Université de Montréal

The Asymmetric Synthesis of L-Azetidine-2-Carboxylic Acid and 3-substituted Analogs

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a été évalué par un jury composé des personnes suivantes:

André Charette	président-rapporteur
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Abstract

This research entails the development of a route to the synthesis of racemic azetidine-2-carboxylic acid (Aze) as well as an asymmetric route to the enantiopure L-Aze. In addition, several 3-substituted analogs: (2*S*,3*R*)-3-phenyl-azetidine-2-carboxylic acid, (2*S*,3*R*)-3-(1-naphthyl)-azetidine-2-carboxylic acid and (2*S*,3*S*)-3-isopropyl-azetidine-2-carboxylic acid were synthesized using Oppolzer's chiral auxiliary as source of chiral induction.

An attempt was made towards the synthesis of *syn*-(2*S*,3*R*)-3-isopropyl-azetidine-2-carboxylic acid yet, in the final step, the required cyclization to obtain the azetidine ring was not successful. Instead, X-ray analysis confirmed that the product of this sequence was the corresponding open chain γ-hydroxy amino acid. With the exception of the known (naturally occurring) parent compound, L-Aze, the structures of all four final products were confirmed by single crystal X-ray analysis.

These cyclic amino acid derivatives are of interest as novel scaffolds in peptidomimetic design, as constained analogs of natural amino acids and as chiral ligands in asymmetric synthesis.

Résumé

Ce mémoire porte sur la synthèse d'acides azétidine-2-carboxyliques (Aze) racémiques, ainsi que sur une voie asymétrique pour la synthèse de L-Aze énantiomériquement purs. De plus, plusieurs analogues substitués en position 3 furent synthétisés, tel le (2*S*,3*R*)-3-phényl Aze, le (2*S*,3*R*)-3-(1-naphthyl) Aze et le (2*S*,3*S*)-3-isopropyl Aze. Nous avons aussi tenté la synthèse du [*syn*] (2*S*,3*R*)-3-isopropyl Aze, mais la réaction finale de cyclization ne put être effectuée. Cette séquence nous a permis cependant d'accéder à des acides aminés portant un groupement hydroxyle en γ.

Aze racémique fut synthétisé par l'addition de dérivés allyl-zinc sur des oximes benzyliques dérivées du glyoxalate de méthyle. En ce qui concerne L-Aze et les analogues substitués en position 3, une version diastéréosélective fut développée en effectuant les mêmes réactions d'allylation sur des oximes derivés de l'acide glyoxalique portant un auxiliaire derivé du camphre d'Oppolzer comme substituant du carboxyle. La réaction d'allylation procède via une réaction de Barbier, soit en ajoutant le Zn° à un bromure allylique qui était dissous dans un mélange de THF-NH_4Cl (sat.). Par la suite, l'auxiliaire chiral fut clivé par saponification avec LiOH pour donner les *N*-benzyloxy esters aminés qui furent par la suite protégés avec un groupement protecteur Cbz.

Plusieurs méthodes furent utilisées pour oxyder le double lien. Dans le cas des oléfine non-substituées, ou substituées par un groupement phényle, l'utilisation d'un protocole d'ozonolyze/réduction avec $NaBH_4$ nous a donné les alcools correspondants avec de bons rendements. Par ailleurs, l'ozonolyze du composé (3*R*)-3-(1-naphthyl) a donné des

produits de décomposition. Cependant, l'utilisation de $OsO_4/NaIO_4$ a permis d'obtenir l'aldéhyde correspondant avec un rendement modéré. L'aldéhyde fut alors réduit à l'alcool par l'action de $LiAl(Ot\text{-}Bu)_3$, suivi par la mésylation de l'alcool, pour générer le mesylate correspondant dans un rendement de 45% sur 3 étapes.

Les isomères *syn* et *anti* des oléfines portant un groupement 3-isopropyle ne purent être séparés avant le clivage oxidatif. Le traitement de ce mélange avec de l'ozone/DMS a fourni les aldéhydes correspondants. Les deux isomères furent séparés avant la réduction au $LiAl(Ot\text{-}Bu)_3$, et les alcools obtenus furent convertis en mésylates de façon quantitative.

Après l'hydrolyse du groupement "Camphorsultam", les acides substitués avec les groupements phényle et naphthyle doivent être protégés sous forme d'esters *tert*-butyliques afin d'éviter la lactonisation lors de la réduction. Cette methodologie à permis la synthèse d'un seul diastéréoisomère de conformation 2(S) et de stéréochimie *syn*.

Dans le cas de l'analogue substitué en position 3 par un groupement iso-propyl, la reaction d'allylation mêne a un melange 1:1 des diastéréoisomères *syn* et *anti*. Leur séparation a pu être realisée lors de leur transformation en aldehyde. La lactonization spontanée, même en presence de l'ester *t*-butylique a pu être evitée en effectuant la reduction à 0 °C, suivie d'une mesylation.

Chacun des mésylates obtenus fut soumis à des conditions d'hydrogénation pour enlever les groupements protecteurs benzyloxy et Cbz, donnant l'amine libre qui fut piégiée sous forme d'un sel de mésylate. La cyclisation à l'azétidine procéda sans problème, sauf dans

le cas du produit syn portant un groupe *iso*-propyle. Il est apparu que dans ce dernier cas, les conditions réactionelles ($NaHCO_3$, MeOH-H_2O), ont produit un intermédiaire qui, après une hydrolyse en condition acide, s'est révélé être un γ-hydroxy acide aminé.

À l'exception d'un produit déjà connu (l'acide L-azétidine-2-carboxylique) la structure de tous nos produits finaux fut confirmée par une étude par diffraction des rayons-X.

En conclusion, ces acides aminés cycliques présentent un intérêt en tant que nouvelles structures de peptidomimétique, comme analogues rigides d'acides aminés, et en tant que catalyseurs de diverses réactions asymétriques.

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Abreviations

$[\alpha]_D$	optical rotation
aq.	aqueous
Aze	Azetidine-2-carboxylic acid
Bn	Benzyl
brs	broad singlet
Cbz	benzyloxycarbonyl
DCM	dichloromethane
d	doublet
dd	doublet of doublet
d.r.	diastereomeric ratio
DIBAL-H	Diisobutylaluminum hydride
ee	enantiomeric excess
FAB	Fast Atom Bombardment
FT-IR	Fourier Transform InfraRed
g	gram
Glu	Glutamic acid
h.	hour
HRMS	High Resolution Mass Spectrometry
IPA	isopropyl alcohol
J	coupling constant
LiHMDS	lithium hexamethyldisilazane
lit.	litterature
m	multiplet

Me	methyl
MeOH	methanol
MHz	megahertz
mL	milliliter
mmol	millimole
M.P.	melting point
Ms	methanesulfonyl
NMR	Nuclear Magnetic Resonance
Ph	phenyl
ppm	parts per million
s	singlet
t	triplet
t-Bu	tert-butyl
TDS	thexyl dimethylsilyl
thexyl	1,1,2-trimethylpropyl
THF	tetrahydrofuran

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CHAPTER 1.0

Azetidine-2-Carboxylic Acid

1.1 Biosynthesis and Discovery of L-Azetidine-2-carboxylic acid

L-Azetidine-2-carboxylic acid (L-Aze) is an amino acid found naturally almost exclusively in plants belonging to the Lilaceae family[1]. In some of these plants, ex. *Convallaria majalis* (lily-of-the valley) and *Gonatum multiflorum* (a solomon's seal) it is present in very high concentrations relative to those of other free amino acids.

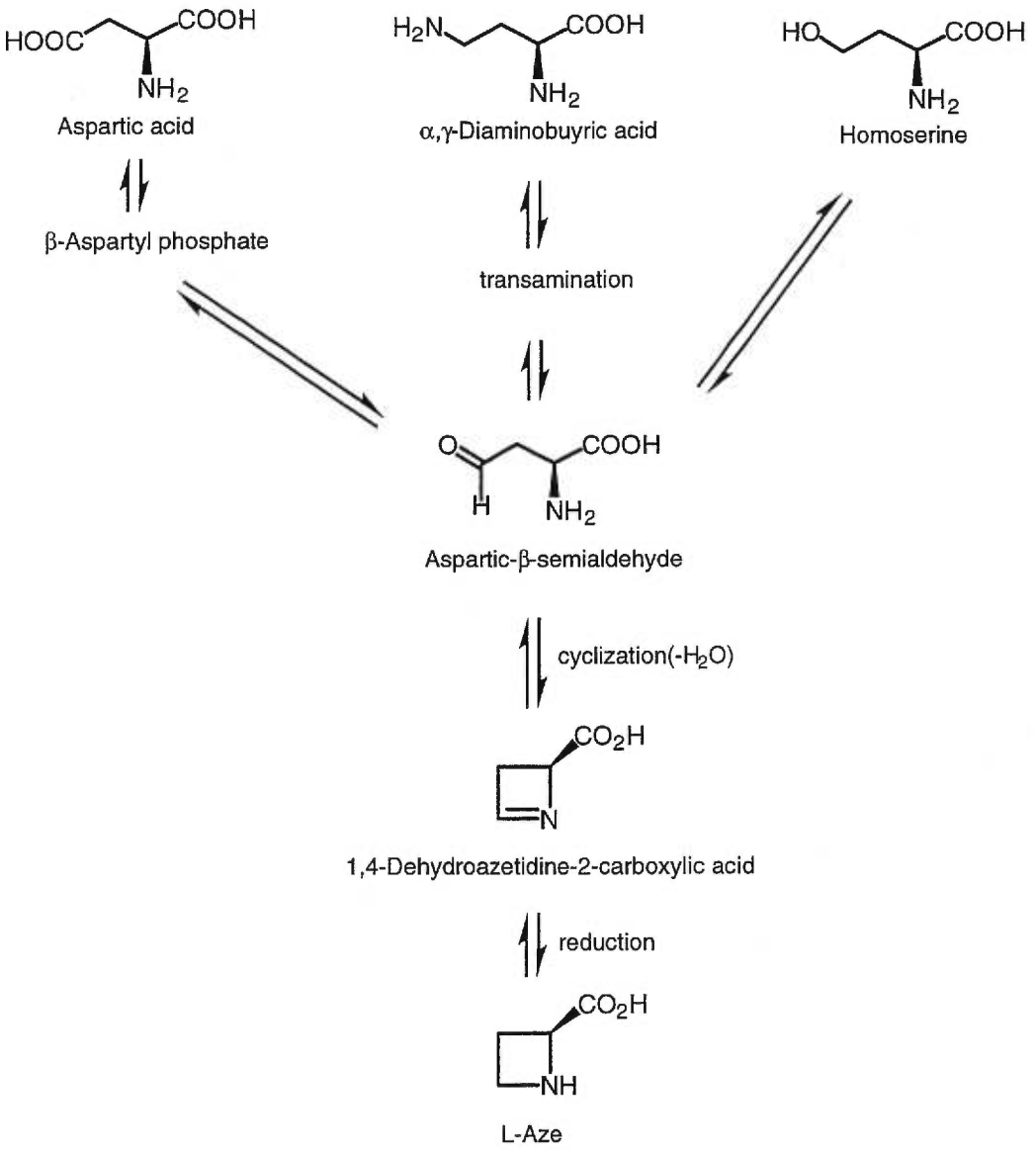
L-Aze was discovered independently by two groups: Fowden (1955)[2], who isolated it from Convallaria majalis and characterized it chemically by comparison with the synthetic material, and Virtanen and co-workers (1955), who isolated the identical substance from Gonatum multiflorum. Virtanen and Linko[3], however, initially proposed an incorrect structural formula, and later[4] acknowledged Fowden's formula as being correct. There had been no reference to this compound in the chemical literature before 1955, although the free azetidine was first described in the latter part of the 19th century by Gabriel and Weiner[5]. This was also the first account of a simple four-atom ring system occurring in plants.

As the lower homologue of proline[6], this amino acid often accumulates in large amounts and may represent the major proportion of non-protein nitrogen of these particular plants. Since it is not known to occur as part of plant proteins, it is considered a non-protein imino acid[7]. Studies examining the effects of L-Aze when administered to other types of plants, for example *Phaseolus aureus*, have found it to cause marked growth inhibition and was lethal at high concentrations. There can be several reasons for this behavior. Because it is a proline analogue, L-Aze may be competing successfully for incorporation into proteins resulting in abnormal proteins that have impaired biological activity. This inhibitory effect

can be reversed by the addition of proline, and the liliaecous plants have evolved a mechanism that excludes L-Aze in favor of proline thus not suffering the toxic effects that other species of plants are susceptible to[7].

The mechanism of differentiation may be occurring at the sub-cellular level where L-Aze is excluded from the sites of protein synthesis or an enzymatic selection between proline and L-Aze. The varying ability of the proline activating enzyme to differentiate between its desired substrate and L-Aze may determine how different plants react. It is still a mystery, though, why the liliaceae synthesize this imino acid in the first place. According to Fowden (1956)[2b], the likely biosynthetic pathway is similar to that leading to proline and that L-Aze possibly originates from 3 possible precursors: aspartic acid, homoserine and diaminobutyric acid as shown in scheme 1.1.

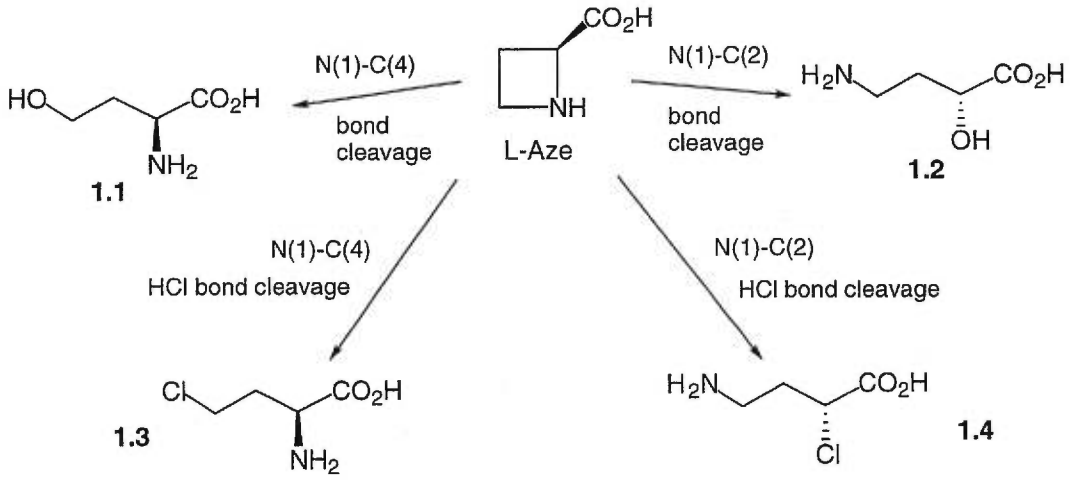
Scheme 1.1: Proposed biosynthetic pathway leading to L-Azetidine-2-carboxylic acid (Aze)



Nevertheless, the products obtained when L-Aze was treated with hydrochloric acid did not give a very clear indication of the degradative process of this imino acid. L-Aze is susceptible to hydrolytic cleavage when heated with 6N HCl to yield homoserine (**1.1**) and α-hydroxy-γ-aminobutyric acid (**1.2**) by cleavage of the N(1)-C(4) and N(1)-C(2) bonds

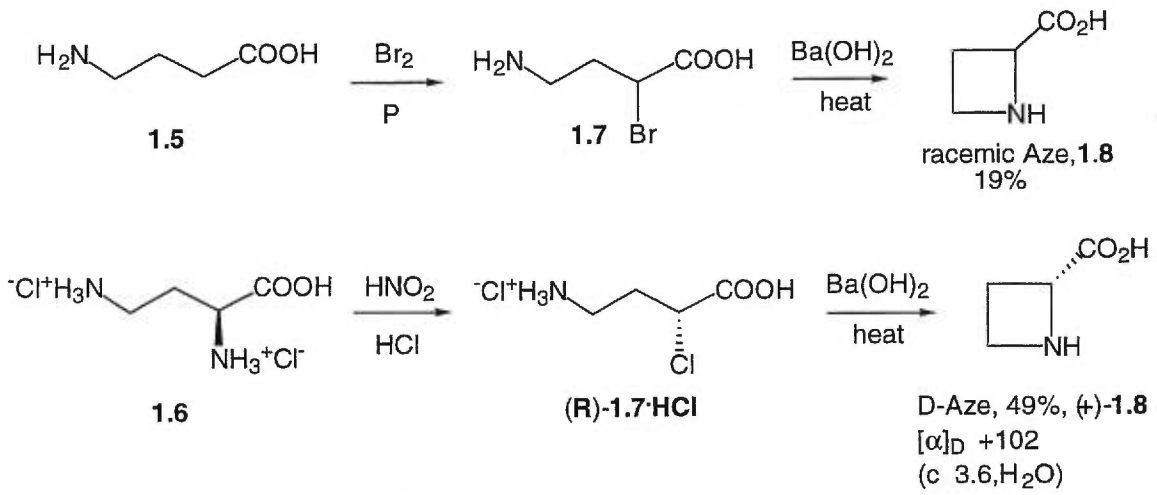
respectively (Scheme 1.2). Similarly, α-amino-γ-chlorobutyic (**1.3**) and α-chloro-γ-aminobutyric acids (**1.4**) were obtained via HCl cleavage of the same bonds (respectively).

Scheme 1.2: Degradation products of L-Aze in the presence of 6N HCl



Lastly, to confirm the structure, Fowden synthesized the first azetidine-2-carboxylic acid via two methods[2b]. Intermediates γ-amino-α-bromobutyric acid (**1.5**) and γ-amino-α–(R)-chlorobutyric acid (**1.6**) were synthesized, and cyclized in the presence of 0.5 N barium hydroxide to yield both the racemic (**1.8**) and optically active ((+)-**1.8**) Aze's (Scheme 1.3).

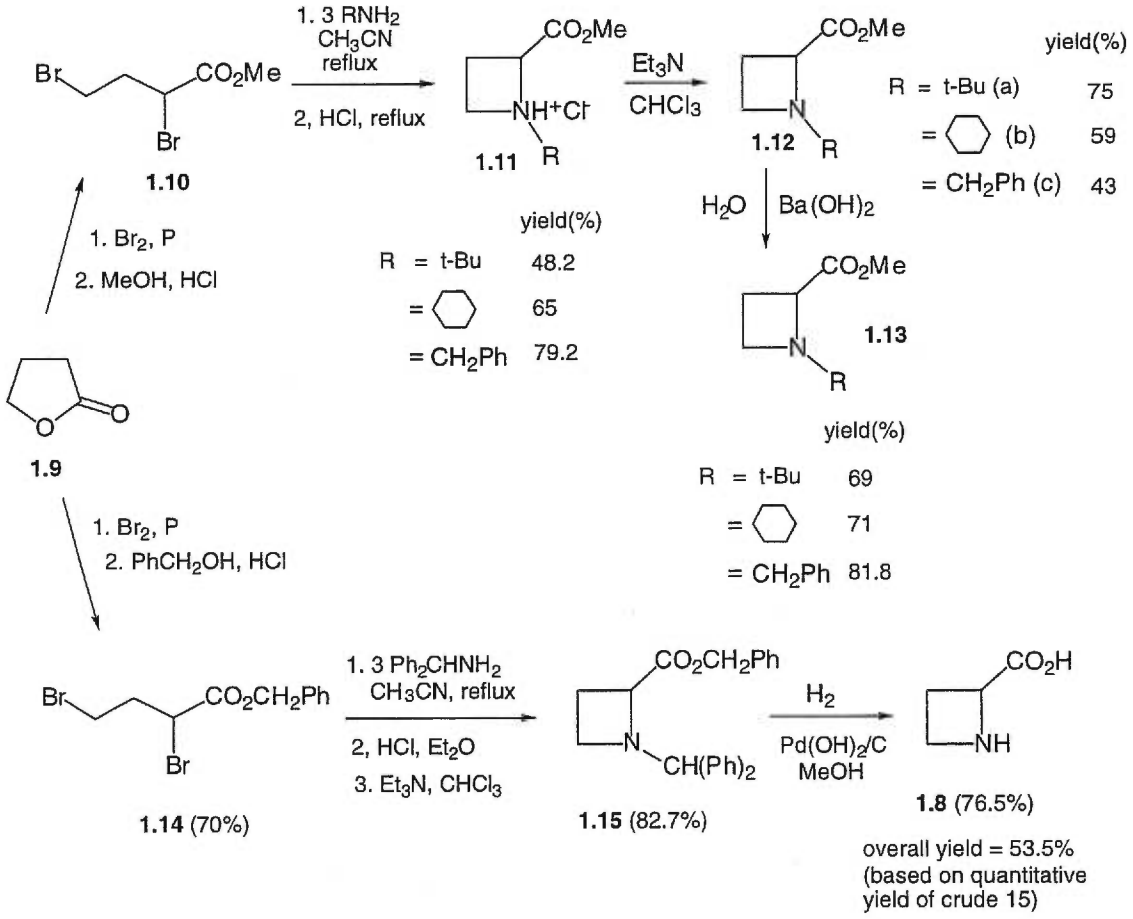
Scheme 1.3: First synthesis of DL and L-Aze's



1.2 Other syntheses of unsubstituted DL- and L-azetidine-2-carboxylic acids

The first practical synthesis of racemic azetidine-2-carboxylic acid was achieved by Rodebaugh and Cromwell[8a]. They also synthesized various *N*-alkyl substituted derivatives of Aze's (**1.13**)[8b] from butyrolactone (**1.9**).

Scheme 1.4: First practical synthesis of racemic and *N*-alkyl Aze's

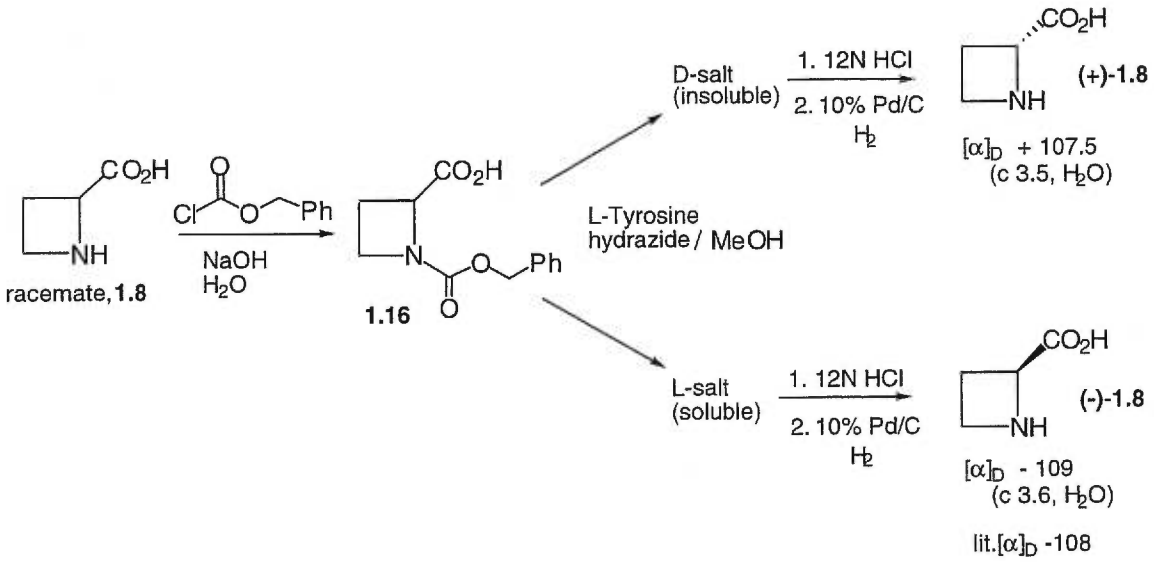


As in the syntheses of DL and D-Aze by Fowden[2b] from γ-amino-α-halo butyric acids, these syntheses relied on the initial formation of γ-amino-α-bromo compounds by displacement of the respective dibromo esters (**1.10**,**1.14**) with a given amine. Subsequently, under reflux conditions, the α-bromide is displaced intramolecularly by the terminal amine while the excess free amines in solution remove the HBr that is produced.

In a later communication[9], Rodebaugh and Cromwell reported the development of a method of resolution of the DL-form (**1.8**) to obtain the enantiopure D- and L-Aze's.

The DL-(*N*-benzyloxycarbonyl) azetidine-2-carboxylic acid (**1.16**) was combined with L-tyrosine hydrazide in methanol to yield two diastereomeric salts, which could be distinguished based on their relative solubilities in methanol. The D-salt (98%) precipitated out while evaporation of the mother liquor yielded the L-salt (92%) as a semisolid.

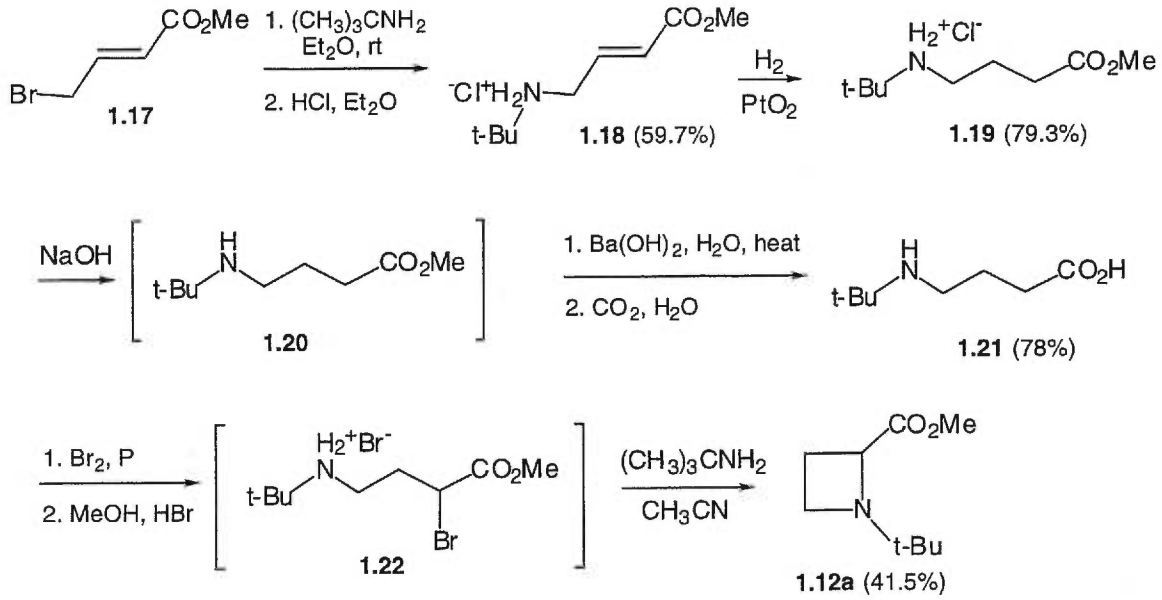
Scheme 1.5: Resolution of *N*-benzyloxy-DL-Aze using L-tyrosine hydrazide



Treatment of the individual salts with concentrated HCl, followed by catalytic hydrogenolysis afforded the D- and L-Aze's in 55% and 61% overall yield respectively. This was the first resolution of the enantiopure L-Aze.

A different synthesis of DL-Aze by this group was published in 1971. In this case the starting material was methyl-γ-bromocrotonate (**1.17**) which was carried through to γ-*t*-butyl-aminobutyric acid (**1.21**), and as opposed to earlier routes, the terminal amino group had been put on before the bromination. Therefore, the next step was treatment with Br_2/P followed by esterification to yield an intermediate (**1.22**) that, although never isolated, was cyclized in the same manner as in previous syntheses to afford *N*-t-butyl-2-carbomethoxy azetidine (**1.12a**) in 15% overall yield.

Scheme 1.6: Synthesis of *N*-(t-butyl) Aze methyl ester from methyl-γ-bromo crotonate

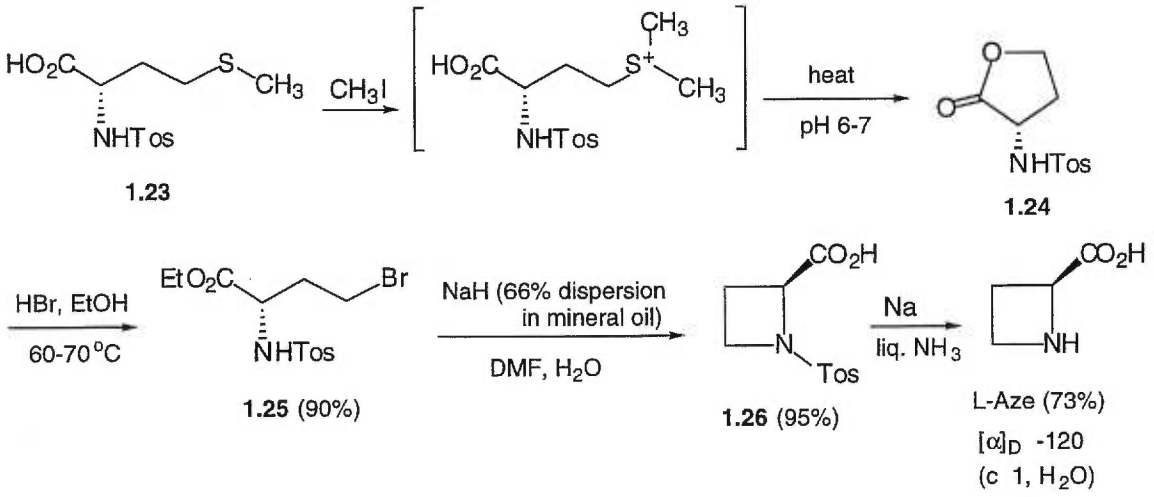


Although the overall yield is all but impressive, this paper[10] attempts rather to demonstrate some of the possible transformations of *N*-alkyl-2-carbomethoxyazetidines (**1.12**) into compounds bearing different functional groups at the 2-position. Reduction with lithium aluminum hydride affords the corresponding alcohol, saponification followed by acidification results in the parent Aze which can further be manipulated through a mixed anhydride to form the amide. This amide can be reduced, once again, to the primary amine.

The first synthesis of enantiopure L-Aze without optical resolution was accomplished by Miyoshi et al[11] from tosyl-L-homoserine lactone (**1.24**) which can be readily prepared from tosyl-L-methionine (**1.23**)[12].

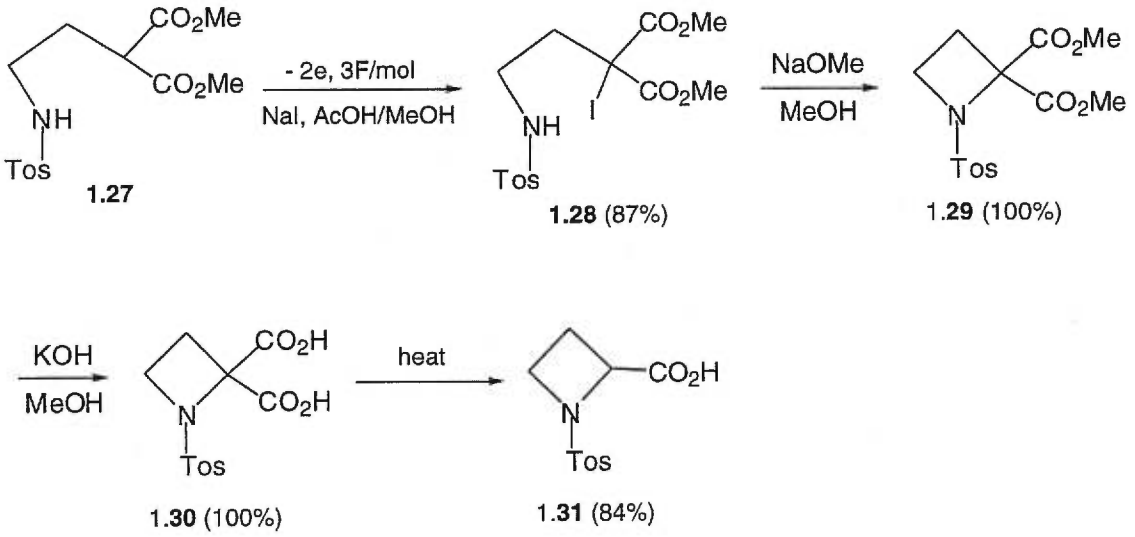
Unlike the previous syntheses where the ring formation involves intramolecular displacement of an α-halide by a γ-amine (substituted or primary), this cyclization relies on the displacement of a γ-bromide by a substituted α-amine.

Scheme 1.7: First asymmetric synthesis of L-Aze from *N*-tosyl-methionine



More recently, a group from Japan reported several novel intramolecular C-N bond forming reactions by anodic oxidation that were used to form aziridine, azetidine and pyrrolidine rings[13]. Using iodide as a mediator, compound **1.27** containing a tosylamine at one end and a dimethyl malonate at the other was cyclized relying on the active methine group of the malonate to form a tertiary alkyl halide (**1.28**) that could be displaced by the amine.

Scheme 1.8: Synthesis of *N*-tosyl-Aze via anodic oxidation

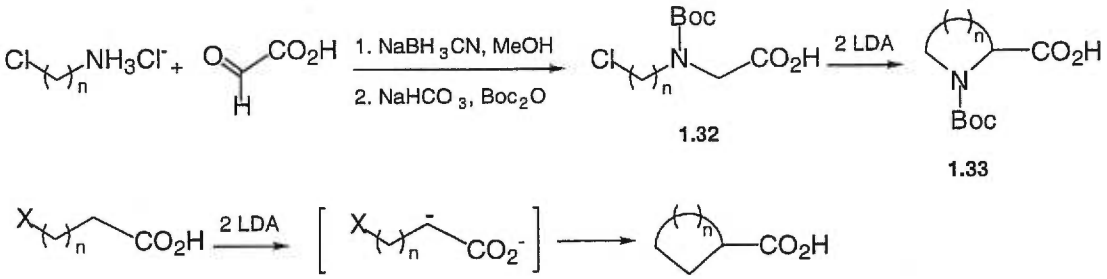


The resulting dimethyl-azetidine-2,2-dicarboxylate (**1.29**) was saponified to yield the dicarboxylic acid (**1.30**), which was then decarboxylated at 150 °C to afford the desired *N*-tosyl-Aze (**1.31**) in remarkably high yield. The supporting electrolyte had a remarkable effect on the yield of **1.29**. When NaI or KI was used to form intermediate **1.28**, then the cyclization step was quantitative. When using KBr or NaBr to form the equivalent halogenated intermediate, the yield of the subsequent cyclization step dropped to 74-76%. In the case of KCl or NaCl, the chlorinated intermediate cyclized with very low yields. It is

noteworthy that the removal of the *N*-tosyl group in this and related syntheses required dissolving metal conditions.

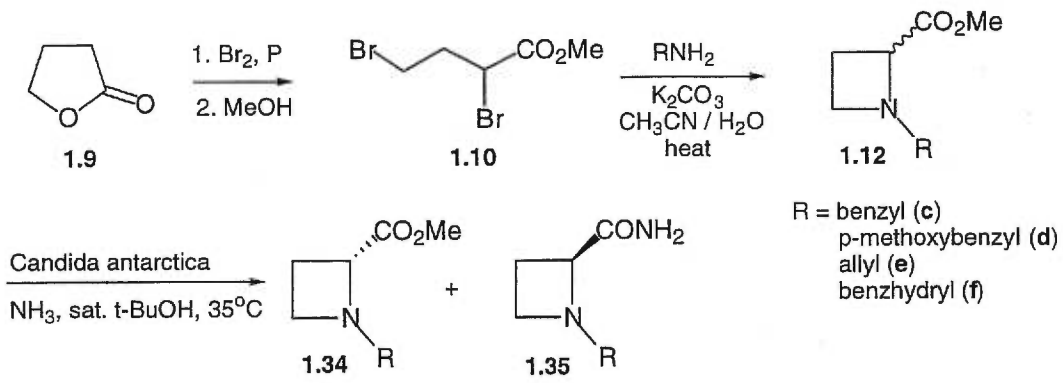
A synthesis of Boc-protected cyclic amino acids has been developed by DeNicola and co-workers[14]. It involves an intramolecular cyclization of dianions derived from n-chloro acids such as **1.32** to form 4, 5 and 6-membered amino acids.

Scheme 1.9: Synthesis of Boc-protected cyclic amino acids



The most recent synthesis of enantiopure D- and L-Aze was reported in 1998 by a group from The Netherlands[15a]. Different racemic Aze's (**1.12c-f**) were first synthesized using the Rodebaugh and Cromwell[8b] method with some modifications to the cyclization step and then enzymatic resolution yielded the pure *R*(**1.34**) and *S*(**1.35**) enantiomers. Methyl-2,4-dibromobutyrate (**1.10**) was obtained from γ-butyrolactone (**1.9**) via a Hell-Volhard-Zelinskii bromination followed by esterification with methanol. The subsequent cyclization step was accomplished with one equivalent of amine and K_2CO_3 as co-base in refluxing CH_3CN/H_2O instead of 3 equivalents of amine in refluxing acetonitrile[8a,b].

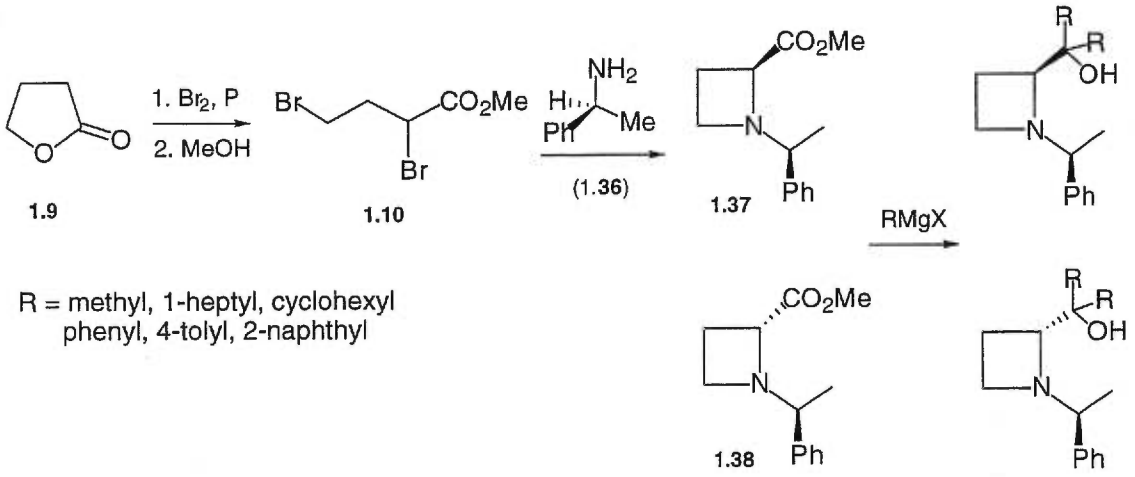
Scheme 1.10: Synthesis of enantiopure D- and L-Aze using enzymatic resolution



Candida antarctica turned out to be a suitable resolving enzyme that forms a carboxamide (**1.35**) from only the (*S*)-ester using ammonia as the nucleophile and leaves the (*R*)-ester (**1.34**) untouched. The *N*-benzyl (**1.34c**) and *N*-p-methoxybenzyl (**1.34d**) (*R*)-esters were both found to have >99% ee's and the (*S*)-amides (**1.35c,d**) had 80% ee (>99% after one crystallization) and 84% ee respectively. The allyl (*R*)-ester (**1.34e**) and (*S*)-amide (**1.35c**) were the most successful with >99% and 97% ee (without crystallization) respectively.

Another method was developed by Starman's group[15b] at about the same time, which allowed the two enantiomers of azetidine-2-carboxylate methyl ester to be formed as separate diastereomers (**1.37**,**1.38**) by cyclizing the common α,γ-dibromo-methyl butyrate (**1.10**) with chiral (*S*)-α-methylbenzylamine (**1.36**).

Scheme 1.11: Synthesis of both enantiomers of azetidine-2-carboxylate methyl ester by cyclizing with (*S*)-α-methylbenzylamine (**1.36**)

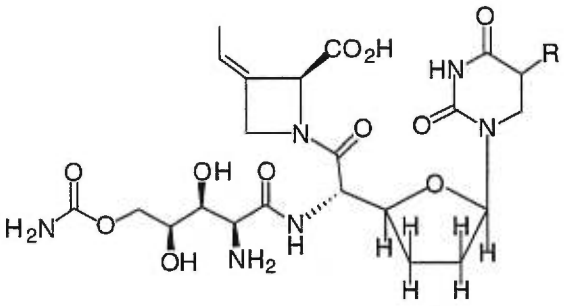


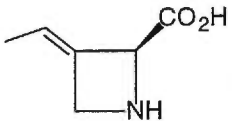
The corresponding tertiary alcohols were then prepared by reaction with Grignard reagents.

1.3 Syntheses of 3-substituted azetidine-2-carboxylic acids

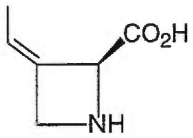
Considerable effort has been put toward the synthesis of (+)-polyoximic acid which is one of the amino acids present in the Polyoxin tripeptides (Polyoxin A, F, H and K).

Figure 1.1: Polyoxin A,F,H,K and *cis/trans* polyoximic acids





trans-Polyoximic acid



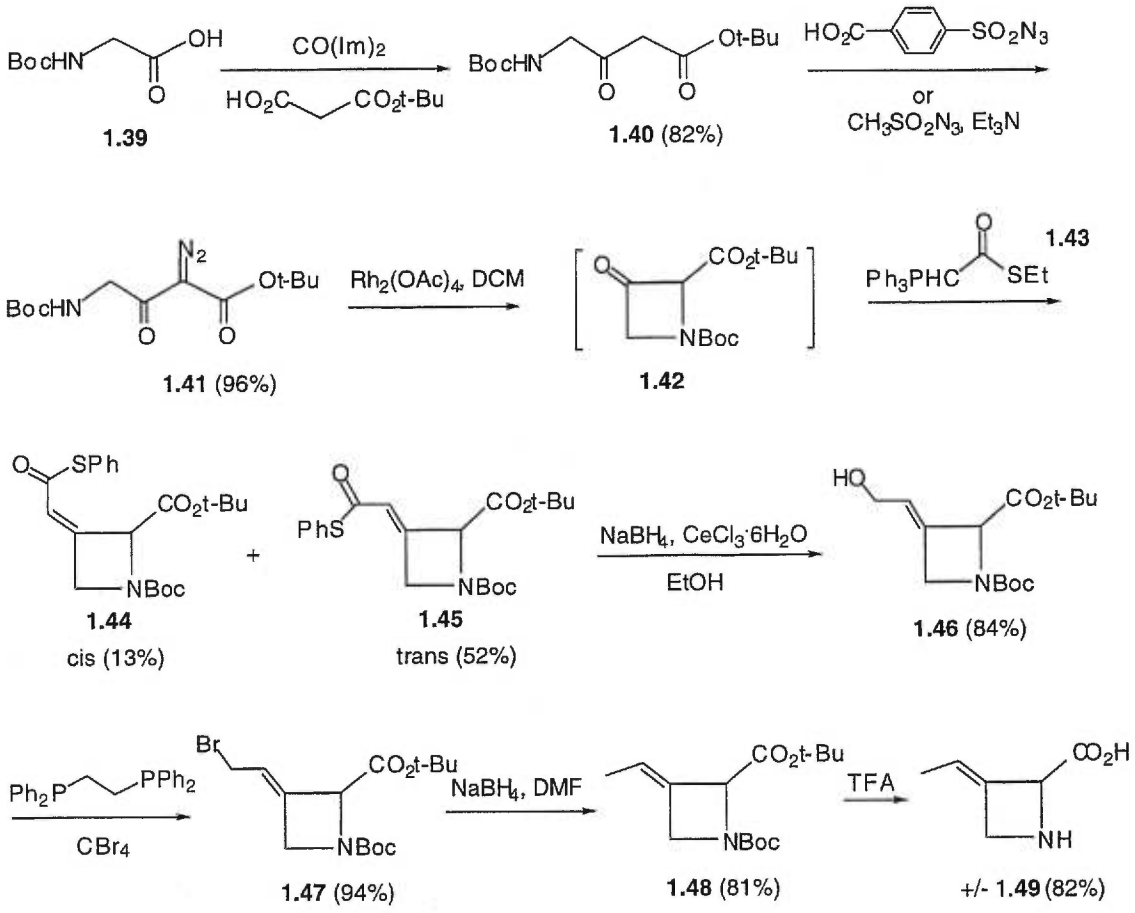
cis-Polyoximic acid

Polyoxin	R
A	CH_2OH
F	COOH
H	CH_3
K	H

It was assumed by Isono and coworkers[16a] that the double bond in Polyoximic acid had a *trans* configuration. Some thirty years later Hanessian et al[16b] reported the total synthesis of *cis* and *trans* Polyoximic acids and established conclusively the *cis* stereochemistry of polyoximic acid (*cis*-3-ethylidene-L-azetidine-2-carboxylic acid). Unaware of the revised structure, Emmer[17] reported the synthesis of racemic *trans* polyoximic acid. *N*-Boc-glycine (**1.39**) was transformed into the β-ketoester (**1.40**) and subsequently cyclized via a rhodium carbenoid intramolecular N-H insertion reaction to afford the four-membered intermediate (**1.42**) that was used without purification for the Wittig reaction. Anticipating

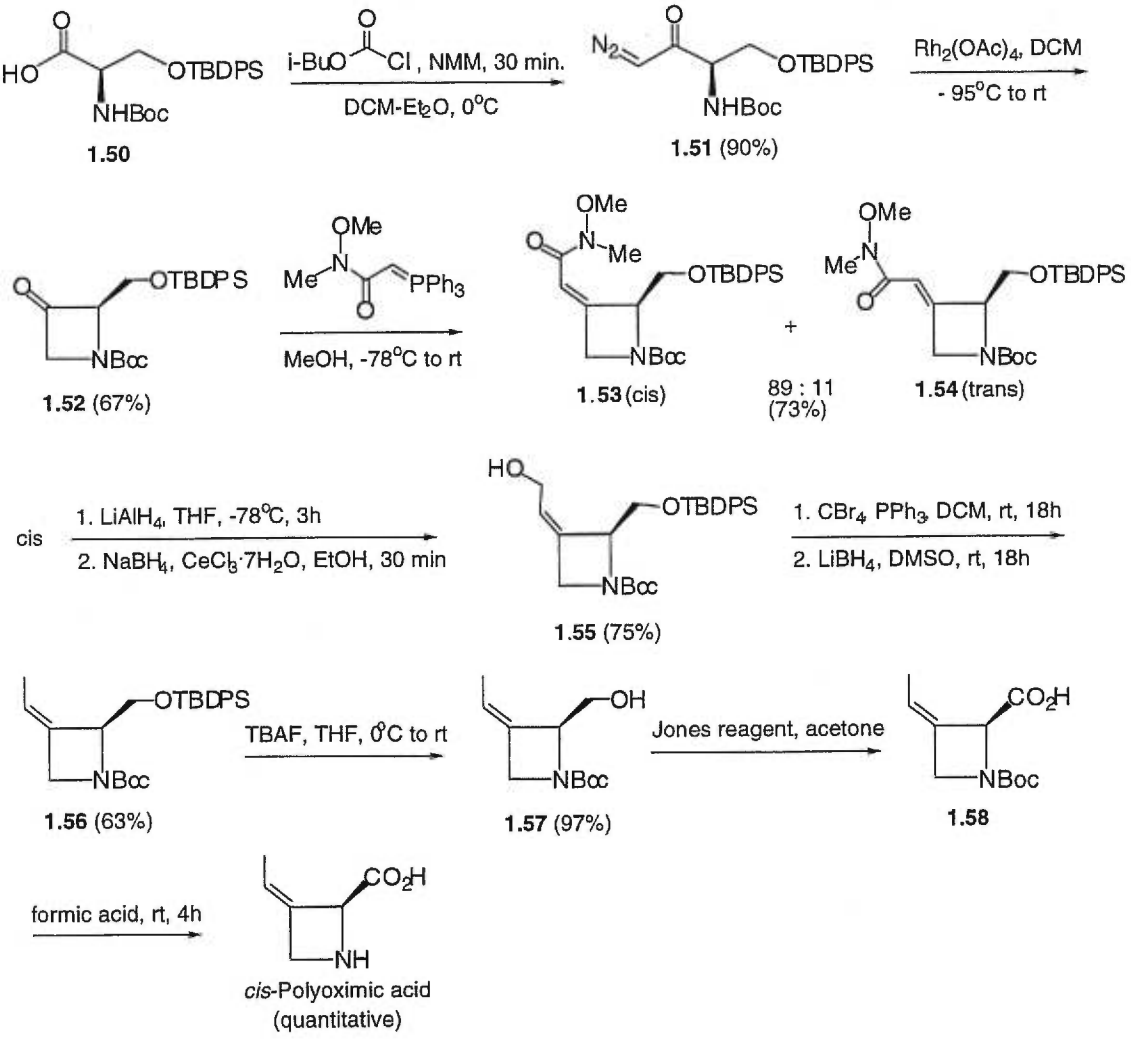
the need for mild reducing conditions, ethylthiocarboxy-methylene-triphenylphosphorane was employed as Wittig reagent since thiol esters are known to be reduced relatively easily. Following the reduction, the *trans* allyl alcohol (**1.46**) was converted to the bromide (**1.47**), then to **1.48** and finally both the Boc and t-butyl ester protecting groups were removed under acidic conditions to yield the desired racemic polyoximic acid (**1.49**) in modest overall yield.

Scheme 1.12: Synthesis of racemic polyoximic acid



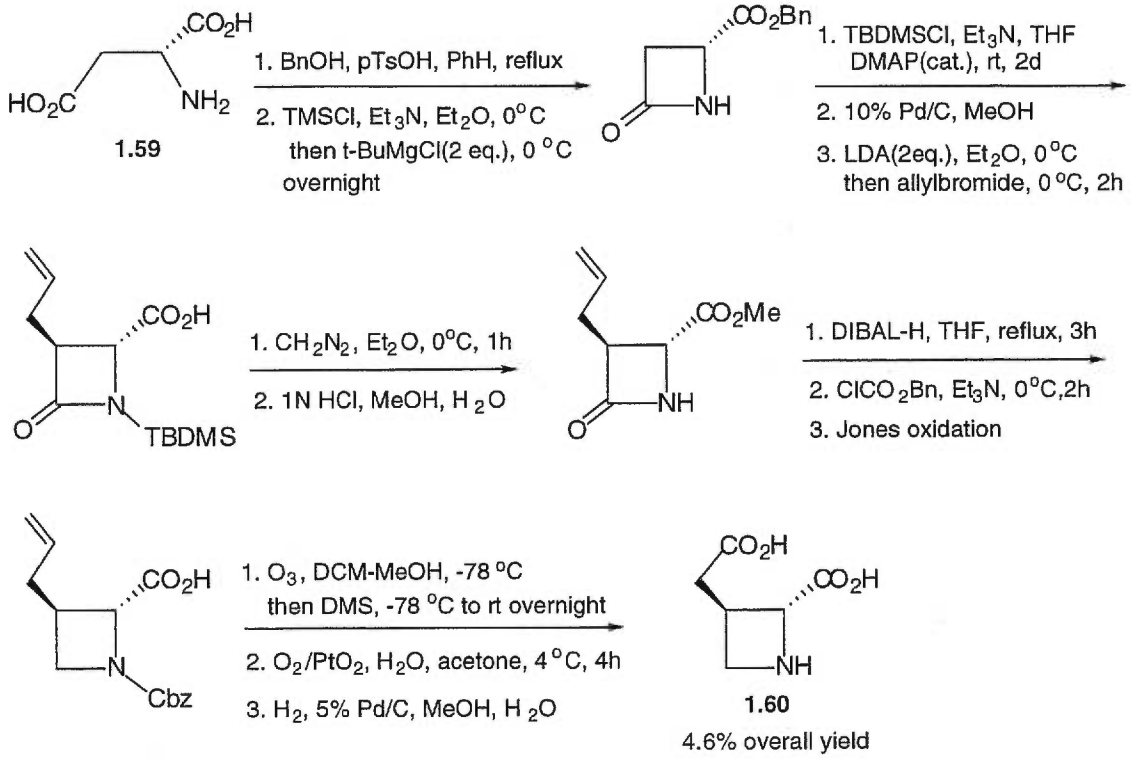
Hanessian et al reported the synthesis of both the *cis* (natural) and *trans* (unnatural)-polyoximic acids[18] from D-serine. Then, the diazoketone **1.51** was subjected to a rhodium-mediated diazoketone insertion reaction to form the 2-hydroxymethyl-L-3-azetidinone intermediate (**1.52**). Using *N*-methoxy-*N*-methyl-2-(triphenyl phosphoranylidene) acetamide as Wittig reagent yielded the exo double bond in a ratio of 89:11 (*cis/trans*). Conversely, sodium diethyl (*N*-methoxy-*N*-methylcarbonylmethyl) phosphonate led to the formation of the major *trans* product in a ratio of 94:6 (*trans/cis*). Although only the route to the *cis* isomer is shown in Scheme 1.13, both isomers (separable by chromatography) were then individually manipulated through to the target cis and trans polyoximic acids.

Scheme 1.13: Synthesis of enantiopure *cis*-polyoximic acid



Another interesting substituted azetidine, *trans*-2-carboxyazetidine-3-acetic acid (**1.60**), was synthesized recently from D-aspartic acid (**1.59**) in an effort to form rigidified analogues of glutamate (glu)[19] and study the glu recognition sites.

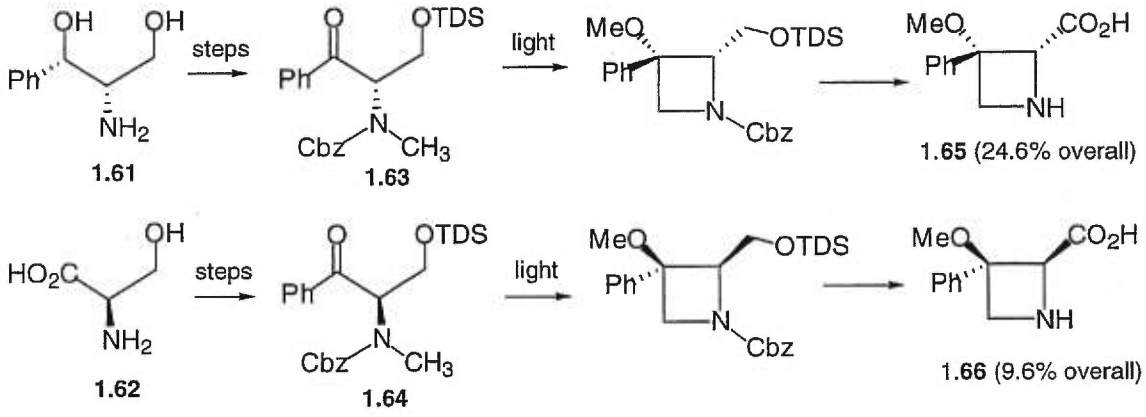
Scheme 1.14: Synthesis of *trans*-2-carboxyazetidine-3-acetic acid from D-aspartic acid



More recently, Wessig and Schwartz[20] reported the preparation of (2*R*,3*S*)-3-methoxy-3-phenylazetidine-2-carboxylic acid (**1.65**) as well as its enantiomer (**1.66**) from the commercially available amino diol (**1.61**) and D-serine (**1.62**) respectively.

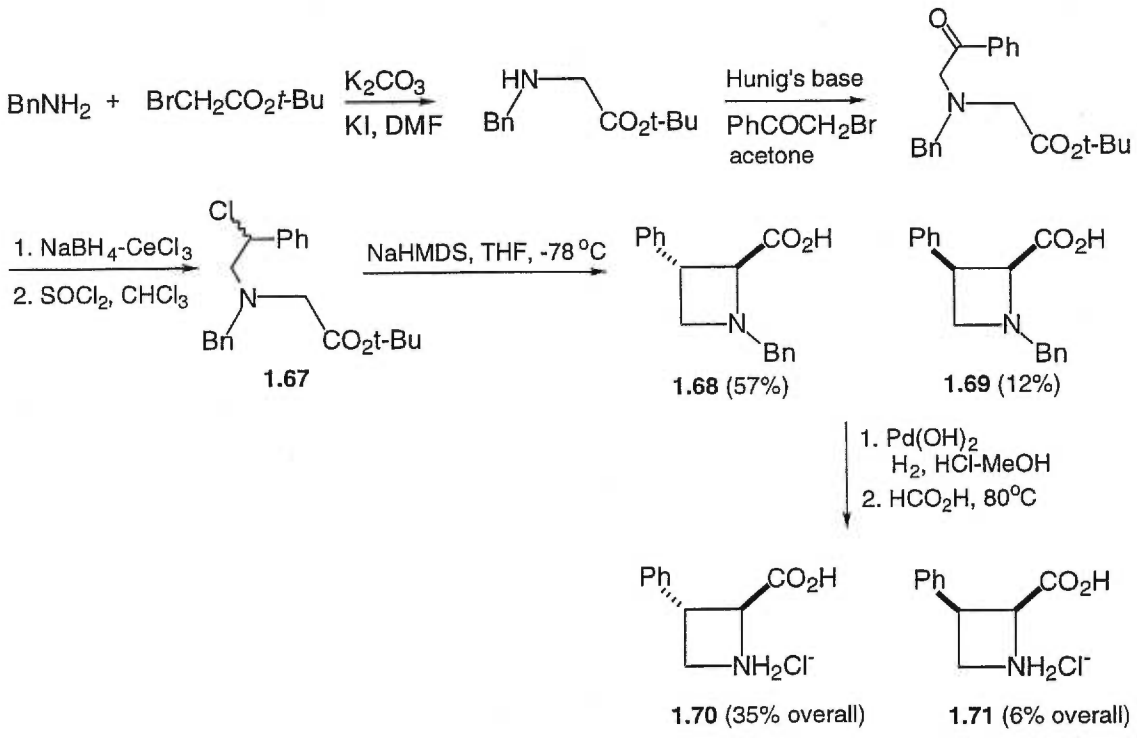
Using a stereoselective photochemical ring closure of the amino ketones **1.63** and **1.64**, they were able to obtain the enantiopure azetidines (**1.65**, **1.66**) in 71% yield each.

Scheme 1.15: Synthesis of azetidines **1.65** and **1.66** from diol **1.61** and *D*-serine (**1.62**)



Lastly, the synthesis that most closely resembles some of the work described in this thesis involves the syntheses of racemic *syn*- and *anti*-3-phenyl azetidine-2-carboxylic acids (**1.70**, **1.71**)[21]. These conformationally restricted phenylalanine analogs may prove to be particularly useful when incorporated into peptides due to the increased resistance to proteolysis of the tertiary amide bonds. A diastereomeric mixture of the *syn* (**1.69**) and *anti* (**1.68**) (*anti* being formed preferentially) azetidines were formed from the same starting materials (**1.67**) that were separable by chromatography and subsequently each isomer was deprotected to afford the corresponding free imino acids.

Scheme 1.16 Synthesis of racemic *syn* and *anti* 3-phenyl Aze's

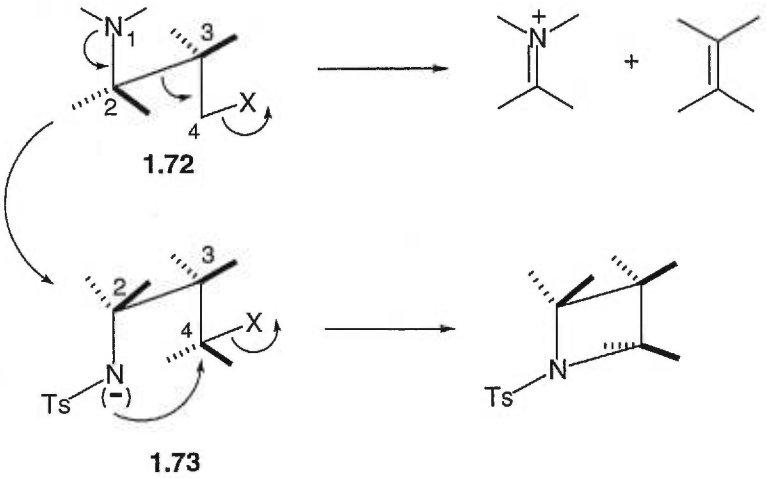


1.4 Conformational effects involved in cyclization to form an azetidine ring

Generally, there have been several common methods used to yield azetidines by cyclization. These include 1) dehydrohalogenation of 3-haloalkylamines 2) reaction of 1.3-dihaloalkanes with amines 3) reaction of 3-aminopropanes bearing a good leaving group with base[22]. The yields though are often low due to competing reactions such as elimination, fragmentation or dimerization. Dimerization tends to occur when C-4 of the precursor is 1° and the reactions are performed at higher concentrations[23,24]. Cyclizations to form azetidine rings are most successful when using high dilution techniques.

Substitution of a given 3-aminopropyl tosylate or sulfonate either on one of the carbons or on the nitrogen can also greatly affect the rate of cyclization[23]. It is understandable that an *N*-unsubstituted chain may undergo Grob fragmentation[24] since the molecule can readily assume a staggered conformation (**1.72**).

Figure 1.2: Fragmentation vs cyclization



Conversely, having a large *N*-substituent on the molecule (**1.73**) prevents fragmentation by impeding rotation about the C(2) - C(3) bond, for steric reasons, thus favoring cyclization.

CHAPTER 2.0

Uses of Azetidine-2-Carboxylic Acids

2.1 Incorporation into peptides and medicinal properties

There are three cyclic amino acids (imino acids) found in nature having 4-,5- and 6-membered rings. Only one of these, proline, occurs naturally in proteins and exerts a major influence on the secondary structure and folding of proteins[25].

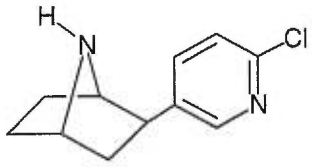
As the lower homologue of proline, L-Aze can be incorporated into proteins in place of L-proline. This can cause alterations in the properties of the protein that makes this toxic for plants that do not naturally contain L-Aze. Plants like Lily-of-the-valley have enzymes that discriminate between L-Pro and L-Aze and will incorporate proline preferentially[26]. This difference in behavior can be largely attributed to the more rigid nature of the 4-membered azetidine ring, and when incorporated in place of the natural proline, it causes an increased flexibility of an Aze-containing polypeptide. It is this entropic effect, in turn, which lessens the stability of the polypeptide conformations[27]. Most studies of Aze incorporation have been carried out on collagen, a fibrous protein whose structure is largely made up of the frequent occurrence of proline and hydroxyproline residues. In the collagen triple helix, substitution of Pro for Aze has a destabilizing effect relative to a statistical coil, since Aze residues can take up more equivalent low energy conformations in the single-stranded form. Incorporation of Aze therefore results in collagen that is more easily digested since the triple helix has been disrupted. As a consequence, there is a decrease in its assembly into higher aggregates which is necessary for the formation of connective tissue[28].

Aze and its derivatives have other potential medicinal uses. Based on the alkaloid (-)-epibatidine, a natural product isolated from the skin of Ecuadorian frogs that has shown

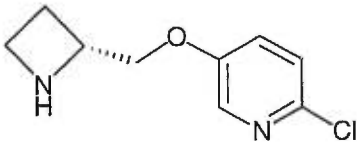
potent non-opioid analgesic properties, several Aze-derived analogs have been synthesized and studied[29,30].

Although (-)-epibatidine is a 200-fold stronger analgesic than morphine, it is toxic or even lethal at doses only slightly higher than the effective analgesic dose. It would therefore be advantageous to find a compound with similar potency and lower toxicity. This has led to the synthesis of 2(*R*)-chloro-5-(2-azetidinylmethoxy)pyridine (ABT-594)[31] which, although not as powerful as the natural product, shows 30-100 times more potency than morphine and is far less toxic than (-)-epibatidine. And since its mode of action is through the acetylcholine and not the opiod receptors, repeated treatment with ABT-594 does not appear to elicit physical dependance.

Figure 2.1: Analgesics: (-)-epibatidine and ABT-594



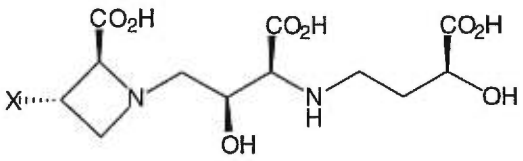
(-)-epibatidine



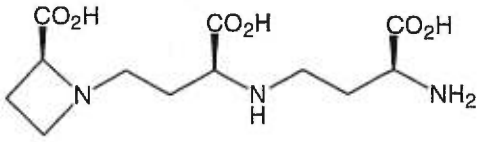
ABT-594

Another series of compounds, some of which contain an L-Aze moiety, exist in nature and are called phytosiderophores. They promote the uptake and transport of iron required for biosynthesis of chlorophyll in higher plants. Mugineic acid, 3-epi-hydroxymugineic acid and nicotianamine are some examples of these iron-chelating compounds isolated from gramineous plants[32].

Figure 2.2: Mugineic acid, 3-*epi*-hydroxymugineic acid and nicotianamine



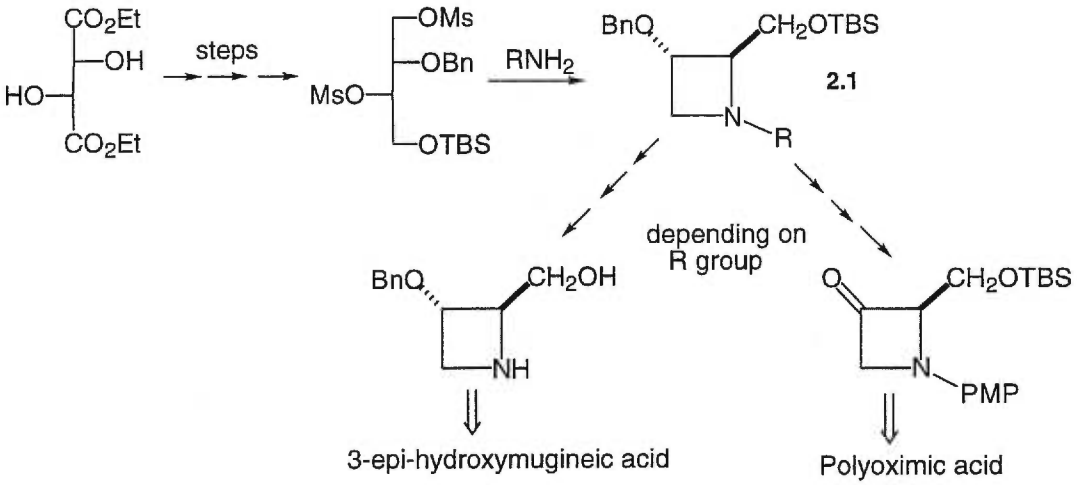
X = H, Mugineic acid
X = OH, 3-epi-Hydroxy mugineic acid



Nicotianamine

Several syntheses of these compounds have been undertaken either from commercially available L-Aze[32a,b] or from an acyclic precursor that cyclizes under basic conditions to form the Aze ring [33a,b]. One group in France[33b] undertook the synthesis of the 3-hydroxy substituted L-Aze moiety of 3-epi-hydroxymugineic acid as well as that of the polyoximic acid moiety of a the polyoxins. Sequential displacement of two mesylates in the presence of an amine led to the anti-3-benzyloxy-2-azetidinol (**2.1**) that would function as the common starting material for the two azetidines.

Scheme 2.1: Synthesis of 3-*epi*-hydroxymugineic acid and polyoximic acid from a common azetidine precursor (**2.1**)

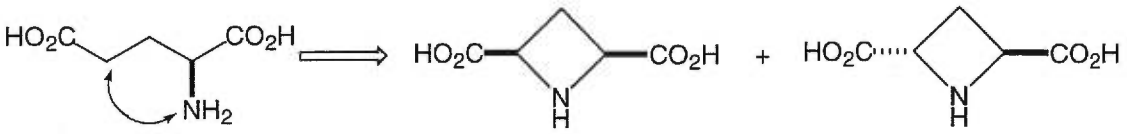


As mentioned, polyoximic acid forms part of a series of polyoxins (A,F,H,K) that, unlike the majority of polyoxins which are dipeptides, are tripeptides and can function as antibiotics. They are referred to as peptidyl nucleoside antibiotics and have been isolated from the culture broth of *Streptomyces cacaoi varasoensis*. They also show a marked activity against phytopathogenic fungi. They inhibit the chitin synthase enzyme of a human pathogen *Candida albicans* at low concentrations in cell-free systems, but much higher concentrations are needed for intact cells. This was the impetus to fine tune the system and create analogues that could be equally effective at lower doses.

Lastly, analogs of L-Aze substituted at the 3- or 4-position have also found a use as rigidified congeners of glutamic acid (Glu) **2.2**. Glu plays a crucial role in a variety of biological processes ranging from memory and learning to neuronal degeneration. Several groups have collaborated to publish the syntheses of constrained glu's in the form of (+) and (-) *trans*-azetidine-2,4-dicarboxylic acids (**2.4**) as well as the corresponding *cis*

compounds (**2.3**). In this case, ring constraint has been introduced without additional atoms [34,35].

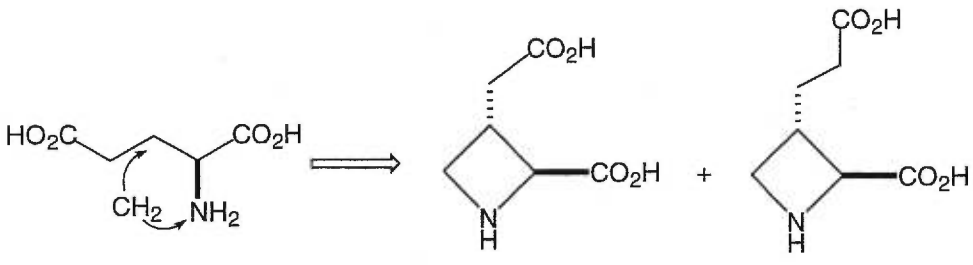
Scheme 2.2: Rigidified congeners of glutamic acid



2.2 (+)**2.3** / (-)**2.3** (+)**2.4** / (-)**2.4**

Another example by some of the same authors involves the synthesis of *trans*-2-carboxyazetidine-3-acetic acid (**2.5**) and their homologues containing a 3-propanoic acid substituent (**2.6**). These azetidines represent constrainted glutamates with one extra methylene group connecting the amine to the β-carbon.

Scheme 2.3: Rigidified congeners of glutamic acid containing one extra carbon



2.2 (+)**2.5** / (-)**2.5** (+)**2.6** / (-)**2.6**

It has been shown that the racemic *cis* isomer of azetidine-2,4-dicarboxylic acid (**2.3**) exibits glutamate-like agonist activity at higher concentrations while the racemic *trans*

isomer (**2.4**) is inactive. Subsequently the (+)- and (-)-*trans* antipodes were tested separately and it was discovered that the (-)-(*S*,*S*)-diacid is active while the (+)-(*R*,*R*) enantiomer is not.

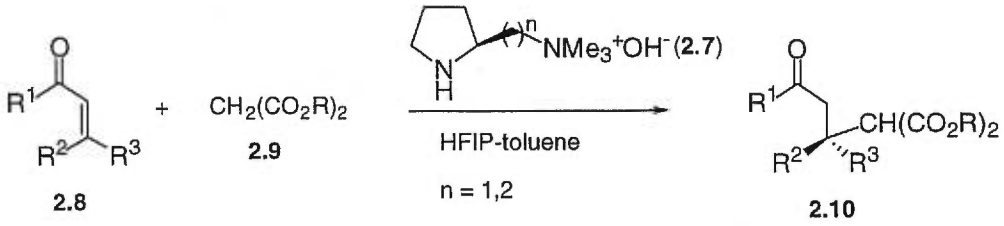
Of the four azetidines [(+)-**2.5**,(-)-**2.5**,(+)-**2.6**,(-)-**2.6**] tested, only one, (+)-**2.5**, was found to exhibit biological activity as a potent KA receptor (subtype of glutamate receptors) agonist as well as a potent inhibitor of Na^+-dependant Glu uptake.

2.2 As chiral catalyst or chiral ligand

Azetidine-2-carboxylic acids have been used as chiral ligands in Michael additions, in the reduction of ketones, in 1,2-additions of alkyl zinc to aldehydes, in cyclopropanation, and in Diels-Alder reactions. In all cases, except the last, the ligand and catalyst were employed in catalytic amounts.

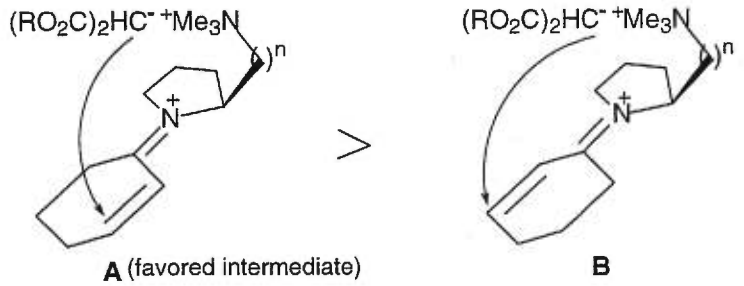
L-Proline and its derivatives (such as **2.7**) have been used as chiral catalysts for the enantioselective Michael addition of soft nucleophiles such as malonates (**2.9**) to enones (**2.8**)[36].

Scheme 2.4: L-Proline as chiral catalyst for the enantioselective Michael addition of malonates to enones



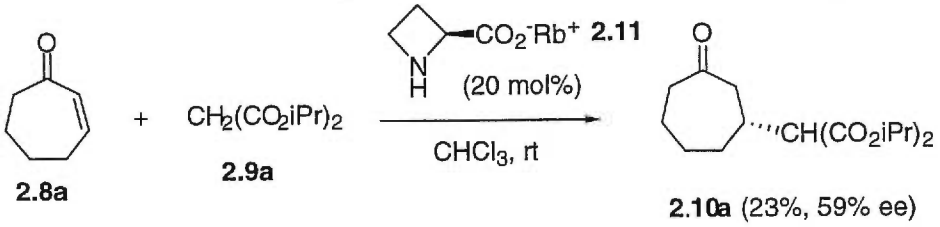
Derivative **2.7** forms an imine with the enone thus allowing the malonate to differentiate between its two faces. Addition from the less hindered face resulted in % ee's of up to 71% depending on the malonate and enone used.

Figure 2.3: Differentiation between two faces of the azadiene complex (**A**, **B**)



Yamaguchi and co-workers[37] were the first to report the results of the asymmetric addition of various simple malonates to prochiral enones and enals using the rubidium salt of L-proline in 5 mol% quantities. They later found that when studying the effect of changing catalyst, rubidium L-azetidine carboxylate (**2.11**) also showed asymmetric induction comparable to that of the L-prolinate[38].

Scheme 2.5: Rubidium L-azetidinecarboxylate as chiral catalyst

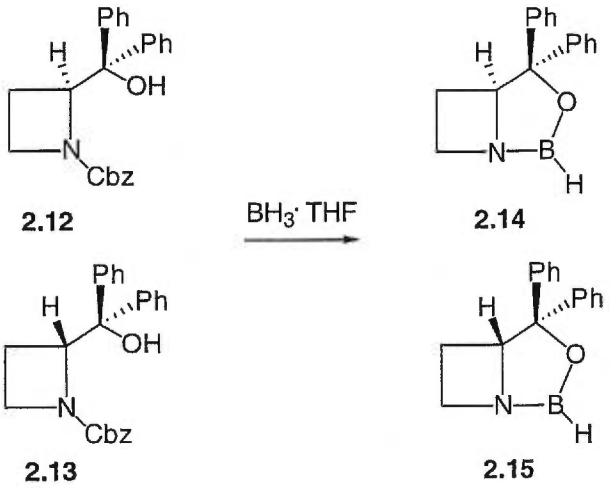


This methodology has also been extended to the use of nitroalkanes as nucleophiles for Michael additions to enones and enals[39a]. Again, rubidium L-Aze was found to be comparable to L-prolinate in terms of asymmetric induction while the 6-membered analog L-piperidine-2-carboxylate gave low yields and low ee's and acyclic amino acid rubidium salts showed essentially no activity. Recently, in our group, (2*S*,3*R*)-3-phenyl-azetidine-

2-carboxylic acid (synthesized as part of this thesis) was found to be a moderately good catalyst (74% ee) in the addition of 2-nitropropane to cyclohexanone[39b].

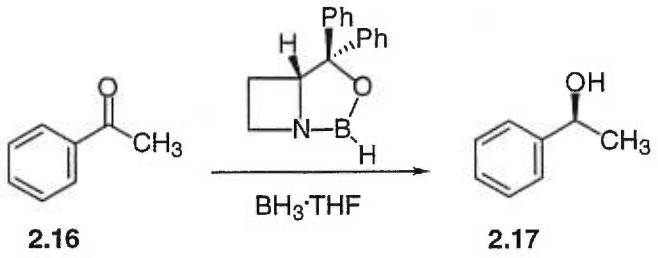
Enantioselective catalytic reduction of ketones[40] has also been accomplished with oxazaborolidine catalysts (**2.14**, **2.15**) including, (2*R*)- and (2*S*)-α,α-diphenyl-2-azetidine methanols (**2.12**, **2.13**) derived from the corresponding (2*R*)- and (2*S*)-azetidine-2-carboxylic acids[41].

Scheme 2.6: Formation of oxazoborolidine catalysts (**2.14**, **2.15**) from Aze's **2.12** and **2.13**



This azetidine catalyst was used in 10 mol% quantities to reduce acetophenone to the corresponding secondary alcohol (**2.17**) in >90% yield and 97% ee.

Scheme 2.7 Enantioselective reduction of acetophenone **2.16** to alcohol **2.17**

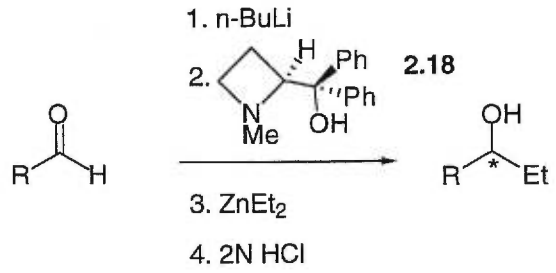


2.16 **2.17**

Oxazoborolidine catalysts derived from aziridines, pyrrolidines and piperidines also showed good to excellent selectivities.

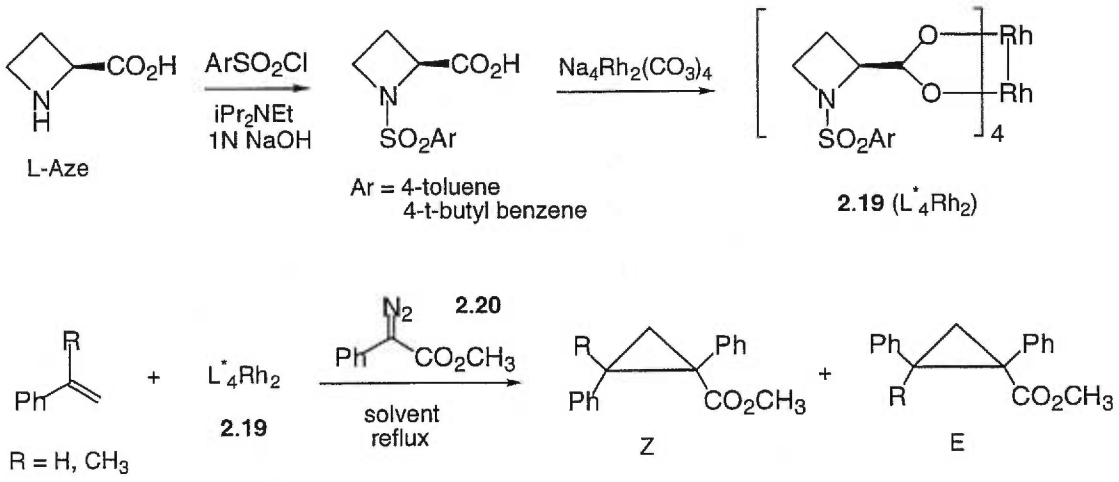
A very similar derivative of L-Aze, N-methyl-α,α-diphenyl-2(*S*)-azetidine methanol (**2.18**) was synthesized by a group in Germany and used as a chiral ligand for the enantioselective addition of diethyl zinc to aldehydes[42]. Various aldehydes were reacted with Et_2Zn in the presence of 5 mol% of the lithium alkoxide derived from the β-amino alcohol to produce the corresponding secondary alcohol in enantioselectivities of up to 100% ee.

Scheme 2.8: Azetidine derivative **2.18** as chiral catalyst for the enantioselective addition of diethyl zinc to aldehydes



Recently, dirhodium (II) azetidine (and aziridine)-2-carboxylate catalysts (**2.19**) have been synthesized and used for asymmetric cyclopropanation reactions with methyl phenyldiazoacetate (**2.20**)[43].

Scheme 2.9: Dirhodium (II) azetidine catalyst (**2.19**) for asymmetric cyclopropanation

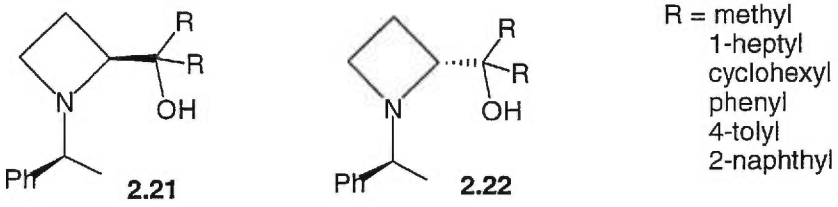


Like some of the previous examples of asymmetric catalysis, the precedent to this is the dirhodium (II) prolinate-catalyzed cyclopropanation reported by Kennedy and Mckervy[44] which showed a remarkable improvement in selectivity for these reactions. While the decrease in ring size showed an improvement in diastereoselectivity (*E*:*Z* ratio), the prolinate catalyst exhibited higher enantiocontrol although, using a very non-polar solvent had a very beneficial effect on enantioselectivity for both catalysts. In addition, the reactions could be performed using only 1 mol% of the catalyst.

Lastly, the rigidity of the azetidine ring is again exploited in the form of a series of (2*S*)- and (2*R*)-azetidine carbinols (**2.21**, **2.22**) which have been used as chiral catalysts in the BBr_3-catalyzed Diels-Alder reaction[15b]. Both diastereomers were synthesized from a

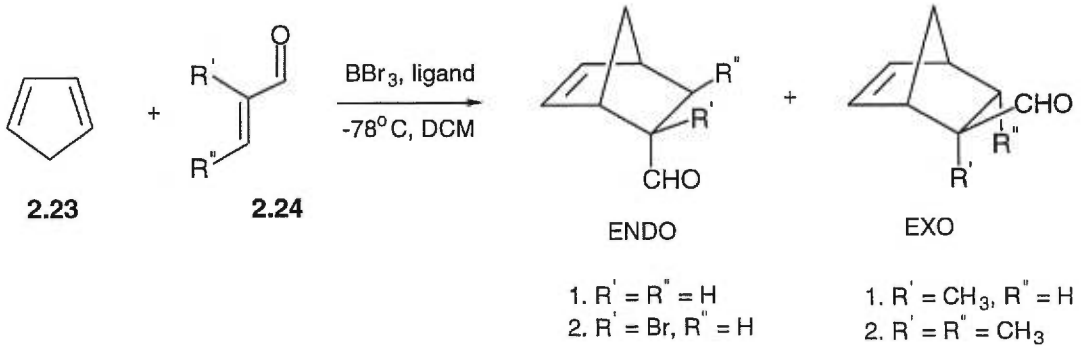
butyrolactone, and ring closure using (*S*)-α-methyl benzylamine led to separation of the two diastereomeric azetidines.

Figure 2.4 : Diastereomeric azetidine carbinols



Most of these catalysts showed good *exo/endo* selectivities, either one or the other being prominent depending on the dienophile but show only poor to moderate enantioselectivities. Cyclopentadiene was used as the diene in all cases and the dienophiles were substituted α,β-unsaturated aldehydes **2.24** such as acrolein (R'=R''=H), crotonaldehyde (R''=CH_3), 2-bromoacrolein (R''=Br) and 2-methyl acrolein (R'=CH_3).

Scheme 2.10: Asymmetric Diels-Alder reaction using azetidine chiral catalysts **2.21** and **2.22**



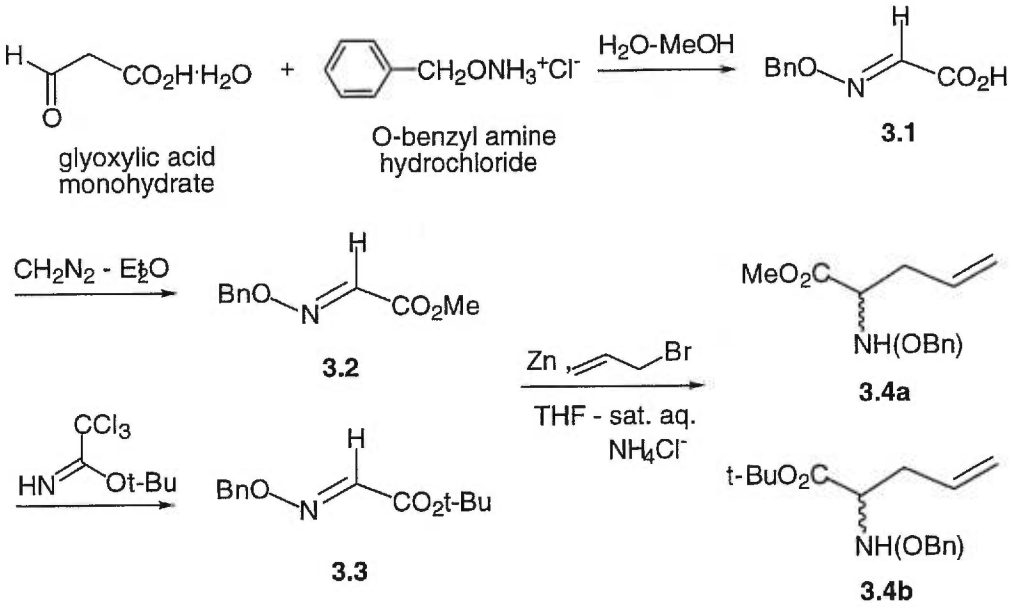
CHAPTER 3.0

Syntheses of Unsubstituted, 3-Aryl or 3-Alkyl 2(*S*)-Azetidine Carboxylic Acids

3.1 Synthesis of DL-Aze

Based on work initiated by R.Y. Yang[45a,b] and later continued by R. Maguire[46], in this laboratory, we set out to complete the synthesis of DL- and L-Aze. Using *O*-benzyl glyoxylic methyl ester oxime **3.2** allylation under Barbier conditions[47] with allyl bromide and Zn powder in a THF-aqueous ammonium chloride emulsion afforded the initial *N*-(*O*-benzyl) amino ester **3.4a**. Similarly ester **3.4b** can be formed from the corresponding t-butyl ester oxime **3.3** .

Scheme 3.1: Allylation of *O*-benzyl glyoxylic methyl (and *t*-butyl) ester oximes

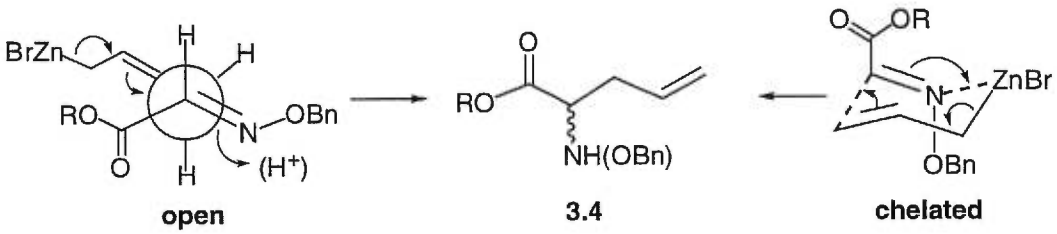


The methyl **3.2** or t-butyl **3.3** ester *O*-benzyl oxime can be formed readily from the corresponding free acid **3.1** by treatment with diazomethane or t-butyl trichloroacetimidate respectively. The free acid oxime in turn is formed in virtually quantitative yield (before

crystallization) from glyoxylic acid monohydrate and *O*-benzyl amine hydrochloride under aqueous conditions attesting to the stability of this oxime relative to imines in general.

Relying on Bronsted acid catalysis by NH_4Cl, one can envision both an open or a closed (chelated) 6-membered transition state model to describe the S_N2' addition of the allyl zinc bromide (formed in situ) to the α-C of the oxime.

Figure 3.1: Open and closed transition state model structures leading to amino esters **3.4**

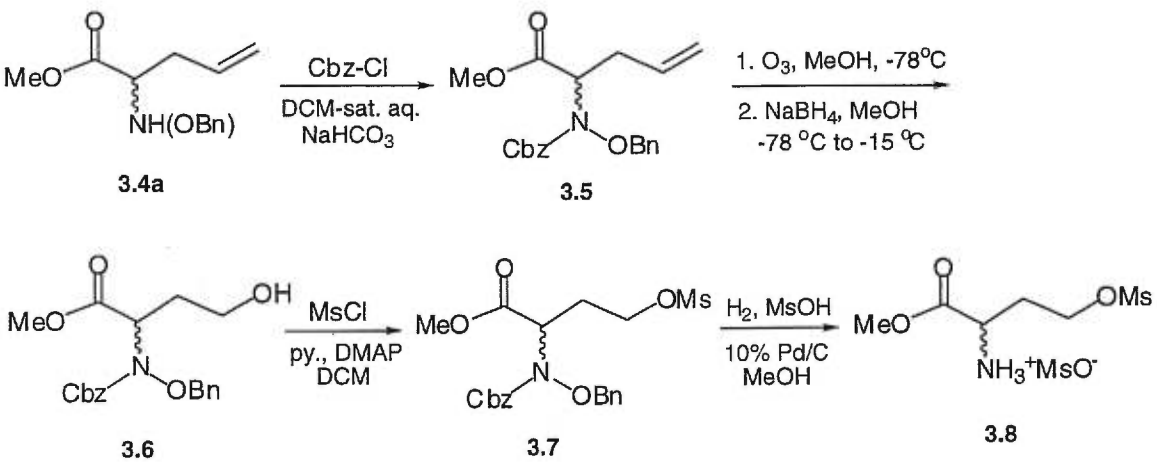


With the amino ester (**3.4a**) in hand, protecting the amino group as the benzyloxy carbonyl derivative (**3.5**) was necessary in order to proceed to the next step (scheme 3.2). Ozonolysis of the double bond was followed by sodium borohydride reduction of the ozonide to the corresponding alcohol **3.6**. It was necessary to monitor the temperature carefully to avoid both lactonization of the alcohol and over-reduction of the methyl ester to the diol yet the reaction had to be performed at a temperature elevated enough to carry the reduction of the aldehyde to completion.

Subsequently, alcohol **3.6** was mesylated to **3.7** so that the mesylate group could be displaced by the free amine resulting from the hydrogenolysis in the following step. Although attempted, it was not possible to achieve both hydrogenolysis and then the cyclization to the azetidine ring in one-pot even under high dilution conditions. What resulted instead was a lot of decomposition, likely due to intermolecular reactions between

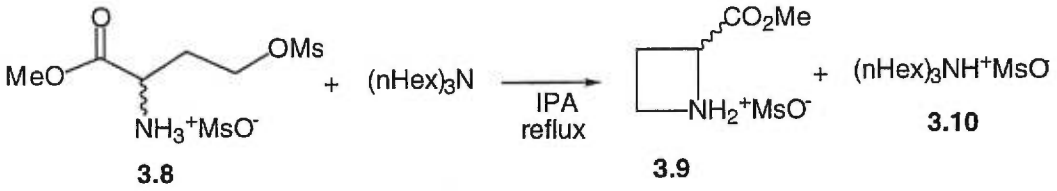
the newly formed free amines and the methyl ester of neighboring molecules resulting in dimers or polymers. As a solution to this problem, one equivalent of methanesulfonic acid was added to the methanol solution during deprotection with H_2 and 10% Pd/C to trap the resultant amine as its ammonium salt **3.8**, thus preventing it from reacting further. The salt, which proved to be quite pure by NMR, could then be used without further purification for the cyclization step.

Scheme 3.2: Conversion of amino ester **3.4a** to mesylate salt **3.8**



Cyclization to form the desired four-membered imino acid proved to be the most daunting task. Initially tri-(*n*-hexyl) amine was used as base in refluxing isopropanol to deprotonate the ammonium salt and effect S_N2 displacement of the terminal mesylate. However, the crude product was not amenable to purification.

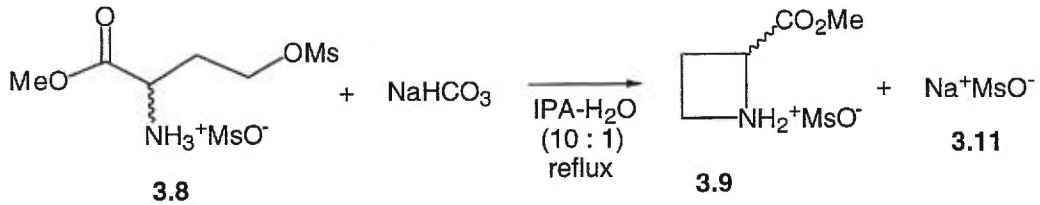
Scheme 3.3: Cyclization of mesylate salt **3.8** to azetidine **3.9** using tri(*n*-hexyl) amine



Chromatography on silica gel eluting with a gradient of methanol in dichloromethane was effective at separating the desired azetidine salt (**3.9**) from the amine mesylate (**3.10**) by-product. Unfortunately this technique was not reproducible. Instead, chromatography tended to result in the decomposition of the azetidine probably by dimerization and/or polymerization.

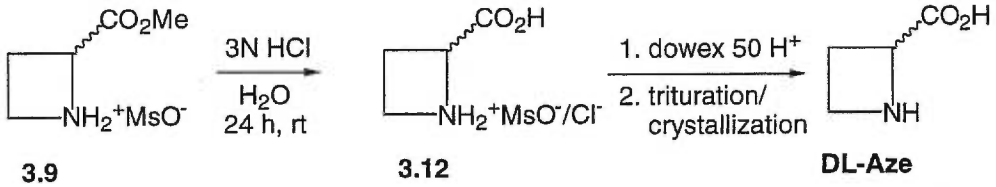
A method had to be found in which the crude cyclization product **3.9** could be purified without the need for chromatography. This led to the use of the inorganic base sodium bicarbonate instead of an organic base and refluxing the reagents in isopropanol containing ~10% H_2O to solubilize the $NaHCO_3$.

Scheme 3.4: Cyclization of mesylate salt **3.8** to azetidine **3.9** using sodium bicarbonate



Under these conditions, the by-products were carbon dioxide and sodium mesylate (**3.11**) which precipitated out by careful trituration of the crude product with an isopropanol-chloroform mixture. The crude methyl azetidine-2-carboxylate **3.9** was converted to the free acid under acidic conditions (3N HCl) and after concentration in vacuo the crude imino acid mesylate/chloride salt (**3.12**) could be passed through a column of Dowex 50 H^+ to remove both methanesulfonic and hydrochloric acid thereby affording the free DL-Aze. Further trituration followed by crystallization yielded the pure product in 40% yield from **3.8**.

Scheme 3.5: Removal of methyl ester and purification to form DL-Aze

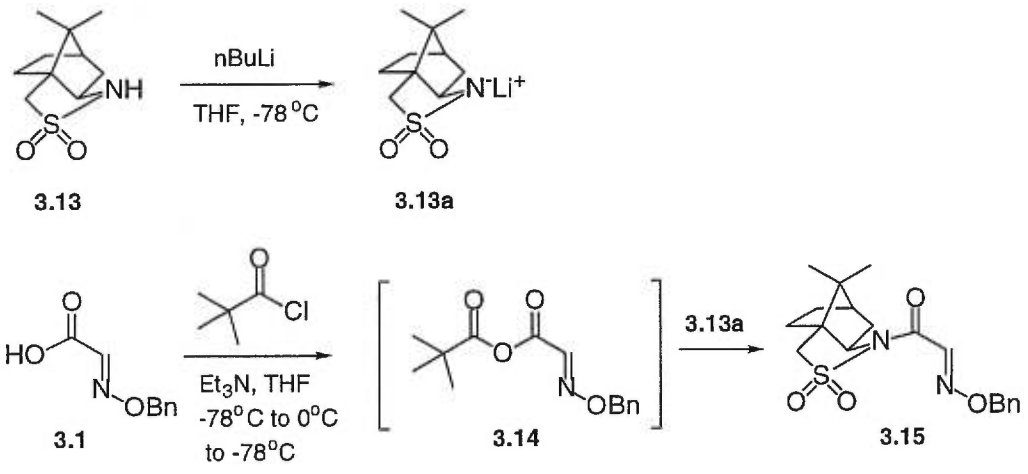


3.9 **3.12** **DL-Aze**

3.2 Asymmetric route to L-Aze

In an effort to achieve an asymmetric allylation, R.Y. Yang investigated several chiral non-racemic ester and amide derivatives of *O*-benzyl glyoxylic acid oxime. Oppolzer's (1*S*)-(-)-2,10-camphorsultam **3.13** was found to be the most suitable. Camphor sultam **3.13** was coupled to the glyoxylic acid oxime **3.1** via the in situ formation of a pivalic mixed anhydride (**3.14**) followed by reaction with lithium camphorsulfonamide **3.13a**.

Scheme 3.6: Formation of camphorsultam oxime **3.15**

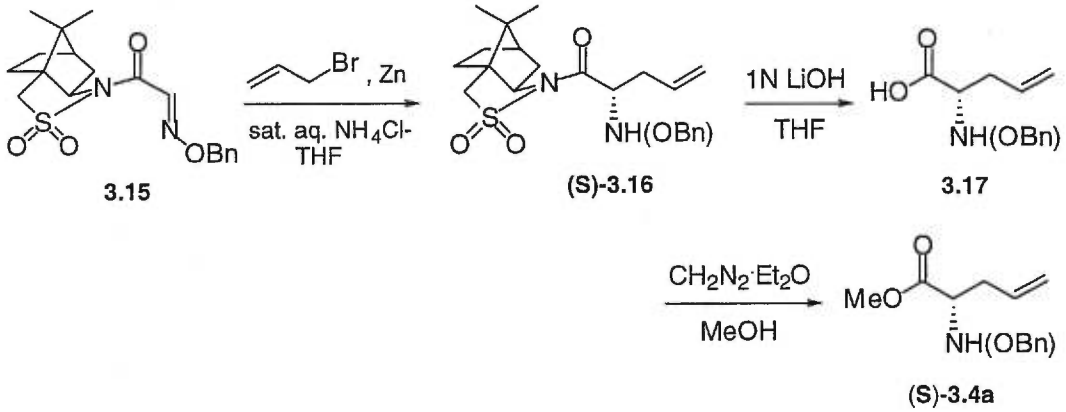


The major product of the allylation was found to be the (*S*)-allylglycine derivative (***S***)-**3.16**. Using this enantiopure material, and following the same sequence as described in chapter 3.1, L-Aze was obtained with an optical rotation of -123.3 (c 3.6, H_2O), (Literature $[\alpha]_D$ -120.0).

When the allylation was carried out at room temperature, the diastereomeric ratio of the products was 91:9 (*S*/*R*) while at 0 °C, the ratio improved only slightly to 93:7, but after

one crystallization, the pure (*S*)-diastereomer could be obtained in 79% yield. This is an improvement over the method of Yamamoto and co-workers[48] who reported that the allylation of 8-(-)-phenylmenthyl ester of *O*-methyl glyoxylic acid oxime with allyl bromide in anhydrous THF at -78 °C produced allylglycine in 74% de (d.r. 87:13).

Scheme 3.7: Asymmetric allylation of camphorsultam oxime **3.15** to form **3.17**



3.15 **(S)-3.16** **3.17** **(S)-3.4a**

Saponification of the amide linkage using a 1N aqueous solution of LiOH in THF afforded the (*S*)-*N*-(*O*-benzyl)allylglycine (**3.17**). The methyl ester (*S*)-**3.4** was carried through via the same series of steps to the final L-Aze in ~15% overall yield.

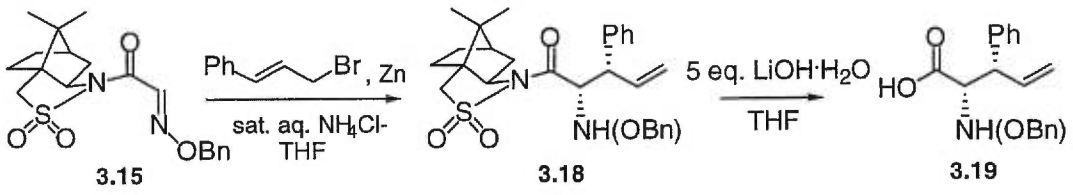
3.3 Syntheses of (2*S*,3*R*)-3-aryl substituted-2-carboxylic acids

Using the same methods developed for the asymmetric synthesis of L-Aze, we set out to make both the 3(*R*)-phenyl and 3(*R*)-naphthyl azetidine-2(*S*)-carboxylic acids (**3.35**, **3.45**). Both routes proceeded relatively smoothly, with a few exceptions, and a single crystal X-ray of each final product was obtained.

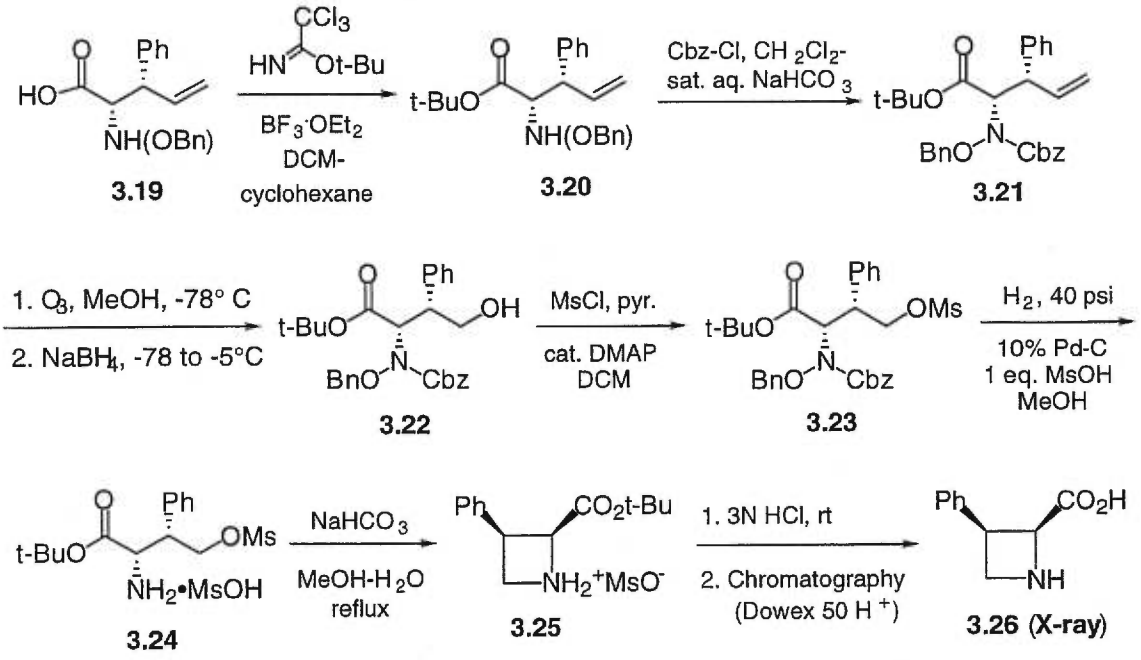
3.3.1 (2*S*,3*R*)-3-Phenyl-2-azetidine carboxylic acid

Beginning with the formation of the phenyl-substituted compound, the reaction sequence is outlined in Schemes 3.8 and 3.9. The first step was the addition of cinnamyl bromide to oxime **3.15** which proceeded with excellent enantioselectivity (99:1 *S*,*S*) and diastereoseletivity (exclusively *syn*) to afford **3.18**.

Scheme 3.8 Formation of camphorsultam adduct **3.18** and saponification to **3.19**



Scheme 3.9: Transformation of acid **3.19** to (2*S*,3*R*)-3-phenyl Aze (**3.26**)



Subsequently, saponification to obtain the free acid **3.19** was followed by esterification and then protection of the amine with a Cbz group. Ozonolysis, reduction and then mesylation of the primary alcohol yielded mesylate **3.23** which was subjected to hydrogenolysis to remove the benzyloxy and Cbz protecting groups. At this point ammonium salt **3.24** was cyclized under the usual basic conditions to yield azetidine **3.25** which was then converted to the desired **3.26** by hydrolysis of the t-butyl ester. Passing the crude product through a Dowex 50H$^+$ column followed by crystallization, afforded a product that could be analyzed by X-ray crystallography.

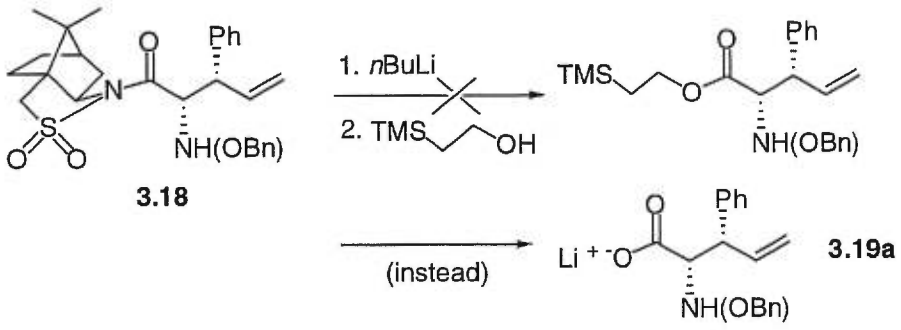
The saponification to remove the camphor sultam auxilliary **3.13** and restore the free carboxylic acid **3.19** was problematic. Using the same method as for the unsubstituted compound (2.5 equivalents of 1N LiOH solution in THF and stirring vigorously at room

temperature until virtually all starting material was consumed) the reaction took up to 4 days. Product **3.19** was isolated in ~25% yield and there was evidence of extensive decomposition as indicated by TLC.

A commonly used technique for the removal of the camphor sultam auxilliary involves basic hydrolysis (with or without H_2O_2)[49,50]. Therefore, we attempted to saponify compound **3.18** using $LiOH{\cdot}H_2O$ and 30% H_2O_2 at 0 °C but unfortunately this also resulted in decomposition.

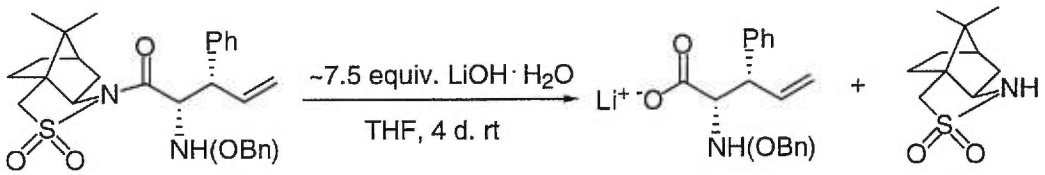
A simple solution was found which increased the yield to ~80% and greatly improved the purity so that there was virtually no contamination with camphor sultam. Through other attempts to remove the auxiliary, we observed that the presence of LiOH under anhydrous conditions resulted in a much cleaner saponification of the amide bond. Based on the example of a lithium p-nitrobenzyl alkoxide displacement of camphor sultam found in the litterature[49,51] we attempted to transesterify the amide to a TMS ethyl ester.

Scheme 3.10 Attempt to transesterify amide **3.18** to TMS ethyl ether



We noticed instead, the formation of a fair amount of the desired carboxylic acid (62% yield after purification) without the usual accompanying decomposition. An old bottle of n-butyl lithium had been used to generate the lithium alkoxide and there must have been some anhydrous LiOH present (from partial quenching of *n*-BuLi) that resulted in a clean hydrolysis of the amide bond. It seemed that the presence of too large a quantity of water as is present when LiOH is used as a 1N solution resulted in more decomposition or side products. Simply using solid LiOH, even in its monohydrate form, gave a much cleaner reaction.

Scheme 3.11: Saponification of camphor sultam amide **3.18**

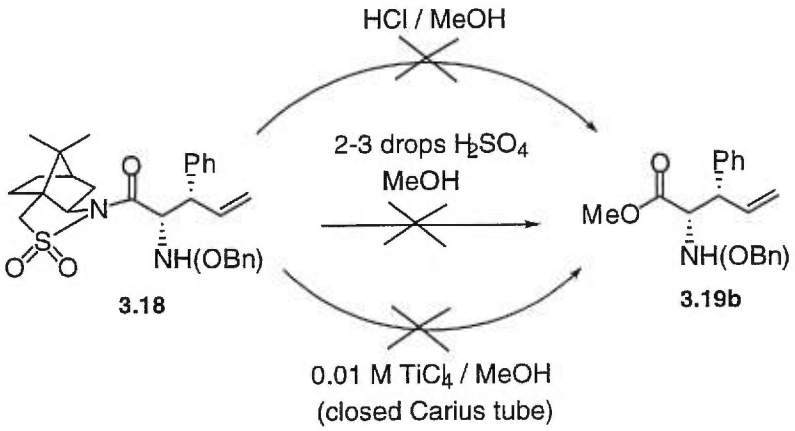


3.18 **3.19a** **3.13**

After removing the THF *in vacuo*, the crude is partitioned between water and dichloromethane. The aqueous layer which is basic and retains the lithium carboxylate salt (**3.19a**) must be extracted repeatedly with DCM (~10% of the aqueous volume) to completely remove the free camphor sultam. Although the extraction process is lengthy, sometimes requiring 10-15 washings, it is less tedious than chromatography and the resulting product needs no further purification. Once this is complete, the basic aqueous solution is acidified with HCl and extracted with dichloromethane to obtain the carboxylic acid **3.19**.

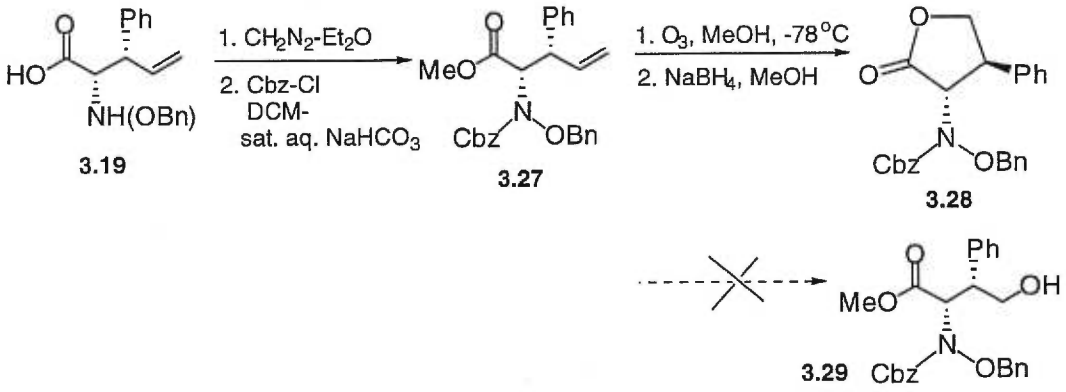
It is worth mentioning that a variety of transesterifications under acidic conditions were also attempted. These include a) stirring camphor sultam amide in methanol with several drops of sulfuric acid, b) bubbling HCl gas into the same type of methanolic solution, c) refluxing the amide in a 0.01M solution of $TiCl_4$ in methanol[52] and even setting up the same reaction in a closed Carius tube and heating at ~140 °C. None of these were successful.

Scheme 3.12: Attempts at transesterification of camphorsultam amide to methyl ester



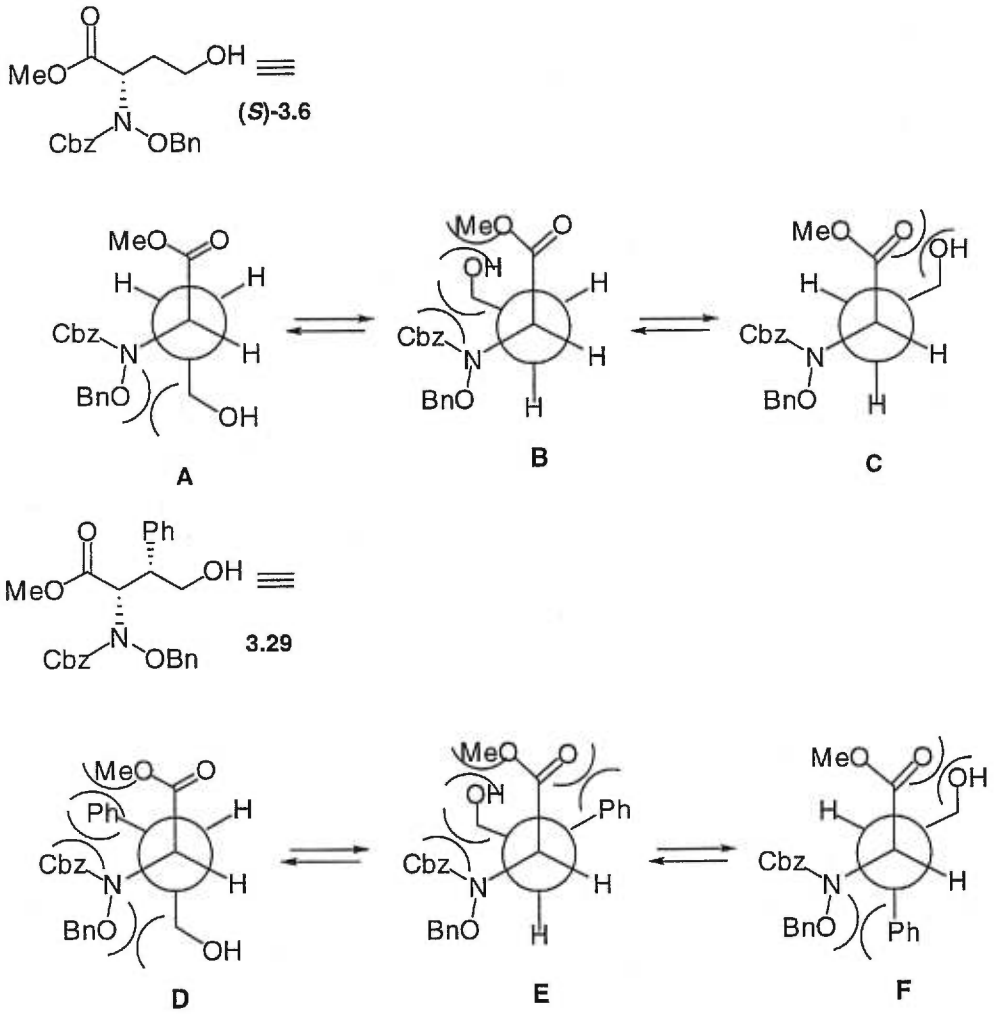
Subsequently, esterification with diazomethane, followed by protection of the amino group with Cbz-Cl resulted in an olefin (**3.27**) that was ready for ozonolysis. At this point appeared the second major obstacle that had to be overcome. During ozonolysis, the ozonide formed as it should but reduction with sodium borohydride resulted in alcohol **3.29** that lactonized to form **3.28**. Therefore, an alternative to the methyl ester had to be found.

Scheme 3.13: Oxidative cleavage of olefin **3.27** and attempted reduction to alcohol **3.29**



Close examination of the possible conformations of the 3-phenyl substituted alcohol (**D-F**) in comparison to those of the unsubstituted alcohol (**A-C**) may give some insight into why a 3-substituted compound such as **3.29** is prone to lactonization so much more readily.

Figure 3.2: Possible conformers for alcohols (*S*)-**3.6** and **3.29**



Alcohol (*S*)-**3.6** can exist in 3 possible low energy conformers (**A** and **C**) but 2 should be lower in energy since gauche interaction is minimized. Only one of these two (**C**) can lead to the lactonized product. In the case of alcohol **3.29** though, there exists only one conformer (**F**) with minimal gauche interaction and it is in this conformation that lactonization can occur most readily.

Therefore, instead of forming a methyl ester, carboxylic acid **3.19** obtained after saponification was converted to the corresponding t-butyl ester (**3.20**) with t-butyl imidate.

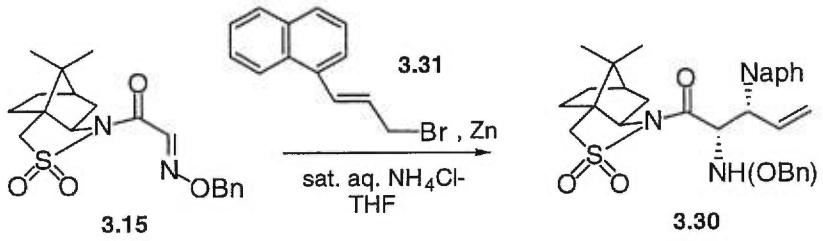
This was followed by Cbz-protection of the amine and then ozonolysis and reduction that yielded the desired alcohol (**3.22**) which did not lactonize even upon chromatography. Subsequent transformations proceeded uneventfully through mesylation of the alcohol, hydrogenolysis under pressure and then cyclization to the *syn* substituted azetidine (**3.26**).

It is noteworthy to mention that cyclization to the 3(*S*)-phenyl substituted azetidine proceeded more readily than cyclization to the L-Aze mesylate salt (***S*-3.9**) and therefore refluxing in methanol (as opposed to the higher boiling IPA) was sufficient to effect ring closure. This is in contrast to the publication by Vaughan[23] stating that 2,3-syn substituents (or 3,4-syn substituents) would retard cyclization to form an azetidine ring.

3.3.2 (2*S*,3*R*)-3-(1-naphthyl)-azetidine-2-carboxylic acid

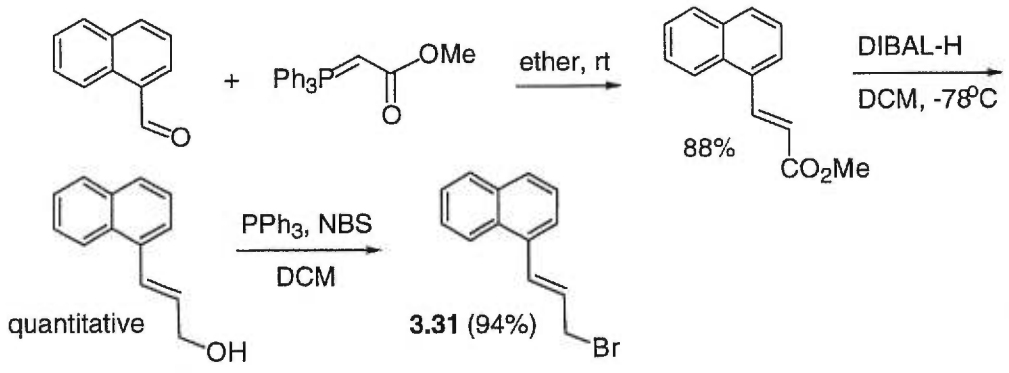
The synthesis of (2*S*,3*R*)-3-(1-naphthyl)-Aze was similar to that of the phenyl compound. Compound **3.15** was allylated under Barbier conditions to afford the desired product **3.30** as a single isomer .

Scheme 3.14 Formation of camphorsultam adduct **3.30**



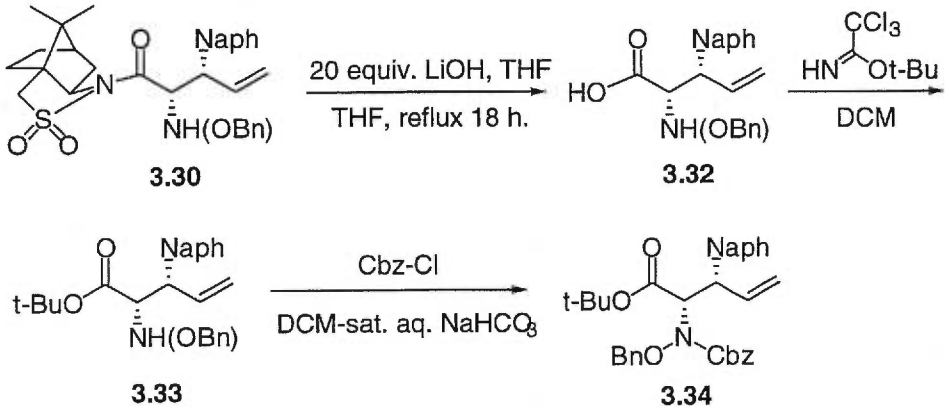
In this case the (1-naphthyl)allyl bromide used was not commercially available and had to be made from the corresponding 1-naphthaldehyde.

Scheme 3.15 Synthesis of (1-naphthyl)allyl bromide



Compound **3.30** was saponified to the corresponding acid **3.32**, then converted to the *t*-butyl ester **3.33** and finally Cbz protected to yield **3.34** which was ready for oxidative cleavage of the terminal double bond.

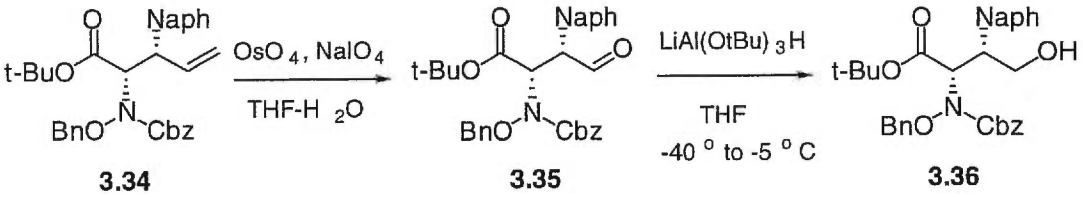
Scheme 3.16: Conversion of camphor sultam amide **3.30** to amino ester **3.34**



3.30 **3.32** **3.33** **3.34**

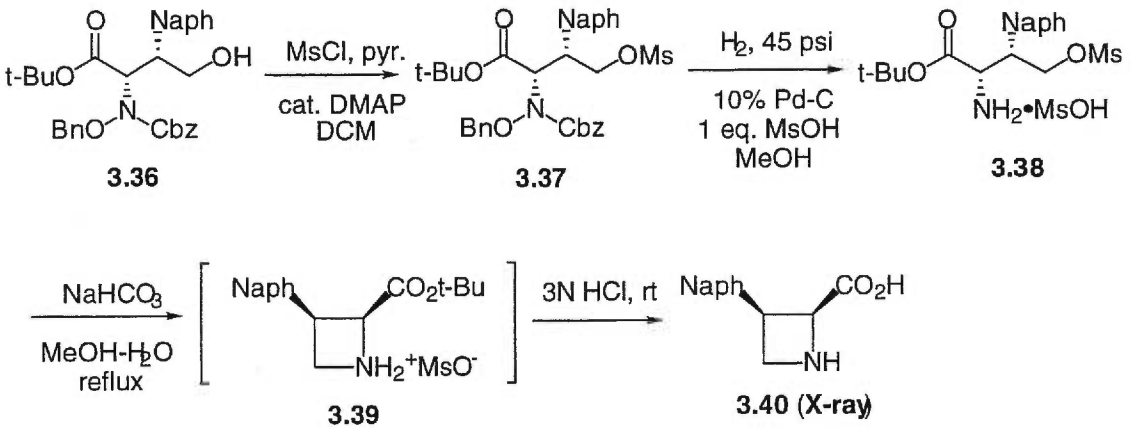
This time the method of choice involved the use of osmium tetroxide and sodium periodate to form aldehyde **3.35**. Reduction was accomplished with lithium (tri-*t*-butoxy)aluminum hydride to yield alcohol **3.36** which was subsequently mesylated.

Scheme 3.17: Oxidative cleavage and subsequent reduction of olefin **3.34**



3.34 **3.35** **3.36**

Scheme 3.18: Transformation of alcohol **3.36** to Aze **3.37**



As with in the synthesis of compound **3.32**, mesylate **3.37** was converted to the corresponding ammonium salt **3.38** by hydrogenolysis and then cyclized by refluxing it in methanol with sodium bicarbonate. The final azetidine **3.40** was obtained by hydrolytic removal of the *t*-butyl ester from intermediate **3.39** followed by Dowex $50H^+$ purification and then crystallization affording crystals suitable for X-ray crystallography.

Several steps in this synthesis proved to be problematic as well. The first difficulty was mechanical in nature in the sense that the lithium carboxylate **3.32a** obtained from the LiOH hydrolysis of the camphor sultam amide (**3.30**) was very difficult to purify. Up to 25 extractions with DCM were required to remove the camphor sultam **3.13** by-product and even then the final product, when isolated, was still shown to contain camphor sultam (5-10% by weight). This was based on mol% which in turn was calculated from NMR integration. One advantage though, of this reaction over the corresponding phenyl compound, was the fact that after refluxing one night with 20 equivalents of $LiOH{\cdot}H_2O$ the reaction was complete.

At this point we discovered that conversion to the t-butyl ester **3.33** could be accomplished more easily and with seemingly fewer side reactions by avoiding the use of $BF_3.OEt_2$ when using t-butyl imidate. Compared to ~60%, the yield was increased to 85% by omitting the Lewis acid and using 3 instead of 2 equivalents of t-butyl imidate.

The next obstacle was encountered when olefin **3.34** was subjected to ozonolysis followed by sodium borohydride reduction. After chromatography we were able to isolate alcohol **3.36** in only ~5% yield. In an attempt to discover the problematic step, a sample of the olefin was ozonolyzed and then quenched with dimethyl sulfide to see whether the aldehyde would be formed in good yield. Ozone completely destroyed the molecule and the NMR of the isolated crude was uninterpretable as any organic compound. It is known that naphthyl groups are succeptible to oxidation resulting in a phthalic acid derivative[53] that in turn may have reacted in either an intra- or intermolecular fashion to yield a variety of products.

An effective alternative to ozonolysis turned out to be the use of a catalytic amount of osmium tetroxide with sodium periodate[54] which both regenerates the OsO_4 and oxidatively cleaves the intermediate diol to yield the desired aldehyde (**3.35**) in 63% yield. In an effort to further improve this yield, we attempted to first synthesize the diol first using OsO_4 and NMO, and then to subject it to oxidative cleavage. Unfortunately the diol was formed in only ~55% yield therefore the original procedure was maintained.

Subsequently, there were many attempts at the reduction of the aldehyde to the corresponding alcohol **3.36**. The most obvious method, being reduction with sodium borohydride in methanol, yielded only 50% of product with a considerable amount of unreacted starting material. Superhydride[55] in THF at -78 °C was fairly successful in the sense that the aldehyde was reduced but not the ester thus affording the desired alcohol in

yields of 60-66%. The reagent of choice though turned out to be lithium (tri-t-butoxy) aluminum hydride[56] whose attenuated activity and steric hindrance were ideal to reduce the aldehyde (but not the t-butyl ester) in THF at temperatures as high as -10 °C to -5 °C. The crude product needed no chromatographic purification and it was formed in nearly quantitative yield.

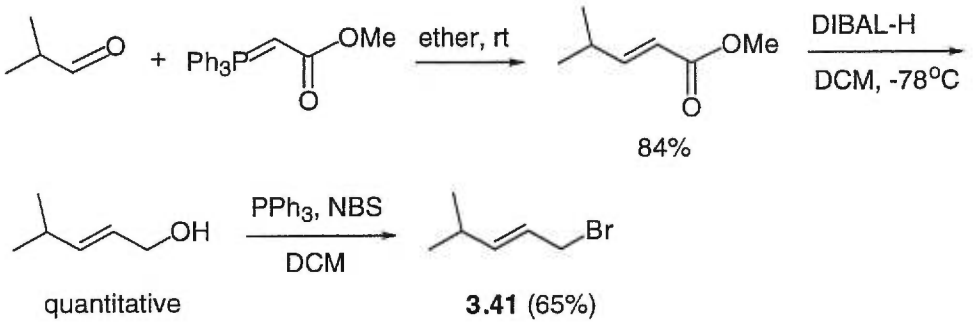
Subsequently, mesylation was accomplished in 80% yield followed by hydrogenolysis of the amino protecting groups in virtually quantitative yield. Cyclization of the ammonium salt **3.39** using sodium bicarbonate as base in refluxing methanol-H_2O afforded the crude cyclized product, which looked rather difficult to interpret by NMR. This may have been due to excess methanesulfonic acid which partially hydrolyzed the t-butyl ester and therefore there may have been a mixture of products at this stage. After being subjected to 2.75N HCl, resulting in complete hydrolysis of the t-butyl ester, the final azetidine mesylate or chloride salt was much less ambiguous by NMR. Nevertheless, due to solubility considerations, purification by Dowex $50H^+$ was not feasible. Instead, trituration followed by crystallization/precipitation using hot acidic (dilute HCl) H_2O afforded the (2*S*,3*R*)-3-(1-naphthyl)-Aze (**3.40**) as the zwitterion (X-ray) even though crystals used for X-ray were obtained by crystallization from acidic (HCl) H_2O.

This is not surprising since, after exhaustive drying of the final imino acid, dissolution in H_2O was no longer possible without the addition of HCl, indicating that the zwitterionic form may be preferable to the hydrochloride salt resulting in the HCl being removed under vacuum.

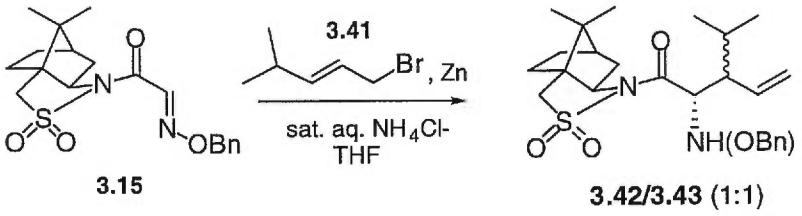
3.4 Synthesis of *syn* and *anti* 3-isopropyl-L-azetidine carboxylic acids

The last two syntheses begin with the formation of a 1:1 diastereomeric mixture of *syn* and *anti* 3-isopropyl substituted camphor sultam amides (**3.42**, **3.43**) by the allylation of camphorsulam oxime **3.15** with 3(*E*)-isopropyl allyl bromide **3.41**.

Scheme 3.19: Synthesis of 3(*E*)-isopropyl allyl bromide from isobutyraldehyde



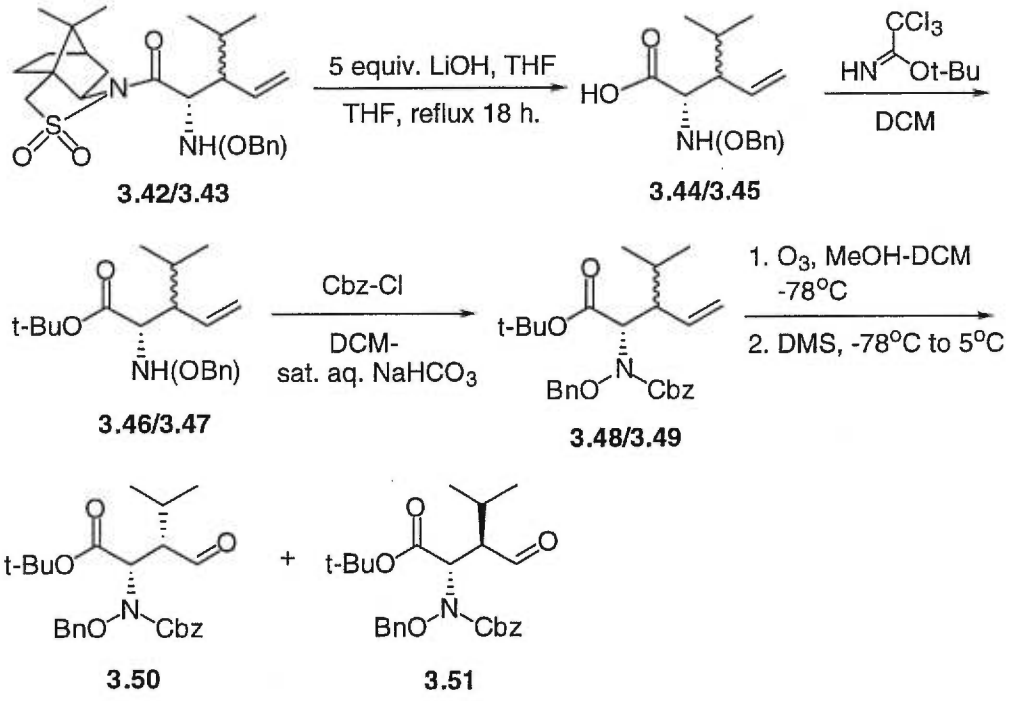
Scheme 3.20: Synthesis of diastereomers **3.42** and **3.43**



Since the two isomers could not by separated at this stage, they were carried through to the corresponding carboxylic acids (**3.44**, **3.45**) by saponification, then esterification to the t-butyl esters (**3.46**, **3.47**) and Cbz-protection to yield compounds **3.48** and **3.49**. After

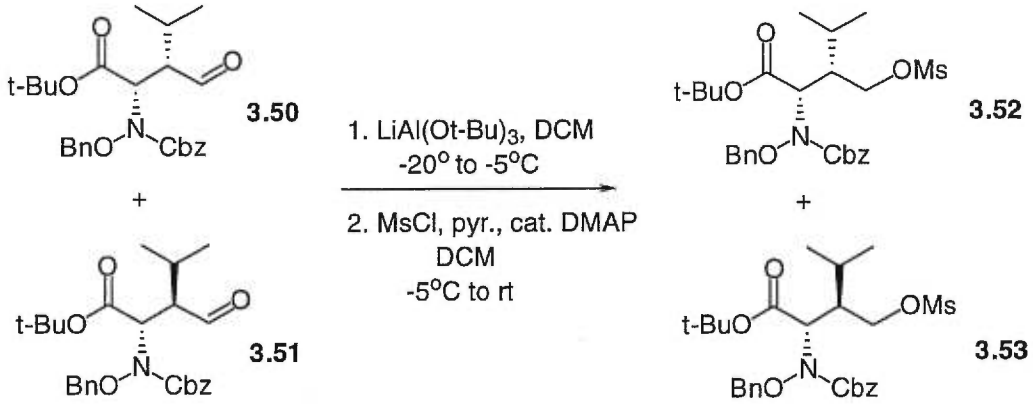
oxidative cleavage with ozone the resulting diastereomeric aldehydes **3.50** and **3.51** were finally separated by chromatography.

Scheme 3.21: Conversion of diastereomers **3.42/3.43** to aldehydes **3.50/3.51**

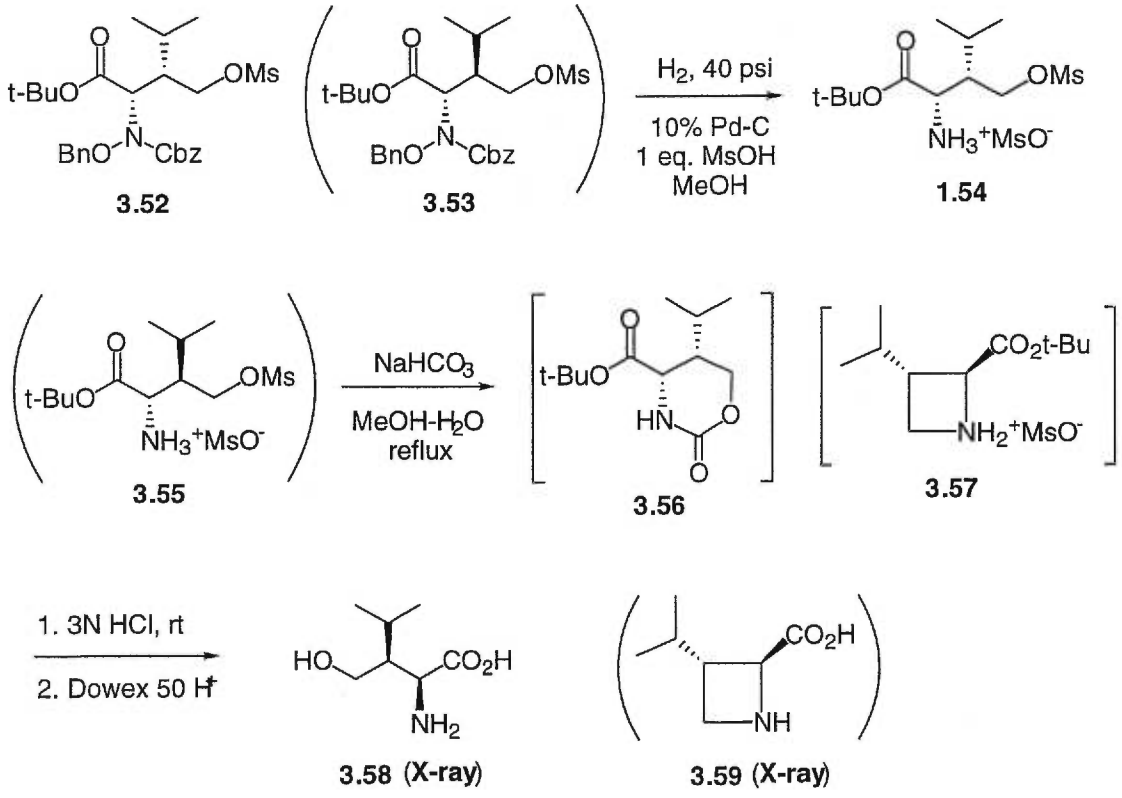


At this point the two aldehydes were carried individually to the end of the synthesis. A one-pot reduction, then mesylation afforded mesylates **3.52** and **3.53** and then hydrogenolysis yielded the ammonium salts **3.54** and **3.55**.

Scheme 3.22: One-pot reduction then mesylation of aldehydes **3.50/3.51**



Scheme 3.23: Transformation of mesylates **3.52/3.53** to final amino acids **3.58/3.59**



Cyclization to the desired azetidine-2-carboxylic acid **3.59** was only successful with the *anti* mesylate. The *syn* compound, after being subjected to the usual cyclization conditions and then acidic hydrolysis, afforded the open chain compound **3.58**. X-ray crystal analysis confirmed the absolute stereochemistry of both compounds.

Generally the synthesis proceeded fairly smoothly until the formation of the Cbz-protected derivative. We attempted ozonolysis followed by reduction with sodium borohydride which was expected to work as well as with the 3-unsubstituted olefin (***S*-3.5**), yet the reduction did not go to completion. Despite the addition of a large excess of reducing agent it appeared, by TLC, that a fair amount of the aldehyde had not reacted. After the usual work-up followed by chromatography only the 2 unreacted aldehydes (**3.50**, **3.51**), now visible as two very close spots by TLC, were isolated. Despite the fact that a new method of reduction had to be found, at least we discovered that at this stage the two diastereomers were separable. Osmium tetroxide and sodium periodate were not successful; the reduction was far from going to completion and mostly unreacted olefin was recovered even after allowing the reaction to proceed for several days with excess reagent.

Finally ozonolysis followed by addition of dimethyl sulfide to decompose the ozonide afforded, after careful chromatography, the pure *syn* (**3.50**) and *anti* (**3.51**) aldehydes in 37% and 33% yields respectively (70% total). As open chain compounds though it was not possible at this stage to discern the relative stereochemistry.

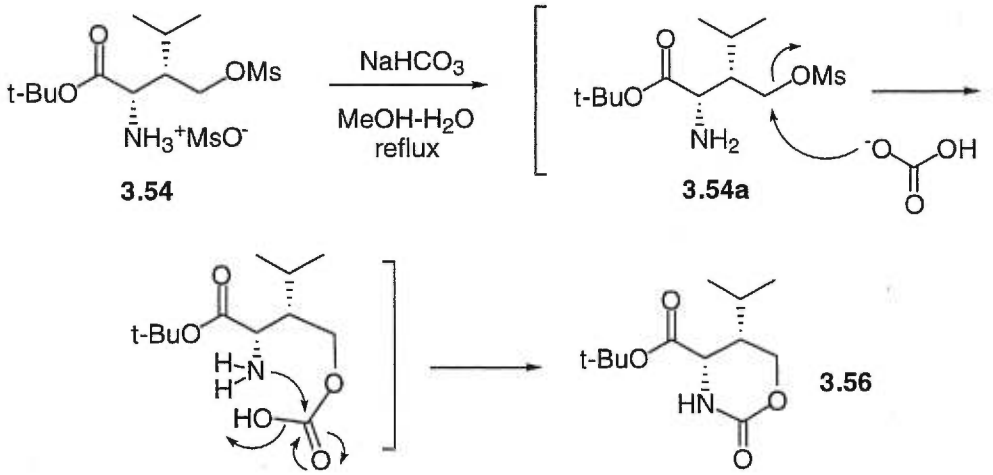
Further reduction to the corresponding alcohols posed another problem in that, despite the presence of a t-butyl ester, the resulting alcohols tended to spontaneously lactonize during

work-up; specifically during concentration on the rotary evaporator. Even when a warming bath was not used and the flask was kept cold during the evaporation of dichloromethane, once the solvent was gone and the crude product reached room temperature, it cyclized. To solve this problem, after quenching the lithium (tri-t-butoxy) aluminum hydride reaction mixture with saturated aqueous ammonium chloride at -10 °C, the aluminum salts were filtered off cold and the filtrate was used directly for the subsequent mesylation step maintaining the temperature between -5 °C and 0 °C and thus avoiding lactonization. This procedure was followed very successfully for both the *syn* and *anti* mesylates (**3.52**, **3.53**) which were formed in 90% and 88% yields respectively without the need for chromatographic purification.

While hydrogenolysis smoothly yielded both mesylate salts (**3.54**, **3.55**), the cyclization step yielded only the *anti* azetidine while the final *syn* product (after employing the same cyclization technique) was proven to be, by X-ray analysis, an open chain γ-hydroxy amino acid.

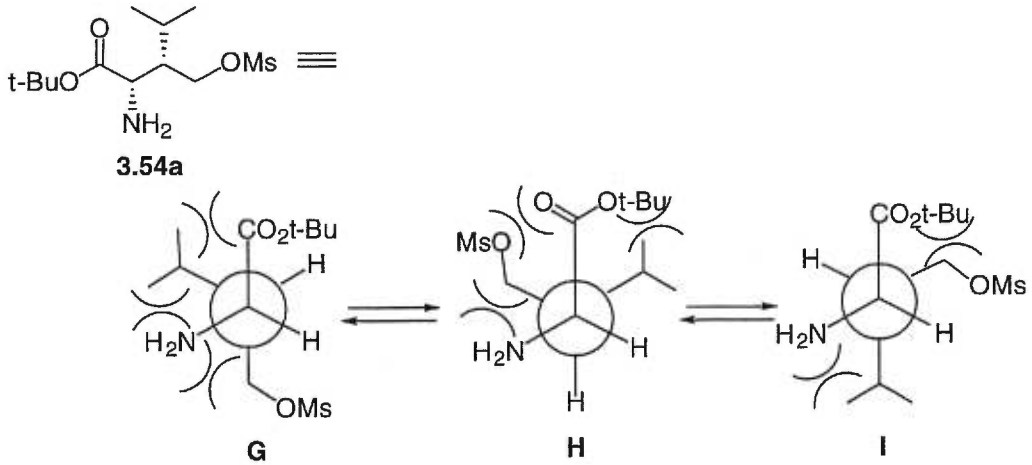
At some point, whether during the cyclization step or during the acidic hydrolysis of the t-butyl ester to a free acid, the problem was occurring. Either the *syn* mesylate salt was not ring closing or if the azetidine ring did form, the following step resulted in hydrolytic ring opening. In order to determine this, we isolated and purified the product of cyclization. According to the FAB mass spectrum results, ^{1}H NMR and especially ^{13}C NMR we determined that it was likely to be compound **3.56** which had probably formed by the mechanism shown in scheme 3.23.

Scheme 3.24: Possible mechanism for formation of **3.56** during attempted cyclization



Since cyclization to form a 2,3-*syn*-substituted four membered ring, when one of the substituents is a bulky aliphatic group, may simply be too sterically challenging, other side reactions may occur. Unlike the flat phenyl or naphthyl groups, which probably do not pose significant steric hindrance to a *syn* cyclization, an isopropyl group may make this impossible. In this case, the detriment of *syn* substitution probably outweighs the advantage of a more substituted ring.

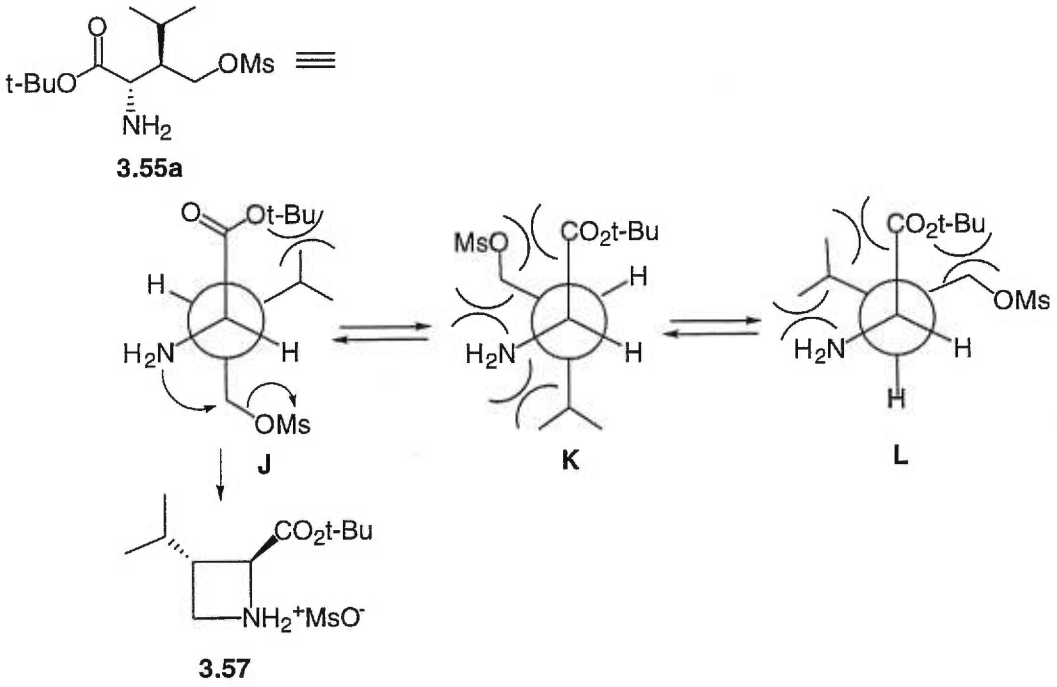
Figure 3.3: Possible conformers of *syn* amino ester **3.54a**



While conformers **G** and **H** can lead to the desired azetidine, it is actually conformer **I** (which is not in the correct orientation to cyclize) that is lower in energy.

In contrast, the lowest energy conformer of the *anti* amino ester (**3.55a**) is **J** which is precisely the conformation that would be required to lead to the cyclized product **3.57**.

Figure 3.4: Possible conformers of *anti* amino ester **3.55a** and cyclization of conformer **J** to Aze **3.57**

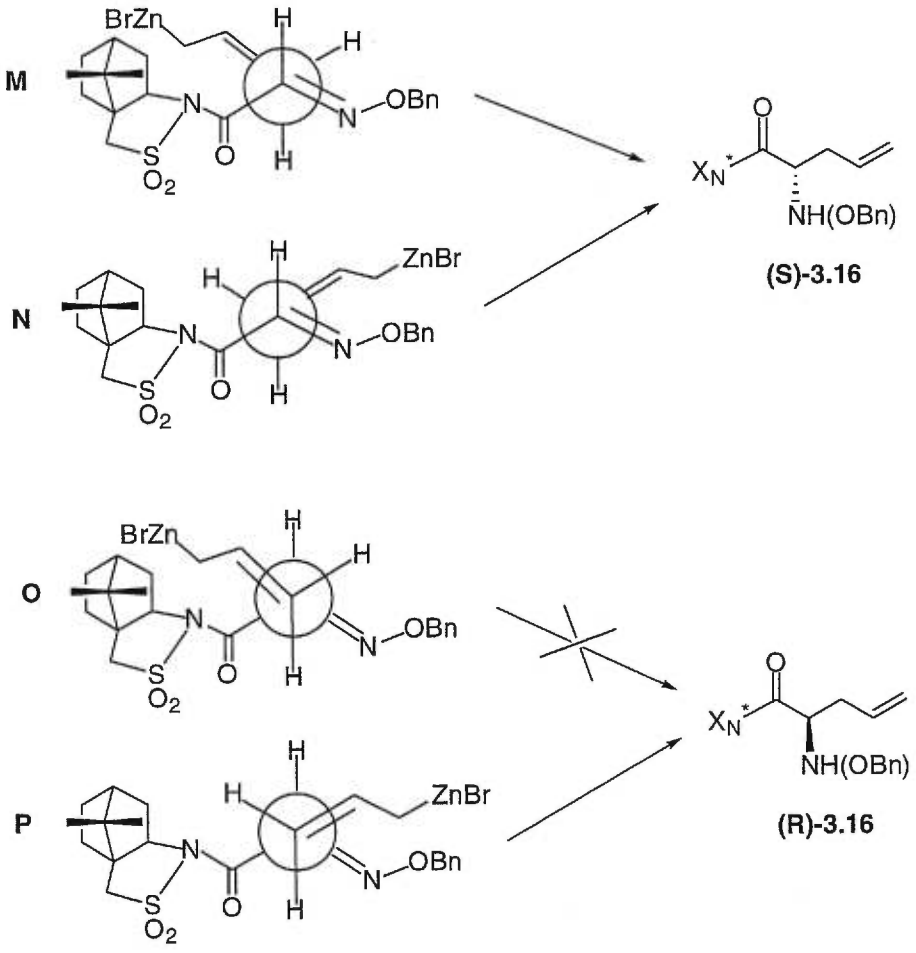


One would expect this cyclization to occur the most readily (Vaughan[23]) since the 2,3 substituents are *anti* to one another and in fact this seems to be the case if one judges by the speed at which this reaction comes to completion.

3.5 Camphor sultam: diastereoselectivity and enantioselectivity

By examining the four possible lowest energy open transition state structures that can lead to the possible (***S*-3.16**) or (***R*-3.16**) isomers, one can readily see how the gem dimethyl group of the camphor sultam auxiliary impedes the conformation (**O**) leading to the isomer (***R*-3.16**).

Figure 3.5: Proposed lowest energy transition state models leading to diastereomers ***S*-3.16** and ***R*-3.16**

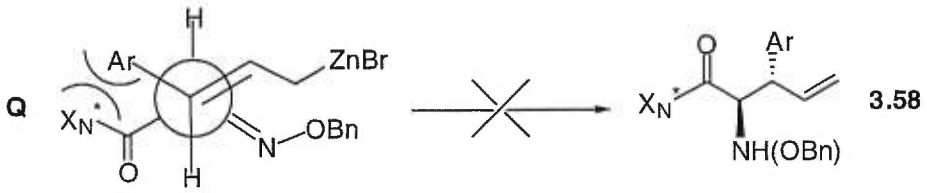


Although conformer **O** is unlikely to exist based on steric considerations, a rotation of 120° results in conformer **P** that can lead to the product ***R*-1.18**. Conformer **P** appears to be energetically less favorable than conformers **M** and **N** which may help to explain the 93:7 ratio observed between the *S*:*R* diastereomers.

The same principle applied to the addition of cinnamyl and 3-(1-naphthyl)-*E*-allyl bromides to the camphorsultam oxime amide (**3.15**). In both cases, only 1 diastereomer was formed, each with 2(*S*) conformation and syn stereochemistry. One explanation is that, while an unsubstituted allyl zinc bromide allows for one possible open transition state (**P**) that can lead to the 2(*R*) isomer, when the allyl zinc bromide is substituted (figure 3.6), the analogous transition state structure (**Q**) becomes too encumbered.

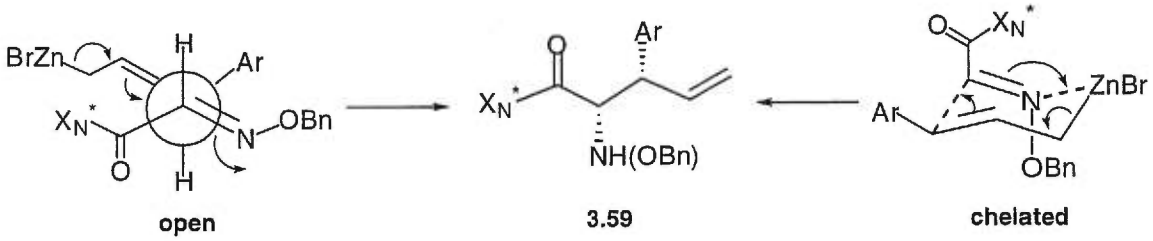
This may explain why the stereochemistry of the product is exclusively (2*S*) even when the cinnallylation is performed at room temperature as compared to the 93:7 (2*S*/2*R*) ratio obtained from the reaction with the unsubstituted allyl bromide (figure 3.5).

Figure 3.6: Open transition state structure **Q**



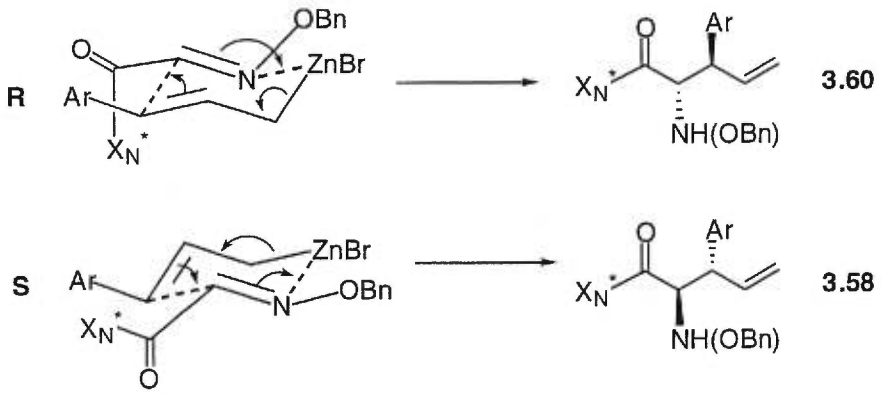
The *syn* stereochemistry in **3.59** can be a result of an open transition state structure or a chelated 6-membered transition as shown Figure 3.7 where the O-benzyl and camphorsultam amide functional groups are placed in a pseudoaxial position .

Figure 3.7: Open and chelated transition state structures leading to *syn* diastereomer **3.59**



Placing these groups in a pseudoequatorial position would result in the *anti* diastereomers (**3.58, 3.60**).

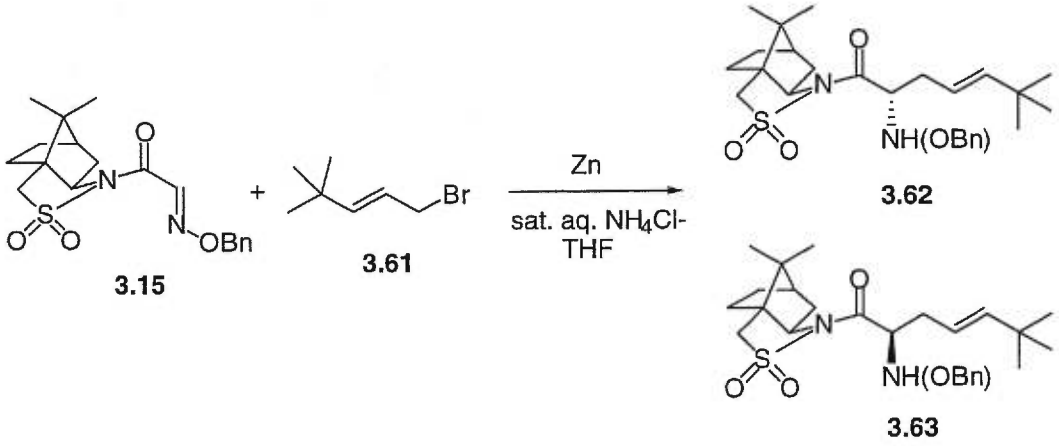
Figure 3.8: Chelated transition state structures



When we set out to make azetidine-2-carboxylic acids with an alkyl substituent at the 3-position, the selectivity of the initial allylation step sharply decreased. R Maguire used crotyl bromide to allylate t-butyl oxime **3.3** and obtained a *syn/anti* ratio of 2-3:1 (assigning *syn* and *anti* was done on the final cyclized Aze's through NMR studies).

Our hope was that a larger bulkier group would improve selectivity and result in a higher ratio of the *syn* over the *anti* product. In fact, allylation with 3-(isobutyl)-E-allyl bromide, which was synthesized in three steps from isovaleraldehyde, resulted in even lower selectivity yielding a product that had a diasereomeric ratio of ~1.5:1. An even bulkier 3-(t-butyl)-E-allyl bromide, synthesized from pivalaldehyde, was less successful and produced what looked like an S_N2 addition to the oxime (instead of S_N2'). Two products were obtained in 26% and 6.6% yields, probably **1.20** and **1.21** respectively.

Scheme 3.25: Asymmetric allylation using 3(*E*)-(t-butyl)-allyl bromide



3.15 **3.61** **3.62** **3.63**

Instead of a terminal olefin, the NMR of the products clearly indicated the presence of an internal double bond. Most of what was recovered was starting material (~50%); it is likely that this allyl zinc bromide was simply too encumbered to react. Finally, 3-(isopropyl)-*E*-allyl bromide (**3.41**) was the reagent of choice, also synthesized in the same manner as the first two but from isobutyraldehyde.

The product consisted of a 1:1 ratio of diastereomers. We suspected that the epimeric center was C-3 since the enantioselectivity dictated by the open transition state structure was

almost exclusively (*S*) at C-2. Nonetheless, since the yield (89%) was quite satisfactory the two isomers, not separable at that stage yet, were taken individually toward the final azetidine compounds.

CHAPTER 4.0

Experimental Procedures

General Information

Instrumentation

Optical rotations were obtained using a Perkin-Elmer 241 apparatus with a sodium lamp (wavelength of 589 nm). All measurements were taken at room temperature (~22 °C) using a 10 cm cell with a 1 ml volume.

Infrared spectroscopy was obtained on Perkin-Elmer FTIR Paragon 1000. The samples were mixed with KBr and formed into pellets. Only those pertinent and/or intense bands are reported.

Melting points were taken on a Buchi apparatus and are uncorrected.

Nuclear Magnetic Resonance (NMR) spectra were performed on Bruker AMX-300 or AMX-400 MHz instruments using the following solvents: deuterated chloroform ($CDCl_3$), methanol (CD_3OD), and deuterium oxide (D_2O). Chemical shifts are expressed in parts per million (ppm), coupling constants (J) are expressed in Hertz (Hz), and splitting patterns are described as follows: s = singlet, d = doublet, dd = doublet of doublet, m = multiplet, br = broad.

High Resolution Mass Spectroscopy (HRMS) was obtained by fast atom bombardment (FAB) of samples on a Kratos MS-50 TCTA or VG Autospec instrument.

X-Ray Diffraction was performed on a Nonius CAD-4 instument using copper (CuK_a) or molybdenum (MoK_a) targets.

Chromatography

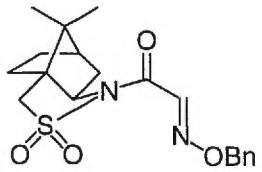
Most products were purified by "flash" chromatography using Kieselgel 60 (Merck 9385, 230-400 mesh) silica gel. Thin Layer Chromatography (TLC) plates were used to follow reactions (glass plates with silica gel of 0.25 mm thickness, Merck, Kieselgel $60F_{254}$).

Most final products (amino acids) were purified with Dowex 50 H^+, 50WX8-100 (100-200 mesh).

Solvents

Anhydrous dichloromethane (DCM) was obtained by distillation over CaH_2. Tetrahydrofuran (THF) was distilled from potassium or sodium using benzophenone as indicator. Spectrograde methanol (MeOH) was used and isopropanol was bought as reagent grade.

(1*S*)-2,10-Camphorsultamyl Benzyloximinoethanoate (**1.15**)



To a solution of oxime **1.1** (3.23 g, 18.1 mmol) in dry THF (100 ml) was added Et_3N (3.0 ml, 21.5 mmol) at room temperature. The mixture was cooled to –78 °C and trimethylacetyl chloride was added dropwise. The subsequent solution was stirred for 10 min. at –78 °C, warmed to 0 °C for 30 min. and then re-cooled to –78 °C. To a solution of (1S)-2,10-camphorsultam (3.0 g, 13.9 mmol) in dry THF (60 ml) at –78 °C was added dropwise n-BuLi (2.3 M in hexanes, 6.1 ml, 14.0 mmol). The solution was stirred at –78 °C for 10 min. and then transferred, via cannula, into the solution of the mixed anhydride prepared separately. The mixture was stirred at –78 °C for 5 min. and allowed to warm to 0 °C over 2 h. and kept at 0 °C for an additional half hour. Sat. aq. NH_4Cl (50 ml) was then added dropwise and the resulting mixture was extracted with ethyl acetate (3X). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The resulting crude solid was crystallized from hexanes-ethyl acetate to yield the desired product as colorless crystals (4.5 g, 86%).

M.P. 122-123 °C

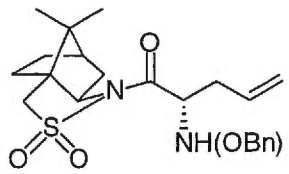
$[\alpha]_D$ –69.0 (c 1.55, $CHCl_3$)

^1H NMR: d (400 MHz, $CDCl_3$): 0.98 and 1.16 (each 3H, s, camphor CMe_2), 1.36-1.46 (2H, m, camphor), 1.88-1.94 (3H, m, camphor), 3.46 and 3.53 (each 1H, d, *J*13.8, camphor $\underline{CH_2}SO_2$), 3.99 (1H, dd, *J*7.6, 5.1, camphor $\underline{CH}N$), 5.3 (2H, s, $O\underline{CH_2}Ph$), 7.33-7.39 (5H, m, Ar$\underline{H}$), 8.2 (1H, s, oxime N$\underline{H}$CO)

^{13}C NMR: (100 MHz, $CDCl_3$): 19.75, 20.76, 26.25, 32.76, 38.15, 44.57, 47.75, 48.82, 52.94, 65.10, 78.24, 128.34, 128.42, 128.54, 135.75, 140.81, 158.97

HRMS: calculated for $C_{19}H_{25}O_4N_2S$: 377.1535, obtained: 377.1551

(1*S*)-2,10-Camphorsultamyl (2*S*)-2-benzyloxyamino-pent-4-enoate (**1.16**)



A solution of camphorsultam oxime **1.15** (1.0 g, 2.66 mmol) in THF (4.8 ml) and sat. aq. NH_4Cl (4.8 ml) was stirred vigorously and cooled to 0 °C. Allyl bromide (0.37 ml, 4.28 mmol) was added followed by the addition of Zn powder (0.35 g, 5.3 mmol) portionwise as it reacted. The mixture was stirred at 0 °C for 30 min and then partitioned between ethyl acetate and H_2O. The aqueous layer was washed with ethyl acetate (2X) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The resulting paste was crystallized from hexanes-ethyl acetate to yield the amide as colorless crystals (0.88 g, 79%). Chromatography of the mother liquor on silica gel eluting with hexanes-ethyl acetate (6:1) yielded additional product (0.067 g, 6%).

M.P. 101.5-103 °C

$[\alpha]_D$ –119.5 (c 0.74, DCM)

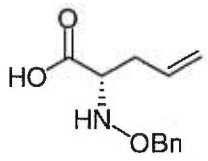
^1H NMR, (400 MHz, $CDCl_3$): 0.97 and 1,14 (each 3H, s, camphor CMe_2), 1.32-1.44 (2H, m, camphor), 1.86-1.91 (3H, m, camphor), 2.06-2.08 (2H, m, camphor), 2.33-2,40 (2H, m, C-$3H_2$), 3.47 and 3.51 (each 1H, d, *J*13.8, camphor CH_2SO_2),

3.97 (1H, t, *J*6.3, camphor CHN), 4.48 (1H, t, *J*6.3, C-2H), 4.68 and 4.75 (each 1H, d, *J*11.7, OCH_2Ph), 5.03-5.10 (2H, m, C-$5H_2$), 5.71-5.78 (1H, m, C-4H), ~6.0-6.4 (1H, brs, NH), 7.25-7.38 (5H, m, ArH).

^{13}C NMR, (100 MHz, $CDCl_3$): 19.79, 20.67, 26.29, 32.65, 34.70, 38.13, 44.44, 47.64, 48.49, 52.91, 62.27, 64.91, 75.75, 118.30, 127.54, 128.07, 128.51, 132.55, 137.55, 172.75

HRMS: calculated for $C_{22}H_{31}O_4N_2S$: 419.2004, obtained: 419.2013

(2*S*)-2-Benzyloxyamino-pent-4-enoic acid (**1.17**)



To a solution of camphorsultam amide **1.16** (0.78 g, 1.86 mmol) in THF (16 ml) was added 1N LiOH (3.9 ml, 3.9 mmol) dropwise. The mixture was stirred vigorously at room temperature for 18 h. Silica gel (~8ml) was subsequently added and the mixture was concentrated in vacuo to dryness. The crude was adsorbed on silica and then was chromatographed using hexanes-ethyl acetate (2:1) as initial eluant to recover camphor sultam (0.35 g, 87%), followed by DCM/MeOH/formic acid (100:10:1) to afford the desired compound as a white solid (0.345 g, 84 %).

M.P. 106-107.5 °C

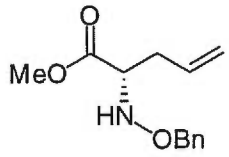
$[\alpha]_D$ –30.8 (c 0.38, MeOH)

^{1}H NMR, (400 MHz, CD_3OD): 2.32-2.37 (2H, m, C-3H_2), 3.63 (1H, t, *J*6.8, C-2H), 4.70 (2H, s, OCH_2Ph), 4.9 (2H, s, COOH, NH), 5.04-5.13 (2H, m, C-5H_2), 5.79 (1H, ddd, *J*17.1, 7.1, 3.1, C-4H), 7.27-7.35 (5H, m, ArH)

^{13}C NMR, (100 MHz, CD_3OD): 33.23, 62.80, 76.34, 76.58, 76.90, 77.22, 118.77, 128.03, 128.31, 128.54, 132.35, 136.73, 177.17

HRMS: calculated for $C_{12}H_{16}O_3N$: 222.1130, obtained: 222.1135

Methyl (2*S*)-2-benzyloxyamino-pent-4-enoate (***S*-1.4a**)



To a stirring solution of acid **1.17** (1.97 g, 8.94 mmol) in MeOH (10-15 ml) was added freshly distilled diazomethane (in diethyl ether) dropwise until a yellow color persisted. TLC (hexanes-ethyl acetate, 1:1) indicated that all the acid had reacted. The solution was allowed to stir 1 h. in fume hood to dissipate excess diazomethane and then concentrated in vacuo to yield the product a clear yellow oil (2.01 g, 96%) that was suitable to be used for the next step.

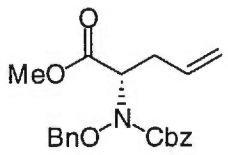
$[\alpha]_D$ –45.6 (c 0.70, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$): 2.34-2.38 (2H, m, C-3H_2), 3.71 (1H, t, *J*6.9, C-2H), 3.75 (3H, s, CO_2CH_3), 4.73 (2H, s, OCH_2Ph), 5.07-5.13 (2H, m, C-5H_2), 5.67-5.78 (1H, m, C-4H), ~5.8-6.2 (1H, brs, NH), 7.26-7.35 (5H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$): 33.68, 51.88, 63.10, 76.15, 118.09, 127.76, 128.21, 128.37, 132.85, 137.39, 173.36

HRMS: calculated for $C_{13}H_{18}O_3N$: 236.1287, obtained: 236.1285

Methyl (2*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-pent-4-enoate (***S*-1.5**)



An emulsion of methyl ester ***S*-1.4a** (2.01 g, 8.58 mmol) and benzyl chloroformate (3.7 ml, 25.7 mmol) in DCM (5 ml) - sat. aq. $NaHCO_3$ (10 ml) was stirred vigorously at room temperature for 48 h. The mixture was partitioned between DCM (~50 ml) and H_2O (~50 ml), and the aqueous layer was extracted with DCM (2X). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude oil was chromatographed on silica gel using a gradient of hexanes-ethyl acetate (12:1 to 5:1) to afford the desired compound as a colorless oil (2.71 g, 85%).

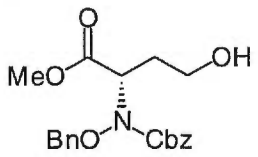
$[\alpha]_D$ –20.5 (c 0.56, DCM)

^1H NMR, (400 MHz, $CDCl_3$): 2.66-2.82 (2H, m, C-3H_2), 3.68 (3H, s, CO_2CH_3), 4.75 (1H, dd, *J*9.8, 5.3, C-2H), 4.91 and 5.00 (each 1H, d, *J*10.0, OCH_2Ph), 5.10 (1H, d, *J*10.2, C-5H_{cis}), 5.17 (1H, dd, *J*17.1, 1,4, C-5H_{trans}), 5.26 (2H, s, OCH_2Ph), 5.76-5.86 (1H, m, C-4H), 7.31-7.42 (10H, m, ArH)

^{13}C NMR, (100MHz, $CDCl_3$): 32.43, 52.31, 62.54, 68.06, 78.10, 118.0, 128.09, 128.22, 128.26, 128.40, 128.42, 129.12, 133.79, 135.08, 135.63, 158.00, 170.13

HRMS: calculated for $C_{21}H_{24}O_5N$: 370.1654, obtained: 370.1664

Methyl (2*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-4-hydroxybutanoate (***S*-1.6**)



A stream of ozone in oxygen was bubbled through a solution of amino ester ***S*-1.5** (0.6 g, 1.63 mmol) in MeOH (20 ml) at –78 °C until a blue color persisted. TLC in hexanes-ethyl acetate (4:1) confirmed that the starting material had completely reacted. The blue color was dissipated by continuing to bubble a stream of O_2 for an additional 20-30 min. $NaBH_4$ (0.62 g, 16.3 mmol) was added portionwise over 4 h., each time adding the reagent at -40 °C and letting the temperature rise to -20 °C. The mixture was allowed to warm to -15 °C * and then poured rapidly into a vigorously stirring mixture of DCM (30 ml) and sat. aq. NH_4Cl (20 ml). The emulsion was stirred until it reached room temperature and then partitioned between DCM and H_2O (enough to dissolve the solids). The aqueous layer was extracted with DCM (3X) and the combined organic extracts were dried over Na_2SO_4, and then concentrated in vacuo (without heat to minimize lactonization). Chromatography on silica gel using hexanes-ethyl acetate (5:2) yielded the desired alcohol as a clear viscous oil (0.46 g, 75%).

*Temp should not be allowed to rise above -15 °C to avoid reduction of ester to form the diol.

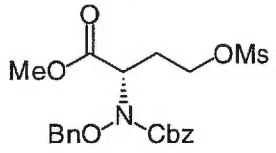
$[\alpha]_D$ –31.3 (c 0.60, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.79 (1H, brs, OH), 2.07-2.11 (1H, m, C-3HH), 2.21-2.24 (1H, m, C-3HH), 3.58-3.61 (1H, m, C-4HH), 3.66-3.71 (1H, m, C-4HH), 3.69 (3H, s, CO_2CH_3), 4.87 (1H, dd, *J*9.8, 5.1, C-2H), 4.93 and 5.02 (each 1H, d, *J*10.0, OCH_2Ph), 5.28 (2H, s, OCH_2Ph), 7.33-7.42 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 31.33, 52.39, 58.84, 59.87, 68.25, 78.13, 128.14, 128.32, 128.48, 128.55, 129.32, 129.61, 134.99, 135.50, 158.20, 170.72

HRMS: calculated for $C_{20}H_{24}O_6N$: 374.1604, obtained: 374.1590

Methyl (2*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-4-methanesulfonyloxy butanoate (***S*-1.7**)



To a solution of alcohol ***S*-1.6** (0.93 g, 2.49 mmol) in dry DCM (10 ml), was added pyridine (0.61 ml, 7.55 mmol), DMAP (~5mg, cat.) followed by mesyl chloride (0.49 ml, 6.34 mmol). The mixture was stirred at room temperature for 18h. Sat. aq. $NaHCO_3$ (~10 ml) was added dropwise and the mixture was stirred vigorously for a half hour. After partitioning between DCM (~20 ml) and H_2O (~20 ml), the aqueous layer was extracted further with DCM (2X). The organic extracts were dried over

Na_2SO_4 and concentrated in vacuo. Chromatography with silica gel using hexane-ethyl acetate (5:2) afforded the desired mesylate as a viscous oil (0.94 g, 84%).

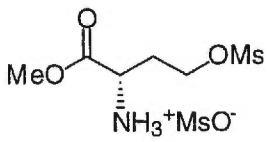
$[\alpha]_D$ –50.3 (c 0.89, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 2.16-2.23 (1H, m, C-3HH), 2.39-2.46 (1H, m, C-3HH), 2.89 (3H, s, OSO_2CH_3), 3.69 (3H, s, CO_2CH_3), 4.08-4.14 (1H, m, C-4HH), 4.21-4.26 (1H, m, C-4HH), 4.78 (1H, *J*9.9, 4.9, C-2H), 4.90 and 5.00 (each 1H, d, *J*10.2, OCH_2Ph), 5.27 (2H, s, OCH_2Ph), 7.31-7.43 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 28.16, 37.13, 52.57, 59.30, 65.98, 68.39, 78.08, 128.20, 128.39, 128.51, 128.70, 129.39, 134.83, 135.39, 157.86, 169.58

HRMS: calculated for $C_{21}H_{26}O_8NS$: 452.1379, obtained: 452.1368

Methyl (2*S*)-2-amino-4-(methanesulfonyloxy)-butanoate Methanesulfonate salt (***S*-1.8**)



To a solution of mesylate ***S*-1.7** (2.27 g, 5.03 mmol) in MeOH (115 ml) was added methanesulfonic acid (0.33 ml, 5.03 mmol) and 10% Pd/C (~350 mg). The mixture was saturated with hydrogen gas and stirred vigorously under a hydrogen atmosphere (balloon) for 24 hrs. TLC using DCM-MeOH (10:1) as eluant confirmed that the hydrogenolysis was complete at which point the mixture was degassed with nitrogen

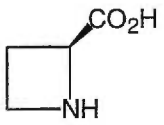
filtered through a celite plug, and then concentrated in vacuo to yield a white solid (1.5 g, 91%) that needed no further purification.

^{1}H NMR, (400 MHz, CD_3OD) : 2.35-2.42 (2H, m, C-3H_2), 2.72 (3H, s, $CH_3SO_3^-$ counterion), 3.14 (3H, s, OSO_2CH_3), 3.88 (3H, s, CO_2CH_3), 4.23 (1H, t, *J*6.5, C-2H), 4.45 (2H, t, *J*6.0, C-4H_2), 4.92 (3H, s, NH_3^+)

^{13}C NMR, (100 MHz, CD_3OD) : 31.27, 37.16, 39.50, 48.36, 48.57, 48.78, 49.00, 49.21, 49.42, 49.63, 50.98, 53.91, 66.83, 170.31

HRMS: calculated for $C_6H_{14}O_5NS$ (cation): 212.0593, obtained: 212.0587

(2*S*)-Azetidine-2-carboxylic acid (**L-Aze**)



A solution of mesylate salt ***S*-1.8** (1.14 g, 3.47 mmol) and $NaHCO_3$ (0.35 g, 4.17 mmol) in isopropanol and was heated to reflux for 2 h. The solution was cooled and concentrated in vacuo (azeotroping the water with ethanol) followed by precipitation of sodium mesylate using IPA (15 ml)-DCM (15 ml). The filtrate was concentrated in vacuo to afford the crude methyl (2S)-azetidine-2-carboxylate mesylate salt (0.70 g, 95%) which was used without purification for the next step.

A solution of the crude azetidine (0.70 g) in 3N HCl (80 ml H_2O, 30 ml 12N HCl) was stirred at room temperature for 24 h., and subsequently concentrated in vacuo (azeotroping the HCl with H_2O). The resulting crude solid was passed through dowex 50 H^+ (100-200 mesh) and eluted using ~5% NH_4OH to yield, after concentration in

vacuo, a white solid. Several triturations with minimal ethanol (to remove most impurities), followed by crystallization from MeOH (~3 ml) and H_2O (3 drops) afforded the pure (2*S*)-azetidine–2-carboxylic acid as colorless crystals (140 mg, 40%).

M.P. ~185 - >200 °C (dec.)

$[\alpha]_D$ –123.0 (c 3.6, H_2O), litt.$[a]_D$ –120.0 (c 3.6, H_2O)

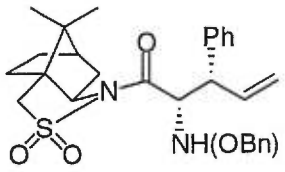
^1H NMR, (400 MHz, D_2O) : 2.46-2.56 (1H, m, C-3HH), 2.70-2.79 (1H, m, C-3HH), 3.88 (1H, ddd, *J*20.4, 10.2, 6.0, C-4HH), 4.02-4.09 (1H, m, C-4HH)

^{13}C NMR, (100 MHz, D_2O) : 24.13, 43.58, 59.83, 174.91

IR (KBr): 2973.4, 1591.7, 1415.1 cm^{-1}

HRMS: calculated for $C_4H_8O_2N$: 102.0555, obtained: 102.0559

(1*S*)-2,10-Camphorsultamyl (2*S*,3*S*)-2-benzyloxyamino-3-phenyl-pent-4-enoate (**1.24**)



To a vigorously stirred emulsion of camphorsultam oxime **1.15** (5.0 g, 13.28 mmol) in THF (25 ml) and sat. aq. NH_4Cl (25 ml) at 0 °C, was added cinnamyl bromide (6.0 ml, 40.49 mmol) and then zinc powder (0.7 g, 10.6 mmol) portionwise as it reacted. The mixture was stirred at 0 °C for an additional 30 min., then partitioned between ethyl acetate and H_2O, and the aqueous layer was extracted with ethyl acetate (2X).

The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was triturated with minimal quantities of hexanes (3X) followed by crystallization from hexanes-ethyl acetate to afford the desired compound as colorless crystals (5.6g, 85%).

M.P. 115-118 °C

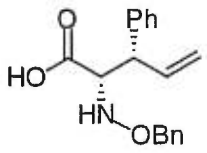
$[\alpha]_D$ –21.6 (c 0.79, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 0.98 and 1.20 (each 3H, s, camphor Cme_2), 1.35-1.40 (2H, m, camphor), 1.86-1.92 (3H, s, camphor), 2.06-2.07 (2H, m, camphor), 3.41-3.57 (3H, m, CH_2SO_2 and camphor CHN), ~3.9-4.05 (1H, br, C-3H), 4.47 and 5.57 (each 1H, d, *J*11.6, OCH_2Ph), 4.78 (1H, d, *J*6.8, C-2H), 5.00 (1H, d, *J*10.0, C-$5H_{cis}$), 5.14 (1H, d, *J*16.8, C-$5H_{trans}$), 6.12-6.21 (1H, m, C-4H), 7.16-7.32 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 19.89, 20.69, 26.30, 32.83, 37.80, 44.48, 47.61, 48.20, 52.22, 53.07, 65.31, 66.02, 75.49, 117.19, 126.83, 127.41, 127.75, 127.88, 128.53, 128.87, 137.45, 140.08, 172.75

HRMS: calculated for $C_{28}H_{35}O_4N_2S$: 495.2318, obtained: 495.2306

(2*S*,3*S*)-2-Benzyloxyamino-3-phenyl-pent-4-enoic acid (**1.25**)



To a solution of camphorsultam amide **1.24** (8.0 g, 16.2 mmol) in THF (300 ml) was added $LiOH{\cdot}H_2O$ (5.9 g, 119.19 mmol) and the mixture was stirred rapidly at room temperature for 4 days until no more starting material was present by TLC (hexanes-ethyl acetate, 3:1). The mixture was concentrated in vacuo to remove all THF and partitioned between H_2O (500 ml) and DCM (50-100 ml). The alkaline aqueous layer was extracted repeatedly with DCM (50-75 ml portions) until camphor sultam could no longer be detected by TLC (DCM-MeOH, 10:1). The aqueous layer was acidified (to pH 1-2) with 12N HCl added dropwise and extracted with DCM (100 ml, 3X). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford a slightly yellow paste (3.9 g, 81%) that was suitable for use without further purification.

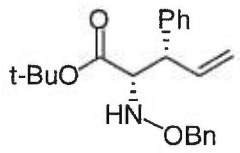
$[\alpha]_D$ +23.8 (c 0.37, MeOH)

^1H NMR, (400 MHz, CD_3OD) : 3.48 (1H, t, *J*8.9, C-3H), 3.90 (1H, d, *J*9.0, C-2H), 4.53 and 4.57 (each 1H, ddd, *J*18.9, 10.2, 8.7, C-4H), 7.16-7.31 (10H, m, ArH)

^{13}C NMR, (100 MHz, CD_3OD) : 51.82, 69.18, 76.81, 117.16, 127.94, 128.75, 129.06, 129.19, 129.61, 129.72, 138.92, 138.98, 141.27, 176.01

HRMS: calculated for $C_{18}H_{20}O_3N$: 298.1443, obtained: 298.1434

tert-Butyl (2*S*,3*S*)-2-benzyloxyamino-3-phenyl-pent-4-enoate (**1.29**)



To a solution of carboxylic acid **1.25** (0.61 g, 2.06 mmol), in dry DCM (2.5 ml)-cyclohexane (5.0 ml) at room temperature was added t-butyl imidate (0.74 ml, 4.12 mmol) followed by $BF_3{\cdot}OEt_2$ (0.05ml, cat.). The mixture was stirred overnight under a N_2 atmosphere at which point it was concentrated in vacuo and then chromatographed on silica gel eluting with hexanes-ethyl acetate (10:1) to afford a clear oil (0.56 g, 77%).

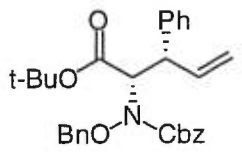
$[\alpha]_D$ +14.7 (c 0.98, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.46 (9H, s, CMe_3), 3.53 (1H, t, *J*8.8, C-3H), 3.88 (1H, d, *J*8.8, C-2H), 4.62 and 4.66 (each 1H, d, *J*11.5, OCH_2Ph), 5.09-5.16 (2H, m, C-5H_2), 6.01 (1H, ddd, *J*19.0, 10.1, 8.9, C-4H), 7.16-7.34 (10H, m, ArH).

^{13}C NMR, (100 MHz, $CDCl_3$) : 27.97, 50.36, 67.95, 75.94, 81.58, 117.14, 126.85, 127.64, 127.80, 128.09, 128.49, 136.83, 137.43, 139.69, 171.46

HRMS: calculated for $C_{22}H_{28}O_3N$: 354.2069, obtained: 354.2083

tert-Butyl (2*S*,3*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-3-phenyl-pent-4-enoate (**1.30**)



To an emulsion of amino ester **1.29** (0.64 g , 1.82 mmol) in DCM (9 ml) and sat. aq. $NaHCO_3$ (18 ml) at room temperature, was added Cbz-Cl (0.8 ml, 5.63 mmol) and it was stirred vigorously for 48 h. TLC (hexanes-ethyl acetate, 9:1) indicated that some starting material was still present so additional Cbz-Cl (0.8 ml) and sat. aq. $NaHCO_3$ (~10 ml) were added and the mixture was stirred for a further 24 h. to allow complete conversion. The mixture was then partitioned between DCM (~25 ml) and H_2O (~30 ml) and the aqueous layer was extracted with DCM (3X). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and chromatographed on silica gel eluting with hexanes-ethyl acetate (12:1) to yield a colorless oil (0.76 g, 86%).

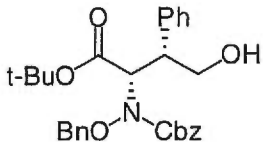
$[\alpha]_D$ –34.6 (c 1.14, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.49 (9H, s, CMe_3), 4.26 (1H, dd, *J*11.3, 8.1, C-3H), 4.64 and 4.82 (each 1H, d, *J*9.6, OCH_2Ph), 5.00 (2H, brs, OCH_2Ph), 5.04 (1H, d, 11.3, C-2H), 5.13-5.19 (2H, m, C-5H_2), 6.08 (1H, ddd, *J*18.3, 10.3, 8.1, C-4H), 7.19-7.42 (15H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 27.86, 48.64, 65.98, 67.77, 71.27, 82.08, 116.82, 126.79, 127.90, 128.06, 128.12, 128.25, 128.35, 128.59, 128.68, 128.98, 135.47, 135.66, 137.90, 139.65, 157.35, 168.08

HRMS: calculated for $C_{30}H_{34}O_5N$: 488.2437, obtained: 488.2446

tert-Butyl (2*S*,3*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-3-phenyl-4-hydroxy-butanoate (**1.31**)



A stream of ozone in oxygen was bubbled through a solution of amino ester **1.30** (0.737 g , 1.51 mmol) in MeOH (15 ml) and DCM (5ml) at –78 °C until a blue color persisted. Running a TLC in hexanes-ethyl acetate (5:1) confirmed that the starting material had been completely consumed. The blue color was discharged with a stream of O_2 for an additional 20 min. $NaBH_4$ (0.57 g , 15.1 mmol) was added portionwise over 2 h., each time adding the reagent at –40 °C and letting the temperature rise to –5 °C. The mixture was allowed to warm to 0 °C and then poured rapidly into a vigorously stirring mixture of DCM (25 ml) and sat. aq. NH_4Cl (20 ml) and stirred until it reached room temperature. The mixture was then partitioned between DCM and H_2O and the aqueous layer was extracted with DCM (3X). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and chromatographed on silica gel eluting with hexanes-ethyl acetate (4:1) to afford the desired alcohol as a clear oil (0.61 g , 83%).

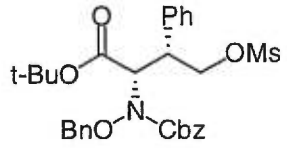
$[\alpha]_D$ –54.2 (c 1.3, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.92 (1H, brs, OH), 3.69 (1H, m C-3H), 3.87-3.97 (2H, m, C-4H_2), 4.41 and 4.70 (each 1H, d, *J*9.9, OCH_2Ph), 5.04-5.13 (1H, d, *J*10.8, C-2H and 2H, each H d, *J*10.8, OCH_2Ph), 7.20-7.38 (15H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 27.76, 47.21, 64.07, 65.20, 67.86, 77.04, 82.60, 127.09, 127.94, 128.00, 128.07, 128.10, 128.38, 128.43, 128.77, 135.39, 135.59, 139.10, 157.76, 168.92

HRMS: calculated for $C_{29}H_{34}O_6N$: 492.2386, obtained: 492.2369

tert-Butyl (2*S*,3*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-4-methanesulfonyloxy-3-phenyl-butanoate (**1.32**)



To a solution of alcohol **1.31** (0.61 g, 1.25 mmol), dry pyridine (0.4 ml, 5.0 mmol) and DMAP (~5mg, cat.) in dry DCM (25 ml) was added mesyl chloride (0.33 ml, 4.25 mmol). The mixture was stirred at room temperature for 18 h. followed by the addition of sat. aq. $NaHCO_3$ (30 ml) and vigorous stirring for 1 h. After partitioning between DCM and H_2O, the aqueous layer was extracted with DCM (2X) and then the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was chromatographed on silica gel eluting with hexanes-ethyl acetate (3.5:1) to obtain the desired product as a viscous oil (0.61 g, 84%).

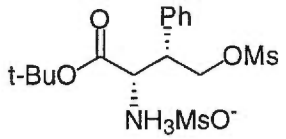
$[\alpha]_D$ – 49.7 (c 0.43, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.44 (9H, s, CMe_3), 2.69 (3H, s, OSO_2CH_3), 3.86 (1H, m, C-3H), 4.42 (1H, d, *J*9,9, OC<u>H</u>HPh), 4.50 (1H, dd, *J*10.1, 3.6, C-4<u>H</u>H), 4.65-4.70 (2H, m, OCH<u>H</u>Ph and C-4H<u>H</u>), 5.03-5.12 (3H, m, OCH_2Ph and C-2H), 7.19-7.38 (15H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 27.72, 36.76, 44.25, 62.88, 68.02, 71.75, 77.10, 82.92, 127.56, 127.96, 128.13, 128.17, 128.40, 128.44, 128.95, 135.15, 135.44, 137.52, 157.25, 167.61

HRMS: calculated for $C_{30}H_{36}O_8NS$: 570.2162, obtained: 570.2176

tert-butyl (2*S*,3*S*)-Methanesulfonate salt (**1.33**)2-Amino-4-(methanesulfonyloxy)-3-phenyl-butanoate.



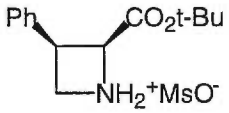
To a solution of mesylate **1.32** (0.58 g, 0.99 mmol) and methanesulfonic acid (0.065 ml, 1.0 mmol) in dry MeOH (40ml), was added 10% Pd/C (~200mg). The mixture was saturated with H_2 gas under pressure (40 psi) and stirred for 2 h. The solution was then filtered through celite and the filtrate concentrated in vacuo to yield a white solid (0.41 g, 94%) that could be used for next step without further purification.

^{1}H NMR, (400 MHz, CD_3OD) : 1.57 (9H, s, CMe_3), 2.72 (3H, s, $CH_3SO_3^-$ counterion), 3.05 (3H, s, OSO_2CH_3), 3.72 (1H, dd, J13.5, 6.8, C-3H), 4.37 (1H, d, J6.9, C-2H), 4.58 (1H, dd, J10.7, 6.5, C-4HH), 4.92 (3H, brs, NH_3^+), 7.37-7.49 (5H, m, ArH)

^{13}C NMR, (100 MHz, CD_3OD) : 28.14, 37.29, 39.52, 47.15, 55.82, 69.89, 86.35, 129.92, 130.07, 130.54, 135.10, 168.09

HRMS: calculated for $C_{15}H_{24}O_5NS$ (cation): 330.1375, obtained: 330.1387

tert-butyl (2*S*,3*R*)-3-Phenyl-azetidinium-2-carboxylate. Methanesulfonate salt (**1.34**)



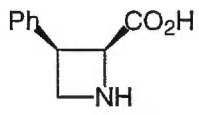
A solution of mesylate salt **1.33** (0.43 g, 0.98 mmol) and $NaHCO_3$ (0.095 g, 1.13 mmol) in MeOH (135ml) and H_2O (11 ml) was refluxed for 1.5 h. The mixture was cooled, concentrated in vacuo to near dryness and then triturated with ethanol (30ml)-chloroform (65 ml) to precipitate out sodium mesylate. The filtrate was concentrated in vacuo to yield a clear solid residue (0.29 g, 89%) that was used without further purification for the next step.

^{1}H NMR, (400 MHz, CD_3OD) : 1.07 (9H, s, CMe_3), 2.73 (3H, s, $CH_3SO_3^-$ counterion), 4.39 (1H, m, C-3H), 4.46-4.53 (2H, m, C-4H_2), 4.93 (2H, brs, NH_2^+), 5.32 (1H, d, J10.2, C-2H)

^{13}C NMR, (100 MHz, CD_3OD) : 27.65, 27.72, 28.12, 39.48, 40.79, 64.55, 85.13, 129.39, 129.54, 129.91, 136.36, 166.56

HRMS: calculated for $C_{14}H_{20}O_2N$ (cation): 234.1494, obtained: 234.1490

(2*S*,3*R*)-3-Phenyl-azetidine-2-carboxylic acid (**1.35**)



A solution of crude azetidine mesylate salt **1.34** (0.29 g, ~0.88 mmol) in 2.75 N HCl (50 ml and 15 ml 12 N HCl) was stirred at room temperature for 18h. and then concentrated in vacuo (the HCl was azeotroped repeatedly with H_2O. The residue was passed through a column of dowex 50 H^+ (100-200 mesh) and eluted using 5% NH_4OH to yield, after concentration in vacuo, a white solid. The crude solid was triturated several times with hot ethanol (~15 ml) to remove the bulk of the impurities and then crystallization from methanol afforded the pure product as a white solid (0.115g, 73%).

M.P. ~235-245 °C (dec.)

$[\alpha]_D$ +70.0 (c 0.09, H_2O)

^1H NMR, (400 MHz, D_2O) : 4.35 (1H, m, C-3H), 4.42-4.51 (2H, m, C-4H_2), 5.09 (1H, m, C-2H), 7.42-7.48 (5H, m, ArH)

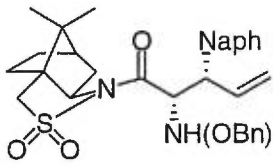
^{13}C NMR, (100 MHz, D_2O) : 39.98, 49.79, 65.37, 128.53, 128.99, 129.53, 136.84, 171.52

IR (KBr): 3289.6, 3030.2, 1607.1, 1467.0, 1498.1, 1394.3 cm^{-1}

HRMS: calculated for $C_{10}H_{12}O_2N$: 178.0868, obtained: 178.0872

single crystal X-ray

(1*S*)-2,10-Camphorsultamyl (2*S*,3*S*)-2-benzyloxyamino-3-(1-naphthyl)-pent-4-enoate (**1.36**)



To a vigorously stirred solution of camphorsultam oxime **1.15** (0.86 g, 2.30 mmol and the allyl bromide (1.95 g, 7.96 mmol) in THF (20 ml) and sat. aq. NH_4Cl (20 ml) at 0 °C, was added Zn (0.60 g, 9.20 mmol) portionwise as it reacted. The mixture was allowed to reach room temperature and stirred for 18 h., at which point it was partitioned between DCM (100 ml) and H_2O (100 ml). The aqueous layer was extracted with DCM (3X) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was triturated first with hexanes-ethyl acetate (~10:1) to remove the bulk of the unreacted allyl bromide, then repeatedly with hexanes and finally crystallized/precipitated form hexanes-ethyl acetate to yield a slightly yellow solid (1.06 g, 85%).

M.P. ~140 °C (dec.)

$[\alpha]_D$ –29.8 (c 0.39, DCM)

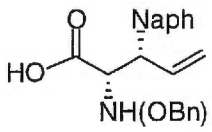
^{1}H NMR, (400 MHz, $CDCl_3$) : 0.47 and 1.08 (each 3H, s, camphor $C(CH_3)_3$), 0.52 and 0.79 (each 1H, br, camphor), 1.12 (1H, m, camphor), 1.31-1.37 (2H, m, camphor), 1.96 and 2.12 (each 1H, brs, camphor), 2.79 and 2.85 (each 1H, d, *J*13.7, camphor CH_2SO_2), 3.65 (1H, brs, camphor CHN), 4.55 and 4.78 (each 1H, d, *J* 11.3, OCH_2Ph), 4.61 (1H, d, *J* 9.2, C-3H), 4.99 (1H, d, *J* 9.8, C-2H), 5.24 (1H, d, *J* 16.9, C-5H_{trans}), 5.61 (1H, br, C-5H_{cis}), 6.51 (1H, d, *J* 11.2, NH), 6.59

(1H, m, C-4H), 7.04-7.41 (8H, m, ArH), 7.57 (1H, d, *J* 8.1, ArH), 7.68 (1H, d, *J* 8.0, ArH), 7.89 (1H, d, *J* 7.3, ArH), 8.13 (1H, d, *J* 8.3, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 19.29, 20.56, 25.90, 32.05, 37.79, 44.35, 46.63, 47.07, 47.48, 52.30, 65.01, 66.67, 75.65, 82.13, 82.37, 116.95, 123.03, 124.72, 125.18, 125.67, 125.86, 127.16, 127.23, 128.89, 128.96, 131.93, 132.22, 134.20, 137.07, 137.84, 172.89

HRMS: calculated for $C_{32}H_{37}O_4N_2S$: 545.2474, obtained: 545.2498

(2*S*,3*S*)-2-Benzyloxyamino-3-(1-naphthyl)-pent-4-enoic acid (**1.37**)



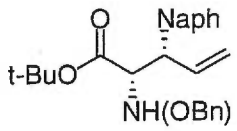
A solution of camphorsultam amide **1.36** (3.43 g, 6.31 mmol) and $LiOH{\cdot}H_2O$ (5.3 g, 126.0 mmol) in dry THF (200 ml) was refluxed for 18 h. The solution was cooled, concentrated in vacuo to remove all solvent (THF) and then partitioned between H_2O (600 ml) and DCM (50 ml). The aqueous layer was extracted repeatedly with DCM (40 ml portions) until there was no longer any indication of camphor sultam by TLC (DCM/MeOH, 10:1) in the DCM washings. The alkaline aqueous layer was acidified to pH 1-2 by adding 12N HCl dropwise and was subsequently extracted with DCM (3X100 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to yield an orange-yellow paste (1.35 g, 62%) that still contained 6% camphorsultam by weight (calculated from ^1H NMR integration), 1.27 g pure, 58% yield.

^{1}H NMR, (400 MHz, $CDCl_3$) : 4.23 (1H, d, *J* 8.5, C-2H), 4.47 (1H, t, *J* 8.3, C-3H), 4.60 and 4.66 (each 1H, d, *J* 11.6, OCH_2Ph), 5.16 (1H, d, *J* 10.6, C-$5H_{cis}$), 5.20 (1H, d, *J* 17.7, C-$5H_{trans}$), 6.14 (1H, ddd, *J* 17.0, 9.8, 8.4, C-4H), 7.20-7.54 (9H, m, ArH), 7.77 (1H, d, *J* 8.2, ArH), 7.87 (1H, d, *J* 7.4, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 44.35, 67.18, 76.31, 118.35, 122.68, 124.62, 125.29, 125.60, 126.26, 127.80, 127.97, 128.22, 128.49, 128.56, 128.70, 128.97, 131.33, 133.95, 134.66, 135.73, 136.62, 175.65

HRMS: calculated for $C_{22}H_{22}O_3N$: 348.1600, obtained: 348.1607

tert-Butyl (2*S*,3*S*)-2-Benzyloxyamino-3-(1-naphyhyl)-pent-4-enoate (**1.38**)



To a solution of amino acid **1.37** (1.3 g, 6% camphorsultam, 3.53 mmol) in dry DCM (12ml) was added t-butyl imidate (2.0 ml, 11.18 mmol) and the mixture was stirred at room temperature for 18h. The mixture was then concentrated in vacuo and chromatographed on silica gel eluting with hexanes-ethyl acetate (10:1) to afford the desired ester as a yellow oil (1.21 g, 85%).

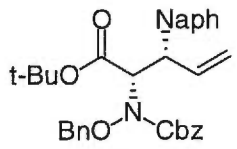
$[\alpha]_D$ +2.3 (1.49, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.40 (9H, s, CMe_3), 4.11 (1H,d, *J* 8.3, C-2H), 4.44 (1H, t, *J* 8.5, C-3H), 4.61 and 4.66 (each 1H, d, *J* 11.5, OCH_2Ph), 5.16 (1H, d, *J* 10.1, C-$5H_{cis}$), 5.21 (1H, d, *J* 17.0, C-$5H_{trans}$), 6.14 (1H, ddd, *J* 17.3, 9.6, 8.8, C-4H), 7.24-7.53 (9H, m, ArH), 7.76 (1H, d, *J* 8.0, ArH), 7.87 (1H, m, ArH), 8.08 (1H, d, *J* 7.6, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 27.55, 27.92, 44.76, 67.59, 76.01, 77.73, 81.62, 117.90, 122.97, 124.61, 125.21, 125.41, 126.03, 127.38, 127.38, 127.65, 128.09, 128.33, 128.52, 128.62, 128.86, 131.45, 133.91, 135.77, 136.14, 137.44, 142.32, 146.98, 171.55

HRMS: calculated for $C_{26}H_{30}O_0N$: 404.2226, obtained: 404.2215

tert-Butyl (2*S*,3*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-3-(1-naphthyl)-pent-4-enoate (**1.39**)



To a vigorously stirred emulsion of amino ester **1.38** (1.14 g, 2.33 mmol) in DCM (10 ml) and sat. aq. $NaHCO_3$ (20 ml) was added Cbz-Cl (4.04 ml, 28.3 mmol). After 7 h., an additional aliquot of Cbz-Cl (4 ml) and sat. aq. $NaHCO_3$ (10 ml) were added and the mixture was allowed to stir another 18 h. After partioning the mixture between DCM and H_2O, the aqueous phase was extracted with DCM (2X). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and chromatographed on silica gel eluting with hexanes-ethyl acetate (10:1) to yield a colorless oil (1.15 g, 92%).

$[\alpha]_D$ +8.4 (c 1.5, DCM)

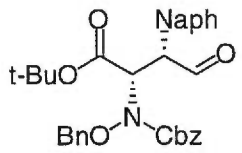
^1H NMR, (400 MHz, $CDCl_3$) : 1.5 (9H, s, CMe_3), 4.18 (1H, brd, *J* 9.0, C-3H), 4.63 (1H, d, *J* 9.6, C-2H), 5.04-5.21 and 5.29-5.34 (6H, m, OCH_2Ph, OCH_2Ph and C-$5H_2$), 6.17 (1H, ddd, *J* 17.6, 10.2, 7.6, C-4H), 7.03 (2H, d, *J* 6.7, ArH), 7.19-

7.52 (12H, m, ArH), 7.77 (1H, d, *J* 8.0, ArH), 7.86 (1H, d, *J* 8.0, ArH), 8.15 (1H, d, *J* 8.5, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 27.90, 42.96, 65.59, 67.83, 71.28, 82.19, 117.22, 123.30, 125.36, 125.92, 127.32, 127.87, 127.90, 128.06, 128.36, 128.45, 128.54, 128.65, 128.80, 128.98, 131.41, 133.99, 135.15, 135.64, 135.67, 137.88, 148.29, 157.69, 168.38

HRMS: calculated for $C_{34}H_{36}O_5N$: 538.2593, obtained: 538.2618

tert-Butyl (2*S*,3*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-3-(1-naphthyl)-4-oxo-butanoate (**1.40**)



To a rapidly stirring solution of olefin **1.39** (0.167 g, 0.31 mmol) in THF (1ml) and H_2O (0.75 ml) was added 6 drops of an OsO_4 solution followed by $NaIO_4$ (0.34 g, 1.55 mmol). The reaction was maintained at room temperature and additional $NaIO_4$ (~1.0 g) was added protionwise over 8 h. until virtually all starting material was gone by TLC (hexanes-ethyl acetate, 3:1) and all diol formed had been converted to aldehyde. The mixture was kept in the freezer for 16 h. at which point it was allowed to warm to room temperature and was partitioned between DCM and H_2O. The aqueous layer was further extracted with DCM (2X) and the combined organic extracts were washed with aq. Sodium thiosulfate, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was chromatographed on silica gel eluting with hexanes-ethyl acetate (4:1) to afford a colorless oil (0.105 g, 63%).

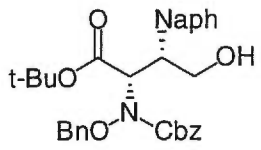
$[\alpha]_D$ –151.6 (c 1.10, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.47 (9H, s, CMe_3), 4.13 (1H, d, *J* 9.6, C-2H), 5.00 (2H, brs, OCH_2Ph), 5.37 and 5.68 (each 1H, d, *J* 10.2 and 10.8, OCH_2Ph), 7.03 (2H, br, ArH), 7.22-7.53 (12H, m, ArH), 7.82-7.90 (2H, m, ArH), 8.19 (1H, d, *J* 7.3, ArH), 9.81 (1H, d, *J* 1.6, CHO)

^{13}C NMR, (100 MHz, $CDCl_3$) : 25.50, 27.75, 63.43, 67.91, 82.97, 123.17, 125.35, 125.89, 126.68, 127.56, 127.89, 128.00, 128.07, 128.12, 128.36, 128.52, 128.87, 128.95, 132.32, 134.89, 135.40, 168.01, 195.90

HRMS: calculated for $C_{33}H_{34}O_6N$: 540.2386, obtained: 540.2403

tert-Butyl (2*S*,3*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-4-hydroxy-3-(1-naphthyl)-butanoate (**1.41**)



To a solution of aldehyde **1.40** (0.277 g, 0.514 mmol) in THF (10ml) at was added 1M $LiAl(Ot\text{-}Bu)_3H$ (0.7 ml, 0.7 mmol) dropwise and the solution was allowed to warm to –20 °C over 2 h. After cooling again to –50 °C, more reducing agent (0.3 ml, 0.3 mmol) was added and the temperature was increased to –5 °C at which point the reaction had reached completion by TLC (hexanes-ethyl acetate, 3:1). Sat. aq. NH_4Cl (6-7 drops) was added and the mixture was stirred for 0.5 h. followed by addition of DCM (10ml) and then filtration through medium frit sintered glass. The filtrate was

concentrated in vacuo to afford the alcohol as a viscous oil (0.265 g, 95%) that was suitable for use without further purification.

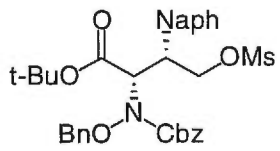
$[\alpha]_D$ - 0.20 (c 3.05, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.47 (9H, s, CMe_3), ~2.0-2.2 (1H, brs, OH), 3.96 (2H, br, C-4HH and C-3H), 4.09 (1H, dd, *J* 11.7, 4.1, C-4HH), 4.48 and 4.62 (each 1H, d, *J* 9.7, OCH_2Ph), 5.10 and 5.20 (each 1H, d, *J* 12.0, OCH_2Ph), 5.41 (1H, d, *J* 11.0, C-2H), 6.94 (2H, d, *J* 7.0, ArH), 7.15-7.52 (12H, m, ArH), 7.79 (1H, d, *J* 8.0, ArH). 7.89 (1H, m, ArH), 8.14 (1H, d, *J* 8.4, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 27.79, 40.69, 63.68, 64.68, 67.92, 77.05, 82.70, 122.83, 125.08, 125.52, 126.29, 127.53, 127.89, 127.95, 128.13, 128.40, 128.50, 128.98, 129.41, 131.59, 134.76, 135.05, 135.61, 158.03, 169.35

HRMS: calculated for $C_{33}H_{36}O_6N$: 542.2543, obtained: 542.2562

tert-Butyl (2*S*,3*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-4-methanesulfonyloxy-3-(1-naphthyl)-butanoate (**1.42**)



To a solution of alcohol **1.41** (0.386 g, 0.712 mmol) and pyridine (0.23 ml, 2.84 mmol) in DCM (10ml) at room temperature was added DMAP (~15 mg, cat.) followed by mesyl chloride (0.193 ml, 2.5 mmol), and the mixture was allowed to stir overnight. After the addition of sat. aq. $NaHCO_3$ (10 ml) the emulsion was stirred for an hour and then partitioned between DCM and H_2O. The aqueous layer was extracted with DCM (2X), the combined organic extracts were dried over Na_2SO_4 and then concentrated in vacuo. The crude residue was chromatographed on silica gel using 2% MeOH in DCM as eluant to yield a viscous oil (0.36 g, 80%).

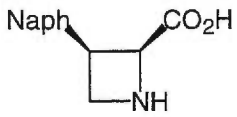
$[\alpha]_D$ –18.2 (c 0.62, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.45 (9H, s, CMe_3), 2.51 (3H, s, OSO_2CH_3), 4.01 and 4.50 (each 1H, d, *J* 9.6, OCH_2Ph), 4.57 (1H, dd, *J* 10.0, 2.7, C-3H or C-4HH), 4.79 (1H, d, *J* 6.2, C-4HH or C-3H), 4.87 (1H, dd, *J* 10.1, 5.2, C-4HH), 5.09 and 5.19 (each 1H, d, *J* 12.2, OCH_2Ph), 5.35 (1H, d, *J* 10.6, C-2H), 6.95 (2H, d, *J* 6.9, ArH), 7.16-7.54 (12H, m, ArH), 7.80 (1H, d, *J* 8.1, ArH), 7.88 (1H, m, ArH), 8.05 (1H, d, *J* 8.0, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 27.74, 29.59, 36.63, 37.76, 62.61, 68.07, 71.29, 82.96, 122.25, 125.00, 125.58, 126.22, 126.56, 127.94, 128.01, 128.07, 128.18, 128.41, 128.48, 129.13, 131.37, 132.94, 133.88, 134.85, 135.45, 157.82, 167.87

HRMS: calculated for $C_{34}H_{38}O_8NS$: 620.2318, obtained: 620.2291

(2*S*,3*R*)-3-(1-Naphthyl)-azetidine-2-carboxylic acid (**1.45**)



Palladium on charcoal (10%, ~250 mg) was added to a solution of mesylate **1.42** (0.287 g, 0.46 mmol) and methanesulfonic acid (0.029 ml, 0.45 mmol) in dry MeOH (25 ml) at room temperature. The mixture was saturated with H_2 gas under pressure (50 psi) and then stirred vigorously for 1.5 h. After filtration through a pad of celite, the filtrate was concentrated in vacuo to afford a white solid (0.22 g, quantitative) that still contained ~60 mol% excess methane sulfonic acid. A portion of the crude mesylate salt (0.076 g, 0.160 mmol) and $NaHCO_3$ (0.0156 g, 0.186 mmol) were dissolved in MeOH (25 ml) and H_2O (1.7 ml) and refluxed for 1.25 h. The mixture was cooled, concentrated in vacuo to near-dryness, and triturated with ethanol-DCM (~3:4 ml) to precipitate out sodium mesylate. The filtrate was concentrated in vacuo to yield a clear solid residue (0.058 g, 95%) that was taken to the next step without further purification. The crude t-butyl (2S,3R)-3-(1-naphthyl)-azetidine-2-carboxylate (0.058 g) was stirred in 2.75 M HCl (10ml and 3 ml 12N HCl) at room temperature for 5 h. The solution was then decanted, the flask rinsed with H_2O (5ml) and the clear filtrate was concentrated in vacuo. The residue was heated to reflux with H_2O (~10ml) and 12N HCl (3 drops) which precipitated/crystallized out ~20 mg of purified material. After hot filtration (~15 ml H_2O, ~5 drops HCl) to remove insoluble solids, the solution was cooled to yield colorless crystals (0.011 g, 30%).

M.P. ~245-255 °C (dec.)

$[\alpha]_D$ +335 (c 0.14, 2N HCl)

^{1}H NMR, (400 MHz, DCl/D_2O) : 3.57 and 3.97 (each 1H, t, *J* 10,1, C-4H_2), 4.46 (1H, dt, *J* 19.0, 9.5, C-3H), 4.66 (1H, d, *J* 9.9, C-2H)

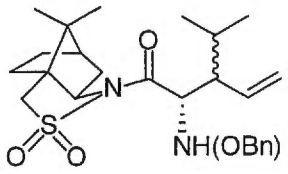
IR (KBr): 3130.6, 3040.0, 1723.0, 1541.9, 1510.2, 1437.7 cm^{-1}

HRMS: calculated for $C_{14}H_{14}O_2N$: 228.1025, obtained: 228.1020

single crystal X-ray

Syn :(1*S*)-2,10-Camphorsultamyl (2*S*,3*S*)-2-benzyloxyamino-3-isopropyl-pent-4-enoate (**1.46**)

Anti : :(1*S*)-2,10-Camphorsultamyl (2*S*,3*R*)-2-benzyloxyamino-3-isopropyl-pent-4-enoate (**1.47**)



To a vigorously stirred solution of camphor sultam oxime **1.15** (1.54 g, 4.08 mmol.) and (3-isopropyl)allyl bromide (2.66 g, 16.3 mmol.) in THF (50ml) and sat. aq. NH_4Cl at 0 oC was added Zn powder (1.2 g, 18.4 mmol) portionwise as it reacted. The mixture was allowed to to reach room temperature and was stirred for 18 h. at which point it was partitioned between DCM and H_2O. The aqueous layer was extracted with DCM(3X) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Chromatography on silica gel eluting with hexanes-ethyl acetate (4:1) afforded a very viscous oil (1.68 g, 89%) that indicated a mixture (~1:1) of inseparable diastereomers by NMR.

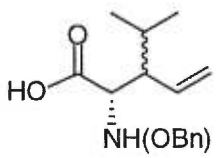
^{1}H NMR, (400 MHz, $CDCl_3$) : (~1:1 mixture of diastereomers), 0.77 and 0.84 (each 3H, d, *J* 6.9, $CH(\underline{CH_3})_2$), 0.83 and 0.96 (each 3H, d, *J* 6.7, $C'H(CH_3)_2$), 0.96 and 0.97 (each 3H, s, camphor CH_3), 1.16 and 1.17 (each 3H, s, camphor' CH_3), 1.33-1.44 (4H, m, 2X camphor CH_2), 1.78-2.22 (14H, 3 multiplets, 2X 5 camphor H, 2X C-3H, 2X $C\underline{H}(Me)_2$), 3.48 (2H, s, $C'H_2SO_2$), 3.49 (2H, d, *J* 1.3, CH_2SO_2), 3.96-3.99 (2H, m, 2X camphor CHN), 4.47 (1H, brd, *J* 9.9, C'-2H), 4.58-5.07 (8H, overlapping multiplets, 2X C-$5H_2$, 2X OCH_2Ph, 1X C-2H), 5.38 (1H, ddd, *J* 27.3, 16.9, 10.3, C'-4H), 5.78 (1H, ddd, *J* 27.1, 16.9, 10.2, C-4H), 7.25-7.40 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : (~1:1 mixture of diastereomers) : 16.15, 19.79, 19.90, 20.12, 20.57, 20.68, 21.04, 21.08, 26.30, 26.36, 27.47, 28.88, 32.68, 32.82, 37.59, 38.54, 44.43, 44.51, 47.54, 47.60, 48.00, 48.40, 52.24, 52.89, 52.94, 53.11, 63.32, 64.87, 65.00, 65.02, 65.28, 75.57, 75.71, 75.76, 77.15, 118.12, 119.25, 127.41, 127.47, 127.98, 128.05, 128.54, 128.68, 133.74, 135.62, 137.87, 138.01, 172.99, 174.49

HRMS: calculated for $C_{25}H_{37}O_4N_2S$: 461.2474, obtained: 461.2466

Syn : (2*S*,3*S*)-2-Benzyloxyamino-3-isopropyl-pent-4-enoic acid (**1.48**)

Anti : (2*S*,3*R*)-2-Benzyloxyamino-3-isopropyl-pent-4-enoic acid (**1.49**)



A solution of camphorsultam amide diastereomers **1.46/1.47** (1.55 g, 3.37 mmol) and $LiOH.H_2O$ (0.71 g, 17.0 mmol) in THF (75ml) was refluxed for 18h. After confirming that there was no more starting material by TLC (hexanes-ethyl acetate, 3:1), the mixture was cooled and concentrated in vacuo to remove all solvent. The residue was partitioned between H_2O (200 ml) and DCM (~30 ml) and the aqueous layer was extracted repeatedly with DCM (~25 ml portions) until there was no longer any indication of camphor sultam by TLC (DCM/MeOH, 10:1) in the DCM washings. At that point, the alkaline aqueous layer was acidified to pH 1-2 using 12N HCl added dropwise and the product was extracted with DCM(3X). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford a yellow paste (0.756 g, 86%) that was used for the next step without further purification.

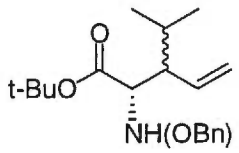
^1H NMR, (400 MHz, $CDCl_3$) : (~1:1 mixture of diastereomers) 0.77 and 0.86 (each 3H, d, *J* 6.8, $CH(\underline{CH_3})_2$), 0.88 and 0.89 (each 3H, d, *J* 6.7, $C'H(\underline{CH_3})_2$), 1.76-1.87 (2H, m, 2X $\underline{CH}Me_2$), 1.98 and 2.10 (each 1H, m, 2X C-3H), 3.73 (1H, d, *J* 7.6, C'-2H), 3.82 (1H, d, *J* 6.6, C-2H), 4.71 (4H, s, 2X OCH_2Ph), 4.99-5.04 (2H, m, C'-$5H_2$), 5.08-5.13 (2H, m, C-$5H_2$), 5.42-5.58 (2H, m, 2X C-4H), 7.26-7.38 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : (~1:1 mixture of diastereomers) 18.30, 18.98, 20.80, 20.89, 27.67, 28.33, 32.23, 51.11, 51.49, 64.55, 65.41, 76.02, 76.20, 77.15, 119.06, 119.11, 120.37, 127.81, 128.22, 128.56, 134.10, 134.59, 137.24, 137.34, 178.79, 178.93

HRMS: calculated for $C_{15}H_{22}O_3N$: 264.1600, obtained: 264.1602

Syn : tert-Butyl (2*S*,3*S*)-2-benzyloxyamino-3-isopropyl-pent-4-enoate (**1.50**)

Anti : tert-Butyl (2*S*,3*R*)-2-benzyloxyamino-3-isopropyl-pent-4-enoate (**1.51**)



A solution of amino acids **1.48/1.49** (0.687 g, 2.62 mmol.) and t-butyl imidate (0.94 g, 5.24 mmol.) in dry DCM (15 ml) was allowed to stir at room temperature for 18h. Another aliquot of t-butyl imidate (0.45 ml., 2.51 mmol.) was then added and the mixture was concentrated by passing a stream of nitrogen through the flask over 4h. until the reaction was virtually complete by TLC (hexanes-ethyl acetate, 3:1). At this point the mixture was concentrated in vacuo to dryness and the residue was chromatographed on silica gel eluting with hexanes-ethyl acetate (10:1) to yield the desired product as a colorless oil (0.666 g, 80%).

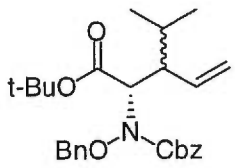
^{1}H NMR, (400 MHz, $CDCl_3$) : (~1:1 mixture of diastereomers) 0.78 and 0.85 (each 3H, d, *J* 6.8, $CH(\underline{CH_3})_2$), 0.88 and 0.89 (each 3H, d, *J* 6.7, $C'H(\underline{CH_3})_2$), 1.46 and 1.49 (each 9H, s, $C(CH_3)_3$) 1.73-1.83 (2H, m, 2X $\underline{CH}Me_2$), 1.93-2.07 (2H, m, 2X C-3H), 3.60 (1H, d, *J* 7.9, C'-2H), 3.67 (1H, d, *J* 6.9, C-2H), 4.70 (2H, s, $OC'H_2Ph$), 4.71 (2H, s, OCH_2Ph), 4.95-5.03 (2H, m, C'-$5H_2$), 5.07-5.12 (2H, m, C-$5H_2$), 5.41-5.57 (2H, m, 2X C-4H), 7.26-7.35 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : (~1:1 mixture of diastereomers) 18.18, 18.72, 20.82, 20.94, 22.83, 27.70, 28.04, 28.26, 51.16, 51.62, 64.81, 65.78, 75.68, 75.90, 81.12, 81.26, 118.33, 118.57, 127.54, 128.07, 128.26, 128.34, 134.54, 135.14, 137.79, 172.23, 172.63

HRMS: calculated for $C_{19}H_{30}O_3N$: 320.2226, obtained: 320.2236

Syn : tert-Butyl (2*S*,3*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-3-isopropyl-pent-4-enoate (**1.52**)

Anti : tert-Butyl (2*S*,3*R*)-2-[(benzyloxy)benzyloxycarbonylamino]-3-isopropyl-pent-4-enoate (**1.53**)



A mixture of amino esters **1.50/1.51** (0.254 g, 0.798 mmol.) and Cbz-Cl (0.6 ml., 4.0 mmol.) in DCM (5 ml.) and sat. aq. $NaHCO_3$ (10 ml.) was stirred vigorously at room temperature for 8h. More Cbz-Cl (0.6 ml.) was added and the emulsion was allowed to stir an additional 48h. until there was virtually no more starting material visible by TLC (hexanes-ethyl acetate, 4:1). The mixture was partitioned between DCM and H_2O and the aqueous layer was extracted with DCM (2X). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and chromatographed on silica gel eluting with hexanes-ethyl acetate (15:1) to yield a viscous oil (0.331 g, 91%)

^{1}H NMR, (400 MHz, $CDCl_3$) : (~1:1 mixture of diastereomers) 0.75 and 0.92 (each 3H, d, *J* 6.8, $CH(\underline{CH_3})_2$), 0.83 and 0.85 (each 3H, d, *J* 7.2, $C'H(\underline{CH_3})_2$), 1.42 and 1.46 (each 9H, s, $C(CH_3)_3$) 1.78-1.94 (2H, m, 2X $\underline{CH}Me_2$), 2.73-2.82 (2H, m, 2X C-3H), 4.64 (1H, d, *J* 10.8, C'-2H), 4.78 (1H, d, *J* 9.9, C-2H), 4.91-5.26 (12H, m, 2X C-$5H_2$, 4X OCH_2Ph), 5.60-5.68 (2H, m, 2X C-4H), 7.30-7.43 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : (~1:1 mixture of diastereomers) 16 15, 17.64, 21.12, 21.44, 22.27, 26.99, 27.85, 27.95, 48.49, 49.74, 64.39, 67.83, 67.97, 69.60, 73.31, 77.68, 81.62, 81.68, 118.95, 119.00, 128.03, 128.09, 128.11, 128.16, 128.36, 128.39, 128.46, 128.71, 128.79, 128.86, 128.92, 129.23, 133.86, 135.19, 135.37, 135.51, 135.77, 135.85, 157.23, 168.68, 168.84

HRMS: calculated for $C_{27}H_{36}O_5N$: 454.2593, obtained: 454.2579

Syn : tert-Butyl (2*S*,3*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-3-isopropyl-4-oxo-butanoate (**1.54**)

Anti : tert-Butyl (2*S*,3*R*)-2-[(benzyloxy)benzyloxycarbonylamino]-3-isopropyl-4-oxo-butanoate (**1.55**)

A stream of ozone in oxygen was bubbled through a solution of olefins **1.52/1.53** (0.303 g, 0.67 mmol.) in MeOH (10 ml.) and DCM (10 ml.) at –78 °C until a blue color persisted. A TLC (hexanes-ethyl acetate, 3:1) confirmed that all starting material had been consumed. The blue color was discharged with a stream of oxygen that was bubbled through for 15 min. Subsequently, DMS (~20 ml, excess) was added in 3 portions over 2h. while the solution was allowed to warm to from –70 °C to 5 °C. The mixture was concentrated in vacuo and chromatographed on silica gel eluting with hexanes-ethyl acetate (13:1) to afford the 2 diastereomers as clear viscous oils (syn: 0.114 g, 37%, anti: 0.10 g, 33%, total yield 70%).

Syn : $[\alpha]_D$ – 81.4 (c 0.63, DCM)

Anti : $[\alpha]_D$ – 4.9 (c 0.65, DCM)

Syn :

^{1}H NMR, (400 MHz, $CDCl_3$) : 0.88 and 1.09 (each 3H, d, *J* 7.0, $CH(C\underline{H}_3)_3$), 1.38 (9H, s, CMe_3), 2.11 (1H, m, $C\underline{H}Me_2$), 3.07 (1H, ddd, *J* 10.3, 4.0, 2.5, C-3H), 4.86 and 4.98 (each 1H, d, *J* 9.8, OCH_2Ph), 5.05 (1H, d, *J* 10.3, C-2H), 5.24 and 5.29 (each 1H, d, *J* 12.2, OCH_2Ph), 7.29-7.42 (10H, m, ArH), 9.85 (1H, d, *J* 2.4, CHO)

^{13}C NMR, (100 MHz, $CDCl_3$) : 17.29, 21.24, 27.33, 27.65, 54.95, 62.42, 68.23, 77.67, 82.68, 128.16, 128.27, 128.39, 128.46, 128.82, 134.97, 135.48, 157.54, 168.03, 202.14

Anti :

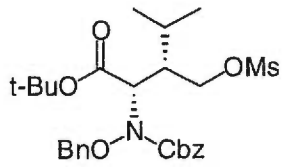
^{1}H NMR, (400 MHz, $CDCl_3$) : 1.01 and 1.06 (each 3H, d, *J* 6.8, $CH(C\underline{H}_3)_2$), 1.48 (9H, s, CMe_3), 2.12 (1H, m, $C\underline{H}Me_2$), 2.77 (1H, ddd, *J* 10.5, 5.9, 2.0, C-3H), 4.80 and 4.97 (each 1H, d, *J* 9.2, OCH_2Ph), 5.09 (1H, brd, *J* 5.3, C-2H), 5.27 (2H, s, OCH_2Ph), 7.30-7.43 (10H, m, ArH), 9.64 (1H, d, *J* 1.7, CHO)

^{13}C NMR, (100 MHz, $CDCl_3$) : 20.44, 20.58, 25.76, 27.80, 29.59, 56.48, 62.97, 68.35, 82.70, 128.20, 128.23, 128.34, 128.39, 128.49, 129.51, 134.59, 135.43, 157.08, 168.33, 201.69

HRMS: <u>syn</u>: calculated for $C_{26}H_{34}O_6N$: 456.2386, obtained: 456.2377

<u>anti</u>: calculated for $C_{26}H_{34}O_6N$: 456.2386, obtained: 456.2367

tert-Butyl (2*S*,3*S*)-2-[(benzyloxy)benzyloxycarbonylamino]-3-isopropyl-4-methanesulfonyloxy-butanoate (**1.56**)



To a solution of syn aldehyde **1.54** (0.058 g, 0.127 mmol.) in DCM (2 ml.) at –40 °C, was added a 1N $LiAl(Ot\text{-}Bu)_3H$ solution (0.65 ml, 0.65 mmol.) in 3 portions over 2 h.; each time adding the reducing agent at –40 °C and letting the solution warm to –15 °C. When the starting material was virtually gone by TLC (2% MeOH in DCM), the mixture was warmed to –10 °C and DCM (1ml) was added followed by sat. aq. NH_4Cl (5 drops). The mixture was stirred vigorously for 10-15 min. maintaining the bath temperature at ~ -5 °C to avoid lactonization. Subsequently, the solution was filtered quickly through medium sintered glass and transferred immediately to a cold bath at –5 °C under a nitrogen atmosphere. A strong stream of nitrogen was passed through the flask to concentrate the solution to a volume of ~1 ml. at which point pyridine (0.5 ml, 6.18 mmol), DMAP (5 mg, cat.) and then mesyl chloride (0.25 ml, 3.23 mmol) were added and the mixture was allowed to stir at 0 °C for 2h. For an additional hour, the mixture was allowed to stir at room temperature.

Sat. aq. $NaHCO_3$ (~3 ml) was added and the solution was stirred vigorously for ~1 h. until no more gas evolved. The emulsion was partitioned between DCM and H_2O, and the aqueous was extracted with DCM (3X). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo, and the excess pyridine was azeotroped with toluene (3X10 ml). The residue was dissolved in toluene, filtered through a cotton

plug and the filtrate was concentrated in vacuo to yield a viscous oil (0.061 g, 90%) that needed no further purification.

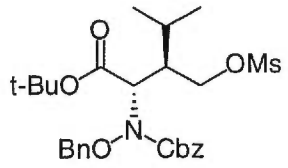
$[\alpha]_D$ –24.35 (c 1.08, DCM)

^{1}H NMR, d_H (400 MHz, $CDCl_3$) : 0.89 and 0.97 (each 3H, d, *J* 6.9, $CH(C\underline{H}_3)_2$), 1.44 (9H, s, CMe_3), 2.01 (1H, m, $C\underline{H}Me_2$), 2.34 (1H, m, C-3H), 2.87 (3H, s, OSO_2CH_3), 4.38 (1H, dd, *J* 10.1, 5.2, C-4H$\underline{H}$), 4.71 (1H, d, *J* 8.5, C-2H), 4.89 and 5.03 (each 1H, d, *J* 9.7, OCH_2Ph), 5.26 (2H, s, OCH_2Ph), 7.31-7.42 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 17.86, 20.96, 27.06, 27.73, 27.74, 36.76, 42.92, 62.36, 67.82, 68.35, 77.84, 82.53, 128.17, 128.27, 128.28, 128.31, 128.34, 128.42, 128.46, 128.50, 128.94, 129.37, 134.98, 135.50, 157.51, 168.07

HRMS: calculated for $C_{27}H_{38}O_8NS$: 536.2318, obtained: 536.2337

tert-Butyl (2*S*,3*R*)-2-[(benzyloxy)benzyloxycarbonylamino]-3-isopropyl-4-methanesulfonyloxy-butanoate (**1.57**)



To a solution of anti aldehyde **1.55** (0.08 g, 0.176 mmol.) in DCM (4 ml.) at –40 °C was added a 1N $LiAl(Ot\text{-}Bu)_3H$ solution (1.25 ml, 1.25 mmol) in 4-5 portions over 2.5 h.: each time adding a portion at –40 °C and letting the solution warm to –15 °C. When the starting material had been completely consumed, the mixture was worked up in the same manner as for the syn compound, using the same quantities.

To a cold (-5 °C) solution of the anti alcohol in DCM (1-2 ml after concentration with a stream of nitrogen) was added pyridine (0.6 ml, 7.4 mmol), DMAP (5 mg, cat.) and then mesyl chloride (0.35 ml, 4.52 mmol).The mixture was allowed to stir at 0 °C for 2 h. and then at room temperature for an additional hour at which point the work-up was the same as for the syn mesylate. Concentration of the final filtrate in vacuo afforded the desired product as a viscous oil (0.083 g, 88%).

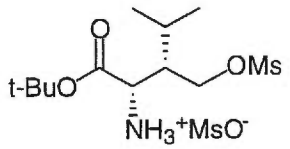
$[\alpha]_D$ –20.0 (c 0.54, DCM)

^{1}H NMR, (400 MHz, $CDCl_3$) : 0.98 and 1.02 (each 3H, d, *J* 6.9, $CH(C\underline{H}_3)_2$), 1.47 (9H, s, CMe_3), 1.87 (1H, m, $C\underline{H}Me_2$), 2.44 (1H, ddd, *J* 10.2, 5.7, 2.3, C-3H), 2.78 (3H, s, OSO_2CH_3), 4.20 (1H, dd, *J* 10.3, 5.6, C-4$\underline{H}$H), 4.30 (1H, dd, *J* 10.3, 3.4, C-4H$\underline{H}$), 4.84 (1H, d, *J* 7.8, C-2H), 4.93 and 5.06 (each 1H, d, *J* 9.3, OCH_2Ph), 5.24 and 5.28 (each 1H, d, *J* 12.1, OCH_2Ph), 7.31-7.44 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 18.81, 21.13, 27.75, 27.91, 36.74, 43.53, 62.70, 68.35, 68.46, 77.70, 82.57, 128.25, 128.33, 128.49, 128.53, 129.26, 134.77, 135.48, 157.15, 168.42

HRMS: calculated for $C_{27}H_{38}O_8NS$: 536.2318, obtained: 536.2337

tert-Butyl (2*S*,3*S*)-2-amino-3-isopropyl-4-methanesulfonyloxy-butanoate Methanesulfonate salt (**1.58**)



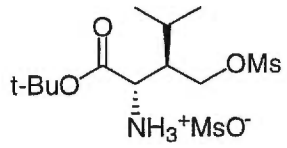
To a solution of syn mesylate **1.56** (0.06 g, 0.11 mmol) and methanesulfonic acid (7.1 microl., 0.11 mmol) in dry MeOH (8 ml) and DCM (2 ml) was added 10% Pd/C (~25 mg). The mixture was saturated with H_2 gas under pressure (45 psi) and allowed to stir for 3 h. Subsequently it was filtered through a pad of celite and the filtrate was concentrated in vacuo to yield the mesylate salt as a white solid (0.042 g, 97%) that was suitable for use without further purification.

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.07 and 1.15 (each 3H, d, *J* 6.4, $CH(C\underline{H}_3)_2$), 1.55 (9H, d, CMe_3), 1.98-2.14 (2H, s, $C\underline{H}Me_2$ and C-3H), 2.71 (3H, s, $CH_3SO_3^-$ counterion), 3.13 (3H, s, OSO_2CH_3), 4.19 (1H, d, *J* 3.4, C-2H), 4.37-4.46 (2H, m, C-4H_2), 4.89 (3H, br, NH_3^+)

^{13}C NMR, (100 MHz, $CDCl_3$) : 20.31, 21.53, 27.42, 28.19, 37.12, 39.49, 47.55, 54.16, 67.72, 85.99

HRMS: calculated for $C_{12}H_{26}O_5NS$ (cation): 296.1532, obtained: 296.1522

tert-Butyl (2*S*,3*R*)-2-amino-3-isopropyl-4-methanesulfonyloxy-butanoate Methanesulfonate salt (**1.59**)



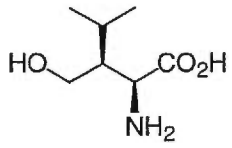
To a solution of anti mesylate **1.57** (0.06 g, 0.11 mmol) and methanesulfonic acid (7.1 microl., 0.11 mmol) in dry MeOH (8 ml) and DCM (2 ml) was added 10% Pd/C (~25 mg). The same protocol was followed as for the syn mesylate to afford the anti mesylate salt as a white solid (0.041 g, 95%).

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.04 and 1.12 (each 3H, d, *J* 6.7, $CH(C\underline{H}_3)_2$), 1.56 (9H, s, CMe_3), 1.97 (1H, m, $C\underline{H}Me_2$), 2.28 (1H, m, C-3H), 2.71 (3H, s, $CH_3SO_3^-$ counterion), 3.17 (3H, s, OSO_2CH_3), 4.21 (1H, d, *J* 3.7, C-2H), 4.36-4.47 (2H, m, C-$4H_2$), 4.88 (3H, br, NH_3^+)

^{13}C NMR, (100 MHz, $CDCl_3$) : 19.38, 21.92, 26.90, 28.14, 37.22, 39.49, 46.73, 54.58, 68.03, 86.17, 168.90

HRMS: calculated for $C_{12}H_{26}O_5NS$ (cation): 296.1532, obtained: 296.1528

(2*S*,3*S*)-2-Amino-4-hydroxy-3-isopropyl-butanoic acid (**1.62**)



To a solution of syn mesylate salt **1.58** (44 mg, 0.108 mmol) in MeOH (20 ml) and H_2O (1.5 ml) was added $NaHCO_3$ (11 mg, 0.131 mmol) and the mixture was heated to reflux for 1.5 h. After cooling the solution was concentrated in vacuo and the H_2O was azeotroped with ethanol (2X10 ml). The resulting residue was triturated with ethanol/DCM (1:3, ~10 ml) and the precipitate was filtered off then washed with DCM (2X5 ml). The filtrate was concentrated in vacuo and the crude intermediate was set to stir with 2N HCl (~12 ml) at r.t. for 12 h. The solution was decanted, concentrated in vacuo, azeotroping the HCl with H_2O repeatedly and then passed through dowex $50H^+$ eluting with 5% NH_4OH. The resulting crude was redissolved in H_2O and filtered to remove insoluble solids and finally triturated with minimal IPA (2-3X) to afford the product as a white solid (7.8 mg, 45%).

M.P 175-178 °C

$[\alpha]_D$ +24.0 (c 0.15, H_2O)

^{1}H NMR (400 MHz, D_2O) : 0.94 and 0.99 (each 3H, d, *J* 6.6, $CH(\underline{CH_3})_2$), 1.81 (1H, m, $C\underline{H}Me_2$), 1.90 (1H, m, C-3H), 3.69 (1H, dd, *J* 11.4, 7.8, C-4H'), 3.86 (1H, dd, *J* 11.5, 3.8, C-4H), 3.96 (1H, d, *J* 2.2, C-2H)

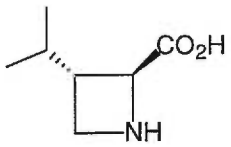
^{13}C NMR (100 MHz, D_2O) : 20.61, 21.58, 26.37, 47.89, 57.25, 62.62, 174.93

IR (KBr): 3411.3, 3184.9, 1614.3, 1410.6 cm^{-1}

HRMS: calculated for $C_7H_{16}O_3N$: 162.1130, obtained: 162.1135

single crystal X-ray

(2*S*,3*S*)-3-Isopropyl-azetidine-2-carboxylic acid (**1.63**)



To a solution of mesylate salt **1.59** (42 mg, 0.103 mmol) in MeOH (20 ml) and H_2O (1.2 ml) was added $NaHCO_3$ (10 mg, 0.12 mmol) and the mixture was heated to reflux for 1.0 h. After cooling the solution was concentrated in vacuo and the H_2O was azeotroped with ethanol (2X10 ml). The same protocol was followed as for the syn compound. The crude intermediate was set to stir with 1.5N HCl (6 ml) at r.t. for 12 h. The same protocol was followed to yield a crude that was redissolved and filtered to remove insoluble solids and then triturated with minimal IPA (2-3X) to afford the desired product as a white solid (3.6 mg, 26%).

M.P 188-191 °C (dec.)

$[\alpha]_D$ -9.5 (c 0.11, H_2O)

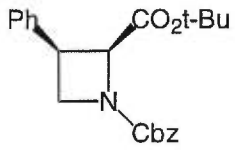
^1H NMR (400 MHz, D_2O) : 0.88 and 0.95 (each 3H, d, *J* 6.7, $CH(\underline{CH_3})_2$), 1.92 (1H, m, $C\underline{H}Me_2$), 2.56 (1H, m, C-3H), 3.78 (1H, t, *J* 9.0, C-4H'), 4.00 (1H, t, *J* 10.0, C-4H), 4.45 (1H, d, *J* 7.3, C-2H)

^{13}C NMR (100 MHz, D_2O) : 18.66, 19.15, 32.02, 44.94, 47.53, 64.35, 174.56

IR (KBr): 3094.3, 1618.9, 1415.1 cm^{-1}

HRMS: calculated for $C_7H_{14}O_2N$: 144.1025, obtained: 144.1020

tert-Butyl (2*S*,3*R*)-N-benzyloxycarbonyl-3-phenyl-azetidine-2-carboxylate (**1.35a**)



A mixture of (2*S*,3*R*)-3-phenyl-azetidine-2-carboxylic acid **1.35** (0.05 g, 0.282 mmol) and Cbz-Cl (0.16 ml, 1.13 mmol) in H_2O (~2ml) and sat. aq. $NaHCO_3$ (~2ml) was allowed to stir vigorously for 18 h. Subsequently, the solution was acidified to pH 1-2 using 2N HCl and then partitioned between H_2O and DCM. The aqueous layer was extracted with DCM (3X) and the combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and then chromatographed on silica gel using 5% MeOH in DCM as eluant. The resulting residue (50 mg) was dried thoroughly and combined with t-butyl imidate (0.09 ml, 0.48 mmol) in DCM (1.5 ml) and allowed to stir for 4 h. The mixture was concentrated in vacuo followed by chromatography on silica gel using a gradient of hexanes-ethyl acetate (10:1 to 5:1) to afford the desired product as a white solid (0.038 g, 37%).

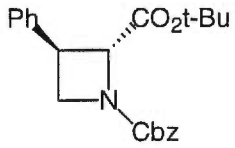
$[a]_D$ +12.2 (c 0.09, $CHCl_3$)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.00 (9H, s, $C(CH_3)_3$), 4.14 (1H, m, C-3H), 4.26 (1H, t, *J* 8.5, C-4HH), 4.42 (1H, t, *J* 7.6, C-4HH), 4.90 (1H, d, *J* 9.4, C-2H), 5.11 and 5.19 (each 1H, d, *J* 12.2, OCH_2Ph), 7.24-7.35 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 27.31, 37.35, 66.78, 77.09, 81.36, 127.49, 127.86, 128.25, 128.29, 132.79, 133.11, 133.43, 136.30, 155.99, 167.06

HRMS: calculated for $C_{22}H_{26}O_4N$: 368.1862, obtained: 368.1846

tert-Butyl (2*R*,3*R*)-N-benzyloxycarbonyl-3-phenyl-azetidine-2-carboxylate (**1.35b**)



To a solution of azetidine **1.35a** (0.0194 g, 0.053 mmol) in THF (2 ml) at –78 °C was added LiHMDS (1M solution, 0.045 ml, 0.045 mmol) and the mixture was allowed to stir for 2h. (bath temperature rose to –60 °C from time to time). At –78 °C, H_2O (0.1 ml) followed by sat. aq. NH_4Cl (0.1 ml) were added and the solution was warmed to 0 °C. The mixture was partitioned between DCM and H_2O, the aqueous layer was extracted with DCM (3X) and the combined organic extracts were dried over Na_2SO_4 and then concentrated in vacuo. The residue (18.5 mg) needed no further purification and, by NMR, showed a ratio of 67:33 for the anti/syn diastereomers. Separation by chromatography on silica gel eluting with hexanes-ethyl acetate (4:1) afforded anti diastereomer **1.35b** as a viscous oil (0.0105 g, 54%) followed by recovery of syn diastereomer **1.35a** as a viscous oil (0.0058 g, 30%).

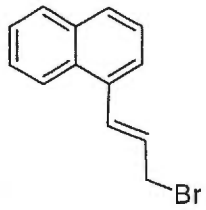
$[\alpha]_D$ -14.5 (c 0.53, $CHCl_3$)

^{1}H NMR, (400 MHz, $CDCl_3$) : 1.47 (9H, s, $C(CH_3)_3$), 3.68 (1H, dd, *J* 8.6, 5.6, C-3H), 4.05 (1H, dd, *J* 8.2, 5.7 C-4HH), 4.46 (1H, t, *J* 8.4, C-4HH), 4.59 (1H, d, *J* 5.3, C-2H), 5.12 and 5.17 (each 1H, d, *J* 12.4, OCH_2Ph), 7.28-7.40 (10H, m, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 27.84, 38.76, 66.82, 81.91, 126.58, 127.37, 127.81, 127.91, 128.31, 128.75, 136.21, 139.98, 155.80, 169.42

HRMS: calculated for $C_{22}H_{26}O_4N$: 368.1862, obtained: 368.1854

1-Bromo-3-(1-naphthyl)-prop-2-ene (**1.23a**)



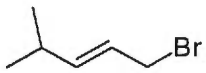
To a solution of the preceding allyl alcohol (9.6 g, 52.7 mmol) in dry DCM (150 ml) at –40 °C, was added PPh_3 (25.3 g, 96.7 mmol) and the mixture was stirred under a nitrogen atmosphere until all solids dissolved. After cooling the solution further to –50 °C, NBS (16.0 g, 90.0 mmol) was added in one portion and the mixture was allowed to stir under N_2 until it warmed to 0 °C. The mixture was concentrated in vacuo to ~ 0.5 of its initial volume, added to a separatory funnel and diluted with ether (~450 ml). The organic mixture was extracted vigorously with sat. aq. $NaHCO_3$ (2X50 ml) and then with aq. sodium thiosulfate (1X50 ml). The organic layer was dried over $MgSO_4$, concentrated in vacuo and the residue was triturated repeatedly with an ether-hexane mixture (~1:1). Each time, the solid that precipitated out was filtered off, the filtrate was concentrated in vacuo and then the process was repeated several times. The final filtrate was concentrated in vacuo to yield a yellowish-brown solid (12.2 g, 94%) that (by NMR) contained traces of PPh_3 and/or PPh_3=O.

^{1}H NMR, (400 MHz, $CDCl_3$) : 4.27 and 4.29 (each 1H, dd, *J* 7.8, 1.2, C-1H_2), 6.42-6.50 (2H, m, C-2H and C-3H), 7.41-7.60 (3H, m, ArH), 7.64 (1H, d, J 7.2, ArH), 7.84 (1H, d, *J* 7.8, ArH), 7.90 (1H, m, ArH), 8.13 (1H, d, *J* 7.7, ArH)

^{13}C NMR, (100 MHz, $CDCl_3$) : 33.46, 123.46, 124.24, 125.51, 125.88, 126.26, 128.19, 128.44, 128.59, 128.63, 131.00, 131.49, 131.99

HRMS: calculated for $C_{13}H_{11}{}^{79}Br$: 246.0044, obtained: 246.0038

1-Bromo-4-methyl-pent-2-ene (**1.23**)



To a solution of the preceding allyl alcohol (6.4 g, 63.9 mmol) in dry DCM (60 ml) at –30 °C was added PPh_3 (17.9 g, 68.4 mmol) and the mixture was stirred under a N_2 atmosphere until all solid dissolved. After cooling the solution to –45 °C, NBS (11.8 g, 66.1 mmol) was added in one portion and stirred under N_2 until it warmed to ~5 °C. The mixture was added to a separatory funnel, diluted with ether (~150 ml) and then extracted vigorously with sat. aq. $NaHCO_3$ (2X50 ml) and then with aq. sodium thiosulfate (1X50 ml). The ether layer was dried over $MgSO_4$, concentrated in vacuo (without water bath) keeping temperature below 10 °C, and the residue was triturated repeatedly with pentane. The precipitate obtained was filtered off, the filtrate was concentrated in vacuo(cold) and the process was repeated several times. The final filtrate was concentrated again to yield a slightly brownish liquid (6.8 g, 65%) that(by NMR) still contained traces of PPh_3 and/or PPh_3=O.

^{1}H NMR, (400 MHz, $CDCl_3$) : 0.98 and 1.00 (each 3H, s, $CH(\underline{CH_3})_2$), 2.32 (1H, m, $CHMe_2$), 3.93 and 3.95 (each 1H, dd, *J* 0.5, 6.8, C-1H_2), 5.63 (1H, m, C-2H), 5.73 (1H, dd, *J* 15.2, 6.3, C-3H)

^{13}C NMR, (100 MHz, $CDCl_3$) : 21.80, 30.53, 33.64, 123.41, 143.11

CRYSTAL AND MOLECULAR STRUCTURE OF
C10 H11 N O2 COMPOUND (HAN224)

Equipe HANESSIAN

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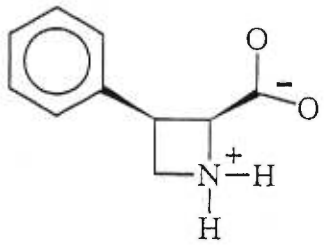


Structure résolue au laboratoire de diffraction des rayons X de l'Université de Montréal par Dr. Michel Simard.

Table 1. Crystal data and structure refinement for C10 H11 N O2.

Identification code	HAN224
Empirical formula	C10 H11 N O2
Formula weight	177.198
Temperature	293(2)K
Wavelength	1.54056Å
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 5.714(2)Å α = 90° b = 5.2950(11)Å β = 92.05(3)° c = 14.196(5)Å γ = 90°
Volume	429.2(2)Å^3
Z	2
Density (calculated)	1.3710 Mg/m^3
Absorption coefficient	0.786 mm^{-1}
F(000)	188.0
Crystal size	0.63 x 0.32 x 0.14 mm
Theta range for data collection	3.11 to 69.82°
Index ranges	-6<=h<=6, -6<=k<=6, -17<=l<=17
Reflections collected	5596
Independent reflections	1612 [R(int) = 0.015]
Absorption correction	Integration
Max. and min. transmission	0.9021 and 0.7342
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1612 / 1 / 163
Goodness-of-fit on F^2	1.095
Final R indices [I>2sigma(I)]	R1 = 0.0230, wR2 = 0.0625
R indices (all data)	R1 = 0.0233, wR2 = 0.0627
Absolute structure parameter	0.12(18)
Extinction coefficient	0.041(2)
Largest diff. peak and hole	0.112 and -0.103 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C10 H11 N O2.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	10646(2)	7991(2)	3749(1)	45(1)
O(2)	7313(2)	7757(2)	4522(1)	38(1)
N(1)	6859(2)	2765(2)	4329(1)	30(1)
C(2)	8692(2)	4079(2)	3777(1)	27(1)
C(3)	7149(2)	3569(2)	2859(1)	30(1)
C(4)	5123(2)	3007(3)	3515(1)	35(1)
C(5)	8928(2)	6863(2)	4040(1)	29(1)
C(6)	6891(2)	5560(2)	2113(1)	32(1)
C(7)	8636(2)	5806(3)	1456(1)	45(1)
C(8)	8474(3)	7617(3)	758(1)	53(1)
C(9)	6567(3)	9211(3)	693(1)	51(1)
C(10)	4819(3)	8984(3)	1332(1)	48(1)
C(11)	4977(2)	7178(2)	2042(1)	39(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C10 H11 N O2.

	x	y	z	U(eq)
H(1A)	7200(3)	1010(4)	4459(12)	55(5)
H(1B)	6390(3)	3550(4)	4855(12)	49(4)
H(2)	10220(2)	3220(3)	3806(9)	31(3)
H(3)	7680(2)	1970(3)	2582(10)	40(4)
H(4A)	4060(3)	4540(3)	3608(11)	46(4)
H(4B)	4270(3)	1460(4)	3420(12)	54(5)
H(7)	10040(3)	4670(4)	1507(12)	57(5)
H(8)	9760(3)	7790(5)	287(13)	78(6)
H(9)	6490(3)	10420(5)	211(15)	74(6)
H(10)	3440(3)	10090(4)	1309(12)	60(5)
H(11)	3710(3)	6980(3)	2512(11)	49(4)

Table 4. Anisotropic parameters ($Å^2 \times 10^3$) for C10 H11 N O2.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$$

	U11	U22	U33	U23	U13	U12
O(1)	46(1)	34(1)	55(1)	-2(1)	6(1)	-14(1)
O(2)	51(1)	22(1)	43(1)	-2(1)	10(1)	1(1)
N(1)	36(1)	23(1)	32(1)	1(1)	7(1)	-1(1)
C(2)	27(1)	23(1)	31(1)	0(1)	4(1)	0(1)
C(3)	33(1)	26(1)	32(1)	-4(1)	2(1)	-2(1)
C(4)	33(1)	32(1)	42(1)	4(1)	2(1)	-6(1)
C(5)	36(1)	23(1)	28(1)	1(1)	-2(1)	-3(1)
C(6)	37(1)	32(1)	28(1)	-4(1)	-2(1)	-5(1)
C(7)	45(1)	52(1)	40(1)	4(1)	7(1)	2(1)
C(8)	58(1)	61(1)	42(1)	10(1)	10(1)	-6(1)
C(9)	68(1)	45(1)	38(1)	10(1)	-6(1)	-9(1)
C(10)	55(1)	40(1)	47(1)	2(1)	-10(1)	4(1)
C(11)	42(1)	37(1)	37(1)	-1(1)	0(1)	2(1)

Table 5. Bond lengths [Å] and angles [°] for C10 H11 N O2

O(1)-C(5)	1.2327(14)	O(2)-C(5)	1.2603(14)
N(1)-C(4)	1.5014(16)	N(1)-C(2)	1.5019(14)
C(2)-C(5)	1.5257(15)	C(2)-C(3)	1.5704(15)
C(3)-C(6)	1.4971(16)	C(3)-C(4)	1.5409(16)
C(6)-C(11)	1.3900(17)	C(6)-C(7)	1.3960(17)
C(7)-C(8)	1.379(2)	C(8)-C(9)	1.379(2)
C(9)-C(10)	1.379(2)	C(10)-C(11)	1.3896(19)
C(4)-N(1)-C(2)	90.68(8)	N(1)-C(2)-C(5)	112.15(9)
N(1)-C(2)-C(3)	88.44(8)	C(5)-C(2)-C(3)	114.34(9)
C(6)-C(3)-C(4)	120.42(10)	C(6)-C(3)-C(2)	120.23(9)
C(4)-C(3)-C(2)	86.72(8)	N(1)-C(4)-C(3)	89.56(9)
O(1)-C(5)-O(2)	127.39(11)	O(1)-C(5)-C(2)	116.76(10)
O(2)-C(5)-C(2)	115.84(9)	C(11)-C(6)-C(7)	118.21(12)
C(11)-C(6)-C(3)	122.89(11)	C(7)-C(6)-C(3)	118.90(11)
C(8)-C(7)-C(6)	120.91(13)	C(7)-C(8)-C(9)	120.43(13)
C(10)-C(9)-C(8)	119.45(13)	C(9)-C(10)-C(11)	120.50(14)
C(10)-C(11)-C(6)	120.50(13)		

Table 6. Torsion angles [°] for C10 H11 N O2.

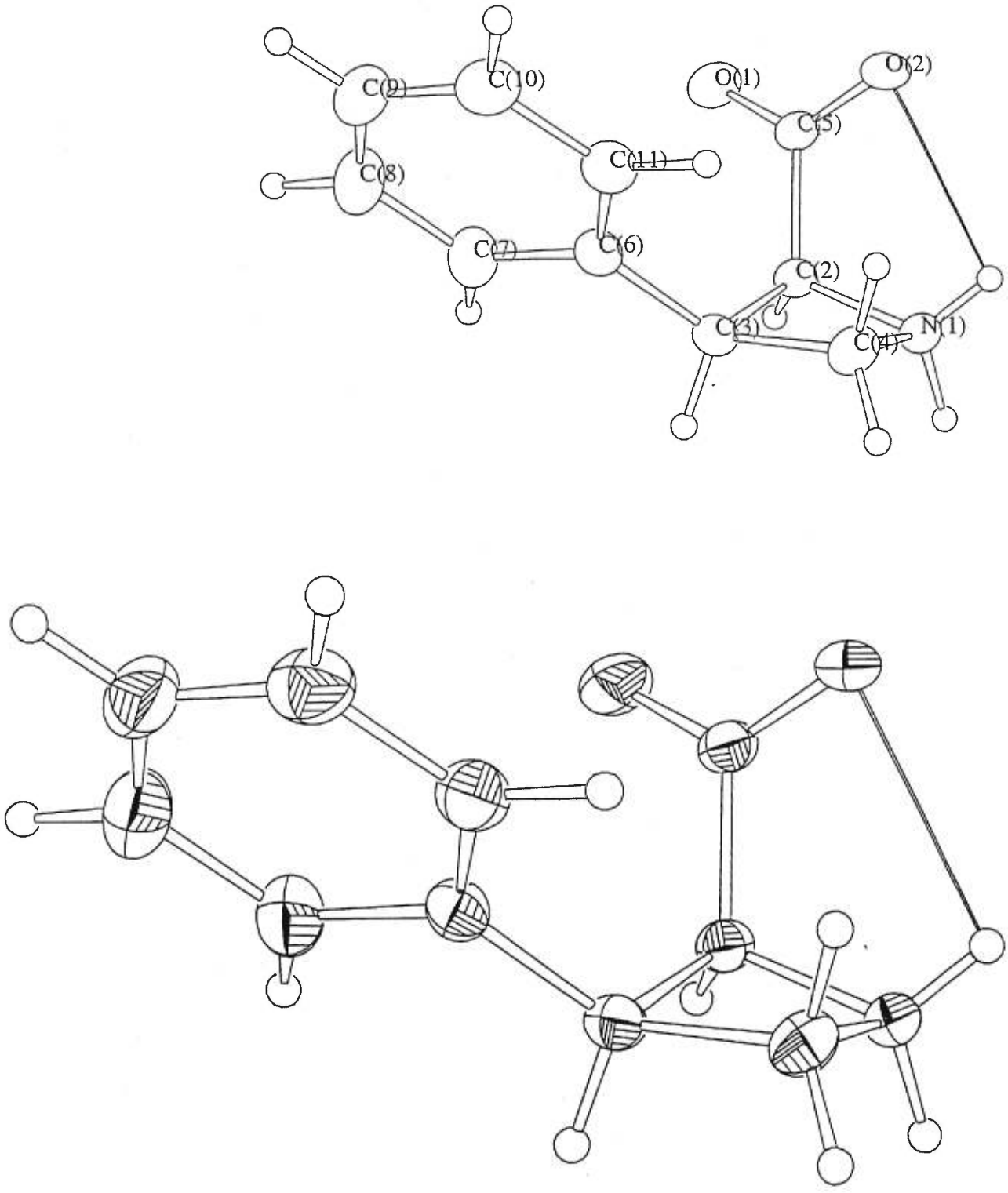
C(4)-N(1)-C(2)-C(5)	99.46(10)
C(4)-N(1)-C(2)-C(3)	-16.26(9)
N(1)-C(2)-C(3)-C(6)	139.47(10)
C(5)-C(2)-C(3)-C(6)	25.79(14)
N(1)-C(2)-C(3)-C(4)	15.86(8)
C(5)-C(2)-C(3)-C(4)	-97.82(10)
C(2)-N(1)-C(4)-C(3)	16.57(9)
C(6)-C(3)-C(4)-N(1)	-139.30(10)
C(2)-C(3)-C(4)-N(1)	-15.86(8)
N(1)-C(2)-C(5)-O(1)	167.78(10)
C(3)-C(2)-C(5)-O(1)	-93.49(12)
N(1)-C(2)-C(5)-O(2)	-13.29(12)
C(3)-C(2)-C(5)-O(2)	85.44(11)
C(4)-C(3)-C(6)-C(11)	7.63(16)
C(2)-C(3)-C(6)-C(11)	-97.75(13)
C(4)-C(3)-C(6)-C(7)	-172.05(11)
C(2)-C(3)-C(6)-C(7)	82.57(14)
C(11)-C(6)-C(7)-C(8)	0.4(2)
C(3)-C(6)-C(7)-C(8)	-179.87(13)
C(6)-C(7)-C(8)-C(9)	-0.5(2)
C(7)-C(8)-C(9)-C(10)	0.1(2)
C(8)-C(9)-C(10)-C(11)	0.4(2)
C(9)-C(10)-C(11)-C(6)	-0.5(2)
C(7)-C(6)-C(11)-C(10)	0.08(18)
C(3)-C(6)-C(11)-C(10)	-179.61(12)

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C10 H11 N O2.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	..A
N(1)-H(1A)	0.96(2)	1.73(2)	167.5(16)	2.677(1)	O(2)#1
N(1)-H(1B)	0.90(2)	2.34(2)	101.3(12)	2.669(1)	O(1)#2
N(1)-H(1B)	0.90(2)	2.36(2)	121.6(13)	2.936(2)	O(2)#3
N(1)-H(1B)	0.90(2)	2.58(2)	112.2(12)	3.034(2)	O(1)#4

Symmetry transformations used to generate equivalent atoms:

#1 x,y-1,z #2 x,y,z #3 -x+1,y-1/2,-z+1
#4 -x+2,y-1/2,-z+1



ORTEP view of the C10 H11 N O2

compound with the numbering scheme adopted. Ellipsoids drawn at

40% probality level. Hydrogens represented by sphere of arbitrary size.

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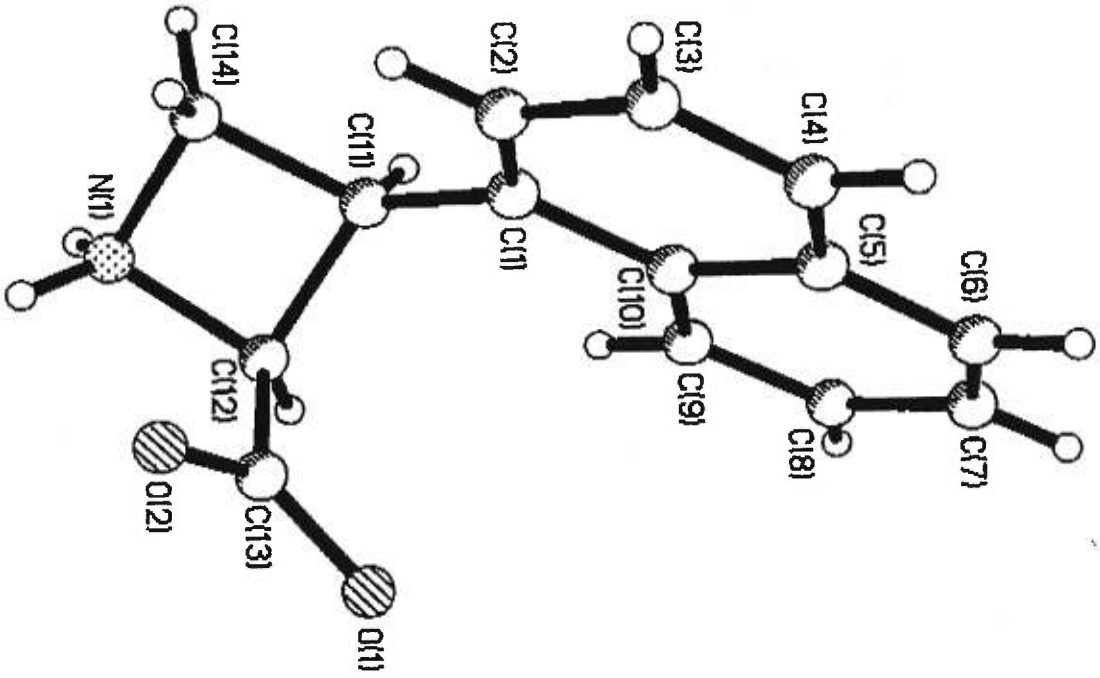


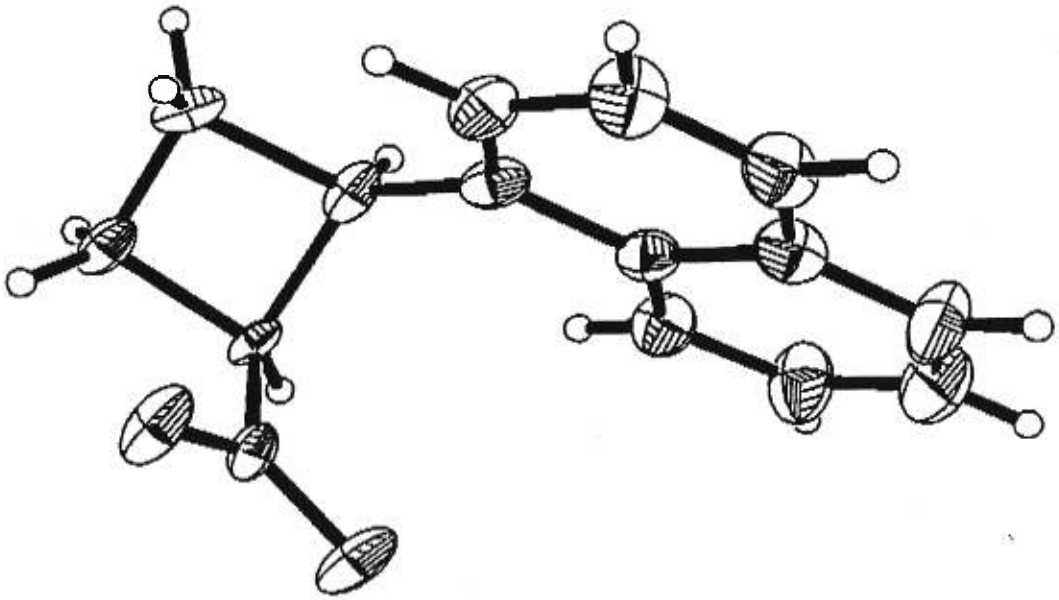


Table 1. Crystal data and structure refinement for mont2s.

Identification code	mont2s
Empirical formula	$C_{14}H_{13}NO_2$
Formula weight	227.25
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 8.3611(6) Å alpha = 90° b = 5.7449(4) Å beta = 98.447(3)° c = 11.9342(8) Å gamma = 90°
Volume, Z	567.03(7) $Å^3$, 2
Density (calculated)	1.331 Mg/m^3
Absorption coefficient	0.722 mm^{-1}
F(000)	240
Crystal size	0.01 x 0.02 x 0.40 mm
θ range for data collection	3.74 to 48.97°
Limiting indices	$-8 \le h \le 6$, $-5 \le k \le 5$, $-9 \le l \le 11$
Reflections collected	1375
Independent reflections	916 (R_{int} = 0.0395)
Completeness to θ = 48.97°	94.4 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	916 / 1 / 167
Goodness-of-fit on F^2	1.076
Final R indices [I>2σ(I)]	R1 = 0.0569, wR2 = 0.1140
R indices (all data)	R1 = 0.0735, wR2 = 0.1257
Absolute structure parameter	-0.3(8)
Largest diff. peak and hole	0.178 and -0.195 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for mont2s. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(1)	7154(9)	-6468(12)	2799(6)	40(2)
C(2)	8559(10)	-5829(14)	3454(6)	47(2)
C(3)	8650(10)	-3983(15)	4238(7)	60(2)
C(4)	7283(11)	-2761(14)	4329(7)	57(2)
C(5)	5787(10)	-3277(14)	3690(7)	51(2)
C(6)	4373(13)	-1991(16)	3786(8)	73(3)
C(7)	2956(13)	-2620(20)	3172(9)	84(3)
C(8)	2822(11)	-4494(18)	2409(8)	71(3)
C(9)	4189(8)	-5712(15)	2270(7)	51(2)
C(10)	5703(8)	-5162(14)	2908(6)	40(2)
C(11)	7105(7)	-8411(11)	1954(6)	36(2)
C(12)	7022(8)	-7898(11)	680(6)	30(2)
C(13)	7749(8)	-5555(11)	441(5)	34(2)
C(14)	8638(9)	-9886(13)	1865(7)	50(2)
N(1)	8216(6)	-9842(9)	621(5)	39(2)
O(1)	6731(5)	-3955(8)	214(4)	54(2)
O(2)	9226(5)	-5368(8)	543(4)	57(2)

Table 3. Bond lengths [Å] and angles [°] for mont2s.

C(1)-C(2)	1.362(8)	C(1)-C(10)	1.449(8)
C(1)-C(11)	1.501(9)	C(2)-C(3)	1.409(10)
C(3)-C(4)	1.359(10)	C(4)-C(5)	1.398(9)
C(5)-C(6)	1.413(10)	C(5)-C(10)	1.424(10)
C(6)-C(7)	1.348(10)	C(7)-C(8)	1.404(12)
C(8)-C(9)	1.371(9)	C(9)-C(10)	1.414(8)
C(11)-C(12)	1.540(8)	C(11)-C(14)	1.553(8)
C(12)-N(1)	1.506(7)	C(12)-C(13)	1.521(8)
C(13)-O(2)	1.228(6)	C(13)-O(1)	1.255(7)
C(14)-N(1)	1.474(8)		
C(2)-C(1)-C(10)	118.2(7)	C(2)-C(1)-C(11)	121.5(7)
C(10)-C(1)-C(11)	120.3(7)	C(1)-C(2)-C(3)	122.8(8)
C(4)-C(3)-C(2)	118.6(8)	C(3)-C(4)-C(5)	122.8(8)
C(4)-C(5)-C(6)	122.5(9)	C(4)-C(5)-C(10)	118.2(8)
C(6)-C(5)-C(10)	119.3(8)	C(7)-C(6)-C(5)	119.6(10)
C(6)-C(7)-C(8)	122.6(10)	C(9)-C(8)-C(7)	118.7(9)
C(8)-C(9)-C(10)	121.2(9)	C(9)-C(10)-C(5)	118.5(7)
C(9)-C(10)-C(1)	122.1(8)	C(5)-C(10)-C(1)	119.4(7)
C(1)-C(11)-C(12)	120.9(5)	C(1)-C(11)-C(14)	120.7(6)
C(12)-C(11)-C(14)	87.4(5)	N(1)-C(12)-C(13)	111.2(5)
N(1)-C(12)-C(11)	88.3(5)	C(13)-C(12)-C(11)	113.2(5)
O(2)-C(13)-O(1)	126.7(6)	O(2)-C(13)-C(12)	118.9(6)
O(1)-C(13)-C(12)	114.3(5)	N(1)-C(14)-C(11)	88.9(5)
C(14)-N(1)-C(12)	91.6(5)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for mont2s.

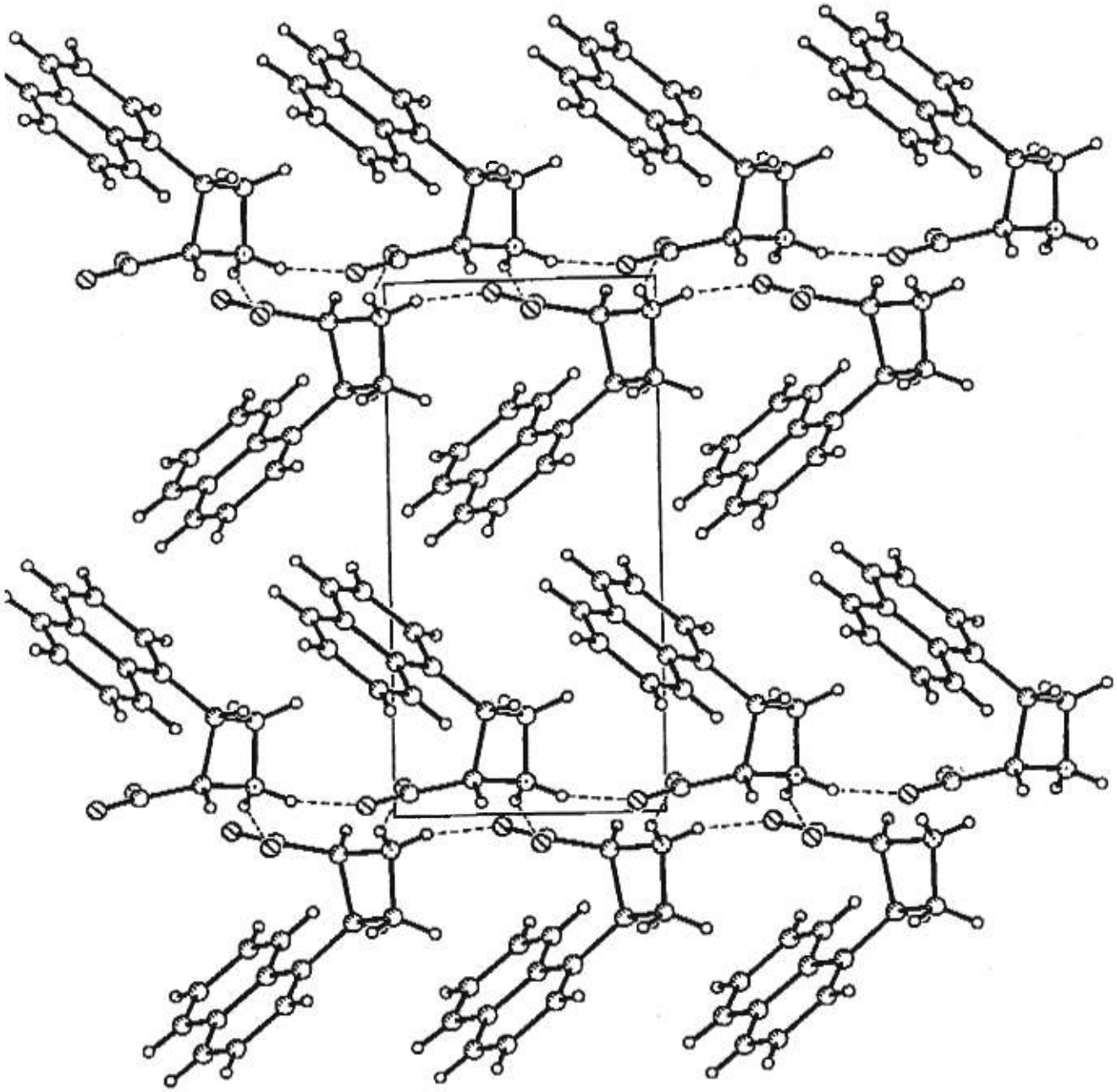
The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
C(1)	35(5)	35(5)	49(6)	12(5)	0(4)	-3(4)
C(2)	37(5)	48(5)	55(6)	-1(5)	0(5)	1(5)
C(3)	53(6)	62(6)	62(7)	-19(6)	-3(6)	-12(5)
C(4)	81(7)	40(5)	49(6)	-14(5)	6(6)	-13(5)
C(5)	59(6)	47(6)	45(6)	-1(5)	3(5)	-9(5)
C(6)	71(7)	61(7)	88(8)	-15(6)	15(7)	23(6)
C(7)	56(8)	102(9)	95(8)	4(8)	12(6)	35(7)
C(8)	45(7)	91(8)	76(7)	-20(6)	3(6)	10(6)
C(9)	40(5)	55(6)	57(6)	-2(6)	3(5)	0(5)
C(10)	36(5)	43(5)	39(5)	6(5)	-1(4)	-1(4)
C(11)	19(4)	25(5)	63(6)	-2(5)	5(4)	-3(4)
C(12)	18(4)	24(4)	46(5)	5(4)	-2(4)	7(3)
C(13)	33(5)	21(4)	47(5)	-9(4)	7(4)	2(4)
C(14)	49(5)	41(5)	56(6)	16(5)	-7(5)	11(5)
N(1)	31(3)	21(4)	63(5)	1(3)	2(4)	1(3)
O(1)	32(3)	24(3)	101(4)	10(3)	-2(3)	0(3)
O(2)	22(3)	34(3)	118(5)	8(3)	19(3)	-3(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for mont2s.

	x	y	z	U(eq)
H(2)	9498	-6646	3380	60(20)
H(3)	9624	-3608	4683	60(20)
H(4)	7346	-1529	4838	80(30)
H(6)	4420	-717	4271	50(20)
H(7)	2031	-1781	3258	100(30)
H(8)	1824	-4901	2005	80(30)
H(9)	4120	-6921	1747	40(20)
H(11A)	6217	-9465	2059	27(17)
H(12A)	5958	-8187	237	15(16)
H(14B)	9644	-9096	2143	40(20)
H(14A)	8613	-11429	2191	80(30)
H(1A)	7755	-11169	333	60(30)
H(1B)	9049	-9440	262	110(40)



CRYSTAL AND MOLECULAR STRUCTURE OF

C7 H15 N O3 COMPOUND (HAN240)

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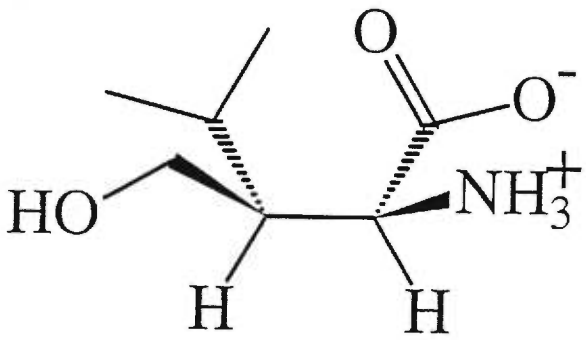


Structure résolue au laboratoire de diffraction des rayons X de l'Université de Montréal par Dr. Michel Simard.

Table 1. Crystal data and structure refinement for C7 H15 N O3.

Identification code	HAN240
Empirical formula	C7 H15 N O3
Formula weight	161.200
Temperature	220(2)K
Wavelength	1.54056Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 4.984(2)Å α = 90° b = 6.489(4)Å β = 91.52(4)° c = 12.767(8)Å γ = 90°
Volume	412.8(4)Å^3
Z	2
Density (calculated)	1.2970 Mg/m^3
Absorption coefficient	0.835 mm^{-1}
F(000)	176.0
Crystal size	0.94 x 0.40 x 0.02 mm
Theta range for data collection	3.46 to 69.72°
Index ranges	-6<=h<=6, -7<=k<=7, -15<=l<=15
Reflections collected	3055
Independent reflections	1549 [R(int) = 0.156]
Absorption correction	Integration
Max. and min. transmission	0.9869 and 0.8231
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1549 / 67 / 101
Goodness-of-fit on F^2	1.602
Final R indices [I>2sigma(I)]	R1 = 0.1371, wR2 = 0.3461
R indices (all data)	R1 = 0.1415, wR2 = 0.3529
Absolute structure parameter	0.5(10)
Largest diff. peak and hole	1.088 and -1.445 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C7 H15 N O3.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(4)	2644(10)	8159(9)	8198(4)	35(1)
O(10)	3161(9)	2088(7)	8829(4)	27(1)
O(11)	7403(9)	1397(8)	9281(4)	29(1)
N(2)	9113(11)	5243(8)	9056(4)	25(1)
C(1)	5583(13)	2574(9)	8969(5)	23(1)
C(2)	6285(13)	4819(10)	8717(4)	23(1)
C(3)	5601(14)	5500(10)	7582(5)	26(1)
C(4)	4915(15)	7798(11)	7578(6)	32(2)
C(5)	7738(16)	4954(11)	6778(5)	33(2)
C(6)	8360(18)	2661(13)	6750(6)	42(2)
C(7)	6910(2)	5689(18)	5679(7)	54(2)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C7 H15 N O3.

	x	y	z	U(eq)
H(4)	2755	9324	8465	53
H(2A)	9524	6560	8909	38
H(2B)	10219	4395	8714	38
H(2C)	9306	5029	9751	38
H(2)	5155	5677	9171	28
H(3)	3942	4760	7364	31
H(4A)	6449	8588	7858	38
H(4B)	4536	8257	6858	38
H(5)	9412	5684	6987	39
H(6A)	8895	2198	7447	62
H(6B)	9807	2412	6273	62
H(6C)	6774	1911	6512	62
H(7A)	6552	7158	5694	82
H(7B)	5304	4962	5443	82
H(7C)	8349	5413	5202	82

Table 4. Anisotropic parameters ($Å^2 \times 10^3$) for C7 H15 N O3.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$$

	U11	U22	U33	U23	U13	U12
O(4)	22(2)	34(2)	49(2)	0(2)	0(2)	0(2)
O(10)	10(2)	30(2)	41(2)	2(1)	-2(1)	-2(1)
O(11)	14(2)	34(2)	39(2)	4(1)	-5(1)	-1(2)
N(2)	15(2)	29(2)	32(2)	-1(2)	-4(2)	-2(2)
C(1)	12(2)	27(2)	31(2)	1(2)	-2(2)	2(2)
C(2)	15(2)	27(2)	27(2)	-1(2)	-1(2)	1(2)
C(3)	18(2)	29(2)	31(2)	1(2)	-2(2)	-2(2)
C(4)	26(2)	31(2)	38(2)	3(2)	-1(2)	0(2)
C(5)	28(2)	35(2)	36(2)	0(2)	0(2)	-3(2)
C(6)	37(4)	45(3)	43(3)	0(3)	6(3)	3(3)
C(7)	54(4)	56(4)	53(4)	9(3)	2(3)	5(3)

Table 5. Bond lengths [Å] and angles [°] for C7 H15 N O3

O(4)-C(4)	1.418(9)	O(10)-C(1)	1.256(8)
O(11)-C(1)	1.243(8)	N(2)-C(2)	1.489(8)
C(1)-C(2)	1.535(9)	C(2)-C(3)	1.544(8)
C(3)-C(4)	1.530(10)	C(3)-C(5)	1.540(10)
C(5)-C(6)	1.520(11)	C(5)-C(7)	1.528(11)
O(11)-C(1)-O(10)	125.6(6)	O(11)-C(1)-C(2)	118.8(6)
O(10)-C(1)-C(2)	115.6(6)	N(2)-C(2)-C(1)	109.5(5)
N(2)-C(2)-C(3)	113.8(5)	C(1)-C(2)-C(3)	115.0(5)
C(4)-C(3)-C(5)	112.4(6)	C(4)-C(3)-C(2)	109.0(5)
C(5)-C(3)-C(2)	114.9(6)	O(4)-C(4)-C(3)	109.9(6)
C(6)-C(5)-C(7)	109.5(7)	C(6)-C(5)-C(3)	112.7(6)
C(7)-C(5)-C(3)	111.4(7)		

Table 6. Torsion angles [°] for C7 H15 N O3.

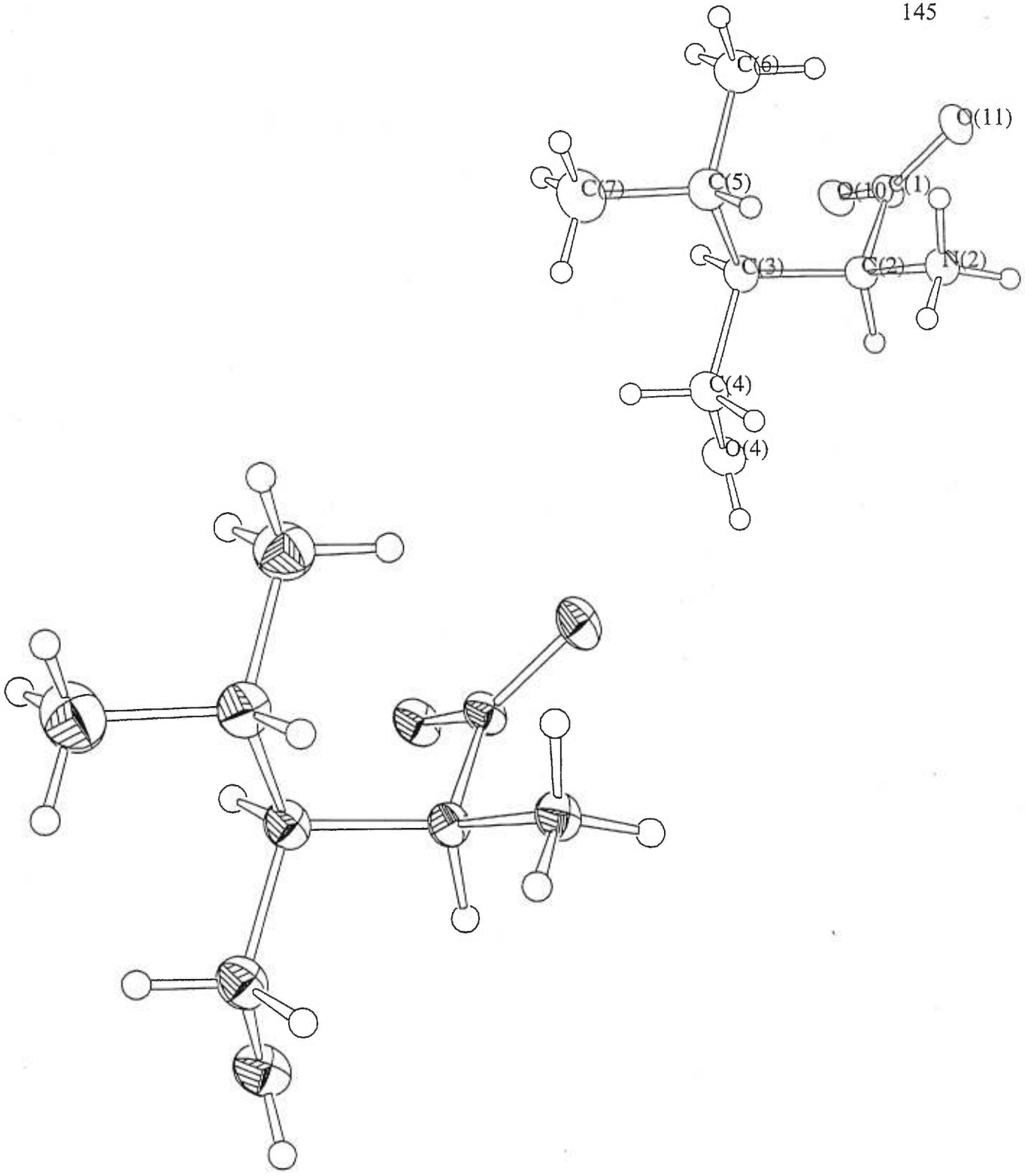
O(11)-C(1)-C(2)-N(2)	-8.2(7)
O(10)-C(1)-C(2)-N(2)	172.3(5)
O(11)-C(1)-C(2)-C(3)	121.4(7)
O(10)-C(1)-C(2)-C(3)	-58.1(7)
N(2)-C(2)-C(3)-C(4)	-83.3(6)
C(1)-C(2)-C(3)-C(4)	149.2(5)
N(2)-C(2)-C(3)-C(5)	43.8(8)
C(1)-C(2)-C(3)-C(5)	-83.7(7)
C(5)-C(3)-C(4)-O(4)	170.3(6)
C(2)-C(3)-C(4)-O(4)	-61.2(7)
C(4)-C(3)-C(5)-C(6)	-178.0(7)
C(2)-C(3)-C(5)-C(6)	56.6(8)
C(4)-C(3)-C(5)-C(7)	-54.4(9)
C(2)-C(3)-C(5)-C(7)	-179.8(7)

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C7 H15 N O3.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	..A
O(4)-H(4)	0.83	1.86	170.0	2.684(7)	O(10)#1
N(2)-H(2A)	0.90	2.10	137.4	2.824(8)	O(4)#2
N(2)-H(2B)	0.90	2.10	146.9	2.894(7)	O(10)#2
N(2)-H(2C)	0.90	2.21	123.1	2.808(7)	O(11)#3
N(2)-H(2C)	0.90	2.59	124.8	3.190(7)	O(10)#4

Symmetry transformations used to generate equivalent atoms:

#1 x,y+1,z #2 x+1,y,z #3 -x+2,y+1/2,-z+2
#4 -x+1,y+1/2,-z+2



ORTEP view of the C7 H15 N O3

compound with the numbering scheme adopted. Ellipsoids drawn at

40% probality level. Hydrogens represented by sphere of arbitrary size.

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CRYSTAL AND MOLECULAR STRUCTURE OF

C7 H13 N O2 COMPOUND (HAN246)

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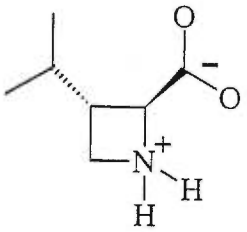


Structure résolue au laboratoire de diffraction des rayons X de l'Université de Montréal par Dr. Michel Simard.

Table 1. Crystal data and structure refinement for C7 H13 N O2.

Identification code	HAN246
Empirical formula	C7 H13 N O2
Formula weight	143.184
Temperature	205(2)K
Wavelength	1.54056Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.721(2)Å α = 90° b = 9.520(6)Å β = 94.65(4)° c = 14.802(9)Å γ = 90°
Volume	803.5(8)$Å^3$
Z	4
Density (calculated)	1.1836 Mg/m^3
Absorption coefficient	0.706 mm^{-1}
F(000)	312.0
Crystal size	0.96 x 0.30 x 0.05 mm
Theta range for data collection	2.99 to 69.84°
Index ranges	-6<=h<=6, -11<=k<=11, -17<=l<=17
Reflections collected	15828
Independent reflections	2995 [R(int) = 0.105]
Absorption correction	Integration
Max. and min. transmission	0.9667 and 0.7594
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2995 / 1 / 253
Goodness-of-fit on F^2	0.997
Final R indices [I>2sigma(I)]	R1 = 0.0674, wR2 = 0.1572
R indices (all data)	R1 = 0.0744, wR2 = 0.1611
Absolute structure parameter	-0.2(4)
Largest diff. peak and hole	0.358 and -0.325 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C7 H13 N O2.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(11)	5171(5)	10472(3)	611(2)	45(1)
O(12)	4839(5)	10975(2)	-855(2)	42(1)
N(11)	2256(4)	8141(3)	406(2)	31(1)
C(12)	3099(5)	8888(3)	-399(2)	29(1)
C(13)	557(5)	8902(3)	-854(2)	32(1)
C(14)	5(6)	7799(4)	-144(3)	37(1)
C(15)	4506(5)	10238(3)	-175(2)	29(1)
C(16)	123(6)	8505(3)	-1834(3)	37(1)
C(17)	934(8)	9653(5)	-2460(3)	57(1)
C(18)	-2462(6)	8174(4)	-2070(3)	43(1)
O(21)	10275(4)	9516(3)	1840(2)	49(1)
O(22)	11985(4)	10178(3)	3183(2)	49(1)
N(21)	5893(5)	9523(3)	2412(2)	35(1)
C(22)	7987(5)	9672(3)	3090(2)	33(1)
C(23)	7570(6)	8141(4)	3426(2)	39(1)
C(24)	5845(7)	7958(4)	2588(3)	46(1)
C(25)	10291(6)	9812(3)	2645(2)	37(1)
C(26)	6561(8)	8030(4)	4335(3)	50(1)
C(27)	8346(11)	8444(7)	5090(3)	83(2)
C(28)	5651(12)	6528(6)	4476(4)	83(2)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C7 H13 N O2.

	x	y	z	U(eq)
H(11A)	3420(8)	7500(5)	600(3)	55(13)
H(11B)	2130(5)	8570(4)	940(2)	19(8)
H(12)	4180(6)	8330(4)	-790(2)	34(9)
H(13)	-250(8)	9660(7)	-710(3)	72(15)
H(14A)	-1200(6)	7940(4)	210(2)	31(9)
H(14B)	70(8)	6620(7)	-490(3)	72(14)
H(16)	1250(8)	7800(6)	-1920(3)	65(13)
H(17A)	77	10512	-2365	110(2)
H(17B)	640	9357	-3086	43(10)
H(17C)	2599	9818	-2326	69(14)
H(18A)	-2935	7411	-1691	75(16)
H(18B)	-2699	7901	-2702	21(8)
H(18C)	-3397	9000	-1967	60(13)
H(21A)	5830(5)	9800(4)	1740(2)	24(8)
H(21B)	4250(7)	9880(5)	2640(2)	45(11)
H(22)	7940(6)	10480(4)	3580(2)	36(9)
H(23)	9240(8)	7680(5)	3450(3)	56(12)
H(24A)	6460(7)	7500(5)	2000(3)	46(11)
H(24B)	4220(9)	7670(7)	2690(3)	83(18)
H(26)	5060(8)	8630(5)	4360(3)	59(13)
H(27A)	8861	9399	4996	90(18)
H(27B)	9681	7814	5098	110(2)
H(27C)	7648	8384	5665	97(19)
H(28A)	6941	5868	4468	110(2)
H(28B)	4463	6299	3994	110(2)
H(28C)	4976	6473	5056	96(19)

Table 4. Anisotropic parameters ($Å^2 \times 10^3$) for C7 H13 N O2.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$$

	U11	U22	U33	U23	U13	U12
O(11)	57(2)	27(1)	49(2)	4(1)	-6(1)	-13(1)
O(12)	57(2)	21(1)	46(1)	4(1)	-6(1)	-13(1)
N(11)	33(1)	17(1)	41(2)	1(1)	2(1)	1(1)
C(12)	30(1)	12(1)	44(2)	2(1)	4(1)	-1(1)
C(13)	27(2)	13(1)	57(2)	0(1)	4(1)	0(1)
C(14)	32(2)	29(2)	49(2)	5(1)	4(2)	-6(1)
C(15)	29(2)	16(1)	40(2)	0(1)	0(1)	1(1)
C(16)	33(2)	26(2)	51(2)	-1(1)	2(1)	-4(1)
C(17)	61(3)	53(3)	55(2)	11(2)	-7(2)	-26(2)
C(18)	40(2)	35(2)	55(2)	-5(2)	0(2)	-8(2)
O(21)	41(1)	50(2)	56(2)	-4(1)	12(1)	2(1)
O(22)	33(1)	47(2)	67(2)	-4(1)	3(1)	-1(1)
N(21)	31(1)	27(1)	46(2)	2(1)	2(1)	1(1)
C(22)	29(2)	25(2)	46(2)	1(2)	2(1)	1(1)
C(23)	38(2)	24(2)	54(2)	2(2)	2(2)	0(1)
C(24)	55(2)	23(2)	59(2)	-2(2)	-2(2)	-3(2)
C(25)	37(2)	25(2)	49(2)	1(1)	2(1)	5(1)
C(26)	59(2)	35(2)	58(2)	8(2)	7(2)	-6(2)
C(27)	103(4)	86(4)	57(3)	14(3)	-3(3)	-11(4)
C(28)	108(4)	47(3)	96(4)	22(3)	26(4)	-20(3)

Table 5. Bond lengths [Å] and angles [°] for C7 H13 N O2

O(11)-C(15)	1.215(4)	O(12)-C(15)	1.254(4)
N(11)-C(12)	1.501(4)	N(11)-C(14)	1.503(4)
C(12)-C(15)	1.539(4)	C(12)-C(13)	1.552(4)
C(13)-C(16)	1.500(5)	C(13)-C(14)	1.536(5)
C(16)-C(18)	1.525(5)	C(16)-C(17)	1.528(5)
O(21)-C(25)	1.222(4)	O(22)-C(25)	1.253(4)
N(21)-C(22)	1.506(4)	N(21)-C(24)	1.514(5)
C(22)-C(25)	1.526(5)	C(22)-C(23)	1.565(5)
C(23)-C(26)	1.510(5)	C(23)-C(24)	1.531(5)
C(26)-C(27)	1.504(6)	C(26)-C(28)	1.542(6)
C(12)-N(11)-C(14)	89.3(2)	N(11)-C(12)-C(15)	114.9(3)
N(11)-C(12)-C(13)	90.0(2)	C(15)-C(12)-C(13)	122.8(2)
C(16)-C(13)-C(14)	117.5(3)	C(16)-C(13)-C(12)	119.6(3)
C(14)-C(13)-C(12)	86.2(2)	N(11)-C(14)-C(13)	90.5(2)
O(11)-C(15)-O(12)	127.6(3)	O(11)-C(15)-C(12)	118.5(3)
O(12)-C(15)-C(12)	113.9(3)	C(13)-C(16)-C(18)	110.8(3)
C(13)-C(16)-C(17)	111.8(3)	C(18)-C(16)-C(17)	110.2(3)
C(22)-N(21)-C(24)	90.1(2)	N(21)-C(22)-C(25)	112.9(3)
N(21)-C(22)-C(23)	89.4(2)	C(25)-C(22)-C(23)	112.2(3)
C(26)-C(23)-C(24)	116.5(3)	C(26)-C(23)-C(22)	115.3(3)
C(24)-C(23)-C(22)	87.3(3)	N(21)-C(24)-C(23)	90.5(3)
O(21)-C(25)-O(22)	128.9(3)	O(21)-C(25)-C(22)	117.5(3)
O(22)-C(25)-C(22)	113.6(3)	C(27)-C(26)-C(23)	111.0(4)
C(27)-C(26)-C(28)	111.0(4)	C(23)-C(26)-C(28)	110.1(4)

Table 6. Torsion angles [°] for C7 H13 N O2.

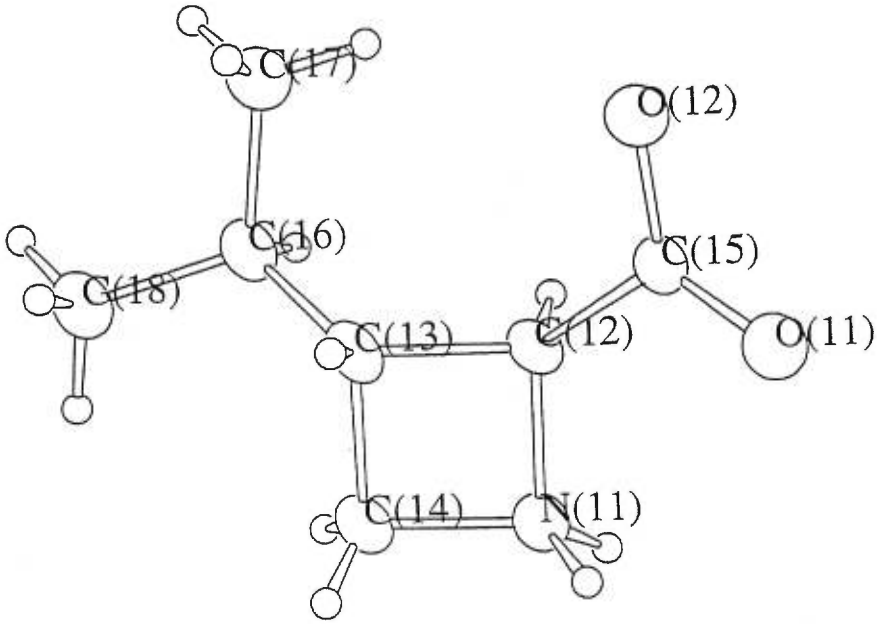
C(14)-N(11)-C(12)-C(15)	141.9(3)
C(14)-N(11)-C(12)-C(13)	15.2(2)
N(11)-C(12)-C(13)-C(16)	-134.6(3)
C(15)-C(12)-C(13)-C(16)	105.4(3)
N(11)-C(12)-C(13)-C(14)	-14.9(2)
C(15)-C(12)-C(13)-C(14)	-134.9(3)
C(12)-N(11)-C(14)-C(13)	-15.4(2)
C(16)-C(13)-C(14)-N(11)	136.4(3)
C(12)-C(13)-C(14)-N(11)	14.9(2)
N(11)-C(12)-C(15)-O(11)	12.3(4)
C(13)-C(12)-C(15)-O(11)	119.6(3)
N(11)-C(12)-C(15)-O(12)	-168.1(3)
C(13)-C(12)-C(15)-O(12)	-60.8(4)
C(14)-C(13)-C(16)-C(18)	61.3(4)
C(12)-C(13)-C(16)-C(18)	163.5(3)
C(14)-C(13)-C(16)-C(17)	-175.3(3)
C(12)-C(13)-C(16)-C(17)	-73.2(4)
C(24)-N(21)-C(22)-C(25)	101.7(3)
C(24)-N(21)-C(22)-C(23)	-12.2(3)
N(21)-C(22)-C(23)-C(26)	-106.1(3)
C(25)-C(22)-C(23)-C(26)	139.3(3)
N(21)-C(22)-C(23)-C(24)	12.1(3)
C(25)-C(22)-C(23)-C(24)	-102.5(3)
C(22)-N(21)-C(24)-C(23)	12.5(3)
C(26)-C(23)-C(24)-N(21)	105.0(3)
C(22)-C(23)-C(24)-N(21)	-12.0(3)
N(21)-C(22)-C(25)-O(21)	-14.0(4)
C(23)-C(22)-C(25)-O(21)	85.2(4)
N(21)-C(22)-C(25)-O(22)	168.3(3)
C(23)-C(22)-C(25)-O(22)	-92.4(4)
C(24)-C(23)-C(26)-C(27)	-171.4(4)
C(22)-C(23)-C(26)-C(27)	-71.2(5)
C(24)-C(23)-C(26)-C(28)	65.3(5)
C(22)-C(23)-C(26)-C(28)	165.5(4)

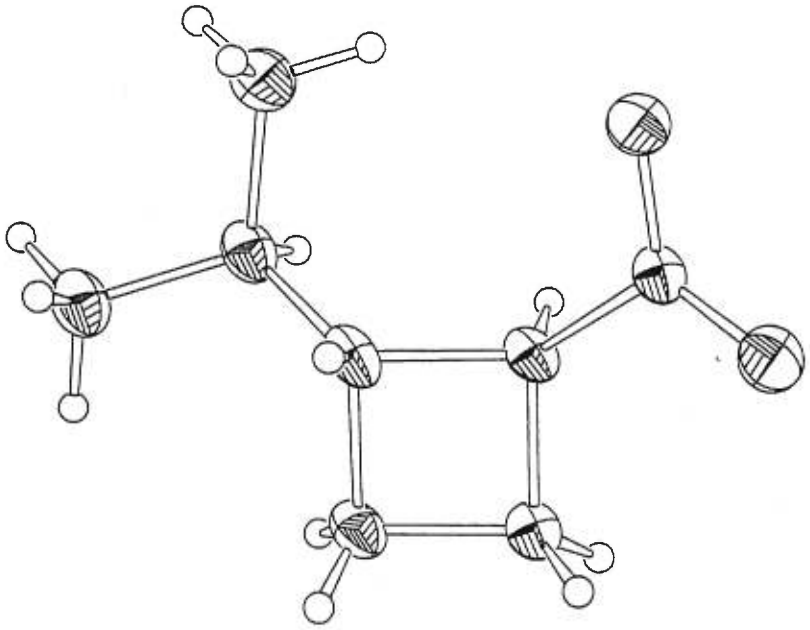
Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C7 H13 N O2.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	..A
N(11)-H(11A)	0.93(5)	1.78(5)	167(4)	2.697(4)	O(12)#1
N(11)-H(11B)	0.89(4)	1.99(4)	152(3)	2.810(4)	O(21)#2
N(21)-H(21A)	1.03(3)	1.80(3)	168(3)	2.813(4)	O(11)#3
N(21)-H(21B)	1.08(4)	1.60(4)	167(3)	2.665(4)	O(22)#2
N(21)-H(21B)	1.08(4)	2.50(4)	126(3)	3.257(4)	O(21)#2

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1/2,-z #2 x-1,y,z #3 x,y,z





ORTEP view of the C7 H13 N O2

compound with the numbering scheme adopted. Ellipsoids drawn at

40% probality level. Hydrogens represented by sphere of arbitrary size.

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