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Enantio- and Diastereoselective Construction of α,α-Disubstituted α-Amino Acids for the Synthesis of Biologically Active Compounds

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Keywords: Aldol reaction / Amino acids / Asymmetric synthesis / Biological activity / Natural products

Natural and unnatural compounds possessing an α,α-disubstituted α-amino acid substructure have received significant attention because of their structural complexity and potent biological activity. Many methods have been developed for the enantio- and diastereoselective synthesis of α,α-disubstituted α-amino acids, many of which are focused on the total synthesis of natural products and related bioactive compounds. This microreview highlights recent advances in synthetic methods utilized for the synthesis of (1) α-substituted serine analogs, which were extensively transformed into glutamate and enkephalin analogs, and (2) natural products such as lactacystin, manzacidins, kaitocephalin, altemicidin, sphingofungins, and neooxazolomycin. The key methods for the construction of these higher-order structures are the asymmetric Strecker synthesis and enolate-Claisen rearrangements used by our group, and aldol condensation of an enolate or bislactim, mercurio- or iodo-cyclization, alkylation of an oxazoline, rearrangement of a trichloroacetimidate, nitrene insertion into a C–H bond, carbene insertion into a C–N bond, a Diels–Alder reaction, Lewis acid-induced epoxide opening, and other methods by other groups.

Introduction

There is ever-growing interest in the synthesis, pharmacology, and conformational properties of non-proteinogenic amino acids.[1,2] In particular, α,α-disubstituted α-amino acids have been the subject of numerous investigations over the decades. The structural feature common to these amino acids is the presence of an additional substituent at the α-position of the amino acid that sterically constrains the free rotation of its side-chain or strictly fixes the conformation by forming a carbo- or heterocyclic ring. α,α-Disubstituted α-amino acids are often found in nature either in their free

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

form or as constituents of biologically active natural products that are known to be enzyme inhibitors, ion-channel blockers, agonists and/or antagonists of neuronal receptors, and antibiotics. In many cases, the sub-structure of the α,α-disubstituted α-amino acid of natural origin is fixed in its rigid skeleton, where the polar functional groups (e.g., amino, carboxy, and hydroxy groups) play an essential role in the biological activity. Therefore, numerous attempts to synthesize such amino acids have been performed, many of which involve optical resolution of the racemic form.[3] Recent efforts to synthesize these amino acids are mainly asymmetric transformations based on the alkylation of enolates from bislactims,[4] oxazinones,[5] imidazolidinones,[6] and other procedures.[7] These methods have been documented by Seebach et al.[8] and Cativiela et al.[9] in their excellent reviews. This microreview will focus on recent works from our laboratory, as well as other groups, regarding the total syntheses of biologically active natural products and their analogous amino acids possessing an α,α-disubstituted α-amino acid, or equivalent structure (Figure 1).

Acyclic and cyclic α,α-disubstituted α-amino acids possessing a β-hydroxy group can be viewed as α-substituted serine or threonine equivalents and are found in many natural products. Our approach was the asymmetric synthesis of α-substituted serine analogs (**1**) using an intramolecular version of the Strecker synthesis.[10,11] Various optically active acyclic and cyclic β-hydroxy-α,α-disubstituted α-amino acids were synthesized from achiral or racemic α-hydroxy ketones. The synthetic α-substituted serine analogs were then used extensively for the synthesis of bioactive compounds such as (+)-LY-354740[12] and Leucine-enkephalin analogs.[13]

Metabotropic glutamate receptors (mGluRs) are implicated in the regulation of many physiological and pathological processes in the mammalian central nervous system, including synaptic plasticity, learning and memory, motor coordination, pain transmission, and neurodegeneration.[14] An agonist of these receptors markedly suppresses postsynaptic excitation. (+)-LY-354740 (**2**), which has a fused bicyclo[3.1.0]hexane skeleton, is a potent and selective mGluR2 agonist and exhibits anticonvulsant and anxiolytic properties in mice.[15] Various leucine-enkephalin analogs incorporating α-substituted serine at the Gly^2 residue have been synthesized to explore the role of these amino acids in affecting peptide conformation as well as their biological activity. The (1*R*,2*S*)-1-amino-2-hydroxycyclohexanecarboxylic acid (Ahh)-containing analog, [Ahh^2]-enkephalin (**3f**), is a potent agonist of δ-opioid receptors;[13] it binds to the receptor 17 times more potently than Leu-Enk.

Most natural products, except altemicidin and sphingofungins, involve the amino group at their cyclic core, and their valuable biological activities mean that they have attracted growing attention from pharmaceutical and synthetic chemists. Lactacystin (**4**),[16] which is a highly functionalized γ-lactam thioester, was first isolated from *Streptomyces* sp. OM6519, and inhibits 20S proteosome, which plays a vital role for removing damaged, misfolded, and mistranslated proteins.[17] Recently, salinosporamide A,[18] which is structurally related to lactacystin, was isolated

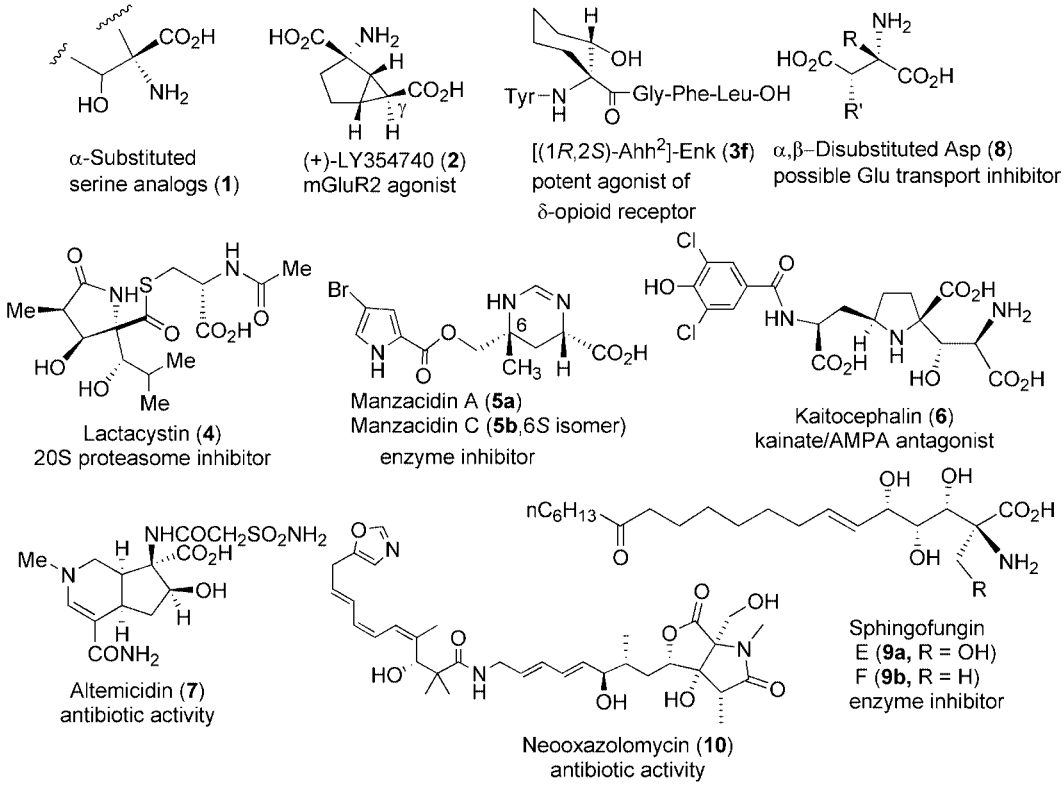


Figure 1. α,α-Disubstituted α-amino acid-containing biologically active natural and unnatural compounds.

from a marine microorganism and subsequently synthesized by Corey et al.[19]

Manzacidin A (**5a**) and C (**5b**) were first isolated from the Okinawan sponge *Hymeniacidon* sp., and exhibit activities as α-adenoceptor blockers, antagonists of serotogenic receptors, and actomyosin ATPase activators similar to those of other bromopyrrole alkaloids.[20] Their structure is unique compared to the class of bromopyrrole alkaloids because they contain an ester-linked bromopyrrole and a tetrahydropyrimidine moiety.

Kaitocephalin (**6**) was first isolated from the filamentous fungus *Eupenicillium shearii* PF1191, and exhibits potent antagonist activities against AMPA [(*S*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid]/KA (kainic acid) receptors, which are a major subtype of ionotropic glutamate receptors.[21] These receptors mediate the majority of excitatory signal transmissions at synapses in the mammalian central nervous system and have been implicated in the construction of memory and learning as well as in profound neuron damage by ischemic injury to cause acute neuronal diseases.[22] Since antagonists of AMPA/KA receptors exhibit potent activities for protection of neuronal death, even when administered after an ischemic attack, kaitocephalin has considerable potential as a promising lead compound for the development of therapeutic agents for ischemia-reperfusion injury such as stroke and epilepsy.[21,22]

Naturally occurring sulfonamide altemicidin (**7**), which was first isolated from the actinomycete strain *Streptomyces sioyaensis* SA-1758, is a unique monoterpene alkaloid with a 6-azaindene skeleton.[23] It possesses strong inhibitory activity against tumor cell growth as well as potent acarcidal activity.

β-Substituted aspartate analogs are known to inhibit or block glutamate transporters in the mammalian central nervous system, where the extracellular glutamate concentration should be maintained below neurotoxic levels.[24] Glutamate transporters play an important role for this purpose. For elucidation of the intrinsic properties and physiological roles of transporters, β-substituted aspartates represented by threo-β-benzyloxyasparte (TBOA) have been developed as a subtype-selective blocker of glutamate transporters.[25] Thus, α,β-substituted aspartate analogs (**8**) are expected to be candidate amino acids as a selective blocker of glutamate transporters.

Sphingofungin E (**9a**) and F (**9b**),[26] isolated from fungi, are known to have potent antifungal activity and inhibitory activity against serine palmitoyltransferase, which is an essential enzyme for sphingosin biosynthesis.[27] The natural antitumor antibiotic neooxazolomycin (**10**) was first isolated from streptomyces strains.[28] Its highly functionalized structure, containing oxazole, polyene, and fused lactam-lactone groups, bears a structural similarity to lactacystin.

The intriguing methods applied to the construction of a quaternary carbon center with an amino group in the target molecule (Figure 1) include a nucleophilic addition of cyanide to the ketimine intermediate using an asymmetric Strecker synthesis for various α-substituted serine analogs (**1**),[29–31] (+)-LY-354740 (**2**),[12] Leu-Enk analogs (**3**),[13] lactacystin (**4**) (Corey's intermediate),[32] manzacidins (**5**),[33] kaitocephalin (**6**),[34] and altemicidin (**7**) intermediate,[35] a sulfonamide-derived nitrene insertion into the C–H bond for manzacidins (**5**),[36] a Diels–Alder cycloaddition to an α,β-unsaturated amino ester for altemicidin (**7**),[37] a Lewis acid-induced Hatakeyama epoxide opening[38] for lactacystin (**4**)[39] and sphingofungins (**9**),[40] an aldol condensation of an enolate derived from an α-amino ester with an aldehyde for lactacystin (**4**),[41–44] kaitocephalin (**6**),[45] and neooxazolomycin (**10**),[46] a mercuriocyclization of an allylic trichloroacetimidate for lactacystin (**4**),[47] an aldol condensation of bislactim[48] and a Pd-catalyzed alkylation of oxazoline ester[49] for sphingofungin F (**9b**), an Overman rearrangement[50] for lactacystin (**4**)[51] and sphingofungin E

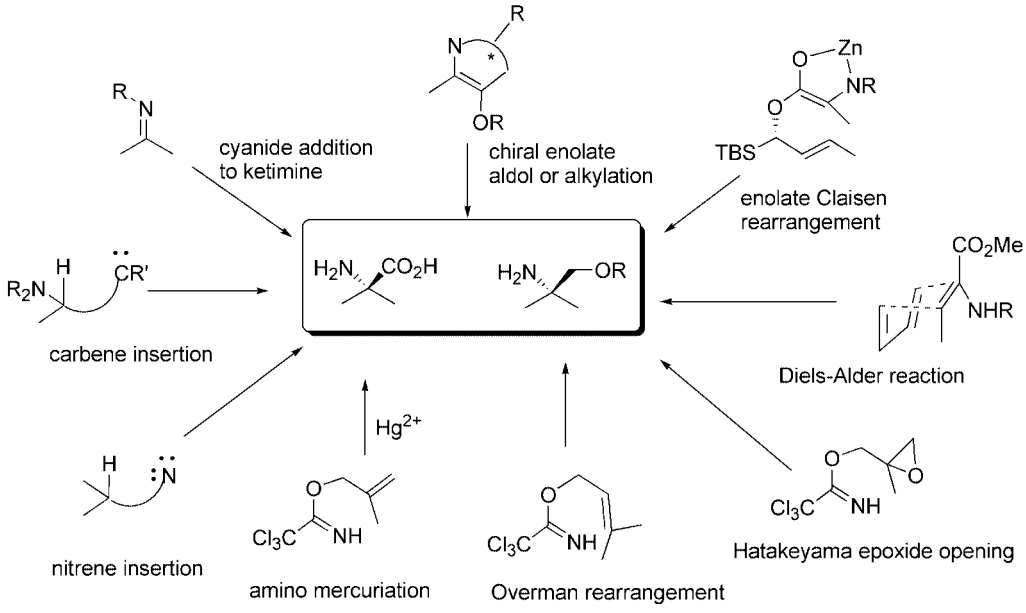


Figure 2. Enantio- and diastereoselective methods for the construction of a quaternary stereogenic center attached to an amino group.

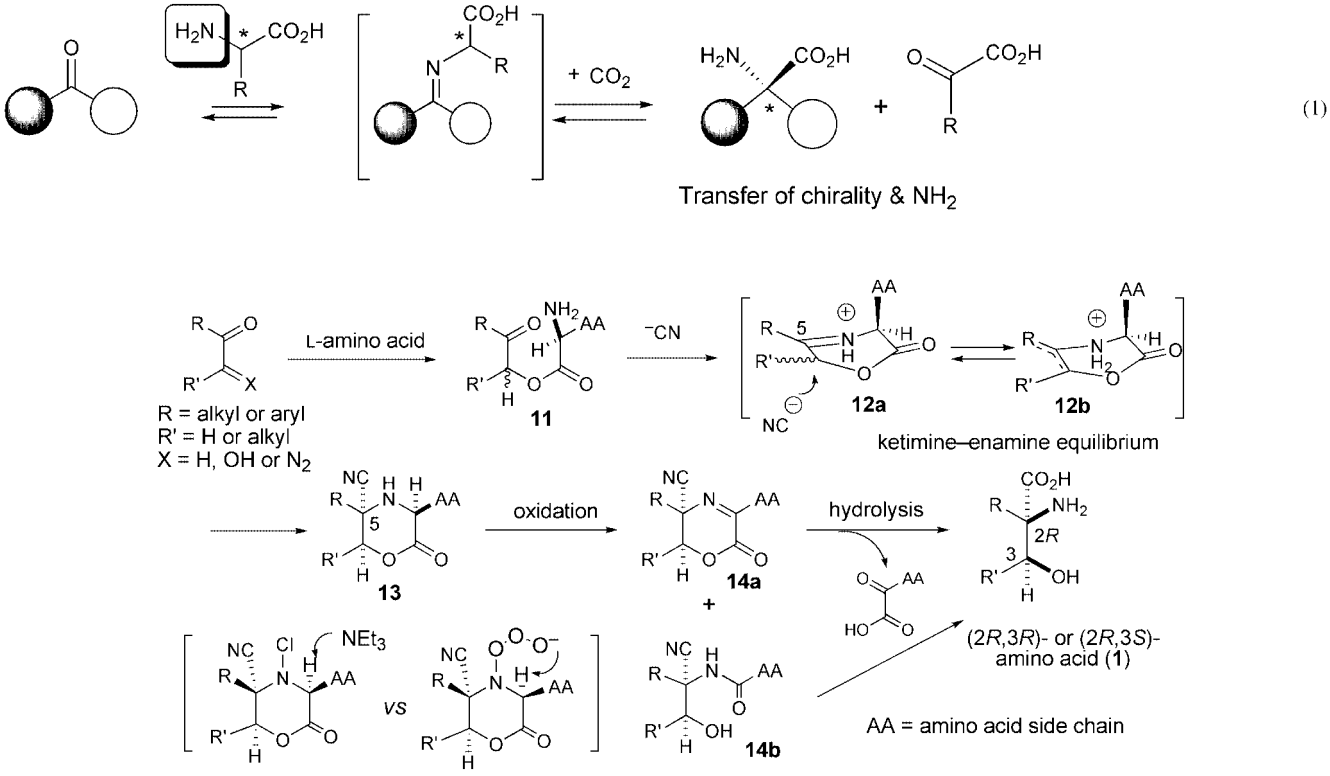
(**9a**),[52] and other methods, as shown in Figure 2. The discussion below is limited mainly to key methods for the construction of a quaternary carbon center attached to an amino group, as employed for the synthesis of the target molecules in Figure 1 based on our work and that of others.

Cyanide Addition to Ketimines: Asymmetric Strecker Synthesis

The biosynthetic pathway of an α,α-disubstituted α-amino acid may involve an asymmetric transfer of an amino group from an α-amino acid to a ketone.[53] 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. A proposed biosynthetic route to α,α-disubstituted α-amino acids is shown in Equation (1).

Influenced by the hypothetical biosynthetic route in Equation (1), our synthetic plan for these amino acids was to use an asymmetric version of the Strecker synthesis.[11] This synthesis consists of the following sequence of transformations: (1) formation of a cyclic ketimine intermediate **12a** from α-acyloxy ketone **11** having an L- or D-amino acid as the acyloxy group; (2) stereoselective addition of a cyanide ion to 1,4-oxazine **12a** to give an α-amino nitrile **13**; (3) oxidative conversion into α-imino nitrile **14a**; and (4) 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 (**1**) (Scheme 1).

The Strecker precursor − the α-amino-α-acyloxy ketone − was prepared by condensation of an *N*-Boc-protected amino acid with an α-hydroxy ketone, a 1,2-diol, followed by oxidation, or copper-catalyzed insertion of an α-diazo ketone into an *N*-Boc-protected amino acid.[54] The stereoselective α-amino nitrile formation involves, in most cases, an imine–enamine equilibrium where protonation to an enamine **12b** occurs from the opposite side to the amino acid (AA) group to give the thermodynamically favored ketimine intermediate **12a**. The cyanide ion then attacks the ketimine from the sterically less hindered side to give (5*S*)-α-amino nitrile **13**, presumably because the ketimine **12a** has a boat-like conformation[55] in which the AA group orients in a pseudo-axial position. The relative configuration of the cyano and the AA groups in α-amino nitrile **13** is always *anti*. The stereochemical outcome of this process has been well elucidated by isotope-labeling experiments using [D]-2-propanol and $Na^{13}CN$.[29] The oxidation step from α-amino nitrile **13** to α-imino nitrile **14a** is performed by initial *N*-chlorination with *t*BuOCl and subsequent dehydrochlorination with a base. However, this step is occasionally very slow or does not proceed at all, particularly in the case where a sterically congested α-amino nitrile was employed. Since an external base such as Et_3N cannot abstract the hydrogen at C2, mainly for steric reasons, bidentate oxidants, which after oxidation of the amino group act as an internal base, were screened. Ozone, which is a strong and less bulky oxidant, was found to an excellent oxidant to give the desired α-imino nitrile **14a** together with α-amide nitrile **14b**.[56] Hydrolysis of each product gave an amino



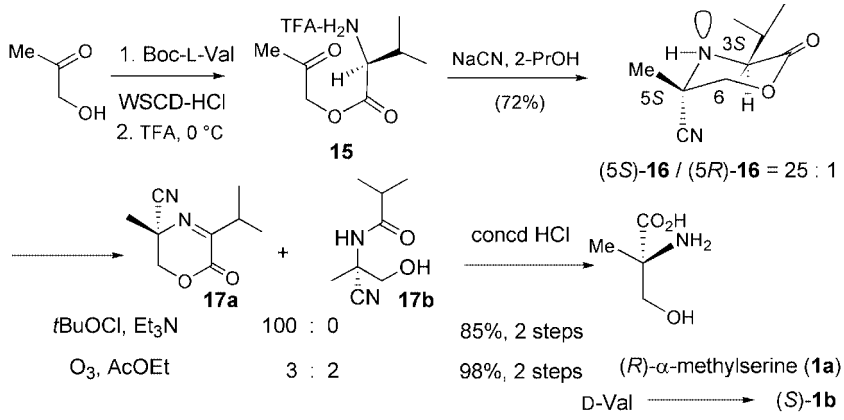
Scheme 1. Asymmetric version of the Strecker synthesis.

acid in excellent yield. Thus, the stereochemical outcome of the asymmetric Strecker synthesis is clearly understood and the problematic oxidation step much improved by the use of ozone.

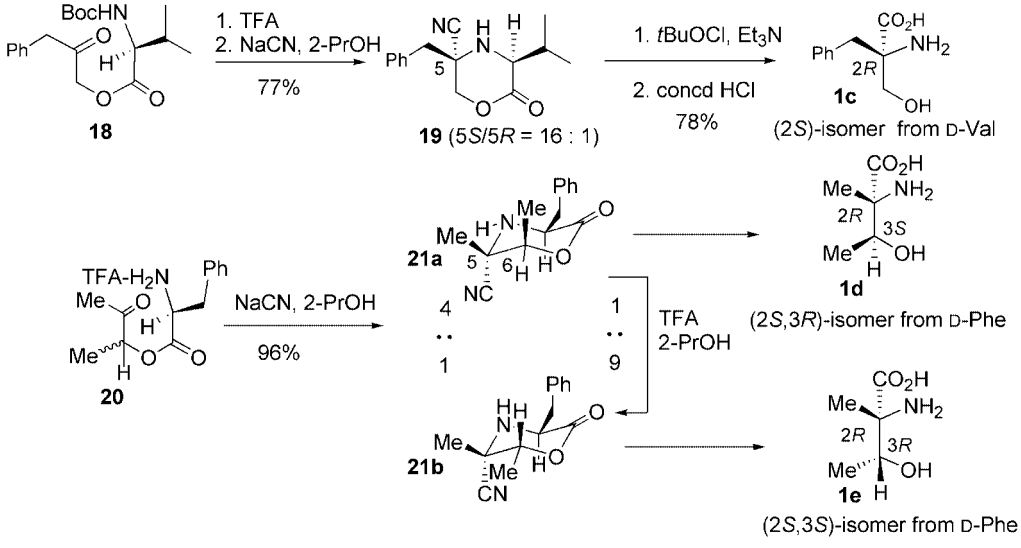
The synthesis of α-methylserine (**1a**) is shown as a representative example of an asymmetric version of the Strecker synthesis in Scheme 2. Treatment of an α-acyloxy ketone **15**, which possesses L-valine as an acyloxy group, with two equivalents of NaCN in 2-propanol gives stereoselective cyanide addition and formation of (5*S*)-α-amino nitrile **16** as the major product (5*S*/5*R* = 25:1). The major isomer (5*S*)-**16** was converted into α-imino nitrile **17a** by treatment with *t*BuOCl and triethylamine, and **17a** was then treated with conc. HCl to give (*R*)-α-methylserine (**1a**; 84% from **16**). The use of ozone gave a mixture of α-imino nitrile **17a** and α-amide nitrile **17b** (3:2), hydrolysis of which gave (*R*)-α-methylserine (**1a**)[57] in 98% yield (2 steps). The use of D-valine afforded (*S*)-α-methylserine (**1b**). Note that the configuration of the new amino acid is opposite to that of valine. Thus, both enantiomers of α-methylserine were prepared in five steps with overall yields of about 55%.[29,56]

α-Benzylserine (**1c**) has attracted significant attention as an enzyme inhibitor.[58] Its synthesis started with phenyl acetol ester **18**. The reaction gave a mixture of α-amino nitriles **19**, in 77% yield, with (5*S*)-**19** as the major product (5*S*/5*R* = 16:1). Conversion into **1c** in an optically active form[30] was performed in the same manner as that of α-methylserine.

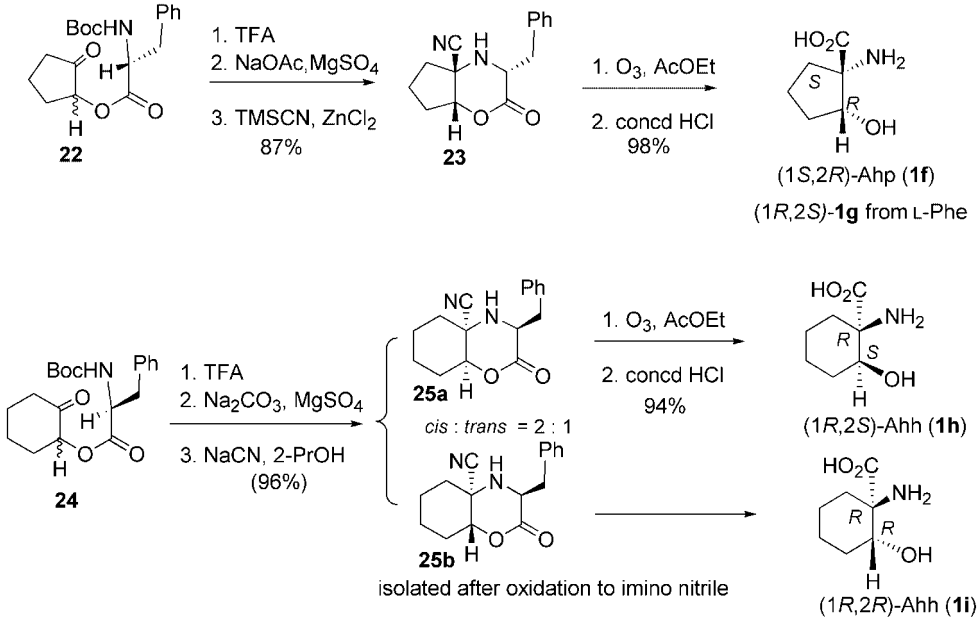
To examine whether the C3 stereogenic center of the ketimine intermediate would affect the stereochemistry of an α-amino nitrile having a substituent at the C6 position, an α-acyloxy ketone **20** derived from (D,L)-acetoin was subjected to the Strecker synthesis. Treatment of **20** with NaCN gave kinetically favored (5*S*,6*S*)-**21a** [(5*S*,6*S*)-**21a**/(5*S*,6*R*)-**21b** = 4:1]. In the presence of an additional equivalent of TFA, the mixture was equilibrated to thermodynamically favored (5*S*,6*R*)-**21b** (**21a**/**21b** = 1:9). Removal of the phenylalanyl moiety and conversion into (2*R*,3*S*)- and (2*R*,3*R*)-α-methyl-



Scheme 2. Asymmetric Strecker synthesis of both enantiomers of α-methylserine (**1a** and **1b**).



Scheme 3. Asymmetric Strecker synthesis of optically active α-benzylserine (**1c**), α-methylthreonine (**1d**), and α-methyl-*allo*-threonine (**1e**).



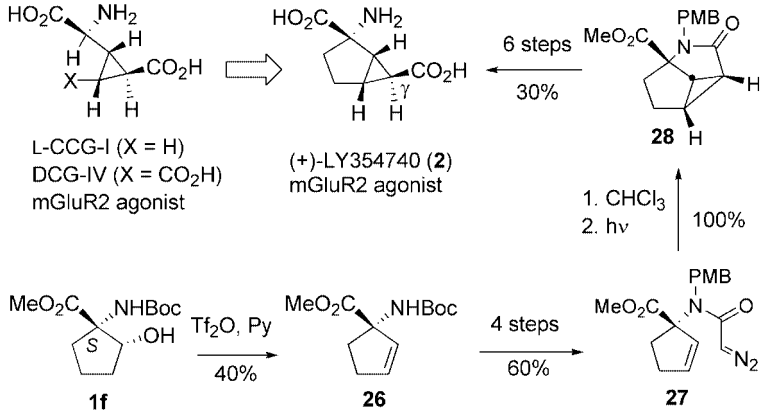
Scheme 4. Asymmetric Strecker synthesis of optically active 1-amino-2-hydroxycyclopentane- and -cyclohexanecarboxylic acids.

threonine (**1d** and **1e**, respectively) were carried out in a manner similar to the preparation of α-methylserine (Scheme 3).[29]

The synthesis of the cyclic analogs with a five-membered ring started with 2-acyloxy cyclopentanone (**22**) and D-Phe. TMSCN/$ZnCl_2$[59] was found to be a superior reagent combination to that of NaCN for the formation of the α-amino nitrile **23** in view of its yield and stereoselectivity (98% *ds* vs. 80% *ds*). Its conversion into (1*S*,2*R*)-1-amino-2-hydroxycyclopentanecarboxylic acid (Ahp, **1f**)[31] was carried out in the same manner as described above. The use of L-Phe afforded (1*R*,2*S*)-Ahp (**1g**). The Strecker synthesis of a six-membered ring analog gave a mixture of the (5*S*,6*S*)-*cis* and (5*S*,6*R*)-*trans* isomers, (*cis*-**25a**/*trans*-**25b** = 2:1). Oxidation of *cis*-**25a** and *trans*-**25b**,[56] followed by hydrolysis, gave both diastereomers of 1-amino-2-hydroxycyclohexanecarboxylic acid (Ahh), namely (1*R*,2*S*)-Ahh (**1h**) and (1*R*,2*R*)-Ahh (**1i**), respectively.[31] Both the five- and six-membered ring amino acids can be viewed as conformational variants of L-serine, as described in the following section (Scheme 4).

Synthesis of (+)-LY354740 (2) and the Potent Enkephalin Analog 3f

Both L-CCG-I[60] and DCG-IV[61] are potent and selective agonists of mGluR2. In particular, DCG-IV exhibits an anesthetic action in rats, inhibits their AOB memory, and confers protection against kainate-induced neuronal death both in vivo and in vitro.[62] These structures fix their glutamate sub-structure to an extended conformation, which has been proposed as a crucial factor for the conformational requirement of mGluRs.[63] These results prompted the design and synthesis of an effective neuroprotecting agent (+)-LY354740 (**2**) by Schoepp et al.[15] Both DCG-IV and **2** have been used as important tools to investigate neurobiological functions of mGluRs. The synthesis



Scheme 5. Diastereoselective transformation of (1*S*,2*R*)-Ahp (**1f**) into (+)-LY354740 (**2**).

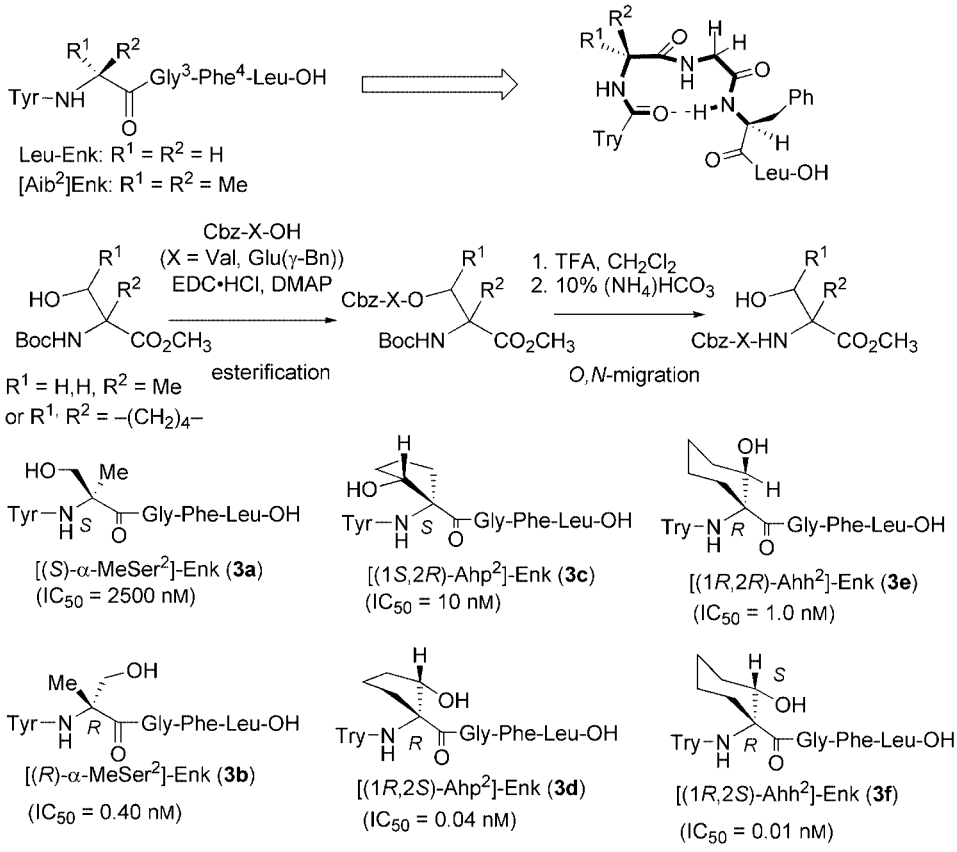
of **2** was performed in racemic form using Bücherer–Burg's second generation of the Strecker synthesis,[64] followed by optical resolution.[15] Our synthesis was started with (1*S*,2*R*)-Ahp (**1f**), which was available in multi-gram quantities as described above. Coupling of an diazoacetamide group to **1f**, followed by intramolecular cyclopropanation, produced cycloadduct **28**. Opening of the γ-lactam followed by epimerization of the resulting γ-ester group gave rise to (+)-**2** (Scheme 5).[12]

Coupling of a 2-amino-2-methylpropanoic acid (Aib) moiety to the Gly^2 residue of leucine-enkephalin (Leu-Enk) fixes its Tyr^1-Aib^2-Gly^3-Phe^4 moiety into a β-turn conformation in solution.[65] However, [Aib^2]Enk exhibits much weaker activity to opioid receptors than that of the native compound, 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-Ser^2]Enk, are known to be potent agonists of opioid receptors.[66] Thus, (*R*)-α-MeSer (**1a**), (*S*)-α-MeSer (**1b**), (1*R*,2*S*)-Ahp (**1f**), (1*S*,2*R*)-Ahp (**1g**), (1*R*,2*S*)-Ahh (**1h**), and (1*R*,2*R*)-Ahh (**1i**) have been incorporated into the Gly^2 residue of enkephalin. It is known that peptide coupling of both the N- and C-termini of sterically congested α,α-disubstituted α-amino acids is relatively slow compared to that of an α-amino acid due to steric reasons. Therefore, incorporation of these amino acids into Leu-Enk was performed in part by an initial esterification and subsequent O,N-migration.[67] Among these analogs, [(1*R*,2*S*)-Ahh^2]-Enk (**3f**) shows the most potent activity (Scheme 6). All the α-substituted analogs possess a β-turn conformation in solution, suggesting that high affinity binding to the receptor requires both the β-turn conformation and the presence of a β-hydroxy group with an appropriate configuration at the Gly^2 residue.[13]

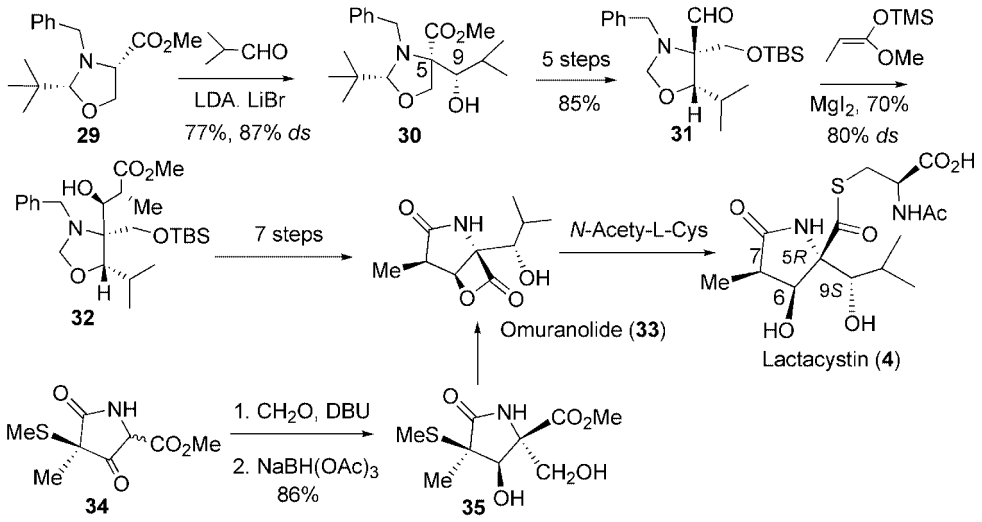
Diastereoselective Construction of an α,α-Disubstituted α-Amino Acid Moiety Focused on the Total Synthesis of Natural Products

Synthesis of Lactacystin (4): Construction of a Key Quaternary Carbon Center

Lactacystin (**4**) has received much attention from synthetic chemists due to its important biological role as well as its unique structure − it has a β,β′-dihydroxy-α,α-disubstituted α-amino acid substructure.[16,17] Therefore, a number of efforts have been made to construct the key quaternary carbon center attached to an amino group. The first total synthesis of lactacystin was reported by Corey et al.,[41] who used 1,3-oxazolidine (**31**) as the key intermediate both for **4**, its biosynthetic precursor omuranolide (**33**), and their derivatives (Scheme 7). The consecutive C5 and C9 stereogenic centers were constructed by an aldol condensa-



Scheme 6. Incorporation of α-substituted serine analogs to Leu-Enk and their binding activity towards δ-opioid receptors using Chinese hamster ovary expressing cloned rat μ-, δ-, and κ-opioid receptors.

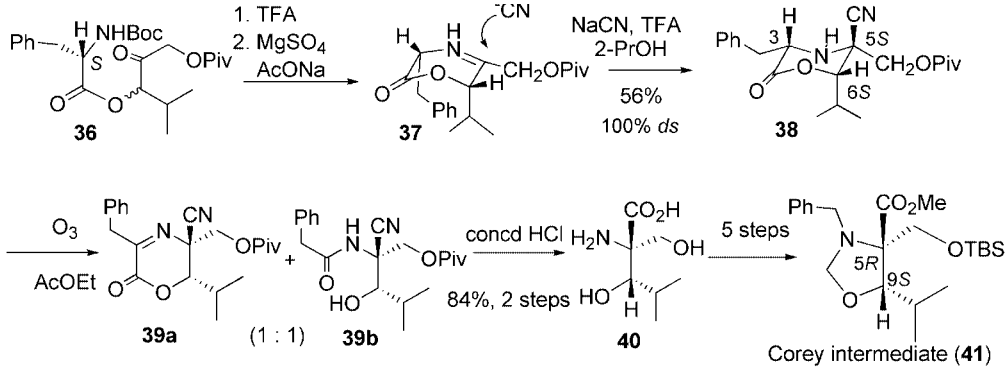


Scheme 7. Corey's total synthesis of lactascystin (**4**).

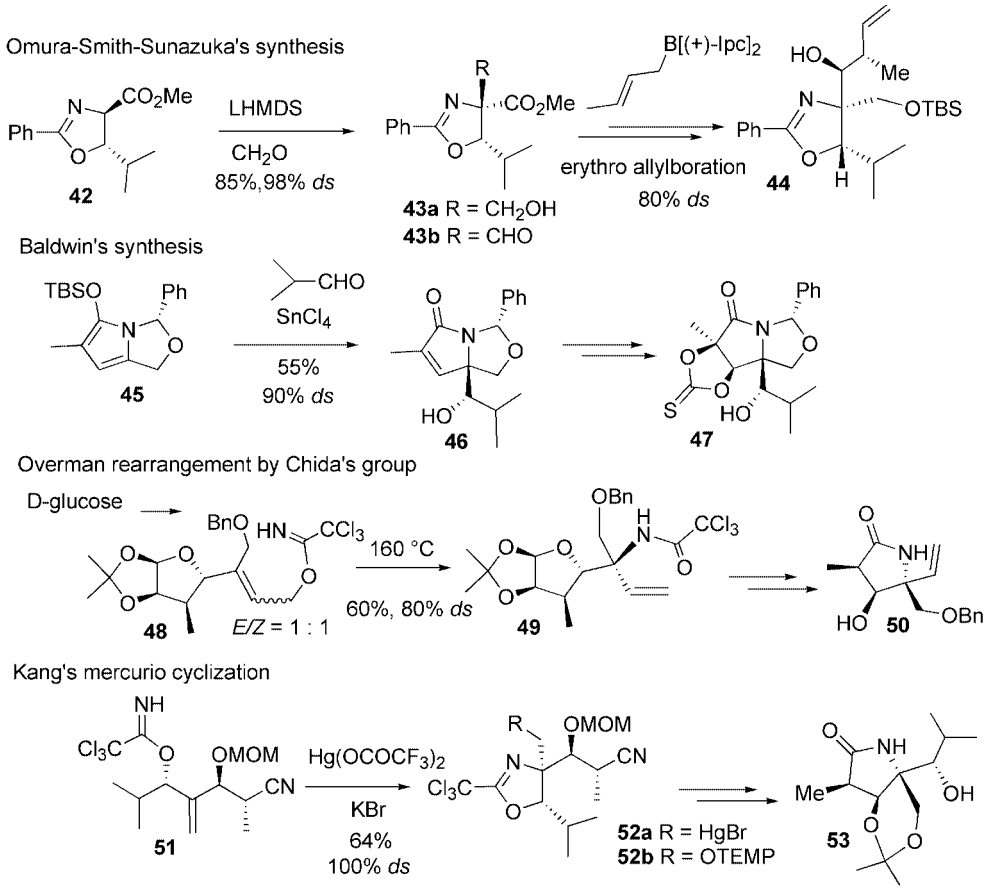
tion of an optically active ester enolate prepared from **29** with isobutylaldehyde, according to the Seebach self-regeneration protocol.[6,8] The presence of added LiBr was required for the diastereoselective formation of **30** (87% *ds*). The transformation into the *anti*-aldol adduct **32** was another key step for the total synthesis. The Mukaiyama aldol condensation[68] of **31** with (*E*)-silylenol ether in the presence of catalytic MgI_2 proceeded stereoselectively to afford the *anti*-aldol product **32** in 77% yield (*anti*/*syn* = 10:1). This was converted into **33** in seven steps. Finally, treatment of **33** with acetyl (*S*)-cysteine produced **4**. Corey and coworkers have also reported an alternative synthesis of lactacystin from chiral keto lactam **34**.[69] Aldol condensation with formaldehyde, followed by reduction of the keto group, afforded the hydroxy lactam **35** with high diastereoselectivity (>99% *ds*).

We considered that an intermediate amino acid of Corey's synthesis,[41] which has two consecutive chiral centers at C5 and C9, can be constructed simultaneously by use of the asymmetric Strecker approach. The key transformation was a cyanide addition to the ketimine intermediate **37**. The reaction occurs from the sterically less-hindered β-face to give kinetically favored (5*S*,6*S*)-α-amino nitrile **38**, exclusively. Ozone was found to be a much superior oxidant than *t*BuOCl/Et_3N for the oxidative removal of the L-Phe moiety to give a mixture of α-imino and α-amide nitriles **39a** and **39b** (84% with ozone vs. 20% with *t*BuOCl/Et_3N).[56] The resulting amino acid **40** was then converted into Corey's intermediate **41** (Scheme 8).[32]

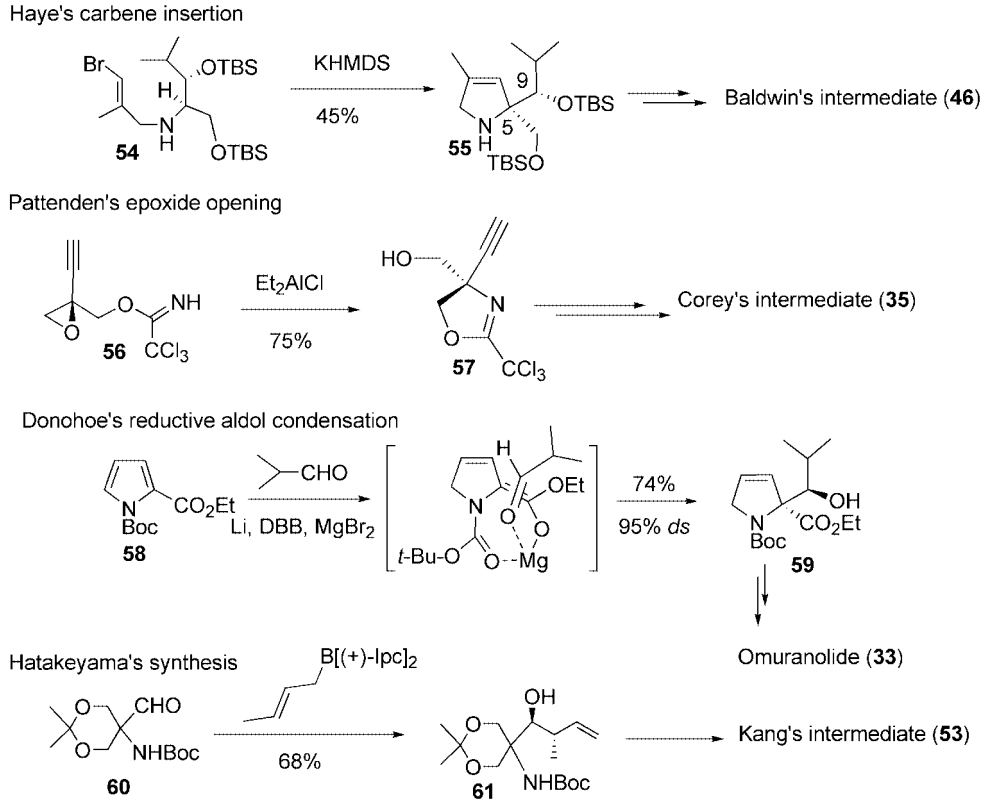
To date, the total synthesis of lactacystin has been accomplished by Omura, Smith III, and Sunazuka et al.,[42] Baldwin et al.,[43] Chida et al.,[51] and Kang et al.[47] Since two reviews on their synthesis, excluding Kang's work, have been reported,[70] this review deals with methods to construct the key quaternary stereogenic center at C5, as shown in Scheme 9. Omura's group[42] has employed the aldol condensation of an ester enolate derived from *trans*-oxazoline **42** with formaldehyde. This reaction gave α-hydroxymethylated adduct **43a** in 98% *ds*. Another key transformation from **43b** to *anti*-aldol adduct **44** was performed by aldol condensation of a chiral crotylborate[71] (*anti*-**44**/*syn*-**44** = 80:20). Baldwin and co-workers[43] have employed the Mukaiyama aldol reaction[68] of chiral pyrrole derivative **45**, which already has the γ-lactam ring of lactacystin. The reaction with isobutylaldehyde gave (5*S*,9*S*)-aldol adduct **46** (90% *ds*). A different mode for the construction of the C5 stereogenic center was employed by Chida and coworkers.[51] Upon heating of trichloroacetimidate **48** derived



Scheme 8. Asymmetric Strecker synthesis of Corey's intermediate of lactacystin.



Scheme 9. Total syntheses of lactacystin (**4**) by other groups.



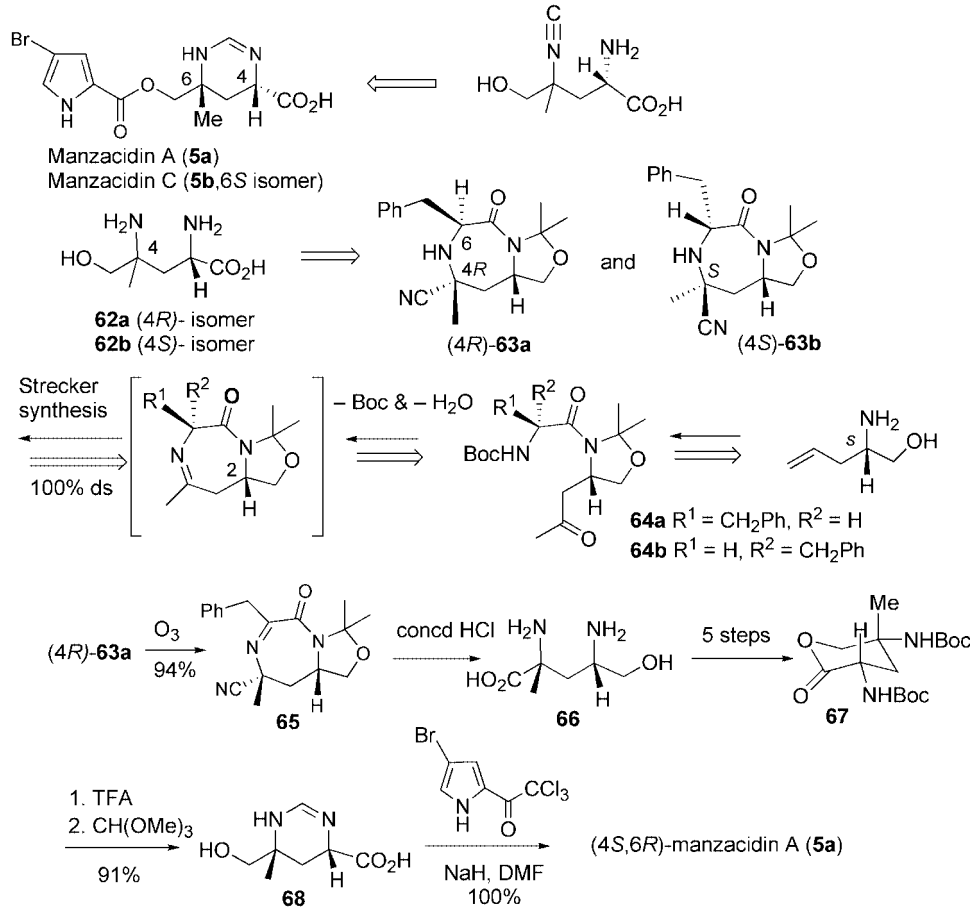
Scheme 10. Other methods for the construction of the α,α-disubstituted α-amino acid substructure of lactacystin (**4**).

from D-glucose, the reaction underwent an Overman rearrangement[50] to give allylamine **49** as a 4:1 mixture of diastereomers. Kang's group[47] has employed the trichloroacetimidate **51** for a mercuriocyclization reaction to construct the key C5 stereogenic center of lactacystin. Treatment of **51** with mercuric trifluoroacetate, followed by oxidative removal of the mercurio group, gave oxazoline **52b** as the only isolable diastereomer.

Other approaches toward the construction of the C5 quaternary stereogenic center are summarized in Scheme 10. Haye et al.[72] have employed vinyl bromide **54** as a precursor to generate a vinyl carbene species. This inserts into the C–H σ bond to give (5*S*,9*S*)-**55**, which was then converted into Baldwin's intermediate **46**.[43] Lewis acid-catalyzed Hatakeyama epoxide opening[38] from an internal trichloroacetimidate has been reported by Pattenden et al.[73] The reaction with **56** gave oxazoline **57**, which was then converted into Corey's intermediate **35**.[69] The Donohoe group[44] has utilized an aldol condensation of the (*Z*)-enolate derived from pyrrole carboxylate **58** with isobutylaldehyde in the presence of $MgBr_2$. The stereochemical outcome − formation of the *anti*-aldol adduct **59** (>95% *ds*) − was explained by assuming a chelation intermediate with Mg, as depicted in Scheme 10. This was successfully converted into Omuranolide (**33**) in 11 steps. Hatakeyama and co-workers[74] have employed an α-aminoaldehyde **60** derived from amino triol as the starting material. Enantioselective crotylboration[75] gave an *anti*-aldol adduct **61**, which was converted in three steps into Kang's intermediate **53**.[47]

Total Synthesis of Manzacidins (5)

The stereochemical relationship between manzacidins A (**5a**) and C (**5b**) has been proposed as either the C4 or the C6 diastereomer.[20] We presumed that their C4 configuration would be the same, namely *S*, by considering a plausible biosynthetic pathway that involves an (*R*)- or (*S*)-isocyanide intermediate, as is often seen in the biosynthesis of marine natural products.[76] Thus, diastereoselective construction of (2*S*,4*S*)- and (2*S*,4*R*)-diamines **62a** and **62b** would lead to **5a** and **5b**, respectively. This route relies on a stereoselective construction of the α-amino nitrile by the Strecker synthesis of the amino ketone. Strecker synthesis of Boc-L-phenylalanine amide (**64a**), after chemoselective removal of the Boc group with TMSOTf/2,6-lutidine,[77] with TMSCN causes stereoselective cyanide addition to give (4*R*)-**63a** as a single diastereomer. The D-Phe isomer **64b** affords (4*S*)-**63b** (87%), exclusively. Thus, the desired α-amino nitriles, which correspond to the stereochemistry of manzacidins A and C, were each obtained with excellent

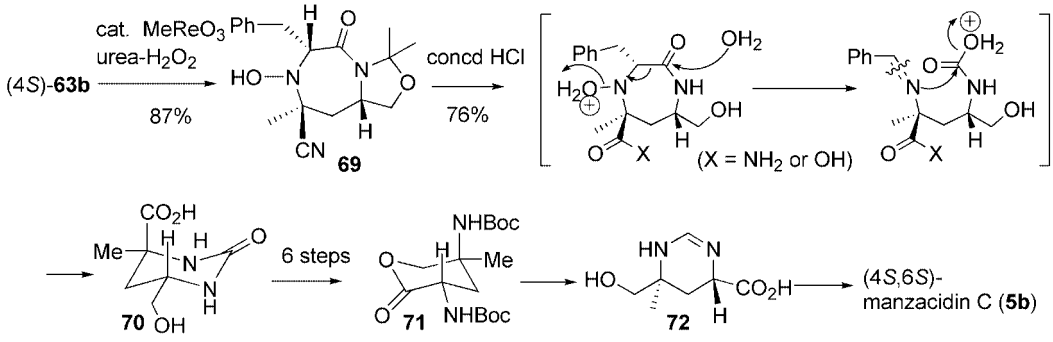


Scheme 11. Total synthesis of (–)-manzacidin A (**5a**).

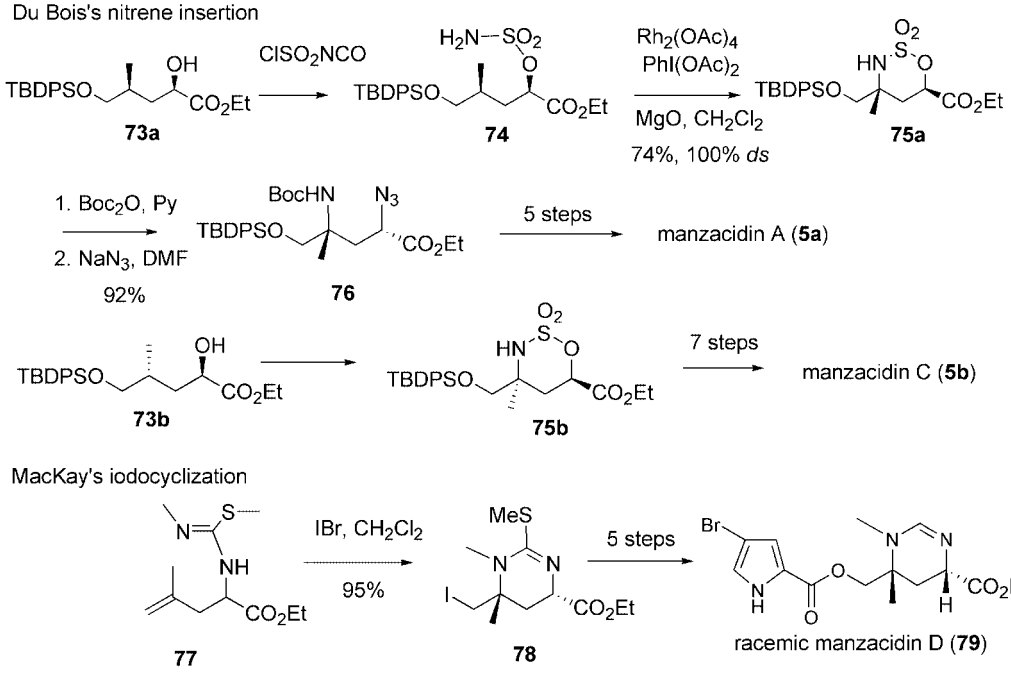
stereocontrol. Upon conversion of (4*R*)-**63a** into the corresponding α-imino nitrile, the oxidation with ozone was quite effective to give the α-imino ketone **65** in 94% yield. In this case, none of the α-amide nitrile was produced.[56] Treatment with conc. HCl afforded diaminocarboxylic acid **66**. This was converted into the δ-lactone **67** in five steps, to which a tetrahydropyrimidine ring was introduced to give **68**. The synthesis of **5a** was accomplished by coupling with the bromopyrrole moiety using 4-bromo-2-trichloroacetylpyrrole. Thus, the absolute structure of natural (–)-manzacidin A could unambiguously be assigned to (4*S*,6*R*)-**5a** (Scheme 11).[33]

Oxidative removal of the D-Phe unit from the (4*S*)-**63b** was performed by trioxorhenium oxidation,[78] followed by hydrolysis of resulting **69** with conc. HCl to give the cyclic urea **70** in 76% yield, since ozone was exceptionally ineffective for this oxidation. This cyclic urea was then hydrolyzed to give lactone **71**, which, upon similar treatment to that of **5a**, gave manzacidin C (**5b**; Scheme 12). Thus, both natural (–)-manzacidin A and (+)-manzacidin C were found to possess the same 4*S* configuration.[33]

Two other intriguing approaches to the total synthesis of manzacidins have been reported (Scheme 13). Du Bois et al.[36] have employed a Rh-catalyzed C–H insertion of nitrene[79] into optically active 2-hydroxy-4-methylpentanoate derivatives **73a** and **73b**. The reaction of **73a** with $ClSO_2NCO$, followed by $Rh(OAc)_2$-catalyzed C–H insertion, proceeded in a highly stereoselective manner to give oxathiazinane **75a**. S_N2 azidation opened the ring to give an azide ester **76** possessing the requisite C4 and C6 stereogenic centers corresponding to manzacidin A (**5a**). The use of (4*R*)-pentanoate (**73b**) led to the synthesis of manzacidin C (**5b**) in the same manner as that of **5a**. A stereoselective iodocyclization protocol has been reported by MacKay et al.[80] Isothiourea was attached to 2-amino-4-methyl-4-pentenoate as a convertible functional group for the 1,3-



Scheme 12. Total synthesis of (+)-manzacidin C (**5b**).



Scheme 13. Total synthesis of manzacidins A (**5a**) and C (**5b**) by Du Bois et al. and manzacidin D (**79**) by Mackay et al.

terahydropyrimidin-2-one moiety of manzacidin D (**79**).[81] The reaction of **77** with IBr gave cyclized product **78** in 95% *ds*. This was converted into racemic **79** in five steps.

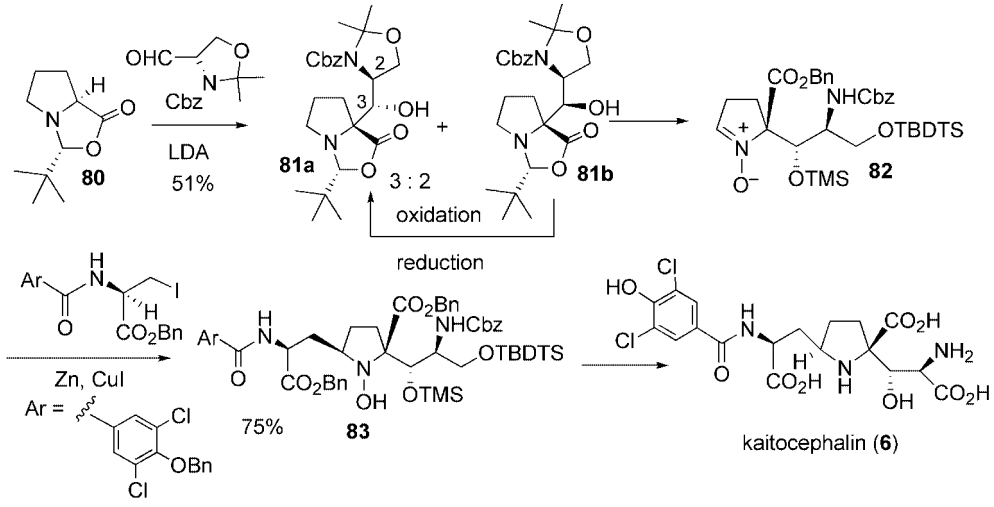
Total Synthesis of Kaitocephalin (6)

The structure of kaitocephalin (**6**) is characterized by its α-substituted proline core assembled from *N*-acylalanine and threonine moieties connected by a carbon–carbon bond. The structure was originally assigned to have a (2*S*,3*S*,4*R*,7*R*,9*S*)-configuration.[21] Recently, the Ma[82] and Kitahara[45] groups have reported the total synthesis of **6**, independently. Kitahara's work has proven the structure revision at C2 to have an (*R*)-configuration,[45] while Ma's work concerned the synthesis of the (2*S*)-isomer of kaitocephalin.[82]

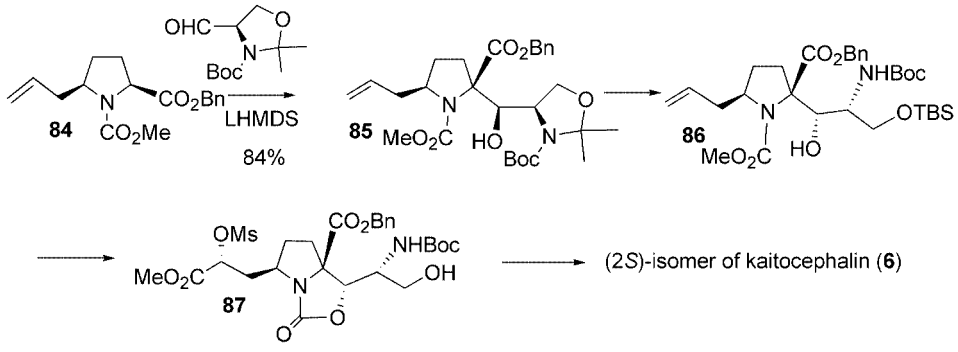
Kitahara and co-workers employed Seebach's aldol condensation of chiral oxazolone **80** with the (*S*)-configured Garner aldehyde[83] for the construction of the (2*R*,3*S*)-2-amino-3-hydroxy moiety. The stereoselectivity upon formation of (3*S*)-3-hydroxypyrrolidine (**81a**) was only 60%, but the undesired (3*R*)-**81b** could be converted into (3*S*)-**81a** by oxidation of the 3-hydroxy group followed by reduction of the resulting ketone. After removal of the acetal group, oxidation with an oxorhenium reagent gave nitrone intermediate **82**, to which an aryl alanyl group was introduced using a copper(I)-activated organozinc reagent to give **83**. Thus, the whole framework of kiatocephalin was efficiently constructed. A sequence of reduction, protection, desilylation, oxidation, and deprotection gave (–)-kaitocephalin (**6**; Scheme 14).[45]

Ma's synthesis[82] is characterized by the use of an allyl group pre-installed on the pyrrolidine compound **84** at its C5, which is an alanine precursor as well as a stereochemical directing group for the aldol condensation at C2. Reaction between the (*R*)-configured Garner aldehyde and LHMDS gave the (3*R*,4*S*)-aldol adduct **85** in 84% yield, while LDA gave an equal mixture of four diastereomers. Since the aldol adduct **85** possesses the undesired (3*R*)-configuration, this compound, after exchange of the protecting groups, was converted into (3*S*)-**86** by oxidation of the hydroxy group to a ketone followed by reduction. Introduction of an α-hydroxy ester group to the allyl group gave **87**, which was converted into the (2*S*)-isomer of **6** (Scheme 15).

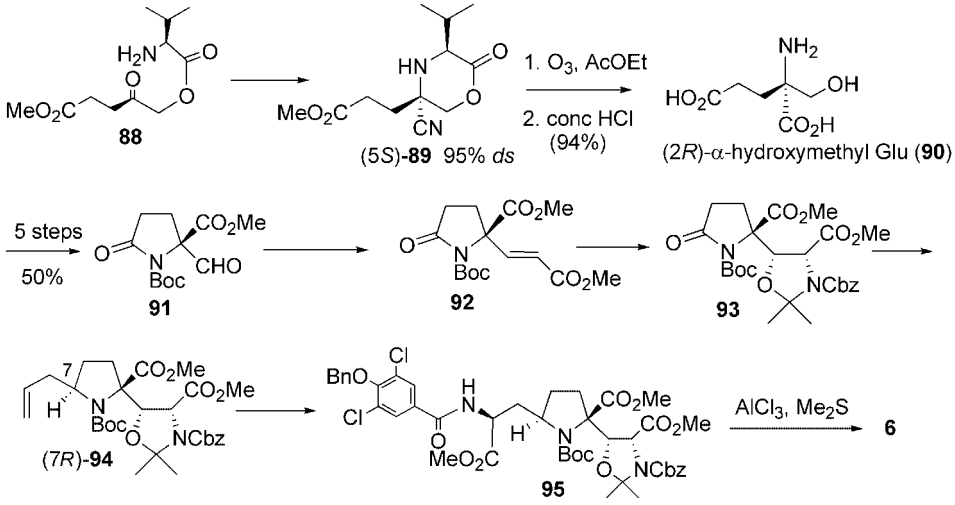
We envisioned that (*R*)-α-formyl pyroglutamate (**91**) could be a key precursor to kaitocephalin, anticipating that its formyl and lactam carbonyl groups would allow introduction of an α,β-unsaturated ester for the C1–C3 threonine unit and an allyl group for the C8–C10 *N*-acylalanine moiety, respectively. The synthesis of α-formyl pyroglutamate (**91**) was started with the Strecker synthesis of α-



Scheme 14. Kitahara's total synthesis of kaitocephalin (**6**).



Scheme 15. Ma's synthesis of the (2*S*)-isomer of kaitocephalin (**6**).



Scheme 16. Total synthesis of kaitocephalin (**6**), asymmetric Strecker approach.

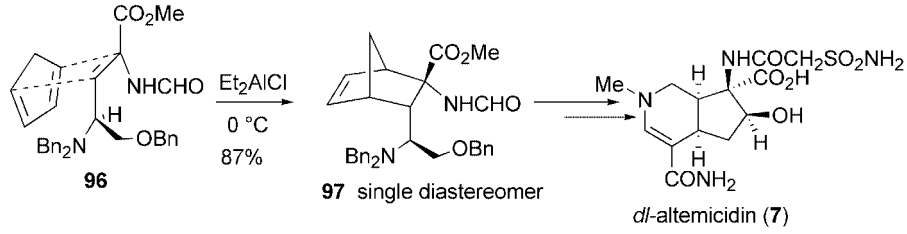
amino acyloxy ketone **88**. This reaction gave (5*S*)-**89** as the major isomer (95% *ds*). Oxidation with ozone gave a mixture of α-imino and α-amide nitrile (1:1), which, upon hydrolysis, gave optically pure (*R*)-α-hydroxymethyl glutamate (**90**).[84,85] Dehydration with Dowex 50Wx4 resin (H^+ form) as an acid catalyst, followed by functional group manipulation, afforded **91**. An acyliminium ion precursor **93** possessing the requisite (2*R*,3*S*)-stereogenic centers was synthesized from **91** using a stereochemically prospective approach via (*E*)-α,β-unsaturated ester **92**, which involves stereoselective dihydroxylation and S_N2 azidation of thionocarbonate. Since Lewis acid-promoted allylation of an acyliminium ion prepared from **93** gave the undesired (7*S*)-isomer of **94**, exclusively, an allylcopper reagent was used for the allylation to give the desired (7*R*)-**94** [(7*S*)-**94**/(7*R*)-**94** = 1:2]. The major isomer was converted into protected kaitocephalin (**95**) by conventional methods. The combined use of a hard Lewis acid ($AlCl_3$) and a soft nucleophile (dimethyl sulfide)[86] effected complete removal of all protecting groups simultaneously to give **6** (Scheme 16).[34]

Other Methods for the Synthesis of Natural and Unnatural Amino Acids

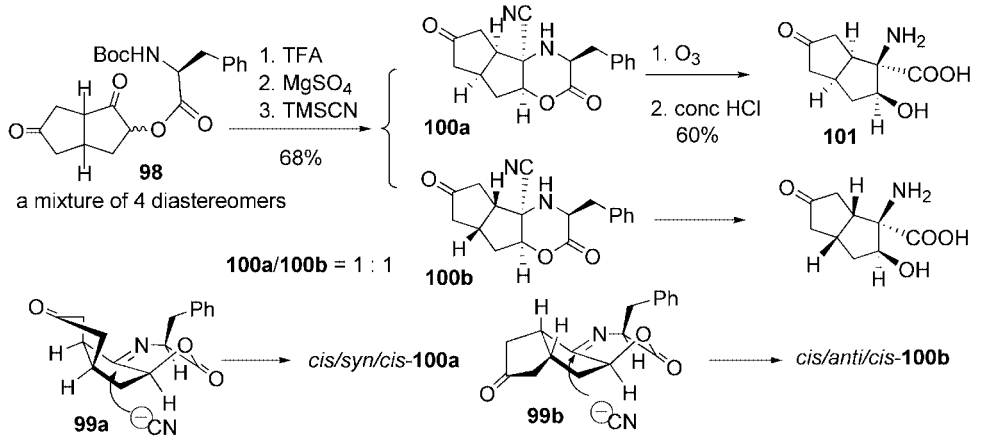
For the total synthesis of altemicidin (**7**; Scheme 17), by Kende et al.,[37] a Diels–Alder reaction was utilized for the construction of the 1-amino-2-hydroxycyclopentanecarboxylate unit. The cycloaddition of an enamine-type dienophile **96**, assembled from an α-amino alcohol and cyclopentadiene, proceeded in a completely diastereoselective and *endo* selective manner to give cycloadduct **97** in 80% yield.

Our approach[35] was the Strecker synthesis of 2-acyloxybicyclo[3.3.0]octanedione (**98**). Strecker synthesis of **98**, as a mixture of four diastereomers, proceeded in a highly stereospecific manner to give a mixture of *cis*/*syn*/*cis* and *cis*/*anti*/*cis* α-amino nitriles **100a** and **100b** (1:1). This reaction involves a rapid imine–enamine equilibrium to give the thermodynamically favored ketimine intermediates **99a** and **99b** in an equal ratio. Cyanide then attacks from their less-hindered side opposite to the benzyl group to give **100a** and **100b**, respectively. The *cis*/*syn*/*cis* adduct **100a**, which has the requisite configuration of altemicidin, was converted into amino acid **101** by sequential ozone oxidation and hydrolysis. Conversion of **101** into optically active altemicidin (**7**) is underway in our laboratory (Scheme 18).

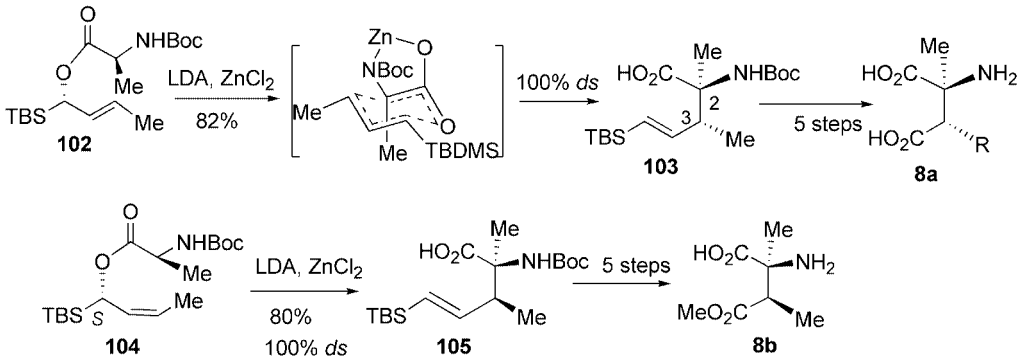
The ester–enolate Claisen rearrangement of chiral α-acyloxytrialkylsilane **102** developed in our laboratory[87] is a novel method for the synthesis of optically active vinylsilane-containing α,α-disubstituted α-amino acids **103** and **105**. This method is characterized by its complete transfer of the chirality from the α-silyloxy group to the newly formed chiral centers at C2 and C3. Oxidative cleavage of its vinylsilane group afforded the α,β-disubstituted aspartates **8**. The reaction of (*E*)-olefin **102** using the Kazmaier protocol (LDA, $ZnCl_2$)[88] proceeds through a chair-like transition state to give (2*S*,3*S*)-α,β-disubstituted vinylsilane **103**, whereas the (*Z*)-isomer **104** affords (2*S*,3*R*)-**105**. Oxi-



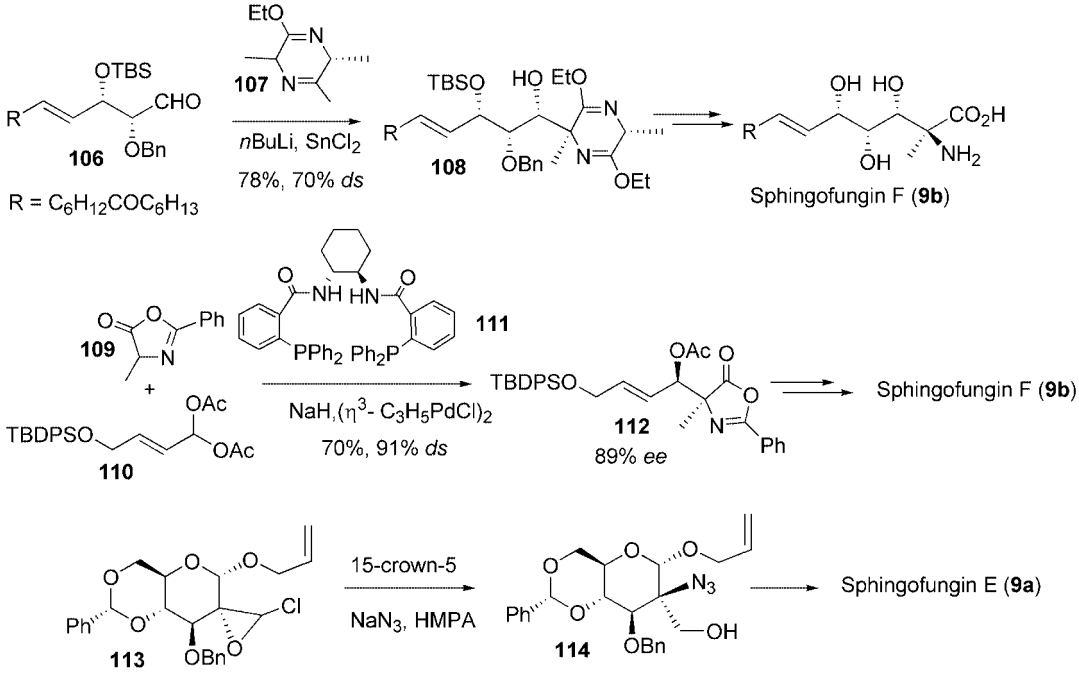
Scheme 17. Total synthesis of racemic altemicidin (**7**).



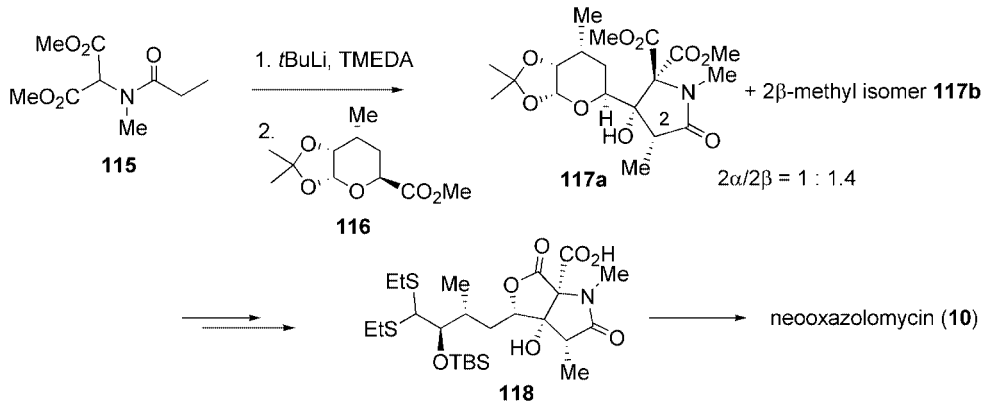
Scheme 18. Asymmetric Strecker approach toward the total synthesis of optically active altemicidin (**7**).



Scheme 19. Enolate–Claisen route to the synthesis of α,β-substituted aspartates **8**.



Scheme 20. Other useful methods for the total synthesis of sphingofungins (**9**).



Scheme 21. Dianion enolate addition to anhydrogalactoside for the synthesis of neooxazolomycin (**10**).

dative cleavage of the vinylsilane group gave amino acids **8a** and **8b**, respectively.[89] While neither **8a** nor **8b** show potent inhibitory activity against the glutamate transport system, this method has significant synthetic potential for the preparation of various α,α,β-trisubstituted α-amino acids (Scheme 19).

Sphingofungins (**9**; Scheme 20) have been target molecules to exploit the enantio- and diastereoselective construction of the amino group attached to a quaternary carbon center. However, methods for the construction are almost the same as those described for lactacystin. In this section, other efficient methods that have not been mentioned above are discussed briefly. Kobayashi et al.[48] have used an aldol condensation of chiral aldehyde **106** with the Sn^{II}-mediated azaenolate of Schöllkopf's bislactim **107**[4] to give the *syn* aldol product **108** in 97% *ds*, and Trost and Lee[49] have utilized a Pd-catalyzed asymmetric allylic alkylation using the (*R*,*R*)-1,2-diaminocyclohexane-derived chiral ligand **111**. The racemic oxazole **109** was alkylated with allylic diacetate **110** in the presence of the Pd^{II} complex of **111** to deliver a 10.5:1 mixture of the coupling product. The major isomer **112** was the desired *threo* compound with 89% *ee*. This was transformed into sphingoshin F (**9b**) in 10 steps. Shiozaki et al.[90] have used a regioselective opening of the chloroepoxy group of **113**. Treatment of **113** with sodium azide effected a regioselective epoxide opening to give **114**, which has an azide attached to the quaternary carbon center. This was converted into sphingofungin E (**9a**).

Neooxazolomycin (**10**), a structurally intriguing congener of oxazolomycin,[91] possesses a novel *cis*-fused azaoxabicyclo[3.3.0]octane containing a γ-lactone and γ-lactam system with chiral substituents at all the ring carbons (Scheme 21). The total synthesis of **10** was accomplished by Kende et al.[46] as only one example since 1990. The key bicyclic core involving a γ-lactam nitrogen was constructed by a condensation of the dianion enolate of **115** with the ester group of anhydrogalactoside **116**. The reaction gave a mixture of the desired lactam **117a** and its 2β-methyl diastereomer **117b** (1:1.4). Sequential glycoside opening and lactone formation allowed the two ester groups to be differentiated to give γ-lactone-γ-lactam **118**. This unit, after several further conversions, was coupled with a triene unit to give the successful total synthesis of **10**.

Concluding Remarks

In conclusion, the selected examples discussed here illustrate recent progress of the enantio- and diastereoselective methods for the construction of α,α-disubstituted α-amino acids that have been employed for the synthesis of natural and unnatural bioactive molecules. An asymmetric version of the Strecker synthesis has proven to be a useful method for the enantio- or diastereoselective transformation of an achiral and racemic substrate to a β-hydroxy-α,α-disubstituted α-amino acid and related natural products. Chiral enolate alkylation or aldol condensation ensure diastereomeric transformations for the construction of the key quaternary stereogenic center that is involved in many natural products. Trichloroacetimidate-assisted allylic rearrangement, epoxide opening, and mercuriocyclization have proven to be widely applicable methods to a diastereoselective N–C bond-forming reaction for the construction of the quaternary stereogenic center. Internal nitrene insertion into a tertiary C–H bond is novel and is expected to be a promising method for the synthesis of a variety of natural products. Other methods have also been demonstrated to be efficient for the successful synthesis of natural products. It should be noted that Pd-catalyzed enantioselective construction of a quaternary carbon center by Trost et al. is an important reaction that represents a future trend for catalytic asymmetric synthesis. However, the structure common to the class of natural products of an amino group attached to a quaternary carbon center can be viewed as one of the most challenging targets in organic synthesis because of their resulting complexity and multi-functionality. To accomplish the total synthesis of these compounds requires not only synthetic efficiency for the construction of the key quaternary stereogenic center but also careful consideration or accumulation of experience in the functional group compatibility of each synthetic sequence. The selected methods of our own approaches and those of other groups described in this microreview should encourage further investigations

focusing on the highly efficient synthesis of biologically active compounds possessing an α,α-disubstituted α-amino acid substructure.

Acknowledgments

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