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UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

For Jiji and Pitaji

ABSTRACT

Chapter 1 contains a very brief overview of 3,3-disubstituted azetidinones. Also included in this chapter are the approaches to 'hybrid' azetidinones, i.e. those which contain the structural features of more than one class of azetidinones. Finally the target molecules for the present studies are listed.

Chapter 2 contains details of use of various 2,3-dihydroxybutyric acid derivatives in enantioselective syntheses of 3-alkoxyazetidinones with an additional substituent at position 3. In chapter 3 similar studies on threonine derivatives for the syntheses of 3-amino-3-hydroxyethylazetidinones are described. These studies were only partially successful.

In chapter 4 a systematic approach towards the syntheses of 3-alkoxyazetidinones is described. The steps involved were the formation of the C-3 carbanion from the parent azetidinones, reaction with acetaldehyde, oxidation of the resulting 3-alkoxy-3-hydroxyethylazetidinones and finally the reduction of the acetyl compound in a non-chelation controlled manner. It has been possible to synthesize protected 3-amino-3-hydroxyethylazetidinones by a similar series of reaction and the results are presented in chapter 5.

Chapter 6 has details of syntheses of 3-hydroxy, 3-hydroxy-3-hydroxyethyl, 3-hydroxy-3-allyl and 3-'epoxy'azetidinones.

Chapter 7 contains results of a detailed study on the impact of various variables on the non-chelation controlled reduction of 3-acylazetidinones (which have an additional substituent at 3-position).

Chapter 8 is about the use of N, N-dimethylchloromethylenimnium chloride for the the purpose of activating carboxylic acids for their final conversion to azetidinones. An attempt was made to determine the nature of the white solid obtained on reaction of DMF with oxaly chloride, and the product of reaction between this white solid and a carboxylic acid.

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LIST OF ABBREVIATIONS

Ac	Acetyl
t-Bu	tertiary butyl
°C	degrees Celsius
ca.	approximately
cat	catalytic quantities (< 5%)
Cbz	carbobenzyloxy
CI	chemical ionization
cm	centimeter
dec	decomposition
d	doublet
DMF	N,N-Dimethylformamide
DMS	dimethyl sulfide
ei	electron impact
ev	electron volt
h	hours
Hz	Hertz (cycles/second)
ir	infrared
LDA	lithium diisopropyl amide
M ⁺	parent molecular ion
m	multiplet
MCPBA	<i>meta</i> -chloroperoxybenzoic acid
min	minutes
Me	methyl
mmol	millimole(s)

mp	melting point
ms	mass spectrum
NBS	N-bromosuccinimide
nmr (NMR)	nuclear magnetic resonance
PCC	pyridinium chlorochromate
PMP	<i>para</i> -methoxyphenyl
psi	pounds per square inch
RT (R.T.)	room temperature (about 25°C)
q	quartet
s	singlet
Selectride	tri(<i>sec</i> -butyl)borohydride
Superhydride	tri(ethyl)borohydride
t	triplet
TBAF	tetra-N-butylammonium fluoride
TBDMS	<i>tert</i> - butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	tetramethylsilane
TMS-	trimethylsilyl
Triflate	trifluoromethanesulfonate

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It is a pleasure to thank Professor Tony Durst for his critical insight and encouragement. He is a wonderful teacher and learning chemistry from him has been a fantastic experience. I would like to believe that I have not misused the tremendous freedom I enjoyed under his guidance.

Dr. Eric Gabe of NRC and his colleagues deserve special thanks for performing all the X-ray diffraction analyses. M. Tremblay performed the early experiments on 3-iminoazetidinones and the oxazoline carboxylic acid. I express my gratitude to him for carrying out a series of experiments in a very careful manner.

Special thanks to Mr. Raj Capoor for recording a large number of NMR spectra. Dr. Dettman's help in connection with the C-13 spectra is much appreciated. Many thanks to Drs. Klem Kazakoff and John Krause who provided arguably the best mass spectral service in the world.

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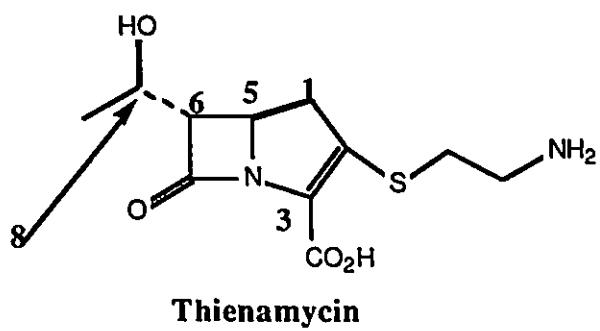
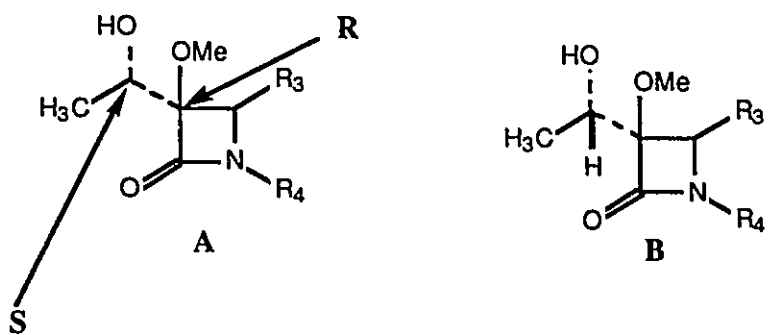
A note of thanks to late Dr. Hari Mohan Saxena for helping me in maintaining my interest in chemistry.

A heartfelt thank to my family for their patience and affection.

General Organization

References are numbered continuously. However, these have been listed at the end of individual chapters. For the sake of brevity no attempt has been made to provide a comprehensive listing of the references, only the leading ones are included. Experimental details pertaining to individual chapters have been included with the respective chapters. Experiments which did not lead to the desirable results have not been included in any detail. Spectral and physical properties of compounds have been included in the pertinent experimental sections. Full spectra are not reproduced in the thesis.

All the azetidinones used and/or synthesized in chapter 4 and subsequently are mixtures of enantiomers, only one enantiomer has been shown. For the sake of simplicity, in several instances hydrogen atoms have been dropped from various structures. Thus structure A is a simplification of the structure B. Thienamycin numbering has been used on several occasions. A fully numbered diagram of this molecule is as follows.

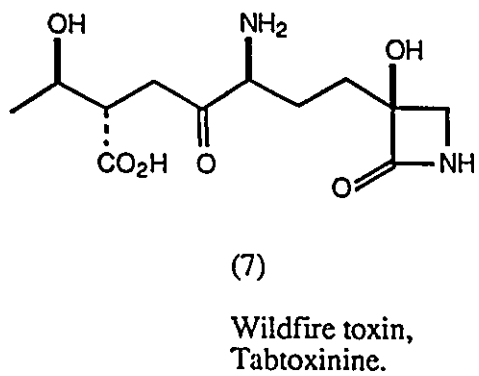
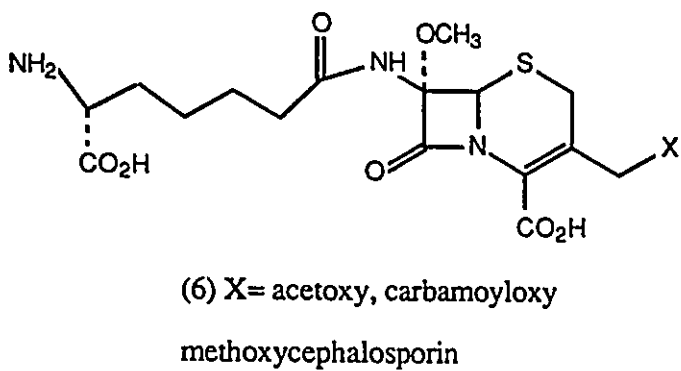
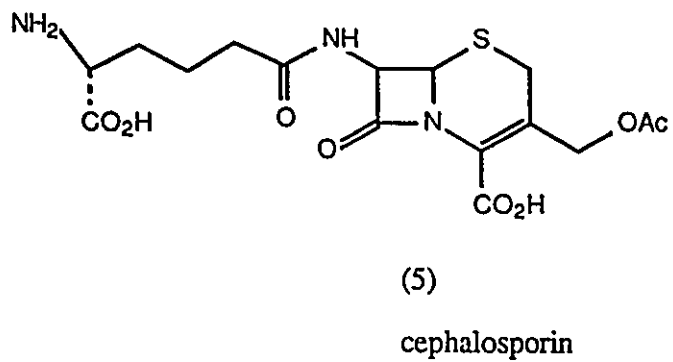
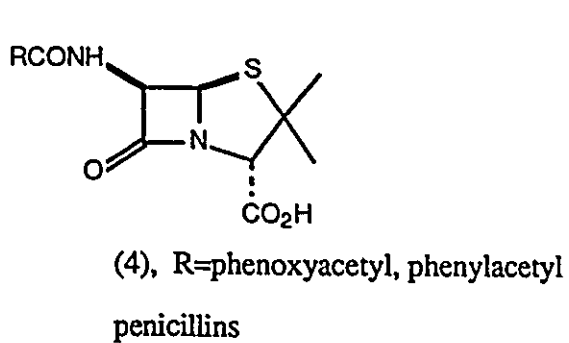
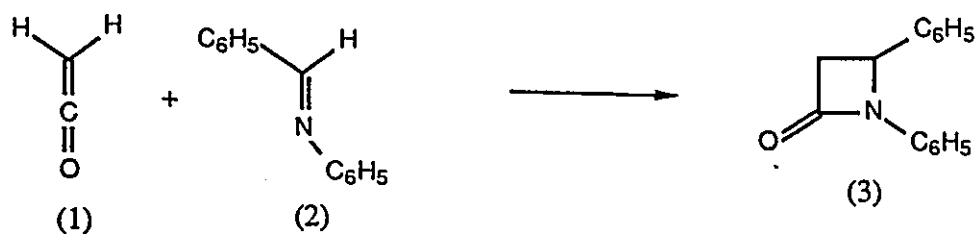


CHAPTER 1

Ever since the first synthesis by Staudinger in 1907, azetidinones have attracted a lot of attention (3, Fig. I)^{1,2}. Initially these compounds were a chemical curiosity. However, discovery of the wonder drug penicillin in 1929 and the fact that the β -lactam ring was the essential component for biological activity changed that attitude (4, Fig. I)^{3,4}. What followed was a period of intense activity encompassing the areas of synthetic, degradative, biological and clinical studies. Just as these hectic activities were beginning to abate in late 1960's cephalosporins were discovered. These compounds are structurally more complex, more stable and clinically more interesting than penicillins (5, Fig. I)⁵. Methoxycephalosporins were discovered shortly afterwards. These were structurally the most complex azetidinones discovered up to that period and were the first one to have a disubstitution pattern (methoxy and acylamino α to the β -lactam carbonyl group) (6, Fig. I)⁶. Within a few years, the correct structure of the Wildfire toxin was established. Though devoid of useful antimicrobial properties, the latter also falls into the category of naturally occurring disubstituted azetidinones (7, Fig. I)⁷.

Currently penicillins along with cephalosporins and methoxycephalosporins are the dominant antibiotics. These compounds may eventually be replaced with the more active and the very broad spectrum carbapenem class of molecules i.e. thienamycin and related compounds.

Fig.I



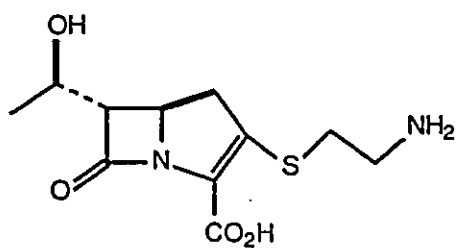
Thienamycin was isolated from *Streptomyces cattleya* by Merck chemists and reported in 1976 (8, Fig.2)⁸. Structurally this was very different from all other azetidinones known to date. Merck and Co. has recently begun to make thienamycin analogs under the trade name Imipenem.

The weakly antimicrobial compound norcardin A was isolated at about the same time (9, Fig. II)⁹. The β -lactamase inhibitor clavulanic acid was discovered during the mid-1970's (10, Fig. II)¹⁰. A large number of structurally similar compounds have been isolated since then¹¹.

In the case of penicillins and cephalosporins synthetic approaches have not been and are not likely to be able to compete effectively with the fermentation process¹². Well-established procedures for large-scale fermentations have provided easy access to these compounds. Even "new-generation" penicillins are fairly accessible via a combination of fermentation techniques and chemical modifications. The production of natural penicillins such as Pen.G and 6APA is efficient enough that such compounds can reasonably be considered as starting materials for the syntheses of thienamycin type compounds (vide-infra).

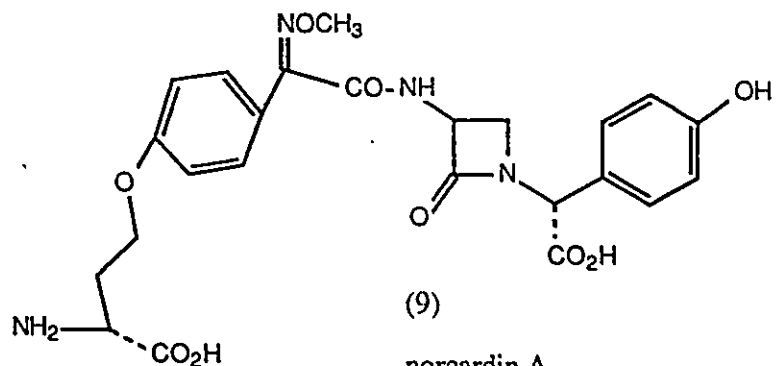
Synthetic approaches to methoxycephalosporins are known. For example Kishi and coworkers have synthesized compounds (14 and 15, Fig. II)¹³. However it does not seem likely that their routes can be useful for large scale production of these compounds. Nor do they seem particularly suited for the purpose of preparing analogs. In this context the methodologies developed by Christensen and

Fig. II



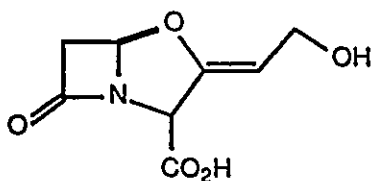
(8)

thienamycin



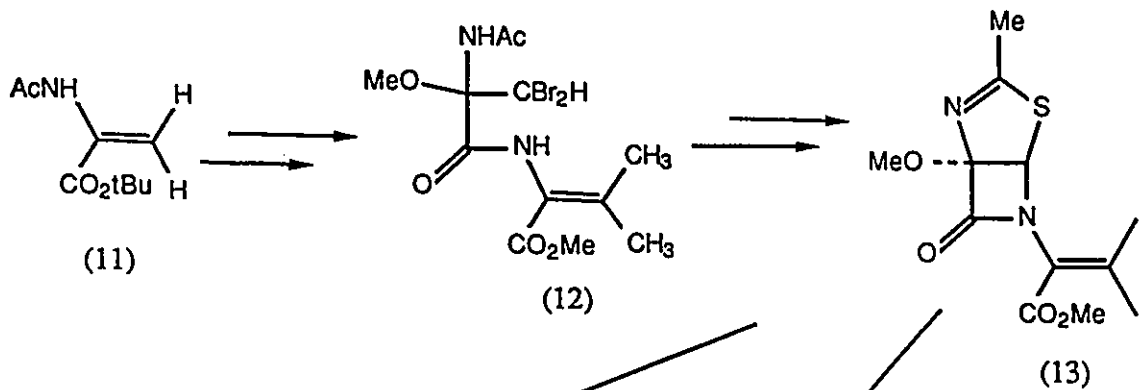
(9)

norcardin A



(10)

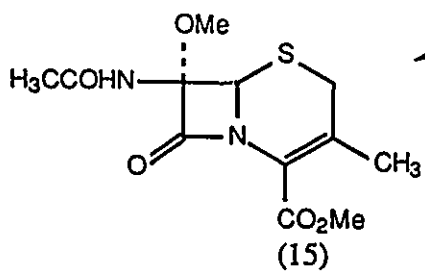
clavulanic acid



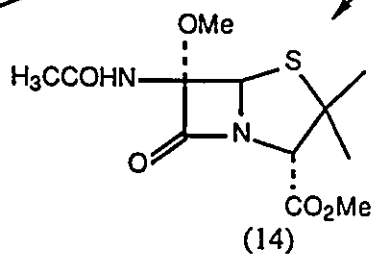
(11)

(12)

(13)



(15)



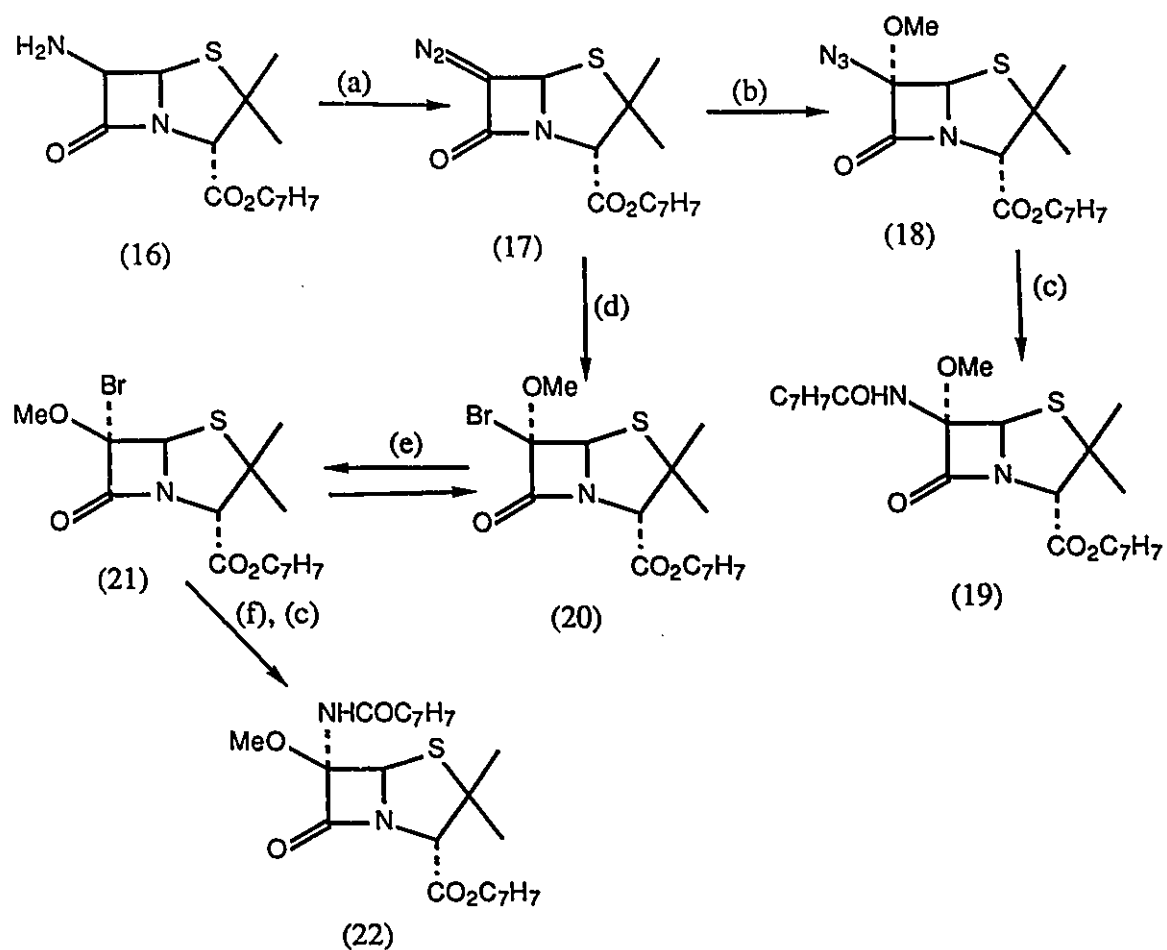
(14)

coworkers at Merck are efficient, versatile and particularly admirable.

These chemists have studied two different approaches. Both of them involve cephalosporins as starting materials. An additional advantage of such approaches is that penicillins can also serve as starting materials thereby allowing access to methoxyphenicillins!. The first route involved use of esters of 6-diazopenicillinic acid (17, Fig. III) (or the corresponding 7-diazocephalosporinate). By a sequence of simple reactions it was possible to obtain either 6-a-azido-6-b-methoxyphenicillinate or its diastereoisomer. Subsequent conversion of the azido group to the corresponding acylamino group provided a series of 6,6-disubstituted penicillins. Similar methodology was applied to obtain 7,7-disubstituted cephalosporins. (18, Fig. III)¹⁴.

The second approach utilized the esters of 6-aminopenicillinic acid. The key step involved the conversion of the amino group to the corresponding imine by reaction with an aromatic aldehyde (23, Fig. IV). Subsequent deprotonation with a strong base and reaction with a series of electrophiles provided access to a large number of 6,6-disubstituted penicillins. 7,7-disubstituted cephalosporins were obtained in a similar fashion. (25 and 26 respectively Fig. IV) Both alkyl and hydroxyalkyl penicillins and cephalosporins have high antimicrobial activity. It is interesting that even before isolation of thienamycin and northienamycin, the side-chain corresponding to these compounds had been incorporated at the 6 and the 7 position in penicillins and cephalosporins respectively.. Such compounds had very desirable biological properties¹⁵. By using a slightly modified

Fig. III



$C_7H_7 = \text{benzyl}$

Similar results were obtained in the cephalosporins series.

(a) HNO_2 , NaOAc, (b) [i] BrN_3 , $Bu_4N^+N_3$, [ii] $AgBF_4$, MeOH,

(c) [i] H_2 , Pd/C, EtOAc, [ii] C_7H_7COCl , (d) MeOH, NBA,

(e) LiBr, DMF, (f), LiN_3 , DMF.

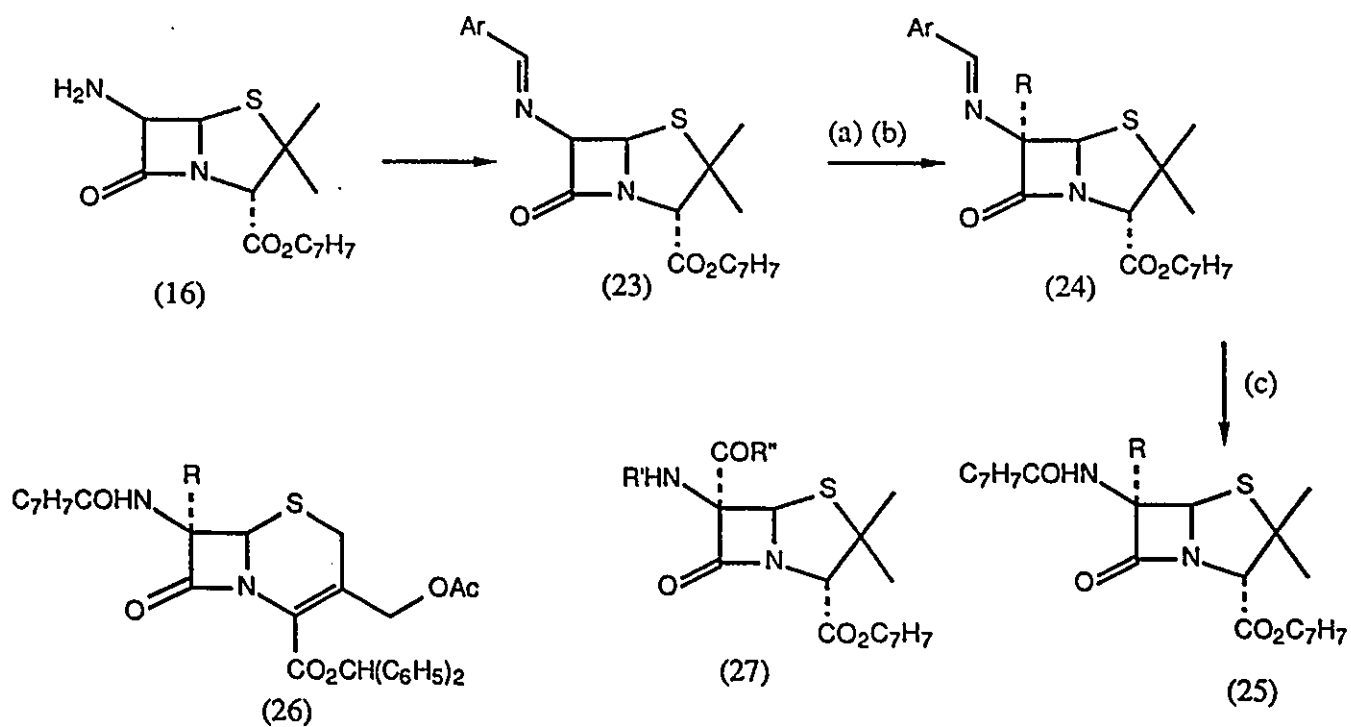
approach these workers provided access to the corresponding methoxy compounds¹⁶.

Using a similar approach, Guest has prepared a series of 6-*a*-carboxy and 6-*a*-carbamoyl penicillins. However, these compounds had poor antimicrobial activities. (27, Fig. IV)¹⁷. Another related area where similar methodologies have been used is the synthesis of 7-(methylthio)cephalosporins. These compounds have served as a source of 7-methoxy and 7-formamido-cephalosporins (30 and 35, Fig. V)^{18,19}. The methylthio compounds have also played a key role in the syntheses of spirocyclic penicillins and cephalosporins (37, 41 and 42, Fig. VI)²⁰.

6,6-Dibromopenicillins constitute another interesting class of useful azetidinones. These are neither found naturally nor do they seem to have any useful antimicrobial activity. Initially these were obtained as by-products in the conversion of esters of 6-diazopenicillinic acid to the corresponding 6-oxo compounds (43 and 44, Fig. VII)²¹. However, they gained significance as intermediates in the conversion of penicillins to thienamycin and analogs²².

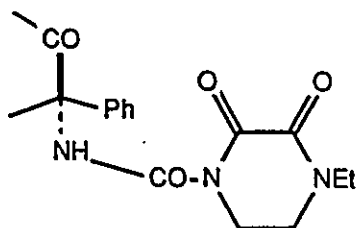
The quest for more stable azetidinones has taken several directions. One successful approach is that of Watanbe and coworkers. The synthesis of 6-methoxy-epi-PS-5 involved several steps. The product was much more resistant toward renal dehydropeptidase but the antimicrobial activity was considerably reduced, when compared to the natural product PS-5(46, Fig. VII)²³. Similarly, 6-hydroxy-epi-PS-5 showed higher resistance towards the

Fig. IV



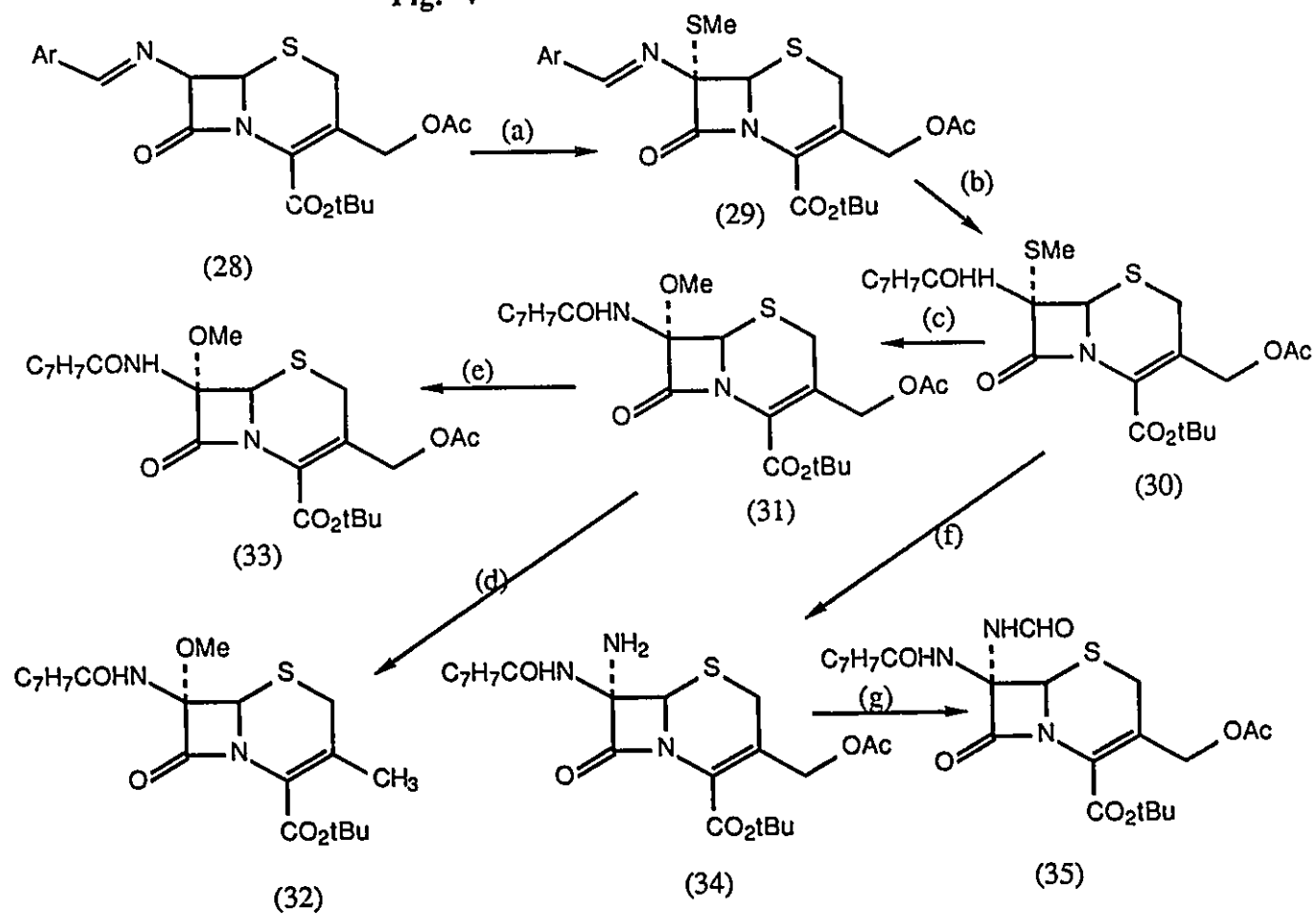
R = CH₃, C₂H₅, CD₃, CH₂OH, CH(OH)CH₃ C₇H₇ = Benzyl

R'' = OC(CH₃)₃, NH₂, R' =



(a) PhLi, DME, -78 °C (b) various electrophiles (c) acylation etc.

Fig. V

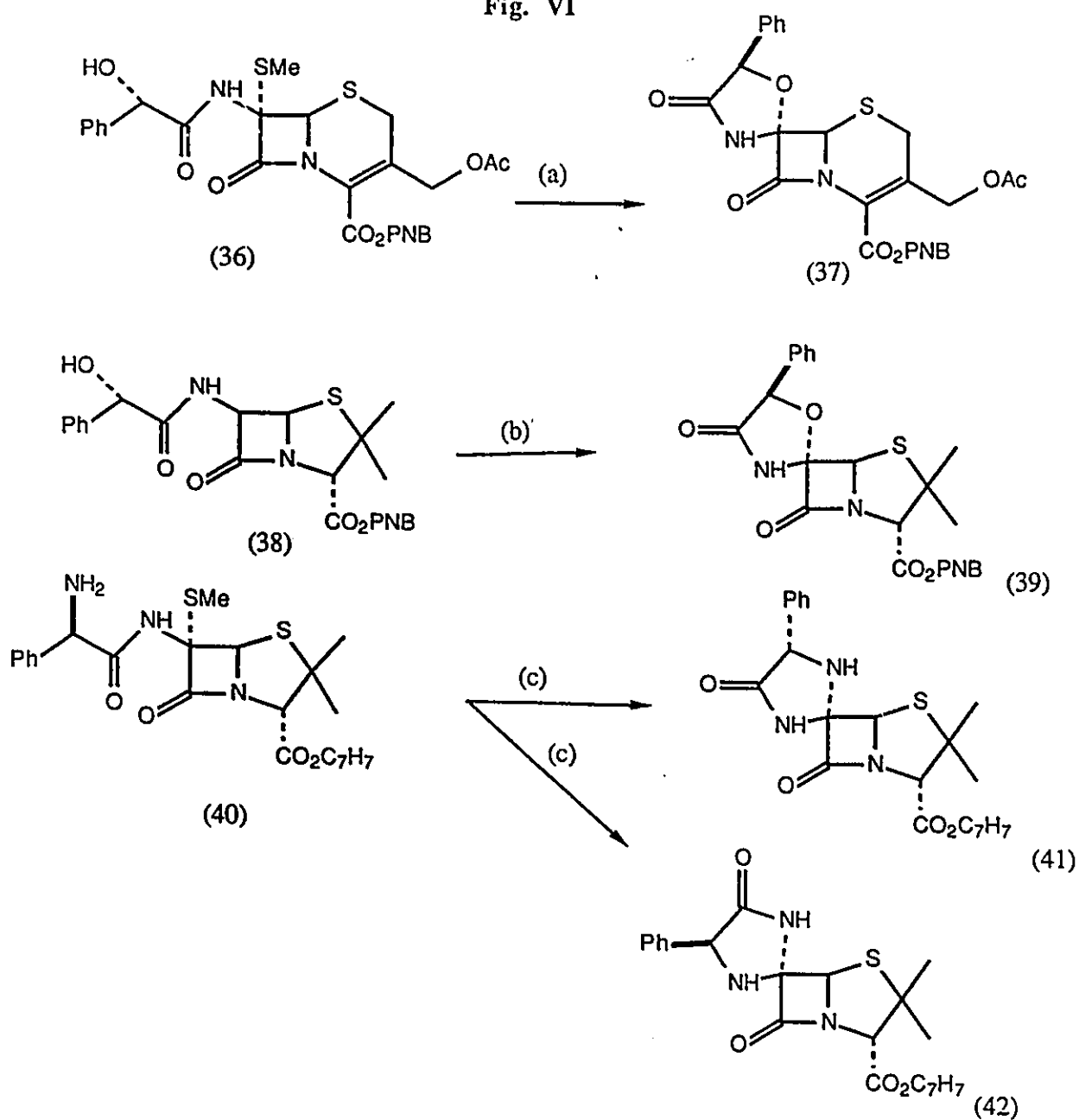


(a) [i] *t*-BuOK, DME, [ii] CH₃SO₂SCH₃, (b) acylation, hydrolysis

(c) Hg(OAc)₂, MeOH, (d) H₂, Pd/C, EtOAc, (e) CF₃CO₂H,

(f) NH₃, Hg(OAc)₂, DMF, (g) CH₃CO₂COH

Fig. VI



(a) HgCl₂, Py. (b) t-C₄H₉ OCl, LiOMe. (c) HgCl₂, THF

Conversion of (40) to (41) and (42) involves attack of the internal nucleophile at both the faces of the azetidinone. This is an exception!.

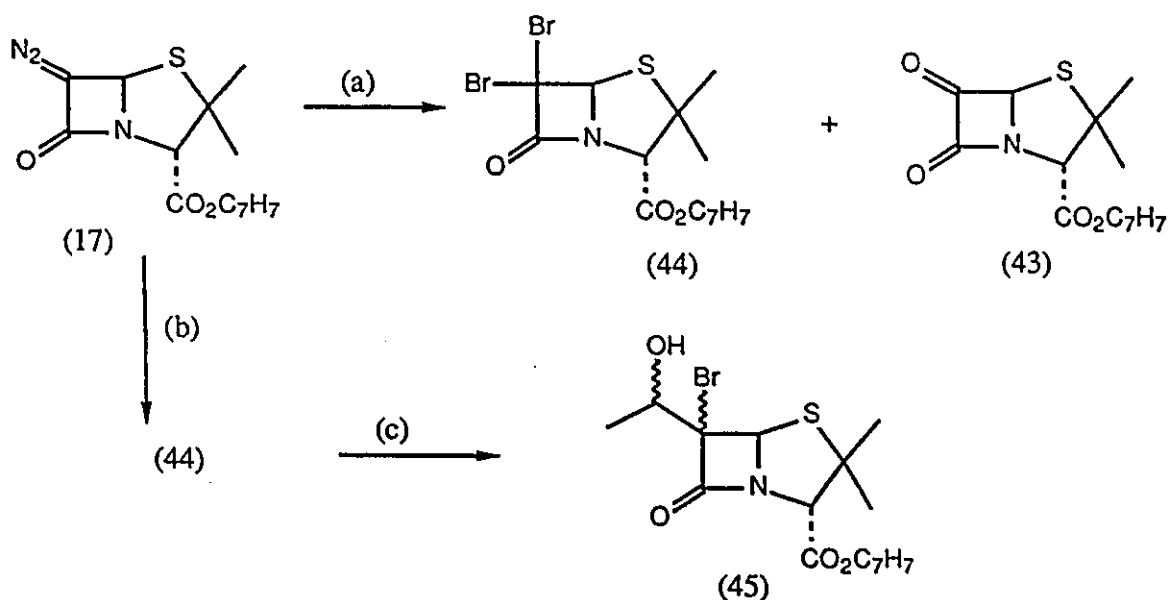
peptidase. Here again the antimicrobial activity was considerably lower (47, Fig. VII)²⁴.

In the area of thienamycin analogs introduction of a 1-b-methyl group into the carbapenam nucleus led to a considerable improvement in the stability towards renal dehydropeptidase; while retaining the excellent biological activity of the parent compound (48 and 49, Fig. VIII)²⁵. On the other hand introduction of 1,1-difluoro group led to a sharp decline in the chemical stability (50, Fig. VIII)²⁶. Similarly introduction of a spirocyclopropyl moiety at C-1 led to good antimicrobial activity. Surprisingly, the stability toward renal dehydropeptidase was significantly reduced(51, Fig. VIII)²⁷. These results serve to illustrate the difficulties encountered in this area.

Yet another interesting approach has involved the syntheses of "hybrid" azetidinones; i.e. those involving structural features from more than one class of b-lactam antibiotics. As mentioned in the context of hydroxyalkyl penicillins and cephalosporins, this approach can often be very successful¹⁶. Obviously, due to the structural diversities in the case of azetidinones numerous combinations are possible. What follows is a simplified overview of the results obtained for several of those "combinations".

Perhaps the earliest hybrid azetidinones were the penems. These contain the structural features of both penicillins (the five-membered ring) and the cephalosporins (the endocyclic double bond). The presence of the double bond leads to increased biological activity (52, Fig. VIII)²⁸. Penems are also totally "synthetic" ; none have yet been isolated from natural sources. It is surprising that

Fig. VII



(a) NBS, H₂O, THF

(b) Excess Br₂, CH₂Cl₂, -40°--0°C

(c)[i] CH₃MgI or n-C₄H₉Li., [ii] CH₃CHO.

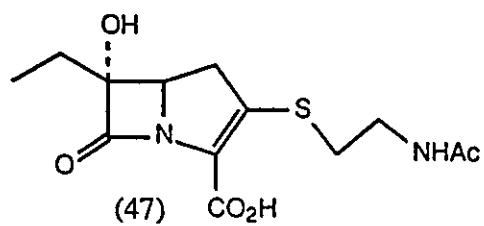
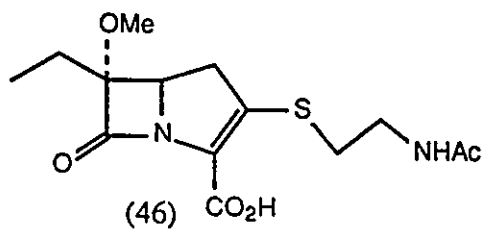
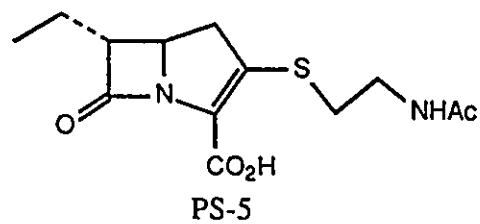
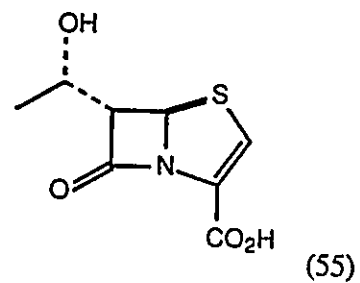
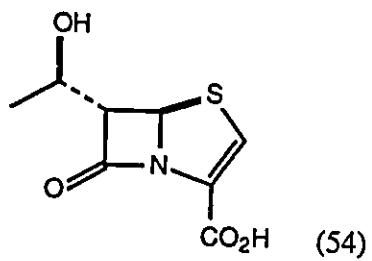
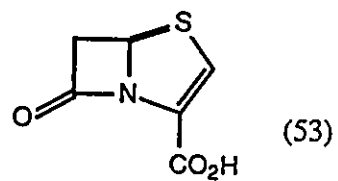
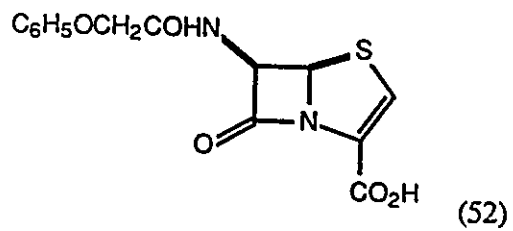
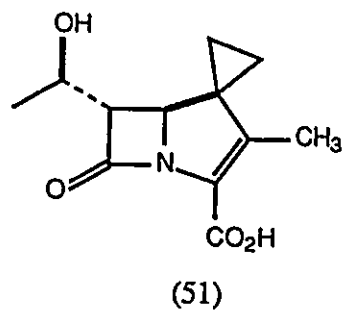
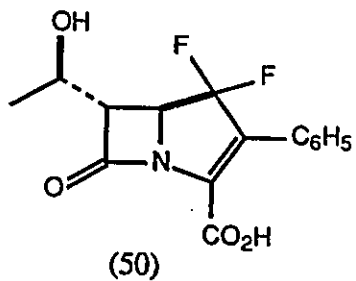
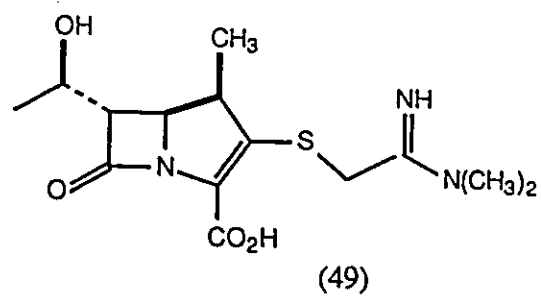
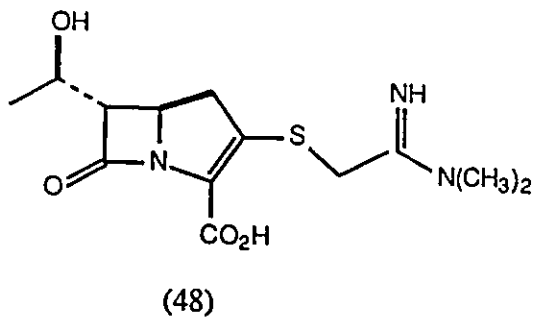


Fig. VIII

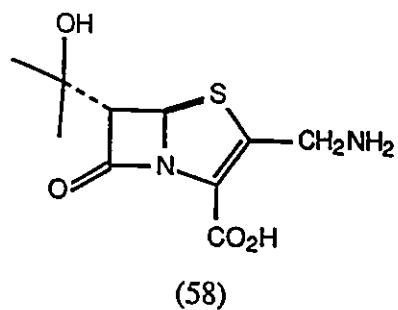
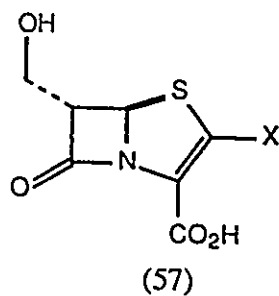
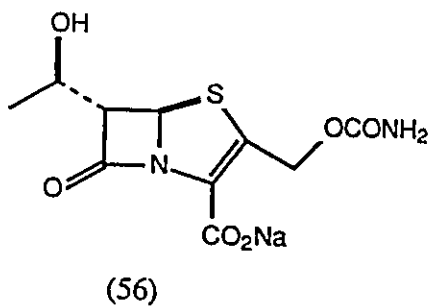


introduction of the 6-acylamino side-chain led to a sharp decline in chemical stability (53, Fig. VIII)²⁹. After the isolation of thienamycin, Woodward and coworkers synthesized the penems with the hydroxyethyl side-chain (54 and 55, Fig. VIII). These compounds had modest biological activity. However, the chemical stability was far superior compared to either the acylamino or the parent penem³⁰. The attention enjoyed by penems as synthetic targets is remarkable for a "non-natural" molecule, a compliment to Woodward's remarkable insight.

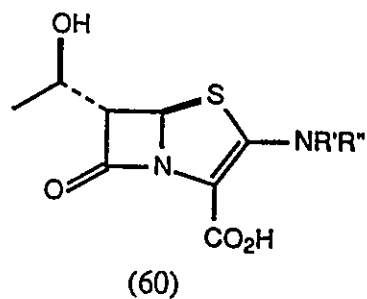
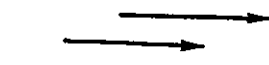
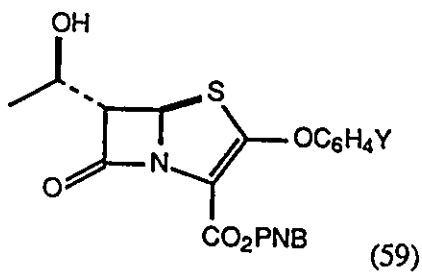
Hanessian and coworkers have synthesized the penems such as (56, Fig. IX). These include structural features of thienamycin and cephalosporins³¹. Chemists at Ciba-Geigy have prepared a series of penems which have structural features of northienamycin and carpetimycins. An additional modification is the presence of the alkylamino substituent at C-2. These compounds showed a "well balanced spectrum of activity"(57 and 58, Fig. IX)³². Barker and colleagues have synthesized penems such as (60, Fig. IX) The key step involved the replacement of a phenol from C-2³³.

In an attempt to include the features of carbapenems and the acylamino side-chain of the classical azetidiones, compounds such as (61, Fig. IX) and (62, Fig. IX) were prepared. Despite the presence of the phthalimido group instead of the more "usual" side-chain, the cis compound had moderate biological activity. The trans compound was devoid of any biological activity³⁴. Evan and Sjogern synthesized the compound (63, FigX). The biological activity of this compound is claimed to be high³⁵.

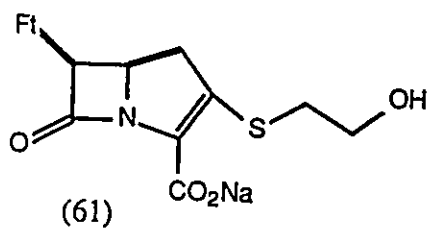
Fig. IX



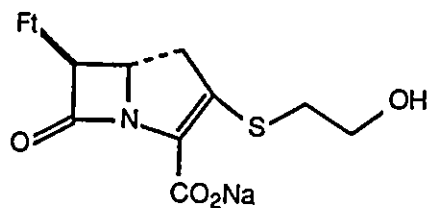
X = various aminoalkyl groups



R' and R'' = various alkyl groups, Y = CN, NO₂



Ft = phthalimido



Glaxo chemists synthesized 6-methoxy-1-carbapen-2-em and 7-methoxy-carbacepeha-1,3-diene type of compounds (64 and 65, Fig. X). Neither of these compounds had any antimicrobial or β -lactamase inhibitory properties³⁶. 6-Methoxy-1,1-dimethylcarbapen-2-em has also been reported. However, the biological activity of this compound is not known.

It is difficult to draw any truly general conclusions from the above discussion. However, one can be fairly certain about the following points:

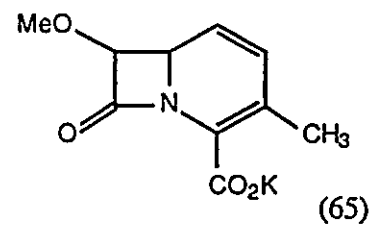
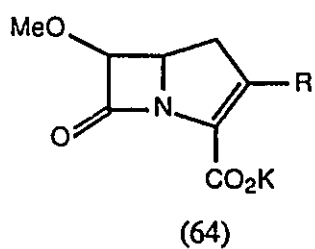
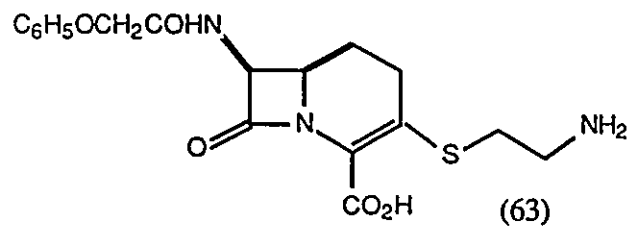
(a) The presence of strain in the molecule is often a desirable factor for biological activity since this helps to activate the β -lactam carbonyl towards nucleophilic attack.

(b) Usually there is a need for a suitable "signature" group on the position adjacent to the carbonyl of the azetidinone. Acylamino or hydroxyalkyl groups often serve as the signature group. The presence of both these group in the molecule often leads to a considerable increase in stability. This is usually accompanied by useful antimicrobial activity.

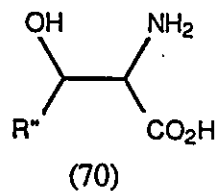
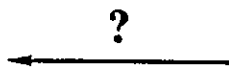
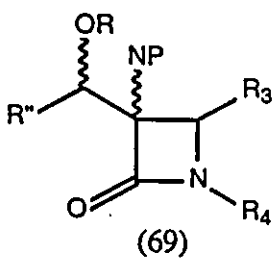
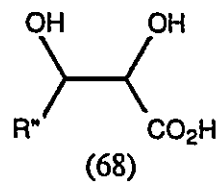
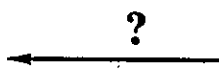
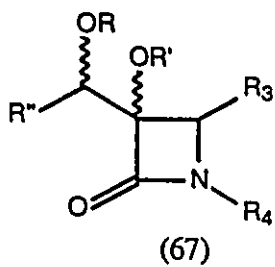
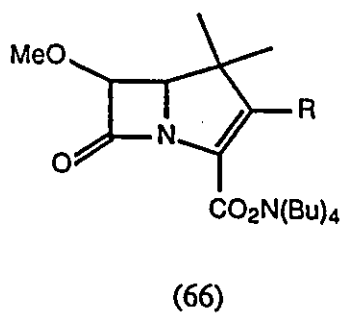
(c) The presence of an inductively electron-withdrawing group such as methoxy, on the position adjacent to the carbonyl of the azetidinone often leads to a desirable shift in terms of stability, while maintaining antimicrobial activity. The methoxy group by itself does not appear to function as the signature group and thus must be accompanied by either of the above groups.

(d) In case of carbapenem class of compounds the relative stereochemistry of C-5 and C-6 is not very crucial. The extra stability gained by the introduction of an additional substituent at

Fig. X



R = H, CH₃



C-6 would lead to a series of disubstituted azetidinones with some potential for biological activity, irrespective of the relative stereochemistry of the substituents at C-5 and C-6.

With these factors in mind it was decided to undertake syntheses of azetidinones bearing both an alkoxy and hydroxyethyl group at C-3. The relative stereochemistry of the substituents is not shown clearly at this stage. The initial anticipation was that methodologies could be devised to obtain either of the two possible relative geometries. Additionally it was expected that suitable precursors to these alkoxy azetidinones could be obtained in enantiomerically pure form by using various dihydroxy acids as starting materials. The basic idea was that the presence of the chiral center would lead to a high degree of asymmetric induction in the azetidinone formation step. Subsequently this chiral center could become an integral part of the molecule (68, Fig.X). An important concern was regarding the nature of the substituents at C-4 and at the nitrogen atom, these should be amenable to elaboration into bicyclic azetidinones.

A related idea was the syntheses of azetidinones bearing a suitably protected amino and a hydroxyalkyl side-chain at C-3. Here again the expectations were similar to the case of 3-alkoxy-3-hydroxyalkyl azetidinones (69 and 70, Fig. X). In the following four chapters details of progress towards achieving these objectives are presented.

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There seems to be some confusion regarding the numbering; part [iii] has been numbered by these authors as part [iv]. A later example is by Hiroka, T. and Marayama, H. *J. Org..Chem.* 1986, 51, 399. For an early study of reaction of benzyl-6,6-dibromopenicillinate with Grignard reagents and n-butyllithium. see DiNinno, F.; Beattie, T.R. and Christensen., B.G. *J. Org. Chem.* 1977, 42, 2960.

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Chapter 2

In this chapter details of the studies related to the enantioselective synthesis of azetidinones such as (67, Fig.XI) are presented. The aim was to synthesize optically active 3-alkoxyazetidinones starting from dihydroxybutyric acid derivatives (68, Fig.XI). From a practical point of view such an approach has certain distinct advantages. Such acids are often relatively easily available in enantiomerically pure form. This should allow access to synthetically useful amounts of the products (*vide infra*). As stated previously, the proximity of the chiral center to the site of ketene formation may lead to a high degree of overall enantioselectivity in the azetidinone formation process. Later on the inducing chiral center will become an integral part of the molecule, providing opportunities for further manipulations.

To meet the requirements outlined at the end of Chapter 1, it was decided that the substituent on the nitrogen atom should be *p*-methoxyphenyl (PMP). This group can be oxidatively removed to furnish the corresponding *N*-unsustituted azetidinone.³⁸ For the substituent at C-4, (*E*)-cinnamyl, (2)-furyl and (*Z*)-1-methyl-2-phenylethenyl (or methylcinnamyl) appeared to be reasonable choices. Each of these groups can be oxidatively modified to furnish functionalities which offer possibilities for further modifications³⁹. A phenyl group has often been a substituent at C-4 since it tends to give higher cycloaddition yields and aids in the structural assignments due to its predictable anisotropic effect. However, oxidative degradation of this group has often proven to be a difficult

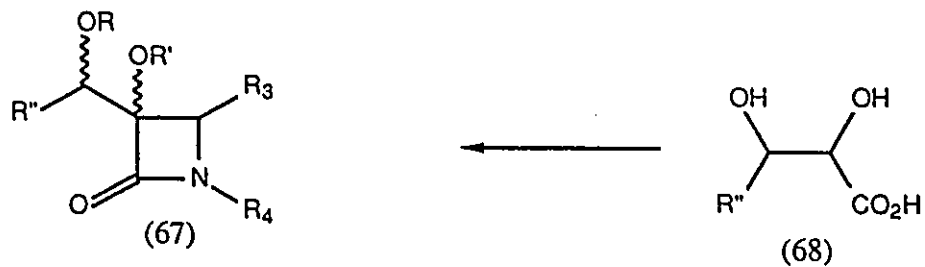
and unreliable procedure and thus this group was used only in some model studies⁴⁰.

There are only a few examples of the direct syntheses of 3,3-disubstituted azetidinones via cycloaddition reactions. Worse still in most of the cases the assignment of the relative stereochemistry is not rigorous. Generally it seems that workers have relied only on chemical shifts to justify the assigned stereochemistry, which in turn necessitated the syntheses of compounds which have groups "unsuitable" for the purpose at hand. The intention here is not to cast doubts or undermine in any way the previous studies in this area, but to point out that these are probably not very relevant in the present context^{41,42}. For the present studies to be meaningful it is very important that the stereochemical assignments be rigorous. Another factor is reliability. Even though the general area of enantioselective syntheses of azetidinones continues to draw considerable attention, paucity of studies relevant to the present context make it difficult, if not outright impossible, to predict the stereochemical outcome of any potential enantioselective cycloaddition sequence to 3,3-azetidinones⁴³.

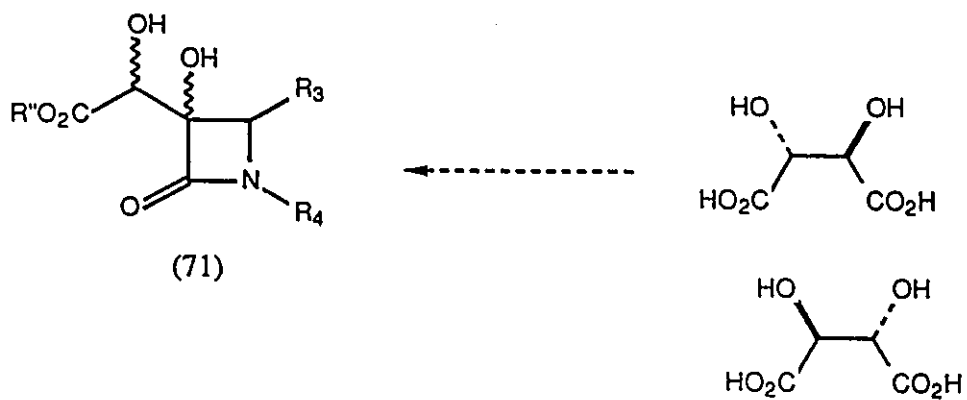
In view of the above discussion, it was decided to adopt a practical approach. The focus was to obtain reasonable quantities of the alkoxyazetidinones. It also seemed reasonable that the absolute configurations of the products be confirmed by X-ray diffraction analysis.

Tartaric acid derivatives seemed well suited for initial studies due to the commercial availability of large quantities of both

Fig. XI



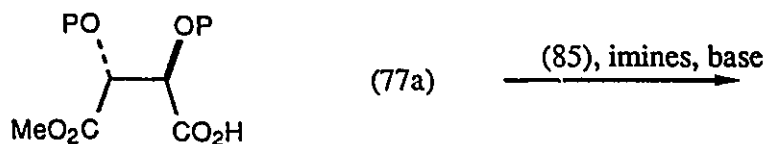
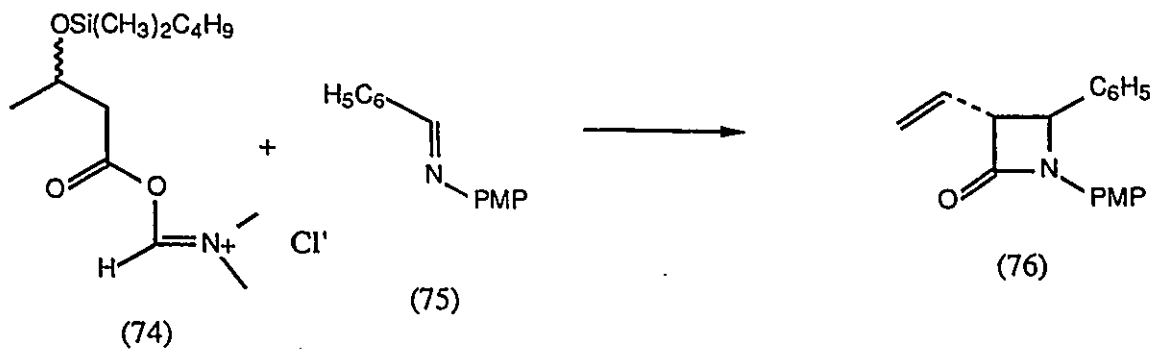
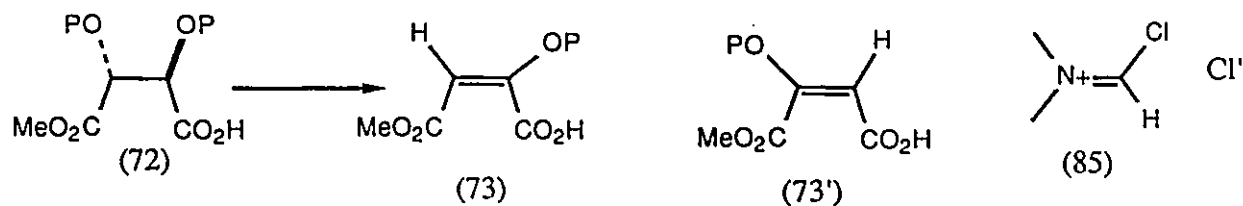
R = various protecting groups
 R' = various alkyl groups
 R'' = Methyl group or a suitable precursor
 R₃ = cinnamyl, 2-furyl or methycinnamyl. Not phenyl
 R₄ = p-Methoxyphenyl (=PMP).



enantiomers . Once assembled azetidinones such as (71, Fig.XI) seem to offer possibilities for subsequent modification. .

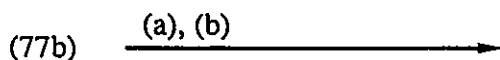
Conventional wisdom would suggest that ketene formation from compounds such as (72, Fig. XII) may be complicated by β -elimination. Indeed our own results with 3-(t-butyldimethylsilyloxy)-butanoic acid (73, Fig.XII) seem to confirm that. As a matter of fact, reaction between the activated acid (74, Fig. XII) and the imine (75, Fig.XII) at 0°C->R.T. has served as a poor source (<5% yield) of 3-vinyl-4-phenyl azetidenone (76, Fig. XII). Perhaps for that reason it was not entirely surprising that acids such as (77a and 77b, Fig. XII) did not furnish any detectable amounts of the corresponding azetidinones when N,N-dimethylchloromethyleniminium chloride (85, Fig. XII) was used as the acid activating agent. The only identifiable reaction products were the starting imine and the corresponding aldehyde. At times the method employed for activation of the carboxylic acid has been shown to have an impact on the outcome of the ketene-imine reaction. For that reason it was decided that an attempt should be made to convert the acid (77b, Fig.XII) into the corresponding acid chloride. The conversion was doubtful at best as judged by infrared monitoring of the reaction mixture. However there was no doubt about the outcome of the attempt to use this "crude acid chloride" in a cycloaddition reaction with the imine; it was an unqualified failure. Attempts to obtain other suitable derivatives such as dimethyl or dibenzyl ethers of monoesters of tartaric acid were not promising. It was found that the monosaponification step is unreliable and affords only small quantities of the desired product in low and

Fig. XII



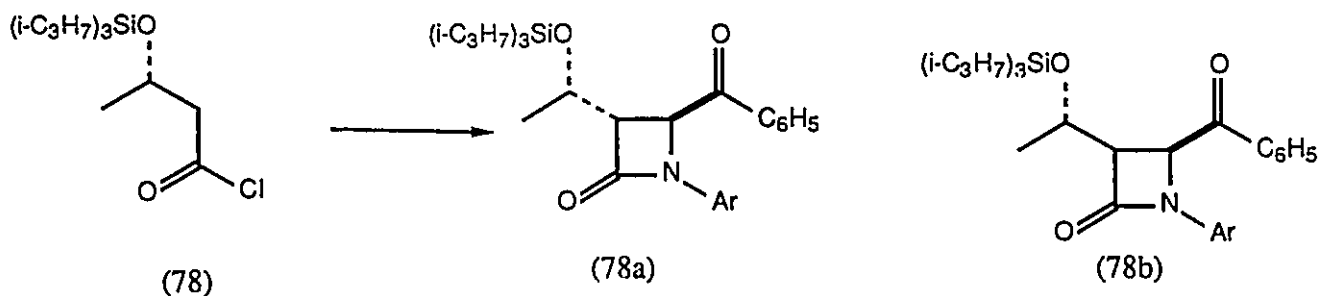
No azetidinones indicated, only the imine and the aldehyde

P = TBDMS (77a), Ac (77b)

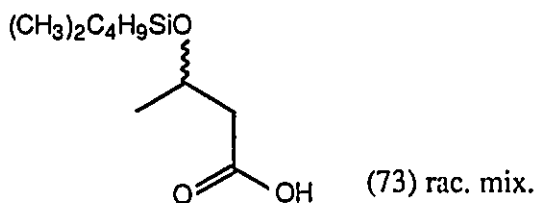


No azetidinones indicated, only the imine and the aldehyde

(a) cat. DMF, 2.2 eq. oxalyl chloride, methylene chloride, reflux, (b) imine, excess amine



(78a) : (78b) = 6:1



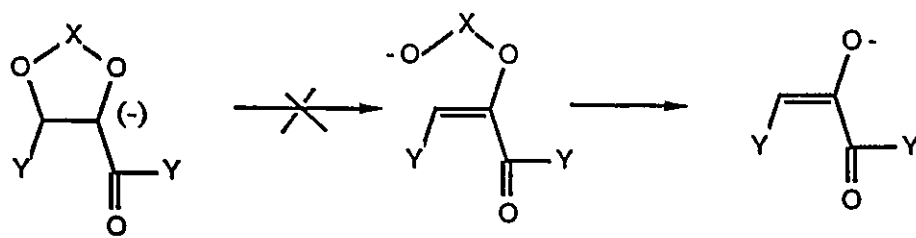
irreproducible yields. For this reason it was decided to abandon this approach. In 1988, chemists at Merck reported that by reacting the acid chloride (78, Fig. XII) with amines at low temperatures followed by reaction with the imine, azetidinones could be obtained with respectable diastereoselectivity. Had we been able to generate the acid chloride of the acid (77b), low temperature ketene generation might have been beneficial in the present context⁴⁴.

On the basis of Baldwin's rules it is reasonable to assume that a concerted b-elimination from systems such as (79, Fig. XIII) is disfavoured⁴⁵. The rationale was used by Sharpless and Masamune to explain the clean epimerization of (80a) to (80b, Fig. XIII); a key step in the syntheses of aldoses⁴⁶. In view of the above the use of cyclic derivatives such as (81 and 82, Fig. XIII) seemed reasonable choices.

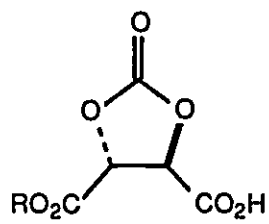
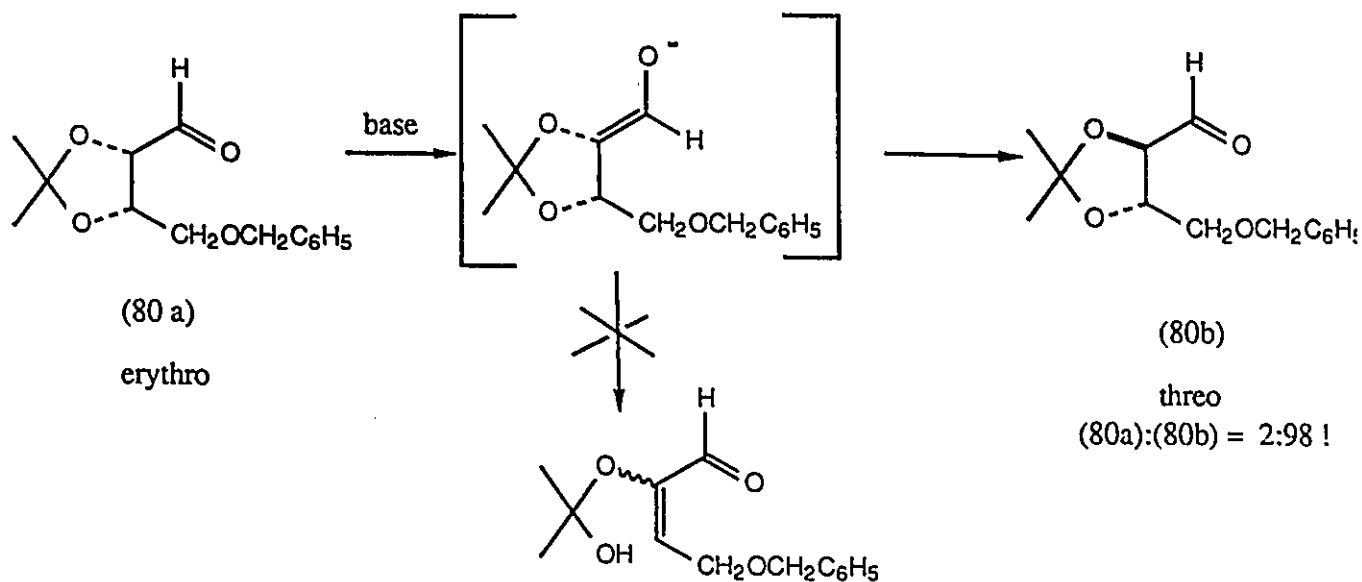
Experiments using the cyclic carbonate proved very frustrating. Monocarbonate (83, Fig. XIV) was difficult to obtain pure, being contaminated with variable amounts of the dicarbonate (83a, Fig. XIV). Subsequent base-catalyzed ring closure of the monocarbonate and the selective saponification was hampered by low yields. Failure to obtain any amount of the azetidinone after attempted activation and the cycloadditions finally led to abandoning this idea.

Rappoport and Musich utilized the acid (84, Fig. XIV) in their synthesis of antholeurine⁴⁷. By following the detailed directions provided by these authors it was possible to obtain large quantities of this acid. Attempted conversion of the acid to the acid chloride using thionyl chloride in refluxing benzene was accompanied by a

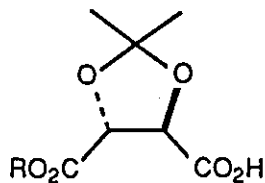
Fig. XIII



(79) X = CH₂, CR₂, CO. Y = H, alkylalkoxy, alkoxyalkyl etc.



(81)

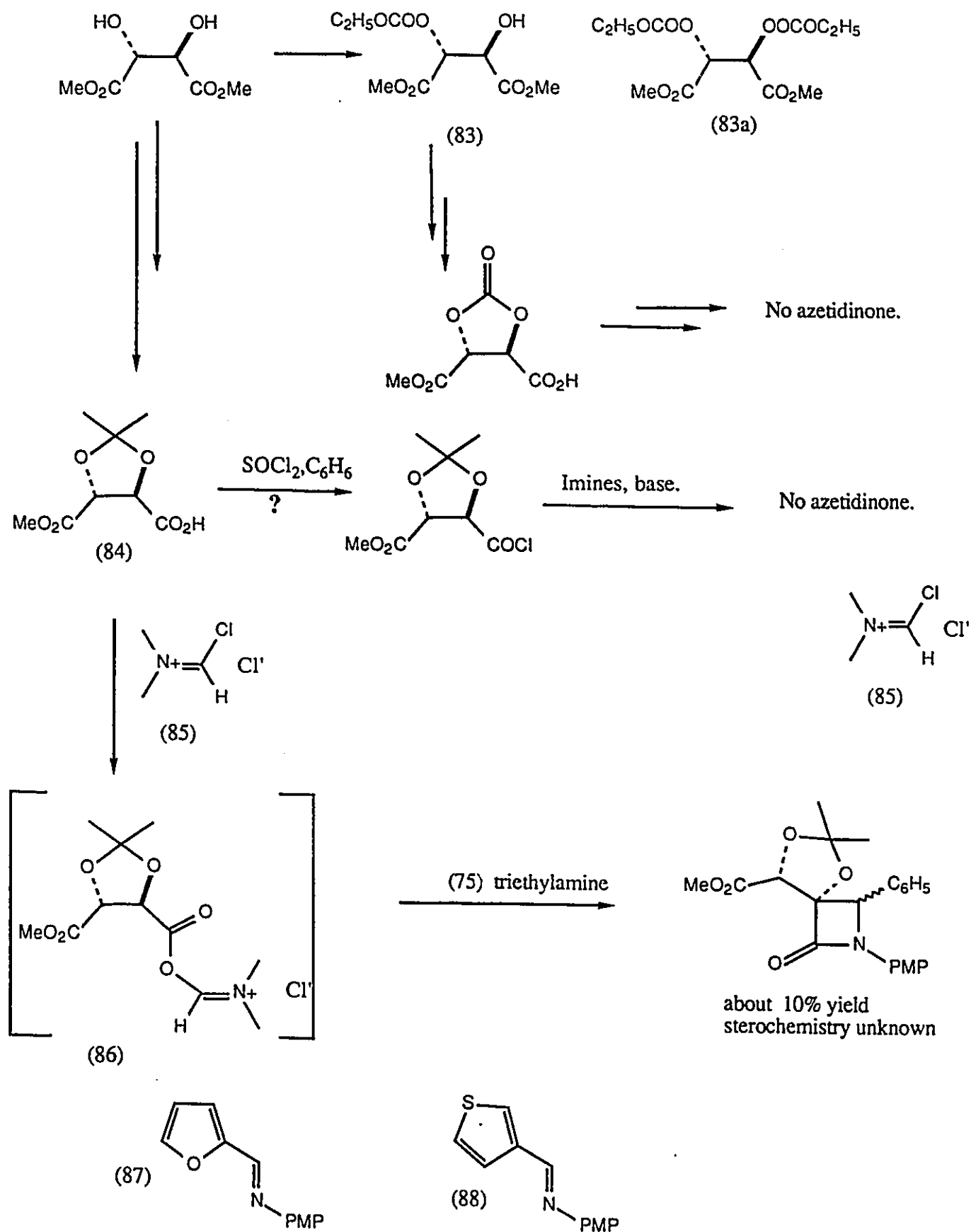


(82)

change in coloration and deposition of a sticky residue. Subsequent reaction of the (unpurifiable) acid chloride with a variety of imines did not seem to furnish any azetidinones.

N,N-dimethylchloromethyleniminium chloride (obtained from DMF and oxalyl chloride) (85, Fig. XIV) has often proven a suitable alternative for activation of carboxylic acids towards ketene formation (see Chapter 8). Usually the reaction between the salt and the acid is rapid and proceeds under much milder conditions than those encountered during acid chloride formation. Indeed the reaction of the acid (84, Fig. XIV) after activation by (85) followed by addition of the imine (75, Fig. XIV) and triethylamine furnished a chromatographically homogeneous azetidinone in poor yields (<10%). The unresolved fractions seemed to show the presence of another azetidinone. In addition, a large amount (about 50% by weight!) of an unresolved mixture of unknown compounds was obtained. The behavior was not limited to this particular imine. Thus reaction of the imines (87 and 88, Fig. XIV) with the acid seems to be even more complicated. In these cases it was not possible to obtain any azetidinone in pure form. The imine (87) furnished what appeared to be an unresolved mixture of two azetidinones, in a total yield of about 10%. It is likely that there was some azetidinone formation in the case of the imine (88). Despite the poor yields obtained in the cycloaddition reaction it seemed that the combination of the acid and the activating agent is a useful one for the purpose. This provided the much needed incentive to explore this area further in terms of variations in the nature of the imines and the conditions of the reaction. At this stage it appeared that there might be

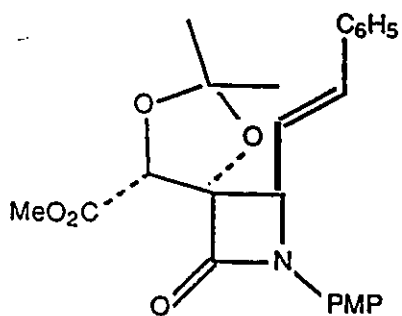
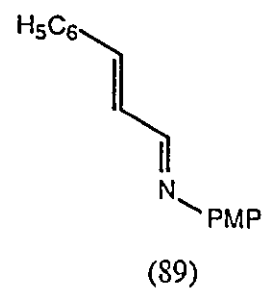
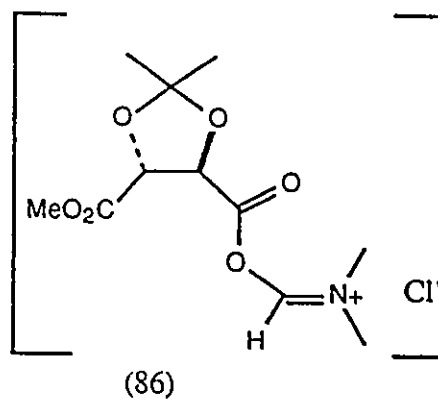
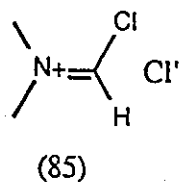
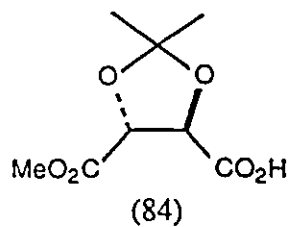
Fig. XIV



significant changes in the course taken by the reaction depending upon the imine employed and considerable experimentations may be required. Nonetheless it was necessary to move away from the imine(75), since as pointed out earlier that the azetidinones obtained from this imine have some serious limitations. .

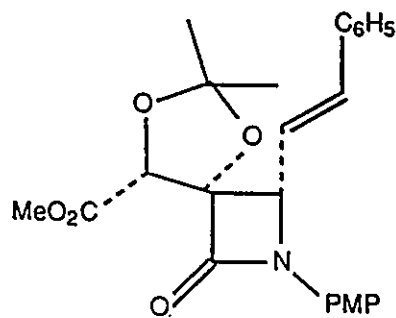
The use of the same combination of the acid (84 Fig.XV) and the iminium salt (85, Fig. XV) as activating agent with the imine (89, Fig. XV) furnished a red-brown oil as in previous cases. However this time it was possible to selectively crystallize one diastereomer from this mixture. The azetidinone obtained was chromatographically and spectroscopically homogeneous. As determined by performing column chromatography on the mother-liquor, the azetidenone isolated by crystallization was also the major product. The isolated yield of this major compound , obviously a function of the efficiency of the crystallization process, is about 20-25%. Column chromatography never furnished a pure sample of the major compound, always affording a mixture of the major product and another product, the latter being designated as the minor azetidinone (91, Fig. XV). The major : minor ratio is variable, ranging from 7:1 to about 4 : 1. Obviously this ratio is dependent upon the exact experimental conditions. Slight variations which might be easily overlooked seem to have a significant bearing on the outcome. It should again be pointed out that replacement of (85) with other activating agents such as mesyl chloride or thionyl chloride was not very successful. The imminium salt (85) is the only reagent which shows any degree of consistency.

Fig.XV



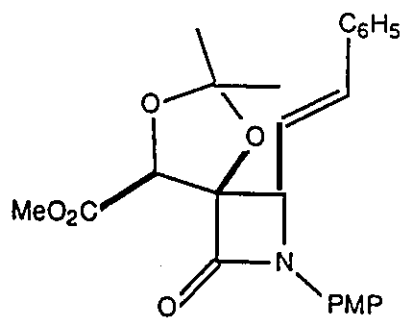
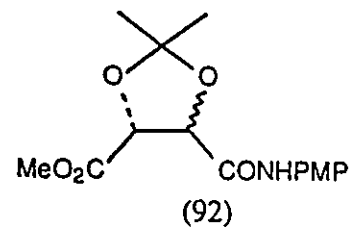
(91)

Minor product tentative structure.

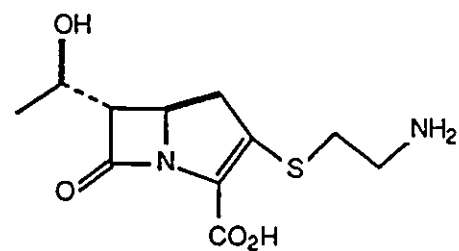


(90)

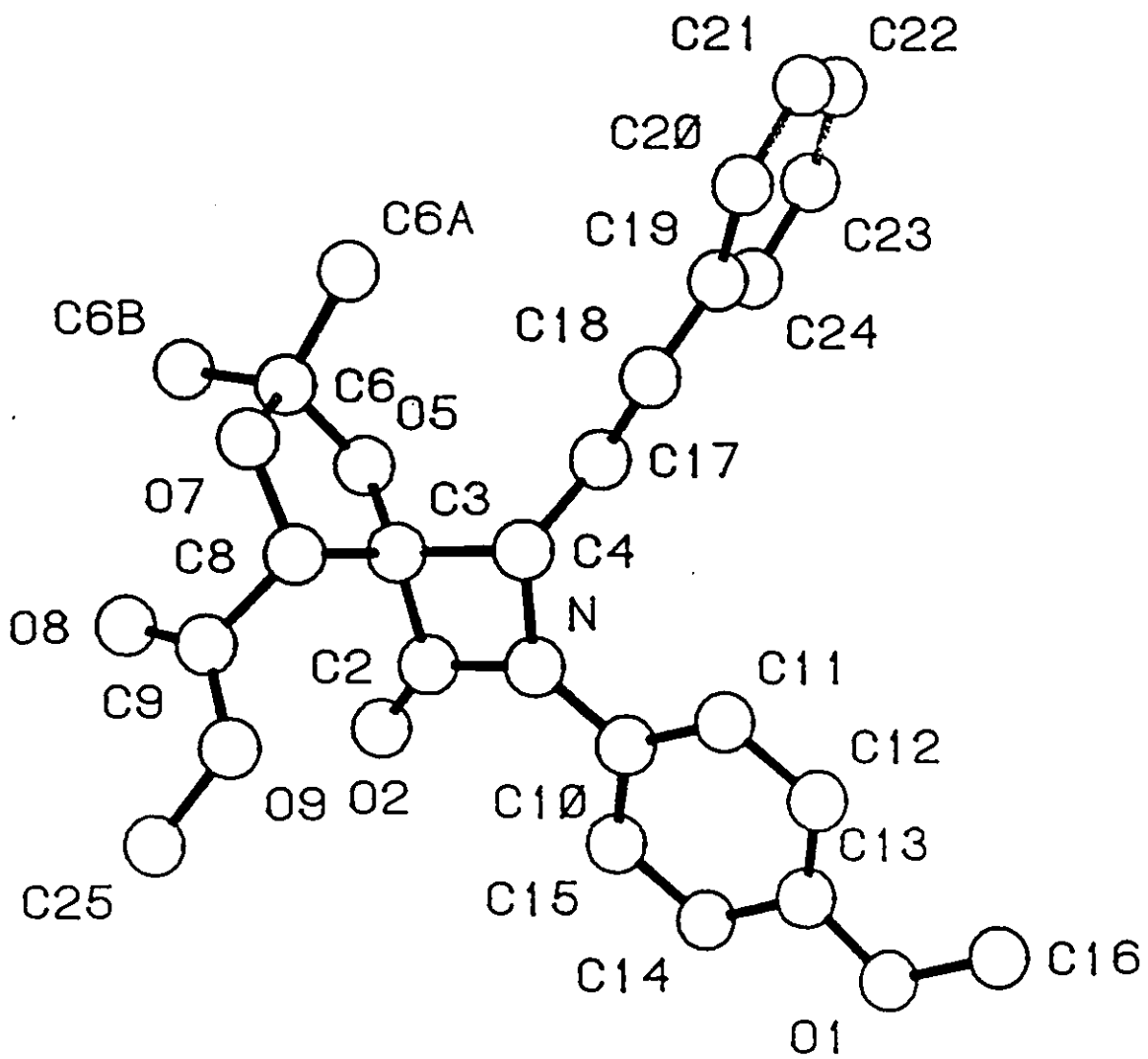
Major product, structure determined by X-ray diffraction



(enantiomer of 90)
from 2S,3S tartaric acid.



Thienamycin



The structure of the major diastereoisomer was determined by single crystal X-ray diffraction analysis (90, Fig. XV). The crystals were obtained by slow evaporation of a concentrated solution of the compound in DMF. Several features are noteworthy. The new carbon-carbon bond formed by "inversion" of geometry. Thus the in the final product the relative stereochemistry of the acetonide residue is "erythro" while that in starting acid (84, Fig.XV) it was "threo". This stereochemistry forces one of the methyl group of the acetonide residue into the deshielding zone of the carbonyl group of the azetidinone. This is manifested in the significant difference in the chemical shifts of the two methyl groups (1.38 and 1.68 ppm).

As in the case for simple 3,4-disubstituted azetidinones, the two bulky groups, the cinnamyl group at C-4 and the alkoxy group at C-3, are cis to each other. Thus it is gratifying that the relative placement of the group which can act as the precursor for the hydroxyalkyl group (in this case the carbomethoxy group) and the cinnamyl substituent at C-4 are trans to each other, parallel to the situation in thienamycin (8, Fig.XV). The absolute stereochemistry at C-3 and C-4 is opposite to that of natural thienamycin (8, Fig. XV). Thus by using the (2S, 3S) tartaric acid the situation will become favorable. Such reactions have been carried out to provide comparable yields of the enantiomer of the compound (90, Fig. XV).

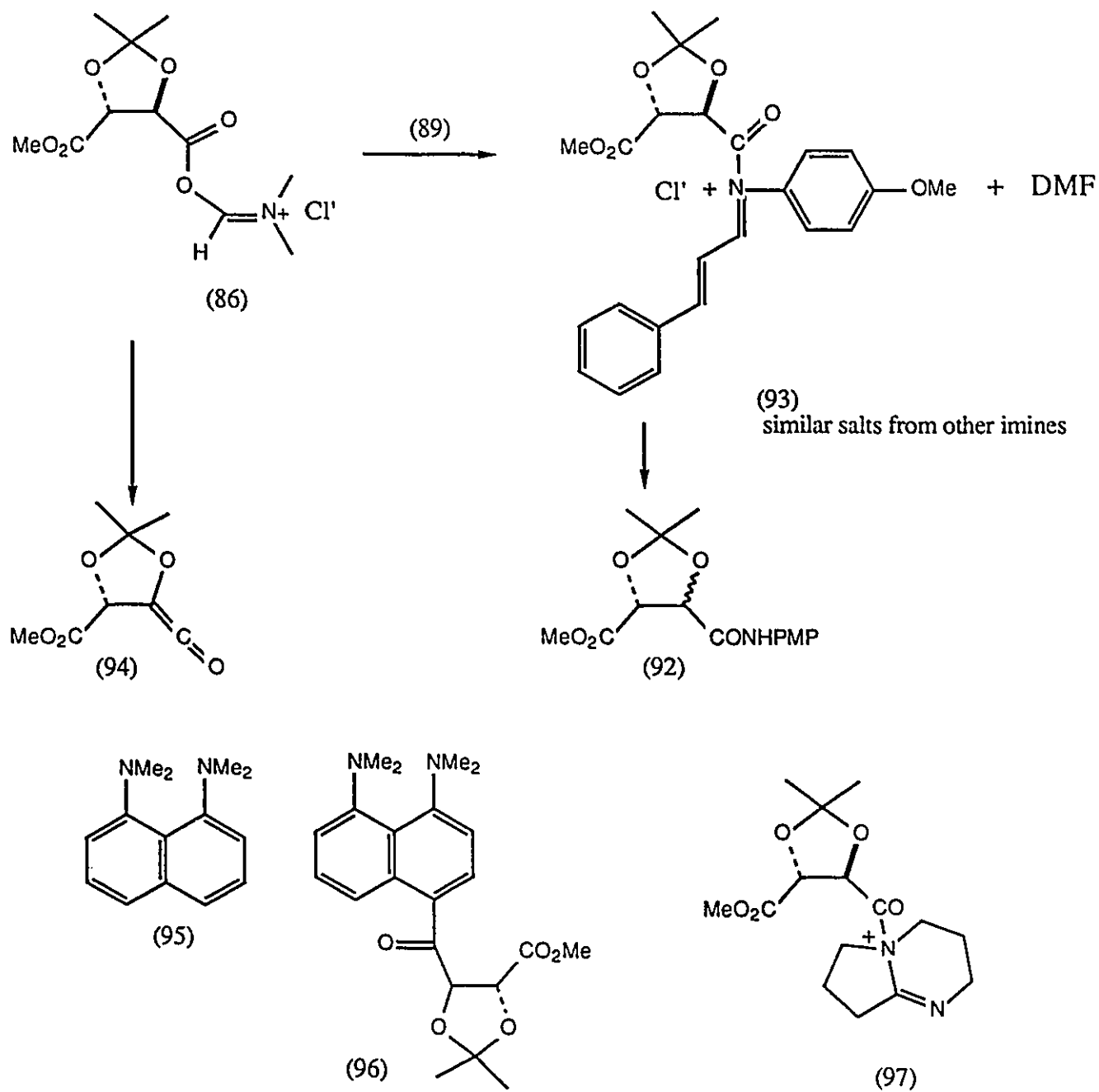
The structure of the minor azetidinone obtained from (2R,3R) tartaric acid has not been established, since this compound could not be obtained pure. However it is very tempting to make a suggestion in this regard. There is again significant difference in the chemical shifts of the methyl groups of the acetonide residue of this compound

(1.45 and 1.55 p.p.m.). This suggests a situation similar to that observed in the case of the major compound; and thus the relative "erythro" stereochemistry for the "left-half" of the molecule. This implies that the major and the minor compound differ only in the stereochemistry at C-4. Thus (91, Fig. XV) becomes a reasonable suggestion for the structure of the minor compound. {However, see Addendum II}.

An unusual feature of these reactions is the formation of significant amounts of the "simple" amide (92, Fig. XV). This can be attributed to somewhat sluggish formation of the ketene from the activated acid. Instead of ketene formation, a reaction may take place directly between the activated acid and the imine to produce the acyliminium salt (93, Fig. XVI). This salt is expected to be fairly stable by virtue of resonance energy. It may revert back to the activated acid and the imine or may stabilize itself by interaction with an "external" nucleophile such as triethylamine, DMF or chloride anion or it may even produce the ketene (94, Fig. XVI) by reacting with triethylamine. Hydrolysis of this salt or the "addition products" upon work-up will produce the simple amide (92, Fig. XVI) and release an equal amount of the corresponding aldehyde. Thus it seems logical that any factor which promotes ketene (94, Fig. XVI) formation is likely to increase the proportion of the azetidinones compared to the simple amide.

It can be argued that the process of ketene formation should be facilitated by addition of a base stronger than triethylamine or by using larger amounts of the amounts of the base. A further way to steer the reaction in the desired direction involves the formation

Fig.XVI



of the ketene at low temperatures prior to the addition of the imine^{44c}.

For reasons that are still not obvious none of these approaches proved useful. Perhaps the most surprising was that the use of the stronger base "Proton Sponge"(95, Fig, XVI) gave no detectable amounts of azetidinone, even by TLC. An unsubstantiated explanation is that the activated acid reacted with this amine to produce an acylated version of the base (96, Fig.XVI) which dissolved in the aqueous phase during the acidic work-up. The use of DBN, a base useful for elimination reactions, might have undergone temporary acylation with the activated acid, and gave no overall improvement in the situation (97, Fig.XVI). Larger amounts of triethylamine again did not lead to any noticeable improvements in terms of either the yield or the diastereoselectivity of azetidinone formation. The process of pre-formation of the ketene is usually carried out at low temperature, especially with easy to form ketenes. In the present case the formation of the ketene seems to be a difficult process even at high temperatures. At low temperatures it seems to slow down considerably, as evidenced by no overall improvement in the situation.

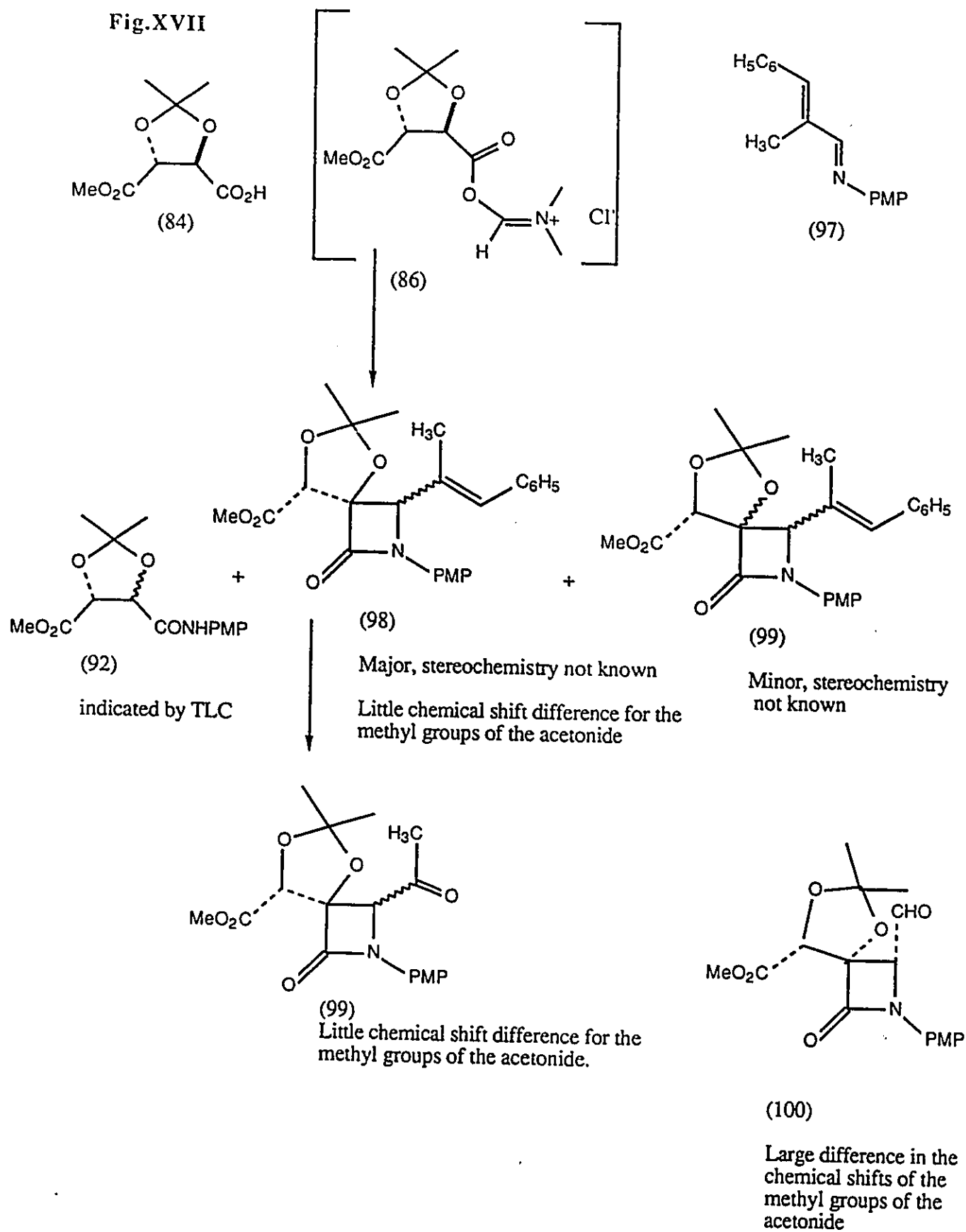
At present the best way to obtain the azetidinone (90) is by carrying out the activation of the acid using N,N-dimethylchloromethyleniminium chloride and the ketene formation using triethylamine, at 0° C. This procedure is perhaps the only one that guarantees access to reasonable quantities of the pure major diastereomer. The situation regarding the yields (20-25% isolated) is tolerable; all the reagents are fairly cheap and accessible in a few

steps. The reaction has been carried out on modest scale to provide upto about 6-7 grams of the major diastereoisomer by simple crystallization of the crude reaction product.

In an effort to determine the influence of the nature of the imine on the stereochemical course of the reaction, the cycloaddition reaction was carried out with the "methylcinnamyl" imine (97, Fig. XVII) and the acid (84, Fig. XVII). The major:minor ratio was about 5:1. Direct crystallization was not successful in this case. The major compound was isolated pure on a small scale by using the chromatotron. The chemical shift differences for the methyl groups of the acetonide residue was much less than in the case of the major diastereoisomer. (90)

Ozonolysis of the major compound produced an acetyl compound (99, Fig. XVII) . Here again there did not seem to be any differences in the chemical shifts of the two methyl groups of the acetonide residue. On the other hand the aldehyde (100, Fig. XVII) obtained from the major compound (90) has considerable differences in the chemical shifts of the two methyl groups of the acetonide residue. This seems to indicate that the major compound from the methylcinnamyl imine has the "threo" stereochemistry for the "left hand side" of the molecule. Thus change in the nature of the imine appears to have significant impact on the stereochemical outcome of the cycloaddition reaction of the acid (84). { On the basis of the structure of compound (98) as determined by X-ray diffraction analysis after the submission of the thesis, the structure of the acetyl compound (99) should be revised. The revised structure has been provided in Addendum II}.

Fig. XVII

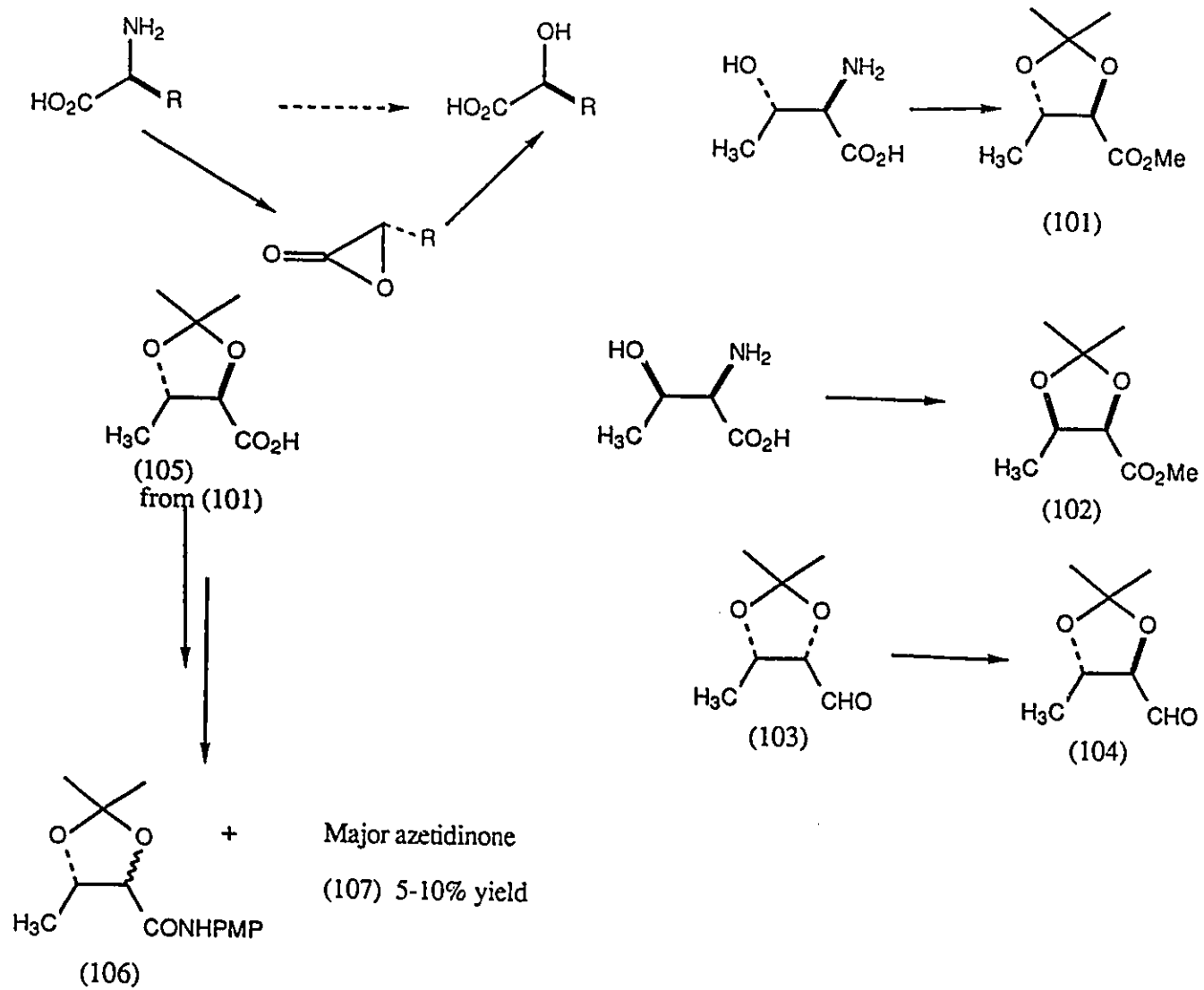


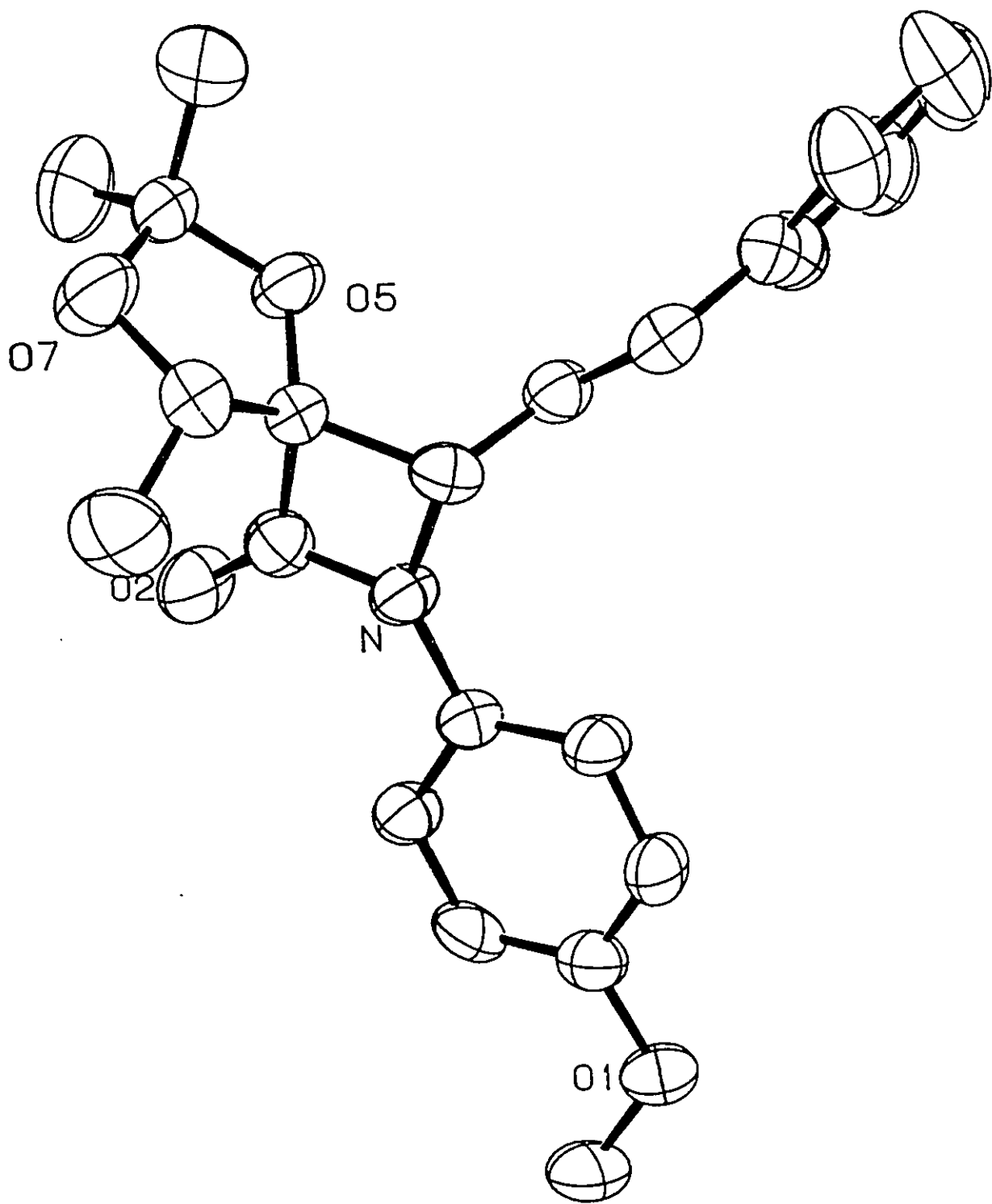
α -Aminoacids have been known to undergo diazotisation to furnish the corresponding α -hydroxyacids. The process takes place with overall retention of the configuration; the result of two inversions (Fig. XVIII). Such a process provides access to derivatives of 2,3-dihydroxybutanoic acids such as (101 and 102, Fig. XVIII). Threonine serves as the starting material for the acid with threo relative stereochemistry whereas erythro acid is obtainable from allo-threonine. Fuganti and colleagues have obtained the corresponding erythro aldehyde by a fermentation process. The threo compound can be obtained by a facile base catalyzed epimerisation of the erythro compound. (103 to 104, Fig. XVIII)⁴⁸.

Following Servi's experimental details, the threo ester acetone (101, Fig.XVIII) was prepared. The corresponding acid (105, Fig.XVIII) was obtained by hydrolysis. On being subjected to the cycloaddition reaction using the usual activating agent and the imine (85 and 89, Fig. XV) the "usual" red brown oil resulted. Here again attempted crystallization did not provide any pure azetidinone. Column chromatography on the other hand furnished a pure azetidinone (107, Fig. XVIII and XIX) in about 5-10% yield. This however was the major azetidinone, the weight of other fractions which might have contained azetidinone was even smaller. The simple amide (106, Fig. XVIII) being also detected in this case, however the yield of this compound was not determined.

The structure of the major azetidinone was determined by single crystal X-ray diffraction analysis (107, Fig.XIX). The chemical shifts of the two methyl groups of the acetone residue are again

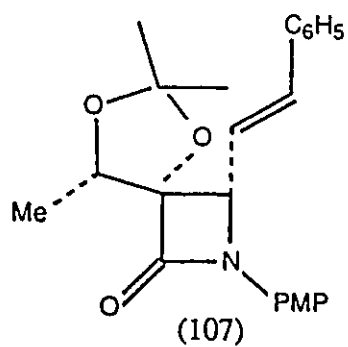
Fig. XVIII



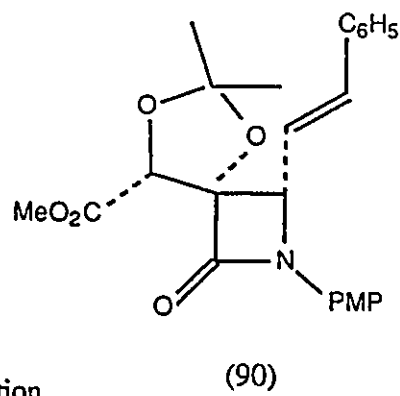


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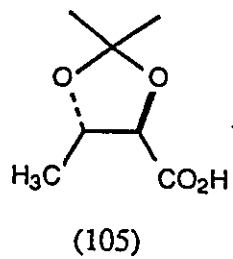
Fig.XIX



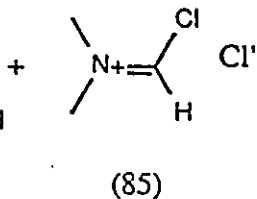
Structure determined by X-ray diffraction



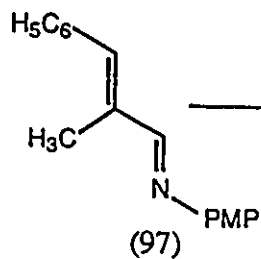
(90)



(105)



(85)



(97)

Unresolved mixture of
azetidinones;
about 2% yield

significantly different (about 0.2 ppm), again a manifestation of the "erythro" stereochemistry of the "left-half" of the molecule. It was interesting to note that the sense of the chirality induction remains the same for both the carbomethoxy and the methyl compound (106 and 94., Fig.XIX).

Efforts to determine the influence of the imine on the stereochemical course (of 2+2 cycloaddition reactions of the ketene derived from the threo acid) were frustrating. Thus the reaction of the methylcinnamyl imine with the acid, using (85, Fig. XIX) as the activating agent, furnished only about 2% yield of unresolvable mixture of the azetidinones. Experiments using the alleged acid chloride were only slightly better, furnishing the similar mixture in about 5% yield. This makes it difficult to comment about the influence of the imine on the stereochemical outcome of this reaction. A major problem in the use of the "threo" acid is that yields of the azetidinone (107) are poor. Compared to the case of the carbomethoxy compound, isolation of this compound is a tedious process. So far it has not been possible to obtain the azetidinone (107) in synthetically useful amounts.

At this stage it was argued that the formation of the ketene from the erythro acid should be somewhat easier than from the corresponding threo acid though the ketene obtained is the same in both the cases. Perhaps somewhat naively it was argued that formation of the ketene from the erythro acid may lower the steric congestion. Thus use of the erythro acid may solve the problem of poor yields associated with the threo acid.

Instead of using expensive allo-threonine as the starting material for the erythro compound, it was decided to use the racemic mixture in this case. Thus epoxidation of benzyl crotonate followed by Lewis acid catalyzed reaction of the epoxide(108, Fig. XX) with acetone furnished the erythro acetonide (109, Fig.XX)⁴⁹. The benzyl group was removed by transfer hydrogenolysis and the resulting acid (110, Fig. XX) was subjected to the ketene-imine reaction using the "usual" combination of the activating agent and the imine. In this case no azetidinone was isolated. The reason for this failure is not known. However in this case TLC revealed the presence of a compound with R_f very similar to the simple amide (106, Fig.XX) obtained from the corresponding threo acetonide. The reasons for this failure are not clear.

The trans epoxy ester could be converted to the corresponding acid(111, Fig.XX) Subjecting the acid to the usual cycloaddition reaction led to no detectable amounts of the azetidinone, TLC and NMR analysis revealed the presence of only the simple amide (112, Fig. XX) and variable quantities of the imine and the aldehyde. Since the aqueous washes were not analyzed, it is difficult to comment about the fate of the starting acid. It appeared that in the case of the epoxy compounds the strain in the final molecule might have been the cause of this failure.

Efforts to remove the acetonide residue from (90, Fig.XX) were unrewarding. Thus whereas exposure of the compound to a 10% solution of HCl in refluxing THF-methanol mixture leads to no change, increasing the amount of the acid leads to total destruction of the compound. Use of TFA did not prove effective. A major

problem in this area is the poor solubility of the compound in various hydroxylic solvents. Use of co-solvents such as acetone, THF or acetonitrile does not seem to improve the situation.

Our inability to obtain the diol (113, Fig. XX) made it impossible to determine if selective alkylation can be carried out to convert this compound into 3-alkoxy compounds such as (114, Fig. XX).

Paucity of the results in this area makes it somewhat difficult to come up with a suitable, general model for the process of chirality induction.

The poor diastereoselectivity makes it obvious that the factors determining the stereochemical course of the reaction are not overwhelming. It is logical to assume that the carbomethoxy group serves to make one of the faces of the ketene less accessible than the other face. On this basis it can be assumed that the preferred zwitterionic intermediate should be (115, Fig. XXI). Inward disrotatory movement is favoured over the outward disrotatory movement. The former will considerably minimise the interaction between the cinnamyl side-chain and one of the methyl groups of the acetonide residue. This will lead to overall "erythro" arrangements of the various substituents of the left-half of the molecule and the compound (90) as the major product. The outward disrotatory movement will lead to the "threo" arrangement for the "left-half" of the molecule. Such an arrangement will manifest itself in terms of neither of the methyl groups being thrust into the shielding zone of the carbonyl group of the azetidinone. Consequently the chemical shifts differences in the compound

Fig. XX

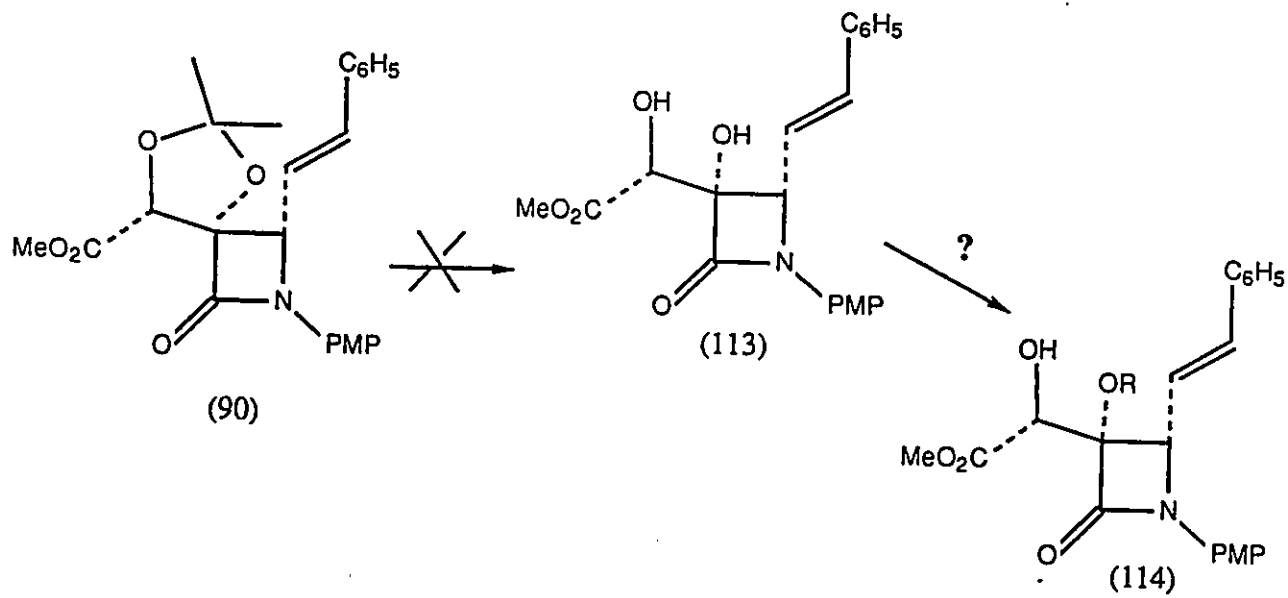
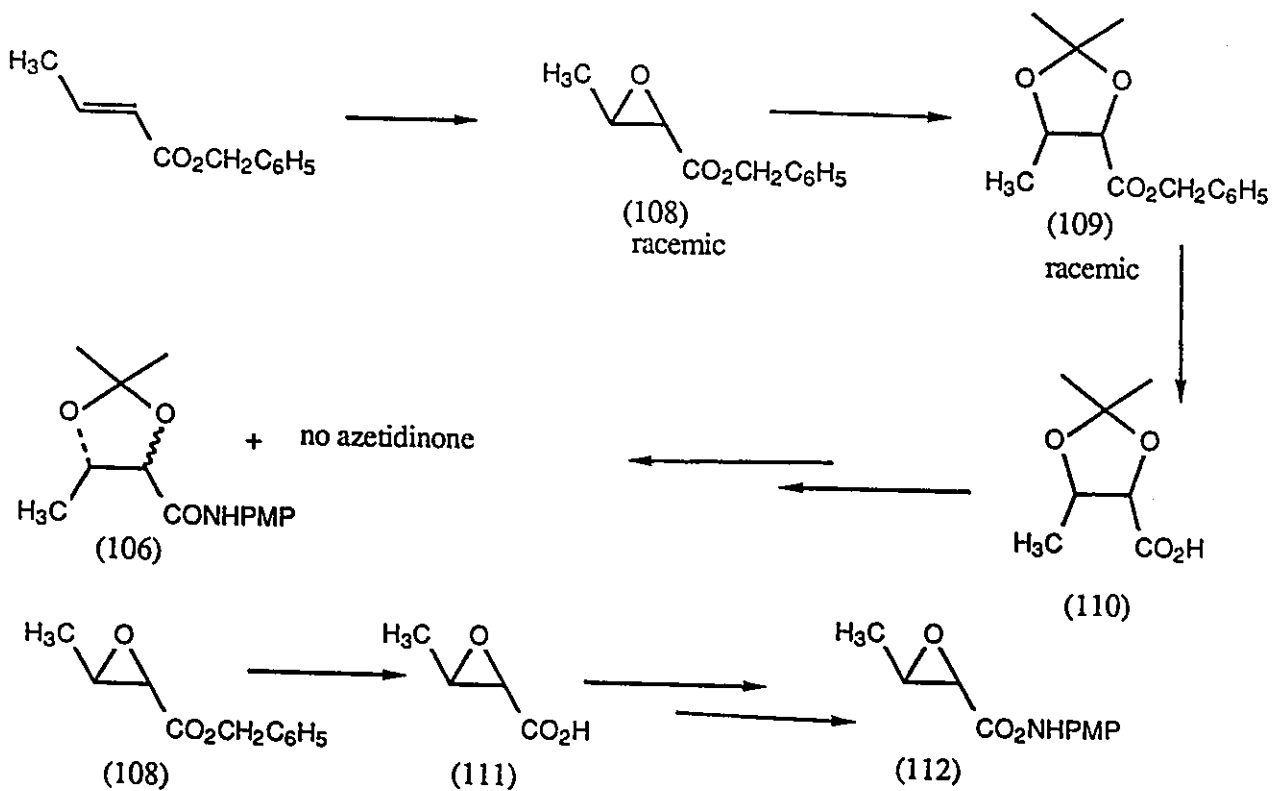
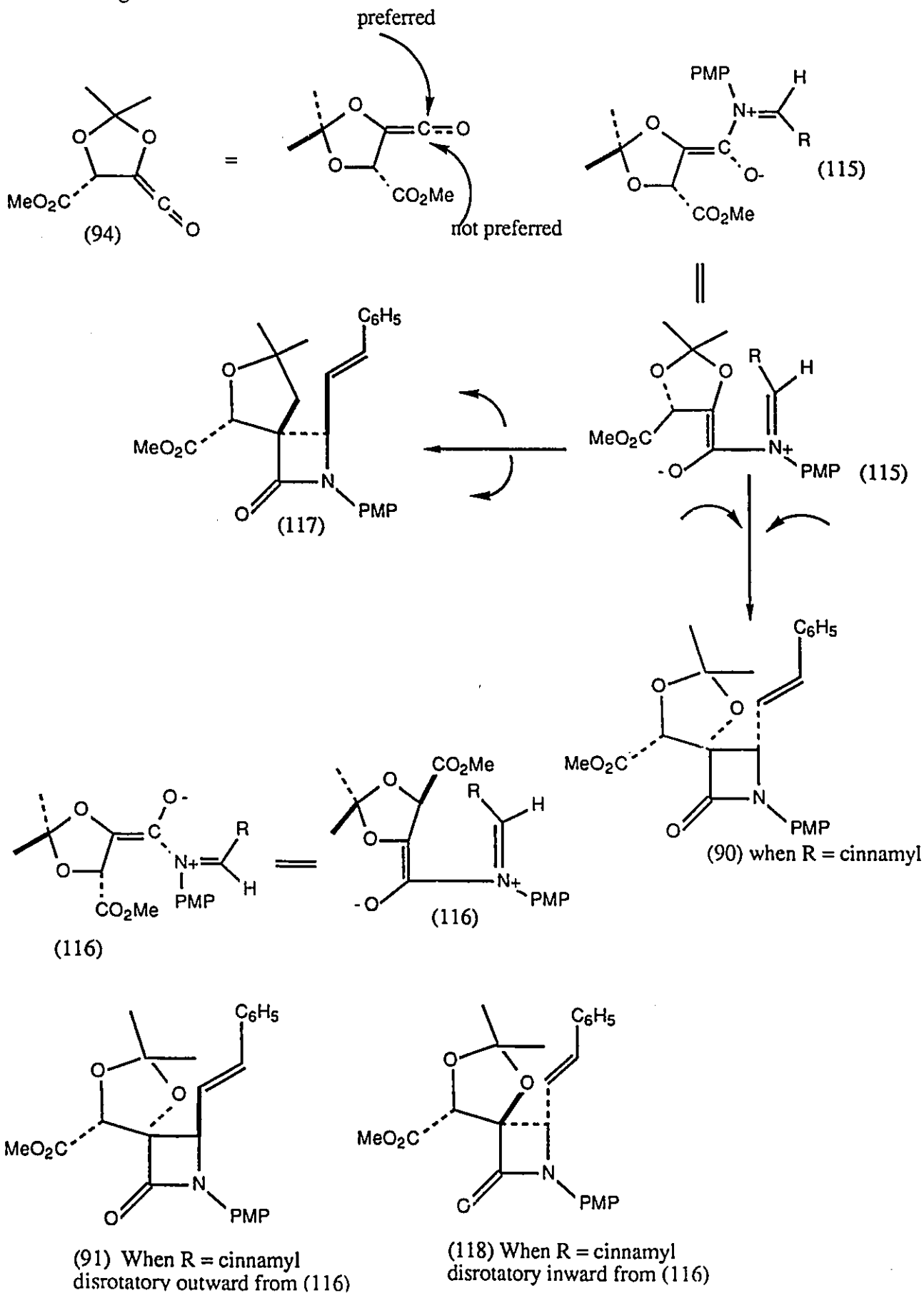


Fig. XXI



arising from outward disrotatory movement will be much smaller (117, Fig. XXI). Even though in the L-tartaric acid series no such compound was isolated, in the D-tartaric acid series, in addition to the comparable quantities of the major and the minor compounds, very small quantities (about 0.5%) of such a compound were isolated. The chemical shift difference in this case is about 0.09 ppm. There is an alternative explanation for the formation of a compound with "threo" stereochemistry for the "left hand side". The "trace" compound obtained from D-tartaric acid is likely to be an enantiomer of the compound (117, Fig. XXI).

The formation of the minor compound (which also has significant differences in the chemical shifts of the methyl groups of the acetonide residue) can be explained by the attack of the imine on the more hindered face of the ketene (116, Fig. XXI) followed by outward disrotatory movement. In this case this movement is preferred because it minimises the interaction between the bulky carbomethoxy and the cinnamyl group. The inward disrotatory movement is highly unlikely due to the severe steric congestion that will accompany such a movement. Thus structure (118, Fig. XXI) is not a likely candidate for the structure of "trace" compound; even though it does have the requisite "threo" stereochemistry for the "left hand" portion of the molecule. Similar analysis explains the formation of the major product in the dihydroxy butyric acid series⁵⁰.

As mentioned previously, it is not possible to come up with a truly general model to predict the stereochemical outcome of these reactions. It has not been possible to "routinely" determine the

actual structure of the minor compounds, by X-ray diffraction analysis, and thus check the far reaching predictions made by this model. However, one can be fairly certain about the assignment of stereochemistry of the "left hand half" of this molecule. Also, this model can be adequate for explaining generally poor yields and poorer diastereoselectivity when methylcinnamyl imine replaces the cinnamyl imine. In the former case following the argument of the proposed model leads to zwitterionic intermediates in which the disrotatory movement to form bonds is hindered by interaction of the "extra" methyl group with various other substituents. This situation seems to prevail for the methylcinnamyl imine, regardless of the face of the ketene, the nature of the other substituents on the ketene or the nature of the disrotatory movement (inward or outward). { However see Addendum II }

The task of enantioselective syntheses of azetidinones from tartaric and 2,3-dihydroxy acids is a qualified success at best. Lack of results from erythro and epoxy acids have shown the severe limitation of such an approach. Failure to hydrolyse the acetonide residue has so far made it impossible to check the viability of the selective alkylation approach. On the positive note it can be added that at least in one case such an approach has provided access to respectable amounts of a functionalisable azetidinone, with proper relative stereochemistry of thienamycin type compounds. It is anticipated that this particular compound will prove useful for the syntheses of bicyclic azetidinones.

The studies described above also serve to underline need for a more systematic approach for syntheses of 3-alkoxy-3-

hydroxyalkylazetidinones. Such studies have been carried out and are presented in a later chapter.

References and notes

(38) Kronenthal, D.R.; Han, C.Y. and Taylor, M.K. *J. Org. Chem.* **1982**, *47*, 2765.

(39) Ozonolysis of the cinnamyl group and the methylcinnamyl group can be expected to be trouble free. The ozonolysis of the 2-furyl group, though not as well-known as that of other groups has served as a source of the corresponding carboxyl group. For an example see: Danishefsky, S. and Maring, C. *J. Am. Chem. Soc.* **1985**, *107*, 7762.

(40) Formation of cis 3,4-disubstituted azetidinones by ketene-imine interaction is almost universal and too well-established to be fully documented here. Some exceptions are known, specifically in the field of the phthaloylglycine as the ketene precursor. When the imine component is derived from benzaldehyde, significant quantities of the trans azetidinones can result. However even in this case use of cinnamaldehyde derived imines furnish cis azetidinone as the major product though not the exclusive product. For an example see: Toutake, N.; Kirisawa, M. and Miyake, M. *Synthesis* **1982**, 1853.

(41) Examples of syntheses of 3,3-disubstitued azetidinones using Staudinger reaction are few. Even in some of these cases no stereochemical assignments have been made. For one such example see, Palomo, C.; Arrieta, A. and Aizpura, J. M. *Syn. Comm.* **1982**, *12*, 967.

(42) Hegedus and coworkers have established a fairly general protocol for the synthesis of various 3-alkoxy-3,4-dialkyl (or arylalkyl or diaryl) azetidinones. Here again it seems that these authors have relied rather heavily on the use of chemical shifts as means of establishing the relative stereochemistry of the substituents. There does not seem to be an independent confirmation of these assignments. Though intrinsically interesting, this approach is not likely to be relevant for the syntheses of the targets such as those under consideration here. For detailed experimental procedure and a compilation of leading references in this area see, Hegedus, L.S.; McGuire, M.A. and Schultz, L.M. *Org. Syn.* 65, 14C 143. (Ed. E. Vedejs). For an approach based upon photocyclisation see: Aoyama, H.; Sakamoto, M. and Omote, Y. *Tet.* 1987, 43, 1513.

(43) This particular area has attracted a lot of attention and the list of the references is extensive. No attempt is being made here to provide a comprehensive listing. What follows is a compilation of some of the examples.

[i] Cooper, R.D.G.; Daugherty, B.W. and Boyd, D.B. *Pure and Appl. Chem.*, 1987, 59, 485.

[ii] Hubschwerlen, C. and Schmid, G. *Helv. Chim. Acta.*, 1983, 66, 2206.

[iii] Evans, D.A. and Sjogern, E.B. *Tet. Lett.* 1985, 26, 3783.

[iv] Evans, D.A. and Williams, J.M. *Tet. Lett.* 1988, 29, 5065.

[v] Morin, C. and Labia, R. *J. Antibio.* 1984, 37, 1104.

[vi] Nagahara, T. and Kametani, T. *Het.* 1987, 25, 729.

- [vii] George, G.I. in "Studies in the Natural Products Chemistry" Vol. 2. (Ed. A-ur Rahman). 1988. Elsevier, Amsterdam.
- (44) Tschaen, D. M.; Fuentes, L.M.; Lynch, J.E.; Laswell, W.I.; Volante, R.P. and Shinkai, I. *Tet. Lett.* **1988**, *29*, 2779.
- (45) Baldwin, J.E. *J. Chem. Soc. Chem. Comm.* **1976**, 734, 736, 738.
- (46) Masamune, S.; Lee, A.W. M.; Sharpless, K.B. and Walker, F.J. *J. Am. Chem. Soc.* **1982**, *104*, 3515. See also the reference 5 in this particular communication.
- (47) Rapoport, H. and Musich, J.A. *J. Am. Chem. Soc.* **1978**, *100*, 4865.
- (48) Diazotisation of threonine has been described with good experimental details by Servi. The author also describes the procedure for epimerisation of the erythro aldehyde to the threo compound. Fuganti's contributions in this area are also listed in this communication.. Servi, S. *J. Org. Chem.* **1985**, *50*, 5865.
- (49) The experimental procedure adopted here was very close to that of Hoffman, R.W. and Ladner, W. *Chem. Ber.* **1983**, *116*, 1633,1638. Bachelor and Miana have described routes which provide access to both erythro and threo 2,3-dihydroxy butyric acids. Bachelor, F.W. and Miana, G.A. *Can. J. Chem.* **1969**, *47*, 4089. However, their procedure involves resolution of the corresponding racemic mixtures and thus provide access to only one enantiomer at a time. These authors do not make any comments regarding the other enantiomer. At least two different attempts to obtain the threo acid in enantiomerically pure form by this procedure failed. Attempts with the erythro acid did not seem any better. These factors forced use to use a racemic mixture in the erythro series.

(50) The use of terms "conrotatory" and "disrotatory" is very restricted and perhaps somewhat arbitrary. These terms are just being used to describe the movement of the substituents for the purpose of bond formation. They are not to be used in the same sense as in concerted reactions which are bound by Woodward-Hoffman rules. Indeed it can be argued that conservation of orbital symmetry rules are not applicable to the ketene-imine reactions since these seems to involve discrete zwitterionic intermediates and thus may not be concerted.

Experimental Section

General

Unless otherwise specified proton NMR spectra were recorded in CDCl_3 with a Varian XL300 or Gemini 200 or EM 360 spectrometer. The chemical shifts are reported in ppm(d) downfield from tetramethylsilane which was used as an internal standard. The shape of the signal (i.e. singlet, doublet, triplet, quartet or multiplet etc.), the number of protons indicated by integration and the coupling constants are reported; in that order. Infrared spectra were recorded with a Perkin-Elmer 783 spectrophotometer by applying the solution of the compound (in dichloromethane or chloroform) as a thin film on NaCl disc. Only intense peaks have been presented; the values indicated are in cm^{-1} . Mass spectra were obtained with a VG ANALYTICAL 7070E mass spectrometer (ei-ms 70ev; ci-ms 70 ev ionizing potential using diethylether as the reagent gas). Unless otherwise indicated the data corresponds to ei-ms spectra. Optical rotations were recorded only for new and pure compounds on a Perkin Elmer 241 polarimeter using Na 5890 A° light; chloroform being the solvent for this purpose. Melting points were recorded on a Gallenkemp melting point apparatus at medium setting (5 -7).

Solvents for the extractions and chromatographic purifications were routinely distilled prior to use. Solvents used in various reactions were dried in usual manner. Dichloromethane was distilled over phosphoric anhydride and stored over 4 A° molecular sieves under an atmosphere of nitrogen. Tetrahydrofuran, diethylether, benzene and toluene were distilled over sodium-benzophenone ketyl under an atmosphere of nitrogen. DMF was distilled over CaH_2

under an atmosphere of nitrogen and stored over 4A^o molecular sieves. Ethanol and methanol were distilled over Mg-I₂ under nitrogen atmosphere and were stored under nitrogen. However for hydrolysis reactions 99% ethanol was used.

Amines used were distilled and stored similar to DMF. Acid chlorides were purified by distillation. Alkyl halides were distilled prior to use, except for methyl iodide which was used as received. Oxalyl chloride and thionyl chloride were used as received from commercial suppliers. NaH (ca.50% dispersion in oil) was not washed free of the oil. Tosylimidazole was prepared as per reference (76). Benzoylimidazole was prepared by a similar method (76, Hodgson and Carey). For preparation of t-butyldimethylsilyl triflate and preparation of TBDMS derivatives using this reagent the procedure outlined by Corey and coworkers (*Tet. Lett.* 1982,22, , 3455) was employed. Ammonium formate and Pd/C were used as received. All other reagent were used as received.

Filtration refers to removal of solid (products or the drying agent) by applying suction from a water aspirator. Removal of solvents, evaporation of the solvent or concentration of a solution implies evaporation under low pressure by using a Rotovap at a temperature of less than 40°C.

Chromatography refers to flash chromatography (Kahn.M. ; Still, W.C. and Mitra, A. *J. Org. Chem.* 1978, 43, 2923) except that Merck 230-400 mesh silica was used and columns were filled to the height of about 25-35 cms. The elution was carried out by applying 10-15 psi nitrogen pressure. Thin layer chromatograms were used to

determine the purity of various samples. The above general comments apply to all other chapters as well.

The acid (84, Fig. XV) was prepared by the literature procedure⁴⁷. Since there was no difference in the $[\alpha]_D$ of the distilled and the undistilled acid, the latter was used for the purpose of azetidinone formation step. The acid (105, Fig. XVIII) was prepared by saponification of the ester (101, Fig. XVIII)⁴⁸ followed by conventional acid-base purification. The unstable acid (105) was obtained in about 80% yield.

Synthesis of azetidinone (90, Fig. XV)

A dry 500 mL two neck round bottomed flask fitted with a stirring bar and a pressure equalizing dropping funnel was charged with 250 mL of dry dichloromethane and 5.8 mL (75 mmol) of dry DMF. The dropping funnel was charged with 6.4 mL (75 mmol) of oxalyl chloride and 25 mL of dry dichloromethane. The flask was cooled to 0°C under nitrogen and the septum on the top of the dropping funnel was quickly replaced with a drying tube. Oxalyl chloride solution from the dropping funnel was added dropwise to the vigorously stirred solution of DMF over a period of about 25 min. The addition was accompanied by precipitation of a white solid and fuming. A solution containing 14 g (68 mmol) of the acid (94, Fig. XV) in 100 mL of dry dichloromethane was introduced via the side arm over a period of 1-2 min. This led to dissolution of the precipitate to furnish a clear colorless solution. To facilitate transfer under nitrogen, the drying tube was replaced with a septum cap.(Flask I).

To a dry 1000 mL round bottomed flask provided with a stirring bar and a pressure equalizing dropping funnel was added 14.6 g (61 mmol) of imine (89, Fig. XV), 21 mL (207 mmol) of dry triethylamine and enough dry dichloromethane (ca. 550 mL) to obtain a clear solution. The solution containing the imine and amine cooled under nitrogen in an ice-bath (FlaskII). The clear solution from (Flask I) was transferred to the dropping funnel on the (Flask II) ;under nitrogen. The septum cap on the FlaskII was quickly replaced with a drying tube. Addition of the solution from the dropping funnel to the vigorously stirred solution in the flask was carried out over a period of about 1 h. The heterogeneous dark solution was allowed to warm up to room temperature over a period of about 2 h and was stirred at this temperature for an additional 18 h. Workup involved successive extraction of the reaction mixture with 500 mL of 10% HCl, 500 mL of water and 500 mL of 5% NaHCO₃ solution. After each extraction, the aqueous layer was washed with another 25 mL of dichloromethane. The combined organic layer was dried with MgSO₄. Removal of the drying agent and the solvent furnished a red tar.

To this red tar was added 100 mL of ether and 10 mL of ethyl acetate to obtain a clear solution on warming. Addition of 25 mL of dichloromethane to the warm solution at this stage led to cloudiness. This solution was allowed to cool undisturbed to room temperature and then 20 mL of hexanes was added. The precipitate thus obtained was removed by filtration and the solid was washed with 2X10 mL of ice-cold ether to provide 4 g of a chromatographically homogeneous azetidinone (90) as a white solid. Solvent was

removed from the mother liquor to furnish a red tar which was dissolved in 25 mL of diethyl ether. Addition of 35 mL of hexanes to this warm solution led to cloudiness. On being allowed to cool undisturbed, a brown solid deposited from this solution. Removal of the solution by filtration and washing of the solid by 2X5 ml of ice-cold solution led to 2 g of a white solid which in addition to the azetidinone (90) contained another more polar material. However the high field NMR(300) spectrum of this particular sample showed only one set of signals i.e. those corresponding to the azetidinone (90). Thus the total yield of the azetidinone (90) was 6 g (13 mmol; 22%). Column chromatography using 3:1: hexane: ethyl acetate also furnished 1.6 g of a mixture of azetidinones which contained the azetidinone (90) and the minor azetidinone (91) in nearly 1:1 ratio. By column chromatography, about 28% of simple amide (92, Fig. XV) and a total of 15 g of a red tar consisting of multitude of compounds was also obtained. As mentioned in the text, this tar was not processed further.

The major azetidinone (90, Fig. XV) has the following physical properties: mp: 181-182°C; ir: 1755 cm^{-1} ; ms: 423 (M^+ , 12.8%), 365 (M^+-48 , 12.8%), 334 (M^+-89 , 3.7%), 309 (M^+-114 , 2.8%), 274 (M^+-149 , 12.2%), 237 (imine⁺, 56.3%), 236 (imine⁺-1, 100%); nmr: δ = 7.4-7.2 (m, 7 H), 6.8 (m, 3 H), 6.3-6.2 (dd, 2 H, J = 9.0 Hz, J = 15.9 Hz), 4.9 (s, 1 H), 4.8 (d, 1 H, J = 9.0 Hz), 3.7 (s, 6 H), 1.6 (s, 3 H), 1.3 (s, 3 H); $[\alpha]_{\text{D}} = (-)3.75^\circ$ (c = 0.02). The minor azetidinone (91, Fig. XV) could not be isolated pure and thus physical data for this compound is not available. By the process of elimination, the following signals could be assigned to the minor azetidinone (91, Fig. XV) in the NMR

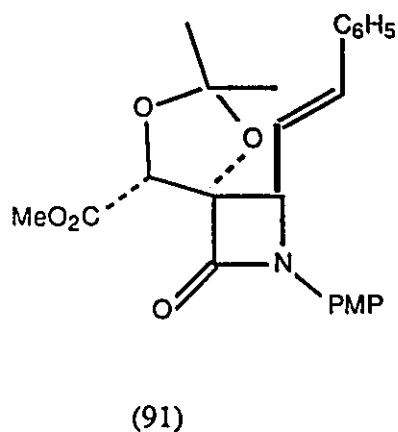
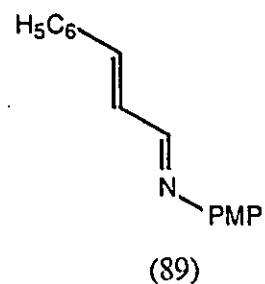
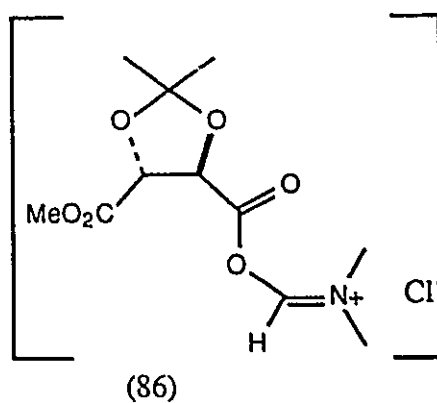
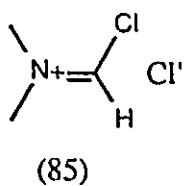
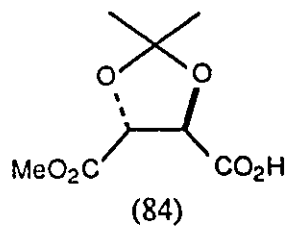
spectrum of the mixture of the azetidinones: δ = 5.0 (s, 1 H), 4.5 (d, 1 H, J = 8.6 Hz), 3.7 (s, 3 H), 1.5 (s, 3 H), 1.4 (s, 3 H). All other signals overlapped with those of the major azetidinone.

For comparison purposes a small sample of the amide (92, Fig. XV) was prepared by activation of the acid (84, Fig. XV) with (85) and subsequent reaction with *p*-anisidine in a manner similar to that mentioned for the synthesis of the azetidinone. The amide was obtained as a red oil in 85% yield. Spectroscopic properties of this compound are as follows: ir: 1670 cm^{-1} ; ms: 309 (M^+ , 5.7%), 268 ($M^+ - 31$, 2.3%), 149 ($C_8H_7NO_2^+$ 100%); nmr: 7.4 (d, 2 H, J = 6.5 Hz), 6.8 (d, 2 H, J = 6.5 Hz), 5.2 (s, 2 H), 3.6 (s, 6 H), 1.3 (s, 6 H). The extent of epimerization during amide bond formation was not determined and thus $[\alpha]_D$ was not recorded.

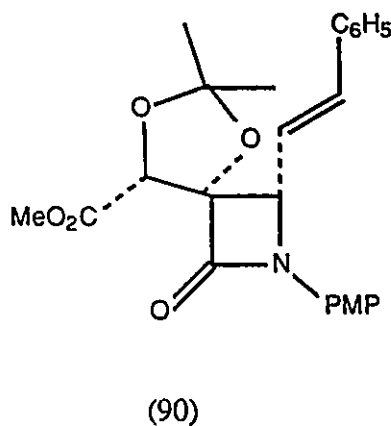
Synthesis of the enantiomer of the azetidinone (90, Fig. XV) involved the steps outlined above and the major azetidinone was obtained as before. Physical properties of this compound are the same as that of the azetidinone (90) and $[\alpha]_D$ was equal in magnitude and opposite in sign.

The 'trace' azetidinone obtained in this series i.e. the enantiomer of (117, Fig. XXI) was obtained from column chromatography on the mother liquor. This compound has the following spectroscopic properties: mp: $146-147^\circ\text{C}$; ir: 1755 cm^{-1} ; 423 (M^+ , 15.1%), 365 ($M^+ - 58$, 16.8%), 306 ($M^+ - 68$, 9.6%), 274 ($M^+ - 149$, 29.4%), 237 (imine⁺, 74.5%), 236 (imine⁺ - 1, 100%); nmr: δ = 7.4-7.2 (m, 7 H), 6.8 (d, 2 H, J = 6.8 Hz), 6.7 (d, 1 H, J = 15.9 Hz), 6.2 (dd, 1 H, J = 8.6 Hz, J = 15.9 Hz), 5.0 (s, 1 H), 4.5 (d, 1 H, J = 8.6 Hz), 3.77 (s, 3 H), 3.74 (s, 3 H), 1.552-1.541 (two s, 6 H); $[\alpha]_D = (+) 45.9^\circ$ ($c = 0.005$).

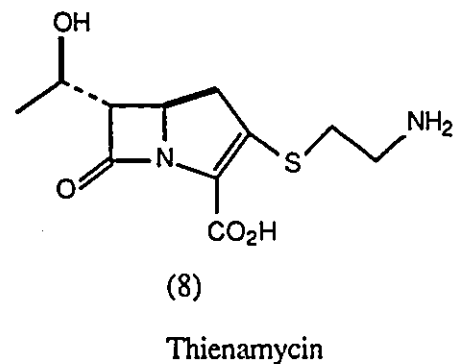
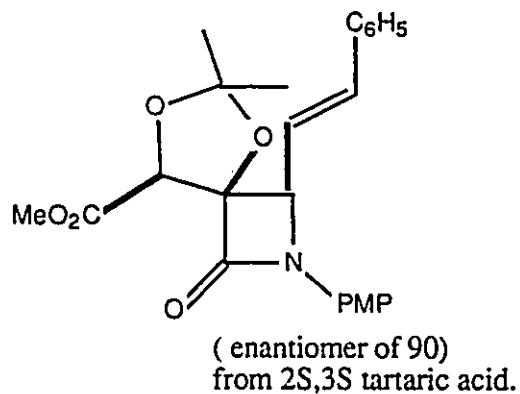
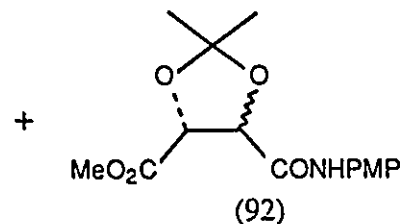
Fig.XV



Minor product tentative structure.



Major product, structure determined by X-ray diffraction



HRMS Calcd for $C_{24}H_{25}NO_6$ 423.1702, found 423.1691. The last two chemical shifts have been reported in more detail than others to emphasize the small difference in the chemical shifts of the methyl groups of the isopropylidene moiety.

A small sample of pure (98, Fig. XVII) was obtained as the less polar fraction by purification of a mixture of this compound with the minor azetidinone using chromatotron. The physical properties of this compound are as follows: mp: 118-119°C; ir: 1750 cm^{-1} ; ms: 437 (M^+ , 15.2%), 379 ($M^+ - 58$, 5.4%), 288 ($M^+ - 149$, 13.1%), 251 (imine⁺, 40.3%), 250 (imine⁺ - 1, 100%); nmr: δ = 7.3-7.2 (m, 7 H), 6.8 (dd, 2 H, J = 2.4 Hz, J = 6.8 Hz), 6.5 (broad s, 1 H), 5.0 (s, 1 H), 4.4 (d, 1 H, J = 0.7 Hz), 3.7 (s, 6 H), 1.8 (d, 3 H, J = 1.3 Hz), 1.549 (s, 3 H), 1.508 (s, 3 H); $[\alpha]_D = (-) 35.9^\circ$ (c = 0.016). HRMS Calcd for $C_{25}H_{27}NO_6$ 437.1836, found 437.1829. The last two chemical shifts have been reported in more details than others to emphasize the very small difference.

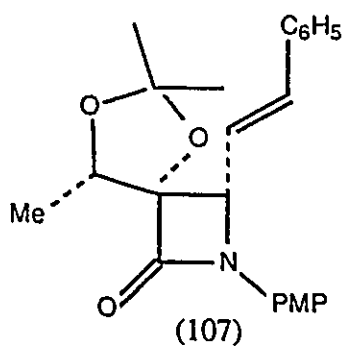
A very small sample of the minor azetidinone (98a, Fig. XVII) was obtained in pure state. The physical properties of this compound are as follows: mp = 114°C; infra red and mass spectrum were similar to that of the major diastereoisomer (98, Fig. XVII); nmr: δ = 7.4-7.3 (m, 7 H), 6.8 (dd, 2 H, J = 2.2, J = 6.8 Hz), 6.6 (s, 1 H), 4.99 (s, 1H), 4.7 (1 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 1.9 (d, 3 H, J = 1.3 Hz), 1.664 (s, 3 H), 1.415 (s, 3 H); $[\alpha]_D = (-) 50.6^\circ$ (c = 0.01). HRMS Calcd for $C_{25}H_{27}NO_6$ 437.1836, found 437.1839. Here again some chemical shifts have been reported in more details than others to emphasize the differences between the two diastereoisomers (98 and 98a, Fig. XVII).

Synthesis of the azetidinones (99 and 100, Fig. XVII) involved the ozonolysis of the corresponding azetidinones. These reactions were carried out in a manner similar to that mentioned for the azetidinone (152, Fig. XXVIII); the details of the latter reaction have been included in the Experimental Section of Chapter 3. The azetidinone (99, Fig. XVII) has the following physical properties: mp:124°C; ir: 1755, 1720 cm^{-1} ; ms: 363 (M^+ , 10.9%), 292 (M^+-71 , 5.0%), 234 (M^+-129 , 13.5%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$ 100%), nmr: δ =7.2 (d, 2 H, $J=8.9$ Hz), 6.8 (d, 2 H, $J=8.9$ Hz), 4.9 (s, 3 H), 4.4 (s, 3 H), 3.7 (s, 6 H), 2.1 (s, 3 H), 1.5 (s, 3 H); $[\alpha]_{\text{D}} = (-) 68.4^\circ$ ($c=0.028$)

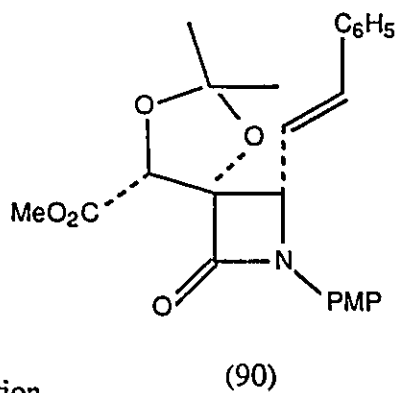
The physical properties of the azetidinone (100, Fig. XVII) are as follows: mp:125-126°C; ir: ms: 349 (M^+ ,), 291 (M^+-58 ,), 200 (M^+-149 ,); nmr: δ = 9.7 (d, 1 H, $J=4.4$ Hz), 7.2 (dd, 2 H, $J=2.0$ Hz, $J=6.3$ Hz), 6.8 (dd, 2 H, $J=2.2$, $J=6.3$ Hz), 5.0 (s, 1 H), 4.5 (d, 1 H, $J=4.4$ Hz), 3.76 (s, 3 H), 3.71 (s, 3 H), 1.62 (s, 3 H), 1.41 (s, 3 H); $[\alpha]_{\text{D}} = (+) 66.3^\circ$ ($c=0.02$).

The azetidinone (107, Fig. XIX) was prepared by activation of the acid (105, Fig. XVIII) with (85) in the manner detailed for the preparation of the azetidinone (90) and purification of the resulting tar by column chromatography using 5 : 1 : hexane : ethyl acetate and the compound has following physical properties: mp: 168°C; ir: 1750 cm^{-1} ; ms: 379 (M^+ , 3.9%), 322 (M^+-57 , 13%), 321 (M^+-58 , 53.4%), 236 (imine $^+-1$, 100%); nmr: δ = 7.4-7.2 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, $J=9.1$ Hz, $J=16.1$ Hz), 4.5 (m, 2 H), 3.7 (s, 3 H), 1.5 (d, 3 H, $J=1.0$ Hz), 1.4 (d, 3 H, $J=6.3$ Hz), 1.3 (d, 3 H, $J=1.0$ Hz); $[\alpha]_{\text{D}} = (+) 64.2^\circ$ ($c=0.019$).

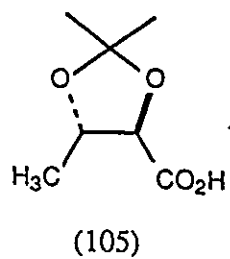
Fig.XIX



Structure determined by X-ray diffraction

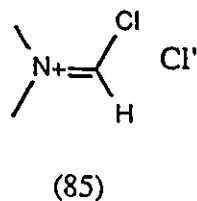


(90)



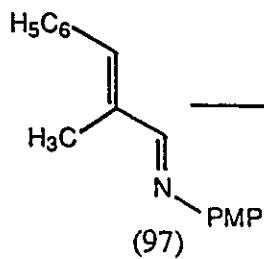
(105)

+



(85)

+



(97)



Unresolved mixture of
azetidinones;
about 2% yield

CHAPTER 3

Having gained some experience with the dihydroxybutyric acids, it was decided to undertake syntheses of 3-amino-3-hydroxyalkyl azetidinones (69, 70, Fig. XXII). Threonine appeared to be an ideal starting point for these enantioselective syntheses. This amino acid belongs to the rare group of acids for which both enantiomers are commercially available at modest prices (119, 120, Fig. XXII). This coupled with the unique placement of the functional groups in the threonine class of molecules, has made them attractive starting materials in various synthetic approaches to thienamycin. The central idea in all these approaches is the conversion of the amino acid into an epoxy amide of defined and predictable stereochemistry by diazotization of the amino group and subsequent internal trapping. Subsequent opening of the epoxide with the internal nucleophile α to the nitrogen of the amide leads to the formation of the azetidinone ring, usually with a high degree of diastereoselectivity. Thus this approach effectively utilizes all the functional groups of threonine including their stereochemical features⁵¹.

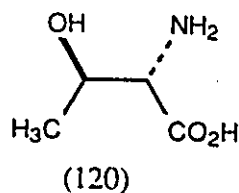
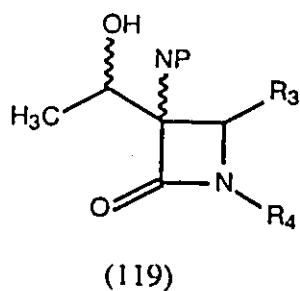
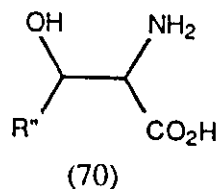
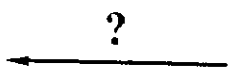
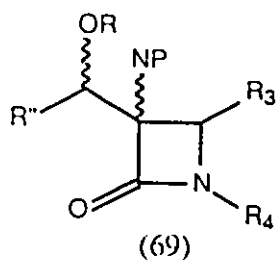
The objective of the studies described here was different. The essential idea, as indicated in the first chapter, was to incorporate intact threonine into the azetidinone moiety. C-1 and C-2 of threonine were to become C-2 and C-3 of the azetidinone respectively. C-3 and C-4 of threonine were to become the 3-hydroxyethyl side chain of the azetidinone. As before the expectation was that the vicinity of the chiral center bearing the

oxygen function α to the site of ketene formation may lead to significant diastereoselectivity in the process of azetidinone formation. Thus 3-amino-3-hydroxyethylazetidinones would become available. With the choice of the proper imine, the azetidinone would have suitable functional groups for subsequent conversion to bicyclic compounds.

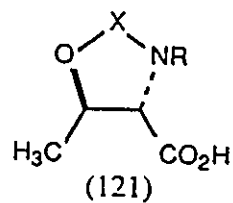
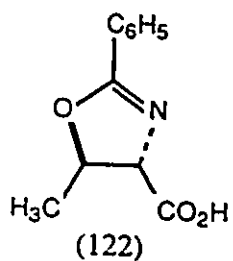
Based upon the studies outlined in Chapter 2, it seemed very appropriate that the amino and the hydroxy group be "tied up" to provide a cyclic derivative. As before, this would minimize the chances for β -elimination (121, Fig. XXII). However in this case it was necessary that the amino group be protected further so as to render it "non-nucleophilic". The latter is necessary so as to overcome any complications due to reaction between the amino group and the activated acid (or the ketene derived from it).

These requirements when considered together are not as stringent as may appear on the first sight. As a matter of fact conversion of the amino alcohol moiety to the corresponding oxazoline would seem to meet all these requirements (122, Fig. XXII). In the oxazoline moiety the amino group has been converted to a cyclic amide and thus is not very nucleophilic but it is known that the α -acetimido acid compounds are not suitable for activation for the ketene-imine reaction (the issue has been raised again in Chapter 8). In this case it seems that the activation of the acid is accompanied by participation of the amide oxygen giving for example (125, Fig. XXIII). The resulting cyclic moiety can be easily deprotonated, but does not seem to form the corresponding ketene easily. However in the case of the cyclic amide such as (122,

Fig. XXII



R_3 = cinnamyl, methyl cinnamyl
 R_4 = p-methoxyphenyl (= PMP)
 P = suitable protecting group, maybe involving the hydroxy group.



$X = CH_2, C(R)_2, CO$

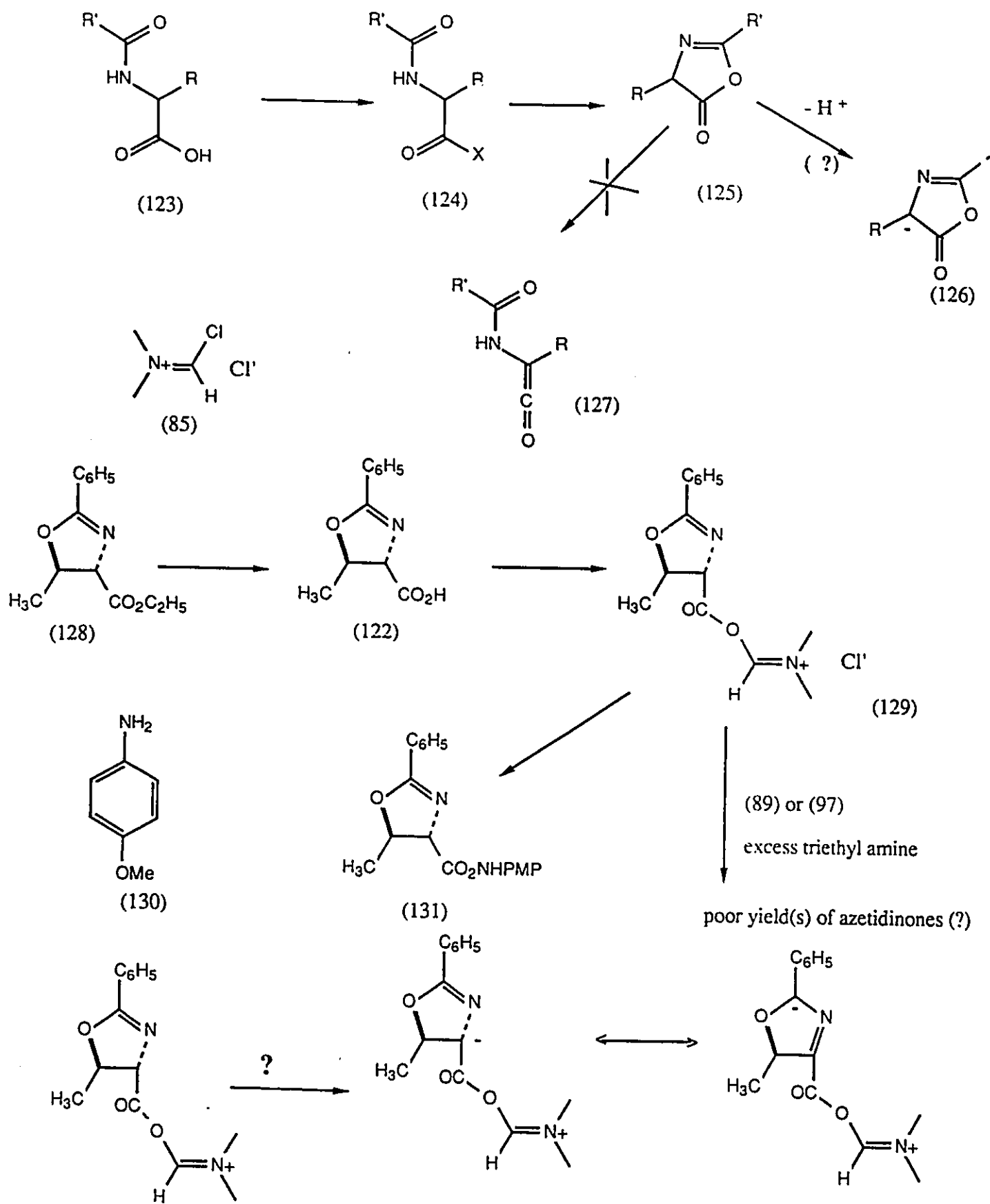
R = suitable substituent.

Fig. XXIII) such as an interaction between the "amide" oxygen and the activated carboxyl group seems stereochemically impossible. Thus in this particular case it might be possible to achieve the desired result without the interference from either the amino or the hydroxyl group. What made this simple choice somewhat more compelling was the fact that the compounds such as (122, Fig. XXII) are well known⁵².

Instead of following Elliot's original procedure it was found that the acid (122, Fig. XXIII) obtained from the ethyl ester could be extracted into THF. This acid seems to have a very poor solubility in majority of other common organic solvents. However when the acid was added to a suspension of N,N-dimethylchloromethyleniminium chloride (85, Fig. XXIII) in methylene chloride an immediate reaction seemed to take place, as indicated by formation of a clear solution. Subsequent addition of triethylamine and p-anisidine led to formation of the amide (131 Fig. XXIII), also referred to as "simple amide" in about 80% isolated yield. This established that despite the poor solubility of both the acid and the salt (85) a reaction between them did take place to provide an activated acid derivative (129, Fig. XXIII)⁵³.

The next step was the reaction of (129, Fig. XXIII) with the typical imines in the presence of at least two equivalents of triethylamine. For reasons that are not clear the yields of the azetidione(s) obtained from several such experiments conducted with various imines under a variety of conditions were never more than 1-2% ! Worse still usually a tedious purification was required and diastereomer ratios varied from one experiment to another

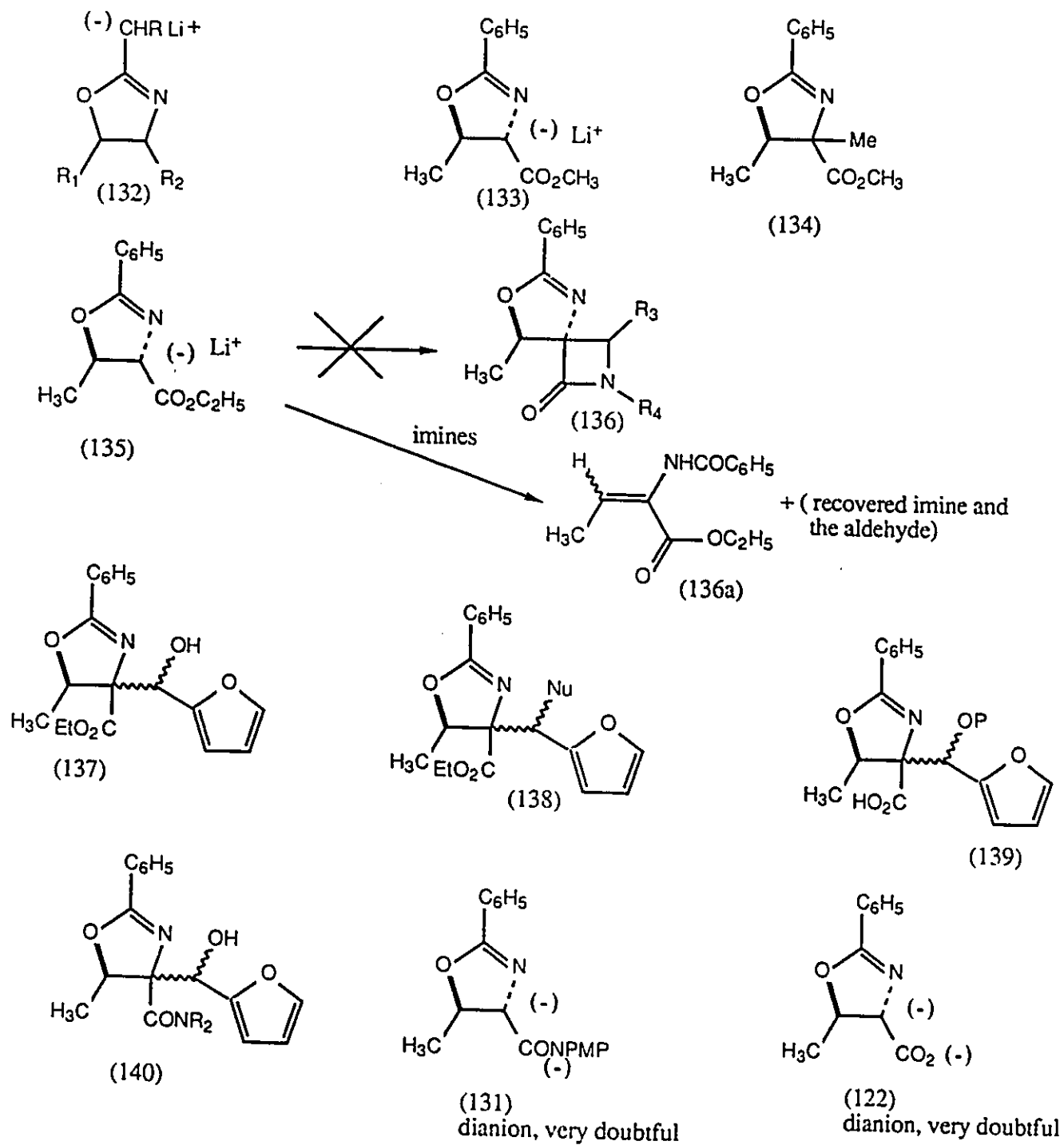
Fig. XXIII



Reactions involving the putative acid chloride were no better in this respect. A probable explanation is that the process of ketene formation was scuttled by easy deprotonation of the activated acid and the subsequent stabilization of the anion by the oxazoline moiety. Perhaps the presence of the phenyl group made this situation worse. Since experiments were not carried out with other oxazolines it is difficult to support this point.

Usually encountered oxazoline anions are of the type (132, Fig. XXIV), made famous by Meyers.⁵⁴ Oxazoline anions were used by Seebach and Aebi in their syntheses of α -alkylated threonines (133 and 134 Fig. XXIV). The latter alkylation reaction proceeds with a high degree of diastereoselectivity⁵⁵. The reaction of (133, Fig. XXIV) with aldehydes furnishes only two compounds, a consequence of high degree of diastereoselectivity in the process of bond formation adjacent to the oxazoline moiety. Thus it was tempting to react the oxazoline anion with an imine, with a view to obtaining the azetidiones such as (136, Fig. XXIV) directly⁴³, [vii]. Exposure of the anion (135, Fig. XXIV) to various imines was accompanied by a marked change in color, from red to blue. Subsequent work-up provided the starting imine, the aldehyde corresponding to the imine and the enamide (136a, Fig. XXIV). The last compound is a consequence of the decomposition of the anion (135, Fig. XXIV). Based upon the quantities of the various products, it would seem that the anion (135) is unreactive towards these imines at low temperatures. Raising the temperature did not help since the anion underwent retrocyclization to provide (136a, Fig. XXIV) at temperatures higher than -30°C .

Fig. XXIV



The anion could be reacted with furaldehyde to furnish an unresolved mixture of hydroxy compounds (137, Fig. XXIV). Subsequent attempts to convert the hydroxy group into a suitable leaving group were erratic and gave variable but generally low yields of the desired products e.g. tosylates or mesylates. Attempted nucleophilic displacement by an external nitrogen nucleophiles on the highly hindered carbon atom were uniformly unsuccessful. In an alternative approach, attempts were made to hydrolyse the ester moiety and to convert the resulting acid into a suitable amide (140, Fig. XXIV). This approach bogged down due to failure of the hydrolysis step. The idea of converting the ester into the amide directly was not much better (137-140, Fig. XXIV)⁵⁶.

A possible reason for failure of these approaches is the highly hindered nature of the carboxyl group and the secondary hydroxyl group in (137). With a view to incorporating the nitrogen atom earlier in the reaction scheme, the amide was (131, Fig. XXIV) prepared. Exposure of this amide to two equivalents of LDA at -78°C in THF led to a deep blue solution. The color faded on addition of furaldehyde. Work-up gave a mixture which contained the aldehyde, and unidentifiable compounds. None of the desired material could be isolated. The attempted formation of a dianion (122, Fig. XXIV) though less colorful than in the above amide case, was equally unrewarding.

At this stage it appeared that it might be better to try an internal carbamate (or cyclic carbamate) for the purpose of protecting the amino and the hydroxyl group. It is known that unlike their amide counterparts, carbamate derivatives of a-

aminoacids are suitable for ketene-imine cycloaddition reactions. It seems that with the use of carbamates interaction between the activated carboxyl function and the carbonyl group of the protecting group. is significantly minimized. This minimized interaction is responsible for wide spread use of carbamate type protecting groups in peptide syntheses⁵⁷.

The process of carbamate formation turned out to be somewhat difficult. The ethyl carbamate did not appear to cyclize to (142, Fig. XXV) under the influence of the base⁵⁸. Use of pyridine-phosgene led to the desired carbamate (141-142 Fig. XXV)⁵⁹. However, the subsequent hydrolysis of the ester portion of this carbamate did not provide the desired acid reliably. Disappointingly the acid proved to a poor partner for the cycloaddition reaction, furnishing largely the unreacted imine and the aldehyde corresponding to the imine when activated with (85).

Having ventured unsuccessfully in the area of cyclic carbamate and amides, it was decided that an effort should be made to obtain amins such as (144, Fig. XXV). Here again the issue of the nucleophilicity of the amino group needed to be addressed. An additional problem is the formation of diastereomers⁶⁰. It was reasonable to expect that the use of compounds such as (146, Fig. XXV) will effectively address both these problems.

Conversion of ethyl L-threoninate to the corresponding benzylcarbamate was straightforward (145, Fig. XXV) but the product was contaminated with variable amounts of benzyl alcohol. The reaction of this impure carbamate with methoxypropene, using phosphorus oxychloride as the catalyst was characterized by it's

highly exothermic nature the range of colors observed, and the mixture of compounds it produced, including starting material⁶¹. Adoption of the procedure similar to that used for conversion of dimethyltartrate to its acetonide appeared better⁴⁷. Even in this case there was formation of more than one product; but consumption of the starting material was total. The spectrum of the crude product indicated the desired material accompanied by variable quantities of dimethoxypropane, the reaction solvent benzene and ethyl acetate (that was used for extraction purpose). Attempted purification of this red oil by vacuum distillation (1-2 mm./ Hg) was unsuccessful. Thus it was decided that it should be directly hydrolysed to the corresponding acid (145-147, Fig. XXV). Unfortunately, the purity and the color of this acid were no better than that of the starting ester. Here again the purification by distillation was futile forcing us to use the impure acid in the subsequent step.

Activation of the acid with the iminium salt seemed successful. However subsequent reaction with triethylamine and imines (89 and 97, separately!) did not seem to lead to any azetidiones. The weight of the chromatographic fractions which might have contained the azetidiones was usually insignificant (< 1%).

At least initially the formation of the acid chloride from this acid seemed to be complicated, as characterized by observations similar to those of the acid (84, Fig. XIV). Subsequent reaction with the imine (89, Fig. XXVI) did not lead to any detectable amounts of the azetidione. Here again, as in the case of the iminium salt, the weight of the fractions which might have contained the azetidione was insignificant. However, the situation with the imine (97,

Fig. XXV

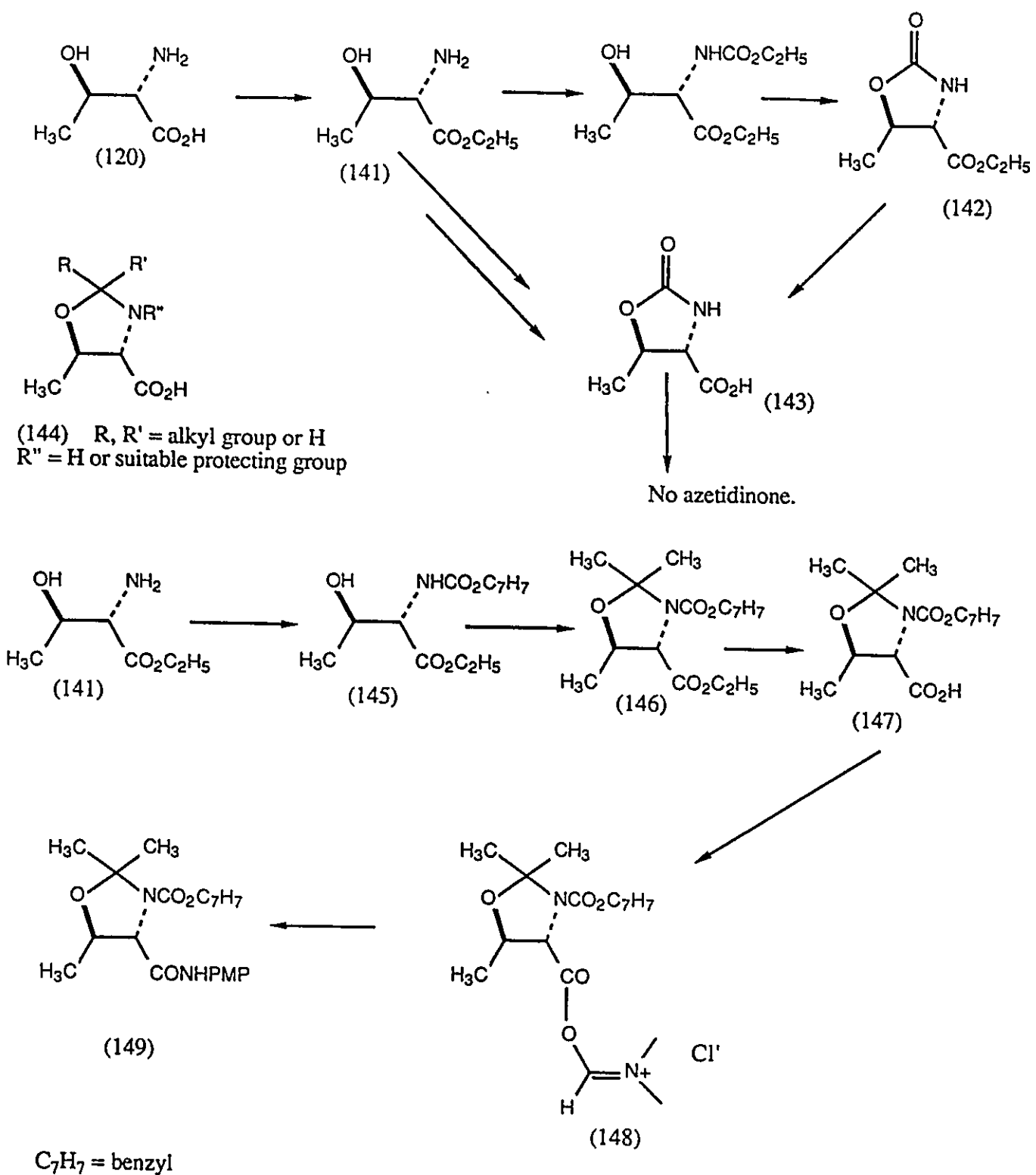
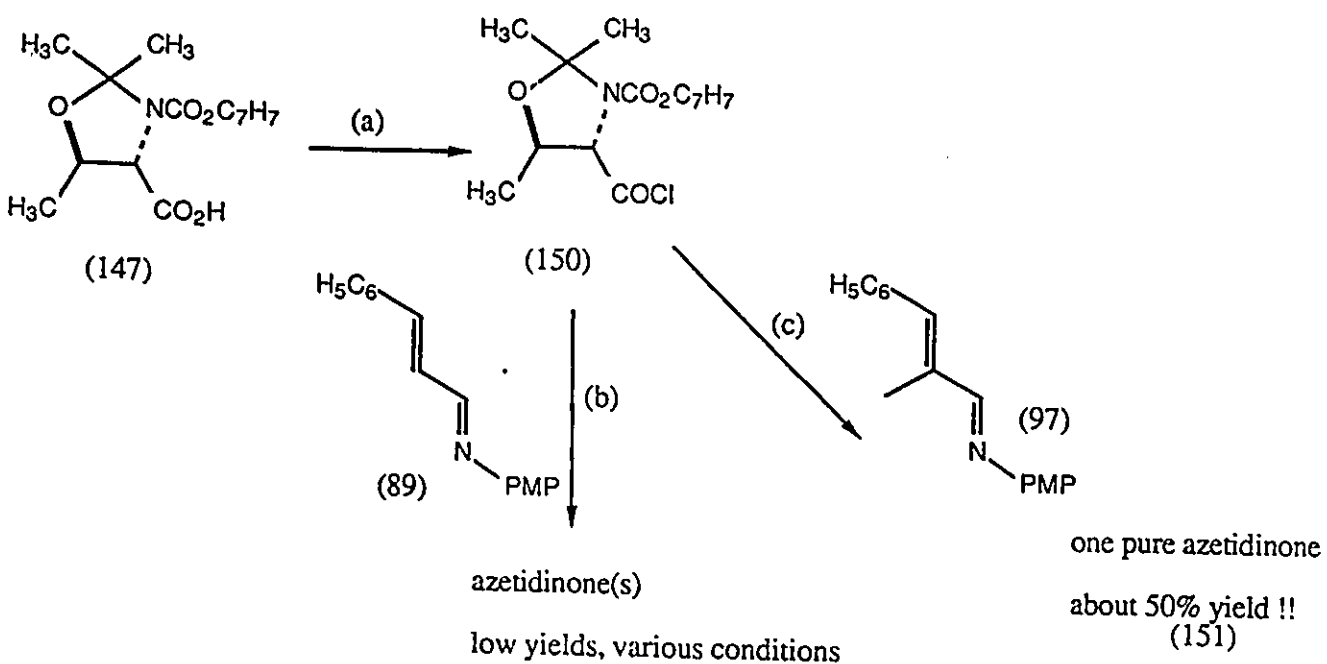
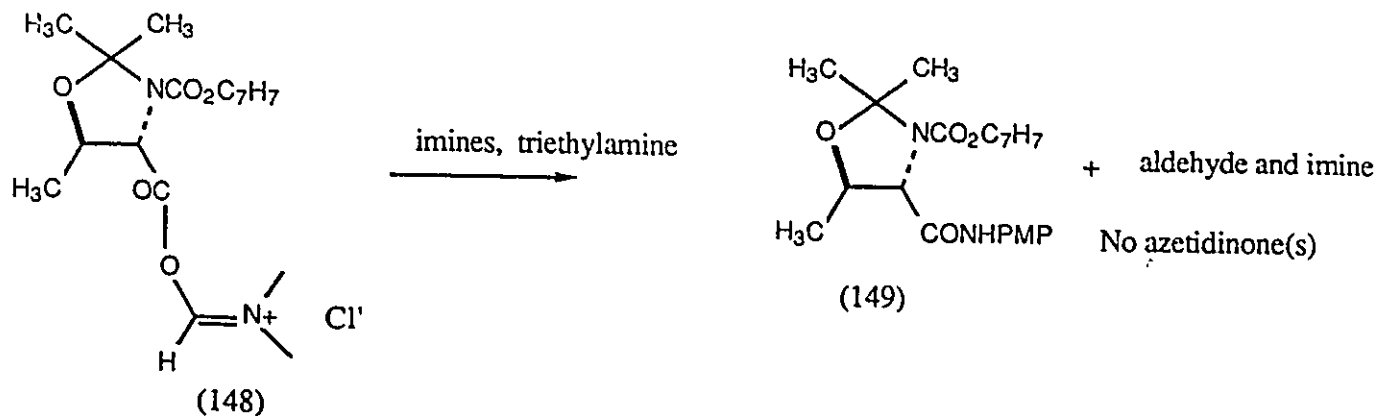


Fig.XXVI) was delightfully different. In this case it was possible to obtain about 50% yield of a chromatographically homogenous compound by simple ether wash of the crude reaction mixture. The mass spectrum of this sharply melting solid indicated a molecular weight of 526 as required for the product of a 2+2 cycloaddition. However, the NMR spectrum of this compound was not very informative, being characterized by multitude of peaks, some of which were very broad. Raising the temperature was not helpful in terms of reducing the number of peaks. Since the usual spectroscopic techniques failed to provide unambiguous proof, it was necessary to turn to single crystal X-ray diffraction analysis. Suitable crystals were easily obtained, they appeared as the solvent evaporated from the fractions collected during column chromatography necessary for removal of colored impurities and the trace amounts (usually < 5%) of simple amide (149, Fig.XXV). This crystalline material was indeed an azetidinone (151).

The structure of the azetidinone (151, Fig.XXVII) has various interesting features. First and the foremost, the relative stereochemistry of the protected amino group at C-3 and the methylcinnamyl group at C-4 is cis. Thus in one cycloaddition reaction, a product with all the correct relative stereochemical features of thienamycin and penicillin class of molecules about the β -lactam ring has been produced. However, the absolute stereochemistry of the entire molecule is opposite to that of both the thienamycin and the penicillin class of molecules. This contrasts sharply the prediction made on the basis of the results in the tartaric and 2,3-dihydroxybutyric acid series. In going from the

Fig. XXVI



(a) cat DMF, 2.2 eq oxalyl chloride, refluxing methylene chloride 1hr. removal of solvent

(b) 0.9 eq. imine (89), triethylamine, various conditions

(c) 0.9 eq. imine (97), triethylamine, 0 \rightarrow R.T., 18 h.

C₇H₇ = benzyl

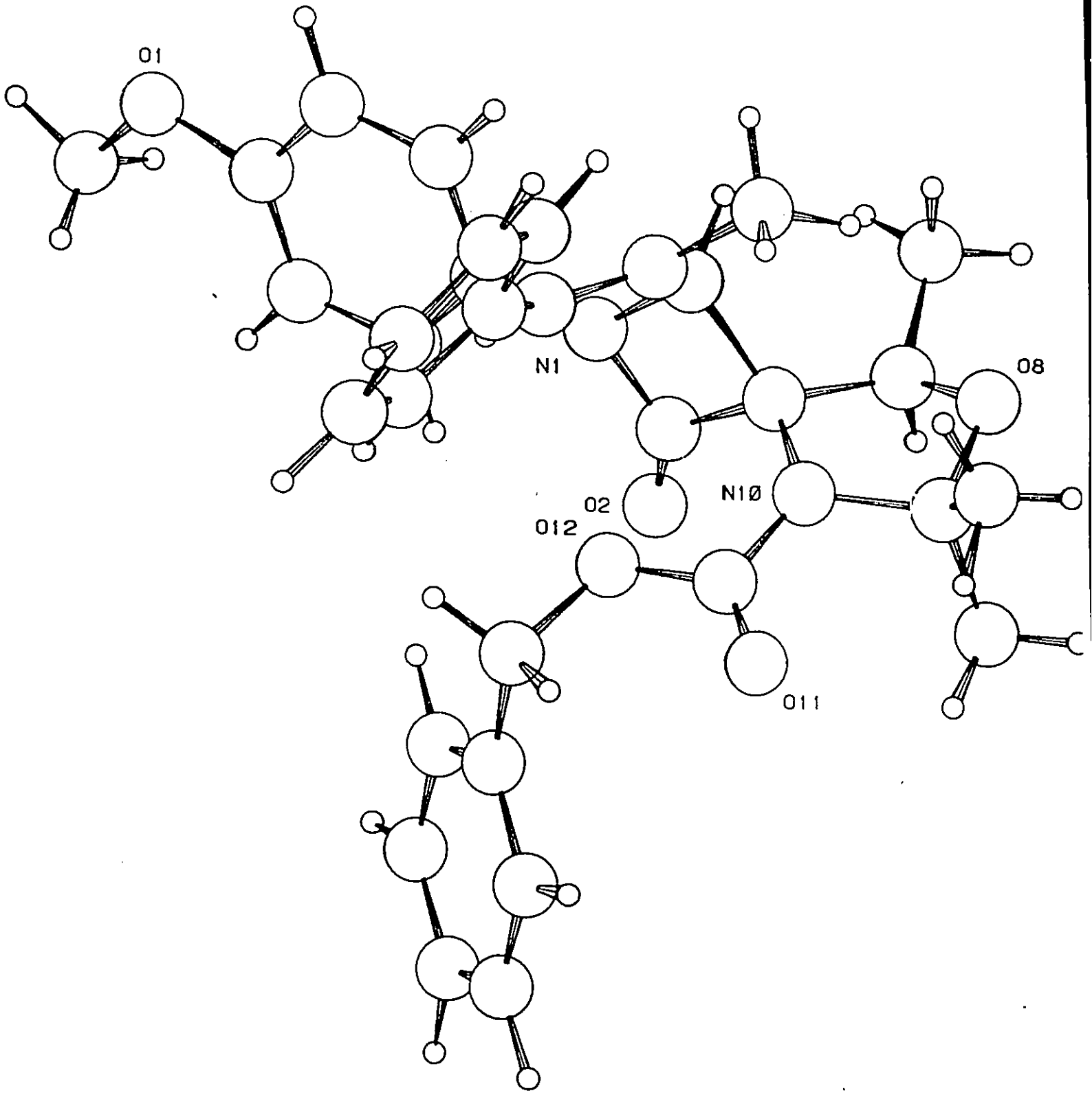
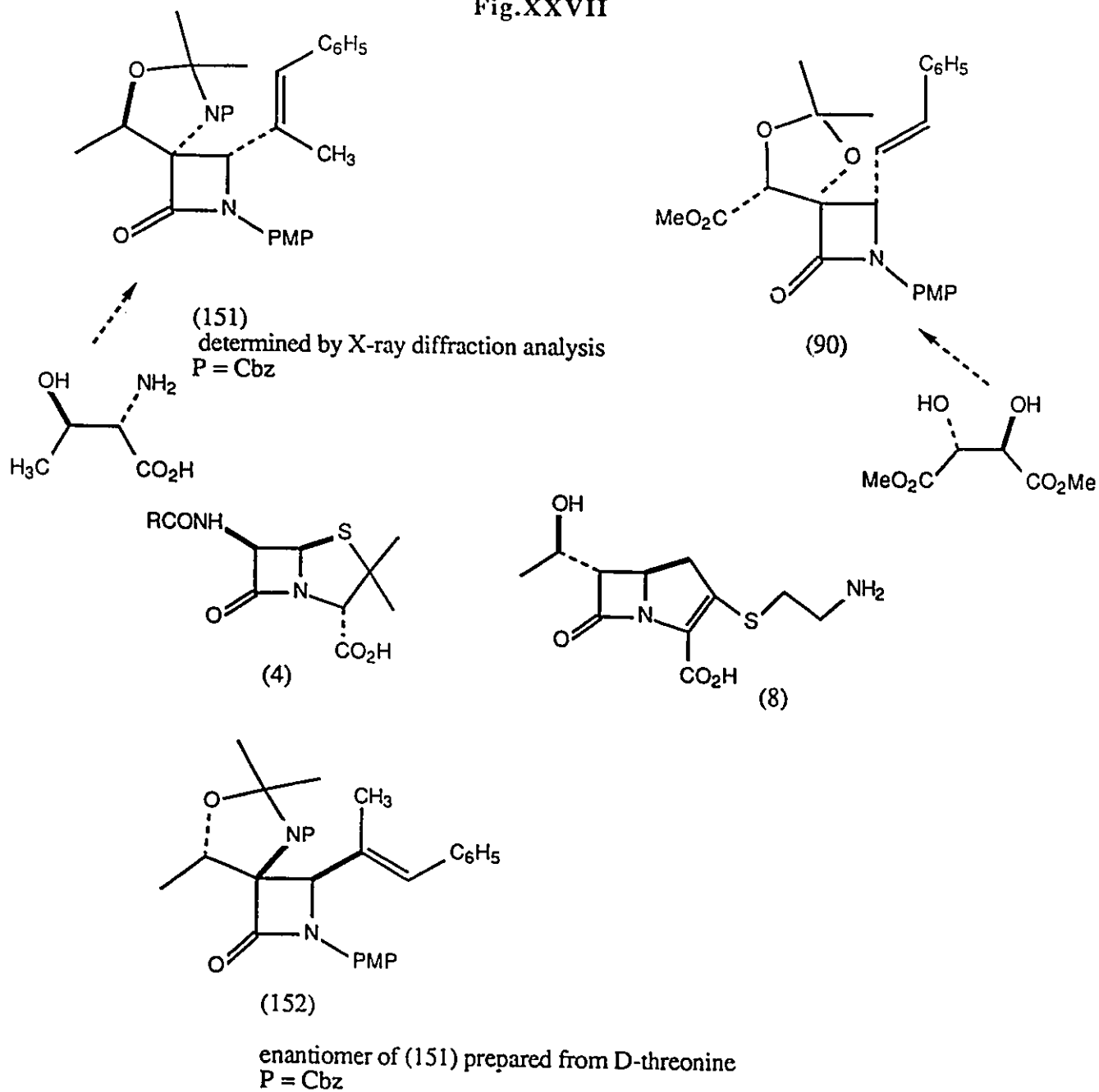


Fig. XXVII



dihydroxy acids to the 2-amino-3-hydroxy acid, the sense of induction of chirality has reversed. Since it will be just about impossible to invert the stereochemistry of C-3 and C-4, it seems better to use D-threonine to synthesize the enantiomer of the compound (152, Fig. XXVII) and then to invert the stereochemistry of the hydroxyethyl group. Indeed such a reaction has been carried out to produce the requisite enantiomer in comparable yields.

Another consequence of this inverted sense of induction of chirality is the production of a compound in which the relative stereochemistry of the "left hand half" is threo. This is same as the relative stereochemistry in the starting threonine derivative. It should be recalled that in the tartaric acid series the carbon-carbon bond formation involves "inversion" at the ketene-formation center while in the case of threonine it involves "retention".

As before, it is impossible to propose a general model for the mode of induction of chirality. However it is obvious that the features that were proposed for the induction of chirality in the case of dihydroxy acid derivatives are being overridden in the cyclic animal. A possible explanation (provided in the the figure XXVIII) involves the methyl group of the hydroxyethyl group, which controls the accessibility of attack on faces of the ketene.

The imine attacks the less hindered face of the ketene (the face opposite to the methyl group), followed by rotation around the acyl-nitrogen bond. A subsequent disrotatory inward rotation precedes the C-C bond formation process. Such a movement is preferred since it serves to minimize the steric interaction between the carbobenzyloxy function and the methyl group of the imine:

these groups move away from each other in the process. This rotation takes place at the expense of the methyl group of the hydroxyethyl moiety and the hydrogen substituent of the imine, being pushed together. The products arising from the attack of the imine on the more hindered face of the ketene have not been isolated from this reaction. In that particular case it seems that either the outward or the inward disrotatory movement will involve serious steric interactions between the methyl group of the hydroxyethyl moiety and the methyl group of the imine (Fig. XXVIII).

The initial plan involved the removal of the acetonide residue from the compound (152, Fig. XXVII) ; an objective that has not yet been realized. Mildly acidic conditions seem to leave the molecule untouched whereas strongly acidic conditions destroy it. Removal of the carbobenzyloxy group is likely to facilitate the removal of the acetonide moiety. Experiments along these lines have not yet been carried out. However, an approach involving the participation of the functional group at C-4 has been partially successful for the removal of the benzyloxy group.

Ozonolysis of the azetidinone (152, Fig. XXVIII) produced the acetyl compound (153, Fig. XXVIII) in about 70% yield after purification. Subsequent reduction with sodium borohydride was sluggish and non-stereoselective and provided a separable 10:7 mixture of secondary alcohols (154 and 155 Fig. XXVIII), respectively. Both the alcohols could be individually or collectively oxidised back to the starting ketone, thereby establishing that no epimerisation took place during the oxidation-reduction cycle. It is

difficult to draw any conclusions regarding the stereochemistry of the newly created chiral centers since even the high field N.M.R. spectra are complicated by hindered rotation phenomena. The stereochemistry shown for the newly created chiral center is arbitrary.

The major less polar alcohol was reacted with tosylimidazole and sodium hydride in DMF⁷⁶. The result was a of cyclic carbamate (157, Fig. XXVIII) and a small amount of the desired tosylate (not shown). Interestingly enough exposure of this tosylate to DBU in DMF converted it into a different cyclic carbamate (158, Fig. XXVIII). Reaction of the more polar alcohol(155, Fig.XXVIII) with NaH and tosylimidazole in DMF was very similar and produced the cyclic carbamate (158, Fig. XXVIII) as the major product.

The process of cyclic carbamate formation might have involved the direct attack of the alkoxide at the carbonyl group of the benzyl carbamate. An alternative process of formation of the cyclic carbamate involves initial formation of the tosylate, followed by nucleophilic attack of the benzyl carbamate moiety on the carbon atom bearing the tosylate group.

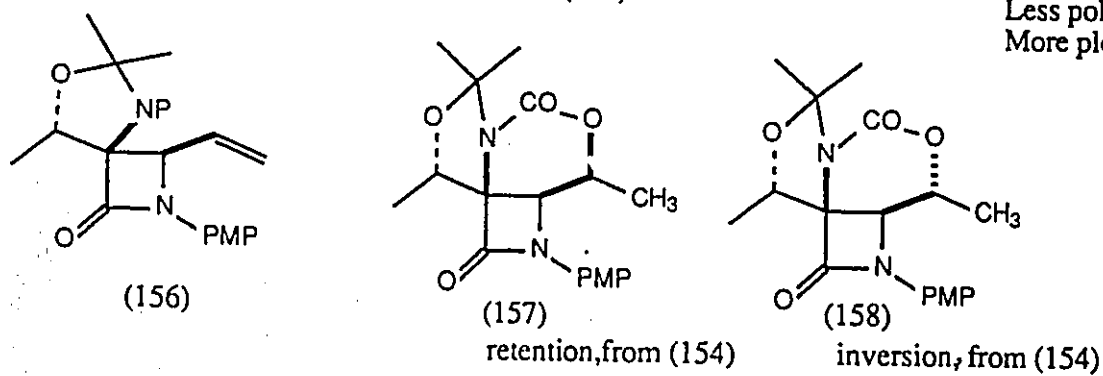
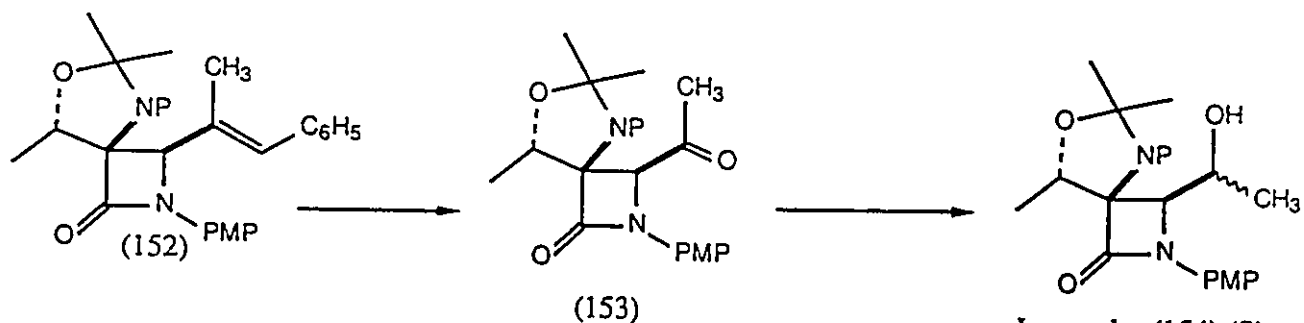
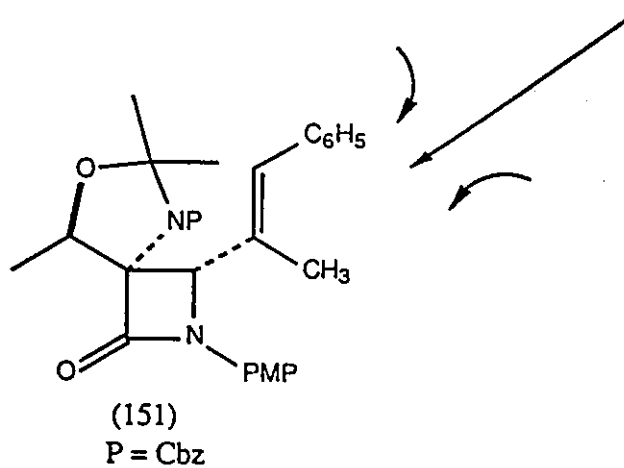
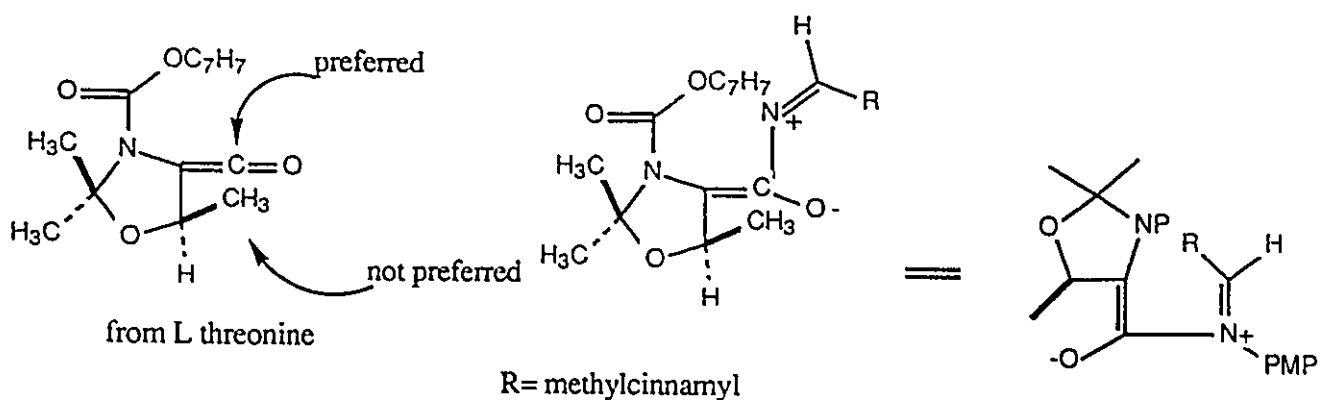
These carbamates are stable towards strong non-nucleophilic bases such as DBU and DBN and do not show any signs of formation of the vinyl azetidinone (156, Fig.XXVIII). In another attempt towards elimination, the less polar hydroxy compound was subjected to successive treatment with sodium hydride, carbon disulfide and methyl iodide, in THF⁶². The only identifiable compounds obtained upon chromatographic separation of the crude product was the cyclic carbamate (157, Fig. XXVIII) and a foul

smelling oil having the NMR spectrum consistent with that of benzylxanthate⁶². This serves to illustrate that it does not require a very polar solvent to affect the cyclization by attack on the carbonyl group of the benzyl carbamate moiety. So far it has not yet been possible to remove the acetonide moiety from these cyclic carbamates.

It is interesting to note that the peaks in the NMR spectra for the cyclic carbamates are sharp, in contrast to the situation encountered for all other compounds earlier in this series. Thus it seems that the multiplication and broadness of the peaks was caused by restricted rotation in the benzyl carbamate residue. This manifestation of the restricted rotation is rather strong in this case, since in the case of the corresponding 'open-chain' benzyl carbamates this problem is not so pronounced and sharper peaks are obtained (Chapter 5).

In summary it has been possible to synthesize an azetidinone which incorporates features of both thienamycin and the classical β -lactams directly from D or L-threonine. Currently the process of converting this compound into bicyclic azetidinones is being hampered by our failure to selectively hydrolyse the acetonide group. It seems very likely that a successful process will involve a reductive cleavage of the Cbz group which may be accompanied by the reduction of the methylcinnamyl residue. Further transformations of azetidinones with a reduced cinnamyl substituent at C-4 will depend upon re-introduction of the functionality in the substituent at C-4. In the context of some unrelated projects, some success has been achieved in this regard by Mr. S.R. Shakya. On the

Fig. XXVIII



other hand one can be fairly confident about the ability to invert the stereochemistry of the C-3 hydroxyethyl group. It is reasonable to expect that once the removal of the acetonide group has been carried out it should be possible to invert the stereochemistry of the C-3 hydroxyethyl group, with the aid of the neighbouring carbamate group. Similar inversions have been carried out for some other compounds in which the C-3 amino group is hindered by the presence of a cis substituent at C-4 (Chapter 5).

It can be concluded that syntheses of enantiomerically pure azetidinones from threonines has been successful to a large extent. The process of azetidinone formation is easy enough to carry out on modest scale since as much as 14-15 grams of the azetidinone (151 and 152) have been made in one attempt. Subsequent developments in this area may require large amounts of these azetidinones. The good news is that such quantities are easily available.

References and Notes.

- (51) For a recent example see : Chackalamannil, S.; Fett, N.; Kirkup, M.; Afonso, A. and Ganguly, A.K. *J. Org. Chem.* **1988**, *53*, 450.
- (52) Elliot, D.F. *J.Chem. Soc. (London)*, [i] **1948**, 310, [ii] **1949**, 589, [iii] **1950**, 62.
- (53) These observations are very similar to the case of phthaloyl glycine. That acid is also not very soluble in methylene chloride but the reaction between the acid and the salt is almost instantaneous. The yields of azetidinones are comparable to the cases where the acid is soluble in methylene chloride.

- (54) For a review see: Meyers, A.I. and Lutomski, K.A. in "Asymmetric Synthesis" Vol. 3, part B. Ed. Morrison, J.D. Academic Press. 1983.
- (55) Seebach, D. and Aebi, J.A. *Tet. Lett.* 1983, 24, 3311. These authors obtained only two compounds from reaction of the oxazoline anion with benzaldehyde, instead of four. Though in this particular communication these authors did not establish that these compounds differed only in the stereochemistry of the hydroxy-bearing carbon atom the probability is strongly implied.
- (56) For a relatively recent example of conversion of esters directly into amides see: Barrett, A.G.M. and Dhanak, D.B. *Tet. Lett.* 1987, 28, 3327. These chemists have used such an approach for conversion of lactones to the corresponding open chain protected hydroxy alcohols. Also included in this communication are references to the early examples of such reactions.
- (57) See for example, [i]. "Protective Groups in Organic Synthesis". Greene, T. John-Wiley and Sons. 1980. [ii] "Organic Synthesis: Concepts, Methods and Starting Materials" Fuhrhop, J. and Penzlin, G. Verlag-Chemie. 1983.
- (58) The actual conditions employed for the attempted ring closure were very close to those used by Evans for similar reactions (ref. 43[iii]). Under those conditions the starting material seemed to survive unchanged.
- (59) King and coworkers have studied the reaction between pyridine and phosgene. King, Jr, J.A.; Donahue, P.E. and Smith, J.E. *J. Org. Chem.* 1988, 53, 6145

(60) Badar and colleagues have carried out reaction between aromatic aldehydes and threonine esters. Though not categorically stated, it is very likely that a mixture of diastereoisomers were formed during this reaction. Since the second step in their sequence involved dehydrohalogenation, diastereoisomer formation was of not much concern to these chemists. Badar, M.Z.A. et. al. *Bull. Chem. Soc. Jpn.* 1981, 54., 1844.

(61) For one such example of use of phosphoryl chloride for the purpose of simultaneous protection of a carbamate and a hydroxy group see, Kleinman, E.F.; Fray, R.L. and Kaye, R.L. *J. Org. Chem.* 1986, 51, 4828.

(62) The actual experimental conditions employed were very close to those of Iacono, S. and Rasmussen, J.R. *Org. Syn.* Vol. 64, 57 Ed. Kende. A.S.

(76) Fraser-Reid, B. and Hicks, D.R. *Synthesis* 1974, 203. The reason for this unusual numbering of references stems from the fact that this very useful tosylation procedure was used first in the context of 3-methoxy-3-hydroxyethylazetidiones, the subject of Chapter 4.

Experimental Section

General

Threonine used in these studies was purchased from Sigma Chemical Company and was used as received. Conversion of threonine to its ethyl ester hydrochloride salt was achieved according to the method described by Elliot ⁵². To obtain free base from ethyl ester hydrochloride of threonine the method of Weinstein and colleagues was used (Weinstein, B.; Crews, O.; Leaffer, M.A.; Baker, B.R. and Goodman, L. *J. Org. Chem.* 1962, 27, 1389). The free base appears to have only limited stability and thus was generated just prior to use. Benzyl chloroformate (95%) was purchased from Aldrich Chemical Company and was used without further purification. General comments mentioned in the beginning of the Experimental Section of Chapter 2 also apply here.

Preparation of Cbz derivative of ethyl threoninate

To a 500 mL two neck round bottomed flask containing a stirring bar and fitted with a pressure equalizing dropping funnel was added 8.25 g (56.1 mmol) of D-threonine ethyl ester. Addition of 125 mL of dry THF and 11.7 mL (85 mmol) of dry triethylamine led to dissolution of most of the solid. The flask was cooled to 0°C (ice bath) under nitrogen. The funnel was charged with 9.2 mL (61 mmol) of benzyl chloroformate and 25 mL of dry THF. Solution from the dropping funnel was added dropwise as the solution in the flask was vigorously stirred. This was accompanied by extensive fuming and formation of thick white precipitate. The addition was complete in about 30 min and the reaction mixture was stirred for an additional 30 min at 0°C. Workup consisted of addition of 100 mL of

10% HCl to the reaction mixture and extraction with 75 mL of ethyl acetate. The aqueous layer was saturated with sodium chloride and extracted with an additional 2X75 mL ethyl acetate. The combined organic layer was washed with 50 mL of 5% NaHCO₃ and then with 50 mL of saturated solution of NaCl. The organic layer was dried with MgSO₄ and after removal of the drying agent by filtration the solvent was evaporated to furnish 16.6 g of a clear mobile oil which had a smell of benzyl chloroformate. This weight amounted to 104% yield. This compound has following spectroscopic properties ir: 3100, 1750, 1720 cm⁻¹; ms: 237 (M⁺-44, 47%), 220 (M⁺-61, 16%), 176 (M⁺-105, 100%); nmr: d = 7.3 (m, 5 H), 5.6 (broad d, 1 H), 5.1 (s, 2 H), 4.5 (m, 4 H), 1.2 (m, 6H). In addition the NMR spectrum showed presence of peaks near 5.0 and 2.0 ppm. Since this compound was not pure it's [α]_D was not recorded. It was used as such in the next step.

Synthesis of enantiomer of (146, Fig. XXV)

The oil obtained in the previous step was transferred to a 250 mL round bottomed flask and was dissolved in 150 mL of regular benzene. 30 mL (24.3 mmol) of 2,2-dimethoxypropane and 0.5 g (catalytic quantity) of pTSA were added. A Soxhlet apparatus containing about 5 g of 4A⁰ molecular sieves was attached to the top of the flask and a reflux condenser was attached to the top of the soxhlet apparatus. The contents of the flask were heated under reflux for 18 h, which led to development of deep red color. The reaction mixture was cooled to room temperature and diluted with 100 mL of ethyl acetate. Solid NaHCO₃ (5 g) was added and the heterogeneous mixture was stirred at room temperature for 20 min.

The solution was removed by decantation and the solid residue was washed with an additional 2X25 mL ethyl acetate. Final separation of the solid was done by filtration through Celite. The solvent was removed from the combined organic layer to furnish a red viscous oil. This oil showed the presence of ethyl acetate and dimethoxypropane as determined by NMR (60 MHz). In addition the spectrum showed the presence of several featureless humps and some absorptions in the region of 7-8 ppm. The weight of this chemically impure oil was about 19 g. Attempted purification of this oil by distillation under reduced pressure (1-2 mm/Hg) led to considerable loss of material and the colored distillate had features which were not very different from the starting material. Therefore $[\alpha]_D$ was not recorded and it was decided to use this oil as such in the next step.

Saponification of enantiomer of (146, Fig. XXV)

Crude ethyl ester (19 g) from the previous step was dissolved in 100 mL of 99% ethanol and a solution of 4.9 g (87.5 mmol) of KOH in 40 mL of water was added in one portion. The homogeneous faint red solution was stirred at room temperature for 3 h. Ethanol was evaporated from the reaction mixture and the resulting semi-solid mass was dissolved in 100 mL of 5% NaHCO₃ solution. The solution was extracted with 3X25 mL ethyl acetate and the organic layers were discarded. The aqueous layer was cooled in an ice bath and was saturated with sodium chloride. Nearly 10 g of crushed ice and 150 mL of ethyl acetate were added to the flask. The heterogeneous mass was stirred vigorously as concentrated H₂SO₄ was slowly released near the bottom of the flask to bring the pH near 2. The

organic layer was separated and the aqueous layer was extracted with 3X25 mL of ethyl acetate. The combined organic layer was washed with saturated NaCl solution and was dried with MgSO₄. Removal of the drying agent and the solvent furnished 10 g of a viscous oil. NMR (60 MHz) showed presence of ethyl acetate and peaks similar to the case of the acetonide (146, Fig. XXV). Attempted distillation under reduced pressure led to results similar to the case of the ethyl ester. Thus it was decided to use this acid as such in the next step.

Synthesis of the azetidinone (152, Fig. XXVII)

To a dry 1000 mL round bottomed flask equipped with a stirring bar was added 39 g of crude acid from previous step (from two reactions carried out on twice the scale mentioned above). If pure this would amount to 126 mmol of the acid. A Claisen tube was attached to the flask and the acid was dissolved in 500 mL of dry dichloromethane and 1 mL of dry DMF. A reflux condenser and a pressure equalized dropping funnel were attached to the Claisen tube. The funnel was charged with 24.3 mL (280 mmol) of oxalyl chloride and 100 mL of dry dichloromethane. The flask was cooled to 0°C under nitrogen. The septum cap on the top of the reflux condenser was replaced with a drying tube while maintaining brisk nitrogen flow through the septum cap on the top of the dropping funnel. The contents in the flask were vigorously stirred as the solution from the funnel was added dropwise. This led to vigorous gas evolution. After the addition was complete (about 40 min) the dropping funnel was washed with 50 mL of dichloromethane and the

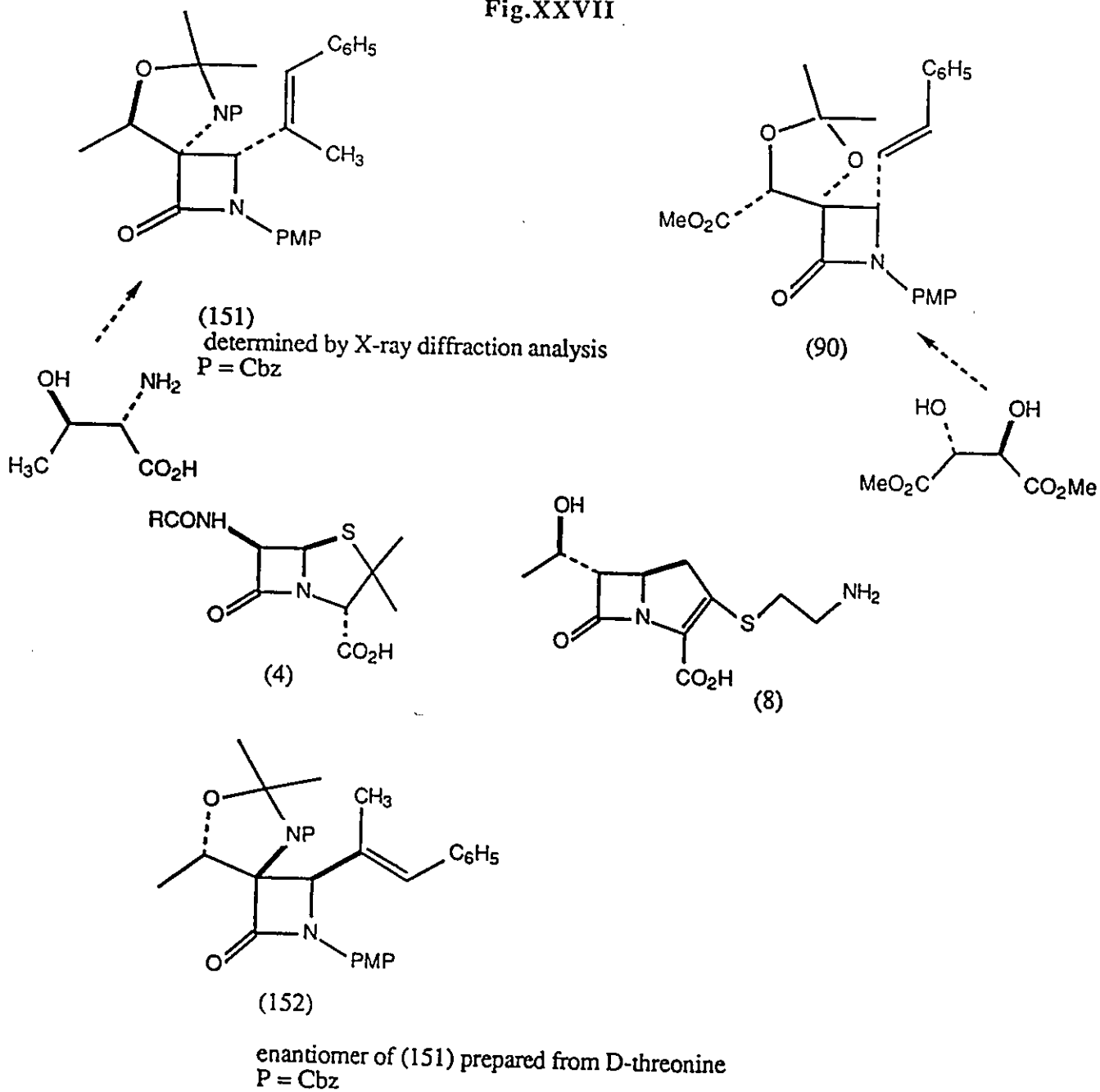
washings were also added to the flask. The Claisen tube was removed and the reflux condenser was attached directly to the flask. The flask was allowed to come to room temperature over a period of about 10 min and then the solution in the flask was heated under reflux for 2h. This led to development of deep red color and formation of some tarry deposits on the sides of the flask. The flask was allowed to cool to room temperature and then the solvent was removed on a rotary evaporator to leave behind a thick red oil. After application of high vacuum(0.1mm/Hg) for 10 min the oil was diluted with 500 mL of dry dichloromethane and was provided with a stirring bar and a pressure equalized dropping funnel. The red solution (with red deposit on the sides of the flask) was cooled to 0°C (ice-bath) under nitrogen. The funnel was charged with a solution of 26.94 g (107 mmol) of the imine (97, Fig. XXVII) and 38.6 mL (277 mmol) of dry triethylamine in 200 mL of dry dichloromethane. The septum cap on the dropping funnel was quickly replaced with a drying tube and the imine solution was added dropwise to the vigorously stirring solution of the acid chloride. After the addition was complete the funnel was washed with 25 mL of dry dichloromethane. The heterogeneous reaction mixture was stirred vigorously and was allowed to come to room temperature over 6 h. After stirring at this temperature for an additional 20 h the reaction was worked up by successive washing with 200 mL of water, 2X200 mL of 10% HCl, 3X200 mL of water and finally with 2X200 mL of 5% NaHCO₃ solution. After each extraction the aqueous layer was extracted with 25 mL of dichloromethane and the new organic layer was added to the main organic layer. To the combined organic layer was added 7 g

of charcoal and 10 g of $MgSO_4$. After vigorous stirring at room temperature the solids were removed by filtration through Celite. The solids were washed with an additional 50 mL of dichloromethane. Removal of the solvent provided a black gum. Addition of 500 mL of warm ether led to deposition of a brown solid (24 g), which was separated by filtration. Removal of ether from the washings led to 28 g of a black viscous oil. TLC (5:1: hexane: ethyl acetate) of this oil showed presence of following compounds [i] imine ($R_f = 0.5$), [ii] unknown compound, weight less than 1% of the imine used ($R_f = 0.25$), [iii] desired compound ($R_f = 0.21$), [iv] simple amide ($R_f = 0.085$). The brown solid showed presence of only the desired azetidinone i.e. [iii] and some base line impurities.

The black oil was dissolved in enough dichloromethane to make 100 mL solution. This solution was applied to a silica column (10' long, 2.2' diameter) and the column was eluted with 4:1 : hexane : ethyl acetate under 10-15 psi nitrogen pressure applied to the top. Several 125 mL fractions were collected and all the fractions which showed the presence of the desired compound (except those which showed the presence of the compound and the simple amide) were pooled together. Removal of the solvent and trituration of the resulting yellow solid with 150 mL of refluxing ether led to 7.7 g of the azetidinone (152, Fig. XXVII) as a white chromatographically homogenous solid.

The brown solid obtained above was dissolved in enough dichloromethane to furnish a 100 mL solution. This was divided in two nearly equal portions and each of these was purified in the manner similar to that used for the black oil. This led to isolation of

Fig. XXVII



a total of 21.5 g of the desired compound. Thus the total yield of the azetidinone (152, Fig. XXVII) was 29.2 g (51%). As mentioned before in the text the NMR spectrum of this azetidinone was not very informative and somewhat dependent upon the exact conditions of recording. Thus it is not being reported here. The assigned structure has been established by X-ray diffraction analysis and thus lack of a suitable NMR spectrum is not a hindrance. This compound has following characteristics mp= 145-145.5°C; ir: 1750, 1720 cm⁻¹; ms: 526 (M⁺, 3.3%), 482 (M⁺-44, 6.9%), 437 (M⁺-89, 4%), 334 (M⁺-192,34.4%), 250 (imine⁺-1, 82.5%), 91 (C₇H₇⁺, 100%);[α]_D = (-) 155.1° (c= 0.016).

The synthesis of the azetidinone (151, Fig. XXVII) was carried out on about 1/ 4th scale as described above starting from L-threonine. The yield was comparable. Spectral properties and mp of this compound was the same as the enantiomer and [α]_D was equal in magnitude but opposite in sign. Crystals suitable for X-ray diffraction analysis were obtained during the purification of the brown solid.

Ozonolysis of (152, Fig, XXVIII)

To a 500 mL dry round bottomed flask was added 15.78 g (30 mmol) of the starting material and enough dry dichloromethane (about 300 mL) to obtain a clear solution. Dry methanol (5 mL) and 1 g of 4A^o molecular sieves were added. A Claisen tube was attached to the flask. One of the openings of the Claisen tube was provided with a drying tube and the other one was capped with a septum cap. The flask was cooled to -78°C (acetone- Dry Ice bath) under nitrogen. Ozonized oxygen was blown through this solution till it acquired a

faint blue color. TLC at this stage showed the absence of starting material. Excess ozone was removed by purging the solution with nitrogen for 5 min and then 5 mL of dimethyl sulfide was added. The solution was allowed to come to room temperature over a period of several hours. The molecular sieves were removed by filtration through Celite and were washed with an additional 50 mL of dichloromethane. The solvent was removed from the combined filtrate to furnish a sticky white solid. Trituration of this solid with 2X75 mL of warm ether followed by filtration led to isolation of the acetyl compound (153, Fig. XXVIII) as chromatographically homogeneous solid. The weight was 10.17 g (22.5 mmol.) which amounts to an isolated yield of 75%. The NMR spectrum of this compound essentially consisted of broad multiplets in the anticipated regions. However it was not very informative and thus is not being reported here. Other physical properties of this compound are as follows mp: 181°C; ir: 1750, 1720 cm^{-1} ; ms: 452 (M^+ , 5%), 268 ($\text{M}^+ - 184$, 2.8%), 217 ($\text{M}^+ - 235$, 6.4%), 91 (C_7H_7^+ , 100%); $[\alpha]_{\text{D}} = (-) 95.3^\circ$ ($c = 0.01$). HRMS calcd for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_6$ 452.1975 observed 452.2005.

Reduction of (153, Fig. XXVIII)

The acetyl compound from the previous step (10 g, 22.1 mmol) was dissolved in 300 mL of 5: 1 : THF: ethanol mixture and the nearly clear solution was cooled in an ice bath. Approximately 2 g of sodium borohydride was added and the reaction mixture was stirred for 3 h at this temperature. TLC at this stage indicated the presence of starting material and therefore another 1g of sodium borohydride was added. After an additional 1 h TLC still indicated the presence of starting material. At this stage enough Amberlite 120(H^+) was

added to bring the pH of the solution to about 2. The solvent was removed by decantation and the resin was washed with an additional 5X50 mL of ethanol. The combined washings were concentrated on rotary evaporator to provide a white semi-solid. This was dissolved in 500 mL of ethyl acetate and the solution was washed successively with 2X100 mL of 5% NaHCO₃ and 2X100 mL of water. The organic layer was dried etc to furnish 10 g of a white solid. This was column chromatographed (2:1: hexane : ethyl acetate) to furnish 5 g of a less polar compound(154, Fig. XXVIII) and 3.5 g of a more polar compound (155, Fig. XXVIII), in addition to 0.2 g of the starting material. Proton NMR of these alcohols consisted of a multitude of broad peaks; the exact position, shape and the number of these peaks varied considerably. Thus the NMR spectra of these compounds are not being reported here. The less polar alcohol has the following physical properties : mp: 117-119°C; ir: 3200, 1755, 1720 cm⁻¹; ms: 454 (M⁺,6.2%), 346 (M⁺-108,17.3%), 318 (M⁺-136,20.7%),149 (C₈H₇NO₂⁺,61%), 91 (C₇H₇⁺, 100%) ; [α]_D= (+) 8.3° (c = 0.016). HRMS calcd for C₂₅H₃₀N₂O₆ 454.2147, observed 454.2106.

The more polar alcohol has these physical properties: mp: 66-67°C; ir: 3200, 1750, 1715 cm⁻¹; ms: 454 (M⁺, 5%), 346 (M⁺-108, 15%), 318 (M⁺-136, 9.3%), 182 (M⁺-272, 59%), 149 (C₈H₇NO₂⁺, 90%), 91 (C₇H₇⁺, 100%); [α]_D = (+) 29.1° (c= 0.02). HRMS calcd for C₂₅H₃₀N₂O₆ 454.2147 observed 454.2107

Synthesis of (157 and 158, Fig. XXVIII)

In a 25 mL dry flask was placed 1 g (2.2 mmol) of the alcohol (154, Fig. XXVIII) and 0.733 g (3.3 mmols.) of tosylimidazole and 10

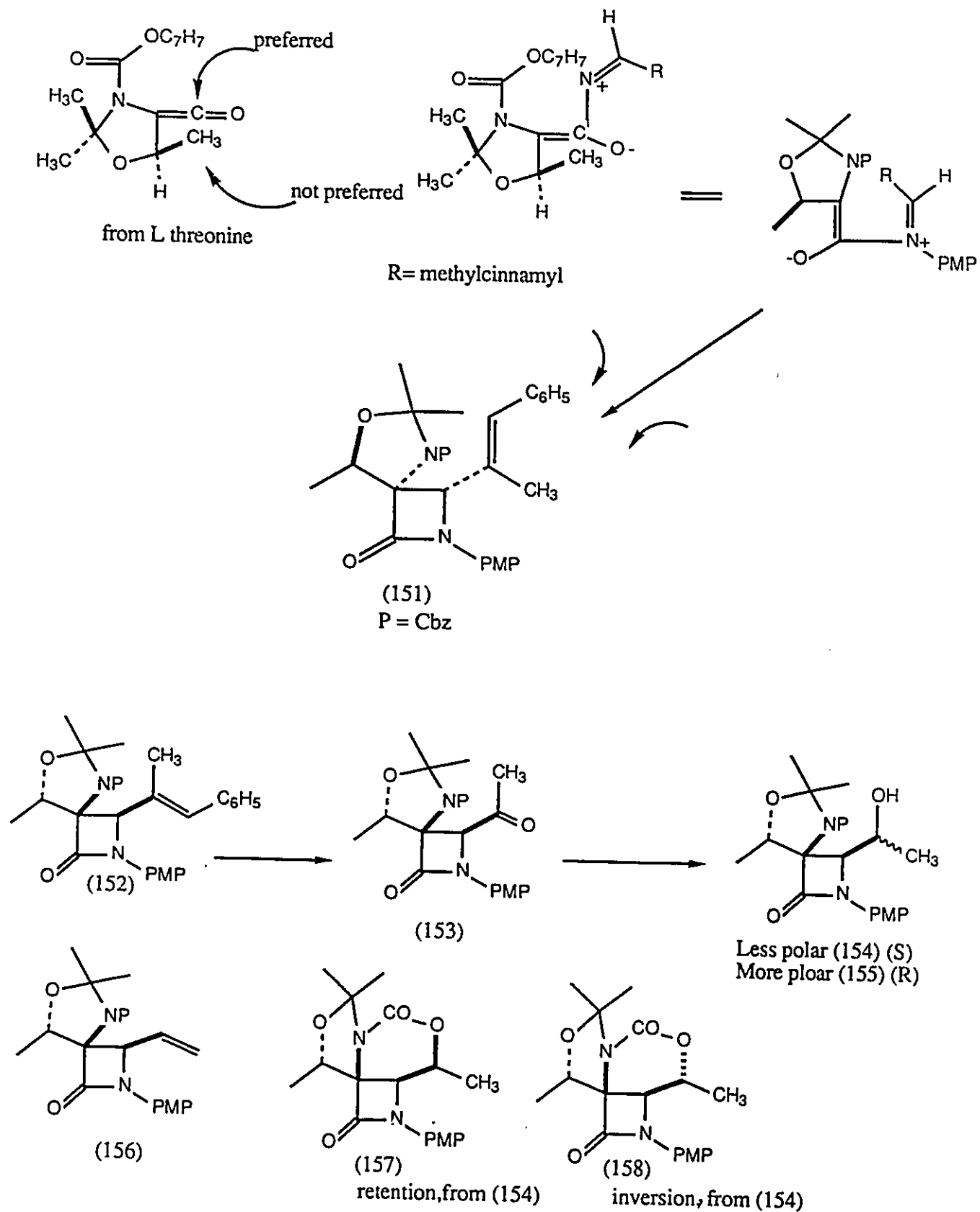
mL of dry DMF to obtain a clear solution. The alcohol solution was added with the help of a cannula to a vigorously stirred suspension of sodium hydride (0.158 g, 50% dispersion in oil, 3.3 mmol) in 20 mL of dry DMF at 0°C. Effervescence ceased within 10 min and the white gelatinous mass was stirred at 5- 7°C (cold room) for an additional 20 h. Work up consisted of cautious addition of 10 mL of 10% HCl. Subsequent extraction of the aqueous layer with 3X50 mL of ether and processing of the organic layer in the usual manner furnished a brownish semi-solid. TLC analysis revealed the absence of the starting material but indicated two less polar compounds. Column chromatography (4:1: hexane : ethyl acetate) furnished 0.6 g of a non polar white foam and 0.4 g of a polar white solid. The NMR spectrum of the foam was not very informative since it consisted of featureless lumps but the mass spectrum suggested that this compound probably was the tosylate of the alcohol (tosylate would require m/e peak at 608, the ci-ms had a peak at 437 which amounts to $M^+ - 171$). When this alleged tosylate was heated in DMF at 120°C in presence of 3-5 equivalents of DBU, it furnished 0.25 g of a compound which had R_f identical with that of the polar compound. This new compound was identified as the cyclic carbamate (158, Fig.XXVIII) on the basis of following properties: mp: 213-214°C; ir: 1750 cm^{-1} ; ms: 336 (M^+ , 16.5%), 318($M^+ - 28$, 11.2%), 259 ($M^+ - 6.7\%$), 197 ($M^+ - 149$, 56%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$, 100%); nmr: δ = 7.2 (m, 2 H), 6.9 (m, 2 H), 4.8 (q, 1 H, $J = 6.9$ Hz), 4.6 (q, 1 H, $J = 6.4$ Hz), 4.2 (s, 1 H), 3.7 (s, 3H), 1.7 (s, 3 H), 1.65 (s, 3 H), 1.4 (dd 6 H, $J = 6.9$ Hz, $J = 6.4$ Hz). This compound has $[\alpha]_D = (-) 210.2^\circ$ ($c = 0.02$). HRMS calc for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5$ 346.1560, observed 346.1525.

The polar white solid was identified as the cyclic carbamate (157, Fig. XXVIII) on the basis of following spectroscopic properties mp: 172-174°C; ir: 1755 cm^{-1} ; ms: 346 (M^+ , 25%), 318 ($\text{M}^+ - 28$, 29.5%), 259 ($\text{M}^+ - 87$, 13.3%), 197 ($\text{M}^+ - 149$, 56%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$, 83%), 43 (100%); nmr: d = 7.3 (dd, 2H, J= 2.2 Hz, J= 9.2 Hz), 6.9 (dd, 2H, J= 2.2 Hz, J= 9.2 Hz), 4.5 (m, 2 H), 4.2 (dq, 1 H, J= 1.5 Hz, J= 6.7 Hz), 3.7 (s, 3 H), 1.6 (s, 6 H), 1.4 (d, 3 H, J= 5.6 Hz), 1.3(d, 3 H, J= 6.7 Hz); $[\alpha]_{\text{D}} = (-) 207.5^\circ$ (c= 0.013). HRMS calc for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5$ 346.1560, observed 346.1518.

As mentioned in the text, the cyclic carbamate (157, Fig. XXVIII) was obtained when an attempt was made to convert the alcohol (154) into its xanthate derivative using NaH.

Attempted tosylation of the more polar alcohol (155, Fig. XXVIII) led to the cyclic carbamate (158, Fig. XXVIII) and another tosylate (not shown). Attempted elimination from that tosylate led to the formation of the carbamate (157, Fig. XXVIII).

Fig. XXVIII

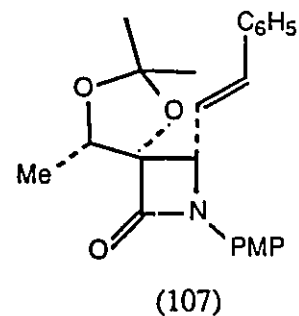
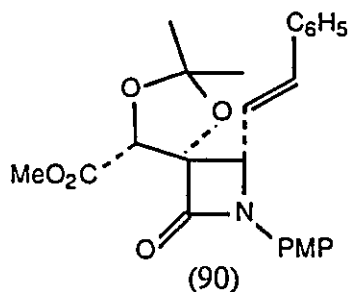
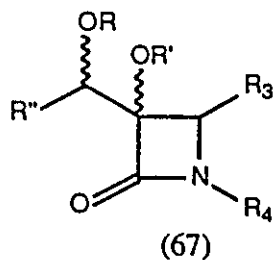


CHAPTER 4

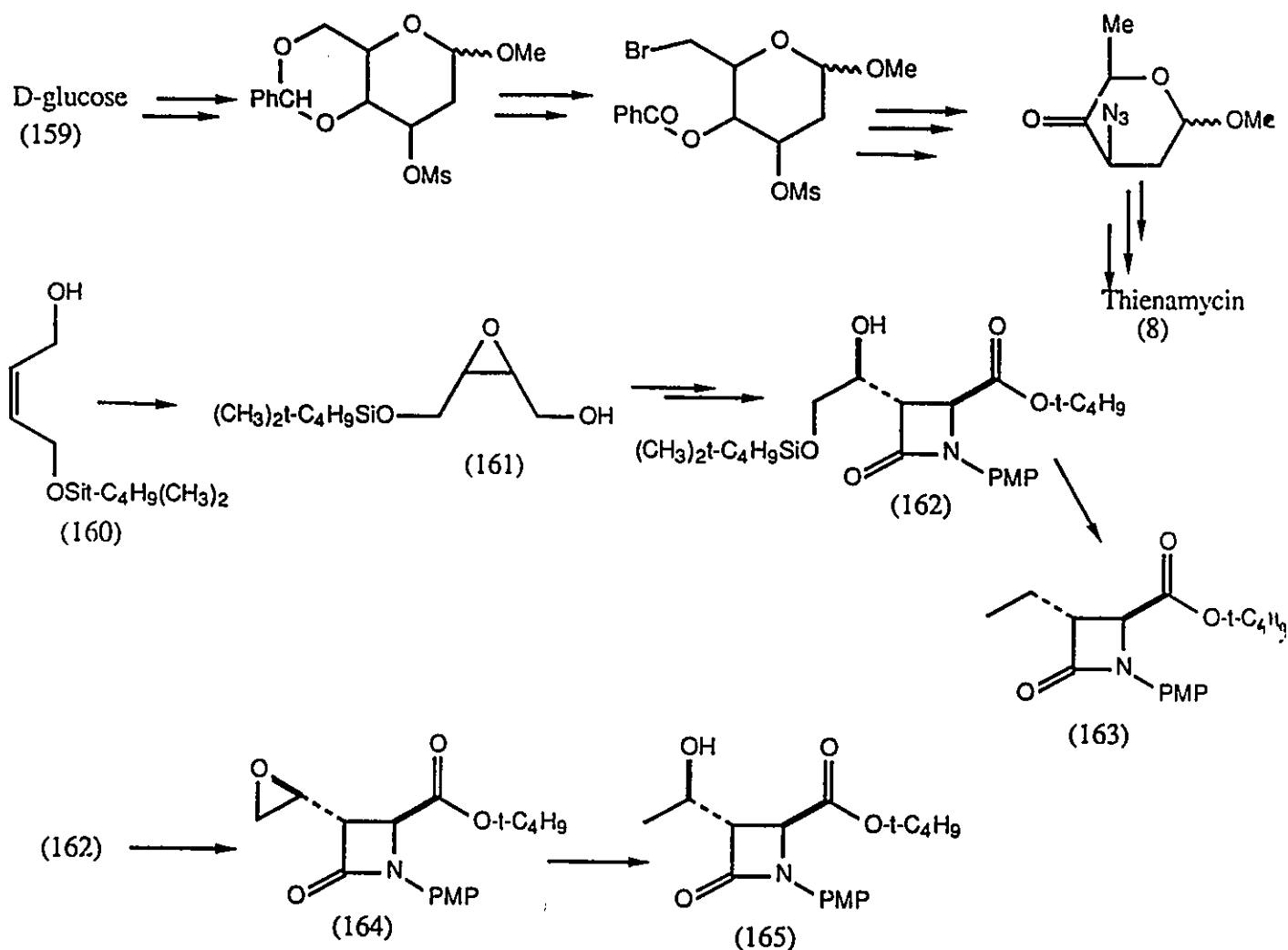
As pointed out at the end of Chapter 1, the dihydroxybutyric acid approach towards the syntheses of 3-alkoxy azetidinones left a lot to be desired. Perhaps the dihydroxybutyric acid approach was too ambitious and not systematic enough ; and it definitely was full of too many surprises. Specifically, our inability to carry out the hydrolysis of the acetonide residue of (90, Fig. XXIX) has placed that approach presently on hold. It can be hoped that suitable conditions might be found to carry out this particular transformation and the subsequent alkylation. Also thus far it has not been possible to obtain synthetically useful amounts of the azetidinone (107, Fig. XXIX). Obviously there was a need to develop a more reliable method to gain access to 3-alkoxy azetidinones such as (67, Fig. XXIX) in quantities large enough to serve as starting materials. As pointed out previously such a systematic approach has been developed. The final solution to this problem is non-enantioselective but highly diastereoselective. What follows is an account of the studies involved in this development.

The isolation of thienamycin led to extensive activity in the area of 3-hydroxyalkyl and 3-acylazetidinones. A variety of synthetic methods have been developed. However, the majority of them are very narrowly focussed. For example, Hanessian's formal synthesis of thienamycin is very elegant and perhaps a classic example the "Chiron" approach. But it seems highly unlikely that it could be used for syntheses of the analogs under consideration here (159 etc. Fig. XXIX)⁶³. The combination of Sharpless epoxidation with

Fig. XXIX



R = various protecting groups
 R' = various alkyl groups
 R'' = methyl group or a suitable precursor
 R₃ = cinnamyl, 2-furyl or methylcinnamyl. not phenyl
 R₄ = p-methoxyphenyl (=PMP).

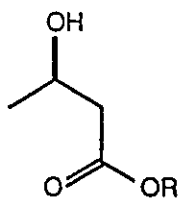
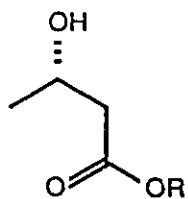


the "typical" ring opening methodology utilized by Bonini and Fabio allowed quick, if somewhat restricted access to thienamycin and PS-5 precursors (160 --> 163, 165, Fig. XXIX)⁶⁴. The utilization of threonine and allothreonines for the purpose of construction of theinamycin precursors is too well established to be fully documented here⁵¹. Relatively easy access to both enantiomers of 3-hydroxybutyric acid esters have made these compounds as suitable starting materials for a large number of diverse syntheses of theinamycin and PS-5 (Fig. XXX)^{43[vii]}. There have been other non-enantioselective methods of construction of thienamycin precursors. For example a nitrile oxide addition approach was developed by Kametani (166 -- 169, Fig. XXX)⁶⁵. Chemists at Merck provided a very innovative solution to the problem of introduction of the acetyl side chain in the enamine used for thienamycin synthesis (170 -- 173, Fig. XXX)⁶⁶.

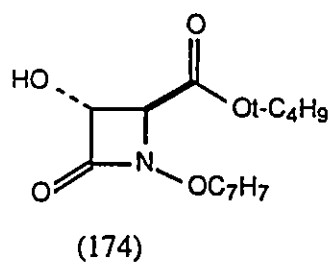
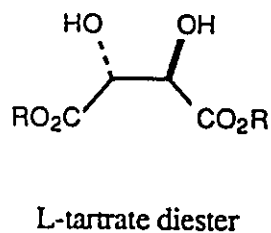
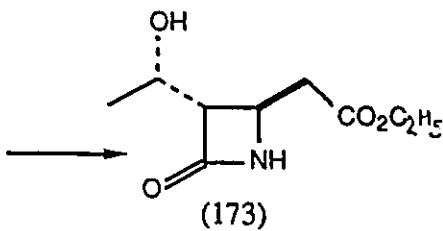
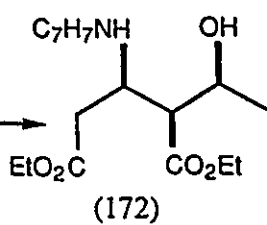
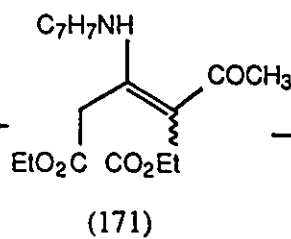
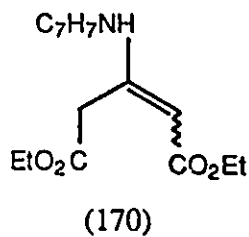
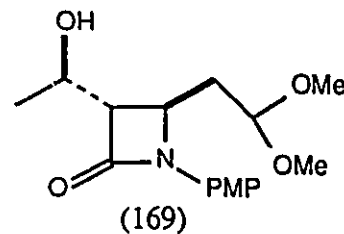
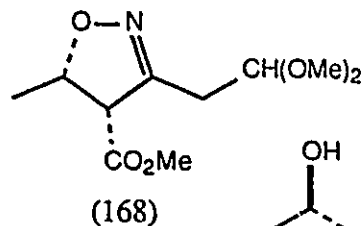
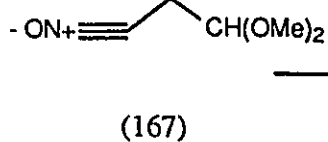
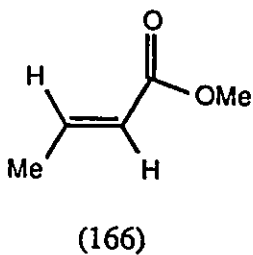
On the other hand the syntheses of 3-alkoxyazetidiones has attracted much less attention. With chemoenzymatic utilization of tartaric acid, French chemists developed a route to 3-hydroxy-4-carboalkoxy azetidiones (175, Fig. XXX)⁶⁷. Later Miller and Kolasa published a non-enzymatic approach to these compounds using the same starting material (174, Fig. XXX)⁶⁸.

It is obvious from the above discussion that most of the approaches to 3-acyl azetidiones are not suitable for syntheses of compounds also containing the 3-alkoxyazetidiones. To synthesize 3-alkoxy-3-acyazetidiones it was clear that a new approach was required. For maximum flexibility it appeared that a carbanion approach involving 3-alkoxyazetidiones might prove useful. Such

Fig. XXX

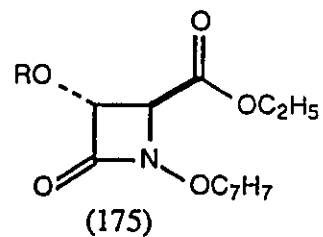


azetidinones.



chemical synthesis

C₇H₇ = benzyl



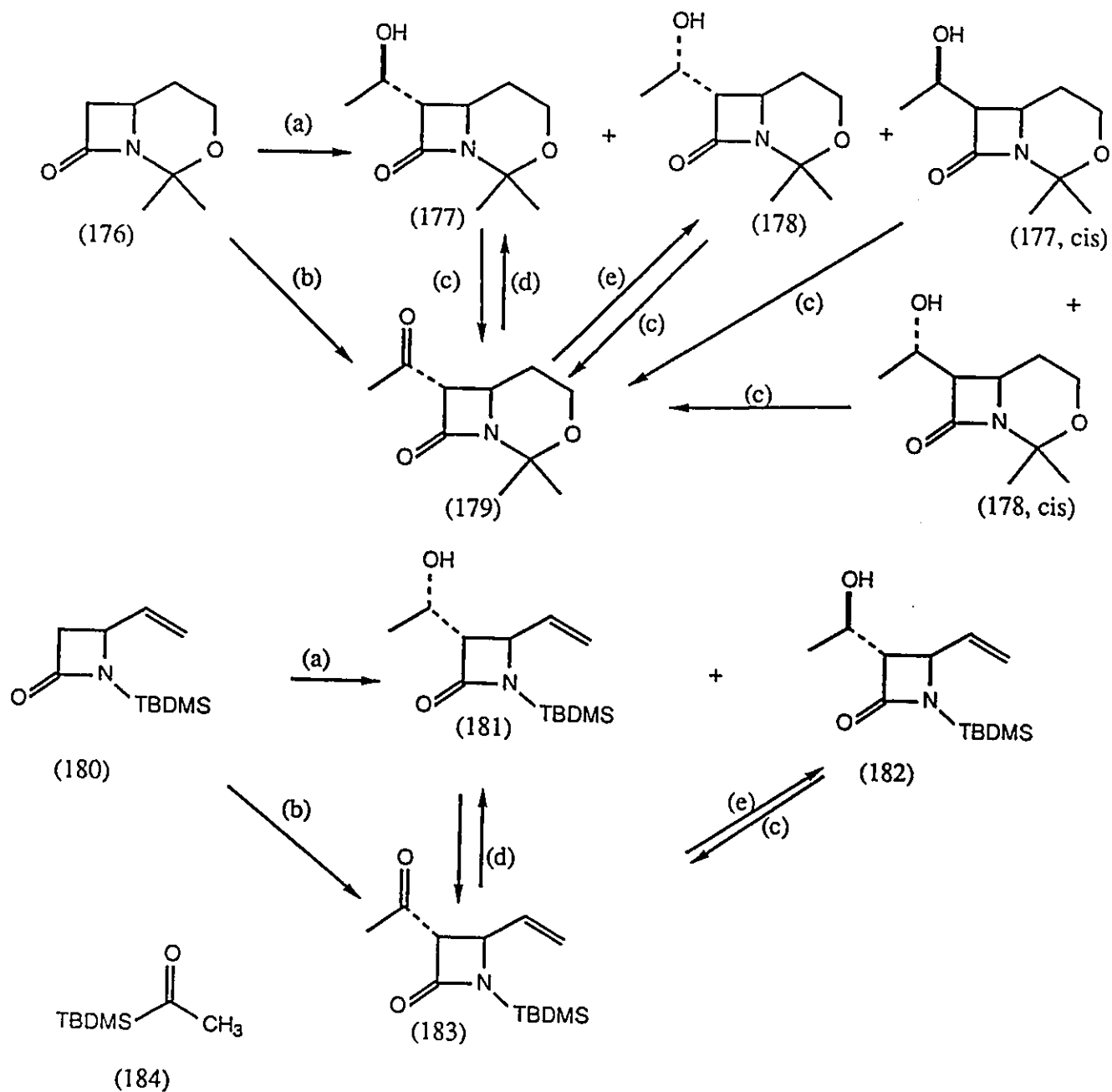
R = methyl, benzyl

chemoenzymatic synthesis

an approach was inspired by the studies carried out by Bouffard and Christensen (176 --> 179, and 180 --> 183, Fig. XXXI)⁶⁹.

In their studies these chemists found that it was straightforward to convert 3-unsubstituted azetidinones to their carbanions by reacting with LDA at -78° C. Subsequent trapping with acetaldehyde provided the trans azetidinones as major product. However the hydroxyethyl group was being generated in a non-stereoselective manner. Subsequent oxidation and a chelation controlled reduction were used to obtain the trans 8(R*) compound (thienamycin numbering system used here and subsequently)⁶⁹. Several features of this work are noteworthy. These chemists observed that it was impossible to introduce the acetyl side chain directly and thus developed a route involving 3-(trimethylsilyl)azetidinone. This required that the carbanion forming step be carried out twice, once on the parent β -lactam and then on the 3-silyl compound. The introduction of the silyl group was stereospecific, providing the trans compound. This sequence also served to establish that it is possible to deprotonate a 3-substituted azetidinone. It was also noted by these chemists that Swern oxidation of a mixture of the cis and trans 3-hydroxyethylazetidinones furnished the trans acylazetidinone exclusively. Finally these chemists observed that by using a chelation controlled reduction of 3-acetylazetidinones, the desired 8(R*) could be obtained as the major product. Reduction using a hindered reducing agent under non-chelating conditions furnished the undesired 8(S*) as the major product. A later solution to this problem was provided by these chemists in the form of a

Fig. XXXI



- (a) [i] LDA, THF, -78 °C. [ii] acetaldehyde.
 (b) [i] LDA, THF, -78 °C. [ii] TMS-Cl. [iii] LDA, THF, -78 °C. [iv] acetylimidazole.
 (c) Swern oxidation.
 (d) KI, K-Selectride, ether or THF, 25 °C. (177) : (178) = 88:12.
 (e) L-Selectride, THF, -78 °C. (177) : (178) = 8:92.

observations for (180) -- (183) were similar..

Brook rearrangement based approach employing silyl ketones such as 184 (Fig. XXXI)⁷⁰. It was claimed that the observed 8(R*) stereochemistry was the result of an unusual Brook rearrangement.

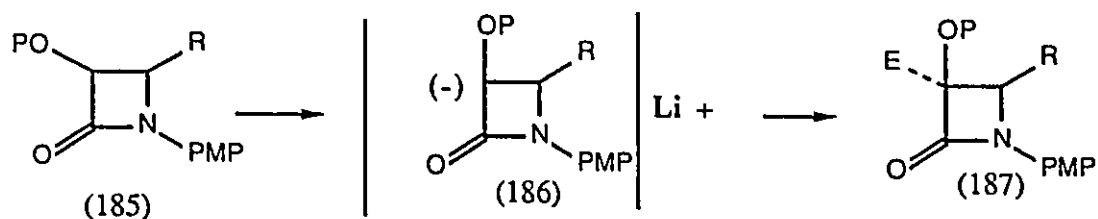
Based on the observations made by these chemists, it appeared reasonable that 3-alkoxyazetidinones could be converted to their corresponding anions. Subsequently it should be possible to convert these anions into various 3,3-disubstituted azetidinones (185 -- 187, Fig. XXXII). For initial experiments, racemic 3-alkoxyazetidinones were utilized. A few of these compounds were available by ketene-imine reaction of the corresponding alkoxyacid and various imines (Chapter 8). Initial experiments were carried out on 3-methoxyazetidinones.

Formation of a carbanion from 1-(p-methoxyphenyl)-cis-3-methoxy-4-phenyl azetidinone (188, Fig. XXXII) was somewhat complicated by its low solubility in THF. Addition of LDA to the suspension of this compound in THF at -78° C did not lead to any perceptible change in color or solubility. Slow increase in the temperature to ambient led to formation of a turbid deep red solution. Subsequent quenching with electrophiles led to no change in color. The isolated product in this case was the unsaturated amide (189, Fig. XXXII). On the other hand exposure of the azetidinone to LDA at 0° C led to a plethora of unresolved compounds, none of which has been fully characterized. This situation was not very different from that of the corresponding β -lactones^{71,72}. Thus at some stage the anion was indeed generated but it decomposed during the warming-up process. This made it necessary that the anion formation reaction be carried out at low temperature.

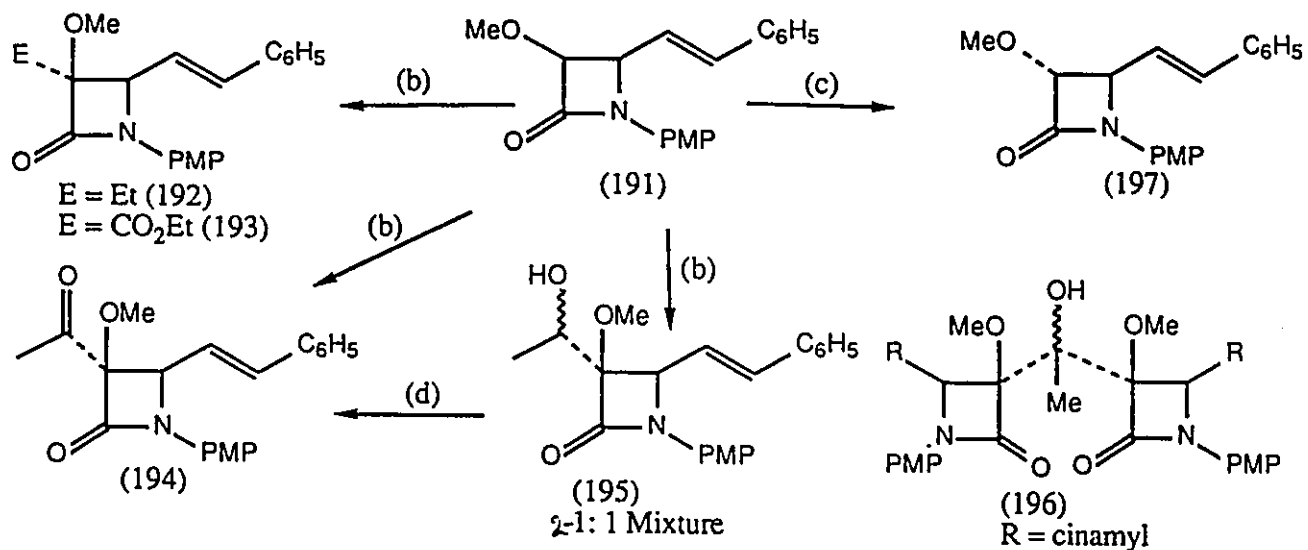
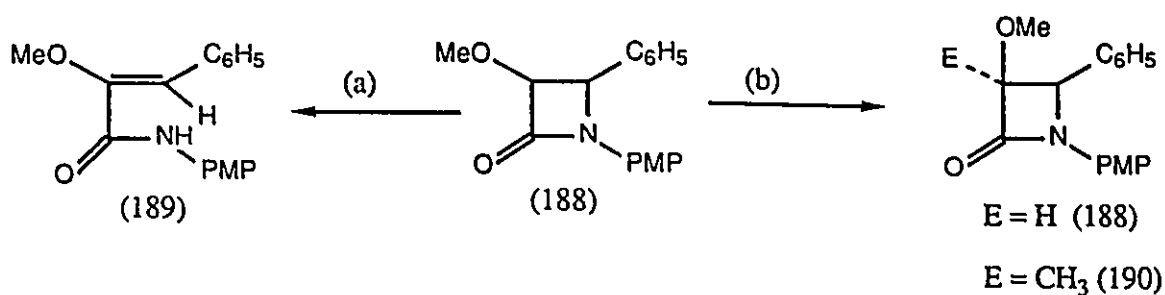
In a subsequent attempt a solution of the azetidinone in a relatively large volume of THF (about 300 mL of THF for about 1g of the azetidinone) at -78° C was exposed to a slight excess of LDA. The formation of the anion seemed to be instantaneous , as indicated by development of a dull-yellow color. Subsequent quenching with methyl iodide led to exclusive formation of the corresponding 3-methyl-3-methoxyazetidinone as the sole product in about 96% isolated yield (190, Fig. XXXII). Addition of acetic acid to the anion led to regeneration of the starting material. These experiments demonstrate that the alkylation and the protonation of the anion was taking place with a very high degree of diastereoselectivity. Regeneration of the starting material on protonation served to establish that the bond formation between the electrophile and the azetidinone anion was taking place on the side opposite to the big substituent at C-4. In case of the 3-methyl-3-methoxyazetidinone a significant upfield shift (about 0.7 ppm) for the methoxy protons seems to corroborate this notion. This assumption regarding the stereoselectivity of bond formation process was later found to be correct.

Having gained some experience with the "model" compound it was decided that the reaction be extended to the compound which will allow elaboration of the side-chain at C-4. For this purpose compounds with a cinnamyl, methylcinnamyl or 2-furyl group are suitable. Fortunately in these cases the solubility problems were not as acute as in the case of the model compound. In these cases 1 gram of azetidinone is typically soluble in about 50 - 60 mL of THF.

Fig. XXXII



R = phenyl, cinnamyl, 2-furyl
methylcinnamyl.
P = various alkyl group.



- (a) azetidinone, THF, -78 °C, slow warm up.
 (b) azetidinone, THF, -78 °C, various electrophiles, direct or inverse quench.
 (c) azetidinone, THF, -78 °C, inverse addition to acetylimidazole.
 (d) PCC, methylene chloride, sodium acetate, 4 A° (191) \rightarrow (195) and (195) \rightarrow (194) is true regardless of substituents.

Generation of the carbanion from the azetidinone (191, Fig. XXXII) was free of any problems. The yellow color of the anion faded instantaneously on the addition of the electrophiles. Reaction of the anion with ethyl iodide provided only one compound, aside from about 0.5% recovered starting material (192, Fig. XXXII).

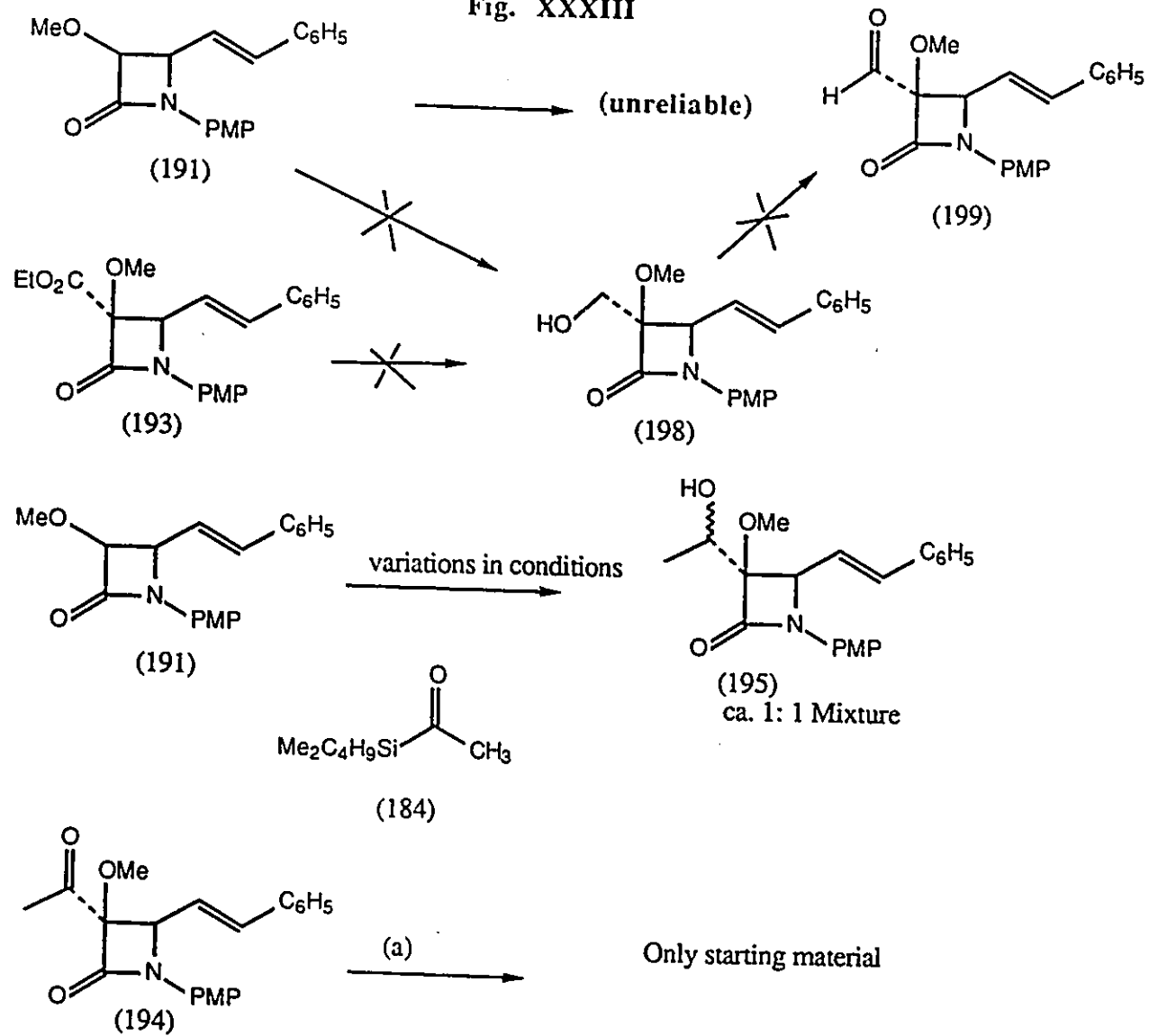
Inverse addition of the anion to a large excess of ethyl chloroformate furnished the corresponding carboethoxy compound (193, Fig. XXXII) in nearly quantitative yield. On the other hand inverse addition of the anion to large excess of acetyl chloride led to the corresponding C-3 acetyl compound in about 60% yield (194, Fig. XXXII). In this particular case some starting material is recovered, in addition to about 10-15% of the 'dimer' (196, Fig. XXXII). Direct addition of acetyl chloride to the solution of the anion led to the recovery of the starting material, and the formation of 'dimer' in about 60% yield. It is interesting to note that in their studies, Bouffard and Christensen did not obtain more than 10 -15% of the C-3 acetyl compound even on inverse addition. In the present case inverse addition of the anion to a large excess of acetylimidazole led to only minute amounts of the acetyl compound. The dimer, the starting material and the corresponding trans azetidinone (197, Fig. XXXII) accounted for the bulk of the product. Despite several attempts, reaction of the anion with ethyl formate or DMF was uniformly unrewarding, typically returning the starting azetidinone and its trans isomer as the major products. The desired C-3 formyl compound (199, Fig. XXXIII) was obtained in about 10% yield and was always contaminated with variable quantities of unidentifiable materials. Reaction with acetic-formic anhydride gave no 3-formyl

azetidinone. Starting material, its trans isomer and the 3-acetyl compound were the only characterisable products which were isolated. The anion did not seem to react with formaldehyde. The reaction product consisted of the starting and the isomerized azetidinone. No 3-hydroxymethyl compound (198, Fig. XXXIII) could be obtained. Reduction of C-3 carboethoxy azetidinone was not useful for obtaining the formyl and the hydroxymethyl compounds. This failure may in part be due to low stability of the formyl compound, though there does not seem to be any reason for such behavior. In a couple of instances when trace quantities of this compound were isolated, the material decomposed within a few hours at room temperature.

On the other hand, reaction of the anion with other aldehydes (acetaldehyde has served as a representative in this study; aromatic aldehydes were also used) was trouble free. The reaction was fast and quantitative as judged by disappearance of the color of the anion and TLC. Almost invariably a mixture of two hydroxyalkyl compounds (195, Fig. XXXII) was isolated, usually in 80-90% yields and as nearly 2 :1 mixture of diastereoisomers. The signals for the C-4 protons are usually well resolved and have served as diagnostic peaks in all the cases examined. On the other hand peaks due to the hydroxyethyl protons or the methyl groups are not always well resolved.

The mixture of the hydroxyethyl compounds could not be resolved. Conversion to a variety of derivatives has not proven useful for this purpose. Obviously an alternate route was required to obtain the individual hydroxyethyl compounds in pure form.

Fig. XXXIII



(a) TMSLi, THF, -78°C , t-BuOK, t-BuOH.

Several variations in the conditions of the anion formation and the quenching were undertaken. Since early experiments had served to establish that variation in terms of the substituents at C-4 has little impact on the stereochemical course of the reaction it was possible to use any of the available azetidinones. Changing the nature of the counteraction did not lead to a significant improvement in diastereoselectivity with respect to the hydroxyethyl group. In all cases the same mixture of diastereomeric hydroxyethyl compounds (191 and 195, Fig. XXXIII) was obtained. Furthermore in all these cases the yield of the mixture (195) was often much poorer than those with the lithium counteraction. Quenching of the anion at a lower temperature (about -90°C) or quick inverse addition of the anion into large excess of acetaldehyde at 0°C proved futile with respect to this aspect. The simple procedure involving the generation of the carbanion at -78°C with LDA and quenching by direct addition of acetaldehyde at that temperature is still the best procedure in terms of the consumption of the starting material, yields of the products and minimal formation of undesirable polar side-products.

The Brook rearrangement approach adopted by Merck chemists when applied to the anion derived from (191) and the silyl ketone (184, Fig. XXXIII) was unsuccessful. Only the starting azetidinone, (and its trans isomer) was isolated. Efforts to induce the rearrangement by addition of TMSLi to the corresponding C-3 acetyl compound were unsuccessful probably due to enolisation of the starting material⁷³.

Having exhausted the available viable options for the preparation of the hydroxyethyl compounds in diastereoselective manner, it was decided to undertake an approach based upon stereoselective reduction of the acetyl compound (194, Fig. XXXIV). In the present case the presence of the additional alkoxy group at C-3 can severely complicate the chelation phenomenon which was used by Merck chemists for the diastereoselective reduction. Thus several of the chelates might be present at the same time, each one of them influencing the course of the reduction in its own way. It is difficult to make any prediction regarding the relative amounts of these chelates and their contribution to the reduction process. On the other hand it can be reasonably argued that in the presence of an excess of an additional strong chelating agent, chelation of cations with the 3-acetylazetidinone will be considerably minimized, if not altogether eliminated. It may be easy to create non-chelating conditions, but it may not be easy to generate a specific chelate reproducibly. If nothing else reductions under non-chelating conditions are likely to be reproducible. With the use of a fairly bulky reducing agent it might be possible to attain a high degree of diastereoselectivity due solely to steric effects.

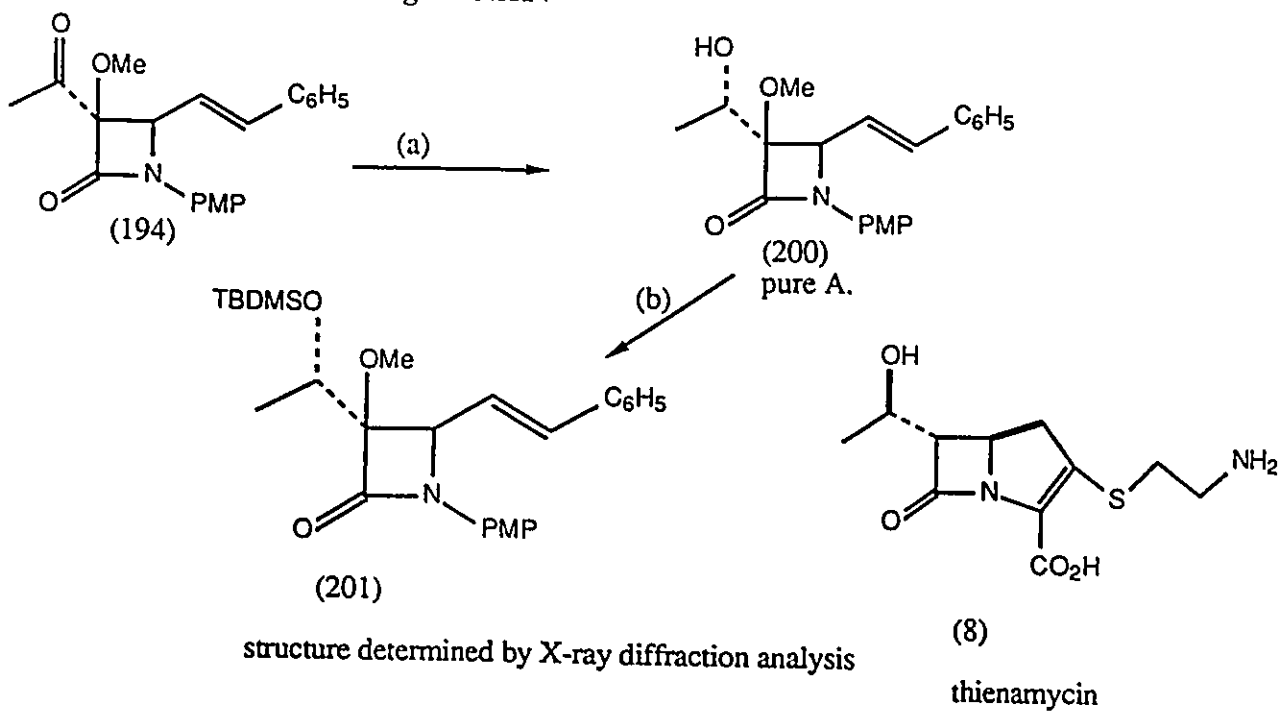
Crown ethers appear to be a logical choice as a strong external chelating agent that will prevent the complexation between the metal cations of the reducing agent and the acetylazetidinone. However crown ethers have severe limitations in terms of high cost, high toxicity and above all the potential difficulties that might be encountered in the removal of the chelating agent from the product(s) of the reduction. N,N,N',N'-Tetramethylethylenediamine

(TMEDA) may not be as effective as crown ethers in terms of its chelating ability, but it does offer some very significant advantages since it is relatively cheap, easy to purify, handle and above all to separate from the products at the end of the reaction.

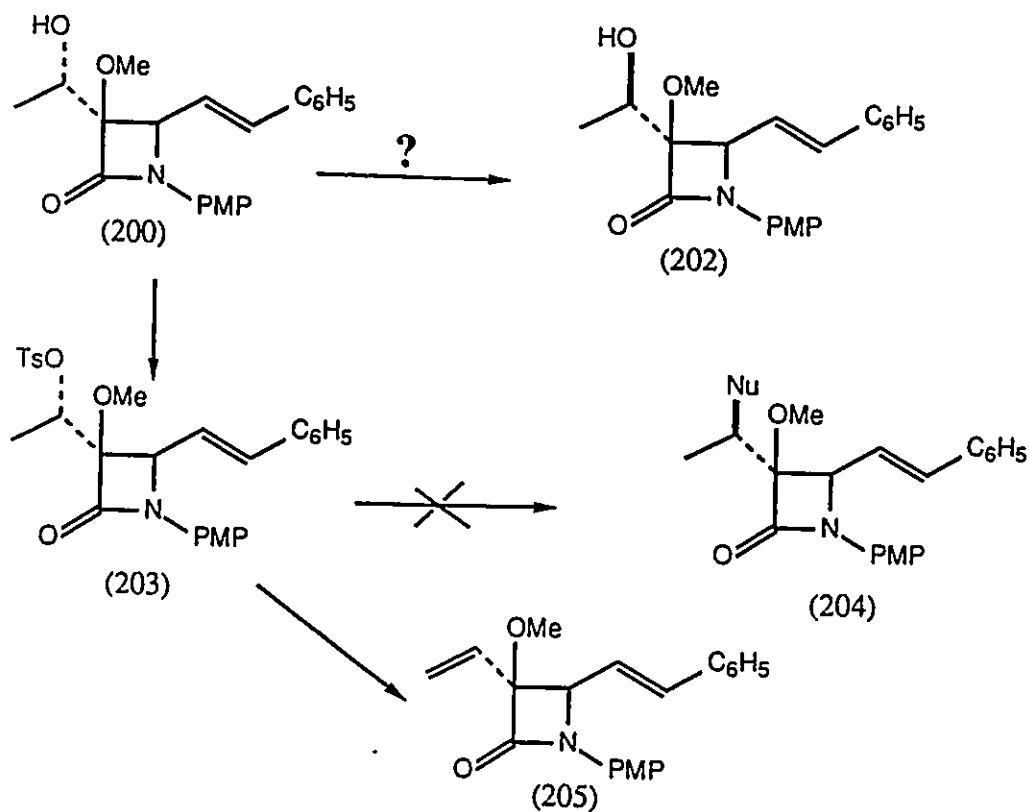
Thus in very early stages an experiment was conducted in which about 2.5 equivalents of TMEDA were added to a solution of the acetyl β -lactam in THF at -78°C , followed by 1.1 equivalents of L-Selectride (Lithium-tri-*sec*-butyl-borohydride) in THF. Even after 2 hours at -78°C the reaction mixture showed the presence of the starting material. However, the isolated hydroxyethyl compound obtained in about 50% yield was diastereomerically pure. The diastereomer isolated in this case had the upfield shift for the C-4 proton. This compound was labelled as the diastereoisomer A. The diastereomer with downfield shift of C-4 proton was labelled as B. This phenomenon of obtaining the "upfield shift isomer" is common to other azetidiones regardless of the substituents (Chapter 7).

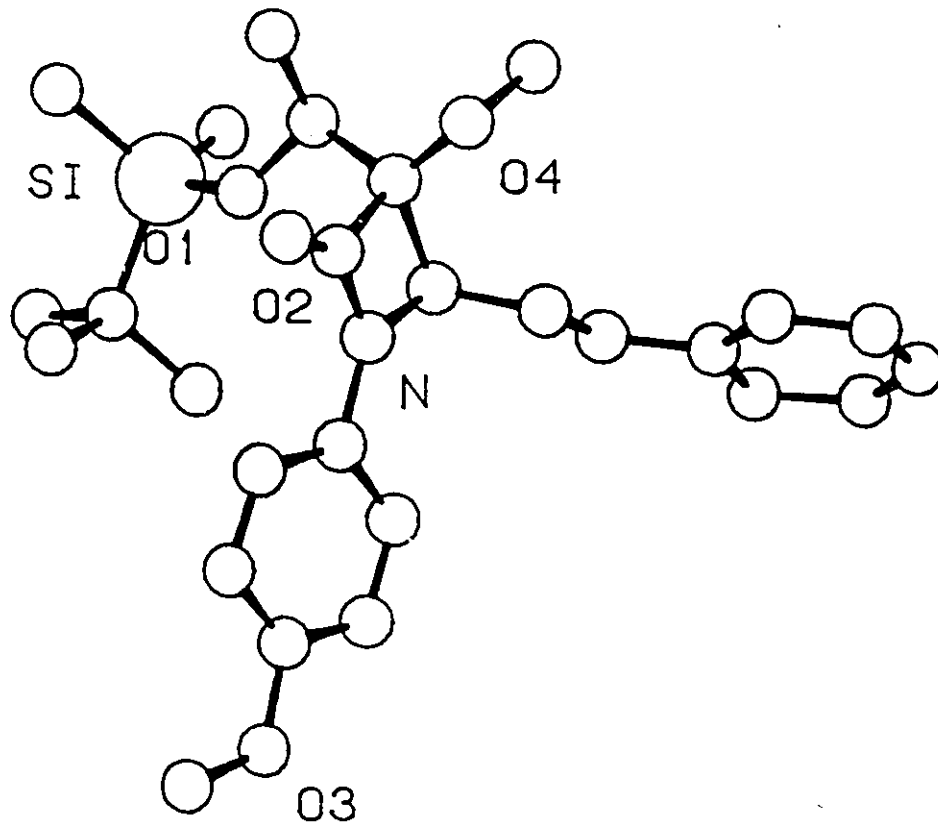
It was decided to convert this pure compound (200, Fig. XXXIV) (a sticky foam) into a derivative suitable for X-ray diffraction analysis. After several attempts the TBDMS derivative of diastereoisomer A (201, Fig. XXXIV) crystallized in a form suitable for X-ray diffraction. The relative trans arrangement of the hydroxyethyl group at C-3 and the cinnamyl substituent at C-4 determined by X-ray diffraction analysis was anticipated on the basis of early methylation experiments. This effectively amounts to replacing the C-3 proton in a thienamycin precursor with a methoxy group with retention of configuration. Incidentally such a replacement

Fig. XXXIV



(a) L-Selectride, THF, 2.5 eq. TMEDA, -78 °C, 2 hrs.
 (b) TBDMS-triflate, 2,6-lutidine, methylene chloride.





201

leads to change in the R-S assignment due to a change in the relative priority of the substituents.

The stereochemistry of the hydroxyethyl group was shown to be "non-thienamycin". This was not entirely surprising. This is very similar to the observation made by Merck chemists in their reduction of C-3 acetyl compounds under non-chelating conditions.⁶⁹ In the present case the diastereoselectivity is much higher.

Despite 'wrong' stereochemistry with respect to thienamycin series the hydroxyethyl compound has proper functionality to allow elaboration into bicyclic azetidinones. Carbapenems which have the unnatural stereochemistry at the hydroxyalkyl position of the C-3 substituent are known ^{11, 46[vi]}. Such efforts are being currently undertaken by a colleague. It is anticipated that soon it shall be possible to obtain a methoxy analog of thienamycin.

As stated before the high degree of diastereoselectivity observed in the non-chelation controlled reduction of C-3 acetyl compounds is independent of the nature of various substituents. At least in one case it has been shown by chemical correlation that C-4 cinnamyl and C-4 methylcinnamyl azetidinones furnish the same stereochemistry at the hydroxyethyl group on Selectride reduction. More detailed studies on the effect of various factors on this non-chelation controlled reduction are described and discussed in Chapter 7.

The focus of current studies shifted to obtaining the azetidinone with the 'proper' i.e. 8 (R*) stereochemistry for the hydroxyethyl side-chain. An obvious answer to the problem would involve an S_N2 reaction at the carbon atom in question

(200 --> 202, Fig. XXXIV). The most obvious choice in this regard is the Mitsunobu reaction⁷⁴. However a Mitsunobu reaction using formic acid as the external nucleophile proved very sluggish even in refluxing toluene. The isolated yields of the formate ester corresponding to (202) was never more than 10-15%, the rest being the starting material. The procedure involving DCCI-CuI combination was not useful either⁷⁵. As subsequent experiments on the tosylate of this azetidinone have shown the hydroxyethyl group is highly hindered, being neo-pentylic and secondary⁷⁶ and thus S_N2 reactions at this position are extremely difficult. In majority of these cases nucleophiles such as acetate and azide do not seem to be able to reach the carbon atom in question. Elimination to form the 3-vinyl products such as (205, Fig. XXXIV) is the annoying side reaction in these cases. S_N1 reactions conditions do not seem to be particularly easy either, after about 15 days exposure to formic acid at room temperature, the tosylate is recovered essentially unchanged!.

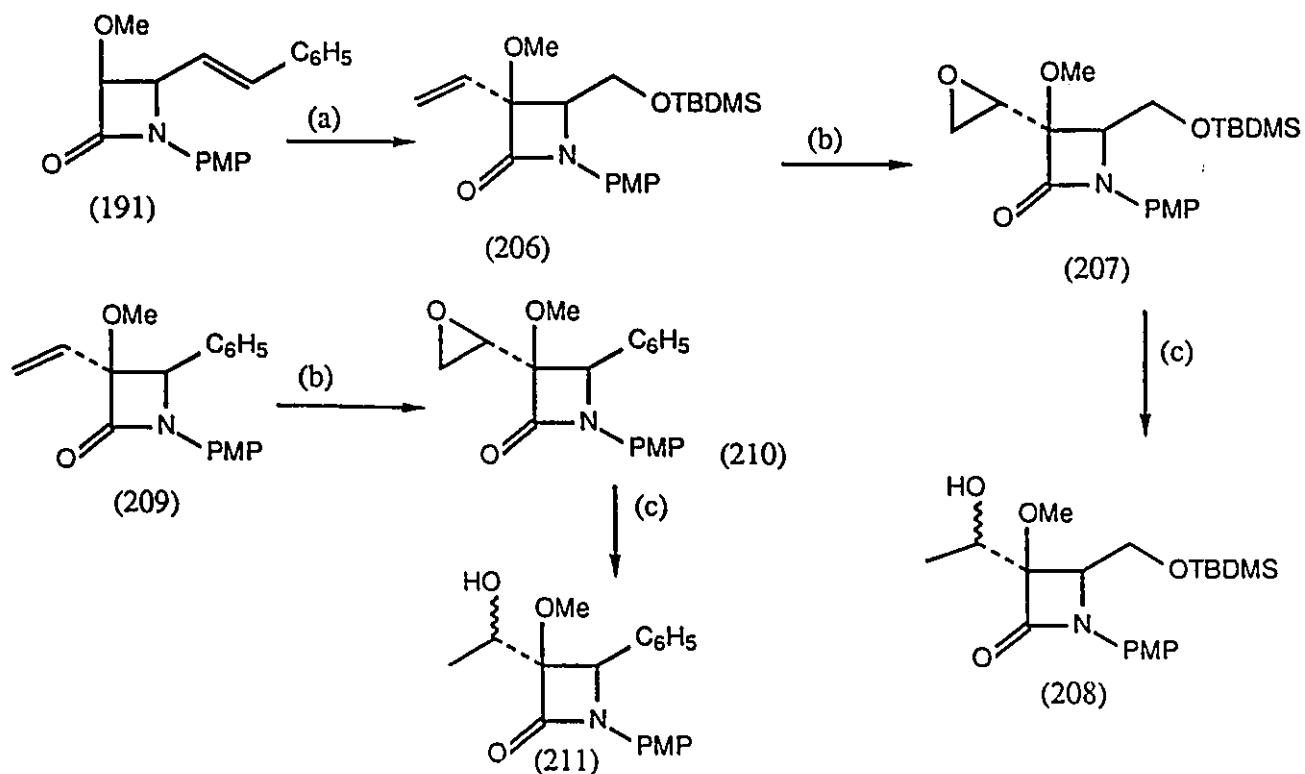
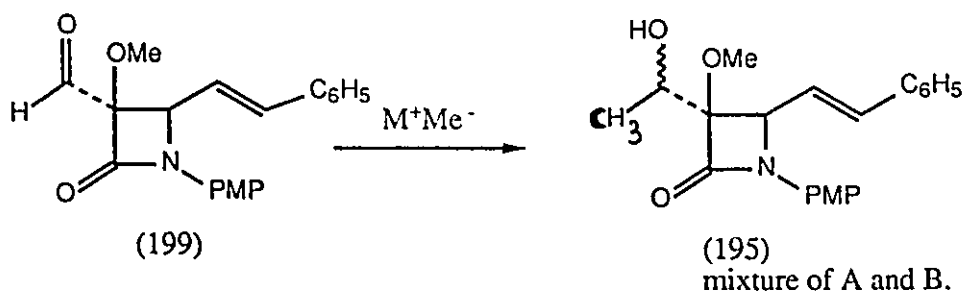
It can be argued that the 'proper' stereochemistry for the hydroxyethyl side-chain can be attained by interchanging the order of introduction of the various groups. Thus instead of introducing the hydrogen residue last (reduction of the acetyl group) one could introduce the methyl residue last (reaction of the corresponding aldehyde with a bulky source of Me⁻), under non-chelating conditions. This approach was partly successful; in one such reaction, the aldehyde was reacted with MeLi in presence of excess TMEDA. The result was about 50% yield of a 1:3 mixture of A:B i.e. the desired diastereoisomer was formed as the major product. Addition of trimethylborate to the MeLi prior to the addition of the

azetidinone with a view to making a borate adduct which might serve as source of 'hindered' methyl group did not prove useful either, the yield and the diastereoselectivity were similar to the first case. As mentioned before the aldehyde is not an easily accessible compound, which realistically speaking made further experiments along these lines, including the possible use of Me_2CuLi ⁷⁷ irrelevant.

Another variation in terms of interchanging the order of introduction of the various substituents involves stereoselective epoxidation of the olefine (205, XXXIV) and regioselective opening of the resulting epoxide. For this purpose it was necessary that the substituent at C-4 be suitably modified (205, Fig. XXXV). Initial studies designed to address these questions studies were carried out on the model compound (209, Fig. XXXV). In the event these olefines were found to be highly resistant towards epoxidation. This required that the epoxidation reactions be carried out under somewhat harsh conditions (3 eq. mCPBA, refluxing dichloroethane, 15 h) and thus the diastereoselectivity for epoxidation was poor. This made it necessary that the epoxides (207, 210 Fig. XXXV) be separated. Despite considerable efforts (211, XXXV) was obtained as was a roughly 1:3 mixture of isomers A:B. It was not possible to separate the mixture into individual diastereomers (207). Overall this approach was at best a partial success. One positive outcome of these studies was that conditions required for the opening of the epoxide were determined; these were effectively used below.

These experiments showed the need for a conceptually different approach to the thienamycin b-lactam building block. Early experiments had established that use of an external

Fig. XXXV



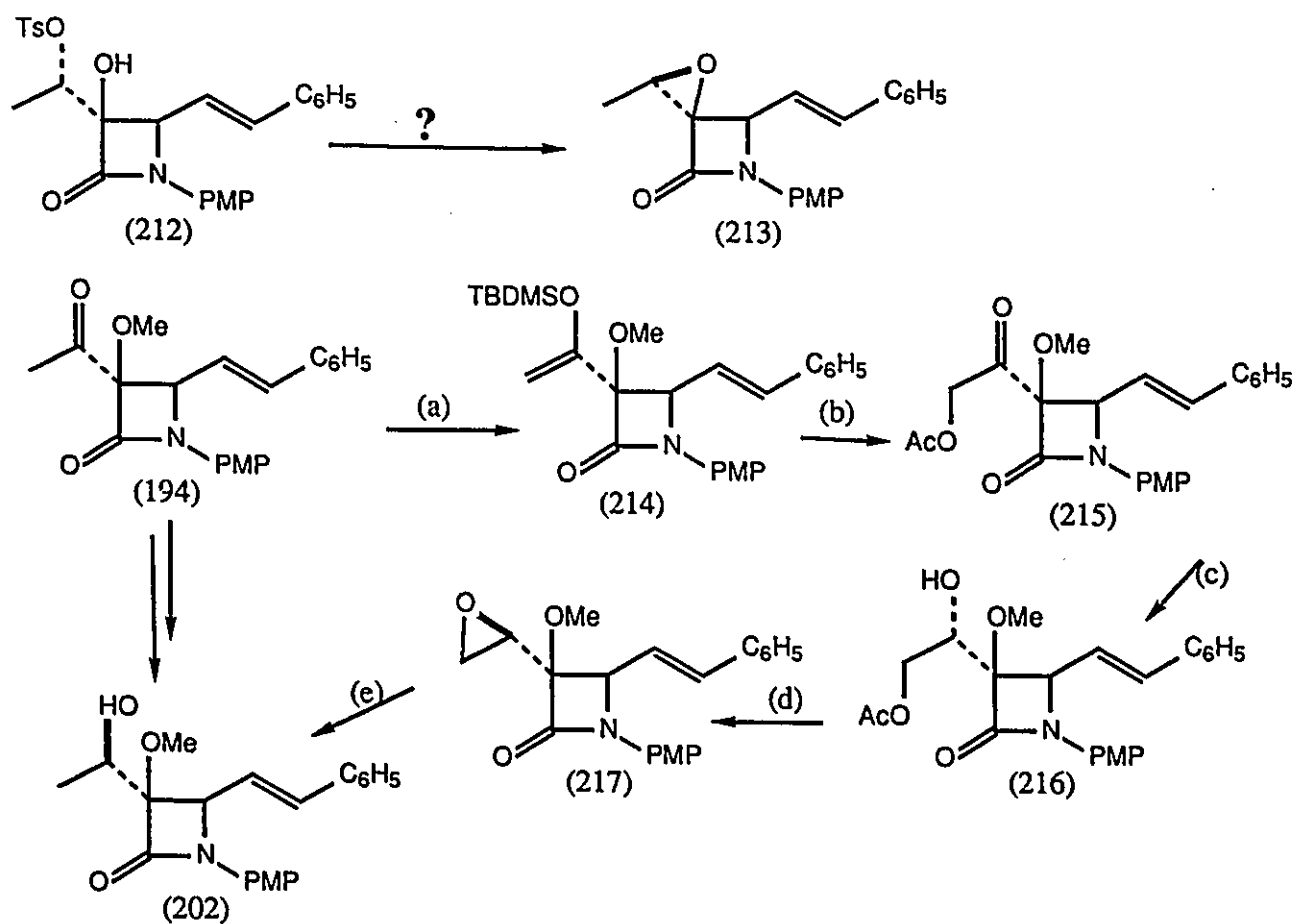
- (a) [i] $O_3 \mid O_2$, $-78^\circ C$. [ii] Sodium borohydride, EtOH, [iii] TBDMS-triflate, 2,6-lutidine, methylene chloride [iv] LDA, THF, $-78^\circ C$, then acetaldehyde, [v] Tosylimidazole, NaH, DMF. [vi] DBU, DMF, reflux. 20% yield from (191).
 (b) mCPBA, dichloroethane, reflux.
 (c) L-superhydride, THF, $0 - 5^\circ C$.

nucleophile for inverting the hydroxyethyl group is unlikely to be fruitful. The question to be addressed was whether an internal nucleophile can be used to invert the stereochemistry of the hydroxyethyl group. An obvious internal nucleophile will be the free hydroxy group at C-3 (212 --> 213, Fig. XXXVI). In the present context such an idea would require that the compound (203, Fig. XXXIV) be demethylated. As studies on the model compounds were to prove, this is not an easy task⁷⁸.

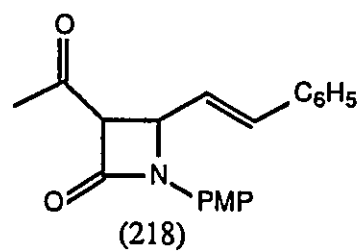
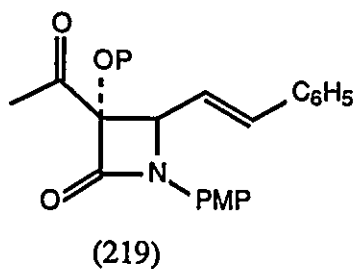
The testing of the concept described above would require an easy access to a C-3-hydroxy-C-3-hydroxyethylazetidinone. Since there did not seem to be a reliable procedure for making these compounds, a sequence was devised. The studies related to these efforts are presented in Chapter 6 of this thesis. The most significant outcome of these experiments was that an internal nucleophile can indeed invert the stereochemistry of the carbon atom in question.

One approach to the 1,2 glycols necessary for this study would be to introduce a hydroxyl group α -to the acetyl group of (194, Fig. XXXVI). Attempted formation of the enol from the β -lactam (194, Fig. XXXVI) and subsequent quenching with MoOPH did not yield the hydroxy compound, the starting material was recovered unchanged⁷⁹. Use of iodoxybenzoic acid under basic conditions led to destruction of the starting material⁸⁰. Attempted Rubottom reaction was not very useful either⁸¹. It appeared that formation of the enol silyl ether from the acetyl compound by LDA/THF/TMSCl combination was the unreliable step. On the other hand refluxing a solution of the acetyl compound in methylene chloride with a slight excess of TBDMS-triflate and 2,6-lutidine led to the formation of the

Fig. XXXVI



- (a) TBDMS-triflate, 2,6-lutidine, methylene chloride, reflux, purify
 (b) [i] Bromine, methylene chloride, 0°C, [ii] DMF, Cesium acetate ca. 10 eq.
 (c) L-Selectride, TMEDA, THF, -78°C
 (d) [i] Tosyl imidazole, DMF, [ii] Sodium methoxide, Methanol, THF.
 (e) L-Superhydride, THF, 2-5°C. ca. 15% overall yield from (194).



corresponding enol ether (214, Fig. XXXVI) in nearly quantitative yield. Subsequent reaction of the enol ether with bromine in methylene chloride appeared to be instantaneous, as judged by the disappearance of bromine color. This crude bromo compound was reacted with an excess of cesium acetate in DMF to furnish after purification the corresponding acetoxy compound (216, Fig. XXXVI) in about 65% overall yield from the acetylazetidinone (194, XXXVI). The compound prepared in this manner was identical with the one prepared from the reaction of the azetidinone (191, Fig. XXXII) anion with acetoxyacetyl chloride (addition of the anion to a large excess of the acid chloride). Subsequent steps in the latter scheme involved the reduction of the acetate with L-Selectride under non-chelating conditions, conversion of the monoacetate to the corresponding secondary tosylate, epoxide formation under the influence of methoxide in methanol and the opening of the epoxide (217, Fig. XXXVI) with the superhydride at low temperature to furnish (202, Fig. XXXVI). This was the diastereoisomer B (202, Fig. XXXIV). The unoptimized yield for this entire sequence of reactions was about 15% from the acetoxyacetyl compound. Thus the overall objective of the inversion of the configuration of the hydroxyethyl group was achieved. Similar reactions have been carried out on the azetidinone bearing the methylcinnamyl substituent at C-4. In the latter case the acetoxyacetyl compound was obtained from the azetidinone via anion /acetoxyacetyl chloride quench method. Thus starting from the acetyl compound ((194) it is possible to obtain either hydroxyethyl compound by using the non-chelation controlled reduction as the key step.

Thus it can be claimed that the objective of obtaining both the diastereoisomers of the 3-hydroxyethyl compound has been realized. Undoubtedly there is room for improvements, especially in the epoxide forming step. For reasons not yet known this step has proven somewhat tricky and may not yet be ready for a large scale reaction. A better approach might involve the corresponding benzyloxyacetyl compound for this purpose (Chapter 6). It has been known that epoxide formation from compounds such as (341, Fig. LII and 344, Fig. LIII) is remarkably facile. Such a route will involve some modifications of the starting materials, i.e. conversion of the cinnamyl substituent at C-4 into the corresponding protected hydroxymethyl compound. Such an undertaking might prove worthwhile since it might also overcome the problems due to the partial loss of the acetate group during the reduction step. It can be stated that problems are essentially of a technical nature, the concept of inversion of the stereochemistry of the hydroxyethyl bearing carbon atom by attack of an internal nucleophile is sound. In due course, by making appropriate modifications it should be possible to prepare synthetically useful amounts of the hydroxyethyl compound with the 'proper' stereochemistry. It seems very likely that the reactions encountered in the synthesis of 3-methoxy-3-hydroxyethyl compound can be used successfully for the synthesis of other 3-alkoxy-3-hydroxyalkyl compounds.

Yet another point concerns the azetidinones in which C-3 alkoxy group is cis to the proton at C-4. Thus far it has not been possible to prepare compounds having such stereochemistry via the anion approach. It is difficult to predict if a methodology involving

anion formation from C-3 acetylazetidinone and subsequent trapping with an oxygen electrophile will be useful in this context (218, 219 etc Fig. XXXVI).

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- (64) Bonini, C. and Fabio, R.D. *Tet. Lett.* **1988**, *29*, 815, 818.
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- (66) Melillo, D.G.; Liu, T.; Ryan, K. Seltzinger, M. and Shinkai, I. *Tet. Lett.* **1980**, *21*, 2783. See also. *Tet. Lett.* **1981**, *22*, 913.
- (67) Gateau, O.A.; Celophax, J. and Gero, S.D. *Tet. Lett.* **1986**, *27*, 41.
- (68) Miller, M.J. and Kolasa, T. *Tet. Lett.* **1987**, *28*, 1862.
- (69) Bouffard, F.A. and Christensen, B.G. *J. Org. Chem.* **1981**, *46*, 2208.
- (70) Bouffard, F.A. and Saltzman, T. N. *Tet. Lett.* **1985**, *26*, 6285.
- (71) Mulzer has observed that β -lactones make anions at -78°C . These anions are quite stable at this temperature and can be reacted with a variety of electrophiles. However, upon raising the temperature these anions decompose to the corresponding α,β -unsaturated acid derivatives. On the other hand, the elimination

from the corresponding open-chain compounds is instantaneous even at -78°C . Mulzer, J. and Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620. It can be stated that any C-3 anion derived from an azetidinone is a candidate for β elimination. On the other hand for a facile and concerted elimination to take place it is necessary that the groups involved in the process meet the requirements set by Baldwin's rules. In the present case this requires considerable distortion of the molecule, and the activation energy for such elimination processes is rather high. Thus the anions under consideration have at least moderate stability at low temperatures.

(72) For examples of ring opening of 4-benzyloxyazetidinones see, Plumet, J.; Alcaide, B.; Dominguez, G.; Monge, A. and Perez-Garcia, V. *Het.* **1987**, *26*, 1461.

(73) For this reaction TMSLi was generated following procedure of Still. Still, W.C. *J. Org. Chem.* **1976**, *41*, 3063. The idea was to obtain the 'silyl alcohol' and then to rearrange it under the influence of base and protic acid, following procedure similar to that adopted by Bouffard and Saltzman. Ref. 70. It was somewhat annoying to find out that the acetyl compound (194) seems to be capable of reacting with relatively hindered anion such as the one obtained from (191) but appears to undergo extensive enolization with TMSLi.

(74) Mitsunobu, O. *Synthesis* **1981**, 1

(75) Kaulen, J. *Angew. Chem. Int. Ed. Eng.* **1987**, *26*, 773.

(76) The classical method of tosylation was not very useful in this case. Even after several days at low temperature, the yield of the tosylate (203) were not more than 40 -50 %. On the other hand use

of tosylimidazole was a marked improvement. Thus the conversion of (200) to (203) was carried out in presence of 1.5 eq. of NaH and about 2 eq. of tosylimidazole in DMF at 0 -5^o C for about 24 hrs. The isolated yield of the tosylate was about 90%. In general, tosylimidazole - NaH combination has proven very useful for tosylation of some very hindered alcohols.(Chapter 6). Fraser-Reid, B. and Hicks, D.R. *Synthesis* 1974, 203. Similar reactions have been used for the preparation of benzoyl esters, without NaH. In our hands both benzoylation and tosylation are best carried out in presence of NaH.for benzoyl ester formation reaction the procedure used for the formation of tosylates was more useful. Hodgson, K. and Carey, F.A. *Carbo. Res.* 1970(12), 463.

(77) Barreiro, E.; Luche, J.L.; Zweig, J. and Crabbe, P. *Tet. Lett.* 1975, (28), 2353.

(78) [i] Olah, G.A.; Narang, S.C.; Gupta, B.G.B. and Malhotra, R. *J. Org. Chem.* 1979, 44, 1247. [ii] Sakurai, H.; Okamoto, Y. and Morita, T. *J. Chem. Soc. Chem. Comm.* 1978, 874. It may be argued that use of more 'exotic' demethylating agents might have solved the problem. There were at least two good reasons for not venturing into that direction. In the case relevant for synthetic purposes it would be required that the substituent on the nitrogen atom be p-methoxyphenyl group; demethylating agents are likely to convert arylmethyl ethers into their corresponding phenol analogs while leaving the alkylmethyl ethers relatively unscathed. Thus a demethylation based approach would require a significant change in terms of the substituent on the nitrogen atom. Secondly, even if such a change were to be carried out it will not guarantee the success of

demethylation step for either the starting material or for the hydroxyethyl compound. The problem is essentially one of steric inaccessibility of the methyl group in question. BBr_3 for demethylation Willard, P.G. and Fryhle, C.B. *Tet. Lett.* 1980, 21, 3731. These authors prefer a stabilized form of this reagent. BCl_3 for demethylation is exemplified by Carvalho, C.F. and Sargent, M.V. *J. Chem. Soc. Chem. Comm.* 1984, 227.

(79) The procedure followed was the one suggested by Vedejs and Larsen, *Org. Syn. Vol 64*, 127. (Ed. Kende, A.S.)

(80) The detailed procedure furnished by Moriarty, Hou, Prakash and Arora in *Org. Syn. Vol. 64*, 138. was followed.

(81) The procedure of Rubottom, Gruber, Juve and Charleson was followed with a minor variation; instead of using triethylamine-hydrogen fluoride salt for desilylation, tetra-n-butylammonium fluoride was used. *Org. Syn. Vol. 64*, 118. Recovery of the starting material seems to suggest that the problem was not with the desilylation step. In this case as well as in the case where MoOPH was used, perhaps the problem lies in the reaction of the enolate with electrophiles.

Experimental Section

General

For handling of various air and moisture sensitive reagents the directions provided in Brown, H.C. 'Organic Synthesis via Boranes' John Wiley & Sons Inc.: New York, 1975 were followed. However the nitrogen gas used for the inert environment was not dried. n-BuLi was titrated at 0°C according to the method described by Kofran, W.G. and Baclawski, L.M. *J. Org. Chem.* 1976, 41, 1879. Acetaldehyde was distilled prior to use according to the directions provided in Fieser and Fieser¹⁴². Ethyl chloroformate was distilled in an inert environment prior to use. Commercial N,N-diethylethylenediamine was used as such. Anhydrous sodium acetate used in the oxidations was fused and kept molten for several minutes, was allowed to solidify, crushed and kept in a tightly stoppered bottle. PCC was obtained from Aldrich Chemical Company and was used as such. Commercial 4A^o molecular sieves were crushed to a fine powder and heated under vacuum for 30-40 min and then maintained under an atmosphere of nitrogen. Commercial L-Selectride and L-Superhydride (Aldrich) were used as such. Bromine and cesium acetate were commercial grade. Purification of other solvents and reagents has been mentioned elsewhere. Various alkoxy azetidiones used in these studies were prepared by the ketene-imine reaction mentioned in Chapter 8.

General comments mentioned at the beginning of the experimental section of Chapter 2 also apply here.

Synthesis of N-(p-methoxy)phenyl-3-ethyl-3-methoxy-4-(2-phenyl)propenylazidin-2-one (192, Fig. XXXII)

Azetidinone (191, Fig. XXXII) (0.618 g 2 mmol) was dissolved in about 125 mL of dry THF in a 250 mL dry round bottomed flask equipped with a magnetic stirring bar. The yellow solution was cooled to -78°C (acetone-Dry Ice bath) under nitrogen. To the vigorously stirred solution was added with the help of a cannula 1.15 equivalents of LDA (prepared by reaction of 1.15 equivalents of *n*-BuLi and 1.32 equivalents of dry diisopropylamine in THF at -78°C). This led to considerable darkening of the color of the solution. After additional stirring for 15 min at this temperature, 0.5 mL of iodoethane (ca. 11 mmol) was added via syringe. This did not lead to any noticeable change in the color. The reaction mixture was stirred at -78°C for an additional 1 h and then was allowed to rise to room temperature over a period of about 3 h. Work up consisted of addition of 100 mL of 10% HCl to the reaction mixture and extraction with 3X50 mL of ethyl acetate. The combined organic layer was washed with saturated NaCl solution and was dried etc. to furnish a yellow solid. TLC revealed the presence of the starting material and a new less polar compound. Column chromatography using 3:1: hexane : ethyl acetate furnished the product as a yellowish solid. Trituration with ether served to remove the color. The yield of the azetidinone (192, Fig. XXXII) was 0.572 g (1.7 mmol) which amounts to 85%. The physical properties of this compound are as follows: mp: $107-108^{\circ}\text{C}$; ir: 1750 cm^{-1} ; ms: 337 (M^+ , 5.3%), 238 (imine⁺⁺, 46%), 237 (imine⁺, 93.9%), 236 (imine⁻, 100%); nmr: $\delta = 7.4$ (m, 7 H), 6.8 (m, 3 H), 6.4 (dd, 2 H, $J = 8.3\text{ Hz}$, $J = 16.0\text{ Hz}$), 4.4 (dd,

1 H, J= 0.7 Hz, J= 8.3 Hz), 3.7 (s, 3 H), 3.5 (s, 3 H), 2.1-2.0 (two m, 2 H), 1.0 (apparent d, 3 H, J=7.4 Hz). HRMS calcd for C₂₁H₂₃NO₃ 337.1676, observed 337.1669.

The azetidinone (190, Fig, XXXII) was prepared by this procedure in 95% yield. This azetidinone has following physical properties: mp: 116-117°C; ir: 1755 cm⁻¹; ms: 297 (M⁺, 10%), 211 (imine⁺, 100%), 196 (M⁺-101, 31.3%), 148(M⁺-149, 71%); nmr: d= 7.4 (m, 7 H), 7.1 (m, 2 H), 5.0 (s, 1 H), 3.6 (s, 3 H), 3.1 (s, 3 H), 1.7 (s, 3 H). HRMS calcd for C₁₈H₁₉NO₃ 297.1365, observed 297.1363.

Synthesis of N-(p-methoxy)phenyl-3-carboethoxy-3-methoxy-4(2-phenyl)propenyl-azetidin-2-one.

In a 250 mL dry round bottomed flask containing a magnetic stirring bar 0.618 (2 mmol) of the azetidinone (191, Fig. XXXII) was dissolved in about 130 mL of dry THF. The clear yellow solution was cooled to -78°C (acetone-Dry Ice bath) under nitrogen. Addition of 1.15 equivalents of LDA to the vigorously stirring solution led to the darkening of the color. This was allowed to stir at this temperature. (Flask I).

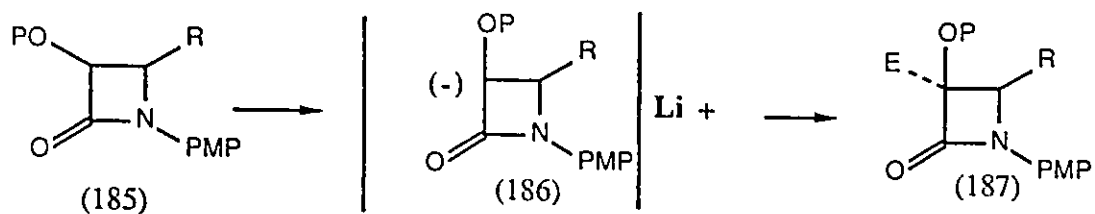
Freshly distilled ethyl chloroformate 1 ml (10.4 mmol) was dissolved in about 50 mL of dry THF in a dry 500 mL round bottomed flask equipped with a magnetic stirring bar.(Flask II)..The chloroformate solution was cooled to -78°C under nitrogen and was kept vigorously stirring at this temperature as the solution from Flask I was added to it with a cannula over a period of about 1-2 min. The resulting colorless homogeneous solution was stirred for another 5 min at the same temperature. At the end of this period the septum

was removed, and 2-3 mL of N,N-diethylethylenediamine were added in one portion. The resulting heterogeneous reaction mixture was brought to room temperature over a period of about 15 min. Work up consisted of addition of 100 mL of 10% HCl solution and extraction with 3X75 mL ethyl acetate. The combined organic layer was washed with 100 mL of saturated NaCl solution and was dried etc to furnish 0.77 g of a yellow oil which revealed the absence of the starting material. This was loaded on a small silica column and was eluted with 4:1: hexane : ethyl acetate to ultimately furnish 0.755 g (1.9 mmol) which amounts to 95% yield. The product azetidinone is a mobile yellow oil with the following properties: ir: 1750 cm^{-1} ; ms: 381 (M^+ , 7.8%), 350 (M^+-31 , 4.4%), 237 (imine⁺, 49%), 236 (imine⁺-1, 100%), 232 (M^+-149 , 61%); nmr: δ = 7.4 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 2 H, J= 8.7 Hz, J= 16.0 Hz), 4.9 (dd, 2 H, J= 8.7 Hz, J= 0.7 Hz), 4.3 (q, 1 H, J= 6.7 Hz), 3.75 (s, 3 H), 3.69 (s, 3 H), 1.3 (t, 3 H, J= 6.7). Since 381 is a reference peak, it was not possible to obtain HRMS for this compound,

The procedure mentioned above for preparation of the ethylazetidinone (192, Fig. XXXII) has served for the direct quench of azetidinone anions with electrophiles. For the inverse addition of anion to electrophile the procedure mentioned for the preparation of the carboethoxyazetidinone (193, Fig. XXXII) was used.

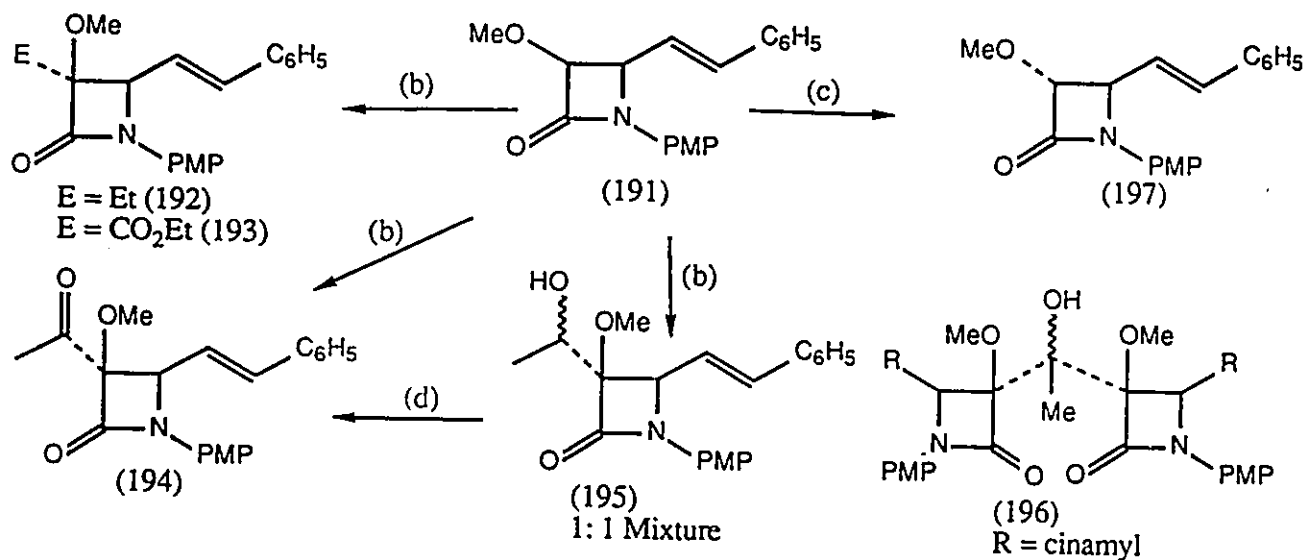
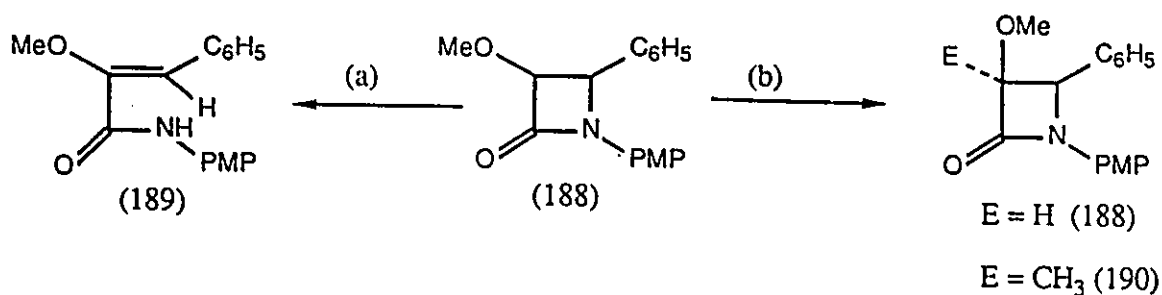
The reaction of the azetidinone (191, Fig. XXXII) with acetaldehyde was done in the manner specified for the direct addition reaction with the difference that a marked fading of the color was observed when acetaldehyde was added to the solution of the anion and thus the reaction mixture was not allowed to come to

Fig. XXXII



R = phenyl, cinnamyl, 2-furyl
methylcinnamyl.

P = various alkyl group.



(a) azetidinone, THF, -78 °C, slow warm up.

(b) azetidinone, THF, -78 °C, various electrophiles, direct or inverse quench.

(c) azetidinone, THF, -78 °C, inverse addition to acetylimidazole.

(d) PCC, methylene chloride, sodium acetate, 4 A° (191) → (195) and (195) → (194) is true regardless of substituents.

room temperature. In this case a yellow foam was obtained which showed absence of starting material and presence of two non-polar and one(!) polar compound by TLC. The non-polar compounds were not identified. The polar compound was obtained 'pure' by column chromatography using 2:1: hexane : ethyl acetate as the eluting solvent. Starting from 2 mmol of the azetidinone(191, XXXII) 0.564 g (1.6 mmol) of (195, Fig. XXXII) was obtained as a yellow foam. (80% yield).

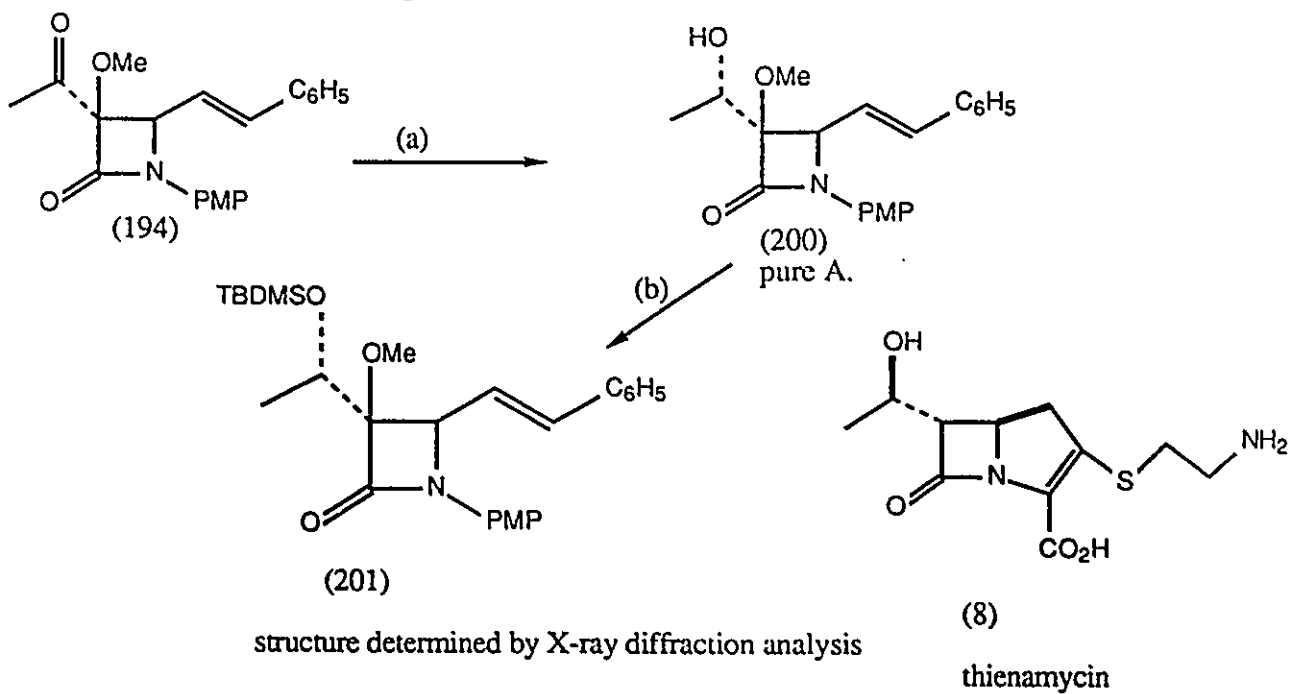
On the basis of appearance of two set of signals for the proton at 4 position of the azetidinone ring (2 dd, 1st set 4.8 ppm, J= 0.6 Hz, J= 8.6 Hz 2nd set 4.7 ppm, J = 0.8 Hz, J= 7.8 Hz); presence of two signals for the methyl group of the methoxy moiety at 3 (3.67 and 3.64 ppm) position and the appearance of a distorted triplet for the methyl group of the hydroxyethyl moiety(1.33 ppm) in the high field (300MHz) proton nmr spectrum of this foam, it was concluded that it was a mixture of two hydroxyethyl compounds. Other signals were not well resolved. The diastereoisomer with C-4 proton appearing at 4.7 ppm was designated as isomer A. The diastereoisomer with C-4 proton appearing at 4.8 ppm was designated as isomer B. The ratio A:B was 2 : 1. The mass psectrum of this mixture had peaks at 353 (M⁺, 21.4%), 309 (M⁺-44, 25.6%), 237 (imine⁺, 99.7%), 236 (imine⁺-1,99.7%), 204 (M⁺-149, 29.9%), 149 (C₈H₇NO₂⁺ 27.5%), 84(M⁺-269, 100%). Infrared spectrum showed peaks at 3300-3200 and 1755 cm⁻¹.

Oxidation of (195) to (194)

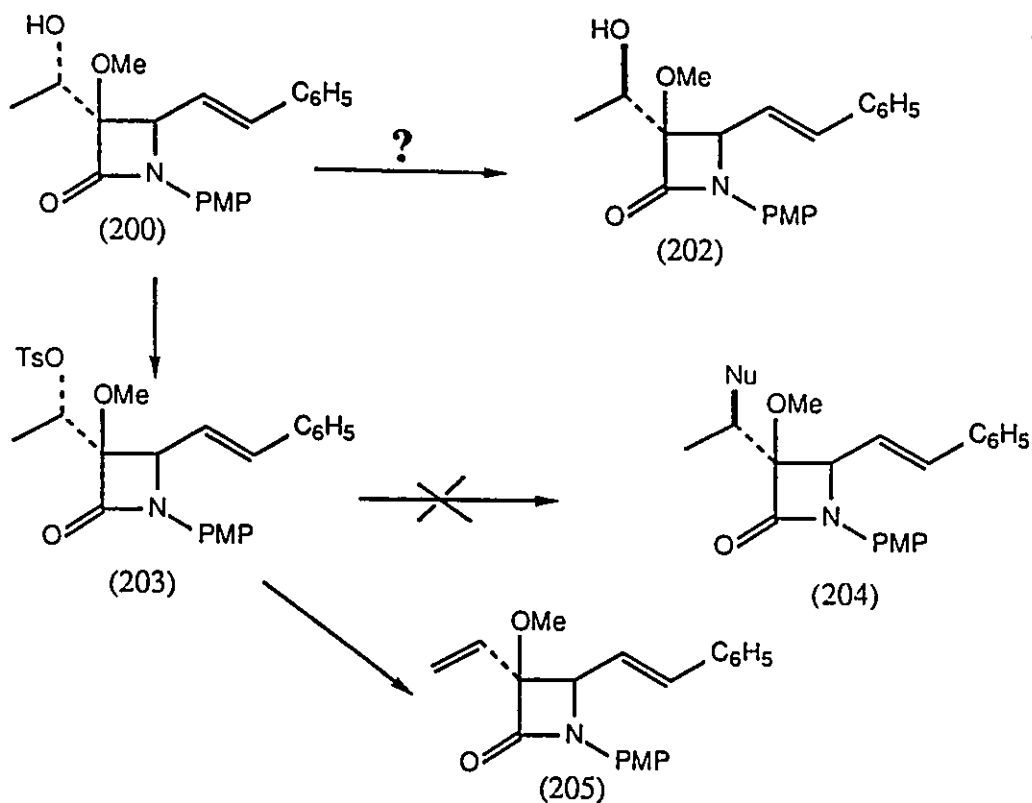
To a solution of 1.059 g (3 mmol) of the mixture of the hydroxyethyl compounds (195) in 10 mL of dry dichloromethane

was added 1 g of powdered fused sodium acetate. The reaction mixture was stirred vigorously as 3 g (13.9 mmol) of PCC was added in 4 equal portions over a period of about 10 min. This led to development of black color and deposition of a tarry residue. The reaction mixture was stirred overnight. TLC at this stage indicated the presence of the starting material and a less polar compound. Another 2 g (ca. 1 mmol) of PCC was added and the reaction mixture was stirred for an additional 2 h. At this stage TLC revealed the absence of starting material. About 50 mL of ether was added to the reaction mixture and the stirring was continued for an additional 15 min. The solvent was decanted and the tarry residue in the flask was washed with 2X50 mL ether. The combined organic layer was filtered through Celite. Removal of the solvent and column chromatography using 3: 1: hexane: ethyl acetate as the eluting solvent furnished 0.884 g (2.5 mmol, 84% yield) of the acetyl compound as a white solid. This compound has following physical properties: mp: 81-82°C (softening at 78-79°C); ir: 1750, 1720 cm^{-1} ; ms: 351 (M^+ , 10.3%), 308 (M^+-43 , 7.4%), 237 (imine⁺, 3.9%), 201 (M^+-149 , 7%), 43($\text{C}_2\text{H}_3\text{O}^+$, 100%); nmr: δ = 7.4-7.2 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J = 7.4 Hz, J = 16.0 Hz), 5.1 (dd, 1 H, J = 0.7 Hz, J = 7.4 Hz), 3.7 (s, 3 H), 3.5 (s, 3 H), 2.4 (s, 3 H). HRMS calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_4$ 351.1468, found 351.1428. The acetyl compound (194, Fig. XXXII) was also prepared by the inverse addition method that was used for the synthesis of the azetidinone (193, Fig. XXXII) with the difference that addition of the diamine was omitted and the work up consisted of washing the organic layer with 2X50 mL of 5% NaHCO_3 in addition to the regular HCl wash. The pure compound was

Fig. XXXIV



(a) L-Selectride, THF, 2.5 eq. TMEDA, -78 °C, 2 hrs.
 (b) TBDMS-triflate, 2,6-lutidine, methylene chloride.



obtained as a solid in about 60% yield after column chromatography using 3:1 : hexane : ethyl acetate as the eluting solvent. The yield of the compound prepared in this way was 60% and it was identical in all regards with the compound prepared by oxidation of the mixture of the hydroxyethyl compound.

Selectride-TMEDA reduction of the acetyl compound(194) To a 50 mL dry round bottomed flask equipped with a stirring bar was added 0.117 g (0.33 mmol) of the acetyl compound and 10 mL of dry THF. The clear solution was cooled to -78°C (acetone-Dry Ice bath) under nitrogen and 0.12 mL (0.88 mmol) of dry TMEDA was added. To the clear solution was added 0.36 mL of a 1M solution of L-Selectride in THF (3.6 mmol). The clear solution was stirred at -78°C for 1 h. Work up consisted of addition of 10 mL of 10% HCl solution, saturation of the aqueous layer with NaCl and extraction with 3X30 mL of ethyl acetate. The combined organic layer was washed with saturated NaCl and was dried over MgSO₄. Filtration to remove the drying agent and removal of the solvent from the filtrate furnished a yellow foam. TLC indicated the presence of the starting material and two other non polar compounds in addition to the hydroxyethylazetidinone(s). Column chromatography using 2 : 1 : hexane : ethyl acetate as the eluting solvent led to isolation of 0.005 g of a compound which had R_f identical to that of the starting material and 0.055 g (0.15 mmol, 45% yield) of the product as a white foam. The high field (300MHz) proton NMR spectrum consisted of the following signals: δ = 7.4-7.2 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J = 7.8 Hz, J = 16.0 Hz), 4.7 (dd, 1 H, J = 0.9, J = 8.0 Hz), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.67 (s, 3 H), 1.340-1.319

(d, 3 H, $J = 6.5$ Hz). HRMS calcd for $C_{21}H_{23}NO_4$ 353.1626, observed 353.1630. On this basis this compound was judged to be diastereomerically pure isomer A. Infra red and mass spectra of this compound were similar to those of the mixture of the diastereoisomers.

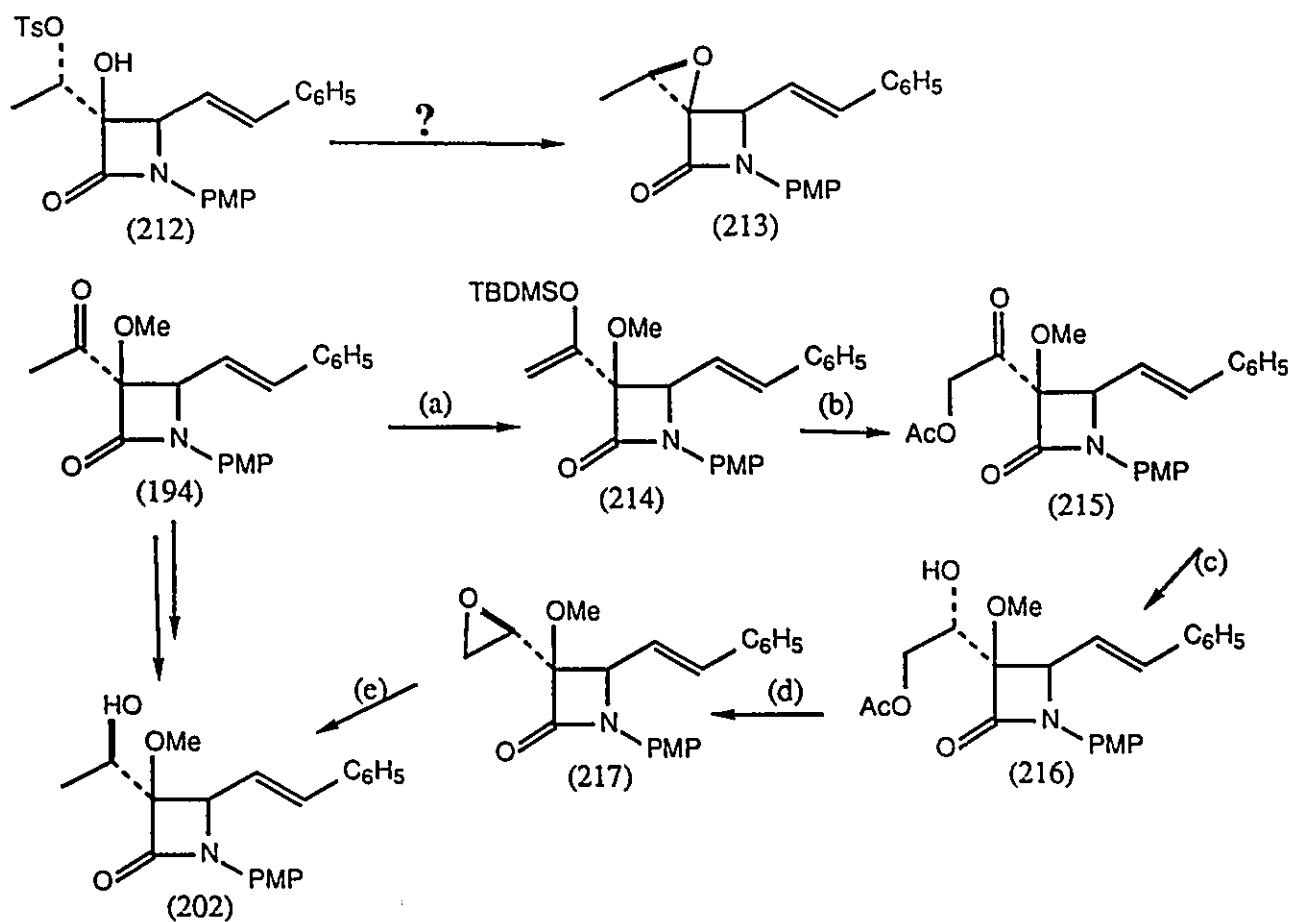
The above procedure has been carried out on preparative scale with the difference that the Selectride solution was added from a pressure equalizing dropping funnel over a period of several minutes. The same procedure has been used for the reduction of a variety of acetyl and acylazetidiones (Chapter 7).

Preparation of the TBDMS derivative of the hydroxyethyl compound was carried out in the standard manner. The product (201, Fig. XXXIV) was purified by column chromatography using 5 : 1: hexane : ethyl acetate in order to remove some polar impurities. The yield of the product, a white solid, was 89-95%. The product has following physical properties: mp: 100-101°C (may require several hours for solidification!); ir: 1750 cm^{-1} ; ms: 467 (M^+ , 4.5%), 436 ($M^+ - 31$, 2.8%), 237 (imine⁺, 94.4%), 236 (imine⁺ - 1, 100%); nmr: $\delta = 7.4-7.2$ (m, 7 H), 6.8 (m, 3 H), 6.2 (dd, 1 H, $J = 7.8$ Hz, $J = 16.0$ Hz), 4.7 (dd, 1 H, $J = 0.9$ Hz, $J = 7.8$ Hz), 4.1 (q, 1 H, $J = 6.3$ Hz), 3.7 (s, 3 H), 3.6 (s, 3 H), 1.3 (d, 3 H, $J = 6.3$ Hz), 0.7 (s, 9 H), 0.06 (s, 6 H). Crystals suitable for X-ray diffraction analysis were obtained from slow evaporation from a methylene chloride-hexane solution.

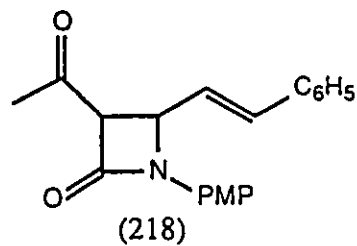
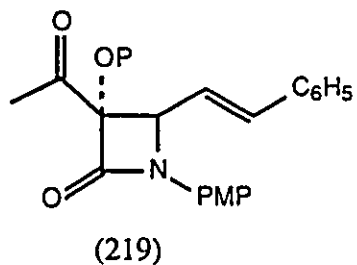
Preparation of the enol silyl ether(214, Fig. XXXVI)

To a 25 mL dry round bottomed flask was added 0.353 g (1 mmol) of the acetyl compound(195, Fig. XXXVI) and about 10 mL of dry dichloromethane. To this clear solution at room temperature was

Fig. XXXVI



- (a) TBDMS-triflate, 2,6-lutidine, methylene chloride, reflux, purify
 (b) [i] Bromine, methylene chloride, 0°C, [ii] DMF, Cesium acetate ca. 10 eq.
 (c) L-Selectride, TMEDA, THF, -78°C
 (d) [i] Tosyl imidazole, DMF, [ii] Sodium methoxide, Methanol, THF.
 (e) L-Superhydride, THF, 2-5°C. ca. 15% overall yield from (194).



added 0.23 mL (2 mmol) of 2,6-lutidine and 0.32 mL (1.5 mmol) of TBDMS-Triflate. The clear homogeneous solution was heated under reflux for 3 h under nitrogen. TLC analysis at this stage revealed the absence of the starting material. The reaction mixture was allowed to come to room temperature and then the solvent was removed under reduced pressure. The resulting yellow oil was subjected to column chromatography using 5 : 1: hexane : ethyl acetate to furnish the enol silyl ether in 95% yield as a yellow semi-solid with following spectral properties: ir: 1745 cm^{-1} ; ms: 465 (M^+ , 6.3%), 434 (M^+-31 , 3.2%), 408 (M^+-57 , 40.5%), 237 (imine⁺, 89%), 236 (imine⁺-1, 100%); nmr: δ = 7.3-7.1 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J = 8.2 Hz, J = 16.0 Hz), 4.6 (d, 1 H, J = 1.9 Hz), 4.3 (d, 1 H, J = 1.9 Hz), 4.0 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 0.8 (s, 9 H), 0.0(-)0.15 (series of singlets). This compound has only moderate stability and reverts to the acetylacetidinone (194) over a period of 2-3 days at room temperature.

Synthesis of (215) from (214, Fig. XXXVI)

A solution of the enol silyl ether (214), 0.93 g (2 mmol) in 25 mL of dry dichloromethane under nitrogen was cooled to 0°C under nitrogen. To this vigorously stirred solution was added a solution of 0.33 g (2.1 mmol) of bromine in 10 mL of dry dichloromethane. The addition was complete the colorless reaction mixture was brought to room temperature over a period of about 5 min and the solvent was removed. The resulting yellow foam was dissolved in 10 mL of dry DMF and 1.5 g (7.8 mmol) of powdered cesium acetate was added in one portion. The resulting heterogeneous reaction mixture was stirred at room temperature for 18 h. The reaction

mixture was worked up by addition of 10 mL of water and extraction with 5X50 mL of ether. The combined organic layer was washed with saturated NaCl solution and was processed in the usual manner to furnish a yellow oil. This oil contained the desired acetoxy compound as revealed by TLC. Purification by column chromatography using 5 : 1 : hexane : ethyl acetate as eluting solvent furnished 0.523 g (1.3 mmol,) of the acetoxyacetylazetidinone (215, Fig. XXXVI) as a yellow oil. This amounts to an overall yield of 65% for two steps. This product was identical in all regard with a sample prepared by reaction of the anion of the azetidinone (191, XXXII) with acetoxyacetyl chloride by inverse addition procedure. This compound has same R_f as starting material! The spectral properties of this compound are as follows: ir: 1750, 1740 cm^{-1} ; ms: 409 (M^+ , 5.3%), 308 (M^+-101 , 10%), 236 (imine $^{+}-1$, 54%), 43($C_2H_3CO^+100\%$); nmr: d = 7.4 (m, 7 H), 6.9 (m, 3 H), 6.3-6.2(dd, 1 H, $J= 8.2$ Hz, $J= 14.0$ Hz), 5.2 (d, 1 H, $J= 17.0$ Hz), 5.1 (d, 1 H, $J= 8.1$ Hz), 4.8 (d, 1 H, $J= 17.0$ Hz), 3.7 (s, 3 H), 3.6 (s, 3 H), 2.1 (s, 3 H).

The Selectride reduction of the above acetoxyacetyl compound was carried out in a manner similar to that used for the reduction of compound (194, Fig. XXXIV). The reaction proceeded in about 50% yield to furnish a yellow oil after column chromatography. This oil has following spectroscopic properties: ir: 3200, 1755, 1740 cm^{-1} ; ci-ms: 412 (M^{++1} , 1.8%), 160 (M^+-252 , 100%); nmr: d=7.4 (m, 7 H), 6.8 (m , 3 H), 6.3 (dd, 2 H, $J= 7.7$ Hz, $J= 16.1$ Hz), 4.8 (dd, 2 H, $J= 0.9$ Hz, $J= 7.8$ Hz), 4.3 (m, 2 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 2.1 (s, 3 H).

The synthesis of the tosyl derivative of this compound was carried out in the usual manner to furnish a yellow foam which

contained a multitude of compounds. Column chromatography and pooling of the fractions whose nmr spectrum was consistent with the desired (singlet about 2.3 ppm as noted in a 60 MHz nmr spectrum) product provided the desired product in about 70% yield. However attempts to obtain this tosylate in chromatographically homogeneous form failed. For this reason this compound could not be completely characterized. When subjected to 2.2 equivalents of sodium methoxide in a THF : methanol mixture at room temperature for 2 h, the tosylazetidinone provided the epoxide (217, Fig. XXXVI) as a yellow semi- solid. The latter was also chromatographically non-homogeneous and thus was not completely characterized. The yield of this epoxyazetidinone was about 80%. The conversion of the epoxide to the azetidinone (202, Fig. XXXVI) involved reaction with 1.5 equivalents of Superhydride in THF at 5-7°C for 48 h. The last step proceeded in about 50% yield after column chromatography using 2:1: hexane : ethyl acetate as the eluting solvent. The azetidinone (202, Fig. XXXVI) is a semi-solid with following properties: ir:3300, 1750 cm^{-1} ; nmr: d = 7.3-7.1 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J= 7.8 Hz, J= 16.0 Hz), 4.8 (dd, 1 H, J= 0.6, J= 7.8 Hz), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.64 (s, 3 H), 1.345-1.323 (d, 3 H, J= 6.4). The chemical shift for the methyl residue of the hydroxyethyl moiety has been mentioned in more details than other peaks. This is to emphasize the difference in the chemical shifts of this set of signals for two diastereoisomer. As mentioned previously in a mixture of diastereoisomers these set of signals are not well resolved.

The methylcinnamyl analog of the above compound was prepared in 85% yield by inverse addition of the corresponding anion

to 10 equivalents of acetoxyacetyl chloride at -78°C . This yellow oil has same R_f as the starting azetidinone and has following physical properties: ir: 1750, 1740 cm^{-1} ; ms: 423 (M^+ , 1.8%), 322 ($\text{M}^+-3.1\%$), 250 (imine $^{+1}$, 9.3%), 84 (M^+-339 , 100%); nmr: d = 7.4 (m, 7 H), 6.8 (dd, 2 H, $J= 2.2$ Hz, $J= 6.8$ Hz), 6.6 (s, 1 H), 5.3 (d, 1 H, $J= 7.9$ Hz), 4.9 (s, 1 H), 4.8 (d, 1 H, $J= 7.9$ Hz), 3.7 (s, 3 H), 2.1 (s, 3 H), 1.9 (d, 3 H, $J= 1.2$ Hz). In converting this compound to the corresponding tosylate and the epoxide problems similar to the case of the simple cinnamyl compound were encountered. The opening of the epoxide to the corresponding secondary alcohol involved reaction with Superhydride in THF at $5-7^{\circ}\text{C}$ for 48 h. The reaction proceeded in about 50% yield.

The properties of diastereoisomer A (a semi-solid prepared in about 50% yield by L-Selectride -TMEDA reduction of the acetyl compound) are as follows : ir: 3300-3200, 1750 cm^{-1} ; ms: 367(M^+ , 9.2%), 252(imine $^{+1}$, 51.7%), 250(imine $^{+1}$, 100%); nmr: d= 7.4-7.2 (m, 7 H), 6.8 (dd, 2 H, $J= 2.1$ Hz, $J= 6.8$ Hz), 6.4 (broad s, 1 H), 4.5 (s, 1 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 1.9 (d, 3 H, $J= 1.6$ Hz), 1.33 (d, 3 H, $J= 6.5$ Hz). Since 367 is a reference peak, it was not possible to obtain HRMS for this compound.

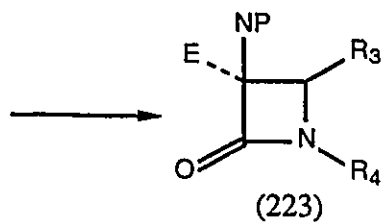
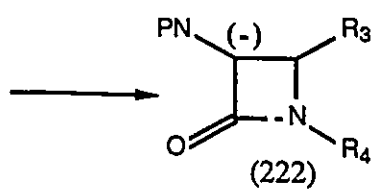
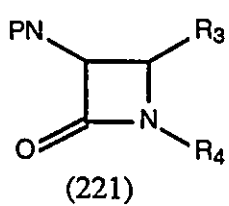
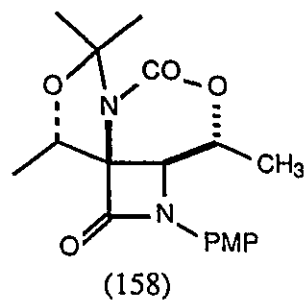
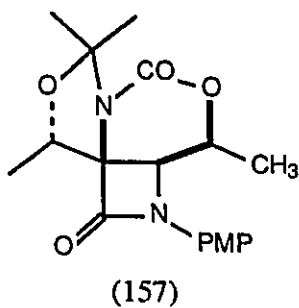
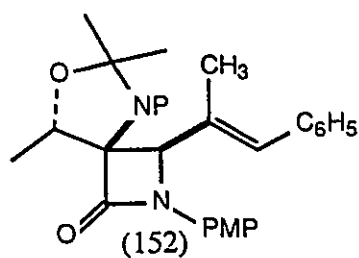
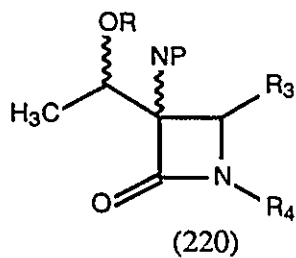
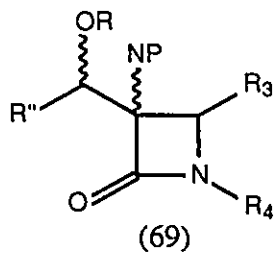
The diastereoisomer B (a semi-solid prepared via opening of the epoxide) has infra red and mass spectra very similar to that of the diastereoisomer A. The NMR spectrum of the diastereoisomer B has following signals: d= 7.4-7.2 (m, 7 H), 6.8 (dd, 2 H, $J= 2.0$ Hz, $J= 8.9$ Hz), 6.4 (broad s, 1 H), 4.6 (s, 1 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 1.9 (s, 3 H), 1.37 (d, 3 H, $J= 6.4$ Hz).

CHAPTER 5

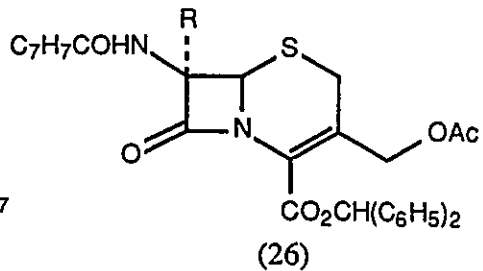
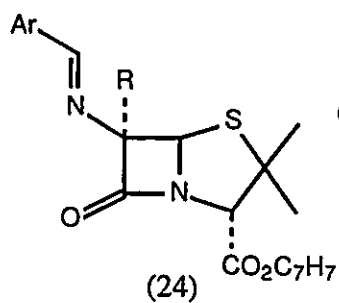
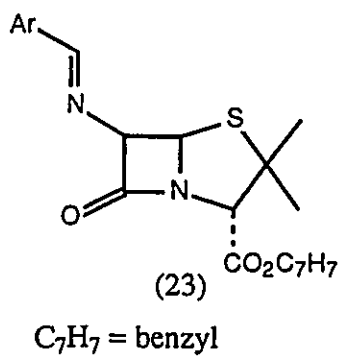
This chapter deals with synthesis of 3-amino-3-hydroxyethyl compounds such as (69 and 220, Fig.XXXVII). The studies presented here involved formation of the anion from azetidinones such as (221, Fig.XXXVII) and the subsequent reaction of these anions with suitable electrophiles. The idea was to provide a back up synthesis of azetidinones such as (69, Fig.XXXVII) since the approach to such compounds beginning with threonine has some limitations. Even though it was possible to obtain significant quantities of the azetidinone (152, Fig.XXXVII) its utilization in subsequent syntheses of bicyclic compounds is being made difficult by the fact that thus far the selective hydrolysis of the acetonide moiety of the cyclic carbamates (157 and 158, Fig.XXXVII) has not been achieved.

Formation of anions at position 6 in 6-aminopenems or at position 7 in 7-aminocephems is a well established procedure^{15,16}. The amino group is converted into the corresponding imine typically by reaction with an aromatic aldehyde. Deprotonation of such imines is usually very facile and both stereo and regioselective introduction of the electrophile at C-6 (or C-7) is the norm. Hydrolysis of the imine to the corresponding substituted aminoazetidinone completes the process. In certain cases hydrolysis is facilitated by acylation of the imine. Such a sequence of reaction has served as a basis of syntheses for several 3,3-disubstituted azetidinones, including methoxyphenicillins, methoxycephalosporins, alkyl and alkoxyalkyl azetidinones (23, 24 and 26, Fig. XXXVII; see also chapter 1).

Fig. XXXVII



P = a suitable protective group.

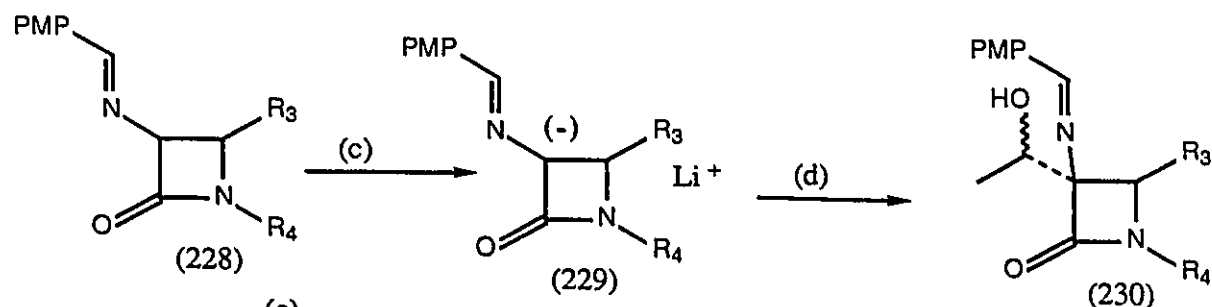
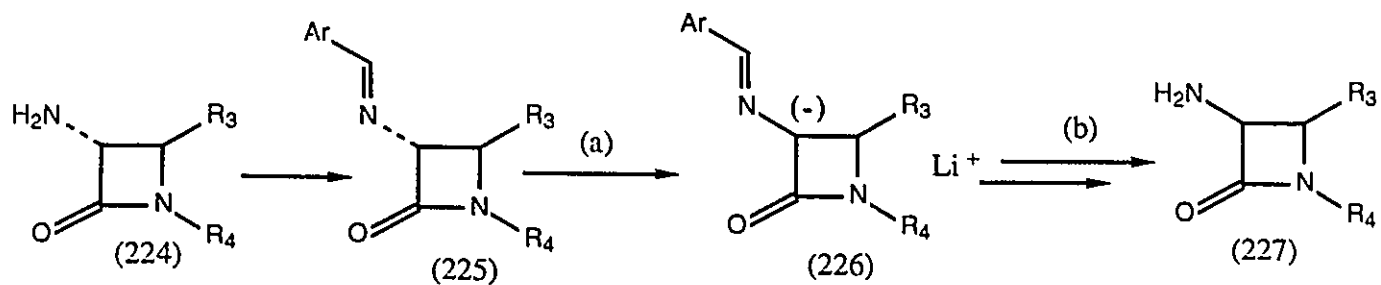


Additionally, the high stereoselectivity observed in the reaction of such anions with electrophiles has served as a means of epimerising trans aminoazetidinones (224, Fig.XXXVIII) to the corresponding cis compounds.(227, Fig.XXXVIII)⁸³.

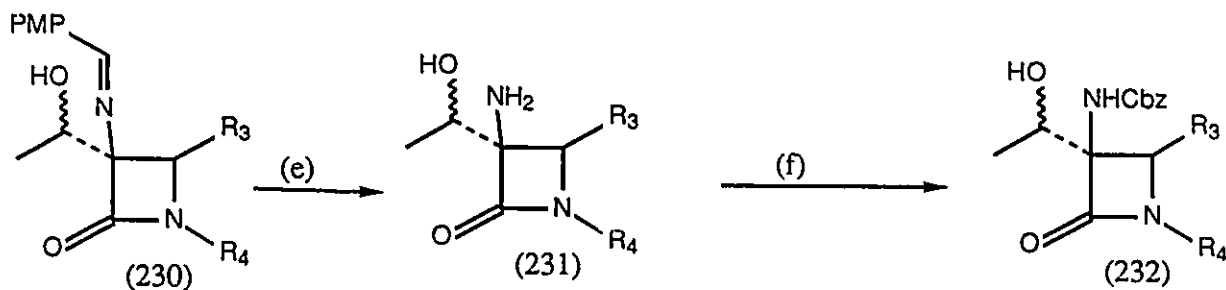
Thus it was tempting to use such methodology to synthesize the azetidinones such as (232, Fig. XXXVIII). On the basis of above results it was anticipated that the incoming electrophile would be trans to the existing substituent at C-4. As before the stereochemistry of the side-chain carbon bearing the hydroxyethyl group was unlikely to be generated selectively in the condensation step.

The formation of anion from the imino compounds appeared to be very quick as indicated by the immediate development of a deep red color when these compounds were added to a solution of LDA in THF at -78°C (229, Fig.XXXVIII). Subsequent reaction with acetic acid regenerated the cis starting material at least in the case examined. Under the same conditions, reaction with acetaldehyde furnished a multitude of compounds. However it appeared on the basis of the a 300 MHz proton spectrum of the crude product that the mixture of the isomeric hydroxyethyl imines (230, Fig.XXXVIII) constituted the bulk of the material. Removal of the impurities by column chromatography was not very successful since the product imines seem to decompose on silica gel. The extent of decomposition might not have been extensive, but it made the purification process by silica gel chromatography very difficult for both the starting imines (228, Fig.XXXVIII) and the hydroxyethyl imines.

Fig. XXXVIII



R₃ = Phenyl



For (228) -- (232) R₃ = furyl, phenyl or cinnamyl R₄ = PMP

(a) PhLi, THF or DME etc. -78 °C.

(b) H⁺

(c) LDA, THF, -78 °C

(d) acetaldehyde

(e) HCl, >2.2 eq. THF - H₂O, 0 -> R.T. ca.1-2 h.

(f) excess Cbz-Cl (10 eq.), THF -H₂O saturated with Na₂CO₃, R.T., 15 - 20 h.

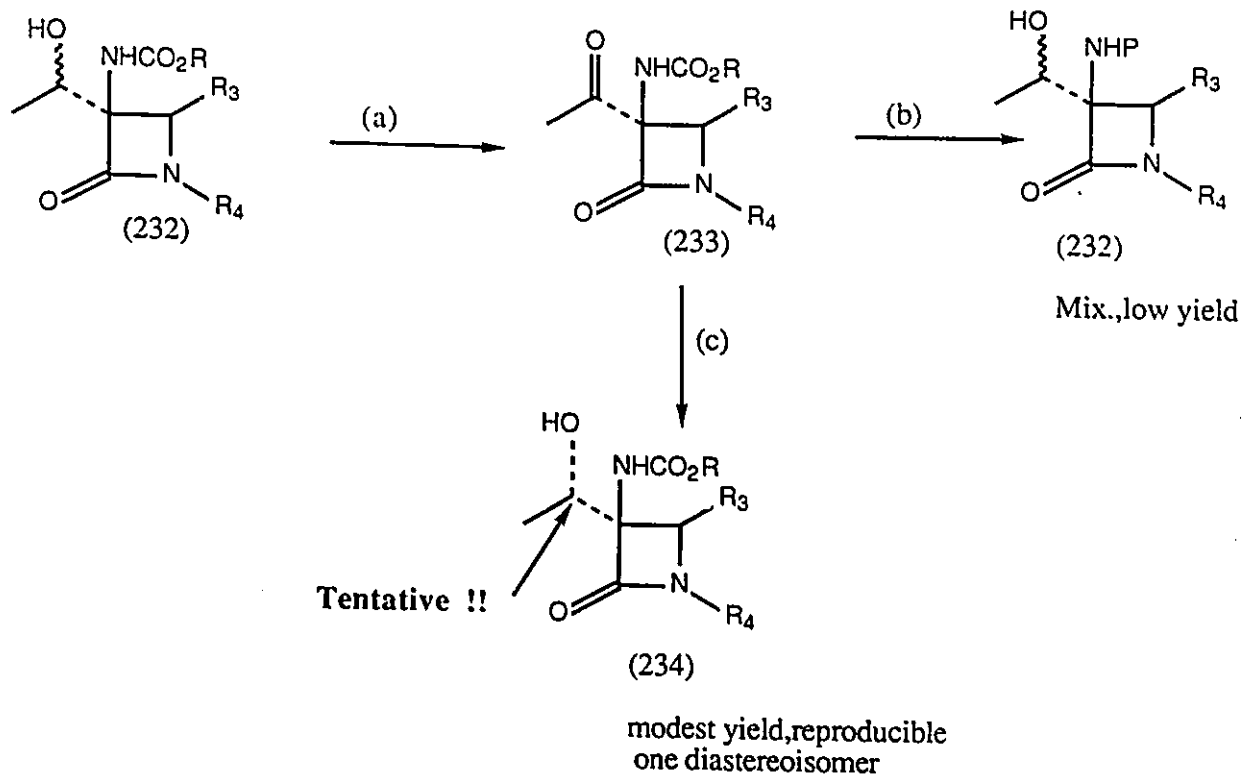
15 - 25 % yield from (230).

With a view to obtaining suitably protected azetidinones, which could later be converted to any of the desired acylated compounds, the hydrolysis of the substituted imine was carried out in absence of such acylating agents⁸⁴. However, it was not possible to isolate the resulting free amino compounds (231, Fig. XXXVIII) since they appear to have rather poor solubility in organic solvents.

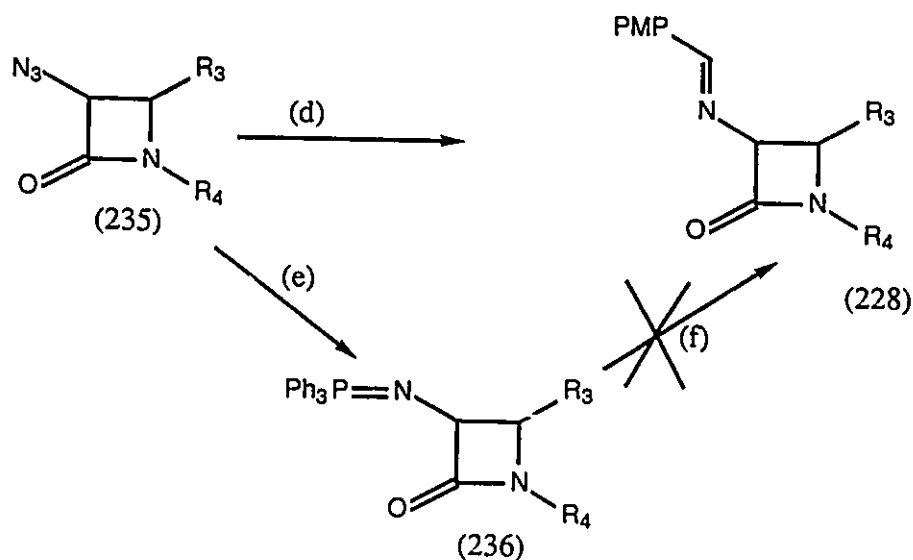
To make the task of isolation of the hydroxyethylazetidinones easier and to keep the option of acylation open, it was decided that the amino compound should be converted to the corresponding carbamate⁸⁵. By using a very large excess of benzyl chloroformate and potassium carbonate, it was possible to isolate the mixture of hydroxyethyl compounds (232, Fig. XXXVIII) in modest (25-30%) yields. Not unexpectedly, the NMR spectrum of isolated hydroxyethyl carbamates indicated presence of two compounds in nearly 1:1 proportion. As before, it appeared unlikely that a change in the reaction conditions would lead to increase in the diastereoselectivity. Thus it seemed more sensible that a scheme involving oxidation-reduction sequence should be undertaken to obtain one hydroxyethylazetidinone, as in the case of 3-methoxy-3-hydroxyethylazetidinones.

PCC oxidation of the crude mixtures of the protected hydroxyethylcarbamates and benzyl chloroformate did not provide the acetyl carbamates (233, Fig. XII) reproducibly. It was necessary to remove the unreacted benzyl chloroformate prior to carrying out the oxidation⁸⁶. Thus a rather difficult purification became very necessary. The oxidation of the purified hydroxyethyl carbamates to the corresponding acetyl compound (232 to 233, Fig. XII) was

Fig. XII



- (a) PCC, 4 Å molecular sieves, methylene chloride. ca. 60% yield from (232)
 (b) 1.1 eq. L-Selectride, 2.2 eq. TMEDA, THF, -78 °C. ca. 25% yield, !
 (c) 2.2 eq. L-Selectride, 4.4 eq. TMEDA, THF, -78 °C ca. 50 -- 60% yield regardless of R, R₃ and R₄



- (d) [i] H₂S, TEA, methylene chloride, [ii] p-anisaldehyde, MgSO₄, R.T. 15-18 h ca. 50% yield
 (e) Ph₃P, THF, reflux, 16-17 h.
 (f) p-anisaldehyde, THF, reflux, 6 -- 7 h.

trouble-free affording the product in about 60-70% yield. The formation of only one acetyl compound confirmed that the two hydroxyethylazetidiones differed only in the configuration of the hydroxyethyl group⁸⁷.

Reduction of the acetyl compound (233, Fig. XIL) under USUAL non-chelating conditions (i.e. 2.5 eq. TMEDA, THF, 1.1 eq. L-Selectride, -78 ° C) was disappointing. The product (232, since it was a mixture!, Fig. XIL) was obtained in only 25% yield. The diastereoselectivity in the reduction step was a disappointing 3:1. It was found that use of at least 2 eq. of L-Selectride and at least 4 eq. of TMEDA served to provide the product in higher yield (ca. 50-60%) and higher diastereoselectivity (234, Fig.XIL) (see below). Above all, reduction conducted in this manner was consistent in terms of the yield and the observed diastereoselectivity.

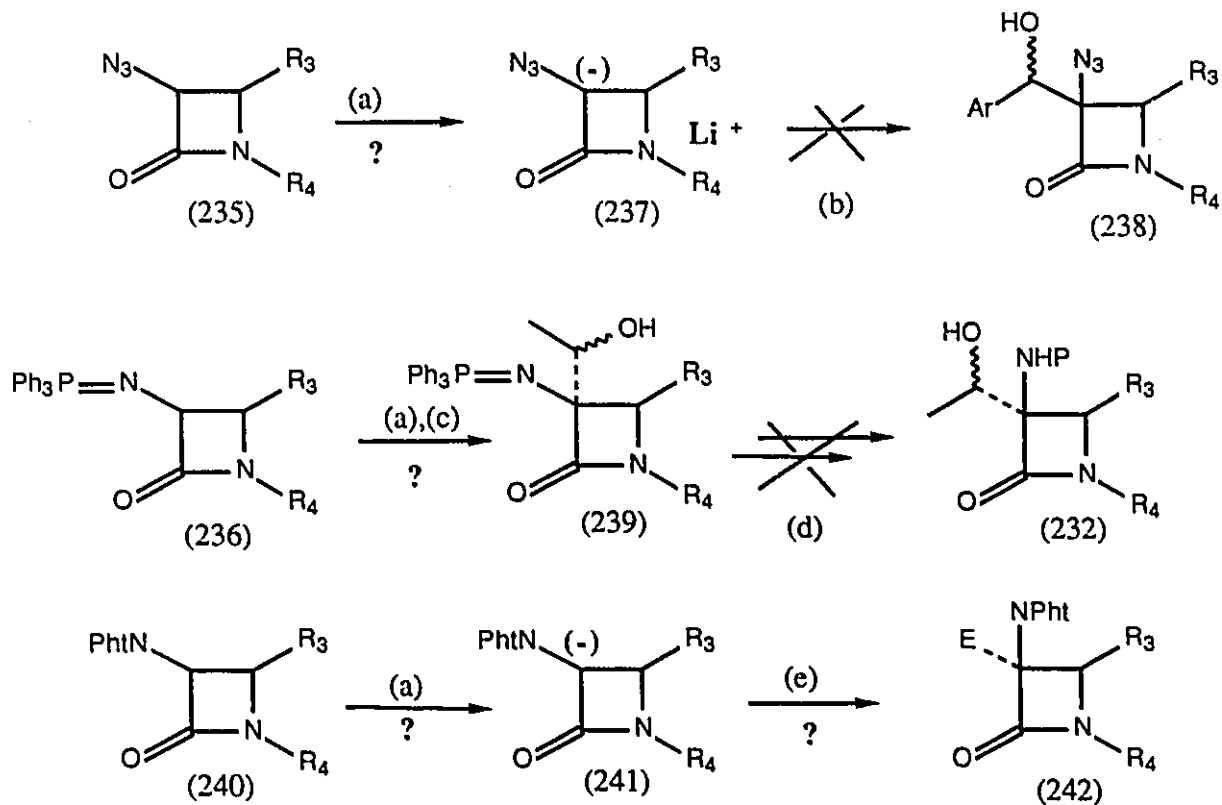
Significant as these early results were , they left a lot to be desired. The aminoazetidiones used as the starting materials were obtained by the reduction of the corresponding azidoazetidiones (235, Fig XIL). This required that large quantities of azidoacetic acid be handled early in the sequence. The conversion of the azido group to the corresponding amino group was carried out by hydrogen sulfide since the reduction using triphenylphosphine was troublesome.⁸⁸ While the reaction of the azidoazetidione with the phosphine appeared slow but trouble-free, attempts to obtain the free amino compound from the aza-ylide (236, Fig,XIL) provided only 5-10% of impure amine. Attempted direct conversion of the aza-ylide to the corresponding imine by reaction with p-anisaldehyde (236 - 228, Fig. XIL) was unsuccessful. Even by TLC, no

product imine could be detected. The reasons for this very frustrating experience are not clear. To make matters worse, the overall yield of the hydroxyethylazetidinones (234, Fig.XIL) from azidoazetidinones (235, Fig.XIL) were very low. Despite several attempts not even a gram of any of the hydroxyethylazetidinone (234) could be obtained. Considering the fact that these are supposed to be starting materials for a reasonably long sequence of reactions, it was very important that an alternative scheme be devised.

Attempted use of the aza-ylides (236, Fig. XIL) directly in the anion formation step were not successful. Neither the addition of LDA to a solution of the ylide in THF at -78°C nor the subsequent addition of acetaldehyde after 1 hr. at the same temperature led to any observable change. However the subsequent hydrolysis and protection step did not lead to any protected hydroxyethyl compound (236, 239 and 232, Fig.XL). Since it was not possible to purify and characterize the alleged hydroxyethyl-aza-ylides,(239, Fig.XL) it is difficult to determine which step did not work.

It was expected that the azidoazetidinones (235, Fig.XL) could be converted to the corresponding carbanion (237, Fig. XL). This might make subsequent steps much easier in terms of handling of the products. Exposure of the azetidinone to LDA at -78°C led to generation of deep red color. Addition of electrophiles did not lead to any observable change. The gum obtained on working up the reaction did not show presence of starting material and was devoid of an azido group as determined by infra red spectrum. This behavior is not restricted to the azidoazetidinones since other

Fig. XL



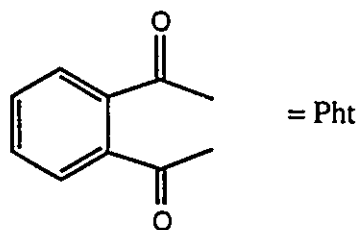
(a) LDA, THF, -78 °C, ca. 1 hr.

(b) m-tolualdehyde. Other electrophiles also used and gave results similar to ArCHO.

(c) acetaldehyde, -78 °C.

(d) [i] acidic hydrolysis, [ii] CbzCl, THF - H₂O, Na₂CO₃

(e) various electrophiles, including acetaldehyde, MeI etc..



α -azido-carbonyl compounds such as t-butylazidoacetate gave similar results⁸⁹. Exposure of the azetidinone (240, Fig. XL) to LDA in THF at -78°C led to development of red colour and deposition of a tarry residue. Addition of either methyl iodide or m-tolualdehyde led to an intractable tar⁵⁵. The situation with other electrophiles was no better.

Since there were problems with the hydrolysis of hydroxyethylimines (230, Fig. XXXVIII) and carbamate formation steps, it was considered that an attempt should be made to use azetidinones such as (243, Fig.XLI) as starting materials. This idea is attractive because such azetidinones are available by direct ketene-imine reaction (except for the t-butylcarbamate). Direct utilization of these compounds would require that they be converted to the corresponding dianions (244, Fig.XLI). Similar reactions are known for the simple esters of the protected aminoacids (245 -- 247, Fig.XLI)⁹⁰.

Formation of the dianion of (243, Fig. XLI) upon reaction with 2 equivalents of LDA at -78°C and its subsequent reaction with acetaldehyde afforded a crude product whose TLC showed the complete consumption of the starting material and the formation of undetermined amounts of some very polar and non-polar impurities in addition to the desired products. The isolated yields of the mixture of hydroxyethylazetidinones (232, Fig.XLI) was typically in the range 80-90%, similar to the case of the alkoxyazetidinones. In the present case it was not necessary to remove the impurities before oxidation with PCC. This oxidation provided a single acetyl compound(233, Fig. XLI) in about 60% overall yield from the parent

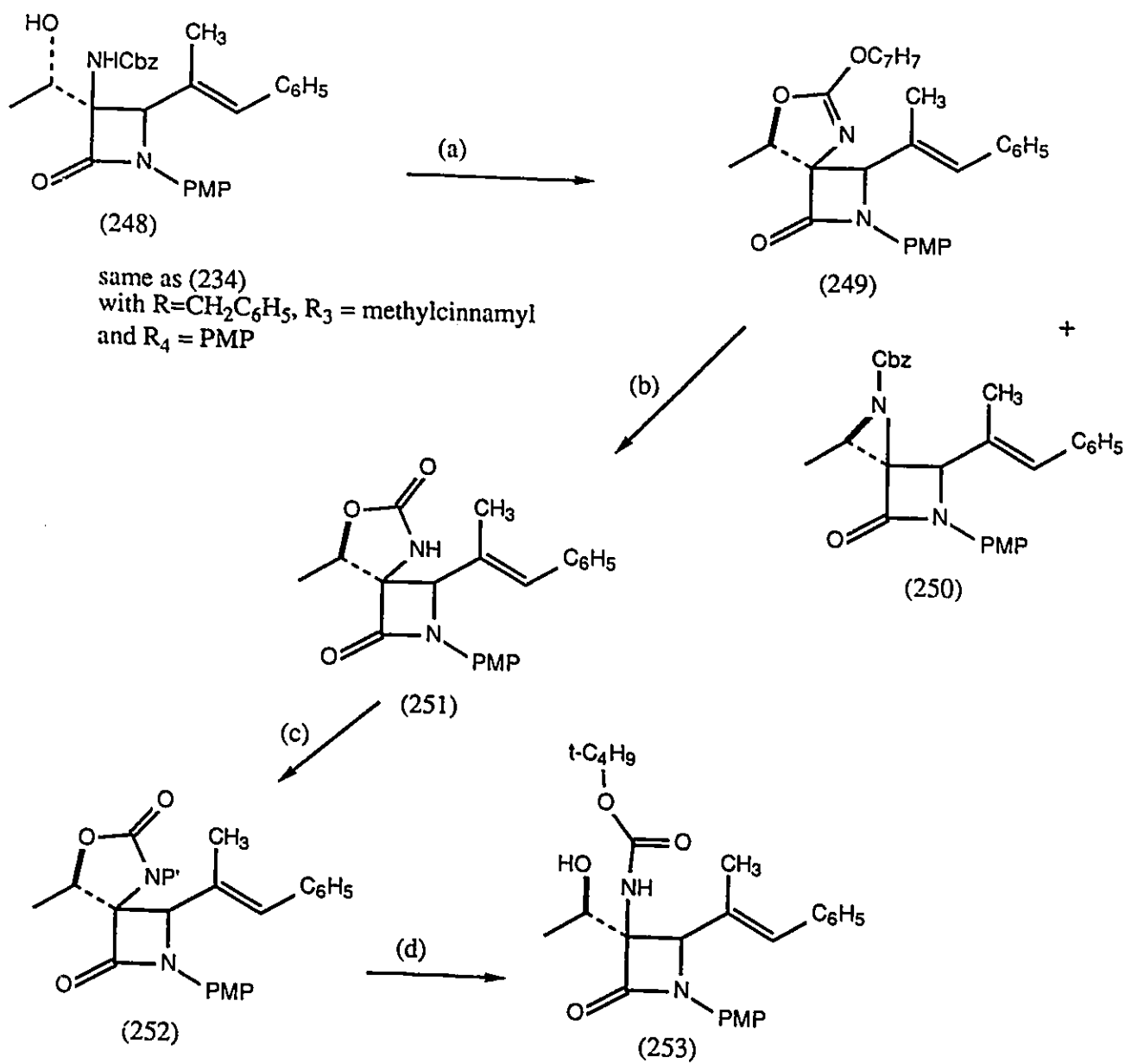
azetidinone. The inverse addition of the azetidinone dianion to large excess of acetyl chloride led to the formation of the same acetyl compound in about 60-70% yield (233, Fig. XLI). The inverse addition sequence was carried out for only one azetidinone but the situation for other azetidinones is expected to be similar. From practical point of view the two step sequence is better than the one step acetylation procedure. This dianion approach allowed access to up to 0.01 moles for the acetyl compounds (233, Fig.41). There is no reason to believe that larger quantities cannot be obtained.

Reduction of the acetyl compound with two equivalents of L-Selectride and 4-5 equivalents of TMEDA in THF at -78°C was very similar to the case of the alkoxyazetidinones (depicted in Figs XII and XXXIV). Whereas the results were very clear cut in the latter case in terms of the chemical shifts of the C-4 protons, the situation was somewhat muddled in the present case. The isolated hydroxyethyl compound was indeed diastereomerically pure as judged by the appearance of only one set of signals in 200 MHz .NMR spectrum. But the spectrum of the mixture of the hydroxyethyl compounds (232, Fig. XXXVIII) was marred by the appearance of rather broad peaks. To make matters worse it was difficult to be confident about the assignments of the individual peaks for the C-4 protons in the mixture of the hydroxyethyl compounds. But as stated earlier the formation of one pure hydroxyethyl compound (234, Fig. XII) as a result of the non-chelation controlled reduction was very certain. Having obtained one pure hydroxyethylazetidinone, it was decided to determine its structure by X-ray diffraction analysis. This task has not yet been completed

due to the lack of a derivative suitable for this purpose⁹¹. Therefore the assignment of configuration of the hydroxyethyl group in (234, Fig XIL) is tentative. But one can be quite certain that the hydroxyethyl group at C-3 and the larger substituent at C-4 are trans to each other.

Having obtained the one pure diastereoisomer via reduction process, the next target was the other diastereoisomer. In the present case it is very likely that the carbamate group at C-3 would interfere with a process involving inversion of stereochemistry at the hydroxyethyl group by an external nucleophile. It was tempting to see if the carbamate moiety can be used productively i.e. can an inversion be carried out at the hydroxyethyl group with the carbamate acting as the internal nucleophile⁹². A subsequent step would involve the hydrolysis of the resulting cyclic urethane or the imidate to the corresponding vicinal amino alcohol. With this view the azetidinone (248, Fig. XLII) was reacted with 2.5 equivalents of NaH and 1.2 equivalents of tosylimidazole in DMF at 0°C for 24 hours⁷⁶. The consumption of the starting material was complete and the reaction mixture contained three new compounds. The two less polar compounds could be only partially separated. Their structures were assigned as the oxazoline derivative (249, Fig.XLII) and the novel aziridine derivative (250, Fig.XLII)⁹³ on the basis of their NMR spectra. In the case of the oxazoline derivative (249) the chemical shift of the α -hydroxyethyl proton is 5.0 ppm which corresponds to the usual range for the chemical shift of the hydroxyethyl proton of the ester derivatives in the alkoxy series (254 Fig. XLII) regardless of the stereochemistry of the hydroxyethyl group. In the case of the

Fig. XLII



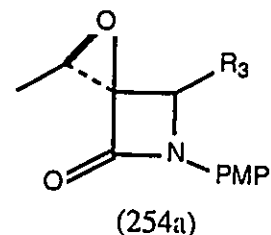
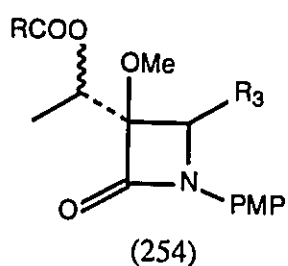
$P' = \text{CO}_2\text{-t-C}_4\text{H}_9$

(a) 2.2 eq NaH, 1.1 eq. tosylimidazole, DMF, 0 --R.T. 24 h.

(b) dil. aq. HCl. ca. 10% in THF-H₂O 2-3 days at R.T. or stir DMF --aq. HCl, 1 h. 0°C --R.T.

(c) 1.1 eq. (t-C₄H₉OCO)₂O, 1.1 eq. DMAP, THF, R.T., 15 -- 20 h.

(d) [i] MeOH, Cs₂CO₃, R.T., [ii] citric acid quench, remove solvent etc.



aziridine compound (250, Fig. XLII) the chemical shift of the α -hydroxyethyl proton is 3.0 ppm. The corresponding hydrogen in the case of epoxyazetidiones (254a, Fig. XLII) is found at 3.3-3.4 ppm. The ratio of (249): (250) was about 4:1. The more polar compound obtained from this reaction mixture has spectral properties in agreement with the oxazolidinone structure, specifically the chemical shift of the hydroxyethyl proton is 5.0 ppm and the spectrum lacks a benzyl group (251, Fig. XLII).

Exposure of (249, Fig. XLII) to dilute aqueous HCl led cleanly to its conversion to the oxazolidinone (251, Fig. XLII). TLC analysis of the reaction mixture indicated the presence of another very non polar compound, presumably benzyl chloride. More significantly it was possible to carry out the hydrolysis on the mixture of the aziridine and the oxazoline to furnish the same oxazolidinone. The aziridine did not survive the acidic treatment. The significant difference in the R_f of the aziridine (250, Fig. XLII) and the oxazolidinone (251, Fig. XLII) made the hydrolysis of the mixture very attractive since the R_f the oxazoline and the aziridine are fairly close. This situation is common to all other benzyl carbamate derivative of hydroxyethylazetidiones regardless of the substituents at C-4.

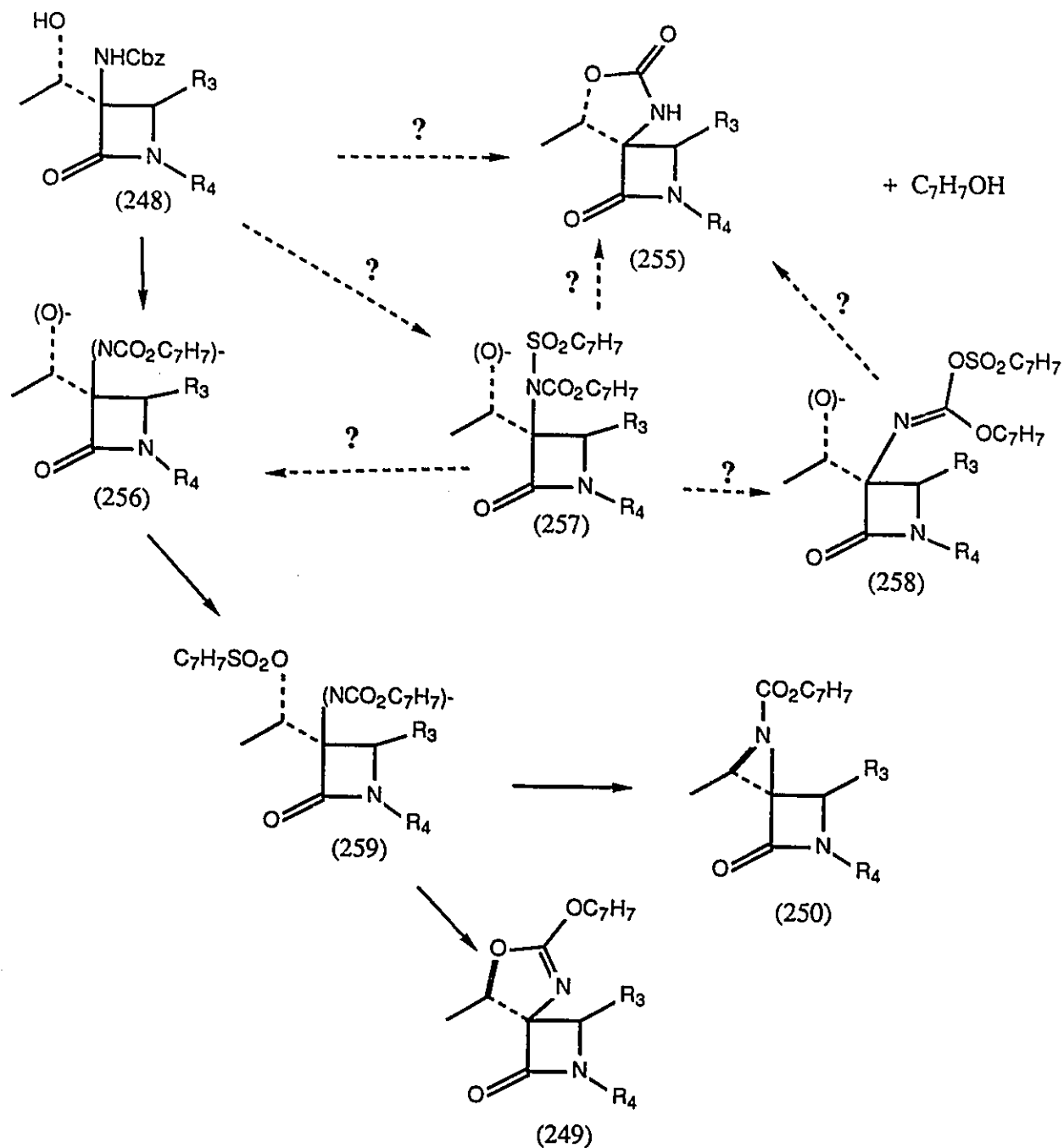
Conversion of the oxazolidinone to the open chain compound involved the sequence of reactions very similar to that used by Schmidt and coworkers⁹⁴. Treatment of the oxazolidinone (251, Fig. XLII) with a slight excess of *t*-butylpyrocarbonate and one equivalent DMAP in THF led to the formation of the 'dicarbamate' derivative (252, Fig. XLII) in about 85% isolated yield. Clean high

yield formation of the dicarbamate derivative from this highly hindered compound was surprising and very satisfying. Subsequent hydrolysis proceeded in roughly 80% yield to furnish the corresponding open chain t-butyl carbamate (253, Fig.XLII). Thus the objective of inversion of the stereochemistry of the hydroxyethyl group had been achieved. The process employed here also leads to change of the protective groups of the amino group.

One may put forward the argument that the formation of the oxazolidinone might have involved the 'direct' attack of the alkoxide on the benzylcarbamate followed by expulsion of benzyl alcohol in a process that does not involve tosylimidazole. That is to say the structure of the oxazolidinone should be (255, Fig.XLIII) and not (251, Fig.XLII). Such a situation will result in retention of the stereochemistry of the hydroxyethyl group. A similar reaction has been seen in the case of formation of compounds such as (157 and 158, Figs XXVIII and XXXVII). In the same vein it can be argued that the formation of the oxazoline might have involved the formation of a tosylate at the carbamate group such as (257, or 258, Fig.XLIII). Ring closure of these tosylates amount to 'direct' ring closure.

However these arguments are not very plausible. Dideprotonation of both the alcohol and the carbamate should occur in presence of 2.5 equivalents of NaH to yield the reactive species (256, Fig. LXIII). The more nucleophilic alkoxide should react preferentially to form the tosylate (259, Fig.LXIII). In the subsequent step the cyclization via the carbamate oxygen yields the oxazoline (249, Fig. XLII). Formation of the azirdine (250, Fig.LXIII)

Fig. XLIII



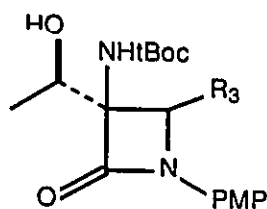
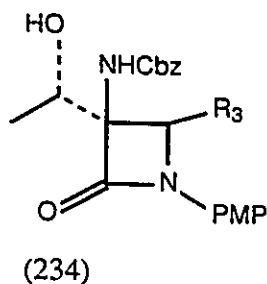
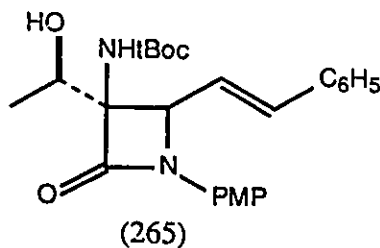
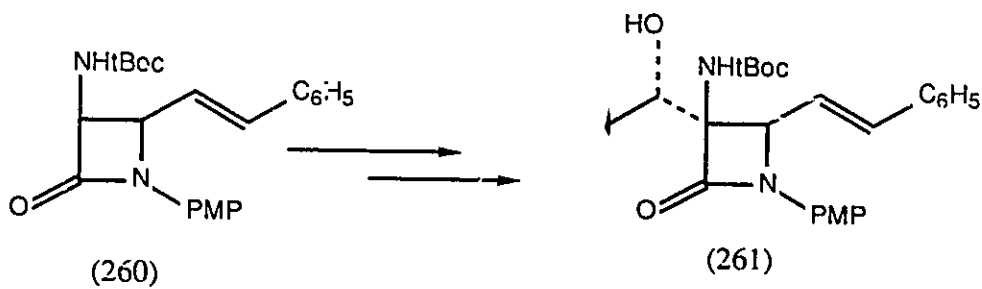
R₃ and R₄ as before

C₇H₇ = benzyl, C₇H₇SO₂ = p-toluenesulfonyl

also requires the intermediacy of (259, Fig. XLIII) and inversion at the carbon bearing the oxygen. It is unlikely but perhaps not impossible for the carbamate and the alkoxide group to compete for the limited amount of the tosylating agent, and thus some quantities of (257 or 258, Fig. LXIII) may be formed. However they may act as tosylating agents in their own right providing the tosylate (259, Fig. LXIII) ready for inversion. Furthermore it will be difficult for (258) to undergo ring closure to provide the oxazolidinone (255, Fig. XLIII) corresponding to the direct ring closure, since this process involves 5-endo trig type cyclisation⁴⁵. Cyclization of (257) should form the N-tosyl derivative of (255). No evidence for formation of this compound was found. Thus there is a very strong reason to believe that the oxazolidinone formation process involves inversion.

To set the matters at rest the azetidinone (260, Fig. XLIV) was taken through the dianion, oxidation and Selectride reduction sequence. The product obtained (261, Fig. XLIV) from this sequence was different from the one obtained from the inversion approach (265, Fig. XLIV). In addition to confirming the mechanism of oxazoline formation this bit of 'old fashioned' chemistry also served to establish that the nature of the carbamate group does not have any influence over the course of the Selectride reduction. Two other azetidinones were also converted to the corresponding 'Selectride reduction' and the 'inverted' hydroxyethyl compounds ({262 263} and {264, 265}). Since the stereochemistry of the hydroxyethyl group of any of these compounds has not been determined by X-ray diffraction analyses the assignments are tentative. But at least in one case the inversion of stereochemistry has been clearly

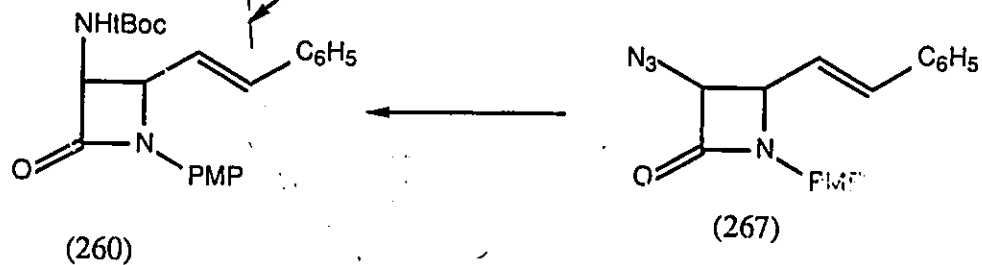
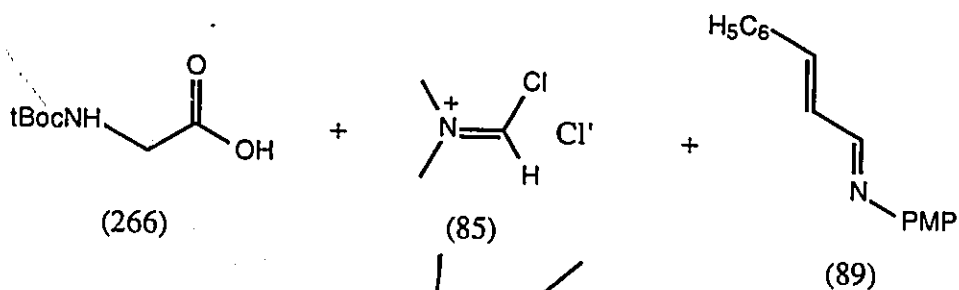
Fig. XLIV



tBoc = C(O)OtC₄H₉

if R₃ = 2-furyl then (262)
if R₃ = cinnamyl then (264)

if R₃ = 2-furyl then (263)
if R₃ = cinnamyl then (265)

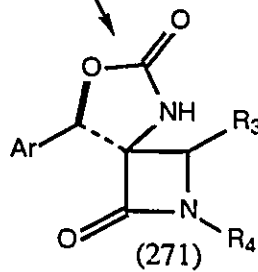
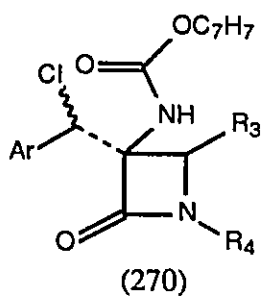
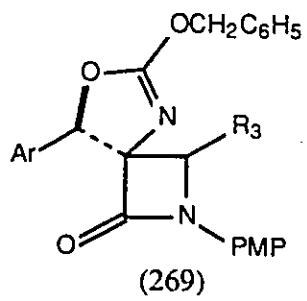
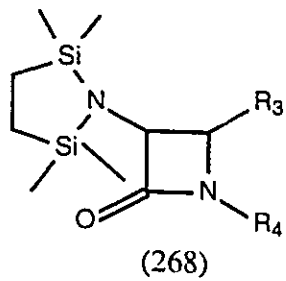


demonstrated. In future it may become possible to carry out X-ray diffraction analysis on one of these compounds. Currently procedures are available to obtain either of the hydroxyethyl compound in respectable quantities.

It may be argued that since the process of inverting the stereochemistry of the hydroxyethyl group starts from a carbobenzyloxy type carbamate and converts it into the corresponding t-butyloxycarbonyl carbamate, why not start with a t-butyloxycarbonyl azetidinone? In adopting such a sequence of reactions, at least the comparisons will be far easier. There were several reasons for not adopting such an approach. Whereas carbobenzyloxyglycine undergoes ketene-imine reaction with a variety of imines (all the precursors for the azetidinones (234) were prepared in this manner), the t-butyloxycarbonyl derivative of glycine (266, Fig.XLIV) does not undergo similar reactions. The reason for this failure is not very clear. However this led to the situation where the azetidinone (260, Fig.XLIV) was synthesized from the corresponding azidoazetidinone(267, Fig. XLIV). The problems associated with the use of 3-azidoazetidinone for the synthesis of compounds such as (260) in large quantities have been described earlier in this chapter.

An unknown factor is the change in the relative proportion of the oxazoline (249) and the aziridine (250) compound as a function of the carbamate group. Studies along those lines may be interesting but may not necessarily prove useful in providing a larger proportion of the 'desired' compound .

Fig. XLV



The possibility of protecting the amino group as in (268, Fig. XLV)⁹⁵ was not investigated. It is likely that monoanion formation can be carried out however it seems that here again new problems regarding the hydrolysis and amino protection will have to be faced.

In conclusion it can be stated that the formation of 3-hydroxyethylazetidiones bearing an additional protected amino group at position 3 has been a success. In this case by use of the 3- carbamate residue it has been possible to carry out the inversion of the stereochemistry of the hydroxyethyl group. This sequence of reactions has provided access to curious aziridine compounds such as (250). Currently the conditions required to maximize the yield of either the aziridine or the oxazoline compounds are not known. Fortunately the currently employed conditions favour the the more 'desirable' compound. Even though the reactions have been attempted only on acetaldehyde, it should be just as easily be applicable to other aliphatic aldehydes. It is not known if the reaction will be successful with formaldehyde (as in the case of the methoxyazetidione). It is likely that it will be possible to prepare the corresponding aryloxy compounds such as (269, Fig. XLV). But it is difficult to predict if the inversion process, involving acidic hydrolysis may lead to the cleavage of the benzyl-oxygen bond (270 and 271, Fig. XLV).

An interesting side-light of the studies carried out to invert the stereochemistry of the hydroxyethyl group is that these might prove useful in the context of the compounds (157 and 158, Fig. XXVIII) provided the acetonide hydrolysis can be carried out!

References and notes

(83). For an early example see, Ratcliffe, R.W. and Christensen, B.G. *Tet. Lett.* **1973**, (46), 4649. The procedure employed here was not very successful. However a similar procedure was employed by these chemists to prepare various substituted penicillins and cephalosporins., Ref. 15, 16, Chapter 1.

(84) In some of the cases cited in Ref. 15 and 16, the 'hydrolysis' of the imine was carried out by first reacting it with a suitable acylating agent. It would appear that conversion to the corresponding acyl-imminium which facilitated the hydrolysis. Though such a procedure is very useful for the hydrolysis there are some shortcomings. Firstly, it would mean that diversification will take place at a rather early stage in the synthetic plan. Secondly, competitive acylation of the amino and the hydroxy group will increase the number of steps involved in obtaining the pure hydroxyethyl compound. Finally, considerable care will be required in terms of the actual conditions employed for the acylation reaction since in absence of an additional tertiary base, the N-acylation process may not go to completion, whereas the presence of excess tertiary base may lead to some ketene formation from the acylating agent and thus may lead to formation of bis-b.-lactams of the type obtained by Ojima (see Chapter 6).

(85) The anticipation was based on the fact that benzyl chloroformate, being less reactive than the acylating agents, should react preferentially with the amino group. The acylation of the amino

group thus could be carried out at a later stage. There are several methods of regenerating the parent amino compound from the benzyl carbamate. Ref. (57) [i], 239-241. For a relatively recent review of removal of the "benzyl" type protecting groups with ammonium formate as hydrogen donor see, Ram, S. and Ehrenkauser, R.E. *Synthesis*, 1988, 91.

(86) The variable amounts of the left over Cbz-Cl and the benzyl alcohol obtained by the slow hydrolysis of the former, seem to be the culprit in this regard.

(87) Reaction of the C-3 imine anions with excess acetyl chloride did not furnish imine acetylazetidiones compounds as judged by attempting the hydrolysis and protection sequence on the red gum obtained on attempted acylation. Since no identifiable product could be isolated from these reactions it is impossible to comment on the course taken by these reactions.

(88) For a relatively recent review on various aspects of azide chemistry, including the Staudinger reaction (reaction of azido compounds with triphenyl phosphine) and reaction of the aza-ylids with various carbonyl compounds see, Turnbull, K. and Scriven, E.F.V. *Chem. Rev.* 1988, 88, 351. At least in this review there is no mention of attempted formation of anions α to either azido groups or α to the aza-ylides of the type used in current studies.

(89) It is likely that the azidoazetidione decomposed with loss of nitrogen on anion formation. Such a reaction has been observed previously. Manis, P.A. and Rathake, M.W. *J. Org. Chem.* 1980, 45, 4952.

(90) Dikshit, D.K. and Singh, S. *Tet. Lett.* 1988, 29, 3109.

- (91) The azetidinone (248, Fig. XLII) was converted to the corresponding p-bromobenzoate in about 75% yield. However various attempts to obtain suitable crystals from this material were not successful. Admittedly the lack of time did not permit formation of other derivatives. As pointed out later, both diastereomers of the hydroxyethyl compound are available.
- (92) There are numerous examples of the use of a carbamate moiety as an internal nucleophile and it will not be possible to list all of them. Two particularly impressive examples are [i] Kishi, Y.; Ko, S.S.; Minami, N. *J. Am. Chem. Soc.* 1982, 104, 1109. In this example it has been shown that depending upon the conditions employed, either the nitrogen or the oxygen atom can act as a nucleophile. [ii] Schlessinger, R.H. and Iwanowicz, E.J. *Tet. Lett.* 1987, 28, 2083 and Harding, K.E. and Burk, S.R. *J. Org. Chem.* 1981, 46, 3921.
- (93) Even though there does not seem to be a very prominent example of formation of aziridine derivatives from carbobenzyloxyamino-alcohols, these aza analogs of epoxides are well known. For a recent example of synthesis of aziridines in an enantioselective manner, see Sharpless, K.B.; Gao, Y. and Lohray, B.B. *Tet. Lett.* 1989, 30, 2623. Perhaps the reason for paucity of such examples lies in the fact that for the purpose of aziridine formation ring-closure by oxygen atom of the amide or the carbamate will be the undesirable. Thus reactions involving sulfate esters or the vic. azido alcohols are more popular. The latter reaction has been covered in the review on the azides (88).
- (94) Schmidt, U.; Respondek, M.; Lieberknecht, A.; Werner, J. and Fischer, P. *Synthesis*, 1989, 256. The various variations on this

theme are mentioned in the original publication by Kunieda, T. and Ishizuka, T. *Tet. Lett.*, 1987, 28, 4185.

(95) Formation of anions of such derivatives of glycine esters has been described by Magnus, P.; Venit, J. and Djuric, S. *Tet. Lett.* 1981, 22, 1787. These authors mention that methyl ester of 6APA could be converted to similar derivatives in a sluggish reaction.

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Experimental Section

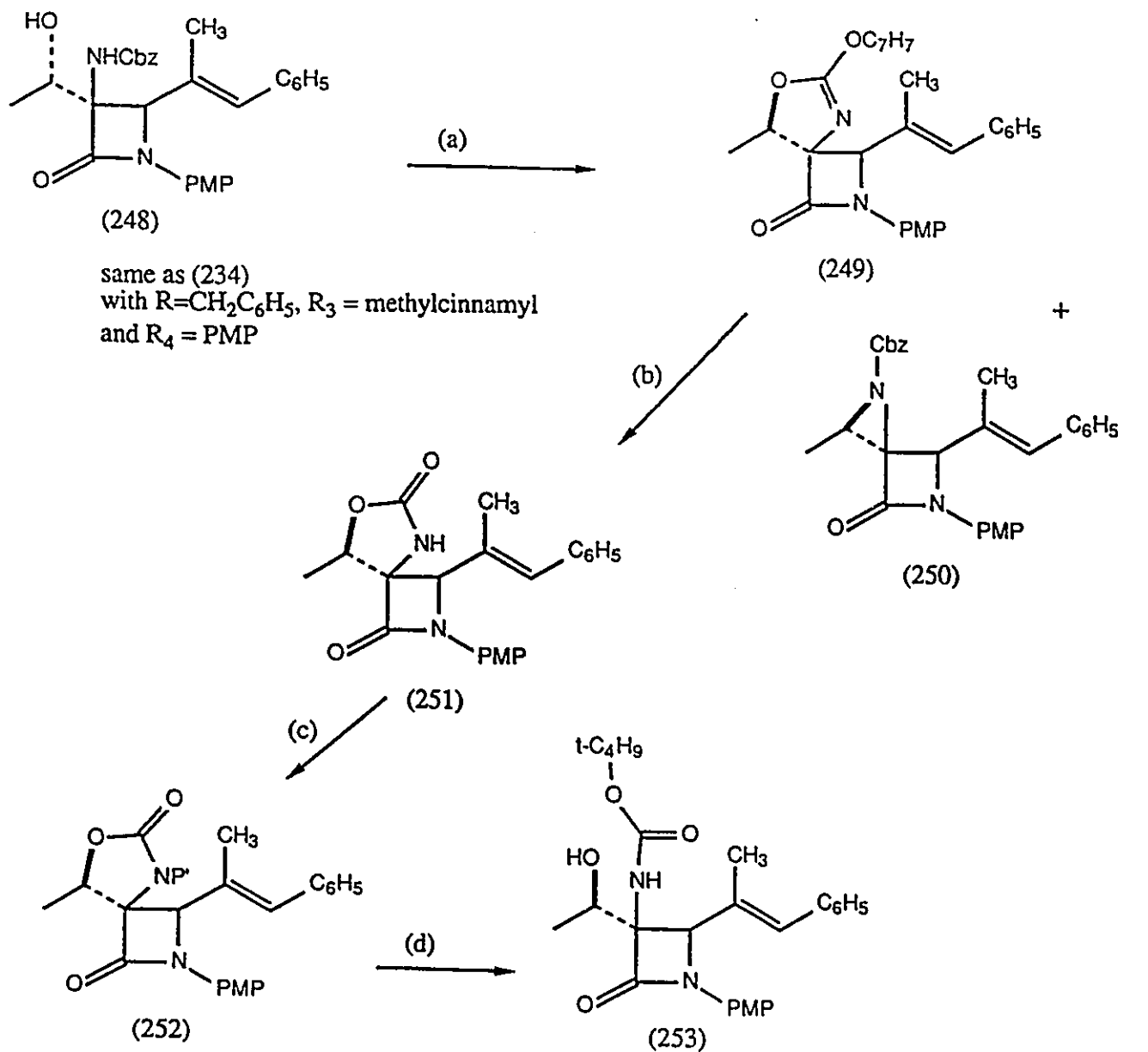
General

The formation of dianions from carbamates and the subsequent reactions of the dianions with electrophiles were carried out following the general procedure mentioned in the Experimental Section of Chapter 4. Oxidation of the hydroxyethylazetidinones by PCC and reduction of the resulting acylazetidinones were carried out following the methods mentioned in Chapter 4. The obvious differences in the dianion and reduction steps have been mentioned in the text. All other general comments mentioned in the beginning of the experimental section of Chapter 2 also apply here.

The hydroxyethylazetidinone (248, Fig. XLII) was inadvertently numbered as (401, Fig. LX). The compound is a white foam with the following properties: ir: 3300-3100, 1750, 1730 cm^{-1} ; ms: 486 (M^+ , 3.3%), 441 ($\text{M}^+ - 45$, 81.8%), 378 ($\text{M}^+ - 108$, 100%), 365 ($\text{M}^+ - 121$, 16.1%), 91 (C_7H_7^+ , 50.8%); nmr: δ = 7.3-7.1 (m, 12 H), 6.8 (m, 2 H), 6.4 (apparent t, 1 H, $J = 1.1$ Hz), 5.5 (d, 1 H, $J = 1.1$ Hz), 4.9 (AB, 2 H, $J = 12$ Hz), 4.7 (d, 1 H, $J = 1.5$ Hz), 4.4 (d, 1 H, $J = 1.1$ Hz), 4.3 (m, 1 H), 3.7 (s, 3 H), 1.8 (d, 3 H, $J = 1.2$ Hz), 1.3 (t, 3 H, $J = 6.6$ Hz).

The attempted tosylation of this compound was carried in the manner used for the hydroxyethylazetidinones (154 and 155, Fig. XXVIII); the crucial difference was that in the present case 2.2 equivalents of sodium hydride were used. Rest of the details were similar to those provided in the Experimental Section of Chapter 2. Starting with 0.972 g (2 mmol) of the hydroxyethylazetidinone 0.652 g (1.39 mmol) of (249, Fig. XLII) was obtained as a white semi-solid. This amounted to an isolated yield of 70%. An additional mixed

Fig. XLII



same as (234)
with $R = \text{CH}_2\text{C}_6\text{H}_5$, $R_3 = \text{methylcinnamyl}$
and $R_4 = \text{PMP}$

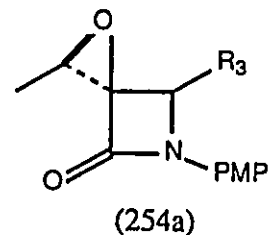
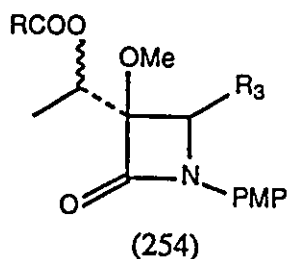
$\text{P}' = \text{CO}_2\text{-t-C}_4\text{H}_9$

(a) 2.2 eq NaH, 1.1 eq. tosylimidazole, DMF, 0 --R.T. 24 h.

(b) dil. aq. HCl. ca. 10% in THF-H₂O 2-3 days at R.T. or stir DMF --aq. HCl, 1 h. 0°C --R.T.

(c) 1.1 eq. (t-C₄H₉OCO)₂O, 1.1 eq. DMAP, THF, R.T., 15 -- 20 h.

(d) [i] MeOH, Cs₂CO₃, R.T., [ii] citric acid quench, remove solvent etc.



fraction was obtained which showed the presence of the aziridine derivative (250, Fig. XLII) in addition to (249). The ratio (249):(250) was roughly 4:1.

Compound (249) has the following spectral properties: ir: 1755, 1745 cm^{-1} ; ms: 468 (M^+ , 12.9%), 377, ($\text{M}^+ - 91$, 6.8%), 333 ($\text{M}^+ - 135$, 35.0%), 250 (imine⁺-1, 54.0%) 91 (C_7H_7^+ , 100%); nmr: δ = 7.4-7.1 (m, 12 H), 6.8 (dd, 2 H, $J = 2.2$ Hz, $J = 8.1$ Hz), 6.3 (broad s, 1 H), 5.3 (d, 1 H, $J = 11.7$ Hz), 5.2 (d, 1 H, $J = 11.7$ Hz), 5.0 (q, 1 H, $J = 6.6$ Hz), 4.4 (s, 1 H), 3.76(s, 3 H), 1.88 (d, 3 H, $J = 1.3$ Hz), 1.6 (d, 3 H, $J = 6.6$ Hz). HRMS calc for $\text{C}_{29}\text{H}_{28}\text{N}_2\text{O}_4$ 468.2090, found 468.2065.

The aziridine derivative (250) could not be obtained in pure state. Infrared and mass spectra of the mixture of these compounds were similar to those of (249). Following peaks have been assigned to this compound: nmr: δ = 4.7 (s, 1 H), 3.78 (s), 3.0 (q, 1 H, $J = 5.6$ Hz), 1.91 (d, 3 H, $J = 1.1$ Hz), 1.6 (m); rest of the peaks overlapped with those of the compound (249). Peaks at 3.78 ppm could not be integrated separate from that at 3.36 ppm.

Hydrolysis of (249, Fig. XLII)

A solution of 10% HCl in 9:1: THF: water was prepared by mixing appropriate quantities of various ingredients. To 5 mL of this solution was added 0.468 g (1 mmol) of (249). The clear yellow solution was stirred at room temperature for 2 days. During this period some of the solution evaporated; thus the volume of the reaction mixture was brought back to 5 mL. At this stage TLC showed presence of some starting material and thus the reaction mixture was allowed to stir for an additional 20 h. Even at this stage the TLC revealed the presence of some starting material. Workup

consisted of addition of 10 mL of saturated NaCl solution and partition with 2x25 mL ethyl acetate. The combined organic layer was washed with 10 mL of 5% NaHCO₃ solution, 10 mL of saturated NaCl solution and was dried over MgSO₄. Filtration to remove the drying agent and the removal of the solvent provided a yellow semi-solid. Column chromatography using 2:1: hexane: ethyl acetate furnished 0.321 g (0.84 mmol) of (251, Fig. XLII) as a white semi-solid. This amounts to an isolated yield of 84%. Compound (251) has the following properties: ir: 3100, 1745, 1720 cm⁻¹; ms: 378 (M⁺, 23.9%), 252 (imine⁺⁺, 46.5%), 250 (imine^{+ -}, 100%); nmr: δ= 7.3-7.1 (series of m, 7 H), 6.8 (d, 2 H, J= 9.0 Hz), 6.4 (broad s, 1 H), 5.4 (s, 1 H), 5.0 (q, 1 H, J= 6.5 Hz), 4.5 (s, 1 H), 3.7 (s, 3 H), 1.9 (s, 3 H), 1.6 (d, 3 H, J= 6.5 Hz). HRMS calc for C₂₂H₂₂N₂O₄ 378.1580, found 378.1564.

Synthesis of (252, Fig. XLII)

To a solution of 0.09 g (0.23 mmol) of (251) in 5 mL of dry THF was added 0.032 g (0.26 mmol) of 4-dimethylaminopyridine. To the vigorously stirring clear solution at room temperature was added 0.057 g (0.26 mmol) of di-*t*-butylpyrocarbonate. The clear solution was stirred at the same temperature for 18 h. TLC analysis of the reaction mixture at this stage revealed absence of the starting material and presence of non-polar product. The reaction mixture was concentrated and the resulting oil was purified by column chromatography using 3 : 1 : hexane: ethyl acetate to remove some base line impurities. This furnished 0.115 g of a clear oil which showed presence of the starting material in addition to the product. This amounts to an isolated yield of greater than 100%. This oil had

the following spectroscopic properties : ir: 1755, 1730 cm^{-1} ; ms: 478 (M^+ , 3.1%), 378 (M^+-100 , 42.6%), 250 (imine $^+-1$, 98.6%), 57 (C_4H_9^+ , 100%); nmr: d=7.4-7.1 (m, 7 H), 6.9 (m, 2 H), 6.3 (broad s, 1 H), 5.0 (broad s, 1 H), 4.9 (m, 1 H), 4.6 (s, 1 H), 3.7 (s, 3 H), 1.9 (d, 3 H, $J=2.0$ Hz), 1.33 (s, 9 H). In addition the NMR spectrum showed peaks at 3.8 (s), 2.2 (m), 1.38 (s) and 1.2 (s). The integration for most of these peaks amounted to about one proton, integration for the last peak amounted to about 3 protons.

Synthesis of (253, Fig. XLII)

The mixture of compounds obtained from the previous step was dissolved in 10 mL of methanol. To the vigorously stirring solution was added 0.117 g (0.38 mmol) of cesium carbonate and the heterogeneous reaction mixture was allowed to stir at room temperature for about 2 h. TLC at this stage showed absence of the starting material. About 0.3 g (1.5 mmol) of citric acid was added and the solvent was removed from the reaction mixture to provide a white solid. This solid was dissolved in about 25 mL of ethyl acetate - 15 mL of water combination. The layers were separated and the aqueous layer was extracted with 2X10 mL of ethyl acetate. The combined organic layer was extracted with 1X10 mL of 5% NaHCO_3 solution, 10 mL of saturated NaCl solution and was dried over MgSO_4 . Filtration to remove the drying agent and removal of the solvent furnished about 0.1 g of a white solid. Column chromatography using 2:1 : hexane : ethyl acetate furnished 0.075 g (0.16 mmol) of (253) as a white solid. The overall yield of (253) from (251) was about 70%. The product has the following spectral properties: mp: 188-190°C; ir: 3300-3100, 1755, 1730 cm^{-1} ; ci-ms: 453 (M^++1 , 21%), 353 (M^+-100 ,

15.9%), 337 ($M^+ - 116$, 12.4%), 252(imine⁺+1, 18.9%), 149 (100%); nmr: d= 7.3-7.2 (m, 7 H), 6.8 (m, 2 H), 6.4 (broad s, 1 H), 5.3 (s, 1 H), 4.8 (d, 1 H, J= 1.1 Hz), 4.1 (m, 1 H), 3.7 (s, 3 H), 1.9 (d, 3 H, J= 0.9 Hz), 1.4 (d, 3 H, J= 5.1 Hz), 1.2 (s, 9 H).

Compound (262, Fig. XLIV) was inadvertently designated as (405, Fig. LX). The compound in question is a white solid with the following physical properties: mp: 169-170°C (dec) ; ir: 3300-3100, 1750, 1720 cm^{-1} ; ms: 436 (M^+ , 4.6%), 328 ($M^+ - 107$, 78%), 202 (imine⁺, 97.3%), 91 (C_7H_7^+ , 100%); nmr: d= 7.3-6.2 (series of m, 12 H), 5.5 (s, 1 H), 5.4 (s, 1 H), 4.9 (s, 2 H), 4.4 (q, 1 H, J= 6.5 Hz), 3.7 (s, 3 H), 1.3 (d, 3 H, J= 6.5 Hz).

Starting with 0.436 g (1 mmol) of the above alcohol and subjecting it to the tosylation-hydrolysis sequence furnished 0.21 g (0.64 mmol) of the furyl analog of the compound (251, Fig. XLII). In addition 0.11 g (0.26 mmol) of the mixture of the furyl analogs of compounds (249 and 250, Fig. XLII). The oxazolidinone-azetidinone (the furyl analog of 251) is a white foam with the following properties: ir: 3100, 1750, 1725 cm^{-1} ; ms: 328 (M^+ , 16.1%) 202 (imine⁺+1, 100%), 179 ($M^+ - 149$, 14.2%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$, 7.4%); nmr ; d= 7.4-6.3 (series of m, 7 H), 5.6 (broad signal, 1 H), 5.0 (m, 2 H), 3.7 (s, 3 H), 1.6 (d, 3 H, J= 3.9 Hz). HRMS calc for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_5$ 328.1059, found 328.1079.

The furyl analog of the compound (252, Fig. XLII) was prepared in about 80% yield from the corresponding oxazolidinone using the procedure mentioned above. In this case it was possible to obtain this compound pure by column chromatography. The physical properties of this compound are mp: 161-162°C (dec) ; ir: 1755, 1725

cm⁻¹; n_{is}: 428 (M⁺, 1.2%), 202 (imine⁺+1, 100%); nmr: d= 7.4-6.2 (series of m, 7 H), 5.1 (s, 1 H), 4.9 (q, 1 H, J= 6.7 Hz), 3.7 (s, 3 H), 1.5 (d, 3 H, J= 6.7 Hz), 1.3 (s, 9 H).

Conversion of the furyl analog of the compound (252, Fig. XLII) to the compound (263, Fig. XLIV) was carried out in about 85% yield following the procedure mentioned above. The product is a white foam with the following properties: ir: 3300-3150, cm⁻¹; ms: 402 (M⁺, 0.6%), 328 (M⁺-74, 3.6%), 302 (M⁺-100, 2.9%), 202 (imine⁺+1, 100%); nmr: d= 7.4-6.3 (series of m, 7 H), 5.4 (s, 1 H), 5.3 (d, 1 H, J= 1.1 Hz), 5.0 (d, 1 H, J= 1.2 Hz), 4.1 (m, 1 H), 3.7 (s, 3 H), 1.3 (d, 3 H, J= 4.2 Hz), 1.2 (s, 9 H).

The hydroxyethylazetidinone(264, Fig. XLIV) was inadvertently designated as (399, LX). This compound is a white solid with the following properties: mp: 155-157°C; ir: 3350-3100, 1755, 1725 cm⁻¹; ci-ms: 473 (M⁺+1, 2.5%), 365 (M⁺-107, 87%), 216 (M⁺-156, 35.9%), 149 (100%); nmr: d= 7.4-7.1 (series of m, 7 H), 6.8 (m, 2 H), 6.7 (dd, 1 H, J= 0.8 Hz, J= 16.6 Hz), 6.5 (dd, 1 H, J= 8.0 Hz, J= 16 Hz), 5.5 (broad signal, 1 H), 5.0 (AB, 2 H, J= 10.1 Hz), 4.8 (dd, 1 H, J= 0.8 Hz, J= 8.0 Hz), 4.3 (m, 1 H), 3.7 (s, 3 H), 3.3 (m, 1 H), 1.3 (d, 3 H, J= 6.6 Hz).

When the tosylation-hydrolysis sequence was applied to 0.6 g (1.27 mmol) of the above hydroxyethylazetidinone (264) 0.351 g (0.96 mmol) of the cinnamyl analog of the compound (251, Fig. XLII) was obtained as a white foam which amounts to a yield of 75%. This compound has the following properties: ir: 3150, 1745, 1720 cm⁻¹; ms: 364 (M⁺, 2.9%), 236 (imine⁺-1, 8.8%), 43 (C₂H₃O⁺, 100%); nmr: d= 7.3-7.2 (series of m, 7 H), 6.9 (broad signal, 1 H), 6.8 (d, 2 H, J= 9 Hz), 6.6 (d, 2 H, J= 16.1 Hz), 6.1 (dd, 1 H, J= 8.0 Hz, J= 16.1 Hz), 4.9 (q, 1 H,

J= 6.5 Hz), 4.5 (d, 1 H, J= 8.0 Hz), 3.7 (s, 3 H), 1.5 (d, 3 H, J= 6.5 H). In addition 0.07 g (0.15 mmol) of a mixture of the cinnamyl analog of the compounds (249 and 250, Fig. XLII) was obtained. In the NMR spectrum of this mixture, the chemical shift for the hydroxyethyl proton of the aziridine compound was assigned at 3.2 ppm. Rest of the signals were unresolved. Mass spectrum of this mixture showed peaks at 454 (M^+ , 5.0%), 364 (M^+-90 , 7.0%), 236 (imine $^+-1$, 31.3%) 91 ($C_7H_7^+$, 100%).

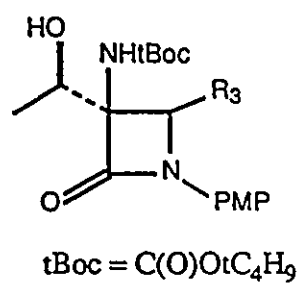
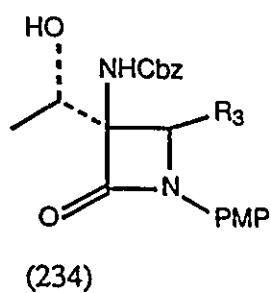
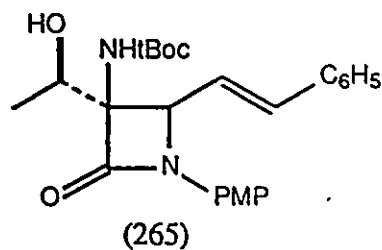
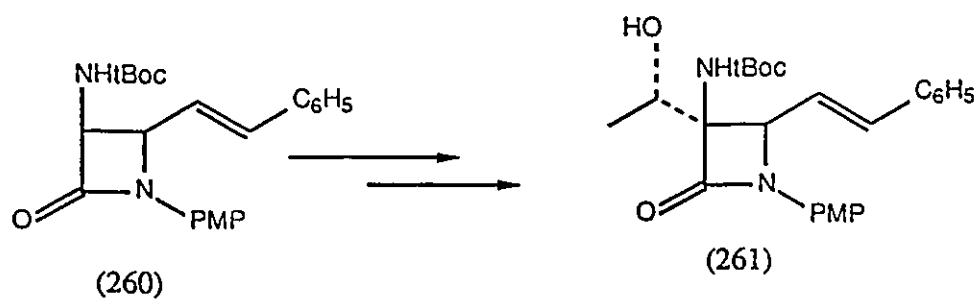
The cinnamyl analog of the compound (252, Fig. XLII) was obtained in 89% yield as an oil. The following spectral properties served to establish the structure: ir: 1755, 1730 cm^{-1} ; ms: 464 (M^+ , 2.3%), 364 (M^+-100 , 98.9%), 237 (imine $^+$, 98.4%), 56($C_4H_8^+$, 100%); nmr: d= 7.4-7.2 (series of m, 7 H), 6.8 (m, 3 H), 6.4 (dd, 1 H, J= 8.2 Hz, J= 16.2 Hz), 4.9 (q, 1 H, J= 6.6 Hz), 4.7 (dd, 1 H, J= 0.8 Hz, J= 8.2 Hz), 3.7 (s, 3 H), 1.5 (d, 3 H, J= 6.6 Hz), 1.4 (s, 9 H).

Hydrolysis of the above compound using cesium carbonate was carried out in the manner indicated above. The product the hydroxyethylazetidinone (265, Fig. XLIV) was obtained in about 80% yield and has the following following properties: mp:154-157°C; ir: 3325-3100, 1750, 1720 cm^{-1} ; ms: 438 (M^+ , 1.7%), 364 (M^+-74 , 18.4%), 338 (M^+-100 , 46.7%), 238 (imine $^++1$, 98.4%), 149 ($C_8H_7NO_2^+$, 22.8%), 57 ($C_4H_9^+$, 100%); nmr: ($CDCl_3+D_2O$) d= 7.3-7.2 (series of m, 7 H), 6.8-6.7 (m, 3 H), 6.3 (dd, 1 H, J= 7.3 Hz, J= 16.2 Hz), 5.3 (broad signal, 1 H), 4.9 (d, 1 H, J= 7.3 Hz), 4.1 (q, 1 H, J= 6.6 Hz), 3.3 (s, 3 H), 1.3 (d, 3 H, J= 6.6 Hz), 1.2 (s, 9H).

Synthesis of the azetidinone (260, Fig. XLIV)

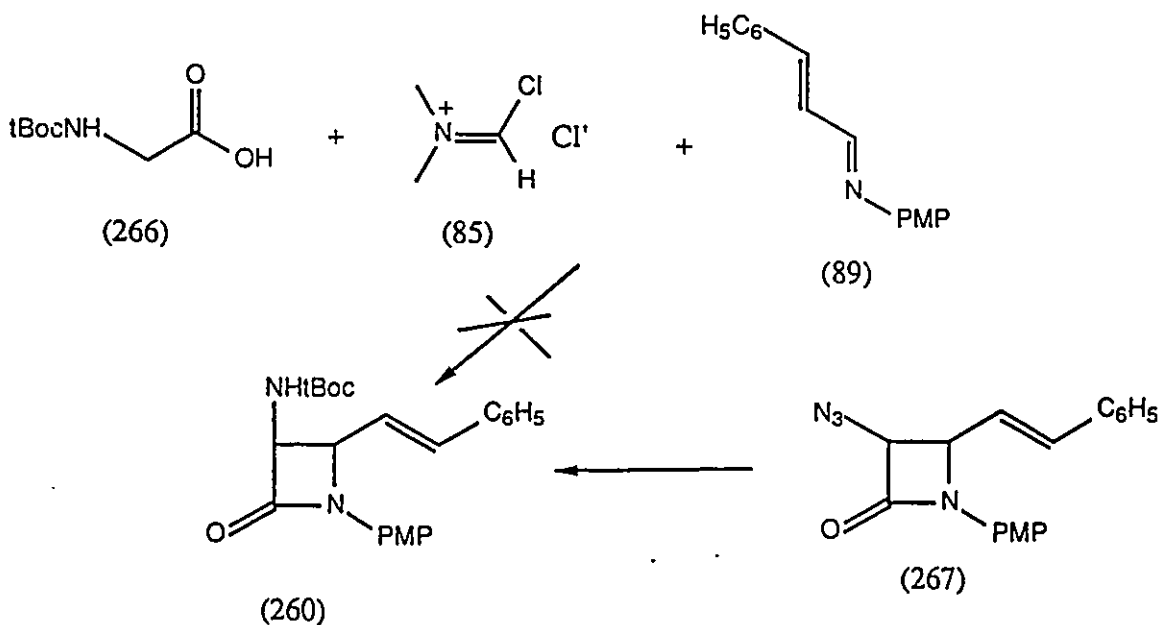
To a dry 500 mL dry round bottomed flask fitted with a Claisen tube and a stirring bar was added 3.2 g (10 mmol) of the azidoazetidinone (267, Fig. XLIV) and 1.5 mL (10.7 mmol) of triethylamine. About 250 mL of dry dichloromethane was added to obtain a clear yellowish solution which was cooled to 0°C under nitrogen. One opening of the Claisen tube was provided with a drying tube and hydrogen sulfide was blown into the solution through the other opening. This was accompanied by vigorous gas evolution and darkening of the color. After about 10 min of gas bubbling the reaction mixture was free of the azide group as determined by infrared spectrum. Nitrogen was blown through the solution for 2 min to remove excess hydrogen sulfide. To the resulting clear solution was added a solution of 2.5 g (11 mmol) of di-t-butylpyrocarbonate in 5 mL of dry dichloromethane and the clear solution was allowed to stir for an additional 3 h at 0°C and then at room temperature for 20 h. Removal of the solvent and trituration of the resulting semi solid with 100 mL of refluxing ether provided 1.37 g (3.3 mmol) the carbamate-azetidinone (260, Fig. XLIV) as a pale yellow solid. The weight of the product amounts to a yield of 33 %. The product has the following physical properties: mp: 202-203°C (dec); ir: 3200, 1750, 1730 cm^{-1} ; ms: 394 (M^+ , 5.2%), 338 (M^+ -56, 11.3%), 320 (M^+ -74, 18.2%), 277 (M^+ -117, 100%); nmr: δ = 7.4-7.2 (series of m, 7 H), 6.9 (m, 3 H), 6.1 (dd, 1 H, J = 7.2 Hz, J = 16.1 Hz), 5.1 (m, 2 H), 4.8 (m, 1 H), 3.7 (s, 3 H), 1.3 (s, 9 H). Even though the ^1H -NMR of H₃-H₄ could not be determined with certainty, it is likely that the stereochemistry of the azetidinone is cis.

Fig. XLIV



if R₃ = 2-furyl then (262)
if R₃ = cinnamyl then (264)

if R₃ = 2-furyl then (263)
if R₃ = cinnamyl then (265)



Conversion of the azetidinone (260, Fig. XLIV) to the hydroxyethylazetidinone (261, Fig. XLIV) involved the formation of dianion, reaction of the dianion with excess acetaldehyde, oxidation of the resulting mixture of hydroxyethyl azetidinones with PCC and reduction of the acetylazetidinone thus obtained with 2.2 equivalent of L-Selectride and 4.4 equivalents of TMEDA. Chromatographically homogenous product was obtained in the overall yield of 25% from the (t-Boc)aminoazetidinone. The compound is a yellowish foam with the following properties: ir: 3200-3100, 1750, 1730 cm^{-1} ; ci-ms: 421 (M^{++1} -18,31%), 365 (M^{++1} -75, 35.4%), 339 (M^{++1} -100,70.8%), 238 (imine^{++1} , 100%); nmr: δ = 7.4-7.2 (series of m, 7 H), 6.8-6.6 (m, 3 H), 6.3 (dd, 1 H, J = 8.1 Hz, J = 16.0 Hz), 5.3 (broad s, 1 H), 4.8 (d, 1 H, J = 8.1 Hz), 4.3 (q, 1 H, J = 6.2 Hz), 3.7 (s, 3 H), 1.2 (m, 12 H). NMR spectrum of this compound remained essentially unaffected in presence of D_2O .

CHAPTER 6

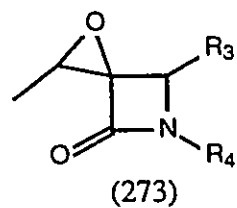
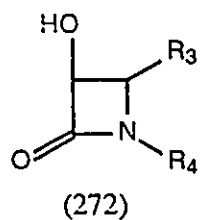
This chapter describes studies concerning the synthesis of 3-hydroxy azetidinones and 3- epoxy azetidinones (272 and 273, Fig. XLVI).

The idea behind the syntheses of these molecules was two-fold. The first goal was to test the feasibility of approach of an internal nucleophile to the side-chain carbon bearing the hydroxyl group (274 \rightarrow 275, Fig. XLVI). It should be recalled that a variety of external nucleophiles can not approach this position and thus carry out an inversion of configuration of this position. Ideally the best internal nucleophile would be the free hydroxy group at C-3. However it was impossible to obtain such a functional group by dealkylation of the 3-alkoxyazetidinones such as (203, Fig. XXXIV). Of necessity an alternate approach needed to be devised in order to study this hypothesis.

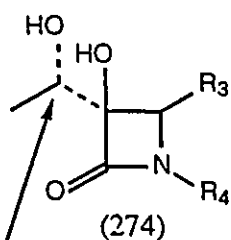
A second, subsidiary purpose of these reactions was to provide reliable access to 3 'epoxyazetidinones' or 'oxirane-azetidinones'. No systematic synthesis of these interesting class of molecule has been reported in the literature ¹²⁰. Specifically the idea was to combine the highly diastereoselective reduction of the 3-acyl-3-alkoxyazetidinones with an internal nucleophilic substitution reaction to obtain these compounds in stereochemically pure form.

These studies required a reliable access to large amounts of various C-3-alkoxyazetidinones. The nature of the protecting group R in (276, Fig. XLVI) should be such as to allow conversion to azetidinones such as (278, Fig. XLVI).

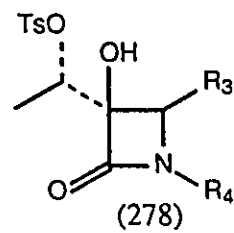
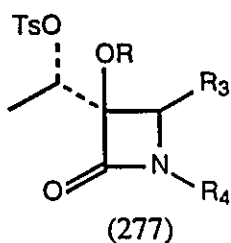
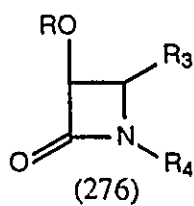
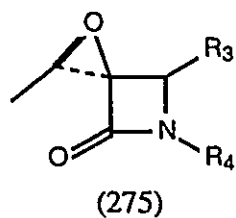
Fig. XLVI



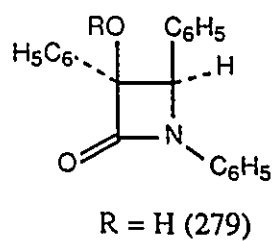
$R_3 = \text{cinnamyl, furyl, methylcinnamyl}$ $R_4 = \text{PMP}$



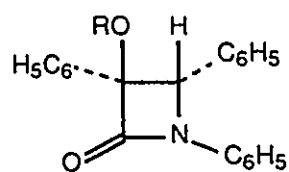
Inversion at this atom.



$R = \text{suitable protective group. } R_3 \text{ and } R_4 \text{ same as in (272)}$



$R = \text{Me}$ (280)



There have been some syntheses of azetidinones with a free hydroxy group at C-3. However majority of these procedures are very limited in scope. For example, Bose and coworkers prepared polyphenylazetidinones such as (279, 280 and 281, Fig. XLVI)⁹⁶. These authors claim that their work is significant in the light of the Sheehan's studies⁹⁷. It is very difficult to comprehend the significance of syntheses of such compounds, specially when for the purpose of further elaboration these compounds seem to be worthless.

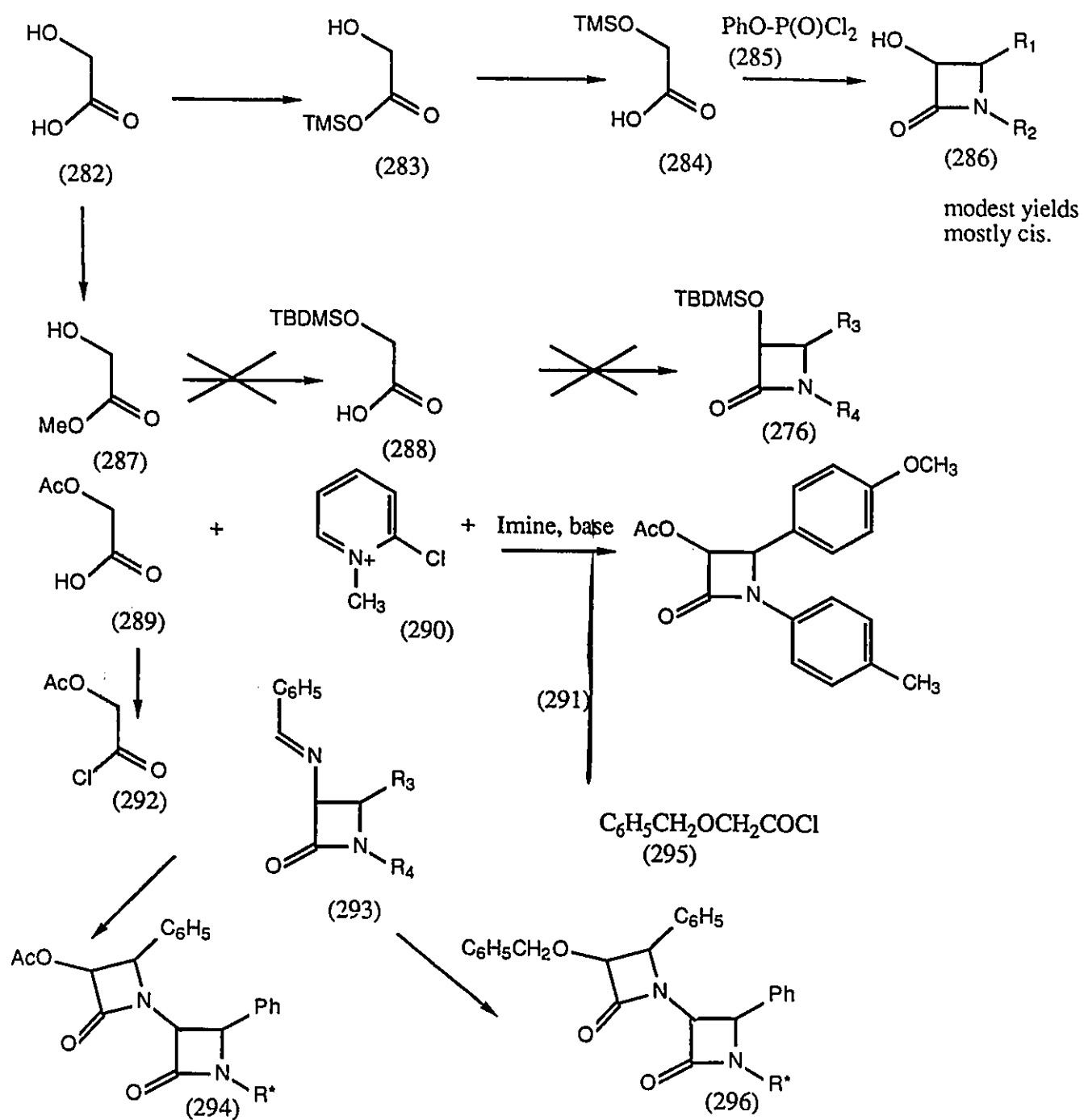
Palomo and coworkers have described the syntheses of 3- hydroxy azetidinones using the trimethylsilyl ether of glycolic acid⁹⁸. These authors also claimed that use of various protected hydroxy acetic acids may not provide C-3 hydroxyazetidinones since epimerisations, hydrolysis(?) and opening of the b- lactam ring may be expected. These authors note the need for a suitable protective group for the hydroxyl group, since according to them hydroxyacetic acids do not provide azetidinones under the conditions used by them.

These authors used phenyl dichlorophosphate as the activating agent. for the TMS derivative of glycolic acid (284, Fig. XLVII). The products obtained were mixtures of cis and trans azetidinones. Perhaps the biggest problem with the procedure outlined by these authors is that it is both non-stereospecific and is unreliable. Based upon the multitude of repetitive publications by these authors⁹⁹ it appeared that the change in the nature of the activating agent should not have any impact on the yield of ketene-imine reactions. However in our hand the use of the iminium salt (85) for

the purpose of activation of (284) did not lead to any detectable quantities of the desired azetidinones (272, Fig. XLVI). The formation of intractable yellow emulsions during the work up (an indicator of non-consumption of the imine in the ketene-imine reaction) was the usual result. One possible reason for such an outcome may be the differences in the quality of glycolic acid employed. In view of scant information provided by these authors we chose to use the commercial (95%, remainder water) glycolic acid and compensate by adding extra TMS-Cl. Since the TMS-ether of glycolic acid was not isolated in any case, it is difficult to draw conclusions regarding its purity. The reaction is possibly very sensitive towards the nature of the activating agent. On the assumption that perhaps the TBDMS-ether of glycolic acid may be easier to prepare and handle, attempts were made to prepare that compound. The rearrangement used for the preparation of the TMS-ether of glycolic acid did not seem to furnish the TBDMS-ether (no product was obtained on careful acidification of the aqueous basic extract). A more methodical approach involved the silylation (TBDMS-triflate) of methylglycolate and subsequent hydrolysis. Here again careful acidification of the basic aqueous layer (obtained after extended exposure of the protected methyl ester to 1.1 eq. of KOH in methanol) did not lead to the desired protected glycolic acid (288, Fig. XLVII).

Acetoxyacetic acid and the corresponding acid chloride are both well known¹⁰⁰. However their use in the field of azetidinone chemistry has been very limited. Specifically Manhas and coworkers had observed that acetoxyacetic acid can be converted to the azetidinone (291, Fig. XLVII) in modest yield¹⁰¹. Ojima and

Fig. XLVII



colleagues in the context of syntheses of bis-azetidinones such as (294, Fig. XLVII) and bis-azetidines reacted the acid chloride (292, Fig. XLVII) with the imine (293, Fig. XLVII). These chemists also used benzyloxyacetyl chloride (295, Fig. XLVII) to gain access to bis-azetidinones with a free hydroxy group at the carbonyl group of azetidinone¹⁰².

In our hands the use of either acetoxyacetyl chloride - triethylamine or acetoxyacetic acid-N,N-dimethylchloromethyleniminium chloride combination reliably furnished the corresponding C-3-acetoxy azetidinones in 60-80% yields. On small scale the procedure has been used as an undergraduate experiment. Details for a relatively large scale experiment are described in the experimental section. Experimentally the use of acid chloride-triethylamine combination is easier and this method was used throughout. The products obtained were pure cis azetidinones (297, Fig. XLVIII)¹⁰³.

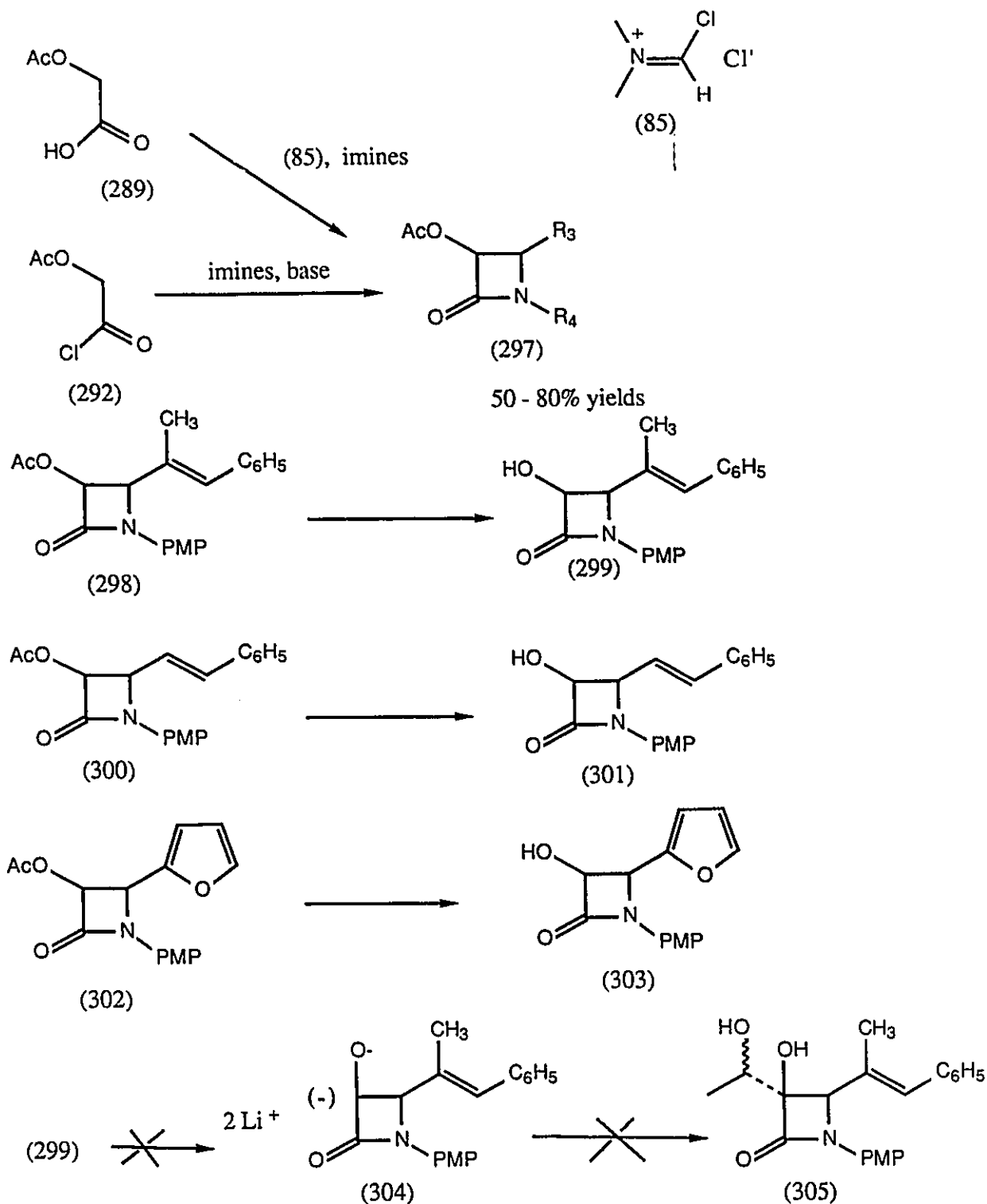
The hydrolysis of these azitidinones was sluggish using the standard saponification conditions, possibly due to the low-solubility of various acetoxyazetidinones in the combination of the hydroxylic solvents used for the purpose. Thus exposure of (298) to about 2 eq. of KOH in methanol-water-THF system for 24 hours at room temperature provided about 85% yield of the corresponding hydroxyazetidinone (299, Fig. XLVIII). The procedure was not amenable to large scale work. On the other hand use of sodium methoxide in a methanol-THF combination (1:1) was much faster (< 1 h. at R.T.). and yield of the crude hydroxyazetidinones were typically in the range of 90%. More importantly the methoxide procedure

was reproducible and could be applied to all the acetoxyazetidiones. This latter saponification method is also applicable for large scale syntheses of hydroxyazetidiones. The saponification of these acetates takes place without any detectable epimerisation at C-3.

Having established a useful route to a variety of 3-hydroxyazetidiones attention was directed towards the formation of carbanions from these compounds. Exposure of the hydroxyazetidione (299, Fig. XLVIII) to an excess of (> 2.2 eq.) of LDA at low temperature did not lead to any detectable formation of the dianion (304, Fig. IL) as evidenced by recovery of the starting material. Additives such as HMPA and TMEDA did not lead to any improvement in this situation. In view of the known thermal instability of C-3 anions of azetidiones the reaction was not attempted at higher temperatures¹⁰⁴.

It was anticipated that the C-3-hydroxy group in the product 3,3-disubstituted azetidiones such as (277, Fig. XLVI) would be highly hindered and thus may not be easily approachable. Thus the protecting group should be such that its removal could be assisted by the secondary hydroxy group. It was argued that use of benzoate esters such as (306, Fig. IL) might be useful since the benzoyl group can potentially be transferred from the tertiary to the secondary hydroxyl group and thus be finally removed (307 - 310, Fig. IL). To check the viability of this idea the hydroxyazetidione (299, Fig. XLVIII), was converted to the corresponding benzoate (311, Fig. IL). Exposure of the ester to LDA in THF at -78°C followed by addition of acetaldehyde produced a significant amount of the parent hydroxyazetidione and some uncharacterisable polar

Fig. XLVIII

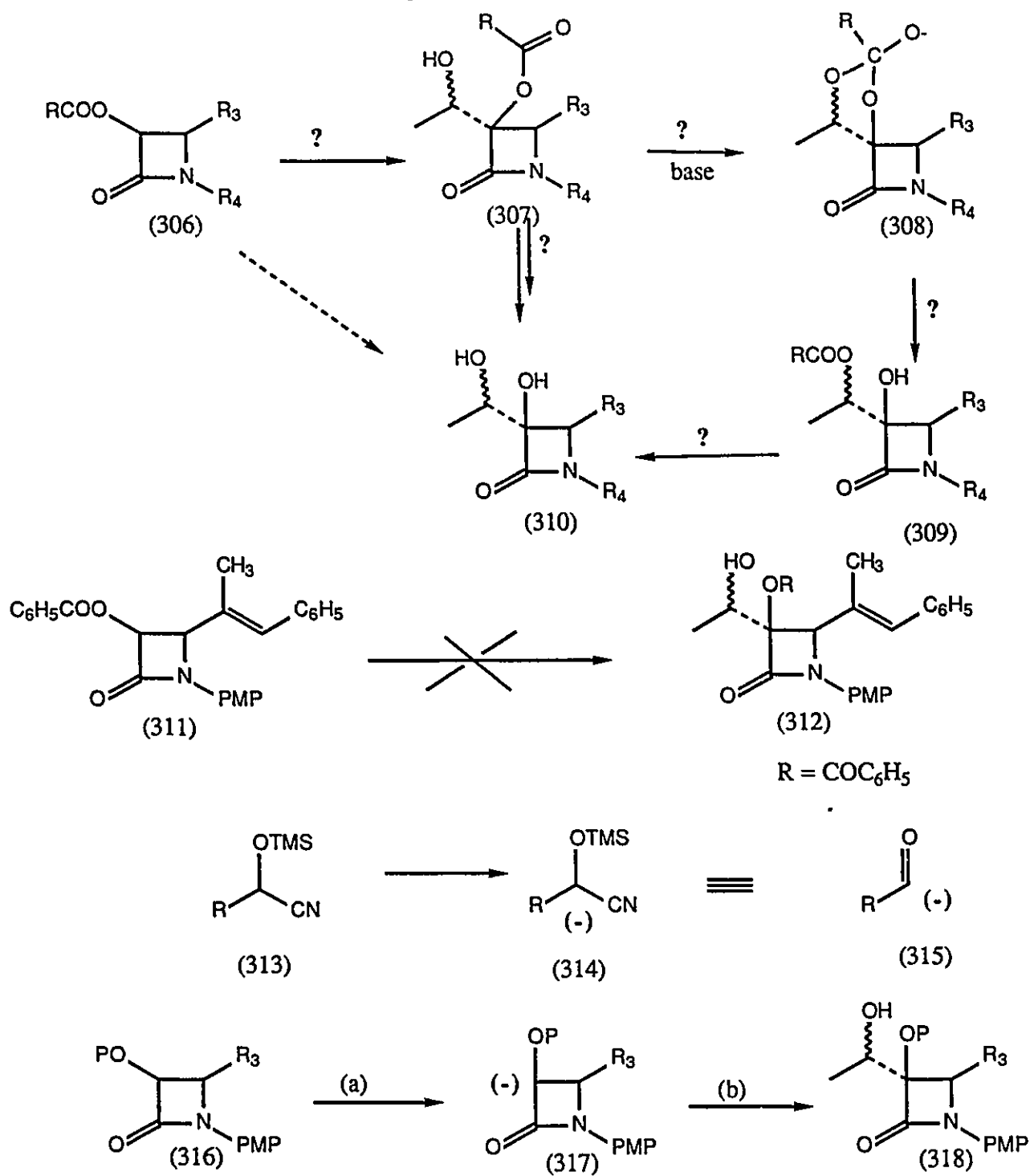


materials. None of the desired 3- hydroxyethyl (307, Fig. IL) compound could be obtained. Admittedly the idea of using the benzoate as the protective group for C-3 hydroxy group as outlined above was optimistic but the potential of the approach made the effort worthwhile.

Protection of the hydroxy group by a silyl protective group was next investigated. Silyl protecting groups can potentially be removed under the influence of protic acid or by the use of fluoride ion a fairly small nucleophile ^{57[i]}. The use of the anions derived from trimethylsilyl protected cyanohydrins (313, Fig. IL) as acyl anion equivalents is well-known¹⁰⁵, such anions are easily generated by exposure to LDA. Therefore the failure of TBDMS protected azetidinone to generate anion under 'usual' conditions was very surprising (316->318, Fig. IL). The yield of the corresponding hydroxyethyl compounds were abysmal (<10% at best, usually close to 0%) and the starting azetidinone was largely recovered.

Alternatively the protective group for the C-3-hydroxy function should be such that it's removal could be 'remote- triggered' i.e. the nucleophile or the electrophile used in the process of deprotection will not have to involve the highly hindered oxygen substituent at C-3. A potential remote triggered group is carbobenzyloxy¹⁰⁶. Conversion of the azetidinone (301, Fig. XLVIII) to the corresponding benzylcarbonate (319, Fig. L) was sluggish and occurred in about 30% yield. The azetidinone (323) could be obtained by direct ketene-imine reaction of the corresponding acid (not shown) in about 40% yield. Attempts to form anion from this

Fig. II



R = COC₆H₅

P = TBDMS, R₃ = methylcinnamyl

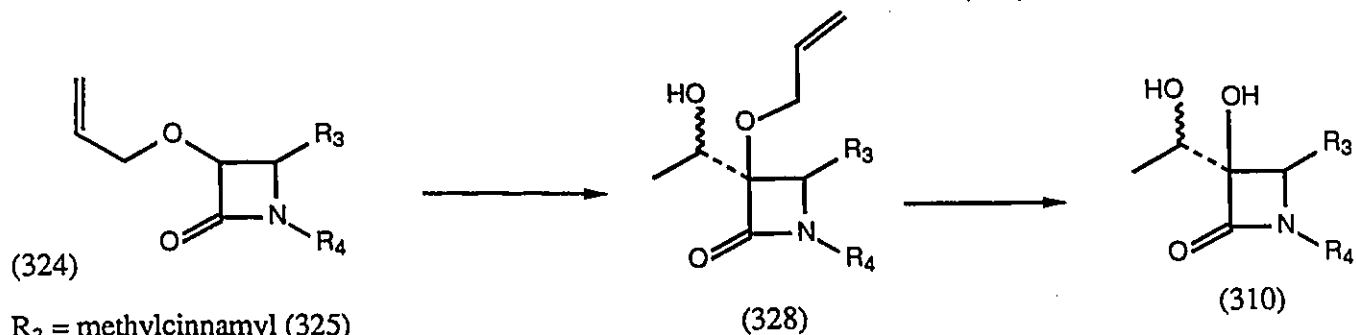
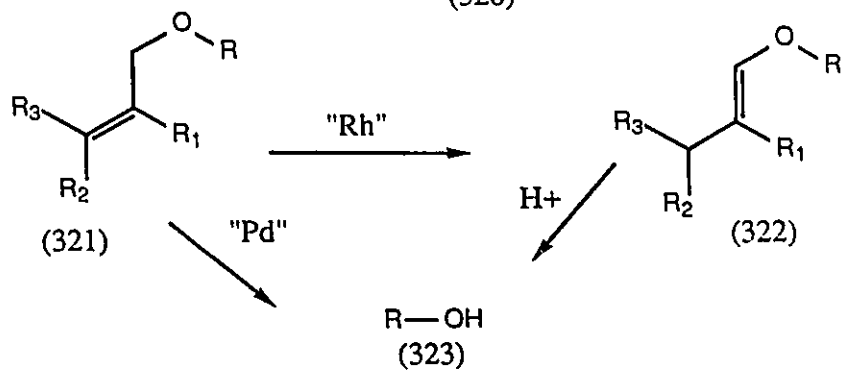
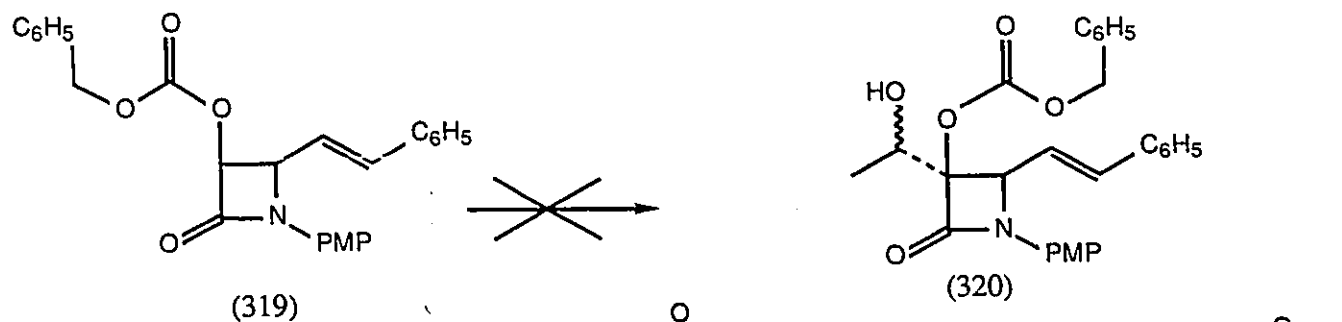
(a) LDA, THF, -78 °C, additives etc.
 (b) Acetaldehyde, low temp. work up.

carbonate were unsuccessful and led to the results similar to those for the ester (311, Fig. IL).

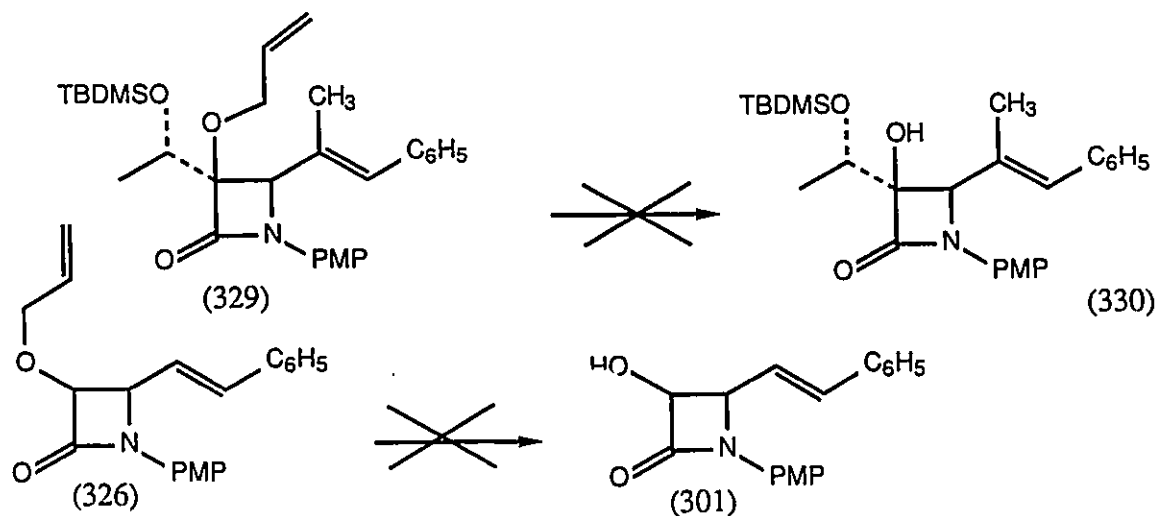
The allyl ether as protective group for the hydroxy function is different from benzylcarbonate but still falls into the category of the protective groups whose removal can be remote-triggered. Various methods for the removal of the allyl group are known, but a common underlying theme is the interaction of the allyl group with a palladium or a rhodium complex¹⁰⁷. Generation of palladium complex leads to direct formation of the parent alcohol (321 and 323, Fig.L). The isomerisation of the double bond and formation of an acid-labile vinyl ether (321 and 323, Fig. L) appears to be the mode of operation of rhodium complexes. It was anticipated that even in highly hindered 3-allyloxy-3-hydroxyethylazetidinones (324, Fig.L) the allyl group would remain available for interaction with the suitable metal complex and thus be potentially removable (328, Fig. L). Thus 3-allyloxyazetidinones (325, 326 and 327, Fig. L) were prepared from the corresponding hydroxyazetidinones.

Formation of anion from the allyloxyazetidinone(325, Fig. L) and the subsequent reaction with acetaldehyde was trouble free. The mixture of the hydroxyethyl compounds could be directly oxidised with PCC to provide the acetyl compound in about 70% overall yield from (325). The stereoselectivity in the non-chelation controlled L-Selectride reduction of 3-acetyl-3-allyloxyazetidinone was comparable to the case of the 3-alkoxyazetidinones and provided the compound (329, Fig.L) after silylation. The yield for these two steps was about 50%. However various attempts to

Fig. L



R₃ = methylcinnamyl (325)
 R₃ = cinnamyl (326)
 R₃ = furyl (327)
 R₄ = PMP for all cases



remove the allyl group from either the disubstituted azetidinones (329 Fig. L) or the azetidinone (326, Fig. L) were unsuccessful¹⁰⁷.

In the next attempted removal of the allyl moiety the idea was to degrade the vinyl residue selectively to the corresponding (nor-) hydroxymethyl compound and then cause a β -elimination from this monoprotected vicinal diol. It was not possible to carry out cleanly the selective ozonolysis of the terminal vinyl group (329 or 326) Despite careful addition of an ozone solution to the azetidinones at -78°C and monitoring by TLC, benzaldehyde was the only identifiable product!¹⁰⁸ An alternative approach involved potential conversion of the allyl group to the corresponding aldehyde with the same number of carbon atoms and then inducing β -elimination. Attempts were made to selectively react the terminal double bond of the allyloxy azetidinone (326, Fig. L) with 9-BBN¹⁰⁹. The reaction was sluggish at ambient temperature. However the use of refluxing THF as the solvent led to almost complete consumption of the starting material, but no identifiable compound could be obtained on subsequent oxidation with H_2O_2 .

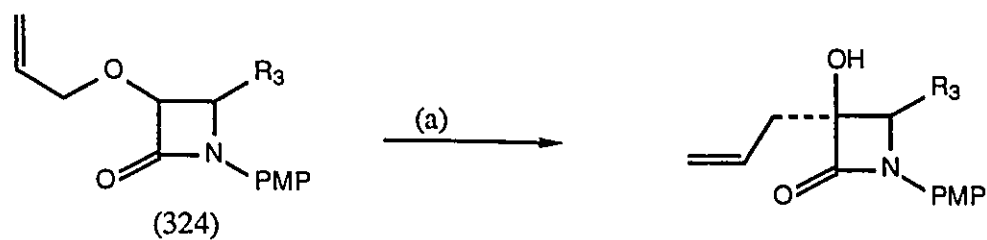
There was one redeeming feature of the studies carried out on these allyloxy compounds. In a preliminary experiment, excess (> 3 eq.) TMEDA was added to the anion obtained by treatment of (324, Fig.LI) with LDA in THF at -78°C . This led to no observable color change. The clear solution was allowed to warm to ambient temperature. As expected there was some decomposition of the anion but the major product obtained from this experiment was the rearranged azetidinone (331, FigLI). Similar results were obtained with azetidinone (327). Even though the conditions for this Wittig

rearrangement have not been optimized, the yields are respectable (65 -75%)¹¹⁰. As indicated by the presence of only one set of signals in the high field N.M.R. of (331 and 332) these products obtained by this Wittig rearrangement are diastereomerically pure. Though the stereochemistry has not been established for any of these azetidinones, it is very likely that the 'electrophilic' allyl group is approaching the azetidinone anion from the side opposite to the large substituent at C-4. If this assignment is correct, the procedure outlined here nicely complements an alternative hydroxylation procedure developed in these laboratories¹¹¹.

Attention was next turned to the benzyl type protective group. Initially it was feared that the removal of the benzyl protective group for the C-3 hydroxy group might be difficult since in the case of the 3,3-disubstituted azetidinones such as (334, Fig. LI) and (336, Fig.LI) this group will be highly hindered. Also the use of such a protective group would require that the side chain at C-4 be properly modified.

Formation of the anion from the benzyloxyazetidinone was straightforward and so were the subsequent steps involving the oxidation and the non-chelation controlled reduction.(333 -> 334, Fig.LI) and (335 -> 336, Fig. LI). The yields for these steps were similar to the case of 3-allyloxy and 3-alkyloxyazetidinones. The removal of the C-3 protective group was attempted using the typical conditions (Pd/C, H₂, 40-50 psi). The reaction was slow , some starting material was recovered but the benzyl protective group was removed to furnish the desired compound (338, Fig. LII) in 90% yield and without any complications. In the case of the disilyl compound

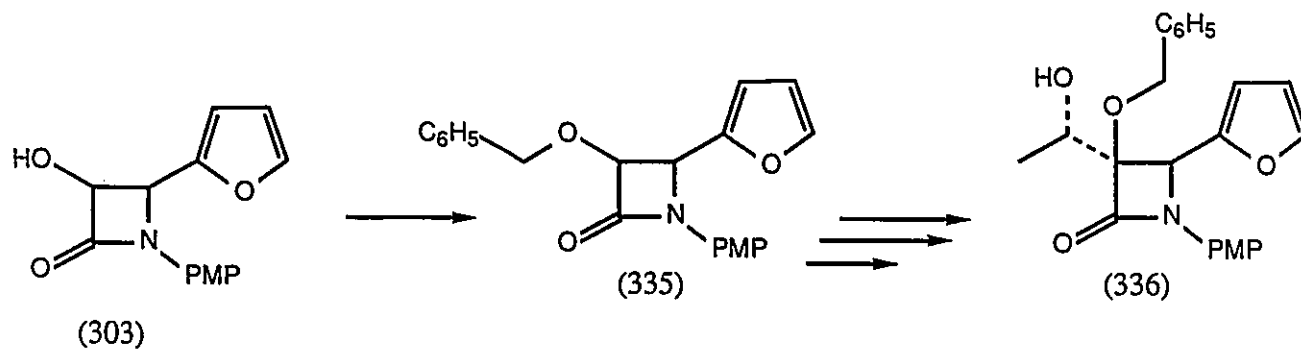
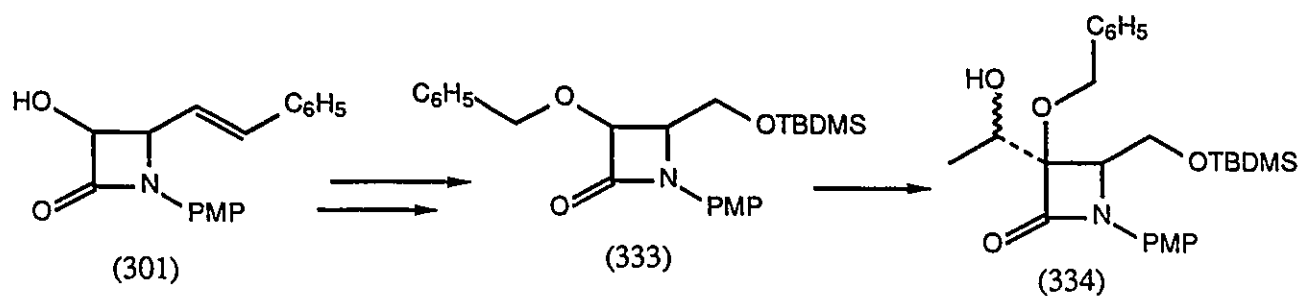
Fig. LI



R₃ = methylcinnamyl (325)
R₃ = furyl (327)

R₃ = methylcinnamyl (331)
R₃ = furyl (332)

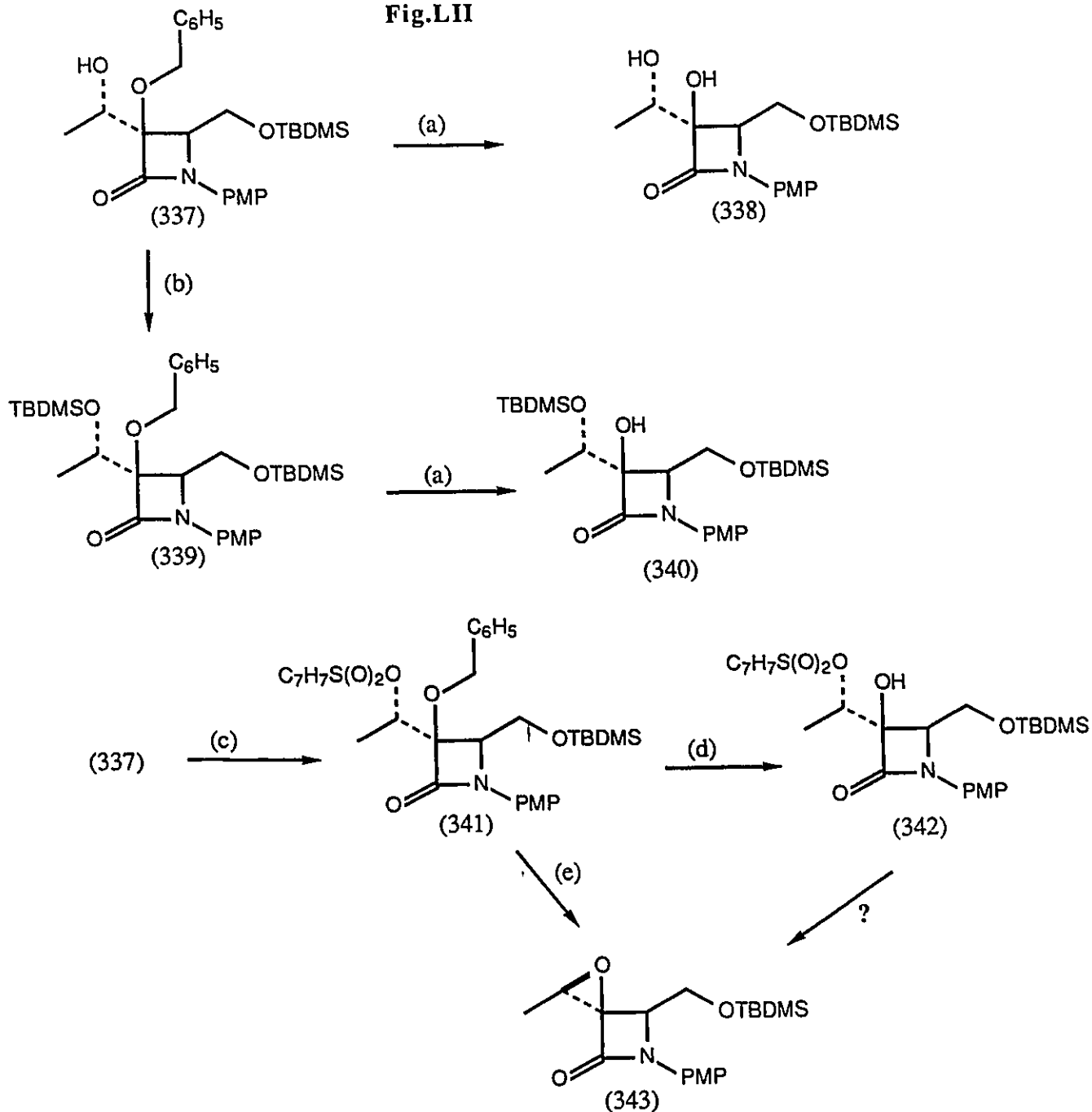
(a) LDA, THF, -78 °C, excess TMEDA, warm up.



the extent of conversion was somewhat lower (50%) but based upon the consumption of the starting material the yield of the product (340, Fig. LII) was excellent (45%). In the latter case perhaps a longer reaction period at a higher pressure might have increased the extent of conversion. As the recovery of substantial amounts of the starting material (339) indicate, this reaction was free of complications. Considering the hindered nature of the benzyloxy group and rather low pressure used these result were encouraging. The next experiments involved the formation of the tosylate (341, Fig. LII) and its debenylation. Under the same conditions, the debenylation process for (341) was much slower than that for (338 and 340). The yield of both the hydroxy azetidinone and the recovery of the starting material were less than 10% (341 and 342, Fig. LII). Additionally it was required that the 'epoxidation' be carried out as a separate step.

Hydrogen transfer debenylation conditions using ammonium formate was much more useful¹¹². Exposing the tosylate (341, Fig. LII) with an equal weight of palladium on charcoal and a large excess of ammonium formate (ca. 20 -30 eq.) in refluxing methanol led to clean debenylation and epoxidation in an overall yield of about 80% (341 -> 343, Fig. LII). The high field N.M.R. spectrum of the chromatographically homogeneous product showed only one set of signals. Since it has been previously demonstrated that S_N1 process is not possible for the hydroxyethyl group,(Chapter 4) the key step must have involved inversion at the carbon atom bearing the tosyloxy group. Thus the central question concerning the feasibility

Fig.LII



- (a) H₂ 40 -50 psi, 5 or 10% Pd-C, EtOH, 24 h
 (b) TBDMS-Triflate, 2,6-lutidine, methylene chloride, 0°C
 (c) NaH, DMF, Tosylimidazole, 0° -> 8° C 24 h.
 (d) same as (a) except 48 h.
 (e) Excess ammonium formate, 10% Pd-C, MeOH, reflux , 15 h.

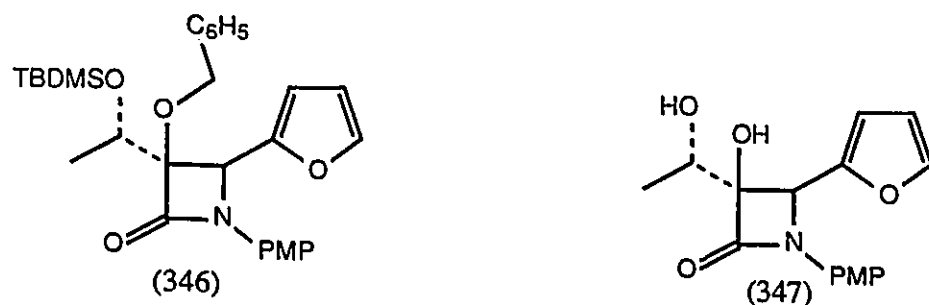
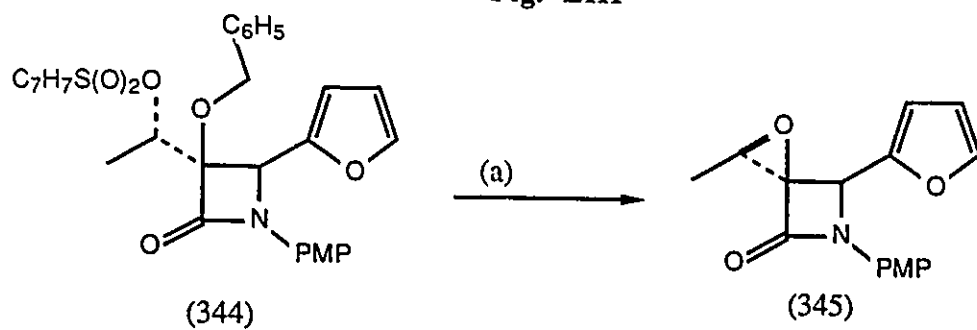
of carrying out the inversion at the hydroxyethyl side chain was answered in the affirmative.

The similar ring closure was carried out for the corresponding C-4-(2-furyl) azetidinone, in about 50% yield (344 \rightarrow 345, Fig. LIII). The corresponding dihydroxy compound was also prepared (347, Fig. LIII) in nearly quantitative yield. This hydroxyazetidinone (347) appears to have only moderate stability, possibly accounting for somewhat low yield observed for oxirane formation.

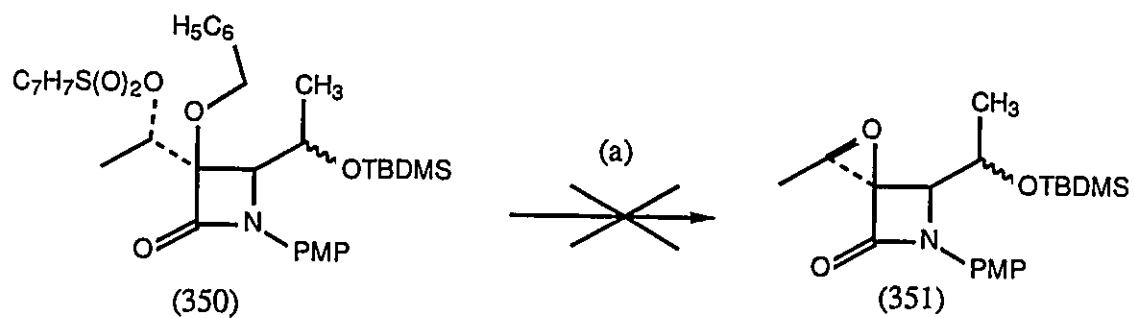
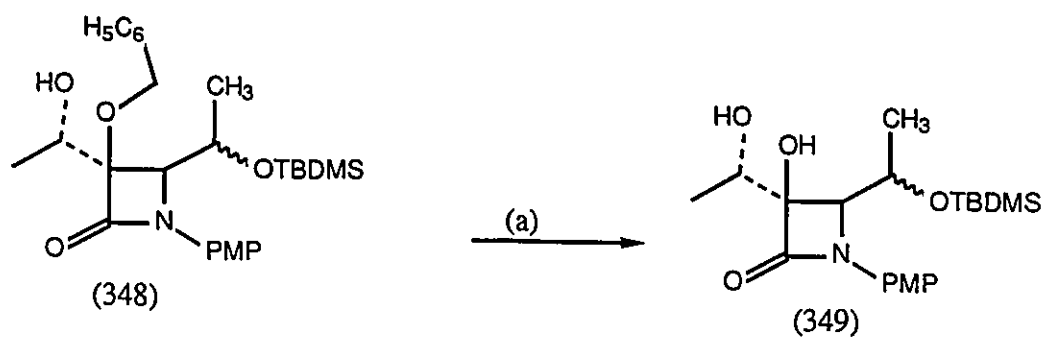
In general the procedure involving the formate hydrogen transfer technique are superior to the low pressure hydrogenolysis in terms of yield and time consumed. However this transfer hydrogenolysis method has its limitations. In case of the mixture of the silyl ethers (348, Fig. LIII) the debenzylation proceeds in good 88% yield. In contrast the compound (350, Fig. LIII) is recovered essentially unchanged on exposure to the typical hydrogen transfer conditions. The acetyl compound (352, Fig. LIV) was also a poor candidate for this epoxidation reaction. The only observed reaction is the partial reduction of the acetyl group to a mixture of hydroxyethyl compounds. There was no sign of oxirane formation in this case either but partial reduction of the acetyl group was observed. In the case of the parent compound (355, Fig. LIV) the transfer debenzylation is essentially a failure. The product in this particular case is mixture consisting of largely (>85%) (356, Fig. LIV) and small amounts (<10%) of (357, Fig. LIV).

Having answered the central question concerning the displacement by an internal nucleophile and obtained the oxiranes in the process it was decided that this idea be further explored.

Fig. LIII



(a) Excess ammonium formate, 5 or 10% Pd-C, MeOH, reflux



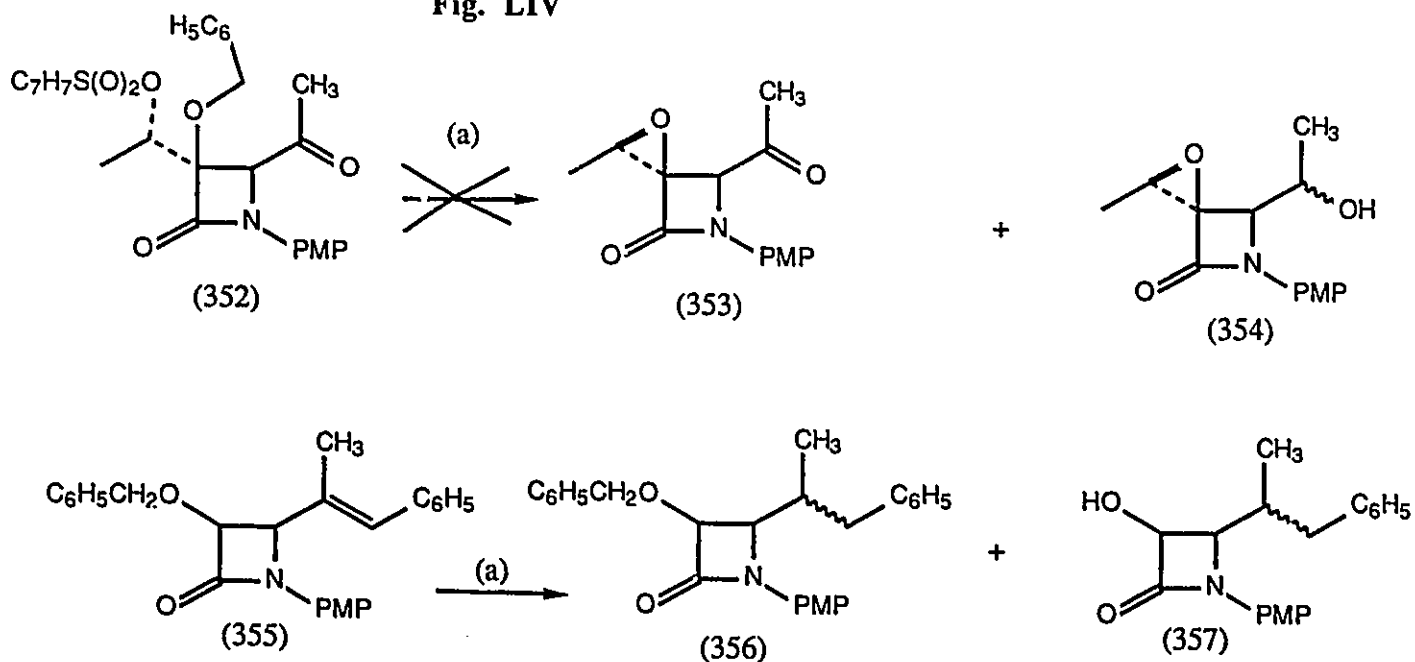
$C_7H_7S(O)_2 = p\text{-toluenesulfonyl}$

The question posed was: can the epoxides corresponding to an inversion at C-3(358 → 359, Fig. LIV) be prepared? The carbon atom in question is very hindered and thus may resist such displacement¹¹³. A dilemma in this regard was should the leaving group be introduced at C-3 early (before the alkoxyalkyl side-chain) or later (after the alkoxyalkyl side-chain). In view of well established nature of Darzen's glycidic ester syntheses it appeared more reasonable that the leaving group (a halogen) be introduced prior to the alkoxyalkyl side-chain.¹¹⁴

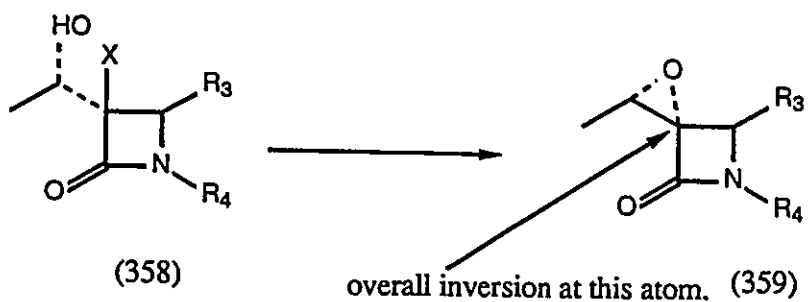
Attempts to prepare the C-3 chloroazetidinones were only partially successful. The sequence involving the reaction of hydroxyazetidinone (299, Fig. LV) with thionyl chloride gave of the desired product (360 Fig. LV) in about only 40% yield despite complete disappearance of the starting material. Furthermore tedious purification was required to remove substantial quantities of uncharacterised impurities in order to obtain (366, Fig.LVI) in pure state. The stereochemistry of the azetidinone was trans. This was considered inconsequential since it was anticipated that the process of anion formation and subsequent reaction with acetaldehyde would 'fix' the relative stereochemistry of various substituents similar to the case of alkoxyazetidinones¹¹⁵.

The situation concerning the preparation of 3-bromoazetidinones from the corresponding hydroxyazetidinone was much worse. The use of thionyl bromide did not provide any of the desired product¹¹⁶. No reaction was observed upon the treatment of 3-hydroxyazetidinone (299, FigLV) with the triphenylphosphine-bromine combination¹¹⁷. Conversion of the hydroxyazetidinones to

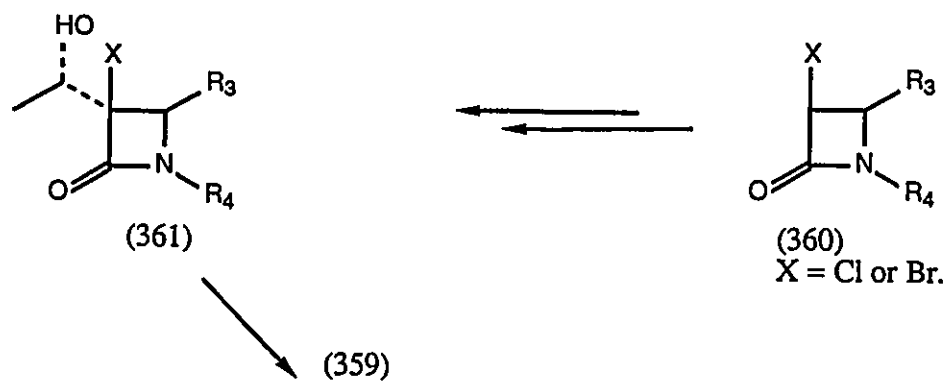
Fig. LIV



(a) Excess ammonium formate, 5 or 10% Pd-C, MeOH, reflux.



X = potential leaving group, R_4 = PMP, R_3 = furyl, protected hydroxymethyl or hydroxyethyl



the corresponding sulfonate esters could be easily carried out (362, Fig. LV) in 80 -90% yields. However the displacement of the sulfonate group with halide anions was unsuccessful. The situation is not unique to the use of halide anions as nucleophiles. In some instances the starting material was recovered in variable amounts and often the consumption was total. But in no case was it possible to reproducibly obtain the products of nucleophilic displacement with any degree of consistency¹¹⁸. Attempts to form 3-halo azetidiones except for 3-fluoroazetidinone from the corresponding acids via ketene-imine reaction were not successful, regardless of the mode of activation(364 -> 360, Fig. LV) .

Deprotonation of the 3-chloroazetidinone (360, Fig. LVI) appeared to be a rather difficult process. Even after extended exposure to LDA at low temperature, the extent of anion formation, as judged by reaction with acetaldehyde, was not significant and up to 50% of the starting azetidinone was recovered unchanged. The mixture of the hydroxyazetidiones (366, Fig. LVI) obtained appeared to be contaminated with some impurities as judged by TLC and thus it is not possible to comment accurately on the yield. The crude mixture was oxidised to the corresponding acetyl compound in about 45% overall yield from the chloroazetidinone (368, Fig. LVI). Surprisingly enough non-chelation controlled reduction of the acetylazetidinone furnished ca. 2:1 mixture of two hydroxyethylazetidiones. The reasons for this behavior are not clear. Perhaps the biggest surprise came at the very end. Subjecting this mixture of hydroxyethyl β -lactams to sodium hydride in DMF led to the formation of the acetyl compound (367, Fig. LVI) as the

only product in about 50% yield!. A possible explanation for the formation of the acetyl compound (367) supposes that major diastereoisomer reacts by a 1,2-hydrogen shift from the alkoxy bearing carbon atom, with concomitant expulsion of the chloride anion. The fate of the minor diastereoisomer is not known. Another explanation would involve the elimination of the elements of HCl followed by ketonization of the enol thus obtained. Failure to secure significant quantities of the starting material (360) precluded other attempts at obtaining the oxirane (359, fig. LIV) by this route.

Since the sulfonate esters (362, Fig. LV) were easily available, it was decided that an attempt should be made to convert them to the corresponding anion. Similar to the experience in the case of the benzoate ester (311, Fig. IL), no protected 3-hydroxyethylazetidinones were obtained.

Having exhausted other possibilities it was decided that an attempt should be made to convert an azetidinone such as (344, Fig. LVII) (available by debenzoylation sequence shown in figure LIII) to their 3-tosyloxy derivative.(369, Fig. LVI). Even though in this and other cases examined, the yields were modest, the tosylation procedure involving tosylimidazole-NaH-DMF combination was uniformly successful and furnished these hindered tosyl derivatives in 50 - 75% yields with complete consumption of the starting materials⁷⁶. In the case of the silyloxytosylate (369, Fig. LVI) use of TBAF in THF led to clean formation of the oxirane (370, Fig. LVI) as the only product in about 65% yield. The product was diastereomerically pure as determined from it's high field NMR spectrum. Starting with a mixture of diastereomeric

Fig.LV

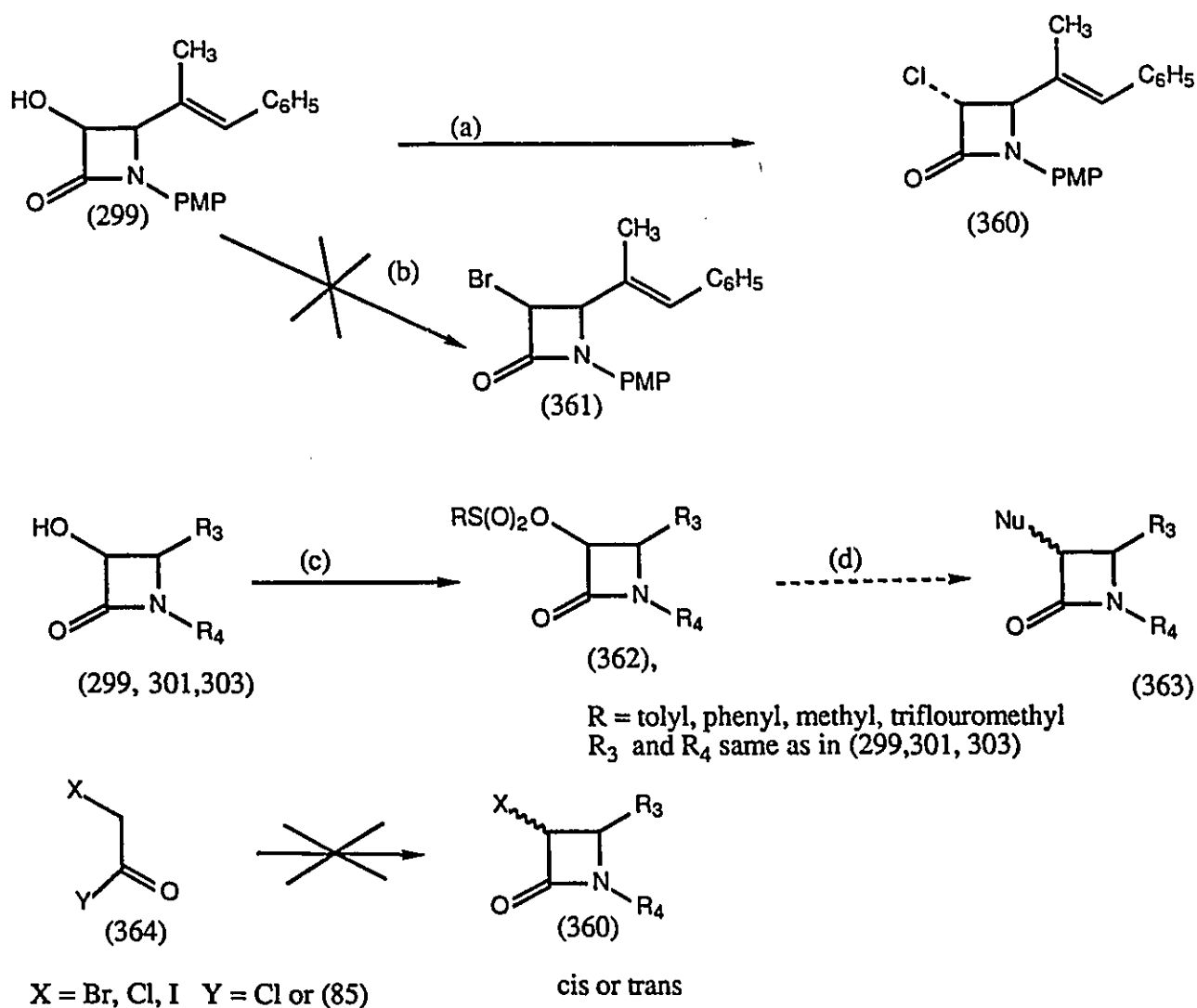
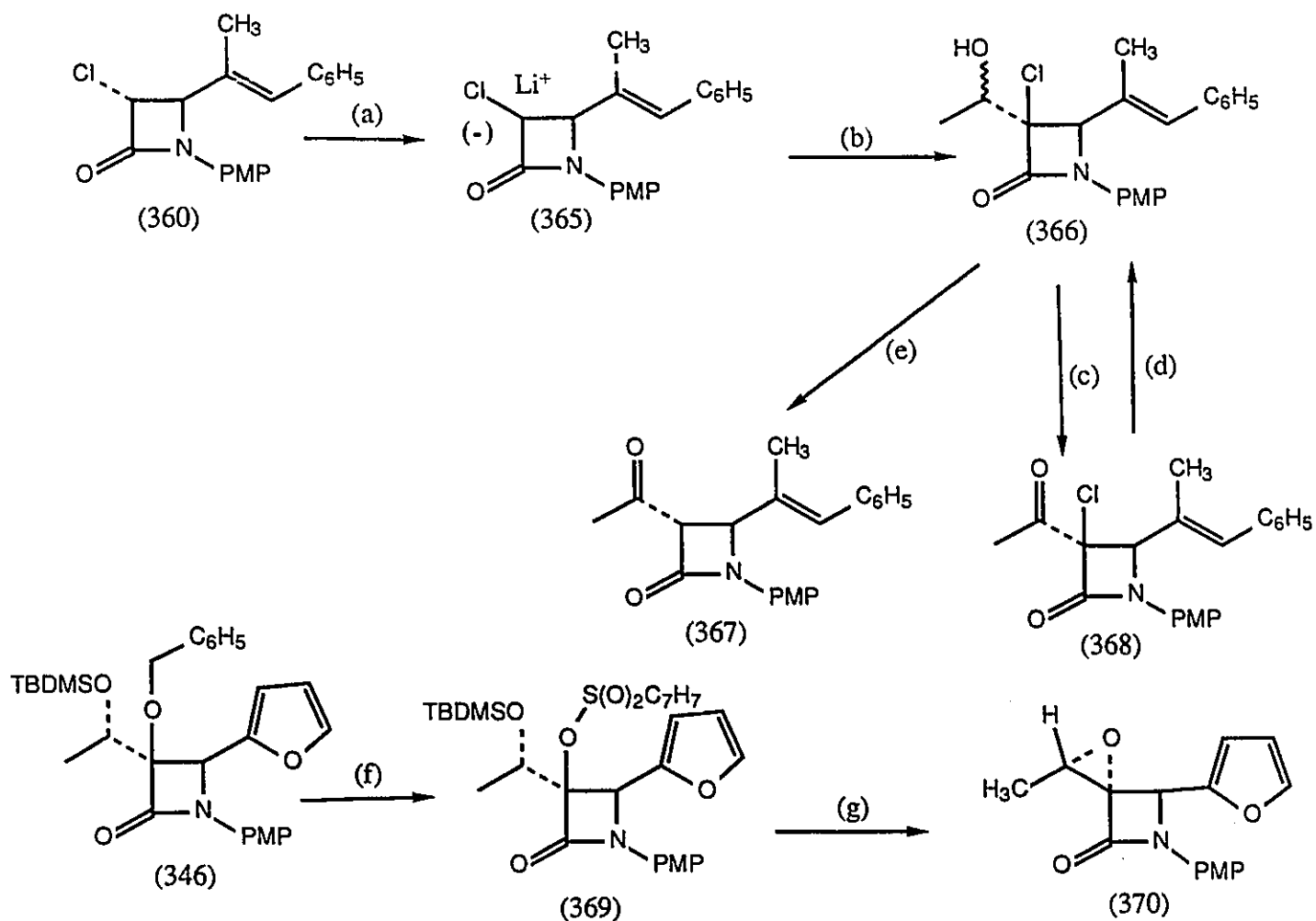


Fig. LVI



- (a) LDA, THF, -78°C, extended period of time.
 (b) Acetaldehyde, modest yield of (366), upto 50% (360) recovered.
 (c) PCC, sodium acetate, 4Å molecular sieves.
 (d) 1.1 eq. L-Selectride, 2.2 eq. TMEDA, THF, -78°C.
 (e) NaH, DMF, R.T.
 (f) [i] Excess ammonium formate, methanol, Pd-C, reflux, [ii] Tosylimidazole, NaH, DMF, 0°C, 24 h.
 (g) 2 eq. TBAF, R.T., 72 h.

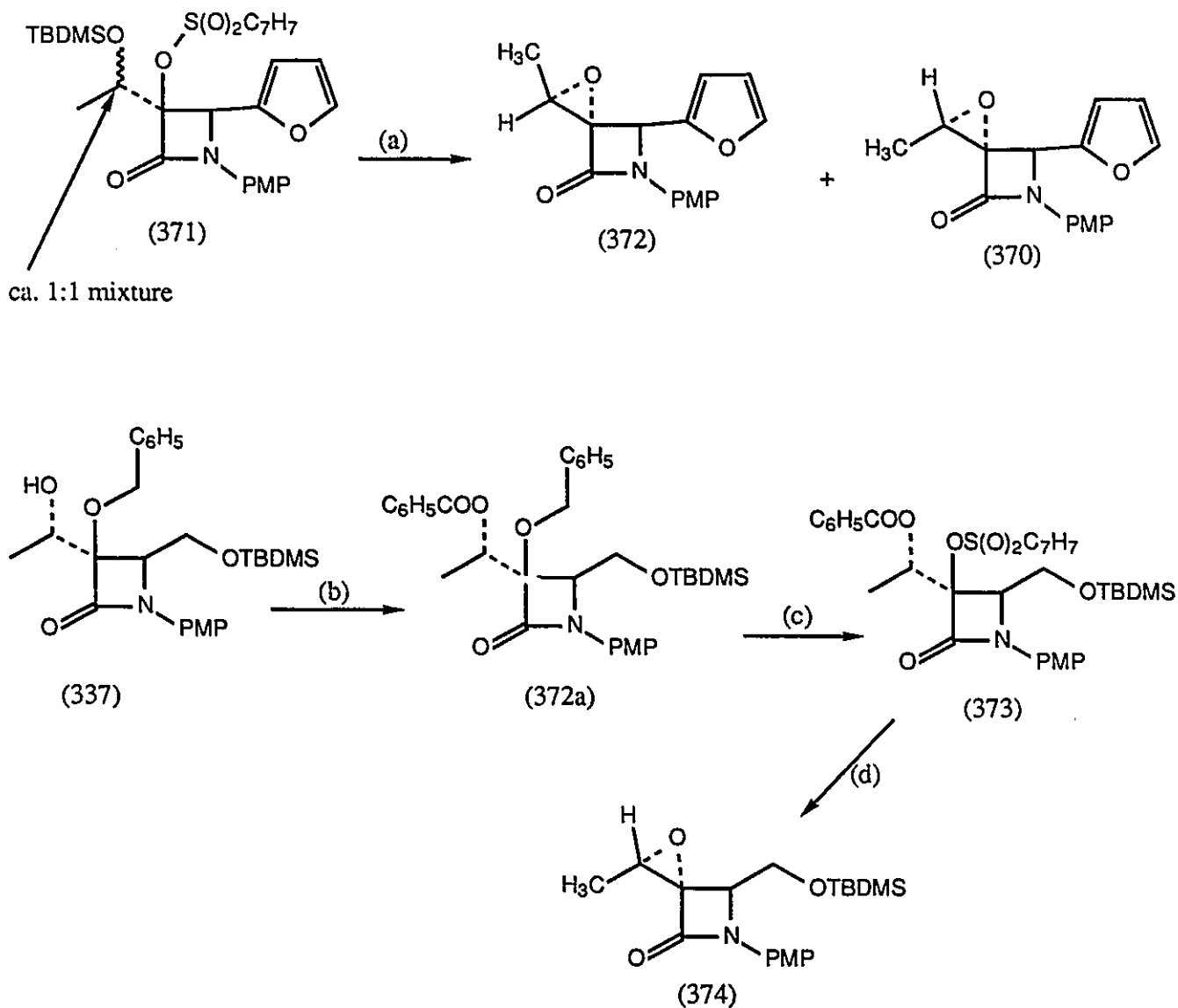
hydroxyethylazetidinones, the 1:1 mixture of the tosylates (371, Fig. LVII) was prepared. Exposure of this mixture to TBAF in THF under conditions used for (369, Fig. LVI) led to the formation of a 1:1 mixture of the azetidinone-oxiranes. (372 and 370, Fig. LVII) in about 80% yield. This mixture could not be resolved into its components. It seems that the stereochemistry of the hydroxyethyl group is of little consequence for these oxirane formation reactions. Thus the unusual elimination observed in the case of (366, Fig. LVI) was perhaps a consequence of the nature of the leaving group and the conditions employed¹¹⁹.

In the case of the azetidinone obtained by debenzoylation of (372a, LVII), the activation of the tertiary alcohol group was uneventful. {The product of debenzoylation step has not been shown.} Subsequent epoxide formation was carried out with sodium methoxide in THF-methanol mixture in about 50% yield. As before only one product was obtained, as determined by high field NMR.

It can be claimed that the nucleophilic inversion at the hydroxyethyl side-chain of azetidinones such as (274, Fig. XLVI) was successfully carried out. In the course of these studies a method for synthesis of 3-hydroxy-3-allylazetidinones was discovered. Even though the stereochemistry of these disubstituted azetidinones has not yet been established, it is obvious that the syntheses is highly diastereoselective.

Another out come of these experiments was the *systematic* syntheses of epoxyazetidinone such as (273, Fig. XLVI)¹²⁰. The issue of the stereochemistry of the hydroxyethyl side chain has not been settled, since no X-ray diffraction analysis has been carried out in

Fig. LVII



$C_7H_7S(O)_2 = p\text{-toluenesulfonyl}$

(a) TBAF, THF, R.T., 72 h.

(b) benzoylimidazole, NaH, DMF, 0°C.

(c) [i] Excess ammonium formate, 10% Pd -C, methanol, reflux.

[i] tosylimidazole, NaH, DMF, 0°C.

(d) 1.1eq. NaOMe, THF, methanol.

this series of experiments. But on the basis of analogy with 3-methoxyazetidinone it can be suggested that these compounds have the stereochemical feature as shown in various figures. One can be fairly certain that these compounds are diastereomerically pure.

A side-light of these studies is that perhaps for the very first time a dependable series of reactions is available for the syntheses of 3-hydroxyazetidinones and thus various alkoxy derivatives.

Another minor point that has emerged from these studies is the extraordinary facility with which hindered hydroxyl groups can be converted to the corresponding esters and sulfonate esters with the help of imidazole derivatives.⁷⁶

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- (97) [i] Sheehan, J.C. and Lo, Y.S. *J. Am. Chem. Soc.* 1972, 94, 8253. [ii] Sheehan, J. C. and Lo, Y.S. *J. Org. Chem.* 1973, 38, 3227.
- (98) Palomo, C. and Cossio, F.P. *Tet. Lett.* 1985, 26, 4239.
- (99) In this particular publication (98) these authors do not mention if the reaction is affected by the nature of the condensing agent used. In several of their earlier publications, these authors have used various condensing agents to prepare various azetidinones, without any noticeable differences in terms of the yields and the geometry of the product azetidinones.
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- (101) Manhas, M.S.; Amin, S.G. and Glazer, R.D. *Synthesis*, 1979, 210.

- (102) Ojima, I. Yamato, T. and Nakahashi, K. *Tet. Lett.* **1985**, *26*, 2035.
- (103) Some of the acetoxy derivatives were taken through the deacetylation-alkylation sequence and the products were compared against those obtained by ketene-imine reaction of the corresponding alkoxyacetic acid. Invariably the azetidinones prepared by these two different procedures were identical and had the H₃-H₄ coupling constants in the range of 5 -6 Hz.
- (104) C-3 deprotonation of azetidinones bearing an additional negatively charged group at C-3 is known (Chapter 5). It seems that the stabilization of the negatively charged nitrogen atom by the carbamate moiety is crucial for the success of deprotonation.
- (105) Hunig, S.; Denchert, K. and Hertenstein, U. *Synthesis* **1973**, 777.
- (106) Removal of the carbobenzyloxy group does not have to involve the C-3 oxygen atom. The carbonic acid derivative resulting from the loss of the benzyl group from the carbonate can lose CO₂ to generate the free hydroxyl group at C-3.
- (107) The procedures attempted for the disubstituted azetidinone were those described by [i] Corey, E.J. and Suggs, W.J. *J. Org. Chem.* **1973**, *38*, 3224. [ii] Gigg, J. and Gigg, R. *J. Chem. Soc. C.* **1968**, 1903. [iii] Boss, R. and Scheffold, R. *Angew. Chem. Inter. Ed. Engl.* **1976**, *15*, 558. In none of these cases any change was observed even after an overnight reaction. In case of the monosubstituted azetidinone (326, Fig. L) only [iii] was attempted and no change was observed.

(108) Ozonolysis of conjugated dienes has been carried out to selectively cleave the terminal (or less substituted or unconjugated) double bond in presence of suitable commercial dyes. Veysoglu, T.; Mitscher, L.A. and Swayze, J.K. *Synthesis* 1980, 807. When applied to the monosubstituted azetidinone (326, Fig. L), again benzaldehyde was the only identifiable product.

It is difficult to come up with an exact explanation of this inability to distinguish between two double bonds. A possible explanation is that the presence of electron withdrawing allyl substituent lowers the reactivity of the terminal double bond. The reactivity of the cinnamyl (or the methylcinnamyl) group at C-4 is perhaps not as significantly lowered by the presence of the allylic nitrogen atom. Moreover the presence of the phenyl group may partially compensate for the electron withdrawal by the amino group. Thus the double bonds may have comparable reactivity toward various reagents. To complicate things further, the two groups are fairly close to each other, specially in the case of the disubstituted azetidione. Any reagent can approach both the double bonds with about equal facility.

(109) 9-BBN is known to be fairly selective for reaction with unhindered double bond. Brown, H.C.; Knights, E.F. and Scouten, C.G. *J. Am. Chem. Soc.* 1974, 96, 7765. b- Elimination as a means of releasing chiral auxiliaries from the products of acetal template based enantioselective reactions has been used. For specific details see, Seebach, D.; Weber, Y. and Imwinkelried R. in "Modern Synthetic Methods" 1986, 4, 128, specifically the pages 196 - 212.

- (110) Nakai and Mikami have reviewed Wittig rearrangement. Nakai, T. and Mikami, K. *Chem. Rev.* 1986, 86, 885.
- (111) Ogilvie, W.W. and Durst, T. *Can. J. Chem.* 1988, 66, 304
- (112) The conditions employed were very similar to those of Bieg, T. and Szeja, W. *Synthesis* 1985, 75.
- (113) It might be expected that nucleophilic displacement at the tertiary carbon atom would not be facile. However internal nucleophilic displacements have been known to take place at such hindered carbon atoms. There are numerous examples and it is not possible to list all of them here. In the context of formation of oxiranes (in which one carbon atom of the oxirane ring is quaternary) see Trost, B. M. and Melvin, L.S. "Sulfur Ylides: Emerging Synthetic Intermediates" 1975, Academic Press. The tables on pages 194 - 197 provide several such examples.
- (114) For a discussion of Darzen's reaction see March, J. "Advanced Organic Chemistry" third edition., 1985, Wiley Interscience. 843.
- (115) It was anticipated that similar to the case of the C-3 iminoazetidinones, formation of a planar anion at C-3 would force the formation of bond between the electrophile and the azetidinone on the side opposite to the substituent at C-4. This would force the chloro group at C-3 and the methylcinnamyl group at C-4 cis to each other.
- (116) Thionyl bromide has been used for conversion of alcohols to the corresponding bromides. Hudson, H.R. and de Spinoza, G.R. *J. Chem. Soc., Perkin Trans. I* 1976, 104.
- (117) For a review of several such reagents see Castro, D.R. *Org. React.* 1983, 29, 964.

(118) The situation is not unique to the use of halide anions as nucleophiles. In some instances the starting material was recovered in variable amounts and in some instances the consumption was total. But in no case it was possible to reproducibly obtain the products of nucleophilic displacement with any degree of consistency. Resistance towards nucleophilic displacement has been noted for several similar derivatives of mono and bicyclic azetidinones. Wagale, D.R.; Garai, C.; Monteleone, M.G. and Bose, A.K. *Tet. Lett.* 1988,29, 1649. (specifically the ref 10.). This publication also mentions use of acetoxyacetyl chloride for the purpose of enantioselective synthesis of azetidinone but provides only one example. Isolated examples of nucleophilic inversions at 3 position of azetidinones are known. For one such example see; Bose, A.K.; Manhas, M.S.; Amin, S.G. and Chawla, H.P.S. *Synthesis*, 1977, 407.

(119) The reaction seems to be unique for the chloroazetidinone. As it stands the reaction is nothing more than a chemical curiosity, largely due to the difficulties associated with obtaining the haloazetidinones and their conversion to the corresponding hydroxyethyl derivatives. However if the successful α - elimination can be carried out on the corresponding C-3 alkoxyazetidinones, it would provide a very quick entry to C-3 acyl azetidinones which are potential precursors for thienamycin and related compounds. At the time of writing several such attempt for 3-alkoxy-3-hydroxyethyl and 3-alkoxy-3-acetylazetidinones have failed.

(120) There have been isolated and non-systematic syntheses of similar epoxides [i] Sebti, S. and Foucaud, A. *Tet.* 1984, 40, 3233 In this case the epoxy azetidinones were the byproducts,

stereochemistry of these compounds is not known. [ii] John, D.I.; Jephcote, V.J.; Edwards, P.D.; Luk, K. and Williams, D.J. *Tet. Lett.* 1984, 25, 2915.

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Experimental section

General

Acetoxyacetyl chloride, used for the preparation of various acetoxyazetidiones, was prepared from glycolic acid. The procedure undertaken was similar to that employed by Bennigton¹⁶⁶. For short periods (up to one week) the acid chloride can be kept under nitrogen at room temperature. However on longer storage under these conditions it tends to develop a faint yellow colour and needs to be distilled prior to use (55 - 57°C/12 mmHg). For reproducibility in the azetidnone formation step it is essential that colourless acid chloride be used. The preparation and purification of other chemicals used has been noted at several other places. General comments mentioned at the beginning of the Experimental Section of Chapter 2 also apply here.

As an example of the synthesis of 3-acetoxyazetidiones and their subsequent manipulations, details of preparation of 3-acetoxy-4-cinnamylazetidione (300, Fig. XLVIII) are presented below.

Synthesis of (300, Fig. XLVII)

To a dry 1000 ml round bottomed flask provided with a stirring bar and a pressure equalizing dropping funnel was added 19.84 g (83.7 mmol) of imine (89) and 17.3 mL (124 mmol) triethylamine. Enough dry dichloromethane was added to obtain a clear solution (ca. 500 - 600 mL). The solution was cooled in an ice-bath under nitrogen. The dropping funnel was charged with 10 mL (93 mmol) of acetoxyacetyl chloride and about 30 mL of dry methylene chloride. The septum cap was quickly replaced with a drying tube. The solution of the acid chloride was added to a

vigorously stirring solution of the imine over a period of about 30 min. The resulting red-brown heterogenous reaction mixture was allowed to come room temperature over 3 h and then stirred at this temperature for an additional 18 - 20 h.

Work up consisted of washing the reaction mixture with 2X100 mL of 10% HCl, 2X100 mL water and 2X100 mL of 5% NaHCO₃. After each extraction the aqueous layer was extracted with 25 - 30 mL of methylene chloride and the organic layers were combined. To the combined organic layer was added 3 g of MgSO₄ and about 100 g of 230-400 mesh silica. After stirring for about 10 min the liquid was filtered to remove the drying agent and silica. The solid residue was washed twice with 50 -75 mL of methylene chloride. Removal of solvent from the combined filtrate provided a brown-white powder with some lumps. The lumps were crushed and the entire mass was triturated with about 150 mL of refluxing ether. Removal of ether by filtration provided 14 - 18 g of the product as a white solid. This amounts to a yield of 50 -62% based on the amount of the imine. The compound has following spectral properties: mp:164-165°C; ir: 1755 cm⁻¹; ms: 337 (M⁺, 3.7%), 236 (M⁺-101, 8.3), 188 (M⁺-149, 23.9%), 146 (M⁺-191, 100%); nmr: δ =7.4-7.2 (m, 7 H), 6.8-6.7 (m, 3 H), 6.17 (dd, 2 H, J= 8.0 Hz, J= 16.0 Hz), 5.8 (d, 1 H, J= 4.9 Hz), 4.9-4.8 (ddd, 1 H, J= 0.7 Hz, J= 4.9 Hz, J= 7.9 Hz), 3.7 (s, 3 H), 2.0 (s, 3 H).

Saponification of the acetoxyazetidinone(300, XLVII)

19 g (56.3 mmols) of the acetoxyazetidinone (300) was dissolved in 500 mL of THF (not rigorously dried but taken from a fresh bottle). To the clear solution was added 500 mL of methanol. The solution was stirred vigorously and 1 g of commercial sodium

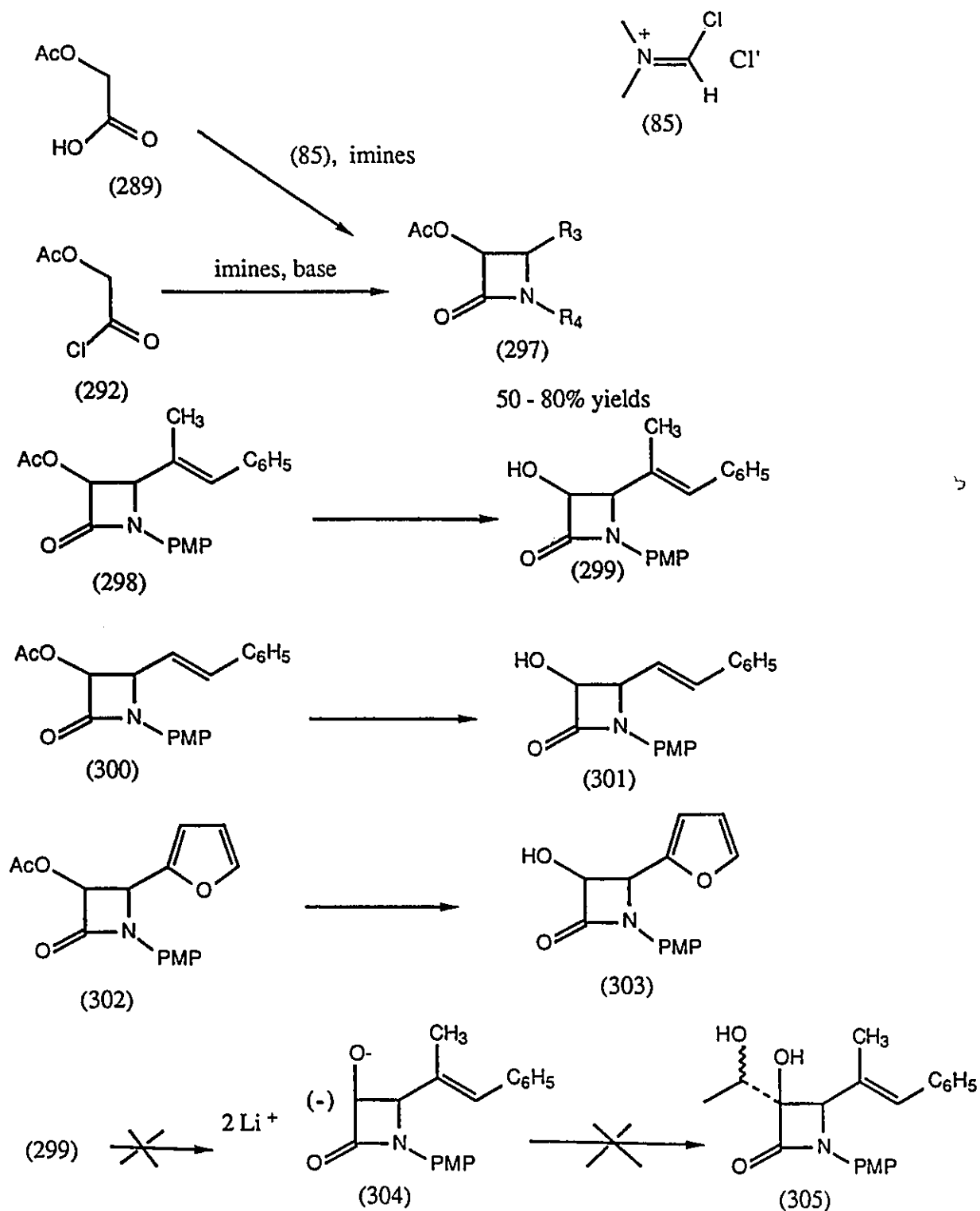
methoxide was added. (Amount of sodium methoxide in milligrams was about the same as the total volume of the solution in mL. This requirement is by no means rigorous). The heterogeneous reaction mixture was stirred at room temperature for an additional 30 min by which time the starting material was completely consumed as revealed by TLC. About 9 g of Amberlite 120 resin (H⁺ form) and about 3 g of charcoal was added to the reaction mixture. (weight of Amberlite in grams was roughly half of the weight of the starting material in grams, again this relationship is not rigorous). After 5- 10 min of stirring at room temperature the Amberlite and charcoal were removed by filtration through Celite. The solid was washed with about 100 mL of methanol. Removal of the solvent from the combined filtrate provided a straw colored solid which was dissolved in a solvent mixture containing ethyl acetate, methylene chloride and THF in an approximately 10:1:1 ratio. The total volume at this stage was roughly 1000 mL. The organic layer was washed successively with 2X50 mL 5% NaHCO₃ saturated with NaCl, saturated NaCl solution and finally with 2X50 mL of 10% HCl saturated with NaCl. The organic layer was dried etc. to provide a brownish solid. Washing with 2X125 mL of ether served to remove the color and left behind 15.8 - 16.2 g of the hydroxyazetidinone(301, Fig. XLVII). The yield was 95 - 97%. The product has following properties mp: 167-168°C; ir: 3400-3200, 1740 cm⁻¹; ms: 295 (M⁺, 10.4%), 266 (M⁺-29, 25.3%), 238 (imine⁺+1, 15%), 236 (imine⁺-1⁺, 14%), 146 (M⁺-149, 100%); nmr: d = 7.3-7.1 (m, 7 H), 6.7-6.6 (m, 3 H), 6.2-6.1 (dd, 1 H, J= 6.6 Hz, J= 16.0 Hz), 5.0 (dd, 1 H, J= 7.7 Hz, J= 5.1 Hz), 4.7 (m, 1 H), 3.6 (s, 3 H), 2.9 (d, 1 H, J= 7.6 Hz). HRMS calc for C₁₈H₁₇NO₃ 295.1233,

found 295.1179. The product was pure enough for subsequent alkylation steps.

Methylation of (301, Fig. XVII)

Hydroxyazetidinone (301), 2 g (6.77 mol) was added to a 250 mL round bottomed flask with a Claisen tube and a stirring bar. One opening of the Claisen tube was provided with a drying tube and the other was capped with a septum cap. About 50 mL of dry THF was added with help of a cannula and the contents were cooled in an ice-bath. NaH (ca. 50% dispersion in oil), 0.36 g (7.5 mmol) was added to the flask in three portions. This required quick removal of the drying tube while maintaining a flow of nitrogen. After the addition was complete and gas evolution had subsided (about 5 - 10 min) a grey suspension was obtained. A solution of about 2 mL of iodomethane in about 10 mL of dry THF was added to the suspension with the help of a cannula (number of milliliters of iodomethane was roughly same as the weight of the hydroxyazetidinone, this ensured a fairly large excess of the alkylating agent). The resulting yellow heterogeneous reaction mixture was stirred vigorously and was allowed to come to room temperature over a period of about 3 h. After a total of about 18 h of stirring, the reaction mixture was worked up by adding it to 150 mL of 1% ice-cold HCl and extracting the aqueous layer with 250 mL of dichloromethane. The aqueous layer was extracted with additional 2X50 mL of dichloromethane and the combined organic layer was dried, the drying agent was removed by filtration and the solvent was removed from the filtrate to provide a yellow-white solid. Trituration of this solid with 50 mL of refluxing ether followed by filtration provided 1.8 - 2 g of 3-

Fig. XLVIII



methoxyazetidinone(191, Fig. XXXII). This amounts to an isolated yield of 85 - 95%. However when the reaction is performed on about 10 times the present scale the yield for this step may be as low as 60 - 65%. The spectral properties of the product are identical with a sample prepared by ketene-imine reaction (Chapter 8).

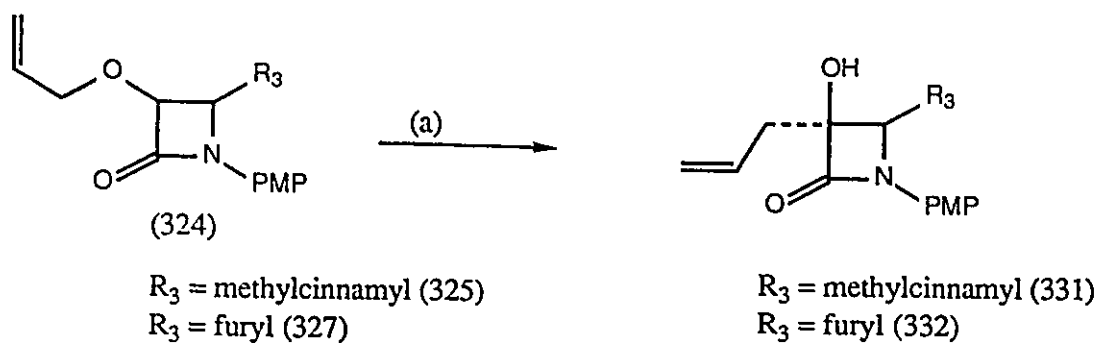
Benylation of (301, Fig. XLVIII)

To a solution of 16 g (54 mmol) of the starting material in 250 mL of THF in a 500 mL round bottomed flask provided with a stirring bar was added 0.25 g of tetra-(n-butyl)ammonium iodide and 14 g (81 mmols.) of benzyl bromide. The contents were stirred vigorously while 4.3 g (75 mmol) of finely powdered KOH were added in one portion. Initially the reaction mixture had a pale yellow color which changed to white within 10 min and a solid began to deposit on the sides of the flask. This solid was washed down with the help of small portions of THF. After stirring for 18 -20 h at room temperature the reaction mixture was poured into a conical flask containing 300 mL of 10% HCl and 500 mL of dichloromethane. The reaction flask was rinsed with the help of additional quantities of the acid and dichloromethane and these washings were added to the conical flask. The contents of the conical flask were stirred for a period of about 30 min during which time the solid lumps dissolved to provide a clear red organic layer and nearly colorless aqueous layer. The layers were separated and the aqueous layer was washed with 5X50 mL of dichloromathane. The combined organic layer was washed with 100 mL of sat. NaCl solution and was dried etc. to provide a brown white solid. Trituration of this solid with 2X125 mL of refluxing ether followed by filtration provided 12.1 g (31 mmol) of

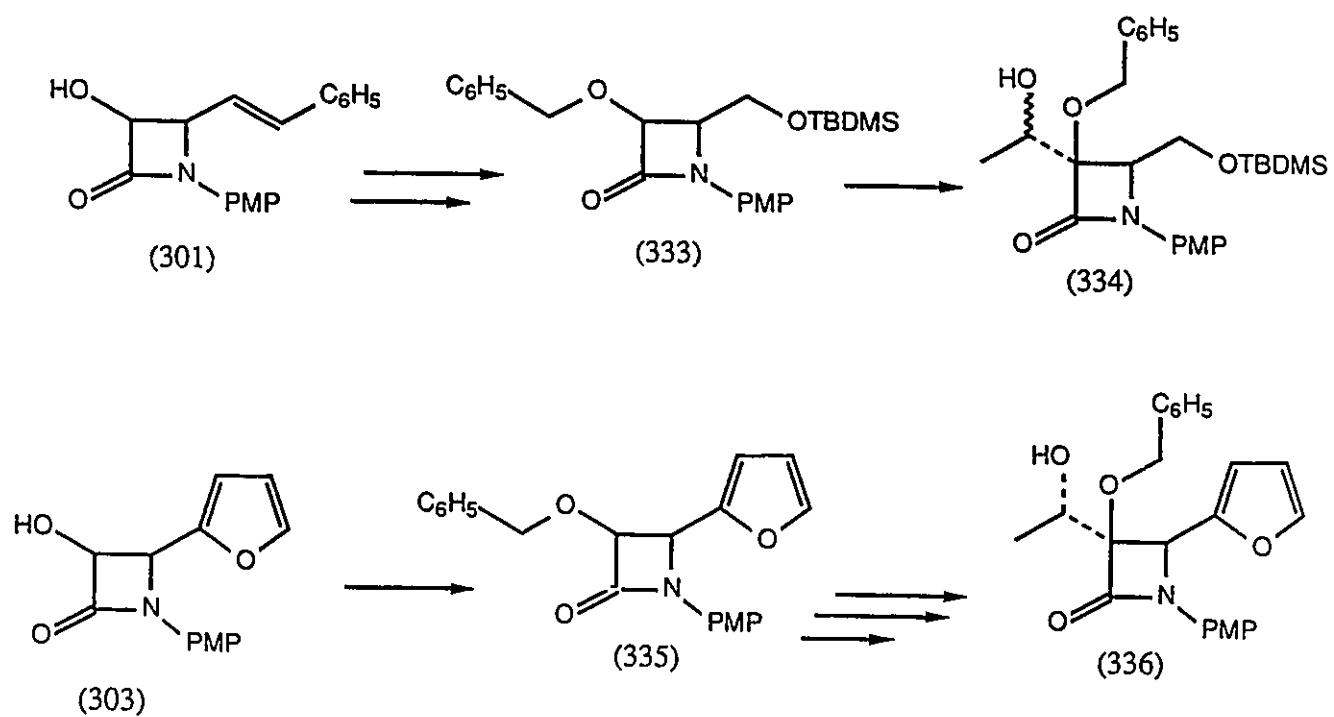
3-benzyloxy-4-cinnamylazetidinone as a white chromatographically homogeneous solid. Removal of the solvent from the filtrate provided 13.2 g of a red oil which showed the presence of the desired product by TLC. This oil was subjected to column chromatography using 5:1:0.1 :: hexane : ethyl acetate: dichloromethane to provide several fractions which showed the presence of the desired product along with other impurities. All such fractions were pooled together and the solid obtained after removal of the solvent was washed with ether to provide 1.0 g of the benzyloxyazetidinone. This brought the total yield to 13.1 g (62% yield). This product was identical with the one prepared by reaction of benzyloxyacetic acid with the imine(89) using (85) for the activation of benzyloxyacetic acid (421, Fig. LXXII, entry no. 26). The same product was obtained in about 50% yield by reaction of benzyloxyacetyl chloride with the imine(89) by a procedure similar to that mentioned for the preparation of the acetoxyazetidinone. mp: 155-156°C; ir: 1750 cm^{-1} ; ms: 385 (M^+ , 3.1%), 294 ($\text{M}^+ - 91$, 13.6%), 237 (imine⁺, 8.9%), 236 (imine⁺-1, 36.4%), 91 (C_7H_7^+ , 100%) ; nmr: δ = 7.4-7.2 (m, 12 H), 6.8-6.7 (m, 3 H), 6.3-6.2 (dd, 2 H, J= 8.8 Hz, J= 16.0 Hz), 4.9 (d, 1 H, J = 4.7 Hz), 4.7 (m, 3 H), 3.7(s, 3 H).

Compound (298, Fig. XLVIII) was prepared from the acid chloride by a procedure similar to the one mentioned above for the preparation of (300). The yield was about 72%. This azetidinone has following properties. mp:139-141°C; ir: 1755-1745 cm^{-1} ; ms: 351 (M^+ , 12.5%), 280 ($\text{M}^+ - 71$, 3.5%), 250 (imine⁺, 100%), 160 ($\text{M}^+ - 191$, 100%); nmr: δ = 7.4-7.2 (m, 7 H), 6.86-6.83 (dd, 2 H, J= 2.1 Hz, J= 6.8 Hz), 6.6 (s, 1 H), 6.0 (d, 1 H, J= 4.1 Hz), 4.8 (d, 1 H, J= 4.1 Hz), 3.76

Fig. LI



(a) LDA, THF, -78 °C, excess TMEDA, warm up.



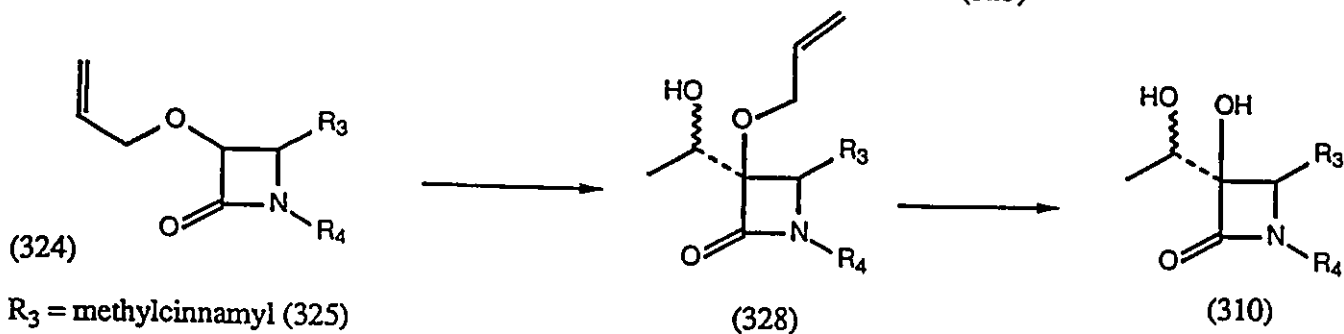
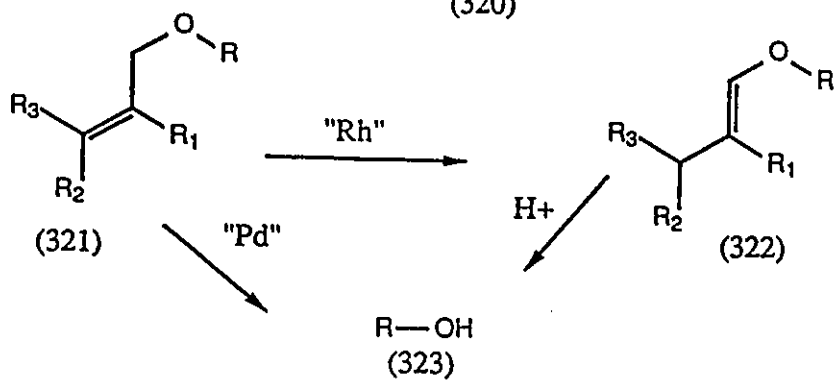
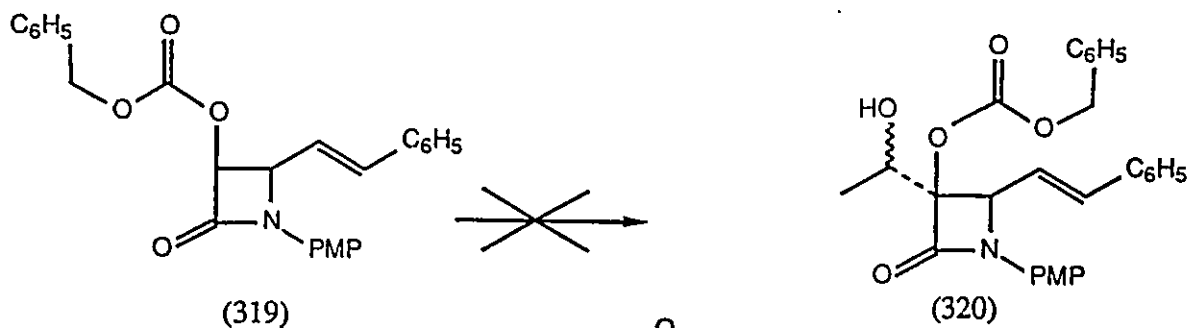
(s, 3 H), 2.0(s, 3 H), 1.8 (d, 3 H, J= 1.2 Hz). HRMS calc for C₂₁H₂₁NO₄ 351.1507 , found 351.1455.

Compound (302, Fig. XLVIII) was prepared in 61% yield by the method used for other acetoxyazetidiones. This compound has following properties mp:136°C; ir: 1755, 1745 cm⁻¹; ms: 301 (M⁺, 4.3%), 202 (imine⁺⁺, 12.7%), 201 (imine⁺, 9.5%), 186 (M⁺-115, 10.5%), 152 (M⁺-149, 21.9%), 149 (C₈H₇NO₂⁺, 17.9%), 110 (M-191, 100%); nmr: d =7.4-6.3 (m, 9 H), 5.9 (d, 1 H, J= 4.7 Hz), 5.3 (d, 1 H, 4.7 Hz), 3.7 (s, 3 H), 1.9 (s, 3 H).

Saponification of the acetoxyazetidione (298, Fig. XLVIII) as above furnished the hydroxyazetidione (299, Fig. XLVIII) in 82% yield. The properties of this compound are as follows mp:172°C; ir: 3450-3100, 1750 cm⁻¹; ms: 309 (M⁺, 24.6%), 280 (M⁺-29, 21%), 250 (imine⁺-1, 19.2%), 160 (M⁺-149, 100%), 159 (M⁺-150, 76%); nmr: d = 7.4-7.2 (m, 7 H), 6.85-6.82 (dd, 2 H, J= 2.1 Hz, J= 6.8 Hz), 6.5 (s, 1 H), 5.13-5.19 (dd, 1 H, J= 5.3 Hz, J= 9.3 Hz), 4.7 (d, 1 H, 5.3 Hz), 3.7 (s, 3 H), 2.6 (d, 1 H, J= 9.3 Hz). HRMS calc for C₁₉H₁₉NO₃ 309.1393, found 309.1304.

Saponification of the acetoxy compound (302) furnished the hydroxyazetidione (303, Fig. XLVIII) in 89% yield. This azetidione has following properties mp:168°C; ir: 3200-3100, 1755 cm⁻¹; ms: 259 (M⁺, 3.7%), 202 (imine⁺⁺, 8.0%), 201 (imine⁺, 3.8%), 149 (C₈H₇NO₂⁺, 15.8%), 110 (M⁺-149, 100%); nmr: d =7.4-6.3 (m, 7H), 5.2 (d, 1 H, J= 5.0 Hz), 3.7-3.6 (m, 4 H), 3.3 (broad signal, 1 H). The high field NMR spectrum also showed presence of a broad signal at 5.19 ppm(less than one proton by integration) which remains unassigned.

Fig. L

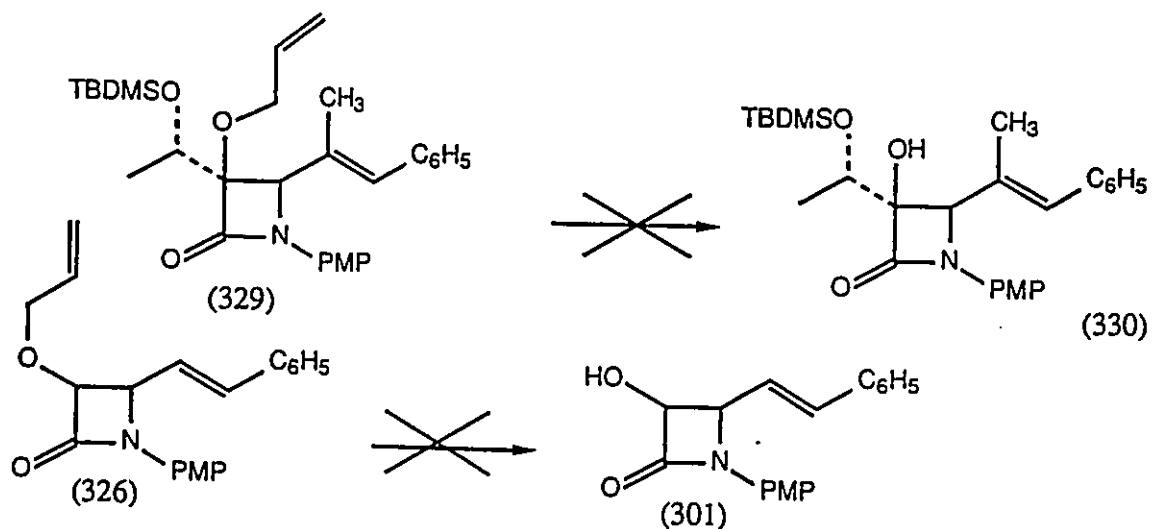


R₃ = methylcinnamyl (325)

R₃ = cinnamyl (326)

R₃ = furyl (327)

R₄ = PMP for all cases



The benzyl ether of the hydroxyazetidinone (299, Fig. XLVIII) was prepared by the benzylation procedure mentioned above. The reaction proceeded in about 75% yield and the product obtained was identical in all regards with that obtained from reaction of benzyloxyacetyl chloride with the corresponding imine, using the procedure mentioned above for the preparation of the acetoxyazetidinones. This azetidinone was characterized by following properties mp:118°C; ir: 1755 cm^{-1} ; ms: 399 (M^+ , 8.2%), 308 (M^+-91 , 20%), 290 (M^+-109 , 10.8%), 251 (imine⁺, 9.2%), 250 (imine⁺-1, 39.3%), 216 (M^+-173 , 39.3%), 129 (M^+-270 , 100%); nmr: δ = 7.4-7.2 (m, 14 H), 6.84-6.81 (dd, 2 H, $J=2.8$ Hz, $J= 6.7$ Hz), 6.5(s, 1 H), 4.9(d, 1 H, $J= 5.0$ Hz), 4.79-4.67 (m, 3 H), 3.7 (s, 3 H), 1.9 (d, 3 H, $J= 1.3$ Hz). HRMs calc for $\text{C}_{26}\text{H}_{25}\text{NO}_3$ 399.1871, found 399.1820.

The properties of the benzyloxyazetidinone (334a, Fig.LI) prepared either by benzylation of the corresponding hydroxyazetidinone (57% yield) or by reaction of benzyloxyacetyl chloride with the corresponding imine (51% yield) are as follows mp:160-161°C; ir: 1755 cm^{-1} ; ms: 349 (M^+ , 2.3%) 258 (M^+-91 , 11.3%), 202 (imine⁺+1, 21.6%), 201 (imine⁺, 17.6%), 200 (imine⁺-1, 27.7%), 91 (C_7H_7^+ , 10%); nmr: δ = 7.4-6.39 (m, 13 H), 5.2 (d, 1 H, $J= 4.6$ Hz), 4.9 (d, 1 H, $J= 4.6$ Hz), 4.5-4.3 (AB, 2 H, $J= 11.3$ Hz), 3.7 (s, 3 H).

Allylation of the hydroxyazetidinones (299, 301 and 303, Fig. XLVIII) was carried out in a manner similar to that used for methylation. The products (325, 326 and 327, respectively, Fig. L) were obtained in 80-90% yields and were identical to those obtained

from reaction of allyloxyacetic acid with the corresponding imines using (85) as activating agent. Their properties are as follows:

(325, Fig. L) mp: 78-79°C; ir: 1750 cm^{-1} ; ms: 349 (M^+ , 16.7%), 308 (M^+-41 , 7.0%), 280 (M^+-69 , 4.6%), 251 (imine⁺, 10.3%), 250 (imine⁺-1, 46.3%), 200 (M^+-149 , 27.9%), 129 (M^+-220 , 100%); nmr: δ = 7.4-7.2 (m, 7 H), 6.8 (m, 2 H), 6.6 (broad s, 1 H), 5.9-5.8 (m, 1 H), 5.3-5.1 (two m, 2 H), 4.89 (d, 1 H, $J= 5.0$ Hz), 4.7 (m, 1 H), 4.2-4.1 (m, 2 H), 3.7 (s, 3 H), 1.9 (d, 3 H, $J= 1.4$ Hz). HRMS calc for $\text{C}_{22}\text{H}_{23}\text{NO}_4$ 349.1661, found 349.1686.

(326, Fig. L) mp:129-130°C; ir: 1745 cm^{-1} ; ms: 335 (M^+ , 7.8%), 294 (M^+-41 , 12.7%), 237 (imine⁺, 10%), 236 (imine⁺-1, 32%), 186 (M^+-149 , 73%), 117 (M^+-218 , 100%); nmr: δ = 7.4-7.2 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 2 H, $J= 8.8$ Hz, $J= 16.0$ Hz), 5.9-5.8 (m, 1 H), 5.3-5.1 (two m, 2 H), 4.8 (d, 1 H, $J= 5.2$ Hz), 4.7 (m, 1 H), 4.1 (m, 2 H), 3.7 (s, 3 H). HRMS calc $\text{C}_{21}\text{H}_{21}\text{NO}_3$ 335.1552, found 335.1519.

(327, Fig. L) mp:77-78°C; ir: 1760 cm^{-1} ; ms: 299 (M^+ , 6.2%), 258 (M^+-41 , 10.5%), 202 (imine⁺+1, 30.9%), 201 (imine⁺, 28.1%), 150 (M^+-149 , 100%); nmr: δ = 7.4-6.3 (m, 7 H), 5.7 (m, 1 H), 5.1 (m, 3 H), 4.9 (d, 1 H, $J= 4.6$), 4.0-3.8 (two m, 2 H), 3.7 (s, 3 H). HRMS calc for $\text{C}_{17}\text{H}_{17}\text{NO}_4$ 299.1233, found 299.1143.

Syntheses of 3-(2-propenyl)-3-hydroxyazetidiones

A solution of 0.698 g (2 mmol) of the allyl ether (325, Fig.LI) in about 25 mL of dry THF was cooled in an acetone-Dry Ice bath under nitrogen atmosphere. LDA (1.1 eq. prepared by reaction of 1.15 equivalents of di-isopropylamine and 1.1 equivalent of n-BuLi, in THF at acetone-dry ice temperature for 10-15 min) was added with the help of a cannula. The resulting clear solution was allowed

to stir for about 10 min and 1 mL of dry TMEDA was added. The resulting clear colorless solution was allowed to come to room temperature over a period of about 3 h and was stirred at that temperature for an additional 15-16h. The reaction mixture was worked up by addition of 50 mL of 10% HCl followed by 50 mL of ethyl acetate. The layers were separated and the aqueous layer was extracted with 3x25 mL ethyl acetate. The combined organic layer was washed with 50 mL of sat. NaCl solution and was dried etc to provide a red-brown tar. TLC showed absence of the starting material and presence of 2 compounds, one with higher and the other compound with lower R_f compared to the starting material. Column chromatography using 2:1: hexane : ethyl acetate for elution furnished 0.445 g (1.27 mmol) (65%) of azetidinone (331, LI) as a clear viscous oil which turned brown on exposure to air as the less polar compound. The product has following properties ir: 3200-3100 (broad signal), 1750 cm^{-1} ; ms: 349 (M^+ , 4.96%), 308 (M^+-41 , 2.2%), 280 (M^+-69 , 45%), 252 (imine $^{+}+1$, 15.1%), 250 (imine $^{+}-1$, 13.4%), 43 (100%); nmr: d = 7.3-7.1 (m, 7 H), 6.8 (m, 2 H), 6.4 (broad s, 1 H), 5.9 (m, 1 H), 5.2 (m, 2 H), 4.5 (s, 1 H), 3.7 (s, 3 H), 2.8 (m, 3 H), 1.9 (d, 3 H, $J= 1.2\text{ Hz}$). HRMS calc for $C_{22}H_{23}NO_4$ 349.1661, found 349.1670. The more polar compound was not identified.

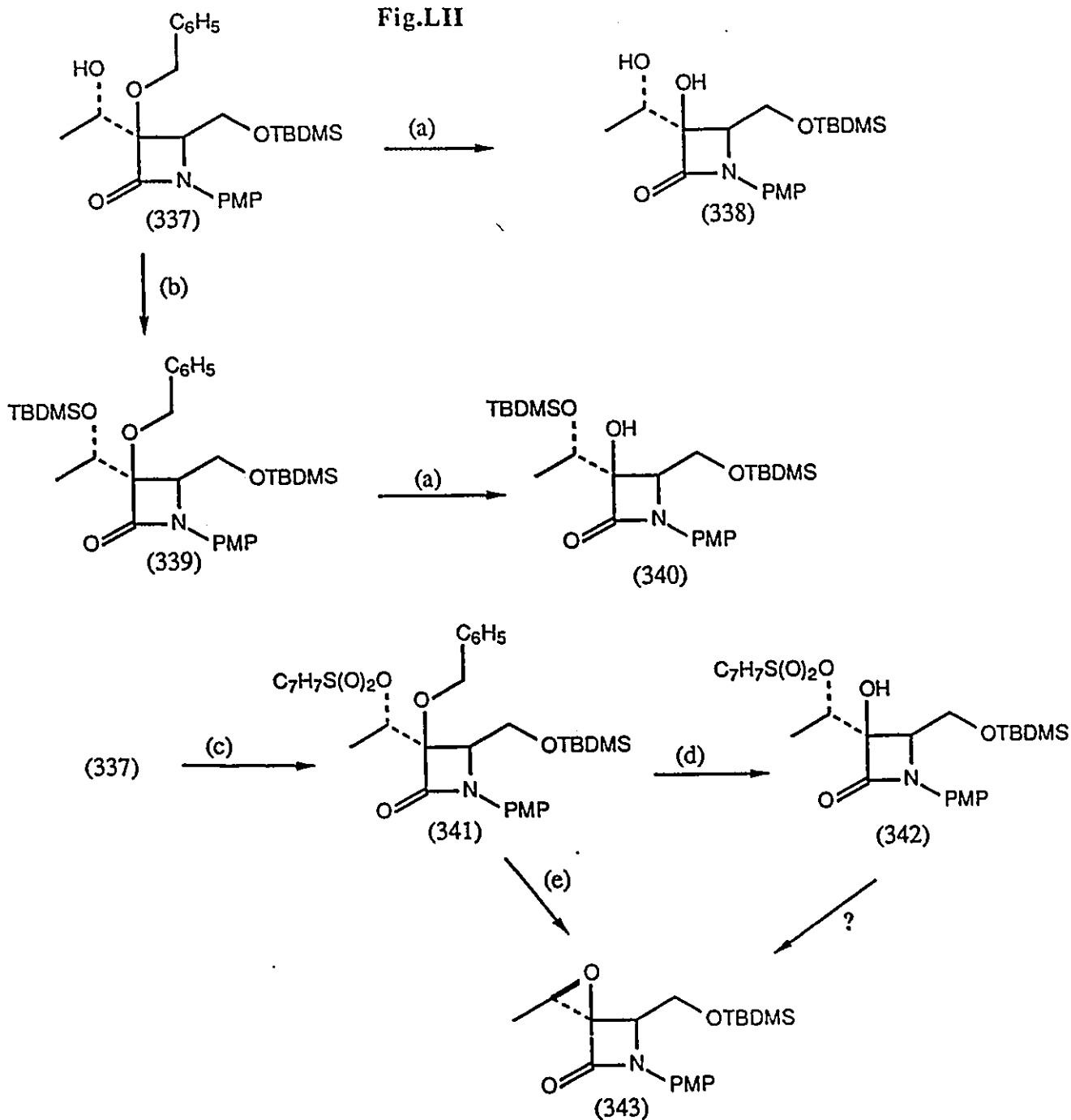
The hydroxyazetidinone (332, Fig. LI) is an oil. It was prepared in a manner similar to that used for preparation of (331) in 75% yield from the allyl ether (327, Fig. LI) and has following properties ir 3300-3200, 1750 cm^{-1} ; ms: 299 (M^+ , 7.9%), 202 (imine $^{+}+1$, 55.3%), 201 (imine $^{+}$, 12.8%), 150 (M^+-149 , 55.5%), 108 (M^+-281 , 100%); nmr: d = 7.4-6.4 (m, 4 H), 5.9-5.8 (m, 1 H), 5.3-5.2 (m, 2 H), 5.0 (s, 1 H), 5.7

(s, 3 H), 2.9 (s, 1 H), 2.7 (m, 2 H). HRMS calc for $C_{17}H_{17}NO_4$ 299.1233, found 299.1154.

Synthesis of (333, Fig. LI)

In a 1000 mL round bottomed flask fitted with a Claisen tube was added 3.85 g (10 mmols) of (427, Fig. LXXII) dissolved in 500 mL of dry dichloromethane and 10 mL of methanol followed by 1.5 g of finely crushed 4A^o molecular sieves. A drying tube and a septum were attached to the Claisen tube and the flask was cooled in an acetone-dry ice bath under nitrogen. Ozonized oxygen was bubbled into the solution until it acquired a dull blue color. Excess ozone was purged with nitrogen. Approximately 5 mL of dimethyl sulfide was introduced and the reaction mixture was allowed to warm up to room temperature over a period of about 3-4 h and was kept at that temperature for an additional 15-16 h. The solution was filtered through Celite to remove molecular sieves and the solid residue was washed with additional 100 mL of dry dichloromethane. The solvent was removed from the combined filtrate to leave behind a brownish solid. This solid was washed with ether (3X50 mL) to provide a white solid. Without further purification this solid was dissolved in about 250 mL of approximately 10:1 mixture of ethanol and THF. The nearly homogeneous solution was cooled in an ice bath and about 2 g (large excess) of sodium borohydride were added. The resulting heterogeneous mixture was stirred at the ice-bath temperature for 2-3 h. Enough Amberlite 120 (H⁺ form) was added to bring the pH of the solution near 2-3 (tested by taking a small sample and diluting it with 2 drops of water). The solvent was

Fig.LII



- (a) H₂ 40 -50 psi, 5 or 10% Pd-C, EtOH, 24 h
 (b) TBDMS-Triflate, 2,6-lutidine, methylene chloride, 0°C
 (c) NaH, DMF, Tosylimidazole, 0° -> 8° C 24 h.
 (d) same as (a) except 48 h.
 (e) Excess ammonium formate, 10% Pd-C, MeOH, reflux, 15 h.

removed by decantation and the resin was washed with 3X50 mL of ethanol. The original solution and the washings were combined and concentrated to provide a white paste. This paste was dissolved in 300 mL of dichloromethane and was washed successively with 100 mL 10% HCl, 100 mL water, 100 mL 5%NaHCO₃ and 100 mL water. Drying, removal of the drying agent and removal of the solvent provided 1.9 g (6 mmol) of 3-benzyloxy-4-hydroxymethylazetidinone as a white, chromatographically homogeneous paste. This was directly converted to the corresponding TBDMS derivative by standard methodology. This afforded 2.4 g (5.7 mmol) of the desired product (333, Fig. LI) following column chromatography (57% yield from compound 427). The product is a white solid mp: 70°C; ir: 1745 cm⁻¹; ms: 427 (M⁺, 2.6%), 370 (M⁺-57, 7.1%), 342 (M⁺-85, 7.0%), 149 (C₈H₇NO₂⁺, 16.4%), 91 (C₇H₇⁺, 100%); nmr: δ =7.5-7.2 (m, 7 H), 6.8 (dd, 2 H, J= 2.3 Hz, J= 6.8 Hz), 4.7 (m, 3 H), 4.2 (m, 1 H), 4.0-3.8 (m, 2 H), 3.7 (s, 3 H), 0.8 (s, 9 H), 0.0-(-)0.98(two s, 6 H).

The synthesis of (334, Fig. LI) from (333, Fig. LI) involved formation of the corresponding anion with LDA, the reaction of the anion with acetaldehyde, oxidation of the product with PCC and reduction of the acetyl compound with L-Selectride under non-chelating conditions. These reactions were carried out in the manner similar to that used in the case of 3-methoxyazetidinone (Chapter 4). The overall yield of the hydroxyethylazetidinone (334, Fig. LI) from (333) was about 40-45%. This compound is an oil and has following spectroscopic properties ir: 3200-3100, 1750 cm⁻¹; ms: 471 (M⁺,3.7%), 386 (M⁺-85, 3.0%), 251 (M⁺-220, 10%), 149 (C₈H₇NO₂⁺,

14.3%), 91 ($C_7H_7^+$, 100%); nmr: d = 7.5-7.2 (m, 7 H), 6.8 (dd, 2 H, $J=2.3$ Hz, $J=6.9$ Hz), 5.0-4.9 (AB, 2 H, $J=11.40$ Hz), 4.25 (m, 1H), 4.2 (dd, 1 H, $J=6.5$ Hz, $J=3.5$ Hz), 4.05 (dd, 1 H, $J=11.4$ Hz, $J=3.5$ Hz), 3.90(dd, 1 H, $J=6.5$ Hz, $J=11.4$ Hz), 3.7(s, 3 H), 1.29(d, 3 H, $J=6.2$ Hz), 0.84(s, 9 H), (-)0.02(s, 3 H), (-)0.04(s, 3 H). The high field nmr spectrum also showed presence of a doublet at 1.30 ppm, the integration for this signal was less one proton. This was not indicative of presence of the other diastereoisomer of the compound since all other signals were not duplicated and the signal in question was absent in the spectrum of the mixture of diastereoisomers.

Silylation of the above hydroxyethylazetidinone (337, Fig. LII) by the usual procedure provided the product azetidinone (339, Fig. LII) as a semi-solid in about 85% yield from (337). This compound has following properties ir: 1750; ms: 585(M^+ , 2.8%), 528 (M^+-57 , 17.7%), 500 (M^+-85 , 2.5%), 450 (M^+-135 , 2.3%), 436 (M^+-149 , 1.3%), 91 ($C_7H_7^+$, 100%); nmr: d = 7.6-7.2 (m, 7 H), 6.8 (m, 2 H), 5.0-4.8 (AB, 2 H, $J=11.3$ Hz), 4.2-3.9 (series of multiplets with shapes and coupling constants similar to those for (337), 3 H), 3.7 (s, 3 H), 1.3 (d, 1 H, $J=6.3$ Hz), 0.8 (s, 9 H), 0.7 (s, 9 H), 0.03-(-) 0.03 (series of singlets).

The synthesis of the tosylate (341, Fig. LII) from the hydroxyethylazetidinone (337) was carried out in the standard manner i.e. using NaH-DMF-tosylimidazole combination. The yield was 75% and the product was a white solid with following properties mp: 89-91°C; ir: 1745 cm^{-1} ; ms: 625 (M^+ , 7.8%), 568 (M^+-57 , 8.7%), 540 (M^+-85 , 5.5%), 453 (M^+-172 , 11.4%), 396 (M^+-229 , 66.4%), 157 (M^+-468 , 69.8%), 91 ($C_7H_7^+$, 100%); nmr: d = 7.7-7.1 (m, 11 H), 6.8

(dd, 2 H, J= 2.2 Hz, J= 8.9 Hz), 5.1 (q, 1 H, J= 6.6 Hz), 4.8-4.7 (AB, 2 H, J= 11.0 Hz), 4.1-3.79 (series of multiplets with shapes and coupling constants similar to those for (337), 3 H), 3.77 (s, 3 H), 2.3 (s, 3 H), 1.4 (d, 3 H, J= 6.6Hz), 0.8 (s, 9 H), (-) 0.06 (s, 3 H), (-) 0.09 (s, 3 H).

Synthesis of 3-hydroxy-3-hydroxyethyl-4-(t-butyldimethylsilyloxy)methylazetidion-2-one (338, Fig. LII)

Azetidione (339, Fig. LII) 0.35 g (0.59 mmol) was dissolved in 10 mL of 99% ethanol and approximately 0.02 g of 10% Pd-C was added. The mixture was hydrogenated at a pressure of 45-40 psi in a Parr hydrogenation apparatus. After an initial drop of about 5 psi there was no noticeable change in the pressure. After 24 h of hydrogenation at room temperature the reaction mixture showed absence of starting material as determined by TLC. The catalyst was removed by filtration through a small pad of Celite and the solid was washed with 10 mL of 99% ethanol. The combined filtrate was concentrated under reduced pressure to furnish a viscous oil with black particles suspended in it. Passage of the oil through a small plug of silica using 3:1: hexane : ethyl acetate for elution furnished 0.266 g (0.53 mmol) of the dihydroxyazetidione (338) as a clear oil. This amounts to 90% yield for debenzoylation step. The product has following properties ir: 3300-3100, 1750 cm^{-1} ; ms: 381 (M^+ , 1.7%), 324 (M^+-57 , 5.5%), 280 (M^+-101 , 29.2%), 252(M^+-129 , 6.4%), 157 (M^+-224 , 100%); nmr: d = 7.34 (dd 2 H, J= 2.3 Hz, J= 6.8 Hz), 6.8 (dd, 2 H, J= 2.3 Hz, J= 6.8 Hz), 4.25-3.97 (series of unresolved multiplets, 3 H), 3.7(s, 3 H), 1.2 (d,3 H, J= 6.5 Hz), 0.8 (s, 9 H),0.06(s, 3 H), 0.03(s, 3 H). HRMS calc for $\text{C}_{15}\text{H}_{22}\text{NO}_5\text{Si}$ (M^+-57) 324.1299, found 324.1267.

Debenzylation of the disilyl ether (339) was similarly carried out. Thus hydrogenation of 0.585 g (1 mmol) of the starting material for 48 h under a pressure of 40-35 psi furnished 0.245 g (0.5 mmol) of the product (340, Fig.LII) as a white solid after chromatography using 4: 1: hexane : ethyl acetate as eluting solvent. The product has following properties mp: 112-114°C; ir: 3210-3100, 1755 cm^{-1} , ms: 495 (M^+ not observed), 438 (M^+-57 , 29%), 410 (M^+-75 , 14%), 280 (M^+-215 , 40.7%), 222 (M^+-273 , 18.6%), 157 (M^+-338 , 71.2%), 73(100%); nmr: δ = 7.3(dd, 2 H, $J= 2.1$ Hz, $J= 7.7$ Hz), 6.8(dd, 2 H, $J= 2.1$ Hz, $J= 7.7$ Hz), 4.5 (s, 1 H), 4.2-4.1(m 1 H), 4.07-3.98 (q, 1 H, $J= 6.2$ Hz), 3.9 (m, 1 H), 3.7(s, 3 H), 1.3 (d, 3 H, $J= 6.2$ Hz), 0.79 (s, 9 H), 0.78 (s, 9 H), 0.075- (-)0.213 (series of singlets). HRMS calc for $\text{C}_{21}\text{H}_{36}\text{NO}_5\text{Si}_2$ (M^+-57) 438.2184, found 438.2128. In addition 0.263 g (0.45 mmol.) of the starting material was recovered.

Hydrogenation of the tosylate (341, Fig. LII) 0.312 g (0.5 mmol) under a pressure of 45 psi for 48 h did not lead to complete consumption of the starting material but formation of a new polar compound was indicated, 0.053 g of the latter was isolated as an oil (yield ca.10%). This compound has following spectral characteristics: ir: 3200, 1745 cm^{-1} , ms: 535 (M^+ , 2.7%), 363 (M^+-172 , 6.4%), 306 (M^+-229 , 100%); nmr: δ = 7.7 (d, 2 H, $J= 8.5$ Hz), 7.2 (m, 6 H), 6.8 (dd, 2 H, $J= 2.1$ Hz, $J= 6.8$ Hz), 4.9 (q, 1 H, $J= 6.6$ Hz), 4.7 (s, 1 H), 4.24-3.93 (series of unresolved multiplets, 3 H), 3.7 (s, 3 H), 2.49 (s, 3 H), 1.3 (d, 3 H, $J= 6.6$ Hz), 0.7 (s, 9 H), (-)0.107-(-)0.25 (series of singlets).

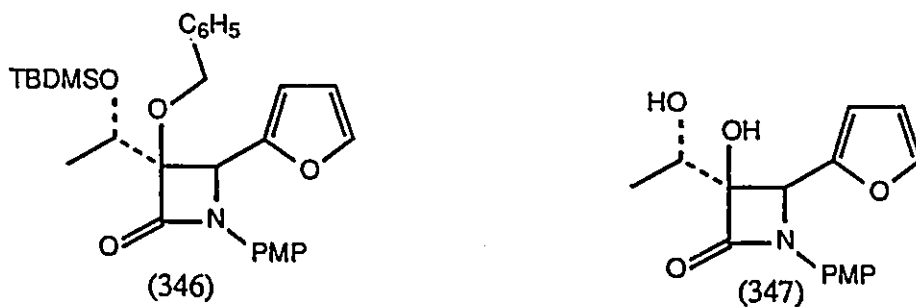
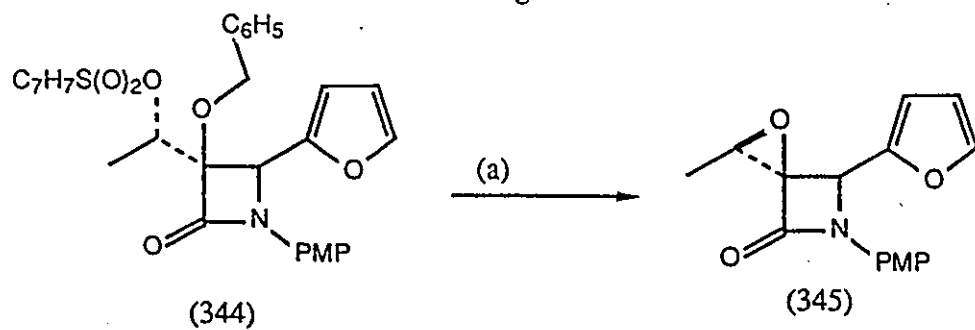
Synthesis of the epoxoyazetidione(343, Fig.LII)

Tosylate (341, Fig. LII) 0.5 g (0.8 mmol) was dissolved in about 25 mL of methanol and 1.1 g (16 mmol) of ammonium formate and

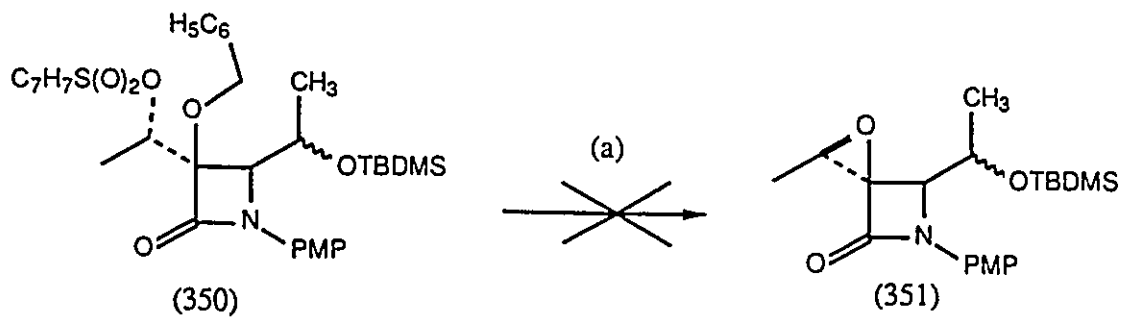
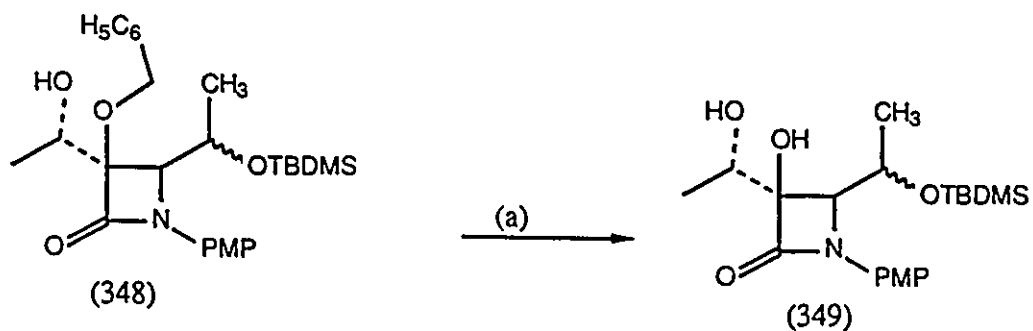
approximately 0.2 g of 5% Pd-C was added. The heterogeneous reaction mixture was heated under reflux with vigorous stirring. Occasionally the white solid that deposited in the reflux column was pushed down with the help of a long glass rod. After 6 h of refluxing the TLC indicated the presence of starting material, thus an additional 0.2 g of the catalyst was added. After about 12 h of refluxing the TLC indicated the absence of the starting material. The reaction mixture was filtered through Celite and the catalyst was washed with 2X10 mL of methanol. The combined filtrate was concentrated to provide a viscous oil with suspended black particles. This oil was dissolved in water and the aqueous layer was extracted with 3X25 mL ethyl acetate. The organic layer was processed in the usual manner to provide a viscous oil. This was column chromatographed using 5:1: hexane : ethyl acetate mixture for elution to provide 0.261 g (0.72 mmol) of the epoxyazetidinone as a viscous oil which partially solidified on standing. The isolated yield was about 80% and the product is characterized by following properties: ir: 1765-1760, 1250, 910 cm^{-1} ; ms: 363 (M^+ , 6.5%), 306 (M^+-57 , 3.1%), 262 (M^+-101 , 14%), 222 (M^+-141 , 31.9%), 157 (M^+-206 , 100%); nmr; δ = 7.5 (dd, 2 H, J = 2.2 Hz, J = 6.7 Hz) 6.8 (dd, 2 H, J = 2.2 Hz, J = 6.8 Hz), 4.3 (m, 1 H), 3.9 (two multiplets, 1 H), 3.7 (s, 3 H), 3.4 (q, 1 H, J = 5.2 Hz), 1.5 (d, 3 H, J = 5.2 Hz), 0.8 s, 9 H), (-)0.015 (s, 3 H), (-)0.04(s, 3 H). HRMS calc for $\text{C}_{19}\text{H}_{29}\text{NO}_4\text{Si}$ 363.1906, found 363.1856.

Preparation of the hydroxyethylazetidinone (336, Fig. LI) from the benzyloxyazetidinone (335, Fig. LI) involved formation of anion, subsequent reaction with acetaldehyde, PCC oxidation, L-Selectride-

Fig. LIII



(a) Excess ammonium formate, 5 or 10% Pd-C, MeOH, reflux



$C_7H_7S(O)_2 = p\text{-toluenesulfonyl}$

TMEDA reduction following the procedure described in Chapter 4 for the corresponding methoxyazetidinone. The overall sequence of reaction produced the product in about 30% yield from the parent azetidinone (335, Fig. LI). The product a white foam, was characterized by following properties: ir: 3400-3210, 1755 cm^{-1} ; ms: 393 (M^+ , 1.8%), 302 (M^+-91 , 31.6%), 202 (imine $^{+}+1$, 100%), 201 (imine $^+$, 19.3%); nmr: d = 7.4-6.3 (series of m, 12 H), 5.2 (s, 1 H), 4.8-4.6 (AB, 2 H, J= 10.6 Hz), 4.2 (m, 1 H), 3.76 (s, 3 H), 2.2 (d, 1 H, J= 4.5 Hz), 1.4 (d, 3 H, J= 6.4 Hz). The high field NMR spectrum also showed presence of unassigned signals 3.7-3.6.(overall integration for these signals amounted to less than one proton) However none of these signals belonged to the other diastereoisomer of the hydroxyethyl compound as determined by comparison with the spectrum of the mixture obtained by reaction of the parent azetidinone with LDA and acetaldehyde.

Tosylation of the hydroxyethylazetidinone (336, Fig. LI) was carried out in the usual manner and produced the tosylate (344, Fig. LII) in 95% yield as a white foam. This compound has following properties: ir: 1755, 1380, 1250 cm^{-1} ; ms: 456 (M^+ , not observed), 375 (M^+-172 , 6.9%), 284 (M^+-263 , 3.0%), 91 (C_7H_7^+ , 34.5%), 43 (100%); nmr: d = 7.8-6.3 (series of m, 17 H), 5.1 (s, 1 H), 5.0 (q, 1 H, J= 5.3 Hz), 3.7 (s, 3 H), 2.3 (s, 3 H), 1.5 (d, 3 H, J= 5.3 Hz).

For preparation of the protected hydroxyethylazetidinone (346, Fig. LIII) the anion formation, trapping with acetaldehyde, PCC oxidation, L-Selectride -TMEDA reduction and silylation sequence mentioned for the corresponding methoxyazetidinone (Chapter 4) was employed to furnish chromatographically and diastereomerically

homogeneous product in about 20% overall yield from the azetidinone (334, Fig. LI). The compound is an oil and has following spectroscopic properties: ir: 1745; ci-ms: 508 ($M^{+}+1$, 21%), 450 ($M^{+}-57$, 6.5%), 416 ($M^{+}-91$, 36%), 350 ($M^{+}-158$, 20.6%), 202 (imine $^{+}+1$, 100%); nmr: δ = 7.4-6.3 (series of m, 12 H), 5.2 (s, 1 H), 4.8-4.6 (AB, 2 H, J = 10.4 Hz), 4.2 (q, 1 H, J = 6.2 Hz), 3.7 (s, 3 H), 1.4(d, 3 H, J = 6.3 Hz), 0.7 (s, 9 H), 0.08-(-)0.004 (series of s).

The synthesis of the epoxyazetidinone (345, Fig. LIII) from the tosylate (344, Fig.LIII) involved debenzoylation using ammonium formate in a manner similar to that used for the preparation of the epoxide (343, Fig. LII). The product was obtained as a foam in about 50% yield. This compound has following spectroscopic properties: ir: 1760 cm^{-1} ; ms: 285 (M^{+} , 1.2%), 259 ($M^{+}-27$, 9.4%), 202 (imine $^{+}+1$, 44.5%), 201 (imine $^{+}$, 18.1%), 154 ($M^{+}-131$, 58.1%), 108 ($M^{+}-177$, 100%); nmr: δ = 7.4-6.4 (series of m, 7 H), 5.1(s, 1 H), 4.2 (q, 1 H, J = 6.4 Hz), 3.8 (s, 3 H), 1.3 (d, 3 H, J = 6.4 Hz). No starting material was recovered in this experiment.

The preparation of the dihydroxyazetidinone (347, Fig. LIII) involved the debenzoylation of the corresponding benzyl ether using ammonium formate. The reaction proceeded in 100% yield to furnish the diol as a semi-solid. This unstable compound has following characteristics: ir: 3400-3100, 1750 cm^{-1} ; ms: 303 (M^{+} , 1.5%), 285 ($M^{+}-18$, 1.4%), 259 ($M^{+}-44$, 3.9%), 202 (imine $^{+}+1$, 8.4%), 201 (imine $^{+}$, 10.1%), 154 ($M^{+}-149$, 11.0%), 83 ($M^{+}-220$, 100%); nmr: δ = 7.4-6.3 (series of m, 7 H), 5.1 s, 1 H), 4.18 (q, 1 H, J = 6.5 Hz), 3.7 (s, 3 H), 1.3 (d, 3 H, J = 6.5 Hz). On storage at room temperature the NMR spectrum of the compound began to show, in addition to the signals mentioned

above, a series of multiplets in the region of 0-2 ppm (total integration indicated more than 10 protons).

Conversion of the azetidinone (346, Fig. LVI) to the tosylate (369, Fig.LVI) was carried via debenzoylation and tosylation sequence. The product of debenzoylation was not rigorously purified. The overall yield for the tertiary tosylate was 75%. This clear oil has following spectroscopic properties: ir: 1760 cm^{-1} ; ci-ms: 572 ($M^{+}+1$, 100%), 529 ($M^{+}-42$, 29.4%), 514 ($M^{+}-57$, 27%); nmr: d = 7.7-6.4 (m, 11 H), 5.3 (s, 1 H), 4.4 (q, 1 H, $J= 6.3\text{ Hz}$), 3.7 (s, 3 H), 2.4 (s, 3 H), 1.1 (d, 3 H, $J= 6.3\text{ Hz}$), 0.73 (s, 9 H), 0.027 (s, 3 H), 0.023 (s, 3 H).

Synthesis of (370, LVI)

The tosylate (369, LVI), 0.2 g (0.67 mmol) was dissolved in 5 mL of dry THF at room temperature. To the vigorously stirred clear solution under nitrogen was added 0.67 mL (0.67 mmol) of solution of tetra-n-butylammonium fluoride (TBAF) in THF. This led to instant development of yellow color. The clear homogeneous solution was left stirring at room temperature for 6h. TLC at this stage indicated presence of the starting material and a non-polar compound. An additional 0.67 mL of TBAF solution was added and the reaction mixture was allowed to stir for additional 65 h. At this stage TLC indicated absence of starting material. The solvent was removed and the viscous yellow oil thus obtained was applied to the top of a small silica column. Elution with 6:1: hexane : ethyl acetate led to isolation of 0.125 g (0.43 mmol) of the epoxyazetidinone (370, Fig. LVI) as a clear colorless viscous oil which partially solidified on standing at room temperature. The spectroscopic properties of this compound are as follows: ir: 1770 cm^{-1} ; ms: 285 (M^{+} , 28%), 201 (imine⁺, 8.8%),

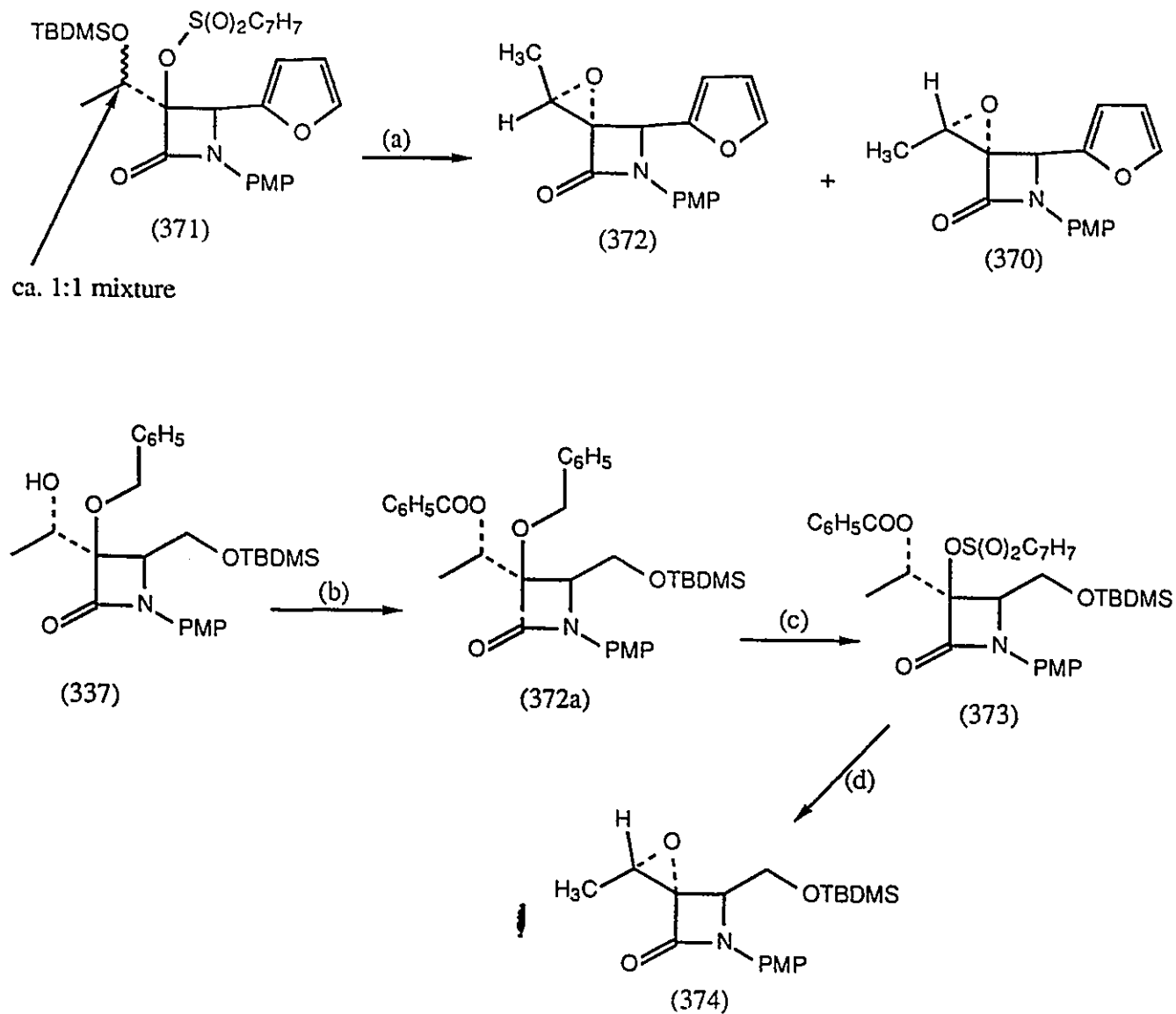
108 (M^+ -177, 100%); nmr: d = 7.3-6.3 (series of m, 7 H), 5.19 (s, 1 H), 3.7 (s, 3 H), 3.2 (q, 1 H, $J=5.0$ Hz), 1.5 (d, 3 H, $J= 5.0$ Hz). HRMS calc for $C_{16}H_{15}NO_4$ 285.1023, found 285.1037.

The mixture of epoxyazetidiones (370 and 372, Fig. LVII), was similarly prepared in comparable yield. In the case of this mixture there are two signals corresponding to the proton at C-4 (5.27 and 5.19 ppm, ratio ca. 1:1), two quartets due to the side-chain proton (3.6 and 3.2 ppm, ratio ca. 1:1). Other signals were not very well resolved. This mixture shows only one spot on TLC.

Benzoylation of the hydroxyethylazetidione (337, Fig. LVII) was carried out in manner similar to that used for the purpose of tosylation (using NaH-benzoylimidazole-DMF combination) in 90% yield to furnish azetidione (372a, Fig. LVII) as a white semi-solid. which has the following spectral characteristics: ir: 1760, 1720 cm^{-1} ; ms: 575 (M^+ , 1%), 396 (M^+ -179, 1.6%), 105 (M^+ -470, 100%); nmr: d =7.9-7.2 (series of m, 12 H), 6.8 (dd, 2 H, $J= 2.2$ Hz, $J= 6.8$ Hz), 5.6 (q, 1 H, $J= 6.5$ Hz), 5.0-4.99 (AB, 2 H, $J= 7.3$ Hz), 4.2 (m, 1 H), 4.09 (dd, 1 H, $J= 3.4$ Hz, $J= 11.6$ Hz), 3.9 (dd, 1 H, $J= 5.0$ Hz, $J= 11.6$ Hz), 3.7 (s, 3 H), 1.5 (d, 3 H, $J= 6.5$ Hz).

Debenzylation of the above benzoate was carried out using ammonium formate and Pd-C in the manner indicated above. The product was obtained as a clear oil in about 80% yield and has following spectroscopic properties: ir: 3300-3200, 1750, 1730 cm^{-1} ; ms: 485 (M^+ , 4.5%), 306 (M^+ -179, 21%), 280 (M^+ -205, 26.3%), 157 (M^+ -328, 100%); nmr: d = 7.8-7.2 (series of m, 7 H), 6.8 (dd, 2 H, $J= 2.4$ Hz, $J= 9.9$ Hz), 5.4 (q, 1 H, $J= 5.5$ Hz), 4.8 (s, 1 H), 4.22-4.03 (series of multiplets with shapes and coupling constants similar to the case

Fig. LVII



$C_7H_7S(O)_2 = p\text{-toluenesulfonyl}$

(a) TBAF, THF, R.T., 72 h.

(b) benzylimidazole, NaH, DMF, 0°C.

(c) [i] Excess ammonium formate, 10% Pd -C, methanol, reflux.

[i] tosylimidazole, NaH, DMF, 0°C.

(d) 1.1eq. NaOMe, THF, methanol.

of the benzoate derivative mentioned in the preceding paragraph, 3 H), 3.7 (s, 3 H), 1.5 (d, 3 H, $J = 5.5$ Hz), 0.8 (s, 9 H), (-)0.084 (s, 3 H), (-)0.2 (s, 3 H). HRMS calc for $C_{26}H_{35}NO_6Si$ 485.2233, found 485.2242.

The synthesis of the azetidinone (373, Fig. LVII) involved tosylation of the aforementioned tertiary alcohol in a manner similar to that utilized for other tosylation. The reaction proceeded in about 75% yield to furnish the product as a semi-solid with following spectroscopic properties: ir: 1765, 1720 cm^{-1} ; ci-ms: 640 ($M^+ + 1$, 100%), 582 ($M^+ - 47$, 13.2%), 468 ($M^+ - 171$, 16.6%), 363 ($M^+ - 276$, 69%); nmr: $\delta = 8.0-6.8$ (series of m, 16 H), 5.4 (q, 1 H, $J = 5.5$ Hz), 4.2-4.1 (m, 3 H), 3.7 (s, 3 H), 2.4 (s, 3 H), 1.5-0 (series of unresolved m). The last set of signals could conceivably contain the signals for the methyl residue of the hydroxyethyl part and the TBDMS group. However the integration for this region suggested far too many protons that could be accounted for by these groups. At present there is no explanation for the presence of these signals. On the basis of the spectral properties of the starting material and the product epoxide it is obvious that the tosylate was indeed obtained.

Synthesis of (374, Fig. LVII)

The above tosylate 0.14 g (0.2 mmol) was dissolved in 4 mL of 3:1: methanol: THF at room temperature. To the vigorously stirred clear solution of the starting material was added in one portion 0.0136 g (0.23 mmol) of commercial sodium methoxide. After 10 min TLC revealed the presence of the starting material and a more polar substance. On continued stirring for an additional 20 min TLC indicated that the more polar material had disappeared and a compound with R_f identical to that of the starting material was

present. Amberlite resin (H⁺ form) 0.2 g was added at this stage and after 5 min of additional stirring the resin was filtered off. The small amounts of the solid residue in the flask and the resin was washed with an additional 15 mL of methanol. The combined filtrate was concentrated to provide a viscous oil. This oil was applied to a small column of silica gel and the column was eluted with 5 :1: hexane : ethyl acetate. The fractions indicating the presence of the compound with R_f identical to the starting material furnished 0.055 g (0.15 mmol) of a semi-solid. The structure of this product was assigned as the epoxyazetidinone (374, Fig. LVII) on the basis of following spectral data: ir: 1770 cm⁻¹; ms: 363 (M⁺, 23.3%), 306 (M⁺-57, 10.6%), 276 (M⁺-87, 7.3%), 262 (M⁺-101, 20.1%), 222 (M⁺-141, 100%); nmr: δ =7.3 (dd, 2 H, J= 2.2 Hz, J= 6.8 Hz), 6.8 (dd, 2 H, J= 2.2 Hz, J= 6.8 Hz), 4.2 (t, 1 H, J= 2.9 Hz), 4.0 (dd, 1 H, J= 2.9 Hz, J= 11.8 Hz), 3.7 (m, 4 H), 3.4 (q, 1 H, J= 5.2 Hz), 1.5 (d, 3 H, J= 5.2 Hz), 0.7 (s, 9 H), 0.0(s). HRMS calc for C₁₉H₂₉NO₄Si 363.1906, found 363.1910. The mass spectrum also showed presence of a peak at m/e= 395 (M⁺+32, 7%). This peak could possibly be accounted for in terms of presence of minute amounts of the product obtained from the opening of the epoxide with methanol.

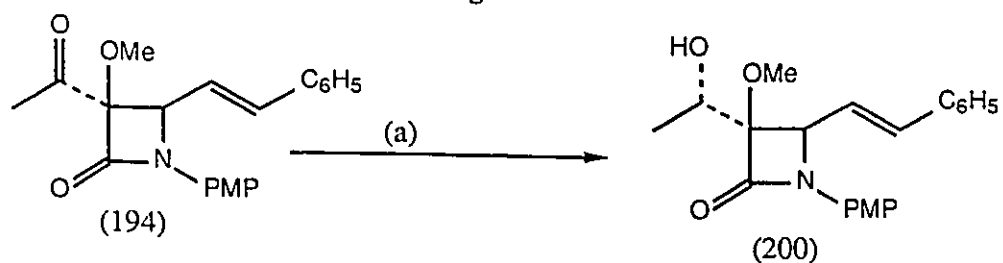
CHAPTER 7

The non-chelation controlled reduction of 3-acetyl-3-methoxyazetidinones was encountered in the context of the synthesis of 3-methoxy-3-hydroxyethylazetidinone (194 → 200, Fig. LVIII). The reaction involved reduction of the starting acetyl compounds by L-Selectride in the presence of slightly more than 2 eq. of TMEDA¹²¹. As indicated earlier this reaction produced only one hydroxyethyl compound i.e. the one with upfield chemical shift for the C-4 proton. The high diastereoselectivity observed under such simple conditions was very gratifying. As determined by X-ray diffraction analysis, the product obtained had 8(S*) stereochemistry (thienamycin numbering used here and subsequently).

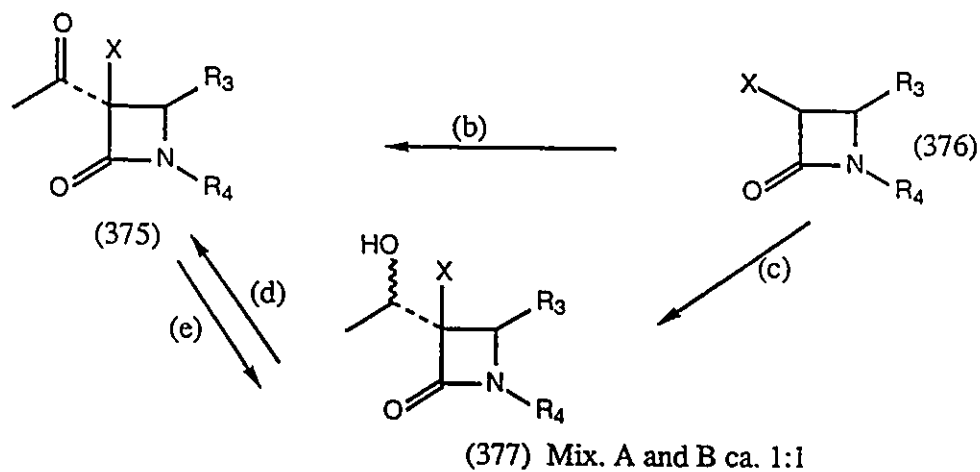
Notwithstanding the high diastereoselectivity observed in the reduction, the thinking behind the non-chelation controlled reduction was somewhat simplistic. Thus it was decided to determine the scope and limitations of this type of reduction. Specifically the issues addressed were:

- (1) The impact of changes in the nature of substituents at various positions of the azetidinone ring;.
- (2) The importance of the bulk of the reducing agent; Can Selectride be replaced by a smaller reducing agent?;.
- (3) The importance of temperature and solvent;.
- (4) The importance of TMEDA;
- (5) The impact of Lewis acids on the course of the reduction. More specifically, is it possible to alter the stereochemical course of the

Fig. LVIII



(a) 1.1 eq. L-Selectride, 2.2 eq. TMEDA, THF, -78°C 1-2 h. 'USUAL' conditions



- (b) [i] LDA, THF, -78°C , variable time. [ii] inverse addition to excess acetyl chloride -78°C .
(c) Excess acetaldehyde.
(d) PCC, 4A^o molecular sieves, methylene chloride.
(e) Sodium borohydride, ethanol, 0°C .

Similar reactions were used for other aldehydes and acid chlorides.

reduction by adding metal salts i.e. is it at all possible to obtain the 8-(R*) hydroxyethylazetidinone by changing the conditions ?.

These studies required access to a large number of 3-acetylazetidinones with an additional substituent at position 3. All of these compounds were prepared by reaction of the appropriate azetidinone anions with acetaldehyde followed by PCC oxidation. In some cases the inverse addition of the anion to a large excess of acetyl chloride at -78°C was carried out to provide the acetyl compound directly. Based upon the method of syntheses the acetylazetidinones should have the trans arrangement of the acetyl group and the larger substituent at position 4 (376 \rightarrow 375, Fig. LIX)¹²².

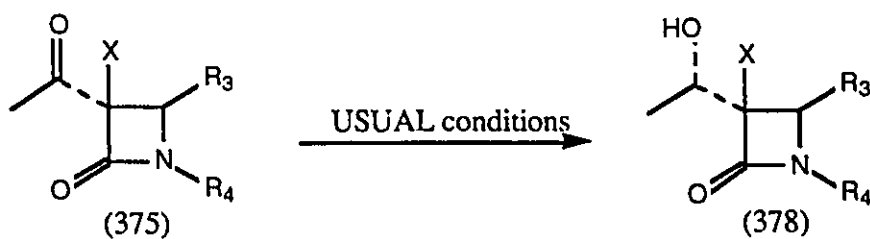
To answer the first question a series of reductions were carried out under standard conditions i.e. 1.1 eq. of L-Selectride, 2.2-2.5 eq. of TMEDA, THF as solvent and temperature at -78°C . Usually the reductions were carried out for 1-3 hours. These were referred to as USUAL conditions of reduction. The diastereoisomeric composition were determined by high field (200 or 300 MHz) NMR spectra recorded on the purified mixture of products. Since it was not possible to resolve the mixtures of diastereoisomeric hydroxyethyl compounds by column chromatography, the diastereoselectivity observed was a consequence of the reduction alone and not an artifact of the chromatography¹²³. It was necessary to carry out chromatographic purification to remove some material with R_f similar to the starting material and some relatively non-polar impurities, neither of these minor impurities were characterised. For comparison purposes, the diastereoisomeric mixture of hydroxyethyl

compounds, obtained either by LDA- acetaldehyde sequence or by reduction of the acetyl compounds with NaBH_4 , were used. Both these procedures furnish nearly 1:1 mixture of diastereoisomeric hydroxyethyl azetidinones.

The results of several such experiments are shown in figures LIX through LXIV. As can be seen from figure LIX the changes in the nature of the substituents at C-4 have little impact on the stereochemical course of the reaction. This point has also been independently verified at least in one case (see below). Changes in the nature of the ether moiety at C-3 also has no noticeable impact on the stereochemical outcome of these reductions. Azetidinones with an electron donating substituent at C-4 behave in a manner similar to those with a simple phenyl group (393 vs. 379, Fig. LIX). However in the case of azetidinones which have (aminoalkyl)aryl substituents (393 and 395, Fig. LIX) some additional uncharacterised substances are present in the crude reaction mixture and rather rigorous purification is required. These uncharacterised impurities do not belong to the diastereoisomer B, since these are absent in the mixtures obtained by reduction of the acetyl compound with sodium borohydride¹²⁴.

The various examples of the reduction of azetidinones with a protected amino group at C-3 are shown in figure LX. As pointed out previously, in these cases the USUAL conditions are not good enough. To obtain hydroxyethyl compounds with high diastereoselectivity in this series it is required that at least 2 equivalents of L-Selectride be used for every equivalent of the azetidinone. The amount of TMEDA has to be increased simultaneously and typically 4.4 equivalents are

Fig. LIX



SM	X	R ₃	R ₄	Yield%	Product
(379)	OCH ₃	C ₆ H ₅	C ₇ H ₇ O	75	(380)
(381)	OCH ₃	C ₆ H ₅	C ₆ H ₅	75	(382)
(383)	OCH ₃	C ₄ H ₃ O	C ₇ H ₇ O	65	(384)
(385)	OC ₇ H ₇	C ₈ H ₇	C ₇ H ₇ O	75	(386)
(387)	OC ₇ H ₇	C ₉ H ₉	C ₇ H ₇ O	70	(388)
(389)	OC ₇ H ₇	C ₄ H ₃ O	C ₇ H ₇ O	50	(390)
(391)	OC ₃ H ₅	C ₉ H ₉	C ₇ H ₇ O	57	(392)
(393)	OCH ₃	C ₁₀ H ₁₀ N	C ₇ H ₇ O	68	(394)
(395)	OCH ₃	C ₈ H ₇	C ₈ H ₁₀ N	65	(396)

OC₇H₇ = benzyloxy, OC₃H₅ = 2-propenyloxy (= allyloxy), C₇H₇O = p-methoxyphenyl (= PMP), C₄H₃O = 2-furyl, C₈H₇ = *t*-cinnamyl, C₉H₉ = methylcinnamyl, C₁₀H₁₀N = p-(diethylamino)phenyl, C₈H₁₀N = p-(dimethylamino)phenyl.

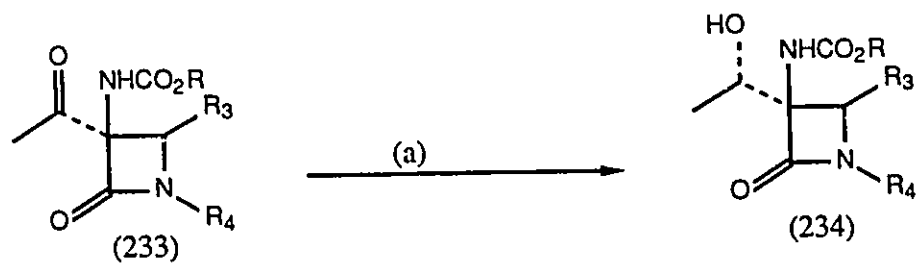
Diastereoisomer A was the sole product as determined by 300 MHz NMR

required for every equivalent of the azetidinone. The reason for this behavior is not entirely clear but it is reasonable to assume that the active hydrogen of the carbamate residue might be consuming one equivalent of the reducing agent. Thus the need for at least two equivalents. The experimental conditions employed were based on the simple assumption that every Li^+ can co-ordinate with two molecules of TMEDA and therefore use of two equivalents of L-Selectride should require four equivalents of TMEDA. It has not yet been determined if lesser number of equivalents of TMEDA might also suffice.

As noted in Chapter 5, the stereochemistry of the Selectride reduction product is not known in the case of azetidinones shown in figure LX. Nor was it possible to comment on the chemical shifts of the predominant diastereoisomer in case of these compounds. But the more significant outcome of the studies presented in Chapter 5 was that the reduction is independent of the nature of the carbamate residue. In one case where direct comparison was possible, the product of the Selectride reduction was indeed diastereoisomer A (408 \rightarrow 261, Fig. LX).

The situation in case of other substituents at C-3 is somewhat confusing. In the case of the methyl substituent at C-3 (409 \rightarrow 410, Fig. LXI) high diastereomeric purity is indicated on the basis of the signals for the C-4 proton. However other signals do not seem to corroborate such an assertion. Unavailability of a mixture of hydroxyethyl compounds made it difficult to directly compare and determine the relative amounts of two diastereoisomers in the mixture obtained from USUAL reduction. In the case of 3-vinyl-3-

Fig. LX



(a) 2.2 eq. L-Selectride, 4.4 eq. TMEDA, THF, -78°C , 1-2 h.

SM	R	R ₃	Yield	Product
(398)	C ₇ H ₇	C ₈ H ₇	80%	(399)
(400)	C ₇ H ₇	C ₉ H ₉	78%	(401)
(402)	C ₇ H ₇	C ₆ H ₅	75%	(403)
(404)	C ₇ H ₇	C ₄ H ₃ O	60%	(405)
(406)	C ₂ H ₅	C ₆ H ₅	72%	(407)
(408)	C ₄ H ₉	C ₈ H ₇	62%	(261)

R₄ = PMP for all cases. C₈H₇ = trans cinnamyl, C₉H₉ = methylcinnamyl,
C₄H₃O = 2-furyl, C₄H₉ = tertiary butyl

acetylazetidinone (411, Fig. LXI) the USUAL reduction did furnish only one compound as determined on the basis of the presence of only one set of signals for the methyl part of the hydroxyethyl residue. However the diagnostic C-4 protons and signals for the vinyl groups were not well resolved in case of either the mixture of hydroxyethyl compounds or the isomer obtained from Selectride reduction. Interestingly enough the Selectride reduction of this acetyl compound in presence of excess LiI furnished the same hydroxyethyl compound (412 Fig. LXI).

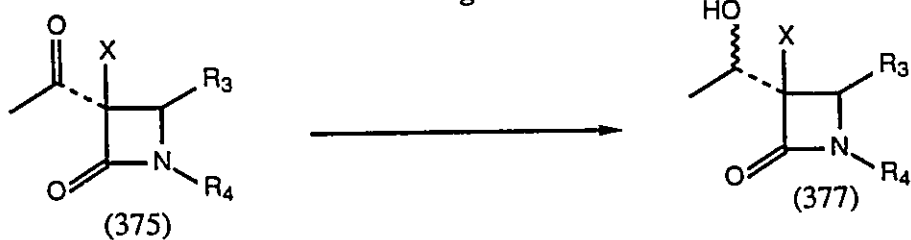
In case of the fluoroazetidinone (413, Fig. LXI) the reduction under non-chelating conditions was somewhat less stereoselective. In case of the chloroazetidinone (374, Fig. LXI) the diastereoselectivity was much poorer. This coupled with the difficulties in obtaining the acetyl compound detract from further use of these interesting compounds.

In the case of azetidinones bearing the acetoxyacetyl group at C-3 (415, and 215, Fig. LXI) it was not possible to assign the signals for the hydroxyethyl compounds with any degree of confidence. However by subsequent chemical manipulation, involving the inversion of configuration at the hydroxyethyl group, it was possible to establish that the additional oxygen atom has no influence on the stereochemical outcome of the reduction.

The USUAL reduction of a 3-acylazetidinone gives results similar to that of 3-acylazetidinone (417, Fig. LXI).

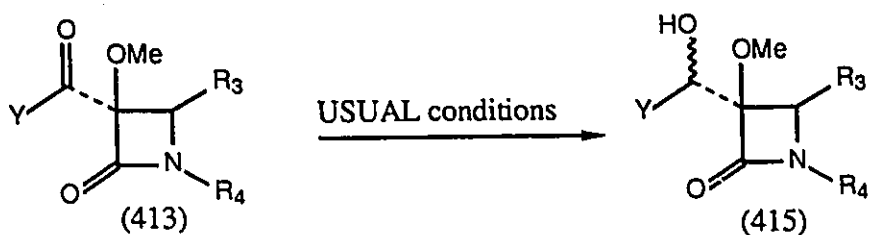
As pointed out earlier, the exact relative configuration is known only in one case. However at least in one other case, the point has been established by subsequent chemical transformation.

Fig.LXI



SM	X	R ₃	Yield	Comments
(409)	Me	C ₈ H ₇	50%	Usual conditions, Only A (410)
(411)	C ₂ H ₃	C ₆ H ₅	85%	Usual conditions, One product (412)
(411)	C ₂ H ₃	C ₆ H ₅	60%	LiI, Ether, -78°C, L-Selectride (412)
(413)	F	C ₉ H ₉	55%	Usual conditions ca. 95:5 :: A:B (414)
(374)	Cl	C ₉ H ₉	50%	Usual conditions 2:1 :: A:B (373)

R₄ = PMP for all cases. C₂H₃ = vinyl Others as before.



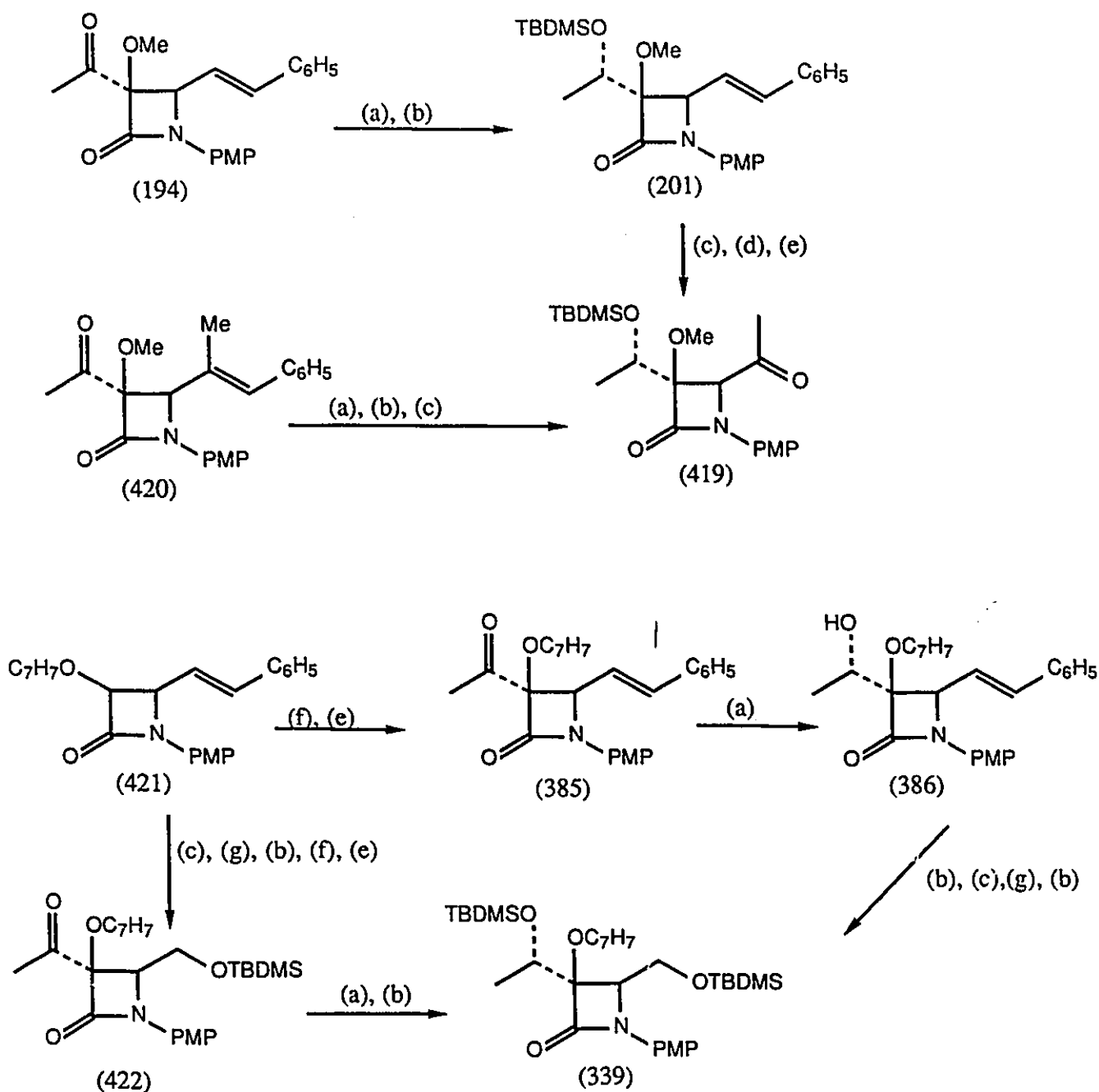
SM	Y	R ₃	Yield	Comment
(415)	C ₃ H ₅ O ₂	C ₉ H ₉	60%	one compound, unassigned at this stage (416)
(215)	C ₃ H ₅ O ₂	C ₈ H ₇	50%	one compound unassigned at this stage (216)
(417)	C ₇ H ₇	C ₈ H ₇	80%	Only diastereomer A. (418)

R₄ = PMP for cases C₃H₅O₂ = acetoxymethyl C₇H₇ = m-tolyl. other as efore

Compound (194, Fig. LXII) could be converted to the acetyl compound (419, Fig. LXII) via silylation, ozonolysis, MeLi addition and PCC oxidation sequence. The same acetyl compound (419) was obtained from the azetidinone (420, Fig. LXII) via a silylation and ozonolysis sequence. This particular comparison was carried out Mr. S. R. Shakya of these laboratories. Similar series of transformations were carried out in the case of the benzyloxy compounds (421 -> 339, Fig. LXII) and (397 -> 352, Fig. LXIII). It was expected that the changes in the nature of the trans substituents at C-4 position would not influence the outcome of the reduction of the acetyl group at C-3. These experiments have supported this hypothesis and made planning of subsequent work easier. Since the reduction of the acetyl group is not influenced by the nature of the substituent at C-4, the steric outcome of the reduction of any one acetylazetidinone can be used in order to extrapolate to other members of the same series.

It is known that at least in certain cases epimerization at C-4 (425 -> 426, Fig. LXIII) is possible under basic conditions¹²⁵. For that reason reliance upon chemical shift and identity of the C-4 proton alone might be considered risky. It is not likely that such epimerizations could possibly take place for the compounds encountered in these studies. Moreover the conditions employed for manipulations of potentially epimerizable compounds are fairly mild. Therefore it is very likely that epimerization took place under the conditions encountered in the case of azetidinones bearing a carbonyl group at C-4. In a series of interconvertible azetidinones into one another the exact correspondence of all the peaks in the high field

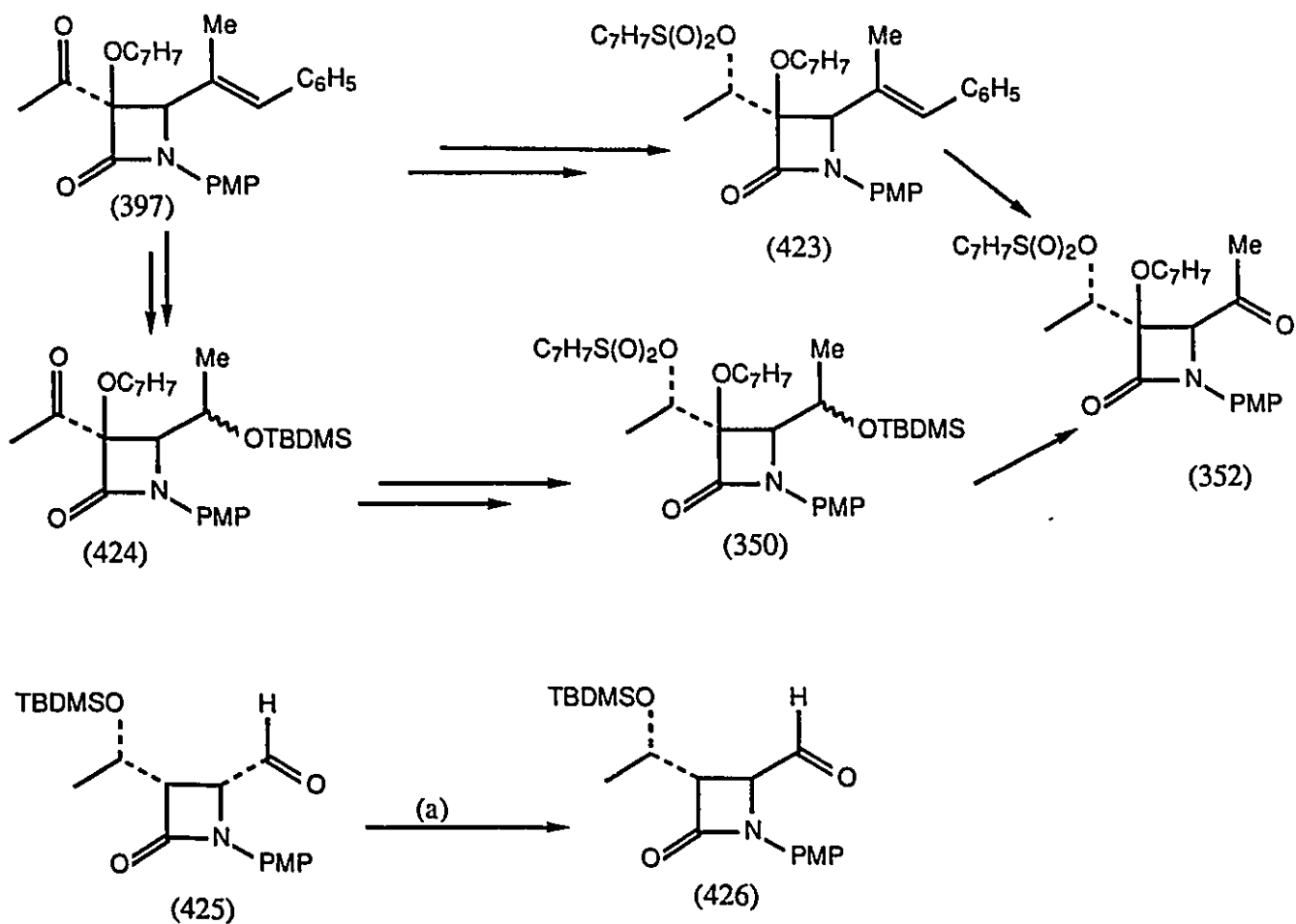
Fig. LXII



- (a) Selectride reduction USUAL conditions.
 (b) TBDMS-Triflate, 2,6-lutidine, methylene chloride, 0° C.
 (c) [i] O₃/O₂, methylene chloride, -78°C, [ii] DMS, -78°C --> R.T.
 (d) MeLi, THF, -78°C.
 (e) PCC, methylene chloride, 4A° molecular sieves.
 (f) [i] LDA, THF, -78°C, [ii] excess acetaldehyde.
 (g) NaBH₄, ethanol, 0°C

Yields [i] (194) -> (201) = 66 - 70% [ii] (420) -> (419) = 45% [iii] (201) -> (419) = 50%
 [iv] (421) -> (422) = 35 - 40% [v] (422) -> (339) = 67% [vi] (385) -> (386) = 55%.

Fig. LXIII



(a) DBU, methylene chloride, R.T. (426) : (425) :: 88 : 9

NMR spectra (Fig. LXIII and LXIV) serves to prove that such an epimerization did not take place.

With a view to determining the impact of the size of the reducing group the acetyl azetidinone (194, Fig.LXIV) was reduced with BH_3 . At -78°C , even after 2 hours of reaction time the yield of the hydroxyethyl compound was only 6%; the diastereomeric ratio was not determined. At room temperature the reduction was somewhat faster and the yields were more respectable (50%) but the diastereoselectivity as measured by integration of signals for C-4 protons was poor.(2:1= A:B) (Entries 1 and 2, Fig. LXIV)¹²⁶. As pointed out earlier, sodium borohydride in ethanol has served as a reliable source of ca.1:1 mixtures of diastereisomeric hydroxyethyl compounds (Entry 3, Fig.LXIV). Thus the size of the reducing agent is a crucial factor.

Use of ether instead of THF for Selectride reduction at -78°C seemed to provide diastereoisomer A as the major product (13:1 :: A:B), in somewhat higher yields than usual. (Entry 4, Fig. LXIV). However this reaction gave results which showed considerable variations in terms of yields and diastereoselectivity. Thus in several attempts to repeat this reduction resulted in yields as low as 50% and the A:B ratio decreased to close to 7-8:1.

Initial experiments appeared to suggest that TMEDA is not particularly important in controlling the stereochemical outcome of the reaction. Thus in the case where the reduction was carried out at -78°C in absence of TMEDA, the observed diastereoselectivity was a highly respectable (25:1 = A:B) and the yields were comparable to the 60-80% obtained under the USUAL conditions. (Entry 5,

Fig.LXIV). However in the absence of TMEDA the reaction shows greater variability with respect to both the yield and diastereoselectivity than under the USUAL conditions. However despite the variations in yields, diastereoisomer A remains the predominant product. Only the experiments carried out at -78°C in presence of at least 2 equivalents of TMEDA per mole of L-Selectride (i.e. the USUAL conditions) give consistent yields and diastereoselectivity. Increasing the amount of TMEDA past 2.2 equivalents at -78°C does not seem to have any beneficial effect. Carrying out the reaction at higher temperatures is deleterious regardless of the presence of TMEDA (Entries 6 and 7, Fig. LXIV).

In terms of variations in the nature of the cation of the Selectride moiety, the use of the K-selectride / ether combination (no TMEDA) was investigated. Under these conditions results were the same as those obtained with L-Selectride/TMEDA combination, i.e. exclusive formation of diastereomer A in about 60-75% yield (Entry 8, Fig LXIV). This might be attributed to poorer complexation of the K^+ cation with the acetylazetidinone .since results were not very different when K-Selectride- KI- ether combination was used (Entry 9, Fig. LXIV). The K-Selectride based reductions are much less effected by the presence of TMEDA and show the diastereoselectivity comparable to L-Selectride-TMEDA combination; regardless of the solvent. It may be recalled that this is contrary to the situation encountered by Merck chemists in their studies on 3-acetylazetidinones⁶⁹.

It seems in general that the idea of involving Lewis acids for the purpose of chelation controlled reduction is not a very useful one.

Fig.LXIV



X = OMe and R₄ = PMP for all cases. for (194) R₃ = C₈H₇ and for (379) R₃ = C₆H₅

No	SM	Reagent	Solvent	Temp	Additives	Yields%(A:B)
1	(194)	BH ₃	THF	RT	None	50 (2:1)
2	(194)	BH ₃	THF	-78°C	None	6 (NA)
3	(194)	NaBH ₄	Ethanol	0°C	None	70 (1:1)
4	(194)	L-Selec	Ether	-78°C	2.2 TMEDA	80 (13:1)

Fig. LXIV (Cont.)

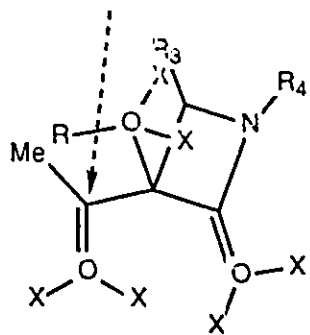
5	(194)	L-Selec.	THF	-78°C	None	81 (25:1)
6	(194)	L-Selec	THF	0°C	None	89 (25:1)
7	(194)	L-Selec	THF	0°C	2.2 TMEDA	84 (10:1)
8	(379)	K-Selec.	Ether	-78°C	None	70 (A only)
9	(379)	K-Selec	Ether	-78°C	ex. KI	80 (A only)
10	(379)	K-Selec	THF	-78°C	4.4 TMEDA	65 (A only)
11	(379)	K-Selec	THF	-78°C	None	70 (A only)
12	(379)	L-Selec	THF	-78°C	2.2 TMEDA	75 (A only)
13	(194)	L-Selec	Ether	-78°C	ex. LiI	34 (3:1)
14	(194)	LiAlH ₄	Ether	-78°C	ex. LiI	76 (1:1)
15	(194)	NaBH ₃ CN	THF-MeOH	-78°C	(pH = 3-4)	50 (1:1)
16	(194)	Zn(BH ₄) ₂	Ether	-78°C	None	55 (1:1)

Regardless of the size of the reducing agent involvement of a Lewis acid led to considerable erosion of diastereoselectivity. Thus when the LiI/ether combination was used both L-Selectride and LiAlH_4 gave disappointing results (Entry 13, 14 Fig. LXIV). With sodium cyanoborohydride, it was essential that the reduction be carried out in presence of protic acid¹²⁷. Here also there was no diastereoselectivity. This result may be due to the small size of the reducing agent (Entry 15, Fig.LXIV). The reduction with zinc borohydride was also nonstereoselective. (Entry 16, Fig.LXIV)¹²⁸. In conclusion any Lewis acid appears to decrease the stereoselectivity observed in the reduction of the 3-acetyl group.

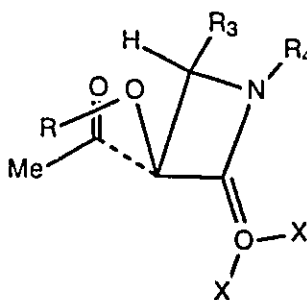
On the basis of the observations so far one can propose a model for the stereochemical course of this reduction. Because of the generality of this reduction, the factors which govern the stereochemical outcome of the reaction must be independent of the nature of various substituents. The only requirements seem to be that the acyl group at C-3 be trans to the larger substituent at C-4, the chelation be disfavored and the reducing agent be fairly bulky. To account for all these facts it can be suggested that the reduction must involve conformational features that are common to all the azetidinones studied.

A plausible conformation is (427, Fig.LXV) the one in which the acetyl group at C-3 and the carbonyl group of azetidinone are nearly orthogonal to each other. The acetyl group is also nearly orthogonal to the alkoxy group at C-3. Such a conformation also implies that in order to avoid significant steric interaction with the substituent at C-4, the alkyl moiety of the alkoxy group is occupying

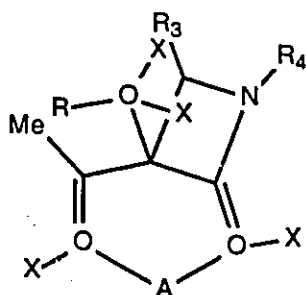
Fig. LXV



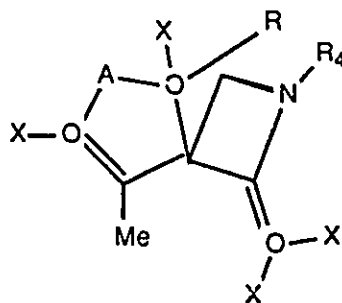
(427)
viewed along C3-C4 bond.
C-4 H not shown



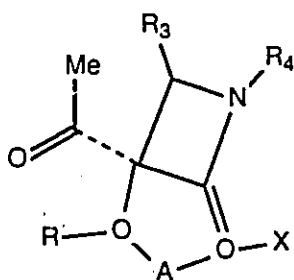
(428)
viewed along C3-C4 bond



(429)

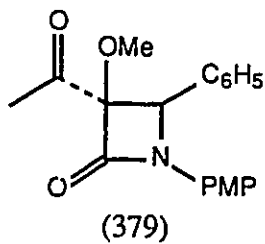


(430),
R₃, H not shown

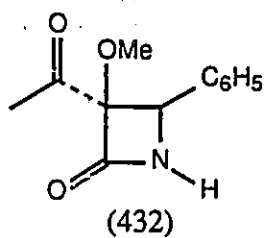


(431)

X = lone pair of electrons A = lewis acid, charge not specified.



(379)



(432)

the position outside the azetidinone ring. As a result the lone pairs of electrons on the alkoxy oxygen atom are occupying the space on the inside of the azetidinone ring. Such an arrangement also allows for maximum separation between various lone pairs. In this conformation one face of the acetyl group is blocked by the alkyl (or benzyl or allyl) moiety of the alkoxy group. The other face is relatively free. The hydride attacks from the 'bottom' side of the conformation (427, Fig. LXV), along the dotted arrow to provide rel.(8S) hydroxyethylazetidinone. Another conformation in which such an arrangement of various oxygen atoms can be achieved is (428, Fig. LXV). It is unlikely that this particular conformation plays significant role in the reduction since approach to one of the faces of the acetyl group is blocked by one of the lone pair of electrons on the azetidinone oxygen atom. The approach to the other face is blocked by the hydrogen atom at C-4.

To explain the observed lowering of diastereoselectivity in presence of Lewis acids it can be suggested that there is chelation of the acid A, charge not specified, by the acetyl group and the carbonyl group, resulting in (429, Fig. LXV). This situation is similar to that for the simple monosubstituted acetylazetidiones. In this case the alkoxy group at C-3 essentially completely blocks only one face. The hydride attack on the available face leads to diastereomer A (rel 8S) is the major product. On the other hand chelation of the Lewis acid by the alkoxy group and the acetyl group would lead to a situation in which both face of the acetyl group appear to be about equally accessible (430, Fig. LXV). In this case both diastereomer A and B may result from the reduction. In a third case the

involvement of the C-3 alkoxy group and the carbonyl of the azetidinone (431, Fig. LXV) would make faces of the acetyl residue open to attack by the hydride, leading to a situation similar to that of that for (430, Fig. LXV). Moreover in any particular case equilibria may exist amongst the (429, 430 and 431). Depending upon the exact experimental conditions the proportion of the various chelates may vary and thus result in the observed low diastereoselectivity.

The situation may not be very different in the case of the carbamate substituted azetidinones. In such cases it is very likely that the carbamate moiety becomes deprotonated under reduction conditions. Aside from that the situation can be treated in a manner similar to that of the alkoxyazetidinones. In the conformational analog of (427, Fig. LXV) the alkoxy carbonyl group blocks one of the faces of the acetyl group.

For 3-vinylazetidinone (411, Fig. LXI) it can be assumed that in order to avoid steric interaction with the substituent at C-4, the vinyl group adopts a conformation in which it effectively blocks one of the faces of the acetyl group. This will lead to a situation similar to (427, Fig. LXV) except that there will be no substituent occupying the inside of the azetidinone ring. As mentioned previously, the lack of clear demarcation between the chemical shifts of the C-4 protons for the 3-hydroxyethyl-3-vinylazetidinone has not allowed for rigorous assignments in this case. The observed diastereoselectivity in the case of C-3-methyl is somewhat doubtful at best. The case of C-3-fluoro azetidinones is not accounted for the model proposed above. In this particular case examination of molecular models does not suggest any particular conformation in which one of the faces of the

acetyl group is effectively blocked. The lack of diastereoselectivity in the case of C-3-chloroazetidinone is also at present unexplained.

In the case of 3-vinyl-3-acetylazetidinone the size of the substituent at C-3 remains comparable to that of methoxyazetidinones. However for the purpose of chelation by LiI the only possibility is the one involving the acetyl and the azetidinone carbonyl groups, a situation similar to (429, Fig. LXV) and thus the formation of the same hydroxyethyl compound regardless of the Lewis acid.

It can be concluded that the non-chelation controlled reduction as a route to 3-hydroxyethyl azetidinones is fairly broad in scope. Azetidinones bearing either a 3-halo and 3-alkyl substituent show lower diastereoselectivity. The suggested mechanism to explain these results is based on rather simple (almost simplistic) considerations. The exact mechanism may be a matter of debate but the usefulness of such a reduction is very real.

It is difficult to predict if such a reduction might be useful for reduction of azetidinones in which the acetyl group and the big substituent at C-4 are cis to each other. Currently the progress along those lines is being hampered by the unavailability of such compounds.

References and notes

(121) L-Selectride and its potassium analog are widely used reagents. It is not possible to list all of their previous applications. For a leading reference describing selective applications see Fieser M ' Reagents for organic synthesis' Vol. 12 page.284.

(122) This is expected on the basis of reactions of several such anions. Specifically the structure of (201).

(123) In certain cases it appeared that chromatography might have led to separation of two diastereoisomers. In such instances, chromatographically non-homogeneous samples were used for high field NMR spectral analyses.

(124) The impact of an electron withdrawing substituent at C-4 or at the nitrogen atom has not been determined thus far due to unavailability of such acetylazetidinones. For example, p-nitrobenzaldehyde reacts with p-anisidine to form the imine relatively easily. The azetidinone obtained by reaction of the imine with methoxyacetic acid, does not furnish any hydroxyethyl compound on successive exposure to LDA and acetaldehyde. Reaction of the alleged anion with acetyl chloride was also not successful and the starting material was recovered unchanged. The use of 2 equivalents of LDA led to complete destruction of the starting azetidinone and formation of an intractable red tar. Also it has not been possible to obtain an acetylazetidinone with an electron withdrawing group on the nitrogen atom. Direct synthesis of the parent azetidinones was not possible due to unavailability of the corresponding imines. The acetylazetidinone (379, Fig. LIX) could be converted to the N-H compound (432, Fig. LXV) by exposure to ceric ammonium nitrate. But several attempts to convert this compound to a suitable derivative failed. Thus reaction of this azetidinone with 2,4-dinitrofluorobenzene led to destruction of the starting material. Reaction (442, Fig. LXVI) with dimethyl acetylene dicarboxylate gave results similar to the case of 2,4-dinitrofluorobenzene.

(125) Hart, D.J. and Ha, D-C. *Tet. Lett.* 1985, 26, 5493. The reaction does not seem to be general. The corresponding N-TBDMS derivative failed to epimerize under these conditions.

(126) Borane and alkylboranes are known to react with both carbon-carbon and carbon-oxygen double bonds. However in the case of compound (192, Fig. XXXII, the precursor of 194, Fig. LXIV) even an extended reaction time with borane-THF complex in refluxing THF led to recovery of the starting material. Indeed the reduction of the acetyl group with borane seems to much faster than that of the cinnamyl group and despite some what low yield at high temperature, the cinnamyl group was intact in the mixture of the hydroxyethyl compounds. For a leading reference on the subject of reaction of borane derivatives with carbon-carbon multiple bonds see, Brown, H.C. and Jadhav, P.K. 'Asymmetric Synthesis' Morrison, J.D. ; Academic Press, New York. 1983, Vol.2, 1.

For some recent studies of reduction of carbonyl group by modified boranes, see, [i] Corey, E.J.; Shibata, S. and Bakshi, R.K. *J. Org. Chem.* 1988, 53, 2861. [ii] Masamune, S.; Kennedy, R.M.; Petersen, J.; Houk, K.N. and Wu, Y. *J. Am. Chem. Soc.* 1986, 108, 7404.

(127) Conditions used for this reduction were similar to those employed by Borch, R.F.; Bernstein, M.D. and Durst, H.D. *J. Am. Chem. Soc.* 1971, 93, 2897.

(128) For a review on use of $Zn(BH_4)_2$ see, Oishi, T. and Nakata, T. *Acc. Chem. Res.* 1984, 17, 338.

Experimental Section

General

L-Selectride was purchased from Aldrich Chemical Company and was used as such. Various acylazetidinones were synthesized using the general procedure outlined in Chapter 4. General comments mentioned at the beginning of the Experimental Section of Chapter 2 also apply here. The general procedure for the reduction was outlined in Chapter 4.

Physical and spectroscopic properties of various azetidinones synthesized by the non-chelation controlled reduction are being mentioned below.

Compound (380, Fig. LIX) has the following physical properties: mp: 175-176°C; ir: 3300, 1750 cm^{-1} ; 327 (M^+ , 18.8%), 282 (M^+-45 , 4.3%), 212 (imine⁺+1, 47.0%), 211 (imine⁺, 100%); nmr: δ = 7.3-7.2 (m, 7 H), 6.8 (dd, 2 H, J= 2.3 Hz, J= 6.8 Hz), 5.1 (s, 1 H), 4.3 (m, 1 H), 3.7 (s, 3 H), 3.2 (s, 3 H), 2.2 (broad s, 1 H), 1.3 (d, 3 H, J= 6.4 Hz). HRMS calc for $\text{C}_{19}\text{H}_{21}\text{NO}_4$ 327.1507 found 327.1476.

Azetidinone (382, Fig. LIX) is a white solid with the following properties: mp: 105-106°C; ir: 3200, 1750 cm^{-1} ; ms: 297 (M^+ , 7.5%), 265 (M^+-32 , 7.2%), 182 (imine⁺+1, 100%), 178 (M^+-119 , 14.2 %); nmr: δ = 7.4-7.0 (m, 10 H), 5.2 (s, 1 H), 4.3 (q, 1 H, J= 6.4 Hz), 3.2 (s, 3 H), 1.4 (d, 3 H, J=6.4 Hz). HRMS calc for $\text{C}_{18}\text{H}_{19}\text{NO}_3$ 297.1393, found 297.1373.

Azetidinone (384, Fig. LIX) is an oil with the following properties: ir: 3310, 1755 cm^{-1} ; ms : 317 (M^+ , 13%), 273 (M^+-44 , 4.6 %), 201 (imine⁺, 100%); nmr: δ = 7.4-6.3 (series of m, 7 H), 5.1 (s, 1 H),

4.2 (q, 1 H, J= 5.2 Hz), 3.7 (s, 3 H), 3.4 (s, 3 H), 1.3 (d, 3 H, J= 5.2 Hz).
HRMS calc for C₁₇H₁₉NO₃ 317.1393, found 317.1271.

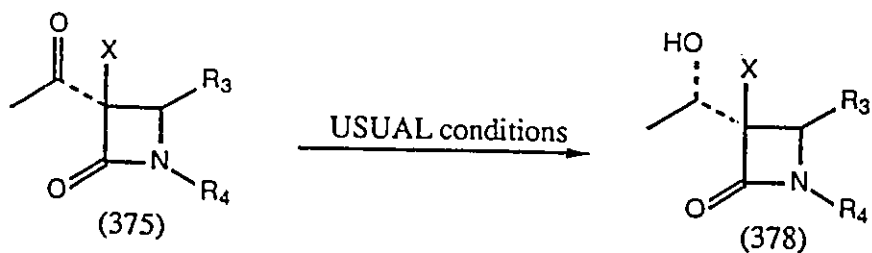
Compound (386, Fig. LIX) is a foam with the following properties: ir: 3300-3200, 1745 cm⁻¹; ms: 429 (M⁺, 5.5 %), 339 (M⁺-90, 100%), 338 (M⁺-91, 100%), 280 (M⁺-149, 3.1%); nmr: δ= 7.4-7.2 (m, 12 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, J= 7.5 Hz, J= 15.9 Hz), 4.9 (broad s, 2 H), 4.8 (dd, 1 H, J= 0.7 Hz, J= 7.5 Hz), 4.3 (q, 1 H, J= 6.5 Hz), 3.7 (s, 3 H), 1.3 (d, 3 H, J= 6.5 Hz).

Azetidinone (388, Fig. LIX) is a white foam with the following properties: ir: 3300, 1750 cm⁻¹; ms: 443 (M⁺, 1.1 %), 352 (M⁺-91, 5.2 %), 308 (M⁺-135, 3.8%), 250 (imine⁺-1, 18.4%), 129 (M⁺-314, 50.8%), 91 (C₇H₇⁺, 69%), 41 (M⁺-402, 100%); nmr: δ= 7.4-7.1 (m, 12 H), 6.8 (dd, 2 H, J= 1.1 Hz, J= 7.8 Hz), 6.5 (broad s, 1 H), 5.0-4.9 (AB, 2 H, J= 10.8 Hz), 4.6 (s, 1 H), 4.4 (m, 1 H), 3.7 (s, 3 H), 1.9 (d, 3 H, J= 1.0 Hz), 1.4 (d, 3 H, J= 6.4 Hz).

Compound (390, Fig. LIX) was inadvertently wrongly numbered, this compound is identical with (336, Fig. LI). The properties of this compound have been described in the Experimental Section of Chapter 6.

Azetidinone (392, Fig. LIX) is a colorless oil with the following properties: ir: 3300-3200, 1750 cm⁻¹; ms: 393 (M⁺, 1.5%), 348 (M⁺-45, 1.2%), 308 (M⁺-85, 1.2%), 250 (imine⁺-1, 25%), 149 (C₈H₇NO₂⁺, 5.9%), 129 (M⁺-264, 32.3%), 45 (M⁺-348, 100%); nmr: δ= 7.4-7.1 (m, 7 H), 6.8 (dd, 2 H, J= 2.2 Hz, J= 6.8 Hz), 6.4 (broad s, 1 H), 5.9-5.8 (m, 1 H), 5.1-5.0 (m, 2 H), 4.5 (s, 1 H), 4.4 (m, 2 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 1.9 (d, 3 H, J= 1.2 Hz), 1.3 (d, 3 H, J= 6.5 Hz).

Fig. LIX



SM.	X	R ₃	R ₄	Yield%	Product
(379)	OMe	C ₆ H ₅	C ₇ H ₇ O	75	(380)
(381)	OMe	C ₆ H ₅	C ₆ H ₅	75	(382)
(383)	OMe	C ₄ H ₃ O	C ₇ H ₇ O	65	(384)
(385)	OBn	C ₈ H ₇	C ₇ H ₇ O	75	(386)
(387)	OBn	C ₉ H ₉	C ₇ H ₇ O	70	(388)
(389)	OBn	C ₄ H ₃ O	C ₇ H ₇ O	50	(390)
(391)	OC ₃ H ₅	C ₉ H ₉	C ₇ H ₇ O	57	(392)
(393)	OMe	C ₁₀ H ₁₀ N	C ₇ H ₇ O	68	(394)
(395)	OMe	C ₈ H ₇	C ₈ H ₁₀ N	65	(396)

OC₃H₅ = 2-propenyloxy (= allyloxy), C₇H₇O = p-methoxyphenyl (= PMP)

C₄H₃O = 2-furyl, C₈H₇ = trans cinnamyl, C₉H₉ = methylcinnamyl

C₁₀H₁₀N = p-(diethylamino)phenyl, C₈H₁₀N = p-(dimethylamino)phenyl

Diastereomer A was the sole hydroxyethyl compound as determined by 300 MHz NMR.

Azetidinone (394, Fig. LIX) is a yellowish foam with the following properties: ir:3250, 1755 cm^{-1} ; ms: 398 (M^+ , 4.3%), 354 (M^+-44 , 10.6%), 282 (M^+-116 , 12.6%), 249 (M^+-149 , 41%), 43 (M^+-355 , 100%); nmr: d= 7.3-6.6 (series of m, 8 H), 5.0 (s, 1 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.35 (s, 3 H), 3.32 (m, 4 H); 1.3 (d, 3 H, $J=6.4$ Hz), 1.1 (m, 6 H).

Compound (396, Fig. LIX) is a semi-solid with the following properties: ir:3300-3200, 1750 cm^{-1} ; ms: 366 (M^+ , 6.0%), 322 (M^+-22 , 1.4%), 350 (M^+-116 , 7.0%), 162 (M^+-204 , 19.7%), 86 (M^+-280 , 100%); nmr: d= 7.4-7.2 (m, 7 H), 6.7-6.6 (m, 3 H), 6.3-6.2 (dd, 1 H, $J=7.7$ Hz, $J=16.0$ Hz), 4.7 (d, 1 H, $J=7.7$ Hz), 4.2 (m, 1 H), 3.6 (s, 3 H), 2.9 (s, 6 H), 1.3 (d, 3 H, $J=6.4$ Hz). HRMS calc for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3$ 366.2015, found 366.1994.

Azetidinones (399,401, 405 and 261, Fig. LX) were encountered in the context of studies described in Chapter 5. Their spectral properties have been mentioned in the Experimental Section of Chapter 5.

Azetidinone (403, Fig. LX) has the following physical properties: mp: 87-88 $^{\circ}\text{C}$, ir:3300-3100, 1760-1745 cm^{-1} ; ms: 446 (M^+ , 1.2%), 338 (M^+-108 , 12.9%), 212 (imine $^{++}1$, 100%) 211 (imine $^+$, 69.4%); nmr: d= 7.2-6.9 (m, 12 H), 6.8 (dd, 2 H, $J=2.2$ Hz, $J=6.9$ Hz), 5.3 (m, 2 H), 4.7 (s, 2 H), 4.4 (m, 1 H), 3.7 (s, 3 H), 1.4 (d, 3 H, $J=6.5$ Hz). In this particular case the proton at C-4 of the azetidinone and the N-H proton of the carbamate moiety have accidentally overlapped (m at 5.3). The diastereoisomeric purity is judged on the basis of the presence of only one doublet for the methyl group of the hydroxyethyl moiety. In the case of the mixture of hydroxyethyl

compounds (obtained by reaction of the anion with acetaldehyde) the signal in question is a distorted triplet.

Compound (407, Fig. LX) is a white solid with following physical properties: mp: 188-189°C; ir: 3300-3100, 1755, 1730 cm^{-1} ; ms: 384 (M^+ , 4.2%), 339 (M^+-49 , 75.0%), 235 (M^+-149 , 1.6%), 212 (imine⁺⁺1, 98.4%), 211 (imine⁺, 98.7%), 43 ($\text{C}_2\text{H}_3\text{O}^+$, 100%); nmr: δ = 7.3-7.2 (m, 7 H), 6.8 (dd, 2 H, $J= 1.8$ Hz, $J= 7.2$ Hz), 5.3 (broad s, 2 H), 4.4 (m, 2 H), 3.7 (m, 5 H), 1.3 (d, 3 H, $J= 6.3$ Hz), 0.8 (t, 3 H, $J= 3.5$ Hz)

In the case of the azetidinone (409, Fig. LXI) the product of the non-chelation controlled reduction was a semi-solid with the following properties: ir: 3200, 1750 cm^{-1} ; ms: 337 (M^+ , 26.7%), 292 (M^+-45 , 17.1%), 237 (imine⁺, 24%), 236 (imine⁺-1, 67%), 188 (M^+-149 , 74.2%), 43 ($\text{C}_2\text{H}_3\text{O}^+$, 100%); nmr: δ = 7.4-7.2 (m, 7H), 6.9 (m, 3 H), 6.2 (dd, 1 H, $J= 8.1$ Hz, $J= 15.9$ Hz), 4.4 (dd, 1 H, $J=0.8$ Hz, $J= 8.1$ Hz), 4.0 (q, 1 H, $J= 6.3$), 3.7 (s, 3 H), 1.29 (d, 3 H, $J= 6.3$ Hz), 1.24 (d, 2 H, $J= 5.6$ Hz). The signal at 1.29 had an adjoining signal the integral for which was about 1/10th that for the main signal.

Azetidinone (412, Fig. LXI) was initially obtained as a colorless oil which solidified on standing at room temperature. The compound has the following physical properties: mp: 122-123°C; ir: 3200, 1750 cm^{-1} ; ms: 323 (M^+ ,21.9%), 279 (M^+-44 ,11.6%) 211 (imine⁺, 100%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$, 30.1%); nmr: δ = 7.3-7.1 (m, 7 H), 6.7 (dd, 2 H, $J= 2.3$ Hz, $J= 5.9$ Hz), 5.5-5.4 (m, 1 H), 5.1 (m, 3 H), 4.1 (m, 1 H), 3.7 (s, 3 H), 2.1 (d, 1 H, $J= 5.3$ Hz), 1.3 (d, 3 H, $J= 6.4$ Hz). HRMS calc for $\text{C}_{20}\text{H}_{21}\text{NO}_3$ 323.1551, found 323.1528.

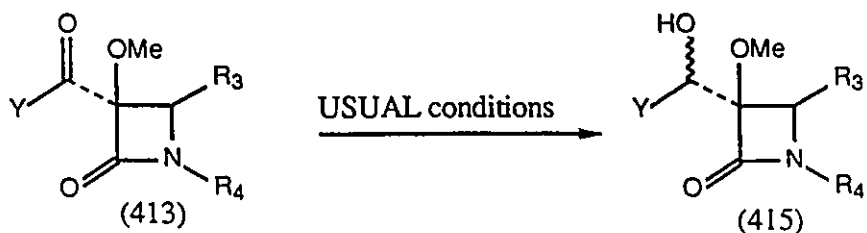
In case of the fluororoazetidinone (413, Fig. LXI) the product of the non-chelation controlled reduction showed following signals in

Fig.LXI



SM	X	R ₃	Yield	Comments
(409)	Me	C ₈ H ₇	50%	Usual conditions, Only A (410)
(411)	C ₂ H ₃	C ₆ H ₅	85%	Usual conditions, One product (412)
(411)	C ₂ H ₃	C ₆ H ₅	60%	LiI, Ether, -78°C, L-Selectride (412)
(413)	F	C ₉ H ₉	55%	Usual conditions ca. 95:5 :: A:B (414)
(374)	Cl	C ₉ H ₉	50%	Usual conditions 2:1 :: A:B (373)

R₄ = PMP for all cases. C₂H₃ = vinyl Others as before.



SM	Y	R ₃	Yield	Comment
(415)	C ₃ H ₅ O ₂	C ₉ H ₉	60%	one compound, unassigned at this stage (416)
(215)	C ₃ H ₅ O ₂	C ₈ H ₇	50%	one compound unassigned at this stage (216)
(417)	C ₇ H ₇	C ₈ H ₇	80%	Only diastereomer A. (418)

R₄ = PMP for cases C₃H₅O₂ = acetoxyethyl C₇H₇ = m-tolyl. other as before

the NMR spectrum: δ = 7.4-7.2 (m, 7 H), 6.8 (dd, 2 H, J = 2.3 Hz, J = 7.0 Hz), 6.6 (broad s, 1 H), 4.7 (d, 1 H, J = 3.9 Hz), 4.3 (m, 1 H), 3.77 (s, 3 H), 1.92 (s, 3 H), 1.42 (dd, 3 H, J = 1.1 Hz, J = 6.5 Hz). In addition the spectrum showed presence of peaks at δ = 4.8, 1.98 and 1.46. These peaks correspond to the diastereoisomer B and were too small in intensity to ascertain their shape or to allow proper integration. For that reason the ratio of diastereoisomers after Selectride reduction is somewhat inaccurate. This mixture has following spectral properties: ir: 3200, 1745 cm^{-1} ; ms: 355 (M^+ , 43.4%), 311 (M^+ -44, 9.6%), 251 (imine⁺, 27.1%), 206 (M^+ -149, 100%).

In the case of the chloroazetidinone (374, Fig. LXI) the product obtained from the non-chelation controlled reduction, (373, Fig. LXI), was a semi-solid with the following spectral characteristics: ir: 3200, 1745 cm^{-1} ; ms: 371 (M^+ , 37.9%) 327 (M^+ -44, 11.4%), 251 (imine⁺, 22.3%), 250 (imine⁺-1, 97.8%), 43 ($C_2H_3O^+$, 100%); nmr: δ = 7.4-7.2 (m, 7 H), 6.8 (m, 2 H), 6.5 (broad s, 1 H), 4.8 (s, < 1 H), 4.7 (s, < 1 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 2.3 (d, < 1 H, J = 4.4 Hz), 2.1 (d, < 1 H, J = 7.6 Hz), 1.9 (d, 3 H, J = 2.8 Hz), 1.4 (m, 3 H). The presence of two sets of signals at 4.8 and 4.7 and a multiplet at 1.4 suggested that the compound (374) was a mixture of two hydroxyethylazetidinone.

Compound (416, Fig. LXI) is a semi-solid with the following properties: ir: 3300, 1755 cm^{-1} ; ms: 425 (M^+ , 15.2%), 322 (M^+ -103, 18.6%), 250 (imine⁺-1, 100%); nmr: δ = 7.4-7.2 (m, 7 H), 6.9 (m, 2 H), 6.5 (broad s, 1 H), 4.7 (s, 1 H), 4.4-4.2 (series of m, 3 H), 3.7 (s, 3 H), 3.68 (s, 3 H), 2.9 (d, 1 H, J = 4.3 Hz), 2.1 (s, 3 H), 1.9 (broad s, 3 H),

The azetidinone (215, Fig. LXI) furnished a clear colorless oil on reduction under non-chelating conditions. The product (216) has the

following properties: ir: 3200, 1750 cm^{-1} ; ci-ms: 412 ($\text{M}^+ + 1$, 1.0%), 160 ($\text{M}^+ - 252$, 100%); nmr: d= 7.4-7.2 (m, 7 H), 6.8 (m, 3 H), 6.3 (dd, 1 H, $J = 7.7$ Hz, $J = 16.1$ Hz), 4.8 (dd, 1 H, $J = 0.9$ Hz, $J = 7.8$ Hz), 4.3-4.22 (m, 2 H), 4.2 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 3 H), 2.1 (s, 3 H).

Compound (418, Fig. LXI) is a semi-solid with the following properties: ir: 3200, 1745 cm^{-1} ; ci-ms: 429 (M^+ , 0.8%), 309 ($\text{M}^+ - 120$, 38%), nmr: d= 7.8 (d, 1 H, $J = 7.0$ Hz), 7.4-7.1 (m, 10 H), 6.7 (m, 3 H), 6.3 (dd, 1 H, $J = 8.4$ Hz, $J = 16.0$ Hz), 5.4 (s, 1 H), 4.8 (dd, 1 H, $J = 0.8$ Hz, $J = 8.0$ Hz), 3.7 (s, 3 H), 3.68 (s, 3 H), 2.4 (s, 3 H).

As indicated in the text, synthesis of the azetidinone (419, Fig. LXII) was carried out by two different procedures. Regardless of the sequence of the reactions employed, the product was obtained as a white solid with following properties: mp: 85-86°C; ir: 1755, 1720 cm^{-1} ; ms: 407 (M^+ , 12.1%) 350 ($\text{M}^+ - 57$, 82.8%) 306 ($\text{M}^+ - 101$, 32.8%) 201 ($\text{M}^+ - 206$, 19.9%) 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$, 43.7%) 73 ($\text{M}^+ - 334$, 100%); nmr: d= 7.2 (dd, 2 H, $J = 1.4$ Hz, $J = 4.7$ Hz), 6.8 (dd, 2 H, $J = 2.3$ Hz, $J = 6.3$ Hz), 4.6 (s, 1 H), 4.2 (q, 1 H, $J = 6.4$ Hz), 3.7 (s, 3 H), 3.5 (s, 3 H), 2.2 (s, 3 H), 1.2 (d, 3 H, $J = 6.4$ Hz), 0.8 (s, 9 H), 0.09-0.086 (broad s, 6 H).

Spectral properties of the azetidinone (339, Fig. LXII) have been described in the Experimental Section of Chapter 6.

The tosylate (352, Fig. LXIII) is a viscous oil with following properties: ir: 1760, 1730 cm^{-1} ; ms : 523 (M^+ , 4.6%), 351 ($\text{M}^+ - 172$, 6.2%), 175 ($\text{M}^+ - 348$, 3.5%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$, 26.4%), 91 (C_7H_7^+ , 100%); nmr: d=7.7 (d, 2 H, $J = 8$ Hz), 7.3-7.1 (series of m, 9 H), 6.8 (dd, 2 H, $J = 2.3$ Hz, $J = 6.8$ Hz), 5.1 (q, 1 H, $J = 6.6$ Hz), 4.8 (s, 1 H), 4.7-4.6 (AB, 2 H, $J = 10.4$ Hz), 3.7 (s, 3 H), 2.3 (s, 3 H), 2.1 (s, 3 H), 1.4 (d, 3 H, $J = 6.6$ Hz).

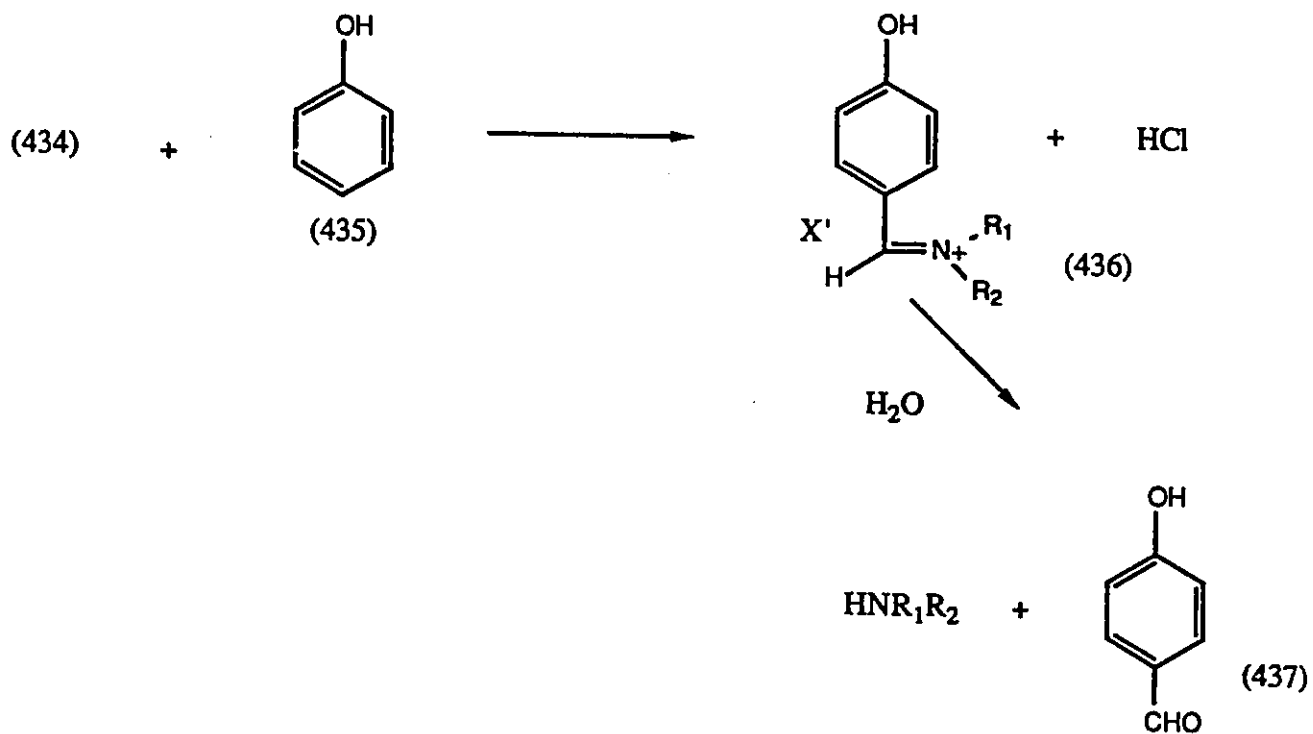
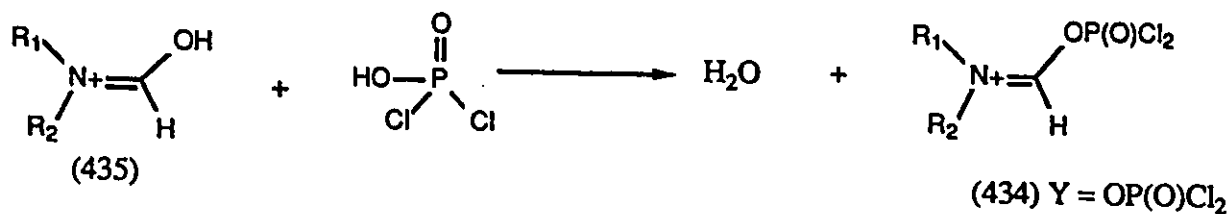
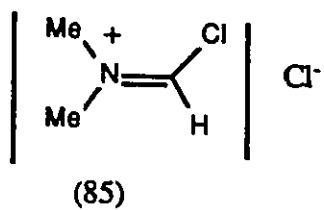
CHAPTER 8

In this chapter use of N,N-dimethylchloromethyleniminium chloride (85, Fig. LXVI) as an activating agent for carboxylic acids is described. Specifically the idea was to use this activating agent to obtain ketenes from carboxylic acids for the purpose of making azetidiones.

In view of the large number of activating agents that have been used for formation of ketenes from carboxylic acids the question might be asked regarding the wisdom of investing time in determining the virtues of yet another condensing agent¹²⁹. The question is valid since none of these more expensive or difficult to handle reagent seems to come close to the cheap and easily prepared acid chlorides in terms of yields. However as has been pointed out here and elsewhere by other authors, continued exploration of condensing agents for the purpose of formation of azetidiones is well justified. Too often there are subtle or even marked differences in the reactivity pattern of acid chlorides and other activating agents. Within the realm of non-acid chloride type activating agents there are interesting differences. As pointed out in the following paragraphs such an exercise has offered opportunities for simplification of some existing experimental procedures.

It has been known for a long time that dehydrating agents such as phosphoryl chloride react with tertiary amides such as (433, Fig. LXVI) to provide compounds such as (434, Fig. LXVI). The products of such reactions can be formally considered as 'mixed anhydrides' of the acid and the dehydrating agent (434, Fig. LXVI).

Fig.LXVI



This has formed the basis of Vilsmeier-Haack reactions¹³⁰. The electrophilic imminium salt (434, Fig. LXVI) reacts with aromatic compounds to provide intermediates such as (436, Fig. LXVI). Subsequent hydrolysis furnishes the corresponding aldehyde. Even though the imminium salt is relatively electrophilic, the reaction is successful only with fairly electron rich aromatic compounds such as anilines and phenols; simple aromatic hydrocarbons fail to react. Although originally N-methylformanilide-POCl₃ was used as a source of the imminium salt, other combinations of tertiary formamides and dehydrating agents can be used. Perhaps from the viewpoint of availability and handling, DMF is the best tertiary amide for this purpose. On the other hand there are many choices in terms of dehydrating agents. Thus iminium salts can be derived from the DMF-COCl₂ combination. Among other dehydrating agents that can be used include SOCl₂, (COCl)₂ and various chlorophosphonates. (see below).

Iminium salts such as (85, Fig. LXVII) can also react with a variety of other nucleophiles. Thus such salts have been reacted with alcohols for the purpose of their conversion to the corresponding halides (438->439, Fig. LXVII)¹³¹. Ketoximes react with such salts to provide the corresponding formate esters (440 -> 441, Fig. LXVII) and aldoximes are dehydrated by these salts to provide nitriles (442->443, Fig. LXVII)¹³². Reaction of nitronates with iminium salts lead to their activation. Subsequent reaction of the activated nitronates has formed the basis of a synthesis of ketoximes (444 -> 447, Fig. LXVII)¹³³. Hutchinson and colleagues have reacted such salts with potassium monomethyl malonate to obtain methyl

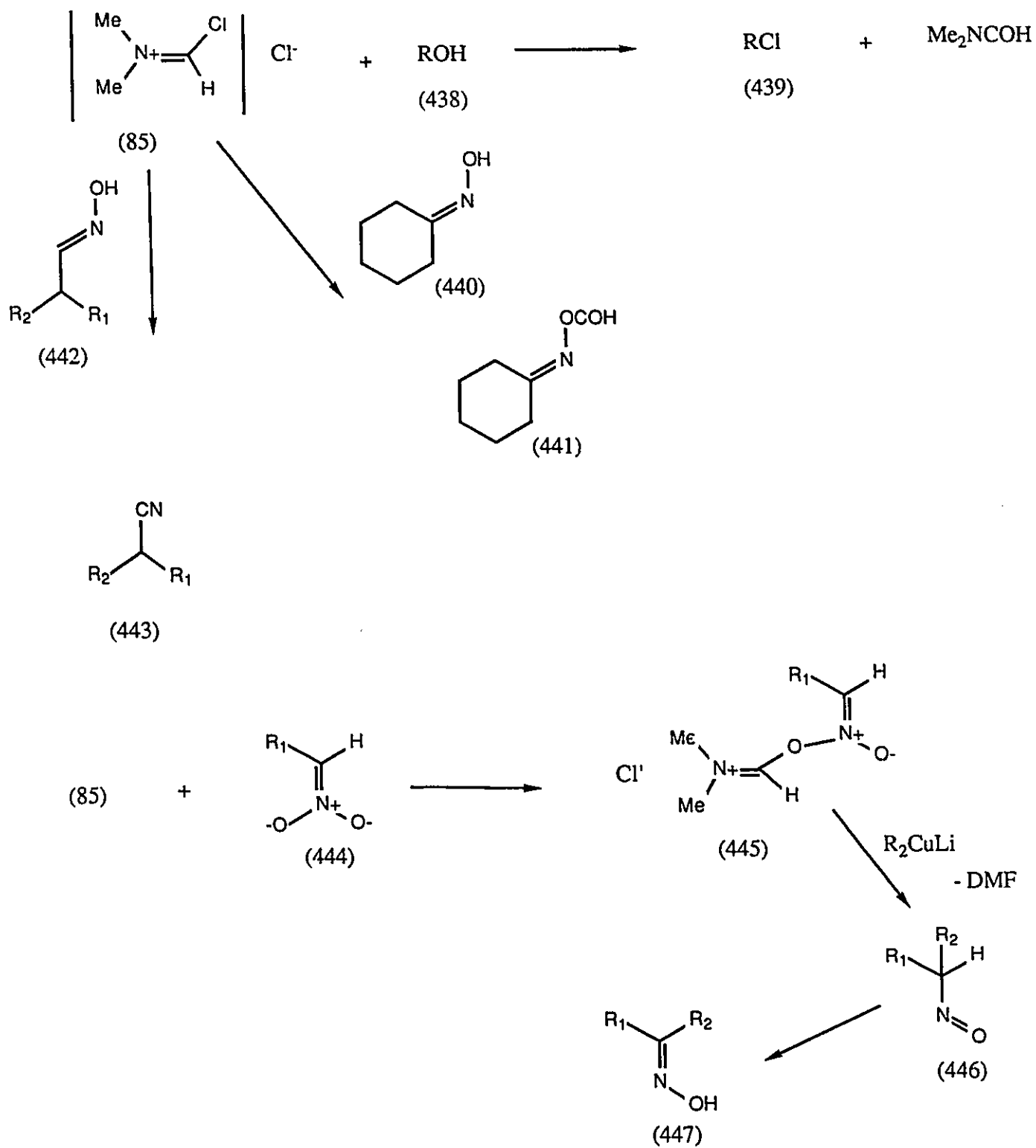
diformylacetate.(448->450, Fig. LXVII)¹³⁴. In a somewhat more intriguing application of the such salts bromoacetic acid was converted to triformylmethane by reaction with (449, 451-> 453, Fig. LXVIII)¹³⁵. A recent publication describes the use of such iminium salts for the purpose of conversion of cyclic 1,3-diketones to the corresponding α -haloenones¹³⁶.

Carboxylic acids can be activated by reacting with these iminium salts. Though some times the results of such reactions are presented as acid chlorides, there is some room for debate regarding the exact structure (see below). Such activated acid derivatives have been used for conversion of the acid to the corresponding alcohols and aldehydes by reduction with an appropriate reducing agent (454 -> 456 and 454 -> 457, Fig. LXVIII)^{137, 138}. Conversion to esters has also been achieved by the means of similar activation (454 -> 459, Fig. LXVIII)¹³⁹. Also by reaction of such activated acids with amines, amides have been obtained in respectable yields ¹⁴⁰.

The structure of the solid product obtained from the reaction of DMF with oxalyl chloride may be expressed as either (85, Fig.LXIX) or (460, Fig. LXIX). {The trioxygenated structure (461, Fig.LXIX) is due to Mewshaw¹³⁶. This structure may be a typing mistake and perhaps the author intended the structure (460)}. However based upon the vigorous gas evolution that takes place upon interaction between DMF and oxalyl chloride the structure (460) does not seem reasonable. In our opinion the adducts should be depicted as (85).

The products of reaction between acids and the iminium salts have sometimes been designated as acid chlorides¹⁴¹. Perhaps the reason for such a representation lies in the often observed catalysis

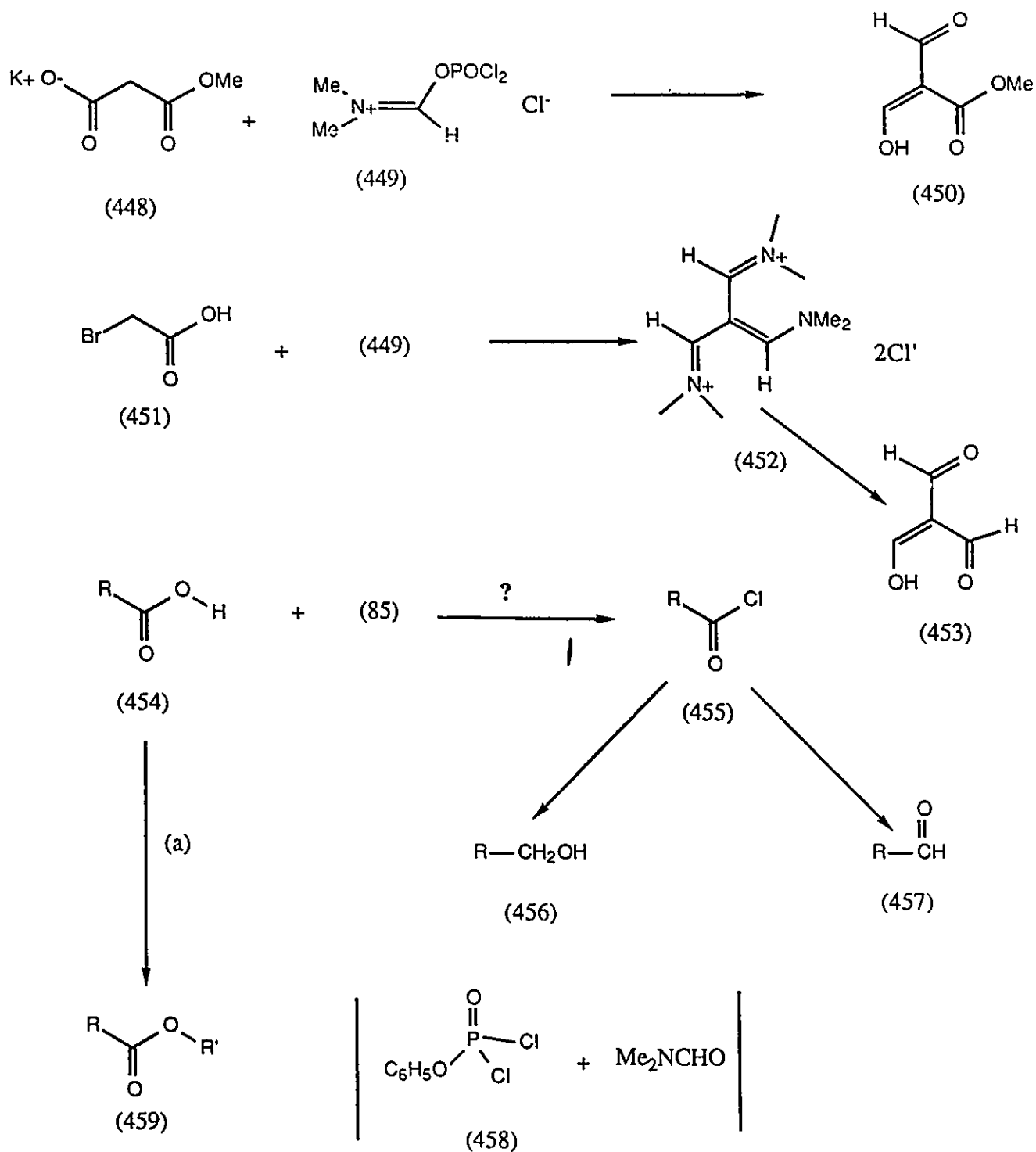
Fig.LXVII



of acid chloride formation reactions by DMF¹⁴². This may not be accurate in the present context since equivalent amounts of (85) and the acid are used. It can be argued that the result of reaction between the acid and the iminium salt should be shown as (462, Fig. LXIX) or its covalent equivalent (463, Fig. LXIX).

With a view to answering these questions it was decided to record C-13 NMR spectra of various compounds related to this discussion. Only the carbonyl region in the decoupled spectra are shown (Fig. LXX). As can be seen by inspection of spectra {1}, {3} and {4} the reaction between DMF and oxalyl chloride is irreversible. Also the presence of only one signal in the carbonyl region gives credence to structure (85) rather than the structure (460, Fig. LXIX). The comparison of spectra {1} , {2} and {6} also shows that there is no noticeable interaction between the acid chloride and DMF. On the other hand addition of less than one equivalent of acid to the iminium salt leads to loss of carbonyl signal due to the carboxylic acid and formation of a product with a signal at 171.458 ppm {7}. The more significant part in the spectrum of this product is the absence of the signal due to the carbonyl group of DMF in {7}. Thus even though the chemical shift of the carbonyl group of the adduct is nearly identical with that of the carbonyl group of the acid chloride, spectra {2} and {6} respectively , the absence of DMF signal in the spectrum {7} points to a structure such as (462, Fig. LXIX). On the basis of the chemical shift of the adduct between the acid and the iminium salt the structure (462, Fig. LXIX) also seems unlikely. The chemical shift for the carbonyl carbon atom which originated from

Fig. LXVIII



(a) [i] Pyridine, (458), [ii] R'OH.

Fig. LXIX

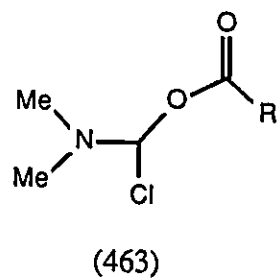
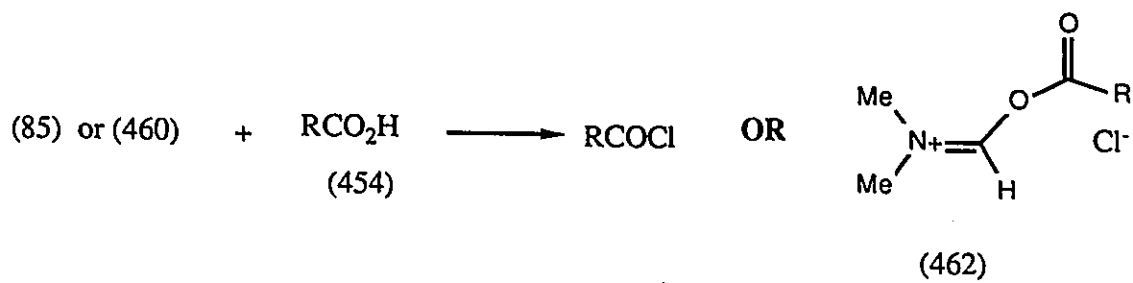
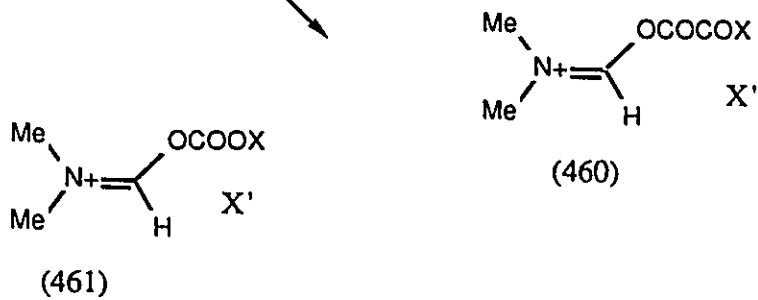
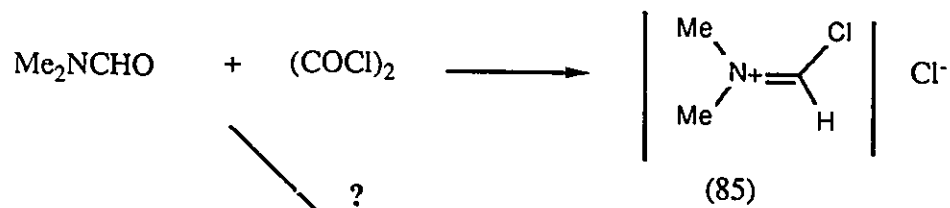


Fig. LXX

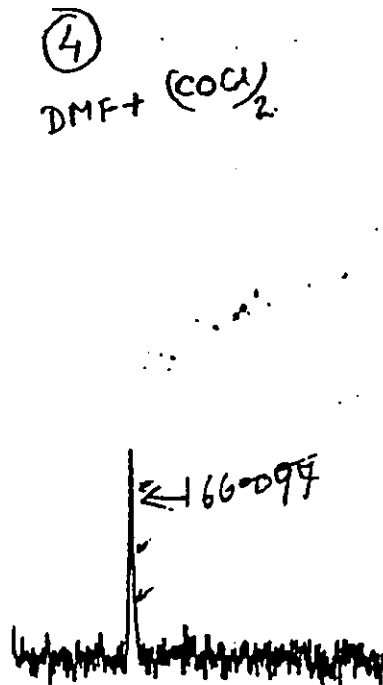
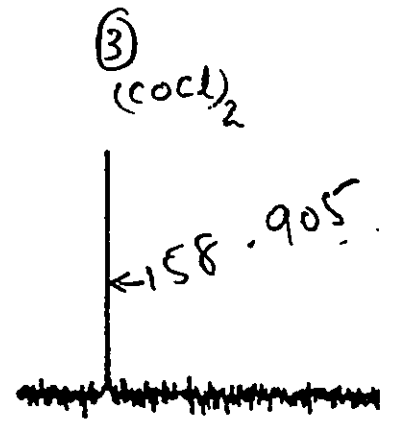
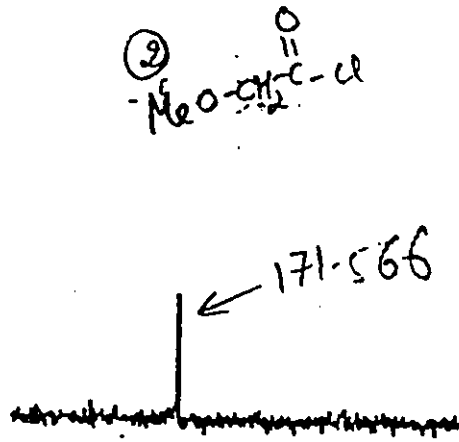
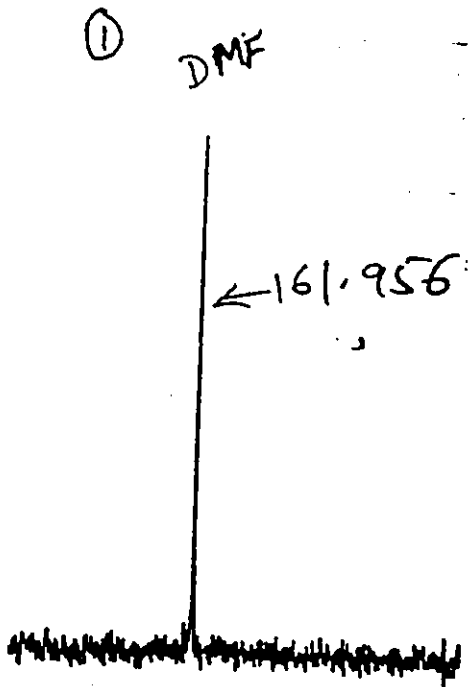
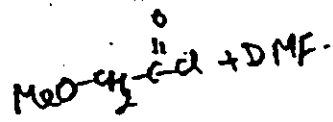
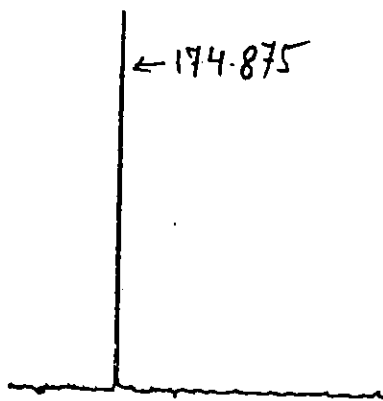
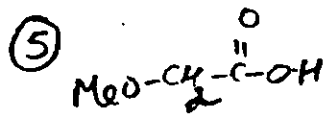
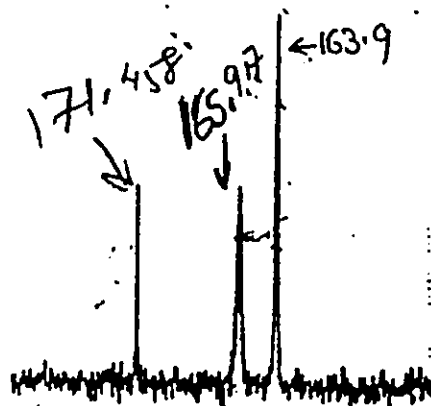
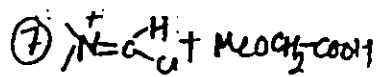
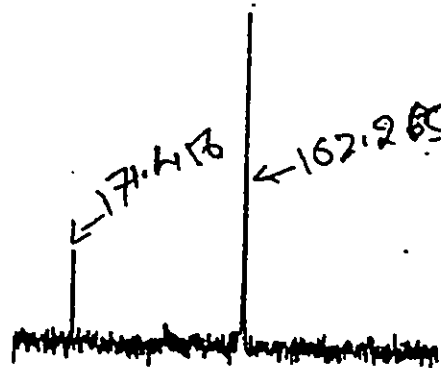


Fig. LXX (cont'd)



⑥



DMF, is much lower than what could be expected for the structure (462)¹⁴³.

The differences in chemical properties of the acid chloride and compounds such as (462, Fig.LXIX) have been noted before. In the case of dihydroxybutyric acids the acid chloride does not lead to azetidiones (Chapter 2). On the other hand in the case of the acid derived from protected threonine, the activation by (85) was futile for the purpose of obtaining azeitinone and conversion to the corresponding acid chloride had to be carried out.

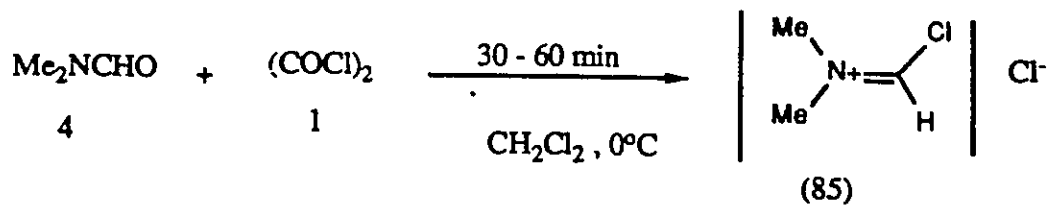
In the context of an unrelated project we had an occasion to use the iminium salt for the activation of carboxylic acids according to Fujisawa procedure. Even though the experiment was successful, yet we were somewhat disappointed by the type of manipulations involved. When the need arose for a reliable procedure for the syntheses of a variety of azetidiones for the studies outlined in Chapter 7, it was decided to examine the role of this activation method and if at all possible to simplify the experimental procedure.

Activation of carboxylic acids by means of iminium salts for azetidione formation has been reported before. Specifically the activation of carboxylic acids by DMF-thionyl chloride¹⁴⁴ and DMF-chlorodiphenylphosphonate¹⁴⁵ was disclosed by Palomo. When these studies were started (Sept. 1985), activation by means of oxalyl chloride was not known. However toward the end of these studies (April 1987), a study by Palomo and coworkers described the limited use of DMF-oxalyl chloride. Essentially a limited study was carried out by these authors to compare the iminium salt (85) and the DMF-thionyl chloride combination for obtaining azetidiones¹⁴⁶.

In the cases where direct comparison was been made reagent (85) was found to be at least as good as other activating agents in terms of the diastereoselectivity of the ketene-imine reaction and the yield of azetidiones thus obtained. There are other significant differences in terms of the type of azetidiones synthesized.

Contrary to Fujisawa's original procedure^{137,138} there does not seem to be any need to let DMF and oxalyl chloride react over an extended period. Nor does it appear necessary to have an excess of DMF over oxalyl chloride or the vice-versa. In our hands the reaction of DMF and oxalyl chloride in 1:1 proportion is quite satisfactory. The reaction is vigorous and instantaneous, though the deposition of the solid salt may not lead to complete reaction. This problem can usually be overcome by conducting the reaction in a rather dilute solution in methylene chloride and adding more solvent as the need arises. An important point concerns the evolution of gases during the reaction and the accompanying dispersion of the solid salt as a fine mist which often clogs the needles. Thus for the process of formation of this salt it was found more beneficial to provide a drying tube rather than a bubbler type outlet for the gases. Activation of various acids does not require the removal of solvent. This is useful from the point of accidental exposure to remaining amounts of CO and minimizing exposure of the moisture sensitive salt to atmosphere. Addition of acids to the suspension of the salt in methylene chloride instantly leads to a clear solution. In our hands it was not necessary to use an excess of the imminium salt over the carboxylic acid. This is true even in those cases where the acid is not soluble in methylene chloride! The formation of a clear solution on

Fig. LXXI

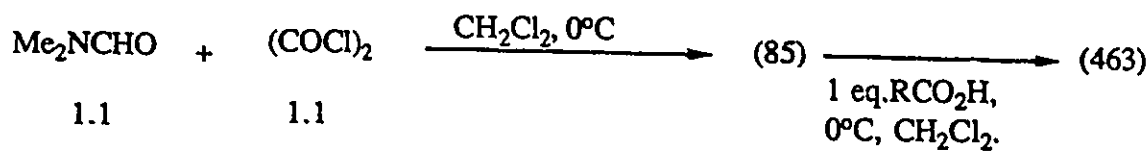
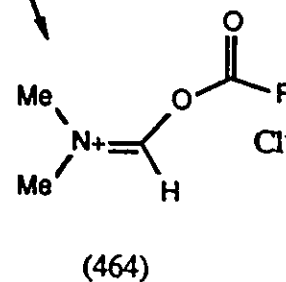


1 1.5

rotovap etc, change of solvent.
0.5 eq. RCO₂H, C₅H₅N, -30°C, 30 min.

Fujisawa

RCOCl OR



Current studies.

Nearly complete dissolution of (85)

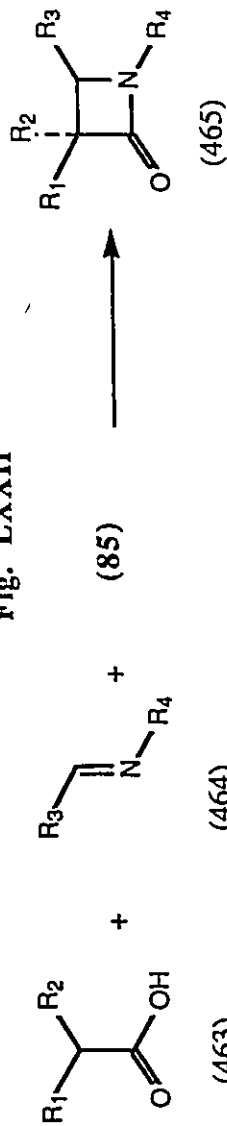
adding one solid (the insoluble acid) to the suspension of the other (the imminium salt) to instantly furnish a clear solution is an indication of the facility of the reaction.⁵³ So contrary to Fujisawa's procedure there is no need to react the acid with the salt at -30°C , nor is it necessary to have a tertiary base present for this reaction. Figure LXXI shows a comparison of our procedure to Fujisawa's procedure. The HCl generated as a result of reaction of the acid with the activating agent is usually taken care of by addition of two equivalents of a tertiary amine during ketene formation step.

Reaction of the activated acid with an imine and at least two equivalents of a strong, non-nucleophilic base (typically triethylamine) over an extended period leads to formation of azetidinones in respectable yields. The results of several such reactions are listed in the Figure LXXII.

As shown in Figure LXXII, the reaction is successful for the preparation of azetidinones from a variety of combinations of acids and imines. Thus acids with a nitrogen substituent at the α position form cis azetidinones in respectable yields. As is the case with many other activating agents, phthaloylglycine leads to formation of significant amounts of the trans azetidinones. The combination of phthaloylglycine activated with (85) and cinnamyl imines leads to mainly cis azetidinones^{146,148}. Hippuric acid does not furnish any azetidinone on activation by the imminium salt (85). Such a behavior is not restricted to the activating agent used here, many other activating agents have also failed¹⁴⁷.

On the other hand benzyl and ethyl carbamate derivatives of glycine reacted with a variety of imines under the influence of the

Fig. LXXII



No.	R ₁	R ₂	R ₃	R ₄	Yield %
1	N ₃	H	C ₆ H ₅	PMP	39
2	N ₃	H	C ₈ H ₇	PMP	68
3	N ₃	H	C ₄ H ₃ O	PMP	55
4	N ₃	H	C ₉ H ₉	PMP	72
5	N ₃	H	C ₉ H ₇ O	PMP	70
6	N ₃	H	CO ₂ (C ₄ H ₉)	PMP	13
7	N ₃	H	CO ₂ CH ₃	PMP	21
8	H	C ₈ H ₄ O ₂ N	C ₆ H ₅	C ₆ H ₅	25
9	C ₈ H ₄ O ₂ N	H	C ₈ H ₇	PMP	49
10	C ₈ H ₄ O ₂ N	H	C ₉ H ₉	PMP	45+10% trans
11	C ₃ H ₆ O ₂ N	H	C ₆ H ₅	PMP	62

No	R1	R2	R3	R4	Yield%
12	(476) C ₈ H ₈ O ₂ N	H	C ₉ H ₉	PMP	45
13	(477) C ₈ H ₈ O ₂ N	H	C ₄ H ₃ O	PMP	50
14	(478) C ₈ H ₈ O ₂ N	H	C ₈ H ₇	PMP	55
15	(188) OCH ₃	H	C ₆ H ₅	PMP	50
16	(190) OCH ₃	CH ₃	C ₆ H ₅	PMP	26
17	(191) OCH ₃	H	C ₈ H ₇	PMP	42
18	(479) OCH ₃	H	C ₉ H ₉	PMP	65
19	(480) OCH ₃	H	C ₅ H ₄ N	PMP	71
20	(481) OCH ₃	H	C ₄ H ₃ S	PMP	72
21	(482) OCH ₃	H	C ₈ H ₇	C ₈ H ₇ N	25
22	(483) OCH ₃	H	C ₁₀ H ₁₄ N	PMP	15
23	(484) OCH ₃	H	C ₆ H ₄ NO ₂	PMP	23
24	(485) OCH ₃	H	C ₆ H ₅	C ₆ H ₅	82
25	(486) OCH ₃	H	C ₄ H ₃ O	PMP	41
26	(421) OC ₇ H ₇	H	C ₈ H ₇	PMP	49
27	(487) OC ₆ H ₅	H	C ₆ H ₅	PMP	42
28	(325) OC ₃ H ₅	H	C ₉ H ₉	PMP	72
29	(326) OC ₃ H ₅	H	C ₈ H ₇	PMP	65

No	R1	R2	R3	R4	Yield%
30 (327)	OC ₃ H ₅	H	C ₄ H ₃ O	PMP	62
31 (300)	OCOCH ₃	H	C ₈ H ₇	PMP	52
32 (488)	OCO ₂ C ₇ H ₇	H	C ₈ H ₇	PMP	37

C_8H_7 = t-cinnamyl, C_4H_3O = 2-furyl, C_9H_9 = methylcinnamyl, $C_8H_4O_2N$ = phthaloyl,
 $C_3H_6O_2N$ = N(carboxyethyl) same as ethylcarbamate of glycine,
 $C_8H_8O_2N$ = N(carobenzoyloxy) same as Cbz-glycine.
 C_5H_4N = 3-pyridyl, C_4H_3S = 3-thienyl, $C_{10}H_{14}N$ = p-(diethylamino)phenyl,
 C_8H_7N = p-(dimethylamino)phenyl, $C_6H_4NO_2$ = p-nitrophenyl, OC_7H_7 = O-benzyl,
 OC_3H_5 = O-allyl.

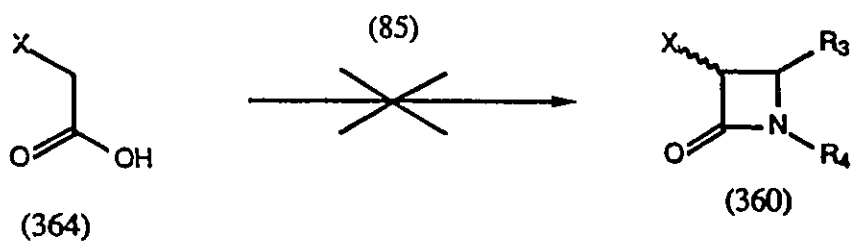
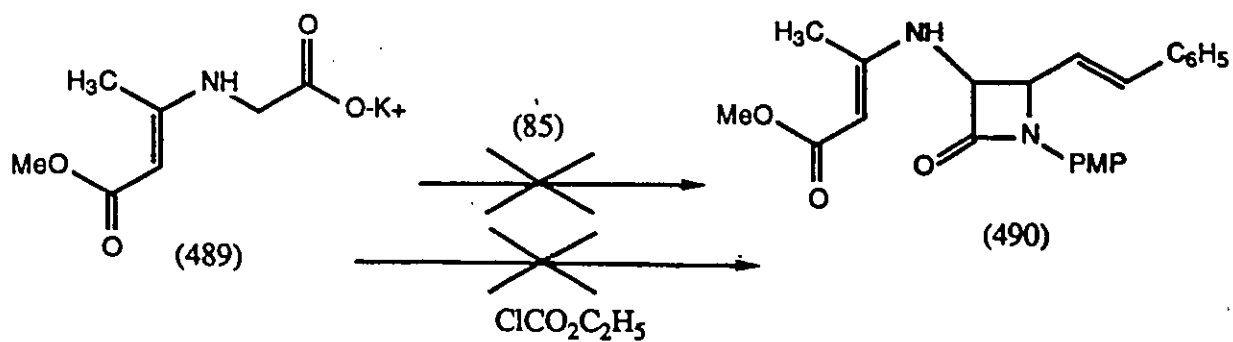
salt (85) to furnish the corresponding protected aminoazetidinones. In contrast the t-Boc derivative of glycine did not furnish azetidinone on activation by and subsequent reaction with the imine.

Dane's salt (489, Fig. LXXIII) also could not be activated with (85) for the purpose of azetidinone formation. In our hands even the use of the recommended condensing agent for this purpose failed to provide the desired azetidinone(490, Fig. LXXIII).¹⁴⁷ Palomo has also noted the failure of such reactions on activation by similar salts^{146,154} . The reasons for such a failure are not obvious.

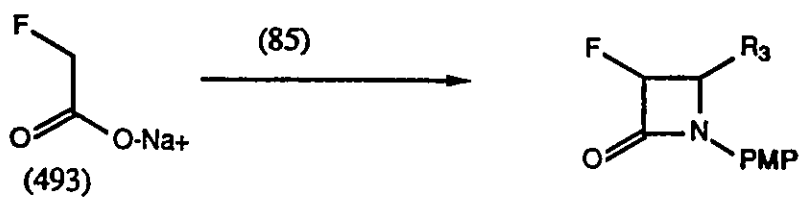
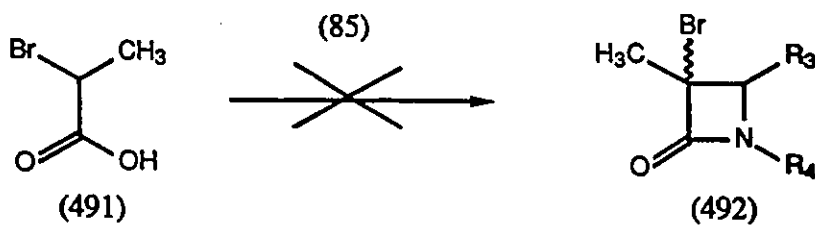
Various ethers of glycolic acids also undergo the ketene-imine reaction under the influence of the imminium salt to furnish exclusively cis azetidinones. Amongst the examples studied are methyl, benzyl, allyl and phenyl ethers. Acetoxyacetic acid similarly undergoes azetidinone formation reaction with a variety of imines. In this particular case the yields of the acetoxyazetidinones are comparable for acetoxyacetyl chloride and the acid-imminium salt combination. Application of these products involve saponification and O-alkylation of the resulting 3-hydroxyazetidinones. Various aspects of these transformations including freedom from epimerization at C-3 during the saponification process have been pointed out in Chapter 6.

The methyl ether of lactic acid undergoes 2+2 cycloaddition reaction to furnish a single 3,3-disubstituted azetidinone in modest yield. This azetidinone is the same as obtained from methylation of the anion form the 3-methoxyazetidinone. However the low yield in the ketene-imine cycloaddition reaction may point towards an 'accidental' purification rather than a high degree of stereoselectivity

Fig.LXXIII



X = Cl, Br or I.



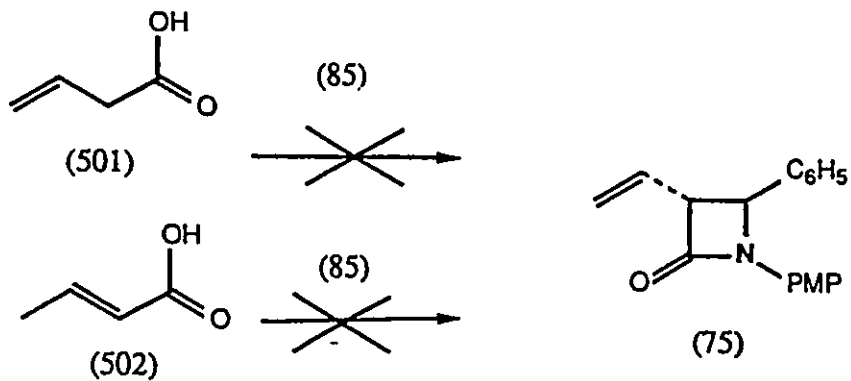
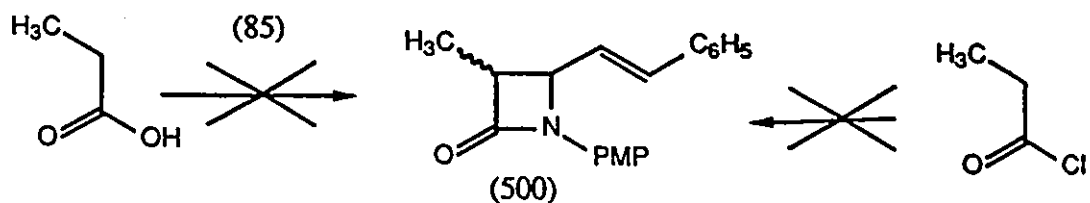
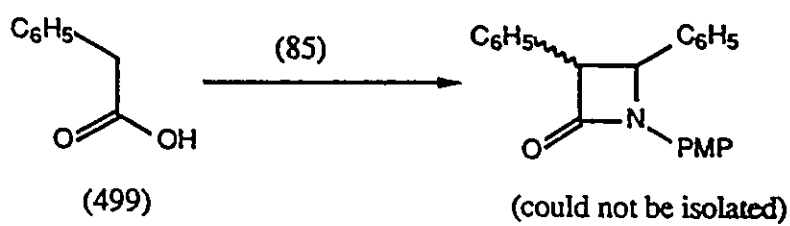
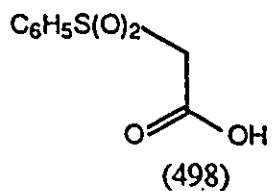
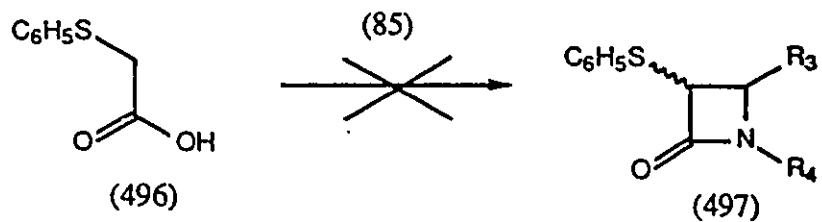
R₃ = 2-furyl (494)

R₃ = methylcinnamyl (495)

during 2+2 cycloaddition reaction. The TBDMS ether of lactic acid was difficult to obtain and failed to furnish any detectable quantities of the azetidinone on activation by the imminium salt (85).

Various attempts to obtain 3-haloazetidiones by direct reactions involving the activated halo acids have been disappointing. The reaction of chloro, bromo and iodo acetic acids with the salt (85) appears to occur as judged by the dissolution of the salt, subsequent reaction with a variety of imines is characterized by formation of intractable emulsions during work-up and isolation of red tars which do not show presence of azetidiones, either by NMR or IR. The behavior of 2-bromopropanoic acid-(85) combination was similar to that for the haloacetic acids. The only identifiable products were the starting imines and the aldehydes obtained by the hydrolysis of the imine during work-up. Similar results are obtained when the combination of the acid chlorides and imines were employed. However the situation with sodium fluoroacetate (493, Fig.LXXIII) was different. The salt could be reacted with the imminium salt and then with imines to furnish the cis azetidiones in poor yields. Despite low yields these reactions were reproducible. On the other hand the attempted conversion of sodium salt into the corresponding acid chloride by reaction with excess thionyl chloride in dichloroethane did not appear to be successful, as judged by lack of any detectable quantities of azetidinone on subsequent reaction with the imine. This example itself perhaps justifies the effort made in developing (85) as an activating agent for the purpose of synthesising azetidiones from carboxylic acids¹⁴⁹.

Fig. LXXIV



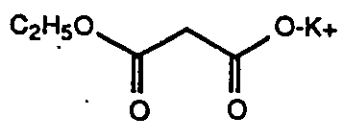
Phenylthioacetic acid (496, Fig. LXXIV) appeared to react with the iminium salt as judged by rapid dissolution of the precipitate. However subsequent reaction with the imine in presence of two equivalents of triethylamine did not furnish any azetidinone (497, Fig. LXXIV). In this case it was decided to preform the ketene by allowing the activated acid and triethylamine to react at a low temperature. A deep red colored solution was obtained instantaneously. However as failure to obtain any azetidinone on subsequent addition of the imine indicated, there did not appear to be any ketene formation. The situation with phenylsulfonylacetic acid (498, Fig. LXXIV) was similar and no azetidinone could be isolated in this case either. The reasons for such a behavior are not clear¹⁵⁰.

Phenylacetic acid (499, Fig.LXXIV) did seem to furnish some azetidinone as indicated by an IR signal at about 1745 cm^{-1} of the crude reaction product but it was not possible to obtain any azetidinone from the red tar. Neither the Propanoic acid-(85) combination nor the propanoylchloride-triethylamine combination furnished the 3-methylazetidinone (500, Fig.LXXIV). The situation in the case of vinylacetic acid (501, Fig. LXXIV) was similar and no azetidinone could be isolated. Crotonic acid also did not furnish any of the 3-vinyl azetidinone (75, Fig. XII), either in the usual manner or via attempted preformation of the ketene. The vinylazetidinone (75, Fig. LXXIV) is best obtained by adding crotonyl chloride to a solution of the imine in refluxing triethylamine, following Manhas's procedure¹⁵¹.

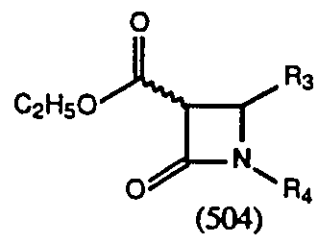
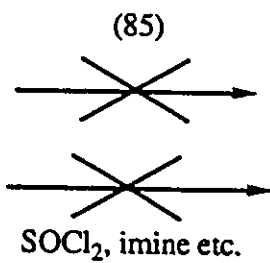
In 1988 Merck chemists disclosed that by using the acid chloride derived from a suitably protected 3-hydroxybutanoic acid and performing the ketene at low temperature, it was possible to obtain protected 3-hydroxyethylazetidinones in respectable yields⁴⁴. In our hands using the TBDMS derivative of butanoic acid and the salt for the purpose of activation led to a mixture of compounds. The only isolable product in this case was the vinylazetidinone in about 5% yield. It is difficult to believe that change from the TIPS (triisopropylsilyl) to TBDMS derivative should make that much of difference in terms of ketene formation, the difference must have been due to the mode of activation. Both these reactions have been shown in figure XII, chapter 2. Thus it would seem that in this particular case the imminium salt (85) is somewhat inferior to the corresponding acid chloride in terms of ketene formation. Another similar case has been noted in Chapter 3.

The activation by (85) has also failed to provide azetidinones in several other instances. For example activation of acetoacetic acid with the imminium salt and subsequent reaction with various imines provided a multitude of products, amongst them were the imines and aldehydes obtained by hydrolysis of the imine during work up¹⁵². None of other compounds had spectral data consistent with the desired azetidinone structures. The activation of the monopotassium salt (503, Fig. LXXV) with (85) and subsequent reaction with the imine also led to a mixture of the imine and the aldehyde. Here again no signals corresponding to the desired structure could be observed. A similar result is obtained when ethylmalonyl chloride was reacted with imines.

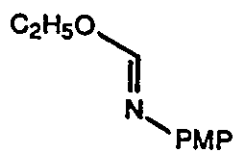
Fig. LXXV



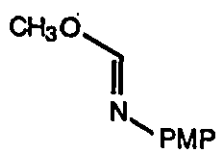
(503)



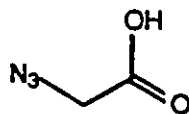
(504)



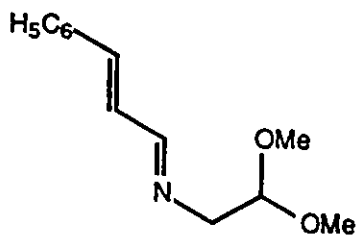
(505)



(506)



(507)



(508)

The use of (85) as an activating agent was unsuccessful in the case of imidates-azidoacetic acid combination (505,506 and 507 Fig. LXXV) as judged by the absence of a signal in the 1700 - 1800 cm^{-1} in the IR spectrum of the red-brown tar obtained on working up the reaction. This is in contrast to the observations made by Palomo using DMF-thionyl chloride combination for the purpose of activation of phenoxyacetic acid and phthaloylglycine^{153,147}. Activation of methoxyacetic acid and subsequent reaction with the imine (508, Fig. LXXIV) led to no identifiable azetidinone. The only identifiable products were the recovered imine and cinnamaldehyde.

The studies outlined above have served to clarify the structure of the product of reaction of DMF with oxalyl chloride as (85). Also the structure of the reaction between the salt (85) and a carboxylic acid has been strongly indicated as (460) rather than the corresponding acid chloride.

They have also served to define the scope and limitations of this imminium salt (85) in the context of azetidinone formation from carboxylic acids. A wide variety of azetidinones have been obtained in the process. The yields of azetidinone obtained by this procedure are comparable to those obtained by other condensing agents. Use of (85) leads to stereospecific cis for azetidinone formation. In view of the generally modest yields of the azetidinones it might be inaccurate to claim that the cis azetidinones are the exclusive products.. In most of the cases the cis azetidinones were obtained by trituration of the crude reaction mixtures with ether. This simple protocol may have missed small amount of any trans isomer and

some remaining cis. product. Thus the actual yields may be considerably higher than those claimed in the table.

The shortcomings of this particular combination of reagents have been pointed out before. Perhaps the biggest objection to the use of such a combination may lie in the generation of one equivalent of carbon monoxide for every equivalent of the reagent (85) synthesised. However our procedure has made the situation much safer in the sense that once the reagent has been synthesised inside the fumehood, there is no need to handle it outside. This improvement has allowed the use of (85) on preparative scales (up to 100 mmols).

Another problem concerns the synthesis of 3-methoxy-4-cinnamylazetidinone. Small scale reactions (involving upto 10 mmoles of various reagents) work well. In contrast the use of the reagent (85) leads to serious complications when the reaction is carried out on a scale larger than 10 mmoles. Whereas small scale reaction furnish a variably colored solid on work-up and removal of the solvent, large scale reaction furnish a red-tar from which the isolation of the azetidinone requires tedious chromatographic purification. In general the yield of the desired azetidinone is usually less than 10% for reactions carried out on the preparative scale. It should be pointed out that such a behavior is not restricted to (85). Other activating agents such as DMF-thionyl chloride have been found to be equally troublesome. Methoxyacetyl chloride has not been any better for this purpose.

Some of the examples indicate that direct access to a particular 3-heteroatom substituted azetidinone by direct 2+2 approach may be

problematic despite the variety of activation methods. In such cases it is often possible to prepare the desired azetidinone by modification of a more accessible azetidinone. A case in point is the preparation of 3-methoxy-4-cinnamylazetidione from the corresponding 3-acetoxiazetidione via saponification-methylation sequence.

References and notes

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- (139) Stadler, P.A. *Helv. Chim. Acta.*, 1978, 61, 1675.
- (140) Such a reaction was carried out to ascertain the activation of various acids by the imminium salt. The reaction has been used in Chapters 2 and 3. The extent of racimisation was not determined.
- (141) A case in point is by Fujisawa and coworkers. In their original publication (137) these authors showed the result of the interaction between the imminium salt and a carboxylic acid as similar to (462, Fig.LXIX). However when these authors submitted their procedure to Organic Syntheses, they chose to show the result as an acid chloride!! Fujisawa, T. and Sato, T. *Org. Syn.* vol. 66, 121 ed. Heathcock, C.H.
- (142) Such beneficial effect of DMF on acid chloride formation reactions has been observed by us in the context of preparation of methoxyacetyl chloride and acetoxycetyl chloride. It has been observed by us (and doubtless by others as well) that in certain cases the addition of catalytic amount of DMF to a mixture of the carboxylic acid and the halogenating agent leads to a vigorous reaction, which often sustains itself. For some examples of application of DMF in the context of acid chloride formation, see Fieser, L. F. and Fieser, M. 'Reagents for organic synthesis' vol. 1, page 286.
- (143) The chemical shift of the comparable carbon atom of trimethylorthoformate is about 100 ppm.
- (144) Aizpura, J.M.; Arrieta, A. and Palomo, C. *Tet. Lett.* 1984, 25, 3365.

(145) Palomo, C.; Arrieta, A. and Garcia, T B. *Syn. Comm.* **1982**, *12*, 681. See also (41), Chapter 2.

(146) Palomo, C. ; Arrieta, A. and Lecea, B. *J. Chem. Soc. Perkin Trans. I* **1987**, 846. In this expanded version of their studies on DMF-thionyl chloride combination, these authors describe their considerable efforts to obtain pure cis azetidinones using their reagent combination. As pointed out later with DMF-oxalyl chloride combination obtention of cis azetidinones is a matter of routine. It seems that these authors have inadvertently switched the substituents in the crucial structures (9 - 20).

(147) Bose and coworkers have noted the failure of α -acylamino acetic acids to form azetidinones on activation by various reagents. These authors have also advocated the use of Dane's salts, essentially as a cheaper substitute for the carbamate derivatives of α -aminoacids. The azetidinones prepared by these authors by this combination were the typically polyaromatic azetidinones. As has often happened in the past , what is true for 4-phenylazetidinones is not necessarily true for 4-cinnamyl or 4-methylcinnamylazetidinones. Besides in our experience the much acclaimed Dane's salts are not easy to obtained in a high enough state of purity. On the other hand the carbamate derivatives of aminoacids are easily prepared in a high state of purity by reliable procedures. Bose, A.K et. al.. *Tet.* **1981**, *37*, 2321.

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- (149) For a recent synthesis of 3,3-difluoroazetidiones see: Taguchi, T.; Kitagawa, O.; Suda, Y.; Hashimoto, A.; Iitaka, Y. and Kobayashi, Y. *Tet. Lett.* **1988**, *29*, 5291.
- (150) For examples of syntheses of some azetidones of this class see [i] Toutake, N.; Miyake, M. and Kirisawa, M. *Synthesis*, **1983**, 66.
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- (151) Manhas, M.S. personal communication.
- (152) Acetoacetic acid preparation Rosenfeld, S.M. and Grande, K.D. *J. Org. Chem.* **1980**, *45*, 1626.
- (153) Some examples of use of imidates as partners in cycloaddition reactions are listed in Claudi, F.; Cardellini, M. and Moracci, F.F. *Synthesis*, **1984**, 1070.
- (154) Palomo, C.; Cossio, F. P. . and Arrieta, A. *Tet.* **1985**, *41*, 1703.

Experimental Section

General

Methoxyacetic acid and phenoxyacetic acid were purchased from Aldrich Chemical Company and were used as received. Acetoxyacetic acid was prepared as per Benington's procedure with the difference that dichloroethane was used as solvent and instead of refluxing the reaction mixture was allowed to stand at room temperature for 18 - 20 hours¹⁰⁰. For the purpose of quick access to benzyloxyacetic acid a small sample of commercially available acid chloride was hydrolysed with 10% aq. NaHCO₃ and the acid was extracted from the acidified aqueous layer into ethyl acetate. Allyloxyacetic acid was prepared by reaction of potassium bromoacetate with allyl alcohol (as solvent) in presence of 1.1 equivalent of NaH at 100°C for 4 -5 hours followed by removal of the solvent and conventional acid base purification. Methyl ether of lactic acid was prepared by methylation of ethyl lactate (NaH, DMF, ex. MeI, 4 - 5 hours), followed by hydrolysis of the ester (1.1 eq. KOH, ethanol - water) and conventional acid base purification. Benzyl carbonate of glycolic acid was prepared by extended exposure of glycolic acid to excess benzyl chloroformate in water -THF (1:1) saturate with Na₂CO₃ at room temperature for several days. Conditions were not optimized for these preparations and yield were variable.

Haloacetic acids and their corresponding acid chlorides were commercial materials. Sodium fluoroacetate, obtained from Aldrich Chemical Company, was used as such.

Azidoacetic acid was prepared from iodoacetic acid by heating it (80 -90 ° C) with excess NaN_3 in water for 2 -3 hours followed by extraction with ether. The hemihydrate of azidoacetic acid obtained on drying and evaporation of the solvent was used as such (the molecular weight was taken as 110, instead of 101). Phthaloylglycine was purchased from Aldrich Chemical Company and was used as such. Carbobenzyloxyglycine was prepared according to established procedure(Carter, H.E.; Frank, R.L. and Johnston, H.W. *Org. Syn. Collected Vol. 3* , 167- 169, Ed. Horning, E.C.) with the exception that instead of precipitation from aqueous acidic layer, the product was extracted into ethyl acetate. Ethyl carbamate of glycine was similarly prepared in comparable yields. The t-BOC derivative of glycine was prepared following the instructions provided in *Organic Synthesis Vol. 63*, 160, Ed. Saucy, G. Dane's salt (489, Fig. LXXIII) was prepared by established procedure¹⁴⁷. It appeared that the product contained some methanol and thus it was crushed under benzene. After removal of the solvent the crystals were dried under vacuum for 4 - 6 hours.

Phenylthioacetic acid and phenylsulfonylacetic acid were prepared by saponification of the corresponding methyl esters. Phenylacetic, vinylacetic and crotonic acids were commercial materials which were used as such. The TBDMS derivative of 3-hydroxybutanoic acid was prepared by reduction of ethyl acetoacetate with sodium borohydride, silylation of the secondary alcohol using TMDMS-Triflate and hydrolysis of the protected ethyl ester with KOH in ethanol. The free acid was obtained by conventional acid-base purification. Ethylpotassium malonate and

the corresponding acid chloride were used as purchased from Lancaster Synthesis.

The imidates used in these studies (505 and 506, Fig. LXXV) were prepared by a slight modification of the procedure mentioned by Vogat and Roberts (*Org. Syn. Vol. 35*, 65). Thus small portions of a solution of the amine in benzene were added to refluxing trialkyl orthoformate followed by refluxing for 3 - 4 hours. After the removal of excess orthoesters the imidates were collected by distillation under reduced pressure.

Other general comments mentioned at the beginning of the Experimental Section of Chapter 2 also apply here.

Syntheses of imines (464, Fig. LXXII)

The various imines used were synthesized by the following general procedure. The details are being provided for one such imine (75, Fig. XII). To a solution of 12.3 (100 mmol) of p-anisidine in 200 mL of dichloromethane was added about 10 g of anhydrous $MgSO_4$ at room temperature. The contents were stirred vigorously as a solution of 10.6 g (100 mmol) of freshly distilled benzaldehyde in 50 mL of dichloromethane was added in one portion. After 30 min of vigorous stirring at room temperature, the solid was removed by filtration. The solid residue was washed with dichloromethane till the filtrate was colorless (3X10 mL). From the combined filtrate the solvent was removed to provide 18.9 - 21.1 g. (90' -100 mmol) of the imine (464, $R_3 = C_6H_5$, $R_4 = PMP$, Fig. LXXII) as shiny brown plates ; mp 49 - 50 C; ir: 1630 cm^{-1} ; ms 211 (M^+ , 100%); nmr: $\delta = 8.5$ (s, 1 H), 7.9 (m, 2 H), 7.5 (m, 5 H), 6.9 (dd, 2 H, $J = 7.0\text{ Hz}$, $J = 1.9\text{ Hz}$),

3.8 (s, 3 H). HRMS calc for C₁₄H₁₃NO 211.1061, found 211.1011.

The compound was used as such.

For preparation of the N-(3-phenyl-2-propenylidene)-4-methoxyaniline (464, R₃ = C₈H₇, R₄ = PMP, Fig. LXXII also mentioned as compound 89 in various figures) a slightly different procedure was used. To a clear solution of 37.3 g (300 mmol) of p-anisidine in about 450 mL of ethyl acetate was added about 50 g of anhydrous MgSO₄. To the vigorously stirring solution was added a solution of 40.7 g (308 mmol) in 100 mL of ethyl acetate. After 30 min of stirring at room temperature, the contents were filtered and the solid was washed with ethyl acetate till the filtrate was clear (5X25 mL). A small portion of the filtrate was evaporated to provide seed crystals. The major portion of the filtrate was heated on a hot plate with stirring till the volume was reduced to nearly half of the original. The clear yellow solution was allowed to come to room temperature and was seeded with a few crystals of the imine. Further cooling in an ice-bath for a period of about 1 h provided plates of the imine. Filtration and subsequent drying in air provided 40 - 50 g (70%) of the imine. Physical properties of this imine were in agreement with the literature data³⁸.

Synthesis of (188, Fig. LXXII, no. 15)

To a dry 500 mL two neck round bottomed flask containing a stirring bar and a pressure equalized dropping funnel was added 100 mL of dry dichloromethane and 4.3 mL (5.5 mmol) of dry DMF under nitrogen atmosphere. The contents were cooled under nitrogen in an ice-bath and the funnel was charged with 25 mL of dry dichloromethane and 4.80 mL (5.5 mmol) of oxalyl chloride. The

septum at the top of the funnel was quickly replaced with a drying tube filled with CaSO_4 . The contents in the flask were vigorously stirred as the oxalyl chloride solution was added at a rate of about 1 - 2 drops per second. The addition was accompanied by precipitation of a white solid and copious gas evolution. After the addition was complete, through the side arm of the flask a solution of 4.5 g (5 mmol) of methoxyacetic acid in 25 mL of dichloromethane was added with via a cannula over a period of about 1 minute. The white precipitate dissolved during this addition to provide a clear colorless solution. (Flask I)

In another set-up similar to the above 9.49 g (4.5 mmol) of the imine (75) and 16.8 mL (12.1 mmol) of dry triethylamine were dissolved in about 100 mL of dry dichloromethane. (Flask II). The contents of Flask I were transferred to the dropping funnel on the Flask II and the latter was cooled in an ice-bath under nitrogen and the septum was quickly replaced with a drying tube. The clear solution from the dropping funnel was added to the vigorously stirring solution over a period of about 20-30 min. The addition was accompanied by fuming and precipitation. The heterogeneous mixture was allowed to come to room temperature over a period of about 3 hours and was stirred at this temperature for an additional 18 h.

The reaction mixture was worked up by successive washing of the organic layer with 2X100 mL of 10% HCl, 100 mL of water and 2X100 mL of 5% NaHCO_3 . After every extraction the aqueous layer was washed with an additional 25 mL of dichloromethane and the organic layers were combined. The combined organic layers was dried over MgSO_4 and the contents were filtered to remove the

drying agent. Removal of the solvent provided a brown-white solid which was triturated with 250 mL of hot ether. Ether was removed by filtration to provide 7-8 g of chromatographically homogeneous product. (55 - 62% based on the imine). The product azetidinone has following physical properties mp: 172 - 173°C; ir: 1745 cm^{-1} ; ms: 283 (M^+ , 13.4%), 211 (imine⁺, 26.6%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$, 9.8%), 134 ($\text{M}^+ - 149$, 100%); nmr: d = 6.7- 7.2 (m, 7H), 5.1 (d, 1 H, J= 6 Hz) , 4.6 (d, 1 H, J= 6 Hz), 3.6 (s, 3 H), 3.0 (s, 3 H). HRMS calc for $\text{C}_{17}\text{H}_{17}\text{NO}_3$ 283.1366, found 283.1220.

Physical properties of other azetidinones prepared by the above method are being presented below

Compound (466, no. 1) is characterized by following properties: mp:102-104°C; ir: 2110, 1750 cm^{-1} ; ms: 294 (M^+ , 2.6%), 266 ($\text{M}^+ - 28$, 2.3%), 211 (imine⁺, 30.5%), 196 ($\text{M}^+ - 149$, 50%), 117 ($\text{M}^+ - 177$, 100%); nmr: 7.2-7.0 (m, 7 H), 6.8 (dd, 2 H, J= 2.1 Hz, J= 6.8 Hz), 5.2 (d, 1 H, J= 5.3 Hz), 4.8 (d, 1 H, J= 5.3 Hz), 3.8 (s, 3 H)

Azetidinone(267, no. 2) has spectral properties which are in agreement with the literature values³⁸.

Compound (467, no. 3) has following properties : mp: 84-85°C; ir: 2100, 1755 cm^{-1} ; ms: 284 (M^+ , 3.5 %), 256 ($\text{M}^+ - 28$, 1.9%), 202 (imine⁺+1, 100%), 201 (imine⁺, 78%); nmr: d=7.3-6.2 (series of m, 7 H), 5.2 (d, 1 H, J= 5.6 Hz), 4.8 (d, 1 H, J= 5.6 Hz), 3.6 (s, 3 H).

Azetidinone (468, no. 4) was obtained as a white solid after ether trituration. mp: 96-97°C; ir: 2200, 1750 cm^{-1} ; ms: 334 (M^+ , 4.3%), 306 ($\text{M}^+ - 28$, 83%), 250 (imine⁺-1, 43%), 157 ($\text{M}^+ - 177$, 100%); nmr: d= 7.4-7.2 (m, 7 H), 6.8 (dd, 2H, J= 2.3 Hz, J= 7.5 Hz), 6.0 (broad s, 1 H), 4.9 (d, 1 H, J= 5.4 Hz), 4.7 (d, 1 H, J= 5.4 Hz), 3.7 (s, 3 H), 1.9

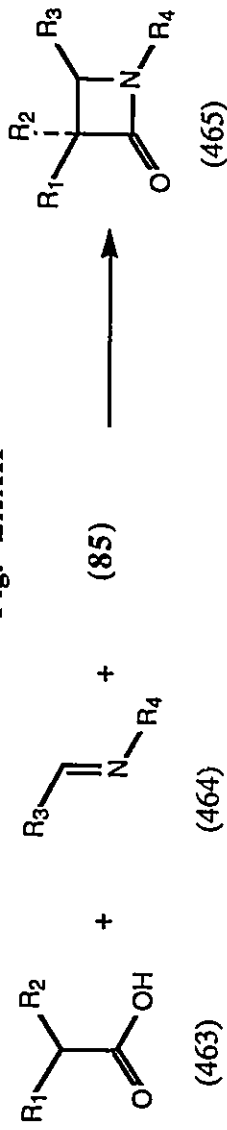
(d, 3 H, J= 1.3 Hz). HRMS calc for C₁₉H₁₈N₄O₂ 334.1460, found 334.1441.

Compound(469,no.5) is a yellowish solid characterized by following properties: mp: 109-110°C; ir: 2105, 1750 cm⁻¹; ms: 350 (M⁺, 3.1%) 322 (M⁺ - 28, 98.6%), 321 (M⁺-1, 78.7%), 173 (M⁺-149, 94%), 145 (M⁺-178, 100%); nmr: d= 7.3-6.9 (series of m, 9 :H), 6.2 (dd,2H, J= 7.6 Hz, J= 15.9 Hz), 4.9 (d, 1H, J= 5.1 Hz), 4.8 (dd, 1 H, J= 5.1 Hz, J= 7.6 Hz), 3.8 (s, 3 H), 3.7 (3 H).

In the case of the azetidinone (470, no. 6) the corresponding imine was obtained by ozonolysis of t-butyl fumrate, reduction of the ozonide with dimethyl sulfide and subsequent reaction with p-anisidine in presence of MgSO₄. The imine itself could not be obtained pure; being contaminated with variable amounts of dimethyl sulfoxide. The products, a brownish semi-solid obtained after column chromatography (using 4: 1: hexane: ethyl acetate) on the red tar obtained after working up the reaction mixture, has following properties: ir: 2110, 1755 cm⁻¹; ms: 318 (M⁺ not observed), 290 (M⁺-28. 10.2%), 261(M⁺-57, 10.2%), 149 (C₈H₇NO₂⁺, 100%); nmr: d= 7.2 (dd, 2 H, J= 2.1 Hz, J= 6.2 Hz), 6.8 (dd, 2 H, J= 2.2 Hz, J= 6.2 Hz), 5.0 (d, 1 H, J= 6.0 Hz), 4.6 (d, 1 H, J= 6.0 Hz), 3.7 (s, 3 H), 1.7 (s, 9 H).

For azetidinone (471, no. 7), the synthesis of the corresponding imine to this azetidinone, problems similar to the case of the previous compound were encountered. The product azetidinone is a semi-solid with following properties: ir: 2110, 1750 cm⁻¹; ms: 276 (M⁺, 3.5 %), 248 (M⁺-28, 4.1%), 211 (imine⁺, 100%), 149 (C₈H₇NO₂⁺, 5.4%); nmr: d= 7.2 (dd, 2 H, J= 2.2 Hz, J= 6.3 Hz), 6.9 (dd, 2 H, J= 2.1 Hz, J= 6.3 Hz), 4.9 (d, 1 H, J= 5.7 Hz), 4.5 (d, 1 H, J= 5.7 Hz), 3.7 (s, 6 H).

Fig. LXXII



No.	R ₁	R ₂	R ₃	R ₄	Yield %
1	N ₃	H	C ₆ H ₅	PMP	39
2	N ₃	H	C ₈ H ₇	PMP	68
3	N ₃	H	C ₄ H ₃ O	PMP	55
4	N ₃	H	C ₉ H ₉	PMP	72
5	N ₃	H	C ₉ H ₇ O	PMP	70
6	N ₃	H	CO ₂ C ₄ H ₉	PMP	13
7	N ₃	H	CO ₂ CH ₃	PMP	21
8	H	C ₈ H ₄ O ₂ N	C ₆ H ₅	C ₆ H ₅	25
9	C ₈ H ₄ O ₂ N	H	C ₈ H ₇	PMP	49
10	C ₈ H ₄ O ₂ N	H	C ₉ H ₉	PMP	45+10% trans
11	C ₃ H ₆ O ₂ N	H	C ₆ H ₅	PMP	62

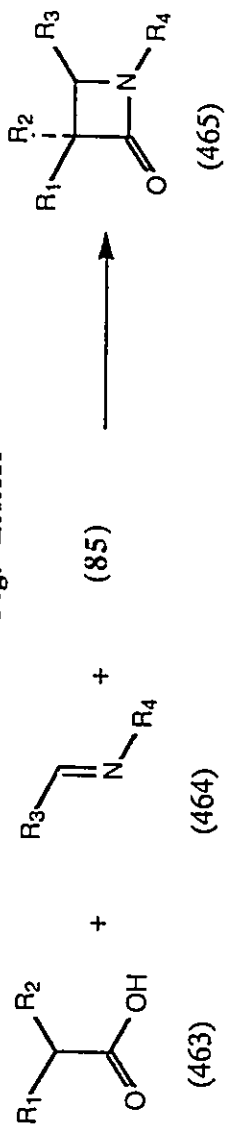
b-lactam (472, no. 8) exhibited physical properties in agreement with the literature values¹⁴⁸.

Compound (473, no. 9) is a white solid with these properties: mp: 197-198°C; ir: 1750, 1730 cm^{-1} ; ms: 424 (M^+ , 9.4%), 275 (M^+ -149, 34.6%), 236 (imine⁺-1, 41%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$, 100%); nmr: δ = 7.8-7.0 (series of m, 11 H), 6.8 (m, 3 H), 6.2 (dd, 1 H, J = 7.8 Hz, J = 16.0 Hz), 5.2 (d, 1 H, J = 5.0 Hz), 4.7 (dd, 1 H, J = 5.0, J = 7.8 Hz), 3.8 (s, 3 H).

Azetidinone (474, no. 10) was obtained as a brownish powder by ether trituration of the semi-solid obtained after removal of the solvent. Following spectral properties served to characterize it as a cis azetidinone: mp: 107-108°C; ir: 1755, 1735 cm^{-1} ; ms: 438 (M^+ , 3.9%), 310 (M^+ -128, 14.6%), 291 (M^+ -147, 40.3%), 250 (imine⁺-1, 84.5%), 142 (M^+ -296, 100%); nmr: δ =7.7-7.2 (series of m, 11 H), 6.8 (dd, 2 H, J = 2.2 Hz, J = 6.8 Hz), 6.5 (broad s, 1 H), 5.5 (d, 1 H, J = 5.7 Hz), 4.8 (d, 1 H, J = 5.7 Hz), 3.8 (s, 3 H), 1.9 (d, 3 H, J =1.3 Hz). The trans azetidinone could not be obtained in pure form. The amount of this compound was judged to be about 10% by comparison of the signals in the nmr spectrum of the mixture obtained by attempted chromatographic purification of the mother liquor. The diagnostic peaks were: 5.3 (d, 1 H, J = 2.0 Hz) and 4.9 (d, 1 H, J = 2.0 Hz). Rest of the peaks overlapped with those of the cis azetidinone.

Compound (475, no. 11) was obtained as a white solid after ether trituration. This azetidinone has following properties: mp: 118-119°C; ir: 1755, 1725 cm^{-1} ; ms: 340 (M^+ , 11.6%), 251 (M^+ -89, 13.7%), 212 (imine⁺+1, 100%), 211 (imine⁺, 82.2%); nmr: δ = 7.3-7.1 (m, 7 H), 6.8 (m, 2 H), 5.4 (dd, 1 H, J = 4.3 Hz, J = 9.5 Hz), 5.3 (m, 1 H), 4.7 (d, 1

Fig. LXXII



No.	R ₁	R ₂	R ₃	R ₄	Yield %
1	N ₃	H	C ₆ H ₅	PMP	39
2	N ₃	H	C ₈ H ₇	PMP	68
3	N ₃	H	C ₄ H ₃ O	PMP	55
4	N ₃	H	C ₉ H ₉	PMP	72
5	N ₃	H	C ₉ H ₇ O	PMP	70
6	N ₃	H	CO ₂ (C ₄ H ₉)	PMP	13
7	N ₃	H	CO ₂ CH ₃	PMP	21
8	H	C ₈ H ₄ O ₂ N	C ₆ H ₅	C ₆ H ₅	25
9	C ₈ H ₄ O ₂ N	H	C ₈ H ₇	PMP	49
10	C ₈ H ₄ O ₂ N	H	C ₉ H ₉	PMP	45+10% trans
11	C ₃ H ₆ O ₂ N	H	C ₆ H ₅	PMP	62

H, $J = 9.5$ Hz), 3.9 (m, 2 H), 3.7 (s, 3 H), 1.0 (t, 3 H, $J = 7.0$ Hz). HRMS calc for $C_{19}H_{20}N_2O_4$ 340.1422, found 340.1452.

β -lactam(476, no. 12) could be obtained pure only after column chromatography (using 4:1: hexane: ethyl acetate) followed by trituration of the resulting brownish solid with refluxing ether. This compound has following physical properties: mp: 148-149°C; ir: 1750, 1720 cm^{-1} ; ci-ms: 443 ($M^{+}+1$, 50.6%), 442 (M^{+} , 2.2%), 335 ($M^{+}-107$, 65.8%), 291 ($M^{+}-152$, 100%), 253 (imine $^{+}+2$, 10.4%); nmr: $\delta = 7.3-7.17$ (m, 12 H), 6.8 (dd, 2 H, $J = 1.9$ Hz, $J = 6.8$ Hz), 6.4 (broad s, 1 H), 5.42-5.39 (broad d, 2 H), 5.09-5.08 (AB, 2 H, $J = 10$ Hz), 4.7 (d, 1 H, 5.0 Hz), 3.7 (s, 3 H), 1.8 (s, 3 H).

Compound (477, no. 13) is a white solid with following physical properties: mp: 115-117°C; ir: 1740, 1720 cm^{-1} ; ms: 392 (M^{+} , 9.7%), 285 ($M^{+}-107$, 100%), 243 ($M^{+}-147$, 7%); nmr: $\delta = 7.3-6.9$ (series of m, 12 H), 5.5 (dd, 1 H, $J = 4.9$ Hz, $J = 5.1$ Hz), 5.3 (m, 2 H), 5.0 (m, 2 H), 3.7 (s, 3 H). HRMs calc for $C_{22}H_{20}N_2O_4$ 392.1454, found 392.1344

Azetidinone (478, no. 14) has following properties: mp: 196-197°C; ir: 1750, 1720 cm^{-1} ; ms: 428 (M^{+} , 2.3%), 279 ($M^{+}-149$, 9.1%), 236 (imine $^{+}-1$, 36.9%), 149 ($C_8H_7NO_2^{+}$; 6.3%), 91 ($C_7H_7^{+}$, 100%); nmr: $\delta = 7.3-7.2$ (m, 12 H), 6.9 (d, 2 H, $J = 8$ Hz), 6.7 (d, 1 H, $J = 14.0$ Hz), 6.2 (dd, 1 H, $J = 7$ Hz, $J = 14.0$ Hz), 5.4 (dd, 1 H, $J = 0.9$ Hz, $J = 5.5$ Hz), 5.3 (m, 1H), 5.0 (s, 2 H), 4.9 (m, 1 H), 3.7 (s, 3 H).

Properties of (190, no. 16) have been mentioned in Chapter 4.

To obtain Compound (191, no. 17) in a pure state required was crystallization from dichloromethane-hexane combination. This compound was identical in all regards with the one obtained on methylation of the corresponding hydroxyaetidione. It has following

No	R ₁	R ₂	R ₃	R ₄	Yield%
12	(476) C ₈ H ₈ O ₂ N	H	C ₉ H ₉	PMP	45
13	(477) C ₈ H ₈ O ₂ N	H	C ₄ H ₃ O	PMP	50
14	(478) C ₈ H ₈ O ₂ N	H	C ₈ H ₇	PMP	55
15	(188) OCH ₃	H	C ₆ H ₅	PMP	50
16	(190) OCH ₃	CH ₃	C ₆ H ₅	PMP	26
17	(191) OCH ₃	H	C ₈ H ₇	PMP	42
18	(479) OCH ₃	H	C ₉ H ₉	PMP	65
19	(480) OCH ₃	H	C ₅ H ₄ N	PMP	71
20	(481) OCH ₃	H	C ₄ H ₃ S	PMP	72
21	(482) OCH ₃	H	C ₈ H ₇	C ₈ H ₇ N	25
22	(483) OCH ₃	H	C ₁₀ H ₁₄ N	PMP	15
23	(484) OCH ₃	H	C ₆ H ₄ NO ₂	PMP	23
24	(485) OCH ₃	H	C ₆ H ₅	C ₆ H ₅	82
25	(486) OCH ₃	H	C ₄ H ₃ O	PMP	41
26	(421) OC ₇ H ₇	H	C ₈ H ₇	PMP	49
27	(487) OC ₆ H ₅	H	C ₆ H ₅	PMP	42
28	(325) OC ₃ H ₅	H	C ₉ H ₉	PMP	72
29	(326) OC ₃ H ₅	H	C ₈ H ₇	PMP	65

properties: mp: 146-147°C; ir: 1750 cm⁻¹; ms: 309 (M⁺, 7.5%), 236 (imine⁺-1, 25%), 197 (M⁺-112, 5%), 160 (M⁺-149, 100%); nmr : d= 7.4-7.2 (m, 7 H), 6.9-6.8 (m, 3 H), 6.3-6.2 (dd, 1 H, J= 8.3 Hz, J= 16 Hz), 4.8 (d, 1 H, J= 4.9 Hz), 4.7 (d, 2 H, J= 4.9 Hz, J= 8.3 Hz), 3.8 (s, 3 H), 3.3 (s, 3 H). HRMS calc for C₁₉H₁₉NO₃ 309.1393 , found 309.1371.

Azetidinone (479, no. 18) is a yellowish solid with following physical properties: mp: 117-118 °C; ir: 1750 cm⁻¹; ms: 323 (M⁺, 49.1%), 292 (M⁺-31, 3.3%), 251 (imine⁺, 17%), 250 (imine⁺-1, 78%), 174 (M⁺-149, 100%); nmr: d= 7.4-7.2 (m, 7 H), 6.8 (dd, 2 H, J= 2.2 Hz, J= 6.8 Hz), 6.6 (broad s, 1H), 4.75 (d, 1 H, J= 4.0 Hz), 4.72 (d, 1 H, J= 4.1 Hz), 3.7 (s, 3 H), 3.5 (s, 3 H), 1.9 (d, 3 H, J= 1.3 Hz). HRMS calc for C₂₀H₂₁NO₃ 323.1552, found 323.1520.

β-lactam (480, no. 19) was obtained in the usual manner except during the work up acid wash was omitted. This white solid has following properties: mp: 128-129°C; ir: 1745 cm⁻¹; ms: 284 (M⁺, 18.7%), 213 (M⁺-71, 17%), 212 (imine⁺, 33.2%), 134 (M⁺-149,100%); nmr: d= 8.8-6.8 (series of m, 8 H), 5.2 (d, 1 H, J= 4.8 Hz), 4.8 (d, 1 H, J= 4.8 Hz), 3.7 (s, 3 H), 3.2 (s, 3 H). HRMS calc for C₁₆H₁₆N₂O₃ 284.1186, found 284.1150.

Compound (481, no. 20) has following properties: mp: 178-179; ir: 1745 cm⁻¹; ms: 289 (M⁺, 8.5%), 217 (M⁺-72, 19%), 140 (M⁺-149, 100 %); nmr: d= 7.5-6.8 (m, 7 H), 5.3 (d, 1 H, J= 5 Hz), 4.8 (d, 1 H, J= 5 Hz), 3.8 (s, 3 H), 3.6 (s, 3 H). HRMs calc for C₁₅H₁₅NO₃S 289.1714, found 289.0766

In the case of azetidinone (482, no. 21) acid wash was omitted during the workup. The product was obtained by column chromatography using 3 : 1 : hexane : ethyl acetate followed by

washing with ether. mp: 160-161°C; ir: 1740 cm⁻¹; ms: 322 (M⁺, 9.3%), 250 (imine⁺, 46%), 162 (M⁺-160, 100%), 160 (M⁺-162, 20.7%); nmr: d= 7.4-7.2 (m, 7 H), 6.8 (d, 1 H, J= 16.1 Hz), 6.2 (dd, 1 H, J= 8.4, J= 16.0 Hz), 4.76 (d, 1 H, J= 4.6 Hz), 4.71 (m, 1 H), 3.4 (s, 3 H), 2.8 (s, 6 H). HRMS calc for C₂₀H₂₂N₂O₂ 322.1715, found 322.1675.

In the case of azetidinone(483, no. 22) , acid wash was omitted during workup. The product was obtained as a yellow solid after ether wash. mp: 159-161°C; ir: 1755 cm⁻¹; ms: 354 (M⁺, 2.3%), 282 (M⁺-72, 3.2%), 267 (M⁺-97, 11%), 205 (M⁺-149, 100%); nmr: d= 7.2-6.7 (series of m, 8 H), 5.1 (d, 1 H, J= 4.8 Hz), 4.7 (d, 1 H, J= 4.8 Hz), 3.7 (s, 3 H), 3.5 (q, 4 H, J= 7.0 Hz), 3.2 (s, 3 H), 1.1 (t, 6 H, J= 7.0 Hz).

Compound (484, no. 23) obtained by ether wash of the solid obtained on removal of the solvent. mp: 145-146°C; ir: 1745, 1510, 1390 cm⁻¹; ms: 328 (M⁺, 14.9%), 285 (M⁺-43, 4.4%), 256 (M⁺-72, 29%), 195 (M⁺-133, 51%), 149 (C₈H₇NO₂⁺, 100%); nmr: d= 8.2 (dd, 2 H, J=2 Hz, J= 6.8 Hz), 7.5 (dd, 2 H, J= 2.2 Hz, J= 6.8 Hz), 6.7 (dd, 2 H, J= 2.2 Hz, J= 6.8 Hz), 5.2 (d, 1 H, J= 4.7 Hz), 4.8 (d, 1 H, J= 4.7 Hz), 3.7 (s, 3 H), 3.2 (s, 3 H). HRMS calc for C₁₇H₁₆N₂O₅ 328.1084, found 328.1062.

Azetidinone (485, no. 24) was obtained as a white solid after trituration with ether. mp: 142-143°C; ir: 1755 cm⁻¹; ms: 253 (M⁺, 11.5%), 181 (M⁺-72, 14.6%), 134 (M⁺-119, 100%), 119 (M⁺-134, 19%); nmr: d= 7.3-7.0 (m , 10 H), 5.2 (d, 1 H, J= 4.8 Hz), 4.8 (d, 1 H, J= 4.8 Hz). HRMS calc for C₁₆H₁₅NO₂ 253.1132, found 253.1080.

b-lactam(486, no. 25) was obtained a brown solid after work up and removal of solvent. Trituration with ether provided a white solid with following properties: mp: 124-125°C; ir: 1755 cm⁻¹; ms:

273 (M^+ , 3.6%), 201 (imine⁺, 14.4%), 124 (M^+-149 , 100%); nmr: δ = 7.4-6.3 (series of m, 7 H), 5.1 (d, 1 H, J = 5 Hz), 4.7 (d, 1 H, J = 5 Hz), 3.8 (s, 3 H), 3.3 (s, 3 H).

Properties of the azetidinone (421, no. 26) have been mentioned in the experimental section of Chapter 6.

In the case of azetidinone (487, no. 27) workup and removal of the solvent furnished a brown-white solid. In this particular case it was necessary to wash this solid with ice-cold acetone to furnish chromatographically homogeneous product. This compound has following physical properties: mp: 196-197°C; ir: 1750 cm^{-1} ; ms: 345 (M^+ , 34%), 211 (imine⁺, 54%), 196 (M^+-149 , 100%); nmr: δ = 7.4-6.7 (series of m, 14 H), 5.7 (d, 1 H, J = 6.0 Hz), 5.4 (d, 1 H, J = 6.0 Hz), 3.8 (s, 3 H). HRMS calc for $\text{C}_{22}\text{H}_{19}\text{NO}_3$ 345.1393, found 345.1375.

Physical properties of compounds (325, 326, 327 and 300; no. 28, 29, 30 and 31 respectively) have been mentioned in the experimental section of Chapter 6.

Azetidinone (488, no. 32) was obtained as a white solid after ether wash. Following physical properties served to establish the assigned structure: mp: 146-147°C; ir: 1760 cm^{-1} ; ms: 429 (M^+ , 1.2%), 315 (M^+-114 , 2.3%), 280 (M^+-149 , 2%), 237 (imine⁺, 7.8%), 236 (imine⁺-1, 19.2%), 91 (C_7H_7^+ , 100%); nmr: δ = 7.4-7.1 (m, 12 H), 6.8-6.79 (m, 3 H), 6.2-6.12 (dd, 1 H, J = 8.4 Hz, J = 16.0 Hz), 5.8 (d, 1 H, J = 4.9 Hz), 5.09 (AB, 2 H, J = 11.0 Hz), 4.9 (m, 1 H), 3.7 (s, 3 H).

The fluoroazetidinone (494, Fig. LXXIII) was obtained as a chromatographically homogeneous solid after trituration of the brown solid obtained after removal of the solvent. The yield based upon the amount of the imine used in the reaction was about 10%

This compound has following physical properties: mp: 153-154°C; ir: 1745 cm^{-1} ; ms: 261 (M^+ , 5.0%), 201 (imine⁺, 1.4%), 188 (M^+-73 , 35%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$, 100%); nmr: δ = 7.4-6.3 (series of m, 7 H), 5.8-5.6 (AB, 1 H, J = 4.5 Hz, J = 55.0 Hz), 5.31-5.28 (dd, 1 H, J = 4.5 Hz, J = 3.5 Hz), 3.7 (s, 3 H). HRMS calc for $\text{C}_{14}\text{H}_{12}\text{FNO}_3$ 261.0819, found 261.0828.

The isolated yield for the fluoroazetidinone (495, Fig. LXXIII) was about 15%. On the basis of the following physical properties support the azetidinone structure: mp: 132-133°C; ir: 1750 cm^{-1} ; ms: 311 (M^+ , 23.1%), 251 (imine⁺, 3.8%), 250 (imine⁺-1, 11.6%), 162 (M^+-149 , 100%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$, 68%), 147 (M^+-164 , 94.3%); nmr: δ = 7.4-7.2 (m, 7 H), 6.8 (m, 2H), 6.6 (broad s, 1 H), 5.7-5.5 (AB, 1 H, J =4.0 Hz, J = 55 Hz), 4.8 (apparent t, 1 H, J = 4.0 Hz), 3.7 (s, 3 H), 1.9 (d, 3 H, J = 1.3 Hz). HRMS calc for $\text{C}_{19}\text{H}_{18}\text{FNO}_2$ 311.1348, found 311.1290.

The 4-phenyl analog of the above fluoroazetidinones was also prepared in 12% yield. This white solid has following properties: mp: 166-167°C; ir:1745 cm^{-1} ; ms: 271 (M^+ , 8.8%), 211 (imine⁺, 3%), 149 ($\text{C}_8\text{H}_7\text{NO}_2^+$,100%); nmr: 7.3-7.2 (m, 7 H), 6.8 (dd, 2 H, J = 2.3 Hz, J = 6.8 Hz), 5.7 (AB, 1 H, J = 4.8 Hz, J = 55 Hz), 5.2 (dd, 1 H, J = 3.6 Hz, J = 4.8 Hz), 3.7 (s, 3 H). HRMS clac for $\text{C}_{16}\text{H}_{16}\text{FNO}_2$ 271.1189, found 271.1033.

Synthesis of N-(p-methoxy)phenyl-3-ethenyl-4-phenylazetidinone (75, LXXIV) .

A solution of 5 g (23.7 mmol) of the imine (75) in 50 mL of dry triethylamine was brought to reflux under nitrogen. The septum cap at the top was replaced with a pressure equalizing dropping funnel containing 10 mL (95 mmol) of crotonyl chloride in 10 mL of dry

dichloroethane. A drying tube was provided on the top of the dropping funnel. The heating bath was removed and the solution from the dropping funnel was added dropwise to a vigorously stirred solution over a period of about 10 - 15 min. The addition was exothermic and the heterogeneous reaction mixture continued to reflux on its own. After completion of addition, the reaction mixture was refluxed for an additional 18 h. Work up consisted of addition of 50 mL of water to the reaction mixture and extraction of the aqueous layer with 5X50 mL of dichloromethane. The organic layer was washed free of triethylamine by extraction with 10% HCl. Excess crotonyl chloride and crotonic acid were removed by washing with 5% NaHCO₃ solution. The organic layer was dried with MgSO₄. Removal of the drying agent and the solvent furnished a brown solid. Washing with ether furnished 2.795 g (10 mmol) of the azetidinone (75) as a white solid. This amounted to an isolated yield of 42%. The product has following physical properties: mp: 127-128°C; ir: 1755 cm⁻¹; ms: 279 (M⁺, 15.8%), 211 (imine⁺, 26.3%), 196 (M⁺-83, 27%), 149 (C₈H₇NO₂⁺, 55%), 130 (M⁺-149, 100%); nmr: d = 7.4-7.2(m, 7 H), 6.7 (dd, 2 H, J= 2.1 Hz, J= 5.4 Hz), 6.0 (m, 1 H), 5.5-5.3 (m, 3 H), 4.7 (d, 1 H, J = 2.4 Hz), 3.7 (s, 3 H). HRMs calc for C₁₈H₁₇NO₂ 279.1284, found 279.1240.

Claims to Original Research

1. The conversion of a suitably protected tartrate monoester to 3,3-disubstituted azetidinones such as (90, Fig. XV) and (98, Fig. XVII) was investigated. This study provided access to synthetically significant quantities of a fully protected and suitably functionalized azetidinone in a straightforward manner. Similar conversion of a protected 2,3-dihydroxybutyric acid to the azetidinone (107, Fig. XIX) was studied. It was observed that the sense of chirality induction is the same in both the cases. (Chapter 2)
2. Conversion of a protected form of threonine to the corresponding spiro azetidinone (151, Fig. XXVII) was studied. The result of this study produced an azetidinone in which structural features of both a 'classical' and a 'new' azetidinones were included, with the proper relative geometry. The Cbz protecting group was removed from this molecule using the hydroxyethyl moiety at C-4 position as an internal nucleophile. (Chapter 3).
3. The formation of C-3 carbanions from 3-alkoxyazetidinones was investigated. This study provided access to various 3,3-disubstituted azetidinones which incorporated the methoxy group of the 'classical' (methoxycephalosporins) and the hydroxyethyl group of the 'new' (thienamycin) at the position α to the carbonyl group of the azetidinone; with proper relative stereochemistry. It was also possible to incorporate alkyl groups at the 3 position of azetidinones using the carbanion methodology. (Chapter 4).
4. To the best of our knowledge, dianions were generated from 3-(carboalkoxyamino)azetidinones for the very first time. This

approach to 3-(protected)amino azetidiones with an additional substituent at position 3 offers significant advantages over the conventional imine-carbanion approach.(Chapter 5).

5. Using the dianion methodology mentioned previously (point 4), various 3-hydroxyethyl-3-(carboalkoxy)aminoazetidiones were prepared in a stereospecific manner. By employing a simple three step inversion sequence, both diastereoisomers of these compounds have become available. (Chapter 5).

6. During the course of the inversion sequence mentioned above (point 5) it was possible to obtain small quantities of structurally novel aziridine-azetidiones. However the goal of synthesizing these molecules on a preparative scale has not yet been met. (Chapter 5).

7. A reliable approach to various 3-hydroxy (and thus alkoxy) azetidiones was devised. (Chapter 6).

8. By combining the synthesis of 3-allyloxyazetidiones with a Wittig rearrangement it was possible to synthesize several 3-hydroxy-3-(2-propenyl)azetidiones. To the best of our knowledge this approach to this type of molecule is unique. (Chapter 6).

9. A systematic synthesis of 3-hydroxy-3-hydroxyethylazetidiones was carried out. (Chapter 6).

10. By combining the above mentioned approach to 3-hydroxy-3-hydroxyethylazetidiones (point 9), it was possible to synthesize spiro oxirane-azetidiones in a stereospecific manner. Thus two different classes of '3-oxiranes' have become available. (Chapter 6).

11. During the course of the syntheses of 3-alkoxy-3-hydroxyethylazetidinones a very highly diastereoselective reduction of 3-acylazetidinones was discovered. The scope of this reaction was studied in some detail. This reduction proceeds in a stereospecific manner under non-chelating conditions and is remarkably insensitive towards the nature of substituents at various positions. (Chapter 7).

12. The nature of the product obtained by reaction of DMF with oxalyl chloride was studied by C-13 NMR spectrum. These studies strongly indicated the structure of the compound as N,N-dimethylchloromethyleniminium chloride, (85). An effort was made to determine the nature of the products obtained on reacting (85) with various carboxylic acids. On the basis of this study, it appears that the acid chlorides are not formed in these reactions. (Chapter 8).

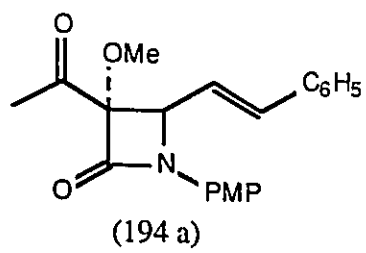
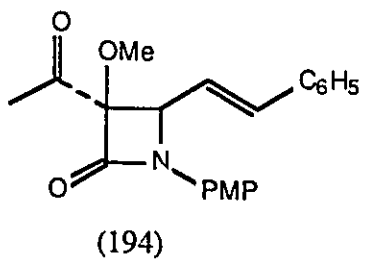
13. The experimental procedure for preparation and utilization of the iminium salt (85) was considerably simplified. (Chapter 8).

14. The scope of (85) as a suitable activating agents for carboxylic acids for the purpose of ketene-imine reactions was studied. This approach provided a large number of azetidinones used in various aspects of the above mentioned studies. To the best of our knowledge, 3-fluoroazetidinones were synthesized for the very first time by using this approach.

Addendum

After the completion of the major portion of this thesis it was brought to our attention by Mr. S. R. Shakya that the formation of the acylazetidinone (194) via the LDA-acetaldehyde-PCC sequence can be complicated by formation of two different acetyl compounds, specially when large quantities of the starting azetidinone are involved. Thus in some instances (but not always) trace quantities (2-5%) of the acylazetidinone (194 a) were obtained in addition to the usual product (194). The main reason for such a behavior appears to be somewhat poor temperature control during the quenching of the corresponding carbanion with acetaldehyde. Purification of the hydroxyethyl compounds has not proven very useful. However it has been possible to take the contaminated acetyl compound (194) through Selectride reduction-silylation sequence. Subsequent careful purification of the silyl derivative (201) serves to remove the products arising from the reduction of the minor acetyl compound (194 a). It should be noted that these observations do not in any way undermine the main conclusions of Chapter 4.

The spectral properties of the minor azetidinone (194 a), a semi-solid, are as follows: ir: 1750, 1720 cm^{-1} ; ms: 351 (M^+ , 5.7%), 308 ($\text{M}^+ - 43$, 15.9%), 236 (imine $^+ - 1$, 100%); nmr: δ = 7.4-7.2 (m, 7 H), 6.8 (m, 3 H), 6.1 (dd, 1 H, $J = 8.9$ Hz, $J = 16.0$ Hz), 4.7 (dd, 1 H, $J = 0.6$ Hz, $J = 8.9$ Hz), 3.7 (s, 3 H), 3.6 (s, 3 H), 2.19 (s, 3 H).



Addendum II

After the submission of this thesis, the structure of the major azetidinone (98) became available. Clearly in this structure, the geometry of the 'left hand side' of the molecule is erythro. This fact indicates that the correlation between the differences in the chemical shift of the methyl groups of the acetonide residue with the geometry of the 'left hand side' is arrangement of molecule is not a useful one. This also puts in doubt the structure assigned to the minor azetidinone (91) in the cinnamyl series. Also in doubt is the structure of the 'trace' azetidinone.

