Supporting Infomation

Asymmetric Synthesis of *anti*-α,β-Disubstituted β-Amino Acid Derivatives by Reaction of *N*-Alkoxycarbonyl-1-methoxyamines with Optically Active 2-Oxazolidinones

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General: IR spectra were recorded with a Hitachi 215 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a JEOL GX-270 spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Optical rotations were recorded with a Jasco DIP-360 digital polarimeter. Column chromatography was performed on silica gel 60 (Merck).

***N*-Alkoxycarbonyl-1-methoxyamines 1a and 1b** were prepared from corresponding *N*-alkoxycarbonyamines by anodic oxidation in methanol.[3]

1b: R_f 0.5 (hexane-ethyl acetate, 5:1); IR (neat) 3350, 1700, 715, 700 cm^{-1}; ^{1}H NMR δ 1.09 (s, 9 H), 1.49 (s, 9 H), 1.69-2.02 (m, 2 H), 3.38 (s, 3 H), 3.63-3.76 (m, 1 H), 3.90-4.06 (m, 1 H), 5.01-5.14 (m, 1 H), 5.99 (d, 1 H, J = 9.0 Hz), 7.34-7.50 (m, 6 H), 7.62-7.77 (m, 4 H); ^{13}C NMR δ 18.8 (s), 26.6 (q), 28.2 (q), 36.4 (t), 55.2 (q), 59.8 (t), 79.3 (s), 80.7 (d), 127.8 (d), 129.8 (d), 133.3 (s), 135.9 (d), 155.8 (s). Anal. Calcd for $C_{25}H_{37}NO_4Si$: C, 67.68; H, 8.41; N, 3.16. Found: C, 67.70; H, 8.36; N, 3.01.

Typical procedure for the reaction of 1 with 5. A mixture of **1b** (0.89g, 2 mmol) and **5** (0.44g, 2.2 mmol) in THF (3 mL) was added to a solution of LDA (4.5 mmol) in THF-hexane (6 mL) at -70 ˚C. After stirring for 15 min, $TiCl_4$ (0.24 mL, 2.2 mmol) was added to the mixture. After being stirred for 3 hr at this temperature, the mixture was diluted with water (20 mL), neutralized with sat. $NaHCO_3$ aq, filtered, and then extracted with CH_2Cl_2 (3 X 10 mL). The product **7** was isolated as a 80:20 mixture of two diastereomers (by ^{1}H NMR analysis) by column chromatography on silica gel (hexane-ethyl acetate = 5:1) in 86% yield.

3 (50:50 mixture of two diastereomers): R_f 0.25 (hexane-ethyl acetate, 5:1); IR (neat) 3300, 1715, 1655 cm^{-1}; ^{1}H NMR δ 0.85-1.02 (m, 15 H), 1.47-1.86 (m, 4 H), 2.56-2.69 (m, 1 H), 3.45-3.60 (m, 1 H), 3.67 (s, 3 H), 3.82-3.98 (m, 2 H), 4.10-4.28 (m, 1 H), 5.94 (d, 0.5 H, J = 9.6 Hz), 6.04 (d, 0.5 H, J = 10.1 Hz); ^{13}C NMR δ 11.6 (q), 17.9 (q), 18.0 (q), 18.4 (q), 18.6 (q), 19.1 (q), 19.5 (q), 19.6 (q), 24.1 (t), 24.2 (t), 31.8 (d), 32.2 (d), 32.3 (d), 41.5 (d), 41.7 (d), 51.6 (q), 57.3 (d), 69.1 (t), 71.5 (d), 71.8 (d), 157.5 (s), 167.9 (s), 168.1 (s).

***anti*-6**: R_f 0.5 (hexane-ethyl acetate, 2:1); IR (neat) 3380, 1760, 1700 cm^{-1}; ^{1}H NMR δ 0.82-1.03 (m, 15 H), 1.50-1.78 (m, 3 H), 2.23-2.47 (m, 1 H), 3.66 (s, 3 H), 3.60-3.77 (m, 1 H), 4.07-4.60 (m, 4 H), 5.78 (d, 1 H, J = 10.6 Hz); ^{13}C NMR δ 11.2 (q), 13.9 (q), 17.5 (q), 18.2 (q), 19.5 (q), 23.6 (t), 28.2 (d), 31.2 (d), 44.2 (d), 51.6 (q), 57.3 (d), 58.4 (d), 62.8 (t), 153.9 (s), 157.2 (s), 178.3 (s).

***syn*-6**: R_f 0.4 (hexane-ethyl acetate, 2:1); IR (neat) 3320, 1760, 1695 cm^{-1}; ^{1}H NMR δ 0.82-1.02 (m, 15 H), 1.50-1.83 (m, 3 H), 2.25-2.45 (m, 1 H), 3.65 (s, 3 H), 3.65-3.75 (m, 1 H), 3.90-4.12 (m, 1

H), 4.15-4.33 (m, 2 H), 4.38-4.60 (m, 2 H); ^{13}C NMR δ 11.1 (q), 14.1 (q), 17.0 (q), 17.8 (q), 19.7 (q), 20.8 (t), 28.1 (d), 30.7 (d), 46.3 (d), 51.9 (q), 57.2 (d), 58.4 (d), 62.9 (t), 154.0 (s), 157.3 (s), 174.3 (s).

7 (80:20 mixture of two diastereomers): R_f 0.3 (hexane-ethyl acetate, 5:1); IR (neat) 3380, 1775, 1705, 1690 cm^{-1}; ^{1}H NMR δ 0.80-1.00 (m, 9 H), 1.04 (s, 9 H), 1.37 (s, 9 H), 1.55-1.95 (m, 4 H), 2.25-2.45 (m, 1 H), 3.60-3.85 (m, 1 H), 3.96-4.10 (m, 1 H), 4.16-4.32 (m, 2 H), 4.40-4.50 (m, 1 H), 5.38 (d, 0.8 H, *J* = 9.3 Hz), 7.32-7.48 (m, 6 H), 7.63-7.73 (m, 4 H); ^{13}C NMR (major) δ 11.3 (q), 14.3 (q), 17.7 (s), 18.8 (s), 26.5 (q), 28.0 (q), 37.1 (t), 47.0 (d), 48.2 (d), 58.5 (d), 60.7 (t), 62.9 (t), 78.5 (s), 127.6 (d), 129.6 (d), 133.7 (s), 133.8 (s), 135.6 (d), 153.9 (s), 155.7 (s), 176.2 (s).

Transformation of 6 to 4. To an ice cooled solution of **6** (328 mg, 1 mmol) in THF (4 mL) and H_2O (1 mL) was added LiOH•H_2O (168 mg, 4 mmol) and 30% H_2O_2 (1 mL) successively. The mixture was stirred for 24 h at 25 ˚C and then quenched with 1.5 M Na_2SO_3 (4 mL) at 0 ˚C. After addition of 1 M HCl (10 mL), the mixture was extracted with CH_2Cl_2. The crude acid was dissolved in sat. HCl-MeOH and the solution was stirred for 12 h at 25 ˚C. After removal of the solvent, The two diastereomers of **4** were isolated by column chromatography on silica gel (hexane-ethyl acetate = 10:1) in 64% (anti) and 14% (syn) yields.. Each isomer of **4** was determined to be >98% ee by ^{1}H NMR analysis with Eu(hfc)$_3$.

***anti*-4**: R_f 0.35 (hexane-ethyl acetate, 5:1); $[\alpha]^{20}_D$ +46.9 (*c* 2.09, $CHCl_3$); IR (neat) 3430, 1720 cm^{-1}; ^{1}H NMR δ 0.87-1.00 (m, 9 H), 1.46-1.79 (m, 3 H), 2.55-2.68 (m, 1 H), 3.47-3.60 (m, 1 H), 3.67 (s, 3 H), 3.69 (s, 3 H), 5.05 (d, 1 H, *J* = 10.2 Hz); ^{13}C NMR δ 11.6 (q), 18.9 (q), 19.5 (q), 23.5 (t), 31.9 (d), 47.7 (d), 51.2 (q), 51.8 (q), 57.2 (d), 157.5 (s), 176.0 (s). Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.42; H, 9.44; N, 5.83.

***syn*-4**: R_f 0.25 (hexane-ethyl acetate, 5:1); $[\alpha]^{20}_D$ +12.9 (*c* 1.67, $CHCl_3$); IR (KBr) 3340, 1730, 1695 cm^{-1}; ^{1}H NMR δ 0.83-0.97 (m, 9 H), 1.55-1.79 (m, 3 H), 2.33-2.46 (m, 1 H), 3.67 (s, 3 H), 3.70 (s, 3 H), 3.78-3.90 (m, 1 H), 4.50 (d, 1 H, *J* = 10.9 Hz); ^{13}C NMR δ 11.6 (q), 15.9 (q), 20.0 (q), 21.5 (t), 30.1 (d), 50.7 (d), 51.3 (q), 51.9 (q), 57.1 (d), 157.4 (s), 174.7 (s). Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 56.86; H, 9.14; N, 5.88.

Transformation of 7 to 8. To an ice cooled solution of **7** (0.61 g, 1 mmol) in THF (4 mL) and H_2O (1 mL) was added LiOH•H_2O (0.17 g, 4 mmol) and 30% H_2O_2 (1 mL) successively. The mixture was stirred for 24 h at 25 ˚C and the solvent was removed *in vacuo*. To the residue were added DMF (5 mL) and MeI (0.5 mL), and the suspension was stirred for 8 h at 25 ˚C. After addition of sat. NH_4Cl aq (10 mL), the mixture was extracted with Et_2O. The two diastereomers of **8** were isolated by column chromatography on silica gel (hexane-ethyl acetate = 10:1) in 60% (anti) and 15% (syn) yields.

(2*R*,3*R*)-8: R_f 0.55 (hexane-ethyl acetate, 5:1); $[\alpha]^{20}_D$ +6.5 (*c* 2.20, $CHCl_3$); ^{1}H NMR δ 0.93 (t, 3 H, *J* = 7.3 Hz), 1.05 (s, 9 H), 1.41 (s, 9 H), 1.48-1.82 (m, 4 H), 2.49-2.60 (m, 1 H), 3.66 (s, 3 H), 3.60-3.81 (m, 2 H), 3.92-4.08 (m, 1 H), 5.25 (d, 1 H, *J* = 9.9 Hz), 7.32-7.48 (m, 6 H), 7.63-7.70 (m, 4H); ^{13}C NMR δ 11.9 (q), 18.9 (s), 22.5 (t), 26.6 (q), 28.2 (q), 36.5 (t), 48.5 (d), 50.5 (d), 51.4 (q),

61.1 (t), 78.8 (s), 127.8 (d), 129.7 (d), 133.7 (s), 133.8 (s), 135.7 (d), 155.8 (s), 175.8 (s). Anal. Calcd for $C_{29}H_{43}NO_5Si$: C, 67.80; H, 8.44; N, 2.73. Found: C, 67.65; H, 8.39; N, 2.66.

(2*R*,3*S*)-8: R_f 0.45 (hexane-ethyl acetate, 5:1); $[\alpha]^{20}_D$ -11.4 (*c* 1.80, $CHCl_3$); ^{1}H NMR δ 0.92 (t, 3 H, *J* = 7.4 Hz), 1.05 (s, 9 H), 1.42 (s, 9 H), 1.40-1.90 (m, 4 H), 2.49-2.63 (m, 1 H), 3.67 (s, 3 H), 3.60-3.86 (m, 2 H), 3.91-4.07 (m, 1 H), 5.00 (d, 1 H, *J* = 9.1 Hz), 7.34-7.50 (m, 6 H), 7.63-7.70 (m, 4 H); ^{13}C NMR δ 11.9 (q), 18.9 (s), 21.8 (t), 26.6 (q), 28.2 (q), 33.9 (t), 49.6 (d), 51.4 (q), 51.7 (d), 61.0 (t), 79.0 (s), 122.8 (d), 129.8 (d), 133.5 (s), 134.9 (s), 135.7 (d), 155.7 (s), 174.8 (s). Anal. Calcd for $C_{29}H_{43}NO_5Si$: C, 67.80; H, 8.44; N, 2.73. Found: C, 67.73; H, 8.46; N, 2.68.

Decarbamation of (2*R*,3*R*)-8 (1 mmol) was accomplished by the treatment with TFA (5 mL) at 0 ˚C for 30 min. After usual work-up, the obtained amine was subjected to cyclization without purification.

Preparation of (3*R*,4*R*)-9: A solution of the amine obtained from **(2*R*,3*R*)-8** (1 mmol) in THF (3 mL) was added to a solution of LDA (1.5 mmol) in THF-hexane (5 mL) at 0 ˚C. The mixture was stirred for 2 hr at this temperature until almost all of the starting amine was consumed (checked by TLC). The mixture was diluted with 1 M NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 X 10 mL). The product **(3*R*,4*R*)-9** was isolated by column chromatography on silica gel (hexane-ethyl acetate) in a 78% yield.

(3*R*,4*R*)-9: R_f 0.35 (hexane-ethyl acetate, 2:1); $[\alpha]^{20}_D$ +11.1 (*c* 2.00, $CHCl_3$); IR (neat) 3270, 1750, 695 cm^{-1}; ^{1}H NMR δ 1.00 (t, 3 H, *J* = 7.5 Hz), 1.06 (s, 9 H), 1.67-1.90 (m, 4 H), 2.70-2.80 (m, 1 H), 3.42-3.51 (m, 1 H), 5.79 (brs, 1 H), 7.36-7.52 (m, 6 H), 7.60-7.70 (m, 4 H); ^{13}C NMR δ 11.1 (q), 18.8 (s), 21.1 (t), 26.6 (q), 37.3 (t), 52.4 (d), 58.2 (d), 61.6 (t), 127.8 (d), 129.9 (d), 133.3 (s), 135.6 (d), 171.2 (s). Anal. Calcd for $C_{23}H_{31}NO_2Si$: C, 72.39; H, 8.19; N, 3.67. Found: C, 72.40; H, 8.08; N, 3.61.

Preparation of (3*R*,4*R*)-10: Desilylation and subsequent *tert*-butyldimethylsilylation of **(3*R*, 4*R*)-9** were carried out by the usual methods with TBAF/THF and TBDMSCl/Et_3N/DMF, respectively.

(3*R*,4*R*)-10: $[\alpha]^{20}_D$ -39.3 (c 1.62, $CHCl_3$) (Lit.[6b] -39.59).

Epimerization of (2*R*,3*R*)-8: A solution of **(2*R*,3*R*)-8** (128 mg, 0.25 mmol) and TBAF (0.25 mmol) in THF (5 mL) was stirred for 6 h at 25 ˚C and the solvent was removed *in vacuo*. To the residue was added $NaHCO_3$ (50 mg) and MeOH (5 mL) and the mixture was stirred for 2 h at 25 ˚C. The solvent was removed and the residue was extracted with CH_2Cl_2 (20 mL). After evaporation of the solvent, the residue was dissolved in DMF (2 mL). To the solution were added TBDMSCl (0.3 mmol) and imidazole (0.3 mmol) successively at 0 ˚C. The mixture was stirred for 6 h at 25˚C, diluted with H_2O (10 mL), and extracted with CH_2Cl_2. The product **(2*S*,3*R*)-8** (25 mg) was isolated by column chromatography on silica gel.

(2*S*,3*R*)-8: $[\alpha]^{20}_D$ +11.5 (*c* 1.00, $CHCl_3$).