Supporting Information

for Asymmetric Skeletal Rearrangement of Symmetrically α,α -Disubstituted α -Amino Aldehydes: A New Entry to Optically Active α -Hydroxy Ketones

Takashi Ooi, Akira Saito, and Keiji Maruoka*

*Department of Chemistry, Graduate School of Science, Kyoto University
Sakyo, Kyoto 606-8502, Japan*

Characterization of α,α -Disubstituted α -Amino Aldehydes.

2-Benzyl-2-benzylamino-3-phenylpropanal: 2aa (Ar = Ph, R = PhCH₂). ¹H NMR (400 MHz, CDCl₃) δ 9.57 (1H, s, CHO), 7.31–7.18 (15H, m, Ar-H), 3.87 (2H, s, PhCH₂N), 3.08 (2H, d, J = 14.4 Hz, PhCH₂), 2.96 (2H, d, J = 14.4 Hz, PhCH₂), 1.70 (1H, br s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 205.0, 139.8, 135.5, 130.3, 128.4, 128.2, 127.9, 127.1, 126.7, 67.4, 47.1, 39.6; IR (liquid film) 3028, 1726, 1602, 1583, 1494, 1454, 1116, 1074, 1030, 912, 750, 698 cm⁻¹. HRMS (ESI-TOF) Calcd for C₂₃H₂₄NO ([M+H]⁺): 330.1852, Found: 330.1864.

2-Benzyl-2-(4-chlorobenzylamino)-3-phenylpropanal: 2ba (Ar = *p*-Cl-Ph, R = PhCH₂). ¹H NMR (400 MHz, CDCl₃) δ 9.55 (1H, s, CHO), 7.26–7.16 (14H, m, Ar-H), 3.80 (2H, s, *p*-Cl-PhCH₂N), 3.06 (2H, J = 14.4 Hz, PhCH₂), 2.93 (2H, J = 14.4 Hz, PhCH₂), 1.65 (1H, br s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 204.5, 138.3, 135.3, 132.6, 130.2, 129.1, 128.4, 128.2, 126.7, 67.4, 46.3, 39.7; IR (liquid film) 3028, 2840, 1726, 1601, 1493, 1454, 1408, 1090, 1015, 912, 839, 752, 700 cm⁻¹. HRMS (ESI-TOF) Calcd for C₂₃H₂₃ClNO ([M+H]⁺): 364.1463, Found: 364.1463.

2-Benzyl-2-(4-methoxybenzylamino)-3-phenylpropanal: 2ca (Ar = *p*-MeO-Ph, R = PhCH₂). ¹H NMR (400 MHz, CDCl₃) δ 9.55 (1H, s, CHO), 7.29–7.17 (12H, m, Ar-H), 6.84 (2H, d, J = 8.8 Hz, Ar-H), 3.80 (2H, s, *p*-MeO-PhCH₂N), 3.79 (3H, s, OCH₃), 3.07 (2H, d, J = 14.4 Hz, PhCH₂), 2.94 (2H, d, J = 14.4 Hz, PhCH₂), 1.63 (1H, br s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 205.0, 158.6, 135.6, 131.9, 130.3, 129.0, 128.2, 126.7, 113.8, 67.4, 55.3, 46.5, 39.6; IR (liquid film) 3028, 2835, 1726, 1612, 1512, 1454, 1302, 1248, 1175, 1034, 824, 752, 700 cm⁻¹. HRMS (ESI-TOF) Calcd for C₂₅H₃₀NO₃ ([M+MeOH+H]⁺): 392.2220, Found: 392.2199.

2-Benzyl-2-[(1-naphthylmethyl)amino]-3-phenylpropanal: 2da (Ar = α -Np, R = PhCH₂). ¹H NMR (400 MHz, CDCl₃) δ 9.64 (1H, s, CHO), 7.90 (1H, d, J = 8.0 Hz, Ar-H), 7.83 (1H, d, J = 8.0 Hz, Ar-H), 7.76 (1H, d, J = 8.0 Hz, Ar-H), 7.51–7.39 (4H, m, Ar-H), 7.30–7.20 (10H, m, Ar-H), 4.28 (2H, s, NpCH₂N), 3.18 (2H, d, J = 14.4 Hz, PhCH₂), 3.02 (2H, d, J = 14.4 Hz, PhCH₂), 1.80 (1H, br s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 204.9, 135.6, 135.3, 133.6, 131.6, 130.4, 128.4, 128.3, 127.8, 126.7, 125.9, 125.8, 125.6, 125.3, 123.9, 67.8, 44.9, 39.8; IR (KBr) 3030, 2910, 2821, 1724, 1595, 1497, 1456, 1391, 1155, 1059, 1030, 968, 824, 779, 750, 698 cm⁻¹. HRMS (ESI-TOF) Calcd for C₂₇H₂₆NO ([M+H]⁺): 380.2009, Found 380.2012.

2-(4-Chlorobenzyl)-3-(4-chlorophenyl)-2-[(1-naphthylmethyl)amino]propanal: 2d (Ar = α -Np, R = *p*-Cl-PhCH₂). ¹H NMR (400 MHz, CDCl₃) δ 9.60 (1H, s, CHO), 7.90 (1H, d, J = 8.0 Hz, Ar-H), 7.86 (1H, d, J = 8.0 Hz, Ar-H), 7.79 (1H, d, J = 8.0 Hz, Ar-H), 7.51–7.41 (4H, m, Ar-H),

7.24 (4H, d, $J = 8.8$ Hz, Ar-H), 7.12 (4H, d, $J = 8.8$ Hz, Ar-H), 4.25 (2H, s, NpCH₂), 3.10 (2H, d, $J = 14.8$ Hz, p -Cl-PhCH₂), 2.95 (2H, d, $J = 14.8$ Hz, p -Cl-PhCH₂), 1.74 (1H, br s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 204.2, 135.0, 133.8, 133.7, 132.8, 131.7, 131.6, 128.6, 128.5, 128.1, 126.0, 125.8, 125.7, 125.4, 123.7, 67.7, 44.9, 38.8; IR (KBr) 3033, 2926, 2843, 1722, 1595, 1491, 1454, 1094, 1013, 833, 798, 777 cm⁻¹. HRMS (ESI-TOF) Calcd for C₂₇H₂₄Cl₂NO ([M+H]⁺): 448.1229, Found: 448.1210.

2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-2-[(1-naphthylmethyl)amino]propanal: 2d (Ar = α -Np, R = p -MeO-PhCH₂). ¹H NMR (400 MHz, CDCl₃) δ 9.64 (1H, s, CHO), 7.93 (1H, d, $J = 8.4$ Hz, Ar-H), 7.83 (1H, d, $J = 8.4$ Hz, Ar-H), 7.76 (1H, d, $J = 8.4$ Hz, Ar-H), 7.51–7.40 (4H, m, Ar-H), 7.12 (4H, d, $J = 8.8$ Hz, Ar-H), 6.81 (4H, d, $J = 8.8$ Hz, Ar-H), 4.26 (2H, s, NpCH₂N), 3.77 (6H, s, OCH₃), 3.10 (2H, d, $J = 14.4$ Hz, p -MeO-PhCH₂), 2.95 (2H, d, $J = 14.4$ Hz, p -MeO-PhCH₂), 1.78 (1H, br s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 205.4, 158.3, 135.5, 133.7, 131.7, 131.3, 128.5, 127.8, 127.5, 125.9, 125.7, 125.6, 125.4, 123.9, 113.7, 67.9, 55.2, 44.8, 38.7; IR (KBr) 3317, 2964, 2835, 1705, 1610, 1510, 1441, 1302, 1252, 1177, 1031, 802, 779 cm⁻¹. HRMS (ESI-TOF) Calcd for C₂₉H₃₀NO₃ ([M+H]⁺): 440.2220, Found: 440.2199.

5-Methyl-2-(3-methyl-2-butenyl)-2-[(1-naphthylmethyl)amino]-4-hexenal: 2d (Ar = α -Np, R = (CH₃)₂C=CHCH₂). ¹H NMR (400 MHz, CDCl₃) δ 9.53 (1H, s, CHO), 8.15 (1H, d, $J = 7.6$ Hz, Ar-H), 7.85 (1H, d, $J = 7.6$ Hz, Ar-H), 7.77 (1H, d, $J = 7.6$ Hz, Ar-H), 7.53–7.40 (4H, m, Ar-H), 5.16 (2H, t, $J = 7.1$ Hz, C=CH), 4.04 (2H, s, NpCH₂), 2.44 (4H, m, C=CCH₂), 1.74 (6H, s, CH₃), 1.66 (7H, s and br s, CH₃ and NH); ¹³C NMR (100 MHz, CDCl₃) δ 204.2, 135.8, 135.0, 133.7, 131.8, 128.5, 127.8, 126.3, 125.9, 125.5, 125.4, 124.0, 117.5, 67.4, 44.8, 30.9, 26.1, 18.2; IR (liquid film) 2914, 1724, 1672, 1626, 1510, 1450, 1377, 1103, 793, 777 cm⁻¹. HRMS (ESI-TOF) Calcd for C₂₃H₃₀NO ([M+H]⁺): 336.2322, Found: 336.2306.

2-[(1-Naphthylmethyl)amino]-5-phenyl-2-(3-phenyl-2-propenyl)-4-pentenal: 2d (Ar = α -Np, R = PhCH=CHCH₂). ¹H NMR (400 MHz, CDCl₃) δ 9.65 (1H, s, CHO), 8.17 (1H, d, $J = 8.4$ Hz, Ar-H), 7.84 (1H, d, $J = 8.4$ Hz, Ar-H), 7.77 (1H, d, $J = 8.4$ Hz, Ar-H), 7.49–7.22 (14H, m, Ar-H), 6.57 (2H, d, $J = 15.8$ Hz, PhCH=), 6.22 (2H, dt, $J = 15.8, 7.5$ Hz, PhCH=CH), 4.20 (2H, s, NpCH₂), 2.77–2.66 (4H, m, PhC=CCH₂), 1.78 (1H, br s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 203.7, 136.9, 135.4, 134.2, 133.7, 131.8, 128.5, 128.5, 128.0, 127.4, 126.5, 126.1, 125.6, 125.4, 124.0, 123.4, 67.1, 45.1, 36.2; IR (KBr) 3057, 3026, 2868, 1724, 1595, 1495, 1448, 1391, 961, 800, 777, 735, 691 cm⁻¹. HRMS (ESI-TOF) Calcd for C₃₁H₃₀NO ([M+H]⁺): 432.2322, Found: 432.2303.

N-(1-Naphthylmethyl) diphenylglycinal: 2d (Ar = α -Np, R = Ph). ¹H NMR (400 MHz, CDCl₃) δ 9.85 (1H, s, CHO), 7.82 (2H, m, Ar-H), 7.75 (1H, d, $J = 8.4$ Hz, Ar-H), 7.58 (1H, d, $J = 8.4$ Hz, Ar-H), 7.49–7.33 (13H, m, Ar-H), 3.85 (2H, s, NpCH₂), 2.56 (1H, br s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 196.7, 138.4, 135.7, 133.6, 131.6, 128.7, 128.7, 128.5, 127.9, 127.6, 125.9, 125.8, 125.5, 125.4, 123.5, 75.7, 45.4; IR (liquid film) 3059, 2850, 1724, 1597, 1510, 1491, 1448, 1396, 1209, 1178, 1076, 1016, 908, 793, 773, 733, 702 cm⁻¹. HRMS (ESI-TOF) Calcd for C₂₅H₂₂NO ([M+H]⁺): 352.1696, Found: 352.1695.

General Procedure for Skeletal Rearrangement of *N*-Benzyl- α,α -dibenzyl- α -amino Aldehydes to α -Hydroxy Ketone with Achiral Lewis Acids. To a solution of 2-benzyl-2-benzylamino-3-phenylpropanal (**2aa**, 98.8 mg, 0.3 mmol) in distilled CH₂Cl₂ (3 mL) was added a 1 M hexane solution of dimethylaluminum chloride (330 μ L, 0.33 mmol) at -78 °C under argon atmosphere. After stirring for 1 h, the whole reaction mixture was allowed to warm to 0 °C, and the stirring was continued for additional 1.5 h. The reaction mixture was poured into 1 N HCl at 0 °C and extractive work-up was performed with CH₂Cl₂. The organic extracts were washed with brine and dried over anhydrous Na₂SO₄. After removal of solvents, the residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:4 as eluant) to give the corresponding rearrangement product, 1,4-diphenyl-3-hydroxy-2-butanone¹ (**3a**, R = PhCH₂) (67.9 mg, 0.282 mmol) as a colorless oil (94% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.14 (10H, m, Ar-H), 4.52 (1H, ddd, J = 7.5, 5.5, 4.7 Hz, C(=O)CH(OH)), 3.81 (1H, d, J = 15.8 Hz, PhCH₂C(=O)), 3.75 (1H, d, J = 15.8 Hz, PhCH₂C(=O)), 3.21 (1H, d, J = 5.5 Hz, OH), 3.15 (1H, dd, J = 14.2, 4.7 Hz, C(OH)CH₂Ph), 2.90 (1H, dd, J = 14.2, 7.5 Hz, C(OH)CH₂Ph); IR (neat) 3462, 3030, 2924, 1717, 1603, 1497, 1454, 1402, 1331, 1078, 1049, 738, 700 cm⁻¹.

General Procedure for Asymmetric Skeletal Rearrangement of α,α -Dialkyl- α -amino Aldehydes to Optically Active α -Hydroxy Ketones. To a solution of (*S*)-2,2'-bis(trifluoromethanesulfonylamino)-1,1'-binaphthyl ((*S*)-**4**, 120.6 mg, 0.22 mmol) in distilled toluene (2 mL) was added a 1 M toluene solution of trimethylaluminum (220 μ L, 0.22 mmol) at room temperature under argon atmosphere and the mixture was stirred for 15 min. Then, the mixture was heated to 110 °C and stirring was continued for additional 15 min. After cooling to -78 °C, 2-benzyl-2-[(1-naphthylmethyl)amino]-3-phenylpropanal (**2da**, 75.9 mg, 0.2 mmol) in toluene (1 mL) was added. The whole reaction mixture was stirred for 4 h at -78 °C and then allowed to warm to -40 °C. After 12 h of stirring at -40 °C, the resulting mixture was poured into 1 N HCl at 0 °C and extractive work-up was performed with ether. The organic extracts were washed with brine and dried over anhydrous Na₂SO₄. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:3 as eluant) gave 1,4-diphenyl-3-hydroxy-2-butanone (**3a**, R = PhCH₂) (44.7 mg, 0.186 mmol) as a colorless oil (93% yield). $[\alpha]_D^{27} +75.96^\circ$ (c 0.62, CHCl₃, 95% ee), HPLC conditions: DAICEL Chiralcel OD-H, hexane/*i*-PrOH = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, retention time: 26.6 min (*R*), 29.4 min (*S*).

Characterization of Optically Active α -Hydroxy Ketones.

1,4-Bis(4-chlorophenyl)-3-hydroxy-2-butanone: **3 (R = *p*-Cl-PhCH₂).** $[\alpha]_D^{28} +28.69^\circ$ (c 1.05, CHCl₃, 86% ee); ¹H NMR (400 MHz, CDCl₃) δ 7.32–7.26 (4H, m, Ar-H), 7.15 (2H, d, J = 8.4 Hz, Ar-H), 7.08 (2H, d, J = 8.4 Hz, Ar-H), 4.47 (1H, ddd, J = 7.6, 5.2, 4.4 Hz, C(=O)CH(OH)), 3.79 (1H, d, J = 16.4 Hz, ArCH₂C(=O)), 3.74 (1H, d, J = 16.4 Hz, ArCH₂C(=O)), 3.17 (1H, d, J = 5.2 Hz, OH), 3.13 (1H, dd, J = 14.4, 4.4 Hz, C(OH)CH₂Ar), 2.86 (1H, dd, J = 14.4, 7.6 Hz, C(OH)CH₂Ar); ¹³C NMR (100 MHz, CDCl₃) δ 207.9, 134.5, 133.3, 132.9, 131.0, 130.7, 130.5,

128.8, 128.7, 44.8, 39.4 ; IR (KBr) 3479, 1717, 1493, 1408, 1331, 1090, 1045, 1015, 851, 800, 746 cm^{-1} . HRMS (ESI-TOF) Calcd for $\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{O}_2\text{Na}$ ($[\text{M}+\text{Na}]^+$): 331.0263, Found: 331.0277. HPLC conditions: DAICEL Chiralcel OB-H, hexane/EtOH = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, retention time: 31.7 min (minor), 35.2 min (major).

3-Hydroxy-1,4-bis(4-methoxyphenyl)-2-butanone: 3 (R = *p*-MeO-PhCH₂). $[\alpha]_{\text{D}}^{29} +71.31^\circ$ (*c* 1.00, CHCl_3 , 94% ee); ^1H NMR (400 MHz, CDCl_3) δ 7.13 (2H, d, J = 8.8 Hz, Ar-H), 7.07 (2H, d, J = 8.8 Hz, Ar-H), 6.87–6.83 (4H, m, Ar-H), 4.46 (1H, m, $\text{C}(=\text{O})\text{CH}(\text{OH})$), 3.79 (6H, s, OCH_3), 3.73 (1H, d, J = 16.4 Hz, $\text{ArCH}_2\text{C}(=\text{O})$), 3.69 (1H, d, J = 16.4 Hz, $\text{ArCH}_2\text{C}(=\text{O})$), 3.19 (1H, d, J = 5.9 Hz, OH), 3.09 (1H, dd, J = 14.2, 5.1 Hz, $\text{C}(\text{OH})\text{CH}_2\text{Ar}$), 2.85 (1H, dd, J = 14.2, 7.5 Hz, $\text{C}(\text{OH})\text{CH}_2\text{Ar}$); ^{13}C NMR (100 MHz, CDCl_3) δ 209.2, 158.6, 158.4, 130.4, 130.2, 128.2, 124.8, 114.1, 113.9, 76.7, 55.3, 44.9, 39.3; IR (KBr) 3415, 2964, 2837, 1713, 1697, 1614, 1514, 1468, 1301, 1250, 1178, 1109, 1034, 812, 777 cm^{-1} . HRMS (ESI-TOF) Calcd for $\text{C}_{18}\text{H}_{20}\text{O}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$): 323.1254, Found: 323.1268. HPLC conditions: DAICEL Chiralcel OD-H, hexane/EtOH = 10:1, flow rate = 0.5 mL/min, λ = 210 nm, retention time: 32.6 min (minor), 34.8 min (major).

6-Hydroxy-2,9-dimethyl-2,8-decadien-5-one: 3 (R = $(\text{CH}_3)_2\text{C}=\text{CH}_2$). $[\alpha]_{\text{D}}^{29} +69.82^\circ$ (*c* 0.63, CHCl_3 , 97% ee); ^1H NMR (400 MHz, CDCl_3) δ 5.28 (1H, t, J = 7.1 Hz, $\text{C}=\text{CH}$), 5.10 (1H, t, J = 7.1 Hz, $\text{C}=\text{CH}$), 4.27 (1H, dt, J = 5.1, 5.1 Hz, $\text{CH}(\text{OH})$), 3.38 (1H, d, J = 5.1 Hz, OH), 3.19 (2H, d, J = 7.1 Hz, $\text{CH}_2\text{C}=\text{O}$), 2.55 (1H, m, $\text{C}(\text{OH})\text{CH}_2$), 2.38 (1H, m, $\text{C}(\text{OH})\text{CH}_2$), 1.76 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.64 (3H, s, CH_3), 1.63 (3H, s, CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 210.2, 136.3, 135.5, 117.8, 114.7, 75.8, 38.1, 33.2, 32.6, 25.9, 25.8, 18.2 ; IR (neat) 3447, 2970, 2918, 2858, 1713, 1632, 1450, 1377, 1309, 1248, 1109, 1063, 984, 843, 733 cm^{-1} . HRMS (ESI-TOF) Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2\text{Na}$ ($[\text{M}+\text{Na}]^+$): 219.1356, Found: 219.1345. HPLC conditions: DAICEL Chiralcel OD-H, hexane/*i*-PrOH = 50:1, flow rate = 0.5 mL/min, λ = 210 nm, retention time: 22.8 min (major), 25.0 min (minor).

5-Hydroxy-1,8-diphenyl-1,7-octadien-4-one: 3 (R = PhCH=CHCH₂). $[\alpha]_{\text{D}}^{30} +11.89^\circ$ (*c* 0.93, CHCl_3 , 96% ee); ^1H NMR (400 MHz, CDCl_3) δ 7.36–7.20 (10H, m, Ar-H), 6.51 (1H, d, J = 16.0 Hz, PhCH=CH), 6.50 (1H, d, J = 16.0 Hz, PhCH=CH), 6.29 (1H, ddd, J = 16.0, 7.2, 7.2 Hz, PhCH=CH), 6.18 (1H, ddd, J = 16.0, 7.6, 7.6 Hz, PhCH=CH), 4.44 (1H, ddd, J = 5.6, 5.6, 5.2 Hz, $\text{C}(=\text{O})\text{CH}(\text{OH})$), 3.45 (3H, m, $\text{C}=\text{CCH}_2\text{C}=\text{O}$ and OH), 2.82 (1H, ddd, J = 14.8, 7.6, 5.6 Hz, $\text{C}=\text{CCH}_2\text{C}(\text{OH})$), 2.62 (1H, ddd, J = 14.8, 7.6, 5.6 Hz, $\text{C}=\text{CCH}_2\text{C}(\text{OH})$); ^{13}C NMR (100 MHz, CDCl_3) δ 209.0, 136.6, 136.4, 134.3, 133.7, 128.5, 128.4, 127.6, 127.4, 126.2, 126.1, 123.5, 120.5, 76.0, 42.5, 37.4 ; IR (liquid film) 3429, 3026, 2926, 1713, 1599, 1496, 1448, 1396, 1217, 1070, 1028, 968, 756, 694 cm^{-1} . HRMS (ESI-TOF) Calcd for $\text{C}_{20}\text{H}_{20}\text{O}_2\text{Na}$ ($[\text{M}+\text{Na}]^+$): 315.1356, Found: 315.1357. HPLC conditions: DAICEL Chiralcel OD-H, hexane/*i*-PrOH = 5:1, flow rate = 0.5 mL/min, λ = 254 nm, retention time: 28.1 min (major), 42.6 min (minor).

NMR Characterization of the Zwitterionic Iminium Intermediate A Derived from 2da and Chiral Aluminum Lewis Acid (S)-1. To a solution of (S)-2,2'-bis(trifluoromethanesulfonylamino)-1,1'-binaphthyl ((S)-4, 30.1 mg, 0.055 mmol) in CDCl_3 (500 μL) was added a 1 M

CDCl₃ solution of trimethylaluminum (55 μ L, 0.055 mmol) at room temperature under argon atmosphere and the mixture was stirred for 15 min. Then, the mixture was heated at reflux temperature and stirring was continued for additional 15 min. After cooling to -78 $^{\circ}$ C, a CDCl₃ (200 μ L) solution of **2da** (19.0 mg, 0.05 mmol) was added to the mixture and the resulting solution was stirred for 30 min. The mixture was transferred into NMR tube *via* cannula, gradually warmed to room temperature, and then 1 H NMR and [1 H, 1 H] COSY were recorded. 1 H NMR (400 MHz, CDCl₃) δ 11.1 (1H, br, N⁺H), 7.77–6.71 (28H, m, Ar-H), 5.92 (1H, d, J = 6.8 Hz, Ar-H), 5.24 (1H, br s, CH-OAl⁺), 4.66 (1H, dd, J = 15.6, 8.8 Hz, PhCH₂N⁺), 4.46 (1H, dd, J = 15.6, 3.2 Hz, PhCH₂N⁺), 3.87 (1H, d, J = 16.0, PhCH₂C=N⁺), 3.71 (1H, d, J = 16.0 Hz, PhCH₂C=N⁺), 3.32 (1H, dd, J = 14.8, 5.2 Hz, PhCH₂C-OAl⁺), 2.99 (1H, dd, J = 14.8, 3.6 Hz, PhCH₂C-OAl⁺), -0.83 (3H, s, Al⁺CH₃); [1 H, 1 H] COSY: 11.1–(4.66, 4.46), 5.24–(3.32, 2.99), 4.66–4.46, 3.87–3.71, 3.32–2.99.

In Situ Reduction of Zwitterionic Iminium Intermediate A with DIBAH: Asymmetric Synthesis of *anti*-1,2-Amino Alcohol 5. To a solution of (*S*)-2,2'-bis(trifluoromethanesulfonylamino)-1,1'-binaphthyl ((*S*)-**4**, 120.6 mg, 0.22 mmol) in distilled toluene (2 mL) was added a 1 M toluene solution of trimethylaluminum (220 μ L, 0.22 mmol) at room temperature under argon atmosphere and the mixture was stirred for 15 min. Then, the mixture was heated to 110 $^{\circ}$ C and stirring was continued for additional 15 min. After cooling to -78 $^{\circ}$ C, 2-benzyl-2-[(1-naphthylmethyl)amino]-3-phenylpropanal (**2da**, 75.9 mg, 0.2 mmol) in toluene (1 mL) was added. The reaction mixture was stirred for 4 h at -78 $^{\circ}$ C and then allowed to warm to -40 $^{\circ}$ C. After 12 h of stirring at -40 $^{\circ}$ C, the mixture was cooled back to -78 $^{\circ}$ C followed by the addition of a 2 M toluene solution of diisobutylaluminum hydride (DIBAH, 330 μ L, 0.66 mmol) and the whole reaction mixture was stirred for 3 h at that temperature. The reaction was quenched with 3 N HCl at 0 $^{\circ}$ C and, after being basified with saturated NaHCO₃ *aq*, extractive work-up was performed with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous Na₂SO₄. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (EtOAc/hexane = 1:2 as eluant) gave (2*S*,3*R*)-3-[(1-naphthylmethyl)amino]-1,4-diphenyl-2-butanol (**5**, 68.7 mg, 0.18 mmol) as a white solid (90% yield). 1 H NMR (400 MHz, CDCl₃) δ 7.79 (1H, d, J = 8.4 Hz, Ar-H), 7.71 (1H, d, J = 8.4 Hz, Ar-H), 7.59 (1H, d, J = 8.4 Hz, Ar-H), 7.43–7.13 (12H, m, Ar-H), 7.05 (2H, d, J = 7.6 Hz, Ar-H), 4.16 (1H, d, J = 12.6 Hz, NpCH₂), 4.13 (1H, m, CH(OH)), 3.91 (1H, d, J = 12.6 Hz, NpCH₂), 3.10 (1H, br, NH), 3.04 (1H, dd, J = 13.6, 4.0 Hz, PhCH₂), 2.98–2.92 (2H, m, CH(NH) and PhCH₂), 2.85 (1H, dd, J = 13.6, 5.0 Hz, PhCH₂), 2.65 (1H, dd, J = 13.6, 10.4 Hz, PhCH₂); 13 C NMR (100 MHz, CDCl₃) δ 138.9, 138.4, 135.0, 133.7, 131.4, 129.1, 128.9, 128.6, 128.5, 127.8, 126.4, 126.3, 126.1, 125.5, 125.1, 123.0, 71.2, 62.1, 49.7, 38.8, 34.3; IR (liquid film) 3119, 2931, 2853, 2749, 1597, 1493, 1458, 1348, 1103, 1042, 880, 800, 777, 754, 702 cm⁻¹. HRMS (ESI-TOF) Calcd for C₂₇H₂₈NO ([M+H]⁺): 382.2166, Found: 382.2180. $[\alpha]_D^{24}$ +109.96 $^{\circ}$ (c 1.20, CHCl₃, recrystallized as hydrochloride). For HPLC analysis, **5** was treated with *t*-BuMe₂SiCl and imidazole in DMF to give *O-t*-butyldimethylsilylated product. 1 H NMR (400 MHz, CDCl₃) δ 8.00 (1H, d, J = 7.2 Hz, Ar-H), 7.82 (1H, d, J = 7.2 Hz, Ar-H), 7.74

(1H, d, $J = 7.2$ Hz, Ar-H), 7.47–7.10 (14H, m, Ar-H), 4.19 (1H, d, $J = 13.0$ Hz, NpCH₂), 4.16 (1H, d, $J = 13.0$ Hz, NpCH₂), 3.87 (1H, ddd, $J = 8.8, 4.0, 2.4$ Hz, CH-OSi), 3.08 (1H, ddd, $J = 9.2, 7.6, 2.4$ Hz, CH(NH)), 2.95 (1H, dd, $J = 13.6, 9.2$ Hz, PhCH₂C(NH)), 2.94 (1H, dd, $J = 13.6, 4.0$ Hz, PhCH₂C-OSi), 2.82 (1H, dd, $J = 13.6, 8.8$ Hz, PhCH₂C-OSi), 2.80 (1H, dd, $J = 13.6, 7.6$ Hz, PhCH₂C(NH)), 1.58 (1H, br, NH), 0.72 (9H, s, Si-*t*Bu), –0.25 (3H, s, Si-CH₃), –0.57 (3H, s, Si-CH₃); HPLC conditions: DAICEL Chiralpak AD-H, hexane/*i*-PrOH = 100:1, flow rate = 0.5 mL/min, $\lambda = 254$ nm, retention time: 7.7 min (2*S*,3*R*), 10.8 min (2*R*,3*S*), 95% ee. The stereochemistry of **5** was assigned by ¹H NMR analysis after conversion to oxazolidin-2-one derivative **7** (Scheme 5). ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.10 (17H, m, Ar-H), 4.96 (1H, ddd, $J = 9.2, 7.2, 5.2$ Hz, CH-O), 4.89 (1H, br, NH), 4.01 (1H, ddd, $J = 11.2, 7.2, 3.6$ Hz, CH-N), 3.23 (1H, dd, $J = 14.8, 9.2$, PhCH₂C-O), 3.02 (1H, dd, $J = 14.8, 5.2$ Hz, PhCH₂C-O), 2.98 (1H, dd, $J = 13.6, 3.6$ Hz, PhCH₂C-N), 2.78 (1H, dd, $J = 13.6, 11.2$ Hz, PhCH₂C-N). The assignment of stereochemistry was based on the vicinal coupling, $J_{\text{vic}} = 7.2$ Hz, which was consistent with that of the *cis*-oxazolidin-2-one derivative.²

NMR Characterization of the Neutral Imine **6 Derived from **2aa** and Dimethylaluminum Chloride.** To a solution of 2-benzyl-2-benzylamino-3-phenylpropanal (**2aa**, 32.9 mg, 0.1 mmol) in CD₂Cl₂ (1 mL) was added 1 M CD₂Cl₂ solution of dimethylaluminum chloride (110 μ L, 0.11 mmol) at –78 °C under argon atmosphere and the mixture was stirred for 15 min at that temperature. Then, the mixture was transferred into NMR tube *via* cannula and gradually warmed to room temperature. At this point, evolution of methane gas was observed and then ¹H and ¹³C NMR and [¹³C, ¹H] COSY were recorded. ¹H NMR (400 MHz, CD₂Cl₂): δ 7.38–6.81 (13H, m, Ar-H), 6.28 (2H, d, $J = 7.2$ Hz, Ar-H), 5.51 (1H, m, CH-OAl), 5.15 (1H, d, $J = 15.6$ Hz, PhCH₂C=), 4.47 (1H, d, $J = 15.6$ Hz, PhCH₂C=), 3.74 (1H, d, $J = 16.2$ Hz, PhCH₂N=), 3.56 (1H, d, $J = 16.2$ Hz, PhCH₂N=), 3.44 (1H, dd, $J = 15.0, 3.2$ Hz, PhCH₂C-OAl), 3.12 (1H, dd, $J = 15.0, 3.3$ Hz, PhCH₂C-OAl) –0.97 (3H, s, Al-CH₃); ¹³C NMR (100 MHz, CD₂Cl₂): δ 184.9, 136.1, 135.9, 133.3, 130.6, 129.6, 129.1, 128.9, 128.7, 127.9, 127.6, 127.2, 127.0, 75.7, 52.0, 38.6, 36.3, –7.2; [¹³C, ¹H] COSY: 75.7–5.51, 52.0–(5.15, 4.47), 38.6–(3.44, 3.12), 36.3–(3.74, 3.56), –7.2–(–0.97).

References

- (1) Guo, Z.; Goswami, A.; Nanduri, V. B.; Patel, R. T. *Tetrahedron: Asymmetry* **2001**, 12, 571.
- (2) (a) Hoffman, R. V.; Maslouh, N.; Carrantes-Lee, F. *J. Org. Chem.* **2002**, 67, 1045, (b) Harris, B. D.; Bhat, K. L.; Joullie, M. M. *Tetrahedron Lett.* **1987**, 28, 2837.

Copies of ¹H and ¹³C spectra for all new compounds (α -amino aldehydes **2**, α -hydroxy ketones **3** and 1,2-amino alcohol **5**) were attached as follows (pp. S7–S20).

2-Benzyl-2-benzylamino-3-phenylpropanal
2aa (Ar = Ph, R = PhCH₂)

FILE: WINDOWS\PROFILES\AKIRAS\COMBILH-Bn-Bn-CHO_1H
 DATE: Oct 13 15:05:30 2002
 OBNUC
 EXMBCN
 OBFQ 395.75 MHz
 OBSF 124.00 KHz
 OBFN 10277.0 Hz
 POINT 32768
 FREQU 7917.6 Hz
 SCANS 8
 ACQTM 4.139 sec
 PD 2.861 sec
 PW1 6.0 us
 IRNLUH
 CTMP 24.2 c
 SLVNDCL3
 EXREF 0.00 ppm
 BF 0.12 Hz
 RGAIN 17

R = PhCH₂

¹H NMR
 400 MHz
 CDCl₃

FILE: WINDOWS\PROFILES\AKIRAS\COMBILH-Bn-Bn-CHO_13C
 DATE: Oct 13 15:01:45 2002
 OBNUC
 EXMBCN
 OBFQ 99.45 MHz
 OBSF 94.00 KHz
 OBFN 10309.0 Hz
 POINT 32768
 FREQU 26881.7 Hz
 SCANS 222
 ACQTM 1.219 sec
 PD 1.781 sec
 PW1 6.0 us
 IRNLUH
 CTMP 25.2 c
 SLVNDCL3
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 25

R = PhCH₂

¹³C NMR
 100 MHz
 CDCl₃

2-Benzyl-2-(4-chlorobenzylamino)-3-phenylpropanal
2ba (Ar = *p*-Cl-Ph, R = PhCH₂)

2-Benzyl-2-(4-methoxybenzylamino)-3-phenylpropanal

2ca (Ar = *p*-MeO-Ph, R = PhCH₂)

2-Benzyl-2-[(1-naphthylmethyl)amino]-3-phenylpropanal
2da (Ar = α -Np, R = PhCH₂)

DFILE: \WINDOWS\PROFILES\AKIRAS\COM\NpCH2.H-Bn.Bn-CHO_1H
 DATE: Jan 24 22:19:46 2003
 OBNUC
 EXMNDON
 OBFQ 395.75 MHz
 OBSE 124.00 kHz
 OBFN 10277.0 Hz
 POINT 32768
 FREQU 7917.6 Hz
 SCANS 4
 ACQTM 4.139 sec
 PD 2.861 sec
 PW1 6.0 us
 IRNUH
 CTEMP 19.2 c
 SLVDCDCL3
 EXREF 0.00 ppm
 BF 0.12 Hz
 RGAIN 14

R = PhCH₂

¹H NMR
 400 MHz
 CDCl₃

DFILE: \WINDOWS\PROFILES\AKIRAS\COM\NpCH2.H-Bn.Bn-CHO_13C
 DATE: Jan 24 22:26:45 2003
 OBNUC
 EXMNDON
 OBFQ 99.45 MHz
 OBSE 94.00 kHz
 OBFN 10309.0 Hz
 POINT 32768
 FREQU 26881.7 Hz
 SCANS 128
 ACQTM 1.219 sec
 PD 1.781 sec
 PW1 6.0 us
 IRNUH
 CTEMP 22.1 c
 SLVDCDCL3
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 24

R = PhCH₂

¹³C NMR
 100 MHz
 CDCl₃

2-(4-Chlorobenzyl)-3-(4-chlorophenyl)-2-[(1-naphthylmethyl)amino]propanal
2d (Ar = α -Np, R = p -Cl-PhCH₂)

DFILE: \WINDOWS\PROFILES\AKIRAS\...
 COMNAME: CH2.H-(pClBn)2-CHO_1H
 DATETIME: Jul 04 15:02:00 2002
 OBNAME: EXMNDON
 OBFRQ: 395.75 MHz
 OBSET: 124.00 kHz
 OBFIN: 10277.0 Hz
 POINT: 32768
 FREQU: 7917.6 Hz
 SCANS: 8
 ACQTM: 4.139 sec
 PD: 2.861 sec
 PW1: 6.0 us
 IRNUH: CTEMP: 24.0 c
 SLV: CDCl₃
 EXREF: 0.00 ppm
 BF: 0.12 Hz
 RGAIN: 20

DFILE: \WINDOWS\PROFILES\AKIRAS\...
 COMNAME: CH2.H-(pClBn)2-CHO_13C
 DATETIME: Jan 23 13:49:07 2003
 OBNAME: EXMBDCM
 OBFRQ: 100.40 MHz
 OBSET: 125.00 kHz
 OBFIN: 10500.0 Hz
 POINT: 32768
 FREQU: 27173.9 Hz
 SCANS: 128
 ACQTM: 1.206 sec
 PD: 1.794 sec
 PW1: 5.5 us
 IRNUH: CTEMP: 24.8 c
 SLV: CDCl₃
 EXREF: 77.00 ppm
 BF: 0.12 Hz
 RGAIN: 33

2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-2-[(1-naphthylmethyl)amino]propanal
2d (Ar = α -Np, R = p -MeO-PhCH₂)

5-Methyl-2-(3-methyl-2-butenyl)-2-[(1-naphthylmethyl)amino]-4-hexenal
2d (Ar = α -Np, R = $(\text{CH}_3)_2\text{C}=\text{CHCH}_2$)

DFILE: \WINDOWS\PROFILES\AKIRAS\...
 COMNAME: CH2.H-(prenyl)2-CHO_1H
 DATIM: May 22 13:32:55 2002
 OBNUH
 EXMNDON
 OBFQ 395.75 MHz
 OBSE 124.00 kHz
 OBFN 10277.0 Hz
 POINT 32768
 FREQU 7917.6 Hz
 SCANS 8
 ACQTM 4.139 sec
 PD 2.861 sec
 PW1 6.0 us
 IRNUH
 CTEMP 22.3 c
 SLVDC13
 EXREF 0.00 ppm
 BF 0.12 Hz
 RGAIN 14

R = $(\text{CH}_3)_2\text{C}=\text{CHCH}_2$
¹H NMR
 400 MHz
 CDCl₃

DFILE: \WINDOWS\PROFILES\AKIRAS\...
 COMNAME: CH2.H-(prenyl)2-CHO_13C
 DATIM: Sep 20 20:56:03 2002
 OBNUH
 EXMNDON
 OBFQ 99.45 MHz
 OBSE 94.00 kHz
 OBFN 10309.0 Hz
 POINT 32768
 FREQU 26881.7 Hz
 SCANS 137
 ACQTM 1.219 sec
 PD 1.781 sec
 PW1 6.0 us
 IRNUH
 CTEMP 26.3 c
 SLVDC13
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 23

R = $(\text{CH}_3)_2\text{C}=\text{CHCH}_2$
¹³C NMR
 100 MHz
 CDCl₃

2-[(1-Naphthylmethyl)amino]-5-phenyl-2-(3-phenyl-2-propenyl)-4-pentenal
2d (Ar = α -Np, R = PhCH=CHCH₂)

N-(1-Naphthylmethyl) diphenylglycinal
2d (Ar = α -Np, R = Ph)

DFILE: \WINDOWS\PROFILES\AKIRAS\COM\Np-CH2-H-Ph-Ph-CHO_1H
 DATIM: Jan 27 16:15:00 2003
 OBNUH
 EXMNDON
 OBFRO 395.75 MHz
 OBSET 124.00 kHz
 OBFIN 10277.0 Hz
 POINT 32768
 FREQU 7917.6 Hz
 SCANS 8
 ACQTM 4.139 sec
 PD 2.861 sec
 PW1 6.0 us
 IRNUH
 CTEMP 21.0 c
 SLVDCCL3
 EXREF 0.00 ppm
 BF 0.12 Hz
 RGAIN 10

R = Ph

¹H NMR
 400 MHz
 CDCl₃

DFILE: \WINDOWS\PROFILES\AKIRAS\COM\Np-CH2-H-Ph-Ph-CHO_13C
 DATIM: Jan 27 16:19:09 2003
 OBNUH
 EXMNDON
 OBFRO 99.45 MHz
 OBSET 94.00 kHz
 OBFIN 10309.0 Hz
 POINT 32768
 FREQU 26881.7 Hz
 SCANS 69
 ACQTM 1.219 sec
 PD 1.781 sec
 PW1 6.0 us
 IRNUH
 CTEMP 23.6 c
 SLVDCCL3
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 23

R = Ph

¹³C NMR
 100 MHz
 CDCl₃

1,4-Bis(4-chlorophenyl)-3-hydroxy-2-butanone
3 (R = *p*-Cl-PhCH₂)

DFILE: \WINDOWS\PROFILES\AKIRAS\COMP\p-Cl-PhCH₂_product_1H
 DATIM: Jan 22 17:33:11 2002
 OBNUEC
 EXMBOM
 OBFREQ 395.75 MHz
 OBSET 124.00 KHz
 OBFIN 10277.0 Hz
 POINT 32768
 FREQQU 7917.6 Hz
 SCANS 8
 ACQTM 4.139 sec
 PD 2.861 sec
 PW1 6.0 us
 IRNUH
 CTEMP 23.1 c
 SLVCDCL3
 EXREF 0.00 ppm
 BF 1.20 Hz
 RGAIN 23

DFILE: \WINDOWS\PROFILES\AKIRAS\COMP\p-Cl-PhCH₂_product_13C
 DATIM: Jan 23 14:30:03 2003
 OBNUEC
 EXMBOM
 OBFREQ 99.45 MHz
 OBSET 94.00 KHz
 OBFIN 10309.0 Hz
 POINT 32768
 FREQQU 26881.7 Hz
 SCANS 103
 ACQTM 1.219 sec
 PD 1.781 sec
 PW1 6.0 us
 IRNUH
 CTEMP 23.2 c
 SLVCDCL3
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 25

3-Hydroxy-1,4-bis(4-methoxyphenyl)-2-butanone
3 (R = *p*-MeO-PhCH₂)

DFILE:WINDOWS\PROFILES\AKIRAS\,
 COMPMcOBn_product_1H
 DATE: Jul 05 10:50:43 2002
 OBNMBC
 EXMBCOM
 OBFREQ 395.75 MHz
 OBSET 124.00 KHz
 OBFIN 10277.0 Hz
 POINT 32768
 FREQ 7917.6 Hz
 SCANS 8
 ACQTM 4.139 sec
 PD 2.861 sec
 PW1 6.0 us
 IRNUH
 CTEMP 24.4 c
 SLVCDCL3
 EXREF 0.00 ppm
 BF 0.12 Hz
 RGAIN 21

R = *p*-MeO-PhCH₂

¹H NMR
 400 MHz
 CDCl₃

DFILE:WINDOWS\PROFILES\AKIRAS\,
 COMPMcOBn_product_13C
 DATE: Jul 19 08:50:40 2002
 OBNMBC
 EXMBCOM
 OBFREQ 99.45 MHz
 OBSET 94.00 KHz
 OBFIN 10309.0 Hz
 POINT 32768
 FREQ 26881.7 Hz
 SCANS 495
 ACQTM 1.219 sec
 PD 1.781 sec
 PW1 6.0 us
 IRNUH
 CTEMP 25.5 c
 SLVCDCL3
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 23

R = *p*-MeO-PhCH₂

¹³C NMR
 100 MHz
 CDCl₃

6-Hydroxy-2,9-dimethyl-2,8-decadien-5-one
3 (R = (CH₃)₂C=CH₂)

D:\FILE\WINDOWS\PROFILES\AKIRAS\COMPM\prenyl_product_1H
 DATE: May 28 20:42:39 2002
 OBNUEC
 EXMBOM
 OBFREQ 395.75 MHz
 OBSET 124.00 KHz
 OBFIN 10277.0 Hz
 POINT 32768
 FREQ 7917.6 Hz
 SCANS 8
 ACQTM 4.139 sec
 PD 2.861 sec
 PW1 6.0 us
 IRNUH
 CTEMP 20.5 c
 SLVCDCL3
 EXREF 0.00 ppm
 BF 0.12 Hz
 RGAIN 19

R = (CH₃)₂C=CHCH₂

¹H NMR
 400 MHz
 CDCl₃

D:\FILE\WINDOWS\PROFILES\AKIRAS\COMPM\prenyl_product_13C
 DATE: Jul 18 09:33:09 2002
 OBNUEC
 EXMBOM
 OBFREQ 99.45 MHz
 OBSET 94.00 KHz
 OBFIN 10309.0 Hz
 POINT 32768
 FREQ 26881.7 Hz
 SCANS 1024
 ACQTM 1.219 sec
 PD 1.781 sec
 PW1 6.0 us
 IRNUH
 CTEMP 27.4 c
 SLVCDCL3
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 25

R = (CH₃)₂C=CHCH₂

¹³C NMR
 100 MHz
 CDCl₃

5-Hydroxy-1,8-diphenyl-1,7-octadien-4-one
3 (R = PhCH=CHCH₂)

(2*S*,3*R*)-3-[(1-naphthylmethyl)amino]-1,4-diphenyl-2-butanol **5**

FILE: WINDOWS\PROFILES\AKIRAS.
 COMNT: Aminolcohol 1H
 DATIM: Med Jan 29 10:18:46 2003
 OBNUIC
 EXMNON
 OBFRQ 399.65 MHz
 OBSET 124.00 KHz
 OBFIN 10500.0 Hz
 POINT 32768
 FREQU 8000.0 Hz
 SCANS 16
 ACQTM 2.000 sec
 PD 1.500 sec
 PW1 6.8 us
 IRNLUH
 CTEMP 22.9 c
 SLVNCDC13
 EXREF 0.00 ppm
 BF 1.20 Hz
 RGAIN 23

¹H NMR
 400 MHz
 CDCl₃

FILE: WINDOWS\PROFILES\AKIRAS.
 COMNT: Aminolcohol 13C
 DATIM: Med Jan 29 11:11:19 2003
 OBNUIC
 EXMNON
 OBFRQ 100.40 MHz
 OBSET 125.00 KHz
 OBFIN 10500.0 Hz
 POINT 32768
 FREQU 27173.9 Hz
 SCANS 1024
 ACQTM 1.206 sec
 PD 1.794 sec
 PW1 5.5 us
 IRNLUH
 CTEMP 22.3 c
 SLVNCDC13
 EXREF 77.00 ppm
 BF 1.20 Hz
 RGAIN 32

¹³C NMR
 100 MHz
 CDCl₃