Synthesis of α-Amino Acids Based on Chiral Tricycloiminolactone Derived from Natural (+)-Camphor

ARTICLE *in* ACCOUNTS OF CHEMICAL RESEARCH · OCTOBER 2010

Impact Factor: 22.32 · DOI: 10.1021/ar100050p · Source: PubMed

4 AUTHORS, INCLUDING:

Yong-Chun Luo
Lanzhou University
32 PUBLICATIONS **404** CITATIONS

SEE PROFILE

Peng-Fei Xu
Lanzhou University
152 PUBLICATIONS **1,463** CITATIONS

SEE PROFILE

ACCOUNTS
of chemical research

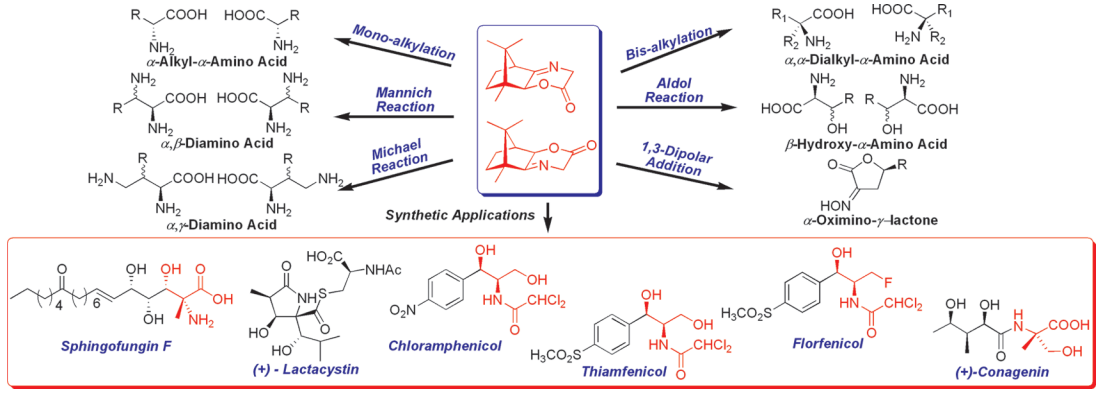
Synthesis of α-Amino Acids Based on Chiral Tricycloiminolactone Derived from Natural (+)-Camphor

YONG-CHUN LUO, HUAN-HUAN ZHANG, YAO WANG, AND PENG-FEI XU*

State Key Laboratory of Applied Organic Chemistry, and College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China

RECEIVED ON MARCH 23, 2010

CONSPECTUS



Amino acids are one of the most important classes of the building blocks of life: they are the structural subunits of proteins, peptides, and many secondary metabolites. In addition to the 20 α-amino acids that constitute the backbone of proteins, hundreds of other natural α-amino acids have been discovered either in free form or as components in natural products. The difference between these molecules is the substituents at the chiral carbon situated between the amino and carboxyl moieties; this carbon (and any atom along a chain attached to it) is thus an important synthetic target.

Because tailor-made α-amino acids are increasingly popular in biochemistry and organic synthesis, further refinement in synthetic methods to generate both natural (L-configuration) and unnatural (D-configuration) amino acids is a very active area of current research. In this Account, we examine the tricycloiminolactones, which are versatile glycine equivalents derived from natural camphor. We have developed the tricycloiminolactones in our laboratory and used them in the synthesis of several kinds of enantiopure α-amino acids.

As nucleophiles, enolated tricycloiminolactones were shown to successfully participate in alkylations, Aldol reactions, Michael additions, and Mannich reactions. These reactions all gave excellent stereoselectivities and high yields. Simple conversion of the products offered α-alkyl-α-amino acids, α,α-dialkyl-α-amino acids, β-hydroxy-α-amino acids, α,γ-diamino acids, and α,β-diamino acids. One particular advantage is that the same electrophile can react with two chiral templates in the same way, thus affording access to both enantiomeric amino acids. In other words, some natural (L-configuration) α-amino acids and their unnatural (D-configuration) counterparts can be prepared very conveniently.

The relation between substrate structures and product stereoconformations derived from our investigations serves as a convenient guide in the synthesis of useful chiral amino acids. In addition, highly stereoselective 1,3-diploar cycloadditions between alkenes and chiral nitrones derived from tricycloiminolactones provide a potential method for the synthesis of γ-hydroxy-α-amino acids.

We also discuss applications of our methods in the synthesis of complex natural products, including conagenin, polyoxamic acid, lactacystin, and sphingofungin F. The preparation of some clinically important drug molecules, such as thiaphenicol, florfenicol, and chloramphenicol, was greatly simplified with our methods. The tricycloiminolactones offer a number of advantages in the synthesis of both natural and unnatural α-amino acids and provide many useful building blocks in the synthetic pursuit of complex molecules.

Published on the Web 07/30/2010 www.pubs.acs.org/acr
10.1021/ar100050p

1. Introduction

Amino acids are widely incorporated in proteins, peptides, and many secondary metabolites. α-Amino acids constitute an important family of natural products[1] and are essential molecules in many areas of research. Usually, they are employed in the construction of peptides and proteins as structural units, ligand design, and total synthesis as chiral pools.[2,3] In the past decade, it was discovered that several α-amino acids could be used to catalyze certain reactions, which opened the door of asymmetric organocatalysis.[3] Apart from 20 proteinogenic α-amino acids, hundreds of α-amino acids have been discovered in the free form or as a component in natural products, and the number of such α-amino acids still grows constantly. Generally speaking, the α-carbon of major natural α-amino acids is of L-configuration. Some of the D-series exist in nonprotein compounds of plants, fungi, and microorganisms but are not common in animals and never in any protein. Furthermore, tailor-made unnatural α-amino acids are widely and increasingly employed in organic synthesis, biochemistry, and some other areas. Thus, the development of α-amino acids synthesis is necessary.

Important applications of the enantiomerically enriched α-amino acids have attracted a great deal of attention among scientists. Particularly, the increasing demand of these optically active compounds has encouraged chemists to develop new synthetic methodologies. In the last 30 years, catalytic asymmetric synthesis of α-amino acids has undergone tremendous growth.[4] Chiral auxiliary-mediated asymmetric synthesis has attracted considerable attention continuously. In many asymmetric synthetic methods of α-amino acids mediated by chiral auxiliaries, chiral templates derived from glycine, alanine, and other α-amino acids were used frequently and widely,[5] because such a process is considered to be one of the most straightforward and reliable methodologies. Our efforts on the development of tricycloiminolactones (**12**, **13**), versatile glycine equivalents, and their applications in the synthesis of α-amino acids (Table 1) and natural products will be reviewed in this Account.

2. Preparation of Tricycloiminolactones from Natural Camphor

As part of our work to develop procedures for the preparation of optically active α-amino acids, we designed the chiral glycine equivalent **12** based on **3** derived from natural camphor.[6] In developing an asymmetric glycine equivalent, we focused our attention on camphor-based tricycloiminolactones for the following reasons: (1) the rigid transition state derived from a cyclic system could enhance the asymmetric steric effect of the auxiliary in controlling the stereochemistry of the reaction; (2) single *Z*-enolate obtained from the lactone provides a single product when the electrophile approaches from one face of the enolate specifically; (3) the C12-methyl group of camphor could block the top face of the enolate, resulting in good stereoselectivity; (4) both the imine and the lactone functionalities can be hydrolyzed easily to form the amino acid and recover the chiral auxiliary; and (5) camphor is inexpensive and readily available. Therefore, iminolactone **12** is expected to form a rigid transition state upon deprotonation, and an electrophile is expected to come in from the less hindered bottom side of the lactone to give the product in high diastereomeric purity.

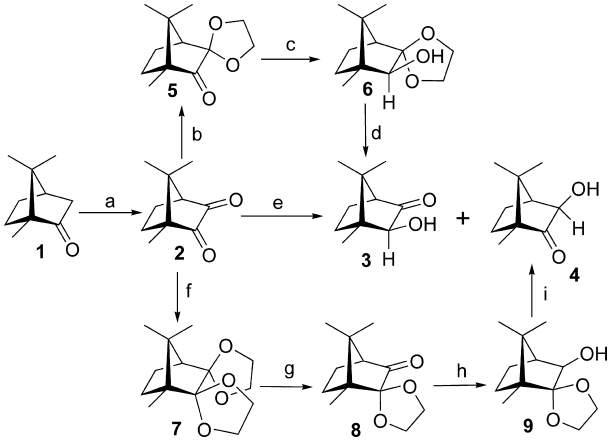
Our route started from natural camphor (Scheme 1). (1*R*)-(+)-Camphor was oxidized with selenium dioxide to give (1*R*)-(+)-camphorquinone **2** quantitatively. Selective protection of the less hindered carbonyl group followed by reduction and hydrolysis afforded 2-*exo*-hydroxyepicamphor **3** as the sole isomer. Hydroxyketone **3** was then transformed into ester **10** with *N*-Cbz-glycine. Removal of the Cbz group and concomitant cyclization to the imine occurred to give rise to the desired chiral template **12** (Scheme 2).

α-Substituted amino acids could be obtained by the reaction of electrophiles and enolated **12** followed by hydrolysis. In principle, the antipode of the α-amino acids can be synthe-

TABLE 1. Reactions of Tricycloiminolactones

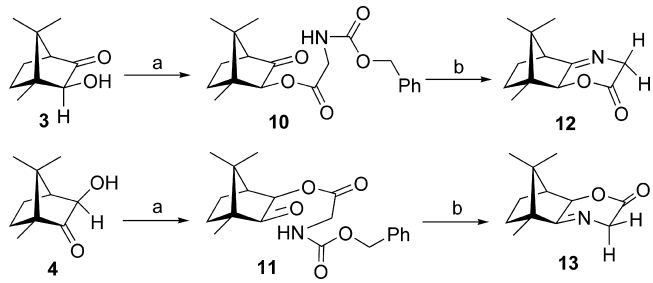
reaction type	reactant	yield and *de* selectivity of product	corresponding amino acids
monoalkylation	**12**/**13** + RX	yield = 59−93%, *de* > 98%	$RCH(NH_2)CO_2H$, yield = 70−82%, *ee* > 94%
bis-alkylation	**12**/**13** + $R^1X + R^2X$	yield = 71−90%, *de* = 71−96%	$R^1R^2C(NH_2)CO_2H$, yield = 82−90%, *ee* > 97%
Aldol	**12**/**13** + RCHO	R = Ar, yield = 73−83%, *de*=85−96%	$RCH(OH)CH(NH_2)CO_2H$, yield = 74−84%, *ee* > 98%
		R = alkyl, yield = 63−86%, *de* = 71−96%	
Michael	**12**/**13** + $RCH{=}CH_2NO_2$	R = Ar, yield = 77−94%, *de* > 92%	$NH_2CHCHRCH(NH_2)\ CO_2H$, yield = 65−82%, *ee* > 99%
		R = alkyl, yield = 71−92%, *de* > 90%	
Mannich	**12**/**13** + RCH=NBoc	yield = 71−94%, *de* = 85−96%	$RCH(NH_2)CH(NH_2)\ CO_2H$, yield = 75−85%, *ee* > 99%

SCHEME 1. Synthesis of 2-*exo*-Hydroxyepicamphor (**3**) and 3-*exo*-Hydroxycamphor (**4**)[a]



[a] Reagents and conditions: (a) SeO_2/Ac_2O, reflux, 17 h, 100%; (b) $HOCH_2CH_2OH$, TsOH, benzene, 78%; (c) $NaBH_4$, Et_2O/CH_3OH (v/v = 1:1); (d) cold H_2SO_4, 94%; (e) $NaBH_4$, MeOH/Et_2O, 0 °C, 30 min, 87% (**3**/**4** =1/1.85); (f) $HOCH_2CH_2OH$, TsOH, *c*-hexane, reflux, 4 days, 88%; (g) cold aq. H_2SO_4 (v/v = 1:1), 91%; (h) $NaBH_4$, Et_2O/CH_3OH (v/v = 1:1); (i) cold aq. H_2SO_4 (v/v = 1:1), 20 minutes, 93%.

SCHEME 2. Synthesis of Tricycloiminolactones **12** and **13**[a]



[a] Reagents and conditions: (a) Z-GlyOH, DMAP, DCC, THF, rt, 16 h, 98%; (b) H_2 (1 atm), Pd/C, rt, 14 h, 76%.

sized if unnatural (1*S*)-(−)-camphor is utilized through the same sequence. Unfortunately, unnatural camphor is much more expensive. So, a more practical method by exchanging the position of the hydroxyl group of the chiral auxiliary from C2 to C3 was probed.[7] In order to accomplish this exchange, a selective hydrolysis of the ketal was employed as a key step (Scheme 1). When compound **7** was converted into **8** successfully, preparation of compound **13** became easy (Scheme 2). Different R_f values were observed for **12** and **13** on TLC, which suggested that a mixture of compounds **12** and **13** could be separated by flash column. Thus, we directly reduced compound **2** with $NaBH_4$, and compounds **3** and **4** were obtained as a mixture. Without separation, the mixture was used in the next two steps to give pure **12** and **13** successfully (Scheme 3).[8]

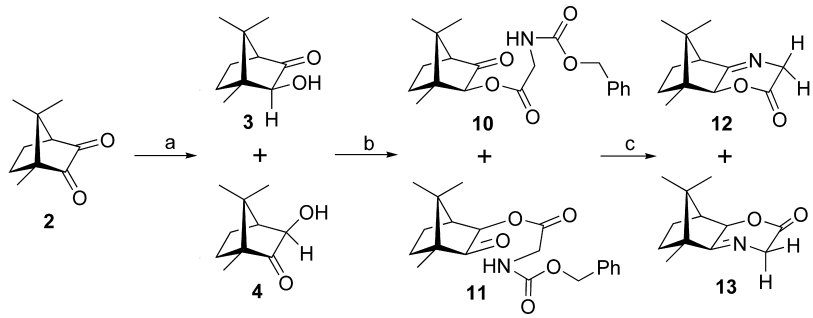
3. Synthesis of α-Alkyl-α-amino Acids and α,α-Dialkyl-α-amino Acids

In many lactone participated reactions, alkylation is the simplest. Thus, alkylation of the deprotonated tricycloiminolactones was investigated first.[6,7,8a] It was expected that the alkylated products could offer optical pure α-alkylated glycines after simple hydrolysis.

Alkylation of tricycloiminolactones was carried out at −78 °C using various combinations of different bases, solvents, additives, and electrophiles. The results of alkylations strongly depended on the reaction conditions employed. It was found that the combination of lithium diisopropylamide (LDA) and hexamethylphosphoramide (HMPA) gave the best yield and excellent stereoselectivity. The scope of electrophiles including methyl iodide, ethyl iodide, butyl iodide, benzyl bromide, and allyl bromide was examined in detail (Scheme 4). NMR coupling patterns and X-ray crystallography confirmed the stereochemistry of alkylated iminolactone and demonstrated that the major product had *endo* configuration. It is noteworthy that methylation of the two iminolactones with KO^{t}Bu as a base resulted in considerably lower facial selectivity compared to LDA. Similarly, benzylation of iminolactones with KO^{t}Bu resulted in a reversal of selectivity but with a poor distereomeric ratio.[6]

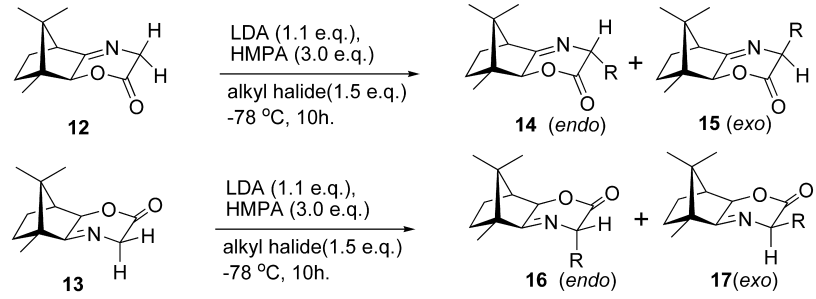
Hydrolysis of the alkylated iminolactones afforded the corresponding α-amino acids in good yields and enantiomeric excesses (Scheme 5). The configurations of the amino acids,

SCHEME 3. Optimized Approach to the Tricycloiminolactones[a]

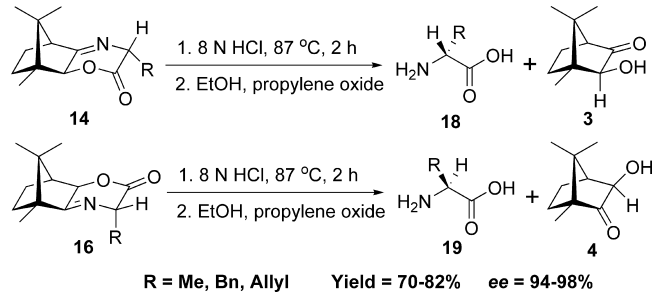


[a] Reagents and conditions: (a) $NaBH_4$, MeOH/Et_2O, 0 °C, 30 min, 87% (**3**/**4** = 1/1.85); (b) Z-GlyOH, DMAP, DCC, THF, rt, 16 h, 98%; (c) H_2 (1 atm), Pd/C, rt, 14 h, 76% (**12**/**13** = 1:1.59).

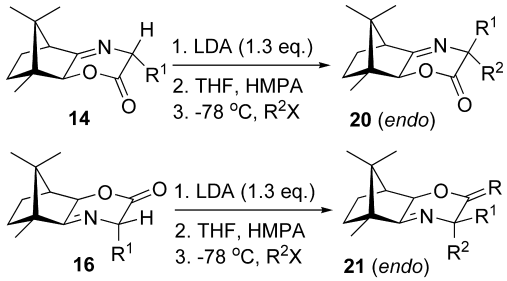
SCHEME 4. Alkylation of Tricycloiminolactones



SCHEME 5. Hydrolysis of Monoalkylated Tricycloiminolactones



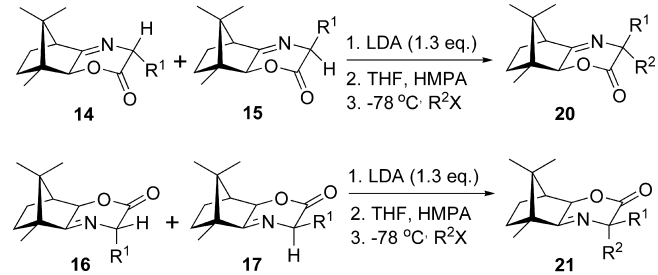
SCHEME 6. Preparation of Dialkylated Tricycloiminolactones



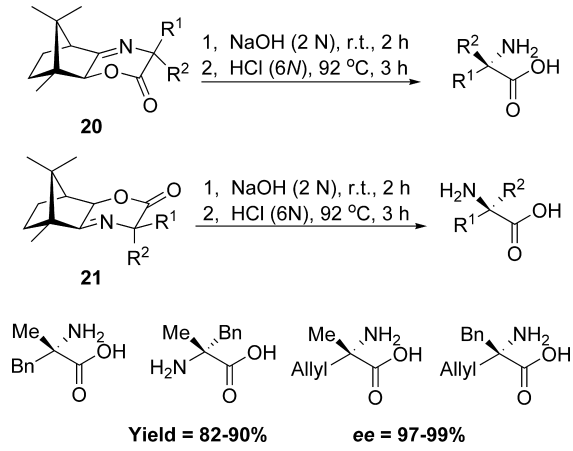
determined by comparing the optical rotation of the products with the literature values, were in accordance with those assigned to the respective precursors. In addition, the chiral auxiliaries **3** and **4** were recovered in excellent yields and could be recycled.

After the preparation of α-monoalkylated glycines, we turned our attention to the synthesis of α,α-disubstituted α-amino acids.[8a] According to our previous results, alkylation of iminolactones **12** and **13** gave the monoalkylated products **14** and **16**, respectively, as the sole products in good yields. If compounds **14** and **16** were alkylated again under the same conditions, compounds **20** and **21** might be furnished. Followed by hydrolysis, corresponding α,α-disubstituted α-amino acids could be obtained. Thus, monoalkylated products **14** and **16** were alkylated again under the condition used in the alkylation of iminolactones **12** and **13** except

SCHEME 7. Direct Alkylation of a Mixture of Monoalkylated Tricycloiminolactones



SCHEME 8. Hydrolysis of Dialkylated Tricycloiminolactones



1.3 equiv of LDA was used. Fortunately, the reaction occurred smoothly and the scope of the electrophiles was as wide as monoalkylation. Good yields and excellent diastereoselectivities were observed (Scheme 6). Interestingly, the enolates of iminolactones **14** and **16** always attacked the electrophiles from the *endo* face regardless of the sizes of the electrophiles to generate the stereocenters with virtually complete diastereoselectivity. Consequently, the configuration of the α,α-disubstituted α-amino acids could be controlled by employing proper order of alkylations. According to the above results, we reasoned if the mixture of compounds **14** and **15**, as well as **16** and **17,** was alkylated directly under the same conditions,

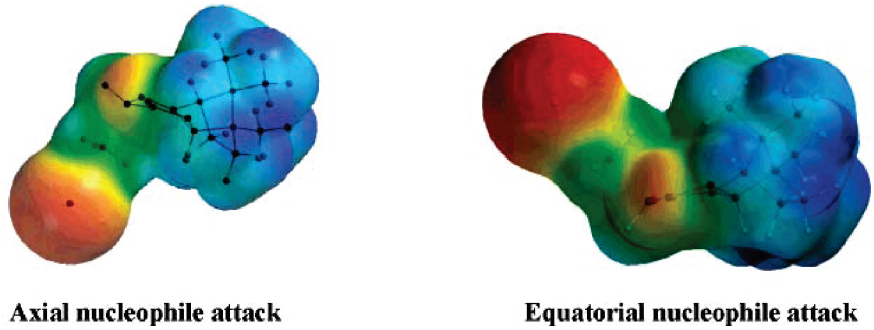


FIGURE 1. Electrostatic potential isodensity surfaces of two transition states obtained from ab initio calculations.

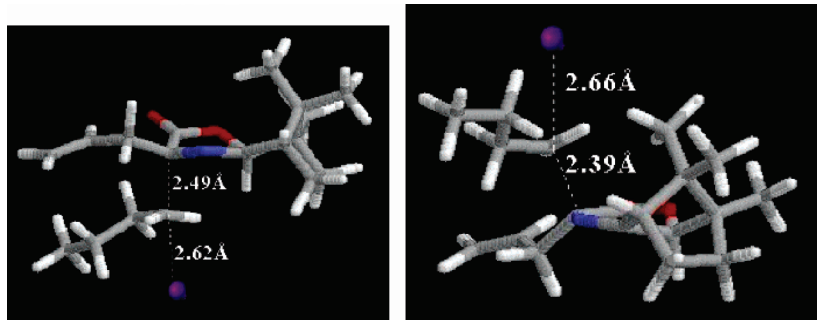


FIGURE 2. Geometries of transition states for alkylation of compound **16** (R^1 = CH2CH=CH2, R^2 = *n*-Bu): (left) axial nucleophile attack; (right) equatorial nucleophile attack.

TABLE 2. Energy Difference between *Exo*- and *Endo*- Attack (kcal/mol)

reaction compd 16				
R^1	R^2	ΔE_{exo}	ΔE_{endo}	$\Delta(\Delta E)^a$
CH_3	$CH_2C_6H_5$	35.58	32.25	3.33
CH_2=$CHCH_2$	$CH_2C_6H_5$	38.80	35.91	2.89
CH_2=$CHCH_2$	*n*-Bu	41.19	39.62	1.57
$CH_2C_6H_5$	CH_3	36.63	31.06	5.57
$CH_2C_6H_5$	CH_2=$CHCH_2$	37.31	35.99	1.32
$CH_2C_6H_5$	$CH_2C_6H_5$	37.02	34.77	2.25

[a] $\Delta(\Delta E) = \Delta E_{exo} - \Delta E_{endo}$.

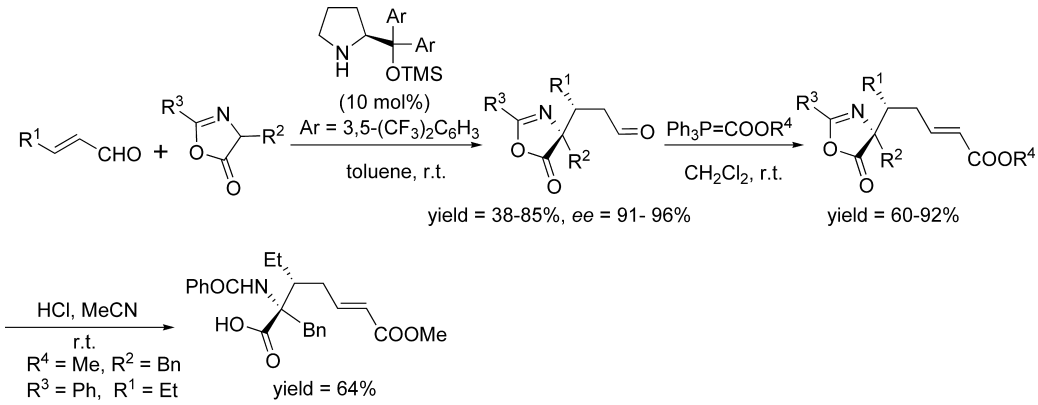
a single diastereoisomer of the product would be obtained (Scheme 7). This presumption was confirmed by experiments.

Representative dialkylated tricycloiminolactones **20** and **21** were hydrolyzed with 2 N NaOH at room temperature for 2 h and then with 6 N HCl at 92 °C for 3 h to afford the corresponding optically active α,α-disubstituted α-amino acids in good yields and enantiomeric excesses (Scheme 8). The configurations of α-amino acids were in agreement with those assigned to the respective dialkylated tricyclominolactone precursors.

The extremely high *endo*-face selectivity for alkylation is discussed using semiempirical (MOPAC 93) calculations (Figures 1 and 2, and Table 2), and the results are in accordance with our conclusion drawn from experiments.

It is noteworthy that Jørgensen reported an excellent method for the synthesis of α,α-disubstituted α-amino acids in 2008 (Scheme 9).[8b] An organocatalyzed Michael addition of α,β-unsaturated aldehydes by racemic oxazolones was employed as the key step. Good yields and stereoselectivi-

SCHEME 9. Organocatalyzed Approach to α,α-Disubstituted α-Amino Acids Developed by Jørgensen



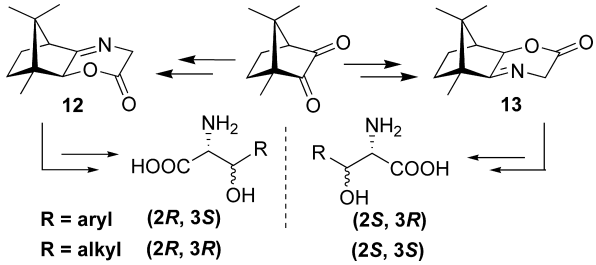


FIGURE 3. Synthesis of β-hydroxy-α-amino acids.

ties were observed. By contrast, our method has obvious advantages in the synthesis of α,α-dialkyl α-amino acids, especially in the regulation of stereochemistry.

4. Synthesis of β-Hydroxy-α-amino Acids

β-Hydroxy-α-amino acids are important constituents of peptides and other complex natural products. Therefore, methods that can control the stereochemistry of α- and β-positions of β-hydroxy-α-amino acids would be highly useful.[9] After we achieved the enantiomeric synthesis of α-alkylated-α-amino acids, we probed the aldol reactions between the enolated iminolactones and aldehydes (Figure 3). The aldol reactions were carried out at −78 °C in THF using LDA as the base. In an attempt to improve the yield and diastereoselectivity, we carried out a series of experiments by varying the additives used. The results demonstrated that the addition of 6.0 equiv of lithium chloride led to remarkably improved diastereoselectivity. Then, a series of aldol reactions was conducted using the above-optimized conditions, and the results are summarized in Scheme 10. As expected, these reactions furnished the aldol adducts in good yields with high stereochemical control for the two newly generated stereogenic centers.[10]

In principle, the aldol reaction of any tricycloiminolactone (**12** or **13**) with an aldehyde will form four diastereoisomeric products. However, in our reactions, the exclusive *endo* addition of the nucleophile to the aldehyde only led to the production of two diastereisomers. It is presumably due to the steric hindrance of the C12-methyl, which effectively blocks the approach from the *exo*-face and thus favors attacking the electrophile from the *endo*-face of the enolate. Additionally, the lone pair of electrons on the auxiliary nitrogen fuses the iminolactone into a boat conformation.

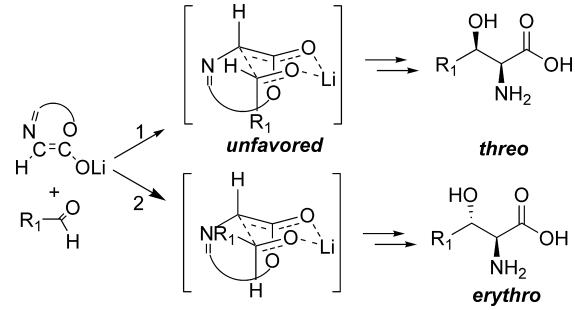


FIGURE 4. Proposed mechanism of the Aldol reaction of **13** with aliphatic aldehydes.

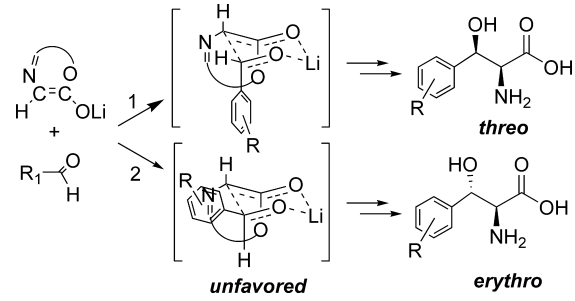
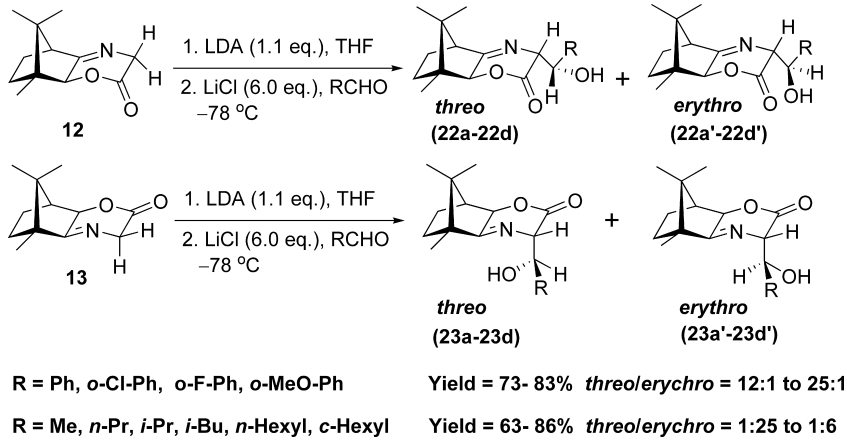


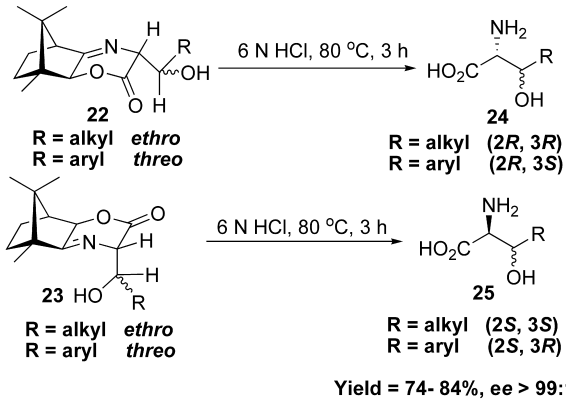
FIGURE 5. Proposed mechanism of the Aldol reaction of **13** with aromatic aldehydes.

It is noteworthy that the aldol reactions of aromatic aldehydes with **12** and **13** produced predominantly *threo*-adducts, while reactions of aliphatic aldehydes gave exclusively *erythro*-adducts. The reason for this selectivity pattern can be explained by the theory of Zimmerman and Traxler (Figure 4),[11] where pathway 2 details the orientation for *erythro*-adducts in the aldol reactions of aliphatic aldehydes with **13**. In this case, the stereoselectivity comes from minimization of

SCHEME 10. Aldol Reactions between Aldehydes and Tricycloiminolactones



SCHEME 11. Hydrolysis of Aldol Adducts



nonbonded interaction in the form of a chairlike transition state, in which the alkyl group of aldehyde (R^1) assumes a pseudoequatorial position. For the reactions of aromatic aldehydes (Figure 5), the transition state in pathway 2 may experience a $\pi-\pi$ interaction between the phenyl ring and the π system of the iminolactone. As a result, the phenyl ring can adopt an orientation parallel with the iminolactone ring, as shown in pathway 1, to reduce the steric interaction. Therefore, pathway 1 is more favorable than pathway 2 in the reactions of aromatic aldehydes. The hydrolysis of the isolated single aldol products afford the corresponding β-hydroxy-α-amino acids in good yields with excellent optical purity (Scheme 11).

5. Synthesis of β-Substituted α,γ-Diaminobutyric Acids

Michael addition of electron-deficient olefins is one of the most important approaches for carbon−carbon bond formation. As excellent Michael acceptors, nitroalkenes were used to synthesize nitro-compounds and amino-compounds frequently. Therefore, we probed the Michael addition of nitroalkenes by tricycloiminolactones and expected to prepare enantiomerically enriched α,γ-diaminobutyric acids after subsequent reduction of the nitro group and removal of the auxiliary.[12]

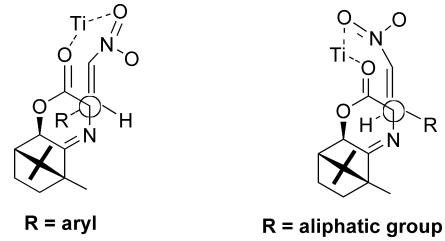


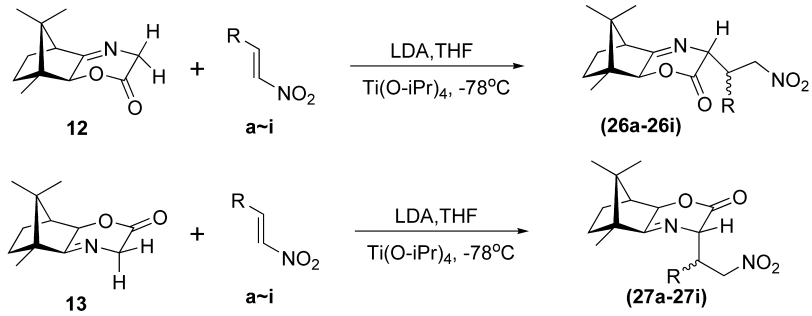
FIGURE 6. Proposed mechanism for the Michael addition.

After optimizing of the reaction conditions, we discovered the Michael addition of nitroalkenes by tricycloiminolactones occurred in THF with LDA as a base and Ti(*i*-PrO)$_4$ as a Lewis acid additive to give excellent yields and stereoselectivities. A range of aromatic and aliphatic nitroalkenes was employed to investigate the scope of the reaction. Results of the reactions are summarized in Scheme 12.

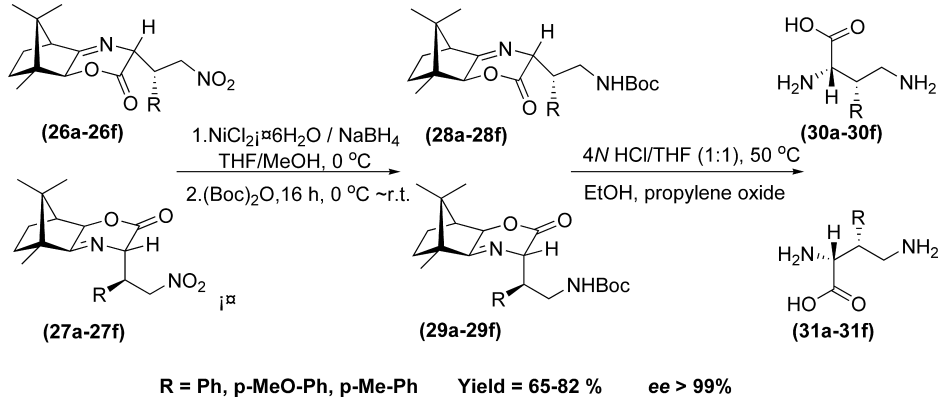
Under similar reaction conditions, excellent diastereoselectivities were also obtained for the reactions of aliphatic nitroalkenes when the addition order of the reagents was changed.

On the basis of above observations, strong correlations between the enolate geometries and the adduct stereostructures were discovered. Predominant *syn* adducts were obtained when R was an aryl group, while *anti*-adducts were preferentially formed when R was an aliphatic group. As with Aldol reaction,[10] the steric hindrance of C12-methyl and boat confirmation of tricycloiminolactones lead to a high *endo*/*exo* ratio at the C5 position. The $\pi-\pi$ interaction between the phenyl ring of aromatic nitroalkenes and C=N in the donor led to the generation of *syn*-adducts. By contrast, when aliphatic nitroalkenes were employed, there existed no $\pi-\pi$ interaction. Thus, the nucleophilic attack occurred from the

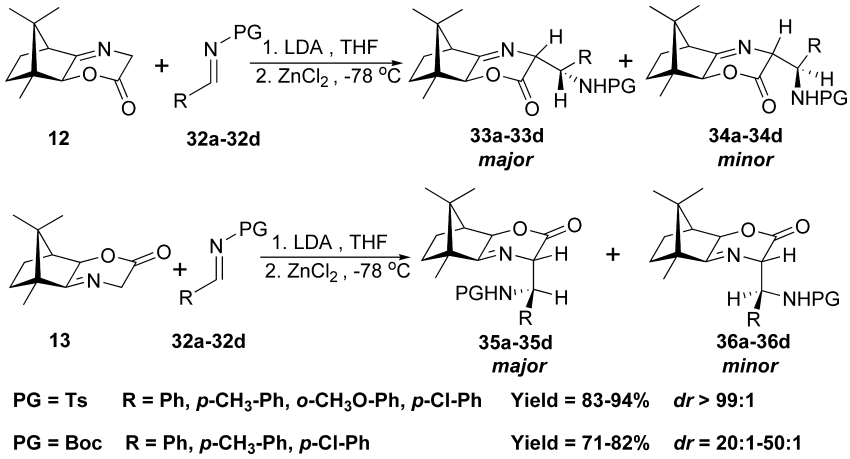
SCHEME 12. Michael Addition between Tricycloiminolactones



SCHEME 13. Synthesis of β-Substituted α,γ-Diaminobutyric Acids



SCHEME 14. Mannich Reaction between Tricycloiminolactones and *N*-Protected Imines



less hindered face of nitroalkenes, and *anti*-adducts were obtained (Figure 6).

In order to prepare α,γ-diaminobutyric acids, the Michael adducts were reduced to amino groups and protected with Boc_2O. Following removal of auxiliary afforded several kinds of α,γ-diaminobutyric acids (Scheme 13).

6. Synthesis of Enantiopure β-Aryl-α,β-diaminopropanoic Acids

Optically active α,β -diamino acids are an important class of compounds due to their presence in a variety of peptide antibiotics, antifungal dipeptides, and other biologically active compounds.[13]

The Mannich reaction is another important carbon−carbon bond forming reaction for the synthesis of nitrogenous molecules, which can lead to the generation of two contiguous nitrogen-bearing stereogenic centers.[14] After investigation of Aldol and Michael reactions, we focused our attention on the Mannich reaction between tricycloiminolactones and imines.[15] Our investigation began with the reactions of iminolactone **12** with various *N*-aryl substituted imines, but no Mannich adducts were detected. Given the low reactivity of the imine in this nucleophilic addition, a strong electron-withdrawing group, such as sulfonyl, was introduced on the nitrogen atom of the imine to activate the C═N bond. Fortunately, we found that *N*-tosyl-*C*-phenyl imine **32a** reacted smoothly with iminolactone **12** at −78 °C in THF using LDA as the base to afford a mixture of diastereomeric adducts. Optimization of the reaction condition demonstrated that addition of 1.2 equiv of zinc chloride dramatically improved both the yield and the diastereoselectivity. We examined the scope of the reaction with a variety of *N*-tosyl imines under the optimized conditions. As revealed in Scheme 14, high yields and excellent diastereoselectivities were obtained with all the substrates.

The high diastereoselectivity led us to propose a mechanism to account for the stereochemical induction of the reaction. The zinc enolate of tricyclic iminolactone **13** is formed in situ from the corresponding lithium enolate via transmetalation with 1 equiv of zinc chloride. As shown in Figure 7, two possible pathways for the reaction are depicted. Obviously, the coordination of the imine via the lone pair of electrons on the nitrogen with the zinc center enables a six-membered cyclic

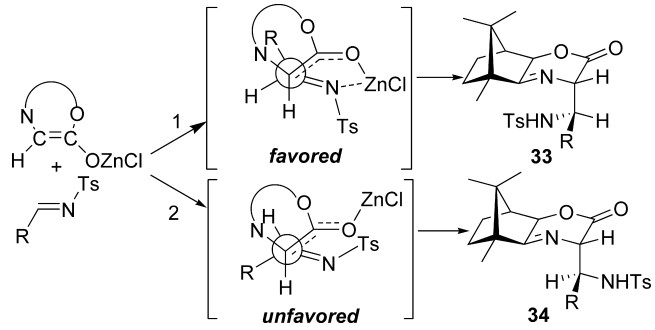
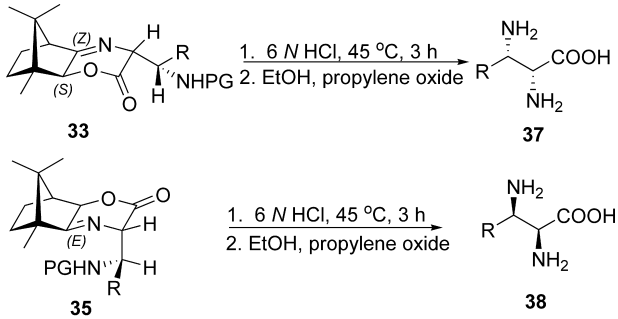


FIGURE 7. Proposed mechanism of Mannich addition.

SCHEME 15. Hydrolysis of Mannich Products



transition state in pathway 1. This model can account for both the *endo*- configuration and the high diastereoselectivity. By contrast, in pathway 2, the bulky sulfonyl group within the imine would not allow for efficient interaction with the zinc center.

Subsequently, we attempted to hydrolyze the Mannich adducts under acidic conditions, but we found the removal of *para*-toluenesulfonate (tosyl) group was difficult and racemization was unavoidable under acidic conditions. Therefore, we turned our attention to *N*-Boc imine as an electrophile.

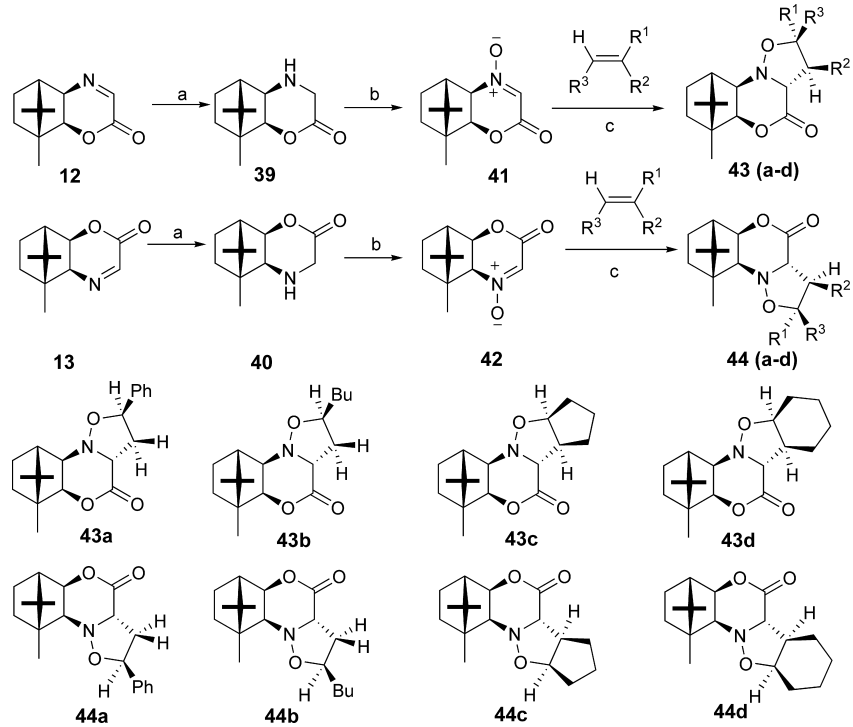
A series of Mannich reactions with *N*-Boc imines was conducted as summarized in Scheme 14. The predominant *endo* configurations were the same as *N*-tosyl imines.

Facile deprotection of the *N*-Boc group and removal of the chiral auxiliary could be achieved under acidic conditions (Scheme 15). It is exciting that racemization was not detected and both the (2*S*,3*R*) and (2*R*,3*S*) forms of β-aryl-α,β-diaminopropanoic acids were obtained in high diastereoselectivities. Diastereo- and enantioselectivies obtained in this manner are higher compared to those obtained by previously reported methods.

7. Investigation for the Synthesis of γ-Hydroxy-α-amino Acids

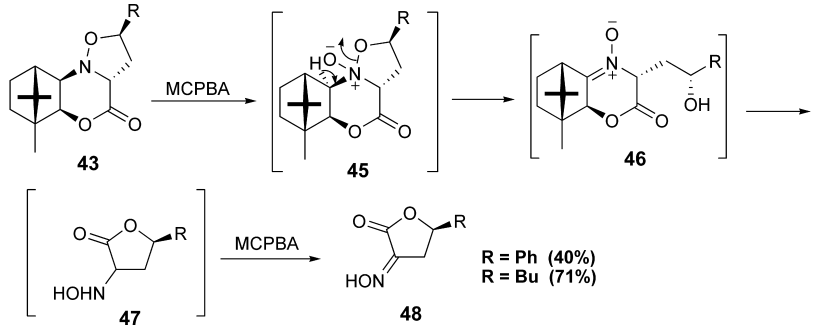
Asymmetric 1,3-dipolar cycloaddition reaction between nitrones and alkenes is one of the most efficient methods for the construction of optically active isoxazolidines, which are readily converted to useful chiral γ-amino alcohols.[16] Therefore, 1,3-diploar cycloaddition between alkenes and the nitrones derived from tricycloiminolactones was investigated,

SCHEME 16. 1,3-Dipolar Addition between Alkenes and the Nitroalkenes Derived from Tricycloiminolactones[a]



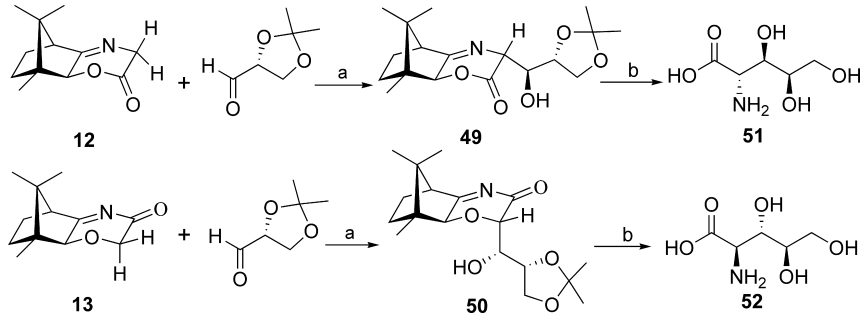
[a] Reagents and conditions: (a) 10% Pd/C, H_2, *i*-PrOH, rt, 100%; (b) MCPBA, Na_2CO_3, 0°C to rt, 44%; (c) toluene, 60°C, yield = 93−100%, *exo*/*endo* = 20:1−99:1.

SCHEME 17. Cleavage of the Chiral Auxiliary



43 45 46 47 48

SCHEME 18. Synthesis of Polyoxamic Acid[a]



12 49 51 13 50 52

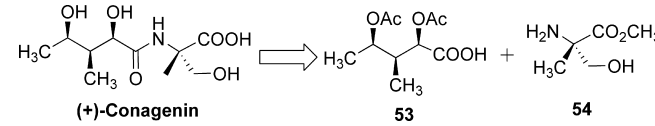
[a] Reagents and conditions: (a) LDA, THF, LiCl, −78°C, **49** (83%, *dr* = 9:1); **50** (85%, *dr* = 12:1) (b) (1) 4 N HCl, rt, 2 h; (2) 0.6 M $NH_3 \cdot H_2O$, Dowex 50W X8 (H^+), 90−95%.

and the transformation of cycloadducts to γ-hydroxy-α-amino acids was probed.[17]

Cyclic nitrones **41** and **42** were prepared by catalyzed hydrogenolysis and oxidation (Scheme 16) from **12** and **13**, respectively. 1,3-Diploar cycloadditions between the cyclic nitrones and alkenes were carried out to give the α-face cycloadducts (**43, 44**) in high *exo*/*endo* ratios.

In all cases studied, the cycloaddition reactions took place from the less hindered face of nitrones, which placed the 5-substituent (R^3) of the major stereoisomer in the *exo*-position. This was due to the steric hindrance of the C12-methyl group. Because of steric hindrance between the substituents on the alkenes and the nitrones, *exo*-transition states were favored to give 5-*exo*-substituted isoxazolidines as the major isomers.

To remove the chiral auxiliary, it is necessary to cleave the N−O and C−N bonds regioselectively. The oxidative procedure developed by Langlois was employed. However, treatment of **44** with MCPBA failed to initiate any reactions. It was postulated that the bridgehead methyl group adjacent to the nitrogen atom blocked the approach of MCPBA. On the other hand, oxidation of the regioisomeric adduct **43** with MCPBA afforded an intermediate *N*-oxide **45**, which underwent a spontaneous elimination to produce nitrone **46**. Subsequent transesterification, hydrolysis, and further oxidation of **47** gave α-oximino-γ-lactone **48** (Scheme 17).



(+)-Conagenin 53 54

FIGURE 8. Retrosynthetic analysis of conagenin.

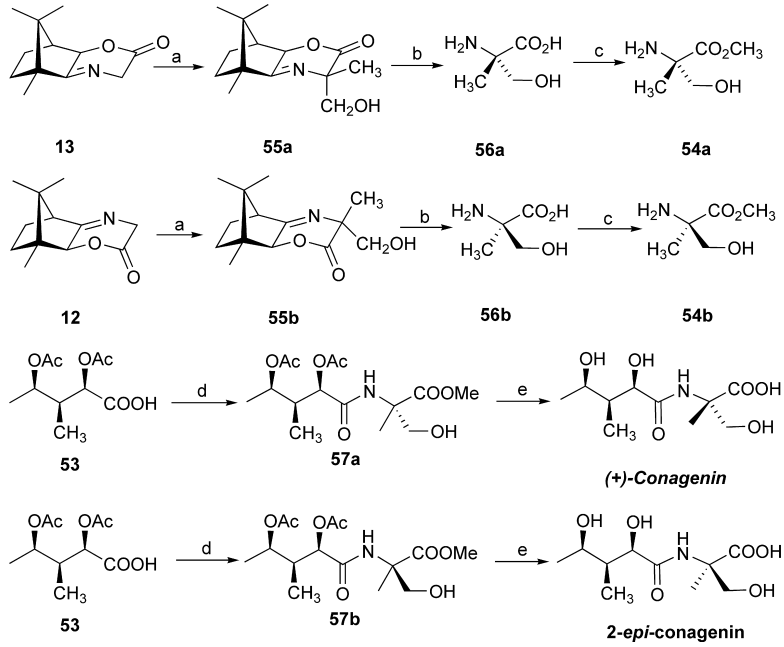
8. Total Synthesis of Natural Products Based on the Tricycloiminolactone Methodology

Following the successful development for the synthesis of β-hydroxy-α-amino acids, we investigated their application in the total synthesis of natural products. Polyoxamic acid, conagenin, lactacystin and sphingofungin F were selected as targets.

Polyoxamic acid is a common fragment in many polyoxins, an important group of nucleoside peptide antibiotics.[18] Our route[19] started with the diastereoselective aldol reaction between tricycloiminolactones and 2,3-*O*-(isopropylidene)-*D*-glyceraldehyde, and afforded amino alcohols **49** and **50**. After hydrolysis of the aldol adducts, two diastereoisomers of polyoxamic acids **51** and **52** were obtained (Scheme 18).

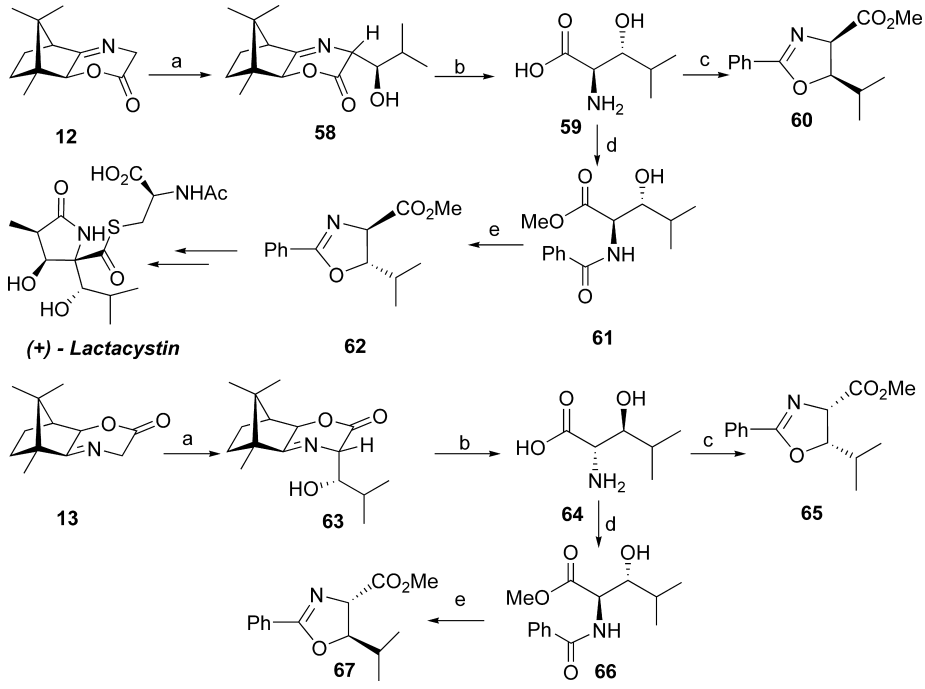
Conagenin is an immunomodulator of antitumor activity.[20] Total synthesis of (+)-conagenin was usually assembled from two fragments **53** and **54** (Figure 8). Synthesis of the α-methylserine reported by many groups was complex and the preparation of its enantiomer was difficult. We employed the aldol reaction between methylated tricycloiminolactones and

SCHEME 19. Synthesis of Conagenin and Its 2-*epi*-Diastereoisomer[a]



[a] Reagents and conditions: (a) (i) LDA (1.1 equiv), DMPU (1.5 equiv), MeI (1.5 equiv), THF, −78 °C, 98%; (ii) LDA (2 equiv), DMPU (1.5 equiv), HCHO/THF, −78 °C, **55a** (64%, *dr* = 2:1), **55b** (83%, *dr* = 7:1); (b) (i) 6 *N* HCl, 90 °C, 6 h; (ii) EtOH, propylene oxide; (c) CH_2N_2/ether, rt, **54a** (83%), **54b** (80%); (d) **54a** or **54b**, DCC, HOBt, DMF, rt, 6 h, **57a** (61%), **57b** (69%); (e) 1 M K_2CO_3, MeOH, conagenin (85%), 2-*epi*-conagenin (83%).

SCHEME 20. Formal Synthesis of Latacystin and the Intermediate of Its Diastereoisomers[a]



[a] Reagents and conditions: (a) (1) LiCl, LDA, −78 °C, $(CH_3)_2CHCHO$, 2 h, **58** (85%), **63** (84%); (b) 6 N HCl, 80 °C, **59** (84%), **64** (87%); (c) (i) HCl (g), MeOH; (ii) $PhC(OMe)_3$, PTSA, DME, reflux, **60** (82%), **65** (82%); (d) (i) HCl (g), MeOH; (ii) Et_3N (3.0 equiv), PhCOCl (1.1 equiv), **61** (77%), **66** (75%); (e) $SOCl_2$, THF, **62** (89%), **67** (80%).

formaldehyde as the key step to construct the stereochemistry of α-methylserine and its enantiomer (Scheme 19).[21] Hydrolysis of the aldol adducts and esterification of the amino acids afforded **56** and its isomers, which were coupled with **53**[22] followed by hydrolysis to give conagenin and its 2-*epi*-diastereoisomer in high yields.

(+)-Lactacystin, a potent and selective 20S and 26S proteasome inhibitor, was isolated from the culture broth of *Strep-*

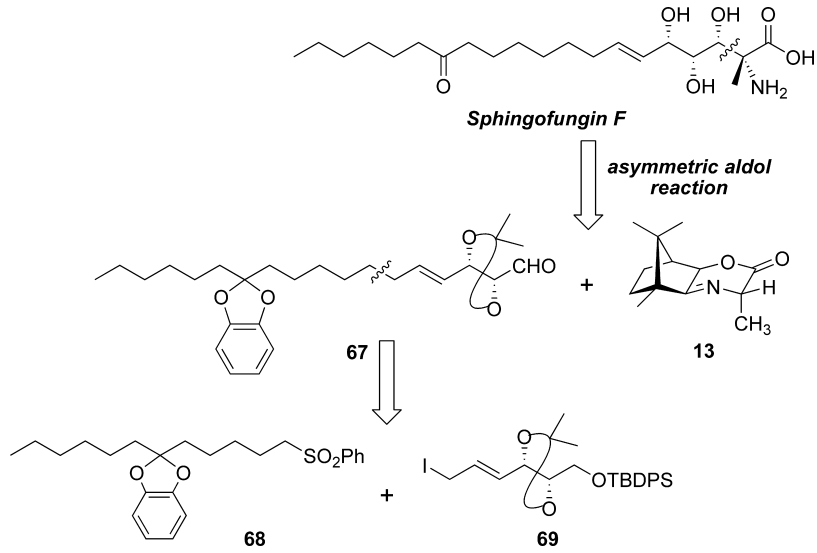
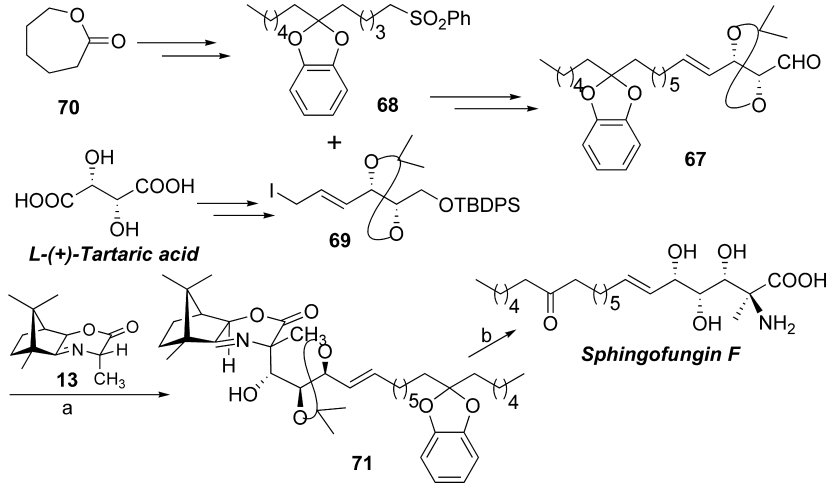


FIGURE 9. Retrosynthetic analysis of sphingofungin F.

SCHEME 21. Synthesis of Sphingofungin F[a]



[a] Reagents and conditions: (a) KHMDS, $BF_3 \cdot Et_2O$, 65% (*dr* = 3:1); (b) 0.2 *N* HCl, EtOH, reflux, 66%.

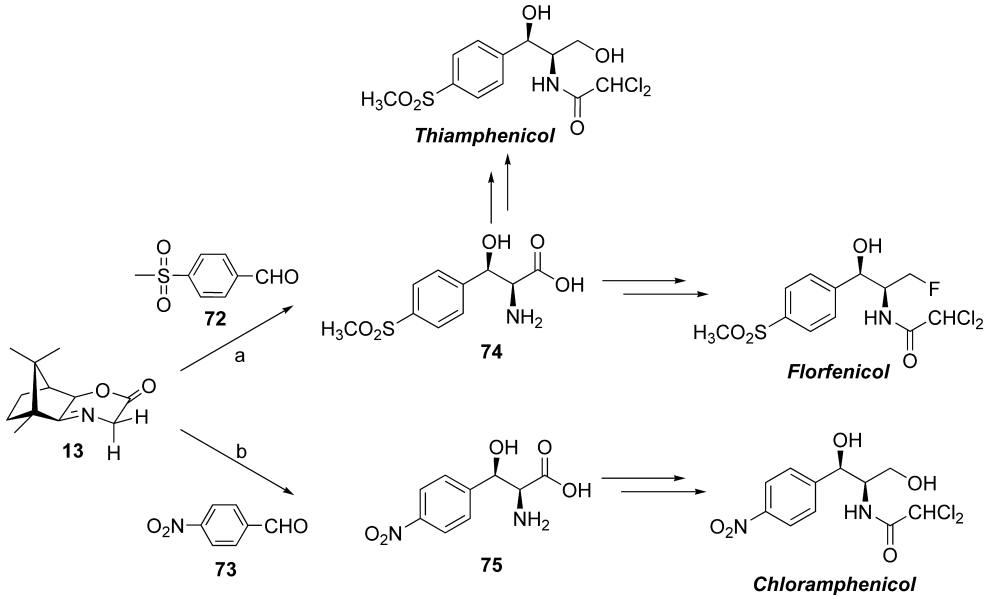
tomyces sp. OM-6519 by Omura et al. in 1991. Its unusual structure along with its remarkable biological activity has attracted the attention of many synthetic chemists.[9c,23,24] Many groups used oxazoline **62** derived from enantioenriched hydroxyleucine as a key intermediate in their total syntheses. Although several approaches for the synthesis of chiral 3-hydroxyleucine have been reported previously, our strategy allows for the most concise preparation of either (2*S*,3*S*) or (2*R*,3*R*) 3-hydroxyleucine. So we can easily prepare *trans*-oxazolidine **62** and the other three isomers. The synthesis of *trans*-oxazoline **62** and its diastereoisomer **67** are outlined in Scheme 20. Iminolactones reacted with isobutyric aldehyde at −78 °C to form compounds **58** and **63** with good yields and selectivities.[10]

Subsequent hydrolysis afforded the corresponding 3-hydroxyleucines **59** and **64**. After esterification, the esters were transformed into amides **61** and **66**, which underwent cyclization to give oxazoline **62** and **67** via reaction with 1.5 equiv of thionyl chloride. Based on the above achievement, formal synthesis of lactacystin has been accomplished and the total synthesis of other diastereoisomers of lactacystin is ongoing.

Sphingofungin F isolated from the fermentation broth of *Paecilomyces variotii* exhibits inhibitory effects toward the serine palmitoyl transferase (SPT).[25] Its novel structure and biological activity attracted considerable attention of synthetic chemists.[26] Based on our method, sphingofungin F can be divided into two parts, methyl tricyclic iminolactone **13** and polyhydroxyl long chain aldehyde **67**. The latter can be obtained by the coupling reaction of long chain lipid **68** and polyhydroxyl *trans*-olefin **69** (Figure 9).

Compound **68** (Scheme 21) was prepared according to our reported method from ε-caprolactone **70**,[27] and compound

SCHEME 22. Application of Tricycloiminolactones in the Synthesis of Some Drug Molecules[a]



[a] Reagents and conditions: (a) (i) LDA, $LiClO_4$, THF, −78 °C, 76%; (ii) 6 N HCl, 70 °C, 91%; (b) (i) LDA, $LiClO_4$, THF, −78 °C, 75%; (ii) 6 *N* HCl, 70 °C, 84%.

69 was synthesized from L-(+)-tartaric acid. Coupling of compound **68** and **69** afforded aldehyde **67** after several steps. With aldehyde **67** in hand, aldol reaction between compound **13** and **67** was carried out and compound **71** was obtained in 65% yield with *dr* = 3:1. Hydrolysis of **71** afforded sphingofungin F in 66% yield. An efficient strategy for the total synthesis of sphingofungin F has been accomplished in 15 steps and with 10% overall yield, which is the highest among all reported routes.[28]

Besides the above natural molecules, the application of our method in the synthesis of some drug molecules such as thiaphenicol, florfenicol, and chloramphenicol was also investigated. As shown in Scheme 22, two kinds of important β-hydroxy-α-amino acids were prepared easily and transformed into our target molecules after several simple steps. By using our method, the preparation of these drug molecules was greatly simplified.

9. Conclusion

In the past few years, our group discovered tricycloiminolactones and probed their usage systematically. Facile approaches to several kinds of α-amino acids were developed and successfully applied in total synthesis of related natural products. The striking advantage of our methodologies is that both enantiomers of α-amino acids can be produced from the same inexpensive and easily accessible chiral source and the chiral auxiliaries can be recovered. From a synthetic viewpoint, a method which provides both enantiomers of products by using chiral auxiliaries derived from a single chiral source is most attractive and desirable. Our methodologies have simplified the synthesis of a few kinds of useful α-amino acids and should provide many useful building blocks for the synthesis of some complex molecules.

We are indebted greatly to co-workers, whose names are shown in the references, for their outstanding contributions. We are grateful to the National Basic Research Program of China (No. 2009CB626604, 2010CB833200), NSFC (20772051, 20972058), the "111" program from MOE of P. R. China, and the Important Science & Technology Specific Projects of Gansu Province (092GKDA015) for their financial support. We also thank Professor T.-J. Lu and Binghe Wang for their support.

BIOGRAPHICAL INFORMATION

Yong-Chun Luo (b. 1982) received his B.S. and Ph.D. degrees under the supervision of Professor Xu from Lanzhou University, where he was appointed Lecturer in 2009. His research focuses on the total synthesis of indole and cyclopeptide alkaloids.

Huan-Huan Zhang (b. 1982) received her B.S. and Ph.D. degrees under the supervision of Professor Xu from Lanzhou University, where she was appointed Lecturer in 2008. Her research focuses on the synthesis of chiral amino acids.

Yao Wang (b. 1984) received his B.S. from Lanzhou University in 2006. He is currently pursuing his Ph.D. degree under the supervision of Professor Xu. His research focuses on the design, development, and application of reaction cascades.

Prof. Peng-Fei Xu received his Ph.D. degree in 1998 at Lanzhou University and conducted postdoctoral studies at National Chung-Hsing University (hosted by Prof. T.-J. Lu) in Taiwan for 2 years. In 2003, he went to Nagoya University in Japan and joined

the group of Prof. Kazuyuki Tatsumi as a visiting professor for 1.5 years. He is presently deputy director of the State Key Laboratory of Applied Organic Chemistry and an advisory board member of the Chinese Chemical Community. His current research interests focus on the synthetic methodologies of amino acids, total synthesis of natural products, and catalyzed cascade reactions. In 2009, Prof. Peng-Fei Xu was awarded the "Thieme Journal Award".

REFERENCES

1 Bhat, S. V.; Nagasampagi, B. A.; Sivakumar, M. E. *Chemistry of Natural Products*; Springer: Narosa, 2005; p 317.

2 (a) Williams, R. M.; Burnett, K. M. New Tricks in Amino Acid Synthesis: Applications to Complex Natural Products. In *Asymmetric Synthesis and Application of α-Amino Acids*; Soloshonok, V. A., Izawa, K., Eds.; ACS: Washington, DC, 2009; pp 420—474. (b) Kaiser, J.; Kinderman, S. S.; van Esseveldt, B. C. J.; van Delft, F. L.; Schoemaker, H. E.; Blaauw, R. H.; Rutjes, F. P. J. T. Synthetic Applications of Aliphatic Unsaturated α-H-α-Amino Acids. *Org. Biomol. Chem.* **2005**, *3*, 3435–3467. (c) Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. Applications of Aliphatic Unsaturated non-Proteingenic α-H-α-Amino Acids. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4197–4212. (d) Sardina, F. J.; Rapoport, H. Enantiospecific Synthesis of Heterocycles from α-Amino Acids. *Chem. Rev.* **1996**, *96*, 1825–1872.

3 (a) Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E.; Etxebarria, J. α-Amino Acids, β-Amino Alcohols and Related Compounds as Chiral Auxiliaries, Ligands and Catalysts in the Asymmetric Aldol Reaction. *Curr. Org. Chem.* **2005**, *9*, 219–235. (b) Jarvo, E. R.; Miller, S. J. Amino Acids and Peptides as Asymmetric Organocatalysts. *Tetrahedron* **2002**, *58*, 2481–2495. (c) Xu, L.-W.; Lu, Y.-X. Primary Amino Acids: Privileged Catalysts in Enantioselective Organocatalysis. *Org. Biomol. Chem.* **2008**, *6*, 2047–2053.

4 (a) Nájera, C.; Sansano, J. M. Catalytic Asymmetric Synthesis of α-Amino Acids. *Chem. Rev.* **2007**, *107*, 4584–4671. (b) Maruoka, K.; Ooi, T. Enantioselective Amino Acid Synthesis by Chiral Phase-Transfer Catalysis. *Chem. Rev.* **2003**, *103*, 3013–3028. (c) Chinchilla, R.; Nájera, C. Asymmetric Synthesis of α-Amino Acids Using Polymer-Supported Cinchona Ammonium Salts as Phase-Transfer Catalysts. In *Asymmetric Synthesis and Application of α-Amino Acids*; Soloshonok, V. A., Izawa, K., Eds.; ACS: Washington, DC, 2009; pp 251—264.

5 (a) Okuro, K.; Saka, Y.; Suzuki, I.; Mitsuda, M. Novel Chiral Template for Preparation of α-Amino Acids: Practical Synthesis and Application. In *Asymmetric Synthesis and Application of α-Amino Acids*; Soloshonok, V. A., Izawa, K., Eds.; ACS: Washington, DC, 2009; pp 89—100. (b) Abellan, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Najera, C.; Sansano, J. M. Glycine and Alanine Imines as Templates for Asymmetric Synthesis of α-Amino Acids. *Eur. J. Org. Chem.* **2000**, *15*, 2689–2697. (c) Li, Zh.-J.; Wang, H.-G.; Wei, P.; Shi, Y.-H. Asymmetric Synthesis of Tailor-made α-Amino Acids by Chiral Auxiliaries: Glycine Equivalent Approach. *Chin. J. Org. Chem* **2005**, *25*, 881–892.

6 Xu, P.-F.; Chen, Y.-S.; Lin, S.-I.; Lu, T.-J. Chiral Tricyclic Iminolactone Derived from (1*R*)-(+)-Camphor as a Glycine Equivalent for the Asymmetric Synthesis of α-Amino Acids. *J. Org. Chem.* **2002**, *67*, 2309–2314.

7 Xu, P.-F.; Lu, T.-J. Selective Synthesis of Either Enantiomer of α-Amino Acids by Switching the Regiochemistry of the Tricyclic Iminolactones Prepared from a Single Chiral Source. *J. Org. Chem.* **2003**, *68*, 658–661.

8 (a) Xu, P.-F.; Li, S.; Lu, T.-J.; Wu, C.-C.; Fan, B.; Golfis, G. Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids by Diastereoselective Alkylation of Camphor-Based Tricyclic Iminolactone. *J. Org. Chem.* **2006**, *71*, 4364–4373. (b) Cabrera, S.; Reyes, E.; Alemcn, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. Organocatalytic Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids and Derivatives. *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037.

9 (a) Amador, M.; Ariza, X.; Garcia, J.; Sevilla, S. Stereodivergent Approach to β-Hydroxy α-Amino Acids from C2-Symmetrical Alk-2-yne-1,4-diols. *Org. Lett.* **2002**, *4*, 4511–4514. (b) Willis, M. C.; Cutting, G. A.; Piccio, V. J.-D.; Durbin, M. J.; John, M. P. The Direct Catalytic Enantioselective Synthesis of Protected Aryl β-Hydroxy-α-Amino Acids. *Angew. Chem., Int. Ed.* **2005**, *44*, 1543–1545. (c) Shibasaki, M.; Kanai, M.; Fukuda, N. Total Synthesis of Lactacystin and Salinosporamide A. *Chem. Asian. J.* **2007**, *2*, 20–38.

10 Li, Q.; Yang, S.-B.; Zhang, Zh.-H.; Li, L.; Xu, P.-F. Diastereo- and Enantioselective Synthesis of β-Hydroxy-α-Amino Acids: Application to the Synthesis of a Key Intermediate for Lactacystin. *J. Org. Chem.* **2009**, *74*, 1627–1631.

11 Zimmerman, H. E.; Traxler, M. D. The Stereochemistry of the Ivanov and Reformatsky Reactions. I. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

12 Huang, Y.; Li, Q.; Liu, T.-L.; Xu, P.-F. Diastereoselective Synthesis of β-Substituted-α,γ-Diaminobutyric Acids and Pyrrolidines Containing Multichiral Centers. *J. Org. Chem.* **2009**, *74*, 1252–1258.

13 Viso, A.; Fernández de la Pradilla, R.; Garcia, A.; Flores, A. α,β-Diamino Acids: Biological Significance and Synthetic Approaches. *Chem. Rev.* **2005**, *105*, 3167–3196, and references cited therein.

14 For recent examples of the asymmetric Mannich reaction to synthesize 2,3-diamino acid derivatives, see, for example Davis, F. A.; Zhang, Y.-F.; Qiu, H. Asymmetric Synthesis of *anti*- and *syn*-2,3-Diamino Esters Using Sulfinimines. Water and Concentration Effects. *Org. Lett.* **2007**, *9*, 833–836, and references cited therein.

15 Zhang, H.-H.; Hu, X.-Q.; Wang, X.; Luo, Y.-C.; Xu, P.-F. A Convenient Route to Enantiopure 3-Aryl-2,3-diaminopropanoic Acids by Diastereoselective Mannich Reaction of Camphor-Based Tricyclic Iminolactone with Imines. *J. Org. Chem.* **2008**, *73*, 3634–3637.

16 For recent reviews, see. Gothelf, K. V.; Jørgensen, K. A. Catalytic Enantioselective 1,3-Dipolar Cycloaddition Reactions of Nitrones. *Chem. Commun.* **2000**, 1449–1458, and references cited therein.

17 Wang, P.-F.; Gao, P.; Xu, P.-F. Synthesis and 1,3-Dipolar Cycloadditions of Two New Chiral Geometrically Fixed α-Alkoxycarbonylnitrones from a Single Chiral Source. *Synlett* **2006**, 1095–1099.

18 Isono, K. Nucleoside Antibiotics: Structure, Biological Activity, and Biosynthesis. *J. Antibiot.* **1988**, *41*, 1711–1739.

19 Li, S.; Hui, X.-P.; Yang, S.-B.; Jia, Z.-J.; Xu, P.-F. A Straightforward Route to the Asymmetric Synthesis of 3,4-Diepipolyoxamic Acid and its Isomers. *Tetrahedron: Asymmetry* **2005**, *16*, 1729–1731.

20 Kawatsu, M.; Yamashita, T.; Ishizuka, M.; Takeuchi, T. Improvement of Efficacy of Antitumor Agents by Conagenin. *J. Antibiot.* **1995**, *48*, 222–225.

21 Wang, H.-F.; Ma, G.-H.; Yang, S.-B.; Han, R.-G.; Xu, P.-F. A Concise Synthesis of (+)-Conagenin and its Isomer Using Chiral Tricycliciminolactones. *Tetrahedron: Asymmetry* **2008**, *19*, 1630–1635.

22 Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; Mcclure, C. K.; Norcross, R. D. Enantio- and Diastereoselective Aldol Reactions of Achiral Ethyl and Methyl Ketones with Aldehydes: the Use of Enol Diisopinocampheylborinates. *Tetrahedron* **1990**, *46*, 4663–4684.

23 (a) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. J. *Anfibiof.* **1991**, *44*, 113–116. (b) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. J. *Anfibiof.* **1991**, *44*, 117–118.

24 Shenvi, R. A.; Corey, E. J. A Short and Efficient Synthesis of (−)-7-Methylomuralide, a Potent Proteasome Inhibitor. *J. Am. Chem. Soc.* **2009**, *131*, 5746–5747.

25 Horn, W. S.; Smith, J. L.; Bills, G. L.; Raghoobar, S. L.; Helms, G. L.; Kurtz, M. B.; Marriana, J. A.; Frommer, B. R.; Thornton, R. A.; Mandala, S. M. Sphingofungin E and F: Novel Serinepalmitoyl Trans-Feranse Inhibitors From *Paecilomyces variotii*. *J. Antibiot.* **1992**, *45*, 1692—1996.

26 Representative examples for the total synthesis of sphingofungin F: (a) Trost, B. M.; Lee, C. B. A New Strategy for the Synthesis of Sphingosine Analogues. Sphingofungin F. *J. Am. Chem. Soc.* **1998**, *120*, 6818–6819. (b) Trost, B. M.; Lee, C. B. gem-Diacetates as Carbonyl Surrogates for Asymmetric Synthesis. Total Syntheses of Sphingofungins E and F. *J. Am. Chem. Soc.* **2001**, *123*, 12191–12201.

27 Yang, S.-B.; Gan, F.-F.; Chen, G.-J.; Xu, P.-F. An Efficient One-Pot Synthesis of ω-Hydroxy Ketones from Lactones. *Synlett* **2008**, *16*, 2532–2534.

28 Gan, F.-F.; Yang, S.-B.; Luo, Y.-C.; Yang, W.-B.; Xu, P.-F. Total Synthesis of Sphingofungin F Based on Chiral Tricyclic Iminolactone. *J. Org. Chem.* **2010**, *75*, 2737–2740.