

NEW ASYMMETRIC SYNTHESIS OF ENANTIOMERIC PAIRS OF THE 2-SUBSTITUTED PYRROLIDINES BBUGAINE AND IRNIINE#

Hiroki Takahata,* Kozue Ihara, Minoru Kubota, and Takefumi Momose*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

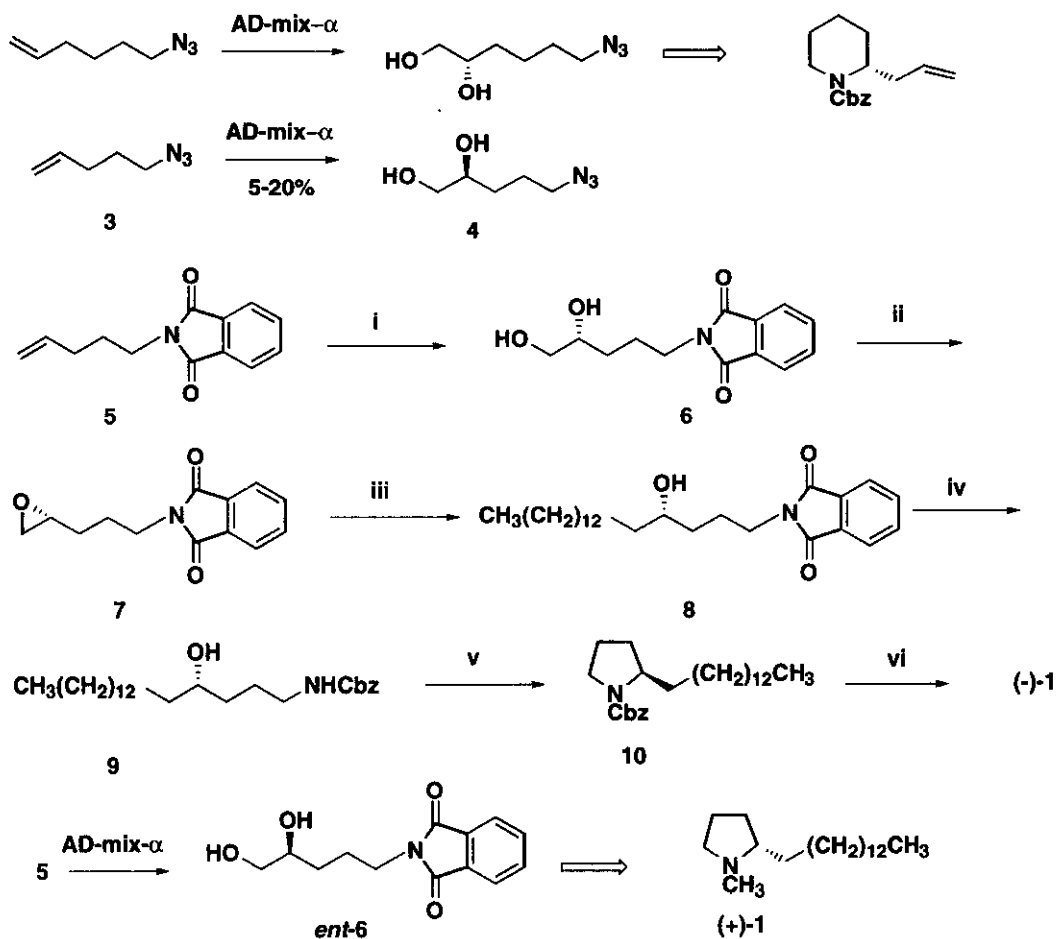
Abstract- A new asymmetric route to 2-substituted pyrrolidines starting with the Sharpless asymmetric dihydroxylation (AD) of 4-pentenylphthalimide (**5**) followed by aminocyclization of the resultant amino alcohol is presented. The application to the asymmetric synthesis has been examined for two 2-substituted pyrrolidine alkaloids, bbugaine (**1**) and irniine (**2**).

The widespread occurrence and intriguing biological activity of pyrrolidine alkaloids make them attractive to synthetic chemists in conjunction with the short supply of many of them from natural sources. Recently, two optically active 2-alkylpyrrolidine alkaloids, (-)-bbugaine (**1**)¹ and (-)-irniine (**2**),² have been isolated from the tubers of *Arisaema vulgare*, a toxic Araceae responsible for human and animal poisonings in Morocco. These alkaloids display antibacterial activity against Gram-positive bacteria and antimycotic activity against some *Candida* and *Cryptococcus* strains. Very recently, both the determination of their absolute configuration and the first asymmetric synthesis have been accomplished on the basis of the Meyers's protocol.³ Herein, we report an alternative synthesis of both enantiomers of **1** and **2**, the strategy constituting a general entry to chiral 2-substituted pyrrolidines.

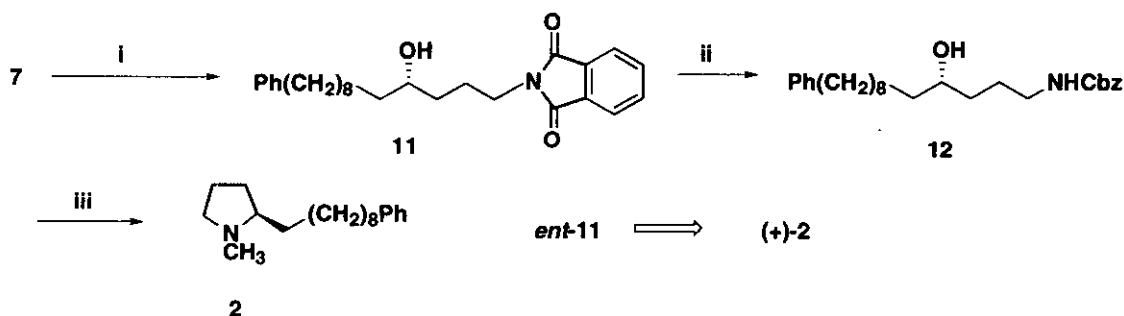


Recent investigation in this laboratory has revealed that the Sharpless asymmetric dihydroxylation (AD)⁴ of 5-hexenyl azide provides a new asymmetric route to 2-substituted piperidines.⁵ According to the method, our synthesis of **1** and **2** was started with the AD reaction of 4-pentenyl azide (**3**). Unfortunately, the AD reaction using (DHQD)₂-PYR⁶ as a ligand afforded the desired diol (**4**) in less than 20 % yield in spite of a long reaction period (4 days). Although the reason remains unknown, it was found the AD reaction using **3** scarcely proceeded with any ligands.^{7,10} Next, we examined the AD reaction using *N*-pentenylphthalimide (**5**) instead of **3**, and obtained the diol (**6**) in 93% yield. The diol (**6**) was converted by the Sharpless' one pot procedure¹¹ into the epoxide (**7**) in 83 % yield. With the epoxide (**7**) in hand, we

carried out the synthesis of (-)-bbugaine (**1**). The regioselective cleavage of the epoxide ring in **7** with tridecanylmagnesium bromide in combination with cuprous iodide was performed to yield the alcohol (**8**) in 75% yield. The treatment of **8** with hydrazine gave an amine, which, without purification, was protected at the terminal nitrogen with benzyloxycarbonyl chloride in the presence of NaOH to provide the carbamate (**9**) in 79% yield. After mesylation of **9**, the intramolecular amino cyclization of the resulting mesylate by action of sodium hydride afforded the pyrrolidine (**10**) in 84% yield. Finally, the reduction of **10** with lithium aluminum hydride (LiAlH_4) yielded the desired **1** $\{[\alpha]^{29}_{\text{D}} -42.5^\circ (c\ 1.65, \text{MeOH}), \text{lit.},^3 [\alpha]^{20}_{\text{D}} -45^\circ (c\ 1.2, \text{MeOH})\}$ in 85% yield. Spectral and physical data were identical with those reported.³ According to the procedure similar to that described above, the synthesis of the enantiomer (+)-**1** was achieved in 25% total yield from the enantiomer of **6**, obtained by the AD of **5** using (DHQD)₂PYR as a ligand.



Having obtained these results, the synthesis of both enantiomers of iriniine (**2**) was carried out starting from the epoxides (**7**). We began with cleavage of the epoxy ring in **7**. The treatment of **7** with 8-phenyloctylmagnesium bromide¹² in the presence of cuprous iodide gave the alcohol (**11**) in 56% yield. In manner analogous to that for **1**, **11** was transformed in five steps into (-)-iriniine (**2**) in 54 % overall yield. Spectral and physical data were consistent with those reported.³ Additionally, the synthesis of (+)-**2** was performed in 65 % overall yield *via* a sequence starting from *ent*-**7**.



i) $\text{Ph(CH}_2)_8\text{MgBr/CuI}$; ii) 1) NH_2NH_2 ; 2) CbzCl/NaOH ; iii) 1) $\text{MsCl/pyridine/DMAP}$; 2) NaH ; 3) LiAlH_4

In summary, a simple procedure has been devised for the asymmetric synthesis of chiral 2-substituted pyrrolidines. The utility of this methodology has been demonstrated by its application to the expeditious synthesis of both enantiomers of **1** and **2**. Additionally, a practical and efficient method for the assembly of pyrrolidines with a functionalized appendage at C2 should be provided by application of the reaction of the epoxide (**7**) with several cuprates. Further studies are in progress.

EXPERIMENTAL

Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Infrared spectra (IR) were measured with a Perkin-Elmer 1600 series FTIR spectrophotometer. Proton magnetic resonance (^1H NMR) spectra were recorded at 500 MHz on a Varian-Unity-500 instrument with CHCl_3 (7.26 ppm) as an internal standard. Carbon-13 NMR spectra were determined on a Varian-Unity-500 instrument with CDCl_3 (77.2 ppm) as an internal standard unless otherwise specified. Mass spectra (MS) and high resolution mass spectra (HRMS) were measured on a JEOL JMS D-200 spectrometer. Optical rotations were measured on a JASCO DIP-140 instrument. Chromatography was performed on a silica gel column [Fuji-Davison BW-200 or Merck 60 (No. 9385)] with a medium pressure apparatus and a mixture of ethyl acetate and hexane was used as eluant unless otherwise specified. The extracts were dried over Na_2SO_4 unless otherwise specified.

(R)-2-(4,5-Dihydroxypentyl)-1H-isoindole-1,3(2H)-dione (6). A solution of *N*-pentenylphthalimide **5** (5.127 g, 23.8 mmol) in *tert*-BuOH (20 mL) was added to a mixture of AD-mix- β [(DHQD) $_2$ PYR ligand] (30.9 g), prepared by a mixture of $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (15 mg), (DHQD) $_2$ PYR (0.187 g), $\text{K}_3\text{Fe(CN)}_6$ (20.50 g), and K_2CO_3 (8.6 g) according to the method described in the literature,¹³ in *tert*-BuOH (94 mL) and H_2O (114 mL) at 0 °C. After the mixture was stirred for 42 h at the same

temperature, sodium sulfite (35.8 g, 285 mmol) was added to the mixture. After being stirred for 30 min, the mixture was filtered through Celite. The organic solvent was separated, and the aqueous solution was extracted with ethyl acetate three times. The combined organic solvents were washed with brine and dried, and the solvent was removed by rotary evaporation. The residue was purified by chromatography using hexane-ethyl acetate (1:3) as eluant to yield **6** (5.51 g, 93%) as a solid: mp 84-86 °C; $[\alpha]_D^{25} +1.73^\circ$ (*c* 1.3, CHCl₃); IR (KBr) 3919, 3840, 3746, 3713, 3287, 2932, 1770, 1722, 1466, 1440, 1396 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48-1.53 (2 H, m), 1.74-1.83 (1 H, m), 1.85-1.92 (1 H, m), 2.04 (1 H, t, *J* = 11.5 Hz), 2.42 (1H, d, *J* = 4.7 Hz), 3.43-3.48 (1 H, m), 3.64-3.68 (1 H, m), 3.74-3.81 (3 H, m), 7.71-7.75 (2 H, m), 7.84-7.88 (2 H, m); Anal. Calcd for C₁₃H₁₅NO₄: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.61; H, 5.95; N, 5.54.

(R)-2-(4,5-Epoxypropyl)-1H-isoindole-1,3(2H)-dione (7). A mixture of **6** (3.41 g, 13.7 mmol), pyridinium *p*-toluenesulfonate (PPTS) (28.0 mg, 0.11 mmol), and trimethyl orthoacetate (2.1 mL, 16.4 mmol) in CH₂Cl₂ (21 mL) was stirred for 20 min at rt. After the solvent was removed by rotary evaporation, CH₂Cl₂ (21 mL) was added to the residue. To the mixture was added acetyl bromide (1.21 mL, 16.4 mmol). After being stirred for 45 min, the solvent was removed by rotary evaporation. To the residue were added methanol (46 mL) and potassium carbonate (2.49 g, 18.0 mmol), and the mixture was stirred for 2.5 h. The reaction was quenched with sat. NH₄Cl, then extracted with CH₂Cl₂ three times. The extracts were washed with brine, dried and evaporated. The residue was purified by chromatography using hexane-ethyl acetate (3:1) as eluant to yield **7** (2.47 g, 78%) as an oil; $[\alpha]_D^{25} +6.55^\circ$ (*c* 1.14, CHCl₃); IR (neat) 3464, 3054, 2939, 1771, 1711, 1615, 1466 cm⁻¹; ¹H NMR (CDCl₃) δ 1.53-1.60 (1 H, m), 1.63-1.70 (1 H, m), 1.81-1.92 (2 H, m), 2.51 (1 H, dd, *J* = 4.9, 2.8 Hz), 2.76 (1 H, dd, *J* = 4.9, 4.1 Hz), 2.95-2.99 (1 H, m), 3.71-3.80 (2 H, m), 7.71-7.75 (2 H, m), 7.83-7.87 (2 H, m); ¹³C NMR (CDCl₃) δ 25.245, 29.895, 37.708, 47.118, 51.761, 123.370, 132.172, 134.113, 168.515. Anal. Calcd for C₁₃H₁₃NO₃: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.89; H, 5.65; N, 5.98.

(S)-2-(4-Hydroxyoctadecanyl)-1H-isoindole-1,3(2H)-dione (8). To a slurry of CuI (809 mg, 4.25 mmol) in THF (7.25 mL) was added a 1 M tridecanylmagnesium bromide-THF solution (6.38 mL, 6.38 mmol) at -30 °C with stirring. After being stirred for 1 h, a solution of **7** (982 mg, 4.25 mmol) in THF (6.35 mL) was slowly added. The mixture was gradually warmed to 0 °C, stirred for 2 h, and quenched with sat. NH₄Cl. The mixture was diluted with ether, washed with brine, dried, and evaporated. The residue was chromatographed using hexane-ethyl acetate (5:1) as eluant to give **8** (3.6 g, 75%) as a solid: mp 93-94 °C $[\alpha]_D^{25} +1.83^\circ$ (*c* 1.1, CHCl₃); IR (KBr) 3488, 2918, 2849, 1765, 1707 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (3 H, t, *J* = 13.9 Hz), 1.26-1.32 (23 H, m), 1.41-1.50 (4 H, m), 1.51-1.56 (2 H, m), 1.67 (2 H, d, *J* = 5.13 Hz), 1.72-1.78 (1 H, m), 1.83-1.88 (1 H, m), 3.62-3.66 (1 H, m), 3.74 (2 H, t, *J* = 14.3 Hz), 7.71-7.74 (2 H, m), 7.83-7.87 (2 H, m); ¹³C NMR (CDCl₃) δ 14.319, 22.872, 25.157, 25.832, 29.543, 29.785, 29.822, 29.836, 29.851, 29.865, 32.099, 34.515, 37.759, 38.111, 71.701, 123.378, 132.267, 134.083, 168.691. Anal. Calcd for C₂₆H₄₁NO₃: C, 75.13; H, 9.94; N, 3.37. Found: C, 75.17; H, 9.77; N, 3.20.

(S)-N-Benzoyloxycarbonyl-1-aminopropylpentadecan-1-ol (9). A solution of **8** (814 mg, 1.96 mmol) and 100% hydrazine hydrate (104 μL, 2.16 mmol) in ethanol (6.05 mL) was refluxed for 3.5 h. To the mixture was added conc. HCl (0.6 mL) at rt. The mixture was filtered through Celite. The filtrate

was evaporated to leave the hydrochloride salt. To a mixture of the salt and 2N NaOH (1.96 mL) was added benzyloxycarbonyl chloride (280 μ L, 1.96 mmol) at 0 °C. The mixture was stirred for 2 h at rt and extracted with ether. The extract was successively washed with 20% KHSO₄, sat. NaHCO₃, and brine, dried, and evaporated. The residue was chromatographed using hexane-ethyl acetate (5:1) as eluant to give **9** (649 mg, 79%) as a solid; mp 73-76 °C; $[\alpha]_D^{27} +1.58^\circ$ (*c* 1.3, CHCl₃); IR (KBr) 3334, 2915, 2848, 1683 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (3 H, t, *J* = 13.9 Hz), 1.27-1.32 (23 H, m), 1.34-1.45 (4 H, br s), 1.47-1.67 (3 H, m), 1.84 (1 H, br s), 3.18-3.25 (2 H, m), 3.56 (1 H, br s), 5.01 (1 H, br s), 5.09 (2 H, s), 7.31-7.38 (5 H, m); ¹³C NMR (CDCl₃) δ 14.290, 22.843, 25.816, 26.365, 29.514, 29.785, 29.829, 29.851, 32.077, 34.340, 37.811, 41.165, 66.743, 71.679, 128.225, 128.247, 128.643, 128.709, 136.734, 156.674. Anal. Calcd for C₂₆H₄₅NO₃: C, 75.41; H, 10.81; N, 3.34. Found: C, 74.87; H, 10.98; N, 3.52.

(R)-N-Benzyloxycarbonyl-2-tetradecylpyrrolidine (10). To a mixture of **8** (329 mg, 0.78 mmol) and DMAP (15 mg, 3.2 mmol) in pyridine (1.6 mL) was added methanesulfonyl chloride (91 μ L, 1.17 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was diluted with ether. The mixture was acidified with 20% KHSO₄. The organic solvent was successively washed with H₂O and brine, dried, and evaporated. The residue was purified by chromatography to yield **9** (336 mg, 87%) as an oil. To a suspension of 60% NaH (17 mg, 0.42 mmol) in THF (1.0 mL) was added a solution of **9** (160 mg, 0.32 mmol) in THF (1.0 mL) at 0 °C. The mixture was stirred for 15 h at 45 °C, quenched with sat. NH₄Cl, and diluted with ether. The mixture was successively washed with water and brine, then the mixture was dried, and evaporated. The residue was chromatographed using hexane-ethyl acetate (20:1) as eluant to give **10** (114 mg, 89%) as an oil; $[\alpha]_D^{26} -23.07^\circ$ (*c* 0.89, CHCl₃); IR (neat) 2922, 2851, 1701 cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (3 H, t, *J* = 13.9 Hz), 1.24-1.33 (25 H, m), 1.68-1.92 (5 H, m), 3.40-3.47 (2 H, m), 3.84 (1 H, s), 5.12-5.20 (2 H, m), 7.29-7.39 (5 H, m); ¹³C NMR (CDCl₃) δ 14.305, 22.972, 23.202, 23.971, 26.380, 26.490, 29.448, 29.543, 29.756, 29.792, 29.836, 29.858, 29.873, 30.686, 31.762, 32.099, 34.039, 34.720, 46.393, 46.713, 57.487, 58.227, 66.523, 66.750, 127.940, 128.284, 128.555, 128.655; Anal. Calcd for C₂₆H₄₃NO₂: C, 77.75; H, 10.79; N, 3.49. Found: C, 77.81; H, 11.19; N, 3.34.

(R)-Bgugaine (1). To a solution of **10** (114 mg, 0.283 mmol) in THF (5.3 mL) was added LiAlH₄ (21 mg, 0.566 mmol) at 0 °C. The reaction mixture was heated at 70 °C for 13 h. The mixture was treated by successive dropwise addition of H₂O (220 μ L), 2N NaOH (220 μ L), and H₂O (440 μ L) at 0 °C. After being stirred for 45 min, ether was added to the mixture. The mixture was dried with K₂CO₃, and the solvent was evaporated. The residue was chromatographed using CHCl₃-MeOH (10:1) as eluant to give **1** (68 mg, 85%) as an oil; $[\alpha]_D^{29} -42.5^\circ$ (*c* 1.65, MeOH), lit.,³ $[\alpha]_D^{20} -45^\circ$ (*c* 1.2, MeOH); IR (neat) 2923, 2852, 2771, 1458, 1215, 1042 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (3 H, t, *J* = 13.5 Hz), 1.19-1.31 (25 H, m), 1.40-1.47 (1 H, m), 1.66-1.71 (1 H, m), 1.75-1.79 (1 H, m), 1.90-2.01 (3 H, m), 2.11-2.18 (1 H, m), 2.32 (3 H, s), 3.06-3.10 (1 H, m); ¹³C NMR (CDCl₃) δ 14.334, 21.954, 22.894, 26.922, 29.565, 29.822, 29.858, 29.880, 30.239, 30.957, 32.128, 33.966, 40.615, 57.531, 66.706. HRMS calcd for C₁₉H₃₉N: 281.3083. Found: 281.3077.

(S)-2-(4,5-Dihydroxypentyl)-1H-isoindole-1,3(2H)-dione (ent-6). (91%); a solid; $[\alpha]_D^{25} -1.3^\circ$ (*c* 1.0, CHCl₃).

(S)-2-(4,5-Epoxypropyl)-1*H*-isoindole-1,3(2*H*)-dione (ent-7). (83%); an oil; $[\alpha]^{25}_D -5.55^\circ$ (c 1.98, CHCl_3).

(R)-2-(4-Hydroxyoctadecan-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (ent-8). (60%); an oil; $[\alpha]^{25}_D -1.95^\circ$ (c 0.99, CHCl_3).

(R)-*N*-Benzyloxycarbonyl-1-aminopropylpentadecan-1-ol (ent-9). (76%); a solid; $[\alpha]^{27}_D -0.98^\circ$ (c 1.1, CHCl_3).

(S)-*N*-Benzyloxycarbonyl-2-tetradecylpyrrolidine (ent-10). (78%); a solid; $[\alpha]^{26}_D +18.93^\circ$ (c 0.98, CHCl_3).

(S)-Bgugaine (ent-1). (84%); an oil; $[\alpha]^{29}_D +38.1^\circ$ (c 1.0, MeOH).

(S)-2-(4-Hydroxy-13-phenyltridecan-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (11). By means of a procedure similar to that for the preparation of 8, a mixture of 7 (664 mg, 2.78 mmol), 1*M* 8-phenyloctylmagnesium bromide-THF solution (4.18 mL, 4.18 mmol), and CuI (0.531 g, 2.79 mmol) in THF (6.9 mL) gave 11 (323 mg, 28 %) as a solid: mp 57-59 °C $[\alpha]^{25}_D +1.83^\circ$ (c 1.1, CHCl_3); IR (KBr) 3850, 3813, 3799, 3742, 3730, 3686, 3667, 3646, 3626, 3500, 2912, 1770, 1705, 1651, 1538, 1403, 1056 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.27-1.31 (11 H, m), 1.41-1.49 (4 H, m), 1.50-1.64 (4 H, m), 1.71-1.78 (2 H, m), 1.83-1.89 (1 H, m), 2.60 (2 H, t, $J = 15.6$ Hz), 3.63-3.65 (1 H, m), 3.74 (2 H, t, $J = 14.3$ Hz), 7.17-7.19 (3 H, m), 7.27-7.30 (2 H, m), 7.70-7.74 (2 H, m), 7.83-7.87 (2 H, m); ^{13}C NMR (CDCl_3) δ 25.142, 25.794, 29.477, 29.646, 29.675, 29.734, 29.778, 31.703, 34.501, 36.141, 37.723, 38.096, 71.657, 123.370, 125.684, 128.357, 128.547, 132.231, 134.083, 143.091, 168.684. Anal. Calcd for $\text{C}_{27}\text{H}_{35}\text{NO}_3$: C, 76.92; H, 8.37; N, 3.32. Found: C, 77.62; H, 8.31; N, 3.91.

(S)-*N*-Benzyloxycarbonyl-1-aminopropyl-10-phenyldecan-1-ol (12). By means of a procedure similar to that for the preparation of 9, a mixture of 11 (136 mg, 0.32 mmol) and 100% hydrazine hydrate (17 μL , 0.36 mmol) in EtOH (1 mL) gave the amine, which was transformed with a mixture of benzyloxycarbonyl chloride (46 μL , 0.32 mmol) and 2*N* NaOH (0.32 mL) to yield 12 (110 mg, 80%) as a solid: mp 77-78 °C; $[\alpha]^{27}_D +1.58^\circ$ (c 1.3, CHCl_3); IR (KBr) 3851, 3325, 3060, 3027, 2926, 2852, 1686, 1603, 1542, 1496, 1467, 1453, 1267, 1146, 1071, 1006 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.29-1.67 (21 H, m), 2.61 (2 H, t, $J = 15.6$ Hz), 3.20-3.27 (2 H, m), 3.61 (1 H, s), 5.11 (2 H, s), 7.17-7.20 (3 H, m), 7.27-7.38 (7 H, m); ^{13}C NMR (CDCl_3) δ 25.809, 26.438, 29.499, 29.668, 29.690, 29.763, 29.807, 31.718, 34.384, 36.156, 37.840, 41.194, 66.794, 71.781, 100.831, 125.714, 128.306, 128.284, 128.379, 128.562, 128.694, 136.749, 143.105. Anal. Calcd for $\text{C}_{29}\text{H}_{39}\text{NO}_3$: C, 76.19; H, 9.24; N, 3.29. Found: C, 76.23; H, 9.09; N, 3.53.

(R)-*N*-Benzyloxycarbonyl-2-(9-phenylnonyl)pyrrolidine (13). By means of a procedure similar to that for the preparation of 10, a mixture of 12 (138 mg, 0.325 mmol), methanesulfonyl chloride (38 mL, 0.49 mmol), pyridine (0.165 mL), and 4-*N,N*-dimethylaminopyridine (6 mg, 0.049 mmol) gave the mesylate, which was converted with 60% NaH (12 mg, 0.49 mmol) in THF (2 mL) to yield 13 (115 mg, 88%) as an oil: $[\alpha]^{26}_D -24.12^\circ$ (c 2.23, CHCl_3); IR (neat) 3062, 3026, 2925, 2853, 2363, 1702, 1603, 1496, 1453, 1410, 1356, 1245, 1186, 1096, 1029 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.23-1.31 (14 H, m), 1.65-1.67 (3 H, m), 1.83-1.90 (3 H, m), 2.61 (2 H, t, $J = 15.4$ Hz), 3.40-3.48 (2 H, br t), 3.84 (1 H, s), 5.10-5.20 (2 H, m), 7.19-7.38 (10 H, m); ^{13}C NMR (CDCl_3) δ 23.187, 23.949, 26.343, 26.460,

29.477, 29.638, 29.668, 29.778, 29.917, 30.671, 31.696, 34.010, 34.684, 36.141, 46.378, 46.708, 57.458, 58.197, 66.501, 66.721, 125.677, 127.923, 128.350, 137.364, 143.103, 154.961; Anal. Calcd for $C_{26}H_{43}NO_2$: C, 77.75; H, 10.79; N, 3.49. Found: C, 77.81; H, 11.19; N, 3.34.

Irniine (2). By means of a procedure similar to that for the preparation of **1**, a mixture of **13** (65 mg, 0.159 mmol) and $LiAlH_4$ (12 mg, 0.31 mmol) in THF (3 mL) gave **2** (34 mg, 76%) as an oil: $[\alpha]^{29}_D -49.4^\circ$ (c 0.35, CH_2Cl_2), lit.,² $[\alpha]^{20}_D -35^\circ$ (c 1, CH_2Cl_2); IR (neat) 2924, 1560, 1458 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.18-1.46 (14 H, m), 1.59-2.15 (8 H, m), 2.31 (3 H, s), 2.61 (2 H, t, $J = 15.6$ Hz), 3.04-3.05 (1 H, m), 7.17-7.30 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 21.950, 26.892, 29.514, 29.682, 29.719, 29.814, 30.217, 30.964, 31.725, 34.032, 36.170, 40.645, 57.546, 66.625, 125.706, 128.374, 128.569, 143.127. HRMS calcd for $C_{20}H_{33}N$: 287.2713. Found: 287.2617.

(R)-2-(4-Hydroxy-13-phenyltridecanyl)-1H-isoindole-1,3(2H)-dione (ent-11). (53%); a solid; $[\alpha]^{25}_D -0.67^\circ$ (c 1.0, $CHCl_3$).

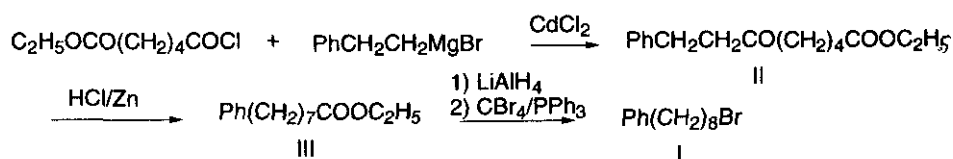
(R)-N-Benzoyloxycarbonyl-1-aminopropyl-10-phenyldecan-1-ol (ent-12). (70%); a solid; $[\alpha]^{27}_D -1.39^\circ$ (c 1.1, $CHCl_3$).

(S)-N-Benzoyloxycarbonyl-2-(9-phenylnonyl)pyrrolidine (ent-13). (78%); an oil; $[\alpha]^{26}_D +21.63^\circ$ (c 1.03, $CHCl_3$)

Irniine (ent-2). (61%); an oil; $[\alpha]^{26}_D +39.4^\circ$ (c 0.69, CH_2Cl_2).

REFERENCES AND NOTES

- # Dedicated to the memory of the late Professor Shun-ichi Yamada.
1. A. Melhaui, M. Mallea, A. Jossang, and B. Bodo, *Nat. Prod. Lett.*, 1993, **2**, 237.
2. A. Melhaui, A. Jossang, and B. Bodo, *J. Nat. Prod.*, 1992, **55**, 950.
3. A. Jossang, A. Melhaui, and B. Bodo, *Heterocycles*, 1996, **43**, 755.
4. For an excellent review, see: H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
5. H. Takahata, M. Kubota, S. Takahashi, and T. Momose, *Tetrahedron: Asymmetry*, 1996, **7**, 3047.
6. G. A. Crispino, K.-S. Jeong, H. C. Kolb, Z.-M. Wang, D. Xu, and K. B. Sharpless, *J. Org. Chem.*, 1993, **58**, 3785.
7. (DHQ)2PHAL⁸ and (DHQD)2AQN⁹ as ligands were examined.
8. K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768.
9. H. Becker and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 448.
10. On the other hand, 3-butenyl azide smoothly underwent the AD reaction [(DHQ)2PYR] of to yield the dihydroxide in 77% yield.
11. H. C. Kolb and K. B. Sharpless, *Tetrahedron*, 1992, **48**, 10515.
12. The requisite 8-phenyloctylbromide (**I**) ¹³ was prepared as shown. The coupling of ethyl chloroadipate with phenetylmagnesium bromide in the presence of cadmium chloride afforded the ketoester (**II**),¹⁴ which was reduced by the Clemmensen protocol to yield the ester (**III**). Reduction of **II** with $LiAlH_4$ followed by bromination of the resulting alcohol with carbon tetrabromide in combination with triphenylphosphine gave the desired bromide (**I**).



13. C. D. Perchonock, I. U. Vzinslas, M. E. McCsrthy, K. F. Erhand, J. G. Gleason, M. A. Wasserman, R. M. Muccilelli, J. F. DeVan, S. S. Tucker, L. M. Vickery, T. KIRchner, B. M. Weichman, S. Mong, M. O. Scott, G. Chi-Rosso, H.-L. Wu, S. T. Crook, and J. F. Newton, *J. Med. Chem.*, 1986, **29**, 1442.
14. J. Hase and H. Ohura, *Chem. Pharm. Bull.*, 1954, **2**, 368.

Received, 25th February, 1997