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Asymmetric Nitroaldol Reaction. Synthesis of Taxotere Side Chain and (−)-Bestatin Using (1*R*)-8-Phenylmenthyl Glyoxylate

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The nitroaldol reaction of (1*R*)-8-phenylmenthyl glyoxylate (**3b**) with 1-nitro-1-phenylmethane (**4**) or with 1-nitro-2-phenylethane (**13**) led stereoselectively to adducts *syn*-**2b** and *syn*-**12b**, which were then transformed into the Taxotere side chain and (−)-bestatin hydrochloride in overall yields of 52% and 31%, respectively.

Introduction

The β-amino α-hydroxy acid moiety is common structural component in a vast group of naturally occurring molecules. The presence of this moiety and the relative (as well as absolute) stereochemistry is essential for biological activity of molecules containing it. The need to prepare these compounds, as well as analogues, has dramatically increased the importance of development of methods for the synthesis. In recent years, stereoselective synthesis of β-amino α-hydroxy acids has attracted much attention due to their presence in various medicinally important molecules.[1] Additionally, a number of their amide derivatives, isolated recently from bacterial cultures, displayed the significant activity against aminopeptidases.[2] For this reason, a variety of stereoselective synthetic methods of formation of β-amino α-hydroxy acids were recently presented,[3] including aminohydroxylation;[4] reduction of α-keto acid derivatives;[5] nucleophilic addition to chiral aldehydes,[6] aminoaldehydes,[7] olefins,[8] amides,[9] or imines;[10] cycloaddition reactions;[11] ring-opening procedures of chiral epoxides[12] and β-lactams;[13] halocyclocarbamation of allylamines;[14] and transformations of chiral sugars[15] or α-amino acids.[16]

Results and Discussion

Very recently, we investigated the nitroaldol reaction of chiral derivatives of glyoxylic acid bearing various auxiliaries, such as (1*R*)-8-phenylmenthol, (2*R*)-bornane-10,2-sultam, (4*R*)-methyl-(5*S*)-phenyloxazolidnone, and 7,7-dimethylnorbornane-(1*S*,2*R*)-oxazolidinone with simple

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nitroalkanes.[17] In most cases, the reaction proceeded with high stereoselectivity. The configuration of major diastereomers formed in these reactions was established as (2*S*,3*R*)—like in most of the biologically important *β*-amino α-hydroxy carboxylic acid derivatives. Thus, the readily available nitro alcohols formed by this facile procedure appeared to be very convenient precursors for *β*-amino α-hydroxy acids.

To illustrate this, we decided to synthesize methyl (3*R*)-*tert*-butoxycarbonylamino-(2*S*)-hydroxy-3-phenylpropionate—known as a side chain of Taxotere (**1**).[18] Taxotere (docetaxel) is a semisynthetic anticancer agent, closely related to palitaxel (Taxol), derived from bacatin III of the needles of European yew *Taxus baccata*.[19] The simple retrosynthetic analysis, shown in Scheme 1, points out that chiral derivatives of glyoxylic acid could serve as a starting material for the synthesis of this compound.

On the basis of our model studies on diastereoselective Henry reaction, we resolved to apply two chiral auxiliaries, (1*R*)-8-phenylmenthol and (2*R*)-bornane-10,2-sultam, and compare their efficacy in the crucial, for the synthesis, reaction of 1-nitro-1-phenylmethane (**4**) with glyoximide **3a** and glyoxylate **3b** (Scheme 2). We performed the reactions using different catalytic systems. The results are summarized in Table 1.

Only moderate yields were obtained for the reactions of glyoximide **3a** with 1-nitro-1-phenylmethane (**4**), promoted by both TBAF·3H_2O and Al_2O_3 (Table 1, entries 1 and 3); substantial amounts of hydrolyzed sultam auxiliary were found in the crude product mixtures. To improve the reaction yields we decided to use Al_2O_3 activated by heating at 120 °C under reduced pressure (method A′) and TBAF dried at 80 °C in a vacuum (method B′). Indeed, it resulted in much better yield for the reactions under investigation, especially for activated Al_2O_3 (entries 2 and 4). Presumably, for the reactions of glyoxylate **3b** we did not observe the influence of the way of preparing catalysts; the ester moiety does not hydrolyze as easily as the imide moiety. Both TBAF and Al_2O_3 led the reactions to the desired nitro alcohols in high yields (entries 5−8). As far as diastereoselectivity is concerned, we found that (1*R*)-8-phenylmenthol is a slightly less efficient chiral auxiliary compared to (2*R*)-bornane-10,2-sultam. The configuration assignments for the major diastereomers **2a** and **2b** were made using X-ray analysis (Figures 1 and 2). They show (2*S*)-absolute configuration for the hydroxylic stereogenic center. The relative configuration of nitro and hydroxy groups is syn. On the basis of our other investigations, we established that minor diastereomers **2a** and **2b** possess an *anti* relative configuration of nitro and hydroxy groups and absolute configuration (2*S*) of the hydroxylic stereogenic centers.[20] For our synthetic application we have chosen (1*R*)-8-phenylmenthyl derivative. Despite the lower chiral induction for this auxiliary we obtained better chemical yields, which gave us finally better yield for the single major diastereomer used in the total synthesis.

Condensation of glyoxylate **3b** with 1-nitro-1-phenylmethane (**4**), catalyzed with activated aluminum oxide,

SCHEME 1. Retrosynthetic Analysis of the Taxotere Side Chain

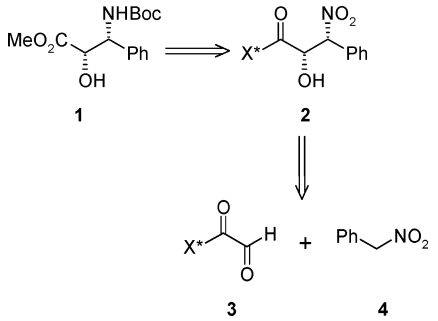

TABLE 1. Results of the Reactions of 3a or 3b with 4

entry	aldehyde	method[a]	time (h)	yield[b] (%)	diastereomeric ratio[c] *syn*-**2**/*anti*-**2**/III/IV
1	**3a**	A	2.5	46	84:16:0:0
2	**3a**	A′	0.5	90	75:20:5:0
3	**3a**	B	2.5	42	93:7:0:0
4	**3a**	B′	1.5	60	92:8:0:0
5	**3b**	A	3	90	89:8:3:0
6	**3b**	A′	1	97	87:13:0:0
7	**3b**	B	20	86	51:35:14:0
8	**3b**	B″	1.5	90	63:23:14: 0

[a] Methods: (A) Al_2O_3, rt; (A′) activated Al_2O_3, rt; (B) TBAF·3H_2O, −78 °C; (B′) dried TBAF, −78 °C; (B″) TBAF·3H_2O, −20 °C. [b] Yield given for isolated products. [c] Calculated by both HPLC (Merck, Nucleosile 100, 3 *μ*m, hexane/*i*-PrOH) and ^1H NMR (Bruker AM-500 MHz, $CDCl_3$).

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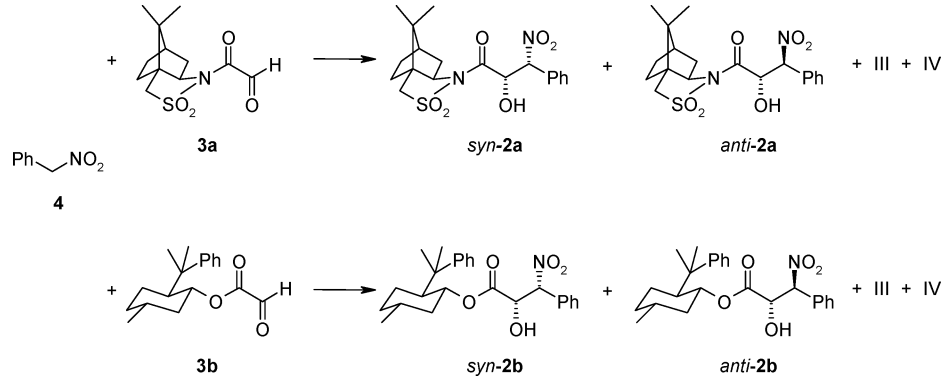
SCHEME 2. Reactions of Chiral Aldehydes 3a or 3b with 1-Nitro-1-phenylmethane (4)



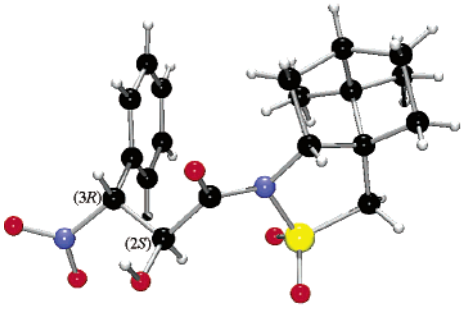


FIGURE 1. X-ray structure of (2′*R*)-*N*-[(2*S*)-hydroxy-(3*R*)-nitro-3-phenylpropanoyl]bornane-10′,2′-sultam (*syn*-**2a**).

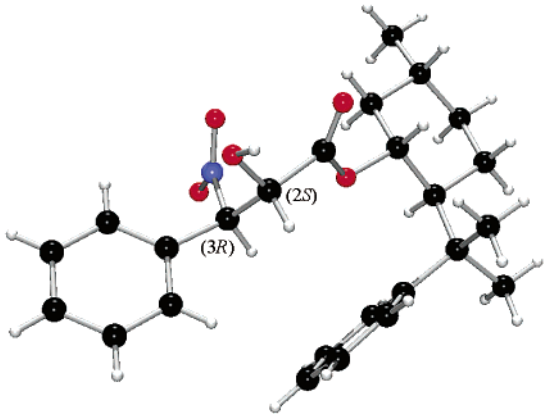


FIGURE 2. X-ray structure of *O*-[(2*S*)-hydroxy-(3*R*)-nitro-3-phenylpropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (*syn*-**2b**).

carried out at 25 °C, afforded the 87:13 mixture of two diastereomeric *syn*/*anti* nitro alcohols in 97% yield (Scheme 3).

Nitro alcohol *syn*-**2b**, isolated by column chromatography in 81% yield, was catalytically reduced and then protected with di-*tert*-butyl dicarbonate to give the appropriate *N*-Boc derivative **5** in 93% overall yield. Subsequent acetylation (95% yield) and hydrolysis of the ester functionality (89% yield) furnished the amino acid **7**, which was esterified with diazomethane to afford the methyl ester **8** in 90% yield. Finally, the acetyl group was removed to give the ester **1** in 90% yield. Both compounds **8** and **1** had the optical rotations and spectral properties identical to those reported in the literature.[18,21]

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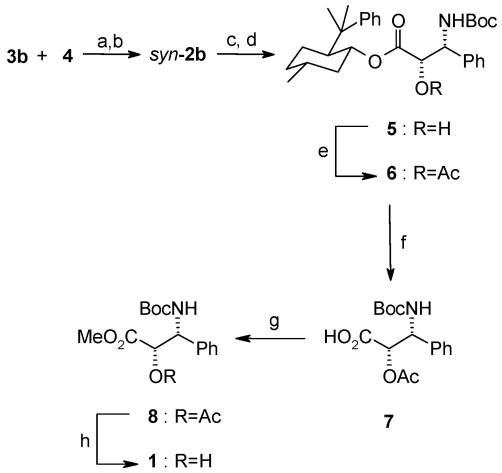
SCHEME 3. Synthesis of Taxotere Side Chain[a]



[a] Reagents and conditions: (a) activated Al_2O_3, dry THF, rt, 1 h; (b) column chromatography; (c) H_2, catalytic Raney-Ni, MeOH, rt, 12 h; (d) $(Boc)_2O$, satd aq $NaHCO_3$, AcOEt, rt, 2 h; (e) Ac_2O, Et_3N, Et_2O, rt, 20 min; (f) MeONa (2 equiv), MeOH, rt, 24 h; (g) CH_2N_2, Et_2O, rt, 16 h; (h) MeONa (3 equiv), MeOH, rt, 1.5 h.

During the retrosynthetic analysis performed for the Taxotere side chain we realized that the use of 1-nitro-2-phenylethane (**13**) instead of 1-nitro-1-phenylmethane (**4**) opens a route to another biologically important compound, namely (−)-bestatin **9**,[22] which contains (3*R*)-amino-(2*S*)-hydroxy-4-phenylbutanoic acid (AHPBA) (**11**) residue (Scheme 4). Bestatin, a dipeptide, isolated from *Streptomyces olivoreticulithe*, is an aminopeptidase inhibitor that exhibits immunomodulatory activity[2c] and is used clinically as an adjuvant in cancer chemotherapy.[23]

Similar to synthesis of the Taxotere side chain, we have also conducted separate experiments to study the effect of chiral auxiliary and catalytic way. We examined the reactions of 1-nitro-2-phenylethane (**13**) with the glyox-

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SCHEME 4. Retrosynthetic Analysis of (−)-Bestatin

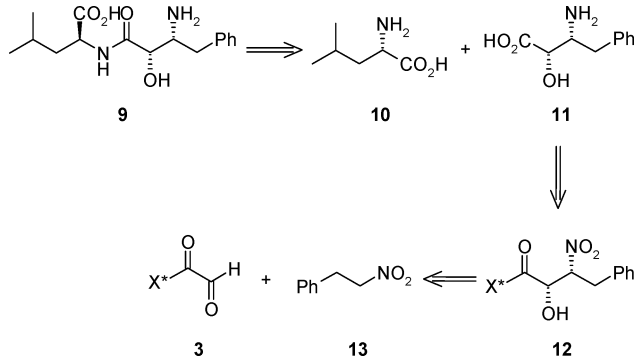


TABLE 2. Results of Reactions of 3a or 3b with 13

entry	aldehyde	method[a]	time (h)	yield[b] (%)	diastereomeric ratio[c] *syn*-**12**/*anti*-**12**/III/IV
1	**3a**	A′	1	91	59:19:16:6
2	**3a**	B	1	6	
3	**3a**	B′	8	50	57:20:13:10
4	**3b**	A	48	60	47:32:14:7
5	**3b**	A′	7	98	62:19:13:6
6	**3b**	A″	24	89	71:19:5:5
7	**3b**	B	2.5	97	28:27:26:19

[a] Methods: (A) Al_2O_3, rt; (A′) activated Al_2O_3, rt; (A″) activated Al_2O_3, −20 °C; (B) TBAF·$3H_2O$, −78 °C; (B′) dried TBAF, −78 °C. [b] Yield given for isolated products. [c] Calculated by both HPLC (Merck, Nucleosile 100, 3 μm, hexane/*i*-PrOH) and ^{1}H NMR (Bruker AM-500 MHz, $CDCl_3$).

imide **3a** and glyoxylate **3b** (Scheme 5). Results are summarized in Table 2.

The reactions of glyoximide **3a** with 1-nitro-2-phenylethane (**13**), promoted by both TBAF·$3H_2O$ and dried TBAF, provided the products in moderate yields (Table 2, entries 2 and 3). The activated catalysts gave much higher yields for the reactions under investigation (entries 1 and 3). Similar relationships were observed for the reactions of glyoxylate **3b** (entries 4−7). As far as diastereoselectivity is concerned, we found that in this case (1*R*)-8-phenylmenthol is a slightly more efficient chiral auxiliary compared to (2*R*)-bornane-10,2-sultam. We did not make the configuration assignments for the major diastereomers **12a** and **12b**. On the basis of our previous investigations made for the synthesis of the Taxotere side chain, we assumed that the absolute configuration of the hydroxylic stereogenic center would be (*2S*) and the relative configuration of nitro and

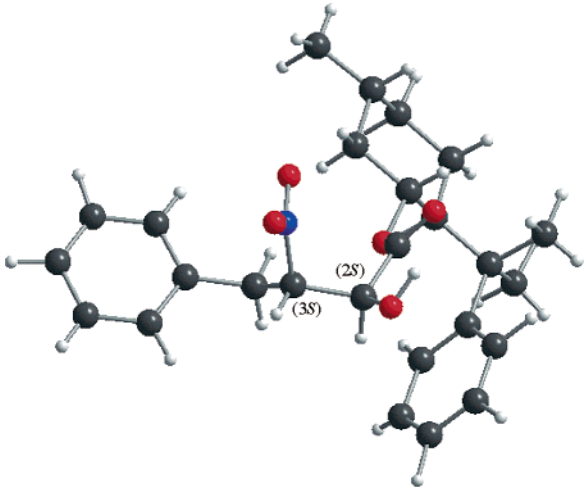


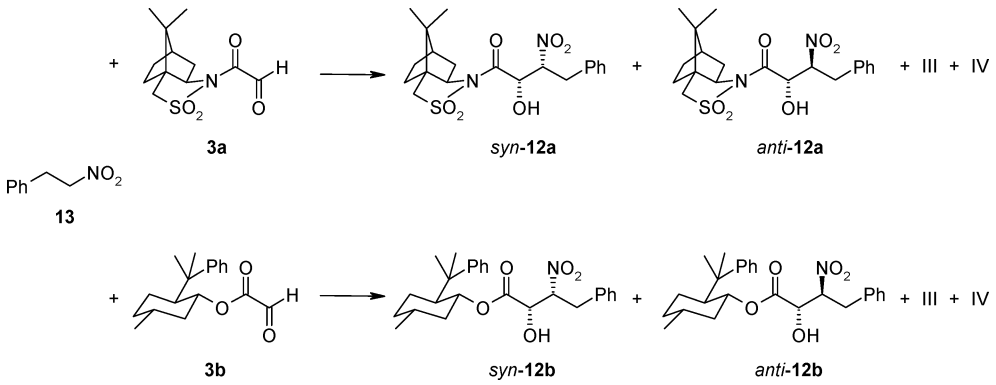
FIGURE 3. X-ray structure of *O*-[(2*S*)-hydroxy-(3*S*)-nitro-3-phenylpropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (*anti*-**12b**).

hydroxy groups would be *syn*. On the other hand, we determined by X-ray analysis the *anti* relative configuration of nitro and hydroxy groups and the absolute configuration (*2S*) of the hydroxylic stereogenic center for the minor diastereomer *anti*-**12b** (Figure 3).

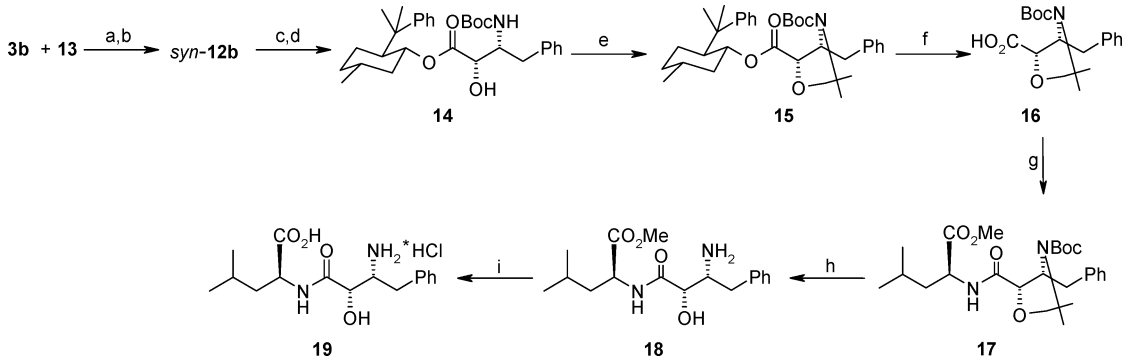
To our synthetic application we have chosen (1*R*)-8-phenylmenthol as a convenient and efficient chiral auxiliary as far as diastereoselectivity and chemical yield are concerned. The reaction of (1*R*)-8-phenylmenthyl glyoxylate (**3b**) with 1-nitro-2-phenylethane (**13**), catalyzed by activated aluminum oxide and carried out at −20 °C, afforded the mixture (71:19:5:5) of diastereomeric nitro alcohols **12** in 89% yield (Scheme 6).

The major diastereomer *syn*-**12b**, which was isolated in 63% yield by column chromatography, was catalytically hydrogenated, followed by protection of the amino group using di-*tert*-butyl dicarbonate to afford product **14** in 95% overall yield. Compound **14** was then subjected to the reaction with dimethoxypropane to give, after hydrolysis of ester functionality, the acid **16** in 78% yield. The protected β-amino α-hydroxy acid **16** was coupled with the methyl ester of L-leucine using the mixed anhydride method to afford in 95% yield dipeptide **17** which was finally deprotected in a two-step reaction sequence with 70% overall yield. (−)-Bestatin hydrochloride **19**, obtained in an eight-step sequence (31% overall yield), was shown to be identical in optical rotation and

SCHEME 5. Reactions of Chiral Aldehydes 3a or 3b with 1-Nitro-2-phenylethane (13)



SCHEME 6. Synthesis of (−)-Bestatin[a]



[a] Reagents and conditions: (a) activated Al_2O_3, dry THF, rt, 7 h; (b) column chromatography; (c) H_2, catalytic Raney-Ni, MeOH, rt, 16 h; (d) $(Boc)_2O$, satd aq $NaHCO_3$, AcOEt, rt, 2 h; (e) DMP, catalytic TsOH, toluene, 50 °C, 5 h; (f) MeONa, MeOH, rt, 24 h; (g) *N*-ethylmorpholine, isobutyl chloroformate, L-LeuOMe, THF (dry), −5 °C → rt, 1 h; (h) catalytic TsOH, MeOH, rt, 24 h; (i) 1 N HCl, rt, 16 h.

^{1}H and ^{13}C NMR data with the product reported in the literature.[22]

In conclusion, we demonstrated that the enantiomerically pure *β*-amino α-hydroxy acids can be readily synthesized by transformation of nitro alcohols obtained from (1*R*)-8-phenylmenthyl glyoxylate (**3b**) via nitroaldol reaction. Taxotere side chain and (−)-bestatin were successfully synthesized in overall yields of 52% and 31%, respectively.

Experimental Section

General Procedure for the Neutral Al_2O_3 (Method A) and Activated Al_2O_3 (Method A′ and A″) Catalyzed Nitroaldol Reactions. The carbonyl compound (1 mmol) and the nitro compound (2 mmol) were added to a solution of a catalyst (2 mmol) in dry THF (5 mL) at appropriate temperature (rt, method A′; −20 °C, method A″) under inert gas atmosphere. Activated Al_2O_3 was prepared just before the reaction by heating at 120 °C under reduced pressure (0.2 mmHg) over 2 h. The reaction was monitored by TLC, and when finished the catalyst was filtered off and the solvent was evaporated. All products were purified by silica gel column chromatography (hexane/AcOEt).

General Procedure for the TBAF·3H$_2$O (Tetrabutylammonium Fluoride) (Method B) and TBAF (Method B′ and B″) Catalyzed Nitroaldol Reactions. A catalyst (0.5 mmol) was added to a solution of the carbonyl compound (1 mmol) in dry THF (5 mL) precooled to −78 °C (−20 °C for B″) under inert gas atmosphere, followed by addition of the nitro compound (2 mmol). Dried TBAF was prepared just before the reaction by heating at 80 °C at reduced pressure (0.2 mmHg) over 2 h. The reaction was monitored by TLC, and when finished it was quenched by addition of saturated aqueous NaCl and extracted with AcOEt. The combined organic extracts were dried ($MgSO_4$), and solvents were evaporated. All products were purified by silica gel column chromatography (hexane/AcOEt).

(2′*R*)-*N*-[(2*S*)-Hydroxy-(3*R*)-nitro-3-phenylpropanoyl]-bornane-10′,2′-sultam (*syn*-2a). ^{1}H NMR (500 MHz; $CDCl_3$): *δ* 7.60−7.35 (m, 5H), 5.95 (d, *J* = 6.6 Hz, 1H), 5.55 (dd, *J* = 6.6, 6.5 Hz, 1H), 3.97 (dd, *J* = 4.7, 7.8 Hz, 1H), 3.66 (d, *J* = 6.5 Hz, 1H), 3.51 (d_{AB}, *J* = 13.8 Hz, 1H), 3.46 (d_{AB}, *J* = 13.8 Hz, 1H), 1.95−1.85 (m, 4H), 1.78−1.74 (m, 1H), 1.67−1.60 (m, 1H), 1.42−1.36 (m, 1H), 1.33−1.23 (m, 1H), 0.92 (s, 3H), 0.79 (s, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): *δ* 168.7, 130.3,130.1, 129.2, 128.8, 92.0, 72.0, 65.1, 52.9, 48.9, 47.7, 44.5, 37.4, 32.7, 26.3, 20.4, 19.7. IR (KBr): 3496, 3291, 2999, 2944, 2909, 1682, 1561, 1367, 1320, 1214, 1137, 1072, 719, 532 cm^{-1}. HRMS-EI: calcd for $C_{19}H_{25}N_2O_6S$ (M + H)$^+$ 409.14333, found 409.14329. Anal. Calcd for $C_{19}H_{24}N_2O_6S$: C, 55.87; H, 5.92; N, 6.86; S, 7.85. Found: C, 55.79; H, 6.08; N, 6.80; S, 7.87. Mp = 169−170 °C (hexane/AcOEt). $[\alpha]^{20}_D$ = −68 (*c* = 1.39; $CHCl_3$). R_f = 0.4 (hexane/AcOEt 7:3).

***O*-[(2*S*)-Hydroxy-(3*R*)-nitro-3-phenylpropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (*syn*-2b).** ^{1}H NMR (500 MHz; $CDCl_3$): *δ* 7.50−7.20 (m, 4H), 7.11−7.06 (m, 1H), 5.14 (d, *J* = 5.1 Hz, 1H), 4.87 (dt, *J* = 10.8, 4.5 Hz, 1H), 3.63 (dd, *J* = 5.1, 6.1 Hz, 1H), 3.05 (d, *J* = 6.1 Hz, 1H), 2.07 (ddd, *J* = 10.8, 3.6, 12.1 Hz, 1H), 1.99 (dd, *J* = 3.6, 13.5 Hz, 1H), 1.78−1.71 (m, 1H), 1.67−1.62 (m, 1H), 1.52−1.41 (m, 1H), 1.30 (s, 3H), 1.26−1.19 (m, 1H), 1.15 (s, 3H), 1.00−0.89 (m, 2H), 0.87 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): *δ* 169.9, 152.3, 131.0, 129.9, 129.1, 128.6, 127.9, 125.4, 124.2, 91.1, 76.9, 71.1, 50.1, 40.5, 39.1, 34.2, 31.1, 30.8, 25.9, 21.6, 21.3. IR (KBr): 3479 2958, 2924, 1730, 1556, 1496, 1456, 1366, 1258, 1121, 957, 766, 701 cm^{-1}. HRMS-LSIMS(+): calcd for $C_{25}H_{31}O_5NNa$ (M + Na)$^+$ 448.20999, found 448.20871. Anal. Calcd: C, 70.57; H, 7.34; N, 3.29, found C. 70.10; H, 7.55; N, 3.32. Mp = 179−180 °C (hexane/AcOEt). $[\alpha]^{20}_D$ = 7.2 (*c* = 0.93; $CHCl_3$). R_f = 0.5 (hexane/AcOEt 8:2).

***O*-[(3*R*)-*tert*-Butoxycarbonylamino-(2*S*)-hydroxy-3-phenylpropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (5).** Hydrogen was bubbled through a solution of nitro alcohol *syn*-**2b** (165 mg, 0.39 mmol) in MeOH (5 mL) containing a catalytic amount of Raney Ni. The progress of the reaction was monitored by TLC. After the mixture was stirred for ca. 16 h at rt, the catalyst was filtered off, solvents were evaporated, and the residue was dissolved in AcOEt and saturated aqueous $NaHCO_3$ (10 mL, 1:1), followed by addition of $(Boc)_2O$ (93 mg, 0.43 mmol). After completion of the reaction, the layers were separated and the water phase was extracted with CH_2Cl_2. After the combined organic layers were dried ($MgSO_4$), the solvents were removed under reduced pressure. Purification was achieved on silica gel column using hexane/AcOEt to produce compound **5** (179 mg, 93%) (R_f = 0.5 hexane/AcOEt 7:3). ^{1}H NMR (500 MHz; $CDCl_3$): *δ* 7.34−7.21 (m, 7H), 7.17−7.04 (m, 3H), 5.21 (d, *J* = 9.4 Hz, 1H), 4.91 (dt, *J* = 10.7, 10.7, 4.4 Hz, 1H), 4.74 (d, *J* = 9.4 Hz, 1H), 3.33 (bs, 1H), 2.84 (bs, 1H), 2.24−2.20 (m, 1H), 1.96−1.92 (m, 1H), 1.84−1.67 (m, 2H), 1.61−1.44 (m, 2H), 1.37 (s, 9H), 1.30 (s, 3H), 1.19 (s, 3H), 1.14−0.92 (m, 2H), 0.86 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): *δ* 172.2, 154.6, 151.9, 139.5, 128.2, 128.0, 127.3, 126.5, 125.2, 79.4, 76.7, 72.9, 55.2, 49.8, 40.7, 39.3, 34.3, 31.3, 30.2, 28.3, 26.1, 22.1, 21.6. IR (film): 3426 2956, 2926, 2869, 1725, 1699, 1504, 1366, 1260, 1172, 1106, 766, 698 cm^{-1}. HRMS-ESI: calcd for $C_{30}H_{41}O_5NNa$ (M + Na)$^+$ 518.28824, found 518.28991. Anal. Calcd: C, 72.70; H, 8.34; N, 2.83. Found: C, 72.63; H, 8.31; N, 2.84. $[\alpha]^{20}_D$ = −12.0 (*c* = 0.1; $CHCl_3$).

***O*-[-(2*S*)-Acetoxy-(3*R*)-*tert*-butoxycarbonylamino-3-phenylpropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (6).** To

a solution of amine **5** (302 mg, 0.61 mmol) in Et_2O (6 mL) was added Ac_2O (287 μL, 3.05 mmol), followed by Et_3N (425 μL, 3.05 mmol). The progress of the reaction was monitored by TLC. After the mixture was stirred at rt for ca. 20 min, solvents were evaporated and the residue was purified on a silica gel column using hexane/AcOEt to afford compound **6** (311 mg, 95%) (R_f = 0.5 hexane/AcOEt 8:2). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.38−7.22 (m, 7H), 7.17−7.05 (m, 3H), 5.23 (d, $J_{2,3}$ = 9.7 Hz, 1H), 4.90 (dd, J = 9.7, 2.3 Hz, 1H), 4.81 (dt, J = 10.8, 10.8, 4.2 Hz, 1H), 4.51 (d, J = 2.3 Hz, 1H), 2.20−2.17 (m, 1H), 2.01 (s, 3H), 1.96−1.77 (m, 2H), 1.72−1.62 (m, 1H), 1.54−1.43 (m, 2H), 1.38 (s, 9H), 1.30 (s, 3H), 1.20 (s, 3H), 1.19−0.90 (m, 2H), 0.84 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 169.3, 166.6, 154.4, 152.2, 138.3, 128.2, 128.0, 127.5, 126.2, 125.4, 79.7, 76.6, 74.7, 54.1, 50.0, 40.4, 39.2, 34.3, 31.3, 29.5, 28.2, 26.2, 22.5, 21.6, 20.3. IR (film): 3452 2959, 2927, 1765, 1744, 1722, 1502, 1368, 1212, 1164, 1088, 765, 701 cm^{-1}. HRMS-ESI: calcd for $C_{32}H_{43}O_6NNa$ $(M + Na)^+$ 560.2983, found 560.2999. Anal. Calcd: C, 71.48; H, 8.06; N, 2.60. Found: C, 71.32; H, 8.09; N, 2.58. $[\alpha]^{20}_D$ = 18.0 (c = 0.79; $CHCl_3$).

Methyl (2*S*)-Acetoxy-(3*R*)-*tert*-butoxycarbonylamino-3-phenylpropionate (8). To a solution of compound **6** (300 mg, 0.61 mmol) in MeOH (10 mL) was added MeONa (69 mg, 1.22 mmol). The progress of the reaction was monitored by TLC. After the mixture was stirred at rt for 24 h, solvents were evaporated, H_2O (1 mL) was added to the residue, and the pH was adjusted with 6 N HCl to ca. 1. The postreaction mixture was extracted with CH_2Cl_2. After drying ($MgSO_4$) of combined extracts, the solvents were removed under reduced pressure. To the residue were added H_2O (3 mL), $CHCl_3$ (0.5 mL), and AcOEt (2.5 mL). The organic layer was separated, and the water phase was extracted with CH_2Cl_2. Combined organic layers were dried ($MgSO_4$), solvents were removed under reduced pressure, and purification was achieved on a silica gel column using CH_2Cl_2/MeOH to give compound **7** (175 mg, 89%) (R_f = 0.1, CH_2Cl_2/MeOH, 8:2). To a precooled (0 °C) solution of acid **7** in Et_2O (10 mL) was added the ethereal solution of CH_2N_2 (5 mmol, 50 mL). After the mixture was stirred for 16 h, solvents were evaporated, and the residue was purified on a silica gel column using hexane/AcOEt to afford compound **8** (165 mg, 90%) (R_f = 0.5 hexane/AcOEt 8:2). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36−7.25 (m, 5H), 5.46−5.35 (m, 1H), 5.31 (bs, 1H), 3.77 (s, 3H), 2.07 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 169.6, 168.2, 154.8, 138.0, 128.5, 127.8, 126.3, 80.1, 74.7, 54.5, 52.6, 28.2, 20.3. $[\alpha]^{25}_D$ = 26.5 (c = 1.44; $CHCl_3$) (lit.[21] $[\alpha]^{25}_D$ = 27.6).

Methyl (3*R*)-*tert*-Butoxycarbonylamino-(2*S*)-hydroxy-3-phenylpropionate (1). To a solution of ester **8** (29 mg, 0.085 mmol) in MeOH (1 mL) was added MeONa (14 mg, 0.25 mmol). The progress of the reaction was monitored by TLC. After the mixture was stirred at rt for ca. 1.5 h, solvents were evaporated, and to the residue were added saturated aqueous NH_4Cl (2 mL) and AcOEt (2 mL). The organic layer was separated, and the water phase was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and solvents were removed under reduced pressure. Purification was achieved on a silica gel column using hexane/AcOEt to give compound **1** (23 mg, 90%) (R_f = 0.1, hexane/AcOEt 8:2). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.37−7.25 (m, 5H), 5.43−5.36 (m, 1H), 5.25−5.18 (m, 1H), 4.46 (bs, 1H), 3.83 (s, 3H), 3.17 (bs, 1H), 1.41 (s, 9H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 173.3, 155.1, 139.1, 128.5, 127.7, 126.7, 79.9, 73.5, 56.0, 53.0, 28.2. $[\alpha]^{25}_D$ = 7.4 (c = 0.67; $CHCl_3$) (lit.[18] $[\alpha]^{25}_D$ = 7.2). Mp = 131−132 °C (hexane/CH_2Cl_2).

(2′*R*)-*N*-[-(2*S*)-Hydroxy-(3*R*)-nitro-4-phenylbutanoyl]-bornane-10′,2′-sultam (*syn*-12a). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.34−7.25 (m, 5H), 5.34 (ddd, J = 2.2, 5.8, 9.1 Hz, 1H), 4.92 (dd, J = 2.2, 7.1 Hz, 1H), 3.96 (dd, J = 4.8, 7.9 Hz, 1H), 3.58 (dd_{AB}, J = 9.1, 14.5 Hz, 1H), 3.27 (dd_{AB}, J = 5.8, 14.5 Hz, 1H), 3.13 (d_{AB}, J = 13.7 Hz, 1H), 3.08 (d_{AB}, J = 13.7 Hz, 1H), 2.01−1.81 (m, 3H), 1.49−1.29 (m, 2H), 1.20−1.08 (m, 1H), 1.19 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.3, 134.9,129.3, 128.6, 127.3, 90.2, 71.3, 65.3, 52.8, 49.2, 47.9, 44.3, 37.2, 35.4, 32.5, 26.4, 20.2, 19.8. IR (film): 3470, 2961, 1694, 1555, 1335, 1294, 1167, 1138, 1061, 753, 700, 535 cm^{-1}. HRMS-ESI: calcd for $C_{20}H_{26}N_2O_6SNa$ $(M + Na)^+$ 445.1404, found 445.1415. Anal. Calcd: C, 56.86; H, 6.20; N, 6.63, S, 7.59. Found: C, 57.09; H, 6.31; N, 6.46, S, 7.71.; $[\alpha]^{20}_D$ = −60 (c = 1.10; $CHCl_3$). R_f = 0.4 (hexane/AcOEt 7:3).

***O*-[(2*S*)-Hydroxy-(3*R*)-nitro-4-phenylbutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (*syn*-12b).** ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.40−7.30 (m, 3H), 7.22−7.19 (m, 4H), 7.07−7.02 (m, 2H), 6.75−6.71 (m, 1H), 4.92 (dt, J = 10.8, 10.8, 4.5 Hz, 1H), 4.35 (ddd, J = 2.7, 6.9, 8.5 Hz, 1H), 4.31 (dd_{AB}, J = 13.9, 6.9 Hz, 1H), 3.07 (dd_{AB}, J = 13.9, 6.9 Hz, 1H), 3.01 (dd, J = 2.7, 6.9 Hz, 1H), 2.95 (d, J = 6.9 Hz, 1H), 2.10 (ddd, J = 10.6, 12.1, 3.7 Hz, 1H), 1.96 (dq, J = 13.5, 3.7, 3.7 Hz, 1H), 1.87−1.84 (m, 1H), 1.75−1.70 (m, 1H), 1.52−1.41 (m, 1H), 1.23−1.16 (m, 1H), 1.24 (s, 3H), 1.12 (s, 3H), 1.00−0.90 (m, 2H), 0.89 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.3, 151.8, 135.0, 129.3, 128.8, 127.6, 127.4, 125.1, 125.0, 88.5, 76.9, 68.7, 50.1, 40.7, 39.1, 35.4, 34.4, 31.2, 30.6, 26.0, 21.6, 21.3. IR (film): 3567, 2960, 2920, 1718, 1546, 1367, 1282, 1126, 986, 758, 695, 491 cm^{-1}. HRMS-ESI: calcd for $C_{26}H_{33}O_5NNa$ $(M + Na)^+$ 462.2251, found 462.2251. Anal. Calcd: C, 71.05; H, 7.57; N, 3.19. Found: C, 70.90; H, 7.61; N, 3.03. $[\alpha]^{20}_D$ = 26 (c = 1.11; $CHCl_3$). R_f = 0.5 (hexane/AcOEt 8:2).

***O*-[(2*S*)-Hydroxy-(3*S*)-nitro-4-phenylbutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (*anti*-12b).** ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.31−7.21 (m, 7H), 7.16−7.12 (m, 1H), 7.08−7.025 (m, 2H), 4.94 (dt, J = 10.8, 10.8, 4.4, 1H), 4.46 (ddd, J = 3.9, 9.7, 4.5 Hz, 1H), 3.47 (dd, J = 3.9, 4.6 Hz, 1H), 3.19 (dd_{AB}, J = 14.9, 9.7 Hz, 1H), 3.01 (d, J = 4.6 Hz, 1H), 2.73 (dd_{AB}, J = 14.9, 4.5 Hz, 1H), 2.16 (ddd, J = 10.8, 12.2, 3.6 Hz, 1H), 1.96 (dq, J = 13.5, 3.6, 3.6 Hz, 1H), 1.80−1.71 (m, 1H), 1.53−1.41 (m, 1H), 1.23−1.16 (m, 1H), 1.29 (s, 3H), 1.18 (s, 3H), 1.10−0.91 (m, 2H), 0.90 (d, J = 6.5, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.0, 151.7, 135.4, 128.9, 128.7, 128.1, 127.4, 125.4, 125.1, 90.2, 77.4, 70.2, 50.2, 41.2, 39.3, 34.3, 34.2, 31.3, 30.4, 26.1, 21.8, 21.6. $[\alpha]^{20}_D$ = −21 (c = 1.27; $CHCl_3$).

***O*-[(3*R*)-*tert*-Butoxycarbonylamino-(2*S*)-hydroxy-4-phenylbutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (14).** Through a solution of nitro alcohol was bubbled *syn*-**12b** (171 mg, 0.39 mmol) in MeOH (5 mL) containing catalytical amounts of Raney Ni hydrogen. The progress of reaction was monitored by TLC. After the mixture was stirred for ca. 16 h at rt, the catalyst was filtered off, solvents were evaporated, and the residue was dissolved in AcOEt and saturated aqueous $NaHCO_3$ (10 mL, 1:1), followed by addition $(Boc)_2O$ (93 mg, 0.43 mmol). After completion of the reaction, the layers were separated, and the water phase was extracted with CH_2Cl_2. After drying ($MgSO_4$) of combined organic layers, solvents were removed under reduced pressure. Purification was achieved on a silica gel column using hexane/AcOEt to give compound **14** (185 mg, 95%) (R_f = 0.5 hexane/AcOEt 7:3). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.34−7.06 (m, 9H), 6.86−6.80 (m, 1H), 4.41 (dt, J = 10.7, 10.7, 4.5 Hz, 1H), 4.62−4.54 (m, 1H), 3.84−3.75 (m, 3H), 2.98−2.93 (m, 1H), 2.86 (J = 3.2 Hz, 1H), 2.70 (dd_{AB}, J = 7.7, 13.4 Hz, 1H), 2.63 (dd_{AB}, J = 8.0, 13.4 Hz, 1H), 2.11 (ddd, J = 12.2, 14.2, 3.6 Hz, 1H), 1.96 (dq, J = 13.5, 3.6, 3.6 Hz, 1H), 1.75−1.60 (m, 2H), 1.47−1.27 (m, 1H), 1.28 (s, 9H), 1.19 (s, 3H), 1.13 (s, 3H), 1.06−0.98 (m, 1H), 0.96−0.80 (m, 2H), 0.81 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 173.5, 155.2, 152.1, 138.3, 128.8, 128.2, 126.9, 125.6, 79.5, 76.7, 70.8, 54.3, 50.3, 41.1, 39.8, 39.4, 34.8, 31.9, 30.5, 28.8, 26.7, 22.8, 22.3. IR (film): 3443 2966, 2927, 1721, 1496, 1456, 1367, 1258, 1170, 1117, 763, 700 cm^{-1}. HRMS-ESI: calcd for $C_{31}H_{43}O_5NNa$ $(M + Na)^+$ 523.3033, found 523.3057. Anal. Calcd: C, 73.05; H, 5.50; N, 2.75. Found: C, 72.85; H, 8.47; N, 2.77. $[\alpha]^{20}_D$ = 63.0 (c = 1.10; $CHCl_3$). Mp = 101−103 °C (hexane/CH_2Cl_2).

***O*-[(3*R*)-*tert*-Butoxycarbonylamino-(2*S*)-hydroxy-2,3-isopropylidene-4-phenylbutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-**

phenylmenthol (15). A solution of compound **14** (99 mg, 0.19 mmol), dimethoxypropane (26μL, 0.21 mmol), and a catalytic amount of TsOH in toluene (2 mL) was heated for 5 h at 50 °C with stirring. Then solvents were evaporated, and the residue was purified on a silica gel column using hexane/AcOEt to afford compound **15** (91 mg, 87%) (R_f = 0.5 hexane/AcOEt 8:2). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.35−7.10 (m, 10H), 4.87−4.75 (m, 1H), 4.18−4.11 (m, 1H), 3.71 (d, J = 3.7 Hz, 1H), 3.03 (dd_{AB}, J = 3.2, 13.3 Hz, 1H), 2.97−2.68 (m, 1H), 2.15−2.08 (m, 1H), 1.98−1.94 (m, 1H), 1.76−1.60 (m, 2H), 1.49−1.28 (m, 1H), 1.48 (s, 9H), 1.22 (s, 3H), 1.14 (s, 6H), 1.13 (s, 3H), 1.07−0.97 (m, 1H), 0.95−0.79 (m, 2H), 0.84 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.8, 151.5, 151.0, 137.6, 128.9, 128.5, 127.1, 125.9, 125.6, 96.3, 80.8, 75.4, 62.3, 60.5, 50.3, 42.0, 40.2, 38.5, 34.9, 31.7, 28.9, 28.0, 27.0, 26.2, 22.3, 22.3. IR (film): 2970, 2927, 1749, 1703, 1496, 1455, 1388, 1367, 1251, 1208, 1172, 1088, 766, 700 cm^{-1}. HRMS-ESI: calcd for $C_{34}H_{47}O_5NNa$ $(M + Na)^+$ 572.3346, found 572.3336. Anal. Calcd: C, 74.28; H, 8.62; N, 2.55. Found: C, 73.99; H, 8.98; N, 2.60. $[\alpha]^{20}_D$ = 20.5 (c = 1.46; $CHCl_3$).

(3*R*)-*tert*-Butoxycarbonylamino-(2*S*)-hydroxy-2,3-isopropylidene-4-phenylbutanoic Acid (16). To a solution of compound **15** (129 mg, 0.23 mmol) in MeOH (5 mL) was added MeONa (24 mg, 0.46 mmol). After the reaction mixture was stirred at r for 24 h, solvents were evaporated, H_2O (1 mL) was added to the residue, and the pH was adjusted with 6 N HCl to ca. 1. The water phase was extracted with CH_2Cl_2, the combined organic layers were dried ($MgSO_4$), and solvents were removed under reduced pressure. Purification was achieved on a silica gel column using CH_2Cl_2/MeOH to give compound **16** (70 mg, 89%) (R_f = 0.5 CH_2Cl_2/MeOH 9:1). ^{1}H NMR (500 MHz; $CDCl_3$, 323 K): δ 7.32−7.17 (m, 5H), 4.54−4.47 (m, 1H), 4.39 (d, J = 3.1 Hz, 1H), 3.21 (dd_{AB}, J = 3.2, 13.6 Hz, 1H), 3.02−2.88 (m, 1H), 1.52 (s, 9H), 1.16 (s, 6H). ^{13}C NMR (125 MHz; $CDCl_3$, 323K): δ 174.7, 151.5, 136.8, 129.7, 128.6, 126.8, 96.6, 80.7, 76.1, 61.1, 38.7, 28.4, 27.4. IR (film): 2979, 2934, 1698, 1390, 1367, 1254, 1172, 1080, 857, 702 cm^{-1}. HRMS-ESI: calcd for $C_{18}H_{25}O_5NNa$ $(M + Na)^+$ 358.1625, found 358.1640. Anal. Calcd: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.42; H, 7.71; N, 3.89. $[\alpha]^{20}_D$ = 16.6 (c = 0.81; $CHCl_3$).

[(3*R*)-*tert*-Butoxycarbonylamino-(2*S*)-hydroxy-2,3-izopropylidene-4-phenylbutanoyl]-L-leucine Methyl Ester (17). To a precooled (−5 °C) solution of acid **16** (42 mg, 0.125 mmol) in THF (15 mL) was added *N*-ethylmorpholine (17 μL, 0.13 mmol), followed by isobutyl chloroformate (17 μL, 0.13 mmol). After 3 min, L-leucine methyl ester was added (20 mg, 0.137 mmol). After the mixture was stirred at rt for 1 h, solvents were evaporated, and to the residue were added H_2O (3 mL), $CHCl_3$ (0.5 mL), and AcOEt (2.5 mL). The organic layer was separated, and the water phase was extracted with CH_2Cl_2. Combined organic layers were dried ($MgSO_4$), and solvents were removed under reduced pressure. Purification was achieved on a silica gel column using hexane/AcOEt to afford compound **17** (55 mg, 95%) (R_f = 0.5 hexane/AcOEt 6:4). ^{1}H NMR (500 MHz; $CDCl_3$, 323K): δ 7.30−7.10 (m, 5H), 4.63−4.54 (m, 1H), 4.29 (d, J = 6.7 Hz, 1H), 3.87−3.84 (m, 1H), 3.70−3.68 (m, 1H), 3.71 (s, 3H), 3.20−3.10 (m, 1H), 1.75−1.55 (m, 3H), 1.52 (s, 9H), 0.96−0.90 (m, 6H), 0.92 (s, 6H). ^{13}C NMR (125 MHz; $CDCl_3$, 323K): δ 172.8, 170.5, 151.6, 136.8, 130.2, 128.4, 126.6, 96.1, 80.4, 71.3, 60.5, 52.1, 50.5, 41.8, 28.4, 26.7, 25.0, 22.5, 22.1. IR (film): 3346, 2959, 2873, 1747, 1698, 1521, 1454, 1388, 1368, 1254, 1208, 1172, 1077, 703 cm^{-1}. HRMS-ESI: calcd for $C_{25}H_{38}O_6N_2Na$ $(M + Na)^+$ 485.2622, found 485.2627. Anal. Calcd: C, 64.91; H, 8.28; N, 6.05. Found: C, 64.92; H, 8.24; N, 5.88. $[\alpha]^{20}_D$ = −3.8 (c = 0.47; $CHCl_3$).

[(3*R*)-Amino-(2*S*)-hydroxy-4-phenylbutanoyl]-L-leucine Methyl Ester (18). To a solution of compound **17** (136 mg, 0.29 mmol) in MeOH (5 mL) was added a catalytic amout of TsOH. The progress of reaction was monitored by TLC. After the reaction mixture was stirred at rt for ca. 24 h, solvents were evaporated, and the residue was purified on a silica gel column using $CHCl_3$/MeOH to give compound **18** (78 mg, 82%) (R_f = 0.5 $CHCl_3$/MeOH 8:2). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36−7.24 (m, 5H), 4.68−4.61 (m, 1H), 3.98 (d, J = 3.1 Hz, 1H), 3.76 (s, 3H), 3.63 (ddd, J = 3.1, 4.6, 10.1 Hz, 1H), 3.00 (dd_{AB}, J = 4.6, 13.6 Hz, 1H), 2.60 (dd_{AB}, J = 10.1, 13.6 Hz, 1H), 1.75−1.55 (m, 3H), 0.96 (d, J = 2.8 Hz, 3H), 0.94 (d, J = 4.0 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 173.1, 173.0 1, 138.3, 129.2, 128.7, 126.6, 72.4, 54.1, 52.2, 50.5, 41.2, 37.9, 25.0, 22.8, 21.7. IR (film): 3292, 2957, 1744, 1666, 1523, 1454, 1207, 1156, 744, 701 cm^{-1}. HRMS-ESI: calcd for $C_{17}H_{27}O_4N_2$ $(M + H)^+$ 323.1965, found 323.1949. Anal. Calcd: C, 63.32; H, 8.13; N, 8.69. Found: C, 63.28; H, 8.30; N, 8.45. $[\alpha]^{20}_D$ = −2.0 (c = 0.53; $CHCl_3$).

[(3*R*)-Amino-(2*S*)-hydroxy-4-phenylbutanoyl]-L-leucine hydrochloride [(−)-Bestatin Hydrochloride, 19)]. Ester **18** (23 mg, 0.07 mmol) was dissolved in 1 N aq HCl (2 mL), and after 16 h of stirring at rt the product was filtered off to give compound **19** (21 mg, 86%) (R_f = 0.1 $CHCl_3$/MeOH 8:2). ^{1}H NMR (500 MHz; CD_3COOD): δ 7.30−7.05 (m, 5H), 4.62−4.60 (m, 1H), 4.57−4.55 (m, 1H), 4.10−4.02 (m, 1H), 3.30−3.20 (m, 1H), 3.15−3.03 (m, 1H), 1.85−1.65 (m, 3H), 0.95 (s, 6H). ^{13}C NMR (125 MHz; CD_3COOD): δ 176.9, 136.1, 130.5, 129.8, 128.3, 70.1, 56.9, 52.2, 40.7, 35.5, 25.7, 23.1, 21.2. HRMS-ESI: calcd for $C_{16}H_{25}O_4N_2$ $(M + H)^+$ 309.1809, found 309.1816 (free amine). Mp = 220 °C dec. $[\alpha]^{20}_D$ = −13.7 (c = 0.51; 1N HCl) (lit.[22] $[\alpha]^{20}_D$ = −14.3).

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Supporting Information Available: X-ray structure data for compounds *syn*-**2a**, *syn*-**2b**, and *anti*-**12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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