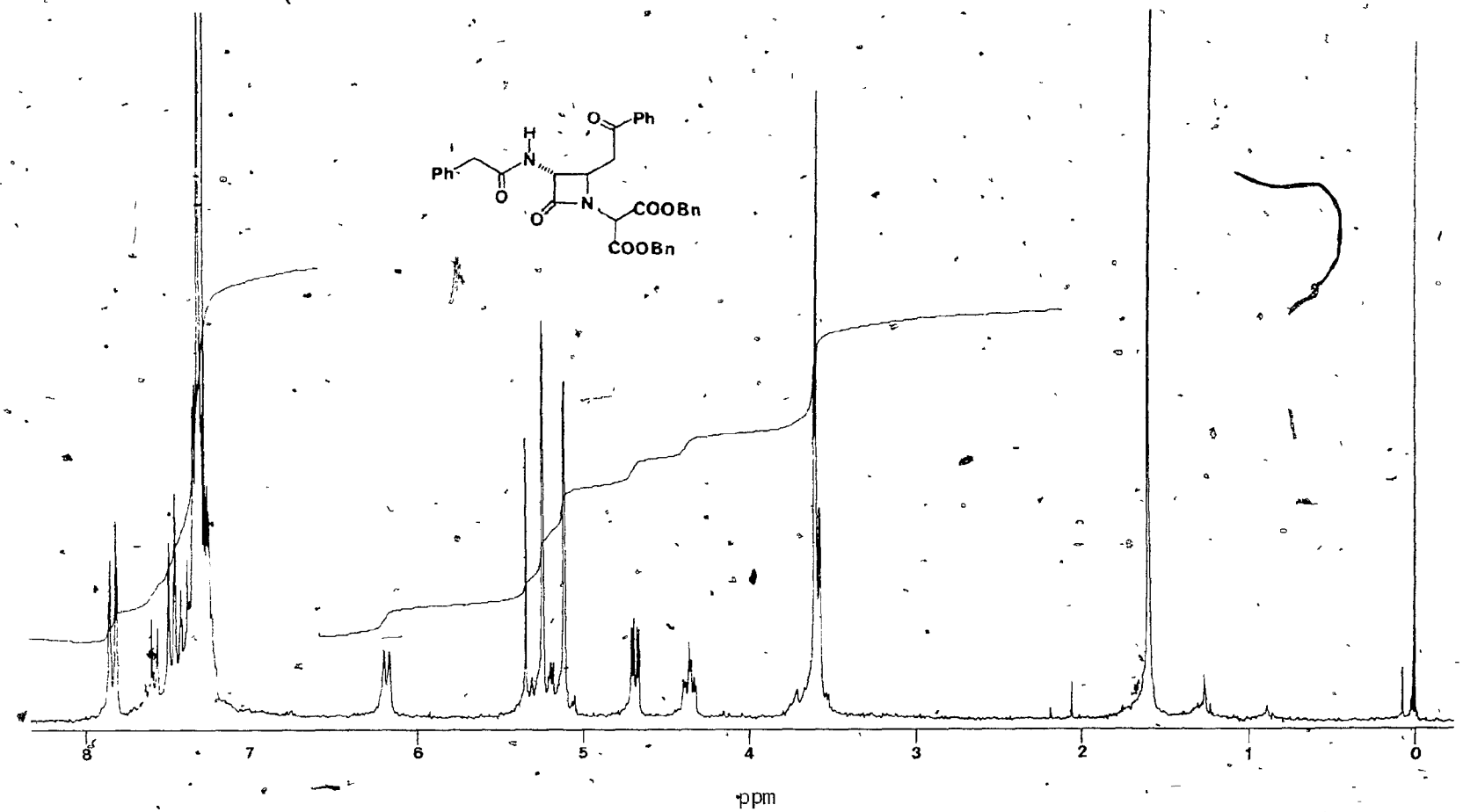


Fig. 19. 200 MHz pmr spectrum of 154, in $CDCl_3$.

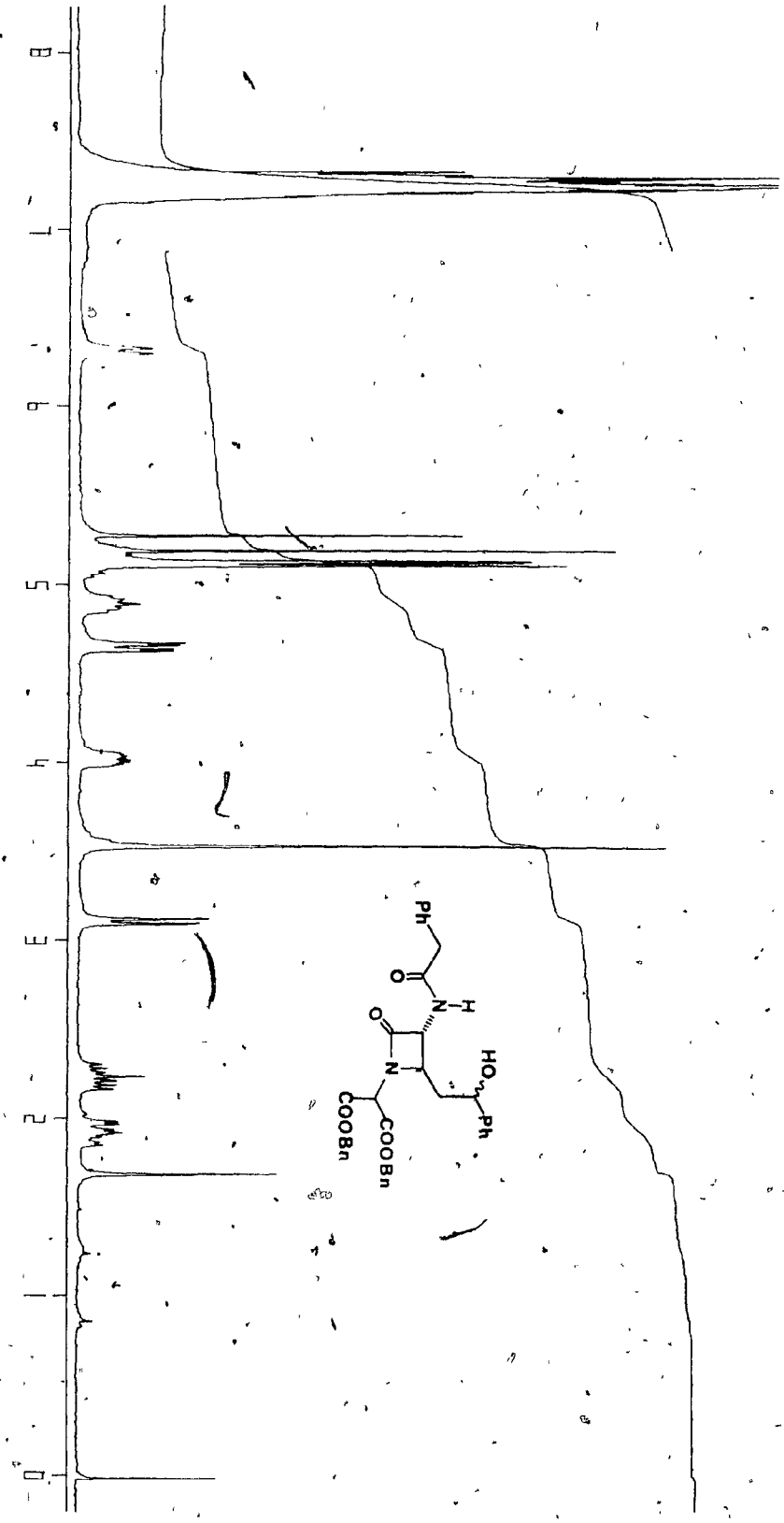


Fig. 20. 200 MHz pmr spectrum of 155, in $CDCl_3$.

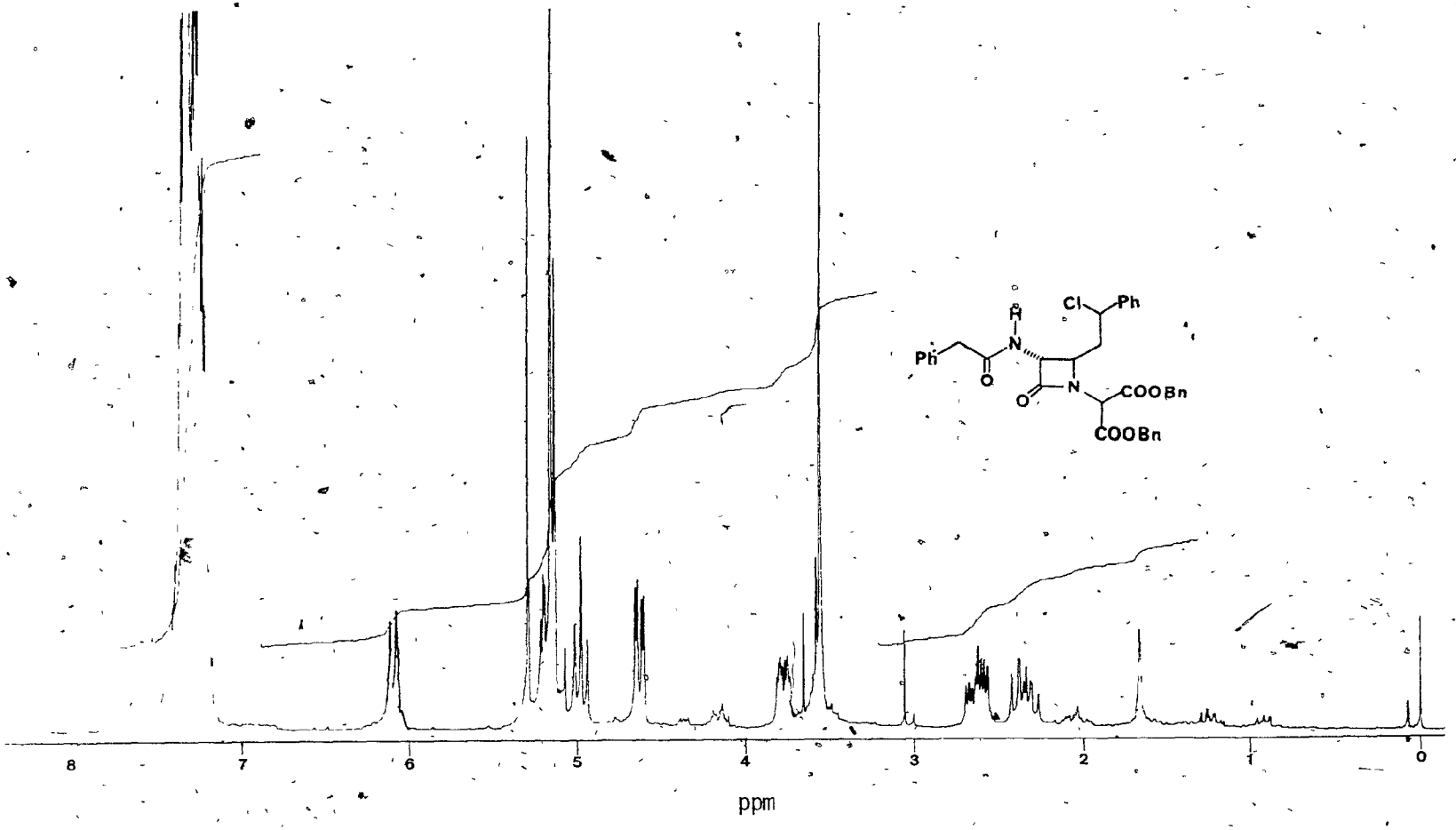


Fig. 21. 200 MHz pmr spectrum of 156, in $CDCl_3$.

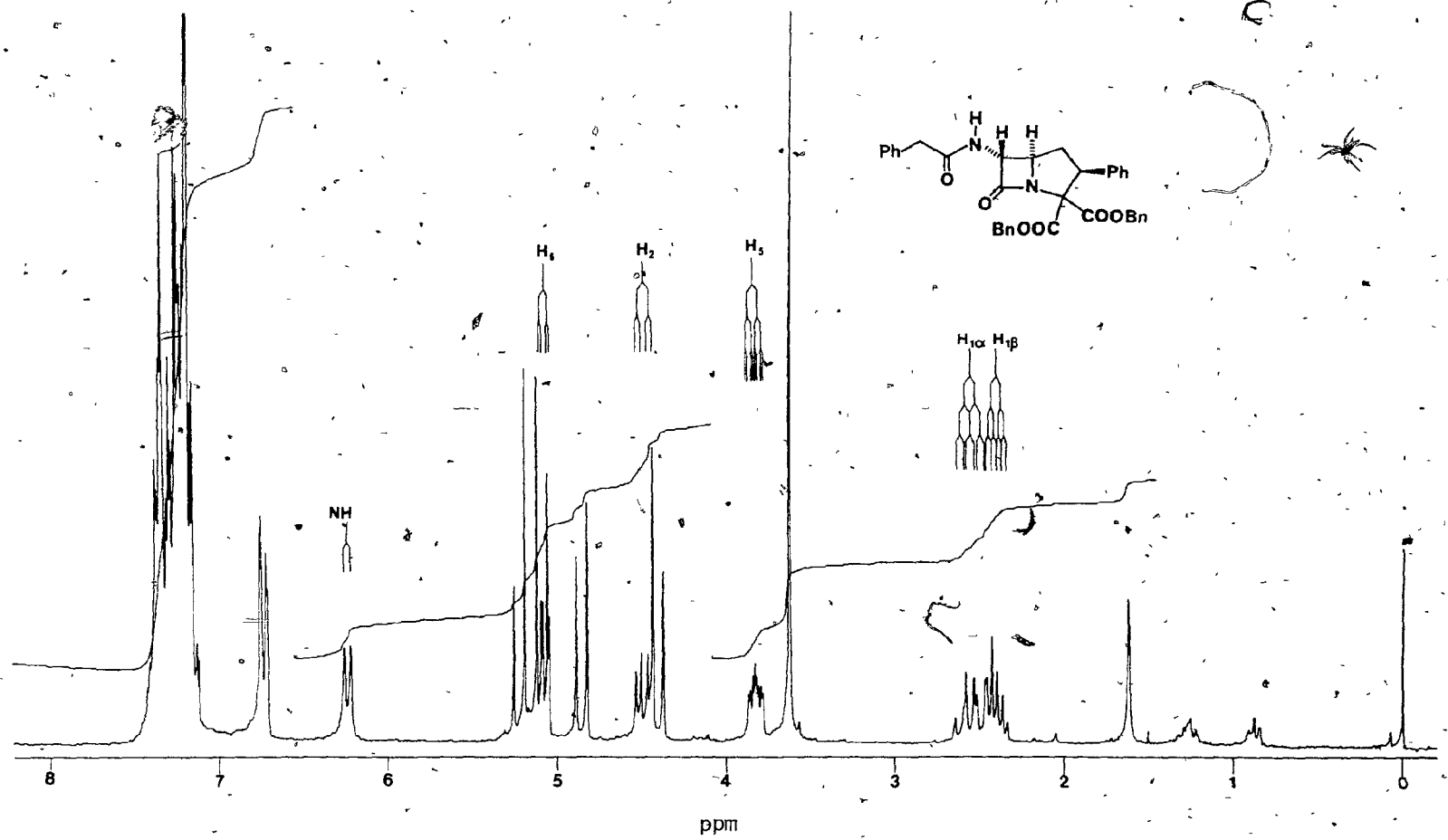


Fig. 22. 200 MHz pmr spectrum of 157, in $CDCl_3$.

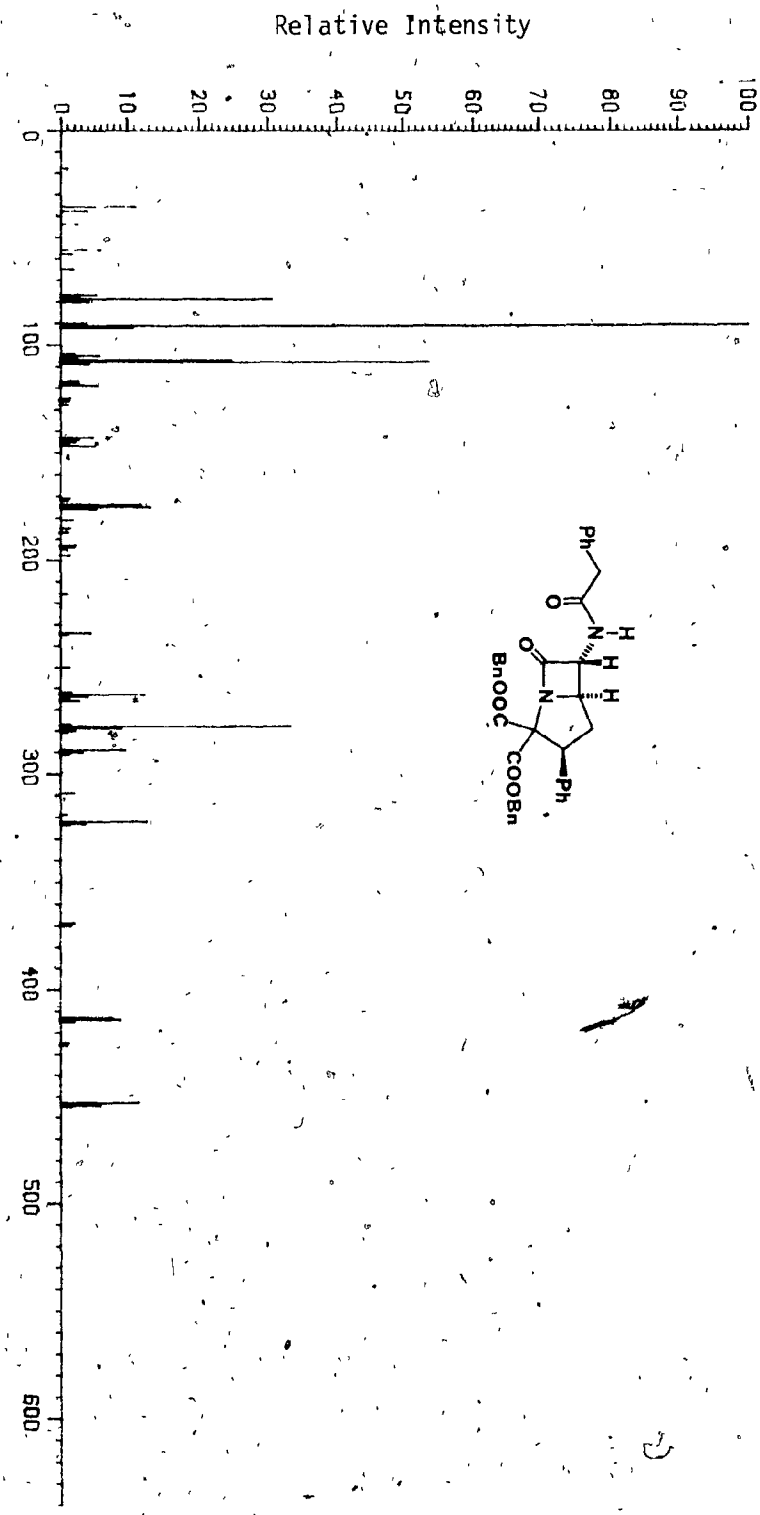
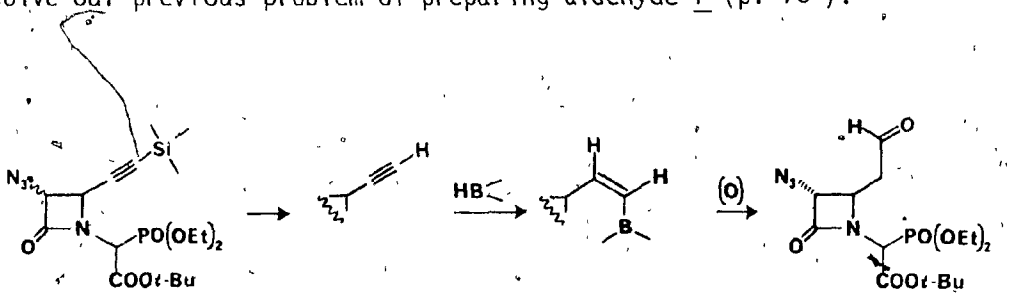


Fig. 23. Mass spectrum of 157.

made throughout this work were aided by homonuclear decoupling experiments.

Although not shown in the mass spectral computer plot (p. 94), a clearly visible molecular ion at m/e 588 was evident in the oscillogram. Attempted hydrogenolysis of 157 at 30 psi using palladium chloride in ethyl acetate afforded only unreacted starting material and degradation products.

One last venture into the chemistry of acetylenes was accomplished through β-lactams 159 and 160, which were prepared from trimethylsilylpropargyl aldehyde in the familiar manner, again as a 1 to 2 mixture of *cis* and *trans* forms. We thought of using these β-lactams to solve our previous problem of preparing aldehyde P (p. 78).



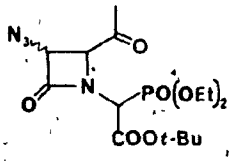
159 *cis* 161 *trans* P

160 *trans*

Cleavage of the silylacetylene in 160 proceeded smoothly with potassium fluoride in methanol[119] to give terminal acetylene 161. Treatment of 161 with catecholborane in THF at 70° for 1 hour followed by oxidation with buffered hydrogen peroxide[120] gave mostly unidentifiable products and

some starting material. Reaction of 161 with 9-BBN[121] in THF followed by oxidative workup afforded some unreacted 161 and other products deficient in β-lactam absorptions in the ir.

As an aside, it is interesting to note that, whereas phenylacetylene *cis* β-lactam 136 (p. 82) could not be hydrated to the corresponding ketone, both *cis* 159 and *trans* 160 could be oxidized to their corresponding methyl ketones 162 and 163, respectively, in one operation using mercuric trifluoroacetate, in the usual manner.



162 *cis*

163 *trans*

In conclusion, the synthesis and reactivity of various allyl-, vinyl- and epoxysilane substituted β-lactams were explored. The reactions of mercuric salts with cinnamyl and phenylacetylenyl azetidinones were examined. From the latter was prepared phenylketone 141, which was shown to undergo rearrangement to acylpyrrole 143 instead of cyclization to a penem. Finally, two new ring systems, the carbapenams 146 and 157 have been prepared. Although we were unable to cleanly deblock the ester functions in 146 and 157, cleavage of the corresponding p-nitrobenzyl

esters should prove to be considerably simpler. However, synthesis of such p-nitrobenzyl esters was not within the scope of this thesis.

CONTRIBUTIONS TO KNOWLEDGE

The stereochemistry of the β-lactams derived from the reaction of azidoacetyl chloride with substituted cinnamylidene anilines was found to depend on the substituent. Schiff bases derived from electron rich anilines (with pK_a's $\geq$ 2.4) afforded exclusively cis β-lactams.

Cephalosporin analogs 37, 59 and 77 were synthesized. The key step in the synthesis of 77 involved a novel intramolecular cyclization, of a t-butyldimethylsilyl ether with either a mesylate or a chloride, mediated by fluoride ion (p. 32, 48).

The one carbon homologation of β-trimethylsilyl-α,β-unsaturated esters with diazomethane was extended to the corresponding β-trimethylsilyl or β-t-butyldimethylsilyl aldehydes (p. 63).

Phosphono ketone β-lactam 141 was shown not to yield the desired carbapenem system upon treatment with base, but to rearrange to N-acyl pyrrole 143.

Two new ring systems, 2-phenylcarbapenams 146 and 157 have been prepared. The former being a key intermediate in the synthesis of phosphonic acid carbapenam 148.

EXPERIMENTAL

GENERAL EXPERIMENTAL

Melting points (mp) were determined on a Gallenkamp block and are uncorrected, unless otherwise specified. Mass spectra (ms) were obtained on HP 5984 or LKB 9000 mass spectrometers and intensities are reported in parts per thousand (‰). Chemical ionization mass spectra (CI-ms) (using isobutane) and gas chromatographic mass spectra (gc-ms) were recorded on the HP 5984 instrument. Infrared (ir) spectra were obtained on Unicam SP 1000, Perkin Elmer 257 and 297 spectrophotometers. Proton magnetic resonance (^{1}Hmr) spectra were acquired on Varian T-60, T-60A, HA-100, XL-200 and Brucker WH-90 spectrometers, with tetramethylsilane (TMS) as internal standard. Chemical shifts are given in the δ scale, in parts per million (ppm). Doublets (d), triplets (t) and quartets (q) are reported by their center positions, while multiplets (m) are described by a range of absorption. Other abbreviations used are: (s) for singlet, (b) for broad and (app) for apparent.

Analytical thin layer chromatography (tlc) was carried out on silica gel 60 F_{254} pre-coated aluminum sheets. "Flash chromatography", described by Still *et al.*[122], was performed using 32-63 μ Woelm silica gel (from ICN Nutritional Biochemicals, Cleveland, Ohio). Analytical gas chromatography was performed on an HP 5750 instrument, using a 3% OV-101 (3 ft) column.

Dry solvents were obtained by storing over molecular sieves[123] (DMF, DME, acetonitrile, benzene, methanol, methylene chloride, toluene),

or by refluxing in the presence of sodium-benzophenone[124] (THF), or were available commercially (Et_2O, EtOH).

All evaporations were done, unless otherwise mentioned, under reduced pressure (water aspirator) with a bath temperature of 25-40°.

Midwest Microlabs (Indianapolis, Indiana) performed the elemental analyses.

CHAPTER I

tetra-n-Butylammonium fluoride

Pless reported a convenient preparation of this fluoride salt[67]. The salt was obtained as an aqueous solution and had to be dried. The solid formed during the evaporation of the water was the trihydrate, which had to be heated at 60° for several hours, under high vacuum, to obtain anhydrous TBAF, as a clear, thick oil. In this way, the commercially available TBAF trihydrate (Fluka) was also used.

Solutions of this salt in THF were found to lose activity, over a period of a few months, when stored in glass bottles, even at -20°. Also, refrigerated solutions, stored in plastic bottles, became more concentrated with time due to the permeability of the plastic to tetrahydrofuran.

Schiff base 30

o-Aminophenol (5.5 g, 50 mmol) and cinnamaldehyde (7.3 g, 55 mmol) were refluxed in benzene (60 mL) for 4 h, using a Dean-Stark trap. After cooling, hexane (40 mL) was added to give 10.5 g (93%) of Schiff base 30 as yellow needles contaminated with a trace of cinnamaldehyde.

^{1}Hmr ($CDCl_3$) δ: 6.5-7.3 (m, 12H, aromatic, CH=CH and OH), 8.2 (dd, 1H, N=CH, J = 4,4 Hz); ir ($CHCl_3$) ν_{max}: 3400 (OH), 1630 (N=C) cm^{-1}.

Schiff base 31

Imine 30 (2.2 g, 10 mmol), t-butyldimethylsilyl chloride (1.8 g, 12 mmol) and imidazole (1.7 g, 25 mmol) were stirred overnight in DMF (20 mL). Then ether (100 mL) was added and the solution was washed with water (3 x 75 mL) and brine (75 mL), dried ($MgSO_4$) and evaporated to give Schiff base 31 (89%), as a thick yellow oil, which was reacted without purification.

^{1}Hmr ($CDCl_3$) δ: 0.15 (s, 6H, $SiMe_2$), 0.95 (s, 9H, t-BuSi), 6.7-7.3 (m, 11H, aromatic, CH=CH), 8.0 (dd, 1H, N=CH, J = 3,6 Hz).

β-Lactam 32

Azidoacetyl chloride (1.6 g, 13 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of Schiff base 31 (3.4 g, 10 mmol) and triethylamine (1.3 g, 13 mmol) in CH_2Cl_2 (50 mL), at -20°, over 15 min. After stirring for 1 h at -20°, the solution was allowed to warm up. Washing with water (2 x 60 mL) and brine (60 mL), then drying ($MgSO_4$) and evaporation of the solvent afforded, after chromatography on silica gel, 2.65 g (63%) of β-lactam 32, as a thick yellow oil which crystallized upon trituration with hexanes; mp 84-85°.

^{1}Hmr ($CDCl_3$) δ: 0.28 (s, 6H, $SiMe_2$), 1.03 (s, 9H, t-BuSi), 4.88 (d, 1H, $CH-N_3$, J = 5 Hz), 5.02 (dd, 1H, $CH-CHN_3$, J = 5,7 Hz), 6.10 (dd, 1H, CH=CHPh, J = 7,15 Hz), 6.57 (d, 1H, CHPh, J = 15 Hz), 6.6-7.5 (m, 9H,

aromatic); ir ($CHCl_3$) ν_{max}: 2100 (N_3), 1760 (β-lactam) cm^{-1}.

Alcohol β-lactam 33

Ozone was bubbled through a solution of β-lactam 32 (2.1 g, 5 mmol) in dry MeOH (100 mL) at -78°. Excess* ozone was flushed out with a stream of N_2 and $NaBH_4$ (0.19 g, 5 mmol) was added, at -40°. After warming to room temperature, pH 4.5 buffer (KH_2PO_4, 100 mL) was added and the methanol removed under reduced pressure. The aqueous residue was extracted with ether (3 x 75 mL) and the ether washed with brine (75 mL), dried and evaporated to afford 1.53 g (88%) of alcohol 33, after chromatography on silica gel. Crystallization from ether-hexanes gave fine white needles; mp 77-77.5°.

^{1}Hmr ($CDCl_3$) δ: 0.25 (s, 6H, $SiMe_2$), 0.98 (s, 9H, t-BuSi), 2.30 (bt, 1H, OH), 3.83 (bdd, 2H, CH_2), 4.46 (dt, 1H, $CH-CH_2$, J = 4,5 Hz), 4.87 (d, 1H, $CH-N_3$, J = 5 Hz), 6.7-7.7 (m, 4H, C_6H_4).

bis Silyl ether 34

Obtained from 33 *via* the procedure for the preparation of 31, as a pale yellow foam, in quantitative yield.

^{1}Hmr ($CDCl_3$) δ: -0.10, -0.15 (2s, 6H, $SiMe_2$), 0.20 (s, 6H, $SiMe_2$), 0.75, 0.92 (2s, 18H, 2t-BuSi), 3.75 (d, 2H, CH_2, J = 5 Hz), 4.40 (dt, 1H, $CH-CH_2$, J = 5,5 Hz), 4.65 (d, 1H, $CH-N_3$, J = 5 Hz), 6.6-7.6 (m, 4H, C_6H_4).

*The presence of ozone was monitored with KI-starch paper.

Amino β-lactam 35 and Acylamino β-lactam 36

Into azide 34 (4.6 g, 10 mmol) dissolved in CH_2Cl_2 (200 mL) and triethylamine (1.0 g, 10 mmol) at 0° was bubbled H_2S for 15 min. The yellow solution was allowed to warm up, and after stirring for 1 h at room temperature, nitrogen was bubbled through the solution for 0.5 h. To this solution at 0° was added triethylamine (1.3 g, 13 mmol), followed by dropwise addition of phenylacetyl chloride (2.0 g, 13 mmol). After stirring for 1 h, at ambient temperature, the solution was washed with water (3 x 100 mL) and brine (100 mL), then treated with $MgSO_4$ and charcoal, filtered and evaporated to give 4.2 g (76%) of amide 36, as a white foam, after chromatography on silica gel (CH_2Cl_2-$CHCl_3$). Amine 35 could be isolated, prior to acylation, by washing the CH_2Cl_2 solution with water (3 x 100 mL) and brine, then stirring with $MgSO_4$ and charcoal followed by filtration and evaporation of the solvent.

Amine 35: ^{1}Hmr ($CDCl_3$) δ: -0.17, -0.03 (2s, 6H, $SiMe_2$), 0.20 (s, 6H, $SiMe_2$), 0.88, 1.05 (2s, 18H, 2t-BuSi), 2.40 (bs, 2H, NH_2), 3.8-4.0 (m, 2H, CH_2), 4.1-4.5 (m, 2H, $C\underline{H}$-$C\underline{H}$-NH_2), 6.7-7.7 (m, 4H, C_6H_4).

Amide 36: -0.37, -0.23 (2s, 6H, $SiMe_2$), 0.20, 0.24 (2s, 6H, $SiMe_2$), 0.80, 0.95 (2s, 18H, 2t-BuSi), 3.52 (s, 2H, $C\underline{H}_2Ph$), 3.72 (bABX, 2H, CH_2O), 4.47 (bddd, 1H, $C\underline{H}$-CH_2, J = 5.5 Hz), 5.60 (dd, 1H, $C\underline{H}$-NH, J = 5.5, 10 Hz), 6.5-7.9 (m, 10H, aromatic, NH); ir ($CHCl_3$) ν_{max}: 3400 (NH), 1755 (β-lactam), 1680 (amide) cm^{-1}.

cis-N-(2'-Hydroxyphenyl)-3-phenylacetamido-4-hydroxymethyl-2-azetidinone (37)

To a solution of 36 (1.1 g, 2 mmol) in dry THF (75 mL) at 0° was added n-Bu_4NF (2.2 mL, 1 M) in dry THF (5 mL), dropwise over 10 min. After stirring for an additional 15 min, pH 4.5 buffer (75 mL) was added, and half the THF removed under reduced pressure. Extraction with ethyl acetate (3 × 50 mL) followed by evaporation afforded 630 mg (97%) of β-lactam 37, as white needles from MeOH-ether, mp 174-175° d (corr.). ^{1}Hmr (acetone d_6) δ: 3.1 (b, 2H, 2OH), 3.80 (s, 2H, CH_2Ph), 3.85 (dd, 1H, CHH-OH, J = 2.5, 12.5 Hz), 4.30 (dd, 1H, CHH-OH, J = 3.0, 12.5 Hz), 4.75 (ddd, 1H, CH-CH_2, J = 2.5, 3.0, 5.0 Hz), 5.72 (dd, 1H, CH-NH, J = 5.0, 10 Hz), 6.8-7.6 (m, 10H, C_6H_4, C_6H_5, NH); ir (KBr) ν_{max}: 3450 (NH), 3250 (OH), 1695 (β-lactam), 1650 (amide) cm^{-1}; ir (CH_3CN) ν_{max}: 1720 (β-lactam), 1680 (amide) cm^{-1}; ir (DMSO) ν_{max}: 1750 (β-lactam), 1680 (amide) cm^{-1}; gc-ms (TMS derivative) (70 eV), m/e (‰): component 1: 542 (4, $M^{+\cdot}$, tri-TMS derivative), 527 (17, $M^{+\cdot}$ - $CH_3\cdot$), 439 (30, $M^{+\cdot}$ - TMS-O-$CH_2\cdot$), 335 (210, $M^{+\cdot}$ - TMS-O-Ar-N=C=O), component 2: 470 (56, $M^{+\cdot}$, di-TMS derivative), 455 (24, $M^{+\cdot}$ - $CH_3\cdot$), 296-(1000, $M^{+\cdot}$ - 174).

Chloride 38

Alcohol 33 (0.5 g, 1.4 mmol) was refluxed for 2 h in benzene (25 mL), containing thionyl chloride (0.2 g, 1.7 mmol) and pyridine (0.14 g, 1.7 mmol). This mixture was added to ether (25 mL) and then washed with

water (2 x 30 mL) and brine (30 mL). Treatment with charcoal and drying ($MgSO_4$), followed by filtration and evaporation of the solvent afforded 0.46 g (87%) of chloride 38, as a white powder from ether-hexanes, mp 77-78°.

^{1}Hmr ($CDCl_3$) δ: 0.32 (s, 6H, $SiMe_2$), 1.03 (s, 9H, t-BuSi), 3.7-3.8 (m, $\underline{A_2}BC$, 2H, CH_2), 4.75 (ddd, $A_2\underline{B}C$, 1H, $C\underline{H}$-CH_2), 5.05 (d, $A_2\underline{B}C$, 1H, CH-N_3, J = 5.0 Hz), 6.8-7.8 (m, 4H, C_6H_4); ir (film) ν_{max}: 2110 (N_3), 1765 (β-lactam) cm^{-1}.

Mesylate 39

To alcohol 33 (0.8 g, 2.3 mmol) in CH_2Cl_2 (25 mL) and triethylamine (0.28 g, 2.8 mmol), at -78°, was added dropwise methanesulfonyl chloride (0.32 g, 2.8 mmol), in CH_2Cl_2 (5 mL). The solution was stirred for 0.5 h at -78° and allowed to warm to room temperature. After 1 h, the solution was washed with water (2 x 25 mL) and brine (25 mL), then dried ($MgSO_4$) and evaporated to afford 832 mg (85%) of mesylate 39 as a semi-solid, after chromatography on silica gel.

^{1}Hmr ($CDCl_3$) δ: 0.28 (s, 6H, $SiMe_2$), 1.02 (s, 9H, t-BuSi), 2.87 (s, 3H, SO_2CH_3), 4.4-4.5 (m, $\underline{A_2}BC$, 2H, CH_2), 4.80 (app q, $A_2\underline{B}C$, 1H, $C\underline{H}$-CH_2), 5.10 (d, $A_2\underline{B}C$, 1H, CH-N_3, J = 4.5 Hz), 6.8-7.8 (m, 4H, C_6H_4); ir (film) ν_{max}: 2110 (N_3), 1770 (β-lactam) cm^{-1}.

Tricyclic β-lactam 40

To mesylate 39 (306 mg, 0.72 mmol) in dry THF (30 mL), at 0°, was added dropwise n-Bu_4NF (0.79 mmol) in dry THF (10 mL), over 15 min. Dilution with pH 4.5 buffer (KH_2PO_4, 40 mL) and extraction with ether (3 x 50 mL) followed by drying ($MgSO_4$) and evaporation afforded, after chromatography of the residue on silica gel, 141 mg (91%) of tricyclic β-lactam 40, as a white solid from ether-hexanes, mp 77-78°.

Procedure B: To mesylate 39 (2.64 g, 6.2 mmol) in dry acetonitrile (80 mL) was added anhydrous KF (0.43 g, 7.4 mmol) and 18-crown-6 (0.49 g, 1.9 mmol). Upon completion of the reaction, as indicated by tlc (6-8 h), the solution was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 x 80 mL), which was then washed with brine (100 mL), dried ($MgSO_4$) and evaporated to give 1.27 g (95%) of tricyclic β-lactam 40, after chromatography on silica gel.

^{1}Hmr 100 MHz (C_6D_6) δ: 3.10 (ddd, 1H, C<u>H</u>-CH_2, J = 3.5, 5.0, 10 Hz), 3.36 (dd, 1H, CH-C<u>H</u>H, J = 10,10 Hz), 3.87 (dd, 1H, CH-CH<u>H</u>, J = 3.5, 10 Hz), 4.18 (d, 1H, CH-N_3, J = 5.0 Hz), 6.6-7.4 (m, 4H, C_6H_4); ir (KBr) ν_{max}: 2120 (N_3), 1780 (β-lactam) cm^{-1}; ms (70 eV, 30°), m/e (‰): 216 (330, $M^{+\cdot}$), 188 (250, $M^{+\cdot} - N_2$), 135 (1000), 133 (455, $M^{+\cdot} - O{=}C{=}CH{-}N_3$), 84.4 (M*, 216 → 135).

Silyl ether 42

Obtained from 2-amino-5-nitrophenol *via* the procedure for the preparation of 31, in quantitative yield, as deep yellow crystals from ether-hexanes, mp 106-107°.

^{1}Hmr ($CDCl_3$) δ: 0.30 (s, 6H, $SiMe_2$), 1.03 (s, 9H, t-BuSi), 3.95 (bs, 2H, NH_2), 6.5-7.5 (m, 3H, C_6H_3); ir (film) ν_{max}: 3500, 3400 (NH_2), 1520, 1340 (NO_2) cm^{-1}.

Schiff base 43

Obtained from 41 *via* the procedure for the preparation of Schiff base 30, and used, as such, for subsequent transformations.

Schiff base 44

Obtained from 42 by treatment with cinnamaldehyde, as for 30, but, requiring reflux for 6 h, in the presence of a trace of p-TsOH, as catalyst. Also obtained from 43 *via* the procedure for the preparation of 31. In either case, 44 was used without any purification.

β-Lactam 45

Obtained from 44 *via* the procedure for the preparation of 32, except that tetrahydrofuran was used as solvent instead of methylene chloride. After completion of the reaction, the THF was removed under

reduced pressure and the residue redissolved in an equivalent amount of ether, prior to the usual work-up. β-Lactam 45 was isolated in 50% yield. ^{1}Hmr ($CDCl_3$) δ: 0.38 (s, 6H, $SiMe_2$), 1.03 (s, 9H, t-BuSi), 4.55 (d, 1H, $CH-N_3$, J = 2 Hz), 4.85 (dd, 1H, $CH-CH-N_3$, J = 2,7 Hz), 6.10 (dd, 1H, $CH=CHPh$, J = 7,16 Hz), 6.63 (d, 1H, $CH=CHPh$, J = 16 Hz), 7.1-7.7 (m, 8H, aromatic); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam) cm^{-1}.

β-Lactams III and IV (Table 4, p. 37)

Obtained from their corresponding Schiff bases *via* the procedure for the preparation of 32.

β-Lactam IIIa: ^{1}Hmr (C_6D_6) δ: 4.05 (dd, 1H, $CH-CH-N_3$, J = 5,7 Hz), 4.15 (d, 1H, $CH-N_3$, J = 5 Hz), 5.90 (dd, 1H, $CH=CHPh$, J = 7,15 Hz), 6.48 (d, 1H, $CHPh$, J = 15 Hz), 6.9-7.6 (m, 10H, aromatic).

β-Lactam IIIb: ^{1}Hmr (C_6D_6) δ: 3.95 (dd, 1H, $CH-CH-N_3$, J = 5,7 Hz), 4.20 (d, 1H, $CH-N_3$, J = 5 Hz), 5.80 (dd, 1H, $CH=CHPh$, J = 7,16 Hz), 6.43 (d, 1H, $CHPh$, J = 16 Hz), 6.9-7.3 (m, 9H, aromatic).

β-Lactam IIId: see β-lactam 32.

β-Lactam IIIf: see β-lactam 70, Chapter II.

β-Lactam IIIg: ^{1}Hmr ($CDCl_3$) δ: 4.20 (dd, 1H, $CH-CH-N_3$, J = 5,8 Hz), 4.43 (d, 1H, $CH-N_3$, J = 5 Hz), 5.97 (dd, 1H, $CH=CHPh$, J = 8,16 Hz), 6.66 (d, 1H, $CHPh$, J = 16 Hz), 6.8-8.2 (m, 9H, aromatic); ir (film) ν_{max}: 2100 (N_3), 1775 (β-lactam) cm^{-1}.

β-Lactam IIIh: ^{1}Hmr (C_6D_6) δ: 3.23 (s, 3H, Ar-OMe), 3.60 (s, 3H,

COOMe), 4.53 (d, 1H, CH-N_3, J = 5.5 Hz), 4.83 (dd, 1H, CH-CH-N_3, J = 5.5, 7 Hz), 6.05 (dd, 1H, CH=CHPh, J = 7,15 Hz), 6.50 (d, 1H, CHPh, J = 16 Hz), 6.9-8.3 (m, 8H, aromatic); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam), 1725 (ester) cm^{-1}.

β-Lactams IIIi and IVi: ^{1}Hmr (C_6D_6) δ: 4.10, 4.43 (2d, 1H; CH-N_3, J = 2.2, 5.5 Hz), 4.65, 4.82 (2dd, 1H, CH-CH-N_3, J = 2.2, 8, 5.5, 8 Hz), 6.07 (dd, 1H, CH=CHPh, J = 8,16 Hz), 6.4-8.4 (m, 9H; C_6H_3, C_6H_5-CH); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam) cm^{-1}.

β-Lactam IIIℓ: see β-lactam 45.

β-Lactam IIIm: ^{1}Hmr (C_6D_6) δ: 4.05 (dd, 1H, CH-CH-N_3, J = 5,8 Hz), 4.30 (d, 1H, CH-N_3, J = 5 Hz), 5.93 (dd, 1H, CH=CHPh, J = 8,16 Hz), 6.57 (d, 1H, CHPh, J = 16 Hz); 7.1-8.0 (m, 9H, aromatic); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam) cm^{-1}.

β-Lactam IVm: ^{1}Hmr (C_6D_6) δ: 4.0-4.2 (m, 2H, CH-CH-N_3; + $Eu(fod)_3$ dd, 1H, J = 2.5,9 Hz and d, 1H, J = 2.5 Hz), 5.77 (dd, 1H, CH=CHPh, J = 9,16 Hz), 6.58 (d, 1H, CHPh, J = 16 Hz), 7.1-8.0 (m, 9H, aromatic); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam) cm^{-1}.

β-Lactam IVn: ^{1}Hmr ($CDCl_3$) δ: 2.43 (s, 3H, CH_3), 4.60 (d, 1H, CH-N_3, J = 2 Hz), 4.66 (dd, 1H, CH-CH-N_3, J = 2,8 Hz), 6.03 (dd, 1H, CH=CHPh, J = 8,16 Hz), 6.68 (d, 1H, CHPh, J = 16 Hz), 7.1-7.9 (m, 8H, aromatic); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam) cm^{-1}.

Azido β-lactam 53

2-t-Butyldimethylsilyloxy-5-nitroaniline (7.5 g, 28 mmol) and cinnamaldehyde (4.1 g, 31 mmol), in benzene (100 mL) containing a trace of p-TsOH, were refluxed for 2 days using a Dean-Stark trap. The solvent was then evaporated and replaced by CH_2Cl_2 (250 mL). To this solution, at -20°, was added triethylamine (3.6 g, 36 mmol) followed by dropwise addition of azidoacetyl chloride (4.3 g, 36 mmol), in CH_2Cl_2 (50 mL), over 1 h. The red brown solution was stirred for an additional hour at -20°, then allowed to warm up. Washing with water (2 x 200 mL) and brine (200 mL), then drying ($MgSO_4$) and treatment with charcoal and evaporation of the solvent afforded 6.9 g (53%) of β-lactam 53, as a pale yellow solid; mp 109-110° (ether-petroleum ether).

^{1}Hmr (C_6D_6) δ: 0.10 (s, 6H, $SiMe_2$), 0.93 (s, 9H, t-BuSi), 4.35 (d, 1H, $CH\text{-}N_3$, J = 5.5 Hz), 4.58 (dd, 1H, $CH\text{-}CHN_3$, J = 5.5, 7.0 Hz), 6.06 (dd, 1H, CH=CHPh, J = 7,16 Hz), 6.42 (d, 1H, $C_6\underline{H}H_2$, J = 9 Hz), 6.52 (d, 1H, CHPh, J = 16 Hz), 6.9-7.2 (m, 5H, C_6H_5), 7.60 (dd, 1H, $C_6\underline{H}H_2$, J = 3,9 Hz), 8.46 (d, 1H, $C_6\underline{H}H_2$, J = 3 Hz); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam) cm^{-1}.

Azido β-lactam 54

t-Butyldiphenylsilyl ether β-lactam 54 was obtained, from 52, using the same procedure as for 53, in 58% yield, as fine white crystals; mp 159.5-160° (corr.) (ether-petroleum ether).

^{1}Hmr (C_6D_6) δ: 1.22 (s, 9H, t-BuSi), 4.3-4.6 (m, 2H, CH-CHN_3), 6.2-6.4 (m, 3H, CH=CHPh, C_6HH_2), 7.0-7.9 (m, 16H, 3 C_6H_5 and C_6HH_2), 8.16 (d, 1H, C_6HH_2); ir (film) ν_{max}: 2100 (N_3), 1780 (β-lactam) cm^{-1}.

Amino β-lactam 55

Hydrogen sulfide was bubbled into a solution of azide 54 (589 mg, 1 mmol) and Et_3N (0.1 g, 1 mmol) in CH_2Cl_2 (30 mL), at 0° for 5 min. The solution was allowed to warm, and after stirring for 1 h at room temperature, N_2 was passed through the solution for 0.5 h. Then, Et_3N (50 mg, 0.5 mmol) was added followed by t-butyldiphenylsilyl chloride (137 mg, 0.5 mmol). After 0.5 h, the solution was washed with water (3 x 30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated to give, after flash chromatography (8:2, EtOAc:petroleum ether), 420 mg (75%) of amine 55, as a pale yellow foam.

^{1}Hmr ($CDCl_3$) δ: 1.18 (s, 9H, t-BuSi), 1.90 (bs, 2H, NH_2), 4.67 (d, 1H, CH-NH_2, J = 5.5 Hz), 5.33 (dd, 1H, CH-CH-NH_2, J = 5.5, 6 Hz), 6.26 (dd, 1H, CH=CHPh, J = 6,16 Hz), 6.46 (d, 1H, C_6HH_2, J = 9 Hz), 6.65 (d, 1H, CHPh, J = 16 Hz), 7.1-7.7 (m, 16H, 3 C_6H_5 and C_6HH_2), 8.62 (d, 1H, C_6HH_2, J = 2.7 Hz); ir ($CHCl_3$) ν_{max}: 3400, 3340 (NH_2), 1760 (β-lactam) cm^{-1}.

Phenylacetamido β-lactam 56

Hydrogen sulfide was bubbled into a solution of azide 53 (2.25 g,

4.8 mmol) and Et_3N (0.48 g, 4.8 mmol) in CH_2Cl_2 (150 mL) at 0° for 15 min. The cooling bath was removed and the stirring continued for 1 h, then N_2 was passed through the solution for 0.5 h, and Et_3N (830 mg, 8.2 mmol) was added, followed by t-butyldimethylsilyl chloride (362 mg, 2.4 mmol). After 0.5 h phenylacetyl chloride (890 mg, 5.8 mmol) was added dropwise at 0° and the solution stirred for an additional hour. The solution was then washed with water (2 x 150 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated to give, after chromatography on SiO_2, 2.1 g (78%) of amide 56 as fine white crystals; mp 165-166° (ether-petroleum ether).

^{1}Hmr (Acetone-d_6) δ: 0.38 (2s, 6H, $SiMe_2$), 1.02 (s, 9H, t-BuSi), 3.56 (s, 2H, CH_2), 5.30 (dd, 1H, CH-CH-NH, J = 5.5, 6.5 Hz), 5.58 (dd, 1H, CH-NH, J = 5.5, 9.0 Hz), 6.30 (dd, 1H, CH=CHPh, J = 6.5, 16 Hz), 6.73 (d, 1H, CHPh, J = 16 Hz), 7.1-7.4 (m, 11H, 2 C_6H_5 and C_6HH_2), 8.03 (dd, b, 2H, C_6HH_2, J = 3,9 Hz, NH), 8.63 (d, 1H, C_6HH_2, J = 3 Hz); ir (KBr) ν_{max}: 3400 (NH), 1765 (β-lactam), 1675 (amide) cm^{-1}; ms (12 eV, 80°), m/e (‰): 557 (399, $M^{+\cdot}$), 500 (60, $M^{+\cdot}$ - t-Bu·), 382 (79, $M^{+\cdot}$ - $PhCH_2CONHCH{=}C{=}O$), 325 (300, $M^{+\cdot}$ - 57 - 175), 263 (1000, PhCH=CH-CH=CH-$NHCOCH_2Ph$).

Phenylacetamido β-lactam 57

t-Butyldiphenylsilyl ether β-lactam 57 was obtained, from 54, *via* the procedure for the preparation of 56, in 75% yield, as fine white crystals; mp 199-200° (corr.) (ether-petroleum ether).

^{1}Hmr ($CDCl_3$) δ: 1.13 (s, 9H, t-BuSi), 3.56 (s, 2H, CH_2), 5.45 (dd, 1H, C<u>H</u>-CH-NH, J = 5.0, 6.0 Hz), 5.70 (dd, 1H, C<u>H</u>-NH, J = 5.0, 8.0 Hz), 6.15 (dd, 1H, C<u>H</u>=CHPh, J = 6.0, 16 Hz), 6.45 (d, 1H, $C_6\underline{H}H_2$, J = 9.0 Hz), 6.60 (d, 1H, C<u>H</u>Ph, J = 16 Hz), 6.9-7.8 (m, 22H, 4 C_6H_5, NH and $C_6\underline{H}H_2$), 8.62 (d, 1H, $C_6\underline{H}H_2$, J = 3 Hz); ir ($CHCl_3$) ν_{max}: 3310 (NH), 1765 (β-lactam), 1670 (amide) cm^{-1}.

<u>Hydroxy β-lactam 58</u>

Into a solution of β-lactam <u>57</u> (1.1 g, 1.6 mmol), in absolute EtOH (100 mL) and CH_2Cl_2 (25 mL), was bubbled ozone at -78°. Excess ozone was flushed out with N_2 and $NaBH_4$ (0.24 g, 6.3 mmol) was added at -78°, then the cooling bath was removed. After stirring for 1 h at room temperature, pH 4.5 buffer (100 mL) was added and the ethanol removed under reduced pressure. The aqueous residue was extracted with EtOAc (3 x 50 mL) and the extract washed with brine (30 mL), dried and evaporated to give 700 mg (71%) of alcohol <u>58</u> as white crystals, mp 125-126°, after chromatography on SiO_2.

^{1}Hmr (CD_3CN) δ: 1.06 (s, 9H, t-BuSi), 2.85 (bs, 1H, OH), 3.63 (s, 2H, $C\underline{H}_2$-Ph), 3.75, 4.10 (2dd, 2H, $C\underline{H}_2$-OH, J = 3, ^{2}J = 12 Hz), 4.82 (dt, 1H, C<u>H</u>-CH_2-OH, J = 3, 5.5 Hz), 5.66 (dd, 1H, C<u>H</u>-NH, J = 5.5, 9.5 Hz), 6.53 (d, 1H, $C_6\underline{H}H_2$, J = 9 Hz), 7.2-7.8 (m, 17H, 3 C_6H_5, $C_6\underline{H}H_2$, NH), 8.26 (d, 1H, $C_6\underline{H}H_2$, J = 3 Hz); ir ($CHCl_3$) ν_{max}: 3350 (OH), 1760 (β-lactam), 1650 (amide) cm^{-1}.

cis-N-(2'-Hydroxy-5'-nitrophenyl)-3-phenylacetamido-4-hydroxymethyl-2-azetidinone (59)

Ozone was bubbled through a solution of β-lactam 56 (280 mg, 0.5 mmol) in absolute EtOH (40 mL) and CH_2Cl_2 (10 mL) at -78°. Excess ozone was flushed out with N_2 and $NaBH_4$ (38 mg, 1 mmol) was added at -78°, and the cooling bath was removed. After stirring for 1 h at room temperature, pH 4.5 buffer (40 mL) was added to the deep orange solution and the ethanol removed under reduced pressure. The aqueous yellow residue was extracted with EtOAc (3 x 20 mL) and the extract washed with brine (20 mL), dried ($MgSO_4$) and evaporated to give 110 mg (59%) of alcohol 59 as white crystals; mp 179-180° (EtOAc).

^{1}Hmr 200 MHz (Acetone-d_6) δ: 3.68 (2s, 2H, CH_2CO), 3.80, 4.16 (2dd, 2H, CH-CH_2, J = 2.5, ^{2}J = 12.8 Hz), 4.80 (dt, 1H, CH-CH_2, J = 2.5, 5.9 Hz), 5.68 (dd, 1H, CH-NH, J = 5.9, 10 Hz), 7.08 (d, 1H, C_6HH_2, J = 9 Hz), 7.2-7.4 (m, 5H, C_6H_5), 7.60 (bd, 1H, NH, J = 10 Hz), 7.95 (dd, 1H, C_6HH_2, J = 3,9 Hz), 8.38 (d, 1H, C_6HH_2, J = 3 Hz); ir (CH_3CN) ν_{max}: 3600 (OH), 3350 (NH), 1720 (β-lactam), 1625 (amide) cm^{-1}; CI-ms (110°), m/e (°/₀₀): 372 (138, MH^+), 218 (1000, $MH^+ - OH^\cdot - NO_2^\cdot - PhCH_2^\cdot$).

Sodium p-nitrophenoxide β-lactam 60

To nitrophenol 59 (100 mg, 0.27 mmol) in THF (25 mL) at 0° was added sodium isopropoxide in isopropanol (2.7 mL, 0.1 M). The mixture was allowed to warm and the orange precipitate filtered and dried *in vacuo*

to give a quantitative yield of the sodium salt 60 as an orange solid; mp 168-171° (corr.).

^{1}Hmr (CD_3CN) δ: 3.6-4.3 (bm, 6H, CH-CH_2OH, CH_2), 5.50 (dd, 1H, C<u>H</u>-NH, J = 5.5, 10 Hz), 6.55 (d, 1H, $C_6\underline{H}H_2$, J = 9 Hz), 7.40 (s, 5H, C_6H_5), 7.76 (bd, 1H, NH, J = 10 Hz), 7.96 (dd, 1H, $C_6\underline{H}H_2$, J = 3,9 Hz), 8.13 (d, 1H, $C_6H\underline{H}_2$, J = 3 Hz); (+D_2O): 3.6-3.8 (m, 4H, 2 CH_2), 4.30 (dt, 1H, C<u>H</u>-CH_2, J = 2.5, 5.5 Hz), 5.45 (d, 1H, CH-ND, J = 5.5 Hz); ir (CH_3CN) ν_{max}: 3520 (OH), 3360 (NH), 1745 (β-lactam), 1670 (amide) cm^{-1}.

<u>Nitrophenyl β-lactam 61</u>

To a solution of β-lactam <u>40</u> (110 mg, 0.51 mmol) in dry acetonitrile (10 mL), containing 2,4,6-collidine (92 mg, 0.76 mmol), was added solid nitronium tetrafluoroborate (102 mg, 0.76 mmol) in portions, under nitrogen atmosphere. After stirring for 4 h, benzene (1 mL) was added and the solution stirred for an additional 20 min. The solution was then poured into ether (50 mL) and washed with water (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to afford 80 mg (60%) of a mixture of isomeric β-lactams <u>61</u>, after chromatography on silica gel.

^{1}Hmr ($CDCl_3$) δ: 3.8-4.5 (m, 2H, C<u>H</u>H-C<u>H</u>), 4.7-4.9 (m, 1H, CH<u>H</u>-CH), 5.40 (d, 1H, CH-N_3, J = 5.0 Hz), 7.0-8.3 (m, 3H, C_6H_3); ir (film) ν_{max}: 2100 (N_3), 1785 (β-lactam), 1530, 1320 (NO_2) cm^{-1}.

Nitrophenoxysilyl ether β-lactams 62

β-Lactams 62 were prepared, from 74, *via* the procedure for the preparation of β-lactams 61, except, using a 0.5 M solution of nitronium tetrafluoroborate in sulfolane instead of the solid reagent.

^{1}Hmr ($CDCl_3$) δ: 0.10, 0.28, 0.33 (s, 2s, 6H, $SiMe_2$), 1.03 (s, 9H, t-BuSi), 3.9-4.3 (m, 2H, CHH-CH), 4.5-4.9 (m, 1H, CHH-CH), 5.22, 5.27 (2d, 1H, CH-N_3, J = 4.5 Hz), 6.55, 6.67 (2d, 1H, C_6HH, J = 9.5 Hz), 7.78 (d, 1H, C_6HH, J = 9.5 Hz); ir (film) ν_{max}: 2100 (N_3), 1790 (β-lactam), 1530, 1330 (NO_2) cm^{-1}.

Note: the pmr spectrum of the crude material, before chromatography, also displayed a multiplet (7.4-7.5) for the two aromatic protons in 62, in which the nitro group is para to the β-lactam nitrogen. This isomer is apparently unstable to silica gel chromatography.

CHAPTER II

2,6-Dibenzyloxynitrobenzene 66

A mixture of 2-nitroresorcinol (1.55 g, 10 mmol), potassium carbonate (3.45 g, 25 mmol) and benzyl bromide (3.42 g, 20 mmol) in DMSO (10 mL) was stirred at room temperature, for 24 h. The mixture was then poured into water (100 mL) and extracted with ether (3 x 50 mL), dried ($MgSO_4$) and evaporated to afford 2.1 g (63%) of 66, as a wax.

^{1}Hmr ($CDCl_3$) δ: 5.0 (s, 4H, 2 CH_2), 6.4-7.4 (m, 13H, aromatic).

Di(t-butyldimethylsilyl)-2-aminoresorcinol (67)

A suspension of 2-nitroresorcinol (15 g, 97 mmol) and PtO_2 (1 g) in absolute ethanol (250 mL) was hydrogenated in a Parr apparatus at 40 psi. Filtration through celite and evaporation of the rapidly darkening filtrate afforded 12 g of amine 65 as a brown solid. This amine was added to t-butyldimethylsilyl chloride (32 g, 212 mmol) and imidazole (33 g, 485 mmol) in dry DMF (75 mL), and let stir overnight at room temperature. Then water (300 mL) was added and the solution extracted thrice with ether (300, 50, 50 mL). The ether extract was washed with water (3 x 100 mL) and brine (100 mL), then dried ($MgSO_4$) and evaporated. Chromatography of the residue on SiO_2 (250 g) afforded 20 g (59%) of amine 67 as a brownish oil.

^{1}Hmr ($CDCl_3$) δ: 0.23 (s, 12H, 2 $SiMe_2$), 1.00 (s, 18H, 2 t-BuSi), 3.47

(bs, 2H, NH_2), 6.27 (s, 3H, C_6H_3); ir (film) ν_{max}: 3350, 3450 (NH_2) cm^{-1}.

Schiff base 69 and Azido β-lactam 70

Amine 67 (14.2 g, 40 mmol) and cinnamaldehyde (5.6 g, 42 mmol), in benzene (150 mL), with a trace of p-TsOH, were refluxed overnight using a Dean-Stark trap. Evaporation of the solvent afforded Schiff base 69 as a thick brown oil. To this Schiff base, in CH_2Cl_2 (250 mL) containing triethylamine (5.3 g, 52 mmol), at -20° was added dropwise azidoacetyl chloride (6.2 g, 52 mmol) in CH_2Cl_2 (50 mL), over 1 h. The red brown solution was stirred for an additional hour at -20°, and then allowed to warm up. Washing with water (2 x 150 mL) and brine (150 mL), then drying ($MgSO_4$) and evaporation of the solvent afforded, after chromatography on SiO_2 (300 g, $CHCl_3$), 13 g (59%) of β-lactam 70 as a thick brown oil, which crystallized upon trituration with petroleum ether; mp 95-96°.

Schiff base 69: ^{1}Hmr ($CDCl_3$) δ: 0.16 (s, 12H, 2 $SiMe_2$), 0.98 (s, 18H, 2 t-BuSi), 6.5-7.6 (m, 10H, C_6H_5, C_6H_3, CH=CH), 8.38 (dd, 1H, N=CH, J = 3,5 Hz); ir (film) ν_{max}: 1640 (N=C) cm^{-1}.

β-Lactam 70: ^{1}Hmr ($CDCl_3$) δ: 0.24, 0.30 (2s, 12H, 2 $SiMe_2$), 1.03 (s, 18H, 2 t-BuSi), 4.8-5.0 (m, 2H, CH-CH-N_3), 6.4-7.3 (m, 10H, C_6H_3, CH=CH-C_6H_5); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam), 1580 cm^{-1}.

Azido alcohol 71

Obtained from β-lactam 70, *via* the procedure for the preparation of 58, as a viscous pale yellow oil, which could be crystallized by addition of a little pentane, giving β-lactam 71, in 74% yield, as white needles; mp 99.5-100°.

^{1}Hmr ($CDCl_3$) δ: 0.26, 0.30 (2s, 12H, 2 $SiMe_2$), 1.05 (s, 18H, 2 t-BuSi), 2.5 (bs, 1H, OH), 3.8 (bs, 2H, CH_2), 4.23 (dt, 1H, CH-CH_2-OH, J = 5, 5 Hz), 4.82 (d, 1H, CH-N_3, J = 5 Hz), 6.4-7.2 (m, 3H, C_6H_3); ir (film) ν_{max}: 3500 (OH), 2100 (N_3), 1765 (β-lactam), 1590 cm^{-1}.

Mesylate 72

Obtained from alcohol 71, *via* the procedure for the preparation of 39, as a pale yellow oil, which could be crystallized by trituration with petroleum ether, affording mesylate 72, in 95% yield, as white crystals; mp 69-70.5°.

^{1}Hmr ($CDCl_3$) δ: 0.24, 0.27 (2s, 12H, 2 $SiMe_2$), 1.0 (s, 18H, 2 t-BuSi), 2.86 (s, 3H, SO_2CH_3), 4.3-4.6 (bm, 3H, CH-CH_2), 4.9-5.0 (m, 1H, CHN_3), 6.4-7.2 (m, 3H, C_6H_3); ir (film) ν_{max}: 2100 (N_3), 1780 (β-lactam) cm^{-1}.

Chloride 73

Collidine (0.4 mL, 3 mmol) and thionyl chloride (0.22 mL, 3 mmol) were added to a solution of alcohol 71 (720 mg, 1.5 mmol) in dry benzene

(30 mL). After refluxing for 3 h, the mixture was poured into pH 4.5 buffer (30 mL), extracted with ether (2 x 15 mL), dried ($MgSO_4$), treated with charcoal, filtered and evaporated to give 670 mg (90%) of chloride 73 as white crystals, mp 74-75°.

^{1}Hmr ($CDCl_3$) δ: 0.23, 0.27 (2s, 12H, 2 $SiMe_2$), 1.0 (s, 18H, 2 t-BuSi), 3.5-4.0 (m, 2H, CH_2), 4.3-4.6 (m, 1H, $CH_2\underline{CH}$), 4.96 (d, 1H, CHN_3, J = 5 Hz), 6.4-7.2 (m, 3H, C_6H_3); ir (film) ν_{max}: 2100 (N_3), 1780 (β-lactam) cm^{-1}.

Tricyclic β-lactam 74

Obtained from mesylate 72, *via* the procedures for the preparation of 40, in 90-95% yield, as a pale yellow oil which crystallized on standing; mp 69-70°.

^{1}Hmr ($CDCl_3$) δ: 0.22, 0.30 (2s, 6H, $SiMe_2$), 1.0 (s, 9H, t-BuSi), 3.8-4.7 (m, 3H, CH-CH_2), 5.24 (d, 1H, CH-N_3, J = 5 Hz), 6.4-7.1 (m, 3H, C_6H_3); ir (film) ν_{max}: 2100 (N_3), 1775 (β-lactam) cm^{-1}.

Amino β-lactam 75

Into azide 74 (2.1 g, 6.1 mmol) dissolved in CH_2Cl_2 (80 mL) and Et_3N (0.61 g, 6.1 mmol), at 0°, was bubbled H_2S for 10 min. The solution was allowed to warm, and after stirring for 1 h at room temperature, nitrogen was bubbled through the solution for 0.5 h. The solution was then washed with H_2O (2 x 50 mL) and brine (50 mL), then dried ($MgSO_4$)

and evaporated. The oily residue was flash chromatographed on silica gel, using ethyl acetate-petroleum ether (3:1), affording 1.65 (85%) of amine 75 as a white solid; mp 135-136° (recrystallized from ether).

^{1}Hmr 200 MHz (C_6D_6) δ: 0.22, 0.30 (2s, 6H, $SiMe_2$), 0.75 (bs, 2H, NH_2), 1.15 (s, 9H, t-BuSi), 3.10 (ddd, 1H, CH_2-CH, J = 3.8, 5.3, 10.0 Hz), 3.42 (dd, 1H, CHH-CH, J = 10.0, 10.0 Hz), 3.90 (bd, 1H, $CHNH_2$, J = 5.3 Hz), 4.02 (dd, 1H, CHH-CH, J = 3.8, 10.0 Hz), 6.5-6.8 (m, 3H, C_6H_3); ir (film) ν_{max}: 3400, 3330 (NH_2), 1770 (β-lactam) cm^{-1}; ms (70 eV, 51°), m/e (°/₀₀): 320 (22, $M^{+\cdot}$), 305 (54, $M^{+\cdot}$ - $CH_3^{\cdot}$), 292 (428), 263 (1000, $M^{+\cdot}$ - 57), 248 (290, $M^{+\cdot}$ - 15-57), 235 (314), 216.2 (M*, 320 → 263), 189.1 (M*, 292 → 235); Anal. calcd. for $C_{16}H_{24}N_2O_3Si$: C 59.97, H 7.55, N 8.74; found: C 59.59, H 7.61, N 8.74.

β-Lactam amide 76

To amine 75 (640 mg, 2 mmol) and Et_3N (242 mg, 2.4 mmol) in CH_2Cl_2 (20 mL) at 0° was added dropwise phenylacetyl chloride (370 mg, 2.4 mmol) in CH_2Cl_2 (5 mL), over a period of 5 min. The solution was allowed to warm and, after stirring for 1 h at room temperature, was washed with pH 4.5 buffer (20 mL) and H_2O (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography, of the residue, afforded 750 mg (86%) of amide 76 as fine needles from ether, mp 161-162°.

^{1}Hmr 200 MHz ($CDCl_3$) δ: 0.15, 0.22 (2s, 6H, $SiMe_2$), 0.96 (s, 9H, t-BuSi), 3.56 (s, 2H, CH_2Ph), 3.62 (dd, 1H, CHH-CH, J = 10.0, 10.0 Hz), 3.93

(ddd, 1H, CH_2-CH, J = 3.5, 5.0, 10.0 Hz), 4.38 (dd, 1H, CHH-CH, J = 3.5, 10.0 Hz), 5.46 (dd, 1H, CHNH, J = 5.0, 7.0 Hz), 6.40, 6.45 (2 dd, 2H, CH-CH-CH in C_6H_3, J = 1,8 Hz), 6.53 (bd, 1H, NH, J = 7.0 Hz), 6.83 (dd, 1H, CH-CH-CH in C_6H_3, J = 8,8 Hz), 7.2-7.4 (m, 5H, C_6H_5); ir (film) ν_{max}: 3300 (NH), 1780 (β-lactam), 1670 (amide) cm^{-1}; ms (70 eV, 91°), m/e (°/₀₀): 438 (311, $M^{+\cdot}$), 423 (26, $M^{+\cdot}$ - $CH_3^{\cdot}$), 381 (130, $M^{+\cdot}$ - t-Bu$^{\cdot}$), 264 (1000), 206 (732), 159.1 (M*, 438 → 264), 111.4 (M*, 381 → 206).

7-β-Phenylacetamido-3'-hydroxybenzo[3,4]-0-2-isocephem (77)

Obtained from 76, 78 or 79, *via* the procedure for the preparation of 37, in 52, 55 and 48% yield, respectively, as fine needles from ethyl acetate-petroleum ether; mp 194-195°.

^{1}Hmr 200 MHz (acetone-d_6) δ: 3.62 (s, 2H, CH_2Ph), 4.07 (dd, 1H, CHH-CH, J = 10.0, 10.0 Hz), 4.18 (ddd, 1H, CH_2-CH, J = 3.3, 4.5, 10.0 Hz), 4.47 (dd, 1H, CHH-CH, J = 3.3, 10.0 Hz), 5.66 (dd, 1H, CHNH, J = 4.5, 8.0 Hz), 6.47, 6.53 (2 dd, 2H, CH-CH-CH in C_6H_3, J = 1,8 Hz), 6.92 (dd, 1H, CH-CH-CH in C_6H_3, J = 8,8 Hz), 7.2-7.4 (m, 5H, C_6H_5), 7.98 (bd, 1H, NH, J = 8.0 Hz); ir (CH_3CN) ν_{max}: 3280 (NH,OH), 1760 (β-lactam), 1655 (amide) cm^{-1}; ms (70 eV), m/e (°/₀₀): 324 (103, $M^{+\cdot}$), 205 (12, $M^{+\cdot}$ - $PhCH_2CO^{\cdot}$), 175 (30), 149 (54), 150 (1000), 91 (398).

Amide mesylate 78

Obtained from 72, *via* the procedure for the preparation of β-lactam

36, as white crystals (hexanes) in 79% yield; mp 129-130°.

^{1}Hmr ($CDCl_3$) δ: 0.20 (s, 12H, 2 $SiMe_2$), 0.95 (s, 18H, 2 t-BuSi), 2.80 (s, 3H, SO_2CH_3), 3.68 (s, 2H, CH_2Ph), 4.2-4.6 (m, 3H, CH_2-CH), 5.35 (dd, 1H, CHNH, J = 4.5, 7.0 Hz), 6.00 (bd, 1H, NH, J = 7.0 Hz), 6.4-7.2 (m, 3H, C_6H_3), 7.37 (s, 5H, C_6H_5); ir (CH_2Cl_2) ν_{max}: 3310 (NH), 1775 (β-lactam), 1685 (amide) cm^{-1}; ms (70 eV, 116°), m/e (°/₀₀): 537 (8), 512 (23, $M^{+\cdot}$ - t-Bu· - SO_2CH_3·), 495 (131), 322 (1000).

Amide chloride 79

Obtained from 73, *via* the procedure for the preparation of β-lactam 36, as white crystals (hexanes) in 86% yield; mp 125-126.5°.

^{1}Hmr ($CDCl_3$) δ: 0.20 (s, 12H, 2 $SiMe_2$), 0.95 (s, 18H, 2 t-BuSi), 3.2-3.6 (m, 2H, CH_2Cl), 3.67 (s, 2H, CH_2Ph), 4.2-4.6 (m, 1H, CH_2-CH), 5.43 (dd, 1H, CHNH, J = 5,8 Hz), 6.03 (bd, 1H, NH, J = 8 Hz), 6.4-7.2 (m, 3H, C_6H_3), 7.33 (s, 5H, C_6H_5); ir (film) ν_{max}: 3400 (NH), 1765 (β-lactam), 1675 (amide) cm^{-1}; ms (70 eV), m/e (°/₀₀): 588, 590 (35, 16, $M^{+\cdot}$), 531, 533 (573, 268, $M^{+\cdot}$ - t-Bu·), 414, 416 (411, 180), 322 (605).

CHAPTER III

Allenic ether 82

Chloromethyltrimethylsilane (4.5 g, 37 mmol) was added to magnesium turnings (0.9 g, 37.5 mmol), suspended in Et_2O (30 mL), and refluxed until most of the magnesium dissolved. The dark grey solution was then added dropwise to 1,1-diethoxy-2-propyne (3.84 g, 30 mmol) and CuBr (0.14 g, 1 mmol) in Et_2O (30 mL), and stirred for 0.5 h at room temperature. The mixture was then poured into a vigorously stirred solution of NaCN (1.5 g) and NH_4Cl (4.5 g) in ice water (75 mL), and extracted with Et_2O (3 x 50 mL), which was washed with brine (100 mL), dried ($MgSO_4$) and distilled under reduced pressure to give 3.3 g (65%) of ethoxy allene 82, bp 40-42° @ 1.5 mm Hg.

^{1}Hmr (CCl_4) δ: 0.03 (s, 9H, $SiMe_3$), 1.16 (t, 3H, $CH_2\underline{CH_3}$), 1.46 (dd, 2H, $\underline{CH_2}$-$SiMe_3$, J = 2.0, 8.0 Hz), 3.53 (q, 2H, $\underline{CH_2}CH_3$), 5.71 (dt, 1H, CH_2-$\underline{CH}$, J = 5.5, 8.0 Hz), 6.48 (dt, 1H, EtO-$\underline{CH}$, J = 2.0, 5.5 Hz).

Aldehyde 83 and Diene 92

To a solution of E-3-trimethylsilylacrolein 90[69] (1.3 g, 10 mmol) in Et_2O (30 mL) was added, in portions, a solution of diazomethane[125] in Et_2O, until gc monitoring (3 ft, 3% OV 101) showed the reaction to be complete. Evaporation under reduced pressure (0° water bath) afforded a pale yellow liquid. Aldehyde 83 was identified as the major product,

in the pmr spectrum of the crude residue. Distillation of this material under reduced pressure afforded none of the desired aldehyde, but gave exclusively diene 92, bp 47° @ 25 mm Hg (0.94 g, 65%).

Aldehyde 83: ^{1}Hmr (CCl_4) δ: 0.10 (s, 9H, $SiMe_3$), 1.98 (dd, 2H, CH_2, J = 1.0, 8.5 Hz), 6.01 (bdd, 1H, CH-CHO, J = 7.8, 15 Hz), 6.95 (dt, 1H, CH_2-CH, J = 8.5, 15 Hz), 9.41 (d, 1H, CHO, J = 7.8 Hz); ir (CH_2Cl_2) ν_{max}: 1680, 1630 (α,β-unsaturated aldehyde) cm^{-1}.

Diene 92: ^{1}Hmr (CCl_4) δ: 0.12 (s, 9H, $SiMe_3$), 4.6-6.1 (m, 2H, CH=CH), 5.5-6.6 (m, 3H, $CH=CH_2$); gc-ms (15 eV, 230°), m/e (‰): 142 (50, $M^{+\cdot}$), 127 (143, $M^{+\cdot}$ - $CH_3^{\cdot}$), 73 (1000, $SiMe_3^{\cdot}$).

Silyl alkyne 94

Obtained from alkyne 93, in 81% yield, by treatment with 1.1 equivalents of n-BuLi followed by 1.1 equivalents of t-$BuMe_2SiCl$, according to the procedure described by Dr. Zamboni (ref. 69, p. 143); bp 96-98° @ 0.05 mm Hg.

^{1}Hmr (CCl_4) δ: 0.10 (s, 6H, $SiMe_2$), 0.95 (s, 9H, t-BuSi), 1.4-1.8 (m, 6H, CH_2-CH_2-CH_2), 3.4-3.9 (m, 2H, CH_2-CH_2-O), 4.25 (s, 2H, C≡C-CH_2), 4.95 (m, 1H, O-CH-O).

Propargyl alcohol 95

Obtained from silyl alkyne 94, in 88% yield, by treatment with

pyridinium p-toluenesulfonate in ethanol, according to the procedure of Grieco and co-workers[126]; bp 87-90° @ 3.5 mm Hg.

^{1}Hmr (CCl_4) δ: 0.08 (s, 6H, $SiMe_2$), 0.88 (s, 9H, t-BuSi), 2.22 (bs, 1H, OH), 4.07 (s, 2H, CH_2).

α,β-Unsaturated aldehyde 96

Obtained from alcohol 95, in 73% yield, by sequential treatment with $LiAlH_4$ and PCC, according to the procedure reported by Dr. Zamboni (ref. 69, p. 144); bp 63-66° @ 5 mm Hg.

^{1}Hmr (CCl_4) δ: 0.13 (s, 6H, $SiMe_2$), 0.92 (s, 9H, t-BuSi), 6.40 (dd, 1H, C<u>H</u>-CHO, J = 7.0, 19 Hz), 7.10 (d, 1H, C<u>H</u>=CH-CHO, J = 19 Hz), 9.45 (d, 1H, CHO, J = 7.0 Hz).

E-4-t-Butyldimethylsilylcrotonaldehyde (97)

Obtained from 96, in 80-85% yield, by treatment with ethereal diazomethane[125], as for the preparation of 83, followed by either flash chromatography or distillation; bp 64-66° @ 2 mm Hg.

^{1}Hmr (CCl_4) δ: 0.08 (s, 6H, $SiMe_2$), 1.00 (s, 9H, t-BuSi), 1.98 (dd, 2H, CH_2, J = 1.0, 8.5 Hz), 5.97 (bddd, 1H, C<u>H</u>-CHO, J = 1.0, 7.8, 15 Hz), 6.96 (dt, 1H, CH_2-C<u>H</u>, J = 8.5, 15 Hz), 9.46 (d, 1H, CHO, J = 7.8 Hz); ir (film) ν_{max}: 1680, 1620 (α,β-unsaturated aldehyde) cm^{-1}.

Schiff base 98 and N-Benzyl β-lactam 99

A suspension of E-4-t-butyldimethylsilylcrotonaldehyde (97) (0.5 g, 2.7 mmol), benzylamine (0.29 g, 2.7 mmol) and $MgSO_4$ (1 g) in CH_2Cl_2 (25 mL) was stirred at room temperature until formation of Schiff base 98 was complete, as indicated by infrared spectroscopy, (≈1.5 h). The mixture was filtered and Et_3N (0.35 g, 3.5 mmol) was added followed by azidoacetyl chloride (0.42 g, 3.5 mmol), dropwise over 15 min. After stirring for 2 h the solution was washed with water (3 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to give 0.66 g (68%) of β-lactam 99, as a waxy, pale, yellow solid, after flash chromatography.

Schiff base 98: ^{1}Hmr (CCl_4) δ: 0.08 (s, 6H, $SiMe_2$), 1.02 (s, 9H, t-BuSi), 1.7-1.9 (m, 2H, CH_2-Si), 4.65 (bs, 2H, CH_2Ph), 6.1-6.3 (m, 2H, CH=CH), 7.34 (s, 5H, C_6H_5), 7.95 (m, 1H, N=CH); ir (CH_2Cl_2) ν_{max}: 1640 (C=N) cm^{-1} (no band at 1680 cm^{-1}).

β-Lactam 99: ^{1}Hmr (CCl_4) δ: 0.20 (s, 6H, $SiMe_2$), 1.13 (s, 9H, t-BuSi), 1.80 (d, 2H, CH_2-Si, J = 7.5 Hz), 4.08, 4.80 (2d, 2H, CH_2-Ph, ^{2}J = 15 Hz), 4.18 (dd, 1H, CH-CH-N_3, J = 5.0, 8.0 Hz), 4.77 (d, 1H, CH-N_3, J = 5.0 Hz), 5.40 (dd, 1H, CH=CH-CH, J = 8.0, 15 Hz), 5.94 (dt, 1H, CH=CH-CH, J = 7.5, 15 Hz), 7.40 (s, 5H, C_6H_5); ir (film) ν_{max}: 2100 (N_3), 1760 (β-lactam), 1650 (C=C) cm^{-1}; CI-ms (70°), m/e (°/₀₀): 357 (615, MH^+), 329 (1000, $MH^+ - N_2$·), 314 (287, $MH^+ - N_2$· - CH_3·).

Schiff base 105 and β-Lactam 106

Benzylamine (2.3 g, 21 mmol) was added to a slurry of E-3-trimethylsilylacrolein 96 (2.56 g, 20 mmol) and $MgSO_4$ (5 g) in CH_2Cl_2 (50 mL) at 0°, then the cooling bath was removed. After stirring at room temperature for 3 h, the solid was removed by filtration. To this solution was added Et_3N (2.4 g, 24 mmol) followed by azidoacetyl chloride (2.8 g, 24 mmol), dropwise, at room temperature. After 1.5 h the mixture was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated affording 3.5 g (58%) of β-lactam 106, as a pale yellow oil, after flash chromatography (2:5.5, EtOAc:petroleum ether).

Schiff base 105: ir (CH_2Cl_2) ν_{max}: 1640 (C=N) cm^{-1}.

β-Lactam 106: ^{1}Hmr 100 MHz (C_6D_6) δ: 0.12 ($SiMe_3$ lock), 3.76 (ddd, 1H, C<u>H</u>-CH-N_3, J = 3.0, 4.0, 5.0 Hz), 4.02, 4.30 (2d, 2H, C<u>H</u>$_2$-Ph, ^{2}J = 15 Hz), 4.28 (d, 1H, C<u>H</u>-N_3, J = 5.0 Hz), 5.85-5.9 (m, 2H, CH=CH), 7.15 (s, 5H, C_6H_5); ir ($CHCl_3$) ν_{max}: 2100 (N_3), 1765 (β-lactam) cm^{-1}.

Epoxysilane β-lactam 107

To a solution of vinylsilane 106 (1.5 g, 5 mmol) in anhydrous ether (15 mL) was added m-CPBA (85%, 1.5 g, 7.5 mmol). The solution was then concentrated, using a stream of nitrogen, until it became viscous. After stirring overnight at 40°, ether (50 mL) was added and the solution washed with aqueous sodium sulfite (5%, 30 mL), aqueous

sodium bicarbonate (5%, 30 mL), and brine (30 mL), then dried ($MgSO_4$) and evaporated. The oily residue was flash chromatographed (2:5, EtOAc:petroleum ether) to give 1.34 g (85%) of diastereomeric epoxides 107.

^{1}Hmr ($CDCl_3$) δ: 0.03, 0.06 (2s, 9H, $SiMe_3$), 1.95, 2.05 (2d, 1H, Si-CH-CH, J = 3.2, 3.2 Hz), 2.82, 2.93 (2dd, 1H, SiCH-CH, J = 3.2, 7.0, 3.2, 4.5 Hz), 3.18, 3.52 (2dd, 1H, CH-CH-N_3, J = 4.6, 7.0, 4.5, 4.6 Hz), 4.05, 4.25, 4.66, 4.71 (4d, 2ABq, 2H, CH_2Ph, ^{2}J = 14, 14 Hz), 4.69, 4.76 (2d, 1H, CH-N_3, J = 4.6, 4.6 Hz), 7.33 (s, 5H, C_6H_5); ir (film) ν_{max}: 2100 (N_3), 1765 (β-lactam) cm^{-1}; CI-ms (45°), m/e (‰): 317 (1000, MH^+), 289 (512, $MH^+ - N_2$).

α-Amino phosphonoacetate 108

Prepared according to the procedure of Dr. Hakimelahi[82], except for the following modifications. The suspension of sodium hydride in THF was added to the solution of Schiff base (from t-butylglyoxylate and benzylamine) and diethyl phosphite, in portions, at 0°. Palladium chloride was used instead of palladium on charcoal for the subsequent debenzylation, as it was found to be considerably more efficient.

β-Lactam 109

Obtained from equimolar amounts of amine 108 and aldehyde 90, *via* the procedure for the preparation of β-lactam 106, in 77% yield, as a pale yellow oil, which solidified upon storage, in the cold.

^{1}Hmr ($CDCl_3$) δ: 0.12 (s, 9H, $SiMe_3$), 1.33 (bt, 6H, 2 CH_2-CH_3), 1.48 (s, 9H, t-Bu), 3.9-4.3 (m, 4H, 2 CH_2-CH_3), 4.53, 4.61 (2d, 1H, P-CH, ^2J = 24,24 Hz), 4.6-4.7 (m, 2H, CH-CH-N_3), 6.0-6.1 (m, 2H, CH=CH); ir (film) ν_{max}: 2100 (N_3), 1775 (β-lactam), 1740 (ester) cm^{-1}; CI-ms (40°), m/e (%): 461 (39, MH^+), 433 (40, $MH^+ - N_2$), 405 (1000, $MH^+ - Me_2C{=}CH_2$); Anal. calcd. for $C_{18}H_{33}N_4O_6PSi$: C 46.94, H 7.22, N 12.16; found: C 46.69, H 7.18, N 11.88.

Carboxylic acid 110

A solution of t-butyl ester 109 (1.1 g, 2.4 mmol) in 30% trifluoroacetic acid-methylene chloride (30 mL) was allowed to stand for 3 h, at room temperature. The solvent was then evaporated and the residue flash chromatographed (6.5:0.5, acetone:water) to afford 740 mg (77%) of carboxylic acid 110.

^{1}Hmr ($CDCl_3$) δ: 0.13 (s, 9H, $SiMe_3$), 1.36 (bt, 6H, 2 CH_2-CH_3), 4.0-4.5 (m, 4H, 2 CH_2-CH_3), 4.7-4.9 (m, 2H, CH-CH-N_3), 4.88, 4.95 (2d, 1H, P-CH, ^2J = 25,25 Hz), 6.0-6.2 (m, 2H, CH=CH), 12.0 (bs, 1H, COOH); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam), 1730 (COOH) cm^{-1}.

Treatment with ethereal diazomethane afforded the corresponding methyl ester 122, p. 133.

Epoxysilane β-lactam 111

Obtained from vinylsilane 109, *via* the procedure for the preparation of 107, in 90% yield, as a clear oil after flash chromatography (6,5:2, EtOAc:petroleum ether) (two components).

Less polar component of 111: ^{1}Hmr 100 MHz (CCl_4) δ: 1.22 (t, 6H, 2 CH_2-CH_3), 1.35 (s, 9H, t-Bu), 2.04, 2.09 (2d, 1H, Si-CH-CH, J = 3.2, 3.2 Hz), 2.80, 2.91 (2dd, 1H, Si-CH-CH, J = 3.2, 7.8, 3.2, 7.8 Hz), 3.41, 3.49 (2dd, 1H, CH-CH-N_3, J = 5.3, 7.8, 5.3, 7.8 Hz), 3.8-4.2 (m, 4H, 2 CH_2-CH_3), 4.48, 4.62 (2d, 1H, P-CH, ^{2}J = 23, 24.5 Hz), 4.72, 4.73 (2d, 1H, CH-N_3, J = 5.3, 5.3 Hz); ir (film) ν_{max}: 2100 (N_3), 1780 (β-lactam), 1740 (ester) cm^{-1}; CI-ms (94°), m/e (°/₀₀): 477 (1000, MH^+), 449 (280, $MH^+ - N_2$), 403 (362, MH^+ - t-BuOH), 393 (584, $MH^+ - N_2 - Me_2C{=}CH_2$).

More polar component of 111: ^{1}Hmr 100 MHz (CCl_4) δ: 1.20, 122 (2t, 6H, 2 CH_2-CH_3), 1.35 (s, 9H, t-Bu), 1.80 (d, 1H, Si-CH-CH, J = 3.2 Hz), 2.89, 2.98 (2dd, 1H, Si-CH-CH, J = 3.2, 7.8, 3.2, 7.8 Hz), 3.4-3.6 (m, 1H, CH-CH-N_3), 3.9-4.2 (m, 4H, 2 CH_2-CH_3), 4.48, 4.62 (2d, 1H, P-CH, ^{2}J = 23.8, 24.2 Hz), 4.68 (bd, 1H, CH-N_3, J = 5.3 Hz); ir (film) ν_{max}: 2100 (N_3), 1780 (β-lactam), 1740 (ester) cm^{-1}; CI-ms (120°), m/e (°/₀₀): 477 (546, MH^+), 449 (67, $MH^+ - N_2$), 421 (1000, $MH^+ - Me_2C{=}CH_2$), 403 (12, MH^+ - t-BuOH), 393 (59, $MH^+ - N_2 - Me_2C{=}CH_2$).

Methyl ester 122

Obtained from acid 110, by treatment with ethereal diazomethane[125], in 89% yield, after evaporation and flash chromatography (6:2, EtOAc: petroleum ether).

^{1}Hmr ($CDCl_3$) δ: 0.12 (s, 9H, $SiMe_3$), 1.34 (bt, 6H, 2 CH_2-CH_3), 3.75, 3.80 (2s, 3H, OCH_3), 3.9-4.4 (m, 4H, 2 CH_2-CH_3), 4.7-4.9 (m, 2H, CH-CH-N_3), 4.83, 4.86 (2d, 1H, P-CH, ^2J = 24,24 Hz), 6.0-6.2 (m, 2H, CH=CH); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam), 1745 (ester) cm^{-1}; ms (70 eV, 43°), m/e (°/₀₀): 403 (27, $M^{+\cdot}$ - $CH_3^{\cdot}$), 390 (123, $M^{+\cdot}$ - $N_2^{\cdot}$), 375 (235, $M^{+\cdot}$ - $CH_3^{\cdot}$ - $N_2^{\cdot}$), 73 (1000, $SiMe_3^{+\cdot}$).

β-Lactam 124

Obtained from 122, *via* the procedure for the preparation of 107, in 47% yield, as a wax after flash chromatography.

^{1}Hmr ($CDCl_3$) δ: 0.12 (s, 9H, $SiMe_3$), 2.10, 2.30 (2d, 1H, Si-CH-CH, J = 3.7, 3.7 Hz), 2.96, 3.00 (2dd, 1H, Si-CH-CH, J = 3.7, 6.3, 3.7, 4.5 Hz), 3.50, 3.94 (2dd, 1H, CH-CH-N_3, J = 5.0, 6.3, 4.5, 5.0 Hz), 4.83, 4.87 (2dd, 1H, CH-N_3, J = 2.0*, 5.0, 2.2*, 5.0 Hz), 6.45, 6.85 (2bs, 1H, NH); ir (film) ν_{max}: 3280 (NH), 2100 (N_3), 1775 (β-lactam) cm^{-1}; CI-ms (36°), m/e (°/₀₀): 227 (1000, MH^+), 199 (774, MH^+ - $N_2^{\cdot}$), 156 (111, MH^+ - O=C=NH - $N_2^{\cdot}$), 144 (664, MH^+ - O=C=CHN_3).

*Through-space coupling with NH.

Cinnamyl β-lactam 127

Obtained from 108 and cinnamaldehyde, *via* the procedure for the preparation of β-lactam 106, in 78% yield after flash chromatography (6:2, EtOAc:petroleum ether).

^{1}Hmr (C_6D_6) δ: 1.0-1.4 (m, 6H, 2 CH_2-CH_3), 1.48, 1.58 (2s, 9H, t-Bu), 3.9-4.4 (m, 4H, 2 CH_2-CH_3), 4.53 (bd, 1H, CH-N_3, J = 5.0 Hz), 4.8-5.0 (m, 1H, CH-CH-N_3), 5.10 (d, 1H, P-CH, ^{2}J = 23 Hz), 6.7-6.8 (m, 2H, CH=CH), 7.1-7.6 (m, 5H, C_6H_5); ir (film) ν_{max}: 2100 (N_3), 1775 (β-lactam), 1740 (ester) cm^{-1}; CI-ms (115°), m/e (%): 437 (190, $MH^+ - N_2$·), 381 (1000, $MH^+ - N_2$· - $Me_2C=CH_2$), 337 (270, $MH^+ - N_2$· - $Me_2C=CH_2$ - CO_2), 238 (497, $MH^+ - Me_2C=CH_2$ - Ph-CH=CH-CH=CH-N_3).

Aldehyde 128

Ozone was bubbled through a solution of 127 (460 mg, 1 mmol) in CH_2Cl_2 (25 mL), at -78°. Upon appearance of the blue color, the bubbling was discontinued and the excess ozone flushed out with a stream of nitrogen, at -78°. Dimethyl sulfide (0.4 mL, 5 mmol) was then added and the solution allowed to stir for 4 h, at room temperature. Evaporation of the solvent followed by flash chromatography (8:1, EtOAc: petroleum ether), of the residue, afforded 310 mg (80%) of aldehyde 128.

^{1}Hmr ($CDCl_3$) δ: 1.40 (t, 6H, 2 CH_2-CH_3), 1.55 (s, 9H, t-Bu), 4.0-4.4 (m, 4H, 2 CH_2-CH_3), 4.4-4.7 (m, 1H, CH-CHO), 4.92-4.95 (2d, 1H, P-CH,

^2J = 20,22 Hz), 5.15 (d, 1H, CH-N_3, J = 5.0 Hz), 9.38 (d, 1H, CHO, J = 4.5 Hz); ir (film) ν_{max}: 3300 (hydrated CHO), 2100 (N_3), 1785 (β-lactam), 1735 (ester) cm^{-1}.

β-Lactams 129 to 131

The following compounds were prepared according to the method of Wollenberg and Miller[110]; 128 → 129, 62% yield, 129 → 131, 48% yield.

β-Lactam 129: ^{1}Hmr ($CDCl_3$) δ: 1.42 (t, 6H, 2 CH_2-CH_3), 1.57 (s, 9H, t-Bu), 4.0-4.5 (m, 5H, 2 CH_2-CH_3, OH), 4.6-5.2 (m, 6H, O_2N-CH_2-CHOH-CH-CH, P-CH); ir (film) ν_{max}: 3320 (OH), 2100 (N_3), 1775 (β-lactam), 1740 (ester), 1560, 1380 (NO_2) cm^{-1}.

β-Lactam 130: ^{1}Hmr ($CDCl_3$) δ: 1.38 (t, 6H, 2 CH_2-CH_3), 1.53 (s, 9H, t-Bu), 3.9-4.5 (m, 4H, 2 CH_2-CH_3), 4.7-5.2 (m, 3H, CH-CH-N_3, P-CH), 7.2-7.4 (m, 2H, CH=CH); ir (film) ν_{max}: 2100 (N_3), 1780 (β-lactam), 1740 (ester), 1530, 1350 (NO_2) cm^{-1}.

β-Lactam 131: ^{1}Hmr ($CDCl_3$) δ: 1.42 (t, 6H, 2 CH_2-CH_3), 1.55 (s, 9H, t-Bu), 2.4-2.9 (m, 2H, O_2N-CH_2-CH_2), 3.9-4.7 (m, 7H, 2 CH_2-CH_3, O_2N-CH_2, CH-CH-N_3), 4.86 (d, 1H, CH-N_3, J = 5.0 Hz), 4.89, 5.91 (2d, 1H, P-CH, ^2J = 22,24 Hz); ir (film) ν_{max}: 2100 (N_3), 1770 (β-lactam), 1740 (ester), 1550, 1380 (NO_2) cm^{-1}.

Acetylenic β-lactams 136 and 137

Obtained from phenylpropargyl aldehyde and amine 108, *via* the procedure for the preparation of β-lactam 106, in 79% yield, as a 1:2 mixture of 136 and 137.

β-Lactam 136: ^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.2-1.4 (m, 6H, 2 CH_2-CH_3), 1.47, 1.52 (2s, 9H, t-Bu), 4.1-4.3 (m, 4H, 2 CH_2-CH_3), 4.71, 4.74 (2d, 1H, CH-CH-N_3, J = 5.0, 5.0 Hz), 4.87, 4.90 (2d, 1H, P-CH, ^{2}J = 23.5, 24.0 Hz), 5.12, 5.30 (2d, 1H, CH-N_3, J = 5.0, 5.0 Hz), 7.3-7.6 (m, 5H, C_6H_5); ir (film) ν_{max}: 2210 (w, C≡C), 2100 (N_3), 1780 (β-lactam), 1740 (ester) cm^{-1}.

β-Lactam 137: ^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.30, 1.38 (2t, 6H, 2 CH_2-CH_3), 1.47, 1.51 (2s, 9H, t-Bu), 4.1 - 4.3 (m, 5H, 2 CH_2-CH_3, CH-CH-N_3), 4.69, 4.76 (2d, 1H, CH-N_3, J = 2.0, 2.0 Hz), 4.83, 4.84 (2d, 1H, P-CH, ^{2}J = 23.5, 24.0 Hz), 7.3-7.5 (m, 5H, C_6H_5); ir (film) ν_{max}: 2210 (w, C≡C), 2100 (N_3), 1780 (β-lactam), 1740 (ester) cm^{-1}.

Phenylketone 138

A mixture of acetylene 137 (434 mg, 0.94 mmol), yellow mercuric oxide (406 mg, 1.9 mmol) and mercuric trifluoroacetate (803 mg, 1.9 mmol) in ethyl acetate (50 mL), containing water (0.5 mL), was stirred at room temperature for 5 h. The mixture was then cooled to 0° and H_2S was bubbled through for 10 min. After stirring at room temperature for

0.5 h, the black mercuric sulfide was removed by filtration and the solvent evaporated to give 361 mg (80%) of phenylketone 138, after flash chromatography (6:3, EtOAc:petroleum ether). The reaction could be followed by tlc, after treatment of an aliquot of reaction mixture with H_2S.

^{1}Hmr 200 MHz (C_6D_6) δ: 0.9-1.1 (m, 6H, 2 CH_2-CH_3), 1.30, 1.37 (2s, 9H, t-Bu), 3.17, 3.25 (2dd, 1H, CHH-CO, J = 10,10 Hz, ^{2}J = 18,18 Hz), 3.8-4.2 (m, 6H, 2 CH_2-CH_3, CHH-CO, CH_2-N_3), 4.50, 4.71 (2bd, 1H, CH-CH-N_3, J = 10,10 Hz), 5.08, 5.14 (2d, 1H, P-CH, ^{2}J = 23,24 Hz), 7.0-7.2, 7.9-8.0 (m, 5H, C_6H_5); ir (film) ν_{max}: 2100 (N_3), 1773 (β-lactam), 1738 (ester), 1680 (ketone) cm^{-1}; CI-ms (106°), m/e (°/₀₀): 425 (1000, MH^+ - $Me_2C=CH_2$); 397 (175, MH^+ - $Me_2C=CH_2$ - N_2), 353 (71, MH^+ - $Me_2C=CH_2$ - N_2 - CO_2).

β-Lactam 139

Obtained, in 20% yield, by treatment of a 0.1 M solution of 138 in THF, at -78°, with 1 equivalent of n-butyllithium, followed by quenching of the cold solution with aqueous ammonium chloride and flash chromatography (6:4, EtOAc:petroleum ether) of the residue; ir (film) ν_{max}: 3400 (OH), 2100 (N_3), 1775 (β-lactam), 1740 (ester) cm^{-1}; CI-ms (98°), m/e (°/₀₀): 521 (71, MH^+ - H_2O), 465 (1000, MH^+ - H_2O - $Me_2C=CH_2$), 437 (237, MH^+ - H_2O - $Me_2C=CH_2$ - N_2). The pmr spectrum ($CDCl_3$) was also consistent with structure 139, showing the extra alkyl methyl at

0.8-0.9 ppm and a decreased range of aromatic resonances (7.2-7.4 ppm) for the phenyl group.

Amide β-lactam 140

Obtained from 137, *via* the procedure for the preparation of amide 36, in 81% yield after flash chromatography (EtOAc).

^{1}Hmr ($CDCl_3$) δ: 1.1-1.3 (m, 6H, 2 CH_2-CH_3), 1.40, 1.43 (2s, 9H, t-Bu), 3.55 (s, 2H, CH_2Ph), 3.9-4.4 (m, 4H, 2 CH_2-CH_3), 4.7-5.2 (m, 2H, CH-CH-N_3), 4.76, 4.87 (2d, 1H, P-CH, ^2J = 24, 24 Hz), 7.1-7.5 (m, 11H, 2 C_6H_5, NH); ir (film) ν_{max}: 3300 (NH), 1780 (β-lactam), 1740 (ester), 1680 (amide) cm^{-1}.

Phenylketone 141

Obtained from 140, in 77% yield after flash chromatography (EtOAc), *via* the procedure for the preparation of 138.

^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.2-1.4 (m, 6H, 2 CH_2-CH_3), 1.42, 1.48 (2s, 9H, t-Bu), 3.56, 3.63 (2dd, 1H, PhCO-CHH, J = 7.0, 7.0 Hz, ^2J = 18.5, 18.5 Hz), 3.62 (s, 2H, Ph-CH_2), 3.88, 3.89 (2dd, 1H, PhCO-CHH, J = 6.0, 6.0 Hz, ^2J = 18.5, 18.5 Hz), 4.1-4.3 (m, 4H, 2 CH_2-CH_3), 4.34, 4.49 (2ddd, 1H, CH-CH-N_3, J = 2.5, 6.0, 7.0, 2.5, 6.0, 7.0 Hz), 4.69, 4.73 (2dd, 1H, CH-N_3, J = 2.5, 8.0, 2.5, 8.0 Hz), 4.97, 4.98 (2d, 1H, P-CH, ^2J = 23.8, 24.6 Hz), 6.62, 6.84 (2d, 1H, NH, J = 8.0, 8.0 Hz), 7.2-8.0

(m, 10H, 2 C_6H_5); ir (film) ν_{max}: 3300 (NH), 1770 (β-lactam), 1738 (ester), 1680 (amide, ketone) cm^{-1}; ms (70 eV, 77°), m/e: 572 ($M^{+\cdot}$), 516 ($M^{+\cdot}$ - $Me_2C{=}CH_2$), 397 ($M^{+\cdot}$ - O=C=CH-NHCO-CH_2-Ph), 105 (Ph-C≡$O^{+\cdot}$).

Amide 142

Obtained from 141, by treatment with 1 equivalent of potassium t-butoxide, in THF at -20°, quenching the cold reaction mixture with aqueous ammonium chloride (upon appearance of the first product by tlc, see p. 83) and flash chromatography of the residue.

^{1}Hmr ($CDCl_3$) δ: 1.32 (t, 6H, 2 CH_2-CH_3), 1.50 (s, 9H, t-Bu), 3.6-3.8 (m, 4H, 2 CH_2), 3.9-4.5 (m, 4H, 2 CH_2-CH_3), 5.05, 5.18 (2d, 1H, P-CH, ^2J = 21,22 Hz), 6.7-8.0 (m, 13H, 2 C_6H_5, NH, CH=CH); ir (film) ν_{max}: 3280 (NH), 1740 (ester), 1690-1640 (b, amide, C=C-C=O) cm^{-1}; ms (70 eV, 88°), m/e: 572 ($M^{+\cdot}$), 516 ($M^{+\cdot}$ - $Me_2C{=}CH$), 454, 397 ($M^{+\cdot}$ - O=C=CH-NHCO-CH_2-Ph).

Pyrrole 143

Obtained from 141, in 45% yield, by allowing the above-mentioned reaction to attain completion, followed by work-up in the same manner.

^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.42 (s, 9H, t-Bu), 3.75 (s, 2H, CH_2-Ph), 4.47 (s, 2H, CO-CH_2-NH), 6.18 (d, 1H, NCH=CH, J = 7.0 Hz), 7.2-7.5 (m, 10H, 2 C_6H_5), 8.40 (bs, 1H, NH), 8.41 (d, 1H, NCH=CH, J = 7.0 Hz); ir (film)

ν_{max}: 3300 (NH), 1740 (ester), 1680 (amides), 1650 (C=C) cm^{-1}; ms (70 eV, 67°), m/e: 418 ($M^{+\cdot}$), 362 ($M^{+\cdot}$ - $Me_2C=CH_2$), 313.5 (M*, 418 → 362), 271 ($M^{+\cdot}$ - $Me_2C=CH_2$ - $PhCH_2^{\cdot}$), 202.9 (M*, 362 → 271).

Alcohol 144

To phenylketone 141 (320 mg, 0.56 mmol) in absolute ethanol (20 mL), at 0°, was added $NaBH_4$ (21 mg, 0.55 mmol). After stirring for 1 h at 0° and 20 min at room temperature, pH 4.5 buffer (20 mL) was added and the solution extracted with CH_2Cl_2 (3 x 40 mL). Drying ($MgSO_4$) and evaporation of the solvent afforded 257 mg (80%) of alcohol 144, after flash chromatography (EtOAc).

^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.2-1.4 (m, 6H, 2 CH_2-CH_3), 1.4-1.5 (4s, 9H, t-Bu), 2.0-2.2 (m, 1H, PhCH-CHH), 2.4-2.6 (m, 1H, PhCH-CHH), 3.61 (s, 2H, CH_2-Ph), 3.9-4.0 (m, 1H, CH-CH-NH), 4.1-4.3 (m, 4H, 2 CH_2-CH_3), 4.8-4.9 (m, 1H, CH-NH), 4.86, 4.88 (2d, 1H, P-CH, ^2J = 24,25 Hz), 5.0-5.2 (m, 1H, PhCH-OH), 6.4-6.5 (m, 1H, NH), 7.2-7.5 (m, 10H, 2 C_6H_5); ir (film) ν_{max}: 3400 (NH), 3300 (OH), 1770 (β-lactam), 1740 (ester), 1670 (amide) cm^{-1}; CI-ms (142°), m/e (‰): 458 (144, MH^+ - $Me_2C=CH_2$ - CO_2 - $OH^{\cdot}$), 440 (172, MH^+ - H_2N-CO-CH_2Ph), 290 (1000).

Mesylate 145

Obtained from 144, in 63% yield, *via* the procedure for the preparation of 39, except that, the reaction was worked-up as soon as it

reached room temperature,

^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.2-1.4 (m, 6H, 2 CH_2-CH_3), 1.44, 1.49 (2s, 9H, t-Bu), 1.9-2.2 (m, 1H, PhCH-CHH), 2.60 (s, 3H, SO_2CH_3), 2.8-3.1 (m, 1H, Ph-CH-CHH), 3.6-3.7 (m, 2H, CH_2-Ph), 4.0-4.3 (m, 5H, 2 CH_2-CH_3, CH-CH-NH), 4.83, 4.92 (2d, 1H, P-CH, ^2J = 23.5, 24.5 Hz), 5.01 (bd, 1H, CH-NH, J = 8.0 Hz), 5.7-5.8 (m, 1H, CH-OMs), 6.68 (bd, 1H, NH, J = 8.0 Hz), 7.2-7.5 (m, 10H, 2 C_6H_5); ir (film) ν_{max}: 3300 (NH), 1765 (β-lactam), 1740 (ester), 1670 (amide) cm^{-1}.

Bicyclic β-lactam 146

A solution of mesylate 145 (25 mg, 0.04 mmol) and Et_3N (40 mg, 0.4 mmol) in acetonitrile (0.3 mL) was stirred, at room temperature, for 48 h. Then, ethyl acetate (25 mL) was added and the solution washed with pH 4.5 buffer (2 x 10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated to afford 11 mg (52%) of bicyclic β-lactam 146, after chromatography (8:2, EtOAc:petroleum ether) on silica gel.

When the above reaction was carried out using potassium acetate in DMF, the reaction required 4 days and 146 was obtained in 59% yield. In both cases, a small amount of the corresponding styryl compound was formed.

^{1}Hmr 200 MHz ($CDCl_3$, 45°) δ: 1.04 (s, 9H, t-Bu), 1.2-1.5 (m, 6H, 2 CH_2-CH_3), 2.17, 2.20 (2ddd, 1H, PhCH-CHH, J = 1.0, 5.0 Hz, ^2J = 12.5 Hz),

2.51, 2.53 (2ddd, 1H, PhCH-CHH, J = 7.5, 11.5 Hz, ^2J = 12.5 Hz), 3.61 (s, 2H, CH_2-Ph), 4.1-4.2 (m, 1H, CH-CH-NH), 4.2-4.4 (m, 4H, 2 CH_2-CH_3), 4.42, 4.49 (2dd, 1H, PhCH, J = 1.0, 7.5, 1.0, 7.5 Hz), 4.95 (dd, 1H, CH-NH, J = 2.0, 7.0 Hz), 6.16 (bd, 1H, NH, J = 7.0 Hz), 7.2-7.4 (m, 10H, 2 C_6H_5); ir (film) ν_{max}: 3300 (NH), 1780 (β-lactam), 1740 (ester), 1680 (amide) cm^{-1}; ms (20 eV, 109°), m/e (°/₀₀): 556 (4, $M^{+\cdot}$), 500 (14, $M^{+\cdot}$ - $Me_2C{=}CH_2$), 455 (337, $M^{+\cdot}$ - COOt-Bu·), 419 (1000, $M^{+\cdot}$ - $PO(OEt)_2$·), 363 (599, $M^{+\cdot}$ - $PO(OEt)_2$· - $Me_2C{=}CH_2$).

Alcohol 149

Obtained from 138, in 77% yield after flash chromatography (6:3, EtOAc:petroleum ether), *via* the procedure for the preparation of 144.

^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.2-1.4 (m, 6H, 2 CH_2-CH_3), 1.4-1.5 (4s, 9H, t-Bu), 2.0-2.3 (m, 1H, PhCH-CHH), 2.4-2.7 (m, 1H, PhCH-CHH), 4.0-4.6 (m, 7H, 2 CH_2-CH_3, CH-CH-N_3, PhCH-OH), 4.9-5.0 (m, 1H, CH-N_3), 4.93, 5.00 (2d, 1H, P-CH, ^2J = 24.25 Hz), 7.3-7.5 (m, 5H, C_6H_5); ir (film) ν_{max}: 3400 (OH), 2100 (N_3), 1772 (β-lactam), 1740 (ester) cm^{-1}; CI-ms (108°), m/e (°/₀₀): 483 (92, MH^+), 455 (307, MH^+ - N_2·), 437 (254, MH^+ - N_2· - H_2O), 409 (796, MH^+ - $Me_2C{=}CH_2$ - H_2O), 381 (1000, MH^+ - $Me_2C{=}CH_2$ - N_2· - H_2O); Anal. calcd. for $C_{21}H_{31}N_4O_7P$: C 52.28, H 6.48, N 11.61; found: C 52.06, H 6.51, N 11.12.

Mesylate 150

Obtained from 149, in 60% yield, *via* the procedure for the preparation of 145.

^{1}Hmr ($CDCl_3$) δ: 1.1-1.4 (m, 6H, 2 CH_2-CH_3), 1.48 (s, 9H, t-Bu), 2.0-2.9 (m, 2H, PhCH-CH_2), 2.7-2.8 (4s, 3H, SO_2CH_3), 3.9-4.4 (m, 6H, 2 CH_2-CH_3, CH-CH-N_3), 3.85, 3.88 (2d, 1H, P-CH, ^2J = 24,25 Hz); 5.6-5.8 (m, 1H, CH-OMs), 7.3-7.5 (m, 5H, C_6H_5); ir (film) ν_{max}: 2100 (N_3), 1772 (β-lactam), 1738 (ester) cm^{-1}; CI-ms (120°), m/e (°/₀₀): 437 (259, MH^+ - N_2 · - $MeSO_3H$), 365 (1000, MH^+ - $MeSO_3H$ - $Me_2C{=}CH_2$ - CO_2).

Bicyclic β-lactam 151

Obtained from 150, in 53% yield, *via* the procedure for the preparation of 146.

^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.05 (s, 9H, t-Bu), 1.36, 1.43 (2t, 6H, 2 CH_2-CH_3), 2.14 (ddd, 1H , PhCH-CHH, J = 1.0, 5.5 Hz, ^2J = 12.5 Hz), 2.52 (ddd, 1H, PhCH-CHH, J = 7.5, 11.5 Hz, ^2J = 12.5 Hz), 4.2-4.4 (m, 5H, 2 CH_2-CH_3, CH-CH-N_3), 4.42, 4.49 (2dd, 1H, PhCH, J = 1.0, 7.5, 1.0, 7.5 Hz), 4.53 (d, 1H, CH-N_3, J = 2.5 Hz), 7.1-7.4 (m, 5H, C_6H_5); ir (film) ν_{max}: 2100 (N_3), 1783 (β-lactam), 1740 (ester) cm^{-1}; CI-ms (102°), m/e (°/₀₀): 465 (252, MH^+), 437 (468, MH^+ - N_2 ·), 409 (155, MH^+ - $Me_2C{=}CH_2$), 381 (1000, MH^+ - N_2 · - $Me_2C{=}CH_2$).

Amide β-lactam 153

Into azide 152 (946 mg, 1.9 mmol) dissolved in CH_2Cl_2 (60 mL) and Et_3N (193 mg, 1.9 mmol), at 0°, was bubbled H_2S for 10 min. The solution was then allowed to warm. After stirring for 1 h at room temperature, nitrogen was bubbled through the solution for 0.5 h. To this solution at 0° was added pyridine (200 mg, 2.5 mmol), followed by dropwise addition of phenylacetyl chloride (386 mg, 2.5 mmol) over 5 min. After stirring for 1 h at ambient temperature, the solution was washed with H_2O (3 x 40 mL) and brine (50 mL), then treated with $MgSO_4$ and charcoal, filtered and evaporated to afford 622 mg (55%) of amide 153, after flash chromatography (3:7, EtOAc:petroleum ether).

^{1}Hmr 200 MHz ($CDCl_3$) δ: 3.62 (s, 2H, $PhCH_2CO$), 4.87 (d, 1H, CH-CH-NH, J = 2.5 Hz), 5.00 (dd, 1H, CH-NH, J = 2.5, 7.5 Hz), 5.09, 5.22 (2AB [2 app. doublets], 4H, 2 $PhCH_2$-O), 5.27 (s, 1H, $CH-CO_2CH_2Ph$), 6.28 (d, 1H, NH, J = 7.5 Hz), 7.1-7.4 (m, 20H, 4 C_6H_5); ir (film) ν_{max}: 3300 (NH), 1785 (β-lactam), 1750 (esters), 1670 (amide) cm^{-1}.

Phenylketone 154

Obtained from 153, in 64% yield after flash chromatography (3:7, EtOAc:petroleum ether), *via* the procedure for the preparation of 138.

^{1}Hmr 200 MHz ($CDCl_3$) δ: 3.60 (d, 2H, PhCO-CH_2, J = 6.5 Hz), 3.61 (s,

2H, $PhCH_2$-CO), 4.36 (dt, 1H, CH-CH-NH, J = 2.5; 6.5 Hz), 4.69 (dd, 1H, CH-NH, J = 2.5, 7.0 Hz), 5.11, 5.24 (2AB, 4H, 2 $PhCH_2$-O), 5.35 (s, 1H, CH-CO_2CH_2Ph), 6.18 (d, 1H, NH, J = 7.0 Hz), 7.2-7.9 (m, 20H, 4 C_6H_5); ir (film) ν_{max}: 3300 (NH), 1775 (β-lactam), 1750 (esters), 1690-1650 (amide, phenylketone) cm^{-1}.

Alcohol 155

To phenylketone 154 (340 mg, 0.56 mmol) in absolute ethanol (20 mL), at 0°, was added $NaBH_4$ (21 mg, 0.56 mmol). After stirring for 1 h at 0° and 20 min at room temperature, pH 4.5 buffer (20 mL) was added and the solution extracted with CH_2Cl_2 (3 x 40 mL). Drying ($MgSO_4$) and evaporation of the solvent afforded a total of 232 mg (68%) of alcohol 155, after flash chromatography (3:7, EtOAc:petroleum ether; 188 mg of less polar and 44 mg of more polar material).

Less polar fraction: ^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.95 (ddd, 1H, PhCH-CHH, J = 3.3, 9.0 Hz, ^2J = 14.5 Hz), 2.26 (ddd, 1H, PhCH-CHH, J = 4.5, 9.5 Hz, ^2J = 14.5 Hz), 3.13 (d, 1H, OH, J = 5.2 Hz), 3.55 (s, 2H, $PhCH_2$-CO), 4.05 (ddd, 1H, CH-CH-NH, J = 2.2, 4.5, 9.0 Hz), 4.68 (dd, 1H, CH-NH, J = 2.2, 6.5 Hz), 4.92 (ddd, 1H, PhCH-OH, J = 3.3, 5.2, 9.5 Hz), 5.14, 5.16 (2AB, 4H, 2$PhCH_2$-O), 5.22, 5.31 (2s, 1H, CH-CO_2CH_2Ph), 6.35 (d, 1H, NH, J = 6.5 Hz), 7.2-7.4 (m, 20H, 4 C_6H_5); ir (film) ν_{max}: 3400 (OH), 3300 (NH), 1775 (β-lactam), 1750 (esters), 1665 (amide) cm^{-1}.

More polar fraction: ^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.92 (ddd, 1H, PhCH-CHH, J = 10.0, 10.0 Hz, ^{2}J = 14.0 Hz), 2.20 (ddd, 1H, PhCH-CHH, J = 3.0, 4.0 Hz, ^{2}J = 14.0 Hz), 3.60 (s, 2H, $PhCH_2$-CO), 4.00 (ddd, 1H, CH-CH-NH, J = 2.2, 4.0, 10.0 Hz), 4.40 (d, 1H, OH, J = 4.4 Hz), 4.68 (m, 1H, PhCH-OH), 4.71 (dd, 1H, CH-NH, J = 2.2, 6.0 Hz), 5.12 (s, 2H, $PhCH_2$-O), 5.18 (AB, 2H, $PhCH_2$-O), 5.26 (s, 1H, $CH-CO_2CH_2Ph$), 6.35 (d, 1H, NH, J = 6.0 Hz), 7.2-7.4 (m, 20H, 4 C_6H_5); ir (film) ν_{max}: 3350 (OH), 3300 (NH), 1775 (β-lactam), 1750 (esters), 1660 (amide) cm^{-1}.

Chloride 156

To a solution of alcohol 155 (121 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) containing pyridine (48 mg, 0.6 mmol) was added $MeSO_2Cl$ (70 mg, 0.6 mmol), at room temperature. After stirring overnight, CH_2Cl_2 (20 mL) was added and the solution washed with water (3 x 5 mL), dried ($MgSO_4$) and evaporated to give 76 mg (61%) of chloride 156 and 25 mg (21%) of the corresponding styryl β-lactam, after flash chromatography (2:8, EtOAc: petroleum ether).

Chloride 156: ^{1}Hmr 200 MHz ($CDCl_3$) δ: 2.35 (ddd, 1H, PhCH-CHH, J = 7.5, 9.5 Hz, ^{2}J = 14.0 Hz), 2.63 (ddd, 1H, PhCH-CHH, J = 4.0, 7.5 Hz, ^{2}J = 14.0 Hz), 3.55 (s, 2H, $PhCH_2$-CO), 3.78 (ddd, 1H, CH-CH-NH, J = 2.5, 4.0, 9.5 Hz), 4.64 (dd, 1H, CH-NH, J = 2.5, 7.7 Hz), 4.98 (dd, 1H, PhCH-Cl, J = 7.5, 7.5 Hz), 5.1-5.2 (m, 4H, 2 $PhCH_2$-O), 5.30 (s, 1H, $CH-CO_2CH_2Ph$), 6.10 (d, 1H, NH, J = 7.7 Hz), 7.2-7.4 (m, 20H, 4 C_6H_5);

ir (film) ν_{max}: 3300 (NH), 1775 (β-lactam), 1750 (esters), 1670 (amide) cm^{-1}; ms (20 eV, 97°), m/e (‰): 624, 626 (0.6, 0.4, $M^{+\cdot}$), 588 (1, $M^{+\cdot}$ - HCl), 454 (6, $M^{+\cdot}$ - $Cl^{\cdot}$ - $CO_2CH_2Ph^{\cdot}$), 91 (1000, $PhCH_2^{+\cdot}$).

Styryl β-lactam side-product: ^{1}Hmr 200 MHz ($CDCl_3$) δ: 3.65 (s, 2H, $PhCH_2$-CO), 4.57 (dd, 1H, CH-CH-NH, J = 2.5, 9.0 Hz), 4.84 (dd, 1H, CH-NH, J = 2.5, 8.0 Hz), 5.08, 5.24 (2s, 4H, 2 $PhCH_2$-O), 5.28 (s, 1H, CH-CO_2CH_2Ph), 6.20 (d, 1H, NH, J = 8.0 Hz), 6.22 (dd, 1H, PhCH=CH, J = 9.0,16 Hz), 6.60 (d, 1H, PhCH=CH, J = 16 Hz), 7.2-7.5 (m, 20H, 4 C_6H_5); ir (film) ν_{max}: 3300 (NH), 1775 (β-lactam), 1750 (esters), 1670 (amide) cm^{-1}.

Bicyclic β-lactam 157

A solution of chloride 156 (63 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) containing triethylamine (50 mg, 0.5 mmol) was stirred for 48 h, at room temperature. Then, CH_2Cl_2 (25 mL) was added and the solution washed with pH 4.5 buffer (2 x 10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated to afford 49 mg (83%) of bicyclic β-lactam 157, after flash chromatography (2:8, EtOAc:petroleum ether).

^{1}Hmr 200 MHz ($CDCl_3$) δ: 2.40 (ddd, 1H, PhCH-CHH, J = 5.5, 6.0 Hz, ^{2}J = 13.0 Hz), 2.56 (ddd, 1H, PhCH-CHH, J = 9.5, 13.5 Hz, ^{2}J = 13.0 Hz), 3.63 (s, 2H, $PhCH_2$-CO), 3.83 (ddd, 1H, CH-CH-NH, J = 2.3, 5.5, 9.5 Hz), 4.44, 4.86 (2d, AB, 2H, $PhCH_2$-O, J = 12.0 Hz), 4.49 (dd, 1H, PhCH-CH_2, J = 6.0, 13.5 Hz), 5.08 (dd, 1H, CH-NH, J = 2.3, 7.3 Hz), 5.10, 5.23

(2d, AB; 2H, $PhCH_2$-O, J = 12.5 Hz), 6.24 (d, 1H, NH, J = 7.3 Hz), 6.7-6.8, 7.1-7.4 (m, 20H, 4 C_6H_5); ir (film) ν_{max}: 3300 (NH), 1785 (β-lactam), 1750 (esters), 1670 (amide) cm^{-1}; ms (20 eV, 96°), m/e (°/₀₀): 588 (9, $M^{+\cdot}$), 453 (118, $M^{+\cdot}$ - $CO_2CH_2Ph^{\cdot}$), 413 (79, $M^{+\cdot}$ - $PhCH_2CONHCH{=}C{=}O$), 322 (130, $M^{+\cdot}$ - 175 - $CH_2Ph^{\cdot}$), 278 (336, $M^{+\cdot}$ - 175 - $CO_2CH_2Ph^{\cdot}$), 187.1 (M*, 413 → 278).

β-Lactams 159 and 160

Obtained from trimethylsilylpropargyl aldehyde and amine 108, in 76% yield, as a 1 to 2 mixture of *cis* (159) and *trans* (160) isomers, *via* the procedure for the preparation of 106.

β-Lactam 159: ^{1}Hmr 200 MHz ($CDCl_3$) δ: 0.21, 0.22, (2s, 9H, $SiMe_3$), 1.3-1.4 (m, 6H, 2 CH_2-CH_3), 1.50, 1.52 (2s, 9H, t-Bu), 4.1-4.4 (m, 4H, 2 CH_2-CH_3), 4.58, 4.61 (2d, 1H, CH-CH-N_3, J = 5.0, 5.0 Hz), 4.76, 4.77 (2d, 1H, P-CH, ^{2}J = 22,23 Hz), 4.86, 5.00 (2d, 1H, CH-N_3, J = 5.0, 5.0 Hz); ir (film) ν_{max}: 2110 (N_3), 1780 (β-lactam), 1735 (ester) cm^{-1}.

β-Lactam 160: ^{1}Hmr 200 MHz ($CDCl_3$) δ: 0.19 (s, 9H, $SiMe_3$), 1.3-1.4 (m, 6H, 2 CH_2-CH_3), 1.51 (s, 9H, t-Bu), 4.1-4.3 (m, 4H, 2 CH_2-CH_3), 4.43, 4.56 (2d, 1H, CH-CH-N_3, J = 2.5, 2.5 Hz), 4.62, 4.65 (2d, 1H, CH-N_3, J = 2.5, 2.5 Hz), 4.64, 4.76 (2d, 1H, P-CH, ^{2}J = 23,23 Hz); ir (film) ν_{max}: 2110 (N_3), 1785 (β-lactam), 1740 (ester) cm^{-1}.

Terminal acetylene 161

Obtained from 160, in 70% yield, according to the procedure described by Kraihanzel and Poist[119].

^{1}Hmr ($CDCl_3$) δ: 1.2-1.5 (m, 6H, 2 CH_2-CH_3), 1.53 (s, 9H, t-Bu), 2.73, 2.75 (2d, 1H, C≡C-H, J = 2.0, 2.0 Hz), 4.0-4.4 (m, 4H, 2 CH_2-CH_3), 4.6-4.8 (m, 2H, CH-CH-N_3), 4.72, 4.80 (2d, 1H, P-CH, ^{2}J = 23,24 Hz); ir (film) ν_{max}: 3280 (C≡C-H), 2110 (N_3), 1785 (β-lactam), 1740 (ester) cm^{-1}.

Methyl ketones 162 and 163

Obtained from 159 and 160, in 63 and 60% yield, respectively, *via* the procedure for the preparation of 138.

Ketone 162: ^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.35, 1.37 (2t, 6H, 2 CH_2-CH_3), 1.48, 1.51 (2s, 9H, t-Bu), 2.25, 2.31 (2s, 3H, $COCH_3$), 4.1-4.3 (m, 4H, 2 CH_2-CH_3), 4.74, 4.89 (2d, 1H, P-CH, ^{2}J = 19,22 Hz), 4.75-4.85 (3d, 1H, CH-CH-N_3, J = 5.5 Hz), 4.9-5.0 (3d, 1H, CH-N_3, J = 5.5 Hz); ir (film) ν_{max}: 2110 (N_3), 1785 (β-lactam), 1735 (ester, ketone) cm^{-1}.

Ketone 163: ^{1}Hmr 200 MHz ($CDCl_3$) δ: 1.3-1.4 (m, 6H, 2 CH_2-CH_3), 1.48, 1.51 (2s, 9H, t-Bu), 2.34, 2.36 (2s, 3H, $COCH_3$), 4.1-4.3 (m, 4H, 2 CH_2-CH_3), 4.45-4.65 (m, 2H, CH-CH-N_3), 4.73, 4.87 (2d, 1H, P-CH, ^{2}J = 20,22 Hz); ir (film) ν_{max}: 2110 (N_3), 1785 (β-lactam), 1735 (ester, ketone) cm^{-1}.

BIBLIOGRAPHY

1. H. Staudinger, Liebigs Ann. Chem., 356, 51 (1907).

2. T.H. Clarke, J.R. Johnson and R. Robinson, *"The Chemistry of Penicillin"*, Princeton University Press, N.Y. (1949).

3. G.G.F. Newton and E.P. Abraham, Nature, 175, 548 (1955); Biochem. J., 62, 651 (1955).

4. D.C. Hodgkin and E.N. Maslen, Biochem. J., 79, 393 (1961).

5. T. Kikuchi and S. Uyeo, Tetrahedron Lett., 3473 (1965).

6. R. Nagarajan, L.D. Boeck, M. Gorman, R.L. Hamill, C.E. Higgens, M.M. Hoehn, W.M. Stark, and J.J. Whitney, J. Am. Chem. Soc., 93, 2308 (1971); G. Albers-Schoenberg, B.H. Arison and J.L. Smith, Tetrahedron Lett., 2911 (1972).

7. T.T. Howarth, A.G. Brown and T.J. King, J.C.S. Chem. Comm., 266 (1976).

8. W.W. Stewart, Nature, 229, 174 (1971).

9. T. Takita, Y. Muraoka, T. Yoshioka, A. Fujii, K. Maeda and H. Umezawa, J. Antibiotics, 25, 755 (1972); 26, 252 (1973).

10. M. Hashimoto, T. Komori and T. Kamiya, J. Antibiotics, 29, 890 (1976); J. Am. Chem. Soc., 98, 3023 (1976).

11. G.A. Schönberg, B.H. Arison, O.D. Hensens, J. Hirshfield, K. Hoogsteen, E.A. Kaczka, R.E. Rhodes, J.S. Kahan, F.M. Kahan, R.W. Ratcliffe, E. Walton, L.J. Ruswinkle, R.B. Morin and B.G. Christensen, J. Am. Chem. Soc., 100, 6491 (1978).

12. D. Butterworth, M. Cole, G. Hanscomb and G.N. Robinson, J. Antibiotics, 32, 287 (1979); J.D. Hood, S.J. Box and M.S. Verrall, *ibid.*, 32, 295 (1979); A.G. Brown, D.F. Corbett, A.J. Eglington and T.T. Howarth, J.C.S. Chem. Comm., 523 (1977).

13. J. ETks, *"Recent Advances in the Chemistry of β-Lactam Antibiotics"*, The Chemical Society, Burlington House, London (1977).

14. P. Actor, R.D. Sitrin and J.V. Uri, *"Annual Reports in Medicinal Chemistry-14"*, H.-J. Hess, ed. in chief, Academic Press, New York (1979).

15. L.D. Cama and B.G. Christensen, *"Annual Reports in Medicinal Chemistry-13"*, F.H. Clarke, Ed. in Chief, Academic Press, N.Y. (1978).

16. B.D. Davis, R. Dulbecco, H.N. Eisen, H.S. Ginsberg and W.B. Wood, *"Microbiology"*, Harper and Row, New York, (1973).

17. E.M. Wise and T.J. Park, Proc. Natl. Acad. Sci. USA, 54, 75 (1965).

18. D.J. Tipper and J.L. Strominger, Proc. Natl. Acad. Sci. USA, 54, 1133 (1965).

19. D.B. Boyd, Proc. Natl. Acad. Sci. USA, 74, 5239 (1977); J. Med. Chem., 22, 533 (1979).

20. J.C. Jászberényi and T.E. Gunda, *"Progress in Medicinal Chemistry"*, Vol. 12, G.P. Ellis and G.B. West, eds., Elsevier, N.Y. (1975).

21. D.J. Tipper, Rev. Infect. Dis., 1, 39 (1979), and references therein.

22. B.G. Spratt, Proc. Natl. Acad. Sci. USA, 72, 2999 (1975); B.G. Spratt and J.L. Strominger, J. Bacteriol., 127, 660 (1976).

23. M. Matsuhashi, I.N. Maruyama, Y. Takagaki, S. Tamaki, Y. Nishimura and Y. Hirota, Proc. Natl. Acad. Sci. USA, 75, 2631 (1978).

24. S.J. Curtis and J.L. Strominger, J. Bacteriol., 145, 398 (1981).

25. L.S. Schmidt, G. Botta and J.T. Park, J. Bacteriol., 145, 632 (1981); G.A. Botta and J.T. Park, J. Bacteriol., 145, 333 (1981).

26. J.R. Rasmussen and J.L. Strominger, Proc. Natl. Acad. Sci. USA, 75, 84 (1978); R.R. Yocum, D.J. Waxman, J.R. Rasmussen and J.L. Strominger, Proc. Natl. Acad. Sci. USA, 76, 2730 (1979).

27. J.M. Ghuysen, Symposium on "Recent Advances in the Chemistry of β-Lactam Antibiotics", abstracts of papers, Cambridge, 30 June, 1980.

28. A. Tomasz, Annuals N.Y. Acad. Sci., 235, 439 (1974); R. Lopez, C.R. Lain, A. Tapia, S.B. Waks and A. Tomasz, Antimicrob. Agents Chemother., 10, 697 (1976).

29. H. Nikaido, Angew. Chem. Int. Ed. Engl., 18, 337 (1979), and references therein.

30. R.B. Sykes and A. Morris, *"Progress in Medicinal Chemistry"*, Vol. 12, G.P. Ellis and G.B. West, eds., Elsevier, N.Y. (1975), and references therein.

31. J.F. Fisher and J.R. Knowles, *"Annual Reports in Medicinal Chemistry-13"*, F.H. Clarke, ed. in chief, Academic Press, New York (1978).

32. M.H. Richmond, Rev. Infect. Dis., 1, 30 (1979).

33. B.S. Orlek, P.G. Sammes, V. Knott-Hunziker and S.G. Waley, J.C.S. Chem. Comm., 962 (1979); also, Symposium on "Recent Advances in the Chemistry of β-Lactam Antibiotics", abstracts of papers, Cambridge, 30 June, 1980.

34. R.F. Pratt and M.J. Loosemore, Proc. Natl. Acad. Sci. USA, 75, 4145 (1978).

35. From a correspondent, Nature, 279, 288 (1979).

36. E.H. Flynn, *"Cephalosporins and Penicillins, Chemistry and Biology"*, Academic Press, N.Y. (1972).

37. T.W. Doyle, B. Belleau, B.Y. Luh, C.F. Ferrari and M.P. Cunningham, Can. J. Chem., 55, 468 (1977).

38. W. Dürckheimer, H. Seliger, N. Klessel, M. Limbert, E. Schrinner and K. Seeger, Symposium on "Recent Advances in the Chemistry of β-Lactam Antibiotics", abstracts of papers, Cambridge, 30 June (1980).

39. J.R. Knowles, 178th ACS National Meeting, abstracts of papers, Washington, 9 Sept. (1979).

40. P. Actor, R.D. Sitrin and J.V. Uri, *"Annual Reports in Medicinal Chemistry-15"*, H.-J. Hess, ed. in chief, Academic Press, N.Y. (1980).

41. G.P. Bodey, S. Weaver and T. Pan, J. Antibiotics, 30, 724 (1977).

42. J.G. Allen, F.R. Atherton, M.J. Hall, C.H. Hassall, S.W. Holmes, R.W. Lambert, L.J. Nisbet and P.S. Ringrose, Nature, 272, 56 (1978).

43. C.W. Thornber, Chem. Rev., 8, 563 (1979).

44. S.J. Cartwright and A.F.W. Coulson, Nature, 278, 360 (1979).

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

46. M. Lang, K. Prasad, W. Holick, J. Gosteli, I. Ernest and R.B. Woodward, J. Am. Chem. Soc., 101, 6296 (1979).

47. A.K. Mukerjee and R.C. Srivastava, Synthesis, 327 (1973); A.K. Mukerjee and A.K. Singh, Synthesis, 547 (1975); P.G. Sammes, Chem. Rev., 76, 113 (1976); A.K. Mukerjee and A.K. Singh, Tetrahedron, 34, 1731 (1978).

48. J. Sheehan and H. Logan, J. Am. Chem. Soc., 84, 2983 (1962).

49. R.B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan and H. Vorbrüggen, J. Am. Chem. Soc., 88, 852 (1966); R.B. Woodward, Science, 153, 487 (1966).

50. A.K. Bose, M.S. Manhas, H.P.S. Chawala and B. Dayal, J.C.S. Perkin Trans. I, 1880 (1975); A.K. Bose, G. Spiegelham and M.S. Manhas, J. Am. Chem. Soc., 90, 4506 (1968).

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

52. a) R.W. Ratcliffe and B.G. Christensen, Tetrahedron Lett., 4645 (1973); b) 4649 (1973); c) 4653 (1973); d) 3567 (1974).

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

54. R.A. Firestone, J.L. Fahey, N.S. Maciejewicz, G. Patel and B.G. Christensen, J. Med. Chem., 20, 551 (1977).

55. T.W. Doyle, J.L. Douglas, B. Belleau, T.T. Conway, C.F. Ferrari, D.E. Horning, G. Lim, B.Y. Luh, A. Martel, M. Menard, L.R. Morris and M. Misiek, Can. J. Chem., 58, 2508 (1980).

56. D.B.R. Johnston, S.M. Schmitt, F.A. Bouffard and B.G. Christensen, J. Am. Chem. Soc., 100, 313 (1978); F.A. Bouffard, D.B.R. Johnston and B.G. Christensen, J. Org. Chem., 45, 1130 (1980).

57. P.H. Bentley, P.D. Berry, G. Brooks, M.L. Gilpin, E. Hunt and I.I. Zomaya, J.C.S. Chem. Comm., 748 (1977).

58. T.N. Salzmann, R.W. Ratcliffe, B.G. Christensen and F.A. Bouffard, J. Am. Chem. Soc., 102, 6161 (1980).

59. W.J. Leanza, K.J. Wildonger, T.W. Miller and B.G. Christensen, J. Med. Chem., 22, 1435 (1979).

60. A.K. Bose, M.S. Manhas, J.C. Kapur, S.D. Sharma and S.G. Amin, J. Med. Chem., 17, 541 (1974); A.K. Bose, B. Anjaneyulu, S.K. Bhattacharya and M.S. Manhas, Tetrahedron, 23, 4769 (1967); A.K. Bose, S.D. Sharma, J.C. Kapur and M.S. Manhas, Synthesis, 216 (1973); A.K. Bose, J.C. Kapur, S.G. Amin and M.S. Manhas, Tetrahedron Lett., 1917 (1974).

61. A. Ugolini, unpublished results.

62. G. Just and R. Zamboni, Can. J. Chem., 56, 2720 (1978); see also ref. 69.

63. J. Sheehan and V.S. Frank, J. Am. Chem. Soc., 71, 1856 (1949).

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

65. E.J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 94, 6190 (1972).

66. H.B. Kagan, J.J. Basselier and J.L. Luche, Tetrahedron Lett., 941 (1964); J.L. Luche, H.B. Kagan, R. Parthasarathy, G. Tsoucaris, C. de Rango and C. Zelwer, Tetrahedron, 24, 1275 (1968).

67. J. Pless, J. Org. Chem., 39, 2644 (1974).

68. P.C. Blanpain, J.B. Nagy, G.H. Laurent and F.V. Durant, J. Med. Chem., 23, 1283 (1980).

69. R. Zamboni, Ph.D. Thesis, McGill University, Montreal, 1978.

70. H.W. Moore, L. Hernandez and A. Sing, J. Am. Chem. Soc., 98, 3728 (1976); H.W. Moore, Acc. Chem. Res., 12, 125 (1979).

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

72. S.J. Kuhn and G.A. Olah, J. Am. Chem. Soc., 83, 4564 (1961).

73. C.A. Cupas and R.L. Pearson, J. Am. Chem. Soc., 90, 4742 (1968).

74. Y.S. Tsantrizos, M.Sc. Thesis, McGill University, Montreal, 1979.

75. M.J. Kamlet and R.R. Minesinger, J. Org. Chem., 36, 610 (1971).

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

77. H. Kauffmann and E. de Pay, Ber., 37, 725 (1904); R.E. Schaffrath, J. Chem. Ed., 47, 224 (1970).

78. G. Hilgetag and A. Martini, ed., *"Preparative Organic Chemistry"*, Wiley, New York, 1972, p. 560.

79. G. Just and R. Zamboni, Can. J. Chem., 56, 2725 (1978).

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

81. R.N. Guthikonda, L.D. Cama and B.G. Christensen, J. Am. Chem. Soc., 96, 7584 (1974).

82. G.H. Hakimelahi and G. Just, Synth. Comm., 10, 429 (1980).

83. M.J. Carter and I. Fleming, J.C.S. Chem. Comm., 679 (1976).

84. R. Mantione and Y. Leroux, J. Organometal. Chem., 31, 5 (1971).

85. Y. Leroux and C. Roman, Tetrahedron Lett., 2585 (1973).

86. G. Tadema, P. Vermeer, J. Meijer and L. Brandsma, Recl. Trav. Chim. Pays-Bas, 95, 66 (1976).

87. L. Brandsma, *"Preparative Acetylenic Chemistry"*, Elsevier, New York (1971).

88. C.R. Hanser and C.R. Hance, J. Am. Chem. Soc., 74, 5091 (1952).

89. P. Sieber, Helv. Chim. Acta, 60, 2711 (1977).

90. F. Bohlmann, Chem. Ber., 90, 1519 (1957).

91. D. Ayalon-Chass, E. Ehlinger and P. Magnus, J.C.S. Chem. Comm., 772 (1977).

92. R.J.P. Corriu, G.F. Lanneau, D. Leclercq and D. Samate, J. Organometal. Chem., 144, 155 (1978); R.J.P. Corriu, J. Masse and D. Samate, J. Organometal. Chem., 93, 71 (1975).

93. L.F. Fieser and M. Fieser, *"Reagents for Organic Synthesis"*, Vol. 1, Wiley, N.Y. (1968), p. 397.

94. R.F. Cunico, H.M. Lee and J. Herbach, J. Organometal. Chem., 52, C7 (1973).

95. G. Stork and E. Colvin, J. Am. Chem. Soc., 93, 2080 (1971).

96. T.H. Chan, M.P. Li, W. Mychajlowski and D.N. Harpp, Tetrahedron Lett., 3511 (1974).

97. Obtained from W.H. Rastetter through Dr. K. Steliou, for preparation and use see W.H. Rastetter, T.J. Richard and M.D. Lewis, J. Org. Chem., 43, 3163 (1978).

98. Ref. 93, p. 821.

99. G. Stork and M.E. Jung, J. Am. Chem. Soc., 96, 3682 (1974).

100. E.W. Colvin, Chem. Soc. Rev., 7, 15 (1978).

101. a) P.F. Hudrlik, R.H. Schwartz and A.K. Kulkarni, Tetrahedron Lett., 2233 (1979); b) M. Obayashi, K. Utimoto and H. Nozaki, Tetrahedron Lett., 1383 (1978); c) P.F. Hudrlik, R.N. Misra, G.P. Withers,

A.M. Hudrlik, R.J. Rona and J.P. Arcoleo, Tetrahedron Lett., 1453 (1976); d) P. Magnus and G. Roy, J.C.S. Chem. Comm., 297 (1978); e) C.M. Robbins and G.H. Whitham, J.C.S. Chem. Comm., 697 (1976); f) P.F. Hudrlik, J.P. Arcoleo, R.H. Schwartz, R.N. Misra and R.J. Rona, Tetrahedron Lett., 591 (1977); g) J.J. Eisch and J.E. Galle, J. Org. Chem., 41, 2615 (1976).

102. P.F. Hudrlik, A.M. Hudrlik, R.J. Rona, R.N. Misra and G.P. Withers, J. Am. Chem. Soc., 99, 1993 (1977).

103. Y.K. Han and L.A. Paquette, J. Org. Chem., 44, 3731 (1979).

104. D.O. Spry, J. Org. Chem., 44, 3084 (1979).

105. M.M. Campbell and D.I. Rawson, Tetrahedron Lett., 1257 (1979).

106. V. VanRheenen, R.C. Kelley and D.Y. Cha, Tetrahedron Lett., 1973 (1976).

107 J.E. McMurry and J. Melton, J. Am. Chem. Soc., 93, 5309 (1971); J.E. McMurry, Acc. Chem. Res., 7, 281 (1974); T.L. Ho, Synthesis, 1 (1979).

108. J.E. McMurry and J. Melton, J. Org. Chem., 38, 4367 (1973).

109. Ref. 78, p. 348.

110. R.H. Wollenberg and S.J. Miller, Tetrahedron Lett., 3219 (1978).

111. I. Ernest, J. Gosteli, C.W. Greengrass, W. Holick, D.E. Jackman, H.R. Pfaendler and R.B. Woodward, J. Am. Chem. Soc., 100, 8214 (1978); I. Ernest, J. Gosteli and R.B. Woodward, J. Am. Chem. Soc., 101, 6301 (1979); H.R. Pfaendler, J. Gosteli and R.B. Woodward, J. Am. Chem. Soc., 101, 6306 (1979); see also reference 46.

112. H.C. Brown and P. Geoghegan Jr., J. Am. Chem. Soc., 89, 1522 (1967); H.C. Brown and W.J. Hammar, J. Am. Chem. Soc., 89, 1524 (1967); H.C. Brown, J.H. Kawakami and S. Ikegami, J. Am. Chem. Soc., 89, 1525 (1967).

113. H.C. Brown and M.-H. Rei, J. Am. Chem. Soc., 91, 5646 (1969).

114. E.J. Corey and M.A. Tius, Tetrahedron Lett., 2081 (1977).

115. W.Y. Liu and G. Just, McGill University, Montreal, unpublished results.

116. H.B. Kagan, A. Marquet and J. Jacques, Bull. Soc. Chim. (France), 1079 (1960).

117. E. Santaniello, F. Ponti and A. Manzocchi, Synthesis, 891 (1978).

118. G.H. Hakimelahi, A. Ugolini and G. Just, submitted 09/1981, Can. J. Chem.

119. C.S. Kraihanzel and J.E. Poist, J. Organometal. Chem., 8, 239 (1967).

120. H.C. Brown and S.P. Rhodes, J. Am. Chem. Soc., 91, 4306 (1969).

121. H.C. Brown, C.G. Scouten and R. Liotta, J. Am. Chem. Soc., 101, 96 (1979).

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

123. Ref. 93, p. 703.

124. A.J. Gordon and R.A. Ford, *"The Chemist's Companion, a Handbook of Practical Data, Techniques and References"*, Wiley, New York (1972).

125. F. Arndt, Org. Synth. Coll. Vol. II, 165 (1943).

126. M. Miyashita, A. Yoshikoshi and P.A. Grieco, J. Org. Chem., 42, 3772 (1977).

127. T. Ohgi and S.M. Hecht, J. Org. Chem., 46, 1232 (1981), and references therein.