One-pot Catalytic Asymmetric Synthesis of Pyranones

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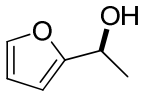
Supporting Information

I. General Methods. All reactions were carried out under a nitrogen atmosphere with oven-dried glassware. The progress of all reactions was monitored by thin-layer chromatography to ensure the reactions had reached completion. All manipulations involving dialkylzinc reagents were carried out using an inert atmosphere in a Vacuum Atmosphere drybox with an attached MO-40 Dritrain or by using standard Schlenk or vacuum line techniques. Dichloromethane and hexanes were dried through alumina columns. All aldehydes were distilled prior to use and stored under N_2. Unless otherwise specified, all chemicals were obtained from Acros, Aldrich, or GFS Chemicals, and all solvents were purchased from Fischer Scientific. The ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectra were obtained on a Bruker AM-500 Fourier transform NMR spectrometer at 500 and 125 MHz, respectively. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane, and all coupling constants are reported in Hertz. The infrared spectra were obtained using a Perkin-Elmer 1600 series spectrometer. Thin-layer chromatography was performed on Whatman precoated silica gel 60 F-254 plates and visualized by ultra-violet light or by staining with ceric ammonium molybdate stain. Silica gel (230-400

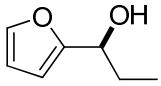
mesh, Silicycle) was used for air-flashed chromatography. Silica gel treated with triethylamine (deactivated silica gel) was prepared by mixing 20 mL of triethyl amine with 800 mL of silica. Analysis of enantiomeric excess was performed using a Hewlett-Packard 1050 or 1100 Series HPLC and a Chiralcel OD-H column or by chiral capillary gas chromatography on a Hewlett-Packard 6890 GC with a Beta-DEX column. High resolution mass spectra were measured using a Waters 2695 Separations Module. Absolute configuration was determined by comparison of optical rotation to literature data for known compounds. $Zn[(CH_2)_4OTBS]_2$ was prepared by the method of Knochel[1] (see page S13). Cautionary note: care should be used in the handling of pyrophoric dialkylzinc reagents.

II. Synthesis and Characterization of Enantioenriched Furyl Alcohols

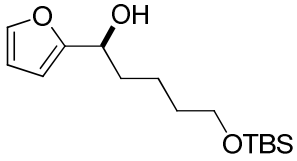


General Procedure A. (1a) (*S*)-1-Furan-2-yl-ethan-1-ol. A 10 mL Schlenk flask was charged with (–)-MIB (4 mg, 0.016 mmol) and purged with dinitrogen. Hexanes (1 mL) was added followed by $ZnMe_2$ (0.4 mL, 2M solution in hexanes, 0.8 mmol). The reaction mixture was cooled to 0 ^oC and 2-furfural (33 μL, 0.4 mmol) was added dropwise. The reaction mixture was stirred at 0 ^oC for 8 h and quenched with saturated aq NH_4Cl. The organic and aqueous layers were separated, and the aqueous layer was extracted with Et_2O (3 X 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica treated with triethylamine (10% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 80% yield (36 mg, 0.32 mmol). $[\alpha]_D^{20}$ = -18.8 (*c* = 0.021 M, $CHCl_3$, 94% ee); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37 (m, 1H), 6.33 (m, 1H), 6.23 (m, 1H), 4.89 (q, *J* = 6.6 Hz, 1H), 1.94 (br, 1H), and 1.55 (d,

3H, *J* = 6.5 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 157.6, 141.9, 110.1, 105.1, 63.7, and 21.3; IR (neat) 3384, 2930, 1505, 1371, 1230, 1150, and 1068 cm^{-1}. HRMS-ESI neg *m/z* 111.0444 [M-H^+; calcd for $C_6H_8O_2$: 111.0446]. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra for this compound match with previously reported literature data.[2]

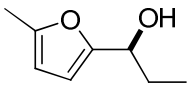


(2a) (*S*)-1–Furan-2-yl-propan-1-ol. The product was prepared by General Procedure A using $ZnEt_2$ (0.4 mL, 2M solution in hexanes, 0.8 mmol), (–)-MIB (4 mg, 0.016 mmol), 2-furfural (33 μL, 0.4 mmol), and 1.0 mL hexanes. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica treated with triethylamine (10% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 98% yield (49 mg, 0.39 mmol). $[\alpha]_D^{20}$ = -19.0 (*c* = 0.033 M, $CHCl_3$, 97% ee); ^{1}H NMR ($CDCl_3$, 500 MHz) δ **7**.37 (m, 1H), 6.33 (m, 1H), 6.23 (d, 1H, *J* = 3.2 Hz), 4.61 (t, 1H, *J* = 6.6 Hz), 1.98 (s, 1H), 1.88 (m, 2H), and 0.96 (t, 3H, *J* = 7.4 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 156.7, 141.9, 110.1, 105.8, 69.2, 28.6, and 9.9; IR (neat) 3376, 2964, 2935, 2878, 1504, 1455, 1402, 1288, 1224, 1150, 1112, and 1068 cm^{-1}. HRMS-ESI neg *m/z* 125.0601 [M-H^+; calcd for $C_7H_{10}O_2$: 125.0603]. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra for this compound match with previously reported literature data.[3]



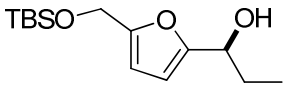
(3a) (*S*)-5-(*tert*-Butyldimethylsilyloxy)-1-(furan-2-yl)-pentan-1-ol. The product was prepared by General Procedure A using $Zn[(CH_2)_4OTBS]_2$ (1.6 mL, 1M solution in hexanes, 1.6 mmol,

prepared by the method of Knochel[1]), (–)-MIB (8 mg, 0.032 mmol), 2-furfural (35 μL, 0.35 mmol), and 1.0 mL hexanes. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica treated with triethylamine (10% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 91% yield (21 mg, 0.73 mmol). $[\alpha]_D^{20}$ = -6.9 (*c* = 0.066 M, $CHCl_3$, 95% ee); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (m, 1H), 6.32 (m, 1H), 6.23 (d, 1H, *J* = 3.3 Hz), 4.68 (t, 1H, *J* = 6.9 Hz), 3.61 (t, 2H, *J* = 7.4 Hz), 1.87 (m, 2H), 1.56 (m, 2H), 1.48 (m, 1H), 1.38 (m, 1H), 0.88 (s, 9H), and 0.04 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 156.8, 141.9, 110.1, 105.8, 67.8, 63.0, 35.3, 32.5, 26.0, 21.9, 18.3, and -5.3; IR (neat) 3361, 2930, 2858, 1597, 1505, 1472, 1463, 1388, 1361, 1255, 1148, and 1099 cm^{-1}. HRMS-ESI pos *m/z* 307.1696 [M+Na^+; calcd for $C_{15}H_{28}O_3Si$: 307.1705].

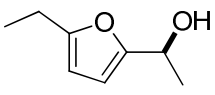


(4a) (*S*)-1-(5-Methyl-furan-2-yl)-propyn-1-ol. The product was prepared by General Procedure A using $ZnEt_2$ (0.7 mL, 1M solution in hexanes, 0.7 mmol), (–)-MIB (3 mg, 0.014 mmol), 5-methyl-2-furfural (35 μL, 0.35 mmol), and 1.0 mL hexanes. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica treated with triethylamine (10% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 85% yield (42 mg, 0.30 mmol). $[\alpha]_D^{20}$ = -12.8 (*c* = 0.041 M, $CHCl_3$, 91% ee); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.10 (d, 1H, *J* = 3.0 Hz), 5.90 (d, 1H, *J* = 3.0 Hz), 4.53 (t, 1H, *J* = 6.6 Hz), 2.3 (s, 3H), 1.85 (m, 2H), and 0.96 (t, 3H, *J* = 7.5 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 154.9, 151.6, 106.7, 105.9, 69.3, 28.5, 13.5, and 10.1; IR (neat) 3364, 2965, 2936, 2878, 1563, 1455, 1382, 1220, 1096, and 1020 cm^{-1}. HRMS-ESI neg *m/z* 139.0749 [M-H^+; calcd for

$C_8H_{12}O_2$: 139.0759]. ^{1}H NMR spectra for this compound matches with previously reported literature data.[4]

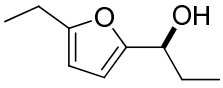


(5a) (*S*)-1-[5-(*tert*-Butyl-dimethylsilanyloxy)-furan-2-yl]-propan-1-ol. The product was prepared by General Procedure A using $ZnEt_2$ (0.33 mL, 1M solution in hexanes, 0.33 mmol), (–)-MIB (2 mg, 0.006 mmol), 5-*tert*-butyl-dimethylsilanyloxy-methyl-2-furfural (39 mg, 0.16 mmol), and 1.0 mL hexanes. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica treated with triethylamine (10% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 87% yield (38 mg, 0.14 mmol). $[\alpha]_D^{20}$ = -12.7 (*c* = 0.024 M, $CHCl_3$, 99% ee); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.16 (s, 2H), 4.62 (s, 2H), 4.57 (t, 1H, *J* = 6.2 Hz), 1.86 (m, 2H), 0.96 (t, 3H, *J* = 7.4 Hz), 0.90 (s, 9H), and 0.08 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 156.2, 153.7, 107.7, 106.5, 69.3, 58.2, 28.5, 25.8, 18.3, 9.9, and -5.2; IR (neat) 3376, 2958, 2931, 2883, 2858, 1727, 1560, 1463, 1371, 1255, 1191, and 1080 cm^{-1}. HRMS-ESI pos *m/z* 293.1540 [M+Na$^+$; calcd for $C_{14}H_{26}O_3Si$: 293.1549].

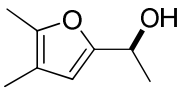


(6a) (*S*)-1-(5-Ethyl-furan-2-yl)-ethan-1-ol. The product was prepared by General Procedure A using $ZnMe_2$ (0.35 mL, 2M solution in hexanes, 0.7 mmol), (–)-MIB (3 mg, 0.014 mmol), 5-ethyl-2-furfural (43 μL, 0.35 mmol), and 1.0 mL hexanes. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica treated with triethylamine (10% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 83% yield (41 mg, 0.29 mmol). $[\alpha]_D^{20}$ = -7.9 (*c* = 0.041 M, $CHCl_3$, 97% ee); ^{1}H

NMR ($CDCl_3$, 500 MHz) δ 6.11 (d, 1H, *J* = 2.9 Hz), 5.90 (d, 1H, *J* = 2.9 Hz), 4.83 (q, 1H, *J* = 6.6 Hz), 2.63 (q, 2H, *J* = 7.6 Hz), 1.52 (d, 3H, *J* = 6.6 Hz), and 1.22 (t, 3H, *J* = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 157.4, 155.7, 105.7, 104.3, 63.7, 21.3, 21.2, and 12.1; IR (neat) 3354, 2975, 2936, 1562, 1452, 1369, 1325, 1288, 1192, and 1078 cm^{-1}. HRMS-ESI neg *m/z* 139.0754 [M-H^+; calcd for $C_8H_{12}O_2$: 139.0759]. This product has previously been reported in the literature but was not fully characterized.[5]

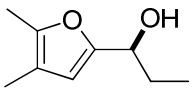


(7a) (*S*)-1-(5-Ethyl-furan-2-yl)-propan-1-ol. The product was prepared by General Procedure A using $ZnEt_2$ (0.35 mL, 2M solution in hexanes, 0.7 mmol), (–)-MIB (3 mg, 0.014 mmol), 5-ethyl 2-furfural (43 μL, 0.35 mmol), and 1.0 mL hexanes. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica treated with triethylamine (10% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 83% yield (45 mg, 0.29 mmol). $[\alpha]_D^{20}$ = -13.0 (*c* = 0.040 M, $CHCl_3$, 97% ee); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.11 (d, 1H, *J* = 3.1 Hz), 5.90 (d, 1H, *J* = 3.1 Hz), 4.54 (t, 1H, *J* = 6.6 Hz), 2.63 (q, 2H, *J* = 7.6 Hz), 1.85 (m, 2H), 1.22 (t, 3H, *J* = 7.6 Hz), and 0.96 (t, 3H, *J* = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 157.3, 154.7, 106.4, 104.3, 69.3, 28.5, 21.4, 12.1, and 10.0; IR (neat) 3359, 2971, 2937, 2878, 1562, 1462, 1377, 1326, 1186, 1096, and 1053 cm^{-1}. HRMS-ESI neg *m/z* 153.0923 [M-H^+; calcd for $C_9H_{14}O_2$: 153.0916]. ^1H NMR spectra for this compound matches with previously reported literature data.[6]



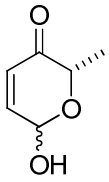
(8a) (*S*)-1-(4,5-Dimethyl-furan-2-yl)-ethan-1-ol. The product was prepared by General Procedure A using $ZnMe_2$ (0.35 mL, 2M solution in hexanes, 0.7

mmol), (–)-MIB (3 mg, 0.014 mmol), 4,5-dimethyl-2-furfural (43 μL, 0.35 mmol), and 1.0 mL hexanes. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica treated with triethylamine (10% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 89% yield (44 mg, 0.31 mmol). $[\alpha]_D^{20}$ = -12.2 (*c* = 0.048 M, $CHCl_3$, 92% ee); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.99 (s, 1H), 4.78 (q, 1H, *J* = 6.8 Hz), 2.18 (s, 3H), 1.91 (s, 3H), and 1.50 (d, 3H, *J* = 6.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 154.5, 146.8, 114.3, 108.4, 63.6, 21.2, 11.3, and 9.8; IR (neat) 3364, 2977, 2924, 2870, 1639, 1573, 1451, 1388, 1370, 1287, 1223, 1167, 1108, 1075, and 1020 cm^{-1}. HRMS-ESI neg *m/z* 139.0765 [M-H^+; calcd for $C_8H_{12}O_2$: 139.0759]. This compound has previously been reported in the literature but was not fully characterized.[7]

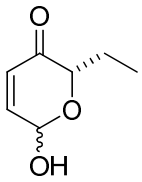


(9a) (*S*)-1-(4,5-Dimethyl-furan-2-yl)-propan-1-ol. The product was prepared by General Procedure A using $ZnEt_2$ (0.35 mL, 2M solution in hexanes, 0.7 mmol), (–)-MIB (3 mg, 0.014 mmol), 4,5-dimethyl-2-furfural (43 μL, 0.35 mmol), and 1.0 mL hexanes. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica treated with triethylamine (10% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 82% yield (44 mg, 0.29 mmol). $[\alpha]_D^{20}$ = -13.7 (*c* = 0.043 M, $CHCl_3$, 95% ee); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.99 (s, 1H), 4.48 (t, 1H, *J* = 6.6 Hz), 2.18 (s, 3H), 1.91 (s, 3H), 1.83 (m, 2H), and 0.95 (t, 3H, *J* = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 153.6, 146.8, 114.3, 109.2, 69.3, 28.5, 11.3, 10.1, and 9.8; IR (neat) 3360, 2965, 2925, 2877, 1640, 1572, 1455, 1387, 1223, 1165, 1114, and 1094 cm^{-1}. HRMS-ESI neg *m/z* 153.0916 [M-H^+; calcd for $C_9H_{14}O_2$: 153.0916].

III. One-pot Synthesis and Characterization of Pyranones

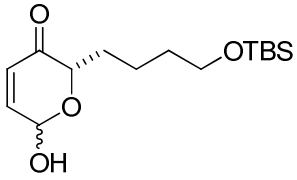


General Procedure B. (1b) (*S*)-6-Hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one. A 10 mL Schlenk flask was charged with (–)-MIB (8 mg, 0.032 mmol) and purged with dinitrogen. Hexanes (1 mL) was added followed by $ZnMe_2$ (0.8mL, 2M solution in hexanes, 1.6 mmol). The reaction mixture was cooled to 0 ^oC and then 2-furfural (66 μL, 0.8 mmol) was added dropwise. The reaction was stirred at 0 ^oC for 12 h, after which 0.3 mL H_2O, 1.2 mL THF, and NBS (157 mg, 0.88 mmol) were added at RT. The reaction was stirred at RT for 4 h and quenched with saturated aq NH_4Cl. The organic and aqueous layers were separated, and the aqueous layer was extracted with Et_2O (3 X 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica treated with triethylamine (20% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 70% yield (71.8 mg, 0.56 mmol) as a mixture of two diastereomers. $[\alpha]_D^{20}$ = –23.4 (*c* = 0.070 M, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.89 (dd, 1H, *J* = 3.4, 10.1 Hz), 6.10 (d, 1H, *J* = 10.2 Hz), 5.63 (d, 1H, *J* = 3.3 Hz), 4.71 (q, 1H, *J* = 6.8 Hz), and 1.38 (d, 3H, *J* = 6.9 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 196.8, 144.3, 127.3, 87.7, 70.4, and 15.3; IR (neat) 3420, 2987, 2940, 1730, 1697, 1447, 1373, 1234, 1159, and 1074 cm^{-1}. HRMS-ESI neg *m/z* 127.0401 [M-H^+ calcd for $C_6H_8O_3$: 127.0395]. ^1H NMR and $^{13}C\{^1H\}$ NMR spectra for this mixture of diastereomers match with previously reported literature data.[8]



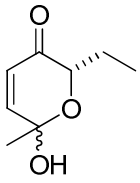
(2b) (*S*)-2-Ethyl-6-hydroxy-2*H*-pyran-3(6*H*)-one. The product was prepared by General Procedure B using $ZnEt_2$ (0.8 mL, 2.0 M solution in hexanes, 1.6 mmol),

(–)-MIB (8 mg, 0.032 mmol), 2-furfural (66 μL, 0.8 mmol), 1.0 mL hexanes, NBS (157 mg, 0.88 mmol), 0.3 mL H_2O, and 1.2 mL THF. The crude product was purified by column chromatography on silica treated with triethylamine (20% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 73% yield (83 mg, 0.58 mmol) as a mixture of diastereomers. $[\alpha]_D^{20}$ = 5.8 (*c* = 0.040 M, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.89 (dd, 1H, *J* = 3.5, 10.3 Hz), 6.10 (d, 1H, *J* = 10.2 Hz), 5.66 (d, 1H, *J* = 3.1 Hz), 4.51 (dd, 1H, *J* = 4.1, 7.4 Hz), 1.95 (m, 1H), 1.77 (m, 1H), and 0.98 (t, 3H, *J* = 7.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 196.5, 144.3, 127.7, 87.7, 75.2, 23.0 and 9.3; IR (neat) 3406, 2971, 2934, 1693, 1458, 1436, 1377, 1268, 1227, 1159 and 1082 cm^{-1}. HRMS-ESI neg *m/z* 141.0557 [M-H$^+$ calcd for $C_7H_{10}O_3$: 141.0552] ^{1}H NMR spectra for this mixture of diastereomers matches with previously reported literature data.[5]

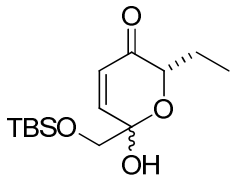


(3b) (*S*)-2-(4-(*tert*-Butyldimethylsilyloxy)butyl)-6-hydroxy-2*H*-pyran-3(6*H*)-one. The product was prepared by General Procedure B using $Zn[(CH_2)_4OTBS]_2$ (1.6 mL, 1.0 M solution in hexanes, 1.6 mmol), (–)-MIB (8 mg, 0.032 mmol), 2-furfural (66 μL, 0.8 mmol), 1.0 mL hexanes, NBS (157 mg, 0.88 mmol), 0.3 mL H_2O, and 1.2 mL THF. The crude product was purified by column chromatography on silica treated with triethylamine (20% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 61% yield (147 mg, 0.49 mmol) as a mixture of two diastereomers. $[\alpha]_D^{20}$ = 1.5 (*c* = 0.045 M, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.79 (dd, 1H, *J* = 3.4, 10.3 Hz), 6.10 (d, 1H, *J* = 10.3 Hz), 5.64 (d, 1H, *J* = 3.6 Hz), 4.56 (m, 1H), 3.62 (t, 2H, *J* = 6.4 Hz), 1.71 (m, 2H), 1.52 (m, 4H), 0.89 (s, 9H), and 0.05 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125

MHz): δ 196.5, 144.3, 127.6, 87.6, 74.1, 63.1, 32.5, 29.4, 26.0, 21.4, 18.4, and -5.3; IR (neat) 3395, 2954, 2930, 2858, 1694, 1632, 1471, 1463, 1435, 1387, 1256, 1188, and 1096 cm^{-1}. HRMS-ESI pos *m/z* 323.1652 [M+Na^+ calcd for $C_{15}H_{28}O_4Si$: 323.1655]

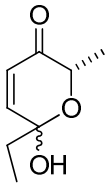


(4b) (*S*)-2-Ethyl-6-hydroxy-6-methyl-2*H*-pyran-3(6*H*)-one. The product was prepared by General Procedure B using $ZnEt_2$ (0.8 mL, 2.0 M solution in hexanes, 1.6 mmol), (–)-MIB (8 mg, 0.032 mmol), 5-methyl-2-furfural (80 μL, 0.8 mmol), 1.0 mL hexanes, NBS (157 mg, 0.88 mmol), 0.3 mL H_2O, and 1.2 mL THF. The crude product was purified by column chromatography on silica treated with triethylamine (20% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 71% yield (89 mg, 0.57 mmol) as a mixture of two diastereomers. $[\alpha]_D^{20}$ = 6.7 (*c* = 0.085 M, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.81 (d, 1H, *J* = 10.2 Hz), 6.00 (d, 1H, *J* = 10.3 Hz), 4.45 (dd, 1H, *J* = 4.1, 7.2 Hz), 1.94 (m, 1H), 1.73 (m, 1H), 1.63 (s, 3H), and 0.96 (t, 3H, *J* = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 196.9, 147.9, 126.6, 92.7, 75.3, 28.9, 22.9 and 9.2; IR (neat) 3418, 2982, 2938, 2880, 1694, 1682, 1456, 1403, 1379, 1235, 1127, and 1088 cm^{-1}. HRMS-ESI pos *m/z* 176.0676 [M+Na^+ calcd for $C_8H_{12}O_3$: 179.0684]. This diastereomeric mixture has previously been reported in the literature but was not fully characterized.[9]



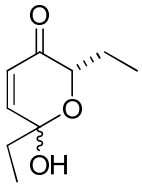
(5b) (*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-2-ethyl-6-hydroxy-2*H*-pyran-3(6*H*)-one. The product was prepared by General Procedure B using $ZnEt_2$ (0.62 mL, 1.0 M solution in hexanes, 0.62 mmol), (–)-MIB (0.12 mL, 0.1 M solution in hexanes, 0.012 mmol), 5-*tert*-butyl-dimethylsilanyloxy-methyl-2-furfural (74.8 mg, 0.31 mmol), 1.0 mL hexanes, NBS (61 mg, 0.34 mmol), 0.3 mL H_2O, and 1.2 mL THF. The

crude product was purified by column chromatography on silica treated with triethylamine (20% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 72% yield (64 mg, 0.22 mmol) as a mixture of two diastereomers. $[\alpha]_D^{20}$ = –20.8 (*c* = 0.021 M, $CHCl_3$, 95% ee); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.74 (d, 1H, *J* = 10.3 Hz), 6.09 (d, 1H, *J* = 10.3 Hz), 4.48 (dd, 1H, *J* = 3.9, 7.3 Hz), 3.76 (d, 1H, *J* = 10.2 Hz), 3.67 (d, 1H, *J* = 10.2 Hz), 1.95 (m, 1H), 1.73 (m, 1H), 0.96 (t, 3H, *J* = 7.5 Hz), 0.93 (s, 9H) and 0.12 (d, 6H, *J* = 4.1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 197.1, 145.0, 128.6, 92.5, 75.4, 68.4, 25.7, 22.9, 18.4, 9.2, and -5.2; IR (neat) 3429, 2955, 2931, 2858, 1694, 1463, 1255, 1121, and 1093 cm^{-1}. HRMS-ESI pos *m/z* 309.1491 [$M+Na^+$ calcd for $C_{14}H_{26}O_4Si$: 309.1498].

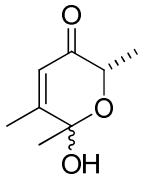


(6b) (*S*)-6-Ethyl-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one. The product was prepared by General Procedure B using $ZnMe_2$ (0.8 mL, 2.0 M solution in hexanes, 1.6 mmol), (–)-MIB (8 mg, 0.032 mmol), 5-ethyl-2-furfural (95 μL, 0.8 mmol), 1.0 mL hexanes, NBS (157 mg, 0.88 mmol), 0.3 mL H_2O, and 1.2 mL THF. The crude product was purified by column chromatography on silica treated with triethylamine (20% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 76% yield (95 mg, 0.61 mmol) as a mixture of two diastereomers. $[\alpha]_D^{20}$ = 24.4 (*c* = 0.081 M, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.78 (d, 1H, *J* = 10.3 Hz), 6.06 (d, 1H, *J* = 10.2 Hz), 4.65 (q, 1H, *J* = 13.3, 6.6 Hz), 1.85 (m, 2H), 1.36 (d, 3H, *J* = 6.7) and 0.99 (t, 3H, *J* = 7.6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 197.3, 147.2, 127.1, 94.7, 70.7, 34.6, 15.3 and 7.7; IR (neat) 3413, 2983, 2940, 1693, 1448, 1405, 1372, 1234, 1117 and 1094 cm^{-1}. HRMS-ESI neg *m/z* 155.0712 [$M-H^+$ calcd for $C_8H_{12}O_3$:

155.0708] ^{1}H NMR and ^{13}C{^{1}H} NMR spectra for this mixture of diastereomers match with previously reported literature data.[5]

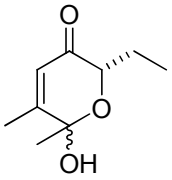


(7b) (*S*)-2,6-Diethyl-6-hydroxy-2*H*-pyran-3(6*H*)-one. The product was prepared by General Procedure B using $ZnEt_2$ (1.6 mL, 1.0 M solution in hexanes, 1.6 mmol), (–)-MIB (8 mg, 0.032 mmol), 5-ethyl-2-furfural (95 μL, 0.8 mmol), 1.0 mL hexanes, NBS (157 mg, 0.88 mmol), 0.3 mL H_2O, and 1.2 mL THF. The crude product was purified by column chromatography on silica treated with triethylamine (20% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 77% yield (105 mg, 0.62 mmol) as a mixture of two diastereomers. $[\alpha]_D^{20}$ = 0.4 (*c* = 0.030 M), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.78 (d, 1H, *J* = 10.3 Hz), 6.07 (d, 1H, *J* = 10.3 Hz), 4.47 (dd, 1H, *J* = 4.1, 6.9 Hz), 1.94 (m, 1H), 1.86 (m, 2H), 1.78 (m, 1H), 1.01 (t, 3H, *J* = 7.6 Hz), and 0.96 (t, 3H, *J* = 7.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 196.9, 147.1, 127.7, 94.4, 75.1, 34.7, 23.0, 9.2, and 7.7; IR (neat) 3417, 2972, 2938, 2881, 1693, 1682, 1463, 1404, 1380, 1228, 1123, 1123, 1089, and 1060 cm^{-1}. HRMS-ESI pos *m/z* 193.0838 [M+Na^{+} calcd for $C_9H_{14}O_3$: 193.0841].



(8b) (*S*)-6-Hydroxy-2,5,6-trimethyl-2*H*-pyran-3(6*H*)-one. The product was prepared by General Procedure B using $ZnMe_2$ (0.8 mL, 2.0 M solution in hexanes, 1.6 mmol), (–)-MIB (8 mg, 0.032 mmol), 4,5-dimethyl-2-furfural (98 μL, 0.8 mmol), 1.0 mL hexanes, NBS (157 mg, 0.88 mmol), 0.3 mL H_2O, and 1.2 mL THF. The crude product was purified by column chromatography on silica treated with triethylamine (20% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 46% yield (57 mg, 0.37

mmol) as a mixture of two diastereomers. $[\alpha]_D^{20}$ = 89.4 (*c* = 0.062 M), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.85 (s, 1H), 4.57 (dd, 1H, *J* = 6.8, 13.4 Hz), 2.02 (s, 3H), 1.61 (s, 3H), and 1.34 (d, 3H, *J* = 6.9 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 197.3, 159.0, 124.0, 95.2, 70.5, 27.1, 19.4, and 15.3; IR (neat) 3349, 2987, 1667, 1435, 1372, 1247, 1185, 1128, and 1105 cm^{-1}. HRMS-ESI pos *m/z* 179.0685 [M+Na^+ calcd for $C_8H_{12}O_3$: 179.0684].

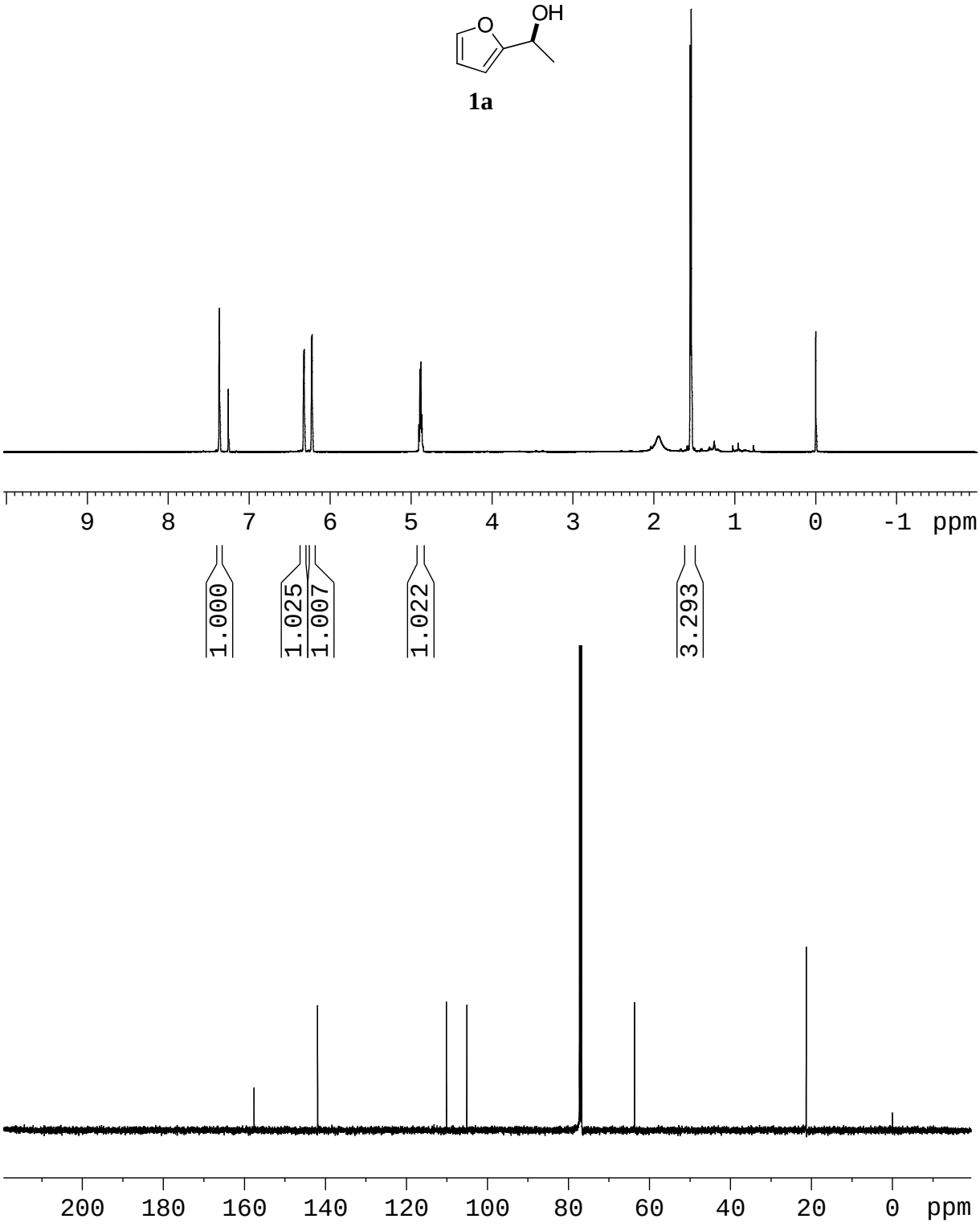


(9b) (*S*)-2-Ethyl-6-hydroxy-5,6-dimethyl-2*H*-pyran-3(6*H*)-one. The product was prepared by General Procedure B using $ZnEt_2$ (1.6 mL, 1.0 M solution in hexanes, 1.6 mmol), (–)-MIB (8 mg, 0.032 mmol), 4,5-dimethyl-2-furfural (98 μL, 0.8 mmol), 1.0 mL hexanes, NBS (157 mg, 0.88 mmol), 0.3 mL H_2O, and 1.2 mL THF. The crude product was purified by column chromatography on silica treated with triethylamine (20% ethyl acetate in hexanes) to afford the title compound as a colorless oil in 63% yield (86 mg, 0.50 mmol) as a mixture of two diastereomers. $[\alpha]_D^{20}$ = 37.7 (*c* = 0.105); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.84 (s, 1H), 4.38 (dd, 1H, *J* = 7.2, 3.95 Hz), 2.97 (br, 1H), 2.01 (s, 3H), 1.92 (m, 1H), 1.71 (m, 1H), 1.61 (s, 3H) and 0.94 (t, 3H, *J* = 7.5 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 197.1, 159.1, 124.4, 95.0, 75.0, 26.9, 22.9, 19.5, and 9.3; IR (neat) 3407, 2980, 2939, 1682, 1435, 1379, 1318, 1297, 1230, 1186, 1135, and 1109 cm^{-1}. HRMS-ESI pos *m/z* 193.0837 [M+Na^+ calcd for $C_9H_{14}O_3$: 193.0841].

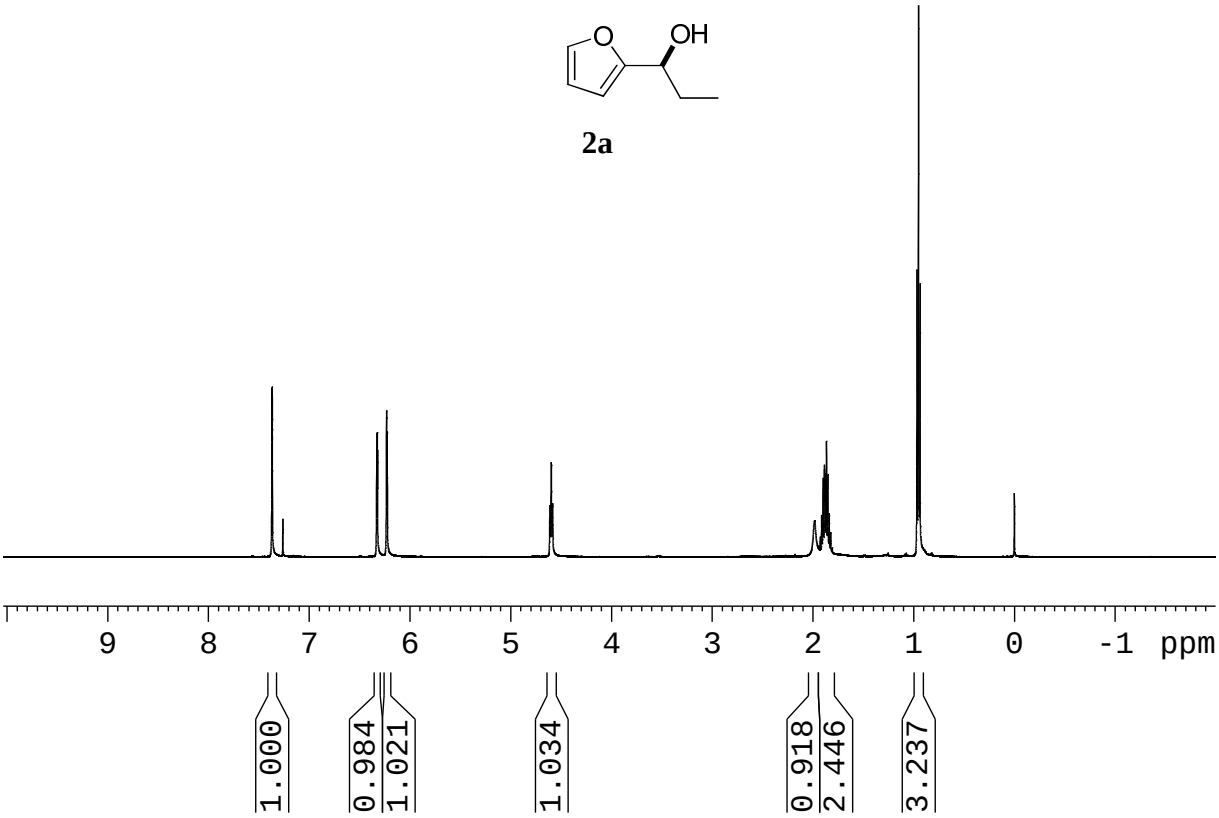
$Zn(CH_2CH_2CH_2CH_2OTBS)_2$ **Bis(4-(*tert*-butyldimethylsilyloxy)butyl)zinc.** The product was prepared by the method of Knochel.[1] A Schlenk flask was charged with (but-3-enyloxy)(*tert*-

butyl)dimethylsilane (1.84 g, 6.35 mmol) and purged with dinitrogen. The reaction mixture was cooled to 0 ^{o}C before the slow addition of diethylborane (6.35 mL, 1M solution in hexanes, 6.35 mmol). The reaction was warmed to room temperature and stirred for 3 h before pumping off all volatiles for 30 min. After cooling to 0 ^{o}C , $ZnEt_2$ (1.29 mL, 12.70 mmol) was slowly added and the reaction was allowed to stir at this temperature for 30 min. All the volatiles were then removed under vacuum for 3 h to give the product in 77% yield (1.07g, 2.44 mmol).

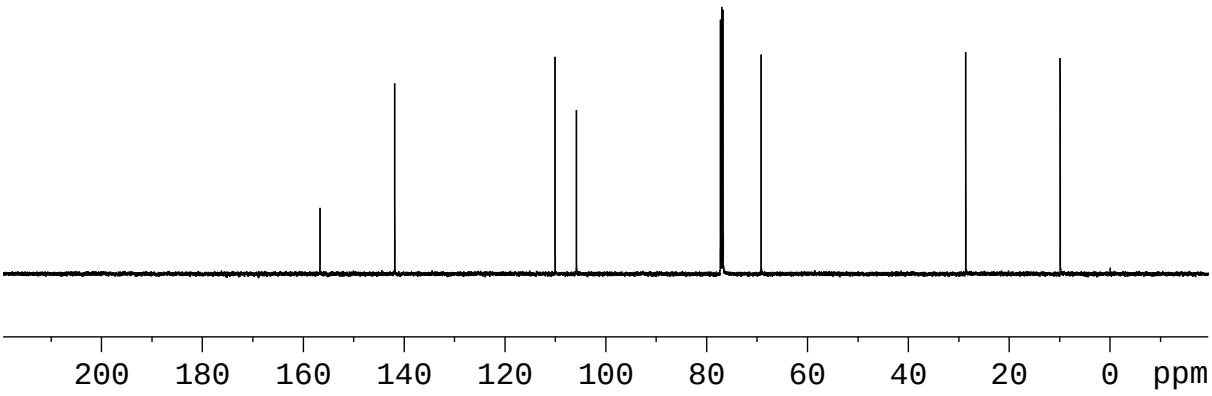
IV. Spectral Data



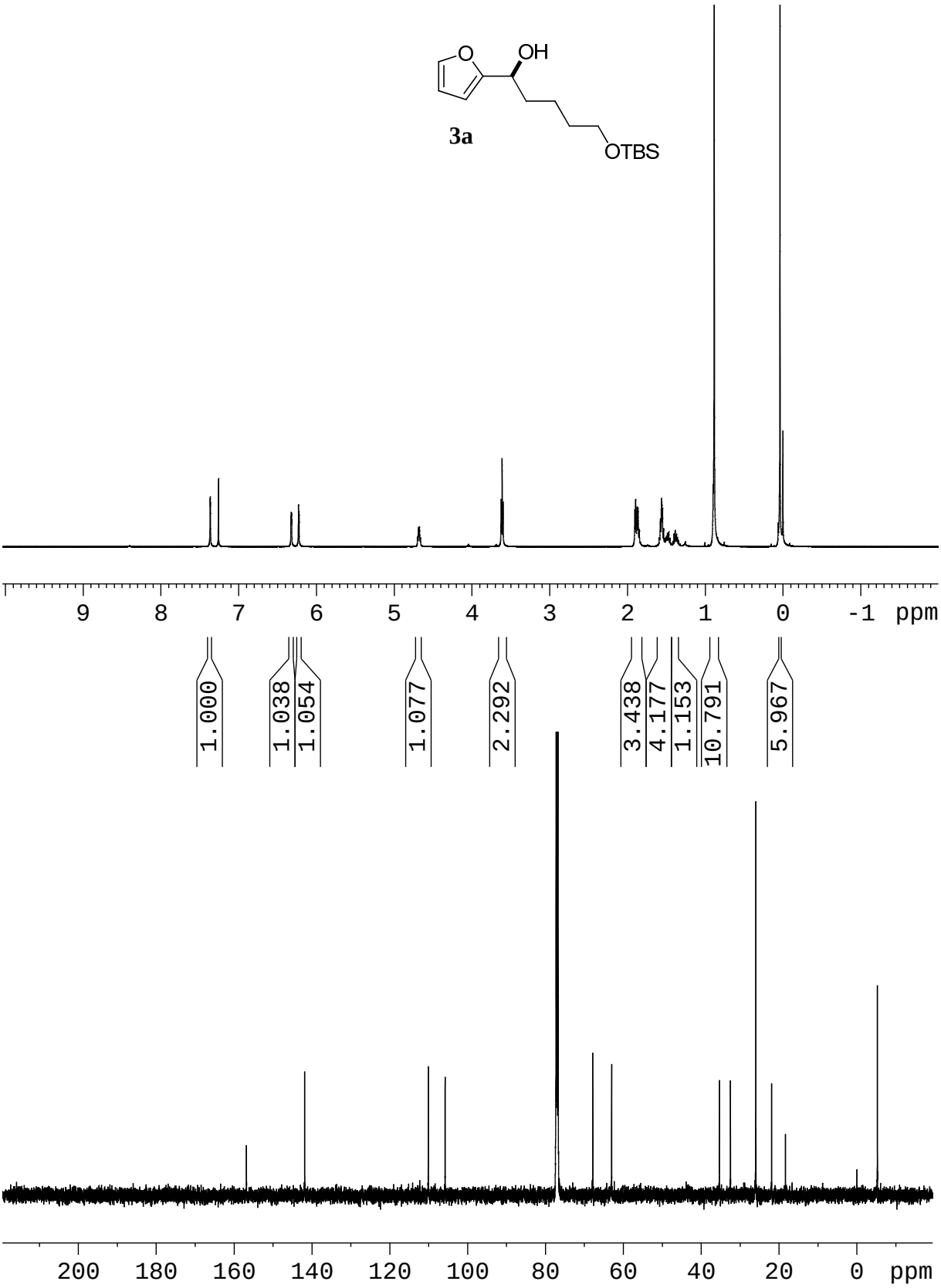
500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$



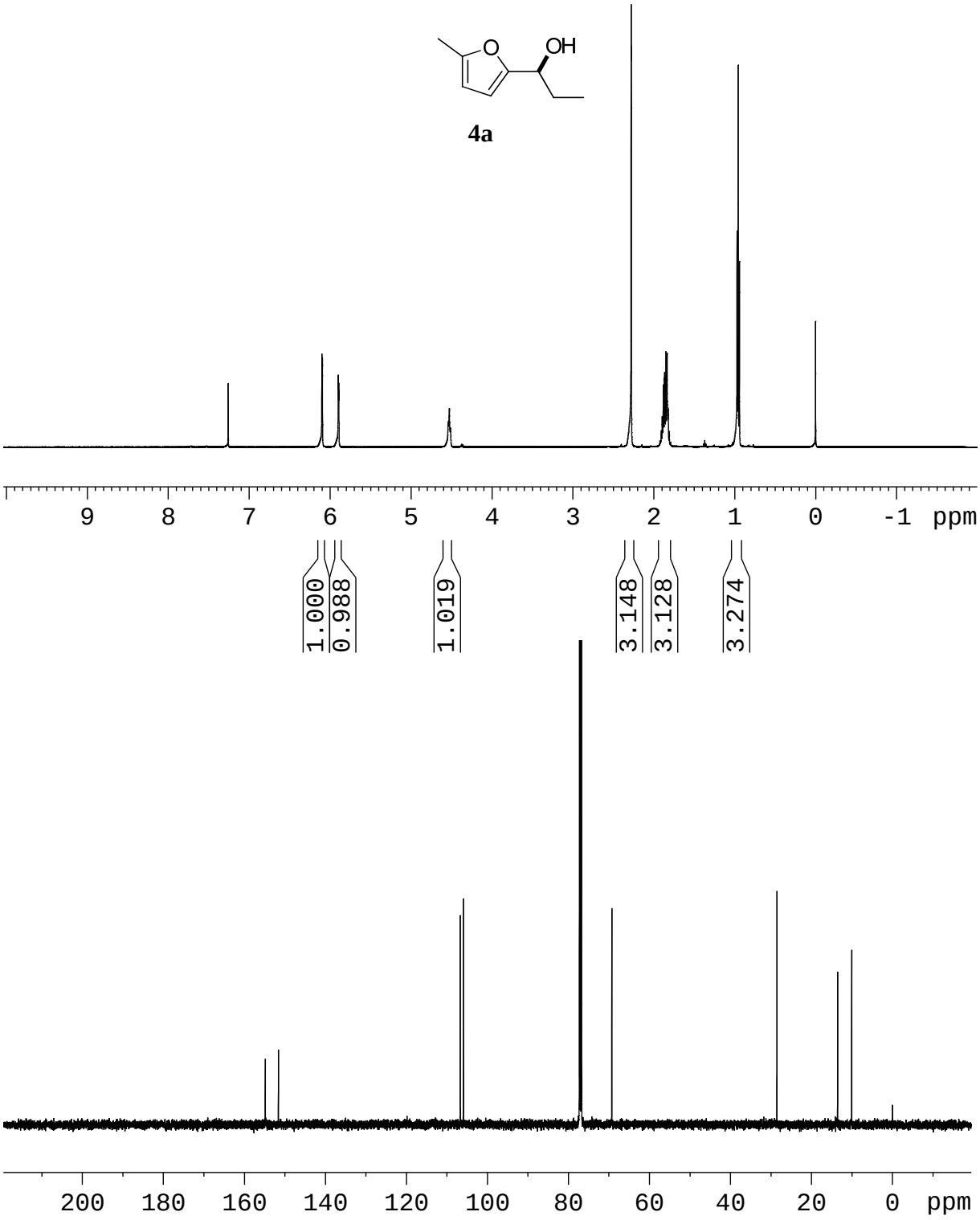
2a



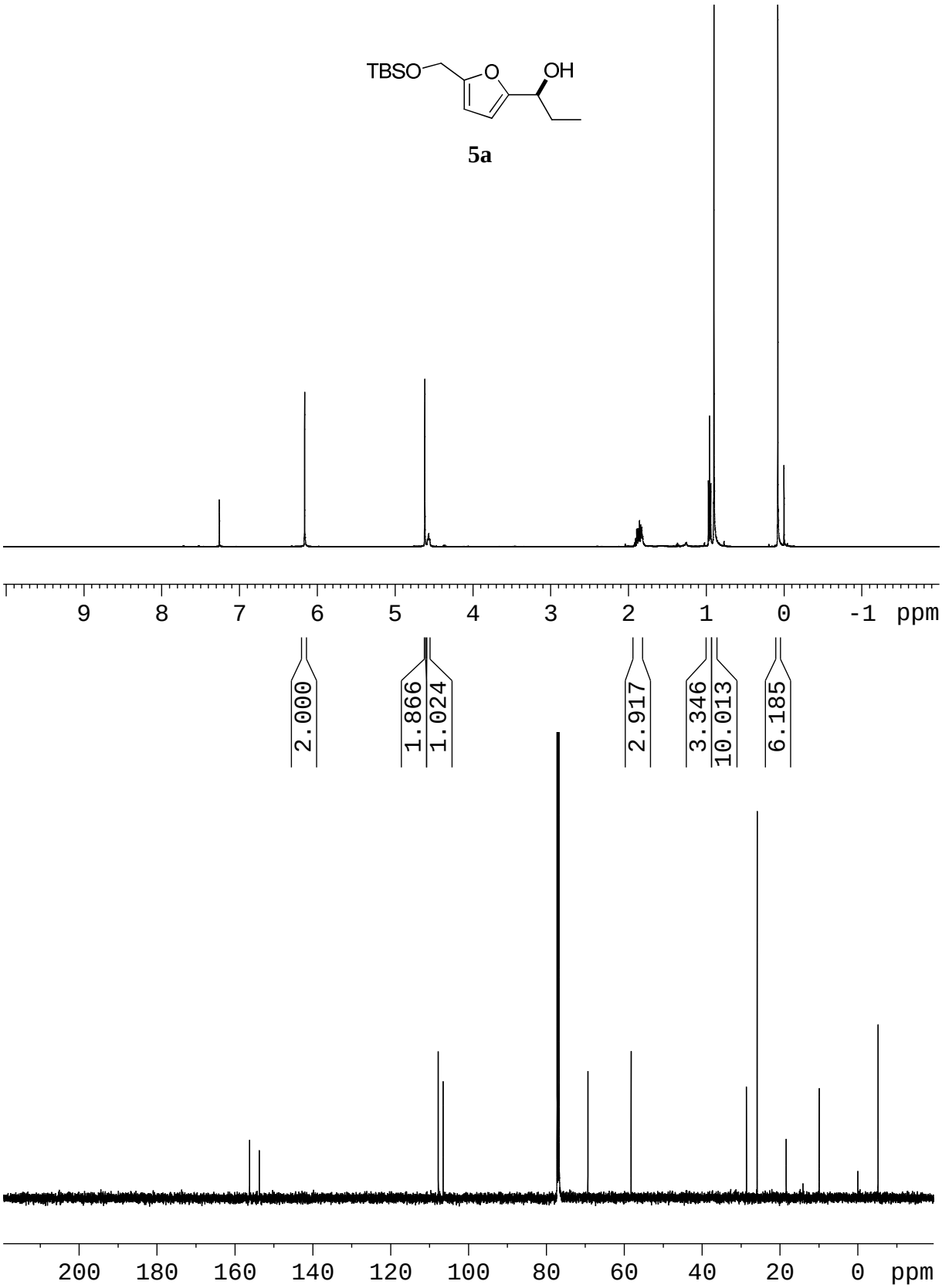
500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$



500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$

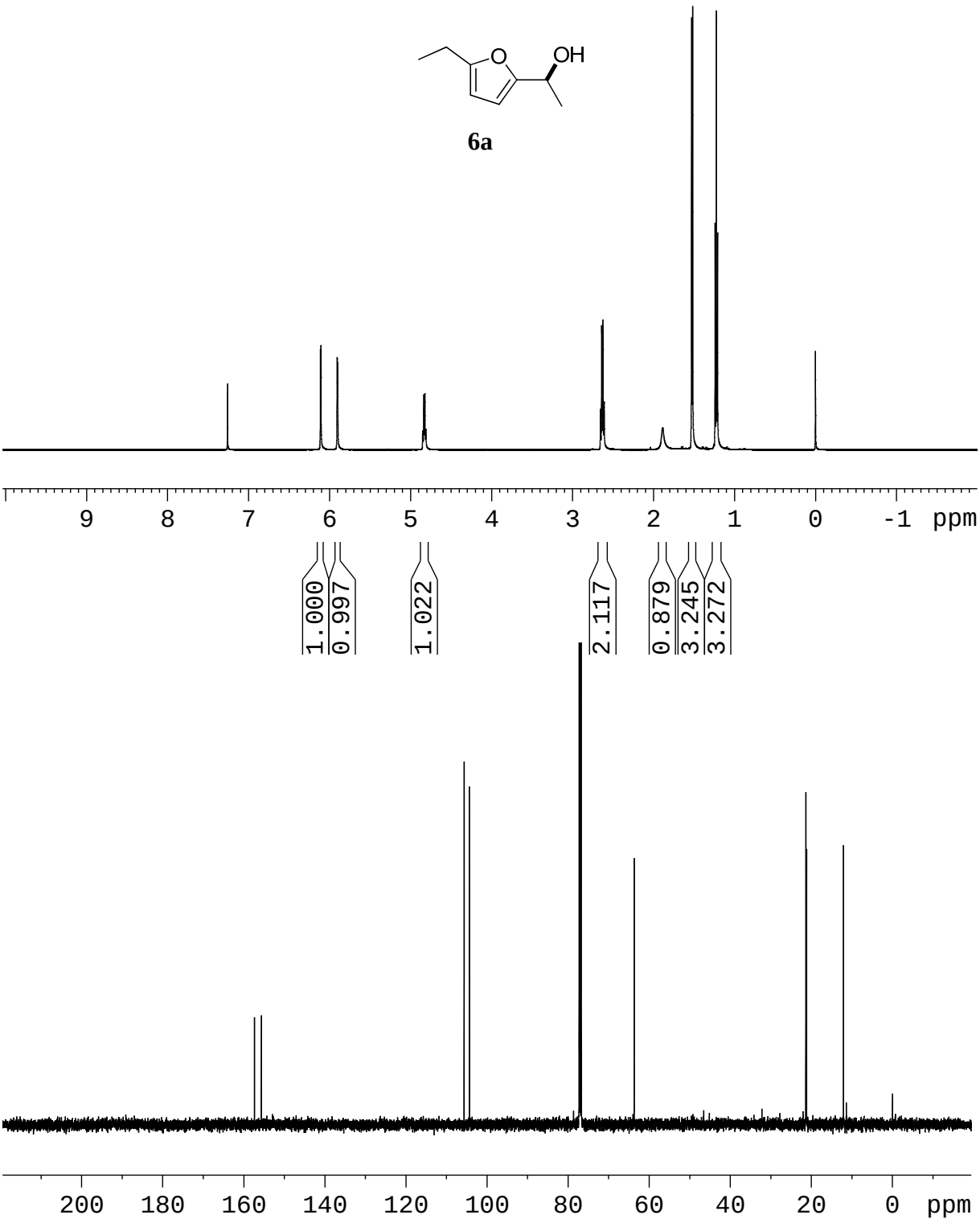


500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$



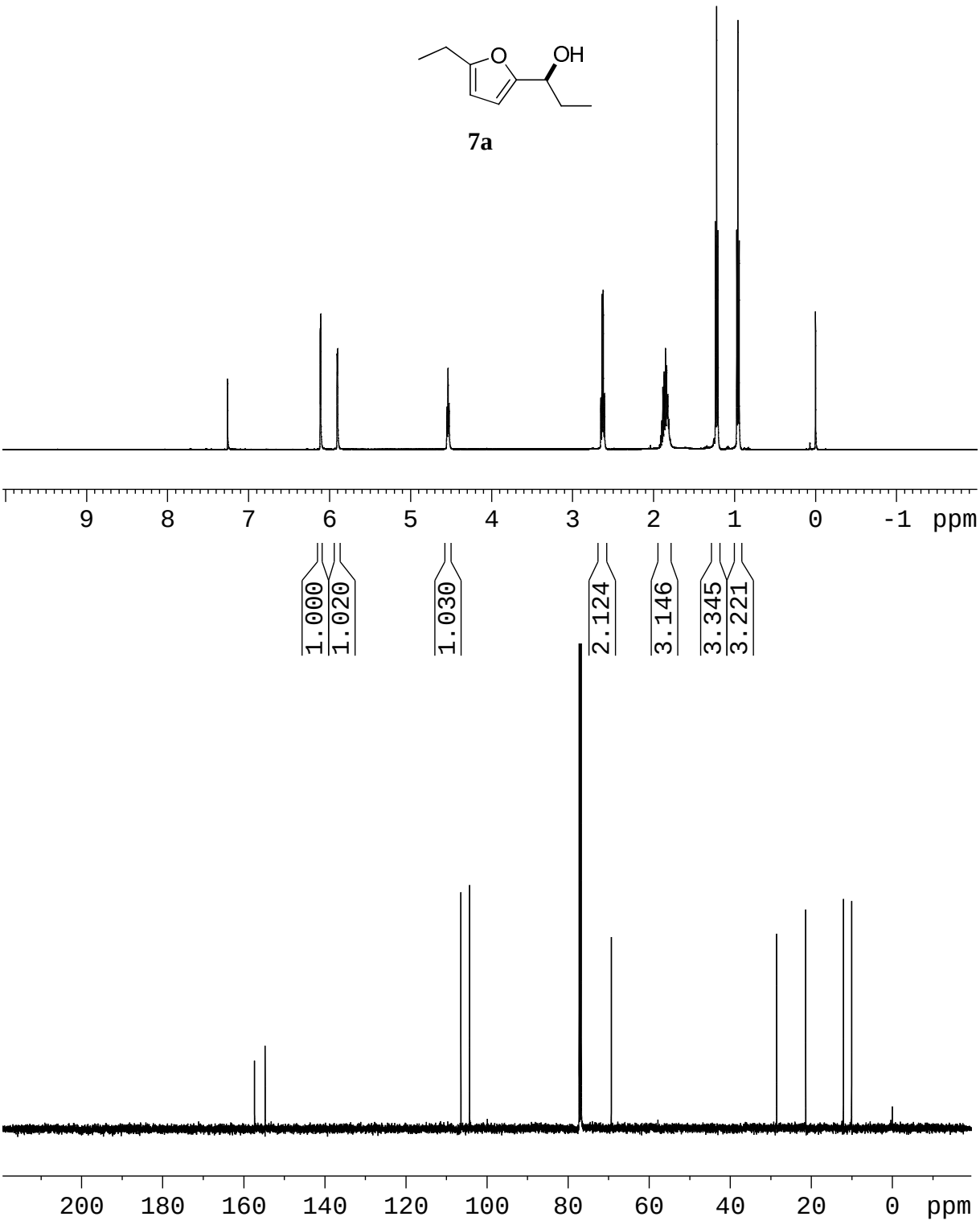
5a

500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$



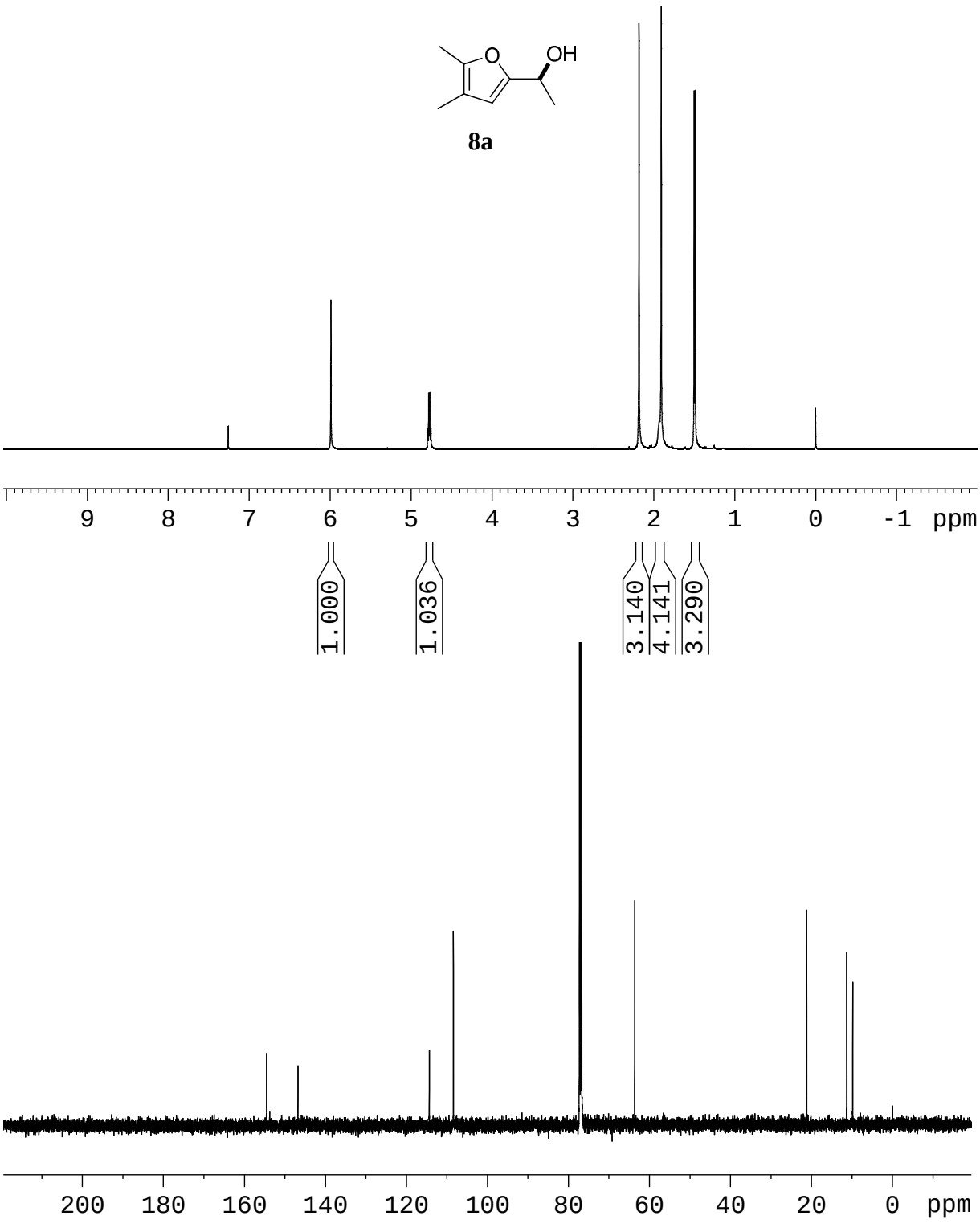
6a

500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$



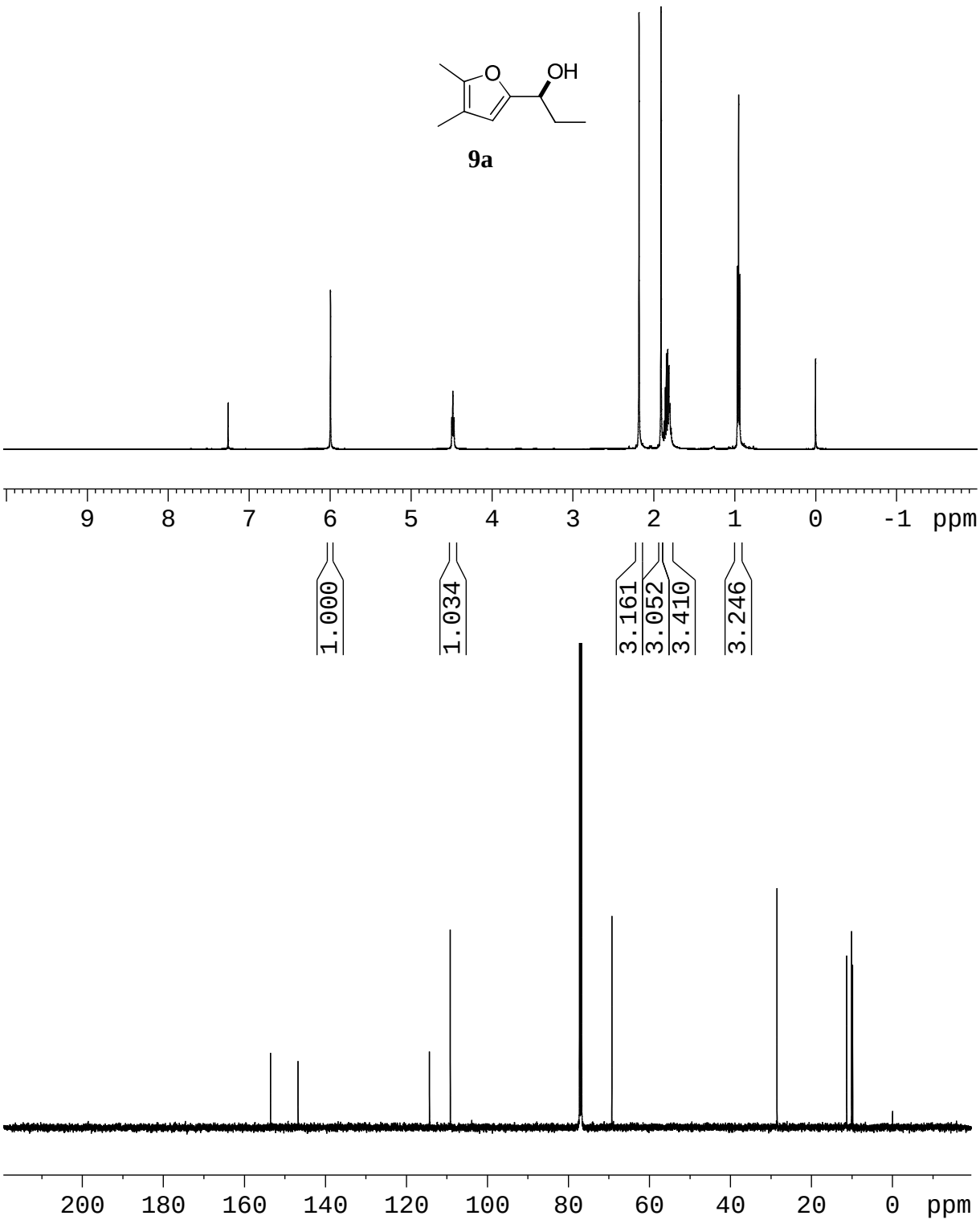
7a

500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$

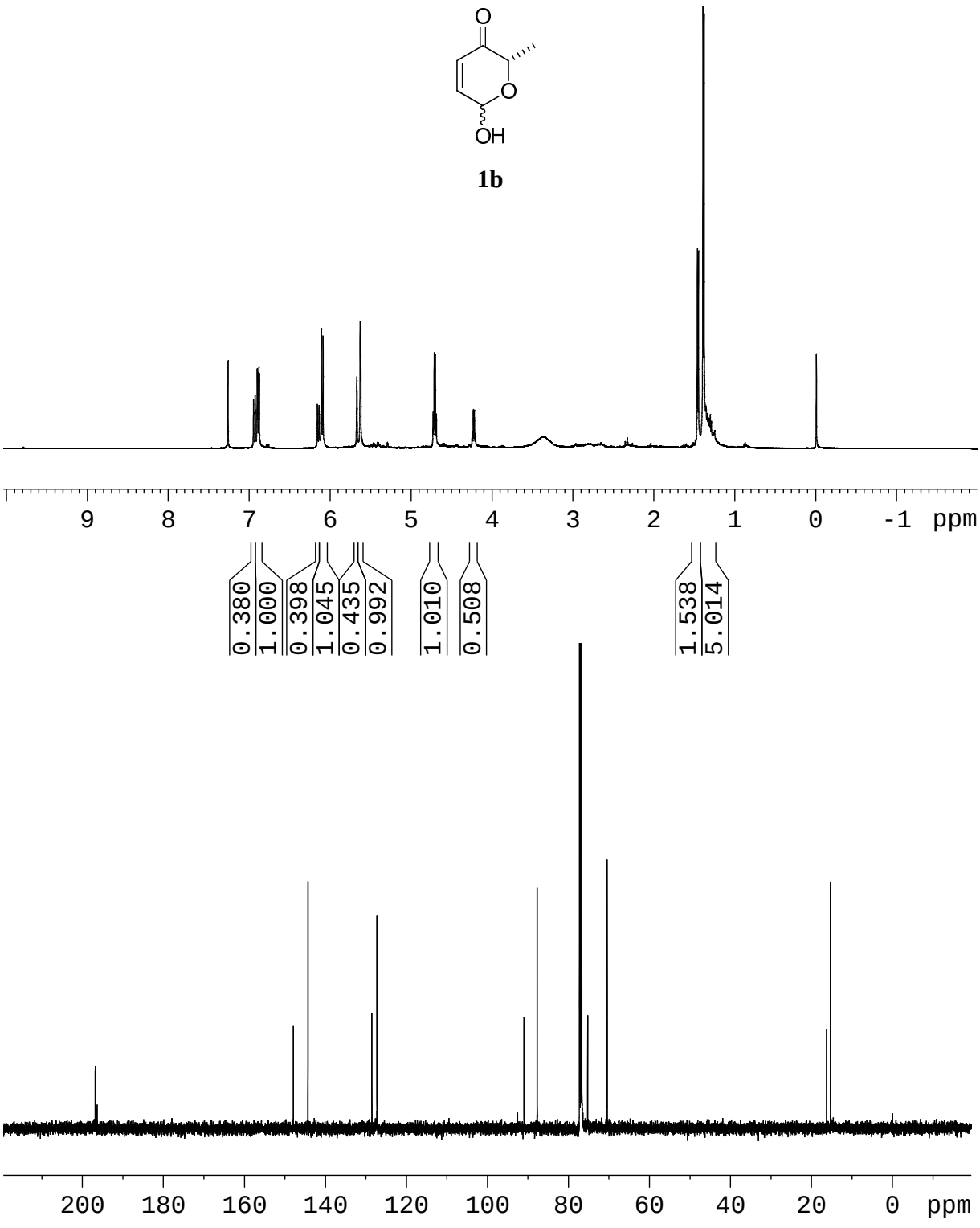


8a

500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$

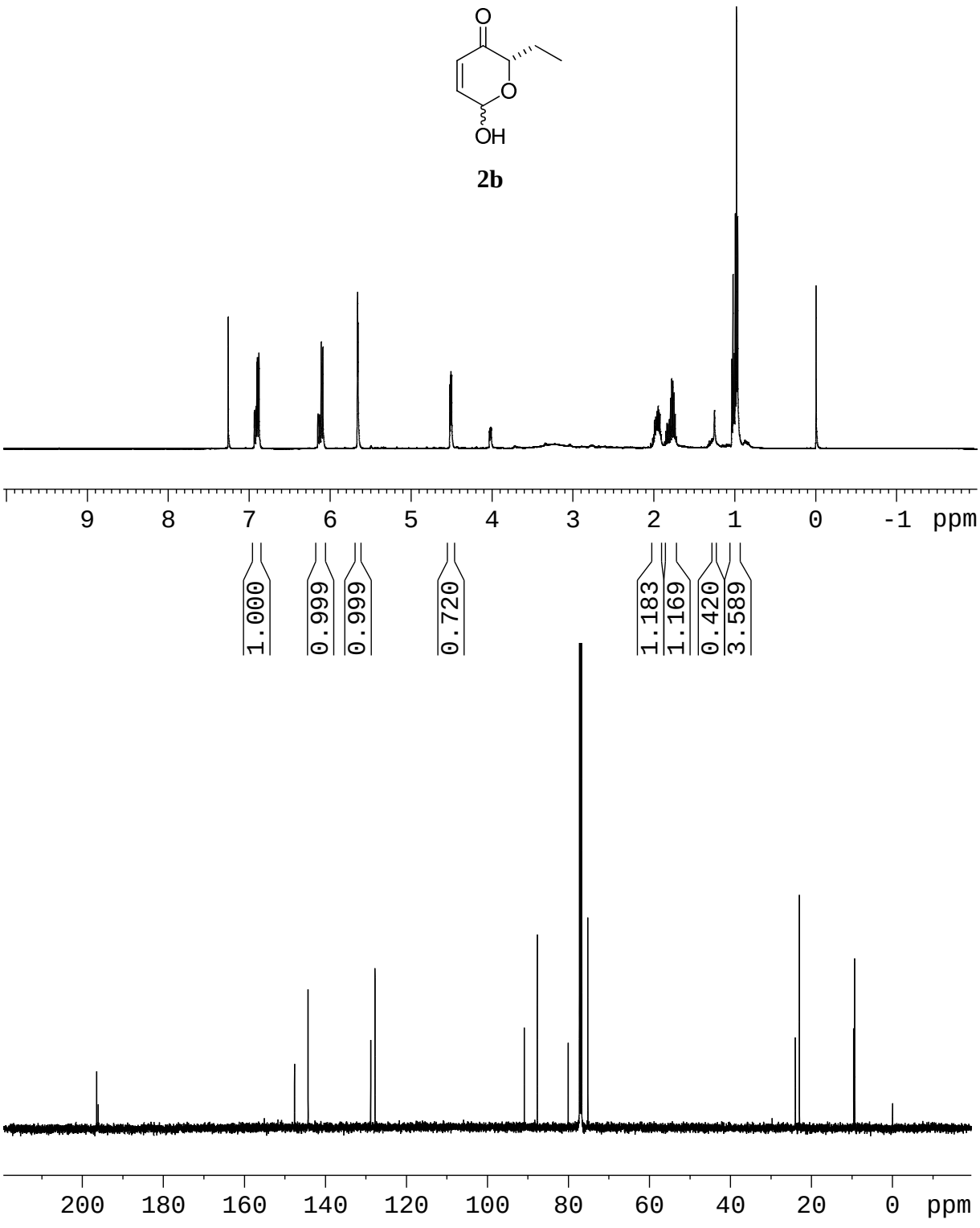


500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$



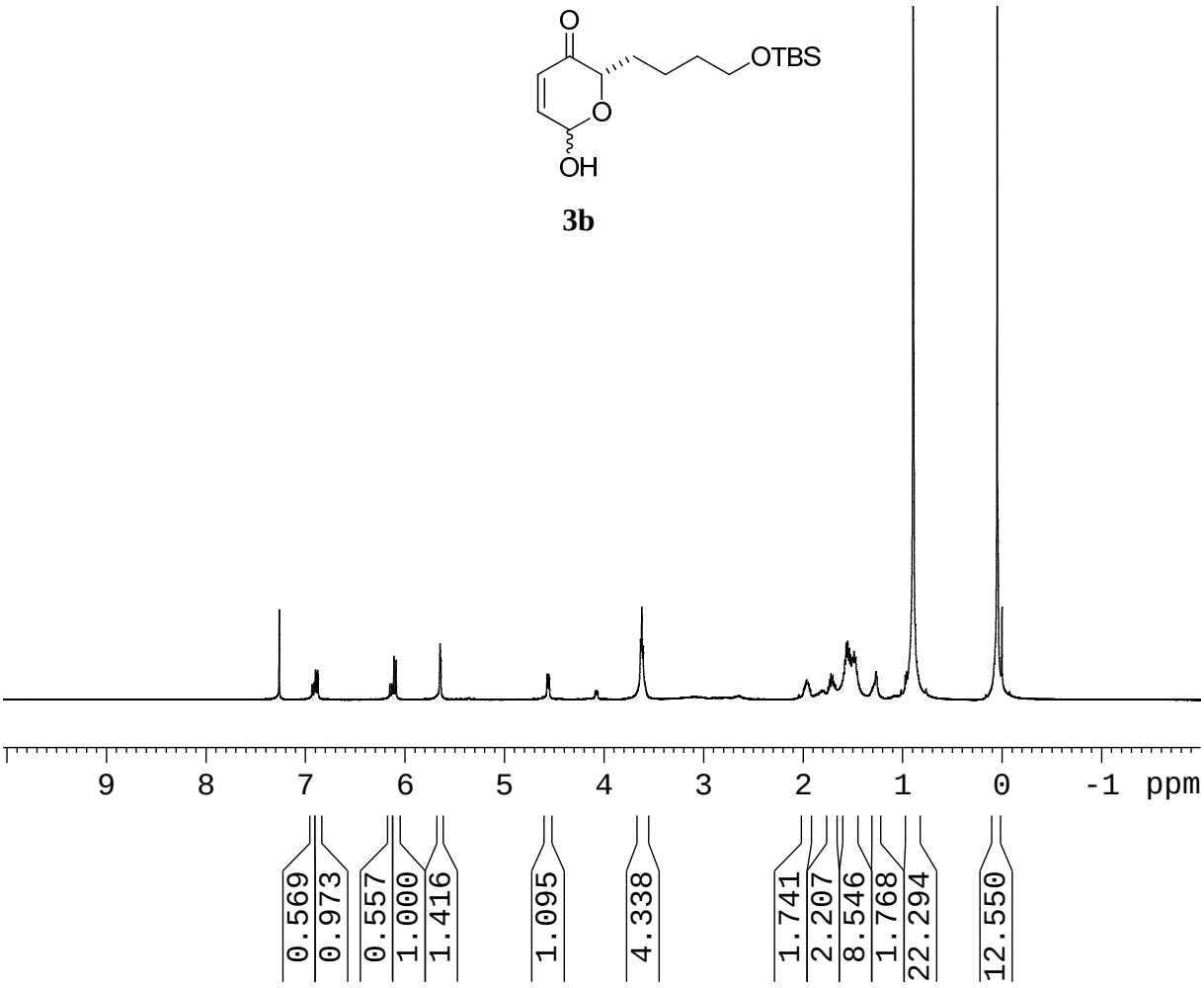
1b

500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$

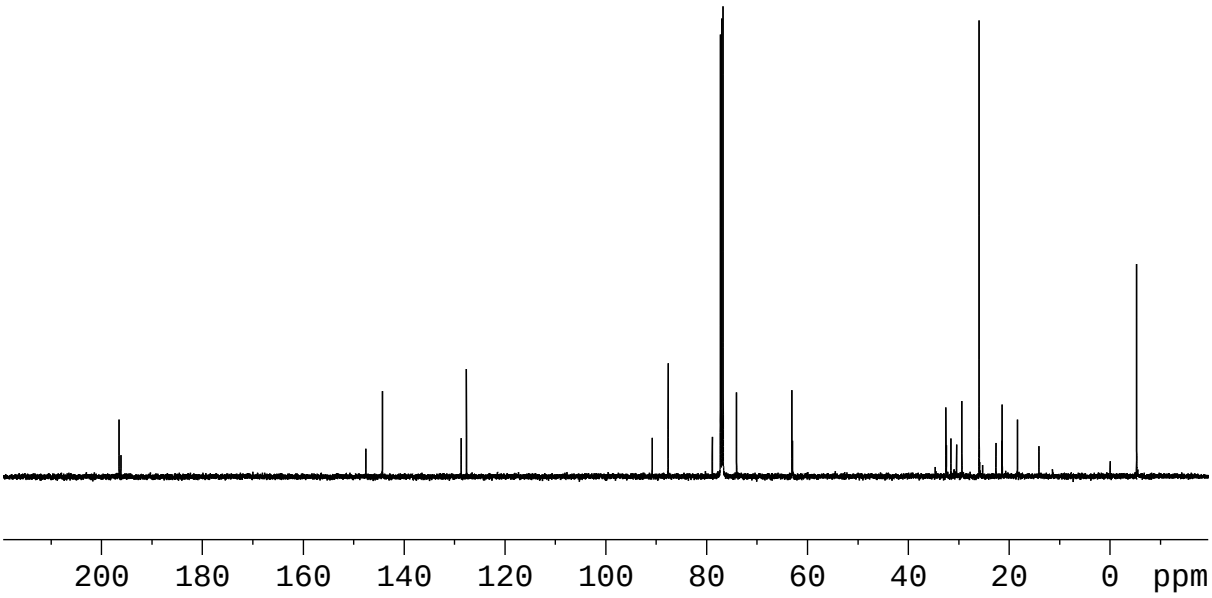


2b

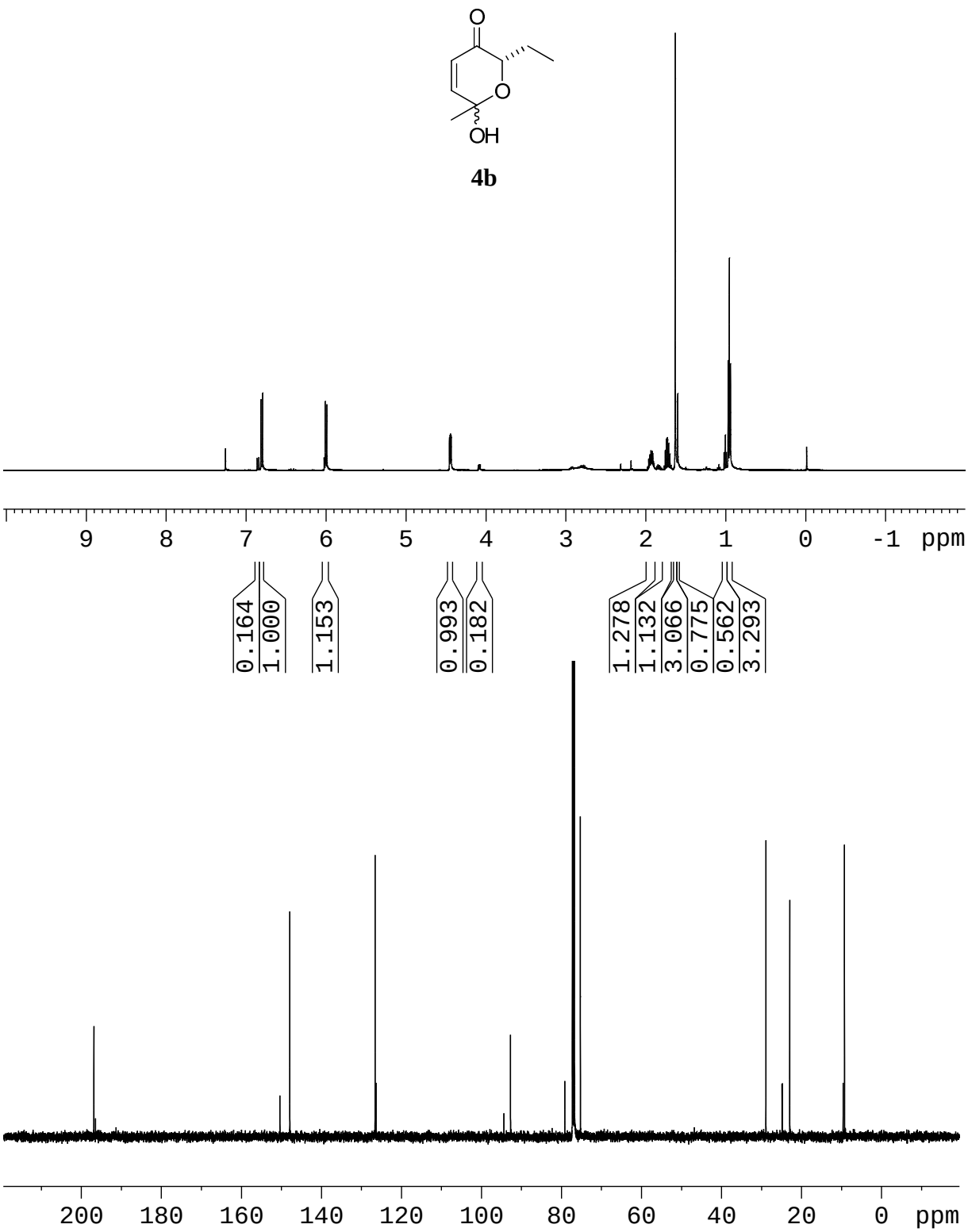
500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$



3b

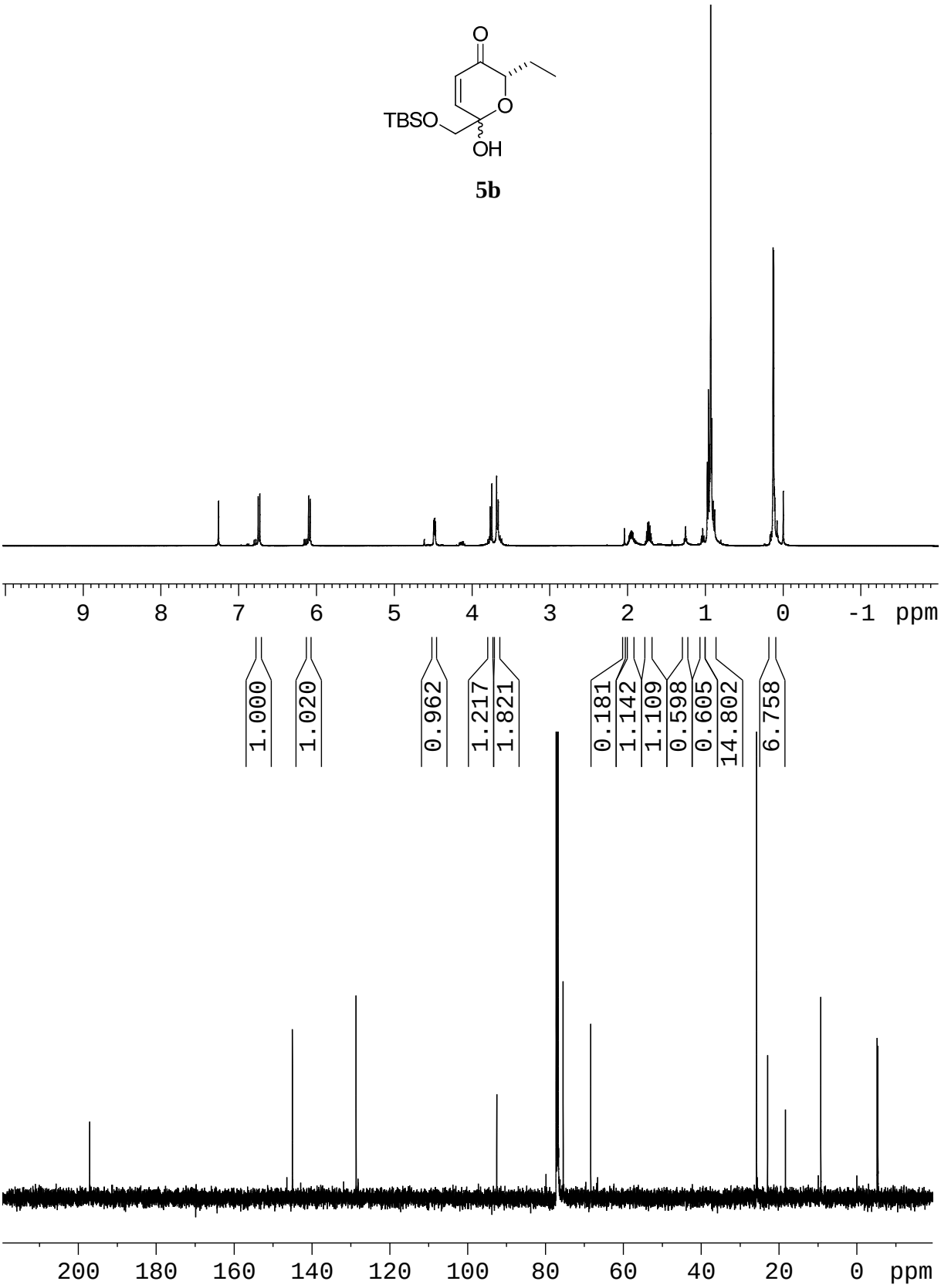


500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$



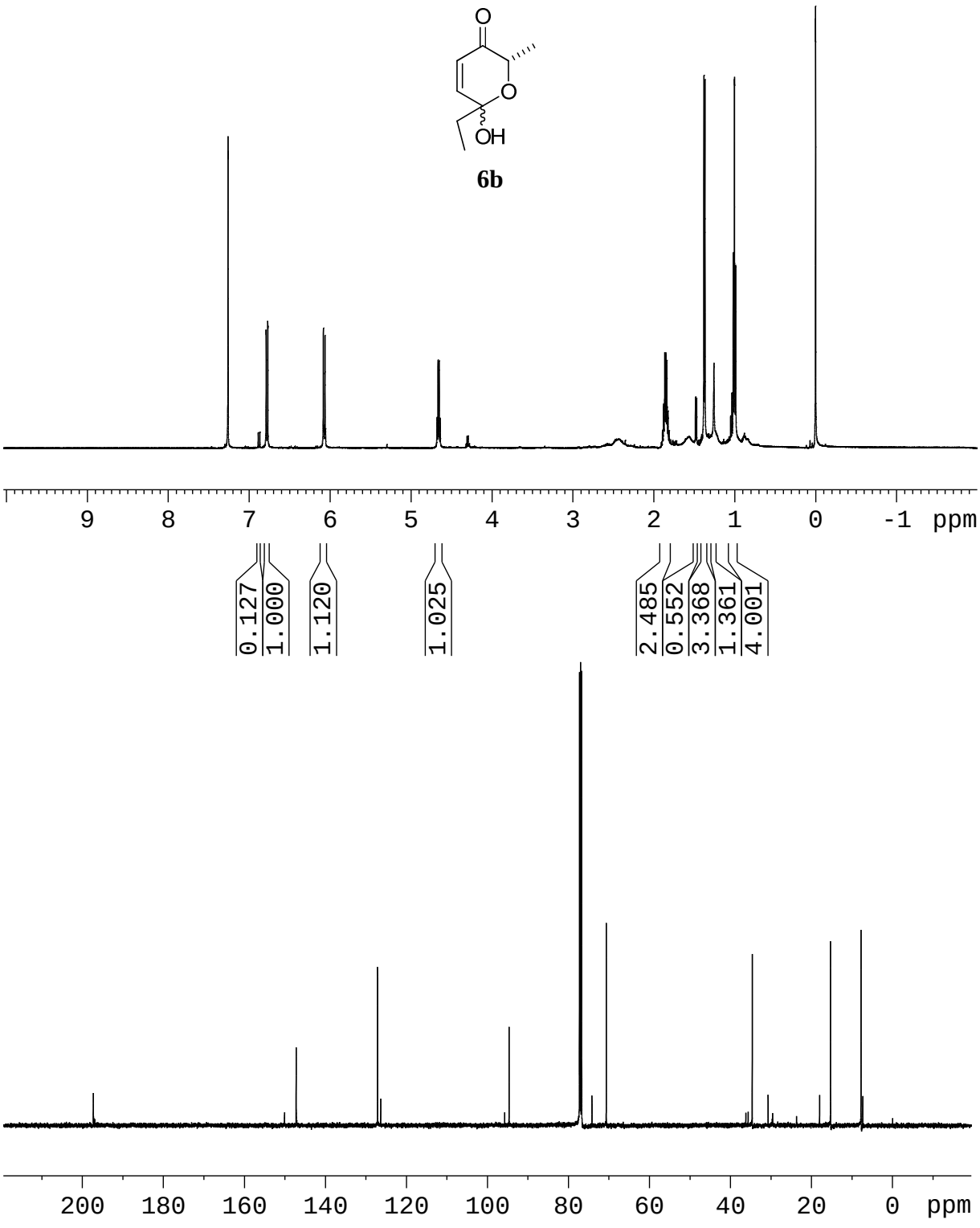
4b

500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$



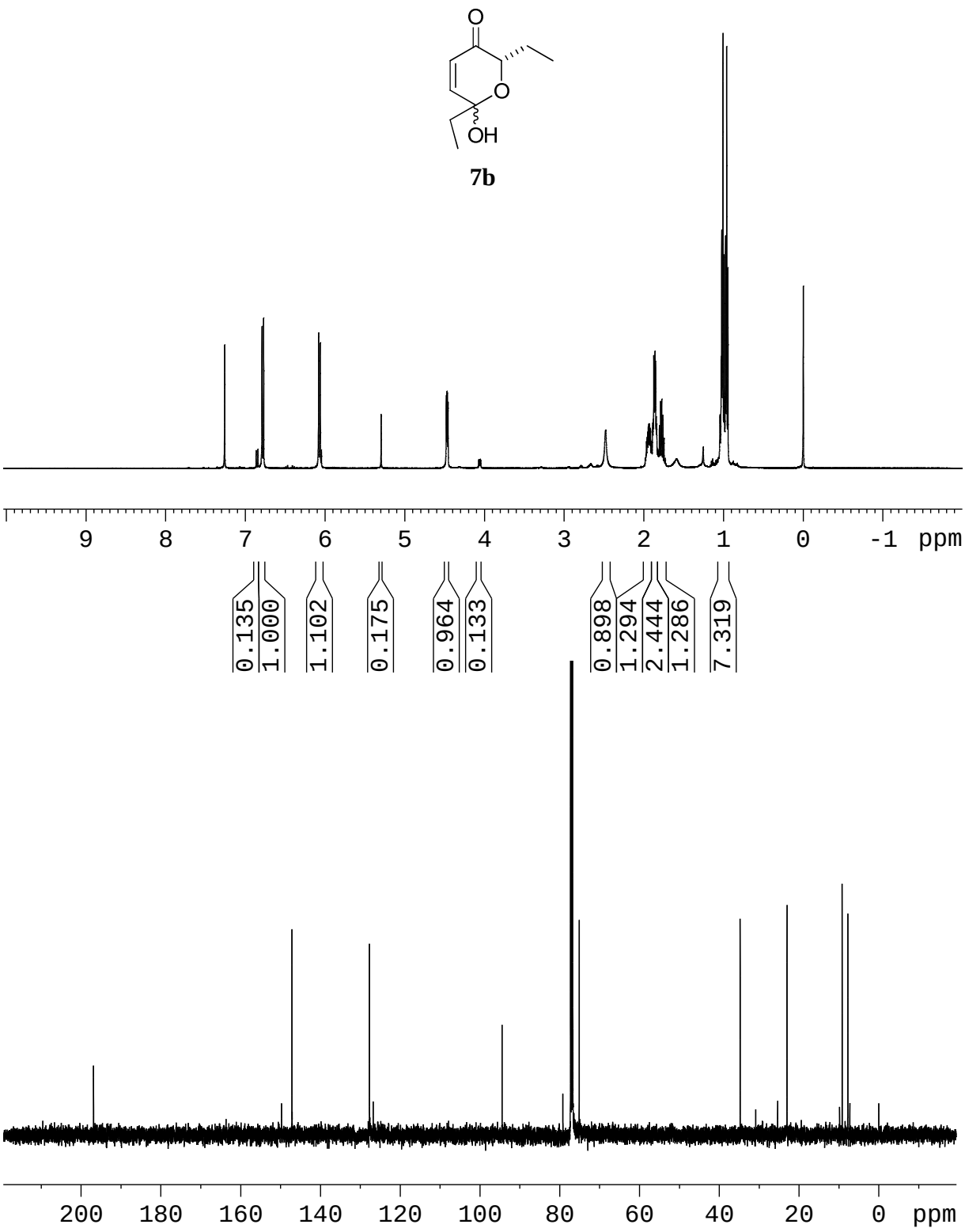
5b

500 MHz ^{1}H and 125 MHz ^{13}C{^{1}H} NMR in $CDCl_3$



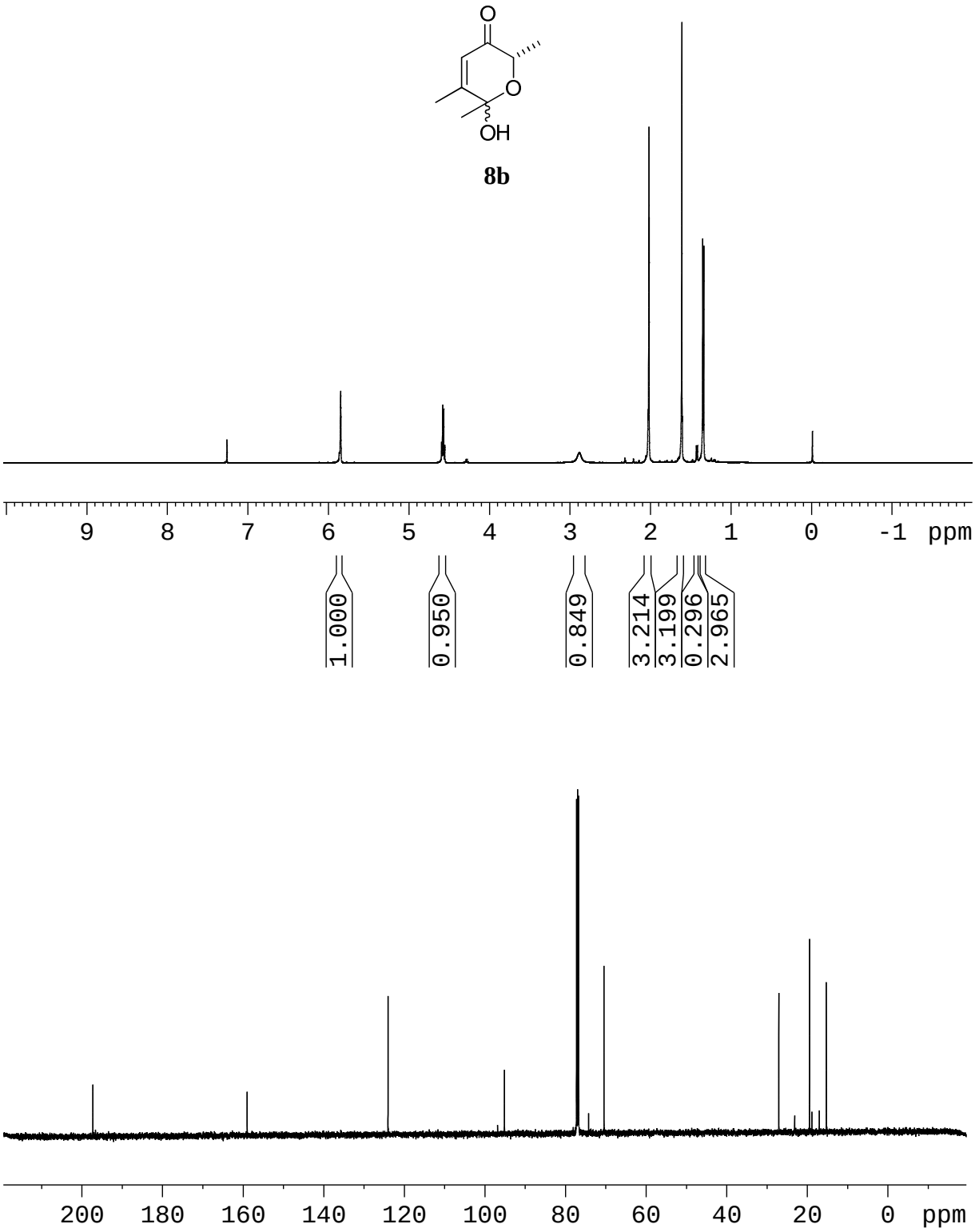
6b

500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$



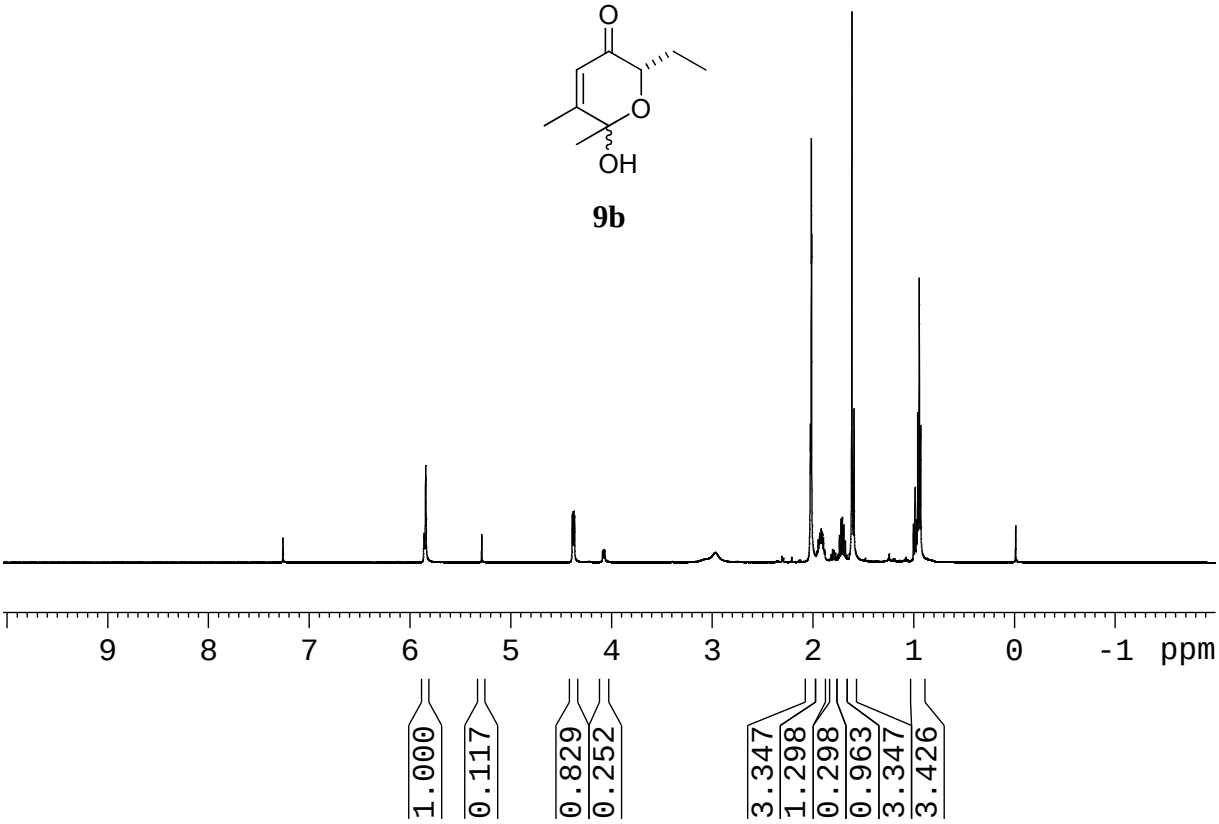
7b

500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$

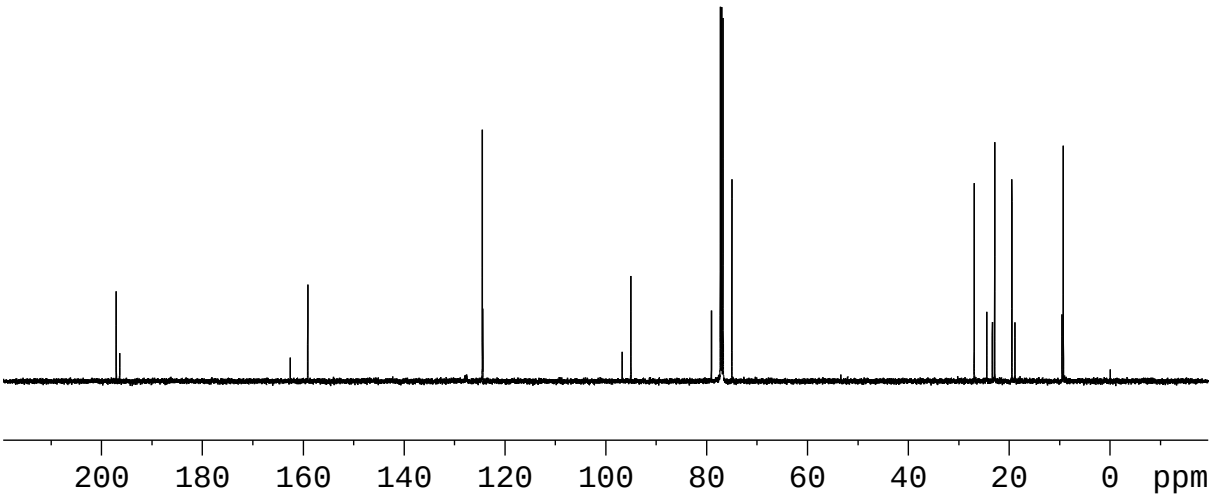


8b

500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$

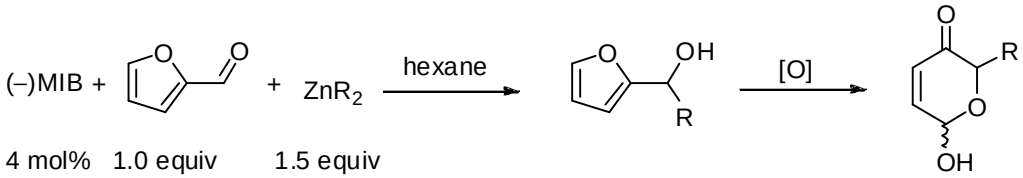


9b



500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR in $CDCl_3$

V. Additional details for Table 1



mixture of anomers

Entry	Oxidation Conditions	Temp	Conversion (%)[a]	Yield (%)
1	5 equiv TBHP, 20 mol% $Ti(O\textit{i}\text{-}Pr)_4$	0 °C	55	50
2	3 equiv TBHP, 40 mol% $VO(acac)_2$ in 10 mL benzene added over 6 h	0 °C	70	50
3	2 equiv TBHP, 10 mol% $VO(acac)_2$ in 10 mL benzene added over 6 h	0 °C	0	0
4	3 equiv TBHP, 30 mol% $VO(acac)_2$ added neat over 24 h	0 °C	70	50
5	3 equiv TBHP, 30 mol% $VO(acac)_2$ in 10 mL toluene added over 6 h	0 °C	100	70
6	3 equiv TBHP, 15 mol% $VO(acac)_2$ in 1 mL CH_2Cl_2 added over 6 h	0 °C	100	70
7	1.1 equiv NBS in 3 portions 4 mL THF, 1 mL H_2O	RT	100	73

[a]Conversion based on NMR analysis of reaction mixture after workup.

VI. References

(1)Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P. Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229-8243.

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