Enantioselective Synthesis of (*R*)-3-(3,4-Dihydroxyphenyl)alanine from *tert*-Butyl Glycinate

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Received February 13, 2001

Since the discovery of L-3-(3,4-dihydroxyphenyl)alanine (L-DOPA) for the treatment of Parkinson's disease, the preparation of this specific compound has attracted considerable synthetic attention.[1] The synthesis of optically active α-amino acids has been intensively investigated in the past couple decades.[2,3] We have reported that enantioselective synthesis of α-amino acids from the asymmetric enolate alkylation of Schiff base, derived from the condensation of *tert*-butyl glycinate with N-substituted or N,N-disubstituted (1*S*)-(+)-10-camphorsulfonamides, could be achieved in high ee.[4] Here, we report an enantioselective synthesis of D-DOPA with high ee employing this method.

Direct condensation of (1*S*)-(+)-*N*,*N*-diisopropyl-10-camphorsulfonamide **1** with excess *tert*-butyl glycinate in refluxing toluene for 48 h could give Schiff base **2** in 71% yield.[4a] Alternatively, Schiff base **2** could be prepared in a more practical sense and avoid the use of excess *tert*-butyl glycinate and purification problems. Condensation of *tert*-butyl glycinate with an equimolar amount of (1*S*)-(+)-*N*,*N*-diisopropyl-10-camphorsulfonamide thione **3** in refluxing toluene for 24 h gave **2** in 98% yield. Thione **3** could be prepared from the treatment of (1*S*)-(+)-*N*,*N*-diisopropyl-10-camphorsulfonamide **1** with Lawesson's reagent[5,6] in 74% yield. Treatment of Schiff base **2** with lithium diisopropylamide followed by 2 equiv of HMPA and 3,4-*O*,*O*-methylenedihydroxybenzyl bromide or 3,4-dimethoxybenzyl bromide gave a single alkylation product **4a**[7] or **4b**[7] in 89% and 87% yield, respectively. The presence of HMPA is essential for this reaction. Without HMPA, the reaction was slow and resulted in low yield of product. On the basis of our previous experience,[4] the newly formed stereogenic center was assigned as *R*. Hydrolysis of Schiff base **4** could be achieved by treatment with hydroxyamine in HOAc−NaOAc[8] to give the corresponding aminoester **5** in high yield. Removal of 3,4-*O*,*O*-dialkyl groups is not a trivial task (Table 1). Treatment of **5a** with 2 N HCl/PhOH/AcOH[1h] at 130−135 °C for 22 h gave *tert*-butyl ester hydrolyzed product where the methylenedioxy moiety remained attached. When aminoester **5a** was treated with 6 N HCl/PhOH/AcOH at 130−135 °C, D-DOPA could be obtained in 70% yield. Thus, a complete deprotection was achieved simply by increasing the concentration of HCl from 2 N to 6 N. However, this condition could not be applied on **5b**. It gave *tert*-butyl ester hydrolyzed product in which the dimethoxy groups remained attached. Treatment of **5b** with BBr_3 at 0 °C gave a mixture that could not give pure DOPA. The removal of methyl groups and hydrolysis of the *tert*-butyl ester for **5b** could be achieved by treating **5b** with 47% HBr/PhOH at 120 °C. Chiral HPLC analysis of D-DOPA from our synthesis showed that it is 96.4% ee. The loss of 3.6% ee might be due to a small amount of racemization at the last stage where a severe acidic reaction condition was required for the removal of *tert*-butyl and 3,4-*O*,*O*-methylene or 3,4-*O*,*O*-dimethyl groups.

Table 1. Deprotection and Hydrolysis of Aminoester 5

	conditions	yield, %
5a	2 N HCl, PhOH, AcOH, 22 h[c]	*a*
5a	6 N HCl, PhOH, AcOH, 36 h[c]	70
5b	6 N HCl, PhOH, AcOH, 24 h[c]	*a*
5b	BBr_3, CH_2Cl_2, 0 °C, 0.4 h	*b*
5b	47% HBr, PhOH, 120 °C, 13 h	50

[a] Only *tert*-butyl ester was hydrolyzed. [b] Contamination by inseparable salts. [c] The reaction temperature is 130−135 °C.

In summary, D-DOPA was synthesized in 96.4% ee from *tert*-butyl glycinate in four short steps and good yields employing (1*S*)-(+)-*N*,*N*-diisopropyl-10-camphorsulfonamide **1** as chiral auxiliary. In principle, L-DOPA could be synthesized in high ee and good yield according to the same operations from *tert*-butyl glycinate when employing (−)-**1** as chiral auxiliary.

Experimental Section

Unless otherwise noted, infrared spectra were run on neat liquids. The NMR spectra were run at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in $CDCl_3$ (unless otherwise noted) and were referenced to internal standard (TMS) in ppm units. Mass spectra were measured with the high-resolution electron impact technique. Column chromatography was performed on Merck 9385 Kieselgel 60 silica gel.

(1*S*)-*N*,*N*-Bis(1-methylethyl)-7,7-dimethyl-2-thioxobicyclo-[2.2.1]heptane-1-methanesulfonamide (3). A two-necked round-bottom flask was charged with camphorsulfonamide **1** (33.6 g, 106 mmol), Lawesson's reagent[6] (25.6 g, 63.9 mmol), and toluene (100 mL). The mixture was heated under reflux for 6 h. After cooling, the mixture was filtered. The filtrate was concentrated and purified by silica gel column chromatography eluted

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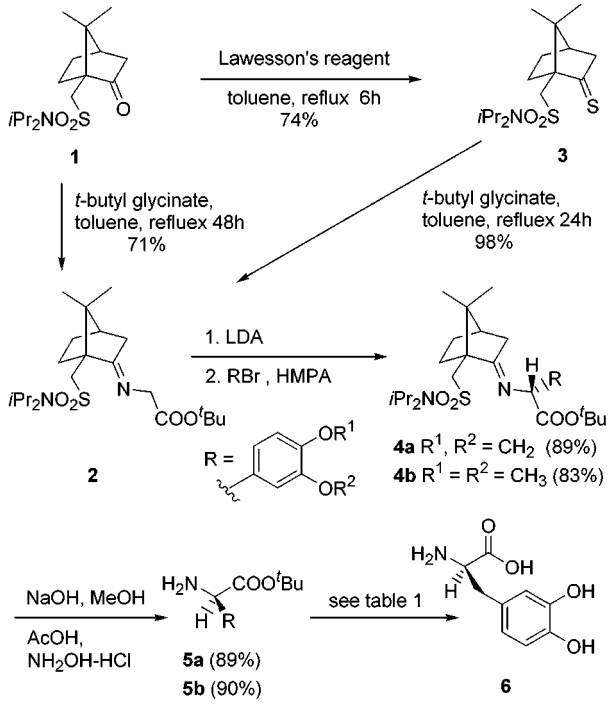
10.1021/jo015569c CCC: $20.00
Published on Web 04/18/2001

Scheme 1



with ethyl acetate−hexane (1:13) to afford thione **3** (25.9 g, 78.8 mmol, 74%) as orange crystals: mp 86.7−87.5 °C (hexane); $[\alpha]^{23}_D$ 181.5 (*c* 2.00, $CHCl_3$); IR (KBr) 1328, 1133 cm^{-1}; ^1H NMR δ 3.89 (d, J = 14.8 Hz, 1H), 3.79 (septet, J = 6.4 Hz, 2H), 2.89 (d, J = 14.8 Hz, 1H), 2.82−2.72 (m, 1H), 2.72−2.65 (m, 1H), 2.46 (d, J = 20.8 Hz, 1H), 2.20−1.95 (m, 2H), 1.50−1.30 (m, 2H), 1.33 (d, J = 6.4 Hz, 6H), 1.32 (d, J = 6.4 Hz, 6H), 1.23 (s, 3H), 0.83 (s, 3H);^{13}C NMR: δ 265.5, 69.5, 54.6, 53.6, 49.4, 48.0, 44.7, 29.4, 26.7, 22.3, 21.8, 20.2, 19.5; HRMS calcd for $C_{16}H_{29}O_2NS_2$ 331.1640, found 331.1640. Anal. Calcd for $C_{16}H_{29}O_2NS_2$: C, 57.96; H, 8.82; N, 4.22; O, 9.65; S, 19.34. Found: C, 57.91; H, 8.81; N, 4.27; O, 9.55; S, 19.45.

(1*S*)-1,1-Dimethylethyl 2-(*N*,*N*-Bis(1-methylethyl)-7,7-dimethyl-1-methanesulfonamidobicyclo[2.2.1]hept-2-ylideneamino)ethanoate (2).[4a,8] A mixture of *tert*-butyl glycinate (157 mg, 1.20 mmol) and thione **3** (331 mg, 1.00 mmol) in toluene (7 mL) was heated under reflux for 24 h. After cooling, the mixture was filtered. The filtrate was concentrated and purified by silica gel column chromatography eluted with ethyl acetate−hexane (1:5) to give Schiff base **2** (417 mg, 98%): mp 68.0−69.5 °C (hexane); $[\alpha]^{23}_D$ 23.5 (*c* 2.00, $CHCl_3$); IR (KBr) 1735, 1684 cm^{-1}; ^1H NMR δ 3.94, 3.92 (ABq, J = 16.0 Hz, 2H), 3.77 (septet, J = 6.8 Hz, 2H), 3.70 (d, J = 14.4 Hz, 1H), 2.86 (d, J = 14.4 Hz, 1H), 2.61 (ddd, J = 12.2, 12.0, 4.4 Hz, 1H), 2.27 (ddd, J = 16.8, 3.6, 3.6 Hz, 1H), 1.97−1.87 (m, 2H), 1.79 (d, J = 16.8 Hz, 1H), 1.56−1.54 (m, 1H), 1.43 (s, 9H), 1.31 (d, J = 6.8 Hz, 6H), 1.30 (d, J = 6.8 Hz, 6H), 1.30−1.20 (m, 1H), 1.16 (s, 3H), 0.83 (s, 3H); ^{13}C NMR δ 183.3, 169.2, 80.7, 55.1, 54.7, 52.8, 48.0, 47.7, 43.8, 34.9, 27.9, 27.2, 27.0, 22.5, 21.9, 20.0, 19.4; HRMS calcd for $C_{22}H_{41}O_4N_2S$ (M + 1), 429.2788, found 429.2796. Anal. Calcd for $C_{22}H_{40}O_4N_2S$: C, 61.65; H, 9.41; N, 6.54; O, 14.93; S, 7.48. Found: C, 61.60; H, 9.45; N, 6.50; O, 13.62; S, 8.84.

(2*R*,1′*S*)-1,1-Dimethylethyl 2-(*N*,*N*-Bis(1-methylethyl)-7,7-dimethyl-1-methanesulfonamidobicyclo[2.2.1]hept-2-ylideneamino)-3-(3,4-methylenedioxylphenyl)propanoate (4a).[4a] To a 50 mL flask containing tetrahydrofuran (5 mL) and diisopropylamine (0.73 mL, 5.6 mmol) was added butyllithium (2.2 M, 2.34 mL, 5.14 mmol) at −78 °C with stirring. The mixture was warmed to 0 °C for 30 min and then was cooled to −78 °C. Schiff base **2** (2.00 g, 4.67 mmol) in THF (5 mL) was dropwise added to the mixture. The resulting mixture was stiired for 30 min, and then a THF solution (5 mL) containing 3,4-methylenedioxylbenzyl bromide (1.14 g, 5.30 mmol) and HMPA (1.65 mL, 9.35 mmol) was added. The mixture was stirred for 1 h, warmed to room temperature, and quenched with the addition of water. The resulting mixture was extracted with ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified with silica gel column chromatography eluted with ethyl acetate−hexane (1:6; containing 0.5% triethylamine) to give white crystals of **4a** (2.34 g, 89%): mp 92.5−93.5 °C (hexane); $[\alpha]^{23}_D$ −2.2 (*c* 2.00, $CHCl_3$); IR (KBr) 1741, 1685, 1328 cm^{-1}; ^1H NMR δ 6.70 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.88 (s, 1H), 5.86 (s, 1H), 3.83 (dd, J = 9.6, 2.8 Hz, 1H), 3.81 (septet, J = 6.8 Hz, 2H), 3.69 (d, J = 14.4 Hz, 1H), 3.07 (dd, J = 13.2, 2.8 Hz, 1H), 2.87 (dd, J = 13.2, 9.6 Hz, 1H), 2.78 (d, J = 14.4 Hz, 1H), 2.43 (td, J = 13.2, 4.4 Hz, 1H), 2.15 (m, 1H), 1.83−1.70 (m, 2H), 1.45−1.40 (m, 1H), 1.37 (s, 9H), 1.33 (d, J = 6.8 Hz, 6H), 1.31 (d, J = 6.8 Hz, 6H), 1.06 (s, 3H), 1.03 (d, J = 17.2 Hz, 1H), 0.84−0.76 (m, 1H), 0.74 (s, 3H); ^{13}C NMR δ 181.3, 170.9, 147.0, 145.9, 132.2, 122.8, 110.4, 107.8, 100.7, 80.6, 66.6, 55.0, 53.2, 48.1, 47.6, 43.4, 38.2, 34.8, 27.9, 27.1, 26.9, 22.5, 22.1, 19.8, 19.2; HRMS calcd for $C_{30}H_{46}O_6N_2S$ 562.3077, found 562.3094. Anal. Calcd for $C_{30}H_{46}O_6N_2S$: C, 64.03; H, 8.24; N, 4.98; O, 17.06; S, 5.07. Found: C, 63.90; H, 8.32; N, 5.01; O, 16.71; S, 5.44.

(2*R*,1′*S*)-1,1-Dimethylethyl 2-(*N*,*N*-bis(1-methylethyl)-7,7-dimethyl-1-methanesulfonamido-bicyclo[2.2.1]Hept-2-ylideneamino)-3-(3,4-dimethoxylphenyl)propanoate (4b). To a 50 mL flask containing tetrahydrofuran (10 mL) and diisopropylamine (0.73 mL, 5.6 mmol) was added butyllithium (2.2 M, 2.34 mL, 5.14 mmol) at −78 °C with stirring. The mixture was warmed to 0 °C for 30 min and then was cooled to −78 °C. Schiff base **2** (2.00 g, 4.67 mmol) in THF (5 mL) was dropwise added to the mixture. The resulting mixture was stirred for 30 min, and then a THF solution (5 mL) containing 3,4-dimethoxylbenzyl bromide (1.17 g, 5.06 mmol) and HMPA (1.65 mL, 9.35 mmol) was added. The mixture was stirred for 2 h, warmed to room temperature, and quenched with the addition of water. The resulting mixture was extracted with ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified with silica gel column chromatography eluted with ethyl acetate−hexane (1:4; containing 0.5% triethylamine) to give white crystals **4b** (2.25 g, 83.3%): mp 115.0−116.0 °C (hexane); $[\alpha]^{23}_D$ 92.5 (*c* 1.00, $CHCl_3$); IR (KBr) 1728, 1690, 1326 cm^{-1}; ^1H NMR δ 6.74 (s, 2H), 6.72 (s, 1H), 3.87 (dd, J = 10.0, 3.6 Hz, 1H), 3.86 (s, 3H), 3.84 (septet, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.73 (d, J = 14.0 Hz, 1H), 3.11 (dd, J = 13.2, 3.6 Hz, 1H), 2.89 (dd, J = 13.2, 10.0 Hz, 1H), 2.74 (d, J = 14.0 Hz, 1H), 2.38 (td, J = 12.4, 3.6 Hz, 1H), 2.13 (dt, J = 16.8, 4.0 Hz, 1H), 1.80−1.60 (m, 2H), 1.40−1.30 (m, 2H), 1.38 (s, 9H), 1.34 (d, J = 7.2 Hz, 6H), 1.31 (d, J = 7.2 Hz, 6H), 1.02 (s, 3H), 0.93 (d, J = 16.8 Hz, 1H), 0.71 (s, 3H); ^{13}C NMR δ 180.7, 170.8, 148.3, 147.3, 131.1, 121.7, 113.1, 110.9, 80.3, 66.6, 55.8, 55.7, 54.7, 52.7, 47.9, 47.5, 43.1, 38.0, 34.5, 27.8, 26.9, 26.6, 22.4, 21.9, 19.5, 19.0; HRMS calcd for $C_{31}H_{50}O_6N_2S$ 578.3390, found 578.3342.

(*R*)-1,1-Dimethylethyl 2-amino-3-(3,4-methylenedioxylphenyl)propanoate (5a).[8] A 25 mL flask was charged with **4a** (1.00 g, 1.79 mmol), sodium hydroxide (86 mg, 2.1 mmol), acetic acid (0.123 mL, 2.14 mmol), $NH_2OH{\cdot}HCl$ (149 mg, 2.14 mmol), methanol (10 mL), and chloroform (6 mL). The mixture was stirred at room temperature for 24 h and then was concentrated, neutralized with 2 N HCl (5 mL), and extracted with ether three times. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to recover chiral auxiliary (510 mg, 91%). Combined aqueous layers were neutralized with NaOH to pH 10−11 and then extracted with ether. Combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give aminoester **5a** (420 mg, 89%) as a pale yellow liquid: $[\alpha]^{23}_D$ −8.2 (*c* 2.00, $CHCl_3$); IR (neat) 3384, 3314, 1729, 1611 cm^{-1}; ^1H NMR δ 6.72 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 1.6 Hz, 1H), 6.63 (dd, J = 8.0, 1.6 Hz, 1H), 5.91 (s, 2H), 3.52 (dd, J = 5.2, 8.0 Hz, 1H), 2.94 (dd, J = 13.6, 5.2 Hz, 1H), 2.73 (dd, J = 13.6, 8.0 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR δ 174.2, 147.6, 146.3, 131.1, 122.3, 109.6, 108.1, 100.8, 81.1, 56.3, 40.7, 28.0; HRMS calcd for $C_{14}H_{19}O_4N$ 265.1314, found 265.1324.

(*R*)-1,1-Dimethylethyl 2-amino-3-(3,4-dimethoxylphenyl)propanoate (5b). A 25 mL flask was charged with **4b** (130 mg, 0.225 mmol), sodium hydroxide (10.8 mg, 0.270 mmol), acetic acid (0.015 mL, 0.27 mmol), $NH_2OH{\cdot}HCl$ (18.8 mg, 0.270 mmol), methanol (3 mL), and chloroform (2 mL). The mixture was

stirred at room temperature for 24 h and then was concentrated, neutralized with 2 N HCl (2 mL), and extracted with ether three times. The organic layer was washed with water, dried over anhydrous sodium sulfate, fitered, and concentrated to recover chiral auxiliary (66.6 mg, 94%). Combined aqueous layers were neutralized with NaOH to pH 10−11 and then extracted with ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give aminoester **5b** (57 mg, 90%) as a pale yellow liquid: $[\alpha]^{23}_D$ 5.5 (*c* 2.02, $CHCl_3$); IR (neat) 3374, 3280, 1731, 1591 cm^{-1}; ^1H NMR δ 6.70−6.68 (m, 3H), 3.84 (s, 6H), 3.57 (dd, J = 7.6 Hz, 5.6 Hz, 1H), 2.98 (dd, J = 13.6 Hz, 5.6 Hz, 1H), 2.77 (dd, J = 13.6 Hz, 7.6 Hz, 1H), 1.63 (b, 2H), 1.42 (s, 9H); ^{13}C NMR δ 174.2, 148.7, 147.7, 129.8, 121.3, 112.3, 111.0, 80.9, 56.1, 55.71, 55.66, 40.5, 27.9; HRMS calcd for $C_{15}H_{23}O_4N$ 281.1627, found 281.1627.

(*R*)-2-Amino-(3,4-dihydroxyphenyl)propanoic Acid (6).[1h] To a 50 mL tanned flask were added **5a** (200 mg, 0.754 mmol), phenol (213 mg, 2.26 mmol), glacial acetic acid (0.130 mL, 2.26 mmol), and 6 N HCl (10 mL). The mixture was heated under reflux for 36 h and then concentrated to give a light pink powder. The residue was dissolved with butyl acetate and extracted with water. The aqueous layer was adjusted to pH 5 with 28% ammonium water and a trace amount of sodium bisulfite and then cooled to 5 °C to give **6** (104 mg, 70%) as white crystals. Chiral HPLC analysis of this sample on a CROWNPAK CR-(+) column eluted with aqueous $HClO_4$ (pH 2.0) at a flow rate of 0.8 mL/min showed that it is 96.4% ee: mp 274.5−276 °C dec (lit.[9] mp 272−275 °C); $[\alpha]^{23}_D$ 12.5 (*c* 1.00, 1 N HCl) [lit.[10] *R*-form, $[\alpha]^{11}_D$ 13.0 (*c* 5.27, 1 N HCl); *S*-form, $[\alpha]^{13}_D$ −13.1 (*c* 5.12, 1 N HCl); lit.[1c] $[\alpha]^{25}_D$ −12.3 (*c* 1.00, 1 N HCl); lit.[1b] $[\alpha]^{20}_D$ −11.0 (*c* 3.7, 4% HCl)]; IR (KBr) 3500−2500, 1654 cm^{-1}; ^1H NMR (D_2O, DCl) δ 6.99 (d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 6.83 (d, J = 8.0 Hz, 1H), 4.43 (dd, J = 7.2 Hz, 5.6 Hz, 1H), 3.32 (dd, J = 14.4 Hz, 5.6 Hz, 1H), 3.20 (dd, J = 14.4 Hz, 7.2 Hz, 1H); ^{13}C NMR (D_2O, DCl) δ 174.1, 147.1, 146.4, 129.1, 124.9, 120.0, 119.6, 57.1, 37.8; HRMS calcd for $C_9H_{11}O_4N$ 197.0688, found 197.0689.

Alternatively, **6** could be prepared from **5b**: To a 15 mL tanned flask wree added **5b** (20.0 mg, 0.0712 mmol), phenol (20.1 mg, 0.214 mmol), and 47% HBr (6 mL). The mixture was heated under reflux for 13 h and then worked up as mentioned previously to give **6** (7.0 mg, 50%) as white crystals.

Acknowledgment. We thank National Science Council, Republic of China, for the support of this work.

JO015569C

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