Supplementary Material (ESI) for Chemical Communications

Supporting Information for

Reaction of 2-Methylenetetrahydropyrans with Activated Aldehydes and Ketones. A Three Component Coupling Protocol

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General Methods:

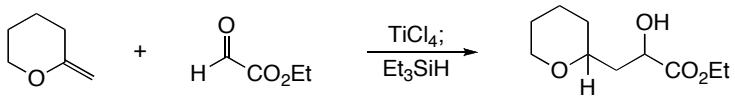
All air sensitive reactions were performed in oven dried glassware under an atmosphere of argon. Reaction solvents were dried over CaH_2 (benzene, dichloromethane), magnesium (methanol), or sodium/benzophenone ketyl (tetrahydrofuran, diethyl ether) and were distilled just prior to use. 2-Methylenetetrahydropyran[1] and 3,4-dihydro-2-methylene-2H-1-benzopyran[2] were prepared according to the literature procedure. Ethyl glyoxylate and 2,3-butanedione were distilled just prior to use. Ethyl glyoxylate was distilled according to the procedure of Evans.[3] All other reagents were reagent grade and were purified as necessary. Analytical thin layer chromatography was performed on EM silica gel 60 F_{254} glass plates (0.25 mm). Melting points were recorded using an Electrothermal melting point apparatus and are uncorrected. Flash column chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) from SiliCycle, Inc. ^{1}H NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual $CHCl_3$ (δ 7.27 ppm) or benzene (δ 7.15 ppm) as the internal standard. ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual $CHCl_3$ as the internal standard (δ

1. McRae, K. J.; Rizzacasa, M. A. *J. Org. Chem*. **1997**, *62*, 1196.
2. (a) Petasis, A. N.; Bzowej, E. I. *J. Am. Chem. Soc*. **1990**, *112*, 6392. (b) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386.
3. D. A. Evans, D. W. C. MacMillan and K. R. Campos, *J. Am. Chem. Soc.* **1997**, *119*, 10859.

77.0 ppm). IR spectra were obtained with a Thermo Nicolet IR-100 spectrometer on NaCl plates. Elemental analyses were performed by Complete Analysis Laboratories, Inc.; Parsippany, NJ. High resolution mass spectra were obtained using the positive ion electrospray mode on a 3-Tesla FT mass spectrometer at The Ohio State University, Columbus, OH.

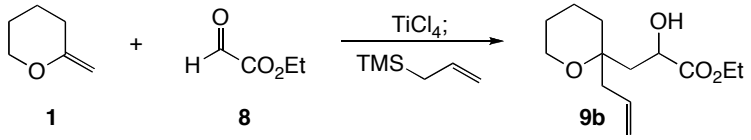
Experimental Procedures:

General Procedure for Three Component Coupling: To a stirred solution of the enol ether (1.00 mmol) in 5 mL CH_2Cl_2 was added the carbonyl derivative (1.20 mmol). The resulting mixture was cooled to -78°C and titanium(IV)chloride (1.0 mL of a 1.0 M solution in CH_2Cl_2, 1.0 mmol) was added dropwise. After the time specified in Table 2, triethylsilane or allyltrimethylsilane (1.00 mmol) was added dropwise and stirring continued for 5 hours at -78°C. Saturated $NaHCO_3$ (2 mL) was then added carefully and the mixture was warmed to room temperature. The layers were separated and the aqueous layer was extracted with additional CH_2Cl_2 (3x). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

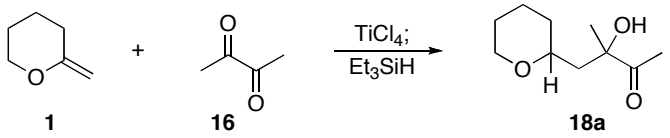


1 **8** **9a**

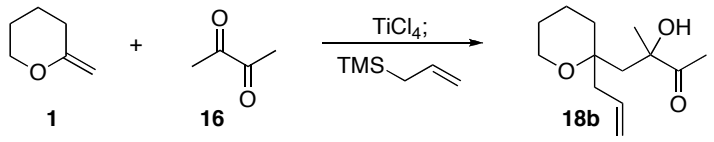
Tetrahydropyran 9a: The reaction of 2-methylenetetrahydropyran, ethyl glyoxylate and triethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 10:1 → 5:1) to afford tetrahydropyran **9a** (86%) as a colorless oil (1:1 mixture of diastereomers). TLC: R_f = 0.46 (hexanes:EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.40 (0.5H, m), 4.32 (0.5H, m), 4.24 (1H, dq, *J* = 7.0, 2.4 Hz), 4.23 (1H, q, *J* = 7.1 Hz), 3.99 (1H, dm, *J* = 11.2 Hz), 3.92 (1H, dm, *J* = 11.2 Hz), 3.56 (1H, m), 3.55 (0.5H, d, *J* = 3.3 Hz), 3.44 (0.5H, br s), 3.42 (1H, m), 1.97 (0.5H, ddd, *J* = 14.4, 10.2, 3.2 Hz), 1.90 (1H, m), 1.82 (1H, m), 1.72 (0.5H, ddd, *J* = 14.4, 8.2, 2.6 Hz), 1.49 (3.5, m), 1.36 (0.5, m), 1.30 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.0, 174.3, 75.5, 74.8, 69.2, 68.5, 68.4, 68.2, 61.3, 61.2, 40.4, 40.1, 32.0, 31.7, 25.8, 25.7, 23.2, 23.2, 14.2, 14.1. IR (film): 3460, 2935, 2856, 1735 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39%; H, 8.97%. Found: C, 59.36%; H, 8.99%.



Tetrahydropyran 9b: The reaction of 2-methylenetetrahydropyran, ethyl glyoxylate and allyltrimethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 15:1 → 8:1) to afford tetrahydropyran **9b** (55%) as a yellow oil (2:1 mixture of diastereomers). TLC: R_f = 0.53 (hexanes:EtOAc, 1:2). δ 5.78 (1H, m), 5.13 (2H, m), 4.52 (1H, m), 4.23 (0.7H, m), 4.23 (1.3H, q, *J* = 7.1 Hz), 4.04 (0.3H, d, *J* = 2.8 Hz), 3.93 (0.7H, d, *J* = 2.9 Hz), 3.73 (2H, m), 2.62 (1H, dd, *J* = 14.2, 6.6 Hz), 2.47 (0.3H, dd, *J* = 14.0, 7.2 Hz), 2.31 (0.7H, dd, *J* = 14.2, 7.9), 1.96 (2H, m), 1.78 (2H, m), 1.63 (1H, m), 1.53 (3H, m), 1.30 (2H, t, *J* = 7.1 Hz), 1.29 (1H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.5, 133.2, 118.6, 118.3, 75.5, 68.5, 68.2, 61.5, 61.3, 41.1, 40.6, 39.4, 38.2, 33.0, 31.4, 29.7, 25.4, 18.8, 18.6, 14.2. IR: 3479, 3075, 2936, 2868, 1730, 1640 cm^{-1}. HRMS (ESI) Calcd for $C_{13}H_{22}O_4$ ($[M+Na]^+$): 265.1410, found 265.1405.

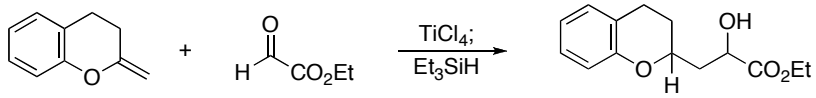


Tetrahydropyran 18a: The reaction of 2-methylenetetrahydropyran, 2,3-butanedione and triethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 15:1 → 10:1) to afford tetrahydropyran **18a** (79%) as a yellow oil (4:1 mixture of diastereomers). TLC: R_f = 0.47 (hexanes:EtOAc, 3:1). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.85 (0.2H, s), 4.36 (0.8H, s), 3.98 (0.2H, dm, *J* = 11.0 Hz), 3.80 (0.8H, dm, *J* = 10.8 Hz), 3.44 (0.8H, m), 3.37 (0.2H, m), 3.24 (1H, m), 2.29 (0.6H, s), 2.22 (2.4H, s), 2.03 (0.2H, dd, *J* = 14.6, 2.0 Hz), 1.98 (0.8H, dd, *J* = 14.6, 10.1 Hz), 1.80 (1H, m), 1.75 (0.8H, dd, *J* = 14.6, 2.0 Hz), 1.71 (0.2H, dd, *J* = 14.4, 10.5 Hz), 1.48 (4H, m), 1.31 (2.4H, s), 1.27 (1H, m), 1.26 (0.6H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.1, 73.5, 68.3, 68.0, 45.7, 44.5, 32.3, 31.9, 29.7, 26.5, 26.2, 26.0, 25.7, 24.1, 23.4, 22.9. IR (film): 3462, 2931, 2857, 1710 cm^{-1}. HRMS (ESI) Calcd for $C_{10}H_{18}O_3$ ($[M+Na]^+$): 209.1148, found 209.1145.



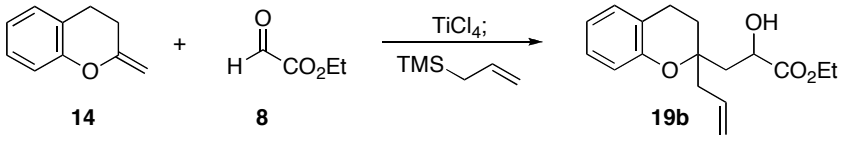
1 **16** **18b**

Tetrahydropyran 18b: The reaction of 2-methylenetetrahydropyran, 2,3-butanedione and allyltrimethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 15:1 → 8:1) to afford tetrahydropyran **18b** (51%) as a colorless oil (2:1 mixture of diastereomers). TLC: R_f = 0.46 (hexanes:EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.77 (1H, m), 5.10 (2H, m), 4.99 (0.7H, s), 4.63 (0.3H, s), 3.68 (1.4H, m), 3.60 (0.6H, m), 2.59 (0.7H, dd, *J* = 14.1, 6.4 Hz), 2.42 (0.3H, dd, *J* = 14.2, 6.1 Hz), 2.32 (2.1H, s), 2.31 (0.7H, dd, *J* = 14.1, 8.0 Hz), 2.31 (0.3H, d, *J* = 14.9 Hz), 2.23 (0.9H, s), 2.22 (0.3H, dd, *J* = 14.4, 5.3 Hz), 2.20 (0.7H, d, *J* = 14.7 Hz), 1.98 (0.3H, m), 1.95 (0.7H, d, *J* = 14.7 Hz), 1.79 (0.3H, d, *J* = 14.9 Hz), 1.60 (2H, m), 1.45 (3.7H, m), 1.26 (0.9H, s), 1.22 (2.1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 215.7, 133.6, 133.4, 118.3, 118.1, 79.3, 78.7, 76.2, 75.0, 61.3, 61.3, 47.0, 45.9, 38.8, 37.8, 33.2, 32.1, 28.5, 28.4, 25.4, 25.2, 24.6, 18.9, 18.7. IR (film): 3445, 3075, 2933, 2863, 1711, 1639 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99%; H, 9.80%. Found: C, 68.92%; H, 10.02%.



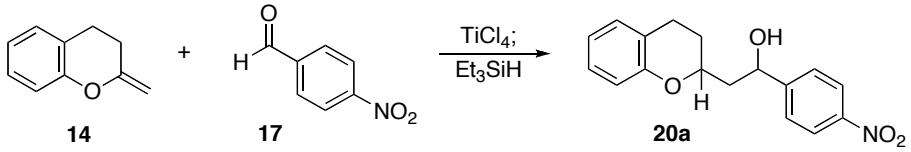
14 **8** **19a**

Dihydrobenzopyran 19a: The reaction of 5,6-benzo-2-methylenetetrahydropyran (**14**), ethyl glyoxylate and triethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 9:1 → 4:1) to afford dihydrobenzopyran **19a** (97%) as a colorless oil (1.5:1 mixture of diastereomers). TLC: R_f = 0.41 (hexanes:EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.08 (2H, m), 6.84 (1.4H, m), 6.72 (0.6H, d, *J* = 8.1 Hz), 4.59 (0.4H, ddd, *J* = 9.9, 6.0, 2.9 Hz), 4.41 (0.6H, *J* = 9.8, 5.2 Hz), 4.35 (1H, m), 4.28 (2H, q, *J* = 7.2 Hz), 3.33 (0.6H, d, *J* = 4.5 Hz), 3.17 (0.4H, d, *J* = 6.0 Hz), 2.84 (2H, m), 2.18 (1.6H, m), 2.02 (1H, m), 1.82 (1.4H, m), 1.32 (1.2H, t, *J* = 7.4 Hz), 1.30 (1.8H, t, *J*= 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.0, 174.7, 154.3, 154.2, 129.4, 127.0, 121.8, 121.7, 120.1, 116.7, 116.5, 72.0, 71.6, 67.6, 67.5, 61.6, 40.0, 38.8, 27.8, 27.1, 24.6, 24.3, 14.1, 14.0. IR (film): 3500, 3039, 2930, 2850, 1731, 1582, 755 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18%; H, 7.25%. Found: C, 66.97%; H, 7.12%.



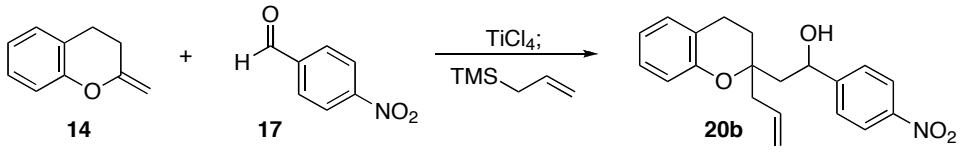
14 8 19b

Dihydrobenzopyran 19b: The reaction of 5,6-benzo-2-methylenetetrahydropyran (**14**), ethyl glyoxylate and allyltrimethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 9:1 → 5:1) to afford dihydrobenzopyran **19b** (96%) as a colorless oil (1:1 mixture of diastereomers). TLC: R_f = 0.59 (hexanes:EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.09 (2H, m), 6.83 (2H, m), 5.88 (1H, m), 5.16 (2H, m), 4.52 (1H, m), 4.23 (1H, q, *J* = 7.1 Hz), 4.20 (1H, m), 3.30 (0.5H, dd, *J* = 14.7 Hz), 3.26 (0.5H, d, *J* = 4.8 Hz), 2.84 (2H, m), 2.60 (0.5H, dd, *J* = 14.2, 6.7 Hz), 2.54 (1H, d, *J* = 7.5 Hz), 2.45 (0.5H, dd, *J* = 14.1, 8.0 Hz), 2.22 (0.5H, dd, *J* = 14.8, 2.9 Hz), 2.16 (0.5H, dd, *J* = 14.7, 2.9 Hz), 1.97 (3H, m), 1.28 (1.5H, t, *J* = 7.1 Hz), 1.26 (1.5H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.9, 174.6, 152.9, 132.8, 132.7, 129.3, 127.3, 127.2, 121.0, 120.8, 120.1, 118.9, 118.6, 117.2, 117.1, 77.4, 77.2, 67.8, 67.6, 61.5, 41.2, 41.0, 40.9, 40.7, 28.7, 28.3, 21.5, 21.4, 14.0. IR: 3524, 3076, 2932, 2855, 1730, 1640, 1582, 755 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32%; H, 7.64%. Found: C, 70.41%; H, 7.59%.



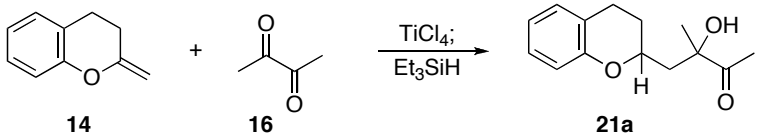
14 17 20a

Dihydrobenzopyran 20a: The reaction of 5,6-benzo-2-methylenetetrahydropyran (**14**), *p*-nitrobenzaldehyde and triethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 7:1 → 3:1) to afford dihydrobenzopyran **20a** (87%) as a yellow oil (1:1 mixture of diastereomers). TLC: R_f = 0.26 (hexanes:EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 300 MHz): 8.23 (2H, d, *J* = 8.8 Hz), 7.60 (1H, d, *J* = 8.8 Hz), 7.59 (1H, d, *J* = 8.8 Hz), 7.11 (2H, m), 6.88 (2H, m), 5.29 (0.5H, m), 5.22 (0.5H, dd, *J* = 8.9, 3.8 Hz), 4.27 (1H, m), 3.66 (0.5H, d, *J* = 1.4 Hz), 3.06 (0.5H, d, *J* = 4.8 Hz), 2.85 (2H, m), 2.03 (4H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.0, 153.6, 152.0, 151.4, 147.2, 129.7, 129.7, 127.4, 127.3, 126.6, 126.4, 123.7, 121.8, 121.7, 120.9, 120.7, 116.6, 77.2, 75.9, 72.9, 72.8, 70.2, 44.8, 44.0, 28.0, 27.6, 24.6, 24.4. IR (film): 3564, 3077, 2925, 1606 , 1582, 1519, 1348 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{17}NO_4$ ([M+Na]$^+$): 322.1050, found 322.1049.



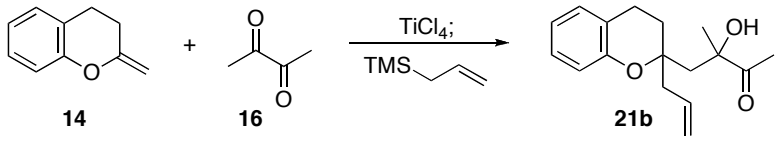
14 17 20b

Dihydrobenzopyran 20b: The reaction of 5,6-benzo-2-methylenetetrahydropyran (**14**), *p*-nitrobenzaldehyde and allyltrimethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 12:1 → 5:1) to afford dihydrobenzopyran **20b** (97%) as a yellow oil (1:1 mixture of diastereomers). TLC: R_f = 0.52 (hexanes:EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.21 (1H, d, *J* = 8.9 Hz), 8.20 (1H, d, *J* = 8.9 Hz), 7.56 (1H, d, *J* = 8.9 Hz), 7.14 (2H, m), 6.92 (1H, m), 6.86 (1H, d, *J* = 8.0 Hz); 5.80 (1H, m), 5.24 (3H, m), 4.09 (0.5H, d, *J* = 0.8 Hz), 3.81 (0.5H, d, *J* = 1.4 Hz), 2.81 (3H, m), 2.45 (1H, m), 2.36 (1H, m), 1.94 (3H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.3, 152.1, 152.1, 152.0, 132.3, 132.2, 129.7, 129.7, 127.7, 127.6, 126.5, 126.3, 123.7 123.7, 121.1, 121.0, 119.7, 119.4, 117.5, 117.1, 79.1, 78.7, 70.1, 70.0, 47.2, 46.2, 41.2, 39.3, 30.0, 27.4, 21.5, 21.2. IR (film): 3564, 3077, 2855, 1640, 1583, 1518, 1347 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78%; H, 6.24%. Found: C, 71.07%; H, 6.44%.



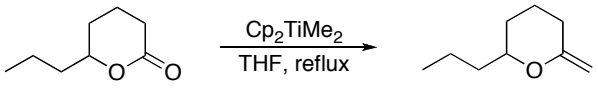
14 16 21a

Dihydrobenzopyran 21a: The reaction of 5,6-benzo-2-methylenetetrahydropyran (**14**), 2,3-butanedione and triethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 9:1 → 4:1) to afford dihydrobenzopyran **21a** (95%) as a yellow oil (5:1 mixture of diastereomers). TLC: R_f = 0.52 (ethyl acetate: hexanes, 1:3). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.07 (2H, m), 6.83 (1H, m), 6.65 (1H, d, *J* = 8.1 Hz), 4.38 (1H, br s), 4.23 (1H, tt, *J* = 10.3, 2.1 Hz), 2.86 (1H, m), 2.74 (1H, m), 2.35 (0.5H, s), 2.34 (2.5H, s), 2.30 (0.83H, dd, *J* = 14.7, 10.3 Hz), 2.18 (0.17H, dd, *J* = 14.5, 3.3 Hz), 2.03 (0.17H, dd, *J* = 14.5, 9.1 Hz), 2.00 (0.83H, dd, *J* = 14.7, 2.0 Hz), 1.94 (1H, m), 1.78 (1H, m), 1.40 (3H, s). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 214.3, 211.2, 154.1, 153.6, 129.7, 129.5, 127.2, 127.1, 121.8, 121.6, 120.8, 120.3, 116.4, 116.2, 79.2, 76.7, 74.2, 71.1, 45.2, 43.8, 28.1, 27.6, 26.8, 26.1, 24.8, 24.5, 24.0. IR (film): 3464, 3022, 2928, 1710, 1582, 755 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77%; H, 7.74%. Found: C, 71.83%; H, 7.82%.



14 16 21b

Dihydrobenzopyran 21b: The reaction of 5,6-benzo-2-methylenetetrahydropyran (**14**), 2,3-butanedione and allyltrimethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 12:1 → 5:1) to afford dihydrobenzopyran **21b** (97%) as a yellow oil (1:1 mixture of diastereomers). TLC: R_f = 0.46 (hexanes:EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.07 (2H, m), 6.84 (0.5H, m), 6.72 (0.5H, d, *J* = 8.1 Hz), 6.65 (1H, d, *J* = 8.2 Hz), 5.82 (1H, m), 5.14 (2H, m), 4.32 (0.5H, s), 4.19 (0.5H, s), 2.72 (2.5H, m), 2.53 (0.5H, d, *J* = 15.2 Hz), 2.38 (1.5H, s), 2.33 (3H, m), 2.22 (1.5H, s), 2.10 (0.5H, d, *J* = 15.2 Hz), 1.89 (0.5H, ddd, *J* = 13.8, 5.8, 4.4 Hz), 1.76 (0.5H, ddd, *J* = 14.1, 6.0, 2.3 Hz), 1.66 (0.5H, m), 1.36 (1.5H, s), 1.34 (1.5H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.3, 211.2, 152.6, 152.5, 133.3, 132.8, 129.5, 129.4, 127.4, 127.2, 121.0, 120.9, 120.3, 120.2, 118.9, 118.8, 116.9, 116.6, 78.3, 78.0, 77.6, 77.3, 46.5, 45.9, 41.5, 39.6, 30.0, 28.4, 27.6, 24.4, 24.3, 21.6, 21.3. IR (film): 3458, 3075, 2930, 1709, 1583, 755 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42%; H, 8.08%. Found: C, 74.62%; H, 8.18%.



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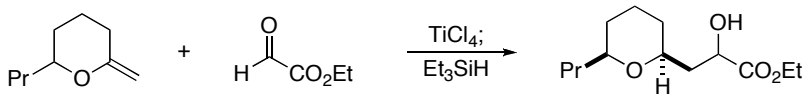
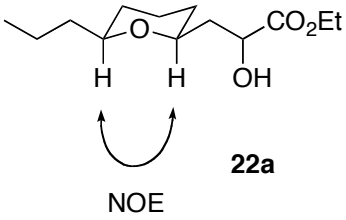
Enol Ether 15: To a solution of δ-octanolactone (1.38g, 9.7 mmol) in 70 mL THF was added Cp_2TiMe_2 (39 mL of a 0.5M solution in THF, 19.5 mmol). The resulting mixture was warmed to reflux and stirred for 24 h in the dark. The solution was then cooled to room temperature, concentrated *in vacuo*, and the resulting residue triturated with hexanes. (100 mL). The hexanes solution filtered was through celite and concentrated again. The residue was purified via flash chromatography (SiO_2; hexanes:triethylamine, 19:1) to afford the exocyclic enol ether **15** as a yellow oil (0.82 g, 68%). TLC: R_f = 0.84 (hexanes: EtOAc, 10:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.30 (1H, d, *J* = 1.4 Hz), 4.04 (1H, d, *J* = 1.4 Hz), 3.59 (1H, m), 2.25 (1H, dt, *J* = 14.0, 3.8 Hz), 2.12 (1H, m), 1.82 (1H, m), 1.74-1.32 (7H, m), 0.93 (3H, t, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 160.6, 90.8, 78.9, 38.1, 30.3, 29.0, 22.7, 18.5, 14.0. IR (film): 3110, 2938, 2870, 1649 cm^{-1}. HRMS (ESI) Calcd for $C_9H_{16}O$ ([2M+Na]$^+$): 303.2294, found 303.2288.



15 **8** **22a**

Tetrahydropyran 22a: The reaction of 2-methylene-6-propyltetrahydropyran (**15**), ethyl glyoxylate and triethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 15:1 → 8:1) to afford tetrahydropyran **22a** (77%) as a colorless oil (5:1 mixture of diastereomers). Relative stereochemistry about the tetrahydropyran was determined by NOE. TLC: R_f = 0.41 (hexanes:EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.42 (0.83H, dt, *J* = 7.4, 3.2 Hz), 4.36 (0.17H, m), 4.23 (2H, m), 3.94 (0.17H, d, *J* = 2.8 Hz), 3.72 (0.83H, d, *J* = 7.4 Hz), 3.62 (0.17H, m), 3.57 (0.83H, m), 3.31 (1H, m), 1.96 (1H, m), 1.80 (2H, m), 1.62-1.25 (9H, m), 1.30 (3H, t, *J* = 7.1 Hz), 0.91 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 174.9, 77.8, 77.8, 76.4, 75.3, 70.2, 69.2, 61.2, 39.8, 39.8, 38.5, 38.5, 31.7, 31.6, 31.4, 31.2, 23.4, 23.4, 18.8, 18.7, 14.2, 14.2, 14.1. IR (film): 3480, 2932, 2863, 1733 cm^{-1}. HRMS (ESI) Calcd for $C_{13}H_{24}O_4$ ([M+Na]$^+$): 267.1567, found 267.1563.

Key NOE enhancements:



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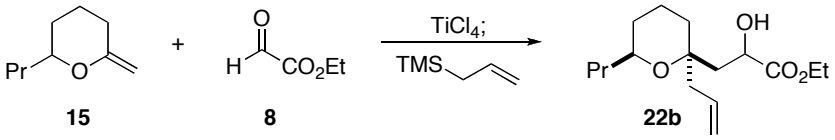
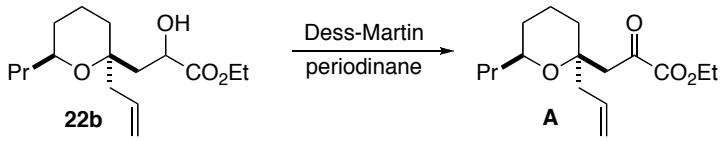


15 **8** **22b**

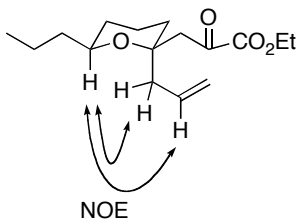
Tetrahydropyran 22b: The reaction of 2-methylene-6-propyltetrahydropyran (**15**), ethyl glyoxylate and allyltrimethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 15:1 → 8:1) to afford tetrahydropyran **22b** (67%) as a yellow oil (1:1 mixture of diastereomers). Relative stereochemistry about the tetrahydropyran ring was determined by NOE studies on the corresponding ketone. TLC: R_f = 0.46 (hexanes:EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.73 (1H, m), 5.12 (2H, m), 4.68

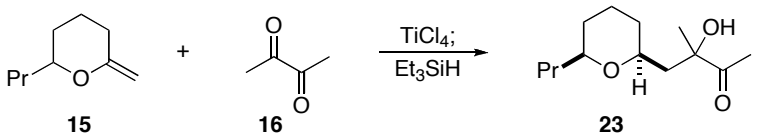
(0.5H, d, *J* = 1.3 Hz), 4.58 (1.5H, m), 4.22 (1H, dq, *J* = 7.1, 0.7 Hz), 4.21 (1H, q, *J* = 7.1 Hz), 3.60 (1H, m), 2.71 (1H, m), 2.45 (0.5H, ddd, *J* = 14.1, 6.9, 1.2 Hz), 2.18 (0.5H, dd, *J* = 14.5, 8.1 Hz), 2.08 (1H, m), 1.75 (3H, m), 1.62 (3H, m), 1.36 (4H, m), 1.30 (1.5H, t, *J* = 7.1 Hz), 1.29 (1.5H, t, *J* = 7.1 Hz), 1.16 (1H, m), 0.88 (1.5H, t, *J* =7.1 Hz), 0.87 (1.5H, t, *J* =7.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.7, 133.2, 132.9, 118.5, 118.4, 77.1, 70.4, 70.1, 69.0, 68.7, 61.0, 61.0, 43.3, 42.2, 39.0, 38.8, 38.5, 35.7, 32.7, 31.1, 31.0, 30.2, 19.1, 19.0, 18.7, 18.6, 14.2, 14.1, 14.0. IR (film): 3468, 3075, 2934, 2871, 1732 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{28}O_4$ ([M+Na]$^+$): 307.1880, found 307.1878.



Ketone A: To a solution of alcohol **22b** (0.020g, 0.070 mmol) in CH_2Cl_2 (0.35 mL) was added Dess-Martin periodinane (0.034g, 0.081 mmol) and $NaHCO_3$ (0.029g, 0.350 mmol). The reaction mixture was stirred at rt for two hours, after which time the reaction was shown to be complete by TLC. Hexanes (4 mL) was added, the resulting solution filtered to remove precipitates, and the filtrate concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2; 50:1; hexanes:EtOAc) to provide ketone **A** (0.013 g, 66%) as a colorless oil. TLC: R_f = 0.79 (hexanes:ethyl acetate, 3:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.79 (1H, m), 5.12 (2H, m), 4.25 (2H, dq, *J* = 7.2, 1.8 Hz), 3.50 (1H, m), 3.43 (1H, d, *J* = 12.6 Hz), 2.69 (1H, ddt, *J* = 14.4, 6.1, 1.4 Hz), 2.44 (1H, d, *J* = 12.6 Hz), 2.27 (1H, dd, *J* = 14.4, 8.3 Hz), 1.66 (2H, m), 1.56 (2H, m), 1.50 (1H, dm, *J* = 14.0 Hz), 1.38 (1H, m), 1.36 (3H, t, *J* = 7.2 Hz), 1.25 (3H, m), 1.09 (1H, m), 0.87 (3H, t, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.4, 162.2, 133.2, 118.5, 76.5, 69.9, 61.9, 47.8, 38.8, 37.3, 31.6, 30.9, 19.2, 18.5, 14.1. 13.9. IR (film): 3077, 2937, 2871, 1728, 1640 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{26}O_4$ ([M+Na]$^+$): 305.1723, found 305.1718.

Key NOE enhancements:

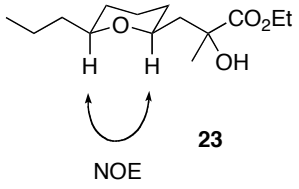




15 **16** **23**

Tetrahydropyran 23: The reaction of 2-methylene-6-propyltetrahydropyran (**15**), 2,3-butanedione and triethylsilane was conducted according to the general procedure. The crude residue was purified by flash chromatography (SiO_2; hexanes:ethyl acetate, 15:1 → 8:1) to afford tetrahydropyran **23** (56%) as a colorless oil (2:1 mixture of diastereomers). Relative stereochemistry about the tetrahydropyran ring was determined by NOE. TLC: R_f = 0.65 (hexanes:EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.16 (0.3H, s), 4.45 (0.7H, s), 3.50 (1H, m), 3.28 (0.3H, m), 3.15 (0.7H, m), 2.30 (1H, s), 2.24 (2H, s), 2.01 (1H, m), 1.77 (1H, dd 14.6, 1.9 Hz), 1.70 (1H, m), 1.57-1.08 (9H, m), 1.31 (2H, s), 1.25 (1H, s), 0.90 (1H, t, *J* = 7.3 Hz), 0.88 (2H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 216.5, 212.0, 80.3, 77.9, 77.6, 77.1, 76.7, 73.3, 45.4, 44.2, 38.4, 38.3, 32.0, 31.7, 31.2, 31.1, 26.3, 26.1, 24.6, 24.2, 23.5, 23.1, 18.9, 18.6, 14.2, 14.0. IR (film): 3463, 2932, 2862, 1711, cm^{-1} HRMS (ESI) Calcd for $C_{13}H_{24}O_3$ ([M+Na]$^+$): 251.1618, found 251.1614.

Key NOE enhancements:



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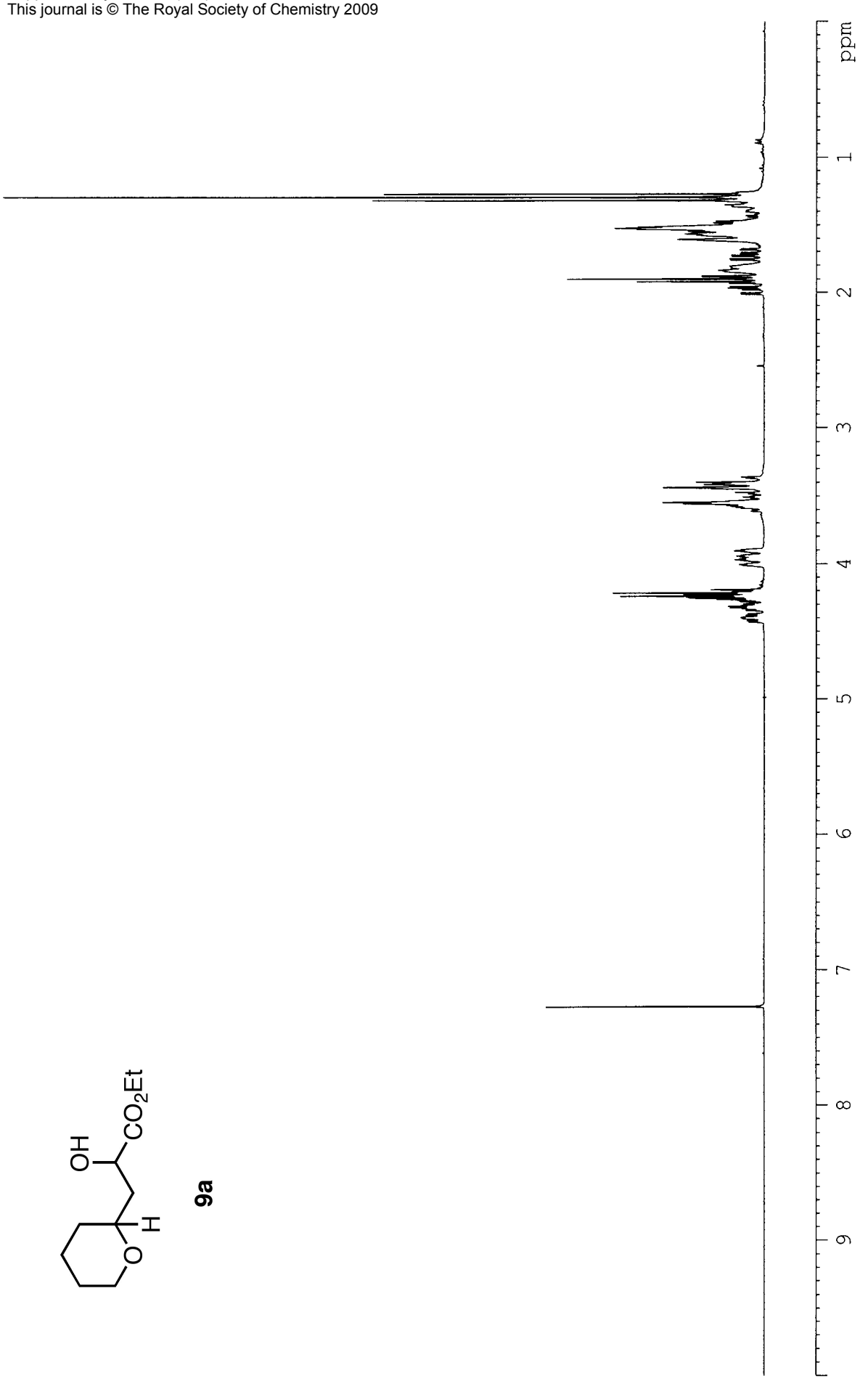

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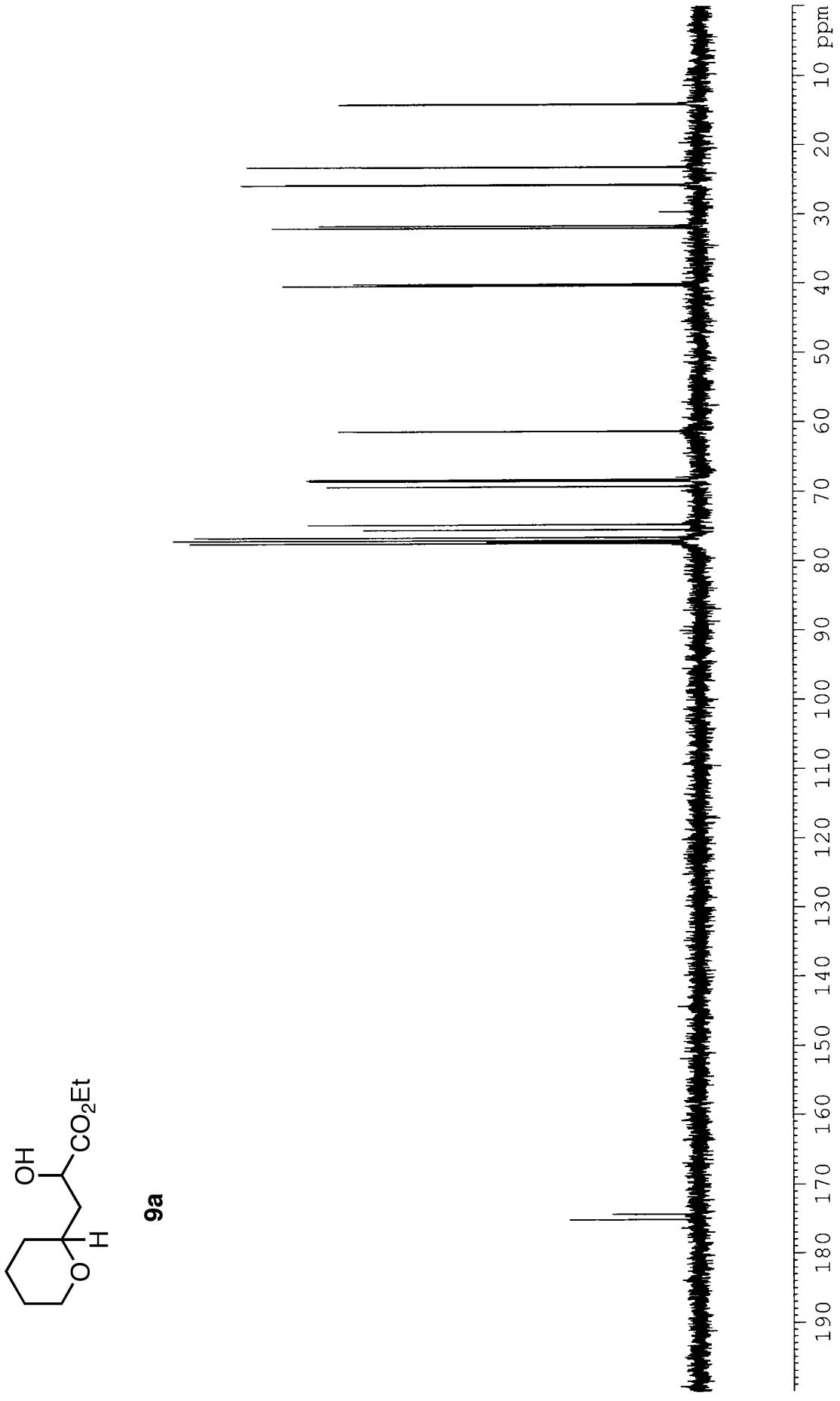

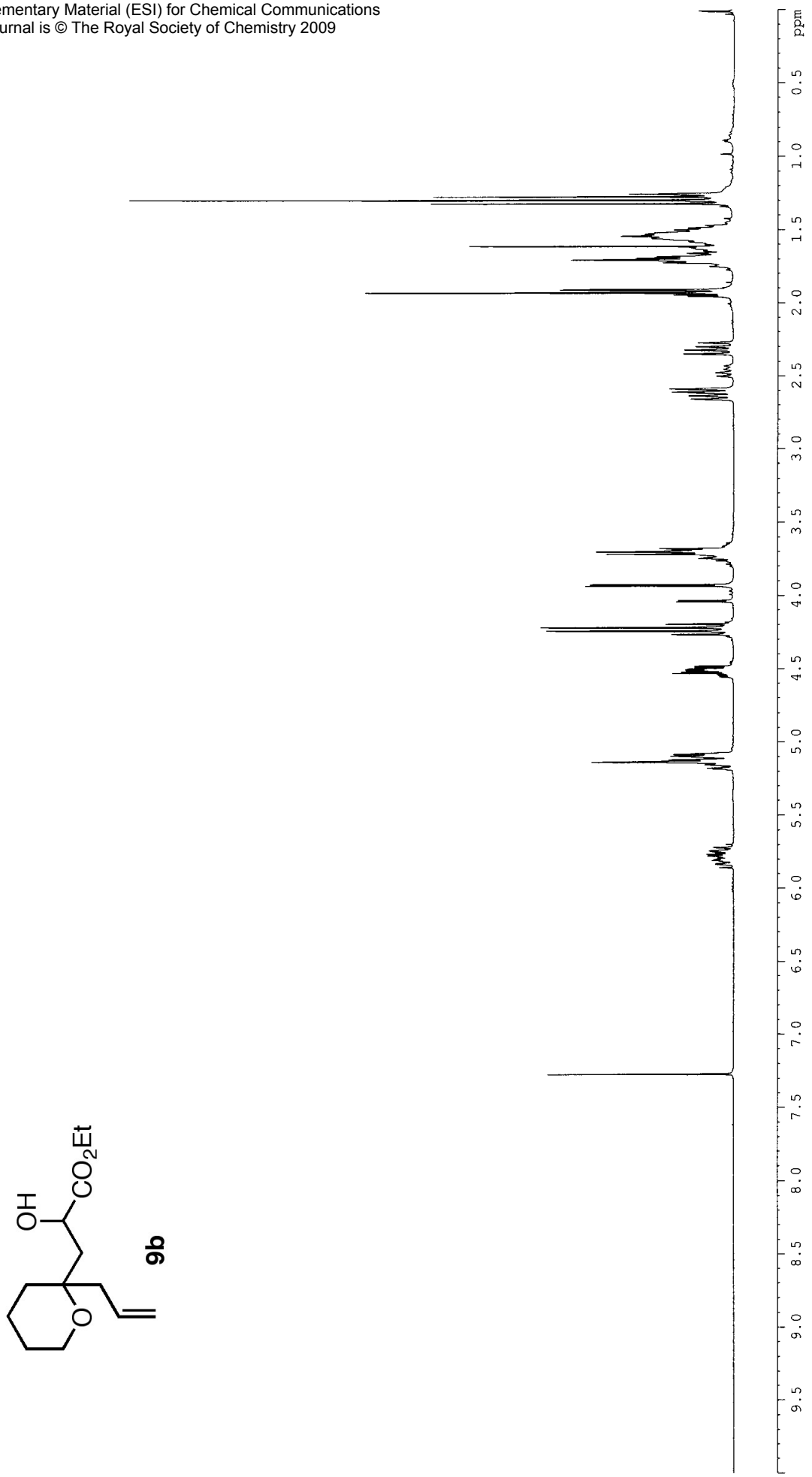

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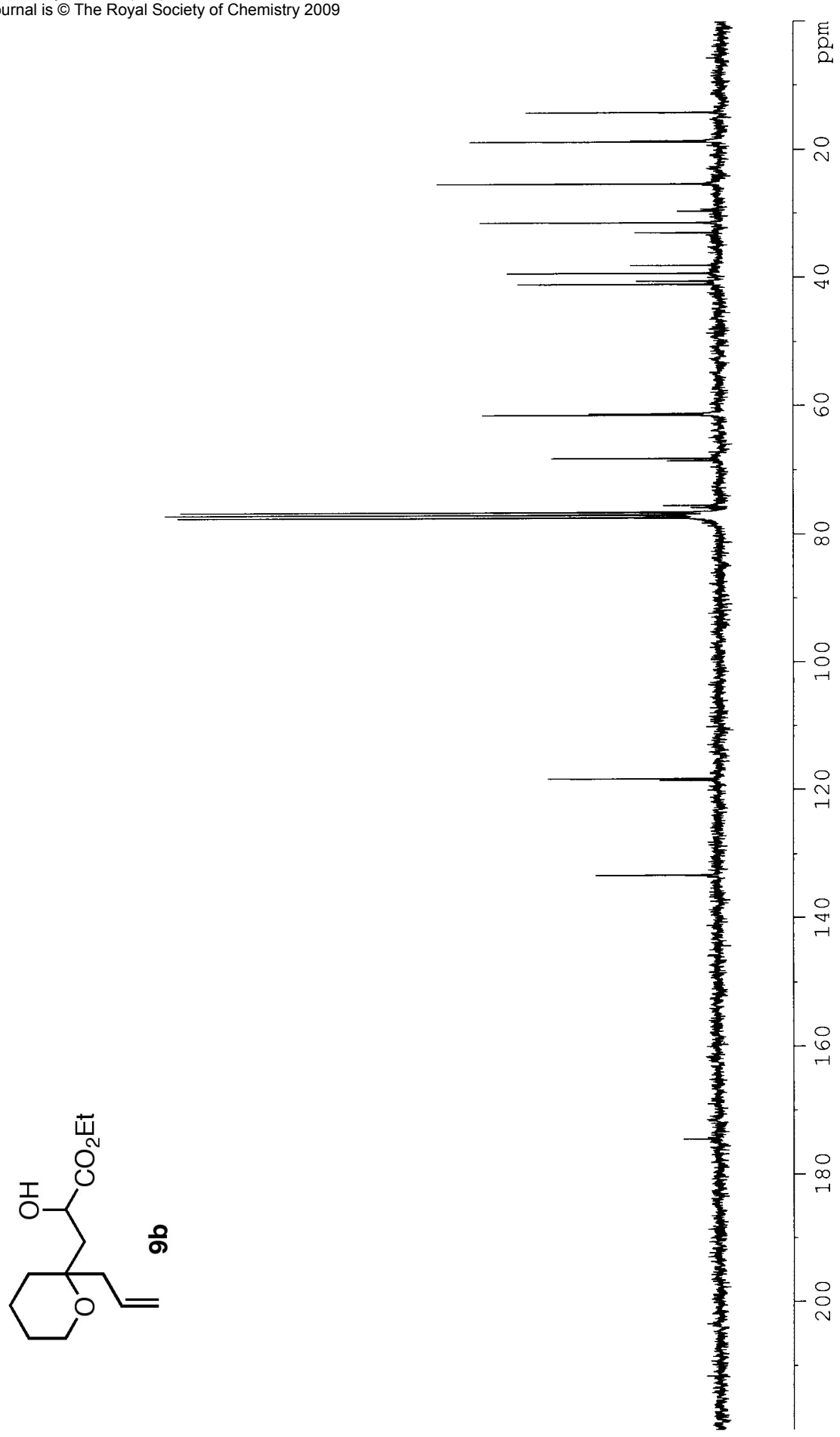

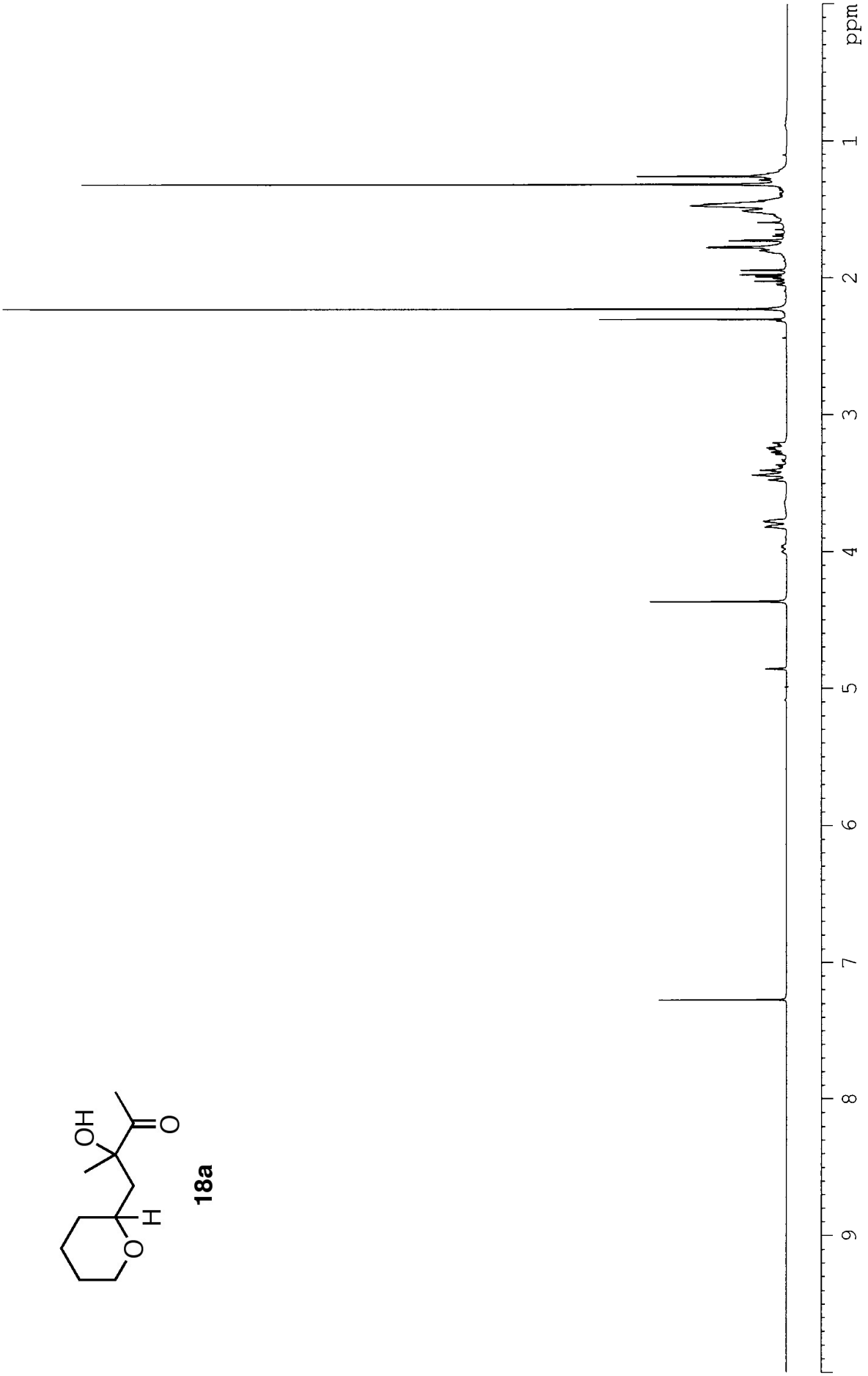

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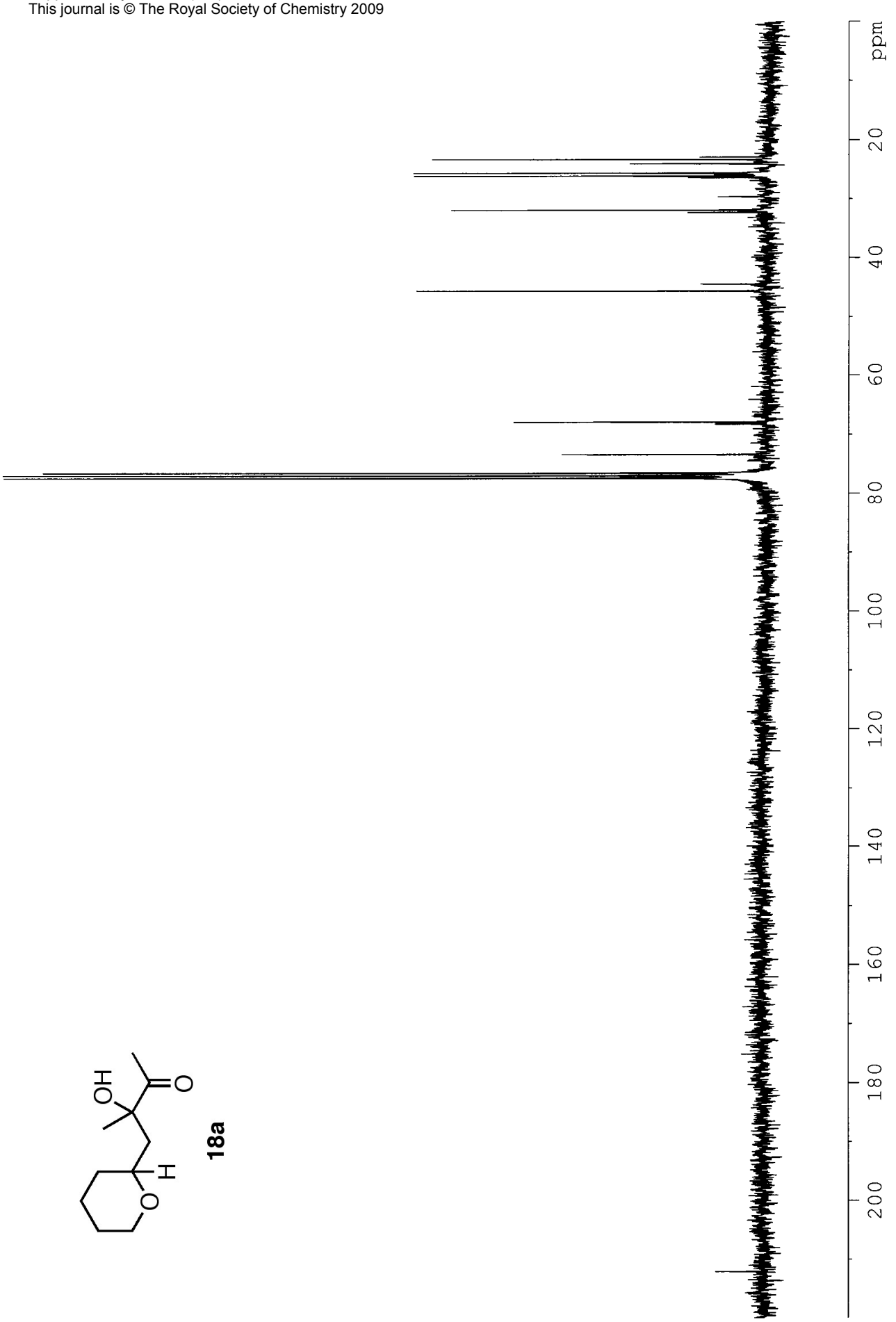

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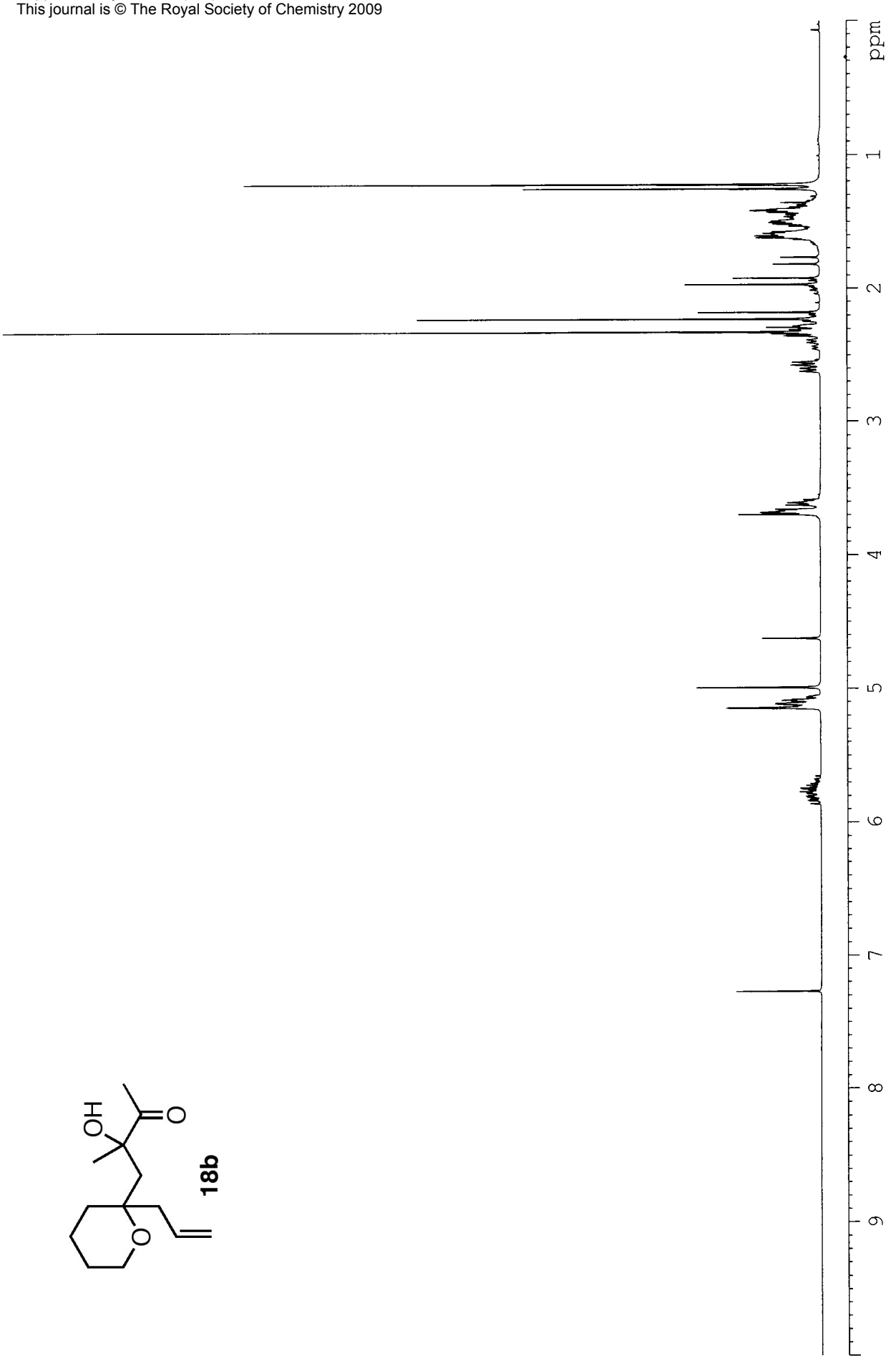

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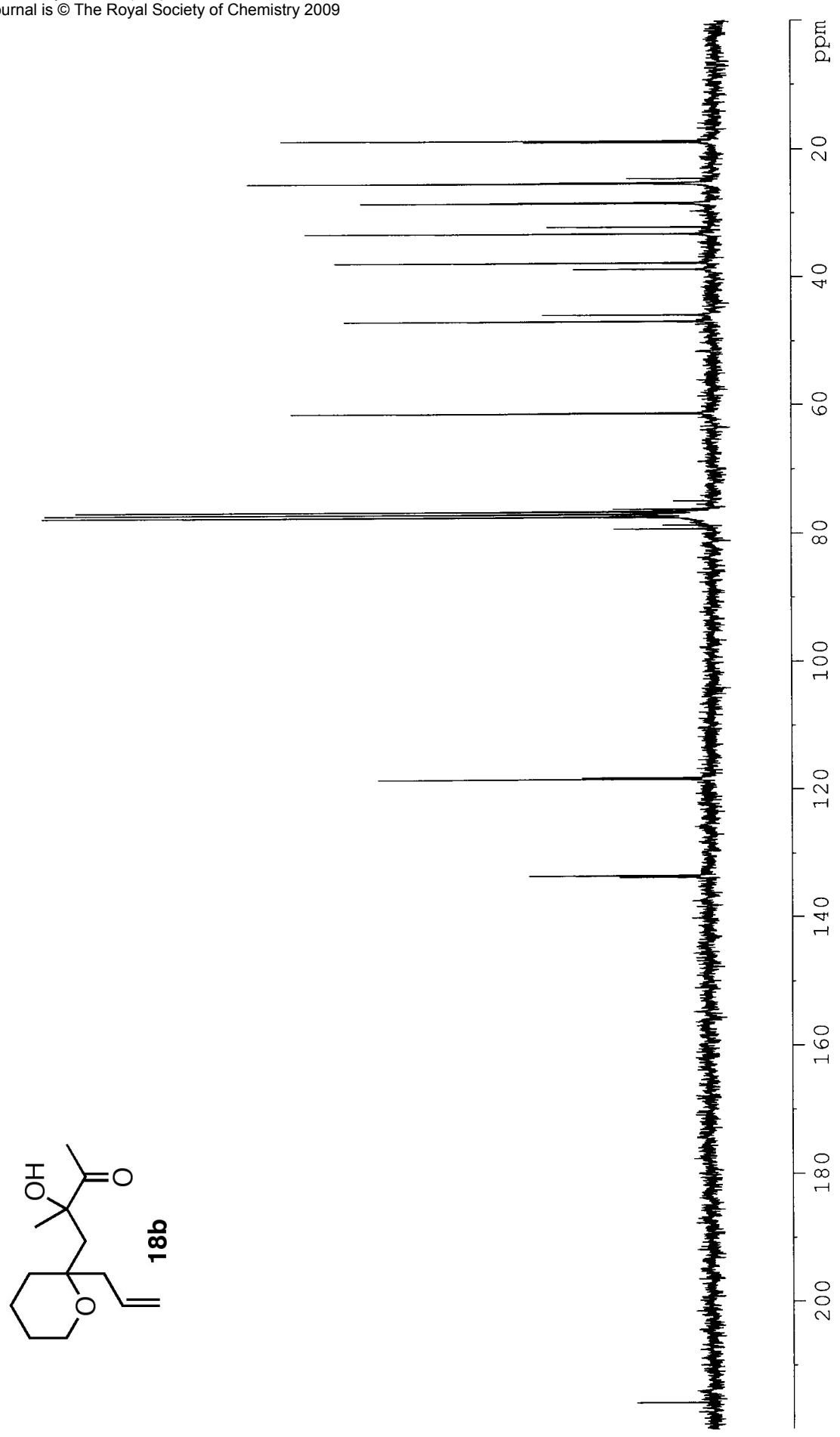

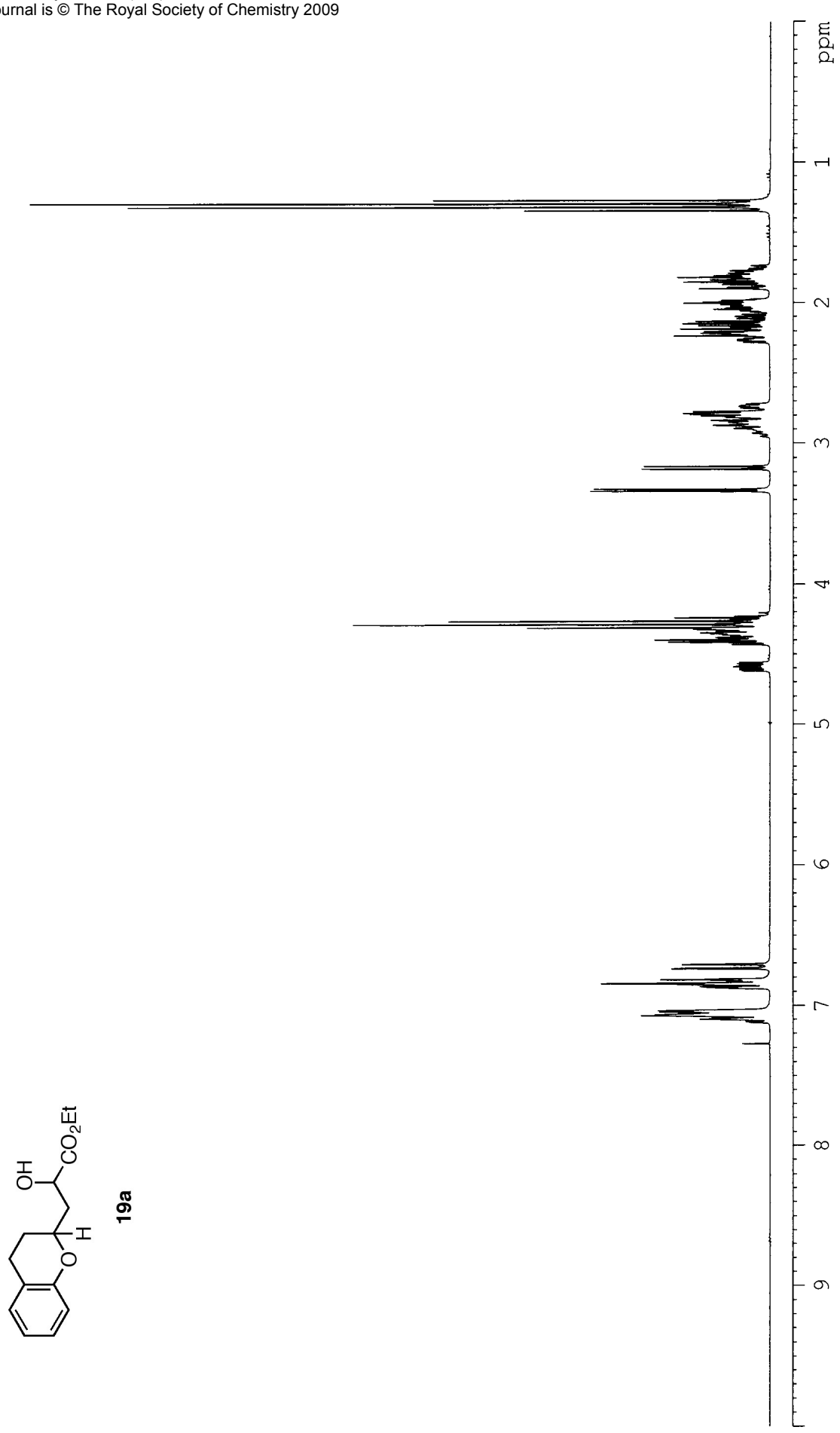

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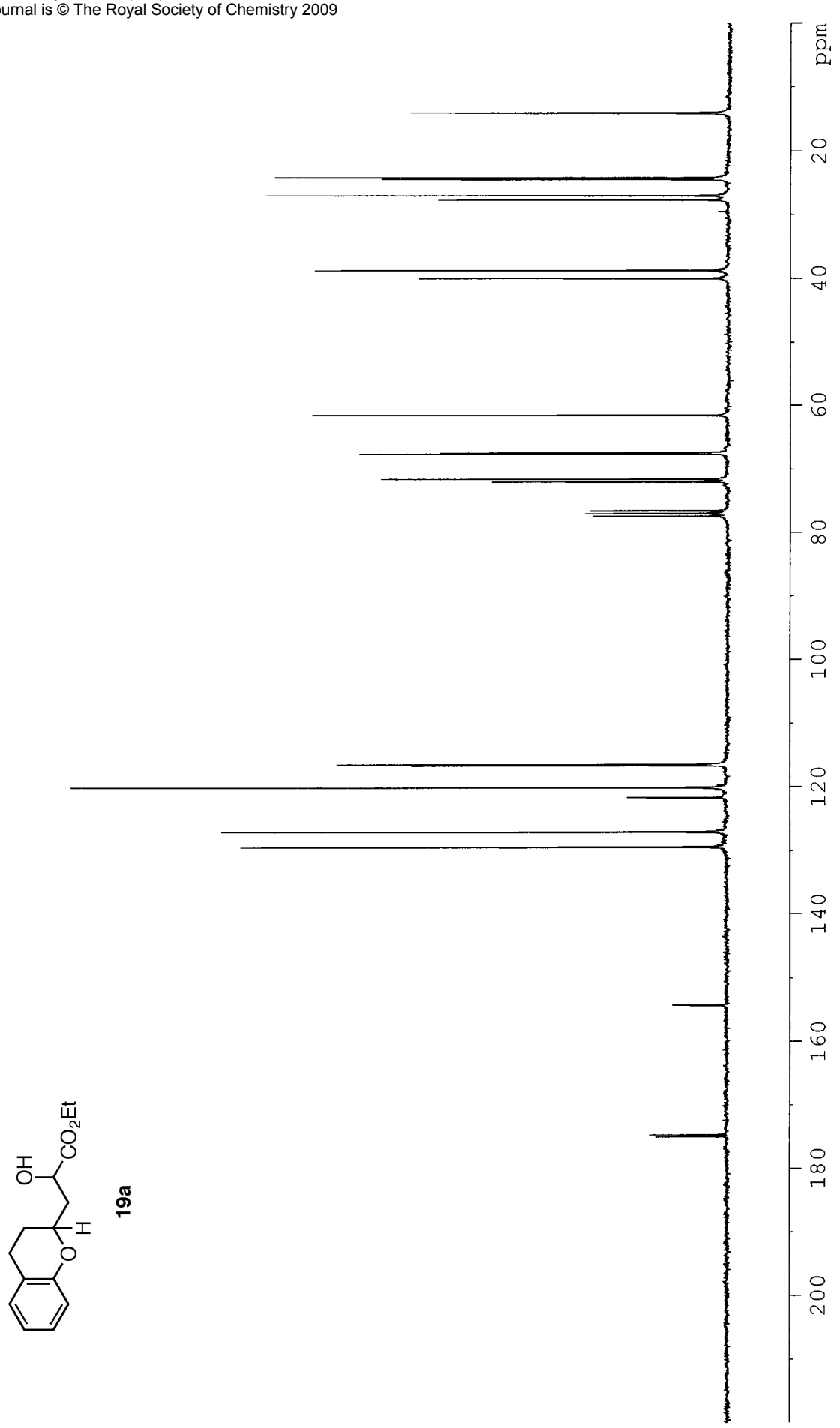

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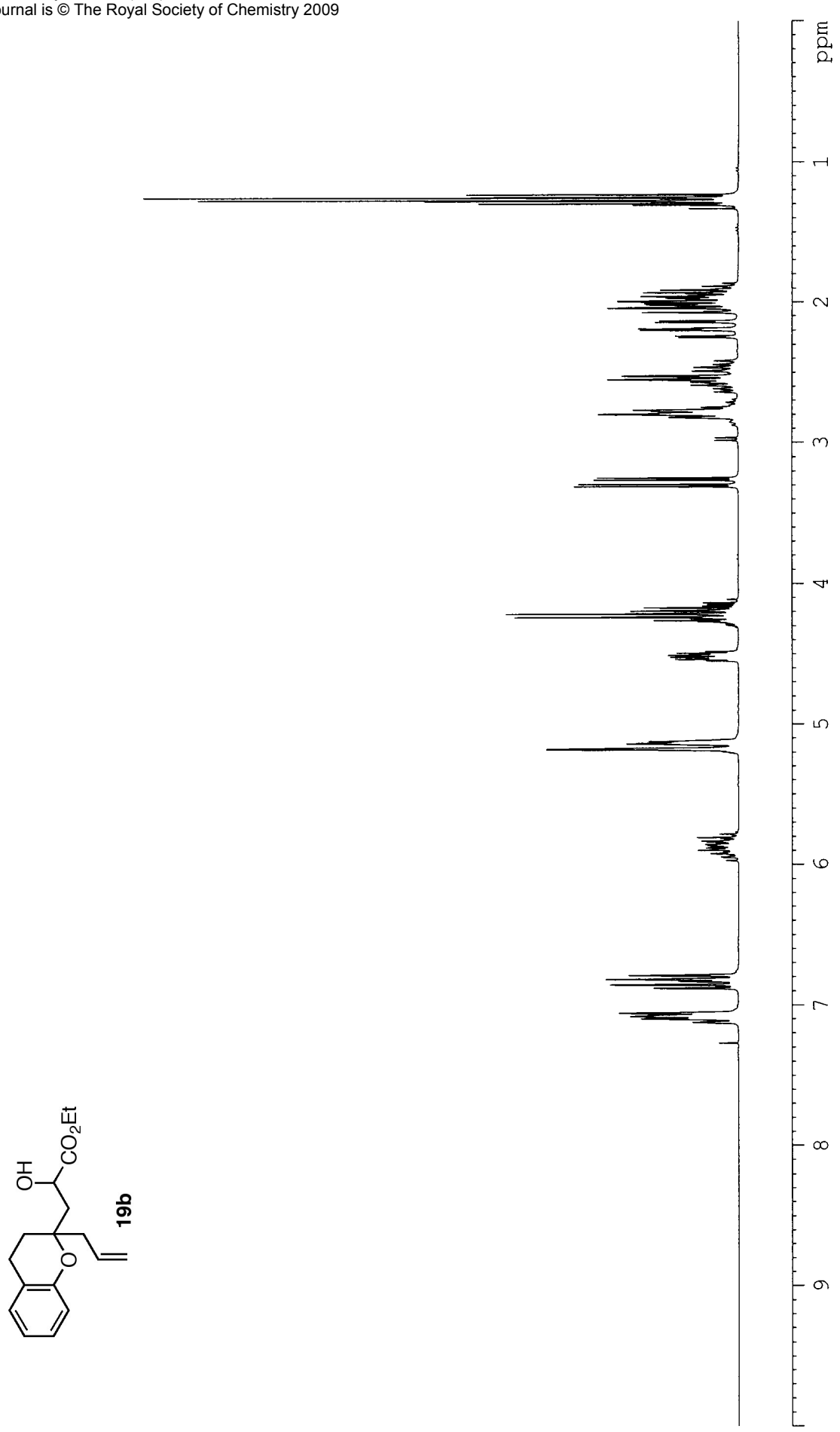

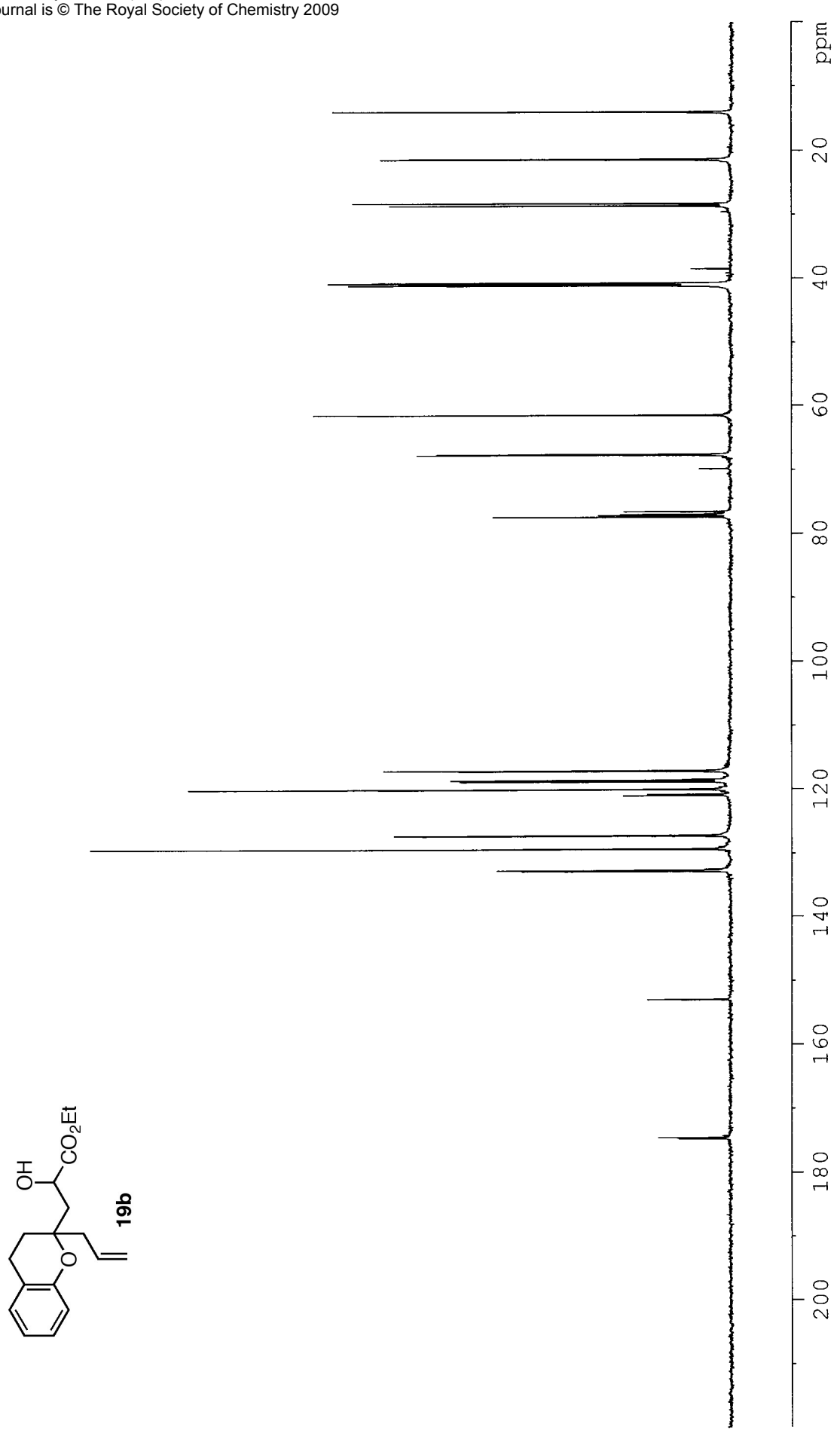

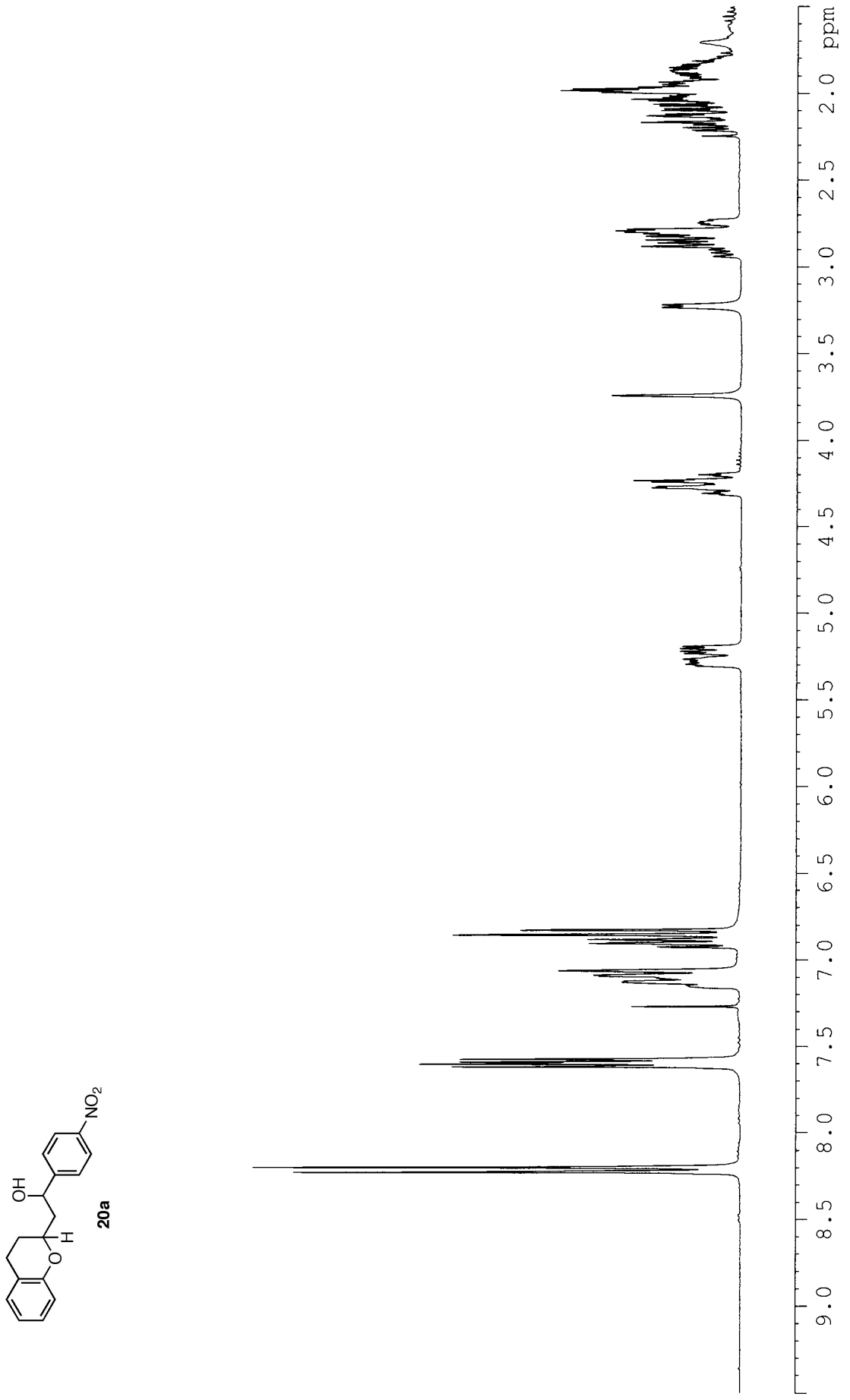

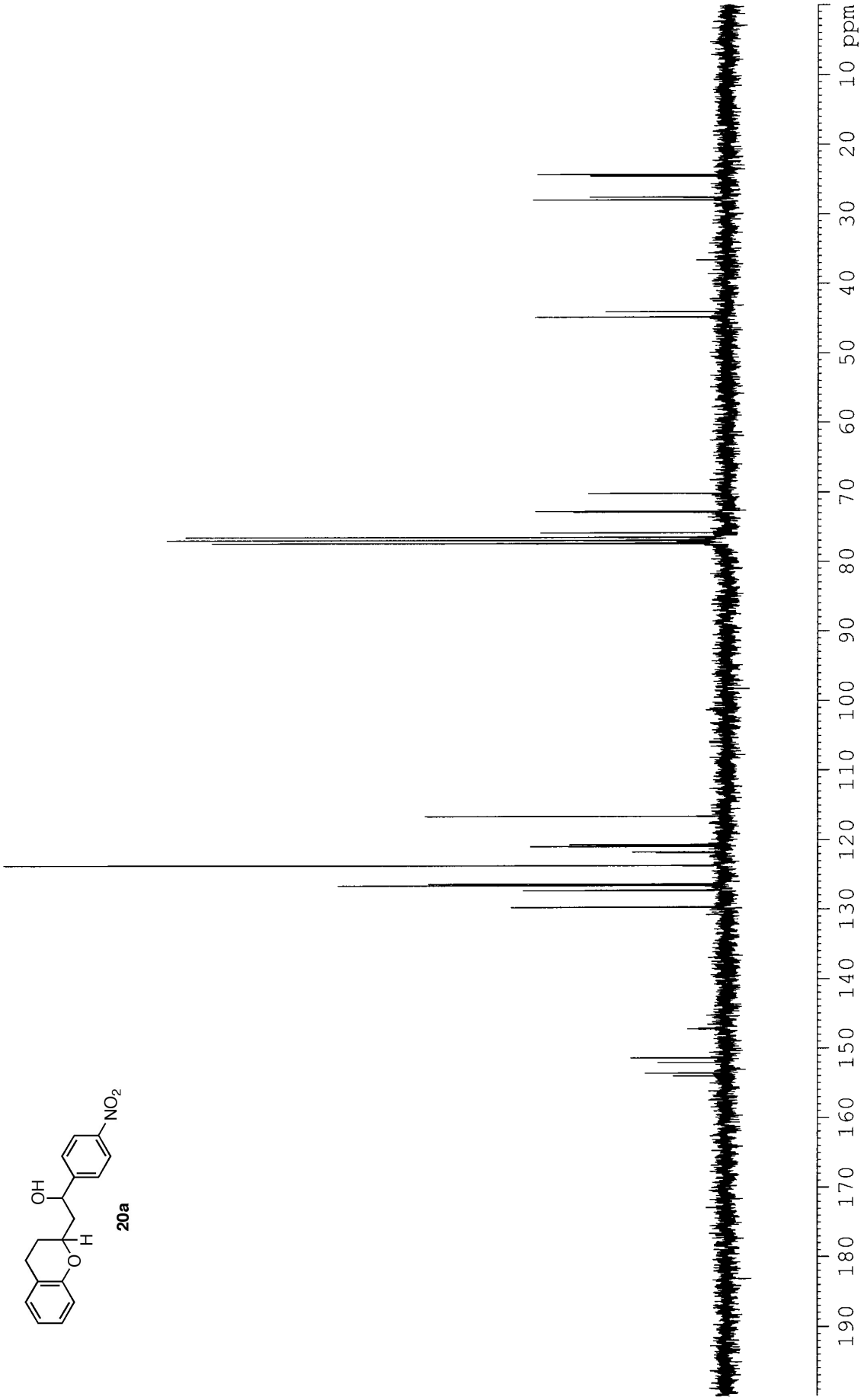

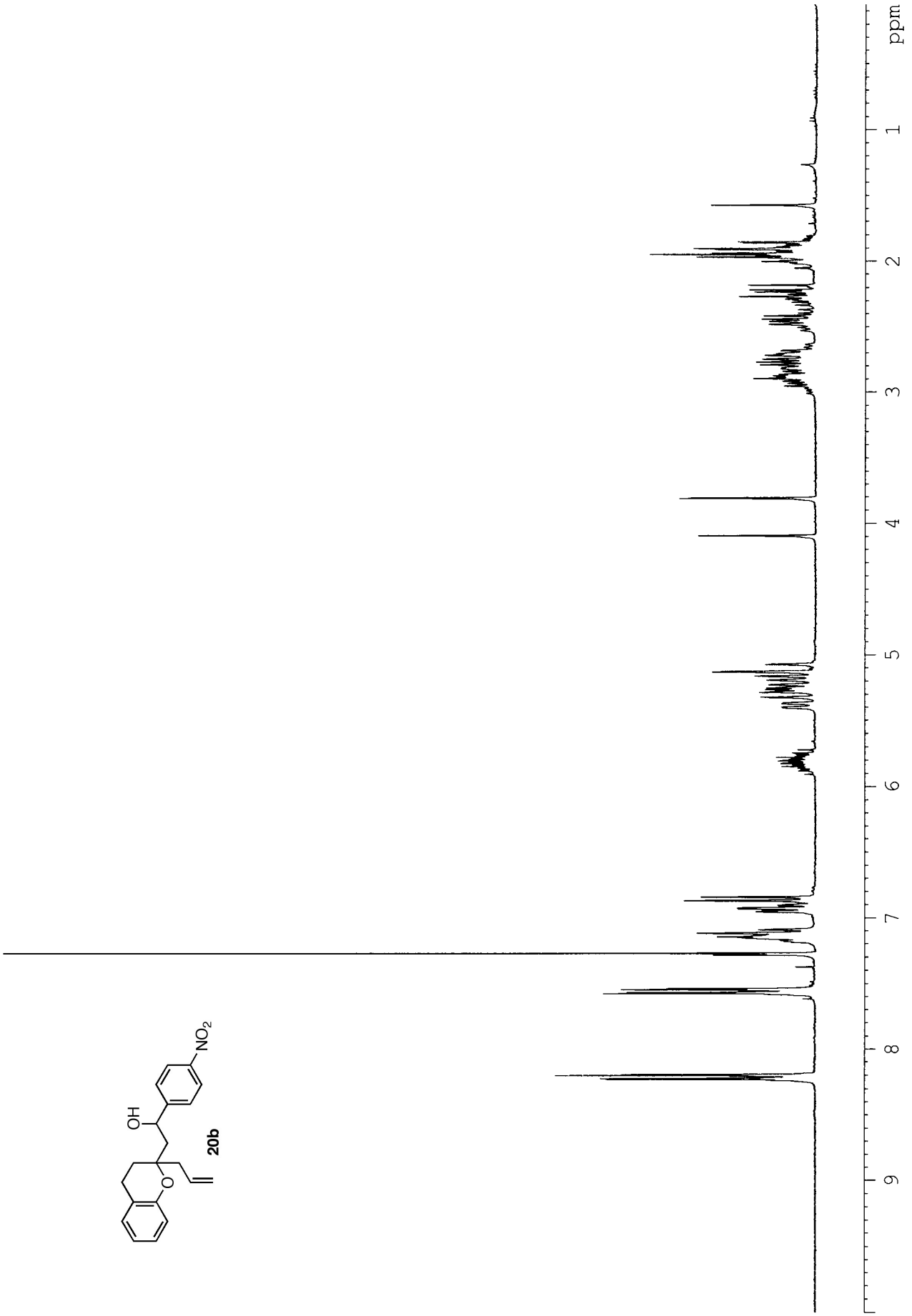

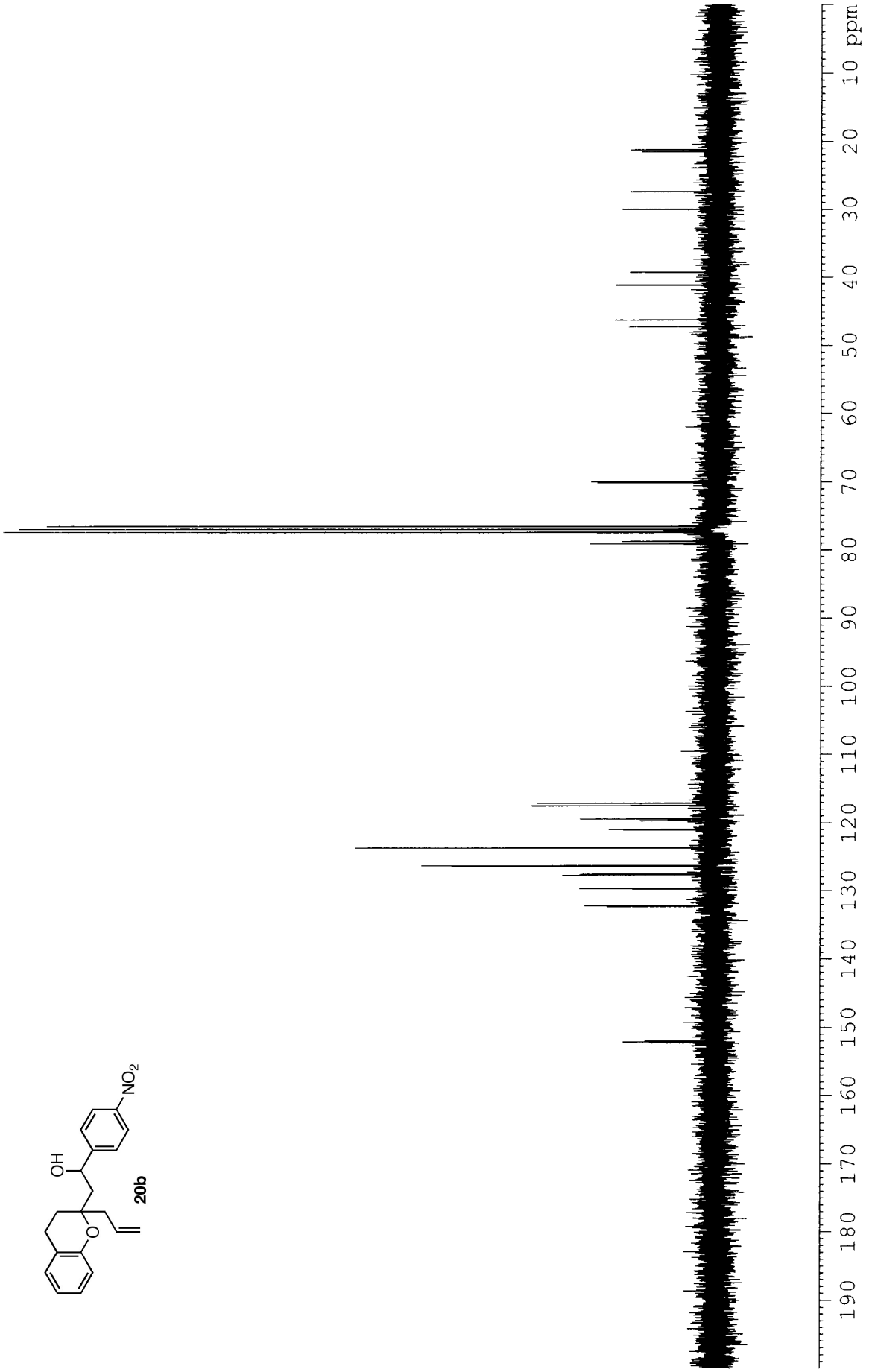

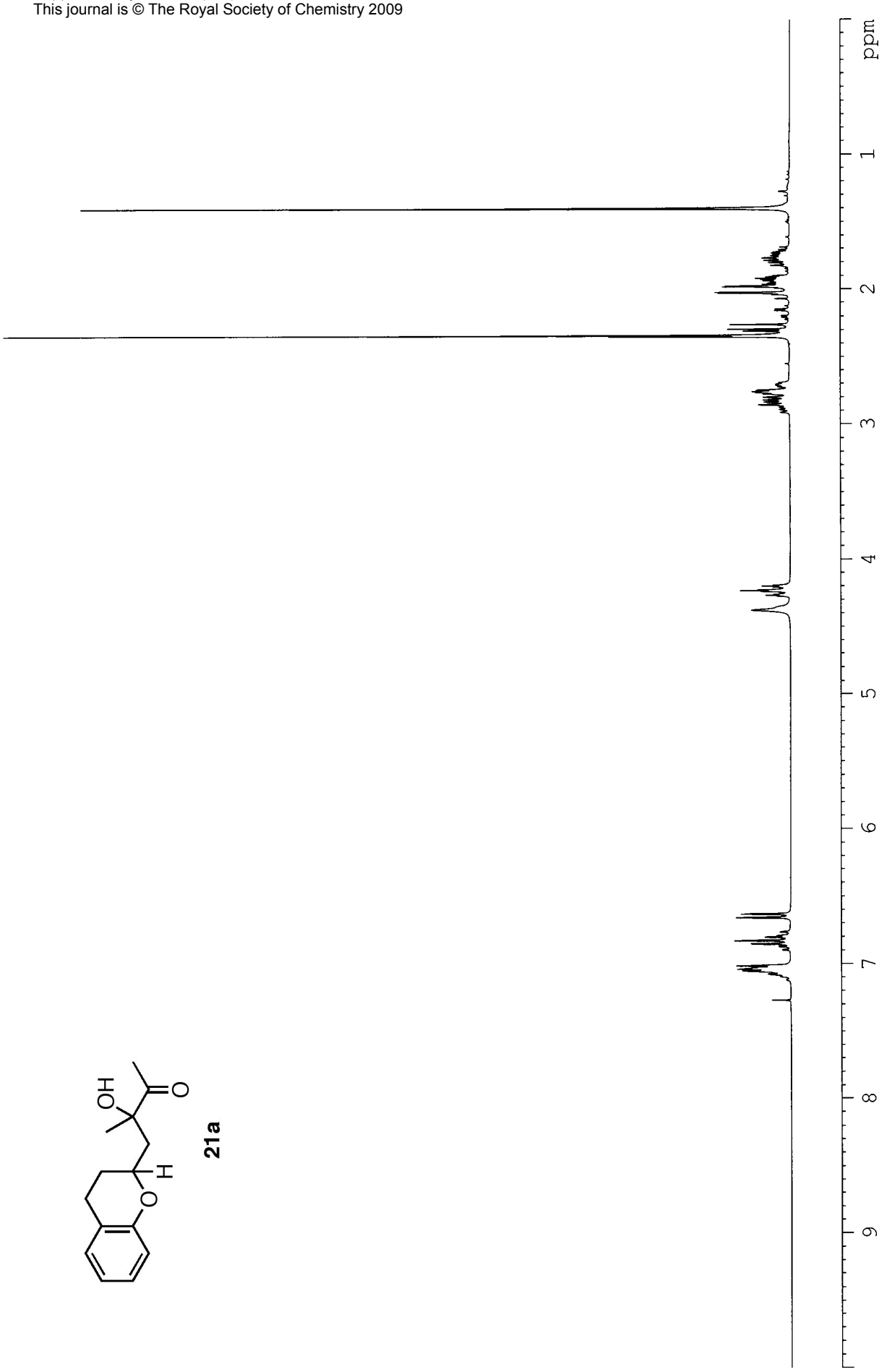

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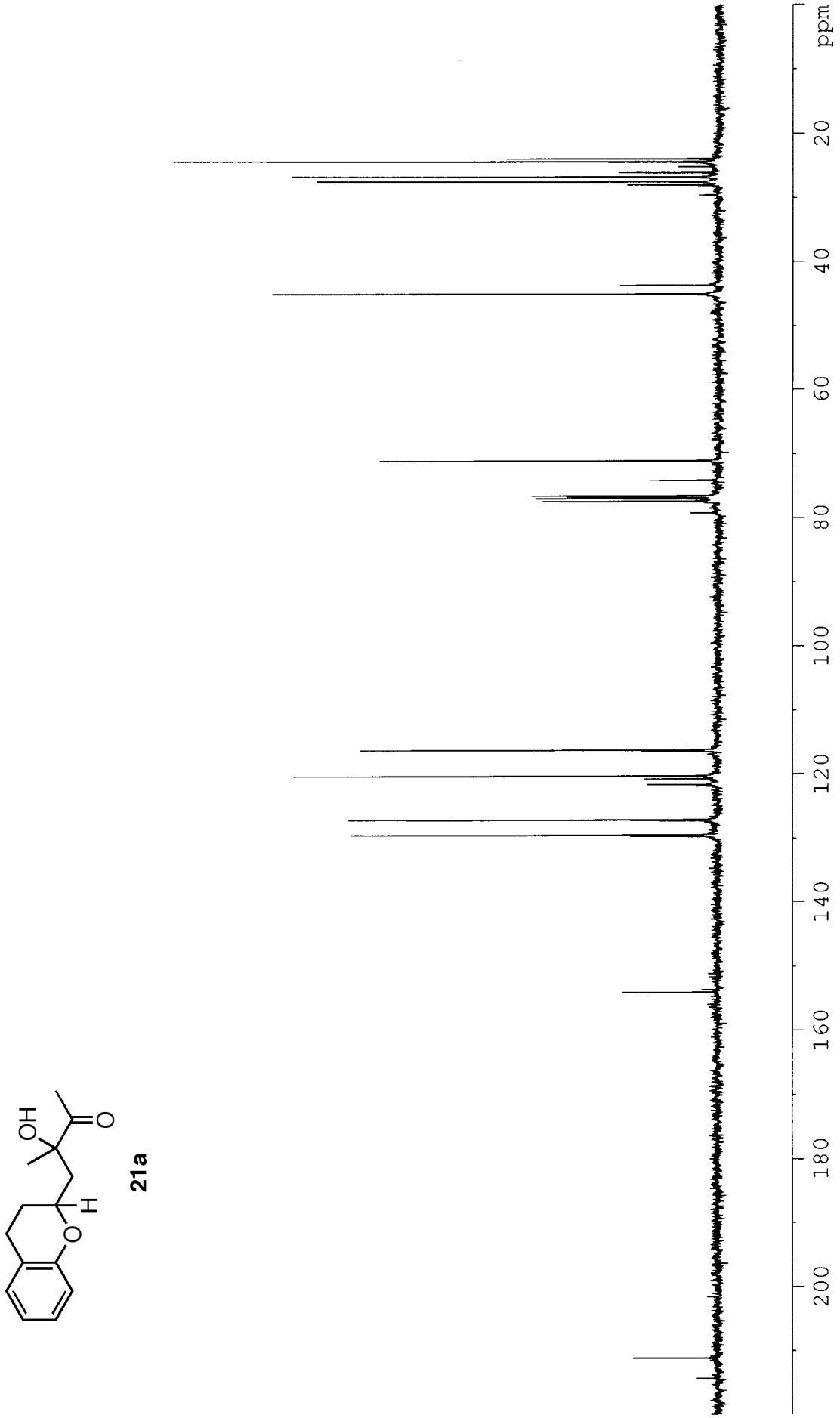

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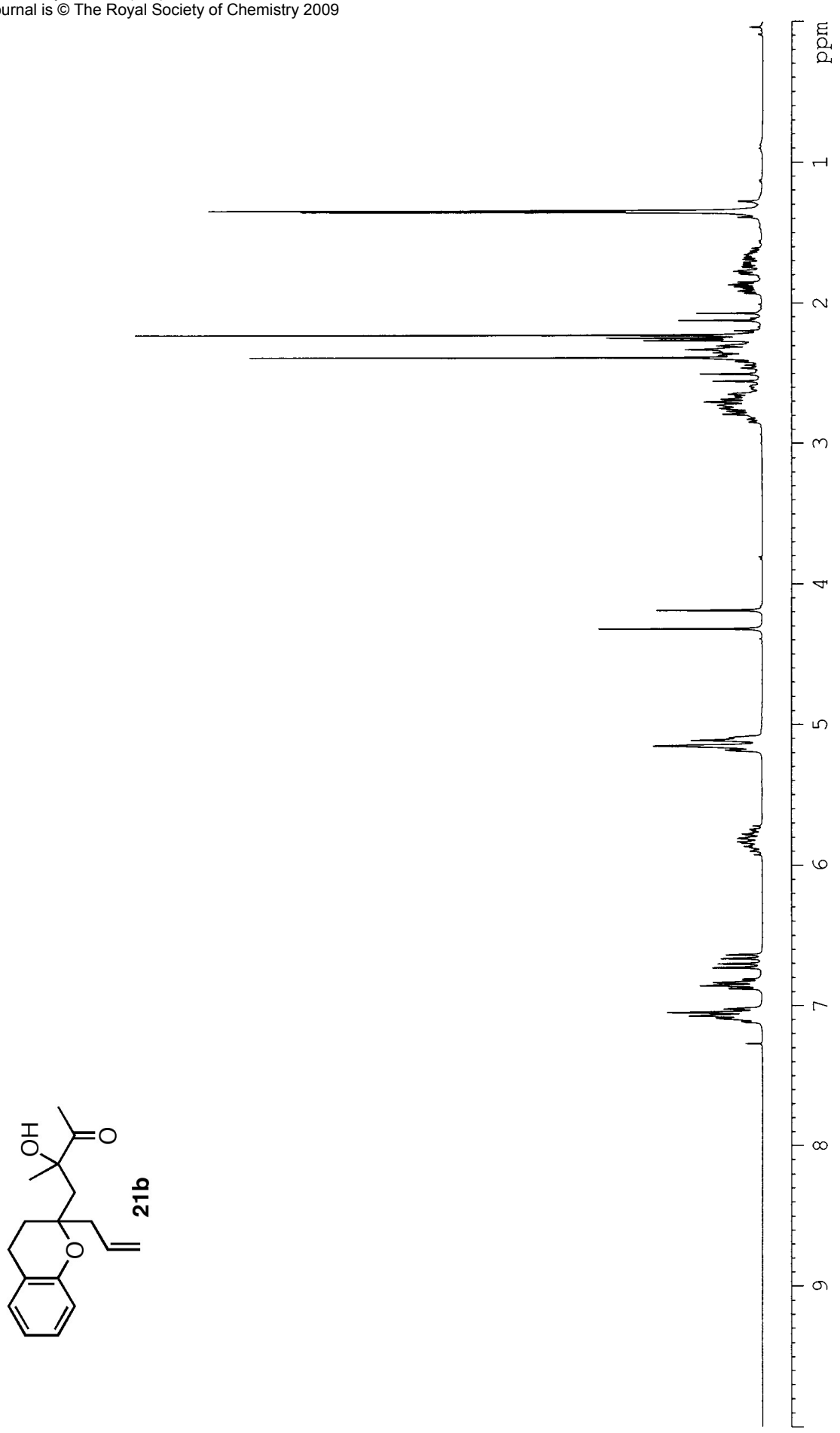

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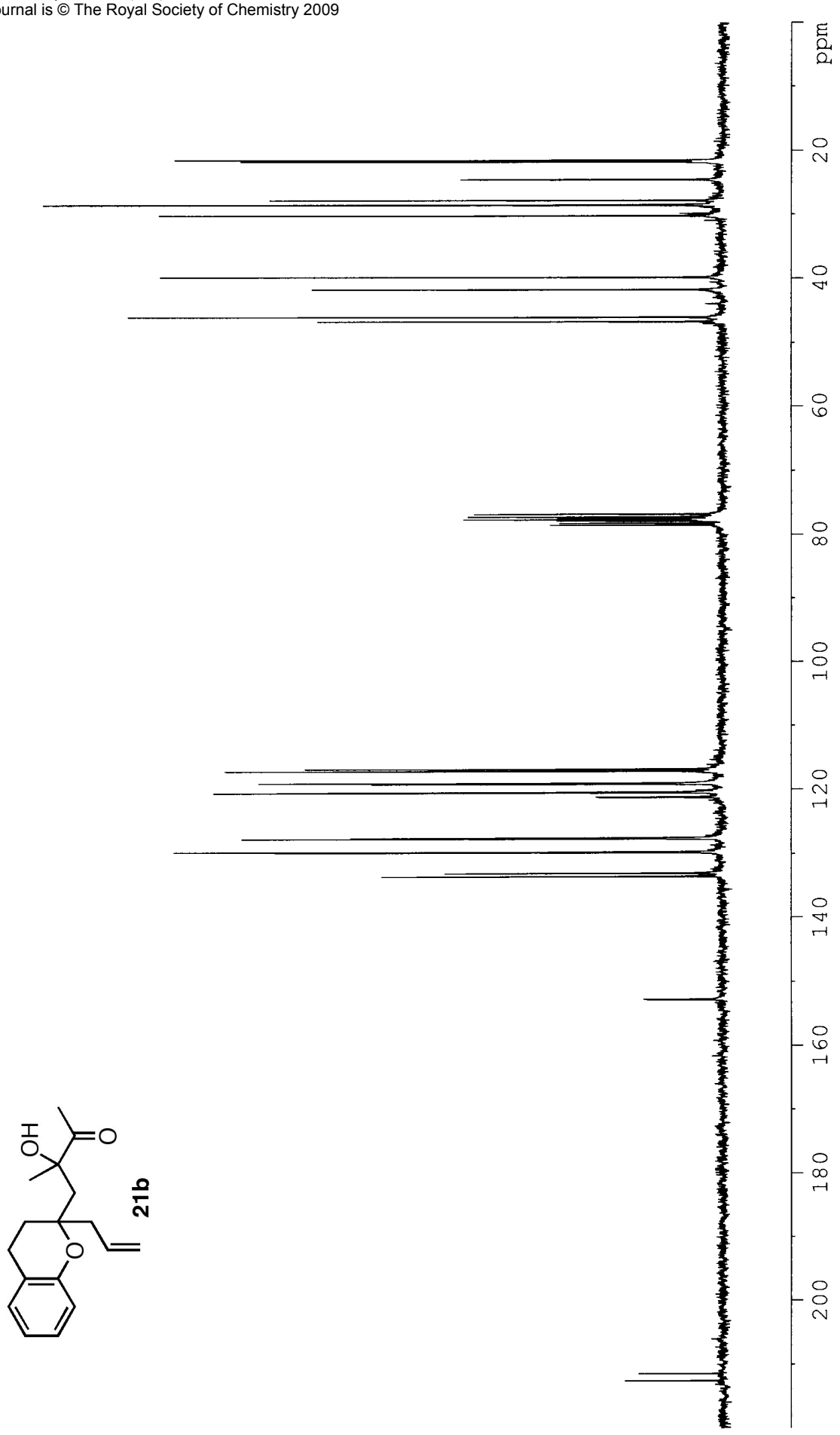

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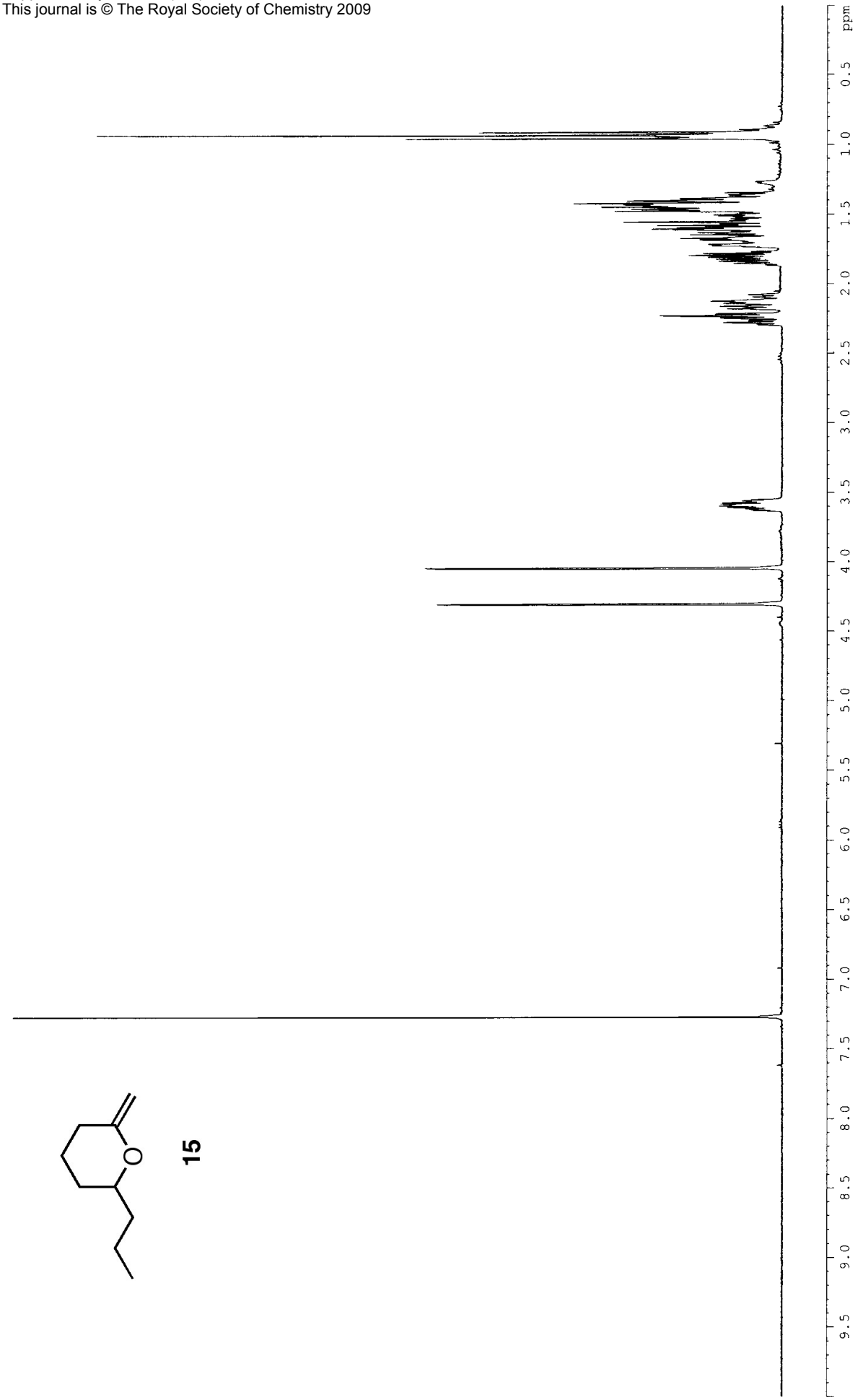

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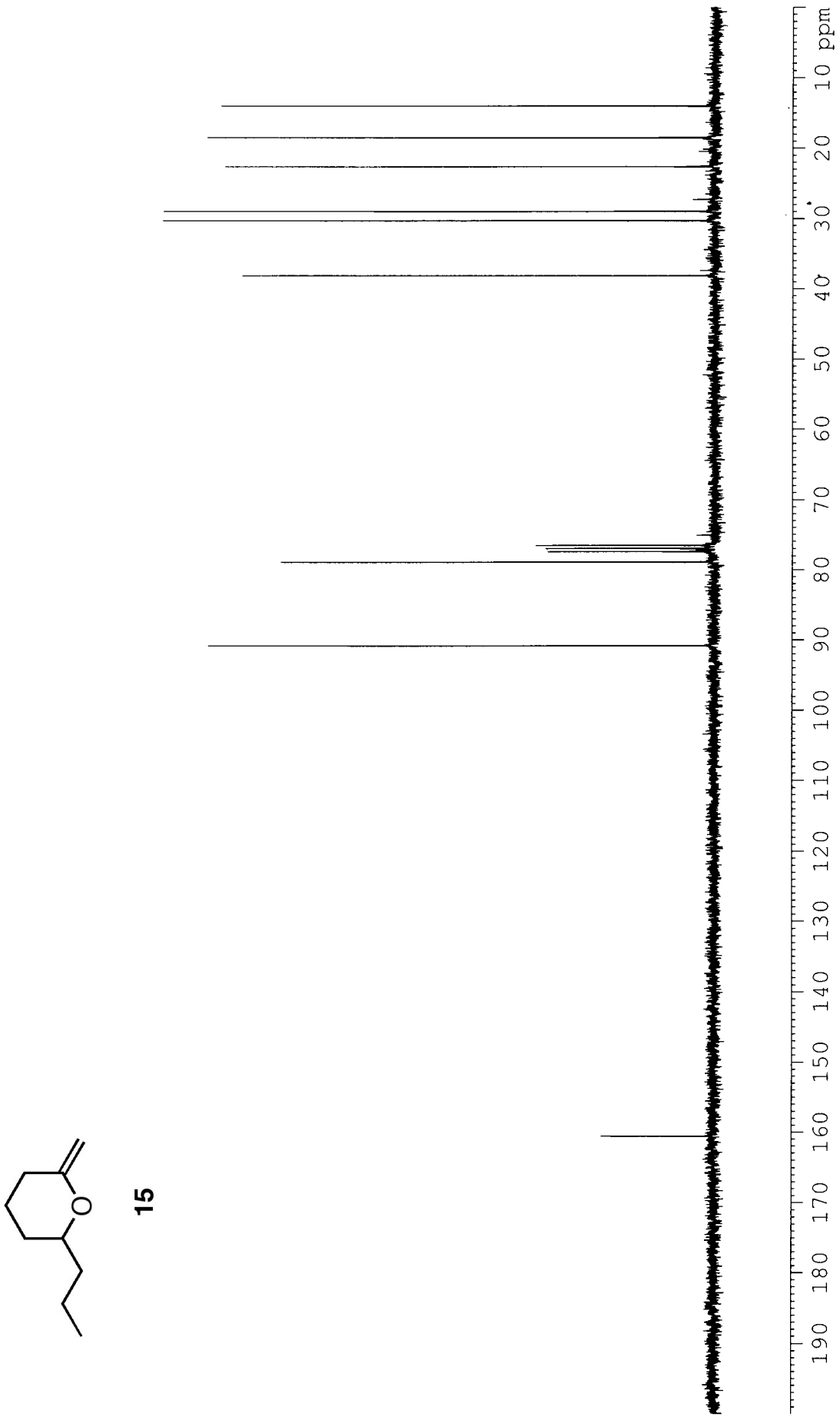

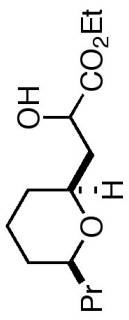

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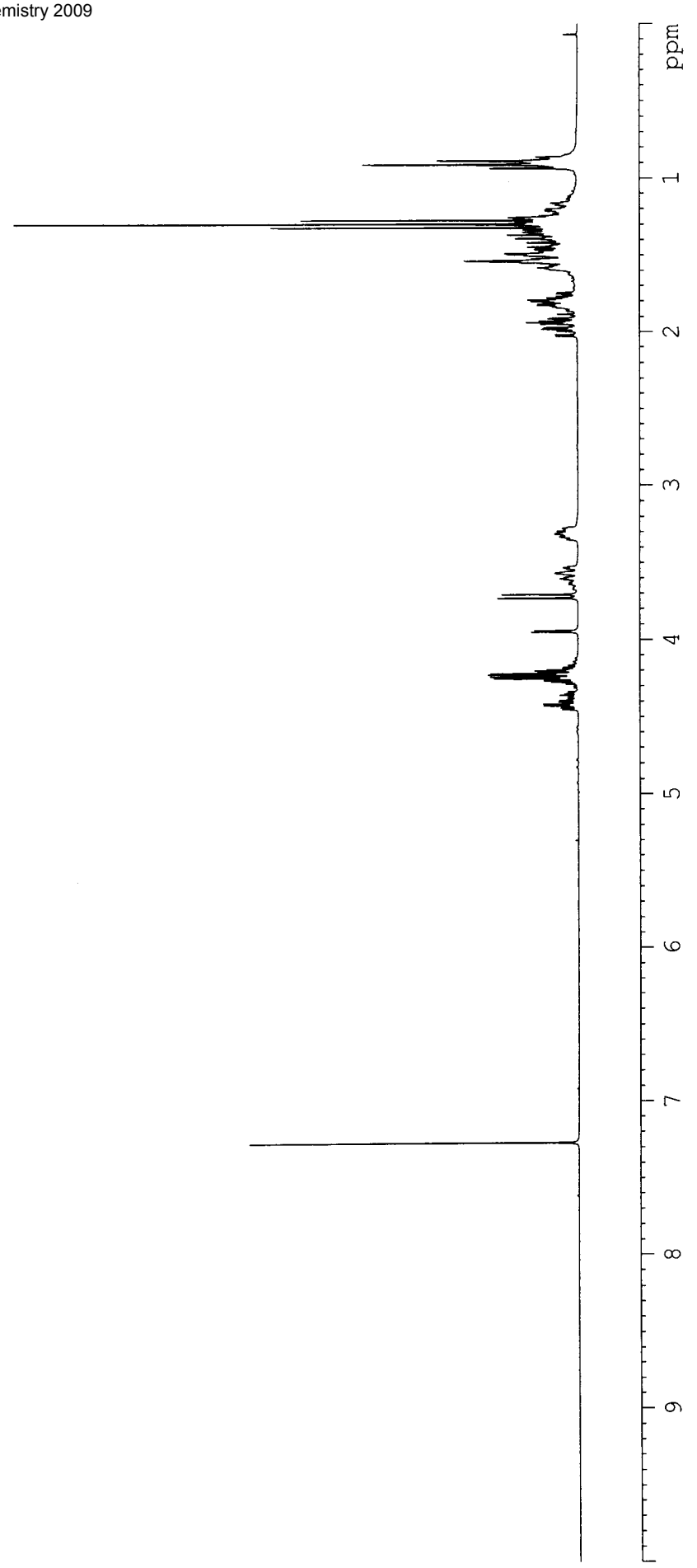

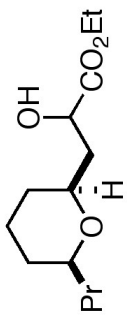

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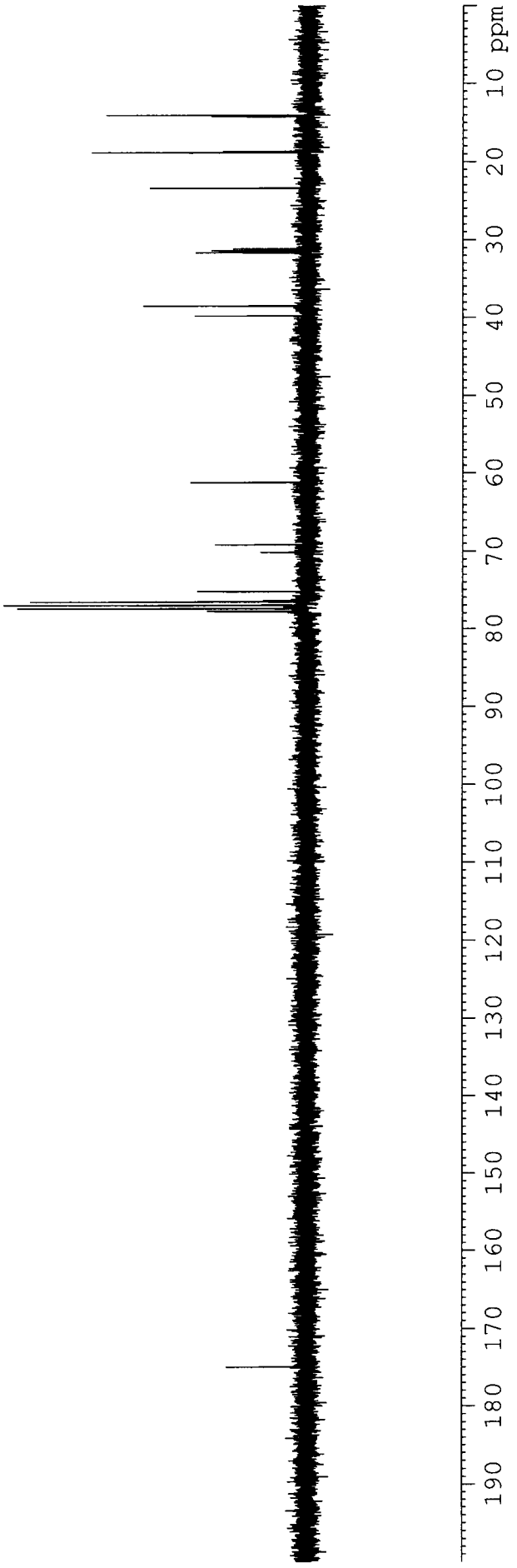

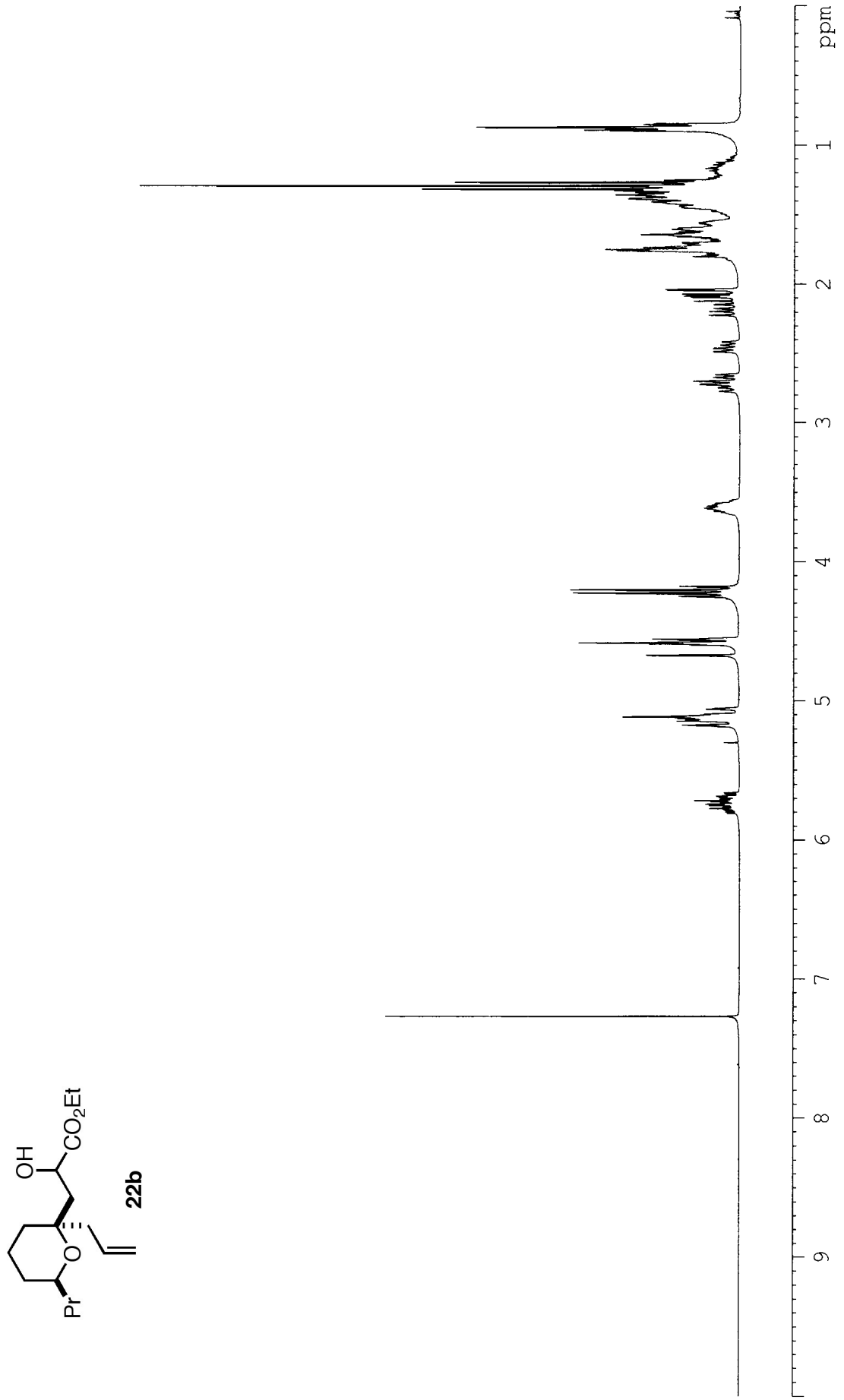

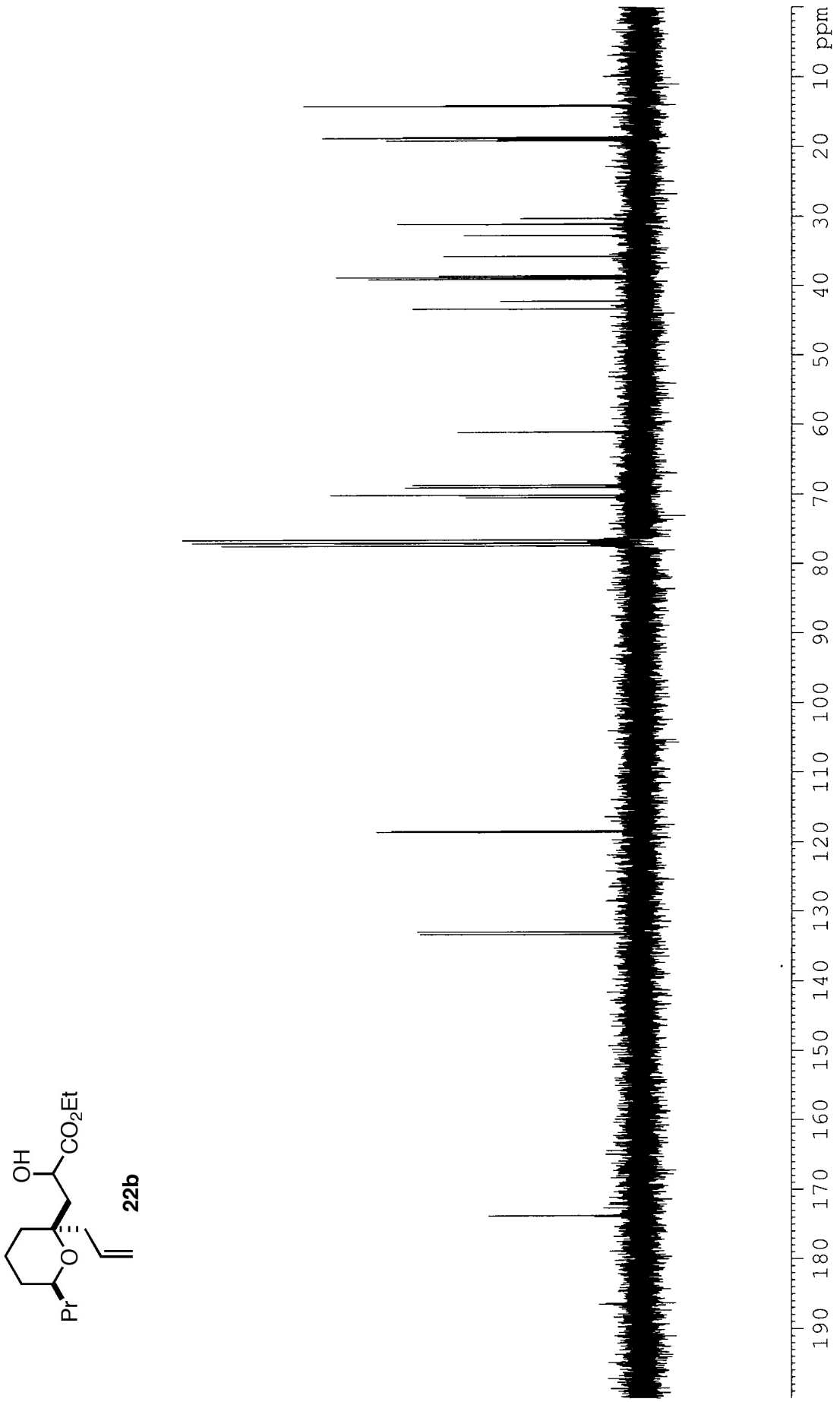

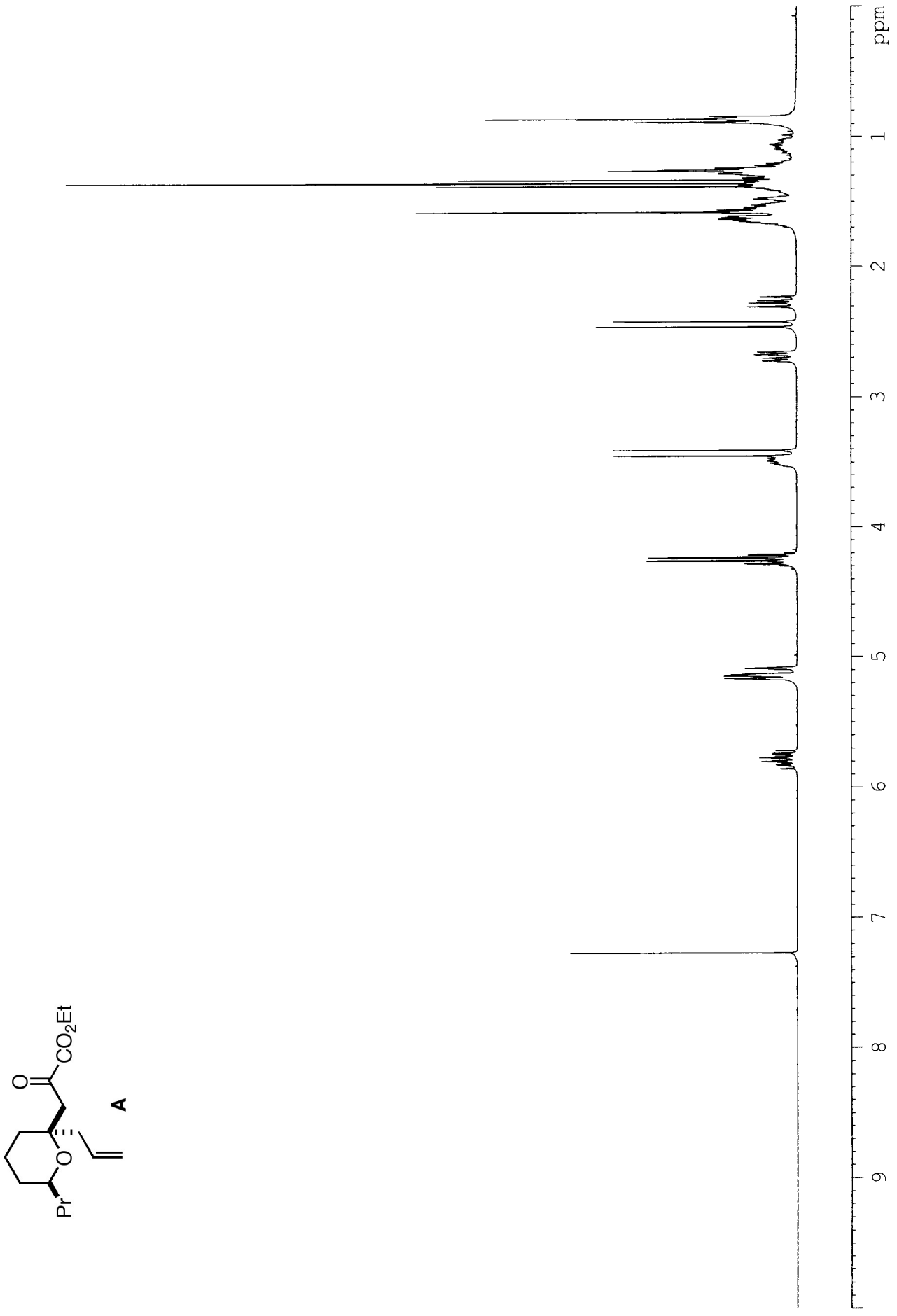

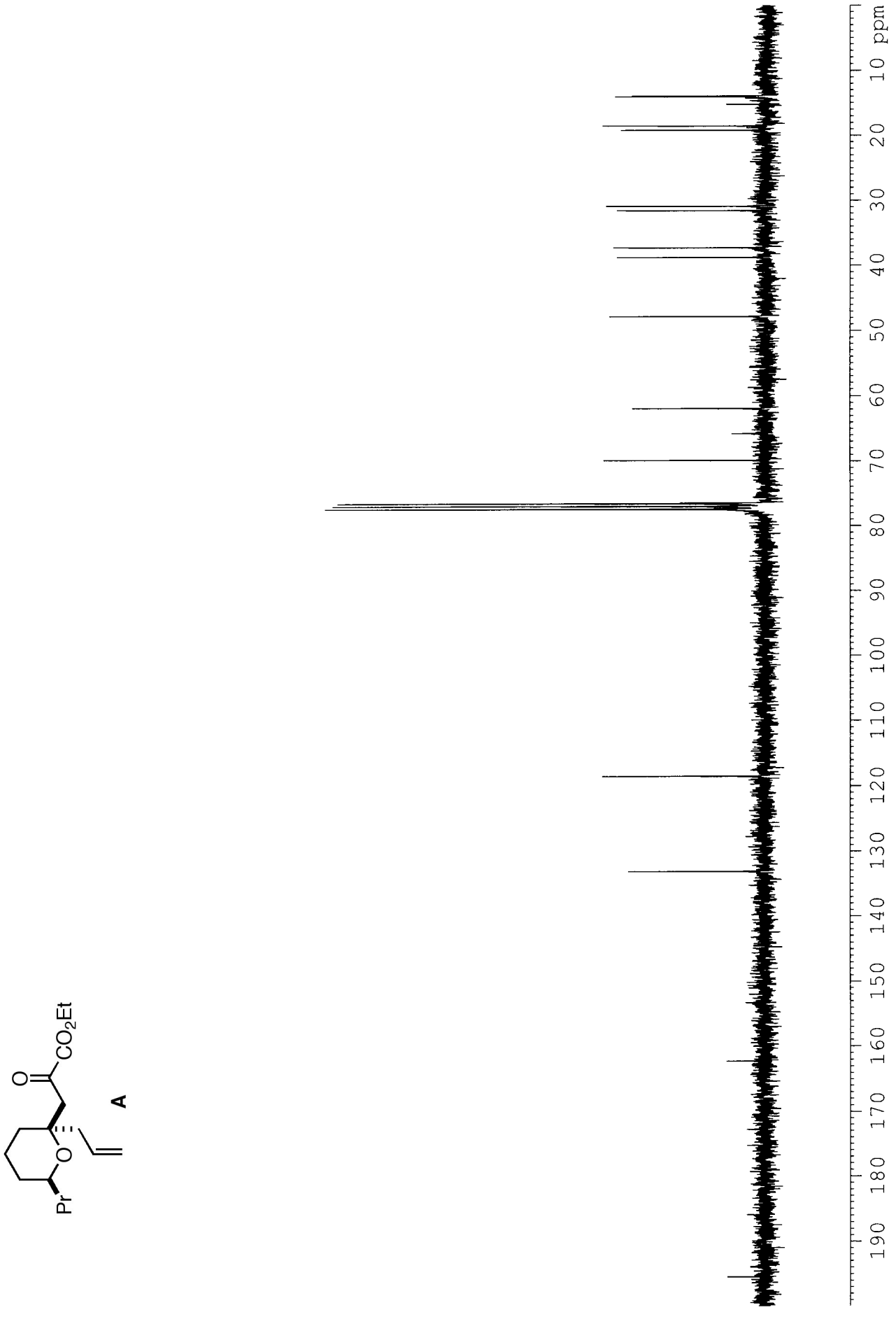

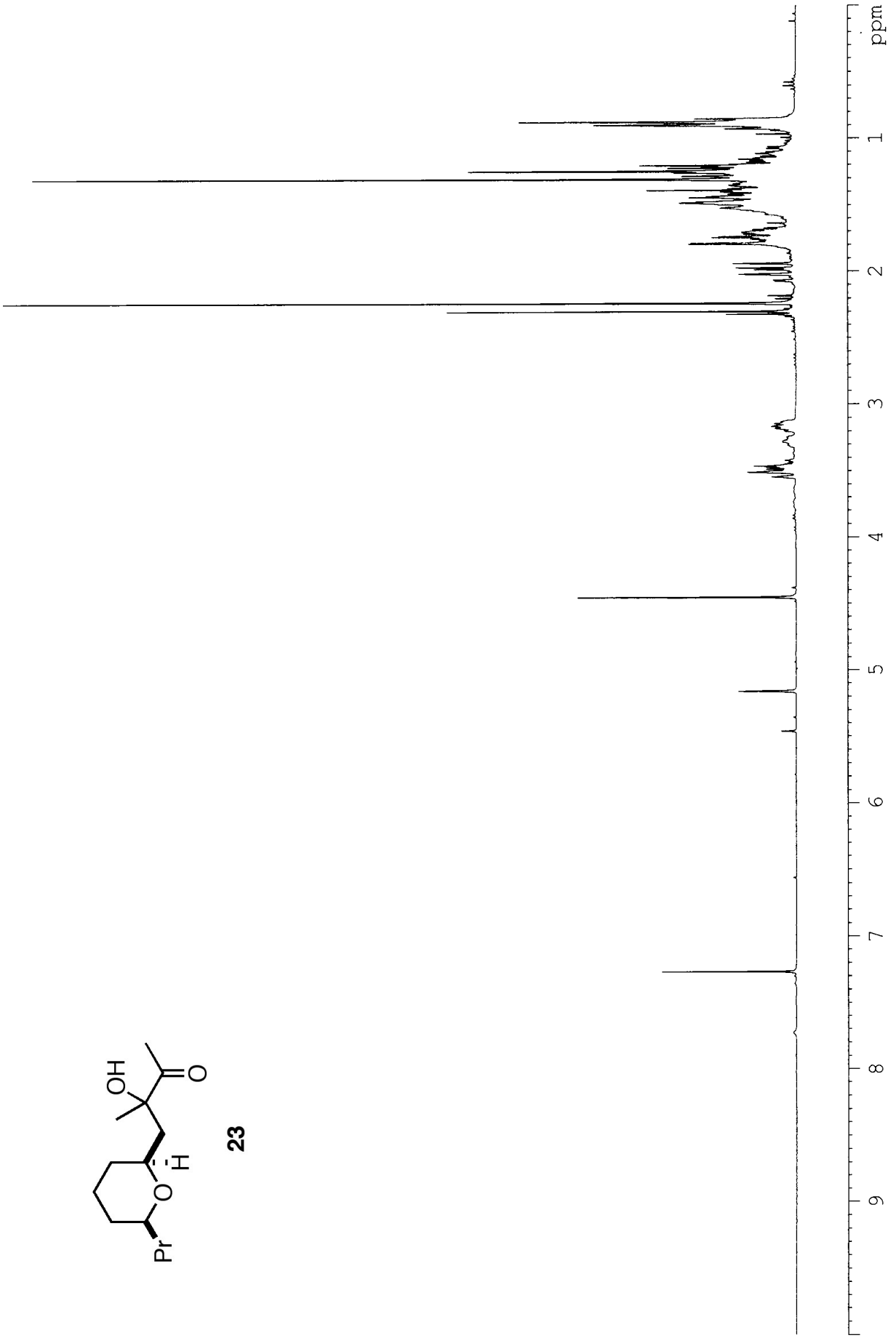

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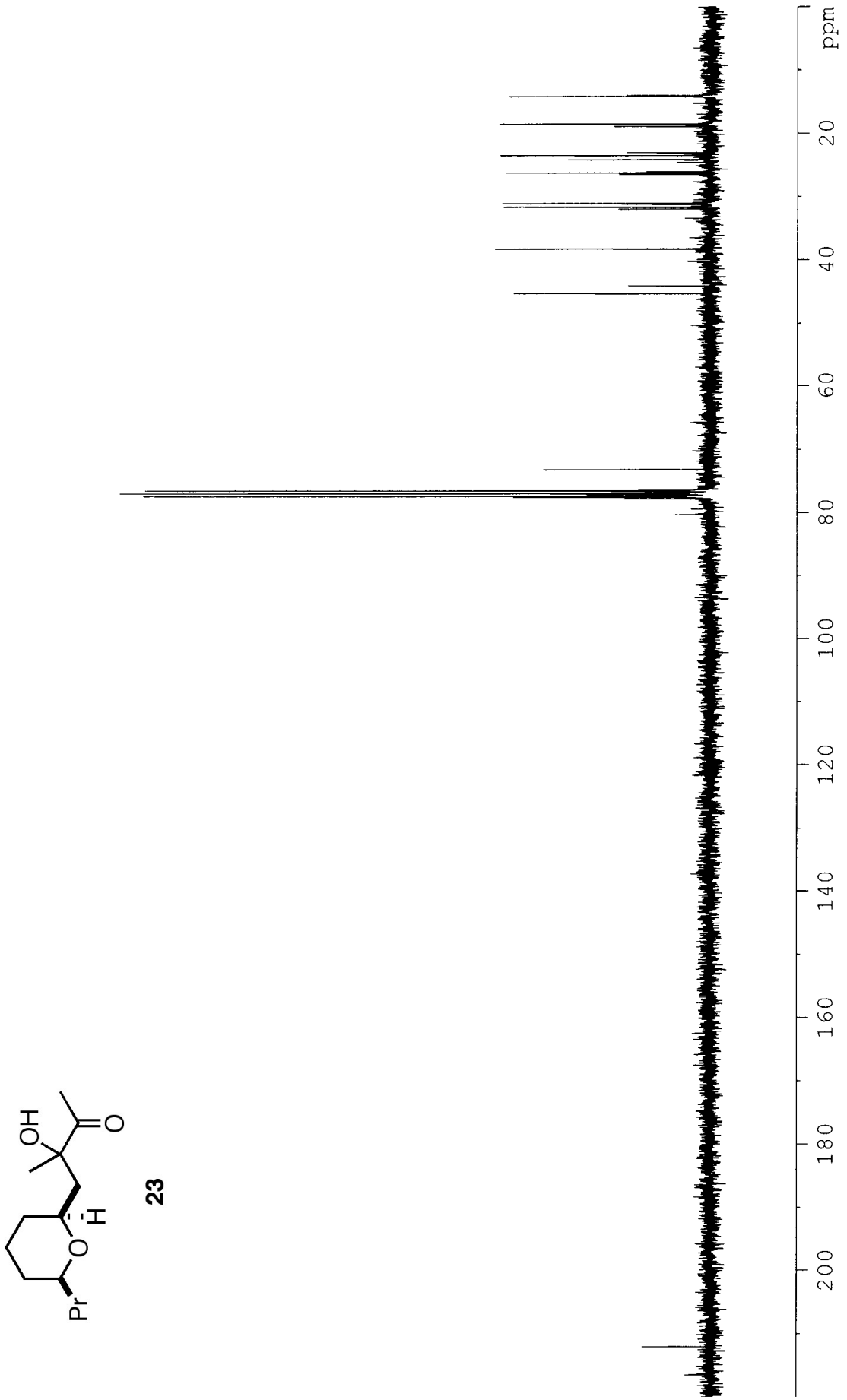

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