Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Electronic Supplementary Information

Transannular Claisen rearrangement reactions for the synthesis of vinylcyclobutanes: formal synthesis of (±)-grandisol

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General experimental

All reactions were performed under nitrogen unless otherwise stated. Melting points were determined using Stuart Scientific SMP1 melting point apparatus and are uncorrected. Infrared spectra were recorded on Mattson 5000 FTIR and Perkin-Elmer Spectrum RX FT-IR System spectrometers. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in CDCl3 unless otherwise stated on a Jeol GX-270, Brüker DRX-300, Brüker AV-400 or Brüker AV-500 spectrometer. Chemical shifts are in parts per million (ppm) and are referenced relative to the residual proton-containing solvent (^{1}H NMR: 7.26 ppm for CDCl3; ^{13}C NMR: 77.0 ppm for CDCl3). Mass spectra (CI, EI and FAB) were recorded using Micromass AutoSpec-Q, Micromass Platform II or Micromass AutoSpec Premier instruments. Elemental analyses were performed at the microanalytical laboratories of the London Metropolitan University. Optical rotations were measured on an Optical Activity Ltd. instrument. Analytical thin layer chromatography (TLC) was performed on pre-coated Aluminium-backed Merck Kieselgel 60 F_{254} plates. Visualisation was effected with ultraviolet light, potassium permanganate or vanillin as appropriate. Column chromatography was performed using BDH (40–63 μm) silica gel unless otherwise stated. Standard solvents were distilled under nitrogen prior to use; Et_2O and THF from sodium-benzophenone ketyl, CH_2Cl_2 from CaH_2 and toluene from sodium. All other solvents were reagent grade. Petrol refers to petroleum ether of the fraction bp 40–60 °C. All liquid reagents were distilled prior to use. BSA was purchased from Alfa Aesar Lancaster and distilled prior to use. Potassium acetate was oven-dried at 120 °C for several days prior to use. Microwave reactions were performed in a Biotage initiator.

Synthesis and Claisen rearrangement reactions of lactones 1, 2 and 3

*5-(Tetrahydro-2*H*-pyran-2-yloxy)pent-2-yn-1-ol*

To 4-(tetrahydro-2*H*-pyran-2-yloxy)-1-butyne (6.78 g, 44.0 mmol, 1.0 equiv.) in THF (70 mL) was added *n*BuLi (2.60 M; 16.9 mL, 44.0 mmol, 1.0 equiv.) dropwise at –78 °C. The mixture was stirred at –78 °C for 10 min, then paraformaldehyde (1.58 g, 52.8 mmol, 1.2 equiv.) was added portionwise. The mixture was warmed to rt and stirred for 3 h before being quenched with sat. $NH_4Cl_{(aq)}$. The reaction mixture was poured onto Et_2O and the aqueous layer further extracted with Et_2O (×2), dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (30% EtOAc–petrol) to give 5-(tetrahydro-2*H*-pyran-2-yloxy)pent-2-yn-1-ol (7.87 g, 97%) as a colourless oil; R_f 0.34 (50% EtOAc–petrol); ν_{max} (film) 3415, 2941, 2871, 2227, 1441, 1353, 1200, 1136, 1120, 1070, 1034, 970, 906, 868 cm^{-1}; δ_H (400 MHz) 4.66 (1H, dd, *J* 4.0, 3.0 Hz, OCHO), 4.26 (2H, m, CH_2OH), [3.87, 3.56] (4H, 2 × m, OCH_2CH_2C and $OCH_2CH_2CH_2$), 2.55 (2H, tt, *J* 7.0, 2.0 Hz, OCH_2CH_2C), 1.89–1.52 (6H, m, $OCH_2CH_2CH_2CH_2$); δ_C (100 MHz) 98.9 (OCHO), 83.3 (CCH_2OH), 79.4 ($CCCH_2OH$), 65.7 (OCH_2CH_2C), 62.4 ($OCH_2CH_2CH_2$), 51.4 (CH_2OH), 30.6 ($OCHCH_2CH_2$), 25.4 ($OCH_2CH_2CH_2$), 20.3 (OCH_2CH_2C), 19.5 ($OCH_2CH_2CH_2$); *m/z* (CI) 202 $[M+NH_4]^+$, 102, 85 (Found $[M+NH_4]^+$, 202.1443. $C_{10}H_{16}O_3$ requires $[M+NH_4]^+$, 202.1443).

*Methyl 5-(tetrahydro-2*H*-pyran-2-yloxy)pent-2-ynyl carbonate*

To a solution of 5-(tetrahydro-2*H*-pyran-2-yloxy)pent-2-yn-1-ol (7.86 g, 42.6 mmol, 1.0 equiv.) and pyridine (13.7 mL, 171 mmol, 4.0 equiv.) in CH_2Cl_2 (85 mL) at 0 °C was added methyl chloroformate (4.28 mL, 55.4 mmol, 1.3 equiv.) dropwise and the reaction stirred at 0 °C for 1 h. The reaction mixture was then diluted with H_2O, extracted with EtOAc and the organic layers washed with sat. $NH_4Cl_{(aq)}$ and sat. $NaCl_{(aq)}$. The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (30% EtOAc–petrol) to give methyl 5-(tetrahydro-2*H*-pyran-2-yloxy)pent-2-ynyl carbonate (9.93 g, 96%) as a colourless oil; R_f 0.63 (50% EtOAc–petrol); ν_{max} (film) 2944, 1754, 1444, 1376, 1263, 1122, 1070, 1033, 951 cm^{-1}; δ_H (400 MHz) 4.74 (2H, t, *J* 2.0 Hz, OCH_2C), 4.65 (1H, t, *J* 3.5 Hz, OCHO), 3.92–3.80 (2H, m, 1 × OCH_2CH_2C and 1 × $OCH_2CH_2CH_2$), 3.82 (3H, s, CH_3), 3.60–3.50 (2H, m, 1 × OCH_2CH_2C and 1 × $OCH_2CH_2CH_2$), 2.55 (2H, tt, *J* 7.0, 2.0 Hz, OCH_2CH_2C), 1.88–1.53 (6H, m, $OCH_2CH_2CH_2CH_2$); δ_C (100 MHz)

155.4 (C=O), 98.8 (OCHO), 85.3 (*C*CH$_2$O), 74.4 (*C*CH$_2$CH$_2$O), 65.3 (O*C*H$_2$CH$_2$C), 62.2 (O*C*H$_2$CH$_2$CH$_2$), 56.1 (O*C*H$_2$C), 55.0 (OCH$_3$), 30.5 (OCH*C*H$_2$CH$_2$), 25.4 (OCH$_2$*C*H$_2$CH$_2$), 20.3 (OCH$_2$*C*H$_2$C), 19.4 (OCH$_2$CH$_2$*C*H$_2$); *m/z* (CI) 260 $[M+NH_4]^+$, 102, 85 (Found $[M+NH_4]^+$, 260.1504. $C_{12}H_{18}O_5$ requires $[M+NH_4]^+$, 260.1498) (Found: C, 59.53; H, 7.41. $C_{12}H_{18}O_5$ requires C, 59.49; H, 7.49%).

5-Hydroxypent-2-ynyl methyl carbonate

A solution of 5-(tetrahydro-2*H*-pyran-2-yloxy)pent-2-ynyl carbonate (1.77 g, 7.3 mmol, 1.0 equiv.) and pyridinium *p*-toluenesulfonate (184 mg, 0.73 mmol, 10 mol%) in EtOH (35 mL) was stirred at 55 °C for 2 h. The reaction mixture was allowed to cool, concentrated under reduced pressure and purified by column chromatography (40% EtOAc–petrol) to give 5-hydroxypent-2-ynyl methyl carbonate (9.72 g, 93%) as a colourless oil; R_f 0.35 (50% EtOAc–petrol); ν_{max} (film) 3400, 2958, 2888, 2236, 1752, 1447, 1377, 1266, 1149, 1046, 956, 902, 791 cm^{-1}; δ_H (400 MHz) 4.76 (2H, t, *J* 2.0 Hz, OCH$_2$C), 3.83 (3H, s, CH$_3$), 3.75 (2H, q, *J* 6.0 Hz, C*H*$_2$OH), 2.53 (2H, tt, *J* 6.0, 2.0 Hz, C*H*$_2$CH$_2$OH), 1.96 (1H, t, *J* 6.0 Hz, OH); δ_C (100 MHz) 155.4 (C=O), 85.1 (*C*CH$_2$O), 75.6 (*C*CH$_2$CH$_2$), 60.9 (CH$_2$OH), 56.1 (C*C*H$_2$O), 55.2 (OCH$_3$), 23.2 (C*C*H$_2$CH$_2$); *m/z* (CI) 176 $[M+NH_4]^+$, 102 (Found $[M+NH_4]^+$, 176.0922. $C_7H_{10}O_4$ requires $[M+NH_4]^+$, 176.0923) (Found: C, 53.22; H, 6.35. $C_7H_{10}O_4$ requires C, 53.16; H, 6.37%).

(Z)-5-Hydroxypent-2-enyl methyl carbonate

To 5-hydroxypent-2-ynyl methyl carbonate (3.12 g, 19.8 mmol, 1.0 equiv.) in THF (120 mL) was added Lindlar's catalyst (156 mg, 5% wt.). With vigorous stirring the reaction vessel was flushed with a balloon of H_2 then allowed to stir for 1 h under a slight positive pressure of H_2. The reaction mixture was then filtered through celite, concentrated under reduced pressure and purified by column chromatography (20–30% EtOAc–petrol) to give (*Z*)-5-hydroxypent-2-enyl methyl carbonate (2.81 g, 89%) as a colourless oil; R_f 0.31 (50% EtOAc–petrol); ν_{max} (film) 3400, 2958, 1749, 1444, 1363, 1265, 1050, 948, 792 cm^{-1}; δ_H (400 MHz) 5.74 (2H, m, C*H*=C*H*), 4.73 (2H, d, *J* 5.5 Hz, OC*H*$_2$CH), 3.80 (3H, s, CH$_3$), 3.71 (2H, q, *J* 6.0 Hz, C*H*$_2$OH), 2.44 (2H, q, *J* 6.0 Hz, C*H*$_2$CH$_2$OH), 1.74 (1H, t, *J* 5.5 Hz, OH); δ_C (100 MHz) 155.9 (C=O), 132.0, 125.7 (CH=CH), 63.6 (CH$_2$OH), 61.7 (CH*C*H$_2$O), 54.9 (OCH$_3$), 31.1 (*C*H$_2$CH$_2$OH);

m/z (CI) 178 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 178.1082. $C_7H_{12}O_4$ requires $[M+NH_4]^+$, 178.1079) (Found: C, 52.59; H, 7.57. $C_7H_{12}O_4$ requires C, 52.49; H, 7.55%).

(Z)-5-(Methoxycarbonyloxy)pent-3-enyl methanesulfonate

A solution of (*Z*)-5-hydroxypent-2-enyl methyl carbonate (1.00 g, 6.24 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) was treated with NEt_3 (2.61 mL, 18.7 mmol, 3.0 equiv.) and MsCl (0.97 mL, 12.5 mmol, 2.0 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, washed with 2 M aq. HCl (× 2) and sat. aq. $NaHCO_3$ (× 2). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give (*Z*)-5-(methoxycarbonyloxy)pent-3-enyl methanesulfonate as an orange oil, which was used crude in the next step; R_f 0.51 (50% EtOAc–petrol); ν_{max} (film) 3027, 2960, 1749, 1444, 1353, 1268, 1174, 956, 915, 794, 734 cm^{-1}; δ_H (400 Hz) 5.72 (2H, m, C*H*=C*H*), 4.69 (2H, d, *J* 6.5 Hz, OCH_2CH), 4.26 (2H, t, *J* 6.5 Hz, CH_2OS), 3.79 (3H, s, OCH_3), 3.02 (3H, s, SCH_3), 2.61 (2H, q, *J* 6.5 Hz, CH_2CH_2O); δ_C (100 MHz) 155.9 (C=O), 129.4, 127.0 (CH=CH), 68.6 (CH_2OS), 63.4 (CH*C*H_2O), 55.1 (OCH_3), 37.7 (SCH_3), 27.8 (*C*H_2CH_2OH); *m/z* (CI) 256 $[M+NH_4]^+$, 178, 52 (Found $[M+NH_4]^+$, 256.0858. $C_8H_{14}O_6S$ requires $[M+NH_4]^+$, 256.0855).

(Z)-5-Iodopent-2-enyl methyl carbonate ***5***

To (*Z*)-5-(methoxycarbonyloxy)pent-3-enyl methanesulfonate (1.41 g, 5.93 mmol, 1.0 equiv.) in MeCN (20 mL) was added sodium iodide (1.78 g, 11.9 mmol, 2.0 equiv.) and the mixture stirred at 70 °C for 16 h. The reaction was then cooled and divided between Et_2O and H_2O. The combined organic layers were washed with sat. aq. $Na_2S_2O_3$, dried ($MgSO_4$) and concentrated under reduced pressure to give (*Z*)-5-iodopent-2-enyl methyl carbonate **5** as a colourless oil, which was used crude in the next step; R_f 0.79 (50% EtOAc–petrol); ν_{max} (film) 2956, 1748, 1443, 1362, 1263, 1175, 965, 903, 791 cm^{-1}; δ_H (400 MHz) 5.72 (1H, m, C*H*CH_2O), 5.63 (1H, m, C*H*CH_2CH_2I), 4.67 (2H, d, *J* 7.0 Hz, OCH_2), 3.78 (3H, s, CH_3), 3.17 (2H, t, *J* 7.0 Hz, CH_2I), 2.72 (2H, dt, *J* 7.0, 6.5 Hz, CH_2CH_2I); δ_C (100 MHz) 155.7 (C=O), 133.6, 125.2 (3°), 63.4 (OCH_2), 54.8 (OCH_3), 31.4 (*C*H_2CH_2I), 4.2 (CH_2I); *m/z* (CI) 288 $[M+NH_4]^+$, 256, 212, 195, 143 (Found $[M+NH_4]^+$, 288.0091. $C_7H_{11}IO_3$ requires $[M+NH_4]^+$, 288.0097).

(Z)-Methyl 7-(methoxycarbonyloxy)-2-tosylhept-5-enoate

Sodium hydride (300 mg, 7.49 mmol, 1.2 equiv.) suspended in THF (10 mL) at 0 °C was treated with methyl tosylacetate (1.42 g, 6.24 mmol, 1.0 equiv.) in THF (7.5 mL) followed by a solution of crude **5** (1.49 g, 6.24 mmol, 1.0 equiv.) in THF (7.5 mL). The reaction mixture was stirred at 0 °C for a further 30 min, then at rt for 16 h. The solution was concentrated under reduced pressure and the crude product suspended in EtOAc, washed with sat. aq. NH_4Cl, H_2O and sat. aq. NH_4Cl. The organic phase was dried ($MgSO_4$), concentrated under reduced pressure to give (*Z*)-methyl 7-(methoxycarbonyloxy)-2-tosylhept-5-enoate as a colourless oil, which was used crude in the next step; R_f 0.55 (50% EtOAc–petrol).

(Z)-Methyl 7-hydroxy-2-tosylhept-5-enoate

To a solution of (*Z*)-methyl 7-(methoxycarbonyloxy)-2-tosylhept-5-enoate (1.0 g, 2.79 mmol, 1.0 equiv.) in dry MeOH (14 mL) at 0 °C was added K_2CO_3 (1.93 g, 13.95 mmol, 5.0 equiv.) and the reaction mixture stirred at 0 °C for 2 h. The solvent was removed under reduced pressure and the residue partitioned between 2 M HCl and EtOAc. The aqueous layer was further washed with EtOAc and the combined organic layers dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (50–75% EtOAc–petrol) to give (*Z*)-methyl 7-hydroxy-2-tosylhept-5-enoate (382 mg, 43% over 4 steps) as a colourless oil; R_f 0.20 (50% EtOAc–petrol); ν_{max} (film) 3539, 2952, 1740, 1597, 1436, 1321, 1198, 1147, 1084, 1036, 816, 729, 667, 570 cm^{-1}; δ_H (400 MHz) 7.73 (2H, d, *J* 8.0 Hz, *o*-SO_2Ar), 7.36 (2H, d, *J* 8.0 Hz, *m*-SO_2Ar), 5.68 (1H, dt, *J* 11.0 7.0 Hz, C*H*CH_2OH), 5.38 (1H, dt, *J* 11.0, 7.0 Hz, SCH_2CH_2CH), 4.01 (2H, d, *J* 6.5 Hz, CH_2OH), 3.94 (1H, dd, *J* 10.5, 3.5 Hz, SCH), 3.68 (3H, s, OCH_3), 2.46 (3H, s, $ArCH_3$), 2.24–1.99 (4H, m, $SCHCH_2CH_2$); δ_C (100 MHz) 166.6 (C=O), 145.6, 134.0 (4°), 131.1, 129.8, 129.5, 129.3 (3°), 70.1 (SCH), 58.2 (CH_2OH), 53.0 (OCH_3), 26.5 ($SCHCH_2CH_2$), 24.6 ($SCHCH_2$), 21.7 ($ArCH_3$); *m/z* (CI) 330 $[M+NH_4]^+$, 174 (Found $[M+NH_4]^+$, 330.1389. $C_{15}H_{20}O_5S$ requires $[M+NH_4]^+$, 330.1375) (Found: C, 57.72; H, 6.51. $C_{15}H_{20}O_5S$ requires C, 57.67; H, 6.45%).

(Z)-7-Hydroxy-2-tosylhept-5-enoic acid 7

A solution of (*Z*)-methyl 7-hydroxy-2-tosylhept-5-enoate (1.45 g, 4.63 mmol, 1.0 equiv.) in THF (11.6 mL) was treated with 2 M LiOH (11.6 mL). The reaction mixture was stirred at rt for 1 h, then partitioned between Et_2O and H_2O and the aqueous layer acidified to pH 1 with 2 M HCl. The aqueous layer was extracted with Et_2O (× 3) and the organic layers combined, dried ($MgSO_4$) and concentrated under reduced pressure to give, without further purification (*Z*)-7-hydroxy-2-tosylhept-5-enoic acid **7** (1.45 g, 90%) as a colourless solid, which was used without further purification; ν_{max} (film) 3367, 974, 2894, 1725, 1451, 1381, 1319, 1148, 1086, 1049, 880 cm^{-1}; δ_H (400 MHz) 7.76 (2H, d, *J* 8.0 Hz, *o*-SO_2Ar), 7.35 (2H, d, *J* 8.0 Hz, *m*-SO_2Ar), 7.05 (1H, br s, OH), 5.67 (1H, dt, *J* 11.0, 7.0 Hz, C*H*CH_2OH), 5.41 (1H, dt, *J* 10.5, 7.5 Hz, $SCHCH_2CH_2CH$), 4.10 (2H, m, CH_2OH), 3.94 (1H, dd, *J* 9.5, 5.0 Hz, SCH), 2.44 (3H, s, $ArCH_3$), 2.18 (2H, m, $SCHCH_2$ and $SCHCH_2CH_2$), 2.04 (2H, m, $SCHCH_2$ and $SCHCH_2CH_2$); δ_C (100 MHz) 168.8 (C=O), 145.7, 133.8 (4°), 130.2, 129.8, 129.4 (3°), 70.0 (SCH), 57.9 (CH_2OH), 26.3 ($SCHCH_2CH_2$), 24.4 ($SCHCH_2$), 21.7 ($ArCH_3$); *m/z* (-ve CI) 297 $[M–H]^-$, 253, 155 (Found $[M–H]^-$, 297.0790. $C_{14}H_{18}O_5S$ requires $[M–H]^-$, 297.0797).

*(Z)-3-Tosyl-3,4,5,6-tetrahydrooxocin-2-one **1***

To a solution of HATU (637 mg, 1.68 mmol, 5.0 equiv.) and DIPEA (598 µL, 3.35 mmol, 10.0 equiv.) in DMF (10 mL) was added **7** (100 mg, 0.34 mmol, 1.0 equiv.) in DMF (7 mL) *via* syringe pump over a period of 12 h. The reaction mixture was allowed to stir for a further 8 h then extracted with EtOAc (× 3). The combined organic phases were washed sequentially with 2 M aq. $HCl_{(aq)}$, 2 M aq. NaOH, sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (30–80% EtOAc–petrol) gave (*Z*)-3-tosyl-3,4,5,6-tetrahydrooxocin-2-one **1** (63 mg, 66%) as a colourless solid; R_f 0.42 (50% EtOAc–petrol); mp 133–134 °C; ν_{max} (film) 3056, 2940, 1754, 1596, 1449, 1316, 1265, 1148, 1086, 1035, 813, 738, 663 cm^{-1}; δ_H (400 MHz) 7.89 (2H, d, *J* 8.0 Hz, *o*-SO_2Ar), 7.37 (2H, d, *J* 8.0 Hz, *m*-SO_2Ar), 5.60–5.50 (2H, m, CH=CH), 4.95 (1H, dd, *J* 15.5, 3.0 Hz, OCH_2), 4.60 (1H, d, *J* 15.5 Hz, OCH_2), 4.06 (1H, dd, *J* 10.0, 6.0 Hz, SCH), 2.46 (3H, s, $ArCH_3$), 2.55–2.35 (3H, m, $SCHCH_2CH_2$ and 1 × $SCHCH_2$), 1.91 (1H, m, $SCHCH_2$); δ_C (100 MHz) 168.4 (C=O), 145.4, 134.2 (4°), 129.8, 129.7, 128.6,

128.2 (3°), 67.4 (SCH), 66.1 (OCH_2), 25.2 ($SCHCH_2CH_2$), 24.7 ($SCHCH_2$), 21.7 ($ArCH_3$); *m/z* (CI) 298 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 298.1114. $C_{14}H_{16}O_4S$ requires $[M+NH_4]^+$, 298.1113) (Found: C, 60.05; H, 5.74. $C_{14}H_{16}O_4S$ requires C, 59.98; H, 5.75%).

*1-Methyl-4-((1*R*,2*S**)-2-vinylcyclobutylsulfonyl)benzene* ***9***

Lactone **1** (42 mg, 0.15 mmol, 1.0 equiv.) in DMF (0.75 mL) was treated with KOAc (1.5 mg, 0.015 mmol, 0.1 equiv.) and BSA (37 μL, 0.15 mmol, 1.0 equiv.) and the mixture subjected to microwave irradiation at 160 °C for 10 min. The reaction mixture was diluted with EtOAc, washed with sat. aq. NaCl (× 3) and H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (20% EtOAc–petrol) gave 1-methyl-4-((1*R**,2*S**)-2-vinylcyclobutylsulfonyl)benzene **9** (30 mg, 85%) as a colourless gum; R_f 0.67 (50% EtOAc–petrol); ν_{max} (film) 2926, 1600, 1493, 1452, 1265, 1146, 740, 702 cm^{-1}; δ_H (400 MHz) 7.76 (2H, d, *J* 8.0 Hz, *o*-SO_2Ar), 7.34 (2H, d, *J* 8.0 Hz, *m*-SO_2Ar), 5.66 (1H, ddd, *J* 17.0, 10.0, 6.0 Hz, $CH=CH_2$), 4.90 (1H, dd, *J* 16.0, 1.5 Hz, $CH=CH_2$ *cis*), 4.90 (1H, dd, *J* 11.5, 1.5 Hz, $CH=CH_2$ *trans*), 3.57 (1H, q, *J* 9.0, Hz, SCH), 3.40 (1H, m, $SCHCH$), 2.43 (3H, s, $ArCH_3$), 2.43 (1H, m, $SCHCH_2$), 2.14 (1H, m, $SCHCH_2CH_2$), 2.03 (1H, m, $SCHCH_2$), 1.84 (1H, m, $SCHCH_2CH_2$); δ_C (100 MHz) 144.6, 135.5 (4°), 138.2 ($CH=CH_2$), 129.8, 128.4 (3°), 115.2 ($CH=CH_2$), 62.0 (SCH), 39.8 ($SCHCH$), 22.9 ($SCHCH_2$), 21.6 ($ArCH_3$), 19.6 ($SCHCH_2CH_2$); *m/z* (CI) 254 $[M+NH_4]^+$, 490 (Found $[M+NH_4]^+$, 254.1212. $C_{13}H_{16}O_2S$ requires $[M+NH_4]^+$, 254.1215) (Found: C, 66.09; H, 6.76. $C_{13}H_{16}O_2S$ requires C, 66.07; H, 6.82%).

*(1*R**,2*S**)-1-Tosyl-2-vinylcyclobutanecarboxylic acid* ***11***

Lactone **1** (98 mg, 0.35 mmol, 1.0 equiv.) in CH_2Cl_2 (1.75 mL) was treated with KOAc (3.4 mg, 0.035 mmol, 0.1 equiv.) and BSA (87 μL, 0.35 mmol, 1.0 equiv.). The reaction mixture was stirred at rt for 16 h, then diluted with CH_2Cl_2, washed with 2 M aq. HCl and H_2O, dried ($MgSO_4$) and concentrated under reduced pressure to give to give (1*R**,2*S**)-1-tosyl-2-vinylcyclobutanecarboxylic acid **11** (97 mg, 99%) as a colourless solid; mp 135–136 °C; ν_{max} (film) 2985, 1728, 1376, 1267, 1046, 737 cm^{-1}; δ_H (400 MHz) 7.76 (2H, d, *J* 8.0 Hz, *o*-SO_2Ar), 7.37 (2H, d, *J* 8.0 Hz, *m*-SO_2Ar), 5.79 (1H, ddd, *J* 17.5, 10.5, 7.5 Hz, $CH=CH_2$), 5.22 (1H, d, *J* 17.5 Hz, $CH=CH_2$ *cis*),

5.21 (1H, d, *J* 10.0 Hz, CH=CH_2 *trans*), 4.05 (1H, br q, *J* 9.0 Hz, SCCH), 2.68 (1H, dt, *J* 11.5, 9.5 Hz, SCCH_2), 2.52 (1H, m, SCCH_2), 2.47 (3H, s, ArCH_3), 2.25 (1H, m, SCCH_2CH_2), 2.14 (1H, m, SCCH_2CH_2); δ_C (100 MHz) 166.9 (C=O), 145.9, 133.0 (4°), 135.0 (*C*H=CH_2), 130.1, 129.3 (3°), 119.0 (CH=*C*H_2), 74.1 (SC), 42.9 (SC*C*H), 23.3 (SC*C*H_2), 21.7 (ArCH_3), 21.2 (SCCH_2*C*H_2); *m/z* (CI) 298 $[M+NH_4]^+$, 254 (Found $[M+NH_4]^+$, 298.1107. $C_{14}H_{16}O_4S$ requires $[M+NH_4]^+$, 298.1113) (Found: C, 60.07; H, 5.80. $C_{14}H_{16}O_4S$ requires C, 59.98; H, 5.75%).

(Z)-Ethyl 5-(tert-butyldiphenylsilyloxy)-2-methylpent-2-enoate

To a solution of ethyl 2-(diphenylphosphinyl)propionate (2.39 g, 7.42 mmol, 1.0 equiv.) in THF (74.2 mL) was added sodium iodide (1.33 g, 8.90 mmol, 1.2 equiv.) and DBU (1.22 mL, 8.16 mmol, 1.1 equiv.) at 0 °C and stirred for 10 min. The mixture was cooled to –78 °C and 3-(*tert*-butyldiphenylsilyloxy)propanal (2.32 g, 7.42 mmol, 1.0 equiv.) added. After 10 min the mixture was warmed to 0 °C over 2 h. The reaction was quenched with sat. aq. NH_4Cl, extracted with EtOAc and the organic layer washed with H_2O and sat. aq. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (10–50% CH_2Cl_2–petrol) gave a mixture of geometric isomers (87:13 *Z*:*E*) of ethyl 5-(tert-butyldiphenylsilyloxy)-2-methylpent-2-enoate (2.64 g, 90%) as a colourless oil.

Z-isomer: R_f 0.27 (50% CH_2Cl_2–petrol); ν_{max} (film) 2958, 2936, 2857, 1714, 1428, 1211, 1143, 1111, 1053, 822, 701 cm^{-1}; δ_H (400 MHz) 7.68 (4H, m, *m*-Ph), 7.42 (6H, m, *o*-/*p*-Ph), 6.05 (1H, td, *J* 7.0, 1.5 Hz, CH), 4.20 (2H, q, *J* 7.0 Hz, CH_2CH_3), 3.76 (2H, t, *J* 6.5 Hz, OCH_2CH_2), 2.77 (2H, td, *J* 7.5, 1.5 Hz, CHCH_2), 1.93 (3H, d, *J* 1.5 Hz, CCH_3), 1.30 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.07 (9H, s, C(CH_3)$_3$); δ_C (100 MHz) 168.0 (C=O), 139.4 (*C*HCH_2), 133.9, 128.5 (4°), 135.6, 129.6, 127.6 (3°), 63.3 (O*C*H_2CH_2), 60.1 (O*C*H_2CH_3), 33.0 (O*C*H_2CH_2), 26.8 (C(*C*H_3)$_3$), 20.7 (C*C*H_3), 19.2 (*C*(CH_3), 14.3 (CH_2*C*H_3); *m/z* (CI) 397 $[M+H]^+$, 414, 330, 170, 125 (Found $[M+H]^+$, 397.2202. $C_{24}H_{32}O_3Si$ requires $[M+H]^+$, 397.2199) (Found: C, 72.63; H, 8.09. $C_{24}H_{32}O_3Si$ requires C, 72.68; H, 8.13%).

E-isomer: R_f 0.20 (50% CH_2Cl_2–petrol); ν_{max} (film) 3073, 2932, 2859, 1713, 1472, 1428, 1391, 1279, 1212, 1111, 823, 740, 702cm^{-1}; δ_H (400 MHz) 7.68 (4H, m, *m*-Ph), 7.42 (6H, m, *o*-/*p*-Ph), 6.83 (1H, td, *J* 7.5, 1.0 Hz, CH), 4.21 (2H, q, *J* 7.0 Hz, CH_2CH_3), 3.76 (2H, t, *J* 6.5 Hz, OCH_2CH_2), 2.45 (2H, q, *J* 7.0 Hz, CHCH_2), 1.82 (3H, s, CCH_3), 1.31 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.07 (9H, s, C(CH_3)$_3$); δ_C (100 MHz) 168.1

(C=O), 138.5 (*C*HCH$_2$), 133.7, 129.3 (4°), 135.6, 129.7, 127.7 (3°), 62.5 (O*C*H$_2$CH$_2$), 60.4 (O*C*H$_2$CH$_3$), 32.1 (OCH$_2$*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 19.2 (*C*(CH$_3$)$_3$), 14.3 (CH$_2$*C*H$_3$), 12.5 (C*C*H$_3$); *m/z* (CI) 397 [M+H]$^+$, 414, 330, 170, 125 (Found [M+H]$^+$, 397.2202. $C_{24}H_{32}O_3Si$ requires [M+H]$^+$, 397.2199) (Found: C, 72.74; H, 8.15. $C_{24}H_{32}O_3Si$ requires C, 72.68; H, 8.13%).

(Z)-5-(tert-Butyldiphenylsilyloxy)-2-methylpent-2-en-1-ol

To (*Z*)-ethyl 5-(*tert*-butyldiphenylsilyloxy)-2-methylpent-2-enoate (2.13 g, 5.36 mmol, 1.0 equiv.) in PhMe (17 mL) at –78 °C was added DIBAL-H (1.2 M in PhMe; 9.83 mL, 11.8 mmol, 2.2 equiv.) dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was again cooled to 0 °C, carefully quenched with sat. Na/K tartrate soln. and the mixture stirred for a further 2 h. The aqueous layer was then extracted with EtOAc and the combined organic layers washed with sat. aq. NaCl (× 2) and H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc–petrol) gave (*Z*)-5-(tert-butyldiphenylsilyloxy)-2-methylpent-2-en-1-ol (1.82 g, 96%) as a colourless oil; R_f 0.66 (50% EtOAc–petrol); ν_{max} (film) 3347, 2930, 2857, 1472, 1427, 1389, 1111, 1007, 938, 823, 736, 701, 614 cm^{-1}; δ_H (400 MHz) 7.70 (4H, m, *m*-Ph), 7.44 (6H, m, *o*-/*p*-Ph), 5.33 (1H, t, *J* 7.5 Hz, CH), 4.09 (2H, s, C*H*$_2$OH), 3.66 (2H, t, *J* 6.5 Hz, OC*H*$_2$CH$_2$), 2.37 (2H, dt, *J* 6.5, 6.5 Hz, CHC*H*$_2$), 1.85 (3H, s, CCH$_3$), 1.79 (1H, br s, OH), 1.08 (9H, s, C(CH$_3$)$_3$); δ_C (100 MHz) 137.3 (*C*HCH$_2$), 133.6, 124.7 (4°), 135.6, 129.7, 127.7 (3°), 63.6 (O*C*H$_2$CH$_2$), 61.7 (CH$_2$OH), 31.0 (CH*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 21.8 (C*C*H$_3$), 19.1 (*C*(CH$_3$)$_3$); *m/z* (CI) 372 [M+NH$_4$]$^+$, 355, 337, 277; data were in accordance with those reported the literature.[1]

(Z)-5-(tert-Butyldiphenylsilyloxy)-2-methylpent-2-enyl methyl carbonate

To (*Z*)-5-(*tert*-butyldiphenylsilyloxy)-2-methylpent-2-en-1-ol (1.82 g, 5.14 mmol, 1.0 equiv.) and pyridine (1.65 mL, 20.6 mmol, 4.0 equiv.) in CH_2Cl_2 (25 mL) at 0 °C was added methyl chloroformate (516 μL, 6.68 mmol, 1.3 equiv.) dropwise and the reaction stirred at 0 °C for 1 h. The reaction mixture was then diluted with H_2O and extracted with EtOAc. The organic layer was washed with sat. aq. NH_4Cl and sat. aq. NaCl, dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (50–80% CH_2Cl_2–petrol) to give (*Z*)-5-(*tert*-butyldiphenylsilyloxy)-

2-methylpent-2-enyl methyl carbonate (1.73 g, 82%) as a colourless oil; R_f 0.38 (50% CH_2Cl_2–petrol); ν_{max} (film) 2954, 2856, 1749, 1442, 1427, 1384, 1261, 1111, 947, 822, 792, 738, 702 cm^{-1}; δ_H (400 MHz) 7.66 (4H, m, *m*-Ph), 7.40 (6H, m, *o*-/*p*-Ph), 5.45 (1H, t, *J* 7.5 Hz, CH), 4.62 (2H, s, CCH_2O), 3.78 (3H, s, OCH_3), 3.65 (2H, t, *J* 6.5 Hz, OCH_2CH_2), 2.36 (2H, dt, *J* 7.0, 7.0 Hz, CHCH_2), 1.77 (3H, s, CCH_3), 1.05 (9H, s, $C(CH_3)_3$); δ_C (100 MHz) 155.9 (C=O), 135.6 ($CHCH_2$), 133.9, 131.1 (4°), 129.6, 127.7, 127.6 (3°), 66.7 (OCH_3), 63.4 (OCH_2CH_2), 54.7 (OCH_2CCH_3), 31.2 ($CHCH_2$), 26.8 ($C(CH_3)_3$), 21.3 (CCH_3), 19.2 ($C(CH_3)_3$); *m/z* (CI) 430 $[M+NH_4]^+$, 337, 81 (Found $[M+NH_4]^+$, 430.2408. $C_{24}H_{32}O_4Si$ requires $[M+H]^+$, 430.2414) (Found: C, 69.93; H, 7.81. $C_{24}H_{32}O_4Si$ requires C, 69.86; H, 7.82%).

(Z)-5-Hydroxy-2-methylpent-2-enyl methyl carbonate

To a stirred solution of (*Z*)-5-(*tert*-butyldiphenylsilyloxy)-2-methylpent-2-en-1-ol (1.73 g, 4.19 mmol, 1.0 equiv.) in MeOH (14 mL) at rt was added conc. HCl (280 µL). The mixture was stirred at rt for 16 h, then solid $NaHCO_3$ was added until effervescence ceased, and the solids removed by filtration. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (30–60% EtOAc–petrol) to give (*Z*)-5-hydroxy-2-methylpent-2-enyl methyl carbonate (673 mg, 92%) as a colourless oil; R_f 0.28 (50% EtOAc–petrol); ν_{max} (film) 3394, 2958, 1748, 1444, 1385, 1351, 1264, 1049, 948 cm^{-1}; δ_H (400 MHz) 5.48 (1H, t, *J* 7.5 Hz, CH), 4.69 (2H, s, OCH_2C), 3.79 (3H, s, OCH_3), 3.67 (2H, t, *J* 6.5 Hz, CH_2OH), 2.40 (2H, dt, *J* 6.5, 6.5 Hz, CHCH_2), 1.89 (1H, s, OH), 1.82 (3H, d, *J* 0.5 Hz, CCH_3); δ_C (100 MHz) 156.0 (C=O), 132.3 (CCH_3), 127.6 (CH), 66.6 (OCH_3), 62.0 (OCH_2CH_2), 54.9 (OCH_2CCH_3), 31.3 ($CHCH_2$), 21.4 (CCH_3); *m/z* (CI) 192 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 192.1228. $C_8H_{14}O_4$ requires $[M+NH_4]^+$, 192.1236) (Found: C, 55.19; H, 8.20. $C_8H_{14}O_4$ requires C, 55.16; H, 8.10%).

(Z)-5-(Methoxycarbonyloxy)-4-methylpent-3-enyl methanesulfonate

(*Z*)-5-HSydroxy-2-methylpent-2-enyl methyl carbonate (650 mg, 3.73 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was treated with NEt_3 (1.56 mL, 11.2 mmol, 3.0 equiv.) and MsCl (577 µL, 7.46 mmol, 2.0 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, washed with 2 M aq. HCl (× 2) and sat. aq. $NaHCO_3$ (× 2). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give

(*Z*)-5-(methoxycarbonyloxy)-4-methylpent-3-enyl methanesulfonate as a yellow oil, which was used crude in the next step; R_f 0.38 (50% EtOAc–petrol); ν_{max} (film) 2960, 1747, 1445, 1351, 1265, 1173, 956, 792 cm^{-1}; δ_H (400 MHz) 5.38 (1H, t, *J* 8.0 Hz, CH), 4.60 (2H, s, OCH_2CCH_3), 4.17 (2H, t, *J* 6.5 Hz, CH_2OS), 3.73 (3H, s, OCH_3), 2.96 (3H, s, SCH_3), 2.53 (2H, dt, *J* 6.5, 6.5 Hz, $CHCH_2$), 1.76 (3H, dd, *J* 2.5, 1.0 Hz, CCH_3); δ_C (100 MHz) 155.6 (C=O), 133.4 (CCH_3), 124.4 (CH), 68.9 ($SOCH_2$), 66.0 (OCH_3), 54.7 (OCH_2CCH_3), 37.2 (SCH_3), 27.7 ($CHCH_2$), 21.2 (CCH_3); *m/z* (CI) 270 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 270.1012. $C_9H_{16}O_6S$ requires $[M+NH_4]^+$, 270.1011).

(Z)-5-Iodo-2-methylpent-2-enyl methyl carbonate ***6***

To (*Z*)-5-(methoxycarbonyloxy)-4-methylpent-3-enyl methanesulfonate (3.73 mmol, 1.0 equiv.) in MeCN (12.5 mL) was added sodium iodide (1.12 g, 7.46 mmol, 2.0 equiv.) and the mixture heated at 70 °C for 16 h. After cooling to rt, the mixture was partitioned between Et_2O and H_2O. The organic layer was washed with sat. aq. $Na_2S_2O_3$ (× 2), dried ($MgSO_4$) and concentrated under reduced pressure to give (*Z*)-5-iodo-2-methylpent-2-enyl methyl carbonate **6** as a colourless oil, which was used crude in the next step; R_f 0.76 (50% EtOAc–petrol); ν_{max} (film) 2955, 1747, 1443, 1383, 1352, 1263, 1170, 954 cm^{-1}; δ_H (400 MHz) 5.37 (1H, t, *J* 7.0 Hz, CH), 4.61 (2H, s, OCH_2CCH_3), 3.77 (3H, s, OCH_3), 3.12 (2H, t, *J* 7.0 Hz, CH_2I), 2.67 (2H, dtd, *J* 7.0, 7.0, 1.0 Hz, $CHCH_2$), 1.77 (3H, dd, *J* 2.5, 1.0 Hz, CCH_3); δ_C (100 MHz) 155.7 (C=O), 132.0 (CCH_3), 129.3 (CH), 66.3 (OCH_3), 54.8 (OCH_2CCH_3), 31.7 (CH_2I), 21.3 (CCH_3), 5.2 (CH_2CH_2I); *m/z* (CI) 302 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 302.0255. $C_8H_{13}O_3I$ requires $[M+NH_4]^+$, 302.0253).

(Z)-Methyl 7-(methoxycarbonyloxy)-6-methyl-2-tosylhept-5-enoate

Sodium hydride (179 mg, 4.48 mmol, 1.2 equiv.) suspended in DMF (7 mL) was treated with a solution of methyl tosylacetate (851 mg, 3.73 mmol, 1.0 equiv.) in DMF (7 mL) followed by a solution of iodide **6** (3.73 mmol, 1.0 equiv.) in DMF (6 mL). The reaction mixture was stirred at 0 °C for a further 30 min, then at rt for 16 h. The solution was concentrated under reduced pressure and the crude product suspended in EtOAc, washed with sat. aq. NH_4Cl, H_2O and sat. aq. NH_4Cl. The organic phase was dried ($MgSO_4$), concentrated under reduced pressure to give to give (*Z*)-methyl 7-(methoxycarbonyloxy)-6-methyl-2-tosylhept-5-enoate, which was used crude in the next step; R_f 0.60 (50% EtOAc–petrol).

(Z)-Methyl 7-hydroxy-6-methyl-2-tosylhept-5-enoate

To a solution of (*Z*)-methyl 7-(methoxycarbonyloxy)-6-methyl-2-tosylhept-5-enoate (905 mg, 2.35 mmol, 1.0 equiv.) in dry MeOH (11.75 mL) was added K_2CO_3 (1.63 g, 11.8 mmol, 5.0 equiv.) at 0 °C and the reaction stirred at 0 °C for 2 h. The reaction was concentrated under reduced pressure, the residue partitioned between 2 M aq. HCl and EtOAc and the aqueous layer further extracted with EtOAc (× 2). The combined organic phase was dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (50–70% EtOAc–petrol) to give (*Z*)-methyl 7-hydroxy-6-methyl-2-tosylhept-5-enoate (416 mg, 42% over 4 steps) as a colourless oil; R_f 0.16 (50% EtOAc–petrol); ν_{max} (film) 3056, 2954, 1740, 1597, 1440, 1322, 1266, 1147, 1085, 1004, 815, 734 cm^{-1}; δ_H (400 MHz) 7.75 (2H, d, *J* 8.0 Hz, *o*-SO_2Ar), 7.39 (2H, d, *J* 8.0 Hz, *m*-SO_2Ar), 5.16 (1H, t, *J* 6.5 Hz, CH), 4.04 (2H, s, C*H*$_2$OH), 3.96 (1H, dd, *J* 10.5, 3.5 Hz, SCH), 3.71 (3H, s, OCH_3), 2.49 (3H, s, $ArCH_3$), 2.20–2.00 (4H, m, SCHC*H*$_2$ and SCHCH$_2$C*H*$_2$), 1.80 (3H, s, CCH_3); δ_C (100 MHz) 166.7 (C=O), 145.5, 137.5, 133.9 (4°), 129.7, 129.3, 125.0 (3°), 70.2 (SCH), 61.2 (CH_2OH), 53.1 (OCH_3), 26.9 (SCHCH$_2$*C*H$_2$), 24.8 (SCH*C*H$_2$), 21.7 ($ArCH_3$), 21.4 (C*C*H$_3$); *m/z* (CI) 344 $[M+NH_4]^+$, 326, 188, 174 (Found $[M+NH_4]^+$, 344.1530. $C_{16}H_{22}O_5S$ requires $[M+NH_4]^+$, 344.1532) (Found: C, 58.94; H, 6.83. $C_{16}H_{22}O_5S$ requires C, 58.87; H, 6.79%).

(Z)-7-Hydroxy-6-methyl-2-tosylhept-5-enoic acid ***8***

(*Z*)-Methyl 7-hydroxy-6-methyl-2-tosylhept-5-enoate (391 mg, 1.20 mmol, 1.0 equiv.) in THF (3.0 mL) was treated with 2 M aq. LiOH (3.0 mL, 2.00 mmol, 5.0 equiv.). The reaction mixture was stirred at rt for 1 h, then partitioned between Et_2O and H_2O and the aqueous layer acidified to pH 1 with 2 M aq. HCl. The aqueous layer was extracted with Et_2O (× 3) and the organic layers combined, dried ($MgSO_4$) and concentrated under reduced pressure to give,to give (*Z*)-7-hydroxy-6-methyl-2-tosylhept-5-enoic acid **8** (360 mg, 92%) as a colourless solid, which was used without further purification; ν_{max} (film) 3487, 2939, 2587, 1726, 1597, 1447, 1317, 1193, 1147, 1084, 1001, 816, 712, 665 cm^{-1}; δ_H (400 MHz; CD_3OD) 7.79 (2H, d, *J* 8.5 Hz, *o*-SO_2Ar), 7.46 (2H, d, *J* 8.0 Hz, *m*-SO_2Ar), 5.20 (1H, t, *J* 7.5 Hz, CH), 4.03 (2H, s, C*H*$_2$OH), 4.02 (1H, dd, *J* 9.0, 5.5 Hz, SCH), 2.48 (3H, s, $ArCH_3$), 2.16 (2H, m, SCHC*H*$_2$ and SCHCH$_2$C*H*$_2$), 1.99 (2H, m, SCHC*H*$_2$ and SCHCH$_2$C*H*$_2$), 1.78 (3H, d, *J* 0.5 Hz, CCH_3); δ_C (100 MHz; CD_3OD) 167.4 (C=O), 145.6, 136.9, 134.4 (4°), 129.4,

129.1, 124.7 (3°), 70.0 (SCH), 59.8 (CH_2OH), 26.9 ($SCHCH_2CH_2$), 24.4 ($SCHCH_2$), 20.3 ($ArCH_3$), 20.1 (CCH_3); *m/z* (CI) 330 $[M+NH_4]^+$, 286, 268, 251, 95 (Found $[M+NH_4]^+$, 330.1387. $C_{15}H_{20}O_5S$ requires $[M+NH_4]^+$, 330.1375) (Found: C, 57.79; H, 6.38. $C_{15}H_{20}O_5S$ requires C, 57.67; H, 6.45%).

*(Z)-7-Methyl-3-tosyl-3,4,5,8-tetrahydro-2*H*-oxocin-2-one* ***2***

To a solution of HATU (362 mg, 0.95 mmol, 3.0 equiv.) and DIPEA (283 μL, 1.58 mmol, 5.0 equiv.) in DMF (9.5 mL) was added acid **8** (99 mg, 0.32 mmol, 1.0 equiv.) in DMF (6.5 mL) *via* syringe pump over a period of 12 h. The reaction mixture was allowed to stir for a further 8 h then extracted with EtOAC (× 3). The combined organic phases were washed sequentially with 2 M aq. HCl, 2 M aq. NaOH, sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (30–50% EtOAc–petrol) gave (*Z*)-7-methyl-3-tosyl-3,4,5,8-tetrahydro-2*H*-oxocin-2-one **2** (80 mg, 85%) as a colourless gum; R_f 0.55 (50% EtOAc–petrol); ν_{max} (film) 3055, 2983, 2937, 1758, 1597, 1449, 1318, 1265, 1152, 1085, 737, 705 cm^{-1}; δ_H (400 MHz) 7.85 (2H, d, *J* 8.0 Hz, *o*-SO_2Ar), 7.34 (2H, d, *J* 8.0 Hz, *m*-SO_2Ar), 5.27 (1H, t, *J* 8.5 Hz, CH), [4.74, 4.47] (2H, 2 × d, *J* 15.0 Hz, OCH_2), 4.00 (1H, dd, *J* 10.0, 6.0 Hz, SCH), 2.44 (3H, s, $ArCH_3$), 2.44–2.28 (3H, m, $SCHCH_2$ and $SCHCH_2CH_2$), 1.90 (2H, m, $SCHCH_2$), 1.59 (3H, s, CCH_3); δ_C (100 MHz) 168.5 (C=O), 145.3, 136.0, 134.5 (4°), 129.7, 122.8 (3°), 68.6 (OCH_2), 67.4 (SCH), 25.4 ($SCHCH_2CH_2$), 24.6 ($SCHCH_2$), 21.7 ($ArCH_3$), 21.3 (CCH_3); *m/z* (CI) 312 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 312.1279. $C_{15}H_{18}O_4S$ requires $[M+NH_4]^+$, 312.1270) (Found: C, 61.19; H, 6.20. $C_{15}H_{18}O_4S$ requires C, 61.20; H, 6.16%).

*1-Methyl-4-((1*R*,2S**)-2-(prop-1-en-2-yl)cyclobutylsulfonyl)benzene* ***10***

Lactone **2** (34 mg, 0.12 mmol, 1.0 equiv.) in DMF (0.6 mL) was treated with KOAc (1.2 mg, 0.012 mmol, 0.1 equiv.) and BSA (29 μL, 0.12 mmol, 1.0 equiv.), and the mixture subjected to microwave irradiation at 160 °C for 10 min. The reaction mixture was diluted with EtOAc, washed with sat. aq. NaCl (× 3) and H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (20% EtOAc–petrol) gave 1-methyl-4-((1*R**,2*S**)-2-(prop-1-en-2-yl)cyclobutylsulfonyl) benzene **10** (26 mg, 90%) as a colourless gum; R_f 0.65 (50% EtOAc–petrol); ν_{max} (film) 2950, 1649, 1597, 1450, 1402, 1312, 1268, 1145, 1087,

893, 816, 665, 591, 564 cm^{-1}; δ_H (400 MHz) 7.76 (2H, d, *J* 8.0 Hz, *o*-SO_2Ar), 7.34 (2H, d, *J* 8.0 Hz, *m*-SO_2Ar), 4.72 (1H, d, *J* 1.0 Hz, C=CH_2), 4.62 (1H, s, C=CH_2), 3.73 (1H, ddd, *J* 9.0, 9.0, 9.0 Hz, SCH), 3.41 (1H, ddd, *J* 9.0, 9.0, 9.0 Hz, SCHC*H*), 2.45 (3H, s, $ArCH_3$), 2.40 (1H, ddd, J 11.5, 9.5, 7.5 Hz, SCHCH_2), 2.17 (1H, ddd, *J* 11.5, 9.0, 2.5 Hz, $SCHCH_2CH_2$), 2.00 (1H, ddd, *J* 8.5, 8.5, 2.5 Hz, SCHCH_2), 1.85 (1H, ddd, *J* 20.0, 9.5, 9.5 Hz, $SCHCH_2CH_2$); δ_C (100 MHz) 144.5, 144.3, 135.5 (4°), 129.8, 128.4 (3°), 110.4 (CH=*C*H_2), 60.9 (SCH), 42.6 (SCH*C*H), 22.7 (SCH*C*H_2), 21.6 ($ArCH_3$), 20.0 (C*C*H_3), 19.5 ($SCHCH_2CH_2$); *m/z* (CI) 268 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 268.1379. $C_{14}H_{18}O_2S$ requires $[M+NH_4]^+$, 268.1371) (Found: C, 67.09; H, 7.30. $C_{14}H_{18}O_2S$ requires C, 67.16; H, 7.25%).

*(1*R**,2*S**)-2-(Prop-1-en-2-yl)-1-tosylcyclobutanecarboxylic acid* ***12***

Lactone **2** (140 mg, 0.48 mmol, 1.0 equiv.) in CH_2Cl_2 (2.4 mL) was treated with KOAc (4.7 mg, 0.048 mmol, 0.1 equiv.) and BSA (235 μL, 0.95 mmol, 2.0 equiv.). The reaction mixture was stirred at rt for 16 h, then diluted with CH_2Cl_2, washed with 2 M aq. HCl and H_2O, dried ($MgSO_4$) and concentrated under reduced pressure to give (1*R**,2*S**)-2-(prop-1-en-2-yl)-1-tosylcyclobutanecarboxylic acid **12** (132 mg, 94%) as a colourless gum; ν_{max} (film) 3195, 2962, 1702, 1596, 1402, 1301, 1154, 1086, 899, 812, 710, 661 cm^{-1}; δ_H (400 MHz) 10.20 (1H, br s, OH), 7.75 (2H, d, *J* 8.0 Hz, *o*-SO_2Ar), 7.32 (2H, d, *J* 8.0 Hz, *m*-SO_2Ar), [4.97, 4.84] (2H, 2 × s, C=CH_2), 3.92 (1H, dd, *J* 9.5, 9.5 Hz, SCCH), 2.69 (1H, ddd, J 11.5, 9.5, 9.5 Hz, $SCCH_2$), 2.43 (3H, s, $ArCH_3$), 2.37 (1H, m, $SCCH_2$), 2.25 (1H, m, $SCCH_2CH_2$), 2.08 (1H, m, $SCCH_2CH_2$), 1.78 (3H, s, CCH_3); δ_C (100 MHz) 170.1 (C=O), 145.6, 142.1, 133.0 (4°), 129.8, 129.6 (3°), 114.2 (CH=*C*H_2), 75.3 (SC), 46.0 (SC*C*H), 23.6 (SC*C*H_2), 22.1 ($SCCH_2CH_2$), 21.7 ($ArCH_3$), 19.7 (C*C*H_3); *m/z* (CI) 312 $[M+NH_4]^+$, 268 (Found $[M+NH_4]^+$, 312.1277. $C_{15}H_{18}O_4S$ requires $[M+NH_4]^+$, 312.1270) (Found: C, 61.29; H, 6.12. $C_{15}H_{18}O_4S$ requires C, 61.20; H, 6.16%).

(Z)-Methyl 2-carbomethoxy-7-methoxycarbonyloxy-2,6-dimethylhept-5-enoate

To a stirred suspension of NaH (60 % in mineral oils, 2.59 g, 64.7 mmol, 1.5 equiv.) in DMF (120 mL) at 0 °C was added a solution of dimethyl 2-methylmalonate (9.45 g, 64.7 mmol, 1.5 equiv.) in DMF (20 mL) dropwise. The reaction was warmed to rt and after 30 min re-cooled to 0 °C and a solution of iodide **6** (12.2 g, 43.1 mmol, 1.0

equiv.) in DMF (20 mL) added dropwise. After 2 h at rt, reaction was treated with sat. aq. NH_4Cl and extracted with EtOAc (× 3), and the combined organic phase dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (10→40 % EtOAc–petrol) gave product (*Z*)-methyl 2-carbomethoxy-7-methoxycarbonyloxy-2,6-dimethylhept-5-enoate (8.21 g, 27.2 mmol, 63%) as colourless oil: R_f 0.22 (20 % EtOAc–petrol); ν_{max} (neat) 2955, 1733, 1442, 1381, 1261, 1166, 1115, 945 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.41 (1H, t, *J* 7.2 Hz, C*H*), 4.65 (2H, s, OCH_2), 3.81 (3H, s, OCH_3), 3.76 (6H, s, (C(O)OCH_3)$_2$), 2.07 (2H, dt, *J* 7.4, 16.4 Hz, OCCHCH_2), 1.93 (2H, m, CHCH_2), 1.78 (3H, s, CCH_3), 1.46 (3H, s, CH_3C=O); δ_C (400 MHz, $CDCl_3$) 172.6 (diester C=O), 155.9 (carbonate C=O), 130.3 (*C*CH_3), 129.8 (*C*H), 66.3 (carbonate O*C*H_3), 54.8 (O*C*H_2CCH_3), 53.4 (*C*CH_3C=O), 52.5 (diester O*C*H_3), 35.7 (*C*H_2CCH_3C=O), 22.9 (CH*C*H_2), 21.3 (C*C*H_3), 19.9 (*C*H_3CC=O); *m/z* (ESI) 325 $[M+Na]^+$ (Found $[M+Na]^+$ 325.1264, $C_{14}H_{22}O_7$ requires $[M+Na]^+$, 325.1258).

(Z)-Methyl 2-carbomethoxy-7-hydroxy-2,6-dimethylhept-5-enoate

To a solution of (*Z*)-methyl 2-carbomethoxy-7-methoxycarbonyloxy-2,6-dimethylhept-5-enoate (684 mg, 2.26 mmol, 1.0 equiv.) in MeOH (9 mL) at 0 °C was added K_2CO_3 (1.56 g, 11.3 mmol, 5.0 equiv.). After 2.5 h, the reaction mixture was neutralised with 2 M aq. HCl, and concentrated under reduced pressure. The resultant aqueous phase was extracted with EtOAc (× 5) and the combined organic phase dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (40→60 % EtOAc–petrol) gave (*Z*)-methyl 2-carbomethoxy-7-hydroxy-2,6-dimethylhept-5-enoate (517 mg, 2.25 mmol, 100%) as a colourless oil: R_f 0.21 (40 % EtOAc–petrol); ν_{max} (neat) 3506 (broad), 2954, 1732, 1435, 1379, 1240, 1165, 1115, 1006, 879 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.22 (1H, t, *J* 7.3 Hz, C*H*), 4.08 (2H, s, OCH_2), 3.81 (3H, s, OCH_3), 3.70 (6H, s, (C(O)OCH_3)$_2$), 2.06 (2H, m, OCCHCH_2), 1.93 (2H, m, CHCH_2), 1.77 (3H, s, CCH_3), 1.42 (3H, s, CH_3C=O), 1.24 (1H, s, OH); δ_C (400 MHz, $CDCl_3$) 173.6, 173.5 (diester *C*=O), 130.2 (*C*CH_3), 127.8 (*C*H), 61.6 (*C*H_2OH), 54.2 (*C*CH_3C=O), 53.4 (diester O*C*H_3), 36.2 (*C*H_2CCH_3C=O), 23.8 (CH*C*H_2), 21.8 (C*C*H_3), 20.9 (*C*H_3CC=O); *m/z* (ESI) 267 $[M+Na]^+$ (Found $[M+Na]^+$ 267.1215, $C_{12}H_{20}O_5$ requires $[M+Na]^+$, 267.1203).

(Z)-Methyl 7-hydroxy-2,6-dimethylhept-5-enoate

To a solution of (*Z*)-methyl 2-carbomethoxy-7-hydroxy-2,6-dimethylhept-5-enoate (697 mg, 3.03 mmol, 1.0 equiv.) in DMSO (6 mL) was added LiCl (257 mg, 6.06 mmol, 2.0 equiv.) and H_2O (360 μL). The reaction was heated under microwave irradiation at 180 °C. After 15 min, the reaction mixture was treated with H_2O (10 mL), extracted with EtOAc (× 3), and the combined organic phase dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (30 % EtOAc–petrol) gave (*Z*)-methyl 7-hydroxy-2,6-dimethylhept-5-enoate (379 mg, 2.04 mmol, 67%) as a colourless oil: R_f 0.24 (40 % EtOAc–petrol); ν_{max} (neat) 3416 (broad), 2970, 2940, 2878, 1736, 1458, 1436, 1378, 1199, 1163, 1107, 1066, 1008, 948, 847, 754 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.24 (1H, t, *J* 7.5 Hz, C*H*), 4.14 (1H, d, *J* 11.8 Hz, OC*H*H), 4.05 (1H, d, *J* 11.8 Hz, OCH*H*), 3.69 (3H, s, OCH_3), 2.52–2.43 (1H, m, C*H*C=O), 2.14–2.03 (2H, m, OCCHCH_2), 1.81 (3H, d, *J* 1.1 Hz, CCH_3), 1.79–1.70 (1H, m, CHCH*H*), 1.70 (1H, broad, OH), 1.53–1.44 (1H, m, CHC*H*H), 1.17 (3H, d, *J* 7.0 Hz, CH_3CC=O); δ_C (400 MHz, $CDCl_3$) 177.3 (*C*=O), 135.5 (*C*CH_3), 127.2 (*C*H), 61.3 (*C*H_2OH), 51.5 (O*C*H_3), 39.0 (CH_3*C*C=O), 33.8 (*C*H_2CH_3C=O), 25.3 (CH*C*H_2), 21.4 (C*C*H_3), 17.3 (*C*H_3CC=O); *m/z* (CI, NH_3) 204 $[M+NH_4]^+$, 169 (Found $[M+NH_4]^+$, 204.1600. $C_{10}H_{18}O_3$ requires $[M+NH_4]^+$, 204.1600).

(Z)-7-Hydroxy-2,6-dimethylhept-5-enoic acid ***13***

To a solution of (*Z*)-methyl 7-hydroxy-2,6-dimethylhept-5-enoate (2.97 g, 16.0 mmol, 1.0 equiv.) in THF (150 mL) at rt was added 2 M aq. LiOH (aq) (5 mL). After 2 h, the reaction was acidified to pH <2 by the addition of 2 M aq. HCl. The mixture was extracted with EtOAc (× 3) and the combined organic phase dried ($MgSO_4$). Concentration under reduced pressure gave crude (*Z*)-7-hydroxy-2,6-dimethylhept-5-enoic acid **13** (2.63 mg, 15.3 mmol, 95%) as a colourless oil: ν_{max} (neat) 3300 (broad), 2970, 2934, 1702, 1456, 1412, 1378, 1286, 1223, 1059, 996, 947 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.77 (2H, broad, OH, CO_2H), 5.28 (1H, t, *J* 7.4 Hz, C*H*), 4.17 (1H, d, *J* 11.8 Hz, OC*H*H), 4.08 (1H, d, *J* 11.9 Hz, OCH*H*), 2.53–2.44 (1H, m, C*H*C=O), 2.19–2.09 (2H, m, OCCHCH_2), 1.81 (3H, s, CCH_3), 1.80–1.72 (1H, m, CHCH*H*), 1.54–1.47 (1H, m, CHC*H*H), 1.21 (3H, d, *J* 7.0 Hz, CH_3CC=O); δ_C (400 MHz, $CDCl_3$) 182.3 (*C*=O), 135.3 (*C*CH_3), 127.4 (*C*H), 61.2 (*C*H_2OH), 38.9 (CH_3*C*C=O), 33.6 (*C*H_2CH_3C=O), 25.3 (CH*C*H_2), 21.3 (C*C*H_3), 17.2 (*C*H_3CC=O); *m/z* (CI, NH_3) 190 $[M+NH_4]^+$, 172, 155 $[M+H]^+$, 109 (Found $[M+NH_4]^+$, 190.1451. $C_9H_{16}O_3$ requires

$[M+NH_4]^+$, 190.1443) (Found C, 62.79; H, 9.28. $C_9H_{16}O_3$ requires C, 62.77; H, 9.36%).

*(Z)-2,7-Dimethyl-3,4,5,8-tetrahydro-2*H*-oxocin-2-one* ***3***

To a solution of 2,4,6-trichlorobenzoyl chloride (2.20 g, 8.36 mmol, 2.0 equiv.) and Et_3N (881 μL, 6.27 mmol, 1.5 equiv.) in CH_2Cl_2 (400 mL) at reflux was added a solution of (*Z*)-7-hydroxy-2,6-dimethylhept-5-enoic acid **13** (720 mg, 4.18 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) *via* syringe pump over 40 h. After 168 h heating under reflux, the reaction mixture was cooled to rt, treated with H_2O (300 mL), extracted with EtOAc (× 3), and the combined organic phase washed with brine (500 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (5 % EtOAc–petrol) gave (*Z*)-2,7-dimethyl-3,4,5,8-tetrahydro-2*H*-oxocin-2-one **3** (510 mg, 3.31 mmol, 79%) as a colourless oil: R_f 0.48 (10 % EtOAc–petrol); ν_{max} (neat) 3079, 2972, 2931, 2865, 1819, 1745, 1576, 1548, 1449, 1869, 1259, 1208, 1150, 1097, 1082, 979 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.33 (1H, t, *J* 8.5 Hz, C*H*), 4.83 (1H, d, *J* 15.0 Hz, OC*H*H), 4.44 (1H, d, *J* 15.5 Hz, OCH*H*), 2.62–2.55 (1H, m, C*H*C=O), 2.53–2.47 (1H, m, OCCHCH*H*), 2.25–2.16 (1H, m, OCCHC*H*H), 1.98–1.90 (1H, m, CHCH*H*), 1.65 (3H, s, CCH_3), 1.31–1.22 (1H, m, CHC*H*H), 1.13 (3H, d, *J* 6.6 Hz, CH_3CC=O); δ_C (400 MHz, $CDCl_3$) 179.0 (*C*=O), 135.4 (*C*CH_3), 124.0 (*C*H), 67.6 (*C*H_2O), 39.0 (CH_3*C*C=O), 34.0 (*C*H_2CH_3C=O), 25.7 (CH*C*H_2), 21.2 (C*C*H_3), 15.4 (*C*H_3CC=O); *m/z* (CI, NH_3) 172 $[M+NH_4]^+$, 155 $[M+H]^+$ (Found $[M+H]^+$, 155.1072. $C_9H_{14}O_2$ requires $[M+H]^+$, 155.1072).

(1R,2R*)-1-Methyl-2-(prop-1-en-2-yl)cyclobutanecarboxylic acid* ***14***

To a solution of (*Z*)-2,7-dimethyl-3,4,5,8-tetrahydro-2*H*-oxocin-2-one **3** (15 mg, 0.0992 mmol, 1.0 equiv.) and Et_3N (69 μL, 0.496 mmol, 5.0 equiv.) in CH_2Cl_2 (1 mL) at rt was added TMSOTf (36 μL, 0.198 mmol, 2.0 equiv.) dropwise. After 16 h, the reaction mixture was diluted with CH_2Cl_2 (3 mL), and the aqueous phase treated with 1 M aq. NaOH to pH >10, and partitioned. The aqueous phase was acidified to pH <2 with 2 M aq. HCl, extracted with CH_2Cl_2 (× 3), and the combined organic phase washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (30 % EtOAc–petrol) gave (1*R**,2*R**)-1-methyl-2-(prop-1-en-2-yl)cyclobutanecarboxylic acid **14** (14 mg, 0.091 mmol, 92 %) as a colourless gum: R_f 0.49 (30 % EtOAc–petrol); ν_{max} (neat) 3100 (broad), 3084, 2964, 1691, 1647,

1461, 1407, 1377, 1311, 1257, 1230, 1170, 1084, 1030, 935, 902, 887, 774 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.85 (1H, d, *J* 1.0 Hz, C=CH*H*), 4.73 (1H, s, C=C*H*H), 2.89 (1H, t, *J* 9.1 Hz, CH), 2.41–2.33 (1H, m, CH*H*CCH_3), 2.35–2.26 (1H, m, CH*H*CH), 1.96–1.89 (1H, m, C*H*HCH), 1.81–1.74 (1H, m, C*H*HCCH_3), 1.74 (3H, s, *C*H_3C=C), 1.50 (3H, s, *C*H_3CC=O); δ_C (400 MHz, $CDCl_3$) 181.5 (C=O), 144.6 (CH_3*C*=C), 110.3 (H_2*C*=C), 52.7 (CH), 50.8 (*C*CH_3C=O), 28.1 (CH_2), 25.5 (CH_2), 22.0 (CH_3), 20.3 (CH_3); *m/z* (CI, NH_3) 172 $[M+NH_4]^+$, 155 $[M+H]^+$, 123, 106 (Found $[M+NH_4]^+$, 172.1338. $C_9H_{14}O_2$ requires $[M+NH_4]^+$, 172.1338).[2]

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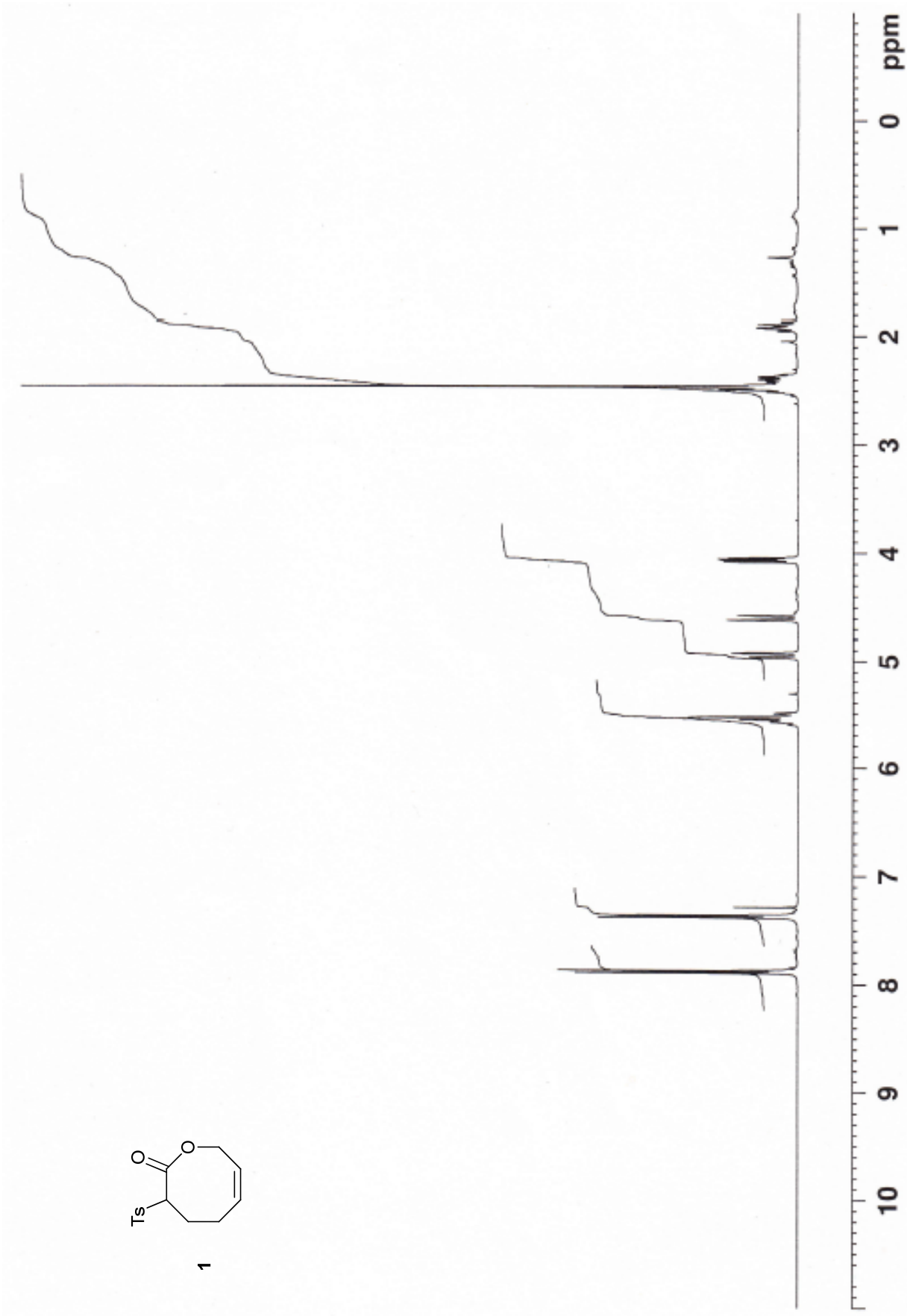
1 Y. K. Chen and P. J. Walsh, *J. Am. Chem. Soc.*, 2004, **126**, 3702.

2 V. Wakchaure and B. List, *Angew. Chem. Int. Ed.,* 2010, **49**, 4136.



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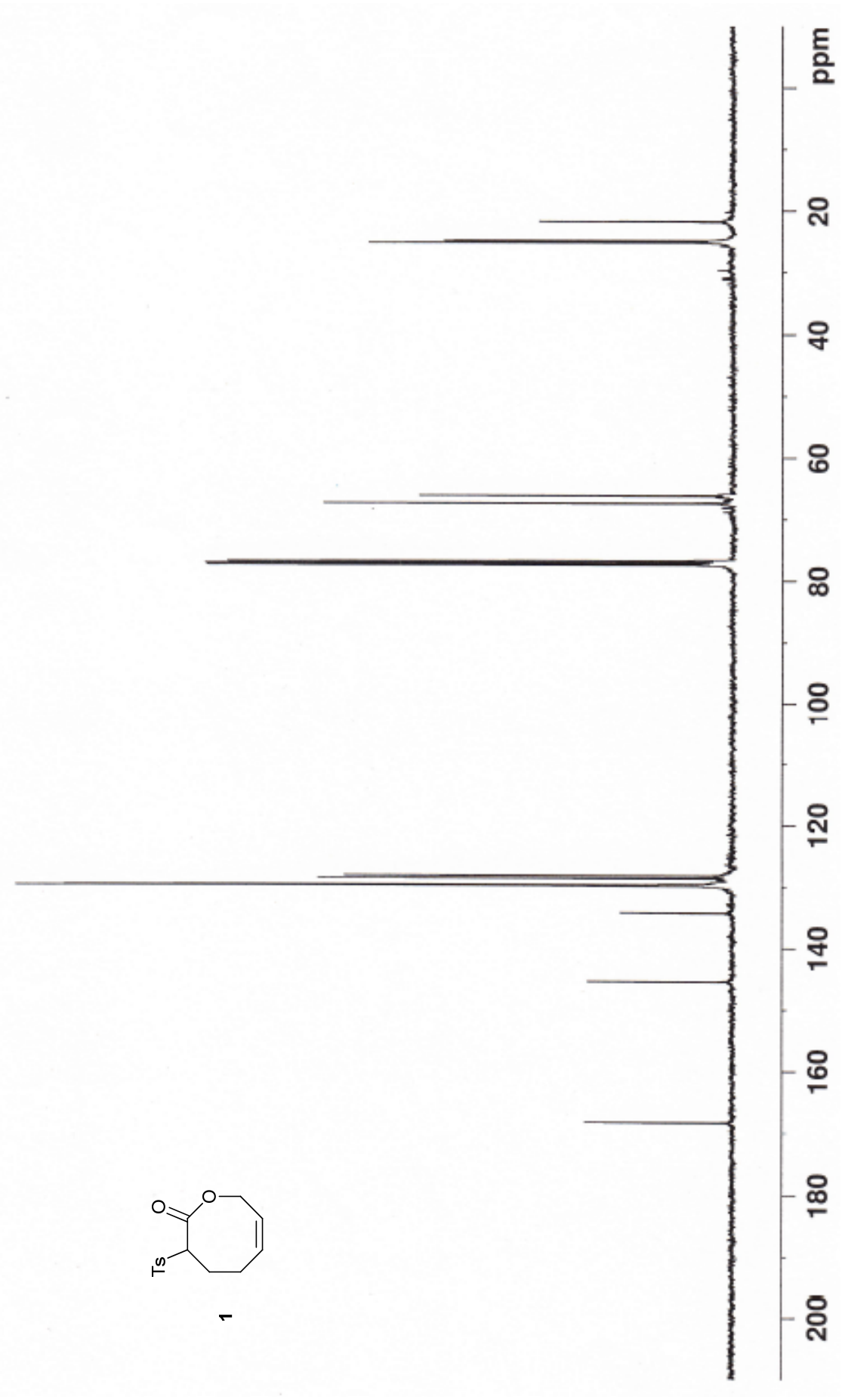

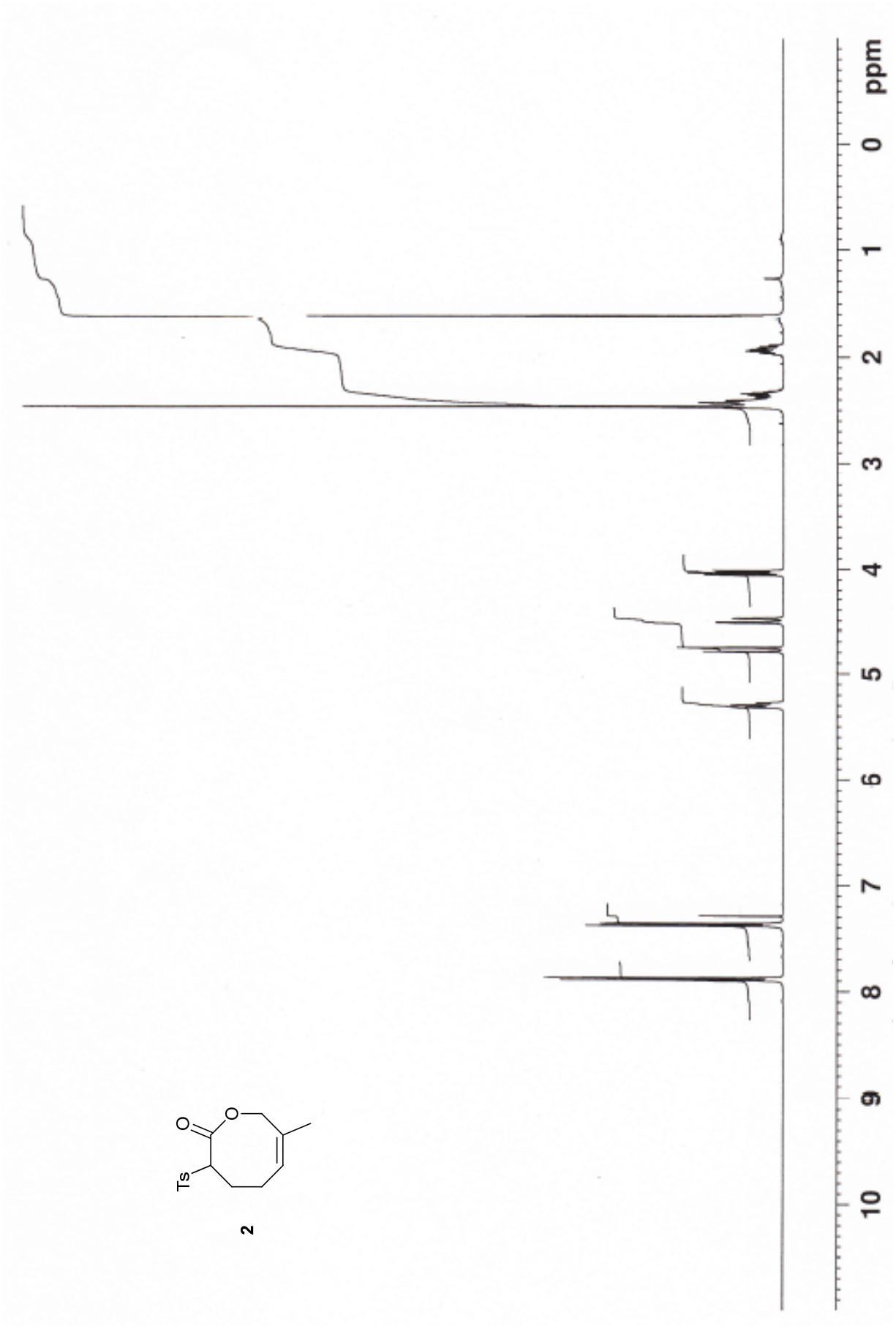

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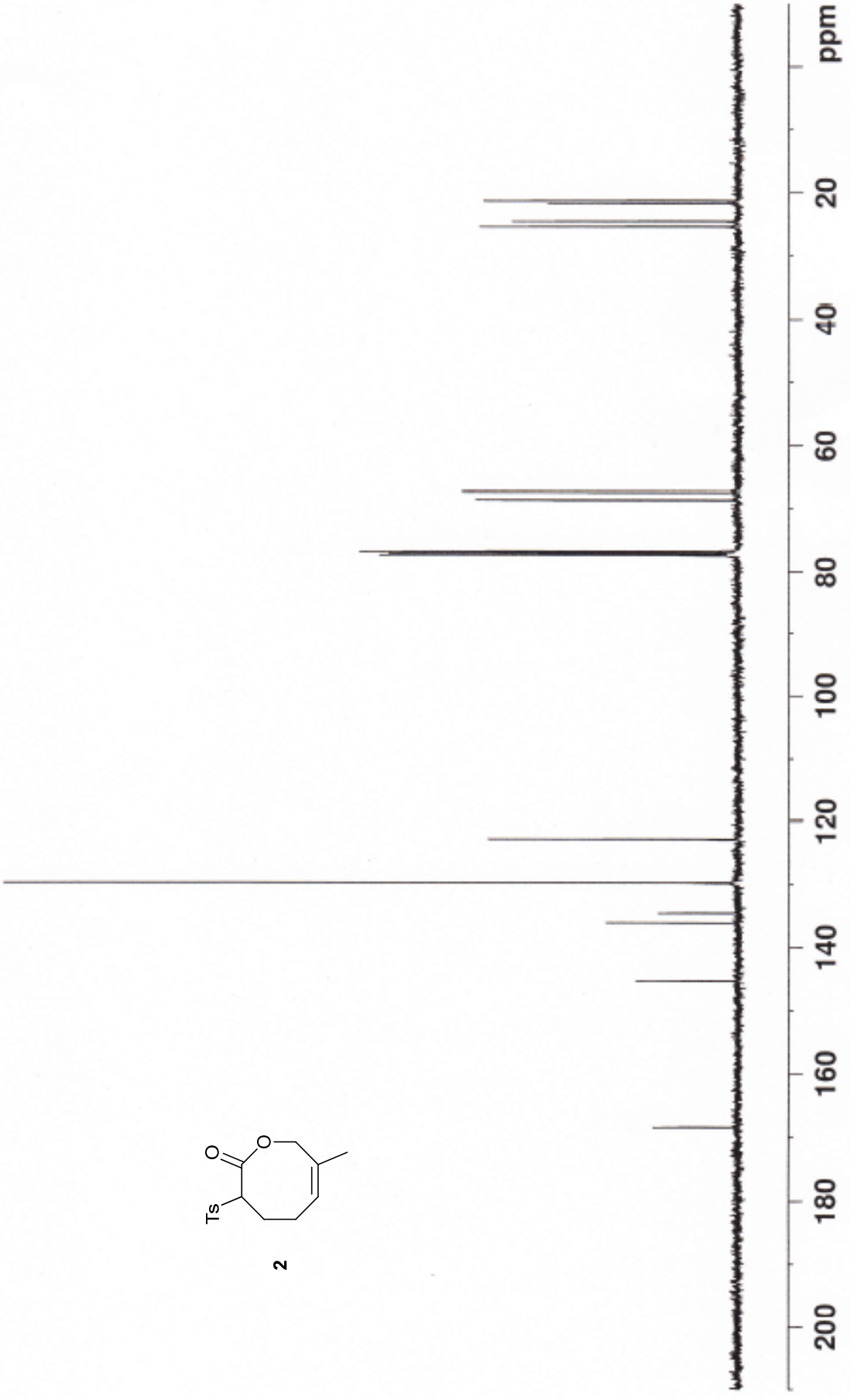

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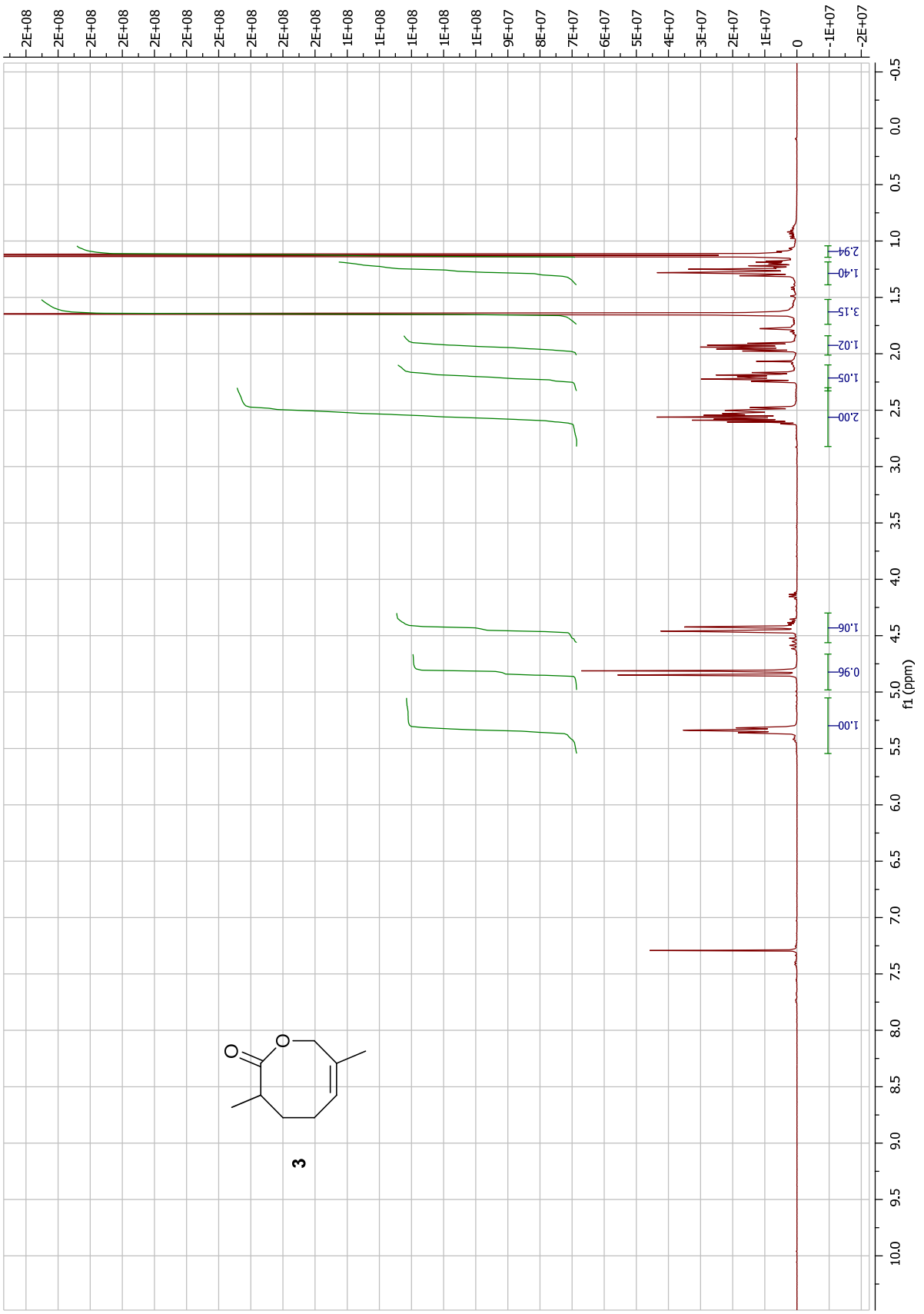
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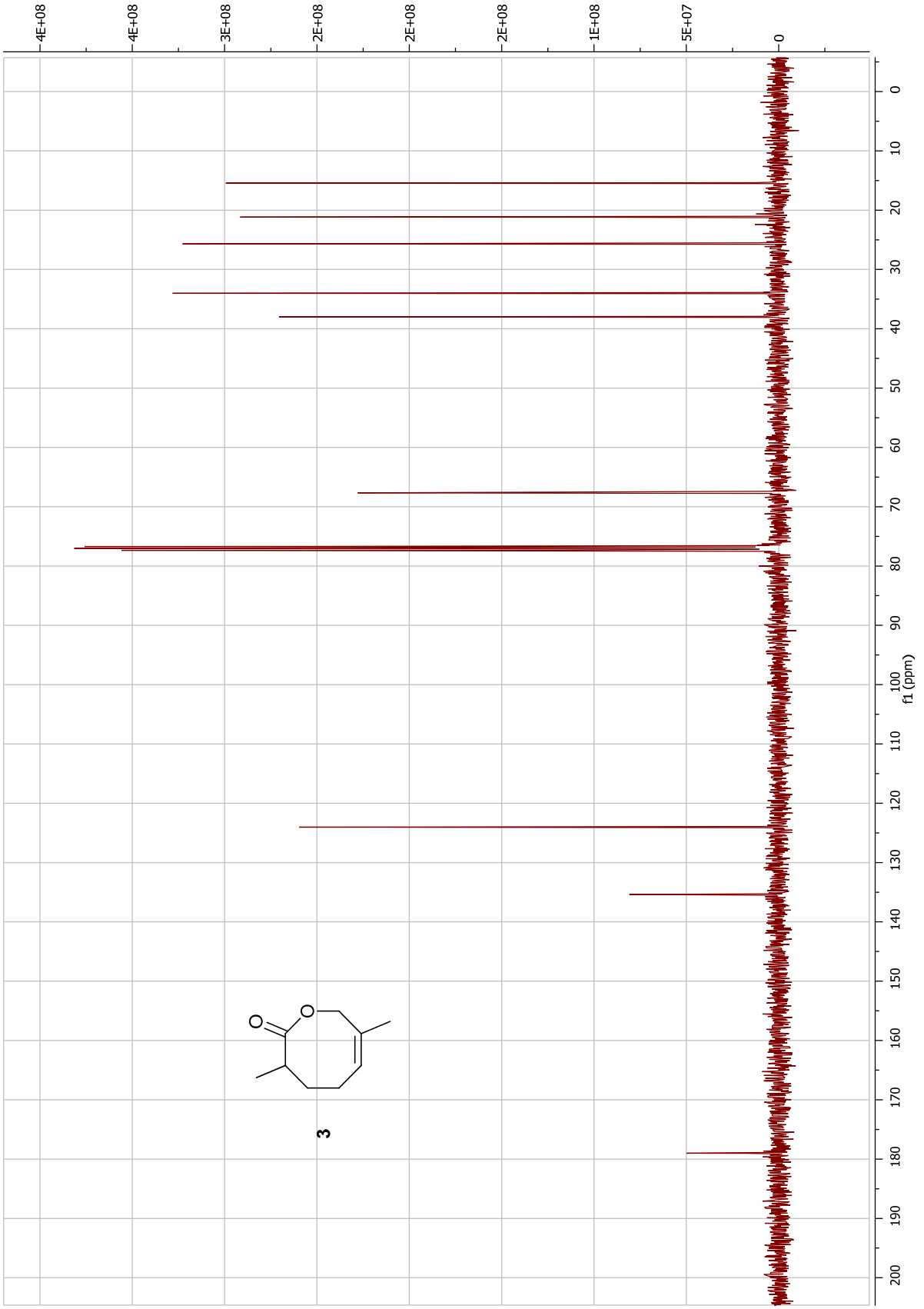

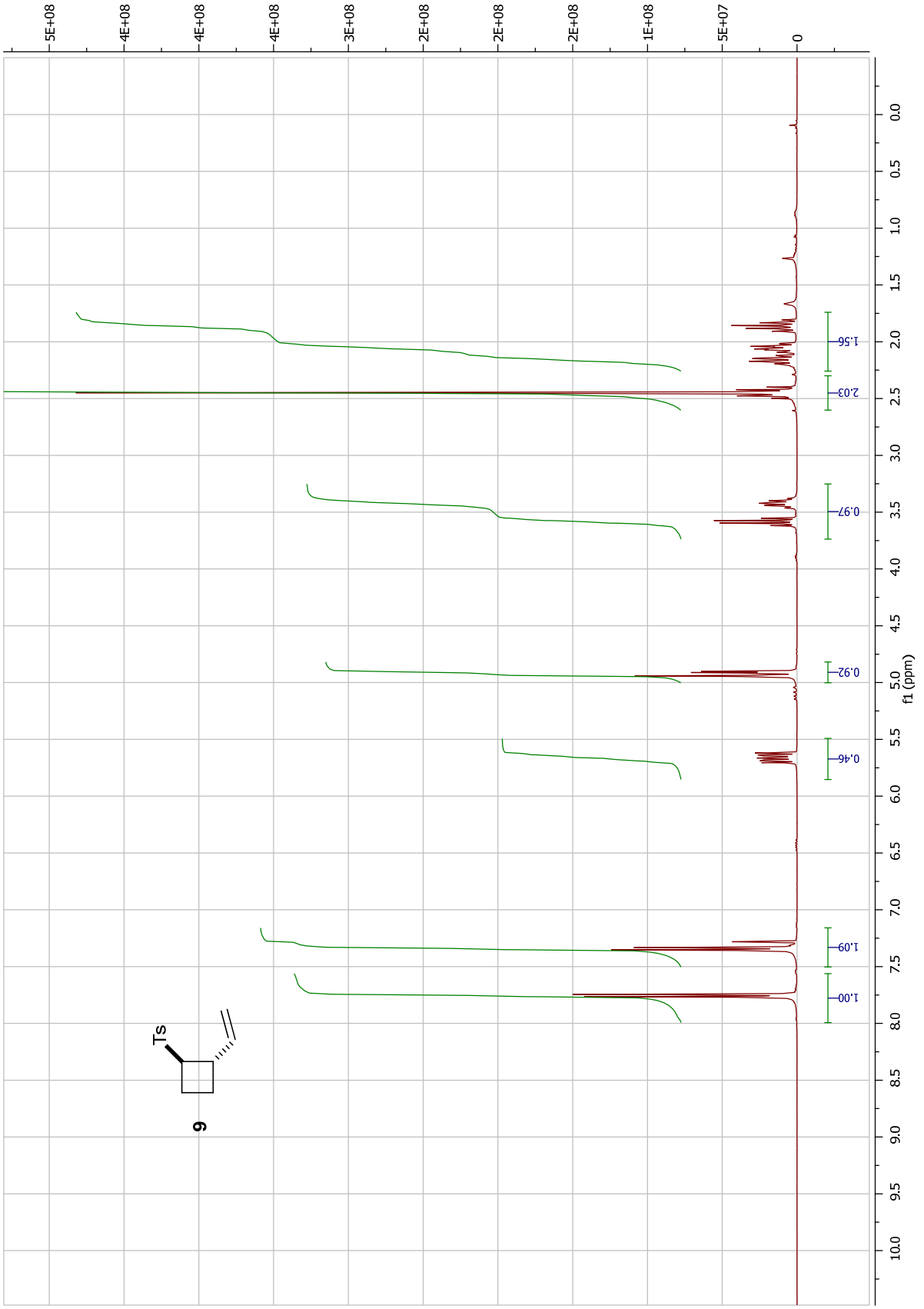
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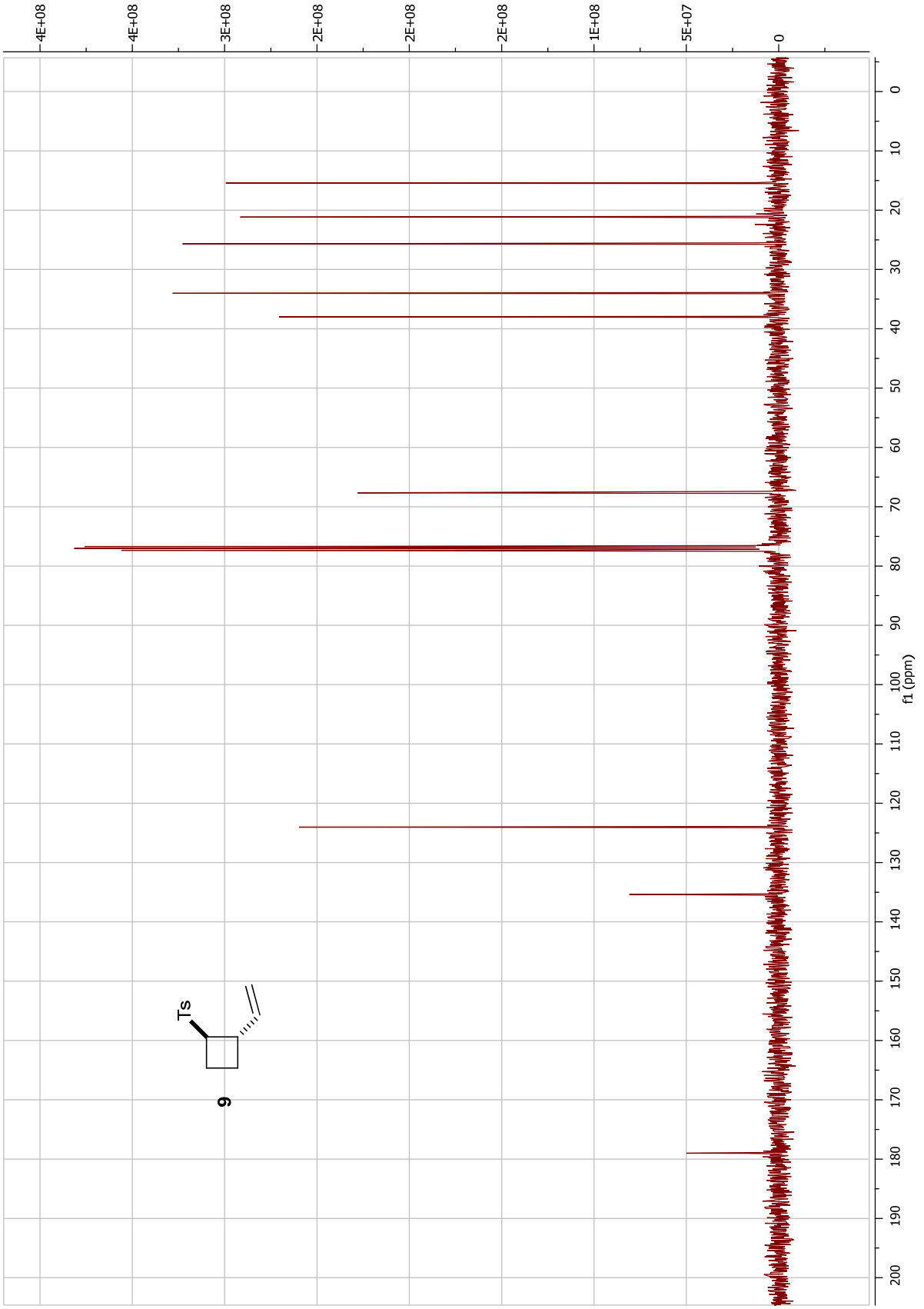

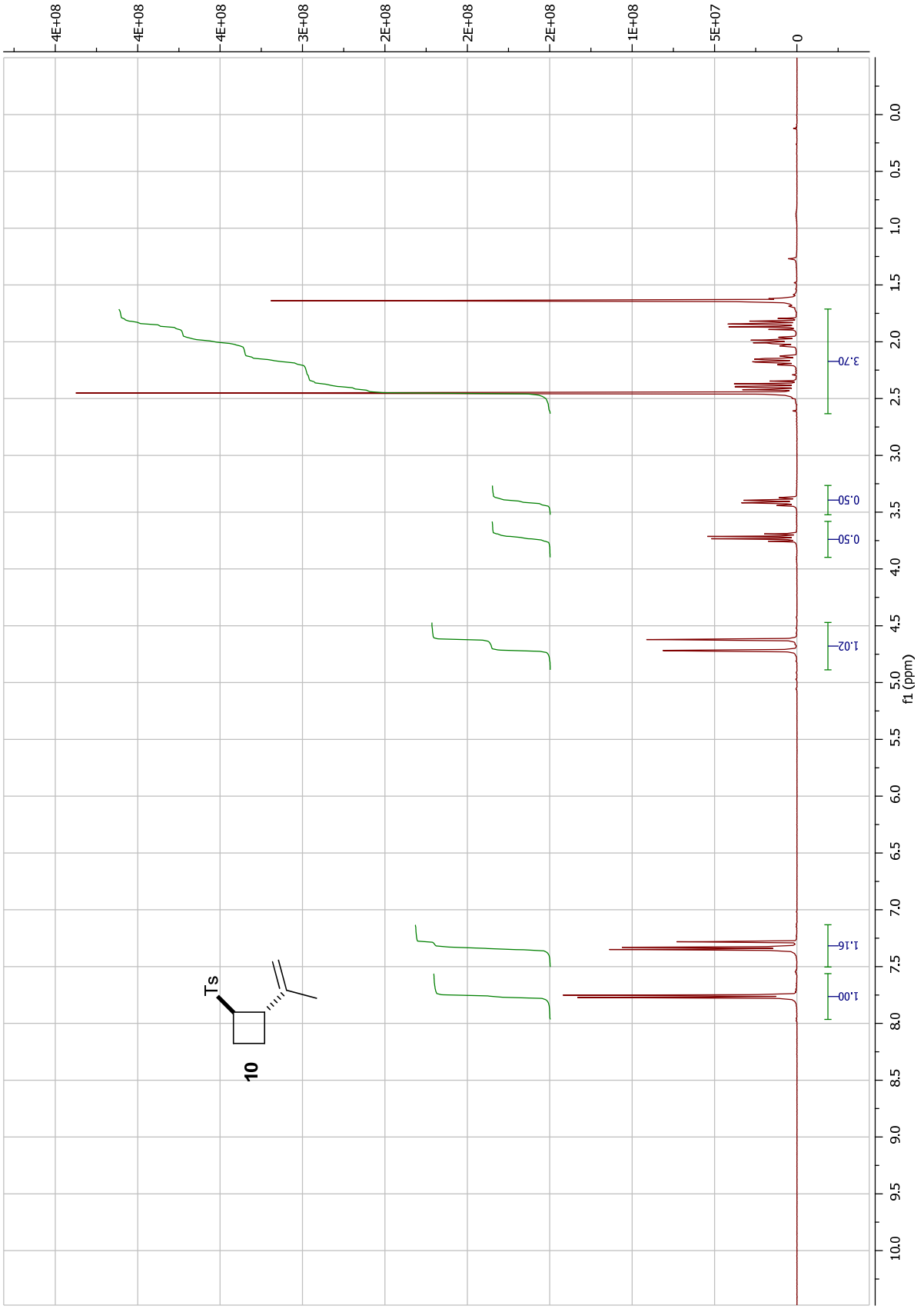
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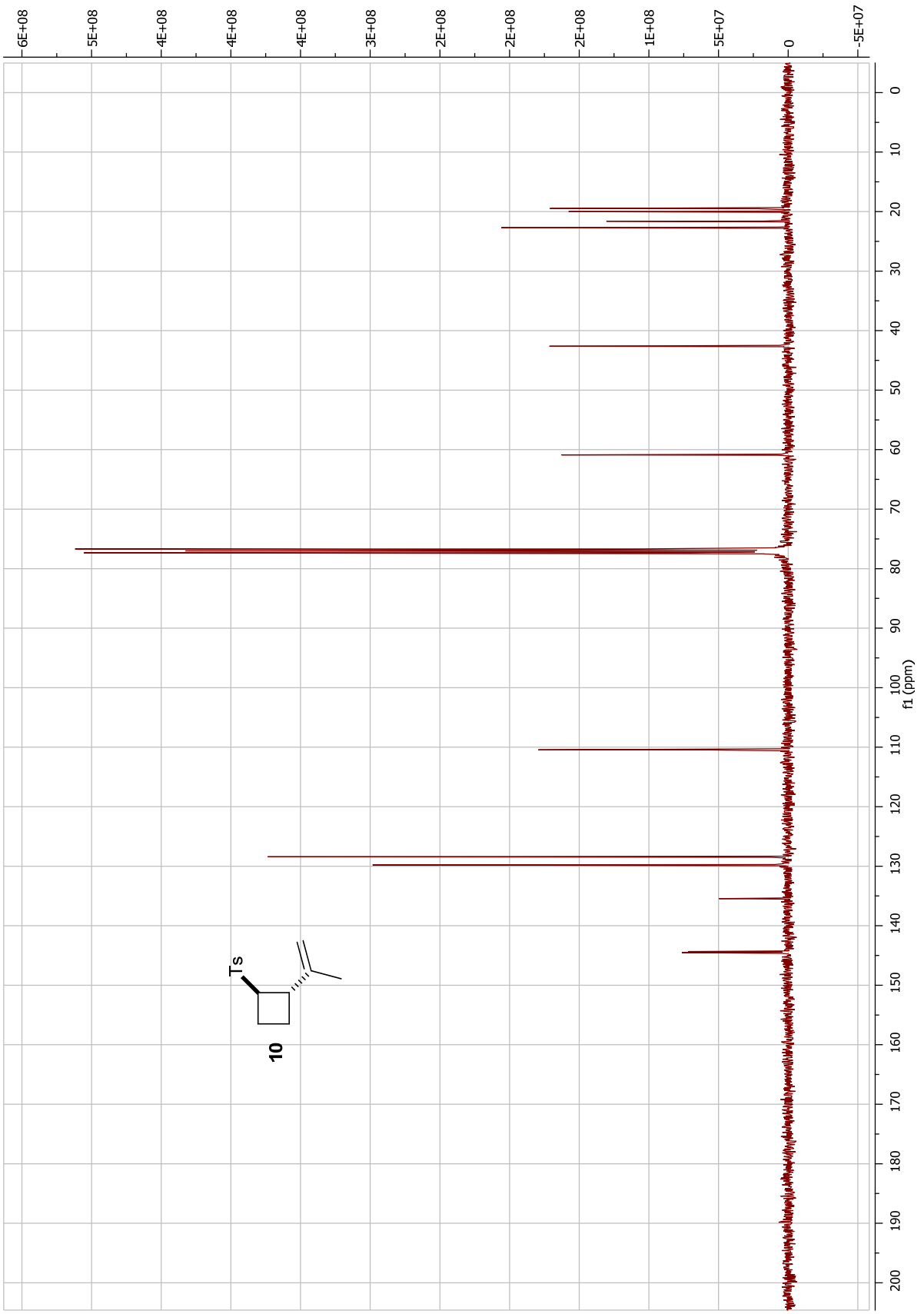
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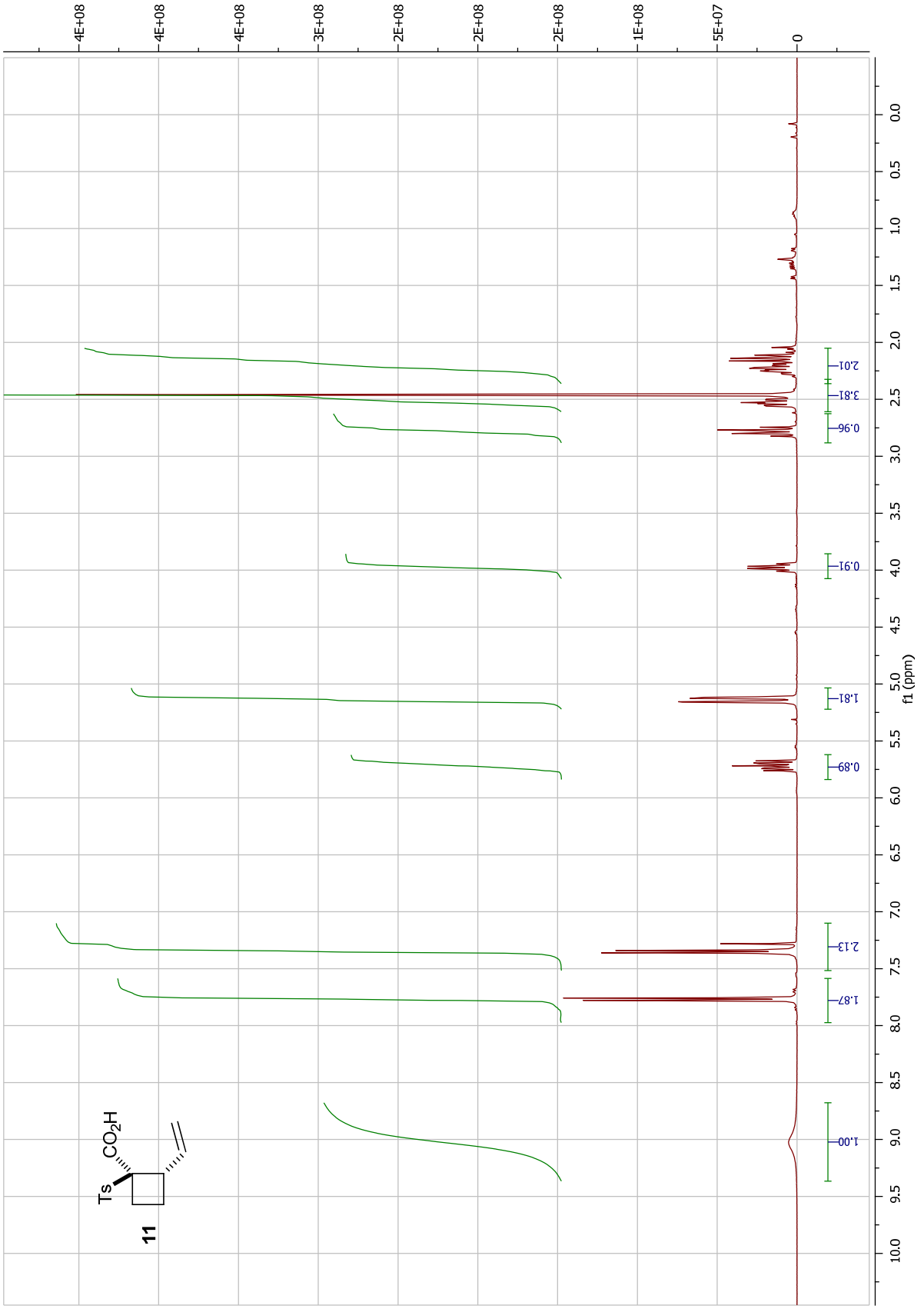
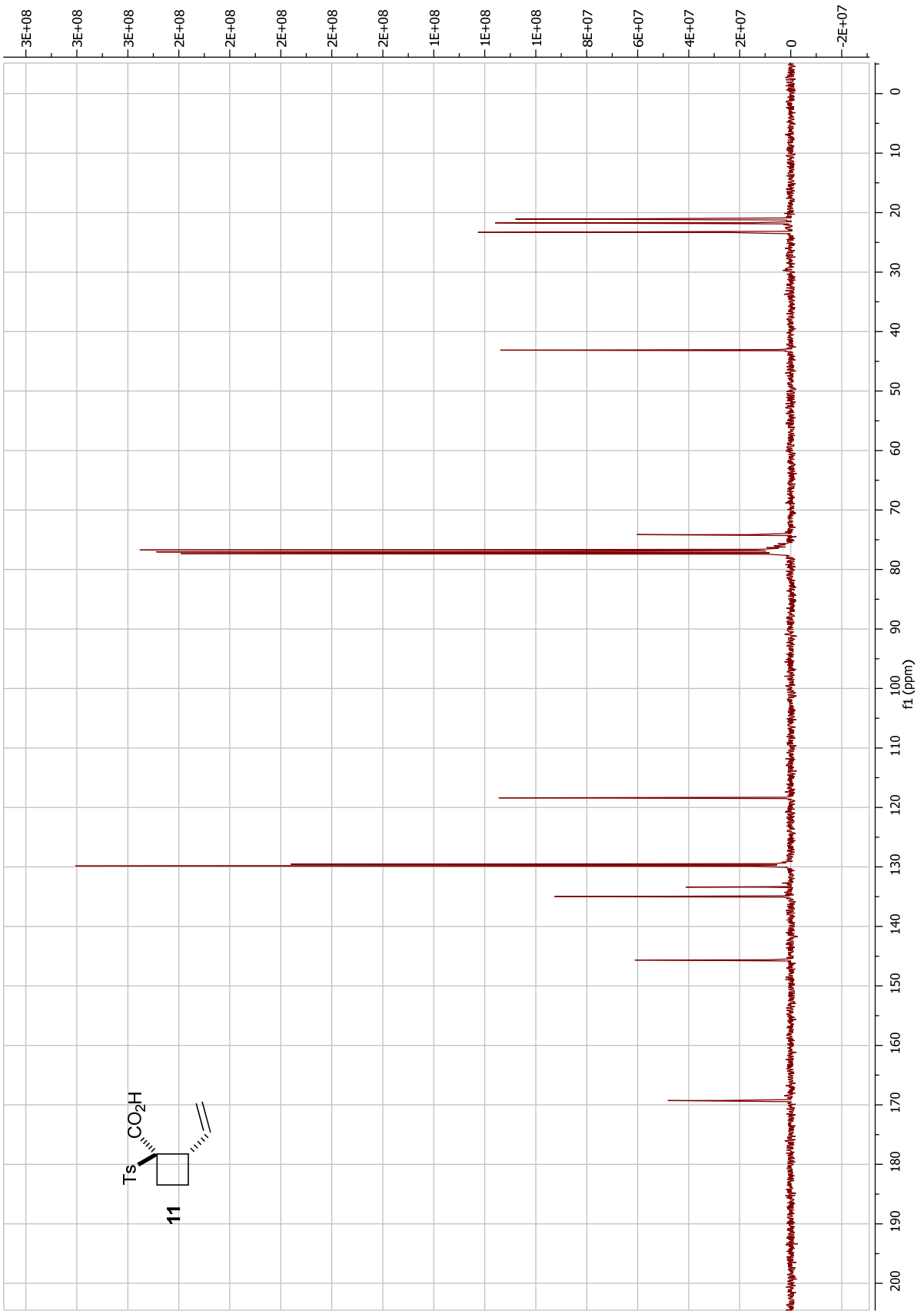
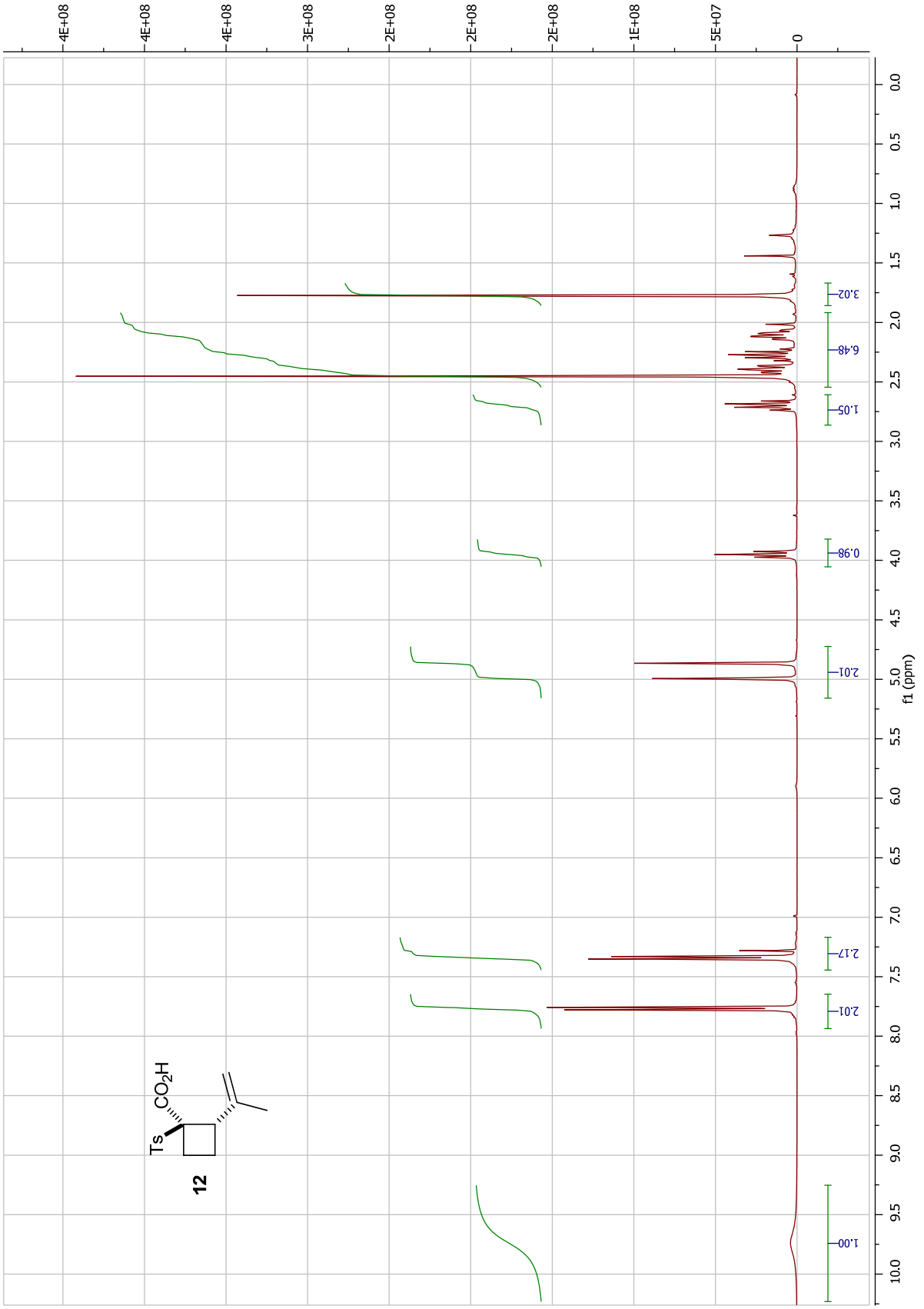
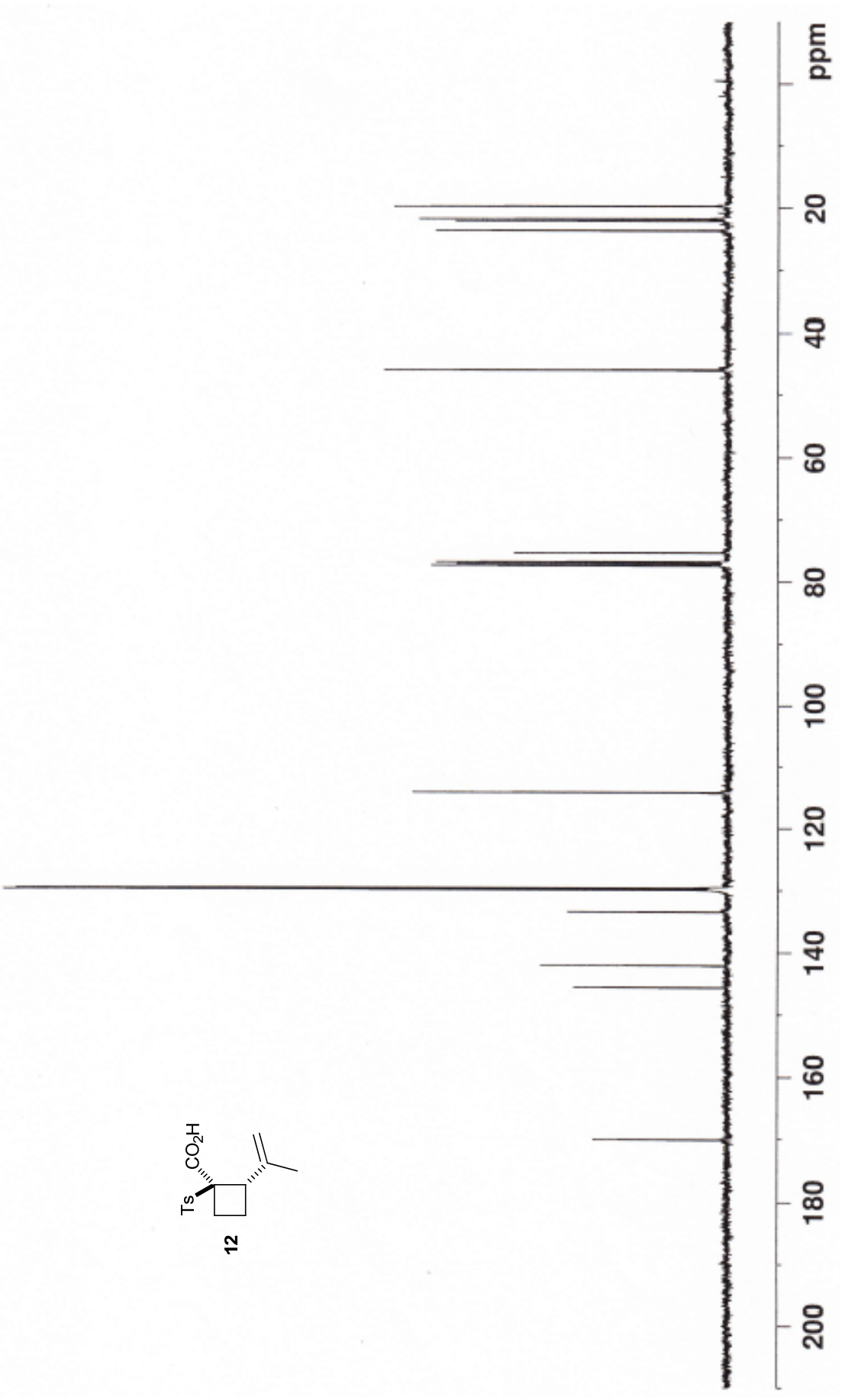
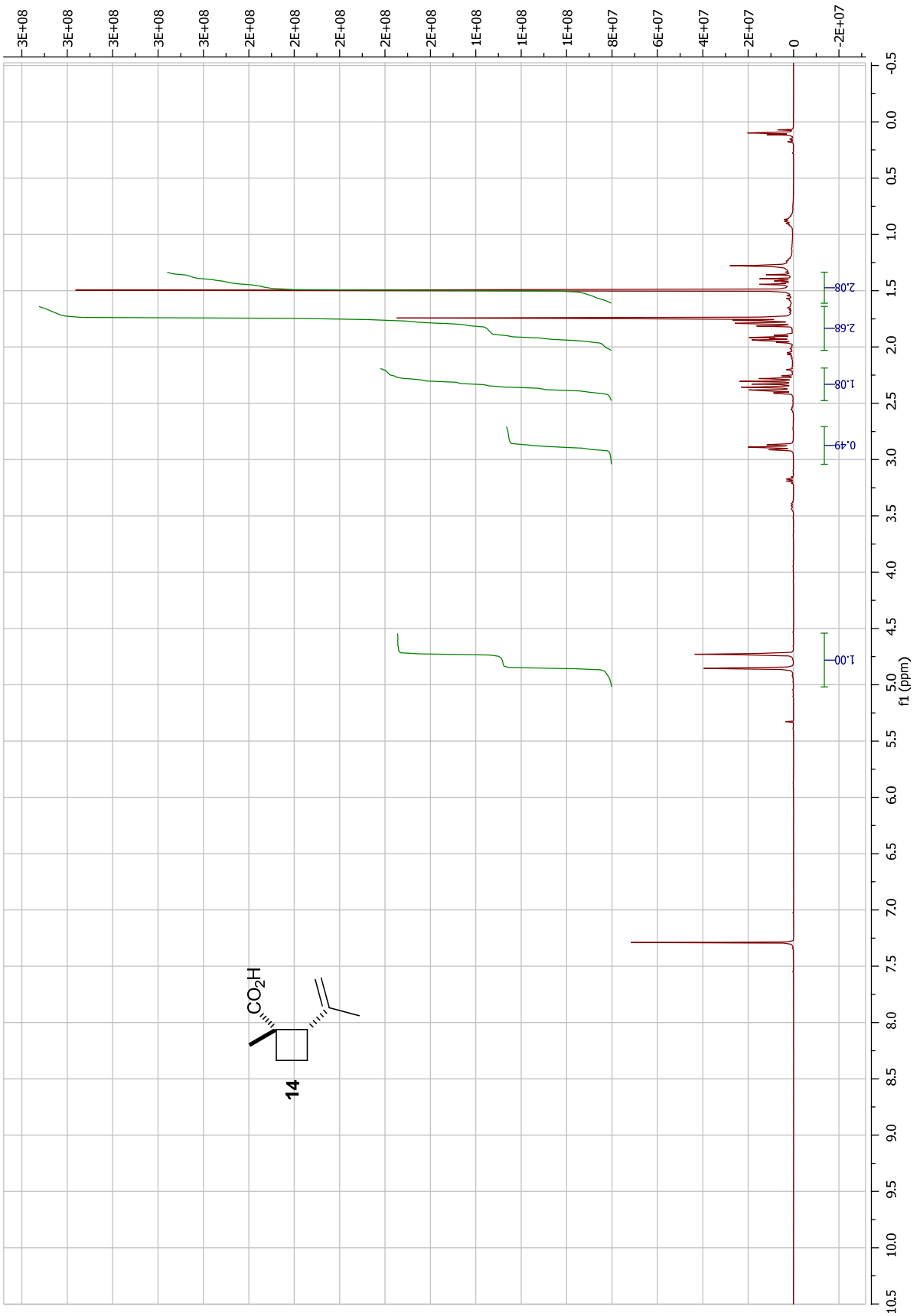


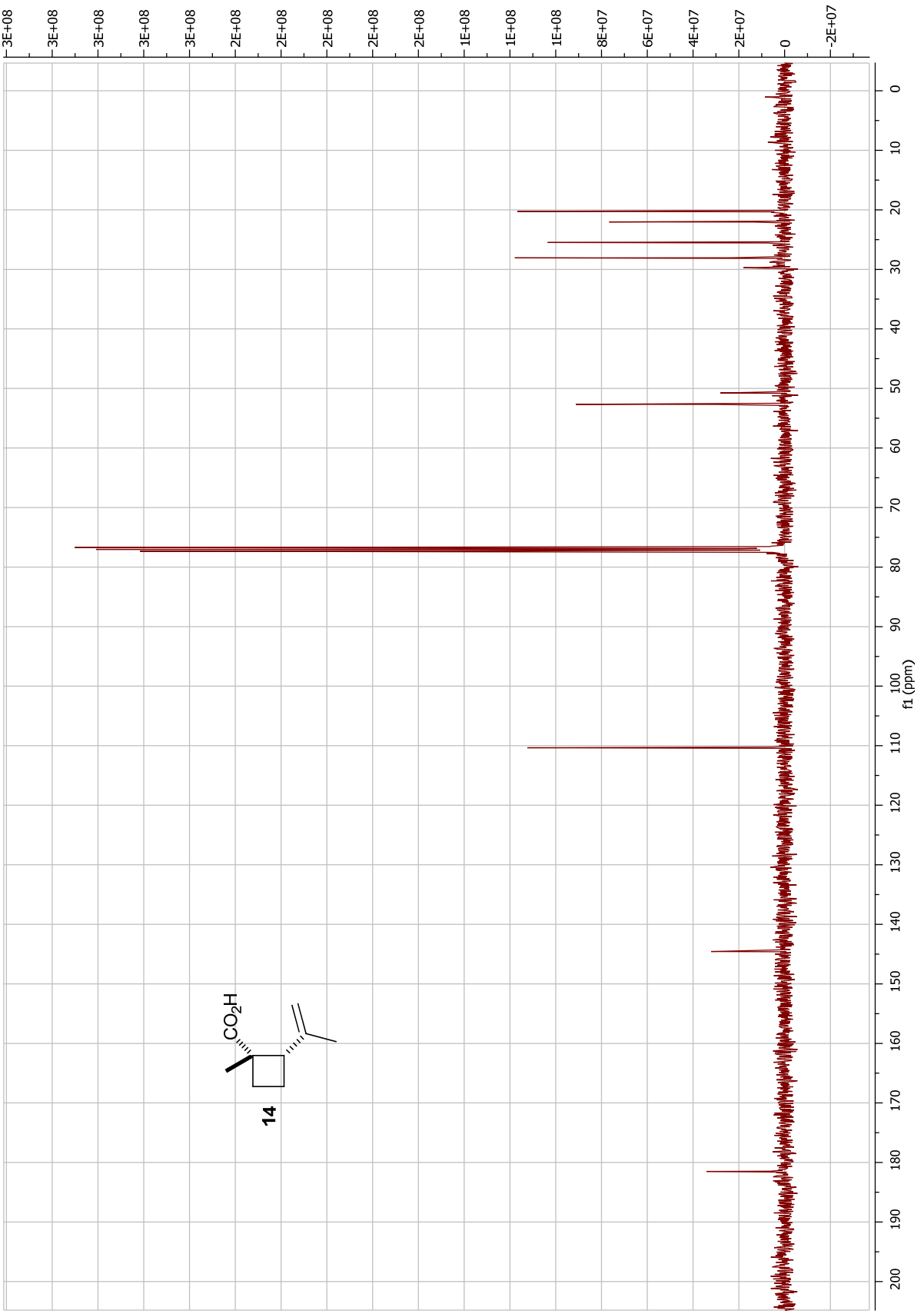






12

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6E+07
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90
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110
120
130
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150
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170
180
190
200
f1 (ppm)
CO2H
14