Chemo- and Enantioselective Rh-Catalyzed Hydrogenation of 3-Methylene-1,2-diazetidines: Application to Vicinal Diamine Synthesis

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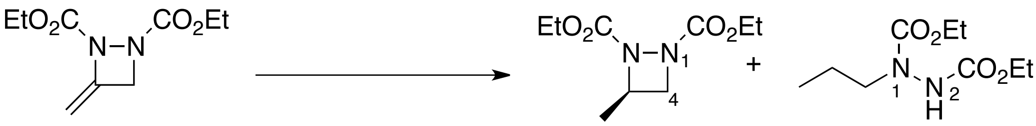
Supplementary Information

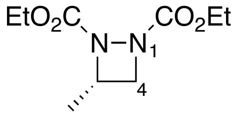
General Hydrogenation Method. To a test tube containing a solution of the 3-methylene-1,2-diazetidine **4** (1 molar equiv.) in EtOAc was added $[Rh(NBD)_2].BF_4$ (0.01 molar equiv.) followed by the ferrocene-based ligand (0.014 molar equiv). The test tube was placed within a high pressure Parr hydrogenator, purged with hydrogen three times and then charged with hydrogen to 50 bar. The reaction was stirred at the specified temperature for the required amount of time, then allowed to cool and concentrated *in vacuo*. Purification on silica gel (EtOAc in hexane) afforded the following compounds.

(*R*)-Diethyl 3-methyl-1,2-diazetidine-1,2-dicarboxylate (5a).

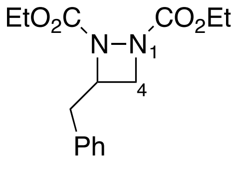


(***R***)**-5a** was synthesized according to the general procedure using **4a** (62 mg, 0.29 mmol), $[Rh(NBD)_2].BF_4$ (1 mg, 2.9 μmol), (*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]ethyl-dicyclohexylphosphine (**6**) (2.5 mg, 4.1 μmol) and ethyl acetate (2 mL). Purification on silica gel (15 % ethyl acetate in hexane) afforded diethyl 1-(propyl)hydrazine-1,2-dicarboxylate (6 mg, 9%) as a colourless oil. IR (film) 3295 (N-H), 2983 (C-H), 1694 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 6.31-6.64 (1H, m, H-2), 4.14-4.22 (4H, m, $CO_2C\underline{H_2}CH_3$), 3.46 (2H, m, $NC\underline{H_2}CH_2CH_3$), 1.59 (2H, sextuplet, J = 7.3 Hz, $NCH_2C\underline{H_2}CH_3$), 1.24-1.28 (6H, m, $CO_2CH_2C\underline{H_3}$), 0.90 (3H, t, J = 7.3 Hz, $NCH_2CH_2C\underline{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) 156.3 (2C, $\underline{C}O_2CH_2CH_3$), 62.4 (1C, $CO_2\underline{C}H_2CH_3$), 62.0 (1C, $CO_2\underline{C}H_2CH_3$), 20.7 (1C, $NCH_2\underline{C}H_2CH_3$), 14.6 (1C, $CO_2CH_2\underline{C}H_3$), 14.5 (1C, $CO_2CH_2\underline{C}H_3$), 11.1 (1C, $NCH_2CH_2\underline{C}H_3$); MS ($ES^+$) m/z = 241 $[M+Na]^+$, HRMS (ES^+) m/z calculated for $C_9H_{18}N_2O_4Na$ $[M+Na]^+$: 241.1159; found: 241.1160. Further elucidation afforded **5a** (56 mg, 89%, 44% ee) as a colourless oil. $[\alpha]^{30}_D$ = 0.0 (c 1.50, EtOAc); IR (film) 2977 (CH_3), 1702 (C=O), 1273 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.39-4.47 (1H, m, H-3), 4.32 (1H, t, J = 8.0 Hz, H-4), 4.15-4.27 (4H, m, $CO_2C\underline{H_2}CH_3$), 3.74 (1H, dd, J = 6.2, 8.0

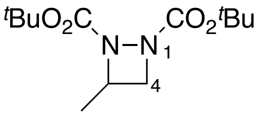
Hz, H-4), 1.48 (3H, d, *J* = 6.3 Hz, $\mathrm{CHC\underline{H}_3}$), 1.28 (6H, t, *J* = 7.2 Hz, $\mathrm{CO_2CH_2C\underline{H}_3}$); ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$) 161.1 (1C, $\mathrm{\underline{C}O_2CH_2CH_3}$), 160.9 (1C, $\mathrm{\underline{C}O_2CH_2CH_3}$), 62.6 (1C, $\mathrm{CO_2\underline{C}H_2CH_3}$), 62.4 (1C, $\mathrm{CO_2\underline{C}H_2CH_3}$), 58.1 (1C, C-3), 56.1 (1C, C-4), 20.7 (1C, $\mathrm{CH\underline{C}H_3}$), 14.4 (2C, $\mathrm{CO_2CH_2\underline{C}H_3}$); MS (ES$^+$) *m/z* = 239 [M+Na]$^+$, HRMS (ES$^+$) *m/z* calculated for $\mathrm{C_9H_{16}N_2O_4Na}$ [M+Na]$^+$: 239.1002; found: 239.1004. Enantiopurity by HPLC analysis on a Chiralcel AD column (1.0 mL min^{-1}, 3% IPA in hexanes): t_R 22.67 (*major*) and 24.85 (*minor*) min.



(*S*)-Diethyl 3-methyl-1,2-diazetidine-1,2-dicarboxylate (5a). (*S*)-5a was synthesized according to the general procedure using **4a** (250 mg, 1.17 mmol), $\mathrm{[Rh(NBD)_2].BF_4}$ (5 mg, 17 μmol), (S_P, S'_P)-1,1′-Bis [bis(4-methoxy-3,5-dimethylphenyl) phosphino]-2,2′-bis [(*R*)-α-(dimethylamino)benzyl]ferrocene **18** (17 mg, 24 μmol) and EtOAc (2 mL). Purification on silica gel (15 % EtOAc in hexane) afforded **280** (244 mg, 98%, 89% ee) as a colourless oil. Spectroscopic data as previously described. Enantiopurity by HPLC analysis on a Chiralcel AD column (1.0 mL min^{-1}, 3% IPA in hexanes): t_R 22.67 (*minor*) and 24.85 (*major*) min.

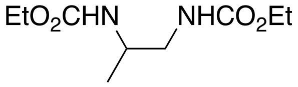


Diethyl 3-benzyl-1,2-diazetidine-1,2-dicarboxylate (5b). 5b was synthesised according to the general procedure using **4b** (50 mg, 0.17 mmol), $\mathrm{[Rh(NBD)_2]BF_4}$ (1 mg, 1.7 μmol), (*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (2 mg, 2.5 μmol), and EtOAc (2 mL). Purification of silica gel (20% EtOAc in hexane) afforded **282** (27 mg, 54% 33% ee) as a colourless oil. $[\alpha]^{30}_{D}$ = +36.0 (*c*. 3.50, EtOAc); IR (film) 2984 ($\mathrm{CH_3}$), 1705 (C=O), 1270 (C-O), 702 (Ar-H) cm^{-1}; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) 7.18-7.30 (5H, m, ArH), 4.52-4.59 (1H, m, H-3), 4.06-4.26 (5H, m, H-4, $\mathrm{CO_2C\underline{H}_2CH_3}$), 3.82 (1H, dd, *J* = 6.0, 8.4 Hz, H-4), 3.11 (1H, dd, J = 5.0, 14.0 Hz, -CH$\underline{H}$Ph), 3.04 (1H, dd, *J* = 7.7, 14.0 Hz, -C$\underline{H}$HPh), 1.25 (3H, t, *J* = 7.1 Hz, $CO_2CH_2C\underline{H_3}$), 1.22 (3H, t, *J* = 7.1 Hz, $CO_2CH_2C\underline{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) 160.8 (2C, $\underline{C}O_2CH_2CH_3$), 135.4 (1C, ArC), 129.5 (2C, ArCH), 128.4 (2C, ArCH), 126.4 (1C, ArCH), 62.5 (2C, $CO_2\underline{C}H_2CH_3$), 62.1 (1C, C-3), 53.8 (1C, C-4), 40.2 (1C, -$\underline{C}H_2$Ph), 14.4 (2C, $CO_2CH_2\underline{C}H_3$); MS (ES$^+$) *m/z* = 315 [M+Na]$^+$, HRMS (ES$^+$) *m/z* calculated for $C_{15}H_{20}N_2O_4Na$ [M+Na]$^+$: 315.1315; found: 315.1311. Enantiopurity by HPLC analysis on a Chiralcel AD column (1.0 mL min^{-1}, 5% IPA in hexanes): t_R 18.22 (*minor*) and 21.32 (*major*) min.

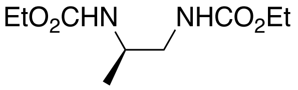


Di-*tert*-butyl 3-methyl-1,2-diazetidine-1,2-dicarboxylate (5c). **5c** was synthesised according to the general procedure using **4c** (50 mg, 0.19 mmol), $[Rh(NBD)_2]BF_4$ (1 mg, 1.9 μmol), (*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]-ethyldicyclohexylphosphine (2 mg, 2.7 μmol) and EtOAc (2 ml). Purification on silica gel (12.5% EtOAc in hexane) afforded **5c** (38 mg, 76%, 60% ee) as a colourless oil. $[\alpha]^{30}_{D}$ = +24.5 (*c* 1.25, EtOAc); IR (neat) 2979 (CH_3), 1700 (C=O), 1158 (C-O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.29-4.36 (1H, m, H-3), 4.21 (1H, t, *J* = 7.9 Hz, H-4), 3.65 (1H, dd, *J* = 6.4, 7.9 Hz), 1.49 (9H, s, $CO_2C(C\underline{H_3})_{\underline{3}}$), 1.48 (9H, s, $CO_2C(C\underline{H_3})_{\underline{3}}$), 1.45 (3H, d, *J* = 6.4 Hz, $CHC\underline{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) 160.1 (1C, $\underline{C}O_2C(CH_3)_3$), 160.0 (1C, $\underline{C}O_2C(CH_3)_3$), 81.8 (1C, $CO_2\underline{C}(CH_3)_3$), 81.7 (1C, $CO_2\underline{C}(CH_3)_3$), 57.4 (1C, C-3), 55.6 (1C, C-4), 28.13 (3C, $CO_2C(\underline{C}H_3)_{\underline{3}}$), 28.12 (3C, $CO_2C(\underline{C}H_3)_{\underline{3}}$), 20.7 (1C, $CH\underline{C}H_3$); MS (ES$^+$) *m/z* = 295 [M+Na]$^+$, HRMS (ES$^+$) *m/z* calculated for $C_{13}H_{24}N_2O_4Na$ [M+Na]$^+$: 295.1652; found: 295.1652. Enantiopurity by HPLC analysis on a Chiralcel AD column (1.0 mL min^{-1}, 1% IPA in hexanes): t_R 9.20 (*minor*) and 9.93 (*major*) min.

Reductive Cleavage of (*S*)-5a to (*S*)-19. Freshly cut pellets of lithium (66 mg, 9.40 mmol) were placed in a flask containing 4,4'-di-*tert*-butylbiphenyl (500 mg, 1.88 mmol). The tube was evacuated and filled with argon 3 times. THF (5 mL) was added and stirring continued for 15 minutes, whereupon the solution turned dark green. The vessel was cooled to –78 °C under an argon atmosphere and the resulting solution of LiDBB used immediately. To (*S*)-**5a** (87 mg, 0.40 mmol, 89%ee) in THF (3 mL) at –78 °C was added the LiDBB solution until the dark green colour persisted. The reaction mixture was stirred for a further 30 minutes, and then quenched by the addition of saturated aqueous NH_4Cl (1 mL). After warming to room temperature, diethyl ether (2 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (20% EtOAc in hexane) afforded (*S*)-**19** (56 mg, 64%, 84%ee) as a white crystalline solid. M.p. 132-133 °C; $[\alpha]^{30}_{D} = -11.1$ (*c* 1.75, EtOAc). IR (neat) 3308 (N-H), 2980 (CH_3), 1681 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), 5.28 (1H, br s, NH), 5.02-5.11 (1H, br m, NH), 4.02-4.10 (4H, m, $CO_2C\underline{H_2}CH_3$), 3.77 (1H, br m, H-2), 3.15-3.29 (2H, m, H-2), 1.19 (6H, br t, *J* = 7.1 Hz, $CO_2CH_2C\underline{H_3}$), 1.12 (3H, d, *J* = 6.7 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) 157.4 (1C, $\underline{C}O_2CH_2CH_3$), 156.6 (1C, $\underline{C}O_2CH_2CH_3$), 60.9 (1C, $CO_2\underline{C}H_2CH_3$), 60.7 (1C, $CO_2\underline{C}H_2CH_3$), 47.6 (1C, C-2), 46.4 (1C, C-1), 18.4 (1C, C-3), 14.6 (2C, $CO_2CH_2\underline{C}H_3$); MS (ES$^+$) *m*/*z* = 241 [M+Na]$^+$, HRMS (ES$^+$) *m*/*z* calculated for $C_9H_{18}N_2O_4Na$ [M+Na]$^+$: 241.1159; found: 241.1157.



Authentic Sample of (±)-19 from 1,2-diaminopropane. To a stirred solution of commercial (±)-1,2-diaminopropane (Aldrich, 1.0 g, 13.5 mmol) and potassium carbonate (2.56 g, 27.0 mmol), in THF (20 mL) was added ethyl chloroformate (2.57 mL, 27.0 mmol) and the reaction was stirred for 4 h at 25 °C. The mixture was poured into water (50 ml) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Recrystallization from hexane afforded (±)-**19** (1.85 g, 63%) as a white crystalline solid. Data as previously described.



Authentic Sample of (*R*)-19 from (*R*)-1,2-diaminopropane. To a stirred solution of commercial (*R*)-1,2-diaminopropane (Aldrich, 0.5 g, 3.40 mmol) and potassium carbonate (1.36 g, 14.28 mmol) in THF (10 mL) and water (10 mL) was added ethyl chloroformate (0.68 mL, 7.14 mmol) and the reaction was stirred for 4 h at 25 °C. The mixture was poured into water (50 ml) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford (*R*)-**19** (734 mg, 99%) as a white crystalline solid. $[\alpha]^{30}_{D} = +12.5$ (*c* 1.75, EtOAc). Data as previously described.

Figure 1. ^{1}H NMR Spectra (400 MHz, d_6-benzene) of (±)-**19** in the presence (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol.

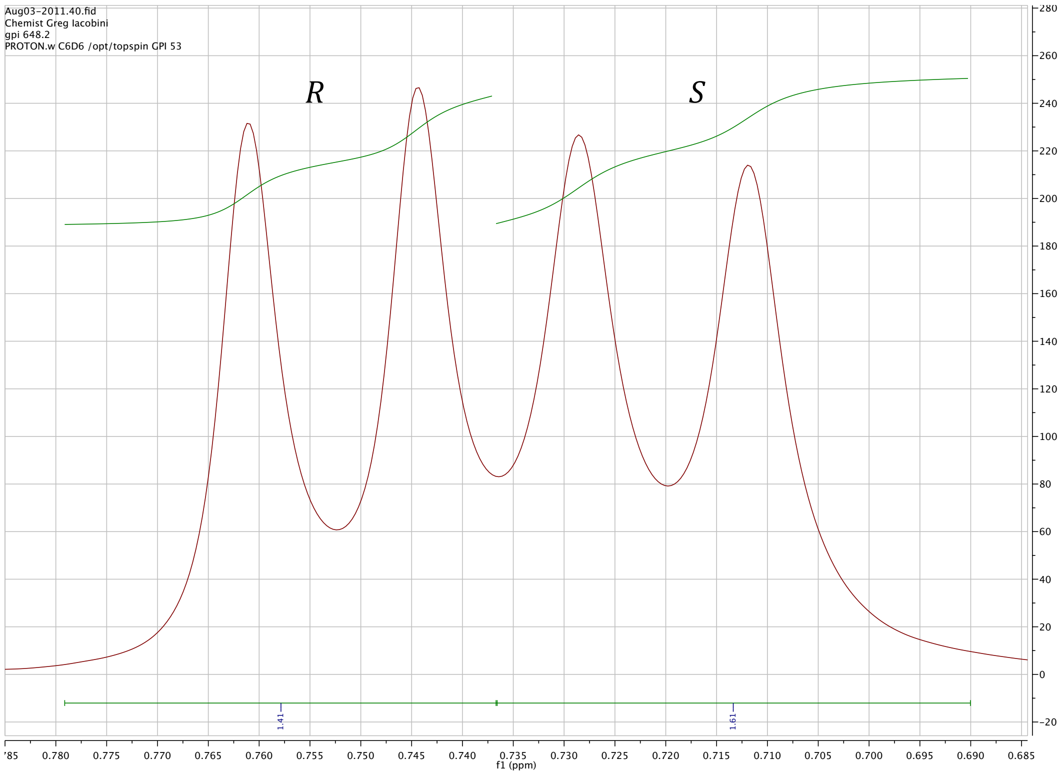


Figure 2. ^{1}H NMR (400 MHz, d_6-benzene) of (*R*)-**19** and (±)-**19** in the presence of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol.

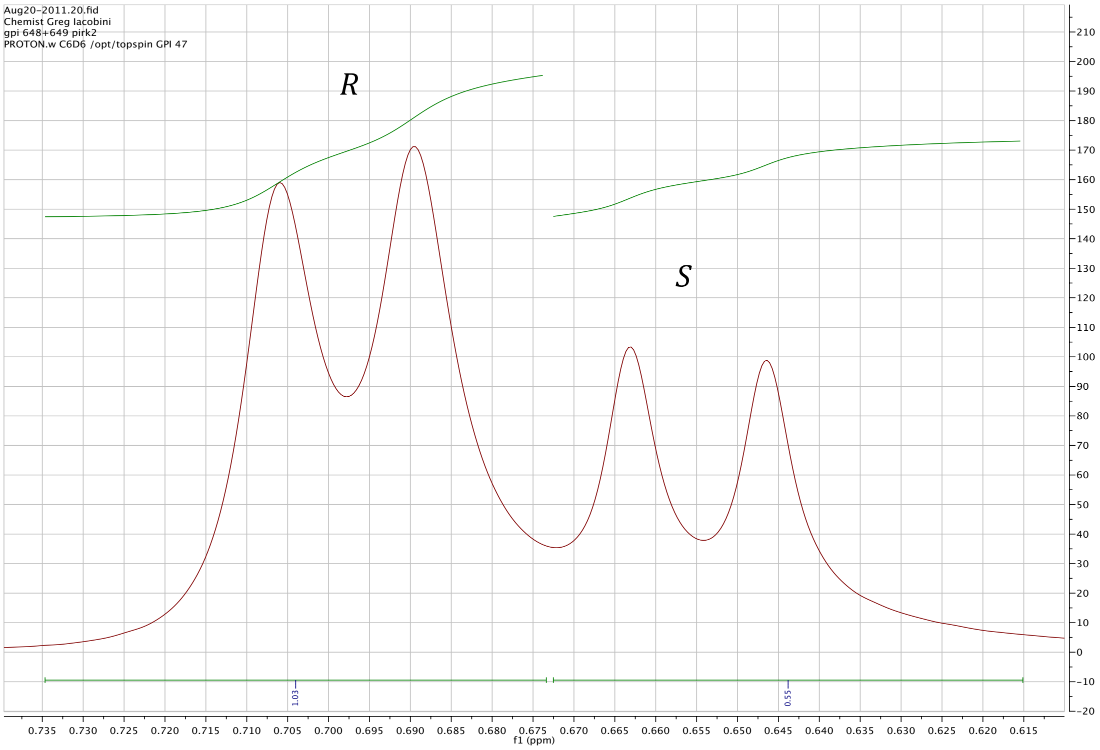


Figure 3. ^{1}H NMR (400 MHz, d_6-benzene) of enantioenriched (*S*)-**19** (from LiDBB reduction) in the presence (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol. Opposite signals enhanced relative to authentic sample derived from (*R*)-1,2-diaminopropane. From integrals, (*S*)-**19** was determined to be 84%ee.

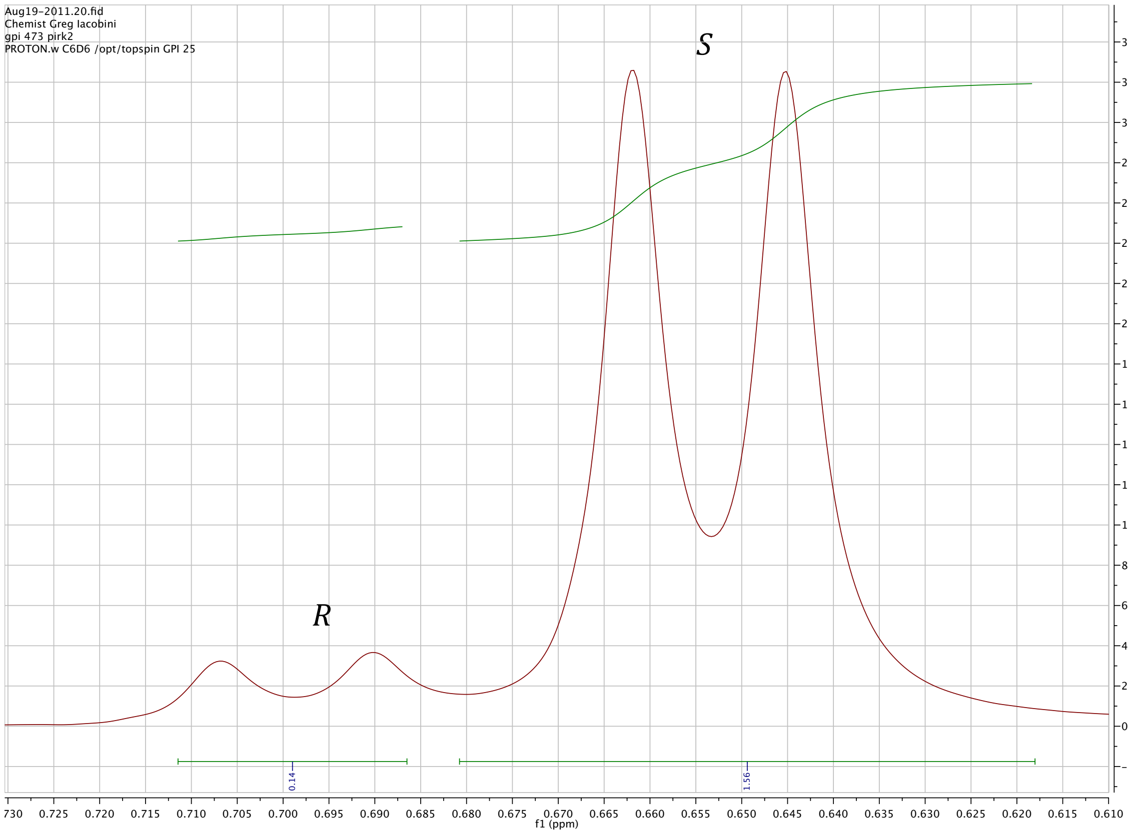


Figure 4. ^{1}H NMR (400 MHz, $CDCl_3$) of **5a**.

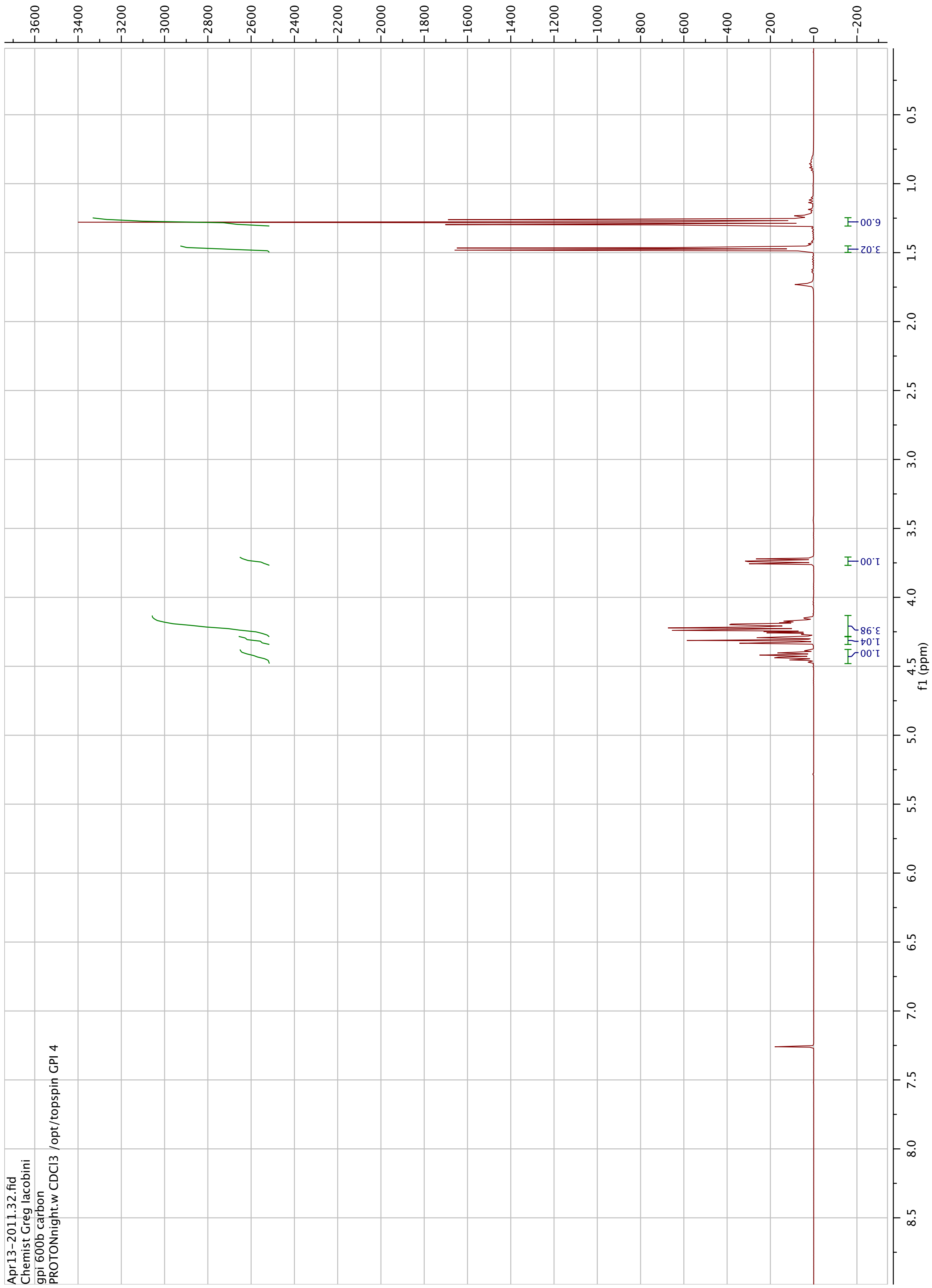


Figure 5. ^{13}C NMR (100 MHz CDCl$_3$) of **5a**.

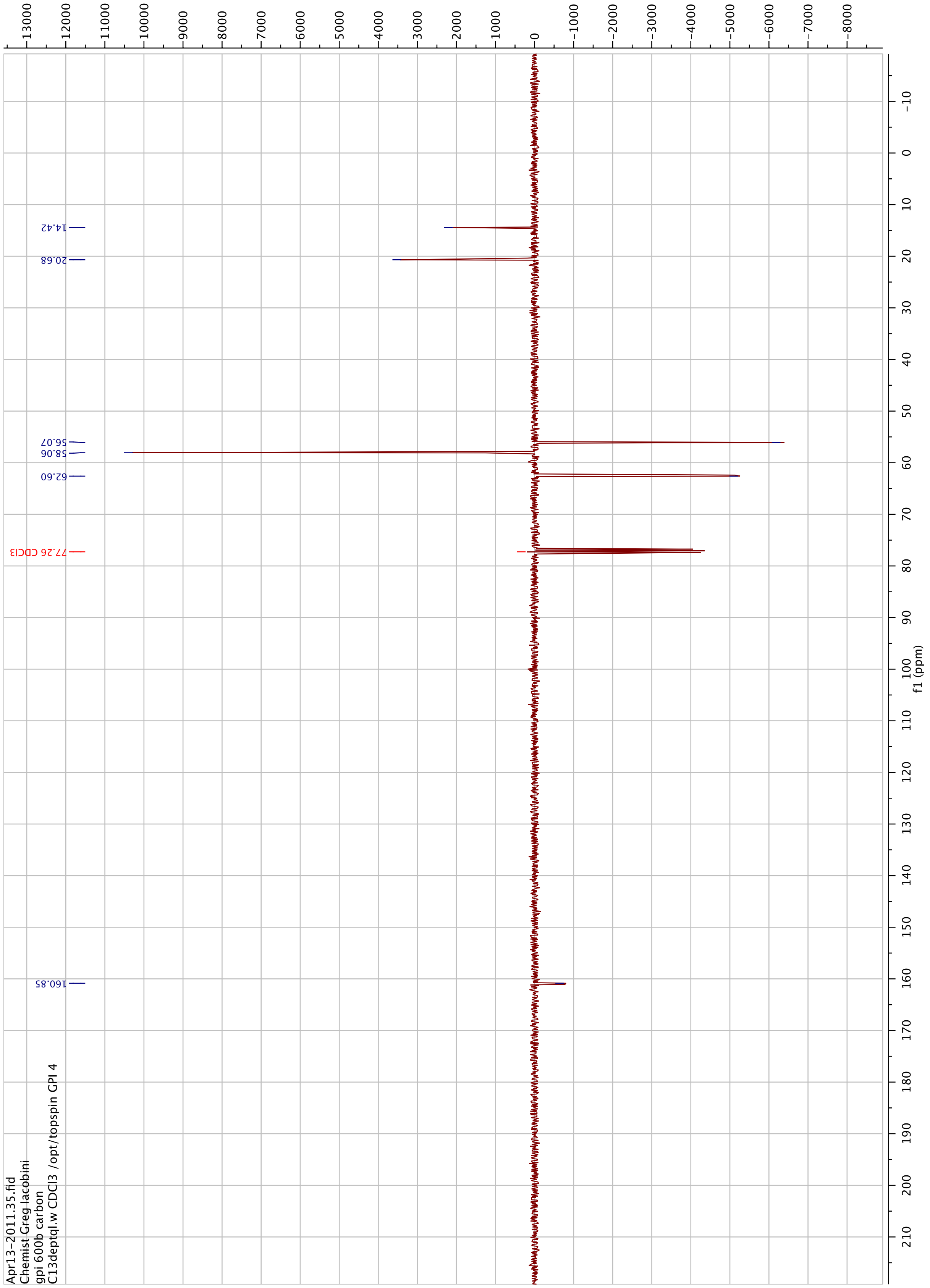


Figure 6. ^{1}H NMR (400 MHz, $CDCl_3$) of **5b**.

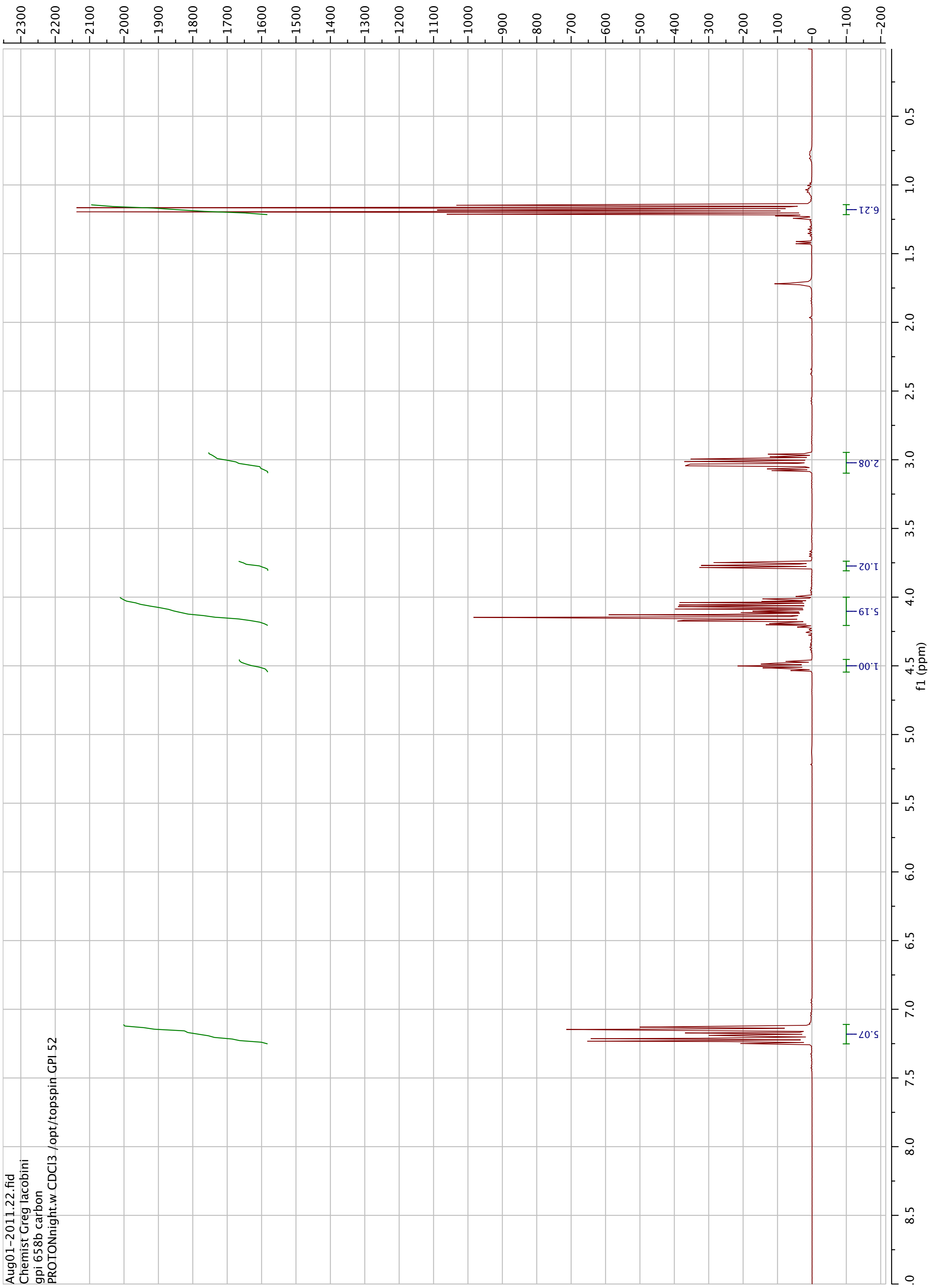


Figure 7. ^{13}C NMR (100 MHz, CDCl$_3$) of **5b**.

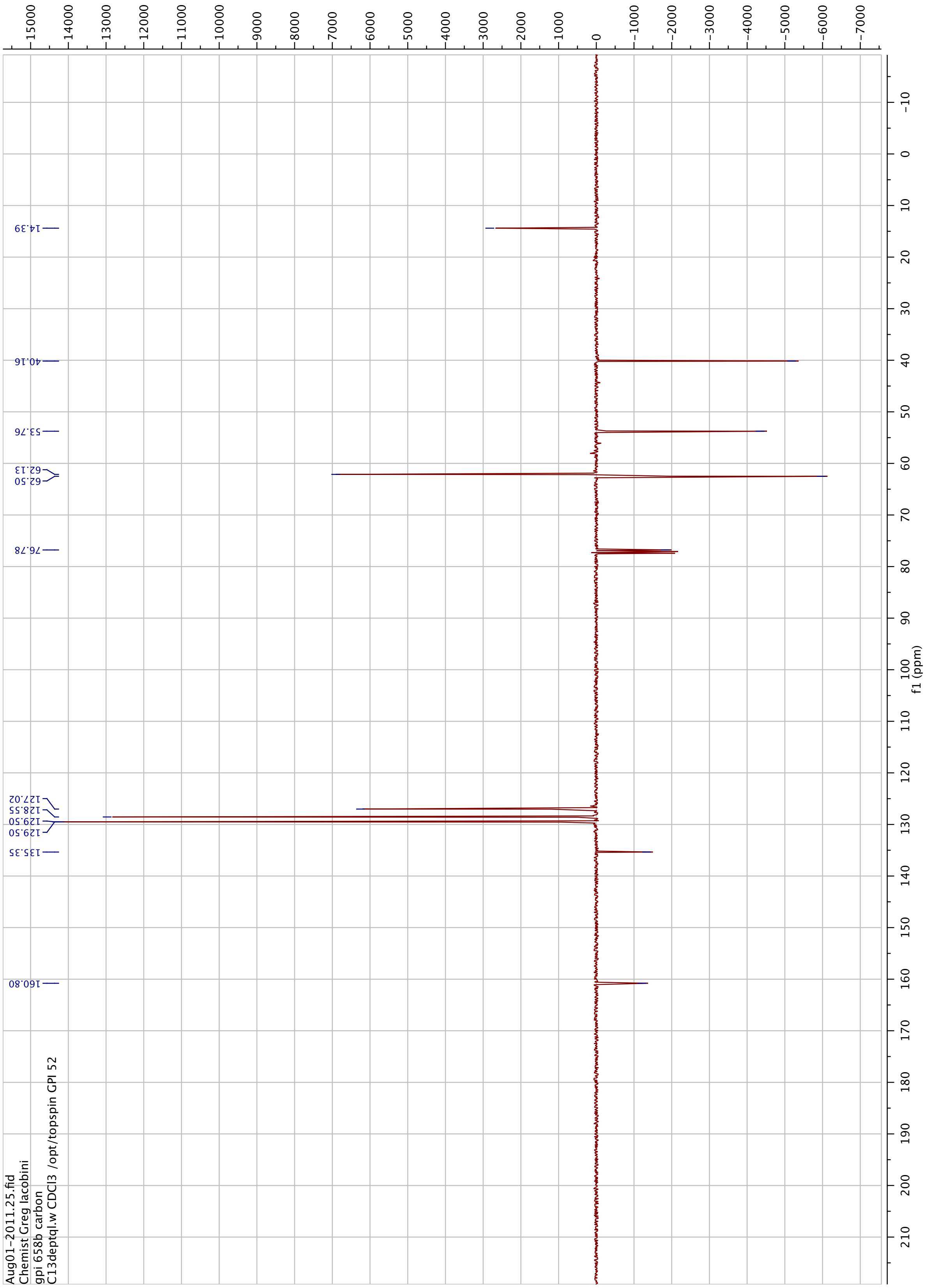


Figure 8. ^{1}H NMR (400 MHz, $CDCl_3$) of **5c**.

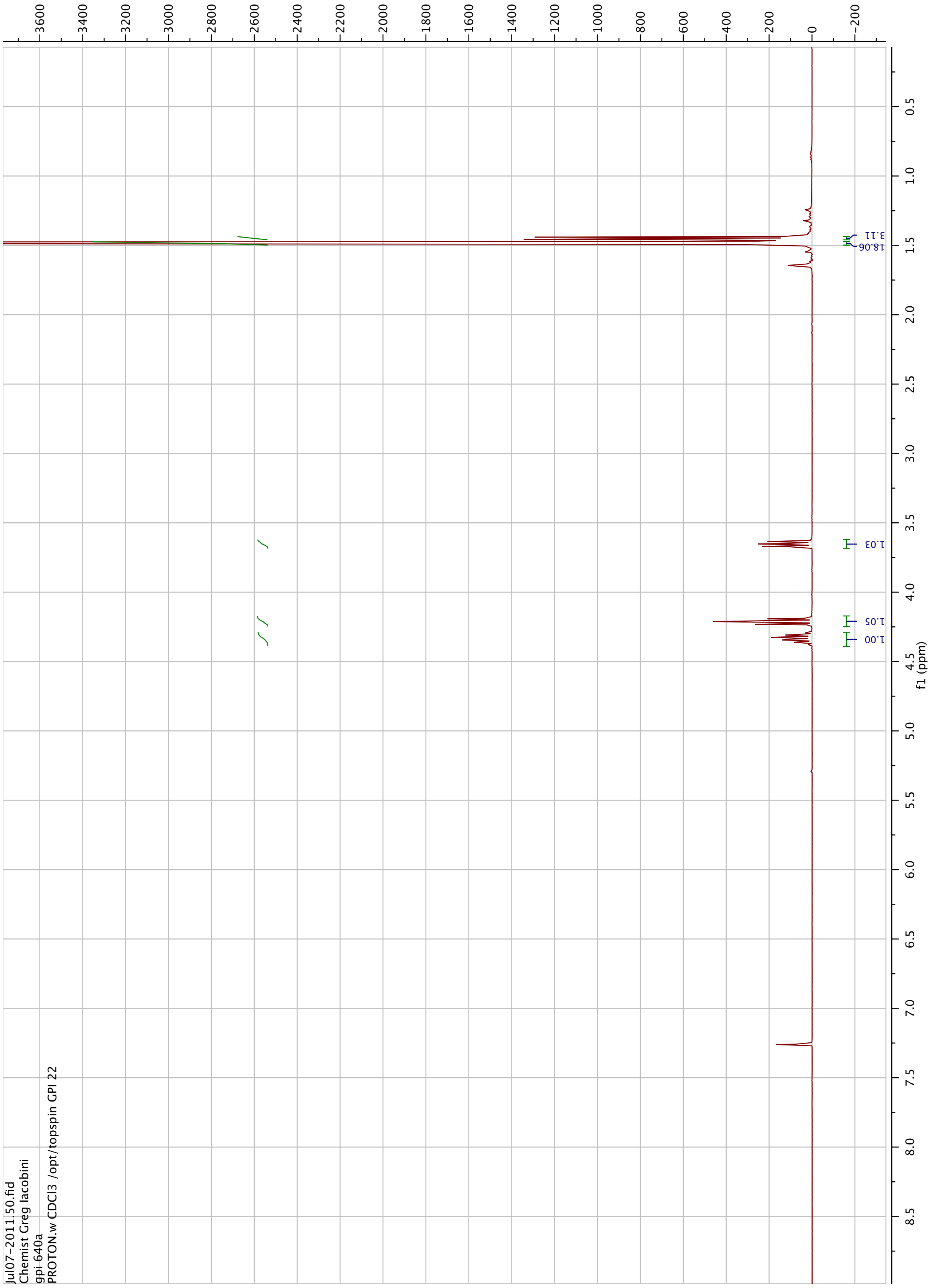


Figure 9. ^{13}C NMR (100 MHz, CDCl$_3$) of **5c**.

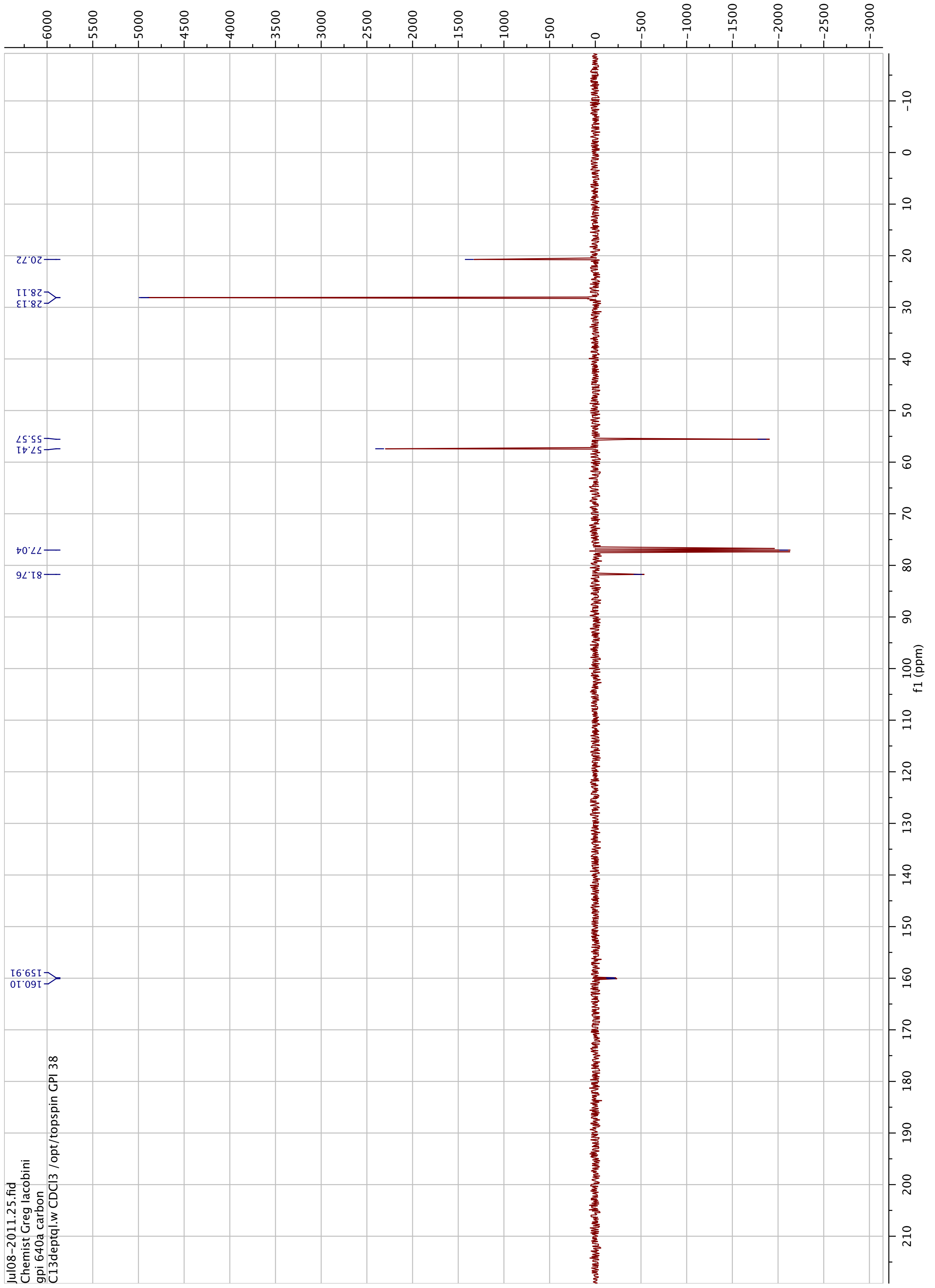


Figure 10. ^{1}H NMR (400 MHz, CDCl$_3$) of (*S*)-**19**.

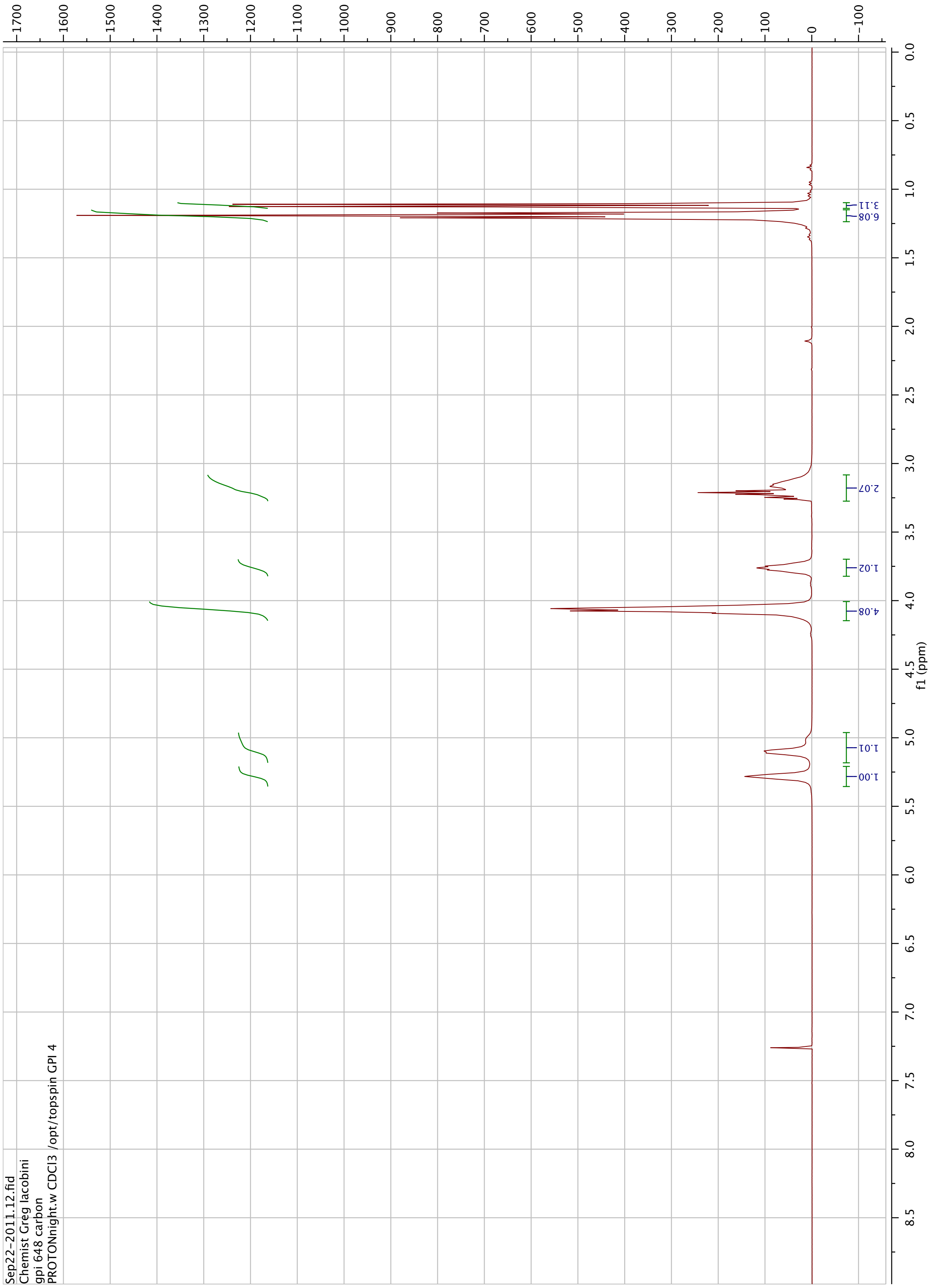


Figure 11. ^{13}C NMR (100 MHz, CDCl$_3$) of (*S*)-**19**.