

An asymmetric dihydroxylation route to (R)-(-)-octopamine, (R)-(-)-tembamide and (R)-(-)-aegeline

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Dedicated to Dr. A. V. Rama Rao on the occasion of his 70th birthday

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Abstract

A simple and efficient asymmetric synthesis of (*R*)-(-)-octopamine **1**, (*R*)-(-)-tembamide **2** and (*R*)-(-)-aegeline **3** is described for the first time employing the Sharpless asymmetric dihydroxylation (AD) as the source of chirality. © 2006 Elsevier Science Ltd. All rights reserved.

Keywords: Asymmetric synthesis, dihydroxylation, octopamine, tembamide, aegeline

Introduction

(*R*)-(-)-Octopamine **1** is a potent chiral drug possessing β -adrenergic activity.¹ (*R*)-(-)-Tembamide **2** and (*R*)-(-)-aegeline **3** are used in traditional Indian medicines and have been shown to have good hypoglycemic activity.² Recent studies have revealed that the two enantiomers of a chiral drug usually display different biological activities³ and in most of the aryl ethanolamine drugs, the biological activity resides mainly in the (*R*)-enantiomer.⁴ The growing need and interest in the asymmetric synthesis of these biologically useful molecules prompted us to take up their synthesis.

Various methods for the synthesis of optically active (*R*)-(-)-octopamine **1**,⁵ (*R*)-(-)-tembamide **2** and (*R*)-(-)-aegeline **3**⁶ have been documented. These include either tedious chemical and biological methods⁷ or require the costly reagents and multistep processes with overall low chemical yields.⁸ Recently the enzymatic reduction of α -bromo ketones^{9a} and α -azido ketones^{9b} has also been reported for their synthesis. Surprisingly there has been no report in the literature about the asymmetric synthesis of these compounds employing the Sharpless asymmetric dihydroxylation (AD) procedure. As part of our research program aimed at developing enantioselective syntheses of naturally occurring lactones,^{10a-c} and amino alcohols,^{10d-k} and the AD was envisaged as a powerful tool to chiral dihydroxy compounds offering

considerable opportunities for synthetic manipulations. Herein we report a new and highly enantioselective synthesis of (*R*)-(-)-octopamine **1**, (*R*)-(-)-tembamide **2** and (*R*)-(-)-aegeline **3** employing the AD reaction as the source of chirality.

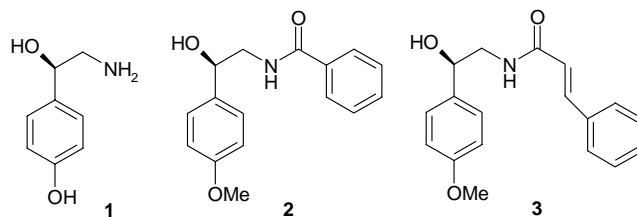
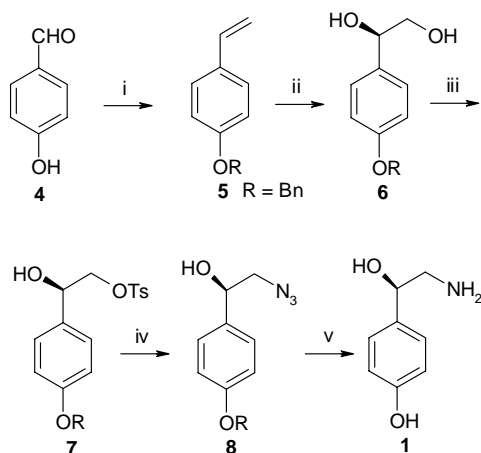


Figure 1. Structures of (*R*)-(-)-octopamine (**1**), (*R*)-(-)-tembamide (**2**), and (*R*)-(-)-aegeline (**3**).

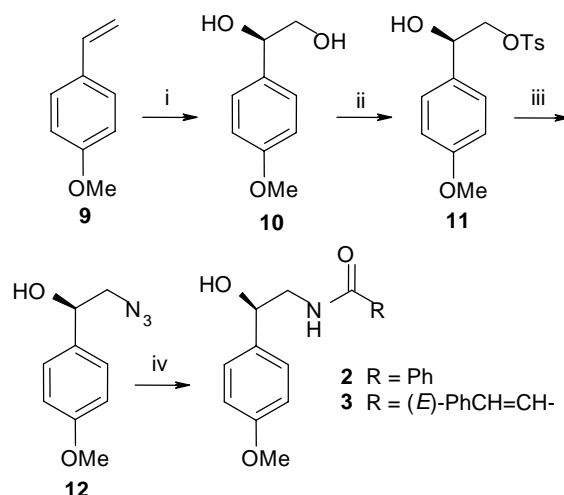
Results and Discussion

Scheme 1, depicts the synthetic route to (*R*)-(-)-octopamine **1** from the commercially available 4-hydroxybenzaldehyde (**4**). The hydroxyl protection of **4** as benzyl ether and subsequent Wittig olefination furnished styrene **5** in excellent yield.¹⁰ⁱ Asymmetric dihydroxylation¹¹ of **5** using osmium tetroxide and $K_3Fe(CN)_6$ as co-oxidant in the presence of 1,4-bis(dihydroquinidin-9-*O*-yl)phthalazine [(DHQD)₂PHAL] gave the diol **6** in 94% yield. Selective conversion of the primary hydroxyl group of **6** into a tosylate was carried out using tosyl chloride in pyridine at $-15^\circ C$ to give **7** in 76% yield. The nucleophilic displacement of tosylate **7** with NaN_3 afforded the azido alcohol **8**, having $[\alpha]_D^{20} -68.4$ (c 0.5, $CHCl_3$)¹² {lit.⁵ $[\alpha]_D^{20} -72.2$ (c 1.1, $CHCl_3$)}. Subsequent reduction of azide and debenzoylation of **8** by catalytic hydrogenation on 10% $Pd(OH)_2/C$ at 60 psi furnished (*R*)-(-)-octopamine having $[\alpha]_D^{20} -35.7$ (c 0.54, H_2O) {lit.⁵ $[\alpha]_D^{20} -37.6$ (c 0.56, H_2O)}.



Scheme 1. (i) (a) $BnBr$, K_2CO_3 , DMF, TBAI (cat), rt, 24 h, 99%, (b) $Ph_3P=CH_2$, THF, rt, 24 h, 78%; (ii) (DHQD)₂-PHAL, $K_3Fe(CN)_6$, K_2CO_3 , OsO_4 , *t*-BuOH/ H_2O (1:1), $0^\circ C$, 18 h, 94%; (iii) *p*-TsCl, pyridine, $-15^\circ C$, 8 h, 76%; (iv) NaN_3 , DMF, $80^\circ C$, 4 h, 88%; (v) $Pd(OH)_2/C$, H_2 60 psi, MeOH, rt, 18 h, 86%.

The synthetic route to (*R*)-(-)-tembamide **2** and (*R*)-(-)-aegeline **3** is shown in Scheme 2. The synthesis starts from 4-methoxystyrene (**9**), a commercially available starting material. Asymmetric dihydroxylation of **9** with (DHQD)₂PHAL ligand gave the diol **10** in 93% yield and 97.5% ee.¹³ Selective conversion of primary hydroxyl into tosylate **11** and nucleophilic displacement with NaN₃ gave the azido alcohol **12**. Reduction of azide **12** by hydrogenation over 10% palladium on charcoal in methanol furnished the amino alcohol which on subsequent acylation with benzoyl chloride in presence of 50% aq. NaOH gave (*R*)-(-)-tembamide **2** in 92% yield having $[\alpha]_D^{20} -60.45$ (c 0.52, CHCl₃) {lit.^{9b} $[\alpha]_D^{25} -59.6$ (c 0.52, CHCl₃)}. In a similar manner, the reaction of amino alcohol with cinnamoyl chloride provided (*R*)-(-)-aegeline **3** in 90% yield having $[\alpha]_D^{20} -35.21$ (c 0.4, CHCl₃) {lit.^{9b} $[\alpha]_D^{25} -36.1$ (c = 0.45, CHCl₃)}. The spectroscopic data of **2** and **3** are in full agreement with the literature data.^{9b}



Scheme 2. (i) (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, OsO₄, *t*-BuOH/H₂O (1:1), 0°C, 18 h, 93%; (ii) *p*-TsCl, pyridine, -15°C, 8 h, 80%; (iii) NaN₃, DMF, 80°C, 4 h, 93%; (iv) (a) Pd/C, H₂, (b) 50% aq. NaOH, CH₂Cl₂, RCOCl, toluene, 10°C, 30 min, 90-92%.

Conclusions

In summary, a practical and highly enantioselective synthesis of (-)-octopamine, (-)-tembamide and (-)-aegeline has been achieved for the first time employing the Sharpless asymmetric dihydroxylation as the source of chirality. Thus, the results described herein constitute a short and efficient route to (-)-octopamine, (-)-tembamide and (-)-aegeline. The synthetic approach can be further extended to the asymmetric synthesis of (*S*)-enantiomers *via* α -dihydroxylation of **5** and **9** and following the reaction sequence, as shown in Schemes 1 and 2.

Experimental Section

General Procedures. Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60-80°C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO P-1020 microprocessor based polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on Bruker AC-200 spectrometer. Mass spectra were obtained with a TSQ 70, Finnigen MAT mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer.

4-Benzyloxystyrene **5**

This was prepared following the literature procedure.¹⁰ⁱ

(R)-1-(4-Benzyloxyphenyl)-1,2-ethanediol (6). To a solution of K₃Fe(CN)₆ (14.09 g, 42.80 mmol), K₂CO₃ (5.91 g, 42.80 mmol), (DHQD)₂PHAL (111 mg, 0.143 mmol, 1 mol%) in *t*-BuOH:H₂O (1:1, 150 mL) was added OsO₄ (0.715 mL, 0.1 M soln in toluene, 0.5 mol%) at 0°C. After stirring for 5 min, 4-benzyloxystyrene **5** (3 g, 14.27 mmol) was added in one portion and the reaction mixture stirred for 18 h at 0°C. Solid Na₂SO₃ (3g) was added and stirred for 1 h. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic layers were washed (brine), dried (Na₂SO₄) and concentrated. The residue was purified by silica gel column chromatography using petrol ether:EtOAc (7:3) as eluent to give **6** (3.276 g, 94%) as colorless solid; mp 143–144°C; [α]_D²⁰ -39.8 (*c* 0.5, CHCl₃); IR (CHCl₃): ν_{max} 3311, 2922, 1613, 1513, 1456, 1378, 1248, 501 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.87 (s, 2H), 3.6–3.75 (m, 2H), 4.76–4.8 (m, 1H), 5.07 (s, 2H), 6.96 (d, *J* = 8 Hz, 2H), 7.3–7.4 (m, 7H); ¹³C NMR (50 MHz, CDCl₃): δ 67.63, 69.28, 73.47, 113.98 (2C), 126.84 (4C), 127.28, 127.91 (2C), 138.64, 136.14, 157.24; EIMS (*m/z*, %): 243 [M⁺-1] (13.2), 226 (12.5), 213 (9.3), 183, (40.3), 91 (100), 65 (13.8); Anal. Calcd for C₁₅H₁₆O₃ (244.29): C, 73.75; H, 6.60. Found: C, 73.82; H, 6.56.

(R)-2-(*O*-Tosyl)-1-(4-benzyloxyphenyl)-1,2-ethanediol (7). To a solution of diol **6** (1.45 g, 5.94 mmol) in CH₂Cl₂ (50 mL) was added pyridine (0.72 mL, 8.91 mmol) and stirred for 15 min at room temperature. The reaction mixture was cooled to -15°C and *p*-TsCl (1.133 g, 5.94 mmol) was added in three portions at time interval of 30 min. The reaction mixture was stirred for 8 h at -15°C and allowed to warm to room temperature. An aqueous solution of CuSO₄·5H₂O (10%, 20 mL) and EtOAc (100 mL) were added and stirred for 30 min. The organic layer was separated and the aqueous layer extracted with EtOAc (2 × 50 mL). The combined organic layers were washed (brine), dried (Na₂SO₄) and concentrated. Silica gel column chromatography of the crude product using petrol ether:EtOAc (17:3) as eluent gave **7** (1.8 g, 76%) as colorless solid; mp 84–85°C; [α]_D²⁰ -34.7 (*c* 0.5, CHCl₃); IR (CHCl₃): ν_{max} 3550, 2925, 1613, 1514, 1463, 1378, 1173, 815, 555 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 2.08 (s, 1H), 2.44 (s, 3H), 3.96–4.11 (m, 2H), 4.89–4.95 (dd, *J* = 4, 8 Hz, 1H), 5.05 (s, 2H), 6.91 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8 Hz, 2H), 7.3–7.5 (m, 7H), 7.75 (d, *J* = 8 Hz, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 21.28, 69.65, 70.93, 73.99,

114.64 (2C), 127.17 (2C), 127.62 (3C), 128.31 (2C), 129.64 (4C), 130.89, 132.39, 136.58, 144.67, 158.49; EIMS (m/z , %): 398 [M^+] (6.2), 380 (22.8), 340 (18.4), 229 (60.6), 197 (86), 91 (100), 77 (28.7), 65 (61.9); Anal. Calcd for $C_{22}H_{22}O_5S$ (398.48): C, 66.31; H, 5.56; S, 8.05. Found: C, 66.12; H, 5.65; S, 8.12.

(R)-2-Azido-1-(4-benzyloxyphenyl)ethanol (8). To a solution of **7** (618 mg, 1.55 mmol) in dry DMF (10 mL) was added NaN_3 (605 mg, 9.3 mmol) and stirred at 80°C for 4 h. The reaction mixture was cooled to room temperature and diluted with water and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were washed (water and then brine) dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petrol ether:EtOAc (17:3) as eluent to give azido alcohol **8** (368 mg, 88%) as a colorless solid; mp 68–69°C [lit.⁵ 69–70°C]; $[\alpha]_D^{20}$ –68.4 (c 0.5, $CHCl_3$) {lit.⁵ $[\alpha]_D^{20}$ –72.2 (c 1.1, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3417, 2926, 2106, 1611, 1512, 1240, 1217, 1174, 769, 668, 475 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$): δ 1.26 (s, 1H), 3.3–3.49 (m, 2H), 4.79–4.85 (dd, $J = 4, 8$ Hz, 1H), 5.06 (s, 2H), 6.95 (d, $J = 8$ Hz, 2H), 7.27 (d, $J = 8$ Hz, 2H), 7.36–7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 57.89, 69.94, 72.81, 114.90 (2C), 127.17 (2C), 127.50 (2C), 127.91, 128.50 (2C), 133.09, 136.77, 158.68; EIMS (m/z , %): 269 [M^+] (11.16), 238 (9.3), 213 (100), 185 (15.8), 170 (40.8), 91 (67.7), 77 (13.8), 65 (20.2).

(R)-(-)-Octopamine (1). To a solution of azido alcohol **8** (302 mg, 1.12 mmol) in EtOH (10 mL) was added 10% $Pd(OH)_2$ (170 mg) on charcoal at room temperature and stirred under a hydrogen atmosphere (60 psi) for 18 h. The catalyst was filtered on a pad of celite and the filtrate concentrated and purified by silica gel column chromatography using n -BuOH/AcOH/ H_2O (3:1:1) as eluent to give (*R*)-(-)-octopamine **1** as colorless solid; mp 246–247°C [lit.⁵ 245–246°C]; $[\alpha]_D^{20}$ –35.7 (c 0.54, H_2O) {lit.⁵ $[\alpha]_D^{20}$ –37.6 (c 0.56, H_2O)}. The spectroscopic data is in full agreement with the literature data.⁵

(R)-1-(4-Methoxyphenyl)-1,2-ethanediol (10). To a solution of $K_3Fe(CN)_6$ (22.1 g, 67.07 mmol), K_2CO_3 (9.26 g, 67.07 mmol), (DHQD)₂-PHAL (174 mg, 0.224 mmol, 1 mol%) in t -BuOH: H_2O (1:1, 200 mL) was added OsO_4 (1.12 mL, 0.1 M soln in toluene, 0.5 mol%) at 0°C. After stirring for 5 min, 4-methoxystyrene **9** (3 g, 22.36 mmol) was added in one portion and the reaction mixture stirred for 18 h at 0°C. Solid Na_2SO_3 (3g) was added and stirred for 1 h. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petrol ether:EtOAc (7:3) as eluent to give **10** (3.5 g, 93%) as colorless solid; mp 103–105°C; $[\alpha]_D^{20}$ –57.7 (c 1, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3279, 2958, 1611, 1513, 1246 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$): δ 2.65 (s, 2H), 3.6–3.7 (m, 2H), 3.81 (s, 3H), 4.73–4.79 (dd, $J = 4, 8$ Hz, 1H), 6.92 (d, $J = 8$ Hz, 2H), 7.26 (d, $J = 8$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3 + DMSO-d_6$): δ 54.03, 67.04, 72.92, 112.4 (2C), 126.29 (2C), 133.24, 157.68; EIMS (m/z , %): 168 [M^+] (3), 150 (1.5), 137 (69.3), 109 (42.3), 94 (71.53), 77 (100), 65 (38); Anal. Calcd for $C_9H_{12}O_3$ (168.19): C, 64.27; H, 7.19. Found: C, 64.45; H, 6.91.

(R)-2-(O-Tosyl)-1-(4-methoxyphenyl)-1,2-ethane diol (11). To a solution of diol **10** (1 g, 5.95 mmol) in CH₂Cl₂ (50 mL) was added pyridine (0.72 mL, 8.91 mmol) and stirred for 15 min at room temperature. The reaction mixture was cooled to -15°C and *p*-TsCl (1.13 g, 5.95 mmol) was added in three portions at time interval of 30 min. The reaction mixture was stirred for 8 h at -15°C and allowed to warm to room temperature. An aqueous solution of CuSO₄·5H₂O (10%, 20 mL) and EtOAc (100 mL) were added and stirred for 30 min. The organic layer was separated and the aqueous layer extracted with EtOAc (2 × 50 mL). The combined organic layers were washed (brine), dried (Na₂SO₄) and concentrated. Silica gel column chromatography of the crude product using petrol ether:EtOAc (17:3) as eluent gave **11** (1.53 g, 80%) as colorless solid; mp 78–80°C; [α]_D²⁰ -53.0 (*c* 1, CHCl₃); IR (CHCl₃): ν_{max} 3518, 2938, 1612, 1514, 1359, 1250, 1176, 971, 832, 666 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 2.2 (s, 1H), 2.45 (s, 3H), 3.81 (s, 3H), 4.06–4.2 (m, 2H), 4.89 (dd, *J* = 4, 8 Hz, 1H), 6.88 (d, *J* = 8 Hz, 2H), 7.25 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H), 7.75 (d, *J* = 8 Hz, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 21.35, 55.02, 71.01, 74.06, 113.76 (2C), 127.32 (2C), 127.69 (2C), 129.71 (2C), 130.56, 132.36, 144.82, 159.34; EIMS (*m/z*, %): 322 [M⁺] (5.2), 304 (42.8), 264 (8.4), 149 (63.6), 121 (100), 91 (98.7), 77 (48.7), 65 (66.9); Anal. Calcd for C₁₆H₁₈O₅S (322.38): C, 59.61; H, 5.62; S, 9.94. Found: C, 59.82; H, 5.52; S, 9.90.

(R)-2-Azido-1-(4-methoxyphenyl)ethanol (12). To a solution of **11** (500 mg, 1.55 mmol) in dry DMF (10 mL) was added NaN₃ (605 mg, 9.3 mmol) and stirred at 80°C for 4 h. The reaction mixture was cooled to room temperature and diluted with water and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were washed (water and then brine) dried (Na₂SO₄) and concentrated. The residue was purified by silica gel column chromatography using petrol ether:EtOAc (17:3) as eluent to give azido alcohol **12** (278 mg, 93%) as a colorless oil; [α]_D²⁰ -77.11 (*c* 1, CHCl₃) {lit.⁵ [α]_D²⁰ -117.4 (*c* 1.30, CHCl₃), lit.^{9b} [α]_D²⁰ -40.1 (*c* 1.02, CHCl₃)}; IR (CHCl₃): ν_{max} 3441, 2934, 2105, 1612, 1513, 1250, 832, 493 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 2.18 (s, 1H), 3.35–3.5 (m, 2H), 3.82 (s, 3H), 4.8–4.87 (dd, *J* = 2, 6 Hz, 1H), 6.94 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 55.17, 57.85, 72.81, 113.94 (2C), 127.1 (2C), 132.8, 159.45; EIMS (*m/z*, %): 193 [M⁺] (7.16), 162 (1.3), 137 (100), 109 (45.8), 94 (43.8), 77 (47.7), 66 (23.8); Anal. Calcd for C₉H₁₁O₂N₃ (193.2): C, 55.95; H, 5.74; N, 21.75. Found: C, 56.1; H, 5.79; N, 21.59.

(R)-(-)-Tembamide (2). To a solution of azido alcohol **12** (500 mg, 2.58 mmol) in MeOH (5 mL) was added 10% Pd/C (20 mg) and the reaction mixture stirred at room temperature under hydrogen atmosphere (filled in a balloon) for 8 h. The catalyst was removed by filtration and the filtrate concentrated to give the amino alcohol. The residue was dissolved in CH₂Cl₂ (4 mL) and a solution of 50% aq NaOH (713 mg) in water (5 mL) was added at 0°C and stirred for 15 min. To the reaction mixture was added a solution of benzoyl chloride (0.37 mL, 3.23 mmol) in dry toluene (2 mL) dropwise and stirred for further 1 h. The solvent was removed in vacuo and the residue was diluted with cold water and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed (brine) dried (Na₂SO₄) and concentrated. The residue was purified by silica gel column chromatography using petrol ether:EtOAc (1:1) to give **2** (645 mg, 92%) as

a colorless solid. It was further recrystallized from petrol ether:EtOAc. Mp 154–156°C [lit.^{9b} 154–155°C]; $[\alpha]_{\text{D}}^{20}$ –60.45 (*c* 0.52, CHCl₃) {lit.^{9b} $[\alpha]_{\text{D}}^{25}$ –59.6 (*c* 0.52, CHCl₃)}. The spectroscopic data is in full agreement with literature data.^{9b}

(R)-(-)-Aegeline (3). Acylation of the intermediate amino alcohol with (*E*)-cinnamoyl chloride under similar condition as described above gave **3** as white solid in 90% yield. Mp 196–198°C [lit.^{9b} 195–196°C]; $[\alpha]_{\text{D}}^{20}$ –35.21 (*c* 0.4, CHCl₃) {lit.^{9b} $[\alpha]_{\text{D}}^{20}$ –36.1 (*c* 0.45, CHCl₃)}. The spectroscopic data is in full agreement with literature data.^{9b}

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References and Notes

1. (a) Kappe, T.; Armstrong, M. D. *J. Med. Chem.* **1964**, *7*, 569. (b) Albonico, S. M.; Deulofeu, V. *J. Chem. Soc. (C)* **1967**, 1327.
2. Shoeb, A.; Kapil, R. S.; Popli, S. P. *Phytochemistry* **1973**, *12*, 2071.
3. (a) Millership, J. S.; Fitzpatrick, A. *Chirality* **1983**, *5*, 573 and references therein. (b) Brittain, R. T.; Farmer, J. B.; Marshall, R. J. *Br. J. Pharmacol.* **1973**, *48*, 144. (c) Chapman, I. D.; Buchneit, K. H.; Manley, P.; Morley, J. *Trends J. Pharmacol Sci.* **1992**, *13*, 231. (d) Stinson, S. C. *Chem. Eng. News* **2000**, *78*, 59.
4. (a) Ruffolo, R. R., Jr. *Tetrahedron* **1991**, *47*, 9953. (b) Lunts, L. H. C.; Main, B. G.; Tucker, H. In *Medicinal Chemistry, The Role of Organic Chemistry in Drug Research*; Roberts, S. M.; Price, B. J., Ed.; Academic Press: New York, 1985; pp 49-92.
5. Cho, B. T.; Kong, S. K.; Shin, S. H. *Tetrahedron: Asymmetry* **2002**, *13*, 1209.
6. Brown, R. F. C.; Jackson, W. R.; McCarthy, T. D. *Tetrahedron: Asymmetry* **1993**, *4*, 205.
7. (a) Ikezaki, M.; Umino, N.; Gaino, M.; Aoe, K.; Iwakuma, T.; Ohishi, T. *Yakugaku. Zasshi* **1986**, *106*, 80. (b) Noguchi, K.; Irie, K. Japan Patent 79 70, 233, 1979, *Chem. Abstr.* **1979**, *91* 630. (c) Kuck, A. M.; Albonico, S. M.; Deulofeu, V. *J. Chem. Soc., Section C* **1967**, 1327. (d) Gu, J.-X.; Zu-Yi, L.; Gou-Qiang, L. *Tetrahedron* **1993**, *49*, 5805.
8. Senuma, M.; Yamato, E.; Koumato, T.; Gaino, M.; Kawaguchi, T.; Iwakuma, T. *Chem. Expt.* **1989**, *4*, 245.
9. (a) Goswami, J.; Bezbaruah, R. L.; Goswami, A.; Borthakur, N. *Tetrahedron: Asymmetry* **2001**, *12*, 3343. (b) Yadav, J. S.; Reddy, T.; Nanda, S.; Rao, A. B. *Tetrahedron: Asymmetry* **2001**, *12*, 3381.
10. (a) Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445. (b) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4349. (c) Fernandes, R. A.; Kumar, P.

- Eur. J. Org. Chem.* **2002**, 2921. (d) Fernandes, R. A.; Kumar P. *Tetrahedron: Asymmetry* **1999**, *10*, 4797. (e) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2000**, 3447. (f) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2000**, *41*, 10309. (g) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425. (h) Fernandes, R. A.; Kumar, P. *Synthesis* **2003**, 129. (i) Fernandes, R. A.; Bodas, M. S.; Kumar, P. *Tetrahedron* **2002**, *58*, 1223. (j) Naidu, S.V.; Kumar, P.; *Tetrahedron Lett.* **2003**, *44*, 1035. (k) Kandula, Subba Rao.;V.; Kumar, P.; *Tetrahedron Lett.* **2003**, *44*, 1957.
11. (a) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 448. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (c) Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeeng K-S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J.Org. Chem.* **1993**, *58*, 844.
12. The enantiomeric purity of the azido alcohol **8** is estimated to be 94% by comparison of optical rotation with the value of $[\alpha]_D^{20} -72.2$ (*c* 1.1, CHCl₃) of 99%ee.
13. Weissman, S. A.; Rossen, K.; Reider, P. J. *Org. Lett.* **2001**, *3*, 2513.