# Enantioselective Assembly of the Benzo[*d*]xanthene Tetracyclic Core of Anti-Influenza Active Natural Products

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## Supplementary Information

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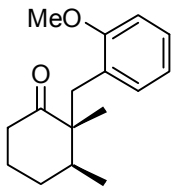
**General Methods:**
All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring, unless otherwise indicated. All other reagents were used as obtained unless otherwise noted. Tetrahydrofuran (THF) was purchased from JT Baker and purified by a Cycle-Tainer Solvent Delivery System. Flash Chromatography was performed with Fluka silica gel 60 (0.040-0.063 µm grade). Analytical thin-layer chromatography was performed with commercial glass plates coated with 0.25 mm silica gel (E. Merck, Kieselgel 60 F254). Compounds were visualized by UV-light at 254 nm and by dipping the plates in an ethanolic vanillin/sulfuric acid solution or an aqueous potassium permanganate solution followed by heating. Melting points were obtained on a Büchi 510 apparatus in open capillary tubes and are uncorrected. Proton nuclear magnetic resonance ($^1$H-NMR) data were acquired on a Varian VXR 300 (300 MHz) or on a Bruker AV400 (400 MHz) spectrometer. Chemical shifts are reported in delta ($\delta$) units, in parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet, br, broad. Proton decoupled Carbon-13 nuclear magnetic resonance ($^{13}$C-NMR) data were acquired at 75 MHz on a Varian VXR 300 or at 100 MHz on a Bruker AV400 spectrometer. Chemical shifts are reported in ppm relative to the center line of a triplet at 77.0 ppm for chloroform-*d.* Infrared (IR) data were recorded on a Perkin Elmer, Spectrum 100, FT-IR Spectrometer. Absorbance frequencies are reported in reciprocal centimeters ($cm^{-1}$). High resolution mass spectra were performed by the MS-service at the Laboratory of Organic Chemistry, ETH Zurich, and are given in *m/z*. Optical rotations were measured on a Jasco P-1000 polarimeter using a 10 cm cell with a Na 589 nm filter. The specific solvents and concentrations (in g/100 mL) are indicated.

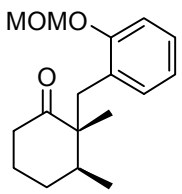
## Experimental Section

### General procedure for the conjugate addition trapping sequence:

To a stirred suspension of copper thiophene carboxylate (3.80 mg, 20.0 µmol) in 2 mL of $Et_2O$ was added (*S*,*R*,*R*)-(+)-(3,5-Dioxa-4-phosphacyclohepta[2,1-a:3,4-a′]di-naphthalen-4-yl)bis(1-phenylethyl)amine (21.6 mg, 40.0 µmol) and stirred for 15 min at 23°C. The mixture was cooled to -30°C and 2-methylcyclohex-2-enone (110 mg, 1.00 mmol) was added. Subsequently, trimethylaluminum (2 M in heptane, 600 µL, 1.20 mmol) was added slowly and the reaction mixture between -30°C and -25°C. When no more 2-methylcyclohex-2-enone was detectable by TLC (2-3 h), most of the solvents were removed *in vacuo* at 0°C and HMPA (2.00 mL) was added, followed by methyllithium (1.6 M in $Et_2O$, 750 µL, 1.20 mmol). After 15 min, the benzyl or propargyl iodide (2.0 equiv.) was added and the reaction mixture was slowly warmed to 23°C and stirred for 1–3 h. The reaction was quenched with a sat. solution of Rochelle's salt and extracted with ethyl acetate. The aq. phase was extracted again with EtOAc. The combined organic layers were washed with sat. aq. $NH_4Cl$ and brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel using the indicated solvent to give ketone **4**.
The *ee* was determined on an aliquot before the solvent was removed. The aliquot was hydrolyzed and briefly purified by a pipette column to give a mixture of cis--(*2S,3S*) and trans-(*2R,3S*)-2,3-dimethylcyclohexanone. The enantiopurity of the invariable 3S-stereocenter was between 94:6-95:5 er by chiral GC, Lipodex E, isotherm 70°C as reported by Alexakis[1]. The *dr* was determined by $^1$H-NMR of the unpurified product and ranges from 6.2:1 to 9.8:1.



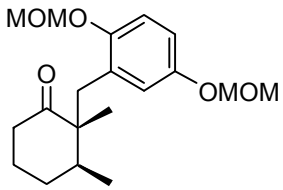

**(*2R,3S*)-2-(2-methoxybenzyl)-2,3-dimethylcyclohexanone (4a), 67 % yield: $^1$H-NMR** (400 MHz, $CDCl_3$) δ = 7.20–7.13 (m, 1H), 7.08 (dd, *J* = 7.5, 1.7, 1H), 6.89–6.77 (m, 2H), 3.73 (s, 3H), 3.22 (d, *J* = 13.6, 1H), 2.93 (d, *J* = 13.6, 1H), 2.76 (ddd, *J* = 14.5, 10.1, 6.8, 1H), 2.32 (dtd, *J* = 14.4, 5.5, 0.6, 1H), 2.13 (ddd, *J* = 18.3, 9.2, 4.5, 1H), 2.04–1.73 (m, 3H), 1.58–1.44 (m, 1H), 0.91 (d, *J* = 7.0, 3H), 0.88 (s, 3H) ppm; **13C-NMR** (101 MHz, CDCl3) δ 216.1, 157.8, 132.2, 127.5, 126.9, 120.1, 110.3, 54.8, 53.5, 40.1, 38.3, 37.3, 28.5, 22.8, 18.7, 16.3 ppm; **IR (ATR):** $\tilde{\nu}$ = 2936, 2874, 1701, 1600, 1494, 1462, 1382, 1290, 1244, 1176, 1053, 1030, 947, 754, 662 cm$^{-1}$; **HRMS (EI)**: calc'd. for $[C_{16}H_{22}O_2]^+$: 246.1620, found: 246.1615; $[\alpha]_D^{20}$ = –51.6 (c = 1.32, $CHCl_3$); $R_f$: 0.46 (Pentane/EtOAc: 90:10); **m.p.**: 36.1-38.3°C.



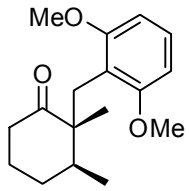

**(*2R,3S*)-2-(2-(methoxymethoxy)benzyl)-2,3-dimethylcyclohexanone (4b), 80 % yield: $^1$H-NMR** (300 MHz, $CDCl_3$) δ = 7.19–7.03 (m, 3H), 6.94–6.84 (m, 1H), 5.13 (d, *J* = 6.8, 1H), 5.10 (d, *J* = 6.9, 1H), 3.47 (s, 3H), 3.22 (d, *J* = 13.6, 1H), 2.98 (d, *J* = 13.6, 1H), 2.83–2.70 (m, 1H), 2.35 (dt, *J* = 14.4, 5.4, 1H), 2.21–2.08 (m, 1H), 2.08–1.97 (m, 1H), 1.97–1.75 (m, 2H), 1.59–1.46 (m, 1H), 0.93 (d, *J* = 7.0, 3H), 0.92 (s, 3H) ppm,

[1] M. Vuagnoux-d'Augustin, A. Alexakis, *Chem. Eur. J.* **2007**, *13*, 9647–9662.

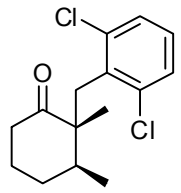
**$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 216.2, 155.9, 132.2, 127.6, 127.3, 121.3, 113.8, 94.6, 56.1, 53.6, 40.0, 38.3, 37.0, 28.6, 22.8, 18.7, 16.3. **IR (ATR):** $\tilde{\nu}$ = 2936, 2876, 1702, 1601, 1492, 1456, 1383, 1312, 1235, 1186, 1154, 1115, 1078, 1002, 922, 756 $cm^{-1}$; **HRMS (EI)**: calc'd. for $[C_{17}H_{24}O_3]^+$: 276.1720, found: 276.1723 $[a]_D^{20}$ = –45.9 (c = 1.50, $CHCl_3$); ***R*$_f$**: 0.21 (Pentane/EtOAc, 10:1)



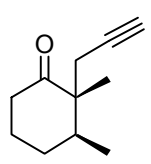

**(*2R,3S*)-2-(2,5-(dimethoxymethoxy)benzyl)-2,3-dimethylcyclohexanone** (**4c**), **78 % yield: $^1$H-NMR** (400 MHz, $CDCl_3$) δ = 6.98–6.88 (m, 1H), 6.80–6.70 (m, 2H), 5.01–4.97 (m, 4H), 3.38 (d, *J* = 3.1, 6H), 3.09 (d, *J* = 13.7, 1H), 2.88 (d, *J* = 13.7, 1H), 2.71–2.57 (m, 1H), 2.27 (dt, *J* = 14.3, 5.7, 1H), 2.08–1.97 (m, 1H), 1.97–1.90 (m, 1H), 1.90–1.78 (m, 1H), 1.78–1.67 (m, 1H), 1.53–1.39 (m, 1H), 0.90–0.83 (m, 6H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 215.9, 151.5, 151.2, 128.7, 120.7, 115.2, 114.9, 95.2, 56.0, 55.8, 53.5, 39.8, 38.3, 36.8, 28.6, 22.9, 18.8, 16.2 ppm; ; **IR (ATR):** $\tilde{\nu}$ = 2935, 2825, 1702, 1608, 15887, 1498, 1460, 1401, 1383, 1316, 1262, 1222, 1191, 1151, 177, 1008, 941, 923, 874, 815, 750 $cm^{-1}$; **HRMS (EI)**: calc'd. for $[C_{19}H_{28}O_5Na]^+$: 359.1829, found: 359.1824; **$[\alpha]_D^{20}$** = +2.3 (c = 1.10, $CHCl_3$); ***R*$_f$**: 0.29 (Pentane/EtOAc, 6:1).




**(*2R,3S*)-2-(2,6-(dimethoxy)benzyl)-2,3-dimethylcyclohexanone** (**4d**), **63 % yield**: **$^1$H-NMR** (300 MHz, $CDCl_3$) δ = 7.11 (t, *J* = 8.3, 1H), 6.48 (d, *J* = 8.3, 2H), 3.71 (s, 6H), 3.30 (d, *J* = 13.6, 1H), 3.18–3.06 (m, 1H), 3.03 (d, *J* = 13.3, 1H), 2.42–2.06 (m, 3H), 1.98–1.82 (m, 2H), 1.52–1.42 (m, 1H), 0.89 (d, *J* = 7.1, 3H), 0.75 (s, 3H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 215.9, 158.7, 127.4, 115.4, 103.5, 55.1, 53.0, 43.0, 37.8, 32.6, 28.0, 22.3, 17.2, 16.4 ppm. **IR (ATR):** $\tilde{\nu}$ = 2937, 2874, 2836, 1699, 1595, 1475, 1381, 1322, 1255, 1206, 1128, 1039, 948, 777, 734 $cm^{-1}$; **HRMS (EI)**: calc'd. for $[C_{17}H_{24}O_3]^+$: 276.1720, found: 276.1723; **$[\alpha]_D^{20}$** = –18.1 (c = 0.91, $CHCl_3$); ***R*$_f$**: 0.43 (DCM/EtOH, 98:2)

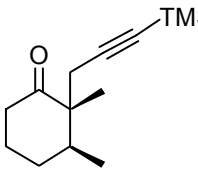



**(*2R,3S*)-2-(2,6-dichlorobenzyl)-2,3-dimethylcyclohexanone (4e)**, **33 % yield**: **$^1$H-NMR** (300 MHz, $CDCl_3$) δ = 7.29–7.26 (m, 1H), 7.26–7.23 (m, 1H), 7.12–7.02 (m, 1H), 3.57 (d, *J* = 14.3, 1H), 3.42 (d, *J* = 14.4, 1H), 3.16–3.00 (m, 1H), 2.42–2.14 (m, 3H), 2.00–1.86 (m, 2H), 1.35–1.19 (m, 1H), 0.89 (dd, *J* = 7.0, 0.9, 3H), 0.85 (d, *J* = 1.0, 3H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 215.5, 136.5, 135.8, 128.3, 128.0, 52.7, 43.9, 39.6, 37.9, 28.0, 22.3, 16.9, 16.1.; **IR (ATR):** $\tilde{\nu}$ = 3943, 2875, 1703, 1561, 1435, 1384, 1310, 1258, 1167, 1094, 918, 777 $cm^{-1}$; **HRMS (EI)** calc'd. for $[C_{15}H_{18}Cl_2O]^+$: 284.0735, found: 284.0728; **$[\alpha]_D^{20}$** = –14.9 (*c* = 0.54, $CHCl_3$); ***R*$_f$**: 0.81 (Pentane/EtOAc, 90:10).

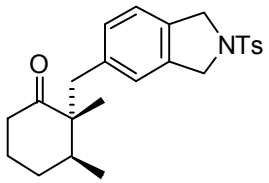



**(*2R,3S*)-2-(2-propinyl)-2,3-dimethylcyclohexanone** (**4f**), **61 % yield**: **$^1$H-NMR** (400 MHz, $CDCl_3$) δ = 2.65 (dd, *J* = 16.6, 2.6, 1H), 2.52–2.40 (m, 1H), 2.40–2.31 (m, 1H), 2.29–2.15 (m, 2H), 2.02–1.91 (m, 2H), 1.79–1.53 (m, 3H), 1.06 (s, 3H), 0.97 (d, *J*=6.9, 3H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 213.4, 81.6, 70.1, 52.0, 38.2, 37.9, 29.2, 25.3, 24.5, 18.1, 15.5 ppm; $\tilde{\nu}$ **IR (ATR):** = 3236, 2956, 2923, 2861, 1697, 1459, 1417, 385, 1320, 1278, 1260, 1142, 1094, 1051, 952, 708 $cm^{-1}$; **HRMS (EI)** calc'd. for $[C_{11}H_{16}O]^+$: 164.1186, found:

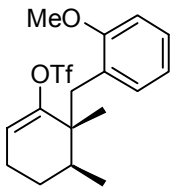
164.1197; $[\alpha]_D^{20}$ = +52.7 (*c* = 2.30, $CHCl_3$); $R_f$: 0.27 (Pentane/EtOAc, 95:5); **m.p.**: 48.5-50.0°C.




**(*2R,3S*)-2-(3-trimethylsilyl-2-propinyl)-2,3-dimethylcyclohexanone (4g), 69 % yield**: **$^1$H-NMR** (400 MHz, $CDCl_3$) δ = 2.64 (d, *J* = 16.8, 1H), 2.48–2.30 (m, 3H), 2.22–2.13 (m, 1H), 1.99–1.89 (m, 1H), 1.80–1.51 (m, 3H), 1.05 (s, 3H), 0.96 (d, *J* = 6.9, 3H), 0.12 (s, *J* = 3.5, 9H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ = 213.3, 104.4, 86.8, 52.1, 38.5, 38.0, 29.2, 27.0, 24.3, 18.1, 15.6, 0.1 ppm; **IR (ATR):** $\tilde{\nu}$ = 2959, 2175, 1708, 1461, 1382, 1248, 1035, 949, 838, 759, 698, 641 $cm^{-1}$; **HRMS (ESI)** calc'd. for $[C_{14}H_{24}OSi]^+$: 236.1591, found: 236.1592; $[\alpha]_D^{20}$ = +2.6 (*c* = 1.45, $CHCl_3$); $R_f$: 0.37 (Pentane/EtOAc, 9:1).

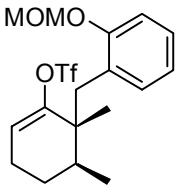



**(*2R*, *3S*)-2,3-dimethyl-2-((2-tosylisoindolin-5-yl) methyl) cyclohexanone (4i):** A solution of *N*-tosyldiprop-2-ynylamine (49.5 mg, 0.20 mmol) in DCE (1.5 ml) was added dropwise over 15 min to a stirred solution of alkyne **3e** (39.4 mg, 0.24 mmol) and Cp*Ru(Cod)Cl (3.80 mg, 10.0 µmol) in DCE (1.5 ml) at 23 °C and then stirred for 1 hr at 23 °C. The mixture was evaporated and purified on silica gel (EtOAc/Pentane 4:1) to give ketone **3g** (64 mg, 78 % yield) as slightly yellow gum.
**$^1$H-NMR** (300 MHz, $CDCl_3$) δ = 7.79–7.72 (m, 2H), 7.34–7.28 (m, 2H), 7.02 (s, 1H), 7.02 (s, 1H), 6.98 (s, 1H), 4.55 (s, 4H), 3.17 (d, *J* = 13.7, 1H), 2.67 (d, *J* = 13.8, 1H), 2.43–2.35 (m, 5H), 1.93–1.74 (m, 3H), 1.68–1.48 (m, 2H), 0.97 (s, 3H), 0.93 (d, *J* = 6.6, 3H). **$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ = 215.5, 143.5, 138.3, 135.9, 133.9, 133.7, 130.1, 129.7, 127.6, 124.6, 122.0, 53.8, 53.6, 53.4, 41.2, 38.5, 37.2, 28.9, 23.4, 21.5, 19.5, 15.9 ppm; **IR (ATR):** $\tilde{\nu}$ = 2928, 2868, 1701, 1462, 1347, 1165, 1097, 1061, 817, 758, 667, 624 $cm^{-1}$; **HRMS (EI)** calc'd. for $[C_{24}H_{29}NO_3S]^+$: 411.1863, found: 411.1861; $[\alpha]_D^{20}$ = +5.8 (*c* = 0.50, $CHCl_3$); $R_f$: 0.35 (Pentane/EtOAc, 4:1).

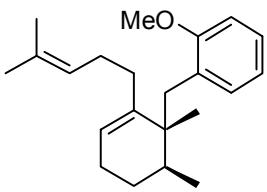



**(*2R,3S*)-2-(2-methoxybenzyl)-2,3-dimethylcyclohex-1-enyltrifluoromethansulfonate** (**8a**):To a 0°C cold solution of diisopropylamine (0.71 ml, 4.95 mmol) in 25 mL dry THF was added dropwise *n*-butyllithium (1.6 M in hexane, 3.10 ml, 4.95 mmol). After 10 min, the solution was cooled down to –78 °C and a solution of ketone **4a** (1.11 g, 3.30 mmol) in 5 mL THF was added dropwise. After 1 h, a solution of *N*-(2-pyridyl)*bis*(trifluoromethanesulfonimide) (1.42 g, 3.96 mmol) in 3 mL THF was added and the mixture was slowly warmed to 0 °C over 1 h. The reaction was quenched with sat. aq. $NH_4Cl$ and was extracted with EtOAc. The aqueous phase was extracted again with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. The resulting brown oil was purified by chromatography on silica gel (DCM/pentane 1:1 and then pentane/EtOAc 4:1) to give 1.03 g (83 %) of triflate **8a** as colorless oil.

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ = 7.23–7.16 (m, 1H), 7.11 (dd, *J* = 7.5, 1.7, 1H), 6.90–6.81 (m, 2H), 5.75 (dd, *J* = 5.2, 3.1, 1H), 3.78 (s, 3H), 3.01 (d, *J* = 13.8, 1H), 2.74 (d, *J* = 13.8, 1H), 2.16–2.01 (m, 1H), 1.99–1.85 (m, 1H), 1.70–1.54 (m, 2H), 1.43–1.30 (m, 1H), 1.10 (s, 3H), 0.96 (d, *J* = 6.8, 3H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 158.2, 154.5, 131.6, 127.6, 126.1, 120.2, 117.6, 116.9, 110.2, 54.9, 43.7, 35.1, 34.5, 26.0, 23.0, 19.9, 16.0.; **IR (ATR):** $\tilde{\nu}$ = 2933, 1601, 1494, 1456, 1410, 1245, 1209, 1144, 1033, 987, 931, 908, 872, 754, 683, 610 cm$^{-1}$; **HRMS (EI)** calc'd. for $[C_{17}H_{21}F_3O_4S]^+$: 378.1113, found: 378.1108; **$[\alpha]_D^{20}$** = –39.4 (*c* = 1.57, $CHCl_3$); ***R*$_f$**: 0.77 (Pentane/EtOAc, 90:10).

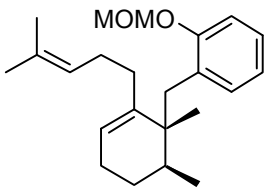



**(*2R,3S*)-2-(2-(methoxymethoxy)benzyl)-2,3-dimethylcyclohex-1-enyl-trifluoromethansulfonate** (**8b**), prepared in 78% yield with using the same procedure: **$^1$H-NMR** (300 MHz, $CDCl_3$) δ = 7.22–7.06 (m, 3H), 6.97–6.87 (m, 1H), 5.77 (dd, *J* = 5.1, 3.3, 1H), 5.18 (d, *J* = 6.8, 1H), 5.14 (d, *J* = 6.8, 1H), 3.47 (s, 3H), 3.01 (d, *J* = 13.9, 1H), 2.78 (d, *J* = 13.9, 1H), 2.10 (dq, *J* = 17.8, 5.2, 1H), 1.95 (m, 1H), 1.78–1.55 (m, 2H), 1.48–1.29 (m, 1H), 1.11 (s, 3H), 0.97 (d, *J* = 6.8, 3H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 156.3, 154.3, 131.7, 127.7, 126.5, 121.4, 117.7, 116.8, 113.8, 94.7, 56.0, 43.6, 35.3, 34.4, 26.0, 22.9, 19.9, 16.1 ppm **IR (ATR):** $\tilde{\nu}$ = 2934, 1674, 1600, 1492, 1407, 1202, 1139, 1077, 984, 907, 870 cm$^{-1}$; **HRMS (EI)** calc'd. for $[C_{18}H_{23}F_3O_5S]^+$: 408.1213, found: 408.1216; **$[\alpha]_D^{20}$** = –49.4 (*c* = 1.10, $CHCl_3$); ***R*$_f$**: 0.36 (Pentane/EtOAc, 25:1);

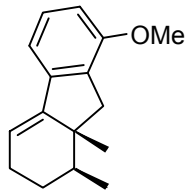



**(1-(((1R,6S)-1,6-dimethyl-2-(4-methylpent-3-enyl)cyclohex-2-enyl)methyl)-2-methoxybenzene (9a):** 4-Methyl-penta-1,3-diene (1.10 mL, 9.61 mmol) was added to a 0 °C solution of 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 18.7 mL, 9.37 mmol) and stirred for 30 min at 0 °C and for 2 h at 23 °C. Subsequently, potassium phosphate (1.49 g, 7.02 mmol) dissolved in 1.5 ml $H_2O$ and triflate **8a** (1.10 g, 2.34 mmol) dissolved in 3.5 ml DMF were added. Triphenylarsine (72 mg, 0.23 mmol), $Pd_2dba_3$•$CHCl_3$ (61 mg, 59.0 µmol) were added as solids and the mixture was degassed and heated to 55 °C. After 2 h the reaction was quenched with sat. aq. $NH_4Cl$ and extracted with $Et_2O$. The organic layer was washed with water, brine and dried over $MgSO_4$. Concentration and column chromatography on silica gel (pentane/EtOAc 15:1) yielded 714 mg (98 % yield) of cross-coupled product **9a** as colorless oil.

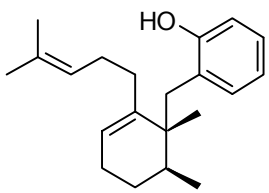
**$^1$H-NMR** (400 MHz, $CDCl_3$) δ = 7.18–7.10 (m, 2H), 6.89–6.79 (m, 2H), 5.46 (t, *J* = 3.7, 1H), 5.22–5.12 (m, 1H), 3.79 (s, 3H), 2.94 (d, *J* = 14.4, 1H), 2.70 (d, *J* = 14.4, 1H), 2.22–1.89 (m, 6H), 1.88–1.77 (m, 1H), 1.74–1.65 (m, 4H), 1.63 (s, *J* = 7.2, 3H), 1.40–1.29 (m, 1H), 0.93 (s, 3H), 0.81 (d, *J* = 6.9, 3H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 158.1, 143.0, 131.4, 131.2, 128.3, 126.7, 125.0, 121.2, 119.8, 110.2, 55.1, 42.0, 36.4, 33.6, 31.4, 27.8, 26.3, 25.7, 23.5, 21.6, 17.7, 15.9 ppm. **IR (ATR):** $\tilde{\nu}$ = 2966, 2925, 1600, 1492, 1458, 1378, 1242, 847, 752, 676 cm$^{-1}$; **HRMS (EI)**: calc'd. for $[C_{22}H_{32}O]^+$: 312.2453, found: 312.2455; **$[\alpha]_D^{20}$** = +5.2 (c = 1.53, $CHCl_3$); ***R*$_f$**: 0.63 (Pentane/EtOAc, 95:5)




**(1-(((*1R,6S*)-1,6-dimethyl-2-(4-methylpent-3-enyl)cyclohex-2-enyl)methyl)-2-(methoxymethoxy)benzene** (**9b**) was prepared in 99 % yield using the same procedure: **$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ = 7.18–7.05 (m, 3H), 6.93–6.86 (m, 1H), 5.50–5.45 (m, 1H), 5.23–5.11 (m, 3H), 3.49 (d, *J* = 3.3, 3H), 2.95 (d, *J* = 14.3, 1H), 2.74 (d, *J* = 14.3, 1H), 2.23–1.95 (m, 6H), 1.91–1.80 (m, 1H), 1.76–1.67 (m, 4H), 1.63 (s, 3H), 1.41–1.32 (m, 1H), 0.96 (s, 3H), 0.82 (d, *J* = 6.9, 3H) ppm. **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 156.1, 142.8, 131.5, 131.2, 128.8, 126.9, 124.9, 121.3, 121.1, 113.8, 94.8, 56.0, 42.0, 36.6, 33.6, 31.4, 27.8, 26.3, 25.7, 23.4, 21.7, 17.7, 15.9; **IR (ATR):** $\tilde{\nu}$ = 2925, 1585, 1489, 1455, 1378, 1233, 1153, 1077, 1007, 753 cm$^{-1}$; **HRMS (EI)**: calc'd. for $[C_{23}H_{34}O_2]^+$: 342.2553, found: 342.2556 **$[\alpha]_D^{20}$** = –2.7 (c = 0.90, $CHCl_3$); ***R*$_f$**: 0.43 (Pentane/EtOAc, 25:1)

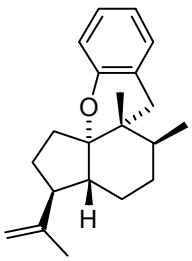



**(1S,9aR)-8-methoxy-1,9a-dimethyl-2,3,9,9a-tetrahydro-1H-fluorene (10a):** 4-Methyl-penta-1,3-diene (23 µL, 0.20 mmol) was added to a 0 °C solution of 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 0.4 mL, 0.20 mmol) and stirred for 30 min at 0 °C and for 2 h at 23 °C. Subsequently, cesium fluoride (30.5 mg, 0.20 mmol) and $Pd(PPh_3)_4$ (2.9 mg, 2.50 µmol) were added. Triflate **8a** (19.0 mg, 0.05 mmol) dissolved in 3 ml dioxane was added and the mixture was degassed and heated to 85 °C. After 2 h the reaction was quenched with sat. aq. $NH_4Cl$ and extracted with $Et_2O$. The organic layer was washed with water, brine and dried over $MgSO_4$. Concentration and column chromatography on silica gel (pentane/EtOAc 95:5) yielded 10.4 mg (91 %) of direct arylation product **10a** as colorless film.
**$^{1}$H-NMR** (400 MHz, $CDCl_3$) δ = 7.16 (t, *J* = 7.8, 1H), 7.01 (d, *J* = 7.5, 1H), 6.69 (d, *J* = 8.0, 1H), 5.87 (t, *J* = 3.7, 1H), 3.84 (s, 3H), 2.81 (d, *J* = 15.5, 1H), 2.56 (d, *J* = 15.5, 1H), 2.31–2.22 (m, 2H), 1.80–1.68 (m, 1H), 1.63–1.55 (m, 2H), 1.01 (d, *J* = 6.8, 3H), 0.96 (s, 3H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 156.7, 149.3, 142.9, 130.3, 128.0, 117.1, 113.1, 108.7, 55.2, 45.5, 42.3, 37.8, 26.9, 25.3, 20.2, 16.9. **IR (ATR):** $\tilde{\nu}$ = 2955, 2928, 2870, 2835, 1585, 1481, 1376, 1282, 1259, 1090, 1070, 1016, 987, 880, 771, 713 cm$^{-1}$; **HRMS (EI)**: calc'd. for $[C_{16}H_{20}O]^+$: 228.1503, found: 228.1509; **$[\alpha]_D^{20}$** = –47.6 (c = 0.38, $CHCl_3$); ***R*$_f$**: 0.36 (Pentane/EtOAc, 95:5).

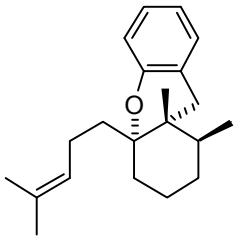



**(2-(((*1R,6S*)-1,6-dimethyl-2-(4-methylpent-3-enyl)cyclohex-2-enyl)methyl)-phenol (3):** Preparation of **3** from **9a**: To a solution of **9a** (360 mg, 1.15 mmol) in HMPA (4mL) was added *n*-BuSLi (1.10 g, 11.5 mmol). The mixture was heated to 110°C and stirred for 2 hours. The mixture was cooled to 23 °, diluted with EtOAc and poured into sat. aq. $NH_4Cl$ / pH 7 buffer 1:1. The aqueous layer was extracted with EtOAc. The combine organic layers were washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (Pentane/EtOAc: 50:1) to give 277 mg (81 %) of phenol **3.**
Preparation of **3** from **9b**: A solution of **9b** (200 mg, 0.497 mmol) in 5 mL 1 M HCl in MeOH was stirred for 18 h at 23 °C. The mixture was quenched with sat. aq. $NH_4Cl$ / pH 7 buffer 1:1 and extracted with EtOAc. The combined organic layers were dried and

evaporated. The residue was purified by chromatography on silica gel (Hexane/EtOAc 4:1) to give 61 mg (41 %) of phenol **3**.
**$^1$H-NMR** (400 MHz, $CDCl_3$) δ = 7.14–7.04 (m, 2H), 6.87–6.74 (m, 2H), 5.58–5.51 (m, 1H), 5.13 (s, 1H), 5.10–5.02 (m, 1H), 3.03 (d, *J* = 14.3, 1H), 2.57 (d, *J* = 14.3, 1H), 2.19–1.93 (m, 5H), 1.88–1.79 (m, 2H), 1.76–1.68 (m, 1H), 1.66 (d, *J* = 0.9, 3H), 1.58 (s, 3H), 1.48–1.37 (m, 1H), 1.01 (s, *J* = 9.2, 3H), 0.87 (d, *J* = 6.9, 3H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 154.6, 143.3, 132.2, 131.4, 127.3, 125.8, 124.5, 122.4, 120.3, 115.8, 41.7, 40.9, 35.7, 31.9, 27.6, 25.8, 25.7, 22.9, 21.5, 17.7, 15.8 ppm; **IR (ATR):** $\tilde{\nu}$ = 3428, 2923, 1587, 1488, 1454, 1378, 1233, 1099, 752 cm$^{-1}$; **HRMS (EI)**: calc'd. for $[C_{21}H_{30}O]^+$: 298.2291, found: 298.2291; $[\alpha]_D^{20}$ = +30.3 (c = 1.10, $CHCl_3$); $R_f$ : 0.29 (Pentane/EtOAc, 25:1).

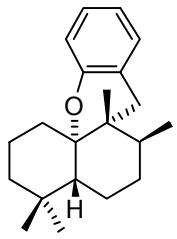



**(*6S,6aR,121S*)-6,6a-dimethyl-3-(prop-1-en-2-yl)-2,3,3a,4,5,6,6a,7-octahydro-1H-cyclopenta[d]xanthene (12):** Benzoquinone (11.6 mg, 107 µmol), lithium chloride (4.6 mg, 107 µmol), sodium carbonate (11.4 mg, 107 µmol) and $Pd(CH_3CN)_2Cl_2$ (5.6 mg, 21.0 µmol) were added to a dry test tube. Phenol **3** (16.0 mg, 50.0 µmol) was added as solution in 500 µL THF. The mixture was degassed and stirred at 60 °C for 48 h. The residue was concentrated and purified by chromatography on silica gel (pentane / ether 100:1) and gave cyclized product **12** (7.0 mg, 44.0 %, 69 % based on 7.3 mg recovered starting material **3**) as colorless film. The stereochemistry was assigned by nOe spectroscopy.
**$^1$H-NMR** (300 MHz, $CDCl_3$) δ = 7.09 (t, *J* = 7.9, 1H), 7.01 (d, *J* = 7.5, 1H), 6.86–6.70 (m, 2H), 4.79–4.76 (m, 1H), 4.76–4.72 (m, 1H), 2.78 (dd, *J* = 19.8, 9.4, 1H), 2.69 (d, *J* = 16.7, 1H), 2.53 (d, *J* = 16.8, 1H), 2.06–1.92 (m, 1H), 1.86–1.64 (m, 6H), 1.64–1.43 (m, 5H), 1.38–1.19 (m, 1H), 0.96 (s, 3H), 0.78 (d, *J* = 6.8, 3H) ppm; **$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 152.4, 147.4, 129.1, 126.9, 121.4, 119.5, 116.9, 109.5, 90.2, 49.2, 45.2, 36.3, 34.5, 31.4, 30.5, 29.4, 27.9, 24.1, 19.9, 16.8, 15.3 ppm; **IR (ATR):** $\tilde{\nu}$ = 3072, 2963, 2933, 1645, 1586, 1488, 1458, 1383, 1247, 1176, 1036, 934, 886, 751 cm$^{-1}$; **HRMS (EI)**: calc'd. for $[C_{21}H_{28}O]^+$: 296.2135, found: 296.2138; **$[\alpha]_D^{20}$** = +68.3 (c = 0.33, $CHCl_3$); $R_f$: 0.85 (Pentane/EtOAc, 95:5).




**(*1S,4aR,9aR*)-1,9a-dimethyl-4a-(4-methylpent-3-enyl)-2,3,4,4a,9,9a-hexahydro-1H-xanthene (11):** Phenol **3** (16.0 mg, 50.0 µmol) in 100 µL $CH_2Cl_2$ was to $PtCl_4$ (1.7 mg, 5.0 µmol) in 400 µL $CH_2Cl_2$ and stirred for 1 h. The residue was concentrated and purified by chromatography on silica gel (pentane / ether 100:1) and gave partially cyclized product 8.6 mg (54 %) **11** as colorless film.
**$^1$H-NMR** (300 MHz, $CDCl_3$) δ = 7.15–7.05 (m, 1H), 7.02–6.94 (m, 1H), 6.86–6.73 (m, 2H), 5.05–4.94 (m, 1H), 2.66 (s, 2H), 2.12–1.93 (m, 3H), 1.85–1.58 (m, 5H), 1.57–1.50 (m, 2H), 1.47 (s, 3H), 1.43–1.23 (m, 4H), 0.93 (s, 3H), 0.79 (d, *J* = 6.8, 3H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 153.2, 131.4, 129.3, 127.1, 124.7, 121.2, 119.5, 116.8, 80.4, 36.9, 33.8, 32.9, 31.9, 30.0, 29.8, 25.6, 21.7, 20.9, 17.4, 16.5, 16.2.; **IR (ATR):** $\tilde{\nu}$ = 3953, 2936, 2856, 1586, 1488, 1456, 1383, 1303, 1255, 1184, 1159,

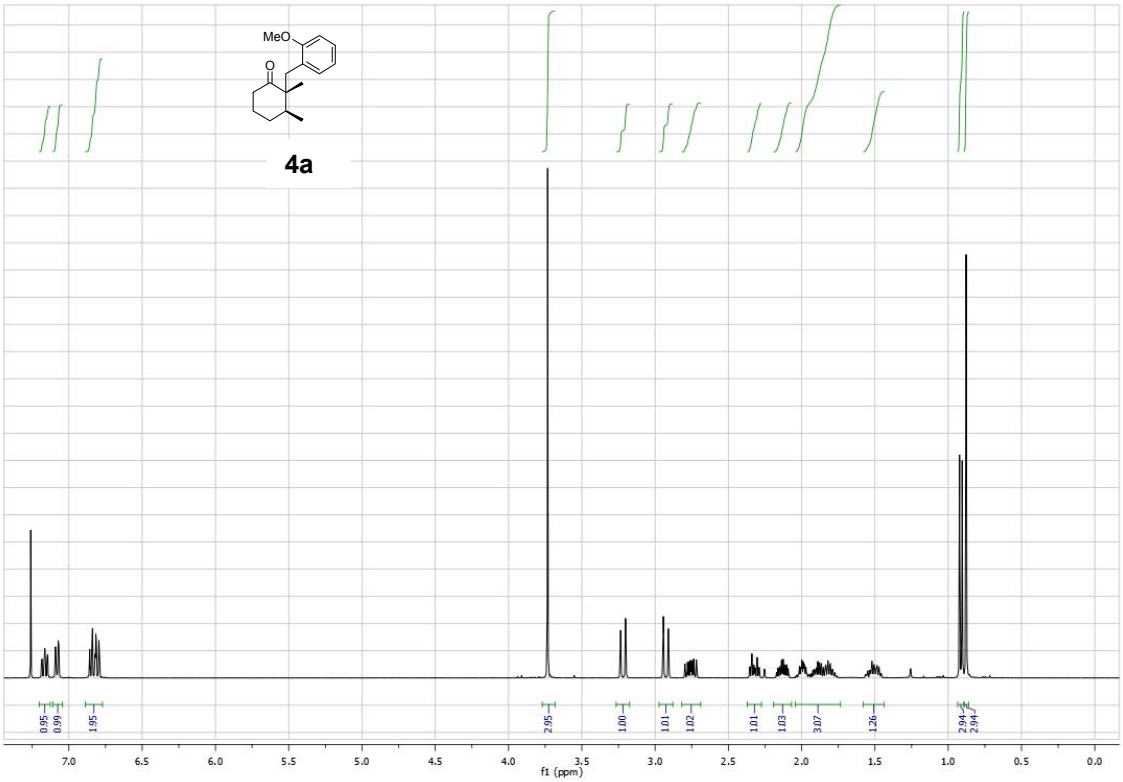
1119, 1036, 995, 934, 840, 752 $cm^{-1}$; **HRMS (EI)** calc'd. for $[C_{21}H_{30}O]^+$: 298.2297, found: 298.2292; $[\alpha]_D^{20}$ = +12.7 (*c* = 0.51, $CHCl_3$); $R_f$: 0.79 (Pentane/EtOAc, 95:5).



**(*4aR,7S,7aR,131S*)-4,4,7,7a-tetramethyl-1,2,3,4,4a,5,6,7,7a,8-deca-hydrobenzo[*d*]xanthene (*trans*-1):** $RuCl_3$•3 $H_2O$ (1.3 mg, 5.00 µmol) and silver triflate (3.9 mg, 15 µmol) were heated in 400 µL acetonitrile for 30 min at 80°C, cooled to 23°C and 2.6 mg (10.0 µmol) triphenylphosphine, 4.5 mg (13.0 µmol) copper(II) triflate and 7.5 mg (25.0 µmol) phenol **3** in 100 µL acetonitrile were added. The reaction mixture was stirred at 80°C for 5 h, cooled and concentrated. The residue was purified by chromatography on silica gel (pentane / ether 100:1) and gave cyclized product 5.2 mg (69 %) ***trans*-1** as colorless film along with 0.8 mg of **11**.

**$^1$H-NMR** (400 MHz, $CDCl_3$) δ = 7.13–7.04 (m, 1H), 7.02–6.92 (m, 1H), 6.85–6.75 (m, 2H), 2.60 (d, *J* = 17.2, 1H), 2.55 (d, *J* = 17.3, 1H), 1.78–1.55 (m, 5H), 1.48–1.14 (m, 7H), 1.12 (s, *J* = 12.0, 3H), 0.92 (d, *J* = 1.5, 6H), 0.75 (d, *J* = 6.8, 3H) ppm; **$^{13}$C-NMR** (101 MHz, $CDCl_3$) δ 152.8, 129.3, 127.0, 121.2, 119.4, 116.9, 81.4, 45.6, 42.0, 37.2, 33.4, 33.4, 32.6, 31.7, 30.5, 28.8, 22.4, 21.9, 17.9, 16.9, 16.2 ppm. **IR (ATR):** $\tilde{\nu}$ = 2925, 2853, 1587, 1488, 1458, 1387, 1254, 1171, 1113, 936, 751 $cm^{-1}$; **HRMS (EI)**: calc'd. for $[C_{21}H_{30}O]^+$: 298.2282, found: 298.2297; $[\alpha]_D^{20}$ = +3.7 (c = 0.23, $CHCl_3$); $R_f$: 0.88 (Pentane/EtOAc, 95:5).

## Spectra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O
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0.95
0.99
1.95
2.95
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1.01
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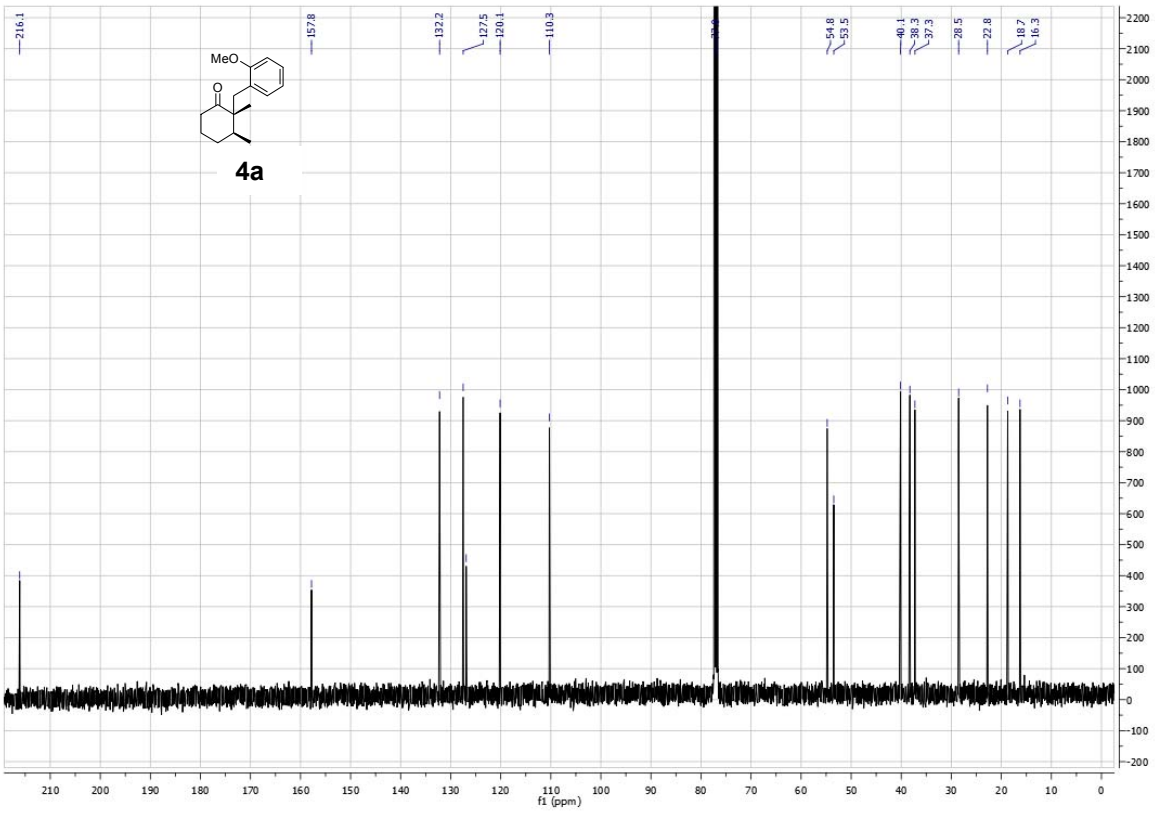
1.01
1.03
3.07
1.26
2.94
2.94
f1 (ppm)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110.3
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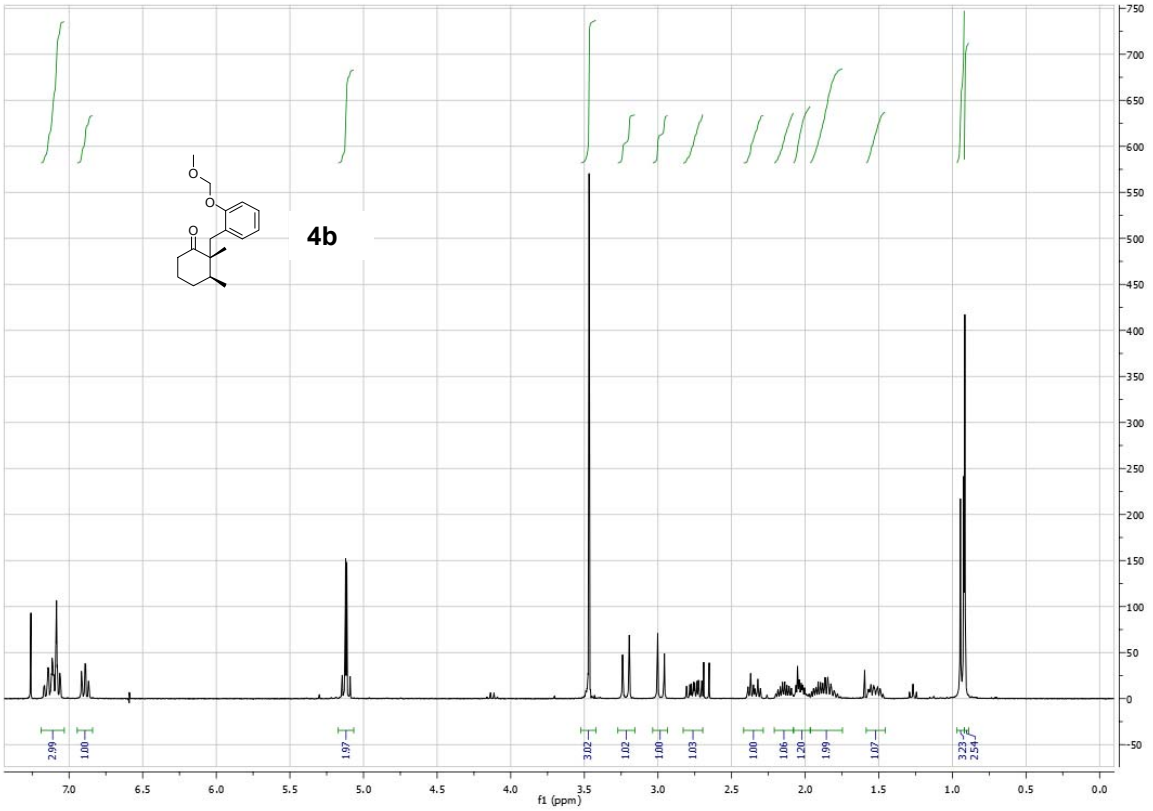
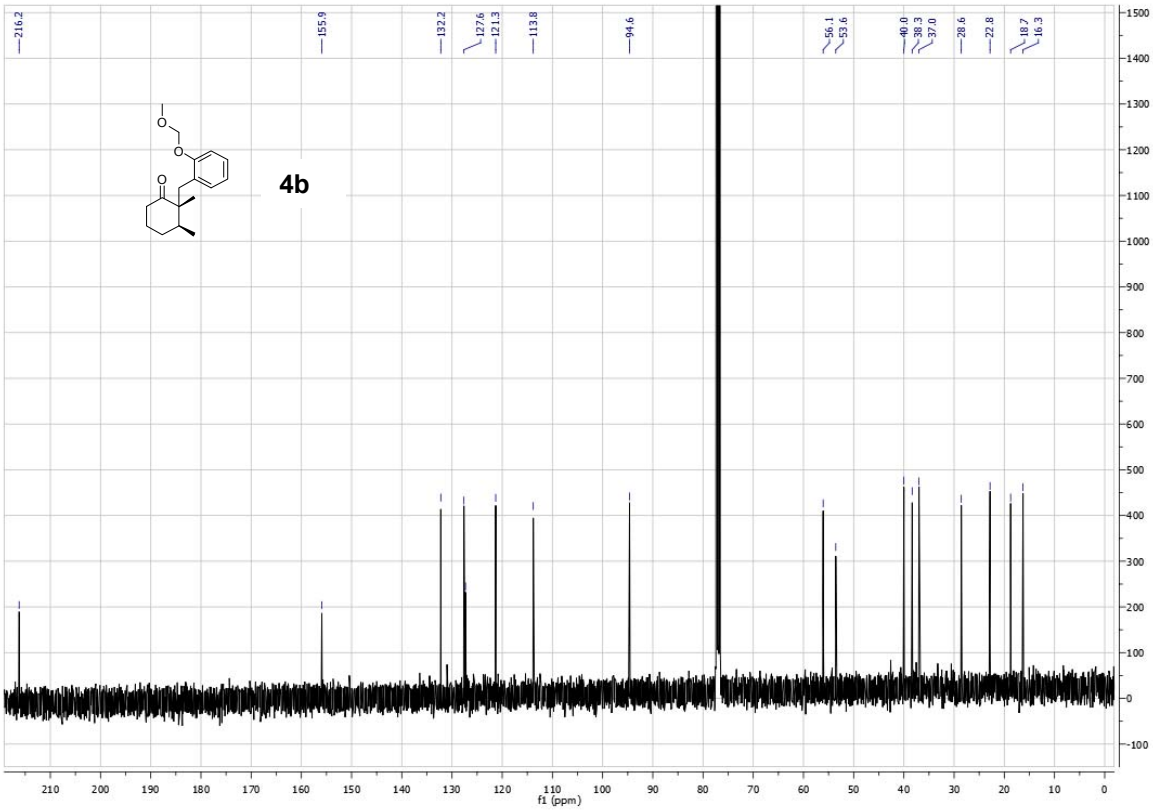
18.7
16.3
MeO
O
4a
f1 (ppm)


4b
f1 (ppm)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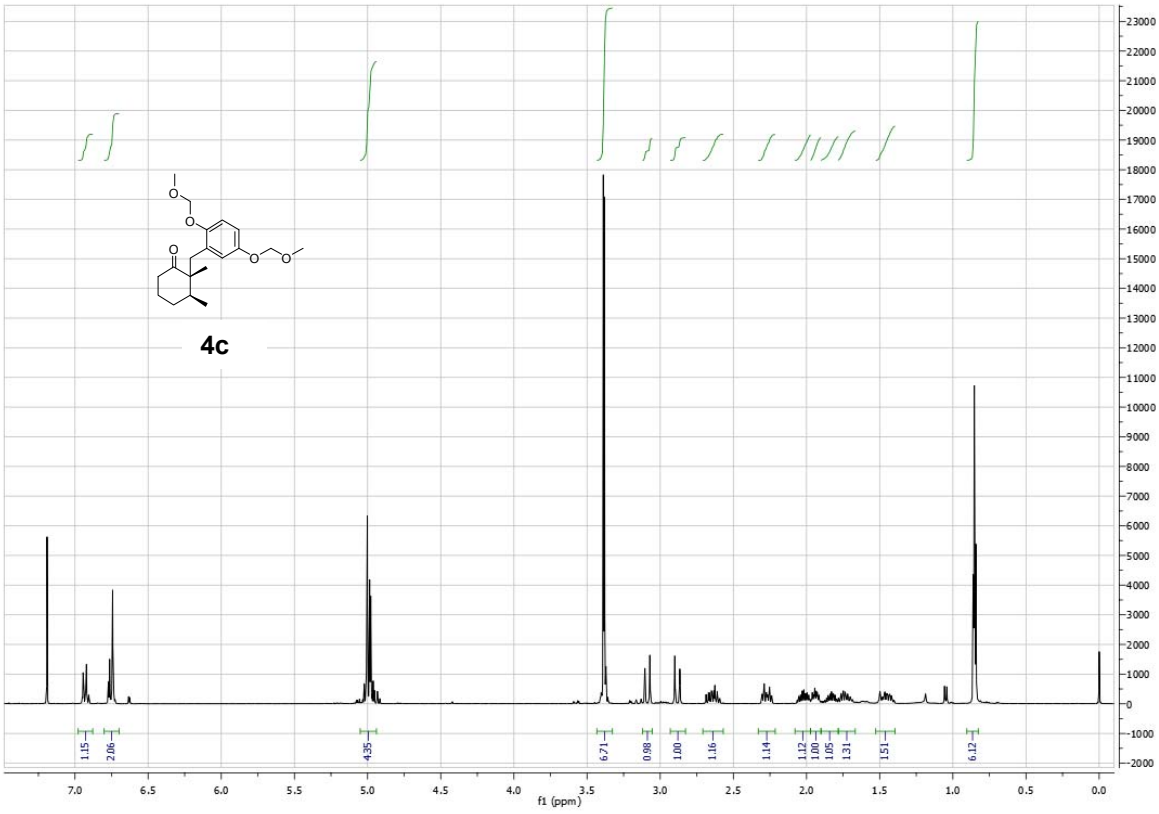
127.6
121.3
113.8
94.6
56.1
53.6
40.0
38.3
37.0
28.6
22.8
18.7
16.3
4b
f1 (ppm)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2.06
4.35
6.71
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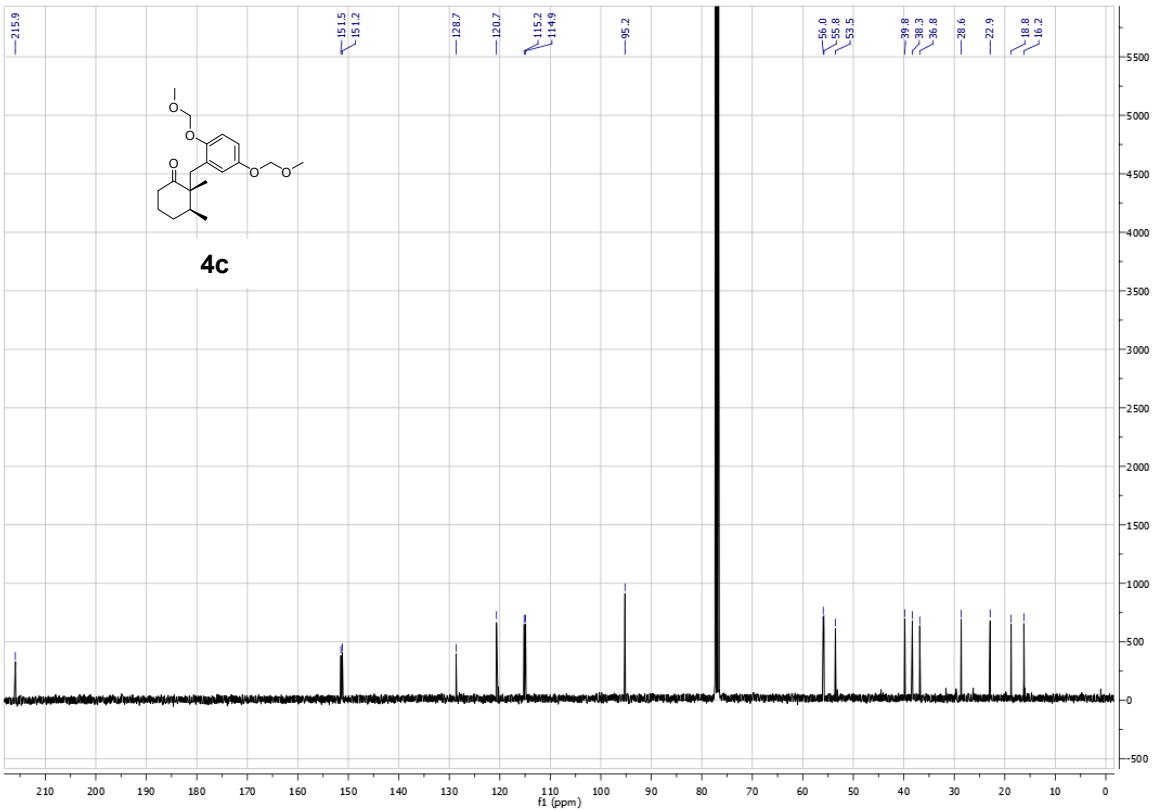
1.12
1.06
1.05
1.31
1.51
6.12
f1 (ppm)


4c
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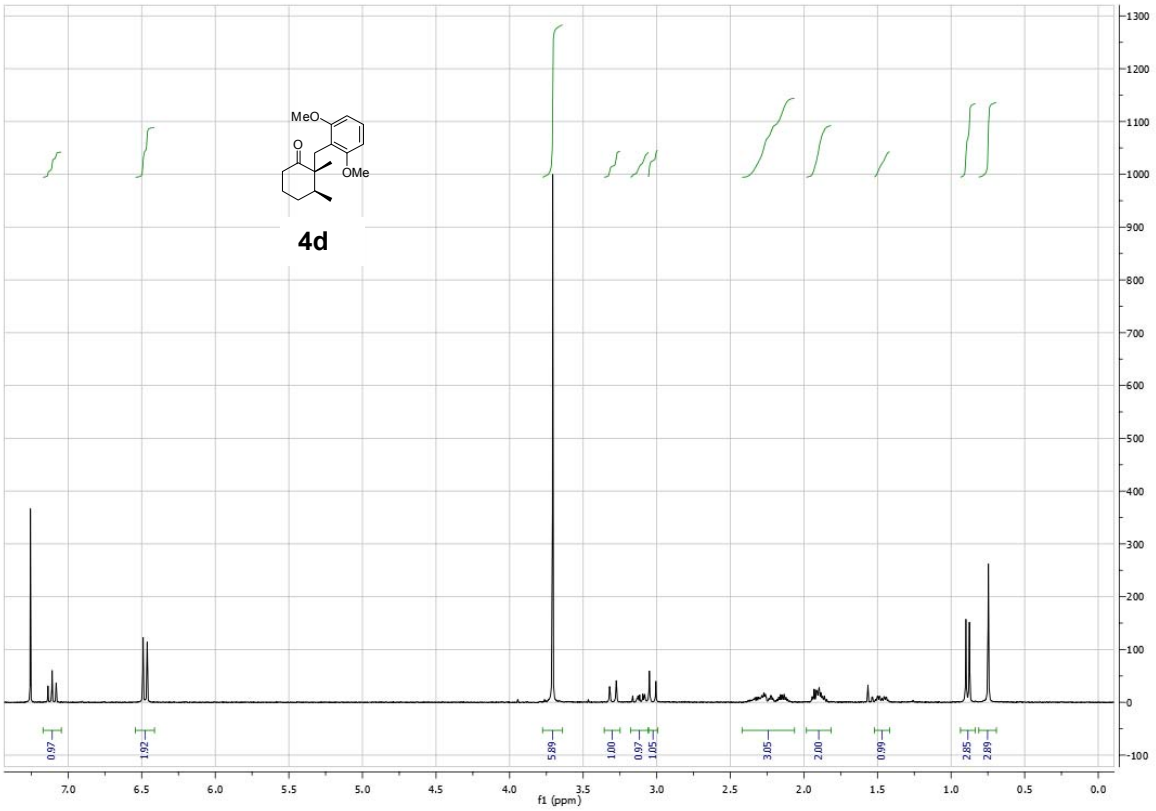
38.3
36.8
28.6
22.9
18.8
16.2
f1 (ppm)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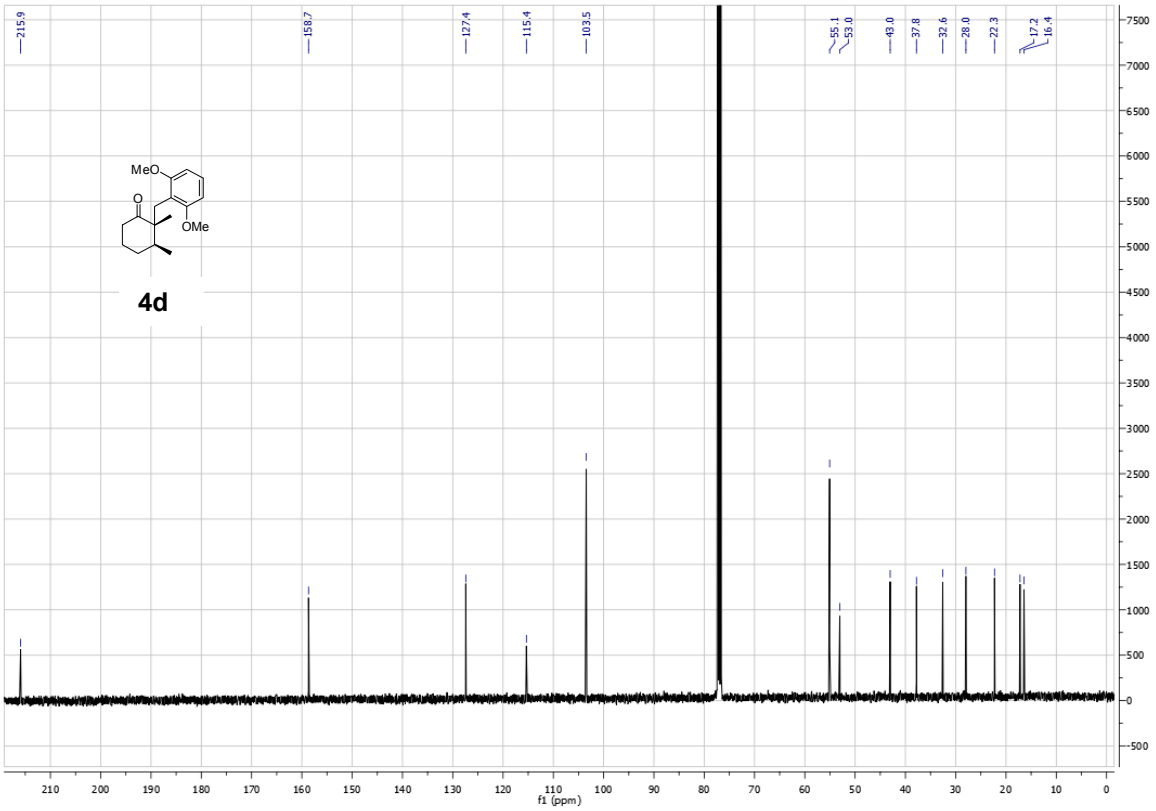
O
OMe
4d
f1 (ppm)


215.9
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115.4
103.5
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43.0
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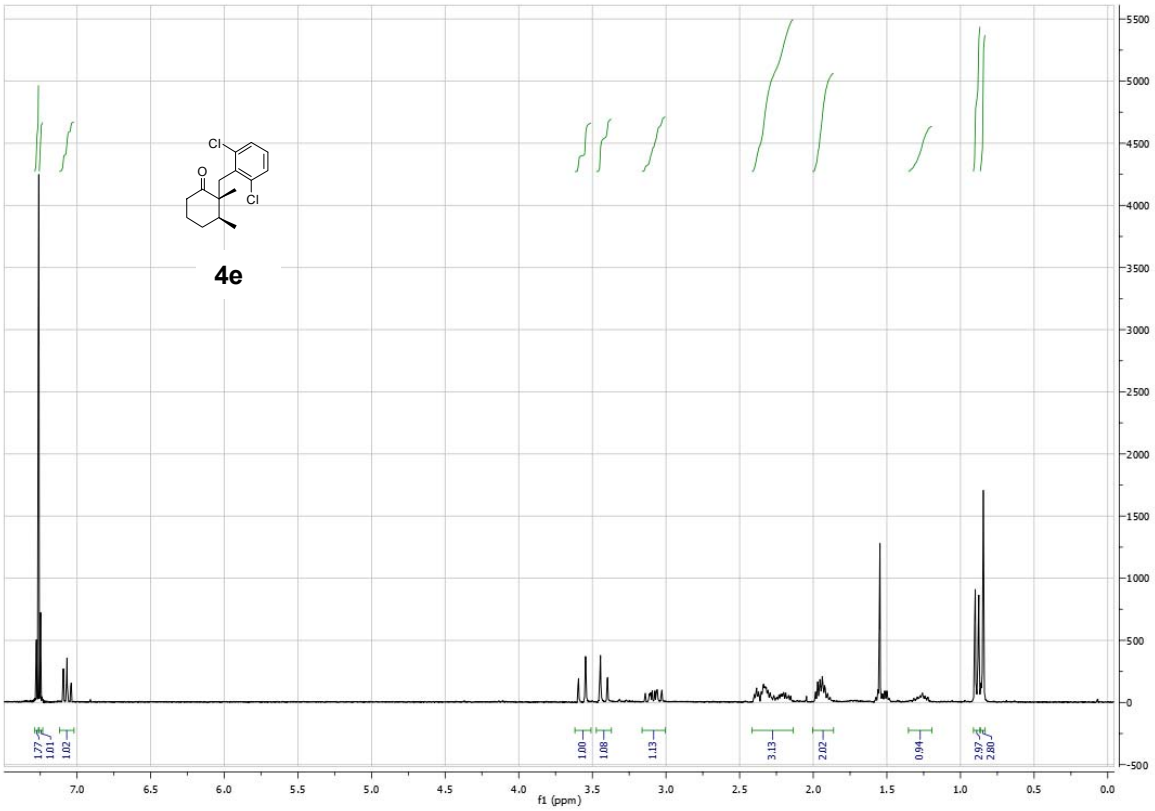
16.4
MeO
O
OMe
4d
f1 (ppm)


Cl
O
Cl
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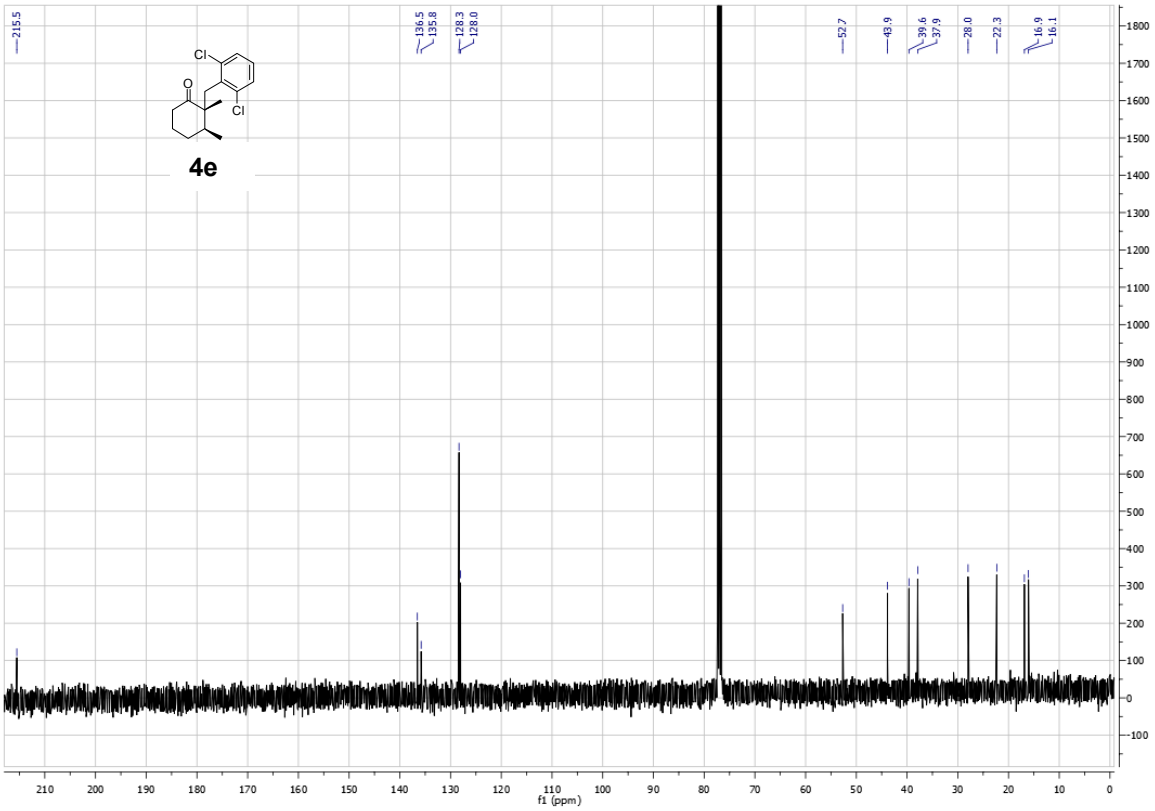
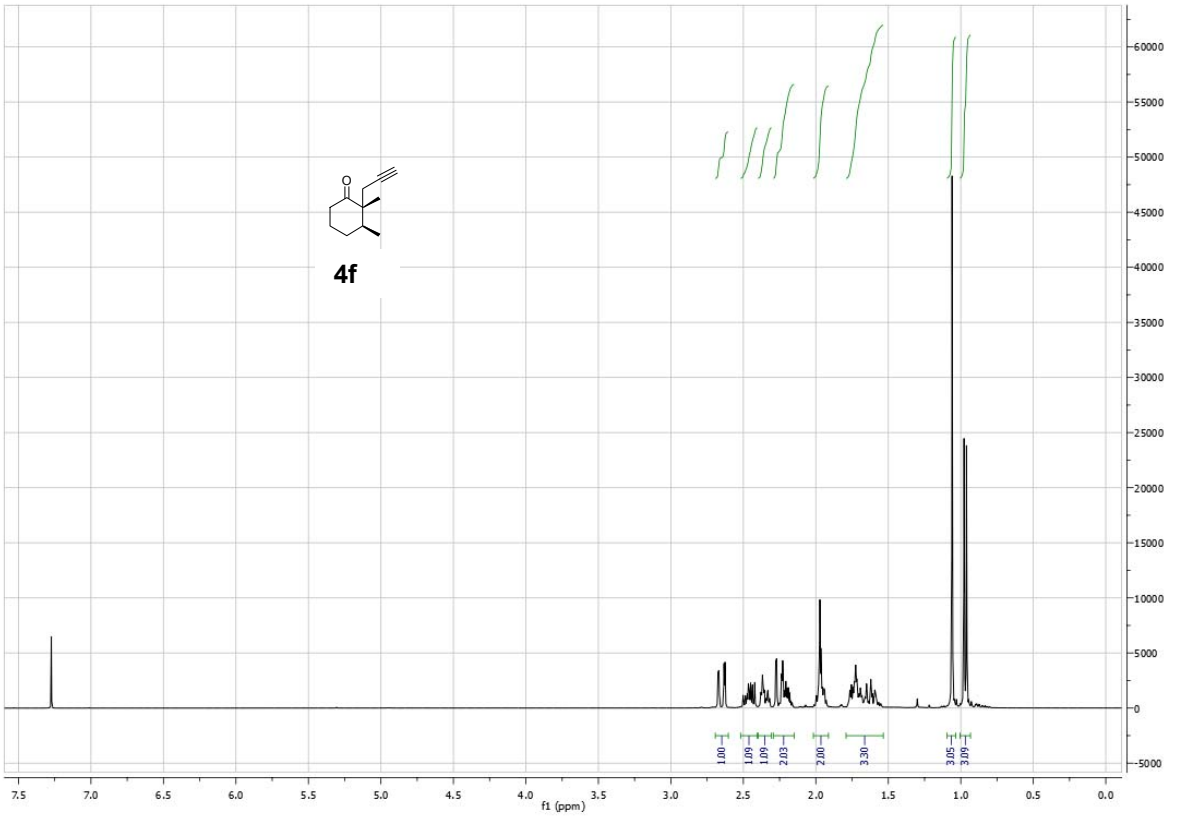
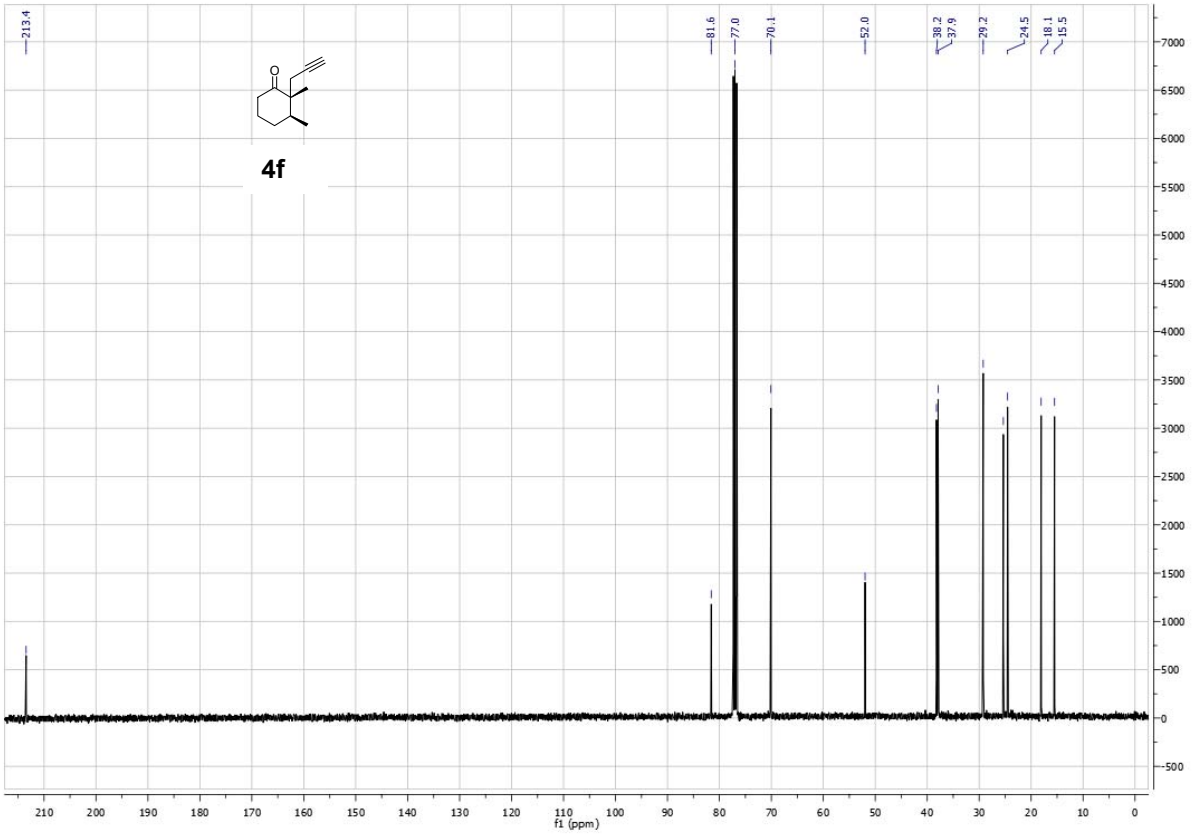
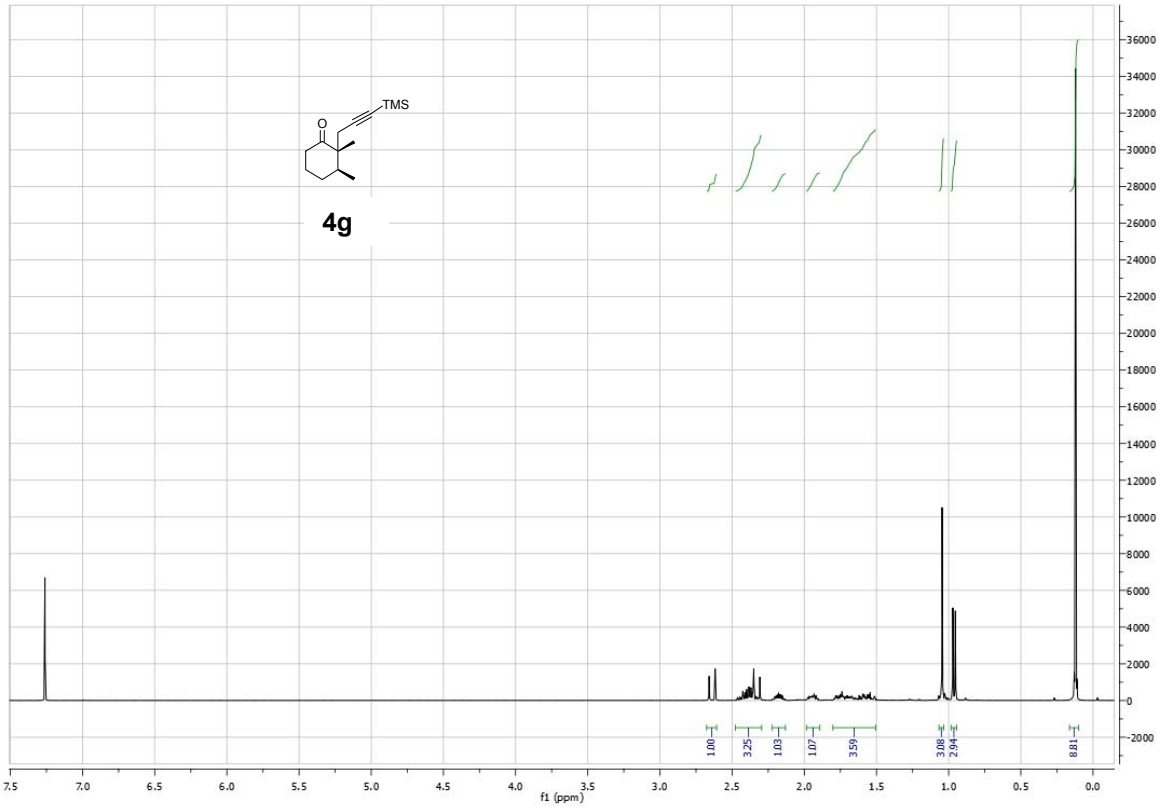
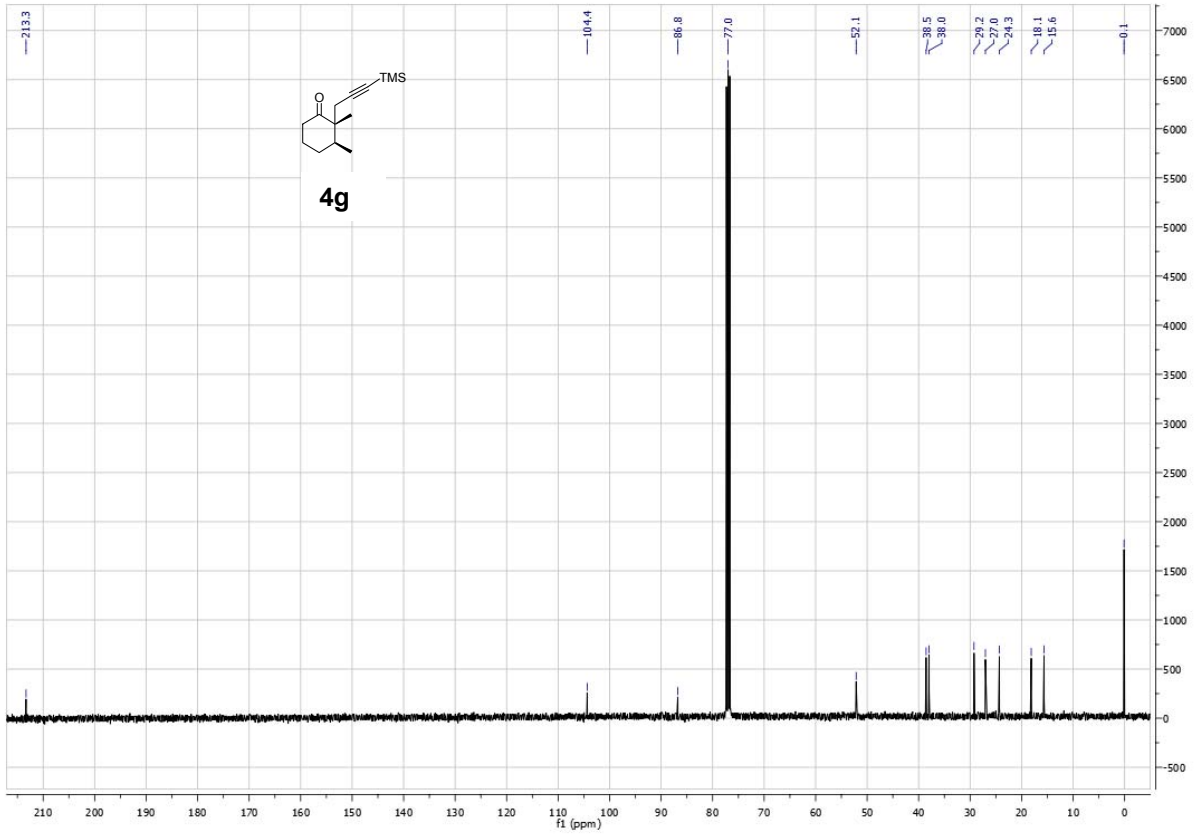
1.02
1.00
1.08
1.13
3.13
2.02
0.94
2.97
2.80
f1 (ppm)

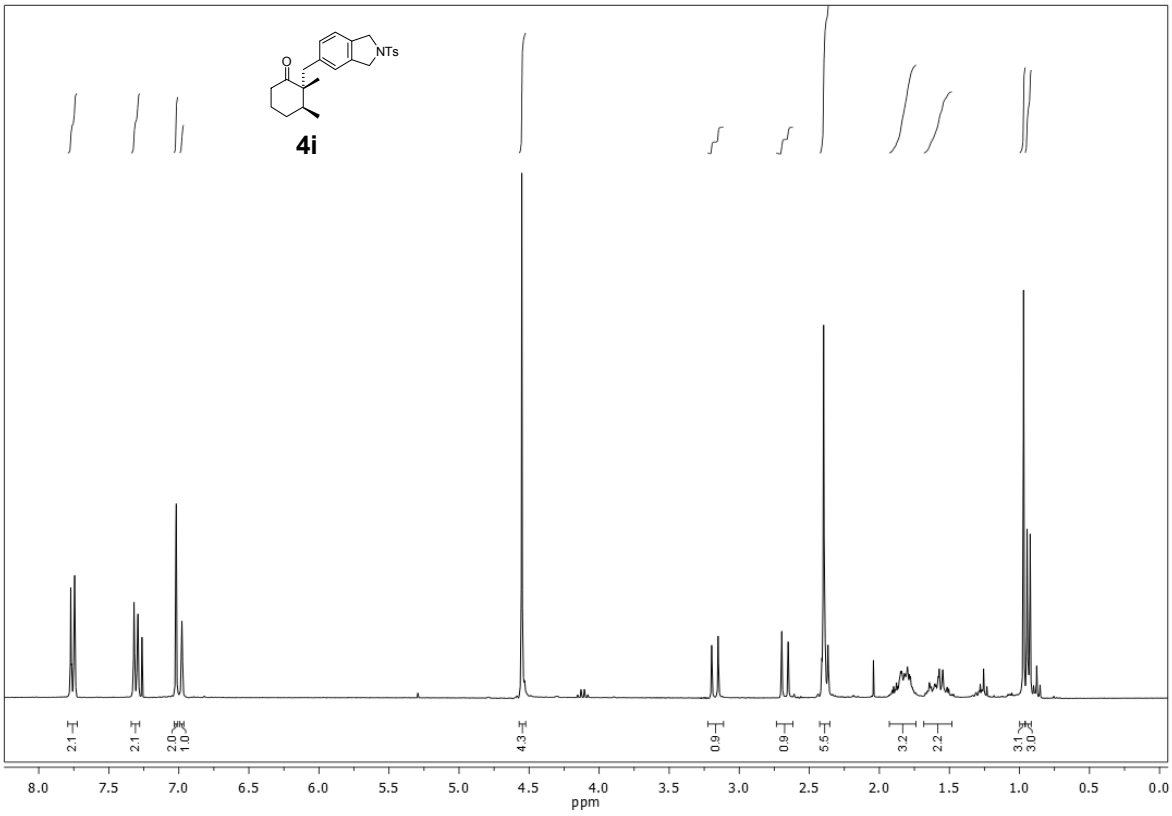

215.5
136.5
135.8
128.3
128.0
52.7
43.9
39.6
37.9
28.0
22.3
16.9
16.1
Cl
O
Cl
4e
f1 (ppm)

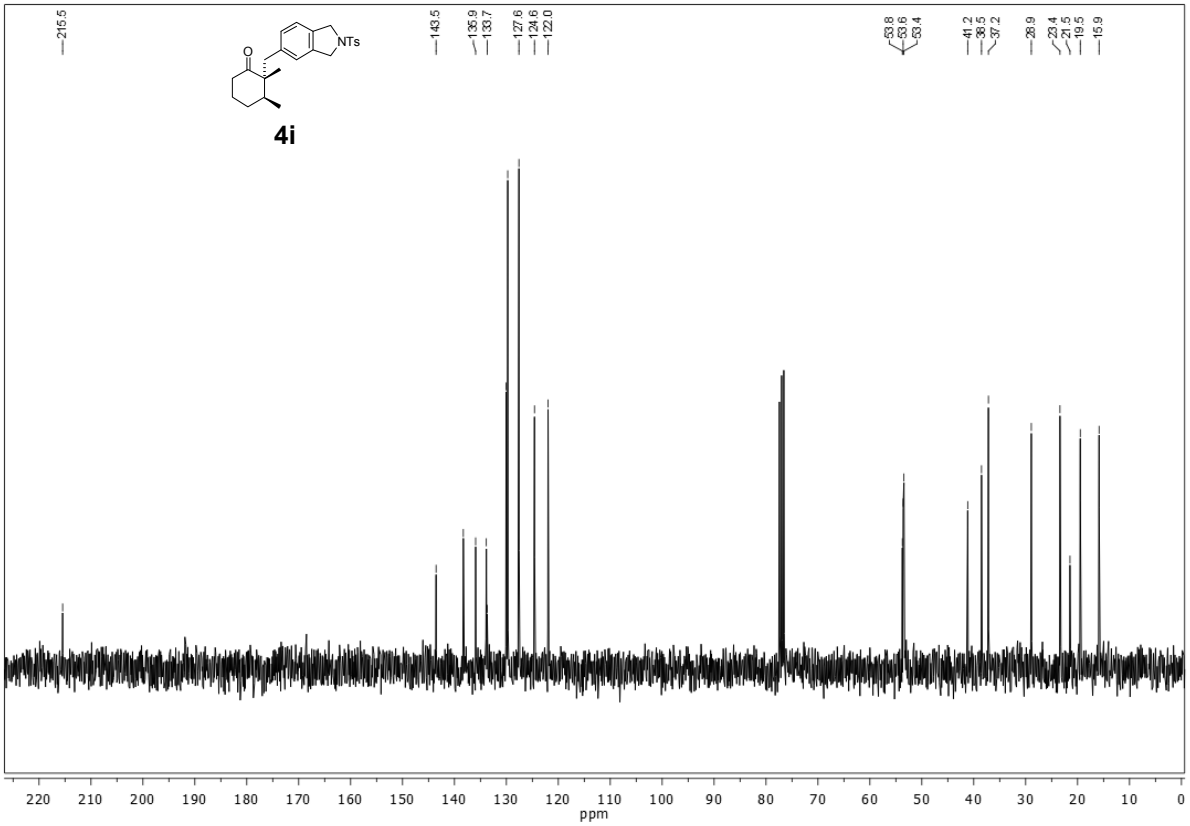

4f
1.00
1.09
1.09
2.03
2.00
3.30
3.05
3.09
f1 (ppm)

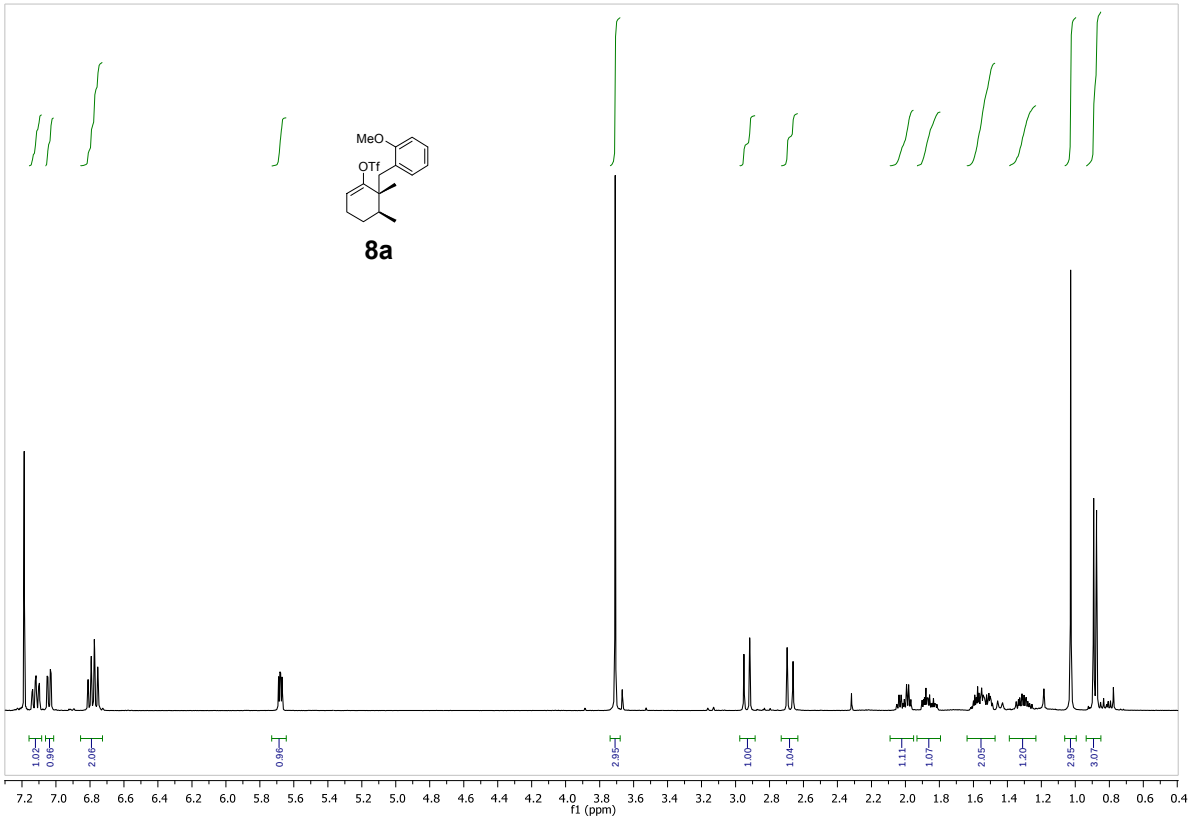

213.4
81.6
77.0
70.1
52.0
38.2
37.9
29.2
24.5
18.1
15.5
4f
f1 (ppm)

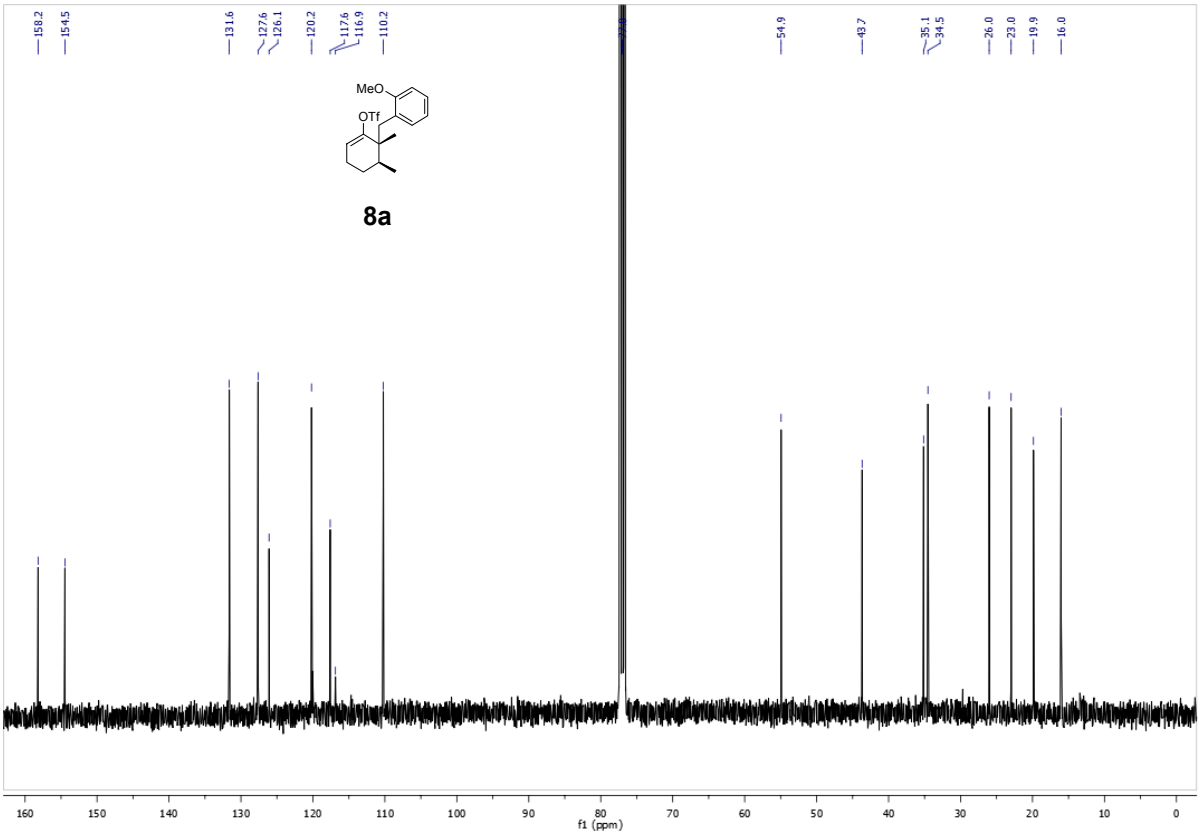

TMS
O
4g
1.00
3.25
1.03
1.07
3.59
3.08
2.94
8.81
f1 (ppm)

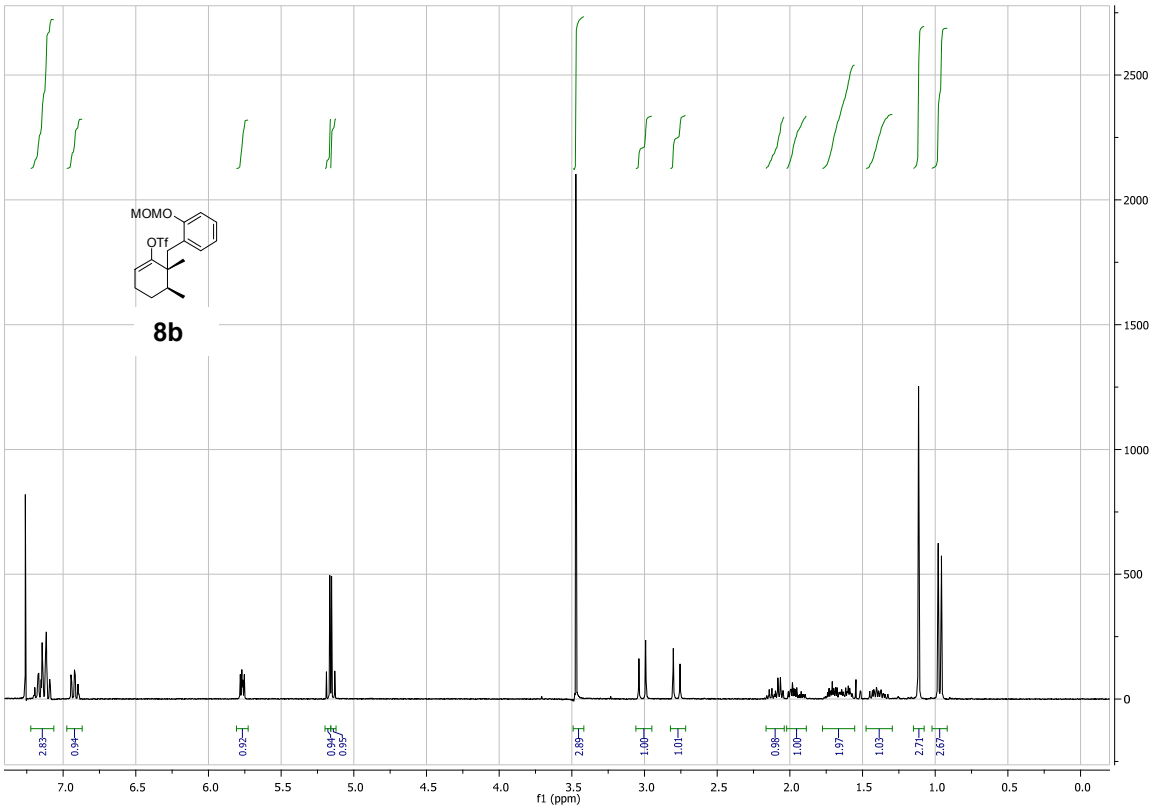

213.3
104.4
86.8
77.0
52.1
38.5
38.0
29.2
27.0
24.3
18.1
15.6
0.1
TMS
O
4g
f1 (ppm)

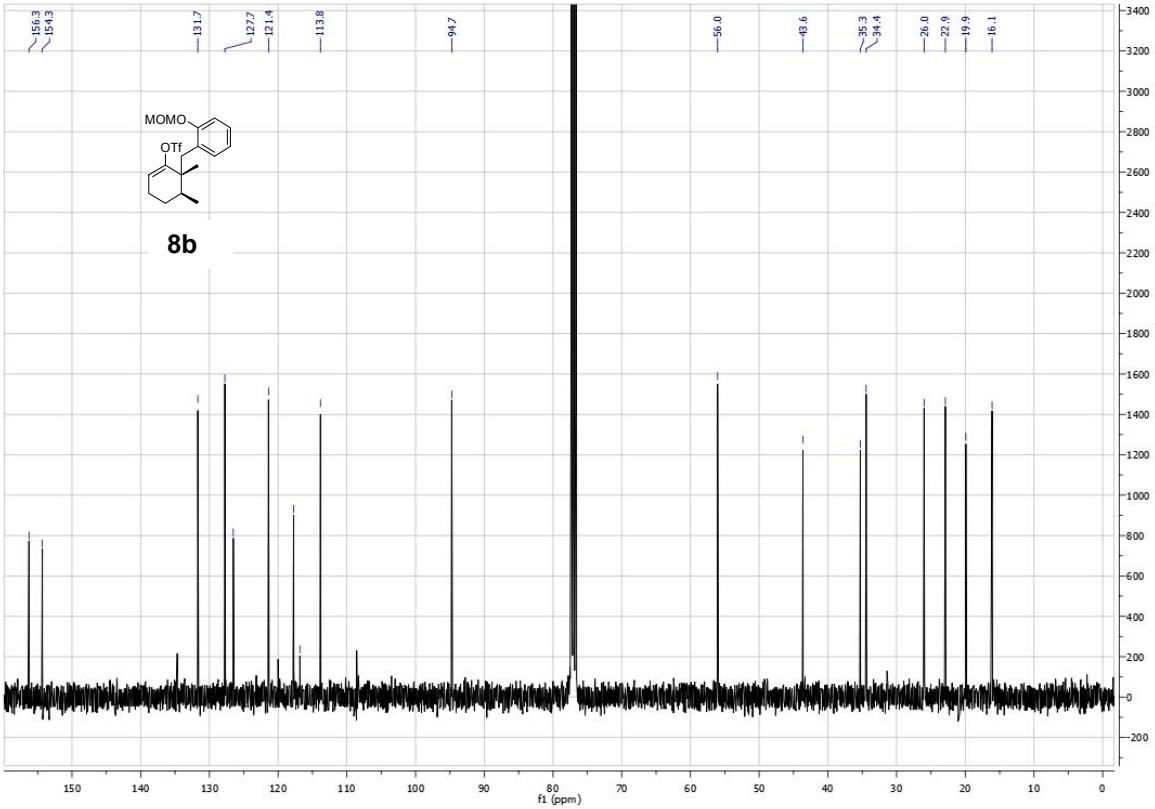

NTs
O
4i
2.1
2.1
2.0
1.0
4.3
0.9
0.9
5.5
3.2
2.2
3.1
3.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

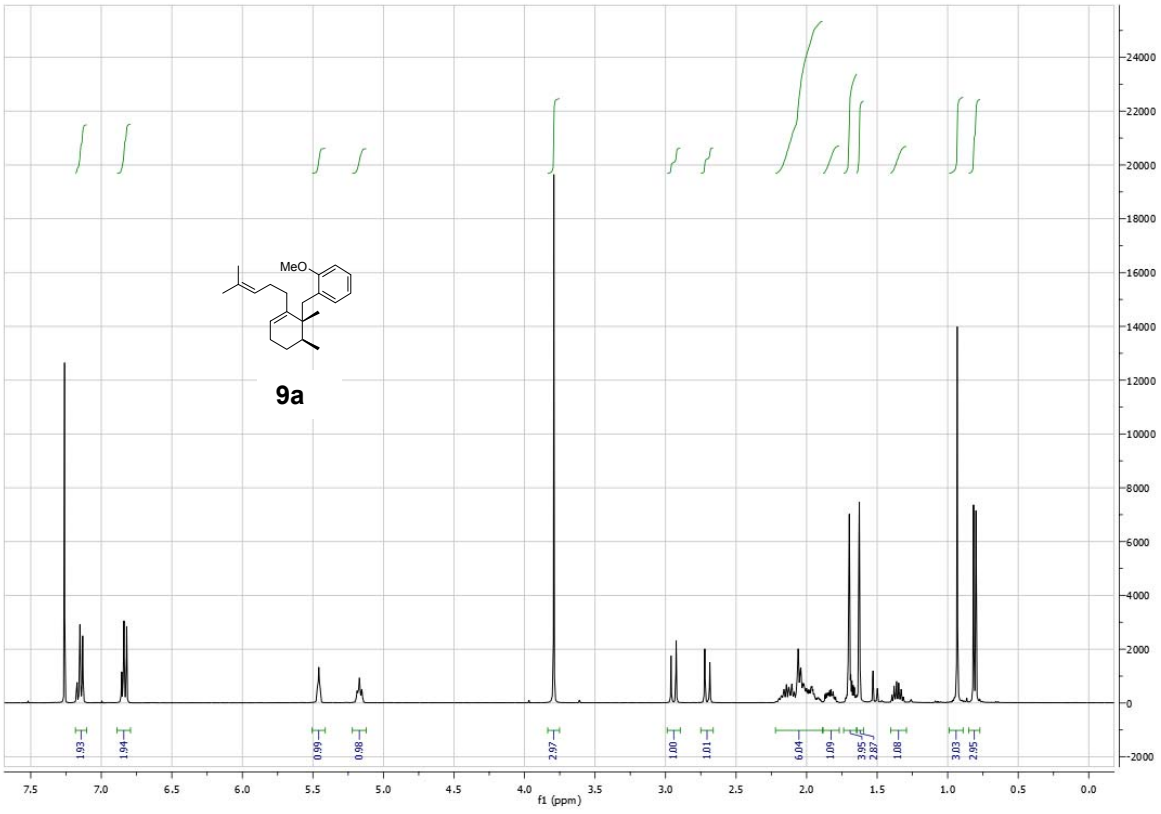

215.5
143.5
135.9
133.7
127.6
124.6
122.0
53.8
53.6
53.4
41.2
38.5
37.2
28.9
23.4
21.5
19.5
15.9
NTs
O
4i
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

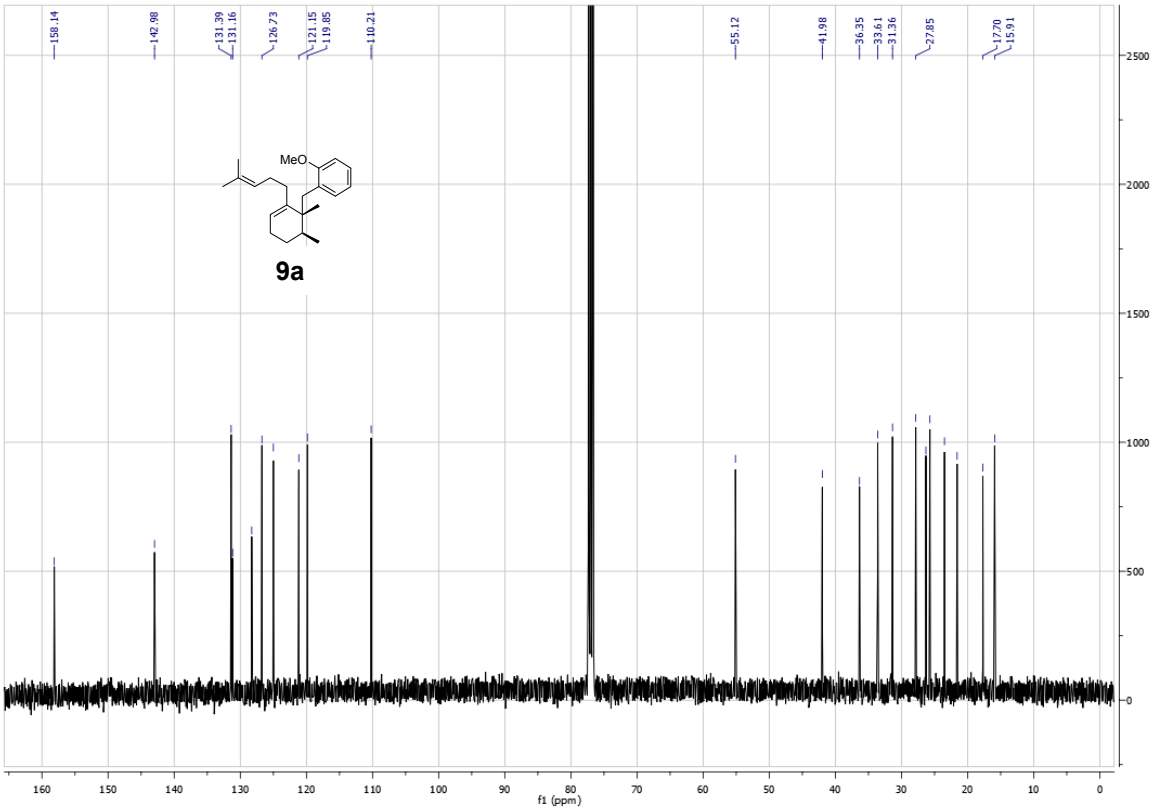

MeO
OTf
8a
1.02
0.96
2.06
0.96
2.95
1.00
1.04
1.11
1.07
2.05
1.20
2.95
3.07
7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
f1 (ppm)

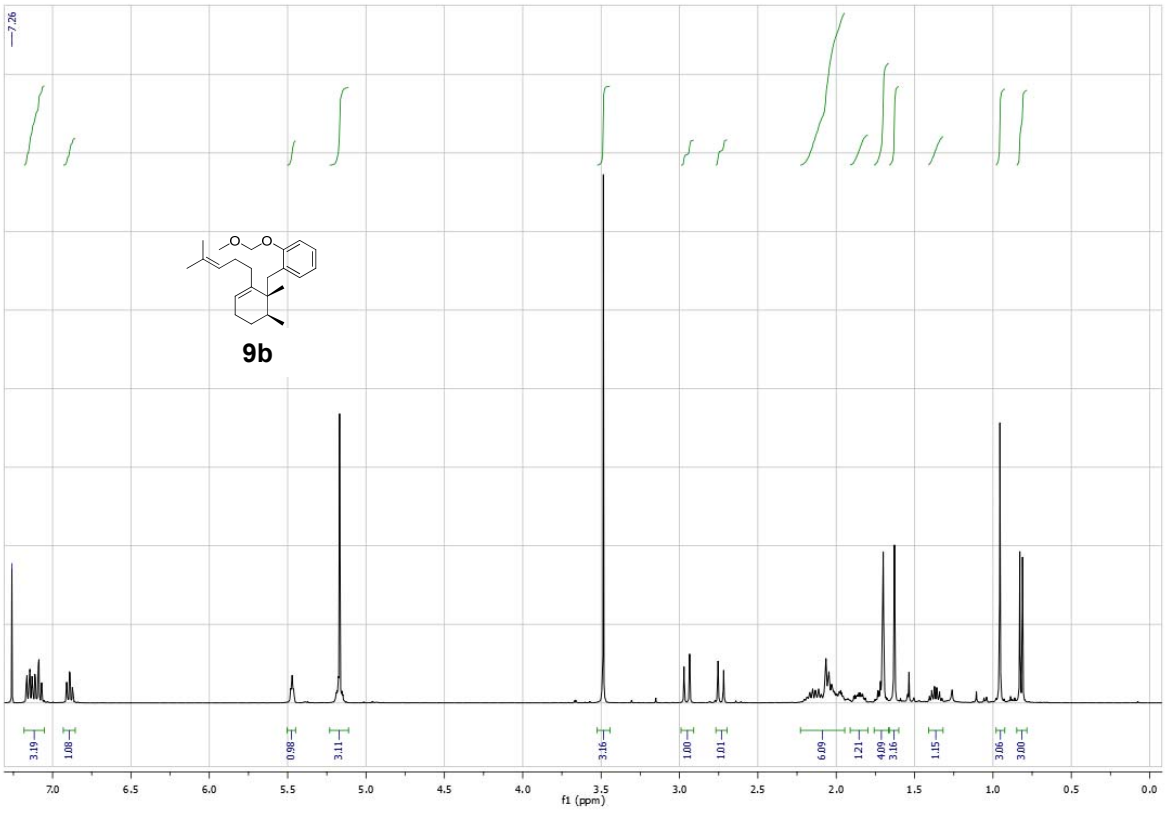

158.2
154.5
131.6
127.6
126.1
120.2
117.6
116.9
110.2
54.9
43.7
35.1
34.5
26.0
23.0
19.9
16.0
MeO
OTf
8a
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

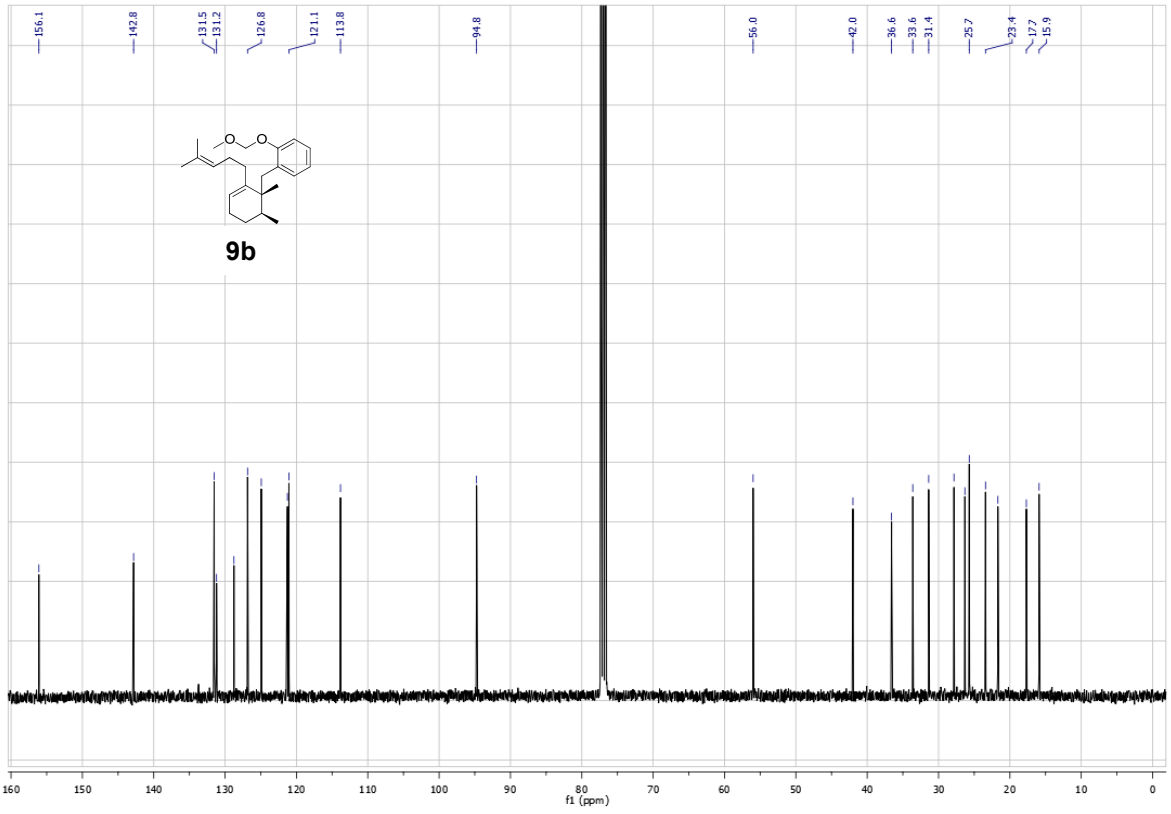

MOMO
OTf
8b
f1 (ppm)

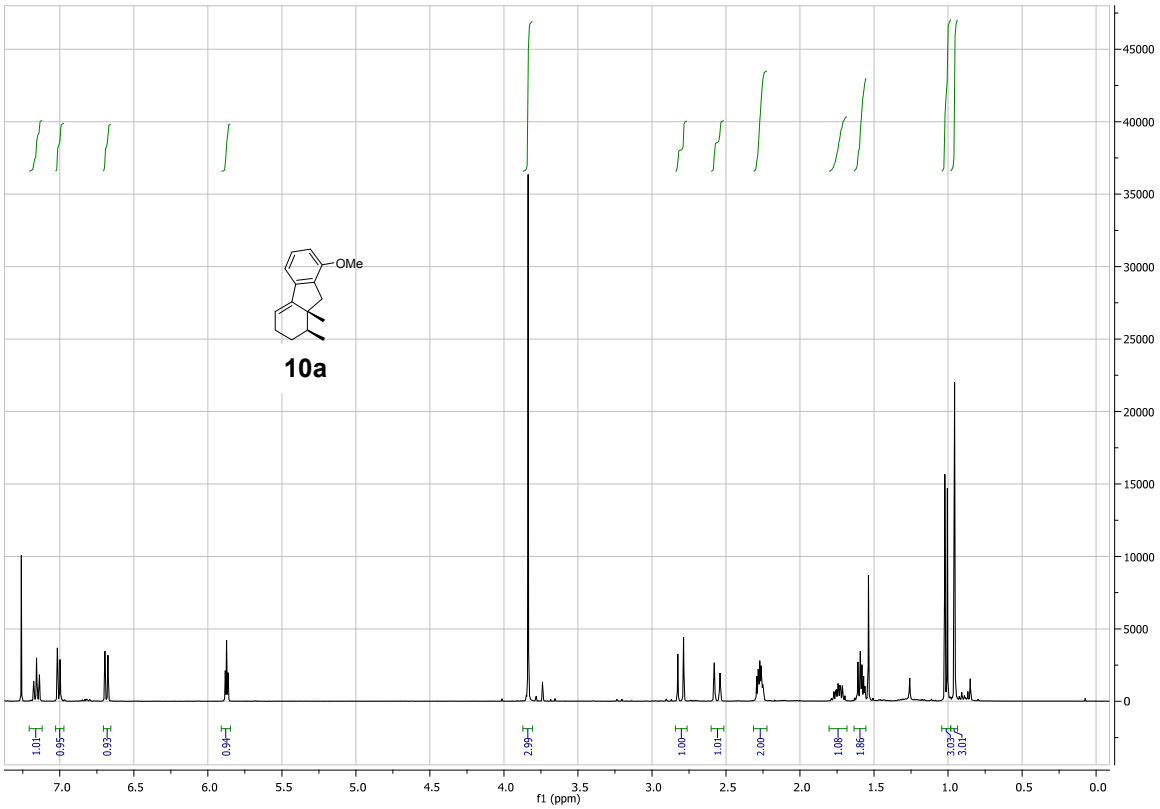

MOMO
OTf
8b
f1 (ppm)

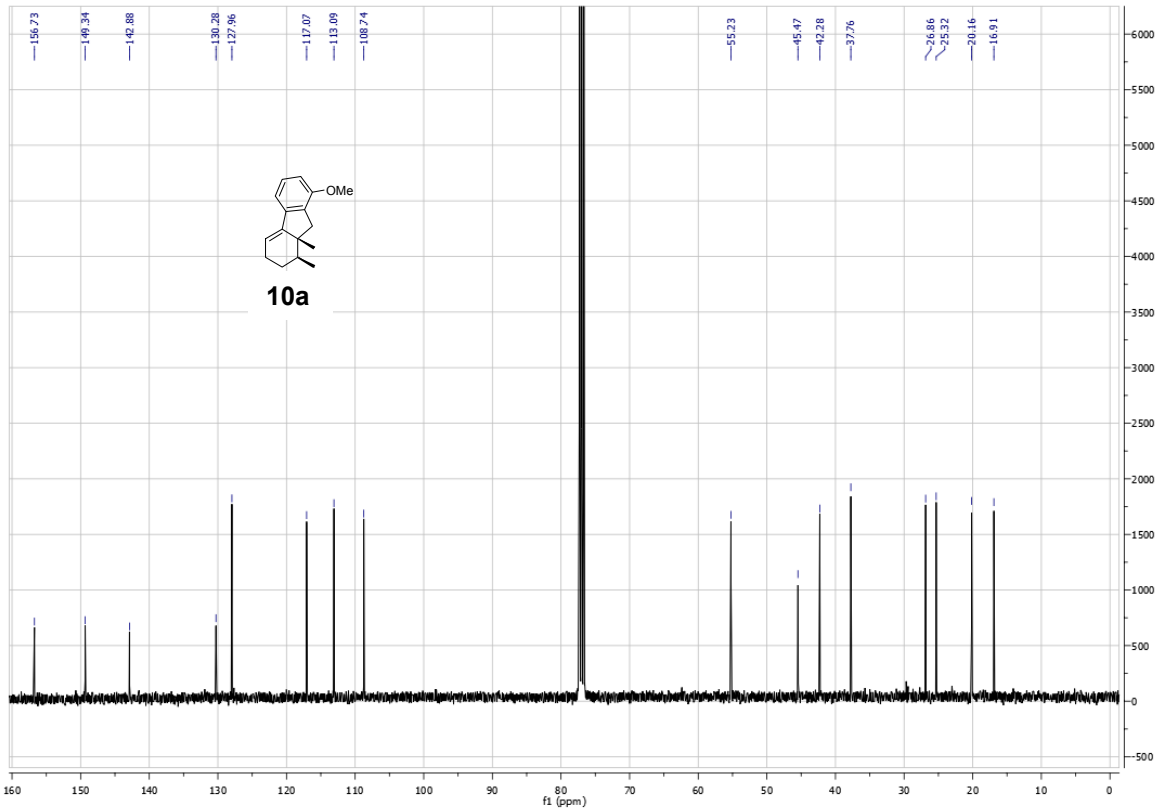

MeO
9a
1.93
1.94
0.99
0.98
2.97
1.00
1.01
6.04
1.09
3.95
2.87
1.08
3.03
2.95
f1 (ppm)

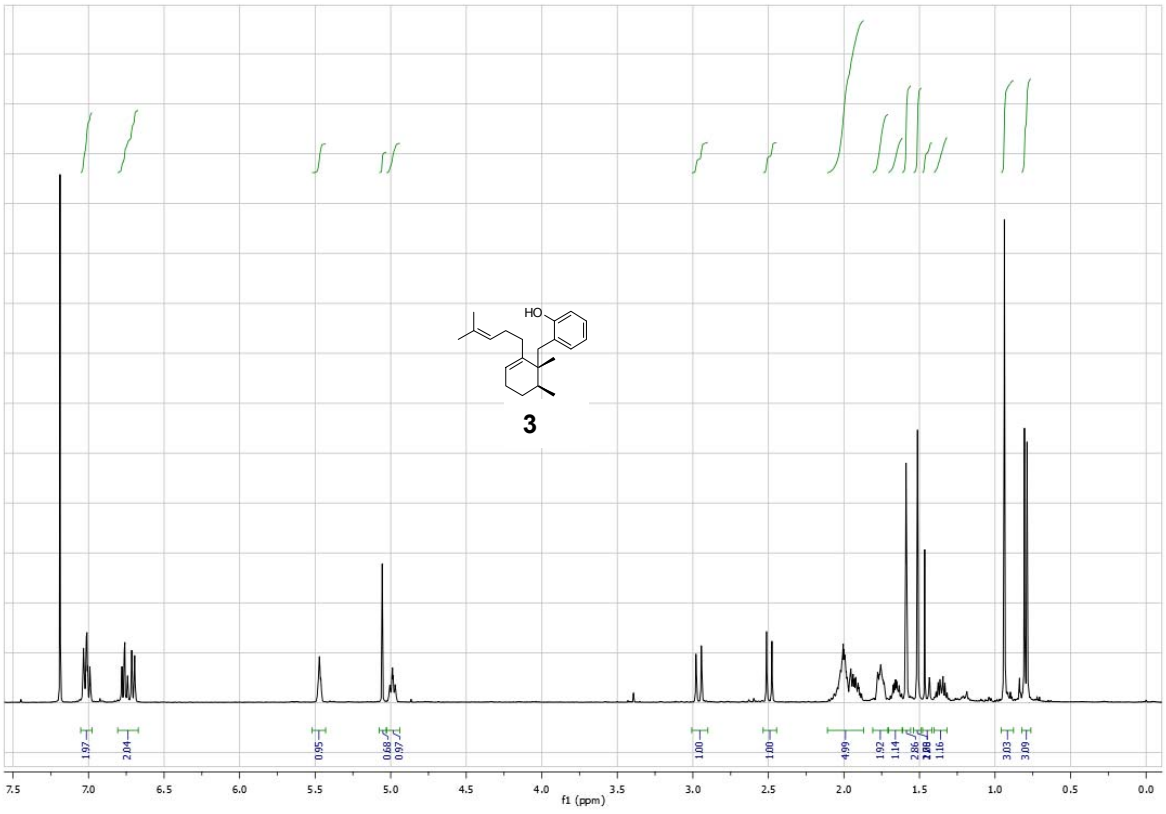

158.14
142.98
131.39
131.16
126.73
121.15
119.85
110.21
55.12
41.98
36.35
33.61
31.36
27.85
17.70
15.91
MeO
9a
f1 (ppm)

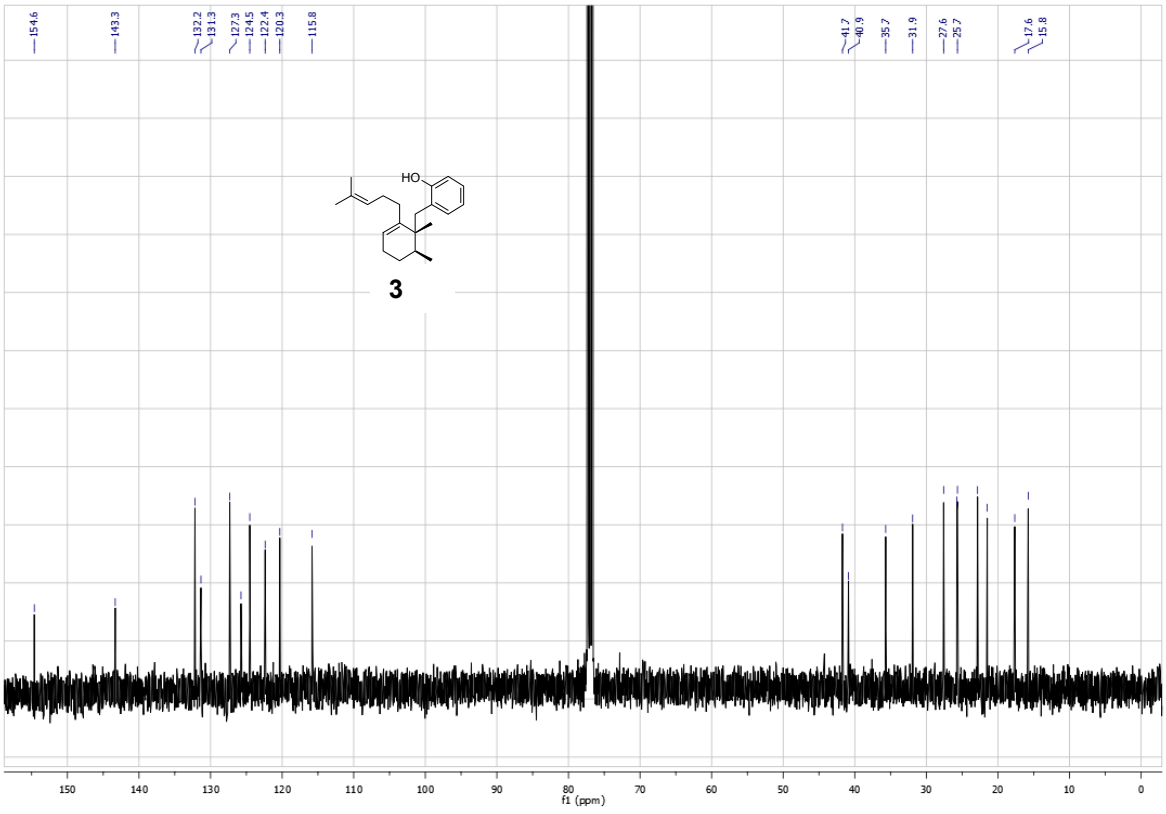

7.26
9b
3.19
1.08
0.98
3.11
3.16
1.00
1.01
6.09
1.21
4.09
3.16
1.15
3.06
3.00
f1 (ppm)

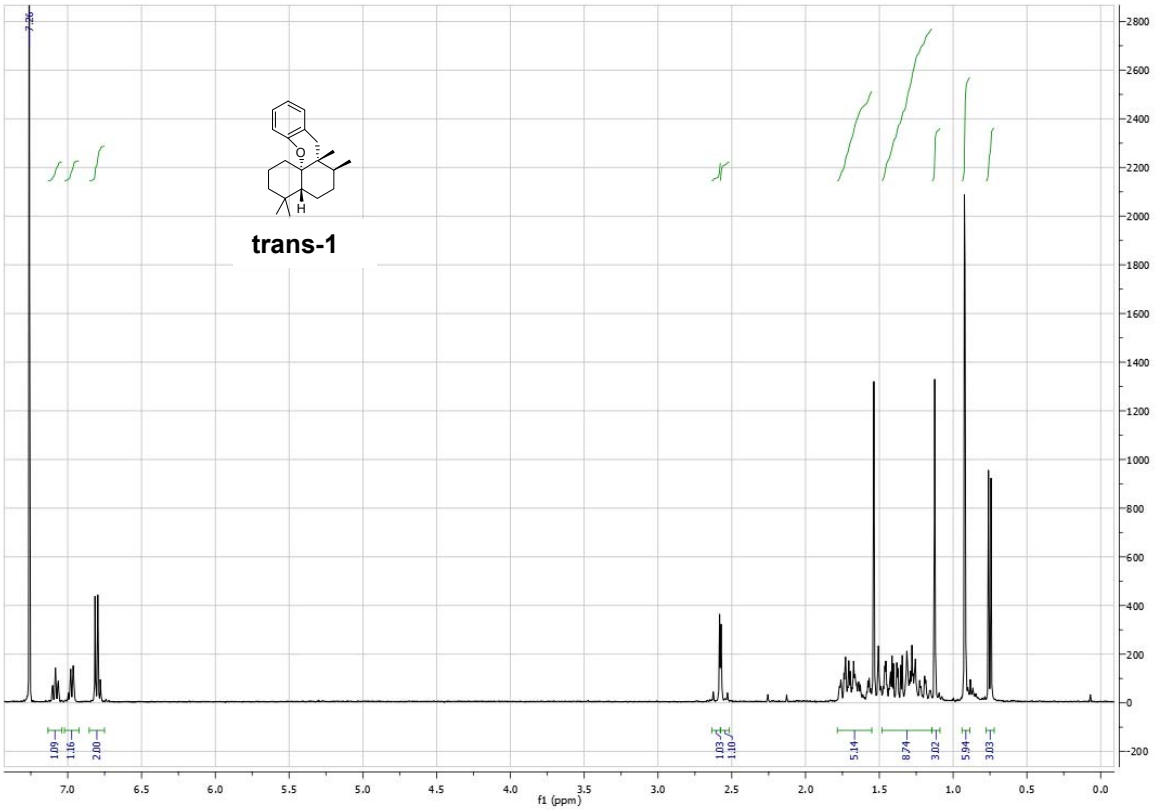

156.1
142.8
131.5
131.2
126.8
121.1
113.8
94.8
56.0
42.0
36.6
33.6
31.4
25.7
23.4
17.7
15.9
9b
f1 (ppm)

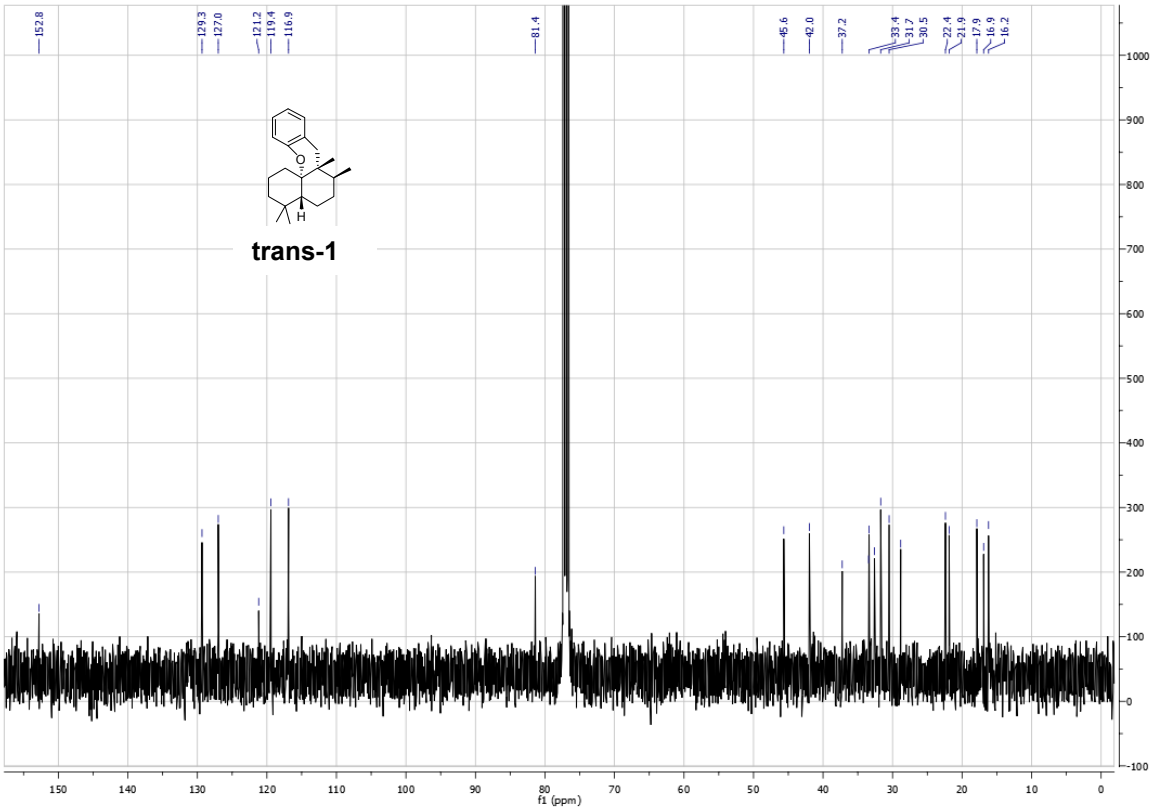

OMe
10a
1.01
0.95
0.93
0.94
2.99
1.00
1.01
2.00
1.08
1.86
3.03
3.01
f1 (ppm)

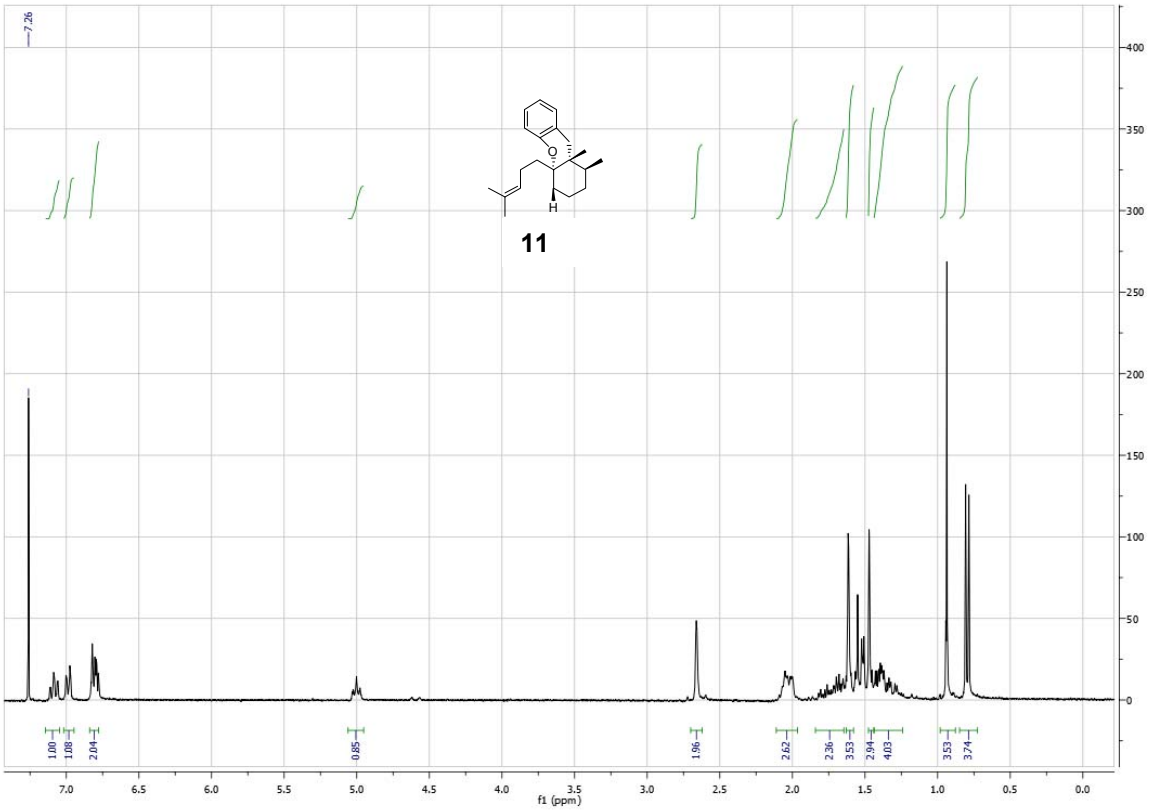

156.73
149.34
142.88
130.28
127.96
117.07
113.09
108.74
55.23
45.47
42.28
37.76
26.86
25.32
20.16
16.91
OMe
10a
f1 (ppm)

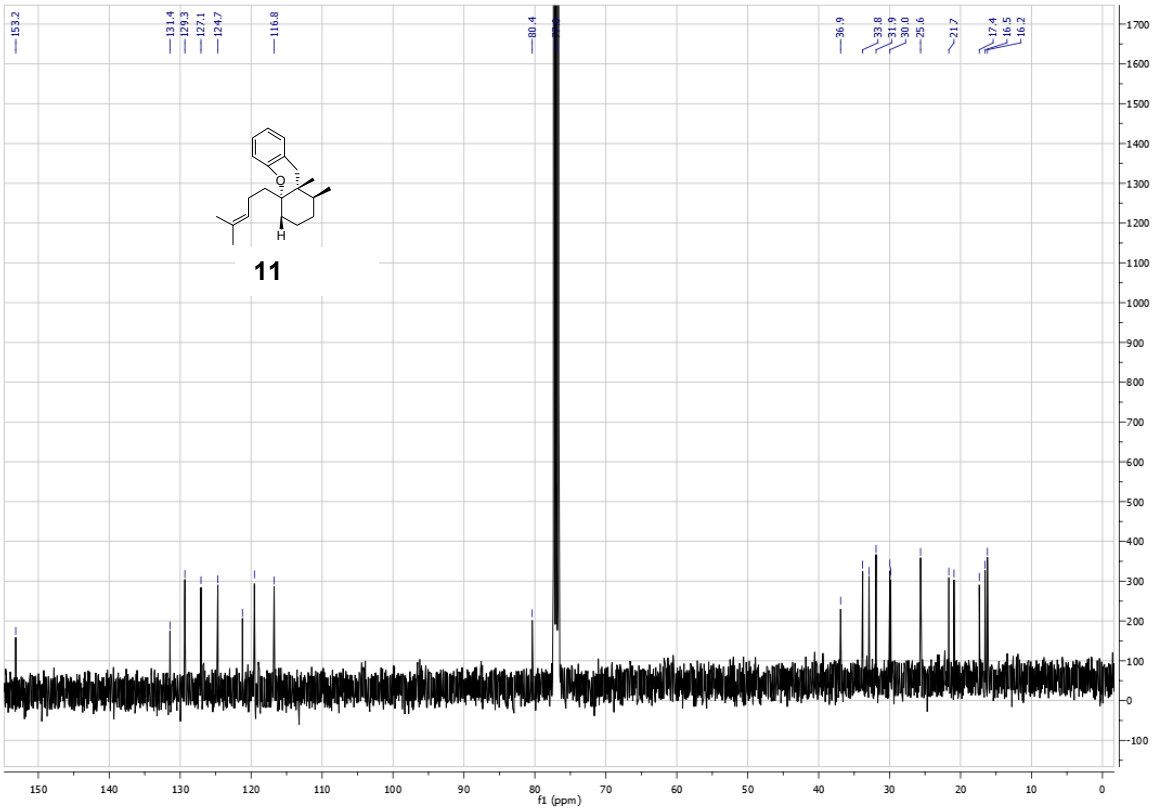

HO
3
1.97
2.04
0.95
0.68
0.97
1.00
1.00
4.99
1.92
1.14
2.86
2.88
1.16
3.03
3.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

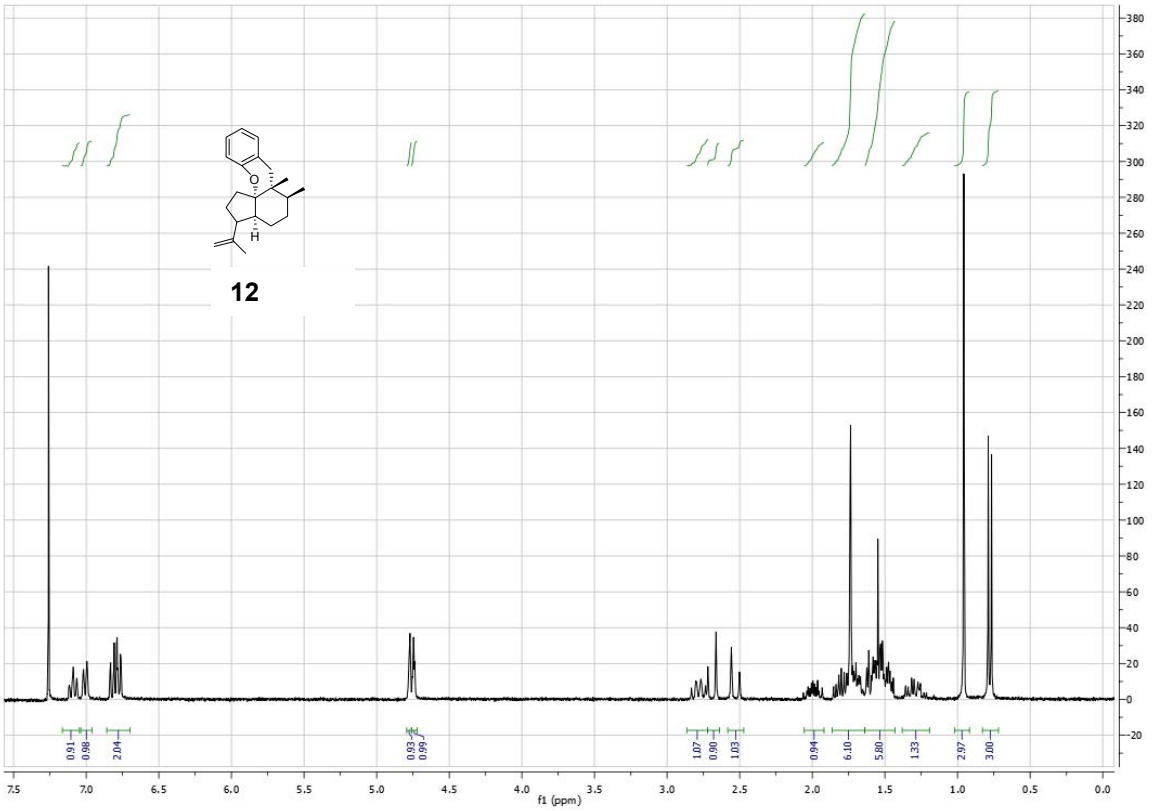

154.6
143.3
132.2
131.3
127.3
124.5
122.4
120.3
115.8
41.7
40.9
35.7
31.9
27.6
25.7
17.6
15.8
HO
3
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

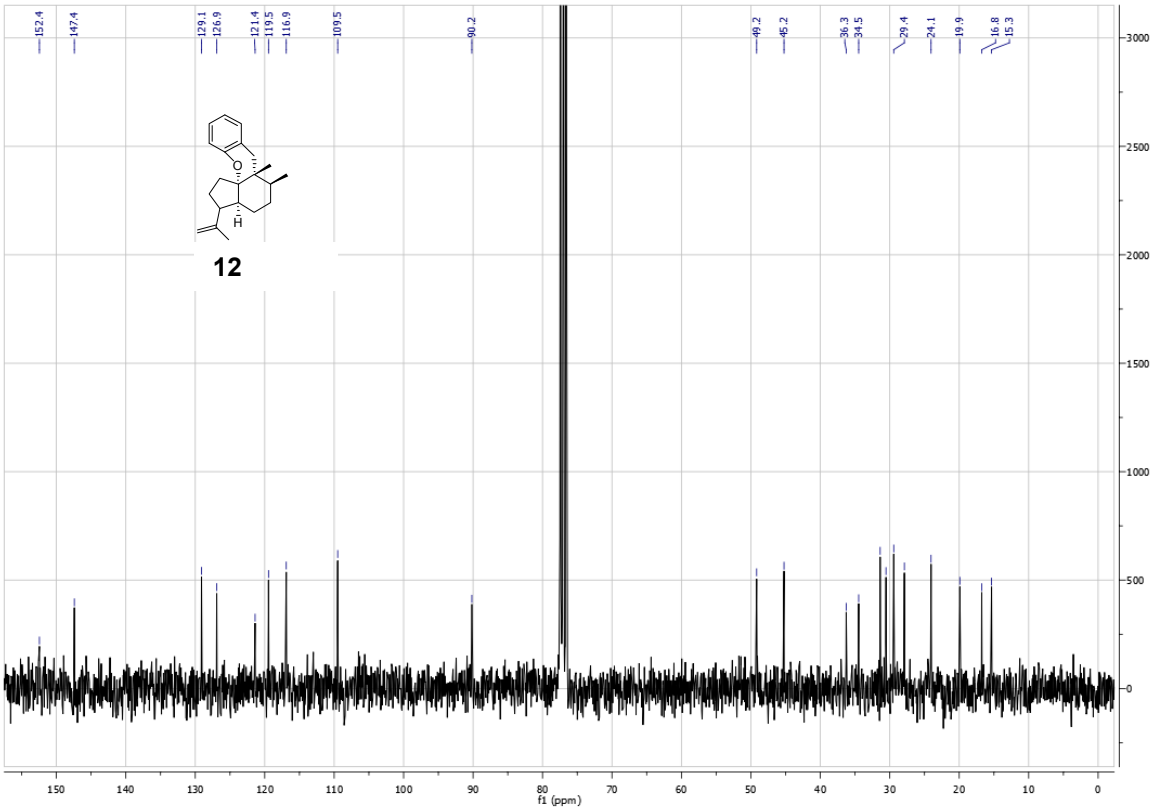

trans-1
f1 (ppm)


trans-1
f1 (ppm)


7.26
11
1.00
1.08
2.04
0.85
1.96
2.62
2.36
3.53
2.94
4.03
3.53
3.74
f1 (ppm)


153.2
131.4
129.3
127.1
124.7
116.8
80.4
36.9
33.8
31.9
30.0
25.6
21.7
17.4
16.5
16.2
11
f1 (ppm)


12
0.91
0.88
2.04
0.93
0.99
1.07
0.90
1.03
0.94
6.10
5.80
1.33
2.97
3.00
f1 (ppm)


12
152.4
147.4
129.1
126.9
121.4
119.5
116.9
109.5
90.2
49.2
45.2
36.3
34.5
29.4
24.1
19.9
16.8
15.3
f1 (ppm)