A Synthesis of Statine Utilizing an Oxidative Route to Chiral α-Amino Aldehydes

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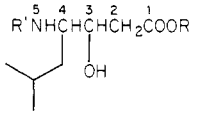
A recent report[1] describing the synthesis of chiral Boc-amino aldehydes by a reduction–oxidation sequence from the corresponding acids prompts us to relate our experience with such a method in the synthesis of the natural product statine.

Statine [(3*S*,4*S*)-1, R = R′ = H] is the key element in



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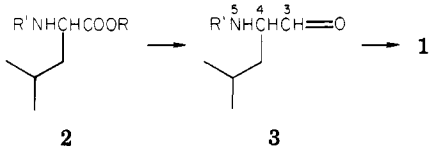
a number of recently discovered protease inhibitors, notably pepstatin.[2] Its potential utility in the synthesis of inhibitors of acid proteases such as pepsin and cathepsin D[3] has spawned considerable interest in practical chemical syntheses of this unusual amino acid. Several statine syntheses have been published.[4-8] The most recent and useful of these[6-8] are based on a similar strategy (Scheme I): namely, use of an N-protected L-amino aldehyde **3** as the source of C_3, C_4, and N_5 with the desired chirality (*S*) fixed at C_4. Addition of a metalated acetic acid derivative to the aldehyde provides **1** as a mixture of N-protected 3*S*,4*S*, and 3*R*,4*S* diastereomers. These have been separated by crystallization[6] and by silica gel chromatography.[7,8] In every case, the protected chiral α-amino aldehyde **3** has been secured by partial reduction of an L-leucine derivative (**2**).

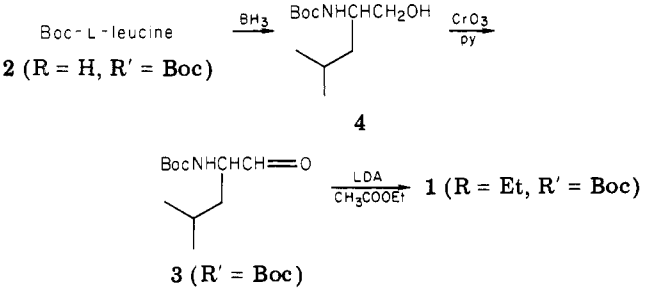
In our search for a preparatively useful alternative to this approach, we have developed a synthesis of statine (Scheme II) which is based on an oxidative route to the requisite chiral Boc-α-amino aldehyde similar to that described by Stanfield et al.[1] In our experience, the chiral lability of such α-amino aldehyde derivatives proved more significant than these authors seem to indicate. In view of this observation, we have also developed chiral purity assays for Boc-L-leucinal (**3** R′ = Boc) and for the product, statine [(3*S*,4*S*)-**1**, R = R′ = H].

Reduction of Boc-L-leucine **2** (R = H, R′ = Boc) to the carbinol **4** with borane/THF took place rapidly and in high yield.[9] Oxidation of **4** with chromium trioxide/pyridine in methylene chloride (Collins oxidation)[10] at −10 °C for 30 min gave aldehyde **3**, (R′ = Boc), again in good yield.

Scheme I



Scheme II



Little information is available regarding the chiral stability of such α-amino aldehyde derivatives.[11] Therefore, we have analyzed the optical purity and stability of samples of the aldehyde **3** (R′ = Boc) taken immediately from the oxidation and samples stored at 0 °C and at ambient temperature. The aldehyde samples were reduced with sodium borohydride to carbinol **4** and then oxidized with permanganate to give Boc-leucine. Following removal of the Boc group with acid, these samples were converted to the corresponding 5-(dimethylamino)naphthalene-1-sulfonyl (dansyl) derivatives by the procedure of Gros and Labouesse,[12] and the chiral purities of the resulting dansyl compounds were determined by a chromatographic method using a chiral eluant.[13] These studies demonstrated that the reduction/oxidation procedure of Scheme II generates aldehdye **3** (R′ = Boc) with complete (>99.5%) retention of chiral integrity. They also showed that the crude aldehyde has some chiral lability,[14] retaining its chirality reasonably well in the cold (≤5% racemization after 9 days at −30 °C) but racemizing relatively rapidly at room temperature (62% racemization of derived leucine after 9 days).

Flash chromatography[15] on silica gel provided pure aldehyde **3** (R′ = Boc), which was combined with α-lithioethyl acetate as described by Rich et al.[8] The resulting

(1) Stanfield, C. F.; Parker, J. E.; Kanellis, P. *J. Org. Chem.* **1981**, *46*, 4797, 4799.
(2) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259.
(3) Aoyagi, T.; Morishima, H.; Nishizawa, R.; Kunimoto, S.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1972**, *25*, 689.
(4) Morishima; H. Takita, T.; Umezawa, H. *J. Antibiot.* **1973**, *26*, 115.
(5) Kinoshita, M.; Hagiwara, A.; Aburaki, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 570.
(6) Stuelmann, R.; Klostermeyer, H. *Justus Liebigs Ann. Chem.* **1975**, *2245*.
(7) Liu, W. S.; Glover, G. I. *J. Org. Chem.* **1978**, *43*, 754.
(8) Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624.
(9) The quality of the commercial borane reagent proved to be capricious. Fresh material stored in a freezer usually, but not always, performed satisfactorily, and loss of reducing power was not accompanied by any observable change in the reagent (sediment, pressure buildup, etc.). Reduction of a sample of benzoic acid to benzyl alcohol was used as a convenient assay for reagent potency.
(10) (a) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, *3363*. (b) Ratcliff, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.
(11) Racemization of N-protected α-amino aldehydes on silica gel has been reported by Rich et al.[8] and by Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull, Jpn.* **1975**, *23*, 3081.
(12) Gros, C.; Labouesse, B. *Eur. J. Biochem.* **1969**, *7*, 463.
(13) Lam, S.; Chow, F.; Karmen, A. *J. Chromatogr.* **1980**, *199*, 295.
(14) The purified aldehyde behaved similarly, losing 10% of its optical rotation after 48 h at room temperature. The chiral lability of Boc-phenylalaninal is more pronounced. Thus, when the oxidation of Boc-L-leucinol was carried out at room temperature, the product (in slightly lower yield) was Boc-L-leucinal of ≥99% chiral purity as reflected in the chiral purity of the derived Boc-statine [$[\alpha]^{24}_D$ −39.3° (*c* 1.5, CH_3OH); lit.[8] $[\alpha]^{24}_D$ −39.6° (*c* 0.31, CH_3OH)]. The same room temperature oxidation procedure applied to Boc-L-phenylalaninol produced extensive racemization in the aldehyde product. This racemization, seen in the resulting purified statine analogue, Boc-4-amino-3-hydroxy-5-phenylpentanoic acid ethyl ester (Boc-AHPPA-OEt) $[\alpha]^{24}_D$ −6.4° (*c*, 2.1, CH_3OH) [lit.[17] $[\alpha]^{24}_D$ −35.9° (*c*, 1.0, CH_3OH)] could be avoided by carrying out the oxidation and workup in the cold (≤0 °C), giving Boc-AHPPA-OEt $[\alpha]^{24}_D$ −34.8 (*c* 1.4, CH_3OH). Under the oxidation conditions reported by Stanfield et al.[1] (room temperature, overnight), extensive racemization of Boc-L-phenylalaninal and some racemization (5–10%) of Boc-L-leucinal might be expected. Since the only criteria of chiral integrity presented by these authors are optical rotations without reference to standard values, the chiral purities of these aldehydes must be regarded as uncertain (see also ref 18 and 19).
(15) Still, W. C.; Kahn M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

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mixture of 3*S*,4*S* and 3*R*,4*S* diastereomers of 1 (R = Et, R′ = Boc) was separated by flash chromatography[15] which allowed processing of considerable material in short order. The Boc ethyl ester (3*S*,4*S*)-1 (R = Et, R′ = Boc) obtained from this procedure was free of the 3*R*,4*S* diastereomer (and its 3*S*,4*R* enantiomer) as shown by gas chromatography (GC).

Since the key intermediate aldehyde **3** (R′ = Boc) showed some chiral lability, we deemed it necessary to verify the chiral purity (i.e., freedom from the 3*R*,4*R* enantiomer) of (3*S*,4*S*)-1 (R = Et, R′ = Boc). Toward this end, we have developed a chiral purity assay for statine, described below.

Saponification of (3*S*,4*S*)-1 (R = Et, R′ = Boc) provided the Boc-amino acid (3*S*,4*S*)-1 (R = H, R′ = Boc) ($[\alpha]^{24}_D$ −39.5°) which was N-deprotected to yield the free amino acid (3*S*,4*S*)-1 (R = R′ = H). Treatment with L-glutamic acid *N*-carboxyanhydride (L-Glu-NCA) according to the procedure of Manning and Moore[16] gave a dipeptide which was shown by high-performance liquid chromatography (HPLC) to contain a single major component (>99.5%) with retention time (t_R) of 11 min, along with a minor fraction (<0.5%) with a t_R of 20 min. Authentic (3*R*,4*R*)-1 (R = R′ = H) (Boc-amino acid $[\alpha]^{24}_D$ +39.1°) was prepared by use of the synthetic methods described above, with Boc-D-leucine as the starting acid. The dipeptide derived from this compound and L-Glu-NCA showed the expected major component (≥99%) with t_R = 20 min by HPLC along with a minor fraction (≤1%) with t_R 11 min.

These experiments demonstrated that the 3*R*,4*R* and 3*S*,4*S* enantiomers of 1 can be distinguished quantitatively. They also showed that the Boc-amino acid 1 (R = H, R′ = Boc) with $[\alpha]^{24}_D$ −39.5° is ca. 99.5% chirally pure 3*S*,4*S* material (Boc-statine).

As a result of the procedures described here, the important natural product statine, (3*S*,4*S*)-1 (R = R′ = H) and its three stereoisomers (3*R*,4*R*; 3*R*,4*S*; 3*S*,4*R*), are available conveniently and in quantity. The chiral purity of statine can be determined quantitatively, an important assay in view of the demonstrated chiral lability of the key intermediate Boc-amino aldehyde.

Experimental Section

Melting points were determined with a Thomas-Hoover melting-point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian T-60 or EM 390 spectrophotometer using $(CH_3)_4Si$ as an internal standard. Optical rotations were measured at the sodium D line, using a Perkin-Elmer 241 polarimeter. Gas chromatography was carried out on a Hewlett-Packard Model 5710A gas chromatograph using glass columns (4 ft × 40 mm) packed with 1% OV-225 on Chromosorb Q (110–120 mesh) at 165 °C. The injection temperature was 255 °C. HPLC assays were run on a Spectra-Physics SP8000 high-performance liquid chromatograph using a 25 × 0.4 cm analytical column packed with Du Pont C-8 resin. Analytical TLC was carried out on 250 μm, 2.5 × 10 cm, silica gel GF plates (Analtech, Inc.), using ninhydrin spray and I_2 for visualization.

Boc-L-leucinol 4. To a solution of Boc-L-leucine hydrate **2** (R = H, R′ = Boc) (100.0 g, 0.401 mol; Bachem) in THF (500 mL) stirred at 0 °C under a nitrogen atmosphere was added dropwise over a 2-h period 1000 mL of 1 M BH_3 in THF (Aldrich). After addition was complete, the resultant suspension was warmed to 25 °C and stirred for 1 h. With cooling, water (100 mL) was added dropwise and the solvent removed under reduced pressure. The white solid residue was slurried with water (500 mL) and extracted with ether (2 × 500 mL). The ethereal extracts were combined, washed with dilute aqueous $NaHCO_3$ (2 × 250 mL) and brine (200 mL), dried over Na_2SO_4, and filtered. Evaporation of the filtrate under reduced pressure gave 70.9 g (81% yield) of **4** as a light-yellow oil homogeneous to TLC (R_f 0.40; elution with 5% MeOH, 95% CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 6 H, $(CH_3)_2$, J = 7 Hz), 1.27–1.75 (m, 3 H, C**H**C**H**$_2$), 1.40 (s, 9 H, $(CH_3)_3$), 3.30–3.80 (m, 4 H, NC**H**C**H**$_2$O; OH, exchanged with D_2O), 4.95 (br d, 1 H, NH, exchanged with D_2O). This compound was used without further purification. A sample was purified for analysis by chromatography on silica gel (elution with 3% MeOH/97% CH_2Cl_2); $[\alpha]^{24}_D$ −27.4° (*c* 2.03, CH_3OH).

Anal. Calcd for $C_{11}H_{23}NO_3$: C, 60.80; H, 10.67; N, 6.45. Found: C, 60.72; H, 11.24; N, 6.11.

Boc-L-leucinal 3 (R′ = Boc). To a solution of dry pyridine (362 g, 4.59 mol) in CH_2Cl_2 (5 L) stirred at 0 °C under a nitrogen atmosphere was added chromium trioxide (229 g, 2.29 mol) portionwise while the temperature was maintained below 5 °C. A 229-g sample of Celite was added and the suspension cooled to −10 °C. (The reaction can be run at room temperature with slight loss of yield. However, see ref 14.) The mixture was stirred vigorously and treated with a solution of Boc-L-leucinol **4** (50.0 g, 0.230 mol) in CH_2Cl_2 (200 mL) added over 5 min. After the mixture was stirred for 30 min at −10 °C, the CH_2Cl_2 was decanted and the residue extracted with fresh CH_2Cl_2 (2 × 200 mL). The organic extracts were combined, and the solvent was removed in vacuo without heat, using a dry ice/acetone condenser. The brown oily residue was treated with ether (1250 mL) and filtered through a pad of Celite. The filtrate was concentrated in vacuo and dried under high vacuum without heat to give **3** as a light purple oil (46.6 g). Flash chromatography[15] on silica (ethyl acetate elution) gave the pure aldehyde as a colorless oil (33 g, 67%): ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 6 H, $(CH_3)_2$, J = 6 Hz), 1.20–1.95 (br m, 3 H, C**H**C**H**$_2$), 1.43 (s, 9 H, $(CH_3)_3$), 4.23 (br, s, 1 H, NCH), 5.13 (br s, 1 H, NH, exchanged with D_2O), 9.60 (s, 1 H, CHO). A sample of this compound in methanol (16.8 mg/mL) had an optical rotation of −0.710°.[18]

Chiral Stability Studies of Boc-leucinal 3 (R′ = Boc). Samples of crude Boc-leucinal prepared as described above were stored at room temperature and at −30 °C for periods of 0 h, 24 h, and 9 days. The samples were assayed for chiral purity as described below.

To a solution of Boc-leucinal (168 mg, 0.780 mmol) in methanol (2 mL) cooled to 0 °C was added sodium borohydride (30 mg, 0.780 mmol). After the mixture was stirred for 15 min, the reaction was complete by TLC. The methanol was removed in vacuo and the resulting residue slurried with water and extracted with ether (3 times). The combined ethereal extracts were washed with saturated NaCl(aq) (2 times), dried over $MgSO_4$, and filtered. The filtrate was stripped to dryness in vacuo to give 130 mg of Boc-leucinol **4** as a colorless oil with properties identical with those described above.

Boc-leucinol **4** (130 mg, 0.598 mmol) was treated with 3.1 mL of 0.25 M NaOH followed by $KMnO_4$ (125 mg, 0.796 mmol) at room temperature and the mixture stirred 15 min. The reaction mixture was treated with methanol and stirred 15 min, and the brown precipitate was removed by filtration through Celite. The filtrate was acidified with solid citric acid and extracted with ether (3 times). The combined ethereal extracts were washed with saturated NaCl(aq) (2 times), dried over $MgSO_4$, and filtered. Evaporation of the filtrate in vacuo gave 130 mg of Boc-leucine **2** (R = H, R′ = Boc) as an oil homogeneous by TLC (R_f 0.34; elution with 5% MeOH/95% CH_2Cl_2).

This material (130 mg, 0.562 mmol) was dissolved in ethyl acetate (2 mL). The solution was cooled to 0 °C, saturated with HCl(g), and stirred 15 min., Evaporation of the solvent in vacuo gave an oil which was repeatedly evaporated in vacuo with ethyl acetate until a white solid precipitated. Filtration gave leucine hydrochloride (75 mg), which was dried in vacuo at room temperature. This hydrochloride (10 μg, 0.06 μmol) in 100 μL of 0.2

(16) Manning, J. M.; Moore, S. *J. Biol. Chem.* **1968**, *243*, 5591.
(17) Rich, D. H.; Sun, E. T. O.; Ulm, E. *J. Med. Chem.* **1980**, *23*, 27.
(18) This is the observed optical rotation of **3** as prepared and used in this work. The compound was obtained as a chirally labile oil which was not rigorously dried. As described in the text, a sample of **3** subjected to any prolonged treatment regimen, including drying, could no longer be regarded as chirally homogeneous unless otherwise verified as such. The liabilities of optical rotation as a standard for chiral purity have been stated by several authors,[19] and they are merely compounded in the case of a material having limited chiral stability.
(19) (a) Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329. (b) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247.

Table I

storage time, day	storage temp, °C	$[\alpha]^{24}_D$, deg	L/D (HPLC)
0		+18.2	100/0
1	-30	+17.9	99/1
9	-30	+17.4	99/1
9	24	+6.9	70/30

M sodium bicarbonate buffer, pH 9.0, was treated with 100 μL of a 0.02 M solution of 5-(dimethylamino)naphthalene-1-sulfonyl chloride in acetone.[12] The mixture was stirred at 37 °C for 30 min and quenched with 0.1 mL of formic acid. The mixture was evaporated to dryness under a stream of nitrogen and the residue dissolved in methanol (0.5 mL). The solution (10 μL) was analyzed by HPLC, using as the mobile phase a solution of arginine (5 mM), copper sulfate pentahydrate (2.5 mM), and ammonium acetate (5 mM) in glass distilled water, adjusted to pH 7.8 with NH_4OH.[13] Fluorescence at 520 nm was monitored with excitation at 340 nm. Samples were run in duplicate, and authentic samples of D- and L-leucine were used as controls. The observed L to D ratios along with measured optical rotations of the leucine hydrochloride samples are summarized in Table I.

Ethyl (3*R*,4*S*)- and (3*S*,4*S*)-Boc-4-amino-3-hydroxy-6-methylheptanoate 1 (R = Et, R′ = Boc). To diisopropylamine (23.2 g, 0.23 mol) in dry tetrahydrofuran (77 mL) cooled to -20 °C under an N_2 atmosphere was added dropwise *n*-butyllithium in hexane (1.46 M, 157.2 mL, 0.23 mol). The solution was stirred 15 min, the temperature lowered to -78 °C, and dry ethyl acetate (20.2 g, 0.23 mol) added dropwise while the temperature was maintained below -75 °C. The solution was stirred 10 min and a precooled (-78 °C) tetrahydrofuran solution (114 mL) of Boc-L-leucinal **3** (R′ = Boc; 33 g, 0.153 mol) was added while the temperature was maintained below -75 °C. After 12 min, 2 M HCl (117 mL) was added while the temperature was held below -65 °C. The mixture was warmed to 10 °C, treated with 2 M HCl to pH 2.5, and extracted with ether (3 × 400 mL). The ethereal extracts were combined, washed with saturated NaCl (2 × 200 mL), dried over $MgSO_4$, and filtered. Evaporation of the filtrate in vacuo gave 42.5 g of a light-purple oil. Chromatography of the crude oil on silica gel (2 kg) by the procedure of Still et al.,[15] eluting with 20% ethyl acetate in hexane, afforded 17.6 g (38%) of Boc-Sta-OEt [(3*S*,4*S*)-1 R = Et, R′ = Boc; R_f 0.32, >99% by GC]: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 6 H, $(CH_3)_2$, *J* = 6 Hz), 1.27 (t, 3 H, CH_2CH_3, *J* = 6 Hz), 1.3-1.75 (m, 3 H, *i*-PrCH_2CH), 1.44 (s, 9 H, $(CH_3)_3$), 2.50 (m, 2 H, CH_2C=O), 3.35 (s, 1 H, OH), 3.63 (br m, 1 H, 1 H, CHNH), 4.03 (br m, 1 H, CHOH), 4.18 (q, 2 H, CH_2CH_3, *J* = 6 Hz), 4.75 (br d, 1 H, NH).

Also isolated were 16.2 g of predominantly (3*R*,4*S*)-1 (R = Et, R′ = Boc; 95% 3*R*,4*S*; 5% 3*S*,4*S*), and 0.8 g of Boc-leucinal **3** (R′ = Boc).

(3*S*,4*S*)-Boc-4-amino-3-hydroxy-6-methylheptanoic Acid [Boc-statine (1, R = H, R′ = Boc)]. Boc-Sta-OEt [(3*S*,4*S*)-1, R = Et, R′ = Boc; 5 g, 16.5 mmol] was dissolved in dioxane (25 mL) and diluted with water (25 mL). Monitored with a meter standardized with 1:1 dioxane/pH 10 buffer, the turbid solution was treated at room temperature with 1 M NaOH(aq) to maintain the pH of the mixture between 12.0 and 12.2. After 1 h, TLC (20% EtOAc/80% hexane) of the clear solution indicated the disappearance of the ester. The pH of the solution was adjusted to 6.5 with 1 M HCl and the dioxane was removed in vacuo. The remaining aqueous solution was acidified to pH 2.5 with 10% citric acid and extracted with ether (3 times). The combined ethereal extracts were washed with saturated NaCl, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil which upon treatment with ether and dilution with hexane gave Boc-statine [(3*S*,4*S*-1, R = H, R′ = Boc] as a white solid (3.9 g, 86% yield): mp 118-120 °C (lit.[8] mp 117-118 °C); $[\alpha]^{24}_D$ -39.5° (*c* 0.12, CH_3OH) [lit.[8] $[\alpha]^{24}_D$ -39.6° (*c* 0.31, CH_3OH)]; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 6 H, $(CH_3)_2$, *J* = 6 Hz), 1.30-1.73 (m, 3 H, *i*-PrCH_2CH), 1.45 (s, 9 H, $(CH_3)_3$), 2.55 (m, 2 H, CH_2C=O), 3.59 (br m, 1 H, CHNH), 4.03 (br m, 1 H, CHOH), 4.79 (br d, 1 H, NH, exchanged with D_2O).

Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.70; H, 9.08; N, 5.09. Found: C, 56.75; H, 9.38; N, 5.23.

Table II

SS/RR by weight[a]	*SS/RR* by HPLC
3*S*,4*S*	99.6/0.4
95.1/4.9	95.5/4.5
96.7/3.3	97.7/2.3
84.3/15.7	84.7/15.3
49.4/50.6	54.6/45.4
3*R*,4*R*	2.3/97.7

[a] Weighed samples of (3*R*,4*R*)- and (3*S*,4*S*)-1 (R = H, R′ = Boc) corrected for the observed contamination of each with the other.

(3*R*,4*R*)-Boc-4-amino-3-hydroxy-6-methylheptanoic Acid (1, R = H, R′ = Boc). The synthetic sequence of Scheme II, described above, was repeated with Boc-D-leucine hydrate in place of the Boc-L-leucine hydrate. The product obtained had physical properties identical with those described above except for $[\alpha]^{24}_D$ +39.1° (*c* 0.12, CH_3OH).

Chiral Integrity Studies of Boc-4-amino-3-hydroxy-6-methylheptanoic Acid (1, R = H, R′ = Boc). Boc-amino acid 1 (R = H, R′ = Boc; 400 mg, 1.45 mmol) was dissolved in ethyl acetate (3 mL) and cooled to 0 °C. The solution was saturated with HCl(g), stirred 15 min, and then saturated with nitrogen for 15 min. Evaporation of the solvent in vacuo gave an oil, which was repeatedly treated with ethyl acetate and evaporated in vacuo. The residue was dried at room temperature under high vacuum for 16 h to give the free amino acid hydrochloride as a sticky solid.

1·HCl (R = R′ = H) (20 μmol) was dissolved in pH 10 borate buffer (2 mL) and cooled to 0 °C. L-Glutamic acid *N*-carboxyanhydride was added,[16] and the solution was vortexed for 2 min and then quenched with 1 M HCl (1 mL). The derivatized samples were assayed by HPLC, using a gradient of phosphate buffer (8.7 mM phosphoric acid adjusted to pH 3.2 with 25% aqueous trimethylamine) with acetonitrile (100/0 → 90/10 over 30 min) on a Waters Associates C-18 column (30 × 0.39 cm). The sample derived from (3*S*,4*S*)-1 (R = H, R′ = Boc) showed a single major component (t_R 11 min) as did that derived from the 3*R*,4*R* material (t_R 20 min). Mixtures of weighed quantities of (3*R*,4*R*) and (3*S*,4*S*)-1 (R = H, R′ = Boc) were assayed by the same procedure. All the results are summarized in Table II.

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Registry No. (3*R*,4*S*)-1 (R = Et, R′ = Boc), 67010-44-0; (3*S*,4*S*)-1 (R = Et; R′ = Boc), 67010-43-9; (3*S*,4*S*)-1 (R = H; R′ = Boc), 58521-49-6; (3*R*,4*R*)-1 (R = H; R′ Boc), 82010-28-4; (3*S*,4*S*)-1·HCl (R = R′ = H), 82010-29-5; 3*R*,4*R*-1·HCl (R = R′ = H), 82010-30-8; L-**2** (R = H; R′ = Boc), 13139-15-6; L-**3** (R′ = Boc), 58521-45-2; **4**, 82010-31-9; H-Leu-OH·HCl, 760-84-9; Boc-D-Leu-OH, 16937-99-8.

Reduction of Aromatic Nitro Compounds by Secondary Alcohols Using Rhodium Complexes as Catalysts

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Both ketones and aromatic amines have been industrially important chemicals. Most of the ketones are made by oxidizing or dehydrogenating the corresponding secondary alcohols, while aromatic amines are manufactured

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