Efficient Enantioselective Synthesis of α-Hydroxy-β-amino Acids Using the Claisen and Curtius Rearrangements

Doo Young Jung, Sol Kang, Sukbok Chang,* Yong Hae Kim*

Center for Molecular Design and Synthesis, School of Molecular Science (BK-21), Korea Advanced Institute of Science and Technology, 373-1 Guseong Dong, Yuseong Gu, Taejon, 305-701, Korea
Fax +82(42)8695818; E-mail: kimyh@kaist.ac.kr

Received 31 August 2005

Abstract: Highly enantioselective and facile synthesis of α-hydroxy-β-amino acids has been achieved using the Claisen and Curtius rearrangements as key reactions. Chiral allylic alcohols were employed, which can be prepared by asymmetric catalysis in both *E*- and *Z*-forms; both *anti*- and *syn*-α-hydroxy-β-amino acids have been synthesized.

Key words: amino alcohols, amino acids, enantioselective synthesis, Claisen rearrangement, Curtius rearrangement

α-Hydroxy-β-amino acids are common structural units found in many biologically active compounds, including both naturally occurring and synthetic pharmaceuticals.[1] As one can see in Figure 1, α-hydroxy-β-amino acids or their derivatives reside in key structural elements of biologically active molecules, including Taxol,[2] a potent antitumor agent; bestatin,[3] an aminopeptidase inhibitor; and KNI-272,[4] a highly potent HIV-protease inhibitor. Due to their widespread occurrence in biologically active molecules, much synthetic effort has been devoted to the development of efficient stereoselective routes to prepare enantiopure α-hydroxy-β-amino acids.[5–8] Traditional synthetic methods toward these molecules have depended heavily on the use of chiral pools, such as amino acids or carbohydrates. In these types of syntheses, diastereoselective addition of nucleophiles to α-aminocarbonyl or α-hydroxyimino compounds is typical. In these syntheses, however, it was hard to obtain both *syn*- and *anti*-α-hydroxy-β-amino acids and thus Mitsunobu inversion of a secondary alcohol was required to obtain both forms of α-hydroxy-β-amino acids.[5] There are some good methods to synthesize α-hydroxy-β-amino acids through asymmetric synthesis. However, in these cases, expensive chiral auxiliaries are needed to obtain enantioenriched products.[6] Recently, some methods employing asymmetric catalysis were reported,[7,8] they include well-known examples of nucleophilic epoxide ring-opening reactions[7] and asymmetric aminohydroxylations.[8] However, in these catalytic systems, substrates that can be used or the stereochemistry of products are quite limited. Also, in the case of aminohydroxylations, the regioselectivity is sometimes problematic. Thus, the development of efficient synthetic routes to α-hydroxy-β-amino acids, which can give products with well-defined stereochemistry (*R*/*S* and *syn*/*anti*) in high yields is urgently needed.

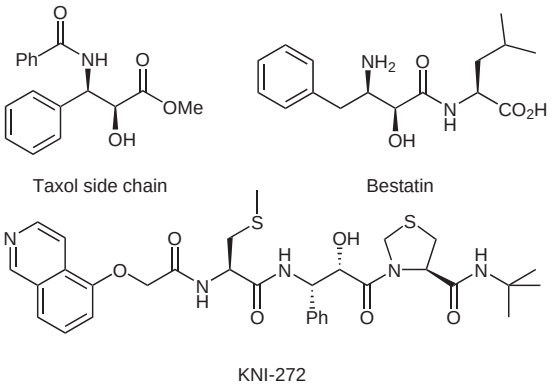
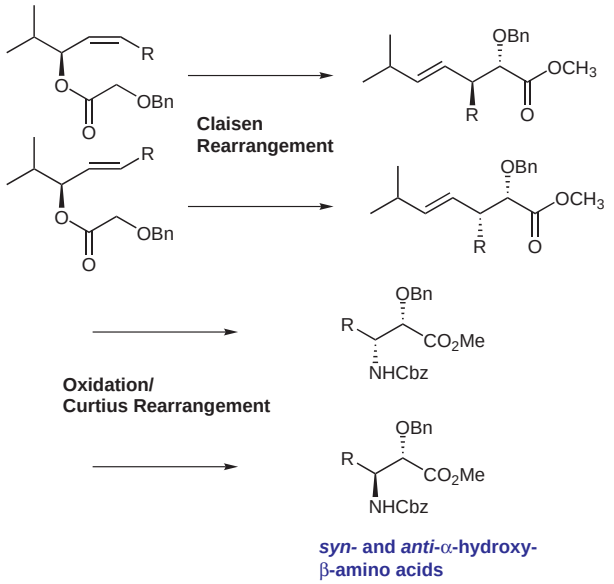


Figure 1

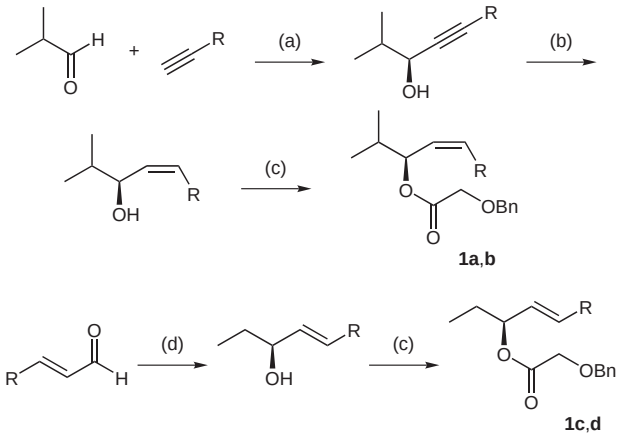
Our synthetic routes are based on both highly stereoselective Claisen rearrangements[9] and stereospecific Curtius rearrangements[10] as shown in Scheme 1. Both *E*-and *Z*-chiral allylic alcohols are starting materials for our synthesis. These allylic alcohols are well-known and easily prepared by various methods including catalytic reactions.[11,12] The stereochemistry of α-hydroxy-β-amino acids will be established through the Claisen rearrangement.[9b] Curtius rearrangement of carboxylic acids is known to introduce nitrogen functionality in a stereospecific manner from carboxylic acids with retention of the stereochemistry of the carboxylic acid, and as a result, the Curtius rearrangement has been employed in the stereoselective synthesis of amino acids.[10a–c]

The starting allylic esters can be easily prepared from simple starting materials in high ee by asymmetric catalysis (Scheme 2). The *Z*-allylic esters were prepared in three steps by initial asymmetric alkynylation developed by Carreira et al.,[11] followed by Lindlar hydrogenation, and subsequent acylation with commercially available benzyloxyacetyl chloride. The *E*-allylic esters were prepared in two steps through the enantioselective addition of a diethyl zinc reagent to α,β-unsaturated aldehydes catalyzed by (1*S*,2*R*)-dibutylnorephedrine,[12] followed by acylation with benzyloxyacetyl chloride. Starting from the corresponding aldehydes, *E*/*Z*-allylic esters can be prepared in high optical purity (Table 1, up to 96% ee) and good yields (>70% in every case).

SYNLETT 2006, No. 1, pp 0086–0090
Advanced online publication: 16.12.2005
DOI: 10.1055/s-2005-922793; Art ID: U26705ST



Scheme 1



Scheme 2 Preparations of *E*- and *Z*-allylic esters. *Reagents and conditions*: (a) $Zn(OTf)_2$, (–)-*N*-methylephedrine, Et_3N, toluene, 25 °C, (b) Lindlar catalyst (5 wt%), quinoline (45 wt%), H_2 (1 atm), MeOH, 25 °C, (c) $BnOCH_2COCl$ (1.1 equiv), pyridine (3 equiv), THF, 25 °C, (d) Et_2Zn (3 equiv), (1*S*,2*R*)-dibutylnorephedrine (5 mol%), hexane, 0 °C.

Then, the allylic esters were treated with a strong base such as LDA and quenched with TMSCl to induce a Claisen rearrangement. The Claisen rearrangement took place in high yields with excellent diastereoselectivity. In each case, only one diastereomer could be observed. Also, the enantiopurity of the starting allylic ester was maintained in every case. This is in accordance with previous reports which showed that the Claisen rearrangement of allylic esters, containing chelating elements such as oxygen, gave γ,δ-unsaturated esters almost stereospecifically.[9] The Claisen rearrangement of allylic esters **1a** and **1c** containing a phenyl group directly attached to a double bond gave the best results when a mixture of **1a** or **1c** and TMSCl were treated with an excess amount of KHMDS. Alternatively, when **1b** and **1d** were employed, the best results were obtained when the allylic esters were treated with 1.1 equivalents of LDA and 1.5 equivalents of TMSCl (Table 2). The crude carboxylic acids were treated with TMS–diazomethane to give methyl esters **2a**–**d**, which were purified by silica gel column chromatography. This reaction proceeded uneventfully to give **2a**–**d** in good yields with excellent stereoselectivity.[13] Their absolute and relative stereochemistries were determined by comparison with the reported data of known compounds.

To synthesize α-hydroxy-β-amino acids from these γ,δ-unsaturated esters, the double bonds could be cleaved to give carboxylic acids, which could then be converted to the amino acids stereospecifically using the Curtius rearrangement. Although various methods to cleave the double bond in **2** were tested, ozonolysis followed by $NaClO_2$ oxidation proved to be optimal to give the carboxylic acid in excellent yields with high purity with no purification required before the final Curtius rearrangement. Using a variant of the Curtius rearrangement developed by Shioiri,[10d,e] **3** was converted to α-hydroxy-β-amino acid **4** in a stereospecific manner (Scheme 3, Table 3).

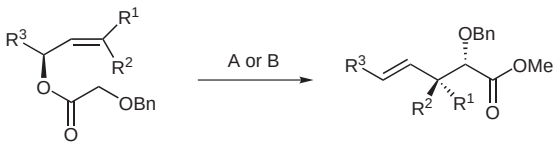
This three-step sequence worked remarkably well regardless of the nature of R (R = Ph, CH_2Ph) or the relative stereochemistry (*syn* or *anti*) of the substrates. Thus, in every case examined, yields were excellent (total yield >67%, 3 steps) and there was no reduction of either diastereopurity or enantiopurity, giving stereochemically pure α-hydroxy-β-amino acids **4a**–**d** efficiently.

Table 1 Preparation of *E*- and *Z*-Allylic Esters

Entry	Product	Configuration (*R*/*S*)	Configuration (*E*/*Z*)	R	Yield (%)[a]	ee (%)[b]
1	**1a**	*S*	Z	Ph	74	95
2	**1b**	*S*	Z	CH_2Ph	71	94
3	**1c**	*S*	E	Ph	83	96
4	**1d**	*S*	E	CH_2Ph	86	95

[a] Isolated yields based on starting aldehydes.
[b] Determined by chiral HPLC analysis by DAICEL OD-H column.

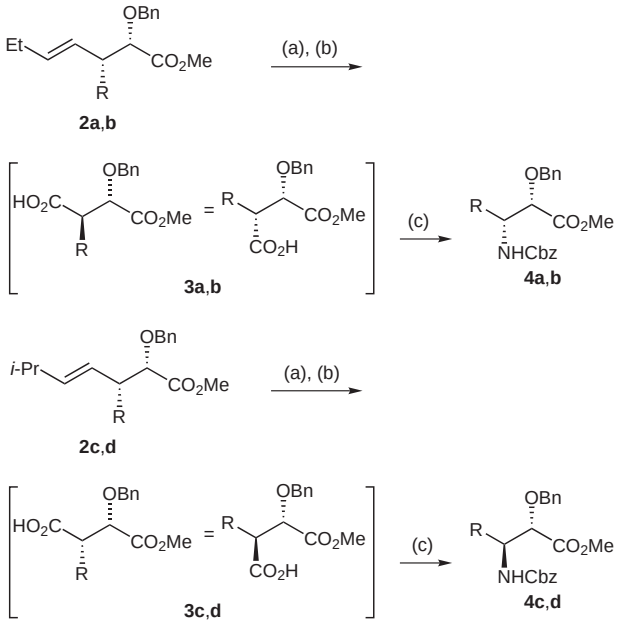
Table 2 Claisen Rearrangement of Allylic Esters



1a–d **2a–d**

Substrate	Product	R^1	R^2	R^3	Conditions[a]	Yield (%)[b]	dr (*syn*/ *anti*)[c]	ee (%)[c]
1a	**2a**	H	Ph	*i*-Pr	A	81	1:99	95
1b	**2b**	H	CH_2Ph	*i*-Pr	B	79	1:99	94
1c	**2c**	Ph	H	Et	A	86	99:1	96
1d	**2d**	CH_2Ph	H	Et	B	77	99:1	95

[a] Conditions A: TMSCl (4.5 equiv) was added to a solution of **1** in THF at –78 °C. Then, KHMDS (4 equiv) was added and stirred for 10 min. The mixture was allowed to warm to r.t. and stirred for an additional 2 h. Conditions B: LDA (1.1 equiv) was added to a THF solution of **1** at –78 °C. After 3 min, TMSCl (2.0 equiv) was added and then allowed to warm to r.t. After work-up, the crude carboxylic acids were treated with TMS–diazomethane to give the corresponding methyl esters.
[b] Isolated yields.
[c] Determined by HPLC analysis with a chiral AD-H column (DAICEL).



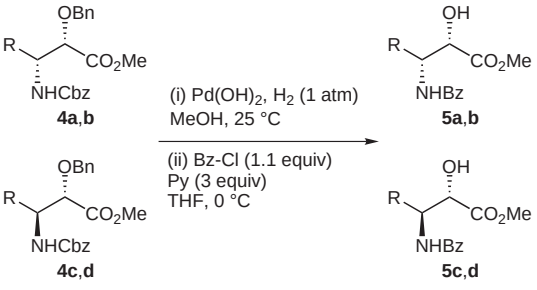
Scheme 3 *Reagents and conditions*: (a) O_3, CH_2Cl_2–MeOH, –78 °C, then Me_2S; (b) $NaClO_2$, 2-methyl-2-butene, *t*-BuOH–H_2O (pH 7 buffer); (c) (i) dppa, Et_3N, toluene, 25 °C, 30 min, then reflux 3 h; (ii) BnOH (3 equiv), reflux 2 d.

To determine the absolute configurations of **4a–d** and examine the applicability of this route to a practical synthesis, **4a–d** were converted to benzoylated α-hydroxy-β-amino acids **5a–d**. Thus, **4a–d** were debenzylated by hydrogenolysis and carefully benzoylated to give *N*-benzoyl-α-hydroxy-β-amino acids **5a–d**.[14] Among these compounds, **5a** is the enantiomer of the side chain of Taxol, one of the most famous, α-hydroxy-β-amino acids (Scheme 4). This method can be applied to the preparation of the Taxol side chain.

Table 3 Stereoselective Synthesis of α-Hydroxy-β-amino Acids

Product	R	Yield (%)[a]	dr (*syn*/*anti*)[b]	Configuration[c]	ee (%)[d]
4a	Ph	71	99:1	(*S*,*S*)	>95
4b	CH_2Ph	67	99:1	(*S*,*S*)	>95
4c	Ph	73	1:99	(*R*,*S*)	>95
4d	CH_2Ph	68	1:99	(*R*,*S*)	>95

[a] Isolated yields over 2 steps.
[b] Determined from derivatives **5a–d** prepared by a known procedure.[5a]
[c] Determined from derivatives **5a–d**.
[d] Determined from derivatives **5c**, **5d**, *ent*-**5c**, and *ent*-**5d** prepared by a known procedure.[5a,15]



5a: R = Ph, 81%, >95% ee
5b: R = CH_2Ph, 86%, >95% ee
5c: R = Ph, 83%, >95% ee
5d: R = CH_2Ph, 87%, >95% ee

Scheme 4 Deprotection and derivatization

In conclusion, we have developed new routes for the highly enantioselective synthesis of α-hydroxy-β-amino acids, including the unnatural enantiomer of the Taxol side chain. Starting from allylic alcohols, α-hydroxy-β-amino acids can be prepared in four steps in better than 45% total yield. The enantiopurity of allylic alcohols are thoroughly reflected in the enantiopurity of the resulting products. There are a lot more *E*- and *Z*-allylic alcohols that can be prepared in high enantiopurity, this newly developed route can be applied to the synthesis of a diverse range of α-hydroxy-β-amino acids.

Acknowledgment

This work was financially supported by grant No. R02-2002-000-00097-0 from the Korea Science & Engineering Foundation and Center for Molecular Design and Synthesis.

References and Notes

(1) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.
(2) (a) Kingston, D. G. I.; Jagtap, P. G.; Yuan, H.; Samala, L. In *Progress in the Chemistry of Organic Natural Products*, Vol. 84; Herz, W.; Falk, H.; Kirby, G. W., Eds.; Springer: Vienna, New York, **2002**, 53–225. (b) Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.
(3) Umezawa, H.; Aoyagi, H.; Suda, H.; Kojima, F.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97.
(4) Mimoto, T.; Imai, J.; Kisanuki, S.; Enomoto, H.; Hattori, N.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1992**, *40*, 2251.
(5) (a) Lee, J. M.; Lim, H. S.; Seo, K. C.; Chung, S. K. *Tetrahedron: Asymmetry* **2003**, *14*, 3639. (b) Hamamoto, H.; Mamedov, V. A.; Kitamoto, M.; Hayashi, N. O.; Tsuboi, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4485. (c) Kayser, M. M.; Mihovilovic, M. D.; Kearns, J.; Feicht, A.; Stewart, J. D. *J. Org. Chem.* **1999**, *64*, 6603. (d) Kang, S. H.; Kim, C. M.; Youn, J. H. *Tetrahedron Lett.* **1999**, *40*, 3581. (e) Jost, J.; Gimbert, Y.; Greene, A. E. *J. Org. Chem.* **1997**, *62*, 6672. (f) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117. (g) Ambroise, L.; Jackson, R. F. W. *Tetrahedron Lett.* **1996**, *37*, 2311. (h) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2385.
(6) (a) Ojima, I.; Park, Y. H.; Sun, C. M.; Brigaud, T.; Zhao, M. *Tetrahedron Lett.* **1992**, *33*, 5737. (b) Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238.
(7) (a) Righi, G.; Rumboldt, G.; Bonini, C. *J. Org. Chem.* **1996**, *61*, 3557. (b) Aggarwal, V. K.; Vasse, J.-L. *Org. Lett.* **2003**, *5*, 3987.
(8) (a) Bruncko, M.; Schilingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483. (b) Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 2045.
(9) (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889. (c) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (d) Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3431.
(10) (a) Spino, C.; Tremblay, M.-C.; Gobdout, C. *Org. Lett.* **2004**, *6*, 2801. (b) Spino, C.; Gobdout, C. *J. Am. Chem. Soc.* **2003**, *125*, 12106. (c) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411. (d) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151. (e) Ninomiya, K.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 1398.
(11) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.
(12) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264.
(13) **Claisen Rearrangement of Allylic Esters 1c; Typical Procedure**
To a cooled solution of **1c** (1 mmol) in THF at –78 °C, was added TMSCl (0.576 mL, 4.5 mmol). The solution was stirred for 5 min and a solution of KHMDS (0.5 M soln in toluene; 8.0 mL) was added rapidly by syringe. The reaction was stirred for 10 min at –78 °C and allowed to warm to r.t. over 1 h. The reaction was quenched with HCl (1 N) and diluted with Et_2O. The resulting mixture was partitioned and the resulting aqueous layer was extracted with Et_2O (× 2). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed to give the crude carboxylic acid. The crude carboxylic acid was dissolve in MeOH–benzene (1:1, 4 mL). TMS–diazomethane (2.0 M solution in hexane, 1.0 mL, 2.0 mmol) was added dropwise and the solution was stirred for 30 min and then the solvent was removed in vacuo. The crude thus obtained was purified by silica gel column chromatography (EtOAc–hexane, 1:10) to give pure **2c** in 86% yield. HPLC (Chiracel AD column, *i*-PrOH–hexane, 2:98, 1 mL/min) t_R 14.1 min, 18.7 min. For *anti*-isomers, **2a**, t_R 17.1 min, 23.2 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, 3 H), 1.96 (m, 2 H), 3.63 (m, 1 H), 3.67 (s, 3 H), 4.10 (d, 1 H), 4.26 (d, 1 H), 4.58 (d, 1 H), 5.56 (m, 2 H), 7.21 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 26.4, 51.5, 53.3, 73.3, 86.2, 125.7, 127.6, 127.7, 127.9, 128.4, 128.7, 129.1, 129.3, 137.2, 140.2, 172.0. MS (EI): *m*/*z* calcd for $C_{21}H_{24}O_3$: 324.1725; found: 323.19.
(14) **α-Hydroxy-β-amino Acids 5a; Typical Procedure**
To a cooled solution of **2a** in CH_2Cl_2–MeOH (1:1) at –78 °C, O_3 was bubbled until the color of the solution changed to a purple color and the bubbling was continued for another 10 min. Then, O_3 bubbling was stopped and a stream of nitrogen was applied to the reaction mixture to drive off any residual O_3 until the solution became colorless. Then, excess Me_2S was added to quench the reaction and the resulting mixture was left to warm to r.t. The solvent was removed in vacuo and the crude mixture was dissolved in *t*-BuOH and 2-methyl-2-butene (1:1 mixture). To the above solution, a solution of NaH_2PO_4 (3 equiv) was added followed by dropwise addition of $NaClO_2$ (2 equiv). After 30 min at r.t., the reaction mixture was diluted with EtOAc and acidified with HCl (1 N). The aqueous layer was extracted again with EtOAc (× 2). The resulting organic layer was washed with a sat. aq solution of Na_2SO_3, dried over $MgSO_4$, filtered, and evaporated in vacuo to give crude **3a**. Then **3a** was dissolved in toluene, dppa (1.5 equiv), and Et_3N (3 equiv) were added, the resulting mixture was stirred for 30 min at r.t., and then heated to reflux. After 3 h, benzyl alcohol (3 equiv) was added and heating was continued for 2 d. The reaction mixture was cooled to r.t. and quenched with an aq solution of NH_4Cl. The resulting mixture was extracted with EtOAc (× 3). The resulting organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give crude **4a**, which was purified by silica gel column chromatography (EtOAc–hexane, 1:6) to give pure **4a** in 71% yield. To confirm the structure and enantiopurity, **4a** was converted to the known compound **5a**, which was converted to *ent*-**5c**. Firstly, it was hydrogenolyzed over $Pd(OH)_2$ under 1 atm of H_2. The crude mixture was dissolved in THF, cooled to 0 °C, treated with pyridine (3 equiv), and benzoyl chloride (1.1 equiv) was added dropwise. After 1 h, the reaction was quenched with HCl (1 N) and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give

crude **5a**, which was purified by silica gel column chromatography (EtOAc–hexane, 1:2) to give pure **5a** in 81% yield (overall yield from **3a**: 58%) The spectra were in accordance with the known compound. $[\alpha]_D^{23}$ +47.1 (*c* 1.00, MeOH) {lit.[5b] $[\alpha]_D^{23}$ –50.2 (*c* 1.00, MeOH)}; ^{1}H NMR (400 MHz, CD_3OD): δ = 3.26 (d, 1 H), 3.86 (s, 3 H), 4.65 (dd, 1 H), 5.75 (dd, 1 H), 6.97 (br d, 1 H), 7.28–7.55 (m, 8 H), 7.78 (d, 2 H). To check the enantiopurity of **5a**, it was converted to the *ent*-**5c**. To a CH_2Cl_2 solution of **5a**, NMO (2.5 equiv) was added, followed by TPAP (10 mol%). After stirring for 1 h, the reaction mixture was filtered through a short pad of silica gel to give the corresponding α-amino ketone. This compound was treated with tetrabutylammonium borohydride as reported previously[15] to give *ent*-**5c**, whose spectral data are identical to those of the known compound **5c**. Then *ent*-**5c** was reacted with Mosher reagent as described.[5a] The enantiomeric purity of **5c** was determined by ^{1}H and ^{19}F NMR spectroscopy.

(15) Li, W.-S.; Thottathil, J. K. US Patent US 5602272 A 19970211, **1997**.