An Improved Enantiospecific Synthesis of Statine and Statine Analogs via 4-(*N*,*N*-Dibenzylamino)-3-keto Esters

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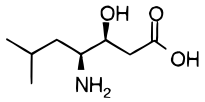
Introduction

Statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid, **1**, is a critical component of pepstatin, a naturally occurring peptidic aspartate protease inhibitor.[1] The 4-amino-3-hydroxy ester functional grouping of statine is thought to mimic the tetrahedral intermediate of peptide hydrolysis, and a *syn* diastereotopic relationship between the amine and hydroxyl groups is required.[2] Replacement of the terminal isobutyl group with other groups has led to derivatives with greatly improved activities.[3]



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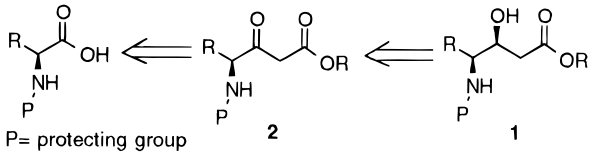
Because of their inhibitory activity toward aspartate proteases, particularly renin,[1] much effort has been directed toward the enantioselective synthesis of statine and statine analogs. In spite of these considerable efforts, there has not emerged a general and reliable strategy for their preparation.[4] Even though they are relatively simple compounds, current methods are compromised by several recurring problems. Often syntheses are overly long (often 7−10 steps from commercial starting materials), in many cases the diastereoselectivities are low (30−70% de), and it is very common for the wrong diastereomer to be formed and an inversion of stereochemistry to be required at C-3. These difficulties have resulted in a continuing search for new methodologies for the synthesis of statine analogs.[4,5]

One of the simplest conceptual approaches to the statine family is the reduction of 4-amino-3-keto esters **2** which are available from α-amino acids (Scheme 1). While a majority of the early work focused on this approach, the reduction step has proven to be somewhat disappointing. In spite of a number of different protecting groups (P = t-Boc,[6] Cbz,[7] and Fmoc[8]) and reducing

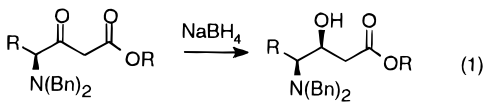
Scheme 1



agents ($NaBH_4$,[6,9] $NaBH_3CN$,[10] KBH_4,[8] and K-Selectride[6]), the diastereoselectivities are usually modest (0−65% de), and the major diastereomer is the incorrect 3*R*,4*S* diastereomer which must be inverted at C-3.

The best success using carbamate protecting groups has come in the synthesis of isostatine (R = sec-butyl). Chain branching at the point of attachment of the R-group improves the diastereoselectivity to >90%, but an inversion of configuration at C-3 is still required.[8,11] Catalytic hydrogenation of the ketone function of **2** (P = Boc) using chiral ruthenium catalysts gives high de's and produces the correct 3*S*,4*S* stereochemistry, but the hydrogenation requires 100 atm of hydrogen and 6 days of reaction time.[12]

The most successful reductive method was that of Reetz, who reported that *N*,*N*-dibenzyl protection of the amino group of the 4-amino-3-keto ester, eg. **3**, led to products with high de's and which had the correct 3*S*,4*S* stereochemistry (eq 1).[13] The improved diastereoselection



was attributed an open Fekin−Ahn transition state for the bulky *N*,*N*-dibenzyl-protected compounds compared to a chelated transition state for the carbamate-protected compounds. The *N*,*N*-dibenzylamino group has been found to give excellent diastereoselectivities in a variety of other reactions as well.[14] Good results were reported for statine and two analogs (R = i-Bu, $CH_2C_6H_{11}$, CH_2-Ph).

In connection with the synthesis of a series of hydroxyethylene peptide isosteres by chiral alkylation,[15] we found it necessary to prepare a series of scalemic 4-(*N*,*N*-dibenzylamino)-3-keto esters, **3**. To do so requires the saponification of an α-(*N*,*N*-dibenzylamino) ester, as had been described by Reetz in the synthesis of statine

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(5) Recent synthetic efforts include: (a) Nebois, P.; Greene, A. G. *J. Org. Chem.* **1996**, *61*, 5210. (b) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248. (c) Kang, S. H.; Rhu, D. H. *Biorg. Med. Chem. Lett.* **1995**, *5*, 2959. (d) Williams, R. M.; Colson, P. J.; Zhai, W. X. *Tetrahedron Lett.* **1995**, *35*, 9371 and references therein. (e) Yamamoto, T.; Ishibuchi, S.; Ishizuka, T.; Haratake, M.; Kunieda, T. *J. Org. Chem.* **1993**, *58*, 1997.
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(11) (a) Harris, B. D.; Jouillé, M. M., *Tetrahedron* **1988**, *44*, 3489. (b) Jouin, P.; Poncet, J.; Dufour, M.-N.; Maugras, I.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1988**, *29*, 2661. c. Hamada, Y.; Kondo, Y.; Shibata, M.; Shioiri, T. *J. Am. Chem. Soc.* **1989**, *111*, 669.
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(13) (a) Reetz, M. T.; Drewes, M. W.; Matthews, B. R.; Lennick, K. *Chem. Commun.* **1989**, 1474. (b) It is not possible to make the *N*,*N*-dibenzylamino *acid* directly from the amino acid by benzylation. The nitrogen is monobenzylated and a second benzyl group then reacts with the carboxylate group. *N*,*N*-Dibenzylation ocurrs in the third benzylation step.
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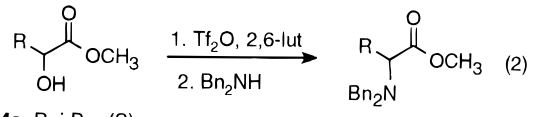
derivatives.[13] To our great surprise we were unable to duplicate this hydrolysis under a variety of experimental conditions. A reexamination of the reaction sequence has led to an improved synthesis of 4-(*N*,*N*-dibenzylamino)-3-keto esters, **3**, and hence statine derivatives, starting from α-hydroxy esters.

Results

A series of scalemic α-hydroxy methyl esters was converted to α-triflyloxy esters and then to α-(*N*,*N*-dibenzylamino) esters by reaction with dibenzylamine (eq 2).[16] It is known that α-triflyloxy esters react with amine



(2)

4a, R=i-Bu (S)
b, R= $PhCH_2$ (R)
c, R=$PhCH_2CH_2$ (R)
d, R= $C_6H_{11}CH_2$ (S)
e, R= C_6H_{11} (R)
f, R= i-Pr (S)
g, R= s-Bu (2S, 3S)
h, R= Me (S)

5a, 97% (R)
5b, 100% (S)
5c, 100% (S)
5d, 100% (R)
5e, 65% (S)
5f, 75% (R)
5g, 80% (2R, 3S)
5h, 100% (R)

nucleophiles with clean inversion of configuration,[16a] and this was confirmed for **5a** and **5b** by a chiral shift reagent study using Eu(hfc)$_3$. By comparison to racemic samples, both **5a** and **5b** were enantiomerically pure within the limits of detection (>97% ee) and it is thus reasonable to assume that **5c**−**h** are also enantiomerically pure. The choice of configuration at C-2 of the starting hydroxy esters **4** was made on the basis of price, commercial availability, and demonstrating the methodology. To obtain *any* particular configuration at C-2 of **5** and ultimately at C-4 of the statine product, the opposite configuration would be chosen for the starting hydroxy ester **4**.

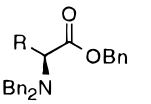
Reaction of amino esters **5a**−**d**,**h** with the lithium enolate of *tert*-butyl acetate gave β-keto esters **3a**−**d**,**h** in high yields (80−90%). The *N*,*N*-dibenzylamino group introduces significant steric congestion around the carbonyl group. Reaction of **5a**−**d**,**h** with lithio *tert*-butyl acetate requires 6 h at room temperature for completion.[17] Amino esters **5e**−**g**, which are even more sterically hindered due to chain branching at the β-position, failed to react. Because of the longer reaction times, it was found that keto esters **3a**−**d**,**h** were racemized to the extent of 78−90% ee. To avoid these structural and stereochemical limitations, hydrolysis of **5** and conversion to a more reactive acylating agent was required.

Saponification of amino esters **5a**,**g**,**h** with a variety of reagents demonstrated the remarkable inertness of the ester function in these compounds toward nucleophilic addition (Table 1). This is certainly a direct result of steric shielding of the ester group; as the steric bulk of the R-group goes up (Me < i-Bu < s-Bu), the reaction time increases and the yield decreases. β-Branching (R = s-Bu) prevents hydrolysis altogether. Moreover, significant racemization of **5h** suggests this would be a serious complication for other members of the series as well.

Table 1. Reactivity of Amino Esters 5 under Various Hydrolysis Conditions

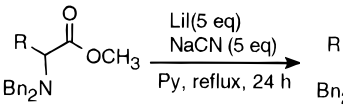
compound	conditions	yield (%)[a]
5h	LiOH, THF/H_2O,reflux, 24 h	92 (45% ee)
5a	LiOH, THF/H_2O, reflux, 4 days	86
5a	KOH, THF/H_2O, reflux 6 days	79
5g	LiOH, THF/H_2O, reflux, 7 days	0
5g	KOH, THF/H_2O. reflux, 7 days	0
6a	KOH, dioxane/H_2O, reflux, 6 days	10 (90% ee)
6b	KOH, dioxane/H_2O, reflux, 7 days	0

These results were disappointing in light of the work of Reetz, who reported that benzyl ester **6a** was saponified by KOH in aqueous dioxane.[13] While no experimental details were given, the hydrolysis was reported to occur without significant racemization. Attempts to reproduce these previous results were unsuccessful (Table 1). After refluxing for 6 days with KOH (5 equiv) in aqueous dioxane, less than 10% hydrolysis was found for **6a** and the starting material had degraded to 90% ee. The β-branched compound **6b** gave no detectable hydrolysis after 7 days under the same conditions.



6a, (R= i-Bu)
b, (R= sec-Bu)

Because nucleophilic attack at the carbonyl group of **5** by either enolates or hydroxide seemed to be sterically retarded, particularly in the β-branched systems, we turned to an iodide-based hydrolysis. Treatment of keto esters **5a**−**h** with a mixture of lithium iodide/sodium cyanide in refluxing pyridine for 24 h[18] gave *N*,*N*-dibenzylamino acids **7a**−**h** in good yields (64−82%) and *without detectable racemization of the chiral center*. Neither the yields nor the optical purities seemed to be affected by branching at the β-position (eq 3).



(3)

5a-h

7a (75%, R)
b (72%, S)
c (75%, S)
d (78%, R)
e (82%, S)
f (79%, R)
g (74%, 2R, 3S)
h (64%, R)

Amino acids **7a**−**h** were converted to the corresponding β-keto esters **3a**−**h** by the carbonyldiimidazole (CDI)-mediated coupling of the amino acid with lithio *tert*-butyl acetate in excellent yields (eq 4).[11a] Determination of the optical purity of **3** was done by a chiral LIS study using Eu(hfc)$_3$ and nearly all the analogs were found to have ≥97% ee, with the exception of **3h**, which had an optical purity of 70% ee.

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(17) Normal methyl and ethyl esters react with lithio *tert*-butyl acetate in 1−2 h. Kim, H.-O.; Saenz, J. unpublished results in these laboratories.

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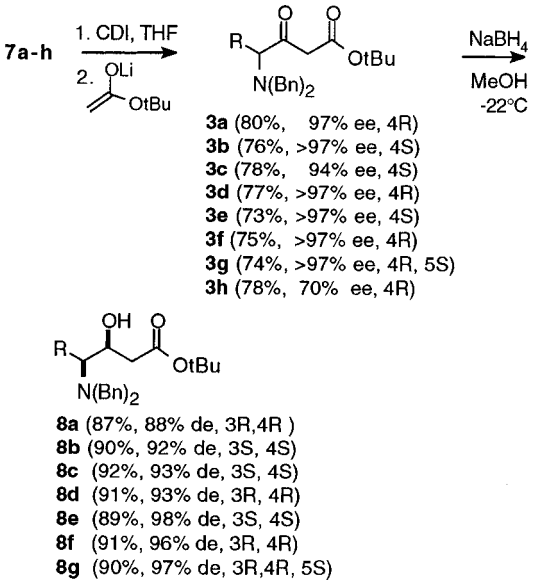


The high optical purities of **3** confirm that neither the hydrolysis nor the CDI coupling causes detectable racemization. Keto esters **3a**−**g** were reduced with $NaBH_4$ in absolute methanol to give protected statine analogs **8a**−**g** in excellent yields and diastereoselectivities.[13] The *syn* diastereomer is presumed to be the major product in all cases on the basis of the known stereochemistry of reduction of (*N,N*-dibenzylamino)carbonyl compounds,[14] and it was readily separable by flash chromatography. Debenzylation of **8** can be accomplished by catalytic hydrogenation.[19]

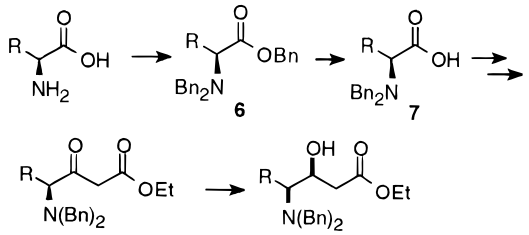
Discussion

The best reductive procedure for the enantioselective preparation of statine analogs was that of Reetz,[13] who converted amino acids to tribenzylated esters **6** and then saponified the benzyl ester to the *N,N*-dibenzylamino acids **7**.[13b] Subsequent conversion to a β-keto ester and borohydride reduction gave statines with the correct relative and absolute stereochemistry (Scheme 2). The advantages of the Reetz approach are that the reduction proceeds with high diastereoselectivity and gives the correct *syn* diastereomer.[14]

On the other hand, that method requires the amine group of an amino acid be converted to the *N,N*-dibenzylamino group, thus the R-group and the chirality of the product are restricted to those available in amino acid precursors. The present methodology utilizes scalemic α-hydroxy methyl esters as starting materials, which are readily available either commercially or from amino acids[20] or from a variety of other sources.[21] A large selection of R-groups may be used since triflate substitution by dibenzylamine to produce the *N,N*-dibenzylamino ester is fairly insensitive to the nature or size of the R-group.

A more serious limitation lies in the saponification of the dibenzylamino esters. The basic hydrolysis of *N,N*-dibenzylamino *methyl* esters **5** by several standard procedures is difficult when the R-group is unbranched at the β-position and impossible when the R-group is β-branched. Moreover, significant amounts of racemization accompany the hydrolysis under these conditions. In our hands *N,N*-dibenzyl *benzyl* esters were virtually inert toward saponification probably because the bulky *N,N*-dibenzylamino group at the α-position inhibits attack of hydroxide at the neighboring ester group. The methyl ester cleavage of **5** using an iodide nucleophile is successful because nucleophilic displacement on the methyl group is removed from the steric congestion at the α-position. The ester cleavage works well even for β-branched substrates, and the conditions do not result in any detectable racemization. Thus the ester cleavage is also tolerant of a wide range of R-groups. This procedure is not suitable for benzyl esters.[18]

Scheme 2



The CDI-mediated coupling to produce **3** takes place normally. Evidently the carbonyl imidazole intermediate is sufficiently reactive, in spite of the steric congestion around the carbonyl carbon, that it reacts with enolates. Stereoselective reduction to protected statine analogs **8** proceeds in high yield and with high diastereoselectivity as described in the literature.[13]

In summary, a diverse set of statine analogs, **8a**−**g**, with both natural and unnatural configurations, and both branched and unbranched R-groups, can be prepared by a four-step sequence from scalemic α-hydroxy esters in excellent overall yields (35−50% for four steps). The sequence is highly *syn*-diastereoselective (>90% de) and produces optically pure products (>97% ee).

Experimental Section

Infrared spectra were recorded as neat liquids or as KBr pellets. ^1H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irridiation and/or iodine. Preparative thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irridiation. Flash chromatography was performed using silica gel 60 (230−400 mesh). Radial chromatography was performed on 2 mm layer plates of silica gel 60 PF_{254} containing gypsum. Tetrahydrofuran was distilled from benzophenone ketyl. Other solvents were HPLC grade and were used without further purification. Starting materials were purchased from Aldrich or Sigma and used as received. Elemental analyses were carried out by M-H-W Laboratories, Phoenix, AZ.

(*S*)-Methyl 2-Hydroxy-4-methylpentanoate (4a).[22] **General Procedure**. A solution of $NaNO_2$ (5.04 g, 73.0 mmol) in H_2O (20mL) was added dropwise to a stirred, ice-cooled (0 °C) solution of L-leucine (6.56 g, 50.0 mmol) in 1 N H_2SO_4 (80.0 mL, 80.0 mmol). The resulting mixture was stirred at the same temperature for 1 h and then at room temperature for 12 h. After extraction with ethyl ether (5 × 100 mL), the etheral extracts were combined and concentrated by rotary evaporator. Then the residue was dried by refluxing in benzene (200 mL). After concentration, the (*S*)-2-hydroxy-4-methylpentanoic acid was dissolved in acetone (100 mL), and K_2CO_3 (7.60 g, 55.0 mmol)

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(22) Miller, M. J.; Kolasa, T. *J. Org. Chem.* **1987**, *52*, 4978. See also Kim, H.-O., Ph.D. Dissertation, New Mexico State University, 1990.

was added. The suspension was stirred at room temperature for 1 h. Iodomethane (4.00 mL, 64.0 mmol) was added, and the milky solution was refluxed overnight, filtered, concentrated, and purified by Kugelrohr distillation (bath temperature 60−65 °C/0.07 mmHg) to provide **4a** as a colorless oil (5.12 g, 70% based on L-leucine): $[\alpha]^{25}_D$ +2.2 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3H, *J* = 2.2 Hz), 0.96 (d, 3H, *J* = 6.5 Hz), 1.54 (t, 2H, *J* = 6.5 Hz), 1.89 (m, 1H), 2.91 (d, 1H, *J* = 6.1 Hz), 3.78 (s, 3H), 4.22 (m, 1H); FTIR (neat) 3478 (br), 2958, 1739, 1213, 1143 cm^{-1}.

(*R*)-Methyl 2-hydroxy-4-phenylpropanoate (4b):[22] yield 95% (based on commercially available D-3-phenyllactic acid) as a white solid after purification by Kugelrohr distillation (bath temperature 120 °C /0.07 mmHg); mp 45.5−46.5 °C; $[\alpha]^{25}_D$ +11.2 (c 2.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.74 (d, 1H, *J* = 9.0 Hz), 3.05 (m, 2H), 3.77 (s, 3H), 4.45 (m, 1H), 7.27 (m, 5H).

(*R*)-Methyl 2-hydroxy-4-phenylbutanoate (4c): yield 89% (based on commmercially available (*R*)-(−)-2-hydroxy-4-phenylbutyric acid) as a colorless oil after purification by Kugelrohr distillation (bath temperature 130−150 °C/0.07 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.20 (m, 2H), 2.74 (d, 1H, *J* = 6.4 Hz), 2.82 (m, 2H), 3.75 (s, 3H), 4.20 (m, 1H), 7.22 (m, 5H).

(*S*)-Methyl 2-hydroxy-3-cyclohexylpropanoate (4d): yield 70% (based on commercially available cyclohexylalanine) as a colorless oil after purification by Kugelrohr distillation (bath temperature 150−180 °C/0.07 mmHg); $[\alpha]^{25}_D$ −0.24 (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.78−1.92 (set of m, 13H), 2.68 (br, 1H), 3.78 (s, 3H), 4.24 (dd, 1H, *J* = 4.5, 9.2 Hz).

(*R*)-Methyl 2-hydroxy-2-cyclohexylacetate (4e): yield 98% (based on commercially available (*R*)-(−)-2-hydroxy-2-cyclohexylacetic acid as a colorless oil after purification by Kugelrohr distillation (bath temperature 100−120 °C /0.07 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.00−1.78 (set of m, 11H), 2.68 (d, 1H, *J* = 6.3 Hz), 3.79 (s, 3H), 4.38 (dd, 1H, *J* = 4.4, 6.3 Hz).

(*S*)-Methyl 2-hydroxy-3-methylbutanoate (4f):[22] yield 93% (based on commercially available (*S*)-(+)-2-hydroxy-3-methylbutyric acid) as a colorless oil after purification by Kugelrohr distillation (bath temperature 50−70 °C /0.07 mmHg); $[\alpha]^{25}_D$ +23.1 (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 3H, *J* = 6.8 Hz), 1.02 (d, 3H, *J* = 7.0 Hz), 2.07 (m, 1H), 2.78 (d, 1H, *J* = 6.1 Hz), 3.80 (s, 3H), 4.05 (dd, 1H, *J* = 3.7, 6.1Hz).

(2*S*,3*S*)-Methyl 2-hydroxy-3-methylpentanoate (4g): yield 70% (based on isoleucine) as a colorless oil after purification by Kugelrohr distillation (bath temperature 50 °C/0.07 mmHg); $[\alpha]^{25}_D$ +25.5 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, *J* = 7.3 Hz), 0.98 (d, 3H, *J* = 7.1 Hz), 1.30 (m, 2H), 1.82 (m, 1H), 2.70 (br, 1H), 3.79 (s, 3H), 4.09 (d, 1H, *J* = 3.8 Hz).

(*R*)-Methyl 2-(*N*,*N*-Dibenzylamino)-4-methylpentanoate (5a). General Procedure. To a stirred solution of (*S*)-methyl 2-hydroxy-4-methylpentanoate (**4a**) (1.46 g, 10.0 mmol) in dichloromethane (20 mL) at 0 °C under a nitrogen was added triflic anhydride (1.90 mL, 11.0 mmol), followed by 2,6-lutidine (1.28 mL, 11.0 mmol). After stirring for 15 min, dibenzylamine (6.00 mL, 31.0 mmol) in dichloromethane (10 mL) was added dropwise to the pink solution. The resulting mixture was stirred for 2 h at room temperature and then concentrated by evaporation under vacuum. The residue was dissolved in pentane (150 mL), passed through a short pad of silica gel, and concentrated again to provide dibenzylamino ester **5a** as a pale yellow oil. This material was carried on to the next step without further purification (3.15 g, 97% based on **4a**): $[\alpha]^{25}_D$ +89.8 (*c* 3.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.59 (d, 3H, *J* = 6.5 Hz), 0.82 (d, 3H, *J* = 6.6 Hz), 1.50 (m, 1H), 1.72 (m, 2H), 3.38 (dd, 1H, *J* = 4.5, 10.0 Hz), 3.50 (d, 2H, *J* = 13.9 Hz), 3.92 (d, 2H, *J* = 13.9 Hz), 3.75 (s, 3H), 7.30 (m, 10H).

An LIS study was carried out on **5a** using $Eu(hfc)_3$ (1 equiv) in chloroform-*d*. A racemic sample was first used to monitor the lanthanide-induced shifts, and then scalemic **5a** prepared above was used. Only a single enantiomer could be detected, and thus the sample is >97% ee.

(*S*)-Methyl 2-(*N*,*N*-dibenzylamino)-3-phenylpropanoate (5b): yield 100% (based on **4b**); $[\alpha]^{20}_D$ −77.8 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.05 (m, 2H), 3.54 (d, 2H, *J* = 14.0 Hz), 3.67 (dd, 1H, *J* = 6.7, 8.9 Hz), 3.95 (d, 2H, *J* = 14.0 Hz), 3.73 (s, 3H), 7.22 (m, 15H). Only a single enantiomer was detected in an LIS study; thus, the sample is >97% ee.

(*S*)-Methyl 2-(*N*,*N*-dibenzylamino)-4-phenylbutanoate (5c): yield 100% (based on **4c**); $[\alpha]^{25}_D$ −82.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.04 (m, 2H), 2.46 (m, 1H), 2.78 (m, 1H), 3.39 (m, 1H), 3.38 (d, 2H, *J* = 13.9 Hz), 3.95 (d, 2H, *J* = 13.9 Hz), 3.74 (s, 3H), 7.29 (m, 15H).

(*R*)-Methyl 2-(*N*,*N*-dibenzylamino)-3-cyclohexylpropanoate (5d): yield 100% (based on **4d**); ^{1}H NMR ($CDCl_3$) δ 0.55−1.80 (set of m, 13H), 3.38 (dd, 1H, *J* = 4.5, 9.0 Hz), 3.50 (d, 2H, *J* = 13.7 Hz), 3.91 (d, 2H, *J* = 13.7 Hz), 3.75 (s, 3H), 7.31 (m, 10H).

(*S*)-Methyl 2-(*N*,*N*-dibenzylamino)-2-cyclohexylacetate (5e): yield 65% (based on **4e**); ^{1}H NMR ($CDCl_3$) δ 1.00−2.35 (set of m, 11H), 3.02 (d, 1H, *J* = 11.1 Hz), 3.30 (d, 2H, *J* = 14.0 Hz), 3.99 (d, 2H, *J* = 14.0 Hz), 3.76 (s, 3H), 7.30 (m, 10H).

(*R*)-Methyl 2-(*N*,*N*-dibenzylamino)-3-methylbutanoate (5f): yield 75% (based on **4f**); ^{1}H NMR ($CDCl_3$) δ 0.78 (d, 3H, *J* = 6.5 Hz), 1.02 (d, 3H, *J* = 6.6 Hz), 2.15 (m, 1H), 2.87 (d, 1H, *J* = 11.0 Hz), 3.28 (d, 2H, *J* = 14.0 Hz), 4.00 (d, 2H, *J* = 14.0 Hz), 3.77 (s, 3H), 7.33 (m, 10H).

(2*R*,3*S*)-Methyl 2-(*N*,*N*-dibenzylamino)-3-methylpentanoate (5g): yield 80% (based on **4g**); $[\alpha]^{25}_D$ +72.8 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.79−1.04 (m, 3H), 1.00 (d, 3H, *J* = 6.6 Hz), 1.21 (m, 2H), 2.01 (m, 1H), 3.00 (d, 1H, *J* = 10.9 Hz), 3.27 (d, 2H, *J* = 14.1 Hz), 3.99 (d, 2H, *J* = 14.1 Hz), 3.77 (s, 3H), 7.36 (m, 10H).

(*R*)-Methyl 2-(*N*,*N*-dibenzylamino)propanoate (5h): yield 100% (based on commercially available (*S*)-(−)-methyl lactate (**4h**)); $[\alpha]^{25}_D$ +88.5 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 3H, *J* = 6.5 Hz), 3.51 (q, 1H, *J* = 6.5 Hz), 3.59 (d, 2H, *J* = 13.9 Hz), 3.84 (d, 2H, *J* = 13.9 Hz), 3.73 (s, 3H), 7.33 (m, 10H).

(*R*)-2-(*N*,*N*-dibenzylamino)-4-methylpentanoic Acid (7a). General Procedure. Dibenzylamino ester **5a** (1.62 g, 5.00 mmol) was refluxed with lithium iodide (3.34 g, 25.0 mmol) and sodium cyanide (1.23 g, 25.0 mmol) in pyridine (25 mL) under a N_2 atmosphere. The reaction was monitored by TLC. After 24 h, the resulting mixture was dissolved in ethyl acetate (150 mL) and then washed with aqueous NH_4Cl (2 × 75 mL), H_2O (100 mL), and brine (100 mL). After concentration, the residue was extracted with pentane (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to afford **7a** as a pale yellow oil (1.17 g, 75% based on **5a**), which was virtually pure by NMR analysis and was carried on without further purification: ^{1}H NMR ($CDCl_3$) δ 0.69 (d, 3H, *J* = 6.4 Hz), 0.85 (d, 3H, *J* = 6.6 Hz), 1.65 (dd, 2H, *J* = 6.7, 9.0 Hz), 1.86 (m, 1H), 3.42 (t, 1H, *J* = 6.7 Hz), 3.70 (d, 2H, *J* = 13.5 Hz), 3.86 (d, 2H, *J* = 13.5 Hz), 7.32 (m, 10H).

(*S*)-2-(*N*,*N*-dibenzylamino)-3-phenylpropanoic acid (7b): yield 72% (based on **5b**); ^{1}H NMR ($CDCl_3$) δ 3.15 (m, 2H), 3.74 (dd, 1H, *J* = 5.1, 7.5Hz), 3.73 (d, 2H, *J* = 14.0 Hz), 3.90 (d, 2H, *J* = 14.0 Hz), 7.21 (m, 15 Hz).

(*R*)-2-(*N*,*N*-dibenzylamino)-4-phenylbutanoic acid (7c): yield 75% (based on **5c**); ^{1}H NMR ($CDCl_3$) δ 2.08 (m, 2H), 2.70 (m, 2H), 3.44 (m, 1H), 3.64 (d, 2H, *J* = 13.9 Hz), 3.79 (d, 2H, *J* = 13.9 Hz), 7.32 (m, 15H).

(*R*)-2-(*N*,*N*-dibenzylamino)-3-cyclohexylpropanoic acid (7d): yield 78% (based on **5d**); ^{1}H NMR ($CDCl_3$) δ 0.62−1.80 (set of m, 13H), 3.44 (dd, 1H, *J* = 6.7, 9.0 Hz), 3.70 (d, 2H, *J* = 14.0 Hz), 3.82 (d, 2H, *J* = 14.0 Hz), 7.34 (m, 10H).

(*S*)-2-(*N*,*N*-dibenzylamino)-2-cyclohexylacetic acid (7e): yield 82% (based on **5e**); ^{1}H NMR ($CDCl_3$) δ 0.72−2.38 (set of m, 11H), 3.04 (d, 1H, *J* = 10.0 Hz), 3.47 (d, 2H, *J* = 14.1 Hz), 4.04 (d, 2H, *J* = 14.1 Hz), 7.26 (m, 10 H).

(*R*)-2-(*N*,*N*-dibenzylamino)-3-methylbutanoic acid (7f): yield 79% (based on **5f**); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3H, *J* = 7.8 Hz), 1.05 (d, 3H, *J* = 8.0 Hz), 2.18 (m, 1H), 2.91 (d, 1H, *J* = 11.3 Hz), 3.46 (d, 2H, *J* = 13.9 Hz), 4.02 (d, 2H, *J* = 13.9 Hz), 7.32 (m, 10 Hz).

(2*R*,3*S*)-2-(*N*,*N*-dibenzylamino)-3-methylpentanoic acid (7g): yield 74% (based on **5g**); ^{1}H NMR ($CDCl_3$) δ 0.86 (m, 3H), 1.03 (d, 3H, *J* = 6.7 Hz), 1.27 (m, 2H), 2.00 (m, 1H), 3.05 (d, 1H, *J* = 11.1 Hz), 3.44 (d, 2H, *J* = 14.1 Hz), 4.02 (d, 2H, *J* = 14.1 Hz), 7.35 (m, 10H).

(*R*)-2-(*N*,*N*-dibenzylamino)propanoic acid (7h): yield 64% (based on **5h**); ^{1}H NMR ($CDCl_3$) δ 1.41 (d, 3H, *J* = 7.0 Hz), 3.56 (q, 1H, *J* = 7.0 Hz), 3.57 (d, 2H, *J* = 11.9 Hz), 3.87 (d, 2H, *J* =11.9 Hz), 7.34 (m, 10 Hz).

Preparation of Amino Acids by Saponification with LiOH or KOH. General Procedure. (*R*)-Methyl 2-(*N*,*N*-dibenzylamino)-4-methylpentanoate (**5a**) (650 mg, 2.00 mmol) was refluxed with $LiOH·H_2O$ (416 mg, 10.0 mmol) in THF (20 mL) and H_2O (10 mL). The reaction was monitored by TLC. After four days the starting material was consumed. The

solution was diluted with ethyl acetate (100 mL), washed with aqueous NH_4Cl (2 × 50 mL), H_2O (100 mL), and brine (100 mL), and then dried ($MgSO_4$), filtered, and concentrated to afford **7a** (535 mg, 86%), which was virtually pure by NMR analysis. Using KOH (560 mg, 10.0 mmol), the saponification took a total of 6 days (yield 79%).

Other *N*,*N*-dibenzylamino esters (**5b**−**d**,**h**) gave similar results; however, this procedure failed to give hydrolysis products **7e**−**g** from **5e**−**g**, which are *β*-branched.

***tert*-Butyl 4-(*N*,*N*-Dibenzylamino)-3-oxo-6-methylheptanoate (3a). General Procedure.** To a stirred solution of *N*,*N*-dibenzylamino acid **7a** (1.34 g, 4.30 mmol) in THF (20 mL) was added CDI (767 mg, 4.70 mmol) at room temperature under a N_2 atmosphere. The resulting solution was stirred at room temperture for 1 h. Meanwhile, a solution of lithium (*tert*-butoxycarbonyl)methanide was made from BuLi (2.50 M, 3.60 mL, 9.00 mmol), diisopropylamine (1.30 mL, 9.00 mmol), and *tert*-butyl acetate (1.22 mL, 9.00 mmol). The imidazole solution was added dropwise to the pale yellow solution of the lithium enloate at −78 °C under a N_2 atmosphere. The resulting mixture was stirred at −78 °C for 50 min, quenched with 1 N HCl (50 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide **3a** as a colorless oil (1.32 g, 80% based on **7a**) after purification by flash chromatography (hexane:ether = 95:5 to 85:10): 97% ee by a chiral LIS study using $Eu(hfc)_3$ in comparison with a racemic sample); $[\alpha]^{25}_D$ +93.8 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.79 (d, 3H, J = 5.8 Hz), 0.88 (d, 3H, J = 6.0 Hz), 1.37 (s, 9H), 1.38 (m, 2H), 1.81 (m, 1H), 3.34 (dd, 1H, J = 3.3, 9.5 Hz), 3.44 (d, 2H, J = 13.7 Hz), 3.70 (d, 2H, J = 13.7 Hz), 3.53 (s, 2H), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 22.7, 23.5, 25.8, 31.3, 48.1, 54.9, 64.8, 82.0, 127.2, 127.7, 128.9, 129.5, 139.7, 167.4, 204.3; FTIR (neat) 2955, 1730, 1710 cm^{-1}.

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxo-5-phenylpentanoate (3b):** yield 76% (based on **7b**) and >97% ee as a colorless oil after purification by flash chromatography (hexane: ether = 95:5 to 85:10); $[\alpha]^{25}_D$ −69.4 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9H), 3.02 (m, 2H), 3.37 (d, 1H, J = 15.4 Hz), 3.54 (d, 2H, J = 13.2 Hz), 3.57 (d, 1H, J = 15.4 Hz), 3.60 (dd, 1H, J = 3.7, 7.5 Hz), 3.82 (d, 2H, J = 13.2 Hz), 7.30 (m, 15H); ^{13}C NMR (CDCl3) δ 28.2, 28.9, 48.2, 55.1, 68.8, 82.0, 126.6, 127.9, 129.0, 129.5, 130.1, 139.2, 140.0, 166.9, 203.0; FTIR (neat) 2976, 1745, 1730 cm^{-1}.

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxo-6-phenylhexanoate (3c):** yield 78% (based on **7c**) and 94% ee as a colorless oil after purification by radial chromatography (hexane:ethyl acetate = 95:5); $[\alpha]^{25}_D$ −35.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (CDCl3) δ 1.38 (s, 9H), 1.88 (m, 1H), 2.19 (m, 1H), 2.33 (m, 1H), 2.70 (m, 1H), 3.28 (dd, 1H, J = 2.8, 9.6 Hz), 3.35 (d, 2H, J = 13.4 Hz), 3.44 (d, 1H, J = 15.8 Hz), 3.54 (d, 1H, J = 15.8 Hz), 3.67 (d, 2H, J = 13.4 Hz), 7.28 (m, 15H); ^{13}C NMR (CDCl3) δ 24.6, 28.4, 28.8, 33.5, 47.9, 55.0, 65.7, 82.0, 126.5, 127.8, 128.1, 129.6, 139.4, 142.4, 167.5, 203.5; FTIR (neat) 2987, 1741, 1716 cm^{-1}.

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxo-5-cyclohexylpentanoate (3d):** yield 77% (based on **7d**) and > 97% ee as a colorless oil after purification by flash chromatography (hexane: ether = 85:10); $[\alpha]^{25}_D$ +113.0 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H), 0.70−1.85 (set of m, 13H), 1.53 (enol) (s, 9H), 3.38 (dd, 1H, J = 4.5, 9.4 Hz), 3.44 (d, 2H, J = 13.5 Hz), 3.47 (d, 1H, J = 15.5 Hz), 3.58 (d, 1H, J = 15.5 Hz), 3.69 (d, 2H, J = 13.5 Hz), 4.80 (enol) (s, 1H), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.7, 28.4, 30.0, 33.5, 34.4, 35.3, 48.2, 54.9, 64.2, 82.0, 127.7, 128.9, 129.5, 140.0, 167.4, 204.5; FTIR (neat) 2937, 1745, 1720 cm^{-1}.

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxo-4-cyclohexylbutanoate (3e):** yield 73% (based on **7e**) and >97% ee as a colorless oil after purification by flash chromatography (hexane:ethyl acetate = 95:5 to 90:10); $[\alpha]^{25}_D$ −200.5 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.70−2.24 (set of m, 11H), 1.46 (s, 9H), 1.53 (enol) (s, 9H), 3.17 (d, 1H, J = 10.4 Hz), 3.18 (d, 1H, J = 15.8 Hz), 3.28 (d, 1H, J = 15.8 Hz), 3.39 (enol) (d, 2H, J = 14.1 Hz), 3.59 (d, 2H, J =14.0 Hz), 3.96 (d, 2H, J = 14.0 Hz), 3.99 (enol) (d, 2H, J = 14.1 Hz), 4.70 (enol) (s, 1H),7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) (keto and enol) δ 26.2, 26.5, 27.1, 28.4, 28.8, 30.5, 30.9, 35.7, 37.3, 52.7, 54.7, 67.3, 70.2, 81.4, 82.0, 94.8, 127.2, 127.6, 128.6, 129.0, 140.0, 140.7, 172.9, 174.0, 205.1; FTIR (neat) 2937, 1745, 1715, 1646 (br) cm^{-1}. Anal. Calcd for $C_{28}H_{37}O_3N$: C, 77.20; H, 8.56; N, 3.22. Found: C, 77.30; H, 8.33; N, 3.15.

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxo-5-methylhexanoate (3f):** yield 75% (based on **7f**) and >97% ee as a colorless oil after purification by flash chromatography (hexane:ethyl acetate = 95:5 to 90:10); $[\alpha]^{25}_D$ +201.7 (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80 (enol) (d, 3H, J = 6.4 Hz), 0.82 (d, 3H, J = 6.5 Hz), 1.08 (enol) (d, 3H, J = 6.5 Hz), 1.12 (d, 3H, J = 6.6 Hz), 1.46 (s, 9H), 1.54 (enol) (s, 9H), 2.28 (m, 1H), 3.07 (d, 1H, J = 10.4 Hz), 3.21 (d, 1H, J = 15.0 Hz), 3.30 (d, 1H, J = 15.0 Hz), 3.38 (enol) (d, 2H, J = 14.0 Hz), 3.60 (d, 2H, J = 13.9 Hz), 3.94 (d, 2H, J = 13.9 Hz), 3.98 (enol) (d, 2H, J = 14.0 Hz), 4.73 (enol) (s, 1H), 7.31 (m, 10H); ^{13} C NMR ($CDCl_3$) (keto and enol) δ 20.4, 20.7, 26.5, 27.6, 28.4, 28.9, 52.4, 54.7, 68.6, 71.4, 81.4, 82.0, 94.7, 127.2, 127.6, 128.6, 129.3, 139.8, 140.7, 174.2, 204.8; FTIR (neat) 2977, 1751, 1721, 1646 (br) cm^{-1}. Anal. Calcd for $C_{25}H_{33}O_3N$: C, 75.91; H, 8.41; N, 3.54. Found: C, 76.07; H, 8.18; N, 3.56.

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxo-5-methylheptanoate (3g):** yield 74% (based on**7g**) and > 97% ee as a colorless oil after purification by flash chromatography (hexane: ethyl acetate = 95:5 to 90:10); $[\alpha]^{25}_D$ +197.3 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, J = 6.9 Hz), 1.08 (d, 3H, J = 6.8 Hz), 1.25 (m, 1H), 1.46 (s, 9H), 1.54 (enol) (s, 9H), 2.08 (m, 2H), 3.17 (d, 1H, J = 6.4 Hz), 3.19 (d, 1H, J = 15.6 Hz), 3.31 (d, 1H, J = 15.6 Hz), 3.37 (enol) (d, 2H, J = 14.0 Hz), 3.59 (d, 2H, J = 13.9 Hz), 3.93 (d, 2H, J = 13.9 Hz), 3.99 (enol) (d, 2H, J = 14.0 Hz), 4.70 (enol) (s, 1H), 7.31 (m, 10H), 12.16 (enol) (s, 1H); ^{13}C NMR ($CDCl_3$) (keto and enol) δ 11.8, 16.2, 16.6, 27.1, 28.5, 28.8, 32.8, 34.2, 52.4, 54.6, 67.2, 70.1, 82.0, 94.8, 127.2, 127.6, 128.6, 128.9, 139.8, 140.7, 166.8, 173.0, 174.2, 204.7; FTIR (neat) 2957, 1751, 1711, 1646 (enol) (br) cm^{-1}. Anal. Calcd for $C_{26}H_{35}O_3N$: C, 76.25; H, 8.61; N, 3.42. Found: C, 76.48; H, 8.42; N, 3.50.

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxo-pentanoate (3h):** yield 78% (based on **7h**) and 70% ee as a colorless oil after purification by flash chromatography (hexane: ether = 85:5 to 80:10); ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 3H, J = 6.7 Hz), 1.37 (s, 9H), 3.41 (d, 2H, J = 13.6 Hz), 3.46 (q, 1H, J = 6.7 Hz), 3.54 (d, 1H, J = 15.6 Hz), 3.68 (d, 1H, J = 15.6 Hz), 3.72 (d, 2H, J = 13.6 Hz), 7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) 6.9, 28.4, 47.3, 55.0, 62.6, 81.9, 127.9, 129.0, 129.3, 139.4, 167.6, 205.7; FTIR (neat) 2996, 1741, 1716 cm^{-1}.

Preparation of 3-Oxo Esters Directly from Esters 5a−**d,h.** ***tert*-Butyl 4-(*N*,*N*-Dibenzylamino)-3-oxo-6-methylheptanoate (3a). General Procedure.** A solution of lithium (*tert*-butylcarbonyl)methanide was prepared using BuLi (2.50 M, 2.10 mL, 5.25 mmol), diisopropylamine (531 mg, 5.25 mmol), and *tert*-butyl acetate (609 mg, 5.25 mmol). To this pale yellow solution at −78 °C was added dropwise (*S*)-methyl 2-(*N*,*N*-dibenzylamino)-4-methylpentanoate (**5a**) (812 mg, 2.50 mmol). The resulting mixture was stirred at −78 °C for 5 min and then warmed to room temperature. The reaction was monitord by TLC. Six hours later, the yellow solution was quenched with 1 N HCl (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated by evaporation in vacuum to provide **3a** as a colorless oil (870 mg, 85% based on **5a**; 87% ee by chiral LIS study using $Eu(hfc)_3$ in comparison with a racemic sample).

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxo-5-phenylpentanoate (3b):** yield 84% (based on 5b) and 92% ee as a colorless oil after purification by radial chromatography (hexane:ether = 85:10).

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxo-6-phenylhexanoate (3c):** yield 88% (based on **5c**) and 88% ee as a colorless oil after purification by radial chromatography (hexane:ether = 95:5).

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxo-5-cyclohexylpentanoate (3d):** yield 85% (based on **5d**) and 90% ee as a colorless oil after purification by radial chromatography (hexane: ethyl acetate = 95:5).

***tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-oxopentanoate (3h):** yield 80% (based on **5h**) and 78% ee as a colorless oil after purification by radial chromatography (hexane:ether = 85:5 to 80:10).

This procedure failed for the synthesis of **3e**−**g** from **5e**−**g**, which are *β*-branched.

(3*R*,4*R*)-*tert*-Butyl 4-(*N*,*N*-Dibenzylamino)-3-hydroxy-6-methylheptanoate, (8a). General Procedure. 3-Oxo ester **3a** (372 mg, 0.910 mmol) was dissolved in methanol (17.0 mL), which was dried using Mg turnings and iodine. The resulting

solution was then cooled to −22 °C and treated with $NaBH_4$ (70.0 mg, 1.84 mmol). The reaction was monitored by TLC. After 3.5 h, the solution was quenched with H_2O (100 mL) at pH = 5−6 (adjusted by 1 N HCl), extracted with ether (3 × 100 mL), washed by brine (100 mL), dried ($MgSO_4$), and concentrated to provide **8a** as a colorless oil (325 mg, 87% based on **3a**); 88% de based on ^{1}H NMR. The diastereomers were separated by flash chromatography (hexane:ether = 85:15) in the ratio of 94:6. The major diastereomer: $[\alpha]^{25}_D$ −2.5 (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 6H, *J* = 6.4 Hz), 1.43 (s, 9H), 1.24 (m, 2H), 1.60 (m, 1H), 2.31 (m, 2H), 2.52 (m, 1H), 3.43 (d, 2H, *J* = 13.4 Hz), 3.92 (d, 2H, *J* = 13.4 Hz), 3.68 (m, 1H), 7.28 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 23.3, 23.8, 26.6, 28.6, 35.2, 41.1, 54.6, 60.1, 69.3, 81.3, 127.6, 128.9, 129.5, 140.0, 172.5; FTIR (neat) 3483 (br), 2955, 1728 cm^{-1}. Anal. Calcd for $C_{26}H_{37}O_3N$: C, 75.87; H, 9.06; N, 3.40. Found: C, 76.04; H, 8.86; N, 3.34.

(3*S*,4*S*)-*tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-hydroxy-5-phenylpentanoate (8b): yield 90% (based on **3b**) and 92% de based on ^{1}H NMR of a colorless oil. The diastereomers were separated by flash chromatography (hexane:ether = 90:10) in the ratio of 96:4. The major diastereomer: $[\alpha]^{25}_D$ +11.5 (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.23 (m, 2H), 2.84 (m, 2H), 2.92 (m, 1H), 3.42 (d, 2H, *J* = 13.3 Hz), 4.07 (d, 2H, *J* = 13.3 Hz), 3.90 (m, 1H), 7.28 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 28.6, 31.3, 41.1, 55.0, 63.5, 68.5, 81.3, 126.6, 127.6, 128.9, 139.8, 140.7, 172.9; FTIR (neat) 3525 (br), 2986, 1736 cm^{-1}. Anal. Calcd for $C_{29}H_{35}O_3N$: C, 78.17; H, 7.92; N, 3.14. Found: C, 77.79; H, 7.69; N, 3.06.

(3*S*,4*S*)-*tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-hydroxy-6-phenylhexanoate (8c): yield 92% (based on **3c**) and 92% de based on ^{1}H NMR of a colorless oil. The diastereomers were separated by flash chromatography (hexane:ether = 85:5 to 90:10) in the ratio of 96:4. The major diastereomer: $[\alpha]^{25}_D$ +77.2 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.79 (m, 1H), 2.05 (m, 1H), 2.40 (m, 2H), 2.50 (m, 1H), 2.71 (m, 1H), 3.42 (d, 2H, *J* = 13.4 Hz), 3.94 (d, 2H, *J* = 13.4 Hz), 4.06 (m, 1H), 7.27 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 27.8, 28.6, 35.0, 41.1, 54.8, 61.6, 69.0, 81.4, 126.6, 127.6, 128.9, 129.6, 139.8, 142.4, 172.5; FTIR (neat) 3505 (br), 2947, 1736 cm^{-1}. Anal. Calcd for $C_{30}H_{37}O_3N$: C, 78.40; H, 8.11; N, 3.05. Found: C, 78.69; H, 8.06; N, 3.02.

(3*R*,4*R*)-*tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-hydroxy-5-cyclohexylpentanoate (8d): yield 91% (based on **3d**) and 94% de by ^{1}H NMR of a colorless oil. The diastereomers were separated by flash chromatography (hexane:ether = 80:20) in the ratio of 97:3. The major diastereomer: $[\alpha]^{25}_D$ −15.7 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.75−1.82 (set of m, 13H), 1.44 (s, 9H), 2.28 (m, 2H), 2.52 (m, 1H), 3.44 (d, 2H, *J* = 13.6 Hz), 3.92 (d, 2H, *J* =13.6 Hz), 3.94 (m, 1H), 4.12 (br) (s, 1H), 7.28 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.9, 28.6, 33.8, 34.0, 34.5, 36.0, 41.4, 54.6, 59.2, 69.4, 81.3, 127.5, 128.8, 129.5, 140.1, 172.5; FTIR (neat) 3495 (br), 2947, 1736 cm^{-1}. Anal. Calcd for $C_{29}H_{41}O_3N$: C, 77.12; H, 9.15; N, 3.10. Found: C, 77.20; H, 8.94; N, 3.12.

(3*S*,4*S*)-*tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-hydroxy-4-cyclohexylbutanoate (8e): yield 89% (based on **3e**) and 98% de by ^{1}H NMR of a colorless oil. The diastereomers were separated by flash chromatography (hexane:ether = 85:15) in the ratio of 99:1. The major diastereomer: $[\alpha]^{25}_D$ +2.25 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.05−1.95 (set of m, 11H), 1.44 (s, 9H), 2.18 (m, 2H), 2.26 (m, 1H), 3.52 (d, 2H, *J* = 13.1 Hz), 3.96 (d, 2H, *J* =13.1 Hz), 4.19 (dd, 1H, *J* = 2.5, 7.5 Hz), 4.25 (br, 1H), 7.27 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.8, 27.3, 28.6, 30.7, 34.2, 36.7, 42.2, 54.9, 65.8, 81.1, 127.6, 128.7, 129.8, 139.7, 172.3; FTIR (neat) 3525 (br), 2947, 1730 cm^{-1}. Anal. Calcd for $C_{28}H_{39}O_3N$: C, 76.85; H, 8.98; N, 3.20. Found: C, 76.89; H, 8.95; N, 3.20.

(3*R*,4*R*)-*tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-hydroxy-5-methylhexanoate (8f): yield 91% (based on **3f**) and 96% de by ^{1}H NMR of a colorless oil. The diastereomers were separated by flash chromatography (hexane:ethyl acetate = 90:10) in the ratio of 98:2. The major diastereomer: $[\alpha]^{25}_D$ +4.4 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3H, *J* = 4.1 Hz), 1.06 (d, 3H, *J* = 6.8 Hz), 1.44 (s, 9H), 2.25 (m, 2H), 2.27 (m, 1H), 2.33 (m, 1H), 3.54 (d, 2H, *J* = 13.2 Hz), 3.98 (d, 2H, *J* = 13.2 Hz), 4.09 (br, 1H), 4.20 (dd, 1H, *J* = 3.4, 6.9 Hz), 7.27 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 20.4, 23.8, 26.4, 28.6, 41.9, 55.0, 65.7, 66.7, 81.1, 127.6, 128.8, 129.4, 129.8, 172.5; FTIR (neat) 3515 (br), 2937, 1726 cm^{-1}. Anal. Calcd for $C_{25}H_{35}O_3N$: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.61; H, 8.80; N, 3.54.

(3*R*,4*R*,5*S*)-*tert*-Butyl 4-(*N*,*N*-dibenzylamino)-3-hydroxy-5-methylheptanoate (8g): yield 90% (based on **3g**) and 97% de by ^{1}H NMR as a colorless oil. The diastereomers were separated by flash chromatography (hexane:ethyl acetate = 85:15) in the ratio of 98.5:1.5. The major diastereomer: $[\alpha]^{25}_D$ +5.0 (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 7.2 Hz), 1.03 (d, 3H, *J* = 7.2 Hz), 1.08 (m, 1H), 1.44(s, 9H), 1.85 (m, 2H), 2.28 (m, 2H), 2.44 (m, 1H), 3.52 (d, 2H, *J* = 13.1 Hz), 3.88 (d, 2H, *J* = 13.1 Hz), 4.09 (br) (s, 1H), 4.26 (m, 1H), 7.28 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 12.6, 19.4, 26.7, 28.6, 33.6, 41.8, 55.2, 65.4, 66.4, 81.3, 127.5, 128.8, 129.8, 140.0, 172.3; FTIR (neat) 3495 (br), 2957, 1721 cm^{-1}. Anal. Calcd for $C_{26}H_{37}O_3N$: C, 75.87; H, 9.06; N, 3.40. Found: C, 76.04; H, 8.91; N, 3.39.

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Supporting Information Available: The ^{13}C NMR spectra of **3a**−**d, h** and the ^{1}H NMR spectra of **4c**−**e, g** and **5a**−**h** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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