UNIVERSITE CATHOLIQUE DE LOUVAIN

FACULTE DES SCIENCES

Unité de Chimie organique et médicinale

Professeur L. GHOSEZ

Synthesis of Phosphinic Acids and Aza-β and γ-lactams as Potential Inhibitors of D,D-Peptidases and β-Lactamases

Dissertation présentée en vue

de l'obtention du grade de

Docteur en Sciences

Par **Jing ZHANG**

October 17, 2003

PhD thesis committee:

Dr G. Dive

Université de Liège

Prof. C. Moody

University of Exeter (UK)

Prof. J. Marchand-Brynaert (President)

Université catholique de Louvain

Prof. I. E. Markó

Université catholique de Louvain

Prof. O. Riant

Université catholique de Louvain

Prof. L. Ghosez (Supervisor)

Université catholique de Louvain

to my parents,

to Pingyu and Zekai

At the end of this work, I would like to thank Professor L. Ghosez for having accepted me in his laboratory. During all these years, I always greatly appreciate his patience, encouragement and advice that made this work realizable.

I would also like to thank all other people who helped me to realize this work:

Professor E. de Hoffmann and Professor Habib Jiwan and all the staff in the laboratory of mass spectrometry; Professor Flammang, at Université de Mons-Hainaut, for high resolution mass spectroscopies;

Mrs J. Maxwell of University College London for elemental analyses;

Dr R. Touillaux for high resolution NMR spectroscopies and Dr D. Chapon for ^{31}P NMR spectroscopies (UCL);

Mrs A. Dekoker, Miss H. Vanlierde and M T. Trien Van for their kindness and their devotion to this work; Mrs C. Delaet for her efficient administrative work and her good humor during all these years;

All the members of Professor Ghosez's and Professor Riant's group, who have left or who are still there, Anouk, Benoît, Chloé, Eric Tam, Jean-Michel, James, Jérôme, Karima, Naouël, Olivier, Patrick P., Patrick S., Prosper, Thierry.... Especially those who worked in the lab c227a, Flo, Déo and Kacém, with whom I spent a wonderful time in ORSY.

Those who made the final corrections of this manuscript, Chloé, Jérôme, Naouël, Kacém, Patrick P. and Yann.

Finally, I would give the special thanks to my parents for their support during all these years. Also to my husband, Pingyu, for his help, his patience, his tolerance and his encouragement. Also to my son, Zekai (Peter), a good boy. I truly appreciate all of these and I would like to say again: thanks for all!

This work was supported by PAI (No P4/03) and UCL.

Abstract

The increasing bacterial resistance to penicillin and cephalosporin antibiotics stimulated intensive reseach aiming at the discovery of non-β-lactam analogs which would bypass the microorganisms' defenses. The present work consists of two parts:

1. Phosphorus(V)-based transition state analogs

Three approaches towards the target molecule, a type of four-membered cyclic phosphinic acid derivative, have been discussed. The first two strategies consisted of performing the cyclization at the end of synthesis. The crucial formation of C-P bond was effected using electrophilic and nucleophilic phosphorus reagents respectively. However, any attempt to effect the cyclization to a four-membered ring failed. The main side reaction was a β-elimination leading to the corresponding dehydro-α-aminophosphinic acid derivative. In the third approach the phosphinic acid ring was formed via a double Arbuzov reaction, whereas successive aminations or alkylations of a phosphorus-stabilized carbanion on the four-membered ring were less effective.

2. RCM in the construction of bicyclic aza-β and γ-lactams (aza-analogs)

Methodology has been established to functionalize regiospecifically two nitrogen atoms which structurally constitute the pyrazolidinone ring. RCM proved to be a good strategy to the preparation of bicyclo [4.3.0] ring systems, whereas this method was less effective towards [3.3.0] ring systems.

The unsubstituted 1,2-diazetidinone ring proved to be rather unstable. We applied a one-pot deprotection-cyclization sequence to prepare an optically active bicyclic 1,2-diazetidinone derivative bearing a (*R*)-hydroxyethyl side chain using RCM. The use of oxazolidinone chiral auxiliary allowed to incorporate an α-carboxyl group contiguous to the lactam nitrogen. In the course of the synthesis of bicyclic [4.2.0] aza-β-lactam carboxylic ester derivatives we encountered a rapid ring expansion reaction via the proton abstraction and N-N cleavage leading to a stable imidazolidinone derivative.

Résumé

La résistance croissante des bactéries vis-à-vis des antibiotiques pénicillines et céphalosporines a stimulé la recherche intensive d'analogues non-β-lactamiques résistants aux enzymes de défense. Notre travail se compose de deux parties:

1. Les analogues d'état de transition à base de phosphore (V)

Trois voies d'accès aux acides phosphiniques cycliques de 4 chaînons ont été étudiées. Les deux premières stratégies ont consisté en l'étude de cyclisation à la fin de synthèse. La formation de la liaison C-P a été effectuée par des réactions d'alkylation de l'espèce phosphorée électrophile et de l'entité phosphorée nucléophile respectivement. Cependant, toutes les tentatives de cyclisation ont échoué. La réaction secondaire principale était une β-élimination qui avait conduit à un dérivé d'acide déhydro-α-aminophosphinique correspondant. Dans la troisième voie, le cycle phosphoré à 4 chaînons a été formé par une double réaction d'Arbuzov. Toutefois, les aminations ou alkylations d'un carbanion stabilisé par le phosphinate étaient moins efficaces.

2. Construction d' aza-β et γ-lactames bicycliques (aza-analogues) par RCM

La méthodologie a été établie afin de fonctionnaliser régiospécifiquement deux atomes d'azote qui constitue le cycle pyrazolidinone. La RCM s'est avéré être une bonne stratégie pour la préparation de bicycles [4.3.0]; cependant, cette méthode est moins efficace pour la préparation de bicycles [3.3.0].

Le cycle 1,2-diazetidinone non-substitué est très instable. L'application d'une séquence one-pot déprotection-cyclisation afin de préparer un dérivé de 1,2-diazetidinone bicyclique optiquement pur portant une chaîne (*R*)-hydroxyéthyl a été réalisée avec succès. L'utilisation d'un auxiliaire chiral d'oxazolidinone nous a permis d'introduire un groupe α-carboxyle contigu à l'azote du lactame. Au cours de la synthèse d'un dérivé bicyclique [4.2.0] d'ester aza-β-lactame carboxylique, nous avons rencontré une réaction d'expansion de cycle qui a conduit à un dérivé d'imidazolidinone stable par l'abstraction du proton et clivage de la liaison N-N.

Abbreviations

Ac	Acetyl
APCI	Atmospheric Pressure Chemical Ionization
Ar	Aromatic
Bn	Benzyl
br.	broad
Boc	*tert*-Butoxycarbonyl
*i*Bu	*iso*-Butyl
BTSP	Bis(trimethylsiloxy)phosphine
cat.	catalyst
Cbz	Benzyloxycarbonyl
CI	Chemical Ionization
δ	chemical shift (ppm)
Δ	heating
d	doublet
DBAD	Di-*tert*-butylazodicarboxylate
DBU	Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	Dichloromethane
d.e.	diastereomeric excess
DEAD	Diethylazodicarboxylate
DIEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulphoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	Electron impact Ionization
Et	Ethyl
equiv.	equivalent
FAB	Fast Atom Bombardment
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoric triamide
Hz	Hertz
IR	Infra-red
J	Coupling constant (Hz)
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
$M^{+\bullet}$	Molecular ion
lit.	literature
m	multiplet
Me	Methyl
Min	Minute
MS	Mass spectrometry
MsCl	Methanesulfonyl chloride
m/z	mass/charge
NMR	Nuclear magnetic resonance
NMM	*N*-Methylmorpholine
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
P.E.	Petroleum ether
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PNB	*para*-Nitrobenzyl
*i*Pr	*iso*-propyl
Py	Pyridine
q	quartet
s	singlet
Rf	Ratio of fronts
rt	room temperature
TBAF	Tetrabutyl ammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Triflyl (SO_2CF_3)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMCE	Tetramethyl-α-chloroenamine
TMS	Trimethylsilyl
*p*TsOH	*p*-Toluenesulfonic acid

Table of Contents

Part I

Part II

Chapter 1

Introduction

1.1 Antibiotics

The classical definition of antibiotics was introduced in 1942 by Waksman, who proposed a narrow concept which restricted the term to those compounds produced exclusively by microorganisms that inhibit the growth of or even destroy other microorganisms. A broader definition was presented by Benedict and Langlyke in 1976, according to which an antibiotic is a substance derived from or produced by a living organism capable of inhibiting the life processes of microorganisms in small concentration.[1] To date, the term antibiotics often includes synthetically produced antibacterial substances. The biological activity includes not only inhibition of the growth of microorganisms but any inhibition of life processes of any types of living objects (viruses, unicellular and multicellular organisms).

1.2 Cell wall synthesis inhibitors

The successful chemotherapeutic management of any host-parasite interaction depends upon the exploitation of biochemical differences between the host and parasite or tumor cells. The greater these differences are, the better the likelihood of finding or designing drugs that exploit them and inhibit some crucial function of the parasite in order to kill it without harming the host cell. The goal has been approximated very closely in the case of cell wall synthesis inhibitors, such as antibacterial agents, for the simple reason that a very fundamental difference exists between bacteria and mammalian cells: the former have cell walls and the latter do not. The rigid cell wall of bacteria encloses and strengthens the vulnerable cell membrane, which is subjected to considerable internal osmotic pressure. If the intergrity of the cell wall is impaired, the bacterial cell will undergo lysis and perish. The antibiotics that inhibit cell wall synthesis can not find an analogous target in animal cells, therefore in many cases they are nontoxic.

1.2.1 Structure and biosynthesis of bacterial cell wall

Of the several constituents in the bacterial cell wall, it is largely the peptidoglycan that determines cell shape and imparts the rigidity necessary to protect the bacterium from osmotic rupture. The basic unit of peptidoglycan is a repeating disaccharide linked through a lactyl ether to a tetrapeptide. The peptides are, in turn, cross-linked (in *Staphylococcus aureus*) by a pentaglycine chain, as shown in Figure 1.[2]

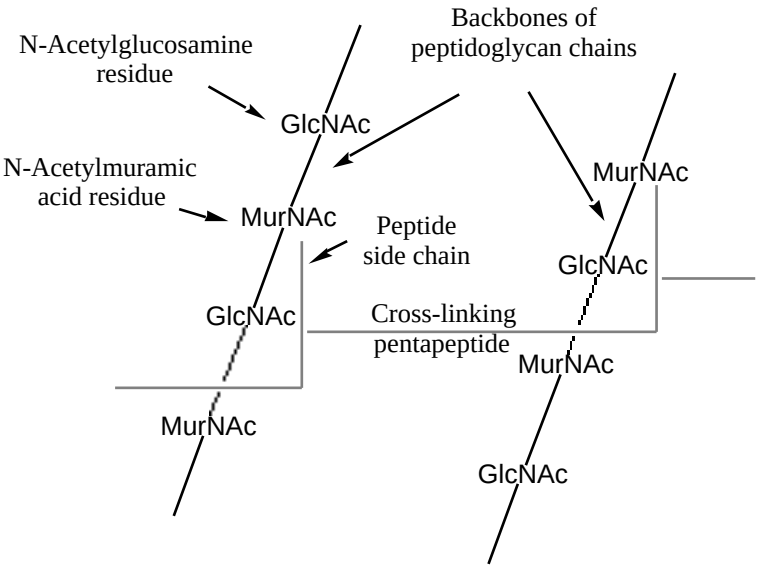
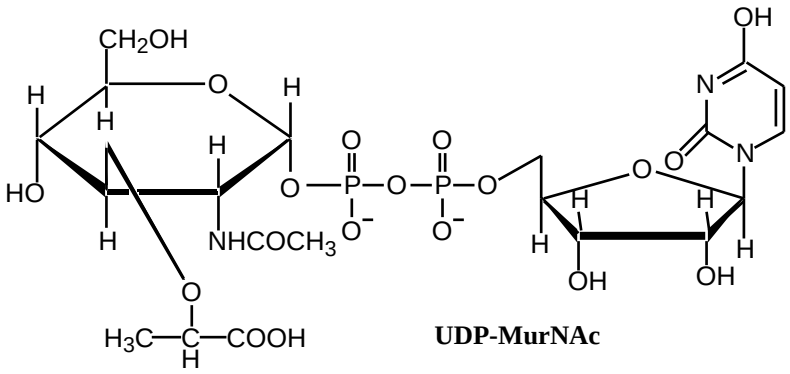


Figure 1

Gram-positive bacteria generally possess a thick (50 to 100 molecular layers) peptidoglycan surrounding the cell membrane, in contrast to gram negatives, which have a peptidoglycan only one or two molecular layers thick, surrounded by an outer membrane. Gram-negative outer membranes constitute a significant permeability barrier for β-lactam antibiotics.[3a]

Peptidoglycan biosynthesis can be divided into three stages:[2]

(1) Synthesis of the two uridine nucleotide precursors, uridine diphospho-N-acetylmuramyl pentapeptide (UDP-MurNAc-pentapeptide) and uridine diphospho-N-acetylglucosamine, by cytoplasmic enzymes. In the former stage, the biosynthesis of the UDP-MurNAc-pentapeptide is completed by successive addition of L-Ala, D-Glu, L-Lys and dipeptide D-Ala-D-Ala to carboxyl group of muramic acid. The dipeptide D-Ala-D-Ala is separately synthesized. A racemase acting on L-Ala gives D-Ala, and a synthetase then joins two molecules giving the dipeptide (Figure 2).



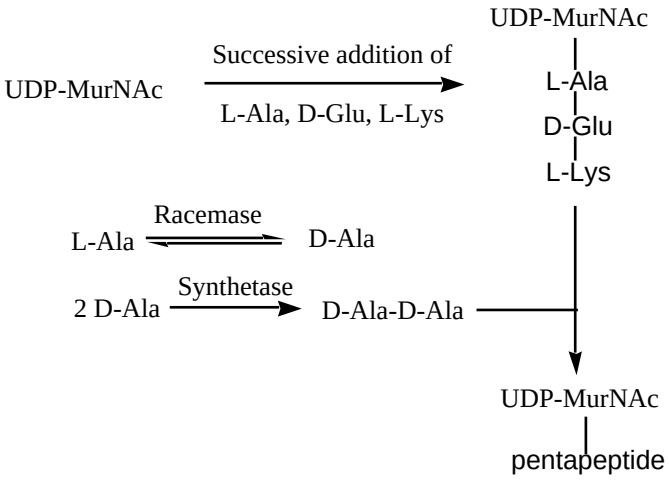


Figure 2

(2) Translocation of the N-acetylmuramyl pentapeptide and N-acetylglucosamine moieties across the cytoplasmic membrane by a lipid-soluble glycosyl carrier (a C_{55} isoprenyl alcohol phosphate) and their subsequent polymerization (transglycosylation) to form a linear peptidoglycan polymer.

(3) Incorporation of the linear polymer into existing peptidoglycan with cross-linking of the peptidoglycan side chains. During this final step, a free amino group on the third residue (L-Lys) of a MurNAc-pentapeptide of one glycan strand displaces the terminal D-Ala from a pentapeptide of a second glycan strand in a transpeptidation reaction (Figure 3). The peptidoglycan of *E. coli* differs in several ways from that of *S. aureus*. As in the other Gram-negative bacteria, the L-Lys residues are replaced by *meso*-diaminopimelic acid and there is no pentaglycine "extending group". Cross-linking occurs between the penultimate D-Ala and the terminal amino group of diaminopimelic acid.

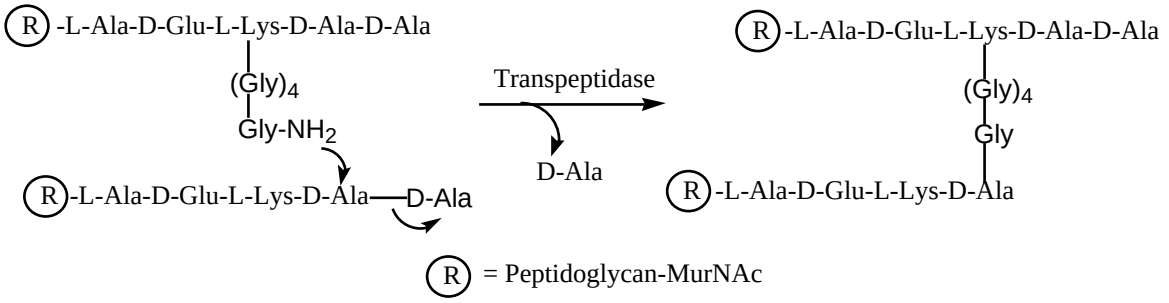
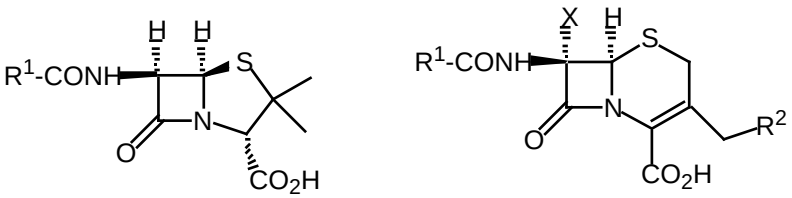


Figure 3

1.2.2 β-lactam antibiotics

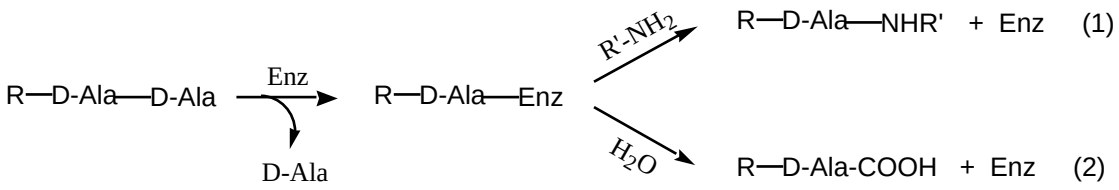
β-Lactam antibiotics, one of the most important contributions of science to human health, account for 50% of the world's total antibiotic market. Such antibiotics as the penicillins and cephalosporins (Figure 4) inhibit the last cross-linking step of bacterial cell wall synthesis.



Penicillins **Cephalosporins**

Figure 4

There are two clearly identifiable groups of penicillin-sensitive activities: D,D-transpeptidation and D,D-carboxypeptidation (Scheme 1):[3b]



(1) D,D-transpeptidation; (2) D,D-carboxypeptidation

Scheme 1

The discovery of more than one penicillin-sensitive enzymatic activity in bacterial membranes resulted in additional complications. In 1972, it was shown that membranes from several bacterial species each contain several distinct proteins that bind penicillins covalently.[4a,b] These so-called "Penicillin-Binding Proteins" (PBPs) fall into two major groups: the low-molecular-mass (LMM) PBPs are monofunctional enzymes acting mainly as D,D-

peptidases, while the high-molecular-mass (HMM) PBPs are multimodular enzymes also displaying a D,D-peptidase activity sometimes associated with a transglycosylase activity. HMM-PBPs are further divided into classes A and B according to their function and the sequence similarities found in their non-penicillin-binding module. The penicillin-binding module of the multimodular PBPs is associated with at least one other domain which is assumed to have a transglycosylase activity in class A HMM-PBPs. The role of the non-penicillin-binding domain of class B HMM-PBPs is not yet understood.[4c]

1.2.2.1 Mode of action

It was suggested that the fixed configuration of the L-cysteinyl-D-valine-derived structure of penicillin is probably very close to the conformation that the D-Ala-D-Ala terminus of the pentapeptide chain must assume for the attachment to the transpeptidase (Figure 5).[5] Thus the penicillin would have a high affinity for the active site of the enzyme.

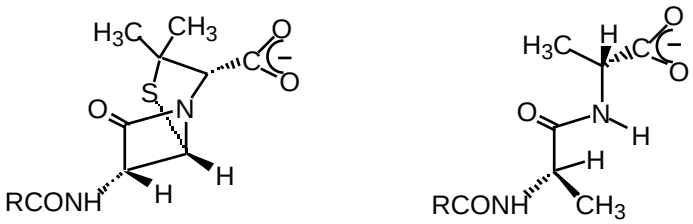
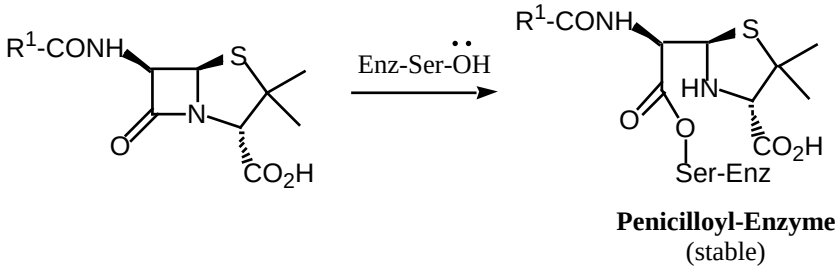


Figure 5 Stereomodels of penicillin (**A**) and D-Ala-D-Ala (**B**)

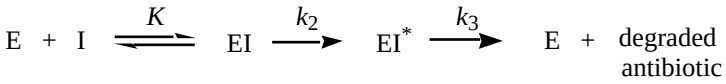
Therefore, penicillin acting as a structural analog of substrate would bind to the enzyme (generally serine peptidases) with its β-lactam bond positioned at the active site. A relatively facile acylation of the catalytically active amino acid residue would then occur with the opening of the β-lactam ring, forming an inactive penicilloyl-enzyme (Scheme 2).



Scheme 2

The present understanding of the interaction between D,D-peptidases and β-lactam antibiotics is largely based on data obtained with soluble enzymes. Frère J. M. and co-workers[6] studied the mode of this interaction at the molecular level and their kinetic analysis demonstrated

that this interaction obeyed a three-step model (Scheme 3): a. the formation of a reversible equimolar enzyme-antibiotic complex (EI); b. the irreversible transformation of this complex into a modified enzyme-antibiotic complex (EI^*); c. the breakdown of this latter complex and the concomitant release of a regenerated enzyme and a modified antibiotic molecule. In this simplest model, K and k_2, k_3 represent dissociation constant and rate constants for the second and third steps respectively.



E: enzyme
I: antibiotic
EI: non-covalent Michaelis complex
EI^*: covalent acyl-enzyme

Scheme 3

Apparently, the efficient inactivation of the enzyme depends on a rapid and nearly quantitative accumulation of the EI^* complex, which is the result both of its stability (low k_3), and of its rapid formation-generally due to high k_2 values.

1.2.2.2 Structure and activity

β-Lactams share a common structural similarity, the four-membered lactam ring. In the bicyclic systems the β-lactam ring is fused through the nitrogen and the adjacent tetrahedral carbon atoms to a secondary ring structure. A thiazolidine ring is present in penicillins, and a dihydrothiazine ring in cephalosporines (Figure 4). Shortly after the introduction of penicillin to the medical world it was suggested that the antibiotic's activity was due to the inherent strain of the four-membered ring leading to reduced amide resonance.[7] In a normal amide the planar arrangement of the O, C and N atoms is generally assumed to be necessary for the effective delocalization of the nitrogen lone pair, and therefore the non-planar butterfly shape of the penicillin molecule could reduce amide resonance (Figure 6), consequently increasing the susceptibility of the carbonyl group to nucleophilic attack.

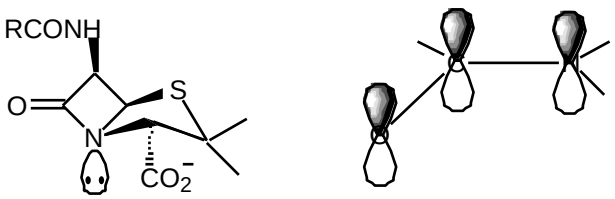


Figure 6

However, biological activity is not directly related to chemical reactivity.[8] A pyramidal geometry of the β-lactam nitrogen does not necessarily give a chemically more reactive β-lactam. Strained bicyclic β-lactams are not necessarily better antibiotics and monocyclic β-lactams with suitable electron-withdrawing substituents may be as reactive as the bicyclic systems.[9]

As a matter of fact, potent β-lactam antibiotics have been developed by systematic modifications of R^1, R^2 and X substituents of the naturally-occurring penicillins and cephalosporines. The intensive search for new microbial β-lactams has led to the discovery of many other active compounds such as oxacephems,[10] clavulanic acid,[10] penems,[11] carbapenems,[11,12] monobactams,[11] and most recently, carbacephems[13,14](Figure 7).

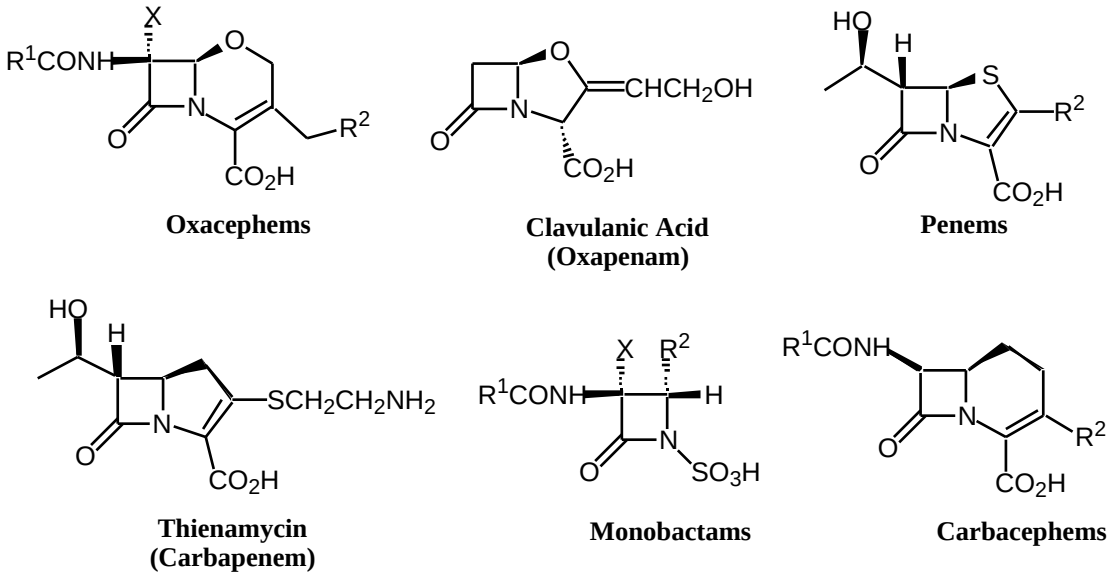


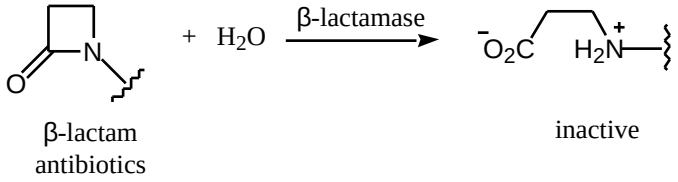
Figure 7

The non-classical structures of these compounds have led to a re-evaluation of the structural requirements for biological activity. In principle, most β-lactams have a carboxyl group on the carbon atom attached to the β-lactam nitrogen. This is because D,D-peptidases have a positively charged residue that can form a salt bridge with a negatively charged entity, *i.e.* the carboxylate function in β-lactams. The "correct molecular shape" requires the presence of an acidic group with a separation of about 3.0-3.6 Å between the lactam carbonyl carbon and the center of the acidic group.[15] For most penicillins, cephalosporins and monobactams, a β-acylamino group is necessary for recognition step to achieve antimicrobial activity; this group is not required for the penems or carbapenems, in which the chemical reactivity of the β-lactam ring appears adequate to achieve high antibacterial activity.

Although in the early 1990s it seemed that the possibilities for new development of β-lactam chemistry had been exhausted, continued efforts have never been stopped, and thus leading to many new and often very fundamental chemistry and applications discovered in this field.[16]

1.2.2.3 Resistance to β-lactam antibiotics: β-lactamases

Two major factors are known to aggravate the problem of antibiotic resistance: overuse of antiobiotics in humans and animals, and noncompliance to the course of treatment by patients. Both the long-term exposure to low doses and the failure to finish a prescription encourage more resistant bacterial strains to flourish. Bacterial resistance to an antibiotic drug is mediated by one or more processes.[17] Of these mechanisms, the β-lactamases[18] are the best known examples of antibiotic-destroying enzymes, which catalyze hydrolysis of the β-lactam bond making most β-lactam antibiotics inactive (Scheme 4). Resistance to β-lactam antibiotics in species where β-lactamases are absent can be mediated by enzymatic targets alterations.[19,20]

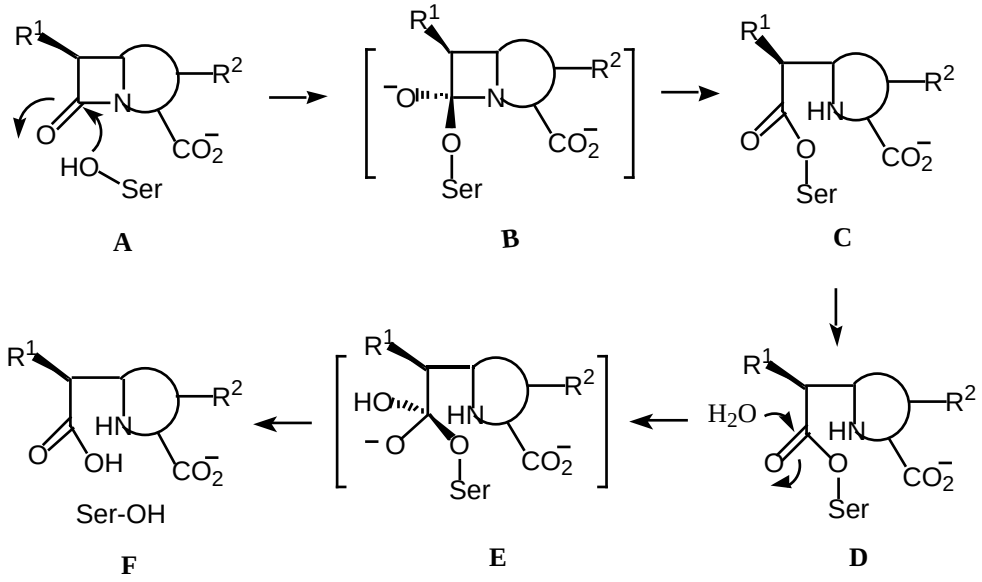


Scheme 4

The main mechanistic division of β-lactamases is into serine enzymes and zinc enzymes. The former have an active site serine residue and the catalytic mechanism involves the formation of an acyl-enzyme intermediate. The metallo-enzymes appear to involve only non-covalently bound intermediates. On the basis of their amino acids sequences, the serine β-lactamases are sub-divided into three classes: A, C and D[21]-whereas the class B β-lactamases consist of the zinc enzymes.[22,23]

The mechanism of hydrolysis mediated by serine β-lactamases is the same as that of D,D-transpeptidases, whereas for β-lactamase activity k_3 must be much larger than k_2/K (Scheme 3). The reaction begins with the formation of a precovalent encounter complex **A** (Scheme 5), and moves through a high energy acylation tetrahedral intermediate **B** to form a transiently stable acyl-enzyme intermediate **C**. Subsequently, the acyl-enzyme is attacked by a hydrolytic water (**D**) to form a high-energy deacylation intermediate **E**, which collapses to form the hydrolyzed product **F**. The product is then expelled, regenerating the free enzyme. It was suggested that the side chains of β-lactams could make considerable contribitions to affinity for β-lactamases.[24]

Formation of the acyl-enzyme intermediate requires at least two proton transfers-proton removal from the attacking serine and proton donation to the departing amine (Scheme 5). Despite the availability of a number of X-ray crystal structures of several class A and class C β-lactamases,[25,26] the identity of the catalytic groups involved in these proton transfer steps remain elusive.[21]



Scheme 5

A recent report by Shoichet *et al.*[27a] provides strong support for the mechanism that Glu166 acts as the catalytic base in the acylation reaction of class A β-lactamases. According to such a mechanism (Figure 8), Glu166 would activate Wat1004, which in turn, would activate Ser70, accepting the proton of the Ser70 nucleophile during the attack on the lactam carbonyl center. Thus, the proton has been shuttled from the serine through the water to end up on the glutamic acid. Meanwhile, the leaving group lactam nitrogen is activated by accepting a proton from Ser130.[27b]

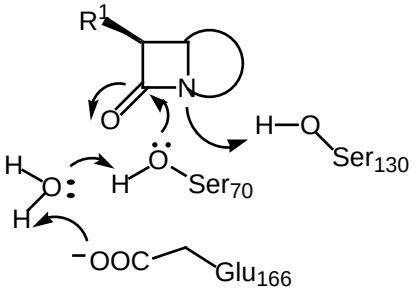


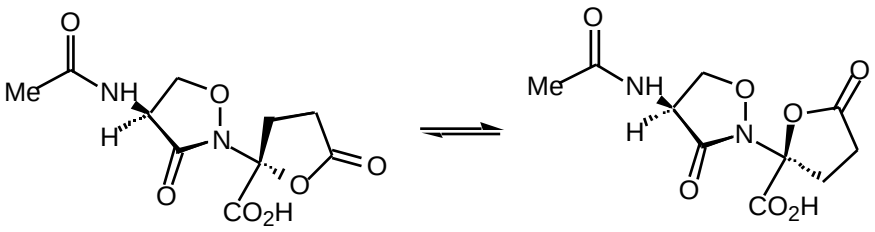
Figure 8

The β-lactamases have evolved from bacterial D,D-peptidases[28,29] along a path where changes in both acylation and deacylation steps have occurred. β-Lactamases have lost the

ability to be acylated by acyl-D-Ala-D-Ala peptides and acquired the ability to catalyze hydrolysis of the acyl-enzyme derived from their acylation by β-lactams. The latter can not apparently be achieved in a D,D-peptidase. It seems unlikely that good, present-day β-lactamases and D,D-peptidases can be functionally interchanged by simple mutations.[30]

1.2.3 Non-β-lactam mimics of β-lactam antibiotics

In recent years there has been a keen interest in the design, synthesis and biological testing of novel structural skeletons which will target the PBPs and also overcome the defense mechanism of bacteria. Non-traditional β-lactams are a possible solution to the problem of bacterial resistance. As a matter of fact, in the 1970s several groups began to question the conventional wisdom that the β-lactam ring itself was essential for the antibacterial activity. Furthermore, the discovery of a naturally occurring γ-lactam antibiotic, lactivicin,[31] which mimics the biological activity and mode of action of β-lactam antibiotics[32] represents a major contribution to the continuing evolution of antibacterial agents. The structure of this novel dipeptide was determined to be composed of the epimeric mixture (Scheme 6).[33]



Scheme 6

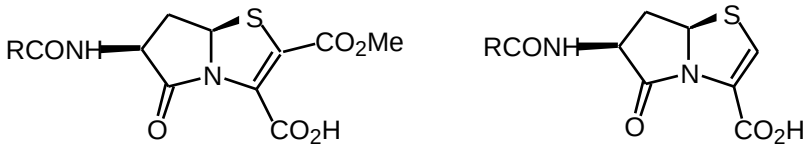
There has been considerable effort by a number of research groups to design or to discover bioisosteres of β-lactams. Two reviews,[34,35] which discuss in detail efforts to prepare non-β-lactam mimics of the β-lactam antibiotics, have appeared in the early 1990s.

1.2.3.1 Irreversible inhibitors

1.2.3.1.1. Acylating agent

The β-lactam mimics discussed here were all designed to acylate the serine residue present in the active site of the PBPs and many β-lactamases. In designing potential β-lactam surrogates, consideration must be given both to molecular shape (for recognition by target PBPs), and to acylation ability. Good inhibitors form acyl-enzyme intermediates (EI^*) that are unable to regenerate the active enzyme by reaction with an exogenous nucleophile. This implies that the ratio k_2/K should be much larger than k_3 (Scheme 3).

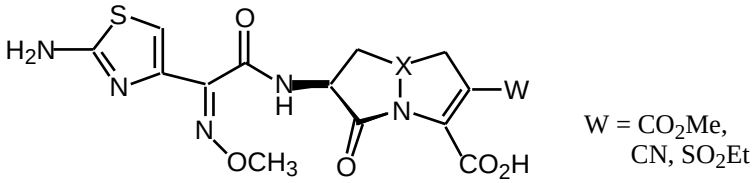
Molecular modeling studies supported the hypothesis that a γ-lactam could be designed to mimic a β-lactam, with regard to chemical reactivity and molecular shape.[36] However, previous attempts dating to the 1940s to prepare biologically active γ-lactam mimics of penicillin met with failure.[37] The Lilly group provided some of the first data that showed the γ-lactam analogues of the β-lactams could exhibit antibacterial activity. Morin and co-workers[38] reported on the synthesis of γ-lactam analogues of penems **1** (Figure 9). A concurrent publication by Baldwin *et al.*[39] described the synthesis of analogue **2**. Both compounds showed weak antibacterial activity against both gram-positive and gram-negative organisms.



1 **2**

Figure 9

The γ-lactam analogues of the carbapenems synthesized by the Lilly group, such as **3a**[36] (Figure 10), were generally devoid of *in vitro* antibacterial activity, although electron-withdrawing substituents (W) might increase the acylating ability of these γ-lactams by delocalization of the lone pair of electrons on the lactam nitrogen through the olefin bond. However, their corresponding aza-γ-lactam analogues **3b** show good binding to bacterial PBPs and exhibit *in vitro* and *in vivo* antibacterial properties at useful levels.[40,41] This exciting discovery firmly established that a viable biological surrogate for the β-lactam ring has been realized.

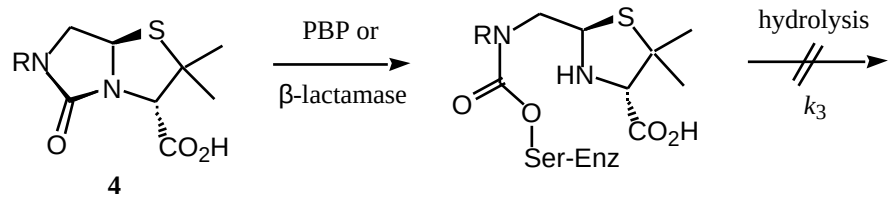


3a: X=C
3b: X=N

Figure 10

Another class of potential β-lactam mimics, the bicyclic imidazolidinones **4** (Scheme 7), has been reported by our laboratory.[34] Upon ring-opening by a PBP or β-lactamase, these compounds form an acyl-enzyme intermediate with a carbamate linkage, which is much less susceptible to nucleophilic hydrolysis than the simple ester linkage formed with a β-lactam. Unfortunately, all of the bicyclic imidazolidinones derived from penicillin were devoid of antibiological activity. We should note that the urea functionality present in the imidazolidinone

is also much less susceptible to the initial nucleophilic attack by the serine residue in the active site of the target enzymes.



Scheme 7

For a similar reason, Nangia *et al.*[42] designed and synthesized mono and bicyclic 1,3-diazetidin-2-ones (Figure 11) as non-natural analogues of β-lactams. These compounds are closer structural mimics of β-lactams and also benefit from resonance stabilization in the carbamoyl-PBP intermediate. A majority of the molecules tested in this article showed higher inhibition of a gram-positive bacterial strain than well-known standard antibiotics, ampicillin and penicillin G.

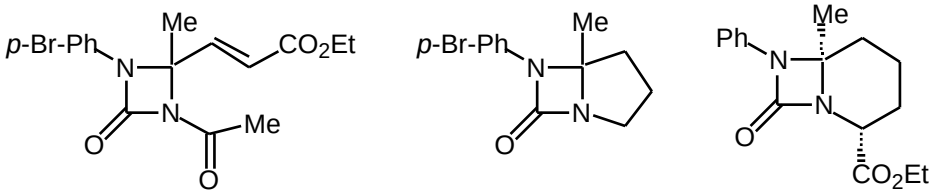
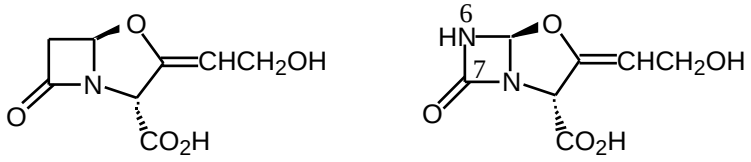


Figure 11

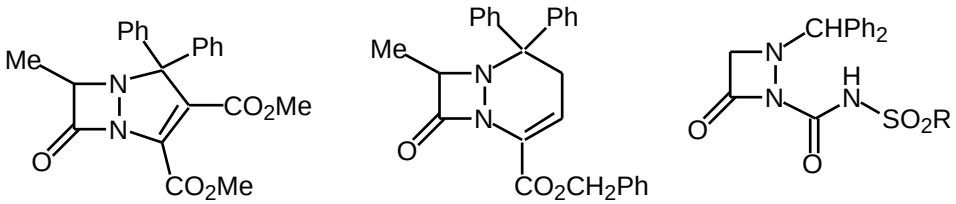
In the theoretical studies on β-lactam structures where the carbon atom next to the β-lactam carbonyl group is substituted by an oxygen, nitrogen or sulphur atom, Munoz *et al.*[43] found the nucleophilic attack of hydroxyl group on the β-lactam carbonyl to yield products possessing the chemical reactivity required from effective antibacterial agents capable of inhibiting β-lactamases. Aza-clavulanic acid could be expected to be a much more powerful inactivator than clavulanic acid (Figure 12). In addition, cleavage of N_6-C_7 bond could also take place during the nucleophilic attack, which allows the enzymes to be inactivated via a rather different pathway relative to classical antibiotics.



Clavulanic acid **Aza-clavulanic acid**

Figure 12

Mono and bicyclic 1,2-diazetidinones (Figure 13) have also been reported in the 1980s. Aza-analogues **5**[44] and **6**[45] were found to be ineffective against representive strains of bacteria, but the sulfonyl derivative **7** displayed some antifungal activity.[42] In light of the fact that these compounds should have sufficient chemical reactivity to acylate the PBPs, it is reasoned that their molecular shape might preclude good "fit" into the PBPs.

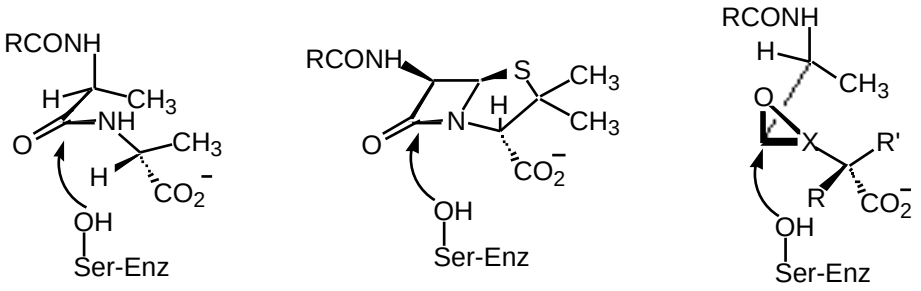


5 **6** **7**

Figure 13

1.2.3.1.2. Alkylating agent

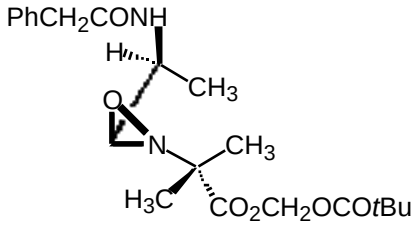
Our group[34] has also been involved in the design and synthesis of potential alkylating agent inhibitors **8**, which mimic the natural substrate D-Ala-D-Ala **9**, or a β-lactam **10** (Figure 14). The target molecules are oxaziridines (X=N) or epoxides ($X=CH_2$) bearing suitably orientated appendages which should allow recognition by the enzyme. Such design has to include the geometrical requirements for the nucleophilic opening of the small ring. The electrophilic center in the three membered heterocycles is a distorted tetrahedral carbon atom and the trajectory of the attacking nucleophile should be antiparallel with respect to the bond to be cleaved.[46]



9 **10** **8**

Figure 14

However, only pivaloyloxymethyl ester **11** (Figure 15) showed weak bacteriostatic activity vs *Klebsiellaaerogenes* and *Klebsiellapneumoniae* when incubated in the presence of serum.



11

Figure 15

Two types of Michael acceptor, cyclopentenones[47] and cyclobutenones,[ZJT0004] have also been designed and synthesized in our laboratory. However, these compounds were devoid of antibacterial activity (Figure 16).

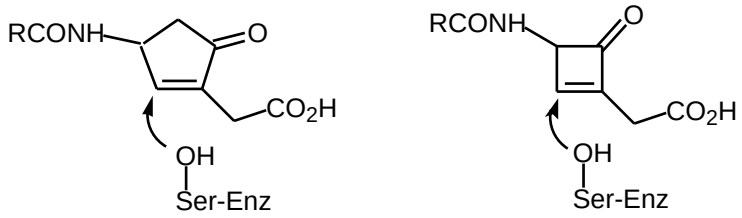


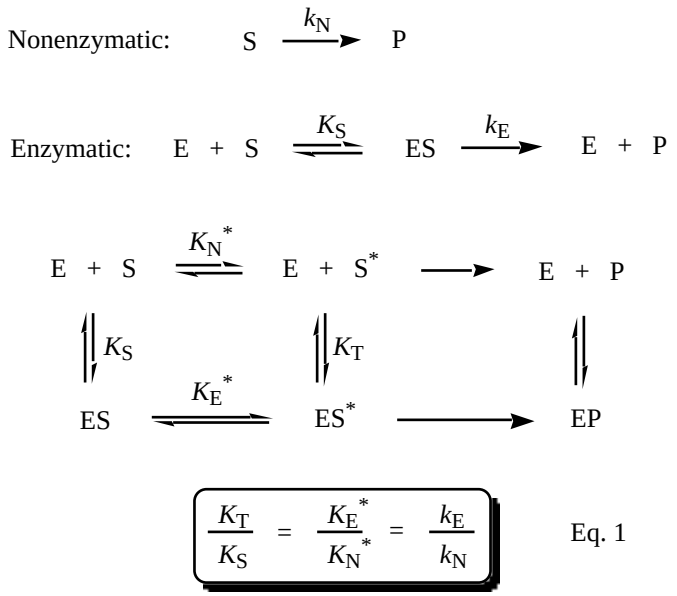
Figure 16

1.2.3.2 Reversible inhibitors: transition-state analogue

1.2.3.2.1 Theory

The function of an enzyme, like that of any other catalysts, is to make the transition state for the reaction easier to reach. This could be achieved if the enzyme did possess an unusual affinity for the altered substrate in the transition state, exceeding that for the substrate itself. This view, originally advanced by Pauling,[48] is easily expressed in terms of the theory of reaction rates.[49]

The system is shown in Scheme 8, where one-substrate reactions are considered for simplicity. In this scheme, K_S is the equilibrium constant for association of the substrate, S, with the enzyme, E; K_N^* and K_E^* are equilibrium constants for the formation of the transition states of the nonenzymatic and enzymatic reactions, S^* and ES^*, respectively; K_T is the equilibrium constant for the binding of S^* to E to form ES^*. The expressions for these four equilibrium constants show that they are related by Eq. 1. Moreover, according to the simplest version of transition-state theory,[50] K_E^* is related to k_E, the first-order rate constant for the conversion of ES to EP, and K_N^* is related to k_N, the first-order rate constant for the corresponding nonenzymatic reaction.



Scheme 8

Thus, transition-state theory yields the important conclusion that enzymatic catalysis, expressed by the ratio k_E/k_N, is equivalent to tighter binding of the transition state than the substrate to the enzyme, expressed by the ratio, K_T/K_S (Eq. 1). The value of k_E/k_N for a typical enzymatic reaction will fall in the range of 10^8 to 10^{14}, since K_S is usually in the range of 10^3 to 10^5 M^{-1}, the values expected for K_T are extremely large, of the order of 10^{15} M^{-1}. These relations are presented in Figure 17 in terms of a free energy-reaction pathway profile for a hypothetical single-substrate enzymatic reaction and the corresponding nonenzymatic reaction.

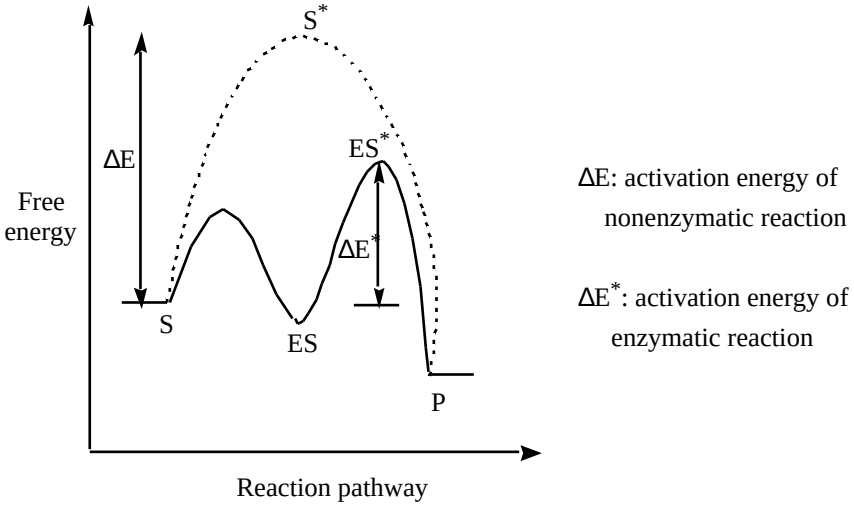


Figure 17

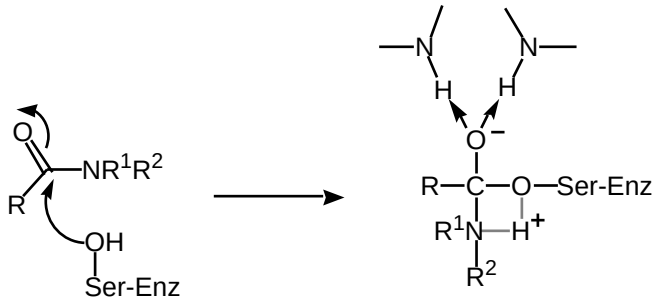
A slight complication arises when the enzymatic reactions involve two substrates, but the factors do not alter the fundamental deductions of the theory discribed above.[50]

The above Wolfenden's quasi-thermodynamic treatment suggests that it may be possible to design stable analogues approaching the structure of the altered substrate in the transition state and that such compounds could be enzyme inhibitors.

1.2.3.2.2 Transition-state analogue inhibitors[51]

A transition-state analogue for an enzyme is a stable compound that resembles in structure the substrate portion of the transition state of the enzymatic reaction. As with acyl-transfer enzymes in general, the aim would be to produce a stable substrate analogue with a tetrahedral and preferably anionic moiety in place of the carbonyl group of the scissile bond. To date, the greater success has been achieved in the development of transition state analogue inhibitors of β-lactamases than D, D-peptidases. This is probably due to the broader specificity of the former enzymes both with respect to the environment of the scissile bond and to the side chain. Development of such inhibitors in the latter case is still slow, reflecting the related unsolved problems of the substrate side chain specificity and active site potentiation of the high MW D, D-peptidases.[30]

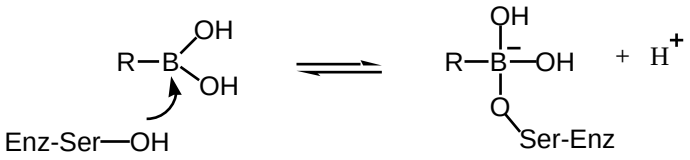
In the simplest structural terms of serine enzymic transition state, the four ligands attached to the substrate's carbonyl carbon atom are constrained by their interactions with the enzyme to be tetrahedrally disposed about that atom. Robertus and co-workers[52] found that a corresponding pair of hydrogen bonds was present in the subtilisin-substrate complex, involving the backbone NH of reactive Ser-221 and the side chain NH_2 of Asn-155. These two hydrogen bonds cannot form in the Michaelis complex or in the acyl-enzyme, but only when the substrate carbonyl is covalently linked to the enzyme and in the tetrahedral configuration. This site of oxyanion binding was called an "oxyanion hole", and it was suggested that this feature supplied much of the required transition state stabilization with respect to both the Michaelis complex and the acyl-enzyme (Scheme 9).



Tetrahedral binding

Scheme 9

According to the transition state theory, serine enzyme should exhibit high affinity for substances that can form stable tetrahedral adducts with the reactive serine. The classic example would be tetrahedral boronate. Borate and boronates inhibit serine enzymes by formation of a negatively charged, tetrahedral adduct with the active site serine hydroxyl group (Scheme 10).



Scheme 10

Indeed, inhibition of β-lactamases by borate and boronates has been known and studied for many years. Both class A[53] and class C[54] β-lactamases can be strongly inhibited by suitably designed boronates. Quite recently, a *m*-carboxyphenylglycylboronic acid[55] (Figure 18) has been designed and synthesized to inhibit class C β-lactamases with *K* value (Scheme 3) as low as 1 nM. In this case the carboxylate group contributed significantly to the binding of this reversible inhibitor, and by extention to the recognition of β-lactam substrates by class C β-lactamases.

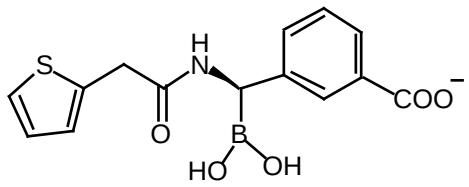
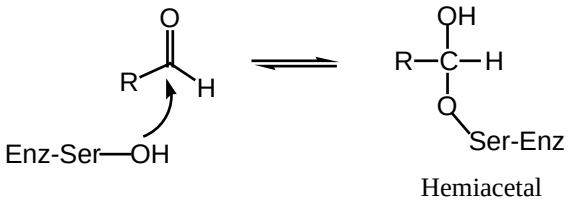


Figure 18

In contrast to the boronates, electrophilic carbonyl species,[54] potentially also leading to tetrahedral adducts (Scheme 11), have proven disappointing as β-lactamase inhibitors.



Scheme 11

On the other hand, peptide aldehydes related to substrates have proven to be potent inhibitors of serine proteases,[56,57] and it has been suggested that the tighter binding of the aldehydes derives from stabilization of a hemiacetal tetrahedral adduct (resembling the transition state) formed between the enzyme active site and the aldehyde carbonyl. The hemiacetal is

relatively stable since breakdown of this complex gives an aldehyde. Aldehydes are unique among carbonyl compounds in preferring to exist as tetrahedral addition complexes and are frequently unstable with respect to their hydrates and hemiacetals in aqueous or alcoholic solution.

1.2.3.2.3 Phosphorus-containing analogues

A successful approach for the inhibition of a number of peptidases has been to utilize phosphorus analogues to mimic unstable tetrahedral intermediates[58,59] or naturally occurring peptides inhibitors.[60] The basis for this inhibition is attributed to the similarity of the tetrahedral phosphorus species to the presumed tetrahedral intermediate arising from addition of a peptidase to the substrate carbonyl group. In the early 1990s the similarity between the tetrahedral intermediates and phosphorus-containing analogues in the ester and amide hydrolysis has been determined by Teraishi and co-workers.[61] Anionic forms showed a fairly good agreement with analogues with regard to both structures and charges (Figure 19). It is generally considered that the P-O bond is longer than C-O bond and mimics the forming and cleaving C-O bond, and also the negative charges on the oxygen atoms of these analogue molecules imitate those of tetrahedral intermediates.

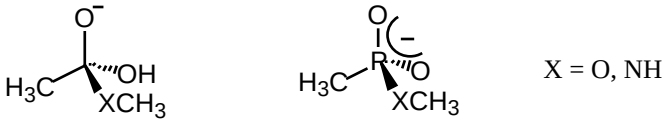
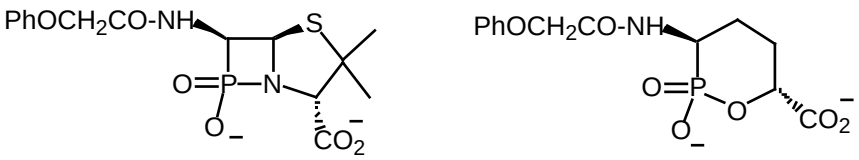


Figure 19

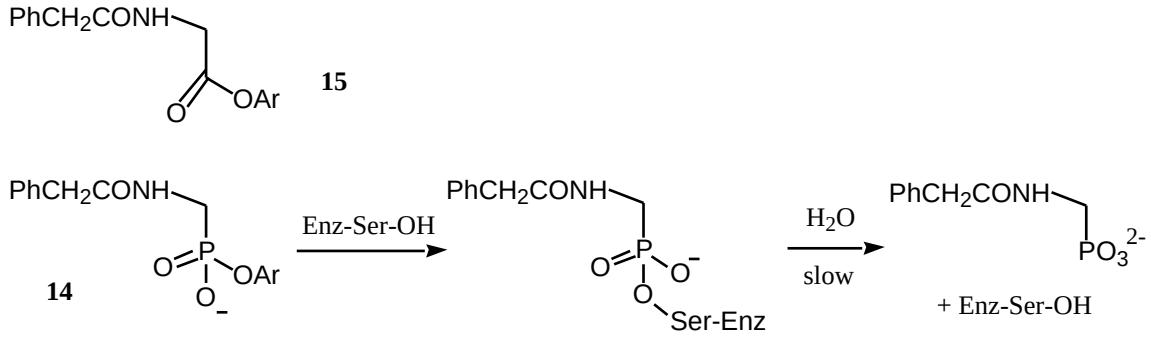
Direct application of the phosphonate-for-carbonyl substitution strategy to mimicry of the presumed tetrahedral intermediate in hydrolysis of a penicillin derivative would necessitate construction of a heterocycle such as **12**, in view of the lability of monocyclic phosphazetidine,[62] Barlett and co-workers[63] considered the monocyclic oxaphosphane **13** as an alternative preserving the basic relationship between the acylamino substituent, the tetrahedral phosphorus atom, and the carboxylate moiety (Figure 20). Both *cis* and *trans* isomers of **13** have been tested as inhibitors of class B β-lactamases and found to be inactive, even at concentrations up to 0.5 mM.



12 **13**

Figure 20

On the other hand, phosphonate monoester **14** was shown to inhibit both class A and class C β-lactamases.[64] This was inspired by the discovery that acyclic dipeptidase **15** was a β-lactamase substrate[65] and the fact that the β-lactamase active site contained considerable positive charge.[28,66] Although it was anticipated on the basis of the general stability of phosphonate monoesters[67] to nucleophilic cleavage that compound **14** would act as a stable transition-state analog, inactivation of β-lactamases by **14** was found to be accompanied by a concerted and stoichiometric release of ArOH. The proposed inactivation reaction involves phosphonylation of an active site of residue, which is most likely to the serine hydroxyl group. As shown in Scheme 12, the dephosphonylation reaction involving release of phenylacetamidomethylphosphonic acid and reactivation of the enzyme is slow.



Scheme 12

Phosph(or/on)yl derivatives have often been considered to be transition-state analog inhibitors of serine proteinases, although it is the phospho(or/on)ylated enzyme that really mimics that acylation or deacylation transition state. They differ from classical transition-state analog inhibitors, however, in that the primary reasons for their effectiveness are kinetic rather than thermodynamic. The inert complex is generated in an essentially irreversible reaction whose transition state is strongly stabilized by the enzyme, yielding a product that interacts with the enzyme active site in a way similar to that of the tetrahedral intermediate of acyl-transfer reactions. This situation should be distinguished from that with aldehyde and boronate inhibitors which rapidly and reversibly form thermodynamically stable and clearly enzyme-stabilized tetrahedral complexes with the active site serine hydroxyl group. In some ways, therefore, phosph(on)ates are perhaps better seen as a class of mechanism-based inhibitors of serine hydrolyses.[64]

(Phenethylphosphonyl)-L-Ala-L-Pro (**b**, Figure 21), a potent inhibitor of the zinc protease angiotensin-converting enzyme (a dipeptidyl carboxypeptidase), was obtained when the scissile carbonyl group of a substrate (**a**) was replaced with a phosphonic moiety. The potency of this compound was presumably due to occupation of the S_1 subsite by the phenethyl side chain, which duplicated the side chain of the phenylalanine at the P_1 position in the natural substrate.

In addition to tetrahedral phosphorus, an ionizable basic oxygen atom was required for tight binding. As shown in Figure 21, the phosphonic amide is positioned at the cationic active site zinc atom.[68a]

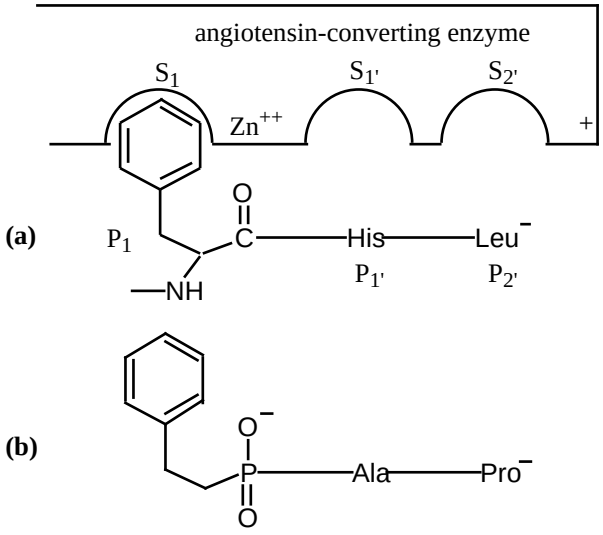
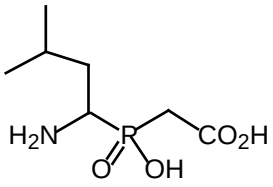


Figure 21

Bartlett[60] described a phosphorus-containing analogue **16** (Figure 22) of the amino acid statine and showed that its incorporation into appropriate oligopeptide sequences afforded a very tight, slow-binding inhibitor of the prototypical aspartic peptidase pepsin. From the chemical nature of the phosphinic acid moiety, they expected that **16** was binding to the enzyme in a reversible and noncovalent fashion. However, accurate determination of its binding affinity is not straightforward.



16

Figure 22

Another good example is a phosphinic acid inhibitor **17** incorporating 4-substiuted proline,[68b] which has the profound effect for angiotensin-converting enzyme. However , the poor oral activity of this compound made it unsuitable for further development as oral antihypertensive agents. Its potential was ultimately realized in a subsequent investigation that culminated in the design of fosinopril, an (acyloxyl)alkyl prodrug of compound **17**, which has entered clinical trials as an orally active antihypertensive (Figure 23).

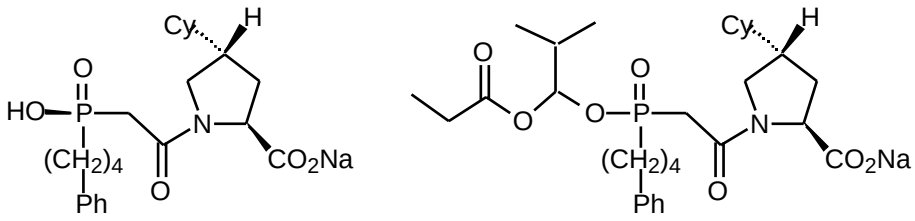
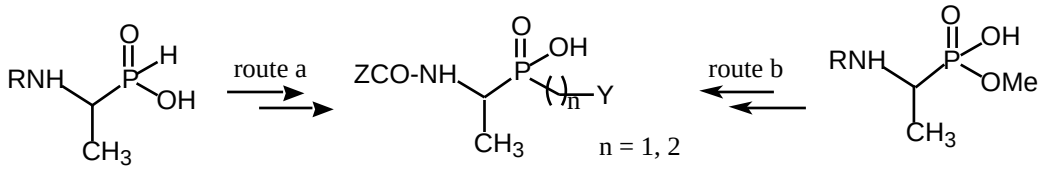


Figure 23

1.3 Objectives of this work

1.3.1 Synthesis of four-membered phosphinic acid derivatives

In our group Kessabi, J.[69a] has developed two complementary methods to prepare acyclic phosphinic acids bearing a carboxylic or sulfonic acid function and an acylamino side chain (Scheme 13).



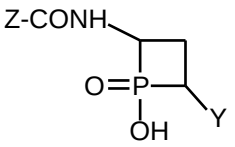
R: protecting groups
Z: side chains of penicillin G and V
($G = PhCH_2$; $V = PhOCH_2$)
Y: CO_2H, SO_3H

Scheme 13

The tetrahedral geometry of phosphinic acid group is thought to mimic the presumed tetrahedral transition state in acylation by nucleophilic attack of the serine residue of a D,D-peptidase on the dipeptidyl substrate D-Ala-D-Ala, by which the final peptidoglycan cross-linking step in bacterial cell wall biosynthesis is accomplished. The design of this kind of analog is based on the reversible and noncovalent binding of the enzyme with analog itself in view of the relatively inert chemical nature of the phosphinic acid moiety (k_2=0, Scheme 3). Although such molecules possess the key elements (*e.g*. carboxylic or sulfonic acid functionality; classic side chains of penicillins) used for recognition step by target PBPs, they are devoid of antibacterial activity.

We thus decide to synthesize one type of four-membered phosphinic acid derivatives (Figure 24) which are believed to resemble more closely the structure of penicillins. Due to the

well-known lability of monocyclic phosphoazetidines that are too unstable for use in aqueous solution,[62] in the target molecule the P-N bond is replaced by a P-C bond.



Z: side chains of penicillins

C_1: Y=CO_2H
C_2: Y=CH_2CO_2H
S_1: Y=SO_3H

Figure 24

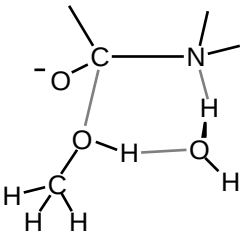
Our first aim is to prepare the four-membered phosphinic acid **C_1** bearing a carboxylic acid group. It is generally considered that the C-P bond is longer than C-N bond, therefore, compared to the classic structure of penicillins where the lactam carbonyl carbon is separated from the center of the acidic group by two atoms (N, C), **C_1** could also possess the "correct molecular shape" despite the separation between phosphorus atom and the center of the acidic group with only one carbon atom. On the other hand, we also tried to prepare its homolog **C_2**. As shown in monobactams, the sulfonic acid function is covalently bound to the lactam nitrogen atom, we thus designed the target molecule **S_1**. The molecular docking performed by our partner Dr G. Dive and his group at Liège University through a simple fit of a four-membered phosphinic acid like **S_1** into the enzymatic cavity of D,D-carboxypeptidase of *Streptomyces* R61 has further confirmed that the distance between phosphorus and the center of sulfonic acid group is adequate.

1.3.2 Synthesis of bicyclic aza-β and γ-lactams

We have shown above that γ-lactam mimics of penicillin, cephalosporin or penem antibiotics did not show any bacterial activity even when the γ-lactam function was made reactive towards hydrolysis. The exciting discovery of the pyrazolidinone-derived antibacterial agents which can be considered as "aza-γ-lactams" by the Lilly group indicated the replacement of a carbon atom by a nitrogen atom was a decisive structural change for the expression of antibacterial activity.

It has been proposed by G. Dive *et al.*[69b] that the acylation reaction between enzymes and β-lactam compounds could proceed according to a concerted one-step mechanism. They have performed *ab initio* studies of several transition state models which are based on the two interacting entities, *i.e.* β or γ-lactam substrates and nucleophile MeOH-H_2O (Figure 25, Table 1). Their calculations demonstrated that the presence of an additional heteroatom (N or O)

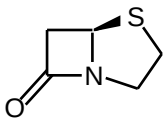
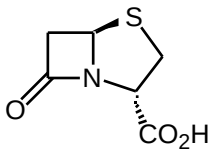
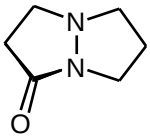
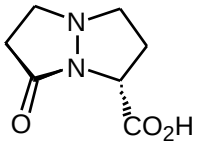
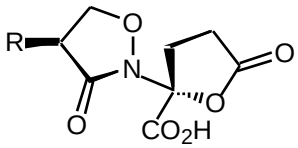
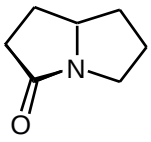
adjacent to the lactam nitrogen greatly decreased the deformation energy in the transition state with respect to that of the parent γ-lactams. As a result, reactions which lead to ring opening should proceed much more readily than do similar reactions on γ-lactams. These so-called *soft* atoms can absorb a geometric deformation much more readily than a sp^3 carbon in the course of the ring opening process, this leading to a lower transition state energy.



TS in the opening of lactam ring by MeOH-H_2O

Figure 25

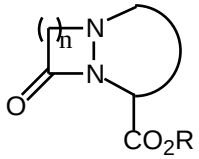
Table 1: Activation barrier calculations of β and γ-lactams*

Substrate	ΔE	ΔG	Substrate	ΔE	ΔG
	21.485	38.729		21.485	38.729
	27.748	44.719		19.144	37.928
 Lactivicin	18.022	37.463		33.181	50.710

* *Ab initio* calculations were performed within the minimal MIN-1' basis set; ΔE (kcal/mol): internal energy difference; ΔG (kcal/mol): free energy difference, calculated at T=298 K and P=1 atm.

Thus bicyclic aza-β-lactam derivatives should also be a class of potential antibacterial agents. Some groups have already been involved in the synthesis of aza-β-lactam derivatives.[34] In this project we shall try to develop practical synthetic routes to scaffolds which could be

readily transformed into molecules inhibiting serine proteases, and in particular bacterial D, D-peptidases and β-lactamases (Figure 26).



n = 1,2
R: protecting group

Figure 26

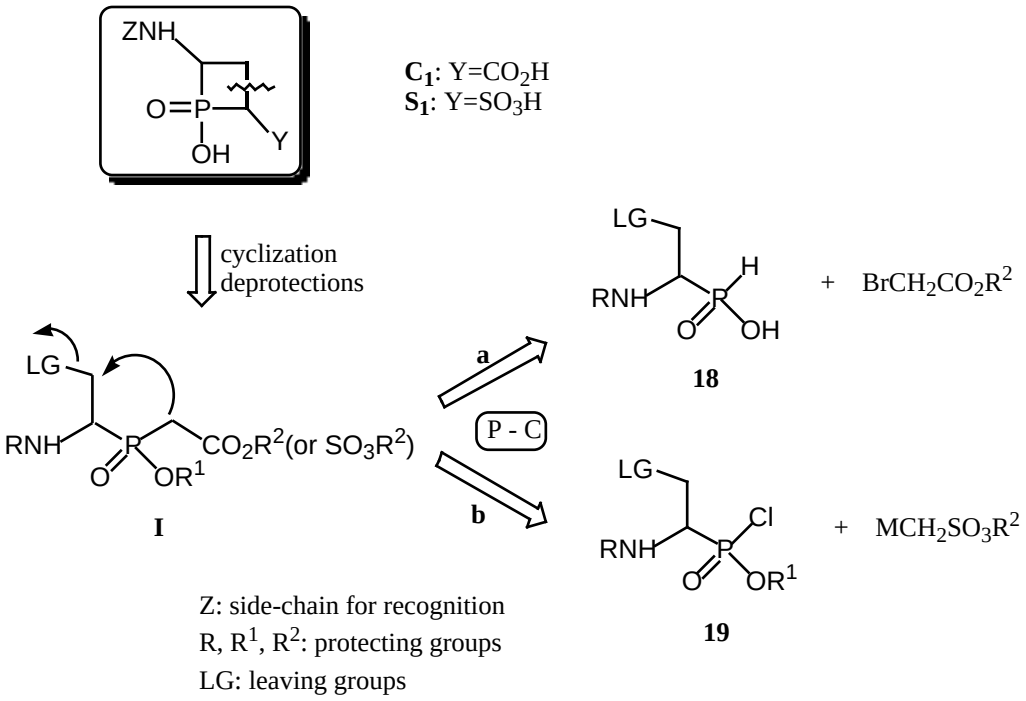
Part I

Chapter 2

Route a: Synthesis of a potential precursor of four-membered cyclic carboxyphosphinic acids via a silylphosphonite

2.1 Strategy: general scheme

Our approach towards target molecules **C_1** and **S_1** consisted of performing the cyclization to a four-membered ring at the end of the synthesis (Scheme 14). The proton of the methylene group between the phosphoryl and ester functionalities shown in the intermediate **I** should be quite acidic so that we could avoid a β-elimination. In the presence of a base, the conjugated carbanion could undergo an entropically favorable intramolecular cyclization. We considered two possible disconnections to form the crucial C-P bond. They correspond respectively to the alkylation of a nucleophilic phosphorus derivative **18** with alkyl bromoacetate (route **a**), or the reaction of an electrophilic phosphorus compound **19** with organometallic reagents (route **b**).



Scheme 14

In this chapter, we shall present our contribution to the preparation of the precursor **I** bearing a carboxylic ester group which could lead to the formation of four-membered **C_1** (route **a**).

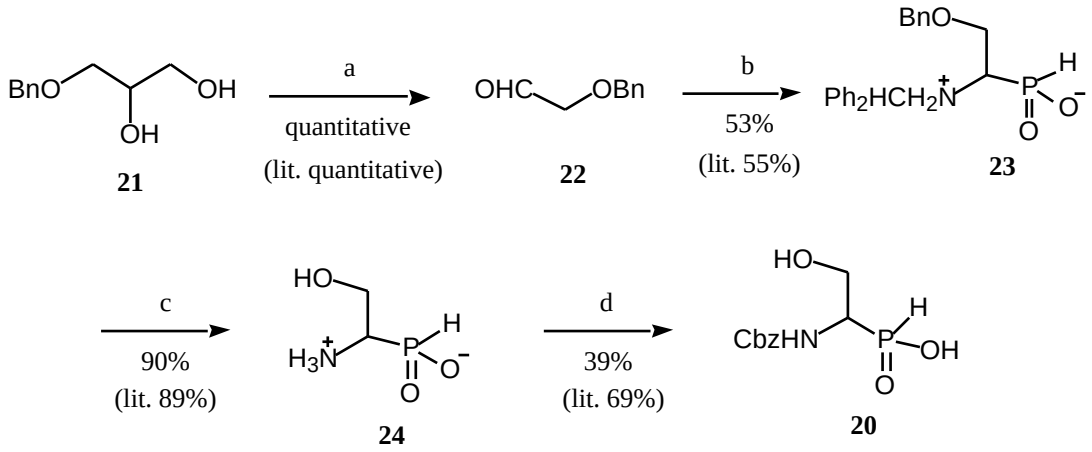
2.2 Synthesis of the phosphonous acid analog of serine 20

Intermediate **18** can be described as a phosphonous acid analog of serine **20** in which the amine group is protected with benzylcarbamate, the hydroxyl group could be transformed into an appropriate leaving group (Scheme 15).

18 **20**

Scheme 15

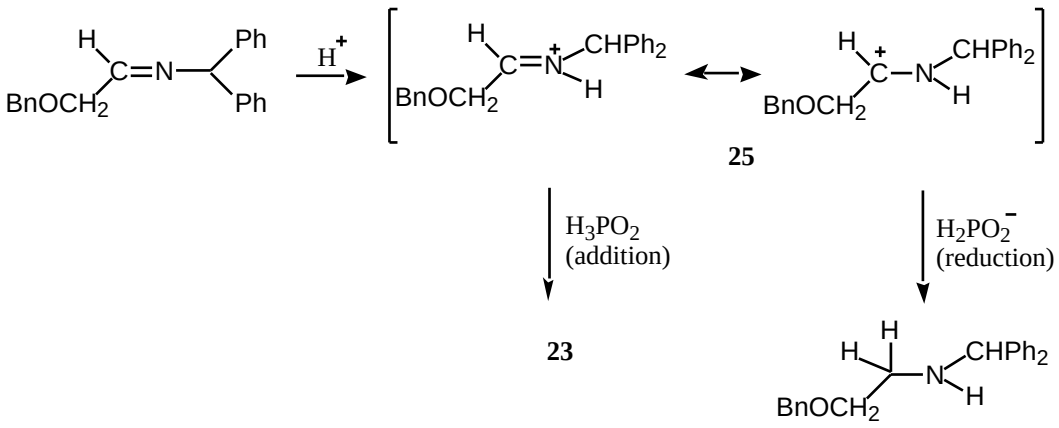
Kessabi J.[69a] has discussed in his dissertation the details of this synthetic sequence. We followed his procedures and obtained **20** in comparable yields, except for the last step which gave a poor yield (Scheme 16).



Reagents and conditions: a. $NaIO_4/SiO_2$, CH_2Cl_2-H_2O, rt, 1 h; b. Ph_2CHNH_2.HCl, 50% aq. H_3PO_2, EtOH/H_2O (1/1), reflux, 4 h; c. 18% HCl, reflux, then EtOH/propylene oxide; d. $ClCO_2Bn$, 2M NaOH, 0°C, 6 h.

Scheme 16

Sodium periodate/wet silica gel in dichloromethane[70] is an efficient reagent for the oxidative cleavage of 1,2-diols (step a). In step b, a Mannich-type one-pot procedure has been applied to generate α-aminoalkylphosphonous acid **23**. The initial step of this reaction was the protonation of the imine to yield **25**. The role of the acid could also be to suppress a competing reduction of the imine by hypophosphite anion[71,72] (Scheme 17). In the present case neutral hypophosphorous acid was sufficiently nucleophilic to add to **25**.

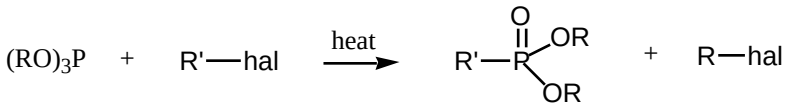


Scheme 17

2.3 Alkylation of 20 with methyl bromoacetate

2.3.1 Michaelis-Arbuzov rearrangement: general aspects

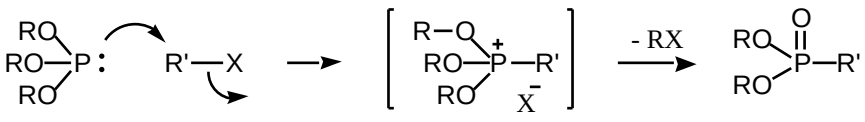
This is one of the most versatile pathways for the formation of C-P bonds and involves the reaction of an ester of trivalent phosphorus with an alkyl halide (Scheme 18):



R, R'=alkyl, aryl etc.
hal=Cl, Br, I

Scheme 18

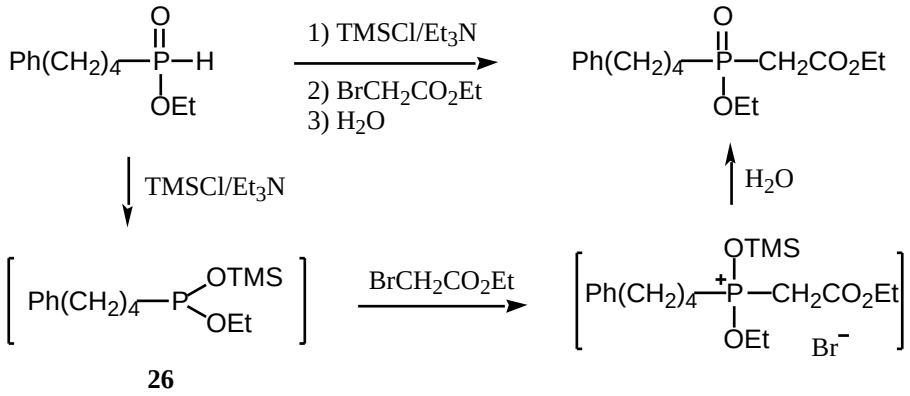
The rearrangement is widely employed for the synthesis of phosphonates, phosphonic acid esters and phosphine oxides. During the transformation, a trivalent phosphorus is converted into a pentavalent phosphorus. Arbuzov formulated a pentacoordinated phosphorus as the intermediate in the rearrangement. In general, the attack of R by X^- is viewed as a S_N2 reaction, whereas a carbonium ion mechanism can also operate (Scheme 19).[73]



Scheme 19

Thottathil and co-workers[74] described a very mild and simple method for the preparation of phosphinic acids from phosphonous acids using an intermediate- silylalkylphosphonite **26** (Scheme 20). Hexamethyldisilazane (HMDS) can also be used as an efficient silylating

reagent.[75] Apparently, the electron-donating TMS group reinforces the nucleophilicity of trivalent phosphite.[76]



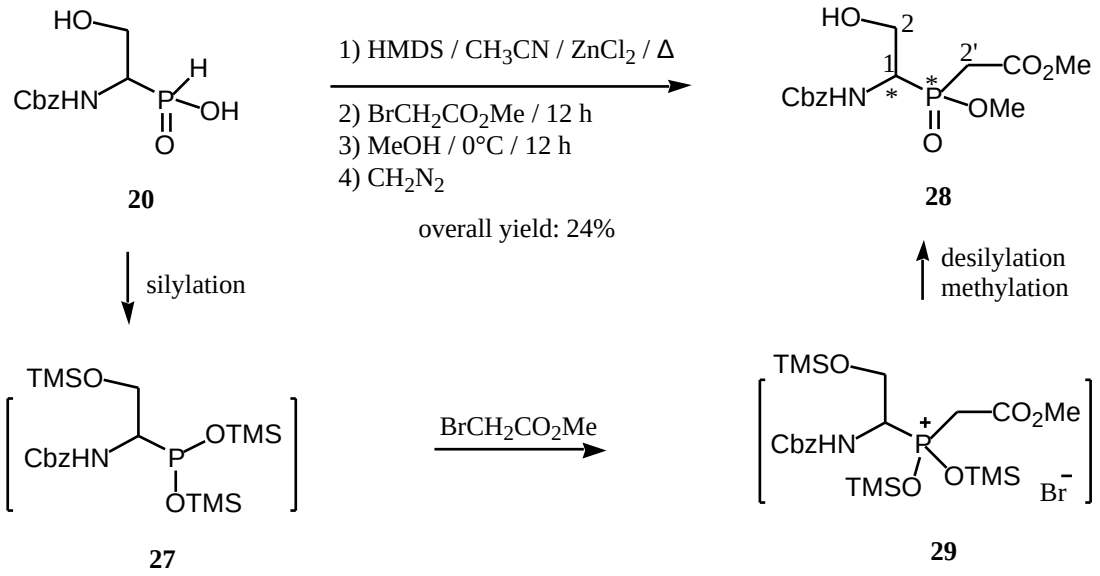
26

Scheme 20

2.3.2 Experimental results

As described in Kessabi's thesis, the alkylation of phosphonous acid **20** could be effected by using a silylalkylphosphite as nucleophile. HMDS was selected for this silylation step since it is a cheap and commercially available reagent and its handling does not need special precaution. However, HMDS is not very reactive and often a Lewis acid such as anhydrous $ZnCl_2$ has to be used.[77,78]

We then performed a one-pot procedure. HMDS was added to a solution of **20** and anhydrous $ZnCl_2$ in refluxing acetonitrile. The silylated intermediate **27** was then treated with $BrCH_2CO_2Me$. Desilylation in methanol yielded the corresponding α-aminoalkylphosphinic acid which was esterified with freshly prepared diazomethane.[79] In this way, methyl α-aminoalkylphosphinate **28** was obtained in 24% overall yield (Scheme 21).

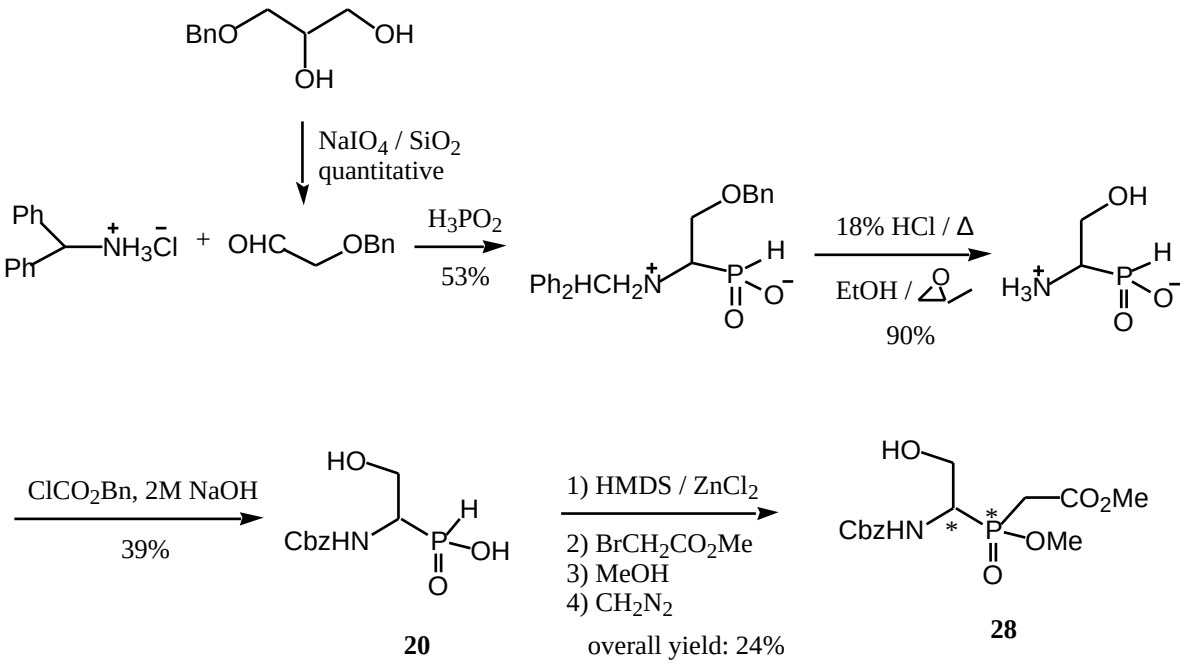


Scheme 21

Two inseparable diastereoisomers (3:2) were detected in the ^{1}H NMR spectroscopy due to the creation of a new chiral phosphorus center in compound **28**. For example, two doublets for NH (δ 6.70, 6.60, *J*=9.4 Hz) and two singlets for CO_2*Me* (δ 3.67, 3.65) were clearly visible in the ^{1}H NMR spectrum. $H_{2'}$ (m, 2H) appeared in the range of δ 3.19-3.09. Another spectral feature of **28** is the doublet of C_1(54.2 ppm, $^{1}J_{PC}$=108.4 Hz) and $C_{2'}$(37.0 ppm, $^{1}J_{PC}$=129.0 Hz) in the ^{13}C NMR spectrum. The large coupling constant values between carbon and phosphorus atoms are quite characteristic for organophosphorus compounds.

2.4 Conclusion

In summary, we described a moderately efficient synthetic pathway to prepare α-aminoalkylphosphinate **28** as a potential precursor towards four-membered carboxyphosphinic acids (5 steps, overall yield: 5%, Scheme 22):



Scheme 22

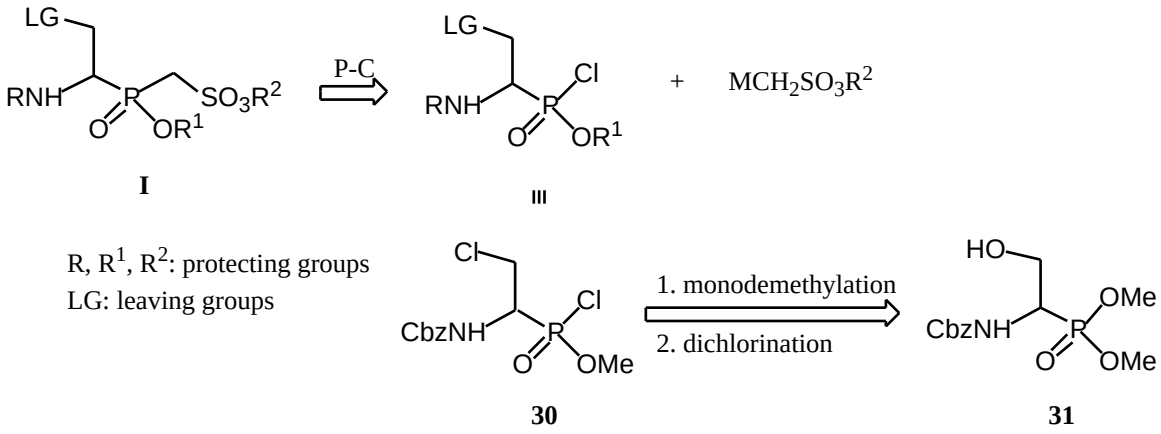
The route outlined above was found to be not very convenient because the yields of some steps were too low and some purifications were difficult. Another strategy (route **b**) will be described in the next chapter.

Chapter 3

Route b: Attempts on the synthesis of four-membered cyclic sulfophosphinic acids via a phosphonochloridate

3.1 Introduction

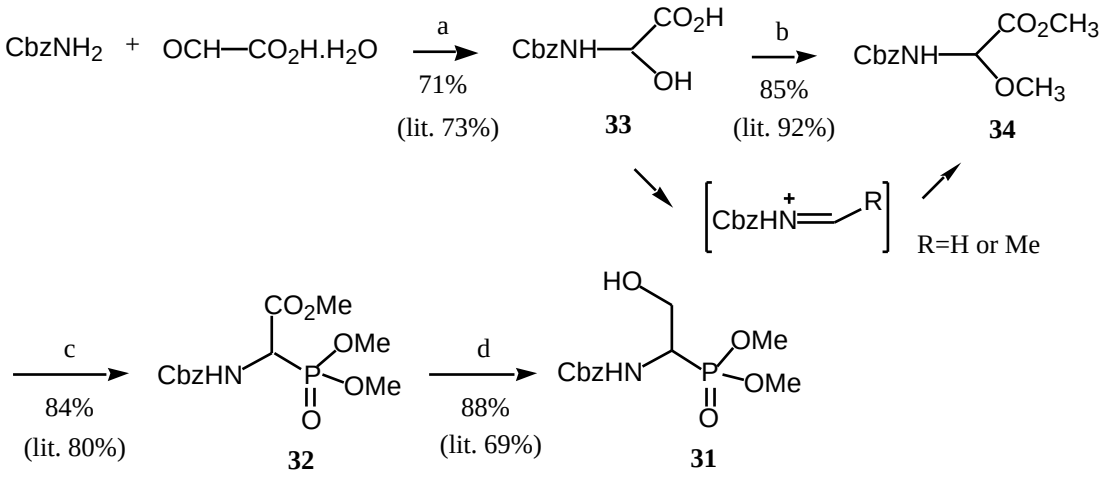
In this chapter, we will report our studies of route **b** (see Chapter 2, Part 2.1) which involves the formation of the P-C bond by the reaction of a phosphinic acid chloride with organometallic reagents. Chlorophosphonite **30** could be derived from compound **31** via a monodemethylation followed by chlorination of both alcohol and phosphinic acid (Scheme 23).



Scheme 23

3.2 Synthesis of dimethyl phosphonate 31

As described in the literature,[69a] the title compound **31** could be readily prepared in four steps starting from the commercially available benzylcarbamate and glyoxylic acid monohydrate (Scheme 24). Step b probably involved an acylimium cation generated by a catalytic amount of sulfuric acid. A type of Arbuzov reaction (see Chapter 2) occurred in step c. The methyl ester in **32** was easily reduced by $NaBH_4$ in the presence of LiCl. Obviously, the enhanced reactivity of $LiBH_4$ (generated *in situ*) is due to the greater Lewis acidity of Li^+ *vs* Na^+ (step d).



Reagents and conditions: a. Et_2O, rt, 12 h; b. MeOH, H_2SO_4, rt, 48 h; c. $P(OMe)_3/PCl_3$, toluene, 70°C, 18 h; d. $NaBH_4$/LiCl, THF/EtOH (1:1), rt, 16 h.

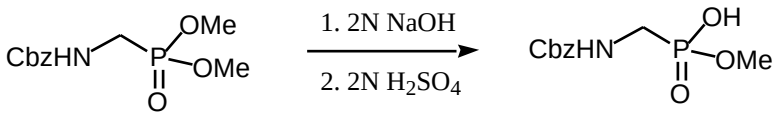
Scheme 24

The method outlined above has the following merits: firstly, the sequence directly leads to the N-protected benzylcarbamate. In view of its easy cleaving properties (*e.g.* by hydrogenolysis), introduction of a variety of acylamino side chains of penicillins and cephalosporins should be achievable, thus providing access to many phamacologically interesting compounds; secondly, in each step the corresponding product could be purified by recrystallization. Compound **31** could be readily prepared in large quantities.

3.3 Monodemethylation of 31

3.3.1 Literature

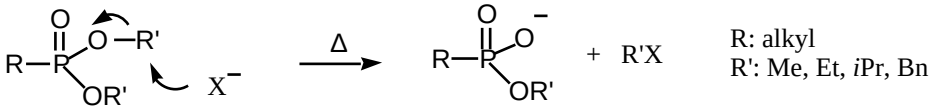
It has been reported that dimethyl phosphonate could undergo partial hydrolysis in aqueous NaOH (Scheme 25).[58] This method is not suitable for compound **31** since a β-elimination could take place under basic conditions.



Scheme 25

We then turned our attention to a S_N2 type of process to effect the monodemethylation. As shown in Scheme 26, the partial cleavage of phosphinic acid diesters by treatment with inorganic salts offers an easy, selective and comparatively mild method for preparation of

monoesters. Clark *et al.*[80] reported that an ethoxyethanol solution of lithium chloride was most effective for monodebenzylation of dibenzyl phosphonates. From a practical standpoint, ethoxyethanol is usually the preferred solvent since most lithium salts being formed crystallize from the reaction solution. This anionic monodealkylation reaction could also be effected by using sodium iodide[81,82] or lithium iodide.[83] Holy[84] mentioned that on treatment with excess lithium azide in dimethylformamide at 100°C, the cleavage to monoester is complete within 1-3 hours, much faster than with LiI or NaI, which reached completion usually after 10-12 hours at 100°C.

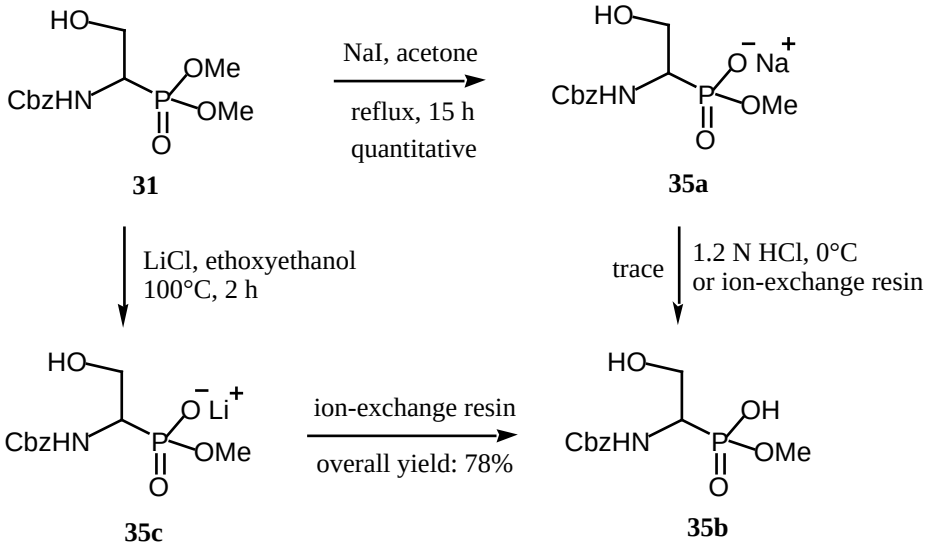


Inorganic salts and solvents:
LiCl/ethoxyethanol, NaI/acetone or 2-butanone,
LiI/THF, or LiN_3/DMF

Scheme 26

3.3.2 Experimental results

We first performed the monodemethylation of **31** by use of NaI in acetone. After refluxing overnight, the sodium salt **35a** was obtained in quantitative yield. However, subsequent acidification (dilute HCl at low temperature or acid-ion exchange resin) only gave a trace of phosphinic acid **35b** (Scheme27).



31 **35a** **35c** **35b**

Scheme 27

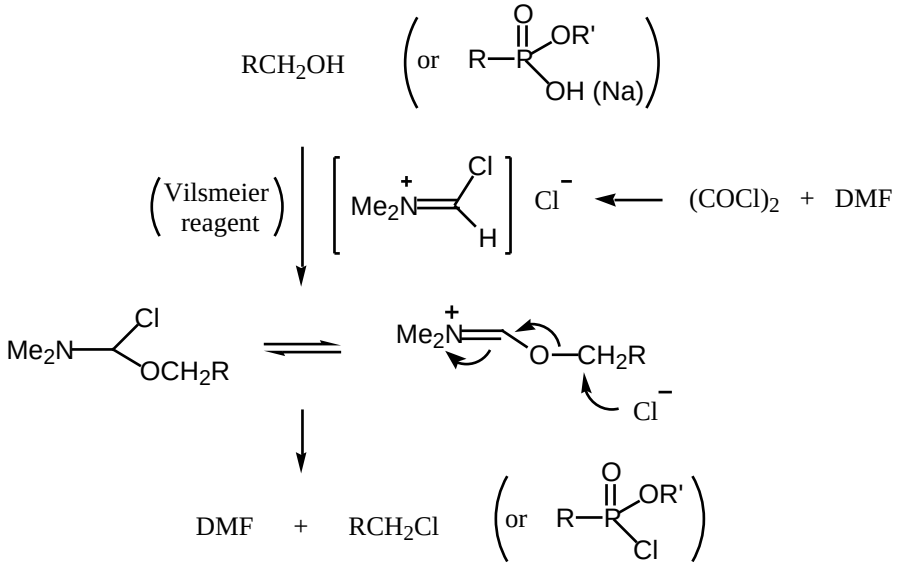
In the course of decomposition, the hemi-ester is probably reduced as shown in Scheme 28.[85] The aqueous solution turned red during workup, which indicated the presence of free iodine.

Scheme 28

On the other hand, LiCl-mediated monodemethylation of **31** worked efficiently in ethoxyethanol. The lithium salt **35c** directly crystallized from the reaction mixture after heating at 100°C for 2 h. Hydroxyphosphinic acid **35b** was obtained in 78% overall yield by the exchange with acid-ion resin (Scheme 27).

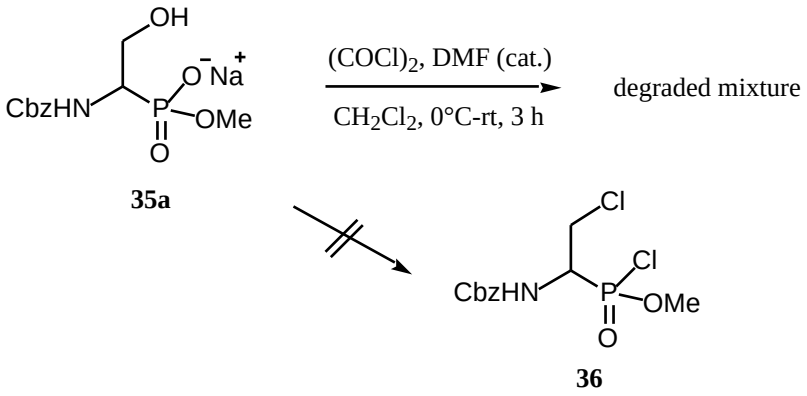
3.4 Attempts on dichlorination

It has been reported that the Vilsmeier reagent (prepared from *N*, *N*-dimethylformamide and oxalyl chloride)[86] could be utilized for the chlorination of both alcohol[87] and phosphinic acid[88] functional groups (Scheme 29).



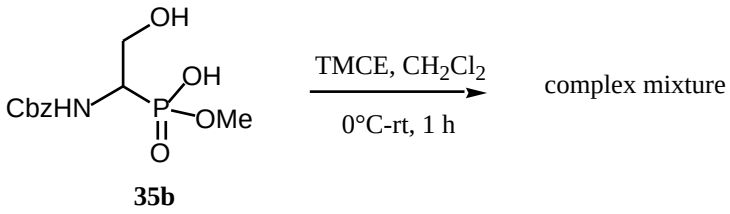
Scheme 29

The sodium salt **35a** was then treated with oxalyl chloride in the presence of a catalytic amount of DMF in CH_2Cl_2 (Scheme 30). The reaction was controlled by ^1H NMR analysis. After 3 h, we only observed a very complex mixture and no more evidence for the presence of the methoxy group.



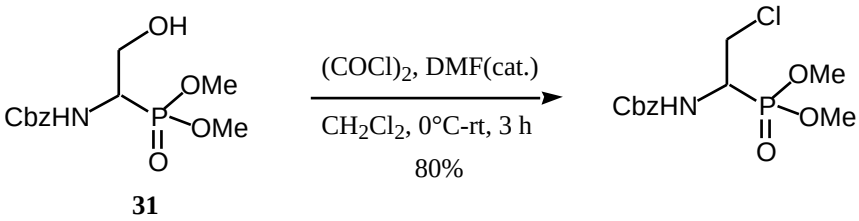
Scheme 30

Tetramethylchloroenamine (TMCE) is an efficient chlorinating agent for preparation of both alkyl chlorides and acyl chlorides.[89,90] We thus attempted the chlorination reaction by using TMCE. Unfortunately, a similar result as with $(COCl)_2$ was observed (Scheme 31).



Scheme 31

Thus, the simultaneous formation of an alkyl chloride and a phosphinic acid chloride could not be achieved although the alcohol group in dimethyl phosphonate **31** could be readily chlorinated by using the same conditions (Scheme 32).



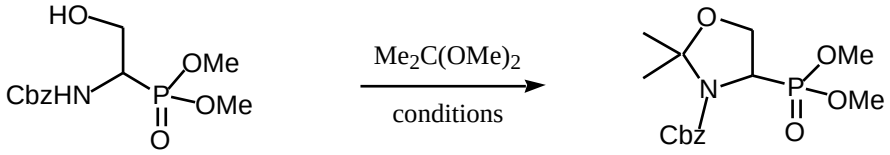
Scheme 32

We then considered to effect the reactions separately. In order to direct the following reactions specifically at the phosphorus center, we decided to protect simultaneously the O-H and CON-H functionalities in **31** by forming an oxazolidine derivative. Another virtue of this tactic is that the deprotected hydroxyl group could be transformed into many other good leaving groups, such as OTs, OMs, OTf *et al.* prior to cyclization.

3.5 Formation of oxazolidine phosphonochloridate 37 and subsequent reaction with carbon-nucleophiles

3.5.1 Synthesis of oxazolidine phosphonate 38

Dimethyl phosphonate **31** reacted readily with 2, 2-dimethoxypropane (DMP) under acid-catalyzed conditions to give the *N*, *O*-acetal **38** (Scheme 33, Table 2). The formation of the oxazolidine ring was better effected with TsOH in refluxing benzene (Entry 2) than with BF_3-Et_2O in acetone (Entry 1).[91]



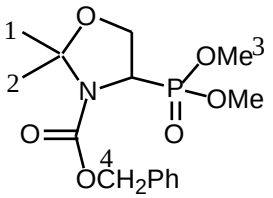
31 **38**

Scheme 33

Table 2: Formation of the oxazolidine ring in **31**

Entry	Conditions	Yield (%)
1	Et_2O-BF_3 (cat.), acetone, rt, 24 h	51
2	TsOH (cat.), benzene, reflux, 9 h	85

The ^1H NMR spectrum of **38** showed two sets of signals at ambient temperature. Upon raising the probe temperature to 50°C, these signals merged into one (Table 3). Slow *pseudo*-rotation of oxazolidine ring relative to the NMR time scale may be responsible for the non-equivalence of the protons.[92]



38

Figure 27

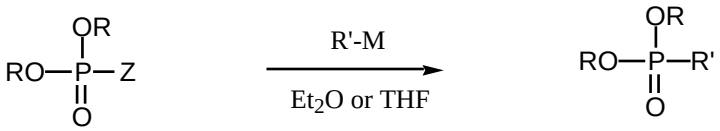
Table 3: ^{1}H NMR data of **38** at 20°C and 50°C

Proton	20°C (δ)	50°C (δ)
4	5.19, 5.15 (s)	5.18 (s)
3	3.75 (d, $^{3}J_{P}$=10.6 Hz)	3.74 (d, $^{3}J_{P}$=10.5 Hz)
	3.59 (d, $^{3}J_{P}$=10.5 Hz)	
1	1.75, 1.70 (s)	1.67 (s)
2	1.56, 1.48 (s)	1.53 (s)

3.5.2 Chlorination and coupling reaction

3.5.2.1 Carbon-nucleophiles: literature survey

Tremendous progresses in the chemistry of carbanionic displacement reactions at an electropositive pentavalent phosphorus center have been made in recent years.[93] This type of nucleophilic substitution at phosphorus has proven to be a powerful method for the generation of a C-P bond (Scheme 34).

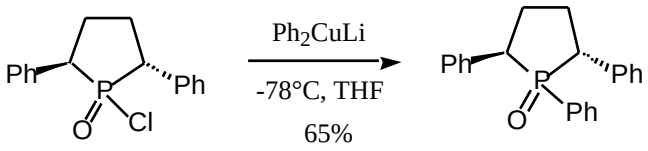


R = alkyl, phenyl
R' = alkyl, alkynyl, aryl, heteroaryl
Z = RO, F, Cl
M = Li, Mg

Scheme 34

Grignard reagents are known to behave as less effective carbanions with respect to their corresponding organolithium reagents and they react with pentavalent phosphorus compounds at relatively high temperature (-20~0°C) with often low selectivity. However, organolithium compounds can readily and smoothly react with P(V)-electrophiles at low temperature (generally -78°C) in a more selective manner, thus avoiding or minimizing the indesired side reactions. Consequently, Grignard reagents have been progressively superseded by lithium reagents, which are nowadays almost exclusively employed.[93]

The coupling reaction of a chlorophosphinite with diphenyl lithiocuprate in the synthesis of a devised chiral phospholanyl ligand has also been reported (Scheme 35).[94]

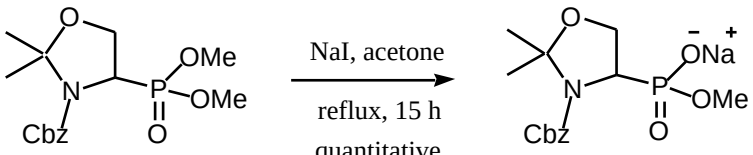


Scheme 35

3.5.2.2 Experimental results

3.5.2.2.1 Chlorination with $(COCl)_2$

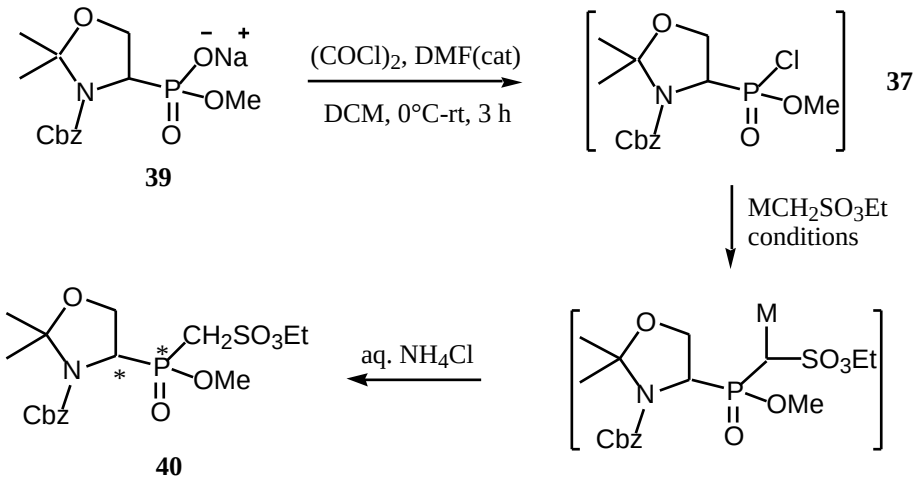
Selective monodemethylation of phosphonate diester **38** with NaI in refluxing acetone gave monoester **39** in essentially quantitative yield (Scheme 36).



38 **39**

Scheme 36

In view of the presence of the acid-sensitive oxazolidine, the sodium salt **39** was directly treated with oxalyl chloride in the presence of a catalytic amount of DMF to generate the crude phosphonochloridate **37**. The first coupling reaction was then carried out with α-lithiatedethyl methanesulfonate (prepared from CH_3SO_3Et and *n*BuLi) in THF at -78°C. It is noteworthy that two equivalents of organolithium reagents were required in this phosphorylation step. This is due to the higher acidity of the coupling product **40** which consumed one equivalent of organolithium reagent. Unfortunately, this procedure only gave **39** in an overall yield of 15% (Scheme 37, Table 4, Entry 1).



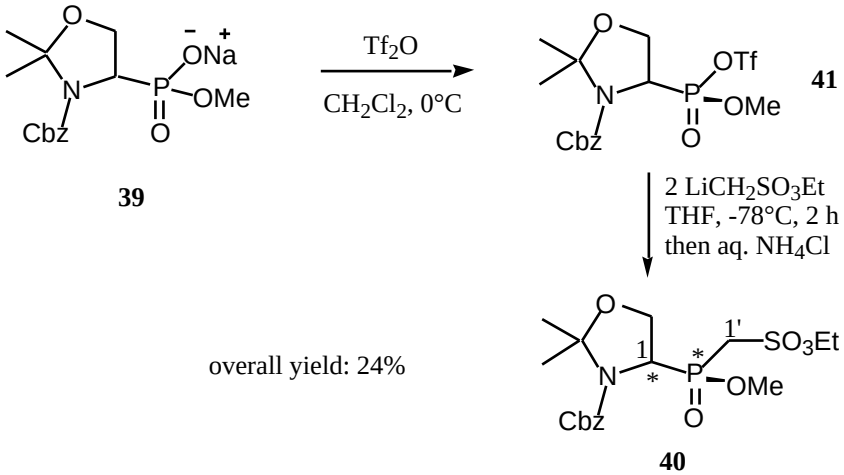
Scheme 37

Table 4: Phosphorylation with organometallic reagents

Entry	MCH_2SO_3Et	Conditions	Overall yield (%)
1	2 equiv $LiCH_2SO_3Et$	-100°C~-78°C, THF, 2 h	15
2	1 equiv Li_2CHSO_3Et	-100°C~-78°C, THF, 2 h	19
3	3 equiv $CuLi(CH_2SO_3Et)_2$	-78°C~-40°C, THF, 2 h	23
4	2 equiv $CuCH_2SO_3Et$	-78°C~-40°C, THF, 2 h	trace

The use of a dianion (Entry 2) or an organocopper reagent (Entry 3, 4) did not give better yields.

The yields were also low when we used the more reactive triflate, which was generated *in situ* from **39** and Tf_2O (Scheme 38).



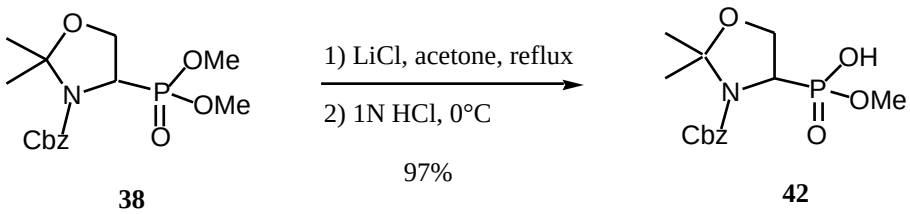
Scheme 38

^{1}H NMR spectrum of **40** showed the presence of two diastereoisomers with a 1:1 ratio. H_1 and $H_{1'}$ appeared as a multiplet in the range of δ 3.98-4.22; in the ^{13}C NMR spectrum the corresponding carbons gave two doublets respectively, with large coupling constant values (C_1: 56.9 ppm, d, $^{1}J_{PC}$=115.7 Hz; $C_{1'}$: 49.9 ppm, d, $^{1}J_{PC}$=75.0 Hz).

3.5.2.2.2 Chlorination with TMCE

3.5.2.2.2.1 Preparation of phosphinic acid 42

As described earlier, the acidification of the sodium salt derived from the corresponding dimethyl phosphonate by reaction with NaI was problematic (see Part 3.3.2). Therefore, in the present case monodemethylation of **38** was effected by treatment with LiCl. Acetone was a good solvent for this reaction since the corresponding lithium salt crystallized from the reaction solution after refluxing overnight. In the course of the acidification, partial cleavage of oxazolidine ring was observed when treated with dilute HCl at rt. Upon lowering the temperature to 0°C, phosphinic acid **42** was obtained in excellent yield (Scheme 39).

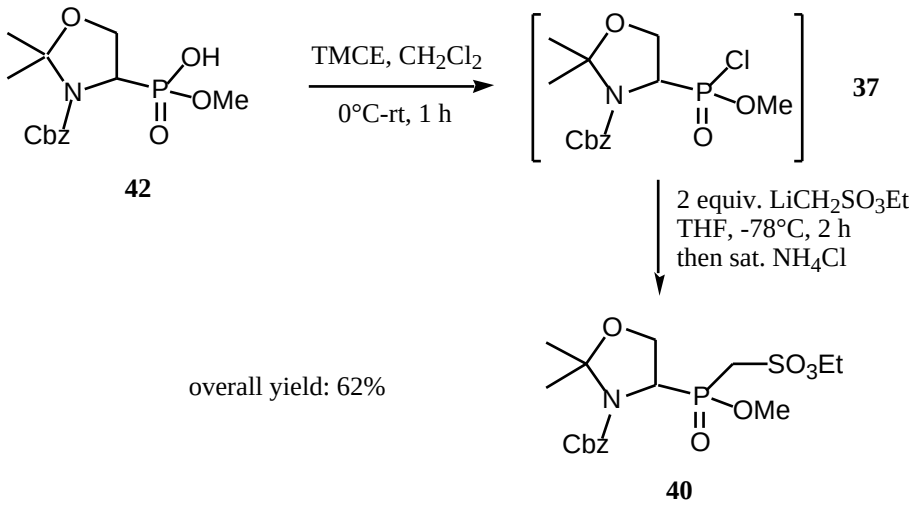


38 **42**

Scheme 39

3.5.2.2.2.2 Chlorination and coupling reaction

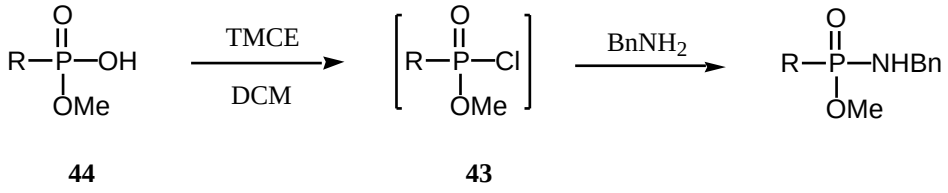
Phosphinic acid **42** was transformed smoothly and cleanly into phosphonochloridate **37** by reaction with TMCE in CH_2Cl_2, then addition of 2 equiv of organolithium reagent $LiCH_2SO_3Et$ gave **40** in a remarkably improved yield (Scheme 40).



Scheme 40

Therefore, chloroenamine also showed its efficiency in phosphorus chemistry. Compared to other classical methods (*e.g.* using PCl_5,[95] $SOCl_2$,[96] $(COCl)_2$[97,98]), it has the following merits: it is specifically applicable to acid-sensitive substrates: the reaction is performed in mild and neutral medium; it is easy to monitor the reaction by ^1H NMR; it produced a relatively inert by-product $Me_2CHCONMe_2$.

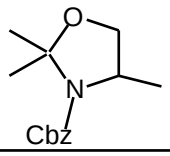
Good results with regard to syntheses of some alkyl halides and acyl halides by using TMCE have been obtained in our group.[90,99] We have demonstrated on a few examples that it is also an excellent chlorinating agent in formation of phosphonochloridate **43** (Scheme 41, Table 5).



Scheme 41

Table 5: Formation of phosphoryl chlorides with TMCE

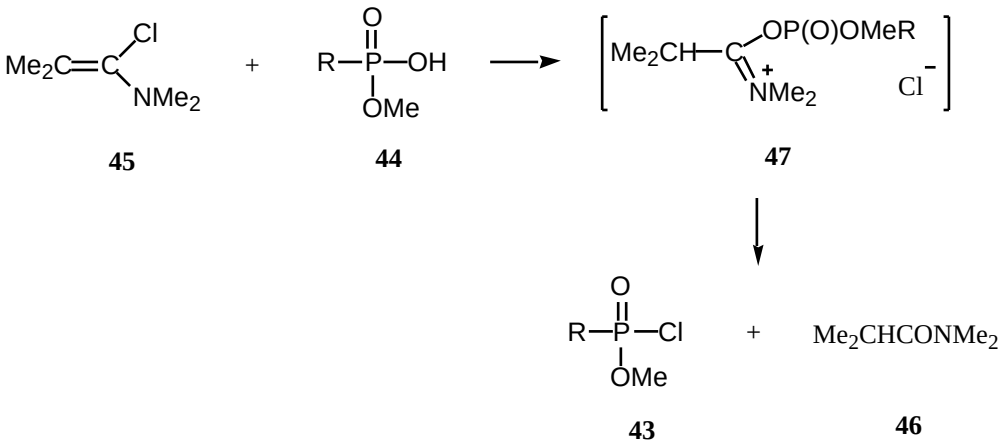
R	Yield (chlorination, %)[a]	Overall Yield (%)[b]
CH_3	100	82
CH_3SCH_2	91	89
EtO_2CCH_2	66	47

	100	85

a) Determined by ^{1}H NMR on the crude mixture with an internal standard; reactions were carried out at rt and were complete within 5 min.

b) Based on the isolated product.

Dichloromethane solutions of phosphinic acids were treated with equimolar amounts of α-chloroenamine **45**. At room temperature, the acids and chloroenamine were instaneously transformed into the phosphoryl chlorides **43** and *N*, *N*-dimethyl isobutyramide **46**. The reaction involves the rapid formation of **47**. Addition of chloride ion to the phosphoryl group in **47** followed by elimination of the amide **46** accounts for the formation of **43** (Scheme 42). Since the only by-product is the relatively inert amide **46**, purification of the phosphoryl chlorides will often be unnecessary.

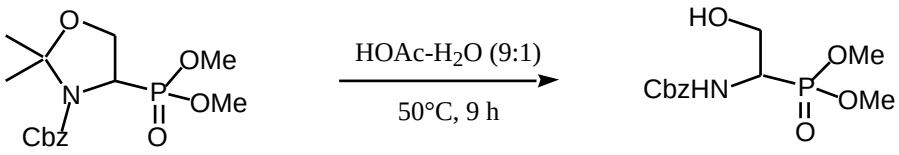


45 **44** **47** **43** **46**

Scheme 42

3.6 Cleavage of oxazolidine ring

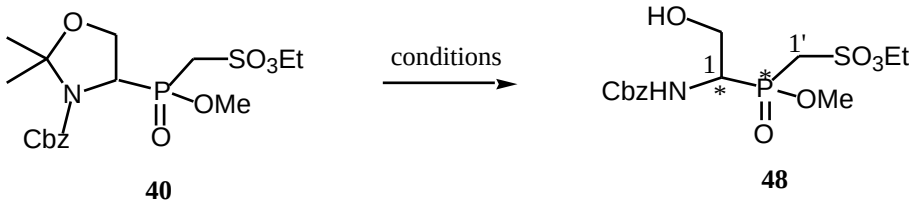
The *N*, *O*-acetal derivative could be hydrolyzed by gentle heating in aqueous acetic acid. Indeed, this reaction worked well with diester **38** (Scheme 43).



38 70%

Scheme 43

However it gave only 34% yield for compound **40** **(**Scheme 44, Table 6**,** Entry 1). Methanolysis of oxazolidine ring in the presence of TsOH[100] led to the recovery of the starting material (Entry 2), but the cleavage was successfully effected by treatment with trifluoroacetic acid at rt (Entry 3). The benzyl carbamate was unaffected under these conditions.[100]



40 **48**

Scheme 44

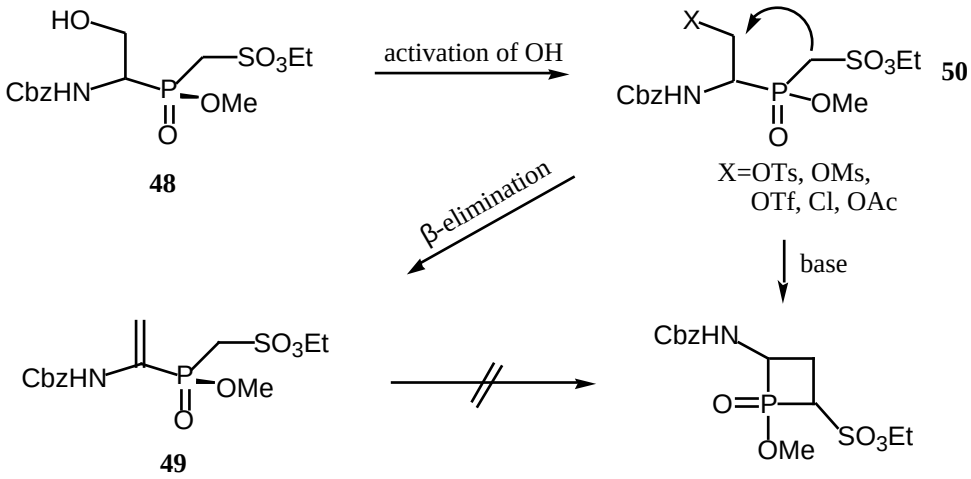
Table 6: Cleavage of oxazolidine ring in **40**

Entry	Conditions	Yield (%)
1	HOAc-H_2O (9:1), 50°C, 9 h	34
2	MeOH, TsOH, rt, 24 h	recovery of **S.M.**
3	DCM/TFA/MeOH (6/3/1), rt, 24 h	84

The ratio of the two inseparable diastereoisomers was 1:1 according to ^{1}H NMR spectroscopy: two doublets ($^3J_{PH}$=10.9 Hz) at δ 3.83 and δ 3.75 were assigned to the methoxy group; two triplets ($^3J_{HH}$=7.1 Hz) of OCH_2CH_3 were also clearly visible at δ 1.37 and δ 1.36 respectively. In the ^{13}C NMR spectrum, $C_{1'}$ gave two doublets (50.0 and 49.0 ppm, d, $^1J_{PC}$=74.9 Hz) corresponding to two diastereoisomers as well.

3.7 Activation of hydroxyl functionality and subsequent cyclization

In this paragraph, we shall describe our efforts to activate the hydroxyl group in **48** then effect cyclization under basic conditions. However, the β-hydroxyl group in **48** should be easily eliminated. Once this competitive reaction occurs, the following cyclization step on the elimination product **49** (4-endo-trigonal cyclization) should be disfavored according to Baldwin's rules[101](Scheme 45).



Scheme 45

Then we try to transform the hydroxyl function into many leaving groups which could help the cyclization (Table 7).

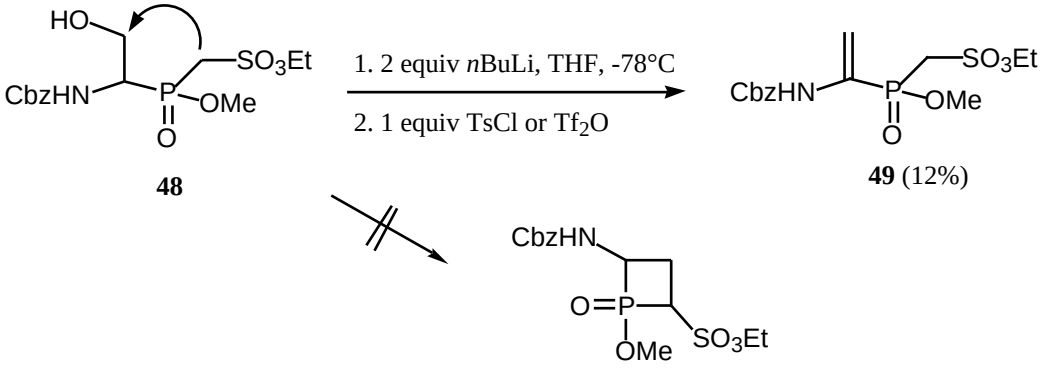
Table 7: Activation of OH in **48**

Entry	X	Reaction Conditions	Result
1	OTs	1.5 equiv TsCl, Py as solvent, 0°C-rt	degradation
2	OTs	1.5 equiv TsCl, 2 equiv Py, DCM, 0°C-rt	trace of **50**
3	OTs	1.2 equiv TsCl, 1.2 equiv Et_3N, DMAP(cat), DCM, 0°C-rt	50% **49**
4	OTs	1 equiv TsCl, 1 equiv *n*-BuLi, -78°C-rt	12% SM, 12% **49**
5	OTs	Ph_3P, DEAD, $Zn(OTs)_2$, benzene, 0°C-rt	trace of **50**
6	OMs	MsCl, Py, DCM, 0°C-rt	degradation
7	OMs	MsCl, Et_3N, DMAP (cat), 0°C-rt	48% **49**
8	Cl	TMCE, DCM, 0°C-rt	20% **50**
9	OAc	Ac_2O, Py, 0°C-rt	33% **50**

In most cases (Entry 1-7), the only product that could be isolated was **49**. We never observed any cyclized product. Compound **50** (X=Cl, OAc) proved to be very sensitive to both base and acid. For instance, the hydroxyl group in **48** could be converted to a chloride in only 20% yield using the mild chlorinating agent-TMCE. Partial degradation of **50** occurred upon purification on silica gel (Entry 8). A similar result was obtained for the acetylation procedure (Entry 9).

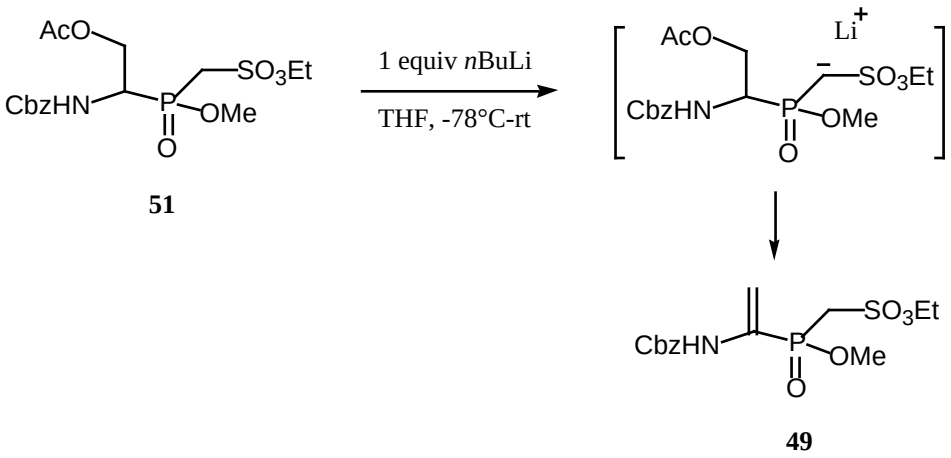
Since we failed to obtain the pure tosylate derived from **48**, we turned our attention to a "one-pot" reaction. Two equivalents of *n*BuLi were added to a solution of **48** in THF at -78°C,

after stirring for 30 min, one equivalent of TsCl or Tf_2O was added. However, this only gave **49** in poor yield. No cyclized product was formed (Scheme 46).



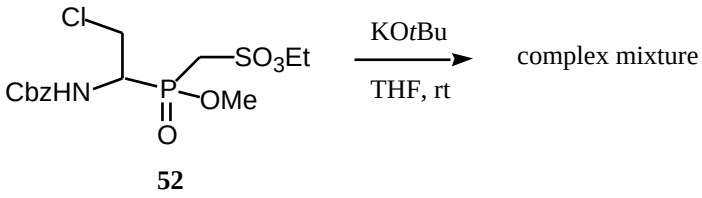
Scheme 46

We also attempt to cyclize **51** in the presence of *n*BuLi. Under these conditions, β-elimination occurred quickly (Scheme 47).



Scheme 47

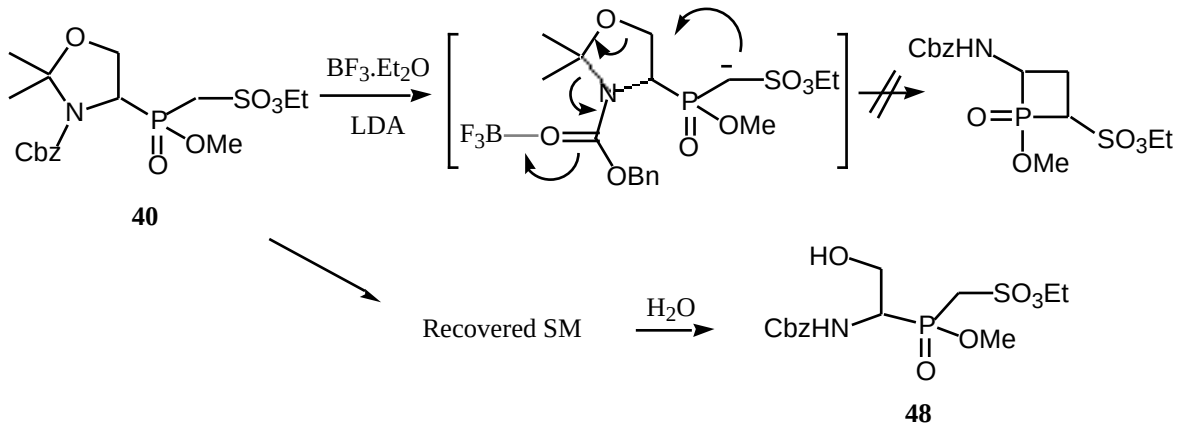
An intramolecular displacement of a tosylate or halide by a carbanion to furnish a cyclobutyl ketone has been studied by Crandall and Dodson.[102,103] KO*t*Bu had been chosen to generate the carbanion. We then utilized **52** as the precursor for cyclization which was run in the presence of KO*t*Bu in THF. After stirring for several hours at room temperature, we obtained a complex mixture of products (Scheme 48).



52

Scheme 48

We then considered to effect the cyclization directly on the oxazolidine ring in the presence of Lewis acid-boron trifluoride etherate complex. However, the starting material **40** was recovered under these conditions and the oxazolidine ring was cleaved after aqueous workup (Scheme 49).

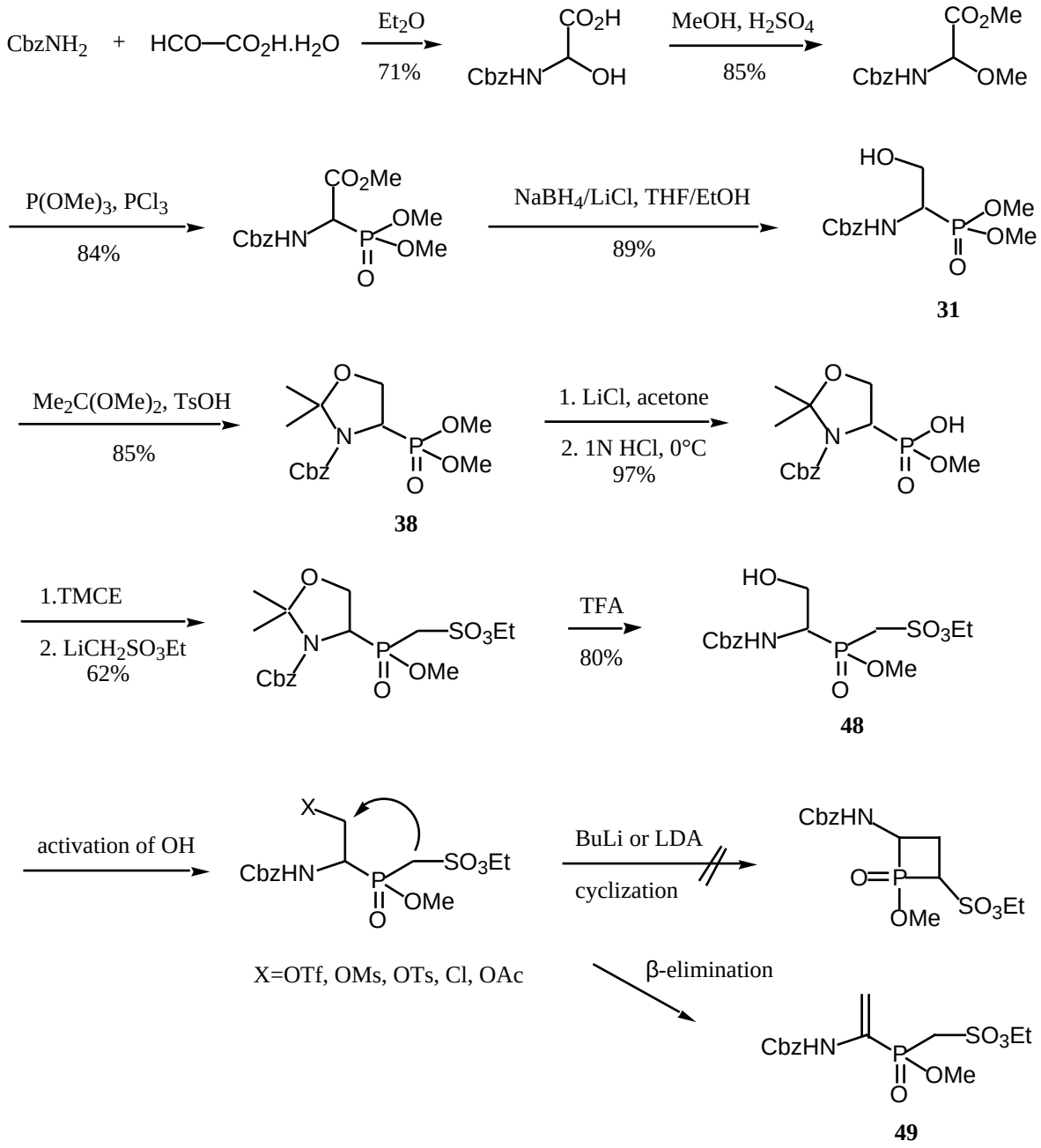


40 **48**

Scheme 49

3.8 Conclusion

In summary, we developed a practical synthetic route to an α-amino-β-hydroxyl phosphinic acid derivative **48** (8 steps, overall yield: 18%, Scheme 50):



Scheme 50

The sequence directly leads to the *N*-protected benzylcarbamate. Selective monoalkylation and chlorination on the dimethyl phosphonate **31** met with failure. In order to specifically direct the reactions at the *P* center, we protected both amino and hydroxyl groups as an oxazolidine derivative **38**. The monoalkylation worked then very well. The chlorination reaction with

classical reagents was problematic. It could be readily solved by the use of a new chlorinating agent developed in our group.

Tetramethylchloroenamine was found a highly effective reagent to prepare phosphinic acid chlorides from phosphinic acids. The reaction occurs under neutral conditions making it suitable for the chlorination of acid- or base-sensitive compounds.

Any attempt to effect the cyclization to a four-membered ring failed. The main side reaction was a β-elimination leading to the corresponding dehydro-α-aminophosphinic acid derivative (Scheme 50). However, the vinylphosphinates being formed in this chapter are probably synthetically useful (see Chapter 5).

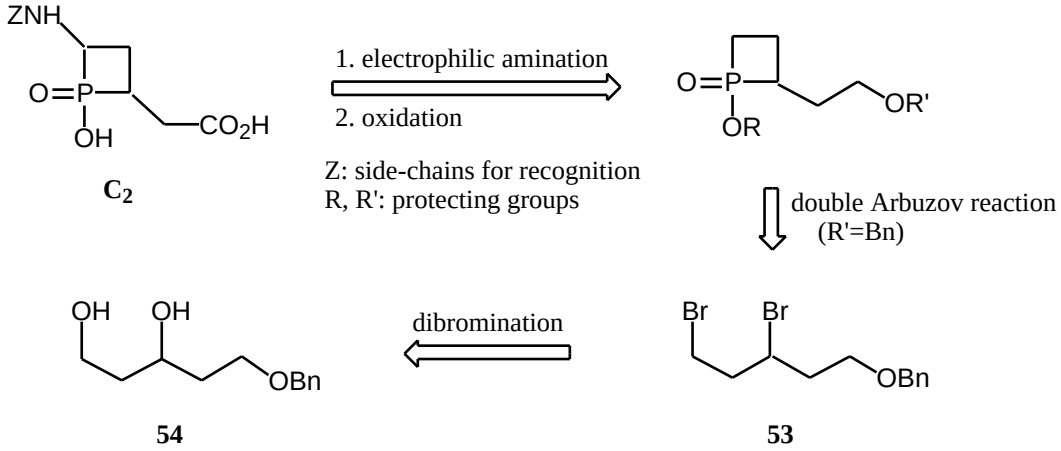
The intramolecular cyclization to a strained four-membered phosphinic acid could not be achieved after modification of substituents. We then decided to form the ring at an earlier stage of the synthesis. This will be discussed in the next chapter.

Chapter 4

Attempts on the synthesis of four-membered cyclic carboxyphosphinic acids via a double Arbuzov reaction

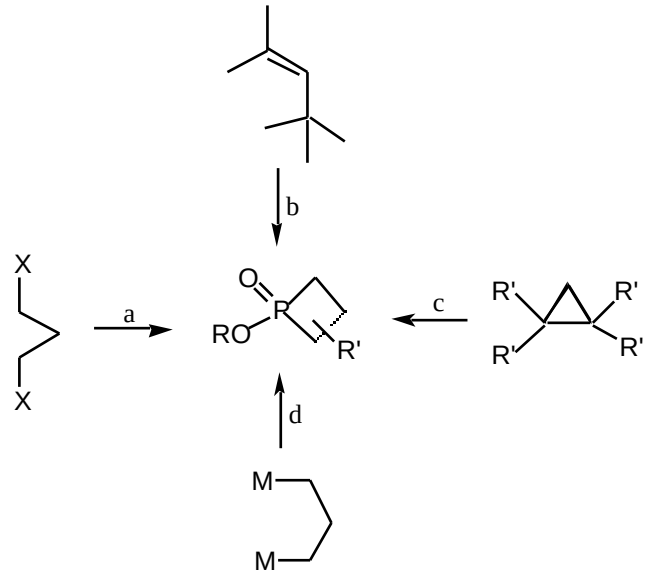
4.1 Strategy and literature survey

We also studied a third route which consists of forming cyclic carboxyphosphinic acids from a dibromide precursor **53** via a double Arbuzov reaction at an early stage of the synthesis. The target molecule **C_2** could then be synthesized after electrophilic amination followed by oxidation of the hydroxyl group. Dibromide **53** should be easily prepared from diol **54** (Scheme 52).



Scheme 52

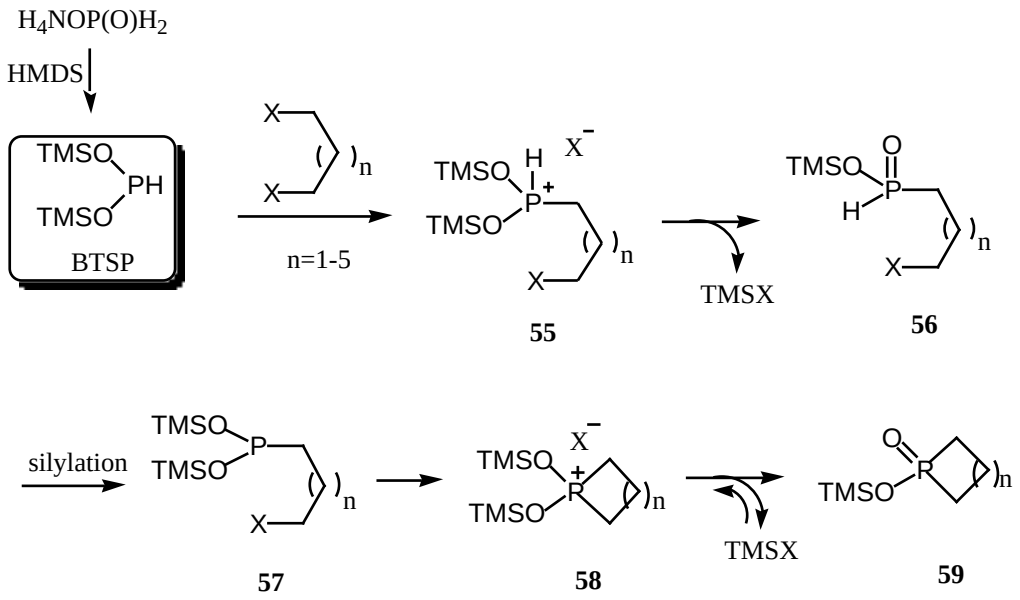
The preferred method for the synthesis of cyclic phosphinic acids varies depending on the ring size and the substitution pattern. Approaches that have been used for four-membered phosphinic acids are summarized in Scheme 53. The intramolecular, nucleophilic attack on a phosphonyl dichloride (reaction a) was one of the early syntheses of a cyclic phosphinic acid, but this strategy requires several steps and the overall yields are low.[104] The reaction of a phosphenium ion with a substituted olefin (reaction b) also provides access to phosphetanic acids.[105,106] This approach is limited to alkylated four-membered cyclic phosphinic acids due to the requirement for a carbocationic rearrangement. The same limitations also characterize the insertion of a phosphenium ion into a cyclopropane ring (reaction c).[107] An approach providing more flexibility in the ring size of the synthesized cyclic phosphinic acid is based on the reaction of the dimetallic species with dichlorophosphonate (reaction d).[108]



a. (i) $P(OR)_3$ (ii) HBr (iii) PCl_5 (iv) Mg (v) H_3O^+;
b. (i) $PCl_3.AlCl_3$ (ii) H_2O;
c. (i) *i*-$Pr_2NPCl_2.AlCl_3$ (ii) HCl, H_2O;
d. $ROP(O)Cl_2$

Scheme 53

Of particular interest is the work of Frost and co-workers,[109] who developed a route to cyclic phosphinic acids which involved the double Arbuzov reaction of bis(trimethylsiloxy)phosphine (BTSP) with dielectrophiles. Generally, alkyl bromides are the best suited electrophilic centers for the reaction. This methodology appears to be the most versatile and convenient so far. As shown in Scheme 54, BTSP was generated from ammonium hypophosphite and hexamethyldisilane (HMDS). The intermolecular reaction of one electrophilic center with the *in situ* generated BTSP could lead to phosphonium ion **55**. In the presence of the silylating agent, intermediate **56** could be converted to bis(trimethylsilyl)phosphonite **57** at a rapid rate. Subsequent intramolecular attack by phosphorus on the second electrophilic center in phosphonite **57** and collapse of the resulting phosphonium ion **58** were the final steps required for the formation of cyclic phosphinic acid **59**.



Scheme 54

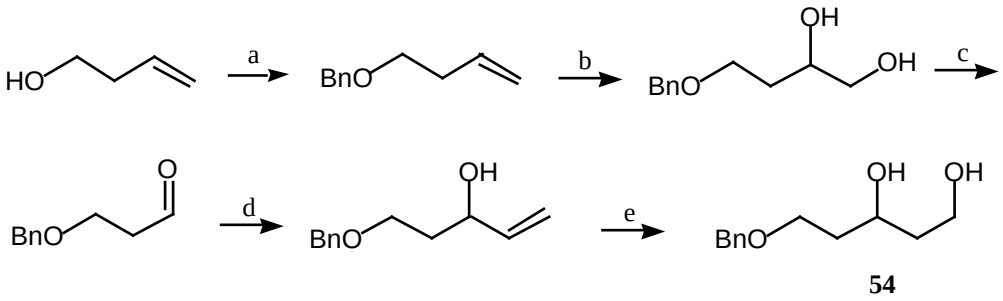
As a result, this double Arbuzov reaction with BTSP became our ultimate choice in the new synthetic plan.

4.2 Synthesis of dibromide precursor 53

4.2.1 Preparation of diol 54

4.2.1.1 A known method

The synthetic procedure of 1,3-diol **54** has been described in the literature (Scheme 55).[110,111]



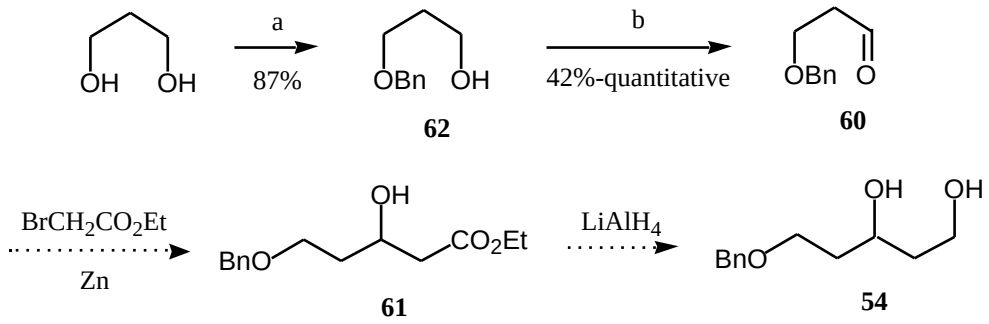
Reagents and conditions: a. BnBr, NaH/THF, rt; b. $KMnO_4$/acetone-H_2O, 0°C; c. $NaIO_4$/THF-H_2O, rt; d. CH_2=CHMgBr/THF, 0°C; e. BH_3.THF/THF, 0°C, then H_2O_2-2M aq. NaOH, rt

Scheme 55

We did not reproduce this rather long sequence, but rather tried a more concise approach.

4.2.1.2 Starting from 1,3-propanediol

Our initial idea was to perform a Reformasky reaction on aldehyde **60** to construct the five-chain skeleton required for **54**. The ester group in **61** should be easily reduced by $LiAlH_4$. Indeed, monobenzylation of 1, 3-propanediol could be readily accomplished in the presence of silver(I) oxide.[112] Subsequent oxidation gave aldehyde **60** in excellent yields (Scheme 56).



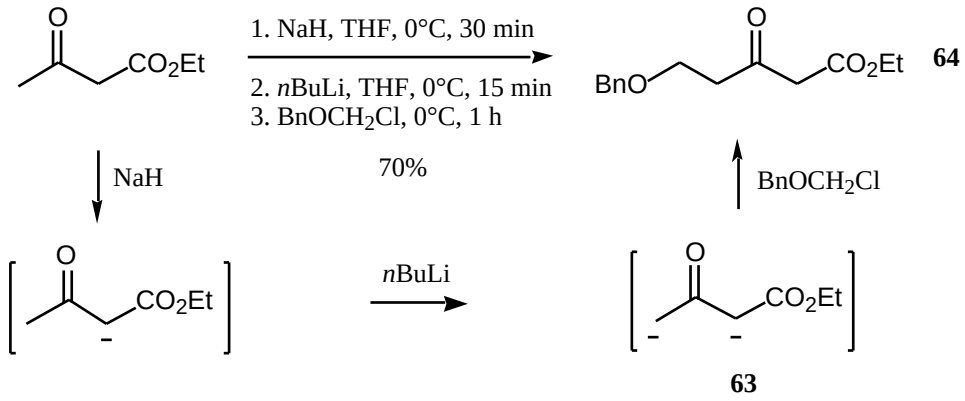
Reagents and conditions: a. Ag_2O, BnBr, DCM, rt; b. oxidation: PCC, DCM, rt, 42%; $(COCl)_2$, DMSO, Et_3N, quantitative; IBX, DMSO, rt, 92%.

Scheme 56

Lithium aluminum hydride can reduce both ketone and ester functionalities simultaneously. We then realized if the hydroxyl group in **61** was replaced with a carbonyl group, the resulting compound could be prepared by a dianion alkylation procedure.

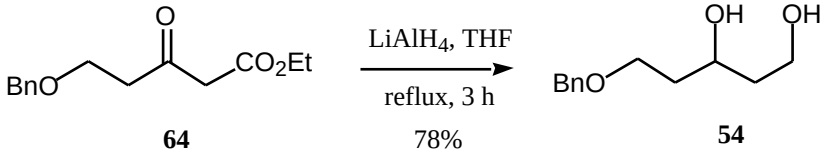
4.2.1.3 A dianion alkylation procedure

One equivalent of sodium hydride converted ethyl acetoacetate into its monoanion. Treatment of this monoanion with *n*-butyllithium gave dianion **63** which then reacted with chloromethyl benzyl ether to produce γ-alkylated product **64** in good yield (Scheme 57).



Scheme 57

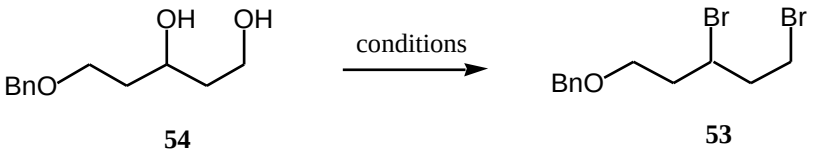
As expected, β-keto ester **64** was readily reduced to 1,3-diol **54** by $LiAlH_4$ (Scheme 58).



Scheme 58

4.2.2 Dibromination

Compound **54** was then converted into dibromide **53** (Scheme 59). The use of phosphorus tribromide in ether[113] was unsatisfactory (Table 8, Entry 1). Tetramethylbromoenamine that had been developed in our group[114] also gave disappointing results (Entry 2). However, **53** could be obtained in high yield by treatment with a suspension of triphenylphosphine and bromine in acetonitrile[115](Entry 3).



Scheme 59

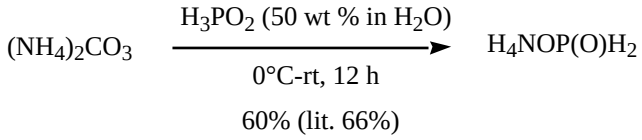
Table 8: Dibromination of 1,3-diol **54**

Entry	Reaction Condition	Yield (%)
1	PBr_3, ether, 0°c-rt, 24 h	13
2	TMBE, DCM, 0°C-rt, 1.5 h	24
3	Br_2, Ph_3P, CH_3CN, 0°C-rt, 1 h	80

One of the important spectral characteristics of **53** is the isotope pattern of Br shown for the molecular ion in the mass spectrum. For dibromide compounds, the relative isotopic abundances are approximately 1/2/1 for $[M-2]^{+\bullet}$ /$[M]^{+\bullet}$ /$[M+2]^{+\bullet}$.

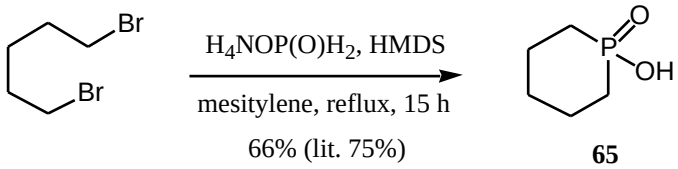
4.3 Cyclization of dibromide precursor

Ammonium hypophosphite $H_2PO_2NH_4$ was prepared according to the literature precedure (Scheme 60).[109] We used a "drying pistol" to remove water which was contained in the material.



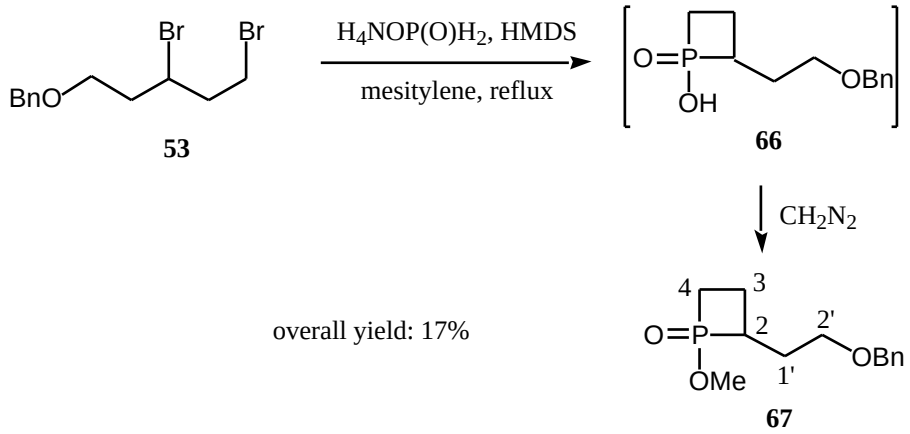
Scheme 60

In order to verify the reactivity of $H_4NOP(O)H_2$ being prepared, we first performed a model reaction to generate a six-membered phosphinic acid which has been described in the literature.[109] The reaction was successfully effected and compound **65** was obtained in a yield comparable to that reported (Scheme 61).



Scheme 61

This method was then applied to prepare four-membered phosphinic acid **66**. The crude mixture of **66** proved difficult to purify, it was then esterified with diazomethane. After flash chromatography on silica, phosphinic acid ester **67** was obtained as a pale yellow oil in 17% overall yield (Scheme 62).

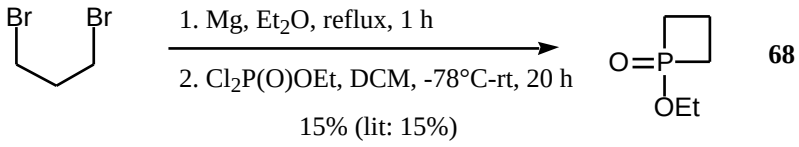


Scheme 62

Two diastereoisomers (1:1) of **67** were detected in the ^{1}H NMR spectrum. The signal of the methoxy group was shown as two distinct doublets (δ 3.73 and 3.72, d, $^{3}J_{PH}$=10.7 Hz). The triplet of $H_{2'}$ appeared at δ 3.46 (J=6.3 Hz), while other protons (H_2, H_3, H_4, and $H_{1'}$) gave a multiplet in the range of δ 1.78-1.46. In the ^{13}C NMR spectrum, two doublets for C_2 (48.5 ppm, $^{1}J_{PC}$=75.6 Hz) and C_4 (27.5 ppm, $^{1}J_{PC}$=70.5 Hz) were clearly visible.

We rationalized that the low yields could be due to the ring strain of four-membered phosphinic acid. Moreover, the hindered secondary bromide group in **53** should also disfavor the ring formation during the nucleophilic attack of BTSP.

We then turned our attention to a di-Grignard strategy to prepare ethyl phosphetanate **68** (Scheme 63).[108] Despite the low yield, this procedure was found to be reproducible, thus allowing us to prepare gram quantities of **68** for further studies.

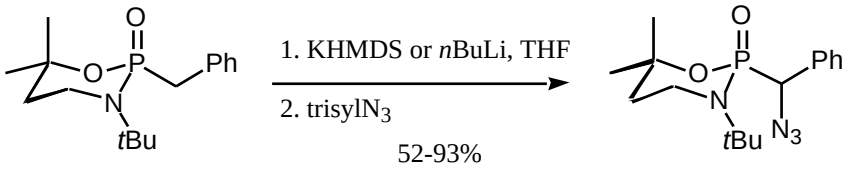


Scheme 63

4.4 Amination and alkylation of phosphorus-stabilized carbanions

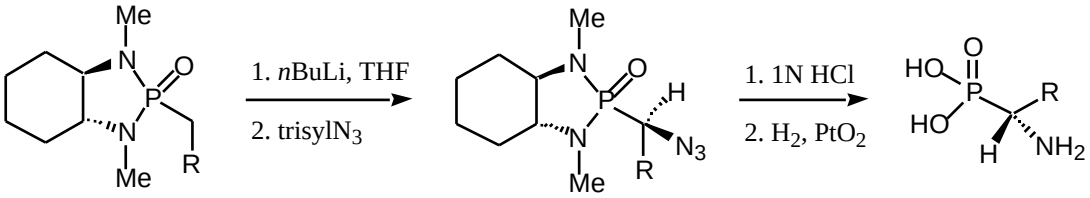
4.4.1 Literature

The electrophilic amination of phosphorus-stabilized anions derived from chiral oxazaphosphorinanes has been described by Denmark *et al.*[116] Trisyl azide (2,4,6-triisopropylbenzenesulfonyl azide) was the reagent of choice for this amination process (Scheme 64).



Scheme 64

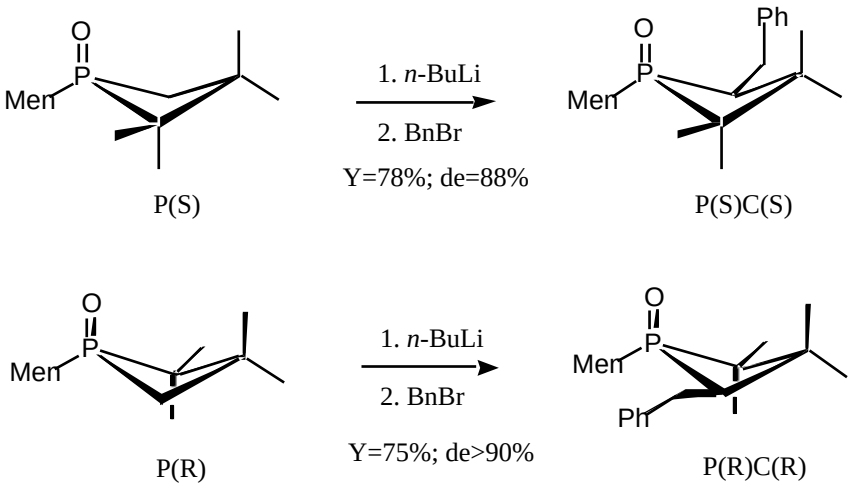
Hanessian *et al.*[117] also reported their results concerning the asymmetric syntheses of α-amino phosphonic acids via the stereoselective electrophilic amination of chiral phosphonamides (Scheme 65).



Scheme 65

In these cases, trisyl azide was chosen as the ideal aminating agent due to its stability and chemoselectivity in azide transfer to enolates.[116] Reactions of enolates with sulfonyl azides were generally known to be sensitive to both the enolate counterion and sulfonyl azide structure. Evans *at al.*[118] mentioned that trisyl azide was found to be superior to both tosyl azide and *p*-nitrobenzenesulfonyl azide.

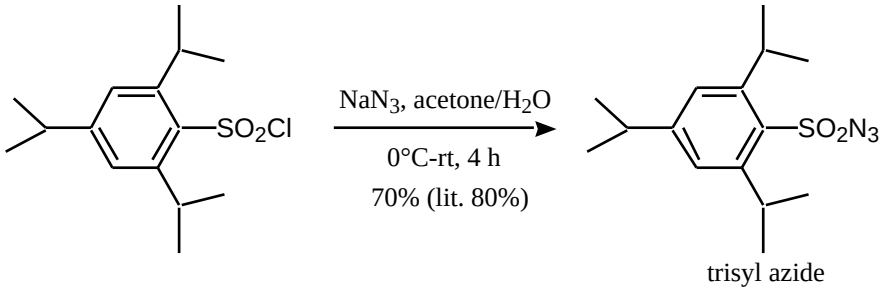
On the other hand, the highly selective and efficient alkylation reactions of phosphorus-stablized phosphetane anion offered a simple way to modify the phosphorus envionment (Scheme 66).[119]



Scheme 66

4.4.2 Preparation of trisyl azide

In the present case trisyl azide was selected as the aminating agent, which was prepared from 2,4,6-triisopropylbenzenesulfonyl chloride and sodium azide according to a method described by Leffler and Tsuno[120,121] (Scheme 67).



Scheme 67

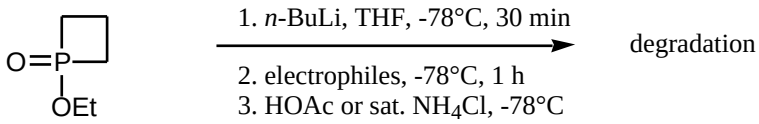
Since sodium azide has low solubility in organic solvents and thus must often be used in aqueous alcohol. Reactive sulfonyl chlorides may be hydrolysed under these conditions and lead to the formation of sulfonic acid esters as an impurity.[122] Aqueous acetone appears to be the solvent of choice at the present time.

4.4.3 Attempts on the electrophilic amination and alkylation

4.4.3.1 Deprotonation by *n*BuLi

*n*BuLi was first used to deprotonate the α-H of ethyl phosphetanate **68**, trisyl azide, ethyl bromoacetate and benzyl bromide were the electrophiles respectively (Scheme 68). The

experimental results were all disappointing and we always detected the degraded starting material.

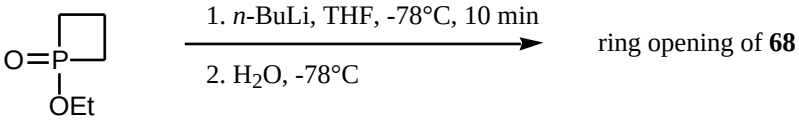


68

Electrophiles: trisyl azide, $BrCH_2CO_2Et$, BnBr

Scheme 68

A blank experiment was then performed (Scheme 69). After deprotonation of **68** with *n*BuLi at -78°C for 10 min, water was added. The ^1H NMR spectral analysis showed that the four-membered ring had been opened.



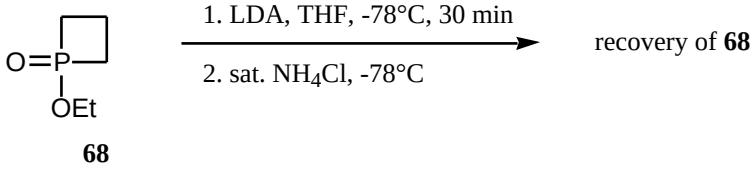
68

Scheme 69

This clearly suggested that *n*BuLi favored the nucleophilic attack on the phosphorus center rather than deprotonation of the α-H of phosphetanate. Therefore, in the present case a more hindered, non-nucleophilic base is required.

4.4.3.2 Deprotonation by LDA

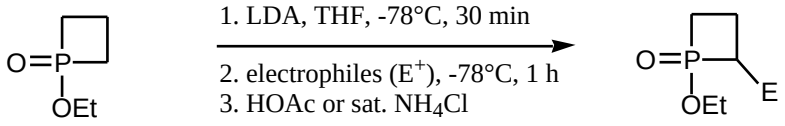
Lithium diisopropylamide (LDA) proved non-destructive to the four-membered phosphinic acid ring. The starting material **68** was thus completely recovered after quenching with sat. NH_4Cl (Scheme 70).



68

Scheme 70

However, when trisyl azide or $BrCH_2CO_2Et$ was added to the carbanion derived from **68** we only observed a complex mixture (Scheme 71, Table 9, Entry 1, 2). Treatment with benzyl bromide gave compound **69** (E=Bn) in 15% yield (Entry 3).



68 **69**

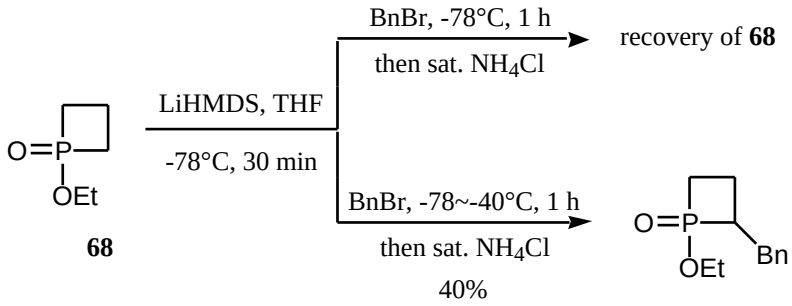
Scheme 71

Table 9: Azidation and alkylation of **68** using LDA

Entry	Electrophiles	Result
1	trisyl azide	complex mixture
2	$BrCH_2CO_2Et$	complex mixture
3	BnBr	15% **69** (E=Bn)

4.4.3.4 Deprotonation by LiHMDS

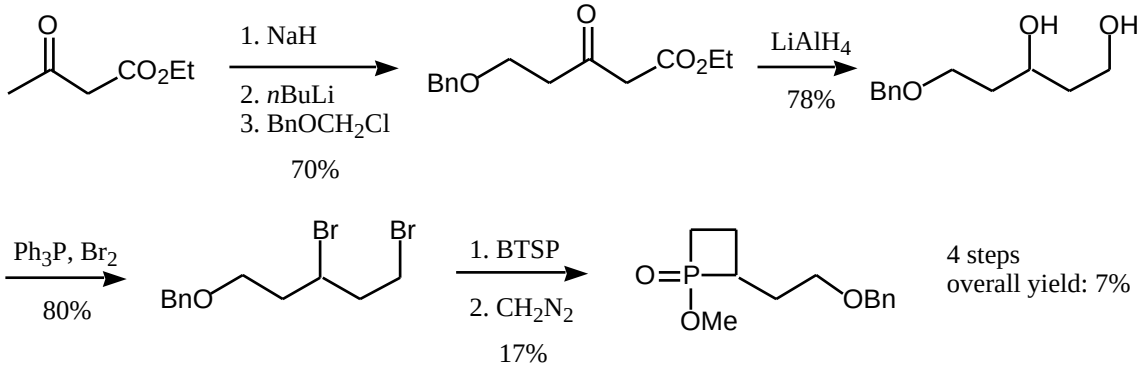
The reaction effected by LiHMDS proved much milder and cleaner than that using LDA. Quenching the benzylation reaction at -78°C led to the recovery of the starting **68**, while a higher temparature (-40°C) gave the benzylated product in 40 % yield (Scheme 72).



Scheme 72

4.5 Conclusion

We have discovered a more convergent method to prepare a dibromide precursor for cyclization to a four-membered cyclic phosphetanic acid derivative. Preliminary studies have been made for the cyclization step. BTSP was found to be sufficiently reactive to prepare such strained compounds but in low yields (Scheme 73).



Scheme 73

Although the alkylation reactions of phosphorus-stablized phosphetane anions were effective, the electrophilic attack on such a carbanion derived from phosphetanate derivatives proved less successful.

So far we have found only two useful references[108,109] concerning the synthesis of four-membered cyclic phosphetanic acids and their esters. This could reflect the difficulties in preparing such structures.

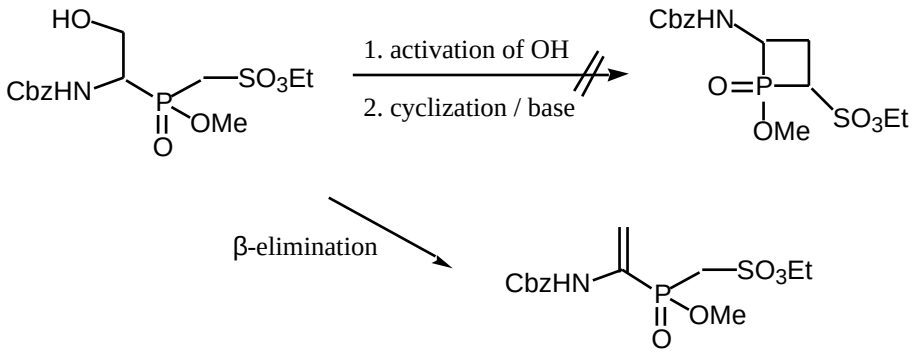
Chapter 5

Conclusions and perspectives

5.1 Concluding remarks

In the course of our studies, two complementary methods have been developped for the construction of a C-P bond using electrophilic and nucleophilic phosphorus reagents respectively.

Kessabi J. has reported in his dissertation the synthesis of acyclic phosphinic acids as transition state analogs of penicillins and cephalosporins. All of these compounds are devoid of biological activity. Although the four-membered phosphinic acid mimics are more promising candidates for biological studies, in the present work they are synthetically inaccessible. The main competitive reaction we encountered in the course of the cyclization was a β-elimination leading to the corresponding dehydro-α-aminophosphinic acid derivative (Scheme 74).



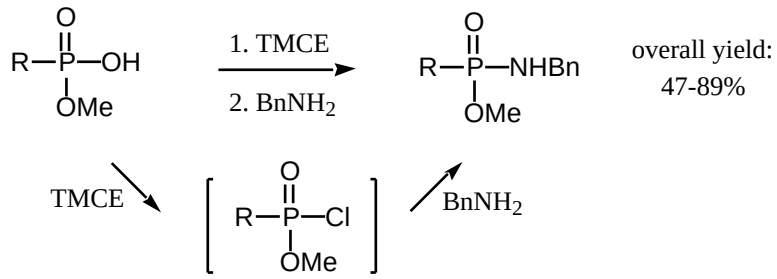
Scheme 74

The formation of a four-membered phosphinic acid ring at an early stage of the synthesis was also less effective.

In spite of the failures we met in the above-mentioned reactions, some useful intermediates being formed in the course of the synthesis could lead to a variety of five or six-membered α-amino *P*-heterocycles. Undoubtedly, these functionalized compounds could also be evaluated as transition state analogs of penicillins and cephalosporins (see below).

It is noteworthy that in our hands the chlorination reaction of phosphinic acids with classical reagents was problematic. It could be readily solved by uisng TMCE. In addition, phosphonochloridates generated with TMCE could readily reacted with amine, thus forming a

relatively weak P-N bond (Scheme 75). To our knowledge, the use of PCl_5,[123] $SOCl_2$,[88,123] or $(COCl)_2$[88] was less effective in the preparation of such a phosphonamide.

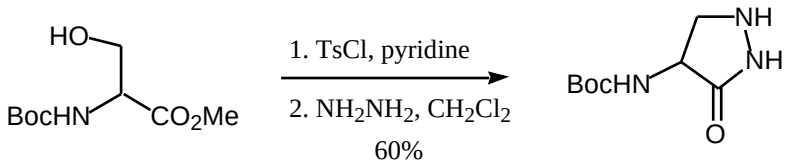


Scheme 75

5.2 Perspectives

5.2.1 Synthesis of *P*-based analogs of α-amino pyrazolidinone

As mentioned earlier, aza-γ-lactam analogs of β-lactam antibiotics exhibit exciting antibacterial activity. The α-amino pyrazolidinone could be readily prepared upon treatment of the corresponding tosylate with anhydrous hydrazine (Scheme 76).[124]

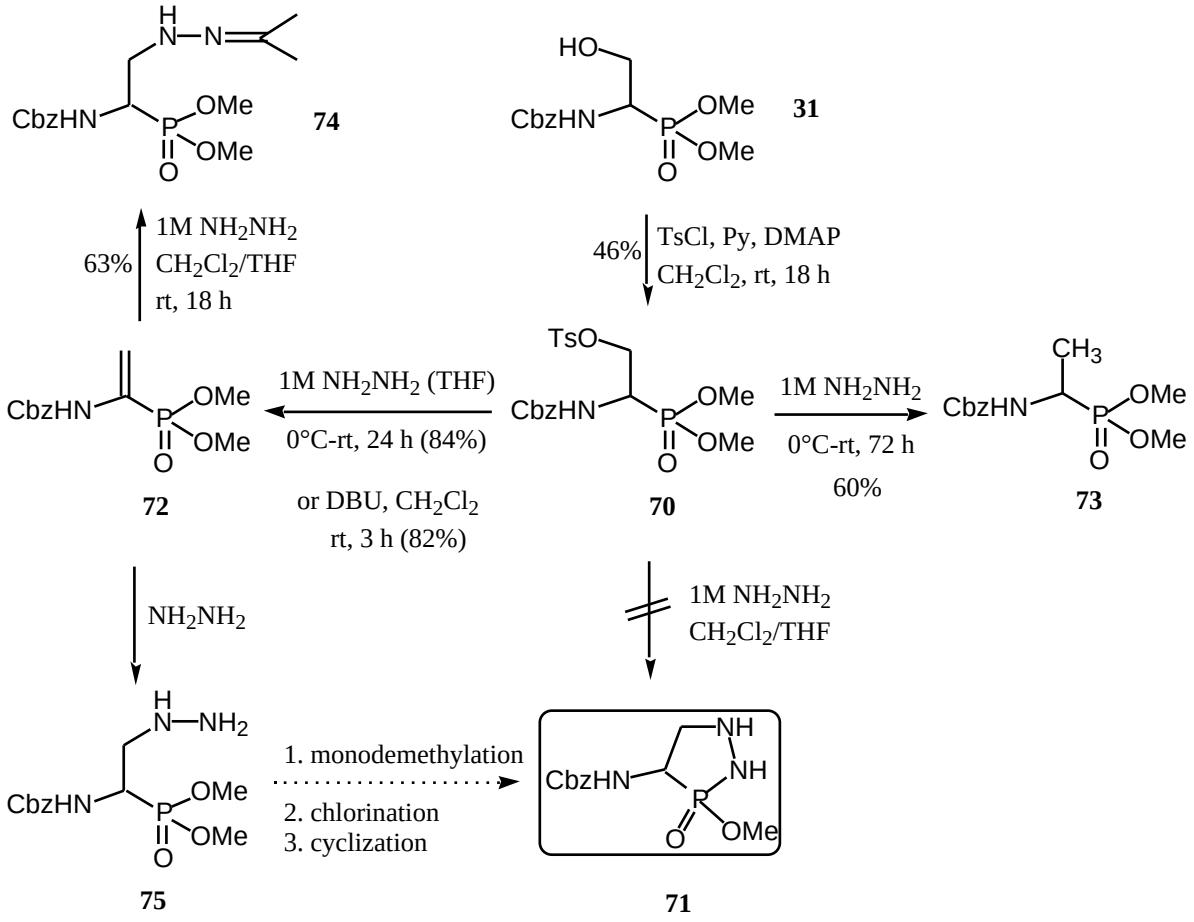


Scheme 76

In our hands, the similar strategy towards a phosphorus-based analog of α-amino pyrazolidinone could thus be conceivable (Scheme 77). Indeed, some preliminary results have already been obtained. In the present case, the reaction of tosylate **70** with hydrazine failed to yield the cyclized compound **71**, but rather a vinylphosphonate **72**. Prolonged reaction times led to compound **73** which resulted from a reductive removal of the tosylhydrazide (generated under the reaction conditions). We thus attempted to add hydrazine onto **72** (it was also available by treatment with DBU). This 1,4-addition reaction of phosphonate-activated alkene was effective and gave **74**[*] in 63% yield. In view of the poor reactivity of phosphonate diester towards the nucleophilic attack of an amine group, in the following step we could perform a monodemethylation to generate the corresponding phosphinic acid, which could in turn be

[*] Formation of **74** was probably due to the presence of trace acetone in the solvents during workup.

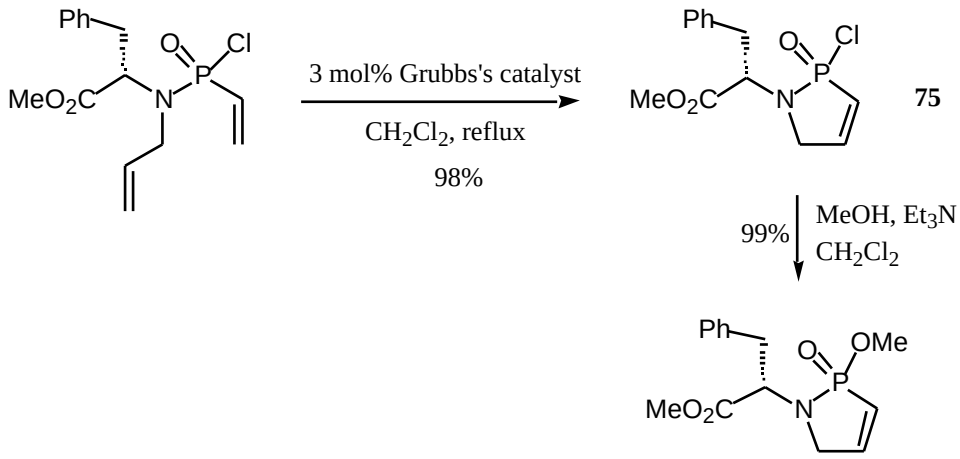
converted to a phosphonochloridate by treatment with a chlorinating agent. It was expected that an intramolecular cyclization could be effected after activation of the phosphonate ester.



Scheme 77

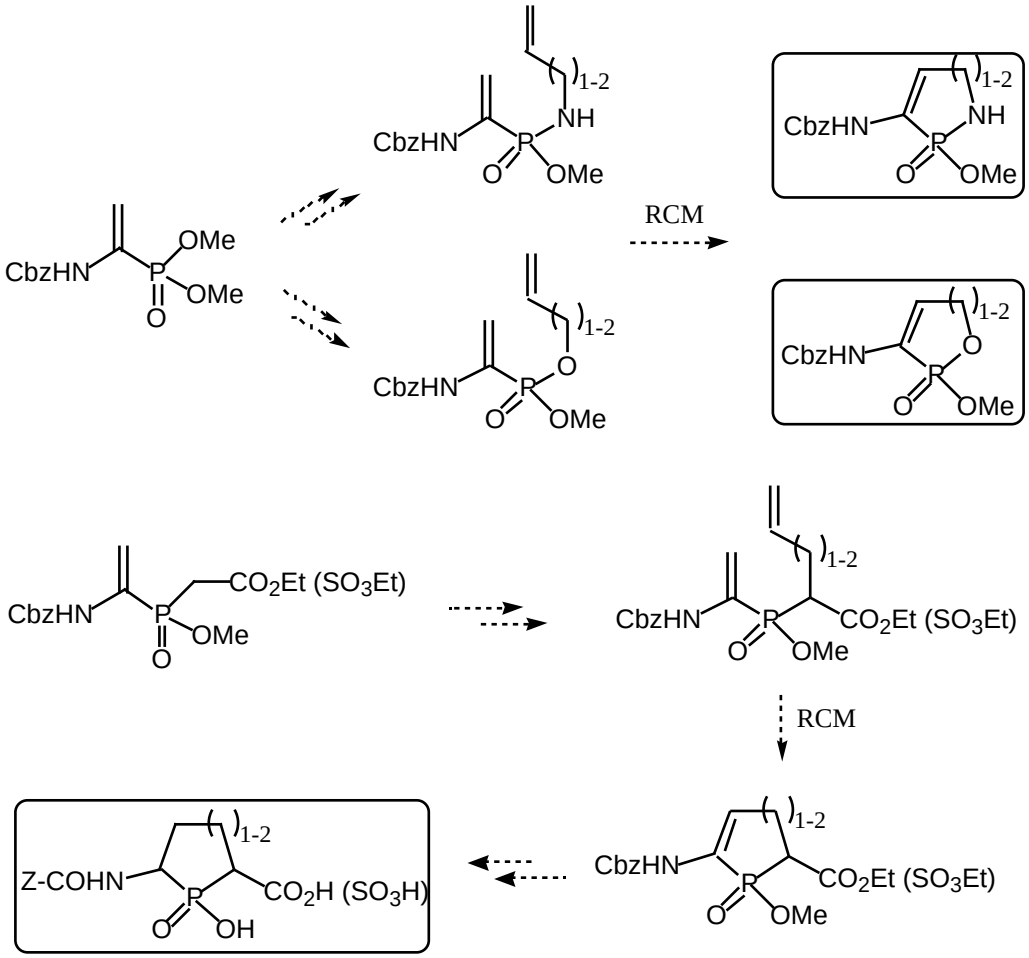
5.2.2 RCM strategy to α-amino *P*-heterocycles

There is only a few examples of RCM reactions on phosphorus-containing compounds in the literature.[125-128] Among them, the formation of an amino acid-derived five-membered *P*-chiral heterocycle **75** should be of particular interest (Scheme 78).[128]



Scheme 78

In our hands, some RCM precursors shown in Scheme 79 should be easily prepared from the corresponding vinylic phosphorus-derivatives. Thus, this RCM strategy could provide ready access to cyclic phosphonamides, phosphonate esters or α-amino phosphinic acid derivatives bearing a carboxylic or sulfonic acid function.



Z: side chains of penicillins

Scheme 79

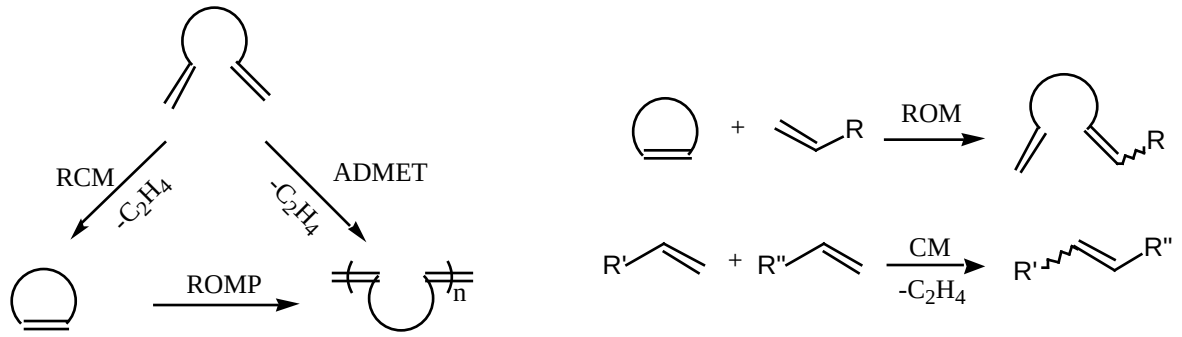
Part II

Chapter 6

Ring-closing metathesis in the construction of bicyclic pyrazolidinone derivatives

6.1 Introduction

Olefin metathesis, a process by which alkylidene groups on alkenes are exchanged, was first reported in 1955 by Anderson and Merckling.[129,130] As shown in Scheme 80, it includes ring-closing metathesis (RCM), ring-opening metathesis polymerization (ROMP), acyclic diene metathesis polymerization (ADMET), ring-opening metathesis (ROM), and cross metathesis (CM).



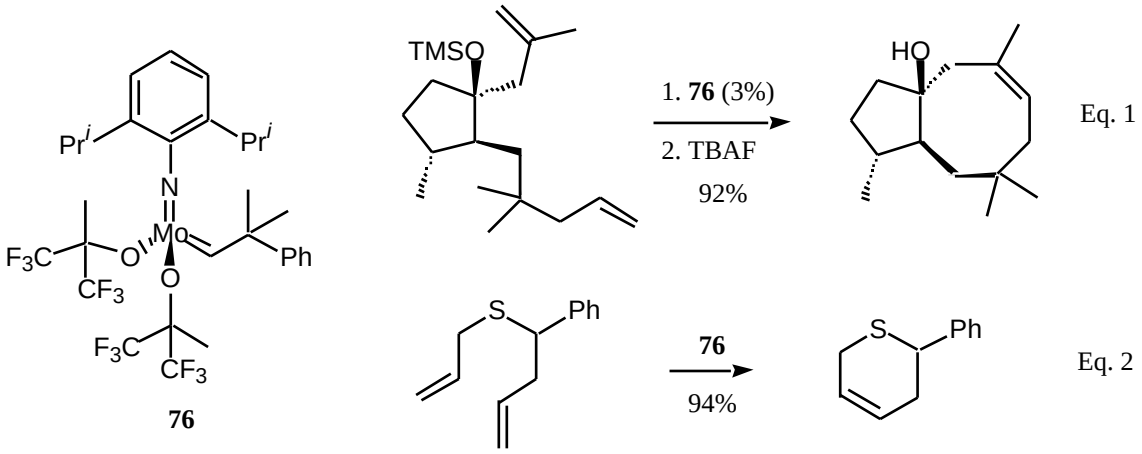
Scheme 80: General types of olefin metathesis reactions

Despite the widespread use of olefin metathesis in industry as a method for producing higher olefins and polymers, it is only recently that the reaction has been applied to organic synthesis.[131,132] This has been primarily driven by the independent discoveries of efficient catalysts by Schrock[133a] and Grubbs.[133b] Undoubtedly, the area of olefin metathesis that has expanded most dramatically in recent years is RCM. The functional-group tolerance and reasonable stability of Schrock's and Grubbs's catalysts have allowed to cyclize a wide variety of substrates. The following chapters will describe the construction of bicyclic aza-γ and β-lactam derivatives using RCM as key step.

6.2 Recent advances in catalyst design: literature survey

6.2.1 Molybdenum-based catalysts and asymmetric metathesis reactions

Schrock's tetracoordinated alkylidene species of the general formula [Mo(=CHCMe$_2$Ph)(=NAr)(OR)$_2$] with bulky Ar and R substituents on the imido and alkoxide ligands are potent and well behaved metathesis (pre)-catalysts which have been thoroughly studied.[134] Among them, compound **76** (Scheme 81) turned out to be particularly active and is now commercially available.



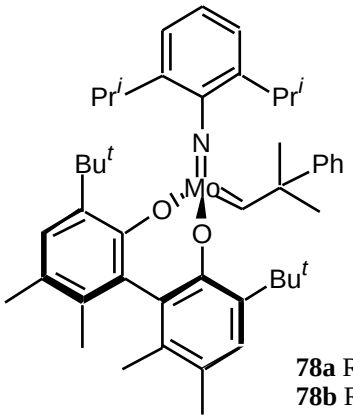
76

Scheme 81

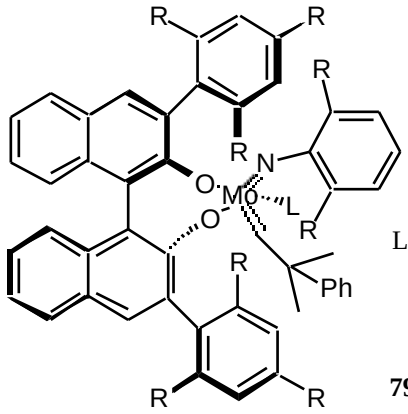
Complex **76** has the major disadvantage of being particularly air- and moisture- sensitive. However, its superb reactivity compensates for this inconvenience and it remains the catalyst of choice for hindered substrates. In a total synthesis of the terpene natural product dactylol, the diene was readily cyclized to a medium-sized ring on exposure to catalyst **76** (Eq. 1, Scheme 81), whereas attempted ring closure with the ruthenium carbene **77** (see Section 6.2.2) completely failed.[135] Moreover, molybdenum complex **76** tolerates certain functional groups which inhibit ruthenium-based metathesis catalysts. A mismatch of the "hard" Mo^{VI} center with "soft" sulfur functionality may explain why the substrate shown in Eq. 2 (Scheme 81) smoothly cyclized in the presence of **76** but failed to react in the presence of the ruthenium carbene **77**.[136]

In addition to its pronounced reactivity, the modular character of Schrock's molybdenum alkylidene complexes constitutes a particularly favorable feature. More specifically, various alkoxides can be readily introduced into the ligand sphere of the Mo center, including chiral scaffolds. This paved the way for different kinds of asymmetric metathesis reactions. Excellent levels of asymmetric induction have been reached with molybdenum complexes **78** and **79**

carrying substituted BINOL- or BIPHEN-derived ligands (Scheme 82). The BIPHEN-derived species **78** are the reagents of choice for the asymmetric formation of five-membered rings by ARCM (Eq. 1),[137] whereas the BINOL-derived analog **79** gives better results in case of six-membered products (Eq. 2).[138]

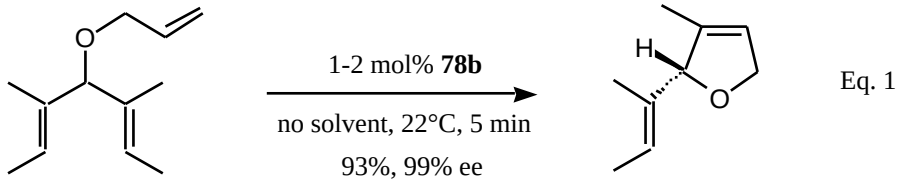


78a R=*i*-Pr
78b R=Me

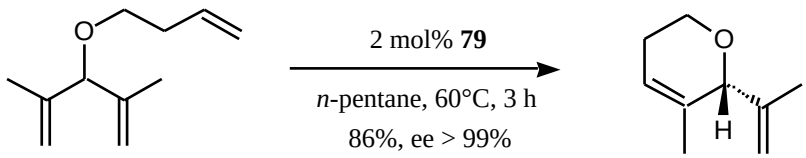


L=thf; R=*i*Pr

79



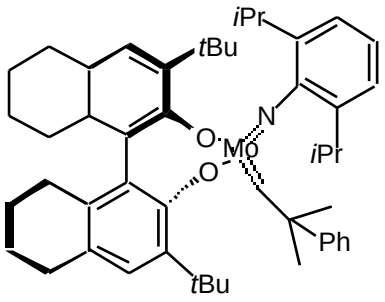
Eq. 1



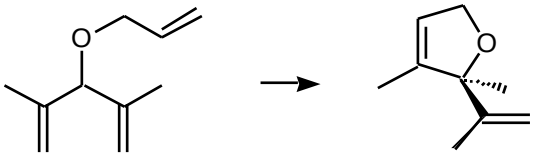
Eq. 2

Scheme 82

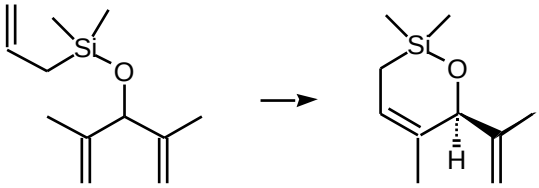
More recently, Schrock and co-workers have reported a chiral catalyst **80** which is readily prepared *in situ* from a commercially available metal complex and a chiral ligand. In addition to being easy to use, complex **80** promotes ARCM reactions with equal or higher levels of efficiency and selectivity than **78**. Moreover, since **80** shares certain structural features with binaptholate **79**, it may also be employed to effect asymmetric olefin metatheses that are typically best performed by **79** (Scheme 83).[139]



80



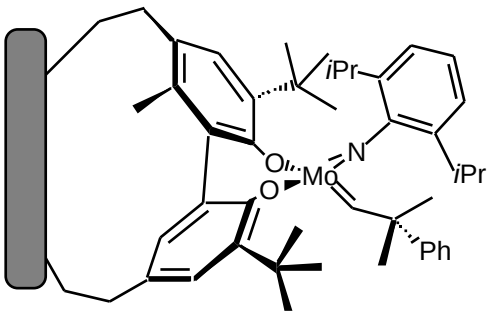
Catalyst	Y (%)	ee (%)
78a	86	93
79	72	90
80	81	92



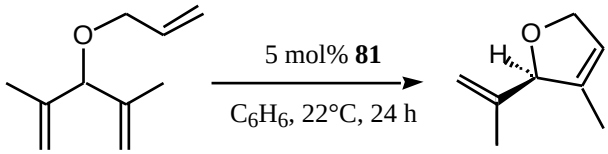
Catalyst	Y (%)	ee (%)
78a	17	65
79	98	>98
80	54	96

Scheme 83

The first polymer-supported and recyclable chiral catalyst **81** bearing substituted BIPHEN-derived ligands has been prepared (Scheme 84).[140] A significant advantage of the polymer-supported chiral catalyst is that simple filtration of the reaction mixture delivers materials that contain noticeably lower amounts of Mo impurity than in cases when homogeneous catalysts are utilized. In most cases, catalyst **81** provides similar levels of enantioselectivity as the corresponding homogeneous variant **78** (Scheme 84).



81

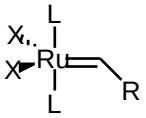


Scheme 84

6.2.2 Ruthenium-based catalysts

6.2.2.1 Variations on a theme by Grubbs

The disclosure of Grubbs that ruthenium carbene complexes of the general type **82** (Figure 28) are highly active (pre)catalysts for all types of alkene metathesis reactions was a real breakthrough in this field.[141]



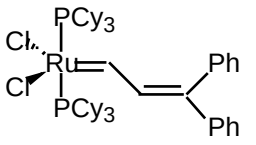
X = Cl, Br, $OOCCF_3$
$L = PR'_3$

82

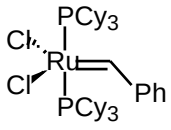
Figure 28

Although the activity of these complexes is usually lower than that of Schrock's molybdenum alkylidene catalysts, their spectacular tolerance towards various functional groups and their ease of handling due to their reasonable stability against air, moisture, or other reaction impurities make them exceedingly practical. Historically, **83** is the first compound of this series but it is complex **77** that has been used in numerous reactions.[131] A selection of these applications is illustrated in Scheme 85: RCM of dienynes have allowed the construction of fused ring systems and bridged bicyclo-alkenes (Eq. 1);[142] one of the major applications of RCM has been the synthesis of medium to large ring systems, such as the total synthesis of Epothilone A;[143] it has also been used in polypeptide chemistry.[144]

Currently, catalysts **83** and **77** are commercially available and details for their syntheses have been reported.[145]

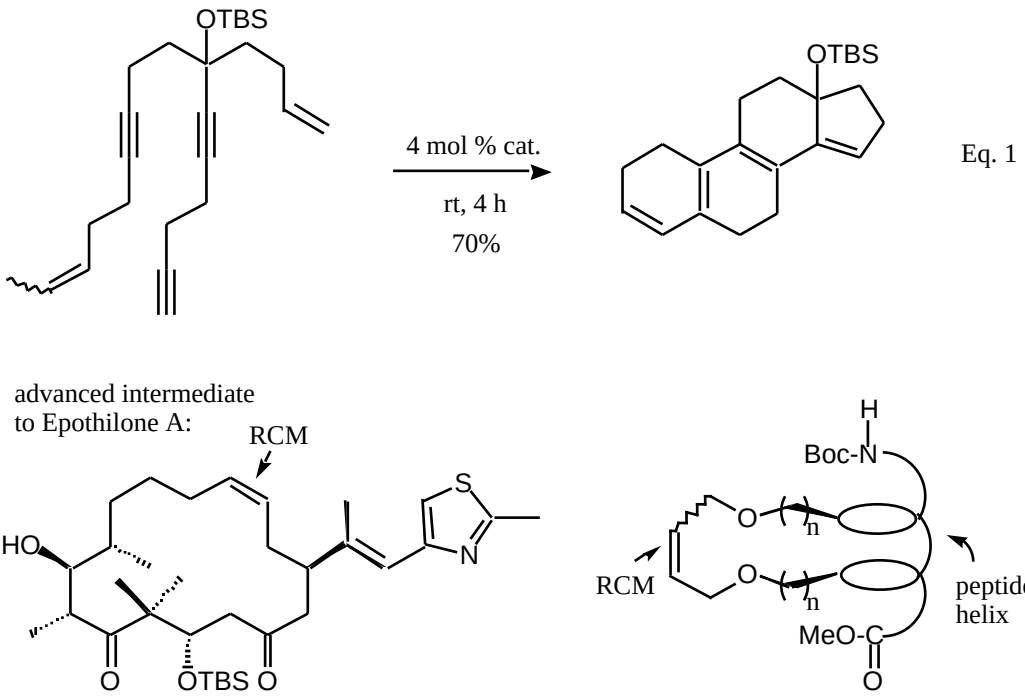


83



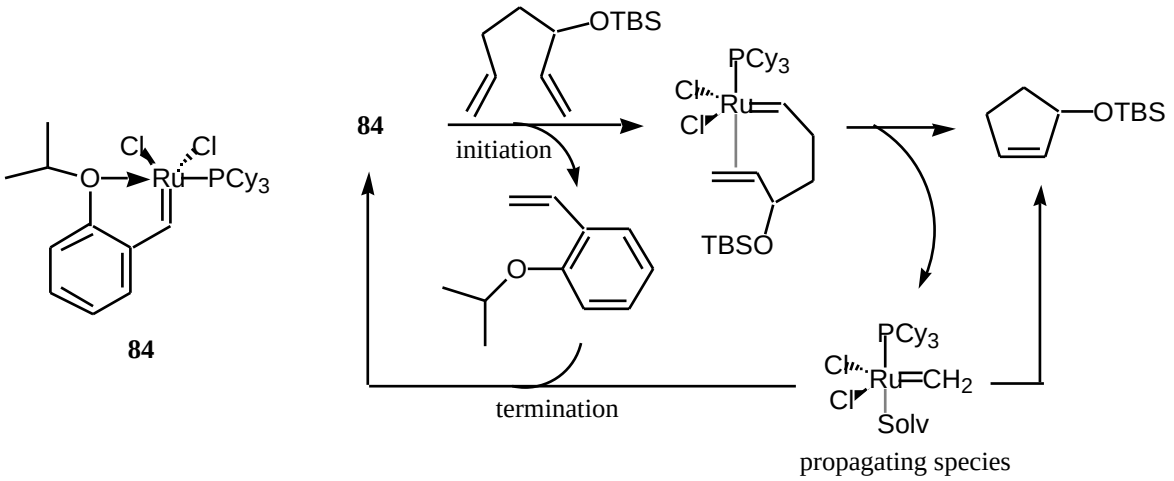
77

Applications using catalyst **77**:



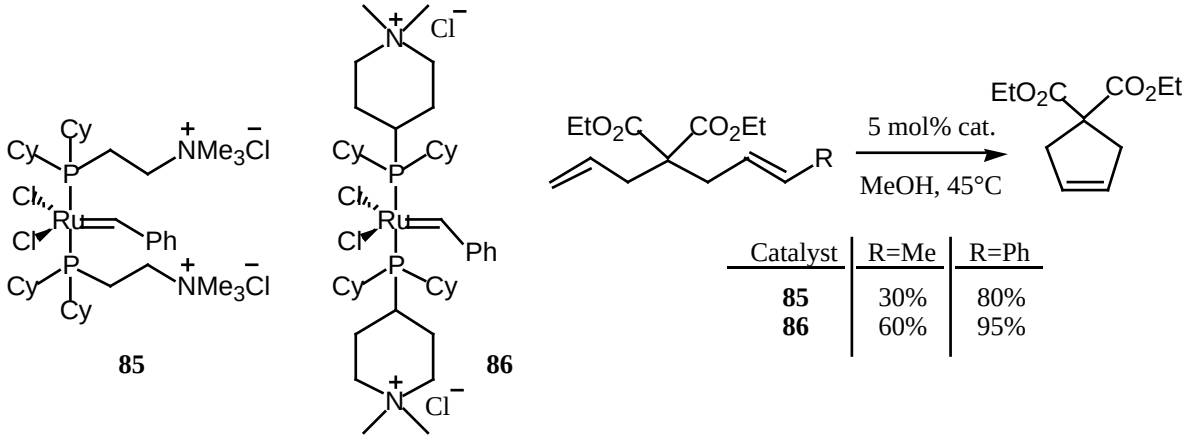
Scheme 85

Hoveyda and co-workers[146] have reported the synthesis and some applications of ruthenium alkylidene **84**. The lateral O*i*Pr group on its phenylcarbene unit stabilizes the complex in its resting state, but readily opens a coordination site in the presence of the substrate. Moreover, this complex is able to regenerate itself once the substrate is depleted and can be recycled by conventional silica chromotography with no detectable loss of activity (Scheme 86).



Scheme 86

Catalysts that allow ring-closing metathesis (RCM) in methanol and water (complexes **85** and **86**, Scheme 87) have also been reported by Grubbs and co-workers.[147,148] The phosphine ligands of these catalysts contain quaternary ammonium salts, which confer enhanced solubility (and hence activity) in protic solvents. This study also revealed that the nature of the substrate has an important influence on the ease of cyclization. Phenyl-substituted substrates are claimed to be best suited to cyclizations, since they yield stable benzylidene systems upon turnover (Scheme 87). The exceptional activity of these catalysts in protic solvents should allow their ready application to systems of biological significance.

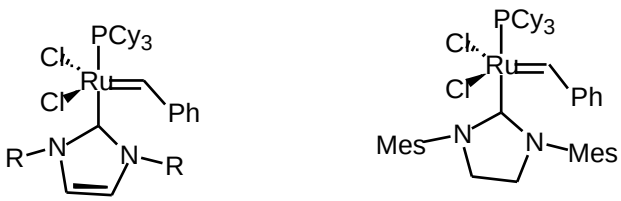


Scheme 87

6.2.2.2 Ruthenium complexes containing *N*-heterocyclic carbene (NHC) ligands

The idea of the use of one kinetically inert, electron-donating NHC ligand in combination with a coordinatively labile ligand was independently pursued by three different research

groups,[149-151] which have almost simultaneously reported on the preparation and the catalytic properties of *N*-heterocyclic complexes such as **87**[152] and **88**[153,154] (Figure 29).

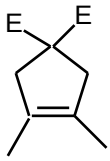
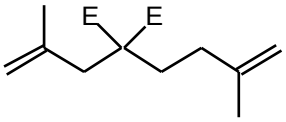
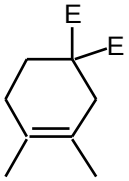
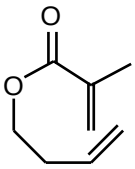
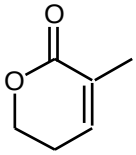


87 **88**

Figure 29

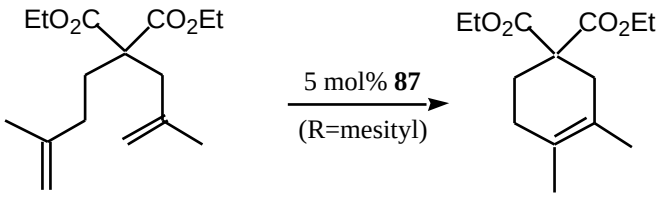
The activity of these catalysts is significantly higher than that of the parent Grubbs carbene **77** and comes close to or even surpasses that of Schrock's molybdenum alkylidene complexes (Table 10). Both **87** and **88** are able to perform the RCM of sterically demanding dienes to form tri- and tetrasubstituted olefins (Entry 1 and 2).[150,153] Similarly, acrylates are problematic substrates for catalyst **77** but were found to cyclize smoothly in the presence of complex **88** (Entry 3).[155] Also as a result of their exceptional thermal stability and resistance towards oxygen and moisture, as well as their compatibility with many functional groups, these complexes have soon become extremely useful tools in organic chemistry.

Table 10: Results of RCM using different catalysts

Entry	Substrate	Product	Yield (%) of product using **76**	**77**	**87**	**88**
1			93	N.R.	40	31
2			52	N.R.	95	90
3						86

E=CO_2Et; N.R.: no reaction; reactions were performed in DCM at reflux using 5 mol% catalysts (for **87**, R=mesityl)

It should be pointed out that the reactivity of **87** can be tuned to some extent by the proper choice of the substituents R on nitrogen as well as by the reaction medium. Particularly high reaction rates are observed in toluene, and this increased activity is not simply an effect of the higher reaction temperature in this medium (Scheme 88). The striking influence of the medium has only been observed for the ruthenium carbene **87** bearing *N*-mesityl substituents on their imidazol-2-ylidene ligand. Related complexes with *N*-cyclohexyl or *N*-isopropyl groups do not show this effect.[152]

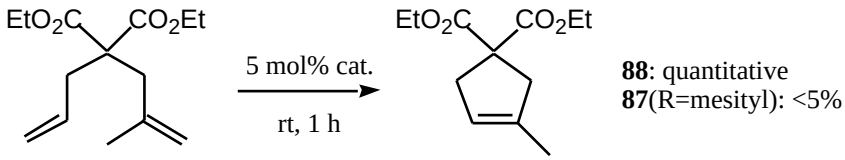


CH_2Cl_2	40°C	60 min	54%
toluene	80°C	15 min	98%

Scheme 88

Complex **88** containing "saturated" NHC ligand seems to be even more reactive than their "unsaturated" analogues **87**.[154] For instance, the conversion to the corresponding trisubstituted cycloolefin using complex **88** was completed within 1 h at room temperature, while little (<5%) product was obtained using complex **87** (Scheme 89).[153] This increased reactivity of catalyst

88 can be explained by an increased basicity of saturated imidazole ligand, in which the carbene center is less stabilized than their unsaturated analogs due to the absence of π-interactions.

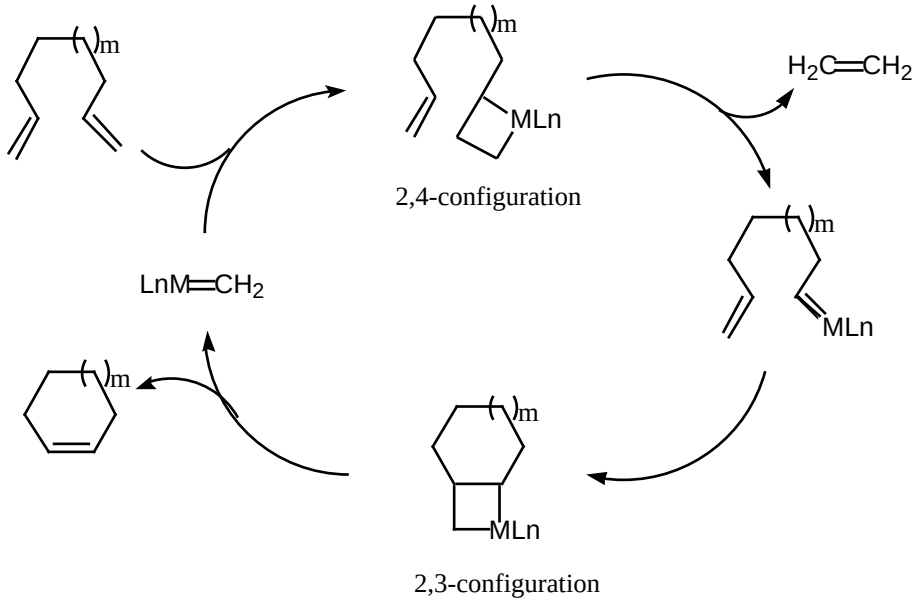


Scheme 89

Studies carried out by Grubbs and co-workers suggest that the bulky mesityl groups in these catalysts may contribute to their high activity, in part because of their interactions with the alkylidene moiety. The mesityl substituents may also provide the metal center with considerable steric protection and contribute to the high thermal stability of these catalysts.[131]

6.3 Mechanism of ring-closing metathesis of acyclic dienes

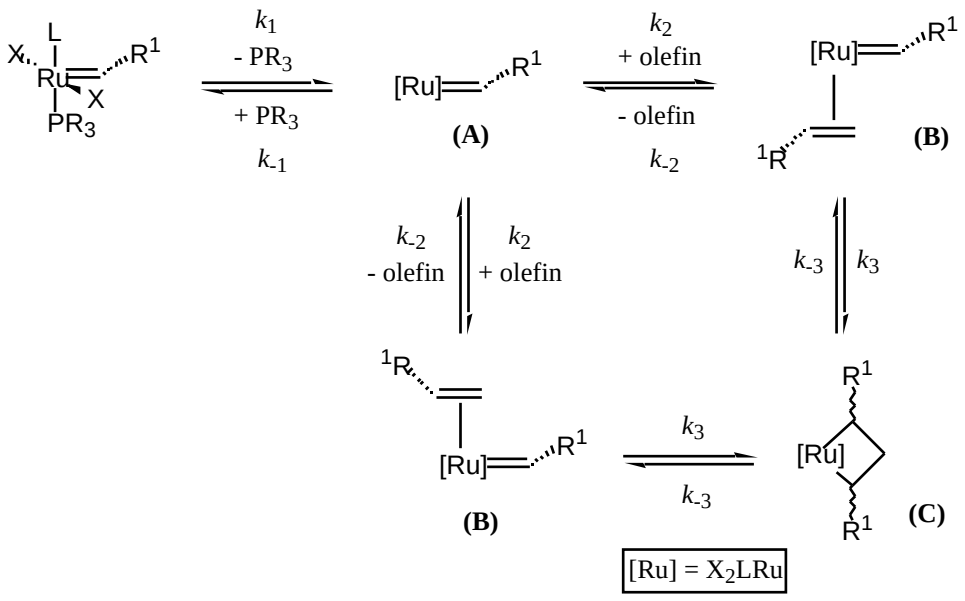
The generally accepted mechanism of metathesis reactions ("Chauvin mechanism")[156] consists of a sequence of formal [2+2] cycloadditions/cycloreversions involving alkenes, metal carbenes, and metallacyclobutanes intermediates (Scheme 90). Since all individual steps of the catalytic cycle are reversible, a thermodynamic mixture of olefins is obtained. Therefore, it is necessary to shift this equilibrium in one direction in order to make metathesis productive in preparative terms. In the case of RCM, the forward process is entropically driven because it cuts one substrate molecule into two products. If one of them is volatile (ethene, propene *etc.*), the desired cycloalkene will accumulate in the reaction mixture.



Scheme 90

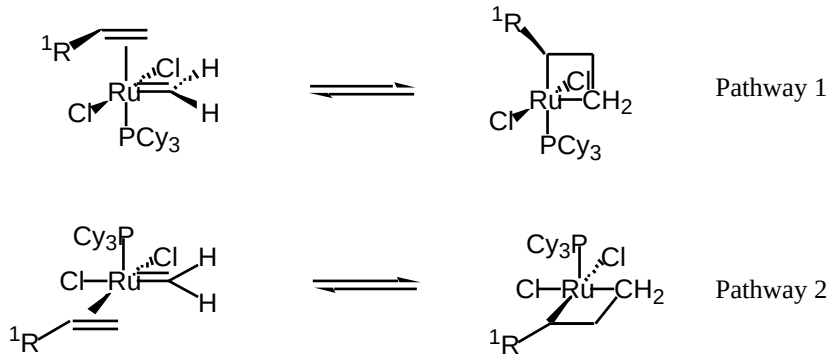
Adam J.-M.[157] has reviewed in his dissertation the kinetic, steric and electronic effects for the metathesis reaction. It has been proposed that the formation of 2, 4-metallacycles is electronically favored while steric effects favor the 2, 3-metallacycle.[158] The kinetic product of the reaction between a sterically unhindered terminal olefin and a ruthenium carbene is usually an alkylidene carbene rather than the methylidene carbene. In other words, the carbene exchange reaction is faster than the productive metathesis. The equilibrium is then driven to the thermodynamic products resulting from self-metathesis (Scheme 90).[145]

Recently, Grubbs and co-workers have described an extensive and systematic evaluation of the effects of ligand variation on the kinetics and mechanism of ruthenium-catalyzed olefin metathesis reactions.[159,160] They proposed a general mechanism as summarized in Scheme 91. The first step of the reaction involves elimination of PR_3 to form a 14-electron intermediate **A**. This intermediate can be trapped by free PR_3 to regenerate the starting alkylidene or can bind substrate and undergo metathesis. As such, the activity of catalysts is not only related to the phosphine dissociation rate k_1, but also to the ratio of k_{-1} to k_2 which determines whether the catalyst binds olefin or returns to its resting states. In the bis-phosphine systems (*e.g.* **77**), **A** is formed rapidly (k_1 is large). However, under the reaction conditions, the recoordination of free PR_3 is competitive with substrate binding ($k_{-1}/k_2 \approx 1$). In contrast, the NHC complexes (*e.g.* **87** and **88**) dissociate phosphine relatively inefficiently (k_1 is small). However, once the phosphine comes off, coordination of olefin is facile compared to rebinding of PR_3 ($k_{-1}/k_2 \sim 1$). Thus, a small amount of initiated 14-electron species is capable of cycling through multiple olefin metathesis reactions before it is deactivated by the rebinding of PR_3.



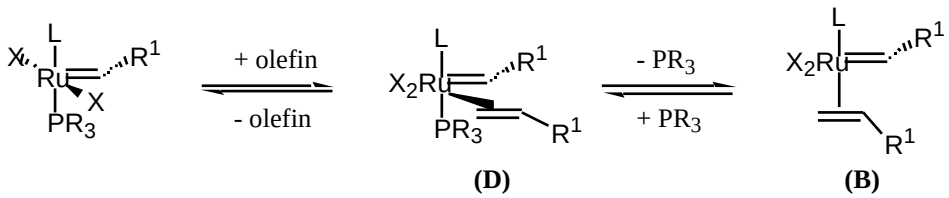
Scheme 91

The above catalytic cycle does not indicate stereochemistry around the ruthenium center for the important catalytic intermediates **B** and **C**. Several possibilities for the geometries of **B** and **C** have been proposed (L=PCy_3, X=Cl; Scheme 92).[161] According to pathway 1, the square pyramidal intermediate in which the carbene occupies the apical position and the olefin an equatorial position, directly precedes metallacyclobutane formation; in pathway 2, the carbene must rotate by 90° before metallacycle formation can occur. However, there is still no experimental evidence supporting either of these possibilities.[160]



Scheme 92

Importantly, the recent experimental results reported by Grubbs *et al.*[160] provide no evidence that an associative reaction pathway (involving the 18-electron olefin adduct **D**, Scheme 93)[161] contributes significantly to the metathesis reactions of any of those ruthenium-based catalysts.



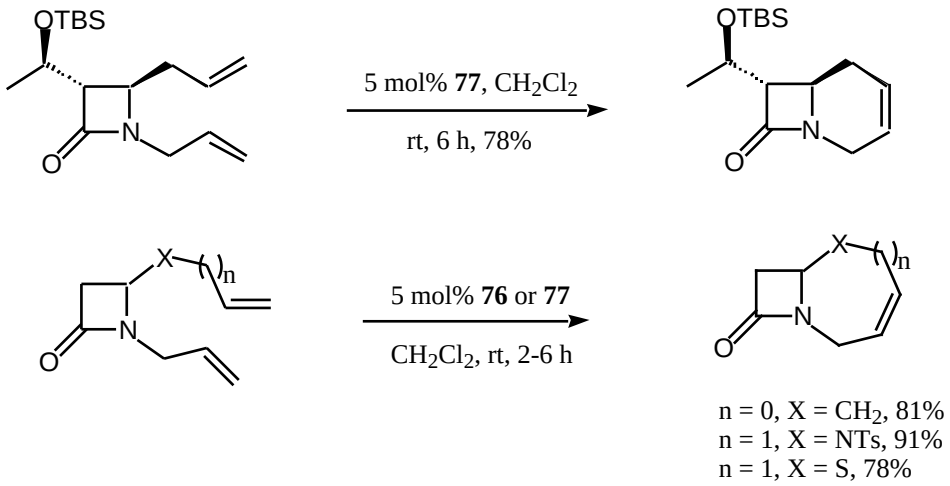
Scheme 93

As mentioned earlier, the huge increase in olefin metathesis activity upon changing the L ligand from a phosphine to a *N*-heterocyclic carbene (*e.g.* **77** *vs.* **88**) has been observed. The high activity of **88** relative to **77** can be understood on the basis of the k_{-1} to k_2 ratios of these two catalysts, which show that the $IMesH_2$ ligand increases selectively for binding olefin substrates over free phosphine by 4 orders of magnitude.[160] This improved selectivity may be explained by the electronic properties of NHC's, which are known to be excellent donor ligands relative to trialkylphosphines.[162,163] The NHC-coordinated complexes show increased affinities for π-acidic olefin substrates relative to σ-donating PR_3. In addition to stabilizing the

olefin complex **B**, electron donation from NHC's is expected to accelerate the oxidative addition required for metallacyclobutane formation.[160]

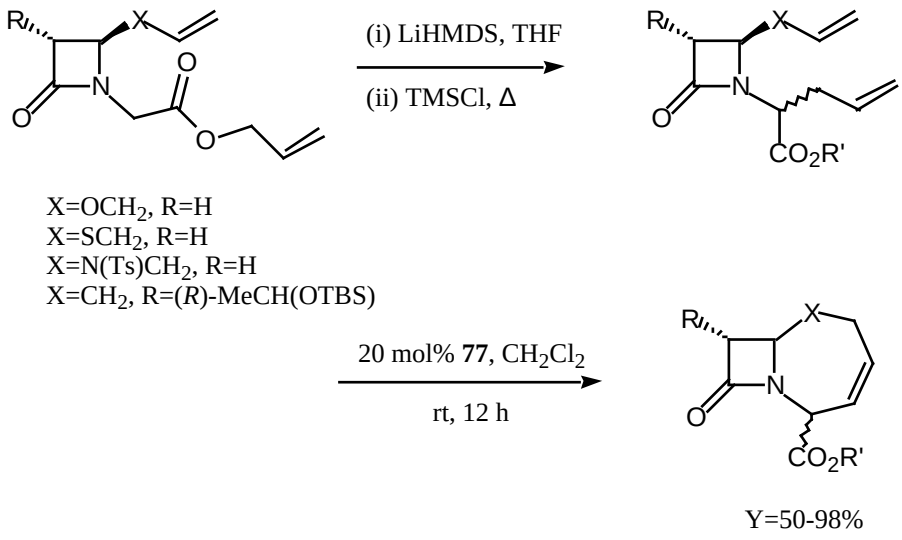
6.4 Applications to the synthesis of bicyclic β- and γ-lactams

Due to their high catalytic activity and functional-group tolerance, catalysts described in Section 6.2 seemed ideally suited to applications involving nitrogen-containing substrates.[164] Indeed, a number of bicyclic β-lactams have been prepared using RCM (Scheme 94).[165,166]



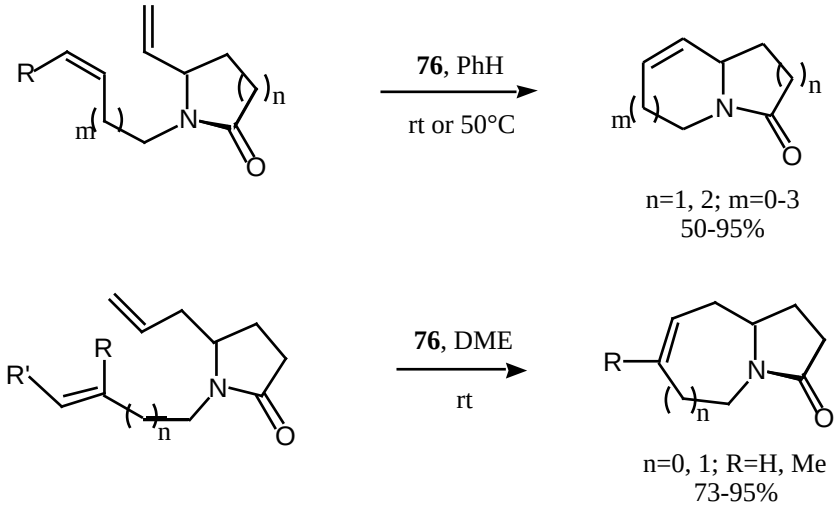
Scheme 94

Of particular interest is the work of Barrett and co-workers[167] who have prepared bicyclic β-lactam carboxylic esters via tandem Ireland-Claisen rearrangement and subsequent alkene metathesis (Scheme 95). It is clear that this strategy represents a powerful and rapid entry into pharmacologically interesting compounds.



Scheme 95

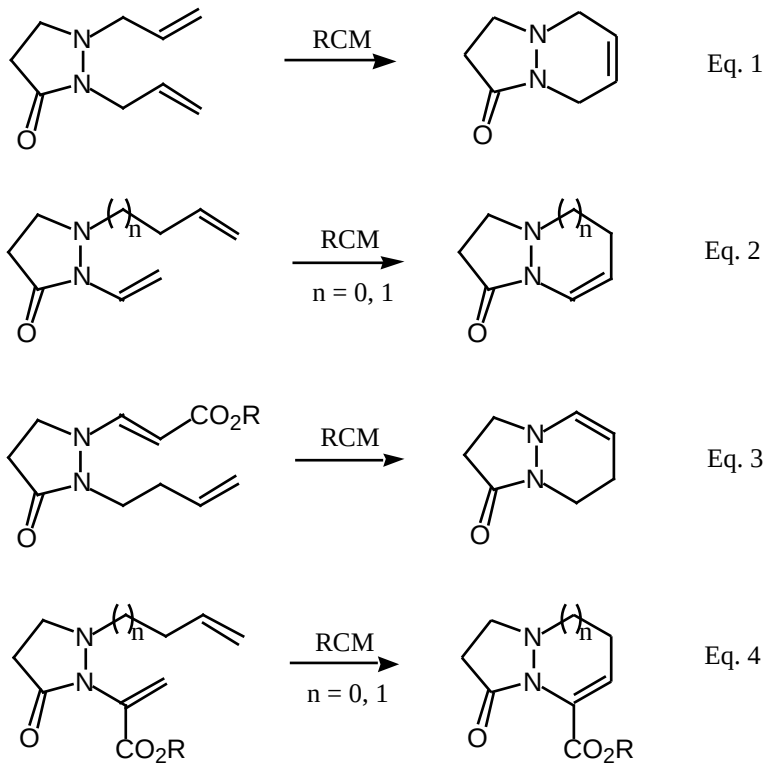
Martin and co-workers have shown the potential of RCM to form the ring systems found in a number of alkaloids (Scheme 96).[168] This work has demonstrated that a number of fused nitrogen heterocycles, including pyrrolizidines, indolizidines, and quinolizidines, can be readily prepared.



Scheme 96

6.5 Objectives

As part of a study of novel potential inhibitors of bacterial D, D-peptidases and β-lactamases, we became interested in RCM reactions as a general route to bicyclic aza-β and γ-lactams. In this chapter, we will focus on the preparation of bicyclic aza-γ-lactams using RCM (Scheme 97). Considering the ready access to RCM precursors, our initial goal was to cyclize a diallylated aza-γ-lactam to form a bicyclo [4.3.0] ring (Eq. 1). On the other hand, examples of RCM reactions with enamides are significantly less abundant.[169] Their application to the synthesis of bicyclic aza-γ-lactams should therefore be of particular interest (Eq. 2). We also tried to prepare a cyclic enamine via RCM (Eq. 3). Finally, our attention will be focused on the preparation of some α-dehydroamino esters. Their corresponding bicyclic derivatives formed by RCM should be of particular interest for the synthesis of aza-analogs of β-lactamantibiotics (Eq. 4).

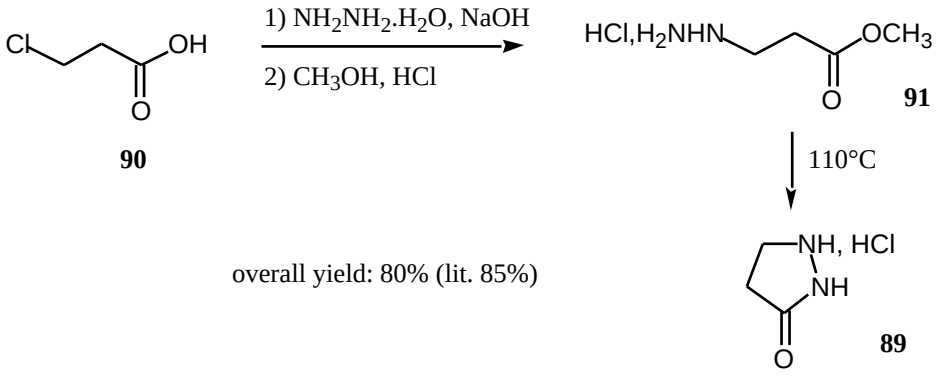


Scheme 97

6.6 Results and discussion

6.6.1 Synthesis of pyrazolidinone hydrochloride 89

The monocyclic pyrazolidinone **89** could readily be prepared in large quantities from 3-chloropropionic acid **90** and hydrazine by a known method.[170] The reaction of the sodium salt of 3-chloropropionic acid and hydrazine yielded the 3-hydrazinopropionate salt which was converted to the methyl ester hydrochloride **91**. 3-Pyrazolidinone hydrochloride **89** was obtained in 80% yield by heating **91** at 110°C (Scheme 98). Currently, this material is also commercially available from Acros Chemical Company.



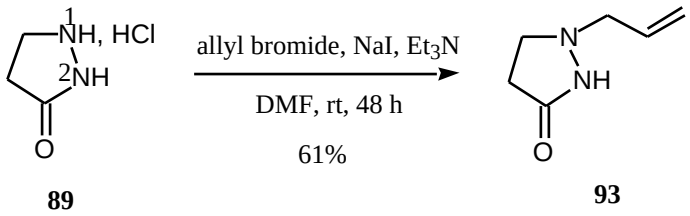
Scheme 98

6.6.2 Preparation of the bis-alkenes, precursors of the RCM

6.6.2.1 Preparation of the N_1, N_2-diallylated pyrazolidinone 92

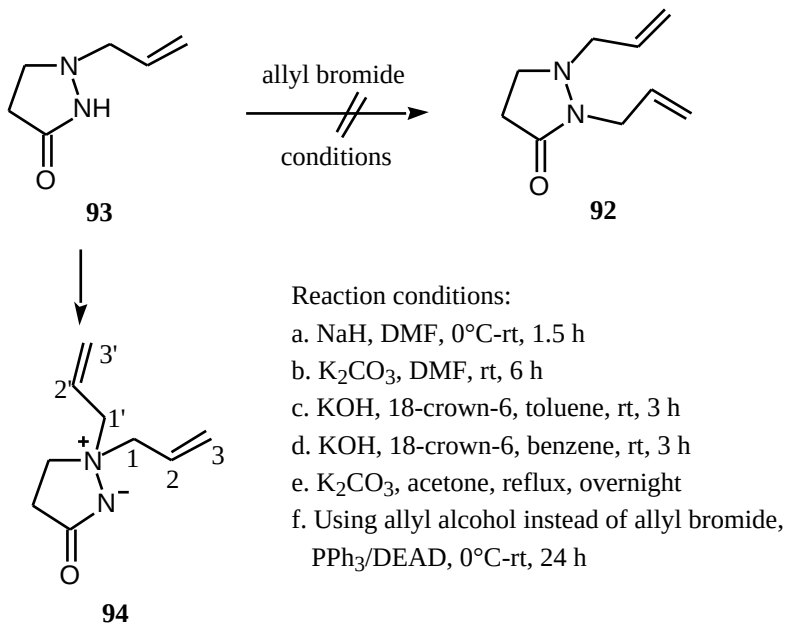
6.6.2.1.1 Attempts to the direct diallylation of pyrazolidinone 89

As expected, the N-1 nitrogen atom exhibited a higher nucleophilicity than N-2. Thus, selective allylation was accomplished at N-1 by the reaction of **89** with allyl bromide in the presence of 2 equiv of Et_3N and 0.25 equiv of NaI in DMF (Scheme 99). The yield was acceptable (61%) and no products resulting from multiple allylation reactions were observed.



Scheme 99

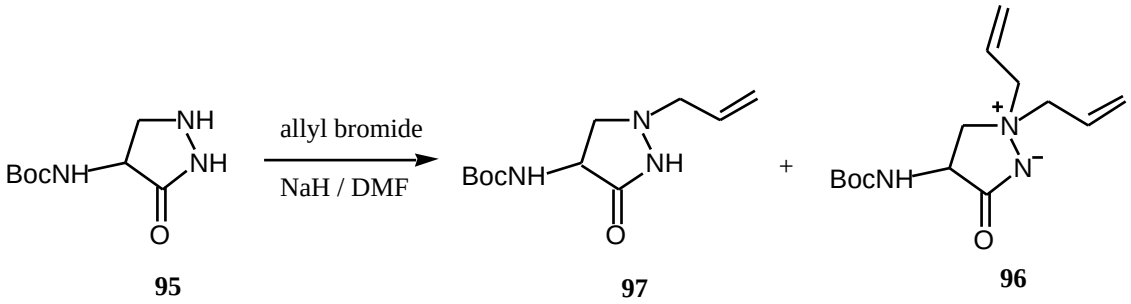
The second allylation at the lactam nitrogen (N-2) was more challenging. Indeed, when we treated **93** with allyl bromide and bases under various reaction conditions, we never obtained the desired bis-alkene **92**. During workup, we could not extract anything from the aqueous phase using standard organic solvents such as ethyl acetate. The formation of ylide **94** which is only slightly soluble in apolar solvents could explain our observed results (Scheme 100).



Scheme 100

This hypothesis was supported by the analysis of the aqueous extracts. After evaporation of water, the salt NaBr (when using NaH as the base) was removed by recrystallization from CH_2Cl_2-EtOH, then evaporation of the organic layer gave a viscous oil in quantitative yield. The structure of **94** was established by spectroscopy. The ^{1}H NMR spectrum (in DMSO-d_6) clearly showed the presence of two allyl groups with identical chemical shifts: a doublet near δ 3.82 (*J*=7.0 Hz, 4H, 1 and 1'), four olefinic protons at δ 5.48 (dm, *J*=9.6 Hz, 2H, 3 and 3' *cis* H) and δ 5.52 (dm, *J*=17.2 Hz, 2H, 3 and 3' *trans* H) respectively and two olefinic protons at δ 5.96 (ddt, *J*=17.0, 10.0, 6.9 Hz, 2H, 2 and 2'). Accordingly, only one set of data has been observed in the ^{13}C NMR spectrum for these two allyl groups: 128.1 ppm (C_2, $C_{2'}$), 125.1 ppm (C_3, $C_{3'}$) and 67.5 ppm (C_1, $C_{1'}$). Furthermore, in the IR spectrum a carbonyl stretch was found at 1576 cm^{-1} of which specially low value must be due to the amide anion.

A similar observation has been made earlier by Ternansky and Draheim[41] when they studied the allylation of pyrazolidinone **95** with allyl bromide and NaH in dimethylformamide (Scheme 101).



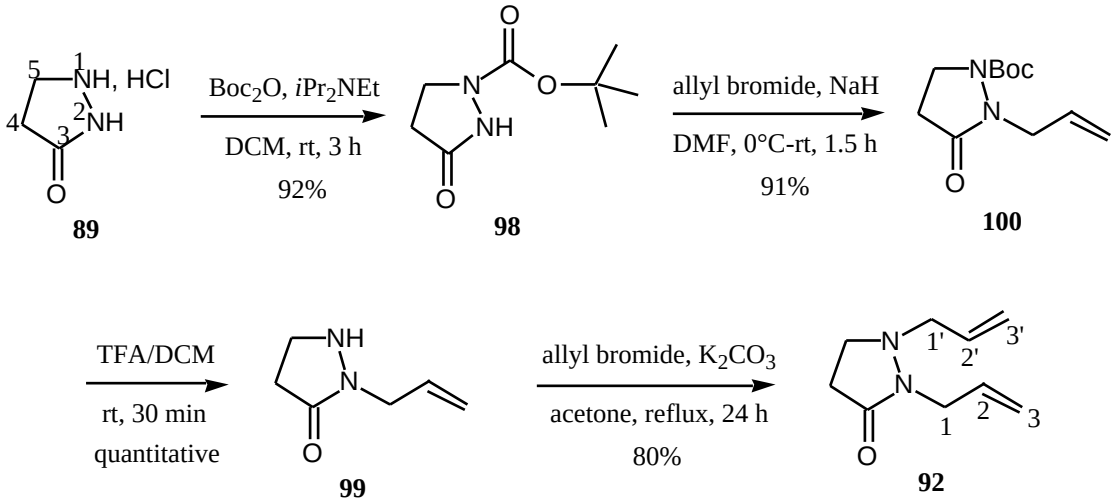
95 **97** **96**

Scheme 101

This can be interpreted by an increase of nucleophilicity of N-1 (in **93** or **97**) due to the strong α-effect[171] of the amide anion.

6.6.2.1.2 Alternative route for the diallylation of 89

A solution was eventually found by protecting the amine nitrogen N-1 with a Boc group, then effecting the allylation at the lactam nitrogen N-2. Thus, treatment of **89** with Boc_2O in the presence of *n, n*-diisopropylethylamine in dichloromethane gave the monoacylated **98** in 92% yield. The allylation at N-2 was then readily accomplished using allyl bromide and NaH in DMF. The yield was excellent (91%). Cleavage of the Boc group with trifluoroacetic acid gave **99** which was transformed into the desired diallylated product **92** in high yield (80%) by treatment with allyl bromide in the presence of potassium carbonate in acetone. Compound **92** was found to be soluble in ethyl acetate and the overall yield of **92** from pyrazolidinone hydrochloride **89** was 67% (Scheme 102).



89 **98** **100**

99 **92**

overall yield: 67%

Scheme 102

An interesting feature is the chemical shift variation of H_5 (adjacent to N-1) in the various compounds of Scheme 102. The triplet appeared at δ 3.95 for **98** and δ 3.97 for **100** when the nitrogen atom carries a Boc group. It is more shielding for the non-substituted compound **99** (δ 3.42) and allylated compound **92** (δ 3.30).

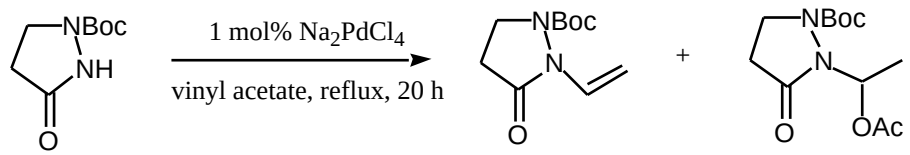
The spectral characteristics of **92** were quite different from those of ylide **94** (Table 11). In the former compound, two allyl groups are attached to two different kinds of nitrogen atoms, thus giving the different ^1H and ^{13}C signals for the corresponding carbon and protons. Due to the deshielding effect of the lactam carbonyl group, H_1 showed a downfield shift (δ 4.05) as compared to $H_{1'}$ (δ 3.40).

Table 11: Spectral comparison of **94** and **92**

	94 (δ)	**92** (δ)
H_1, $H_{1'}$	3.82 (d, *J*=6.9 Hz)	H_1: 4.05 (br. s);
		$H_{1'}$: 3.40 (d, *J*=6.2 Hz)
H_2, $H_{2'}$	5.96 (ddt, *J*=17.0, 10.0, 6.9 Hz)	5.98-5.72 (m)
H_3, $H_{3'}$	5.52 (d, J_{trans}=17.2 Hz);	5.34-5.19 (m)
	5.48 (d, J_{cis}=9.6 Hz)	
C_1, $C_{1'}$	67.5	59.3; 46.1
C_2, $C_{2'}$	128.1	133.5; 133.3
C_3, $C_{3'}$	125.1	120.5; 118.5
IR (C=O)	1576 cm^{-1}	1685 cm^{-1}

6.6.2.2 Preparation of enamide 101a and its homolog 101b

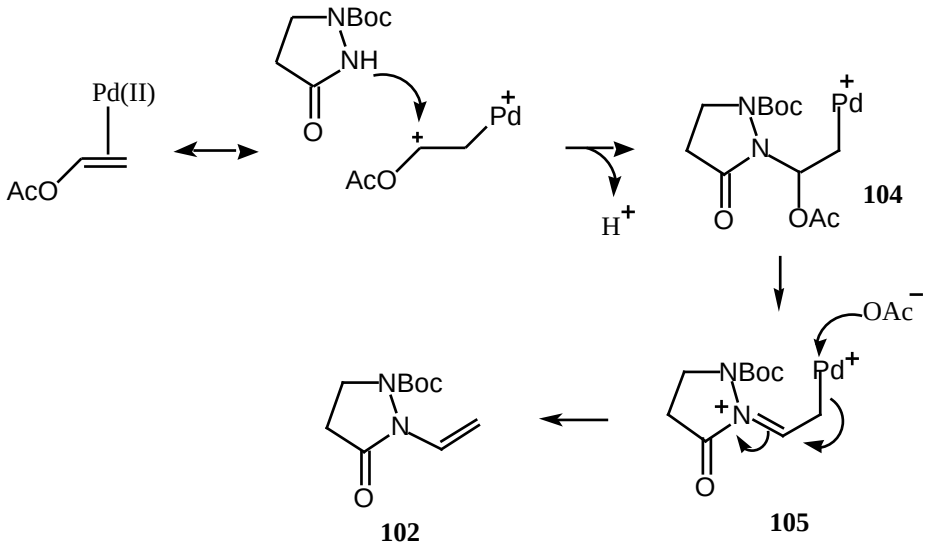
Several procedures have been developed for the preparation of enamide compound.[172,173] We selected to apply the homogeneous catalytic transvinylation between cyclic imides or lactams and vinyl acetate.[174] This method is not suitable for amines which could form a stable complex with the catalyst (generally Pd^{2+}).[175] Thus, a solution of **98** in vinyl acetate in the presence of a catalytic amount of sodium tetrachloropalladate was refluxed to yield a mixture of **102** and **103** in 62% and 28% yield respectively (Scheme 103).



98 **102** (62%) **103** (28%)

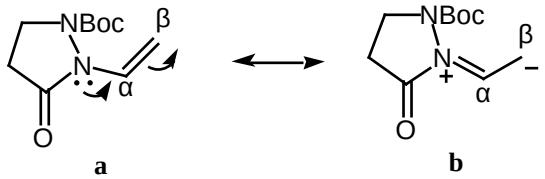
Scheme 103

The mechanism of this transformation probably involves the prior formation of a π complex between vinyl acetate and Pd (II) followed by nucleophilic attack of the amide nitrogen on the complex to generate **104**. These reactions are closely related to the solvomercuration reactions. The formation of the exocyclic iminium ion **105** followed by nucleophilic attack of acetate on Pd(I) accounts for the generation of enamide **102** (Scheme 104).



Scheme 104

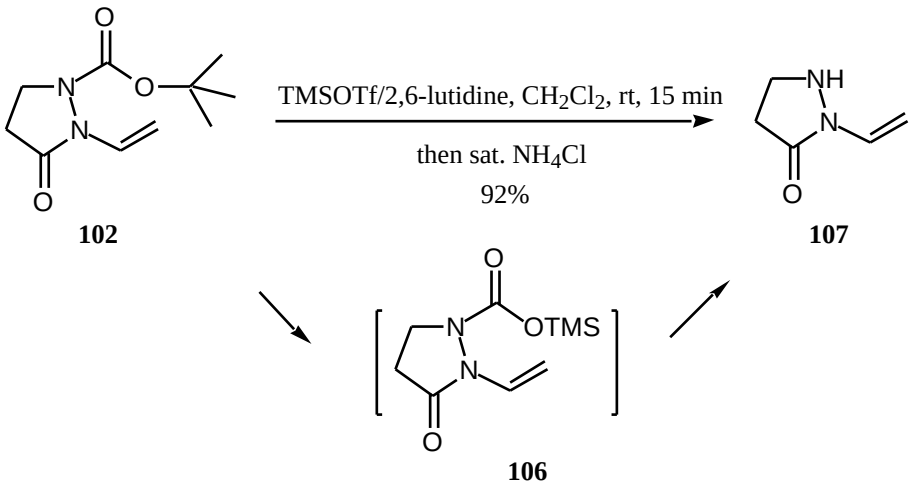
Compound **103** probably resulted from the addition of HOAc (generated during the reaction) to enamide **102** (Scheme 103). Both compounds could be easily separated by flash chromatography on silica gel. An important feature of the NMR spectra of enamide **102** is the upfield shift of the β olefinic protons (δ 4.54, d, J_{cis}=9.3 Hz; δ 4.61, d, J_{trans}=15.3 Hz) and carbon (95.5 ppm) compared to the α-proton (δ 6.91, dd, *J*=15.3, 9.3 Hz) and carbon (127.6 ppm) adjacent to the lactam nitrogen atom. This observation is in agreement with a contribution from the canonical form **b** (Scheme 105). The ^{1}H NMR spectrum of **103** clearly showed the doublet near δ 1.64 (*J*=6.4 Hz, 3H) for methyl group, and the quartet near δ 6.39 (*J*=6.3 Hz, 1H) for α-proton adjacent to the lactam nitrogen.



Scheme 105

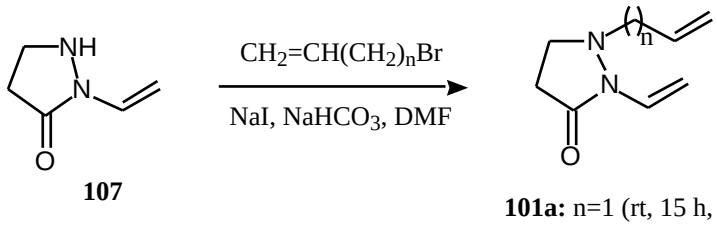
The acidic cleavage of the Boc group in trifluoroacetic acid could not be used here as a result of the presence of the acid-sensitive enamide **102**. However, it was readily effected by addition of 1.5 equiv of TMSOTf in the presence of 2 equiv of 2,6-lutidine in a solution of

CH_2Cl_2.[176] This reaction involved the formation of a labile *O*-silyl carbamate **106**, which was cleaved during aqueous workup (Scheme 106). Compound **107** could be purified by column chromatography on silica gel. A triplet (δ 4.67, *J*=7.9 Hz, 1H) for the amine proton was clearly visible in the ^{1}H NMR spectrum, and the N-H stretch was found at 3217 cm^{-1} in the IR spectrum.



Scheme 106

The alkylations at N-1 of the resulting 2*N*-vinyl pyrazolidinone **107** were then effected by using allyl bromide (n=1) or 4-bromo-1-butene (n=2) in the presence of NaI and $NaHCO_3$ in DMF (Scheme 107). As expected, the allylation easily occurred and compound **101a** was obtained in 90% yield. The reaction of **107** with 4-bromo-1-butene did not take place at ambient temperature and heating at 80°C gave product **101b** in 51% non-optimized yield along with a 28% recovered yield of **107**.

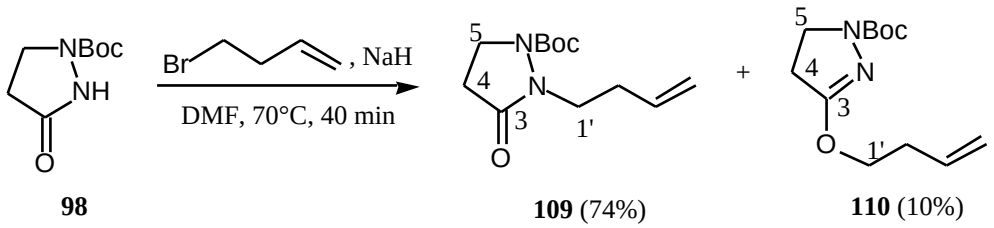


Scheme 107

6.6.2.3 Preparation of β-enamino ester 108

Treatment of pyrazolidinone **98** with NaH and 4-bromo-1-butene in DMF at rt only led to the recovery of the two starting materials. The reaction took place at 70°C. Two products

derived from *N*- and *O*- alkylation were obtained in 74% and 10% yield respectively (Scheme 108).



98 **109** (74%) **110** (10%)

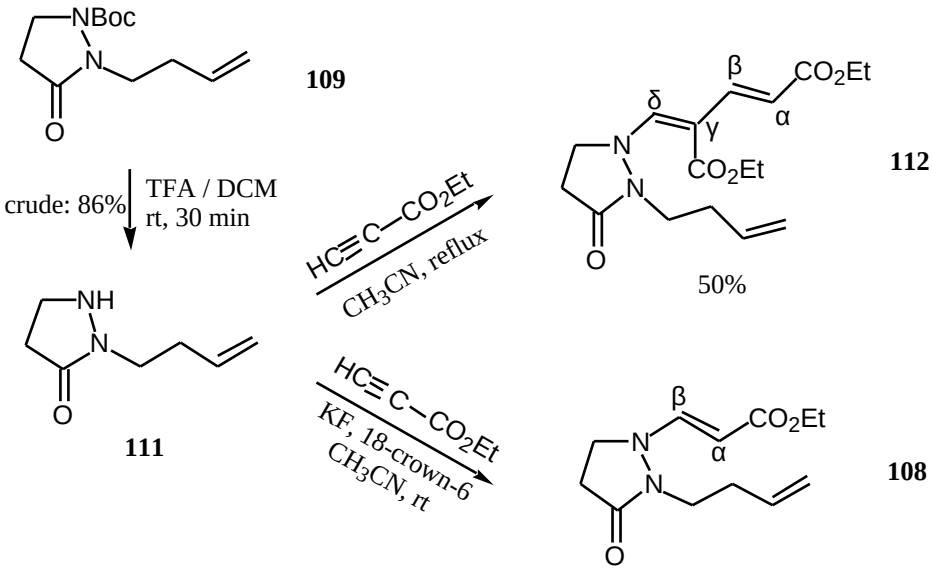
Scheme 108

109 and **110** were easily distinguished by examination of their proton and carbon NMR spectra as well as their IR stretching frequencies (Table 12). Thus, $H_{1'}$ in **110** (δ 4.29) was deshielded with respect to that in **109** (δ 3.81) due to the connection of $C_{1'}$ with an oxygen atom. The same observation was made for $C_{1'}$ (69.4 *vs* 47.8 ppm). The coupling constant value between H_4 and H_5 in **110** is larger (9.7 *vs* 7.7 Hz). In the IR spectrum, the lactam carbonyl stretch appeared at a high frequency (1731 cm^{-1}) than the imine stretch (1637 cm^{-1}).

Table 12: Spectral data for **109** and **110**

	109	**110**
$H_{1'}$	3.81 δ (t, *J*=6.7 Hz)	4.29 δ (t, *J*=6.7 Hz)
H_4	2.54 δ (t, *J*=7.7 Hz)	2.83 δ (t, *J*=9.7 Hz)
C_3	172.3 ppm	165.0 ppm
$C_{1'}$	47.8 ppm	69.4 ppm
C_4	32.0 ppm	33.7 ppm
IR (cm^{-1})	1731 (C=O)	1637 (C=N)

Cleavage of the Boc group in trifluoroacetic acid gave crude **111** which was directly treated with ethyl propiolate in refluxing acetonitrile.[177] This led to a 50% yield of yellow product **112** resulting from a double Michael addition (Scheme 109). In the ^1H NMR spectrum of **112**, a singlet at δ 7.78 for olefinic proton δ was clearly visible; the *trans* H_α and H_β appeared at δ 7.46 and δ 6.34 respectively, with a typical coupling constant of 15.9 Hz.



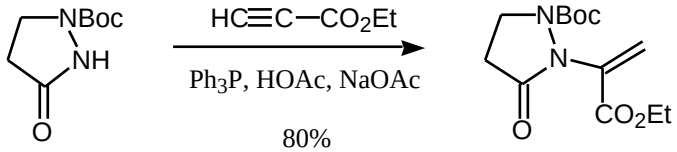
Y: 57% (recovered **S.M.**: 40%)

Scheme 109

Belsky[178] reported that in aprotic solvents containing 18-crown-ether, KF is an efficient and powerful catalyst for Michael additions. Acetonitrile gave a combination of high yields and short reaction times. We then performed the Michael reaction in the presence of 20% anhydrous KF and 0.6% 18-crown-6 in CH_3CN. The conjugate addition took place at rt and gave **108** in 57% non-optimized yield (Scheme 109). The coupling constant value between two olefinic protons (H_α and H_β) was 13.5 Hz, which is typical of a *trans* configuration. The special upfield shift of α-H (δ 4.99) and downfield shift of β-H (δ 7.39) could be due to the electronic effects of the amine nitrogen and the ester functionality.

6.6.2.4 Preparation of dehydroamino ester 113a and its homolog 113b

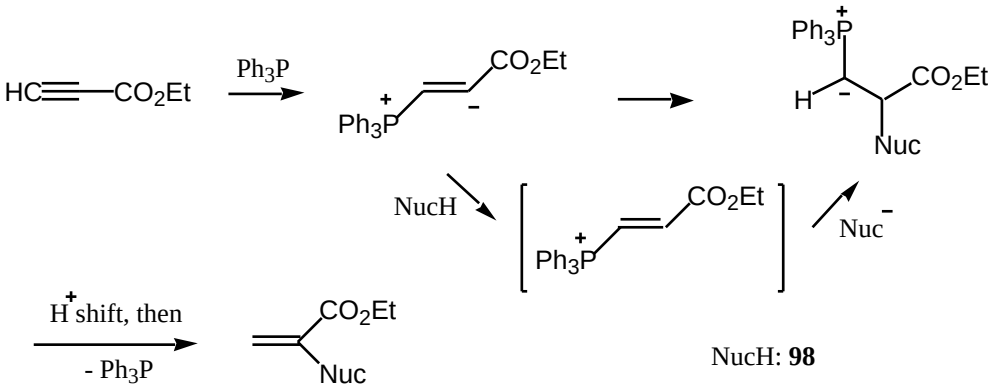
N-α-Acryl derivatives of pyrazolidinone **98** should be of particular interest in the conduct of the synthesis of aza-analogs of penicillins and cephalosporins. A potentially useful approach could be the nucleophilic addition to the α-carbon of an alkynoate.[179] The synthesis of the first representative of this class was readily performed by heating a 1:1 mixture of ethyl propiolate and **98** at 105°C in toluene with 10 mol% triphenylphosphine, 50 mol% acetic acid, and 50 mol% sodium acetate (Scheme 110). The adduct **114** was obtained in 80% yield, and its structure was unambiguously confirmed by the spectroscopy. The ^1H NMR spectrum gave two distinct singlets at δ 6.33 and δ 5.95 for the two non-equivalent vinylic protons.



98 **114**

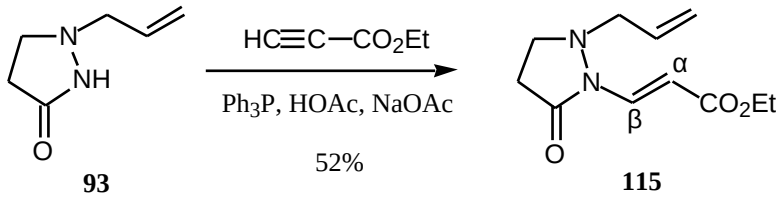
Scheme 110

The mechanism of the reaction is shown in Scheme 111. The proposed route requires both general acid and base catalysis explaining the use of a 1:1 sodium acetate - acetic acid buffer.



Scheme 111

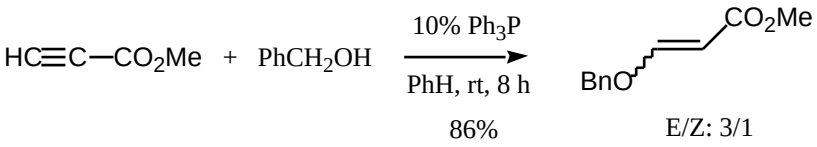
Interestingly, when we ran the reaction under the same conditions using 1*N*-allyl pyrazolidinone **93** as the nucleophile, only β-amino-α, β-unsaturated ester **115** was obtained in 52% yield (Scheme 112). In the ^{1}H NMR spectrum of **115**, the *trans* olefinic protons appeared at δ 7.44 (H_β, d) and δ 4.96 (H_α, d) respectively, with a typical coupling constant value of 13.2 Hz.



93 **115**

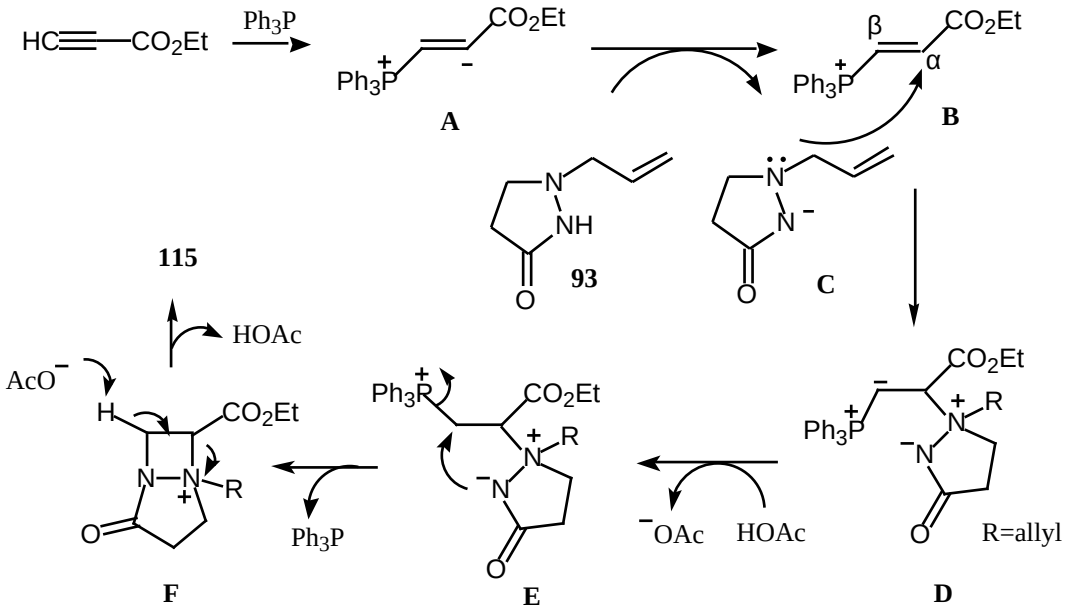
Scheme 112

Compound **115** seemed to result from the simple conjugate addtion. A similar observation had been made by Inanaga and co-workers[180] in the study of the addition of benzyl alcohol to methyl propiolate in the presence of a catalytic amount of Ph_3P (Scheme 113). However, this Michael addition had been run in the absence of HOAc/NaOAc.



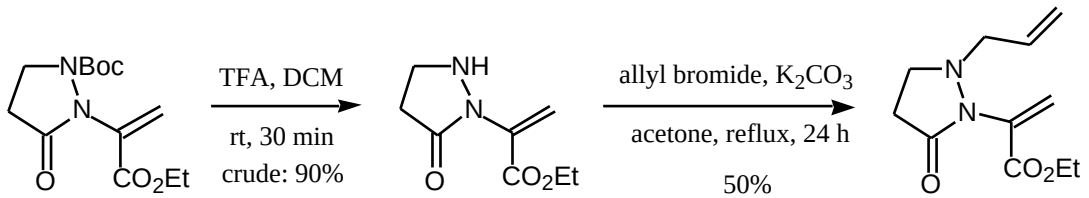
Scheme 113

Based on our previous observation, we assumed the following mechanism for the formation of **115** (Scheme 114): triphenylphosphine attacked the β-carbon of ethyl propiolate to give the intermediate **A**, which then abstracted a proton from **93** to form the corresponding phosphonium **B**. As discussed earlier, the amine nitrogen in **C** exhibited highly increased nucleophilicity and its attack on the α-carbon of **B** generatedintermediate **D**. Abstraction of a proton from HOAc followed by the nucleophilic attack of the amide anion in **E** and elimination of Ph_3P gave the bicyclic intermediate **F**. The final β-elimination of ammonium would yield **115**.



Scheme 114

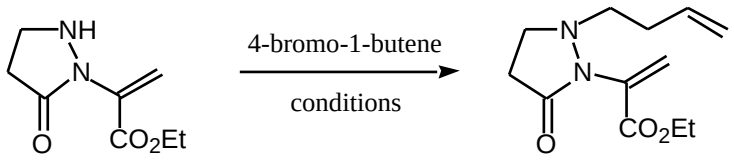
We met no difficulties in effecting the acidic cleavage of the Boc group and allylation at N-1 with allyl bromide. The dehydroamino ester **113a** was obtained in 50% non-optimized yield (Scheme 115).



114 **116** **113a**

Scheme 115

We also tried to prepare the homolog **113b** (Scheme 116, Table 13). However, the alkylation reaction with 4-bromo-1-butene in acetone in the presence of K_2CO_3 only gave the starting material (Entry 1). We got the same result using 4-bromo-1-butene and NaI/$NaHCO_3$ in DMF at room temperature (Entry 2), but the product could be obtained in 50% yield by heating at 50°C overnight (Entry 3).



116 **113b**

Scheme 116

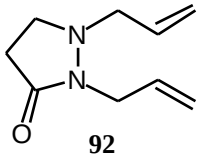
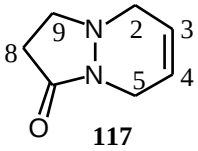
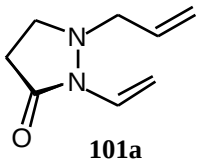
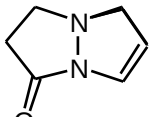
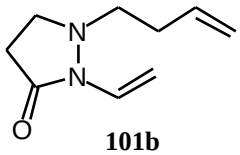
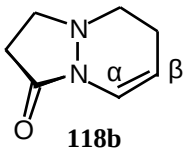
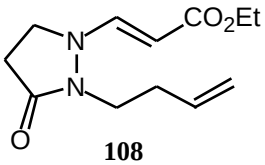
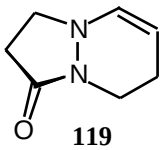
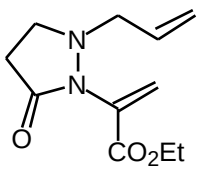
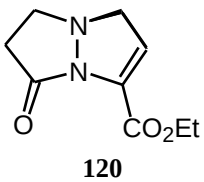
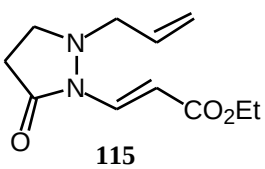
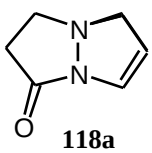
Table 13: Alkylation of **116** with 4-bromo-1-butene

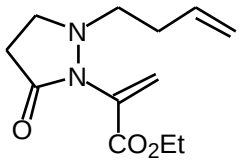
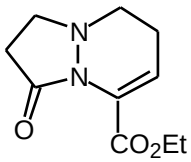
Entry	Conditions	Results
1	K_2CO_3, acetone, reflux, 16 h	Recovered **S.M.**
2	NaI, $NaHCO_3$, DMF, rt, 16 h	Recovered **S.M.**
3	NaI, $NaHCO_3$, DMF, 50°C, 16 h	50% **113b**

6.6.3 Ring-closing metathesis

With a range of diolefinic substrates in hand, we began our studies of the metathesis reactions (Table 14).

Table 14: RCM to bicyclo aza-γ-lactams

Entry	Substrate	Cat. (mol%)	Conditions	Product	Yield (%)
1	 **92**	**77** (5X5)	CH_2Cl_2 (0.07 M), rt, 3 h, then reflux, 18 h; or toluene, 80°C, 24 h	 **117**	0
		88 (5)	toluene (0.2 M), 50°C, 2 h		92
2	 **101a**	**88** (3X10)	toluene (0.06 M), 50°C, 15 h; 80°C, 48 h	 **118a**	trace
3	 **101b**	**88** (2X10)	toluene (0.07 M), 50°C, 16 h; 80°C, 6 h	 **118b**	72
4	 **108**	**88** (2X10)	toluene (0.07 M), 50°C, 15 h; 80°C, 24 h	 **119**	trace
5	 **113a**	**88** (2X10)	toluene (0.06 M), 50°C, 15 h; 80°C, 24 h	 **120**	30
6	 **115**	**88** (2X10)	toluene (0.06 M), 50°C, 16 h; 80°C, 24 h	 **118a**	trace

7	 **113b**	**88** (3X10)	toluene (0.07 M), 50°C, 10 h; 80°C, 17 h	 **121**	61

Diallylated pyrazolidinone **92** was first exposed to a catalytic amount of standard Grubbs ruthenium catalyst **77** (5 mol%) in dichloromethane. After 3 h at rt, the starting material remained unchanged. We failed to obtain any bicyclic aza-γ-lactam **117** even at higher catalyst loadings (catalysts were added at intervals) or under severe reaction conditions (Entry 1).

The stable and more reactive second-generation ruthenium catalyst **88** was then used. To our delight, substrate **92** underwent a clean and rapid cyclization in the presence of 5 mol% catalysts in toluene. After column chromatography, **117** was obtained in 92% yield (Entry 1). In the present case, the RCM reaction was very effective even at a 0.2 M concentration.

The sharp contrast in reactivity between ruthenium carbene **77** and **88** probably originates from the amine nitrogen lone pair in **92**, which could complex the catalyst metal center in **77** with consequent deactivation.

The ^{1}H NMR spectrum of **117** obtained at 20°C was largely uninterpretable, whereas the corresponding spectrum recorded at 50°C was well resolved. The olefinic protons H_3 and H_4 gave rise to a multiplet in the range of δ 5.82-5.72; as a result of the deshielding effect of the carbonyl group, H_5 gave a broad singlet at δ 4.02, while H_2 appeared at δ 3.25; two broad singlets at δ 3.31 and δ 2.55 were assigned to H_9 and H_8 respectively.

The formation of bicyclo [3.3.0] ring systems by RCM reaction was more difficult. Enamide **101a** was totally recovered in the presence of 10 mol% **88** in toluene after heating at 50°C overnight; only traces of product were observed at high catalyst loadings and under more severe conditions (Entry 2). RCM reaction of enamino ester **113a** worked better, and the corresponding bicyclic pyrazolidinone was obtained in 30% yield under relatively forcing conditions (Entry 5). However, β-enamino ester **115** gave a disappointing result (Entry 6). This was probably due to the steric hindrance of the terminal ester group. In all three cases, we considered the sterically unhindered allylic olefin as the initiation site for RCM.

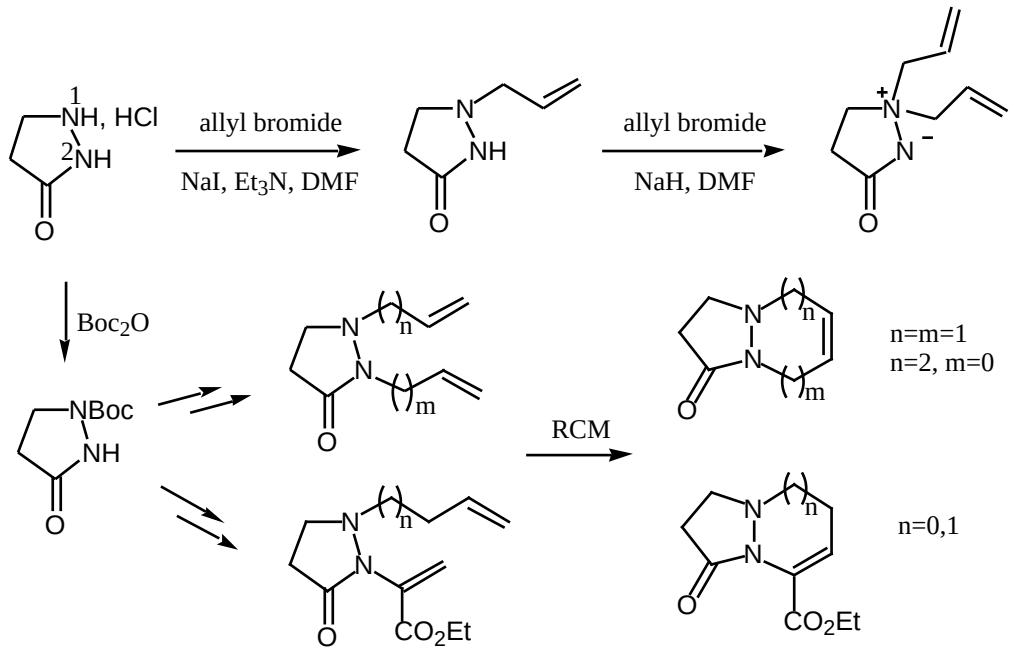
Attempted RCM reaction of β-enamino ester **108** met with no success (Entry 4).

As expected, bicyclo [4.3.0] aza-γ-lactams were more readily accessible via RCM reactions than the corresponding [3.3.0] ring systems. **118b** was obtained in 72% yield in the presence of 20 mol% catalyst **88** (Entry 3). The *cis* olefinic protons in the ^{1}H NMR spectrum

appeared at δ 6.83 (H_α, d, *J*=8.1 Hz) and δ 5.14 (H_β, dt, *J*=8.1, 3.9 Hz) respectively; the corresponding carbons were clearly visible at 119.4 ppm (C_α) and 106.2 ppm (C_β) in the ^{13}C NMR spectrum. In a similar way, RCM of **113b** gave **121** in 61% yield (Entry 7). A typical triplet at δ 6.18 for olefinic proton was observed in the ^1H NMR spectrum, with a coupling constant value of 3.9 Hz.

6.7 Conclusion

Direct diallylation at two different nitrogen atoms in pyrazolidinone ring failed due to the increased nucleophilicity of N-1 when an amide anion was formed. Thus, N-1 was protected with a Boc group, then various functionalizations at N-2 were readily accomplished. This methodology allowed us to prepare a variety of bis-alkenes used as the precursors of the RCM reaction. The ruthenium complex bearing a saturated NHC ligand could tolerate the common aza-γ-lactam functionality. RCM proved to be a good strategy to construct the bicyclo [4.3.0] pyrazolidinones. However, the formation of bicyclo [3.3.0] ring systems was less successful (Scheme 117).



Scheme 117

The increasing clinical importance of drug-resistant bacterial pathogens has lent additional urgency to microbiological and antibacterial research. The preliminary studies of bicyclic pyrazolidinone derivatives using olefin ring-closing metathesis methodology prompted us to investigate its synthetic utility to another type of highly reactive β-lactam: aza-β-lactams. Our ultimate goal is to develop a new synthetic methodology that would provide ready access to a

diverse array of structural derivatives. It was our hope that the availability of such analogs would allow us to prepare compounds having improved biological activities. The following three chapters will detail the results of our synthetic studies.

Chapter 7

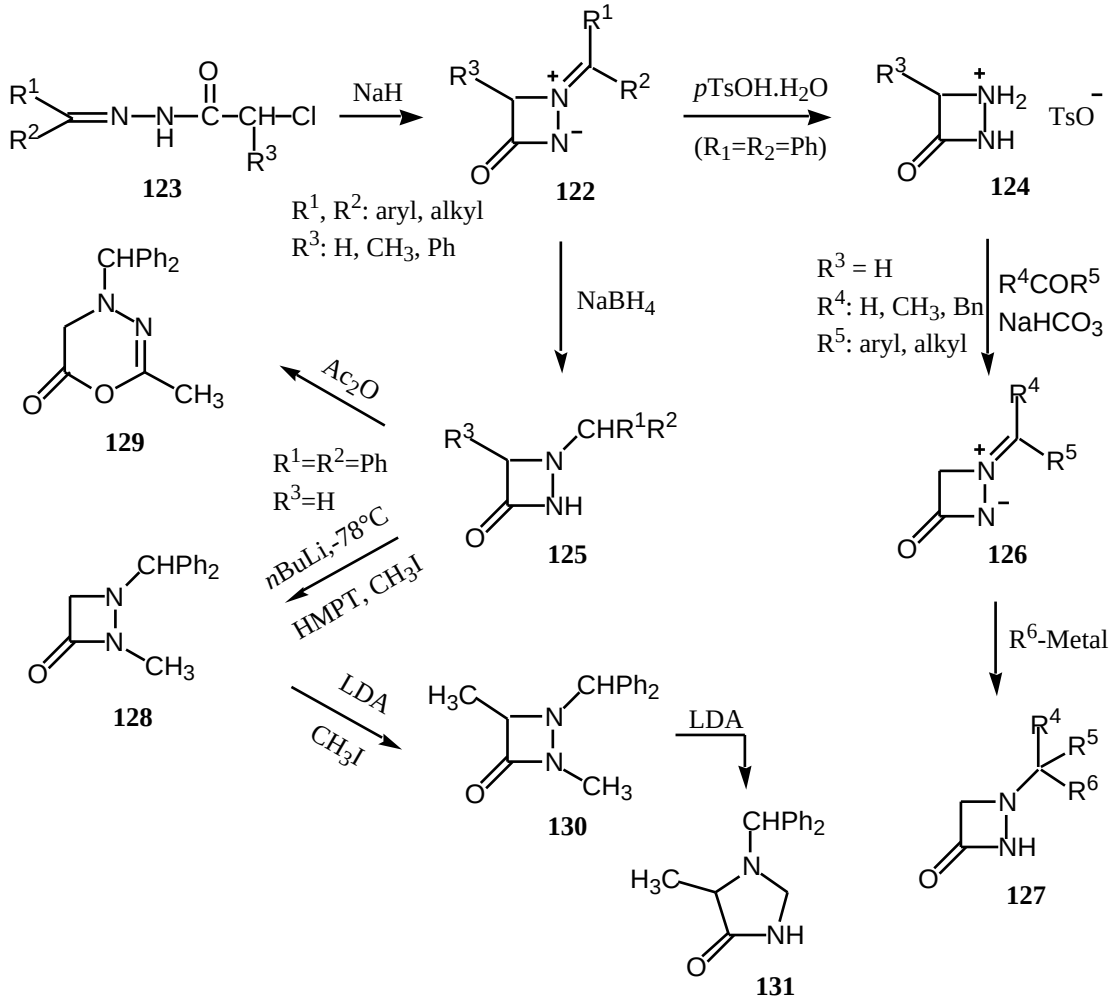
RCM approach towards bicyclo [4.2.0] 1, 2-diazetidin-3-one

7.1 Synthetic studies of monocyclic and bicyclic 1,2-diazetidin-3-one derivatives: literature survey

Synthetic studies of highly strained 1, 2-diazetidin-3-one derivatives (aza-β-lactams) have been undertaken by only a few research groups. Among them, Taylor *et al.* have made significant contributions.[34,44]

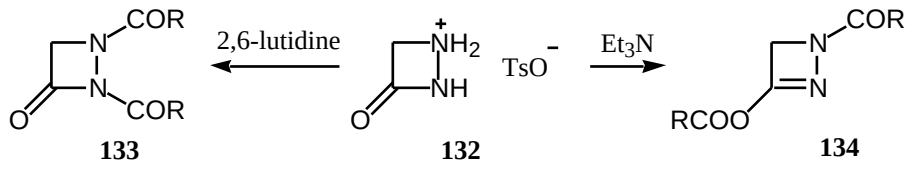
7.1.1 Taylor's work

The early work of Taylor's group in this field is summerized in Scheme 118. 3-Oxo-1,2-diazetidinium ylides **122** were readily prepared by the intramolecular dehydrohalogenation of α-haloacyl hydrazones **123** derived from certain diaryl, aralkyl, and dialkyl ketones. Furthermore, these ylides could be easily converted to 3-oxo-1,2-diazetidinium tosylates **124** by hydrolysis, or to 1-substituted diazetidin-3-ones **125** by reduction.[181] Treatment of **124** (R^3=H) with aromatic aldehydes or ketones in the presence of $NaHCO_3$ effected reconversion to azomethine ylides **126**.[182] Certain organometallic reagents (*e.g.* CH_3MgBr) could be added to the iminium function of **126** to yield 1-substituted 1,2-diazetidin-3-ones **127**.[183] On the other hand, the 2-methylated derivative **128** was readily obtained by reaction of the corresponding lithium salt of **125** with 1 equiv of CH_3I in the presence of 1 equiv of hexamethylphosphoric triamide, whereas the reaction of **125** with acetic anhydride led to ring expansion with the exclusive formation of **129**. 1-Benzhydryl-2-methyl-1,2-diazetidin-3-one **128** could be substituted at C-4 by deprotonation with LDA, followed by addition of MeI to give **130**. Remarkably, addition of 1 equiv of LDA to a solution of **130** in anhydrous THF at -78°C brought about instantaneous ring expansion to 1-benzhydryl-5-methylimidazolidin-4-one **131**.



Scheme 118

Attempts to effect the monoacylation of **132** under a variety of reaction conditions only led to a polymeric solid. Treatment of **132** with 2 equiv of acyl chlorides in the presence of 2,6-lutidine yielded 1,2-diacyl derivatives **133**, whereas acylations in the presence of Et_3N gave *N*, *O*-diacylated derivatives **134** (Scheme 119).[184]

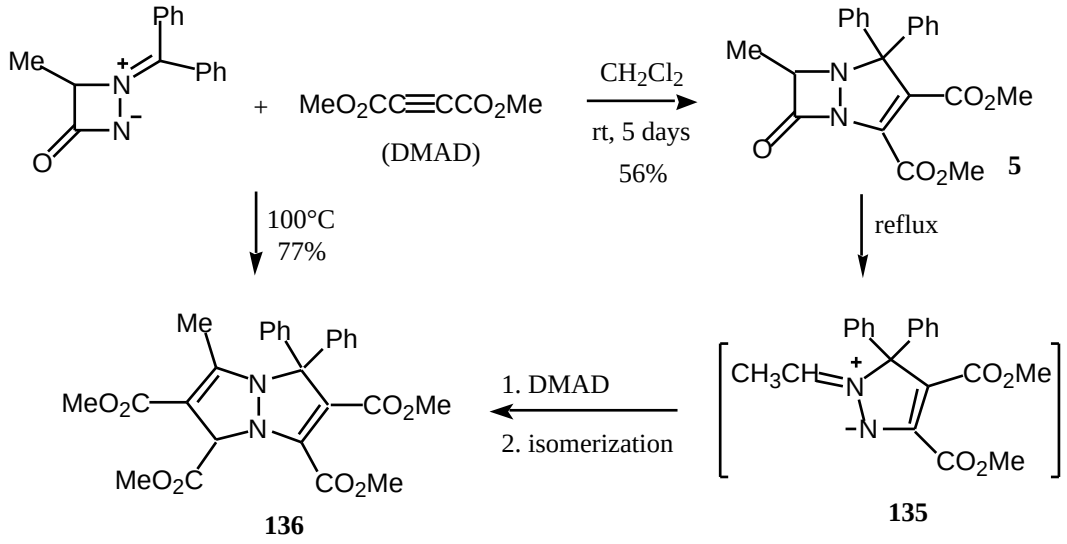


R= aryl, cyclohexyl, *t*-butyl

Scheme 119

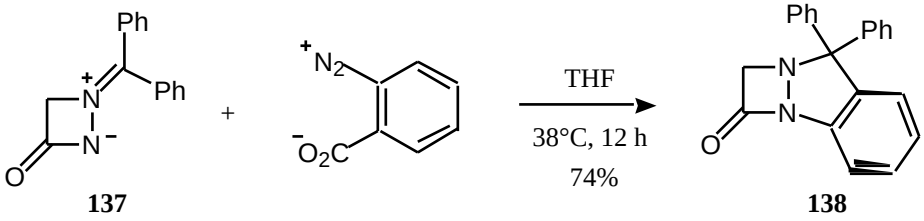
It should also be noted that attempts to alkylate **132** with a variety of alkyl halides resulted only in extensive polymerization, apparently due to the instability of 1,2-diazetidin-3-one in the absence of an effective electrophilic trapping agent.[185]

The reaction of ylide **122** (R^1=R^2=Ph, R^3=Me) with dimethyl acetylenedicarboxylate (DMAD) at rt gave cycloadduct **5** in moderate yield (56%). Refluxing resulted in the loss of carbon monoxide to give ylide intermediate **135**. Addition of a second equivalent of DMAD followed by isomerization yielded **136**, identical with the product obtained upon reaction of the starting ylide with DMAD at 100°C (Scheme 120).[181]



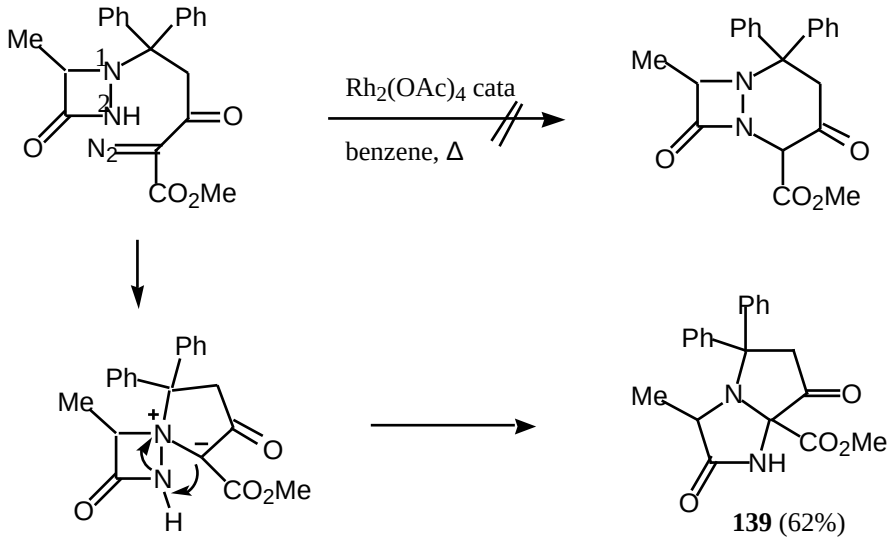
Scheme 120

The 1,3-dipolar cycloaddition of benzyne with 3-oxo-1,2-diazetidinium, inner salt **137** could also be effected to give the tricyclic adduct **138** (Scheme 121).[44]



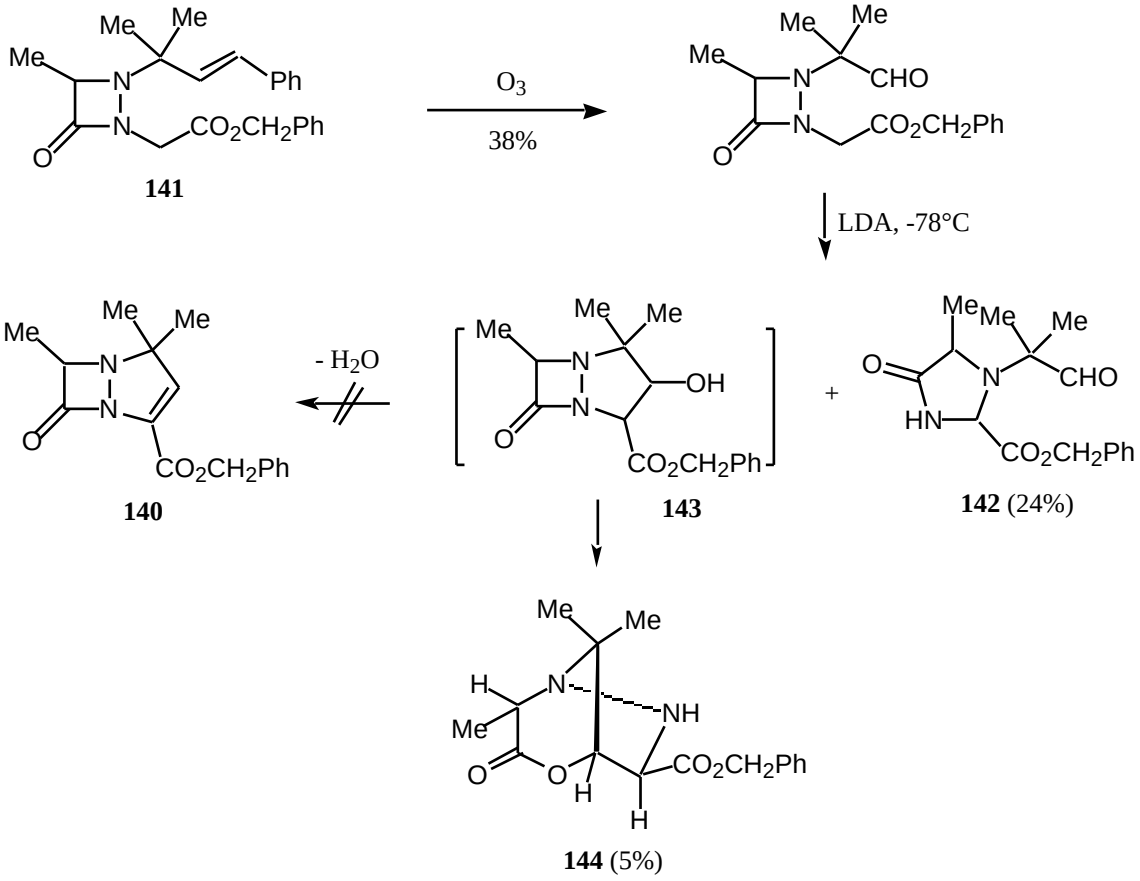
Scheme 121

However, the above [3+2] cycloaddition method was not applicable to the preparation of diazetidinones related to the carbapenem antibiotics. Other strategies were investigated which were inspired by well-established methods in the β-lactam field. Thus, an attempt to apply the "normal" α-diazo ketone carbene insertion reaction to an aza-β-lactam gave the "wrong" product **139** derived from interception of the intermediate carbene by N-1 which is much more nucleophilic than N-2. This was followed by a ring expansion (Scheme 122).[186]



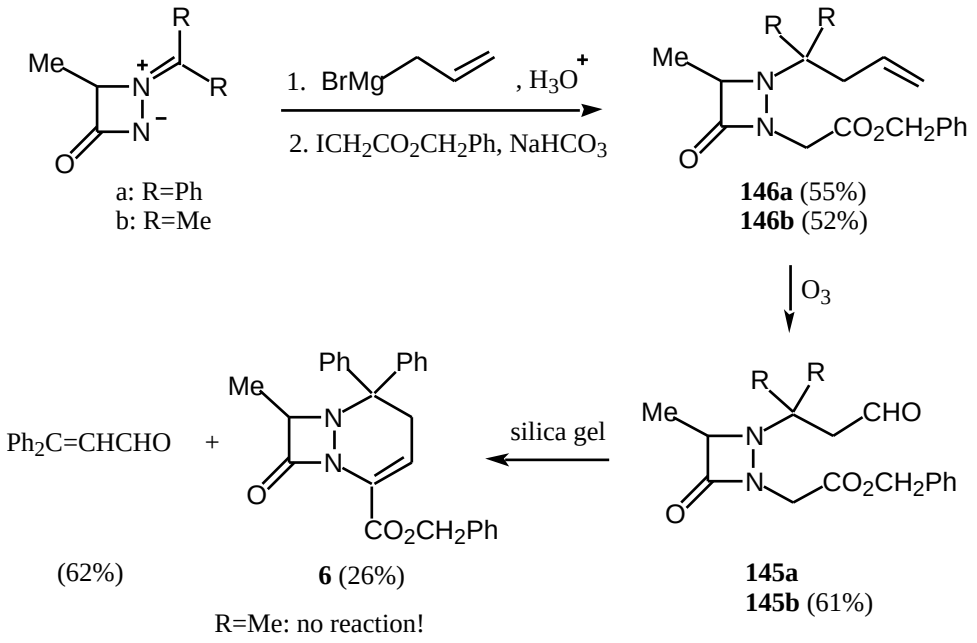
Scheme 122

Attempts to synthesize aza-penem analog **140** by intramolecular aldol condensation also failed.[45] As shown in Scheme 123, ozonolysis of **141** gave the corresponding aldehyde in 38% yield. Treatment with LDA yielded imidazolidinone **142** and an "aldol" product **143** which was inert under a variety of dehydrating conditions. The formation of **144** involved the intramolecular opening of the aza-β-lactam ring by the secondary hydroxyl group.



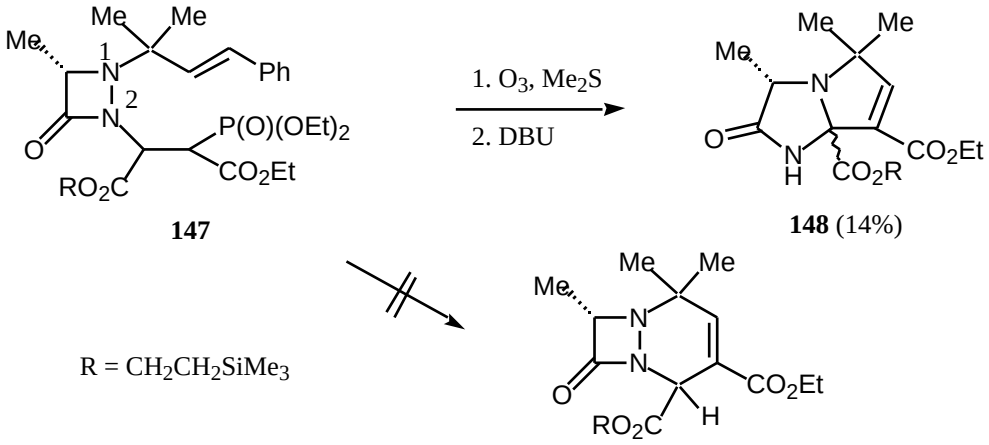
Scheme 123

Extensions of the above reactions to homologous precursors were only partially successful. Attempts to isolate the aldehyde **145a** by column chromatography on silica gel led surprisingly to a mixture of β-phenylcinnamaldehyde (62%) and the dehydrated aldol product **6** (26%), whereas the acid-catalyzed aldol condensations of **145a** were unsuccessful. Aldol condensations of **145b** (R=Me) could not be effected under many attempted conditions, including treatment with silica gel (Scheme 124).[187]



Scheme 124

Woodward's "Wittig strategy" was also applied to the preparation of aza-β-lactams.[188] However, ozonolysis of compound **147** followed by treatment with DBU led only to the rearranged bicyclic imidazolidinone **148** in poor yield. Removal of an α-proton to N-2 in 1,2-disubstituted diazetidinone resulted in an instantaneous ring-expansion reaction, analogous to the Stevens rearrangement (Scheme 125).

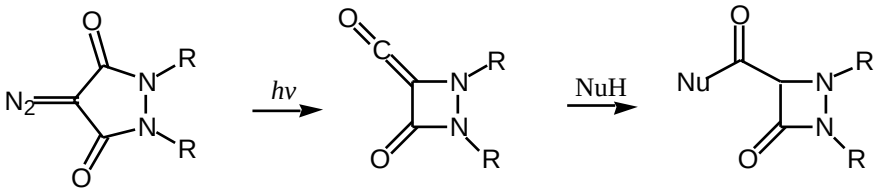


Scheme 125

The above results provide further evidence that the structural similarity of 1,2-diazetidin-3-ones with β-lactams is more apparent than real and that even simple extentions of standard β-lactam chemistry to its aza-analogs can be fraught with unexpected chemistry.

7.1.2 Moody's work

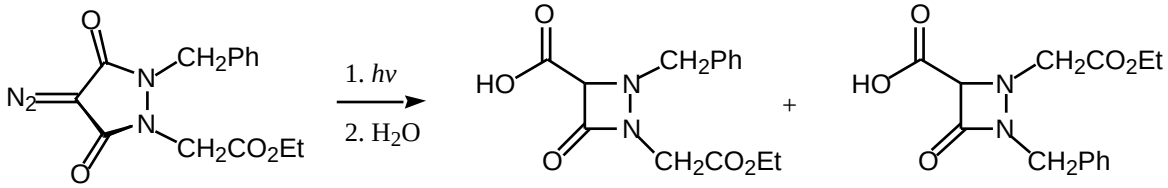
Moody *et al.* have also been engaged in the development of synthetic strategies towards 1,2-diazetidinones. They reported a concise route based on the photochemical ring contraction of 4-diazopyrazolidine-3,5-diones **149** and subsequent trapping of the intermediate ketenes with nucleophiles (Scheme 126).[189,190]



149 **150**

Scheme 126

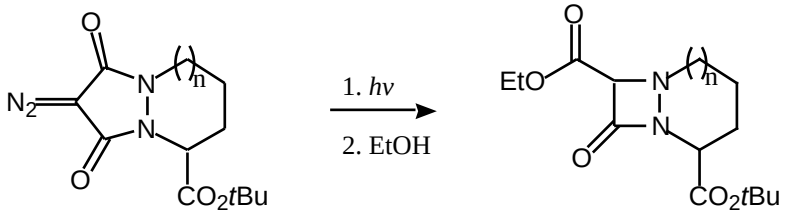
Some selectivity has been observed in the photolysis of the diazopyrazolidinedione **151**, the *N*-benzyl group migrating more readily than the *N*-alkyl group bearing an electron-withdrawing ester substituent (Scheme 127).[191]



151

Scheme 127

This ring contraction reaction gave monocyclic derivatives **150** in moderate yields (*e. g.* R=CH_2Ph, Nu=EtO: Y=45% in Scheme 126). It was however less successful in the preparation of bicyclic derivatives. The aza-cepham analog **152a** was obtained in low yield (12%) and the more strained aza-penam **152b** was not formed at all (Scheme 128).[192]

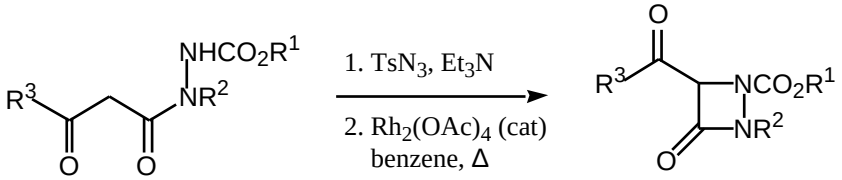


153

152a: 12% (n=1)
152b: 0 (n=0)

Scheme 128

As an alternative route towards aza-β-lactams **154**, Moody *et al.*[193,194] exploited the intramolecular nucleophilic attack of the amide NH on the rhodium carbenoid (generated from the corresponding diazo-compound). The monocyclic 1,2-diazetidin-3-ones were obtained in high yields (Scheme 129). The synthesis of bicyclic products by this method has not been reported.



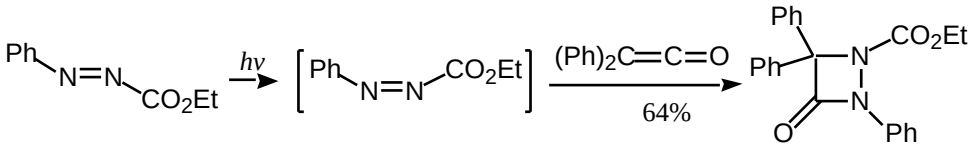
R^1: *t*Bu, CH_2Ph
R^2: CH_2Ph, CH_2CO_2Et
R^3: OEt, Me

154 (75-100%)

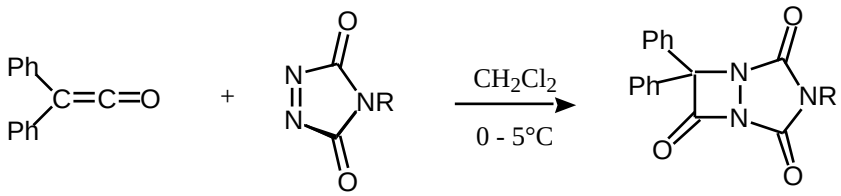
Scheme 129

7.1.3 Investigations by other groups

The formation of a 1,2-diazetidinone by reaction of a ketene with an azo compound was first reported by Staudinger.[195] This kind of cycloaddition reaction was often run by irradiating mixtures of *trans*-azo compound and ketene, the ketene trapping the more reactive, *in situ* photogenerated *cis*-azo compound.[196,197] It has been postulated that the reaction proceeded by a $[\pi 2_s + \pi 2_a]$ concerted pathway.[198] Although there are several examples of this type of reactions in the literature (Scheme 130), for the most part the resulting 1,2-diazetidinones were not suitable for further elaboration to β-lactam antibiotic analogs.



Kerber, R. C.; Ryan, T. J.; Hsu, S. D. *J. Org. Chem.* **1974**, *39*, 1215-1221



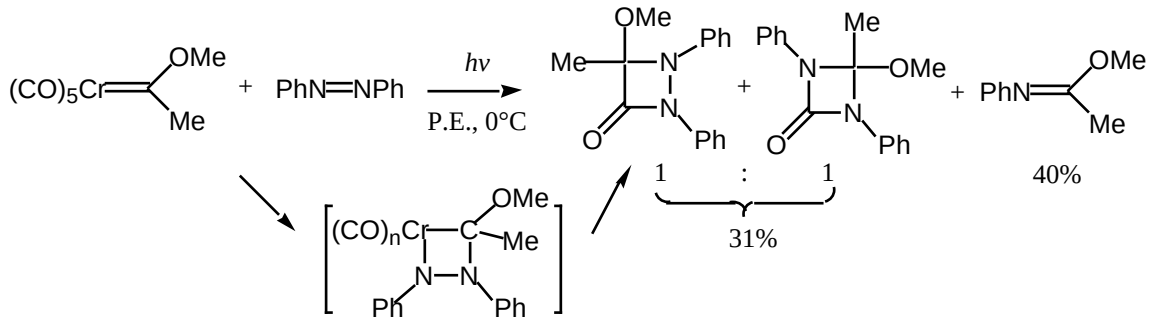
R: alkyl, Ph

Y: 49-54%

Hall, J. H.; Krishnan, G. *J. Org. Chem.* **1984**, *49*, 2498-2500

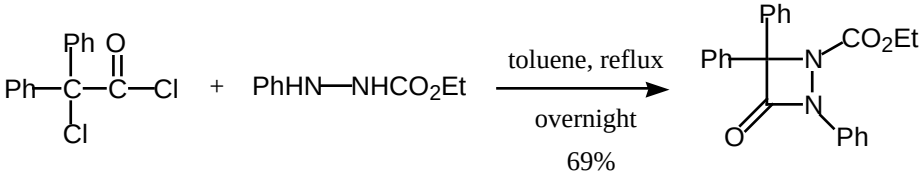
Scheme 130

Hegedus *et al.*[199] have reported that photolysis of a solution of azobenzene and chromium carbene complex in petroleum ether produced an inseparable mixture of 1,2- and 1,3-diazetidinones and an imino ether (Scheme 131). The first step was probably the photocycloaddition of the azobenzene to the chromium carbene complex to generate a diazemetallacyclobutane. This was followed by CO insertion and reductive elimination to form the 1,2-diazetidinone.

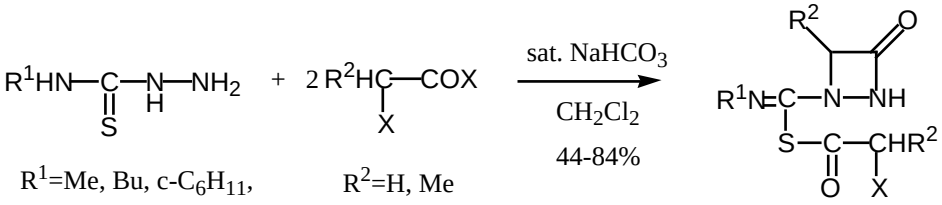


Scheme 131

1,2-Diazetidinones could also be formed by two displacement reactions (Scheme 132).



Bird, C. W. *J. Chem. Soc.* **1963**, 674-677



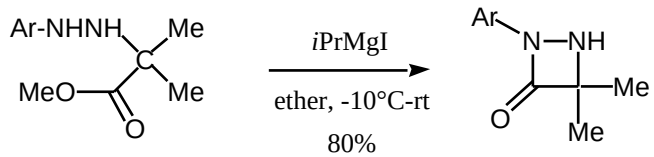
R[1]=Me, Bu, c-C_6H_{11}, $PhCH_2$, Ph

R[2]=H, Me
X=Cl, Br

Okawara, T.; Kato, R.; Yamasaki, T.; Yasuda, N.; Furukawa, M.
Heterocycles **1986**, *24*, 885-888

Scheme 132

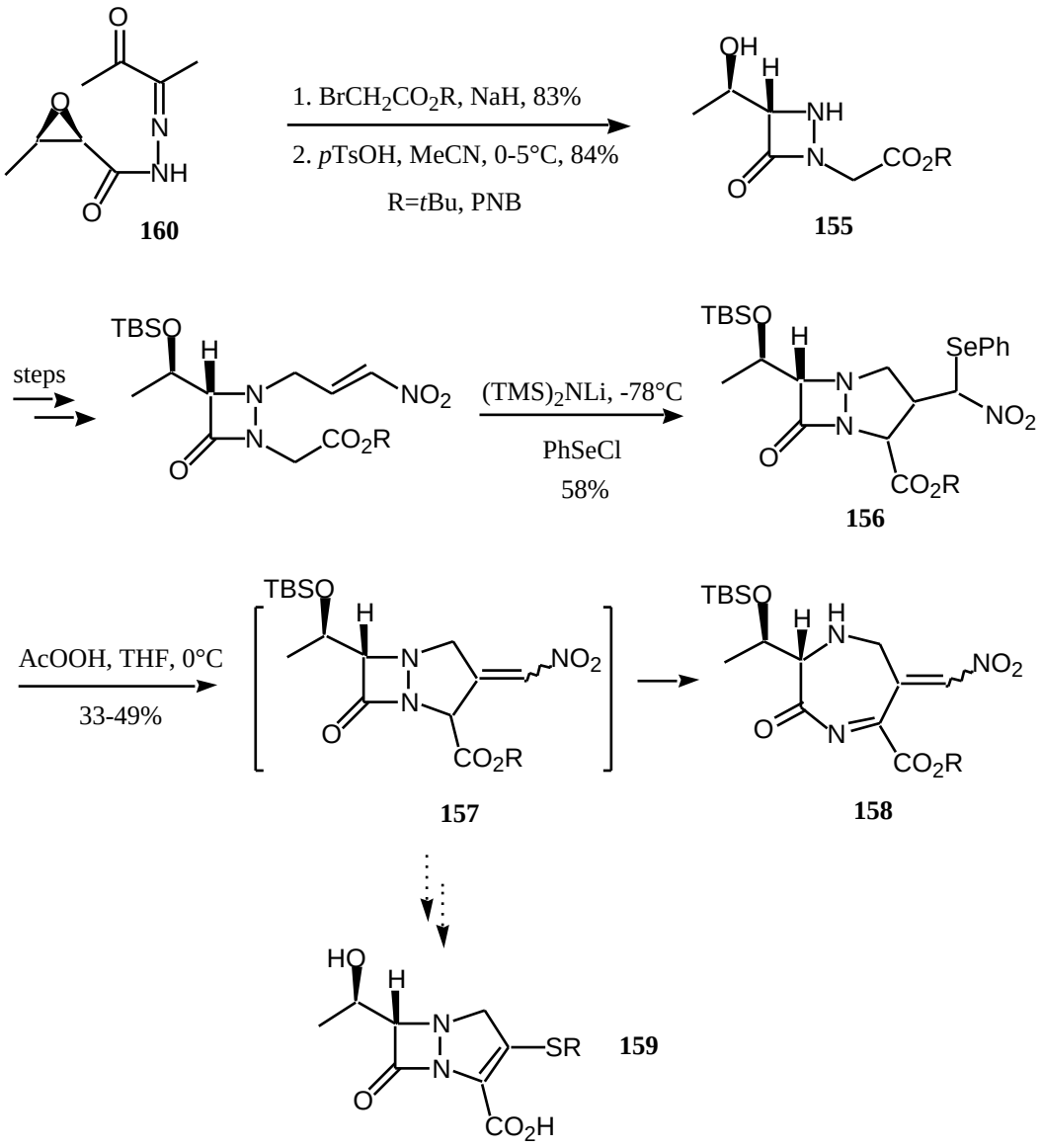
Grignard-induced cyclization of α-(2-arylhydrazino)-esters offered an access to the less known N_1-unsubstituted 1,2-diazetidinone derivatives (Scheme 133). The presence of a magnesium ion was essential for the ring closure: other bases, *e.g.* NaH did not yield a heterocyclic product.[200] The known effect of the geminal methyl groups [201] probably assisted the ring formation.



Ar: C_6H_5; 4-ClC_6H_4

Scheme 133

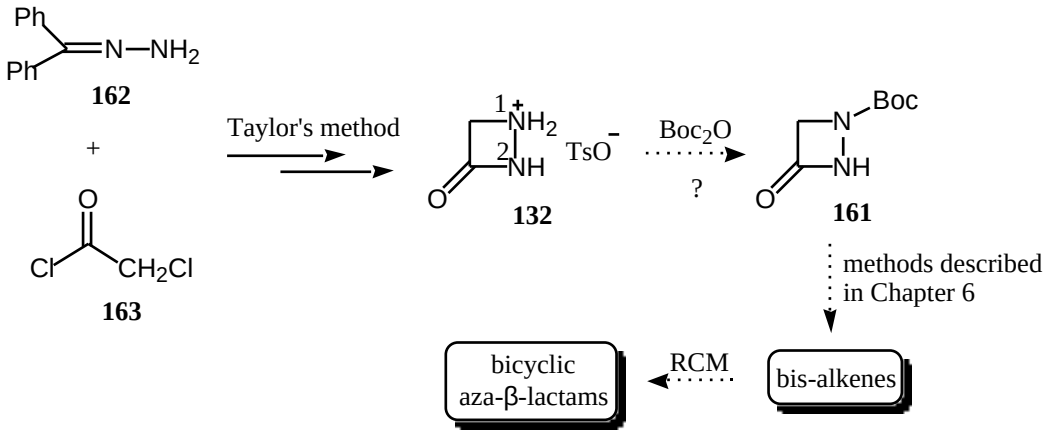
Of particular interest is the work of Oda *et al.*[202] who reported an acidic one-pot deprotection-cyclization sequence to prepare 4(*S*)-(1(*R*)-hydroxyethyl)-1,2-diazetidinone **155**, which was then converted to the bicyclic aza-β-lactam **156** by an intramolecular Michael cyclization reaction. However, the exocyclic nitro olefin **157** thus formed was found to be labile at room temperature and gradually decomposed to the seven-membered lactam **158**. The transformation of **157** to 5-azacarbapenem **159** has not been reported (Scheme 134).



Scheme 134

7.2 Our strategy

As described in Chapter 6, methodology has been established for the selective functionalization of substituted pyrazolidinone heterocycles. This has provided the basis for the preparation of bicyclic aza-γ-lactam derivatives using RCM reaction. Thus, our initial idea was to apply the same methodology to construct the bicyclic aza-β-lactams. We preferably choosed the synthetic method reported by Taylor *et al.*[181] to prepare 1,2-diazetidinone **132**. Further monoacylation at the amine nitrogen (N-1) would provide an intermediate **161** for the preparation of a number of bis-alkenes using the methods described in Chapter 6. They would then be submitted to RCM (Scheme 135).

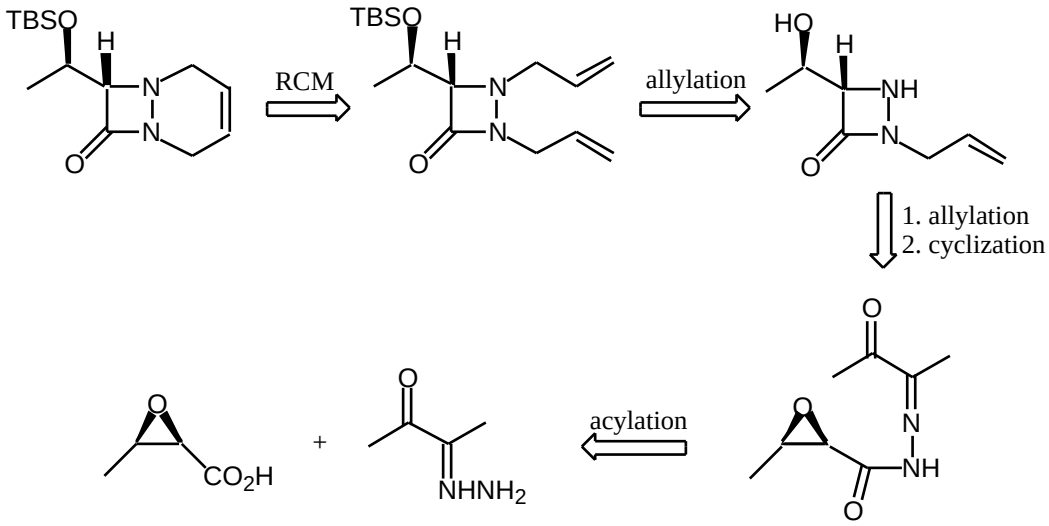


Scheme 135

This strategy should allow to introduce a variety of acylamino side chains or a hydroxylethyl function at the α-position of the lactam carbonyl group using methods known in β-lactam chemistry.

Although Taylor *et al.*[184] mentioned that monoacylation of unsubstituted 1,2-diazetidinone led only to a polymeric solid, detailed reaction conditions have not been reported. On the other hand, since we have successfully introduced a Boc group at the amine nitrogen atom of an unsubstituted pyrazolidinone (see Chapte 6), it could be expected that the reaction worked for the four-membered ring as well.

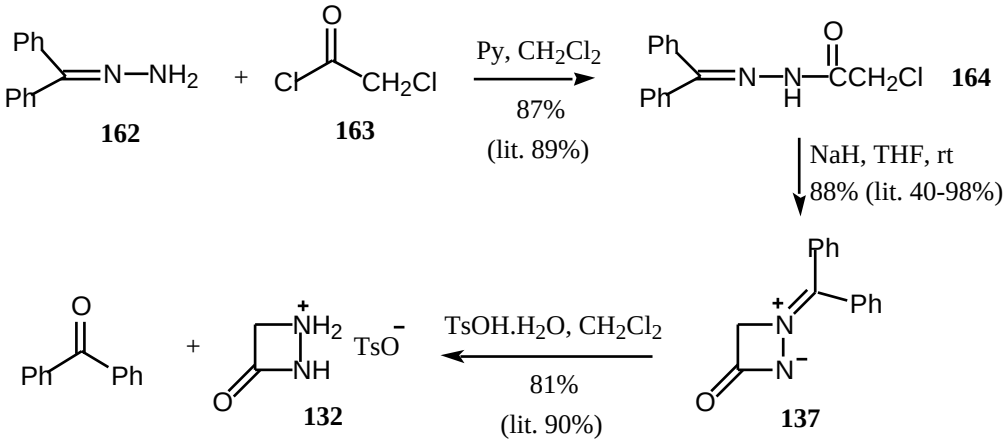
We were also interested in Oda's synthetic approach[202] since it would allow us to prepare stereospecifically an optically active 1, 2-diazetidinone bearing a (*R*)-hydroxyethyl side chain which is the structural requirement for biological activity of penems and carbapenems (see Chapter 1).[203] Another attractive feature was that this strategy could introduce desired substituents at the lactam nitrogen atom under basic conditions prior to the formation of 1,2-diazetidinone ring. This could provide a solution to the selective nitrogen functionalizations of highly strained 4-membered aza-β-lactam ring (Scheme 136).



Scheme 136

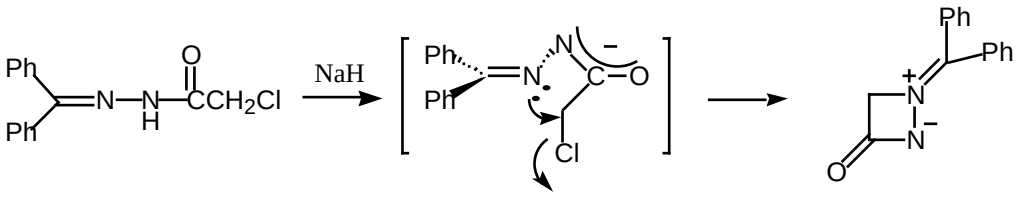
7.3 Preliminary results: synthesis of 1,2-diazetidinone 132 and attempted monoacylation

Following Taylor's method,[181] benzophenone α-chloroacetylhydrazone **164** was readily prepared from benzophenone hydrazone **162** and chloroacetyl chloride **163** in the presence of pyridine in dichloromethane. Treatment of **164** with sodium hydride in anhydrous tetrahydrofuran gave 3-oxo-1,2-diazetidinium ylide **137** in 88% yield. Selective cleavage of the iminium bond with retention of the labile β-lactam group could be achieved by treatment of **137** with 1 molar equiv of water. Thus, reaction of **137** with 1 equiv of *p*-toluenesulfonic acid monohydrate in a methylene chloride solution resulted in the precipitation of 3-oxo-1,2-diazetidinium tosylate **132** in 81% yield (Scheme 137).



Scheme 137

A mechanism for the above intramolecular dehydrohalogenation of **164** is outlined in Scheme 138. The initial result of the treatment of α-haloacyl hydrazone **164** with a strong base must be the removal of the amide proton to give anion **165** which cyclizes.[181]

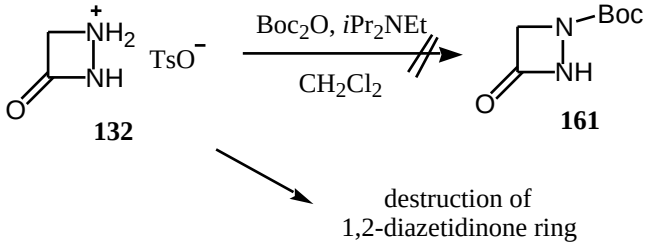


164 **165** **137**

Scheme 138

An important spectral characteristic of 1,2-diazetidinones is the carbonyl absorption in the IR spectrum, which is often higher than that of β-lactams (generally 1730-1760 cm^{-1}). This indicates less resonance interaction between the carbonyl group and the nitrogen lone pair in the more strained four-membered aza-β-lactam ring.[204] For 1,2-diazetidinone **132**, for instance, the C=O band appeared at 1820 cm^{-1}.

The subsequent monoacylation of the amine group in **132** proved quite difficult. Treatment of **132** with Boc_2O in the presence of *i*Pr_2NEt only gave a complex mixture of products, which did not show infrared CO stretching absorptions at high frequency (Scheme 139).



132 **161**

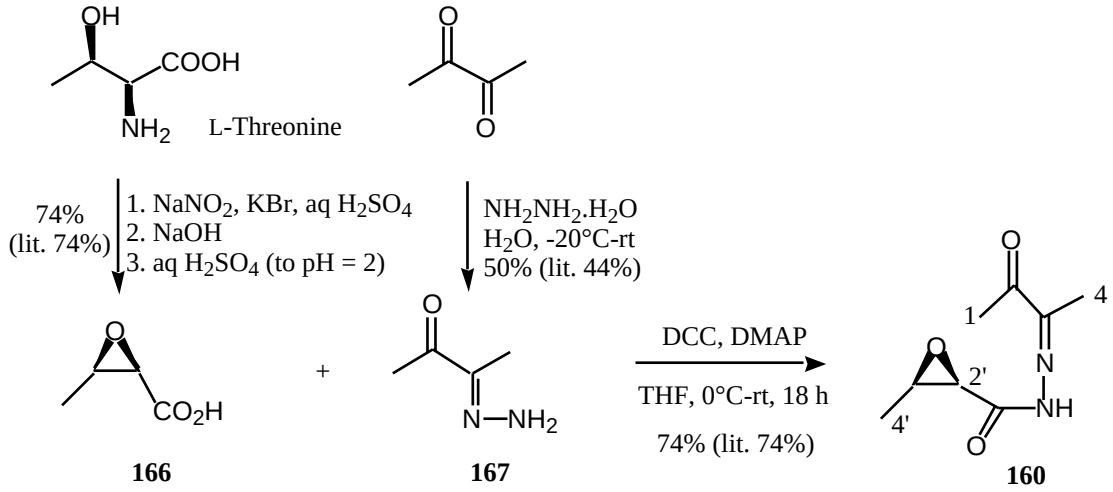
Scheme 139

We did not carry out the detailed studies for this monoacylation reaction, but rather moved to Oda's method.

7.4 An acidic one-pot deprotection-cyclization sequence towards bicyclic 1,2-diazetidinone

7.4.1 Preparation of hydrazone 160

Hydrazone **160** was prepared according to the sequence described by Oda (Scheme 140).[202] The readily available L-threonine was converted into (2*R*, 3*R*)-epoxybutanoic acid **166** via the corresponding α-bromide[205] in a one-pot procedure.[206] It is noteworthy that compound **166** was relatively labile at room temperature and gradually decomposed upon storage. On the other hand, treatment of 2,3-butanedione with 1 equiv of hydrazine monohydrate gave diacetyl monohydrazone **167**.[207] Subsequent coupling reaction worked well in the presence of *N*, *N'*-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in THF.

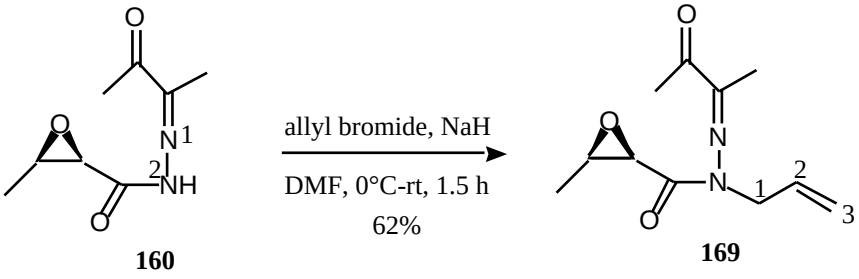


Scheme 140

The ^{1}H NMR spectral characteristics of **160** are in good agreement with that described in the literature.[202] It showed the presence of two rotamers in the spectrum recorded in $CDCl_3$, such as two singlets for NH (δ 10.08, 9.18); two doublets for $H_{2'}$ (δ 4.29, 3.72, *J*=4.8 Hz); two singlets for Me_1 (δ 2.50, 2.42), Me_4 (δ 2.07, 2.02) respectively and two doublets for $Me_{4'}$ (δ 1.41, 1.33, *J*=5.4 Hz). This is probably due to the restricted rotation around the C(O)-N amide bond.

7.4.2 Preparation of bis-alkene 168

The introduction of an allyl group at the amide nitrogen (N-2) of **160** was then effected. Compound **169** was obtained as a colorless oil in 62% yield (Scheme 141).

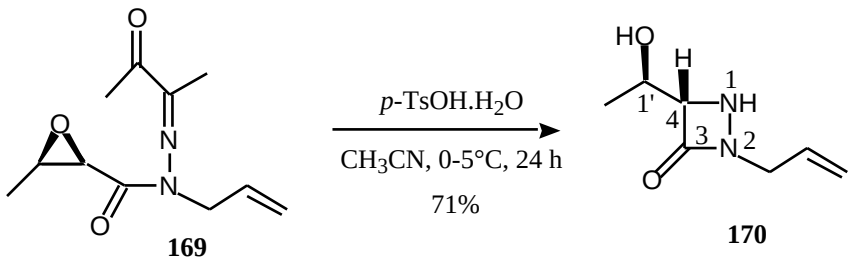


160 **169**

Scheme 141

In the mass spectrum of **169**, the base peak (with 100% intensity) corresponded to the pseudo-molecular ion ($[M+1]^+$); the protons of allyl group in the ^{1}H NMR spectrum were clearly visible: two doublets for H_1 (δ 4.65, 4.76, ^2J=17.7 Hz), two doublets for olefinic protons H_3 (δ 5.24 $^3J_{cis}$=10.5 Hz; δ 5.05, $^3J_{trans}$=17.1 Hz) and a multiplet for H_2 (δ 5.79-5.89). In the ^{13}C NMR spectrum, C_1 appeared at 48.8 ppm, C_2 at 132.3 ppm and C_3 at 117.5 ppm.

The key deprotection-cyclization reaction of **169** was run under mild acidic conditions. Thus, two equivalents of *p*-toluenesulfonic acid monohydrate was added to a cold solution of **169** in acetonitrile. After one day at 0-5°C, 4(*S*)-(1(*R*)-hydroxyethyl)-1, 2-diazetidinone **170** was obtained as a colorless oil in 71% yield after separation on standard grade silica gel (Scheme 142).



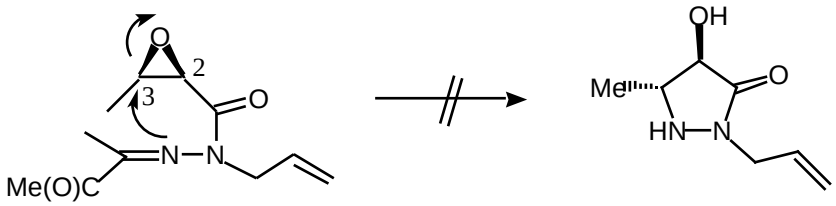
169 **170**

Scheme 142

As expected, the optical rotation of **170** ($[\alpha]_D$=-58.1° $CHCl_3$) was identical with that of the related 1,2-diazetidinones reported by Oda's group (Scheme 134, for **155** (R=*t*Bu), $[\alpha]_D$=-56.2° $CHCl_3$).[202] In the ^{1}H NMR spectrum, $H_{1'}$ appeared in the range of δ 4.23-4.10 (m); a doublet at δ 4.41 was assigned to H_4, with a typical coupling constant value of 5.1 Hz.[202] The carbonyl carbon (C_3) in the ^{13}C NMR spectrum appeared at 167.8 ppm, in the range of carbonyls reported for the 1,2-diazetidinones.[181,182] In addition, the aza-β-lactam carbon (C_4) was deshielded to 77.1 ppm due to the adjacent amine nitrogen atom (N-1) and the lactam carbonyl group in the highly strained four-membered ring. In the IR spectrum, the carbonyl

stretch was found at 1748 cm^{-1};* O-H and N-H bands appeared at 3434 cm^{-1} and 3228 cm^{-1}, respectively.

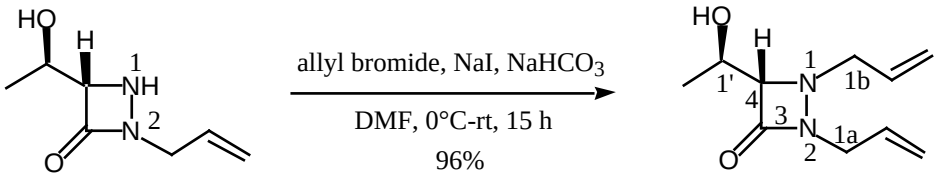
The intramolecular ring-opening of chiral epoxide is a stereocontrolled process useful for the preparation of various carbocycles[208] and heterocycles.[206,209] The epoxide function behaves as an electrophile that can be attacked by nucleophilic reagents at C-2 or C-3 (Scheme 143). In the present case, pyrazolidinone **172** resulting from *N*-nucleophilic attack on oxirane C-3 position was never isolated nor detected in the crude reaction mixture according to the NMR analyses.



169 **172**

Scheme 143

The selective allylation at N-1 in **170** by using allyl bromide in the presence of NaI and $NaHCO_3$ gave the diallylated aza-β-lactam **173** in excellent yield (Scheme 144). These mild reaction conditions were specially suitable for the functionalized 1,2-diazetidinone **170**, and no ring-cleavage was observed (C_3: 167.4 ppm; C=O: 1750 cm^{-1}).



170 **173**

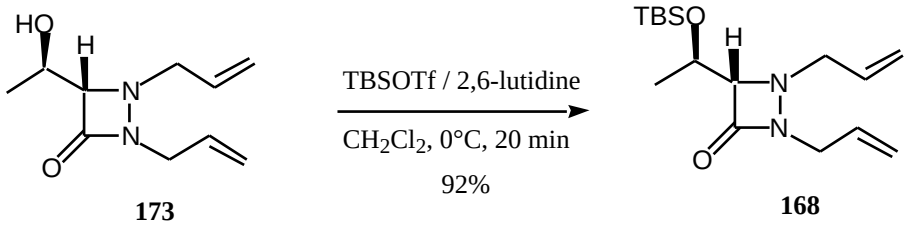
Scheme 144

We found that the β-lactam proton (H_4, d) in **173** were upshielded (δ 3.77) with respect to that in **170** (δ 4.41). This is obviously due to the shielding effect of the allyl group at N-1. We thus further proved that N-1 must be adjacent to C-4, as shown in the structure of a four-membered 1,2-diazetidinone ring. Apparently, the downfield shift of H_{1a} (δ 3.95-4.08, m)

* The carbonyl frequency of 1-unsubstituted and 1-alkyl-1,2-diazetidinones are lower than that of 1-acyl and 1-aryl derivatives.[200,202]

related to H_{1b} (δ 3.60, 3.37, dd, *J*=12.9, 6.6 Hz) is due to the deshielding effect of the carbonyl group.

In order to prevent the destruction of the RCM catalyst,[135] the hindered secondary hydroxyl group in **173** was protected as a *t*-butyldimethylsilyl ether by using *t*-butyldimethylsilyltriflate in the presence of 2 equivalents of 2, 6-lutidine in CH_2Cl_2. The reaction proved very efficient and the silylated bis-alkene **168** was obtained in an isolated yield of 92% (Scheme 145). The special aza-β-lactam carbonyl stretch was found at 1773 cm^{-1} in the IR spectrum.

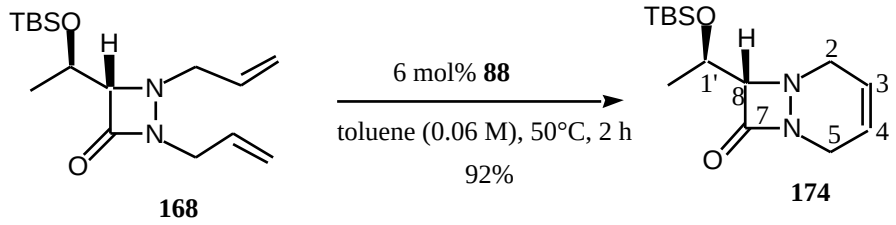


173 **168**

Scheme 145

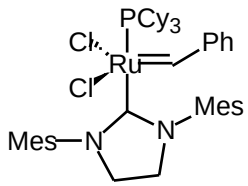
7.4.3 RCM reaction towards bicyclic 1,2-diazetidinone 174

In view of the inertness of the standard Grubbs catalyst **77** in the construction of bicyclic pyrazolidinone derivatives (see Chapter 6), substrate **168** was then directly exposed to a catalytic amount of ruthenium complex **88** in a dilute solution (0.06 M) of degassed toluene. After 2 h at 50°C, bis-alkene **168** had been consumed completely. Direct column chromatography on silica gel gave bicyclic aza-β-lactam **174** in 92% yield (Scheme 146). The 1,2-diazetidinone functionality was well tolerated by the ruthenium catalyst **88**.



168 **174**

cat. **88** :



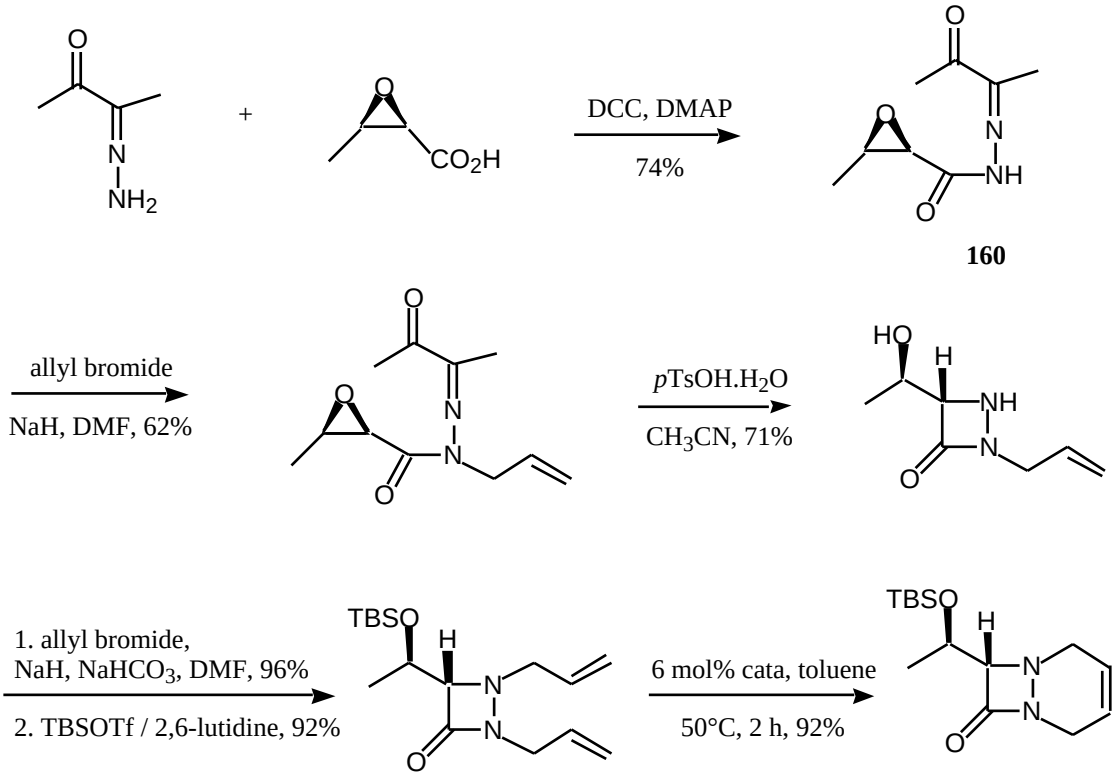
Scheme 146

The structure of **174** was fully confirmed by the spectral analysis. Particularly, in the ^{1}H NMR spectrum, the downfield signals (δ 5.72-5.88, m) were assigned to the two olefinic protons (H_3 and H_4); the signals of H_2 and H_5 were distinctly splitted (δ 4.16 for H_5 and δ 3.86 for $H_{5'}$, dm, ^{2}J=17.7 Hz; δ 3.62 for H_2 and δ 3.16 for $H_{2'}$, dm, ^{2}J=14.7 Hz); a doublet (J=7.8 Hz) for H_8 appeared at δ 3.57. The structure showed in ^{13}C NMR one carbonyl function (161.1 ppm), two monosubstituted olefinic carbons corresponding C_3 (119.8 ppm) and C_4 (123.3 ppm) respectively, and downfield shift of C_8 (88.0 ppm). In addition, the C=O band in the IR spectrum was clearly visible at 1761 cm^{-1}.

7.5 Conclusion

Monoacylation at the amine nitrogen atom in an unsubstituted 1, 2-diazetidinone ring met with failure, thus making further derivatizations impossible.

In this chapter, we have shown a practical synthetic way in the construction of 4(*S*)-(1(*R*)-hydroxyethyl)-1, 2-diazetidinone using L-threonine as a chiral template. The one-pot deprotection-cyclization sequence has provided the basis for the easy preparation of a bicyclic aza-β-lactam derivative using a RCM strategy (8 steps, overall yield: 10%; Scheme 147).



Scheme 147

This stereocontrolled route has the following merits:

1) The hydoxyethyl substituent has been installed during the construction of the aza-β-lactam ring, thereby minimizing the manipulations of the labile products;

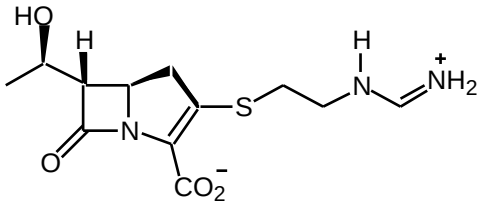
2) It is operationally simple and inexpensive.

Chapter 8

RCM approach towards bicyclo [5.2.0] aza-β-lactam carboxylic ester

8.1 Introduction

Carbapenems bearing an α-oriented (*R*)-1-hydroxyethyl side chain express much higher levels of antibacterial activity and β-lactamase stability than the related penicillins and cephalosporins.[210] The hydroxyl group of imipenem (a clinically important carbapenem antibiotic, Figure 30) can make a strong hydrogen bond to the side chain of Asn-132, positioning the methyl group into a cavity at the bottom of the active site.[211] The methyl group can also block the approach of the hydrolytic water,[9] thus producing a stable covalent acyl-enzyme (see Chapter 1). Another important structural element is a carboxyl group contiguous to the lactam nitrogen, which is also a prerequisite for biological activity.



Imipenem

Figure 30

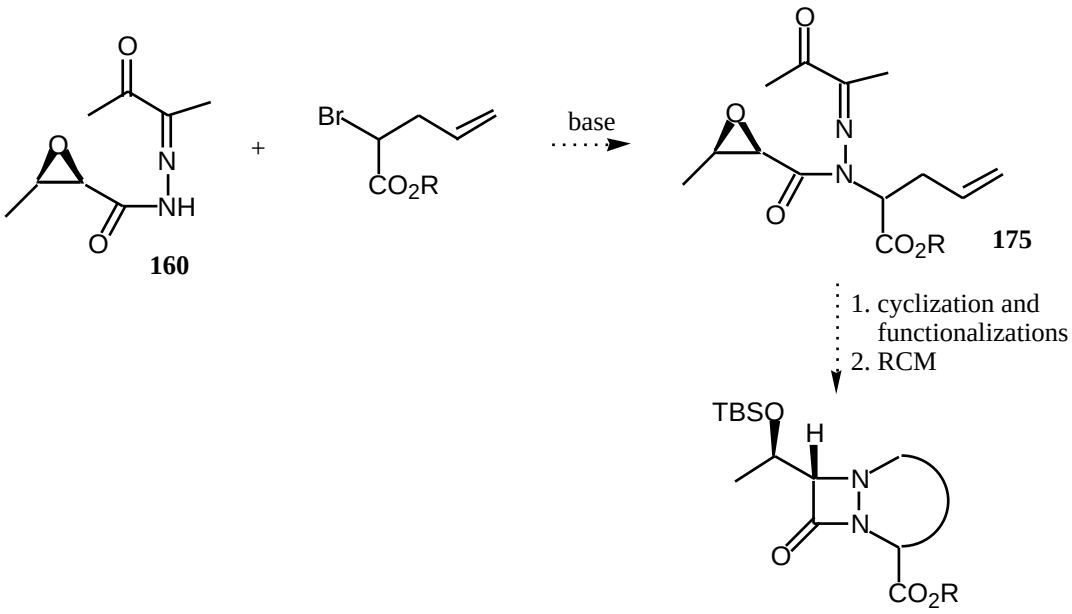
As described in the previous chapter, we have successfully synthesized a bicyclic aza-β-lactam possessing the required hydroxyethyl side chain. In this chapter we present our efforts to incorporate the carboxyl group. Our aim is now to prepare bicyclic aza-β-lactam carboxylic acid derivatives which could serve for the syntheses of promising candidates for biological studies.

8.2 First approach: direct alkylation of monohydrazone 160 with an α-bromo ester

8.2.1 Strategy

In view of the ready access of monohydrazone **160** and the established synthetic method, our initial goal was to directly alkylate the lactam nitrogen in **160** with an α-bromo ester bearing an allylic chain. Then successive cyclization of **175** under acidic conditions and

functionalizations on the resulting 1,2-diazetidinone ring should easily provide a substrate for RCM which could lead to the bicyclic aza-β-lactam carboxylic ester (Scheme 148).

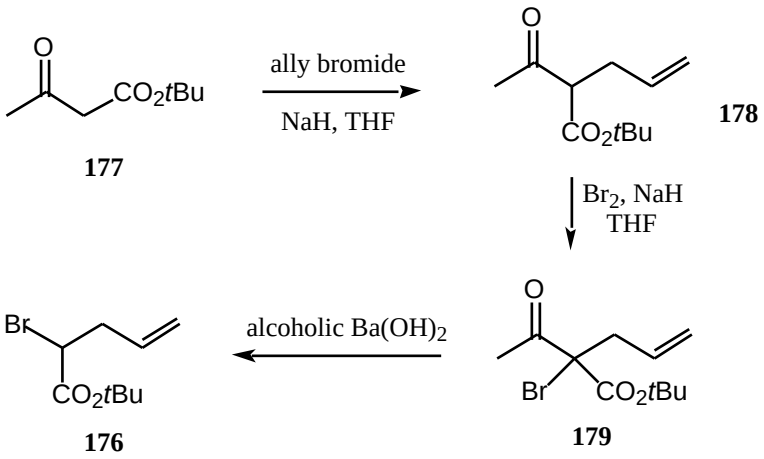


Scheme 148

8.2.2 Experimental results

8.2.2.1 Preparation of α-bromo ester 176

α-Bromo-ester **176** was readily prepared according to a known precedure.[212] Commercially available *t*-butyl acetoacetate **177** was converted to **178** in quantitative yield by alkylating a solution of the sodium enolate in tetrahydrofuran (from NaH on **177**) with 1.1 equiv of allyl bromide. The crude product **178** obtained by normal aqueous workup was sufficiently pure for use in the next step. The tetrahydrofuran solution of **178** was brominated exclusively and quantitatively at the α-position via its sodium enolate. The α-bromo-α-alkylacetoacetate **179** was directly transformed into α-bromo-ester **176** by deacetylation using a suspension of anhydrous barium hydroxide in alcohol (Scheme 149).

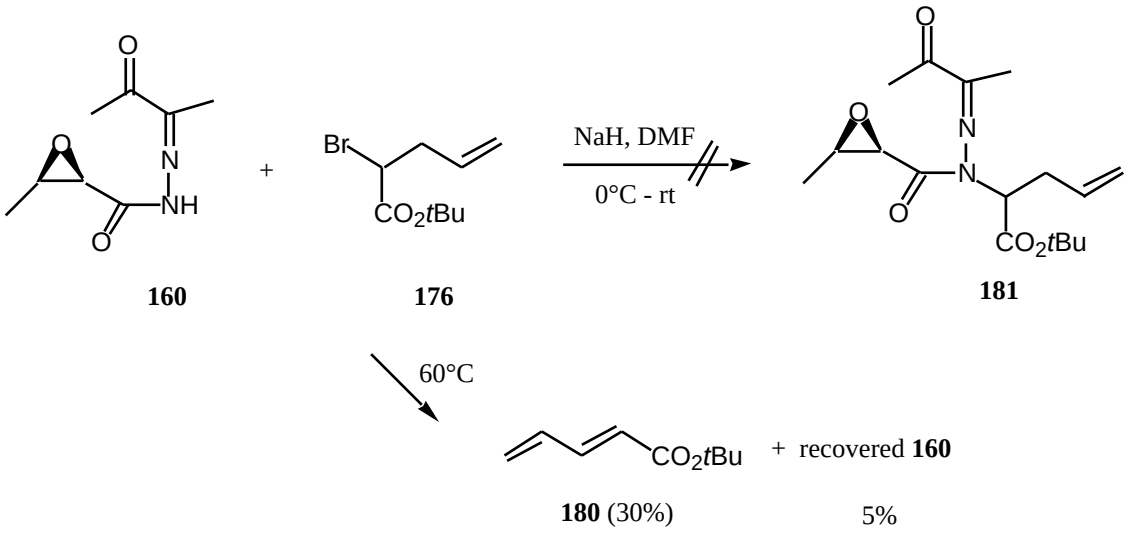


overall yield: 80% (lit. 85%)

Scheme 149

8.2.2.2 Alkylation reaction

The alkylation reaction of hydrazone **160** with α-bromo-ester **176** was then carried out under basic conditions, such as using NaH in DMF (Scheme 150). At 60°C, a β-elimination of **176** readily took place and conjugated ester **180** was obtained in 30% yield. The starting hydrazone **160** was recovered in only small quantities (5%). With benzyltrimethylammonium hydroxide (40% solution in MeOH, Triton B),[213] a similar result was obtained.



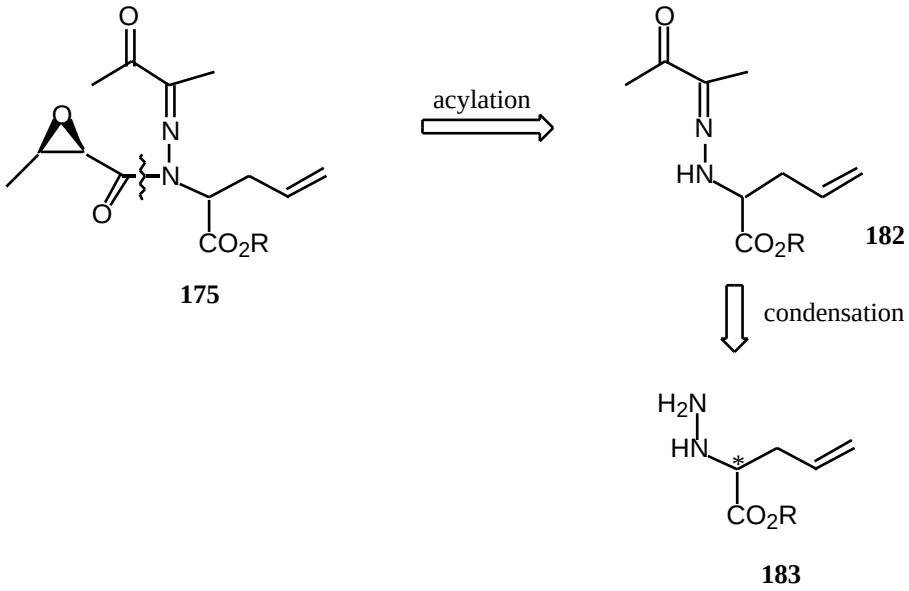
Scheme 150

We then carried out an alternative retrosynthetic analysis to prepare **175**.

8.3 Second approach: an asymmetric strategy using 2-oxazolidinone as chiral auxiliary

8.3.1 Strategy and literature survey

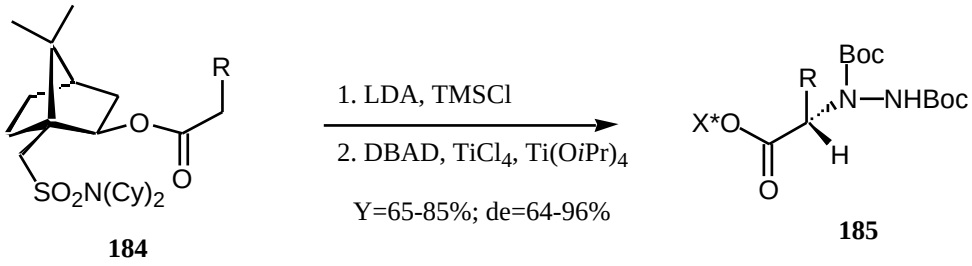
We decided to perform the acylation reaction of hydrazone **182** with the epoxyacid at a later stage. Compound **182** could be further disconnected to the corresponding α-hydrazino ester **183** and 2,3-butanedione (Scheme 151).



Scheme 151

α-Hydrazino acids have aroused wide interest as a result of their activity as potential antimetabolites,[214] as inhibitors of amino acid decarboxylase,[215] and also as inhibitors of cell growth.[216] They are closely related to the naturally occurring α-amino acids and they are also found in nature.[217] Substitution of hydrazino acids for α-amino acids in biologically active peptides has sometimes enhanced certain biological properties.[218]

Several methods to access to α-hydrazino acids have been reported. Currently available methods for obtaining α-hydrazino acids in enantiomerically pure form are limited either to classical resolution,[219] or to multistep procedures starting from the requisiteenantiomerically pure α-amino acid precursor.[220-222] The type of electrophilic hydrazination of chiral enolate might be expected to provide an expedient approach to the asymmetric synthesis of α-hydrazino esters. Oppolzer and co-workers[223] reported that successive treatment of chiral esters **184** with LiN(*i*-Pr)$_2$/Me$_3$SiCl and di(*tert*-butyl)azodicarboxylate(DBAD)/TiCl$_4$/Ti(*i*-PrO)$_4$ gave *N,N'*-di[(*tert*-butoxy)carbonyl]hydrazino esters **185** in high enantiomeric purity (Scheme 152).

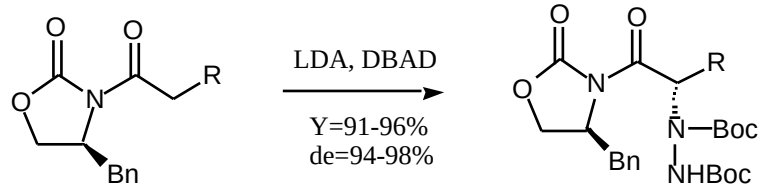


184 **185**

R: CH_3, C_2H_5, C_3H_7, iC_3H_7, iC_4H_9, C_4H_9,
Hexyl, $PhCH_2$, 1-Adamantyl-CH_2

Scheme 152

One can also rely on Evans oxazolidinone chiral auxiliaries for absolute stereochemical control of the electrophilic hydrazination with an (+)NH-NH_2 synthon (Scheme 153).[224] We preferably chosed this strategy in view of its efficacy (high yields and high de%) with respect to Oppolzer's method.



R: Me, $CH_2CH{=}CH_2$, CH_2Ph,
Ph, $CHMe_2$, CMe_3

Scheme 153

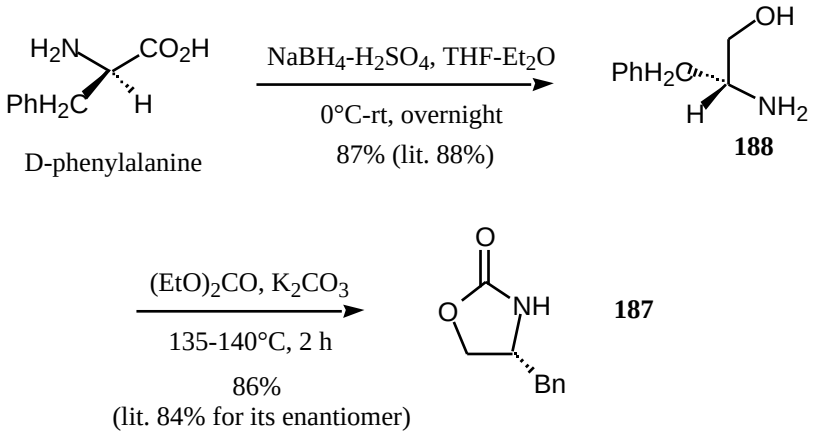
8.3.2 Results and discussion

8.3.2.1 Synthesis of carboximide substrate 186

8.3.2.1.1 Preparation of 2-oxazolidinone 187

Oxazolidinones prepared from amino alcohols derived from natural L-amino acids such as phenylalanine, phenylglycine, valine, norephedrine and *tert*-leucine, are commercially available[225] and relatively inexpensive. However, the structural requirement necessary for exhibiting biological activity in penicillins is a carboxyl group on the α-side of the ring system (see Chapter 1) which corresponds to the configuration of an oxazolidinone derived from a D-amino acid. In the present case we selected D-phenylalanine as the starting material to synthesize the oxazolidinone chiral auxiliary.

(*R*)-4-Benzyl-2-oxazolidinone **187** was prepared according to a known method. D-Phenylalanine was readily reduced to the corresponding 1,2-amino alcohol **188** by $NaBH_4$-H_2SO_4 which generated B_2H_6 *in situ.*[226] This convenient procedure offers definite advantages, such as operational simplicity, ease of scaling up the reaction and the use of inexpensive reagents. Among the methods leading to oxazolidinones,[225] the reaction between an amino alcohol and diethyl carbonate has proven to be particularly efficient. Diethyl carbonate could be used as solvent and ethanol was allowed to distill as it was formed. In this way, the desired oxazolidinone **187** was obtained in 86% yield (Scheme 154). Its optical rotation was identical with that of the commercial material ($[\alpha]_D^{20}$ +64.0°, c=1 in $CHCl_3$).

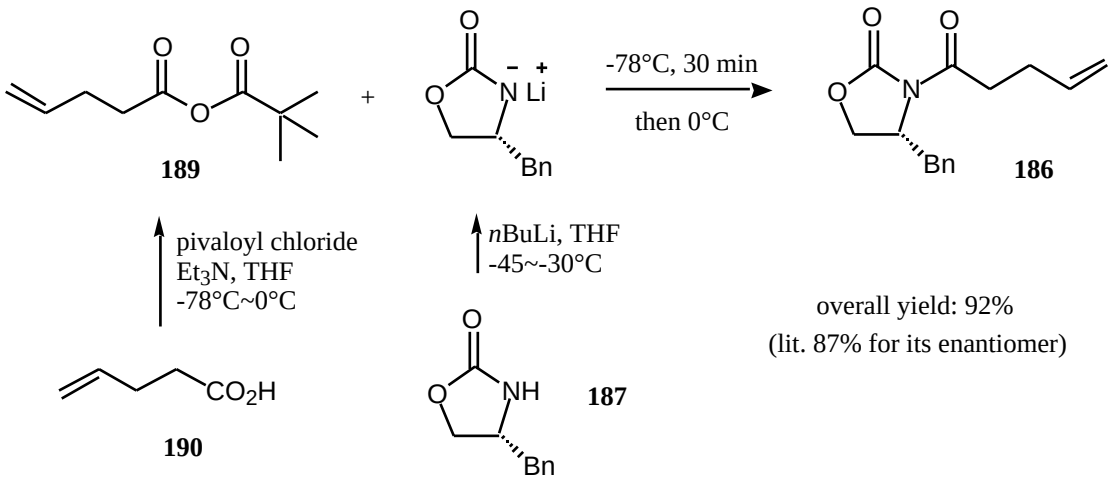


Scheme 154

8.3.2.1.2 Synthesis of *N*-acyloxazolidinone 186

N-Acyloxazolidinones are readily accessible from the reaction of the corresponding oxazolidinone with *n*-butyl lithium followed by the addition of an acid chloride,[227,228] or a mixed anhydride.[229,230]

N-Acyloxazolidinone **186** was prepared from the reaction of lithiated oxazolidinone and anhydride **189**, which had been generated by the reaction of 4-pentenoic acid **190** and pivaloyl chloride in the presence of triethylamine (Scheme 155).



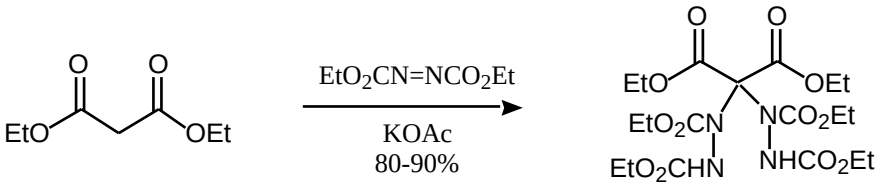
Scheme 155

In this procedure, a little of triphenylmethane was added to the solution of oxazolidinone **187** in THF to control the amount of *n*-butyl lithium (added at -45°C to -30°C till an orange color persisted). The resulting solution was cooled to -78°C and then added, via rapid cannulation, to the stirred mixture containing the mixed anhydride **189** (precooled to -78°C). This method gave the carboximide substrate **186** in excellent yield.

8.3.2.2 Electrophilic hydrazination of chiral imide enolate

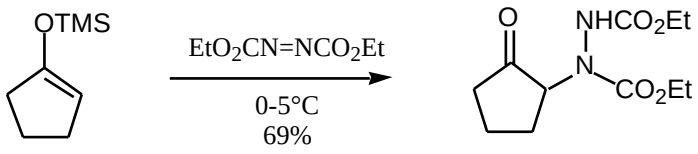
8.3.2.2.1 Selection of di-*tert*-butylazodicarboxylate as (+)NH-NH_2 synthon

The exceptional electrophilic reactivity of azodicarboxylate esters has been widely recognized.[231] The first documented example of application of this reagent to the electrophilic hydrazination of carbon nucleophiles appeared in 1924 (Scheme 156).[232]



Scheme 156

Such a hydrazination reaction could also take place with an enol ether (Scheme 157).[233]



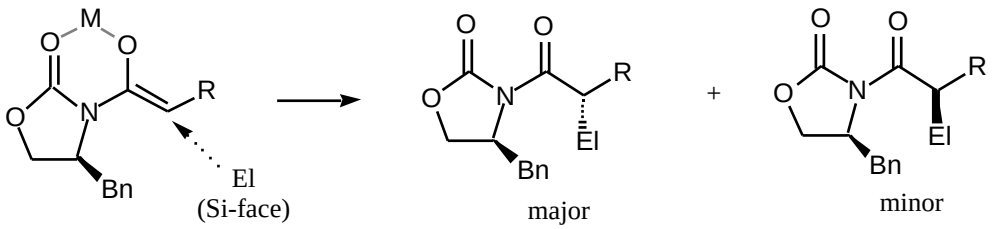
Scheme 157

Our selection of di-*tert*-butylazodicarboxylate as the reagent of choice was motivated by several factors. Firstly, it is a stable, crystalline yellow solid (mp 90-92°C) that is readily prepared[234] and is also commercially available. Secondly, since the *tert*-butoxycarbonyl (Boc) group is a widely used protecting group in peptide chemistry, methods for its removal under mild, nonracemizing conditions have been well established. Finally, studies carried out by Evans's group suggested that this reagent possessed the required high reactivity towards chiral imide enolates.[224]

8.3.2.2.2 Electrophilic α-hydrazination

8.3.2.2.2.1 Asymmetric induction of oxazolidinone chiral auxiliary

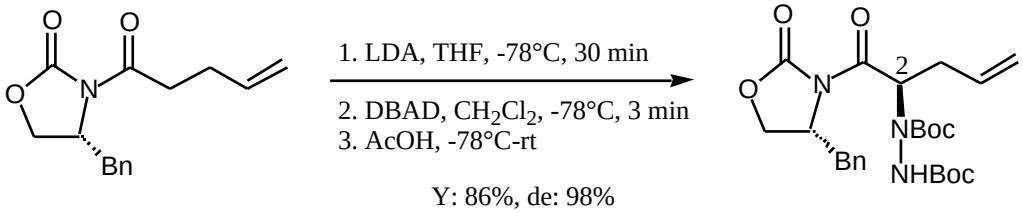
Evans and co-workers have demonstrated that the chelated *Z*-enolate fixed the chiral auxiliary in a specific conformation forcing electrophiles to attack on the least hindered diastereoface. One isomer should be obtained in high diastereoselectivity as shown for alkylation,[235] acylation,[236] hydroxylation,[237] hydrogenation,[238] azidation[239] and hydrazination[224,240] reactions (Scheme 158).



Scheme 158

8.3.2.2.2.2 Experimental results

Treatment of the lithium enolate of **186** (generated with 1.05 equiv of lithium diisopropylamide in THF) with 1.15 equiv of BocN=NBoc (DBAD) at -78°C instantaneously gave the corresponding hydrazino imide, as evidenced by the immediate decoloration of the cooled (-78°C) solution of DBAD in CH_2Cl_2 upon addition to the enolate solution. The mixture was then quenched with glacial acetic acid (2.6 equiv) to give adduct **191** in 86% yield (Scheme 159).

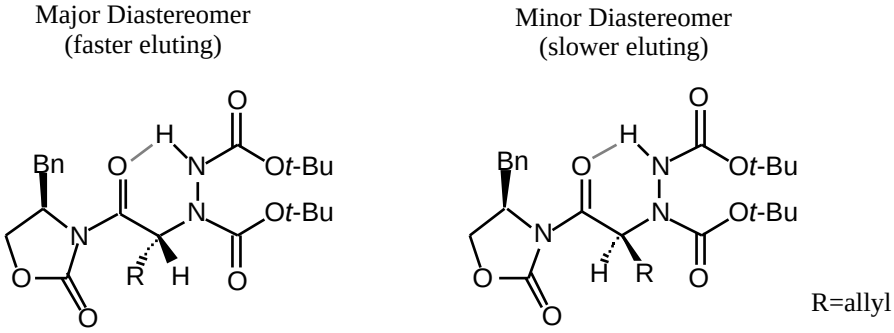


186 **191**

Scheme 159

The diastereomeric mixture proved to be readily separable by TLC, and the fast-eluting component was found to correspond to the major diastereomer. Thus, the flash column chromatography on silica gel of the crude product yielded a 2(*R*):2(*S*) ratio of 99:1. The major diastereomer was assigned the 2(*R*) configuration on the basis of the earlier examples.

The possible ground state conformations which could help rationalizing the chromatographic behavior displayed by the diastereomeric α-hydrazino carboximide adduct **191** are shown in Figure 31. It is suggested that the major, faster-eluting diastereomer adopts the conformation in which the lipophlic moieties, R (allyl) and Bn, shield both faces of the molecule from the polar adsorbant. On the other hand, the minor diastereomer could adopt the conformation in which the substituents reside on the same molecular face. Since the opposite, more polar face is exposed to the absorbant, this diastereomer is more strongly retained. In each case, conformational organization is achieved by a combination of both intramolecular hydrogen bonding and the preferential opposition of the carbonyl dipoles.[241]



191

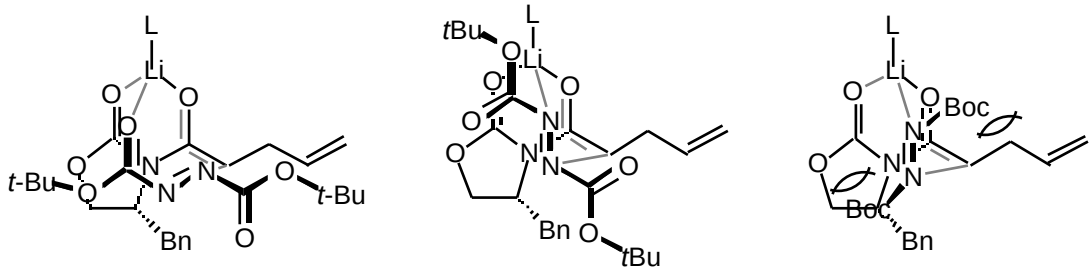
Figure 31

8.3.2.2.2.3 Mechanistic considerations

Evans and co-workers[224] have speculated that these highly exothermic reactions proceed through an early, reactant-like, but highly ordered, transition state. Since DBAD can be considered a nitrogen analog of a conventional α,β-unsaturated ester, these reactions probably

bear a strong mechanistic relationship to the Michael addition reactions of enolates to such esters.

We thus propose several possible transition structures which are illustrated below. Studies have appeared in support of a pericyclic process, in which the enone carbonyl is coordinated to the enolate metal. It is evident that a high degree of organization can be achieved through coordination of the lithium atom with either the ester carbonyl (structure **T_1**) or the azo nitrogen of DBAD (structure **T_2** and **T_3**).



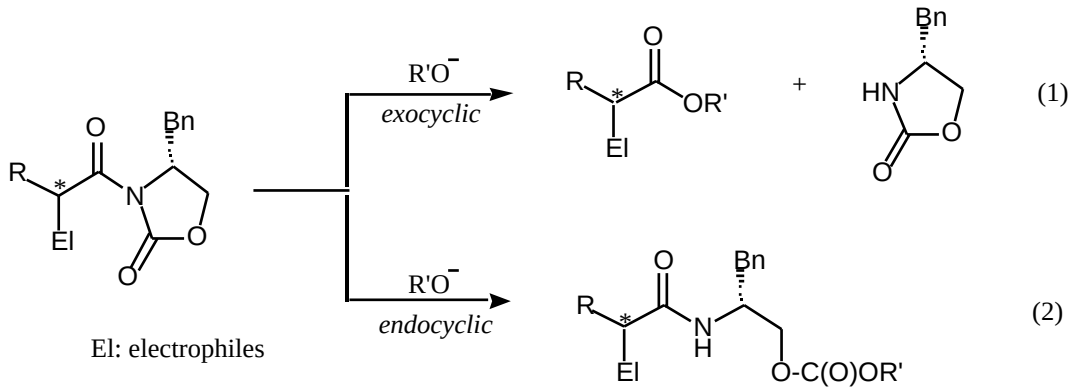
T_1 **T_2** **T_3**

Figure 32

In the former case, an 8-centered pericyclic transition state would be involved, while in the latter more plausible cases, 6-centered-pericyclic structures directly analogous to the now commonly accepted Zimmerman-Traxler aldol transition state[242] would be formed. Although DBAD could, in principle, assume two possible orientations as illustrated in **T_2** and **T_3**, it appears that the former transition structure **T_2** might be favored on steric grounds (Figure 32).

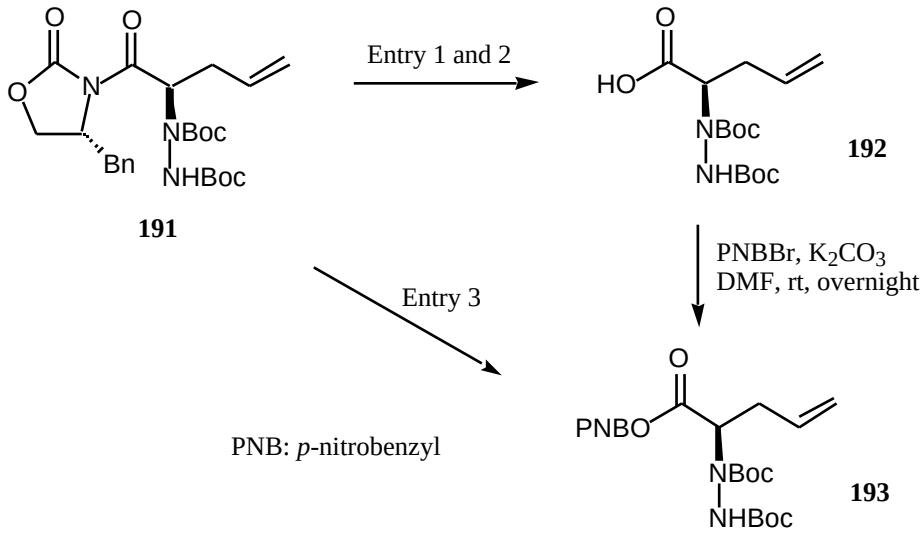
8.3.2.3 Imide hydrolysis and transesterification

The next step was the hydrolytic cleavage of the auxiliary which could occur either at the exo- or endocyclic carbonyl group (Scheme 160).[243] The site of nucleophilic cleavage of *N*-acyloxazolidinones is subject to both steric and electronic factors. In the absence of significant steric crowding in the vicinity of the exocyclic carbonyl function, electronic factors direct hydrolysis or transesterification in the desired fashion giving the carboxylic acid along with the recovered chiral auxiliary (Eq. 1). However, as the steric requirement of the R group is increased, attack on the endocyclic auxiliary carbonyl becomes preferred (Eq. 2).



Scheme 160

From the studies of Evans's research group, it was known that hydrolytic cleavage at the exocyclic C=O group could be effected with lithium hydroperoxide in water.[244,245] Thus, a solution of substrate **191** in 3:1-THF/H_2O* was treated at 0°C with 4 equiv of 30% H_2O_2 followed by 2 equiv of LiOH. After aqueous workup and acidification, carboxylic acid **192** was obtained in high yield without racemization and the oxazolidinone chiral auxiliary was quantitatively recovered (Scheme 161, Table 15, Entry 1).



191 **192** **193**

Scheme 161

* To minimize possible side reactions resulting from hydroxy radical formation due to trace transition metals, we have routinely employed BHT-stablized THF and redistilled water.

Table 15: Hydrolysis and transesterification of hydrazide adduct **191**

Entry	Conditions	Yield of **193** (%)
1	LiOOH, THF-H_2O (3:1), 0°C, 3 h then quenched with aq Na_2SO_3	82
2	LiOH, THF-H_2O (2:1), 0°C, 3 h	80
3	LiOPNB, THF, -78~-50°C, 2 h	89

Actually, in our case the reaction with LiOH (2.4 equiv) in 2:1 THF-H_2O at 0°C also led to the exocyclic cleveage to give the corresponding acid **192** in good yield with no detectable racemization. The chiral auxiliary was also recovered in quantitative yield (Table 15, Entry 2).

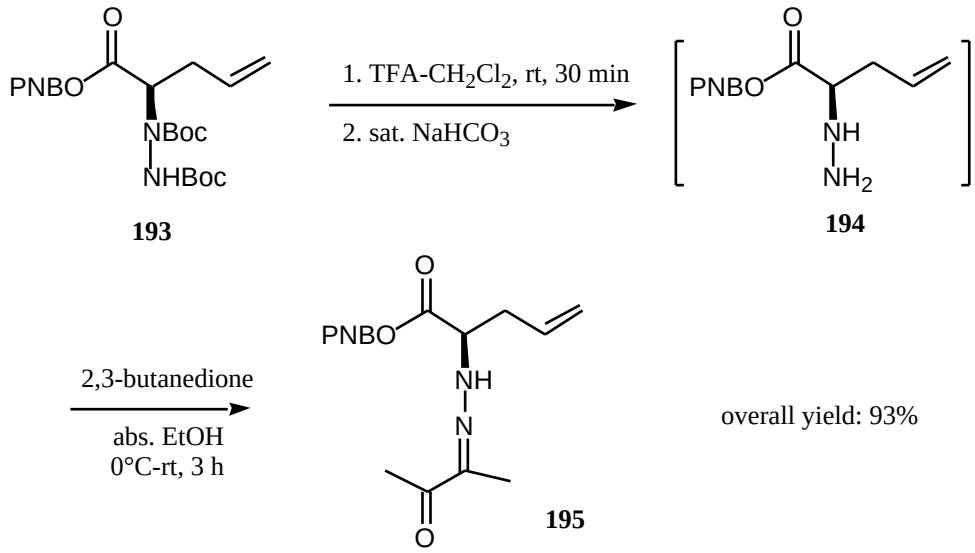
The resulting acid **192** was directly esterified with *p*-nitrobenzyl bromide in the presence of potassium carbonate in DMF. This two-step, one-pot procedure gave the protected hydrazino ester **193** in good yields (Entry 1 and Entry 2).

Removal of the oxazolidinone chiral auxiliary can also be accomplished with lithium alkoxides.[225] Lithium *p*-nitrobenzyloxide (LiOPNB) was prepared from *p*-nitrobenzyl alcohol and *n*-butyl lithium. The resulting alkoxide was then added to a solution of imide **191** in THF at -78°C. This direct transesterification reaction gave the hydrazino ester **193** in 89% yield without detectable racemization (Entry 3).

8.3.2.4 Removal of Boc groups and condensation with 2,3-butanedione

8.3.2.4.1 Experimental results

The Boc groups were detached from the nitrogen atoms of **193** by treatment with anhydrous trifluoroacetic acid in CH_2Cl_2 at 25°C for 30 min to give the free hydrazino ester **194** in quantitative yield. The product needed no further purification for the next step. The condensation of crude **194** with 2,3-butanedione was effected in a solution of absolute ethanol.[246] High yields were obtained when the solution of hydrazino ester **194** in EtOH was added slowly to a mixture of 2,3-butanedione in EtOH at 0°C followed by standing at room temperature for 3 h. The yield of **195** was 93%. When the addition was carried out at ambient temperature the yield dropped significantly (41%) (Scheme 162).



Scheme 162

8.3.2.4.2 Chelated structure of 195

It has been reported that monophenylhydrazone **196** remained unchanged on treatment with either refluxing acetic anhydride or acetyl chloride in *N*, *N*-dimethylaniline. This was assigned to a hydrogen-bond (Figure 33).[247,248] In our case, compound **195** could also exist in the *syn* form, which is stablised by a six-membered chelated ring (Figure 33). This hypothesis was supported by the IR spectrum of **195**: the carbonyl band appeared at low frequency (1669 cm^{-1}) with respect to that of 2,3-butanedione (1718 cm^{-1}).[249]

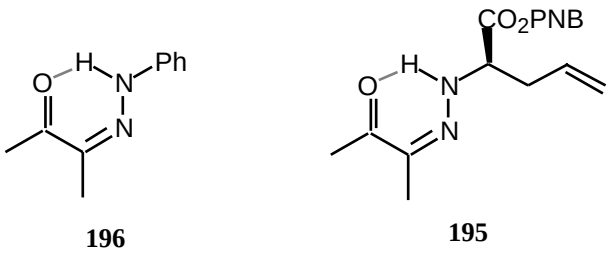


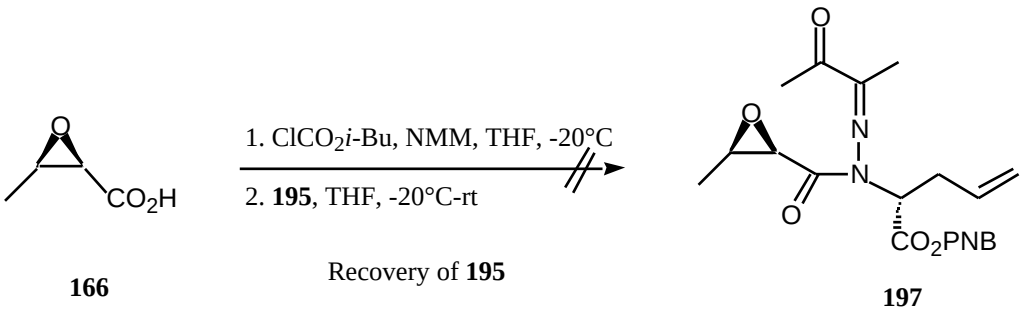
Figure 33

8.3.2.5 Acylation of 195

8.3.2.5.1 Acylation under common coupling conditions

i-Butyl chloroformate/*N*-methylmorpholine (NMM) have been successfully used to activate epoxyacid **166** in the formation of epoxyamide, a precursor of penems.[206] In the present case, addition of NMM and *i*-butyl chloroformate to a solution of epoxyacid **166** in THF at -20°C led to the precipitation *N*-methylmorpholine hydrochloride. However, treatment

of the resulting mixture with monohydrazone **195** did not give any epoxyamide **197**. The starting hydrazone **195** was recovered in quantitative yield (Scheme 163).



166 Recovery of **195** **197**

Scheme 163

Our attention had also been drawn on some efficient coupling reagents, such as PyBrop (bromotris(pyrrolidino)phosphonium hexafluophosphate)[250] and HATU(O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluophosphate),[251] which have been successfully used for the acylation of hindered secondary amines and acyl hydrazides (Figure 34).[252]

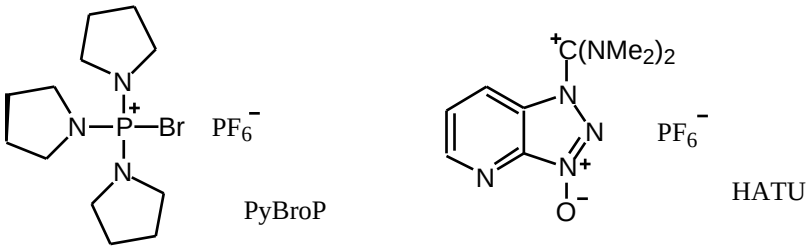
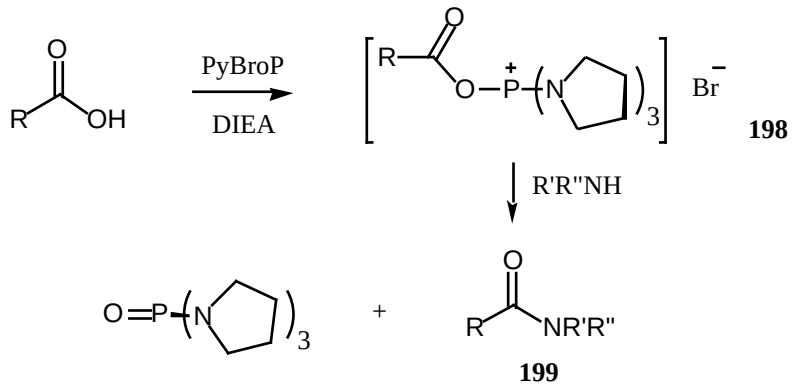


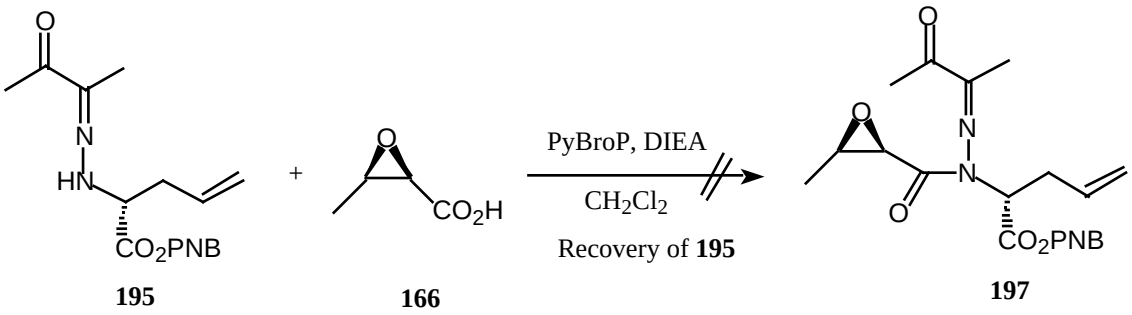
Figure 34

The active intermediate of the PyBroP-induced coupling reaction is presumed to be the acyloxyphosphonium salt **198**. The subsequent aminolysis gives amide **199**. One advantage to the use of PyBroP is that the coupling reaction does not involve the carcinogen HMPA as a by-product (Scheme 164).[253]



Scheme 164

We thus decided to investigate the coupling reaction of hydrazone **195** with PyBroP. *N*, *N*-Diisopropylethylamine (DIEA) was added to a mixture of PyBroP, epoxyacid **166** and hydrazone **195** in CH_2Cl_2 at 0°C. After 2 days at rt, the acylation had not taken place and we completely recovered the starting material **195** (Scheme 165).



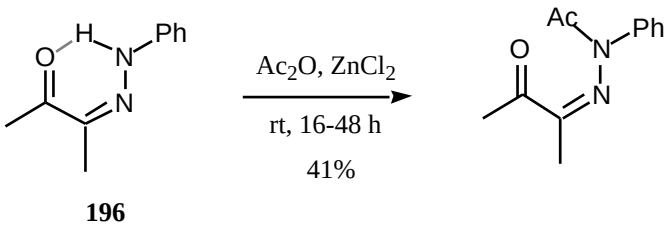
Scheme 165

The resistance of monohydrazone **195** to acylation was probably due to the low reactivity of secondary hydrogen-bonded amine group for both electronic and steric reasons, We then decide to attempt other conditions which would disrupt the chelated structure.

8.3.2.5.2 Acylation by disrupting the chelated structure of 195

8.3.2.5.2.1 Literature

It was described by Somogyi *et al.*[248] that the stability of chelated monoarylhydrazone **196** has been shown to depend on temperature, solvent polarity,[254] and pH of the solution.[255,256] Its transformation could be initiated by the complexing effect of metal ions (Scheme 166).

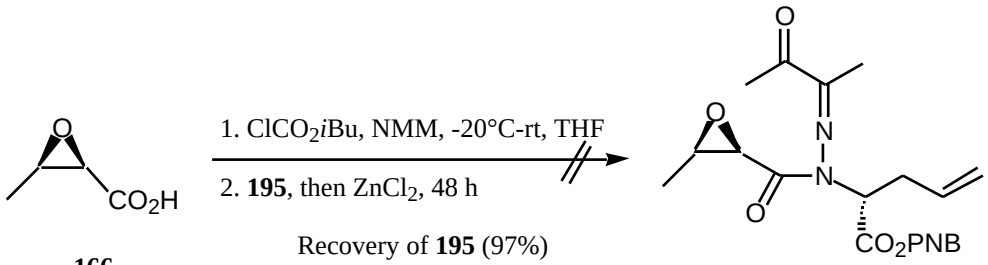


196

Scheme 166

8.3.2.5.2.2 Experimental results

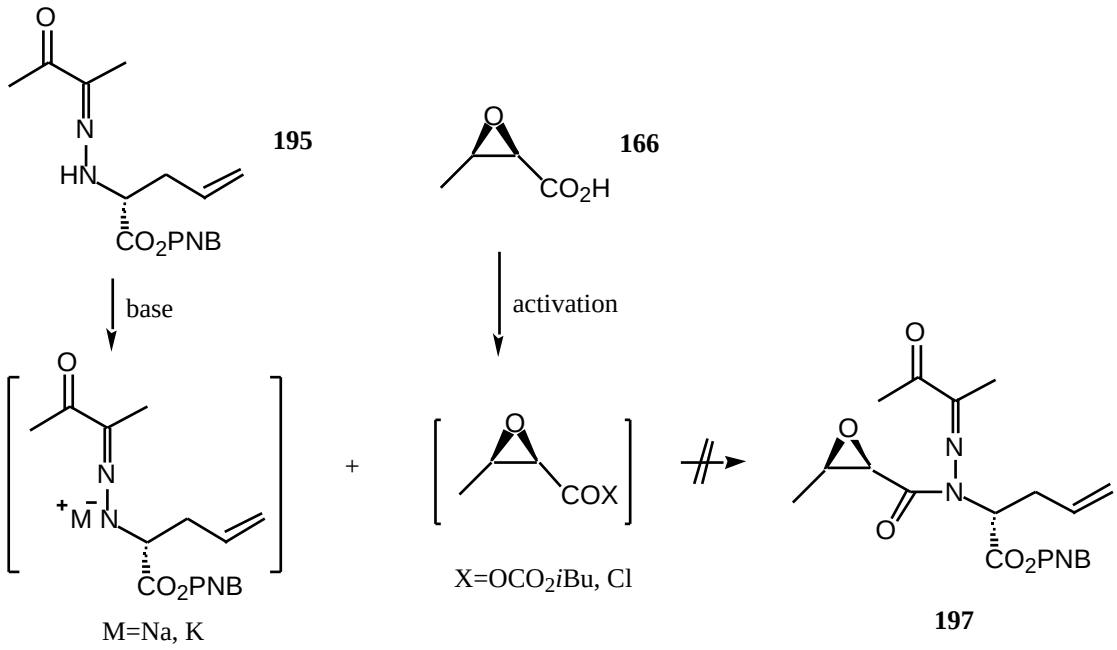
The *N*-acylation of hydrazone **195** with epoxyacid **166** could not be accomplished by disrupting chelation of six-membered ring via zinc-complex formation (Scheme 167).



166 **197**

Scheme 167

We then decide to deprotonate **195** with a strong base and react the resulting anion with an activated derivative of **166** (Scheme 168, Table 16). *i*-Butylchloroformate/*N*-methylmopholine were first used to activate epoxyacid **166**. The reactive intermediate was added to a cooled THF solution of metalated monohydrazone **195** (generated with sodium hydride). In this instance there was no epoxyamide **197**, only monohydrazone **195** was recovered in 56% yield (Entry 1). Similar results were obtained using the acid chloride derived from the reaction of **166** with TMCE (Entry 2 and 3).

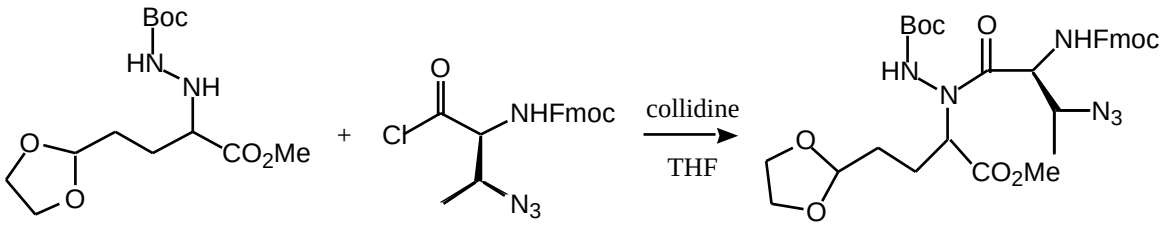


Scheme 168

Table 16: Acylation of monohydrazone **195** with epoxyacid **166**

Entry	Base	Activation of epoxyacid **166**	Conditions	Recovered **195**
1	NaH	$ClCO_2$*i*-Bu/NMM	THF -20°C-rt, 24 h	56%
2	NaH	TMCE	CH_2Cl_2-THF 0°C-rt, 3 h	26%
3	KH	TMCE	CH_2Cl_2-THF 0°C-rt, 3 h	20%

These disappointing results indicated that the diacetyl protecting group in **195** was unsuitable for the subsequent acylation reaction with the epoxyacid. In the course of our literature studies, we became aware of a coupling reaction between a mono-Boc protected hydrazide and an acid chloride in the presence of collidine (Scheme 169).[257] We then anticipated that the replacement of diacetyl group by a Boc function in **195** could provide a solution to our problem. Also successive one-pot deprotection-cyclization procedure leading to a four-membered aza-β-lactam ring could be carried out in TFA. This was found to be the case.



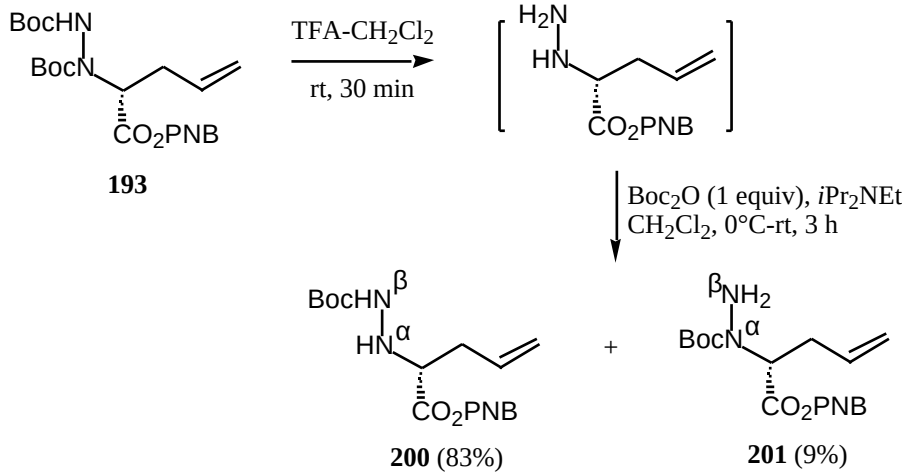
Scheme 169

8.3.2.6 Acylation of mono-Boc hydrazide 200

8.3.2.6.1 Regioselective *N*-protection of α-hydrazino ester

In general the site of acylation of an unsymmetrically-substituted hydrazine depends on steric crowding both in the hydrazine and in the acylating agent.[258] For example, the direct coupling of an α-hydrazino ester ($NH_{2(\beta)}$-$NH_{(\alpha)}$-CHR-CO_2R') with a *N*-protected amino acid essentially leads to the Nβ-acylation, especially in the case of R ≠ H.[259] This is exactly the situation encountered in our synthetic sequence, where a selective protection of Nβ was required.

Both Boc groups were removed in **193** in a 1:1 mixture of TFA-CH_2Cl_2. Monoprotection of the corresponding hydrazino ester was performed with 1 equiv of Boc_2O in the presence of *i*-Pr_2NEt. After 3 h at rt, the desired hydrazide **200** was isolated in an overall yield of 83%. Only small amounts (9%) of Nα-protected amino amide **201** were observed (Scheme 170).



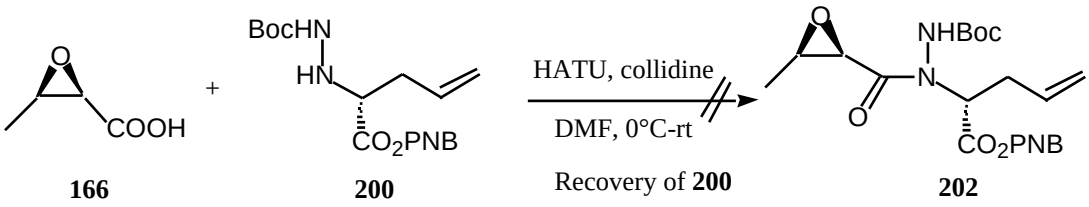
Scheme 170

Compounds **200** and **201** were easily distinguished from the ^{1}H NMR spectroscopy. The former showed a doublet at δ 6.28 (*J*=3.1 Hz) and a triplet at δ 4.29 (*J*=4.0 Hz)

corresponding to the amide and amine proton respectively, whereas for the latter only a broad singlet at δ 3.85 was observed.

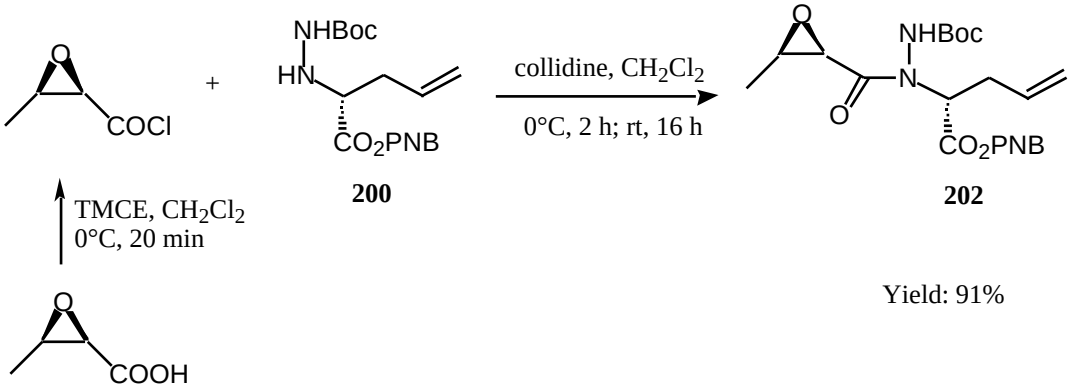
8.3.2.6.2 Acylation reaction

Nβ-Protection in **200** was expected to reduce nucleophilic properties for the vicinal non-acylated N_α. As a matter of fact, the direct acylation of **200** with epoxyacid **166** in the presence of HATU (see Section 8.3.2.5.1) failed to provide any epoxyamide **202** (Scheme 171).



Scheme 171

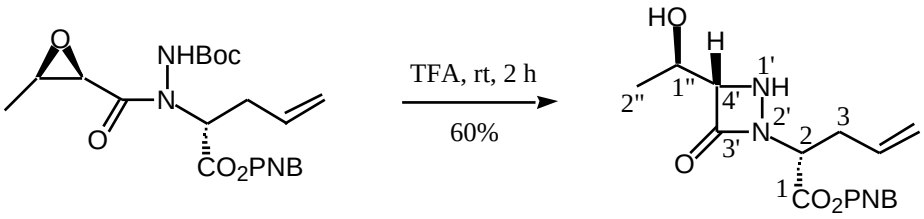
The epoxyacid **166** was then transformed to the corresponding acid chloride with tetramethylchloroenamine (TMCE). A solution of hydrazide **200** and collidine in CH_2Cl_2 was added to the epoxyacid chloride at 0°C. Much to our delight, the acylation was successful and gave epoxyamide **202** in excellent yield (Scheme 172).



Scheme 172

8.3.2.7 Cyclization and subsequent functionalization

With epoxyamide **202** in hand, we were ready to examine the acidic one-pot deprotection-cyclizationprocedure for the construction of 1,2-diazetidinone ring. **202** was treated with trifluoroacetic acid at ambient temperature. No starting material could be detected (TLC) after 2 h. The cyclized product **203** was obtained in 60% yield after flash chromatography on standard grade silica (Scheme 173).



202 **203**

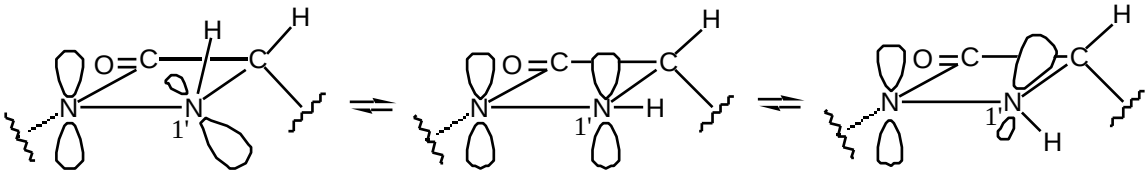
Scheme 173

The ^{1}H and ^{13}C NMR spectroscopies of **203** (in *d*-DMSO) showed two sets of signals at 20°C. These signals merged into one upon raising the probe temperature to 77°C (Table 17).

Table 17: Spectral properties of **203** at 20°C and 77°C

	20°C (δ)	77°C (δ)
H_2	4.69 (4.51): dd, *J*=9.1, 5.1 Hz	4.49: t, *J*=7.3 Hz
$H_{1''}$	3.71 (3.94): dq, *J*=6.5, 6.3 Hz	3.87: dq, *J*=6.5, 6.3 Hz
H_3	2.59 (2.59), dd, *J*=6.9, 8.9 Hz	2.63: t, *J*=7.2 Hz
	2.45 (2.73), dd, *J*=6.6, 5.1 Hz	
$H_{2''}$	1.01 (1.10): d, *J*=6.3Hz	1.10: d, *J*=6.3 Hz
C_1	169.2 (168.4)	168.2
$C_{3'}$	168.5 (168.8)	167.7
$C_{4'}$	75.3 (75.0)	75.9
$C_{1''}$	65.0 (64.4)	64.5
C_2	57.7 (58.1)	57.8
C_3	32.0 (33.3)	32.2
$C_{2''}$	19.9 (19.1)	19.1

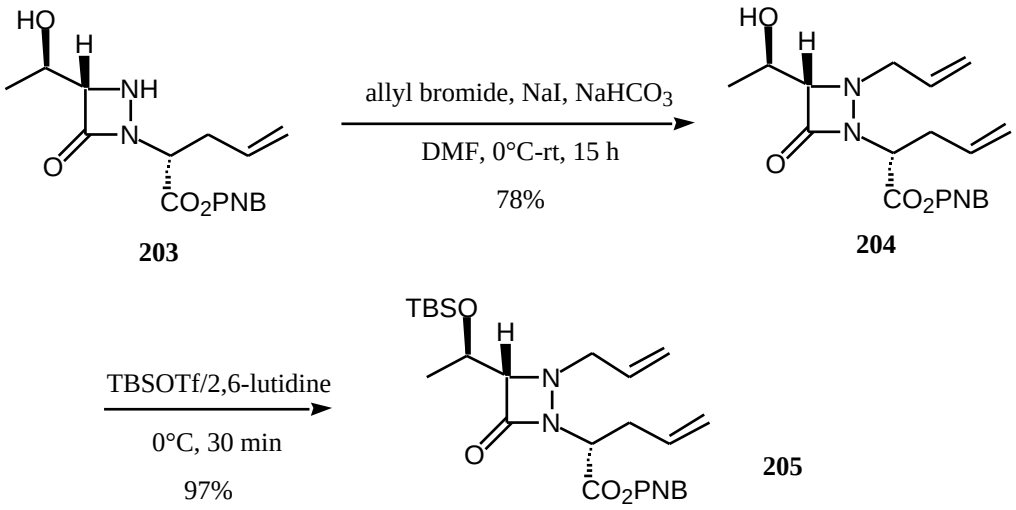
Slow inversion of the sp^3 hybridized $N_{1'}$-atom in **203** relative to the NMR time scale[260] could be responsible for the nonequivalence of the protons and carbons (Scheme 174).



Scheme 174

The selective allylation of the secondary amine was readily achieved by treatment of **203** with allyl bromide in the presence of sodium iodide and sodium bicarbonate in DMF. The bis-alkene **204** wa formed in 78% yield. To minimize possible side reactions or catalyst's

deactivation in the following olefin ring-closing metathesis, the secondary hydroxyl group in **204** was protected as *tert*-butyldimethylsilyl (TBS) ether. The transformation was fast and clean with TBSOTf in the presence of 2,6-lutidine in dichloromethane at 0°C (Scheme 175).

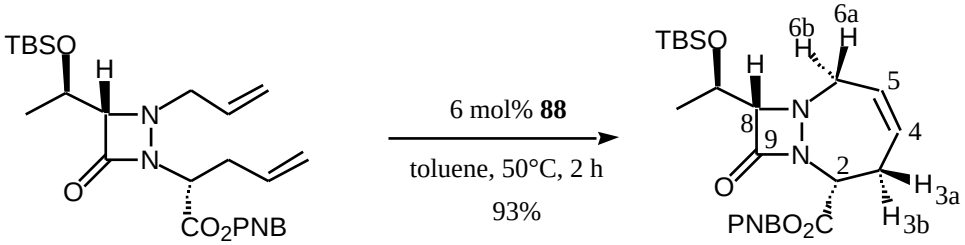


203 **204** **205**

Scheme 175

8.3.2.8 Ring-closing metathesis

The RCM of **205** cleanly occurred with using 6 mol% of secondary generation ruthenium catalyst **88**. The bicyclic aza-β-lactam **206** was isolated in 93% yield after column chromatography on silica gel (Scheme 176).



205 **206**

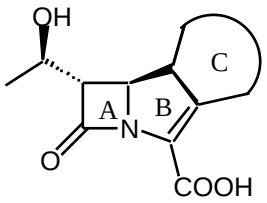
Scheme 176

An important feature of **206** in the ^{1}H NMR spectrum is the distinct splitting of signals of H_6 (6a: δ 3.85, dd, *J*=15.3, 5.4 Hz; 6b: δ 3.56, d, *J*=15.3 Hz) and H_3 (3a: δ 3.17, dt, *J*=15.0, 7.5 Hz; 3b: δ 2.60, dt, *J*=15.0, 4.8 Hz) respectively. A doublet of doublet at δ 4.82 was assigned to H_2 (*J*=7.5, 4.8 Hz). Two olefinic protons (H_4 and H_5) gave a multiplet in the range of δ 6.01-5.03, and the corresponding carbons appeared at 129.8 ppm and 127.1 ppm respectively. As said before, the aza-β-lactam carbons showed characteristic signals at 85.3 ppm (C_8) and 165.9 ppm (C_9). The carbonyl stretching frequency was found at 1773 cm^{-1}.

8.3.2.9 Double-bond migration

8.3.2.9.1 Background: tricyclic β-lactams

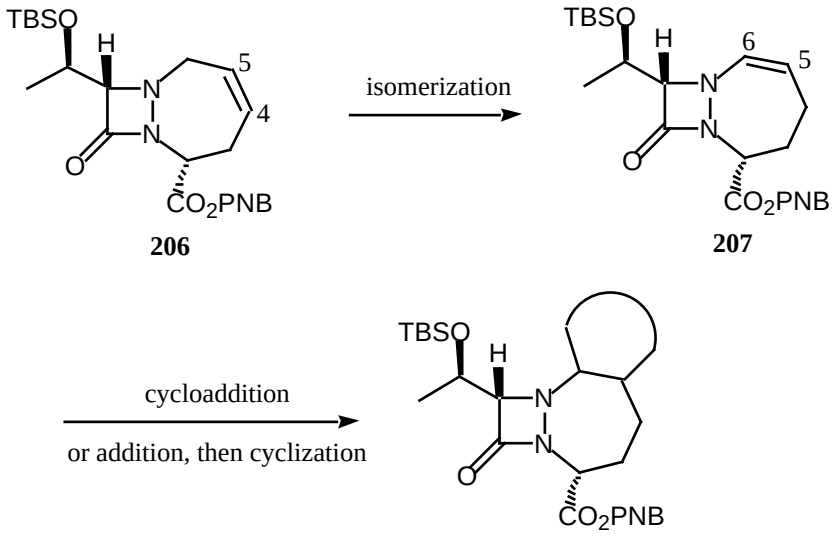
Tricyclic β-lactam antibiotics, generally referred to as trinems,[261,262] are a new family of synthetic antibacterial agents discovered by GlaxoWellcome laboratories. Trinems are promising substances which possess a broad spectrum of activity against Gram-positive and -negative bacterial strains and good resistance to β-lactamases and dehydropeptidases. The general structure of trinems is characterised by a tricyclic ring system in which ring C may be 5, 6 or 7-membered and may contain heteroatoms (Figure 35).



Trinems

Figure 35

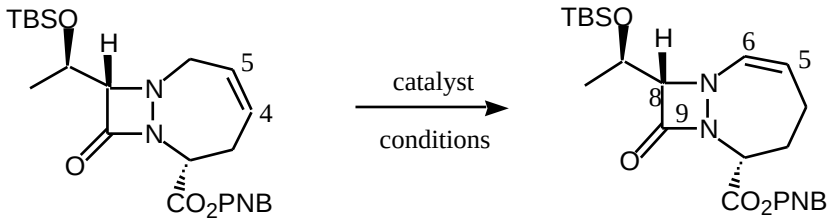
Since bicyclic aza-β-lactam **206** has already possessed the key elements (such as hydroxyethyl side chain and carboxylic acid ester) necessary for biological activity, we then consider to introduce the third ring onto its bicyclic structure. The resulting tricyclic compounds could be another type of pharmacologically interesting substances. Our initial idea was to migrate the double bond $\Delta^{5(4)}$ to $\Delta^{6(5)}$ to generate the corresponding enamine **207** which could be a key intermediate for the introduction of a third ring at the C_5 and C_6 positions (Scheme 177).



Scheme 177

8.3.2.9.2 Formation of enamine via catalytic double-bond migration

Olefin double-bond migration is one of the most extensively studied catalytic reactions. The isomerization catalyzed by soluble transition-metal compounds has found useful applications in organic synthesis. The Rh(I)-catalyzed isomerization of an allylamide to the corresponding enamide has been described by Stille and co-workers in 1980.[263] Meanwhile, the enantioselective isomerization of prochiral allylamines to the corresponding optically active enamines has been reported by Noyori *et al.*[264] We preferably chosed $HRh(PPh_3)_4$ and $HRh(CO)(PPh_3)_3$ as catalysts in view of their ready availability and high efficacy in such reactions.[263] The reaction must be conducted under an inert atmosphere. Allylamine **206** was first exposed to a catalytic amount of $HRh(PPh_3)_4$ in degassed refluxing *m*-xylene. The isomerization did not occur even after prolonged reaction times and additions of more catalyst. The starting allylamine **206** was recovered in 92% yield (Scheme 178, Table 18, Entry 1). Much to our delight, the isomerization was successfully effected at 60°C with a catalytic quantitity of $HRh(CO)(PPh_3)_3$ (Entry 2).



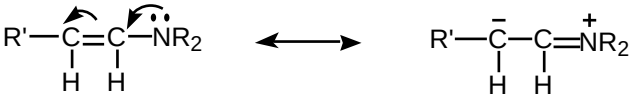
206 **207**

Scheme 178

Table 18: Catalytic double-bond migration of **206**

Entry	Catalyst	Conditions	Result
1	$HRh(PPh_3)_4$ (1-5 mol%)	*m*-xylene, 140°C, 40 h	Recovered **206** (92%)
2	$HRh(CO)(PPh_3)_3$ (1 mol%)	*m*-xylene, 60°C, 2 h	**207** (80%)

The spectral characteristic of an enamine is the upfield shift of the β olefin proton (H_5) relative to the α-proton (H_6) adjacent to nitrogen (Table 19). This is obviously due to the contribution of the canonical form **b** (Scheme 179). This trend was also observed in the ^{13}C NMR spectrum (Table 19).



a **b**

Scheme 179

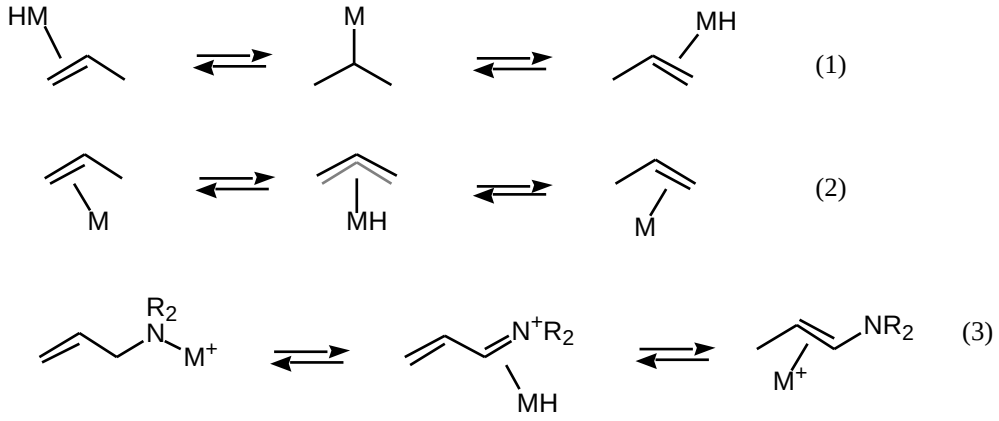
Table 19: ^{1}H and ^{13}C NMR spectra of isomeric enamine **207**

^{1}H NMR	^{13}C NMR
H_5: δ 4.79 (dt, J=8.8, 8.1, 6.1 Hz)	5-C: 108.6 ppm
6-H: δ 6.01 (dd, J=8.8, 2.3 Hz)	6-C:139.8 ppm

The characteristic signals of 1,2-diazetidinone ring were also found: a doublet at δ 3.89 (*J*=9.6 Hz) for H_8, the corresponding carbon at 84.4 ppm; carbonyl carbon (C_9) at 165.9 ppm;, and the carbonyl stretching frequency at 1781 cm^{-1}.

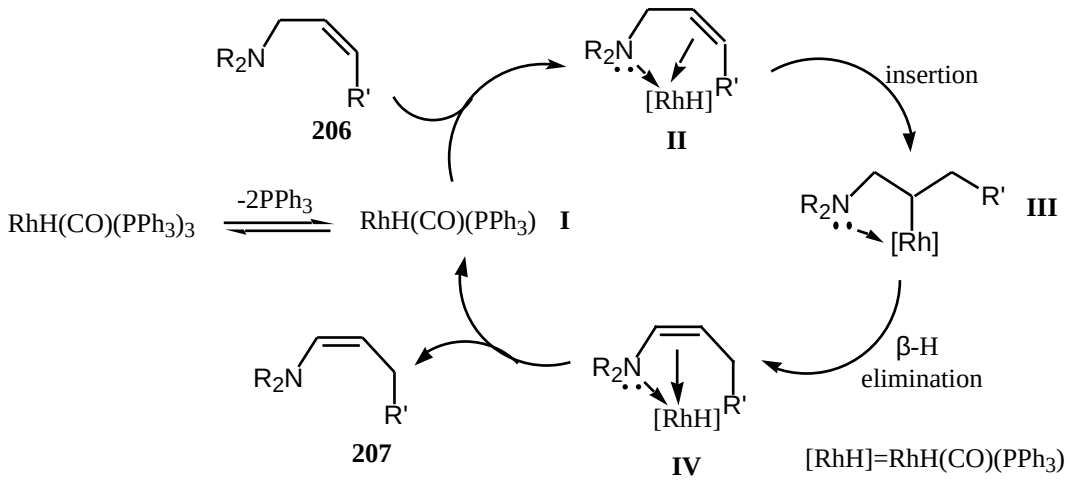
8.3.2.9.3 Mechanistic considerations

Several mechanisms have been proposed for transition-metal catalyzed isomerization of olefins.[265,266] Of these, two mechanisms have experimentally been proven. One is the metal hydride addition-elimination (Scheme 180, Eq. 1)[267,268] and the other is π-allyl mechanism resulting in an intramolecular 1,3-hydrogen shift (Eq. 2).[269,270] Noyori has postulated a nitrogen-triggered mechanism for isomerization of allylamine to enamine catalyzed by cationic Rh complexes containing BINAP ligand (Eq. 3).[271]



Scheme 180

In the present case, since we did not isolate the corresponding conjugated ester, a mechanism involving coordination of the allylamine nitrogen lone pair to the rhodium atom[263] could be written. As shown in Scheme 181, the reactive species **I** (14 e) could bind allylamine **206** to generate intermediate **II**. Subsequent insertion of the olefin into the Rh-H bond is the key step in this isomerization reaction. It is noteworthy that the presence of a strong π-acceptor ligand CO (*i.e.* low electron density on rhodium) should facilitate this olefin insertion process. β-Hydride elimination in the rhodium-alkyl intermediate **III** leads to the isomerized **IV**. Enamine **207** would be liberated after dissociation of rhodium complex **I**, thus making the catalytic cycle possible.



Scheme 181

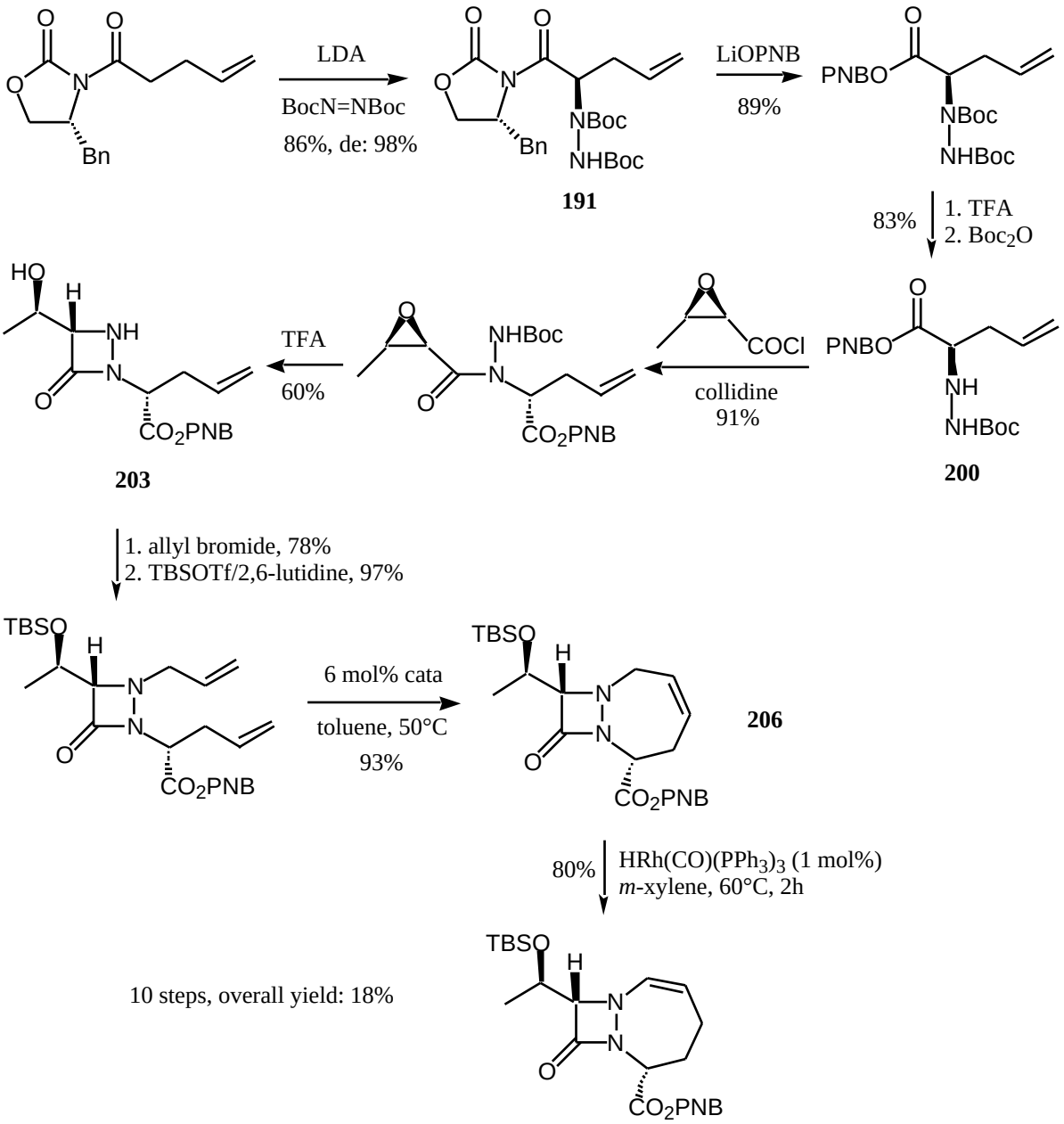
This catalytic process is reversible. The higher stability of the enamine[272] relative to the allylamine drives the reaction to the forward direction.

The lack catalytic activity of $HRh(PPh_3)_4$ could be explained by difficulties in substrate coordination caused by steric hindrance.

8.4 Conclusion

In summary, we developed a convergent asymmetric synthetic approach for the construction of the optically active bicyclo [5.2.0] aza-β-lactam carboxylic acid ester derivative by using RCM as a key step (10 steps, overall yield: 18%, Scheme 182). The electrophilic hydrazination of chiral imide enolate with BocN=NBoc (DBAD) provides an expedient approach to the asymmetric synthesis of α-hydrazino acid derivative **191** in excellent diastereoselectivity. Mono-Boc hydrazide **200** could be readily acylated with the epoxyacid chloride. Much to our delight, the one-pot deprotection-cyclization procedure towards 1,2-diazetidinone **203** in trifluoroacetic acid smoothly occurred at ambient temperature. Finally, the olefin ring-closing metathesis gave the bicyclo aza-β-lactam carboxylic ester **206** in excellent yield upon exposure of bis-alkene to 6 mol% second generation ruthenium complex.

It is noteworthy that the additional double-bond migration step provided an alternate means for the synthesis of bicyclic enamines via RCM. Considering the numerous examples, it becomes apparent that RCM of olefins connected directly to a heteroatom are significantly less abundant. To the best of our knowledge, ring-closing metathesis of enamines so far has not been reported in the literature.[169] On the other hand, the bicyclic aza-β-lactam enamine derivative prepared in this chapter is a versatile structural intermediate, which is amenable to further transformation.


LDA
BocN=NBoc
86%, de: 98%
LiOPNB
89%
191
83%
1. TFA
2. Boc2O
collidine
91%
TFA
60%
200
203
1. allyl bromide, 78%
2. TBSOTf/2,6-lutidine, 97%
6 mol% cata
toluene, 50°C
93%
206
80%
HRh(CO)(PPh3)3 (1 mol%)
m-xylene, 60°C, 2h
10 steps, overall yield: 18%

Scheme 182

Chapter 9

Attempts on the synthesis of bicyclo [4.2.0] aza-β-lactam carboxylic ester

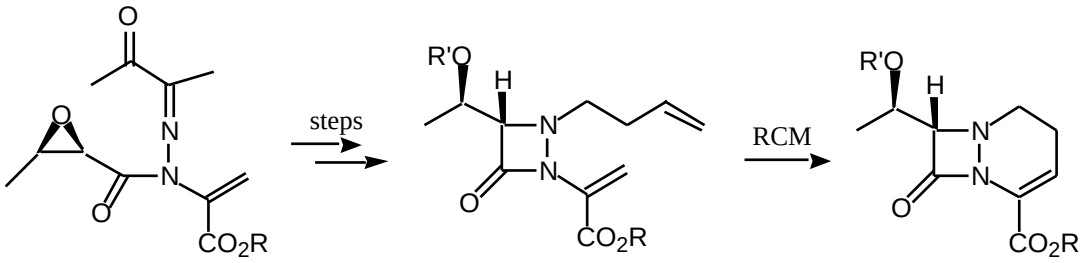
9.1 Introduction and strategies

The results of Chapter 8 encouraged us to apply the sequence to the possibly pharmacologically more interesting bicyclo [4.2.0] aza-β-lactam carboxylic ester derivatives.

Our initial idea was to construct the bicyclic aza-β-lactam **208** via olefin metathesis of substrate **209** in view of the good result obtained for the related pyrazolidinone ring (see Chapter 6). The key intermediate **210** should be easily prepared by a nucleophilic α-addition to alkynoate, a method described in details in Chapter 5 (Scheme 183).

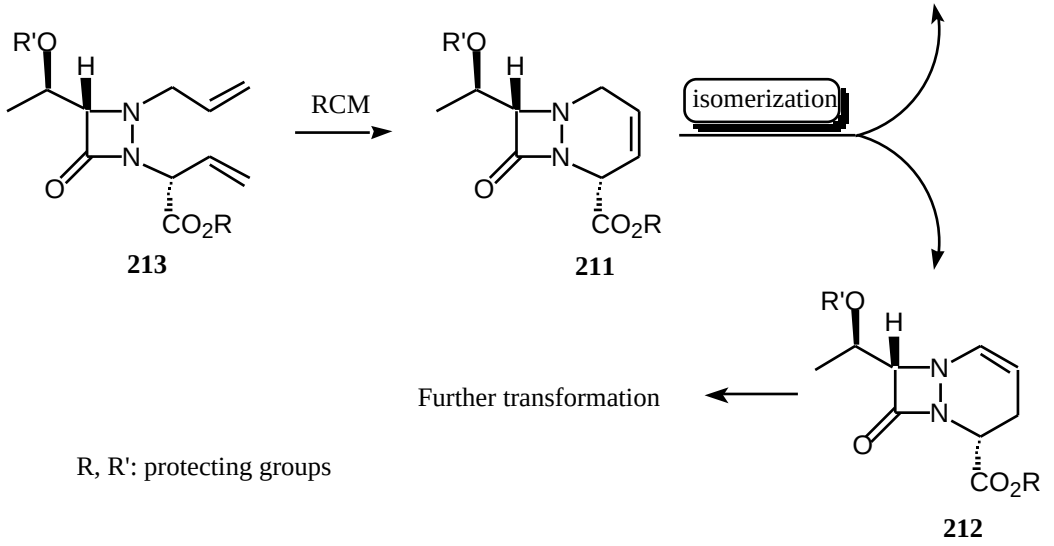
On the other hand, the asymmetric synthetic strategy described in Chapter 8 was also attractive. This sequence should allow us to produce a bicyclic ring system like **211** via RCM. Subsequent double bond migration could lead to the conjugated aza-β-lactam carboxylic ester **208**, or an interesting enamine **212** which would be amenable to further transformation (Scheme 183). In the second and third approach we will present our efforts in the preparation of the key compound **213** using two different methods.

First approach:



210 **209** **208**

Second and third approach:



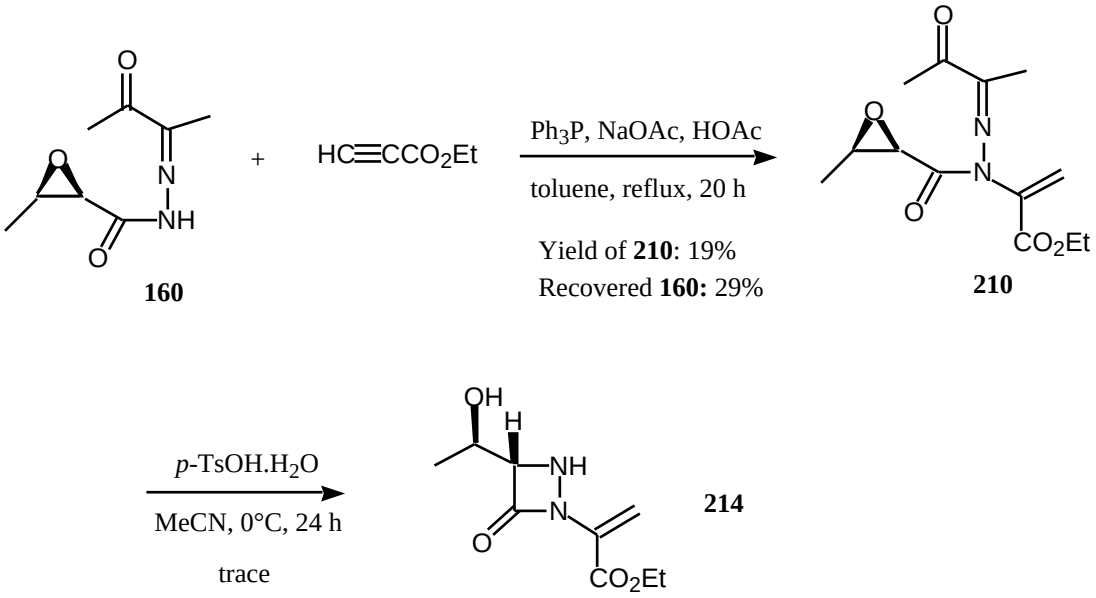
213 **211** **212**

R, R': protecting groups

Scheme 183

9.2 First approach: via a dehydrohydrazino ester

We applied the same conditions as utilized before to effect the α-addition of hydrazone **160** to ethyl propiolate. However, compound **210** was only obtained in 19% yield along with a 29% recovery of the starting hydrazone **160**. Longer reaction times did not improve the yields. Subsequent treatment of **210** with *p*-TsOH.H_2O in a cooled solution of acetonitrile only gave traces of aza-β-lactam carboxylic ester **214**. The starting material **210** was largely decomposed under the reaction conditions probably as a result of the presence of the acid-sensitive enamide structure (Scheme 184).

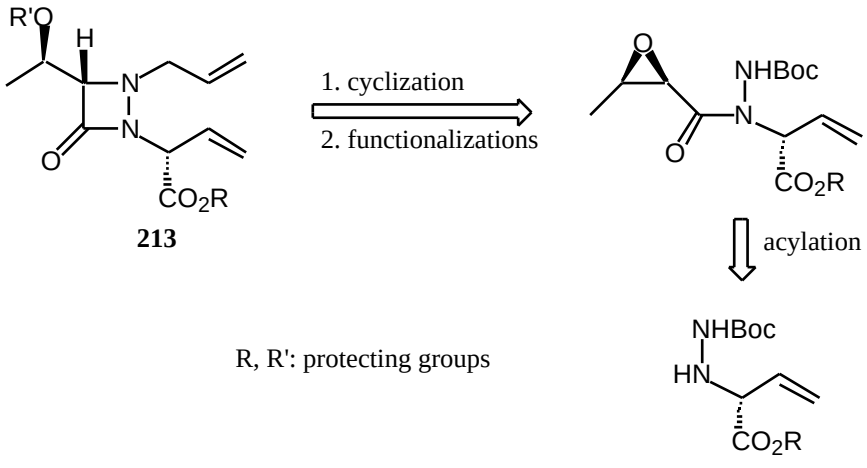


Scheme 184

We then turned our attention to the asymmetric synthetic strategy described in Chapter 8.

9.3 Second approach

In this sequence, we shall attempt to prepare a β,γ-unsaturated mono-Boc hydrazino ester which could be acylated with the epoxyacid, subsequent cyclization and functionalizations should provide bis-alkene **213** (Scheme185).

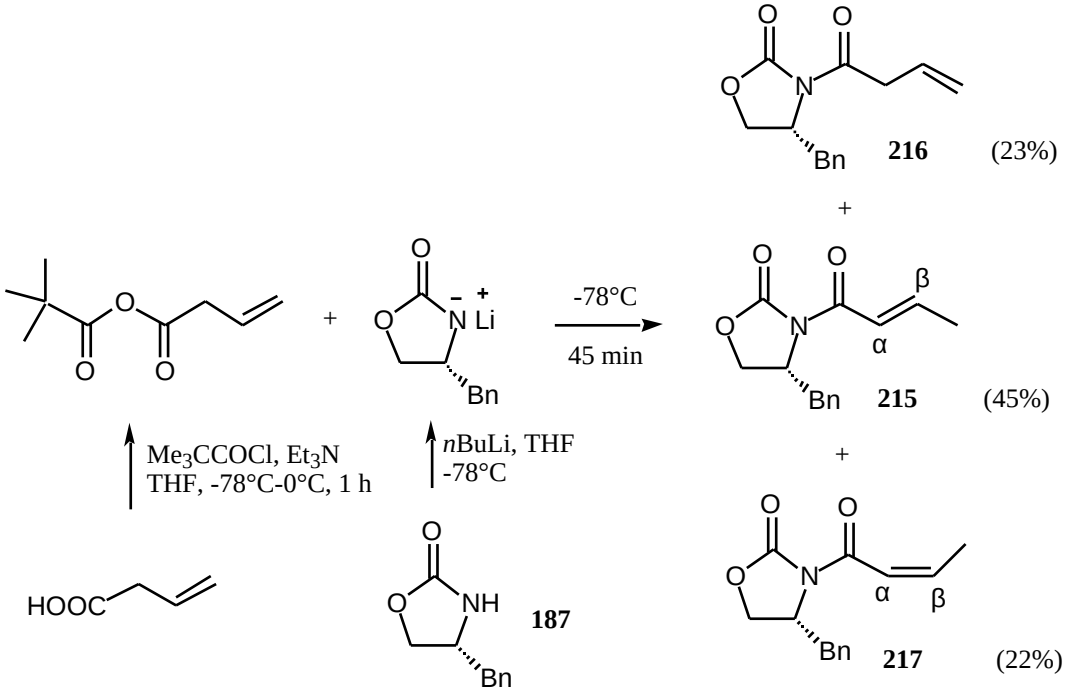


Scheme 185

9.3.1 Electrophilic hydrazination of *N*-acyl-2-oxazolidinone

9.3.1.1 Acylation of 2-oxazolidinone with vinyl acetic acid

We first prepared the carboximide substrate via the reaction of lithiated oxazolidinone **187** (see Chapter 8) and mixed pivalic acid anhydride, which was generated *in situ* from vinyl acetic acid and pivaloyl chloride in the presence of Et_3N. This acylation procedure yielded a mixture of *N*-acyl-2-oxazolidinones resulting from the partial isomerization of the double bond to the conjugated imides. The most stable *E*-conjugated isomer **215** was the major product (Scheme 186).



Scheme 186

Table 20: ^{1}H NMR spectra comparison of **215** and **217**

Proton	**215** (*E*)	**217** (*Z*)
Phenyl	δ 7.34-7.19 (m)	δ 7.34-7.24 (m)
α−H	δ 7.34-7.19 (m)	δ 7.05 (dq, *J*=11.6, 1.7 Hz)
β−H	δ 7.34-7.19(m)	δ 6.49 (dq, *J*=11.5, 7.3 Hz)
Methyl	δ 1.97 (d, *J*=5.7 Hz)	δ 2.19 (dd, *J*=7.1, 1.6 Hz)

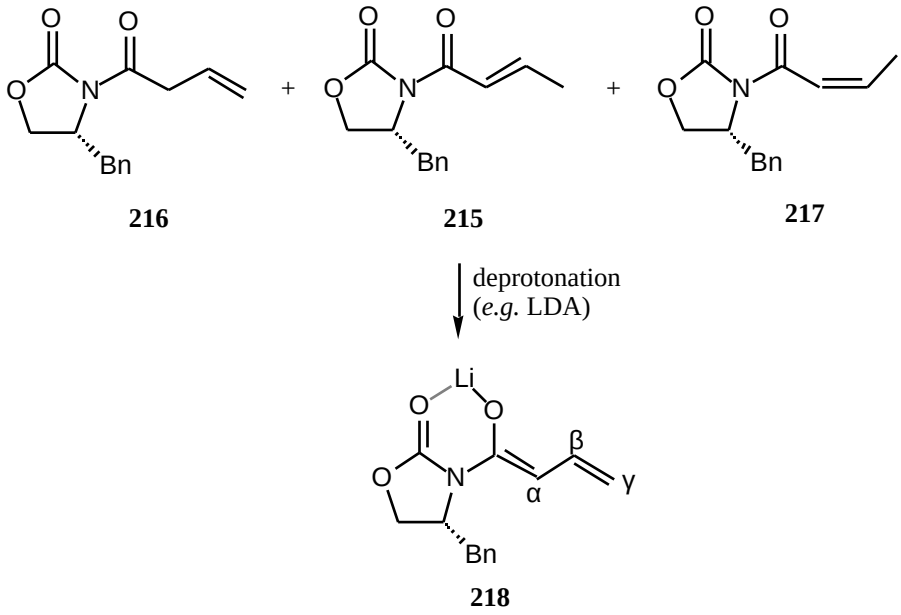
217 eluted faster on standard grade silica than components **216** and **215** which were inseparable. The ^{1}H NMR spectra of **215** and **217** showed significant differences (Table 20). For **215**, the signals of two olefinic protons appeared in the same range of chemical shifts as

that of aromatic protons, which made them impossible to analyze; on the other hand, the signals of *Z* olefinic protons in **217** appeared upfield. The coupling constant value between the *cis*-H is 11.5 Hz. Also the methyl group in **217** gave downshield doublet (δ 2.19, *J*=7.1 Hz) with respect to that in **215** (δ 1.97, *J*=5.3 Hz).

A method using *N*-methylmorpholine as a base allows the preparation of β,γ-unsaturated *N*-acyl-2-oxazolidinones without isomerization of the double bond.[273] However, we decided to perform the hydrazination step on the mixture of imides since they will lead anyway to the same enolate.

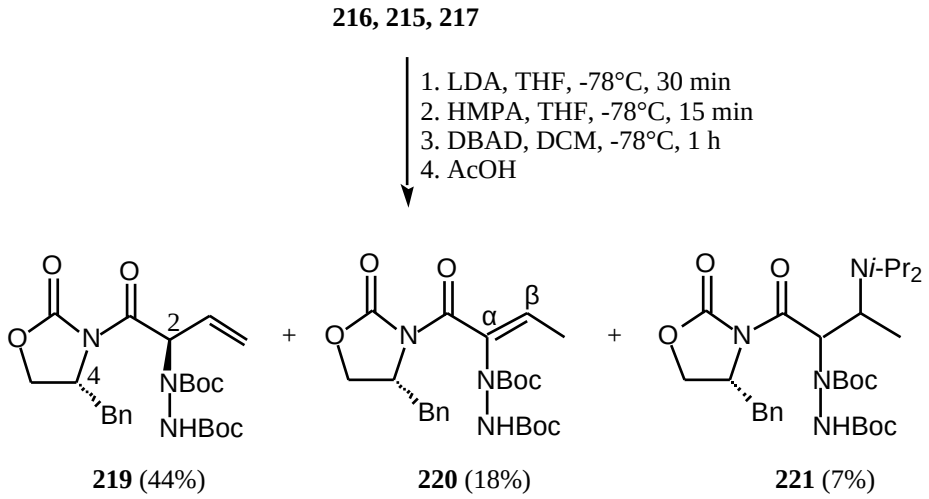
9.3.1.2 Hydrazination of the imide mixture

Deprotonation of carboximides **216**, **215** and **217** will generate the fully conjugated enolate **218**. As discussed earlier, the chelated (*Z*)-enolate is the reactive species for the diastereofacial hydrazination process (Scheme 187).



Scheme 187

The mixture of imides was treated with lithium diisopropylamide (LDA) in THF at -78°C for 30 min. One equivalent of HMPA was added to effect the hydrazination predominantly at the α-position.[274,275] A precooled solution of DBAD in CH_2Cl_2 was then reacted to the enolate solution (Scheme 188).



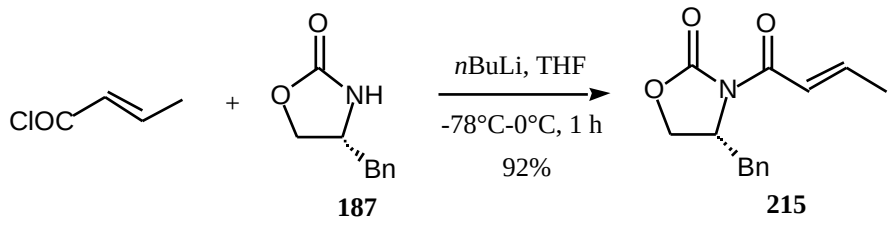
219 (44%) **220** (18%) **221** (7%)

Scheme 188

In enolate **218**, the kinetically preferred site for hydrazination is the α-carbon. We obtained the less stable β,γ-unsaturated hydrazide **219** (2*R*, 4*R*) predominantly as would be expected. In this case we did not detect the corresponding minor diastereomer (2*S*, 4*R*), which further proved the efficacy of oxazolidinone as a chiral auxiliary in the utility of such electrophilic hydrazinations. α,β-Unsaturated hydrazide **220** must result from the double bond migration of **219** under the basic conditions. Based on the earlier results (Table 20), the methyl group in **220** was assigned *trans* to the carbonyl function (δ 1.90, d, *J*=7.5 Hz). On the other hand, the conjugate addition[276] of diisopropylamine anion to **215** or **217** generated the corresponding lithium enolate which could be quenched with electrophile DBAD to give by-product **221**. In its ^{1}H NMR spectrum, two dinstinc doublets (δ 1.04, *J*=6.3 Hz; δ 0.88, *J*=6.6 Hz) for isopropyl methyl groups were clearly visible (Scheme 188).

9.3.1.3 Synthesis of imide 215 and subsequent hydrazination

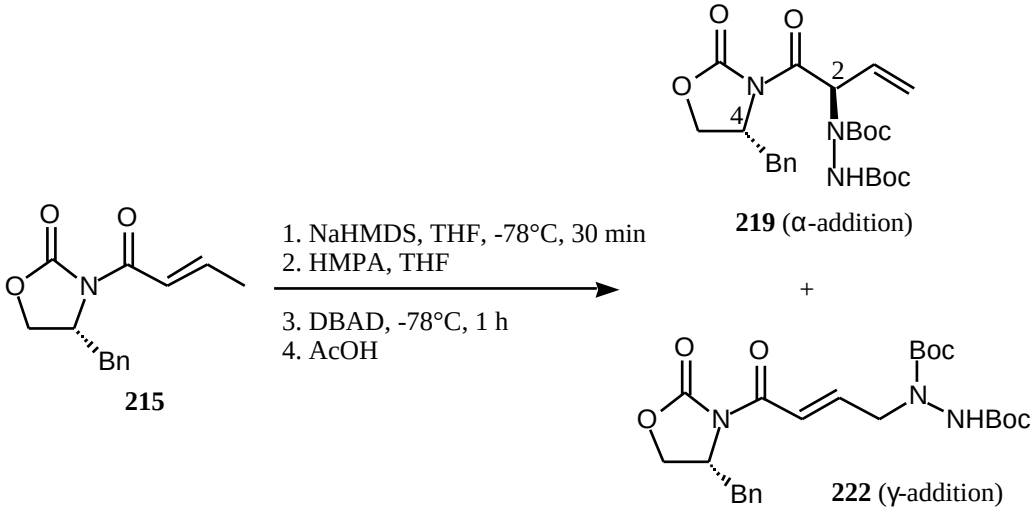
In order to study the role of HMPA on the regioselectivity of addition of DBAD to the conjugated enolate **218**, we prepared *Z*-crotonyl imide **215** in pure form. Freshly distilled crotonyl chloride was added to a solution of lithiated (*R*)-4-benzyloxazolidin-2-one **187** in anhydrous THF at -78°C, and the reaction was allowed to warm to 0°C during 1 h. The imide **215** was obtained in excellent yield after column chromatography (Scheme 189).



Scheme 189

The electrophilic hydrazination with DBAD was conducted on the enolate generated with NaHMDS. Evans and co-workers[235] have indeed reported that for the "small" alkyl halides (*e.g.* MeI) α-alkylations of the sodium enolates (-78°C) of the carboximides exhibited higher diastereoselectivity than that using lithium enolates (0°C).

The reaction was first carried out without addition of HMPA. The sodium enolate of the α,β-unsaturated imide **215** was treated with DBAD to give 51% of the α-adduct **219** along with 33% of the γ-addition product **222** with a *E*-double bond (Scheme 190, Table 21, Entry 1). Addition of 1 equiv of HMPA favoured α-addition of DBAD (Entry 2). In the presence of 5 equiv of HMPA, the major reaction pathway for anion was α-addition, with detectable γ-addition (11%) also taking place (Entry 3). In all three instances, the α-adduct **219** (2*R*, 4*R*) was formed with excellent stereoselectivity and we did not detect the other diastereomer (2*S*, 4*R*) by column chromatography.



Scheme 190

Table 21: HMPA-mediated α- and γ-addition of DBAD to **215**

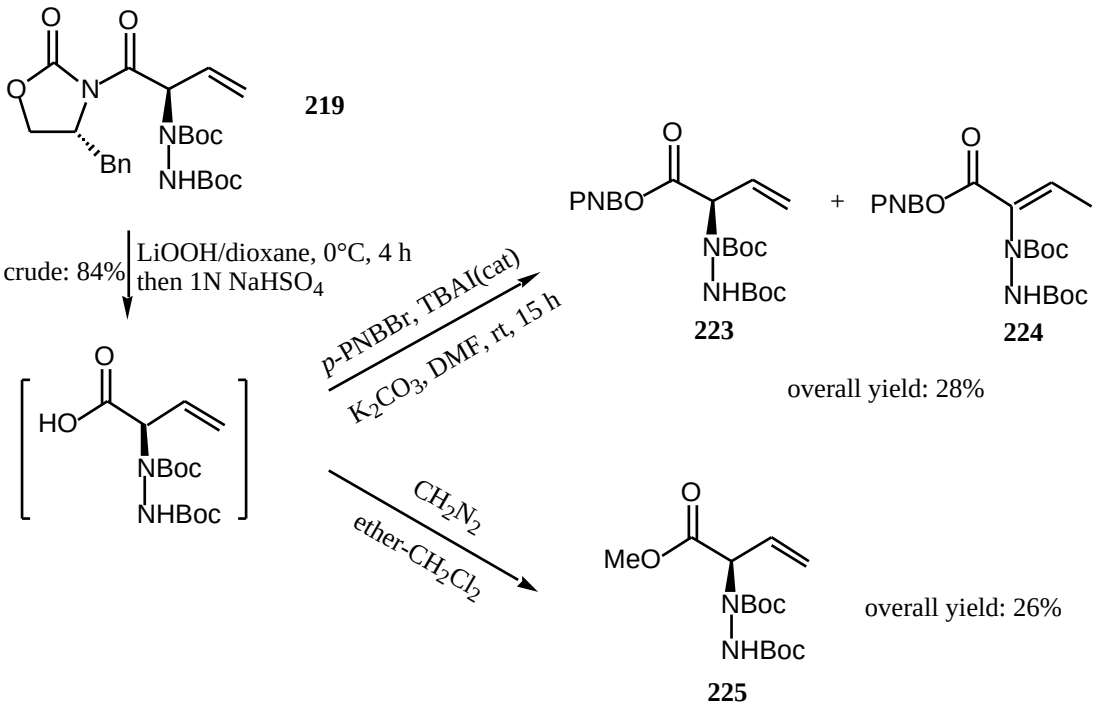
Entry	HMPA	Yield of **219**	Yield of **222**
1	without HMPA	51%	33%
2	1 equiv	61%	21%
3	5 equiv	52%	11%

HMPA is a dipolar aprotic solvent which has been extensively used as an additive in organolithium chemistry. It can dramatically enhance the rates of a wide variety of organolithium reactions and significantly influence regio- or stereoselectivities. The reactivity or selectivity effects of HMPA are usually rationalized in terms of changes in either aggregation state or ion pair structure.[277,278] The breaking up of aggregates to form reactive monomers or solvent-separated ion pairs is often invoked. In the present case, we observed a pronounced α-regioselectivity upon addition of DBAD to the carboximide enolate in the presence of HMPA. However, insufficient literature data do not allow to make a prediction on the role of HMPA in the reactions of conjugated carboximide enolates with various electrophiles.

9.3.2 Removal of oxazolidinone auxiliary

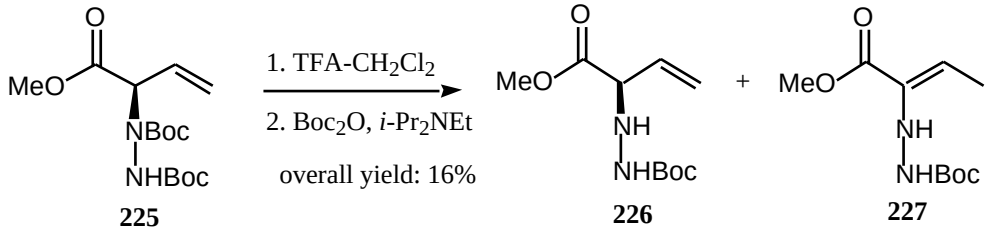
9.3.2.1 Imide hydrolysis

It has been mentioned that the LiOOH-mediated hydrolysis of carboximides not only displayed excellent exocyclic cleavage regioselectivity, but also resulted in the suppression of olefin conjugation, which is a major problem with more basic reagents, *e.g.* LiOH.[245] This was also the case for the cleavage of the auxiliary from **219**. However, the esterification step (*p*-nitrobenzyl bromide in the presence of K_2CO_3 and a catalytic amount of tetrabutylammonium iodide in DMF) gave a low yield (28%) of a 1:1 inseparable mixture of the desired **223** and the conjugated **224**. We also treated the crude acid which was derived from peroxide hydrolysis with CH_2N_2. The overall yield of hydrazide **225** was only 26% but we did not detect any double bond migration (Scheme 191).



Scheme 191

The Boc groups were then cleaved in a solution of TFA in CH_2Cl_2. The crude hydrazine was obtained in 52% yield. Subsequent treatment with 1 equiv of Boc_2O in the presence of iPr$_2$NEt gave an inseparable mixture of β,γ-unsaturated and conjugated hydrazide **226** and **227** (3:1) in very low yield (Scheme 192).



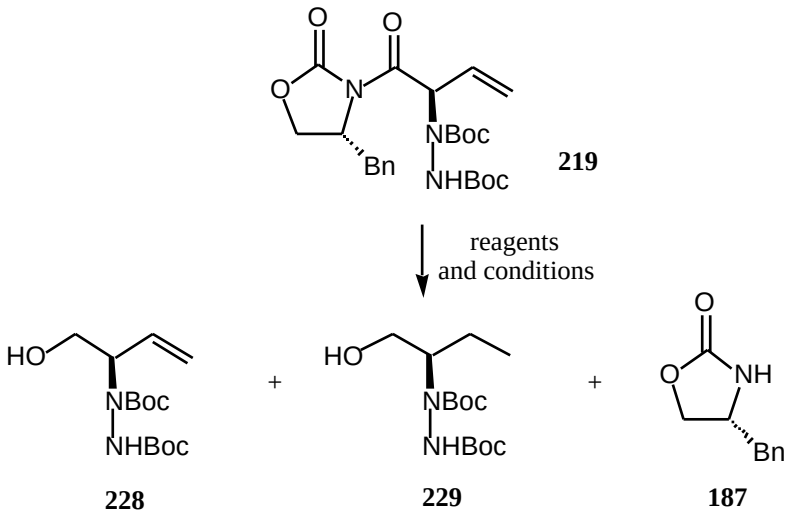
Scheme 192

9.3.2.2 Reductive cleavage

In view of the facile double bond isomerization of β,γ-unsaturated hydrazino esters, we then considered to effect a reductive cleavage of the carboximide to the alcohol which could then be reoxidized to the corresponding ester at a later stage. Sterically hindered and alkene-containing *N*-acyloxazolidinones have been reduced to the corresponding primary alcohols using $LiBH_4$ in Et_2O containing water or ethanol (1 equiv) in better yields than $LiBH_4$ alone.[279] It is possible that a 1:1 ratio of $LiBH_4$ and H_2O forms a hydroxyborohydride ion which then

acts as reducing agent. This reduction procedure was tried on our substrate **219** (Scheme 193, Table 22). However, we only obtained the desired hydrazide **228** in 19% yield along with 25% of a compound **229** resulting from the simultaneous reduction of the double bond (Entry 1). The use of ethanol instead of water gave a similar result (Entry 2).

The reductions performed in THF gave **228** predominantly (Entry 3). Addition of 1 equiv of MeOH was also effective, the maximum yield of **228** has been obtained under these conditions (Entry 4).



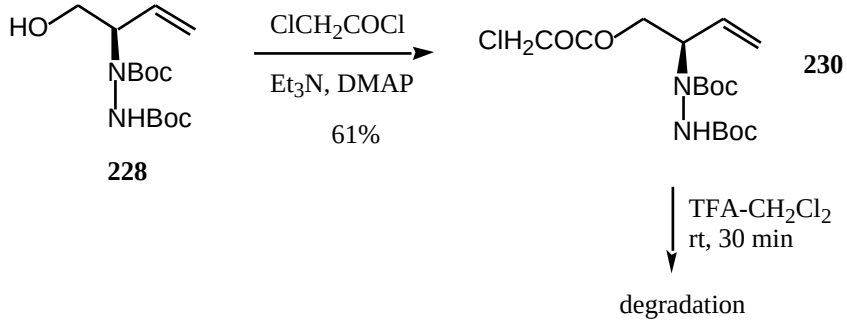
Scheme 193

Table 22: $LiBH_4$-mediated reductive removal of oxazolidinone

Entry	Reagents and conditions	Result (%)		
		228	**229**	**187**
1	$LiBH_4/H_2O$ (1.1/1.1), Et_2O, 0°C, 15 h	19	25	65
2	$LiBH_4$/EtOH (1.1/1.1), Et_2O, 0°C, 20 h	18	31	quantitative
3	$LiBH_4$/EtOH (1.1/1.1), THF, 0°C, 20 h	30	17	quantitative
4	$LiBH_4$/MeOH (1.1/1.1), THF, 0°C-rt, 2 d	35	17	98

In all cases, the chiral auxiliary was recovered in good to quantitative yields (Table 22).

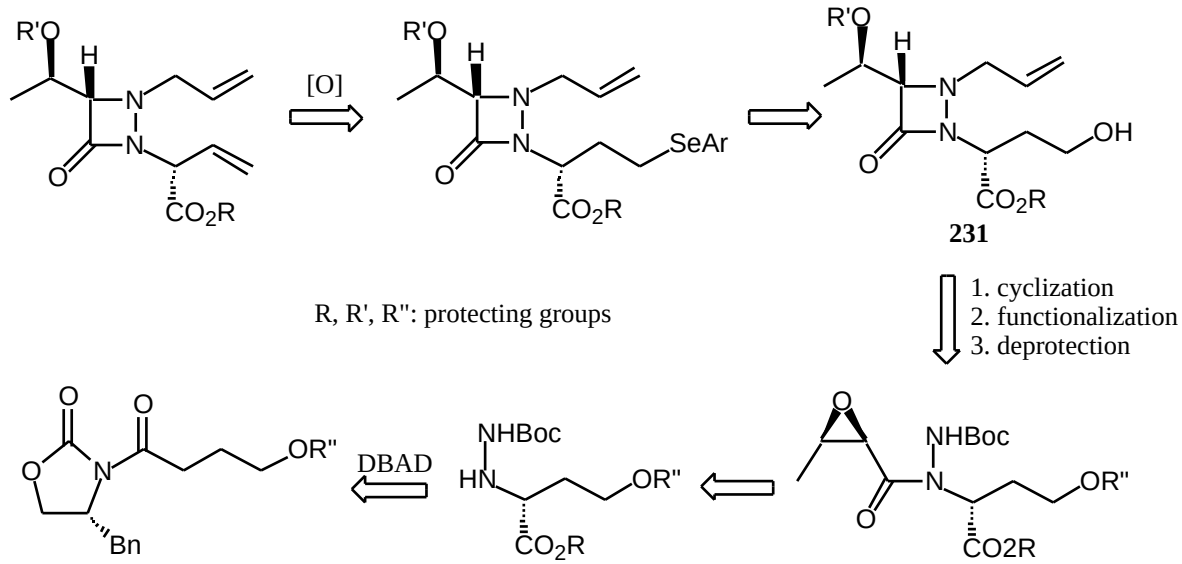
The primary alcohol group in **228** could be efficiently protected as the α-chloroacetate. However, the following acidic cleavage of Boc groups under the usual conditions destroyed hydrazide **230** (Scheme 194).



Scheme 194

9.4 Third approach

In this new synthesis plan, we shall attempt to form the double bond after the cyclization step. This will be done by an oxidative elimination reaction involving a selenide. This mild procedure could be applied to aza-β-lactam ester **231** bearing a hydroxyl group which can be easily transformed into the selenide. The synthesis of **231** should be achievable utilizing the method described in Chapter 8 (Scheme 195).



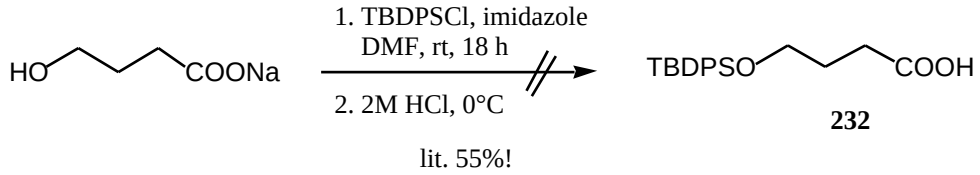
Scheme 195

9.4.1 Synthesis of carboximide derivative bearing a silyl ether

9.4.1.1 Preparation of 4-(*tert*-butyldiphenylsiloxy)butyric acid 232

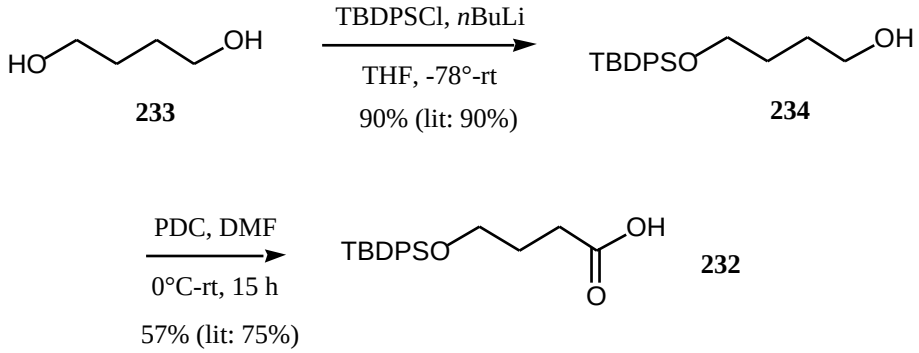
The *tert*-butyldiphenylsilyl ether (TBDPS) has been chosen as the suitable protecting group in the present case in view of its relative stability under acidic conditions. In our hands

the known procedure[280] for the preparation of **232** did not work and TBDPSCl was recovered in quantitative yield (Scheme 196).



Scheme 196

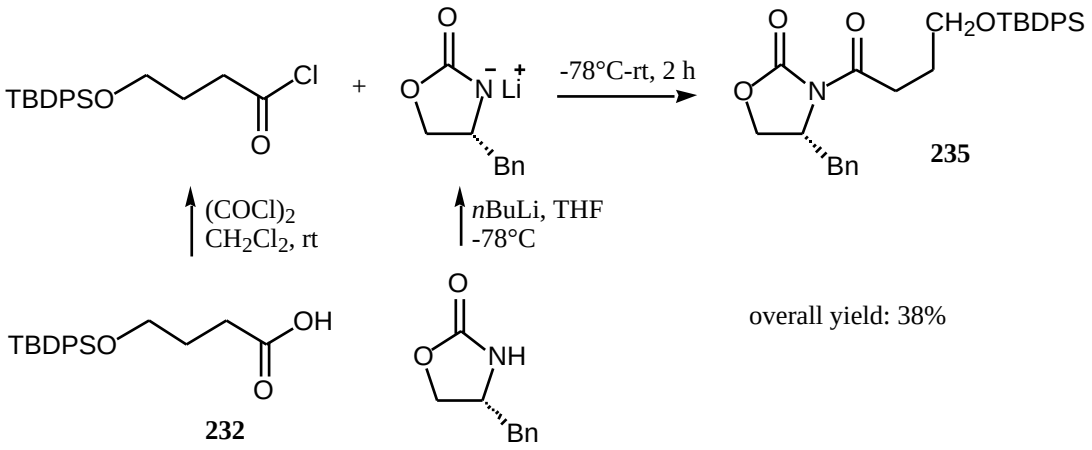
We did not vary the conditions but rather employed a two-step procedure[281] (Scheme 197) starting from 1,4-butanediol **233**. Thus, the selective monoprotection of **233** with TBDPSCl gave a 90% yield of the corresponding alcohol **234**, which upon oxidation with PDC in DMF gave carboxylic acid **232** in 57% yield.



Scheme 197

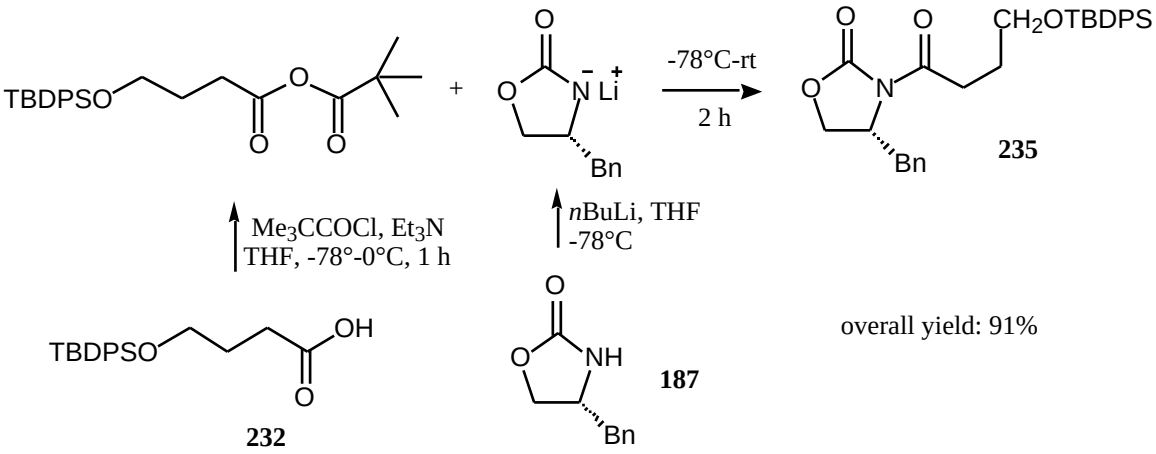
9.4.1.2 Condensation with lithiated oxazolidinone

We first transformed acid **232** into the corresponding acid chloride which was reacted with lithiated oxazolidinone in THF. This procedure gave carboximide **235** in a moderate overall yield (38%, Scheme 198).



Scheme 198

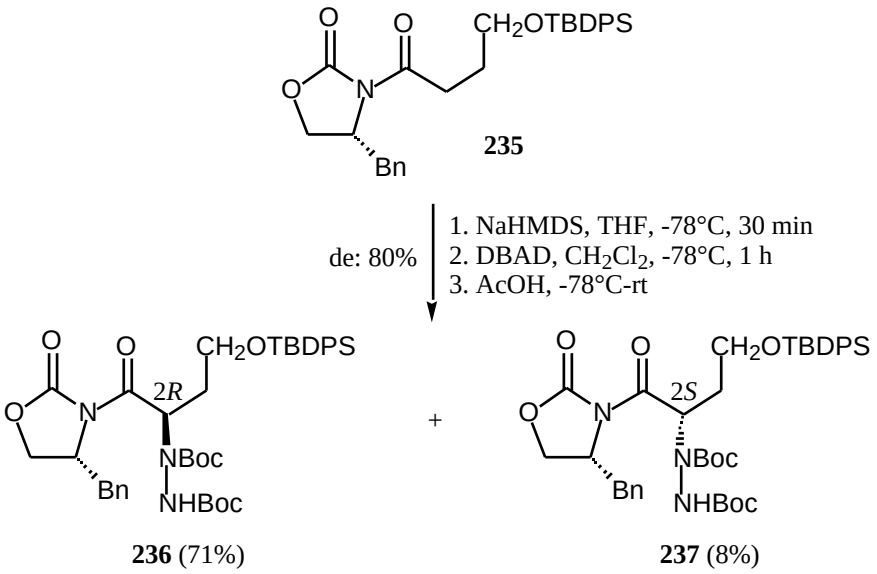
4-Silyloxybutyric acid **232** was then activated as a mixed pivalic acid anhydride. Treatment of the resulting mixed anhydride with the lithiated oxazolidinone **187** gave **235** in excellent yield (Scheme 199).



Scheme 199

9.4.2 Electrophilic hydrazination and subsequent imide hydrolysis

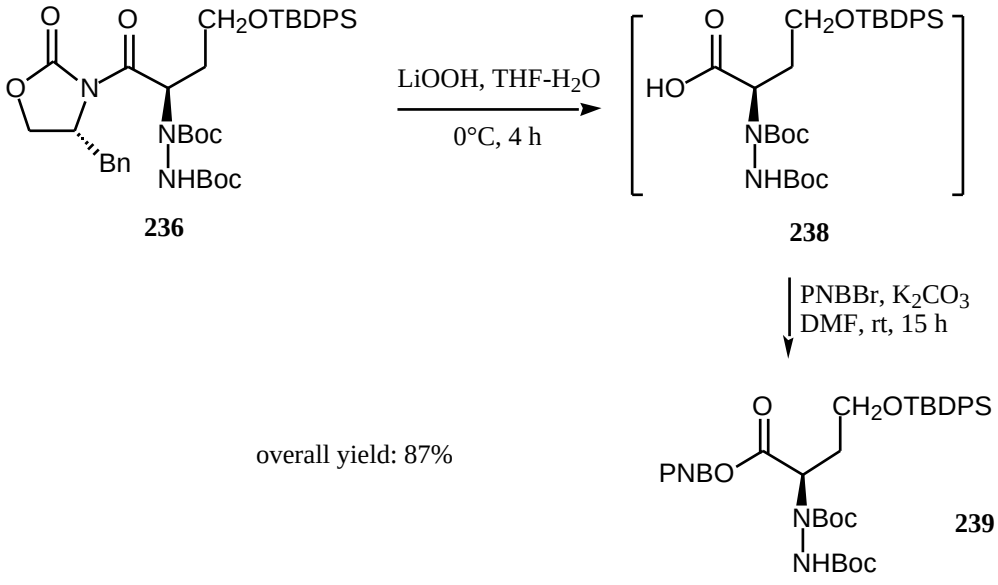
Carboximide **235** was readily converted into the corresponding sodium enolate with NaHMDS in THF at -78°C. This enolate underwent smooth electrophilic hydrazination with BocN=NBoc (DBAD) to give the desired hydrazide **236** (71% yield), together with small amounts of diastereomer **237** (8% yield, Scheme 200).



Scheme 200

The two diastereomers proved to be readily separable by column chromatography on standard grade silica. The faster-eluting component of this diastereomeric mixture was found to correspond to the major diastereomer **236**, which was assigned the 2(*R*) configuration on the basis of the some arguments cited earlier for compound **191** (see Chapter 8).

LiOOH-mediated hydrolysis of **236** under the standard conditions (0°C, 3:1 THF/H_2O) gave the corresponding carboxylic acid **238** which was directly converted into the carboxylic ester **239** by reaction with *p*-nitrobenzyl bromide (PNBBr) in the presence of K_2CO_3 in DMF (87% yield from **236**, Scheme 201).

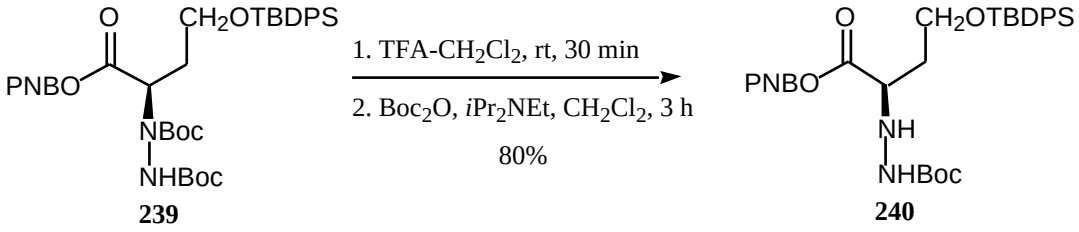


Scheme 201

In a typical procedure of hydrolysis of oxazolidinone by LiOOH, the excess peroxide was quenched with aq Na_2SO_3. After buffering to pH 9-10 with aq $NaHCO_3$ and evaporation of THF, the oxazolidinone chiral auxiliary and the corresponding sodium salt of carboxylic acid **238** could not be separated by simple CH_2Cl_2 extraction as described earlier (see Chapter 8). Probably, the high solubility of the sodium salt of **238** in organic phase is due to the lipophilicity of the OTBDPS functionality. Thus, we directly acidified the CH_2Cl_2 extracts with 1 N aq. $NaHSO_4$ and the crude acid **238** was isolated in quantitative yield.

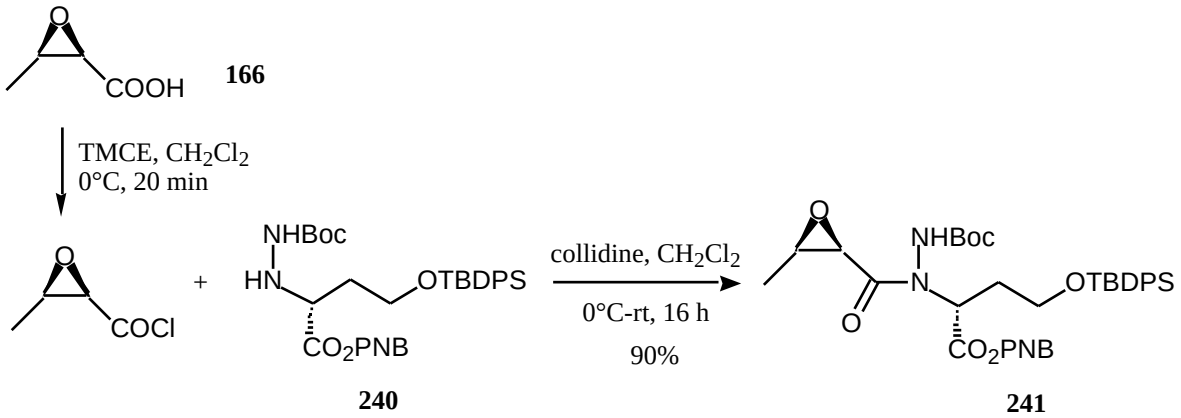
9.4.3 Synthesis of the aza-β-lactam derivative

Upon treatment with TFA hydrazide **239** gave a quantitative yield of the corresponding hydrazine, which in turn yielded 80% of the desired Boc-monoprotected hydrazide **240** by reaction with Boc_2O in the presence of *i*Pr_2NEt (Scheme 202).



Scheme 202

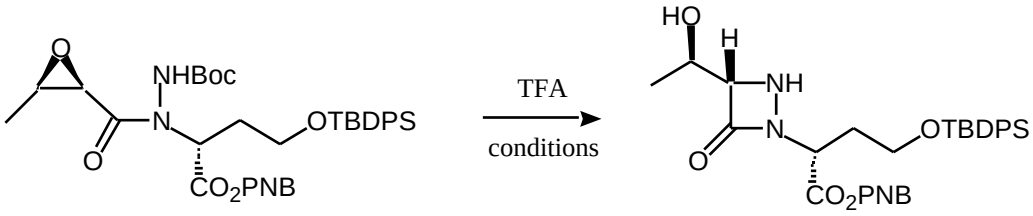
The acylation reaction of **240** with epoxyacid chloride (derived from epoxyacid **166** on treatment with TMCE) proceeded extremely well and gave compound **241** in excellent yield (Scheme 203).



Scheme 203

The one-pot deprotection-cyclization reaction of **241** was then carried out in the large excess of TFA (Scheme 204). Due to the presence of the silyl ether, we first performed the

reaction at 0°C. After 3 h the starting material was completely consumed, whereas the cyclized compound **242** was separated in poor yield (35%, Table 23, Entry 1). As a matter of fact, the TFA-catalyzed deprotection-cyclization of **241** was rather fast at room temperature, and the reaction was best effected after stirring for 30 min (Entry 2).



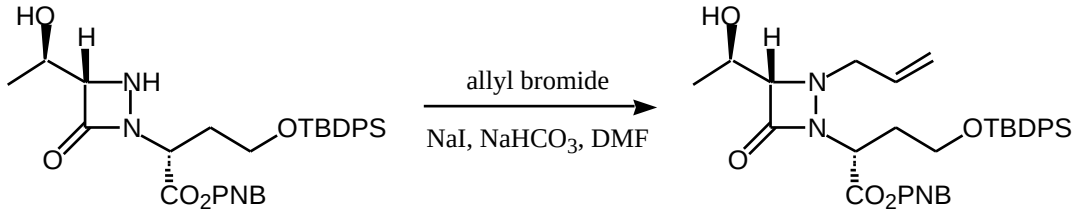
241 **242**

Scheme 204

Table 23: TFA-mediated deprotection-cyclization of **241**

Entry	Conditions	Yield of **242** (%)
1	0°C, 3 h	35
2	rt, 30 min	56

The functionalized aza-β-lactam **242** was then treated with allyl bromide in the presence of NaI and $NaHCO_3$ in DMF (Scheme 205). The allylation proceeded slowly at ambient temperature, and only 27% of allylated **243** was isolated after stirring for 40 h along with a 57% recovered yield of the starting material **242** (Table 24, Entry 1). We reasoned that the steric hindrance of OTBDPS functionality could be critical for the reactivity. Gentle heating was found to be non-destructive in this case, and the allylation was greatly accelerated. The starting compound **242** was totally consumed by heating the reaction mixture at 50°C for 36 h and the desired aza-β-lactam **243** was obtained in 85% yield (Entry 2).



242 **243**

Scheme 205

Table 24: Allylation of **242**

Entry	Conditions	Recovered **242** (%)	Yield of **243** (%)
1	rt, 40 h	57	27
2	50°C, 36 h	/	85

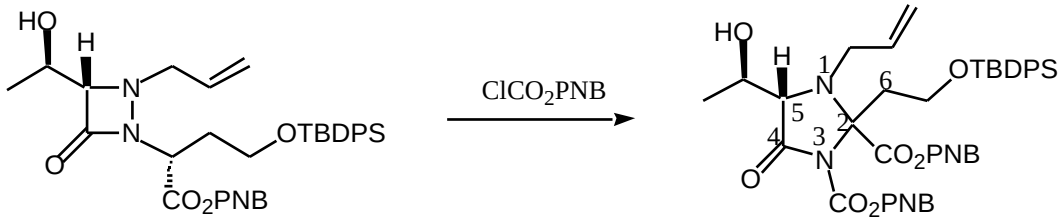
9.4.4 Protection of hydroxyl function and subsequent desilylation

9.4.4.1 Protection of hydroxyl function with *p*-nitrobenzyloxycarbonyl group

Our initial idea was to protect the hydroxyl function in **243** with *p*-nitrobenzyloxycarbonyl group, thus the final deprotections leading to an aza-β-lactam carboxylic acid derivative bearing a hydroxyethyl side chain could be effected simultaneously. This methodology has been well established in the organic chemistry of β-lactams.[213]

The protection of hydroxyl group in **243** with *p*-nitrobenzyl chloroformate in the presence of NaH in DMF was found to be destructive (Scheme 206, Table 25, Entry 1). In fact, the pale yellow solution of **243** in DMF turned immediately green upon addition of NaH at 0°C. We isolated the ring expanded product **244** in 17% yield after treatment of green solution with *p*-nitrobenzyl chloroformate.

The imidazolidinone structure of **244** was fully confirmed by the spectroscopies. Particularly, in the ^{1}H NMR spectrum the doublet at δ 3.70 (*J*=6.2 Hz) was assigned to H_5; due to the absence of proton at C_2 position, H_6 gave two distinct triplets of doublets (δ 2.81, dt, *J*=15.8, 6.8 Hz; δ 2.32, dt, *J*=15.8, 5.3 Hz). In the ^{13}C NMR spectrum, C_4 appeared at 172.2 ppm; the quaternary C_2 was clearly visible at 82.7 ppm.



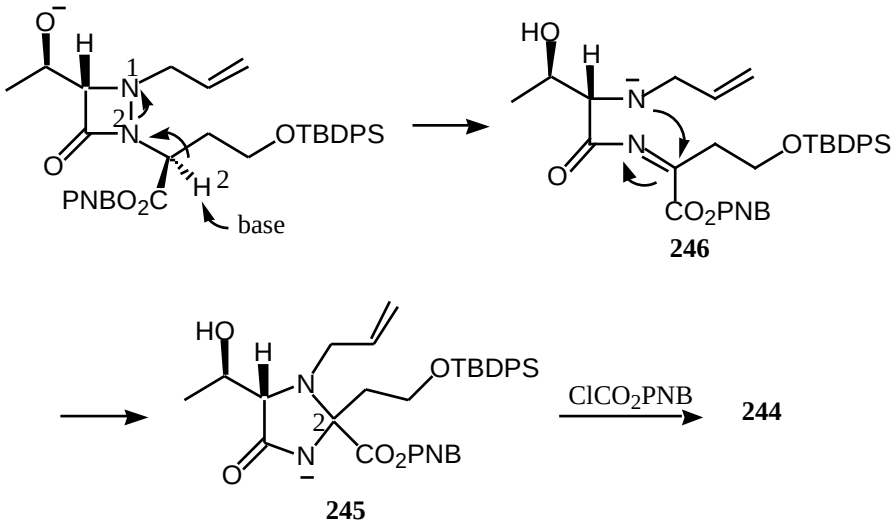
243 **244**

Scheme 206

Table 25: Protection of hydroxyl group in **243** with $ClCO_2PNB$

Entry	Conditions	Recovered **243**	Yield of **244**
1	NaH, DMF, 0°C	/	17%
2	1.2 equiv Et_3N, 0.1 equiv DMAP CH_2Cl_2,, 0°C-rt, 16 h	100%	/
3	1.2 equiv Et_3N, 1.1 equiv DMAP CH_2Cl_2,, 0°C-rt, 16 h	50%	25%

It was observed in the earlier work of Taylor *et al.* that treatment of 1,2-disubstituted 1,2-diazetidinone with strong base (*e.g.* LDA) resulted in proton abstraction from the α-carbon atom of the N-2 substituent and a subsequent extremely rapid ring expansion, analogous to the Stevens rearrangement, to give an imidazolidinone.[183] This reaction was also observed in the present work. The sodium alkoxide derived from the deprotonation of the starting material **243** by NaH can abstract H-2, then cleavage of N-N bond and subsequent cyclization to give the imidazolidinone derivative **245**. Treatment of this intermediate with $ClCO_2PNB$ gave **244** (Scheme 207).



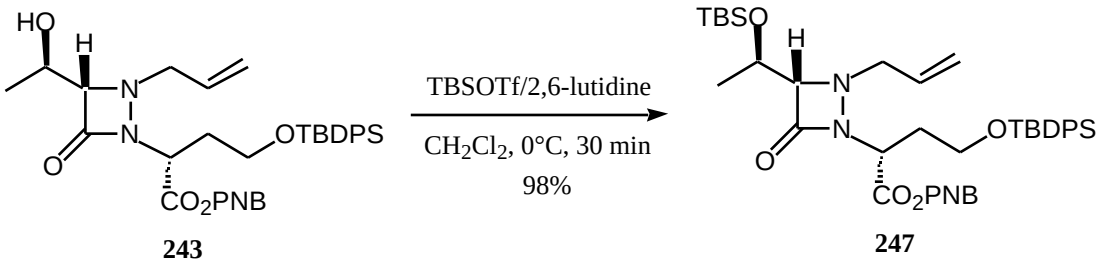
Scheme 207

In this case the methine group adjacent to N-2 is incorporated into the 2-position of the imidazolidinone ring. The extraordinary ease with which this reaction takes place is probably due to the ring strain of 1,2-diazetidinone structure and the weak N-N bond energy. The presence of a carboxylic ester group at C_2 should also facilitate this transformation since it makes H-2 more acidic.

A possible way to avoid the above ring-expansion would be to use a weaker base. Treatment of **243** with 1 equiv of $ClCO_2PNB$ in the presence of 1.2 equiv of Et_3N and 0.1 equiv of DMAP in CH_2Cl_2 led to the complete recovery of the starting material (Table 25, Entry 2). Additional one equivalent of DMAP[282] caused ring-expansion along with a 50% recovered yield of **243** (Entry 3).

9.4.4.2 Protection of hydroxyl function with *tert*-butyldimethylsilyl (TBS) group

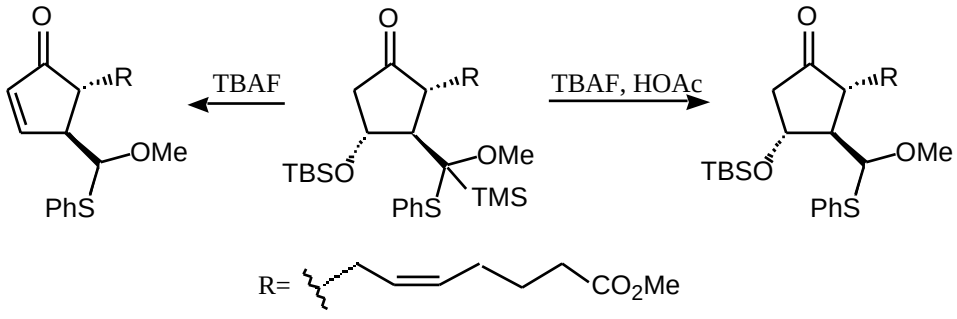
The TBDPS group is cleaved at a comparable rate to the TBS group with TBAF but is more stable to acid hydrolysis. Thus for the fully protected aza-β-lactam derivative **247**, selective removal of a primary TBDPS group in the presence of a hindered secondary TBS group was conceivable. We then employed a method described earlier to protect the hydroxyl group as OTBS functionality (Scheme 208). The reaction was extremely clean and rapid and gave product **247** in excellent yield.



243 **247**

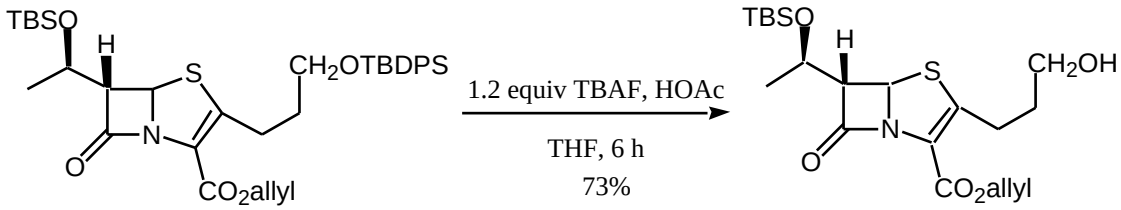
Scheme 208

The subsequent selective desilylation presented a more difficult challenge. As we know, the main drawback of TBAF is its comparatively high basicity which can cause undesirable side reactions. For example, Otera *et al.*[283] reported that in a synthesis of prostaglandin derivative, elimination of TBSO group competed with removal of TMS group. They mentioned that this undesired β-elimination reaction could be suppressed by buffering the reaction with HOAc (Scheme 209).



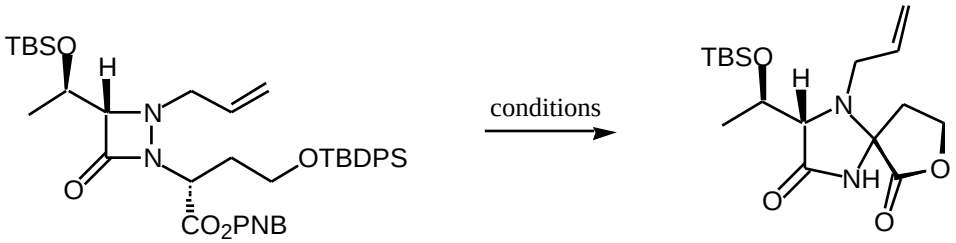
Scheme 209

Moreover, in a synthetic approach towards 2-(heteroatom-substituted)methyl penem Alpegiani *et al.*[284] did achieve the selective cleavage of a primary silyl ether (TBDPS) on the fully protected penem by using TBAF in the presence of HOAc (Scheme 210).



Scheme 210

In the present case, the selective desilylation was really effective in the presence of TBAF, but its basicity caused aza-β-lactam ring expansion accompanied by formation of a γ-lactone even in the presence of HOAc (Scheme 211, Table 26, Entry 1).



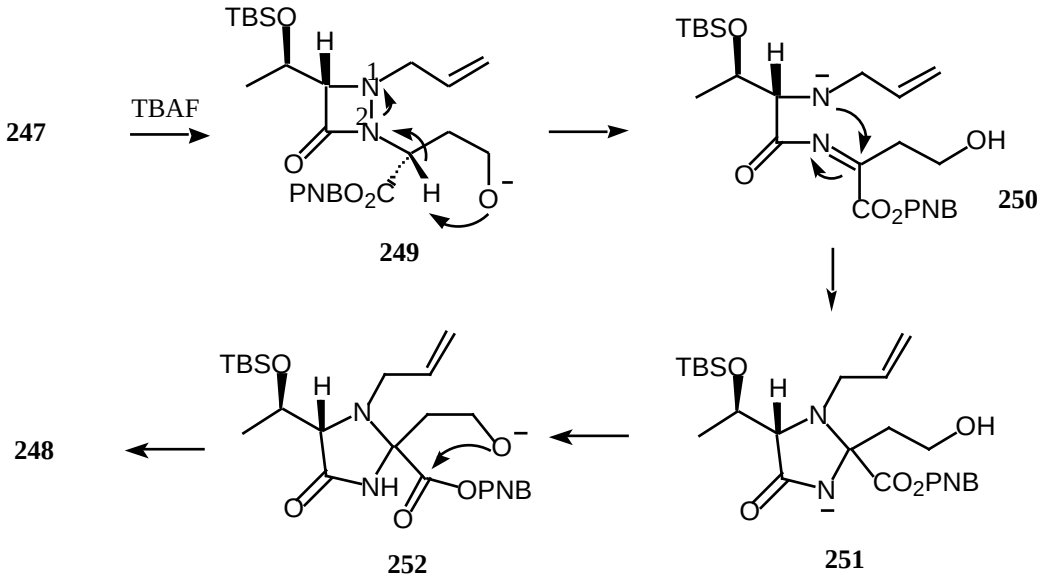
247 **248**

Scheme 211

Table 26: Selective desilylation of **247**

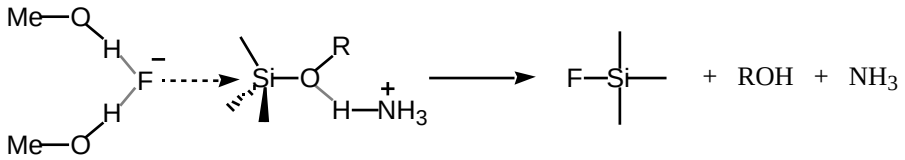
Entry	Conditions	Recovered **247** (%)	Yield of **248** (%)
1	TBAF/HOAc (1.1/1.1) THF, 0°C-rt, 2 h	/	74
2	NH_4F, MeOH, rt, 24 h	35	42

The mechanism of generation of spiro-compound **248** could be as follows (Scheme 212): alkoxide **249** generated by desilylation of OTBDPS functionality with TBAF could abstract the proton adjacent to the lactam nitrogen (N-2). Subsequent N-N cleavage and cyclization of intermediate **250** could lead to an imidazolidione derivative **251**, just as described earlier. Intramolecular transesterification under basic condition then occurred to give product **248**. It should be noted that this 1,2-diazetidinone ring enlargement caused by an intramolecular proton abstraction is so rapid it could not be suppressed by addition of HOAc.



Scheme 212

It was reported[285] that ammonium fluoride could be expected to function as an effective silyl cleaving agent since the weakly acidic ammonium ion might participate in hydrogen bonding to the ether oxygen during nucleophilic attack on silicon by the fluoride counter anion. Methanol was used as the solvent in view of its good solvating properties for silyl ether as well as the polar ammonium fluoride (Scheme 213).



Scheme 213

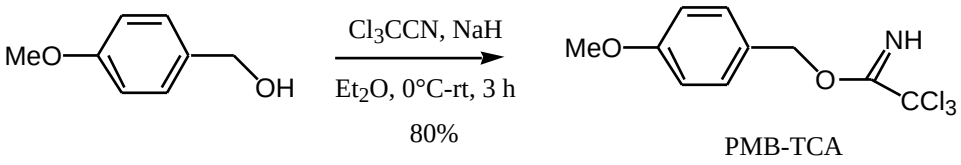
In our case, the deprotection of silyl ether **247** with excess NH_4F in MeOH at ambient temperature was very slow. After one-day stirring, the ring expanded **248** was obtained in 42% yield along with a 35% recovered yield of **247** (Table 26, Entry 2).

9.4.4.3 Protection of hydroxyl function with *p*-methoxybenzyl (PMB) group

9.4.4.3.1 PMB protection under acidic conditions

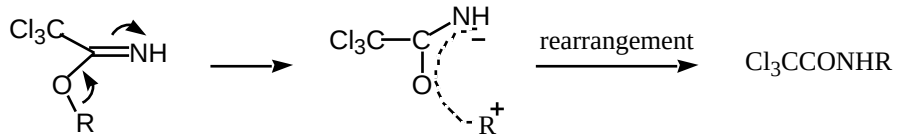
p-Methoxybenzyl ethers can be formed under acid-catalyzed conditions, which would be particularly suitable for the base-sensitive alcohol **247**. PMB trichloroacetimidate (PMB-TCA)

was easily prepared from PMB alcohol and trichloroacetonitrile in the presence of NaH (10 mol%) and purified by distillation (b.p. 135-137°C/0.7 mmHg) (Scheme 214).[286,287]



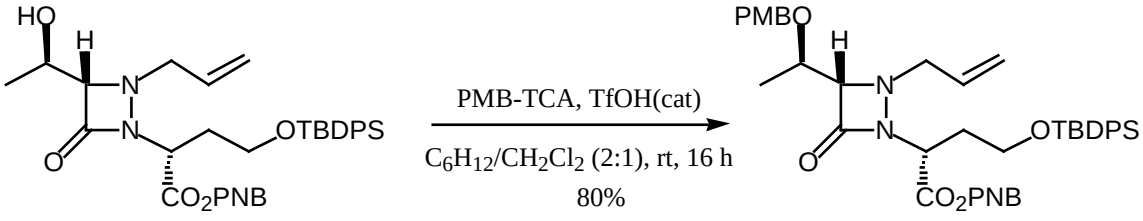
Scheme 214

Alkyl and aryl imidates have been shown to rearrange to the corresponding *N*-alkyl or *N*-aryl amides most probably by an ionic mechanism (Scheme 215).[288]



Scheme 215

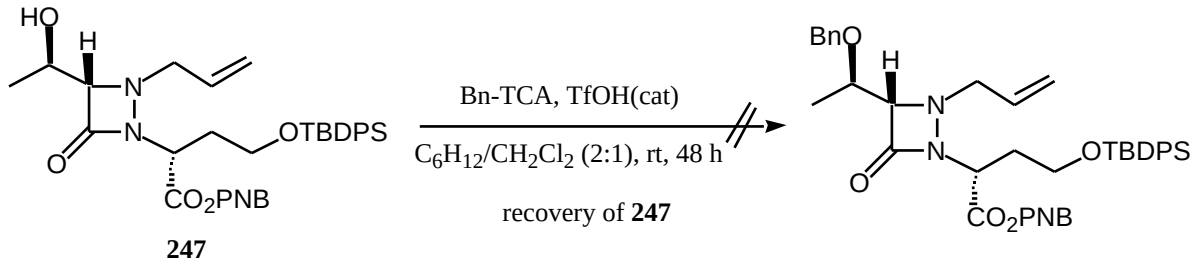
This suggested that *O*-alkylation reactions using these imidates should be conducted in non-polar solvents. Thus, alcohol **247** was dissolved in a minimum volume of CH_2Cl_2, two volumes of cyclohexane and trichloroacetimidate (2 mol per mol of free hydroxyl group) were added together with a catalytic quantity of TfOH (0.3 mol%). We obtained the fully protected aza-β-lactam derivative **254** in 80% yield (Scheme 216).



247 **254**

Scheme 216

PMB trichloroacetimidate proved much more reactive than its benzyl analog and extremely sensitive to acids. The protection with Bn-TCA failed even for prolonged reaction times (Scheme 217).

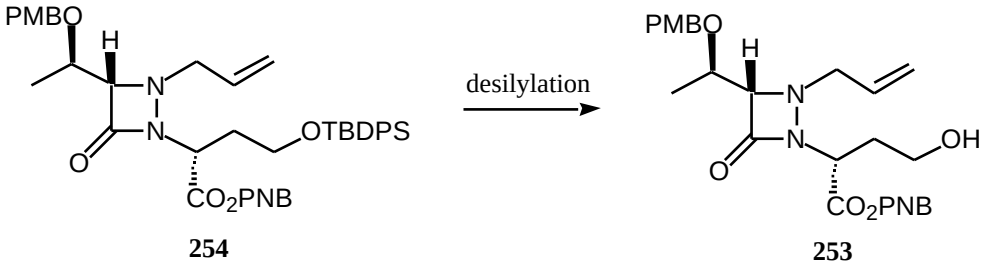


Scheme 217

9.4.4.3.2 Desilylation of 254

Since the desilylation effected by TBAF caused the ring expansion of the aza-β-lactam, we turned to acidic cleavage by using HF or HF-pyridine. This usually requires longer reaction times. The well known reaction of HF with glass may generate species which can be deleterious to the fragile structure,[289] we thus replaced the standard laboratory glassware with a polypropylene tube.* The cleavage was accomplished using an excess of aqueous HF in acetonitrile at ambient temperature. The reaction indeed proved quite clean even after stirring for 48 h and gave **253** in 60% yield (Scheme 218, Table 27, Entry 1).

The mildly acidic HF-pyridine complex has also been suggested for the removal of silyl ethers in acid- and base-sensitive substrates.[290] The desilylation of **254** was effected rapidly by using excess HF-pyridine complex to give an even better yield of **253** (Table 27, Entry 2).



Scheme 218

* The desilylation performed in a normal glassware only gave **253** in 44% yield after stirring at rt overnight.

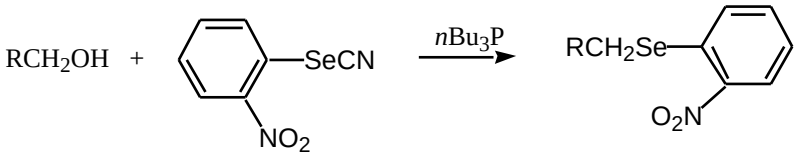
Table 27: Desilylation of **254**

Entry	Conditions	Yield of **253** (%)
1	HF, CH_3CN, polypropylene tube, rt, 48 h	60
2	HF-Py, THF, rt, 7 h	78

9.4.5 Conversion of 253 to *o*-nitrophenyl selenide and subsequent oxidative elimination

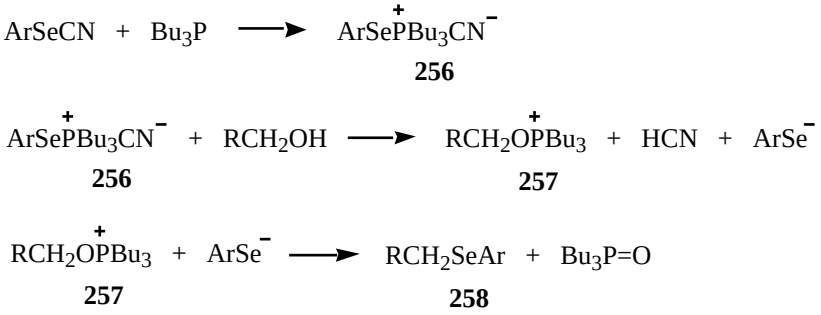
9.4.5.1 One-step synthesis of selenide 255

Alcohols can be converted to *o*-nitrophenyl selenides by reaction with *o*-nitrophenyl selenocyanate (ArSeCN) and tri-*n*-butylphosphine (Scheme 219).[291]



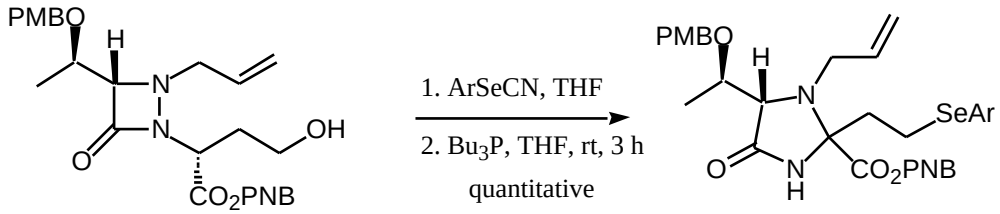
Scheme 219

The above reaction can be rationalized as indicated in Scheme 220 by formation of a selenophosphonium salt **256** which reacts with the alcohol to yield an oxaphosphonium salt **257**. Reaction of the aryl selenium anion with the oxaphosphonium species **257** gives the corresponding alkyl aryl selenide **258** along with tributylphosphine oxide.



Scheme 220

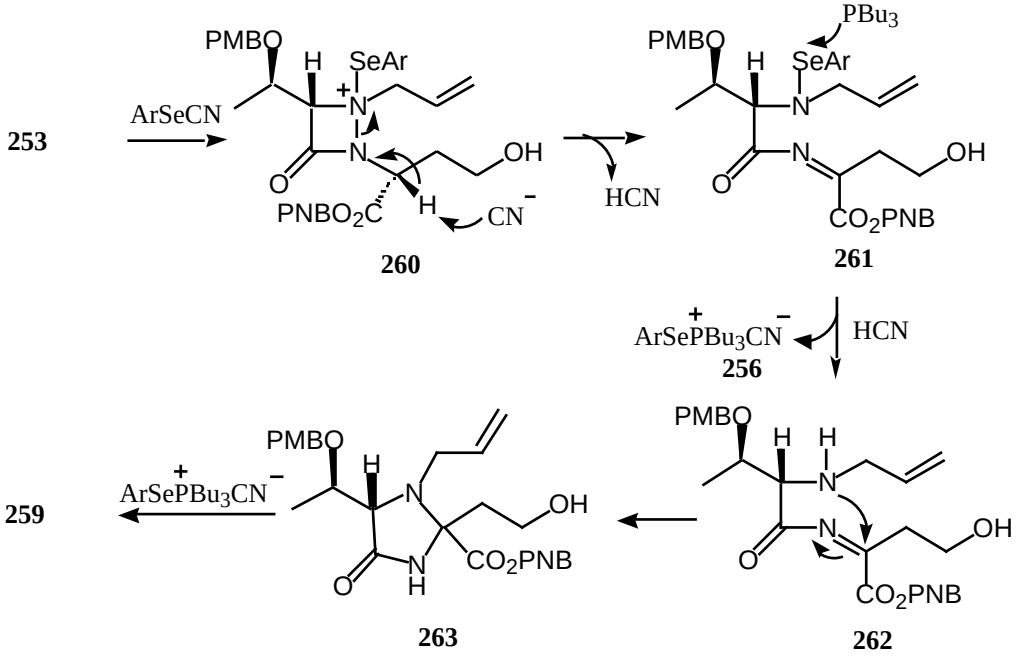
The following experimental procedure indicates the simplicity of this convenient method. A solution of alcohol in THF containing ArSeCN under argon was treated dropwise with Bu_3P at ambient temperature. When applied to **253**, we only obtained the ring expanded product **259** in quantitative yield (Scheme 221).



253 **259**

Scheme 221

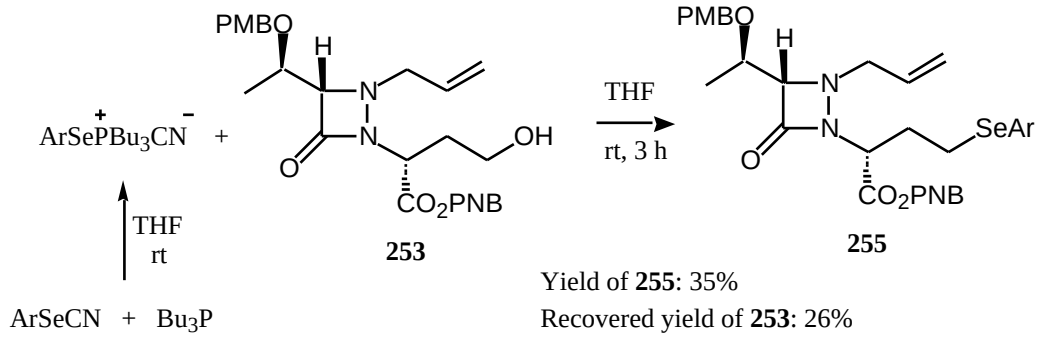
A possible mechanism for formation of **259** is outlined in Scheme 222. Under the experimental conditions, a solution of compound **253** and ArSeCN could generate selenoammonium salt **260**. Proton abstraction by the cyanide anion and cleavage of N-N bond could take place to give selenide **261**. The following addition of Bu_3P could liberate selenophosphonium salt **256** and generate the corresponding ester **262** which underwent the cyclization to form the more stable imidazolidinone **263**. The primary alcohol function in **263** could then be converted to aryl selenide **259** via the general mechanism described above.



Scheme 222

Thus, the experimental procedure was modified (Scheme 223). We first added Bu_3P in a solution of ArSeCN in THF at ambient temperature to generate the selenophosphonium salt **256**. We did observe the formation of a precipitate in the reaction medium. Then a solution of **253** in THF was added and the precipitate disappeared immediately. The reaction mixture was stirred at room temperature for 3 h. This modified procedure gave the desired selenide **255** in

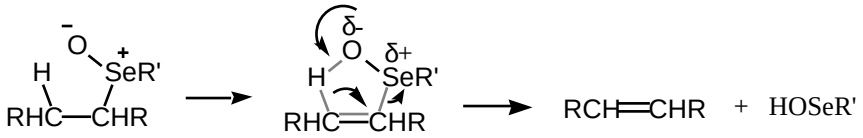
35% yield along with a 26% recovered yield of the starting alcohol **253**. Prolonged reaction times resulted in formation of a complex mixture.



Scheme 223

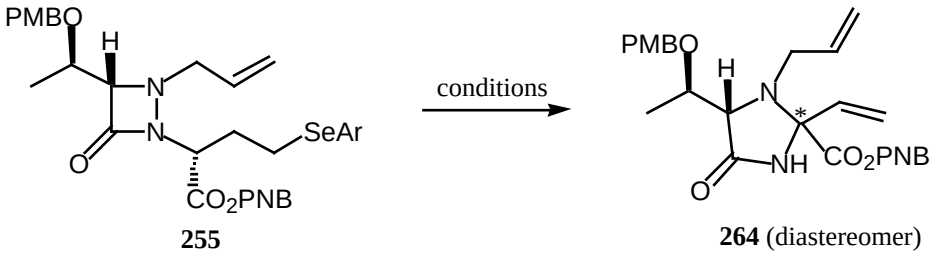
9.4.5.2 Selenoxide elimination

The selenides can be converted to selenoxides by such oxidants as hydrogen peroxide, peroxycarboxylic acids *et al.*. Selenoxides are very reactive towards β-elimination involving a cyclic transition state in which an intramolecular proton transfer accompanies elimination to form a new carbon-carbon double bond. The cyclic transition state dictates that elimination will occur with *syn* stereochemistry (Scheme 224).



Scheme 224

The selenide **255** was then treated with an excess of H_2O_2 in a solution of THF. After stirring at room temperature for 3 h, the ring expanded bis-alkene **264** was obtained as a 3:2 inseparable mixture of diastereomers (Scheme 225, Table 28, Entry 1). Milder conditions using peracetic acid gave **264** in 37% yield (Entry 2).

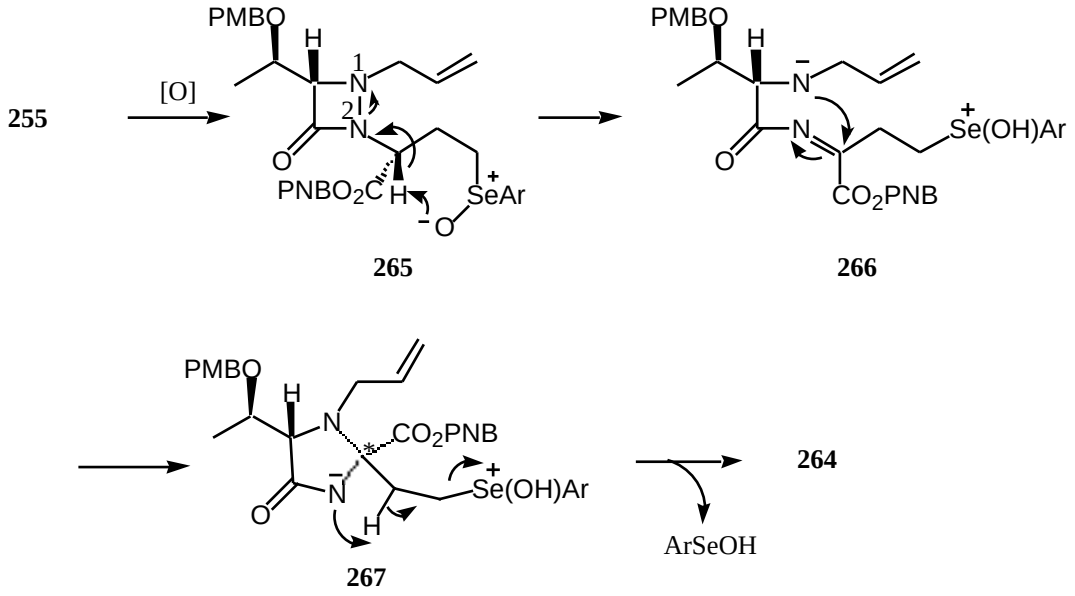


Scheme 225

Table 28: Oxidative elimination of selenide **255**

Entry	Conditions	Yield of **264** (%)
1	10 equiv H_2O_2, THF, 0°C-rt, 3 h	66
2	2.5 equiv AcOOH, THF, 0°C, 3 h	37

Although many selenoxides often react spontaneously at rt to give the eliminated product, this was not the case for the corresponding selenoxide of **255**. The mechanical considerations for formation of **264** are outlined in Scheme 226. We believe that proton abstraction from the α-carbon atom of the N-2 substituent was effected by seleoxide **265** leading to the cleavage of the N-N bond. Nucleophilic attack of nitrogen anion in **266** led to the formation of imidazolidinone **267**. The following proton transfer and elimination of ArSeOH gave the bis-alkene **264**. This procedure further illustrated that the highly strained 1,2-diazetidinone ring can be easily destroyed even in the absence of a strong base.



Scheme 226

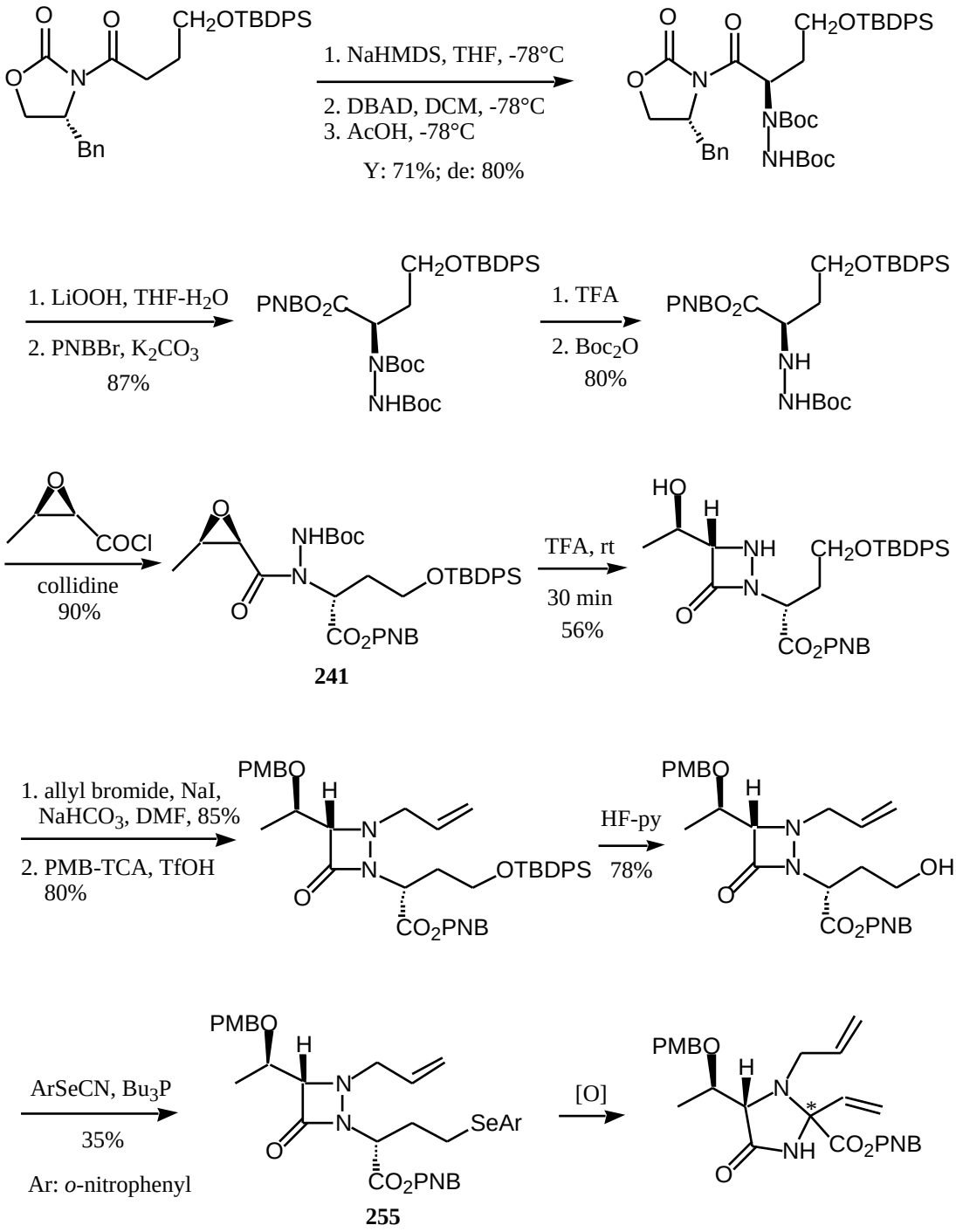
9.5 Conclusion

Three synthetic approaches towards a bicyclo [4.2.0] aza-β-lactam carboxylic acid ester derivative have been described. Unfortunately, none of them provided the desired product.

The first strategy by using an acidic one-pot deprotection-cyclization procedure failed to yield the key 1,2-diazetidinone derivative.

In the second approach, a main side reaction is a ready double bond conjugation of β,γ-unsaturated hydrazino ester, which made impossible the synthesis of a bis-alkene substrate used as the RCM precursor.

We carried out more detailed studies in the third approach involving formation of a double bond via an oxidative elimination of a selenide derivative at the end of the synthesis (Scheme 227). The methodology containing the formation of 1,2-diazetidinone ring by a cyclization of mono Boc-protected hydrazide substrate **241** using trifluoroacetic acid provided the basis for subsequent transformations on aza-β-lactam ring. However, in the following synthetic procedure we encountered a ring expansion reaction via the proton abstraction and N-N fission leading to a stable imidazolidinone derivative. Although we solved several problems and succeeded in preparing an aza-β-lactam derivative **255** bearing a selenide function, the deleterious ring expansion took place again during the oxidative elimination of selenide.


1. NaHMDS, THF, -78°C
2. DBAD, DCM, -78°C
3. AcOH, -78°C
Y: 71%; de: 80%
1. LiOOH, THF-H2O
2. PNBBr, K2CO3
87%
1. TFA
2. Boc2O
80%
COCl
collidine
90%
TFA, rt
30 min
56%
241
1. allyl bromide, NaI,
NaHCO3, DMF, 85%
2. PMB-TCA, TfOH
80%
HF-py
78%
ArSeCN, Bu3P
35%
Ar: o-nitrophenyl
[O]
255

Scheme 227

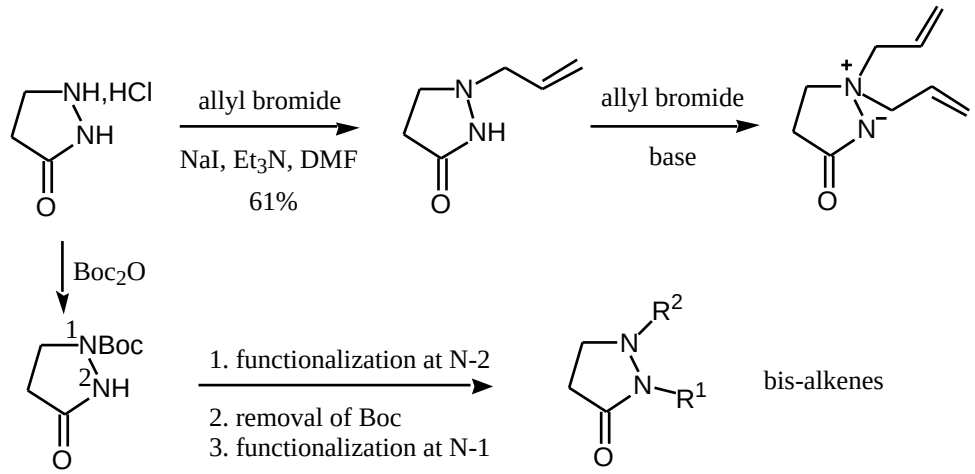
Chapter 10

Conclusions and perspectives

The main contribution of this work (Part II) is the development of a practical synthetic route to an optically active 1,2-diazetidinone derivative bearing the α-oriented (*R*)-hydroxyethyl side chain and carboxyl group contiguous to the lactam nitrogen atom, this providing access to the syntheses of promising candidates for biological studies. On the other hand, RCM proved to be a good method to the construction of bicyclic aza-β and γ-lactams. The second generation ruthenium complex bearing a saturated NHC ligand was much more effective than the standard Grubbs carbene on our nitrogen-containing substrates.

10.1 Preparation of bicyclic pyrazolidinones

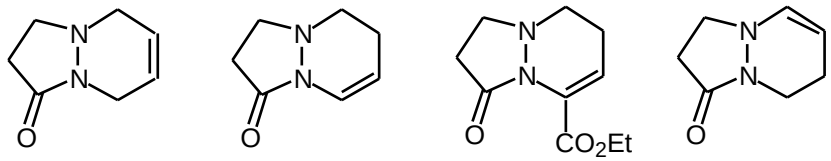
Methodology has been established to functionalize regiospecifically two nitrogen atoms which structurally constitute the pyrazolidinone ring. Direct diallylation only led to a ylide, thus the use of a protecting group was necessary. A Boc substituent readily solved this problem, this providing access to a variety of bis-alkenes as RCM precursors (Scheme 228).



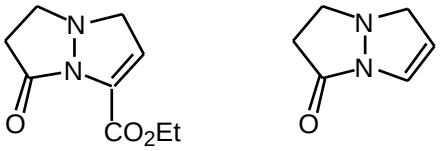
Scheme 228

RCM proved to be a good strategy to the preparation of bicyclo [4.3.0] ring systems except when the double bond became part of an enamine. However, this method was less effective for the preparation of [3.3.0] ring systems (Scheme 229).

[4.3.0] ring systems:



[3.3.0] ring systems:

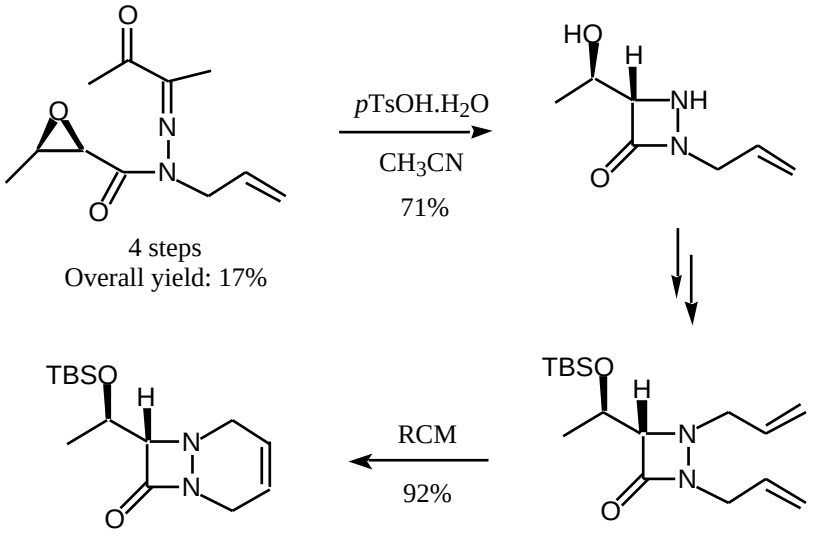


Scheme 229

10.2 Preparation of bicyclic 1,2-diazetidinones

10.2.1 One-pot deprotection-cyclization sequence

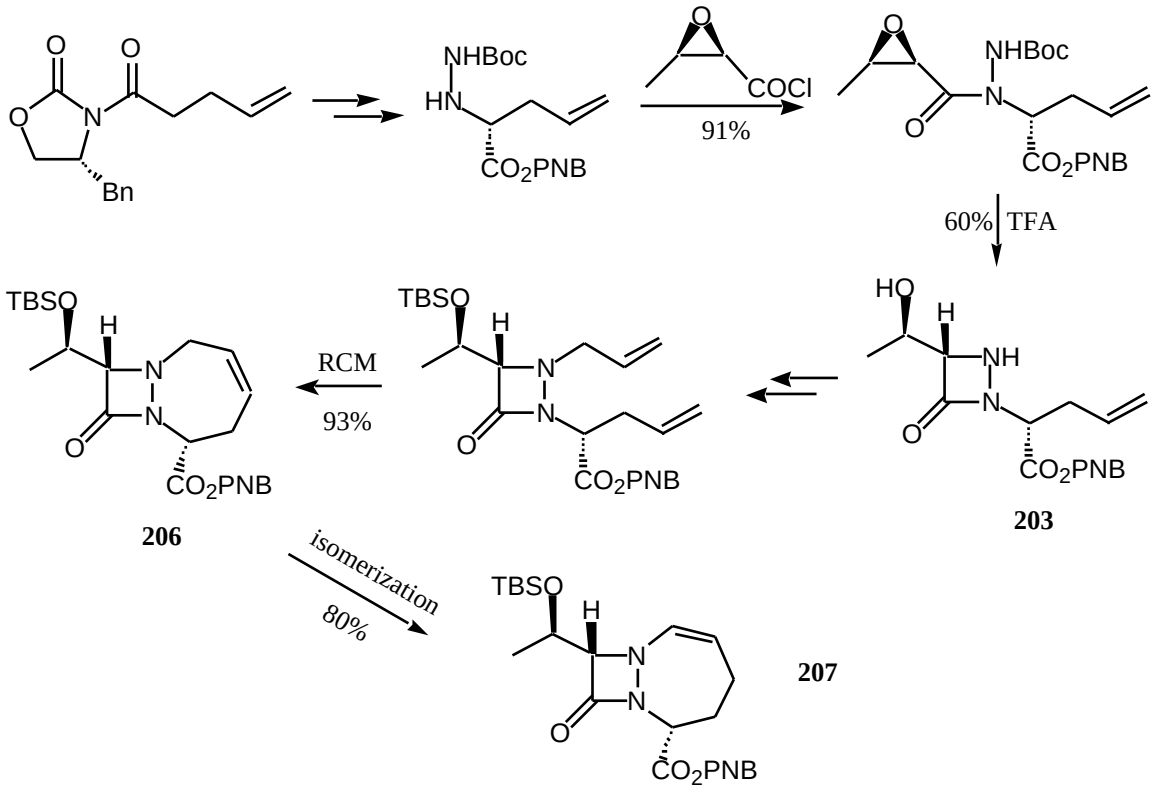
The unsubstituted 1,2-diazetidinone ring proved to be rather unstable. To our delight, a one-pot deprotection-cyclization sequence successfully yielded a 1,2-diazetidinone derivative carrying an α-oriented (*R*)-1-hydroxyethyl side chain. RCM gave the bicyclic aza-β-lactam in excellent yield (Scheme 230). This sequence allowed us to selectively introduce an allyl group at the lactam nitrogen prior to cyclization. Furthermore, since the hydroxyethyl substituent was installed during the ring formation, manipulations of the labile products have been minimized.



Scheme 230

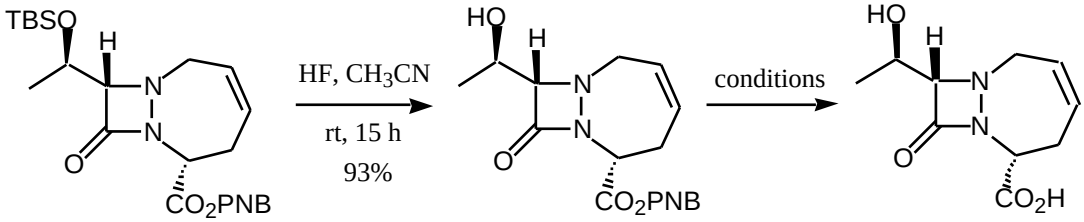
10.2.2 Incorporation of a carboxyl group

The use of oxazolidinone chiral auxiliary allowed to prepare an optically active α-hydrazino ester. One-pot deprotection-cyclization procedure could be readily accomplished in trifluoroacetic acid on an epoxyamide derived from a mono-Boc hydrazide. Ring-closing metathesis and subsequent double bond migration gave bicyclic aza-β-lactams **206** and **207** in excellent yields (Scheme 231).



Scheme 231

Since both hydroxyl and carboxylic acid functions are structural requirements for biological activity, the cleavage of the protecting groups (TBS and PNB) is necessary before carrying out biological studies. Some preliminary results have been obtained for this final step (Scheme 232, Table 29). The desilylation was readily effected by using excess HF to give compound **268** in excellent yield. However, subsequent cleavage of PNB group proved quite difficult. In view of the presence of the double bond in the molecule, hydrogenolysis can not be used. Other methods gave the disappointing results.



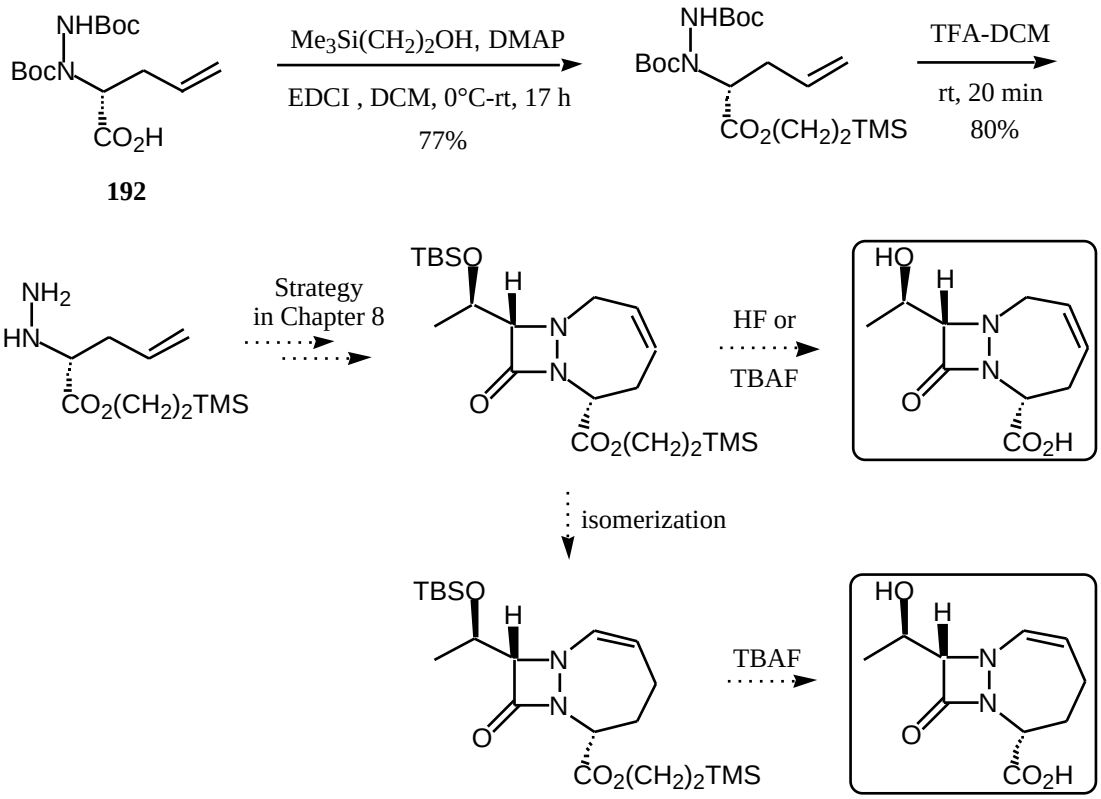
206 **268**

Scheme 232

Table 29: Cleavage of PNB group

Entry	Conditions	Result
1	1 equiv Na_2S, THF-H_2O, 0°C, 30 min	destruction of aza-lactam ring
2	6 equiv $Na_2S_2O_4$, THF-H_2O, 0°C, 3 h; rt, 24 h	recovered **S.M.** (60%)
3	Zn, HOAc-THF, 0°C, 1 h; rt, 17 h	traces of product
4	5 equiv TBAF, HOAc, rt, 17 h	recovered **S.M.** (100%)

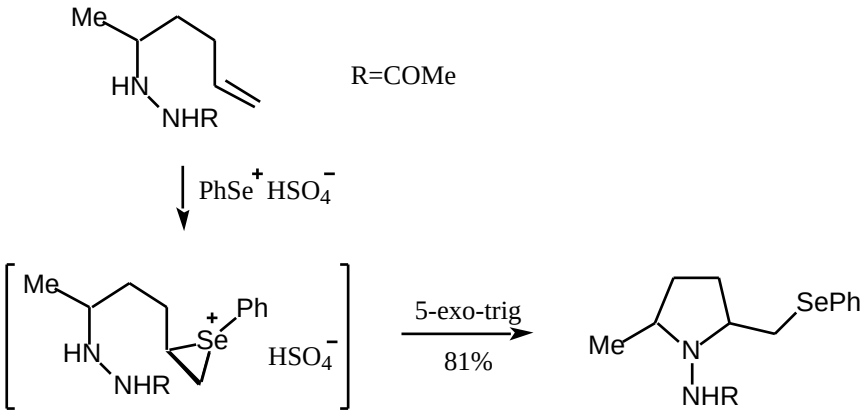
We then considered replacing the PNB group by a trimethylsilylethyl ester. Thus, the final deprotection of hydroxyl and ester functions could be effected instantaneously in the presence of HF or TBAF. Indeed, the coupling reaction of acid **192** with trimethylsilylethanol proceeded quite well and the resulting hydrazino ester can tolerate the acidic conditions used for removing Boc groups. The bicyclic aza-β-lactam carboxylic esters could then be prepared according to the method described in Chapter 8. After deprotections, the corresponding aza-β-lactam carboxylic acids could serve for the promising candidates for biological studies. At this stage, we could further evaluate the role of the double bond in the ring opening reactions of an aza-β-lactam by nucleophilic attack of enzymes (Scheme 233).



Scheme 233

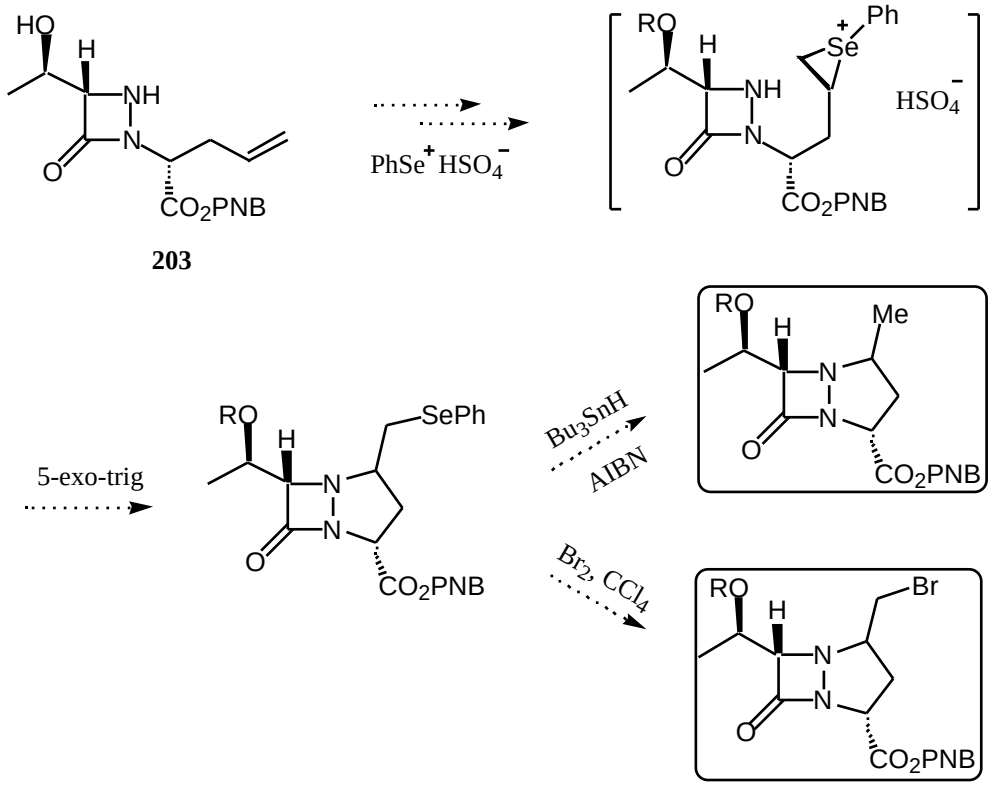
10.2.3 Derivatizations of 203 and related transformations

1,2-Diazetidinone **203** should be an important precursor for cyclization involving the internal amine nitrogen as nucleophile since it contains a suitably positioned alkene. As shown in Scheme 234, the selenium-induced cyclization (5-exo-trig) of an alkenyl hydrazide led to a pyrrolidinamine derivative.[292]



Scheme 234

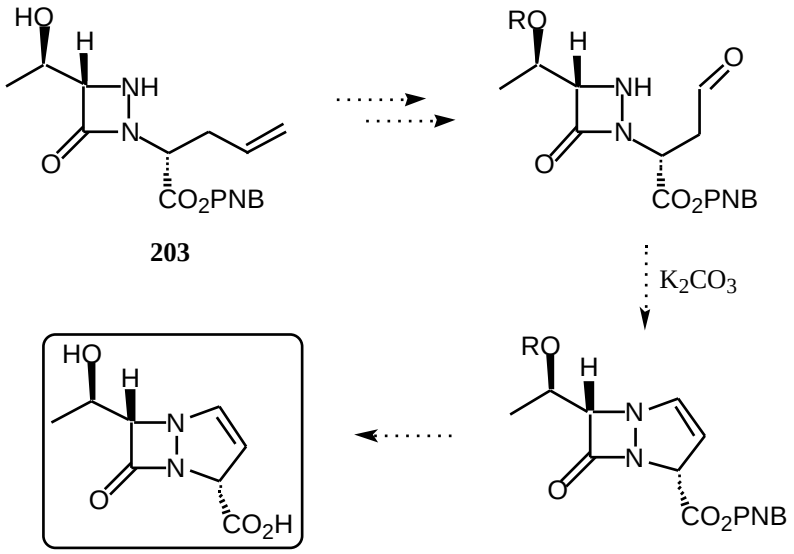
The similar reaction on **203** could thus form a bicyclo [3.2.0] aza-β-lactam carboxylic ester. The selenide could be reduced or brominated to give the pharmacologically interesting compounds.



203

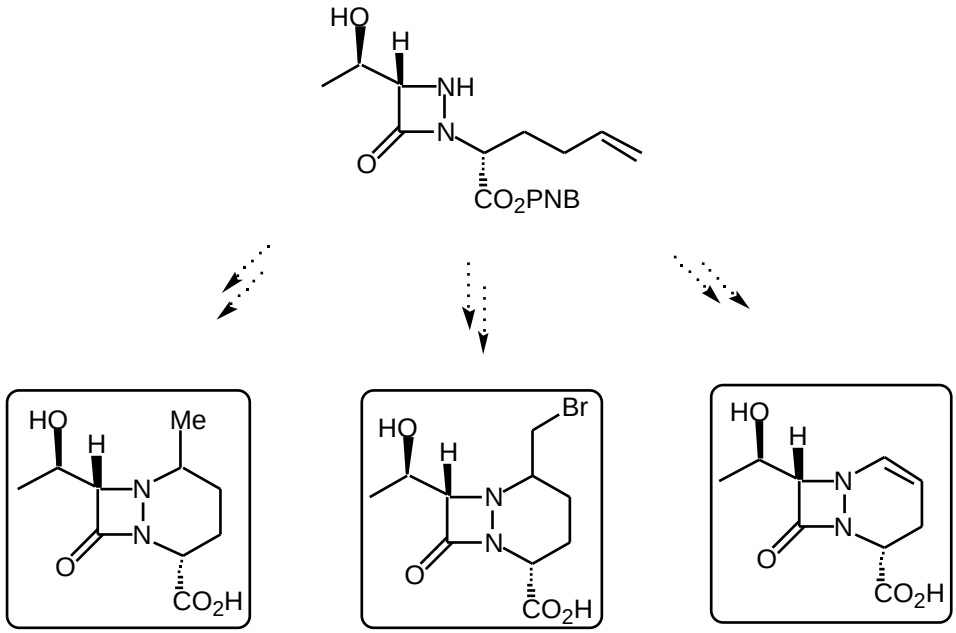
Scheme 235

On the other hand, oxidative cleavage of the double bond in **203** could yield an aldehyde which could condense with the amine group under basic conditions to generate a bicyclic enamine. Undoubtedly, this class of substances should also be of interest (Scheme 236).



Scheme 236

In a similar way, we could also prepare the corresponding homologs of above-mentioned compounds (Scheme 237).

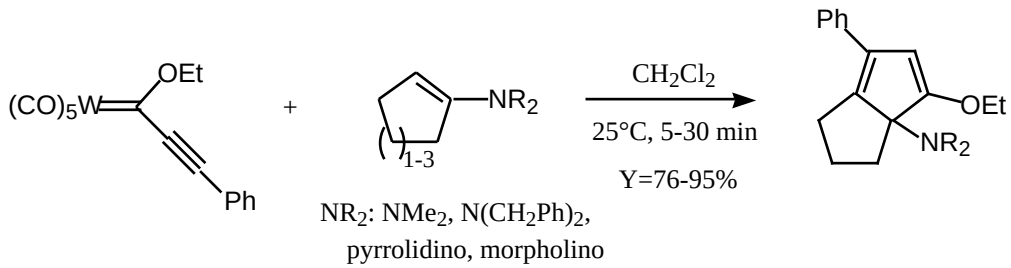


Scheme 237

10.2.4 [C_3 + C_2] Cyclopentadiene annulation to enamine

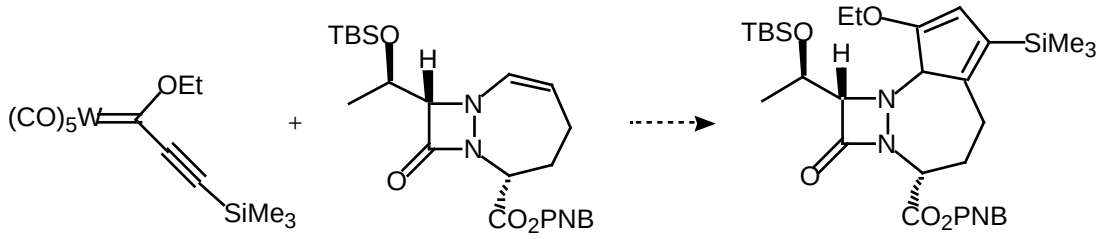
Due to the importance of five-membered carbocycles as part of biologically relevant compounds, *e.g.* steroids and prostaglandins, methods for their preparation remain an area of continuous attention in organic chemistry. Among them, a type of [C_3+C_2] cyclopentadiene

annulation to enamines with an alkynylcarbene complex of tungsten has drawn our attention (Scheme 238).[293]



Scheme 238

In our hands, a similar reaction on enamine **207** could thus be conceivable (Scheme 239). Here an alkynylcarbene complex bearing a trimethylsilyl group would be used since further derivatizations could be available. The tricyclic aza-β-lactam being formed could be another type of pharmacologically interesting compounds.

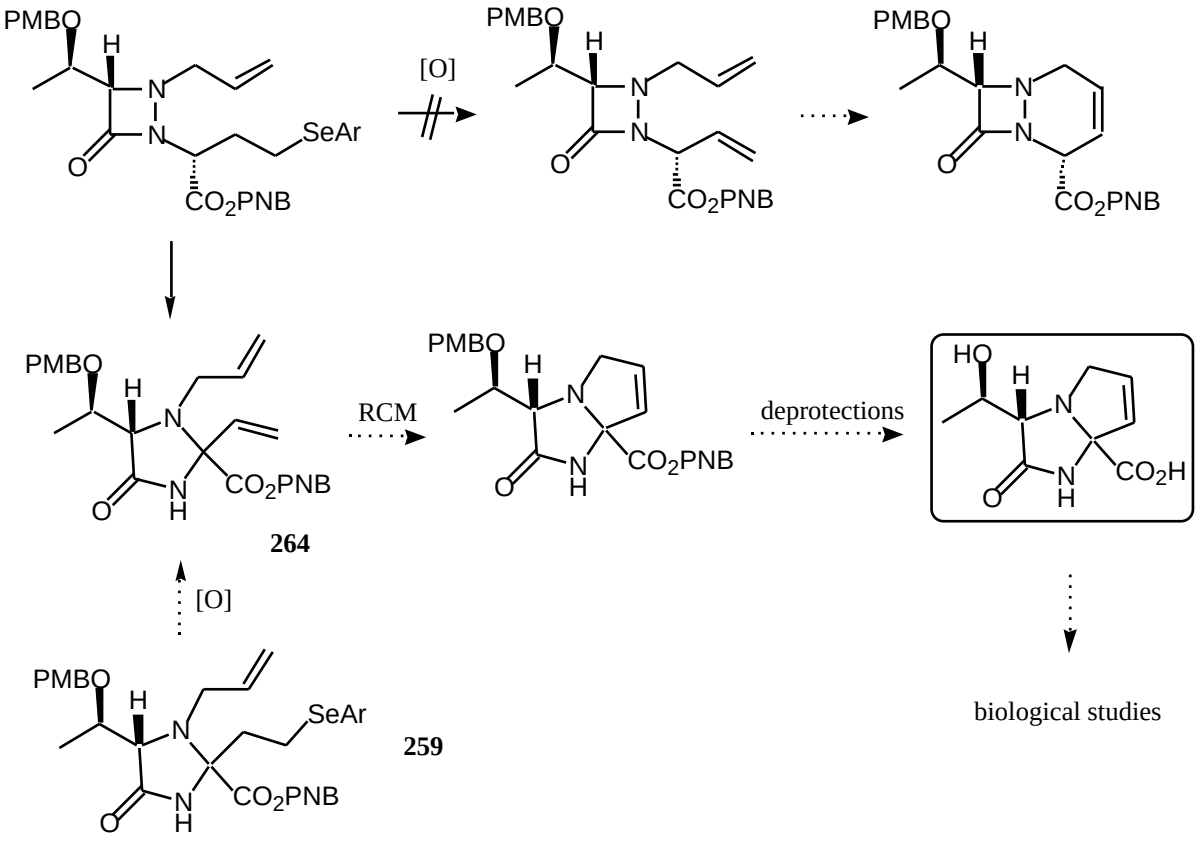


207

Scheme 239

10.3 Synthesis of bicyclic imidazolidinone derivatives

In the course of the synthesis of a bicyclo [4.2.0] aza-β-lactam carboxylic acid derivative, we encountered a rapid ring expansion reaction via the proton abstraction and N-N fission leading to a stable imidazolidinone derivative (Scheme 240). Although the initial target molecule could not be prepared at this stage, we happily found that the resulting diolefinic imidazolidinone could also undergo a RCM reaction to yield a well-substituted bicyclic imidazolidinone. After deprotections, the resulting imidazolidinone carboxylic acid could serve for biological studies as well. Bis-alkene **264** could also be prepared from selenide **259** via oxidative elimination.



Scheme 240

Thus, our unexpected results could provide ready access to prepare a type of bicyclic imidazolidinone carboxylic acid derivatives with the amine nitrogen atom at the fused angular position and bearing an α-oriented (*R*)-1-hydroxyethyl side chain. Such a compound is probably difficult to prepare via other means.

Experimental Section

General Information

1. Apparatus

Infrared spectra were recorded on a BIORAD FTS-135.

NMR spectra were recorded on a Varian Gemini 300BB (300 MHz for ^{1}H and 75 MHz for ^{13}C) and a Varian Germini 200BB (200 Mhz for ^{1}H and 50 MHz for ^{13}C). High resolution spectra were recorded by R. Touillaux on a Brucker AM-500 (500 MHz for ^{1}H and 125 MHz for ^{13}C). ^{31}P NMR spectra were recorded on a Brucker WM-250 (101.3 MHz). Chemical shifts are given in ppm relative to the internal reference. Coupling constants are given in Hz.

MS spectra were recorded on a Varian MAT-44 or FINNIGAN MAT-TSQ 70 apparatus in the Mass Spectrometry Laboratory of Prof. E. de Hoffmann and Prof. Habib-Jiwan (UCL).

High resolution mass spectra (HRMS) were performed in the laboratory of Prof. Flammang (Université de Mons-Hainaut).

Elemental analyses were realized in the laboratory of Dr. Stone (University College-London).

Optical rotation values were measured on a PERKIN-ELMER 241 MC polarimeter. Concentration are given in g/100mL.

Melting points were measured with a BUCHI apparatus (oil bath) and are uncorrected.

Thin layer chromatographic analyses were performed on MERCK 60 F_{254} silica gel plates (coated on aluminium). Visualization was realized under UV lamp or with *p*-anisaldehyde, $KMnO_4$ or phosphomolybdic revelators after heating.

Flash chromatography separations were performed using MERCK 60 40-63mm silica and technical grade solvents.

2. Techniques

Unless otherwise noted, reactions requiring anhydrous conditions were performed using flame-dried glassware under a positive pressure of Argon.

Solvents used for reactions were of analytical grade. Unless otherwise noted, solvents for reactions requiring anhydrous conditions were purified:

dichloromethane and acetonitrile were distilled on CaH_2;

Et_2O, toluene and THF were distilled on Na with benzophenon as indicator;

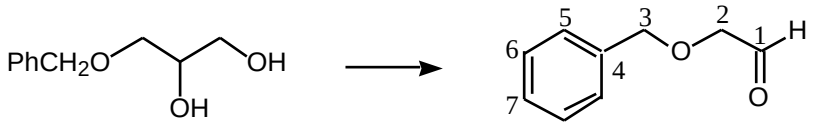
DMF was dried over 4ÅMS.

Concentrated under reduced pressure means that solvents are removed under water aspirator pressure (10 mmHg) with a BUCHI rotavap. Remaining traces of solvents were removed under 1 mmHg until constant weight.

Chapter 1

Towards four-membered phosphinic acid derivatives

1.1 Synthesis of (benzyloxy)acetaldehyde 22



Reference:

Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Le Goffic, F. *Synthesis* **1989**, 64-65

RN: 60656-87-3

Procedure:

To a vigorously stirred suspension of chromatographic grade silica gel (50 g) in CH_2Cl_2 (400 mL) in a 1 L erlenmeyer flask was added an aqueous solution (50 mL) of sodium periodate (6.951 g; 32.5 mmoles; 1.3 equiv) dropwise with stirring, then a flaky suspension was formed. 3-Benzyloxy-1,2-propanediol (4.555 g; 25 mmoles; 1 equiv) in CH_2Cl_2 (5 mL) was then added, and the reaction was monitored by TLC until disappearance of the initial product (14 min). The mixture was then filtered and the silica gel was thoroughly washed with CH_2Cl_2 (3X50 mL). Evaporation of the solvent gave the product.

TLC: Rf=0.30 (ether/petrol ether 4/1, UV, $KMnO_4$)

Yield: 3.76 g (quantitative, lit. quantitative)

Mol. formula: $C_9H_{10}O_2$

FW: 150.17

Physique aspect: colorless oil

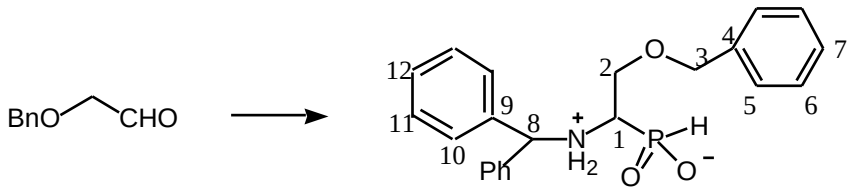
^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
1	9.70	s		1
PhH	7.38-7.30	m		5
2	4.62	s		2
3	4.08	s		2

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 200.9 (C_1), 137.5 (C_4), 129.2, 128.8, 128.6 (C_5, C_6, C_7), 75.9 (C_2), 74.3 (C_3).

1.2 Synthesis of 1-(benzhydrylamino)-2-(benzyloxy)ethylphosphinic acid 23



Reference:

Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc. Perkin Trans I* **1984**, 2845-2852

RN: 65577-51-7

Procedure:

A solution of **22** (8.493 g; 56.55 mmoles; 1.12 equiv) in ethanol (20 mL) was added dropwise to a refluxing solution of aminodiphenylmethane hydrochloride (11.08 g; 50.46 mmoles; 1 equiv) and hypohposphorous acid (50% aqueous solution, 6.436 mL; 8.2 g; 62.12 mmoles; 1.23 equiv) in a mixture of ethanol-water (1/1, 75 mL). Addition was complete within 1.5 h, then heating was continued for 2 h. Precipitation commenced during the heating. The solution was cooled and the white solid was filtered off, washed with EtOH and EtOAc.

Yield: 10.29 g (53%, lit. 55%)

Mol. formula: $C_{22}H_{24}NO_3P$

FW: 381.41

Physique aspect: white solid

Melting point: 216-218°C (lit. 212-214°C)

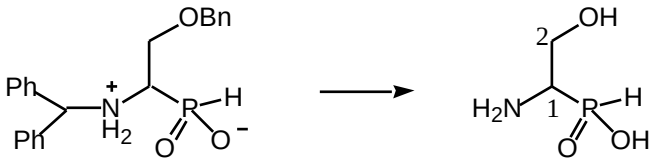
^{1}H NMR (200MHz, DMSO, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.46-7.23	m		15
P-H	6.96	dd	^1J_P=527.0, $^3J_{PH-1}$=1.0	1
8	5.49	br. s		1
3	4.44	s		2
2	3.78-2.68	m		2
1	2.79-2.73	m		1

^{13}C NMR (50MHz, DMSO and CF_3COOD, 20°C)

δ = 137.5 (C_4), 136.5, 135.7 (C_9), 129.0, 128.9, 128.8, 128.7, 128.3, 127.6 (C_{5-7}, C_{10-12}), 72.4 (C_3), 65.6 (C_2), 65.1 (C_8, d, $^3J_{P-C}$=2.6), 56.5 (C_1, d, $^1J_{P-C}$=91.9).

1.3 Synthesis of 1-amino-2-hydroxyethylphosphinic acid 24



Reference:

Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc. Perkin Trans I* **1984**, 2845-2852

RN: 71937-30-9

Procedure:

23 (15.39 g; 40.35 mmoles; 1 equiv) was refluxed together with an excess of 96 g HCl (18% aqueous solution, about 6 times by weight) for 26 h until two distinct phases had separated. The mixture was evaporated to dryness under reduced pressure and the residue was taken up in water (140 mL). The aqueous solution was washed 4 times with ether to remove diphenylmethyl chloride and then evaporated to dryness. The oily residue of 1-amino-2-hydroxyethylphosphinic acid hydrochloride was dissolved in ethanol (10 mL/g, about 80 mL) and propylene oxide was added (80 mL) dropwise until precipitation started. The mixture was stirred for one night. Then the solid was filtered off and dried.

Yield: 4.56 g (90%, lit. 89%)

Mol. formula: $C_2H_8NO_3P$

FW: 125.06

Physique aspect: white solid

Melting point: 206-208°C (lit. 210°C)

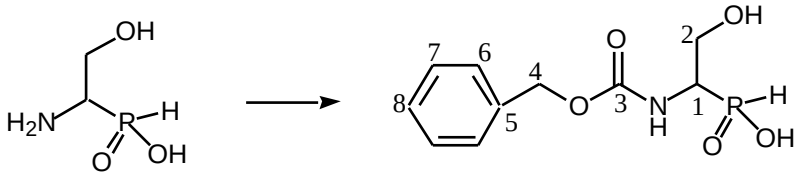
^{1}H NMR (200MHz, D_2O, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
P-H	6.98	dd	^1J_P=540.7, $^3J_{PH-1}$=1.7	1
2	3.98-3.73	m		2
1	3.21-3.11	m		1

^{13}C NMR (50MHz, D_2O+CD_3COCD_3, 20°C)

δ = 58.0 (C_2, d, $^2J_{P-C}$=4.1), 53.4 (C_1, d, $^1J_{P-C}$=87.9).

1.4 Synthesis of 1-((benzyloxycarbonyl)amino)-2-hydroxyethylphosphinic acid 20



Reference:

1. Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc. Perkin Trans I* **1984**, 2845-2852

2. Thesis of Kessabi, J. **1998**, 254

Procedure:

24 (3.795 g; 30.34 mmoles; 1 equiv) was dissolved in water (15 mL), the pH of the solution was adjusted to 9-10 with 2M NaOH and the mixture was cooled to 0°C. Benzyl chloroformate (4.912 mL; 33.37 mmoles; 1.1 equiv) was added dropwise and the mixture was stirred for a further 6 h while the pH was maintained at 9-10 by periodic addition of 2M NaOH. The mixture was then allowed to warm to room temperature and washed with ether. The aqueous solution was then slowly added to a mixture of water, concentrated HCl, and ice (8 mL, 12 mL, 15 g respectively). The aqueous phase was extracted with EtOAc (3X60 mL), and then the organic phases were collected, washed with saturated brine, dried over $MgSO_4$, filtered and evaporated.

Purification: recrystallization from EtOAc/hexane

Yield: 3.09 g (39%, lit. 69%)

Mol. formula: $C_{10}H_{14}NO_5P$

FW: 259.19

Physique aspect: white solid

Melting point: 110-112°C (lit. 110-112°C)

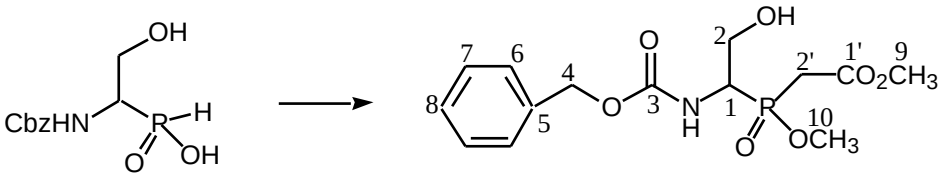
^{1}H NMR (200MHz, DMSO, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
P-H	6.86	d	^1J_P=538.6	1
NH	7.58	d	$^3J_{NH-1}$=8.5	1
PhH	7.38-7.30	m		5
4	5.04	s		2
OH	4.71	br. s		2
1 + 2	3.74-3.62	m		3

^{13}C NMR (50MHz, DMSO, 20°C)

δ = 156.3 (C_3, d, $^3J_{P-C}$=4.6), 136.9 (C_5), 127.8, 128.4, 127.9 (C_6, C_7, C_8), 65.7 (C_4), 58.7 (C_2, d, $^2J_{P-C}$=7.2), 53.8 (C_1, d, $^1J_{P-C}$=102.1).

1.5 Synthesis of methyl ((1-((benzyloxycarbonyl)amino)-2-hydroxyethyl)(methoxy)phosphoryl)acetate 28



Reference:

1. Firouzabadi, H.; Karimi, B. *Synth. Commun*. **1993**, *23(12)*, 1633-1641

2. Thottathil, J. K.; Przybyla, C. A.; Moniot, J. L. *Tetrahedron Lett.* **1984**, *25(42)*, 4737-4740

3. Thesis of Kessabi, J. **1998**, 261

Preparation of CH_2N_2:

In a 250 mL of erlenmeyer were placed 30 mL of 40% aqueous KOH solution and 100 mL of ether. The mixture was cooled to 5°C, and 10 g of *N*-nitroso-*N*-methylurea was added in small portions with stirring. The deep yellow ether layer can be decanted readily; it contained 2.8 g of CH_2N_2, together with some dissolved impurities and water. To remove the water, the ether layer was moved to another 250 mL of erlenmeyer containing some pellets of pure KOH.

Procedure:

To a solution of **20** (389 mg; 1.5 mmoles; 1 equiv) in dry acetonitrile (10 mL), anhydrous zinc chloride (20.45 mg; 150 µmoles; 0.1 equiv) was added. The mixture was refluxed and mangnetically stirred. To the resulting mixture HMDS (1.938 mL; 9.004 mmoles; 6 equiv) was added dropwise with stirring under reflux condition. The reaction was complete within 30 minutes. Then the mixture was cooled to 0°C, methyl bromoacetate (287 µL; 3.001 mmoles; 2 equiv) was added slowly. The stirring was continued at rt for 12 h. After filteration and concentration, the residue was diluted with 10 mL of dry CH_2Cl_2, then 5 mL of MeOH was added slowly. After 3 h of stirring (desilylation), the solvent was removed and the free acid was obtained as an oil. To this oil 10 mL of MeOH were added in a 100 mL of erlenmeyer and then cooled to 0°C, the solution of CH_2N_2 in ether was added slowly until a yellow color persisted. After stirring at rt for 1 h, HOAc was added to destruct the excess CH_2N_2. MeOH was removed under reduced pressure, then ether was added and the solution was dried over $MgSO_4$, filtered and evaporated.

TLC: Rf=0.31 (DCM/acetone/MeOH 18/1/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (DCM/acetone/MeOH 18/1/1)

Yield: 0.125 g (24%)

Mol. formula: $C_{14}H_{20}NO_7P$

FW: 345.28

Physique aspect: pale yellow oil

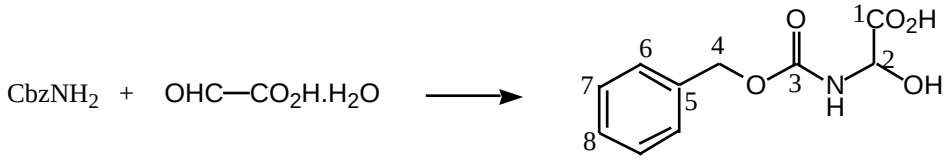
^{1}H NMR (200MHz, CD_3COCD_3, 20°C, two isomers)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.39-7.34	m		5
NH	6.70 (6.60)	d	$^3J_{NH-1}$=9.4	1
4	5.12	s		2
1	4.38-4.12	m		1
2	3.85-3.95	m		2
10	3.75	d	^3J_P=10.8	3
9	3.67 (3.66)	s		3
2'	3.19-3.09	m		2

^{13}C NMR (50MHz, CD_3COCD_3, 20°C, two isomers)

δ = 167.9 ($C_{1'}$), 157.9 (C_3), 138.7 (C_5), 129.9, 129.7, 129.4 (C_6, C_7, C_8), 67.7 (C_4), 61.7, 61.4 (C_2, d, $^2J_{P-C}$=4.7), 54.2 (C_1, d, $^1J_{P-C}$=108.4), 53.2 (C_9), 53.3 (C_{10}, d, $^2J_{P-C}$=6.6), 37.0 ($C_{2'}$, d, $^1J_{P-C}$=129.0).

1.6 Synthesis of ((benzyloxycarbonyl)amino)(hydroxy)acetic acid 33



Reference:

Ben-Ishai, D.; Zoller, U. *Tetrahedron* **1975**, *31*, 863-866

RN: 56538-57-9

Procedure:

A mixture of benzyl carbamate (32.29 g; 213.6 mmoles; 1 equiv) and glyoxylic acid monohydrate (21.64 g; 235.1 mmoles; 1.1 equiv) in ether (200 mL) was stirred at rt for 12 h. During this period a white precipitation was formed (around 5 h), it was filtered, washed with ether (2X) and then dried.

Yield: 34.13 g (71%, lit. 73%)

Mol. formula: $C_{10}H_{11}NO_5$

FW: 225.20

Physique aspect: white solid

Melting point: 196-198°C (lit. 196-198°C)

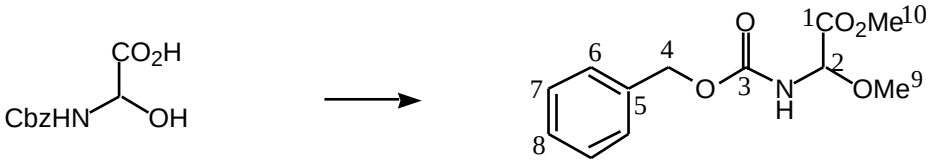
^{1}H NMR (300MHz, DMSO, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
NH	8.15	d	$^{3}J_{NH\text{-}2}$ = 8.5	1
PhH	7.37-7.30	m		5
2	5.23	d	$^{3}J_{2\text{-}NH}$ = 8.8	1
4	5.05	s		2
OH	3.34	br. s		1

^{13}C NMR (75MHz, DMSO, 20°C)

δ = 171.1 (C_1), 155.5 (C_3), 136.9 (C_5), 128.4, 127.9, 127.8 (C_6, C_7, C_8), 73.2 (C_2), 65.5 (C_4).

1.7 Synthesis of methyl ((benzyloxycarbonyl)amino)(methoxy)acetate 34



Reference:

Ben-Ishai, D.; Zoller, U. *Tetrahedron* **1975**, *31*, 863-866

RN: 58237-86-8

Procedure:

To an ice bath cooled and stirred solution of **33** (18.04 g; 80.14 mmoles; 1 equiv) in abs. methyl alcohol (180 mL) was added conc. sulfuric acid (3.008 mL; 35.77 mmoles; 0.446 equiv). The mixture was stirred at rt for 48 h and then poured into ice-saturated aq. $NaHCO_3$, the organic material was extracted with EtOAc (3X). The organic phases were combined and dried over $MgSO_4$. Filtering and evaporation of the solvent.

Purification: crystallization from light petroleum

Yield: 17.21 g (85%, lit. 92%)

Mol. formula: $C_{12}H_{15}NO_5$

FW: 253.25

Physique aspect: white solid

Melting point: 75-77°C (lit. 76-78°C)

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.37-7.33	m		5
NH	5.92	d	$^3J_{NH\text{-}2}$ = 9.1	1
2	5.36	d	$^3J_{2\text{-}NH}$ = 9.1	1
4	5.15	s		2
10	3.80	s		3
9	3.46	s		3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 168.6 (C_1), 156.3 (C_3), 136.5 (C_5), 129.3, 129.0, 128.8 (C_6, C_7, C_8), 81.5 (C_2), 68.1 (C_4), 56.9 (C_{10}), 53.5 (C_9).

1.8 Synthesis of methyl ((benzyloxycarbonyl)amino)(dimethoxyphosphoryl)acetate 32

Reference:

Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53-60

RN: 88568-95-0

Procedure:

34 (12.3 g; 48.56 mmoles; 1 equiv) was dissolved in toluene (50 mL) at 70°C, then phosphorus trichloride (4.324 mL; 6.806 g; 48.56 mmoles; 1 equiv) was added, and the mixture was kept at 70°C for 18 h. Then, trimethyl phosphite (5.905 mL; 6.212 g; 48.56 mmoles; 1 equiv) was added dropwise to the stirred mixture at 70°C and stirring was continued for a further 2 h at 70°C. The solvent was removed under reduced pressure, the residual product redissolved in ethyl acetate (150 mL), this solution was washed with saturated $NaHCO_3$ (3X30 mL), and dried over $MgSO_4$. The solution was concentrated to a volume of about 25 mL and hexane was added with vigorous stirring to precipitate product as fine crystals.

Yield: 13.55 g (84%, lit. 80%)

Mol. formula: $C_{13}H_{18}NO_7P$

FW: 331.26

Physique aspect: white solid

Melting point: 78-80°C (lit. 80°C)

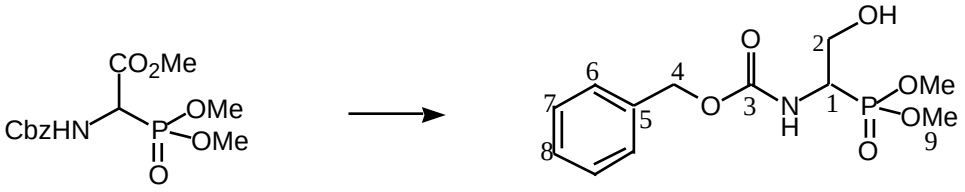
^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.39-7.27	m		5
NH	5.67	d	$^3J_{NH-2}$ = 9.1	1
4	5.14	s		2
2	4.94	dd	$^3J_{2-NH}$=9.3, ^2J_P=22.3	1
10	3.84	s		3
9	3.82	d	^3J_P=11.0	3
9	3.79	d	^3J_P=11.0	3

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 167.9 (C_1, d, ^2J_p=2.6), 156.3 (C_3, d, ^3J_p=7.5), 136.5 (C_5), 129.2, 129.0, 128.8 (C_6, C_7, C_8), 68.3 (C_4), 54.8 (C_9, d, ^2J_p=6.8), 54.6 ($C_{9'}$, d, ^2J_p=6.9), 54.0 (C_{10}), 52.7 (C_2, d, ^1J_p=147.2).

1.9 Synthesis of dimethyl 1-((benzyloxycarbonyl)amino)-2-hydroxyethyl phosphonate 31



Reference:

1. Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252-1255

2. Thesis of Kessabi, J. **1998**, 244

RN: 150649-37-9

Procedure:

32 (6.031 g; 18.2 mmoles; 1 equiv) was dissolved in THF (30 mL) under argon, anhydrous lithium chloride (1.559 g; 36.41 mmoles; 2 equiv) and sodium borohydride (2.108 g; 54.61 mmoles; 3 equiv) were added. After addition of ethanol (30 mL), the mixture was stirred at room temperature overnight. The mixture was cooled with ice-water, adjusted to pH 4 by the gradual additon of 10% aqueous citric acid (ca. 40 mL), and concentrated in vacuo. Water (60 mL) was added to the residue, which was extracted with CH_2Cl_2 (3X100 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated.

Purification: recrystallization from DCM-hexane

Yield: 4.89 g (88%, lit. 69%)

Mol. formula: $C_{12}H_{18}NO_6P$

FW: 303.25

Physique aspect: white solid

Melting point: 103-105°C (lit. 104-105°C)

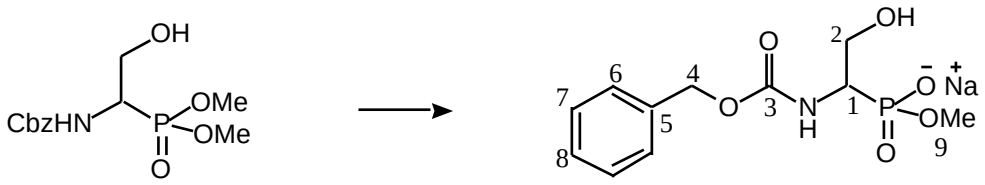
^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.38-7.27	m		5
NH	5.91	d	$^3J_{NH-1}$=10.1	1
4	5.13	s		2
1	4.29-4.16	m		1
2	4.01-3.90	m		2
9	3.79	d	^3J_p=10.0	3
9'	3.73	d	^3J_p=10.0	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ =156.8 (C_3, d, ^3J_p=6.5), 136.8 (C_5), 129.2, 128.9, 128.8 (C_6, C_7, C_8), 68.0 (C_4), 62.5 (C_2), 54.2 (C_9, d, ^2J_p=6.8), 53.8 ($C_{9'}$, d, ^2J_p=5.6), 50.3 (C_1, d, ^1J_p=153.3).

1.10 Synthesis of sodium 1-((benzyloxycarbonyl)amino)-2-hydroxyethyl (methoxy)phosphonate 35a



Reference:

Jacques, J.; Leclercq, M.; Brienne, M.-J. *Tetrahedron* **1981**, *37*, 1727-1733

Procedure:

A mixture of **31** (2 g; 6.595 mmoles; 1 equiv), sodium iodide (1.482 g; 9.892 mmoles; 1.5 equiv) in 60 mL of acetone (dried over molecule sieves) was refluxed at 65°C for 12 h. The precipitation was formed during the stirring. The solid was filtered and washed with acetone.

Yield: 2.02 g (98%)

Mol. formula: $C_{11}H_{15}NaNO_6P$

FW: 311.20

Physique aspect: pale yellow solid

Melting point: 117-120°C

^{1}H NMR (200MHz, D_2O, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.32	m		5
4	5.04	s		2
2	3.85-3.75	m		2
1	3.58-3.50	m		1
9	3.44	d	^3J_P=10.3	3

^{13}C NMR (75MHz, DMSO, 20°C)

δ =155.9 (C_3, d, ^3J_p=7.5), 137.1 (C_5), 128.3, 127.7 (C_6, C_7, C_8), 65.5 (C_4), 61.3 (C_2, br. s), 51.4 (C_9, d, ^2J_p=5.4), 49.7 (C_1, d, ^1J_p=142.4).

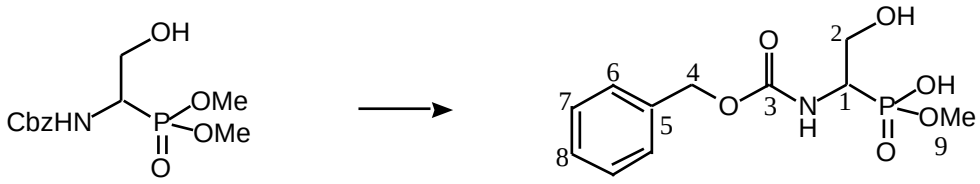
^{31}P NMR (101.3MHz, DMSO, 20°C, ref. 85% aq. H_3PO_4): δ =18.0 ppm

IR (KBr, cm^{-1}): 3527 (OH and NH), 3038 (arom. CH), 2950, 2896, 2852, 2782 (sat. CH), 1722 (C=O), 1030 (P-O).

MS (CI/CH_4-N_2O):

m/z (%): +c: 257 (34) [M-ONa-Me] $^{+\bullet}$, 246 (100) [M-65]$^+$, 205 (22) [M+1-$PhCH_2O$] $^{+\bullet}$, 136 (17) [BnOCO+1] $^{+\bullet}$.

1.11 Synthesis of methyl hydrogen 1-((benzyloxycarbonyl)amino)-2-hydroxyethylphosphonate 35b



Reference:

Clark, V. M.; Todd, A. R. *J. Chem. Soc.* **1950**, 2030-2034

Procedure:

A mixture of anhydrous lithium chloride (838.7 mg; 19.78 mmoles; 3 equiv) and **31** (2 g; 6.595 mmoles; 1 equiv) in freshly distilled 30 mL of 2-ethoxyethanol was heated at 100°C for 2 h. The solvent was removed in vacuo. The residue was dissolved in 30 mL of MeOH. Then Dowex 5X8-100 (cation-exchange resin) was added to the above mixture. The mixture was stirred at rt for 3 h. The resin was filtered and wash with MeOH until pH7. The organic layers were combined and evaporated to give an oil.

Purification: recrystallization from acetone-hexane

Yield: 1.49 g (78%)

Mol. formula: $C_{11}H_{16}NO_6P$

FW: 289.22

Physique aspect: white solid

Melting point: 108-110°C

^{1}H NMR (200MHz, CD_3COCD_3, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.39-7.32	m		5
NH	6.58	d	$^3J_{NH-1}$=8.5	1
4	5.10	s		2
1	4.28-4.08	m		1
2	3.90-3.80	m		2
9	3.70	d	^3J_P=10.7	3

^{13}C NMR (75MHz, CD_3COCD_3, 20°C)

δ =156.3 (C_3, d, ^3J_p=5.7), 136.1 (C_5), 128.4, 128.1, 128.0 (C_6, C_7, C_8), 67.2 (C_4), 61.5 (C_2, d, ^2J_p=14.5), 52.9 (C_9, br. s), 49.1 (C_1, d, ^1J_p=153.9).

^{31}P NMR (101.3MHz, DMSO, 20°C, ref. 85% aq. H_3PO_4): δ =22.1 ppm

IR (KBr, cm^{-1}): 3285 (OH and NH), 3067 (arom. CH), 2945, 2893 (sat. CH), 2291 (PO-H), 1688 (C=O), 1042 (P-O).

MS (FAB):

m/z (%): +Q1MS: 307 (28) $[M+H_2O]^{\bullet\bullet}$, 289 (16) $[M]^{\bullet\bullet}$, 154 (100) $[M\text{-}BnOCO]^+$, 136 (66) $[BnOCO+1]^{\bullet\bullet}$, 91 (34) $[PhCH_2]^+$, 77 (40) $[C_6H_5]^+$;

-Q1MS: 305 (100), 288 (68) $[M-1]^+$, 153 (40) $[M\text{-}BnOCO-1]^{\bullet\bullet}$;

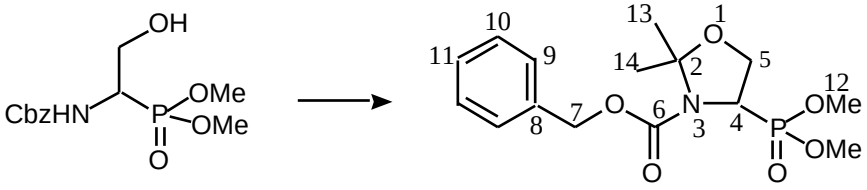
+DAU: 290 (2) $[M+1]^+$, 137 (100) $[BnOCO+2]^+$, 91 (60) $[PhCH_2]^+$;

-DAU: 288 (4) $[M-1]^+$, 180 (100) $[M\text{-}BnO-2]^+$.

Elemental analysis calcd for $C_{11}H_{16}NO_6P$:

C 45.681, H 5.575, N 4.842, P 10.709; found: C 45.67, H 5.50, N 4.80, P 11.34

1.12 Synthesis of benzyl 4-(dimethoxyphosphoryl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate 38



Reference:

Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361-2364

Procedure:

A solution of **31** (2.1 g; 6.924 mmoles; 1 equiv), 10.42 mL of 2,2-dimethoxypropane (12 equiv) and *para*-toluenesulfonic acid monohydrate (66.5 mg; 346.2 μmoles; 0.05 equiv) in

benzene (100 mL) was heated under reflux for 9 h (80°C). The solvent was evaporated, then 25 mL of EtOAc was added to the residue. This solution was washed with sat $NaHCO_3$ followed by brine, then dried over $MgSO_4$, filtered and concentrated.

TLC: Rf=0.20 (EtOAc/hexane 8/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 8/1)

Yield: 2.01 g (85%)

Mol. formula: $C_{15}H_{22}NO_6P$

FW: 343.31

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C, two rotamers)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.38-7.34	m		5
7	5.18 (5.15)	s		2
5a + 4	4.40-4.30	m		2
5b	4.20-4.02	m		1
12	3.75 (3.59)	d	^3J_p=10.5	6
13	1.75 (1.70)	s		3
14	1.64 (1.48)	s		3

^{1}H NMR (300MHz, $CDCl_3$, 50°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.38-7.28	m		5
7	5.18	s		2
5a	4.37	dm	$^2J_{5a\text{-}5b}$=9.8	1
4	4.33	m		1
5b	4.11	dd	$^2J_{5b\text{-}5a}$=9.7, $^3J_{5b\text{-}4}$=6.8	1
12	3.75	d	^3J_p=10.5	6
13	1.67	s		3
14	1.53	s		3

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ =152.5 (C_6, d, ^3J_p=5.6), 136.5 (C_8), 128.8, 128.6, 128.5 (C_9, C_{10}, C_{11}), 95.8 (C_2), 67.8 (C_7), 64.6 (C_5, d, ^2J_p=14.5), 53.5 (C_{12a}, d, ^2J_p=6.8), 53.3 (C_{12b}, d, ^2J_p=4.2), 52.6 (C_4, d, ^1J_p=162.5), 26.5 (C_{13}), 26.4 (C_{14}).

^{31}P NMR (101.3MHz, $CDCl_3$, 20°C, ref. 85% aq. H_3PO_4):

δ =25.7, 25.3 ppm (two rotamers)

IR (film, cm^{-1}): 3050 (arom. CH), 2987, 2953 (sat. CH), 1704 (C=O), 1245 (P=O), 1029 (P-O).

MS (FAB):

m/z (%): +Q1MS: 344 (20) $[M+1]^+$, 286 (24) $[M+1-C_3H_6O]^+$, 109 (8) $[P(O)(OMe)_2]^+$, 91 (100) $[PhCH_2]^+$;

-Q1MS: 328 (100) $[M-Me]^+$, 305 (52), 252 (30) $[M-PhCH_2]^+$, 153 (46) $[C_4H_9NO_3P]^{\bullet\bullet}$;

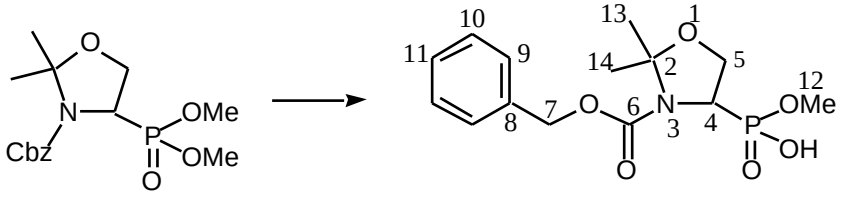
+DAU: 344 (2) $[M+1]^+$, 176 (100) $[C_5H_9NO_5P]^+$, 91 (100) $[PhCH_2]^+$;

-DAU: 342 (100) $[M-1]^+$, 206 (100) $[M-PhCH_2O-2Me]^+$.

HRMS (CI) calcd. for $C_{15}H_{23}NO_6P$:

344.126301; found: 344.127272

1.13 Synthesis of benzyl 4-(hydroxy(methoxy)phosphoryl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate 42



Procedure:

A mixture of **38** (9.117 g; 26.55 mmoles; 1 equiv), lithium chloride (3.411 g; 79.66 mmoles; 3 equiv) in 200 mL of acetone was refluxed at 70°C for 12 h. The white precipitation was formed during the stirring. The lithium salt was then filtered and washed with ether. The solid was dissolved in 50 mL of water, then the aqueous solution was washed with 30 mL of EtOAc. The aqueous layer was cooled to 0°C and acidified with 40 mL of 1.2 N aq. HCl. Extraction with EtOAc (3X50 mL). The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered and evaporated.

Yield: 8.47 g (97%)

Mol. formula: $C_{14}H_{20}NO_6P$

FW: 329.28

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
OH	10.23	br. s		1
PhH	7.35-7.32	m		5
7	5.18	s		2
5a + 4	4.35-4.31	m		2
5b	4.08-4.05	m		1
12	3.74, 3.62	d	^3J_p=10.5	3
13	1.69 (1.61)	s		3
14	1.54 (1.46)	s		3

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ =152.0 (C_6, d, ^3J_p=5.6), 135.8 (C_8), 128.0, 127.9, 127.8 (C_9, C_{10}, C_{11}), 95.1 (C_2), 67.2 (C_7), 64.0 (C_5, d, ^2J_p=14.5), 52.9 (C_{12}, d, ^2J_p=6.0), 51.8 (C_4, d, ^1J_p=154.1), 26.1 (C_{13}), 26.0 (C_{14}).

^{31}P NMR (101.3MHz, $CDCl_3$, 20°C, ref. 85% aq. H_3PO_4): δ =19.2 ppm

IR (film, cm^{-1}): 3303 (OH), 3025 (arom. CH), 2935 (sat. CH), 1705 (C=O), 1238 (P=O), 1043 (P-O).

MS (FAB):

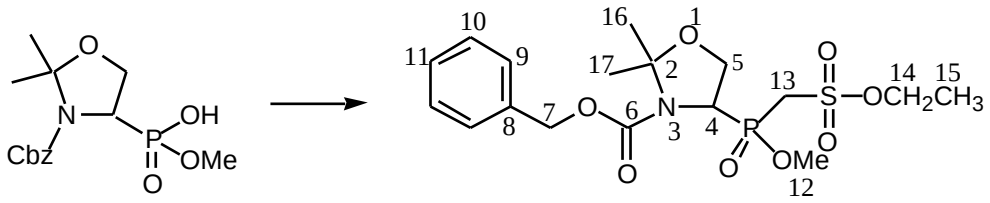
m/z (%): +Q1MS: 330 (15) $[M+1]^+$, 272 (15) $[M+1-C_3H_6O]^+$, 154 (42), 137 (40) $[C_2H_5NO_3P]^{+\bullet}$, 91 (100) $[PhCH_2]^+$;

-Q1MS: 328 (100) $[M-1]^+$, 288 (30) $[M+1-CMe_2]^+$;

+DAU: 330 (2) $[M+1]^+$, 176 (30) $[M-C_3H_6O]^+$, 91 (100) $[PhCH_2]^+$;

-DAU: 328 (100) $[M-1]^+$, 162 (40) $[C_4H_5NO_4P]^+$, 107 (16) $[PhCH_2O]^+$.

1.14 Synthesis of benzyl 4-(((ethoxysulfonyl)methyl)(methoxy)phosphoryl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate 40



Procedure:

A solution of **42** (2.44 g; 7.409 mmoles; 1 equiv) in 30 mL of dry CH_2Cl_2 was cooled to 0°C, then 1-chloro-N,N,2-trimethylpropenylamine (1.383 mL; 8.891 mmoles; 1.2 equiv) was added slowly. The mixture was left to rt progressively and then stirred at this temperature for 3 h (TLC showed the disappearance of TMCE). The solvent was evaporated away from humidity (a

P_2O_5 trap). A solution of ethyl methanesulfonate (1.592 mL; 14.81 mmoles; 2 equiv) in THF (30 mL) was cooled to -78°C, then 2.5 M *n*-butyllithium (6.52 mL; 16.3 mmoles; 2.2 equiv) was added. The mixture was stirred at -78°C for 1 h. Then this anion solution was added via cannulation to a solution of above prepared phosphinic acid chloride in 10 mL of dry THF at -78°C. The reaction was kept stirring at this temperature for 3 h, then quenched with sat. NH_4Cl. The mixture was extracted with EtOAc (3X). The organic layers were combined, washed with the water, dried over $MgSO_4$, filtered and evaporated.

TLC: Rf=0.29 (EtOAc/cyclohexane 9/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 9/1)

Yield: 1.98 g (62%)

Mol. formula: $C_{17}H_{26}NO_8PS$

FW: 435.42

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C, two isomers)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.36	br. s		5
7	5.18	s		2
5 + 14	4.62-4.35	m		4
4 + 13	4.22-3.98	m		3
12	3.93 (3.84)	d	^3J_p=8.7	3
16	1.64 (1.59)	s		3
17 + 15	1.50-1.37	m		6

^{13}C NMR (75MHz, $CDCl_3$, 20°C, two isomers)

δ =154.0 (C_6), 136.1 (C_8), 128.9, 128.8, 128.5 (C_9, C_{10}, C_{11}), 96.0 (C_2), 68.6 (C_{14}), 68.3 (C_7), 63.1 (C_5, d, ^2J_p=52.5), 56.9 (C_4, d, ^1J_p=115.7), 53.6 (C_{12}, d, ^2J_p=7.7), 53.2 (C_{12}, d, ^2J_p=7.4), 49.9 (C_{13}, d, ^1J_p=75.0), 26.5, 26.1 (C_{16}), 25.1, 24.6 (C_{17}), 15.3, 15.2 (C_{15}).

^{31}P NMR (101.3 MHz, $CDCl_3$, 20°C, ref. 85% aq. H_3PO_4):

δ =44.8, 45.4 ppm (two isomers)

IR (film, cm^{-1}): 3073 (arom. CH), 2960, 2934, 2880 (sat. CH), 1717 (C=O), 1235 (P=O), 1027 (P-O).

MS (FAB):

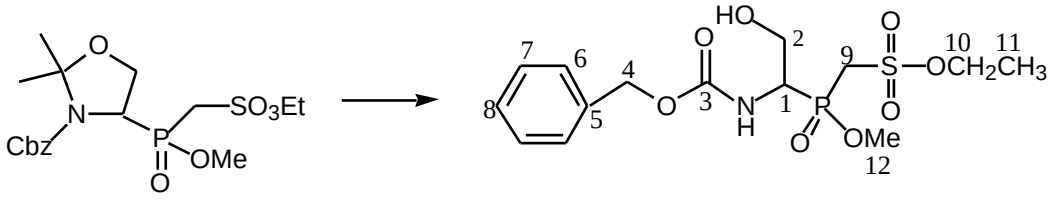
m/z (%): +Q1MS: 436 (15) $[M+1]^+$, 390 (2) $[M\text{-}OEt]^+$, 176 (20), 91 (100) $[PhCH_2]^+$;

-Q1MS: 434 (56) $[M-1]^+$, 406 (100) $[M\text{-}OEt]^+$, 328 (20) $[M\text{-}OBn]^+$, 326 (12) $[M\text{-}SO_3Et]^+$, 300 (8) $[M\text{-}Cbz]^+$;

+DAU: 176 (100) $[BnOCO_2NCCH_3]^+$, 91 (36) $[PhCH_2]^+$;

-DAU: 326 (52) $[M\text{-}SO_3Et]^+$, 296 (100) $[M\text{-}SO_3Et\text{-}2Me]^+$.

1.15 Synthesis of ethyl ((1-((benzyloxycarbonyl)amino)-2-hydroxyethyl)(methoxy)phosphoryl) methanesulfonate 48



Procedure:

40 (1.331 g; 2.414 mmoles; 1 equiv) was taken up in CH_2Cl_2/TFA/MeOH (6:3:1) (20 mL) and stirred at room temperature for 18 h. The solvent was removed by vacuum, and residual TFA was removed by covaporation with toluene.

TLC: Rf=0.26 (CH_2Cl_2/MeOH 95/5, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (CH_2Cl_2/MeOH 95/5)

Yield: 0.81 g (84%)

Mol. formula: $C_{14}H_{22}NO_8PS$

FW: 395.36

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C, two isomers: 1:1)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.33	br. s		5
NH	6.78 (6.34)	d	$^3J_{NH-1}$=9.3	1
4	5.10	s		2
2 + 10	4.41-4.29	m		4
1 + 9	4.14-3.88	m		3
12	3.83 (3.75)	d	^3J_p=10.9	3
11	1.37 (1.36)	t	$^3J_{11-10}$=7.1	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C, two isomers)

δ =157.0, 156.9 (C_3, d, ^3J_p=4.1), 136.5 (C_5), 129.1, 128.9, 128.7 (C_6, C_7, C_8), 68.9 (C_4), 68.1 (C_{10}), 61.1 (C_2, d, ^2J_p=19.2), 54.2 (C_{12}, d, ^2J_p=7.7), 54.0 (C_{12}, d, ^2J_p=7.1), 53.5 (C_1, d, ^1J_p=108.4), 50.0, 49.0 (C_9, d, ^1J_p=74.9), 15.5 (C_{11}).

IR (film, cm^{-1}): 3410 (OH), 3291 (NH), 3030 (arom. CH), 2980, 2852 (sat CH), 1699 (C=O), 1357, 1177 (S=O), 1230 (P=O), 1035(P-O).

MS (FAB):

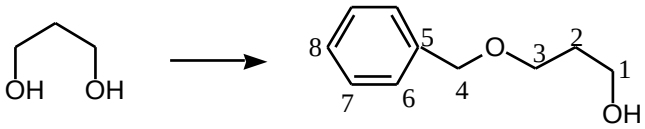
m/z (%): +Q1MS: 396 (5) $[M+1]^+$, 150 (21) $[CbzNH]^+$, 135 (40) $[Cbz]^+$, 107 (22) $[BnO]^+$, 91 (100) $[PhCH_2]^+$, 77 (22) $[Ph]^+$;

-Q1MS: 394 (60) $[M-1]^+$, 266 (100) $[M-Et]^+$, 304 (20) $[M-Bn-1]^+$;

+DAU: 150 (100) $[CbzNH]^+$, 91 (100) $[PhCH_2]^+$;

-DAU: 394 (16) $[M-1]^+$, 286 (28) $[M-SO_3Et]^+$, 240 (12) $[M-1-CH_2SO_3Et-CH_2OH]^+$, 208 (100) $[M-1-Ph-SO_3Et]^+$, 123 (16) $[CH_2SO_3Et]^+$.

1.16 Synthesis of 3-(benzyloxy)-1-propanol 62



Reference:

Bouzide, A.; Sauvé, G. *Tetrahedron Lett.* **1997**, *38(34)*, 5945-5948

RN: 4799-68-2

Procedure:

To a stirred solution of 1,3-propanediol (1 mL; 1.053 g; 13.83 mmoles; 1 equiv) in CH_2Cl_2 was added silver(I) oxide (4.81 g; 20.75 mmoles; 1.5 equiv) and benzyl bromide (1.81 mL; 15.22 mmoles; 1.1 equiv). The reaction was stirred for 5 h and filtered through a celite pad. The solvent was evaporated.

TLC: Rf=0.23 (P.E./EtOAc 3/2, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (P.E./EtOAc 3/2)

Yield: 2.0 g (87%)

Mol. formula: $C_{10}H_{14}O_2$

FW: 166.21

Physique aspect: colorless oil

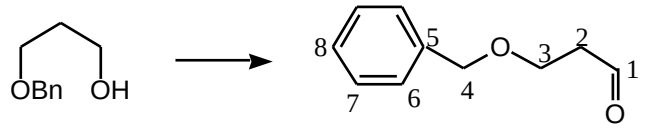
^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.40-7.25	m		5
4	4.51	s		2
3	3.75	t	$^3J_{3-2}$=5.6	2
1	3.65	t	$^3J_{1-2}$=5.8	2
OH	2.45	br. s		1
2	1.86	quint	$^3J_{2-3}$=$^3J_{2-1}$=5.8	2

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 138.6 (C_5), 128.9, 128.2 (C_6, C_7, C_8), 73.7 (C_4), 69.4 (C_3), 61.7 (C_1), 32.7 (C_2).

1.17 Synthesis of 3-(benzyloxy)propanal 60



RN: 19790-60-4

Procedure:

1) PCC oxidation: To a stirred solution of **62** (530 mg; 3.188 mmoles; 1 equiv) in 20 mL of CH_2Cl_2 was added pyridinium chlorochromate (1.052 g; 4.782 mmoles; 1.5 equiv) in small portions. The reaction was stirred at rt for 4 h. Then 50 mL of ether was added and the solution was filtered through a celite pad. The celite was washed with Et_2O (3X). The organic solutions were combined, dried ($MgSO_4$), filtered and evaporated. (**Yield:** 0.2 g, 42%)

2) Dess-Martin reaction: To a solution of *o*-iodoxybenzoic acid (IBX) (1.516 g; 5.414 mmoles; 3 equiv) in DMSO (5 mL) at rt was added dropwise a solution of **62** (300 mg; 1.804 mmoles; 1 equiv) in DMSO (10 mL). The resulting slurry mixture was stirred for 2.5 h. Then 10 mL of water was added at 0°C and the mixture was extracted with diethyl ether. The organic layer was washed with water (3X), dried over $MgSO_4$, filtered and concentrated in vacuo. (**Yield:** 0.25 g, 92%)

3) Swern oxidation: To a solution of oxalyl chloride (0.386 mL; 4.331 mmol; 1.2 equiv) in 8 mL of DCM at -78°C was added a solution of DMSO (0.615 mL; 8.662 mmol; 2.4 equiv) in 1 mL of DCM. After 20 min, a solution of **62** (0.6 g; 3.609 mmol; 1 equiv) in 3 mL of DCM was added and the reaction mixture was stirred for 2 h. Triethylamine (2 mL; 14.44 mmol; 4 equiv) was added and the reaction was warmed to 0°C. The solvent was removed in vacuo and the resulting residue was suspended in diethylether, filtered through a pad of silica gel. The filtrate was dried ($MgSO_4$) and evaporated. (**Yield:** quantitative)

TLC: Rf=0.31 (P.E./EtOAc 7/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (P.E./EtOAc 7/3)

Mol. formula: $C_9H_{10}O_2$

FW: 150.17

Physique aspect: colorless oil

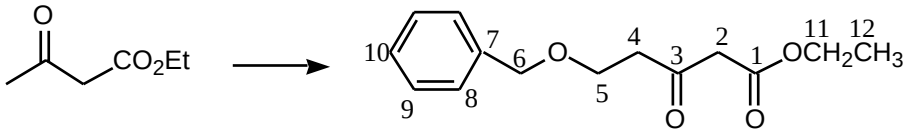
^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
1	9.80	t	$^3J_{1\text{-}2}$=1.8	1
PhH	7.40-7.25	m		5
4	4.53	s		2
3	3.81	t	$^3J_{3\text{-}2}$=6.0	2
2	3.65	td	$^3J_{2\text{-}3}$=6.0, $^3J_{2\text{-}1}$=1.8	2

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 201.6 (C_1), 138.5 (C_5), 129.0, 128.3, 128.2 (C_6, C_7, C_8), 73.8 (C_4), 64.4 (C_3), 44.4 (C_2).

1.18 Synthesis of ethyl 3-oxo-5-(benzyloxy)pentanoate 64



Reference:

Taylor, E. C.; LaMattina, J. L. *J. Org. Chem.* **1978**, *43(6)*, 1200-1204

RN: 64714-79-0

Procedure:

To sodium hydride (60% dispersion in mineral oil, 5.207 g; 130.2 mmoles; 1.1 equiv) in a three-necked flask was added 8 mL of hexane under an argon atmosphere. The mixture was stirred briefly and allowed to settle, and the hexane was carefully decanted off to remove most of the mineral oil. The NaH was then suspended in 10 mL of dry THF with stirring at 0°C, a solution of ethyl acetoacetate (15 mL; 15.4 g; 118.3 mmoles; 1 equiv) in 10 mL of THF was added dropwise over 15 min. The mixture was stirred for 15 min, 2.3 M of *n*-butyllithium (56.61 mL; 130.2 mmoles; 1.1 equiv) was added dropwise, and the dianion solution was stirred for 15 min at 0°C. A solution of benzyl chloromethyl ether (60%, 30.18 mL; 33.98 g; 130.2 mmoles; 1.1 equiv) in 8 mL of THF was then added, and the mixture was stirred at 0°C for 1 h and then 15 mL of cold water was added. The mixture was acidified with cold 1N HCl and the organic layer was separated. The aqueous solution was extraxted twice with ether, and the combined organic layers were dried over $MgSO_4$, filtered and evaporated.

TLC: Rf=0.24 (P.E./EtOAc 4/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (P.E./EtOAc 4/1)

Yield: 20.73 g (70%, lit. 70%)

Mol. formula: $C_{14}H_{18}O_4$

FW: 250.29

Physique aspect: colorless oil

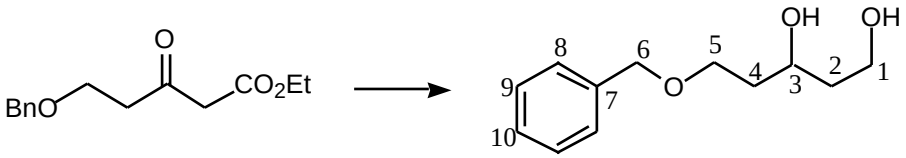
^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.37-7.25	m		5
6	4.49	s		2
11	4.17	q	$^{3}J_{11\text{-}12}$=7.2	2
5	3.74	t	$^{3}J_{5\text{-}4}$=6.2	2
2	3.47	s		2
4	2.81	t	$^{3}J_{4\text{-}5}$=6.2	2
12	1.26	t	$^{3}J_{12\text{-}11}$=7.2	3

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 201.9 (C_3), 167.7 (C_1), 138.5 (C_7), 128.9, 128.3 (C_8, C_9, C_{10}), 73.8 (C_6), 65.5 (C_{11}), 61.9 (C_5), 50.3 (C_2), 43.6 (C_4), 14.7 (C_{12}).

1.19 Synthesis of 5-(benzyloxy)-1, 3-pentanediol 54



RN: 83458-87-1

Procedure:

A solution of **64** (168 mg; 671.2 µmoles; 1 equiv) in 6 mL of dry THF was added slowly to a suspension of lithium aluminum hydride (80.44 mg; 2.013 mmoles; 3 equiv) in 8 mL of dry THF at rt under argon atmosphere. The resulting mixture was refluxed for 3 h. Cold water was added to quench the reaction. $Li(OAl)_2$ was dissolved by addition of little dilute HCl and the mixture was extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and evaporated.

TLC: Rf=0.24 (P.E./EtOAc 1/9, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (P.E./EtOAc 1/9)

Yield: 0.11 g (78%)

Mol. formula: $C_{12}H_{18}O_3$

FW: 210.27

Physique aspect: colorless oil

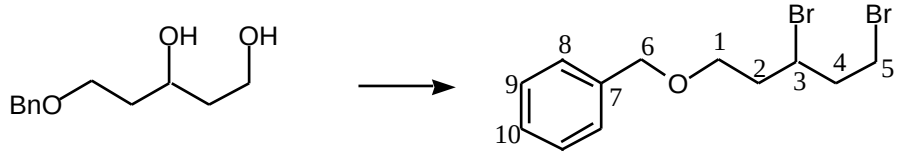
^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	J (Hz)	Integr.
PhH	7.38-7.28	m		5
6	4.50	s		2
3	4.10-4.00	m		1
5 + 1	3.82-3.60	m		4
OH	3.52	br. s		2
4 + 2	1.90-1.66	m		4

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 138.5 (C_7), 129.1, 128.4, 128.3 (C_8, C_9, C_{10}), 73.9 (C_6), 71.5 (C_3), 69.4 (C_5), 61.7 (C_1), 39.1 (C_4), 37.3 (C_2).

1.20 Synthesis of (((3, 5-dibromopentyl)oxy)methyl)benzene 53



Reference:

Hanack, M.; Auchter, G. *J. Am. Chem. Soc.* **1985**, *107*, 5238-5245

Procedure:

To a suspension of triphenylphosphine (2.408 g; 9.089 mmoles; 2.3 equiv) in dry acetonitrile (30 mL) was added dropwise with stirring and under ice-cooling bromine (449.9 uL; 1.403 g; 8.694 mmoles; 2.2 equiv). The inside temperature should not exceed 5°C. After removal of the ice bath, **54** (831 mg; 3.952 mmoles; 1 equiv) in acetonitrile (8 mL) was added in 15 min. The mixture was stirred for 1 h, and acetonitrile was removed on a rotary evaporator.

TLC: Rf=0.45 (hexane/EtOAc 9/1, UV, phosphomolybdic acid)

Purification: flash column chromatography on silica gel (hexane/EtOAc 9/1)

Yield: 1.06 g (80%)

Mol. formula: $C_{12}H_{16}Br_2O$

FW: 336.06

Physique aspect: pale yellow oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.38-7.26	m		5
6	4.52	s		2
3	4.42-4.35	m		1
1	3.66	dd	$^3J_{1\text{-}2a}$=5.3, $^3J_{1\text{-}2b}$=5.1	2
5a	3.59	t	$^3J_{5a\text{-}4}$=5.9	1
5b	3.58	t	$^3J_{5b\text{-}4}$=6.8	1
2	2.32	q	$^3J_{2\text{-}1}$=5.6, $^3J_{2\text{-}3}$=6.0	2
4	2.22-2.04	m		2

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 138.8 (C_7), 129.1, 128.4, 128.3 (C_8, C_9, C_{10}), 73.9 (C_6), 68.3 (C_1), 52.6 (C_3), 42.3 (C_5), 39.6 (C_2), 31.6 (C_4).

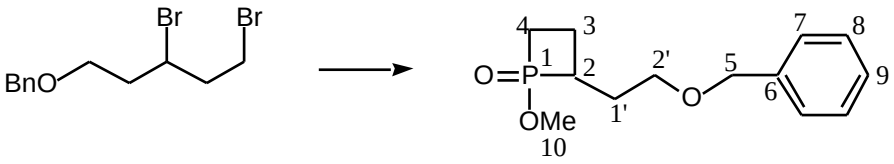
IR (film, cm^{-1}): 3050 (arom. CH), 2980, 2950, 2850 (sat. CH), 1103 (C-O), 735, 697.

MS (EI, 70 ev):

m/z(%): +Q1MS: 338 (10) [M+2]$^{+\bullet}$, 336 (20) [M]$^{+\bullet}$, 334 (10) [M-2]$^{+\bullet}$, 229 (6) [M-OBn]$^+$, 175 (12) [M-1-2Br]$^+$, 107 (6) [OBn]$^+$, 91 (100) [Bn]$^+$;

+DAU: 336 (32) [M]$^{+\bullet}$, 229 (100) [M-OBn]$^+$, 92 (78) [BnO+1]$^{+\bullet}$.

1.21 Synthesis of methyl 2-(2'-(benzyloxy)ethyl)phosphetanate 67



Reference:

Montchamp, J.-L.; Tian, F.; Frost, J. W. *J. Org. Chem.* **1995**, *60*, 6076-6081

Procedure:

Preparation of ammonium hypophosphite ($H_2PO_2NH_4$):

A 50% hypophosphorous acid solution in water (100 mL; 965.2 mmoles; 1 equiv) was treated at 0°C with ammonium carbonate (46.37 g; 482.6 mmoles; 0.5 equiv) in portions. After addtion was completed, the ice bath was removed and the mixture was stirred at rt for 12 h. The colorless solution was concentrated in vacuo to afford a white paste which was recrystallized from water-acetone. The crystals were dried at 60°C under high vacuum and stored over P_2O_5 in a desicator. (**Yield:** 60.1 g, 75%**)**

A mixture of **53** (980 mg; 2.916 mmoles; 1 equiv), HMDS (5.708 mL; 26.24 mmoles; 9 equiv) and ammonium hypophosphite (0.968 g; 11.31 mmol; 4 equiv) was refluxed in mesitylene (10 mL/mmol dielectrophile) overnight under argon atmosphere. After cooling, the reaction mixture

was concentrated in vacuo to a heterogeneous mixture consisting of a yellow oil and a white solid. The crude reaction mixture was hydrolyzed with brine at rt, filtered, then extracted with EtOAc for 24 h in a continuous extractor. Concentration afforded the phosphinic acid.

This crude and 10 mL of MeOH were added in an erlenmeyer and the solution was cooled to 0°C, CH_2N_2 in ether was added slowly until the reaction was complete. After stirring at rt for 1 h, HOAc was added to destruct the excess CH_2N_2. After removal of MeOH, the CH_2Cl_2 was added and the solution was dried over $MgSO_4$, filtered and evaporated.

TLC: Rf=0.45 (CH_2Cl_2/MeOH 95/5, phosphomolybdic acid)

Purification: flash column chromatography on silica gel (CH_2Cl_2/MeOH 95/5)

Yield: 0.126 g (17%, overall)

Mol. formula: $C_{13}H_{19}O_3P$

FW: 254.26

Physique aspect: pale yellow oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C, two isomers)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.25-7.33	m		5
5	4.49	s		2
10	3.73 (3.72)	d	^3J_P=10.7	3
2'	3.46	t	$^3J_{2'-1'}$=6.3	2
2, 3, 4, 1'	1.78-1.46	m		7

^{13}C NMR (75MHz, $CDCl_3$, 20°C, two isomers)

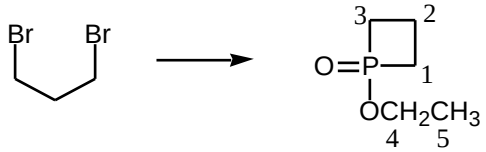
δ = 139.1 (C_6), 129.0, 128.3, 128.2 (C_7, C_8, C_9), 73.7, 73.6 (C_5), 70.7, 70.5 ($C_{2'}$), 52.8 (C_{10}, d, ^2J_p= 7.0), 50.5, 48.5 (C_2, d, ^1J_p= 114.9), 29.9, 29.8 ($C_{1'}$, d, ^2J_p= 8.6), 27.5 (C_4, d, ^1J_p= 108.0), 16.0 (C_3, d, ^2J_p= 23.9).

IR (film, cm^{-1}): 3069 (arom. CH), 2947, 2864 (sat. CH), 1214 (P=O), 1030 (P-O).

MS (EI, 70 ev):

m/z(%): +Q1MS: 254 (2) [M]$^{+\bullet}$, 163 (12) [M-Bn]$^+$, 148 (24) [M-OBn]$^{+\bullet}$, 119 (26) [M-CH_2CH_2OBn]$^+$, 91 (100) [Bn]$^+$.

1.22 Synthesis of ethyl phosphetanate 68



Reference:

Wong, S. C.; Carruthers, N. I.; Chan, T. M. *J. Chem. Research (S)* **1993**, *7*, 268

RN: 150786-92-8

Procedure:

Magnesium (10 g; 411.4 mmoles; 2.07 equiv) in dry ether (150 mL) was treated with 1,3-dibromopropane (20.31 mL; 40.4 g; 198.1 mmoles; 1 equiv) and a crystal of I_2. The mixture was heated at reflux temperature for 1 h then diluted with 1.2 L dichloromethane and cooled to -78°C. To the solution was then added ethyl dichlorophosphate (24.03 mL; 33 g; 196.4 mmoles; 0.991 equiv) in one portion. The reaction mixture was stirred at -78°C for a further 4 h then allowed to warm to room temperature overnight (17 h) and poured into saturated NH_4Cl solution (600 mL). After stirring for 4 h the organic portion was separated and the aqueous layer was extracted with DCM (3X150 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to afford an oil.

TLC: Rf=0.31 (CH_2Cl_2/MeOH 98/2, $KMnO_4$)

Purification: flash column chromatography on silica gel (CH_2Cl_2/MeOH 98/2)

Yield: 4.0 g (15%)

Mol. formula: $C_5H_{11}O_2P$

FW: 134.11

Physique aspect: colorless oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
4	4.12	dq	^3J_P=8.4, $^3J_{4\text{-}5}$=7.1	2
1 + 3	2.75-2.49	m		4
2	2.10-1.60	m		2
5	1.37	td	$^3J_{5\text{-}4}$=7.0, ^4J_P=2.5	3

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 60.4 (C_4, d, ^2J_p= 6.3), 37.3 (C_1, C_3, d, ^1J_p= 69.5), 16.6 (C_5, d, ^3J_p= 5.5), 7.5 (C_2, d, ^2J_p= 26.8).

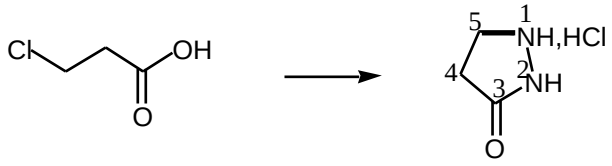
MS (EI, 70 ev):

m/z(%): +Q1MS: 135 (40) $[M+1]^+$, 106 (100) $[M+1\text{-}C_2H_5]^{\bullet\bullet}$, 90 (15) $[M+1\text{-}OEt]^{\bullet\bullet}$.

Chapter 2

Towards bicyclic pyrazolidinone derivatives

2.1 Synthesis of pyrazolidinone hydrochloride 89*



Reference:

Howard, J. C.; Gever, G.; Wei, P.H.L. *J. Org. Chem.* **1963**, *28*, 868-870

RN: 1752-88-1

Procedure:

To 7.44 g (186.1 mmoles; 2.0 equiv) of NaOH dissolved in 31.47 mL (32.47 g; 635.8 mmoles; 6.9 equiv) of 98% hydrazine hydrate was added slowly with stirring 10 g (92.14 mmoles; 1 equiv) of 3-chloropropionic acid in 8.17 mL (453.5 mmoles; 4.9 equiv) of water. The temperature was kept between 90 and 95°C during addition. Introduction of acid was completed in 10 min and the mixture was stirred with heating for 1 h longer. Water and excess hydrazine were then removed at reduced pressure and a semisolid residue remained. To this was added 100 mL of methanol. The solution was saturated with anhydrous hydrogen chloride, heated for 30 min, then filtered to remove NaCl. The methanolic filtrate gave colorless crystals after cooling and scratching. These were collected and washed with amounts of cold methanol and ether. The crude methyl 3-hydrazinopropionate hydrochloride was heated overnight at 110°C.

Purification: recrystallization from MeOH

Yield: 80% (lit. 85%)

Mol. formula: $C_3H_7ClN_2O$

FW: 122.55

Physique aspect: white solid

Melting point: 200-205°C (lit. 200-205°C)

^{1}H NMR (200MHz, DMSO, 20°C)

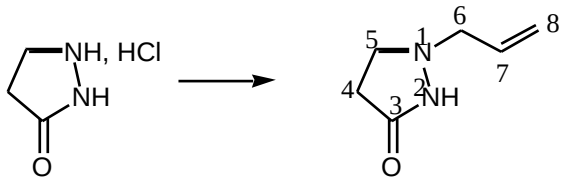
Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
5	3.64	t	$^3J_{5\text{-}4}$ = 8.3	2
4	2.56	t	$^3J_{4\text{-}5}$ = 8.3	2

^{13}C NMR (50MHz, DMSO, 20°C)

δ = 173.7 (C_3), 42.7 (C_5), 28.5 (C_4)

* Currently, this product is also commercially available from Acros Chemical Co..

2.2 Synthesis of 1-allyl-pyrazolidin-3-one 93



Procedure:

To a solution of 300 mg (1.958 mmoles; 1 equiv) of pyrazolidinone hydrochloride in 10 mL of DMF was added 544.4 µL (3.916 mmoles; 2 equiv) of triethylamine, 186.4 µL (2.154 mmoles; 1.1 equiv) of allyl bromide and 73.4 mg (489.5 µmoles; 0.25 equiv) of sodium iodide. The resulting mixture was stirred at ambient temperature for 48 h. The reaction mixture was concentrated under high vacuum, and the residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted twice with CH_2Cl_2 and the organic layers were combined, washed with brine, and dried over $MgSO_4$. Filtration followed by concentration in vacuo provided an oil.

TLC: Rf = 0.15 (DCM/MeOH 95/5, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (DCM/MeOH 95/5)

Yield: 0.15 g (61%)

Mol. formula: $C_6H_{10}N_2O$

FW: 126.15

Physique aspect: pale yellow oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
NH	7.60	br. s		1
7	5.87	ddt	$^3J_{7\text{-}8a(trans)}$=17.3, $^3J_{7\text{-}8b(cis)}$=10.2 $^3J_{7\text{-}6}$=6.4	1
8a	5.31	dm	$^3J_{8a\text{-}7(trans)}$=17.3	1
8b	5.26	dm	$^3J_{8b\text{-}7(cis)}$=10.2	1
5 + 6	3.34	dm	$^3J_{6\text{-}7}$ =6.4	4
4	2.54	t	$^3J_{4\text{-}5}$ =7.8	2

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 175.3 (C_3), 133.6 (C_7), 120.5 (C_8), 63.2 (C_6), 52.5 (C_5), 30.6 (C_4).

IR (film, cm^{-1}): 3409 (NH), 3080 (unsat. CH), 2985, 2931, 2841 (sat. CH), 1682 (C=O), 934.

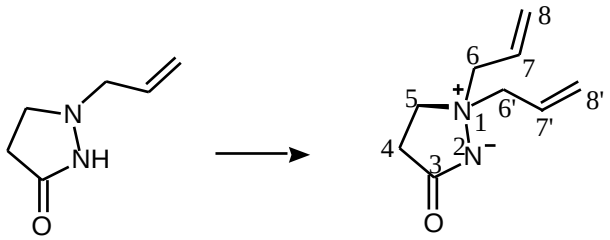
MS (EI, 70 eV):

m/z (%): 126 (90) $[M]^{+\bullet}$, 85 (100) $[M\text{-allyl}]^+$, 57 (20) $[C_3H_5O]^+$.

HRMS (EI) calcd. for $C_6H_{10}N_2O$:

126.079313; found: 126.078764

2.3 Synthesis of 1,1-diallyl-3-oxopyrazolidinium ylide 94



Procedure:

To a suspension of 34.87 mg (871.9 µmoles; 1.1 equiv) of sodium hydride (60% dispersion in mineral oil) in 1 mL of THF was added a solution of **93** (100 mg; 792.6 µmoles; 1 equiv) in 2 mL of THF at 0°C. The mixture was stirred for 30 min prior to the addition of allyl bromide (82.31 µl; 951.1 µmoles; 1.2 equiv). The reaction was allowed to warm to rt (around 2 h) and then quenched with H_2O. The aqueous layer was washed with DCM (2X), separated and evaporated.

Purification: recrystallization from DCM-EtOH

Yield: quantitative

Mol. formula: $C_9H_{14}N_2O$

FW: 166.22

Physique aspect: viscous oil

^{1}H NMR (200MHz, DMSO, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
7 + 7'	5.962, 5.956	ddt	$^3J_{7\text{-}8a(trans)}$=17.0 $^3J_{7\text{-}8b(cis)}$=10.0, $^3J_{7\text{-}6}$=6.9	2
8a + 8'a	5.52	d	$^3J_{8a\text{-}7(trans)}$=17.2	2
8b + 8'b	5.48	d	$^3J_{8b\text{-}7(cis)}$=9.6	2
6 + 6'	3.82	d	$^3J_{6\text{-}7}$=6.9	4
5	3.57	t	$^3J_{5\text{-}4}$=8.9	2
4	2.36	t	$^3J_{4\text{-}5}$=8.6	2

^{13}C NMR (50MHz, DMSO, 20°C)

δ = 177.6 (C_3), 128.1 (C_7, $C_{7'}$), 125.1 (C_8, $C_{8'}$), 67.5 (C_6, $C_{6'}$), 57.4 (C_5), 32.9 (C_4).

IR (KBr, cm^{-1}): 3034 (unsat. CH), 2983, 2932 (sat. CH), 1576 (C=O).

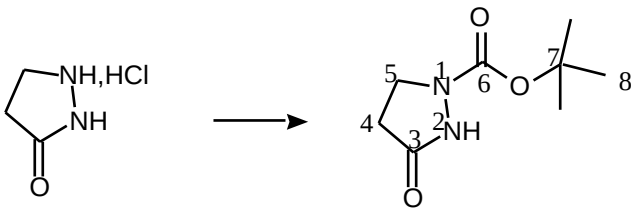
MS (CI, CH_4/N_2O):

m/z (%): +c: 167 (28) $[M+1]^+$, 125 (41) [M-allyl]$^+$, 85 (100) [M+1-2(allyl)]$^+$.

HRMS (CI) calcd for $C_9H_{14}N_2O$:

166.110613; found: 166.110339

2.4 Synthesis of 1-*tert*butyloxycarbonyl pyrazolidin-3-one 98



Reference:

Kemp, D. S.; Carey, R. I. *J. Org. Chem.* **1989**, *54(15)*, 3640-3646

Procedure:

To a suspension of 2 g (16.31 mmoles; 1 equiv) of pyrazolidinone hydrochloride and 4.63 g (21.21 mmoles; 1.3 equiv) of di-*t*-butyl dicarbonate in dry CH_2Cl_2 (30 mL) was added 3.13 mL (17.95 mmoles; 1.1 equiv) of *n,n*-diisopropylethylamine at 0°C. Then the suspension was allowed to stir at rt for 3 h. The reaction mixture was washed with water. Then the aqueous layer was back extracted with DCM. Evaporated the organic layer to give a yellow oil.

TLC: Rf = 0.3 (DCM/MeOH 95/5, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (DCM/MeOH 95/5)

Yield: 2.8 g (92%)

Mol. formula: $C_8H_{14}N_2O_3$

FW: 186.21

Physique aspect: white solid

Melting point: 101-103°C

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
5	3.95	t	$^3J_{5\text{-}4}$ = 8.4	2
4	2.56	t	$^3J_{4\text{-}5}$ = 8.4	2
8	1.50	s		9

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 171.4 (C_3), 154.2 (C_6), 83.0 (C_7), 45.3 (C_5), 31.7 (C_4), 28.9 (C_8).

IR (KBr, cm^{-1}): 3207 (NH), 2979 (sat. CH), 1684 (C=O).

MS (CI, CH_4/N_2O):

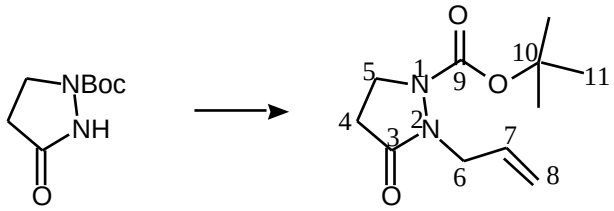
m/z (%): +c: 187 (4) $[M+1]^+$, 159 (12) $[M+1\text{-}CO]^+$, 131(100) $[M+2\text{-}CMe_3]^+$;

-c: 185 (100) $[M-1]^+$, 153 (35) $[M\text{-}3\text{-}2Me]^+$, 129 (15) $[M\text{-}CMe_3]^+$, 84 (25) [M-1-Boc] .

Elemental analysis calcd for $C_8H_{14}N_2O_3$:

C 51.60, H 7.58, N 15.04; found: C 51.55, H 7.63, N 15.00

2.5 Synthesis of 1-*tert*butyloxycarbonyl-2-allyl-pyrazolidin-3-one 100



Procedure:

To a cold (0°C), magnetically stirred suspension of NaH (60% dispersion in mineral oil, 95.4 mg; 2.384 mmoles; 1 equiv) in DMF (2 mL) under argon was added 444 mg (2.384 mmoles; 1 equiv) of **98** dissolved in DMF (2 mL) over 5 min. The cold mixture was stirred for 30 min, 226.9 µL (2.622 mmoles; 1.1 equiv) of allyl bromide was added and stirring was continued for 1.5 h allowing the cooling bath to warm to room temperature. Water was added to quench the reaction, then the mixture was extracted with EtOAc (3X15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo.

TLC: Rf = 0.4 (EtOAc/hexane 3/2, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 3/2)

Yield: 0.49 g (91%)

Mol. formula: $C_{11}H_{18}N_2O_3$

FW: 226.27

Physique aspect: white solid

Melting point: 58-60°C

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
7	5.78	ddt	$^3J_{7\text{-}8a(trans)}$=17.2	1
			$^3J_{7\text{-}8b(cis)}$=10.2, $^3J_{7\text{-}6}$=6.9	
8a	5.27	dm	$^3J_{8a\text{-}7(trans)}$=17.2	1
8b	5.25	dm	$^3J_{8b\text{-}7(cis)}$=10.2	1
6	4.31	d	$^3J_{6\text{-}7}$=6.3	2
5	3.97	t	$^3J_{5\text{-}4}$=7.8	2
4	2.57	t	$^3J_{4\text{-}5}$=7.8	2
11	1.51	s		9

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

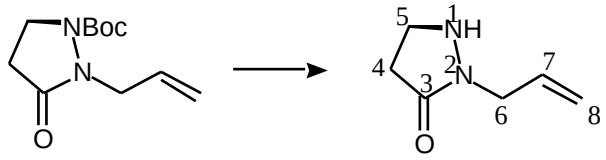
δ = 172.2 (C_3), 157.3 (C_9), 132.3 (C_7), 119.7 (C_8), 83.4 (C_{10}), 48.6 (C_6), 48.2 (C_5), 31.9 (C_4), 28.8 (C_{11}).

IR (KBr, cm^{-1}): 3083 (unsat. CH), 2979, 2935 (sat. CH), 1707 (C=O), 1395, 1157.

MS (EI, 70 eV): m/z (%): 226 (100) [M]$^{+\bullet}$

Elemental analysis calcd for $C_{11}H_{18}N_2O_3$:
C 58.39, H 8.02, N 12.38; found: C 58.38, H 8.13, N 12.45

2.6 Synthesis of 2-allyl pyrazolidin-3-one 99

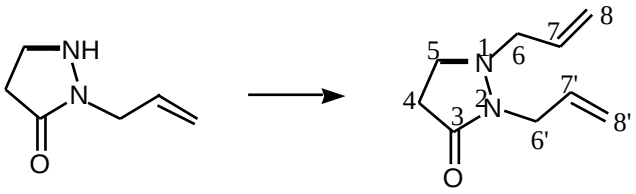


Procedure:
A solution of **100** (64 mg, 282.8 µmoles; 1 equiv) in 5 mL of TFA and 2.5 mL of DCM was stirred at rt for 30 min. The reaction mixture was concentrated. Then about 20 mL of DCM was added, the solution was washed with sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated. (^{1}H NMR: crude is pure enough for the next step.)
Yield: 0.032 g (90%)
Mol. formula: $C_6H_{10}N_2O$
FW: 126.15
Physique aspect: pale yellow oil
^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
7	5.78	ddt	$^3J_{7\text{-}8a(trans)}$=17.3	1
			$^3J_{7\text{-}8b(cis)}$=10.1, $^3J_{7\text{-}6}$=6.3	
8b	5.29	dm	$^3J_{8b\text{-}7(cis)}$=10.1	1
8a	5.27	dm	$^3J_{8a\text{-}7(trans)}$=17.3	1
NH	5.26	br. s		1
6	4.06	d	$^3J_{6\text{-}7}$=6.2	2
5	3.42	t	$^3J_{5\text{-}4}$=7.8	2
4	2.60	t	$^3J_{4\text{-}5}$=7.8	2

^{13}C NMR (50MHz, $CDCl_3$, 20°C)
δ = 172.5 (C_3), 132.4 (C_7), 118.9 (C_8), 47.0 (C_6), 44.2 (C_5), 33.6 (C_4).
IR (film, cm^{-1}): 3427 (NH), 3216 (unsat. CH), 2986 (sat. CH), 1667 (C=O), 1408.
MS (EI, 70 eV): m/z (%): 126 (45) [M]$^{+\bullet}$, 85 (76) [M-allyl]$^+$, 55 (100) $[C_3H_3O]^+$.
HRMS (EI) calcd for $C_6H_{10}N_2O$:
126.079313; found: 126.079367

2.7 Synthesis of 1, 2-diallylpyrazolidin-3-one 92



Procedure:

234 mg (1.694 mmoles; 3 equiv) of potassium carbonate was added to 75 mg (564.7 µmoles; 1 equiv) of **99** in 2 mL of acetone at rt. The mixture was stirred for 5 min, prior to the addition of 97.74 µl (1.129 mmoles; 2 equiv) of allyl bromide. The mixture was refluxed for 24 h, then the reaction mixture was filtered to remove excess K_2CO_3. The filtrate was dried ($MgSO_4$) and evaporated to dryness.

TLC: Rf = 0.2 (EtOAc/hexane 9/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 9/1)

Yield: 0.075 g (80%)

Mol. formula: $C_9H_{14}N_2O$

FW: 166.22

Physique aspect: colorless oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
7 + 7'	5.98-5.72	m		2
8 + 8'	5.34-5.19	m		4
6'	4.05	br. s		2
6	3.40	d	$^3J_{6\text{-}7}$ = 6.2	2
5	3.30	t	$^3J_{5\text{-}4}$ = 8.0	2
4	2.54	br. s		2

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 172.4 (C_3), 133.5, 133.3 (C_7, $C_{7'}$), 120.5, 118.5 (C_8, $C_{8'}$), 59.3 (C_6), 49.3 (C_5), 46.1 ($C_{6'}$), 30.4 (C_4).

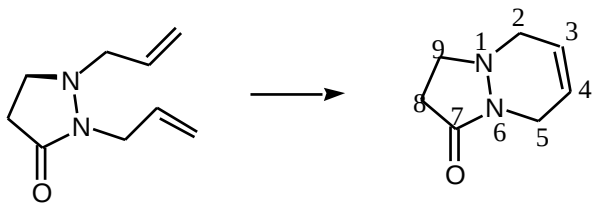
IR (film, cm^{-1}): 3083 (unsat. CH), 2924, 2853 (sat. CH), 2360, 2342 (C-N), 1685 (C=O).

MS (EI, 70 eV): m/z (%): 166 (22) [M]$^{+\bullet}$, 125 (100) [M-allyl]$^+$, 55 (33) $[C_3H_3O]^+$.

HRMS (EI) calcd. for $C_9H_{14}N_2O$:

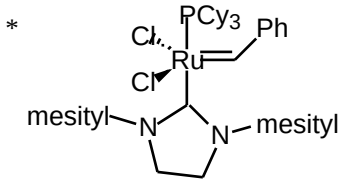
166.110613; found: 166.111229

2.8 Synthesis of 1,6-diazabicyclo[4.3.0]non-3-en-7-one 117



Procedure:

20 mg of cat.* (6 mol%) was added to a solution of 65 mg (391 µmoles; 1 equiv) of *N*,*N*-diallylpyrazolidin-3-one in 2 mL of toluene. The resulting mixture was heated at 50°C for 2 h. The solvent was removed under reduced pressure.



TLC: Rf = 0.2 (DCM/MeOH 95/5, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (DCM/MeOH 95/5)

Yield: 0.05 g (92%)

Mol. formula: $C_7H_{10}N_2O$

FW: 138.01

Physique aspect: pale black oil

^{1}H NMR (500MHz, $CDCl_3$, 52°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3 + 4	5.82-5.72	m		2
5	4.02	br. s		2
9	3.31	br. s		2
2	3.25	br. s		2
8	2.55	br. s		2

^{13}C NMR (125MHz, $CDCl_3$, 52°C)

δ = 170.5 (C_7), 123.3 (C_4), 122.4 (C_3), 54.3 (C_2), 50.1 (C_9), 41.9 (C_5), 29.6 (C_8).

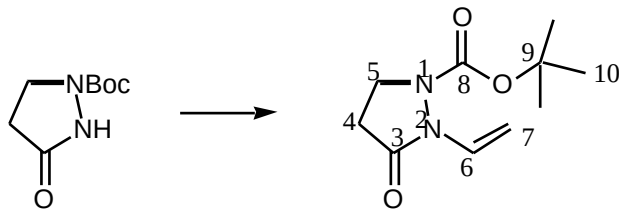
IR (film, cm^{-1}): 3083 (unsat. CH), 2935, 2847 (sat. CH), 1684 (C=O), 1437.

MS (EI, 70 eV): m/z (%): 138 (100) [M] $^{+\bullet}$

HRMS (EI) calcd. for $C_7H_{10}N_2O$:

138.079313, found: 138.078652

2.9 Synthesis of 1-(*tert*-butyloxycarbonyl)-2-vinyl-pyrazolidin-3-one 102



Reference:

Baret, N.; Dulcere, J. P.; Rodriguez, J.; Pons J-M.; Faure, R. *Eur. J. Org. Chem.* **2000**, 1507-1516

Procedure:

To a stirred solution of 717 mg (3.85 mmoles; 1 equiv) of **98** in 21.75 mL of vinyl acetate under argon was added 11.3 mg (38.5 µmoles; 0.01 equiv) of sodium tetrachloropalladate(II) and the mixture was heated under reflux for 20 h. The solvent was removed in vacuo.

TLC: Rf = 0.34 (EtOAc/hexane 2/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 2/3)

Yield: 0.5 g (62%)

Mol. formula: $C_{10}H_{16}N_2O_3$

FW: 212.24

Physique aspect: pale yellow oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
6	6.91	dd	$^3J_{6\text{-}7a(trans)}$ =15.3, $^3J_{6\text{-}7b(cis)}$ =	1
7a	4.61	d	9.3	1
7b	4.54	d	$^3J_{7a\text{-}6(trans)}$ =15.3	1
5	4.04	t	$^3J_{7b\text{-}6(cis)}$ = 9.3	2
4	2.63	t	$^3J_{5\text{-}4}$ = 7.2	2
10	1.49	s	$^3J_{4\text{-}5}$ = 7.5	9

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 170.8 (C_3), 156.5 (C_8), 127.6 (C_6), 95.5 (C_7), 84.0 (C_9), 48.5 (C_5), 32.4 (C_4), 28.6 (C_{10}).

IR (film, cm^{-1}): 2979, 2935 (sat. CH), 1733 (C=O), 1291, 1156.

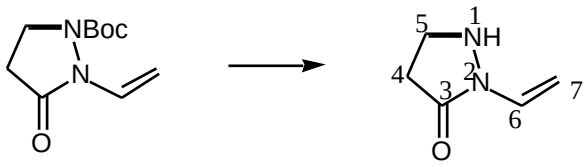
MS (EI, 70 eV):

m/z (%), +c: 212 (12) [M]$^{+\bullet}$, 156 (6) [M-*t*Bu+1]$^{+\bullet}$, 112 (16) [M-Boc+1]$^{+\bullet}$, 57 (100) [*t*Bu]$^+$.

HRMS (EI) calcd. for $C_{10}H_{16}N_2O_3$:

212.116093, found: 212.115248

2.10 Synthesis of 2-vinyl-pyrazolidin-3-one 107



Reference:

Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55(3)*, 870-876

Procedure:

To a stirred solution of **102** (860 mg; 4.051 mmoles; 1 equiv) and 2,6-lutidine (943.8 mL; 8.103 mmoles; 2 equiv) in 12 mL of dry CH_2Cl_2 at 0°C was added dropwise TMSOTf (1.174 mL; 6.077 mmoles; 1.5 equiv). The reaction mixture was sirred at rt for 30 min, then quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (3X). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo.

TLC: Rf = 0.20 (EtOAc/hexane 9/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 9/1)

Yield: 0.418 g (92%)

Mol. formula: $C_5H_8N_2O$

FW: 112.34

Physique aspect: colorless oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
6	6.94	dd	$^3J_{6\text{-}7a(trans)}$ =15.6, $^3J_{6\text{-}7b(cis)}$ =	1
7a	4.72	d	9.0	1
NH	4.67	t	$^3J_{7a\text{-}6(trans)}$ =15.6	1
7b	4.47	d	$^3J_{NH\text{-}5}$ = 7.9	1
5	3.45	q	$^3J_{7b\text{-}6(cis)}$ = 9.0	2
4	2.62	t	$^3J_{5\text{-}4}$ = $^3J_{5\text{-}NH}$ = 7.9	2
			$^3J_{4\text{-}5}$ = 7.8	

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 170.1 (C_3), 126.5 (C_6), 94.0 (C_7), 42.8 (C_5), 33.1 (C_4).

IR (film, cm^{-1}): 3466 (NH), 3088 (unsat. CH), 2989, 2947, 2897 (sat. CH), 1716 (C=O), 1635 (CH=CH_2), 1350, 1049, 857.

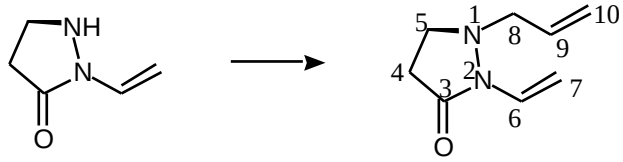
MS (CI/CH_4-N_2O):

m/z (%), +c: 113 (100) $[M+1]^+$, 85 (3) $[M\text{-}CHCH_2]^+$, 71 (87) $[M+1\text{-}NCHCH_2]^{\bullet\bullet}$.

HRMS (CI) calcd. for $C_5H_9N_2O$:

113.071488; found: 113.071219

2.11 Synthesis of 1-allyl-2-vinyl-pyrazolidin-3-one 101a



Reference:

Oda, K.; Nakano, T.; Morimoto, H.; Takamura, N. *Heterocycles* **1996**, *42*, 577-588

Procedure:

To a solution of **107** (90 mg; 802.6 mmoles; 1 equiv) and allyl bromide (83.34 mL; 963.1 mmoles; 1.2 equiv) in DMF (2 mL) was added sodium iodide (144.3 mg; 963.1 mmoles; 1.2 equiv) and sodium bicarbonate (80.9 mg; 963.1 mmoles; 1.2 equiv) at 0°C. After stirring at rt overnight, the mixture was diluted with water (10 mL) and extracted (AcOEt, 2X20 mL). The extracts were dried ($MgSO_4$), filtered and evaporated.

TLC: Rf = 0.25 (EtOAc/hexane 1/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 1/1)

Yield: 0.11 g (90%)

Mol. formula: $C_8H_{12}N_2O$

FW: 152.19

Physique aspect: colorless oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
6	6.85	dd	$^3J_{6\text{-}7a(trans)}$ =15.7, $^3J_{6\text{-}7b(cis)}$ =	1
9	5.89	ddt	9.1	1
			$^3J_{9\text{-}10a(trans)}$ =16.9	
10a	5.34	dm	$^3J_{9\text{-}10b(cis)}$ = 10.6, $^3J_{9\text{-}8}$ = 6.3	1
10b	5.26	dm	$^3J_{10a\text{-}9(trans)}$ =16.9	1
7a	4.71	d	$^3J_{10b\text{-}9(cis)}$ = 10.6	1
7b	4.51	d	$^3J_{7a\text{-}6(trans)}$ =15.7	1
5 + 8	3.65-3.18	m	$^3J_{7b\text{-}6(cis)}$ = 9.1	4
4a	2.88	br. s		1
4b	2.40	br. s		1

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 170.2 (C_3), 132.7 (C_9), 124.9 (C_6), 119.6 (C_{10}), 94.6 (C_7), 55.9 (C_8), 47.1 (C_5), 29.5 (C_4).

IR (film, cm^{-1}): 3079 (unsat. CH), 2985, 2942, 2894, 2844 (sat. CH), 1716 (C=O), 1633 ($CH=CH_2$), 1416, 1312.

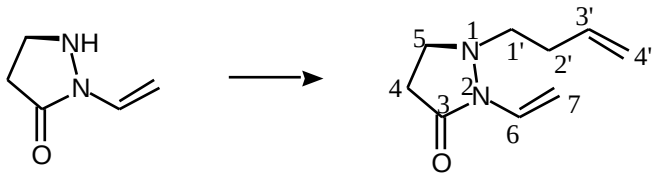
MS (CI/CH_4-N_2O):

m/z (%), +c: 153 (24) $[M+1]^+$, 125 (16) $[M\text{-vinyl}]^+$, 111 (46) $[M\text{-allyl}]^+$, 99 (100) $[M+1\text{-}2(\text{vinyl})]^+$.

HRMS (CI) calcd. for $C_8H_{12}N_2O$:

152.094963; found: 152.095172

2.12 Synthesis of 1-(but-3'-enyl)-2-vinyl-pyrazolidin-3-one 101b



Reference:

Oda, K.; Nakano, T.; Morimoto, H.; Takamura, N. *Heterocycles* **1996**, *42*, 577-588

Procedure:

To a solution of **107** (100 mg; 891.8 µmoles; 1 equiv) and 4-bromo-1-butene (108.6 µL; 144.4 mg; 1.07 mmoles; 1.2 equiv) in DMF (2 mL) was added sodium iodide (43.74 µL; 160.4 mg; 1.07 mmoles; 1.2 equiv) and sodium bicarbonate (41.64 µL; 89.9 mg; 1.07 mmoles; 1.2 equiv) at 0°C. After stirring at rt overnight, **107** was recovered. The reaction was then heated at 80°C for 8 h, diluted with water (10 mL) and extracted (AcOEt, 2X15 mL). The extracts were dried ($MgSO_4$), filtered and evaporated.

TLC: Rf = 0.32 (EtOAc/hexane 7/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 7/3)

Yield: 0.075 g (51%; recovered **107**: 0.028g, 28%)

Mol. formula: $C_9H_{14}N_2O$

FW: 166.22

Physique aspect: colorless oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
6	6.83	dd	$^3J_{6\text{-}7a(trans)}$ =15.7, $^3J_{6\text{-}7b(cis)}$ =	1
3'	5.85	ddt	9.1	1
			$^3J_{3'\text{-}4'a(trans)}$ =17.0	
4'a	5.12	dm	$^3J_{3'\text{-}4'b(cis)}$ = 10.1, $^3J_{3'\text{-}2'}$ = 6.8	1
4'b	5.08	dm	$^3J_{4'a\text{-}3'(trans)}$ =17.1	1
7a	4.70	d	$^3J_{4'b\text{-}3'(cis)}$ = 10.1	1
7b	4.49	d	$^3J_{7a\text{-}6(trans)}$ =16.0	1
5	3.35	br. s	$^3J_{7b\text{-}6(cis)}$ = 9.1	2
1'	2.85	br. s		2
4	2.32	br. s		2
2'	2.30	q		2
			$^3J_{2'\text{-}3'}$ = $^3J_{2'\text{-}1'}$ = 6.9	

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 170.1 (C_3), 134.9 ($C_{3'}$), 125.2 (C_6), 116.7 ($C_{4'}$), 94.7 (C_7), 52.8 ($C_{1'}$), 47.7 (C_5), 31.9 ($C_{2'}$), 29.3 (C_4).

IR (film, cm^{-1}): 3078 (unsat. CH), 2979, 2955, 2930, 2849 (sat. CH), 1713 (C=O), 1633 ($CH=CH_2$), 1415, 1313.

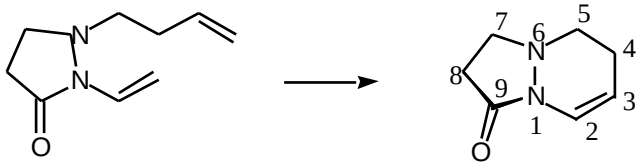
MS (CI/CH_4-N_2O):

m/z (%), +c: 167 (72) $[M+1]^+$, 139 (9) [M-vinyl]$^+$, 125 (100) [M-ally]$^+$.

HRMS (CI) calcd. for $C_9H_{15}N_2O$:

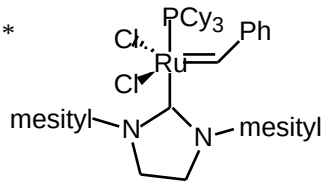
167.118438; found: 167.117658

2.13 Synthesis of 1,6-diazabicyclo[4.3.0]non-2-en-9-one 118b



Procedure:

25 mg of cat.* (10 mol%) was added to a solution of 50 mg (300 μmoles; 1 equiv) of **101b** in 4 mL of toluene. The resulting mixture was heated at 80°C for 16 h. Then another 25 mg of cat.* was added, the mixture was heated at 80°C for further 6 h. The solvent was removed under reduced pressure.



TLC: Rf = 0.13 (EtOAc/cyclohexane/*i*PrOH 8/1/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane/*i*PrOH 8/1/1)

Yield: 0.03 g (72%)

Mol. formula: $C_7H_{10}N_2O$

FW: 138.16

Physique aspect: pale black oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
2	6.83	d	$^3J_{2\text{-}3}$=8.1	1
3	5.14	dt	$^3J_{3\text{-}2}$=8.1, $^3J_{3\text{-}4}$=3.9	1
5	3.19	br. s		2
7	2.98	br. s		2
8	2.61	t	$^3J_{8\text{-}7}$=7.8	2
4	2.34	br. s		2

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 164.5 (C_9), 119.4 (C_2), 106.2 (C_3), 53.0 (C_7), 51.9 (C_5), 31.0 (C_8), 23.7 (C_4).

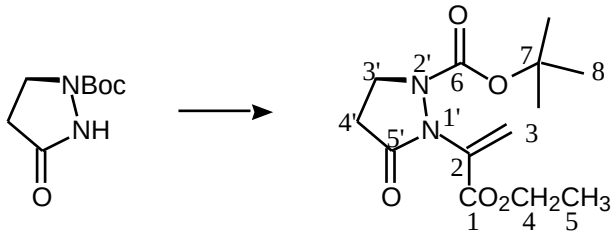
IR (film, cm^{-1}): 3086 (unsat. CH), 2926, 2852 (sat. CH), 1699 (C=O), 1647 (C=C), 1414.

MS (CI/CH_4-N_2O): m/z (%): +c: 139 (100) $[M+1]^+$; -c: 137 (100) $[M-1]^+$.

HRMS (CI) calcd. for $C_7H_{11}N_2O$:

139.087138; found: 139.087340

2.14 Synthesis of ethyl 2-(2'-*tert*butyloxycarbonyl-5'-oxo-1'-pyrazolidinyl)-propenoate 114



Reference:

Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119(32)*, 7595-7596

Procedure:

To a solution of **98** (100 mg; 537 µmoles; 1 equiv), triphenylphosphine (14.1 mg; 53.7 µmoles; 0.1 equiv), and sodium acetate (22.1 mg; 268.5 µmoles; 0.5 equiv) in 2 mL of toluene at 105°C were added sequentially acetic acid (15.4 µL; 268.5 µmoles; 0.5 equiv) and ethyl propiolate (54.4 µL; 537 µmoles; 1 equiv). After 18 h, the cooled reaction mixture was directly chromatographed on silica gel.

TLC: Rf = 0.40 (EtOAc/hexane 1/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 1/1)

Yield: 0.122 g (80%)

Mol. formula: $C_{13}H_{20}N_2O_5$

FW: 284.31

Physique aspect: pale yellow oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3a	6.33	s		1
3b	5.95	s		1
4	4.25	q	$^3J_{4\text{-}5}$ = 7.3	2
3'	4.15	t	$^3J_{3'\text{-}4'}$ = 7.6	2
4'	2.68	t	$^3J_{4'\text{-}3'}$ = 7.6	2
8	1.47	s		9
5	1.32	t	$^3J_{5\text{-}4}$ = 7.3	3

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 173.8 ($C_{5'}$), 163.1 (C_1), 157.2 (C_6), 135.7 (C_2), 125.0 (C_3), 83.5 (C_7), 62.3 (C_4), 47.7 ($C_{3'}$), 31.7 ($C_{4'}$), 28.6 (C_8), 14.6 (C_5).

IR (film, cm^{-1}): 2980, 2935 (sat. CH), 1723 (C=O), 1369, 1157.

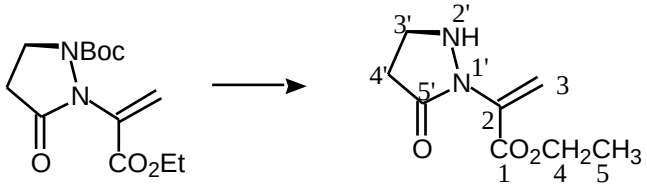
MS (EI, 70 eV):

m/z (%), +c: 284 (12) [M]$^{+\bullet}$, 211 (15) [M-O*t*Bu]$^+$, 184 (100) [M-Boc+1]$^{+\bullet}$, 138 (25) [M-Boc-OEt]$^{+\bullet}$, 109 (12) [M-Boc-CO_2Et]$^+$, 57 (100) [*t*Bu]$^+$.

HRMS (EI) calcd. for $C_{13}H_{20}N_2O_5$:

284.137222, found: 284.135667

2.15 Synthesis of ethyl 2-(5'-oxo-1'-pyrazolidinyl)propenoate 116



Procedure:

A solution of **114** (471 mg; 1.656 mmoles; 1 equiv) in 10 mL of trifluoroacetic acid and 10 mL of dichloromethane was stirred at rt for 30 min. The reaction mixture was evaporated to remove excess TFA. The residue was diluted with 30 mL of DCM, then the organic layer was washed with sat. $NaHCO_3$, dried over $MgSO_4$ and evaporated.

TLC: Rf = 0.18 (EtOAc/hexane 9/1, UV, $KMnO_4$)

Yield: 0.274 g (90%)

Mol. formula: $C_8H_{12}N_2O_3$

FW: 184.19

Physique aspect: pale yellow oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3a	6.10	s		1
3b	6.85	s		1
4	4.27	q	$^3J_{4\text{-}5}$ = 7.1	2
3'	3.46	t	$^3J_{3'\text{-}4'}$ = 7.6	2
4'	2.67	t	$^3J_{4'\text{-}3'}$ = 7.6	2
5	1.33	t	$^3J_{5\text{-}4}$ = 7.1	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

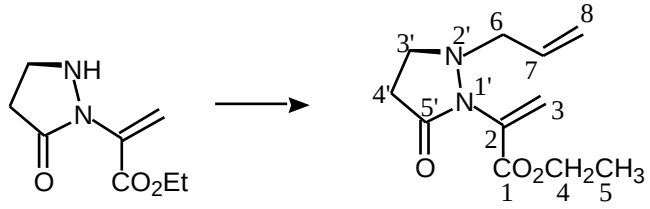
δ = 173.0 ($C_{5'}$), 163.5 (C_1), 134.7 (C_2), 118.4 (C_3), 62.2 (C_4), 44.5 ($C_{3'}$), 30.0 ($C_{4'}$), 14.6 (C_5).

IR (film, cm^{-1}): 3227 (NH), 2983, 2932 (sat. CH), 1731 (C=O), 1210.

MS (EI, 70 eV):

m/z (%), +c: 185 (7) $[M+1]^+$, 148 (100), 111 (23) $[M\text{-}CO_2Et]^+$, 99 (35) $[CH_2CCO_2Et]^+$, 70 (50) $[CH_2CCO_2]^{+\bullet}$, 56 (91) $[CH_2CH_2N_2]^{+\bullet}$, 44 (95) $[CO_2]^{+\bullet}$.

2.16 Synthesis of ethyl 2-(2'-allyl-5'-oxo-1'-pyrazolidinyl)-2-propenoate 113a



Procedure:

Potassium carbonate (90.0 mg; 651.4 µmoles; 3 equiv) was added to a solution of **116** (50 mg; 217.1 µmoles; 1 equiv) in 2 mL of acetone at rt, then allyl bromide (37.58 µL; 434.3

µmoles; 2 equiv) was added. The resulting mixture was allowed to stir for 24 h under reflux. The reaction mixture was filtered to remove excess K_2CO_3 and evaporated to dryness.

TLC: Rf = 0.17 (EtOAc/hexane 1/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 3/2)

Yield: 0.024 g (50%, non- optimized)

Mol. formula: $C_{11}H_{16}N_2O_3$

FW: 224.25

Physique aspect: pale yellow oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3a	6.04	s		1
3b	5.68	s		1
7	5.89	ddt	$^3J_{7\text{-}8a(trans)}$=17.3, $^3J_{7\text{-}8b(cis)}$=10.1 $^3J_{7\text{-}6}$=6.5	1
8a	5.28	dm	$^3J_{8a\text{-}7(trans)}$=17.2	1
8b	5.24	dm	$^3J_{8b\text{-}7(cis)}$=10.0	1
4	4.27	q	$^3J_{4\text{-}5}$ = 7.0	2
3' + 6	3.42	apparent d	^3J = 6.5	4
4'	2.65	br. s		2
5	1.32	t	$^3J_{5\text{-}4}$ = 7.2	3

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 172.9 ($C_{5'}$), 164.0 (C_1), 134.9 (C_2), 133.6 (C_7), 120.6 (C_8), 120.3 (C_3), 62.3 (C_4), 59.4 (C_6), 49.1 ($C_{3'}$), 30.4 ($C_{4'}$), 14.7 (C_5).

IR (film, cm^{-1}): 3070 (unsat. CH), 2990, 2930 (sat. CH), 1733, 1716 (C=O), 1314, 1199.

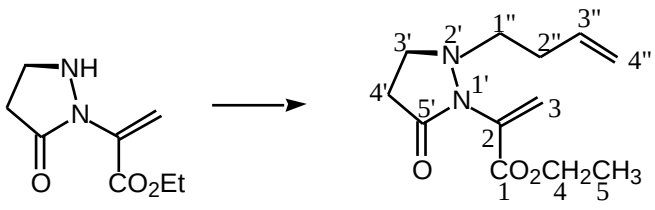
MS (EI, 70 eV):

m/z (%): 224 (85) [M] $^{+\bullet}$, 183 (73) [M-allyl]$^+$, 137 (96) [M-allyl-OEt-1]$^+$, 109 (100) [M-allyl-CO_2Et-1]$^+$.

HRMS (EI) calcd. for $C_{11}H_{16}N_2O_3$:

224.116093, found: 224.116689

2.17 Synthesis of ethyl 2-(2'-(but-3"-enyl)-5'-oxo-1'-pyrazolidinyl)-2-propenoate 113b



Procedure:

To a solution of **116** (220 mg; 1.194 mmoles; 1 equiv) and 4-bromo-1-butene (149.9 µL; 1.433 mmoles; 1.2 equiv) in DMF (5 mL) was added sodium iodide (219.2 mg; 1.433 mmoles; 1.2 equiv) and sodium bicarbonate (122.8 mg; 1.433 mmoles; 1.2 equiv) at 0°C. After stirring at 50°C overnight, the mixture was diluted with water (10 mL) and extracted (AcOEt, 20 mL). The extract was washed (brine), dried ($MgSO_4$) and filtered. The filtrate was evaporated.

TLC: Rf = 0.26 (EtOAc/cyclohexane 3/2, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 3/2)

Yield: 0.15 g (53%, non- optimized)

Mol. formula: $C_{12}H_{18}N_2O_3$

FW: 238.28

Physique aspect: pale yellow oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3a	5.99	s		1
3b	5.67	s		1
3"	5.89	ddt	$^3J_{3"\text{-}4"a(trans)}$=17.0, $^3J_{3"\text{-}4"b(cis)}$=10.2 $^3J_{3"\text{-}2"}$=6.7	1
4"a	5.06	dm	$^3J_{4"a\text{-}3"(trans)}$=17.0	1
4b	5.03	dm	$^3J_{4"b\text{-}3"(cis)}$=10.2	1
4	4.27	q	$^3J_{4\text{-}5}$ = 7.0	2
3'	3.44	t	$^3J_{3'\text{-}4'}$ = 7.3	2
1"	2.89	t	$^3J_{1"\text{-}2"}$ = 7.1	2
4'	2.68	t	$^3J_{4'\text{-}3'}$ = 7.5	2
2"	2.25	q	$^3J_{2"\text{-}1"}$ = 6.9, $^3J_{2"\text{-}3"}$ = 6.7	2
5	1.31	t	$^3J_{5\text{-}4}$ = 7.1	3

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 172.3 ($C_{5'}$), 163.4 (C_1), 135.2 ($C_{3"}$), 134.7 (C_2), 118.3 (C_3), 116.5 ($C_{4"}$), 61.6 (C_4), 55.9 ($C_{1"}$), 49.5 ($C_{3'}$), 31.6 ($C_{4'}$), 29.6 ($C_{2"}$), 14.0 (C_5).

IR (film, cm^{-1}): 3078 (unsat. CH), 2976, 2928, 2851 (sat. CH), 1734, 1707 (C=O), 1260.

MS (CI/CH_4-N_2O)):

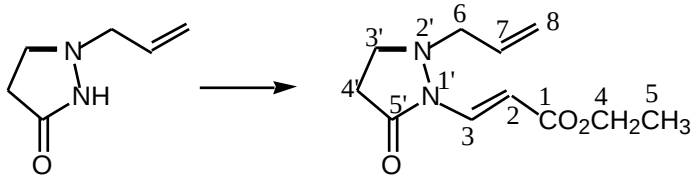
m/z (%), +c: 239 (100) $[M+1]^+$, 197 (30) $[M\text{-}CH_2CHCH_2]^+$, 193 (6) $[M\text{-}OEt]^+$, 123 (6) $[M\text{-}CHCH_2\text{-}CH_2CCO_2Et+1]^+$;

-c: 238 (100) $[M]^{+\bullet}$, 197 (14) $[M\text{-}CH_2CHCH_2]^+$.

HRMS (EI) calcd. for $C_{12}H_{19}N_2O_3$:

239.139568, found: 239.138989

2.18 Synthesis of ethyl (2*E*)-3-(2'-allyl-5'-oxo-1'-pyrazolidinyl)-2-propenoate 115



Reference:

Trost, B.M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119(32)*, 7595-7596

Procedure: see Section 2.14

1*N*-(allyl)pyrazolidin-3-one: 150 mg; 1.188 mmoles; 1 equiv

Triphenylphosphine: 31.2 mg; 118.8 µmoles; 0.1 equiv

Sodium acetate: 48.8 mg; 594.4 µmoles; 0.5 equiv

Acetic acid: 34.03 µL; 594.4 µmoles; 0.5 equiv

Ethyl propiolate: 120.4 µL; 1.188 mmoles; 1 equiv

2 mL of toluene, 105°C, 18 h.

TLC: Rf = 0.24 (EtOAc/cyclohexane 3/2, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 3/2)

Yield: 0.14 g (52%)

Mol. formula: $C_{11}H_{16}N_2O_3$

FW: 224.25

Physique aspect: pale yellow oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3	7.44	d	$^3J_{3\text{-}2}$=12.9	1
7	5.77	ddt	$^3J_{7\text{-}8a(trans)}$=17.4, $^3J_{7\text{-}8b(cis)}$=10.5 $^3J_{7\text{-}6}$=5.7	1
8b	5.30	dm	$^3J_{8b\text{-}7(cis)}$=10.5	1
8a	5.28	dm	$^3J_{8a\text{-}7(trans)}$=17.4	1
2	4.96	d	$^3J_{2\text{-}3}$=13.2	1
4 + 6	4.16	m		4
3'	3.77	t	$^3J_{3'\text{-}4'}$ = 8.1	2
4'	2.67	t	$^3J_{4'\text{-}3'}$ = 8.4	2
5	1.28	t	$^3J_{5\text{-}4}$ = 6.6	3

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 172.0 ($C_{5'}$), 168.2 (C_1), 148.5 (C_3), 131.4 (C_7), 120.1 (C_8), 94.7 (C_2), 60.4 (C_5), 51.3 ($C_{3'}$), 47.1 (C_6), 31.5 ($C_{4'}$), 15.1 (C_5).

IR (film, cm^{-1}): 3084 (unsat. CH), 2981, 2935, 2902 (sat. CH), 1700, 1617 (C=O), 1252, 1147.

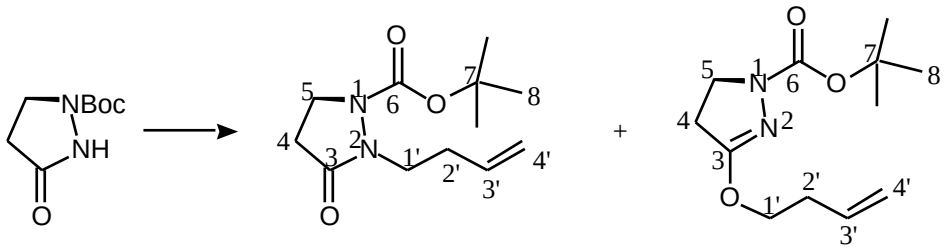
MS (CI/CH_4-N_2O):

m/z (%): 224 (12) $[M]^{+\bullet}$, 179 (5) $[M\text{-}OEt]^+$, 100 (16) $[CHCHCO_2Et+1]^{+\bullet}$, 85 (21) $[CH_2CH_2CON_2+1]^+$, 59 (100) $[CO_2CH_2+1]^+$.

HRMS (CI) calcd. for $C_{11}H_{17}N_2O_3$:

225.123918, found: 225.123445

2.19 Synthesis of 1-(*tert*-butyloxycarbonyl)-2-(but-3'-enyl)-pyrazolidin-3-one 109 and 1-(*tert*-butyloxycarbonyl)-3-((but-3'-enyl)hydroxy)-1,2-diazolid-2-ene 110



Procedure:

To a cold (0°C), magnetically stirred suspension of NaH (60% dispersion in mineral oil, 214.7 mg; 5.37 mmoles; 1 equiv) in DMF (6 mL) under argon was added a solution of **98** (1 g; 5.37 mmoles; 1 equiv) dissolved in DMF (4 mL). The flask was washed with two-portion of 1 mL of DMF. The cold mixture was stirred for 30 min, 599.6 µL (5.907 mmoles; 1.1 equiv) of 4-bromo-1-butene was added and the reaction was allowed to warm to rt. The solid-like reaction mixture was not soluble, the flask was then heated at 70°C around 40 min. Water was added to quench the reaction, then the mixture was extracted with EtOAc (3X). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo.

TLC: Rf = 0.24, **109**

Rf = 0.38, **110** (EtOAc/cyclohexane 2/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 2/3)

Yield: 0.95 g (74%, **109**); 0.13 g (10%, **110**)

Mol. formula: $C_{12}H_{20}N_2O_3$

FW: 240.30

Physique aspect: both are colorless oils

Compound **109:**

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3'	5.75	ddt	$^3J_{3'\text{-}4'\text{a}(trans)}$=17.0, $^3J_{3'\text{-}4'\text{b}(cis)}$=10.1 $^3J_{3'\text{-}2'}$=6.9	1
4'b	5.10	dm	$^3J_{4'\text{b}\text{-}3'(cis)}$=9.8	1
4'a	5.09	dm	$^3J_{4'\text{a}\text{-}3'(trans)}$=17.4	1
5	3.94	t	$^3J_{5\text{-}4}$ = 7.7	2
1'	3.81	t	$^3J_{1'\text{-}2'}$ = 6.7	2
4	2.54	t	$^3J_{4\text{-}5}$ = 7.7	2
2'	2.35	qt	$^3J_{2'\text{-}1'}$=$^3J_{2'\text{-}3'}$=6.7, $^3J_{2'\text{-}4'}$=1.2	2
8	1.51	s		9

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 172.3 (C_3), 157.5 (C_6), 135.7 ($C_{3'}$), 117.7 ($C_{4'}$), 83.2 (C_7), 47.8 ($C_{1'}$), 45.1 (C_5), 32.0 (C_4), 31.5 ($C_{2'}$), 28.8 (C_8).

IR (film, cm^{-1}): 3078 (unsat. CH), 2978, 2934, 2909 (sat. CH), 1731, 1694 (C=O), 1160.

MS (EI, 70 ev):

m/z (%), +c: 240 (15) $[M]^{+\bullet}$, 184 (22) $[M\text{-}t\text{Bu}+1]^{+\bullet}$, 143 (15) $[M\text{-}t\text{Bu-}CH_2CHCH_2+1]^+$, 140 (23) $[M\text{-Boc}+1]^{+\bullet}$, 99 (11) $[M\text{-Boc-}CH_2CHCH_2+1]^+$, 57 (100) $[t\text{Bu}]^+$, 55 (13) $[CH_2CH_2CHCH_2]^+$.

HRMS (EI) calcd. for $C_{12}H_{20}N_2O_3$:

240.147393, found: 240.147381

Compound **110:**

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3'	5.81	ddt	$^3J_{3'\text{-}4'\text{a}(trans)}$=17.1, $^3J_{3'\text{-}4'\text{b}(cis)}$=10.2 $^3J_{3'\text{-}2'}$=6.7	1
4'a	5.13	dm	$^3J_{4'\text{a}\text{-}3'(trans)}$=17.1	1
4'b	5.08	dm	$^3J_{4'\text{b}\text{-}3'(cis)}$=10.2	1
1'	4.29	t	$^3J_{1'\text{-}2'}$ = 6.7	2
5	3.89	t	$^3J_{5\text{-}4}$ = 9.8	2
4	2.83	t	$^3J_{4\text{-}5}$ = 9.7	2
2'	2.46	qt	$^3J_{2'\text{-}1'}$=$^3J_{2'\text{-}3'}$=6.7, $^3J_{2'\text{-}4'}$=1.4	2
8	1.51	s		9

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 165.0 (C_3), 153.3 (C_6), 134.6 ($C_{3'}$), 117.7 ($C_{4'}$), 81.0 (C_7), 69.4 ($C_{1'}$), 46.6 (C_5), 33.7 (C_4), 31.0 ($C_{2'}$), 29.1 (C_8).

IR (film, cm^{-1}): 3079 (unsat. CH), 2977, 2932 (sat. CH), 1687 (C=O), 1637 (C=N), 1434, 1123.

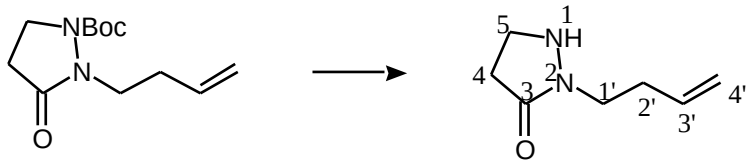
MS (EI, 70 ev):

m/z (%), +c: 240 (26) $[M]^{+\bullet}$, 184 (18) $[M\text{-}t\text{Bu}+1]^{+\bullet}$, 143 (15) $[M\text{-}t\text{Bu-}CH_2CHCH_2+1]^+$, 140 (15) $[M\text{-Boc}+1]^{+\bullet}$, 99 (22) $[M\text{-Boc-}CH_2CHCH_2+1]^+$, 85 (41) $[M\text{-Boc-}CH_2CH_2CHCH_2+1]^+$, 57 (100) $[t\text{Bu}]^+$, 55 (45) $[CH_2CH_2CHCH_2]^+$.

HRMS (EI) calcd. for $C_{12}H_{20}N_2O_3$:

240.147393, found: 240.147522

2.20 Synthesis of 2-(but-3'-enyl)-pyrazolidin-3-one 111



Procedure:

A solution of **109** (396 mg, 1.75 mmoles; 1 equiv) in 10 mL of TFA and 10 mL dichloromethane was stirred at rt for 30 min. The reaction mixture was evaporated. Then *ca.* 30 mL of CH_2Cl_2 was added to the residue, the organic layer was washed with sat. $NaHCO_3$. Back-extracted from aqueous layer by CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$) and concentrated.

TLC: Rf = 0.25 (DCM/MeOH 95/5, UV, $KMnO_4$)

Yield: 0.212 g (86%)

Mol. formula: $C_7H_{12}N_2O$

FW: 140.18

Physique aspect: pale yellow oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3'	5.80	ddt	$^3J_{3'\text{-}4'a(trans)}$=17.0, $^3J_{3'\text{-}4'b(cis)}$=10.1 $^3J_{3'\text{-}2'}$=6.8	1
4'a	5.12	dm	$^3J_{4'a\text{-}3'(trans)}$=17.1	1
4'b	5.05	dm	$^3J_{4'b\text{-}3'(cis)}$=10.1	1
NH	4.42	br. s		1
1'	3.52	t	$^3J_{1'\text{-}2'}$ = 6.8	2
5	3.35	t	$^3J_{5\text{-}4}$ = 7.7	2
4	2.53	t	$^3J_{4\text{-}5}$ = 7.7	2
2'	2.36	qt	$^3J_{2'\text{-}1'}$=$^3J_{2'\text{-}3'}$=6.8, $^3J_{2'\text{-}4'}$=1.0	2

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 172.9 (C_3), 135.9 ($C_{3'}$), 117.6 ($C_{4'}$), 44.7 ($C_{1'}$), 43.9 (C_5), 34.1 (C_4), 32.4 ($C_{2'}$).

IR (film, cm^{-1}): 3440 (NH), 3078 (unsat. CH), 2979, 2933 (sat. CH), 1684 (C=O), 1409.

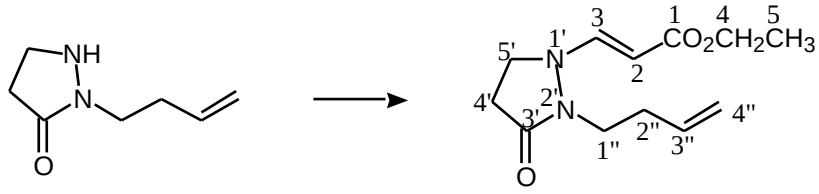
MS (EI, 70 ev):

m/z (%), +c: 140 (15) $[M]^{+\bullet}$, 99 (43) $[M\text{-}CH_2CHCH_2]^+$, 57 (100) $[CH_2CH_2CO+1]^+$, 55 (15) $[CH_2CH_2CHCH_2]^+$.

HRMS (EI) calcd. for $C_7H_{12}N_2O$:

140.094963, found: 140.094230

2.21 Synthesis of ethyl (2*E*)-3-(3'-oxo-2'-(but-3"-enyl)-1'-pyrazolidinyl)-2-propenoate 108



Reference:

Belsky; I. *J. Chem. Soc. Chem.Comm.* **1977**, 237

Procedure:

To a solution of 0.792 mg (2.996 mmoles; 0.006 equiv) of 18-crown-6 in dry CH_3CN (2 mL), dry KF (5.8 mg; 99.86 mmoles; 0.2 equiv) was added followed by 70 mg (499.3 mmoles; 1 equiv) of **111** and 55.66 mL (549.2 mmoles; 1.1 equiv) of ethyl propiolate. The mixture was stirred at rt for 19 h. The solvent was removed in vacuum.

TLC: Rf = 0.3 (EtOAc/Cyclohexane 4/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 4/1)

Yield: 0.068 g (57%; 40% recovery of **111**)

Mol. formula: $C_{12}H_{18}N_2O_3$

FW: 238.28

Physique aspect: yellowish oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3	7.39	d	$^3J_{3\text{-}2}$=13.5	1
3"	5.73	ddt	$^3J_{3"\text{-}4"a(trans)}$=16.5, $^3J_{3"\text{-}4"b(cis)}$=9.9 $^3J_{3"\text{-}2"}$=7.2	1
4"a	5.09	dm	$^3J_{4"a\text{-}3"(trans)}$=16.5	1
4"b	5.05	dm	$^3J_{4"b\text{-}3"(cis)}$=9.9	1
2	4.99	d	$^3J_{2\text{-}3}$=13.5	1
4	4.16	q	$^3J_{4\text{-}5}$ = 7.2	2
5'	3.74	t	$^3J_{5'\text{-}4'}$ = 8.1	2
1"	3.66	t	$^3J_{1"\text{-}2"}$ = 6.9	2
4'	2.61	t	$^3J_{4'\text{-}5'}$ = 7.8	2
2"	2.34	q	$^3J_{2"\text{-}1"}$=$^3J_{2"\text{-}3"}$=6.9	2
5	1.28	t	$^3J_{5\text{-}4}$ = 7.2	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 172.6 ($C_{3'}$), 168.1 (C_1), 149.3 (C_3), 135.1 ($C_{3"}$), 118.3 ($C_{4"}$), 95.5 (C_2), 60.5 (C_4), 51.8 ($C_{5'}$), 43.7 ($C_{1"}$), 31.9 ($C_{4'}$), 31.8 ($C_{2"}$), 15.1 (C_5).

IR (film, cm^{-1}): 3079 (unsat. CH), 2979, 2940, 2902 (sat. CH), 1701, 1684 (C=O), 1305, 1143.

MS (CI, CH_4-N_2O):

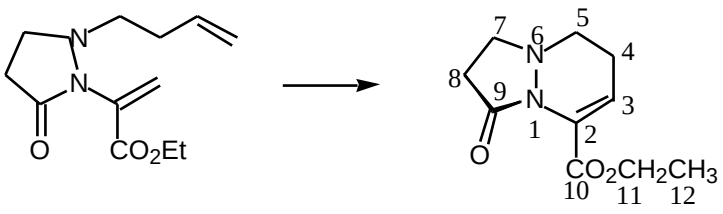
m/z (%), +c: 239 (3) $[M+1]^+$, 193 (2) $[M\text{-}OEt]^+$, 168 (5) $[M\text{-}Me\text{-}CH_2CH_2CHCH_2]^{+\bullet}$, 140 (60) $[M\text{-}CHCHCO_2Et+1]^+$, 99 (100) $[CHCHCO_2Et]^+$, 56 (34) $[CH_2CH_2CHCH_2+1]^{+\bullet}$;

-c: 238 (100) $[M]^{+\bullet}$, 127 (48) $[NNCHCHCO_2Et]^+$, 112 (30) $[NCHCHCO_2Et\text{-}1]^+$, 84 (22) $[CH_2CH_2CON_2]^{+\bullet}$.

HRMS (CI) calcd. for $C_{12}H_{19}N_2O_3$:

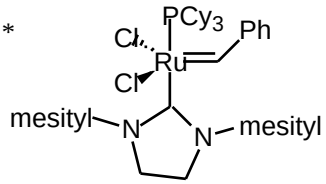
239.139568; found: 239.139230

2.22 Synthesis of ethyl 9-oxo-1,6-diazabicyclo[4.3.0]non-2-ene-2-carboxylate 121



Procedure:

16 mg of cat.* (15 mol%) was added to a solution of 30 mg (125 µmoles; 1 equiv) of **79** in 1.8 mL of toluene. The resulting mixture was heated at 50°C for 10 h. Then another 16 mg of cat* was added, the mixture was heated at 80°C for further 17 h. The solvent was removed under reduced pressure.

* 

TLC: Rf = 0.2 (DCM/MeOH 95/5, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (DCM/MeOH 95/5)

Yield: 0.016 g (61%)

Mol. formula: $C_{10}H_{14}N_2O_3$

FW: 210.23

Physique aspect: pale black oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
3	6.18	t	$^3J_{3\text{-}4}$=3.9	1
11	4.29	q	$^3J_{11\text{-}12}$=6.9	2
5	3.56-3.32	m		2
7	3.03	br. s		2
8	2.66	t	$^3J_{8\text{-}7}$=8.1	2
4	2.47	m		2
12	1.32	t	$^3J_{12\text{-}11}$=6.9	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 170.1 (C_9), 162.0 (C_{10}), 129.2 (C_2), 120.9 (C_3), 61.5 (C_{11}), 52.3 (C_7), 49.5 (C_5), 29.6 (C_8), 25.1 (C_4), 14.2 (C_{12}).

IR (film, cm^{-1}): 3065 (unsat. CH), 2982, 2928, 2843 (sat. CH), 1716 (C=O), 1275.

MS (CI/CH_4-N_2O): m/z (%): +c: 210 (100) $[M]^{+\bullet}$, 165 (97) $[M\text{-}OEt]^+$, 138 (10) $[M\text{-}CO_2Et+1]^{+\bullet}$, 85 (23) $[pyrazolidinone+1]^+$;

-c: 224 (100) $[M\text{-}1+Me]^{+\bullet}$, 209 (60) $[M\text{-}1]^+$.

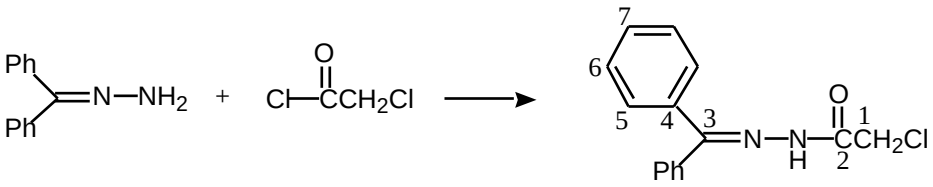
HRMS (CI) calcd. for $C_{10}H_{14}N_2O_3$:

210.100442, found: 210.099781

Chapter 3

Towards bicyclo [4.2.0] 1,2-diazetidinones

3.1 Synthesis of benzophenone α-chloroacetylhydrazone 164



Reference:

Taylor, E. C.; Haley, N. F.; Clemens, R. J. *J. Am. Chem. Soc*. **1981**, *103,* 7743-7752

RN: 29043-58-1

Procedure:

To a solution of benzophenone hydrazone (20 g; 101.9 mmoles; 1 equiv) and pyridine (8.2 mL; 101.9 mmoles; 1 equiv) in 100 mL of dry methylene chloride was added dropwise chloroacetyl chloride (8.1 mL; 101.9 mmoles; 1 equiv), the rate of addition was regulated to afford a gentle reflux. The mixture was heated externally for 15 min following the addition. Extraction with 100 mL of water followed by drying the methylene chloride layer over $MgSO_4$ and evaporation in vacuo afforded the product.

Purification: recrystallization from ethanol.

Yield: 24.2 g (87%; lit. 89%)

Mol. formula: $C_{15}H_{13}ClN_2O$

FW: 272.73

Physique aspect: white solid

Melting point: 101°C (lit. 101°C)

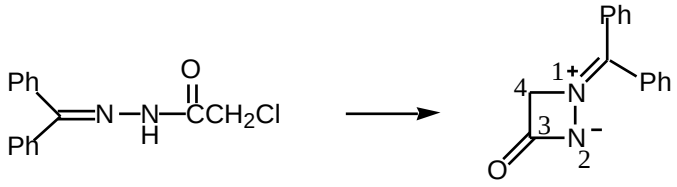
^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
NH	8.49	s		1
PhH	7.59-7.27	m		10
1	4.71	s		2

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 168.1 (C_2), 152.7 (C_3), 136.8 (C_4), 130.9-128.0 ($C_{5\text{-}7}$), 42.6 (C_1).

3.2 Synthesis of 1-(diphenylmethylene)-3-oxo-1,2-diazetidinium inner salt 137



Reference:

Taylor, E. C.; Haley, N. F.; Clemens, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 7743-7752

RN: 29058-76-3

Procedure:

To a solution of benzophenone α-chloroacetylhydrazone (6 g; 21.99 mmoles; 1 equiv) in 50 mL of dry THF was added sodium hydride (60% dispersion in mineral oil, 879.8 mg; 21.99 mmoles; 1 equiv) in small portions. After the addition was complete, the solution was stirred at rt for 24 h. Following the addition of 30 mL of sat. NH_4Cl, the organic layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure.

Purification: recrystallization from ethanol.

Yield: 4.56 g (88%; lit. 40-98%)

Mol. formula: $C_{15}H_{12}N_2O$

FW: 236.27

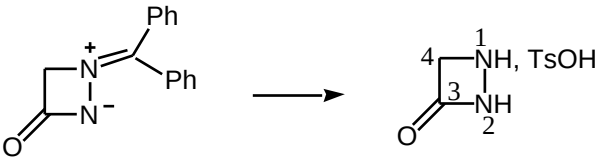
Physique aspect: white solid

Melting point: 198-200°C (lit. 199-200°C)

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	8.02-7.96	m		2
PhH	7.58-7.38	m		8
4	5.35	s		2

3.3 Synthesis of 3-oxo-1,2-diazetidinium tosylate 132



Reference:

Taylor, E. C.; Haley, N. F.; Clemens, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 7743-7752

RN: 79289-49-3

Procedure:

To **137** (2.68 g; 11.34 mmoles; 1 equiv) in 55 mL of dry CH_2Cl_2 was added *p*-toluenesulfonic acid monohydrate (2.157 g; 11.34 mmoles; 1 equiv). The solution was stirred at rt for 1 h. The solid being formed was collected by filtration and washed with ether.

Yield: 2.26 g (81%; lit. 90%)

Mol. formula: $C_9H_{12}N_2O_4S$

FW: 244.26

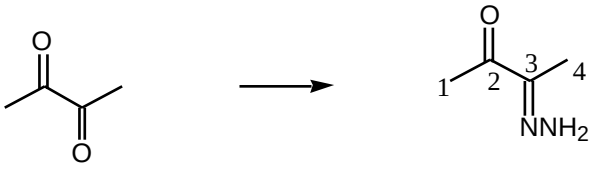
Physique aspect: white solid

Melting point: 147-149°C (lit. 147-149°C)

^{1}H NMR (300MHz, MeOH, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.62	d	^3J=7.5	2
PhH	7.14	d	^3J=7.5	2
4	4.95	s		2
Me	2.28	s		3

3.4 Synthesis of diacetyl monohydrazone 167



Reference:

Diels, O.; Pflaumer, K. *Ber.* **1915**, 223-231

RN: 33487-48-8

Procedure:

A solution of hydrazine monohydrate (6 g; 117.4 mmoles; 1 equiv) in water (3 mL) was added dropwise to 2,3-butanedione (10.3 mL; 117.4 mmoles; 1 equiv) at -20°C, then the reaction was left to room temperature. The yellow solid was filtered.

Purification: recrystallization from Et_2O-hexane

Yield: 5.88 g (50%, lit. 44%)

Mol. formula: $C_4H_8N_2O$

FW: 100.12

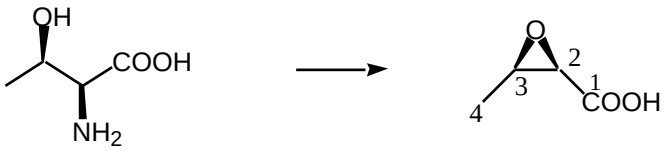
Physique aspect: yellow solid

Melting point: 66-68°C (lit. 67°C)

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
NH	6.00	br. s		2
1	2.34	s		3
4	1.84	s		3

3.5 Synthesis of (2*R*, 3*R*)-2,3-epoxybutanoic acid 166



Reference:

Hanessian, S.; Bedeschi, A.; Battistini, C.; Monngelli, N. *J. Am. Chem. Soc.* **1985**, *107*, 1438-1439

RN: 86561-72-0

Procedure:

L-Threonine (3.5 g; 29.38 mmoles; 1 equiv) and potassium bromide (12.29 g; 103.2 mmoles; 3.51 equiv) were dissolved in ice-cold H_2SO_4 (1.25 M; 59 mL; 2.50 equiv). The colorless solution was stirred at 0°C. Sodium nitrite (3.3 g; 47.82 mmoles; 1.62 equiv) was added portionwise over a period of 30 min. After addition was complete, the reaction mixture was stirred at rt for 2 h . Air was bubbled in order to eliminate nitrogen oxides. To the almost colorless solution, cooled at 0°C, chunks of ice were added followed by solid NaOH (10.43 g; 8.87 equiv). The reaction was kept cold by adding ice. After complete dissolution of NaOH, the resulting yellow solution was stirred at rt for 2 h. The reaction was acidified with aq. H_2SO_4 (1.25M; ≈ 75 mL) to pH 2 and extracted with EtOAc (3X100 mL). The extracts were combined, dried ($MgSO_4$) and evaporated under vacuum. The residue was coevaporated three times with CCl_4 to give a colorless oil.

Yield: 2.23 g (74%, lit. 74%)

Mol. formula: $C_4H_6O_3$

FW: 102.08

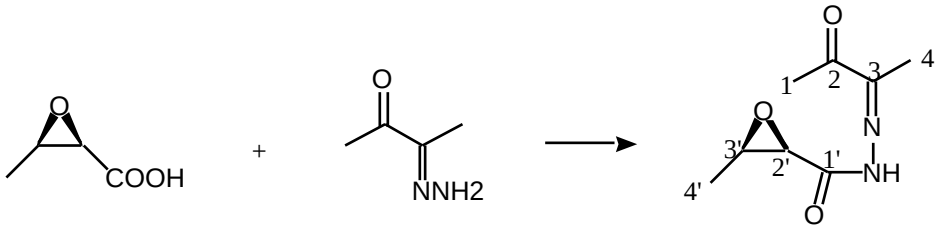
^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
CO_2H	10.85	br. s		1
2	3.59	d	$^3J_{2\text{-}3}$=4.8	1
3	3.39	dq	$^3J_{3\text{-}2}$=4.8, $^3J_{3\text{-}4}$=5.4	1
Me	1.44	d	$^3J_{4\text{-}3}$=5.1	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 174.1 (C_1), 54.6 (C_2), 53.2 (C_3), 13.4 (C_4).

3.6 Synthesis of 2,3-butanedione (2'*R*, 3'*R*)-2',3'-epoxybutanomonohydrazone 160



Reference:

Oda, K.; Nakano, T.; Morimoto, H.; Takamura, N. *Heterocycles*, **1996**, *42(2)*, 577-588

RN: 174787-24-7

Procedure:

To a solution of (2*R*, 3*R*)-2,3-epoxybutanoic acid (459.4 mg; 4.5 mmoles; 1 equiv), diacetyl monohydrazone (300.3 mg; 3 mmoles; 0.666 equiv) and 4-dimethylaminopyridine (73.3 mg; 600 µmoles; 0.133 equiv) in THF (10 mL) was added *N*,*N'*-dicyclohexylcarbodiimide (928.4 mg; 4.5 mmoles; 1 equiv) at 0°C. The mixture was stirred at 0°C for 1 h, at room temperature for 17 h and filtered to remove the precipitated DCU. The filtrate was evaporated.

TLC: Rf = 0.3 (EtOAc/hexane 3/2, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 3/2)

Yield: 0.41 g (74%, lit. 74%)

Mol. formula: $C_8H_{12}N_2O_3$

FW: 184.19

Physique aspect: white solid

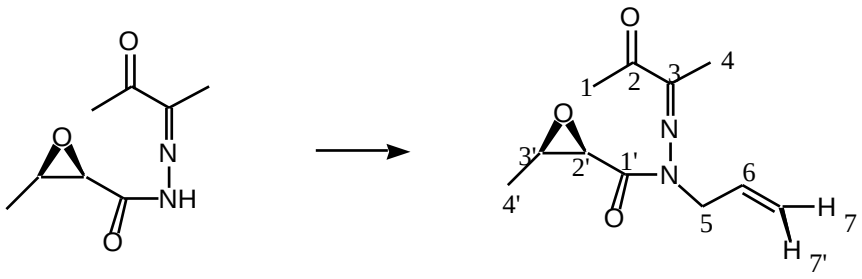
Melting point: 74-76°C (lit. 75-76°C)

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
NH	10.08 (9.18	br.s		1
2'	4.29 (3.72)	d	$^3J_{2'-3'}$=4.8	1
3'	3.46	dq	$^3J_{3'-2'}$=4.9, $^3J_{3'-4'}$=5.1	1
1	2.50 (2.42)	s		3
4	2.07 (2.02)	s		3
4'	1.41 (1.33)	d	$^3J_{4'-3'}$=5.4	3

$[\alpha]_D^{20}$ = +90.3° (c=1.0 in $CHCl_3$)

3.7 Synthesis of 2,3-butanedione *N*-allyl-*N*-((2'*R*, 3'*R*)-2',3'-epoxybutano)monohydrazone 169



Procedure:

To a cold (0°C), magnetically stirred suspension of 55.57 mg (1.389 mmoles; 1.2 equiv) of sodium hydride in DMF (2 mL) under argon was added 237 mg (1.158 mmoles; 1 equiv) of **160** dissolved in DMF (2 mL) over 5 min. The cold mixture was stirred for 30 min, then 120.2 µL (1.389 mmoles; 1.2 equiv) of allyl bromide was added and stirring was continued for 1.5 h allowing the cooling bath to warm to room temperature. Water was added to quench the reaction, then the mixture was extracted with EtOAc (3X15 mL), dried over $MgSO_4$ and concentrated in vacuo.

TLC: Rf = 0.3 (EtOAc/hexane 1/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 1/1)

Yield: 0.16 g (62%)

Mol. formula: $C_{11}H_{16}N_2O_3$

FW: 224.25

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
6	5.89-5.79	m		1
7	5.24	d	$^3J_{7\text{-}6(cis)}$=10.5	1
7'	5.05	d	$^3J_{7'\text{-}6(trans)}$=17.1	1
5a	4.76	d	$^2J_{5a\text{-}5b}$=17.7	1
5b	4.65	d	$^2J_{5b\text{-}5a}$=17.7	1
2'	4.21	d	$^3J_{2'\text{-}3'}$=4.2	1
3'	3.45	dq	$^3J_{3'\text{-}2'}$=5.1, $^3J_{3'\text{-}4'}$=5.1	1
1	2.41	s		3
4	2.21	s		3
4'	1.33	d	$^3J_{4'\text{-}3'}$=5.1	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 198.0 (C_2), 170.3 ($C_{1'}$), 150.0 (C_3), 132.3 (C_6), 117.5 (C_7), 56.2 ($C_{2'}$), 53.8 ($C_{3'}$), 48.8 (C_5), 25.7 (C_1), 14.1 (C_4), 13.8 ($C_{4'}$).

IR (film, cm^{-1}): 3086 (unsat. CH), 2989, 2930 (sat. CH), 1716 (C=O), 1615 (C=N), 1429, 1261, 1153.

MS (CI/CH_4-N_2O):

m/z (%): +c: 225 (100) $[M+1]^+$, 197 (12) $[M-C_2H_3]^+$, 183 (12) $[M-C_3H_5]^+$, 181 (29) $[M-CH_3CO]^+$, 141 (20) $[C_7H_{10}NO_2+1]^+$;

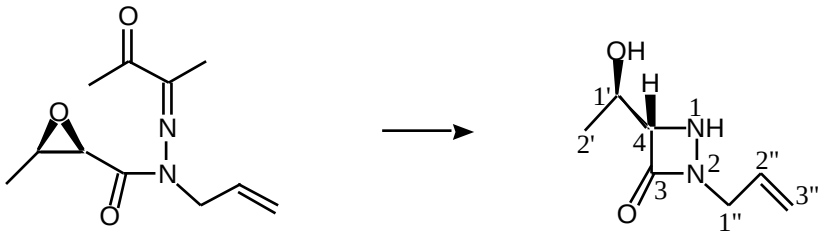
-c: 223 (8) $[M-1]^+$, 140 $[C_7H_{10}NO_2]^+$.

HRMS (CI) calcd. for $C_{11}H_{17}N_2O_3$:

225.123918; found: 225.123721

$[\alpha]_D^{20}$ = +256.0° (c=1.0 in $CHCl_3$)

3.8 Synthesis of (4*S*, 4(1'*R*))-2-allyl-4-(1'-hydroxyethyl)-1,2-diazetidin-3-one 170



Reference:

Oda, K.; Nakano, T.; Morimoto, H.; Takamura, N. *Heterocycles*, **1996**, *42(2)*, 577-588

Procedure:

To a solution of 150 mg (668.8 µmoles; 1 equiv) of **169** in MeCN (8 mL) was added 254.4 mg (1.337 mmoles; 2 equiv) of *p*-TsOH.H_2O at 0°C. After stirring for 24 h, the mixture was evaporated, neutralized (sat. $NaHCO_3$) and extracted (AcOEt). The extract was washed (brine 2X10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated.

TLC: Rf = 0.13 (DCM/MeOH 95/5, weak UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (DCM/MeOH 95/5)

Yield: 0.074 g (71%)

Mol. formula: $C_7H_{12}N_2O_2$

FW: 156.18

Physique aspect: colorless oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
2"	5.82	ddt	$^3J_{2"-3"(trans)}$=17.0, $^3J_{2"-3"(cis)}$=10.0, $^3J_{2"-1"}$=6.2	1
3"	5.30	dm	$^3J_{3"-2"(trans)}$=17.0, $^3J_{3"-2"(cis)}$=10.0	2
4	4.41	d	$^3J_{4-1'}$=5.1	1
1'	4.23-4.10	m		1
1"	4.04-3.99	m		2
NH, OH	3.4-2.6	br. s		2
2'	1.29	d	$^3J_{2'-1'}$=6.4	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 167.8 (C_3), 131.4 ($C_{2"}$), 119.7 ($C_{3"}$), 77.1 (C_4), 65.8 ($C_{1'}$), 49.0 ($C_{1"}$), 20.2 ($C_{2'}$).

IR (film, cm^{-1}): 3434 (OH), 3228 (NH), 3080 (unsat. CH), 2967, 2934 (sat. CH), 1748 (C=O), 1521, 1254 (C-O).

MS (EI, 70 eV):

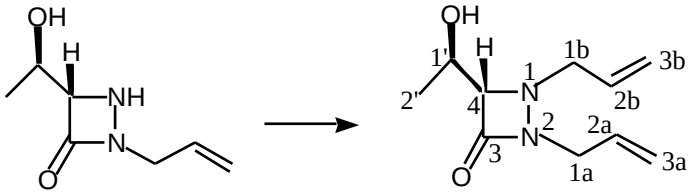
m/z (%): 156 (26) [M]$^{+\bullet}$, 128 (26) [M-1-CH=CH_2]$^{+\bullet}$, 85 (85) $[C_3H_4N_2O+1]^+$, 70 (25) $[C_2H_2N_2O]^{+\bullet}$, 56 (62) $[C_2H_2NO]^+$, 45 (100) $[C_2H_5O]^+$.

HRMS (EI) calcd. for $C_7H_{12}N_2O_2$:

156.089878; found: 156.090264

$[\alpha]_D^{20}$ = -58.1° (c=1.0 in $CHCl_3$)

3.9 Synthesis of (4*S*, 4(1'*R*))-1,2-diallyl-4-(1'-hydroxyethyl)-1,2-diazetidin-3-one 173



Reference:

Oda, K.; Nakano, T.; Morimoto, H.; Takamura, N. *Heterocycles*, **1996**, *42(2)*, 577-588

Procedure:

To a solution of 86 mg (550.6 µmoles; 1 equiv) of **170** and 57.17 µL (660.7 µmoles; 1.2 equiv) of allyl bromide in DMF (2 mL) was added 99.04 mg (660.7 µmoles; 1.2 equiv) of sodium iodide and 55.5 mg (660.7 µmoles; 1.2 equiv) of sodium bicarbonate at 0°C. After stirring at room temperature for 15 h, the mixture was diluted with water (2 mL) and extracted (AcOEt, 2X5 mL). The extracts were washed (brine), dried ($MgSO_4$) and filtered. The filtrate was evaporated.

TLC: Rf = 0.3 (EtOAc/cyclohexane 7/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 7/3)

Yield: 0.104 g (96%)

Mol. formula: $C_{10}H_{16}N_2O_2$

FW: 196.24

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
2a+2b	6.00-5.80	m		2
3a+3b	5.35-5.20	m		4
1a+1'	4.08-3.95	m		3
4	3.77	d	$^3J_{4\text{-}1'}$=5.7	1
1b	3.60	dd	$^3J_{1b\text{-}1b'}$=12.9, $^3J_{1b\text{-}2b}$=6.6	1
1b'	3.37	dd	$^3J_{1b'\text{-}1b}$=12.9, $^3J_{1b'\text{-}2b}$=6.6	1
OH	3.4	br. s		1
2'	1.27	d	$^3J_{2'\text{-}1'}$=6.6	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 167.4 (C_3), 132.9, 132.3 ($C_{2a,}$ C_{2b}), 120.4, 119.3 ($C_{3a,}$ C_{3b}), 83.4 (C_4), 65.9 ($C_{1'}$), 63.2 (C_{1b}), 48.8 (C_{1a}), 20.1 ($C_{2'}$).

IR (film, cm^{-1}): 3446 (OH), 3082 (unsat. CH), 2979, 2930 (sat. CH), 1750 (C=O), 1245 (C-O).

MS (EI, 70 eV):

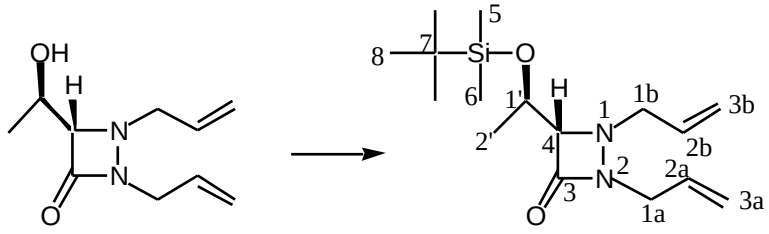
m/z (%): 196 (85) $[M]^{\bullet\bullet}$, 155 (5) $[M\text{-allyl}]^+$, 151 (5) $[M\text{-}C_2H_5O]^+$, 123 (100) $[M\text{-allyl-}CH_3OH]^+$, 81 (20) $[C_3HN_2O]^+$, 69 (36) $[C_3H_5N_2]^+$, 55 (40) $[C_3H_5N]^{\bullet\bullet}$, 45 (53) $[C_2H_5O]^+$.

HRMS (EI) calcd. for $C_{10}H_{16}N_2O_2$:

196.121178; found: 196.121671

$[\alpha]_D^{20}$ = -86.1° (c=1.22 in $CHCl_3$)

3.10 Synthesis of (4*S*, 4(1'*R*))-1,2-diallyl-4-(1-*tert*-butyldimethylsilyloxyethyl)-1,2-diazetidin-3-one 168



Reference:

Oda, K.; Nakano, T.; Morimoto, H.; Takamura, N. *Heterocycles*, **1996**, *42(2)*, 577-588

Procedure:

To a solution of 31 mg (157.9 µmoles; 1 equiv) of **173**, 36.79 µL (315.9 µmoles; 2 equiv) of 2,6-lutidine in CH_2Cl_2 (1 mL) was added dropwise 47.16 µL (205.3 µmoles; 1.3 equiv) of *t*-butyldimethylsilyl triflate at -8°C. After stirring at 0°C for 20 min, the mixture was quenched (ice-cold sat. $NaHCO_3$, 2 mL) and extracted (AcOEt, 2X5 mL). The combined extracts were washed (brine), dried ($MgSO_4$) and filtered. The filtrate was evaporated.

TLC: Rf = 0.5 (EtOAc/cyclohexane 1/4, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 1/4)

Yield: 0.045 g (92%)

Mol. formula: $C_{16}H_{30}N_2O_2Si$

FW: 310.51

Physique aspect: colorless oil

^{1}H NMR (200MHz, $CDCl_3$, without TMS, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
2a+2b	6.20-5.90	m		2
3a+3b	5.51-5.34	m		4
1a+1'	4.28-4.09	m		3
1b	3.84	d	$^3J_{1b\text{-}2b}$=7.5	1
1b'+4	3.62	d	$^3J_{1b'\text{-}2b}$=$^3J_{4\text{-}1'}$=6.6	2
2'	1.42	d	$^3J_{2'\text{-}1'}$=6.3	3
8	1.08	s		9
5 + 6	0.28	s		6

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 168.1 (C_3), 134.1, 133.0 ($C_{2a,}$ C_{2b}), 119.9, 119.1 ($C_{3a,}$ C_{3b}), 84.1 (C_4), 68.0 ($C_{1'}$), 63.9 (C_{1b}), 49.5 (C_{1a}), 26.5 (C_8), 20.9 ($C_{2'}$), 18.7 (C_7), -3.9 ($C_{5,}$ C_6).

IR (film, cm^{-1}): 3082 (unsat. CH), 2961, 2920, 2861 (sat. CH), 1773 (C=O), 1254 (C-O).

MS (EI, 70 eV):

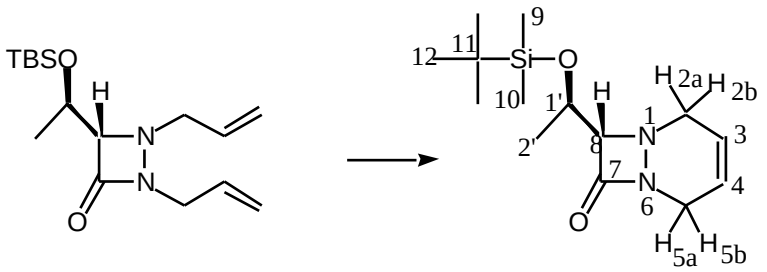
m/z (%): 310 (18) $[M]^{+\bullet}$, 253 (100) $[M\text{-}CMe_3]^+$, 225 (76) $[M+2\text{-}CMe_3\text{-}2Me]^+$, 181 (33) $[M+2\text{-}OTBDMS]^+$, 115 (40) $[t\text{BuMe}_2\text{Si}]^+$, 73 (81) $[C_2H_4OSi+1]^+$.

HRMS (EI) calcd. for $C_{16}H_{30}N_2O_2Si$:

310.207657; found: 310.207592

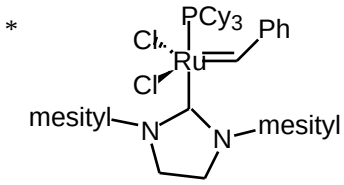
$[\alpha]_D^{20}$ = -75.3° (c=0.58 in $CHCl_3$)

3.11 Synthesis of (8*S*, 8(1'*R*))-8-(1'-*tert*-butyldimethylsilyloxyethyl)-1,6-diazabicyclo[4.2.0]oct-3-ene-7-one 174



Procedure:

6 mg (6 mol%) of cat.* was added to a solution of **168** (37 mg; 119.1 µmoles; 1 equiv) in 2 mL of toluene. The resulting mixture was heated at 50°C for 2 h. The residue was directly purified by flash column chromatography.



TLC: Rf = 0.3 (EtOAc/cyclohexane 2/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 2/3)

Yield: 0.031 g (92%)

Mol. formula: $C_{14}H_{26}N_2O_2Si$

FW: 282.46

Physique aspect: colorless oil

^{1}H NMR (500MHz, $CDCl_3$,without TMS, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
4	5.88-5.82	m		1
3	5.77-5.72	m		1
1'+5a	4.20-4.12	m		2
5b	3.86	dm	$^2J_{5b\text{-}5a}$=17.7	1
2a	3.62	dm	$^2J_{2a\text{-}2b}$=14.7	1
8	3.57	d	$^3J_{8\text{-}1'}$=7.8	1
2b	3.16	dm	$^2J_{2b\text{-}2a}$=14.7	1
2'	1.28	d	$^3J_{2'\text{-}1'}$=6.4	3
12	0.87	s		9
9	0.088	s		3
10	0.078	s		3

^{13}C NMR (125MHz, $CDCl_3$, 20°C)

δ = 161.1 (C_7), 123.3 (C_4), 119.8 (C_3), 88.0 (C_8), 67.3 ($C_{1'}$), 53.7 (C_2), 40.7 (C_5), 25.6 (C_{12}), 20.0 ($C_{2'}$), 17.9 (C_{11}), -4.8, -4.5 ($C_{9,}$ C_{10}).

IR (film, cm^{-1}): 3054 (unsat. CH), 2954, 2930, 2856 (sat. CH), 1761 (C=O).

MS (EI, 70 eV):

m/z (%): 282 (20) $[M]^{\bullet\bullet}$, 253 (40) $[M+1-2Me]^+$, 225 (42) $[M-CMe_3]^+$, 197 (83) $[M+2-CMe_3-2Me]^+$, 151 (100) $[t BuMe_2Si]^+$, 73 (61) $[C_2H_4OSi+1]^+$.

HRMS (EI) calcd. for $C_{14}H_{26}N_2O_2Si$:

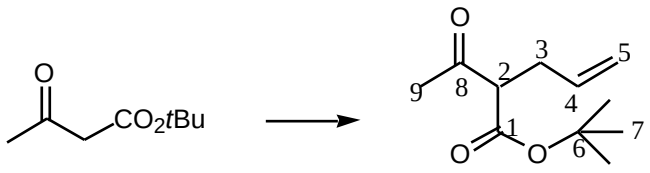
282.176357; found: 282.176042

$[\alpha]_D^{20}$ = +82.9° (c=1.05 in $CHCl_3$)

Chapter 4

Towards bicyclo [5.2.0] aza-β-lactam carboxylic ester derivatives

4.1 Synthesis of *tert*-butyl 2-acetyl-4-pentenoate 178



Reference:

Stotter, P. L.; Hill, K. A. *Tetrahedron Lett.* **1972**, *40*, 4067-4070

R.N.: 39149-69-4

Procedure:

To a cold (0°C), magnetically stirred suspension of sodium hydride (2.411 g; 60.3 mmoles; 1 equiv; 60% dispersion in mineral oil) in THF (20 mL) under argon was added 10 mL (9.54 g; 60.3 mmoles; 1 equiv) of *t*-butyl acetoacetate dissolved in THF (20 mL) dropwise. Allowing the cooling bath to warm to room temperature, 5.74 mL (66.33 mmoles; 1.1 equiv) of allyl bromide was added and stirring was continued for one day at 40°C. Water was added to quench the reaction, then the mixture was extracted with ether (3X), dried over $MgSO_4$ and concentrated in vacuo.

Yield: 11.95 g (quantitative; lit. quantitative)

Mol. formula: $C_{11}H_{18}O_3$

FW: 198.26

Physique aspect: colorless oil

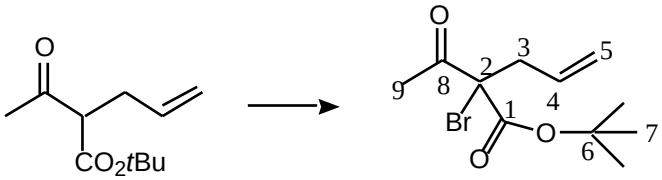
^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
4	5.73	ddt	$^3J_{4\text{-}5a(trans)}$=16.1	1
			$^3J_{4\text{-}5b(cis)}$=10.1, $^3J_{4\text{-}3}$=6.9	
5a	5.10	dm	$^3J_{5a\text{-}4(trans)}$=16.1	1
5b	5.04	dm	$^3J_{5b\text{-}4(cis)}$=10.1	1
2	3.43	t	$^3J_{2\text{-}3}$=7.3	1
3	2.55	t	$^3J_{3\text{-}2}$=$^3J_{3\text{-}4}$=7.2	2
9	2.23	s		3
7	1.46	s		9

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 203.4 (C_8), 169.0 (C_1), 135.1 (C_4), 117.8 (C_5), 82.6 (C_6), 60.8 (C_2), 32.7 (C_3), 29.5 (C_9), 28.5 (C_7).

4.2 Synthesis of *tert*-butyl 2-bromo-2-acetyl-4-pentenoate 179



Reference:

Stotter, P. L.; Hill, K. A. *Tetrahedron Lett.* **1972**, *40,* 4067-4070

R.N.: 39149-76-3

Procedure:

To a cold (0°C), magnetically stirred suspension of sodium hydride (2.411 g; 60.3 mmoles; 1 equiv; 60% dispersion in mineral oil) in THF (20 mL) under argon was added 11.95 g (60.3 mmoles; 1 equiv) of *tert*-butyl 2-acetyl-4-pentenoate dissolved in THF (20 mL) dropwise. After 5 min, bromine (3.089 ml; 60.3 mmoles; 1 equiv) was added rapidly as a solution in CH_2Cl_2 at 0°C. The reaction was monitored by TLC. Water was added to quench the reaction, then the mixture was extracted with ether (3X), dried over $MgSO_4$ and concentrated in vacuo.

Yield: 16.71 g (100%; lit. 100%)

Mol. formula: $C_{11}H_{17}BrO_3$

FW: 277.15

Physique aspect: pale yellow oil

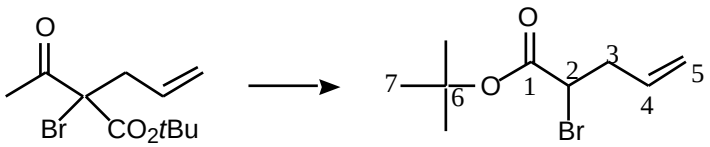
^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
4	5.74	ddt	$^3J_{4\text{-}5a(trans)}$=15.9	1
			$^3J_{4\text{-}5b(cis)}$=10.3, $^3J_{4\text{-}3}$=6.9	
5a	5.18	dm	$^3J_{5a\text{-}4(trans)}$=15.9	1
5b	5.16	dm	$^3J_{5b\text{-}4(cis)}$=10.3	1
3	2.55	m		2
9	2.39	s		3
7	1.48	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 197.7 (C_8), 166.2 (C_1), 132.4 (C_4), 120.5 (C_5), 85.1 (C_6), 69.9 (C_2), 42.2 (C_3), 30.4 (C_9), 28.6 (C_7).

4.3 Synthesis of *tert*-butyl 2-bromo-4-pentenoate 176



Reference:

Stotter, P. L.; Hill, K. A. *Tetrahedron Lett.* **1972**, *40*, 4067-4070

R.N.: 39149-84-3

Procedure:

$Ba(OH)_2$ was previously dried to constant weight under vacuum at 125°C.

16.71 g (60.3 mmoles; 1 equiv) of **179** was added as a solution in absolute EtOH (20 mL) to a suspension of barium hydroxide (5.166 g; 30.15 mmoles; 0.5 equiv) in abs. ethanol (30 mL) at 0°C, the mixture was stirred at this temperature for 30 min. After filtering insoluble barium salts, the product was isolated by partitioning the alcohol filtrate between pentane and brine. The pentane layers were combined and dried over $MgSO_4$.

TLC: Rf=0.43 (pentane/EtOAc 96/4, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (pentane/EtOAc 96/4)

Yield: 11.34 g (80%, lit. 85%)

Mol. formula: $C_9H_{15}BrO_2$

FW: 235.12

Physique aspect: pale yellow oil

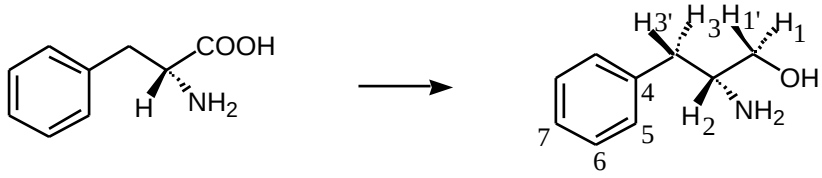
^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
4	5.76	ddt	$^3J_{4\text{-}5a(trans)}$=17.1	1
			$^3J_{4\text{-}5b(cis)}$=10.2, $^3J_{4\text{-}3}$=6.6	
5a	5.18	dm	$^3J_{5a\text{-}4(trans)}$=17.1	1
5b	5.17	dm	$^3J_{5b\text{-}4(cis)}$=10.2	1
2	4.13	t	$^3J_{2\text{-}3}$=7.5	1
3	2.87-2.63	m		2
7	1.48	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 168.8 (C_1), 133.8 (C_4), 119.5 (C_5), 83.1 (C_6), 46.7 (C_2), 39.8 (C_3), 28.5 (C_7).

4.4 Synthesis of (*R*)-2-amino-3-phenylpropan-1-ol 188



Reference:

Abico, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33(38)*, 5517-5518

R.N.: 5267-64-1

Procedure:

To a stirred suspension of sodium borohydride (3.24 g; 85.65 mmoles; 2.5 equiv) in THF (100 mL) was added d-phenylalanine (5.66 g; 34.26 mmoles; 1 equiv). The flask was immersed in an ice-water bath, and a solution of sulfuric acid (2.377 mL; 42.82 mmoles; 1.25 equiv) in ether (total volume of 20 mL) was added dropwise at such a rate as to maintain the reaction mixture below 20°C (addition time, approximately 5 min). Stirring of the reaction time was continued at rt overnight and MeOH (10 mL) was added carefully to destroy excess BH_3. The mixture was concentrated to *ca.* 50 mL and 5N NaOH (100 mL) was added. After removing the solvent that distilled below 100°C, the mixture was heated at reflux for 3 h. The turbid aqueous mixture was cooled and filtered through a thin pad of Celite which was washed with water. The filtrate and the washings were combined and diluted with additional water to *ca.* 100 mL. The DCM extraction (4X50 mL) followed by evaporation of the solvent left solid which has not been purified further.

Yield: 4.52 g (87%, lit. 88%)

Mol. formula: $C_9H_{13}NO$

FW: 151.20

Physique aspect: white solid

Melting point: 94-96°C (lit. 90-94°C)

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

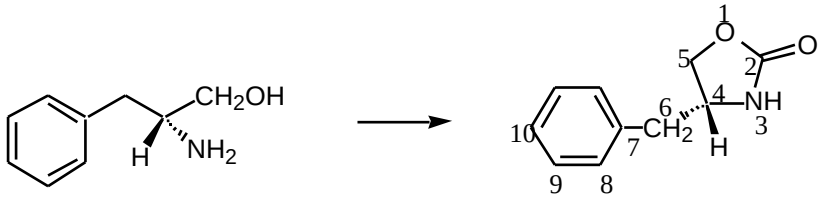
Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.30-7.16	m		5
1	3.62	dd	$^2J_{1\text{-}1'}$=17.5, $^3J_{1\text{-}2}$=3.9	1
1'	3.38	dd	$^2J_{1'\text{-}1}$=17.5, $^3J_{1'\text{-}2}$=7.2	1
2	3.14-2.89	m		1
3	2.77	dd	$^2J_{3\text{-}3'}$=13.2, $^3J_{3\text{-}2}$=5.4	1
3'	2.50	dd	$^2J_{3'\text{-}3}$=13.5, $^3J_{3'\text{-}2}$=8.7	1
OH+NH_2	2.44	br. s		3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 139.1 (C_4), 129.7, 129.0, 126.9 ($C_{5\text{-}7}$), 66.8 (C_1), 54.8 (C_2), 41.3 (C_3).

$[\alpha]_D^{20}$ = +22.8° (c=1.2 in 1N HCl; lit. +23.0 c=1.2 in 1N HCl)

4.5 Synthesis of (*R*)-4-benzyl-2-oxazolidinone 187



Reference:

Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108(21)*, 6757-6761

RN: 102029-44-7

Procedure:

A dry, 100 mL flask equipped with a thermometer and a column with a distillation head was charged with (*R*)-2-amino-3-phenylpropan-1-ol (3.03 g; 20.03 mmoles; 1 equiv), potassium carbonate (276.9 mg; 2.003 mmoles; 0.1 equiv) and diethyl carbonate (4.855 mL; 40.07 mmoles; 2 equiv). The mixture was carefully heated to 135-140°C, and ethanol was allowed to distill as it was formed. After 2 h, the light brown slurry was cooled to rt, diluted with 300 mL of DCM, and filtered to remove most of the remaining K_2CO_3. The solution was washed with 1N aq. $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a pale yellow oil.

TLC: Rf = 0.26 (EtOAc/hexane 7/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 7/3)

Yield: 3.06 g (86%, lit. 84% for its enantiomer)

Mol. formula: $C_{10}H_{11}NO_2$

FW: 177.20

Physique aspect: white solid

Melting point: 88-90°C (lit. 87-90°C)

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

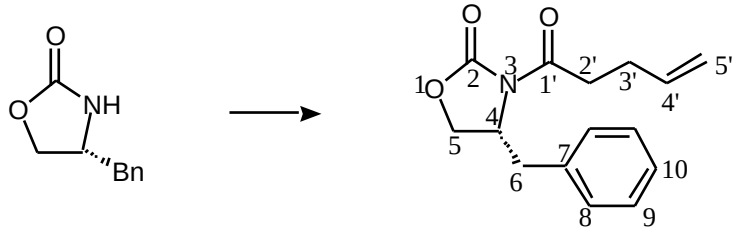
Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.34-7.16	m		5
NH	5.90	br. s		1
4	4.46-4.41	m		1
5	4.17-4.07	m		2
6	2.88	dd	$^3J_{6\text{-}4}$=7.2, $^3J_{6'\text{-}4}$=3.3	2

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 160.0 (C_2), 136.5 (C_7), 129.6, 129.5, 127.8 ($C_{8\text{-}10}$), 70.3 (C_5), 54.5 (C_4), 42.1 (C_6).

$[\alpha]_D^{20}$ = +64.0° (c=1.0 in $CHCl_3$; lit. +62.0° c=1.0 in $CHCl_3$)

4.6 Synthesis of (4*R*)-3-(1'-oxo-4'-pentenyl)-4-benzyl-2-oxazolidinone 186



Reference:

Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria Jr., J. F. *Tetrahedron* **1988**, *44(17)*, 5525-5540

RN: 155399-10-3

Procedure:

To a mechanically stirred solution of 4-pentenoic acid (1.497 mL; 14.67 mmoles; 1.1 equiv) and triethylamine (2.466 mL; 17.74 mmoles; 1.33 equiv) in 40 mL of dry THF, cooled to -78°C under argon was added trimethylacetyl chloride (1.889 mL; 15.34 mmoles; 1.15 equiv). The mixture was warmed to 0°C for 1 h, and then recooled to -78°C. A solution of (*R*)-4-benzyloxazolidin-2-one (2.364 g; 13.34 mmoles; 1 equiv) and 6 mg of triphenylmethane (indicator) in 35 mL of dry THF, stirred at -30°C to -45°C under argon, was treated dropwise with *n*-butyllithium (2.5 M in hexane) until an orange color persisted (5.336 mL; 13.34 mmoles; 1 equiv). The resulting solution was cooled to -78°C and then added, via rapid cannulation, to the above stirred mixture containing the mixed anhydride. The residual metalated oxazolidinone was rinsed in with two 5-mL portions of dry THF and the resulting mixture was stirred at -78°C for 30 min. After warming to 0°C, the mixture was partitioned between DCM and pH7 phosphate buffer. The DCM phase was washed with 5% aq. $NaHCO_3$ followed by saturated aq. NaCl, dried ($MgSO_4$) and evaporated in vacuo.

TLC: Rf = 0.32 (EtOAc/hexane 1/4, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/hexane 1/4)

Yield: 2.88 g (83%, on 5 g oxazolidinone: 92%; lit. 87% for its enantiomer)

Mol. formula: $C_{15}H_{17}NO_3$

FW: 259.30

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

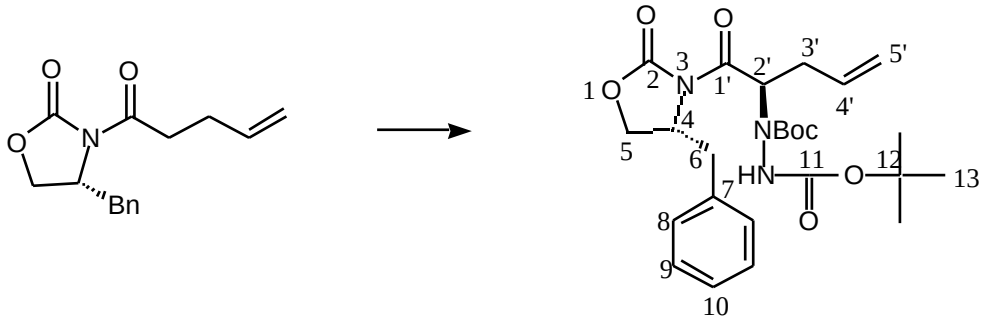
Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.33-7.19	m		5
4'	5.88	ddt	$^3J_{4'\text{-}5'\text{a}(trans)}$=17.4, $^3J_{4'\text{-}5'\text{b}(cis)}$=10.2, $^3J_{4'\text{-}3'}$=6.6	1
5'a	5.11	dm	$^3J_{5'\text{a}\text{-}4'(trans)}$=17.4	1
5'b	5.03	dm	$^3J_{5'\text{b}\text{-}4'(cis)}$=10.2	1
4	4.70-4.62	m		1
5	4.19-4.10	m		2
6a	3.29	dd	$^2J_{6\text{a}\text{-}6\text{b}}$=13.2, $^3J_{6\text{-}4}$=3.2	1
2'a	3.10	dt	$^2J_{2'\text{a}\text{-}2'\text{b}}$=17.4, $^3J_{2'\text{a}\text{-}3'}$=7.5	1
2'b	3.01	dt	$^2J_{2'\text{b}\text{-}2'\text{a}}$=17.4, $^3J_{2'\text{b}\text{-}3'}$=7.2	1
6b	2.76	dd	$^2J_{6\text{b}\text{-}6\text{a}}$=13.5, $^3J_{6\text{b}\text{-}4}$=9.6	1
3'	2.49-2.42	m		2

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 173.0 ($C_{1'}$), 153.9 (C_2), 137.2 ($C_{4'}$), 135.8 (C_7), 129.9, 129.5, 127.9 ($C_{8\text{-}10}$), 116.3 ($C_{5'}$), 66.8 (C_5), 55.8 (C_4), 38.6 (C_6), 35.5 ($C_{2'}$), 28.8 ($C_{3'}$).

$[\alpha]_D^{20}$ = -63.4° (c=1.42 in $CHCl_3$)

4.7 Synthesis of (3(2'*R*), 4*R*)-3-(2'-(*N*, *N'*-bis-(*t*-butoxycarbonyl)hydrazino)-1'-oxo-4'-pentenyl)-4-benzyl-2-oxazolidinone 191



Reference:

Evans, D. A.; Britton, T. C.; Dorow R. L.; Dellaria Jr., J. F. *Tetrahedron* **1988**, *44(17)*, 5525-5540

RN: 174497-79-1

Procedure:

To a freshly prepared solution of 1.05 mmol of LDA in 30 mL of THF, stirred at -78°C under argon, was added via cannula a precooled (-78°C) solution of **186** (2.621 g; 10.1 mmoles; 1 equiv) in 30 mL of THF. Residual imide was rinsed in with two 5-mL portions of THF and

stirring continued at -78°C for 30 min. A precooled (-78°C) solution of di-*tert*-butyl azodicarboxylate (2.676 g; 11.62 mmoles; 1.15 equiv) in 40 mL of dry DCM was added via cannula to the above enolate solution and after an additional 3 min the reaction was quenched with acetic acid (1.504 mL; 26.28 mmoles; 2.6 equiv). The mixture was partitioned between DCM and pH 7 phosphate buffer. The aqueous phase was washed with three portions of DCM. The DCM phases were combined, washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$) and evaporated in vacuo.

TLC: 2'(*R*), major: Rf = 0.26; 2'(*S*), minor: Rf = 0.14 (EtOAc/cyclohexane 1/4, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 1/4)

Yield: 4.25 g (86%, major isomer); 43 mg (0.87%, minor isomer); **de**: 98%

Mol. formula: $C_{25}H_{35}N_3O_7$

FW: 489.57

Physique aspect: colorless glass foam

^{1}H NMR (300MHz, $CDCl_3$, 20°C, major isomer 2'(*R*))

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.40-7.20	m		5
NH	6.64	br. s		1
4' + 2'	6.10-5.82	m		2
5'a	5.14	dm	$^3J_{5'a\text{-}4'(trans)}$=17.1	1
5'b	5.07	dm	$^3J_{5'b\text{-}4'(cis)}$=10.5	1
4	4.64-4.54	sym. m		1
5	4.18	apparent d	*J*=4.8	2
6a	3.40-3.20	m		1
6b + 3'	2.80-2.42	m		3
13	1.48, 1.47	s		18

^{13}C NMR (75MHz, $CDCl_3$, 20°C, major isomer 2'(*R*))

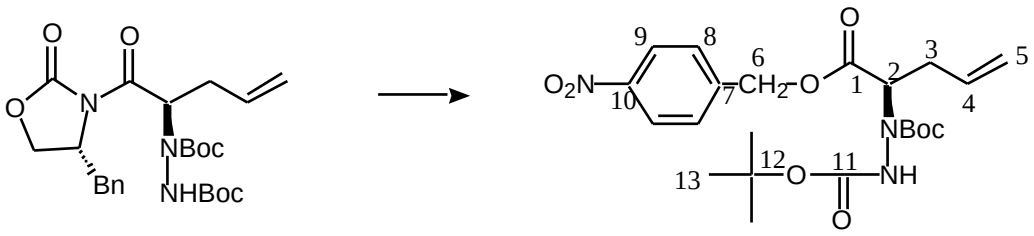
δ = 172.9 ($C_{1'}$) 156.1, 156.0 (C_{11}), 153.2 (C_2), 135.8 (C_7), 134.4 ($C_{4'}$), 129.9, 129.6, 127.9 ($C_{8\text{-}10}$), 118.5 ($C_{5'}$), 82.7 (C_{12}), 67.2 (C_5), 60.8 ($C_{2'}$), 56.3 (C_4), 38.3 (C_6), 34.0 ($C_{3'}$), 28.9, 28.8 (C_{13}).

Elemental analysis calcd for $C_{25}H_{35}N_3O_7$:

C 61.33, H 7.21, N 8.58; found: C 61.32, H 7.26, N 8.47

$[\alpha]_D^{20}$ = -50.5° (c=1.05 in $CHCl_3$)

4.8 Synthesis of (2*R*) *p*-nitrobenzyl 2-(*N*, *N'*-bis-(*t*-butoxycarbonyl)hydrazino)-4-pentenoate 193



Reference:

Evans, D. A.; Britton, T. C.; Dorow R. L.; Dellaria Jr., J. F. *Tetrahedron* **1988**, *44(17)*, 5525-5540

LiOOH-mediated hydrolysis:

A solution of **191** (250 mg; 510.6 µmoles; 1 equiv) in 3:1-THF/H_2O (4 mL) was treated at 0°C with 30% H_2O_2 (0.179 mL, 2.042 mmol, 4 equiv) followed by LiOH.H_2O (42.8 mg; 1.021 mmoles; 2 equiv). The mixture was stirred at 0°C for 3 h. The excess peroxide was quenched at 0°C with a 10% excess of 1.5 N aq. sodium sulfite. After buffering to pH 9-10 with aq. $NaHCO_3$ and evaporation of THF, the oxazolidinone chiral auxiliary was recovered by DCM extractions (2X) in quantitative yield. The aqueous phase was acidified with 1 N aq. $NaHSO_4$ and extracted with DCM (3X). The organic phases were combined, dried ($MgSO_4$) and concentrated in vacuo to give the corresponding carboxylic acid.

LiOH-mediated hydrolysis:

An ice cold solution of **191** (250 mg; 510.6 µmoles; 1 equiv) in THF (2 mL) was treated in one portion with a cold (0°C) solution of LiOH.H_2O (51.4 mg; 1.225 mmoles; 2.4 equiv) in H_2O (1 mL). The resulting two-phase mixture was stirred at 0°C for 3 h. The mixture was partitioned between 1N aq. $NaHSO_4$ and DCM. The aqueous phase was extracted with DCM (3X10 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated in vacuo.

Esterification:

Potassium carbonate (105.8 mg; 765.9 µmoles; 1.5 equiv), 4-nitrobenzyl bromide (220.6 mg; 1.021 mmoles; 2 equiv) and tetrabutylammonium iodide (1.886 mg; 5.106 µmoles; 0.01 equiv) were added to a solution of the above acid in 5 mL of DMF. The mixture was stirred for 12 h prior to dilution with Et_2O and H_2O. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated.

TLC: Rf = 0.42 (EtOAc/cyclohexane 1/4, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 1/4)

Yield: 0.195g (82%, using LiOOH); 0.190 g (80%, using LiOH)

Mol. formula: $C_{22}H_{31}N_3O_8$

FW: 465.50

Physique aspect: pale yellow oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
9	8.22	d	$^3J_{9\text{-}8}$=8.7	2
8	7.53	d	$^3J_{8\text{-}9}$=8.7	2
NH	6.41	br. s		1
4	5.98-5.83	m		1
6a	5.28	d	$^3J_{6a\text{-}6b}$=13.8	1
6b	5.22	d	$^3J_{6b\text{-}6a}$=13.8	1
5a	5.14	d	$^3J_{5a\text{-}4(trans)}$=16.8	1
5b	5.08	d	$^3J_{5b\text{-}4(cis)}$=10.5	1
2	4.95	br. s		1
3	2.65	t	^3J=6.9, ^3J=7.2	2
13	1.48,1.47	s		18

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 171.5 (C_1), 155.7, 154.9 (C_{11}), 148.3 (C_{10}), 143.1 (C_7), 134.4 (C_4), 128.9 (C_9), 124.3 (C_8), 118.2 (C_5), 82.8, 81.7 (C_{12}), 66.1 (C_6), 60.1 (C_2), 33.9 (C_3), 28.8, 28.7 (C_{13}).

IR (film, cm^{-1}): 3334 (NH), 3080 (unsat. CH), 2980, 2934 (sat. CH), 1749, 1705 (C=O), 1523, 1347 (NO_2), 1156, 855.

MS (CI/CH_4-NO_2):

m/z (%): 451 (<1) [M+1-Me]$^{\bullet\bullet}$, 319 (1) [M-2($OCMe_3$)]$^{\bullet\bullet}$, 264 (8) [M-2(CO_2CMe_3)+1]$^+$, 260 (100) [$CH_2CHNBocNHBoc$+2]$^{\bullet\bullet}$, 236 (66) [M-2(NBoc)+1]$^+$, 152 (35) [$NO_2C_6H_4CH_2O$]$^+$, 74 (54) [$OCMe_3$+1]$^{\bullet\bullet}$.

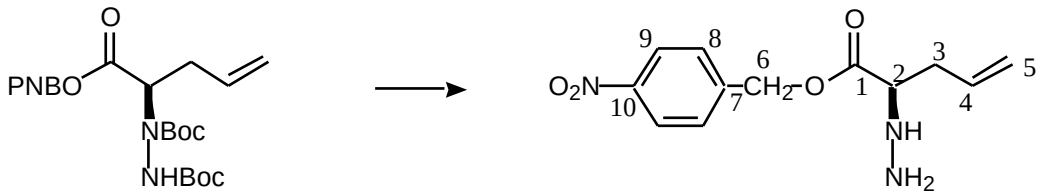
$[\alpha]_D^{20}$ = +12.2° (c=0.5 in $CHCl_3$)

Transesterification:

To a cold (-78°C) solution of PNBOLi (prepared from 4-nitrobenzyl alcohol (243.9 mg; 1.593 mmoles; 3 equiv) and *n*-butyllithium (2.5 M in hexane, 424.8 µL; 1.062 mmoles; 2 equiv)) in 3.0 mL of dry THF) was added via cannula a precooled (-78°C) solution of **191** (260 mg; 531 µmoles; 1 equiv) in 2 mL of THF. Residual imide was rinsed in with two 1 mL portions of THF, and the resulting solution was stirred at -50°C for 2 h prior to quenching with 3 mL of aq. pH 7 phosphate buffer. The mixture was partitioned between H_2O and DCM. The aq. phase was extracted with DCM (3X) and the organic phases were combined, dried ($MgSO_4$) and evaporated in vacuo.

Yield: 0.22 g (89%)

4.9 Synthesis of (2*R*) *p*-nitrobenzyl 2-hydrazino-4-pentenoate 194



Procedure:

A solution of **193** (142 mg; 305 µmoles) in 5 mL of trifluoroacetic acid and 5 mL of dichloromethane was stirred at rt for 30 min. The reaction mixture was concentrated. Then about 15 mL of DCM (PA) was added and the organic layer was washed with sat. $NaHCO_3$, dried over $MgSO_4$ and evaporated in vacuo.

Yield: 0.08 g (crude, 95%)

Mol. formula: $C_{12}H_{15}N_3O_4$

FW: 265.26

Physique aspect: pale yellow oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
9	8.23	dd	^3J=8.4, ^4J=1.8	2
8	7.53	dd	^3J=8.7, ^4J=2.1	2
4	5.72	ddt	$^3J_{4\text{-}5a(trans)}$=17.1	1
			$^3J_{4\text{-}5b(cis)}$=9.9, $^3J_{4\text{-}3}$=7.2	
6	5.29	s		2
5b	5.12	dm	$^3J_{5b\text{-}4(cis)}$=9.9	1
5a	5.10	dm	$^3J_{5a\text{-}4(cis)}$=17.1	1
2	3.66	t	$^3J_{2\text{-}3}$=6.6, $^3J_{2\text{-}3'}$=6.3	1
NH+NH_2	3.66	br. s		3
3	2.50-2.41	m		2

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 174.0 (C_1), 148.3 (C_{10}), 143.3 (C_7), 133.4 (C_4), 129.0, 128.9 (C_9), 124.4, 124.3 (C_8), 119.1 (C_5), 65.7 (C_6), 65.3 (C_2), 35.9 (C_3).

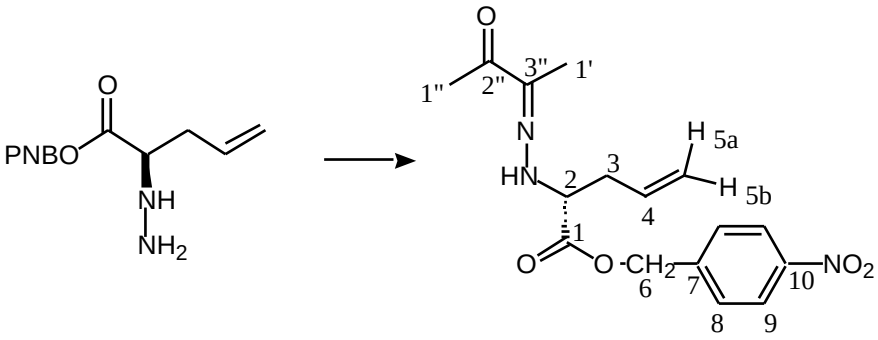
IR (film, cm^{-1}): 3349, 3266 (NH), 3075 (unsat. CH), 2930, 2859 (sat. CH), 1738 (C=O), 1522, 1347 (NO_2), 1183(C-O).

MS (CI/CH_4-NO_2):

m/z (%), +c: 265 (4) [M]$^{+\bullet}$, 260 (35), 236 (27) [M-N_2H_3+2]$^+$, 224 (11) [M-C_3H_5]$^+$, 206 (18) [M-N_2H_3-C_2H_3-1]$^+$, 178 (86) [$C_8H_4NO_4$]$^+$, 154 (43) [$NO_2C_6H_4CH_2O$]$^+$, 136 (15) [$NO_2C_6H_4CH_2$]$^+$, 114 (18) [M-$NO_2C_6H_4CH_2O$+1]$^{+\bullet}$, 86 (27) [M-$NO_2C_6H_4CH_2CO_2$+1]$^{+\bullet}$, 58 (99) [$C_2H_2O_2$]$^{+\bullet}$, 57 (100) [OCOCH]$^+$.

-c: 248 (3) $[M\text{-}NH_2\text{-}1]^{+\bullet}$, 234 (8) $[M\text{-}N_2H_3]^+$, 152 (100) $[NO_2C_6H_4CH_2CO_2]^+$, 98 (55) $[C_5H_6O_2]^{+\bullet}$.

4.10 Synthesis of (2*R*) *p*-nitrobenzyl 2-(*N'*-(1'-methyl-2"-oxo)propylidene)hydrazino)-4-pentenoate 195



Procedure:

To a solution of 2,3-butanedione (396.9 µL; 4.523 mmoles; 1 equiv) in 15 mL of abs. EtOH was added slowly a solution of **194** (1.2 g; 4.523 mmoles; 1 equiv) in 10 mL of abs. EtOH at 0°C. The flask was washed with two 5 mL-portions of EtOH. The resulting mixture was allowed to warm to rt and stirred at this temperature for 4 h. The solvent was evaporated.

TLC: Rf = 0.24 (EtOAc/cyclohexane 3/7, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 3/7)

Yield: 1.4 g (93%)

Mol. formula: $C_{16}H_{19}N_3O_5$

FW: 333.34

Physique aspect: yellowish oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
9	8.23	dd	^3J=8.7, ^4J=2.1	2
8	7.52	d	^3J=8.4	2
NH	6.01	d	$^3J_{NH-2}$=7.2	1
4	5.75	ddt	$^3J_{4-5a(trans)}$=16.2, $^3J_{4-5b(cis)}$=9.6, $^3J_{4-3}$=6.9	1
6	5.29	s		2
5b	5.14	dm	$^3J_{5b-4(cis)}$=9.6	1
5a	5.13	dm	$^3J_{5a-4(trans)}$=16.2	1
2	4.41	q	$^3J_{2-NH}$=6.9, $^3J_{2-3}$=6.3	1
3	2.72-2.66	m		2
1"	2.29	s		3
1'	1.85	s		3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 197.5 ($C_{2"}$), 172.5 (C_1), 148.2 (C_{10}), 144.3 ($C_{3"}$), 142.9 (C_7), 132.6 (C_4), 129.2, (C_9), 124.5 (C_8), 119.9 (C_5), 66.2 (C_6), 62.4 (C_2), 36.8 (C_3), 24.7 ($C_{1"}$), 8.3 ($C_{1'}$).

IR (film, cm^{-1}): 3299 (NH), 3068 (unsat. CH), 2942, 2851 (sat. CH), 1747 (C=O of ester), 1669 (C=O), 1635 (C=N), 1523, 1348 (NO_2), 1216, 1140(C-O).

MS (CI/CH_4-NO_2):

+c: m/z (%): 155 (100) $[M-CH=CH_2-NO_2C_6H_4CH_2O+1]^+$, 85 (30) $[CH_3COCNCH_3+1]^+$;

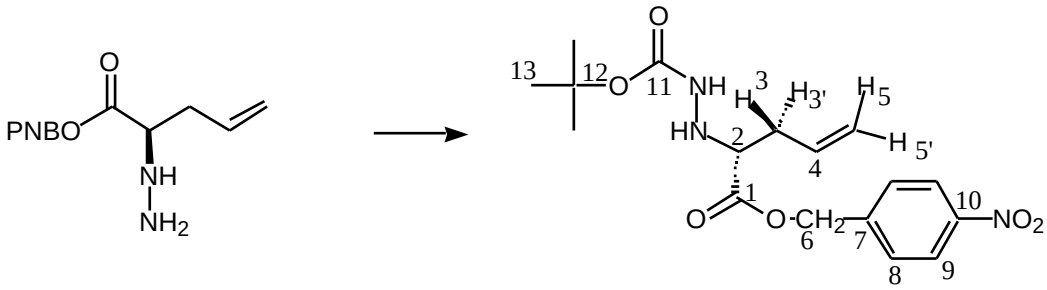
-c: 171 (100) $[M-NO_2C_6H_4-CH_2CHCH_2+1]^+$, 152 (66) $[NO_2C_6H_4CH_2O]^+$.

Elemental analysis calcd for $C_{16}H_{19}N_3O_5$:

C 57.650, H 5.745, N 12.605; found: C 57.54, H 5.74, N 12.58

$[\alpha]_D^{20}$ = -10.8° (c=1.02 in $CHCl_3$)

4.11 Synthesis of (2*R*) *p*-nitrobenzyl 2-(*N'*-(*tert*-butoxycarbonyl)hydrazino)-4-pentenoate 200



Reference:

Kemp, D. S.; Carey, R. I. *J. Org. Chem.* **1989**, *54(15)*, 3640-3646

Procedure:

To a solution of 55 mg (207.3 µmoles; 1 equiv) of **194** and 45 mg (207.3 µmoles; 1 equiv) of di-*t*-butyl dicarbonate in dry DCM (2 mL) was added 36.11 µL (207.3 µmoles; 1 equiv) of *n,n*-diisopropylethylamine at 0°C. The reaction was allowed to stir at rt for 3 h. The reaction mixture was washed (brine), dried ($MgSO_4$) and evaporated.

TLC: Rf = 0.29 (EtOAc/cyclohexane 3/7, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 3/7)

Yield: 0.063g (83%)

Mol. formula: $C_{17}H_{23}N_3O_6$

FW: 365.39

Physique aspect: pale yellow oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
9	8.24	d	$^3J_{9\text{-}8}$=8.8	2
8	7.54	d	$^3J_{8\text{-}9}$=8.6	2
NH-Boc	6.25	br. s		1
4	5.80	ddt	$^3J_{4\text{-}5(trans)}$=17.3 $^3J_{4\text{-}5'(cis)}$=9.9, $^3J_{4\text{-}3}$=6.9	1
6	5.28	s		2
5	5.15	dm	$^3J_{5\text{-}4(trans)}$=17.3	1
5'	5.13	dm	$^3J_{5'\text{-}4(cis)}$=9.9	1
NH	4.29	br. s		1
2	3.85	dd	$^3J_{2\text{-}3}$=7.3, $^3J_{2\text{-}3'}$=5.5	1
3	2.65-2.36	m		2
13	1.45	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 172.8 (C_1), 156.9 (C_{11}), 148.3 (C_{10}), 143.3 (C_7), 133.2 (C_4), 129.1 (C_9), 124.4 (C_8), 119.6 (C_5), 81.6 (C_{12}), 65.9 (C_6), 62.9 (C_2), 35.8 (C_3), 29.0 (C_{13}).

IR (film, cm^{-1}): 3323 (NH), 3081 (unsat. CH), 2979, 2932 (sat. CH), 1741, 1716 (C=O), 1523, 1348 (NO_2), 1165(C-O).

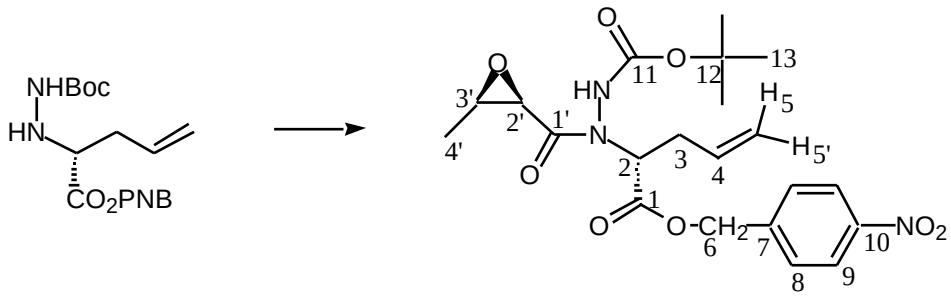
MS (CI/CH_4-NO_2):

+c: m/z (%): 320 (60) $[M\text{-}3Me]^+$, 310 (100) $[M\text{-}C_4H_8\text{+}1]^+$, 267 (14) [M-*t*Bu-$CH_2CHCH_2$] $^{+\bullet}$, 223 (10) [M-CO_2*t*Bu-CH_2CHCH_2] $^{+\bullet}$, 153 (15) [OPNB+1] $^{+\bullet}$, 137 (23) [PNB+1] $^{+\bullet}$, 57 (73) $[t\text{Bu}]^+$;

-c: 229 (100) $[M\text{-PNB}]^+$, 183 (14) $[M\text{-}CO_2\text{PNB-2}]^+$.

HRMS (CI) calcd. for $C_{13}H_{16}N_3O_6$ [M+H-C_4H_8]:
310.103911; found: 310.104316
$[\alpha]_D^{20}$ = +11.4° (c=1.05 in $CHCl_3$)

4.12 Synthesis of (2'*R*, 3'*R*, 2*R*) *p*-nitrobenzyl 2-(*N*-(2',3'-epoxybutano)-*N'*-(*tert*-butoxycarbonyl)hydrazino)-4-pentenoate 202



Procedure:
To a stirred solution of 293.3 mg (2.873 mmoles; 1.5 equiv) of (2*R*, 3*R*)-2, 3-epoxybutanoic acid in anhydrous DCM (10 mL) maintained at 0°C, 506.9 µL (3.831 mmoles; 2 equiv) of 1-chloro-*N*,*N*,2-trimethylpropenylamine was added in one portion and the resulting mixture was stirred at 0°C. After 20 min a solution of 700 mg (1.915 mmoles; 1 equiv) of **200** and 632.9 µL (4.789 mmoles; 2.5 equiv) of 2,4,6-collidine in 6 mL of DCM was added. The flask was washed with two portions of 1 mL of DCM.The mixture was stirred at 0°C for 30 min, then allowed to warm up slowly to rt (around 1 h) and stirred at this temperature for 16 h. 20 mL of DCM was added to the reaction mixture, then this solution was washed with 5% aq. $NaHCO_3$, the aqueous layer was back extracted with DCM (2X15 mL). The organic phases were combined and washed with sat. NH_4Cl, dried over $MgSO_4$ and concentrated under vacuum.
TLC: Rf = 0.24 (EtOAc/cyclohexane 2/3, UV, $KMnO_4$)
Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 2/3)
Yield: 0.78g (91%)
Mol. formula: $C_{21}H_{27}N_3O_8$
FW: 449.46
Physique aspect: pale yellow foam

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
9	8.22	dd	^3J=8.7, ^4J=2.1	2
8	7.52	d	^3J=8.4	2
NH	6.90	br. s		1
4	5.84	ddt	$^3J_{4\text{-}5(trans)}$=17.1 $^3J_{4\text{-}5'(cis)}$=9.9, $^3J_{4\text{-}3}$=6.9	1
6	5.23	s		2
5	5.17	dm	$^3J_{5\text{-}4(trans)}$=17.1	1
5'	5.13	dm	$^3J_{5'\text{-}4(cis)}$=9.9	1
2'	3.72	d	$^3J_{2'\text{-}3'}$=4.2	1
3'+2	3.40-3.22	m		2
3	2.65	t	^3J=6.6, ^3J=7.2	2
13	1.48	s		9
4'	1.25	d	$^3J_{4'\text{-}3'}$=5.1	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 170.7 (C_1), 169.3 ($C_{1'}$), 154.6 (C_{11}), 148.3 (C_{10}), 142.7 (C_7), 133.3 (C_4), 129.1, 128.9 (C_9), 124.4, 124.3 (C_8), 119.1 (C_5), 83.2 (C_{12}), 66.5 (C_6), 59.5 (C_2), 54.8 ($C_{2'}$), 53.9 ($C_{3'}$), 32.9 (C_3), 28.8 (C_{13}), 14.1 ($C_{4'}$).

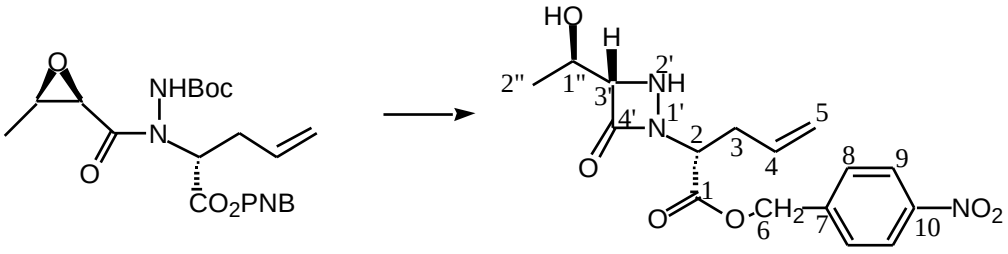
IR (film, cm^{-1}): 3293 (NH), 3083 (unsat. CH), 2981, 2930 (sat. CH), 1734, 1685 (C=O), 1523, 1348 (NO_2), 1159(C-O).

MS (D/APCI):

m/z (%): 394 (3) $[M\text{-}CMe_3+2]^+$, 350 (5) $[M\text{-}Boc+2]^+$, 297 (7) $[M\text{-}NO_2C_6H_4CH_2O]^+$, 283 (18) $[M\text{-}NO_2C_6H_4CH_2\text{-}2Me]^+$, 282 (100) $[M\text{-}3Me\text{-}NO_2C_6H_4]^{\bullet+}$.

$[\alpha]_D^{20}$ = +50.0° (c=0.34 in $CHCl_3$)

4.13 Synthesis of (2*R*, 3'*S*, 1"*R*) *p*-nitrobenzyl 2-(3'-(1"-hydroxyethyl)-4'-oxo-1',2'-diazetidin-1'-yl)-4-pentenoate 203



Procedure:

411 mg (914.4 µmoles; 1 equiv) of **202** was dissolved into 10 mL of trifluoroacetic acid, then the solution was stirred at rt for 2 h. TFA was removed in vacuo. 15 mL of DCM was added to

the residue, and the solution was washed with sat. $NaHCO_3$. The aqueous phase was back extracted with 10 mL of DCM. The organic phases were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated.

TLC: Rf = 0.31 (EtOAc/cyclohexane 9/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 9/1)

Yield: 0.19g (60%)

Mol. formula: $C_{16}H_{19}N_3O_6$

FW: 349.34

Physique aspect: colorless oil

^{1}H NMR (500MHz, DMSO, 20°C, two rotamers, 3:2)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
9	8.23 (8.23)	d	$^3J_{9\text{-}8}$=8.7	2
8	7.66 (7.66)	d	$^3J_{8\text{-}9}$=8.7	2
4	5.80 (5.80)	ddt	$^3J_{4\text{-}5a(trans)}$=17.4, $^3J_{4\text{-}5b(cis)}$=10.2 $^3J_{4\text{-}3}$=6.8	1
6	5.31 (5.31)	s		2
5a	5.18 (5.18)	dt	$^3J_{5a\text{-}4(trans)}$=17.4, $^4J_{5a\text{-}3}$=1.6	1
5b	5.07 (5.07)	dm	$^3J_{5b\text{-}4(cis)}$=10.2	1
2	4.69 (4.51)	dd	$^3J_{2\text{-}3a}$=9.1, $^3J_{2\text{-}3b}$=5.1	1
3'	4.13(4.13)	d	$^3J_{3'\text{-}1''}$=6.5	1
1"	3.71(3.94)	dq	$^3J_{1''\text{-}3'}$=6.5, $^3J_{1''\text{-}2''}$=6.3	1
3a	2.59 (2.59)	dd	$^3J_{3a\text{-}4}$=6.9, $^3J_{3a\text{-}2}$=8.9	1
3b	2.45 (2.73)	dd	$^3J_{3b\text{-}4}$=6.6, $^3J_{3b\text{-}2}$=5.1	1
2"	1.01 (1.10)	d	$^3J_{2''\text{-}1''}$=6.3	3

^{1}H NMR (500MHz, DMSO, 77°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
9	8.20	d	$^3J_{9\text{-}8}$=8.7	2
8	7.65	d	$^3J_{8\text{-}9}$=8.7	2
4	5.82	ddt	$^3J_{4\text{-}5a(trans)}$=17.4, $^3J_{4\text{-}5b(cis)}$=10.2 $^3J_{4\text{-}3}$=6.8	1
6	5.30	s		2
5a	5.17	dt	$^3J_{5a\text{-}4(trans)}$=17.4, $^4J_{5a\text{-}3}$=1.6	1
5b	5.07	dm	$^3J_{5b\text{-}4(cis)}$=10.2	1
2	4.49	t	$^3J_{2\text{-}3}$=7.3	1
3'	4.17	d	$^3J_{3'\text{-}1''}$=6.5	1
1''	3.87	dq	$^3J_{1''\text{-}3'}$=6.5, $^3J_{1''\text{-}2''}$=6.3	1
3	2.63	t	$^3J_{3\text{-}4}$=$^3J_{3\text{-}2}$=7.2	2
2''	1.10	d	$^3J_{2''\text{-}1''}$=6.3	3

^{13}C NMR (125MHz, DMSO, 20°C, two rotamers, 3:2)

δ = 169.2 (168.4) (C_1), 168.5 (168.8) ($C_{4'}$), 147.2 (147.2) (C_{10}), 143.4 (143.4) (C_7), 133.8 (133.5) (C_4), 128.6 (128.6) (C_8), 123.5 (123.6) (C_9), 118.3 (118.6) (C_5), 75.3 (75.0) ($C_{3'}$), 65.3 (65.3) (C_6), 65.0 (64.4) ($C_{1''}$), 57.7 (58.1) (C_2), 32.0 (33.3) (C_3), 19.9 (19.1) ($C_{2''}$).

^{13}C NMR (125MHz, DMSO, 77°C)

δ = 168.2 (C_1), 167.7 ($C_{3'}$), 147.0 (C_{10}), 142.8 (C_7), 133.1 (C_4), 128.2 (C_8), 122.9 (C_9), 117.6 (C_5), 75.9 ($C_{3'}$), 64.9 (C_6), 64.5 ($C_{1''}$), 57.8 (C_2), 32.2 (C_3), 19.1 ($C_{2''}$).

IR (film, cm^{-1}): 3446 (OH), 3243 (NH), 3081 (unsat. CH), 2975, 2880 (sat. CH), 1749 (C=O), 1521, 1348 (NO_2), 1190(C-O).

MS (D/APCI):

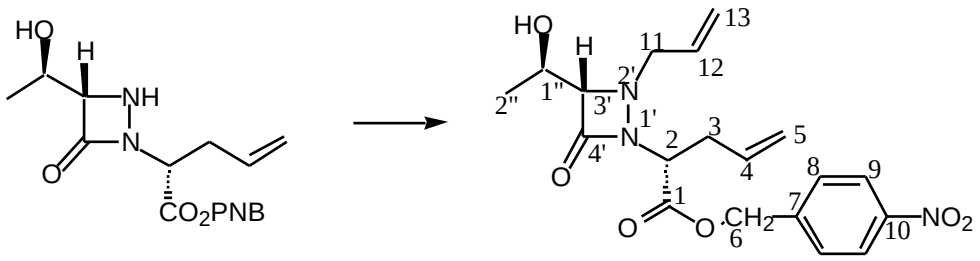
m/z (%) 350 (39) $[M+1]^+$, 322 (100) $[M\text{-}C_2H_4]^+$, 304 (25), $[M\text{-}H_2O\text{-}CH_3CH]^+$, 198 (4) $[M\text{-}NO_2C_6H_4CH_2O+1]^{\bullet\bullet}$, 181 (5) $[CO_2PNB+1]^{\bullet\bullet}$.

HRMS (EI) calcd. for $C_{16}H_{19}N_3O_6$:

349.127386; found: 349.126950

$[\alpha]_D^{20}$ = -24.2° (c=1.0 in $CHCl_3$)

4.14 Synthesis of (2*R*, 3'*S*, 1"*R*) *p*-nitrobenzyl 2-(2'-allyl-3'-(1"-hydroxyethyl)-4'-oxo-1',2'-diazetidin-1'-yl)-4-pentenoate 204



Reference:

Oda, K.; Nakano, T.; Morimoto H.; Takamura, N. *Heterocycles*, **1996**, *42(2)*, 577-588

Procedure:

To a solution of **203** (40 mg; 114.5 µmoles; 1 equiv) and allyl bromide (11.89 µL; 137.4 µmoles; 1.2 equiv) in DMF (1 mL) was added sodium iodide (20.6 mg; 137.4 µmoles; 1.2 equiv) and sodium bicarbonate (11.6 mg; 137.4 µmoles; 1.2 equiv) at 0°C. After stirring at room temperature for 15 h, the mixture was diluted with water (5 mL) and extracted (AcOEt, 10 mL). The extract was washed (brine), dried ($MgSO_4$) and filtered. The filtrate was evaporated.

TLC: Rf = 0.27 (EtOAc/cyclohexane 3/2, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 3/2)

Yield: 0.035g (78%)

Mol. formula: $C_{19}H_{23}N_3O_6$

FW: 389.41

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
9	8.23	d	$^3J_{9\text{-}8}$=8.1	2
8	7.55	d	$^3J_{8\text{-}9}$=8.1	2
4, 12	5.94-5.73	m		2
6a	5.32	dd	$^3J_{6a\text{-}6b}$=13.5	1
6b	5.26	dd	$^3J_{6b\text{-}6a}$=13.5	1
5, 13	5.23	dm	$^3J_{cis}$=9.6, $^3J_{trans}$=17.1	4
2	5.17	t	$^3J_{2\text{-}3a}$=7.2, $^3J_{2\text{-}3b}$=8.1	1
1"	4.46	dq	$^3J_{1''\text{-}3'}$=6.9, $^3J_{1''\text{-}2''}$=6.3	1
3'	4.06	d	$^3J_{3'\text{-}1''}$=7.2	1
11a	3.76	dd	$^2J_{11a\text{-}11b}$=12.6, $^3J_{11a\text{-}12}$=6.4	1
11b	3.63	dd	$^2J_{11b\text{-}11a}$=12.9, $^3J_{11b\text{-}12}$=7.2	1
3	3.34	sym. m		2
OH	2.75	d	$^3J_{OH\text{-}1''}$=5.7	1
2"	1.20	d	$^3J_{2''\text{-}1''}$=6.3	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 168.9 (C_1), 168.1 ($C_{4'}$), 148.4 (C_{10}), 142.7 (C_7), 133.3 (C_4), 132.6 (C_{12}), 129.2 (C_8), 124.5 (C_9), 121.7 (C_{13}), 119.6 (C_5), 83.9 ($C_{3'}$), 66.6 (C_6), 66.4 ($C_{1''}$), 64.3 (C_{11}), 60.3 (C_2), 33.9 (C_3), 20.4 ($C_{2''}$).

IR (film, cm^{-1}): 3478 (OH), 3092 (unsat. CH), 2974, 2932, 2847 (sat. CH), 1772 (lactam C=O), 1732 (ester C=O), 1522 (NO_2), 1183 (C-O).

MS (CI/CH_4-N_2O):

m/z (%) +c: 390 (20) $[M+1]^+$, 362 (3) $[M\text{-}C_2H_3]^+$, 277 (5) $[M\text{-}2C_3H_5\text{-}CH_3OH+2]^{+\bullet}$, 255 (5) $[M\text{-}NO_2C_6H_4CH_2+2]^+$, 211 (3) $[M\text{-}NO_2C_6H_4\text{-}C_3H_5\text{-}Me]^+$, 154 (39) $[C_7H_{10}N_2O_2]^{+\bullet}$, 137 (12) $[NO_2C_6H_4CH_2+1]^{+\bullet}$, 122 (12) $[NO_2C_6H_4]^+$, 114 (17) $[C_4H_6N_2O_2]^{+\bullet}$, 98 (11) $[C_4H_5N_2O+1]^{+\bullet}$, 59 (100) $[C_3H_6O+1]^+$;

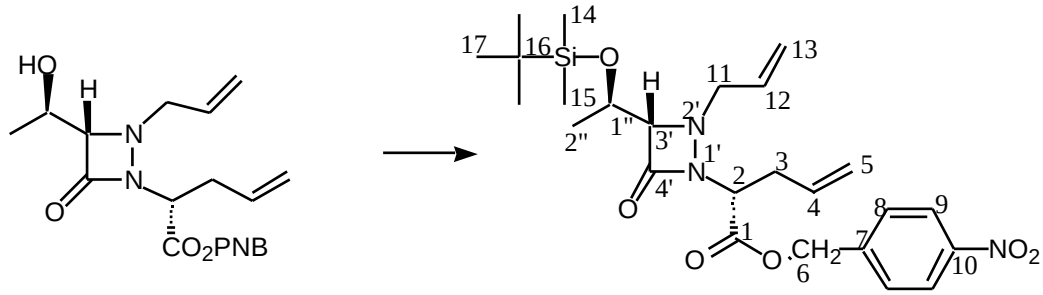
-c: 253 (30) $[M\text{-}NO_2C_6H_4CH_2]^+$, 153 (100) $[C_7H_{10}N_2O_2\text{-}1]^+$.

HRMS (CI) calcd. for $C_{19}H_{24}N_3O_6$:

390.166511; found: 390.164697

$[\alpha]_D^{20}$ = -29.8° (c=1.2 in $CHCl_3$)

4.15 Synthesis of (2*R*, 3'*S*, 1"*R*) *p*-nitrobenzyl 2-(2'-allyl-3'-(1"-*tert*-butyldimethylsilyloxyethyl)-4'-oxo-1',2'-diazetidin-1'-yl)-4-pentenoate 205



Reference:

Oda, K.; Nakano, T.; Morimoto H.; Takamura, N. *Heterocycles*, **1996**, *42(2)*, 577-588

Procedure:

To a solution of 20 mg (51.35 µmoles; 1 equiv) of **204**, 11.96 µL (102.7 µmoles; 2 equiv) of 2,6-lutidine in CH_2Cl_2 (1 mL) was added dropwise 15.33 µL (66.76 µmoles; 1.3 equiv) of *t*-butyldimethylsilyl triflate at -8°C. After stirring at 0°C for 20 min, the mixture was quenched (ice-cold sat. $NaHCO_3$, 2 mL) and extracted (DCM, 2X5 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and filtered. The filtrate was evaporated.

TLC: Rf = 0.39 (EtOAc/cyclohexane 1/4, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 1/4)

Yield: 0.025g (97%)

Mol. formula: $C_{25}H_{37}N_3O_6Si$

FW: 503.67

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
9	8.41	d	$^3J_{9\text{-}8}$=9.0	2
8	7.70	d	$^3J_{8\text{-}9}$=9.0	2
4, 12	6.15-5.90	m		2
6	5.48	s		2
5, 13	5.50	dm	$^3J_{trans}$=16.5	4
	5.33	dm	$^3J_{cis}$=10.8	
2	4.56	t	$^3J_{2\text{-}3a}$=7.2, $^3J_{2\text{-}3b}$=8.4	1
1"	4.20	dq	$^3J_{1''\text{-}3'}$=9.0, $^3J_{1''\text{-}2''}$=6.3	1
3'	3.85	d	$^3J_{3'\text{-}1''}$=9.0	1
11	3.62	m		2
3	2.91	tm	$^3J_{3\text{-}2}$=$^3J_{3\text{-}4}$=7.2	2
2"	1.35	d	$^3J_{2''\text{-}1''}$=6.3	3
17	1.02	s		9
14, 15	0.19, 0.17	s		6

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 168.9 (C_1), 168.5 ($C_{4'}$), 148.3 (C_{10}), 142.9 (C_7), 133.7 (C_4, C_{12}), 128.8 (C_8), 124.5 (C_9), 120.3 (C_{13}), 119.3 (C_5), 83.9 ($C_{3'}$), 68.2 ($C_{1''}$), 66.4 (C_6), 64.1 (C_{11}), 60.9 (C_2), 33.9 (C_3), 26.4 (C_{17}), 20.7 ($C_{2''}$), 18.7 (C_{16}), -3.75, -3.94 (C_{14}, C_{15}).

IR (film, cm^{-1}): 3081 (unsat. CH), 2955, 2930, 2857 (sat. CH), 1774 (lactam C=O), 1752 (ester C=O), 1525, 1347 (NO_2), 834.

MS (CI/CH_4-N_2O):

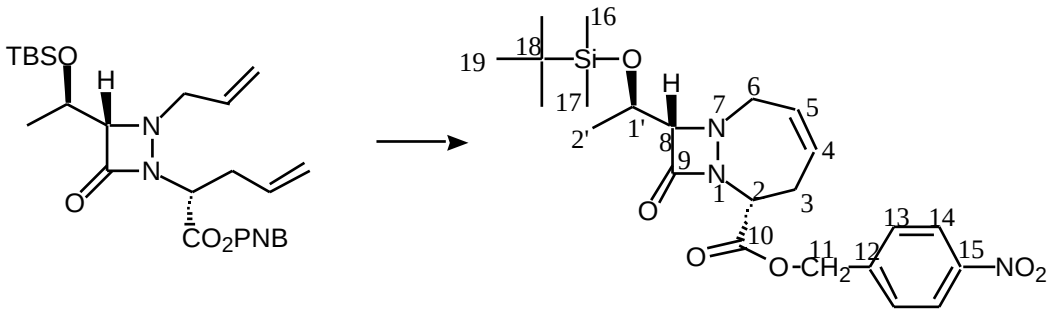
m/z (%) +c: 504 (100) $[M+1]^+$, 488 (7) $[M\text{-}CH_3]^+$, 446 (6) $[M\text{-}C_3H_5OH+1]^+$, 369 (2) $[M\text{-}NO_2C_6H_4CH_2+2]^+$, 154 (3) $[C_7H_{10}N_2O_2]^{+\bullet}$, 58 (7) $[t\text{Bu}+1]^{+\bullet}$.

HRMS (CI) calcd. for $C_{25}H_{38}N_3O_6Si$:

504.252990; found: 504.254770

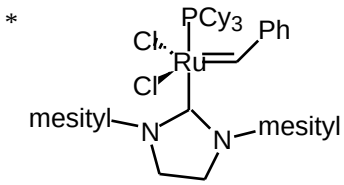
$[\alpha]_D^{20}$ = -55.5° (c=0.56 in $CHCl_3$)

4.16 Synthesis of (2*R*, 8*S*, 8(1'*R*)) *p*-nitrobenzyl 8-(1'-*tert*-butyldimethylsilyloxyethyl)-9-oxo-1,7-diazabicyclo[5.2.0]non-4-ene-2-carboxylate 206



Procedure:

3 mg (6 mol%) of cat.* was added to a solution of **205** (25 mg; 119.1 µmoles; 1 equiv) in 2 mL of toluene. The resulting mixture was heated at 50°C for 2 h. The residue was directly purified by flash column chromatography.



TLC: Rf = 0.15 (EtOAc/cyclohexane 1/4, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 1/4)

Yield: 0.022g (93%)

Mol. formula: $C_{23}H_{33}N_3O_6Si$

FW: 475.62

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$ without TMS, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
14	8.40	d	$^3J_{14\text{-}13}$=8.7	2
13	7.69	d	$^3J_{13\text{-}14}$=8.7	2
4, 5	6.01-5.83	m		2
11a	5.51	d	$^2J_{11a\text{-}11b}$=13.8	1
11b	5.37	d	$^2J_{11b\text{-}11a}$=13.8	1
2	4.82	dd	$^3J_{2\text{-}3a}$=7.5, $^3J_{2\text{-}3b}$=4.8	1
1'	4.21	dq	$^3J_{1'\text{-}8}$=9.6, $^3J_{1'\text{-}2'}$=6.3	1
6a	3.85	dd	$^2J_{6a\text{-}6b}$=15.3, $^3J_{6a\text{-}5}$=5.4	1
8	3.73	d	$^3J_{8\text{-}1'}$=9.6	1
6b	3.56	d	$^2J_{6b\text{-}6a}$=15.3	1
3a	3.17	dt	$^2J_{3a\text{-}3b}$=15.0, $^3J_{3a\text{-}2}$=$^3J_{3a\text{-}4}$=7.5	1
3b	2.60	dt	$^2J_{3b\text{-}3a}$=15.0, $^3J_{3b\text{-}2}$=$^3J_{3b\text{-}4}$=4.8	1
2'	1.36	d	$^3J_{2'\text{-}1'}$=6.3	3
19	1.00	s		9
16, 17	0.15, 0.13	s		6

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 169.1 (C_{10}), 165.9 (C_9), 148.4 (C_{15}), 142.9 (C_{12}), 129.8 (C_4), 129.0 (C_{13}), 127.1 (C_5), 124.4 (C_{14}), 85.3 (C_8), 68.2 ($C_{1'}$), 66.6 (C_{11}), 61.8 (C_6), 58.9 (C_2), 28.9 (C_3), 26.4 (C_{19}), 20.7 ($C_{2'}$), 18.8 (C_{18}), -3.9, -4.1 (C_{16}, C_{17}).

IR (film, cm^{-1}): 3030 (unsat. CH), 2955, 2929, 2856 (sat. CH), 1773 (lactam C=O), 1750 (ester C=O), 1525, 1347 (NO_2), 834.

MS (CI/CH_4-N_2O):

m/z (%) +c: 476 (25) $[M+1]^+$, 418 (3) [M-*t*Bu]$^+$, 391 (8) [M-*t*BuSi+1]$^{+\bullet}$, 341 (5) [M-$NO_2C_6H_4CH_2$+2]$^+$, 165 (33) [M-CO_2PNB-OTBS+1]$^+$, 153 (21) [$OCH_2C_6H_4NO_2$+1]$^{+\bullet}$, 88 (55) [MeSiOCHCH$_3$+1]$^{+\bullet}$, 58 (100) [*t*Bu+1]$^{+\bullet}$;

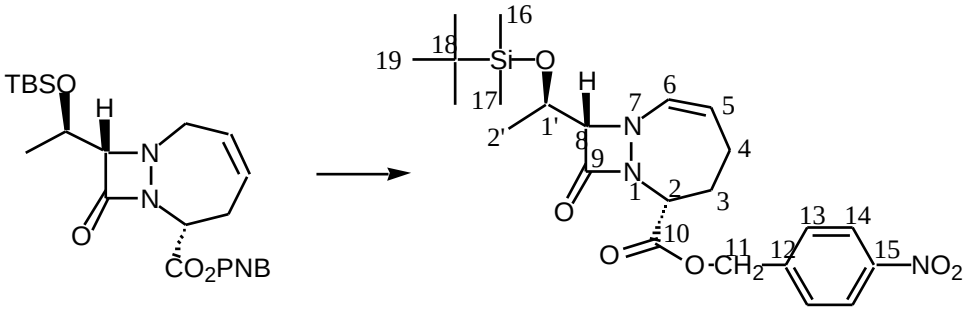
-c: 339 (100) [M-$CH_2C_6H_4NO_2$]$^+$, 208 (3) [M-OPNB-SiMe$_2$*t*Bu]$^{+\bullet}$.

HRMS (CI) calcd. for $C_{23}H_{34}N_3O_6Si$:

476.221690; found: 476.219157

$[\alpha]_D^{20}$ = +144.6° (c=1.0 in $CHCl_3$)

4.17 Synthesis of (2*R*, 8*S*, 8(1'*R*)) *p*-nitrobenzyl 8-(1'-*tert*-butyldimethylsilyloxyethyl)-9-oxo-1,7-diazabicyclo[5.2.0]non-5-ene-2-carboxylate 207



Procedure:

15 mg (31.53 mmoles; 1 equiv) of **206** and 0.3 mg (0.3153 mmole; 0.01 equiv) of carbonyltris-(triphenylphosphine)-rhodium(I)hydride in degassed *m*-xylene (0.6 mL) were heated at 60°C under argon for 2 h.

TLC: Rf = 0.36 (EtOAc/cyclohexane 3/7, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 3/7)

Yield: 0.012g (80%)

Mol. formula: $C_{23}H_{33}N_3O_6Si$

FW: 475.62

Physique aspect: colorless oil

^{1}H NMR (500MHz, $CDCl_3$, without TMS, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
14	8.23	d	$^3J_{14\text{-}13}$=8.7	2
13	7.52	d	$^3J_{13\text{-}14}$=8.7	2
6	6.01	dd	$^3J_{6\text{-}5}$=8.8, $^3J_{6\text{-}4a}$=2.3	1
11a	5.37	d	$^2J_{11a\text{-}11b}$=12.7	1
11b	5.20	d	$^2J_{11b\text{-}11a}$=12.7	1
5	4.79	dt	$^3J_{5\text{-}6}$=8.8, $^3J_{5\text{-}4a}$=8.1, $^3J_{5\text{-}4b}$=6.1	1
2	4.59	dd	$^3J_{2\text{-}3a}$=9.7, $^3J_{2\text{-}3b}$=5.6	1
1'	4.10	dq	$^3J_{1'\text{-}8}$=9.6, $^3J_{1'\text{-}2'}$=6.3	1
8	3.89	d	$^3J_{8\text{-}1'}$=9.6	1
3 + 4	2.42-2.27	m		4
2'	1.21	d	$^3J_{2'\text{-}1'}$=6.3	3
19	0.84	s		9
16, 17	0.16, 0.14	s		6

^{13}C NMR (125MHz, $CDCl_3$, 20°C)

δ = 168.9 (C_{10}), 165.9 (C_9), 147.8 (C_{15}), 142.2 (C_{12}), 139.8 (C_6), 128.5 (C_{13}), 123.8 (C_{14}), 108.6 (C_5), 84.4 (C_8), 67.6 ($C_{1'}$), 65.8 (C_{11}), 58.5 (C_2), 28.3 (C_3), 25.6 (C_{19}), 24.9 (C_4), 19.6 ($C_{2'}$), 17.9 (C_{18}), -4.8, -4.9 (C_{16}, C_{17}).

IR (film, cm^{-1}): 3040 (unsat. CH), 2959, 2920, 2851 (sat. CH), 1781(lactam C=O), 1744 (ester C=O), 1522, 1348 (NO_2), 833.

MS (CI/CH_4-N_2O):

m/z (%) +c: 476 (2) $[M+1]^+$, 243 (35), 137 (20) $[CH_2C_6H_4NO_2+1]^{\bullet\bullet}$, 88 (20) $[MeSiOCHCH_3+1]^{\bullet\bullet}$, 58 (100) $[t\text{Bu}+1]^{\bullet\bullet}$;

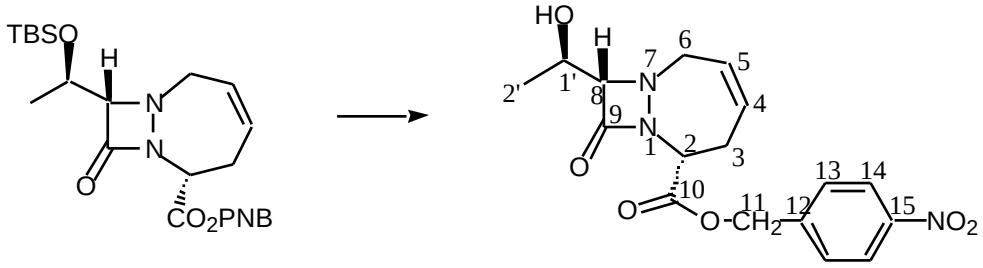
-c: 339 (100) $[M-CH_2C_6H_4NO_2]^+$, 151 (48) $[OPNB-1]^{\bullet\bullet}$.

HRMS (CI) calcd. for $C_{23}H_{34}N_3O_6Si$:

476.221690; found: 476.219499

$[\alpha]_D^{20}$ = -125.0° (c=0.04 in $CHCl_3$)

4.18 Synthesis of (2*R*, 8*S*, 8(1'*R*)) *p*-nitrobenzyl 8-(1'-hydroxyethyl)-9-oxo-1,7-diazabicyclo[5.2.0]non-4-ene-2-carboxylate 268



Procedure:

10% Hydrofluoric acid in acetonitrile (371.2 µl; 426.9 mg; 2.134 mmoles; 7 equiv) was added to a solution of **206** (145 mg; 304.8 µmoles; 1 equiv) in acetonitrile (3 mL). The mixture was stirred at rt overnight. The solvent was evaporated and the residue was directly purified by flash column chromatography.

TLC: Rf = 0.28 (EtOAc/cyclohexane 9/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (EtOAc/cyclohexane 9/1)

Yield: 0.102 g (93%)

Mol. formula: $C_{17}H_{19}N_3O_6$

FW: 361.35

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
14	8.37	d	$^3J_{14\text{-}13}$=8.4	2
13	7.69	d	$^3J_{13\text{-}14}$=8.7	2
4, 5	6.07-5.96	m		2
11a	5.49	d	$^2J_{11a\text{-}11b}$=13.5	1
11b	5.43	d	$^2J_{11b\text{-}11a}$=13.5	1
2	4.88	dd	$^3J_{2\text{-}3a}$=6.9, $^3J_{2\text{-}3b}$=4.6	1
1'	4.26	dq	$^3J_{1'\text{-}8}$=6.3, $^3J_{1'\text{-}2'}$=6.3	1
8	3.93	d	$^3J_{8\text{-}1'}$=6.3	1
6a	3.83	dd	$^2J_{6a\text{-}6b}$=15.9, $^3J_{6a\text{-}5}$=5.4	1
6b	3.67	d	$^2J_{6b\text{-}6a}$=15.9	1
3a	3.14	dt	$^2J_{3a\text{-}3b}$=15.0	1
			$^3J_{3a\text{-}4}$=7.5, $^3J_{3a\text{-}2}$=6.6	
OH	2.87	d	$^3J_{OH\text{-}1'}$=6.3	1
3b	2.68	dt	$^2J_{3b\text{-}3a}$=15.3,	1
			$^3J_{3b\text{-}2}$=4.8, $^3J_{3b\text{-}4}$=4.2	
2'	1.42	d	$^3J_{2'\text{-}1'}$=6.3	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 168.9 (C_{10}), 164.8 (C_9), 148.2 (C_{15}), 142.7 (C_{12}), 129.7 (C_4), 129.2 (C_{13}), 128.1 (C_5), 124.4 (C_{14}), 85.3 (C_8), 66.7 ($C_{1'}$), 66.2 (C_{11}), 61.4 (C_6), 57.9 (C_2), 29.3 (C_3), 20.2 ($C_{2'}$).

IR (film, cm^{-1}): 3455 (OH), 3038 (unsat. CH), 2976, 2922 (sat. CH), 1773 (lactam C=O), 1740 (ester C=O), 1522, 1344 (NO_2).

MS (CI/CH_4-N_2O):

m/z (%) +c: 362 (22) $[M+1]^+$, 153 (19) $[OCH_2C_6H_4NO_2+1]^{\bullet\bullet}$, 137 (5) $[CH_2C_6H_4NO_2+1]^{\bullet\bullet}$, 122 (11) $[C_6H_4NO_2+1]^+$, 88 (66) $[C_4H_6O_2+2]^{\bullet\bullet}$, 60 (100) $[CO_2CH_2+2]^{\bullet\bullet}$;

-c: 225 (100) $[M\text{-}CH_2C_6H_4NO_2]^+$.

HRMS (CI) calcd. for $C_{17}H_{20}N_3O_6$:

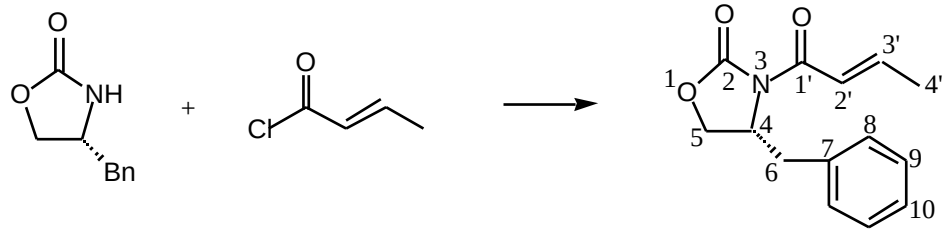
362.135211; found: 362.135906

$[\alpha]_D^{20}$ = -191.9° (c=0.37 in $CHCl_3$)

Chapter 5

Towards bicyclo [4.2.0] aza-β-lactam carboxylic ester derivatives

5.1 Synthesis of (4*R*)-3-((*E*)-2'-butenoyl)-4-benzyl-2-oxazolidinone 215



Reference:

Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256

RN: 151215-01-9

Procedure:

To a solution of (*R*)-4-benzyloxazolidin-2-one (3.672 g; 20.72 mmoles; 1 equiv) in anhydrous THF (*ca.* 0.3M, 69 mL) at -78°C was added 2.5M *n*-butyllithium (8.288 mL; 20.72 mmoles; 1 equiv). After 15 min, freshly distilled crotonyl chloride (2.184 mL; 22.79 mmoles; 1.1 equiv) was added. The mixture was stirred at -78°C for 30 min and at 0°C for 15 min. The reaction is quenched with excess sat. NH_4Cl. The reaction mixture was diluted with ether, then was washed successively with sat. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo.

TLC: Rf = 0.28 (cyclohexane/EtOAc: 7/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 7/3)

Yield: 4.69 g (92%)

Mol. formula: $C_{14}H_{15}NO_3$

FW: 245.28

Physique aspect: white solid

Melting point: 78-80°C

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH, 2', 3'	7.34-7.19	m		7
4	4.75-4.67	m		1
5	4.22-4.07	m		2
6a	3.31	dd	$^2J_{6a\text{-}6b}$=13.5, $^3J_{6a\text{-}4}$=3.3	1
6b	2.80	dd	$^2J_{6b\text{-}6a}$=13.2, $^3J_{6b\text{-}4}$=9.3	1
4'	1.97	d	$^3J_{4'\text{-}3'}$=5.7	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 165.4 ($C_{1'}$), 153.9 (C_2), 147.4 ($C_{3'}$), 135.9 (C_7), 129.9, 129.4, 127.8 (C_8, C_9, C_{10}), 122.3 ($C_{2'}$), 66.7 (C_5), 55.8 (C_4), 38.5 (C_6), 19.2 ($C_{4'}$).

IR (film, cm^{-1}): 3038 (unsat. CH), 2959, 2927 (sat. CH), 1777, 1684 (C=O), 1353.

MS (CI/CH_4-N_2O):

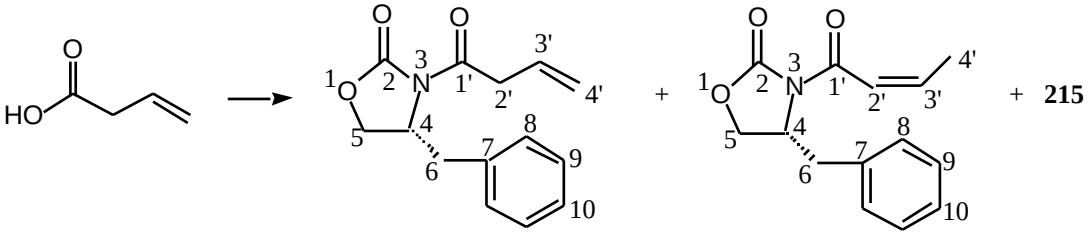
m/z (%) +c: 246 (38) $[M+1]^+$, 178 (15) $[M\text{-}COCHCHCH_3+2]^+$, 99 (7) $[CH_2OCONCHCH_2]^{\bullet\bullet}$, 88 (28) $[OCONCO+2]^+$, 59 (100) $[OCON+1]^{\bullet\bullet}$.

Elemental analysis calcd. for $C_{14}H_{15}NO_3$:

C 68.556, H 6.164, N 5.710; found: C 68.45, H 6.09, N 5.72

$[\alpha]_D^{20}$ = -76.2° (c=1.05 in $CHCl_3$)

5.2 Synthesis of (4*R*)-3-(3'-butenoyl)-4-benzyl-2-oxazolidinone 216 and (4*R*)-3-((*Z*)-2'-butenoyl)-4-benzyl-2-oxazolidinone 217



216 **217**

Procedure: see Experimental Section 4.6

(*R*)-4-benzyloxazolidin-2-one: 1.0 g (5.643 mmol, 1.0 equiv)

Vinyl acetic aicd: 0.544 mL (6.207 mmol, 1.1 equiv)

Triethyl amine: 1.043 mL (7.505 mmol, 1.33 equiv)

Trimethylacetyl chloride: 0.807 mL (6.489 mmol, 1.15 equiv)

n-Butyl lithium (2.4 M): (2.351 mL, 1.0 equiv)

The reaction was quenched by addition of sat. NH_4Cl.

TLC: Rf = 0.34 (**217**);

Rf=0.31 (**216** +**215**) (cyclohexane/EtOAc: 4/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 4/1)

Yield: 0.226 g (22%, **217**); 1.013g (45% **215**; 23% **216**)

Mol. formula: $C_{14}H_{15}NO_3$

FW: 245.28

Compound **216**:

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.34-7.12	m		5
3'	6.03	ddt	$^3J_{3'\text{-}4'\text{a}(trans)}$=17.6	1
			$^3J_{3'\text{-}4'\text{b}(trans)}$=9.9, $^3J_{3'\text{-}2'}$=6.8	
4'a	5.24	dm	$^3J_{4'\text{a}\text{-}3'(trans)}$=17.6	1
4'b	5.22	dm	$^3J_{4'\text{b}\text{-}3'(cis)}$=9.9	1
4	4.78-4.61	m		1
5	4.20-4.13	m		2
2'	3.75-3.70	m		2
6a	3.30	dd	$^2J_{6\text{a}\text{-}6\text{b}}$=13.5, $^3J_{6\text{a}\text{-}4}$=3.3	1
6b	2.80	dd	$^2J_{6\text{b}\text{-}6\text{a}}$=13.5, $^3J_{6\text{b}\text{-}4}$=9.3	1

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 171.6 ($C_{1'}$), 153.9 (C_2), 135.9 ($C_{3'}$), 135.7 (C_7), 129.9, 129.4, 127.8 (C_8, C_9, C_{10}), 119.7 ($C_{4'}$), 66.8 (C_5), 55.7 (C_4), 40.8 ($C_{2'}$), 38.4 (C_6).

Compound **217**:

Physique aspect: white solid

Melting point: 52-54°C

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.34-7.24	m		5
2'	7.05	dq	$^3J_{2'\text{-}3'}$=11.6, $^4J_{2'\text{-}4'}$=1.7	1
3'	6.49	dq	$^3J_{3'\text{-}2'}$=11.5, $^3J_{3'\text{-}4'}$=7.3	1
4	4.78-4.66	sym. m		1
5	4.23-4.12	m		2
6a	3.34	dd	$^2J_{6\text{a}\text{-}6\text{b}}$=13.3, $^3J_{6\text{a}\text{-}4(trans)}$=3.3	1
6b	2.79	dd	$^2J_{6\text{b}\text{-}6\text{a}}$=13.3, $^3J_{6\text{b}\text{-}4(cis)}$=9.5	1
4'	2.19	dd	$^3J_{4'\text{-}3'}$=7.1, $^4J_{4'\text{-}2'}$=1.6	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 165.3 ($C_{1'}$), 153.7 (C_2), 147.1 ($C_{3'}$), 135.9 (C_7), 129.9, 129.4, 127.8 (C_8, C_9, C_{10}), 120.6 ($C_{2'}$), 66.6 (C_5), 55.7 (C_4), 38.5 (C_6), 16.9 ($C_{4'}$).

IR (film, cm^{-1}): 3061 (unsat. CH), 2980, 2919 (sat. CH), 1793, 1674 (C=O), 1195.

MS (CI/CH_4-N_2O):

m/z (%) +c: 246 (100) $[M+1]^+$, 154 (10) $[M-Bn]^+$, 86 (26) $[M+1-COC_2H_4CH_3-Bn]^+$;

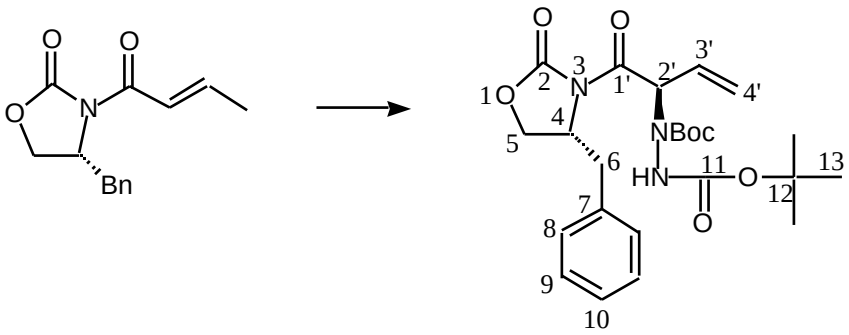
-c: 244 (57) $[M-1]^+$, 216 (35) $[M-1-Me-CH]^+$, 153 (14) $[M-1-Bn]^{\bullet\bullet}$.

HRMS (CI) calcd. for $C_{14}H_{16}N_1O_3$:

246.113019; found: 246.113647

$[\alpha]_D^{20}$ = -65.8° (c=1.11 in $CHCl_3$)

5.3 Synthesis of (3(2'*R*), 4*R*)-3-(2'-((*N*, *N'*-bis-*t*-butoxycarbonyl)hydrazino)-1'-oxo-3'-propenyl)-4-benzyl-2-oxazolidinone 219



Procedure:

To a solution of **215** (532 mg; 2.168 mmoles; 1 equiv) and hexamethylphosphoramide (1.886 mL; 10.84 mmoles; 5 equiv) in dry THF (8 mL) stirred at -78°C under argon, was added sodium bis-(trimethylsilyl)-amide (2.168 mL; 2.168 mmoles; 1 equiv) slowly. The stirring continued at -78°C for 30 min. A precooled (-78°C) solution of di-*tert*-butyl azodicarboxylate (549.3 mg; 2.385 mmoles; 1.1 equiv) in 8 mL of dry DCM was added via cannula to the above enolate solution and after an additional 1 h the reaction was quenched with acetic acid (322.8 µL; 5.639 mmoles; 2.6 equiv). The mixture was partitioned between DCM and sat. NH_4Cl. The aqueous phase was washed with three portions of DCM. The DCM phases were combined, washed with sat. $NaHCO_3$, dried ($MgSO_4$), and evaporated in vacuo.

TLC: Rf = 0.16 (cyclohexane/EtOAc: 4/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 4/1)

Yield: 0.52 g (52%); **γ-addition product:** 0.12 g (11%)

Mol. formula: $C_{24}H_{33}N_3O_7$

FW: 475.54

Physique aspect: colorless glass foam

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.35-7.22	m		5
NH	6.73	s		1
2'	6.46	br. s		1
3'	6.08-5.86	m		1
4'a	5.36	d	$^3J_{4'a\text{-}3'(cis)}$=10.5	1
4'b	5.31	d	$^3J_{4'b\text{-}3'(trans)}$=17.7	1
4	4.66-4.58	m		1
5	4.18	apparent d	^3J=5.7	2
6a	3.44-3.20	m		1
6b	2.88-2.64	m		1
13	1.48	s		9
13'	1.46	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 172.1 ($C_{1'}$), 155.7 (C_{11}), 152.9 (C_2), 135.6 (C_7), 130.3 ($C_{3'}$), 129.9, 129.6, 127.9 (C_8, C_9, C_{10}), 121.8 ($C_{4'}$), 82.6, 81.3 (C_{12}), 67.1 (C_5), 63.5 ($C_{2'}$), 56.2 (C_4), 38.3 (C_6), 28.6, 28.9 (C_{13}).

IR (film, cm^{-1}): 3342 (NH), 3088, 3055 (unsat. CH), 2979, 2937 (sat. CH), 1789, 1699 (C=O), 1392, 1156.

MS (CI/CH_4-N_2O):

m/z (%) +c: 476 (4) $[M+1]^+$, 420 (5) $[M\text{-}t\text{Bu}+2]^+$, 375 (6) $[M\text{-}CO_2t\text{Bu}+1]^{+\bullet}$, 364 (100) $[M\text{-}2t\text{Bu}+3]^+$, 320 (30) $[M\text{-}Ot\text{Bu}\text{-}t\text{Bu}\text{-}C_2H_3+2]^+$, 276 (7) $[M\text{-NHBoc}\text{-}t\text{Bu}\text{-}C_2H_3+1]^{+\bullet}$, 205 (5) $[BnCHCH_2OCONCO+1]^{+\bullet}$, 57 (12) $[t\text{Bu}]^+$;

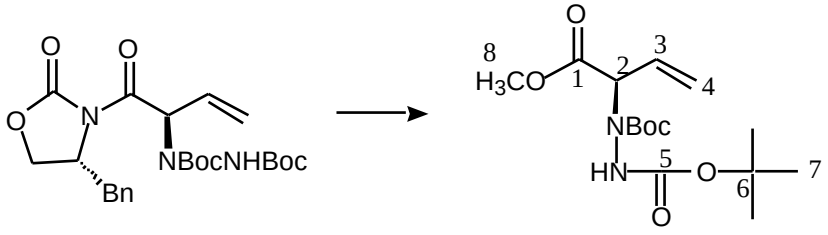
-c: 475 (15) $[M]^{+\bullet}$, 231 (100).

HRMS (CI) calcd. for $C_{24}H_{34}N_3O_7$:

476.239676; found: 476.238121

$[\alpha]_D^{20}$ = -16.5° (c=1.15 in $CHCl_3$)

5.4 Synthesis of (2*R*) methyl 2-((*N*, *N'*-bis-*t*-butoxycarbonyl)hydrazino)-3-butenoate 225



Procedure:

To a solution of **219** (1.936 g; 4.071 mmoles; 1 equiv) in 40 mL of dioxane (ca 0.1 M) at 0°C was added 4.277 mL of H_2O_2 (30% aqueuse solution) and lithium hydroxide monohydrate (512.5 mg; 12.21 mmoles; 3 equiv). The mixture was stirred at 0°C for 4 h, then was treated with a solution of 6.773 g sodium sulfite in 36 mL of H_2O (*ca.* 1.5 M). Following the addition of 45 mL of 5% aqueous $NaHCO_3$, the resulting solution was extracted with EtOAc (2X100 mL) (**100% recovery of oxazolidinone**). The aqueous residue was acidified with 1N $NaHSO_4$ (*ca.* pH 1-2) and extracted with four portions of DCM. The DCM extracts were combined, dried ($MgSO_4$) and concentrated in vacuo. The resulting DCM solution of the above crude was treated dropwise at 0°C with ethereal CH_2N_2 until a yellow color persisted. The stirring was continued for another 30 min at 0°C. The solution was decolorized with glacial HOAc, washed with sat. $NaHCO_3$, dried ($MgSO_4$) and evaporated in vacuo.

TLC: Rf = 0.25 (cyclohexane/EtOAc: 4/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 4/1)

Yield: 0.35 g (26%)

Mol. formula: $C_{15}H_{26}N_2O_6$

FW: 330.38

Physique aspect: pale yellow oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
NH	6.63	s		1
3	5.94	ddd	$^3J_{3\text{-}4a(trans)}$=17.3, $^3J_{3\text{-}4b(cis)}$=10.3, $^3J_{3\text{-}2}$=6.8	1
4a	5.40	d	$^3J_{4a\text{-}3(trans)}$=17.2	1
4b	5.35	d	$^3J_{4b\text{-}3(cis)}$=10.3	1
2	5.34	d	$^3J_{2\text{-}3}$=6.5	1
8	3.76	s		3
7	1.46	s		9
7'	1.43	s		9

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 171.3 (C_1), 155.3 (C_5), 130.3 (C_3), 120.7 (C_4), 82.3, 81.2 (C_6), 62.8 (C_2), 52.7 (C_8), 28.4, 28.3 (C_7).

IR (film, cm^{-1}): 3330 (NH), 3089 (unsat. CH), 2979, 2934 (sat. CH), 1733 (C=O), 1394, 1156.

MS (CI/CH_4-N_2O):

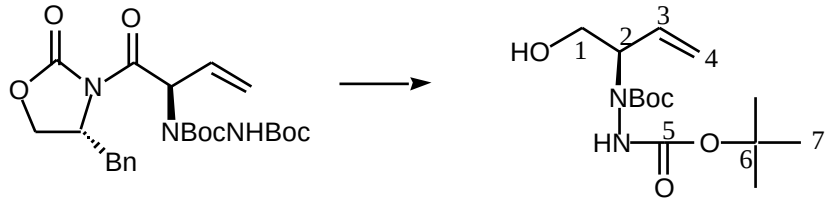
m/z (%) +c: 230 (5) $[M\text{-}NHBoc+1]^+$, 218 (100) $[M\text{-}2t\text{Bu}+2]^{\bullet\bullet}$, 175 (40) $[NHBocNCO_2+1]^+$, 131 (10) $[NNHBoc+1]^+$, 115 (8) $[NBoc]^{\bullet\bullet}$, 57 (20) $[t\text{Bu}]^+$;

-c: 329 (100) $[M-1]^+$, 273 (32) $[M-t\text{Bu}]^+$, 231 (36) $[\text{NBocNHBoc}]^{+\bullet}$, 229 (28) $[M-\text{NHBoc}]^{+\bullet}$, 196 (34) $[\text{M-Boc-OMe-2}]^{+\bullet}$, 157 (17) $[\text{M-NHBoc-}t\text{Bu}]^{+\bullet}$.

HRMS (CI) calcd. for $C_{15}H_{27}N_2O_6$:

331.186912; found: 331.186315

5.5 Synthesis of (2*R*)-((*N*, *N'*-bis-*t*-butoxycarbonyl)hydrazino)-3-buten-1-ol 228



Reference:

Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114 (24)*, 9434-9453

Procedure:

To a solution of **219** (250 mg; 525.7 µmoles; 1 equiv) in 10 mL of dry THF at 0°C was added methyl alcohol (23.42 µL; 578.2 µmoles; 1.1 equiv) and 2.0 M of lithium borohydride in THF (289.1 µL; 259 mg; 578.2 µmoles; 1.1 equiv). The resulting solution was stirred at rt for two days. The reaction was quenched by addition of 10 mL of 0.5 M aq. sodium potassium tartrate and 10 mL of ether. The mixture was stirred for 2 h, and the layers were separated. The aqueous layer was extracted with two 15-mL portions of ether. The combined organic layers were dried ($MgSO_4$), filtered and concentrated.

TLC: Rf = 0.25 (cyclohexane/EtOAc: 7/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 7/3)

Yield: 0.056 g (35%)

Mol. formula: $C_{14}H_{26}N_2O_5$

FW: 302.37

Physique aspect: colorless oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
NH	6.24	s		1
3	5.66	ddd	$^3J_{3\text{-}4a(trans)}$=17.4, $^3J_{3\text{-}4b(cis)}$=10.7, $^3J_{3\text{-}2}$=5.6	1
4b	5.20	d	$^3J_{4b\text{-}3(cis)}$=10.7	1
4a	5.16	d	$^3J_{4a\text{-}3(trans)}$=17.2	1
2	3.70-3.46	m		1
1	3.58	t	$^3J_{1\text{-}2}$=6.9	2
OH	1.78	s		1
7	1.49	s		9
7'	1.48	s		9

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 155.8 (C_5), 129.6 (C_3), 118.6 (C_4), 83.4, 83.1 (C_6), 62.8 (C_2), 62.1 (C_1), 28.8, 28.7 (C_7).

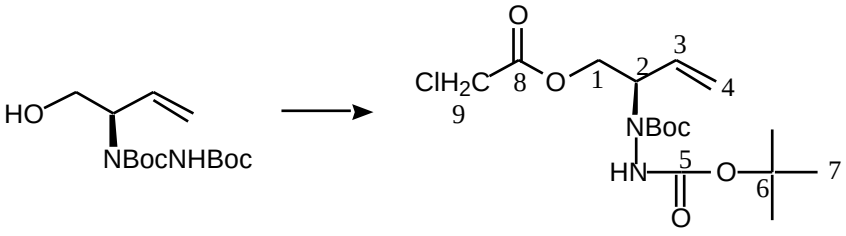
IR (film, cm^{-1}): 3459 (OH), 3299 (NH), 3092 (unsat. CH), 2979, 2936 (sat. CH), 1716 (C=O), 1368, 1158 (C-O).

MS (CI/CH_4-N_2O):

m/z (%) +c: 303 (1) $[M+1]^+$, 190 (100) [M-2*t*Bu+2] $^{+\bullet}$, 175 (15) $[NHBocNCO_2+1]^+$, 146 (42) [M-CO_2*t*Bu-*t*Bu+2] $^{+\bullet}$, 115 (8) [NBoc] $^{+\bullet}$, 73 (18) $[OtBu]^+$, 57 (48) $[tBu]^+$.

$[\alpha]_D^{20}$ = -22.2° (c=0.36 in $CHCl_3$)

5.6 Synthesis of (2*R*)-((*N*, *N'*-bis-*t*-butoxycarbonyl)hydrazino)-3-buten-1-ol, α-chloroacetate 230



Procedure:

To a solution of **228** (234 mg; 773.8 µmoles; 1 equiv) in 4 mL of DCM, triethylamine (118.3 µL; 851.2 µmoles; 1.1 equiv) and 4-dimethylaminopyridine (9.5 mg; 77.38 µmoles; 0.1 equiv) were added at 0°C, then chloroacetyl chloride (69.08 µL; 851.2 µmoles; 1.1 equiv) was added dropwise. The mixture was stirred at rt for 15 h. The reaction mixture was then diluted with DCM, washed with water. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated.

TLC: Rf = 0.27 (cyclohexane/EtOAc: 4/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 4/1)

Yield: 0.178 g (61%)

Mol. formula: $C_{16}H_{27}ClN_2O_6$

FW: 378.85

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
NH	6.24	s		1
3	5.81	ddd	$^3J_{3\text{-}4a(trans)}$=17.4	1
			$^3J_{3\text{-}4b(cis)}$=10.5, $^3J_{3\text{-}2}$=6.9	
4a	5.27	d	$^3J_{4a\text{-}3(trans)}$=17.1	1
4b	5.26	d	$^3J_{4b\text{-}3(cis)}$=11.4	1
1 + 2	5.01-4.13	m		3
9	4.07	s		2
7	1.46	s		18

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 168.1 (C_8), 155.3 (C_5), 132.4 (C_3), 119.6 (C_4), 82.5, 80.8 (C_6), 65.1 (C_1), 58.1 (C_2), 41.6 (C_9), 28.9 (C_7).

IR (film, cm^{-1}): 3325 (NH), 3085 (unsat. CH), 2979, 2933 (sat. CH), 1748, 1706 (C=O), 1368, 1162 (C-O).

MS (CI/CH_4-N_2O):

m/z (%) +c: 278 (6) [M-Boc+1] $^{+\bullet}$, 267 (100) [M+2-2*t*Bu+1]$^+$, 233 (12) [M-2(O*t*Bu)+1]$^+$, 222 (86) [M+2-Boc-*t*Bu+1] $^{+\bullet}$, 173 (38) [NBocNCO$_2$]$^+$, 57 (80) [*t*Bu]$^+$;

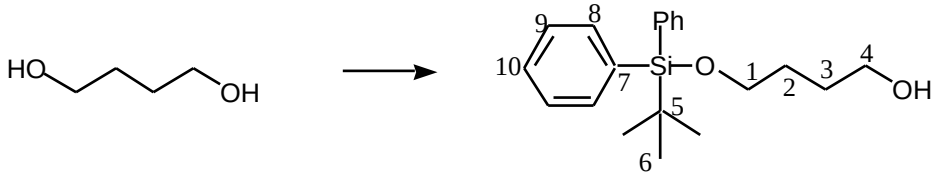
-c: 380 (20) [M+2] $^{+\bullet}$, 378 (51) [M] $^{+\bullet}$, 342 (3) [M-Cl-1] $^{+\bullet}$, 234 (16) [M+2-2(O*t*Bu)] $^{+\bullet}$, 116 (16) [NHBoc]$^+$, 83 (100) [OCH$_2$CHNCHCH$_2$-1] $^{+\bullet}$.

HRMS (CI) calcd. for $C_{16}H_{28}N_2O_6Cl$:

379.163590; found: 379.164197

$[\alpha]_D^{20}$ = -16.7° (c=0.30 in $CHCl_3$)

5.7 Synthesis of 1-*O*-(*tert*-butyldiphenylsilyl)-1,4-butanediol 234



Reference:

Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. J. *J. Org. Chem.* **1996**, *61*, 2413-2417

RN: 130372-07-5

Procedure:

A solution of 1,4-butanediol (3.066 mL; 34.6 mmoles; 3 equiv) in 18 mL of tetrahydrofuran was cooled to -78°C under argon, and the resulting white suspension was treated dropwise with 2.2M *n*-butyllithium (5.243 mL; 11.53 mmoles; 1 equiv). The reaction mixture became very viscous. After being stirred for additional 5 min, the reaction mixture was treated dropwise with *t*-butylchlorodiphenylsilane (3 mL; 3.171 g; 11.53 mmoles; 1 equiv), and the resulting mixture was allowed to warm to rt to give a white suspension. After being stirred at rt for 40 min, the reaction mixture was quenched with 20 mL of water and 20 mL of sat. NH_4Cl, and the separated aqueous layer was extracted with ether (3X30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated.

TLC: Rf = 0.20 (cyclohexane/EtOAc: 4/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 4/1)

Yield: 3.4 g (90%; lit. 90%)

Mol. formula: $C_{20}H_{28}O_2Si$

FW: 328.52

Physique aspect: colorless oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

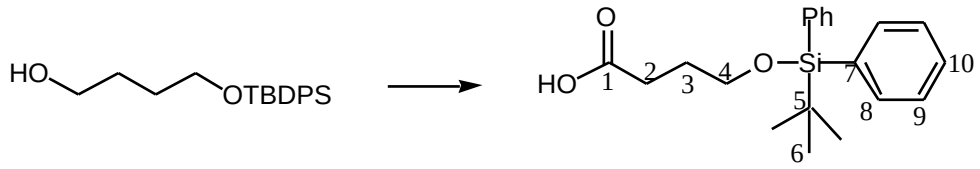
Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
9	7.70-7.65	m		4
8 + 10	7.43-7.37	m		6
1 + 4	3.73-3.61	m		4
OH	2.18	t	$^3J_{OH-4}$=8.4	1
2 + 3	1.71-1.61	m		4
6	1.05	s		9

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 136.3 (C_9), 134.4 (C_7), 130.3 (C_{10}), 128.4 (C_8), 64.7 (C_4), 63.4 (C_1), 30.5 (C_3), 29.9 (C_2), 27.6 (C_6), 19.8 (C_5).

IR (film, cm^{-1}): 3340 (OH), 3070, 3044 (arom. CH), 2931, 2858 (sat. CH), 1472, 1428, 1389, 1111, 1063.

5.8 Synthesis of 4-((*tert*-butyldiphenylsilyl)oxy)butanoic acid 232



Reference:

Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. J. *J. Org. Chem.* **1996**, *61*, 2413-2417

RN: 118715-16-5

Procedure:

A solution of **234** (2.528 g; 7.694 mmoles; 1 equiv) in 20 mL of DMF was cooled to 0°C under argon and was treated protionwise with pyridinium dichromate (10.13 g; 26.93 mmoles; 3.5 equiv). The resulting mixture was allowed to warm to rt and was stirred overnight (15 h). The reaction was then poured into a separatory funnel containing 50 mL of water and extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure.

TLC: Rf = 0.31 (cyclohexane/EtOAc: 7/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 7/3)

Yield: 1.5 g (57%; lit. 75%)

Mol. formula: $C_{20}H_{26}O_3Si$

FW: 342.51

Physique aspect: colorless oil

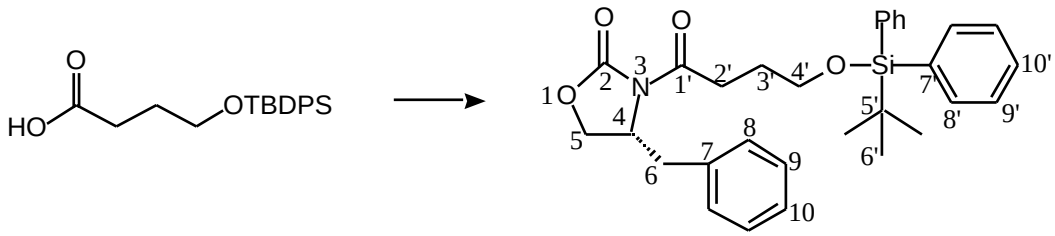
^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
COOH	11.36	br. s		1
9	7.69-7.65	m		4
8 + 10	7.42-7.36	m		6
4	3.70	t	$^3J_{4\text{-}3}$=6.0	2
2	2.51	t	$^3J_{2\text{-}3}$=7.4	2
3	1.89	quint	^3J=6.5	2
6	1.05	s		9

^{13}C NMR (50MHz, $CDCl_3$, 20°C)

δ = 181.0 (C_1), 136.2 (C_9), 134.3 (C_7), 130.3 (C_{10}), 128.4 (C_8), 63.4 (C_4), 31.4 (C_2), 28.1 (C_3), 27.5 (C_6), 19.8 (C_5).

5.9 Synthesis of (4*R*)-3-(4'-((*tert*-butyldiphenylsilyl)oxy)butanoyl)-4-benzyl-2-oxazolidinone 235



Reference:

Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria Jr., J-F. *Tetrahedron* **1988**, *44(17)*, 5525-5540

Procedure:

To a mechanically stirred solution of **232** (4.22 g; 12.32 mmoles; 1 equiv) and triethylamine (2.055 mL; 14.78 mmoles; 1.2 equiv) in 60 mL of dry THF, cooled to -78°C under argon was added trimethylacetyl chloride (1.517 mL; 12.32 mmoles; 1 equiv). The mixture was warmed to 0°C for 1 h, and then recooled to -78°C. A solution of (*R*)-4-benzyloxazolidin-2-one (2.183 g; 12.32 mmoles; 1 equiv) and 10 mg of triphenylmethane (indicator) in 35 mL of dry THF, stirred at -30°C to -45°C under argon, was treated dropwise with *n*-butyllithium (4.928 mL; 12.32 mmoles; 1 equiv) until an orange color persisted. The resulting solution was cooled to -78°C and then added, via rapid cannulation , to the above stirred mixture containing the mixed anhydride. The residual metalated oxazolidinone was rinsed in with two 5-mL portions of dry THF and the resulting mixture was stirred at -78°C for 30 min. After warming to 0°C (2 h), the mixture was partioned between DCM and sat. NH_4Cl. The DCM phase was washed with 5% aq. $NaHCO_3$, followed by half-saturated aq. NaCl, dried ($MgSO_4$) and evaporated in vacuo.

TLC: Rf = 0.21 (cyclohexane/EtOAc: 9/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 9/1)

Yield: 5.65 g (91%)

Mol. formula: $C_{30}H_{35}NO_4Si$

FW: 501.69

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.

PhH	7.69-7.17	m		15
4	4.66-4.56	m		1
5	4.13	apparent d	$^3J_{5\text{-}4(cis)}$=5.1	2
4'	3.75	t	$^3J_{4'\text{-}3'}$=6.0	2
6a	3.26	dd	$^2J_{6a\text{-}6b}$=13.5, $^3J_{6a\text{-}4}$=3.3	1
2'	3.08	t	$^3J_{2'\text{-}3'}$=7.3	2
6b	2.72	dd	$^2J_{6b\text{-}6a}$=13.5, $^3J_{6b\text{-}4}$=9.3	1
3'	1.97	quint.	$^3J_{3'\text{-}2'}$=7.2, $^3J_{3'\text{-}4'}$=6.6	2
6'	1.06	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 173.6 ($C_{1'}$), 153.9 (C_2), 136.1 ($C_{8'}$), 135.9 (C_7), 134.3 ($C_{7'}$), 130.1 ($C_{10'}$), 129.9 (C_8), 129.5 (C_9), 128.2 ($C_{9'}$), 127.9 (C_{10}), 66.8 (C_5), 63.5 ($C_{4'}$), 55.8 (C_4), 38.6 (C_6), 32.9 ($C_{2'}$), 27.7 ($C_{3'}$), 27.6 ($C_{6'}$), 19.9 ($C_{5'}$).

IR (film, cm^{-1}): 3070, 3029 (arom. CH), 2958, 2931, 2858 (sat. CH), 1789, 1700 (C=O), 1472, 1428, 1388, 1111.

MS (CI/CH_4-N_2O):

m/z (%) +c: 247 (40) $[M+1\text{-OTBDPS}]^{+\bullet}$, 205 (100) $[M+1\text{-}(CH_2)_3OTBDPS]^{+\bullet}$, 121 (35) $[OSiPh]^+$, 105 (42) $[SiPh]^+$, 86 (65) $[C_2H_4CO_2N+1]^+$, 58 (45) $[t\text{Bu}+1]^{+\bullet}$;

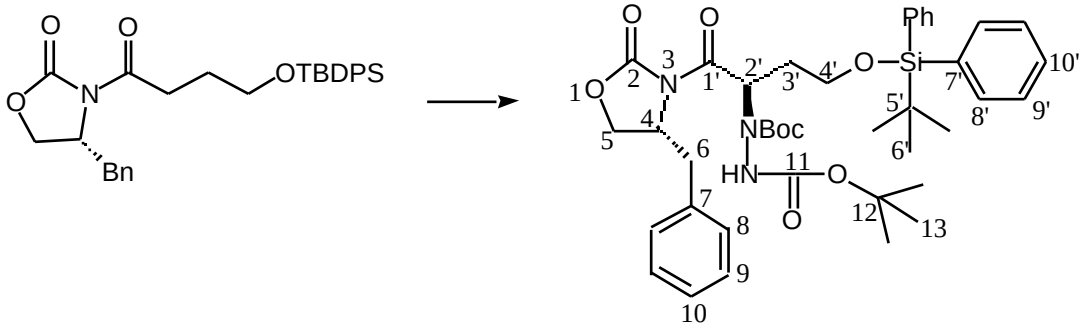
-c: 246 (50) $[M\text{-OTBDPS}]^+$, 143 (100) $[C_6H_9O_3N]^{+\bullet}$.

Elemental analysis calcd. for $C_{30}H_{35}NO_4Si$:

C 71.822, H 7.031, N 2.791; found: C 71.70, H 7.03, N 3.40

$[\alpha]_D^{20}$ = -32.9° (c=0.76 in $CHCl_3$)

5.10 Synthesis of (3(2'*R*), 4*R*)-3-(2'-((*N*, *N'*-bis-*tert*-butoxycarbonyl)hydrazino)-4'-((*tert*-butyldiphenylsilyl)oxy)butanoyl)-4-benzyl-2-oxazolidinone 236



Procedure:

To a solution of **235** (330 mg; 657.7 mmoles; 1 equiv) in dry THF (6 mL) stirred at -78°C under argon atmosphere, was added sodium bis-(trimethylsilyl)-amide (1.0 M in THF, 723.5 mL; 629.4 mg; 723.5 mmoles; 1.1 equiv) slowly. The stirring was continued at -78°C for 30 min. A precooled (-78°C) solution of di-*tert*-butyl azodicarboxylate (166.6 mg; 723.5 mmoles; 1.1 equiv) in 3 mL of dry CH_2Cl_2 was added via cannula to the above enolate solution and after an additional 1h the reaction was quenched with acetic acid (97.9 mL; 1.71 mmoles; 2.6 equiv). The mixture was partitioned between DCM and sat. NH_4Cl. The aqueous phase was washed with three portions of DCM. The DCM phases were combined, washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$) and evaporated in vacuo.

TLC: Rf = 0.22 (cyclohexane/EtOAc: 85/15, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 85/15)

Yield: 0.34 g (71%, major isomer 2'*R*); **de:** 2'(*R*):2'(*S*) 9:1

Mol. formula: $C_{40}H_{53}N_3O_8Si$

FW: 731.96

Physique aspect: colorless foam

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
PhH	7.67-7.21	m		15
4	4.52-4.48	m		1
5, 4', 2'	4.10-3.90	m		5
6a	3.40-3.34	m		1
6b	2.70-2.65	m		1
3'	2.21-2.19	m		2
13	1.46	s		18
6'	1.05	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 174.2 ($C_{1'}$), 155.9, 156.1 (C_{11}), 153.1 (C_2), 136.1 ($C_{8'}$), 134.3 (C_7), 134.3 ($C_{7'}$), 130.1 ($C_{10'}$), 129.9 (C_8), 129.5 (C_9), 128.2 ($C_{9'}$), 127.8 (C_{10}), 82.8, 81.6 (C_{12}), 67.0 (C_5), 61.6 ($C_{4'}$), 58.6 ($C_{2'}$), 56.2 (C_4), 38.3 (C_6), 32.5 ($C_{3'}$), 28.9, 28.8 (C_{13}), 27.5 ($C_{6'}$), 19.9 ($C_{5'}$).

IR (film, cm^{-1}): 3367 (NH), 3070, 3029 (arom. CH), 2977, 2931, 2858 (sat. CH), 1789, 1750, 1715 (C=O), 1474, 1428, 1392, 1111.

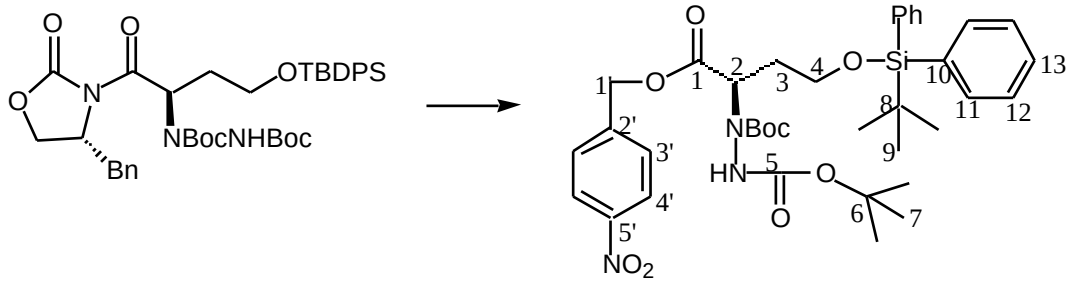
MS (D-APCI):

m/z (%) +c: 603 (5) [M-O*t*Bu-*t*Bu+2] $^{\bullet\bullet}$, 577 (9) [M-2Ph] $^{\bullet\bullet}$, 534 (100) [M-2CO_2*t*Bu+2]$^+$, 453 (7) [M-2CO_2*t*Bu-Ph+1] $^{\bullet\bullet}$, 424 (15) [M-NBoc-NHBoc-Ph+1]$^+$, 346 (16) [M-NBoc-NHBoc-2Ph]$^+$, 276 (20) [M-Boc-NHBoc-TBDPS+1] $^{\bullet\bullet}$, 249 (60) [$COCHCH_2CH_2OSiPh$*t*Bu+2]$^+$.

Elemental analysis for $C_{40}H_{53}N_3O_8Si.1/2C_6H_{12}$(cyclohexane):

C 66.72, H 7.68, N 5.42; found: C 66.82, H 7.41, N 5.55
$[\alpha]_D^{20}$ = -23.7° (c=0.59 in $CHCl_3$)

5.11 Synthesis of (2*R*) *p*-nitrobenzyl 2-((*N*, *N'*-bis-*t*-butoxycarbonyl)hydrazino)-4-((*tert*-butyldiphenylsilyl)oxy)butanoate 239



Procedure:

To a solution of **236** (340 mg; 464.5 mmoles; 1 equiv) in 7 mL of tetrahydrofuran and 2 mL of water at 0°C was added hydrogen peroxide (30% aqueous solution, 0.244 mL; 2.787 mmoles; 6 equiv) and lithium hydroxide monohydrate (39.0 mg; 929 mmoles; 2 equiv). The mixture was stirred for 4 h at 0°C, and was then treated with a solution of sodium sulfite (386.3 mg; 3.065 mmoles; 6.6 equiv) in 2 mL of H_2O (ca. 1.5 M). The mixture was partitioned between 1N $NaHSO_4$ and DCM. The aqueous phase was extracted with DCM(3X). The DCM extracts were combined, dried ($MgSO_4$) and concentrated in vacuo.

Potassium carbonate (96.3 mg; 696.7 mmoles; 1.5 equiv), 4-nitrobenzyl bromide (200.6 mg; 929 mmoles; 2 equiv) and tetrabutylammonium iodide (1.7 mg; 4.645 mmoles; 0.01 equiv) were added to the above residue in 6 mL of DMF. The mixture was stirred for 12 h, then excess K_2CO_3 was filtered. The filtrate was diluted with ether and water. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated.

TLC: Rf = 0.22 (cyclohexane/EtOAc: 9/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 9/1)

Yield: 0.29 g (87%)

Mol. formula: $C_{37}H_{49}N_3O_9Si$

FW: 707.89

Physique aspect: colorless foam

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.

4'	8.19	d (AB)	$^3J_{4'-3'}$=8.4	2
11	7.68	d	$^3J_{11-12}$=6.6	4
3'	7.49	d (AB)	$^3J_{3'-4'}$=8.4	2
12, 13	7.41-7.35	m		6
NH	6.53	br. s		1
1'	5.24	s		2
2	5.33-5.29	m		1
4	3.97-3.76	m		2
3	2.14-2.03	m		2
7	1.42	s		18
9	1.06	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 172.2 (C_1), 155.8, 155.4 (C_5), 148.2 ($C_{5'}$), 143.1 ($C_{2'}$), 136.1 (C_{11}), 134.1 (C_{10}), 130.2 (C_{13}), 128.7 ($C_{4'}$), 128.2 (C_{12}), 124.3 ($C_{3'}$), 82.5, 81.4 (C_5), 66.1 ($C_{1'}$), 60.5 (C_4), 57.5 (C_2), 32.4 (C_3), 28.8 (C_7), 27.6 (C_9), 19.9 (C_8).

IR (film, cm^{-1}): 3364 (NH), 3072, 3050 (arom. CH), 2978, 2931, 2857 (sat. CH), 1748, 1715 (C=O), 1525 (NO_2), 1474, 1428, 1392, 1111.

MS (D-APCI):

m/z (%) +c: 707 (10) [M]$^{+\bullet}$, 651 (12) [M-*t*Bu+1]$^{+\bullet}$, 595 (42) [M-2*t*Bu+2]$^{+\bullet}$, 552 (100) [M-2Ph-1]$^+$, 508 (75) [M-2Ph-*t*Bu+1]$^+$, 474 (35) [M-CO_2*t*Bu-Ph-*t*Bu+1]$^+$;

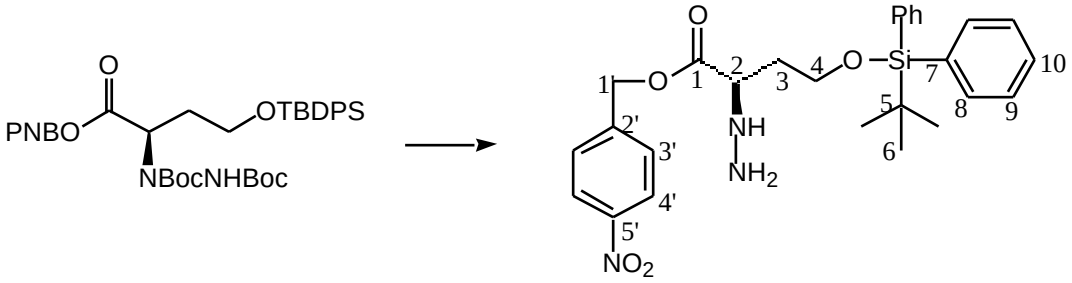
-c: 706 (50) [M-1]$^+$, 650 (5) [M-*t*Bu]$^+$, 571 (15) [M-PNB]$^+$, 255 (14) [OTBDPS]$^+$.

Elemental analysis calcd. for $C_{37}H_{49}N_3O_9Si$:

C 62.778, H 6.976, N 5.935; found: C 62.05, H 6.96, N 6.09

$[\alpha]_D^{20}$ = +7.0° (c= 0.57 in $CHCl_3$)

5.12 Synthesis of (2*R*) *p*-nitrobenzyl 2-hydrazino-4-((*tert*-butyldiphenylsilyl)oxy)butanoate



Procedure:

10 mL of trifluoroacetic acid was added to a solution of **239** (1.336 g; 1.887 mmoles; 1 equiv) in 20 mL of dichloromethane at 0°C, then the mixture was stirred at rt for 30 min. The excess

TFA was removed in vacuo. 30 mL of DCM (PA) was added to the residue, then was washed with sat. $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to give a pale yellow oil.

Yield: quantitative

Mol. formula: $C_{27}H_{33}N_3O_5Si$

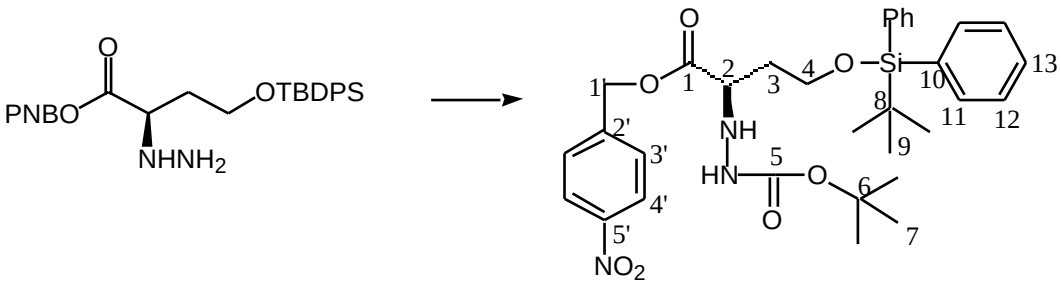
FW: 507.66

Physique aspect: pale yellow oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
4'	8.18	d (AB)	$^3J_{4'-3'}$=8.7	2
3', 8, 9,	7.65-7.33	m		12
10	5.23	s		2
1'	3.80-3.72	m		6
2, 4, NH	2.00-1.78	m		2
3	1.05	s		9
6				

5.13 Synthesis of (2*R*) *p*-nitrobenzyl 2-((2*N'*-*t*-butoxycarbonyl)hydrazino)-4-((*tert*-butyldiphenylsilyl)oxy)butanoate 240



Procedure:

To a suspension of the hydrazino ester and di-*t*-butyl dicarbonate (420.3 mg; 1.887 mmoles; 1 equiv) in dry CH_2Cl_2 (15 mL) was added *n,n*-diisopropylethylamine (335.4 µL; 1.887 mmoles; 1 equiv). The suspension was allowed to stir at rt for 3 h. The reaction mixture was washed with brine. Then the organic layer was dried over $MgSO_4$, filtered and evaporated.

TLC: Rf = 0.31 (cyclohexane/EtOAc: 3/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 3/1)

Yield: 0.92 g (80%, overall)

Mol. formula: $C_{32}H_{41}N_3O_7Si$

FW: 607.77

Physique aspect: pale yellow oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
4'	8.16	d (AB)	$^3J_{4'-3'}$=9.0	2
11	7.66	d	$^3J_{11-12}$=7.8	4
3'	7.45	d (AB)	$^3J_{3'-4'}$=8.7	2
12 + 13	7.41-7.35	m		6
NH-Boc	6.25	br. s		1
1'	5.19	d	$^2J_{1'a-1'b}$=13.2	2
NH	4.61	br. s		1
2	3.96	q	$^3J_{2-3}$=5.4, $^3J_{2-NH}$=6.6	1
4	3.82	t	$^3J_{4-3}$ = 6.0	2
3	1.98	quint	$^3J_{3-4}$=$^3J_{3-2}$=5.7	2
7	1.44	s		18
9	1.04	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 173.4 (C_1), 156.8 (C_5), 148.1 ($C_{5'}$), 143.4 ($C_{2'}$), 136.1 (C_{11}), 133.8 (C_{10}), 130.2 (C_{13}), 128.8 ($C_{4'}$), 128.2 (C_{12}), 124.2 ($C_{3'}$), 81.1 (C_6), 65.8 ($C_{1'}$), 61.7 (C_2), 61.4 (C_4), 33.9 (C_3), 28.9 (C_7), 27.4 (C_9), 19.8 (C_8).

IR (film, cm^{-1}): 3319 (NH), 3088, 3029 (arom. CH), 2970, 2931, 2857 (sat. CH), 1742 (ester C=O), 1716 (carbamate C=O), 1524 , 1347 (NO_2), 1111.

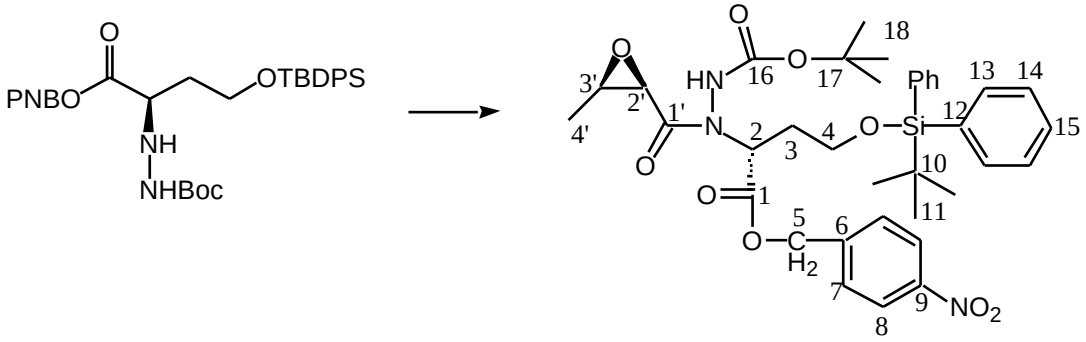
MS (CI/CH_4-N_2O):

m/z (%) +c: 608 (3) $[M+1]^+$, 552 (2) $[M-t\text{Bu}+2]^+$, 453 (4) [M-2Ph] $^{+\bullet}$, 257 (12) $[OTBDPS+2]^+$, 172 (17) $[NHBocNHC_3H_5]^{+\bullet}$, 153 (35) [OPNB+1] $^{+\bullet}$, 57 (100) $[t\text{Bu}]^+$;

-c: 471 (32) $[M-PNB]^+$, 354 (8) $[M-OPNB-CO_2t\text{Bu}]^{+\bullet}$, 278 (13) $[M-OTBDPS-Ot\text{Bu}-1]^+$, 201 (100) $[M-OTBDPS-PNB-Me]^+$.

$[\alpha]_D^{20}$ = +10.4° (c=1.25 in $CHCl_3$)

5.14 Synthesis of (2*R*, 2'*R*, 3'*R*) *p*-nitrobenzyl 2-(1*N*-(2', 3'-epoxybutano)-2*N'*-(*t*-butoxycarbonyl)hydrazino)-4-((*tert*-butyldiphenylsilyl)oxy)butanoate 241



Procedure:

To a stirred solution of (2*R*, 3*R*)-2, 3-epoxybutanoic acid (171.5 mg; 1.68 mmoles; 1.5 equiv) in anhydr. DCM (10 mL) maintained at 0°C, 296.4 µL (2.24 mmoles; 2 equiv) of 1-chloro-*N*,*N*,2-trimethylpropenylamine was added in one portion and the resuting mixture was stirred at 0°C. After 20 min, a solution of **240** (681 mg; 1.12 mmoles; 1 equiv) and 2,4,6-collidine (370.1 µL; 2.801 mmoles; 2.5 equiv) in 6 mL of DCM was added. The flask was washed with two portions of 2 mL of DCM. The mixture was stirred for 30 min at 0°C, then allowed to warm up slowly to rt (around 1 h). The reaction mixture was stirred at rt overnight (16 h). 20 mL of DCM was added to the reaction mixture. Then this solution was washed with 5% aq. $NaHCO_3$, the aqueous layer was back-extracted with DCM (2X15 mL). The organic phases were combined and washed with sat. NH_4Cl, dried over $MgSO_4$ and concentrated under vacuum.

TLC: Rf = 0.29 (cyclohexane/EtOAc: 65/35, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 65/35)

Yield: 0.7 g (90%)

Mol. formula: $C_{36}H_{45}N_3O_9Si$

FW: 691.85

Physique aspect: colorless foam

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.

8	8.20	d (AB)	$^3J_{8\text{-}7}$=8.8	2
7 + PhH	7.67-7.37	m		12
2	5.23	dd	$^3J_{2\text{-}3a}$=6.2, $^3J_{2\text{-}3b}$=5.8	1
5	5.21	s		2
4	3.87-3.68	m		2
2'	3.71	d	$^3J_{2'\text{-}3'}$=4.7	1
3'	3.30	quint	$^3J_{3'\text{-}2'}$=5.1, $^3J_{3'\text{-}4'}$=5.4	1
3	2.15-2.04	m		2
18	1.42	s		9
4'	1.26	d	$^3J_{4'\text{-}3'}$=5.3	3
11	1.06	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 171.9 (C_1), 170.8 ($C_{1'}$), 154.7 (C_{16}), 148.3 (C_9), 143.0 (C_6), 136.3, 136.2 (C_{13}), 134.2 (C_{12}), 130.5, 130.4 (C_{15}), 128.9 (C_8), 128.5, 128.4 (C_{14}), 124.5 (C_7), 83.5 (C_{17}), 66.5 (C_5), 60.6 (C_2), 56.3 (C_4), 54.8 ($C_{2'}$), 53.9 ($C_{3'}$), 31.4 (C_3), 28.7 (C_{18}), 27.6 (C_{11}), 19.8 (C_{10}), 13.9 ($C_{4'}$).

IR (film, cm^{-1}): 3299 (NH), 3072, 3050 (arom. CH), 2962, 2933, 2858 (sat. CH), 1740, 1700 (C=O), 1523, 1348 (NO_2), 1112, 703.

MS (CI/CH_4-N_2O):

m/z (%) +c: 153 (16) [OPNB+1]$^{\bullet\bullet}$, 137 (8) [PNB+1]$^{\bullet\bullet}$, 57 (100) [*t*Bu]$^+$;

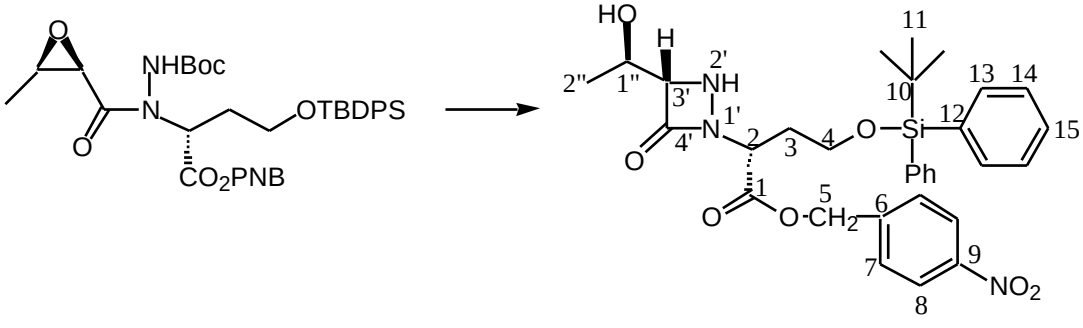
-c: 555 (15) [M-PNB]$^+$, 278 (8) [M-OTBDPS-O*t*Bu-1]$^+$, 201 (87) [M-OTBDPS-PNB-Me]$^+$, 171 (34) [NHBocNCHCH_2CH_2]$^+$, 152 (100) [OPNB]$^+$.

Elemental analysis calcd. for $C_{36}H_{45}N_3O_9Si$:

C 62.498, H 6.555, N 6.073; found: C 62.96, H 6.81, N 6.01

$[\alpha]_D^{20}$ = +17.6° (c=0.34 in $CHCl_3$)

5.15 Synthesis of (2*R*, 3'*S*, 1"*R*) *p*-nitrobenzyl 2-(3'-(1"-hydroxyethyl)-4'-oxo-1',2'-diazetidin-1'-yl)-4-((*tert*-butyldiphenylsilyl)oxy)butanoate 242



Procedure:

500 mg (722.6 µmoles; 1 equiv) of **241** was dissolved into 10 mL of dichloromethane, then 5 mL of trifluoroacetic acid was added at 0°C. The solution was stirred at rt for 30 min. TFA was removed under reduced pressure. The residue was diluted with 20 mL of DCM, then the resulting solution was washed with sat. aq. $NaHCO_3$, the water phase was back-extracted with 10 mL of DCM. The organic phases were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated.

TLC: Rf = 0.22 (cyclohexane/EtOAc: 2/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 2/3)

Yield: 0.24 g (56%)

Mol. formula: $C_{31}H_{37}N_3O_7Si$

FW: 591.73

Physique aspect: colorless oil

^{1}H NMR (200MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
8	8.22	d (AB)	$^3J_{8\text{-}7}$=8.8	2
14	7.67-7.63	m		4
7	7.50	d (AB)	$^3J_{7\text{-}8}$=8.8	2
13 + 15	7.42-7.38	m		6
5	5.26	s		2
2	4.74	dd	$^3J_{2\text{-}3a}$=9.9, $^3J_{2\text{-}3b}$=4.9	1
3'	4.21	d	$^3J_{3'\text{-}1''}$=5.7	1
1''	4.14	dq	$^3J_{1''\text{-}3'}$=5.8, $^3J_{1''\text{-}2''}$=6.2	1
4	3.77	t	$^3J_{4\text{-}3}$=5.8	2
3	2.35-2.08	m		2
2''	1.23	d	$^3J_{2''\text{-}1''}$=6.3	3
11	1.06	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 170.1 (C_1), 168.5 ($C_{4'}$), 148.3 (C_9), 142.7 (C_6), 136.2, 136.1 (C_{13}), 133.8, 133.6 (C_{12}), 130.5 (C_{15}), 129.1 (C_8), 128.4 (C_{14}), 124.5 (C_7), 76.8 ($C_{3'}$), 66.6 (C_5), 66.1 ($C_{1''}$), 60.9 (C_4), 56.5 (C_2), 31.9 (C_3), 27.6 (C_{11}), 20.4 ($C_{2''}$), 19.9 (C_{10}).

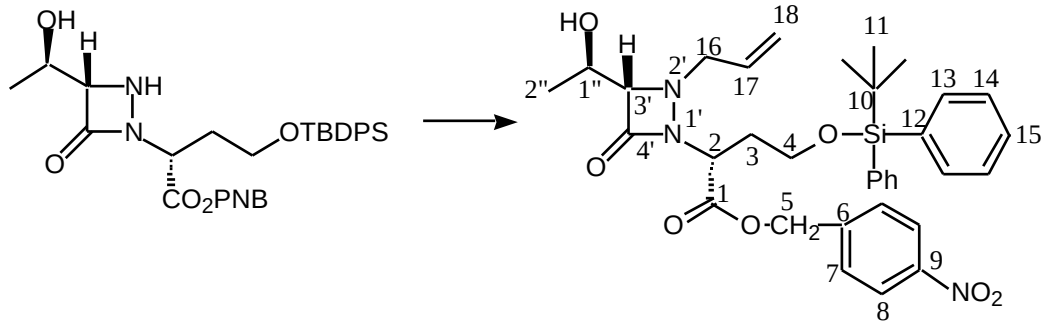
IR (film, cm^{-1}): 3451 (OH), 3243 (NH), 3071, 3054 (arom. CH), 2958, 2931, 2857 (sat. CH), 1771 (lactam C=O), 1748 (ester C=O), 1522, 1347 (NO_2), 1111, 703.

MS (D-APCI):

m/z (%) +c: 591 (8) $[M]^{+\bullet}$, 564 (50) $[M\text{-}2Me+3]^+$, 546 (35) $[M\text{-}CH_3CHOH]^+$, 514 (22) $[M\text{-}Ph]^+$, 468 (56) $[M\text{-}Ph\text{-}CH_3CHO]^+$, 440 (6) $[M\text{-}OPNB+1]^{+\bullet}$, 413 (17) $[M\text{-}t\text{Bu-}Ph\text{-}CH_3CHOH+1]^{+\bullet}$, 308 (65) $[M\text{-}C_2H_4OTBDPS]^+$, 291 (100) $[M\text{-}OTBDPS\text{-}CH_3CHO]^{+\bullet}$.

$[\alpha]_D^{20}$ = -18.5° (c=0.65 in $CHCl_3$)

5.16 Synthesis of (2*R*, 3'*S*, 1"*R*) *p*-nitrobenzyl 2-(2'*N*-allyl-3'-(1"-hydroxyethyl)-4'-oxo-1',2'-diazetidin-1'-yl)-4-((*tert*-butyldiphenylsilyl)oxy)butanoate 243



Procedure:

To a solution of **242** (563 mg; 951.4 µmoles; 1 equiv) and allyl bromide (99.79 µL; 1.141 mmoles; 1.2 equiv) in DMF (8 mL) was added sodium iodide (171.1 mg; 1.141 mmoles; 1.2 equiv) and sodium bicarbonate (95.9 mg; 1.141 mmoles; 1.2 equiv) at 0°C. After stirring at 50°C for 36 h, the mixture was diluted with water (10 mL) and extracted (AcOEt, 20 mL). The extract was washed (brine), dried ($MgSO_4$) and filtered. The filtrate was evaporated.

TLC: Rf = 0.45 (cyclohexane/EtOAc: 2/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 2/3)

Yield: 0.511 g (85%)

Mol. formula: $C_{34}H_{41}N_3O_7Si$

FW: 631.80

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
8	8.22	d (AB)	$^3J_{8\text{-}7}$=9.0	2
14	7.67-7.63	m		4
7	7.51	d (AB)	$^3J_{7\text{-}8}$=8.7	2
13 + 15	7.43-7.36	m		6
17	5.81	ddt	$^3J_{17\text{-}18a(trans)}$=16.8, $^3J_{17\text{-}18b(cis)}$=10.5 $^3J_{17\text{-}16}$=6.9	1
5	5.27	s		2
18a	5.22	dm	$^3J_{18a\text{-}17(trans)}$=16.8	1
18b	5.20	dm	$^3J_{18b\text{-}17(cis)}$=10.5	1
2	4.80	dd	$^3J_{2\text{-}3a}$=9.0, $^3J_{2\text{-}3b}$=5.7	1
1"	3.98	dq	$^3J_{1''\text{-}3'}$=6.8, $^3J_{1''\text{-}2''}$=6.3	1
4	3.77	t	$^3J_{4\text{-}3}$=4.8	2
3'	3.72	d	$^3J_{3'\text{-}1''}$=6.9	1
16a	3.52	dd	$^2J_{16a\text{-}16b}$=12.6, $^3J_{16a\text{-}17}$=6.6	1
16b	3.21	dd	$^2J_{16b\text{-}16a}$=12.6, $^3J_{16b\text{-}17}$=7.2	1
3	2.34-2.05	m		2
OH	2.20	d	$^3J_{OH\text{-}1''}$=6.0	1
2"	1.19	d	$^3J_{2''\text{-}1''}$=6.3	3
11	1.06	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 169.6 (C_1), 168.2 ($C_{4'}$), 148.8 (C_9), 142.8 (C_6), 136.2, 136.1 (C_{13}), 133.8, 133.7 (C_{12}), 132.7 (C_{17}), 130.4 (C_{15}), 129.1 (C_8), 128.3 (C_{14}), 124.4 (C_7), 121.5 (C_{18}), 84.0 ($C_{3'}$), 66.6 (C_5), 66.2 ($C_{1''}$), 64.3 (C_{16}), 60.3 (C_4), 57.2 (C_2), 32.4 (C_3), 27.5 (C_{11}), 20.4 ($C_{2''}$), 19.9 (C_{10}).

IR (film, cm^{-1}): 3481 (OH), 3072, 3042 (unsat. CH), 2958, 2932, 2891, 2858 (sat. CH), 1772 (lactam C=O), 1749 (ester C=O), 1524, 1347 (NO_2), 1112, 703.

MS (D-APCI):

m/z (%) +c: 632 (30) $[M+1]^+$, 605 (100) $[M\text{-}C_2H_3+1]^{\bullet\bullet}$, 554 (5) $[M\text{-}Ph]^+$, 376 (3) [M-OTBDPS]$^+$, 348 (9) $[M\text{-TBDPS-}CH_3CHOH+1]^+$;

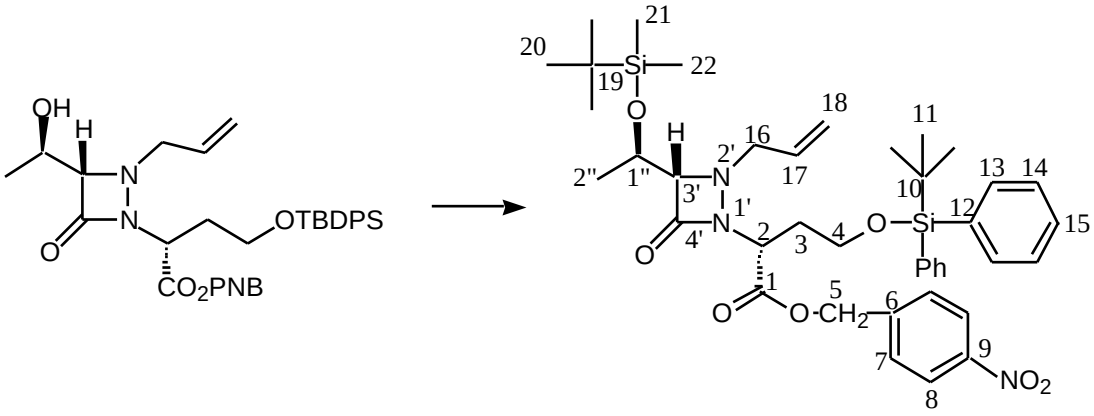
-c: 630 (5) $[M-1]^+$, 495 (100) [M-PNB]$^+$, 451 (6) $[M\text{-}CO_2PNB]^+$, 255 (18) [OTBDPS]$^+$.

Elemental analysis calcd. for $C_{34}H_{41}N_3O_7Si$:

C 64.636, H 6.540, N 6.650; found: C 64.47, H 6.72, N 6.48

$[\alpha]_D^{20}$ = -22.8° (c=0.79 in $CHCl_3$)

5.17 Synthesis of (2*R*, 3'*S*, 1"*R*) *p*-nitrobenzyl 2-(2'*N*-allyl-3'-(1"-((*tert*-butyldimethylsilyl)oxy)ethyl)-4'-oxo-1',2'-diazetidin-1'-yl)-4-((*tert*-butyldiphenylsilyl)oxy)butanoate 247



Procedure:

To a solution of 111 mg (175.6 mmoles; 1 equiv) of **243**, 40.92 mL (351.3 mmoles; 2 equiv) of 2,6-lutidine in CH_2Cl_2 (2 mL) was added dropwise 52.45 mL (228.3 mmoles; 1.3 equiv) of *t*-butyldimethylsilyl triflate at -8°C (salt-ice bath). After stirring at 0°C for 20 min, the mixture was quenched (ice-cold sat. $NaHCO_3$, 5 mL) and extracted (DCM, 2X10 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and filtered. The filtrate was evaporated.

TLC: Rf = 0.31 (cyclohexane/EtOAc: 9/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 9/1)

Yield: 0.129 g (98%)

Mol. formula: $C_{40}H_{55}N_3O_7Si_2$

FW: 745.36

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$ without TMS, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
8	8.39	d (AB)	$^3J_{8\text{-}7}$=8.4	2
14	7.84-7.79	m		4
7	7.67	d (AB)	$^3J_{7\text{-}8}$=8.7	2
13 + 15	7.58-7.53	m		6
17	6.00	ddt	$^3J_{17\text{-}18a(trans)}$=16.5, $^3J_{17\text{-}18b(cis)}$=11.3, $^3J_{17\text{-}16}$=5.4	1
5a	5.49	d	$^2J_{5a\text{-}5b}$=13.6	1
5b	3.37	d	$^2J_{5b\text{-}5a}$=13.6	1
18a	5.29	d	$^3J_{18a\text{-}17(trans)}$=16.2	1
18b	5.28	d	$^3J_{18b\text{-}17(cis)}$=11.4	1
2	4.98	dd	$^3J_{2\text{-}3a}$=8.7, $^3J_{2\text{-}3b}$=6.1	1
1"	4.20	dq	$^3J_{1''\text{-}3'}$=9.0, $^3J_{1''\text{-}2''}$=6.0	1
4	3.91	t	$^3J_{4\text{-}3}$=5.1	2
3'	3.86	d	$^3J_{3'\text{-}1''}$=9.3	1
16a	3.58	dd	$^2J_{16a\text{-}16b}$=13.9, $^3J_{16a\text{-}17}$=6.6	1
16b	3.51	dd	$^2J_{16b\text{-}16a}$=13.6, $^3J_{16b\text{-}17}$=7.5	1
3	2.48-2.28	m		2
2"	1.36	d	$^3J_{2''\text{-}1''}$=6.0	3
11	1.23	s		9
20	1.01	s		9
21	0.17	s		3
22	0.14	s		3

^{13}C NMR (75MHz, $CDCl_3$ without TMS, 20°C)

δ = 169.4 (C_1), 169.2 ($C_{4'}$), 148.3 (C_9), 142.9 (C_6), 136.2, 136.1 (C_{13}), 133.9 (C_{12}), 133.8 (C_{17}), 130.3 (C_{15}), 128.6 (C_8), 128.3 (C_{14}), 124.4 (C_7), 120.0 (C_{18}), 84.2 ($C_{3'}$), 67.9 ($C_{1''}$), 66.3 (C_5), 64.2 (C_{16}), 60.4 (C_4), 57.2 (C_2), 32.5 (C_3), 27.5 (C_{11}), 26.4 (C_{20}), 20.6 ($C_{2''}$), 19.9 (C_{10}), 18.7 (C_{19}), -3.76, -3.98 (C_{21}, C_{22}).

IR (film, cm^{-1}): 3073, 3051 (unsat. CH), 2956, 2926, 2891, 2857 (sat. CH), 1778 (lactam C=O), 1747 (ester C=O), 1526, 1347 (NO_2), 1112, 703.

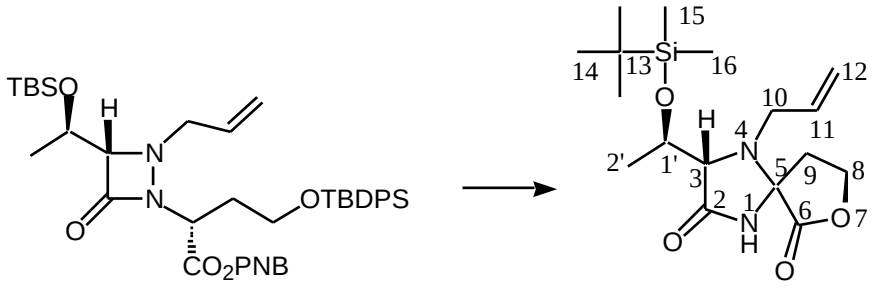
MS (CI/CH_4-N_2O):

m/z (%) +c: 746 (8) $[M+1]^+$, 495 (5) $[M\text{-TBS-PNB}+1]^+$, 454 (6) $[M\text{-TBS-PNB-}CH_2CHCH_2+1]^{+\bullet}$, 436 (22) $[M\text{-TBDPS-}CH_2CHCH_2\text{-2Me}+1]^+$, 171 (63) $[M\text{-TBS-TBDPS-}CO_2PNB\text{-}CH_2CHCH_2]^+$, 75 (100) $[C_6H_3]^+$;

-c: 609 (100) $[M\text{-PNB}]^+$, 255 (5) $[OTBDPS]^+$, 151 (14) $[OPNB\text{-}1]^{+\bullet}$.

$[\alpha]_D^{20}$ = -37.5° (c=0.16 in $CHCl_3$)

5.18 Synthesis of (3*S*, 3(1'*R*))-4-allyl-3-(1'-(*tert*-butyldimethylsilyloxy)ethyl)-7-oxa-1,4-diazaspiro-[4.4]nonane-2,6-dione 248



Procedure:

109.1 uL (96.8 mg; 109.1 mmoles; 1.1 equiv) of tetrabutylammonium fluoride (1M solution in tetrahydrofuran) was added to a solution of 74 mg (99.18 mmoles; 1 equiv) of **247** and 5.678 uL (5.956 mg; 99.18 mmoles; 1 equiv) of acetic acid in 2 mL of THF at 0°C, then the reaction was allowed to warm to rt and stirred for 2 h. The reaction mixture was diluted with ether, washed with sat. $NaHCO_3$ and brine. The organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo.

TLC: Rf = 0.41 (cyclohexane/EtOAc: 3/2, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 3/2)

Yield: 0.026 g (74%)

Mol. formula: $C_{17}H_{30}N_2O_4Si$

FW: 354.52

Physique aspect: colorless oil

^{1}H NMR (500MHz, $CDCl_3$ without TMS, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
NH	7.87	s		1
11	5.89	ddt	$^3J_{11\text{-}12a(trans)}$=17.1, $^3J_{11\text{-}12b(cis)}$=10.0 $^3J_{11\text{-}10a}$=5.6, $^3J_{11\text{-}10b}$=6.6	1
12a	5.33	dq	$^3J_{12a\text{-}11(trans)}$=17.1, $^2J_{12a\text{-}12b}$=1.8, $^3J_{12a\text{-}10}$=1.4	1
12b	5.16	dq	$^3J_{12b\text{-}11(cis)}$=11.4 $^2J_{12b\text{-}12a}$=1.8, $^3J_{12b\text{-}10}$=1.4	1
8	4.35	t	$^3J_{8\text{-}9}$=7.0	2
1'	4.10	dq	$^3J_{1'\text{-}3}$=3.0, $^3J_{1'\text{-}2'}$=6.4	1
10	3.51-3.48	m		2
3	3.45	d	$^3J_{3\text{-}1'}$=3.2	1
9a	2.63	dt	$^3J_{9a\text{-}9b}$=14.0, $^3J_{9a\text{-}8}$=7.0	1
9b	2.31	dt	$^3J_{9b\text{-}9a}$=14.0, $^3J_{9b\text{-}8}$=7.0	1
2'	1.23	d	$^3J_{2'\text{-}1'}$=6.4	3
14	0.87	s		9
15	0.061	s		3
16	0.037	s		3

^{13}C NMR (125MHz, $CDCl_3$ without TMS, 20°C)

δ = 174.2 (C_6), 173.9 (C_2), 135.6 (C_{11}), 110.3 (C_{12}), 78.4 (C_5), 69.3 (C_3), 68.5 ($C_{1'}$), 64.8 (C_8), 54.4 (C_{10}), 35.5 (C_9), 25.7 (C_{14}), 20.0 ($C_{2'}$), 17.9 (C_{13}), -4.61, -4.91 (C_{15}, C_{16}).

IR (film, cm^{-1}): 3328 (NH), 3051 (unsat. CH), 2952, 2927, 2885, 2856 (sat. CH), 1760 (lactone C=O), 1686 (lactam C=O), 835.

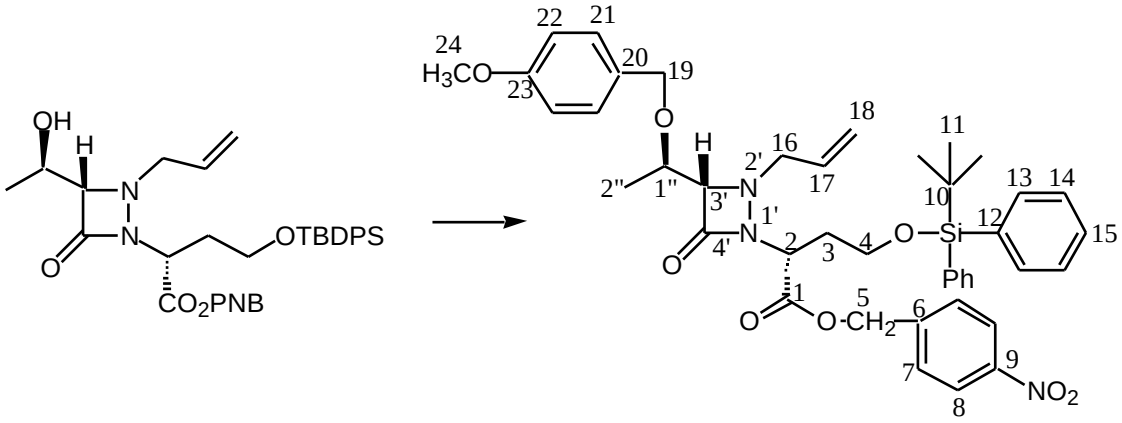
MS (D-APCI):

m/z (%) +c: 355 (40) $[M+1]^+$, 257 (15) [M-*t*Bu-CH_2CHCH_2]$^+$, 229 (32) [M-*t*Bu-CH_2CHCH_2-CO]$^+$, 223 (18) $[M\text{-OTBS}]^+$.

HRMS (CI) calcd. for $C_{17}H_{31}N_2O_4Si$:

355.205311; found: 355.205491

5.19 Synthesis of (2*R*, 3'*S*, 1"*R*) *p*-nitrobenzyl 2-(2'*N*-allyl-3'-(1"-((*p*-methoxybenzyl)oxy)ethyl)-4'-oxo-1',2'-diazetidin-1'-yl)-4-((*tert*-butyldiphenylsilyl)oxy)butanoate 254



Reference:

Widmer, U. *Synthesis*, **1987**, 568-570

Procedure:

To a stirred solution of 86 mg (136.1 µmoles; 1 equiv) of **247** and 76.9 mg (272.2 µmoles; 2 equiv) of *para*-methoxybenzyl trichloroacetimidate in a mixture of 1.3 mL of cyclohexane and 0.65 mL of dichloromethane was added under an argon atmosphere, 54.44 µL (5.444 µmoles; 0.04 equiv) of trifluoromethanesulfonic acid (0.1 M solution in CH_2Cl_2) dropwise at 0°C. The reaction mixture was then allowed to warm to rt overnight (16 h). The reaction mixture was diluted with ether (crystalline trichloroacetamide was dissolved). The solution was washed with sat. $NaHCO_3$, then back-extracted from aqueous layer with ether (2X10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo.

TLC: Rf = 0.25 (cyclohexane/EtOAc: 4/1, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 4/1)

Yield: 0.082 g (80%)

Mol. formula: $C_{42}H_{49}N_3O_8Si$

FW: 751.95

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
8	8.17	d (AB)	$^3J_{8\text{-}7}$=8.7	2
14	7.67-7.62	m		4
7, 13, 15	7.45-7.36	m		8
21	7.17	d (AB)	$^3J_{21\text{-}22}$=8.7	2
22	6.81	d (AB)	$^3J_{22\text{-}21}$=8.7	2
17	5.82	ddt	$^3J_{17\text{-}18a(trans)}$=16.8, $^3J_{17\text{-}18b(cis)}$=10.5 $^3J_{17\text{-}16}$=6.3	1
5a	5.22	d	$^2J_{5a\text{-}5b}$=13.5	1
5b	5.04	d	$^2J_{5b\text{-}5a}$=13.5	1
18a	5.15	d	$^3J_{18a\text{-}17(trans)}$=17.1	1
18b	5.12	d	$^3J_{18b\text{-}17(cis)}$=10.5	1
2	4.82	dd	$^3J_{2\text{-}3a}$=9.0, $^3J_{2\text{-}3b}$=6.0	1
19a	4.47	d	$^2J_{19a\text{-}19b}$=11.6	1
19b	4.36	d	$^2J_{19b\text{-}19a}$=11.6	1
4, 1", 3'	3.83-3.69	m		4
24	3.77	s		3
16a	3.46	dd	$^2J_{16a\text{-}16b}$=13.2, $^3J_{16a\text{-}17}$=7.4	1
16b	3.33	dd	$^2J_{16b\text{-}16a}$=13.2, $^3J_{16b\text{-}17}$=5.9	1
3	2.33-2.04	m		2
2"	1.19	d	$^3J_{2"\text{-}1"}$=6.3	3
11	1.05	s		9

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 169.4 (C_1), 168.8 ($C_{4'}$), 159.6 (C_{23}), 148.2 (C_9), 142.9 (C_6), 136.2, 136.1 (C_{13}), 133.9, 133.8 (C_{12}), 133.3 (C_{17}), 130.9 (C_{20}), 130.3 (C_{15}), 129.6 (C_{21}), 128.7 (C_8), 128.3 (C_{14}), 124.3 (C_7), 120.3 (C_{18}), 114.3 (C_{22}), 83.2 ($C_{3'}$), 73.4 ($C_{1"}$), 71.3 (C_{19}), 66.3 (C_5), 64.3 (C_{16}), 60.3 (C_4), 57.2 (C_2), 55.9 (C_{24}), 32.4 (C_3), 27.6 (C_{11}), 19.9 (C_{10}), 16.8 ($C_{2"}$).

IR (film, cm^{-1}): 3075(unsat. CH), 2973, 2936, 2858 (sat. CH), 1784 (lactam C=O), 1750 (ester C=O), 1522, 1347 (NO_2), 1112, 703.

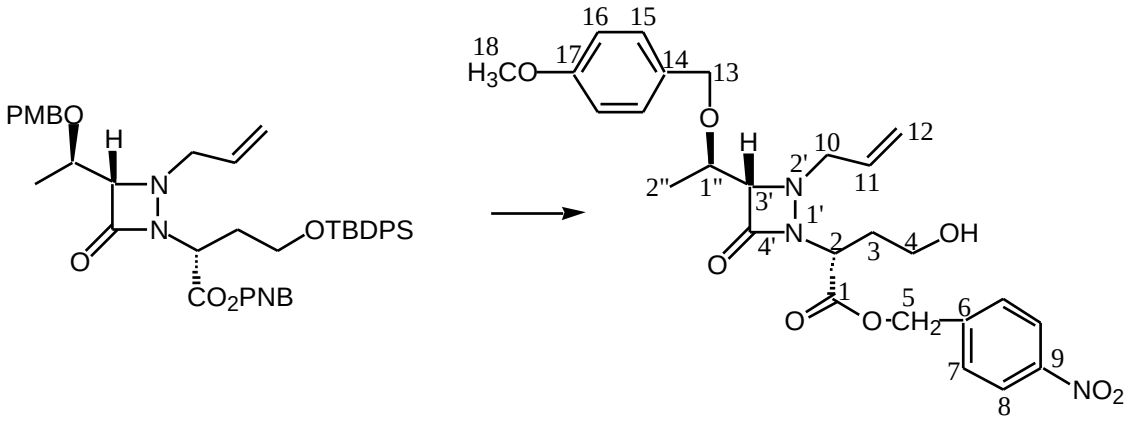
MS (CI/CH_4-N_2O):

m/z (%) +c: 165 (50) [M-CO_2PNB-CH_2OTBDPS-OPMB]$^+$, 136 (30) [OPNB]$^+$, 121 (43) [PMB]$^+$, 101 (20) [OSi*t*Bu]$^+$, 89 (100), 83 (94) [CHCHCON_2+1]$^+$;

-c: 283 (75) [M-PMB-Ph_2*t*Bu-PNB]$^+$, 151 (100) [OPNB-1]$^{\bullet-}$.

$[\alpha]_D^{20}$ = -25.4° (c=1.18 in $CHCl_3$)

5.20 Synthesis of (2*R*, 3'*S*, 1"*R*) *p*-nitrobenzyl 2-(2'*N*-allyl-3'-(1"-((*p*-methoxybenzyl)oxy)ethyl)-4'-oxo-1,2-diazetidin-1'-yl)-4-hydroxybutanoate 253



Procedure:

Hydrogen fluoride-pyridine (58.39 µL; 58.39 mg; 383 µmoles; 8 equiv) was added in a solution of **254** (36 mg; 47.87 µmoles; 1 equiv) in 0.6 mL of THF. The resulting solution was stirred at rt for 6 h. Another 8 equiv of HF-Py was added, the stirring was continued for 1 h. The reaction mixture was diluted with DCM, washed with sat. $NaHCO_3$. The aqueous phase was extracted with DCM (3X). The organic layers were combined, dried ($MgSO_4$) and concentrated.

TLC: Rf = 0.20 (cyclohexane/EtOAc: 3/2, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 3/2)

Yield: 0.019g (78%)

Mol. formula: $C_{26}H_{31}N_3O_8$

FW: 513.54

Physique aspect: colorless oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
8	8.21	d (AB)	$^3J_{8\text{-}7}$=8.7	2
7	7.48	d (AB)	$^3J_{7\text{-}8}$=9.0	2
15	7.23	d (AB)	$^3J_{15\text{-}16}$=8.8	2
16	6.85	d (AB)	$^3J_{16\text{-}15}$=8.8	2
11	5.82	ddt	$^3J_{11\text{-}12a(trans)}$=17.1, $^3J_{11\text{-}12b(cis)}$=10.5, $^3J_{11\text{-}10}$=6.6	1
5a	5.26	d	$^2J_{5a\text{-}5b}$=13.2	1
5b	5.15	d	$^2J_{5b\text{-}5a}$=13.2	1
12a	5.23	d	$^3J_{12a\text{-}11(trans)}$=17.1	1
12b	5.18	d	$^3J_{12b\text{-}11(cis)}$=10.5	1
2	4.50	dd	$^3J_{2\text{-}3a}$=7.8, $^3J_{2\text{-}3b}$=7.2	1
13a	4.53	d	$^2J_{13a\text{-}13b}$=11.4	1
13b	4.40	d	$^2J_{13b\text{-}13a}$=11.4	1
4	3.86-3.83	m		2
18	3.80	s		3
1"	3.70	dq	$^3J_{1''\text{-}3'}$=5.4, $^3J_{1''\text{-}2''}$=5.7	1
3'	3.68	d	$^3J_{3'\text{-}1''}$=5.4	1
10a	3.55	dd	$^2J_{10a\text{-}10b}$=12.8, $^3J_{10a\text{-}11}$=7.6	1
10b	3.43	dd	$^2J_{10b\text{-}10a}$=12.9, $^3J_{10b\text{-}11}$=6.3	1
3+OH	2.28-2.18	m		3
2"	1.21	d	$^3J_{2''\text{-}1''}$=5.7	3

^{13}C NMR (75MHz, $CDCl_3$, 20°C)

δ = 169.5 (C_1), 167.5 ($C_{4'}$), 159.8 (C_{17}), 148.5 (C_9), 142.9 (C_6), 133.0 (C_{11}), 130.6 (C_{14}), 130.0 (C_{15}), 128.9 (C_8), 124.4 (C_7), 120.9 (C_{12}), 114.4 (C_{16}), 82.9 ($C_{3'}$), 73.0 ($C_{1''}$), 71.6 (C_{13}), 66.5 (C_5), 64.1 (C_{10}), 59.3 (C_4), 58.4 (C_2), 55.9 (C_{18}), 32.5 (C_3), 17.0 ($C_{2''}$).

IR (film, cm^{-1}): 3451 (OH), 3077(unsat. CH), 2980, 2934, 2870, 2822 (sat. CH), 1772 (lactam C=O), 1750 (ester C=O), 1521, 1347 (NO_2), 1247.

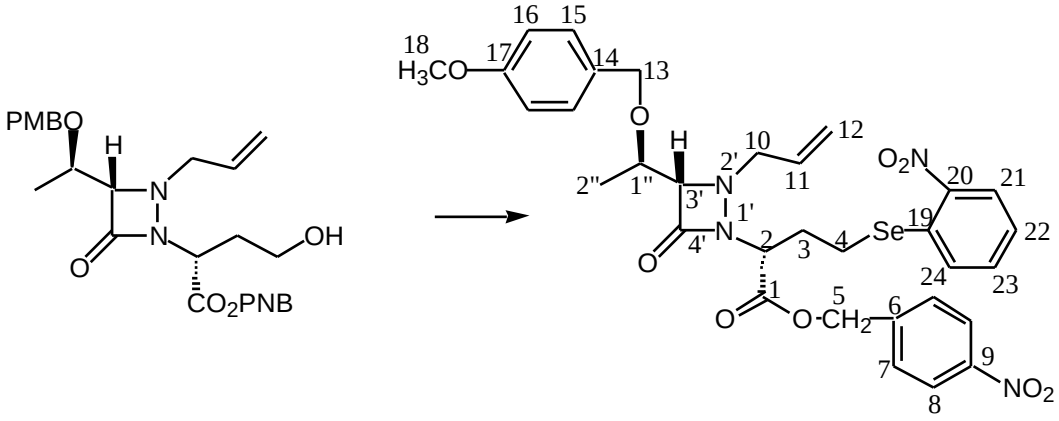
MS (CI/CH_4-N_2O):

m/z (%) +c: 361 (5) $[M\text{-}OPNB]^+$, 333 (2) $[M\text{-}CO_2PNB]^+$, 319 (3) $[M\text{-}CO_2PNB\text{-}Me]^+$, 212 (3) $[M\text{-}PMB\text{-}CO_2PNB]^+$, 153 (100) $[OPNB+1]^{\bullet\bullet}$, 136 (10) $[PNB]^+$, 121 (90) $[PMB]^+$;

-c: 360 (1) $[M\text{-}OPNB\text{-}1]^{\bullet\bullet}$, 153 (100) $[HOPNB]^{\bullet\bullet}$.

$[\alpha]_D^{20}$ = -60.0° (c=0.1 in $CHCl_3$)

5.21 Synthesis of (2*R*, 3'*S*, 1"*R*) *p*-nitrobenzyl 2-(2'*N*-allyl-3'-(1"-((*p*-methoxybenzyl)oxy)ethyl)-4'-oxo-1,2-diazetidin-1'-yl)-4-((*o*-nitrophenyl)selanyl)butanoate 255



Procedure:

Tri-*n*-butylphosphine (20.4 uL; 79.44 mmoles; 1.2 equiv) was added dropwise at rt and under an argon atmosphere to a stirred suspension of 2-nitrophenyl selenocyanate (18.22 mg; 79.44 mmoles; 1.2 equiv) in THF (0.4 mL). After 30 min, a solution of **253** (34 mg; 66.2 mmoles; 1 equiv) in 0.6 mL of THF was added at rt. Stirring was continued for 3 h. The solvent was removed in vacuo.

TLC: Rf = 0.30 (cyclohexane/EtOAc: 3/2, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 3/2)

Yield: 0.016g (35%)

Mol. formula: $C_{32}H_{34}N_4O_9Se$

FW: 697.60

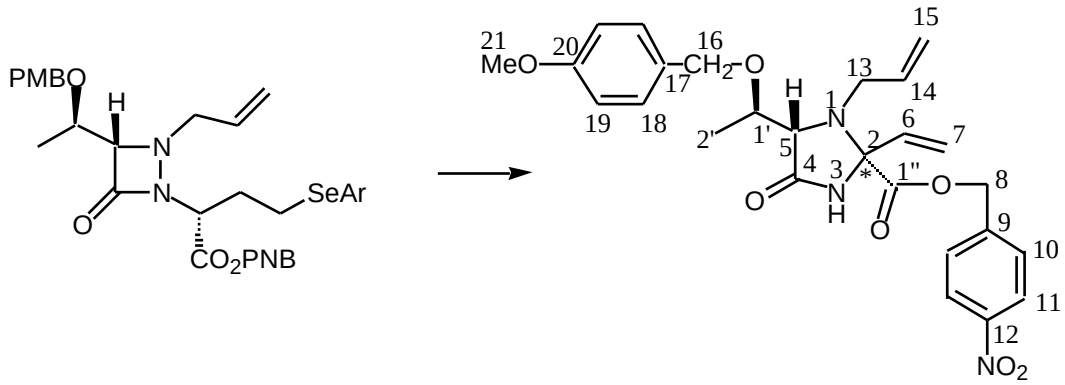
Physique aspect: yellow oil

^{1}H NMR (300MHz, $CDCl_3$, 20°C)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
21	8.29	d	$^3J_{21\text{-}22}$=8.1	1
8	8.19	d (AB)	$^3J_{8\text{-}7}$=8.7	2
22 + 24	7.51-7.50	m		2
7	7.45	d (AB)	$^3J_{7\text{-}8}$=9.0	2
23	7.36-7.30	m		1
15	7.19	d (AB)	$^3J_{15\text{-}16}$=8.7	2
16	6.82	d (AB)	$^3J_{16\text{-}15}$=9.0	2
11	5.90	ddt	$^3J_{11\text{-}12a(trans)}$=16.5, $^3J_{11\text{-}12b(cis)}$=10.5, $^3J_{11\text{-}10}$=6.0	1
5a	5.25	d	$^2J_{5a\text{-}5b}$=13.2	1
5b	5.10	d	$^2J_{5b\text{-}5a}$=13.2	1
12a	5.22	dm	$^3J_{12a\text{-}11(trans)}$=16.5	1
12b	5.18	dm	$^3J_{12b\text{-}11(cis)}$=10.5	1
2	4.46	dd	$^3J_{2\text{-}3a}$=5.7, $^3J_{2\text{-}3b}$=3.3	1
13a	4.51	d	$^2J_{13a\text{-}13b}$=11.4	1
13b	4.37	d	$^2J_{13b\text{-}13a}$=11.4	1
3'	3.87	d	$^3J_{3'\text{-}1''}$=6.6	1
1"	3.79	dq	$^3J_{1''\text{-}3'}$=6.6, $^3J_{1''\text{-}2''}$=6.0	1
18	3.78	s		3
10	3.50	dd	$^2J_{10a\text{-}10b}$=15.3, $^3J_{10\text{-}11}$=5.7	2
4	3.00-2.92	m		2
3	2.46-2.28	m		2
2"	1.20	d	$^3J_{2''\text{-}1''}$=6.0	3

IR (film, cm^{-1}): 3081 (unsat. CH), 2942, 2922, 2849 (sat. CH), 1772 (lactam C=O), 1748 (ester C=O), 1507, 1346 (NO_2), 1238.

5.22 Synthesis of (5*S*, 5(1'*R*)) *p*-nitrobenzyl 1-allyl-5-(1'-((*p*-methoxybenzyl)oxy)ethyl)-4-oxo-2-vinyl)-2-imidazolidinecarboxylate 264



Procedure:

Hydrogene peroxide, 30% aqueous solution (18.82 uL; 215 mmoles; 10 equiv) was added to a solution of **255** (15 mg; 21.5 mmoles; 1 equiv) in 0.5 mL of THF at 0°C. The reaction mixture was allowed to warm to rt and stirred at this temperature for 3 h. The reaction mixture was diluted with DCM and washed with brine. The organic layer was separated, dried ($MgSO_4$) and evaporated in vacuo.

TLC: Rf = 0.25 (cyclohexane/EtOAc: 2/3, UV, $KMnO_4$)

Purification: flash column chromatography on silica gel (cyclohexane/EtOAc: 2/3)

Yield: 0.007g (66%)

Mol. formula: $C_{26}H_{29}N_3O_7$

FW: 495.53

Physique aspect: colorless oil

^{1}H NMR (500MHz, $CDCl_3$, 20°C, two isomers 2:3)

Proton	δ (ppm)	Mult.	*J* (Hz)	Integr.
11	8.23 (8.14)	dm	$^3J_{11\text{-}10}$=8.8	2
10	7.51 (7.38)	dm	$^3J_{10\text{-}11}$=8.8	2
18	7.24 (7.14)	dm	$^3J_{18\text{-}19}$=8.9	2
19	6.84 (6.76)	dm	$^3J_{19\text{-}18}$=8.7	2
NH	6.74 (6.56)	s		1
6	6.22 (6.05)	dd	$^3J_{6\text{-}7a(trans)}$=16.9, $^3J_{6\text{-}7b(cis)}$=10.6	1
14	5.63 (5.75)	ddt	$^3J_{14\text{-}15a(trans)}$=16.9, $^3J_{14\text{-}15b(cis)}$=10.6, $^3J_{14\text{-}13}$=6.4 (6.9)	1
7a	5.58 (5.43)	d	$^3J_{7a\text{-}6(trans)}$=16.9	1
7b	5.37 (5.46)	d	$^3J_{7b\text{-}6(cis)}$=10.6	1
8a	5.30 (5.03)	d	$^2J_{8a\text{-}8b}$=13.6 (13.4)	1
8b	5.25 (4.74)	d	$^2J_{8b\text{-}8a}$=13.6 (13.4)	1
15a	4.94 (5.09)	dq	$^3J_{15a\text{-}14(trans)}$=16.9 $^2J_{15a\text{-}15b}$=$^3J_{15a\text{-}13}$=1.2	1
15b	4.93 (5.08)	dq	$^3J_{15b\text{-}14(cis)}$=10.6 $^2J_{15b\text{-}15a}$=$^3J_{15b\text{-}13}$=1.2	1
16a	4.56 (4.40)	d	$^2J_{16a\text{-}16b}$=12.2 (11.2)	1
16b	4.46 (4.33)	d	$^2J_{16b\text{-}16a}$=12.2 (11.2)	1
1'	3.74 (3.84)	dq	$^3J_{1'\text{-}5}$=3.7 (2.7), $^3J_{1'\text{-}2'}$=6.5	1
21	3.79 (3.74)	s		3
13a	3.33 (3.64)	ddt	$^2J_{13a\text{-}13b}$=15.0, $^3J_{13a\text{-}14}$=6.4 (6.9) $^3J_{13a\text{-}15a}$=$^3J_{13a\text{-}15b}$=1.2	1
5	3.60 (3.43)	d	$^3J_{5\text{-}1'}$=3.7 (2.7)	1
13b	3.22 (3.39)	ddt	$^2J_{13b\text{-}13a}$=15.0, $^3J_{13b\text{-}14}$=6.4 (6.9) $^3J_{13b\text{-}15a}$=$^3J_{13b\text{-}15b}$=1.2	1
2'	1.23 (1.21)	d	$^3J_{2'\text{-}1'}$=6.5	3

^{13}C NMR (125MHz, $CDCl_3$, 20°C)

δ = 171.1 (173.2) ($C_{1''}$), 170.2 (170.4) (C_4), 159.0 (158.9) (C_{20}), 147.8 (147.5) (C_{12}), 141.8 (142.5) (C_9), 134.9 (135.6) (C_{14}), 134.3 (133.8) (C_6), 130.5 (130.4) (C_{17}), 129.2 (129.4) (C_{18}), 128.6 (128.0) (C_{10}), 123.8 (123.5) (C_{11}), 118.2 (119.8) (C_7), 117.6 (118.1) (C_{15}), 113.6 (113.3) (C_{19}), 78.5 (80.9) (C_2), 73.1 (74.9) ($C_{1'}$), 70.4 (71.1) (C_{16}), 65.8 (66.6) (C_5), 65.8 (65.3) (C_8), 55.1 (55.0) (C_{21}), 51.9 (54.1) (C_{13}), 14.9 (14.1) ($C_{2'}$).

IR (film, cm^{-1}): 3202 (NH), 3080 (unsat. CH), 2974, 2940, 2859 (sat. CH), 1734 (ester C=O), 1714 (amide C=O), 1521, 1347 (NO_2), 1247.

MS (CI/CH_4-N_2O):

m/z (%) +c: 153 (100) [OPNB+1]$^{+\bullet}$, 138 (33) [OPMB+1]$^{+\bullet}$, 121 (65) $[PMB]^+$.

Bibliography

(1) Betina, V. *The Chemistry and Biology of Antibiotics*; Elsevier Scientific Publishing Co.: Amsterdam-Oxford-New York, **1983**, pp 35.

(2) Franklin, T. J.; Snom, G. A. *Biochemistry of Antimicrobial Action*; Chapman and Hall: London, **1975**, pp 22.

(3) a. Waxman, D. J.; Strominger, J. L. in *Chemistry and Biology of beta-lactam Antibiotics*; Morin, R. B.; Gorman, M., Ed.; Academic Press: New York-London, **1982**, vol. 3, pp 209; b. Frère, J. M.; Nguyen-Distèche, M.; Coyette, J.; Joris, B. in *The Chemistry of beta-Lactams*; Page, M. I., Ed.; Blackie Academic & Professional: London, **1992**, pp 148

(4) a. Suginaka, H.; Blumberg, P. M.; Strominger, J. L. *J. Biol. Chem.* **1972**, *247*, 5279-5288; b. Blumberg, P. M.; Strominger, J. L. *J. Biol. Chem.* **1972**, *247*, 8107-8113; c. Goffin, C.; Ghuysen, J.-M. *Microbiol. Mol. Biol. Rev.* **2002**, *66*, 702-738

(5) Burger, A. *Medicinal Chemistry Part I*; Wiley-Interscience: New York-London-Sydney-Toronto, **1970**, Chapter 18.

(6) Frère, J. M.; Ghuysen, J. M.; Iwatsubo, M. *Eur. J. Biochem.* **1975**, *57*, 343-351.

(7) Page, M. I. in *The Chemistry of beta-Lactams*; Page, M. I., Ed.; Blackie Academic & Professional: Chapman & Hall, **1992**, pp 79.

(8) Neu, H. C. in *The Chemistry of beta-Lactams*; Page, M. I., Ed.; Blackie Academic & Professional: Chapman & Hall, **1992**, pp 101.

(9) Page, M. I.; Laws, A. P. *Tetrahedron* **2000**, *56*, 5631-5638.

(10) Nagata, W.; Narisada, M.; Yoshida, T. in *Chemistry and Biology of beta-Lactam Antibiotics*; Morin, R. B.; Gorman, M., Ed.; Academic: New York, **1982**, vol. 2, pp 1.

(11) Dürckheimer, W.; Blumbach, J.; Lattrell, R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 180-202.

(12) Nagao, Y.; Tamai, S.; Tanigawa, N.; Sano, S.; Kumagai, T.; Kishi, I. *Heterocycles* **1998**, *48*, 617-620.

(13) Cooper, R. D. G. in *The Chemistry of beta-Lactams*; Page, M. I., Ed.; Blackie Academic & Professional: Chapman & Hall, **1992**, pp 272.

(14) Jackson, B. G.; Pedersen, S. W.; Fisher, J. W.; Misner, J. W.; Gardner, J. P.; Staszak, M. A.; Doecke, C.; Rizzo, J.; Aikins, J.; Farkas, E.; Trinkle, K. L.; Vicenzi, J.; Reihard, M.; Kroeff, E.; Higginbotham, C. A.; Gazak, R. J.; Zhang, T. Y. *Tetrahedron* **2000**, *56*, 5667-5677.

(15) Boyd, D. B. in *The Chemistry and Biology of beta-Lactam Antibiotics*; Morin, R. B.; Gorman, M., Ed.; Academic press: New York, **1982**, pp 437.

(16) Miller, M. J. *Tetrahedron* **2000**, *56*, 5553-5742.

(17) Betina, V. *The Chemistry and Biology of Antibiotics*; Elsevier Scientific Publishing Co.: Amsterdam-Oxford-New York, **1983**, pp 431.

(18) Waley, S. G. in *The Chemistry of beta-Lactams*; Page, M. I., Ed.; Blackie Academic & Professional: Chapman & Hall, **1992**, pp 198.

(19) Spratt, B. G. *Science* **1994**, *264*, 388-392.

(20) Davies, J. *Science* **1994**, *264*, 375-380.

(21) Page, M. I.; Laws, A. P. *Chem. Comm.* **1998**, 1609-1617.

(22) Diaz, N.; Suarez, D.; Merz, J. K. M. *J. Am. Chem. Soc.* **2000**, *122*, 4197-4208.

(23) Kaminskaia, N. V.; Spingler, B.; Lippard, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6411-6422.

(24) Caselli, E.; Powers, R. A.; Blasczcak, L. C.; Wu, C. Y. E.; Prati, F.; Shoichet, B. K. *Chemistry & Biology* **2001**, *8*, 17-31.

(25) Kelly, J. A.; Dideberg, O.; Charlier, P.; Wery, J.; Libert, M.; Moews, P.; Knox, J.; Duez, C.; Fraipont, C.; Joris, B.; Dusart, J.; Frère, J.-M.; ghuysen, J. M. *Science* **1986**, *231*, 1429-1431.

(26) Oefner, C.; Darcy, A.; Daly, G. G.; Gubernator, K.; Charnes, R. L.; Heinze, I.; Hubschwerlen, C.; Winkler, F. K. *Nature* **1990**, *343*, 284-288.

(27) a. Minasov, G.; Wang, X. J.; Shoichet, B. *J. Am. Chem. Soc.* **2002**, *124*, 5333-5340;
b. Nukaga, M.; Mayama, K.; Hujer, A. M.; Bonomo, R. A.; Knox, J. R. *J. Mol. Biol.* **2003**, *328*, 289-301

(28) Herzberg, O.; Moult, J. *Science* **1987**, *236*, 694-701.

(29) Knox, J. R.; Moews, P. C.; Frere, J. M. *Chemistry & Biology* **1996**, *3*, 937-947.

(30) Pratt, R. F. *J. Chem. Soc. Perkin Trans. 2* **2002**, 851-861.

(31) Nozaki, Y.; Katayama, N.; Ono, H.; Tsubotani, S.; Harada, S.; Okazaki, H.; Nakao, Y. *Nature* **1987**, *325*, 179-180.

(32) Nakao, Y. in *Recent Advances in the Chemistry of beta-Lactam Antibiotics*; Bently, P. H.; Southgate, R., Ed.; Royal Society of Chemistry Special Publication: London, **1989**, pp 119.

(33) Harada, S.; Tsubotani, S.; Hida, T.; Koyama, K.; Kondo, M.; Ono, H. *Tetrahedron* **1988**, *44*, 6589-6606.

(34) Marchand-Brynaert, J.; Ghosez, L. in *Recent Progress in the Chemical Synthesis of Antibiotics*; Ohno, M.; Lukais, G., Ed.; Springer-Verlag: Berlin, **1990**, pp 727.

(35) Baldwin, J. E.; Lynch, G. P.; Pitlik, J. *J. Antibiot.* **1991**, *44*, 1-24.

(36) Allen, N. E.; Boyd, D. B.; Campbell, J. B.; Deeter, J. B.; Elzey, T. K. *et al.Tetrahedron* **1989**, *45*, 1905-1928.

(37) Du Vigneaud, V.; Carpenter, F. H. in *The Chemistry of Penicillin*; Clarke, H. T.; Johnson, J. R.; Robinson, R., Ed.; Princeton University Press: Princeton, New Jersey, **1949**, pp 1004.

(38) Boyd, D. B.; Elzey, T. K.; Hatfield, L. D.; Kinnick, M. D.; Morin, J. M. *Tetrahedron Lett.* **1986**, *27*, 3453-3456.

(39) Baldwin, J. E.; Lowe, C.; Schofield, C. J.; Lee, E. *Tetrahedron Lett.* **1986**, *27*, 3461-3464.

(40) Jungheim, L. N.; Ternansky, R. J. in *The Chemistry of beta-Lactams*; Page, M. I., Ed.; Blackie Academic & Professional: Chapman & Hall, **1992**, pp 307.

(41) Ternansky, R. J.; Draheim, S. E. *Tetrahedron* **1992**, *48*, 777-796.

(42) Chandrakala, P. S.; Katz, A. K.; Carrell, H. L.; Sailaja, P. R.; Podile, A. R.; Nangia, A.; Desiraju, G. R. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2597-2608.

(43) Garcias, R. C.; Coll, M.; Donoso, J.; Munoz, F. *Chem. Phys. Lett.* **2003**, *372*, 275-281.

(44) Taylor, E. C.; Sobieray, D. M. *Tetrahedron* **1991**, *47*, 9599-9620.

(45) Taylor, E. C.; Davies, H. M. L.; Hinkle, J. S. *J. Org. Chem.* **1986**, *51*, 1530-1536.

(46) Allinger N. L.; Tai J. C.; Wu F. T.; *J. Am. Chem. Soc*. **1970**, *92*, 579-583.

(47) Durand, T. *Ph. D Thesis UCL-ORSY* **1993**.

(48) Pauling, L. *Nature* **1948**, *161*, 707-709.

(49) Wolfenden, R. *Nature* **1969**, *223*, 704-705.

(50) Wolfenden, R. *Acc. Chem. Res.* **1972**, *5*, 10-18.

(51) Kraut, J. *Annu. Rev. Biochem.* **1977**, *46*, 331-358.

(52) Robertus, J. D.; Kraut, J.; Alden, R. A.; Birktoft, J. J. *Biochemistry* **1972**, *11*, 4293-4303.

(53) Ness, T.; Martin, R.; Kindler, A. M.; Paetzel, M.; Gold, M.; Jensen, S. E.; Jones, J. B.; Strynadka, N. C. J. *Biochemistry* **2000**, *39*, 5312-5321.

(54) Curley, K.; Pratt, R. F. *J. Am. Chem. Soc*. **1997**, *119*, 1529-1538.

(55) Morandi, F.; Caselli, E.; Morandi, S.; Focia, P. J.; Blazquez, J.; Shoichet, B. K.; Prati, F. *J. Am. Chem. Soc.* **2003**, *125*, 685-695.

(56) Thompson, R. C.; Bauer, C.-A. *Biochemistry* **1979**, *18*, 1552-1558.

(57) Shah, D. O.; Gorenstein, D. G. *Biochemistry* **1983**, *22*, 6096-6101.

(58) Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc*. **1981**, *103*, 654-657.

(59) Bartlett P. A.; Marlowe C. K.; *Biochemistry* **1983**, *22*, 4618-4624.

(60) Bartlett, P. A.; Kezer, W. B. *J. Am. Chem. Soc*. **1984**, *106*, 4282-4283.

(61) Teraishi, K.; Saito, M.; Fujii, I.; Nakamura, H. *Tetrahedron Lett.* **1992**, *33*, 7153-7156.

(62) Rahil, J.; Haake, P. *J. Am. Chem. Soc*. **1981**, *103*, 1723-1734.

(63) Bartlett, P. A.; Vanmaele, L. J.; Kezer, W. B. *Bull. Soc. Chim. Fr.* **1986**, 776-780.

(64) Rahil, J.; Pratt, R. F. *Biochemistry* **1992**, *31*, 5869-5878.
(65) Govardhan, C. P.; Pratt, R. F. *Biochemistry* **1987**, *26*, 3385-3395.
(66) Knap, A. K.; Pratt, R. F. *Biochem. J.* **1991**, *273*, 85-91.
(67) Maveyraud, L.; Pratt, R. F.; Samama, J.-P. *Biochemistry* **1998**, *37*, 2622-2628.
(68) a. Galardy, R. E.; Kontoyiannidou-Ostrem, V.; Kortylewicz, Z. P. *Biochemistry* **1983**, *22*, 1990-1995; b. Krapcho, J.; Turk, C. *et al. J. Med. Chem.* **1988**, *31*, 1148-1160
(69) a. Kessabi, J. *Ph. D Thesis, UCL-ORSY,* **1998**; b. Dive, G.; Dehareng, D. *Int. J. Quant. Chem.* **1999**, *73*, 161-174
(70) Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Goffic, F. L. *Synthesis* **1989**, 64-65.
(71) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2845-2852.
(72) Redmore, D. *J. Org. Chem.* **1978**, *43*, 992-996.
(73) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.
(74) Thottathil, J. . K.; Przybyla, C. . A.; Moniot, J. . L. *Tetrahedron Lett.* **1984**, *25*, 4737-4740.
(75) Dingwall, J. G.; Ehrenfreund, J.; Hall, R. G. *Tetrahedron* **1989**, *45*, 3787-3808.
(76) Chojnowski, J.; Cypryk, M.; Michalski, J. *J. Organomet. Chem.* **1981**, *215*, 355-365.
(77) Bruynes, C. A.; Jurriens, T. K. *J. Org. Chem.* **1982**, *47*, 3966.
(78) Firouzabadi, H.; Karimi, B. *Synth. Commun* **1993**, *23*, 1633-1641.
(79) Arndt, F. *Org. Synth, II*, **1943**, pp 165.
(80) Clark, V. M.; Todd, A. R. *J. Chem. Soc.* **1950**, 2030-2034.
(81) Jacques, J.; Leclercq, M.; Brienne, M. J. *Tetrahedron* **1981**, *37*, 1727-1733.
(82) Murakami, K.; Molitor, E. J.; Liu, H. W. *J. Org. Chem.* **1999**, *64*, 648-651.
(83) Parsons, W. H.; Patchett, A. A.; Bull, H. G.; Schoen, W. R.; Taub, D.; Davidson, J.; Combs, P. A. *et al. J. Med. Chem.* **1988**, *31*, 1772-1778.
(84) Holy, A. *Synthesis* **1997**, 381-385.
(85) Hudson, R. F.; Harper, D. C. *J. Chem. Soc.* **1958**, 1356-1360.
(86) Mewshaw, R. E. *Tetrahedron Lett.* **1989**, *30(29)*, 3753-3756.
(87) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285-3294.
(88) Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengeler, P. A.; Phillips, B. W.; Moore, W.; Smith, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 8177-8190.
(89) Colens, A.; Demuylder, M.; Techy, B.; Ghosez, L. *Nouveau J. Chim.* **1977**, *1*, 369-70.
(90) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc. Chem. Commun.* **1979**, 1180-1181.

(91) Schmidt, U.; Meyer, R.; Leitenberger, V.; Stabler, F.; Lieberknecht, A. *Synthesis* **1991**, 409-413.
(92) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361-2364.
(93) Eymery, F.; Iorga, B.; Savignac, P. *Tetrahedron* **1999**, *55*, 13109-13150.
(94) Guillen, F.; Fiaud, J. C. *Tetrahedron Lett.* **1999**, *40*, 2939-2942.
(95) Balreddy, K.; Dong, L.; Simpson, D. M.; Titmas, R. *Tetrahedron Lett.* **1993**, *34*, 3037-3040.
(96) Gross, H. *J. Prakt. Chem.* **1971**, 265.
(97) Lin, H. K.; Gelb, M. H. *J. Am. Chem. Soc.* **1993**, *115*, 3932-3942.
(98) Biller, S. A.; Forster, C. *Tetrahedron* **1990**, *46*, 6645-6658.
(99) Munyemana, F.; Frisque-Hesbain, A.-M.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* **1989**, *30*, 3077-3080.
(100) Feng, X. Q.; Olsen, R. . K. *J. Org. Chem.* **1992**, *57*, 5811-5812.
(101) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734-736.
(102) Crandall, J. K.; Huntington, R. D.; Brunner, G. L. *J. Org. Chem.* **1972**, *37*, 2911-2913.
(103) Dodson, R. M.; Lewis, J. R.; Webb, W. P.; Wenkert, E.; Youssefyeh, R. D. *J. Am. Chem. Soc.* **1961**, *83*, 938-943.
(104) Kosolapoff, G. M.; Struck, R. F. *J. Chem. Soc.* **1957**, 3739.
(105) McBride, J. J. ,.; Jungerman, E.; Killheffer, J. V.; Clutter, R. J. *J. Org. Chem.* **1962**, *27*, 1833-1836.
(106) Jungerman, E.; McBride, J. J. ,.; Clutter, R.; Mais, A. *J. Org. Chem.* **1962**, *27*, 606-610.
(107) Weissman, S. A.; Baxter, S. G. *Tetrahedron Lett.* **1988**, *29*, 1219-1222.
(108) Wong, S. C.; Carruthers, N. I.; Chan, T. M. *J. Chem. R.-S.* **1993**, 268.
(109) Montchamp, J. L.; Tian, F.; Frost, J. W. *J. Org. Chem.* **1995**, *60*, 6076-6081.
(110) Matsumoto, K.; Fuwa, S.; Shimojo, M.; Kitajima, H. *Bull. Chem. Soc. Japan.* **1996**, *69*, 2977-2987.
(111) Yu, M.; Pagenkopf, B. L. *J. Org. Chem.* **2002**, *67*, 4553-4558.
(112) Bouzide, A.; Sauve, G. *Tetrahedron Lett.* **1997**, *38*, 5945-5948.
(113) Dhar, P.; Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1992**, *57*, 1699-1702.
(114) Ghosez, L.; GeorgeKoch, I.; Patiny, L.; Houtekie, M.; Bovy, P.; Nshimyumukiza, P.; Phan, T. *Tetrahedron* **1998**, *54*, 9207-9222.
(115) Hanack, M.; Auchter, G. *J. Am. Chem. Soc.* **1985**, *107*, 5238-5245.
(116) Denmark, S. E.; Chatani, N.; Pansare, S. V. *Tetrahedron* **1992**, *48*, 2191-2208.
(117) Hanessian, S.; Bennani, Y. L. *Synthesis* **1994**, 1272-1274.
(118) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030.

(119) Marinetti, A.; Ricard, L. *Tetrahedron* **1993**, *49*, 10291-10304.
(120) Leffler, J. E.; Tsuno, Y. *J. Org. Chem.* **1963**, *28*, 902-906.
(121) Harmon, R. E.; Wellman, G.; Gupta, S. K. *J. Org. Chem.* **1973**, *38*, 11-16.
(122) Kumar, S. M. *Synth. Commun* **1987**, *17*, 1015-1020.
(123) Malachowski, W.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7616-7624.
(124) Jungheim L. N.; Sigmund S. K.; *J. Org. Chem.* **1987**, *52*, 4007-4013.
(125) Hetherington, L.; Greedy, B.; Gouverneur, V. *Tetrahedron* **2000**, *56*, 2053-2060.
(126) Schuman, M.; Trevitt, M.; Redd, A.; Gouverneur, V. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2491-2493.
(127) Sorensen, A. M.; Nielsen, P. *Org. Lett.* **2000**, *2*, 4217-4219.
(128) Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Synthesis* **2001**, 612-620.
(129) Anderson, A. W.; Merckling, N. G. ; U.S. Patent 2,721,189, **1955**.
(130) *Chem. Abs.* **1956**, *50*, 3008i.
(131) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18-29.
(132) Fürstner, A. *Angew. Chem. Int. Ed. Engl.* **2000**, 3012-3043.
(133) a. Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141-8153; b. Grubbs, R.; Miller, S.J.; Fu G. C. *Acc. Chem. Res.* **1995**, *28*, 446-452
(134) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875-3886.
(135) Furstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746-8749.
(136) Armstrong, S. K. *J. Chem. Soc. Perkin Trans. 1* **1998**, 371-388.
(137) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720-9721.
(138) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251-8259.
(139) Aeilts, S. L.; Cefalo, D. R.; Bonitatebus, P. J.; Houser, J. H.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1452-1455.
(140) Hultzsch, K. C.; Jernelius, J. A.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 589-593.
(141) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450.
(142) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291-4298.
(143) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960-7973.
(144) Blackwell, H. E.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3281-3284.
(145) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.
(146) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791-799.
(147) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904-9909.

(148) Lynn, D. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 3187-3193.

(149) Huang, J. K.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674-2678.

(150) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247-2250.

(151) Ackermann, L.; Furstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787-4790.

(152) Furstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204-2207.

(153) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

(154) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T. L.; Ding S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546-2558.

(155) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, 3783.

(156) Hérrison, J.-P.; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161-176.

(157) Adam, J.-M. *Ph.D Thesis, UCL-ORSY,* **2000**.

(158) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484-2489.

(159) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749-750.

(160) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543-6554.

(161) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887-3897.

(162) Hermann, W. A.; Kocher, C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162.

(163) Huang, J. K.; Schanz, H. J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370-2375.

(164) Phillips, A. J.; Abell, A. D. *AldrichimicaActa* **1999**, *32*, 75-89.

(165) Barrett, A. G. M.; Baugh, S. P. D.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A. *Chem. Comm.* **1997**, 155-156.

(166) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 7893-7907.

(167) Barrett, A. G. M.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. C.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 3716-3721.

(168) Martin, S. F.; Chen, H. J.; Courtney, A. K.; Liao, Y. S.; Patzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251-7264.

(169) Kingderman, S. S.; Van Marrseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjies, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045-2048.

(170) Howard, J. C.; Gever, G.; Wei, P. H. L. *J. Org. Chem.* **1963**, *28*, 868-870.
(171) Klopman, G.; Tsuda, K.; Louis, J. B.; Davis, R. E. *Tetrahedron* **1970**, *26*, 4549-4554.
(172) Bayer, E.; Geckeler, K. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 533-534.
(173) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927-4931.
(174) Baret, N.; Dulcere, J.-P.; Rodriguez, J.; Pons, J.-M.; Faura, R. *Eur. J. Org. Chem.* **2000**, 1507-1516.
(175) Pugin, B.; Venanzi, L. M. *J. Organomet. Chem.* **1981**, *214*, 125-133.
(176) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870-876.
(177) Kanner, C. B.; Pandit, U. K. *Tetrahedron* **1982**, *38*, 3597-3604.
(178) Belsky, I. *J. Chem. Soc. Chem. Commun.* **1977**, 237.
(179) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595-7596.
(180) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241-244.
(181) Taylor, E. C.; Haley, N. F.; Clemens, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 7743-7752.
(182) Taylor, E. C.; Clemens, R. J.; Davies, H. M. L. *J. Org. Chem.* **1983**, *48*, 4567-4571.
(183) Taylor, E. C.; Clemens, R. J.; Davies, H. M. L.; Haley, N. F. *J. Am. Chem. Soc.* **1981**, *103*, 7659-7660.
(184) Taylor, E. C.; Davies, H. M.; Lavell, W. T. *J. Org. Chem.* **1984**, *49*, 2204-2208.
(185) Taylor, E. C.; davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 4415-4419.
(186) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113-116.
(187) Smith, K.; Hou, D. J. *J. Org. Chem.* **1996**, *61*, 1530-1532.
(188) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1986**, *51*, 1537-1540.
(189) Lawton, G.; Moody, C. J.; Pearson, C. J. *J. Chem. Soc. Chem. Commun.* **1984**, 754-756.
(190) Lawton, G.; Moody, C. J.; Pearson, C. J. *J. Chem. Soc. Perkin Trans. 1* **1987**, 877-884.
(191) Moody, C. J.; Pearson, C. J.; Lawton, G. *Tetrahedron Lett.* **1985**, *26*, 3167-3170.
(192) Lawton, G.; Moody, C. J.; Pearson, C. J.; Williams, D. J. *J. Chem. Soc. Perkin Trans. 1* **1987**, 885-897.
(193) Moody, C. J.; Pearson, C. J.; Lawton, G. *Tetrahedron Lett.* **1985**, *26*, 3171-3172.
(194) Lawton, G.; Moody, C. J.; Pearson, C. J. *J. Chem. Soc. Perkin Trans. 1* **1987**, 899-902.
(195) Staudinger, H. *Helv. Chim. Acta* **1922**, *5*, 103.
(196) Hall, J. H.; Kellogg, R. *J. Org. Chem.* **1966**, *31*, 1079-1082.
(197) Kerber, R. C.; Ryan, T. J. *Tetrahedron Lett.* **1970**, *10*, 703-706.
(198) Kerber, R. C.; Ryan, T. J.; Hsu, S. D. *J. Org. Chem.* **1974**, *39*, 1215-1221.

(199) Hegedus, L. S.; Kramer, A. *Organometallics* **1984**, *3*, 1263-1267.
(200) Schantl, J. G.; Decristoforo, M.; Daly, J. J. *Tetrahedron Lett.* **1987**, *28*, 6577-6580.
(201) Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701-704.
(202) Oda, K.; Nakano, T.; Morimoto, H.; Takamura, N. *Heterocycles* **1996**, *42*, 577-588.
(203) Albers-Schönberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491-6499.
(204) Timberlake, J. W.; Elder, E. S. in *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Lwowski, W., Ed.; Pergamon Press: Oxford, **1984**, vol. 7, pp 449.
(205) Yanagisawa, H.; Ando, A.; Shiozaki, M.; Hiraoka, T. *Tetrahedron Lett.* **1983**, *24*, 1037-1040.
(206) Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N. *J. Am. Chem. Soc.* **1985**, *107*, 1438-1439.
(207) Diels, O.; Pflaumer, K. *Ber.* **1915**, *48*, 223-231.
(208) Benedetti, F.; Berti, F.; Fabrissin, S.; Gianferrara, T. *J. Org. Chem.* **1994**, *59*, 1518-1524.
(209) Fukatsu, K.; Fuji, N.; Okkawa, S. *Tetrahedron Asymmetry* **1999**, *10*, 1512.
(210) Ratcliffe, R. W.; Albers-Schonberg, G. in *Chemistry and Biology of beta-Lactam Antibiotics*; Morin, R. B.; Gorman, M., Ed.; Academic Press: New York, London, **1982**, vol. 2, pp 227.
(211) Taibi, P.; Mobashery, S. *J. Am. Chem. Soc.* **1995**, *117*, 7600-7605.
(212) Stotter, P. L.; Hill, K. A. *Tetrahedron Lett.* **1972**, *40*, 4067-4070.
(213) Gunda. I. Georg *The Organic Chemistry of beta-Lactams*; VCH Publishers, Inc.: New York, **1993**.
(214) Carmi, A.; Pollak, G.; Hellin, H. *J. Org. Chem.* **1960**, *25*, 44-46.
(215) Sletzinger, M.; Fireston, R. A.; Reinhold, D. F.; Rooney, C. S.; Nicholson, W. H. *J. Med. Chem.* **1968**, *11*, 261.
(216) Anraku, Y.; Naraki, T.; Kanzaki, S. *J. Biochem. (Tokyo)* **1973**, *73*, 1149-1161.
(217) Klosterman, H. J.; lamoureux, G. L.; Parsons, J. L. *Biochemistry* **1967**, *6*, 170-176.
(218) Bentley, P. H.; Morley, J. S. *J. Chem. Soc.* **1966**, 60-64.
(219) Karady, S.; Ly, M. G.; Pines, S. H.; Sletzinger, M. *J. Org. Chem.* **1971**, *36*, 1946-1948.
(220) Achiwa, K.; Yamada, S.-I. *Tetrahedron Lett.* **1975**, *31*, 2701-2704.
(221) Viret, J.; Gabard, J.; Collet, A. *Tetrahedron* **1987**, *43*, 891-894.
(222) Vidal, J.; Drouin, J.; Collet, A. *J. Chem. Soc. Chem. Commun.* **1991**, 435-437.
(223) Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* **1986**, *69*, 1923-1926.

(224) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525-5540.
(225) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835-875.
(226) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517-5518.
(227) Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725-2737.
(228) Hale, K. J.; Cai, J. Q.; Delisser, V.; Manaviazar, S.; Peak, S. A.; Bhatia, G. S.; Collins, T. C.; Jogiya, N. *Tetrahedron* **1996**, *52*, 1047-1068.
(229) Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1958-1961.
(230) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434-9453.
(231) Fahr, E.; Lind, H. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 372-384.
(232) Diels, O.; Behncke, H. *Chem. Ber.* **1924**, *57*, 653-656.
(233) Moriarty, R. M.; Prakash, I. *Synth. Commun* **1985**, *15*, 649-656.
(234) Carpino, L. A.; Terry, P. H.; Crowley, P. J. *J. Org. Chem.* **1961**, *26*, 4336-4340.
(235) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.
(236) Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154-1156.
(237) Evans, D. A.; Morissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346-4348.
(238) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123-1126.
(239) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881-6883.
(240) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395-6397.
(241) Noe, E. A.; Raban, M. *J. Am. Chem. Soc.* **1975**, *97*, 5811-5820.
(242) Heathcock, C. E. in *Asymmetric Synthesis*; Morrison, J. D., Ed.: New York, **1984**, vol. 3, Chapter 2.
(243) Davies, S. G.; Doisneau, G. J. M.; Prodger, J. C.; Sanganee, H. J. *Tetrahedron Lett.* **1994**, *35*, 2369-2372.
(244) Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957-4960.
(245) Evans, D. A.; Britton, T. C.; Ellman Jon A. *Tetrahedron Lett.* **1987**, *28*, 6141-6144.
(246) Simon, D.; Lafont, O. *J. Heterocy Chem.* **1985**, *22*, 1551-1557.
(247) El Khadem, H. S.; Kreishman, G. P.; El Ashry, E. H. *J. Org. Chem.* **1975**, *40*, 3149-3151.
(248) Somogyi, L. *Carbohydr Res.* **1985**, *142*, 315-320.
(249) Khadem, H. E.; El-Shafei, Z. M.; Hashem, M. M. *J. Chem. Soc.* **1968**, 949-951.
(250) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205-208.
(251) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243-2266.
(252) Kim, H. O.; Gardner, B.; Kahn, M. *Tetrahedron Lett.* **1995**, *36*, 6013-6016.

(253) Coste, J.; Dufour, M.-N.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 669-672.

(254) Chapman, O. L.; King, R. W.; Welsread, W. J.; Murphy, T. J. *J. Am. Chem. Soc.* **1964**, *86*, 4968-4973.

(255) Mester, L. *J. Am. Chem. Soc.* **1955**, *77*, 4301-4305.

(256) Spassov, A. W.; Christova, N. I. *J. Prakt. Chem.* **1982**, *324*, 987-992.

(257) Schmidt, U.; Riedl, B. *Synthesis* **1993**, 809-814.

(258) Patai, S. *The Chemistry of the Hydraza, Azo and Azoxy Groups*, **1975**, vol. 2, pp 643.

(259) Lecoq, A.; Marraud, M.; Aubry, A. *Tetrahedron Lett.* **1991**, *32*, 2765-2768.

(260) Mannschreck, A.; Jonas, V.; Kolb, B. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 583-584.

(261) Biondi, S.; Pecunioso, A.; Busi, F.; Contini, S. A.; Donati, D.; Maffeis, M.; pizzi, D. A.; Rossi, L. *Tetrahedron* **2000**, *56*, 5649-5655.

(262) Hanessian, S.; Rozema, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 9884-9891.

(263) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139-2145.

(264) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; et al. *J. Am. Chem. Soc.* **1984**, *106*, 5208-5217.

(265) Parshall, G. W. *Homogeneous Catalysis*: Wiley: New York, **1980**, vol. Chapter 3.

(266) Rylander, P. N. *Organic Syntheses with Noble Metal Catalysts* : Academic Press: New York, **1973**, vol. Chapter 5.

(267) Tolman, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 2994-2999.

(268) Hendrix, W. T.; Von Rosenberg, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 4850-4852.

(269) Cowherd, F. G.; Von Rosenberg, J. L. *J. Am. Chem. Soc.* **1969**, *91*, 2157-2158.

(270) Casey, C. P.; Cyr, C. R. *J. Am. Chem. Soc.* **1973**, *95*, 2248-2253.

(271) Inoue, S.-i.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 4897-4905.

(272) Doering, W. V. E.; Birladeanu, L.; Andrews, D. W.; Pagnotta, M. *J. Am. Chem. Soc.* **1985**, *107*, 428-432.

(273) Dobarro, A.; Velasco, D. *Tetrahedron* **1996**, *52*, 13733-13738.

(274) Binns, M. R.; Haynes, R. K.; Houston, T. L.; Jackson, W. *Tetrahedron Lett.* **1980**, *21*, 573-576.

(275) Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *46*, 3790-3795.

(276) Boteju, L. W.; Wegner, K.; Qian, X. H.; Hruby, V. J. *Tetrahedron* **1994**, *50*, 2391-2404.

(277) Newcomb, M.; Varick, T. R.; Goh, S.-H. *J. Am. Chem. Soc.* **1990**, *112*, 5186-5193.

(278) Seebach D.; Amstutz R.and Dunitz J.D. *Helv. Chim. Acta* **1981**, *64*, 2622.

(279) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; et al. *Synth. Commun* **1990**, *20*, 307-312.

(280) Binns, F.; Roberts, S. M.; Taylor, A.; Williams, C. F. *J. Chem. Soc. Perkin Trans. 1* **1993**, 899-904.

(281) Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413-2427.

(282) Shiozaki, M.; Masuko, H. *Bull. Chem. Soc. Japan.* **1987**, *60*, 645-648.

(283) Otera, J.; Niibo, Y.; Nozaki, H. *Tetrahedron Lett.* **1992**, *33*, 3655-3658.

(284) Alpegiani, M.; Perrone, E.; Franceschi, G. *Heterocycles* **1988**, *27*, 49-55.

(285) Zhang, W. J.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177-1180.

(286) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139-4142.

(287) Wessel, H.-P.; lveersen, T.; Bundle, D. R. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2247-2250.

(288) Cramer, F.; Hennrich, N. *Chem. Ber.* **1961**, *94*, 976.

(289) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583-5601.

(290) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453-461.

(291) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485-1486.

(292) Tiecco, M.; Testaferri, L.; Marini, F.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron* **1997**, *53*, 10591-10602.

(293) Aumann, R.; Meyer, A. G.; Frohlich, R. *Organometallics* **1996**, *15*, 5018-5027.