Enantioselective Total Syntheses of the Proposed Structures of Prevezol B and Evaluation for Anti-Cancer Activity.

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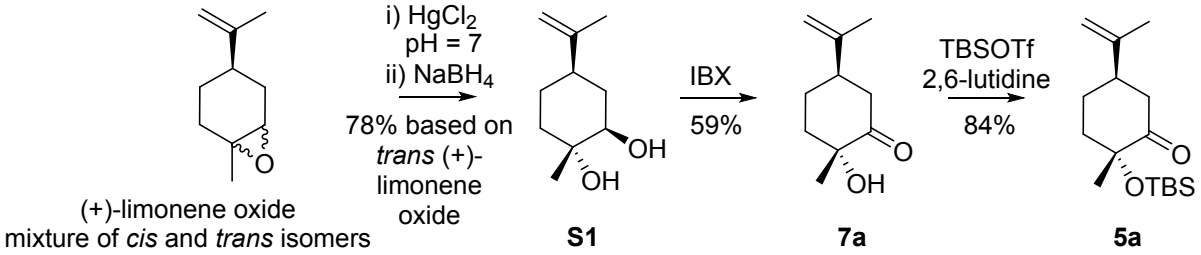
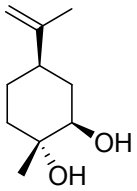


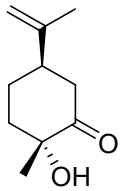
Scheme S1

(1R,2R,4R)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol ***S1***.



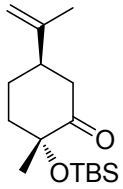
To a solution of $HgCl_2$ (125 mL, 67 mM in 330 mM tris buffer, pH 7) was added (+)-limonene oxide (mixture of *cis*/*trans*, 1.86 g, 12.22 mmol). The mixture was stirred at rt for 1 h, then extracted with hexane (3 × 40 mL) to remove unreacted *cis*-(+)-limonene oxide (1.08 g, 58% based on initial *cis*- and *trans*-(+)-limonene oxide). The aqueous phase was treated slowly with $NaBH_4$ (1.61 g, 42.56 mmol) and stirred at rt for 3 h, then extracted with EtOAc (3 × 40 mL). The organic extracts were dried and concentrated to provide the crude title compound as a white solid. Flash column chromatography (50% EtOAc in hexane) provided the diastereomerically pure title compound (676 mg, 78% based on initial *trans*-(+)-limonene oxide). **Mp** 71-73 °C. $[\alpha]_D^{20} = -6.6$ (c 1.099, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.21 (d, *J* = 0.5 Hz, 3 H), 1.24-1.36 (complex, 2 H), 1.49 (m, 1 H), 1.67-1.73 (complex, 4 H), 1.80 (dt, *J* = 12.8, 3.3 Hz, 1 H), 1.93 (m, 1 H), 2.08 (tt, *J* = 12.3, 3.6 Hz, 1 H), 3.58 (dd, *J* = 11.8, 4.5 Hz, 1 H), 4.72 (m, 2 H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 19.1, 21.1, 28.3, 36.2, 38.7, 43.8, 74.1, 77.4, 109.2, 148.6. **MS** (ESI+) 193.2 (100%). **IR** (ATR, solid) ν_{max} 3336 (s), 3075 (w), 2935 (s), 2863 (m), 1644 (m), 1438 (m), 1368 (m), 1340 (m), 1137 (s), 1077 (s), 880 (s).

(2R,5R)-2-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexanone ***7a***.



To a solution of (1*R*,2*R*,4*R*)-1-methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol **S1** (676 mg, 3.97 mmol) in EtOAc (40 mL) was added IBX (2.88 g, 10.29 mmol). The heterogeneous mixture was heated to reflux for 15 h, then cooled and filtered. The residue was washed with EtOAc (40 mL), and the combined organic extracts were dried and concentrated to afford the crude title compound as a yellow oil. Flash column chromatography (15% EtOAc in hexane) provided the pure title compound as a clear oil (393 mg, 59%). $[\alpha]_D^{20}$ = +100.4 (c 1.034, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.42 (s, 3 H), 1.62-1.76 (complex, 5 H), 1.91 (m, 1 H), 2.18 (m, 1 H), 2.36 (m, 1 H), 2.50-2.60 (complex, 2 H), 3.94 (br s, 1 H), 4.76 (s, 1 H), 4.80 (t, *J* = 1.3 Hz, 1 H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 20.6, 25.2, 28.5, 40.8, 42.5, 47.2, 76.2, 110.4, 146.9, 213.9. **MS** (ESI+) 191.2 (100%). **IR** (ATR, neat) ν_{max} 3481(m), 3081 (w), 2938 (m), 2864 (m), 1710 (s), 1646 (m), 1452 (m), 1373 (m), 1244 (m), 1197 (m), 1136 (s), 1068 (w), 988 (m), 940 (w), 891 (s) cm^{-1}.

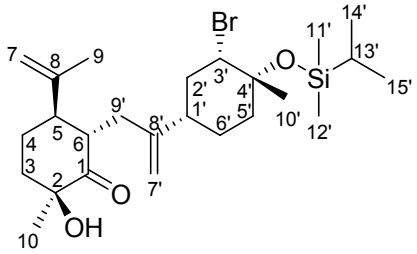
(2R,5R)-2-((tert-Butyldimethylsilyl)oxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone ***5a***.



To a −78 °C solution of (2*R*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexanone **7a** (393 mg, 2.34 mmol) in dry DCM (50 mL) was added 2,6-lutidine (1.05 mL, 9.07 mmol) and TBSOTf (1.05 mL, 4.57 mmol). The reaction mixture was allowed to warm to rt whilst stirring for 15 h, then quenched with 1 M HCl (50 mL), washed with brine (3 × 40 mL), dried

and concentrated to provide the crude title compound as an orange oil. Flash column chromatography (2% EtOAc in hexane) provided the pure title compound as a clear oil (557 mg, 84%). $[\alpha]_D^{20}$ = +34.5 (c 0.772, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.09 (s, 3H), 0.13 (s, 3H), 0.88 (s, 9H), 1.37 (s, 3H), 160-1.71 (m, 1H), 1.73-1.83 (complex, 4H), 1.90-1.99 (complex, 2H), 2.42-2.58 (complex, 3H), 4.73 (s, 1H), 4.79 (t, *J* = 1.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ −2.5, −2.2, 18.5, 21.1, 25.7, 26.1, 27.3, 41.1, 43.5, 45.7, 79.2, 110.6, 147.0, 211.2. **MS** (ESI+) 305.2 (80%). **IR** (ATR, neat) ν_{max} 2932 (m), 2856 (m), 1727 (s), 1647 (w), 1371 (w), 1249 (m), 1206 (m), 1174 (m), 1141 (s), 1053 (s), 1007 (w), 893 (m), 776 (s).

(2S,5R,6S)-6-(2-((1S,3S,4R)-3-Bromo-4-((isopropyldimethylsilyl)oxy)-4-methylcyclohexyl)allyl)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexanone ***(17)***.



To a solution of the mixture of (2*S*,5*R*,6*S*)-6-(2-((1*S*,3*S*,4*R*)-3-bromo-4-((isopropyldimethylsilyl)oxy)-4-methylcyclohexyl)allyl)-2-((*tert*-butyldimethylsilyl)oxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone[1] and (2*S*,5*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone[1] (45 mg, 88% purity w/w of diterpene, 64 μmol) in dry THF (2 mL) was added a solution of TBAF (1.0 M in THF, 80 μL, 80 μmol). The reaction mixture was stirred at rt for 5 min, then filtered through a silica plug, dried and concentrated to afford the crude title compound. Flash column chromatography (DCM) provided the pure title compound as a white solid (27 mg, 85%). $[\alpha]_D^{20}$ = −7.3 (c 0.917,

$CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.11 (s, 3H, H11′ or H12′), 0.15 (s, 3H, H11′ or H12′), 0.76 (septet, *J* = 7.2 Hz, 1H, H13′), 0.98-1.01 (complex, 6H, H14′ and H15′), 1.33(s, 3H, H10), 1.36 (s, 3H, H10′), 1.41-1.72 (complex, 8H, H3a, H4a, H9, H5′a and H6′a), 1.86-2.34 (complex, 9H, H3b, H4b, H5, H1′, H2′, H5′b and H9′), 3.39 (dt, *J* = 10.4, 2.6 Hz, 1H, H6), 3.92 (dd, *J* =12.1, 3.9 Hz, 1H, H3′), 4.56 (s, 1H, H7′a), 4.73 (s, 2H, H7′b and H7a), 4.82 (s, 1H, H7b). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ -1.1 (C11′ or C12′), -0.8 (C11′ or C12′), 16.3 (C13′), 17.3 (C14′ or C15′), 17.4 (C14′ or C15′), 18.7 (C9), 24.6 (C10), 26.5 (C5′ or C6′), 26.7 (C5′ or C6′), 30.1 (C10′), 31.0 (C9′), 39.1 (C2′), 39.9 (C3 or C4), 40.5 (C3 or C4), 46.6 (C1′), 47.2 (C6), 54.1 (C5), 64.7 (C3′), 73.5 (C2), 76.3 (C4′), 107.5 (C7′), 113.0 (C7), 146.1 (C8), 151.6 (C8′), 212.8 (C1). **HRMS** (ESI+) *m*/*z* calculated for $C_{25}H_{43}{}^{81}BrNaO_3Si^+$ $[M+Na]^+$ as 523.2037; found: 523.2042. **IR** (ATR, $CHCl_3$ solution) ν_{max} 3485 (br, m), 3074 (w), 2933 (s), 2863 (s), 1713 (s), 1643 (w), 1450 (s), 1375 (s), 1250 (s), 1176 (s), 1140 (s), 1051 (s), 986 (m), 884 (s), 854 (m), 830 (m), 804 (m), 772 (s), 707 (w), 680 (w) cm^{-1}.

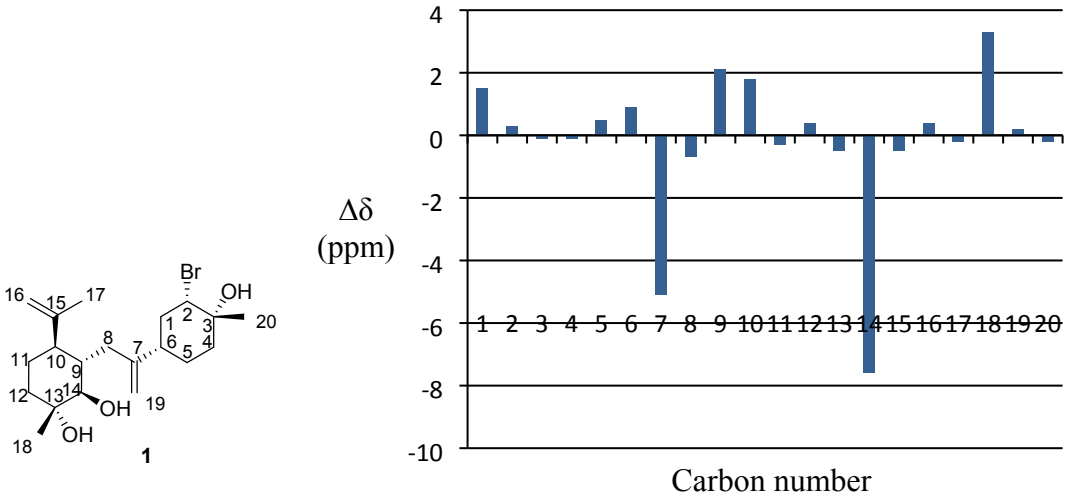
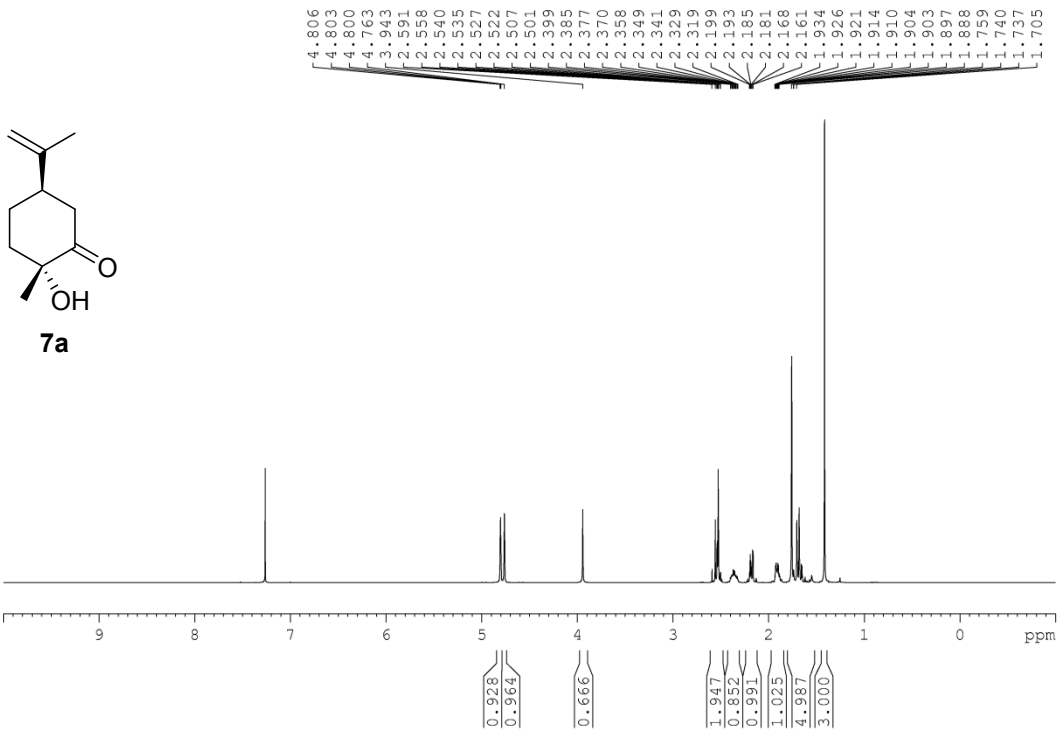
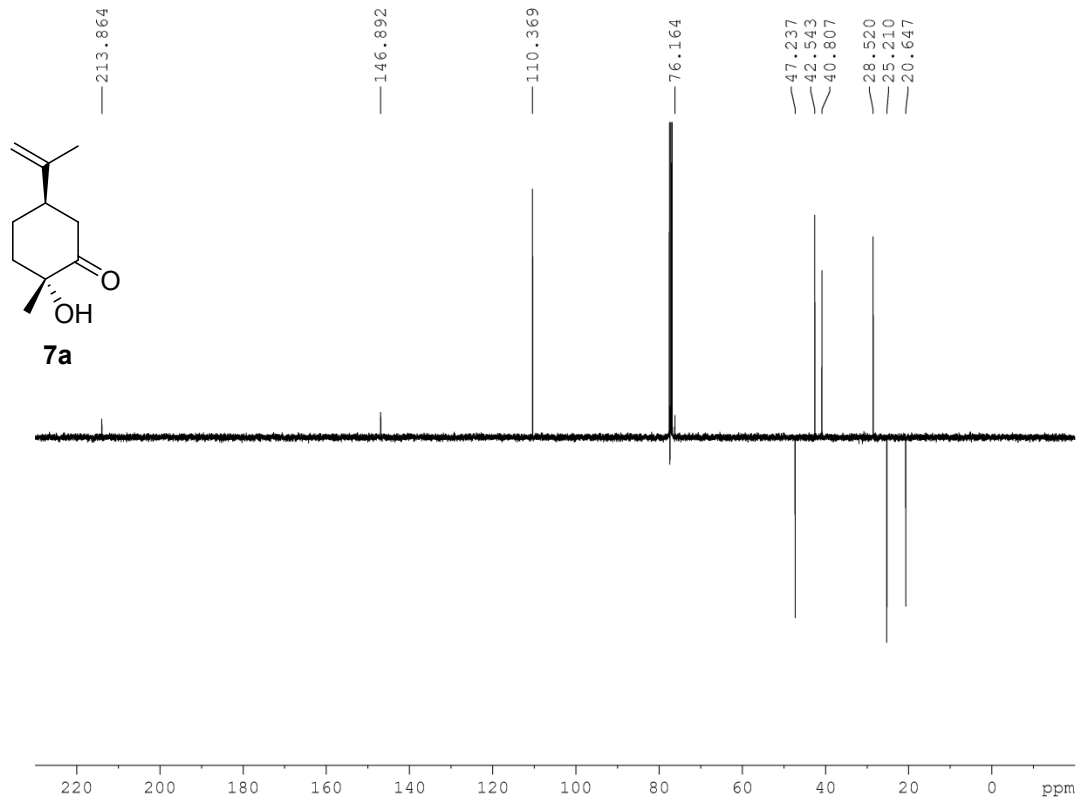


Figure S1: Comparison of the ^{13}C NMR spectroscopic signals of compound **1** and the natural product. Horizontal and vertical axes show carbon number and Δδ values. The numbering of carbon atoms is consistent with that of Roussis and co-workers.[2]

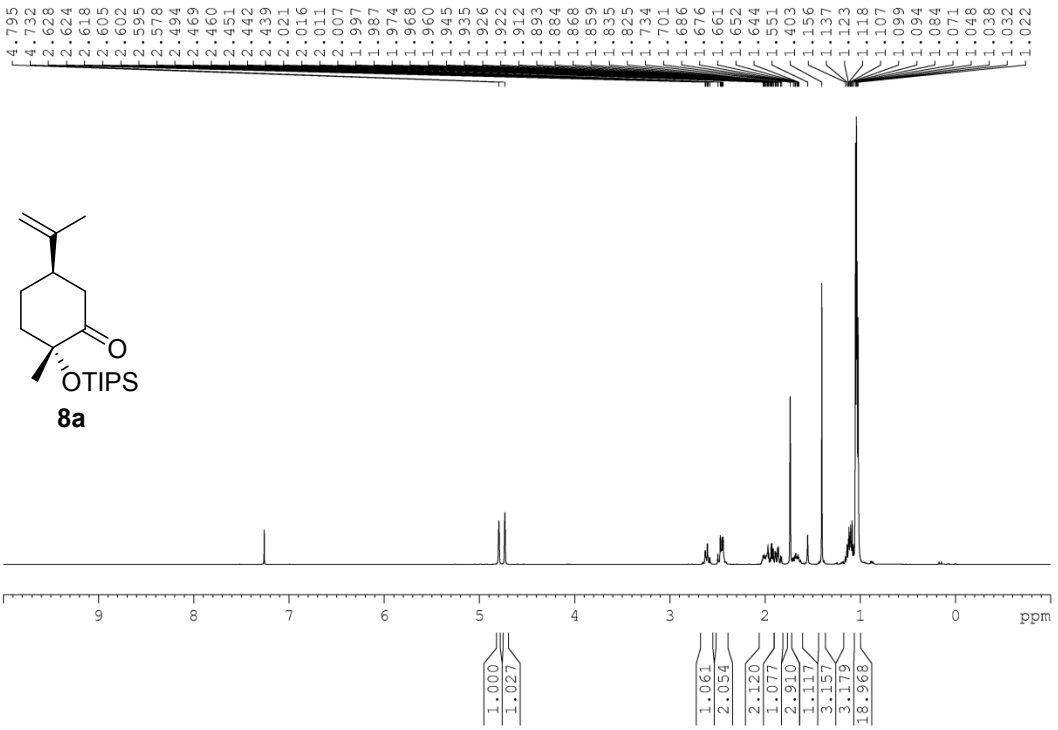
^{1}H NMR, 400 MHz, $CDCl_3$



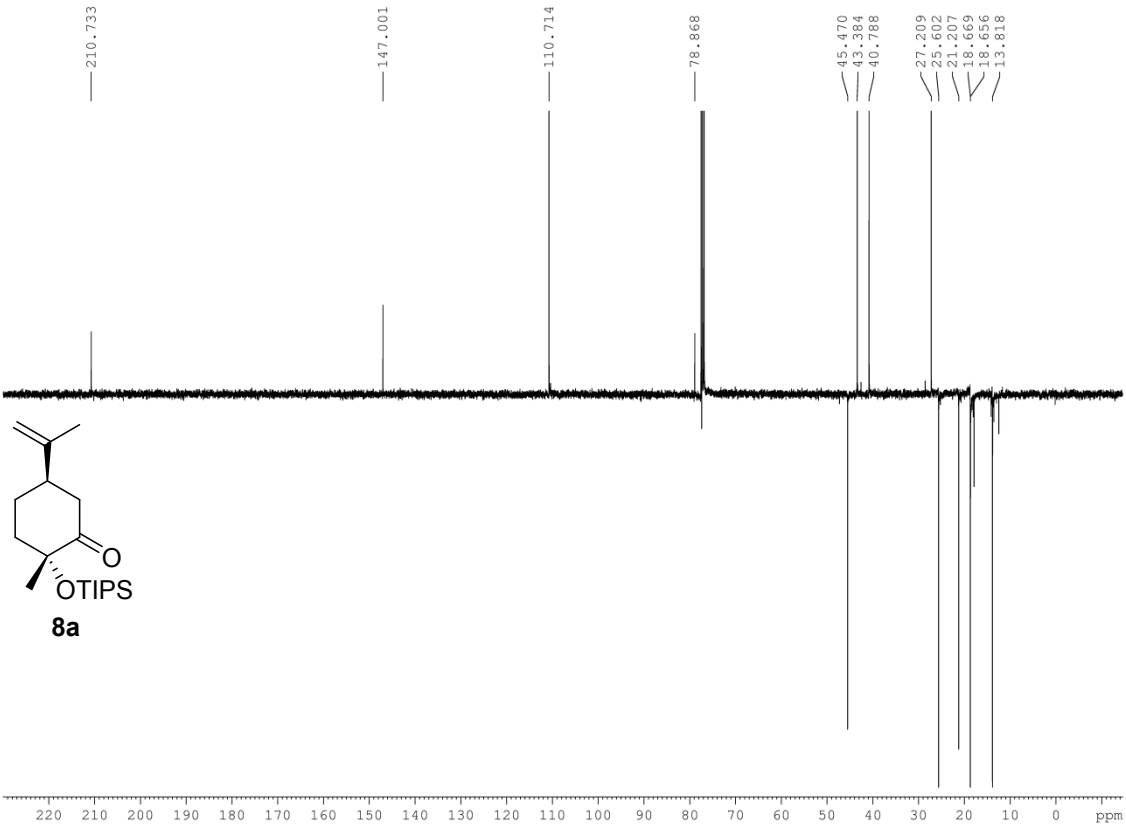
^{13}C NMR, 100 MHz, $CDCl_3$



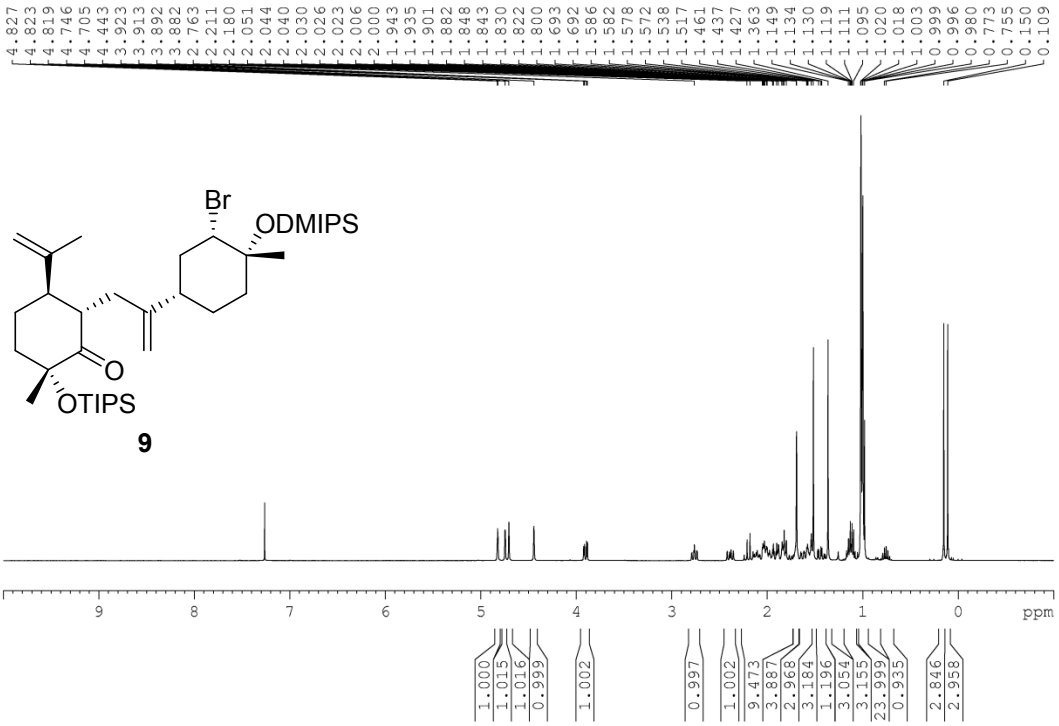
^{1}H NMR, 400 MHz, $CDCl_3$



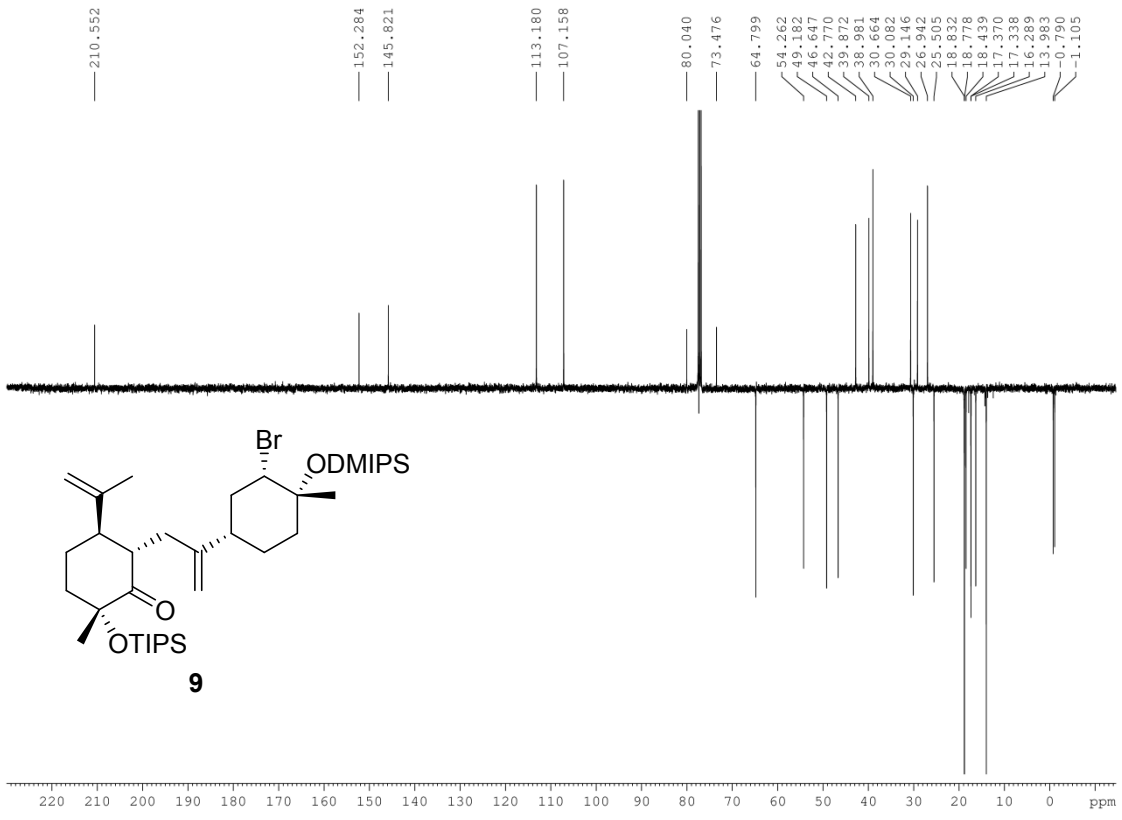
^{13}C NMR, 100 MHz, $CDCl_3$



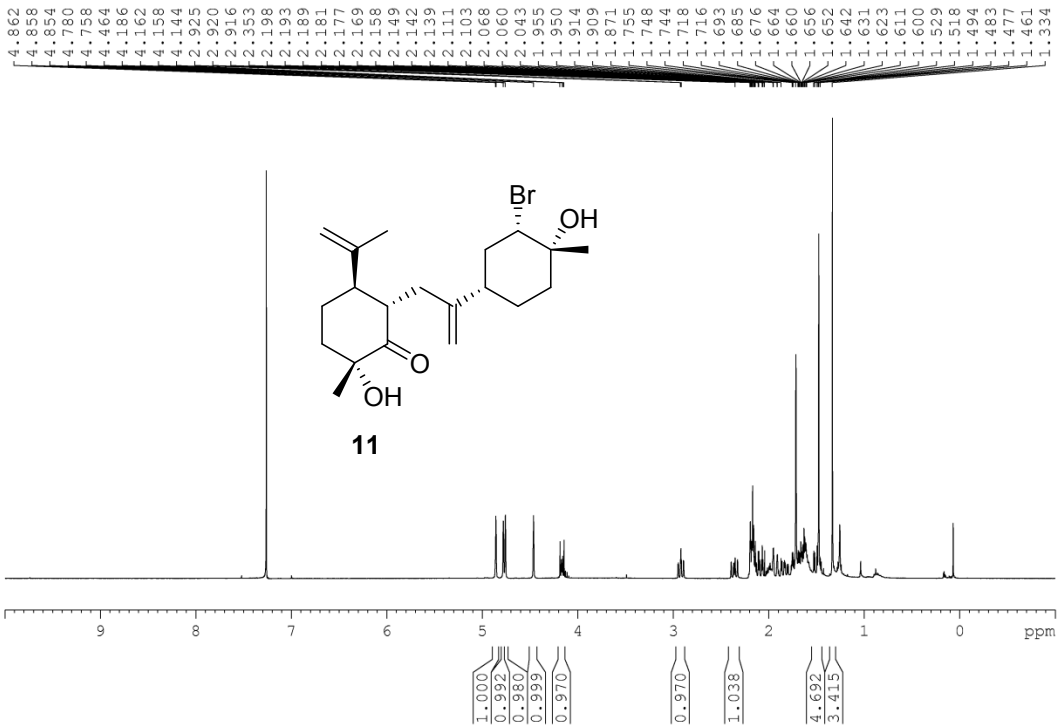
^{1}H NMR, 400 MHz, $CDCl_3$



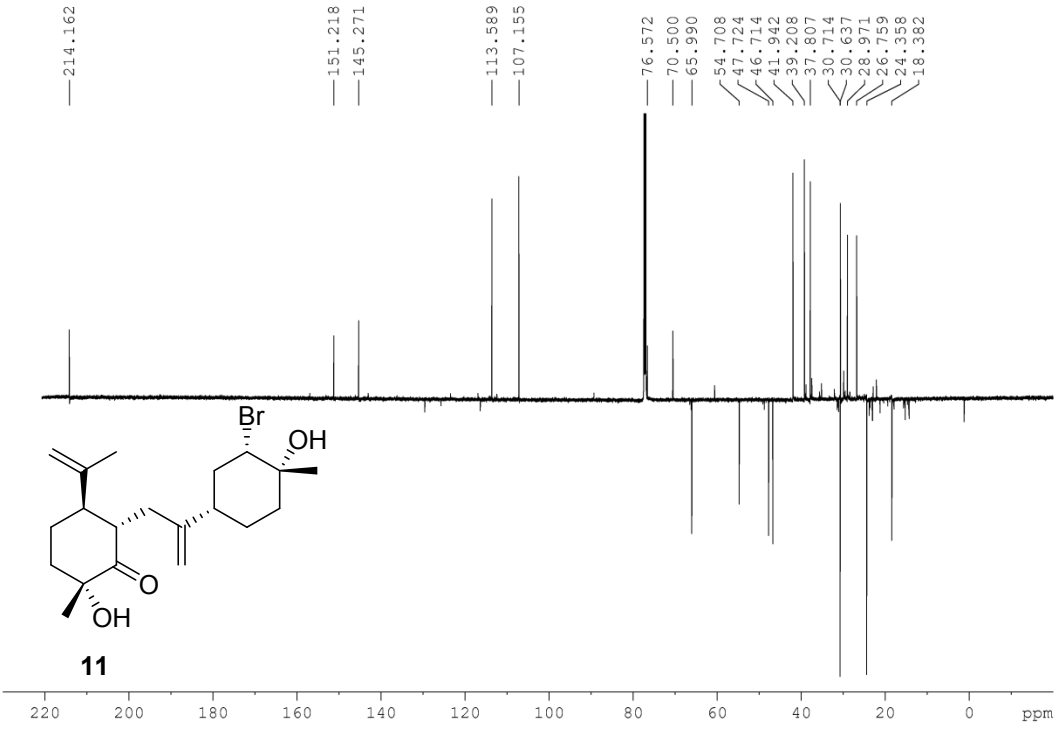
^{13}C NMR, 100 MHz, $CDCl_3$



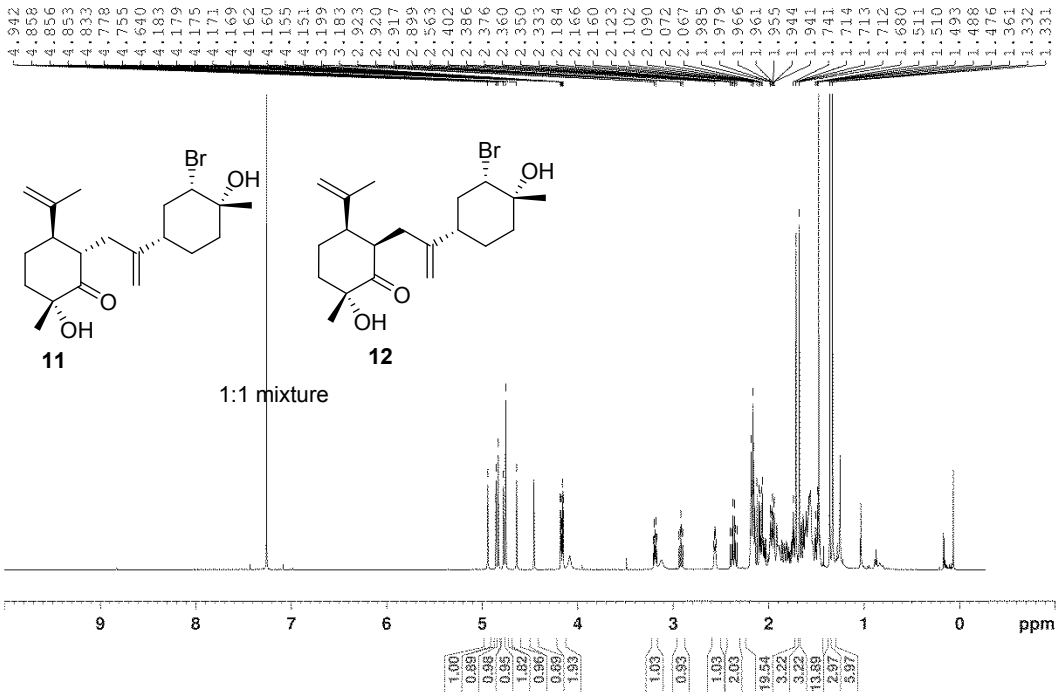
^{1}H NMR, 400 MHz, $CDCl_3$



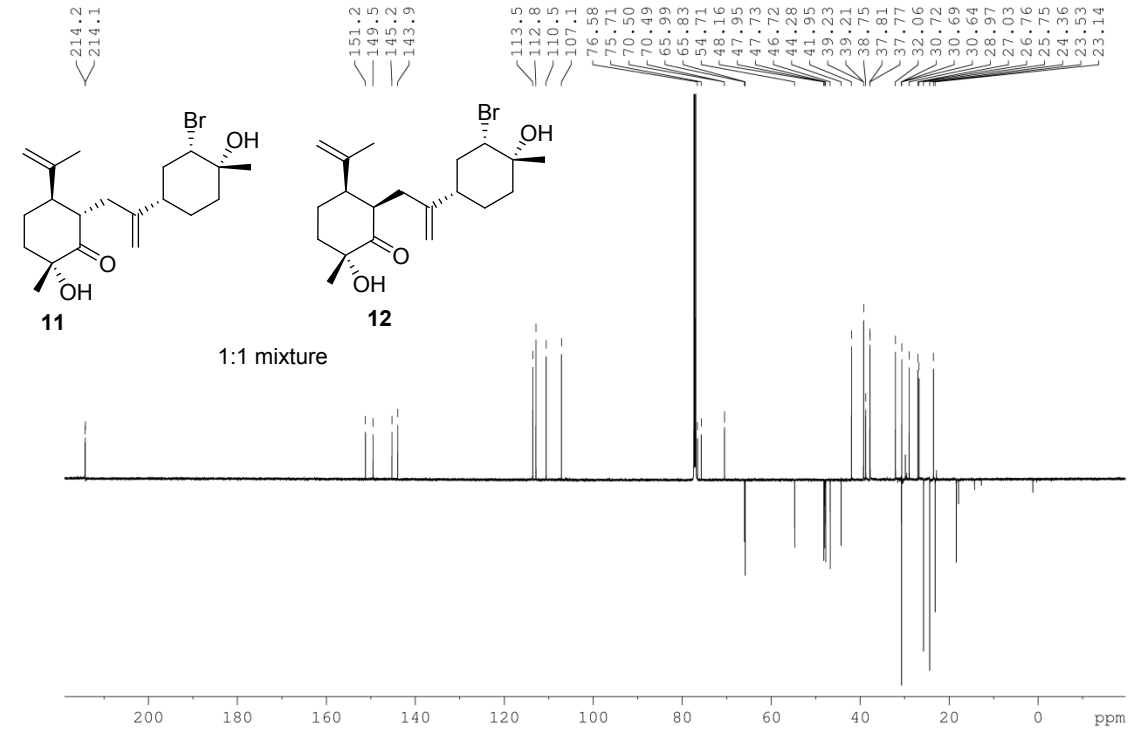
^{13}C NMR, 150 MHz, $CDCl_3$



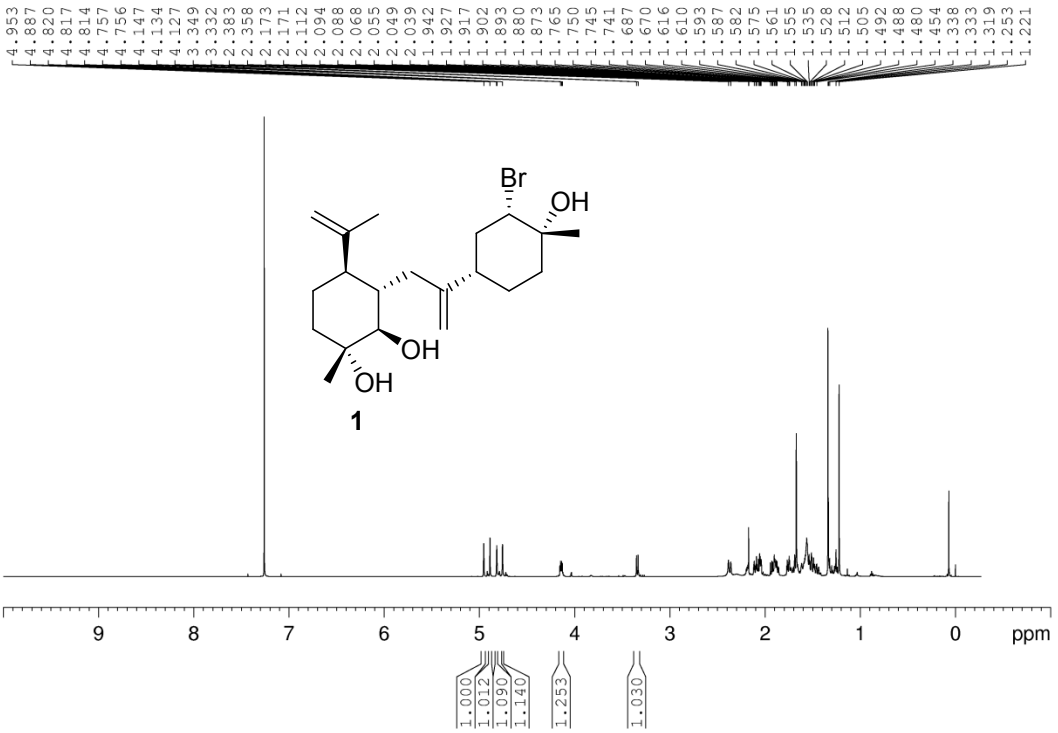
^{1}H NMR, 600 MHz, $CDCl_3$



^{13}C NMR, 150 MHz, $CDCl_3$



^{1}H NMR, 600 MHz, $CDCl_3$



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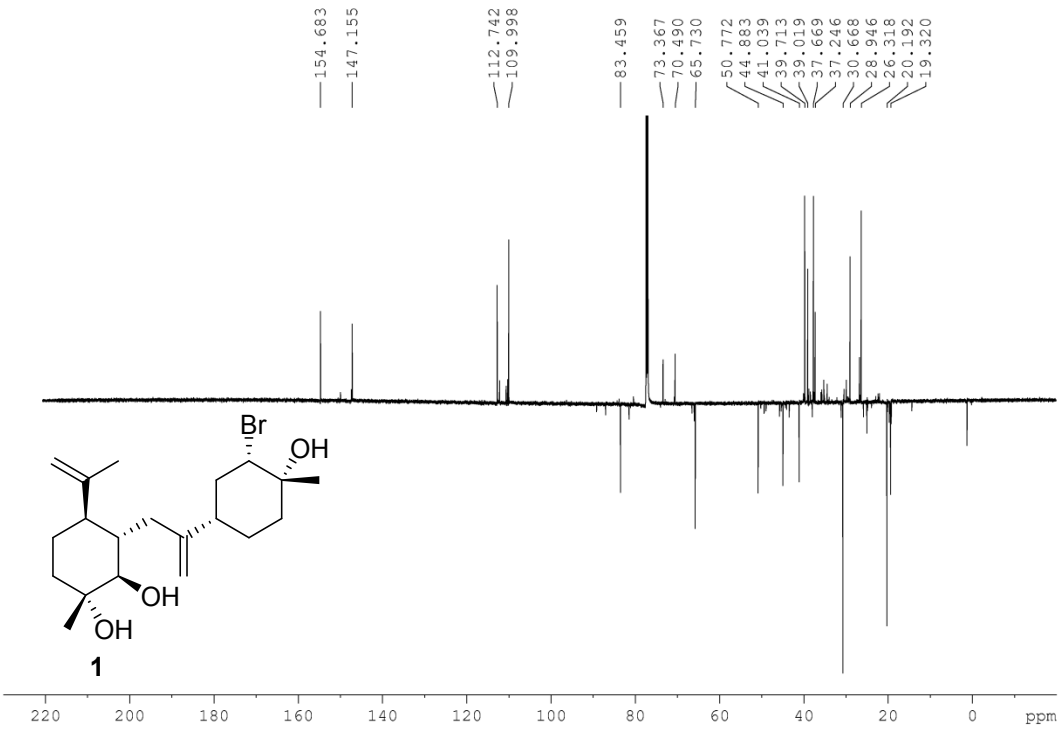
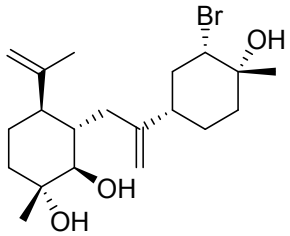


COSY, 600 MHz, $CDCl_3$



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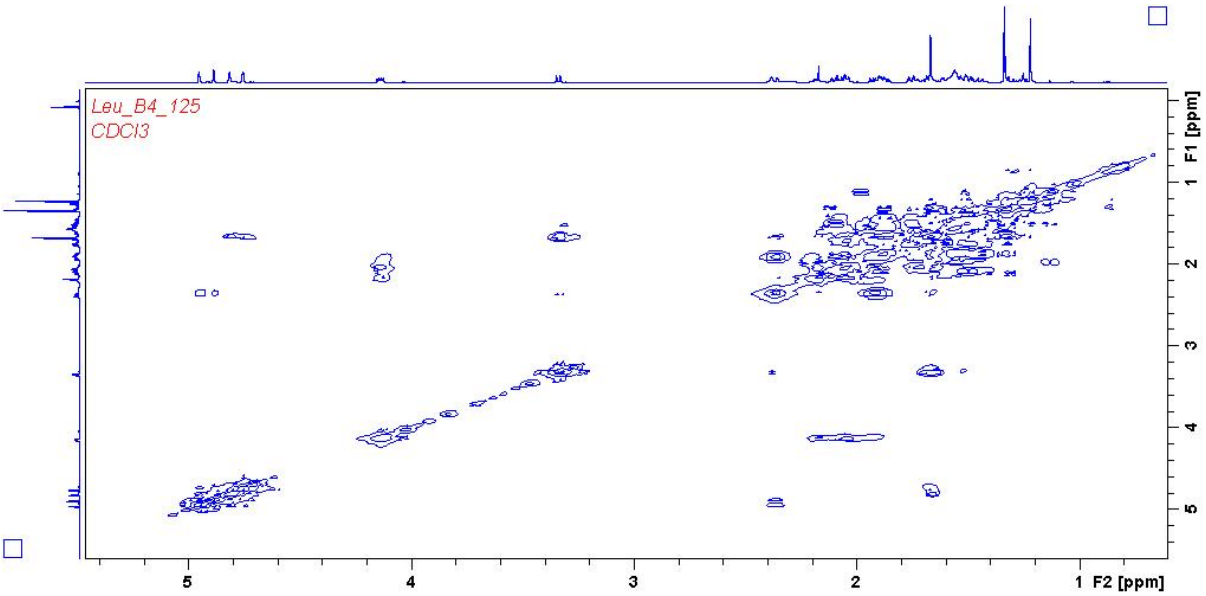
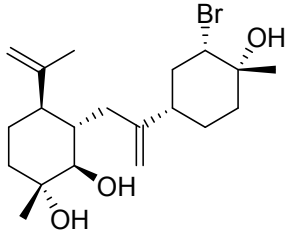


HSQC, 600 MHz, $CDCl_3$



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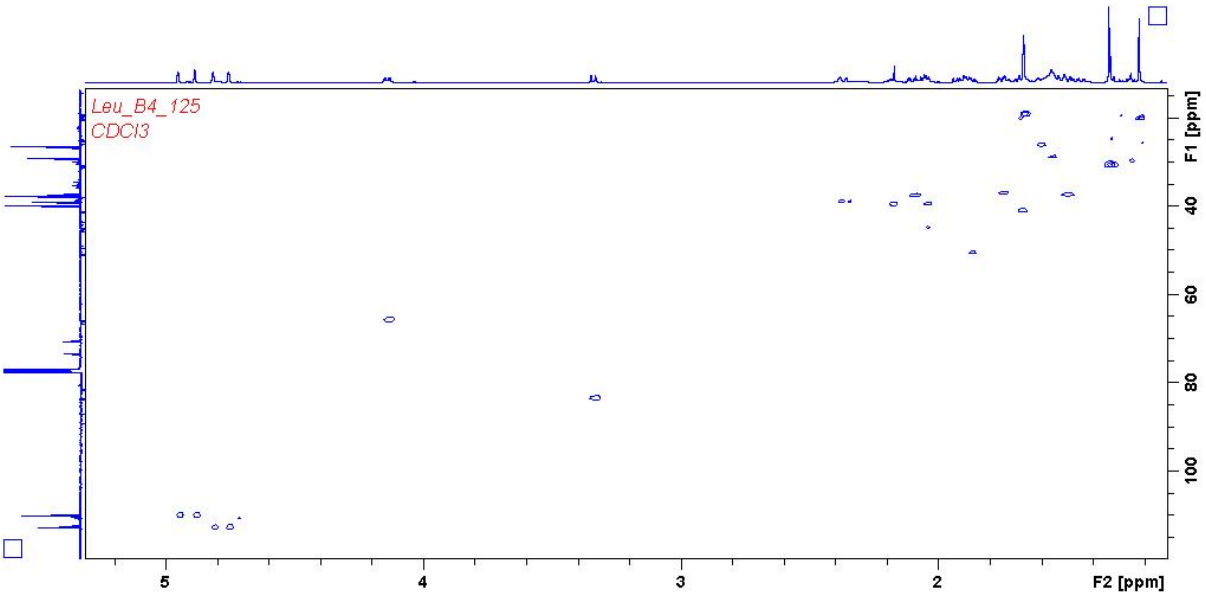

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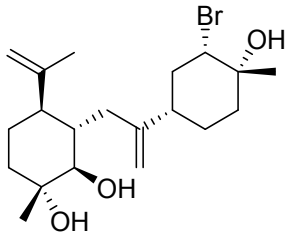

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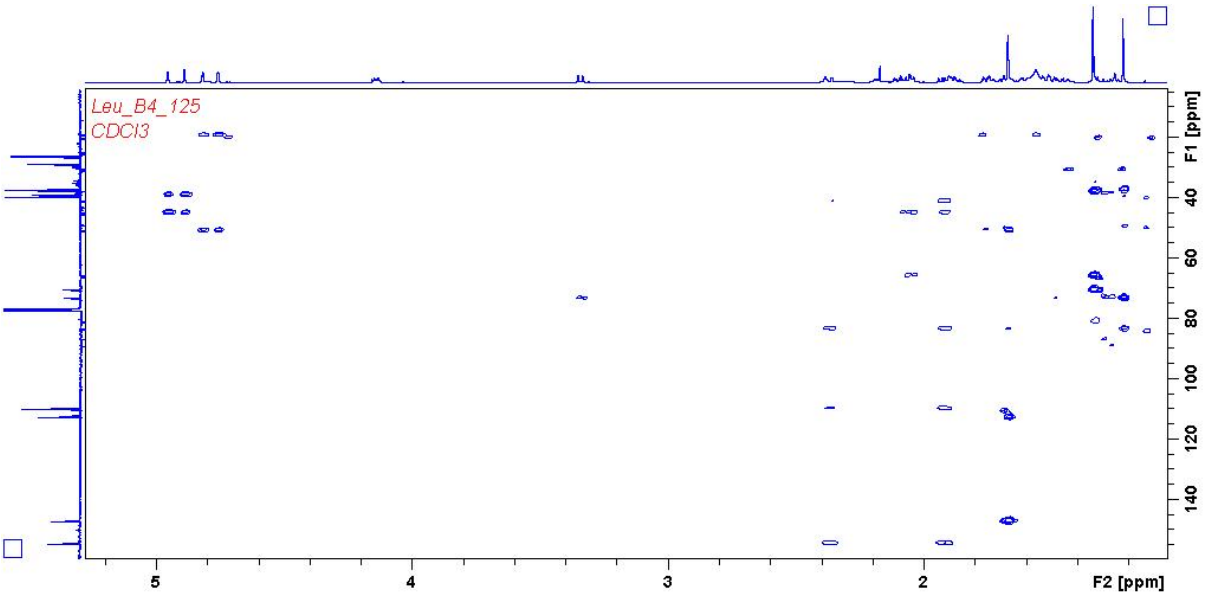
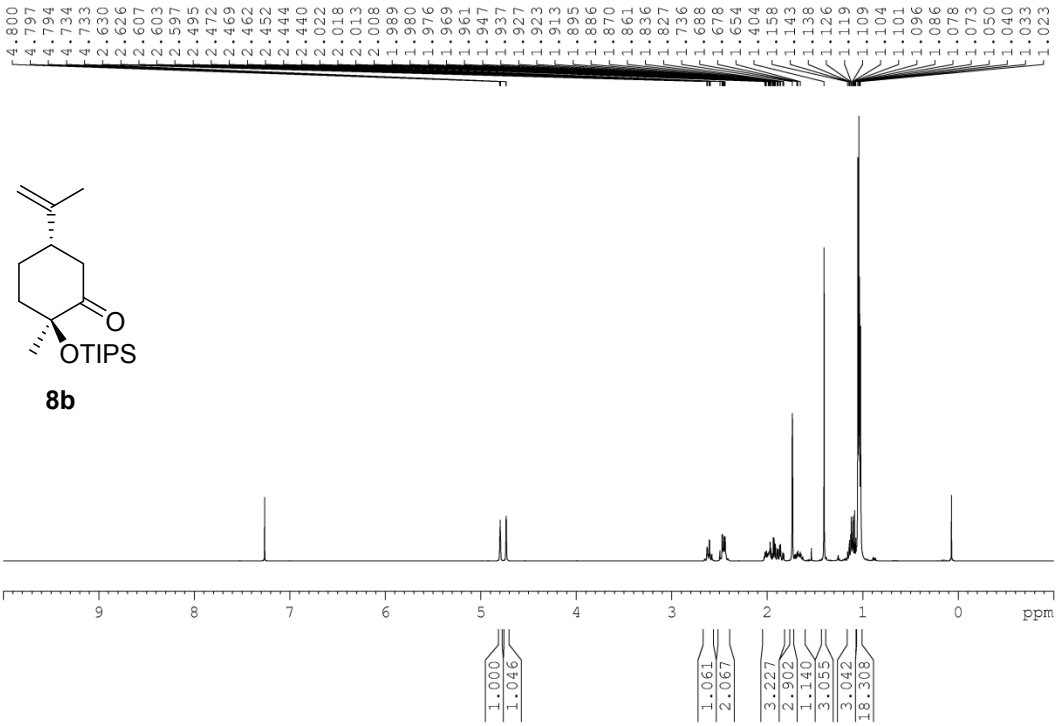


^{1}H NMR, 400 MHz, $CDCl_3$



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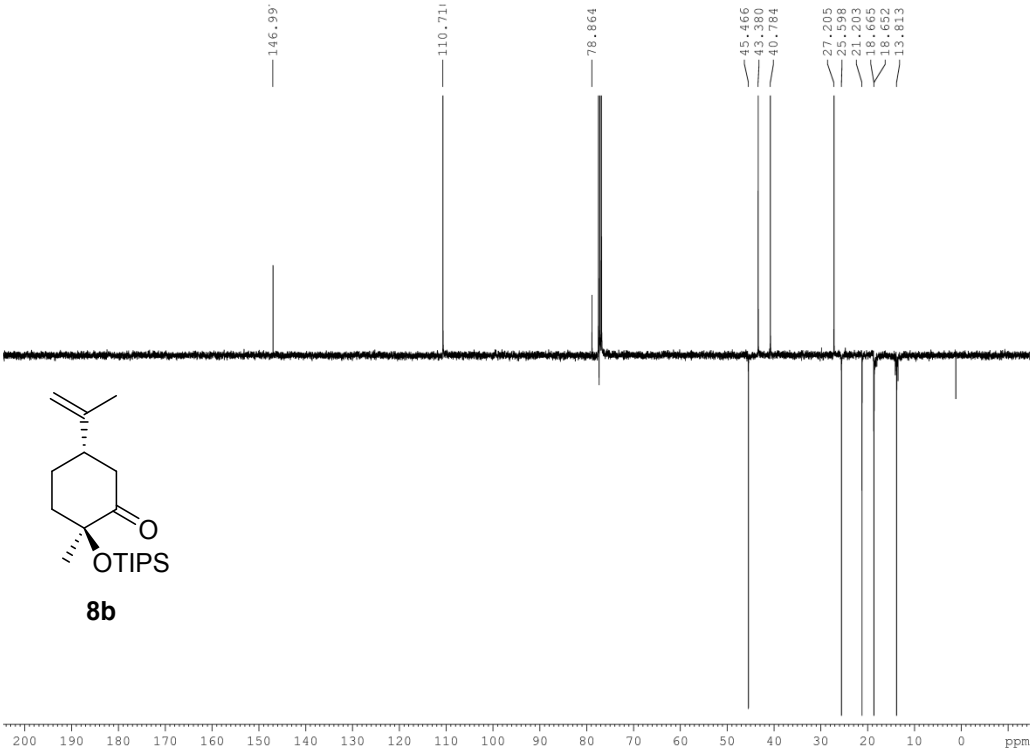

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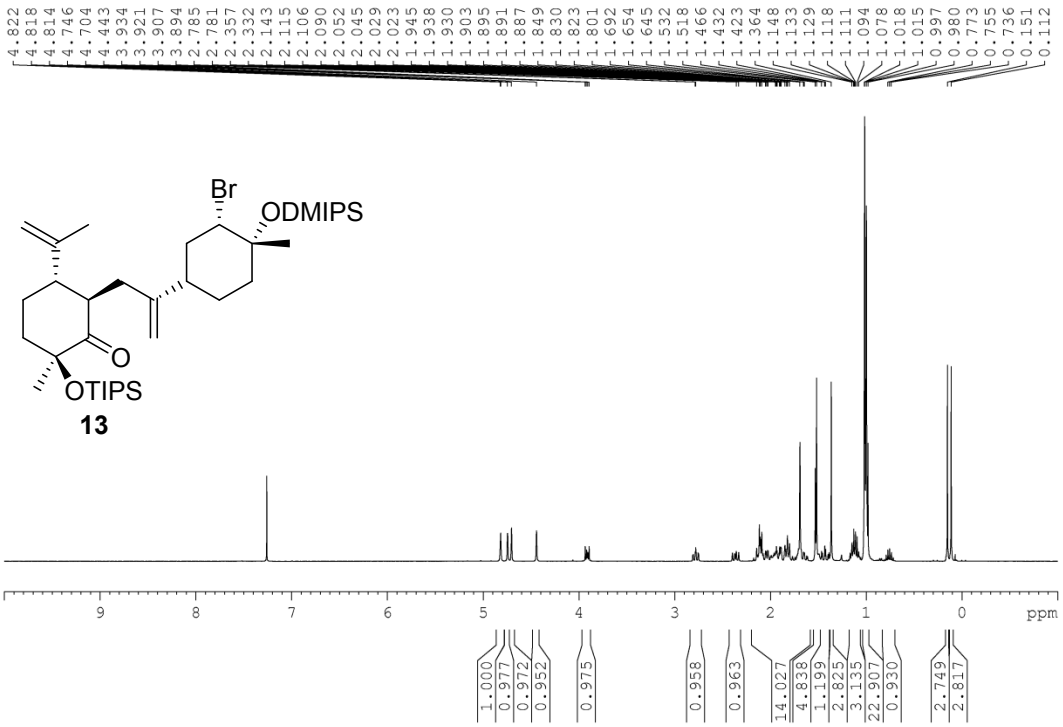
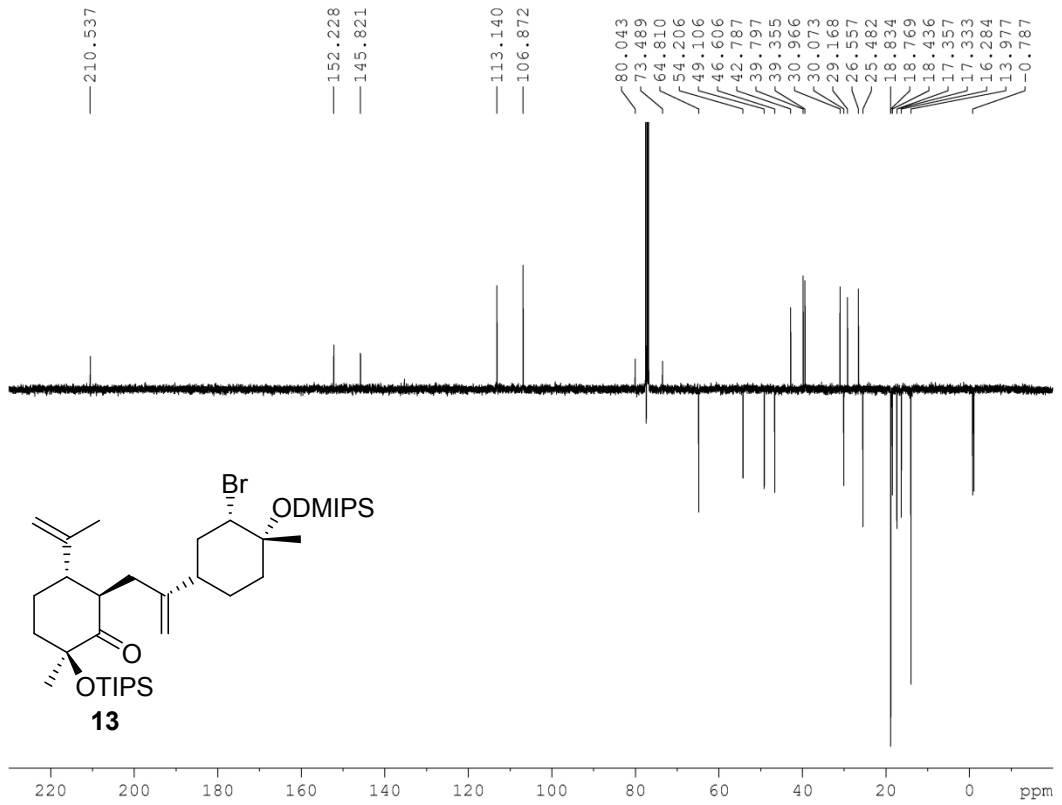


^{13}C NMR, 100 MHz, $CDCl_3$



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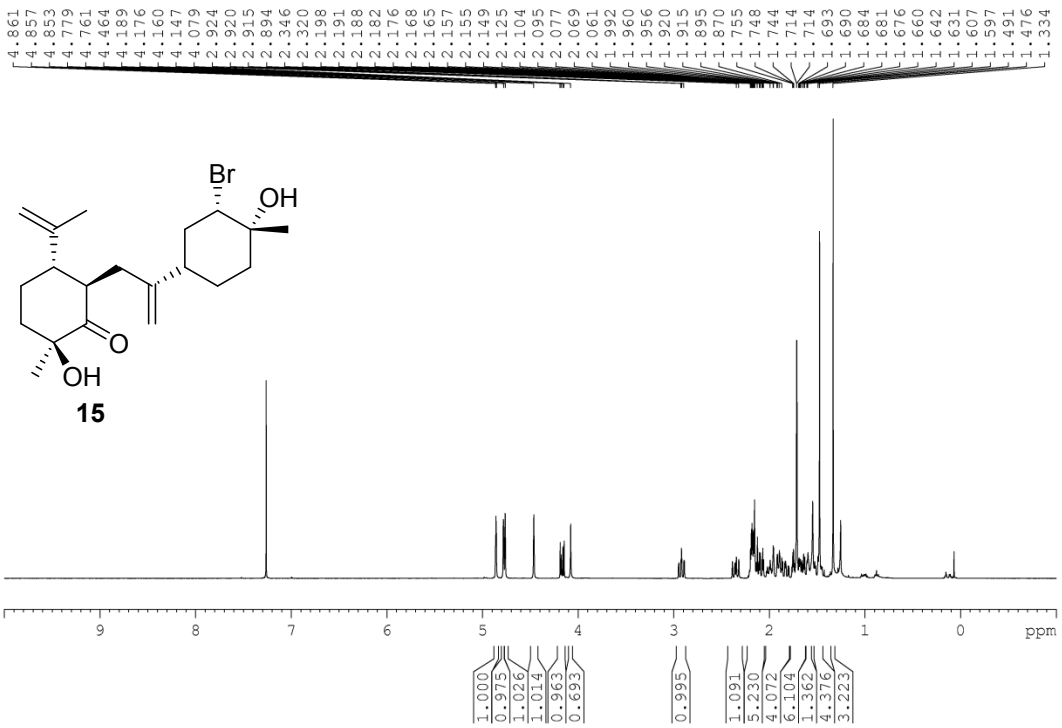

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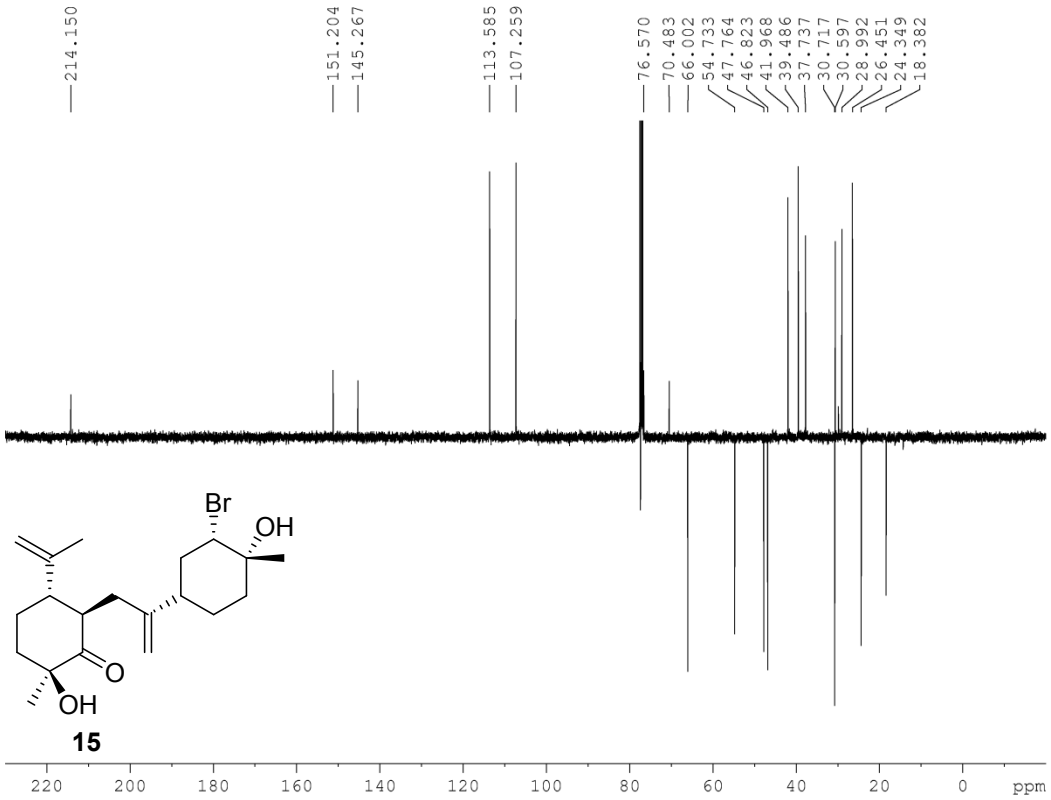

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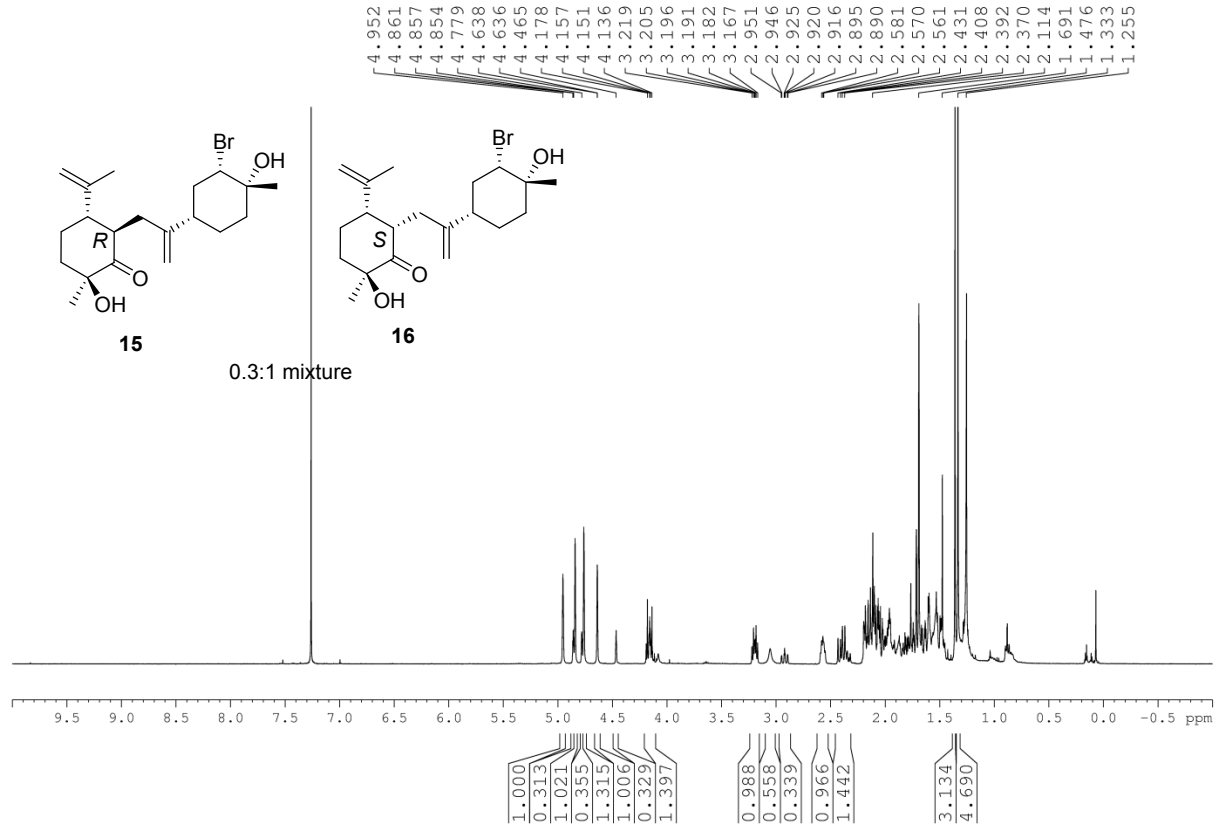

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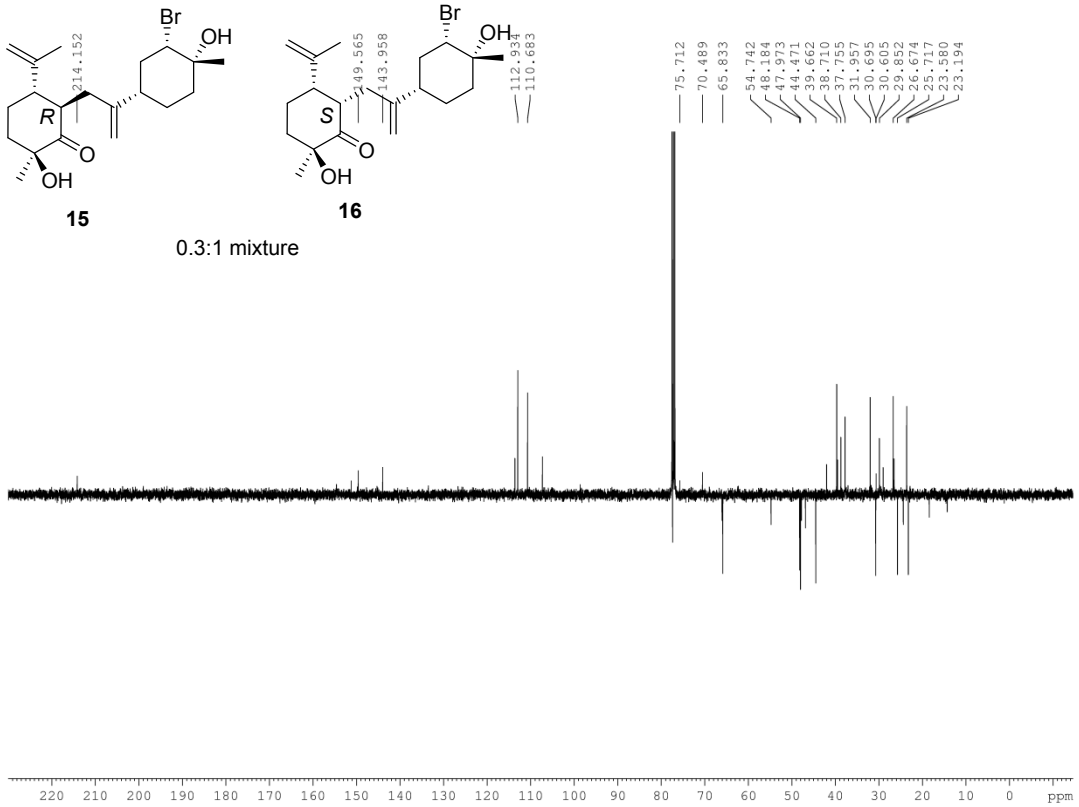

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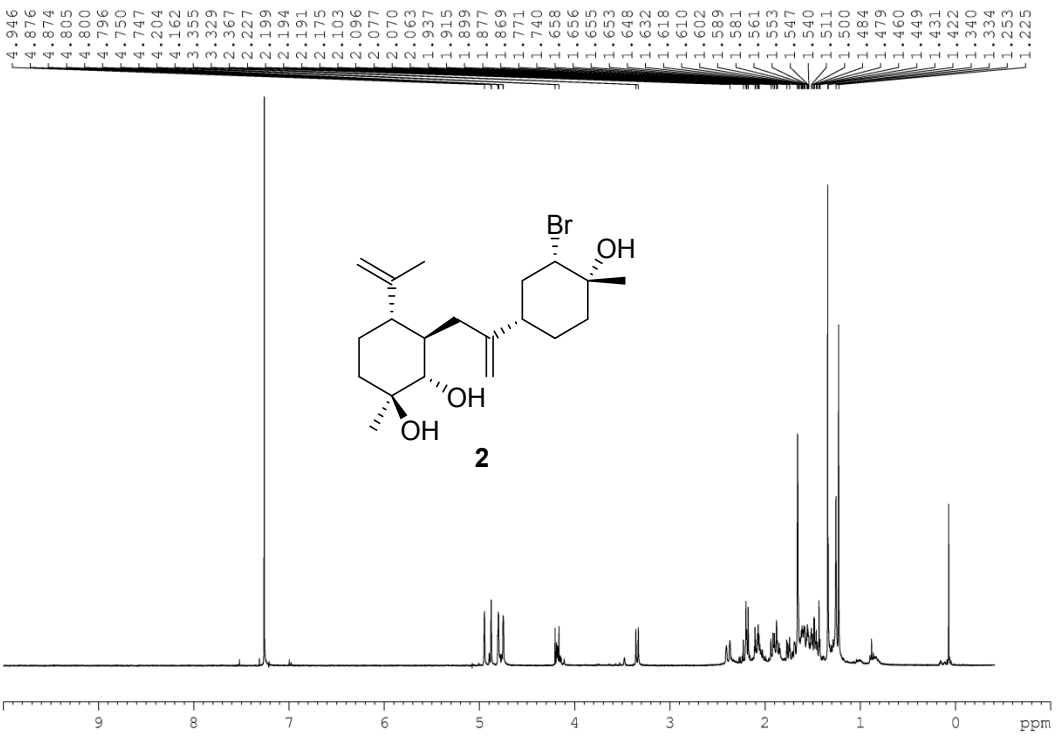

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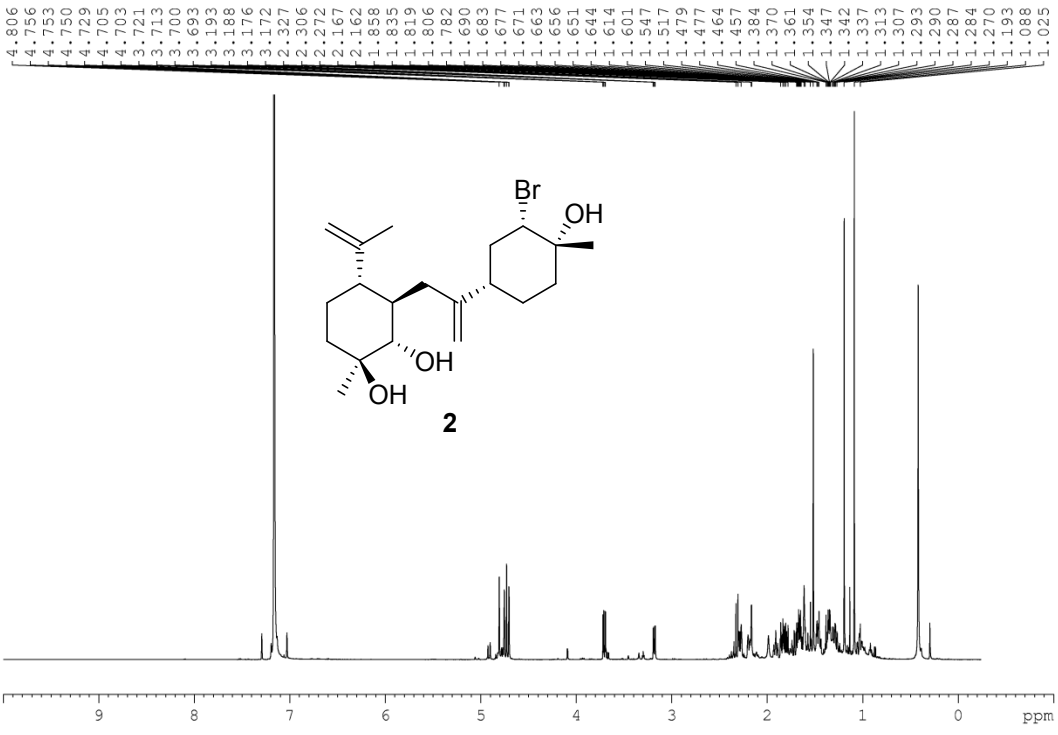

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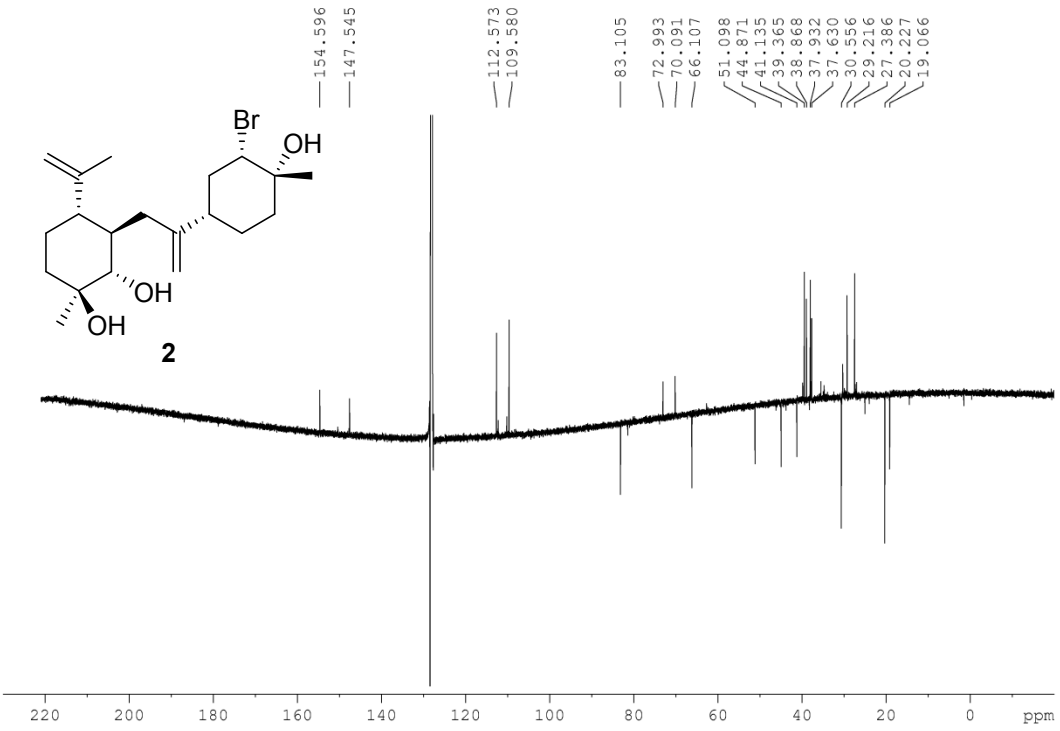
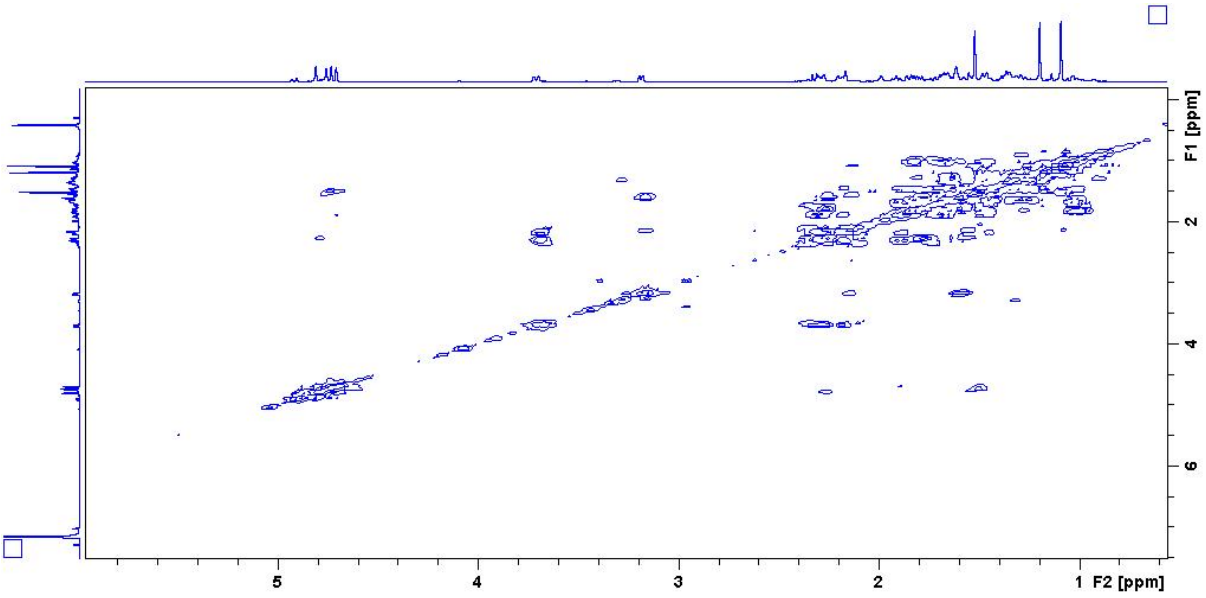
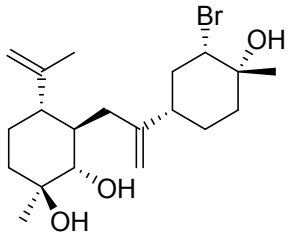


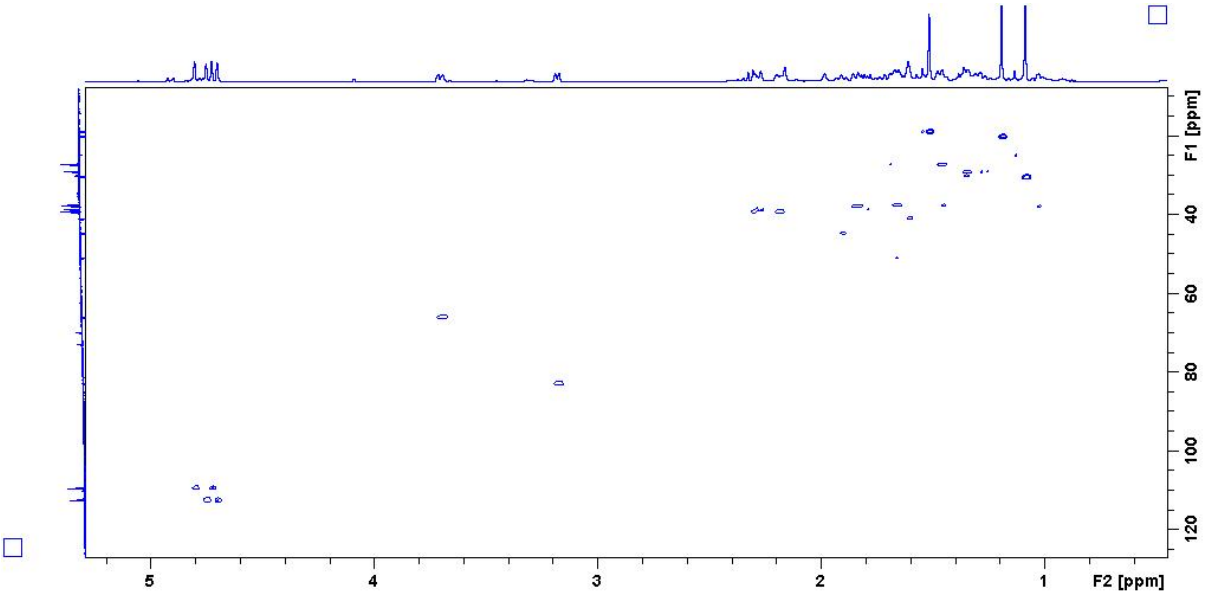
COSY, 600 MHz, $CDCl_3$



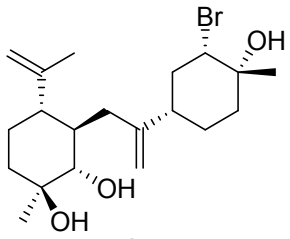
HSQC, 600 MHz, C_6D_6



2



HMBC, 600 MHz, C_6D_6



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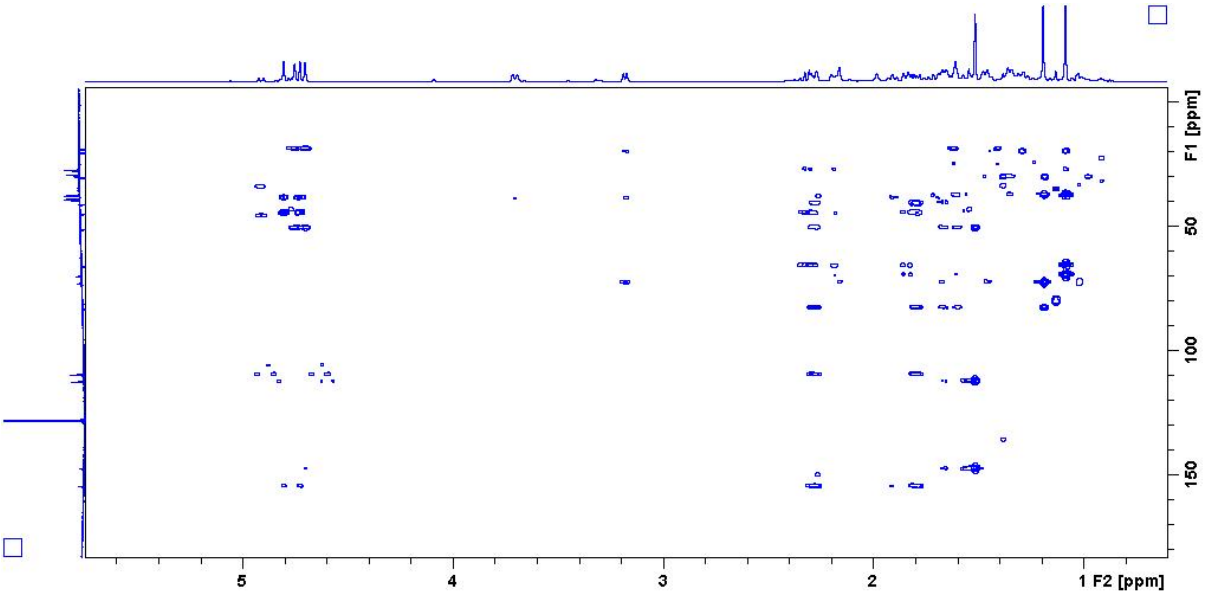
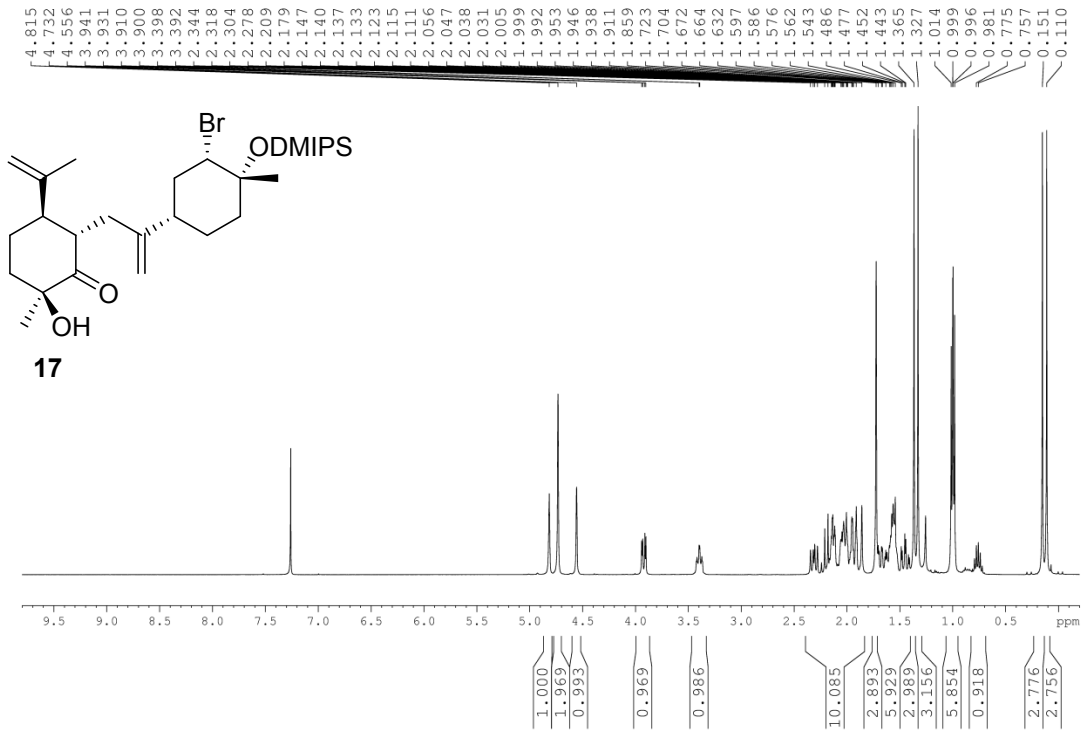
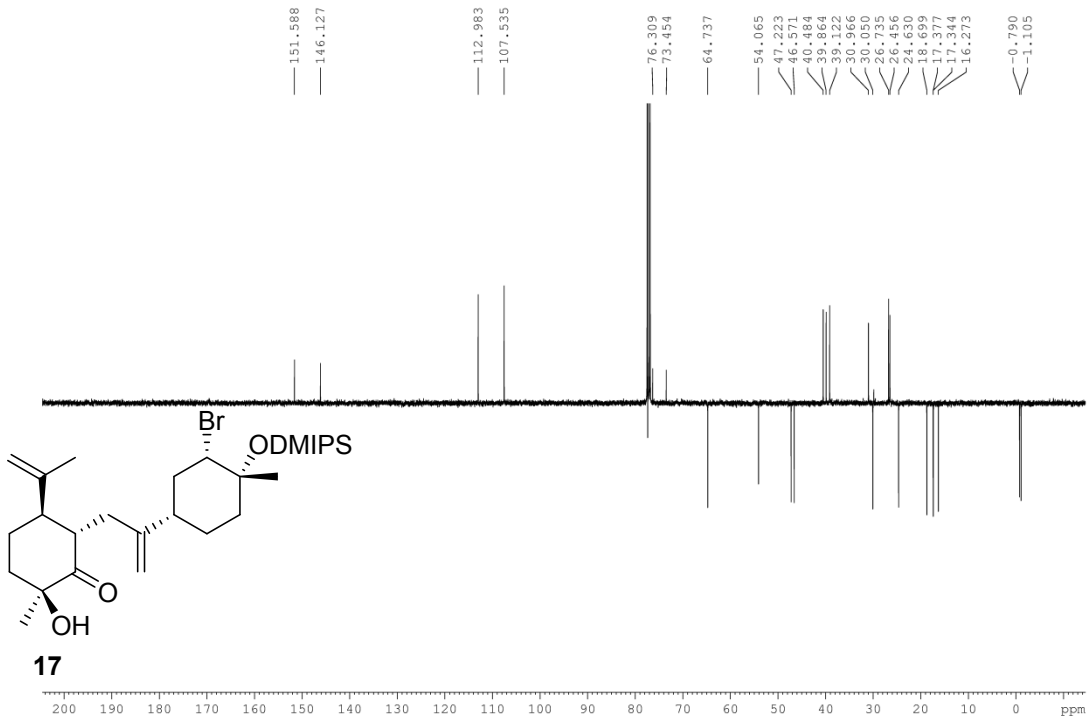


^{1}H NMR, 400 MHz, $CDCl_3$



^{13}C NMR, 100 MHz, $CDCl_3$



1. A. E. Leung, M. Blair, C. M. Forsyth and K. L. Tuck, *Organic Letters*, 2013, **15**, 2198-2201.
2. D. Iliopoulou, N. Mihopoulos, C. Vagias, P. Papazafiri and V. Roussis, *J. Org. Chem*, 2003, 7667-7674.