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

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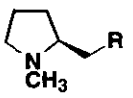
Abstract- A new asymmetric route to 2-substituted pyrrolidines starting with the Sharpless asymmetric dihydroxylation (AD) of 4-pentenylphthalimide (**5**) followed by aminocyclization of the resultant amino alcohol is presented. The application to the asymmetric synthesis has been examined for two 2-substituted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

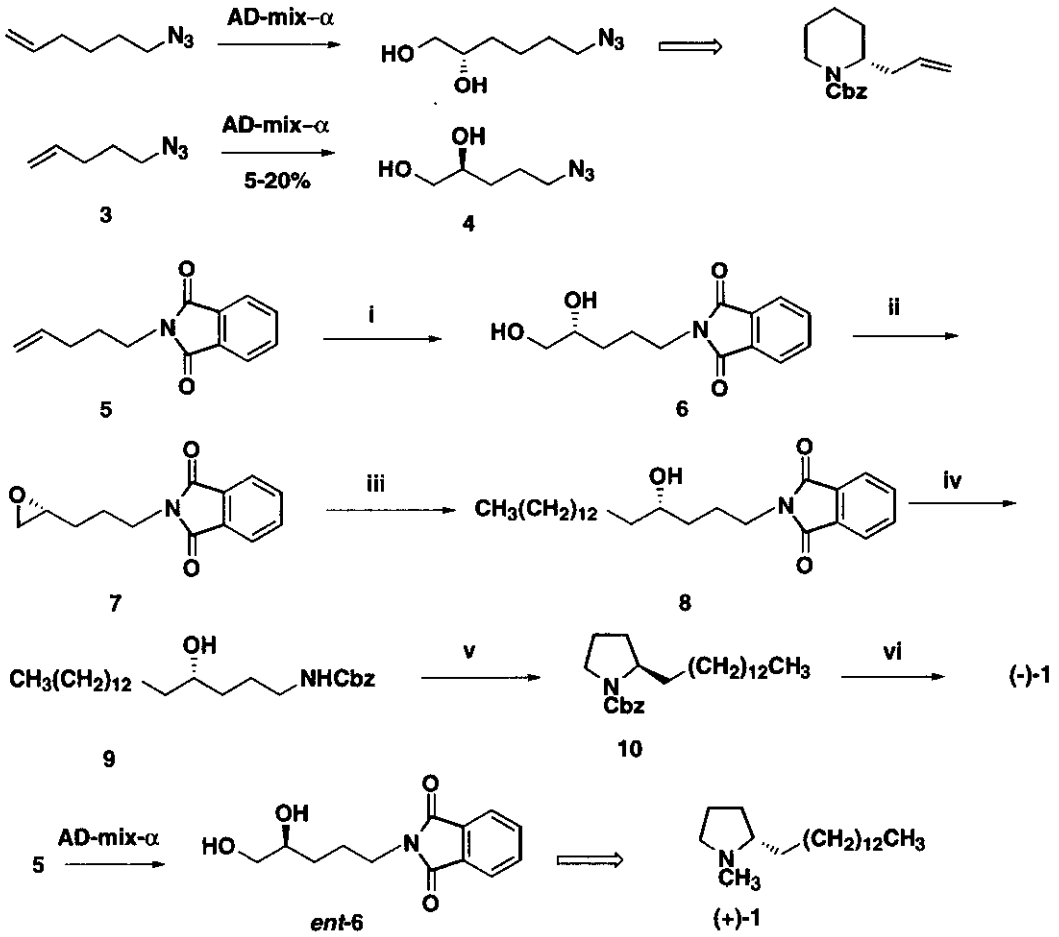
The widespread occurrence and intriguing biological activity of pyrrolidine alkaloids make them attractive to synthetic chemists in conjunction with the short supply of many of them from natural sources. Recently, two optically active 2-alkylpyrrolidine alkaloids, (-)-bgugaine (**1**)[1] and (-)-irniine (**2**),[2] have been isolated from the tubers of *Arisaum 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.



1 R = -$(CH_2)_{12}CH_3$
2 R = -$(CH_2)_8Ph$

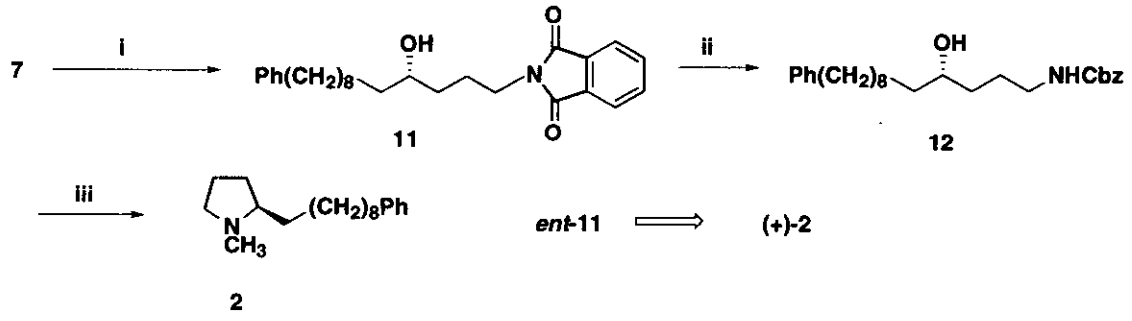
Recent investigation in this laboratory has revealed that the Sharpless asymmetric dihydroxylation (AD)[4] of 5-hexenyl azide provides a new asymmetric route to 2-substituted piperidines.[5] According to the method, our synthesis of **1** and **2** was started with the AD reaction of 4-pentenyl azide (**3**). Unfortunately, the AD reaction using $(DHQD)_2$-PYR[6] 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*-pentenylphtalimide (**5**) instead of **3**, and obtained the diol (**6**) in 93% yield. The diol (**6**) was converted by the Sharpless' one pot procedure[11] into the epoxide (**7**) in 83 % yield. With the epoxide (**7**) in hand, we

carried out the synthesis of (-)-bgugaine (**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 (LiAlH4) yielded the desired **1** {$[\alpha]^{29}_D$ -42.5° (*c* 1.65, MeOH), lit., [3] $[\alpha]^{20}_D$ -45° (*c* 1.2, 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 $(DHQ)_2PYR$ as a ligand.



i AD-mix-β (PYR ligand); ii 1) $(CH_3O)_3CCH_3$/PPTS; 2) CH_3COBr; 3) K_2CO_3/CH_3OH; iii $CH_3(CH_2)_{12}MgBr$/CuI; iv 1) NH_2NH_2; 2) CbzCl/NaOH; v 1) MsCl/pyridine/DMAP; 2) NaH; vi $LiAlH_4$

Having obtained these results, the synthesis of both enantiomers of irniine (**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 bromide[12] 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 (-)-irniine (**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 $Ph(CH_2)_8MgBr$/CuI; ii 1) NH_2NH_2; 2) CbzCl/NaOH; iii 1) 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 C_2 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-Davision 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)-1*H*-isoindole-1,3(2*H*)-dione (6).** A solution of *N*-pentenylphtalimide **5** (5.127 g, 23.8 mmol) in *tert*-BuOH (20 mL) was added to a mixture of AD-mix-β [$(DHQD)_2PYR$ ligand] (30.9 g), prepared by a mixture of $K_2OsO_4{\cdot}2H_2O$ (15 mg), $(DHQD)_2PYR$ (0.187 g), $K_3Fe(CN)_6$ (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; $[\alpha]^{25}_{D}$ +1.73° (*c* 1.3, $CHCl_3$); IR (KBr) 3919, 3840, 3746, 3713, 3287, 2932, 1770, 1722, 1466, 1440, 1396 cm^{-1}; ^1H NMR ($CDCl_3$) 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 $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.61; H, 5.95; N, 5.54.

(*R*)-2-(4,5-Epoxypentyl)-1*H*-isoindole-1,3(2*H*)-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 CH_2Cl_2 (21 mL) was stirred for 20 min at rt. After the solvent was removed by rotary evaporation, CH_2Cl_2 (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. NH_4Cl, then extracted with CH_2Cl_2 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; $[\alpha]^{25}_{D}$ +6.55° (*c* 1.14, $CHCl_3$); IR (neat) 3464, 3054, 2939, 1771, 1711, 1615, 1466 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 25.245, 29.895, 37.708, 47.118, 51.761, 123.370, 132.172, 134.113, 168.515. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.89; H, 5.65; N, 5.98.

(*S*)-2-(4-Hydroxyoctadecanyl)-1*H*-isoindole-1,3(2*H*)-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. NH_4Cl. 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 $[\alpha]^{25}_{D}$ +1.83° (*c* 1.1, $CHCl_3$); IR (KBr) 3488, 2918, 2849, 1765, 1707 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{26}H_{41}NO_3$: C, 75.13; H, 9.94; N, 3.37. Found: C, 75.17; H, 9.77; N, 3.20.

(*S*)-*N*-Benzyloxycarbonyl-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 μL, 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% $KHSO_4$, sat. $NaHCO_3$, 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; $[\alpha]^{27}_D$ +1.58° (*c* 1.3, $CHCl_3$); IR (KBr) 3334, 2915, 2848, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{26}H_{45}NO_3$: 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 μL, 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% $KHSO_4$. The organic solvent was successively washed with H_2O 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. NH_4Cl, 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; $[\alpha]^{26}_D$ -23.07° (*c* 0.89, $CHCl_3$); IR (neat) 2922, 2851, 1701 cm-1; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{26}H_{43}NO_2$: C, 77.75; H, 10.79; N, 3.49. Found: C, 77.81; H, 11.19; N, 3.34.

(*R*)-Bgugaine (1). To a solution of **10** (114 mg, 0.283 mmol) in THF (5.3 mL) was added $LiAlH_4$ (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 H_2O (220 μL), 2N NaOH (220 μL), and H_2O (440 μL) at 0 °C. After being stirred for 45 min, ether was added to the mixture. The mixture was dried with K_2CO_3, and the solvent was evaporated. The residue was chromatographed using $CHCl_3$-MeOH (10:1) as eluant to give **1** (68 mg, 85%) as an oil; $[\alpha]^{29}_D$ -42.5° (*c* 1.65, MeOH), lit.,[3] $[\alpha]^{20}_D$ -45° (*c* 1.2, MeOH); IR (neat) 2923, 2852, 2771, 1458, 1215, 1042 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{19}H_{39}N$: 281.3083. Found: 281.3077.

(*S*)-2-(4,5-Dihydroxypentyl)-1*H*-isoindole-1,3(2*H*)-dione (*ent*-6). (91%); a solid; $[\alpha]^{25}_D$ -1.3° (*c* 1.0, $CHCl_3$).

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

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

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

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

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

(*S*)-2-(4-Hydroxy-13-phenyltridecanyl)-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), 1M 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° (*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 $C_{27}H_{35}NO_3$: 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 2N NaOH (0.32 mL) to yield **12** (110 mg, 80%) as a solid: mp 77-78 °C; $[\alpha]^{27}_D$ +1.58° (*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 $C_{29}H_{39}NO_3$: 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° (*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° (*c* 0.35, CH_2Cl_2), lit.,[2] $[\alpha]^{20}_D$ -35° (*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)-1*H*-isoindole-1,3(2*H*)-dione (*ent*-11). (53%); a solid; $[\alpha]^{25}_D$ -0.67° (*c* 1.0, $CHCl_3$).

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

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

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

REFERENCES AND NOTES

Dedicated to the memory of the late Professor Shun-ichi Yamada.

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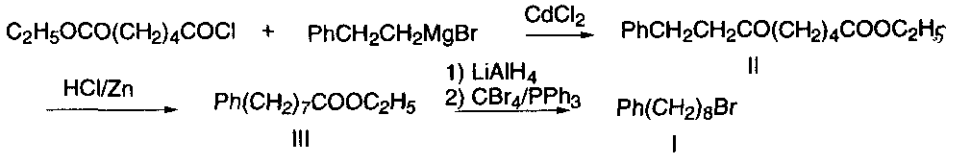

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