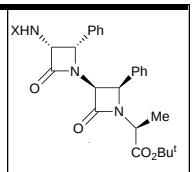
Asymmetric synthesis of building-blocks for peptides and peptidomimetics by means of the β-lactam synthon method



CHEMICAL SOCIETY REVIEWS

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Recent advances in the syntheses of enantiopure synthetic building blocks useful for non-protein amino acids, dipeptides, oligopeptides using solid state peptide synthesis, isoserines (norstatines), dipeptide isosteres [hydroxy(keto)ethylene, hydroxyethylamine, hydroxyethylene and dihydroxyethylene isosteres], taxoids, polyamines, poly(amino alcohol)s and poly(amino ether)s, and other biologically active compounds through applications of the *β-lactam synthon method* is reviewed.

1 Introduction

The β-lactam skeleton has attracted significant interest among synthetic and medicinal chemists over the years mainly because it is the core structure of natural and synthetic β-lactam antibiotics.[1] The importance of β-lactams as synthetic intermediates, however, had not been widely recognized when we started the development of the *β-lactam synthon method* in the early 1980s. Through the 1980s and 1990s, we and others have successfully demonstrated the usefulness of enantiopure β-lactams as versatile intermediates for the asymmetric synthesis of a variety of protein and non-protein amino acids, peptides, peptide turn mimetics, peptidomimetics, taxoid antitumour agents, heterocycles and other types of compounds of biological and medicinal interest. Thus, the *β-lactam synthon method* has now been fully established as a powerful synthetic method.[2,3] We will describe here recent advances in the asymmetric synthesis of useful building blocks for peptides and peptidomimetics by means of the β-*lactam synthon method*.

2 Preparation of enantiopure β-lactams as key intermediates

Enantiopure 3-amino- and 3-hydroxy-β-lactams are the key intermediates for the synthesis of peptides and peptidomimetics. Thus, we describe first the currently available methods for the synthesis of 3-amino- and 3-hydroxy-β-lactams with high enantiopurity. Asymmetric ketene–imine [2 + 2] cycloaddition and ester enolate–imine cyclocondensation are the two major methods that have been successfully used for this purpose.

2.1 Through [2 + 2] cycloaddition of achiral ketenes to chiral imines

The asymmetric Staudinger reaction, *i.e.*, ketene–imine [2 + 2] cycloaddition, using enantiopure imines has been studied for some time, but it is rather difficult to achieve extremely high diastereoselectivity in general, mainly because of the unfavourable arrangement of chiral moieties in the transition state.[4] Nevertheless, enantiopure diastereomers can be isolated without difficulty. Several recent examples are shown below.

3-Phthalimido-β-lactam **3a** with 80% de (de = diastereomeric excess) was obtained by using imine **1** derived from (*R*)-phenylethylamine (Scheme 1).[5]

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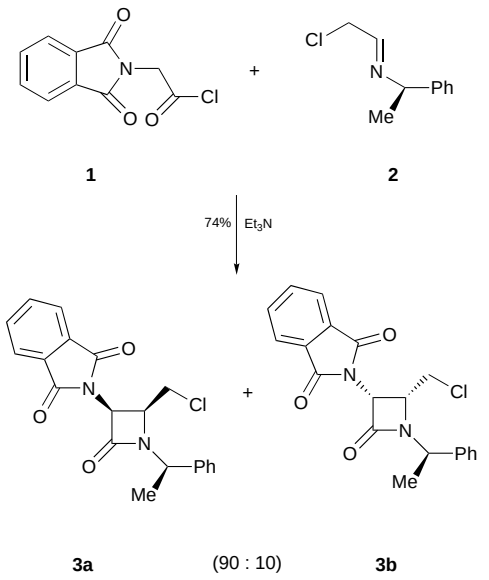
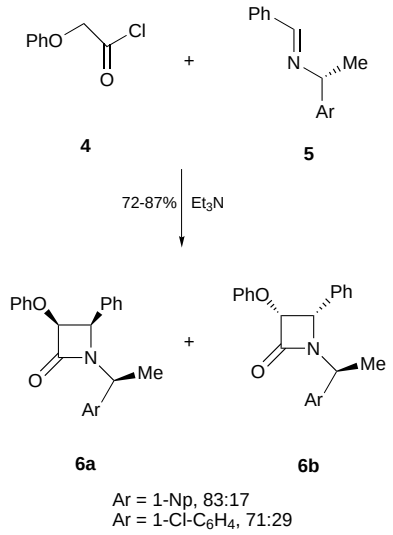
Francette Delaloge and Iwao Ojima

Francette Delaloge was born in Auxerre, France in 1970. She studied at Ecole National Supérieure de Chimie de Paris and received her DEA degree in chemistry from Université Pierre & Marie Curie (Paris VI) under the direction of Dr E. Rose in 1992. She performed her graduate study at Ecole Polytechnique, Paris, France on new approaches to the total synthesis of Taxol with a fellowship from Rhône-Poulenc Rorer and obtained her PhD degree in 1995 under the direction of Professor Jean-Yves Lallemand. She has been working for Professor Iwao Ojima at the Department of Chemistry, State University of New York at Stony Brook as a postdoctoral associate on the development of new synthetic methodologies by expanding the β-lactam synthon method as well as the design and synthesis of non-protein farnesyl transferase inhibitors. She has coauthored three original papers and one book chapter.



Scheme 1

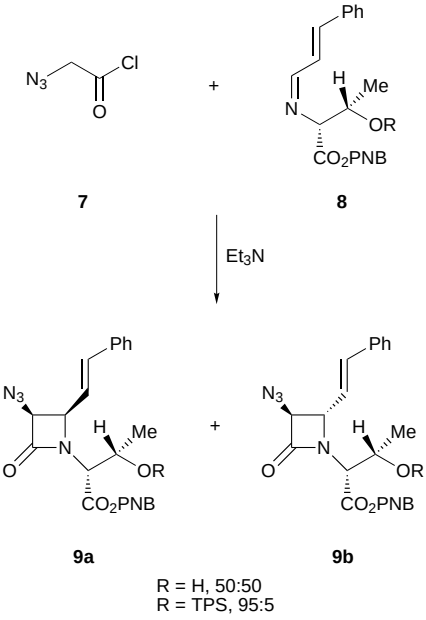
(*R*)-1-Naphthylethylamine was used as the chiral auxiliary for the synthesis of 3-phenoxy-β-lactam **6a** with 66% de.[6] The separation of the two diastereomers by column chromatography on silica gel is reported to be facile (Scheme 2). When (*S*)-1-(2-chlorophenyl)ethylamine was used as the chiral auxiliary, the reaction proceeded with only 42% de (Scheme 2).[7]



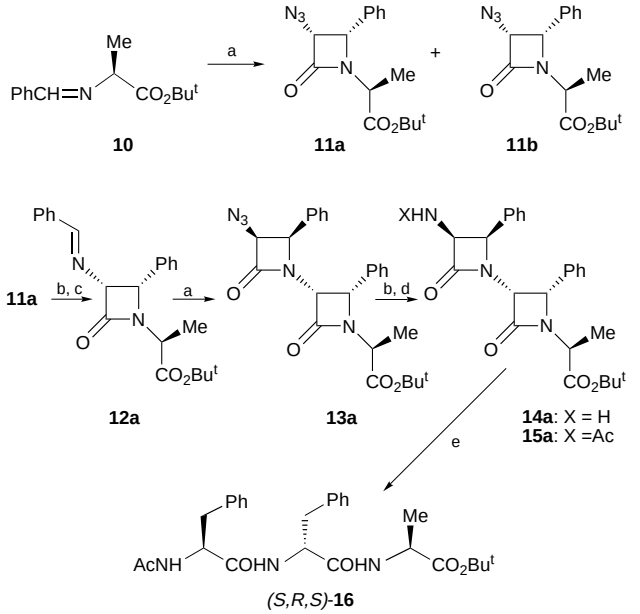
Scheme 2

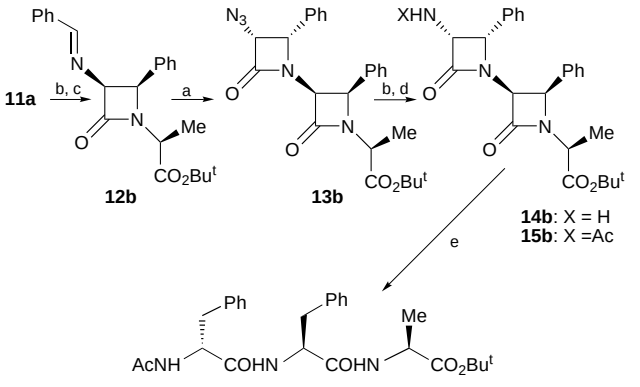
O-TPS-(*R*,*R*)-Threonine PNB ester (TPS = triphenylsilyl; PNB = 4-nitrobenzyl) was employed as the chiral auxiliary in the synthesis of 3-azido-β-lactam **9a** to achieve 90% de (Scheme 3).[8] Interestingly, when the chiral auxiliary has a free β-hydroxy group, no selectivity is observed.

The [2 + 2] cycloaddition of azidoketenes to benzylideneamines bearing a chiral β-lactam backbone was found to be extremely stereoselective (> 99% de), leading to the formation of enantiopure bis-β-lactams (Scheme 4).[9] 3-Benzylideneamino-β-lactams, **12a** (*3R,4S*) and **12b** (*3S,4R*), were obtained through the [2 + 2] cycloaddition of azidoketene to the enantiopure imino ester **10** followed by chromatographic separation of two diastereomers, **11a** and **11b** (80%, **11a**/**11b** = 51/49), followed by reduction of the azido moiety and then imine formation. Each 3-benzylideneamino-β-lactam **12** was converted into the corresponding bis-β-lactam **13a** or **13b** through [2 + 2] cycloaddition with azidoketene to give **13a** or **13b**. In these cycloadditions, only one of the two possible



Scheme 3

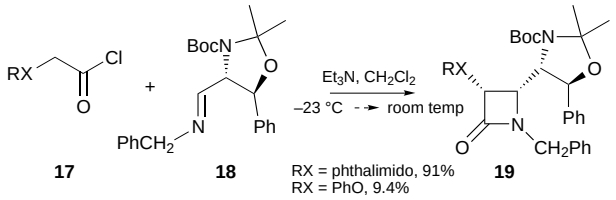




Scheme 4 Reagents: (*a*) N_3CH_2COCl, Et_3N, CH_2Cl_2, −78 °C to room temp. (*b*) H_2 (1 atm), 5% Pd–C, MeOH, 0–5 °C. (*c*) PhCHO, Na_2SO_4, CH_2Cl_2. (*d*) Ac_2O, *N*-methylmorpholine, $CHCl_3$. (*e*) H_2 (1 atm), 10% Pd–C, EtOH, 50 °C.

stereoisomers was formed in each case. The relative stereochemistry was determined by ^{1}H NMR and the absolute configuration was determined by converting **13a** and **13b** to known tripeptides (*S*,*R*,*S*)-and (*R*,*S*,*S*)-**16**.

When a chiral auxiliary is attached to the C-terminus of an imine such as **18** derived from (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol, excellent diastereoselectivity is achieved and the predominant isomers are isolated in > 90% yields (Scheme 5).[10]



Scheme 5

2.2 Through [2 + 2] cycloaddition of chiral ketenes to imines

Another approach to the asymmetric ketene–imine [2 + 2] cycloaddition is to attach a chiral auxiliary to a ketene. This strategy has been shown to be very successful for the asymmetric synthesis of 3-amino-β-lactams.

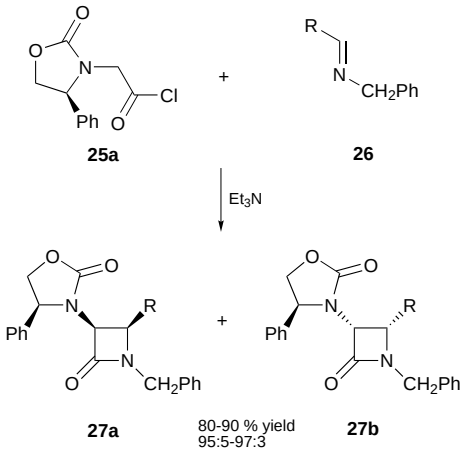
With the use of (+)-tartaric acid derivative **20** as the ketene precursor, β-lactam **22** (PMP = 4-methoxyphenyl) was obtained with 72% de (Scheme 6).[11,12] When ephedrine derived chiral ketene precursor **23** was used, > 90% de was achieved for the synthesis of β-lactam **24** (Scheme 6).

Oxazolidinones derived from (*S*)- and (*R*)-phenylglycine are excellent chiral auxiliaries for the asymmetric ketene–imine [2 + 2] cycloaddition.[13] For example, the reaction of (*S*)-oxazolidinon-3-ylacetyl chloride **25a** with *N*-benzylaldimines **26** gave β-lactam **27a** with 90–94% de in 80–90% yield (Scheme 7).[13]

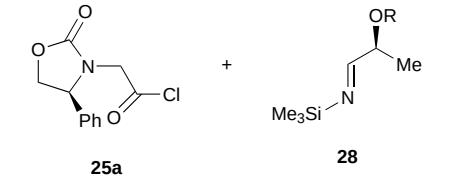
The same oxazolidinone chiral auxiliary was used for the asymmetric synthesis of *trans*-β-lactam **29**. By the introduction of a bulky α-siloxy group (TIPS = triisopropylsilyl; TBDPS = *tert*-butyldiphenylsilyl) to an imine, the relative stereochemistry of the resulting β-lactam **29a** was switched to completely *trans* with 60–80% de (Scheme 8).

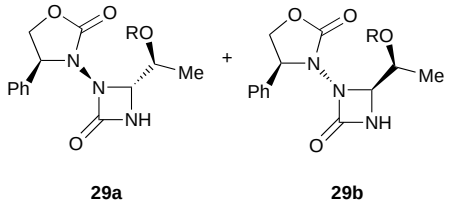
Usually, enolizable imines cannot be used for the ketene–imine [2 + 2] cycloaddition because of its facile isomerization to enamines. However, *N*-bis(trimethylsilyl)methylaldimines such as **30** were found to circumvent this problem. Accordingly, the reaction of **25a** with **30** in the presence of triethylamine gave *cis*-4-benzyl-β-lactam **31a** with > 96% de in 55% yield (Scheme 9).[14]

For the [2 + 2] cycloaddition of chiral ketenes **32** generated from **25** (**a**: *S*, **b**: *R*) with chiral imino esters **33** derived from alanine, valine, phenylalanine and methionine, it has been shown that no appreciable double induction is observed and

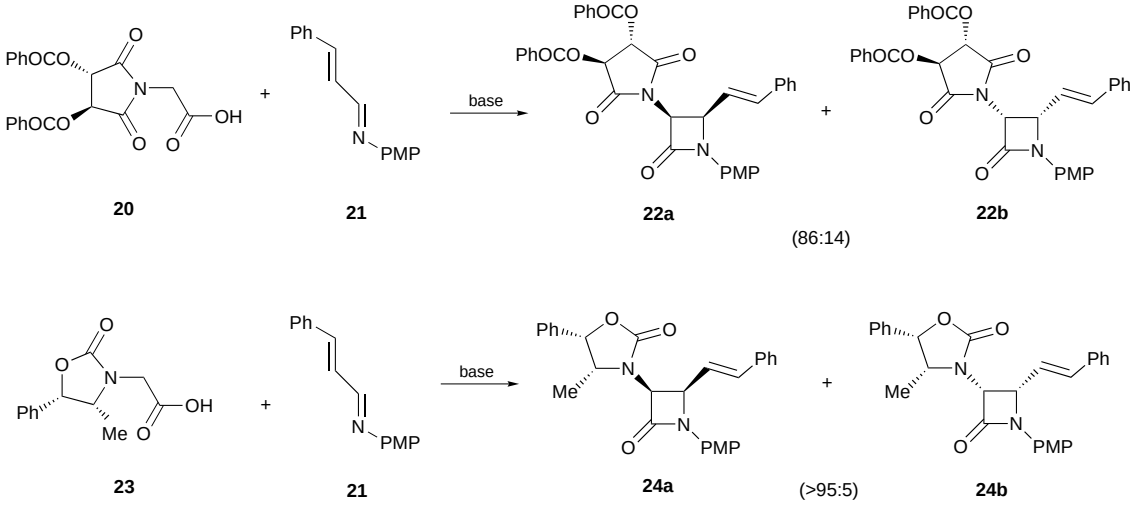


Scheme 7

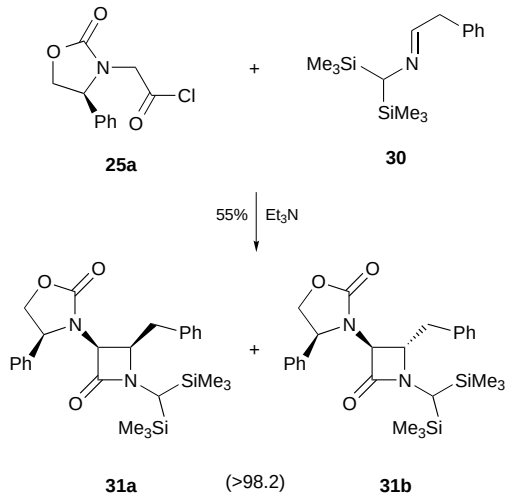




Scheme 8



Scheme 6

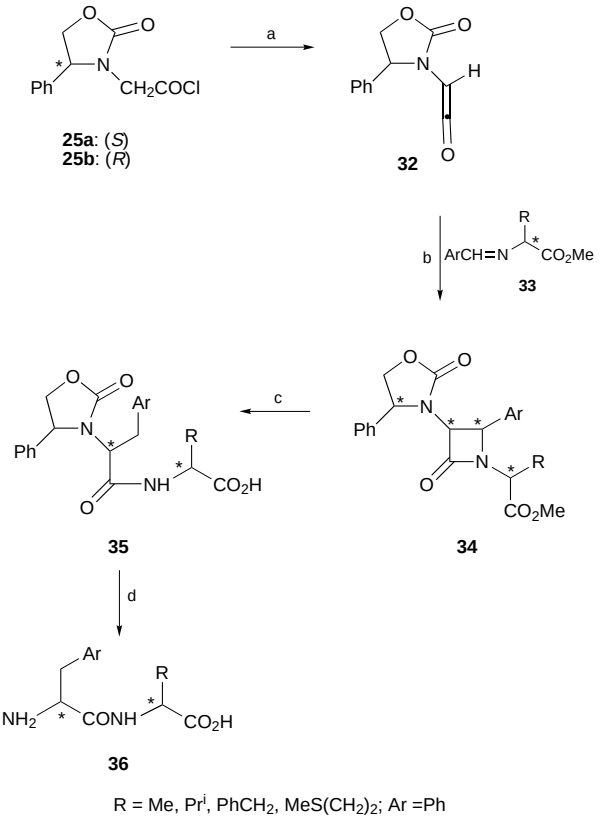


25a **30**

31a (>98.2) **31b**

Scheme 9

only the chiral centre in the ketene played a key role in the asymmetric synthesis (Scheme 10).[2] The reaction gave only one of the two possible diastereomers in all cases examined. The β-lactams **34** thus obtained were converted to the corresponding *N*-protected dipeptides through hydrogenolysis over Pd/C in MeOH and then saponified. The *N*-protected dipeptides **35** can be used for fragment condensation with other *N*-terminus-free peptide units. Removal of the chiral auxiliary was carried out by a modified Birch reduction with lithium in liquid NH_3/THF/Bu^tOH to afford enantiopure dipeptides **36** in excellent yields (Scheme 10).[2]



25a: (*S*)
25b: (*R*)

32 **33** **34** **35** **36**

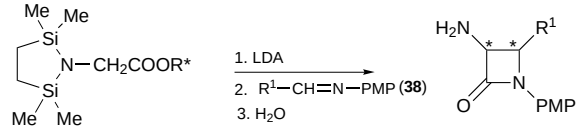
R = Me, Pr^i, $PhCH_2$, $MeS(CH_2)_2$; Ar =Ph

Scheme 10 Reagents: (*a*) NEt_3, CH_2Cl_2, −78 °C. (*b*) CH_2Cl_2, −78 to 0 °C, 2 h. (*c*) (i) H_2, Pd–C, MeOH, 50 °C, 5 h, (ii) 1 M NaOH/THF, room temp., 1 h, H_3O^+. (*d*) Li/NH_3/Bu^tOH, −78 °C, 15 min.

2.3 Through asymmetric cyclocondensation of chiral ester enolates with achiral imines

The ester enolate–imine cyclocondensation provides another efficient route to β-lactams, which can be applied to asymmetric synthesis of 3-amino- and 3-hydroxy-β-lactams.

The cyclocondensation of chiral lithium enolates generated *in situ* from *N*,*N*-bis(silyl)glycinates **37** with *N*-PMP-imines **38** gave *trans*-3-amino-β-lactams **39** exclusively or as the predominant product depending on the chiral auxiliary R* used (Scheme 11). Among the chiral auxiliaries examined, the best results were obtained with (−)-menthyl and (+)- or (−)-*trans*-2-phenylcyclohexyl, which gave **39** with > 99% ee.[3]



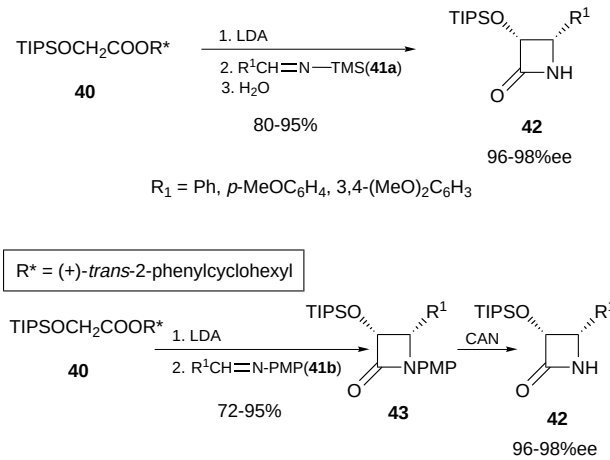
37 **39**

R^1 = Ph, *p*-F-C_6H_4, *p*-CF_3-C_6H_4, 4-MeO-C_6H_4, 3,4-$(MeO)_2C_6H_3$

Scheme 11

3-Hydroxy-β-lactams **42** with high enantiomeric purity (90–98% ee) have been obtained through highly efficient chiral ester enolate–imine cyclocondensation of enantiopure *O*-TIPS-hydroxyacetate **40** with *N*-TMS-imines **41a** or *N*-PMP-imines **41b** (Scheme 12). A variety of aryl, alkenyl and alkyl substituents can be introduced to the C-4 position of 3-hydroxy-β-lactams.[2,15–17] Among the chiral auxiliaries examined, (+)- and (−)-*trans*-2-phenylcyclohexyl gave the best results. *N*-TMS-imines of aromatic aldehydes work very well in this reaction, giving β-lactam **42** in one step. *N*-PMP-imines are suitable for alkenyl-, alkyl-, and fluoroalkyl aldimines that are rather labile. The resulting *N*-PMP-β-lactams **43** are readily converted to **42** by oxidative cleavage using CAN [cerium(IV) ammonium nitrate]. The *N*-acylated derivatives of β-lactam **42** have been successfully used for the practical syntheses of Taxol (paclitaxel) and Taxotere (docetaxel) as well as for the development of highly potent new taxoid antitumour agents.[2,18–20]

As described above, a variety of 3-amino- and 3-hydroxy-β-lactams with excellent enantiopurities are now available based on asymmetric ketene–imine [2 + 2] cycloaddition and chiral ester enolate–imine cyclocondensation. This forms the foundation for the applications of these β-lactams to the asymmetric syntheses of non-protein amino acids, peptides, dipeptide isosteres and peptidomimetics that are not easily prepared by conventional methods. The next section reviews recent applications of the *β-lactam synthon method* along these lines.



40 **42**

R_1 = Ph, *p*-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$

40 **43** **42**

R^1 = Aryl, Alkenyl, Alkyl, *etc.*

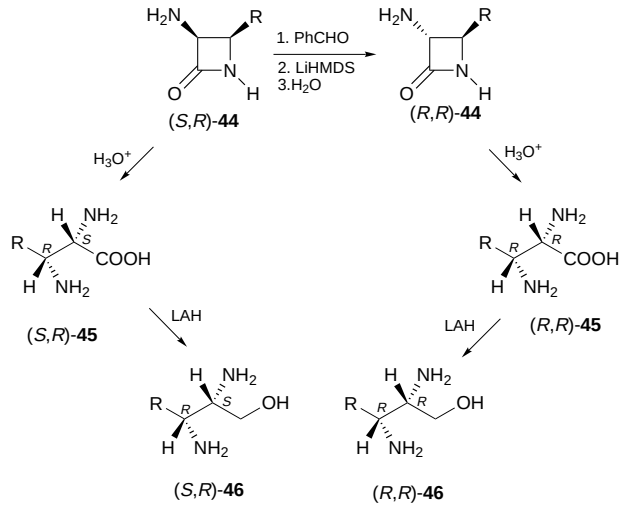
Scheme 12

3 Synthesis of enantiopure non-protein amino acids, their derivatives, and dipeptide isosteres from β-lactam intermediates

Non-protein amino acids are defined as the amino acids which are not found in protein main chains because they do not have a specific transfer-RNA and codon triplet or they do not arise from protein amino acids by post-translational modification. Their origins and functions are so diverse that many things remain to be explored. The majority of naturally occurring non-protein amino acids originate in plants and micro-organisms. Many of them are important components of therapeutic drugs and compounds of medicinal interest such as antibiotics, decarboxylate inhibitors, aminotransferase inhibitors, protease inhibitors and anticancer agents. Thus, the development of efficient methods for the synthesis of enantiopure non-protein amino acids is significant in organic synthesis and medicinal chemistry.

3.1 α,β-Diamino acids and their derivatives

Enantiopure α,β-diamino acids are often components of peptidic antibiotics such as lavendomycin or glumamycin.[21] It has been shown that the hydrolysis of enantiopure 3-amino-β-lactams affords the corresponding α,β-diamino acids.[2] As Scheme 13 illustrates, the acid hydrolysis of (*S*,*R*)-**44** gives (*S*,*R*)-**45** in quantitative yield as hydrochlorides, that is reduced to (*S*,*R*)-diamino alcohol **46** in high yield with $LiAlH_4$ (LAH). The *cis*-β-lactam (*S*,*R*)-**44** is readily converted to the *trans*-β-lactam (*R*,*R*)-**44** through imine formation, deprotonation and protonation. Then, (*R*,*R*)-**44** is transformed to (*R*,*R*)-**45** and (*R*,*R*)-**46** in the same manner as (*S*,*R*)-**44**. Since the other set of diastereomeric β-lactams, (*R*,*S*)-**44** can be obtained by using the other enantiomer of the chiral auxiliary in the chiral ketene–imine [2 + 2] cycloaddition process (see Scheme 7), four diastereomers of α,β-diamino acids **45** and diamino alcohols **46** are accessible by this method.[3] The *trans*-β-lactams (*R*,*R*)-**44** and (*S*,*S*)-**44** can also be obtained through chiral ester enolate–imine cyclocondensation (see Scheme 11). This protocol has been combined with the alkylations at C-3 position (*vide supra*) and applied to the syntheses of enantiopure α-alkyl-α,β-amino acids.

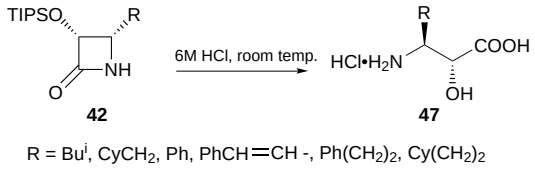


Scheme 13

3.2 β-Hydroxy-β-amino acids (isoserines), their dipeptides and dipeptide isosteres

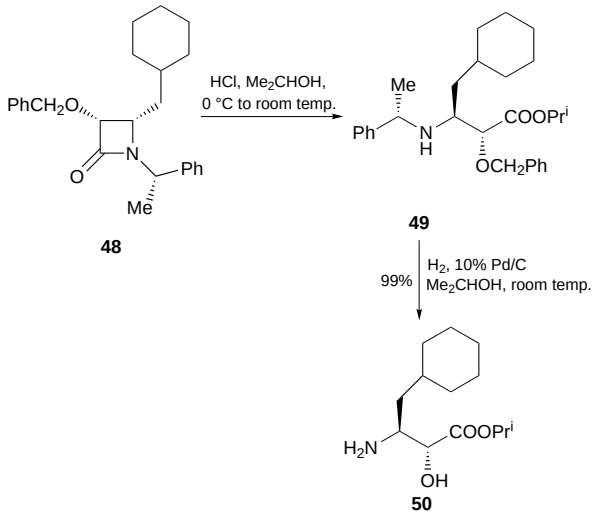
α-Hydroxy-β-amino acids (isoserines) with correct relative and absolute configurations are key components of a large number of therapeutically important compounds. For example, (2*R*,3*S*)-3-amino-2-hydroxy-5-methylhexanoic acid (norstatine), (3*R*,4*S*)-4-amino-3-hydroxy-5-methylheptanoic acid (statine), and their analogues have been used extensively as crucial amino acid residues in peptide-based inhibitors of enzymes such as renin[22] and HIV-I protease.[23] *N*-Benzoyl-(2*R*,3*S*)-3-phenylisoserine and *N*-*tert*-butoxycarbonyl-(2*R*,3*S*)-3-phenylisoserine moieties are at the C-13 positions of the exciting anticancer agents paclitaxel and docetaxel.[24,25] Accordingly, it is very important to develop efficient methods for the syntheses of isoserines with excellent enantiopurity.

As Scheme 14 shows, norstatine (**47**, R = Bu^i) and cyclohexylnorstatine (**47**, R = cyclohexylmethyl), key components of renin inhibitors, have been prepared quantitatively through ring-opening hydrolysis of the corresponding β-lactams **42** obtained through highly efficient chiral ester enolate–imine cyclocondensation (see Scheme 12).[2] Other norstatine analogues are obtained in the same manner.[2]



Scheme 14

Cyclohexylnorstatine isopropyl ester **50** has also been prepared through ring opening hydrolysis of β-lactam **48** obtained by chromatographic separation of the desired diastereomer from ketene–imine [2 + 2] cycloadducts, followed by hydrogenolysis on Pd/C (Scheme 15).[26]

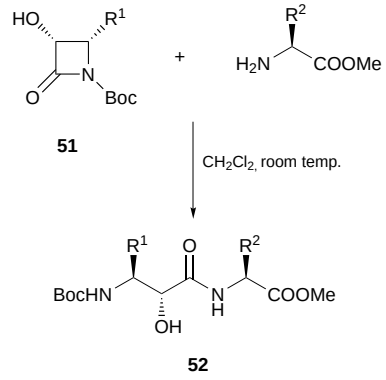


Scheme 15

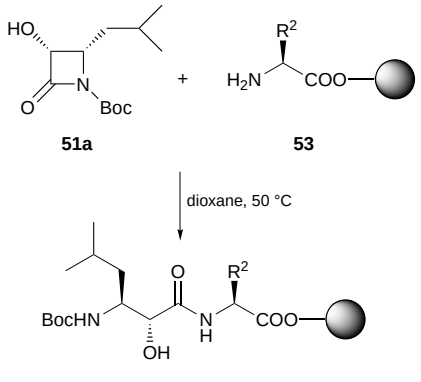
N-Acylation of β-lactams with, *e.g.*, benzoyl and *tert*-butoxycarbonyl (Boc), increases the electrophilic nature of β-lactams. Thus, 1-acyl-β-lactams readily react with various nucleophiles such as amines, alcohols, metal alkoxides and metal enolates.[2,27] For instance, the ring-opening coupling of 1-acyl-β-lactams **51** with α-amino acid methyl esters proceeds smoothly at ambient temperature under neutral conditions to give *N*-Boc-dipeptides containing isoserine residues **52** in excellent yields (Scheme 16).[2] This novel peptide coupling method has been successfully applied to a solid-phase peptide synthesis using the Wang resin-bound amino acid residues **53** (Scheme 16).[2]

It is worth mentioning that (3*R*,4*S*)-1-benzoyl-3-siloxy-4-phenylazetidin-2-one and (3*R*,4*S*)-1-Boc-3-siloxy-4-phenylazetidin-2-one have successfully been applied to the practical syntheses of paclitaxel and docetaxol, through highly efficient ring-opening coupling with metalated baccatin III derivatives.[2,20]

The reaction of 1-Boc-3-(protected hydroxy)-β-lactam **55** with Grignard reagents affords the corresponding α-hydroxy-

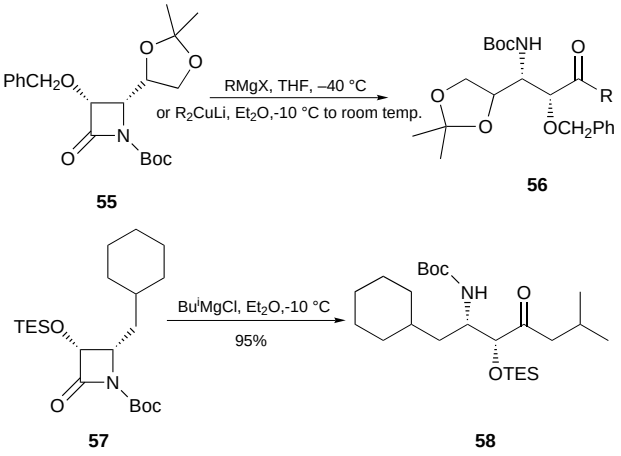


R^1 = Bu^i, Ph, $CyCH_2$, PhCH = CH;
R^2 = $PhCH_2$, Bu^i, Pr^i, Indolemethyl;
R^3 = Me, Bu^t



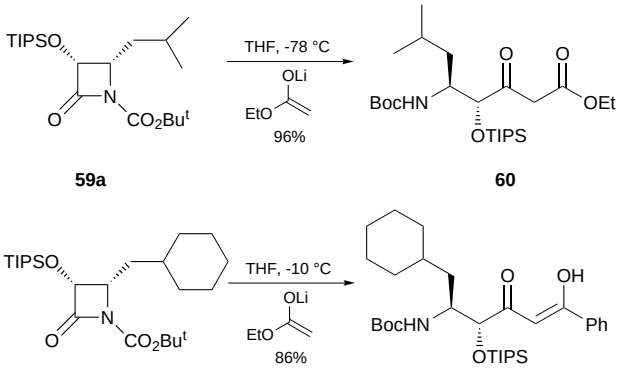
Scheme 16

β-amino ketones **56** in high yields (Scheme 17). Cuprates can be used as highly chemoselective alkylating agents for this reaction, but yields are moderate.[28] This reaction has been successfully applied to a practical synthesis of a key component **58** of a potent renin inhibitor (Scheme 17).[29]



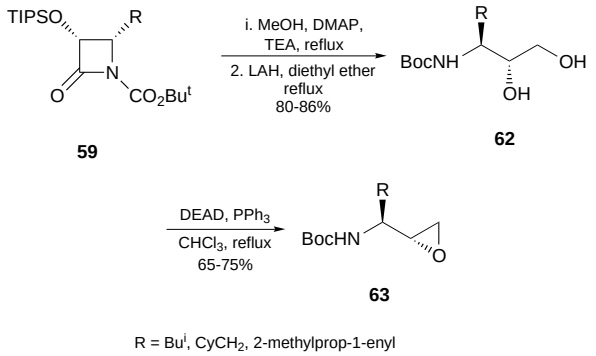
Scheme 17

N-Boc-β-lactams **59** react with ketone and ester enolates to yield hydroxy(keto)ethylene dipeptide isosteres.[30] Two examples are shown in Scheme 18: 4-isobutyl-β-lactam **59a** and 4-cyclohexylmethyl-β-lactam **59b** give ring-opening coupling products **60** and **61**, respectively, in good to excellent yields through reactions with lithium enolates.[30] Lithium enolates of ketones and esters such as acetone, acetophenone, phenyl ethyl ketone, ethyl acetate, ethyl propionate and methyl 2-methylpropanoate have been employed. The reaction is faster with ester enolates than ketone enolates.



Scheme 18

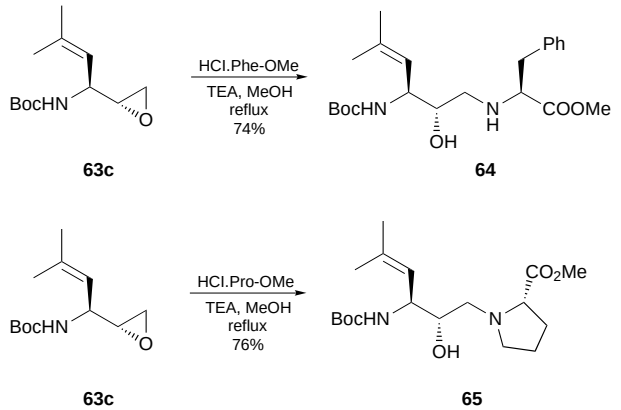
The *N*-Boc-epoxides **63** are important intermediates for the synthesis of various non-protein amino acids. The epoxides **63** can be readily prepared from the corresponding β-lactams **59** in two steps (Scheme 19).[31]



R = Bu^i, $CyCH_2$, 2-methylprop-1-enyl

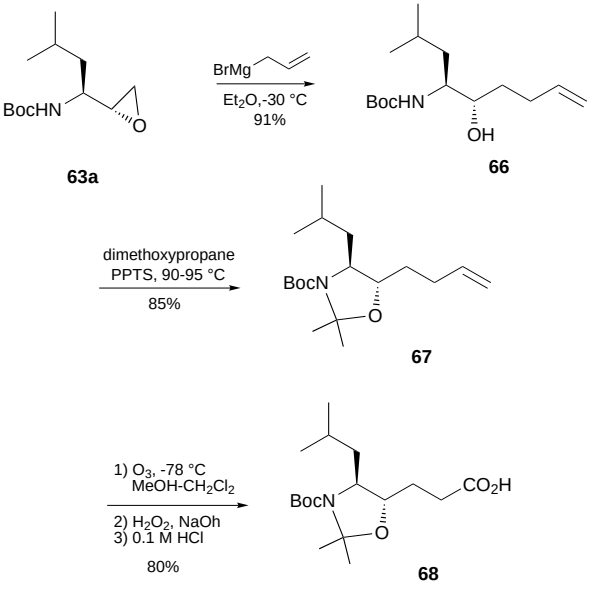
Scheme 19

Hydroxyethylamine isosteres are readily synthesized from epoxides **63**. For example, epoxide **63c** undergoes facile ring-opening reactions with methyl esters of (*S*)-phenylalanine and (*S*)-proline to give the corresponding dipeptide isosteres **64** and **65**, respectively in good isolated yields (Scheme 20).[31]



Scheme 20

Hydroxyethylene isosteres are also easily obtained from epoxides **63**. An example is shown in Scheme 21.[31] The reaction of an allyl-Grignard reagent with epoxide **63a** gives alcohol **66** in excellent yields. The hydroxy and the amino groups are protected as an oxazolidine and the subsequent ozonolysis and oxidative work-up afford the corresponding *N*,*O*-protected hydroxyethylene isostere **68** in good isolated yield.[31]

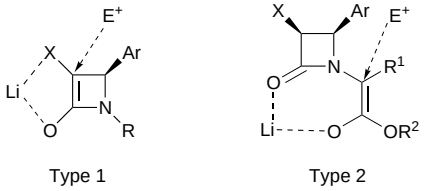


Scheme 21

3.3 α-Alkyl-α-amino acids, their derivatives, and their dipeptides

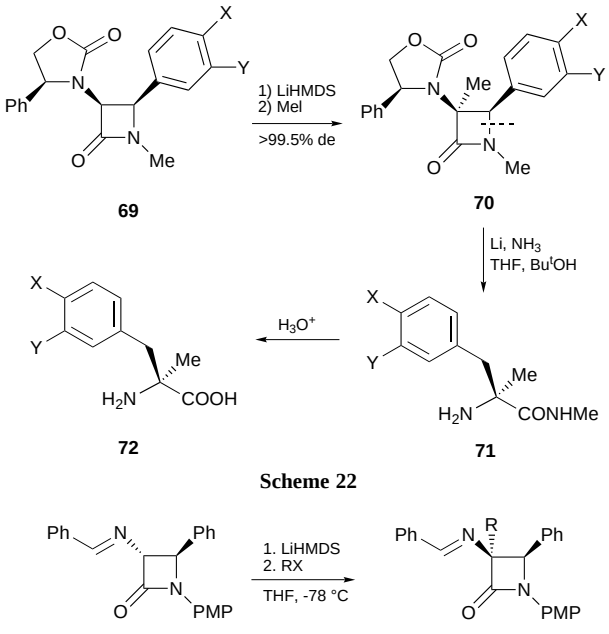
Among the non-protein amino acids, α-alkyl-α-amino acids have been attracting medicinal and biochemical interest because many of them serve as powerful substrate-based inhibitors of enzymes such as decarboxylases and aminotransferases.[21] α-Alkyl-α-amino acid residues also serve as conformational modifiers of physiologically active peptides, bringing in conformational restraints. α-Alkyl amino acids also provide a challenging synthetic problem since conventional enzymatic resolution in combination with racemization cannot be applied effectively. Accordingly, the asymmetric synthesis of α-alkyl-α-amino acids with excellent enantiopurity has been extensively investigated, and the *β-lactam synthon method* provides one of the most efficient routes to these amino acids.[2,3]

Two types of extremely stereoselective alkylations of β-lactams have been studied: (*i*) the alkylation of the C-3 carbon (Type 1), and (*ii*) the alkylation of the side chain ester enolate (Type 2). For Type 1 alkylation, an electrophile should attack the C-3 position of the β-lactam enolate from the opposite side of the C-4-aryl group to avoid steric conflict. In the Type 2 alkylation, the lithium enolate forms a chelate with the β-lactam oxygen and then the electrophile attacks from the back side of the aryl group at C-4.

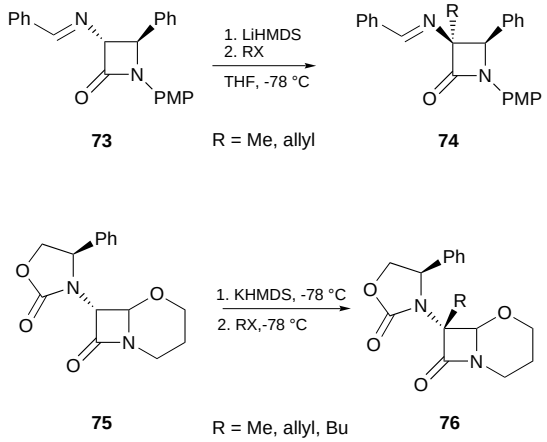


The Type 1 alkylation has been applied to the asymmetric synthesis of (*S*)-α-methylphenylalanine **72a** (X = Y = OMe) and (*S*)-α-methyldopa **72b** (X = Y = OH) with > 99.5% ee as shown in Scheme 22.[2] The methylation at C-3 of *cis*-β-lactam **69** gave **70** with > 99.5% de.

The Type 1 alkylation is applicable to *trans*-β-lactam **73** (Scheme 23) since the reaction goes through the same Type 1 enolate as that from the corresponding *cis*-β-lactam. The alkylation proceeded smoothly for methylation or allylation to give **74** with > 99.5% de in > 90% yield.[2] This protocol has been applied to bicyclic β-lactam **75** to give **76** with ⩾97% de in 51–89% yield (Scheme 23).[32]

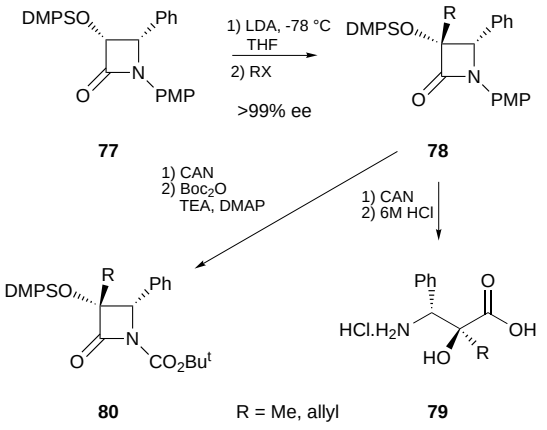


Scheme 22



Scheme 23

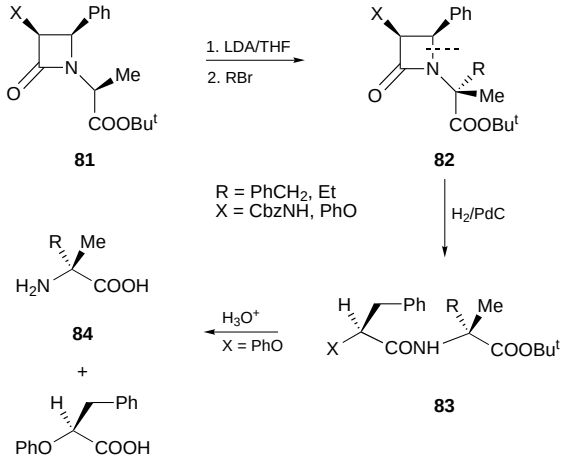
The Type 1 alkylation has also been applied to 3-DMPSO-β-lactam **77** (DMPSO = dimethylphenylsiloxy) to afford **78**, which is transformed to α-methyl- and α-allylphenylisoserines **79** as well as 1-Boc-β-lactams **80** with > 99% ee (Scheme 24).[33] 1-Boc-3-methyl-β-lactam **80a** has been used for the synthesis of the 2′-methyl analogue of docetaxel.[34]



Scheme 24

The Type 2 alkylation was applied to the asymmetric synthesis of (*R*)-α-alkylalanines **84** (X = PhO) as well as (*S*)-phenylalanyl-(*R*)-α-alkylalanines **83** (X = CbzNH) (Cbz = benzyloxycarbonyl) (Scheme 25).[2]

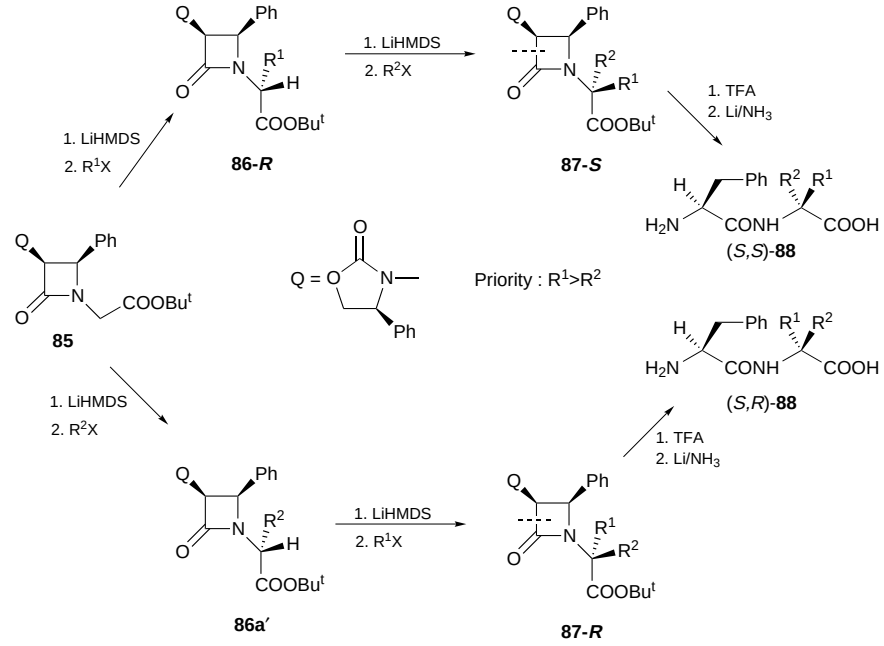
The Type 2 alkylation has been applied to the sequential asymmetric double alkylation of chiral β-lactam ester **85** that is a chiral glycinate as well as a phenylglycinate equivalent (Scheme 26).[2] The β-lactam ester **85** (> 99% ee) was prepared



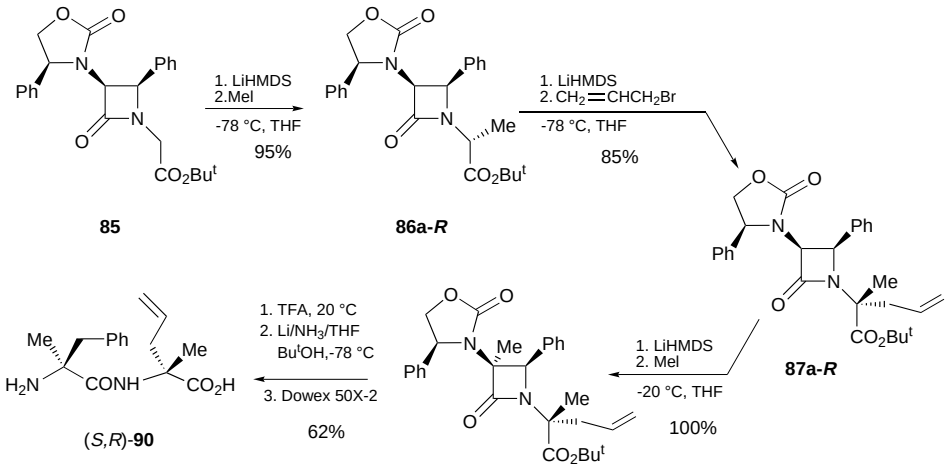
Scheme 25

through asymmetric [2 + 2] cycloaddition of a chiral ketene to *tert*-butyl-*N*-benzylideneglycinate (see Scheme 10). As shown in Scheme 26, the salient feature of this method is that the quaternary chiral centre of the desired configuration can be achieved just by changing the order of the addition of two alkyl halides used ($R^1 \neq R^2$). The reactions were carried out using the combinations of methyl iodide, allyl bromide, and benzyl bromide, and doubly alkylated β-lactam esters **87** with > 99% de were obtained in high yields. The β-lactam esters **87** were converted to the corresponding (*S*,*S*)- and (*S*,*R*)-phenylalanyl-α-alkylalanines **88**.[2]

The sequential asymmetric triple alkylation of **85** was performed through the combination of Type 2 and Type 1 alkylations (Scheme 27).[2] After the completion of the sequential Type 2 asymmetric double alkylations of the glycinate moiety with methyl iodide and allyl bromide, the side chain of the resulting β-lactam ester **87** had no acidic protons. Thus, the Type 1 alkylation with methyl iodide took place at the C-3 of β-lactam **87**. It was found that the first Type 2 double alkylation as well as the subsequent Type 1 alkylation proceeded with virtually complete stereoselectivity to give **89**, which is converted to (*S*)-α-methylphenylalanyl-(*R*)-α-allylalanine **90** in good yield.



Scheme 26



Scheme 27

3.4 Polyamines, poly(amino alcohols), and poly(amino ethers) *via* bis-β-lactams

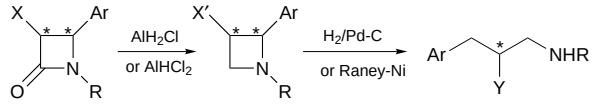
Polyamines, poly(amino alcohols) and poly(amino ethers) are very useful compounds which can be directly synthesized from azetidines with various substitution patterns. However, the azetidine skeleton has been one of the most difficult amines to synthesize because of its ring strain. Only a few effective synthetic methods have been developed to date, and the selective reduction of β-lactams serves as one of the most straightforward and efficient routes to enantiopure azetidines.[35]

It has been shown that monochloroalane (AlH_2Cl) and dichloroalane ($AlHCl_2$) are the best reducing agents that can convert enantiopure β-lactams **91** to the corresponding azetidines **92** in high yields without racemization (Scheme 28).[35] The reductive cleavage of N–C^2 bond of the resulting azetidines **92** affords the corresponding amino alcohols or diamines **93** in virtually quantitative yields (Scheme 28).[35]

This protocol has been successfully applied to bis-β-lactams. Two types of bis-β-lactams, *i.e.*, bis-β-lactams in which two β-lactam rings are directly connected and bis-β-lactams that have an alkanamide linker between two β-lactam rings, have been examined. As Scheme 29 shows, the chloroalane reduction of these two types of bis-β-lactams exemplified as **94** and **96** gives the corresponding bisazetidines **95** and **97**, respectively.[35]

The reductive N–C^2 bond fission and removal of benzyl group through hydrogenolysis of azetidines and bisazetidines on Pd-C or Raney nickel affords the corresponding hydroxylamines, diamines, polyamines, poly(amino alcohols) and poly(amino ethers) in high to quantitative yields as exemplified in Scheme 30.[35] It should be noted that the reductive cleavage of azetidines and bisazetidines is much faster than that of benzyl–oxygen bond, and thus the poly(amino alcohols) can be obtained as their benzyl ethers.[35]

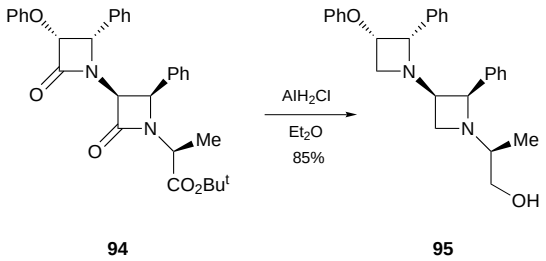
These hydroxylamines, diamines, polyamines, poly(amino alcohols) and poly(amino ethers) serve as chiral chelating agents or catalysts as well as versatile enantiopure building blocks for peptidomimetics and chiral macrocycles.



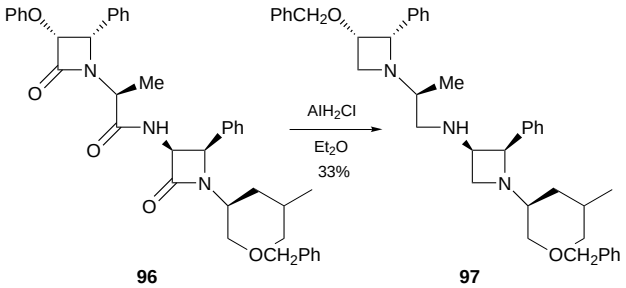
90 **91** **92**

X = $PhCH_2O$, N_3 Y = OH, NH_2, AcNH

Scheme 28

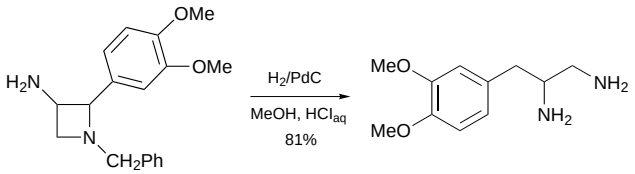


94 **95**

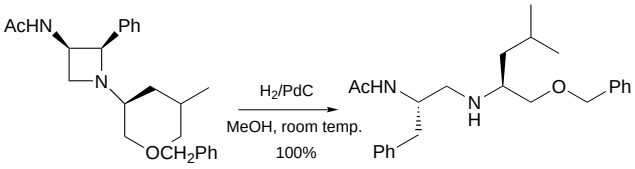


96 **97**

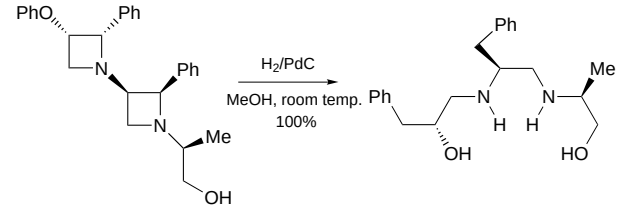
Scheme 29



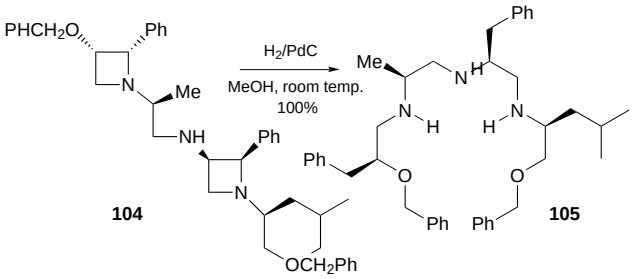
98 **99**



100 **101**



102 **103**



104 **105**

Scheme 30

4 Conclusion

This short review has described recent advances in the asymmetric synthesis of enantiopure building blocks for peptides and peptidomimetics by means of the *β-lactam synthon method*. 3-Amino- and 3-hydroxyl-β-lactams with excellent enantiopurity can be obtained *via* asymmetric ketene–imine [2+2] cycloaddition or chiral ester enolate–imine cyclocondensation. The reductive cleavage of the N–C^4 bonds of 3-amino-β-lactams provides non-protein amino acids, their derivatives, and their dipeptides. Extremely stereoselective Type 1 and Type 2 asymmetric alkylations as well as sequential double and triple asymmetric alkylations of 3-amino-β-lactams, followed by selective hydrogenolysis afford a variety of α-alkyl-α-amino acids, their derivatives, and their dipeptides, that cannot easily be achieved by other methods. The Type 1 asymmetric alkylation has also been successfully applied to 3-hydroxy-β-lactams which give α-alkyl-α-hydroxy-β-amino acids and their derivatives. Facile hydrolysis of 3-hydroxy-β-lactams as well as *N*-acyl-3-hydroxy-β-lactams affords α-hydroxy-β-amino acids (isoserines or norstatins). The ring-opening coupling of *N*-acyl-3-hydroxy-β-lactams with α-amino esters and enolates and further manipulations provide isoserine-containing dipeptides and various dipeptide isosteres. The selective reduction of enantiopure β-lactams and bis-β-lactams with chlorohydroalanes, followed by reductive ring cleavage of the resulting azetidines and bisazetidines furnishes a unique and efficient route to hydroxylamines, diamines, polyamines, poly(amino alcohols) and poly(amino ethers) which are also

useful and versatile building blocks for peptidomimetics and chiral macrocycles.

5 Acknowledgments

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6 References

1 G. I. Georg, *The Organic Chemistry of β-Lactams*, VCH, New York, 1992, and references cited therein.
2 I. Ojima, *Acc. Chem Res.* 1995, **28**, 383.
3 I. Ojima, in *Advances in asymmetric synthesis*, J. P. Inc., New York, 1995, vol. 1, pp. 95–146.
4 G. I. Georg and V. T. Ravikumar, in *The Organic Chemistry of β-Lactams*, ed. G. I. Georg, VCH Publishers, New York, 1992; p. 295.
5 J. Aszodi, A. Bonnet and G. Teusch, *Tetrahedron*, 1990, **46**, 1579.
6 G. I. Georg and Z. Wu, *Tetrahedron Lett.*, 1994, **35**, 381.
7 Y. Hashimoto, A. Kai, and K. Saigo, *Tetrahedron Lett.*, 1995, **36**, 8821.
8 A. K. Bose, M. S. Manhas, J. M. V. D. Veen, S. S. Bari and D. R. Wagle, *Tetrahedron* 1992, **48**, 4831.
9 I. Ojima, K. Nakahashi, S. M. Brandstadter and N. Hatanaka, *J. Am. Chem. Soc.*, 1987, **109**, 1798.
10 M. Jayaraman, A. R. Deshmukh and B. M. Bhawal, *Tetrahedron*, 1996, **52**, 8989.
11 N. Ikota and A. Hanaki, *Heterocycles*, 1984, **22**, 2227.
12 R. D. G. Cooper, B. W. Daugherty and D. B. Boyd, *Pure Appl. Chem.*, 1987, **59**, 485.
13 D. A. Evans and E. B. Sjogren, *Tetrahedron Lett.*, 1985, **26**, 3783.
14 C. Palomo, J. M. Aizpurua, M. Legido, R. Galarza, P. M. Deya, J. Dunoguès, J. P. Picard, A. Ricci and G. Seconi, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1239.
15 I. Ojima, S. D. Kuduk, J. C. Slater, R. H. Gimi and C. M. Sun, *Tetrahedron*, 1996, **52**, 209.
16 I. Ojima, S. D. Kuduk, P. P. Pera, J. M. Veith and R. J. Bernacki *J. Med. Chem.*, 1997, **40**, 279.
17 I. Ojima, J. C. Slater, P. Pera, J. M. Veith, A. Abouabdellah, J.-P. Bégué and R. J. Bernacki, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 133.
18 I. Ojima, J. C. Slater, E. Michaud, S. D. Kuduk, P.-Y. Bounaud, P. Vrignaud, M.-C. Bissery, J. Veith, P. Pera and R. J. Bernacki, *J. Med. Chem.*, 1996, **39**, 3889.
19 I. Ojima, J. C. Slater, S. D. Kuduk, C. S. Takeuchi, R. H. Gimi, C.-M. Sun, Y. H. Park, P. Pera, J. M. Veith and R. J. Bernacki, *J. Med. Chem.*, 1997, **40**, 267.
20 R. A. Holton, R. J. Biediger and P. D. Boatman, in *Taxol: Science and Applications*, ed. M. Suffness, CRC Press, New York, 1995, pp. 97–121.
21 M. J. Jung, in *Chemistry and Biochemistry of Amino Acids*, ed. G. C. Barrett, Chapman and Hall, New York, 1985, p. 227.
22 S. Thaisrivongs, D. T. Pals, L. T. Kroll, S. R. Turner and F.-S. Han, *J. Med. Chem.*, 1987, **30**, 976.
23 J. R. Huff, *J. Med. Chem.*, 1991, **34**, 2305.
24 *Taxane Anticancer Agents: Basic Science and Current Status*, ed. G. I. Georg, T. T. Chen, I. Ojima, and D. M. Vyas, ACS, Washington DC, 1995.
25 M. Suffness *Taxol: Science and Applications*, CRC Press, New York, 1995.
26 Y. Kobayashi, Y. Takemoto, T. Kamijo, H. Harada, Y. Ito and S. Terashima, *Tetrahedron*, 1992, **48**, 1853.
27 E. W. Ng, *Dissertation*, State University of New York at Stony Brook, 1996.
28 C. Palomo, J. M. Aizpurua, J. M. Garcia, M. Iturburu and J. M. Odriozola, *J. Org. Chem.*, 1994, **59**, 5184.
29 D. M. Spero, S. Kapadia and V. Farina, *Tetrahedron Lett.*, 1995, **36**, 4543.
30 I. Ojima, E. W. Ng and C. M. Sun, *Tetrahedron Lett.*, 1995, **36**, 4547.
31 I. Ojima, H. Wang, T. Wang and E. Ng, *217th American Chemical Society National Meeting, San Francisco, April 13–17, 1997; Abstr.* ORGN 52.
32 P.-J. Colson and L. S. Hegedus, *J. Org. Chem.*, 1993, **58**, 5918.
33 T. Wang, F. Delaloge and I. Ojima, *218th American Chemical Society National Meeting, Las Vegas, September 7–11, 1997; Abstr.* ORGN 210.
34 J. Kant, W. S. Schwartz, C. Fairchild, Q. Gao, S. Huang, B. H. Long, J. F. Kadow, V. Farina and D. Vyas, *Tetrahedron Lett.*, 1996, **37**, 6495.
35 I. Ojima, M. Zhao, T. Yamato, K. Nakahashi, M. Yamashita and R. Abe, *J. Org. Chem.*, 1991, **56**, 5263.

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