Synthesis of β-Amino Alcohols Derived from L-Valine

P. Delair, C. Einhorn,* J. Einhorn, and J. L. Luche*,†

LEDSS, Batiment Chimie Recherche, Université J. Fourier, BP 53X, 38041 Grenoble Cedex, France

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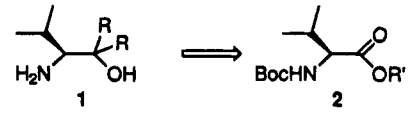
In recent years, β-amino alcohols with various types of structures were used with success as chiral inductors in various enantioselective reactions, e.g., reductions and nucleophilic additions to the carbonyl group.[1,2] We became interested in the preparation of such compounds from natural amino acids, especially L-valine, the derivatives of which (besides those of proline) appear to be quite promising. A straightforward and simple method to achieve this goal corresponds to the addition of Grignard reagents to amino acid esters (Scheme 1).

The addition of organometallics to amino acids and derivatives has been described for the synthesis of α-amino ketones in a number of papers,[3] but less frequently for amino alcohols. For example, phenylmagnesium bromide adds to L-proline in 20% yield[4] and to L-valine methyl ester hydrochloride[5] in 56% yield. In our hands this reaction gave the desired compound **1** (R = Ph) in 73% yield by the direct addition technique, a poor 17% yield using the inverse addition of the Grignard reagent. Extension to alkylmagnesium reagents resulted in the formation of useless mixtures. We began a study of the envisaged synthetic route because it was simple and attractive in its principle despite being difficult to handle.

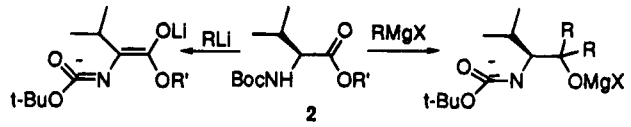
Results and Discussion

The requirements for such a synthesis are simplicity, high yields, and more importantly, the absence of racemization. The literature data suggest the necessity of a protecting group on nitrogen and detail the properties necessary for that protecting group.[6] Monosubstitution with electron-withdrawing groups is suitable.[7] Deprotonation of the acidic N-hydrogen protects efficiently the chiral center when Grignard reagents are employed. Use

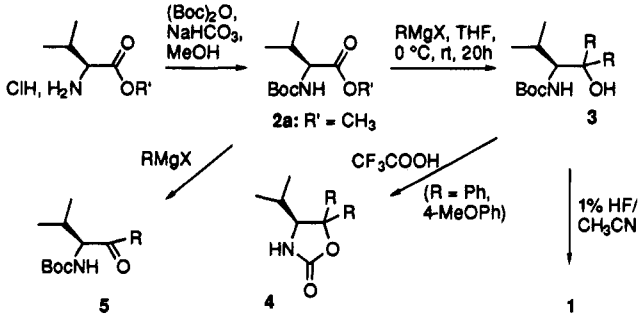
Scheme 1



Scheme 2



Scheme 3



of the more basic lithium reagents leads to extensive racemization (Scheme 2).[8]

The synthetic pathway we chose is shown in Scheme 3. The convenient Boc protecting group was introduced by conventional methods in quantitative yields.[9] Other protecting groups, e.g., benzenesulfonyl, were unsatisfactory in the subsequent steps of the synthesis. The N-protected amino ester was then treated with various Grignard reagents in THF. After addition of the reagent, the reaction was left to proceed at room temperature. The expected compounds **3** are generally obtained in good to high yields (Table 1).

The reaction was efficient with diverse aryl and alkyl reagents. The exceptions were those branched in the α position (e.g., isopropyl) or with a strong steric congestion (entry 5, R = neopentyl). In these cases, the reaction leads to unseparable mixtures. No racemization occurs, as shown by the absence of splitting of the NMR signals in the presence of chiral shift reagents.[10] This preservation of stereochemical integrity was fully demonstrated after the last step of the synthesis (see below).

The last step, the deprotection of the amino group, was more difficult than expected, probably due to the presence of a vicinal tertiary alcohol. Common reagents, such as protic acids in various standard media (HBr in acetic acid, aqueous HCl),[11] lead to degradation. Fortuitously, trifluoroacetic acid[12] leads to quantitative formation of the oxazolidinone **4** for R = Ph or 4-MeOPh, an interesting chiral inductor.[13] This transformation is probably favored by the disubstitution at the carbinol carbon atom, since valinol **1** (R = H) is obtained by deprotection of its Boc derivative in 68% yield using the same acid. Silyl-

† Present address: Laboratoire AMPERES, Bat. 2R1, Université P. Sabatier, 118 Route de Narbonne, 31062 Toulouse Cedex, France.

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Table 1. Grignard Reactions on Methyl *N*-Boc-L-valinate and Deprotection to Amino Alcohol 1

entry	RMgX	product **3** (yield, %)[a]	ketone (yield, %)[a]	deprotection of **3** (yield, %)[a]	overall yield (%) from **2**
1	CH_3	**3a** (84)	**5a** (11)		
2	n-C_4H_9	**3b** (71)	**5b** (11)	**1b** (89)	63
3	n-$C_{10}H_{21}$	**3c** (48)	**5c** (25)	**1c** (92)	44
4	i-C_4H_9	**3d** (87)	**5d** (0)	**1d** (90)	78
5	neo-C_5H_{11}	**3e** (10)[b]	**5e** (70)[b]		
6	C_6H_5	**3f** (78)	(0)	**1f** (81)	63
7	$4FC_6H_4$	**3g** (82)	(0)	**1g** (89)	73
8	4-$MeOC_6H_4$	**3h** (72)	(0)		52[c]
9	2,4,6-$Me_3C_6H_2$	complex	mixture		

[a] Isolated yields. [b] VPC estimation. The mixture could not be separated on analytical and preparative TLC with all the eluents tested. [c] Deprotection is difficult. Compound **1h** was obtained by direct Grignard reaction on **2**.

ating reagents (trimethylsilyl triflate followed by fluoride anion treatment;[14] trimethylsilyl chloride in the presence of phenol[15]) were equally unsuccessful. Ultimately, the desired transformation was effected by a 1% solution of hydrofluoric acid in acetonitrile (Table 1).[16]

The amino alcohols **1** are obtained in satisfactory yields (44–78%) and excellent purity. The only contaminant, easily separated in most cases,[17] is the *N*-*tert*-butylacetamide, deriving from a Ritter reaction of the *tert*-butyl cation with the solvent.[18] The optical purities of the final products were determined by NMR and VPC after transformation to the amide with Mosher's acid.[19] Only monoacylation at nitrogen is observed. NMR spectra consist in only one set of signals, in comparison to the two clearly separated sets displayed by the diastereomeric amides prepared from the racemic amino alcohol. Capillary column VPC analyses exhibit only one peak, and the loss of stereochemical integrity at the chiral center was estimated to be <0.2% (see Experimental Section). The diisobutyl derivative **1d** deserves a special mention since its "rotatory power" is equal to zero at all the wavelengths available on a common polarimeter (except at 365 nm: $[\alpha]_{365}$ +3°).

The method described in this paper constitutes a simple and reasonably rapid preparation for chiral β-amino alcohols. The synthesis is achieved in three steps starting from commercially available L-valine methyl ester hydrochloride using simple reaction conditions and inexpensive reagents without racemization.

Experimental Section

L-Valine methyl ester hydrochloride was purchased from Sigma and used as received. The other reagents, Boc anhydride, acetonitrile, and 40% aqueous HF, were obtained from Aldrich. *N*-Boc L-valine methyl ester **2** was prepared from L-valine methyl ester hydrochloride according to the literature.[8] THF was distilled from sodium benzophenone ketyl. Grignard reagents were prepared in THF following standard procedures. Analytical chromatographies (TLC) were effected on silica gel on aluminum plates (Merck). Preparative column chromatographies were effected on silica gel (Merck, 70–230 mesh), with ethyl acetate in hexane (from 2 to 20% v/v) as the usual eluents. Chromatographies of amino alcohols were effected on silica gel with a mixture of ethyl acetate in hexane (2:8), added with 2% of a saturated solution of NH_3 in methanol. Usual workup implies hydrolysis with aqueous saturated NH_4Cl, washing with brine, drying (Na_2SO_4), and evaporation of the solvent. IR spectra were recorded on a Perkin-Elmer 357 spectrometer as films or Nujol suspensions. Melting points were measured on a Büchi Tottoli apparatus and are not corrected. ^1H NMR and ^{13}C NMR spectra were, respectively, recorded on Brucker 200-MHz and 50-MHz spectrometers unless otherwise specified, in $CDCl_3$ solution with TMS as internal standard. Usual symbols describe the multiplicity of signals (h stands for heptuplet). Mass spectra were taken on a Nermag R-1010-C spectrometer (chemical ionization using ammonia–isobutane, quadrupole detection). Optical rotations were measured on a Perkin-Elmer 241 polarimeter, in chloroform solution (unless specified otherwise) at 25 °C. Combustion analyses were effected at the Service Central de Microanalyse du CNRS, Vernaison, France. High-resolution mass spectra were effected by the FAB technique (positive mode).

3(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-3-amino-2,4-dimethylpentan-2-ol (3a). **2** (1.31 g, 5.66 mmol) was reacted with 7.5 mL of a 3 M solution of methyl magnesium bromide at 0 °C and then stirred at rt overnight. After workup, the crude (1.28 g) was chromatographed. The pure *N*-Boc-amino alcohol **3a** (1.10 g, 84%) was obtained as a white solid, mp 46–48 °C. ^1H NMR: δ 0.94 (m, 6H), 1.23 (s, 3H), 1.27 (s, 3H), 1.46 (s, 9H), 2.12 (hd, 1H, J = 6.8 and 2.6 Hz), 3.39 (dd, 1H, J = 10.3 and 2.6 Hz), 4.99 (br. d, 1H, J = 10.2 Hz). ^{13}C NMR: δ 16.8, 22.2, 26.9, 28.0, 28.3, 28.9, 61.6, 73.4, 78.8, 156.8. IR (Nujol): 3450, 1680, 1490, 1380, 1360 cm^{-1}. MS: m/e 249 ($M + NH_4^+$), 232 (MH^+, 100), 176, 158. $[\alpha]_D$: −14.7° (c 2.3). Anal. Calcd for $C_{12}H_{25}NO_3$: C, 62.30; H, 10.89; N, 6.05. Found: C, 61.99; H, 10.99; N, 6.19.

3(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-3-amino-4-butyl-2-methyloctan-4-ol (3b). Following the above procedure, using n-butylmagnesium bromide (30 mL, 1.68 M THF solution) and compound **2** (3.4 g, 14.7 mmol), there was obtained 4.34 g of a yellow oil, purified by chromatography to give 3.26 g of **3b** (71%), mp 82–83 °C. ^1H NMR: δ 0.9–1.0 (m, 12H), 1.1-1.3 (m, 12H), 1.45 (s, 9H), 2.05 (hd, 1H, J = 6.7 and 2.1 Hz), 3.48 (dd, 1H, J = 10.4 and 2.2 Hz), 4.89 (d, 1H, J = 10.3 Hz). ^{13}C NMR (20 MHz): δ 14.0, 16.9, 22.1, 23.2, 23.3, 25.6, 25.8, 27.7, 28.4, 35.8, 36.6, 58.5, 77.6, 78.7, 156.7. IR (Nujol): 3430, 1680, 1490, 1450, 1380, 1360 cm^{-1}. MS: m/e 316 (MH^+, 100), 298, 259, 242. $[\alpha]_D$: −3.4° (c 2.1). Anal. Calcd for $C_{18}H_{37}NO_3$: C, 68.53; H, 11.82; N, 4.44. Found: C, 68.14; H, 11.42; N, 4.41.

3(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-3-amino-4-decyl-2-methyltetradecan-4-ol (3c). At −78 °C, n-decylmagnesium bromide (7.5 mL of a 0.87 M THF solution) was added to **2** (250.8 mg, 1.08 mmol) in 10 mL of THF and then left to react overnight at rt. After workup, the crude (550 mg) was chromatographed to give 250 mg of pure **3c** (oil, 48%) along with 96 mg of aminoketone **5c** (25%). **3c**. ^1H NMR: δ 0.85–0.94 (m, 12H), 1.26 (m, 36H), 1.4 (s, 9H), 2.05 (m, 1H), 3.48 (dd, 1H, J = 10.3 and 2.0 Hz), 4.89 (d, 1H, J = 10.4 Hz). ^{13}C NMR: δ 14.1, 16.9, 22.1, 22.6, 23.4, 23.6, 27.7, 28.4, 29.3, 29.5, 29.6, 30.1, 30.2, 31.9, 36.1, 36.8, 58.5, 77.6, 78.7, 156.7. IR (film): 3420, 1690, 1490, 1460, 1380, 1360 cm^{-1}. MS: m/e 484 (MH^+), 410 (100), 427. $[\alpha]_D$: +3.5° (c 81.1). Anal. Calcd for $C_{30}H_{61}NO_3$: C, 74.48; H, 12.71; N, 2.89. Found: C, 74.40; H, 12.43; N, 3.37.

3(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-3-amino-2,6-dimethyl-4-(2-methylpropyl)heptan-4-ol (3d). Using the above procedure, isobutyl magnesium bromide (18 mL of a 0.3 M THF solution) was reacted with **2** (249.4 mg, 1.08 mmol), and the

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resulting crude oil (421 mg) was chromatographed to give **3d** (white crystals, 276 mg, 81%), mp 89–91 °C. ^{1}H NMR: δ 0.89–1.00 (m, 12H), 1.45 (s, 9H), 1.71–1.84 (m, 2H), 2.06 (h, 1H, J = 6.2), 3.52 (d, 1H, J = 10.8 Hz), 4.85 (br. d, 1H, J = 10.1 Hz). ^{13}C NMR: δ 17.1, 22.4, 23.9, 24.23, 24.25, 24.4, 24.9, 25.0, 28.0, 28.4, 45.4, 45.6, 59.8, 78.6, 156.8. IR (Nujol): 3440, 3400, 1710, 1695 cm^{-1}. MS: m/e 316 (MH$^+$, 100), 298, 259, 242. [α]$_D$: +1.2° (c 1). Anal. Calcd for $C_{18}H_{37}NO_3$: C, 68.52; H, 11.82; N, 4.44. Found: C, 68.24; H, 11.63; N, 4.40.

3(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-α-(1-amino-2-methylpropyl)-α-phenylbenzenemethanol (3f). Using the above procedure, **2** (164 mg, 0.7 mmol) was treated with phenylmagnesium bromide to give 315 mg of crude material which was recrystallized at −30 °C in CH_2Cl_2/pentane to give **3f** (white crystals, 72.4 mg). Chromatography of the mother liquors followed by recrystallization gives a further portion of 122 mg for a total yield of 78%, mp 192–193 °C. ^{1}H NMR: δ 0.87 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.8 Hz), 1.33 (s, 9H), 1.80 (hd, 1H, J = 6.7 and 2.0 Hz), 2.61 (br. s, 1H), 4.60 (dd, 1H, J = 10.3 and 2.0 Hz), 5.00 (br.d, 1H, J = 9.8 Hz), 7.1–7.5 (m, 8H). ^{13}C NMR: δ 17.4, 22.7, 28.3, 28.8, 59.0, 79.0, 82.4, 125.3, 125.7, 126.7, 126.8, 128.2, 128.3, 145.2, 146.3, 156.3. IR (Nujol): 3440, 3420, 3400, 3040, 1670, 1500, 1460 cm^{-1}. MS: m/e 356 (MH$^+$), 338, 299, 282 (100). [α]$_D$: −61.7° (c 58.6). Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.32; H, 8.00; N, 3.93.

3(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-α-(1-amino-2-methylpropyl)-α-(4-fluorophenyl)-4-fluorobenzenemethanol (3g). With the above procedure, from **2** (3.162 g, 13.69 mmol) and 4-fluorophenyl magnesium bromide (55 mL of a 1 M THF solution), a yellow oil was obtained which was recrystallized at −30 °C (CH_2Cl_2/pentane) to give **3g** (white crystals, 4.39 g, 11.2 mmol, 82%), mp 205–206 °C dec. ^{1}H NMR: δ 0.88 (d, 3H, J = 6.7 Hz), 0.89 (d, 3H, J = 6.8 Hz), 1.32 (s, 9H), 1.80 (m, 1H), 2.73 (s, 1H), 4.50 (d, 1H, J = 10.0 Hz), 4.95 (d, 1H, J = 10.0 Hz), 6.8–7.1 (m, 4H), 7.3–7.5 (m, 4H). ^{13}C NMR: δ 17.3, 22.6, 28.2, 28.7, 59.2, 79.4, 81.7, 114.7, 115.0, 115.1, 115.4, 126.9, 127.1, 127.8, 141.1, 142.0, 156.2, 159.2, 164.0. IR (Nujol): 3450, 3400, 1670, 1595, 1510, 1460 cm^{-1}. MS: m/e 392 (MH$^+$), 374, 335, 318, 219. [α]$_D$: + 80.4° (c 64.8). Anal. Calcd for $C_{22}H_{27}F_2NO_3$: C, 67.50; H, 6.95; N, 3.58; F, 9.72. Found: C, 67.44; H, 6.90; N, 3.66; F, 9.65.

3(S)-*N*-[(1,1-Dimethylethoxy)carbonyl]-α-(1-amino-2-methylpropyl)-α-(4-methoxyphenyl)-4-methoxybenzenemethanol (3h). Twenty-one mL of a 0.94 M solution of (4-methoxyphenyl)magnesium bromide is added dropwise to **2** (920 mg, 3.98 mmol) in 2 mL of dry THF at −60 °C, and then the mixture was stirred at rt for 3 h. After workup, the crude oil was chromatographed and then recrystallized in CH_2Cl_2/hexane to give 1.2 g of pure **3h** (2.88 mmol, 72%), mp 165–166 °C. ^{1}H NMR: δ 0.85 (d, 3H, J = 6.9 Hz), 0.89 (d, 3H, J = 6.8 Hz), 1.34 (s, 9H), 1.80 (hd, 1H, J = 6.8 and 1.9 Hz), 2.50 (s, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 4.49 (dd, 1H, J = 10.3 et 1.7 Hz), 4.99 (br. d, 1H, J = 10.3 Hz), 6.76–6.85 (m, 5H), 7.25–7.42 (m, 5H). ^{13}C NMR: δ 17.2, 22.6, 28.2, 28.7, 55.1, 59.0, 79.0, 81.8, 113.4, 113.5, 126.5, 127.0, 138.1, 138.9, 156.2, 158.0. IR (CH_2Cl_2): 3550, 3450, 3050,1700, 1600 cm^{-1}. MS: m/e 415 (M$^+$), 398, 359, 342 (100%), 243. [α]$_D$: −48.8° (c 1). Anal. Calcd for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.22; H, 7.78; N, 3.58.

Standard Procedure for the Deprotection of the Amino Group. One vol of 40% aqueous HF was diluted in 40 vol of acetonitrile. This solution was directly poured onto the pure *N*-Boc-amino alcohol. The reaction was left to continue stirring overnight. The resulting solution was concentrated under vacuum, diluted with ethyl acetate, and washed two times with aqueous $NaHCO_3$ and then brine. The organic phase was dried (Na_2SO_4) to give the crude product.

Estimation of the Optical Purity of Amino Alcohols. After quantitative transformation to Mosher's amides by literature methods,[19] the sample was analyzed by capillary column VPC (Perkin-Elmer Autosystem GC, FID detector, OV17, 30 m, oven temperature 220 °C, injector temperature 280 °C). Only one peak was present. Addition of 1% of the amides prepared from the racemic compound to the optically pure sample leads to the apparition of a second peak clearly detected. With a 0.2% amount, the peak was detected but not integrated.

(3*S*)-3-Amino-4-butyl-2-methyl-octan-4-ol (1b). From **3b** (350 mg, 1.11 mmol) and 40 mL of 1% HF. The crude oil (315 mg) was distilled (150 °C, 2 Torr) yielding **1b** (colorless oil, 214 mg, 0.99 mmol, 89%). ^{1}H NMR: δ 0.8–1.0 (m, 12H), 1.1–1.6 (m, 14H), 1.97 (hd, 1H, J = 6.85 and 2.25 Hz), 2.5 (d, 1H, J = 2,3 Hz). ^{13}C NMR: δ 14.11, 16.3, 22.9, 23.42, 23.58, 25.75, 25.79, 27.60, 34.73, 37.03, 59.93, 75.11. IR (film): 3400, 1580, 1460, 1370 cm^{-1}. MS: m/e 216 (MH$^+$, 100%), 198. [α]$_D$: −9.0° (c 2.0). Anal. Calcd for $C_{13}H_{29}NO$: C, 72.50; H, 13.57; N, 6.50. Found: C, 72.35; H, 13.84; N, 6.32.

(3*S*)-3-Amino-2-methyl-4-decyltetradecan-4-ol (1c). From **3c** (500 mg, 1.03 mmol) and 50 mL of 1% HF. The crude oil (398 mg) was distilled (220 °C, 2 Torr) to give **1c** (365 mg, 0.95 mmol, 92%) as a colorless oil. ^{1}H NMR: δ 0.84–0.99 (m, 12H), 1.26 (s, 36H), 1.97 (hd, 1H, J = 6.85 and 2.25 Hz), 2.56 (d, 1H, J = 2.3 Hz). ^{13}C NMR: δ 14.0, 16.3, 22.6, 22.9, 23.5, 23.6, 27.7, 29.30, 29.58, 29.63, 30.4, 30.6, 31.9, 35.2, 37.4, 60.1, 75.3. IR (film): 3400, 1460, 1370 cm^{-1}. MS: m/e 384 (MH$^+$, 100%), 366, 242. [α]$_D$: −6.2° (c 3.1). HRMS: calcd for $C_{25}H_{54}NO$ 384.4205 (MH$^+$), found 384.4187.

(3*S*)-3-Amino-2,6-dimethyl-4-(2-methylpropyl)heptan-4-ol (1d). From **3d** (2.01 g, 6.38 mmol) and 100 mL of 1% HF. The crude oil (2.23 g) was distilled (120 °C, 2 Torr) to give **1d** (1.23 g, 5.74 mmol, 90%)as a colorless oil. ^{1}H NMR: δ 0.88–1.00 (m, 18H), 1.21–1.56 (m, 4H), 1.63–2.01 (m, 3H), 2.58 (d, 1H, J = 2.4 Hz). ^{13}C NMR: δ 16.6, 23.1, 23.8, 23.9, 24.5, 24.7, 24.9, 25.3, 27.7, 44.3, 45.4, 60.8, 76.4. IR (film): 3400, 1610, 1460, 1360 cm^{-1}. MS: m/e 216 (MH$^+$, 100%), 198. [α]$_D$ 0.0 ° (c 3.5; CH_2Cl_2, 25 °C). HRMS: calcd for $C_{13}H_{30}NO$ 216.2327 (MH$^+$), found: 216.2344.

(*S*)-α-(1-Amino-2-methylpropyl)-α-phenylbenzenemethanol (1f). From **3f** (1.14 g, 3.62 mmol) and 100 mL of 1% HF. After workup, the white solid (1.07 g) was chromatographed to give **1f** (752 mg, 2.95 mmol, 81%), mp 93–94 °C (lit.[5] mp 94–95 °C). ^{1}H NMR: δ 0.88 (d, 3H, J = 7.1 Hz), 0.92 (d, 3H, J = 7.5 Hz), 1.6–1.8 (hd, 1H, J = 6.94 and 2.06 Hz), 3.83 (d, 1H, J = 2.1 Hz), 7.1–7.6 (m, 10H). ^{13}C NMR: δ 16.06, 22.95, 27.8, 60.1, 79.6, 125.4, 126.2, 126.5, 128.0, 128.4, 144.8, 148.0. IR (Nujol): 3350, 3050, 1440, 1230 cm^{-1}. MS: m/e 256 (MH$^+$, 100), 238. [α]$_D$: −126° (c 0.7).

(*S*)-α-(1-Amino-2-methylpropyl)-α-(4-fluorophenyl)-4-fluorobenzenemethanol (1g). From **3g** (2.10 g, 5.35 mmol) and 50 mL of 1% HF for 72 h. After workup the white solid (1.92 g) was chromatographed to give **1g** (1.39 g, 4.77 mmol, 89%), mp 118–119 °C. ^{1}H NMR: δ 0.86 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 7.0 Hz), 1.6–1.8 (hd, 1H, J = 6.9 and 2.0 Hz), 3.75 (d, 1H, J = 2.1 Hz), 7.01–7.90 (m, 5H), 7.4–7.6 (m, 5H). ^{13}C NMR: δ 15.9, 22.8, 27.8, 60.3, 79.1, 86.5, 114.6, 114.9, 115.2, 127.1, 127.2, 127.5, 127.6, 140.6, 143.7, 160.0 (J_{CF} = 57.9 Hz), 163.2 (J_{CF} = 57.3 Hz). IR (Nujol): 3425, 3300, 1650, 1520, 1460 cm^{-1}. MS: m/e 292 (MH$^+$, 100), 274. [α]$_D$: −125° (c 1.7; CH_2Cl_2). Anal. Calcd for $C_{17}H_{19}F_2NO$: C, 70.08; H, 6.57; N, 4.81; F, 13.06. Found: C, 70.26; H, 6.69; N, 4.93; F, 12.34.

(*S*)-α-(1-Amino-2-methylpropyl)-α-(4-methoxyphenyl)-4-methoxybenzenemethanol (1h). L-Valine methyl ester hydrochloride (1.47 g, 7.5 mmol) was treated with (4-methoxyphenyl)magnesium bromide (58 mL, 1.12 M, 8 equiv) at 0 °C and then 3 h at room temperature. After workup and chromatography the oil (1.23 g) was crystallized in hexane/AcOEt (9/1) to give **1h** (white solid, 1.10 g, 3.49 mmol, 46%), mp 130–131 °C. ^{1}H NMR: δ 0.83 (d, 3H, J = 6.8Hz), 0.91 (d, 3H, J = 7.0Hz), 1.75 (hd, 1H, J = 6.9 and 1.9 Hz), 3.71 (d, 1H, J = 2.0 Hz), 3.75 (s, 3H), 3.76 (s, 3H), 6.78–6.85 (m, 4H), 7.35–7.51 (m, 4H). ^{13}C NMR: δ 16.0, 22.9, 27.7, 55.08, 55.14, 60.2, 79.1, 113.2, 113.6, 126.5, 126.9, 137.4, 140.3, 157.8, 158.0. IR (CH_2Cl_2): 3350, 3050, 1600, 1500 cm^{-1}. MS: m/e 316 (MH$^+$), 298 (100), 243. [α]$_D$: −109.0° (c 1). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 71.97; H, 7.96; N, 4.75.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of compounds **1c** and **1d**. Description of compounds **5c** and **4** (5 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.