A Catalytic Asymmetric Synthesis of *N*-Boc-*β*-Methylphenylalanines

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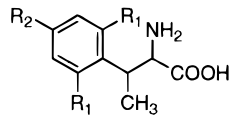
An efficient, stereodivergent, and enantioselective synthesis of the *syn* and *anti* diastereomers of *N*-Boc-*β*-methylphenylalanine has been developed. Starting from enantiomerically pure (2*S*,3*S*)-2,3-epoxy-3-phenyl-1-propanol, a three-step sequence, consisting of the oxidation of the primary alcohol up to the carboxyl stage, ring opening of the epoxy acid with $Me_2CuCNLi_2$, and esterification of the resulting hydroxy acid with methyl iodide, leads to the hydroxy ester *anti*-**10**, which has been converted in a stereodivergent manner into both the (2*S*,3*R*) and the (2*R*,3*R*) diastereomers of *N*-Boc-*β*-methylphenylalanine, *syn*-**1** and *anti*-**1**, respectively. Activation of the secondary hydroxy group in *anti*-**10** as a mesylate, followed by nucleophilic displacement with sodium azide, hydrogenolysis with simultaneous protection of the amino group, and saponification with LiOH, affords *syn*-**1**. The same reaction sequence applied to *syn*-**10**, obtained in turn by Mitsunobu reaction of *anti*-**10** with *p*-nitrobenzoic acid followed by the hydrolysis of the resulting *p*-nitrobenzoate, leads to *anti*-**1**. Both products have been obtained with ⩾99% enantiomeric excess.

Introduction

Unnatural, enantiomerically pure amino acids are gaining an increasing interest as components of biologically active peptides.[1] Hruby and co-workers have shown that the incorporation of conformationally constrained amino acids into peptides results in an increased rigidity, leading to enhanced resistance toward protease enzymes and to different biological activity and selectivity.[2] *β*-Methyl-α-amino acids such as *β*-methylphenylalanine (**I**),[3] *β*-methyltyrosine **II**),[4] and 2′,6′-dimethyl-*β*-methyltyrosine (**III**)[5] have been incorporated into peptides conferring them a conformational side-chain rigidity that has allowed the study of both the bioactive peptide conformation[6,7] and the synthesis of new receptor-selective peptide ligands.[7] On the other hand, *β*-methylphenylalanine {**I**) has been found to be a component of the peptidic antibiotic Bottromycin.[8]

The preparation of these amino acids in homochiral form has been performed by classical resolution,[8b] by using threonine as starting material,[9] by the chiral auxiliary approach[3,4,5,10] or by enantioselective hydrogenation.[11] Due to its importance, a practical and efficient asymmetric synthesis of these compounds is a subject of current interest.



I R_1=R_2=H
II R_1=H, R_2=OH
III R_1=CH_3, R_2=OH

In a project devoted to the enantioselective synthesis of modified amino acids from chiral epoxy alcohols[12] we envisaged the preparation of the *N*-Boc derivatives of *syn*- and *anti*-*β*-methylphenylalanine **I** (*syn*-**1** and *anti*-**1**), through a regio and stereoselective ring-opening of cinnamyl epoxides **2** and **3** by a methyl nucleophilic equivalent to give, after the necessary functional group manipulation, mesylates *syn*-**4** and *anti*-**4** which, in turn, would afford the target *β*-methylphenylalanines *via* a S_N2 substitution with an amino synthetic equivalent (Scheme 1).

We report in the present paper a new approach to the asymmetric synthesis of both the 2*S*,3*R* and the 2*R*,3*R* diastereomers of *N*-Boc-*β*-methylphenylalanine *syn*-**1** and

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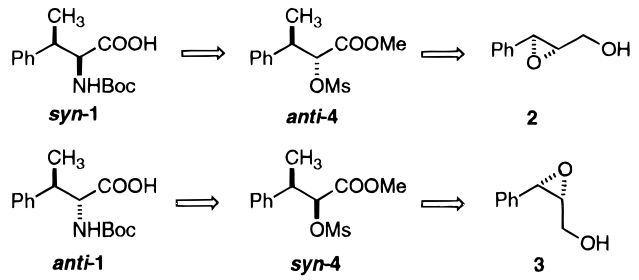
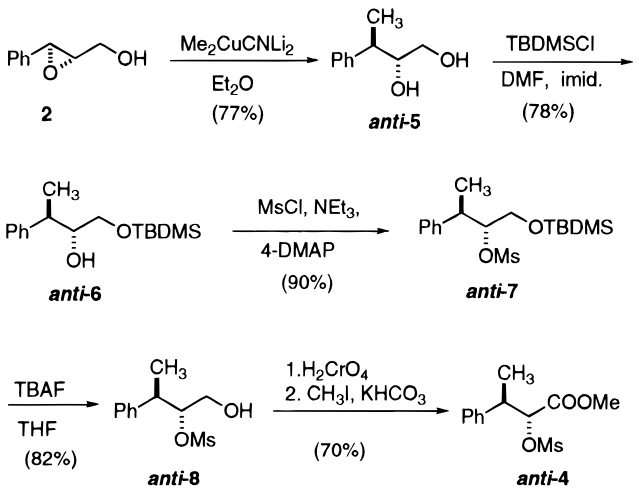
Scheme 1



Scheme 2



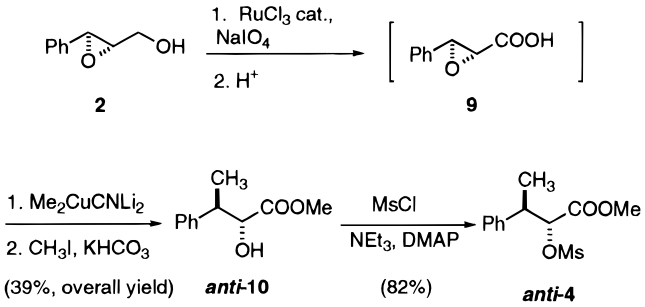
anti-**1**, respectively, based on the retrosynthetic analysis shown in Scheme 1, by using the Sharpless catalytic epoxidation[13] as the sole source of chirality. Obviously, by simply changing the enantiomeric series of the tartrate ester employed in the epoxidation, the 2*R*,3*S* and the 2*S*,3*S* diastereomers, which are enantiomers of *syn*-**1** and *anti*-**1**, respectively, would be equally available.

Results and Discussion

(A) Preparation of Methyl (2*R*,3*R*)-2-(Methanesulfonyloxy)-3-phenylbutanoate, *anti*-4. According to our retrosynthetic scheme, mesylate *anti*-**4** is the key intermediate in the synthesis of *syn (threo) N*-Boc-β-methyl-L-phenylalanine (*syn*-**1**). For the preparation of this intermediate, (2*S*,3*S*)-2,3-epoxy-3-phenyl-1-propanol (**2**), readily accessible in multigram scale and in high enantiomeric purity by the Sharpless asymmetric epoxidation,[13d,g] seemed to be an excellent starting material (Scheme 2).

In our initial approach the planned regioselective ring-opening at the benzylic center was performed using $Me_2CuCNLi_2$ as described by Takano,[14] yielding diol *anti*-**5** in good yield (77%) and with excellent diastereoselectivity. Chemoselective protection of the primary hydroxy group was easily achieved (78% yield) by treatment of *anti*-**5** with *tert*-butyldimethylsilyl chloride/imidazole in DMF. Subsequent treatment with methanesulfonyl chloride in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine provided access to *anti*-**7** in 90% yield. To allow oxidation at the primary hydroxyl site, the silyl ether was selectively cleaved by treatment with tetrabutylammonium fluoride in THF. The resulting alcohol *anti*-**8**, obtained in 82% yield, was then oxidized with Jones reagent[15] in acetone, and the free acid was finally converted into its methyl ester by using methyl iodide in the presence of potassium hydrogen carbonate in dimethylformamide at room temperature[16] (Scheme 2).

Scheme 3



Although the preparation of mesylate *anti*-**4** through this route is practical and convenient, taking place in 31% overall yield, we decided to explore shorter synthetic routes to this important intermediate. We reasoned that by simply inverting the sequence of the ring opening and oxidation operations, protecting group manipulation could be avoided. Obviously, if the epoxide ring-opening could be conveniently performed on the corresponding epoxy acid,[17] the protection of the primary alcohol would be no longer necessary. To test this possibility, epoxy alcohol **2** was first oxidized using ruthenium trichloride–sodium periodate,[18] and, because of its unstability, the resulting free acid **9** was directly submitted to ring-opening by $Me_2CuCNLi_2$ without purification (Scheme 3). Quite interestingly, the reaction took place with complete regioselectivity and with excellent diastereoselectivity, and the single hydroxy acid isomer formed was converted into its methyl ester *anti*-**10** by treatment with methyl iodide in the presence of potassium hydrogen carbonate. The overall yield for the preparation of *anti*-**10** from **2** is 39%, and the final mesylation of the secondary hydroxy group took place in 82% yield leading to *anti*-**4**. In summary, the mesylate *anti*-**4** has been prepared by two alternative routes. Although both took place with similar overall yield, the sequence involving the epoxy acid is substantially shorter both in number of steps and in execution time, involving a single intermediate purification.

(B) Preparation of Methyl (2*S*,3*R*)-2-(Methanesulfonyloxy)-3-phenylbutanoate, *syn*-4. The application of the same methodologies to *cis*-2,3-epoxy-3-phenyl-1-propanol (**3**) should similarly allow the preparation of

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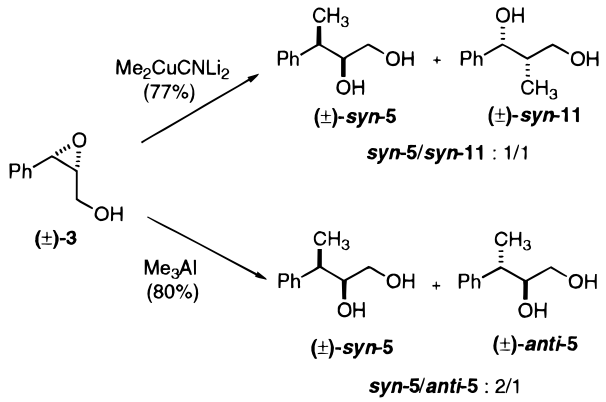
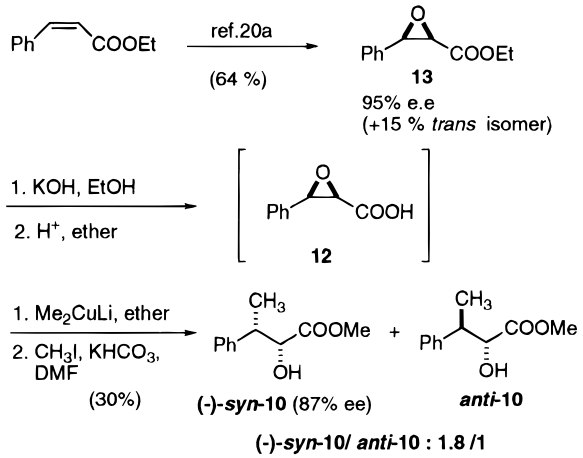
Scheme 4



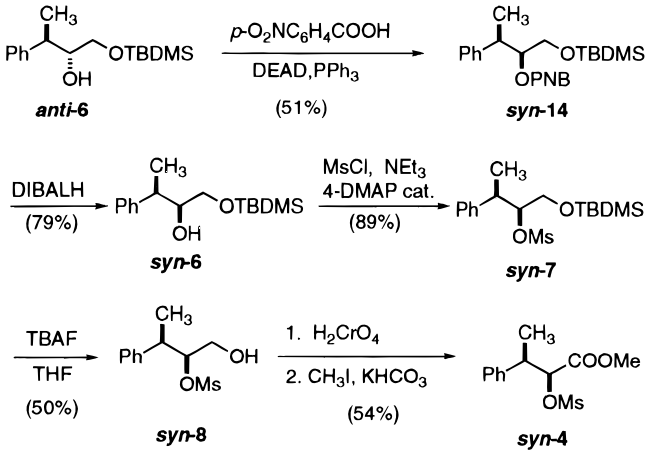
the stereoisomeric mesylate *syn*-**4**, the key intermediate for the preparation of *anti (erythro) N*-Boc-*β*-methyl-D-phenylalanine (*anti*-**1**) (Scheme 1). Consequently, the synthesis should involve an asymmetric epoxidation of (*Z*)-3-phenyl-2-propen-1-ol followed by a regioselective ring-opening of the epoxide by a methyl nucleophile and a selective oxidation of the primary hydroxyl, or the reversal in the order of these operations. This approach, however, encountered unavoidable difficulties. In first place, the Sharpless epoxidation of (*Z*)-3-phenyl-2-propen-1-ol proceeds slowly and with low enantioselectivity even in the presence of stoichiometric amounts of catalyst.[19] Moreover, when the nucleophilic ring opening of the *cis*-epoxy alcohol **3** was attempted by using $Me_2CuCNLi_2$, the reaction showed to be not regioselective, affording a 1:1 mixture of the 1,2- and 1,3-diols *syn*-**5** and *syn*-**11**, respectively. In an attempt to circumvent this difficulty, the use of trimethylaluminum as nucleophilic reagent was also tested. However, the reaction was not stereoselective, yielding a 2:1 mixture of the diastereomeric 1,2-diols *syn*-**5** and *anti*-**5** (Scheme 4).

The alternative procedure, involving oxidation of the primary hydroxy group in **3** and subsequent ring opening, would be hampered by the low enantiomeric purity in which **3** is available through Sharpless epoxidation.[19] This fact prompted us to consider a change in the source of chirality employed in our synthesis. Thus, besides the epoxidation/oxidation route, the *cis*-epoxy acid **12** is directly available in high enantiomeric purity through Jacobsen's catalytic epoxidation of *cis*-ethyl cinnamate (**13**).[20] However, when we performed the oxidation, we could observe that the corresponding *trans*-epoxide, co-generated with low enantiomeric purity, is a significant byproduct of the epoxidation reaction, and that the complete separation of the diastereomeric epoxides by flash chromatography is extremely difficult. When *cis*-2,3-epoxy-3-phenyl-1-propanoic acid (**12**) (contaminated with 15% of its *trans* isomer), generated by saponification of **13**, was allowed to react with Me_2CuLi, the nucleophilic ring opening of both epoxy acid diastereomers took place in low yield (Scheme 5). Disappointingly, the *syn*/*anti* ratio in the derived diastereomeric methyl esters **10** was much lower than the *cis*/*trans* ratio in the starting material (1.8:1 vs 5.4:1), thus indicating that either the ring-opening of the *trans*-epoxy acid **9** takes place more efficiently than that of *cis*-**12** or the ring opening of **9** was

Scheme 5



Scheme 6



not stereoselective. Moreover, the enantiomeric excess of the final hydroxy ester *syn*-**10** (87% ee) was lower than that of the starting epoxy ester **13**, probably as a combination of two factors: low enantiomeric purity of **9** and low stereoselectivity in the ring-opening of this byproduct.

In view of these results, we turned our attention to the possibility of performing an inversion of configuration at C-2 on some intermediate in the routes to *anti*-**4**. The derived synthetic routes to mesylate *syn*-**4**, albeit less straightforward, could benefit in this way from an optimal stereocontrol, as already discussed for the preparation of *anti*-**4**.

Alcohol *anti*-**6** was first chosen as the substrate for the inversion through the use of Mitsunobu methodology.[21] Accordingly, *anti*-**6** was treated with *p*-nitrobenzoic acid in benzene in the presence of triphenylphosphine and diethyl azodicarboxylate, yielding (51%) the inverted *p*-nitrobenzoate *syn*-**14**, which was reduced with DIBALH in CH_2Cl_2 to afford (79% yield) the secondary alcohol *syn*-**6** without any loss of stereochemical purity (Scheme 6).[12f] With the inverted alcohol in hand, the preparation of *syn*-**4** only required the application of the methodology that we had already applied with success to the preparation of *anti*-**4**. The required conversion into mesylate *syn*-**7** took place with excellent yield (89%) by treatment with methanesulfonyl chloride in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine, the primary

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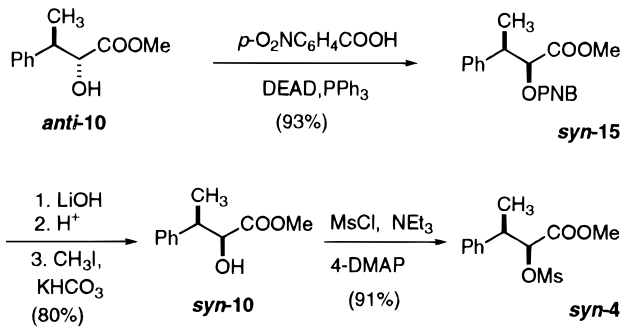
Scheme 7



hydroxy group was then selectively deprotected by treatment with tetrabutylammonium fluoride in THF, and the resulting alcohol *syn*-**8** was oxidized and finally converted to the target mesylate *syn*-**4** by nucleophilic esterification. Whereas the present sequence takes place with full stereochemical control, it suffers from nonoptimal yields in its final steps. The main chemoselectivity problem in these steps resides in the conversion of *syn*-**7** to *syn*-**8**, which is accompanied by a competing intramolecular cyclization reaction leading to the corresponding terminal epoxide.

Once again, the sequence could be shortened in its number of steps and significantly improved in terms of yield by simply performing the inversion of configuration at C-2 on *anti*-**10**, where the oxidation of C-1 has already been performed, instead of performing it on *anti*-**6**. Using *p*-nitrobenzoic acid as the nucleophile, the inverted *p*-nitrobenzoate *syn*-**15** was obtained in an excellent (93%) yield. In comparing with the parallel reaction performed on *anti*-**6** (see above), it is clear that the presence of the adjacent alkoxycarbonyl group greatly facilitates the Mitsunobu inversion. To avoid ester reduction, the elaboration of *syn*-**15** was performed by saponification with LiOH. Although the methyl ester was also affected, the resulting hydroxy acid was converted back to this ester by treatment with methyl iodide in the presence of $KHCO_3$. Hydroxy ester *syn*-**10**, which was obtained in this way in 80% yield from *syn*-**15**, was finally converted to the target mesylate *syn*-**4** in 91% yield (Scheme 7).

(C) Synthesis of (2*S*,3*R*)-*N*-Boc-*β*-Methylphenylalanine, *syn*-1. With mesylate *anti*-**4** in hands, the preparation of *syn*-**1** only required the introduction of the amino functionality and hydrolysis of the methyl ester. The amino group was incorporated by S_N2 substitution with sodium azide in DMF followed by reduction and in situ protection by treatment with H_2/Pd−C in the presence of Boc_2O. In this way, the *N*-Boc-amino ester *syn*-**16** was obtained in 83% yield from *anti*-**4**. The enantiomeric excess was determined at this point by chiral HPLC (Chiralcel OD and OD-R) against the racemic compound (prepared from racemic **2**). According to our expectations, only one enantiomer was detected (>99% ee), in good agreement with the optical purity of the starting material. The methyl ester *syn*-**16** could be easily hydrolyzed in quantitative yield to the target (2*S*,3*R*)-*N*-Boc-*β*-methylphenylalanine *syn*-**1**, which is ready for use in peptide synthesis (Scheme 8).

(D) Synthesis of (2*R*,3*R*)-*N*-Boc-*β*-Methylphenylalanine, *anti*-1. The preparation of the (2*R*,3*R*) diastereomer of the target *N*-Boc-*β*-methylphenylalanine, *anti*-**1**, could be performed in the same way described above for *syn*-**1**, but starting from mesylate *syn*-**4**. Despite the different relative stereochemistry of the two adjacent chiral centers, the introduction of the amino group took place as expected to afford (2*R*,3*R*)-*N*-Boc-*β*-methylphenylalanine methyl ester *anti*-**16** in good yield. To check its enantiomeric purity, this ester was reduced to alcohol by treatment with DIBALH, and the corresponding Mosher ester was analyzed by ^{19}F NMR. In full agreement with the enantiomeric purity of the starting material, a single peak was observed. Finally, basic hydrolysis of *anti*-**16** with lithium hydroxide in THF afforded the target *anti N*-Boc-*β*-methyl-D-phenylalanine *anti*-**1** in excellent yield (Scheme 8).

Conclusions

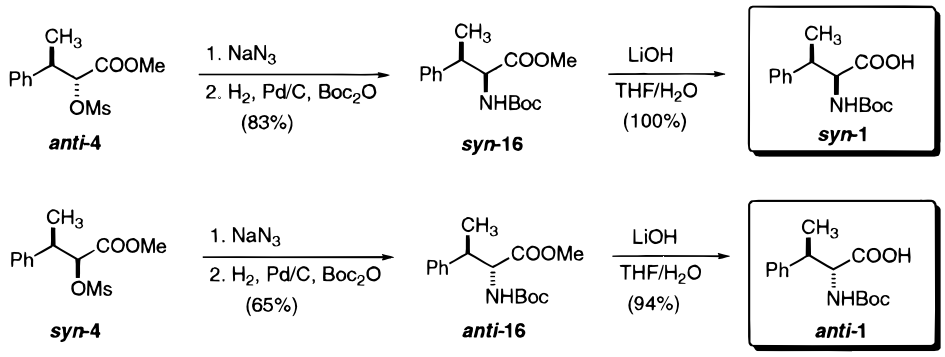
In summary, we have developed a general and efficient method for the stereodivergent preparation of the (2*S*,3*R*) (*syn*) and the (2*R*,3*R*) (*anti*) diastereomers of *N*-Boc-*β*-methylphenylalanine from readily available (2*S*,3*S*)-2,3-epoxy-3-phenyl-1-propanol. The synthesis of the *syn* diastereomer involves only four synthetic operations, taking place in 26,5% overall yield, whereas the synthesis of the *anti* diastereomer involves six synthetic operations and takes place in 16% overall yield. Both routes are characterized by an excellent stereocontrol, the final products being obtained with ⩾99% enantiomeric excess starting from an epoxy alcohol of the same enantiomeric purity. It is worth noting that, since the sole source of chirality in these synthetic sequences is a catalytic Sharpless epoxidation, a simple reversal in the enantiomeric series of the tartrate ester employed at that stage would provide access to the (2*R*,3*S*) and the (2*S*,3*S*) diastereomers of *N*-Boc-*β*-methylphenylalanine. Moreover, when the regio- and stereoselective introduction of the *β*-methyl substituent is considered, the present procedure appears as a very promising alternative for the general synthesis of *β*-alkyl-*β*-aryl-α-amino acids in diastereomerically and enantiomerically pure form. Work along these lines is in progress in our laboratories and will be published in due course.

Experimental Section

General. Melting points were determined in an open capillary tube and are uncorrected. Optical rotations were measured at room temperature (23 °C) on a Perkin-Elmer 241 MC polarimeter. Infrared spectra were recorded on a Perkin-Elmer 681 or on a Nicolet 510 FT-IR instrument using NaCl film or KBr pellet techniques. ^1H NMR spectra were recorded at 200 or 300 MHz in $CDCl_3$ unless specified otherwise (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet). *J* values are given in hertz. ^{13}C NMR spectra were recorded at 50.3 or 75.4 MHz in $CDCl_3$ unless specified otherwise. Signal multiplicities have been assigned by DEPT experiments. In all cases, chemical shifts are in ppm downfield of TMS. Mass spectra were recorded at 70 eV ionizing voltage; ammonia was used for chemical ionization (CI). Elemental analyses were performed by the "Servei d'Anàlisis Elementals del CSIC de Barcelona". THF and diethyl ether were distilled from sodium benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2 and triethylamine from KOH. All reactions were performed in oven-dried glassware under a N_2 atmosphere. Reaction progress was followed by TLC (Merck DC-Alufolien KIESELGEL 60 F254). Chromatographic separations were carried out using Et_3N pretreated (2.5% v/v) silica gel 60 (particle size: 60−200 *μ*m for column chromatography and 35−70 *μ*m for flash chromatography), eluting with hexane/ethyl acetate mixtures of increasing polarity. HPLC analyses were performed with Chiralcel OD and OD-R (25 cm) columns.

(2*R*,3*R*)-3-Phenyl-1,2-butanediol, *anti*-5. To a stirred slurry of CuCN (2.69 g, 0.03 mol) in anhydrous diethyl ether

Scheme 8



at −68 °C was added MeLi (37.5 mL, 1.6 M in diethyl ether), and the mixture was stirred at this temperature for 1 h. A solution of (2*S*,3*S*)-2,3-epoxy-3-phenyl-1-propanol (**2**) (1.5 g, 0.01 mol, ⩾99% ee) in diethyl ether (36 mL) was added via cannula to the cyanocuprate solution at −68 °C, and the mixture was allowed to warm to 0 °C over 3 h under N_2. When no starting material could be detected by TLC, saturated aqueous NH_4Cl (80 mL) and NH_4OH (10 mL) were added to the reaction mixture, and the organic layer was extracted with diethyl ether. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography, yielding 1.28 g of *anti*-**5** (77% yield) as an oil: $[\alpha]_D = 16.3$ ($c = 0.82$, $CHCl_3$). IR (film) ν_{max} 3400, 3100, 3070, 3040, 2980, 2940, 2890, 1500, 1460, 1105, 1460, 1105, 1090, 1060, 1020, 1010, 765 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (d, 3H, $J = 7.1$ Hz), 1.85 (m, 1H, OH), 2 (m, 1H, OH), 2.88 (pseudo quint, $J = 7$ Hz), 3.4−3.6 (m, 1H), 3.7−3.9 (m, 2H), 7.2−7.5 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.7 (CH_3), 42.6 (CH), 64.4 (CH_2), 76.2 (CH), 126.6 (CH), 127.9 (CH), 128.5 (CH), 148.2 (C) ppm. MS (EI) *m/e* = 166 (M^+, 1%), 106 (100%), 105 (70%), 91 (77%), 77 (32%).

(2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-phenyl-2-butanol, *anti*-6. To a solution of *anti*-**5** (1.26 g, 7.6 mmol) in *N*,*N*-dimethylformamide (37 mL) were added *tert*-butyldimethylsilyl chloride (1.72 g, 11.4 mmol) and imidazole (1.14 g, 16.7 mmol), and the reaction progress was monitored by TLC. After 24 h, the mixture was diluted with diethyl ether (40 mL) and washed with saturated aqueous NH_4Cl. The organic layer was separated, dried over $MgSO_4$, and evaporated in vacuo. The residue (2.5 g) was purified by column chromatography to afford 1.45 g of *anti*-**6** (78% yield) as an oil, along with 0.04 g (2% yield) of (2*R*,3*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-3-phenyl-1-butanol and 0.17 g of starting material (87% conversion). $[\alpha]_D = 7.25$ ($c = 1.05$, $CHCl_3$). IR (film) ν_{max} 3500, 3030, 2960, 2930, 2860, 1470, 1260, 1120, 1100, 840, 780 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.29 (d, $J = 7.3$ Hz, 3H), 2.2−2.4 (m, 1H, OH), 2.89 (pseudo quint, $J = 7.1$ Hz, 1H), 3.49 (dd, $J = 9.8$ Hz, $J = 7.2$ Hz, 1H), 3.62−3.84 (m, 2H), 7.1−7.5 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4 (CH_3), −5.3 (CH_3), 17.7 (CH_3), 19.0 (C), 25.8 (CH_3), 42.3 (CH), 65.1 (CH_2), 75.7 (CH), 126.4 (CH), 128.0 (CH), 128.3 (CH), 143 (C) ppm. MS (EI) *m/e* = 280 (M^+, 0.01%), 131 (20%), 105 (100%).

(2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(methanesulfonyloxy)-3-phenylbutane, *anti*-7. To a solution of *anti*-**6** (1.45 g, 5.2 mmol) in CH_2Cl_2 (8 mL) at 0 °C were added triethylamine (1.8 mL, 12.8 mmol), 4-(*N*,*N*-dimethylamino)-pyridine (30 mg), and methanesulfonyl chloride (0.9 mL, 11.4 mmol). The mixture was stirred for 5 h at room temperature, the reaction progress being monitored by TLC. When no starting material could be detected, water (10 mL) was added, the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography to afford 1.7 g (90% yield) of *anti*-**7** as an oil: $[\alpha]_D = 19.3$ ($c = 0.83$, $CHCl_3$). IR (film) ν_{max} 3050, 3020, 2920, 2880, 2840, 1490, 1460, 1350, 1250, 1170, 1115, 960, 910, 830, 770, cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.9 (s, 9H), 1.38 (d, $J = 7$ Hz, 3H), 2.54 (s, 3H), 3.1−3.4 (m, 1H), 3.77 (d, $J = 4.4$ Hz, 2H), 4.6−4.8 (m, 1H), 7.2−7.4 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.6 (CH_3), −5.5 (CH_3), 16.7 (CH_3), 19 (C), 25.8 (CH_3), 37.8 (CH_3), 40.7 (CH), 63.3 (CH_2), 88.3 (CH), 127.0 (CH), 128.2 (CH), 128.4 (CH), 141.9 (C) ppm. MS (EI) *m/e* = 153 (97%), 131 (100%), 105 (77%).

(2*R*,3*R*)-2-(Methanesulfonyloxy)-3-phenyl-1-butanol, *anti*-8. To a solution of *anti*-**7** (1.67 g, 4.66 mmol) in THF (47 mL) at 0 °C was added tetrabutylammonium fluoride (8.5 mL, 1.1 M in THF), and the reaction progress was monitored by TLC. After stirring for 20 min, the starting material could be no longer detected; the mixture was then concentrated in vacuo, the residue diluted with CH_2Cl_2, and the resulting solution washed with saturated aqueous NH_4Cl. The organic phase was dried over $MgSO_4$ and concentrated in vacuo, and the residue was purified by flash chromatography to yield 0.93 g (82% yield) of *anti*-**8** as a white solid: $[\alpha]_D = 21.9$ ($c = 1.43$, $CHCl_3$). Mp: 74−75 °C. IR (KBr) ν_{max} 3550, 3030, 2980, 2950, 1490, 1450, 1410, 1380, 1330, 1170, 1135, 1075, 1060, 1020, 970, 945, 920, 830, 760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (d, $J = 7.2$ Hz, 3H), 2.1−2.3 (m, 1H, OH), 2.47 (s, 3H), 3.20 (pseudo quint, $J = 7.4$ Hz, 1H), 3.75−3.92 (dd ABX, $J_{AB} = 12.8$ Hz, $J_{AX} = 5.9$ Hz, $J_{BX} = 2.6$ Hz, 2H), 4.8 (m, 1H), 7.1−7.5 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.2 (CH_3), 37.7 (CH_3), 40.7 (CH), 63.0 (CH_2), 88.7 (CH), 127.2 (CH), 128.1 (CH), 128.6 (CH), 142.1 (C) ppm. MS (CI) *m/e* = 148 (18%), 105 (100%). Anal. Calcd for $C_{11}H_{16}O_4S$: C, 54.08%; H, 6.60%; S, 13.13%. Found: C, 54.16%; H, 6.65%; S, 13.03%.

Methyl (2*R*,3*R*)-2-(Methanesulfonyloxy)-3-phenylbutanoate, *anti*-4. (a) From *anti*-8: To a solution of *anti*-**8** (0.87 g, 3.56 mmol) in acetone (75 mL) freshly prepared Jones reagent (7.35 mL, 14 mmol) was added dropwise. The reaction mixture was stirred at room temperature until no starting material could be detected by TLC (ca. 4 h), 2-propanol (5 mL) was added, and acetone was removed under reduced pressure. The residue was partitioned between water and CH_2Cl_2; the aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford 1.0 g of (2*R*,3*R*)-2-(methanesulfonyloxy)-3-phenylbutanoic acid as an oil. To a solution of the crude acid in *N*,*N*-dimethylformamide (6.2 mL) were added $KHCO_3$ (0.77 g, 7.7 mmol) and methyl iodide (0.4 mL, 6.42 mmol), and the reaction mixture was stirred at room temperature for 5 h. Water was then added, and the organic layer was extracted with ethyl acetate. The combined organic phases were successively washed with saturated aqueous Na_2SO_3 and brine and dried over $MgSO_4$. Removal of the solvent gave an oil that was purified by column chromatography to yield 0.68 g (70% yield) of *anti*-**4** as a colorless oil.

(b) From *anti*-10: The same procedure described above for the preparation of *anti*-**7** was followed starting from *anti*-**10** (8.0 mg, 0.04 mmol). After purification by column chromatography, *anti*-**4** (9.0 mg, 82% yield) was obtained as a colorless oil, identical in all respects to the product obtained from *anti*-**8**: $[\alpha]_D = 23.5$ ($c = 1.24$, $CHCl_3$). IR (film) ν_{max} 3020, 2980, 2940, 1750, 1490, 1450, 1435, 1360, 1210, 1175, 1095, 1020, 960, 840, 790 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.44 (d, $J = 7.2$ Hz, 3H), 2.88 (s, 3H), 3.3−3.5 (m 1H), 3.72 (s, 3H), 5.11 (d, $J = 5.9$ Hz, 1H), 7.2−7.4 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.4 (CH_3), 38.6 (CH_3), 41.7 (CH), 52.5 (CH_3),

81.9 (CH), 127.5 (CH), 128.0 (CH), 128.5 (CH), 139.9 (C), 168.5 (C) ppm. MS (EI) *m/e* = 213 (2%), 176 (17%), 105 (100%).

Methyl (2*R*,3*R*)-2-Hydroxy-3-phenylbutanoate, *anti*-10. To a vigorously stirred mixture of the epoxy alcohol **2** (0.41 g, 2.73 mmol) and 20 mL of a 1/1/1.5 $CCl_4/CH_3CN/H_2O$ mixture were added sodium bicarbonate (1.16 g, 13.8 mmol), sodium periodate (1.77 g, 8.27 mmol), and ruthenium trichloride trihydrate (21 mg, 0.08 mmol). The reaction mixture was stirred for 48 h, the acidic material was carefully extracted into diethyl ether at 0 °C, and the ethereal solution was briefly dried over sodium sulfate. Evaporation to dryness gave a residue (epoxy acid **9**) that was dissolved again in ether (10 mL) and added via cannula to a stirred suspension of $Me_2CuCNLi_2$ prepared in situ from CuCN (0.74 g, 8.26 mmol) in ether (80 mL) and MeLi (10 mL, 16 mmol, 1.6 M in hexanes) at 0 °C. After 4 h at 0 °C, the reaction mixture was acidified with 5% aqueous HCl. The resulting mixture was filtered through a pad of Celite, and the filtrate was extracted with diethyl ether. The organic layer was dried over sodium sulfate, and the solvent was evaporated. The oily residue was dissolved in *N*,*N*-dimethylformamide (4.5 mL), and $KHCO_3$ (0.55 g, 5.54 mmol) and methyl iodide (0.27 mL, 4.33 mmol) were added. This reaction mixture was stirred at room temperature for 12 h, water was added, and the organic layer was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were successively washed with a saturated aqueous Na_2SO_3 solution and with brine and dried over $MgSO_4$. Removal of the solvents gave an oil that was purified by column chromatography to yield 0.18 g (39% yield) of *anti*-**10** as an oil: $[\alpha]_D$ = 8.4 (*c* = 2.21, $CHCl_3$). IR (film) ν_{max} 3500, 3040, 2980, 2940, 1745, 1500, 1460, 1440, 1275, 1220, 1130 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (d, *J* = 7.2 Hz, 3H), 2.4−2.7 (m, 1H, OH), 3.2−3.4 (m, 1H), 3.70 (s, 3H), 4.3−4.4 (m, 1H), 7.1−7.5 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5 (CH_3), 43.4 (CH), 52.2 (CH_3), 75.0 (CH), 127.0 (CH), 128.0 (CH), 128.2 (CH), 140 (C), 174 (C) ppm. MS (CI−NH_3) *m/e* = 212 (M^+ + 18, 100%).

(2*S*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-phenyl-2-[(*p*-nitrobenzoyl)oxy]butane, *syn*-14. To a solution of *anti*-**6** (0.17 g, 0.61 mmol) in benzene (12 mL) were added PPh_3 (0.77 g, 2.93 mmol), *p*-nitrobenzoic acid (0.44 g, 2.63 mmol), and diethyl azodicarboxylate (0.46 mL, 2.92 mmol). The reaction mixture was stirred at room temperature for 12 h and was subsequently concentrated in vacuo and the residue submitted to column chromatography to yield 0.135 g of *syn*-**14** (51% yield) as an oil: $[\alpha]_D$ = −27.5 (*c* = 1.25, $CHCl_3$). IR (film) ν_{max} 2980, 2950, 2910, 2880, 1740, 1620, 1540, 1470, 1360, 1280, 1130, 1110, 845, 790, 730 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.00 (s, 3H), 0.89 (s, 9H), 1.42 (d, 3H, *J* = 7 Hz), 3.38 (m, 1H), 3.60−3.75 (dd ABX, J_{AB} = 11.2 Hz, J_{AX} = 5 Hz, J_{BX} = 3.4 Hz, 2H), 5.3−5.5 (m, 1H), 7.4 (s, 5H), 8.35 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.6 (CH_3), 17.6 (CH_3), 25.7 (CH_3), 40.0 (CH), 62.4 (CH_2), 80.2 (CH), 123.5 (CH), 126.9 (CH), 127.7 (CH), 128.2 (CH), 128.6 (CH), 130.7 (CH), 135.9 (C), 142.6 (C), 150.5 (C), 164.3 (C) ppm. MS (EI) *m/e* = 447 (M^+ + 18, 100%), 430 (M^+ + 1, 60%).

(2*S*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-phenyl-2-butanol, *syn*-6. To a solution of *syn*-**14** (0.06 g, 0.14 mmol) in CH_2Cl_2 (1 mL) at − 20 °C was added DIBALH (0.4 mL, 0.4 mmol, 20% in hexanes). The mixture was stirred at −20 °C until no starting material was observed by TLC (approximately 1 h), CH_2Cl_2 (0.5 mL) was then added, and the resulting solution was treated with 10% hydrochloric acid (0.8 mL). The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash cromatography to afford 0.03 g (79% yield) of *syn*-**6**: $[\alpha]_D$ = 11.8 (*c* = 1.25, $CHCl_3$). IR (film) ν_{max} 3500, 3060, 2980, 2960, 2910, 2890, 1475, 1260, 1130, 1110, 1090, 1030, 840, 785 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.80 (s, 9H), 1.30 (d, *J* = 6.8 Hz, 3H), 2.48 (m, 1H, OH), 2.71 (pseudo quint, *J* = 7.5 Hz, 1H), 3.21−3.34 (dd ABX, J_{AB} = 10 Hz, J_{AX} = 6.6 Hz, J_{BX} = 3.4 Hz, 2H), 3.6 (m, 1H), 7−7.3 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.5 (CH_3), 18.0 (CH_3), 25.8 (CH_3), 42.8 (CH), 65.2 (CH_2), 76.1 (CH), 126.4 (CH), 127.6 (CH), 128.5 (CH), 144(C) ppm.

(2*S*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-phenyl-2-(methanesulfonyloxy)butane, *syn*-7. Following the procedure described for the preparation of *anti*-**7**, *syn*-**6** (0.05 g, 0.18 mmol) was converted into *syn*-**7** (0.06 g, 89% yield). Colorless oil: $[\alpha]_D$ = −5.9 (*c* = 2.2, $CHCl_3$). IR (film) ν_{max} 3060, 2980, 2960, 2920, 2890, 1475, 1370, 1270, 1190, 1130, 980, 920, 845, 790 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ-0.02 (s, 3H), 0.00 (s, 3H), 0.86 (s, 9H), 1.39 (d, 3H, *J* = 7.2 Hz), 2.81 (s, 3H), 3.17 (pseudo quint, *J* = 7 Hz, 1H), 3.5−3.8 (m, 2H), 4.6−4.8 (m, 1H), 7.2−7.4 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.6 (CH_3), 16.3 (CH_3), 19 (C), 25.8 (CH_3), 38.2 (CH_3), 40.1 (CH), 63.1 (CH_2), 88.2 (CH), 127.1 (CH), 127.8 (CH), 128.7 (CH), 142.2 (C) ppm.

(2*S*,3*R*)-3-Phenyl-2-(methanesulfonyloxy)-1-butanol, *syn*-8. Following the procedure described for the preparation of *anti*-**8**, *syn*-**7** (0.05 g, 0.14 mmol) was converted into *syn*-**8** (18 mg, 50% yield). Colorless oil: $[\alpha]_D$ = −30.4 (*c* = 0.89, $CHCl_3$). IR (film) ν_{max} 3536, 2938, 1495, 1454, 1335, 1173, 1068, 1014, 970, 906, 766 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (d, 3H, *J* = 7 Hz), 2−2.2 (m, 1H, OH), 2.93 (s, 3H), 3−3.2 (m, 1H), 3.5−3.8 (m, 2H), 4.7−4.9 (m, 1H), 7.1−7.5 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.0 (CH_3), 38.2 (CH_3), 40.9 (CH), 63.2 (CH_2), 88.3 (CH), 127.3 (CH), 127.7 (CH), 128.9 (CH), 141.7 (C) ppm.

Methyl (2*S*,3*R*)-2-(Methanesulfonyloxy)-3-phenylbutanoate, *syn*-4. (a) From *syn*-8: The same procedure described above for the preparation of *anti*-**4**, was followed starting from *syn*-**8** (18 mg, 0.07 mmol). After purification by chromatography *syn*-**4** (11 mg, 54% yield) was obtained as a colorless oil.

(b) From *syn*-10: The same procedure described above for the preparation of *anti*-**7** was followed starting from *syn*-**10** (0.12 g, 0.61 mmol). After purification by chromatography, *syn*-**4** (0.15 g, 91% yield) was obtained as a colorless oil. The product was spectroscopically identical with the one obtained from *syn*-**8**. Colorless oil. $[\alpha]_D$ = −11.5 (*c* = 1.93, $CHCl_3$). IR (film) ν_{max} 1761, 1454, 1369, 1177, 1086, 957, 848, 773 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (d, 3H, *J* = 7.2 Hz), 2.73 (s, 3H), 3.4−3.6 (m, 1H), 3.73 (s, 3H), 5.02 (d, 1H, *J* = 4.2 Hz), 7.2−7.4 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4 (CH_3), 38.2 (CH_3), 41.5 (CH), 52.6 (CH_3), 82.3 (CH), 127.6 (CH), 127.8 (CH), 128.6 (CH), 140.1 (C), 168.6 (C) ppm. MS (EI) *m/e* = 290 (M^+ + 18, 100%).

Methyl (2*S*,3*R*)-3-Phenyl-2-[(*p*-nitrobenzoyl)oxy]butanoate, *syn*-15. To a solution of *anti*-**10** (0.2 g, 1.03 mmol) in benzene (20 mL) were added 1.29 g of PPh_3 (4.9 mmol), *p*-nitrobenzoic acid (0.73 g, 4.37 mmol), and diethyl azodicarboxylate (0.8 mL, 5 mmol). The reaction mixture was stirred at room temperature for 12 h and then concentrated in vacuo, and the residue purified by column chromatography to yield 0.33 g of *syn*-**15** (93% yield) as an oil: $[\alpha]_D$ = −72.9 (*c* = 1.46, $CHCl_3$). IR (film) ν_{max} 2960, 1760, 1735, 1615, 1535, 1510, 1355, 1300, 1280, 1260, 1220, 1120, 1110, 1020, 720 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.51 (d, 3H, *J* = 6.8 Hz), 3.5−3.7 (m, 1H), 3.70 (s, 3H), 5.37 (d, 1H, *J* = 4.8 Hz), 7.2−7.4 (m, 5H) 8.21 (d, 2H, *J* = 9.2 Hz), 8.31 (d, 2H, *J* = 9.2 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.3 (CH_3), 41.1 (CH), 52.4 (CH_3), 77.7 (CH), 123.6 (CH), 127.3 (CH), 127.6 (CH), 128.6 (CH), 130.9 (CH), 134.8 (C), 140.9 (C), 169.2 (C) ppm. MS (EI) *m/e* = 361 (M^+ + 18, 100%).

Methyl (2*S*,3*R*)-2-Hydroxy-3-phenylbutanoate, *syn*-10. To a solution of *syn*-**15** (0.33 g, 0.96 mmol) in THF (10 mL) was added 2 mL of a 2 M LiOH aqueous solution. The mixture was warmed to 70 °C and stirred at that temperature for 35 min and then cooled to room temperature and acidified with 10% aqueous HCl. Phases were separated, the aqueous one was extracted with CH_2Cl_2, and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude hydroxy acid (0.29 g) was dissolved in dimethylformamide (3 mL) and treated with $KHCO_3$ (0.39 g, 3.9 mmol) and methyl iodide (0.19 mL, 3.05 mmol) at room temperature for 5 h. Water (5 mL) was then added, and the aqueous layer was extracted with ethyl acetate. The combined organic phases were successively washed with saturated aqueous Na_2SO_3 and brine and dried over $MgSO_4$. Solvent removal and purification by column chromatography yielded 0.15 g of *syn*-**10** (80% yield) as white solid: $[\alpha]_D$ = 34.7 (*c* = 1.09, $CHCl_3$). IR (film) ν_{max} 3498, 2956, 1744, 1495, 1452, 1261, 1126, 1049,

1014, 769 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, 3H, J = 6.8 Hz), 3.23 (dq, 1H, J = 7.3 Hz, J = 3.8 Hz), 3.76 (s, 3H), 4.33 (d, 1H, J = 3.6 Hz), 7.2−7.4 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4 (CH_3), 43.2 (CH_3), 52.5 (CH), 75.0 (CH), 126.8 (CH), 127.7 (CH), 128.3 (CH), 142.4 (C), 174.6 (C) ppm. MS (CI−NH_3) m/e = 212 (M^+ + 18, 100%). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02%; H, 7.26%. Found: C, 68.12%; H, 7.44%.

Methyl (2*S*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-phenylbutanoate, *syn*-16. To a solution of *anti*-**4** (0.36 g, 1.3 mmol) in dimethylformamide (2 mL) was added sodium azide (0.17 g, 2.6 mmol), and the mixture was heated to 80 °C under stirring. After 12 h the reaction mixture was cooled to room temperature, water (5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to yield an oil that was dissolved in ethyl acetate (4.4 mL). To this solution were added Boc_2O (0.38 g, 1.74 mmol) and 10% Pd/C (35 mg), and the mixture was hydrogenated at atmospheric pressure. After 12 h, the reaction mixture was filtered through a pad of Celite, evaporated, and submitted to column chromatography to afford 0.32 g (83%yield) of *syn*-**16** as a white solid: $[\alpha]_D$ = 33 (c = 1.03, $CHCl_3$). Mp: 58−60 °C. IR (KBr) ν_{max} 3360, 2980, 1745, 1680, 1510, 1365, 1295, 1240, 1170, 1155 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (d, 3H, J = 7.4 Hz), 1.40 (s, 9H), 3.18 (pseudo quint, J = 6.9 Hz, 1H), 3.56 (s, 3H), 4.49 (m, 1H), 5−5.2 (m, 1H, NH), 7.1−7.4 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5 (CH_3), 28.2 (CH_3), 42.8 (CH), 51.9 (CH_3), 59.0 (CH), 80 (C), 127.0 (CH), 127.6 (CH), 128.3 (CH), 142 (C), 156 (C), 172 (C) ppm. MS (EI) m/e = 293 (M^+, 2%), 176 (26%), 105 (71%). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51%; H, 7.90%; N, 4.77%. Found: C, 65.54%; H, 7.84%; N, 4.76%. Conditions for Chiral HPLC analysis: CHIRALCEL OD (25 cm) column, hexane/2-propanol 98/2, 0.5 mL/min λ = 220 nm. t_R(2*R*,3*S*): 17.5 min, t_R(2*S*,3*R*): 16.3 min. CHIRALCEL® OD-R (25 cm) column, 35% MeOH/0.5 M $NaClO_4$, 0.5 mL/min, λ = 220 nm. t_R(2*R*,3*S*): 31.1 min, t_R(2*S*,3*R*): 33.0 min.

(2*S*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-phenylbutanoic acid, *syn*-1. To a solution of *syn*-**16** (0.04 g, 0.14 mmol) in THF (1.5 mL) were added 0.3 mL of a 3.5 M LiOH aqueous solution. The mixture was heated to 70 °C and stirred for 60 min at that temperature. The reaction mixture was then cooled to room temperature and acidified by addition of a aqueous 5% HCl solution. Phases were separated, the aqueous one was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated to yield 0.04 g (100% yield) of *syn*-**1** as a white solid: $[\alpha]_D$ = 17 (c = 1.7, $CHCl_3$). Mp: 117 °C. IR (KBr) ν_{max} 3300, 3200−2600 (b), 2969, 1728, 1659, 1410, 1371, 1269, 1167, 1068, 771 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.2 (b s, 3H), 1.4 (s, 9H), 3.3 (m, 1H), 4.4 (m, 1H), 4.6 (m, 1H, rotamer), 5.1 (m, 1H, NH), 6.5 (m, 1H, NH, rotamer), 7.1−7.3 (m, 5H), 9.2−9.4 (m, broad, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) Rotamer 1: δ 16.1 (CH_3), 28.2 (CH_3), 42.1 (CH), 58.6 (CH), 80.1 (C), 127.0 (CH), 127.7 (CH), 128.4 (CH), 141.3 (C), 155 (C), 176.2 (C) ppm. Rotamer 2: δ 14.5 (CH_3), 27.8 (CH_3), 41.8 (CH), 60.1 (CH), 81 (C), 142 (C), 156 (C), 176 (C) ppm. MS (EI) m/e = 178 (13%), 119 (26%), 105 (100%), 91 (21%). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50%; H, 7.58%; N, 5.01%. Found: C, 63.97%; H, 7.60%; N, 4.95%.

Methyl (2*R*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-phenylbutanoate, *anti*-16. To a solution of *syn*-**4** (0.1 g, 0.37 mmol) in *N*,*N*-dimethylformamide (0.6 mL) was added sodium azide (0.05 g, 0.77 mmol), and the mixture was heated to 80 °C under stirring. After 12 h, the reaction mixture was allowed to cool to room temperature and quenched with water (0.5 mL). The mixture was then extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to yield an oil that was dissolved in ethyl acetate (1.6 mL). To this solution, Boc_2O (0.1 g, 0.46 mmol) and 10% Pd/C (10 mg) were added, and the resulting mixture was hydrogenated at atmospheric pressure. When no starting material could be detected by TLC, the mixture was filtered through a short pad of Celite and evaporated. The residue was purified by column chromatography to yield 0.07 g (65%yield) of *anti*-**16** as an oil: $[\alpha]_D$ = −32 (c = 1.72, $CHCl_3$). IR (film) ν_{max} 3372, 2979, 1752, 1713, 1495, 1454, 1368, 1157, 1074, 764 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (d, J = 7 Hz, 3H), 1.40 (s, 9H), 3.2−3.4 (m, 1H), 3.69 (s, 3H), 4.6−4.8 (m, 1H), 4.7−4.9 (m, 1H, NH), 7.1−7.5 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.6 (CH_3), 28.2 (CH_3), 42.1 (CH), 52.0 (CH_3), 58.7 (CH), 79.8 (C), 127.2 (CH), 127.6 (CH), 128.5 (CH), 140.8 (C) ppm. MS (CI−NH_3) m/e = 311 (M^+ + 18, 100%), 294 (M^+ + 1, 16%).

Determination of the Optical Purity of *anti*-16. To a solution of *anti*-**16** (0.027 g, 0.092 mmol) in CH_2Cl_2 (0.8 mL) at −20 °C was added DIBALH (0.4 mL, 0.4 mmol, 20% in hexanes). After 5 h at −20 °C, the solution was treated with 5% aqueous HCl, phases were separated, and the organic one was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo, and the residue was purified by flash chromatography to yield 0.02 g (81% yield) of (2*R*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenylbutanol: ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 (d, 3H, J = 7.2 Hz), 1.37 (s, 9H), 2−2.2 (m, 1H, OH), 3.1 (m, 1H), 3.5−3.9 (m, 3H), 4.4−4.5 (m, 1H, NH), 7.1−7.4 (m, 5H) ppm.

To a solution of this alcohol (0.03 g, 0.11 mmol) in dry CH_2Cl_2 (0.35 mL) at room temperature were sequentially added 4-(*N*,*N*-dimethylamino)pyridine (0.014 g), triethylamine (0.073 mL), and (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.022 mL), and the resulting orange solution was stirred for 60 min, until no starting material could be detected by TLC. The reaction was then quenched by addition of 3-(dimethylamino)propylamine, and the solvent was removed under vacuum. Filtration of the residue through a short pad of silica gel afforded 0.031 g (58% yield) of the corresponding Mosher ester. According to ^{19}F NMR (282.2 MHz, $CDCl_3$) only one signal (−72.3 ppm) was obseved. The ^{19}F NMR spectra (282.2 MHz, $CDCl_3$) of a racemic mixture consists of two well resolved signals: δ −72.3(2*R*,3*R*), −72.4(2*S*,3*S*) ppm.

(2*R*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-phenylbutanoic acid, *anti*-1. Following the procedure described for the preparation of *syn*-**1**, *anti*-**16** (36 mg, 0.12 mmol) was converted into *anti*-**1** (32 mg, 94% yield). Colorless oil. $[\alpha]_D$ = −9.5 (c = 1.58, $CHCl_3$). IR (film) ν_{max} 3400−2600 (b), 2979, 1719, 1497, 1454, 1396, 1369, 1163, 1074, 1024, 854, 762 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.2 (b s, 3H), 1.40 (s, 9H), 3.3−3.5 (m, 1H), 4.4−4.6 (m, 1H), 4.8 (m, 1H), 7.2−7.4 (m., 5H), 9−9.4 (m, broad, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8 (CH_3), 28.2 (CH_3), 41.6 (CH), 58.8 (CH), 80 (C), 127.3 (CH), 127.7 (CH), 128.6 (CH), 141 (C), 156 (C), 176.6 (C) ppm. MS (EI) m/e = 178 (10%), 119 (18%), 105 (100%), 91 (43%).

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Supporting Information Available: Copies of ^1H and ^{13}C NMR of *syn* and/or *anti* stereoisomers of compounds **1**, **4**−**8**, **10**, and **14**−**16**, experimental procedures for the preparation of *syn*-**5** and *syn*-**10** according to Schemes 4 and 5, ^{19}F NMR spectrum used for enantiomeric purity determination of *anti*-**16**, and HPLC chromatogram of *syn*-**16** on a Chiralcel-ODR column (39 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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