An Enantioselective Formal Synthesis of (+)-(*R*)-α-Lipoic Acid by an L-Proline-Catalyzed Aldol Reaction

Shilei Zhang,[a] Xiaobei Chen,[b] Jiangang Zhang,[b] Wei Wang,*[a,c] Wenhu Duan*[a,b]

[a] Department of Medicinal Chemistry, School of Pharmacy, East China University of Science & Technology, Shanghai 200237, P. R. of China

[b] Shanghai Institute of Materia Medica, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Graduate School of the Chinese Academy of Sciences, Shanghai 201203, P. R. of China

[c] Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, NM 87131-0001, USA
Fax +1(505)2772609; E-mail: wwang@unm.edu

Received 12 September 2007; revised 7 November 2007

Abstract: An efficient, highly stereocontrolled formal synthesis of (+)-(*R*)-α-lipoic acid was achieved, which utilizes an L-proline-catalyzed highly enantio- and diastereoselective cross-aldol reaction as the key step.

Key words: aldehyde, aldol reaction, ketone, lipoic acid, proline

The significance of (+)-(*R*)-α-lipoic acid is manifested by its broad spectrum of biological activity (Figure 1). It is an important growth factor, acting as a coenzyme in many biological processes found in animal tissues, plants, and microorganisms.[1] In addition, it serves as an effective scavenger for reactive oxygen species (ROS),[2] which have been implicated in a number of pathological conditions such as carcinogenesis, inflammation, ischemia-reperfusion injury, and aging. Despite the fact that lipoic acid is often used in its racemic form since the *S*-enantiomer shows tolerable side effects, it has been reported that naturally occurring (+)-(*R*)-α-lipoic acid (**1**) and its derivatives possess more potent anti-HIV[3] and antitumor[4] activities than its *S*-counterpart and analogues. Accordingly, the development of enantioselective methods for the preparation of enantiomerically pure lipoic acid is of particular interest from the standpoint of medicinal and organic chemistry.[5–8] Examination of the reported asymmetric synthetic methods reveals that, generally, they rely on using chiral auxiliaries or precursors,[6] and enzymatic reactions or kinetic resolutions;[7] asymmetric synthesis catalyzed by organometallic reagents also has been described.[8] In this communication, we wish to report the first organocatalytic enantioselective approach to the formal synthesis of (+)-(*R*)-α-lipoic acid by using an L-proline-catalyzed cross-aldol reaction as the key step.

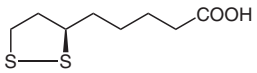
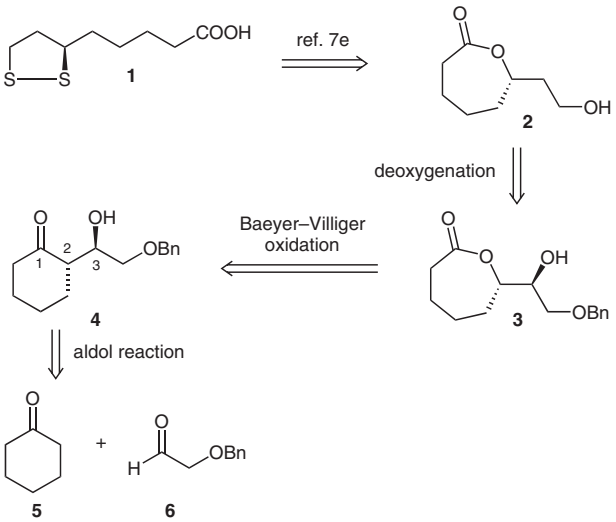


Figure 1 (+)-(*R*)-α-Lipoic acid (**1**)

In recent years, small-organic-molecule-based organocatalysis has received considerable interest as a result of the operational simplicity and environmental friendliness of the technology.[9–12] Organocatalyzed asymmetric processes are particularly attractive for the synthesis of biologically interesting chiral molecules and clinically useful pharmaceuticals since they eliminate the use of toxic transition metals. Recently, we have successfully developed a novel approach to the efficient total synthesis of the potent histone deacetylases (HDACs) inhibitor, natural product (+)-trichostatin A by employing an L-proline-catalyzed cross-aldol reaction as the key step.[12a] In our continuing effort to explore powerful asymmetric aldol reactions for the synthesis of biologically significant molecules, herein we described a strategy, as outlined in Scheme 1, for the formal total synthesis of (+)-(*R*)-α-lipoic acid (**1**) from readily available starting materials.



Scheme 1 Retrosynthetic analysis of (+)-(*R*)-α-lipoic acid (**1**)

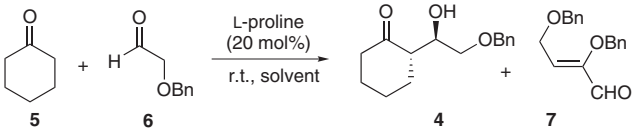
We envisioned that the target molecule **1** could be attained from precursor lactone **2** since its racemic form has been synthesized by Segre and co-workers (Scheme 1).[5a] This disconnection raised a synthetic challenge related to the installation of the stereogenic center in the lactone. We were intrigued by the possibility offered by L-proline-promoted cross-aldol reaction between ketone **5** and alde-

SYNTHESIS 2008, No. 3, pp 0383–0386
Advanced online publication: 10.01.2008
DOI: 10.1055/s-2008-1032022; Art ID: M06507SS

hyde **6** to form chiral aldol adduct **4**. Regioselective Baeyer–Villiger oxidation of ketone **4** would give rise to lactone intermediate **3**, which could be reduced to **2**.[5a] As demonstrated, the tactics enabled us to synthesize efficiently the chiral compound **2** in five steps from readily available achiral compounds.

The synthesis started with commercially available compounds cyclohexanone (**5**) and (benzyloxy)acetaldehyde (**6**) (Scheme 2). Despite the fact that numerous organocatalyzed asymmetric aldol reactions have been developed,[10–12] organocatalytic cross-aldol reactions between cyclohexanone (**5**) and aldehyde **6** created a significant challenge since the highly active aldehyde **6** readily undergoes self-aldol reaction to give the product **7**. As shown in Scheme 2, under the same reaction conditions that we used previously in *N*,*N*-dimethylformamide,[12a] the desired compound **4** was obtained as the major product, but in low yield (26%) together with a significant amount of **7** (7%). After considerable experimentation, we were delighted to find that the use of cyclohexanone (**5**) as a reaction medium led to a dramatic improvement in the yield of the cross-aldol reaction **4** (65%) and, at the same time, the formation of side product **7** was minimized. Notably, an excellent level of enantio- (>95% ee) and diastereoselectivity (29:1 dr) was observed based on chiral HPLC and ^{1}H NMR analysis.

With compound **4** in hand, we completed the synthesis of key intermediate **2** in four steps in a straightforward manner (Scheme 3). β-Hydroxy ketone **4** was regioselectively transformed exclusively into lactone **3** through a Baeyer–Villiger oxidation with 3-chloroperoxybenzoic acid in 86% yield.[13] Treatment of **3** with iodine/triphenylphosphine/imidazole furnished iodide **8**.[14] Deiodination and debenzylation were achieved in a one-pot reaction in



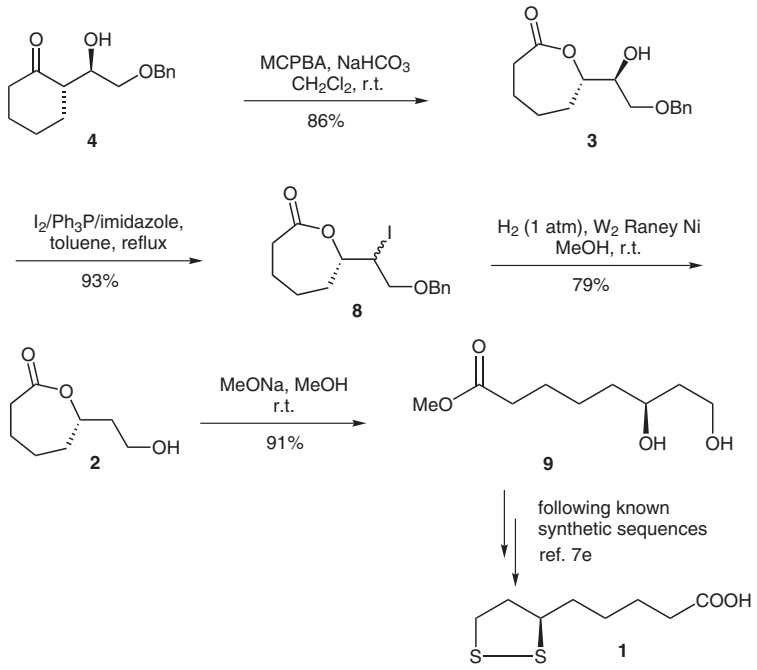
5 6 4 7

Solvent	Yield of **4** (%)	Yield of **7** (%)
DMF	26	7
5	65	–

Scheme 2 Optimization of L-proline-catalyzed cross-aldol reactions: synthesis of β-hydroxy ketone **4**

methanol to afford compound **2** by reaction of **8** under a hydrogen atmosphere in the presence of W2 Raney nickel for 24 hours.[8f] It was interesting to find that the reaction solvent played a significant role in the conversion. When the hydrogenation reaction was carried out in ethanol instead of methanol, the reaction was not clean. Finally, the treatment of **2** in sodium methoxide in methanol afforded known chiral compound **9** in 91% yield. The analytical data of the synthesized substance **9** is identical with those reported,[7g] thus confirming the absolute *S*-configuration. Following known synthetic sequences, compound **2** could be converted into the target (+)-(*R*)-α-lipoic acid (**1**).[7e]

In conclusion, we have developed an approach to the efficient synthesis of key intermediate **9**, which can led to the preparation of (+)-(*R*)-α-lipoic acid, in six steps from readily available achiral starting materials. In the synthesis, an L-proline-catalyzed highly enantio- and stereoselective cross-aldol reaction serves as the key step for the construction of the stereogenic centers. The general strategy can be explored for the synthesis of *S*-enantiomer of lipoic acid and its analogues.



4 3 8 2 9 1

Scheme 3 Synthesis of key intermediate lactone **2**

Commercial reagents were used as received unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz NMR, respectively, with TMS as reference.

(*S*)-2-[(*R*)-2-(Benzyloxy)-1-hydroxyethyl]cyclohexanone (4)
To a soln of **6** (500 mg, 3.3 mmol) in cyclohexanone (10 mL) was added L-proline (80 mg, 0.70 mmol) and the mixture was stirred at r.t. for 16 h. Cyclohexanone was removed under reduced pressure at 60 °C. Flash chromatography of the residue (silica gel, petroleum ether–EtOAc, 5:1) afforded **4** (540 mg, 65%) as a colorless oil; dr 29:1 (^{1}H NMR); 97% ee [HPLC (Chiralcel OD-H, *i*-PrOH–hexane, 10:90, flow rate 1.0 mL/min, λ = 220 nm): t_R = 11.30 (major), 13.10 min (minor)].

$[\alpha]_D^{23}$ –5.5 (*c* 0.95, $CHCl_3$).

IR (KBr): 3460, 3030 2935, 2864, 1705, 1497, 1452, 1365, 1311, 1101, 1028, 739, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H), 4.63–4.49 (m, 2 H), 3.93 (m, 1 H), 3.63–3.48 (m, 3 H), 2.70 (m, 1 H), 2.42–2.23 (m, 2 H), 2.09–2.00 (m, 2 H), 1.86 (m, 1 H), 1.75–1.59 (m, 2 H), 1.52–1.39 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.0, 138.0, 128.2, 127.6, 127.5, 73.3, 71.1, 70.8, 52.4, 42.5, 30.1, 27.6, 24.6.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{20}O_3$: 248.1412; found: 248.1408.

(*S*)-7-[(*S*)-2-(Benzyloxy)-1-hydroxyethyl]oxepan-2-one (3)
To a soln of **4** (990 mg, 4.0 mmol) in CH_2Cl_2 (10 mL) was added $NaHCO_3$ (1.01 g, 12 mmol) and MCPBA (85%, 1.63 g, 8.0 mmol) and the mixture was stirred at r.t. for 5 h. The mixture was then filtered, and the filtrate was washed sequentially with sat. aq $NaHSO_3$, H_2O, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, petroleum ether–EtOAc, 5:1 to 1:1) afforded **3** (910 mg, 86%) as a colorless oil.

$[\alpha]_D^{21}$ +23.8 (*c* 2.04, $CHCl_3$).

IR (KBr): 3439, 2933, 2864, 1713, 1452, 1348, 1329, 1277, 1257, 1180, 1095, 1059, 1016, 741, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H), 4.54 (m, 2 H), 4.39 (m, 1 H), 3.83 (m, 1 H), 3.59 (m, 2 H), 2.63 (m, 2 H), 2.05–1.85 (m, 3 H) 1.73–1.48 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 137.7, 128.4, 127.8, 127.7, 79.9, 73.4, 72.5, 70.1, 34.6, 30.3, 27.9, 22.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1373.

(*S*)-7-(1-Hydroxy-2-iodoethyl)oxepan-2-one (8)
To a soln of **3** (128 mg, 0.485 mmol) in toluene (8 mL) was added imidazole (133 mg, 1.96 mmol), Ph_3P (390 mg, 1.49 mmol), and I_2 (250 mg, 0.98 mmol) and the mixture was stirred at reflux for 5 h. The resulting mixture was concentrated under reduced pressure. Flash chromatography of the residue (silica gel, petroleum ether–EtOAc, 10:1 to 5:1) afforded **8** (170 mg, 93%) as a colorless oil.

$[\alpha]_D^{21}$ –5.2 (*c* 1.77, $CHCl_3$).

IR (KBr): 3030, 2933, 2862, 1738, 1452, 1254, 1178, 1094, 1013, 741, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5 H), 4.56 (m, 2 H), 4.34 (m, 2 H), 3.88 (m, 1 H), 3.73 (m, 1 H), 2.65 (m, 2 H), 2.17 (m, 1 H) 1.97 (m, 2 H), 1.75–1.53 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 137.4, 128.5, 127.9, 127.7, 79.4, 73.0, 71.9, 34.7, 33.5, 33.2, 27.6, 22.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{19}INaO_3$: 397.0277; found: 397.0246.

(*S*)-7-(2-Hydroxyethyl)oxepan-2-one (2)
To a soln of **8** (94 mg, 0.25 mmol) in MeOH (4 mL) was added W2 Raney Ni (0.3 g). The resulting mixture was then stirred under an H_2 atmosphere for 8 h. The mixture was filtered and washed with MeOH. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica gel, petroleum ether–EtOAc, 1:1) to afford **2** (31 mg, 79%) as a colorless oil.

$[\alpha]_D^{23}$ +61.1 (*c* 1.28, $CHCl_3$).

IR (KBr): 3417, 2933, 2864, 1722, 1444, 1348, 1329, 1286, 1257, 1178, 1146, 1053, 1016, 852, 694, 563 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.52 (m, 1 H), 3.81 (m, 2 H), 3.60 (s, 1 H), 2.67 (m, 2 H), 1.95 (m, 4 H), 1.82 (m, 1 H), 1.64 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2, 77.0, 58.3, 38.8, 34.8, 34.6, 28.1, 22.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_8H_{14}NaO_3$: 181.0841; found: 181.0838.

Methyl (*S*)-6,8-Dihydroxyoctanoate (9)
To a soln of **2** (10 mg, 0.063 mmol) in MeOH (0.5 mL) was added MeONa in MeOH [3 drops; Na (0.3 g) dissolved in MeOH (5 mL)] and the mixture was stirred at r.t. for 0.5 h. The resulting mixture was quenched with H_2O and extracted with EtOAc. The organic layer was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, EtOAc) afforded **9** (11 mg, 91%) as a colorless oil.

$[\alpha]_D^{23}$ –3.7 (*c* 0.65, $CHCl_3$) [Lit.[7g] $[\alpha]_D^{25}$ –3.8 ($CHCl_3$)].

IR (KBr): 3363, 2943, 1736, 1442, 1412, 1379, 1225, 1173, 1055, 1020, 989, 953, 868, 663 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.93–3.78 (m, 3 H), 3.67 (s, 3 H), 2.81–2.69 (br, 2 H), 2.34 (t, *J* = 7.4 Hz, 2 H), 1.73–1.60 (m, 4 H), 1.56–1.30 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 71.5, 61.4, 51.5, 38.1, 37.2, 33.9, 24.9, 24.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{18}NaO_4$: 213.1103; found: 213.1093.

Acknowledgment

This work was supported by Shanghai Basic Research Project from the Shanghai Science and Technology Commission (Grants 06JC14080) and start-up funding from School of Pharmacy, East China University of Science & Technology.

References

(1) (a) Sigel, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 389. (b) Yadav, J. S.; Mysorekar, S. V.; Garyali, K. *J. Sci. Ind. Res.* **1990**, *49*, 400; and references cited therein.
(2) Packer, L.; Tritschler, H. J.; Wessel, K. *Free Rad. Biol. Med.* **1997**, *22*, 359.
(3) Baur, A.; Harrer, T.; Peukert, M.; Jahn, G.; Kalden, J. R.; Fleckenstein, B. *Klin. Wochenschr.* **1991**, *69*, 722; *Chem. Abstr.* **1992**, *116*, 207360.
(4) Bingham, P. M.; Zachar, Z. WO 0024734, **2000**; *Chem. Abstr.* **2000**, *132*, 3081921.
(5) For examples of racemic syntheses of lipoic acid, see: (a) Segre, A.; Viterbo, R.; Parisi, G. *J. Am. Chem. Soc.* **1957**, *79*, 3503. (b) Tsuji, J.; Yasuda, H.; Mandai, T. *J. Org. Chem.* **1978**, *43*, 3606. (c) Menon, R. B.; Kumar, M. A.; Ravindranathan, T. *Tetrahedron Lett.* **1987**, *28*, 5313. (d) Crevisy, C.; Herbage, B.; Marrel, M.-L.; Toupet, L.; Gree, R. *Eur. J. Org. Chem.* **1998**, 1949. (e) Chavan, S. P.;

Shivsankar, K.; Pasupathy, K. *Synthesis* **2005**, 1297.
(6) For examples of using chiral auxiliaries or precursors for asymmetric syntheses of lipoic acid, see: (a) Brookes, M. H.; Golding, B. T.; Howes, D. A.; Hudson, A. T. *J. Chem. Soc., Chem. Commun.* **1983**, 1051. (b) Elliott, J. D.; Steele, J.; Johnson, W. S. *Tetrahedron Lett.* **1985**, *26*, 2535. (c) Rama Rao, A. V.; Mysorekar, S. V.; Gurjar, M. K.; Yadav, J. S. *Tetrahedron Lett.* **1987**, *28*, 2183. (d) Brookes, M. H.; Golding, B. T.; Hudson, A. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 9. (e) Silks, L. A. III; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2495.
(7) For examples of enzymatic reactions for asymmetric syntheses of lipoic acid, see: (a) Brooks, D. W.; Kellogg, R. P.; Cooper, C. S. *J. Org. Chem.* **1987**, *52*, 192. (b) Gopalan, A. S.; Jacobs, H. K. *Tetrahedron Lett.* **1989**, *30*, 5705. (c) Dasaradhi, L.; Fadnavis, N. W.; Bhalerao, U. T. *J. Chem. Soc., Chem. Commun.* **1990**, 729. (d) Gopalan, A. S.; Jacobs, H. K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1897. (e) Adger, B.; Bes, M. T.; Grogan, G.; McCague, R.; Pedragosa-Moreau, S.; Roberts, S. M.; Villa, R.; Wan, P. W. H.; Willetts, A. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1563. (f) Laxmi, Y. R. S.; Lyengar, D. S. *Synthesis* **1996**, 594. (g) Bezbarua, M. S.; Saikia, A. K.; Barua, N. C.; Kalita, D.; Ghosh, A. C. *Synthesis* **1996**, 1289. (h) Adger, B.; Bes, M. T.; Grogan, G.; McCague, R.; Pedragosa-Moreau, S.; Roberts, S. M.; Villa, R.; Wan, P. W. H.; Willetts, A. J. *Bioorg. Med. Chem.* **1997**, *5*, 253. (i) Fadnavis, N. W.; Babu, R. L.; Vadivel, S. K.; Deshpande, A. A.; Bhalerao, U. T. *Tetrahedron: Asymmetry* **1998**, *9*, 4109.
(8) For examples of asymmetric syntheses of lipoic acid catalyzed by organometallic reagents, see: (a) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1986**, 1408. (b) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1615. (c) Zimmer, R.; Hain, U.; Berndt, M.; Gewald, R.; Reissig, H.-U. *Tetrahedron: Asymmetry* **2000**, *11*, 879. (d) Upadhya, T. T.; Nikalje, M. D.; Sudalai, A. *Tetrahedron Lett.* **2001**, *42*, 4891. (e) Zimmer, R.; Peritz, A.; Czerwonka, R.; Schefzig, L.; Reissig, H.-U. *Eur. J. Org. Chem.* **2002**, 3419. (f) Chavan, S. P.; Praveen, C.; Ramakrishna, G.; Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 6027. (g) Bose, D. S.; Fatima, L.; Rajender, S. *Synthesis* **2006**, 1863.
(9) For selected recent reviews of organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (c) List, B. *Tetrahedron* **2002**, *58*, 5573. (d) Notz, W.; Tanaka, F.; Barbas, C. F. III *Acc. Chem. Res.* **2004**, *37*, 580. (e) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (f) Special issue on Asymmetric Organocatalysis: *Acc. Chem. Res.* **2004**, *37*, 487.
(10) For L-proline-promoted aldol reactions, see: (a) List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (c) Enders, D.; Grondal, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1210. (d) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1343. (e) Pan, Q.; Zou, B.; Wang, Y.; Ma, D. *Org. Lett.* **2004**, *6*, 1009. (f) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752. (g) Suri, J. T.; Ramachary, D. B.; Barbas, C. F. III *Org. Lett.* **2005**, *7*, 1383.
(11) For selected examples of aldol reactions catalyzed by proline derivatives, see: (a) Mase, N.; Tanaka, F.; Barbas, C. F. III *Angew. Chem. Int. Ed.* **2004**, *43*, 2420. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. III *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167. (d) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262. (e) Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6722. (f) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101. (g) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 1983. (h) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84. (i) Wang, W.; Li, H.; Wang, J. *Tetrahedron Lett.* **2005**, *46*, 5077. (j) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 958. (k) Dziedzic, P.; Zou, W.; Hafren, J.; Córdova, A. *Org. Biomol. Chem.* **2006**, *4*, 38. (l) Chimni, S. S.; Mahajan, D.; Babu, V. V. S. *Tetrahedron Lett.* **2005**, *46*, 5617. (m) Bellis, E.; Vasilatou, K.; Kokotos, G. *Synthesis* **2005**, 2407. (n) Chen, J.-R.; Lu, H.-H.; Li, X.-Y.; Cheng, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543.
(12) (a) Zhang, S.-L.; Duan, W.-H.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 1228; and other examples using L-proline-catalyzed aldol reactions in natural product synthesis for total synthesis. (b) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696. (c) Pihko, P. M.; Erkkila, A. *Tetrahedron Lett.* **2003**, *44*, 7607.
(13) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216.
(14) Akita, H.; Chen, C. Y.; Kato, K. *Tetrahedron* **1998**, *54*, 11011.