JOC Article

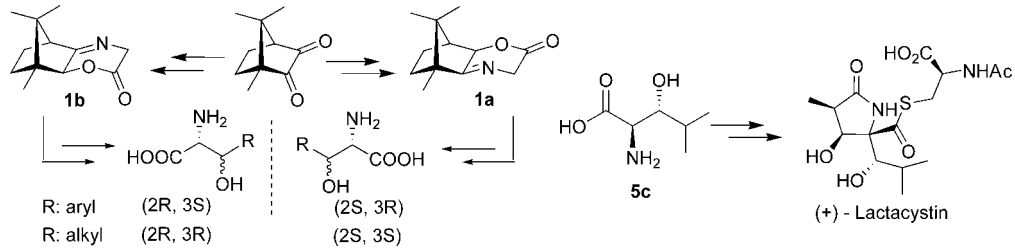
Diastereo- and Enantioselective Synthesis of β-Hydroxy-α-Amino Acids: Application to the Synthesis of a Key Intermediate for Lactacystin

Qiong Li,[†] Shao-Bo Yang,[†] Zhihui Zhang,[‡] Lei Li,[†] and Peng-Fei Xu*,[†]

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, PRC

xupf@lzu.edu.cn

Received October 27, 2008



The development of a highly efficient and stereoselective methodology for the preparation of β-hydroxy-α-amino acids is described. Nucleophilic addition of enolates of tricyclic iminolactones **1a** and **1b** to aldehydes in the presence of 6 equiv of lithium chloride in THF at −78 °C leads to aldol adducts in good yield (63−86%) and high diastereoselectivity (up to >25:1 dr). Subsequently, hydrolysis of the aldol adducts under acidic conditions leads to the corresponding β-hydroxy-α-amino acids in good yields (up to 83%) and excellent enantiomeric excesses (99% ee) with good recovery yields of the chiral auxiliaries **6** and **7**. This methodology was applied to the facile synthesis of the key intermediate for lactacystin along with several isomers.

Introduction

β-Hydroxy-α-amino acids are important constituents of peptides and related compounds[1] as well as other complex natural products.[2] Additionally, they may serve as useful precursors and chiral auxiliaries in organic synthesis.[3] For example (+)-lactacystin is a potent and selective proteasome inhibitor isolated from the culture broth of *Streptomyses* sp. OM-6519 by Omura et al.[4] Its interesting structure contains hydroxyls at both β-positions of the α-amino acid. As a consequence of the essential role played by β-hydroxy-α-amino acids in biological systems and their utilities as synthetic building blocks, a number of useful strategies utilizing chemical and enzymatic methods have been devised for their preparations.[5] However, some problems limit these protocols for the synthesis of enantioenriched β-hydroxy-α-amino acids. For example, the generation of enantioenriched products has been achieved through dynamic kinetic resolution of racemic precursors, while other synthetic approaches afford only one of the diastereomers (*threo*- or *erythro*-β-hydroxy-α-amino acid).[6] Therefore, methods that can control the stereochemistry of α- and β-positions of β-hydroxy-α-amino acids would be highly useful. Our group

* Corresponding author. Tel: 86-931-8912281. Fax: 86-931-8915557.
† Lanzhou University.
‡ Current address: Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, GA 30322.

(1) (a) Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y.; Lajoie, G. A. *J. Org. Chem.* **1998**, *63*, 3631–3646. (b) Palian, M. M.; Polt, R. *J. Org. Chem.* **2001**, *66*, 7178–7183. (c) Belokon, Y. N.; Kochetkov, K. A.; Ikonnikov, N. S.; Strelkova, T. V.; Harutyunyan, S. R.; Saghiyan, A. S. *Tetrahedron: Asymmetry* **2001**, *12*, 481–485.

(2) (a) Amador, M.; Ariza, X.; Garcia, J.; Sevilla, S. *Org. Lett.* **2002**, *4*, 4511–4514. (b) Mettath, S.; Srikanth, G. S. C.; Dangerfield, B. S.; Castle, S. L. *J. Org. Chem.* **2004**, *69*, 6489–6492. (c) Willis, M. C.; Cutting, G. A.; Piccio, V. J.-D.; Durbin, M. J.; John, M. P. *Angew. Chem.* **2005**, *117*, 1567−1569; *Angew. Chem., Int. Ed.* **2005**, *44*, 1543−1545. (d) Shibasaki, M.; Kanai, M.; Fukuda, N. *Chem. Asian J.* **2007**, *2*, 20–38.

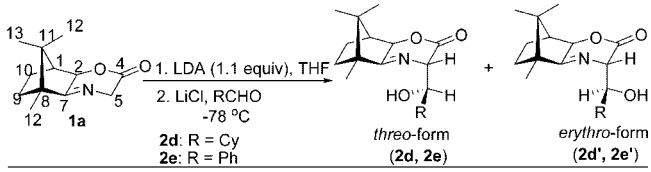
(3) (a) Evans, D. A.; Dinsmore, C. J.; Ratz, A. M.; Evrard, D. A.; Barrow, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 3417–3418. (b) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D. J.; Gálvez, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1015–1025.

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

(5) (a) Herbert, R. B.; Wilkinson, B.; Ellames, G. J.; Kunec, E. K. *J. Chem. Soc., Chem. Commun.* **1993**, 205–206. (b) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem.* **1996**, *108*, 449−452; *Angew. Chem., Int. Ed.* **1996**, *35*, 451−454. (c) Kimura, T.; Vassilev, V. P.; Shen, G. J.; Wong, C. H. *J. Am. Chem. Soc.* **1997**, *119*, 11734–11742. (d) Kuwano, R.; Okuda, S.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 3499–3503. (e) Wang, M.-X.; Deng, G.; Wang, D.-X.; Zheng, Q.-Y. *J. Org. Chem.* **2005**, *70*, 2439–2444.

10.1021/jo8023973 CCC: $40.75 © 2009 American Chemical Society
Published on Web 01/13/2009

TABLE 1. Aldol Reaction of Tricyclic Iminolactones 1a and 1b with Aldehydes



entry	additive	substrate	R	products	yield (%)[a]	*threo*/*erythro*[b]
1		**1a**	Cy[c]	**2d** + **2d′**	80	1:4
2	HMPA (3 equiv)	**1a**	Cy	**2d** + **2d′**	81	1:4
3	HMPA (3 equiv), LiCl (3 equiv)	**1a**	Cy	**2d** + **2d′**	80	1:6
4	LiCl (3 equiv)	**1a**	Cy	**2d** + **2d′**	83	1:15
5	LiCl (6 equiv)	**1a**	Cy	**2d** + **2d′**	82	<1:25
6		**1a**	Ph	**2e** + **2e′**	70	1.5:1
7	LiCl (4 equiv)	**1a**	Ph	**2e** + **2e′**	76	6:1
8	LiCl (6 equiv)	**1a**	Ph	**2e** + **2e′**	75	10:1
9	LiCl (6 equiv)	**1b**	Cy	**3e** + **3e′**	82	<1:25

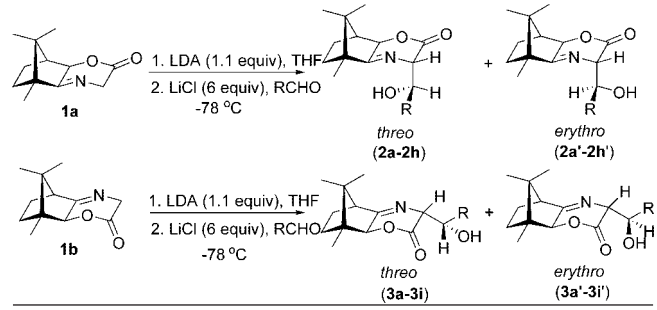
[a] The reported yields are isolated combined yields after column chromatographic separation, except for entry 5. [b] The ratios were estimated by ^{1}H NMR integrations of the crude reaction mixtures on a 400 NMR spectrometer. [c] Cy: cyclohexyl.

has developed an aldol reaction between aldehydes and the enolates of tricyclic iminolactones **1a** and **1b**, which are derived from natural (1*R*)-(+)-camphor as chiral glycine templates,[7,8] to generate optically pure β-hydroxy-α-amino acids in good yield and high diastereoselectivity (up to >25:1 dr) and applied this methodology to the synthesis of the key intermediate of (+)-lactacystin along with several isomers. In addition, an interesting reversal of diastereoselectivity between alkyl and aryl aldehydes was observed with our methodology.

Results and Discussion

The aldol reactions were carried out at −78 °C in THF using LDA as the base, and we observed that the stereoselectivity of the product was strongly dependent on the additives applied. In an attempt to improve the yield and diastereoselectivity, we carried out a series of experiments varying the additives used. The results in Table 1 clearly demonstrate that the addition of 6 equiv of lithium chloride (LiCl) leads to remarkably improved diastereoselectivity.

TABLE 2. Aldol Reaction of Tricyclic Iminolactones 1a and 1b[a] with Aldehydes



entry	substrate	R	yield (%)[b]	product	*threo*/*erythro*[c]
1	**1a**	Me	85	**2a** + **2a′**	1:6
2	**1a**	*n*-propyl	80	**2b** + **2b′**	1:15
3	**1a**	*i*-propyl	84	**2c** + **2c′**	<1:25
4	**1a**	Cy[d]	82	**2d** + **2d′**	<1:25
5	**1a**	Ph	80	**2e** + **2e′**	10:1
6	**1a**	*o*-F-Ph	75	**2f** + **2f′**	>25:1
7	**1a**	*o*-Cl-Ph	73	**2g** + **2g′**	>25:1
8	**1a**	*o*-MeO-Ph	78	**2h** + **2h′**	12:1
9	**1b**	Me	63	**3a** + **3a′**	1:6
10	**1b**	*n*-propyl	80	**3b** + **3b′**	1:19
11	**1b**	*i*-propyl	86	**3c** + **3c′**	<1:25
12	**1b**	*n*-hexyl	83	**3d** + **3d′**	1:19
13	**1b**	Cy	82	**3e** + **3e′**	<1:25
14	**1b**	Ph	83	**3f** + **3f′**	>25:1
15	**1b**	*o*-F-Ph	82	**3g** + **3g′**	>25:1
16	**1b**	*o*-Cl-Ph	80	**3h** + **3h′**	>25:1
17	**1b**	*p*-MeO-Ph	77	**3i** + **3i′**	19:1

[a] The reaction was carried out in the presence of 6 equiv of LiCl. [b] The reported yields are isolated major single product yields after column chromatographic separation, except for entries 1 and 9. [c] The ratios were estimated by ^{1}H NMR integrations of the crude reaction mixtures on a 400 NMR spectrometer (<1:25 means only one diastereomer was found). [d] Cy: cyclohexyl.

Encouraged by the above results, a series of aldol reactions were then conducted using the above optimized conditions, and the results are summarized in Table 2. All aldol reactions were conducted at −78 °C in THF in the presence of 6 equiv of lithium chloride (LiCl) as the additive with 1.1 equiv of LDA as the base. As anticipated, these reactions furnished the aldol adducts in good yields with high stereochemical control of the two newly formed chiral centers.

In principle, the aldol reaction of any tricyclic iminolactone (**1a** or **1b**) with an aldehyde can form four diastereoisomeric products resulting from two newly formed chiral centers. However, in our reactions, the exclusively *endo* addition of the nucleophile to the aldehyde leads to the production of only two diastereomers. It is presumably due to the steric hindrance of the C_{12}-methyl, which effectively blocks the approach from the *exo*-face and thus favors the attack of the electrophile from the *endo*-face of the enolate.[9] Additionally, the lone pair of electrons on the auxiliary nitrogen fuses the iminolactone into a boat conformation. However, it is very difficult to confirm the absolute configuration of the newly formed hydroxyl carbon directly from NMR spectral analysis. Therefore, these configurations were determined by hydrolysis of aldol adducts to the known amino acids (see below). Furthermore, the structures of the aldol products **2c′**, **3c′** (please see the Supporting Informa-

(6) For recent examples, see: (a) Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 9192–9193. (b) Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. *Angew. Chem.* **2004**, *116*, 900−902; *Angew. Chem. Int. Ed.* **2004**, *43*, 882−884. (c) Bourdon, L. H.; Fairfax, D. J.; Martin, G. S.; Mathison, C. J.; Zhichkin, P. *Tetrahedron: Asymmetry* **2004**, *15*, 3485–3487. (d) Makino, K.; Hiroki, Y.; Hamada, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5784–5785. (e) Makino, K.; Fujii, T.; Hamada, Y. *Tetrahedron Lett.* **2006**, *17*, 481–484. (f) Chrich, D.; Banerjee, A. *J. Org. Chem.* **2006**, *71*, 7106–7109.

(7) (a) Xu, P.-F.; Chen, Y.-S.; Lin, S.-I.; Lu, T.-J. *J. Org. Chem.* **2002**, *67*, 2309–2314. (b) Xu, P.-F.; Lu, T.-J. *J. Org. Chem.* **2003**, *68*, 658–661. (c) Li, S.; Hui, X.-P.; Yang, S.-B.; Jia, Z.-J.; Xu, P.-F.; Lu, T.-J. *Tetrahedron: Asymmetry* **2005**, *16*, 1729–1731. (d) Xu, P.-F.; Li, S.; Lu, T.-J.; Wu, C.-C.; Fan, B.; Golfis, G. *J. Org. Chem.* **2006**, *71*, 4364–4373. (e) Wang, P.-F.; Gao, P.; Xu, P.-F. *Synlett* **2006**, *7*, 1095–1099. (f) Zhang, H.-H.; Hu, X.-Q.; Wang, X.; Luo, Y.-C.; Xu, P.-F. *J. Org. Chem.* **2008**, *73*, 3634–3637. (g) Wang, H.-F.; Ma, G.-H.; Yang, S.-B.; Han, R.-G.; Xu, P.-F. *Tetrahedron: Asymmetry* **2008**, *19*, 1630–1635. From (1*R*)-(+)-camphor, we can prepare both **1a** and **1b** (1:1.59) and only need four steps with 55% overall yield. .

(8) For references to early work on asymmetric synthesis of β-hydroxy-α-amino acids through glycine enolates, see: (a) Belokon, Y. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Y. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsyryapkin, V. A.; Ryzhov, M. G.; Lysova, L. A.; Bakhmutov, V. I.; Belikov, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 4252–4259. (b) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761. (c) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843–3846.

(9) The theoretical explanation for the high stereoselectivity of substitution reactions of **1a** and **1b** with alkyl halides has been made by quantum chemistry study; see ref 6d.

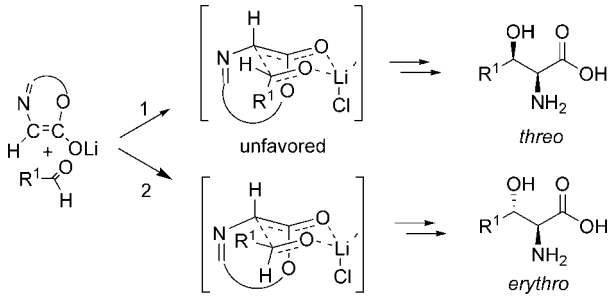


FIGURE 1. Proposed mechanism of the aldol reaction of **1a** with aliphatic aldehydes.

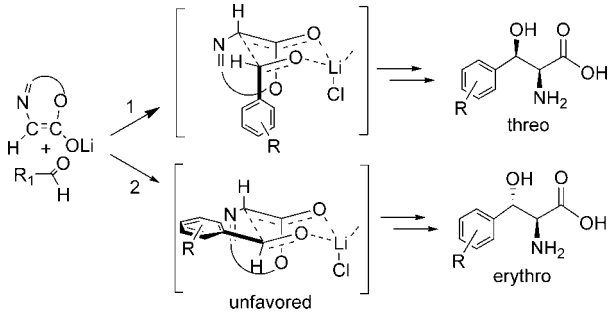


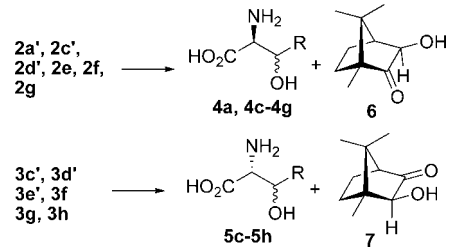
FIGURE 2. Proposed mechanism of the aldol reaction of **1a** with aromatic aldehydes.

tion), **2d′**, **2f**, **2h**, **3f**, **3g**, and **3i** were unambiguously ascertained via X-ray crystallography.[10]

It is noteworthy that the aldol reactions of aromatic aldehydes with **1a** produced predominantly *threo*-adducts, while reactions of aliphatic aldehydes gave exclusively *erythro*-adducts. Similarly, **1b** reacts with aromatic aldehydes to yield *threo*-adducts, while its reaction with aliphatic aldehydes gave *erythro*-adducts with good stereoselectivities. The reason for this selectivity pattern can be explained by the theory of Zimmerman and Denmark[11] (Figure 1), where pathway 2 details the orientation for *erythro*-adducts in the aldol reactions of aliphatic aldehydes with **1a**. In this case, the stereoselectivity comes from minimization of 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 2), the transition state in pathway 2 would enforce a $\pi-\pi$ interaction between the benzene ring and the π system of the iminolactone. As a result, the benzene ring can adjust to be 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 was carried out by heating in 6 N HCl at 80 °C for 3 h[12] to afford the corresponding β-hydroxy-α-amino acids in good yields with enantiomeric excess (Table 3). The configurations of the α-positions and β-positions of the β-hydroxy-α-amino acids are consistent with the stereochemistry assigned to the respective tricyclic iminolactone

TABLE 3. Hydrolysis of Aldol Products



entry	substrate	R	product	yield (%)	$[\alpha]^{20}_D$[a]	ee (%)
1	**2a′**	Me	**4a**	77	+8.9[b] (+8.7)	
2	**2c′**	*i*-propyl	**4c**	87	+20[b] (+22)	
3	**2d′**	Cy	**4d**	74	+33[c]	
4	**2e**	Ph	**4e**	65	−30[b,d] (−32.8)	99:1
5	**2f**	*o*-F-Ph	**4f**	70	−20[b,d] (−18.5)	99:1
6	**2g**	*o*-Cl-Ph	**4g**	76	−34[b,d]	99:1
7	**3c′**	*i*-propyl	**5c**	84	−20[c]	
8	**3d′**	*n*-hexyl	**5d**	81	−6.7[c]	
9	**3e′**	Cy	**5e**	76	−33[c], [d]	
10	**3f**	Ph	**5f**	80	+31[b,d] (+30.6)	99:1
11	**3g**	*o*-F-Ph	**5g**	83	+21[b,d] (+20.6)	99:1
12	**3h**	*o*-Cl-Ph	**5h**	81	+34[b,d]	99:1

[a] Literature values are in parentheses. [b] The optical rotations were recorded in H_2O solution. [c] The optical rotations were recorded in aqueous HCl. [d] Compounds **4e**, **4f**, **4g**, **5f**, **5g**, and **5h** were determined by HPLC analysis on a CR (+) column.

precursors. The structures of β-hydroxy-α-amino acids were further confirmed by comparison of their optical rotations and ^{1}H NMR data with those of the corresponding amino acids reported in the literature.[13] In addition, the chiral auxiliaries **6** and **7** were recovered in excellent yield. The recovered chiral auxiliaries **6** and **7** were recycled to prepare the tricyclic iminolactones **1a** and **1b**, which exhibited the same optical purity as that of the one derived from freshly synthesized compounds **6** and **7**.

The **20S** proteasome is essential for the turnover of cellular proteins and for removing damaged, misfolded, and mistranslated proteins in cells. It also plays a vital role in the turnover of many regulatory proteins that control cell growth and metabolism.[14] So, (+)-lactacystin may have a therapeutic use in animal models of myocardial infarction, stroke, asthma, and arthritis. (+)-Lactacystin's unusual structure and remarkable biological activity has caught the attention of many synthetic chemists. Many have used oxazoline **9** derived from hydroxyleucine as a key intermediate in their total synthesis, including Adams, Corey, and others.[15] Fortunately, we found that using our methodology we can prepare either (2*S*,3*S*)- or (2*R*,3*R*)-3-hydroxyleucine only with two steps from tricyclic iminolactone **1a** or **1b**. We can easily prepare *trans*-oxazoline **9** and the other three isomers. *trans*-Oxazoline **9** was frequently used in the synthesis of (+)-lactacystin, and it was envisaged based upon an asymmetric aldol reaction using a tricyclic iminolactone. The

(10) The X-ray structure of aldol products CCDC Nos. 266588 (**2c′**), 266589 (**3c′**), 221192 (**2d′**), 221193 (**2f**), 266590 (**3f**), 266591 (**3g**), 221191 (**2h**), and 266592 (**3i**) contain the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.ac.uk/conts/ retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K. Fax: (+44) 1223/336−033.

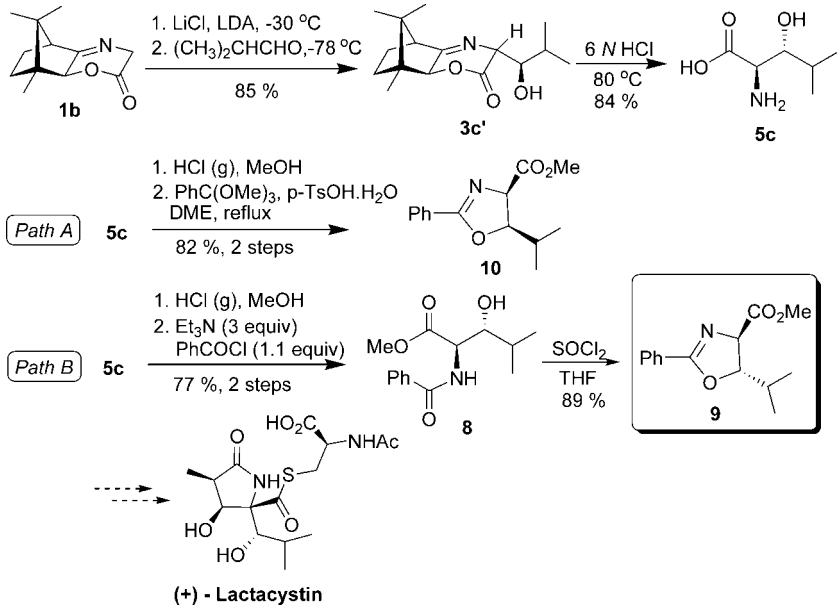
(11) (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8032–8034.

(12) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 2223–2227.

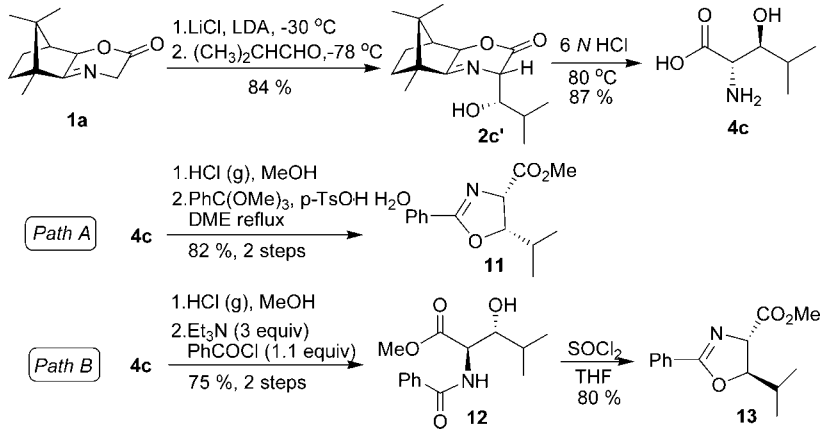
(13) (a) Sheehan, J. C.; Maeda, K.; Sen, A. K.; Stork, J. A. *J. Am. Chem. Soc.* **1962**, *84*, 1303–1305. (b) Yasuo, A.; Naohiko, Y.; Tetsuo, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 326–330. (c) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553–5562. (d) Blaser, D.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1067–1078. (e) Soloshonok, V. A.; Kukhar, V. P.; Galushko, S. V.; Svistunova, N.; Avilov, D. V.; Kuzmina, N. A.; Raevski, N. I.; Struchkov, Y. T.; Pysarevsky, A. P.; Belokon, Y. N. *J. Chem. Soc., Perkin Trans.* **1993**, 3143–3155. (f) Hale, K. J.; Manaviazar, S.; Delisser, V. M. *Tetrahedron* **1994**, *50*, 9181–9188. (g) Alker, D.; Hamblett, G.; Harwood, L. M.; Robertson, S. M.; Watkin, D. J.; Williams, C. E. *Tetrahedron* **1998**, *54*, 6089–6098. (h) Davis, F. A.; Srirajan, V.; Fanelli, D. L.; Portonovo, P. *J. Org. Chem.* **2000**, *65*, 7663–7666.

(14) (a) Rock, K. L.; Gramm, C.; Rothstein, L.; Clark, K.; Stein, R.; Dick, L.; Hwang, D.; Goldberg, A. L. *Cell* **1994**, *78*, 761–771. (b) King, R. W.; Deshaies, R. J.; Peters, J. M.; Kirschner, M. W. *Science* **1996**, *274*, 1652–1659.

SCHEME 1. Synthesis of *trans*-Oxazoline 9 and Its Diastereoisomer 10



SCHEME 2. Synthesis of the Other Two Isomers of *trans*-Oxazoline 9



synthesis of *trans*-oxazoline **9** and its diastereoisomer **10** is outlined in Scheme 1. Treatment of iminolactone **1b** with LDA at −30 °C generated the corresponding anions that reacted with isobutyraldehyde at −78 °C to form compound **3c′** with good yields and diastereoselectivity. Subsequent hydrolysis of compound **3c′** in a 6 N HCl solution at 80 °C for 3 h afforded the corresponding (2*R*,3*R*)-3-hydroxyleucine **5c**. Esterification of **5c** into its methyl ester through acidic methanolysis proceeded in quantitative yield. The resultant product was then N-acylated with benzoyl chloride in methanol at 0 °C to form the amide **8**, which underwent cyclization to oxazoline **9** via reaction with 1.5 equiv of thionyl chloride. Syntheses of the other two isomers of oxazoline **9** were accomplished only by using the corresponding tricyclic iminolactone **1a** as shown in Scheme 2.

Conclusion

In summary, we have developed a novel and practical method for the preparation of enantioenriched β-hydroxy-α-amino acids from inexpensive and readily available (1*R*)-(+)-camphor. The transformations, which occur via the coupling of aldehydes with tricyclic iminolactones **1a** and **1b**, proceed with good diastereoselectivity and yield to afford the corresponding aldol products. Additionally, the chiral auxiliaries (**6** and **7**) can be recovered in high yield and preserve their stereochemical integrity throughout the reaction sequence. Moreover, a stereoselective rule can be deduced as: (1) For tricyclic iminolactone **1a**, the *threo*-isomers are the major products after the aldol reactions with aromatic aldehydes, and the adducts have *S*,*R*-configuration, while the *erythro*-isomers are the major products in the reactions of aliphatic aldehydes and the adducts have *S*,*S*-configuration. (2) For tricyclic iminolactone **1b**, the adducts of tricyclic iminolactone **1b** with aromatic aldehydes have *R*,*S*-configuration, and the adducts of tricyclic iminolactone **1b** with aliphatic aldehydes have *R*,*R*-configuration. Therefore, we can control the configuration of the β-position for new β-hydroxy-α-amino acids using this rule. Application of this method to total synthesis of several natural products, such as sphingofungins, polyoxins, lactacystin, will be reported in due course.

Experimental Section

General Procedure for Aldol Reaction of Iminolactone and Aldehydes: Preparation of iminolactones **1a** and **1b** is described

(15) (a) Sunazuka, T.; Nagamitsu, T.; Matsuzaki, K.; Tanaka, H.; Omura, S. *J. Am. Chem. Soc.* **1993**, *115*, 5302–5302. (b) Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith, A. B, III. *J. Am. Chem. Soc.* **1996**, *118*, 3584–3590. (c) McCormack, T. A.; Adams, J.; Plamondon, L. *J. Am. Chem. Soc.* **1999**, *121*, 9967–9976. (d) Saravanan, P.; Corey, E. J. *J. Org. Chem.* **2003**, *68*, 2760–2764. (e) Panek, J. S.; Masse, C. E. *Angew. Chem.* **1999**, *111*, 1161−1163; *Angew. Chem. Int. Ed.* **1999**, *38*, 1093−1095.

in the literature.[7] Lithium chloride (383 mg, 9 mmol, 6 equiv) was added to a dry 50 mL long-neck flask under argon. Diisopropylamine (0.234 mL, 1.65 mmol, 1.1 equiv) was added to dry THF (8 mL) in a long-neck flask. After the solution was cooled to −30 °C, *n*-BuLi (2.8 M, 0.589 mL, 1.65 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at −30 °C for 30 min. Tricyclic iminolactone (310 mg, 1.5 mmol) in dry THF (10 mL) was added dropwise over a period of 10 min into the above freshly prepared LDA solution at −30 °C, and then the reaction mixture was subsequently cooled to −78 °C and stirring was continued for 30 min followed by the addition of the solution of aldehyde (1.8 mmol) in dry THF (10 mL) over a period of 10 min. The well-stirred reaction was kept at −78 °C for another 1−12 h (after TLC analysis showed the reaction was complete). Saturated NH_4Cl (1 mL) solution was added to the mixture to quench the reaction. The reaction was warmed up to rt; the solvent was removed under reduced pressure, and the residue was diluted with water and extracted with ethyl acetate (3 × 15 mL). The combined organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated to give the crude product. The crude product was purified by column chromatography to yield desired compounds.

(1*S*,2*R*,5*S*,8*R*,1′*S*)-5-(1′-Hydroxyethyl)-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (2a′): White solid (320 mg, 85%); $[\alpha]^{20}_D$ +52 (*c* 1.61, $CHCl_3$); mp 139−141 °C; IR (KBr) 3354 (s), 2990 (m), 1745 (s), 1702 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.43 (d, *J* = 4.4 Hz, 1H), 4.18−4.17 (m, 1H), 2.20 (d, *J* = 4.8 Hz, 1H), 2.10−2.02 (m, 2H), 1.81−1.74 (m, 1H), 1.66−1.59 (m, 1H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.41−1.35 (m, 2H), 1.07 (s, 3H), 0.97 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 169.8, 80.1, 69.4, 68.2, 52.9, 48.4, 47.7, 29.3, 25.9, 21.8, 20.1, 19.5, 10.1; HRMS (ESI) calcd for $C_{14}H_{22}NO_3$ [M + H]$^+$ 252.1597, found 252.1594.

(1*S*,2*R*,5*S*,8*R*,1′*R*)-5-(1′-Hydroxy-*o*-fluorobenzyl)-8,11,11-trimethyl-3-oxa-6-azatricyclo [6.2.1.0^{2,7}]undec-6-en-4-one (2f): White solid (372 mg, 75%); $[\alpha]^{20}_D$ −33 (*c* 1.24, $CHCl_3$); mp 138−140 °C; IR (KBr) 3194 (b), 2990 (m), 1740 (s), 1690 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.43 (m, 1H), 7.33−7.26 (m, 1H), 7.19−7.15 (m, 1H), 7.05−7.00 (m, 1H), 5.63 (d, *J* = 4 Hz, 1H), 4.82 (d, *J* = 4.4 Hz, 1H), 4.30 (s, 1H), 3.06 (s, 1H), 2.13 (d, *J* = 4.4 Hz, 1H), 2.04−1.97 (m, 1H), 1.78−1.71 (m, 1H), 1.62−1.55 (m, 1H), 1.27−1.21 (m, 1H), 1.00 (s, 3H), 0.93 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 170.3, 129.9, 128.1, 127.0, 124.4, 115.4, 115.2, 79.8, 69.4, 66.9, 53.1, 48.2, 47.7, 29.3, 26.0, 20.1, 19.5, 10.1; HRMS (ESI) calcd for $C_{19}H_{23}FNO_3$ [M + H]$^+$ 332.1656, found 332.1660.

(1*R*,2*S*,5*R*,8*S*,1′*R*)-5-(1′-Hydroxyethyl)-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (3a′): Oil (237 mg, 63%); IR (KBr) 3385 (s), 2964 (m), 1743 (s), 1704 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (s, 1H), 4.38 (d, *J* = 4.4 Hz, 1H), 4.16 (m, 1H), 2.43 (d, *J* = 4.4 Hz, 1H), 2.05−1.98 (m, 1H), 1.92−1.87 (m, 1H), 1.63−1.57 (m, 1H), 1.45 (d, *J* = 6.4 Hz, 3H), 1.42−1.36 (m, 1H), 1.05 (s, 3H), 0.97 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 169.5, 82.0, 69.2, 68.0, 53.9, 49.5, 48.2, 34.5, 21.8, 21.4, 20.0, 19.3, 9.7; HRMS (ESI) calcd for $C_{14}H_{22}NO_3$ [M + H]$^+$ 252.1594, found 252.1588.

(1*R*,2*S*,5*R*,8*S*,1′*S*)-5-(1′-Hydroxybenzyl)-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (3f): White solid (389 mg, 83%); $[\alpha]^{20}_D$ +93 (*c* 2.52, CH_2Cl_2); mp 152−153 °C; IR (KBr) 3245 (s), 2960 (s), 1744 (s), 1697 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.32 (m, 3H), 7.28−7.26 (m, 2H), 5.23 (t, *J* = 4.4 Hz, 1H), 4.70 (d, *J* = 3.6 Hz, 1H), 3.59 (s, 1H), 3.40 (d, *J* = 4.8 Hz, 1H), 2.32 (d, *J* = 4.4 Hz, 1H), 1.96−1.88 (m, 1H), 1.80−1.72 (m, 1H), 151−1.45 (m, 1H), 1.12−1.03 (m, 1H), 0.94 (s, 3H), 0.89 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 170.7, 139.8, 128.42, 128.40, 126.3, 81.7, 75.1, 67.1, 53.9, 49.1, 48.0, 34.5, 21.3, 19.8, 19.1, 9.5; HRMS (ESI) calcd for $C_{19}H_{24}NO_3$ [M + H]$^+$ 314.1751, found 314.1759.

General Procedure for Hydrolysis of Aldol Products: The aldol product (1.2 mmol) was dissolved in 6 N HCl (3 mL) in a sealed tube with a Teflon screw cap and heated at 80 °C for 3 h. After cooling to rt, water (5 mL) was added and the mixture was extracted with diethyl ether (3 × 5 mL). The chiral auxiliary **6** or **7** was recovered when the ether layer was concentrated. The aqueous layer was evaporated under reduced pressure, and the residue was dissolved in EtOH (5 mL). Propylene oxide (3 mL) was then added and stirred at rt for 30 min during which time white solids precipitated. The precipitate was collected by filtration, washed successively with cold EtOH (2 × 2 mL) and Et_2O (1 × 4 mL), and air-dried to give the desired free β-hydroxy-α-amino acids.

(2*S*,3*S*)-2-Amino-3-hydroxybutanoic Acid (4a): White solid (97 mg, 77%); $[\alpha]^{20}_D$ +8 (*c* 1.1, H_2O); mp 264−266 °C; ^{1}H NMR (400 MHz, D_2O) δ 4.37 (dd, *J* = 6.4, 4 Hz, 1H), 3.84 (d, *J* = 4 Hz, 1H), 1.20 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, D_2O) δ 171.8, 65.3, 59.6, 16.1.

(2*R*,3*R*)-3-Hydroxyleucine (5c): White solid (148 mg, 84%); $[\alpha]^{20}_D$ −20 (*c* 1.26, H_2O); mp 187 °C (dec); ^{1}H NMR (400 MHz, D_2O) δ 3.92 (d, *J* = 3.2 Hz, 1H), 3.53 (dd, *J* = 9.2, 3.2 Hz, 1H), 1.94 (m, 1H), 0.98 (m, 6H); ^{13}C NMR (100 MHz, D_2O) δ 171.7, 76.1, 57.1, 30.2, 18.5.

Methyl (4*R*,5*S*)-5-Isopropyl-2-phenyl-4,5-dihydrooxazole-4-carboxylate 9: A solution of amide **8** (398 mg, 1.5 mmol) in THF (15 mL) was cooled to 0 °C. Thionyl chloride (0.16 mL, 2.25 mmol) was added to the solution at 0 °C. The reaction mixture was warmed gradually to 25 °C. After stirring 12 h, the reaction mixture was heated to 60 °C for 1.5 h. Then the reaction mixture was cooled to 0 °C and quenched with saturated $NaHCO_3$ (15 mL). The aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic phase was washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (8:1 petrol ether/EtOAc) afforded **9** (330 mg, 89%) as light yellow oil: $[\alpha]^{20}_D$ −113 (*c* 0.04, $CHCl_3$); IR υ_{max} (film) 2922, 1741, 1646, 1449, 1385; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.4 Hz,3H), 1.03 (d, *J* = 6.4 Hz, 3H), 1.94−1.99 (m, 1H), 3.81 (s, 3H), 4.57 (d, *J* = 7.2 Hz, 1H), 4.68 (apparent t, *J* = 6.8 Hz, 1H), 7.40−7.43 (m, 2H), 7.48−7.52 (m, 1H), 7.98−8.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 17.4, 32.4, 52.6, 71.3, 87.2, 127.2, 128.3, 128.5, 131.7, 165.7, 172.0; HRMS (ESI) calcd for $C_{14}H_{18}NO_3$ [M + H]$^+$ 248.1281, found 247.1283.

Methyl (4*R*,5*R*)-5-Isopropyl-2-phenyl-4,5-dihydrooxazole-4-carboxylate 13: Following the procedure described for **9**, the only change was (2*R*,3*R*)-3-hydroxyleucine **5c** into (2*S*,3*S*)-3-hydroxyleucine **4c**: Colorless oil; $[\alpha]^{20}_D$ + 113 (*c* 0.04, $CHCl_3$); IR υ_{max} (film) 2923, 1733, 1636, 1439, 1383; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.92−1.97 (m, 1H), 3.79 (s, 3H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.66 (apparent t, *J* = 6.8 Hz, 1H), 7.38−7.41 (m, 2H), 7.46−7.50 (m, 1H), 7.97−7.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 17.3, 32.3, 52.5, 71.2, 87.1, 127.1, 128.2, 128.5, 131.7, 165.7, 172.0; HRMS (ESI) calcd for $C_{14}H_{18}NO_3$ [M + H]$^+$ 248.1281, found 247.1286.

Acknowledgment. We are grateful for the financial support of the National Natural Science Foundation of China (NSFC, 20572039, 20772051), the Program for NCET-05-0880, and the Doctoral Funds from Chinese Ministry of Education of P.R. China. We also thank Professor T.-J. Lu for his support.

Supporting Information Available: General methods for the synthesis of racemic β-hydroxy-α-amino acids, spectra data for compounds **2d′**, **2e′**, **2g**, **2h**, **3a**, **3d′**, **3e′**, **3h**, **3i**, **4e**−**4g**, **5e**−**5h**, and **11**−**13**, as well as copies of ^{1}H and ^{13}C NMR spectra and HPLC results. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8023973