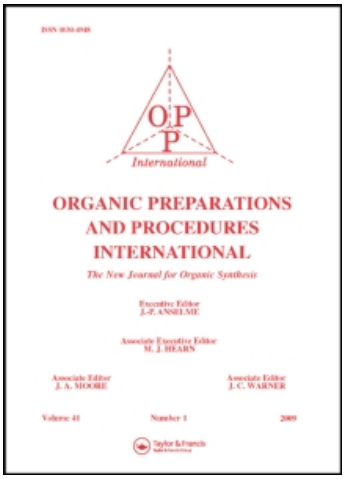

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AZETIDINE-2-CARBOXYLIC ACID. FROM LILY OF THE VALLEY TO KEY PHARMACEUTICALS. A JUBILEE REVIEW

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To cite this Article Couty, Françis and Evano, Gwilherm(2006) 'AZETIDINE-2-CARBOXYLIC ACID. FROM LILY OF THE VALLEY TO KEY PHARMACEUTICALS. A JUBILEE REVIEW', Organic Preparations and Procedures International, 38: 5, 427 — 465
To link to this Article: DOI: 10.1080/00304940609356436
URL: http://dx.doi.org/10.1080/00304940609356436

ORGANIC PREPARATIONS AND PROCEDURES INT., 38 (5), 427-465 (2006)

AZETIDINE-2-CARBOXYLIC ACID. FROM LILY OF THE VALLEY TO KEY PHARMACEUTICALS. A JUBILEE REVIEW

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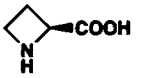
INTRODUCTION

L-Azetidine-2-carboxylic acid **1**, also commonly named L-Aze or L-A-2-C (*Fig.1*) is a non proteinogenic amino acid homologue of proline and it was first isolated fifty years ago (1955), by Fowden from the liliaceae *Convallaria Majalis* (lily-of-the-valley); it was the first known example of naturally occurring azetidine.[1] Virtanen and Linko are credited with independent discovery of the compound[2] but they proposed an incorrect formula and later acknowledged Fowden's one as correct.[3] Although **1** is quite rarely found in nature, its derivatives have been found in different natural products and are of significant importance as active pharmaceutical ingredients.

As a constrained amino acid, L-Aze has found many applications in the modification of peptides conformations[4] as well as in the area of asymmetric synthesis which include its use in asymmetric reduction of ketones,[5] Michael additions,[6] cyclopropanations,[7] Diels-Alder reactions[8] and α-amination of carbonyl compounds.[9]



1: L-Azetidine-2-carboxylic acid *(L-Aze)*

Fig. 1

L-Aze is white crystalline solid quite stable to strong basic,[1] reducing[10] and oxidizing conditions.[1] It has been reported to decompose (mainly to homoserine lactone) upon treatment with 6M HCl at reflux.[1] Analytical characterizations include X-ray diffraction,[11] which show that the azetidine ring is buckled 11° from a plane, ^{1}H NMR spectra,[12,13] ^{13}C NMR spectra,[12,13] melting point,[12-14] IR spectra,[12] optical rotation,[12] and pK_A values.[15] Its natural occurrence and biological activity will be briefly overviewed in the first part of this review, followed by a survey of L-Aze as part of natural and synthetic compounds.

The (*S*) enantiomer of **1** is commercially available, but only in small quantities. Although **1** is readily prepared as a racemate, only few methods allow for its asymmetric preparation. After a brief and non-exhaustive overview describing the syntheses of racemic **1**, the following sections of this review will focus on the enantioselective syntheses and

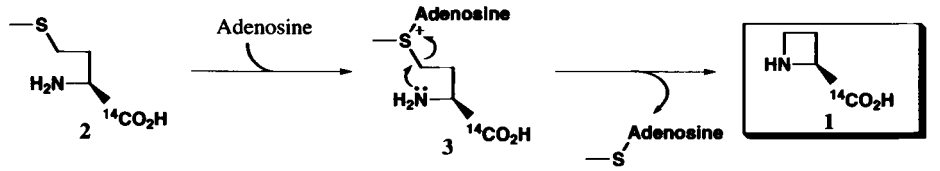
reactivity of the (*S*) enantiomer. The last section will be dedicated to the synthesis of substituted derivatives.

I. NATURAL OCCURRENCE, BIOLOGICAL ACTIVITY AND BIOSYNTHESIS

As mentioned in the Introduction, **1** was first isolated by Fowden from 70% aqueous ethanol extracts of fresh leaves or seeds of *Convallaria Majalis* (lily-of-the-valley);[1,14] at the same time, **1** was found as well in the rhizomes of *Polygonatum officianilis*,[2,3,16] and as the principal free amino acid in several plants of the *Liliaceae* and *Agavaceae* families including species of the genera *Rhodea*, *Bowiea* and *Dracanea*, and has been identified as a constituent of more than 20 of 90 species examined.[17] Later, **1** was also isolated from *Delonix regia*,[18] sugar beet,[19] *Haliclona sp.* and *Chalinopsilla sp.*[20]

Compound **1**, which is believed to be an antagonist of proline,[21] does not participate in protein synthesis. As most non-proteinogenic amino acids, **1** serves as poison for predators and has a wide range of biological activities. First, it has been reported to inhibit the proliferation of *E. Coli*.[22] Since that time, it has been demonstrated that the incorporation of **1** in place of proline changes the folding of proteins[23] and alters the structure of collagen,[24] keratin[25] and hemoglobin.[26] Moreover, **1** was found to have teratogenic effects and to cause various malformations in animals (lung, palate, etc).[27,28,29]

Concerning the biosynthesis of this non-proteinogenic amino acid, in 1964 Leete and coworkers established that L-Aze is formed in the plant *Convallaria Majalis* from methionine (**2**).[30] By administration of methionine labeled with ^{14}C at the carboxylic acid group, the authors isolated radioactive **1**. Decarboxylation and analysis of the evolved carbon dioxide, further established that all the radioactivity of **1** was located on the carboxyl group. Based on these observations and other studies with ^{15}N-labelled precursors,[31] it was considered that **1** may be formed by intramolecular displacement of thiomethyladenosine by the α-amino group of S-adenosylmethionine **3** as illustrated in *Scheme 1*. Sung and Fowden reported that in the legume *Delonix regia*, **1** might be formed from 2,4-diaminobutanoic acid.[32]



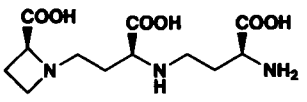
Biosynthesis of L-Azetidine-2-carboxylic acid in *Convallaria Majalis*.

Scheme 1

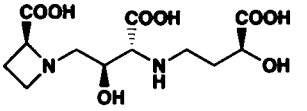
II. NATURAL AND SYNTHETIC COMPOUNDS INCORPORATING AZETIDINE-2-CARBOXYLIC ACID

Since the discovery of **1**, a few natural products containing this amino acid have been isolated. They include phytosiderophores nicotianamine **4**,[33] mugineic **5**,[34] 2'-deoxymugineic **6**[35]

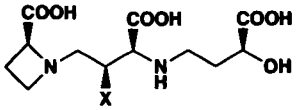
and isomugineic 7[34b] acids as well as medicanine **8** (*Fig. 2*).[36] Natural products possessing a substituted azetidine-2-carboxylic acid, such as the antifungal and cytotoxic vioprolides A and C,[37] the antibiotic polyoxins[38] and substituted azetidine-2,4-dicarboxylic acids have also been isolated.[39]



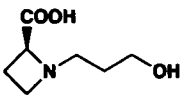
4: nicotianamine



7: isomugineic acid



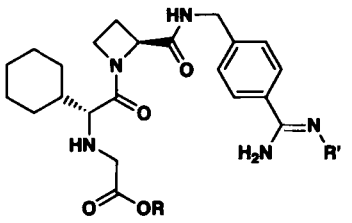
5: X = OH, mugineic acid
6: X = H, 2'-deoxymugineic acid



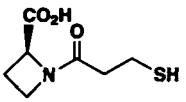
8: medicanine

Fig. 2

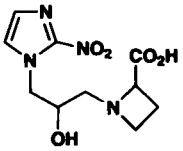
Due to its unique structure, **1** has been recently used in the formulation of many compounds with significant and various biological activities. The most recent and well-known examples are the thrombin inhibitors *melagatran*® (**9**) or *exenta*® (**10**).[40] In 1982, Petrillo and coworkers showed that mercaptoacyl compound **11** was an inhibitor of the angiotensin-



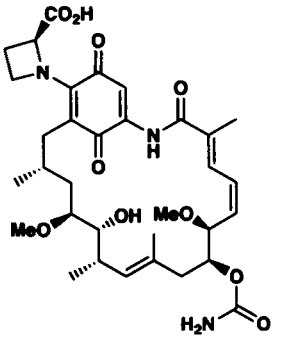
9: R = R' = H: Melagatran®
10: R = Et, R' = OH: Exenta®



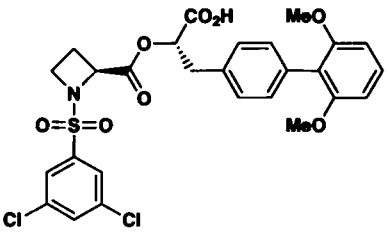
11: ACE inhibitor



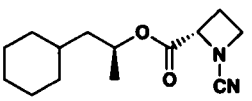
12: selective hypoxic cell cytotoxic agent and radiosensitizer



13: inhibit the p185 phosphotyrosine in human breast cancer cells



14: antagonist of VLA-4



15: cathepsin K inhibitor

Fig. 3

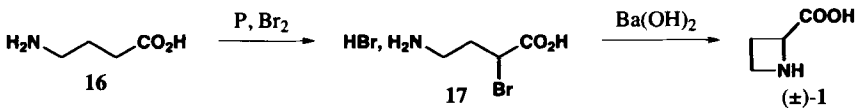
converting enzyme (ACE).[41] After this first report, Suto and coworkers at Parke-Davis found that compound **12** incorporating the L-Aze moiety was an efficient selective hypoxic cell cytotoxic agent and radiosensitizer[42] while the geldanamycin/L-Aze adduct **13** was found to inhibit the p185 phosphotyrosine in human breast cancer SKBR-3 cells.[43] More recently, researchers from Merck reported on the discovery, synthesis, and biological evaluation of **14** as antagonist of VLA-4, a key cell surface integrin playing an important role in inflammation by promoting leukocyte attachment and extravasation from the vasculature into the peripheral tissues.[44] Finally, Deaton and coworkers at GlaxoSmithKline demonstrated that cyanamide **15** was an especially efficient picomolar cathepsin K (a cysteine protease playing a key role in osteoroposis) inhibitor.[45]

III. SYNTHESES OF AZETIDINE-2-CARBOXYLIC ACID

Due to the simplicity of its structure, there are not many possibilities or bond disconnections that can be used for the synthesis of **1**. However, due to its high added value and potential, there are many variations for each synthetic route and every single synthesis, especially the asymmetric types, have been extensively patented. For clarity, only new and original syntheses will be discussed in this section while not all possible variations will be systematically surveyed, unless a new concept was used or a significant improvement to an existing method or procedure was reported.

1. Syntheses of Racemic Azetidine-2-carboxylic Acid[46]

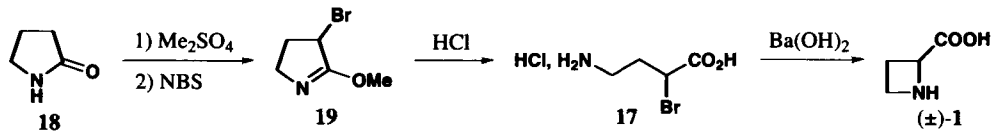
To verify the proposed structure of **1**, Fowden developed a simple and efficient racemic synthesis from γ-aminobutyric acid **16**. Hell-Volhard-Zelinski bromination of **16** allows for the preparation of bromide **17** which is cyclized to (±)-**1** upon treatment with barium hydroxide (*Scheme 2*).[1]



Racemic Synthesis from γ-Aminobutyric Acid

Scheme 2

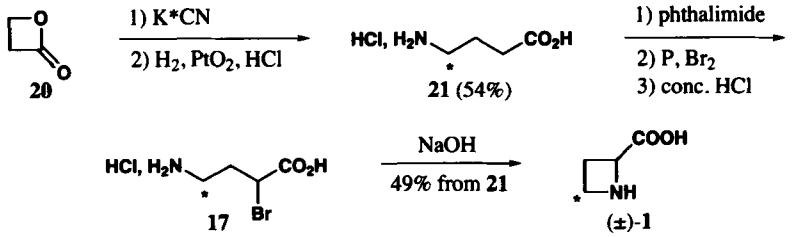
Aiming at improving the overall yield of this procedure, several publications have been reported for the synthesis of bromide **17**, the direct precursor or **1**. Okada and coworkers reported the synthesis of (±)-**1** from 2-pyrrolidinone **18** *via* 3-bromo-2-methoxy-1-pyrroline **19**. Treatment of **18** with dimethyl sulfate followed by subsequent bromination with NBS yields **19**; hydrolysis of **19** gave the required α-bromoacid **17** which was cyclized with barium hydroxide as in Fowden's procedure (*Scheme 3*).[47]



Racemic Synthesis from 2-Pyrrolidinone

Scheme 3

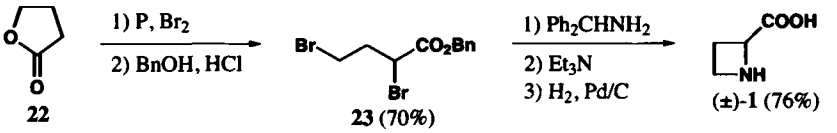
A final modification of Fowden's synthesis reported by Pichat and coworkers was used for the synthesis of **1** labeled with ^{14}C at the C-4 position. Ring opening of β-propiolactone **20** with labeled potassium cyanide followed by hydrogenation gives labeled γ-aminobutyric acid **21** which is following Fowden's synthesis with an additional protection-deprotection step provided labeled **1** with improved the overall yield (*Scheme 4*).[48]



Racemic Synthesis of Labeled Azetidine-2-carboxylic Acid from β-Propiolactone

Scheme 4

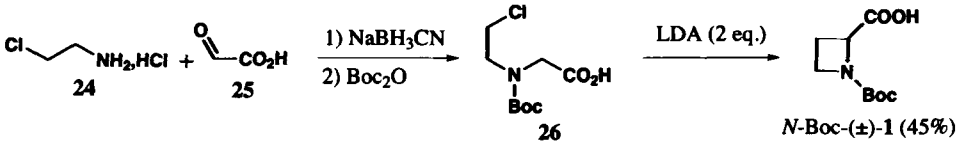
An improved method was reported by Cromwell and Rodebaugh who synthesized (±)-**1** from γ-butyrolactone **22** in 53% overall yield. Benzyl α,γ-dibromobutyrate **23** was prepared from **22** by a bromination-transesterification sequence. The reaction of **23** with benzhydrylamine allows for the formation of *N,O*-protected azetidine-2-carboxylic acid which can be hydrogenated directly over Pearlman's catalyst to give (±)-**1** (*Scheme 5*).[49] Many variants of this route using other esters or amines have been reported later and can be used to synthesize various protected derivatives of (±)-**1** such as PMB-(±)-Aze-OMe,[50] Ph_2CH-(±)-Aze-OMe,[49] allyl-(±)-Aze-OEt[51] or *p*-tolyl-(±)-Aze-OBn.[52]



Racemic Synthesis from γ-Butyrolactone

Scheme 5

Finally, Einhorn and Luche reported an efficient original racemic synthesis of *N*-Boc-(±)-**1** using an intramolecular alkylation of an acyclic amino acid derivative.[53] Reductive amination of glyoxylic acid **25** with 2-chloroethylamine hydrochloride **24** followed by Boc protection gave *N*-Boc, *N*-(2-chloroethyl)glycine **26**. Treatment of **26** with excess LDA generates a dianion which leads to the formation of the four-membered ring in 45% yield (*Scheme 6*).



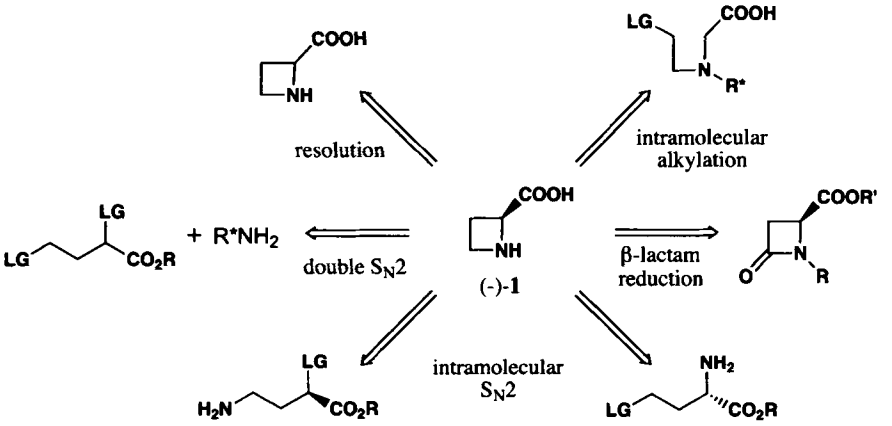
Racemic Synthesis by Intramolecular Alkylation of a Glycine Derivative

Scheme 6

Not surprisingly, **1** has been the focus of asymmetric syntheses since the 1980s. Many synthetic ways have been developed and will be surveyed in the following paragraphs.

2. Asymmetric Syntheses of L-Azetidine-2-carboxylic Acid

Development of an efficient, simple and commercially advantageous process for producing optically active **1** by asymmetric synthesis has been a subject of growing interest and numerous recently approved patents, all aiming at providing an azetidine-2-carboxylic acid. Synthetic routes or processes developed for the synthesis of **1** can be classified according to the bonds that are formed in the key step and/or the origin of the stereoselectivity (*Scheme 7*). Asymmetric syntheses of **1** will be described according to this classification.



Asymmetric Syntheses of 1: the Possibilities

Scheme 7

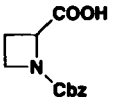
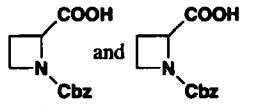
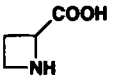
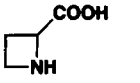
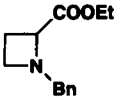
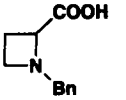
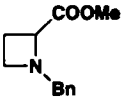
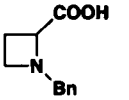
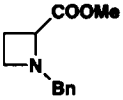
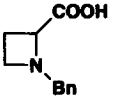
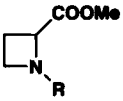
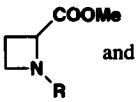
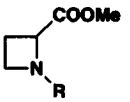
a) Resolution of Racemic Azetidine-2-carboxylic Acid

A trivial way to obtain **1** in an enantiomerically pure form is the resolution of the DL-form of this acid. After screening various common resolving bases such as brucine, strychnine, etc., Rodebaugh and Cromwell reported the use of L-tyrosine hydrazide on the *N*-carbobenzyloxy derivative of (±)-**1** (*Table 1, Entry 1*).[54] Using Vogler's conditions, the D-amino acid salt precipitates first from methanol and can therefore be isolated in an enantiomerically enriched form. This process, however, has the major disadvantage of using L-tyrosine hydrazide, an expensive resolving agent impractical for industrial scale. An excellent alternative was found in the direct and simple resolution of (±)-**1** with D-tartaric acid: in two steps, enantiomerically pure **1** is obtained in 36% yield (*Table 1, Entry 2*).[55]

Another convenient method for producing enantiomerically enriched *N*-alkyl derivatives of **1** rely on the use of an enzymatic hydrolysis. Among the enzymatic systems used for this resolution, *Arthrobacter* SC-6-98-28,[56] Chirazyme L-2[57] and Novozyme 435[57] have proved to be the most efficient ones (*Table 1, Entries 3-5*). If an enantiomerically pure amide derivative is needed, enzymatic ammoniolysis with *Candida Antartica* can be used in place of enzymatic

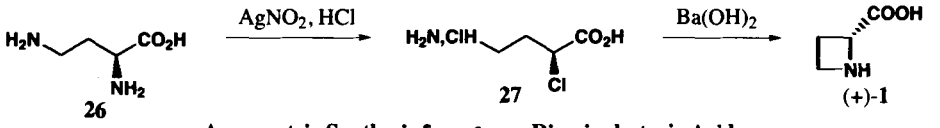
hydrolysis (*Table 1, Entry 6*).[50] In all cases, enantiomeric excesses of products are good or excellent. The major drawback of these methods is mostly the cost of the required enzyme: "classical" asymmetric syntheses making use of chiral induction are therefore excellent alternatives, especially for large scale synthesis.

Table 1. Chemical and Enzymatic Resolution Protocols for Azetidine-2-Carboxylic acid

Entry	Substrate	Conditions	Products	Reference
1		1) L-tyrosine hydrazide 2) recrystallization 3) 3M HCl, H_2O	 from mother liquors 46% and from precipitate 44%	54, 5a
2		1) D-tartaric acid, C_3H_7CHO, AcOH 2) recrystallization 3) KOH, H_2O	 36%, ee = 99%	55
3		*Arthrobacter* SC-6-98-28	 46%, ee = 96.4%	56
4		Chirazyme L-2	 46%, ee = 98.4%	57
5		Novozyme 435	 47%, ee = 97.4%	57
6	 R = Bn, PMB, allyl	NH_3, *Candida Antartica*	 and  ee > 99% 80 <ee <97%	50

b) Asymmetric Syntheses with Chiral Induction

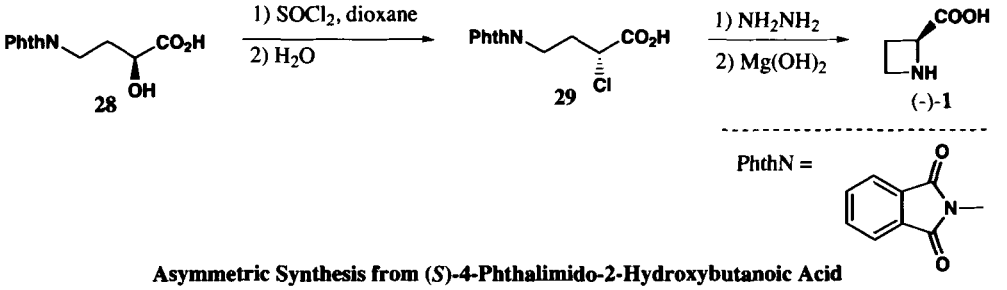
The first asymmetric syntheses of **1** was reported in 1956 by Fowden starting from L-α,γ-diaminobutyric acid **26**.[1,14] Nitrosation of **26** in the presence of hydrochloric acid gave α-chloroacid **27** resulting from a double inversion of configuration. Treatment of this hydrochloride with barium hydroxide initiated cyclization and allowed for the isolation of the unnatural enantiomer, *i. e.* (+)-**1** (*Scheme 8*). This synthesis was later revised and all possible combinations of reagents (various esters and protected amines) were patented in 2003 by the Kaneka Corporation.[58]



Asymmetric Synthesis from L-α,γ-Diaminobutyric Acid

Scheme 8

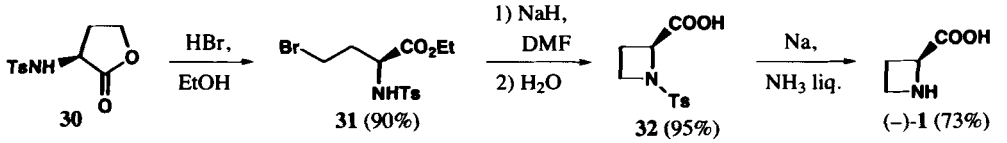
Kondo and Ueyama recently reported a very similar synthesis in which the α-chloroacid required for the cyclization was obtained from (*S*)-4-phthalimido-2-hydroxybutanoic acid, an inexpensive, readily available enantiopure starting material (*Scheme 9*).[59]



Asymmetric Synthesis from (*S*)-4-Phthalimido-2-Hydroxybutanoic Acid

Scheme 9

A simple variation of these syntheses consists in reversing the location of the leaving group and of the nucleophile on the precursor's skeleton by switching from α-halo-γ-aminobutyric acid to α-amino-γ-halobutyric acid. The first report using this strategy published in 1973 by Miyashi and coworkers is summarized below. Treatment of tosyl-L-homoserine lactone **30** with hydrobromic acid, followed by recyclization of **31** with sodium hydride gave tosyl-protected azetidine-2-carboxylic acid **32**. After removal of protecting group by sodium in liquid ammonia, the optically active (-)-**1** was obtained (*Scheme 10*).[60]

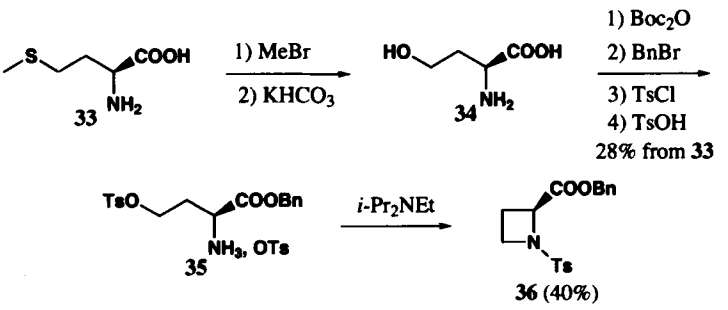


Asymmetric Synthesis from Tosyl-L-Homoserine Lactone

Scheme 10

Similarly, Baldwin and coworkers reported the cyclization of homoserine tosylate **35**. L-methionine **33** was initially converted into homoserine **34**, which by simple functional group transformations gave **35**, the substrate of the cyclization reaction step. Treatment of this compound with diisopropylethylamine did not give the expected L-azetidine-2-carboxylic acid benzyl ester but its *N*-tosyl derivative **36** (*Scheme 11*).[61]

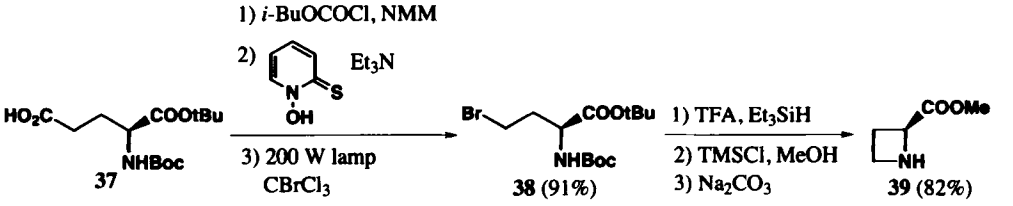
Another variation used a starting material other than L-glutamic acid. A photochemically induced radical decarboxylation of Barton's ester of (*S*)-*N*-Boc-glutamic acid α-*tert*-butyl ester in the presence of $CBrCl_3$[62] afforded bromide **38** in 91% yield. Protecting group



Asymmetric Synthesis from L-Methionine

Scheme 11

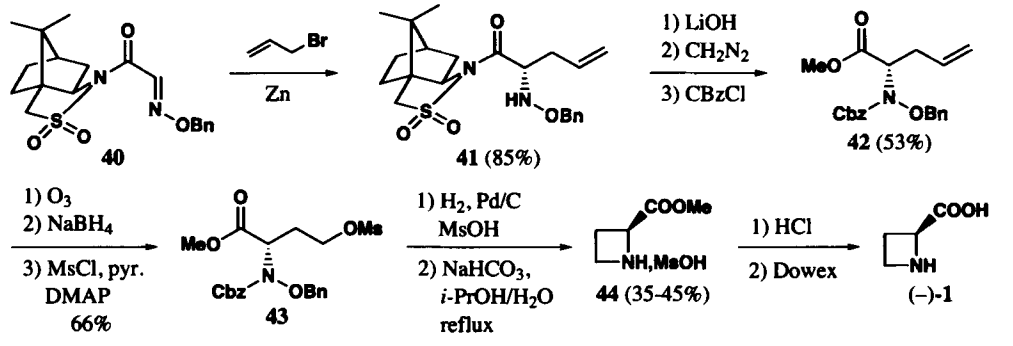
manipulation followed by a base-induced cyclization finally gave the methyl ester **39** of L-Aze (*Scheme 12*).[63]



Asymmetric Synthesis from L-Glutamic acid

Scheme 12

Finally, the most recent synthesis of L-azetidine-2-carboxylic acid, relying on a similar strategy reported by Hanessian, is depicted in *Scheme 13*. This lengthy synthesis based on a zinc-mediated asymmetric addition of allyl bromide to the Oppolzer's sultam derivative of O-benzyloxime **40** is not particularly convenient for the synthesis of (–)-**1** but gives interesting results for the synthesis of substituted derivatives (see *Scheme 22*).[64]

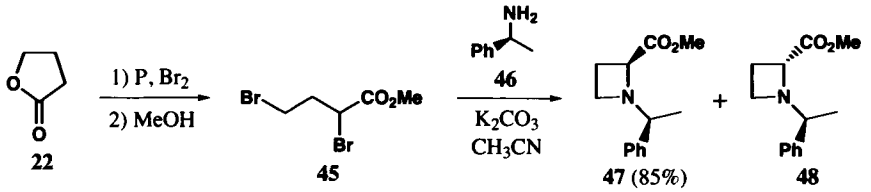


Asymmetric Synthesis using Oppolzer's Sultam

Scheme 13

In 1981, Wasserman and coworkers adapted Cromwell's racemic synthesis[49] by reacting 2,4-dibromobutyrates with chiral amines in excellent yields.[65] Zwanenburg and

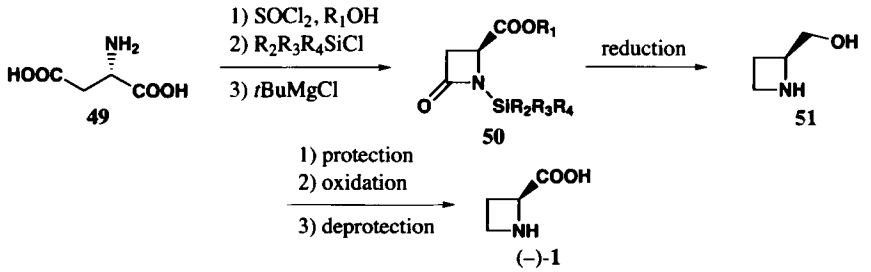
coworkers later reported the application of this procedure to (*S*)-α-methylbenzylamine **46** and obtained diastereoisomeric esters **47** and **48** which where separated by column chromatography (*Scheme 14*).[8] Once again, all variations of this process have been patented by the Sumimoto Chemical Company.[66]



Asymmetric Synthesis from α-Methylbenzylamine and γ-Butyrolactone

Scheme 14

An entirely different procedure based on the reduction of β-lactams according to Ojima's protocol[67] was reported by the Kaneka Corporation in 2000.[68] The required β-lactams **50** were obtained in three steps from (*S*)-aspartic acid **49** by esterification, protection of the amine and cyclization of its magnesium salt. Reduction of lactams **50** gave chiral azetidinol **51** which was further transformed to (–)-**1** (*Scheme 15*).[69]



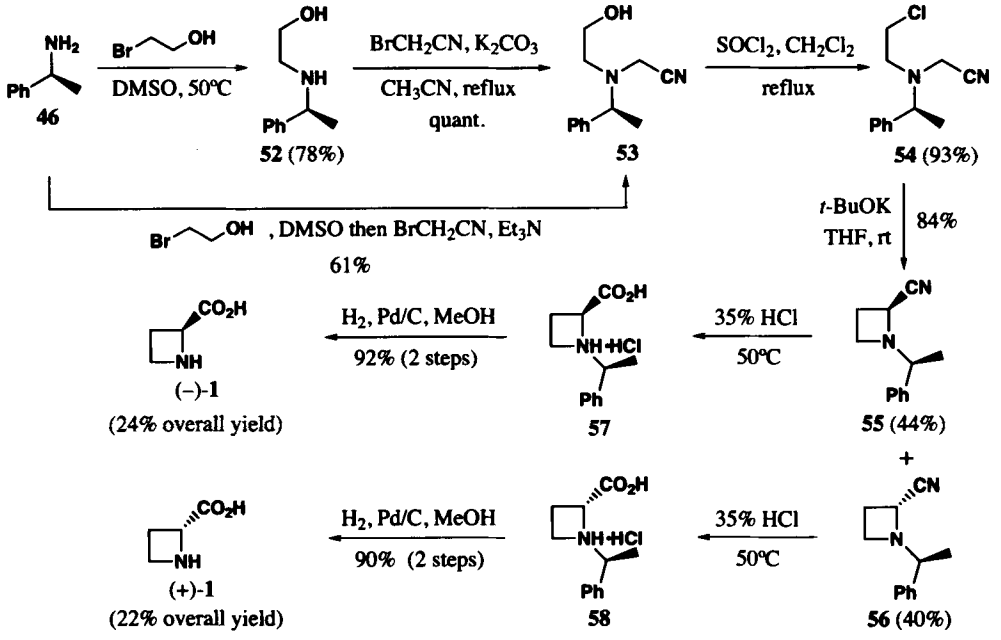
Asymmetric Synthesis from (*S*)-Aspartic Acid *via* β-Lactams

Scheme 15

Except for Zwanenburg's synthesis, these syntheses do not allow for the preparation of both enantiomers of azetidine-2-carboxylic acid. Moreover, none of them are ideal for large-scale preparation in terms of cost, safety issues, or number of steps involved. For specific research interests, a cost-effective, safe synthesis of both enantiomers of azetidine-2-carboxylic acid that is amenable to large-scale preparation was required;[70] such a synthesis was designed for this cyclic amino acid.

A very short method to form the four-membered ring could make use of an intramolecular 4-exo-*tet*-alkylation[71] starting from compound **54** (*Scheme 16*) possessing both leaving and electron-withdrawing groups required for the cyclization. Therefore chloride **54** was synthesized in a three steps sequence starting from commercially available α-methylbenzylamine **46** as the source of chirality. Chloride **54** was next subjected to the key cyclization step (*t*BuOK, THF, rt) to form the four membered ring and gave a crude 6:4 mixture of diastereoisomers **55** and **56**

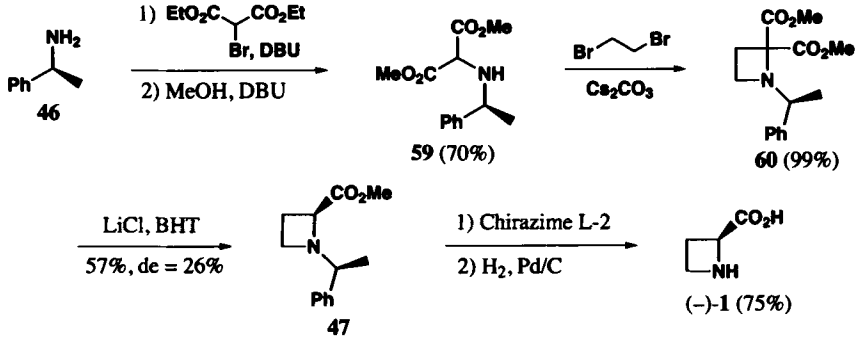
which were easily separated by flash column chromatography. Further functional group transformations (nitrile hydrolysis to carboxylic acid followed by debenzylation) from either **55** or **56** provided access to both enantiomers of the desired cyclic amino acid **1** (*Scheme 16*).



Asymmetric Synthesis from α-Methylbenzylamine using a 4-*exo-tet*-Alkylation

Scheme 16

Finally, Sugai and coworkers[72] reported a related approach to L-azetidine-2-carboxylic acid from aminodiester **59** prepared in two steps from α-methylbenzylamine **46** and ethyl bromomalonate.[73] The key step, azetidine ring formation by double alkylation with 1,2-dibromoethane, was successful and Krapcho decarboxylation using BHT as proton source gave monoester **47** in 57% yield with 26% diastereoisomeric excess. After ester hydrolysis with Chirazime L-2 and debenzylation, L-Aze (−)-**1** was obtained (*Scheme 17*).



Asymmetric Synthesis from α-Methylbenzylamine using a Double Alkylation

Scheme 17

All syntheses of **1** described in the preceding paragraphs have contributed to the study and development of its reactivity which interestingly combines the effects of the amino acid group and of the strained heterocycle. This reactivity will be briefly surveyed in the next section.

IV. REACTIVITY OF AZETIDINE-2-CARBOXYLIC ACID

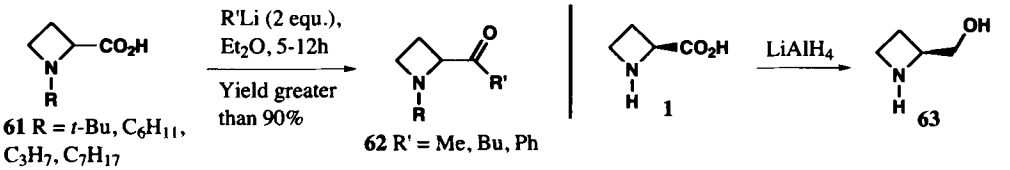
1. L-Aze in Peptide Chemistry

L-Aze is a non-proteinogenic amino acid which has been used for the preparation of modified peptides. Its behavior in peptide chemistry, recently summarized in the excellent Houben-Weyl series,[74] appears to be close to that of proline. However, some differences mainly due to the ring strain, should be mentioned. First, the formation of NCA (*N*-carboxyanhydride) is strongly disfavored due to the steric requirement for the closure of the fused NCA ring. Similarly, the formation of piperazin-2,5-dione resulting from the self-condensation of two amino acids is also disfavored because the central ring piperazin-2,5-dione is forced to adopt a boat conformation that induces a non-planar conformation of the amide bonds.[75] Therefore, poly-(L-Aze) can be conveniently prepared by simple polycondensation of its pentachlorophenyl ester. Conventional deprotection by hydrogenolysis can be achieved, although it was reported that *N*-benzyl deprotection of the free carboxylic acid using Pearlman's catalyst was sluggish. However, the *N*-benzhydryl-*O*-benzyl ester can be selectively deprotected.[76]

As previously stated, an important characteristic of this amino acid, resulting from its ring strain, is its instability towards strong acids. Under the conditions typically required for complete peptide hydrolysis (6N HCl, 110°C, 24 h or more), L-Aze decomposes completely, giving mainly homoserine, resulting from ring opening by water, and other ninhydrin-positive products, formed by the ring opening by chloride ion. This instability, initially reported by Fowden,[14] should not be however considered as a general rule since it has been shown (see *Schemes 16*, *27b* and *32*), that azetidinic amino acids resulting from the corresponding amino nitriles survived the harsh acidic conditions required for nitrile hydrolysis.

2. Reactivity of the Carboxylic Acid Moiety

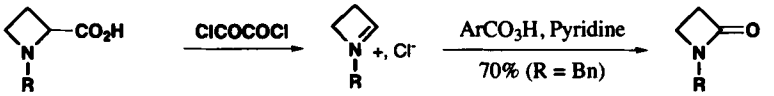
Cromwell reported[77] that the carboxylic acid moiety in *N*-alkyl derivatives **61** could serve as excellent precursors of ketones under Tegner's conditions (reaction with organolithium reagents), yielding 2-acylazetidines **62** in good yields. Complete reduction of the carboxylic acid group with $LiAlH_4$ to L-azetidine-2-methanol **63**, has been reported in unstated yield (*Scheme 18*).[78]



Partial or Total Reduction of the Carboxylic Acid Group

Scheme 18

Apart from these "classical" functional group interconversions, Wasserman[79] studied in details the generation of strained iminium ions **65** from the reaction of *N*-alkyl derivatives **64** with chlorinating agents. Oxidation of these iminium ions with a peracid in the presence of pyridine ultimately afforded the corresponding β-lactams **66** (*Scheme 19*). This efficient methodology was subsquently used in a synthesis of (+)-3-aminonocardicinic acid, the core structure of the nocardicin antibiotic.[80] The efficiency of the decarboxylation process was however shown to be dependent of the substitution pattern of the azetidine ring.[81]



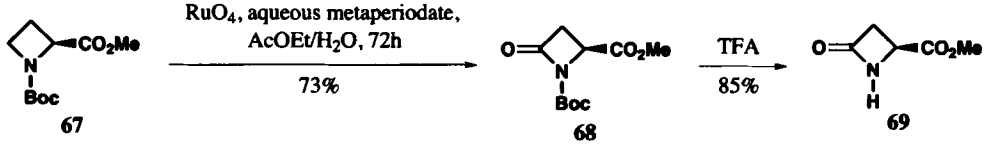
64 R = *t*-Bu, C_6H_{11}, Bn, $PhCH_2CH_2$ — **65** — **66**

Oxidative Decarboxylation of Azetidine-2-carboxylic Acid Derivatives to β-Lactams

Scheme 19

3. Oxidation to β-Lactams

Due to the importance of the β-lactam ring, other oxidation protocols of L-Aze derivatives to azetidin-4-one-2-carboxylic acid esters have been studied. During a general study directed at the oxidation of cyclic amino acids derivatives by catalytic amounts of RuO_4 and $NaIO_4$ as co-oxidant, Tanaka and co-workers showed that high efficiency could be reached when *N*-Boc derivatives were used.[82,83] Thus, oxidation of **67** occurred in good yield and selectivity (only C4 position oxidized), giving *N*-Boc protected lactam **68** which could be further deprotected to **69** through cleavage with TFA (*Scheme 20*).



67 — **68** — **69**

Oxidation to Functionalized β-Lactams

Scheme 20

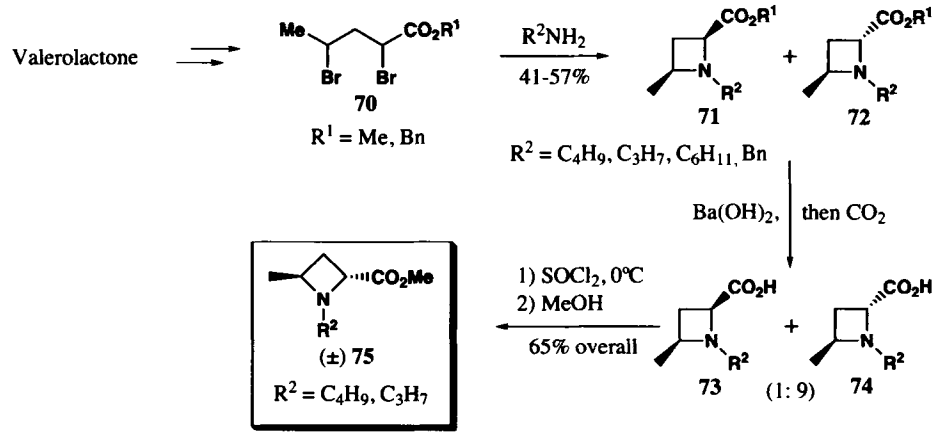
V. SYNTHESIS OF AZETIDINE-2-CARBOXYLIC ACID DERIVATIVES

This section will report on the synthesis of some derivatives of L-azetidine-2-carboxylic acid. Preparation of the natural derivatives such as mugineic acids **5-7** and nicotianamine **4**, whose total syntheses have been extensively studied will not be covered here; it will focus on simple derivatives that can be envisioned as conformationally restricted analogues of natural amino acids. Syntheses in this section will be classified according to the substitution pattern of the derivatives obtained, starting with alkyl-substituted derivatives.

1. Alkyl-substituted Derivatives

a) 4-Alkyl-substituted Derivatives

Early reports in this area were disclosed by Cromwell who reported the reaction of α,γ-dibromovaleryl esters **70** with various primary amines.[84] This reaction afforded fair yields (41-57%) of racemic azetidines with virtually no selectivity since nearly equimolar mixtures of *cis* **71** and *trans* **72** isomers were obtained. Partial epimerization occurred during saponification of ester groups which led to mixtures of carboxylic acids in which the *trans* isomer was the major one (*trans/cis*: 9/1). Treatment of this mixture with thionyl chloride followed by reaction with methanol then afforded pure *trans*-isomer of 1-alkyl-2-carbomethoxy-4-methylazetidines **75** *Scheme 21a*. Formation of the *cis* derivative as a single isomer was attributed by the authors to its higher thermodynamic stability. To the best of our knowledge, no asymmetric synthesis of related 4-alkyl-substituted derivatives have been reported so far.



Synthesis of 4-Methyl Derivatives

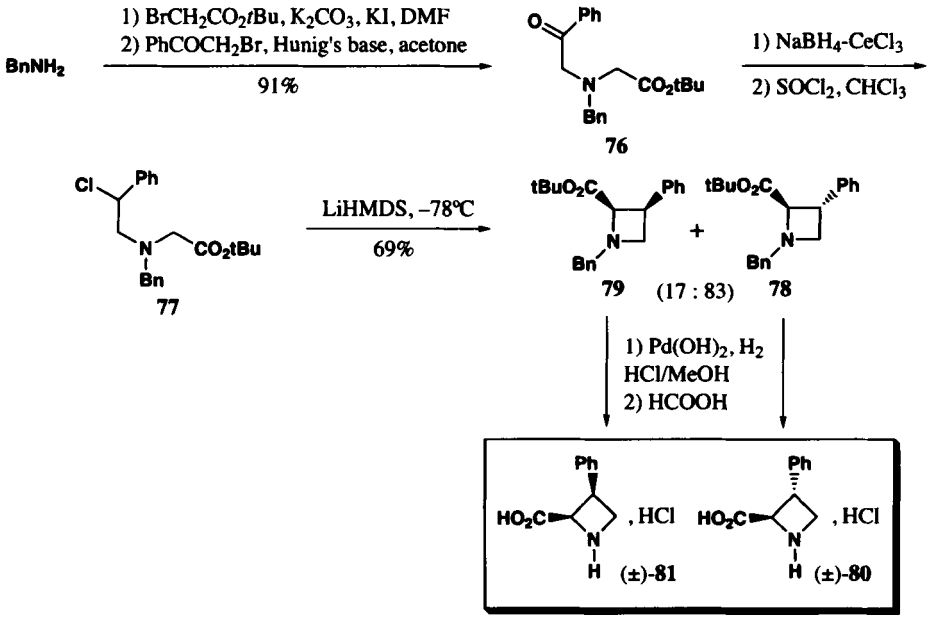
Scheme 21a

b) 3-Alkyl- and Aryl-substituted Derivatives

The synthesis of 3-alkyl- and aryl-substituted derivatives of azetidine-2-carboxylic acid is well documented. The first report of such compounds appeared a decade ago in the work of Shue and co-workers,[85] who described the preparation of racemic amino acids **80** and **81** that can be viewed as conformationally restricted analogues of phenylalanine. The synthesis of these amino acids involves an original and unprecedented intramolecular alkylation as a key step for building the four-membered ring. The starting material of this synthesis was obtained by two consecutive alkylation reactions of benzylamine, first with *t*-butyl bromoacetate, then with bromoacetophenone, which gave aminoketone **76**. Reduction of the ketone followed by chlorination gave chloride **77** that was treated with LiHMDS: after generation of the enolate, intramolecular alkylation occurred and gave *trans*-isomer **78** and *cis*-isomer **79** which were separated by

flash chromatography. Relative configurations of these esters were attributed on the basis of NOE experiments. Removal of protecting groups by hydrogenolysis with Pearlman's catalyst and hot formic acid hydrolysis finally provided amino acid hydrochlorides **80** and **81** in good overall yields (*Scheme 21b*).

In 1999, Hanessian and co-workers described for the first time the diastereo- and enantioselective synthesis of 3-substituted derivatives of azetidine-2-carboxylic acid.[86] This synthesis, which was first applied to the preparation of **1** itself (*Scheme 13*), relies on the

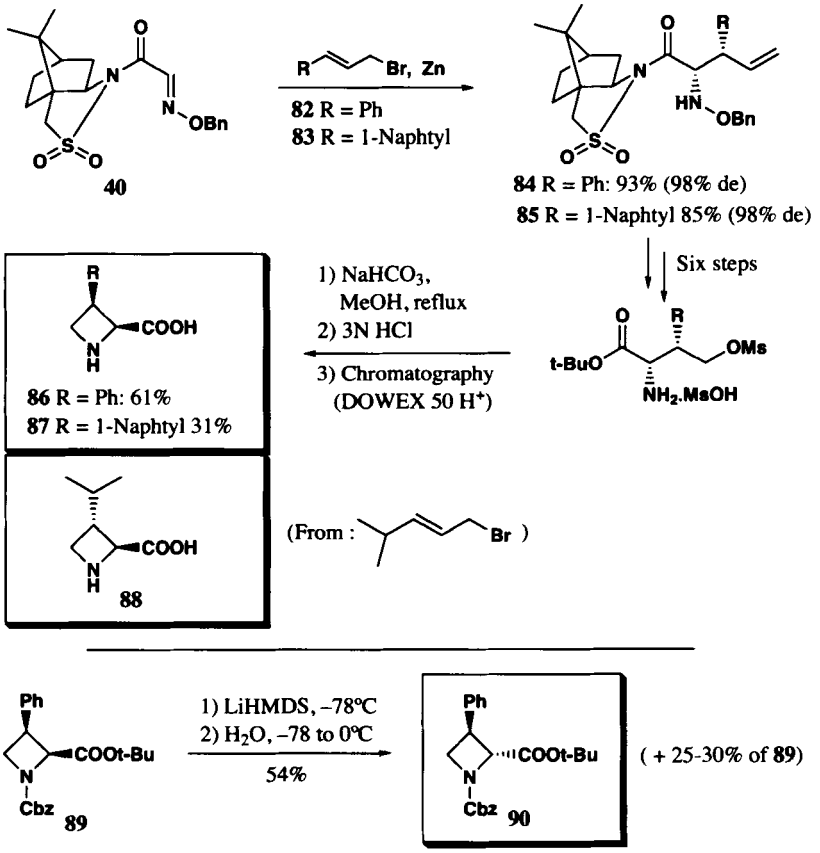


Synthesis of 4-Phenyl-substituted Derivatives

Scheme 21b

stereoselective allylation of Oppolzer's sultam **40** derived from glyoxylic acid *O*-benzyl oxime. Treatment of this sultam with Zn dust and allylic bromides **82** or **83** led to adduct **84** or **85** in high yields with total *syn* diastereoselectivity. Simple functional group transformations (six steps) eventually afforded functionalized mesylates that were cyclized and further hydrolyzed to give 2,3-*cis*-azetidinic amino acids **86** and **87** whose stereochemistries were proven by X-ray crystallography. However, when the same protocol was applied to a starting alkene bearing an *i*-Pr group, both *syn* and *anti* adducts were obtained in equimolar ratio. From the mixture of adducts, only the *anti* diasteroisomer could be cyclized to 2,3-*trans*-azetidine amino acid **88**. Interestingly, the epimerization of the *N*-Cbz derivative **89** was also reported, and gave *trans*-isomer **90** in 54% isolated yield, together with 25-30% of recovered **89** (*Scheme 22*).

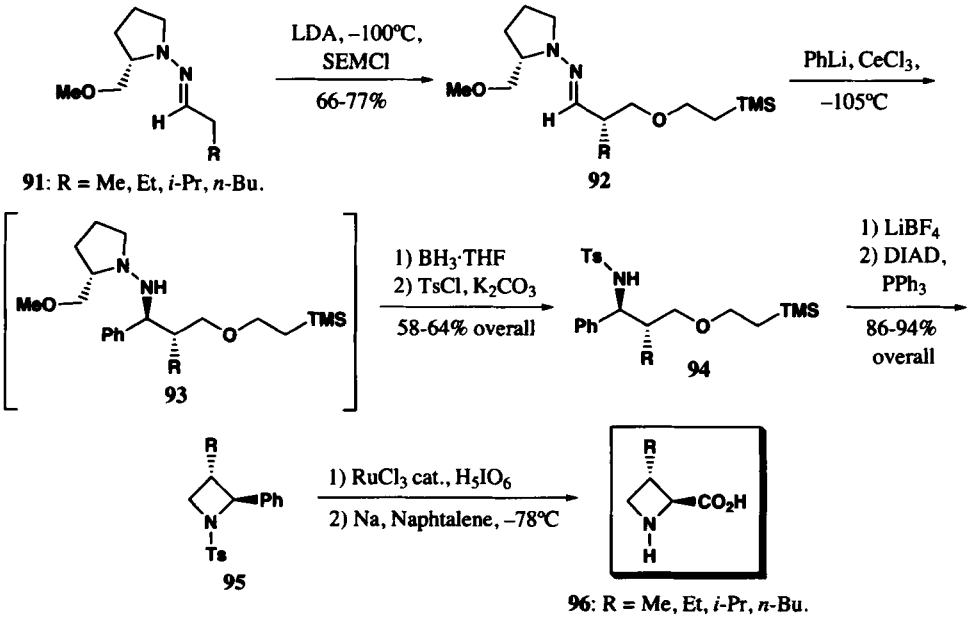
Very recently, Enders applied his well-known SAMP/RAMP hydrazone methodology for the synthesis of alkyl-substituted 2,3-*trans* derivatives.[87] In this event, hydrazone **91** was stereoselectively alkylated with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl), yielding **92** with high diastereoselectivity. Stereoselective addition of phenyllithium to the hydrazone moiety gave hydrazines **93** that were subjected to reductive cleavage, the released primary amines being further protected as their tosylsulfamides **94**. Cyclization to azetidines was performed *via* a two-step sequence involving cleavage of the TMS-ethyl protecting group with $LiBF_4$ followed by a Mitsunobu reaction. By use of this sequence, azetidines **95** were obtained in high overall yields and could serve as precursors to the corresponding azetidinic amino acids



Hanessian's Asymmetric Synthesis of 3-substituted Derivatives

Scheme 22

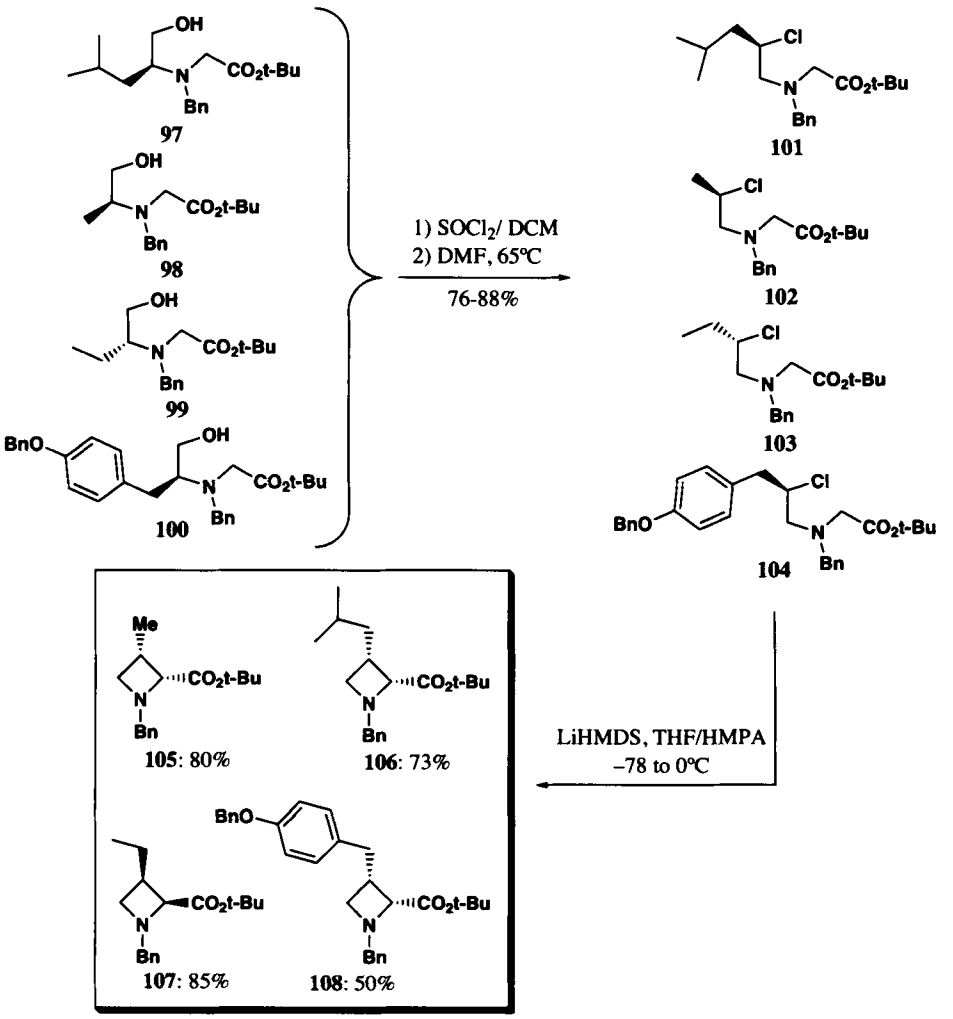
by oxidation of the 2-phenyl to the carboxylic acid group followed by *N*-deprotection with sodium naphtalenide. Azetidinic amino acids with various substituents at C-3 could be prepared using this sequence (*Scheme 23*).



Enders' Asymmetric Synthesis of 3-substituted Derivatives

Scheme 23

If Enders methodology allowed for the synthesis of *trans* 3-substituted derivatives of azetidine-2-carboxylic acid, their *cis* isomers can be conveniently obtained using a recently reported method,[88] based on an intramolecular 4-*exo-tet* alkylation strategy for the synthesis of azetidines from β-amino alcohols.[89] The sequence starts with enantiomerically pure β-amino alcohols **97-100**, easily prepared in two steps from commercially available substrates. Chlorination of these amino alcohols with thionyl chloride gives a mixture of regioisomeric chlorides resulting from the non-selective opening of a transient aziridinium ion by its chloride counteranion. Fortunately, it was found that this mixture could be equilibrated to the more substituted isomers **101-104** by simple heating at 60°C in DMF, in high overall yield and with no loss of the optical purity. Intramolecular alkylation of these chlorides was next effected by treatment with LiHMDS in THF, in the presence of HMPA (*Scheme 24*). This intramolecular alkylation was found to be highly diastereoselective and produced only the 2,3-*cis* isomers **105-108**. The efficiency of this reaction was found to be highly dependent on the steric crowding around the electrophilic center since the cyclization did not proceed with an isopropyl group. The orthogonally protected amino acids produced in this process were shown to be suitable for peptide synthesis. From a mechanistic point of view, it should be noted that the origin of this high 2,3-diastereoselectivity is still a matter of debate and that related compounds bearing a nitrile moiety in place of the *t*-butyl ester cyclized with no stereoselectivity.

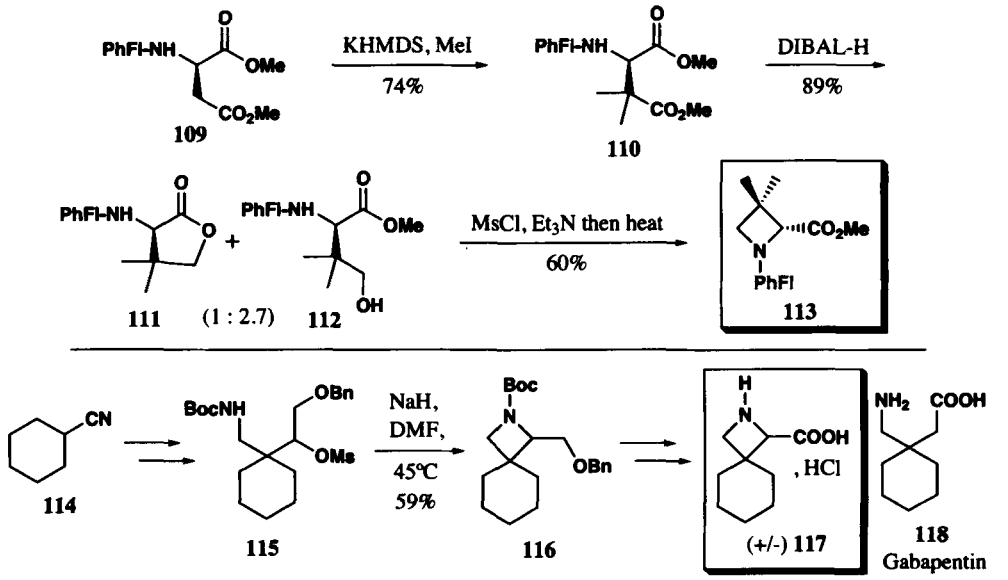


Couty's Asymmetric Synthesis of 3-Substituted Derivatives

Scheme 24

3,3-Dialkyl-substituted azetidinic amino acids have also been reported. The first example was disclosed by Goodman *et al.*[90] who reported the synthesis of azetidinic amino acid **113**, protected as *N*-PhFl (9-phenylfluorenyl) from aspartic acid: alkylation of **109** with methyl iodide yielded **110**, whose DIBAL-H mediated reduction gave **112**, together with some amounts of lactone **111**. Mesylation of **112** followed by heating eventually provided fair yield of **113** (*Scheme 25*). Bicyclic amino acid **117** was synthesized by Bryans and coworkers[91] and tested as a conformationally restricted analogue of the anticonvulsant drug *gabapentin* (**118**). The synthesis of **117** in

its racemic form required eight linear steps from cyclohexanecarbonitrile **114**, the key step for the ring closure being a conventional intramolecular *N*-alkylation (**115** → **116**, *Scheme 25*).

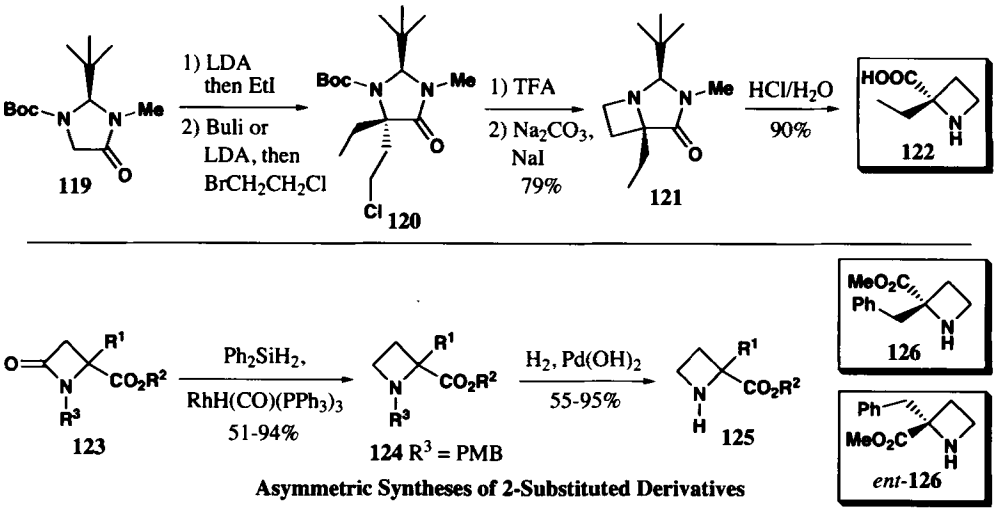


Synthesis of 3,3-Dialkyl-substituted Derivatives

Scheme 25

c) *2-Alkyl-substituted Derivatives*

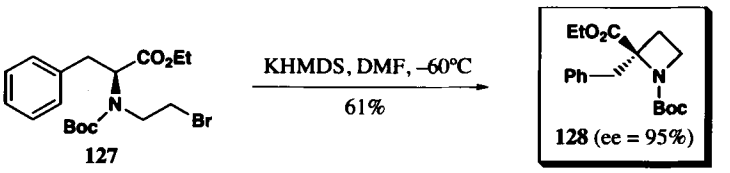
The well-known methodology developed by Seebach for the asymmetric synthesis of amino acids was successfully applied to the preparation of α-substituted derivatives of azetidine-2-carboxylic acid.[92] To this end, sequential alkylation of Boc derivative **119** with ethyl iodide and 1-bromo-2-chloroethane stereoselectively gave **120**. *N*-Boc deprotection initiated intramolecular alkylation and furnished bicyclic imidazolidinone **121** whose acidic hydrolysis finally gave enantiopure azetidinic amino acid **122**. More recently, access to this 2-alkyl substituted derivatives based on a chemoselective reduction of β-lactams **123** was reported by Cativiela *et al.*[93], a transformation that is best achieved using diphenylsilane in the presence of a rhodium catalyst. These conditions were found to be compatible with the presence of the ester group and allowed various substituents to be introduced at the 2-position of the heterocycle. However, access to enantiopure amino acids first required the resolution of the starting lactam, which was performed on a single example by HPLC for the synthesis of optically pure amino acids **126** and *ent*-**126**, compounds that can be envisioned as conformationally constrained derivatives of phenylalanine (*Scheme 26*).



Asymmetric Syntheses of 2-Substituted Derivatives

Scheme 26

The same amino acid was obtained through asymmetric cyclization involving memory of chirality, as depicted in *Scheme 27a*.[94] Treatment of *N*-Boc protected amino ester **127** with KHMDS gave azetidine **128** directly in 61% yield and with 95% ee. Although the absolute configuration of this compound was not ascertained, this straightforward synthesis is particularly elegant and implies the formation of enantiomerically enriched transient enolate with a chiral C-N axis.

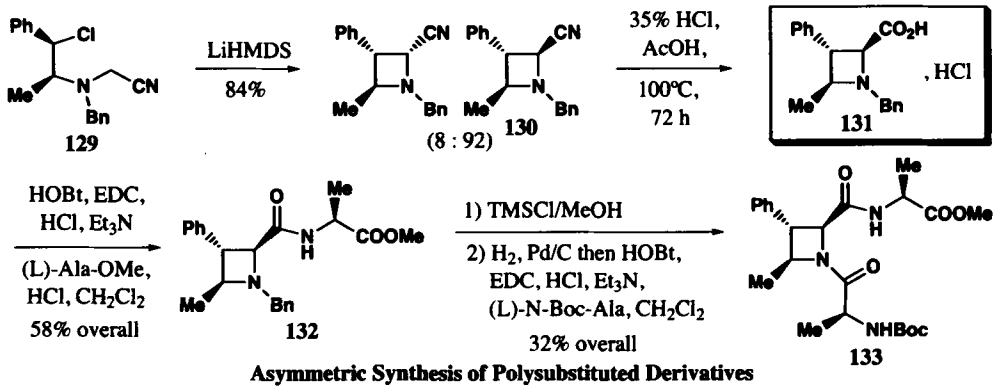


Asymmetric Syntheses of 2-substituted Derivatives using Memory of Chirality

Scheme 27a

d) Polysubstituted Derivatives

The synthesis of polysubstituted azetidinic amino acids is not a well documented topic. In 2003, it was reported[95] that intramocular alkylation of the ephedrine-derived *N*-cyanomethyl chloride **129** produces azetidinic amino nitrile **130**. The diastereoselectivity of this cyclization was proven to arise from a thermodynamic control operating during the anionic ring-closure. Hydrolysis of the amino nitrile required quite harsh conditions but allowed the isolation of azetidinic amino acid **131** in good yield, without epimerization or ring cleavage. This amino acid could be utilized in peptide synthesis, as exemplified in *Scheme 27b*.



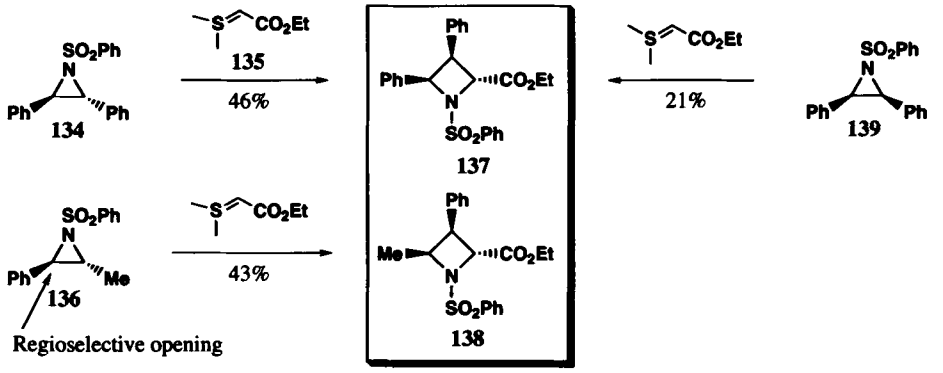
129 130 131 132 133

Asymmetric Synthesis of Polysubstituted Derivatives

Scheme 27b

The reaction of dimethylsulfonium methylide **135** with phenyl-substituted *N*-tosyl aziridines provides a general strategy for the synthesis of polysubstituted azetidine-2-carboxylic acid derivatives. Following the pioneering work of Vaultier and Carrié,[96] Nadir[97] quite recently reported the preparation of a series of *N*-tosyl azetidines **137-138**. This reaction which first involves a nucleophilic opening of the aziridine by the ylide followed by 4-*exo-tet* ring closure, was found to be highly regioselective (exclusive attack of the ylide at a benzylic position in **136**) and stereoselective, as illustrated with the selected examples shown in *Scheme 28a*.

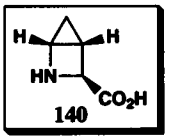
Finally, azetidinic amino acid SF-1836 **140** (*Fig. 4*), a cyclopropyl fused azetidine derivative, was isolated from the culture filtrate of *Streptomyces zaomyceticus*, and its peculiar structure was determined by an X-ray radiocrystallography.[98]



134 136 137 138 139

Synthesis of Polysubstituted Derivatives through Ring Expansion of Aziridines

Scheme 28a



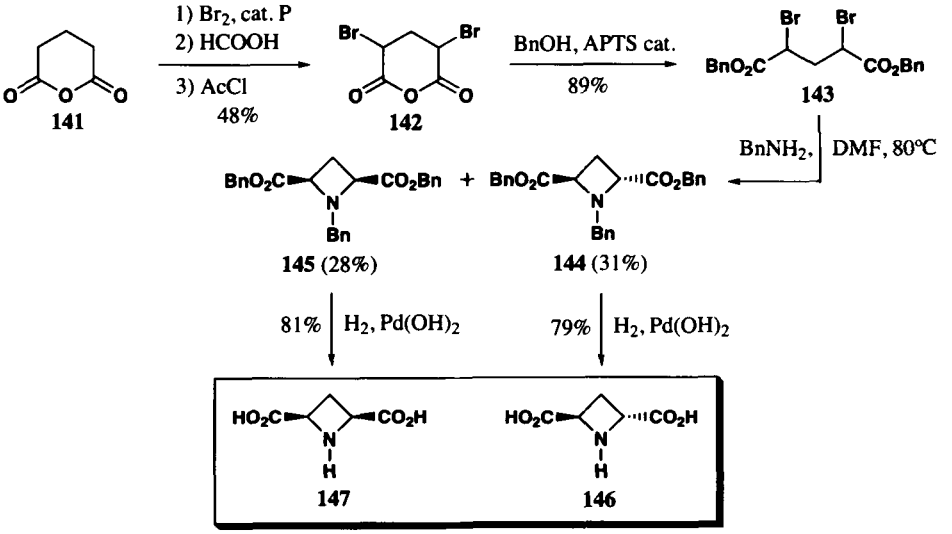
140

Fig. 4

2. Other Functionalized Derivatives

a) Additional Moiety: Carboxylic Acid

The synthesis of derivatives of azetidine-2-carboxylic acid bearing an extra carboxylic group is well-documented. Early work in this field was conducted by Baldwin[99] and followed by Kozykowski[100] who reported the preparation of both *cis*-2,4-azetidinedicarboxylic acid **147** and *trans*-2,4 azetidinedicarboxylic acid **148**, using an adaptation of the procedure initially developed by Cromwell (*vide supra*). The synthesis depicted in *Scheme 28b* starts from glutaric anhydride **141** which is first brominated and transesterified to give dibenzyl ester **143**. Reaction of the



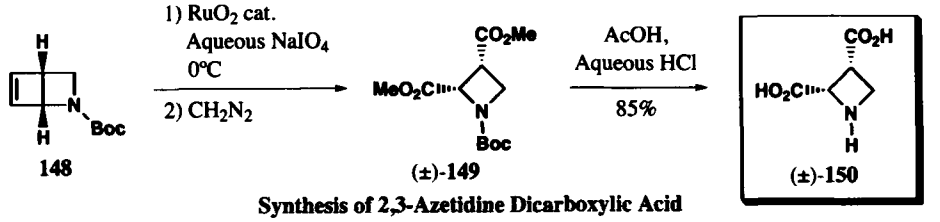
Synthesis of 2,4-Azetidinedicarboxylic Acid

Scheme 28b

latter with benzylamine affords a mixture of *cis*-**145** and *trans*-**144** that could be separated by flash chromatography. Finally, subsequent concurrent hydrogenolysis of both amine and ester groups gives the free amino acid in one step. Biological studies of these amino acids towards NMDA receptors revealed that **147** is a selective ligand for NMDA subtypes excitatory amino acid receptors, but not for kainate or quisqualate receptors. Subsequently, the *trans*-isomer of this diacid was resolved through its (–)-8-phenylmenthyl diesters,[101] and it was demonstrated that the (–)-(*S*,*S*) enantiomer was an activator of the metabotropic receptors.

The synthesis of racemic azetidine 2,3-dicarboxylic acid **150** through the oxidative cleavage of the double bond of **148** (*Scheme 29*) has been described recently.[102] To our knowledge, no biological evaluation of this compound has been reported so far.

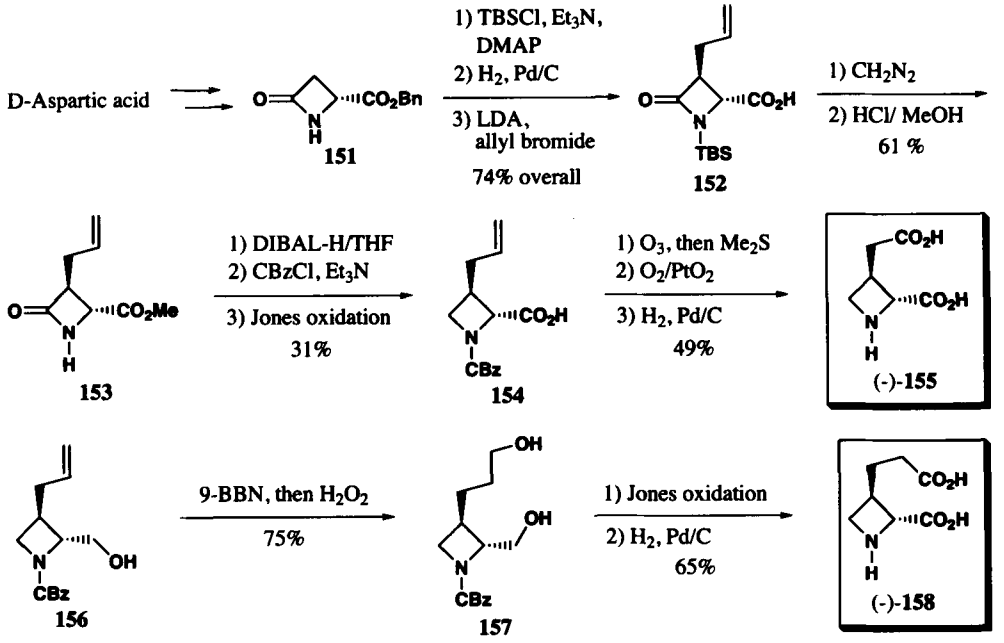
Derivatives in which the additional carboxylic acid is not directly linked to the azetidine ring have also been reported. Kozikowski's pioneering work in this area described the synthesis of azetidinic amino diacids **155** and **158**.[103] In this sequence, β-lactam **151**, prepared in several steps



Synthesis of 2,3-Azetidine Dicarboxylic Acid

Scheme 29

from (D)-aspartic acid, was *N*-silylated and the benzyl ester was cleaved by hydrogenolysis. An efficient and highly stereoselective alkylation with allyl bromide was next conducted, to give, after *N*-desilylation, the azetidin-2-one **153**. Simultaneous reduction of ester and amide groups with DIBAL-H followed by *N*-protection and Jones oxidation eventually furnished azetidine **154**. A three step sequence gave the fully deprotected diacid: (*i*) oxidative cleavage of the alkene with ozone, (*ii*) oxidation of the intermediate aldehyde and (*iii*) deprotection by hydrogenolysis. Alternatively, hydroboration of **156** followed by oxidation gave diol **157** that was converted into homologous diacid **158** through conventional chemistry (*Scheme 30*). It should be



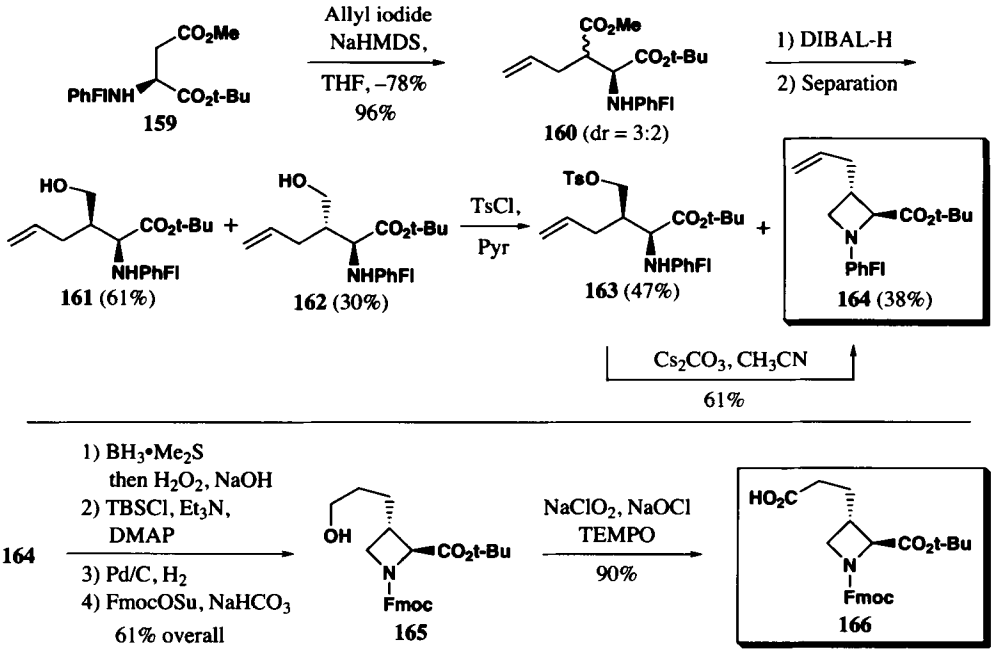
Kozikowski's Synthesis of 3-Substituted Derivatives

Scheme 30

noted that the enantiomers of **155** and **158** were also prepared following the same route, starting from (L)-aspartic acid.

These amino acids are conformationally constrained analogues of glutamic acid and were prepared in order to study their binding with neuroexcitatory amino acids receptors. *Ent*-**155** was found to be a potent kainic acid receptor agonist, as well as a potent inhibitor of Na^+-dependent glutamic acid uptake.

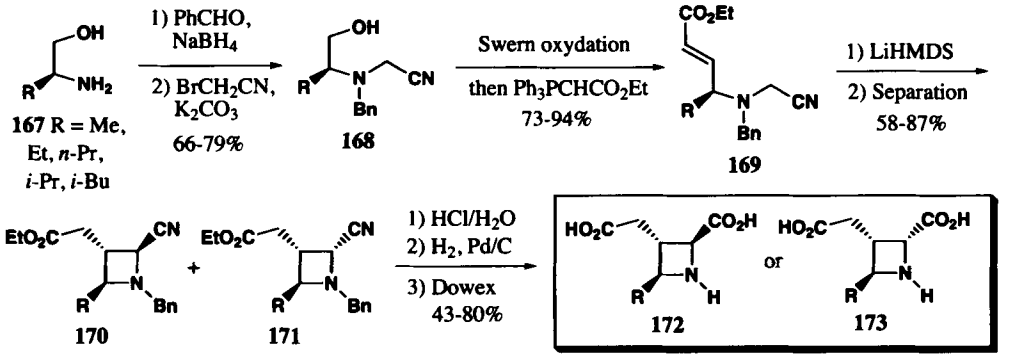
The lengthy procedure described above (11 linear steps and 8% overall yield from **151**) to prepare (–)-**155** was recently improved by Lubell,[104] who described the preparation of azetidines *trans*-**164** (and *cis* from **162**), starting from orthogonally protected aspartic acid **159**. The key step is based on an alkylation with allyl iodide, affording **160** in a non-stereoselective manner. DIBAL-H reduction of the diasteroisomeric mixture afforded *syn*-**161** and *anti*-**162** that could be separated at this stage by flash chromatography. After activation of the alcohol as a tosylate, ring closure eventually afforded in each case the corresponding azetidine (*trans*-**164** only shown) whose relative configurations were determined on the basis of NOESY spectra. Functionalization of the allyl side-chain in **164** by hydroboration was followed by protective group exchange to give *N*-Fmoc derivative **165**. Oxidation of the primary alcohol finally afforded **166** in nine linear steps and 19% overall yield from **159**, in spite of the low stereoselectivity of the allylation step (*Scheme 31*).



Lubell's Synthesis of 3-Substituted Derivatives

Scheme 31

A new route to azetidine dicarboxylic derivatives bearing an additional alkyl substituent at C-4 was recently proposed.[105] This methodology affords in a straightforward manner the four-membered ring through an intramolecular Michael addition of amino nitrile anion on unsaturated esters **169**. The required substrates are prepared in a three step sequence from commercially available enantiomerically pure β-amino alcohols. The cyclization step gives a mixture of 2,3-*cis* and 2,3-*trans* isomers, resulting from thermodynamic control, and these compounds could be conveniently separated by flash chromatography. Transformation of these azetidines into free amino acids only required two steps: (i) acidic hydrolysis of the ethyl ester and nitrile groups and (ii) hydrogenolysis of the *N*-benzyl protecting group. Using this reaction sequence, a set of ten new amino acids of general structure **172** or **173** was prepared and these compounds were evaluated as new ligands for the glutamate receptors and transporters;[106] amino diacids **172** (R = Me and R = *n*-Pr) were found to be selective inhibitors of the glutamate transporter EAAT-2 (*Scheme 32*).



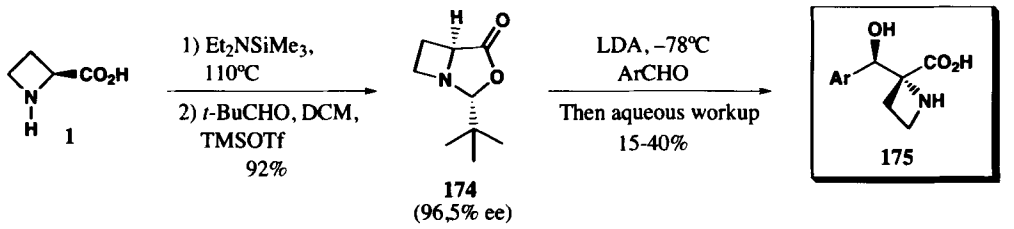
Synthesis of 3,4 Substituted Derivatives through Intramolecular Michael Addition

Scheme 32

b) *Additional Moiety: Hydroxyl Group (or derivatives) or Halogen*

Apart from hydroxylated derivative **165** described in the previous section, other related compounds bearing a hydroxyl-substituted side-chain, have been prepared. Seebach[107] reported the synthesis of **175** *via* the generation of a highly strained enolate from bicyclic acetal **174** and its trapping with aromatic aldehydes. The low yields of these reactions can be attributed to the extreme sensitivity of the strained acetal **174** that was obtained in diastereo- and enantiomerically pure form only through the "silyl" methodology depicted in *Scheme 33* (previous attempts to prepare this compound led to total racemization).[108]

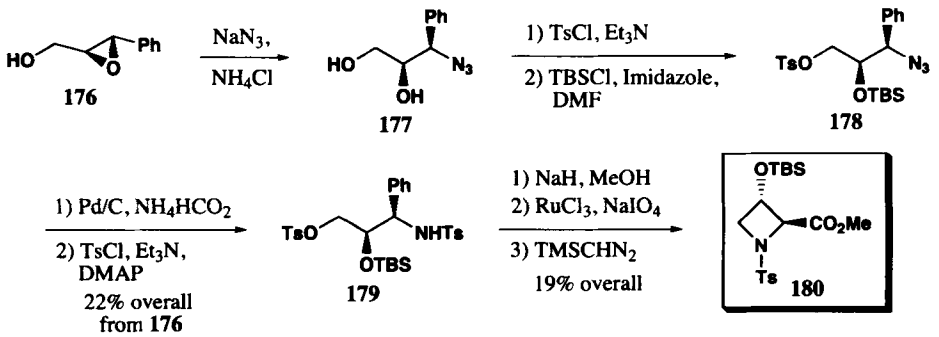
The preparation of 3-hydroxylated derivatives of azetidinic amino acids has also been described, since it is a constituent of 3-*epi*-hydroxymugineic acid, a natural phytosiderophore acting as an iron transporter in plants. Early work in this area was reported by Hamada and coworkers,[109] and starts with enantiopure epoxy alcohol **176**, easily available through a Sharpless's epoxidation of cinnamyl alcohol. Regioselective opening of the latter with azide anion was followed by chemoselective tosylation of the primary alcohol and TBS protection of the secondary one. The



Seebach's Asymmetric Synthesis of a 2-Substituted Derivative

Scheme 33

azide moiety in **178** was then reduced with ammonium formate and the amine was next protected as a sulfonamide. Ring closure of **179** then allowed for the formation of the azetidine ring. Finally, the phenyl group in this compound was oxidatively cleaved to give the acid that was esterified with trimethylsilyldiazomethane (*Scheme 34*). Deprotection of the *N*-tosyl protecting group in **180** was not described in the publication.

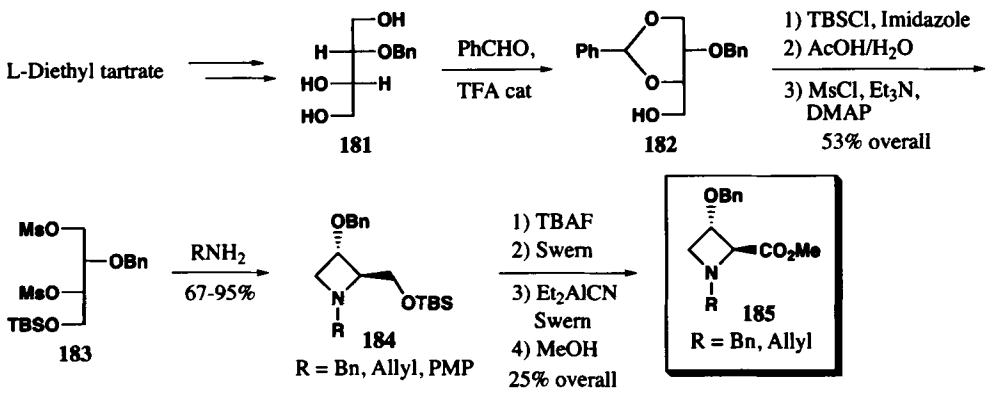


Synthesis of an Intermediate *en route* to 3-*epi*-Hydroxymugineic Acid

Scheme 34

Dureault *et al*[110] also reported a synthesis of this amino acid starting from L-diethyl tartrate. Transformation of the latter into triol **181** was followed by acetalization with benzaldehyde to give **182**. Silylation of the primary alcohol and cleavage of the acetal gave a diol that was mesylated in good yield. Reaction of **183** with various amines then gave excellent yields of azetidines. Due to the presence of tertiary amine prone to oxidation, the oxidation of the side-chain was carried out in two consecutive Swern oxidation steps and *via* an intermediate cyanohydrin (*Scheme 35*). However, it should be noted that attempts at selectively deprotecting the amine without cleaving the O-benzyl group failed.

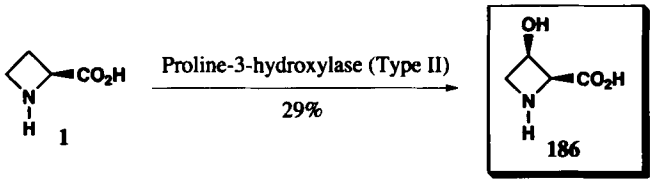
A few years later, in the course of a study directed to the selectivity of proline hydroxylase, Ozaki reported the selective hydroxylation of L-Aze by proline 3-hydroxylase (type I or II), producing hydroxylated analogues of L-Aze **186**.[111] Although the enzyme was shown to be espe-



Dureault's Synthesis of a 3-Hydroxylated Derivative

Scheme 35

cially selective, the amino acid was isolated in low yield (29%) and the reaction was performed on only a small scale (2.5 mg) (*Scheme 36*).

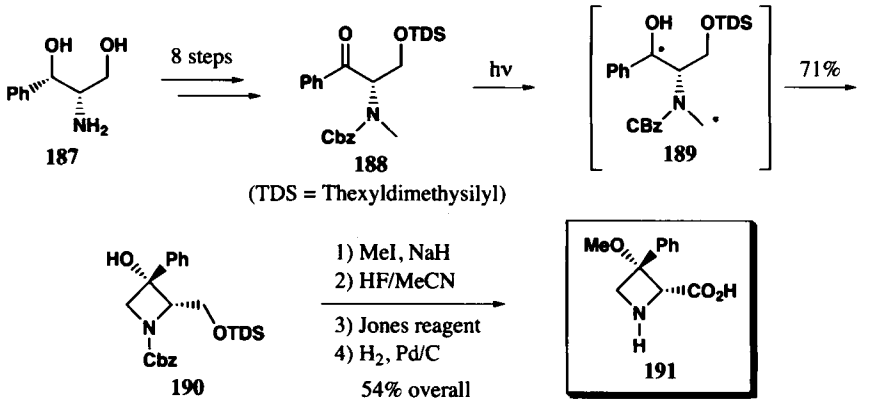


Enzymatic Hydroxylation of L-Aze

Scheme 36

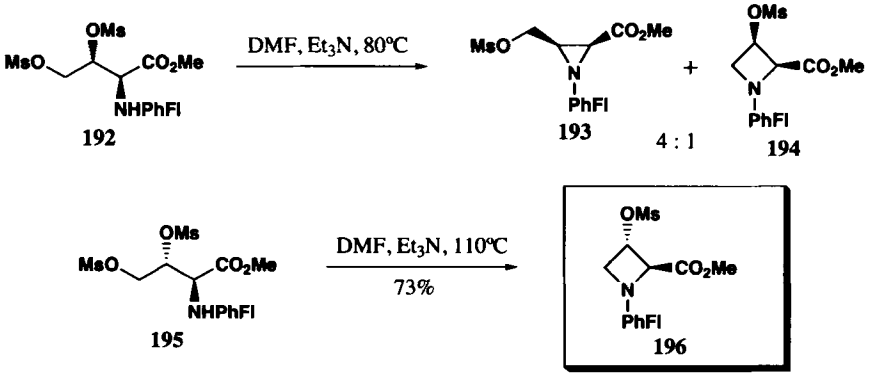
A photochemical cyclization involving the diradical **189** was described by Wessig.[112] This reaction led to azetidinol **190**, obtained with high diastereoselectivity and in enantiomerically pure form. Methylation of the tertiary alcohol, O-desilylation of the primary hydroxyl and Jones oxidation gave, after deprotection, amino acid **191**. From a practical point of view, this synthesis is however quite tedious since the required substrate **188** for the photochemically induced ring-closure was prepared in eight steps from Meyer's amino diol **187**. The enantiomer of **191** could also be prepared from *ent*-**188**, but the latter required ten steps from D-serine (*Scheme 37*).

The formation of azetidine ring, involving intramolecular alkylation of 1,3-amino alcohols is a quite conventional method and has been illustrated through numerous examples in this review. The efficiency of this method is, however, greatly influenced by the nature and relative stereochemistries of the substituents in the produced azetidine. The following work illustrates this point perfectly.[113] When *syn* dimesylate **192** was subjected to intramolecular alkylation, azetidine **194** was produced as a minor product, aziridine **193** being formed almost exclusively through a 3-*exo-tet* ring closure. On the other hand, when *anti* **195** (obtained in five steps from L-aspartic acid) was reacted in the same conditions, azetidine **196** was now produced exclusively through a preferred 4-*exo-tet* process (*Scheme 38*).



A Photochemical Ring Closure to a 3-Substituted Derivative

Scheme 37



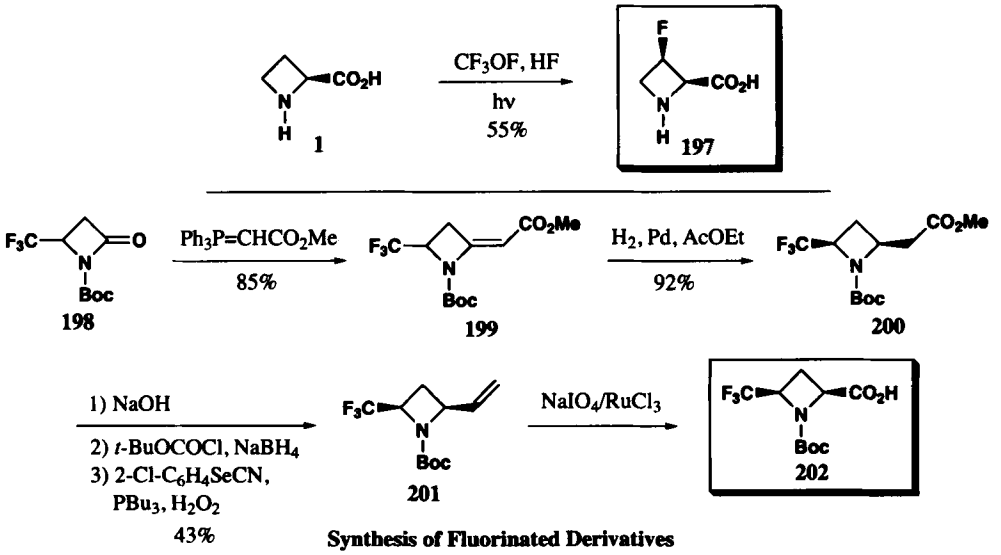
Synthesis of a 3-Substituted Azetidine through Chemoselective Intramolecular Alkylation

Scheme 38

To our knowledge, a single example of 3-halogenated derivative of L-Aze has been reported so far. This fluorinated derivative was obtained by treatment of the latter with CF_3OF under irradiation in liquid HF as solvent and produced *cis*-3-fluoro-azetidine-2-carboxylic acid **197** in 53% yield (*Scheme 39*). Despite the astonishing selectivity of this reaction, the experimental protocol is not especially convenient and probably precluded the development of this interesting process.[114]

Recently, the synthesis of amino acid **202**, bearing a trifluoromethylated side-chain has been described.[115] Its preparation summarized in *Scheme 39* relies on a Wittig olefination of β-lactam **198** followed by stereoselective hydrogenation of the exocyclic double bond to give azetidine **200**. After reduction of the ester moiety in this compound, the primary alcohol was dehydrated and the resulting alkene was oxidatively cleaved, to furnish racemic **202** in good yield. Since the intermediate **200** has also been prepared in optically pure form, an enantioselective

synthesis of **202** is therefore possible. Moreover, 4-substituted derivatives of this amino acid should also be available using the chemistry described in this work.

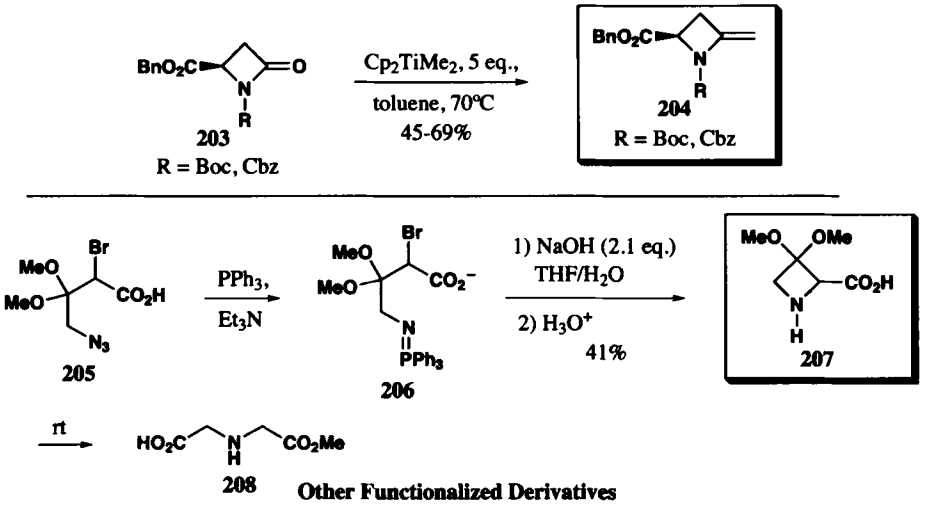


Synthesis of Fluorinated Derivatives

Scheme 39

c) Miscellaneous Derivatives

If a Wittig olefination was used in the preceding synthesis, olefination of β-lactams was also reported to proceed well with dimethyltitanocene (Petasis' reagent). In 2000, Martinez and Howell[116] reported the methylenation of **203**, affording in moderate yield the unsaturated derivatives **204** (*Scheme 40*). In view of the diastereoselectivity of the hydrogenation step described in



Other Functionalized Derivatives

Scheme 40

Scheme 39, these compounds appear to be excellent candidates for the preparation of 2,4-*cis* derivatives of azetidine-2-carboxylic acid. Very recently, De Kimpe *et al.*[117] reported the preparation of 3,3-dimethoxyazetidine-2-carboxylic acid **207** through an intramolecular *N*-alkylation under carefully controlled conditions. To this end, hydrolysis of iminophosphorane **206**, generated from the corresponding azide **205** in basic medium, induced the formation of amino acid **207** after acidification. It should be noted however, that this compound was unstable and gave the acyclic amino acid **208** upon storage at room temperature, probably *via* a retro-Dieckman reaction (*Scheme 40*).

VI. CONCLUSION

The publication year of this review, 2006, marks the jubilee of 50 years since the discovery of **1** by Fowden.[1,14] A retrospective look reveals that the interesting history of **1** to be typical for an azetidine: interest in this amino acid was initially restricted to isolated research groups and this constrained amino acid has been considered for long as a "lab curiosity". However, in the past decade, a renewed interest has grown, as clearly demonstrated by the amount of synthetic work devoted to this molecule and its derivatives: among the 120 references cited in this review article, 56 were published in the last decade. The growing interest originates from the discovery by medicinal chemists of many bioactive molecules which incorporate L-Aze or its derivatives in their structure.

As illustrated in this review, synthetic challenges aimed at the preparation of this simple molecule and its substituted derivatives in diastereo- and enantiomerically pure form have excited the imagination of synthetic chemists, even if a lot of work is yet to be done. From a more general point of view, there is absolutely no doubt that the growing interest in this field will continuously extend the knowledge in the chemistry of azetidines, an understudied yet highly promising class of heterocycles.[118,119]

Acknowledgements.- The authors acknowledge the assistance of Dr. Mangaleswaran Sivaprakasam for careful proofreading of the manuscript.

REFERENCES

1. L. Fowden, *Nature*, **176**, 347 (1955).

2. A. I. Virtanen, and P. Linko, *Acta Chem. Scand.*, **9**, 551 (1955).

3. A. I. Virtanen, *Nature*, **176**, 984 (1955).

4. A. Zagari, G. Nemethy, and H. A. Scheraga, *Biopolymers*, **30**, 951 (1990). (b) A. Zagari, G. Nemethy, and H. A. Scheraga, *Biopolymers*, **30**, 967 (1990). (c) T. J. Deming, M. J. Fournier, T. L. Mason, and D. A. Tirrell, *Macromolecules*, **29**, 1442 (1996). (d) G. Schlechtingen, R. N. Dehaven, J. D. Daubert, J. Cassel, and M. Goodman, *Biopolymers*, **71**, 71 (2003).

5. (a) A. V. Rama Rao, M. K. Gurjar, and V. Kaiwar, *Tetrahedron: Asymmetry*, **3**, 859 (1992). (b) W. Behnen, C. Dauelsberg, S. Wallbaum, and J. Martens, *Synth. Commun.*, **22**, 2143 (1992). (c) E. J. Corey and C. J. Helal, *Angew. Chem., Int. Ed.*, **37**, 1986 (1998).

6. M. Yamaguchi, T. Shiraishi, and M. Hirama, *J. Org. Chem.*, **61**, 3520 (1996).

7. W. A. J. Starmans, L. Thijs, and B. Zwanenburg, *Tetrahedron*, **54**, 629 (1998).

8. W. A. J. Starmans, R. W. A. Walgers, L. Thijs, R. de Gelder, J. M. M. Smits, and B. Zwanenburg, *Tetrahedron*, **54**, 4991 (1998).

9. C. Thomassigny, D. Prim, and C. Greck, *Tetrahedron Lett.*, **47**, 1117 (2006).

10. M. Miyoshi, H. Sugano, T. Fujii, T. Ishihara, and N. Yoneda, *Chem. Lett.*, 5 (**1973**).

11. H. M. Berman, E. L. McGandy, J. W. Burgner II, and R. L. VanEtten, *J. Am. Chem. Soc.*, **91**, 6177 (1969).

12. A. G. M. Barrett, P. Dozzo, A. J. P. White, and D. J. Williams, *Tetrahedron*, **58**, 7303 (2002).

13. F. Couty, G. Evano, M. Vargas-Sanchez, and G. Bouzas, *J. Org. Chem.*, **70**, 9028 (2005).

14. L. Fowden, *Biochem J.*, **64**, 323 (1956).

15. G. Anderegg and H. Ripperger, *J. Chem. Soc., Chem. Commun.*, 647 (**1989**).

16. L. Fowden and M. Bryant, *Biochem J.*, **70**, 626 (1958).

17. L. Fowden and F. C. Stewart, *Ann. Bot.*, **21**, 53 (1957).

18. M.-L. Sung and L. Fowden, *Phytochem.*, **8**, 2095 (1969).

19. L. Fowden, *Phytochem.*, **11**, 2271 (1972).

20. B. Bach, R. P. Gregson, G. S. Holland, R. J. Quinn, and J. L. Reichert, *Experientia*, **34**, 688 (1978).

21. L. Fowden and M. H. Richmond, *Biochim. Biophys. Acta.*, **71**, 459 (1963).

22. P. J. Peterson and L. Fowden, *Nature*, **200**, 148 (1963).

23. F. H. Tsai, C. G. Overberger, and R. Zand, *Biopolymers*, **30**, 1039 (1990).

24. M. Tan, L. Ryhanen, and J. Uitto, *J. Invest. Dermatol.*, **80**, 261 (1983).

25. A. Lubec, A. Pollak, H. Coradello, H. Aschinger, A. Wagendristl, H. Bangert, K. Seifert, and E. Ratzenhoger, *Wien Klin. Wochenschr.*, **97**, 401 (1985).

26. S. Trasko, E. Franzblau, and R. F. Troxler, *Biochim. Biophys. Acta*, **447**, 425 (1976).

27. N. Moullect, V. Karcher-Djuricic, and J. V. Ruch, *C. R. Seances Soc. Biol. Fil.*, **169**, 767 (1975).

28. M. G. Joneja, *Teratology*, **23**, 365 (1981).

29. I. R. Adamson and G. M. King, *Lab. Invest.*, **57**, 439 (1987).

30. (a) E. Leete, *J. Am. Chem. Soc.*, **89**, 3162 (1964). (b) E. Leete, G. E. Davis, C. R. Hutchinson, K. W. Woo, and M. R. Chedekel, *Phytochem.*, **13**, 427 (1974).

31. E. Leete, L. L. Louters, and H. S. P. Rao, *Phytochem.*, **25**, 2753 (1986).

32. (a) M.-L. Sung and L. Fowden, *Phytochem.*, **10**, 1523 (1971). (b) R. Laske, H. Schoenenberger, and E. Holler, *Arch. Pharm.*, **322**, 847 (1989).

33. (a) M. Budesinsky, H. Budzikiewicz, Z. Prochazka, H. Ripperger, Axel Römer, and K. Schreiber, *Phytochem.*, **19**, 2295 (1980). (b) S. Fushiya, K. Takahashi, S. Nakatsuyama, Y. Sato, S. Nozoe, and S.-I. Takagi, *Phytochem.*, **21**, 1907 (1982). (c) E. Kinoshita, J. Yamakoshi, and M. Kikuchi, *Biosci. Biotechnol. Biochem.*, **57**, 1107 (1993). (d) K. Suzuki, K. Shimada, S. Nozoe, K. Tanzawa, and T. Ogita, *J. Antibiot.*, **49**, 1284 (1996).

34. (a) T. Takemoto, K. Nomoto, S. Fushiya, R. Ouchi, G. Kusano, H. Hikino, S. Takagi, Y. Matsuura, and M. Kakudo, *Proc. Jpn. Acad., Ser. B*, **54**, 469 (1978). (b) Y. Sugiura, Y. Mino, T. Iwashita, and K. Nomoto, *J. Am. Chem. Soc.*, **107**, 4667 (1985).

35. T. Murakami, K. Ise, M. Hayakawa, S. Kamei, and S.-I. Takagi, *Chemistry Lett.*, 2137 (**1989**).

36. S. Fushiya, T. Tamura, T. Takashi, and S. Nozoe, *Heterocycles*, **22**, 1039 (1984).

37. D. Schummer, E. Forche, V. Wray, T. Domke, H. Reichenbach, and G. Höfle, *Liebigs Ann. Chem.*, 965 (**1996**).

38. S. Suzuki, K. Isono, J. Nagatsu, T. Mizutani, Y. Kawashima, and T. Mizuno, *J. Antibiotics, Ser. A*, **18**, 131 (1965).

39. T. Akihisa, S. Mafune, M. Ukiya, Y. Kimura, K. Yasukawa, T. Suzuki, H. Tokuda, N. Tanabe, and T. Fukuoka, *J. Nat. Prod.*, **67**, 479 (2004).

40. (a) B. I. Ericksson, S. Carlsson, M. Halvarsson, B. Risberg, and C. Mattsson, *Thromb. Haemostasis*, **78**, 1404 (1997). (b) I. Kirk (AstraZeneca AB), PCT Int. Appl. WO 2000041716, (**2000**). *Chem. Abstr.*, **123**, 99559 (2000).

41. M. E. Condon, E. W. Petrillo, Jr., D. E. Ryono, J. A. Reid, R. Neubeck, M. Puar, J. E. Heikes, E. F. Sabo, K. A. Losee, D. W. Cushman, and M. A. Ondetti, *J. Med. Chem.*, **25**, 250 (1982).

42. M. J. Suto, M. A. Stier, L. M. Werbel, C. M. Arundel-Suto, W. R. Leopold, W. E. Elliott, and J. S. Sebolt-Leopold, *J. Med. Chem.*, **34**, 2484 (1991).

43. R. C. Schnur, M. L. Corman, R. J. Gallaschun, B. A. Cooper, M. F. Dee, J. L. Doty, M. L. Muzzi, J. D. Moyer, C. I. DiOrio, E. G. Barbacci, P. E. Miller, A. T. O'Brien, M. J. Morin, B. A. Foster, V. A. Pollack, D. M. Savage, D. E. Sloan, L. R. Pustilnik, and M. P. Moyer, *J. Med. Chem.*, **38**, 3806 (1995).

44. T. M. Kamenecka, Y.-J. Park, L. S. Lin, S. de Laszlo, E. D. McCauley, G. Van Riper, L. Egger, U. Kidambi, R. A. Mumford, S. Tong, W. Tang, A. Colletti, Y. Teffera, R. Stearns, M. MacCoss, J. A. Schmidt and William K. Hagmann, *Bioorg. Med. Chem. Lett.*, **14**, 2323 (2004).

45. D. N. Deaton, A. M. Hassell, R. B. McFadyen, A. B. Miller, L. R. Miller, L. M. Shewchuk, F. X. Tavares, D. H. Willard, Jr., and L. L. Wright, *Bioorg. Med. Chem. Lett.*, **15**, 1815 (2005).

46. For an old review, see: N. H. Cromwell and B. Phillips, *Chem. Rev.*, **79**, 331 (1979).

47. Y. Yamada, T. Emori, S. Kinoshita and H. Okada, *Agric. Biol. Chem.*, **37**, 649 (1973).

48. L. Pichat, P. N. Liem, and J.-P. Guermont, *Bull. Chim. Soc.*, 4079 (**1968**).

49. R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, **6**, 435 (1969).

50. W. A. J. Starmans, R. G. Doppen, L. Thijs, and B. Zwanenburg, *Tetrahedron: Asymmetry*, **9**, 429 (1998).

51. W.-L. Wu, M. A. Caplen, M. S. Domalski, H. Zhang, A. Fawzi, and D. A. Burnett, *Bioorg. Med. Chem. Lett.*, **12**, 3157 (2002).

52. E. Juaristi and D. Madrigal, *Tetrahedron*, **45**, 629 (1989).

53. A. De Nicola, C. Einhorm, J. Einhorn, J. L. Luche, *J. Chem. Soc. Chem. Comm.*, 879 (**1994**).

54. R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, **6**, 993 (1969).

55. P. Barth and A. Pfenninger (Astra Aktiebolag), WO 9 741 084, (**1997**). *Chem. Abstr.*, **128**, 13193 (1997).

56. Y. Takashima, J. Kudo, M. Hazama, and A. Inoue (Sumimoto Chemical Company), EP 974 670, (**2000**). *Chem. Abstr.*, **132**, 107 041 (2000).

57. J. Kudo, M. Hazama, and N. Hirata (Sumimoto Chemical Company), EP 855 446, (**1998**). *Chem. Abstr.*, **129**, 160706 (1998).

58. N. Nagashima (Kaneka Corporation), WO 2001055104, (**2003**). *Chem. Abstr.* **135**, 137391 (2001).

59. T. Kondo and N. Ueyama, PCT US Appl. US 0 171 849 A1, (**2003**).

60. M. Miyoshi, H. Sugano, T. Fujii, T. Ishihara, and N. Yoneda, *Chemistry Lett.*, 5 (**1973**).

61. J. E. Baldwin, M. North and A. Flinn, *Tetrahedron*, **44**, 637 (1988).

62. P. Ciapetti, F. Soccolini, and M. Taddei, *Tetrahedron*, **53**, 1167 (1997).

63. P. Ciapetti, A. Mann, A. Shoenfelder, and M. Taddei, *Tetrahedron Lett.*, **39**, 3843 (1998).

64. S. Hanessian, N. Bernstein, R.-Y. Yang, and R. Maguire, *Bioorg. Med. Chem. Lett.*, **9**, 1437 (1999).

65. H. H. Wasserman, B. H. Lipshutz, A. W. Temper, and J. S. Wu., *J. Org. Chem.*, **46**, 2991 (1981).

66. H. Ushio, N. Takano, Y. Honda, S. Seko, and M. Hazama (Sumimoto Chemical Company), EP 827 954, (**1998**). *Chem. Abstr.*, **128**, 230235 (1998).

67. I. Ojima, M. Zhao, T. Yamato, and K. Nakahashi, *J. Org. Chem.*, **56**, 5263 (1991).

68. H. Awaji, S. Matsumoto, K. Inoue, and K. Matsuo, WO 9 847 867, (**1998**). *Chem. Abstr.*, **129**, 316132 (1998).

69. Scheme 15 is adapted from the patent cited in ref. 68, no yields or reagents are specified on this scheme since many different reagents and reactants were used in the patent publication. See ref. 68 for details.

70. (a) C. Agami, F. Couty, and G. Evano, *Tetrahedron: Asymmetry*, **13**, 297 (2002). (b) F. Couty, G. Evano, and N. Rabasso, *Tetrahedron: Asymmetry*, **14**, 2407 (2003).

71. F. Couty, G. Evano, M. Vargas-Sanchez, and G. Bouzas, *J. Org. Chem.*, **70**, 9028 (2005).

72. Y. Futamura, M. Kurokawa, R. Obata, S. Nishiyama, and T. Sugai, *Biosci. Biotechnol.*, **69**, 1892 (2005).

73. (a) S. Sugiyama, S. Watanabe, T. Inoue, R. Kurihara, T. Itou, and K. Ishii, *Tetrahedron*, **59**, 3417 (2003). (b) Note that the transesterification was necessary since the cyclization step does not proceed as well with the ethyl esters.

74. P. Thanon, M-J. Musiol, and L. Moroder "*Houben-Weyl, vol. E22c p 62: Synthesis of Peptidomimetics*", M. Goodman, A. Felix, L. Moroder, and C. Toniolo Eds. Thieme: Stuttgart, New-York, 2002.

75. R. Boni, and A. S. Verdini, *J. Chem. Soc. Perkin Trans. 1*, 2173 (**1974**).

76. R. M. Rodebaugh, and N. H. Cromwell, *J. Heterocyclic Chem.*, **6**, 435 (1969).

77. N. H. Cromwell, and K. F. Prodasa, *J. Heterocyclic Chem.*, **17**, 1277 (1980).

78. C. Pasquier, J. Eilers, I. Reiners, J. Martens, A. Mortreux, and F. Agbossou, *Synlett*, 1164 (**1998**).

79. H. H. Wasseman, and A. W. Tremper, *Tetrahedron Lett.*, **18**, 1449 (1977).

80. H. H. Wasserman, A. W. Tremper, and J. S. Wu, *Tetrahedron Lett.*, **20**, 1089 (1979).

81. H. H. Wasserman, W. T. Han, J. M. Schaus, and J. W. Faller, *Tetrahedron Lett.*, **25**, 3111 (1984).

82. S. Yoshifuji, K-I. Tanaka, T. Kawai, and Y. Nitta, *Chem. Pharm. Bull.*, **33**, 5515 (1985).

83. S. Yoshifuji, K-I. tanaka, and Y. Nitta, *Heterocycles*, **24**, 2539 (1986)

84. (a) D. S. Soriano, K. F. Podraza, and N. H. Cromwell, *J. Heterocyclic Chem.*, **17**, 1389 (1980). (b) D. S. Soriano, K. F. Podraza, and N. H. Cromwell, *J. Heterocyclic Chem.*, **17**, 623 (1980).

85. D. J. Blythin, M. J. Green, M. J. R. Lauzon, and H. O. Shue, *J. Org. Chem.*, **59**, 6089 (1994).

86. S. Hanessian, N. Bernstein, R. Y. Yang, and R. Maguire, *Bioorg. Med. Chem. Lett.*, **9**, 1437 (1999).

87. D. Enders and J. Gries, *Synthesis*, 3508 (**2005**).

88. M. Sivaprakasham, F. Couty, G. Evano, B. Srinivas, R. Sridhar, and K. Rama Rao, *Synlett*, 781 (**2006**).

89. C. Agami, F. Couty, and G. Evano, *Tetrahedron: Asymmetry*, **13**, 297 (2002).

90. N. Kawahata, M. Weisberfg, and M. Goodman, *J. Org. Chem.*, **64**, 4362 (1999).

91. J-M. Receveur, J. S. Bryans, M. J. Field, L. Singh, and D. C. Horwell, *Bioorg. Med. Chem. Lett.*, **9**, 2329 (1999).

92. D. Seebach, E. Dziadulewicz, L. Behrendt, S. Cantoreggi, and R. Fitzi, *Liebigs Ann. Chem.*, 1215 (**1989**).

93. G. Gerona-Navarro, M. A. Bonache, M. Alías, M. Jesús Pérez de Vega, M. T. García-López, P. Lopez, C. Cativiela, and R. Gonzàles-Muñiz, *Tetrahedron Lett.*, **45**, 2193 (2004).

94. T. Kawabata, S. Kawakami, and S. Majundar, *J. Am. Chem. Soc.*, **125**, 13012 (2003).

95. F. Couty, G. Evano, and N. Rabasso, *Tetrahedron: Asymmetry*, **14**, 2407 (2003).

96. M. Vaultier, R. Danion-Bougot, D. Danion, J. Hamelin, and R. Carrié, *J. Org. Chem.*, **40**, 2990 (1975).

97. U. K. Nadir and A. Arora, *J. Chem. Soc. Perkin Trans. 1*, 2605 (**1995**).

98. Y. Kodama and I. Yoshio, *Agric. Biol. Chem.*, **44**, 73 (1980).

99. J. E. Baldwin, R. M. Adlington, R. H. Jones, C. J. Shofield, and C. Zaracostas, *Tetrahedron*, **42**, 4879 (1986).

100. A. P. Kozikowski, W. Tückmantel, I. J. Reynolds, and J. T. Wroblewski, *J. Med. Chem.*, **33**, 1561 (1990).

101. A. P. Kozikowski, W. Tückmantel, Y. Liao, H. Manev, S. Ikonomovic, and J. T. Wroblewski, *J. Med. Chem.*, **36**, 2706 (1993).

102. Y. Arakawa, T. Murakami, Y. Arakawa, and S. Yoshifuji, *Chem. Pharm. Bull.*, **51**, 96 (2003).

103. A. P. Kozikowski, Y. Liao, W. Tückmantel, S. Wang, S. Pshenichkin, A. Surin, C. Thomsen, and J. T. Wroblewski, *Bioorg. Med. Chem. Lett.*, **6**, 2559 (1996).

104. Z. Sajjadi and W. D. Lubell, *J. Peptide Res.*, **65**, 298 (2005).

105. F. Couty and N. Rabasso, *Synlett*, 726 (**2003**).

106. H. Braüner-Osborne, L. Bunch, N. Chopin, F. Couty, G. Evano, A. A. Jensen, M. Kusk, B. Nielsen,and N. Rabasso, *Org. Biomol. Chem.*, **3**, 3926 (2005).

107. D. Seebach, T. Vettiger, H-M. Müller, D. A. Platner, and W. Petter, *Liebigs Ann. Chem.*, 687 (**1990**).

108. D. Seebach, M. Boes; R. Naef, and W. B. Schweizer, *J. Am. Chem. Soc.*, **105**, 5390 (1983).

109. F. Matsuara, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, **33**, 7921 (1992).

110. A. Dureault, M. Portal, F. Carreaux,and J-C. Depezay, *Tetrahedron*, **49**, 4201 (1993).

111. T. Shibasaki, W. Sakurai, A. Asegawa, Y. Uosaki, H. Mori, M. Yoshida, and A. Ozaki, *Tetrahedron Lett.* **40**, 5227 (1999).

112. P. Wessig and J. Schwarz, *Helv. Chim. Acta*, **81**, 1803 (1998).

113. E. Fernandez-Megia, M. A. Montaos, and F. J. Sardina, *J. Org. Chem.*, **65**, 6780 (2000).

114. J. Kollonitsch, L. Barash, and G. A. Doldouras, *J. Am. Chem. Soc.*, **92**, 7495 (1970).

115. J. Jiang, H. Shah, and R. J. DeVita, *Org. Lett.*, **5**, 4101 (2003).

116. I. Martinez and A. R. Howell, *Tetrahedron Lett.*, **41**, 5607 (2000).

117. S. Mangelinckx, M. Boeykens, M. Vlkiegen, J. Van der Eycken, and N. De Kimpe, *Tetrahedron Lett.*, **46**, 525 (2005).

118. F. Couty, G. Evano, and D. Prim, *Minireviews in Organic Chemistry*, **1**, 133 (2004).

119. F. Couty, F. Durrat, and G. Evano in *Targets in Heterocyclic Systems*, Royal Society of Chemistry publishing, O. A. Attanasi, D. Spinelli, (Eds.), 9, p. 186 (**2005**).

(Received February 7, 2006; in final form April 17, 2006)