Synthesis of Different Chiral Amino γ -Butyrolactones and Amino γ -Butenolides

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EXPERIMENTAL PROCEDURE FOR THE SYNTHESIS OF 6 FROM AZETIDINIUM SALTS

To a solution of the corresponding azetidinium salt **7** (1 mmol) in acetonitrile (2 mL) was added KI (1.7 g, 10 mmol). The mixture was stirred at reflux temperature for 24 h. Then, the reaction was hydrolyzed and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Flash column chromatography (silica gel, hexane:ethyl acetate = 5:1) provided pure compound **6**.

SPECTROSCOPIC DATA OF COMPOUNDS 2

(–)-(4R,1'S)-4-[1'-(Dibenzylamino)ethyl]-4-hydroxyoxolan-2-one (**2a**): R_f = 0.21 (hexane/ethyl acetate 5/1); $[\alpha]_D^{20}$ = –1.6 (c 0.56, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 7.39–7.28 (10 H, m), 4.52 (1 H, s), 4.08 (2 H, AB syst., J = 9.7), 3.63 (2 x 2 H, AB syst., J = 13.2), 2.82 (1 H, q, J = 6.9), 2.50 (2 H, AB syst., J = 17.4), 1.20 (3 H, d, J = 6.9); ^{13}C NMR (CDCl_3 , 75 MHz) δ 175.9 (C), 138.5 (C), 128.8, 128.5, and 127.4 (3 x CH), 78.4 (CH_2), 78.3 (C), 56.7 (CH), 54.7 (CH_2), 40.0 (CH_2), 7.0 (CH_3); IR (neat) 3444, 1773; HRMS Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_2$ ($\text{M} - \text{H}_2\text{O}^+$) 307.1572, found 307.1550.

(–)-(4R,1'S)-4-[1'-(Dibenzylamino)-3'-(methyl)butyl]-4-hydroxyoxolan-2-one (**2b**): R_f = 0.34 (hexane/ethyl acetate 5/1); $[\alpha]_D^{20}$ = –23.0 (c 0.56, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 7.36–7.25 (10 H, m), 4.41 (1 H, s), 4.05 (2 H, AB syst., J = 10.0), 3.72 (2 x 2 H, AB syst., J = 13.4), 2.82 (1 H, t, J = 6.1), 2.44 (2 H, AB syst., J = 17.2), 1.90–1.77 (2 H, m), 1.38–1.24 (1 H, m), 1.02 (6 H, d, J = 5.1); ^{13}C NMR (CDCl_3 , 75 MHz) δ 175.9 (C), 138.7 (C), 128.9, 128.5, and 127.5 (3 x CH), 78.8 (CH_2), 78.3 (C), 58.9 (CH), 55.4 (CH_2), 40.4 (CH_2), 35.0 (CH_2), 25.8 (CH), 23.2 (CH_3), 22.7 (CH_3); IR (neat) 3444, 1770; HRMS Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_3$ 367.2147, found 367.2130.

(+)-(4R,1'S)-4-[1'-(Dibenzylamino)-2'-(phenyl)ethyl]-4-hydroxyoxolan-2-one (**2c**): R_f = 0.37 (hexane/ethyl acetate 3/1); $[\alpha]_D^{20}$ = +5.0 (c 0.49, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 7.39–7.21 (15 H, m), 4.10 (2 H, AB syst., J = 10.2), 3.64 (2 x 2 H, AB syst., J = 13.4), 3.28 (1 H, dd, J = 12.8, 4.0), 3.05–2.92 (2 H, m), 2.01 (2 H, AB syst., J = 17.6); ^{13}C NMR (CDCl_3 , 75 MHz) δ 176.1 (C), 139.2 and 138.9 (2 x C), 129.0, 128.8, 128.5, 127.4 and 126.7 (5 x CH), 79.4 (CH_2), 79.4 (C), 63.9 (CH), 55.2 (CH_2), 42.2 (CH_2), 29.8 (CH_2); IR (neat) 3454, 1778; HRMS Calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_3$ 401.1991, found 401.1990.

(+)-(4R,1'S)-4-[1'-(Dibenzylamino)-3'-(methyl)butyl]-4-hydroxy-3,3-dimethyloxolan-2-one (**2d**): R_f = 0.40 (hexane/ethyl acetate 3/1); $[\alpha]_D^{20}$ = +14.7 (c 0.72, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 7.40–7.08 (10 H, m), 6.2 (1 H, s), 4.14 (2 H, AB syst., J = 9.4), 3.89 (2 H, t, J = 13.9), 3.64 (2 H, dd, J = 13.0, 5.3), 3.13 (1 H, dd, J = 12.0, 2.3), 2.05–1.93 (2 H, m), 1.38–1.21 (1 H, m), 1.11 (3 H, d, J = 6.6), 1.08 (3 H, d, J = 6.6), 0.87 (3 H, s), 0.76 (3 H, s); ^{13}C NMR (CDCl_3 , 75 MHz) δ 180.9 (C), 138.0, and 137.6 (2 x C), 129.3, 129.2, 128.6, 128.4, 127.8, and 127.6 (6 x CH), 77.1 (C), 73.3 (CH_2), 57.2 (CH_2), 55.7 (CH), 54.0 (CH_2), 45.3 (C), 37.7 (CH_2), 25.7 (CH), 24.3 (CH_3), 21.2 (CH_3), 19.6 (CH_3), 18.6 (CH_3); IR (neat) 3453, 1780; HRMS Calcd for $\text{C}_{25}\text{H}_{33}\text{NO}_3$ 395.2460, found 395.2466.

SPECTROSCOPIC DATA OF COMPOUNDS 6

(+)-(4S,5R)-4-[(Dibenzylamino)methyl]-4-hydroxy-5-methyloxolan-2-one (6a): $R_f = 0.28$ (hexane/ethyl acetate 3/1); $[\alpha]_D^{20} = +7.2$ (c 0.74, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.39-7.27 (10 H, m), 4.12 (1 H, q, $J = 6.3$), 3.97 (1 H, s), 3.67 (2 x 2 H, AB syst., $J = 13.2$), 2.65 (2 H, AB syst., $J = 14.0$), 2.48 (2 H, AB syst., $J = 17.1$), 1.04 (3 H, d, $J = 6.3$); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 175.1 (C), 137.8 (C), 128.9, 128.4, and 127.5 (3 x CH), 82.5 (CH), 75.2 (C), 59.5 (CH_2), 56.9 (CH_2), 43.5 (CH_2), 12.0 (CH_3); IR (neat) 3404, 1774; HRMS Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_3$ 325.1678, found 325.1675.

(+)-(4S,5R)-4-[(Dibenzylamino)methyl]-4-hydroxy-5-iso-butyloxolan-2-one (6b): $R_f = 0.25$ (hexane/ethyl acetate 3/1); $[\alpha]_D^{20} = +14.0$ (c 0.82, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 200 MHz) δ 7.43-7.28 (10 H, m), 4.06 (1 H, s), 3.98 (1 H, dd, $J = 9.6, 2.2$), 3.69 (2 x 2 H, AB syst., $J = 13.2$), 2.64 (2 H, AB syst., $J = 13.8$), 2.47 (2 H, AB syst., $J = 17.0$), 1.66-1.50 (3 H, m), 0.84 (3 H, d, $J = 6.4$), 0.76 (3 H, d, $J = 6.4$); $^{13}\text{C NMR}$ (CDCl_3 , 50 MHz) δ 175.2 (C), 137.6 (C), 129.1, 128.7, and 127.8 (3 x CH), 85.0 (CH), 74.8 (C), 59.6 (CH_2), 57.2 (CH_2), 44.5 (CH_2), 36.1 (CH_2), 24.9 (CH), 23.1 (CH_3), 21.6 (CH_3); IR (neat) 3322, 1772. Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.09; H, 7.98; N, 3.79.

(+)-(4S,5R)-5-Benzyl-4-[(dibenzylamino)methyl]-4-hydroxyoxolan-2-one (6c): $R_f = 0.18$ (hexane/ethyl acetate 3/1); $[\alpha]_D^{20} = +13.5$ (c 1.22, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.41-7.11 (15 H, m), 4.20 (1 H, s), 4.15 (1 H, dd, $J = 8.7, 3.8$), 3.65 (2 x 2 H, AB syst., $J = 13.2$), 2.96 (1 H, dd, $J = 14.9, 8.7$), 2.63 (2 H, AB syst., $J = 14.0$), 2.54-2.39 (3 H, m); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) 174.6 (C), 137.6, and 137.5 (2 x C), 129.1, 129.0, 128.7, 128.4, 127.8, and 126.5 (6 x CH), 87.2 (CH), 74.9 (C), 59.4 (CH_2), 57.6 (CH_2), 44.4 (CH_2), 34.1 (CH_2); IR (neat) 3453, 1780; HRMS Calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_3$ 401.1991, found 401.1972.

(3S,4S,5R)-3-Benzyl-4-[(dibenzylamino)methyl]-4-hydroxy-5-methyloxolan-2-one (6d): $R_f = 0.26$ (hexane/ethyl acetate 3/1); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.38-7.19 (15 H, m), 4.22 (1 H, q, $J = 6.3$), 3.46 (2 x 2 H, AB syst., $J = 14.0$), 3.09 (1 H, dd, $J = 14.2, 5.1$), 2.79 (1 H, dd, $J = 14.2, 7.4$), 2.70 (1 H, dd, $J = 7.4, 5.1$), 2.55 (2 H, AB syst., $J = 14.5$), 1.18 (3 H, d, $J = 6.3$); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 176.7 (C), 139.5 (C), 137.6 (C), 129.1, 128.8, 128.5, 128.4, 127.5, and 126.3, 81.9 (CH), 77.8 (C), 59.6 (CH_2), 58.1 (CH_2), 50.1 (CH), 29.7 (CH_2), 13.2 (CH_3); IR (neat) 3423, 1781.

SPECTROSCOPIC DATA OF COMPOUND 8

(-)-(1'S)-4-[1'-(Dibenzylamino)ethyl]-5H-furan-2-one (8a): $R_f = 0.32$ (hexane/ethyl acetate 3/1); $[\alpha]_D^{20} = -77.3$ (c 0.51, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.44-7.26 (10 H, m), 5.96 (1 H, d, $J = 1.7$), 5.12 (1 H, dd, $J = 17.9, 1.7$), 4.70 (1 H, d, $J = 17.9$), 3.70 (1 H, q, $J = 6.5$), 3.60 (2 x 2 H, AB syst., $J = 14.0$), 1.35 (3 H, d, $J = 6.5$); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 173.6 (C), 173.5 (C), 138.6 (C), 128.4, 128.1, and 127.2 (3 x CH), 116.5 (CH), 72.7 (CH_2), 53.5 (CH_2), 51.6 (CH), 9.1 (CH_3); IR (neat) 1781, 1754, 1638; HRMS Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_2$ 307.1572, found 307.1572.

(-)-(1'S)-4-[1'-(Dibenzylamino)-3'-(methyl)butyl]-5H-furan-2-one (8b): $R_f = 0.50$ (hexane/ethyl acetate 3/1); $[\alpha]_D^{20} = -88.6$ (c 0.57, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.38-7.27 (10 H, m), 5.94 (1 H, d, $J = 1.8$), 5.12 (1 H, dd, $J = 17.5, 1.8$), 4.66 (1 H, d, $J = 17.5$), 3.64-3.51 (5 H, m), 1.78-1.73 (1 H, m), 1.62-1.55 (2 H, m), 0.91 (3 H, d, $J = 5.3$), 0.84 (3 H, d, $J = 5.3$); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 173.5 (C), 171.1 (C), 138.7 (C), 128.4 (CH), 127.2 (CH), 116.9 (CH), 73.1 (CH_2), 54.2 (CH), 53.7 (CH_2), 35.6 (CH_2), 25.2 (CH), 23.1 (CH_3), 22.2 (CH_3); IR (neat) 1779, 1757, 1632. Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 79.27; H, 7.78; N, 4.03.

(-)-(1'S)-4-[1'-(Dibenzylamino)-2'-(phenyl)ethyl]-5H-furan-2-one (8c): $R_f = 0.36$ (hexane/ethyl acetate 3/1); $[\alpha]_D^{20} = -44.7$ (c 0.64, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 7.41-7.09 (15 H, m), 6.01 (1 H, d, $J = 0.9$), 5.04 (1 H, dd, $J = 17.4, 0.9$), 4.56 (1 H, d, $J = 17.4$), 3.92 (1 H, dd, $J = 9.2, 4.8$), 3.72 (2 x 2 H, AB syst., $J = 13.5$), 3.41 (1 H, dd, $J = 14.0, 4.8$), 2.93 (1 H, dd, $J = 14.0, 9.2$); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 173.5 (C), 170.5 (C), 138.4, and 137.9 (2 x C), 128.7, 128.6, 128.5, 128.3, 127.4, and 126.6 (6 x CH), 117.6 (CH), 73.1 (CH_2), 57.8 (CH), 53.8 (CH_2), 32.5 (CH_2); IR (neat) 1781, 1753, 1635; HRMS Calcd for $\text{C}_{26}\text{H}_{25}\text{NO}_2$ 383.1885, found 383.1897. Chiral HPLC analysis: ee >99% (Chiralcel OD-RH, UV detector 210 nm, 0.5 mL/min, 85:15 acetonitrile/water, t_R 13.2 min).

¹³C NMR SPECTRA

NOESY ^1H NMR SPECTRA