Bull. Chem. Soc. Jpn., **76**, 1115–1129 (2003)

Accounts

Asymmetric Strecker Route toward the Synthesis of Biologically Active α,α-Disubstituted α-Amino Acids

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(Received December 24, 2002)

A series of optically active α,α-disubstituted α-amino acids have been synthesized starting with an achiral or a racemic α-hydroxy or α-diazo ketone. In the present synthesis, the key transformation is an asymmetric version of the Strecker synthesis. An α-acyloxy ketone having a chiral amino acid as the acyloxy group afforded cyclic α-amino nitrile in a highly stereoselective manner; in this reaction the amino group and the chirality were diastereoselectively transplanted into the internal ketone group via an imine-enamine equilibrium of the cyclic ketimine intermediate. Oxidation of the amino group followed by removal of the resulting imino group and hydrolysis of the nitrile group afforded α-hydroxymethyl α-amino acid. The use of L-amino acid as the acyloxy group gave *R* enantiomer, and its *S* enantiomer was obtained when D-amino acid was employed. Some problematic processes that remained in the Strecker synthesis, i.e., preparation of the starting α-acyloxy ketone and oxidative conversion of α-amino nitrile into α-imino nitrile, are much improved as regards efficiency by the development of a Cu-catalyzed insertion of α-diazo ketone into *N*-protected α-amino acid, and as regards yields by the use of ozone as the oxidant. With these methods, various types of α,α-disubstituted α-amino acids have been synthesized including cyclic analogs, which can be viewed as a conformational variant of serine. Their incorporations into Leu-enkephalin have revealed that these amino acids play an important role not only to constrain the peptide conformation but also for high affinity bindings to the opioid receptors. Applications to the synthesis of biologically active natural products have been exemplified by the syntheses of the Corey intermediate of lactacystin and of marine natural products, manzacidin A and C.

There is an ever-growing interest in the synthesis, pharmacology, and conformational properties of non-proteinogenic amino acids.[1] In particular, α,α-disubstituted α-amino acids of type A or B have been the subject of numerous investigations over the decades (Chart 1). The structural feature common to these amino acids is the presence of an additional substituent at the α-position of amino acid that sterically constrains the free rotation or conformational flexibility of its side chain (type A) or strictly fixes the conformation by a carbo- or a heterocyclic ring (type B). When an amino acid of type A is incorporated into a peptide, it imparts well-defined conformational constraints to a peptide backbone preferring folded conformations and inducing α-helical secondary structures.[2] Furthermore, they stabilizes the neighboring peptide bond against chemical or enzymatic hydrolysis due mainly to steric reasons.[3] These facts promote the design of a sterically constrained tailor-made amino acid in peptide chemistry. On the other hand, α,α-disubstituted α-amino acids are often found in nature either in free form or as constituents of biologically active compounds that are known as enzyme inhibitors, ion channel blockers, and antibiotics.[4] In many cases, the substructure of α,α-disubstituted α-amino acid in natural origin is

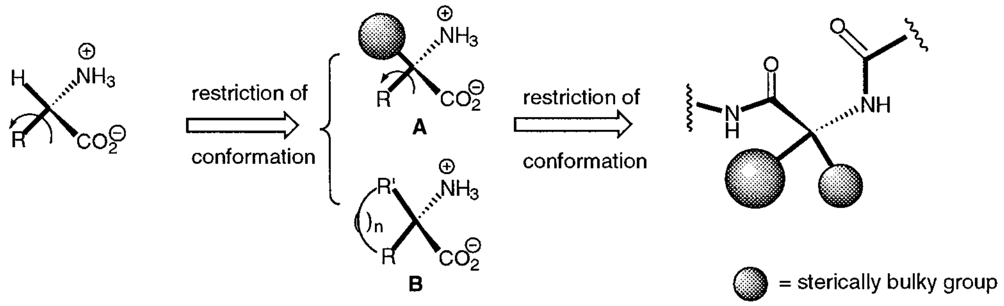


Chart 1.

fixed in its rigid skeleton (type B) where the polar functional groups (e.g., amino, carboxy, and hydroxy groups) play an essential role for the biological activity.

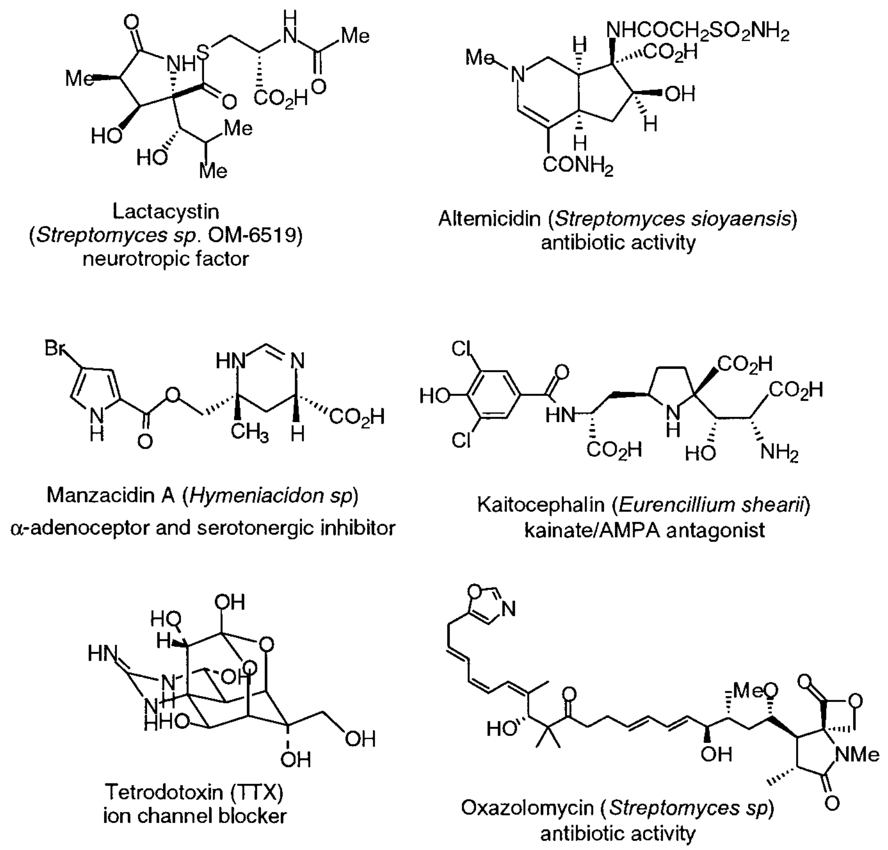
Therefore, numerous attempts to synthesize the amino acids of types A and B have been performed,[5] many of which involved an optical resolution of the racemic form.[6] Recent efforts to synthesize these amino acids are mainly asymmetric transformations based on the alkylation of enolates from bislactims, oxazinones, imidazolidinones, and other procedures.[2,5,7] Among these amino acids, we focused on their β-hydroxy congeners. These can be viewed as the analogous amino acids of serine or threonine and would have marked effects on peptide conformation as well as biological activity.[8] Furthermore, a number of natural products possess β-hydroxy α,α-disubstituted α-amino carboxylic acid as their partial structures.[4] These facts prompted us to study a new method for the synthesis of these novel classes of amino acids (Fig. 1).

The biosynthetic pathway of α,α-disubstituted α-amino acid may involve an asymmetric transformation of an amino group of an α-amino acid to a ketone.[9] As a result, the chirality of the starting amino acid would be transferred to the prochiral ketone group and that of the amino acid would be oxidatively removed as the corresponding pyruvate derivative (Chart 2).

Influenced by the hypothetical biosynthetic route in Chart. 2, our synthetic plan for these amino acids was an asymmetric version of the Strecker synthesis. The synthesis consists of the following sequence of transformations: (i) formation of a cyclic ketimine intermediate from α-acyloxy ketone, having L or D-amino acid as the acyloxy group; (ii) stereoselective addition of a cyanide ion to 1,4-oxazine to give an α-amino nitrile; (iii) oxidative conversion to α-imino nitrile; and (iv) removal of the chirality transferring amino acid as a pyruvate derivative and hydrolysis of the nitrile group under acidic conditions to give a β-hydroxy α,α-disubstituted α-amino acid (Scheme 1).[10]

Syntheses of Both Enantiomers and Diastereomers of α-Methylserine and α-Methylthreonine

We have examined the synthesis of α-methylserine as the representative example of an asymmetric version of the Strecker synthesis to exploit its feasibility as well as efficiency.



Lactacystin (*Streptomyces sp.* OM-6519) neurotropic factor

Altemicidin (*Streptomyces sioyaensis*) antibiotic activity

Manzacidin A (*Hymeniacidon sp*) α-adenoceptor and serotonergic inhibitor

Kaitocephalin (*Eurencillium shearii*) kainate/AMPA antagonist

Tetrodotoxin (TTX) ion channel blocker

Oxazolomycin (*Streptomyces sp*) antibiotic activity

Fig. 1. Natural products possessing an α,α-disubstituted α-amino acid or its related substructure.

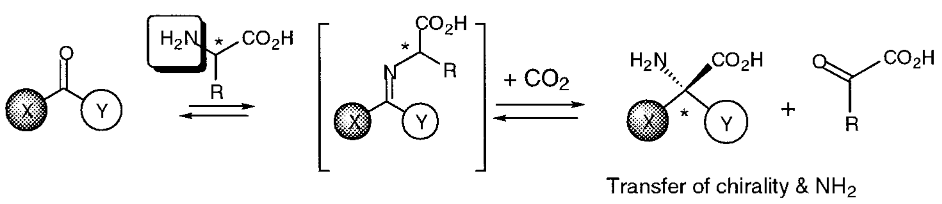
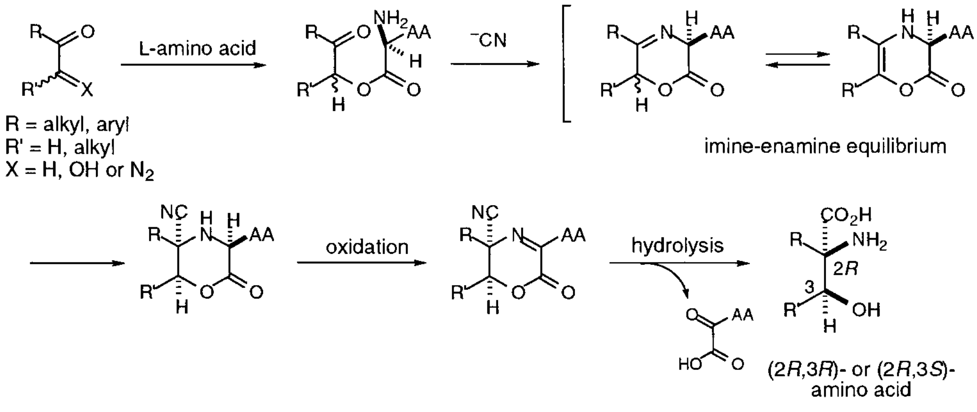


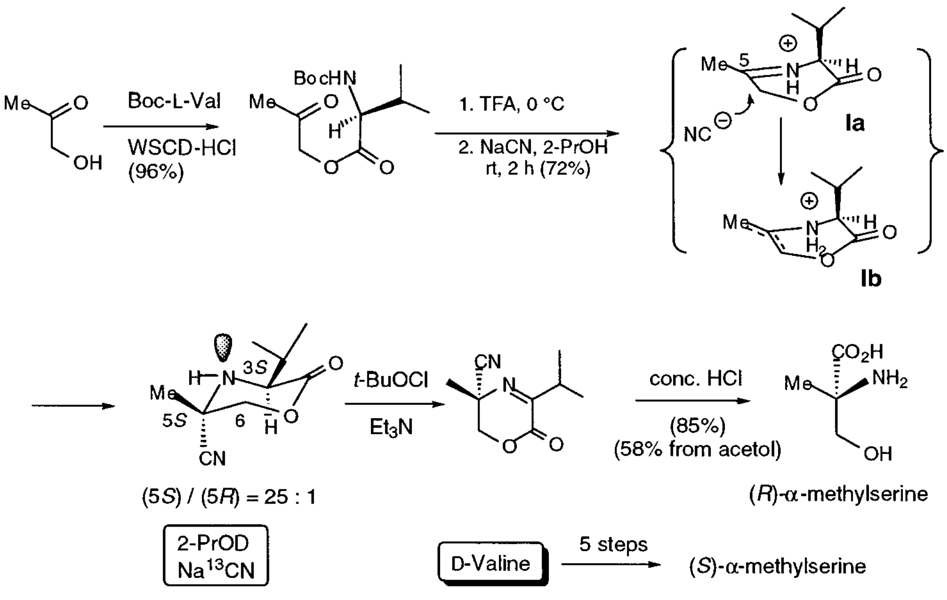
Chart 2.

According to Scheme 1, acetol was condensed with *N*-*t*-butoxycarbonyl (Boc)-L-valine using 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide (WSCD) HCl salt to give *N*-Boc-L-valine acetol ester in 96% yield. After removal of the Boc group with trifluoroacetic acid (TFA), treatment of the resulting TFA salt with 2 equiv of NaCN in 2-propanol for 2 h gave a mixture of cyclic α-amino nitriles in 72% isolated yield (Scheme 2). The mixture was composed of 5*S* isomer as the major product and a small amount of its 5*R* isomer (5*S*:5*R* = 25:1). The latter was removed by recrystallization or column chromatography on silica gel. The structure of the major product possessing a 5*S* configuration was determined by converting it to the known (*R*)-α-methylserine.[11] The choice of the amino acid side chain on the 5*S*/5*R* stereoselectivity was examined by the use of other amino acids with a sterically less bulky side chain. Reaction of L-alanine acetol ester gave a mixture of 5*S* and 5*R* cyclic amino nitriles in 3:1 ratio, and L-phenylalanine acetol ester afforded the mixture in 10:1 ratio, respectively. Thus, valine was found to be an excellent chirality-transferring group in this case in the stereoselective formation of the α-amino nitrile.

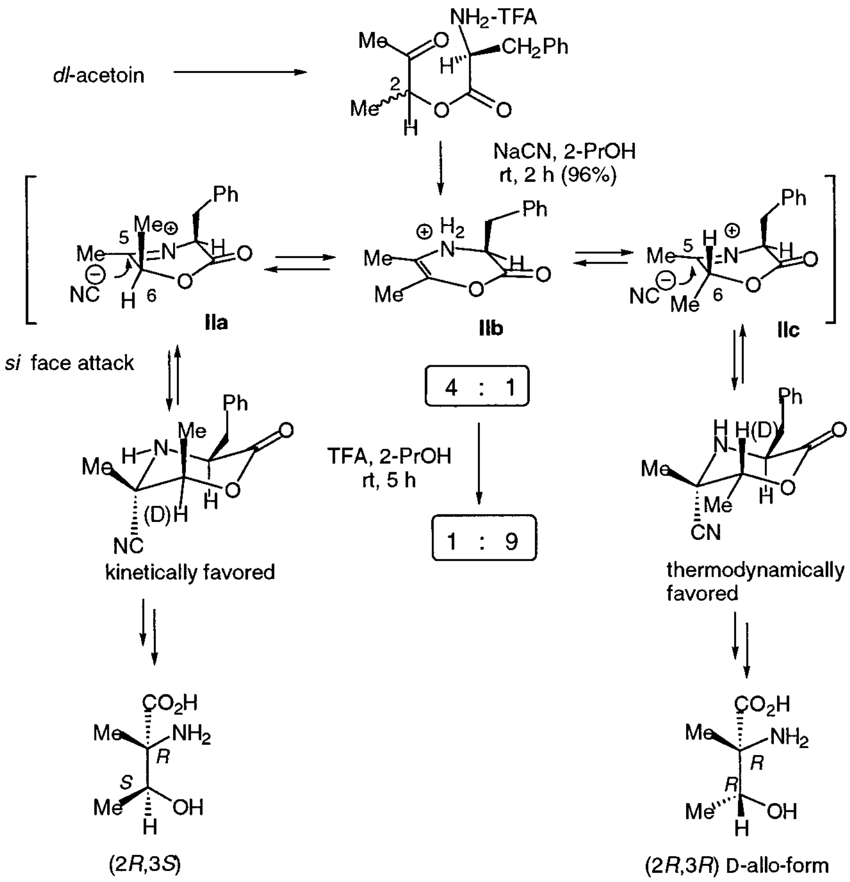
In order to understand the present reaction mechanisms and to estimate the extent of racemization at C3 under the reaction conditions, we examined the following experiments using 2-propanol-*d* and Na^{13}CN: (i) the use of 2-propanol-*d* as the solvent afforded the Strecker product where the deuterium atom was partially incorporated into the methyl group (15%) and into the C6 methylene group (25%); and (ii) treatment of the 5*S* adduct using Na^{13}CN in 2-propanol in the presence of TFA (1 equiv) gave, after 8 h, a mixture of ^{12}C and ^{13}C products (55:45). Based on these experimental results, the reaction is clearly understood to involve an ketimine intermediate **Ia**, coexisting at equilibrium via an enamine-type intermediate **Ib**. We also see that both the 5*S* and 5*R* products are equilibrated via the ketimine intermediate. The highly diastereoselective formation of 5*S*-isomer would be due to an attack of the cyanide ion to the sterically less hindered *si*-face of the ketimine intermediate **Ia**, where a boatlike conformation[12] with the isopropyl group oriented to a pseudoaxial position seemed to be plausible (Scheme 2). Therefore, the 5*S* isomer is a kinetically as well as thermodynamically more favored product than the 5*R* isomer.[13] In addition, the high stereoselectivity would also attributed to stereoelectronic stabilization of the axial nitrile group that is perpendicular to the lone pair electrons of the amino group. The fact that no deuterium atom was incorporated into the C3 methine group clearly indicates that no



Scheme 1. Asymmetric version of the Strecker synthesis: General scheme.



Scheme 2. Asymmetric Strecker synthesis of α-methylserine.



Scheme 3. Synthesis of 4 enantiomers and diastereomers of α-methylthreonine.

racemization occurred under the reaction conditions to give an enantiomerically pure adduct.

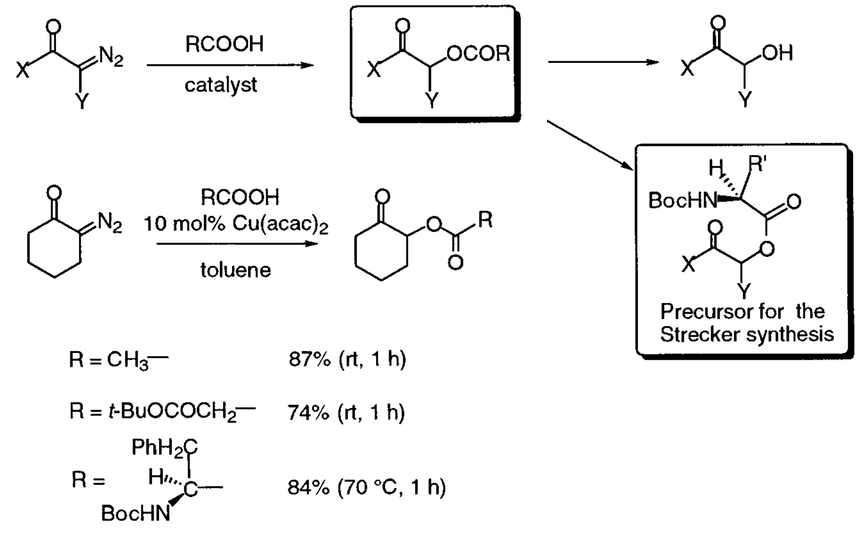
Removal of the valine moiety from the 5*S* isomer and its conversion into (*R*)-α-methylserine were carried out by the following sequence of reactions: (i) oxidation of the α-amino nitrile with *tert*-butyl hypochlorite and triethylamine; and (ii) hydrolytic removal of the resulting α-imino nitrile and hydrolysis of the nitrile group with concentrated HCl. These treatments gave in 84% yield the desired (*R*)-α-methylserine. The use of D-valine afforded (*S*)-α-methylserine. Note that the configuration of the new amino acid is opposite to that of valine. Thus, both enantiomers of α-methylserine were prepared in 5 steps, and their overall yields were ~55%.[10]

Since certain imine-enamine equilibria were involved in the above-mentiond α-amino nitrile formation, we were interested in examining whether the C3 stereogenic center of the ketimine intermediate would affect the stereochemistry of an α-amino nitrile having a substituent at the C6 position. Thus, our next approach was the syntheses of four enantiomers and diastereomers of α-methylthreonine from DL-acetoin. Treatment of the acyloxy ketone having Boc-L-phenylalanyl group with TFA followed by 2 equiv of NaCN in 2-propanol gave a 4:1 mixture of the α-amino nitriles, 5*S*,6*S* isomer and its 5*S*,6*R* isomer. In the presence of an additional 1 equiv TFA in 2-propanol, the mixture was further equilibrated to afford a 1:9 mixture of 5*S*,6*S* isomer and its 5*S*,6*R* isomer. These results suggested that the reaction involves an enamine type intermediate **IIb** and that both the ketimine-type intermediates, **IIa** and **IIc**, coexist at equilibrium via **IIb**. This was proven by the fact that the reaction using 2-propanol-*d* as the solvent gave a 4:1 mixture of the mono-deuterated products in which the C6-H was completely exchanged with a deuterium atom. Therefore, the rate-determining step of the reaction would be an attack of the cyanide ion to the ketimine intermediates, where a boatlike conformation[12] with a pseudoaxial benzyl group might sterically hinder the *re*-face. An attack of the cyanide ion to the *si*-face on C5 of the ketimines would yield, exclusively, the 5*S* products. No deuterium atom was incorporated at C3 of the products, indicating that no racemization at C3 accompanied the reaction process. Thus, the α-amino nitriles with the 6*S* and 6*R* configuration were obtained from DL-acetoin using phenylalanine in an enantiomerically convergent manner, respectively (Scheme 3).

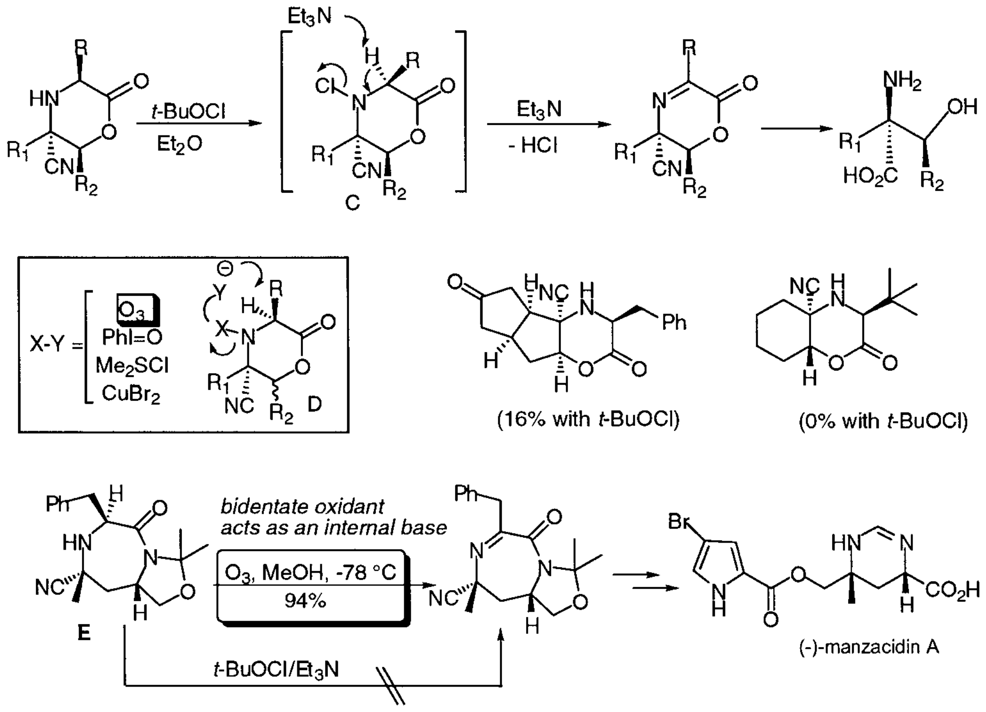
Removal of the phenylalanyl moiety and their conversions into (2*R*,3*S*)- and (2*R*,3*R*)-α-methylthreonine[11] were carried out in a manner similar to the preparation of α-methylserine. The use of D-phenylalanine afforded (2*S*,3*R*)- and (2*S*,3*S*)-α-methylthreonine, respectively, in the same manner as for the 2*R*-isomers. Thus, α-methylated threonine and its allo isomers were prepared in a short number of steps; their overall yields were 44–50%.[10]

Cu(acac)$_2$-Catalyzed Synthesis of α-Acyloxy Ketones

Upon further application of the asymmetric version of the Strecker synthesis into various classes of α,α-disubstituted α-amino acids, conventional preparation of an α-acyloxy ke-



Scheme 4. Cu(acac)$_2$-catalyzed synthesis of α-acyloxy ketones.



Scheme 5. Oxidation of α-amino nitrile to α-imino nitrile.

tone is an important issue. The starting ketones can be prepared by esterification of an α-ketol with an *N*-protected amino acid or mono-esterification of a vicinal diol followed by oxidation. Occasionally, these methods incurred a problem, which is represented by the resistance of the hydroxy group to the esterification with an α-amino acid. We examined an alternative method that is based on the insertion reaction of an α-diazo ketone into the carboxyl group of an α-amino acid. Without any metal-catalyst, the reaction usually required a large excess of the carboxylic acid and high temperature.[14] After a survey of many metal-catalysts, we found that Cu(acac)$_2$ effectively catalyzes the insertion reaction under mild reaction conditions (Scheme 4). Most of the diazo ketones reacted with a stoichiometric amount of carboxylic acid to give the corresponding α-acyloxy ketones. Thus, various types of α-acyloxy ketones as the precursor of the Strecker synthesis became available from α-diazo ketones.[15]

Improved Process for the Conversion of α-Amino Nitriles into α-Imino Nitriles

Better efficiency of the asymmetric version of the Strecker synthesis was demonstrated by the synthesis of optically active α-methylserine and α-methylthreonine. The entire Strecker process depicted in Scheme 1 proceeded smoothly to give the corresponding amino acid, in particular, stereoselectivity in the formation of α-amino nitrile is excellent. In the course of the studies to extend this method for further applications, however, we observed that the oxidation of sterically congested α-amino nitriles to α-imino nitriles depicted in Scheme 5 resulted in a serious decrease in yields or did not give any

α-imino nitrile at all.[16] These results led us to investigate an alternative method to improve the oxidation process. The oxidation of α-amino nitrile to α-imino nitrile is often performed by initial *N*-chlorination with *t*-BuOCl and subsequent dehydrochlorination with Et_3N. However, the latter step is occasionally very slow or does not proceed at all. Since an external base such as Et_3N could not abstract the hydrogen at C2 (**C**) due mainly to steric reasons, we postulated that a bidentate oxidant would act as the internal base after oxidation of the amino group (**D**).[17] After numerous unsuccessful attempts for the oxidation of α-amino nitrile **E**, we found that the oxidation with ozone (a strong and less bulky oxidant) gave the desired α-imino nitrile, which led to our successful total synthesis of manzacidin A (vide infra).[16]

To our surprise, oxidation of structurally simple α-amino nitrile with ozone afforded a mixture of desired α-imino nitrile and an unexpected α-amide nitrile. Hydrolysis of each product with concd hydrochloric acid gave α-methylserine in $> 99\%$ yield, respectively. The choice of ethyl acetate as the solvent gave the best yield of the mixture, and the overall yield to α-methylserine (2 steps) was 97%, much superior to that attained in the previous three step conversion (87%).[10] Treatment of the isolated α-imino nitrile with ozone resulted in a complete recovery of starting material even at 0 °C, indicating that the α-amide nitrile was not produced from α-imino nitrile under the reaction conditions (Scheme 6). From these results, we propose the following reaction pathway to produce the mixture: (i) abstraction of the C2 hydrogen from a trioxo species to give an enol; (ii) formation of the α-imino nitrile via an elimination of O_2 and H_2O (path A); (iii) further oxidation of the enol with ozone to give an epoxide; and (iv) carbon–carbon bond cleavage to form a carbonate, whose work-up gave α-amide nitrile (path B).

The present method was proven to be extremely effective for the conversion of other α-amino nitriles (Table 1). Not only mono-cyclic amino nitrile but also bi- and tri-cyclic substrates having sterically bulky substituents gave a mixture of the corresponding α-imino and amide nitriles in good to excellent yields. It is noteworthy that the yields of the mixtures, including their conversions to the corresponding amino acids, were dramatically improved, while previous conversions using the *t*-BuOCl/base system were 0% to moderate yields. Thus, the problematic oxidation of α-amino nitrile in the Strecker synthesis was much improved by the use of ozone. This method is advantageous in view of its simple operation and high yields.[18]

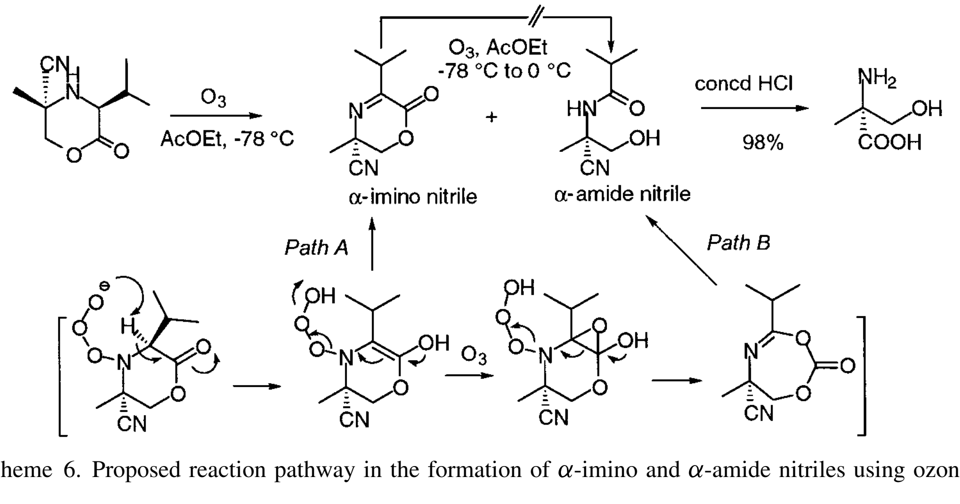
Application of the Asymmetric Strecker Synthesis to Biologically Active α-Substituted Serine Analogs

It was considered that the use of α-hydoxymethyl ketones with various substituents instead of a methyl group would undergo stereoselective α-amino nitrile formation under the Strecker synthesis to give the corresponding α-substituted serines. Next, we examined the synthesis of optically active α-benzylserine [α-(hydroxymethyl)phenylalanine] and α-carboxyethylserine [α-(hydroxymethy)glutamate]; these have attracted significant attention as an enzyme inhibitor[7j] and as a useful ligand for excitatory amino acid receptors,[19,20] respectively.

The synthesis of α-benzylserine was started with phenyl acetol (Scheme 7). The Strecker synthesis of the acyloxy ketone with L-valine gave in 77% yield a mixture of α-amino nitriles; the mixture involved the 5*S* isomer as the major product (5*S*:5*R* = 16:1). No racemization and the presence of a certain imine-enamine equilibrium was ascertained using 2-propanol-*d* as the solvent (vide supra). Conversion of the α-amino nitrile into the target amino acid was performed in the same manner as that of α-methylserine. Thus, α-benzylserine was synthesized in an optically active form.[21] The acyloxy ketone having a 2-carboxyethyl group gave (5*S*)-amino nitrile as the major product (5*S*:5*R* = 18:1). Removal of the chirality transferring group requires oxidation of α-amino nitrile to α-imino nitrile, followed by acidic hydrolysis. The classical method (*t*-BuOCl/Et_3N) gave α-imino nitrile in 78% yield. On the other hand, the use of ozone as the oxidant gave a mixture of α-imino and α-amide nitriles in 94% yield.[18] The mixture was subjected to acidic hydrolysis to give optically active (2*R*)-α-(hydroxymethyl)glutamate in 98% yield.[22]

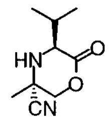
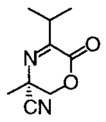
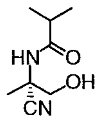
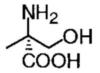
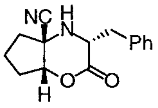
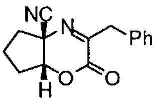
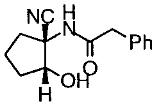
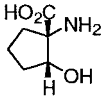
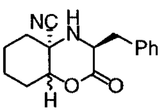
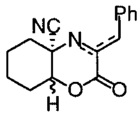
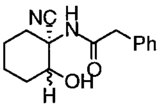
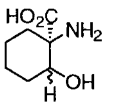
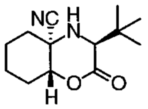
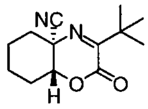
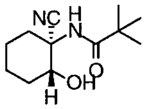
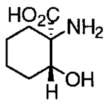
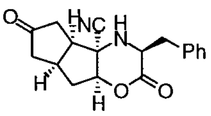
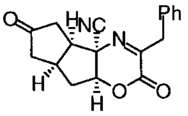
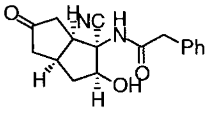
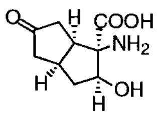
Incorporation of α-Substituted Serine Analogs into Leucine-Enkephalin

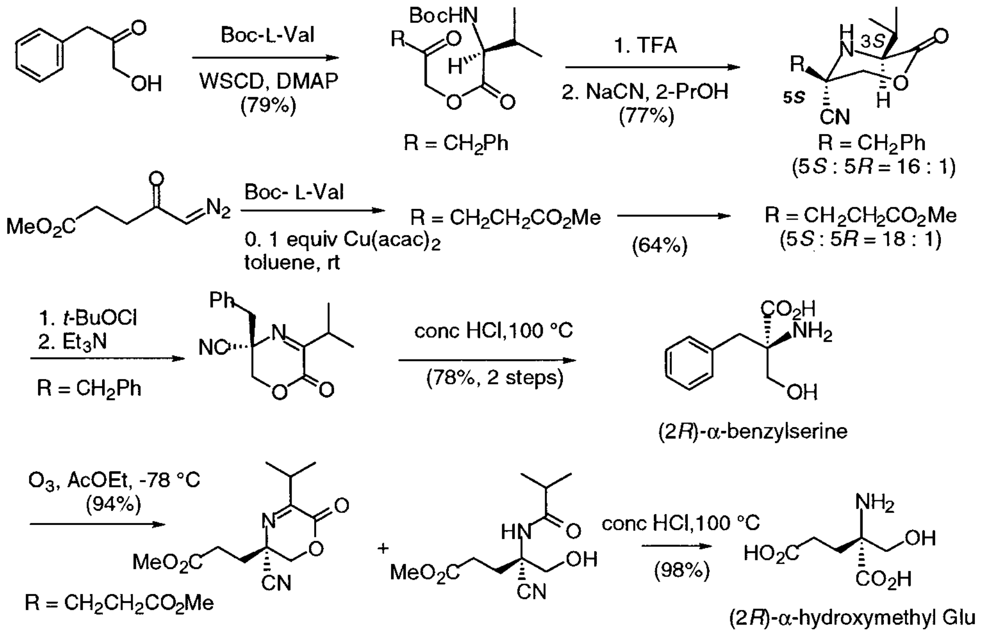
The synthesis of α-methylthreonine has demonstrated that the newly introduced two consecutive chiral centers could be stereochemically controlled by the chirality-transferring amino



Scheme 6. Proposed reaction pathway in the formation of α-imino and α-amide nitriles using ozone.

Table 1. Conversion of α-Amino Nitriles into α-Imino and α-Amide Nitriles with Ozone Oxidation

α-Amino nitrile	α-Imino nitrile	Combined yield (%) (product ratio)	α-Amide nitrile	Yield of α-amino acid (2 steps, %) (yield % using t-BuOCl/Et_3N)
		98 (3:2)		 97 (5)
		98 (3:2)		 98 (61)
 cis/trans=3/2	 cis/trans=1/1	95 (2:1)	 cis/trans=2/1	 cis/trans=3/2 94 (62)
		93 (2:1)		 90 (0)
		64 (1:1)		 60 (6)



Scheme 7. Synthesis of α-benzylserine and (2R)-α-(hydroxymethyl)glutamate.

acid. Its application to cyclic systems, prompted by these results, was of particular interest. Optically active 1-amino-2-hydroxycyclopentanecarboxylic acid and its cyclohexyl analogs were target amino acids starting from 2-hydroxycyclopentanone, and 1-amino-2-hydroxycyclohexanecarboxylic acid from 2-hydroxycyclohexanone, respectively. The details of the successful syntheses of these amino acids have been reported in the previous papers.[10,23] In addition to these reports, their improved Strecker processes, i.e., preparation of the acyloxy ketones using $Cu(acac)_2$-catalyzed insertion reaction and oxidation of α-amino nitriles with ozone, are depicted in Scheme 4 and Table 1. Moreover, α-substituted serine analogs, in particular cyclic amino acids, can be viewed as conformational variants of L-serine, which in peptides and proteins plays a crucial role not only as a hydrophilic residue but also as either an active site or a catalytic site of a variety of enzymatic transformations and biochemical signal transductions in the cell. Thus, their incorporations into biologically important peptides are demonstrated next (Chart 3).[9,24]

An incorporation of 2-amino-2-methylpropanoic acid (Aib) to the Gly^2 residue of leucine-enkephalin (Leu-Enk) fixes its Tyr^1-Aib^2-Gly^3-Phe^4 moiety to a β-turn conformation in solution (Fig. 2).[25] The result resembles the crystal structure of Leu-Enk.[26] However, [Aib^2]Enk exhibits much weaker activity to opioid receptors than that of native one,[27] suggesting that the β-turn conformation is not a crucial factor for the activity. On the other hand, other substituted analogs at the Gly^2 residue such as [D-Ala^2]Enk or [D-Ser^2]Enk are known to be a potent agonist of opioid receptors.[27] We envisaged that an incorporation of serine analogs into the Gly^2 residue, in particular into cyclic serine analogs, would provide important insights into the structure–activity relationship of Leu-Enk.

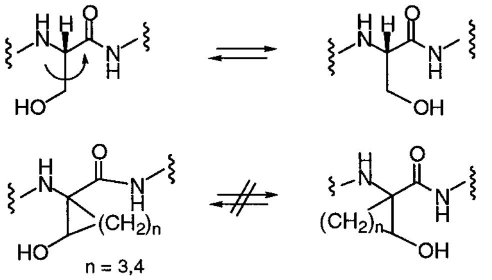
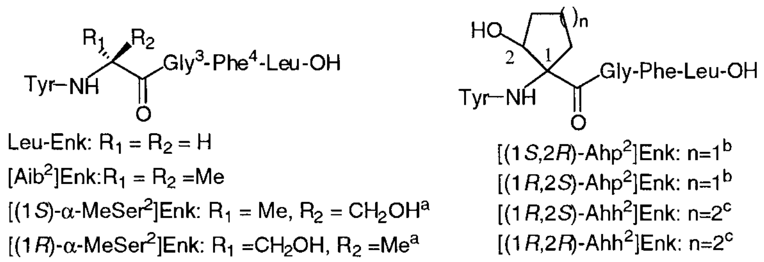


Chart 3.

The synthesis of the *N*-Boc-tetrapeptides was performed by the condensation of H-Gly-Phe-Leu residues, common to all synthetic analogs, with the *C*-terminal of the *N*-Boc-α-substituted serines. Since the coupling of the *N*-terminal of the α-substituted serine residue with Boc-Tyr(*t*-Bu)-OH encountered difficulty, due probably to the presence of the sterically bulky substituents at the α position, we used the following sequence of reactions which have recently been developed by us:[28] (i) ester formation of the *C*-terminal of the tyrosine residue with the hydroxy group of the *N*-Boc-α-substituted serine residue; (ii) removal of the Boc group; and (iii) internal migration of the ester group to the amino group (*O*,*N*-migration).[29] The syntheses of Leu-Enk analogs possessing cyclic serines using the *O*,*N*-migration method are depicted in Scheme 8.

The binding affinities of the synthetic enkephalin analogs and their inhibitory effects on the cAMP production were examined using chinese hamster ovary (CHO) cells expressing cloned rat μ-, δ- or κ-opioid receptors[30] which were determined by a competitive inhibition of the radioligands, [^{3}H]DAMGO (Leu-Enk: $IC_{50} = 1.8$ nM) , [^{3}H]DPDPE (Leu-Enk: $IC_{50} = 0.13$ nM) and [^{3}H]U69593 (Leu-Enk: $IC_{50} =$ 400 nM), respectively. The IC_{50} values of the synthetic analogs for the δ-opioid receptors are shown in Scheme 9. The binding characteristics of the synthetic analogs indicated the following points: (i) all the synthetic analogs had higher affinities for δ-opioid receptors than for μ-opioid receptors, and exhibited very weak binding affinities for κ-opioid receptors; (ii) the (*R*)-isomers potently activated the δ-opioid receptors, in particular, [(1*R*,2*S*)-Ahh^2]Enk had the highest affinity for δ-opioid receptors, which was 17 times more potent than native Leu-Enk; (iii) the (*S*)-isomers showed much lower activity than those of the corresponding (*R*)-isomers; and (iv) (*R*)-isomers also activated μ-opioid receptors to almost the same degree as that of Leu-Enk.

These binding studies revealed that the α-substituted serine residue with the 1*R* configuration is a crucial factor for the high affinity binding to δ-opioid receptors. Next, we examined the conformation of the peptide in which an α-substituted serine is incorporated into the Gly^2 residue. The temperature coefficient values ($-d\delta/dT$, ppm/K) using ^{1}H NMR in DMSO-d_6 as the solvent provide useful information on the inter- or intramolecular hydrogen bonding of the NH group.[31] Thus, the NH groups of the residue-2, Gly^3, and Leu^5 in all peptides tested were exposed to the solvent. On the other

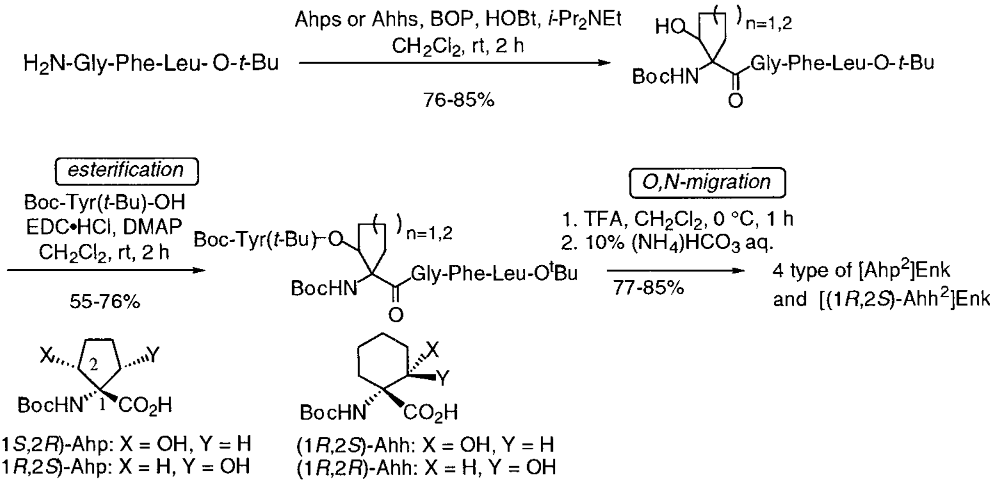


[a] α-MeSer: α-methylserine

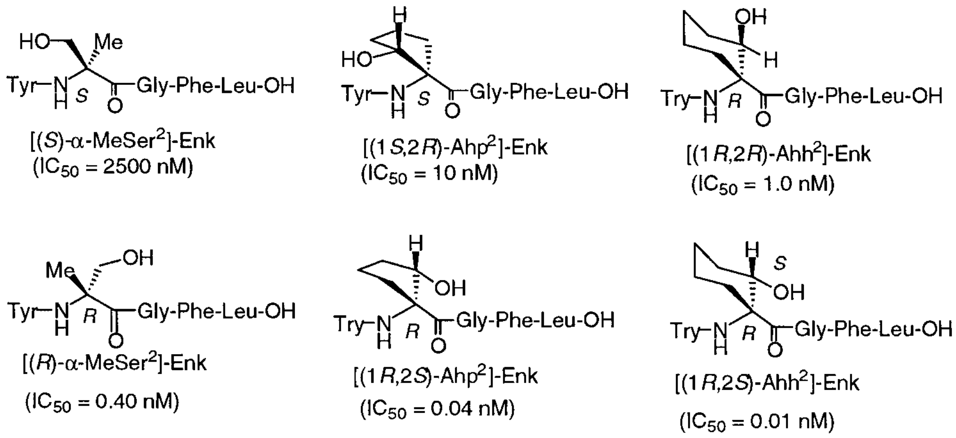
[b] Ahp: 1-amino-2-hydroxycyclopentanecarboxylic acid

[c] Ahh: 1-amino-2-hydroxycyclohexanecarboxylic acid

Fig. 2. Leucine-enkephalin and its α-substituted serine analogs at the Gly^2 position.



Scheme 8. Synthesis of [Ahp^2 or Ahh^2]Enk using *O*,*N*-migration method.



Scheme 9. Radio ligand binding affinities of the synthetic Leu-Enk analogs for δ-opioid receptors.

hand, the NH group at the Phe residue formed an intramolecular hydrogen bonding. Since these results were quite similar to those of the Aib^2 analog of Lue-Enk,[32] all the peptides with α-substituted serine would have β-turn conformation. The α-substituted serine residue employed in this study would play a role in fixing the conformation of the peptides to the β-turn conformation. It is of particular interest to note that [(1*R*,2*S*)-Ahh^2]Enk, the most potent isomer among the tested analogs, fixed its hydroxy group to an equatorial orientation on the cyclohexane ring (chair conformation: δ 3.7, dd, $J = 4.4$, 11.2 Hz in D_2O), indicating the importance of the conformation of the hydroxy group at the α-substituted serine residue (Scheme 9). Therefore, the high affinity binding to δ-opioid receptors would require both the β-turn conformation and the presence of a β-hydroxy group with an appropriate configuration and conformation at the Gly^2 residue. These results suggest an active conformation of Leu-Enk, in particular, the conformation of [(1*R*,2*S*)-Ahh^2]Enk. Thus, they led us to propose an active local conformation of Leu-Enk to δ-opioid receptors that is similar to that of [(1*R*,2*S*)-Ahh^2]Enk, as depicted in Fig. 3. The role of the hydroxy group can not be determined at this stage, i.e., whether this group functions as a binding group or simply as a stabilizing factor of the β-turn conformation. Thus, the conformational variants of L-serine were found to be effective conformational modifiers of biologically active peptides.[33]

Stereocontrolled Synthesis of the Corey Intermediate of Lactacystin

Lactacystin,[4a] isolated from the culture broth of *Streptomyces* sp. OM-6519, has attracted growing interests in the field of life sciences because it inhibits cell proliferation and induces neurite outgrowth in the murine neuroblastoma cell line (Neuro-2a cells) as the result of an inhibition of proteosome-mediated peptidase.[34] Due to its important biological role as well as its unique structure having a β,β'-dihydroxy-α,α-disubstituted α-amino acid substructure, a number of efforts for the total synthesis of lactacystin have been reported.[35] Among these syntheses, Corey et al. have employed 1,3-oxazolidine as the key intermediate for both the natural product and its potent active derivatives.[35a] We considered that the intermediate amino acid having two consecutive chiral centers can be constructed simultaneously by the use of the asymmetric Strecker approach as shown in Scheme 10. The key transformation is whether addition of a nitrile group to the ketimine intermediate would occur from the sterically less hindered β-face to give kinetically favored (5*S*,6*S*)-α-amino nitrile.[10]

The acyloxy ketone as the Strecker precursor was synthe-

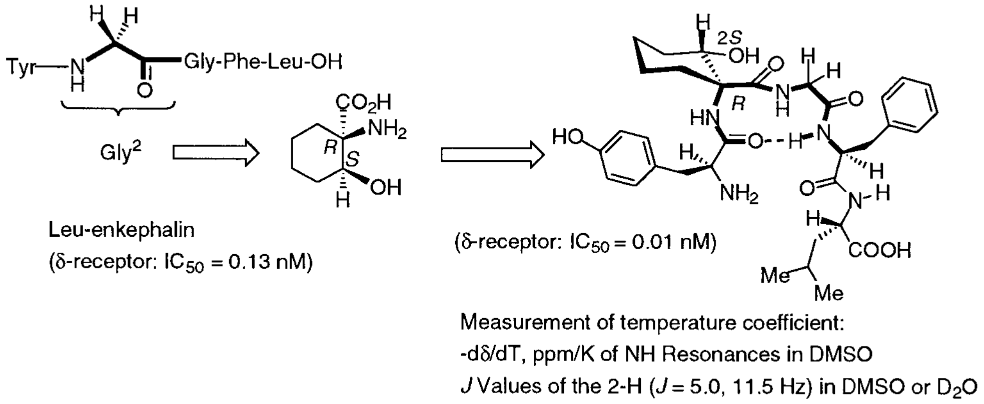
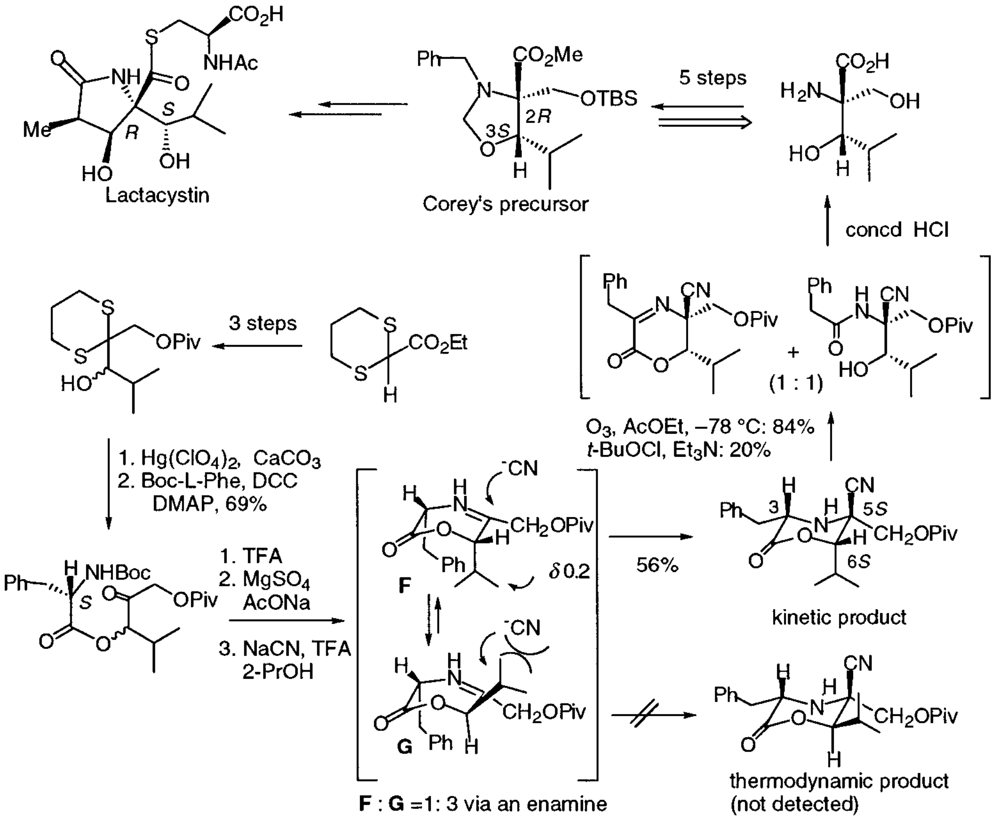


Fig. 3. Proposed conformation of [(1*R*,2*S*)-Ahh$_2$]Enk.



Scheme 10. Synthesis of the Corey intermediate of lactacystin.

sized by the following sequence of reactions: (i) condensation of ethyl 1,3-dithiane-2-carboxylate with isobutyraldehyde; (ii) reduction of the resulting β-hydroxy ester with $LiAlH_4$; (iii) selective protection of the primary hydroxy group with a pivaloyl group; (iv) conversion of the thioacetal group to α-hydroxy ketone; and (v) introduction of Boc-L-Phe to the secondary hydroxy group. After removal of the Boc group with TFA, successive treatments of the resulting amine with (1) $MgSO_4$/AcONa and (2) 10 equiv NaCN/TFA gave in 56% yield the desired (5*S*,6*S*)-α-amino nitrile as a single diastereomer. The exclusive formation of the kinetically controlled product was accounted for by a preferential attack of cyanide ion to the ketimine intermediate **F** having a boatlike conformation as depicted, where an unusually high field shift of one of the methyl groups (^{1}H NMR δ 0.2, s, 3H) was observed.[12a] The presence of an equilibrium between **F** and **G** via an enamine was ascertained by the treatment with NaCN/CF_3COOD in 2-propanol-*d*. The reaction gave deuterated α-amino nitrile in which the C6 hydrogen was completely exchanged with a D atom. Removal of the L-Phe moiety was performed by the use of ozone to give a mixture of α-imino and α-amide nitriles (1:1, 84%), while the classical method gave α-imino nitrile only in 20% yield.[13] Treatment of the mixture with concd HCl allowed simultaneous removal of the pivaloyl group and hydrolysis of the nitrile group to give the desired amino acid. This was converted into Corey's precursor in 5 steps. Thus, Strecker synthesis of α-acyloxy ketone led to an enantioselective synthesis of Corey's precursor of lactacystin under excellent stereocontrol. The intermediate amino acid will be a potential precursor for the synthesis of other variants of lactacystin analogs.[36]

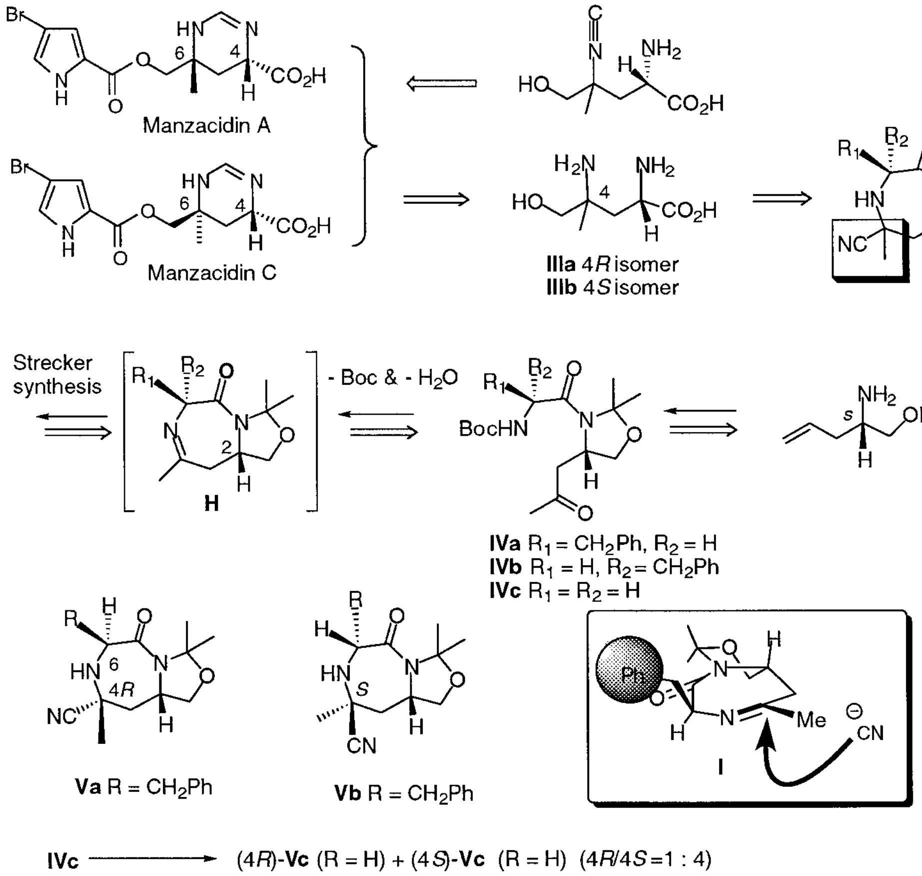
Total Synthesis and Absolute Structure of Manzacidin A and C

A novel class of bromopyrrole alkaloids, manzacidin A–C, was isolated from an Okinawan sponge *Hymeniacidon* sp. by Kobayashi et al.[4g] Manzacidins possess a unique structure consisting of an ester-linked bromopyrrolecarboxylic acid and a 3,4,5,6-tetrahydropyrimidine ring, in which one of the amino groups is attached to the C4 quarternary carbon center. Although they exhibit pharmacologically useful activities such as α-adrenoceptor blockers, antagonists of serotonergic receptor, and actomyosin ATPase activators, only preliminary tests have been carried out, owing to the extremely small amounts of samples available from marine sources.[4g]

The stereochemical relationship between manzacidin A and C has been proposed as either the C4 or the C6 diastereomer. We presumed that their C4 configuration would be the same *S* by considering a plausible biosynthetic pathway which involves (*R*)- or (*S*)-isocyanide intermediate as often seen in the structure of marine natural products.[37] Thus, diastereoselective construction of (2*S*,4*S*)- and (2*S*,4*R*)-diamines **IIIa** and **IIIb** would lead to manzacidin A and C, respectively (Scheme 11). This route relies on a stereoselective construction of the α-amino nitrile by the Strecker synthesis of the amino ketone. However, an asymmetric version of the Strecker synthesis using an amide substrate is unknown, and the stereochemistry of a cyanide addition to the imine **H** is unpredictable in this case because its C2 chiral center also affects the facial selectivity, while in our previous works the nitrile addition to a 6-membered ketimine intermediate occurred from the sterically less demanding α-face (Scheme 11).[10,21–23,36]

We prepared Strecker precursors having Boc-L-phenylalanine amide **IVa**, its D-Phe isomer **IVb**, and Boc-glycine amide **IVc**, respectively, from (2*S*)-allylglycinol to examine the stereochemical outcome of the nitrile addition to the imine **H**. After chemoselective removal of the Boc group with TMSOTf/2,6-lutidine,[38] the resulting amine was treated with TMSCN to give the α-amino nitrile (4*R*)-**Va** as a single diastereomer. The D-Phe isomer afforded (4*S*)-**Vb** (87%), exclusively. These results clearly indicated that in each case the nitrile addition to the imine occurred from the opposite side of the C6 benzyl group, e.g., **I**, similar to the 6-membered case. On the other hand, the glycyl amide **IVc** gave a 1:5 mixture of (4*R*)-**Vc** and (4*S*)-**Vc**, indicating that the cyanide preferentially attacks from the sterically less hindered β-face when the C6 substituent is absent. Thus, not only was the stereochemical outcome of the amino nitrile formation clearly understood, but also the desired α-amino nitriles, which correspond to the stereochemistry of manzacidin A and C, were each obtained with excellent stereocontrol.

As depicted in Scheme 5 (vide supra), the conversion of the α-amino nitrile **Va** into the corresponding α-imino nitrile was problematic because the amino group is sterically congested



Scheme 11. Stereoselective synthesis of the α-amino nitriles.

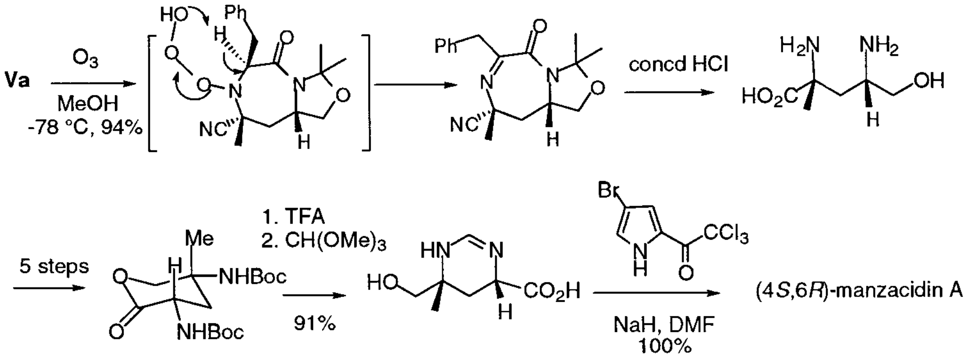
and because the acidity of the neighboring hydrogen is decreased due to the α-amide position. The oxidation with ozone was quite effective for this conversion to give in 94% yield the α-imino ketone. In this case, none of α-amide nitrile was produced. Treatment with concd HCl afforded diamino carboxylic acid. This was converted into δ-lactone in 5 steps, to which a tetrahydropyrimidine ring was introduced. The synthesis of manzacidin A was accomplished by coupling with the bromopyrrole moiety using 4-bromo-2-trichloroacetylpyrrole.[39] Thus, the absolute structure of natural (−)-manzacidin could unambiguously be assigned to (4*S*,6*R*)-enantiomer (Scheme 12).

Next, the synthesis of manzacidin C from the (4*S*)-amino nitrile **Vb** was examined (Scheme 13). We faced difficulty upon oxidative removal of the D-Phe moiety of **Vb**, which did not produce the desired α-imino nitrile even by ozone. Fortunately, treatment of the hydroxylamine prepared by trioxorhenium oxidation[40] with concd HCl unexpectedly produced cyclic urea in 76% yield. We propose that the carbon-carbon fragmentation between C6 and C7 of the protonated hydroxylamine **J** occurred to give **K**, which re-cyclized to cyclic urea (Scheme 13). Treatment of the urea with 10% H_2SO_4 gave a mixture of hydrolyzed products which, upon 5 step conversion, gave the desired δ-lactone whose conversion into manzacidin C was successfully performed in the same manner as that of manzacidin A. Thus, both natural (−)-manzacidin A and (+)-manzacidin C were found to possess the same 4*S* configuration. Not only was sufficient synthetic material (14 steps, 14% overall for manzacidin A, and 15 steps, 3.5% for manzacidin C) obtained to permit further pharmacological studies on these alkaloids, but also the present route enables the synthesis of the enantiomers or diastereomers using the combination of (*R*)-allylglycinol with D- or L-Phe.[16,41]

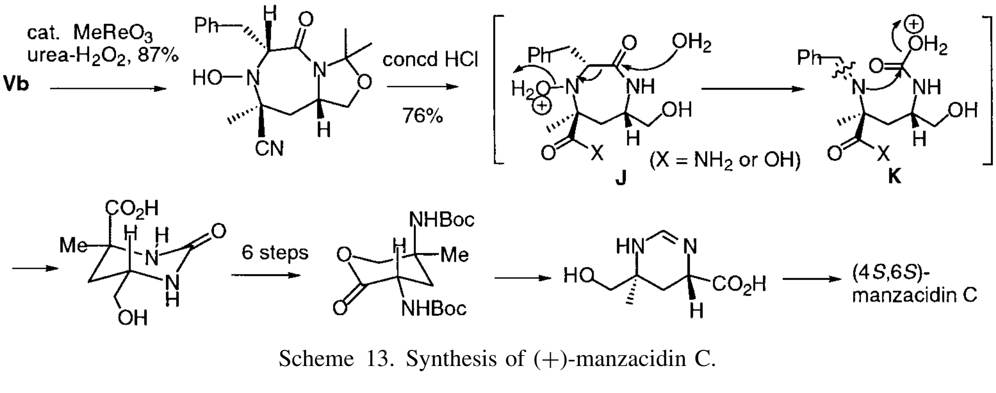
Conclusion

Several types of optically pure α-substituted serine and threonine including their cyclic analogs and natural products were synthesized from achiral or racemic starting material. The chiral transfer process from the acyloxy amino acid moiety, which involved diastereoselective construction of one or two consecutive chiral centers, was found to be highly efficient. Its reaction process was clearly understood by an incorporation experiment of a deuterium atom or ^{13}CN. In all cases that we examined in the present studies, the nitrile group attacked the ketimine intermediates from the opposite side of the C3 substituent. These events would be explained as a result not only of steric reasons but also of stereoelectronic factors. The present efficiency of the chirality transfer from valine or phenylalanine and the overall yields were excellent. The preparation of the starting α-acyloxy ketones and the problematic oxidation process of structurally congested or highly functionalized α-amino nitriles were much improved. These improvements allowed the successful synthesis of biologically active α,α-disubstituted α-amino acids and natural products. Incorporations of α-substituted serines and its cyclic analogs into peptides were represented by the synthesis of highly potent agonists for opioid receptors. Extensive studies regarding the synthesis of related amino acids and natural products are continuing in our laboratories.

We wish to acknowledge the contributions of our colleagues whose names are reported in the references. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technolo-



Scheme 12. Synthesis of (−)-manzacidin A.



Scheme 13. Synthesis of (+)-manzacidin C.

gy, and the Project for the Future Program (JSPS 99L01204).

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