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Supporting Information

# Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone through Gold(I)-Catalyzed Cycloisomerization

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***Supporting Information***

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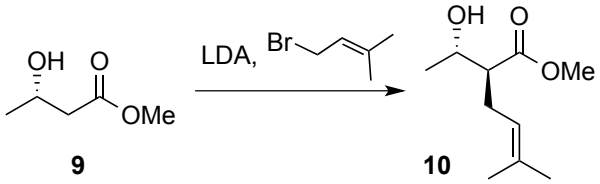
## Experimental Procedures

Unless otherwise stated, reactions were carried out under argon atmosphere in solvents dried by passing through an activated alumina column on a PureSolvTM solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography was carried out using TLC-aluminium sheets with 0.2 mm of silica gel (Merck GF234) using UV light as visualizing agent or an acidic solution of vanillin in ethanol as developing agent. Chromatograpy purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 mm). Preparative TLC was performed on 20 cm × 20 cm silica gel plates (2.0 mm thick, catalogue number 02015, Analtech). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. NMR spectra were recorded at 298 K on a Bruker Avance 400 Ultrashield or a Bruker Avance 500 Ultrashield. $^{1}H$ and $^{13}C$ chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale. Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI). Melting points were determined using a Büchi melting point apparatus. Optical rotations were obtained using a Jasco P-1030 polarimeter and concentrations are given in g/mL. Crystal structure determinations were carried out using a Bruker-Nonius diffractomer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoKa radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = -173 ºC). Full-sphere data collection was used with w and j scans. Programs used: Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. Structure Solution and Refinement: Crystal structure solution was achieved using direct methods as implemented in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters.

## Characterization of new compounds

### (*S*)-Methyl 2-((*S*)-1-hydroxyethyl)-5-methylhex-4-enoate (10)



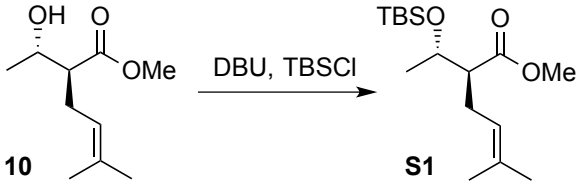

**9** **10**

LDA was prepared by adding n-BuLi (32.0 mL, 80.0 mmol, 2.5 M in hexanes, 2 eq.) to a solution of di*iso*propylamine (11.2 mL, 80.0 mmol, 2 eq.) in 60 mL of THF, at 0 °C. The solution was stirred 30 min at 0 °C and then cooled to –70 °C. (+)-Methyl (*S*)-3-hydroxybutyrate (**9**, 4.5 mL, 40.0 mmol, 1 eq.) in THF (30 mL) was added to the LDA solution at -70 ºC and stirred for 1 h. The reaction mixture was allowed to warm up to -10 ºC (45 min) and recooled to -70 ºC for the addition of HMPA (14 mL, 80.0 mmol, 2 eq.) and 3,3-dimethylallylbromide (7.0 mL, 60.0 mmol, 1.5 eq.) in THF (10 mL). The reaction mixture was allowed to warm up to -10 ºC and stirred in total for 3 h. The reaction was treated with saturated solution of $NH_4Cl$ (50 mL) and the aqueous phase was extracted with $Et_2O$ (2×30 mL). The combined organic phases were dried over $Na_2SO_4$. Column chromatography (cyclohexane/EtOAc 9:1) yielded alcohol **10** (6.0 g, 81%) as a colorless oil. The dr was measured by GC analysis (98:2), see page S-83.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 5.08 - 5.00 (m, 1H), 3.90 (h, $J$ = 6.4 Hz, 1H), 3.68 (s, 3H), 2.62 (d, $J$ = 7.3 Hz, 1H), 2.44 - 2.28 (m, 3H), 1.67 (d, $J$ = 1.5 Hz, 3H), 1.60 (s, 3H), 1.21 (d, $J$ = 6.4 Hz, 3H) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 175.7, 134.4, 120.4, 67.9, 52.8, 51.7, 28.1, 25.9, 21.7, 17.8 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -6.8º (c = 0.98, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{10}H_{18}O_3Na$ [*M*+Na]$^+$ 209.1154, found 209.1158.

Procedure according to: G. Koza, C. Theunissen, J. R. Al Dulayymi, M. S. Baird *Tetrahedron* **2009**, *65*, 10214-10229. NMR data were in accordance with those previously reported for **(*R*)-10**, $[\alpha]_D^{20}$ = +7.2º (c = 1.05, $CHCl_3$): A. Kramer, H. Pfander *Helvetica Chimica Acta* **1982**, 65, 293-301.

### (*S*)-Methyl 5-methyl-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)hex-4-enoate (S1)

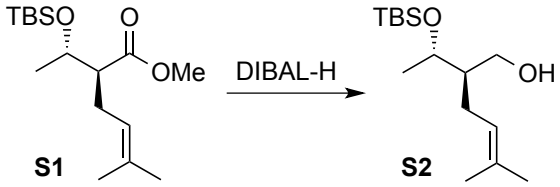



**10** **S1**

DBU (4.9 mL, 33.1 mmol, 1.1 eq.) and TBSCl (4.76 g, 31.6 mmol, 1.05 eq.) were added to a solution of **10** (5.6 g, 30.1 mmol) in $CH_2Cl_2$ (50 mL) in an open flask. The reaction was stirred overnight at 25 ºC. The mixture was quenched with 10% HCl solution (30 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (2×15 mL). The combined organic phases were washed with brine, dried over $Na_2SO_4$ and purified by column chromatography (cyclohexane/EtOAc 25:1) to give ester **S1** (8.0 g, 89%) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.06 - 5.00 (m, 1H), 4.00 (dq, $J$ = 7.4, 6.2 Hz, 1H), 3.63 (s, 3H), 2.40 (ddd, $J$ = 10.4, 7.3, 4.4 Hz, 1H), 2.29 - 2.21 (m, 1H), 2.17 - 2.10 (m, 1H), 1.66 (s, 3H), 1.59 (s, 3H), 1.16 (d, $J$ = 6.2 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 174.8, 133.5, 121.2, 69.8, 55.0, 51.4, 27.0, 25.9, 25.8, 21.5, 18.0, 17.8, -4.1, -5.0 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +12.7º (c = 0.95, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{16}H_{32}O_3NaSi$ [*M*+Na]$^+$ 323.2018, found 323.2031.

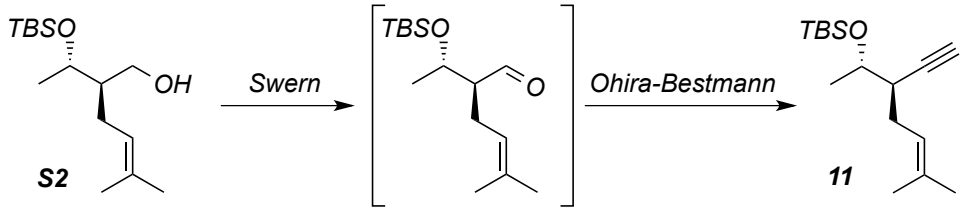
### (*R*)-5-Methyl-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)hex-4-en-1-ol (S2)




A solution of DIBAL-H (50.6 mL, 50.6 mmol, 1M in hexane, 2 eq.) was added to a stirred solution of methyl ester **S1** (7.6 g, 25.3 mmol) in toluene (50 mL) at -78 ºC. The reaction was allowed to warm up to -50 ºC and stirred for 2 h. A second portion of DIBAL-H (50.6 mL, 2 eq.) was added and stirred for additional 2 h at -50 ºC. The mixture was quenched with Rochelle solution (c.a. 150 mL), stirred for 1 h and the aqueous phase was extracted with $Et_2O$ (3×40 mL). The combined organic phases were dried over $Na_2SO_4$ and purified by column chromatography (cyclohexane/EtOAc 10:1) to give alcohol **S2** (5.8 g, 84%) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.14 (ddt, *J* = 7.9, 6.6, 1.4 Hz, 1H), 3.96 (qd, *J* = 6.3, 4.0 Hz, 1H), 3.90 (ddd, *J* = 11.2, 3.8, 2.8 Hz, 1H), 3.59 - 3.53 (m, 1H), 3.00 (dd, *J* = 7.3, 3.7 Hz, 1H), 2.20 (dt, *J* = 15.8, 8.3 Hz, 1H), 2.05 (dt, *J* = 13.5, 6.1 Hz, 1H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.62 (s, 3H), 1.38 (dt, *J* = 8.9, 3.5 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 6H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 133.2, 122.7, 72.9, 63.0, 47.2, 27.9, 25.9, 22.5, 18.0, 18.0, -4.1, -4.9 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +12.8º (c = 1.07, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{15}H_{32}O_2NaSi$ $[M+Na]^+$ 295.2069, found 295.2060.

**(((2*S*,3*R*)-3-Ethynyl-6-methylhept-5-en-2-yl)oxy) *tert*-butyldimethylsilane (11)**




DMSO (1.9 mL, 26.4 mmol, 2.4 eq.) was added to a solution of oxalyl chloride (0.9 mL, 11.0 mmol, 1 eq.) in $CH_2Cl_2$ (50 mL) at -60 ºC and stirred for 10 min. Then, a solution of alcohol **S2** (3.0 g, 11.0 mmol, 1 eq.) in $CH_2Cl_2$ (20 mL) was added and stirred for 15 min. After addition of $Et_3N$ (8.4 mL, 60.5 mmol, 5.5 eq.) the reaction mixture was stirred at 25 ºC for 1 h. The reaction was quenched with 10% HCl solution (30 mL) and after extractive work up ($CH_2Cl_2$), aldehyde was isolated as a colorless oil and used without further purification.

**$^1$H NMR** (400 MHz, $CDCl_3$) *δ* 9.68 (d, *J* = 3.1 Hz, 1H), 5.05 (m, 1H), 4.17 - 4.00 (m, 1H), 2.44 (dd, *J* = 14.9, 8.9 Hz, 1H), 2.28 - 2.12 (m, 2H), 1.67 (s, 3H), 1.61 (s, 4H), 1.22 (d, *J* = 6.3 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 6H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 205.5, 133.9, 120.8, 69.0, 59.8, 25.9, 25.9, 25.8, 25.2, 22.4, 18.0, -4.0, -4.9.

Dimethyl (1-diazo-2-oxopropyl)phosphonate (2.5 g, 13.2 mmol, 1.2 eq.) and $K_2CO_3$ (3.1 g, 22.0 mmol, 2 eq.) were added to a solution of the aldehyde in MeOH (50 mL) and the reaction mixture was stirred for 5 h at 25 ºC. The solvent was evaporated and extractive work-up ($CH_2Cl_2/H_2O$) was performed. The combined organic phases were washed with brine, dried over $Na_2SO_4$ and purified by column chromatography (cyclohexane/EtOAc 20:1) to give alkyne **11** (1.5 g, 51%, 2 steps) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) *δ* 5.26 (ddt, *J* = 8.4, 5.5, 1.5 Hz, 1H), 3.93 (qd, *J* = 6.2, 3.9 Hz, 1H), 2.39 - 2.27 (m, 2H), 2.17 - 2.09 (m, 1H), 2.04 (d, *J* = 2.4 Hz, 1H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.63 (s, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) *δ* 133.1, 122.2, 85.7, 70.4, 69.7, 40.6, 28.1, 26.0, 26.0, 20.3, 18.2, 18.1, -4.2, -4.7 ppm;

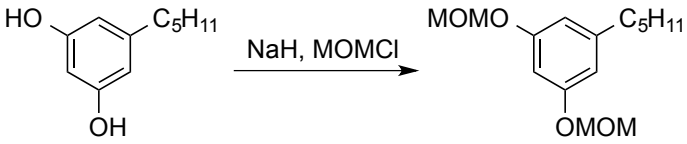
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -32.5º (c = 0.97, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{16}H_{30}ONaSi$ $[M+Na]^+$ 289.1964, found 289.1964.

*Dimethyl (1-diazo-2-oxopropyl)phosphonate* (Bestmann-Ohira reagent) was synthesized according to reported procedure: E. Quesada, S. A. Raw, M. Reid, E. Roman, R. J.K. Taylor *Tetrahedron* **2006**, *62*, 6673-6680.

Alternately, Dess-Martin periodinane instead of Swern oxidation can be used.

$NaHCO_3$ (210 mg, 2.5 mmol, 2.5 eq.) was added to a solution of alcohol **S2** (273 mg, 1 mmol, 1 eq.) in $CH_2Cl_2$ (5 mL) under argon atmosphere and cooled down to 0°C. Dess-Martin periodinane (466 mg, 1.1 mmol, 1.1 eq.) was added to the reaction mixture in 3 portions. After stirring at 25 °C for 3 hours, Fluorisil was added (≈4 g) and all volatiles were removed under reduced pressure. The residue was filtered through a pad of silica gel eluting with $CH_2Cl_2$ to give aldehyde as colourless oil, which was directly used in the following step. Dimethyl (1-diazo-2oxopropyl)phosphonate (192 mg, 1.0 mmol, 1.0 eq.) and $K_2CO_3$ (166 mg, 1.2 mmol, 1.2 eq.) were added to a solution of aldehyde in dry methanol (5 mL) under argon atmosphere and at 0 °C. The reaction mixture was stirred for 5 hours at 25 °C. Then the solvent was evaporated under reduced pressure and extractive work up ($CH_2Cl_2$/water) was performed. Combined organic phases were washed with brine, dried over $Na_2SO_4$ and purified by column chromatography (cyclohexane/EtOAc 20:1) to give alkyne **11** (207 mg, 0.78 mmol, 78% over 2 steps) as a colourless oil.

**1,3-Bis(methoxymethoxy)-5-pentylbenzene (S3)**



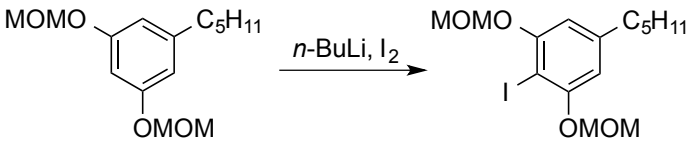

***Olivetol*** **S3**

NaH (1.25 g, 31.2 mmol, 2.5 eq.) was added to a solution of olivetol (2.25 g, 12.5 mmol) in DMF (60 mL) at 0 ºC. After 30 min methoxymethylchloride (2.4 mL, 31.2 mmol, 2.5 eq.) was added and the reaction mixture was stirred overnight at 25 ºC. After extractive work-up ($Et_2O/H_2O$), the residue was purified by column chromatography (cyclohexane/EtOAc 9:1) to yield **S3** (3.25 g, 97%) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.60 (t, *J* = 2.2 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 2H), 5.17 (s, 4H), 3.51 (s, 6H), 2.63 - 2.50 (m, 2H), 1.67 - 1.55 (m, 2H), 1.42 - 1.31 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 158.3, 145.7, 110.0, 102.3, 94.6, 56.2, 36.3, 31.7, 31.1, 22.7, 14.2 ppm; **HRMS-ESI** *m/z* calcd for $C_{15}H_{24}O_4Na$ $[M+Na]^+$ 291.1567, found 291.1556.

$^1$H NMR data were in accordance with those previously reported: J. W. Huffman, X. Zhang, M. J. Wu, H. H. Joyner, W. T. Pennington *J. Org. Chem., **1991, 56,*** 1481-1489.

**2-Iodo-1,3-bis(methoxymethoxy)-5-pentylbenzene (12)**

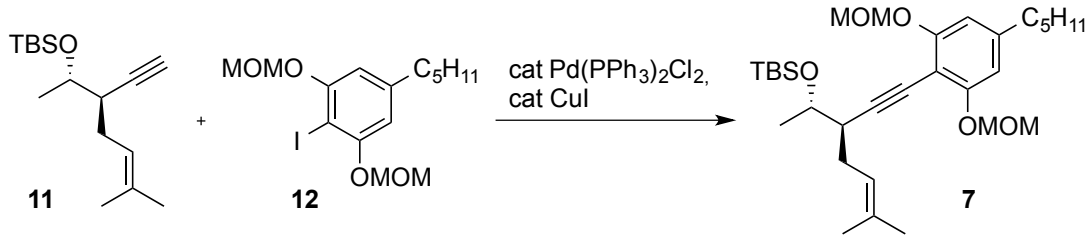



**S3** **12**

*n*-BuLi (5.8 mL, 14.5 mmol, 2.5 M in hexanes, 1.2 eq.) was added to a solution of 1,3-bis(methoxymethoxy)-5-pentylbenzene (**S3**, 3.25 g, 12.1 mmol) in THF (50 mL) at 0 ºC and stirred for 15 min. Then, $I_2$ (3.7 g, 14.5 mmol, 1.2 eq.) was added and the reaction mixture was stirred for 2 h. MeOH (15 mL) was added and the crude was concentrated. After extractive work-up ($EtOAc/H_2O$), the organic layer was washed with saturated $Na_2S_2O_3$ (20 mL) and brine (20 mL), dried with $Na_2SO_4$ and evaporated. The residue was purified by column chromatography (cyclohexane/EtOAc 9:1) to yield **12** (3.91 g, 82%) as a yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.23 (s, 4H), 3.52 (s, 6H), 2.62 - 2.47 (m, 2H), 1.61 - 1.58 (m, 2H), 1.34 - 1.31 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 157.3, 145.7, 109.1, 95.2, 56.6, 36.3, 31.7, 31.2, 22.6, 14.2 ppm; **HRMS-ESI** *m/z* calcd for $C_{15}H_{23}O_4NaI$ $[M+Na]^+$ 417.0539, found 417.0536.

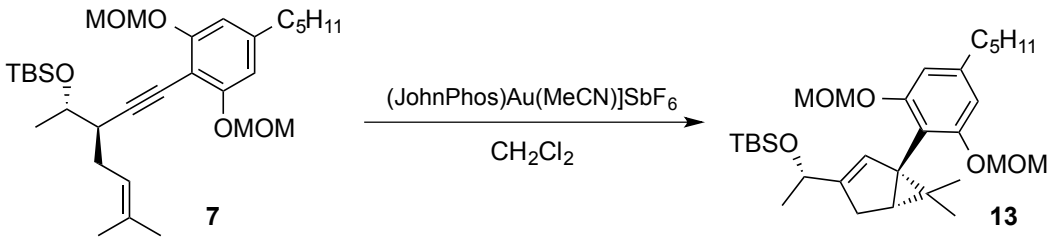
**(((2*S*,3*R*)-3-((2,6-Bis(methoxymethoxy)-4-pentylphenyl)ethynyl)-6-methylhept-5-en-2-yl)oxy)*tert*-butyldimethylsilane** (**7**)




To a solution of 2-iodo-1,3-bis(methoxymethoxy)-5-pentylbenzene (**12**, 1.95 g, 5.0 mmol, 1 eq.) in a mixture of degassed $Et_3N$ and $^iPr_2NH$ (1:1, 20 mL) was added $[Pd(PPh_3)_2Cl_2]$ (174 mg, 0.25 mmol, 0.05 eq.) and stirred for 15 min, CuI (94 mg, 0.50 mmol, 0.1 eq.) and stirred for 15 min and finally enyne **11** (1.52 g, 5.7 mmol, 1.15 eq.) in solution ($Et_3N/^iPr_2NH$ 1:1, 10 mL) dropwise. The mixture was stirred at room temperature for 16 h. The reaction was treated with saturated solution of $NH_4Cl$ (20 mL) and extracted with $CH_2Cl_2$ (3×30 mL). The combined organic phases were washed with brine (40 mL), dried over $Na_2SO_4$ and purified by column chromatography (pentane to pentane/ether 95:5) to give enyne **7** (2.2 g, 83%) as a pale yellow oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.61 (s, 2H), 5.46 - 5.41 (m, 1H), 5.23 (s, 4H), 4.09 (qd, *J* = 6.2, 4.0 Hz, 1H), 3.53 (s, 6H), 2.71 (dt, *J* = 10.2, 4.2 Hz, 1H), 2.58 - 2.53 (m, 2H), 2.47 (ddd, *J* = 12.8, 7.4, 4.5 Hz, 1H), 2.27 - 2.20 (m, 1H), 1.74 (d, *J* = 0.8 Hz, 3H), 1.67 (s, 3H), 1.65 - 1.55 (m, 2H), 1.40 - 1.30 (m, 4H+3H), 0.95 - 0.88 (m, 9H+3H), 0.10 (s, 3H), 0.09 (s, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 158.9, 144.5, 132.3, 123.1, 109.7, 103.4, 99.1, 95.2, 75.0, 70.1, 56.3, 41.7, 36.6, 31.7, 31.0, 27.9, 26.0, 26.0, 22.7, 19.9, 18.2, 18.0, 14.2, -4.3, -4.7 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = -55.9° (c = 1.01, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{31}H_{52}O_5NaSi$ $[M+Na]^+$ 555.3482, found 555.3483.

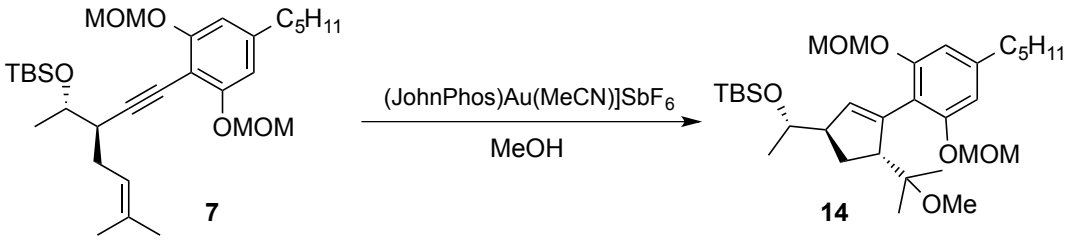
**((*S*)-1-((1*R*,5*S*)-1-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-6,6-dimethylbicyclo[3.1.0]hex-2-en-3-yl)ethoxy)(*tert*-butyl)dimethylsilane (13)**




(JohnPhos)Au(MeCN)]$SbF_6$ (3.8 mg, 0.05 mmol, 0.05 eq.) was added to a solution of **7** (53 mg, 1 mmol, 1 eq.) in $CH_2Cl_2$ (1 mL) and stirred at 25 °C for 30 min. The reaction was quenched with 10 µL of $Et_3N$ and concentrated under reduced pressure. The residue was purified by preparative TLC (pentane/ether 98:2) to give bycicle **13** (26 mg, 49%) as colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.63 (d, *J* = 1.5 Hz, 1H), 6.52 (d, *J* = 1.5 Hz, 1H), 5.39 (bs, 1H), 5.19 - 5.13 (m, 2H), 5.10 - 5.01 (m, 2H), 4.39 - 4.32 (m, 1H), 3.50 (s, 3H), 3.45 (s, 3H), 2.66 (ddd, *J* = 18.2, 7.7, 1.6 Hz, 1H), 2.57 - 2.48 (m, 2H), 2.23 (d, *J* = 17.8 Hz, 1H), 1.76 - 1.71 (m, 1H), 1.62 - 1.57 (m, 2H), 1.37 - 1.29 (m, 4H), 1.22 (d, *J* = 6.4 Hz, 3H), 0.97 (s, 3H), 0.92 - 0.85 (m, 9H+3H), 0.77 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 158.2, 157.8, 147.1, 142.6, 128.2, 116.9, 110.4, 108.0, 95.6, 94.8, 67.7, 56.2, 56.2, 41.3, 36.4, 33.3, 31.9, 31.5, 31.2, 26.0, 25.6, 24.1, 23.8, 22.7, 18.4, 14.7, 14.2, -4.7 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +61.1º (c = 0.96, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{31}H_{52}NaO_5Si$ [*M*+Na]$^+$ 555.3476, found 555.3478.

**((*S*)-1-((1*R*,4*R*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(2-methoxypropan-2-yl)cyclopent-2-en-1-yl)ethoxy)(*tert*-butyl)dimethylsilane (14)**




(JohnPhos)Au(MeCN)]$SbF_6$ (3.8 mg, 0.05 mmol, 0.05 eq.) was added to a solution of **7** (53 mg, 1 mmol, 1 eq.) in methanol (1 mL) and stirred at 25 °C for 30 min. The reaction was quenched with 10 µL of $Et_3N$ and concentrated under reduced pressure. The residue was purified by preparative TLC (pentane/ether 95:5) to give cyclopentene **14** (52 mg, 93%) as colourless oil.

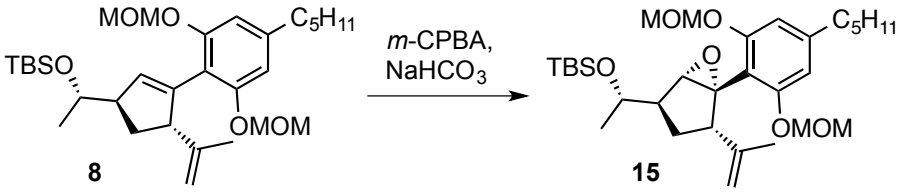
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.55 (s, 1H), 5.81 (t, *J* = 1.7 Hz, 1H), 5.17 - 5.06 (m, 4H), 3.62 - 3.54 (m, 2H), 3.46 (s, 3H), 3.44 (s, 3H), 3.09 (s, 3H), 2.92 - 2.80 (m, 1H), 2.59 - 2.47 (m, 2H), 2.09 (ddd, *J* = 13.5, 8.1, 2.4 Hz, 1H), 1.73 - 1.62 (m, 1H), 1.66 - 1.53 (m, 2H), 1.38 - 1.26 (m, 4H), 1.14 (d, *J* = 6.1 Hz, 3H), 1.12 (s, 3H), 0.91 - 0.87 (m, 9H+3H), 0.82 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.5, 155.1, 143.3, 137.3, 136.3, 117.2, 108.9, 108.5, 95.0, 94.7, 78.3, 73.2, 56.2, 56.1, 54.7, 53.8, 48.8, 36.4, 31.8, 31.1, 29.0, 26.0, 23.3, 22.7, 21.8, 21.8, 18.2, 14.2, -4.1, -4.5 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$ = +99.0º (c = 1.02, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{32}H_{56}NaO_6Si$ [*M*+Na]$^+$ 587.3738, found 587.3748.

**((*S*)-1-((1*R*,4*S*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethoxy)(*tert*-butyl)dimethylsilane (8)**


(JohnPhos)Au(MeCN)]$SbF_6$ (152 mg, 0.20 mmol, 0.05 eq.) was added to a solution of enyne **7** (2.1 g, 3.94 mmol, 1 eq.) in DMSO (7 mL, 0.5 M) and stirred at 25 ºC for 3 h. The reaction mixture was treated with brine (15 mL) and extracted with $CH_2Cl_2$ (3×20). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane/EtOAc 50:1) to give cyclopentene **8** (1.85 g, 88%) as a yellow oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) $\delta$ 6.62 (s, 2H), 5.87 (t, $J$ = 1.9 Hz, 1H), 5.11 (s, 4H), 4.63 (d, $J$ = 2.6 Hz, 1H), 4.50 (dd, $J$ = 2.6, 1.4 Hz, 1H), 4.04 - 3.97 (m, 1H), 3.75 - 3.66 (m, 1H), 3.46 (s, 6H), 3.03 - 2.93 (m, 1H), 2.59 - 2.45 (m, 2H), 1.93 (ddd, $J$ = 13.1, 9.0, 6.6 Hz, 1H), 1.87 (ddd, $J$ = 12.9, 8.3, 4.3 Hz, 1H), 1.64 (s, 3H), 1.62 - 1.55 (m, 2H), 1.39 - 1.26 (m, 4H), 1.17 (d, $J$ = 6.0 Hz, 3H), 0.93 – 0.88 (s, 9H+3H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 155.8, 148.5, 143.4, 138.6, 134.5, 115.2, 110.0, 108.6, 94.9, 72.5, 56.0, 55.5, 53.9, 36.5, 32.6, 31.9, 31.1, 26.0, 22.7, 21.6, 19.3, 18.3, 14.2, -4.1, -4.5 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +110.4º (c = 0.99, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{31}H_{52}O_5NaSi$ [$M$+Na]$^+$ 555.3482, found 555.3459.

**((*S*)-1-((1*S*,2*R*,4*S*,5*S*)-5-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)-6-oxabicyclo[3.1.0]hexan-2-yl)ethoxy)(*tert*-butyl)dimethylsilane (15)**

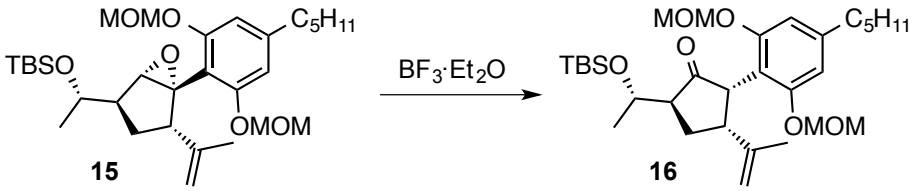



$NaHCO_3$ (583 mg, 6.94 mmol, 2 eq.) and *m*-CPBA (689 mg, 3.99 mmol, 1.15 eq.) were added to a solution of cyclopentene **8** (1.85 g, 3.47 mmol, 1 eq.) in $CH_2Cl_2$ (50 mL) at 0ºC in an open flask. The mixture was stirred for 3 h, allowing the ice bath to slowly warm up to 25 ºC. The reaction mixture was diluted with $CH_2Cl_2$ (10 mL), then washed with aqueous saturated $NaHCO_3$ (2×20 mL), followed by brine (30 mL). The organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (pentane/ether 95:5) to give epoxide **15** (1.1 g, 57%) as a pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.59 (s, 1H), 5.35 - 5.02 (m, 4H), 4.69 (bs, 1H), 4.54 (s, 1H), 4.08 (s, 1H), 3.86 (dq, $J$ = 9.5, 6.1 Hz, 1H), 3.56 (m, 3H+1H), 3.46 (s, 3H), 2.58 - 2.49 (m, 2H), 2.43 (q, $J$ = 10.0 Hz, 1H), 1.62 (s, 3H), 1.61 - 1.54 (m, 2H), 1.54 - 1.48 (m, 1H), 1.47 - 1.40 (m, 1H), 1.37 - 1.30 (m, 4H), 1.19 (d, $J$ = 6.1 Hz, 3H), 0.92 (s, 9H+3H), 0.12 (s, 3H), 0.11 (s, 3H) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 158.8, 155.9, 146.5, 145.6, 111.8, 111.3, 108.2, 107.6, 94.7, 94.5, 69.9, 66.3, 65.4, 56.3, 56.2, 50.4, 49.5, 36.7, 31.8, 31.1, 29.8, 26.0, 22.9, 22.7, 21.0, 18.2,

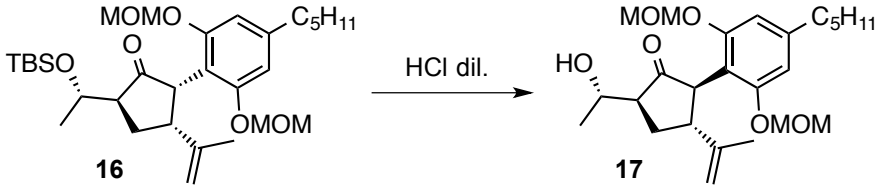
14.2, -4.1, -4.6 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = -27.1º (c = 0.95, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{31}H_{53}O_6Si$ $[M+H]^+$ 549.3606, found 549.3601.

**(2*S*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(prop-1-en-2-yl)cyclopentan-1-one (16)**




$BF_3{\cdot}Et_2O$ (0.49 mL, 3.94 mmol, 2 eq.) was added to a solution of **15** (1.1 g, 1.97 mmol, 1 eq.) in THF (25 mL) at 25 ºC and the mixture was stirred for 30 min. Saturated $NaHCO_3$ solution (15 mL) was added and stirred for 15 min. The reaction mixture was diluted and extracted with AcOEt (2×20 mL) and the organic phase washed with brine (25 mL). The organic phase was then dried over $Na_2SO_4$ and concentrated. The residue was purified by column chromatography (pentane/ether 9:1) giving ketone **16** as a pale yellow oil (1.0 g, 93%).
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.65 (bs, 2H), 5.20 - 5.03 (m, 4H), 4.76 (bs, 1H), 4.69 (bs, 1H), 4.45 (qd, *J* = 6.3, 4.6 Hz, 1H), 4.13 (dd, *J* = 12.2, 1.7 Hz, 1H), 3.51 - 3.35 (bs, 6H), 3.29 (ddd, *J* = 12.2, 10.4, 7.7 Hz, 1H), 2.86 (dtd, *J* = 10.8, 4.4, 1.7 Hz, 1H), 2.60 - 2.52 (m, 2H), 2.38 (ddd, *J* = 13.7, 7.8, 4.3 Hz, 1H), 2.01 (ddd, *J* = 13.8, 11.1, 10.3 Hz, 1H), 1.78 (s, 3H), 1.65 - 1.58 (m, 2H), 1.40 - 1.30 (m, 4H), 1.22 (d, *J* = 6.3 Hz, 3H), 0.92 (bs, 9H+3H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 215.0, 146.7, 144.0, 112.1, 110.8, 108.2, 95.2, 93.8, 67.9, 56.2, 55.9, 53.7, 51.6, 47.5, 36.6, 31.9, 31.1, 26.6, 26.0, 22.7, 19.6, 19.4, 18.2, 14.2, -4.4, -4.7 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = +4.1º (c = 1.09, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{31}H_{52}NaO_6Si$ $[M+Na]^+$ 571.3425, found 571.3416.

**(2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentan-1-one (17)**

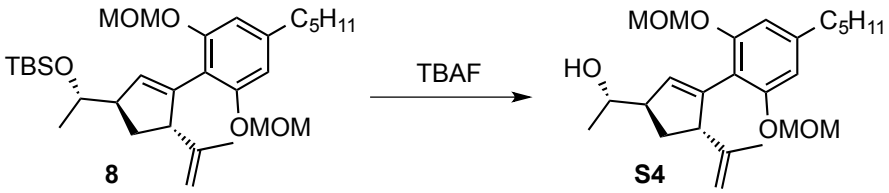



HCl 10% (8 mL) was added to a solution of **16** (1.0 g, 1.82 mmol) in THF (16 mL) at 25 ºC in an open flask and the mixture was stirred for 1 h. $NaHCO_3$ was added to neutralize the solution. After extractive work-up (EtOAc), the organic layer was washed with brine (15 mL), dried with $Na_2SO_4$ and evaporated. The residue was purified by column chromatography (cyclohexane/EtOAc 7:3) to yield ketone **17** (690 mg, 87%) as a yellow oil.
The same product was obtained in other two different ways:
- Starting from epoxide **18** (12.5 mg, 0.03 mmol) and $BF_3{\cdot}Et_2O$ (7 μL, 0.06 mmol) following the procedure described to obtain ketone 16 (**17**, 6 mg, 48%).
- $ZnI_2$ (22 mg, 0.07 mmol, 2 eq.) and $NaBH_4$ (6.5 g, 0.17 mmol, 5 eq.) were added to a solution of **21** (15 mg, 0.03 mmol, 1 eq.) in dichloroethane (5 mL) at 25 ºC and the mixture was stirred for 14 h. The crude was filtrated to remove the remaining salts, the solvent was evaporated and the

residue was purified by column chromatography (cyclohexane/EtOAc 8:2) to yield ketone **17** (9.5 mg, 63%). Note: Same product was obtained in absence of $NaBH_4$, however lower yields and more decomposition products were obtained.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.63 (s, 2H), 5.16 - 5.03 (m, 4H), 4.74 (bs, 1H), 4.70 (bs, 1H), 4.09 (s, 1H), 4.03 (dd, *J* = 10.9, 1.8 Hz, 1H), 4.03 - 3.95 (m, 1H), 3.42 (s, 6H), 3.19 (td, *J* = 10.5, 7.5 Hz, 1H), 2.55 - 2.48 (m, 2H), 2.38 (tdd, *J* = 9.7, 3.8, 1.6 Hz, 1H), 2.13 (dt, *J* = 13.5, 9.9 Hz, 1H), 1.99 (ddd, *J* = 13.5, 7.5, 3.9 Hz, 1H), 1.76 (s, 3H), 1.62 - 1.54 (m, 2H), 1.35 - 1.31 (m, 4H), 1.30 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 221.3, 145.9, 144.3, 113.1, 111.3, 108.1, 95.1, 94.4, 68.7, 56.3, 53.9, 50.9, 47.9, 36.6, 31.8, 31.1, 30.2, 22.7, 22.1, 19.6, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = -18.6º (c = 0.90, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{25}H_{38}NaO_6$ $[M+Na]^+$ 457.2561, found 457.2547.

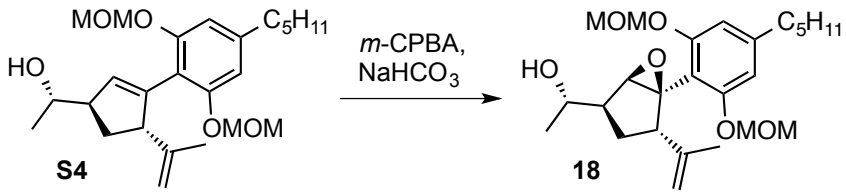
**(*S*)-1-((1*R*,4*S*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethan-1-ol (S4)**




TBAF (0.31 mL, 1 M in THF, 1.1 eq.) was added to a solution of cyclopentene **8** (150 mg, 0.28 mmol, 1 eq.) in THF (2 mL). The reaction mixture was stirred at 25 ºC for 14 h. The solvent was evaporated and the residue was purified by column chromatography (cyclohexane/EtOAc 8:2) to give alcohol **S4** (98 mg, 83%) as a colorless oil

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 6.62 (s, 2H), 5.82 (t, *J* = 2.1 Hz, 1H), 5.11 (s, 4H), 4.65 - 4.61 (m, 1H), 4.57 - 4.49 (m, 1H), 4.11 - 3.98 (m, 1H), 3.75 (q, *J* = 6.1 Hz, 1H), 3.45 (s, 6H), 3.06 - 2.93 (m, 1H), 2.58 - 2.45 (m, 2H), 2.08 - 1.95 (m, 1H), 1.86 (d, *J* = 6.5 Hz, 1H), 1.62 (s, 3H), 1.60 - 1.51 (m, 2H), 1.41 - 1.29 (m, 4H), 1.20 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm; **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 155.5, 147.9, 143.8, 142.3, 131.1, 114.6, 110.7, 108.3, 94.8, 71.8, 56.1, 55.7, 52.7, 36.5, 33.5, 31.8, 31.1, 22.6, 22.0, 19.1, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = +116.1º (c = 1.02, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{25}H_{38}O_5Na$ $[M+Na]^+$ 441.2617, found 441.2608.

**(*S*)-1-((1*R*,2*S*,4*S*,5*R*)-5-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)-6-oxabicyclo[3.1.0]hexan-2-yl)ethan-1-ol (18)**

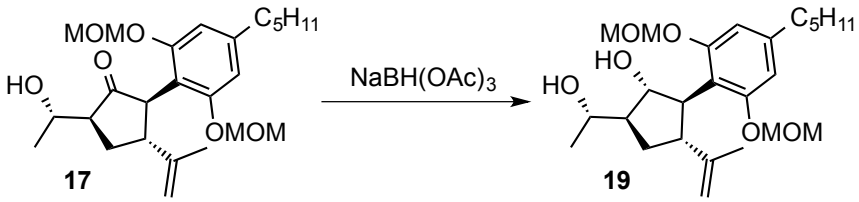



$NaHCO_3$ (19 mg, 0.22 mmol, 2 eq.) and *m*-CPBA (22 mg, 0.13 mmol, 1.15 eq.) were added to a solution of cyclopentene **S4** (46 mg, 0.11 mmol, 1 eq.) in $CH_2Cl_2$ (2 mL) at 0ºC in an open flask. The mixture was stirred for 4 h, allowing the ice bath to slowly warm up to rt. The reaction mixture was diluted with $CH_2Cl_2$ (10 mL), then washed with aqueous saturated $NaHCO_3$ (2×10 mL), followed by brine (10 mL). The organic phase was dried over $Na_2SO_4$ and concentrated

under reduced pressure. The residue was purified by column chromatography (cyclohexane/EtOAc 6:4) to give epoxide **18** (28 mg, 58%) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.60 (s, 1H), 5.35 - 5.22 (m, 2H), 5.17 - 5.08 (m, 2H), 4.70 (dd, *J* = 1.5, 0.7 Hz, 1H), 4.57 (t, *J* = 1.8 Hz, 1H), 4.10 (d, *J* = 1.3 Hz, 1H), 3.98 - 3.88 (m, 1H), 3.57 - 3.53 (m, 3H+1H), 3.47 (s, 3H), 2.59 - 2.50 (m, 2H), 2.43 (q, *J* = 9.1, 8.6 Hz, 1H), 1.63 (s, 3H), 1.61 - 1.54 (m, 4H), 1.39 - 1.31 (m, 4H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 158.7, 156.0, 146.2, 145.7, 112.0, 111.2, 108.3, 107.8, 94.8, 94.7, 69.3, 65.5, 65.4, 56.3, 50.2, 48.3, 36.6, 31.7, 31.0, 30.5, 29.9, 22.7, 22.6, 21.1, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -11.6º (c = 1.07, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{25}H_{38}NaO_6$ $[M+Na]^+$ 457.2561, found 457.2567.

**(1*R*,2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentan-1-ol (19)**

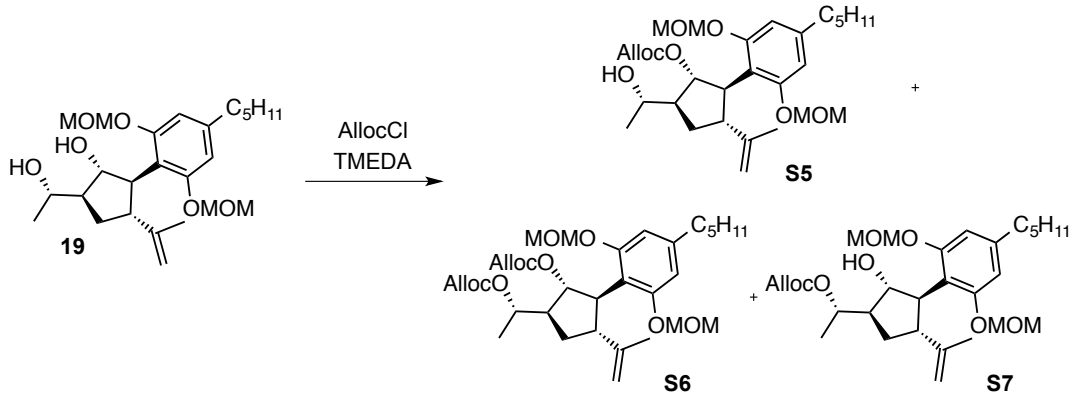



Sodium triacetoxyborohydride (258 mg, 1.22 mmol, 1.1 eq.) was added to a solution of **17** (480 mg, 1.11 mmol, 1 eq.) in $CH_2Cl_2$ (37 mL, 0.03 M) at 25 ºC and the mixture was stirred for 48 h. Saturated $NaHCO_3$ solution (20 mL) was added. After extractive work-up ($CH_2Cl_2$), the organic layer was dried with $Na_2SO_4$ and evaporated. The residue was purified by column chromatography (cyclohexane/EtOAc 8:2 to 6:4) to yield diol **19** (230 mg, 48%, 77% brsm) as a colorless oil. 180 mg of the hydroxy ketone **17** was also recovered.

Note: The use of tetramethylammonium triacetoxyborohydride and/or $CH_3CN$ or $CH_3CN$/HAcO mixtures as solvent lead mainly to the epimerization of the hydroxyethyl substituent.

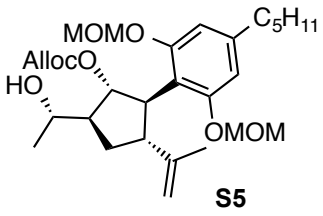
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.16 (s, 4H), 4.68 - 4.63 (m, 1H), 4.58 (dd, *J* = 2.1, 1.3 Hz, 1H), 4.53 (dd, *J* = 9.7, 8.7 Hz, 1H), 3.85 - 3.74 (m, 1H), 3.67 (t, *J* = 9.8 Hz, 1H), 3.48 (s, 6H), 3.16 (td, *J* = 10.1, 5.2 Hz, 1H), 2.60 - 2.45 (m, 2H), 1.89 (p, *J* = 9.0 Hz, 1H), 1.79 (ddd, *J* = 14.5, 9.2, 5.4 Hz, 1H), 1.71 (s, 3H), 1.64 (dt, *J* = 13.3, 10.2 Hz, 1H), 1.61 - 1.54 (m, 2H), 1.36 - 1.29 (m, 4H), 1.21 (d, *J* = 6.1 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.9, 148.2, 143.4, 115.8, 109.4, 109.1, 95.2, 80.9, 73.6, 56.4, 52.5, 47.9, 45.6, 36.4, 31.8, 31.1, 30.4, 22.7, 22.4, 20.1, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = -26.1º (c = 1.09, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{25}H_{40}NaO_6$ $[M+Na]^+$ 459.2717, found 459.2707.

**Alloc protection of diol 19**



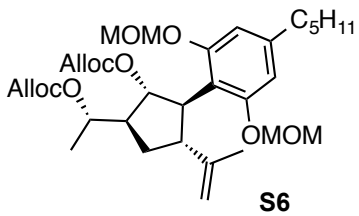

TMEDA (37 μL, 0.25 mmol, 1.2 eq.) was added to the solution of diol **19** (90 mg, 0.21 mmol, 1 eq.) in $CH_2Cl_2$ (4 mL) at -40 ºC. Then, allyl chloroformiate (23 μL, 0.22 mmol, 1.05 eq.) in $CH_2Cl_2$ (1 mL) was added dropwise and the solution was stirred at -40 ºC for 1.5 h. The solvent was evaporated and the residue was purified by column chromatography (cyclohexane/EtOAc 8:2 to 6:4) to obtain monocarbonate **S5** (44 mg, 41%, 72% brsm), dicarbonate **S6** (20 mg), monocarbonate **S7** (11 mg) and diol **19** (30 mg).
Protected alcohol **S6** and **S7** were hydrolyzed with $K_2CO_3$ in methanol to recover 20 mg of diol **19** (92% brsm for **S5**).

**Allyl ((1*R*,2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentyl) carbonate (S5)**




Colorless oil.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.82 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.57 (dd, *J* = 7.8, 3.6 Hz, 1H), 5.32 - 5.12 (m, 4H+2H), 4.61 (bs, 1H), 4.58 (bs, 1H), 4.56 - 4.42 (m, 2H), 4.04 - 3.80 (m, 2H), 3.49 (s, 6H), 3.19 (td, *J* = 11.3, 6.9 Hz, 1H), 2.56 - 2.45 (m, 2H), 2.08 (tt, *J* = 9.2, 3.3 Hz, 1H), 2.00 (ddd, *J* = 13.1, 10.9, 9.4 Hz, 1H), 1.72 (ddd, *J* = 13.1, 6.9, 3.0 Hz, 1H), 1.67 (s, 3H), 1.62 - 1.54 (m, 2H), 1.35 – 1.28 (m, 4H), 1.26 (d, *J* = 6.1 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.3, 155.9, 145.9, 143.5, 131.6, 118.9, 114.5, 111.0, 108.1, 94.6, 85.7, 69.4, 68.5, 56.3, 53.2, 47.8, 45.8, 36.5, 33.0, 31.9, 31.1, 22.7, 22.4, 19.5, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = +12.6º (c = 1.04, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{29}H_{44}NaO_8$ $[M+Na]^+$ 543.2928, found 543.2934.

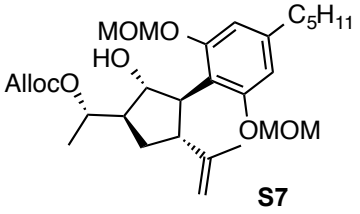
**Allyl ((*S*)-1-((1*S*,2*R*,3*R*,4*R*)-2-(((allyloxy)carbonyl)oxy)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopentyl)ethyl) carbonate (S6)**




Colorless oil.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.59 (bs, 2H), 5.92 (ddt, *J* = 17.3, 10.5, 5.7 Hz, 1H), 5.80 - 5.68 (m, 2H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.28 – 5.04 (m, 3H+2H+2H), 4.95 (p, *J* = 6.4 Hz, 1H), 4.65 (bs, 1H), 4.60 (dq, *J* = 5.8, 1.6 Hz, 2H), 4.59 (bs, 1H), 4.47 - 4.34 (m, 2H), 3.87 (dd, *J* = 11.2, 9.3 Hz, 1H), 3.49 (s, 6H), 3.26 (dt, *J* = 11.3, 8.7 Hz, 1H), 2.54 - 2.47 (m, 2H), 2.45 (dt, *J* = 10.4, 6.6 Hz, 1H), 1.96 (ddd, *J* = 13.5, 10.4, 8.9 Hz, 1H), 1.80 (ddd, *J* = 13.4, 8.6, 6.1 Hz, 1H), 1.67 (s, 3H), 1.61 - 1.54 (m, 2H), 1.35 (d, *J* =

6.3 Hz, 3H), 1.34 - 1.27 (m, 4H), 1.25 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 154.9, 154.5, 146.5, 143.4, 132.0, 131.9, 118.7, 118.2, 113.9, 110.5, 108.2, 94.9, 82.7, 76.9, 68.3, 68.1, 56.2, 47.7, 46.5, 45.6, 36.5, 31.8, 31.0, 31.0, 29.8, 22.7, 19.7, 17.9, 14.2 ppm; $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{27}}$ = -11.2º (c = 1.10, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{33}H_{48}NaO_{10}$ $[M+Na]^+$ 627.3140, found 627.3155.

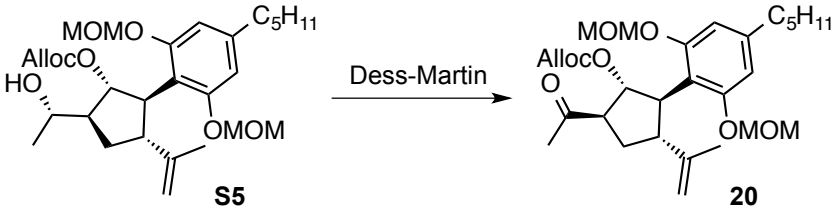
**Allyl ((*S*)-1-((1*R*,2*R*,3*R*,4*R*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-2-hydroxy-4-(prop-1-en-2-yl)cyclopentyl)ethyl) carbonate (S7)**



**S7**

Colorless oil.
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 6.63 (s, 2H), 5.94 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.36 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.19 (s, 4H), 4.97 - 4.88 (m, 1H), 4.67 (bs, 1H), 4.65 - 4.62 (m, 2H), 4.62 - 4.58 (m, 2H), 3.69 (dd, *J* = 11.0, 9.3 Hz, 1H), 3.50 (s, 6H), 3.30 (dt, *J* = 10.9, 8.6 Hz, 1H), 2.58 - 2.48 (m, 2H), 2.22 (dq, *J* = 10.2, 7.0 Hz, 1H), 1.95 (ddd, *J* = 13.4, 10.2, 8.3 Hz, 1H), 1.76 (ddd, *J* = 13.3, 8.9, 6.8 Hz, 1H), 1.70 (s, 3H), 1.64 - 1.56 (m, 2H), 1.39 (d, *J* = 6.3 Hz, 3H), 1.37 - 1.31 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.9, 155.0, 147.4, 143.3, 131.9, 118.8, 115.5, 109.9, 108.8, 94.9, 78.4, 68.3, 56.3, 50.4, 48.6, 46.2, 36.4, 31.9, 31.4, 31.1, 22.7, 20.0, 18.6, 14.2 ppm; $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{28}}$ = -13.4º (c = 0.83, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{29}H_{44}NaO_8$ $[M+Na]^+$ 543.2928, found 543.2933.

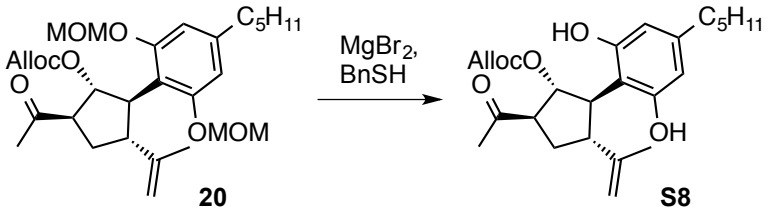
**(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl allyl carbonate (20)**



**S5** **20**

$NaHCO_3$ (14 mg, 0.17 mmol, 2 eq.) and Dess-Martin periodinane (70 mg, 0.17 mmol, 2 eq.) were added to a stirred solution of alcohol **S5** (43 mg, 0.08 mmol, 1 eq.) in $CH_2Cl_2$ (2 mL) at 25 ºC and the mixture was stirred for 1.5 h. Saturated $NaHCO_3$ solution (10 mL) was added. After extractive work-up ($CH_2Cl_2$), the organic layer was dried with $Na_2SO_4$ and evaporated. The residue was purified by column chromatography (cyclohexane/EtOAc 8:2) to yield ketone **20** (37 mg, 87%) as a colorless oil.
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 6.60 (bs, 2H), 5.82 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.75 (dd, *J* = 7.6, 4.2 Hz, 1H), 5.30 - 5.16 (m, 2H), 5.18 - 5.09 (m, 4H), 4.64 (bs, 1H), 4.62 - 4.58 (m, 1H), 4.53 - 4.46 (m, 2H), 3.87 (dd, *J* = 11.6, 7.6 Hz, 1H), 3.52 - 3.45 (m, 6H), 3.25 (td, *J* = 11.2, 7.1 Hz, 1H), 3.09 (dt, *J* = 9.6, 3.8 Hz, 1H), 2.57 - 2.45 (m, 2H), 2.32 (s, 3H), 2.17 (ddd, *J* = 12.8, 7.1, 3.4 Hz, 1H), 1.96 (ddd, *J* = 12.8, 10.9, 9.6 Hz, 1H), 1.66 (s, 3H), 1.62 – 1.53 (m, 2H), 1.37 - 1.27 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 207.8, 156.3, 154.8, 145.6, 143.6, 131.7, 118.9, 114.3, 111.1, 108.2, 94.7, 84.4, 68.4, 57.2, 56.2, 48.0, 45.8, 36.5, 31.9, 31.7, 31.0, 29.0, 22.7, 19.7, 14.2 ppm; $[\boldsymbol{a}]_{\boldsymbol{D}}^{\mathbf{26}}$ = -14.6º (c = 1.02, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{29}H_{42}NaO_8$ $[M+Na]^+$ 541.2772, found 541.2768.

**(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-dihydroxy-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl allyl carbonate (S8)**

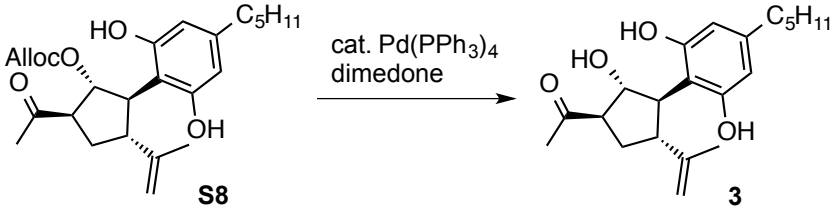



**20** **S8**

$MgBr_2$ (124 mg, 0.68 mmol, 10 eq.) and BnSH (79 μL, 0.68 mmol, 10 eq.) were added to a solution of ketone **20** (35 mg, 0.07 mmol, 1 eq.) in $Et_2O$ (1.5 mL) in an open flask, and stirred for 30 h at 25 ºC. The crude was filtrated to remove the salts and the residue was purified by column chromatography (cyclohexane/EtOAc 8:2) to yield ketone **S8** (18 mg, 62%) as a colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.19 (s, 2H), 5.86 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.61 (dd, *J* = 7.5, 3.4 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.72 (bs, 1H), 4.65 (bs, 1H), 4.59 - 4.48 (m, 2H), 3.81 (dd, *J* = 12.1, 7.5 Hz, 1H), 3.27 - 3.20 (m, 1H), 3.17 (dt, *J* = 7.5, 3.7 Hz, 1H), 2.45 - 2.39 (m, 2H), 2.34 (s, 3H), 2.11 - 2.05 (m, 2H), 1.68 (s, 3H), 1.57 - 1.50 (m, 2H), 1.34 - 1.27 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 210.7, 155.1, 154.8, 144.9, 143.5, 131.6, 119.2, 111.7, 109.8, 84.2, 68.7, 57.0, 47.4, 45.3, 35.6, 32.4, 31.7, 30.7, 29.9, 29.0, 22.7, 19.7, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$ = -0.2º (c = 1.05, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{25}H_{34}NaO_6$ $[M+Na]^+$ 453.2248, found 453.2247.

**Cannabimovone (3)**




**S8** **3**

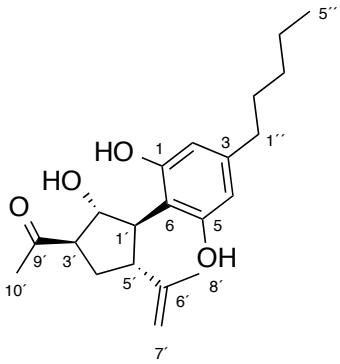
$Pd(PPh_3)_4$ (2.1 mg, 0.002 mmol, 0.05 eq.) and dimedone (10 mg, 0.07 mmol, 2 eq.) were added to a solution of ketone **S8** (16 mg, 0.04 mmol, 1 eq.) in THF (2 mL), and stirred for 1 h at 25 ºC. The solvent was evaporated and the residue was purified by column chromatography (pentane/$Et_2O$ 3:7) to yield cannabimovone **3** (11 mg, 85%) as a colorless oil.

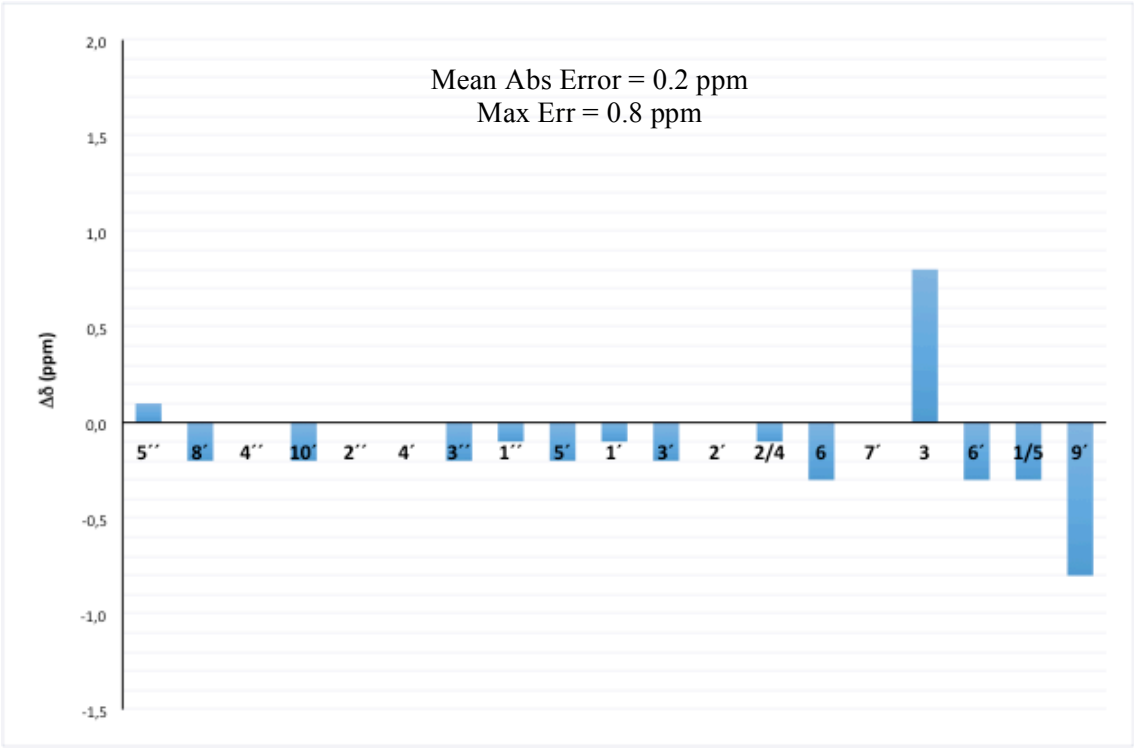
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.19 (s, 2H), 5.66 (s, 2H), 4.76 (dd, *J* = 9.0, 6.8 Hz, 1H), 4.71 (bs, 1H), 4.63 (bs, 1H), 3.52 (dd, *J* = 11.3, 9.0 Hz, 1H), 3.33 (dt, *J* = 11.3, 8.7 Hz, 1H), 3.04 (dt, *J* = 10.4, 6.5 Hz, 1H), 2.45 - 2.37 (m, 2H), 2.27 (s, 3H), 2.12 (ddd, *J* = 13.1, 8.5, 6.2 Hz, 1H), 2.00 (ddd, *J* = 13.2, 10.4, 9.0 Hz, 1H), 1.69 (m, 3H), 1.58 - 1.51 (m, 2H), 1.34 - 1.27 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 211.9, 155.7, 146.6, 143.3, 110.4, 110.3, 109.1, 77.9, 58.2, 48.5, 45.5, 35.6, 31.7, 31.2, 30.7, 29.7, 22.7, 20.2, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = -6.8º (c = 0.70, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{21}H_{30}NaO_4$ $[M+Na]^+$ 369.2036, found 369.2023.

NMR data were in accordance with those previously reported: O. Taglialatela-Scafati, A. Pagani, F. Scala, L. De Petrocellis, V. Di Marzo, G. Grassi, G. Appendino, *Eur. J. Org. Chem.* **2010**, 2067-2072.

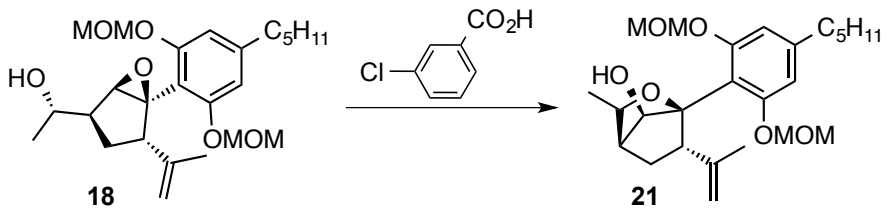
**Table S1**. Comparison of the recorded $^{13}C$ NMR data of **3** with those reported in the literature for Cannabimovone (*Eur. J. Org. Chem.* **2010**, 2067-2072).

| | **Isolated** | **$\delta_C$ (3)** | **Δδ(Isolated - 3)** | **[Δδ]** |
|---|---|---|---|---|
| **5´´** | 14,3 | 14,2 | 0,1 | 0,1 |
| **8´** | 20,0 | 20,2 | -0,2 | 0,2 |
| **4´´** | 22,7 | 22,7 | 0,0 | 0 |
| **10´** | 29,5 | 29,7 | -0,2 | 0,2 |
| **2´´** | 30,7 | 30,7 | 0,0 | 0 |
| **4´** | 31,2 | 31,2 | 0,0 | 0 |
| **3´´** | 31,5 | 31,7 | -0,2 | 0,2 |
| **1´´** | 35,5 | 35,6 | -0,1 | 0,1 |
| **5´** | 45,3 | 45,5 | -0,2 | 0,2 |
| **1´** | 48,4 | 48,5 | -0,1 | 0,1 |
| **3´** | 58,0 | 58,2 | -0,2 | 0,2 |
| **2´** | 77,9 | 77,9 | 0,0 | 0 |
| **2/4** | 109,0 | 109,1 | -0,1 | 0,1 |
| **6** | 110,0 | 110,3 | -0,3 | 0,3 |
| **7´** | 110,4 | 110,4 | 0,0 | 0 |
| **3** | 144,1 | 143,3 | 0,8 | 0,8 |
| **6´** | 146,3 | 146,6 | -0,3 | 0,3 |
| **1/5** | 155,4 | 155,7 | -0,3 | 0,3 |
| **9´** | 211,1 | 211,9 | -0,8 | 0,8 |
| | | **Average** | -0,1 | 0,2 |



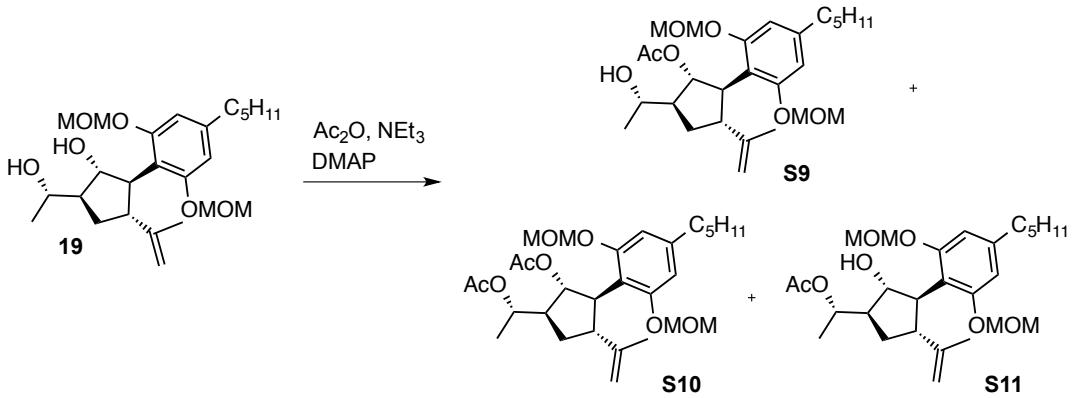



**(1*R*,3*S*,4*R*,6*S*,7*R*)-1-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-3-methyl-6-(prop-1-en-2-yl)-2-oxabicyclo[2.2.1]heptan-7-ol (21)**



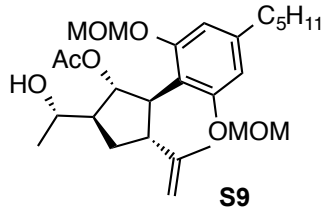

*m*-Chlorobenzoic acid (11 mg, 0.07 mmol, 2 eq.) was added to a solution of epoxide **18** (15.4 mg, 0.04 mmol, 1 eq.) in $CH_2Cl_2$ (1 mL). The mixture was stirred for 1 h at 25 ºC, diluted with $CH_2Cl_2$ (10 mL), and washed with brine (10 mL). The organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane/EtOAc 8:2) to give bicycle **21** (12 mg, 77%) as a white solid.
Single crystals suitable for X-ray diffraction were grown by evaporation of a saturated solution in $CH_2Cl_2/Et_2O$.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 6.61 (s, 1H), 5.23 - 5.13 (m, 4H), 4.68 - 4.63 (m, 1H), 4.61 - 4.56 (m, 1H), 4.58 - 4.54 (m, 1H), 3.92 (q, *J* = 6.5 Hz, 1H), 3.60 (s, 3H), 3.56 (s, 3H), 3.50 (dd, *J* = 9.9, 7.7 Hz, 1H), 3.47 (d, *J* = 2.7 Hz, 1H), 2.56 - 2.45 (m, 2H), 2.23 - 2.14 (m, 1H), 1.75 (dd, *J* = 22.6, 10.9 Hz, 1H), 1.68 (ddd, *J* = 12.0, 7.7, 3.4 Hz, 1H), 1.58 - 1.53 (m, 2H), 1.47 (s, 3H), 1.44 (d, *J* = 6.5 Hz, 3H), 1.37 - 1.27 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159.3, 154.6, 146.4, 145.1, 113.7, 112.1, 109.2, 96.3, 96.2, 89.8, 78.7, 77.7, 56.9, 56.5, 51.8, 45.0, 36.2, 32.7, 31.6, 31.0, 27.1, 22.7, 21.5, 21.3, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = -74.5º (c = 1.03, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{25}H_{38}NaO_6$ $[M+Na]^+$ 457.2561, found 457.2582; **m.p.** 60-62 ºC.

**Acetilation of diol 19**




$Et_3N$ (84 µL, 0.61 mmol, 3 eq.) and DMAP (catalytic amount) were added to the solution of diol **19** (88 mg, 0.20 mmol, 1 eq.) in $CH_2Cl_2$ (3 mL) at -30 ºC. Then, $Ac_2O$ (20 µL, 0.21 mmol, 1.05 eq.) in $CH_2Cl_2$ (1.5 mL) was added dropwise and the solution was stirred at -30 ºC for 1h. The solvent was evaporated and the residue was purified by column chromatography (cyclohexane/EtOAc 8:2 to 6:4) to obtain monoacetate **S9** (48 mg, 50%, 56% brsm), diacetate **S10** (14 mg), monoacetate **S11** (24 mg) and diol **19** (10 mg).
Protected diols **S10** and **S11** were hydrolyzed with $K_2CO_3$ in methanol to recover 28 mg of diol **19** (88% brsm for **S5**).

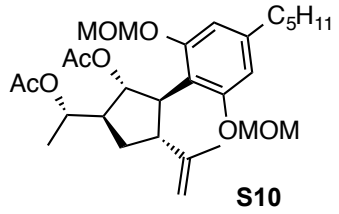
**(1*R*,2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentyl acetate (S9)**



**S9**

Colorless oil.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.59 (s, 2H), 5.66 (dd, *J* = 7.9, 3.0 Hz, 1H), 5.17 (bs, 4H), 4.62 (bs, 1H), 4.59 (bs, 1H), 3.91 - 3.81 (m, 2H), 3.50 (s, 6H), 3.24 - 3.13 (m, 1H), 2.67 - 2.44 (m, 2H), 2.05 - 1.97 (m, 2H), 1.95 (s, 3H), 1.75 - 1.68 (m, 1H), 1.67 (s, 3H), 1.62 - 1.53 (m, 2H), 1.35 - 1.28 (m, 4H), 1.24 (d, *J* = 6.1 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 4H) ppm; **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 172.9, 156.3, 146.0, 143.4, 114.6, 110.9, 108.3, 94.6, 82.2, 69.6, 56.3, 53.5, 47.6, 45.9, 36.4, 33.2, 31.9, 31.0, 22.7, 22.3, 21.6, 19.6, 14.2 ppm;$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = -0.9º (c = 0.95, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{27}H_{42}NaO_7$ $[M+Na]^+$ 501.2823, found 501.2825.

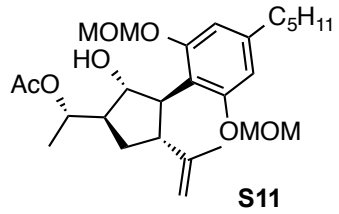
**(*S*)-1-((1*S*,2*R*,3*R*,4*R*)-2-acetoxy-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopentyl)ethyl acetate (S10)**



**S10**

Colorless oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.56 (bs, 2H), 5.86 (dd, *J* = 9.4, 6.8 Hz, 1H), 5.16 (bs, 4H), 5.01 (dq, *J* = 7.9, 6.3 Hz, 1H), 4.64 (bs, 1H), 4.58 (bs, 1H), 3.77 (dd, *J* = 11.4, 9.4 Hz, 1H), 3.49 (s, 6H), 3.23 (dt, *J* = 11.4, 8.8 Hz, 1H), 2.57 - 2.40 (m, 2H), 2.37 - 2.27 (m, 1H), 2.00 (s, 3H), 1.97 - 1.89 (m, 1H), 1.87 (s, 3H), 1.75 (ddd, *J* = 13.2, 8.4, 5.8 Hz, 1H), 1.67 (s, 3H), 1.61 - 1.52 (m, 2H), 1.37 - 1.28 (m, 4H), 1.27 (d, *J* = 6.3 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 170.8, 170.1, 146.6, 143.3, 114.1, 110.5, 108.4, 94.9, 78.5, 72.8, 56.1, 47.9, 46.6, 45.8, 36.4, 31.9, 31.1, 30.9, 22.7, 21.5, 21.3, 19.7, 18.1, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = -14.7º (c = 0.95, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{29}H_{44}NaO_8$ $[M+Na]^+$ 543.2928, found 543.2909.

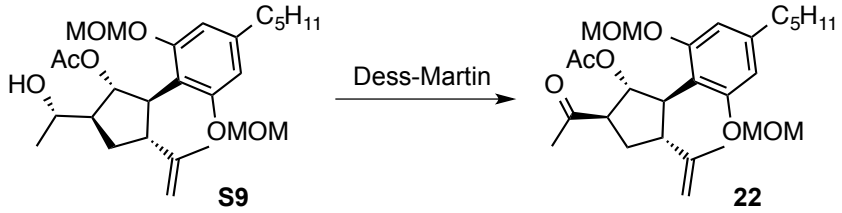
**(*S*)-1-((1*R*,2*R*,3*R*,4*R*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-2-hydroxy-4-(prop-1-en-2-yl)cyclopentyl)ethyl acetate (S11)**



**S11**

Colorless oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.16 (s, 4H), 5.02 (dq, *J* = 8.2, 6.2 Hz, 1H), 4.65 (bs, 1H), 4.58 (bs, 1H), 4.48 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.65 (dd, *J* = 10.9, 9.3 Hz, 1H), 3.48 (s, 6H), 3.25 (dt, *J* = 10.9, 8.5 Hz, 1H), 2.60 - 2.43 (m, 2H), 2.14 (dq, *J* = 9.9, 7.4 Hz, 1H), 2.04 (s, 3H), 1.97 - 1.83 (m, 1H), 1.76 - 1.69 (m, 1H), 1.68 (s, 3H), 1.63 - 1.52 (m, 2H), 1.35 - 1.31 (m, 4H), 1.30 (d, *J* = 6.2 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 170.9, 156.8, 147.4, 143.3, 115.4, 109.9, 108.8, 95.0, 78.8, 74.2, 56.3, 50.5, 48.5, 46.0, 36.4, 31.8, 31.4, 31.1, 22.7, 21.6, 19.9, 18.9, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = -27.3º (c = 0.96, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{27}H_{42}NaO_7$ $[M+Na]^+$ 501.2823, found 501.2824.

**(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl acetate (22)**

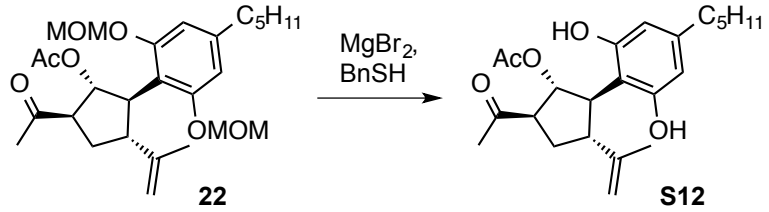



**S9** **22**

$NaHCO_3$ (17 mg, 0.20 mmol, 2 eq.) and Dess-Martin periodinane (85 mg, 0.20 mmol, 2 eq.) were added to a stirred solution of alcohol **S9** (48 mg, 0.10 mmol, 1 eq.) in $CH_2Cl_2$ (2 mL) and the mixture was stirred for 1 h at 25 ºC. Saturated $NaHCO_3$ solution (5 mL) was added. After extractive work-up ($CH_2Cl_2$), the organic layer was dried with $Na_2SO_4$ and evaporated. The residue was purified by column chromatography (cyclohexane/EtOAc 8:2) to yield ketone **22** (35 mg, 73%) as a colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.59 (s, 2H), 5.79 (dd, *J* = 7.8, 4.4 Hz, 1H), 5.20 - 5.09 (m, 4H), 4.65 (bs, 1H), 4.60 (bs, 1H), 3.81 (dd, *J* = 11.6, 7.8 Hz, 1H), 3.48 (s, 6H), 3.27 (td, *J* = 11.2, 7.1 Hz, 1H), 2.97 (dt, *J* = 9.6, 3.9 Hz, 1H), 2.57 - 2.42 (m, 2H), 2.31 (s, 3H), 2.21 - 2.11 (m, 1H), 1.95 (s, 3H), 1.99 - 1.87 (m, 1H), 1.66 (s, 3H), 1.62 - 1.52 (m, 2H), 1.39 - 1.25 (m, 4H), 0.96 - 0.82 (t, *J* = 7.0 Hz, 3H) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 208.3, 171.0, 156.4, 145.8, 143.5, 114.5, 110.9, 108.3, 94.5, 80.8, 57.4, 56.2, 47.8, 45.7, 36.5, 31.9, 31.9, 31.0, 28.8, 22.6, 21.3, 19.8, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -24.2º (c = 1.00, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{27}H_{40}NaO_7$ $[M+Na]^+$ 499.2666, found 499.2655.

**(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-dihydroxy-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl acetate (S12)**

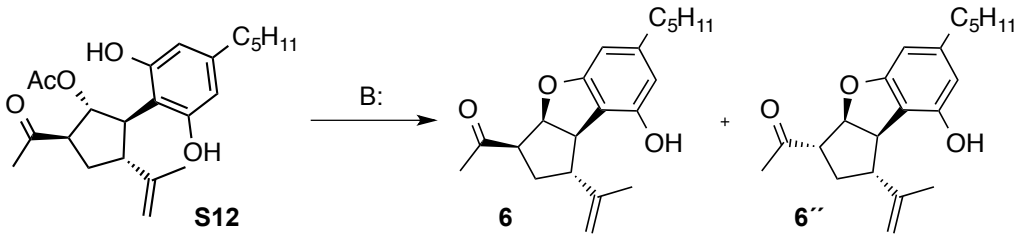



**22** **S12**

$MgBr_2$ (135 mg, 0.73 mmol, 10 eq.) and BnSH (86 μL, 0.73 mmol, 10 eq.) were added to solution of ketone **22** (35 mg, 0.07 mmol, 1 eq.) in $Et_2O$ (1.5 mL) in an open flask, and stirred for 24 h at 25 ºC. The crude was filtrated to remove the salts and the residue was purified by column chromatography (cyclohexane/EtOAc 7:3) to yield ketone **S12** (26 mg, 82%) as a colorless oil.

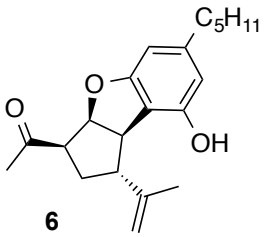
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.19 (s, 2H), 5.65 (dd, *J* = 7.6, 3.5 Hz, 1H), 4.73 (dt, *J* = 1.9, 0.9 Hz, 1H), 4.65 (t, *J* = 1.6 Hz, 1H), 3.76 (dd, *J* = 12.0, 7.6 Hz, 1H), 3.23 (td, *J* = 11.6, 6.9 Hz, 1H), 3.06 (dt, *J* = 9.4, 3.2 Hz, 1H), 2.47 - 2.37 (m, 2H), 2.34 (s, 3H), 2.12 - 2.03 (m, 2H), 2.01 (s, 3H), 1.69 (s, 3H), 1.57 - 1.50 (m, 2H), 1.35 - 1.24 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 211.4, 171.3, 155.2, 145.2, 143.4, 128.7, 111.5, 110.0, 80.9, 57.2, 47.3, 45.4, 35.6, 32.6, 31.7, 30.7, 28.9, 22.7, 21.3, 19.8, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = -3.8º (c = 0.97, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{23}H_{32}NaO_5$ $[M+Na]^+$ 411.2142, found 411.2142.

**Oxy-Michael addition**



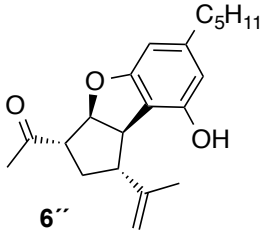

$K_2CO_3$ (17 mg, 0.12 mmol, 4 eq.) was added to a solution of ketone **S12** (12 mg, 0.03 mmol, 1 eq.) in MeOH (1 mL), and stirred for 15 min at 25 ºC. The crude was filtrated to remove the remaining $K_2CO_3$, the solvent was evaporated and the residue was purified by column chromatography (cyclohexane/EtOAc 8:2) to yield anhydrocannabimovone **6** (6.1 mg, 60%) and anhydrocannabimovone **6´´** (1.9 mg, 19%).
Using other conditions, selectivity drop off: DBU in $CH_2Cl_2$ or THF, ratio **6**:**6´´** = 4:6 after 24 h; pyrrolidine in $CH_2Cl_2$ (using Cannabimovone **3** as substrate), ratio **6**:**6´´** = 6:4 after 14 h.

**Anhydrocannabimovone (6)**




White solid.
Single crystals suitable for X-ray diffraction were grown in a saturated solution in $CH_2Cl_2$/cyclohexane.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.16 (s, 1H), 6.12 (s, 1H), 5.53 (dd, *J* = 7.8, 5.9 Hz, 1H), 4.87 (bs, 1H), 4.71 (bs, 1H), 3.95 (dd, *J* = 7.7, 2.2 Hz, 1H), 3.22 (dt, *J* = 12.0, 6.2 Hz, 1H), 2.83 (d, *J* = 7.5 Hz, 1H), 2.49 - 2.42 (m, 2H), 2.32 (s, 3H), 2.10 (ddd, *J* = 13.4, 11.8, 7.6 Hz, 1H), 1.88 - 1.86 (m, 1H), 1.85 (s, 3H), 1.84 - 1.78 (m, 1H), 1.55 - 1.52 (m, 2H), 1.35 - 1.26 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 206.2, 161.6, 151.9, 148.1, 145.7, 112.8, 109.6, 108.3, 102.4, 88.5, 57.5, 50.5, 49.6, 36.1, 31.6, 31.1, 30.1, 29.0, 22.7, 22.5, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +40.6º (c = 0.29, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{21}H_{28}NaO_3$ $[M+Na]^+$ 351.1931, found 351.1930; **m.p.** 45 - 47 ºC.

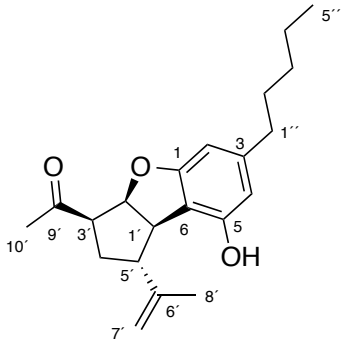
**Anhydrocannabimovone (6´´)**

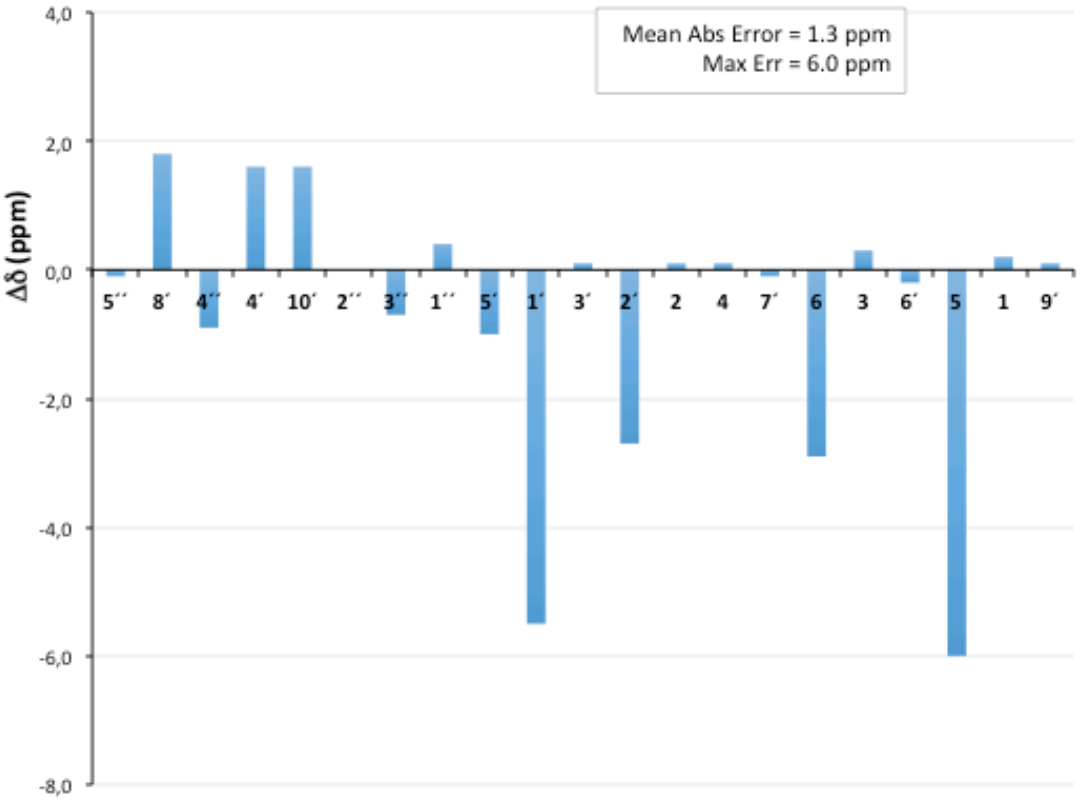



White solid.
**$^1$H NMR (**500 MHz, $CDCl_3$) δ 6.25 (s, 1H), 6.23 (s, 1H), 5.28 (dd, *J* = 10.1, 6.8 Hz, 1H), 5.16 (bs, 1H), 5.02 (bs, 1H), 5.01 (s, 1H), 3.83 (dd, *J* = 10.1, 8.9 Hz, 1H), 3.18 (dt, *J* = 13.0, 6.5 Hz, 1H), 2.80 (ddd, *J* = 12.5, 8.8, 5.7 Hz, 1H), 2.53 - 2.46 (m, 2H), 2.33 (s, 3H), 2.06 (dt, *J* = 12.3, 6.0 Hz, 1H), 1.88 (s, 3H), 1.80 (q, *J* = 12.6 Hz, 1H), 1.62 - 1.55 (m, 2H), 1.35 - 1.27 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 2H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 208.1, 160.7, 152.8, 147.9, 146.1, 112.9, 112.5, 108.9, 102.7, 89.2, 60.5, 54.9, 48.6, 36.2, 34.1, 31.6, 31.1, 30.2, 22.7, 19.8, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +97.0º (c = 0.38, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{21}H_{28}NaO_3$ $[M+Na]^+$ 351.1931, found 351.1923; **m.p.** 124 -127 ºC.

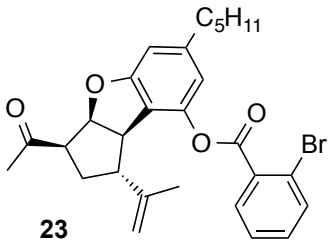
**Table S2**. Comparison of the recorded $^{13}C$ NMR data of **6** with those reported in the literature for Anhydrocannabimovone (*Eur. J. Org. Chem.* **2010**, 2067-2072).

| | Reported | $\delta_C$ (6) | Δδ(Isolated - 6) | [Δδ] |
|---|---|---|---|---|
| **5´´** | 14,3 | 14,2 | -0,1 | 0,1 |
| **8´** | 20,7 | 22,5 | 1,8 | 1,8 |
| **4´´** | 23,6 | 22,7 | -0,9 | 0,9 |
| **4´** | 27,4 | 29,0 | 1,6 | 1,6 |
| **10´** | 28,5 | 30,1 | 1,6 | 1,6 |
| **2´´** | 31,1 | 31,1 | 0,0 | 0,0 |
| **3´´** | 32,3 | 31,6 | -0,7 | 0,7 |
| **1´´** | 35,7 | 36,1 | 0,4 | 0,4 |
| **5´** | 50,6 | 49,6 | -1,0 | 1,0 |
| **1´** | 56,0 | 50,5 | -5,5 | 5,5 |
| **3´** | 57,4 | 57,5 | 0,1 | 0,1 |
| **2´** | 91,2 | 88,5 | -2,7 | 2,7 |
| **2** | 102,3 | 102,4 | 0,1 | 0,1 |
| **4** | 108,2 | 108,3 | 0,1 | 0,1 |
| **7´** | 109,7 | 109,5 | -0,2 | 0,2 |
| **6** | 115,7 | 112,8 | -2,9 | 2,9 |
| **3** | 145,4 | 145,7 | 0,3 | 0,3 |
| **6´** | 148,3 | 148,1 | -0,2 | 0,2 |
| **5** | 157,9 | 151,9 | -6,0 | 6,0 |
| | | **Average** | -0,7 | 1,3 |



**(1*R*,3*R*,3a*S*,8b*R*)-3-acetyl-6-pentyl-1-(prop-1-en-2-yl)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-8-yl 2-bromobenzoate (23)**



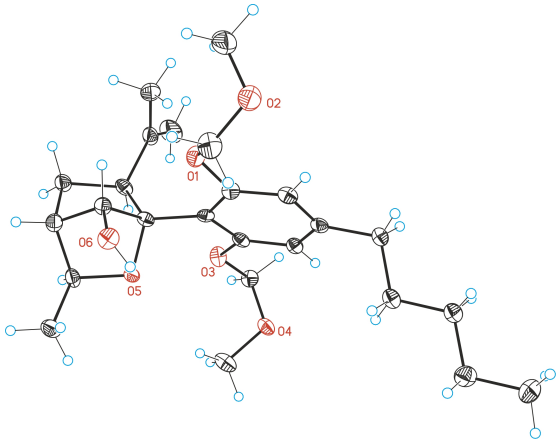
**23**

DMAP (1.2 mg, 0.01 mmol, 0.5 eq.), 2-bromobenzoic acid (4.4 mg, 0.02 mmol, 1.1 eq.) and EDC·HCl (5.7 mg, 0.03 mmol, 1.5 eq.) was added to a solution of anhydrocannabimovone **6** (6.5 mg, 0.02 mmol, 1 eq.) in $CH_2Cl_2$ (1.2 mL). After stirring for 24 h, $CH_2Cl_2$ (10 mL) was added and the organic layer was washed with HCl 10% (5 mL), $NaHCO_3$ (5 mL) and brine (5 mL). Then, the solution was dried over $Na_2SO_4$ and evaporated. The residue was purified by column chromatography (pentane/$Et_2O$ 9:1 to 8:2) to afford ester **23** (7.2 mg, 71%) as a white solid.

Single crystals suitable for X-ray diffraction were grown by evaporation of a saturated solution in $Et_2O$/pentane.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.97 - 7.93 (m, 1H), 7.76 - 7.71 (m, 1H), 7.44 - 7.37 (m, 2H), 6.58 (s, 1H), 6.48 (s, 1H), 5.60 - 5.54 (m, 1H), 4.75 (s, 1H), 4.59 (s, 1H), 4.02 (d, *J* = 7.5 Hz, 1H), 3.17 (dt, *J* = 12.4, 6.1 Hz, 1H), 2.77 (d, *J* = 7.8 Hz, 1H), 2.57 - 2.52 (m, 2H), 2.33 (s, 3H), 2.10 (td, *J* = 13.0, 7.6 Hz, 1H), 1.81 (ddd, *J* = 13.5, 6.3, 1.3 Hz, 1H), 1.64 (s, 3H), 1.61 - 1.55 (m, 2H), 1.35 - 1.28 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm; **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 205.8, 163.8, 161.6, 147.2, 146.7, 145.7, 134.9, 133.4, 132.0, 131.2, 127.4, 122.6, 119.3, 114.2, 109.8, 107.4, 88.7, 57.5, 50.7, 50.1, 36.1, 31.6, 31.0, 29.9, 28.8, 22.7, 22.5, 14.2 ppm; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = +71.7º (c = 0.67, $CHCl_3$); **HRMS-ESI** *m/z* calcd for $C_{28}H_{31}BrNaO_4$ $[M+Na]^+$ 533.1298, found 533.1285; **m.p.** 99 - 102 ºC.

## X-ray structure analyses



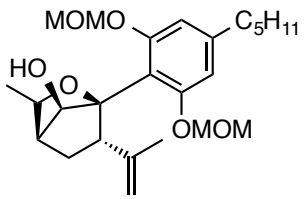
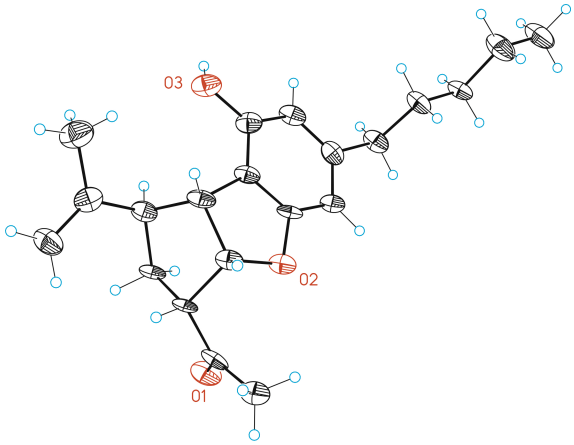




Table S3. Crystal data and structure refinement for **21**.

| | | |
|---|---|---|
| Empirical formula | C25 H38 O6 | |
| Formula weight | 434.55 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2 | |
| Unit cell dimensions | a = 9.7960(10)Å | α= 90°. |
| | b = 9.2718(9)Å | β = 92.067(3)°. |
| | c = 13.2383(13)Å | γ = 90°. |
| Volume | 1201.6(2) Å3 | |
| Z | 2 | |
| Density (calculated) | 1.201 Mg/m3 | |
| Absorption coefficient | 0.084 mm-1 | |
| F(000) | 472 | |
| Crystal size | 0.35 x 0.15 x 0.10 $mm^3$ | |
| Theta range for data collection | 1.539 to 25.101°. | |
| Index ranges | -11<=h<=11,0<=k<=10,0 <=l<=15 | |
| Reflections collected | 4709 | |
| Independent reflections | 4709[R(int) = ?] | |
| Completeness to theta = 25.101° | 98.0% | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.992 and 0.548 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 4709/ 1/ 287 | |
| Goodness-of-fit on $F^2$ | 1.129 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0618, wR2 = 0.1605 | |
| R indices (all data) | R1 = 0.0833, wR2 = 0.1865 | |
| Flack parameter | x =1.3(12) | |
| Largest diff. peak and hole | 0.251 and -0.374 e.$Å^{-3}$ | |



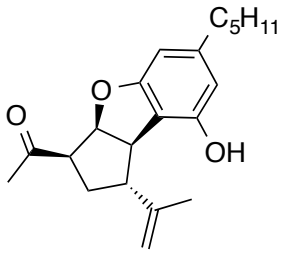




Table S4. Crystal data and structure refinement for **6** as solvate.

| | | |
|---|---|---|
| Empirical formula | C24 H34 O3 | |
| Formula weight | 370.51 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | P2(1)2(1)2 | |
| Unit cell dimensions | a = 16.937(3)Å | α= 90°. |
| | b = 25.771(5)Å | β = 90°. |
| | c = 4.9287(10)Å | γ = 90°. |
| Volume | 2151.3(7) Å3 | |
| Z | 4 | |
| Density (calculated) | 1.144 Mg/m3 | |
| Absorption coefficient | 0.073 mm-1 | |
| F(000) | 808 | |
| Crystal size | 0.25 x 0.10 x 0.02 $mm^3$ | |
| Theta range for data collection | 1.580 to 23.294°. | |
| Index ranges | -18<=h<=15,-28<=k<=19,-4<=l<=5 | |
| Reflections collected | 6653 | |
| Independent reflections | 3067[R(int) = 0.0684] | |
| Completeness to theta =23.294° | 97.6% | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.999 and 0.768 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3067/ 60/ 275 | |
| Goodness-of-fit on $F^2$ | 1.051 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0648, wR2 = 0.1473 | |
| R indices (all data) | R1 = 0.1104, wR2 = 0.1782 | |
| Flack parameter | x =-0.8(10) | |
| Largest diff. peak and hole | 0.290 and -0.348 e.$Å^{-3}$ | |

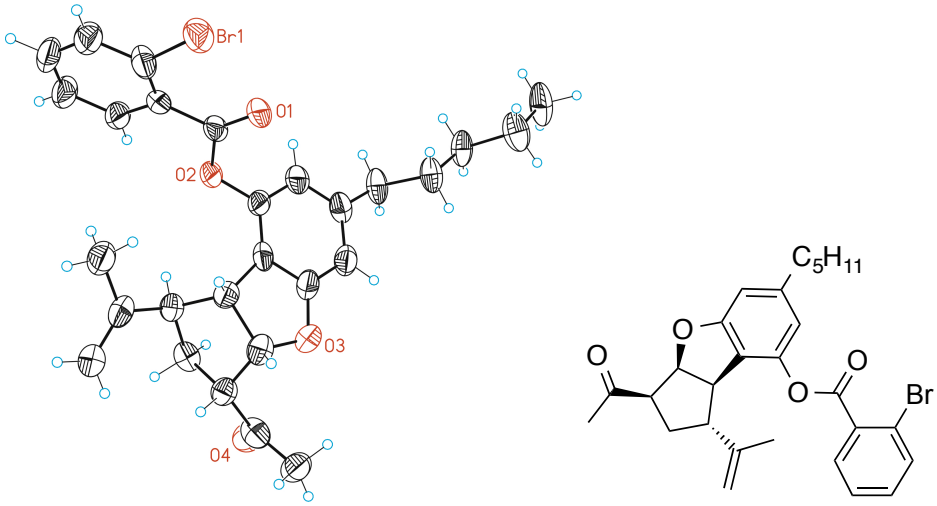



Table S5. Crystal data and structure refinement for **23** as solvate.

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| | | |
|---|---|---|
| Empirical formula | C29.25 H34 Br O4 | |
| Formula weight | 529.47 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | P2(1)2(1)2 | |
| Unit cell dimensions | a = 5.0032(4)Å | α= 90°. |
| | b = 14.3132(9)Å | β = 90°. |
| | c = 38.066(3)Å | γ = 90°. |
| Volume | 2725.9(3) Å3 | |
| Z | 4 | |
| Density (calculated) | 1.290 Mg/m3 | |
| Absorption coefficient | 1.539 mm-1 | |
| F(000) | 1106 | |
| Crystal size | 0.10 x 0.05 x 0.05 $mm^3$ | |
| Theta range for data collection | 2.570 to 25.386°. | |
| Index ranges | -6<=h<=4,-17<=k<=17,-45<=l<=45 | |
| Reflections collected | 23921 | |
| Independent reflections | 4955[R(int) = 0.0940] | |
| Completeness to theta =25.386° | 99.5% | |
| Absorption correction | Multi-scan | |
| Max. and min. transmission | 0.927 and 0.507 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 4955/ 209/ 437 | |
| Goodness-of-fit on $F^2$ | 1.080 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0735, wR2 = 0.1520 | |
| R indices (all data) | R1 = 0.1183, wR2 = 0.1686 | |
| Flack parameter | x =0.014(10) | |
| Largest diff. peak and hole | 0.848 and -0.511 e.$Å^{-3}$ | |

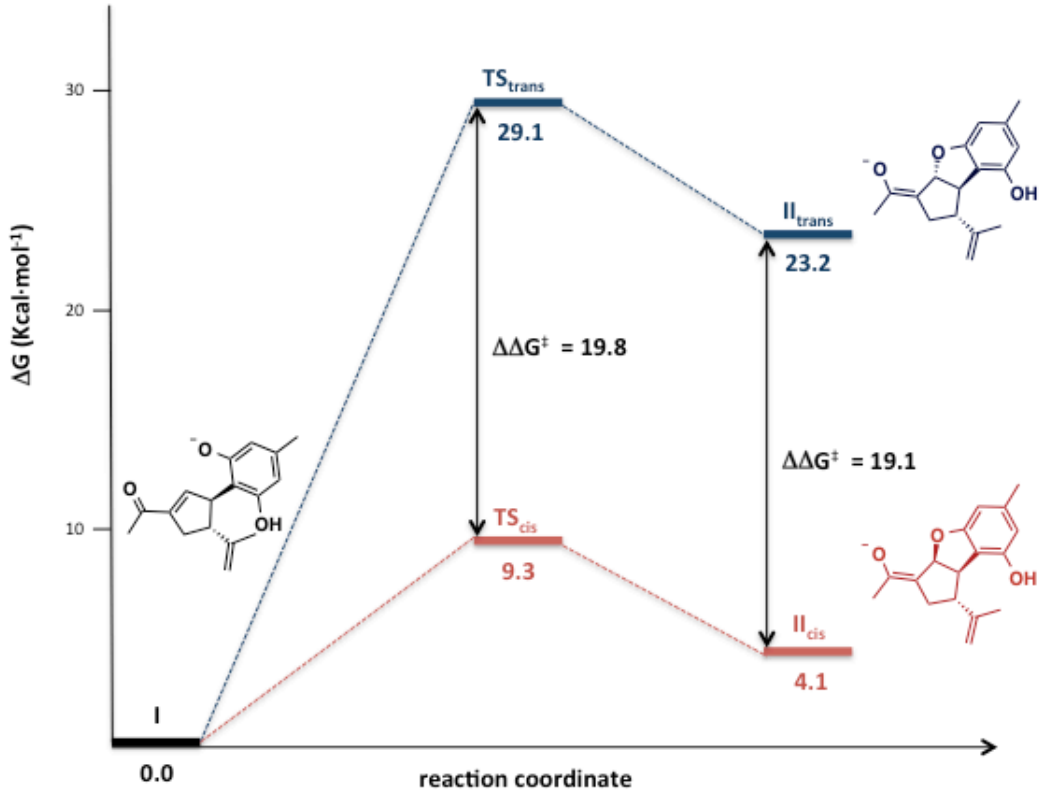
## Computational Details

All calculations were carried out with the Gaussian 09 package.[1] The meta-hybrid M06-2X[2] and 6-31G(d,p) basis set in conjunction with ultrafine integration grids were used for conformational searches, full geometry optimizations and geometry scans. Frequency analyses were carried out at the same level used in the geometry optimizations, and the nature of the stationary points (minima or transition states) was determined according to the appropriate number of negative eigenvalues of the Hessian matrix. Scaled frequencies were not considered. Zero-point vibrational energy, thermal and entropic corrections to energy at 298 K were calculated from vibrational frequencies.
Bulk solvent effects (in dichloromethane and methanol for geometry optimizations and in chloroform for NMR calculations) were considered during optimization through the IEF-PCM polarizable continuum model.[3]
All possible rotamers and ring isomers were investigated. Some structures converged to the same stationary point upon optimization; redundant isomers were discarded and only the unique structures were included in the Boltzmann distribution of Gibbs free energies.
Cartesian coordinates, electronic energies, entropies, enthalpies, Gibbs free energies, and lowest frequencies of the minimum energy conformations of all structures are available in this Supporting Information. All the optimized geometries are available from the authors upon request.
NMR chemical shifts were calculated at the equilibrium geometries for all conformers with the GIAO[4] method at the IEF-PCM/mPW1PW91/6-311+G(2d,p) level[5].

[1] M. J. Frisch, G. W. T., H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox; Gaussian, I., Wallingford CT, 2009., Ed. 2009.
[2] Y. Zhao, D. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215-241.
[3] G. Scalmani, M. J. Frisch *J. Chem. Phys.* **2010**, *132*, 114110-114125.
[4] (a) F. J. London, *Phys. Radium* **1937**, *8*, 397-409; (b) K. Wolinski, J. F. Hinton, P. Pulay, *J. Am. Chem. Soc.* **1990**, *112*, 8251-8260; (c) Cheeseman, J. R.; Trucks, G. W.; Keith, T. A.; Frisch, M. J. *J. Chem. Phys.* **1996**, *104*, 5497.
[5] C. Adamo, V. Barone, *J. Chem. Phys.* **1998**, *108*, 664-75.

**Uncatalyzed oxy-Michael cyclization**

**Figure S1.** Minimum energy profile and optimized geometries for the oxy-Michael cyclization calculated with IEF-PCM(MeOH)/M06-2X/6-31G(d,p).



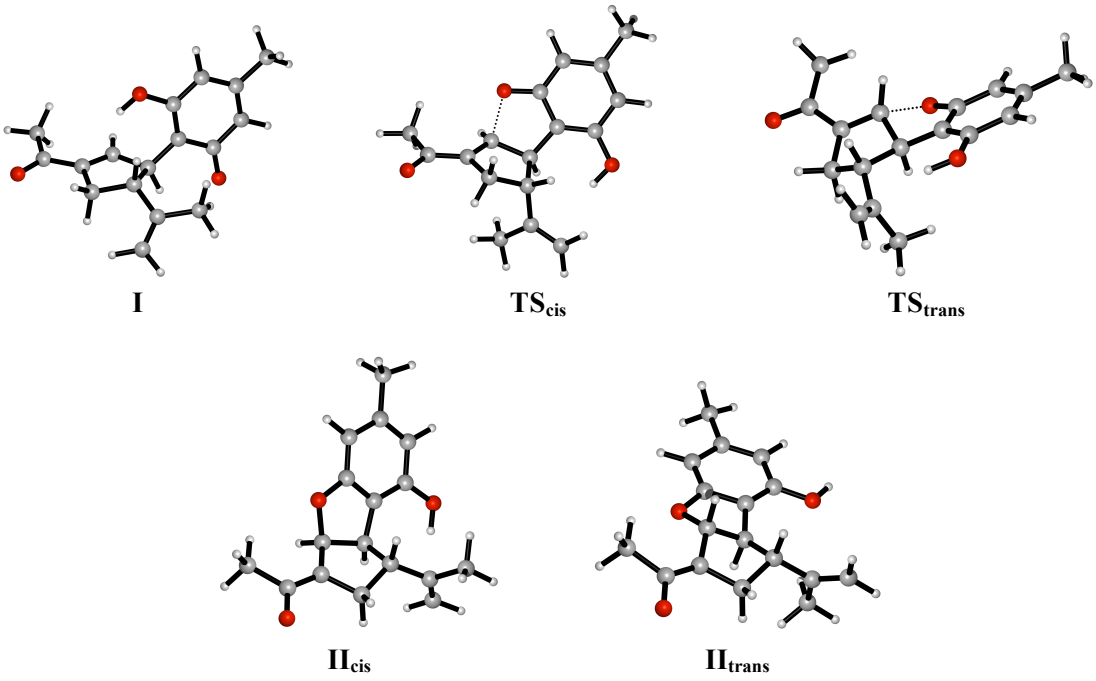



**Table S6.** Energies, enthalpies, free energies, entropies, and lowest frequencies of all the calculated structures at the M06-2X/6-31G(d,p) level. Different isomers of the same stationary point in the potential energy surface are labeled with numbers.

**sm** = starting material (phenoxide). I corresponds to the lowest energy isomer.
**pcis** = *cis*-Michael adduct (enolate). $II_{cis}$ corresponds to the lowest energy isomer.
**ptrans** = *trans*-Michael adduct (enolate). $II_{trans}$ corresponds to the lowest energy isomer.
**TScis** = *cis*-Michael addition transition state. $TS_{cis}$ corresponds to the lowest energy isomer.
**TStrans** = *trans*-Michael addition transition state . $TS_{trans}$ corresponds to the lowest energy isomer.

| Structure | $E_{elec}$ (Hartree)[a] | $E_{elec}$ + ZPE (Hartree)[a] | H (Hartree)[a] | G (Hartree)[a,b] | S (cal $mol^{-1}$ $K^{-1}$)[b] | Lowest freq. ($cm^{-1}$) |
|---|---|---|---|---|---|---|
| **sm1** | –884.656939 | –884.334650 | –884.313647 | –884.383905 | 147.9 | 33.3 |
| **sm2** | –884.659253 | –884.336974 | –884.315969 | –884.386334 | 148.1 | 32.9 |
| **sm3** | –884.655126 | –884.333216 | –884.312110 | –884.383351 | 149.9 | 30.1 |
| **sm4** | –884.657399 | –884.335399 | –884.314360 | –884.385216 | 149.1 | 32.5 |
| **sm5** | –884.656827 | –884.334319 | –884.313432 | –884.383382 | 147.2 | 34.8 |
| **sm6** | –884.659081 | –884.336630 | –884.315711 | –884.385759 | 147.4 | 37.5 |
| **sm7** | –884.654915 | –884.332714 | –884.311729 | –884.382751 | 149.5 | 18.8 |
| **sm8** | –884.657191 | –884.334797 | –884.313914 | –884.383998 | 147.5 | 38.2 |
| **sm9** | –884.660606 | –884.338244 | –884.317286 | –884.388039 | 148.9 | 31.8 |
| **sm10** | –884.660105 | –884.337808 | –884.316806 | –884.387165 | 148.1 | 34.8 |
| **sm11** | –884.658515 | –884.336122 | –884.315268 | –884.385632 | 148.1 | 33.5 |
| **sm12** | –884.657968 | –884.335855 | –884.314867 | –884.385278 | 148.2 | 35.4 |
| **sm13 (I)** | –884.664339 | –884.341513 | –884.320904 | –884.389943 | 145.3 | 39.4 |
| **sm15** | –884.658869 | –884.336269 | –884.315543 | –884.384981 | 146.1 | 40.0 |
| **sm16** | –884.660111 | –884.337411 | –884.316728 | –884.387202 | 148.3 | 23.7 |
| | | | | | | |
| **pcis1** | –884.658081 | –884.334156 | –884.314162 | –884.381833 | 142.4 | 35.4 |
| **pcis2** | –884.654961 | –884.331442 | –884.311217 | –884.379462 | 143.6 | 41.8 |
| **pcis3** | –884.656395 | –884.332752 | –884.312634 | –884.380992 | 143.9 | 24.1 |
| **pcis4** | –884.653448 | –884.330309 | –884.309902 | –884.379125 | 145.7 | 34.1 |
| **pcis5 ($II_{cis}$)** | –884.657025 | –884.333276 | –884.313162 | –884.383450 | 147.9 | 3.6 |
| **pcis6** | –884.653206 | –884.329864 | –884.309600 | –884.378360 | 144.7 | 24.6 |
| **pcis7** | –884.655433 | –884.331550 | –884.311548 | –884.379315 | 142.6 | 26.8 |
| **pcis8** | –884.651629 | –884.328410 | –884.308087 | –884.376865 | 144.8 | 30.0 |
| **pcis9** | –884.658060 | –884.333626 | –884.313863 | –884.381286 | 141.9 | 26.2 |
| **pcis10** | –884.656883 | –884.332463 | –884.312721 | –884.379527 | 140.6 | 29.2 |
| **pcis11** | –884.656270 | –884.332202 | –884.312172 | –884.381576 | 146.1 | 8.1 |
| **pcis12** | –884.655034 | –884.331223 | –884.311131 | –884.379385 | 143.7 | 24.6 |
| **pcis13** | –884.657161 | –884.333402 | –884.313304 | –884.381614 | 143.8 | 28.2 |
| **pcis14** | –884.655057 | –884.331263 | –884.311186 | –884.379418 | 143.6 | 28.5 |
| **pcis15** | –884.655520 | –884.331889 | –884.311701 | –884.380504 | 144.8 | 25.2 |
| **pcis16** | –884.653982 | –884.330284 | –884.310157 | –884.378475 | 143.8 | 31.6 |
| | | | | | | |
| **ptrans1** | –884.628771 | –884.304620 | –884.284694 | –884.351982 | 141.6 | 40.0 |

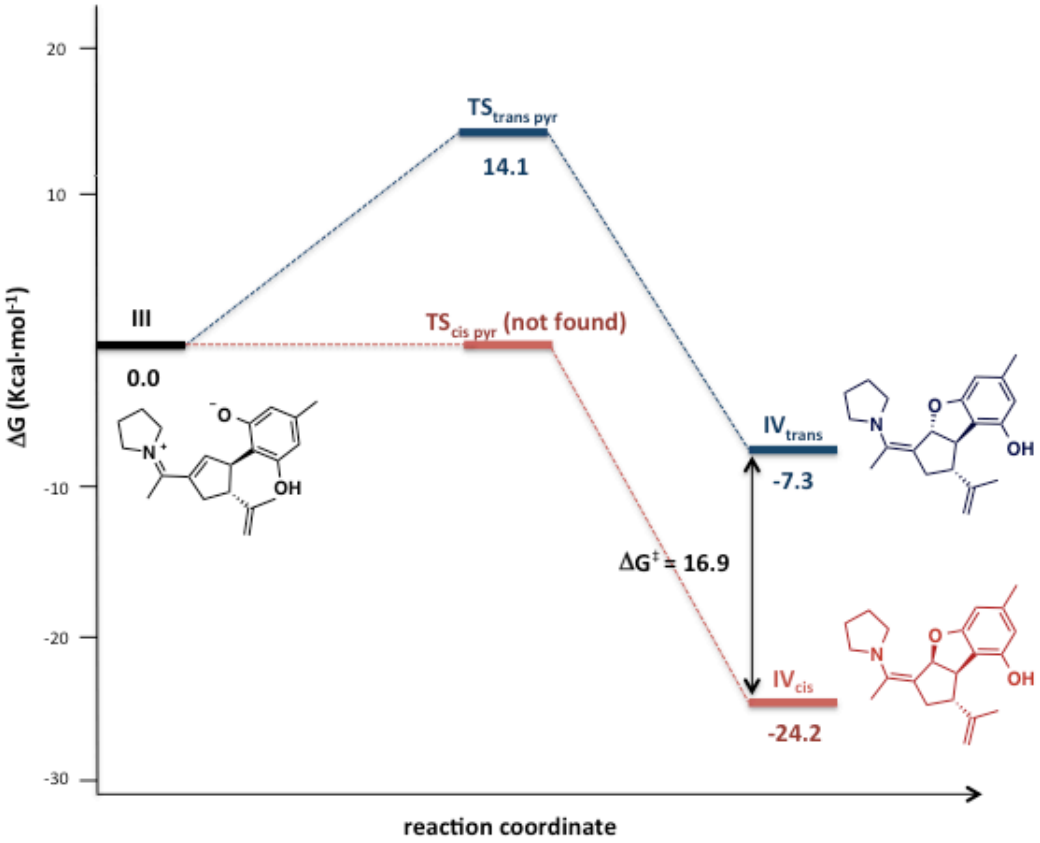
| | | | | | | |
|---|---|---|---|---|---|---|
| **ptrans2** | –884.624767 | –884.301059 | –884.280944 | –884.349331 | 143.9 | 22.1 |
| **ptrans3** | –884.622090 | –884.298463 | –884.278312 | –884.346444 | 143.4 | 30.1 |
| **ptrans4** | –884.625998 | –884.301865 | –884.281913 | –884.349274 | 141.8 | 45.5 |
| **ptrans5** | –884.629853 | –884.305735 | –884.285874 | –884.352904 | 141.1 | 37.2 |
| **ptrans6** | –884.623918 | –884.300181 | –884.280125 | –884.347642 | 142.1 | 37.7 |
| **ptrans7** | –884.621072 | –884.297614 | –884.277335 | –884.346161 | 144.9 | 26.3 |
| **ptrans8** | –884.626972 | –884.302956 | –884.282979 | –884.350750 | 142.6 | 27.0 |
| **ptrans9** | –884.628771 | –884.304620 | –884.284693 | –884.351986 | 141.6 | 40.0 |
| **ptrans10** | –884.624768 | –884.301067 | –884.280945 | –884.349444 | 144.2 | 19.7 |
| **ptrans11** | –884.622090 | –884.298460 | –884.278311 | –884.346425 | 143.4 | 30.4 |
| **ptrans12** | –884.625998 | –884.301866 | –884.281914 | –884.349273 | 141.8 | 45.6 |
| **ptrans13 ($II_{trans}$)** | –884.629853 | –884.305737 | –884.285875 | –884.352909 | 141.1 | 37.2 |
| **ptrans14** | –884.623918 | –884.300181 | –884.280125 | –884.347646 | 142.1 | 37.5 |
| **ptrans15** | –884.621072 | –884.297614 | –884.277335 | –884.346162 | 144.9 | 26.4 |
| **ptrans16** | –884.626972 | –884.302956 | –884.282979 | –884.350745 | 142.6 | 27.1 |
| | | | | | | |
| **TScis1** | –884.647574 | –884.325203 | –884.305420 | –884.372194 | 140.5 | –264.7 |
| **TScis2** | –884.649794 | –884.327625 | –884.307670 | –884.375191 | 142.1 | –277.4 |
| **TScis3 ($TS_{cis}$)** | –884.645579 | –884.323519 | –884.303680 | –884.370666 | 141.0 | –265.6 |
| **TScis4** | –884.647933 | –884.325820 | –884.305960 | –884.372937 | 141.0 | –273.5 |
| **TScis5** | –884.646931 | –884.324774 | –884.304980 | –884.371639 | 140.3 | –271.1 |
| **TScis6** | –884.646140 | –884.324062 | –884.304055 | –884.371795 | 142.6 | –261.7 |
| **TScis7** | –884.644926 | –884.323266 | –884.303356 | –884.370298 | 140.9 | –271.5 |
| **TScis8** | –884.647950 | –884.326154 | –884.306288 | –884.373181 | 140.8 | –283.2 |
| | | | | | | |
| **TStrans1** | –884.613429 | –884.291217 | –884.271394 | –884.338101 | 140.4 | –323.9 |
| **TStrans2 ($TS_{trans}$)** | –884.618134 | –884.295807 | –884.275930 | –884.343570 | 142.4 | –322.9 |
| **TStrans3** | –884.611146 | –884.289242 | –884.269319 | –884.336740 | 141.9 | –321.3 |
| **TStrans4** | –884.615744 | –884.293425 | –884.273646 | –884.340487 | 140.7 | –321.2 |
| **TStrans5** | –884.610864 | –884.288674 | –884.268885 | –884.335343 | 139.9 | –326.5 |
| **TStrans6** | –884.618629 | –884.296193 | –884.276509 | –884.342844 | 139.6 | –325.6 |
| **TStrans7** | –884.608554 | –884.286643 | –884.266768 | –884.333785 | 141.0 | –324.6 |
| **TStrans8** | –884.616257 | –884.294097 | –884.274410 | –884.340617 | 139.3 | –322.1 |

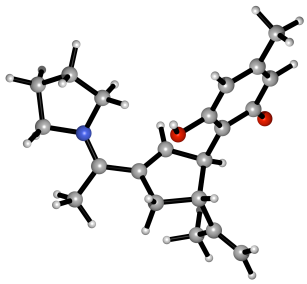
[a] 1 Hartree = 627.51 kcal $mol^{-1}$. [b] Thermal corrections at 298.15 K.

**Catalyzed oxy-Michael cyclization**

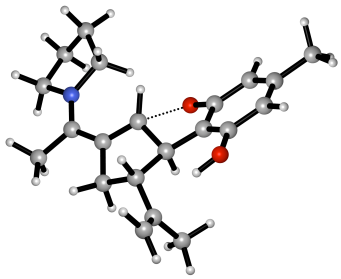
**Figure S2.** Minimum energy profile and optimized geometries for the pyrrolidine-catalyzed oxy-Michael cyclization calculated with IEF-PCM(DCM)/M06-2X/6-31G(d,p).

Note that the TS geometry for the *cis*-Michael addition ($TS_{cis\ pyr}$) could not be optimized in any conformation. The reaction was continuously downhill from the starting phenoxide (III) as revealed by relaxed scan calculations, suggesting an enthalpically barrierless pathway.

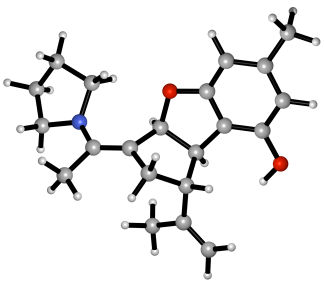


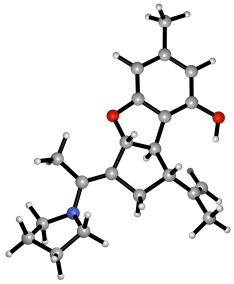
III



$TS_{trans\ pyr}$



$IV_{cis}$



$IV_{trans}$

**Table S7.** Energies, enthalpies, free energies, entropies, and lowest frequencies of all the calculated structures at the M06-2X/6-31G(d,p) level. Different isomers of the same stationary point in the potential energy surface are labeled with numbers.

| Structure | $E_{elec}$ (Hartree)[a] | $E_{elec}$ + ZPE (Hartree)[a] | H (Hartree)[a] | G (Hartree)[a,b] | S (cal $mol^{-1}$ $K^{-1}$)[b] | Lowest freq. ($cm^{-1}$) |
|---|---|---|---|---|---|---|
| **sm1** | –1021.209715 | –1020.766587 | –1020.741994 | –1020.820926 | 166.1 | 19.2 |
| **sm2** | –1021.208058 | –1020.764932 | –1020.740428 | –1020.817942 | 163.1 | 25.5 |
| **sm3** | –1021.208674 | –1020.765120 | –1020.740736 | –1020.818801 | 164.3 | 25.2 |
| **sm4 (III)** | –1021.215501 | –1020.773023 | –1020.748240 | –1020.827307 | 166.4 | 22.5 |
| **sm5** | –1021.215442 | –1020.771898 | –1020.747642 | –1020.824654 | 162.1 | 29.8 |
| **sm6** | –1021.214334 | –1020.771368 | –1020.746761 | –1020.825710 | 166.2 | 20.6 |
| **sm7** | –1021.210700 | –1020.766863 | –1020.742627 | –1020.820381 | 163.6 | 22.8 |
| **sm8** | –1021.213734 | –1020.770559 | –1020.746021 | –1020.825981 | 168.3 | 10.3 |
| | | | | | | |
| **pcis1** | –1021.255187 | –1020.810355 | –1020.786643 | –1020.862886 | 160.5 | 26.3 |
| **pcis2** | –1021.250013 | –1020.806146 | –1020.781962 | –1020.861615 | 167.6 | 5.1 |
| **pcis3** | –1021.252693 | –1020.808163 | –1020.784352 | –1020.860549 | 160.4 | 30.2 |
| **pcis4** | –1021.250599 | –1020.806146 | –1020.782145 | –1020.859435 | 162.7 | 22.2 |
| **pcis5** | –1021.254168 | –1020.809434 | –1020.785595 | –1020.863350 | 163.7 | 15.8 |
| **pcis6** | –1021.250904 | –1020.806468 | –1020.782515 | –1020.859674 | 162.4 | 26.2 |
| **pcis7** | –1021.251403 | –1020.807016 | –1020.783051 | –1020.861204 | 164.5 | 11.8 |
| **pcis8** | –1021.248619 | –1020.804524 | –1020.780467 | –1020.857559 | 162.3 | 31.8 |
| **pcis9** | –1021.255579 | –1020.810824 | –1020.786926 | –1020.864796 | 163.9 | 14.4 |
| **pcis10** | –1021.256034 | –1020.811107 | –1020.787311 | –1020.864108 | 161.6 | 19.2 |
| **pcis11 ($IV_{cis}$)** | –1021.257804 | –1020.813065 | –1020.789185 | –1020.865856 | 161.4 | 27.4 |
| **pcis12** | –1021.257398 | –1020.812759 | –1020.788851 | –1020.865684 | 161.7 | 28.8 |
| **pcis13** | –1021.254373 | –1020.809510 | –1020.785650 | –1020.862799 | 162.4 | 19.0 |
| **pcis14** | –1021.255315 | –1020.810453 | –1020.786627 | –1020.863464 | 161.7 | 20.3 |
| **pcis15** | –1021.256428 | –1020.811996 | –1020.787957 | –1020.865282 | 162.7 | 27.7 |
| **pcis16** | –1021.256897 | –1020.812521 | –1020.788475 | –1020.865807 | 162.8 | 28.4 |
| | | | | | | |
| **ptrans1** | –1021.228654 | –1020.783984 | –1020.760095 | –1020.836979 | 161.8 | 35.6 |
| **ptrans2** | –1021.227421 | –1020.782681 | –1020.758834 | –1020.835234 | 160.8 | 32.2 |
| **ptrans3** | –1021.225530 | –1020.781630 | –1020.757498 | –1020.835163 | 163.5 | 22.2 |
| **ptrans4** | –1021.228677 | –1020.784482 | –1020.760380 | –1020.838402 | 164.2 | 23.2 |
| **ptrans5 ($IV_{trans}$)** | –1021.231829 | –1020.786765 | –1020.763109 | –1020.838909 | 159.5 | 33.7 |
| **ptrans6** | –1021.224590 | –1020.780307 | –1020.756337 | –1020.832903 | 161.1 | 37.3 |
| **ptrans8** | –1021.229675 | –1020.785323 | –1020.761426 | –1020.837808 | 160.8 | 30.5 |
| **ptrans9** | –1021.230874 | –1020.785797 | –1020.762016 | –1020.838641 | 161.3 | 33.5 |
| **ptrans10** | –1021.227421 | –1020.782698 | –1020.758836 | –1020.835365 | 161.1 | 32.1 |
| **ptrans11** | –1021.225530 | –1020.781610 | –1020.757495 | –1020.834872 | 162.9 | 27.4 |
| **ptrans12** | –1021.228676 | –1020.784479 | –1020.760379 | –1020.838357 | 164.1 | 24.6 |
| **ptrans13** | –1021.231830 | –1020.786760 | –1020.763107 | –1020.838882 | 159.5 | 33.7 |
| **ptrans14** | –1021.226774 | –1020.782260 | –1020.758332 | –1020.835097 | 161.6 | 33.0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **ptrans16** | –1021.229675 | –1020.785334 | –1020.761426 | –1020.837929 | 161.0 | 30.2 |
| | | | | | | |
| **TStrans1** | –1021.194018 | –1020.751335 | –1020.727578 | –1020.803461 | 159.7 | –269.9 |
| **TStrans3** | –1021.194467 | –1020.751483 | –1020.727849 | –1020.803188 | 158.6 | –271.1 |
| **TStrans4** | –1021.188518 | –1020.745948 | –1020.722093 | –1020.798001 | 159.8 | –281.5 |
| **TStrans5 ($TS_{trans\ pyr}$)** | –1021.194315 | –1020.751607 | –1020.727905 | –1020.804814 | 161.9 | –272.0 |
| **TStrans6** | –1021.190851 | –1020.748188 | –1020.724509 | –1020.800006 | 158.9 | –280.0 |
| **TStrans7** | –1021.194808 | –1020.751593 | –1020.728174 | –1020.802719 | 156.9 | –275.8 |

[a] 1 Hartree = 627.51 kcal mol-1. [b] Thermal corrections at 298.15 K.

Cartesian Coordinates of the lowest energy structures for the oxy-Michael cyclization calculated with M06-2X/6-31G(d,p).

**Structure I**

| | | | |
|---|---|---|---|
| C | -1.034500 | 1.199900 | -0.532100 |
| C | -0.348800 | 0.328800 | 0.582200 |
| C | -1.351800 | -0.781400 | 0.779100 |
| C | -2.522700 | -0.539000 | 0.169700 |
| C | -2.529900 | 0.824200 | -0.479300 |
| H | -0.630500 | 0.836000 | -1.489100 |
| H | -0.273600 | 0.907100 | 1.515000 |
| H | -1.118200 | -1.666900 | 1.365300 |
| H | -3.092500 | 1.514900 | 0.161400 |
| H | -3.015100 | 0.829500 | -1.459200 |
| C | -3.722200 | -1.403700 | 0.190500 |
| C | -3.620700 | -2.761400 | 0.847300 |
| H | -2.823400 | -3.350100 | 0.385800 |
| H | -3.375500 | -2.649900 | 1.907300 |
| H | -4.571700 | -3.282800 | 0.745600 |
| O | -4.763400 | -1.015600 | -0.315500 |
| C | -0.707900 | 2.673600 | -0.460900 |
| C | -1.634700 | 3.631800 | -0.530300 |
| H | -1.349700 | 4.679800 | -0.502800 |
| H | -2.694000 | 3.418300 | -0.625100 |
| C | 0.755800 | 3.009200 | -0.342500 |
| H | 1.163600 | 2.627800 | 0.601600 |
| H | 1.326500 | 2.528300 | -1.145500 |
| H | 0.915200 | 4.089000 | -0.397600 |
| C | 1.059200 | -0.141200 | 0.303100 |
| C | 1.360100 | -1.005900 | -0.752000 |
| C | 2.113200 | 0.322100 | 1.175500 |
| C | 2.661400 | -1.429300 | -1.026800 |
| C | 3.434800 | -0.136100 | 0.859900 |
| C | 3.704500 | -0.979500 | -0.207100 |
| H | 2.837800 | -2.105500 | -1.857300 |
| H | 4.244000 | 0.207000 | 1.501300 |
| O | 0.385200 | -1.485500 | -1.602200 |
| H | -0.486700 | -1.337500 | -1.212500 |
| O | 1.882600 | 1.108700 | 2.154800 |
| C | 5.122300 | -1.405200 | -0.510200 |
| H | 5.785700 | -1.209000 | 0.335700 |
| H | 5.174300 | -2.472300 | -0.746800 |
| H | 5.519300 | -0.865400 | -1.377100 |

**Structure $TS_{cis}$**

| | | | |
|---|---|---|---|
| C | 0.899600 | 1.238500 | 0.509900 |
| C | 0.181100 | 0.504000 | -0.672300 |
| C | 0.967300 | -0.795500 | -0.842700 |
| C | 1.932900 | -0.905100 | 0.146200 |
| C | 1.698600 | 0.122200 | 1.232300 |
| H | 0.147700 | 1.682700 | 1.168100 |
| H | 0.245900 | 1.114200 | -1.584500 |
| H | 1.127300 | -1.235100 | -1.821700 |
| H | 2.623900 | 0.520600 | 1.667900 |
| H | 1.108200 | -0.273700 | 2.072600 |
| C | 3.000200 | -1.851600 | 0.085100 |
| C | 4.046800 | -1.785500 | 1.192000 |
| H | 4.566700 | -0.820900 | 1.173000 |
| H | 3.581300 | -1.876400 | 2.178700 |
| H | 4.774400 | -2.586500 | 1.055500 |
| O | 3.134500 | -2.694800 | -0.819000 |
| C | 1.798800 | 2.352100 | 0.020900 |
| C | 1.558000 | 3.622800 | 0.350800 |
| H | 2.195000 | 4.431700 | 0.002600 |
| H | 0.710600 | 3.891300 | 0.975200 |
| C | 2.965900 | 1.978800 | -0.856900 |
| H | 3.633700 | 1.276100 | -0.346400 |
| H | 2.627400 | 1.471700 | -1.767700 |
| H | 3.538500 | 2.863900 | -1.144600 |
| C | -1.257500 | 0.172100 | -0.379100 |
| C | -2.271500 | 1.089900 | -0.149100 |
| C | -1.527100 | -1.215300 | -0.331000 |
| C | -3.573500 | 0.667100 | 0.140600 |
| C | -2.844800 | -1.636400 | -0.029900 |
| C | -3.852100 | -0.702900 | 0.203800 |
| H | -4.358300 | 1.399700 | 0.313800 |
| H | -3.060300 | -2.700800 | 0.008900 |
| O | -1.942900 | 2.418700 | -0.223700 |
| H | -2.733700 | 2.945000 | -0.052300 |
| O | -0.537500 | -2.022400 | -0.576400 |
| C | -5.245400 | -1.164900 | 0.559300 |
| H | -5.455300 | -2.149900 | 0.134700 |
| H | -5.368200 | -1.242700 | 1.645200 |
| H | -6.001800 | -0.464400 | 0.195000 |

**Structure $TS_{trans}$**

| | | | |
|---|---|---|---|
| C | -1.308200 | 1.364200 | -0.288600 |
| C | -0.327900 | 0.301100 | 0.208500 |
| C | -2.403800 | -0.753900 | 0.116800 |
| C | -2.608600 | 0.745600 | 0.327000 |
| H | -1.398400 | 1.316100 | -1.381700 |
| H | -0.426500 | 0.348300 | 1.307600 |
| H | -2.699200 | 1.056400 | 1.379500 |
| H | -3.515200 | 1.081900 | -0.184900 |
| C | -3.478500 | -1.614500 | -0.212100 |
| C | -3.160700 | -3.061700 | -0.575900 |
| H | -2.092200 | -3.274900 | -0.638400 |
| H | -3.595800 | -3.721200 | 0.181300 |
| H | -3.641900 | -3.303000 | -1.528000 |
| C | -0.967800 | 2.778000 | 0.113300 |
| C | -0.980800 | 3.767500 | -0.786900 |
| H | -0.732000 | 4.788800 | -0.512800 |
| H | -1.254000 | 3.582900 | -1.822400 |
| C | -0.555800 | 3.019500 | 1.543200 |
| H | -1.287500 | 2.609400 | 2.246200 |
| H | 0.399800 | 2.523900 | 1.753300 |
| H | -0.438600 | 4.086100 | 1.744200 |
| C | 1.121000 | 0.026600 | -0.029900 |
| C | 2.190300 | 0.793700 | -0.450900 |
| C | 1.321300 | -1.304700 | 0.439800 |
| C | 3.480800 | 0.240700 | -0.457500 |
| C | 2.612100 | -1.845400 | 0.432100 |
| C | 3.687400 | -1.064900 | -0.015500 |
| H | 4.310500 | 0.850800 | -0.801400 |
| H | 2.774300 | -2.861100 | 0.782100 |
| O | 2.061500 | 2.091900 | -0.865000 |
| H | 1.133000 | 2.367400 | -0.818800 |
| C | 5.075800 | -1.658700 | -0.040500 |
| H | 5.305400 | -2.163000 | 0.902700 |
| H | 5.169700 | -2.405600 | -0.835900 |
| H | 5.834200 | -0.891300 | -0.211800 |
| O | 0.228300 | -1.933600 | 0.853800 |
| C | -1.035300 | -0.993700 | -0.127500 |
| H | -0.713900 | -1.565200 | -0.998000 |
| O | -4.677300 | -1.266200 | -0.205700 |

**Structure $II_{cis}$**

| | | | |
|---|---|---|---|
| C | 0.889400 | 1.299700 | 0.364900 |
| C | 0.315000 | 0.427900 | -0.776500 |
| C | 2.413700 | -0.508200 | -0.055200 |
| C | 2.391100 | 0.949800 | 0.355300 |
| H | 0.470200 | 0.900100 | 1.298000 |
| H | 0.446000 | 0.923800 | -1.744600 |
| H | 2.909800 | 1.611000 | -0.360600 |
| H | 2.855600 | 1.132900 | 1.332100 |
| C | 3.533200 | -1.305300 | 0.095900 |
| C | 3.455500 | -2.766800 | -0.355000 |
| H | 3.667000 | -3.416300 | 0.501300 |
| H | 2.487300 | -3.054800 | -0.771100 |
| H | 4.238100 | -2.960400 | -1.096900 |
| C | 0.524400 | 2.766900 | 0.278300 |
| C | 0.638400 | 3.475500 | -0.851600 |
| H | 0.388200 | 4.532000 | -0.880100 |
| H | 1.015300 | 3.035900 | -1.771200 |
| C | 0.021000 | 3.389300 | 1.552400 |
| H | -0.907000 | 2.898400 | 1.868300 |
| H | 0.746600 | 3.240200 | 2.359600 |
| H | -0.168100 | 4.459100 | 1.441600 |
| C | -1.082100 | -0.049300 | -0.517600 |

| | | | |
|---|---|---|---|
| C | -2.303100 | 0.603900 | -0.549600 |
| C | -1.009700 | -1.356300 | -0.023400 |
| C | -3.461300 | -0.086000 | -0.162400 |
| C | -2.141900 | -2.052200 | 0.382100 |
| C | -3.382300 | -1.400500 | 0.297500 |
| H | -4.416100 | 0.428400 | -0.207200 |
| H | -2.066300 | -3.068000 | 0.756300 |
| O | -2.427700 | 1.903300 | -0.942800 |
| H | -1.545900 | 2.300800 | -1.031100 |
| C | -4.636400 | -2.138800 | 0.697400 |
| H | -4.904000 | -2.888200 | -0.054500 |
| H | -4.496600 | -2.666600 | 1.644800 |
| H | -5.481900 | -1.456100 | 0.805200 |
| O | 0.253700 | -1.834300 | 0.031500 |
| C | 1.140500 | -0.873400 | -0.716800 |
| H | 1.228500 | -1.350600 | -1.702000 |
| O | 4.636600 | -0.926300 | 0.601100 |

**Structure II$_{trans}$**

| | | | |
|---|---|---|---|
| C | 1.372000 | -1.300600 | -0.347000 |
| C | 0.301500 | -0.378300 | 0.208500 |
| C | 2.226000 | 0.977300 | 0.073500 |
| H | 1.332900 | -1.291900 | -1.446300 |
| H | 0.453900 | -0.368800 | 1.301600 |
| C | 3.142300 | 2.003800 | -0.004100 |
| C | 2.613500 | 3.422300 | -0.231600 |
| H | 3.089000 | 3.842600 | -1.124900 |
| H | 1.527500 | 3.472000 | -0.345700 |
| H | 2.904000 | 4.062600 | 0.608800 |
| C | 1.364200 | -2.732400 | 0.121000 |
| C | 0.568500 | -3.176700 | 1.101000 |
| H | 0.608800 | -4.210100 | 1.431700 |
| H | -0.125700 | -2.522400 | 1.622500 |
| C | 2.358200 | -3.632700 | -0.561900 |
| H | 2.189300 | -3.644000 | -1.644000 |
| H | 3.375800 | -3.258100 | -0.404700 |
| H | 2.303600 | -4.656600 | -0.187100 |
| C | -1.178900 | -0.215200 | -0.010700 |
| C | -2.265900 | -1.052600 | -0.189500 |
| C | -1.402500 | 1.166600 | 0.172500 |
| C | -3.559600 | -0.503600 | -0.203700 |
| C | -2.668700 | 1.721900 | 0.177700 |
| C | -3.763900 | 0.860100 | -0.013300 |
| H | -4.401600 | -1.170500 | -0.361600 |
| H | -2.809600 | 2.789400 | 0.312100 |
| O | -2.148800 | -2.397800 | -0.366500 |
| H | -1.216400 | -2.655500 | -0.287300 |
| C | -5.160200 | 1.431600 | -0.030800 |
| H | -5.373200 | 1.970700 | 0.897100 |
| H | -5.280700 | 2.143900 | -0.852800 |
| H | -5.909300 | 0.646300 | -0.149400 |
| O | -0.238300 | 1.875200 | 0.335600 |
| O | 4.403100 | 1.874600 | 0.123600 |
| C | 0.775600 | 0.987400 | -0.259900 |
| H | 0.569600 | 1.078400 | -1.345700 |
| C | 2.644400 | -0.494500 | 0.109100 |
| H | 2.930600 | -0.857100 | 1.111400 |
| H | 3.504100 | -0.693900 | -0.542900 |

**Structure III**

| | | | |
|---|---|---|---|
| C | -0.609600 | 2.093100 | 0.701500 |
| C | -0.898100 | 1.105200 | -0.478300 |
| C | 0.455600 | 0.571900 | -0.828200 |
| C | 1.402200 | 0.916000 | 0.062400 |
| C | 0.852600 | 1.813500 | 1.151800 |
| H | -1.296100 | 1.886700 | 1.525500 |
| H | -1.353000 | 1.622400 | -1.331500 |
| H | 0.612500 | -0.055200 | -1.700600 |
| H | 1.425400 | 2.739100 | 1.277100 |
| H | 0.872400 | 1.283000 | 2.108000 |
| C | 2.787800 | 0.487500 | 0.013400 |
| C | 3.879900 | 1.470300 | 0.306500 |
| H | 3.478800 | 2.479900 | 0.364000 |
| H | 4.356900 | 1.222500 | 1.261400 |
| H | 4.649200 | 1.437400 | -0.468400 |
| C | -0.788500 | 3.530100 | 0.265100 |
| C | -1.682300 | 4.327200 | 0.851600 |
| H | -1.819400 | 5.356800 | 0.533300 |
| H | -2.309500 | 3.971100 | 1.663700 |
| C | 0.082800 | 4.012500 | -0.866600 |
| H | 1.146700 | 3.920200 | -0.618700 |
| H | -0.081200 | 3.417200 | -1.771200 |
| H | -0.121400 | 5.058500 | -1.103800 |
| C | -1.835400 | -0.051800 | -0.217800 |
| C | -1.669300 | -0.936300 | 0.847100 |
| C | -2.921600 | -0.243500 | -1.155400 |
| C | -2.535300 | -2.002200 | 1.082200 |
| C | -3.798600 | -1.349100 | -0.871200 |
| C | -3.615700 | -2.197200 | 0.204600 |
| H | -2.374400 | -2.666700 | 1.928100 |
| H | -4.630800 | -1.505000 | -1.554000 |
| O | -0.592200 | -0.722800 | 1.684800 |
| H | -0.656600 | -1.342800 | 2.421600 |
| O | -3.089000 | 0.516300 | -2.157200 |
| C | -4.567000 | -3.343400 | 0.454700 |
| H | -5.328900 | -3.404300 | -0.325800 |
| H | -4.034300 | -4.299600 | 0.486300 |
| H | -5.076500 | -3.229900 | 1.417500 |
| C | 2.162500 | -1.887300 | -0.354200 |
| C | 4.513100 | -1.226500 | -0.317100 |
| C | 3.027900 | -3.076300 | 0.047200 |
| H | 1.835000 | -1.979600 | -1.393100 |
| H | 1.297100 | -1.691100 | 0.282700 |
| C | 4.382500 | -2.727900 | -0.574600 |
| H | 4.993600 | -1.015100 | 0.642800 |
| H | 5.047100 | -0.690800 | -1.104100 |
| H | 3.107100 | -3.132100 | 1.136800 |
| H | 2.615500 | -4.015800 | -0.321100 |
| H | 5.214800 | -3.280500 | -0.138800 |
| H | 4.364000 | -2.922600 | -1.650200 |
| N | 3.108900 | -0.746500 | -0.248300 |

**Structure $TS_{trans\ pyr}$**

| | | | |
|---|---|---|---|
| C | 0.640000 | 2.127800 | -0.373000 |
| C | 0.794500 | 0.712200 | 0.193000 |
| C | -1.512300 | 1.053100 | -0.076300 |
| C | -0.817200 | 2.412600 | 0.099400 |
| H | 0.637000 | 2.101700 | -1.470400 |
| H | 0.681600 | 0.847400 | 1.283300 |
| H | -0.818000 | 2.766200 | 1.139700 |
| H | -1.272400 | 3.195400 | -0.512700 |
| C | -2.913400 | 0.899900 | -0.098500 |
| C | -3.789800 | 2.100200 | 0.143000 |
| H | -4.123700 | 2.111900 | 1.186200 |
| H | -3.250800 | 3.025400 | -0.042400 |
| H | -4.675600 | 2.076200 | -0.494200 |
| C | 1.671000 | 3.126000 | 0.095500 |
| C | 2.231600 | 3.977100 | -0.769600 |
| H | 2.973500 | 4.702900 | -0.449700 |
| H | 1.956900 | 3.976400 | -1.821000 |
| C | 2.066600 | 3.091700 | 1.548700 |
| H | 1.193700 | 3.153200 | 2.206800 |
| H | 2.576200 | 2.149300 | 1.782800 |
| H | 2.740600 | 3.915400 | 1.790000 |
| C | 1.863000 | -0.318200 | 0.020900 |
| C | 3.149200 | -0.254200 | -0.486400 |
| C | 1.355500 | -1.534900 | 0.584400 |
| C | 3.961800 | -1.397800 | -0.479200 |
| C | 2.188000 | -2.669500 | 0.577900 |
| C | 3.481100 | -2.594000 | 0.051800 |
| H | 4.966100 | -1.326200 | -0.884300 |
| H | 1.814400 | -3.600900 | 0.994800 |
| O | 3.698800 | 0.883100 | -1.014800 |
| H | 3.110100 | 1.640400 | -0.885800 |
| C | 4.353100 | -3.827500 | 0.039900 |
| H | 4.332800 | -4.333200 | 1.009700 |
| H | 4.003300 | -4.548300 | -0.706900 |
| H | 5.390900 | -3.579800 | -0.195600 |
| O | 0.134700 | -1.501700 | 1.057400 |
| C | -0.513900 | 0.079100 | -0.192000 |
| H | -0.549000 | -0.771900 | -0.852100 |
| C | -2.895100 | -1.543900 | -0.555400 |
| C | -4.993300 | -0.442800 | -0.017900 |
| C | -4.046000 | -2.553000 | -0.598400 |
| H | -2.146400 | -1.775200 | 0.213700 |
| H | -2.386600 | -1.465100 | -1.519300 |
| C | -5.107300 | -1.928300 | 0.307300 |
| H | -5.542600 | -0.190700 | -0.933300 |
| H | -5.342800 | 0.199900 | 0.790400 |
| H | -4.429500 | -2.638700 | -1.619300 |
| H | -3.726400 | -3.542400 | -0.269800 |
| H | -6.112000 | -2.311000 | 0.123800 |
| H | -4.857200 | -2.093700 | 1.359300 |
| N | -3.545000 | -0.261300 | -0.236500 |

**Structure $IV_{cis}$**

| | | | |
|---|---|---|---|
| C | 0.758600 | 1.942100 | -0.463300 |
| C | -1.169000 | 0.474500 | -0.613200 |
| C | -0.289900 | 1.375400 | -1.450400 |
| H | 1.719700 | 2.078700 | -0.971100 |
| H | -0.815500 | 2.174400 | -1.977700 |
| H | 0.238100 | 0.787200 | -2.213600 |
| C | -2.519100 | 0.364400 | -0.648700 |
| C | -3.376000 | 1.251000 | -1.519300 |
| H | -4.126300 | 1.772400 | -0.916900 |
| H | -2.783000 | 2.000700 | -2.038000 |
| H | -3.913900 | 0.662400 | -2.269300 |
| C | 0.372200 | 3.265400 | 0.155900 |
| C | 1.228500 | 4.289800 | 0.154000 |
| H | 0.980900 | 5.238000 | 0.622100 |
| H | 2.200400 | 4.214600 | -0.327300 |
| C | -0.986100 | 3.364600 | 0.798500 |
| H | -1.779300 | 3.235500 | 0.053800 |
| H | -1.133300 | 2.573900 | 1.543200 |
| H | -1.120300 | 4.332800 | 1.285400 |
| C | 2.082900 | -0.069300 | 0.394900 |
| C | 3.441800 | 0.198300 | 0.433600 |
| C | 1.643800 | -1.334400 | 0.019100 |
| C | 4.349800 | -0.820300 | 0.121200 |
| C | 2.518500 | -2.361700 | -0.302100 |
| C | 3.893600 | -2.088500 | -0.241700 |
| H | 5.412400 | -0.603700 | 0.160300 |
| H | 2.150000 | -3.339300 | -0.593500 |
| O | 3.930500 | 1.428700 | 0.756400 |
| H | 3.198600 | 2.022600 | 0.973300 |
| C | 4.880800 | -3.185600 | -0.555100 |
| H | 4.915700 | -3.919000 | 0.256800 |
| H | 4.596300 | -3.721000 | -1.464800 |
| H | 5.887900 | -2.786600 | -0.690700 |
| O | 0.290400 | -1.434300 | -0.008300 |
| C | -0.293200 | -0.158600 | 0.426000 |
| H | -0.826900 | -0.363300 | 1.357000 |
| C | 0.900800 | 0.825500 | 0.619300 |
| H | 0.895600 | 1.259500 | 1.625900 |
| C | -4.677100 | -0.525300 | 0.235300 |
| C | -2.708900 | -1.927400 | 0.347200 |
| C | -5.017700 | -1.850600 | 0.914900 |
| H | -5.164500 | -0.473700 | -0.748100 |
| H | -5.006200 | 0.341600 | 0.817900 |
| C | -3.967500 | -2.794700 | 0.327800 |
| H | -2.208500 | -2.016500 | 1.319800 |
| H | -1.976800 | -2.187000 | -0.422400 |
| H | -4.880400 | -1.764900 | 1.997800 |

| | | | |
|---|---|---|---|
| H | -6.046100 | -2.160600 | 0.720900 |
| H | -3.846600 | -3.720500 | 0.893500 |
| H | -4.232200 | -3.050500 | -0.703600 |
| N | -3.214800 | -0.564500 | 0.114500 |

**Structure IV$_{trans}$**

| | | | |
|---|---|---|---|
| C | 0.166300 | 1.755300 | -0.431500 |
| C | 0.879800 | 0.546400 | 0.145600 |
| C | -1.301000 | -0.254900 | -0.232800 |
| C | -1.333700 | 1.277000 | -0.336800 |
| H | 0.428500 | 1.854300 | -1.494300 |
| H | 0.618300 | 0.491900 | 1.215000 |
| H | -1.810200 | 1.692700 | 0.561300 |
| H | -1.900900 | 1.644300 | -1.197300 |
| C | -2.310100 | -1.047700 | 0.169900 |
| C | -2.107700 | -2.526800 | 0.394800 |
| H | -2.870700 | -3.105900 | -0.136200 |
| H | -1.124800 | -2.834200 | 0.043900 |
| H | -2.176300 | -2.786400 | 1.456200 |
| C | 0.404500 | 3.087200 | 0.233900 |
| C | 1.124400 | 3.225200 | 1.352300 |
| H | 1.265600 | 4.199900 | 1.808700 |
| H | 1.573500 | 2.377300 | 1.862900 |
| C | -0.251900 | 4.260600 | -0.441900 |
| H | 0.080100 | 4.342700 | -1.482300 |
| H | -1.339300 | 4.126500 | -0.465400 |
| H | -0.031100 | 5.197700 | 0.072000 |
| C | 2.281900 | 0.028300 | -0.018100 |
| C | 3.553100 | 0.577200 | 0.014600 |
| C | 2.147200 | -1.371100 | -0.079800 |
| C | 4.665600 | -0.278700 | -0.031500 |
| C | 3.225200 | -2.231900 | -0.111200 |
| C | 4.510600 | -1.661100 | -0.084500 |
| H | 5.656300 | 0.164400 | -0.020500 |
| H | 3.084100 | -3.305900 | -0.166800 |
| O | 3.785200 | 1.914600 | 0.080800 |
| H | 2.943100 | 2.393900 | 0.129000 |
| C | 5.719300 | -2.561800 | -0.136600 |
| H | 5.691300 | -3.298500 | 0.671400 |
| H | 5.751700 | -3.115600 | -1.079700 |
| H | 6.644600 | -1.989600 | -0.046700 |
| O | 0.826300 | -1.775700 | -0.106000 |
| C | 0.129500 | -0.592200 | -0.532300 |
| H | 0.309600 | -0.508900 | -1.619700 |
| C | -4.196200 | 0.326900 | -0.659200 |
| C | -4.645600 | -1.295500 | 1.047900 |
| C | -5.702900 | 0.024100 | -0.605500 |
| H | -3.764700 | 0.059300 | -1.632900 |
| H | -4.004800 | 1.392200 | -0.494500 |
| C | -5.767400 | -1.372200 | 0.015000 |
| H | -4.995300 | -0.762300 | 1.942900 |
| H | -4.286300 | -2.271400 | 1.371200 |
| H | -6.206300 | 0.741000 | 0.050900 |
| H | -6.166100 | 0.088400 | -1.591900 |
| H | -6.739900 | -1.607600 | 0.452500 |
| H | -5.526000 | -2.134800 | -0.734100 |
| N | -3.591600 | -0.520200 | 0.384700 |

## NMR calculations

**Scheme S1.** Oxy-Michael addition structures considered for the $^{13}C$ NMR calculations.

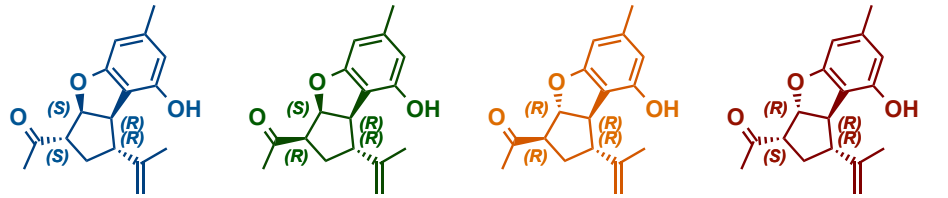



**Table S8.** Energies, enthalpies, free energies, entropies, and lowest frequencies of all the calculated isomers calculated at the M06-2X/6-31G(d,p) level.

| | Structure | $E_{elec}$ (Hartree)[a] | $E_{elec}$ + ZPE (Hartree)[a] | H (Hartree)[a] | G (Hartree)[a,b] | S (cal $mol^{-1}$ $K^{-1}$)[b] | Lowest freq. ($cm^{-1}$) |
|---|---|---|---|---|---|---|---|
| A (SSRR) | **cis_1** | –885.167299 | –884.828736 | –884.808910 | –884.875893 | 141.0 | 33.6 |
| | **cis_2** | –885.165720 | –884.826954 | –884.807293 | –884.873709 | 139.8 | 35.4 |
| | **cis_3** | –885.170123 | –884.831359 | –884.811734 | –884.878014 | 139.5 | 37.0 |
| | **cis_4** | –885.171354 | –884.832607 | –884.813005 | –884.879060 | 139.0 | 37.4 |
| | **cis_5** | –885.171157 | –884.832847 | –884.812976 | –884.880544 | 142.2 | 24.3 |
| | **cis_6** | –885.167133 | –884.828738 | –884.808901 | –884.875835 | 140.9 | 35.3 |
| | **cis_7** | –885.169399 | –884.831046 | –884.811105 | –884.878356 | 141.5 | 35.6 |
| | **cis_8** | –885.168435 | –884.829898 | –884.810096 | –884.876794 | 140.4 | 37.1 |
| | **cis_9** | –885.168372 | –884.830183 | –884.810032 | –884.878701 | 144.5 | 24.7 |
| | **cis_10** | –885.166476 | –884.827930 | –884.807933 | –884.876387 | 144.1 | 20.5 |
| | **cis_11** | –885.172142 | –884.833869 | –884.813752 | –884.882539 | 144.8 | 30.4 |
| | **cis_12** | –885.168549 | –884.830466 | –884.810310 | –884.878925 | 144.4 | 32.4 |
| | **cis_13** | –885.168204 | –884.829763 | –884.809709 | –884.880287 | 148.5 | 3.0 |
| | **cis_14** | –885.164838 | –884.826499 | –884.806490 | –884.874333 | 142.8 | 33.3 |
| | **cis_15** | –885.164533 | –884.826303 | –884.806217 | –884.874170 | 143.0 | 38.6 |
| | **cis_16** | –885.162226 | –884.823606 | –884.803682 | –884.871148 | 142.0 | 41.8 |
| | | | | | | | |
| B (RSRR) | **cis2_1** | –885.168269 | –884.830293 | –884.810158 | –884.879180 | 145.3 | 21.6 |
| | **cis2_2** | –885.166637 | –884.828522 | –884.808521 | –884.876347 | 142.8 | 35.1 |
| | **cis2_3** | –885.167731 | –884.829614 | –884.809555 | –884.877854 | 143.7 | 24.9 |
| | **cis2_4** | –885.168615 | –884.830595 | –884.810491 | –884.879252 | 144.7 | 22.4 |
| | **cis2_5** | –885.171602 | –884.833448 | –884.813345 | –884.881464 | 143.4 | 30.8 |
| | **cis2_6** | –885.172670 | –884.834567 | –884.814464 | –884.882659 | 143.5 | 28.9 |
| | **cis2_7** | –885.172038 | –884.833771 | –884.813717 | –884.882199 | 144.1 | 19.3 |
| | **cis2_8** | –885.170368 | –884.832117 | –884.812075 | –884.880289 | 143.6 | 26.9 |
| | **cis2_9** | –885.168971 | –884.830659 | –884.810601 | –884.878520 | 142.9 | 25.6 |
| | **cis2_10** | –885.165632 | –884.826801 | –884.807044 | –884.873754 | 140.4 | 34.7 |
| | **cis2_11** | –885.171543 | –884.832954 | –884.812958 | –884.881386 | 144.0 | 16.8 |
| | **cis2_12** | –885.167490 | –884.829180 | –884.809120 | –884.877285 | 143.5 | 21.1 |
| | **cis2_15** | –885.168959 | –884.830780 | –884.810616 | –884.881097 | 148.3 | 3.1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C (RRRR) | **trans_1** | –885.139132 | –884.800975 | –884.780800 | –884.849650 | 144.9 | 31.5 |
| | **trans_2** | –885.137755 | –884.799084 | –884.779152 | –884.847075 | 143.0 | 36.4 |
| | **trans_3** | –885.149395 | –884.810948 | –884.790911 | –884.858908 | 143.1 | 29.6 |
| | **trans_4** | –885.144506 | –884.806658 | –884.786271 | –884.855984 | 146.7 | 18.7 |
| | **trans_5** | –885.147599 | –884.809276 | –884.789121 | –884.857821 | 144.6 | 21.5 |
| | **trans_6** | –885.142992 | –884.805092 | –884.784687 | –884.854460 | 146.9 | 20.8 |
| | **trans_7** | –885.143563 | –884.805521 | –884.785214 | –884.854114 | 145.0 | 32.6 |
| | **trans_9** | –885.136665 | –884.798510 | –884.778313 | –884.847585 | 145.8 | 24.5 |
| | **trans_10** | –885.136171 | –884.797562 | –884.777630 | –884.845572 | 143.0 | 33.3 |
| | **trans_11** | –885.146118 | –884.807561 | –884.787592 | –884.855228 | 142.4 | 34.8 |
| | | | | | | | |
| D (SRRR) | **trans2_1** | –885.134583 | –884.795956 | –884.776044 | –884.843618 | 142.2 | 34.8 |
| | **trans2_2** | –885.134701 | –884.796051 | –884.776067 | –884.844247 | 143.5 | 26.8 |
| | **trans2_3** | –885.145427 | –884.806835 | –884.786798 | –884.854955 | 143.4 | 22.6 |
| | **trans2_4** | –885.138404 | –884.800029 | –884.780079 | –884.847750 | 142.4 | 24.9 |
| | **trans2_5** | –885.150260 | –884.811509 | –884.791610 | –884.858766 | 142.3 | 46.1 |
| | **trans2_6** | –885.145101 | –884.806843 | –884.786731 | –884.854569 | 142.8 | 42.3 |
| | **trans2_7** | –885.139614 | –884.801172 | –884.781121 | –884.849262 | 143.4 | 31.6 |
| | **trans2_9** | –885.134153 | –884.795093 | –884.775309 | –884.842773 | 142.0 | 31.9 |
| | **trans2_10** | –885.132672 | –884.793383 | –884.773724 | –884.840679 | 140.9 | 39.6 |
| | **trans2_11** | –885.144161 | –884.805219 | –884.785399 | –884.852593 | 141.4 | 39.4 |
| | **trans2_16** | –885.138370 | –884.799528 | –884.779665 | –884.847490 | 142.7 | 34.0 |

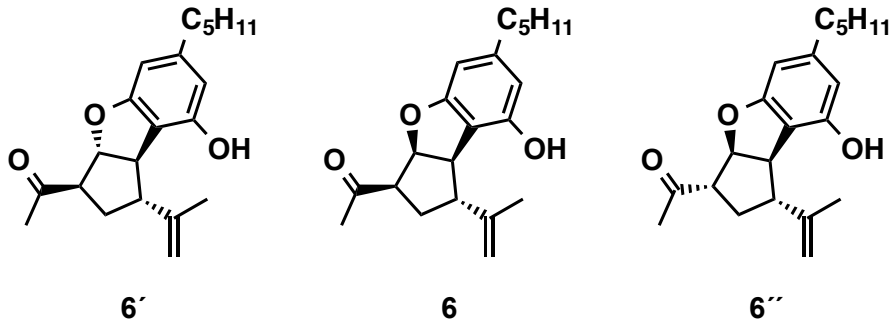
[a] 1 Hartree = 627.51 kcal mol-1. [b] Thermal corrections at 298.15 K.

**Table S9.** Conformers populations calculated at 298 K for structures **A**, **B**, **C** and **D**. The lowest energy conformer is highlighted in boldface.

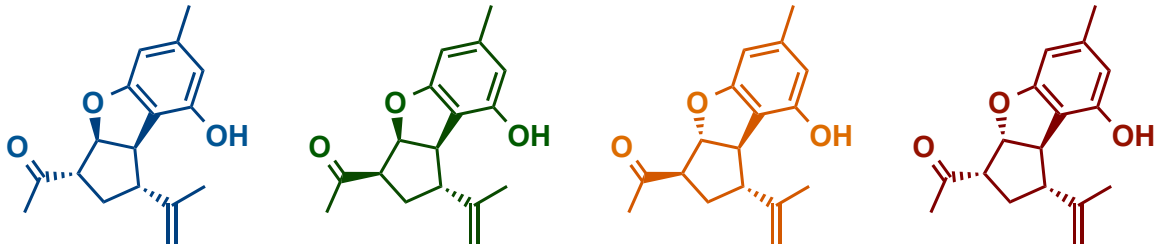
| | | ΔG | $e^{(-\Delta G/RT)}$ | % mol |
|---|---|---|---|---|
| **A** (SSRR) | **cis_1** | 4.2 | 0.0 | 0.1 |
| | **cis_2** | 5.5 | 0.0 | 0.0 |
| | **cis_3** | 2.8 | 0.0 | 0.6 |
| | **cis_4** | 2.2 | 0.0 | 1.9 |
| | **cis_5** | 1.3 | 0.1 | 9.3 |
| | **cis_6** | 4.2 | 0.0 | 0.1 |
| | **cis_7** | 2.6 | 0.0 | 0.9 |
| | **cis_8** | 3.6 | 0.0 | 0.2 |
| | **cis_9** | 2.4 | 0.0 | 1.3 |
| | **cis_10** | 3.9 | 0.0 | 0.1 |
| | **cis_11** | **0.0** | **1.0** | **76.7** |
| | **cis_12** | 2.3 | 0.0 | 1.7 |
| | **cis_13** | 1.4 | 0.1 | 7.1 |
| | **cis_14** | 5.1 | 0.0 | 0.0 |
| | **cis_15** | 5.3 | 0.0 | 0.0 |
| | **cis_16** | 7.1 | 0.0 | 0.0 |
| | | | | |
| **B** (RSRR) | **cis2_1** | 2.2 | 0.0 | 1.0 |
| | **cis2_2** | 4.0 | 0.0 | 0.1 |
| | **cis2_3** | 3.0 | 0.0 | 0.2 |
| | **cis2_4** | 2.1 | 0.0 | 1.1 |
| | **cis2_5** | 0.7 | 0.3 | 11.3 |
| | **cis2_6** | **0.0** | **1.0** | **39.9** |
| | **cis2_7** | 0.3 | 0.6 | 24.5 |
| | **cis2_8** | 1.5 | 0.1 | 3.3 |
| | **cis2_9** | 2.6 | 0.0 | 0.5 |
| | **cis2_10** | 5.6 | 0.0 | 0.0 |
| | **cis2_11** | 0.8 | 0.3 | 10.4 |
| | **cis2_12** | 3.4 | 0.0 | 0.1 |
| | **cis2_15** | 1.0 | 0.2 | 7.6 |

| | | ΔG | $e^{(-\Delta G/RT)}$ | % mol |
|---|---|---|---|---|
| **C** (RRRR) | **trans_1** | 8.7 | 0.0 | 0.0 |
| | **trans_2** | 7.4 | 0.0 | 0.0 |
| | **trans_3** | **0.0** | **1.0** | **71.6** |
| | **trans_4** | 1.8 | 0.0 | 3.2 |
| | **trans_5** | 0.7 | 0.3 | 22.7 |
| | **trans_6** | 2.8 | 0.0 | 0.6 |
| | **trans_7** | 3.0 | 0.0 | 0.4 |
| | **trans_9** | 7.1 | 0.0 | 0.0 |
| | **trans_10** | 8.4 | 0.0 | 0.0 |
| | **trans_11** | 2.3 | 0.0 | 1.5 |
| | | | | |
| **D** (SRRR) | **trans2_1** | 9.5 | 0.0 | 0.0 |
| | **trans2_2** | 9.1 | 0.0 | 0.0 |
| | **trans2_3** | 2.4 | 0.0 | 1.7 |
| | **trans2_4** | 6.9 | 0.0 | 0.0 |
| | **trans2_5** | **0.0** | **1.0** | **97.0** |
| | **trans2_6** | 2.6 | 0.0 | 1.1 |
| | **trans2_7** | 6.0 | 0.0 | 0.0 |
| | **trans2_9** | 10.0 | 0.0 | 0.0 |
| | **trans2_10** | 11.3 | 0.0 | 0.0 |
| | **trans2_11** | 3.9 | 0.0 | 0.1 |
| | **trans2_16** | 7.1 | 0.0 | 0.0 |

**Table S10**. $^{13}C$ NMR chemical shifts (in ppm) measured for **6´**, **6**, and **6´´** and calculated (conformationally-weighted values) for **A**, **B**, **C** and **D**.




**6´** **6** **6´´**




**A** **B** **C** **D**

| | 6´ [a] | 6 | 6´´ | A | B | C | D |
|---|---|---|---|---|---|---|---|
| **C1** | 27.4 | 29.0 | 30.2 | 28.5 | 27.2 | 34.0 | 34.8 |
| **C2** | 56.0 | 50.5 | 55.0 | 50.3 | 49.0 | 39.3 | 38.6 |
| **C3** | 50.6 | 49.6 | 48.6 | 46.5 | 49.7 | 51.8 | 46.2 |
| **C4** | 91.2 | 88.5 | 89.2 | 88.0 | 86.8 | 91.3 | 90.3 |
| **C5** | 57.4 | 57.5 | 60.5 | 59.9 | 56.7 | 48.4 | 46.0 |
| **C6** | 206.1 | 206.2 | 208.1 | 213.3 | 212.6 | 212.0 | 213.6 |
| **C7** | 28.5 | 30.1 | 31.1 | 26.1 | 27.8 | 26.8 | 29.0 |
| **C8** | 148.3 | 148.1 | 147.9 | 155.9 | 156.9 | 160.4 | 159.4 |
| **C9** | 109.7 | 109.6 | 112.5 | 109.9 | 108.0 | 107.3 | 108.0 |
| **C10** | 20.7 | 22.5 | 19.9 | 20.5 | 20.5 | 20.1 | 20.2 |
| **C11** | 161.4 | 161.6 | 160.7 | 163.0 | 163.6 | 169.5 | 168.7 |
| **C12** | 115.7 | 112.8 | 112.9 | 110.6 | 111.5 | 110.1 | 109.8 |
| **C13** | 157.9 | 151.9 | 152.8 | 154.7 | 153.8 | 153.6 | 153.8 |

[a] Data from O. Taglialatela-Scafati, A. Pagani, F. Scala, L. De Petrocellis, V. Di Marzo, G. Grassi, G. Appendino, *Eur. J. Org. Chem.* **2010**, 2067–2072.

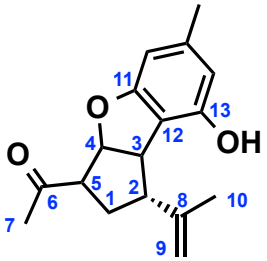
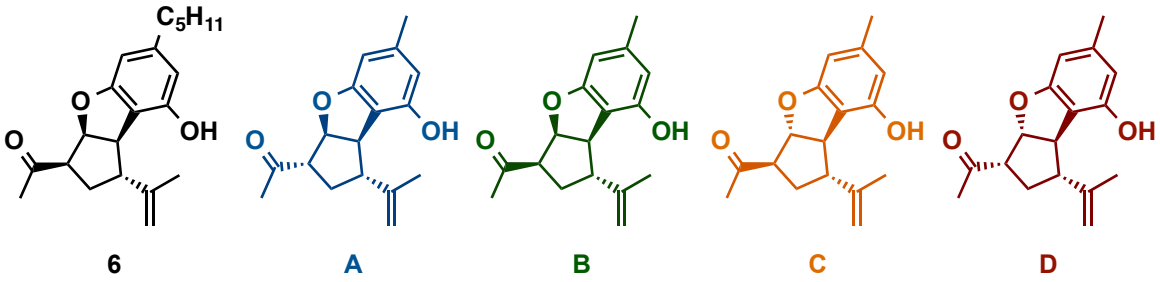


**Table S11**. Comparison between $^{13}C$ NMR chemical shifts calculated (conformationally-weighted values in ppm) for **A**, **B**, **C** and **D** and observed for **6**.



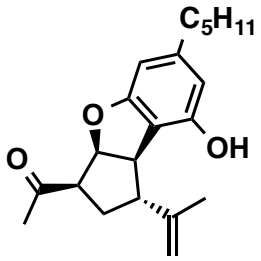

| | 6 | A | Abs error |
|---|---|---|---|
| **C1** | 29.0 | 28.5 | 0.5 |
| **C2** | 50.5 | 50.3 | 0.2 |
| **C3** | 49.6 | 46.5 | 3.1 |
| **C4** | 88.5 | 88.0 | 0.5 |
| **C5** | 57.5 | 59.9 | 2.4 |
| **C7** | 30.1 | 26.1 | 4.0 |
| **C9** | 109.6 | 109.9 | 0.3 |
| **C10** | 22.5 | 20.5 | 2.0 |
| **C11** | 161.6 | 163.0 | 1.4 |
| **C12** | 112.8 | 110.6 | 2.2 |
| **C13** | 151.9 | 154.7 | 2.8 |
| | | | |
| | | **Mean Abs Error =** | 1.8 |

| | 6 | C | Abs error |
|---|---|---|---|
| **C1** | 29.0 | 34.0 | 5.0 |
| **C2** | 50.5 | 39.3 | 11.2 |
| **C3** | 49.6 | 51.8 | 2.2 |
| **C4** | 88.5 | 91.3 | 2.8 |
| **C5** | 57.5 | 48.4 | 9.1 |
| **C7** | 30.1 | 26.8 | 3.3 |
| **C9** | 109.6 | 107.3 | 2.3 |
| **C10** | 22.5 | 20.1 | 2.4 |
| **C11** | 161.6 | 169.5 | 7.9 |
| **C12** | 112.8 | 110.1 | 2.7 |
| **C13** | 151.9 | 153.6 | 1.7 |
| | | | |
| | | **Mean Abs Error =** | 4.6 |

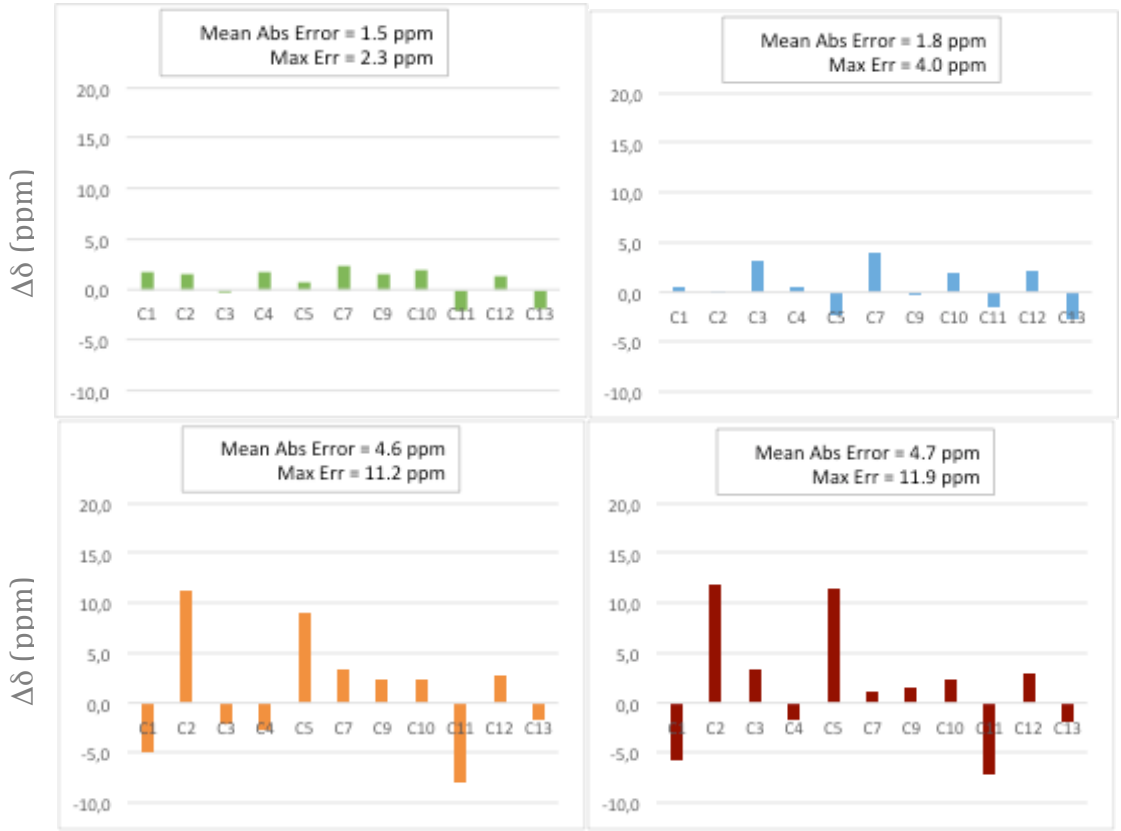
| | 6 | B | Abs error |
|---|---|---|---|
| **C1** | 29.0 | 27.2 | 1.8 |
| **C2** | 50.5 | 49.0 | 1.5 |
| **C3** | 49.6 | 49.7 | 0.1 |
| **C4** | 88.5 | 86.8 | 1.7 |
| **C5** | 57.5 | 56.7 | 0.8 |
| **C7** | 30.1 | 27.8 | 2.3 |
| **C9** | 109.6 | 108.0 | 1.6 |
| **C10** | 22.5 | 20.5 | 2.0 |
| **C11** | 161.6 | 163.6 | 2.0 |
| **C12** | 112.8 | 111.5 | 1.3 |
| **C13** | 151.9 | 153.8 | 1.9 |
| | | | |
| | | **Mean Abs Error =** | 1.5 |

| | 6 | D | Abs error |
|---|---|---|---|
| **C1** | 29.0 | 34.8 | 5.8 |
| **C2** | 50.5 | 38.6 | 11.9 |
| **C3** | 49.6 | 46.2 | 3.4 |
| **C4** | 88.5 | 90.3 | 1.8 |
| **C5** | 57.5 | 46.0 | 11.5 |
| **C7** | 30.1 | 29.0 | 1.1 |
| **C9** | 109.6 | 108.0 | 1.6 |
| **C10** | 22.5 | 20.2 | 2.3 |
| **C11** | 161.6 | 168.7 | 7.1 |
| **C12** | 112.8 | 109.8 | 3.0 |
| **C13** | 151.9 | 153.8 | 1.9 |
| | | | |
| | | **Mean Abs Error =** | 4.7 |

**Figure S3**. Comparative plots between $^{13}C$ NMR chemical shifts (conformationally-weighted values in ppm) calculated for **A**, **B**, **C** and **D** and observed for **6**.




**6**



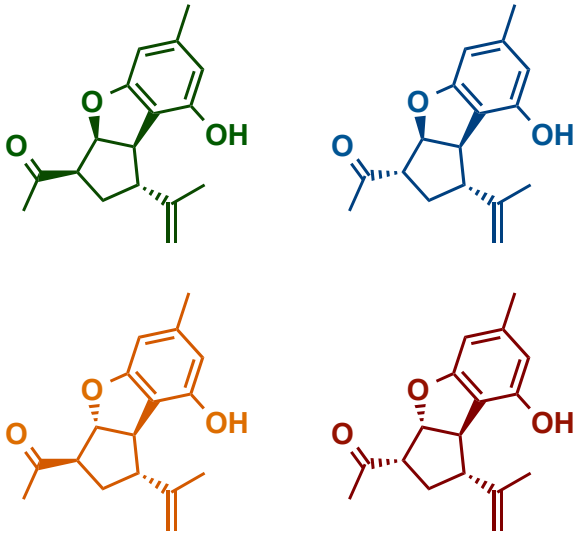
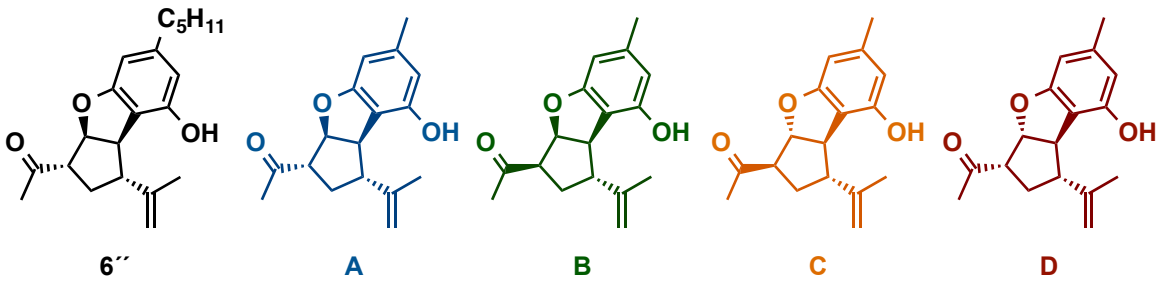



**Table S12**. Comparison between $^{13}C$ NMR chemical shifts calculated (conformationally-weighted values in ppm) for **A**, **B**, **C** and **D** and observed for **6´´**.



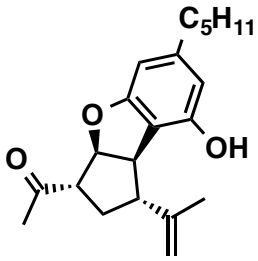

| | 6´´ | A | Abs error |
|---|---|---|---|
| **C1** | 30.2 | 28.5 | 1.7 |
| **C2** | 55.0 | 50.3 | 4.7 |
| **C3** | 48.6 | 46.5 | 2.1 |
| **C4** | 89.2 | 88.0 | 1.2 |
| **C5** | 60.5 | 59.9 | 0.6 |
| **C7** | 31.1 | 26.1 | 5.0 |
| **C9** | 112.5 | 109.9 | 2.6 |
| **C10** | 19.9 | 20.5 | 0.6 |
| **C11** | 160.7 | 163.0 | 2.3 |
| **C12** | 112.9 | 110.6 | 2.3 |
| **C13** | 152.8 | 154.7 | 1.9 |
| | | | |
| | | **Mean Abs Error =** | 2.3 |

| | 6´´ | C | Abs error |
|---|---|---|---|
| **C1** | 30.2 | 34.0 | 3.8 |
| **C2** | 55.0 | 39.3 | 15.7 |
| **C3** | 48.6 | 51.8 | 3.2 |
| **C4** | 89.2 | 91.3 | 2.1 |
| **C5** | 60.5 | 48.4 | 12.1 |
| **C7** | 31.1 | 26.8 | 4.3 |
| **C9** | 112.5 | 107.3 | 5.2 |
| **C10** | 19.9 | 20.1 | 0.2 |
| **C11** | 160.7 | 169.5 | 8.8 |
| **C12** | 112.9 | 110.1 | 2.8 |
| **C13** | 152.8 | 153.6 | 0.8 |
| | | | |
| | | **Mean Abs Error =** | 5.4 |

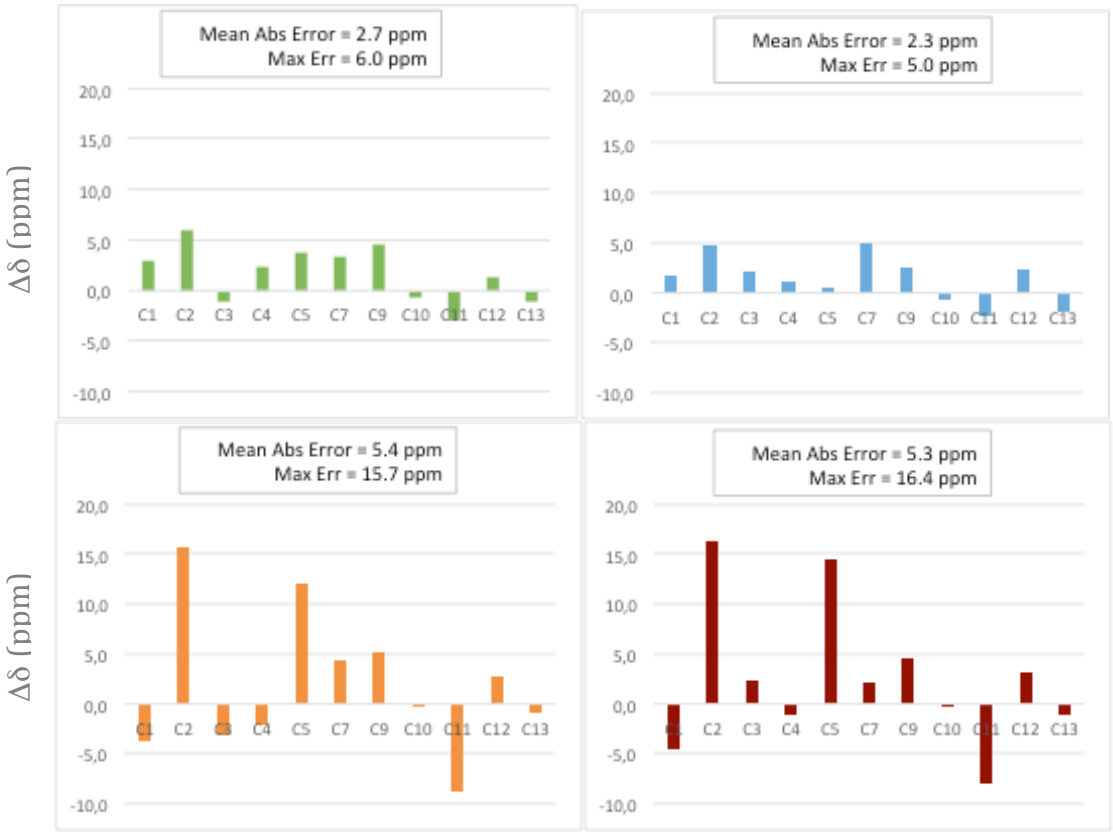
| | 6´´ | B | Abs error |
|---|---|---|---|
| **C1** | 30.2 | 27.2 | 3.0 |
| **C2** | 55.0 | 49.0 | 6.0 |
| **C3** | 48.6 | 49.7 | 1.1 |
| **C4** | 89.2 | 86.8 | 2.4 |
| **C5** | 60.5 | 56.7 | 3.8 |
| **C7** | 31.1 | 27.8 | 3.3 |
| **C9** | 112.5 | 108.0 | 4.5 |
| **C10** | 19.9 | 20.5 | 0.6 |
| **C11** | 160.7 | 163.6 | 2.9 |
| **C12** | 112.9 | 111.5 | 1.4 |
| **C13** | 152.8 | 153.8 | 1.0 |
| | | | |
| | | **Mean Abs Error =** | 2.7 |

| | 6´´ | D | Abs error |
|---|---|---|---|
| **C1** | 30.2 | 34.8 | 4.6 |
| **C2** | 55.0 | 38.6 | 16.4 |
| **C3** | 48.6 | 46.2 | 2.4 |
| **C4** | 89.2 | 90.3 | 1.1 |
| **C5** | 60.5 | 46.0 | 14.5 |
| **C7** | 31.1 | 29.0 | 2.1 |
| **C9** | 112.5 | 108.0 | 4.5 |
| **C10** | 19.9 | 20.2 | 0.3 |
| **C11** | 160.7 | 168.7 | 8.0 |
| **C12** | 112.9 | 109.8 | 3.1 |
| **C13** | 152.8 | 153.8 | 1.0 |
| | | | |
| | | **Mean Abs Error =** | 5.3 |

**Figure S4**. Comparative plots between $^{13}C$ NMR chemical shifts calculated (conformationally-weighted values in ppm) for **A**, **B**, **C** and **D** and observed for **6´´**.




**6´´**



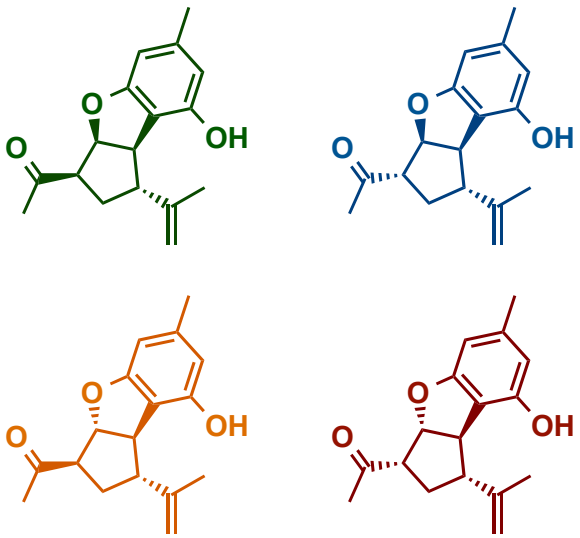
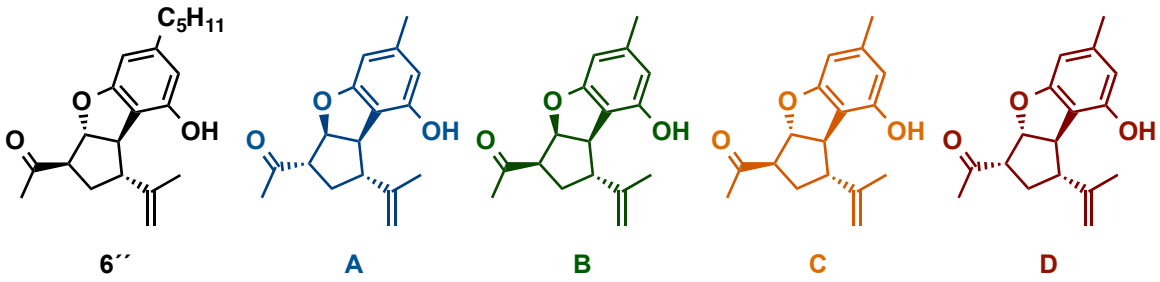



**Table S13**. Comparison between $^{13}C$ NMR chemical shifts calculated (conformationally-weighted values in ppm) for **A**, **B**, **C** and **D** and observed for **6´**.



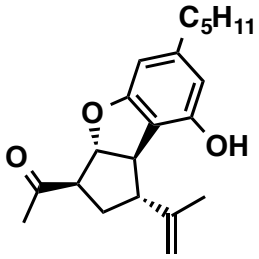

| | 6´ | A | Abs error |
|---|---|---|---|
| **C1** | 27.4 | 28.5 | 1.1 |
| **C2** | 56.0 | 50.3 | 5.7 |
| **C3** | 50.6 | 46.5 | 4.1 |
| **C4** | 91.2 | 88.0 | 3.2 |
| **C5** | 57.4 | 59.9 | 2.5 |
| **C7** | 28.5 | 26.1 | 2.4 |
| **C9** | 109.7 | 109.9 | 0.2 |
| **C10** | 20.7 | 20.5 | 0.2 |
| **C11** | 161.4 | 163.0 | 1.6 |
| **C12** | 115.7 | 110.6 | 5.1 |
| **C13** | 157.9 | 154.7 | 3.2 |
| | | | |
| | | **Mean Abs Error =** | 2.7 |

| | 6´ | C | Abs error |
|---|---|---|---|
| **C1** | 27.4 | 34.0 | 6.6 |
| **C2** | 56.0 | 39.3 | 16.7 |
| **C3** | 50.6 | 51.8 | 1.2 |
| **C4** | 91.2 | 91.3 | 0.1 |
| **C5** | 57.4 | 48.4 | 9.0 |
| **C7** | 28.5 | 26.8 | 1.7 |
| **C9** | 109.7 | 107.3 | 2.4 |
| **C10** | 20.7 | 20.1 | 0.6 |
| **C11** | 161.4 | 169.5 | 8.1 |
| **C12** | 115.7 | 110.1 | 5.6 |
| **C13** | 157.9 | 153.6 | 4.3 |
| | | | |
| | | **Mean Abs Error =** | 5.1 |

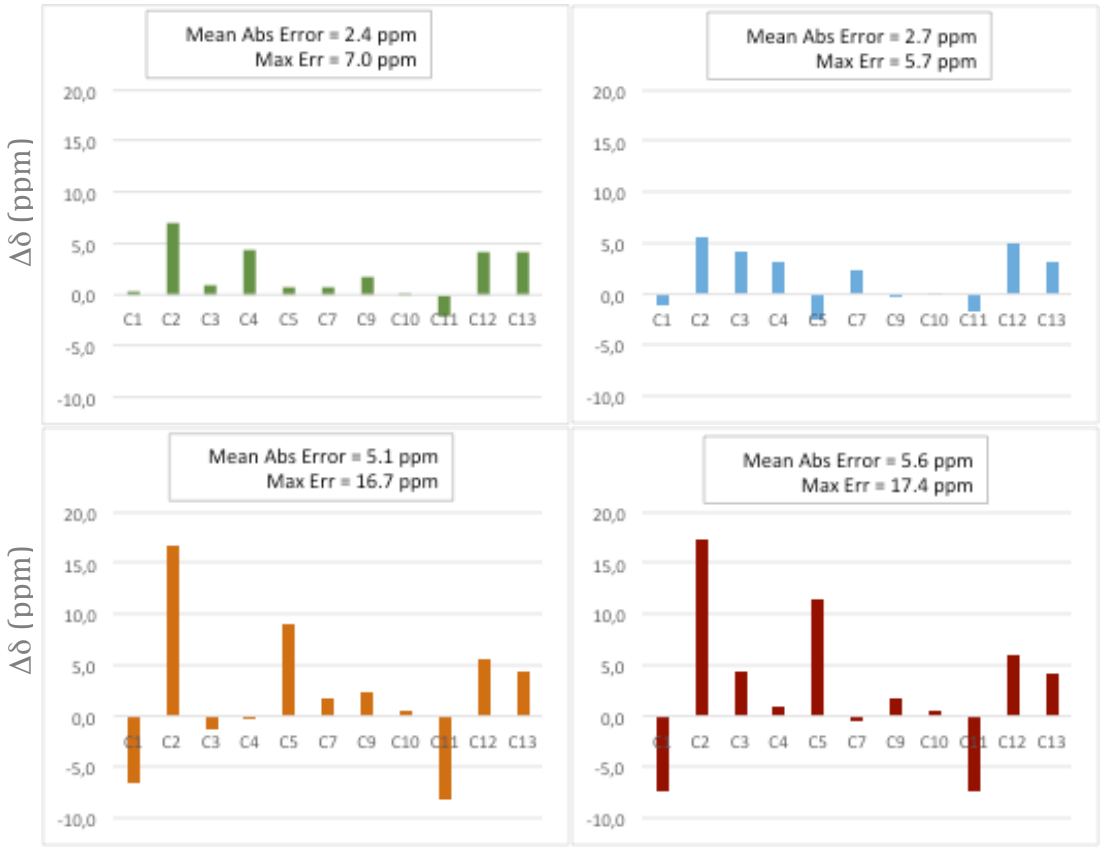
| | 6´ | B | Abs error |
|---|---|---|---|
| **C1** | 27.4 | 27.2 | 0.2 |
| **C2** | 56.0 | 49.0 | 7.0 |
| **C3** | 50.6 | 49.7 | 0.9 |
| **C4** | 91.2 | 86.8 | 4.4 |
| **C5** | 57.4 | 56.7 | 0.7 |
| **C7** | 28.5 | 27.8 | 0.7 |
| **C9** | 109.7 | 108.0 | 1.7 |
| **C10** | 20.7 | 20.5 | 0.2 |
| **C11** | 161.4 | 163.6 | 2.2 |
| **C12** | 115.7 | 111.5 | 4.2 |
| **C13** | 157.9 | 153.8 | 4.1 |
| | | | |
| | | **Mean Abs Error =** | 2.4 |

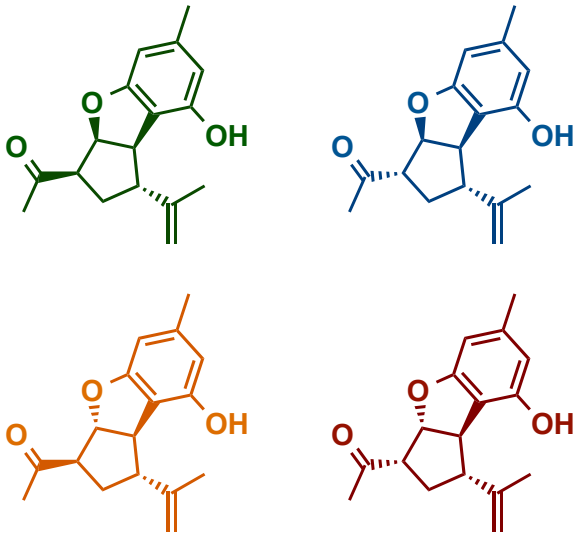
| | 6´ | D | Abs error |
|---|---|---|---|
| **C1** | 27.4 | 34.8 | 7.4 |
| **C2** | 56.0 | 38.6 | 17.4 |
| **C3** | 50.6 | 46.2 | 4.4 |
| **C4** | 91.2 | 90.3 | 0.9 |
| **C5** | 57.4 | 46.0 | 11.4 |
| **C7** | 28.5 | 29.0 | 0.5 |
| **C9** | 109.7 | 108.0 | 1.7 |
| **C10** | 20.7 | 20.2 | 0.5 |
| **C11** | 161.4 | 168.7 | 7.3 |
| **C12** | 115.7 | 109.8 | 5.9 |
| **C13** | 157.9 | 153.8 | 4.1 |
| | | | |
| | | **Mean Abs Error =** | 5.6 |

**Figure S5**. Comparative plots between $^{13}C$ NMR chemical shifts calculated (conformationally-weighted values in ppm) for **A**, **B**, **C** and **D** and observed for **6´**.




**6´**



Cartesian Coordinates of the lowest energy structures used for the NMR calculations calculated with M06-2X/6-31G(d,p).

**Structure cis_11**

| | | | |
|---|---|---|---|
| C | 2.406700 | 0.404300 | 0.465600 |
| C | 1.138400 | 1.264300 | 0.289500 |
| C | 0.311000 | 0.496600 | -0.768900 |
| C | 0.873500 | -0.955400 | -0.796000 |
| H | 3.107800 | 0.581500 | -0.358100 |
| H | 2.933400 | 0.598700 | 1.402300 |
| H | 0.586200 | 1.213500 | 1.240500 |
| H | 0.414200 | 0.954400 | -1.756600 |
| H | 1.369000 | -1.194900 | -1.741500 |
| O | -0.225300 | -1.864800 | -0.647400 |
| C | -1.125600 | 0.236300 | -0.405500 |
| C | -1.344300 | -1.137900 | -0.346100 |
| C | -2.169800 | 1.096800 | -0.091900 |
| C | -2.565600 | -1.698900 | -0.017600 |
| C | -3.420700 | 0.557600 | 0.235900 |
| C | -3.622600 | -0.821600 | 0.268400 |
| H | -2.694700 | -2.774900 | 0.019500 |
| H | -4.229400 | 1.240700 | 0.474300 |
| C | -4.982800 | -1.381500 | 0.601700 |
| H | -5.474700 | -1.763100 | -0.298600 |
| H | -4.903000 | -2.212900 | 1.306900 |
| H | -5.629400 | -0.618700 | 1.039700 |
| O | -2.039100 | 2.448600 | -0.079800 |
| H | -1.119200 | 2.707100 | -0.245100 |
| C | 1.409500 | 2.728500 | 0.027400 |
| C | 0.989200 | 3.398900 | -1.050900 |
| H | 0.438200 | 2.937400 | -1.864200 |
| H | 1.209300 | 4.456100 | -1.160600 |
| C | 2.204100 | 3.415500 | 1.107700 |
| H | 1.759300 | 3.234800 | 2.092100 |
| H | 3.225000 | 3.020200 | 1.141200 |
| H | 2.259400 | 4.492400 | 0.940300 |
| C | 2.922000 | -2.094400 | 0.167800 |
| O | 4.068500 | -1.808400 | -0.109700 |
| C | 2.449800 | -3.521900 | 0.291800 |
| H | 1.512200 | -3.662600 | -0.253700 |
| H | 3.217000 | -4.205400 | -0.070400 |
| H | 2.238800 | -3.734500 | 1.345200 |
| C | 1.871100 | -1.021900 | 0.381800 |
| H | 1.284300 | -1.266200 | 1.277900 |

**Structure cis2_6**

| | | | |
|---|---|---|---|
| C | 1.572400 | -0.030100 | 1.144600 |
| C | 1.284300 | 1.269900 | 0.362200 |
| C | 0.411000 | 0.771100 | -0.813200 |
| C | 0.809600 | -0.721400 | -1.052000 |
| C | 1.844800 | -1.050800 | 0.040700 |
| H | 2.402000 | 0.057900 | 1.849800 |
| H | 0.686300 | -0.335500 | 1.711100 |
| H | 0.710000 | 1.973700 | 0.975300 |
| H | 0.540100 | 1.396700 | -1.700600 |
| H | 1.172200 | -0.932400 | -2.061300 |
| H | 2.840800 | -0.872000 | -0.386900 |
| O | -0.378500 | -1.526400 | -0.856300 |
| C | -1.039900 | 0.624900 | -0.449400 |
| C | -1.407000 | -0.712300 | -0.487000 |
| C | -1.991100 | 1.572000 | -0.097500 |
| C | -2.686600 | -1.159600 | -0.193900 |
| C | -3.292400 | 1.155600 | 0.204800 |
| C | -3.639700 | -0.197600 | 0.160500 |
| H | -2.934000 | -2.214300 | -0.236800 |
| H | -4.040700 | 1.895400 | 0.477900 |
| C | -5.038700 | -0.628100 | 0.524700 |
| H | -5.364700 | -1.467900 | -0.093500 |
| H | -5.083000 | -0.952500 | 1.569300 |
| H | -5.751300 | 0.189800 | 0.399300 |
| O | -1.602300 | 2.875100 | -0.068400 |
| H | -2.347800 | 3.428600 | 0.195500 |
| C | 2.575800 | 1.947000 | -0.051700 |
| C | 3.139300 | 1.799400 | -1.252200 |
| H | 2.687200 | 1.202900 | -2.039800 |
| H | 4.082300 | 2.281800 | -1.490700 |
| C | 3.213200 | 2.791900 | 1.020100 |
| H | 2.560000 | 3.632900 | 1.277900 |
| H | 3.362300 | 2.215800 | 1.939700 |
| H | 4.179100 | 3.187500 | 0.700500 |
| C | 1.796200 | -2.502000 | 0.484200 |
| O | 1.648100 | -2.797600 | 1.651100 |
| C | 1.953000 | -3.547600 | -0.594700 |
| H | 2.792000 | -3.303900 | -1.252400 |
| H | 2.100300 | -4.527800 | -0.141900 |
| H | 1.044300 | -3.560500 | -1.204300 |

**Structure trans_3**

| | | | |
|---|---|---|---|
| C | 2.659300 | 0.442200 | -0.135900 |
| C | 1.381000 | 1.273900 | 0.274500 |
| C | 0.288400 | 0.425400 | -0.356700 |
| C | 0.755700 | -0.964400 | 0.025200 |
| C | 2.190200 | -1.004900 | -0.491000 |
| H | 3.132800 | 0.903900 | -1.006200 |
| H | 3.395200 | 0.406000 | 0.669200 |
| H | 1.278700 | 1.239400 | 1.367800 |
| H | 0.399900 | 0.510900 | -1.450600 |
| H | 0.777300 | -1.033200 | 1.126000 |
| H | 2.171900 | -1.172400 | -1.574200 |
| O | -0.270000 | -1.847200 | -0.433800 |
| C | -1.175500 | 0.256500 | -0.050700 |
| C | -1.426600 | -1.120200 | -0.202500 |
| C | -2.241400 | 1.108800 | 0.187200 |
| C | -2.688300 | -1.670700 | -0.124500 |
| C | -3.533600 | 0.568700 | 0.284900 |
| C | -3.760800 | -0.795000 | 0.124100 |
| H | -2.842800 | -2.738100 | -0.238100 |
| H | -4.358200 | 1.244900 | 0.486700 |
| C | -5.157200 | -1.353200 | 0.237600 |
| H | -5.421100 | -1.926600 | -0.655600 |
| H | -5.236700 | -2.029900 | 1.093700 |
| H | -5.893600 | -0.557400 | 0.364000 |
| O | -2.102400 | 2.450800 | 0.340100 |
| H | -1.170100 | 2.700800 | 0.247200 |
| C | 1.461800 | 2.721600 | -0.140000 |
| C | 0.689800 | 3.250500 | -1.094900 |
| H | -0.040400 | 2.663400 | -1.645700 |
| H | 0.782800 | 4.295700 | -1.372500 |
| C | 2.498100 | 3.532300 | 0.590100 |
| H | 2.313600 | 3.512100 | 1.669400 |
| H | 3.496000 | 3.108500 | 0.431300 |
| H | 2.507000 | 4.571000 | 0.255500 |
| C | 2.993900 | -2.118600 | 0.163200 |
| O | 3.850000 | -1.896900 | 0.992900 |
| C | 2.619100 | -3.517700 | -0.260400 |
| H | 2.883800 | -3.659900 | -1.313100 |
| H | 3.144000 | -4.249300 | 0.352700 |
| H | 1.536000 | -3.655900 | -0.182100 |

**Structure trans2_5**

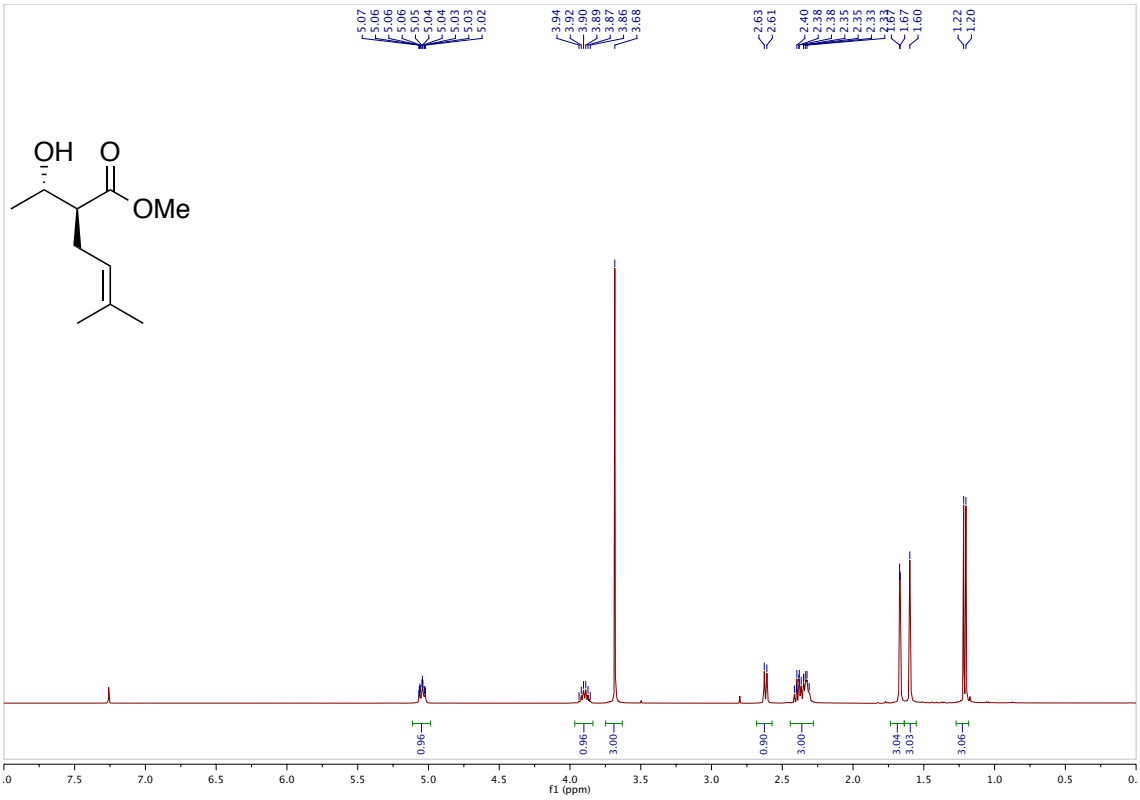
| | | | |
|---|---|---|---|
| C | 2.719000 | -0.022200 | 0.763400 |
| C | 1.573000 | 1.059700 | 0.665900 |
| C | 0.461100 | 0.216800 | 0.065200 |
| C | 0.581700 | -1.039300 | 0.905100 |
| C | 2.052000 | -1.436800 | 0.753800 |
| H | 3.363200 | 0.062900 | -0.116000 |
| H | 3.329500 | 0.121700 | 1.656200 |
| H | 1.289600 | 1.363900 | 1.683200 |
| H | 0.770400 | -0.042300 | -0.959900 |
| H | 0.406500 | -0.773400 | 1.958800 |
| H | 2.383600 | -2.063800 | 1.585800 |
| O | -0.506200 | -1.873000 | 0.493100 |
| C | -1.037200 | 0.350100 | 0.085100 |
| C | -1.521900 | -0.959300 | 0.260900 |
| C | -1.942100 | 1.372000 | -0.150400 |
| C | -2.861300 | -1.282400 | 0.211500 |
| C | -3.312700 | 1.069600 | -0.190000 |
| C | -3.769900 | -0.234100 | -0.022200 |
| H | -3.198800 | -2.302400 | 0.359500 |

| | | | |
|---|---|---|---|
| H | -4.012300 | 1.881500 | -0.360700 |
| C | -5.246900 | -0.535800 | -0.069600 |
| H | -5.466200 | -1.286400 | -0.834400 |
| H | -5.593300 | -0.936500 | 0.887800 |
| H | -5.828000 | 0.360600 | -0.293400 |
| O | -1.572500 | 2.665000 | -0.337900 |
| H | -0.606200 | 2.742100 | -0.302900 |
| C | 1.994800 | 2.293900 | -0.091200 |
| C | 1.517900 | 2.605300 | -1.300600 |
| H | 0.803400 | 1.976300 | -1.824900 |
| H | 1.854600 | 3.496800 | -1.820300 |
| C | 3.020400 | 3.146600 | 0.605800 |
| H | 2.654600 | 3.467800 | 1.587000 |
| H | 3.937700 | 2.573100 | 0.780500 |
| H | 3.274600 | 4.031500 | 0.019900 |
| C | 2.261900 | -2.204700 | -0.548200 |
| O | 2.622800 | -1.652000 | -1.566400 |
| C | 1.953500 | -3.679500 | -0.496200 |
| H | 0.931900 | -3.820500 | -0.130500 |
| H | 2.064800 | -4.119600 | -1.486400 |
| H | 2.628200 | -4.173400 | 0.209700 |

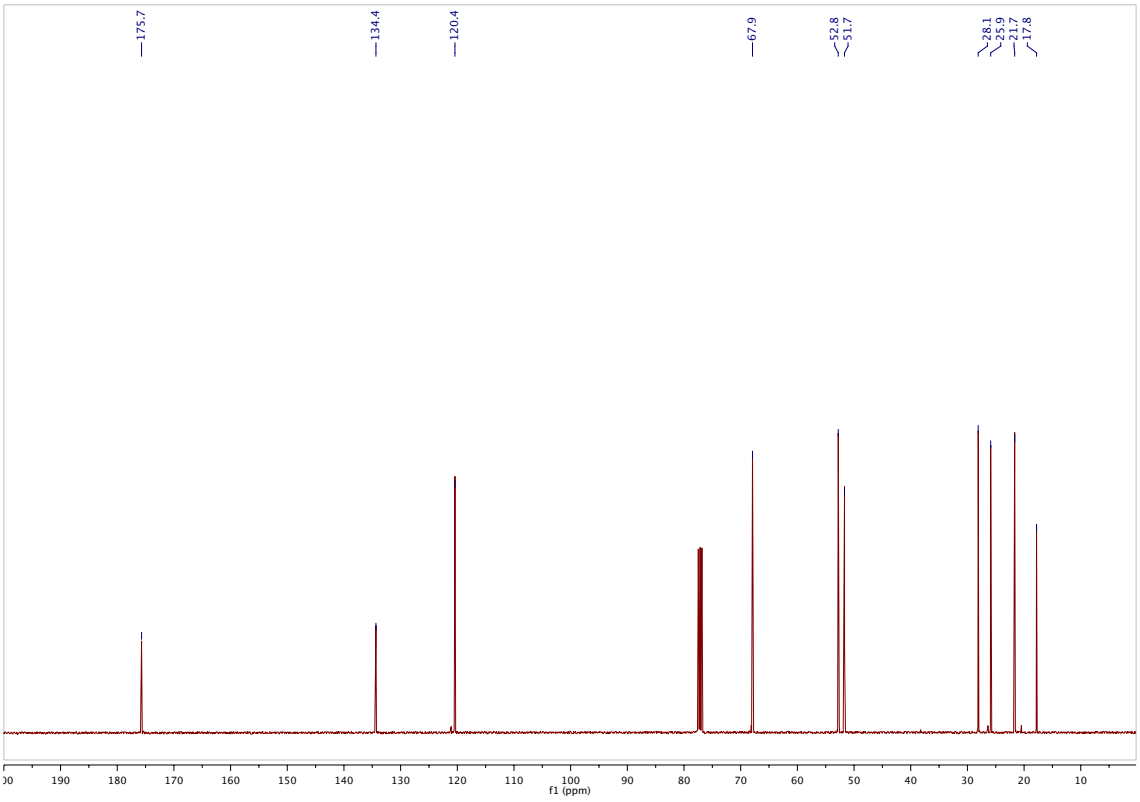
## NMR Spectra

### (*S*)-Methyl 2-((*S*)-1-hydroxyethyl)-5-methylhex-4-enoate (10)

$^{1}$H NMR

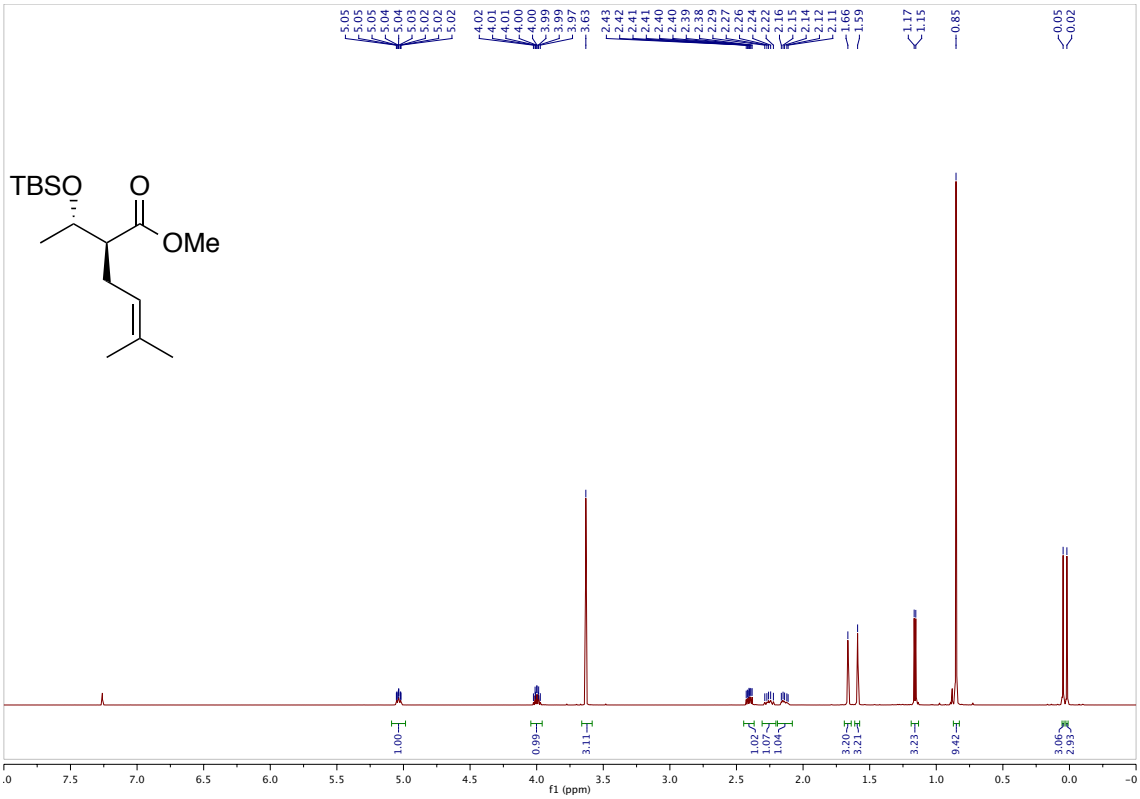



$^{13}$C NMR

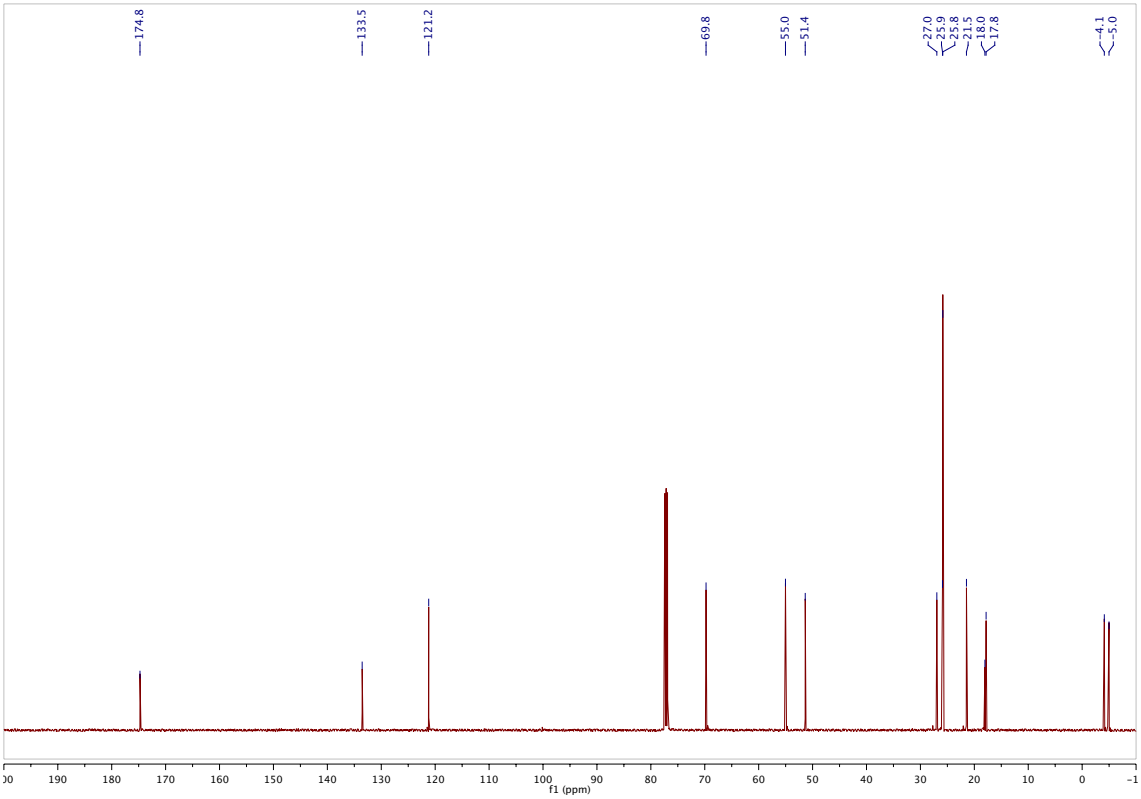


**(*S*)-Methyl 5-methyl-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)hex-4-enoate (S1)**

$^{1}$H NMR

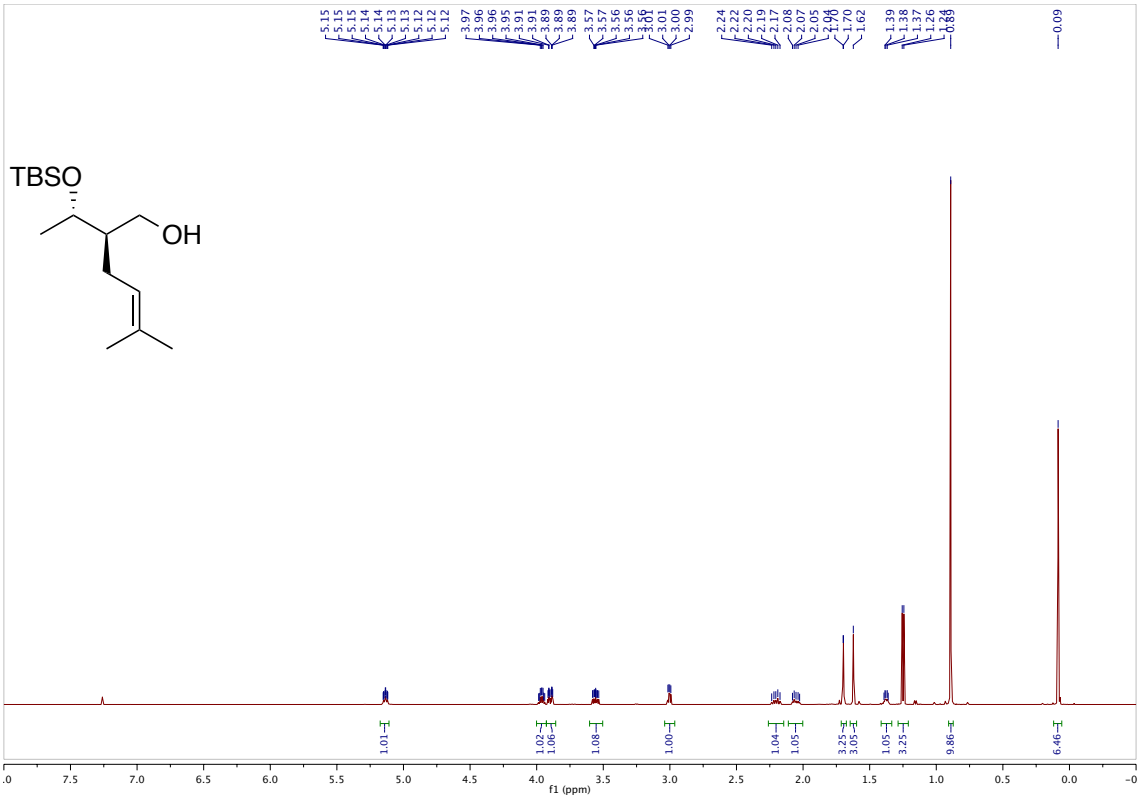



$^{13}$C NMR

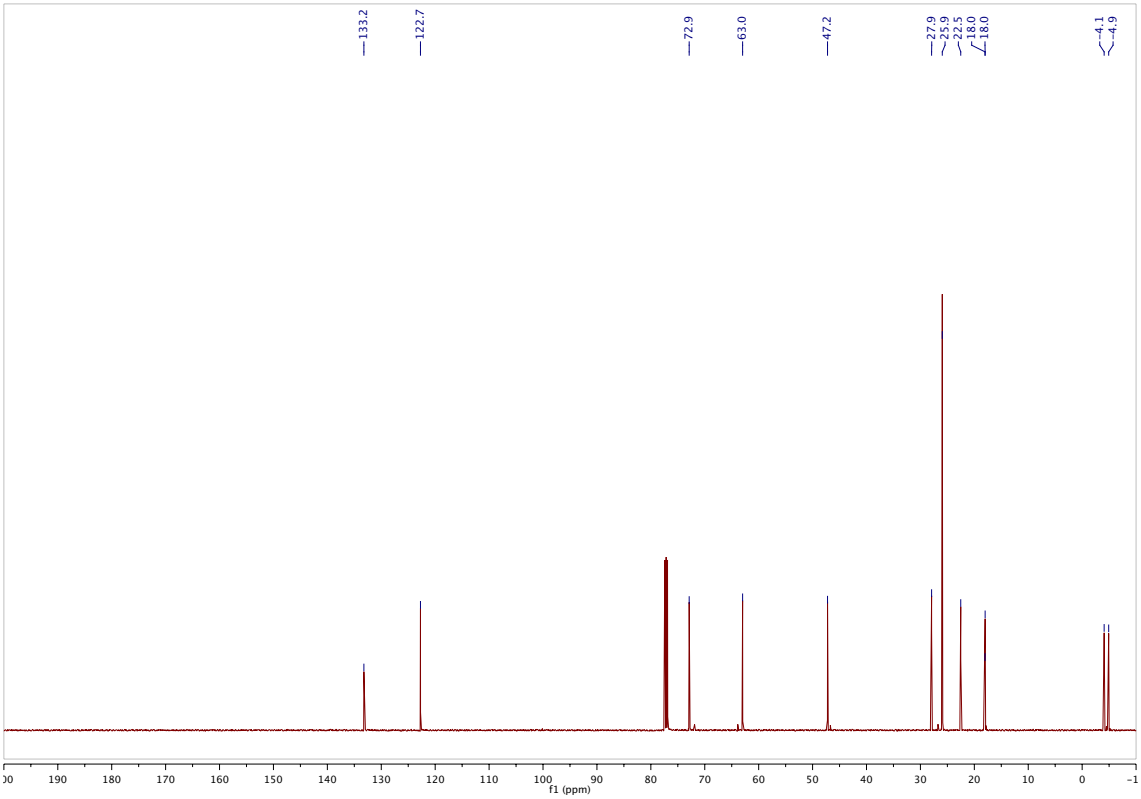


**(*R*)-5-Methyl-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)hex-4-en-1-ol (S2)**

$^{1}$H NMR

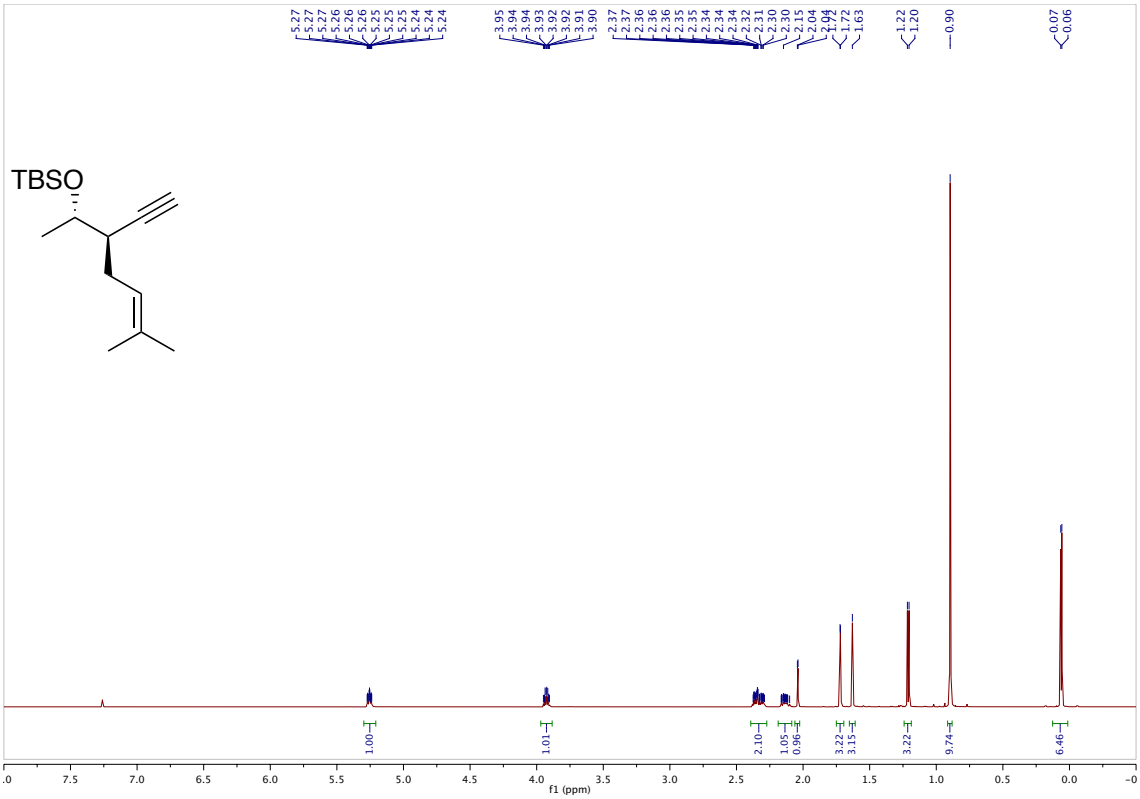



$^{13}$C NMR

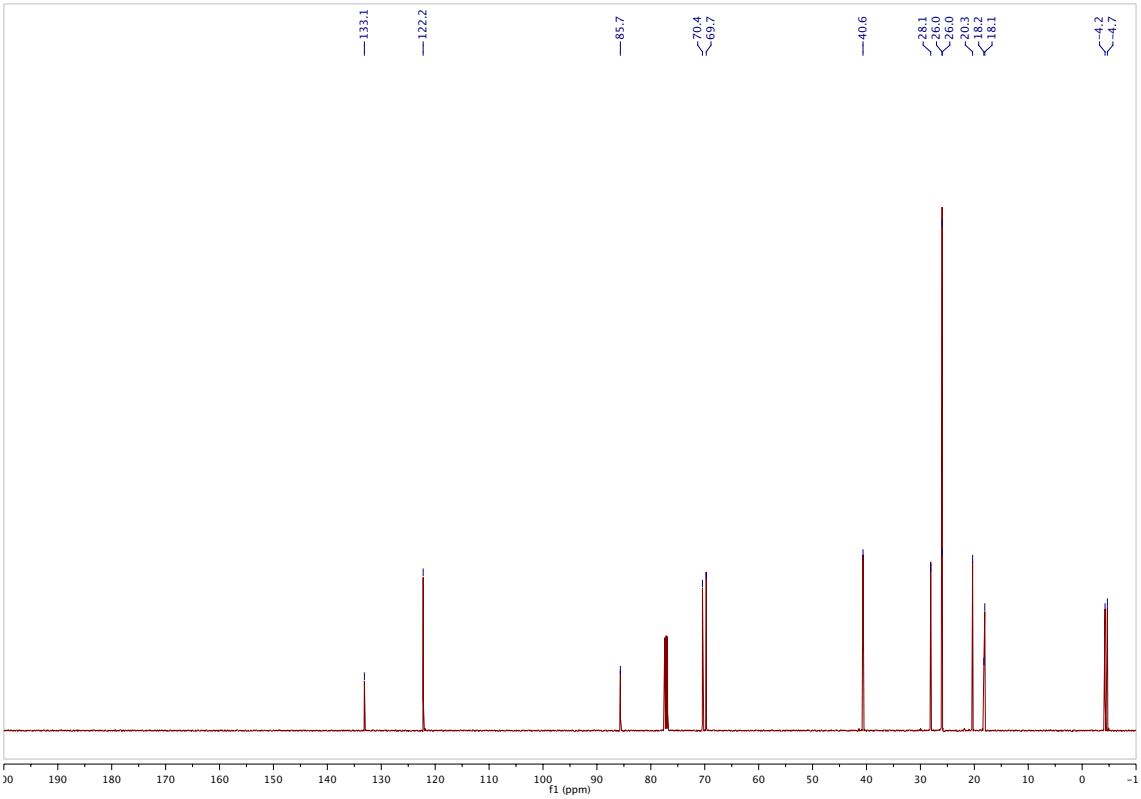


**(((2*S*,3*R*)-3-Ethynyl-6-methylhept-5-en-2-yl)oxy) *tert*-butyldimethylsilane (11)**

$^{1}$H NMR

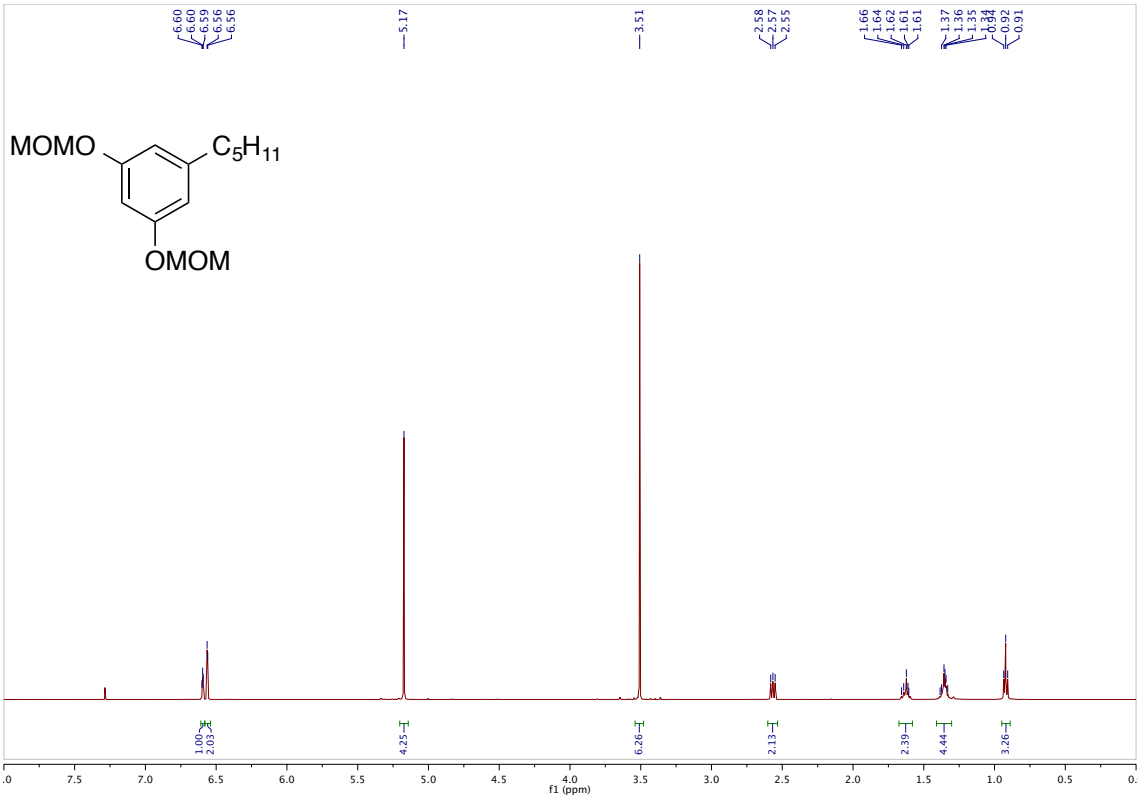



$^{13}$C NMR

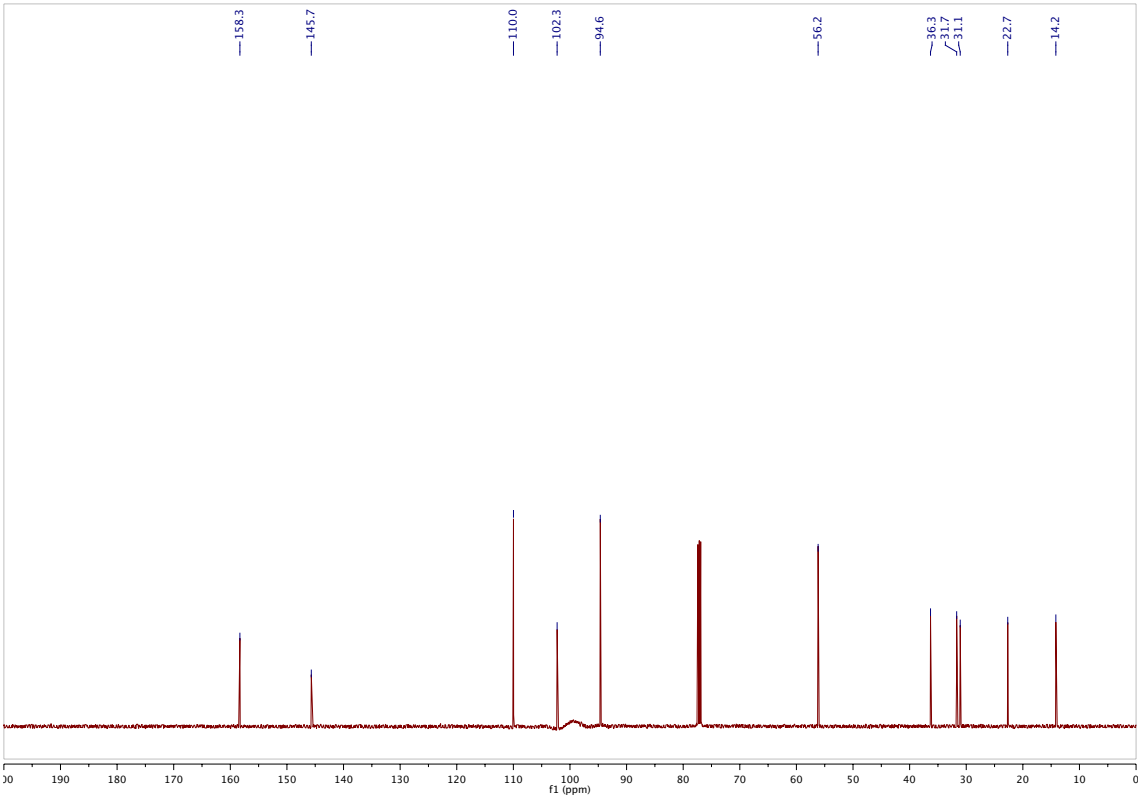


**1,3-Bis(methoxymethoxy)-5-pentylbenzene (S3)**

$^{1}$H NMR

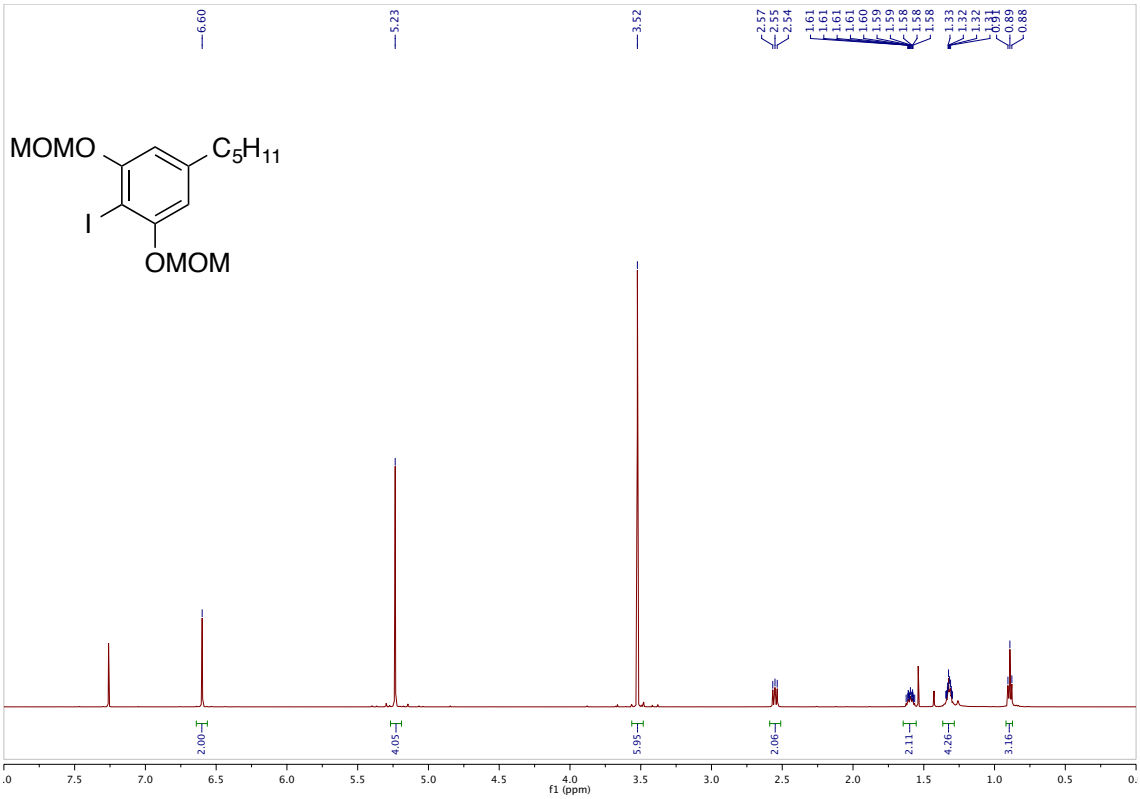



$^{13}$C NMR

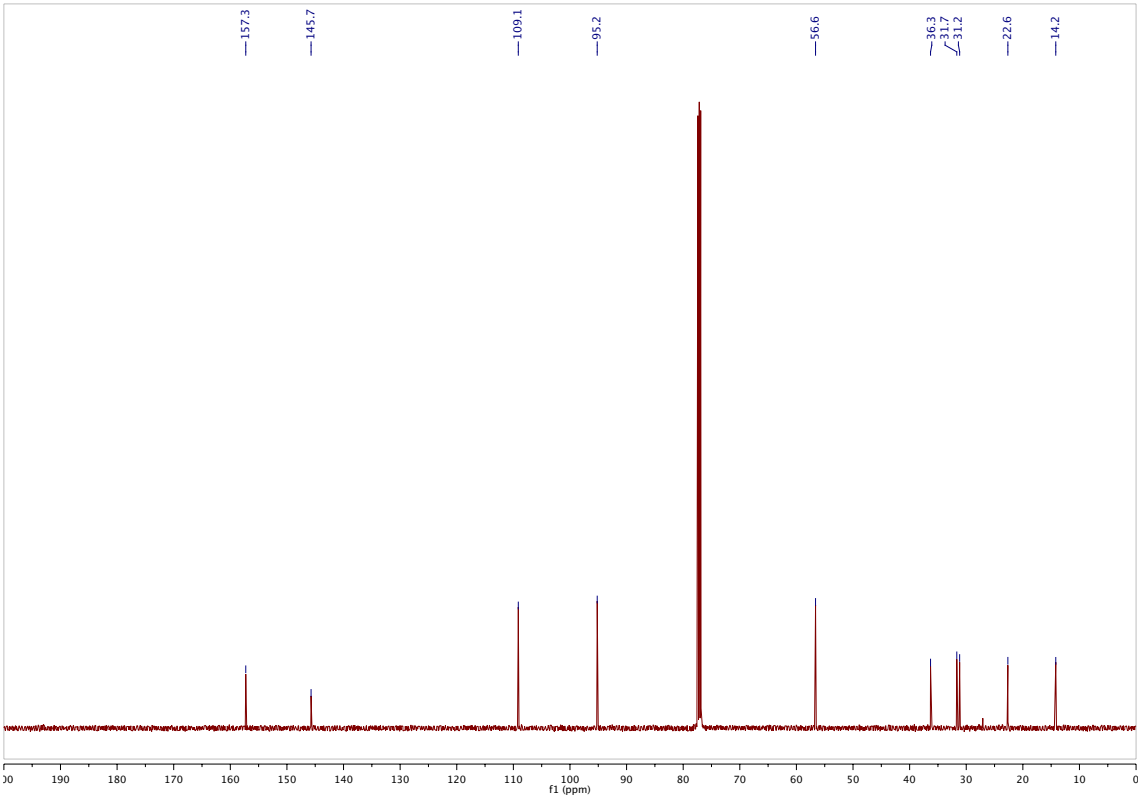


**2-Iodo-1,3-bis(methoxymethoxy)-5-pentylbenzene (12)**

$^{1}$H NMR

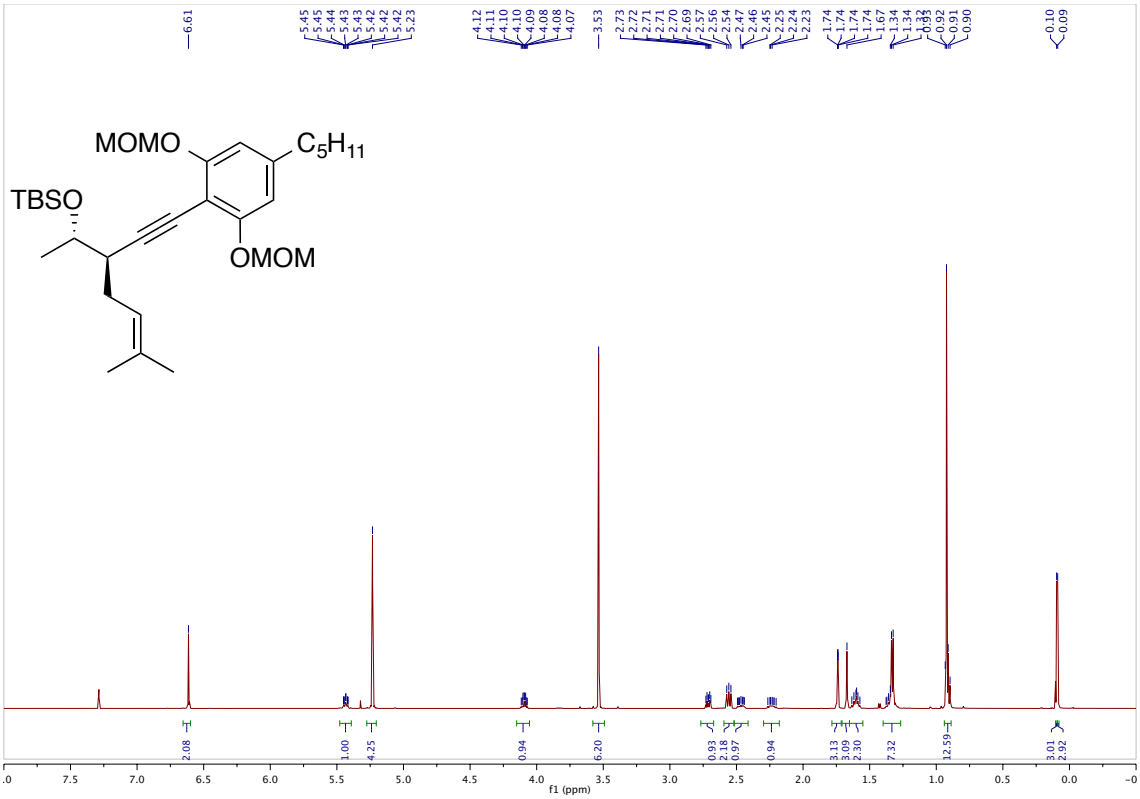



$^{13}$C NMR

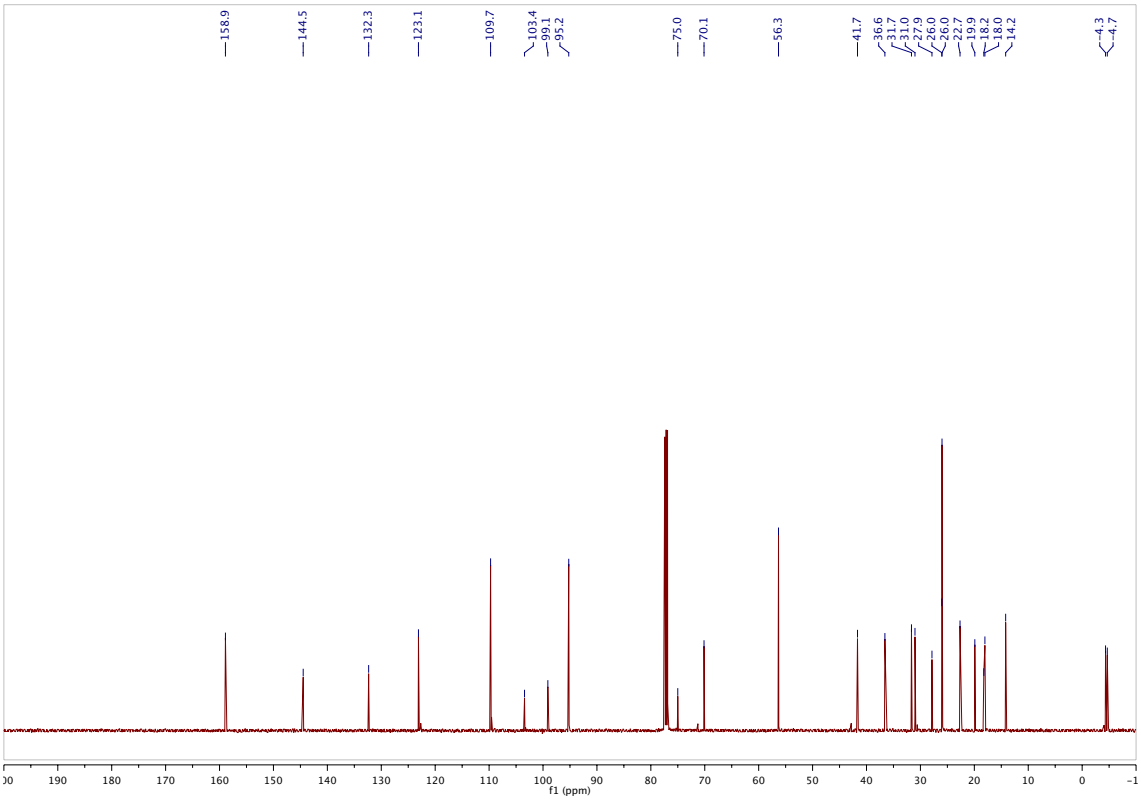


**(((2*S*,3*R*)-3-((2,6-Bis(methoxymethoxy)-4-pentylphenyl)ethynyl)-6-methylhept-5-en-2-yl)oxy)*tert*-butyldimethylsilane (7)**

$^{1}$H NMR

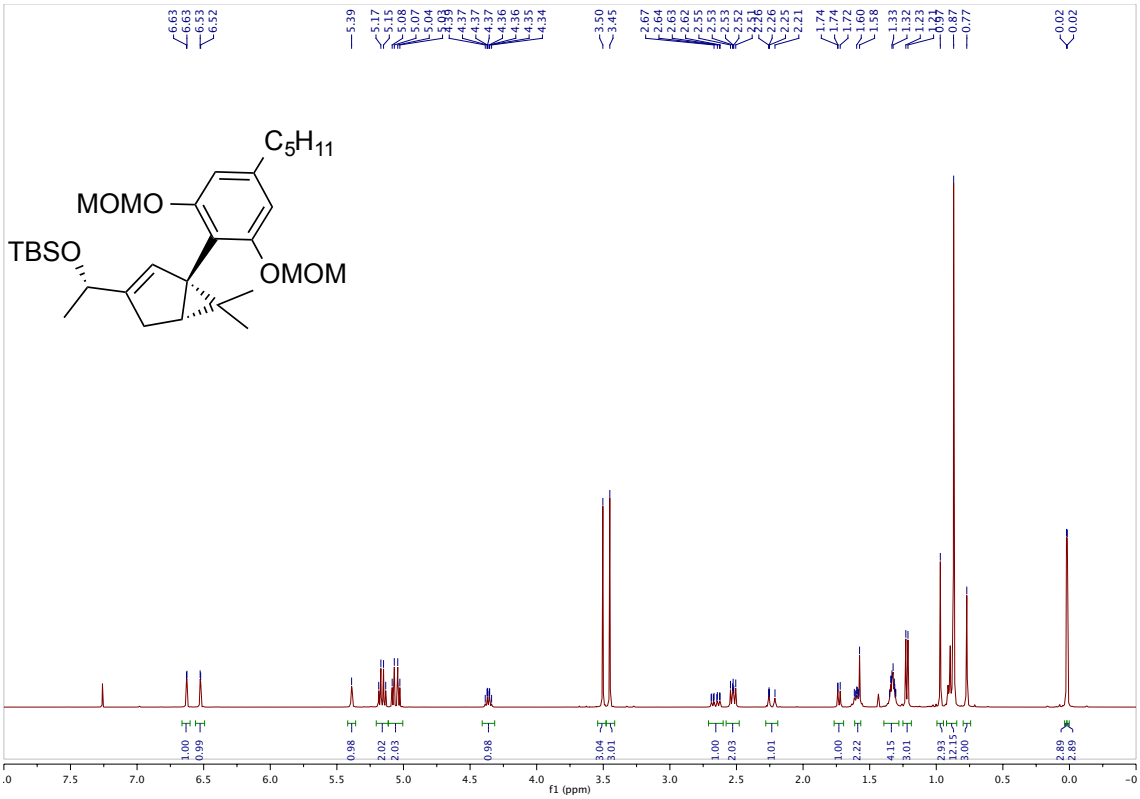



$^{13}$C NMR

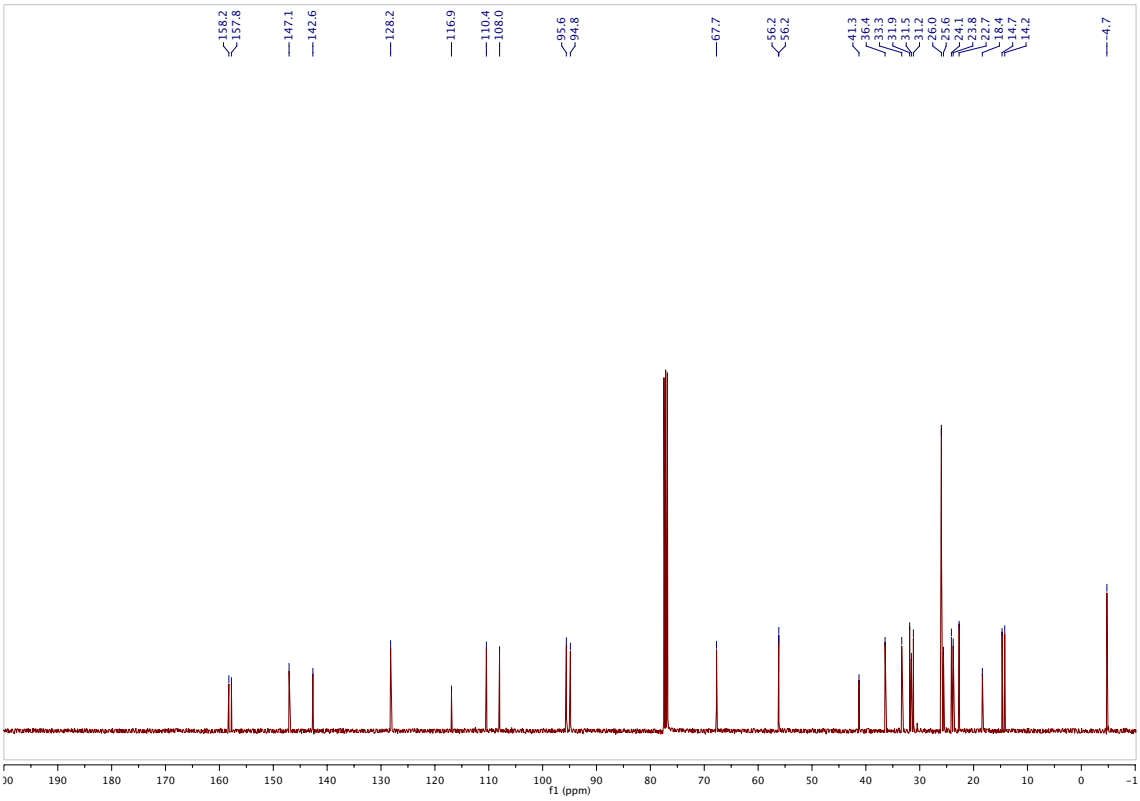


**((*S*)-1-((1*R*,5*S*)-1-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-6,6-dimethylbicyclo[3.1.0]hex-2-en-3-yl)ethoxy)(*tert*-butyl)dimethylsilane (13)**

$^{1}$H NMR

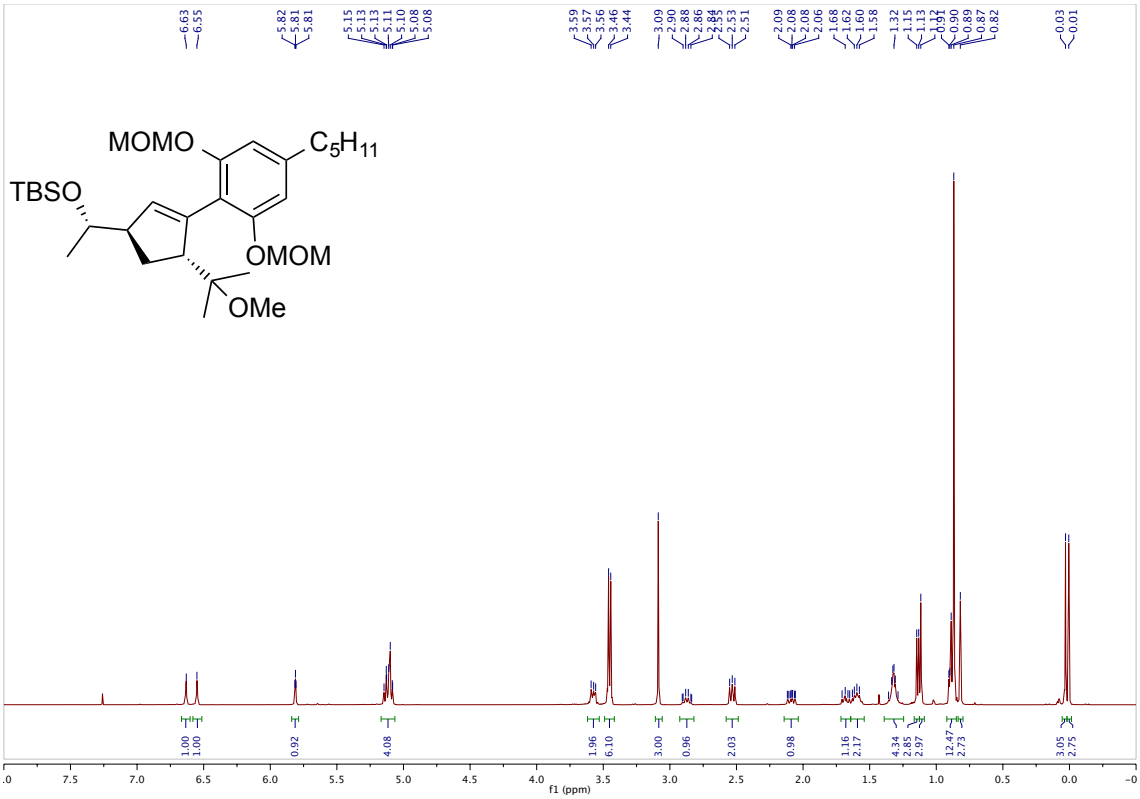



$^{13}$C NMR

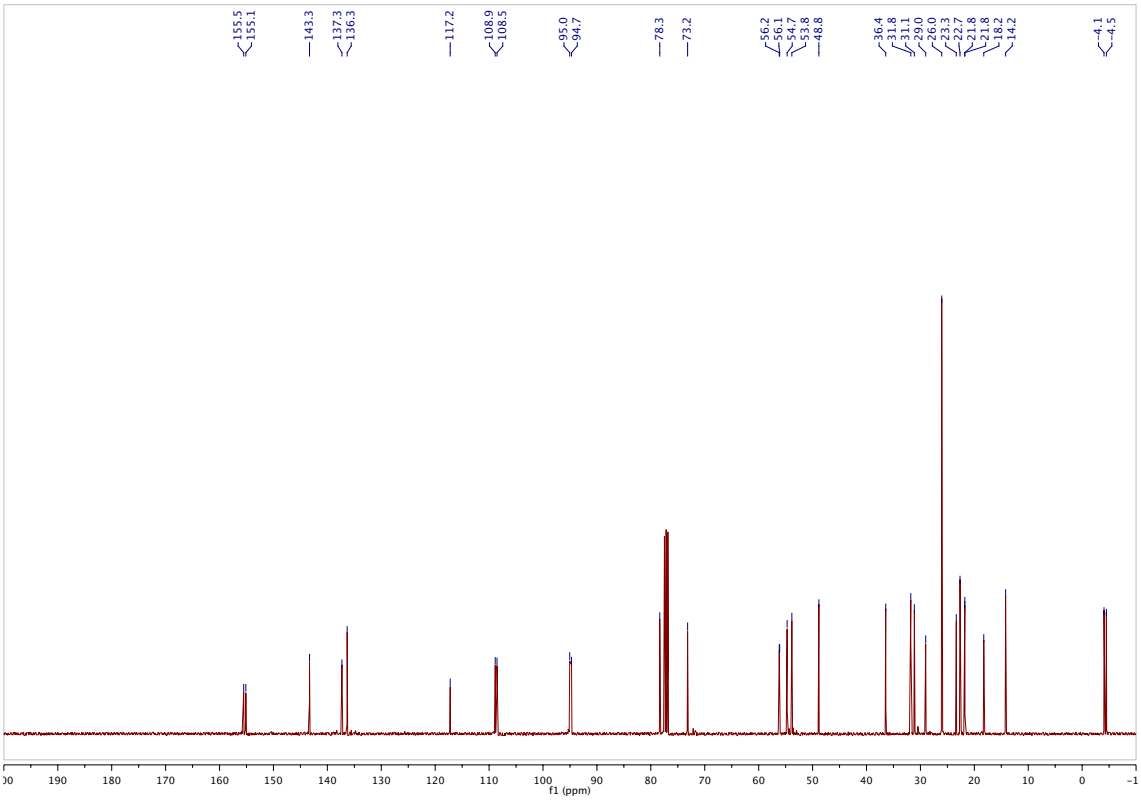


**((*S*)-1-((1*R*,4*R*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(2-methoxypropan-2-yl)cyclopent-2-en-1-yl)ethoxy)(*tert*-butyl)dimethylsilane (14)**

$^{1}$H NMR

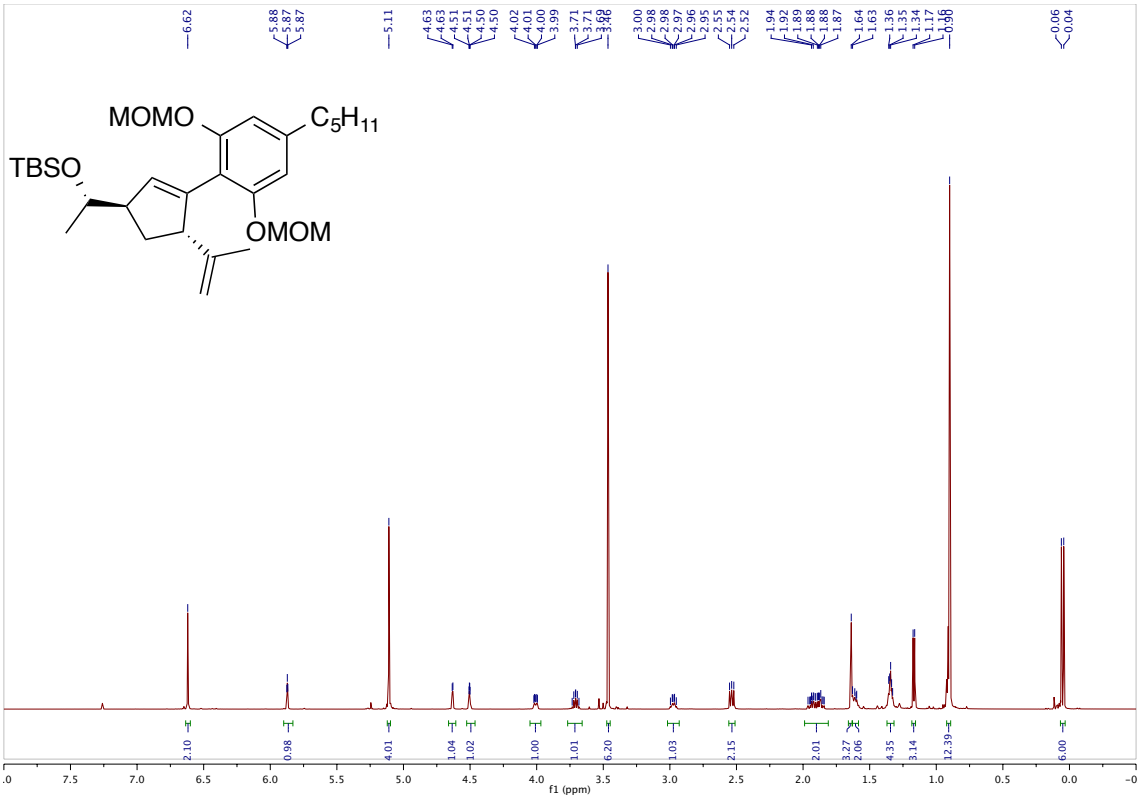



$^{13}$C NMR

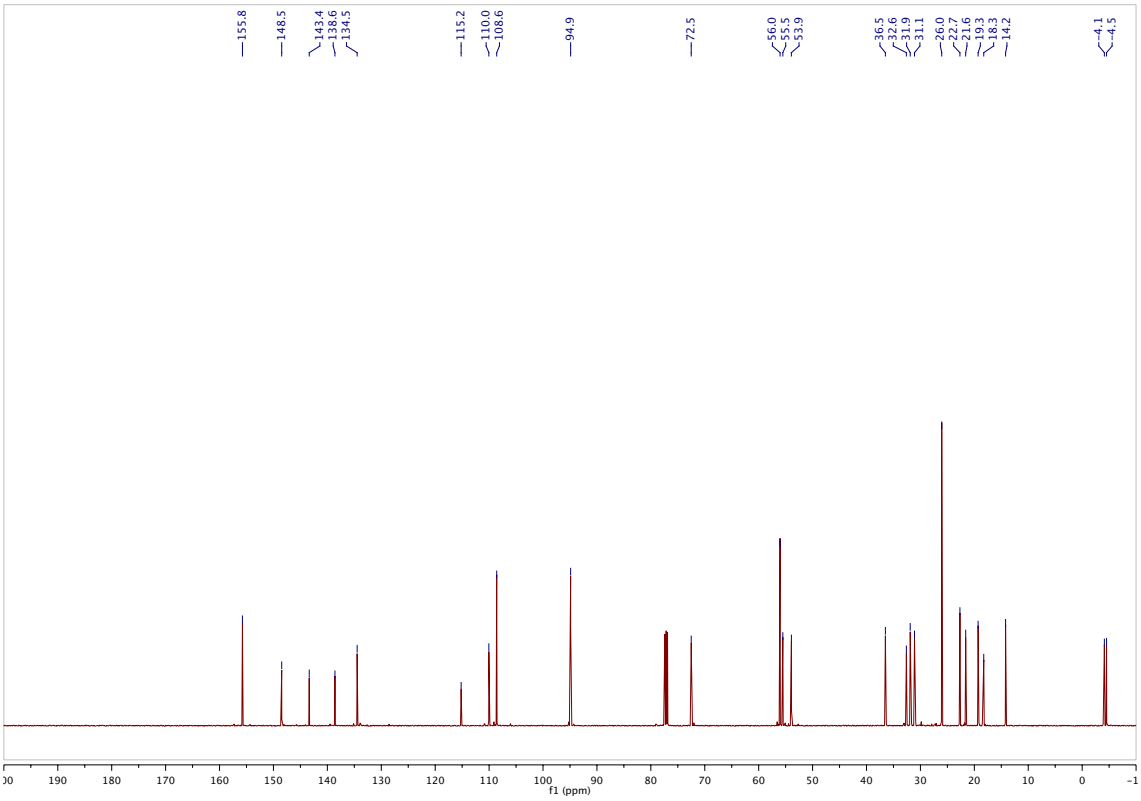


**((*S*)-1-((1*R*,4*S*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethoxy)(*tert*-butyl)dimethylsilane (8)**

$^{1}$H NMR

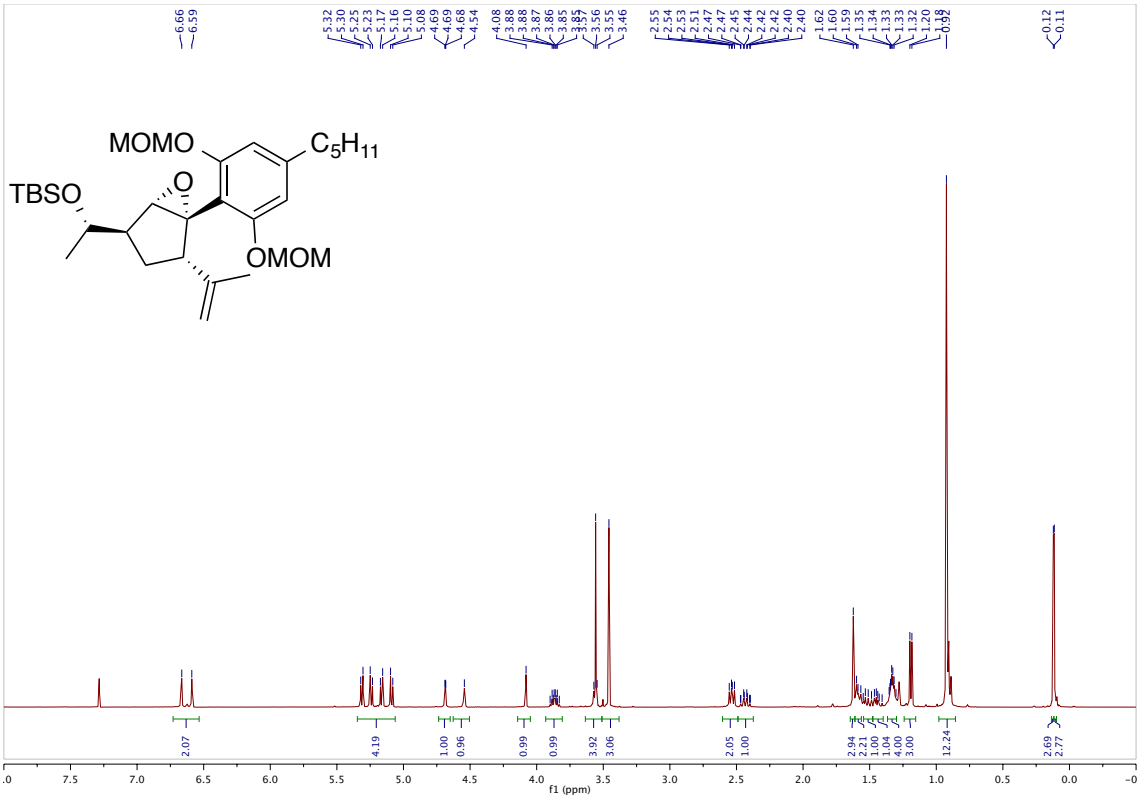



$^{13}$C NMR

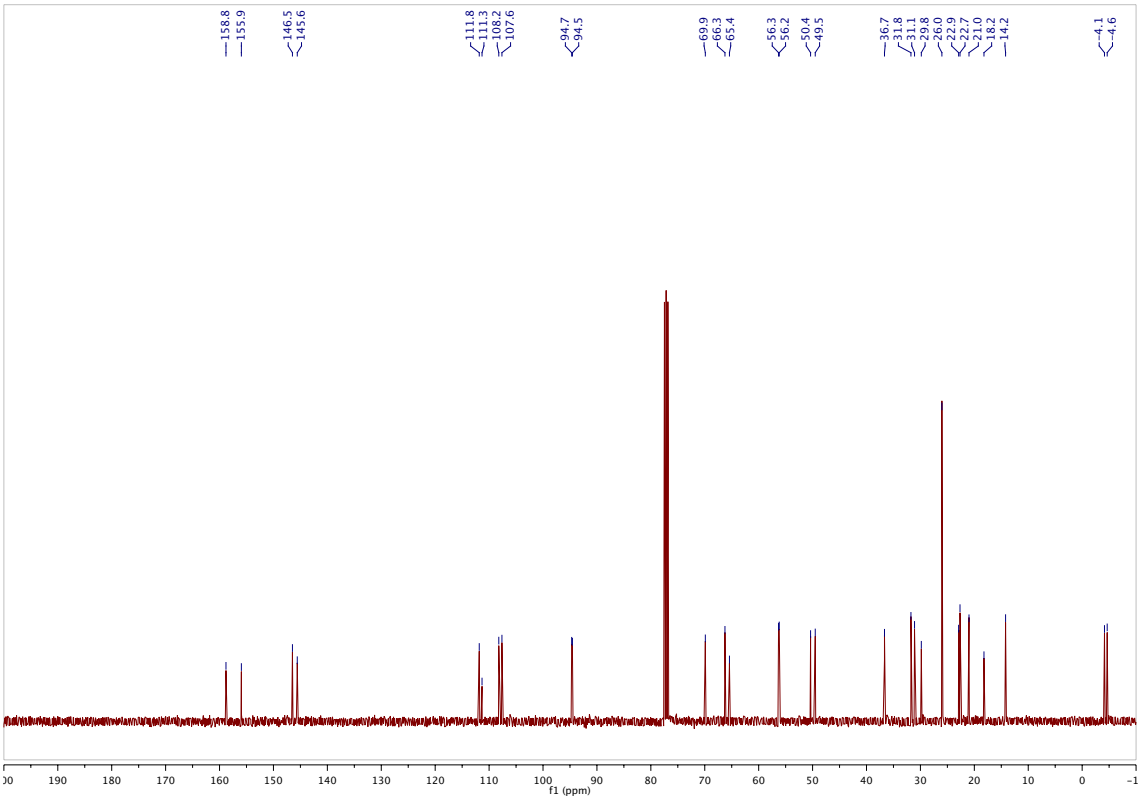


**((*S*)-1-((1*S*,2*R*,4*S*,5*S*)-5-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)-6-oxabicyclo[3.1.0]hexan-2-yl)ethoxy)(*tert*-butyl)dimethylsilane (15)**

$^{1}$H NMR

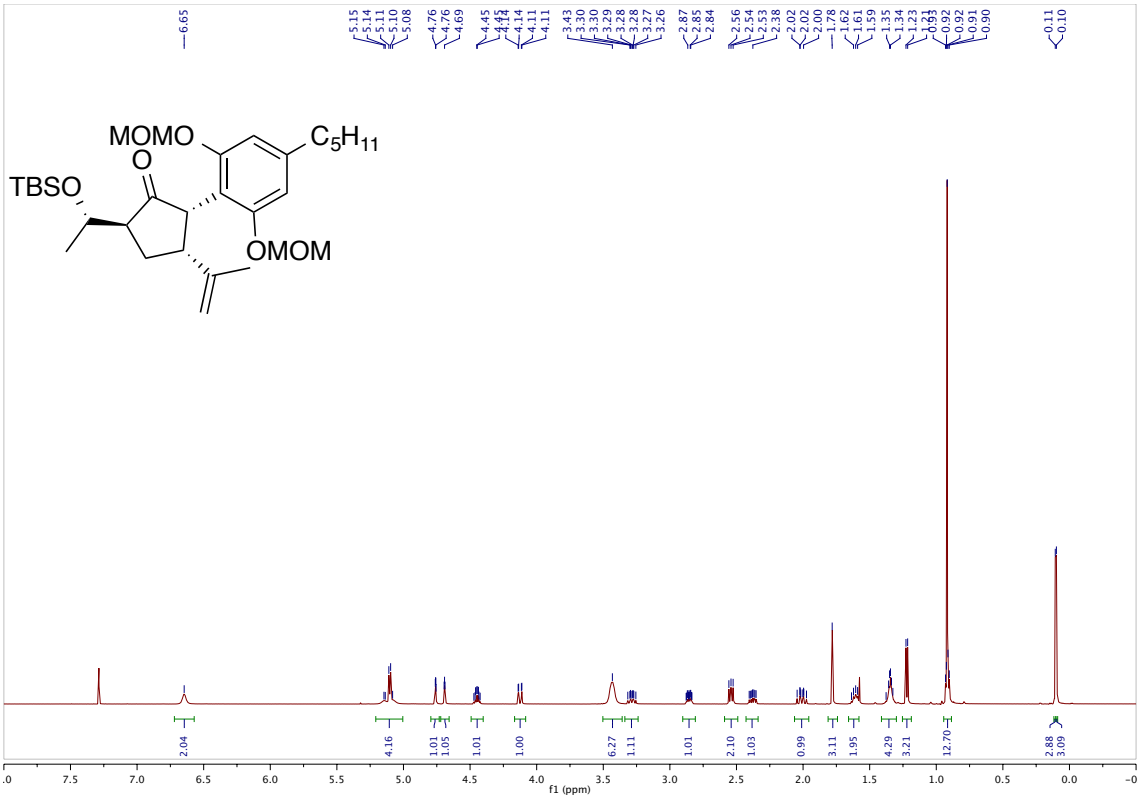



$^{13}$C NMR

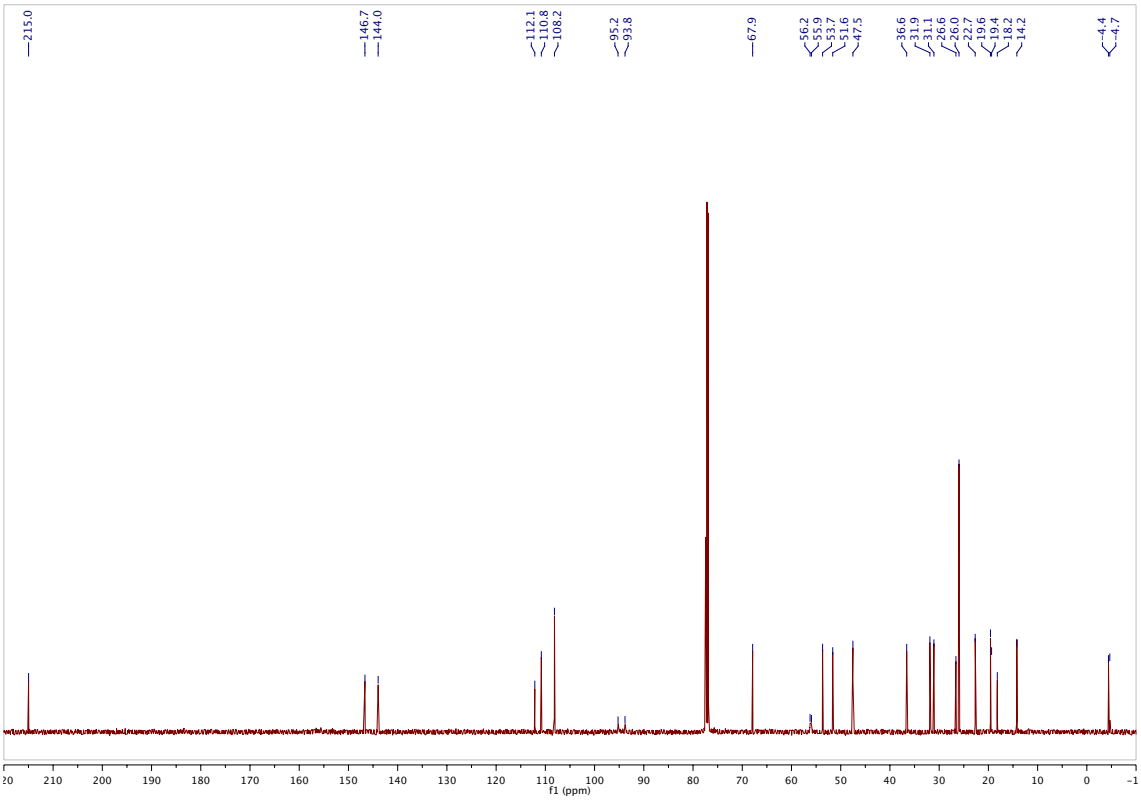


**(2*S*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(prop-1-en-2-yl)cyclopentan-1-one (16)**

$^{1}$H NMR

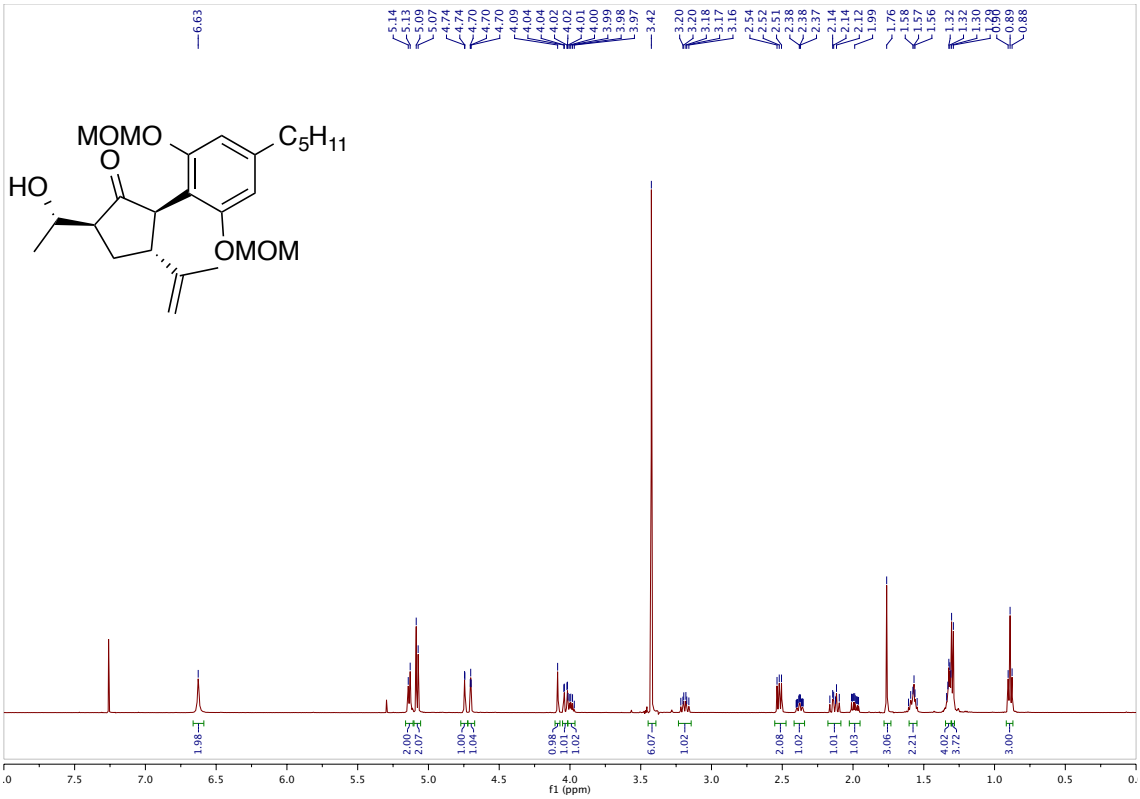



$^{13}$C NMR

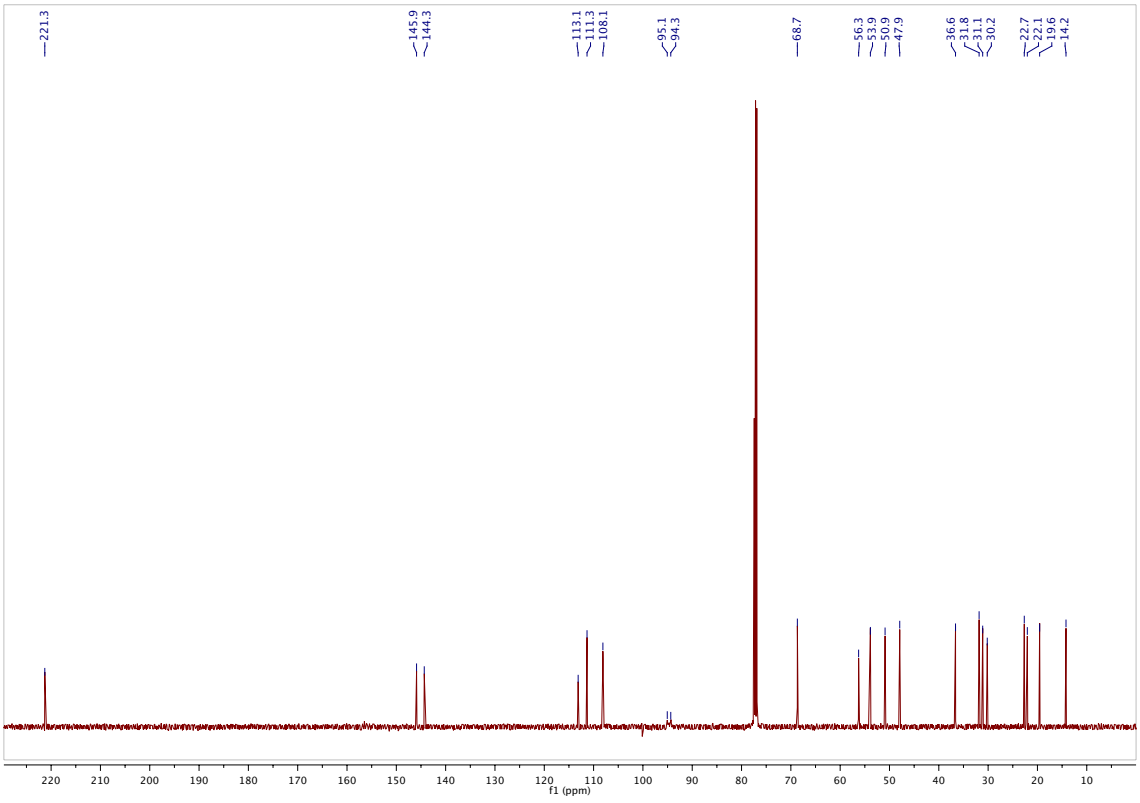


**(2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentan-1-one (17)**

$^{1}$H NMR

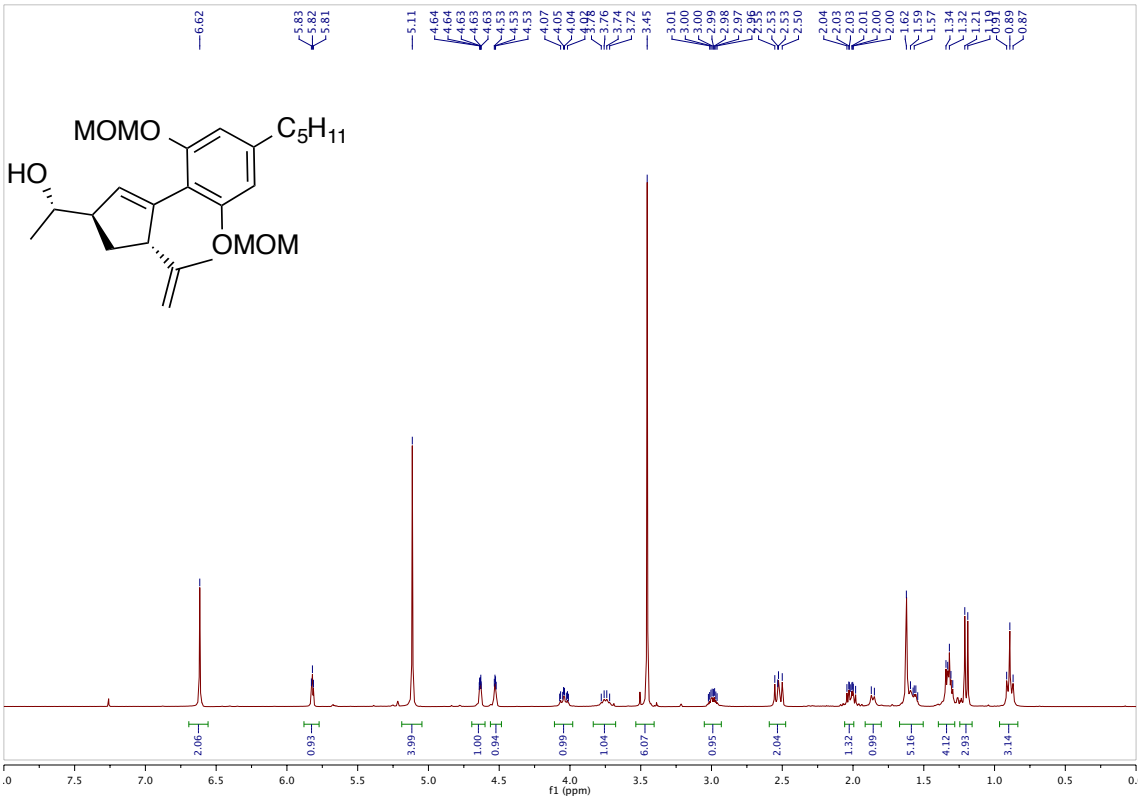



$^{13}$C NMR

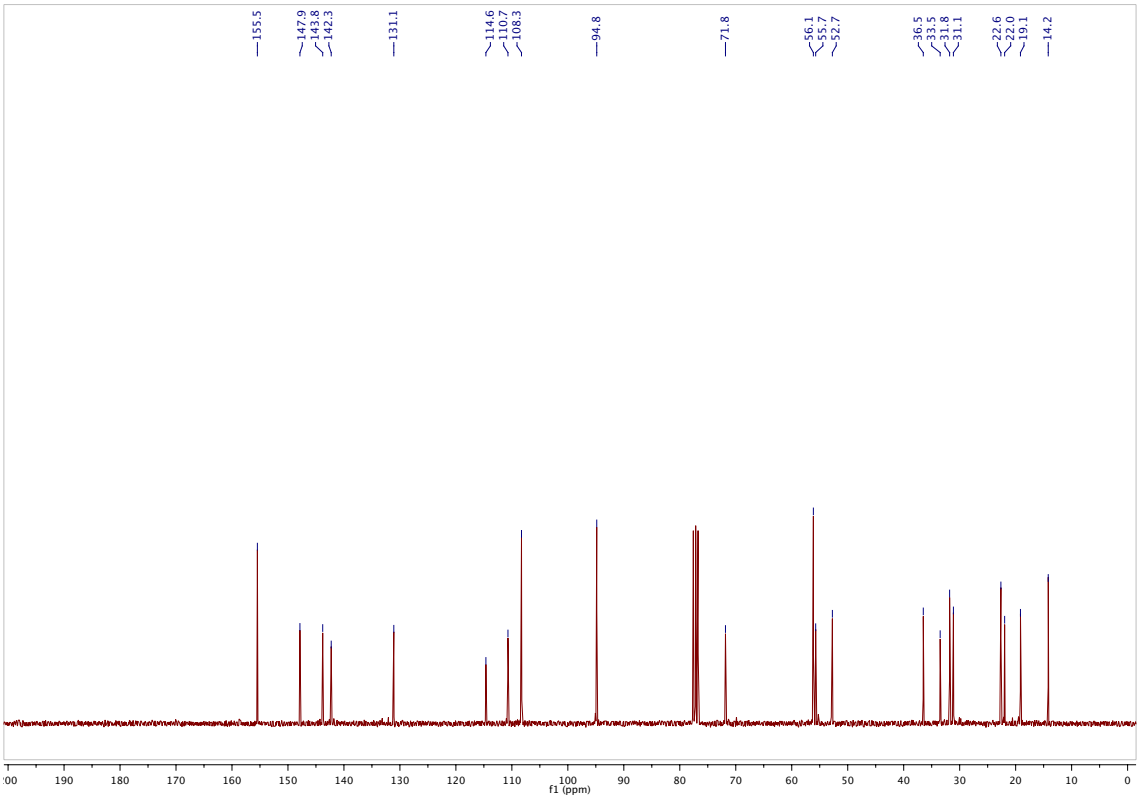


**(*S*)-1-((1*R*,4*S*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethan-1-ol (S4)**

$^{1}$H NMR

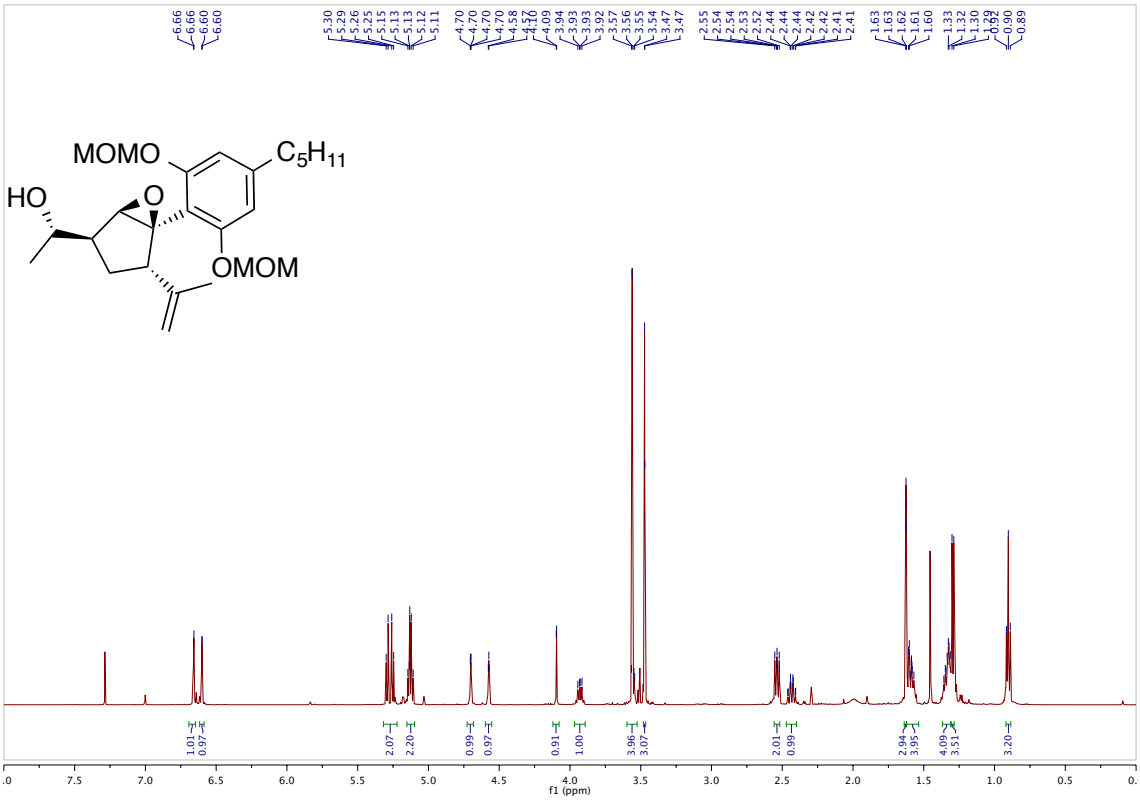



$^{13}$C NMR

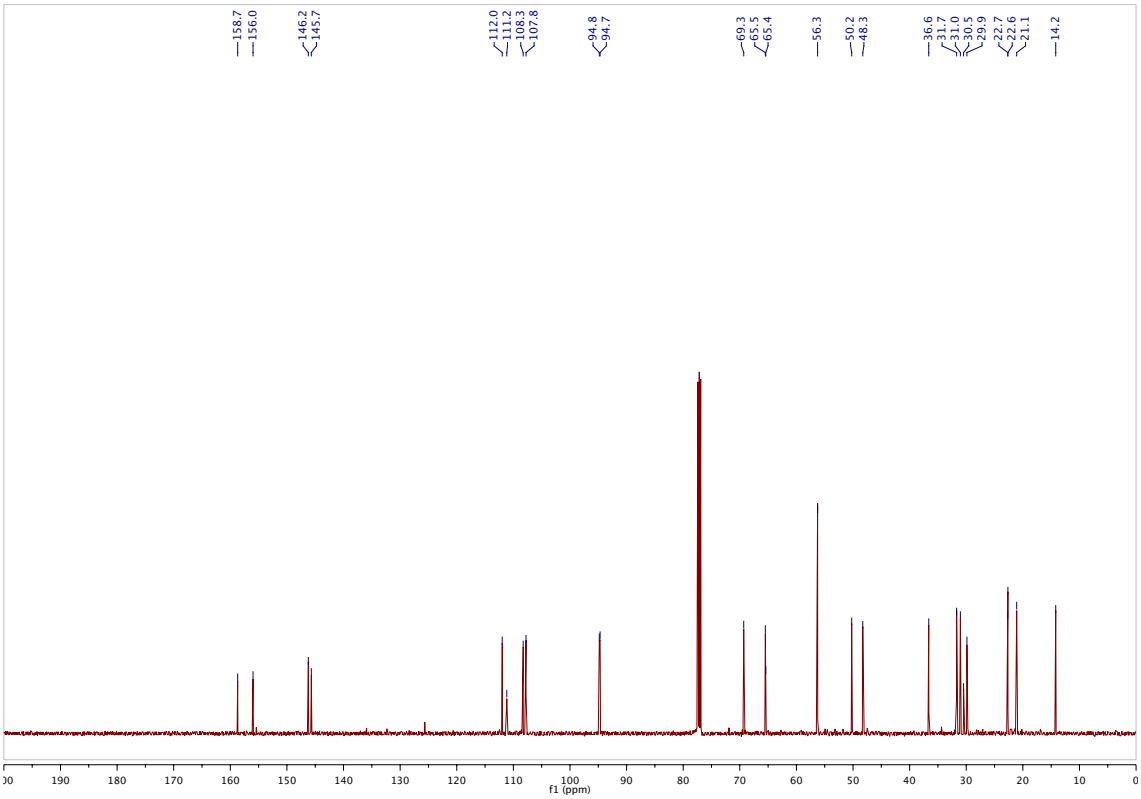


**(*S*)-1-((1*R*,2*S*,4*S*,5*R*)-5-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)-6-oxabicyclo[3.1.0]hexan-2-yl)ethan-1-ol (18)**

$^{1}$H NMR

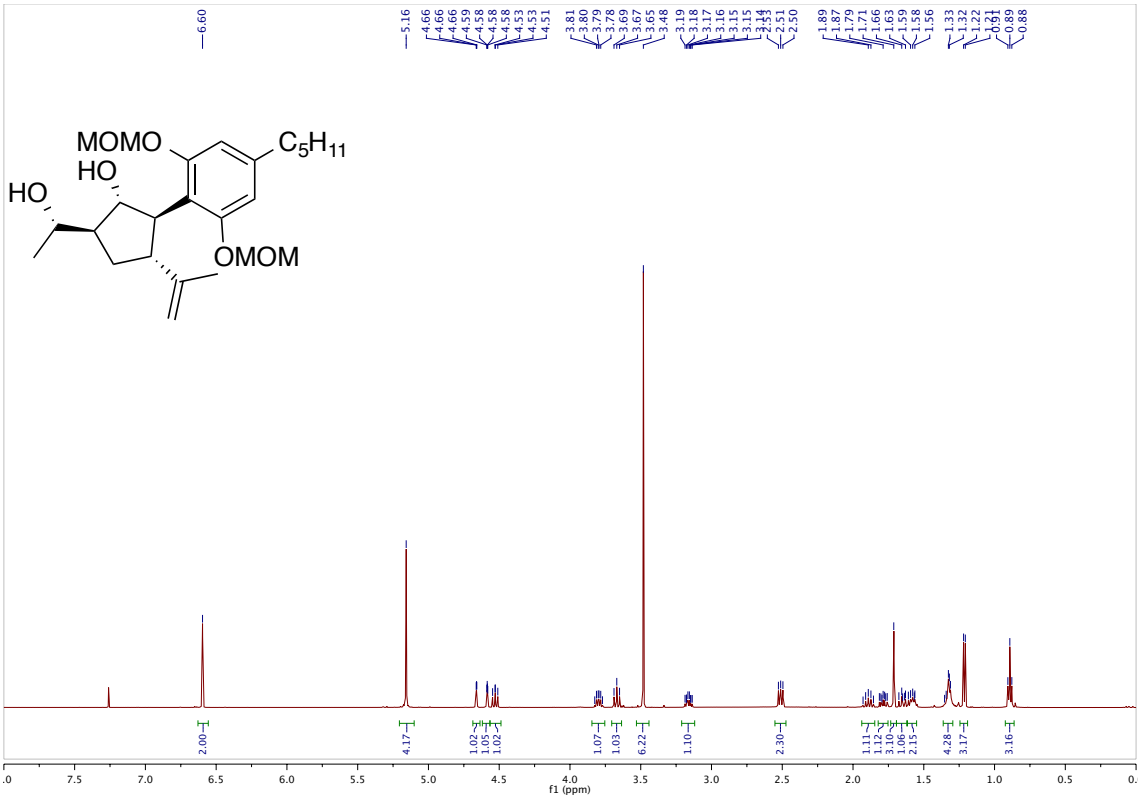



$^{13}$C NMR

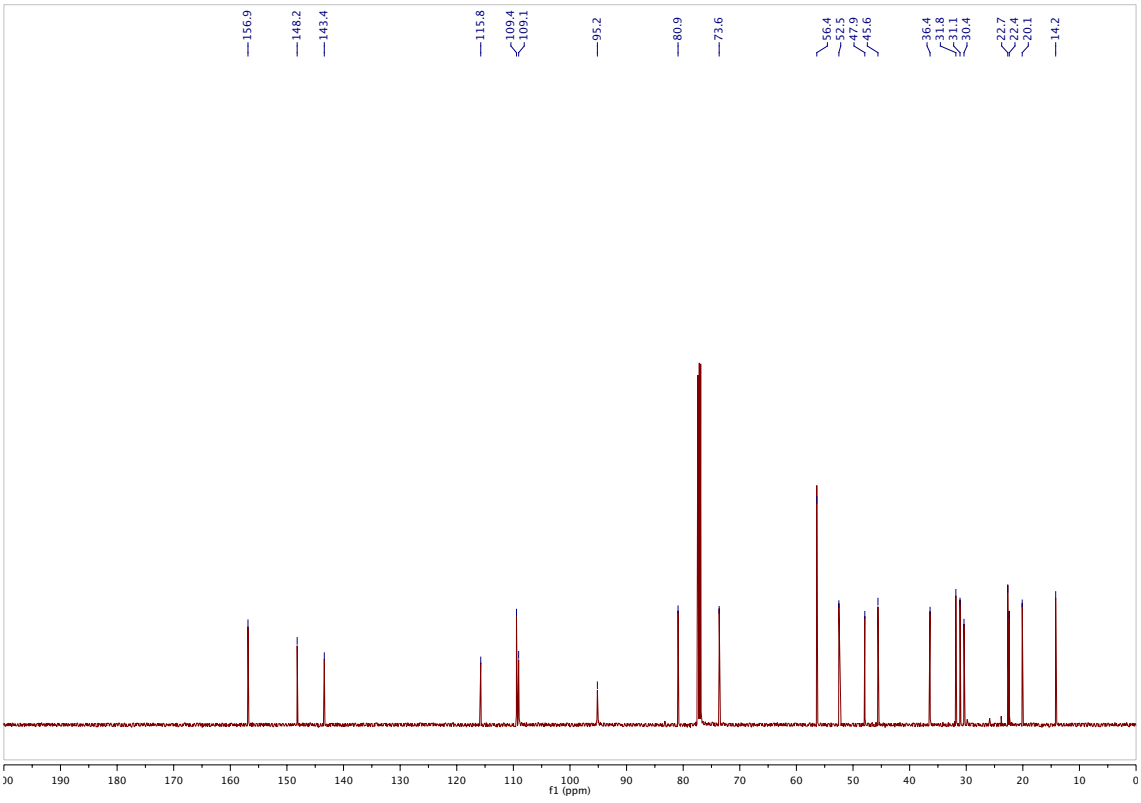


**(1*R*,2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentan-1-ol (19)**

$^{1}$H NMR

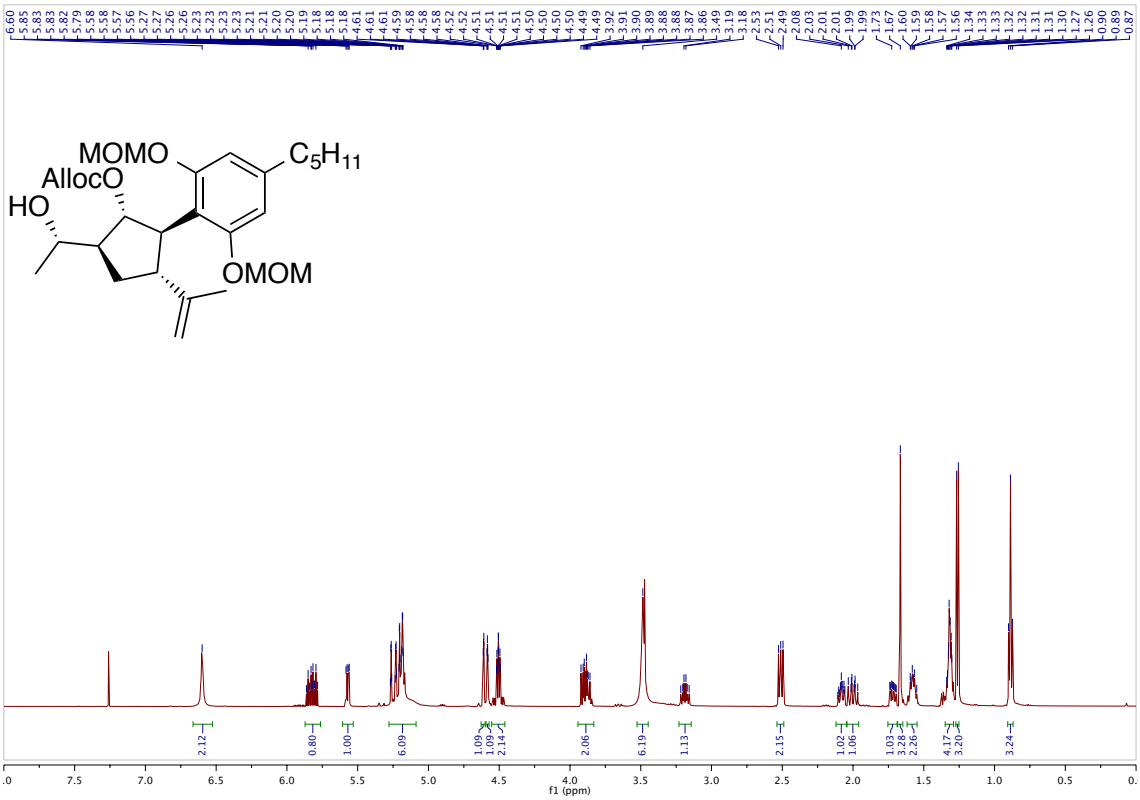



$^{13}$C NMR

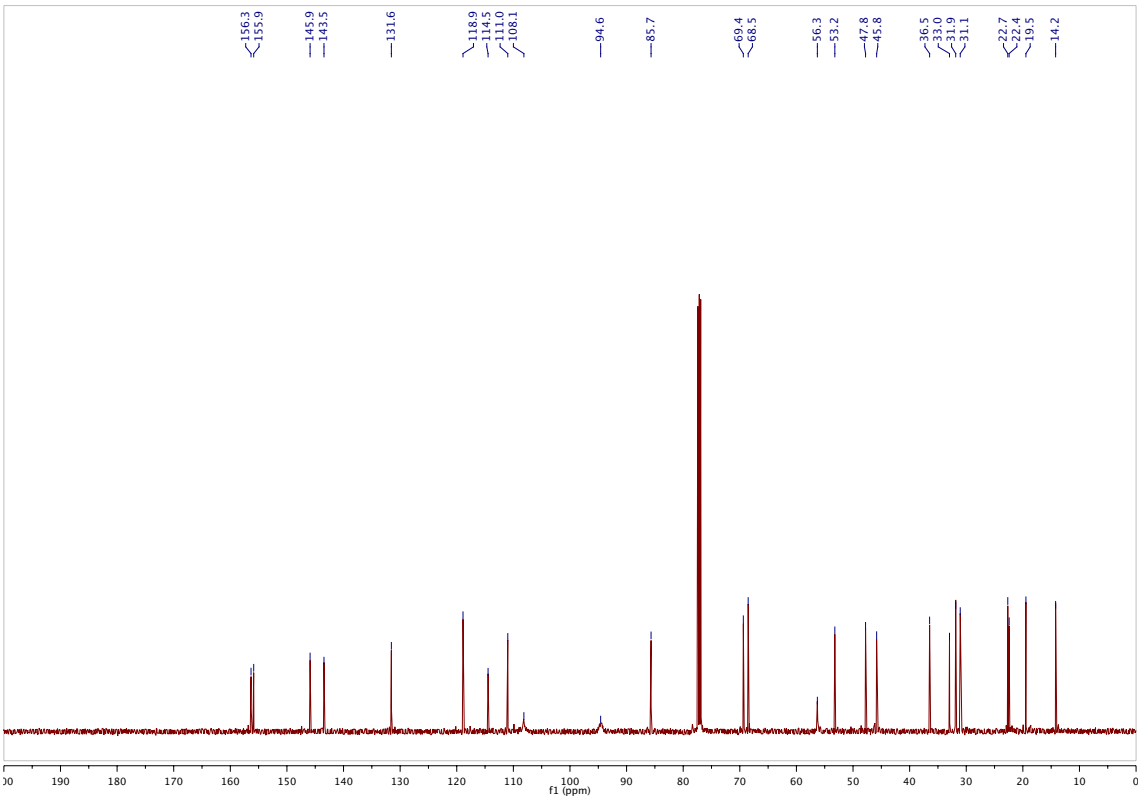


**Allyl ((1*R*,2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentyl) carbonate (S5)**

$^{1}$H NMR

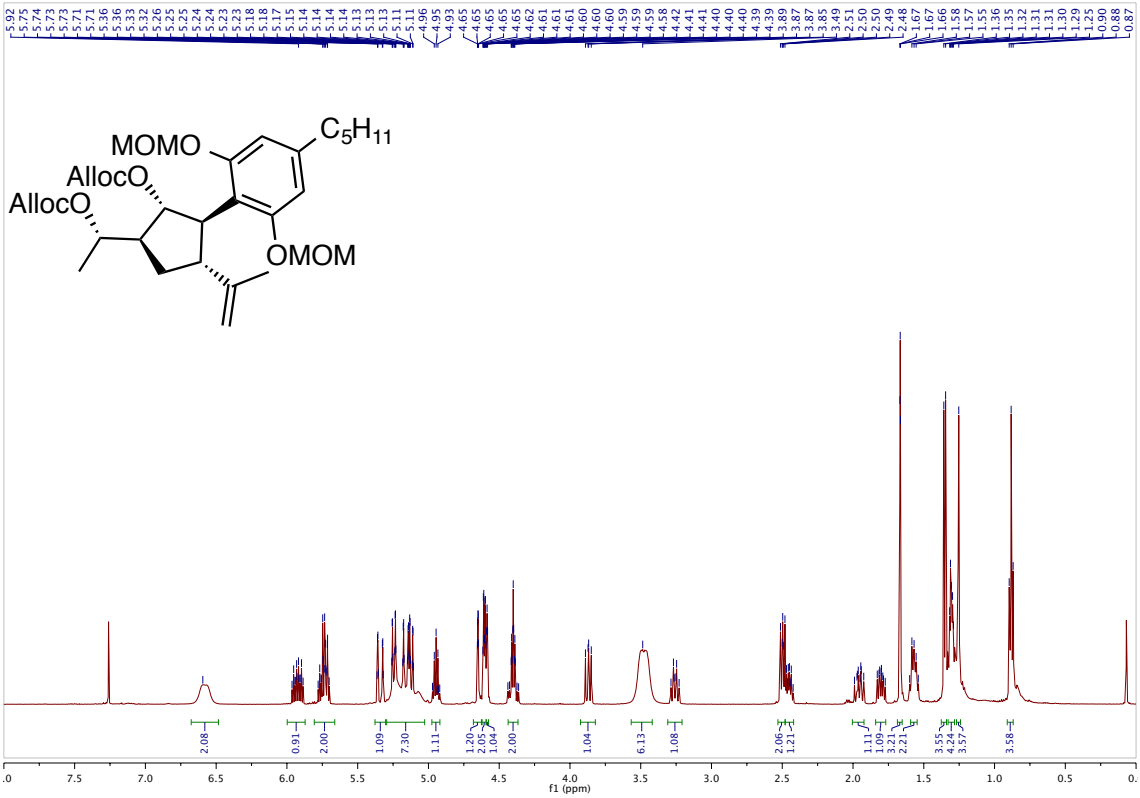



$^{13}$C NMR

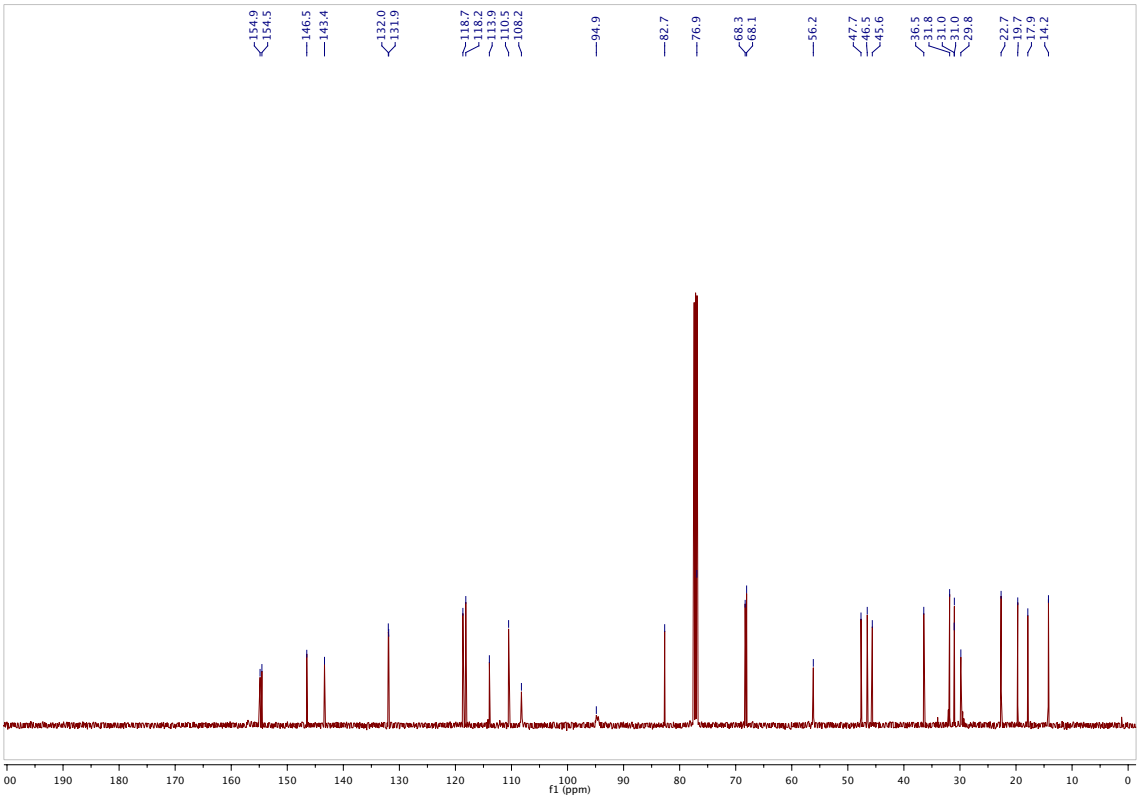


**Allyl ((*S*)-1-((1*S*,2*R*,3*R*,4*R*)-2-(((allyloxy)carbonyl)oxy)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopentyl)ethyl) carbonate (S6)**

$^{1}$H NMR

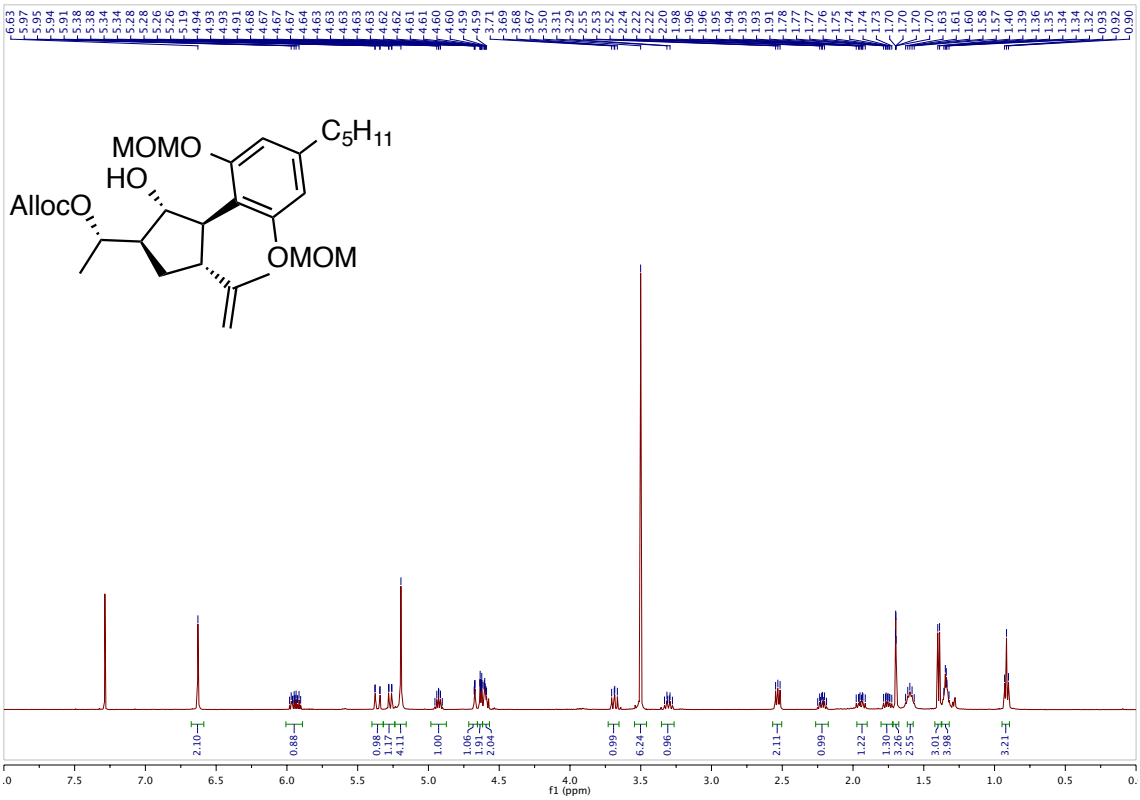



$^{13}$C NMR

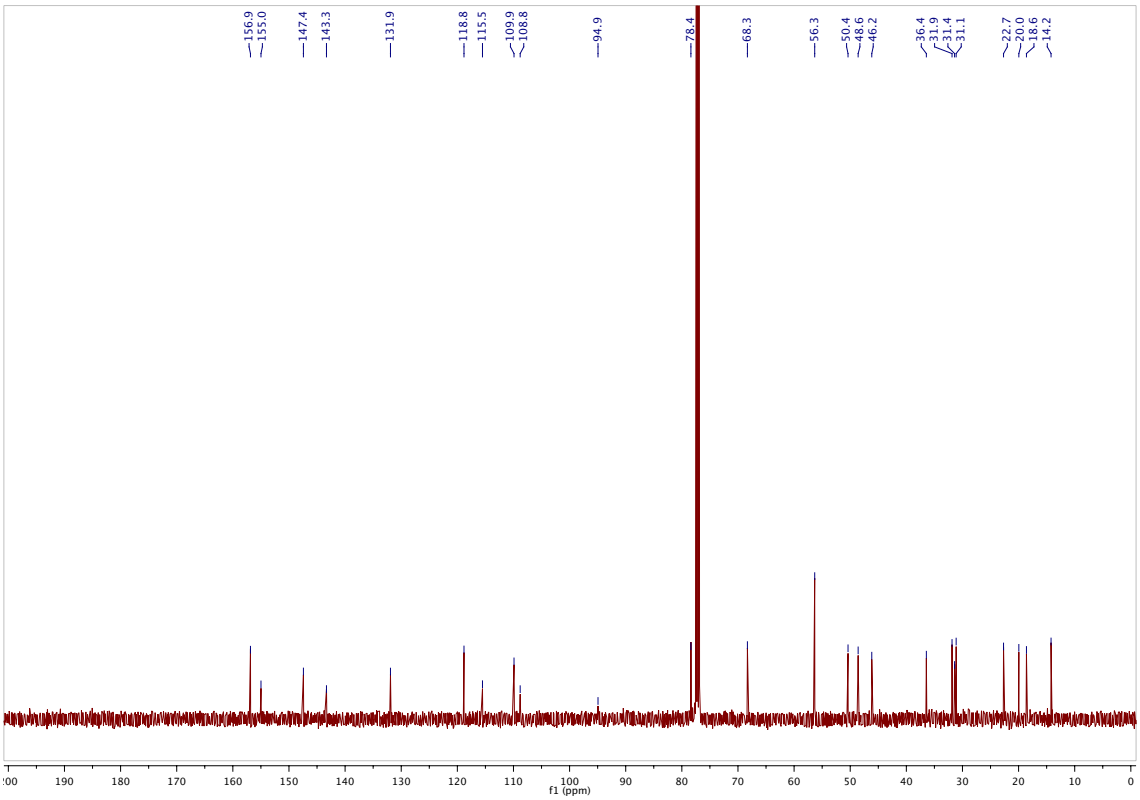


**Allyl ((*S*)-1-((1*R*,2*R*,3*R*,4*R*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-2-hydroxy-4-(prop-1-en-2-yl)cyclopentyl)ethyl) carbonate (S7)**

$^{1}$H NMR

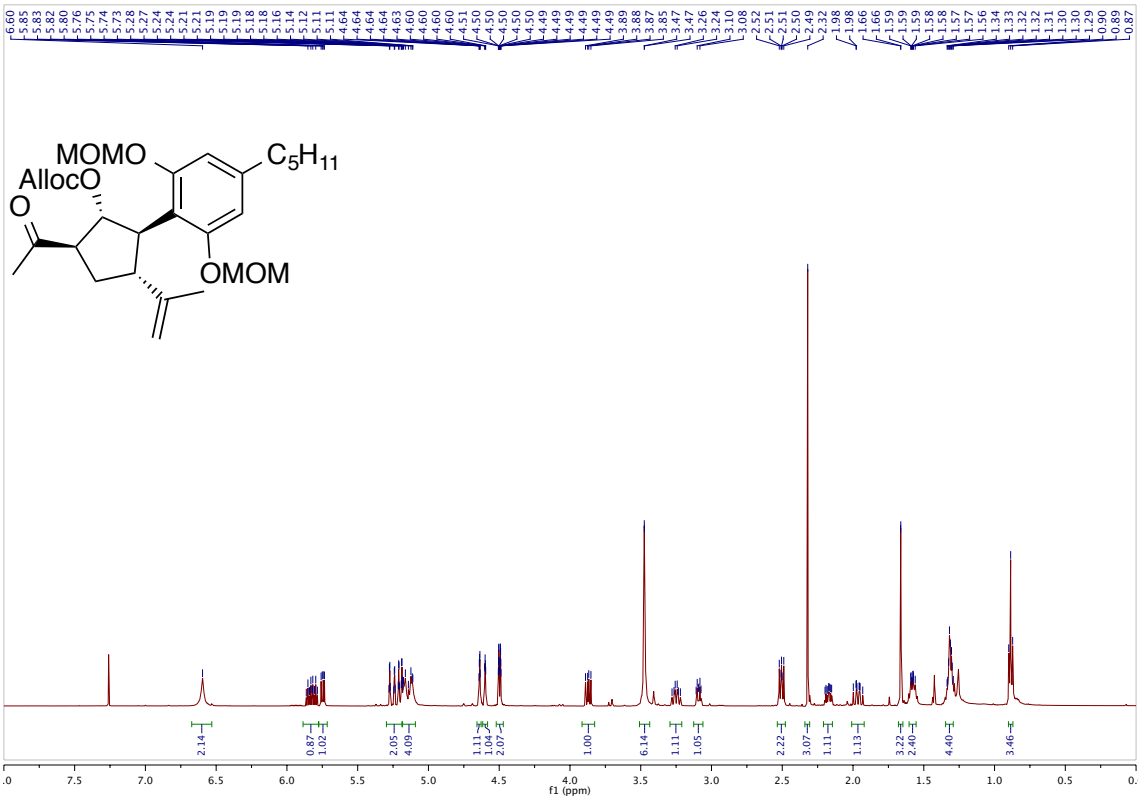



$^{13}$C NMR

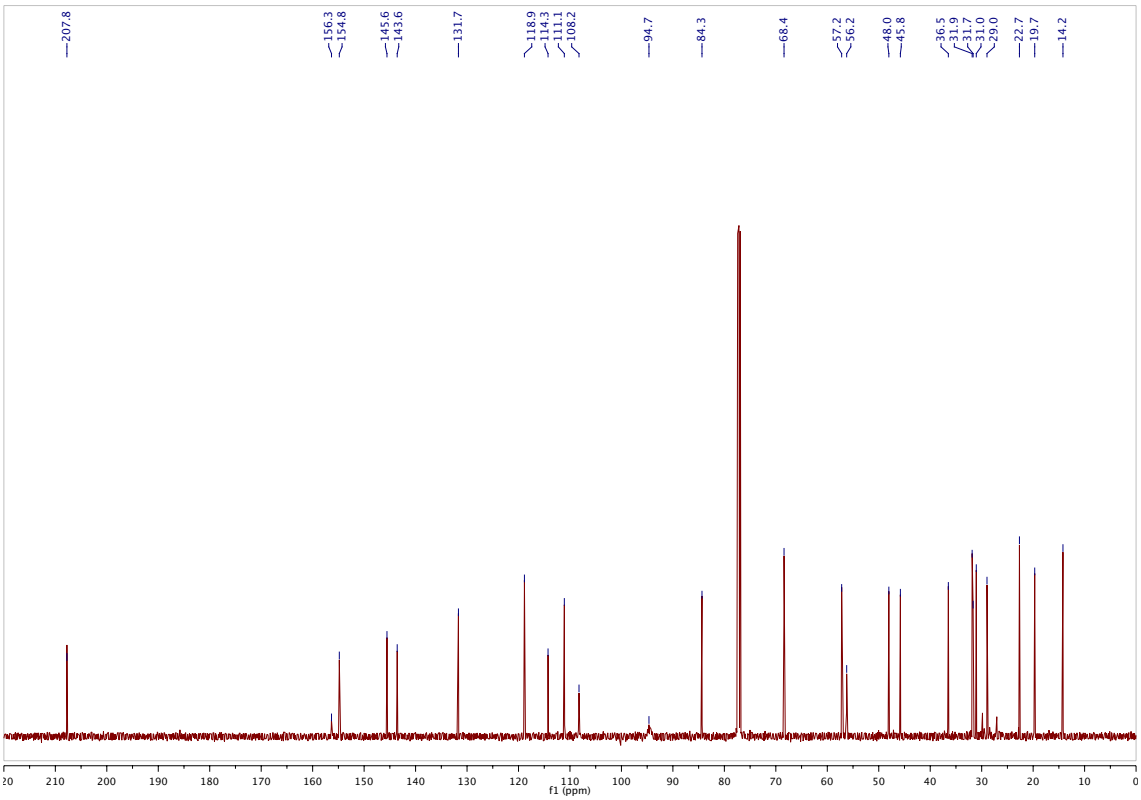


**(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl allyl carbonate (20)**

$^{1}$H NMR

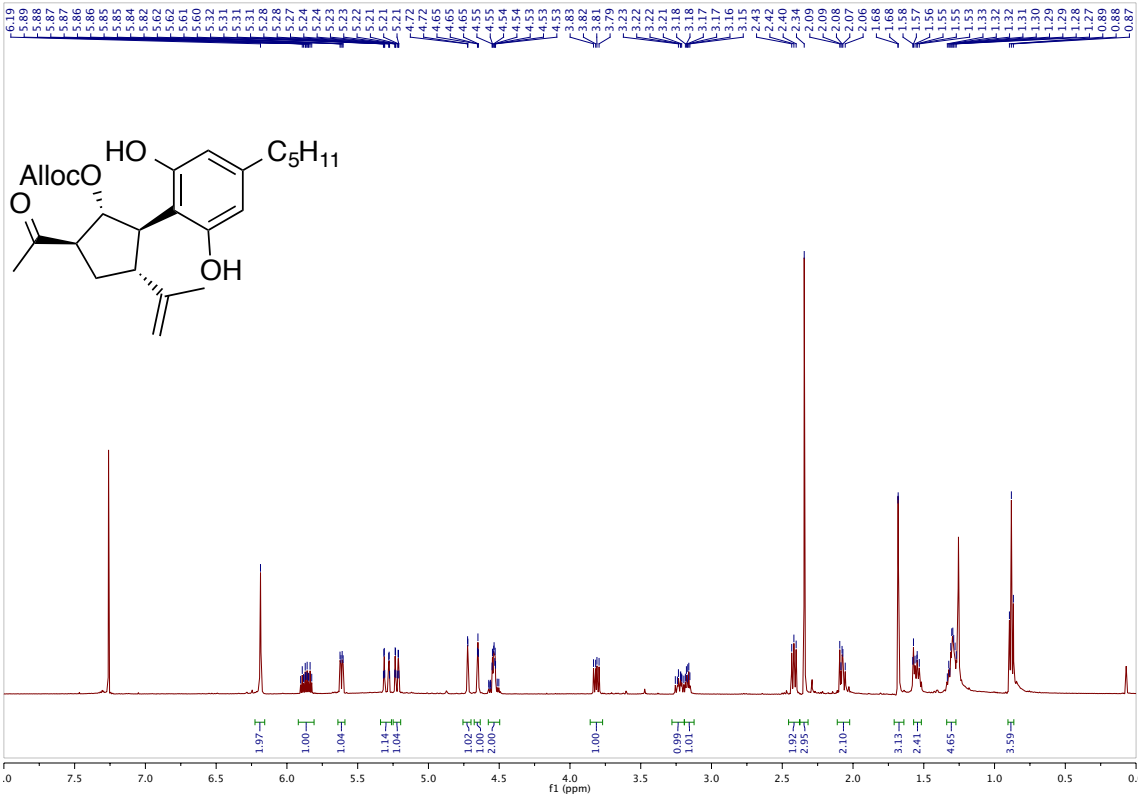



$^{13}$C NMR

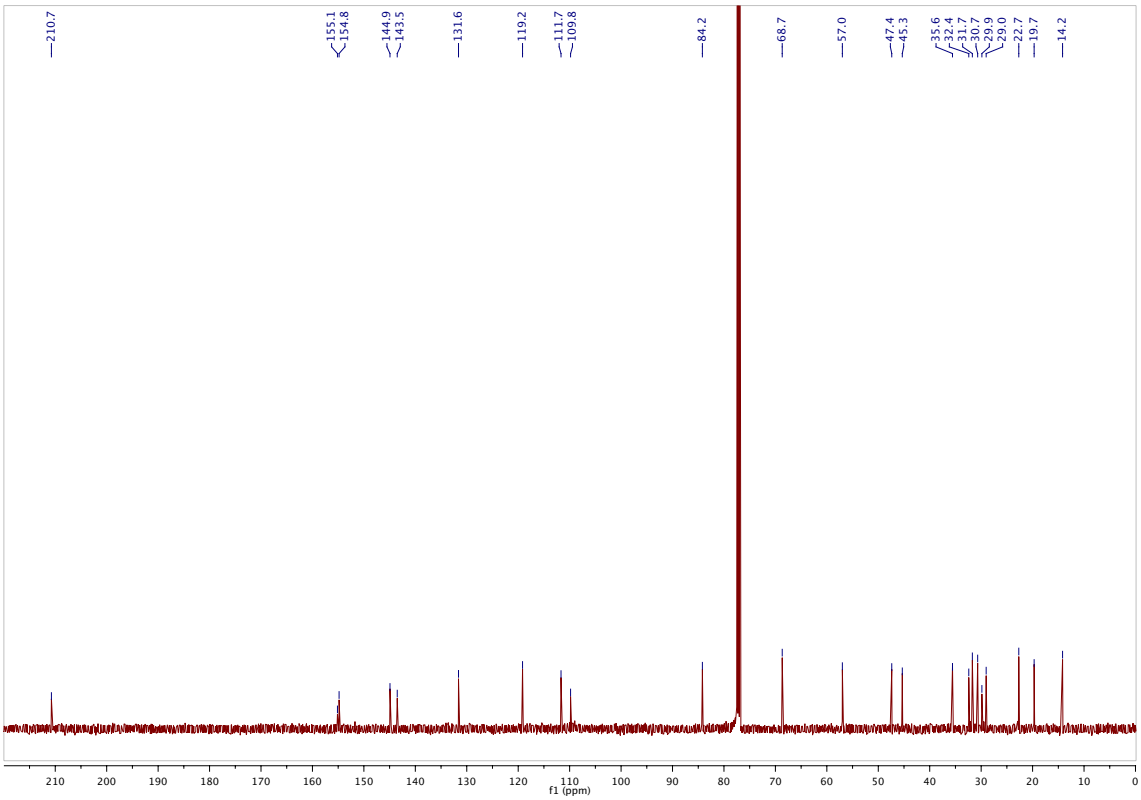


**(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-dihydroxy-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl allyl carbonate (S8)**

$^{1}$H NMR

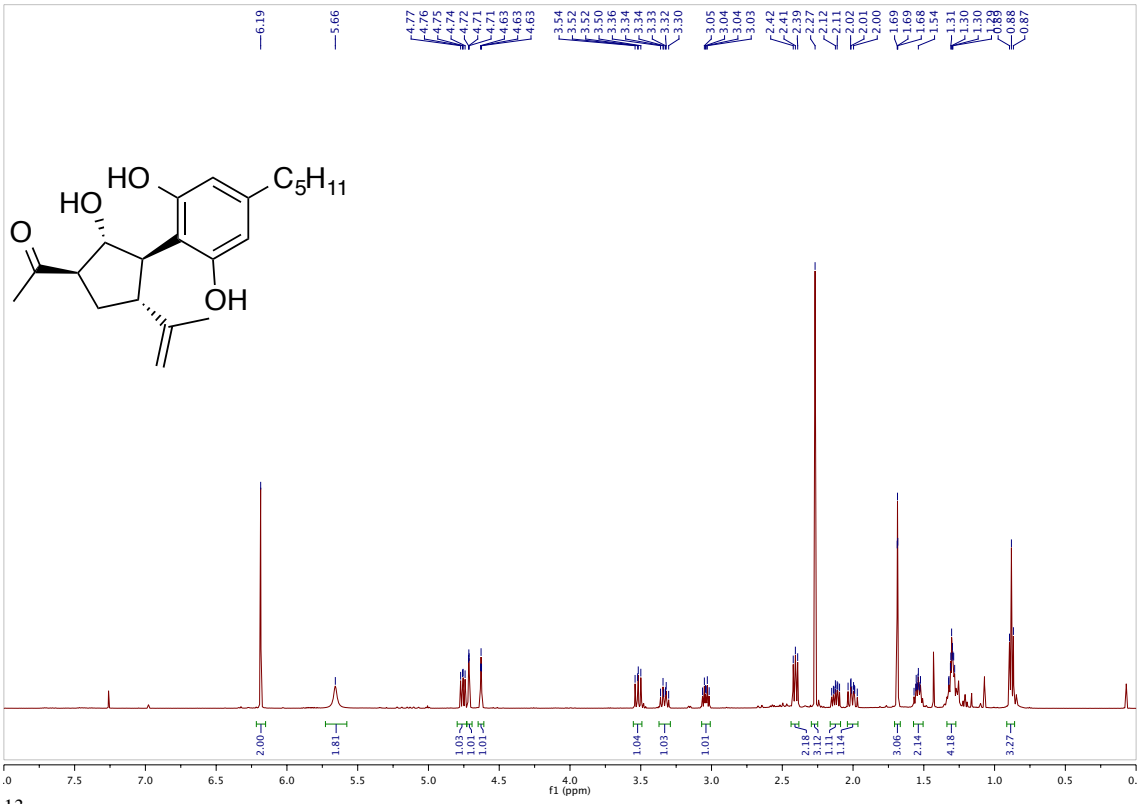



$^{13}$C NMR

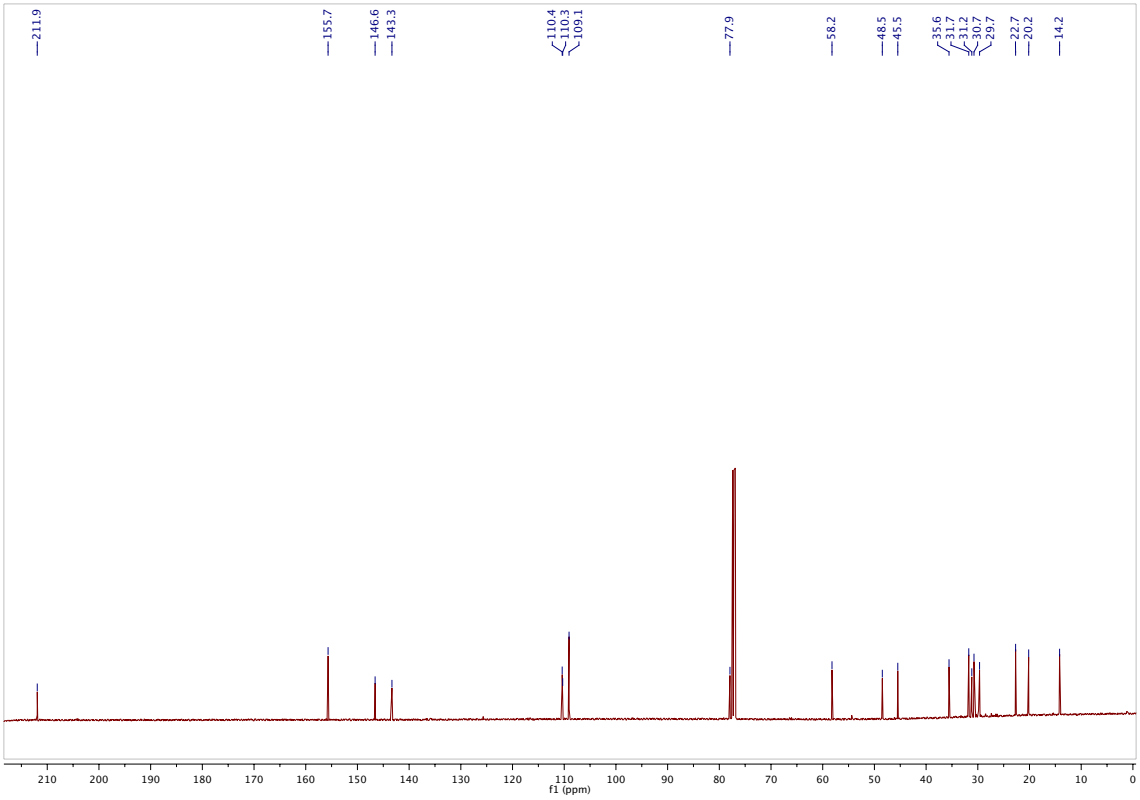


**Cannabimovone (3)**

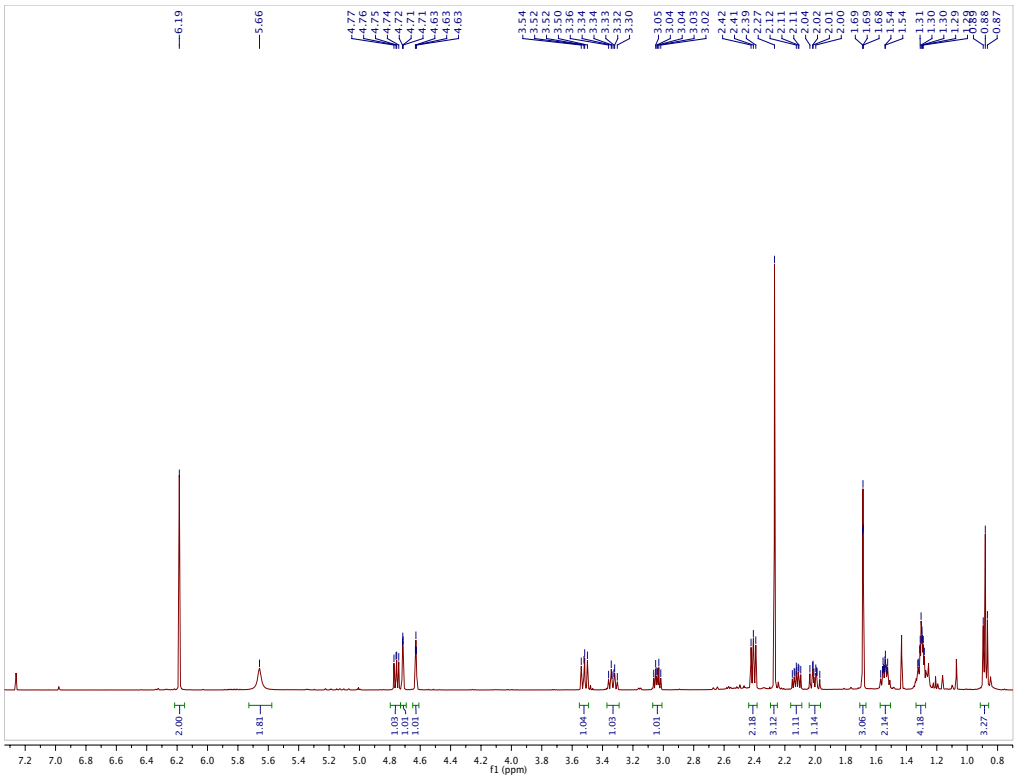
$^{1}$H NMR

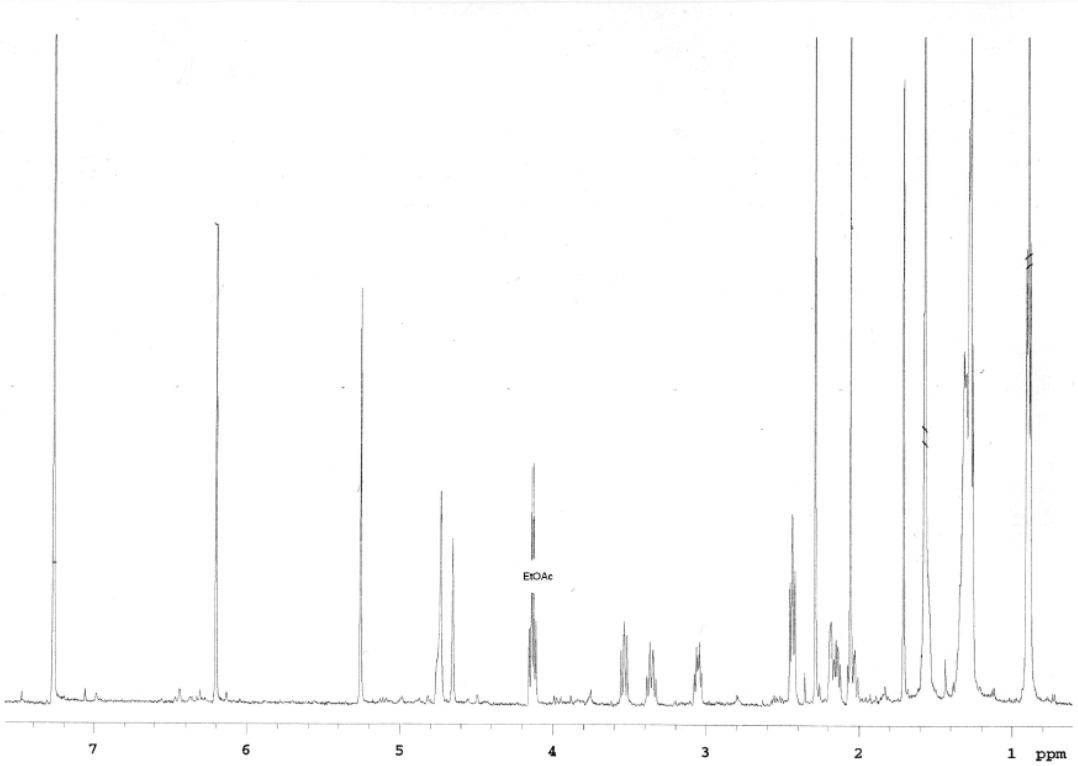



$^{13}$C NMR



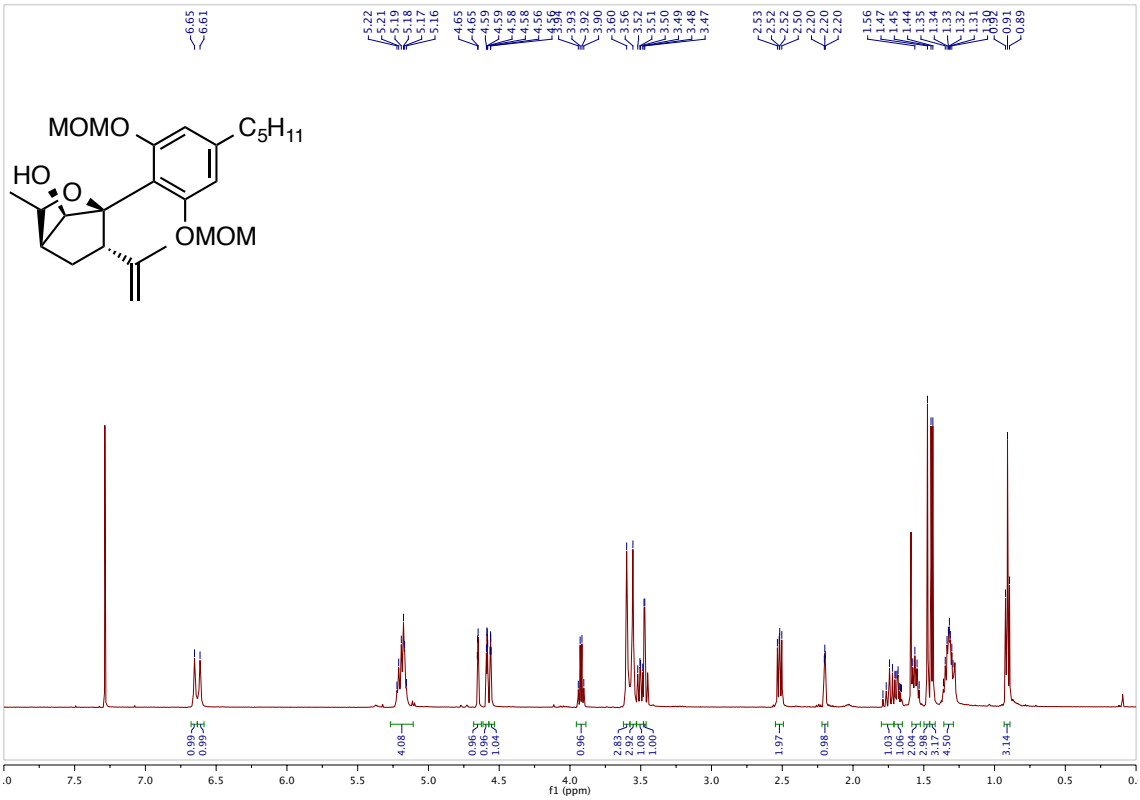
$^{1}$H NMR comparative of synthetic Cannabimovone **3** and reported natural Cannabimovone (*Eur. J. Org. Chem.* **2010**, 2067)



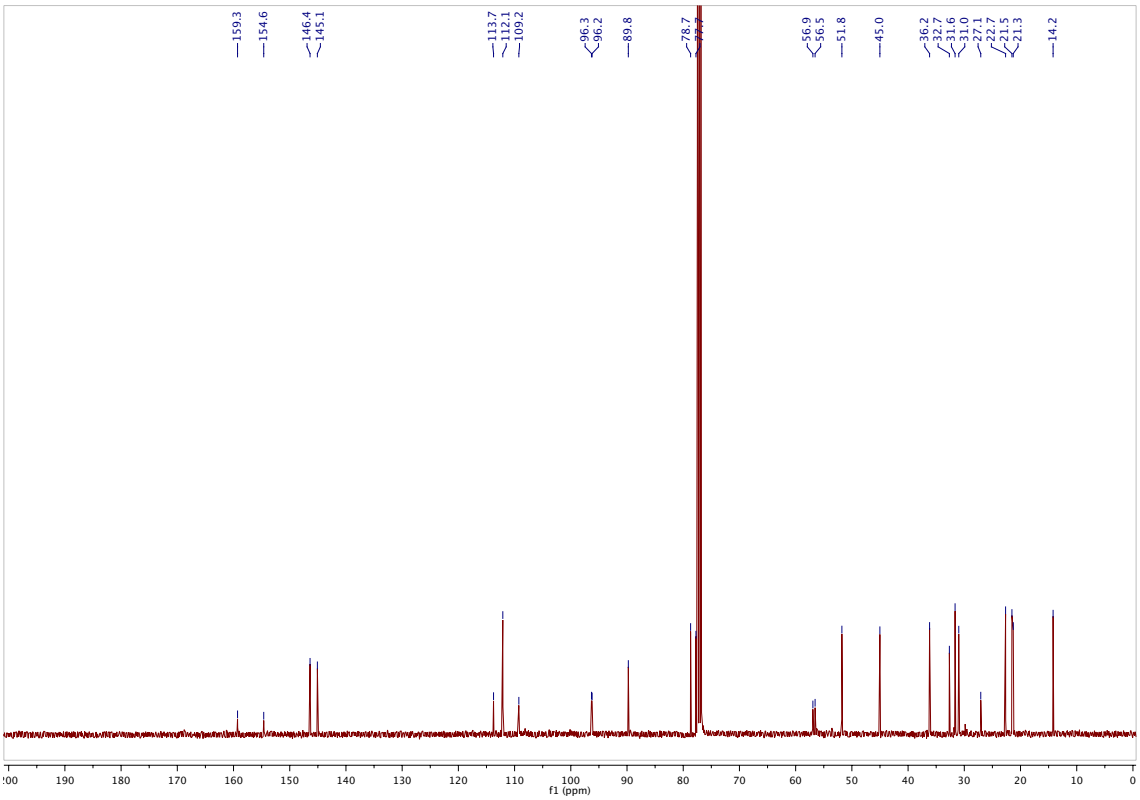


**(1*R*,3*S*,4*R*,6*S*,7*R*)-1-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-3-methyl-6-(prop-1-en-2-yl)-2-oxabicyclo[2.2.1]heptan-7-ol (21)**

$^{1}$H NMR

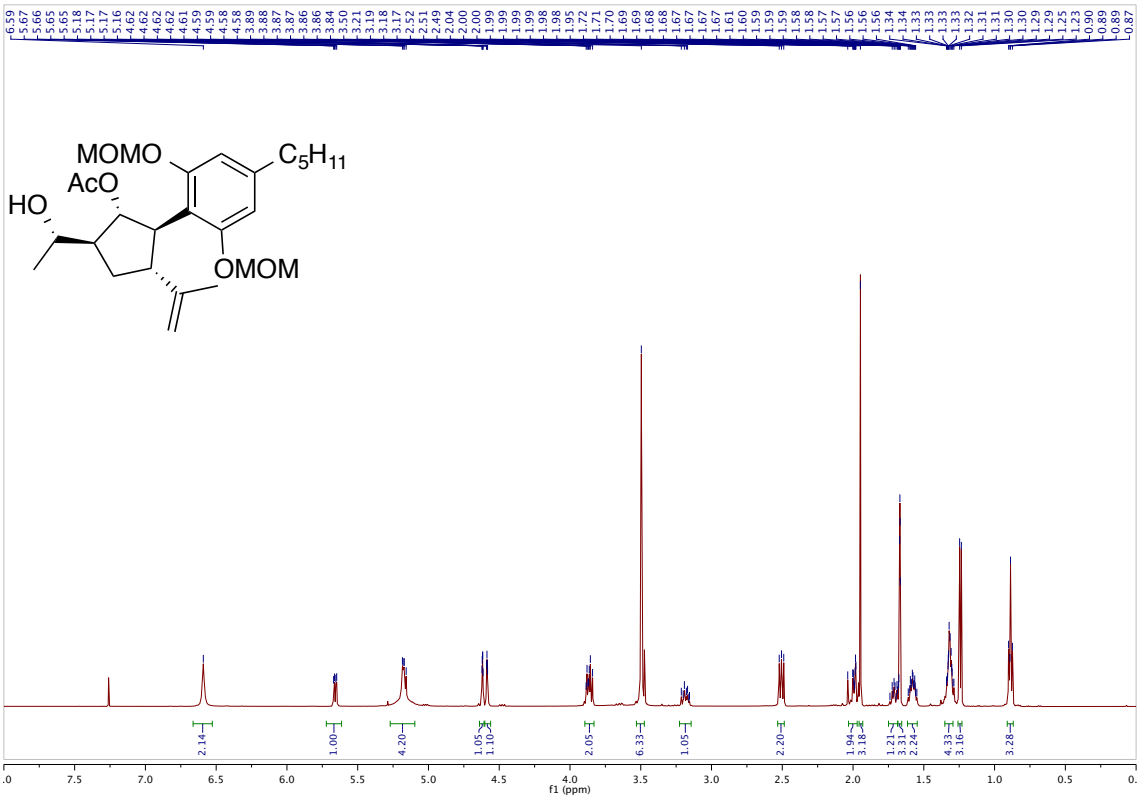



$^{13}$C NMR

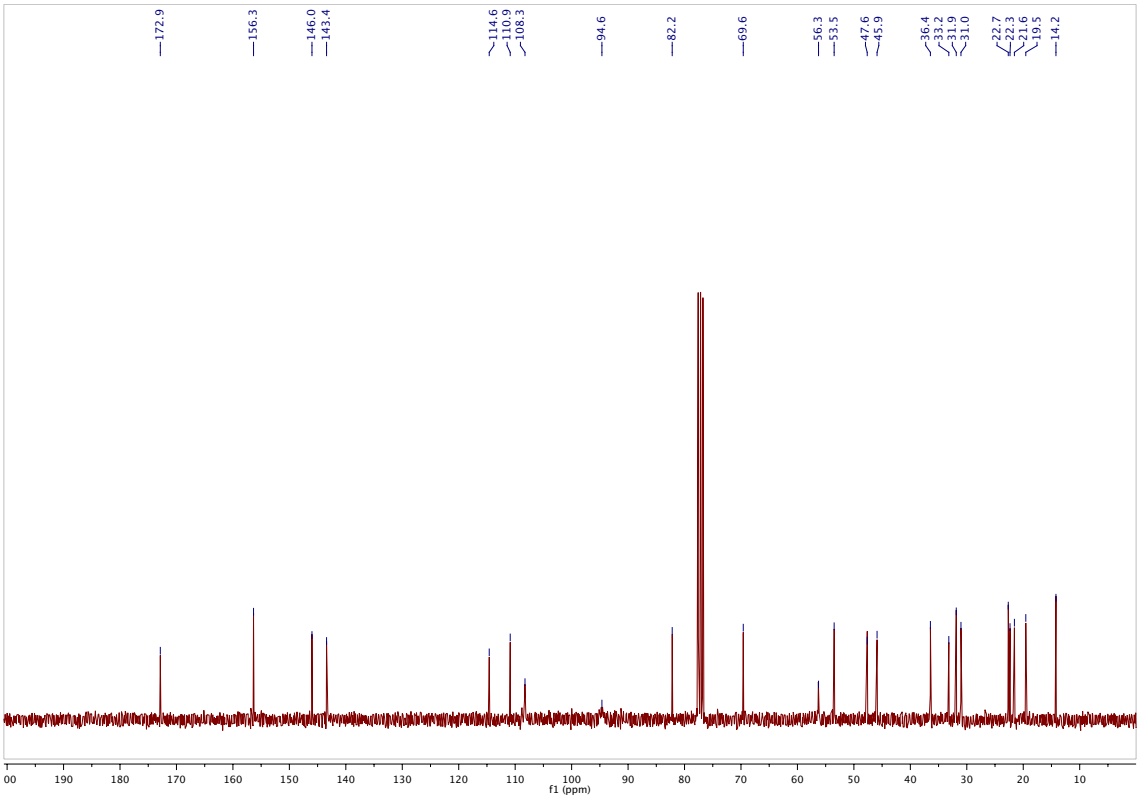


**(1*R*,2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentyl acetate (S9)**

$^{1}$H NMR

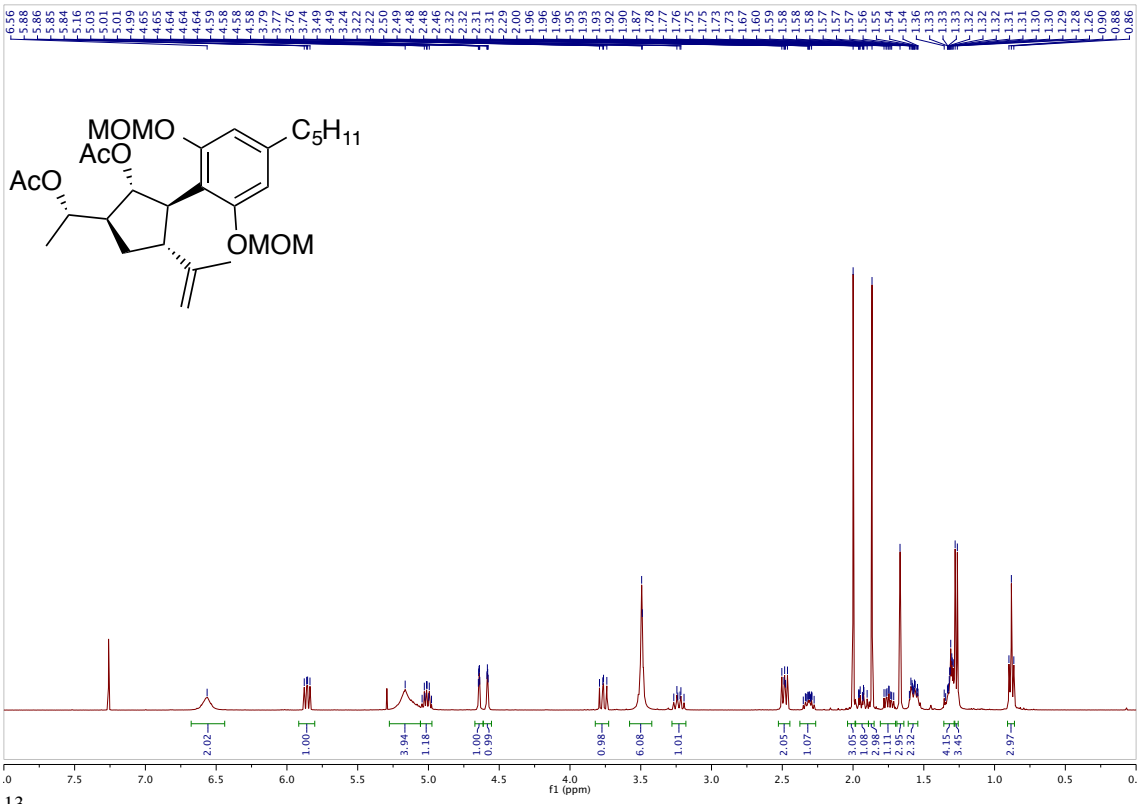



$^{13}$C NMR

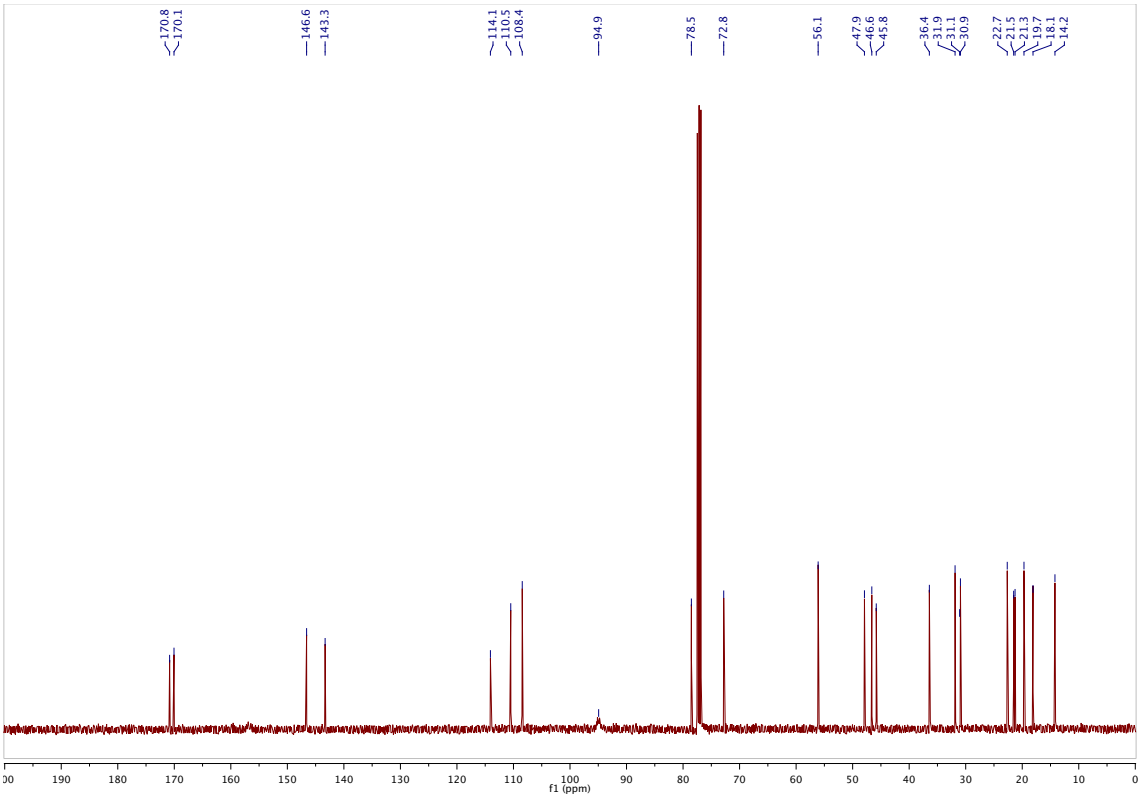


**(*S*)-1-((1*S*,2*R*,3*R*,4*R*)-2-acetoxy-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopentyl)ethyl acetate (S10)**

$^{1}$H NMR

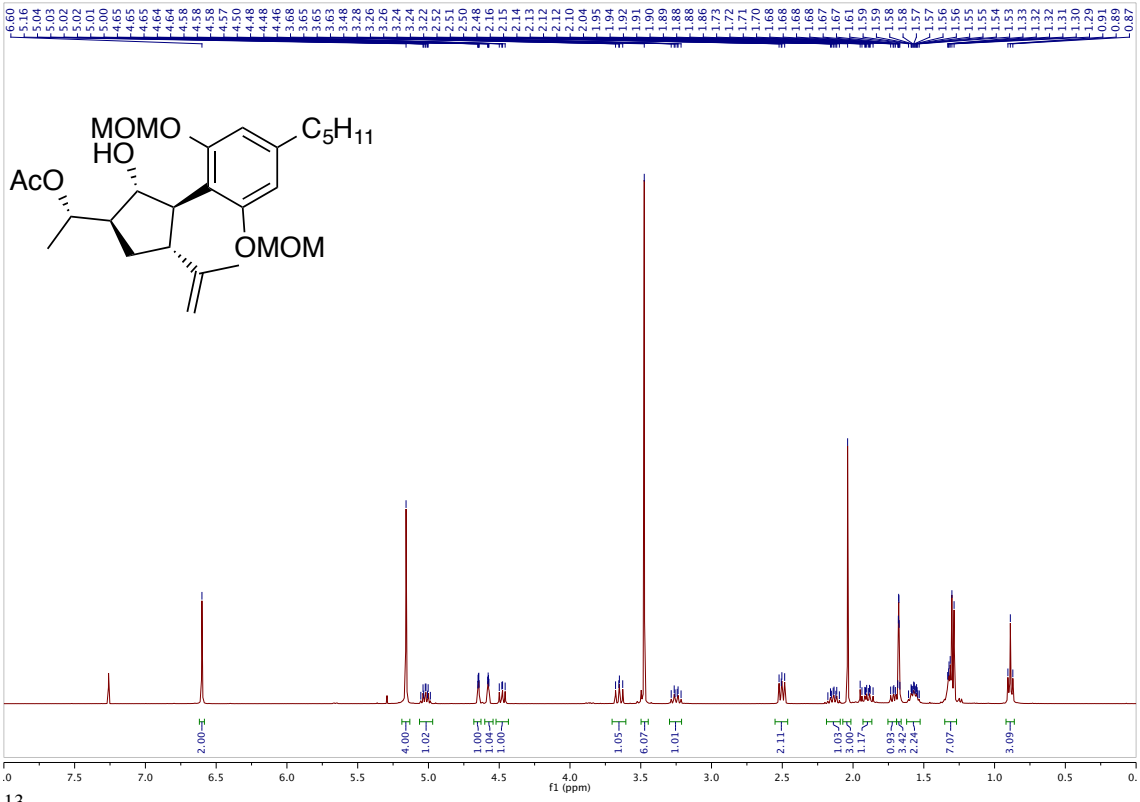



$^{13}$C NMR

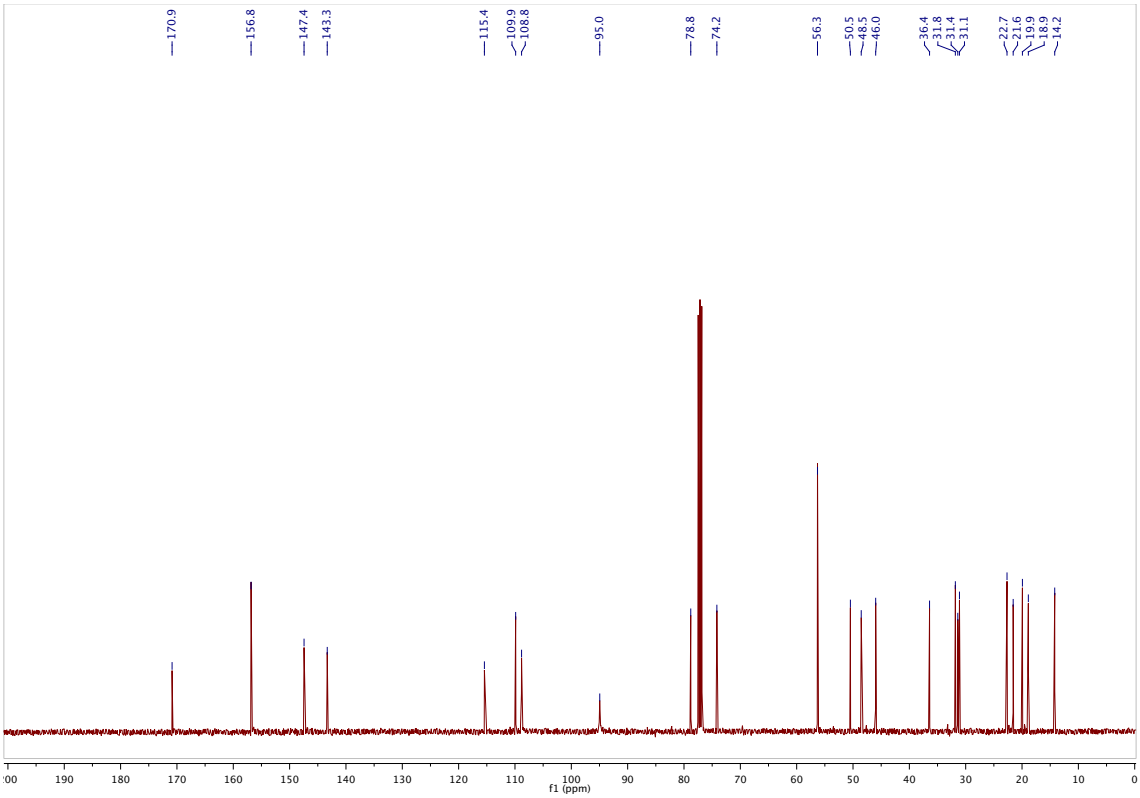


**(*S*)-1-((1*R*,2*R*,3*R*,4*R*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-2-hydroxy-4-(prop-1-en-2-yl)cyclopentyl)ethyl acetate (S11)**

$^{1}$H NMR

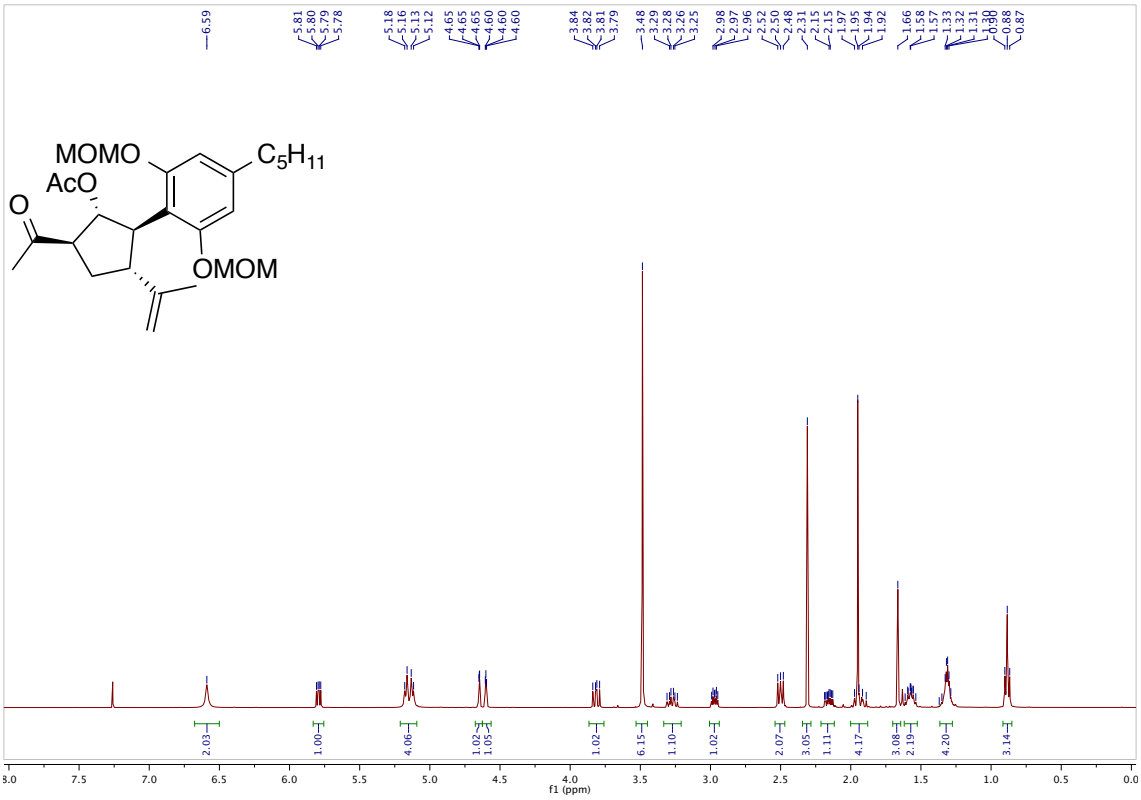



$^{13}$C NMR

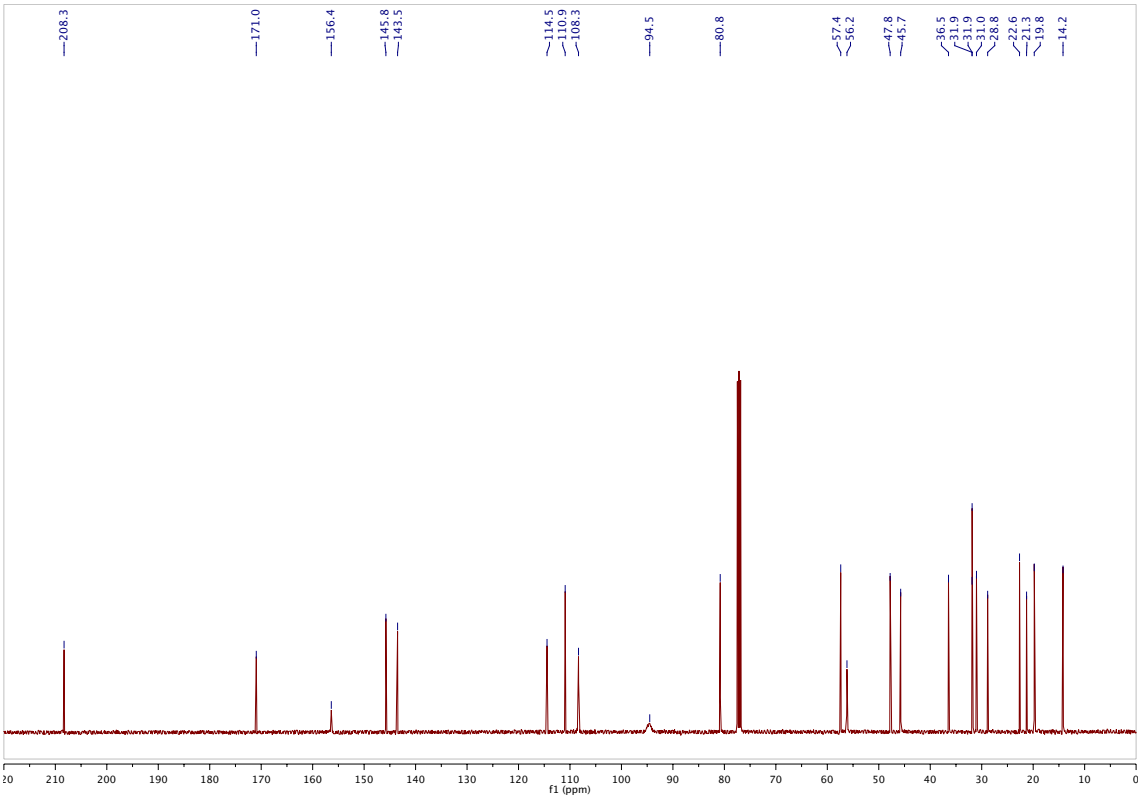


**(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl acetate (22)**

$^{1}$H NMR

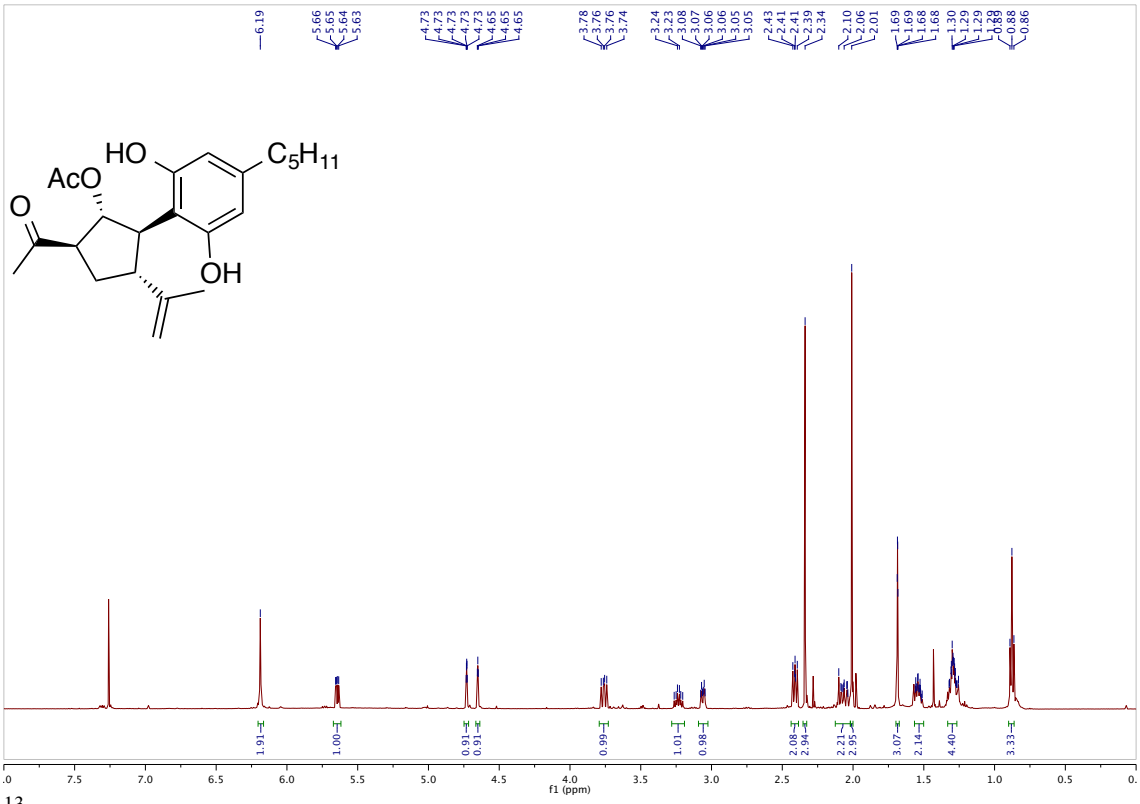



$^{13}$C NMR

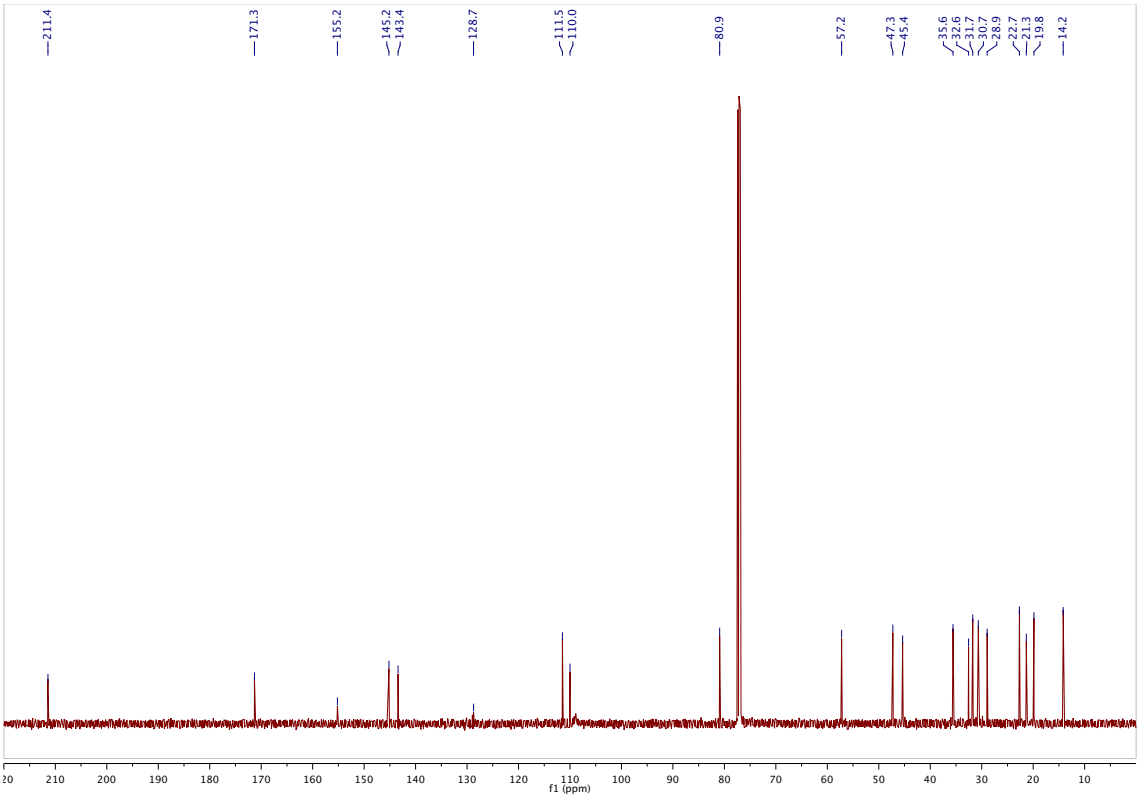


**(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-dihydroxy-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl acetate (S12)**

$^{1}$H NMR

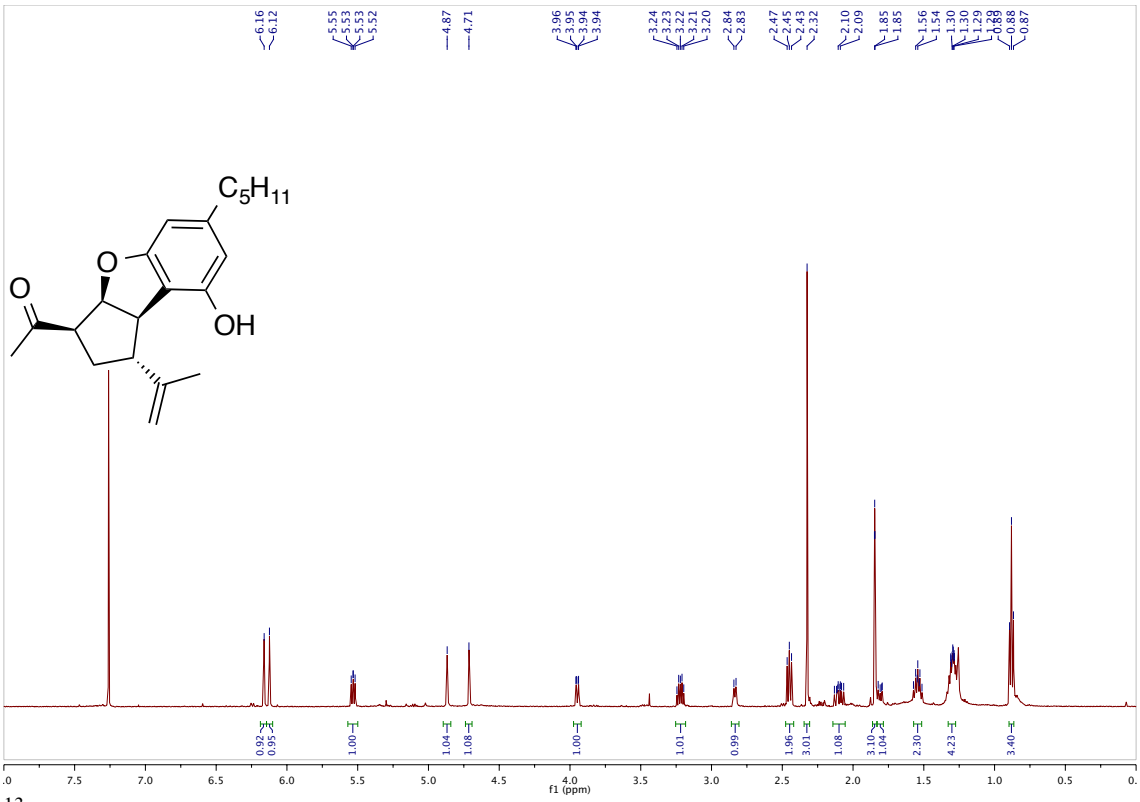



$^{13}$C NMR

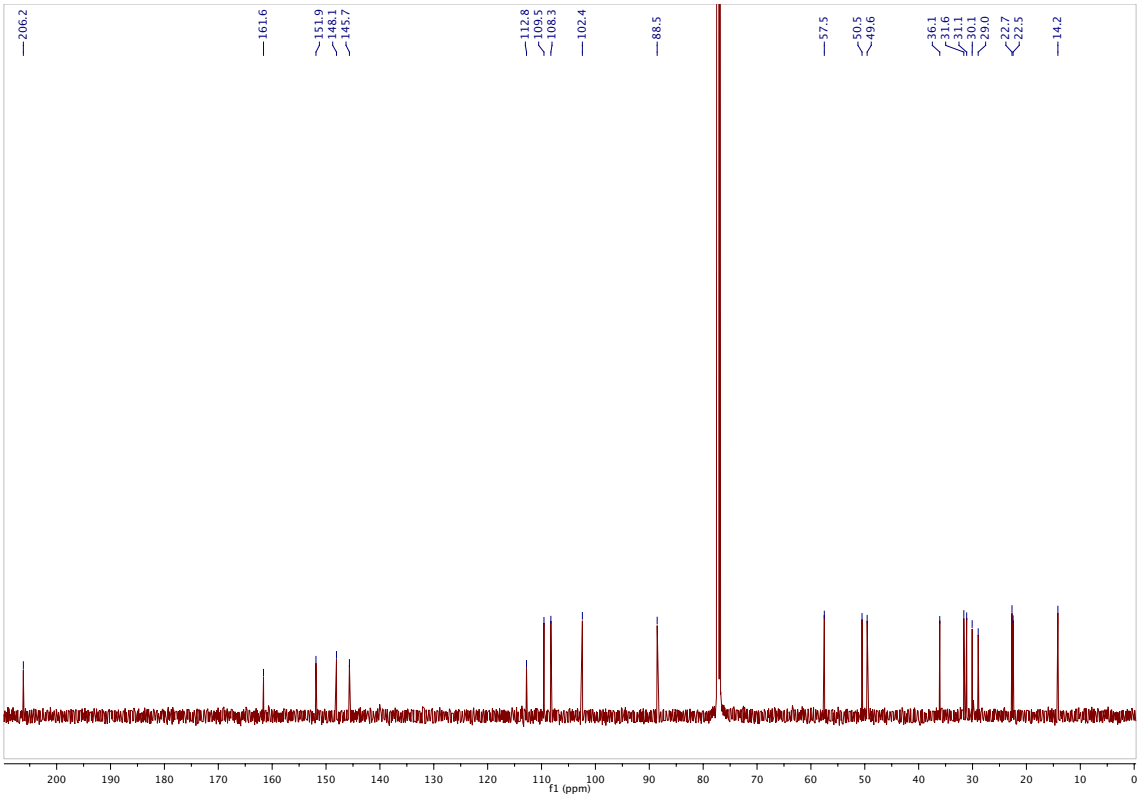


**Anhydrocannabimovone (6)**

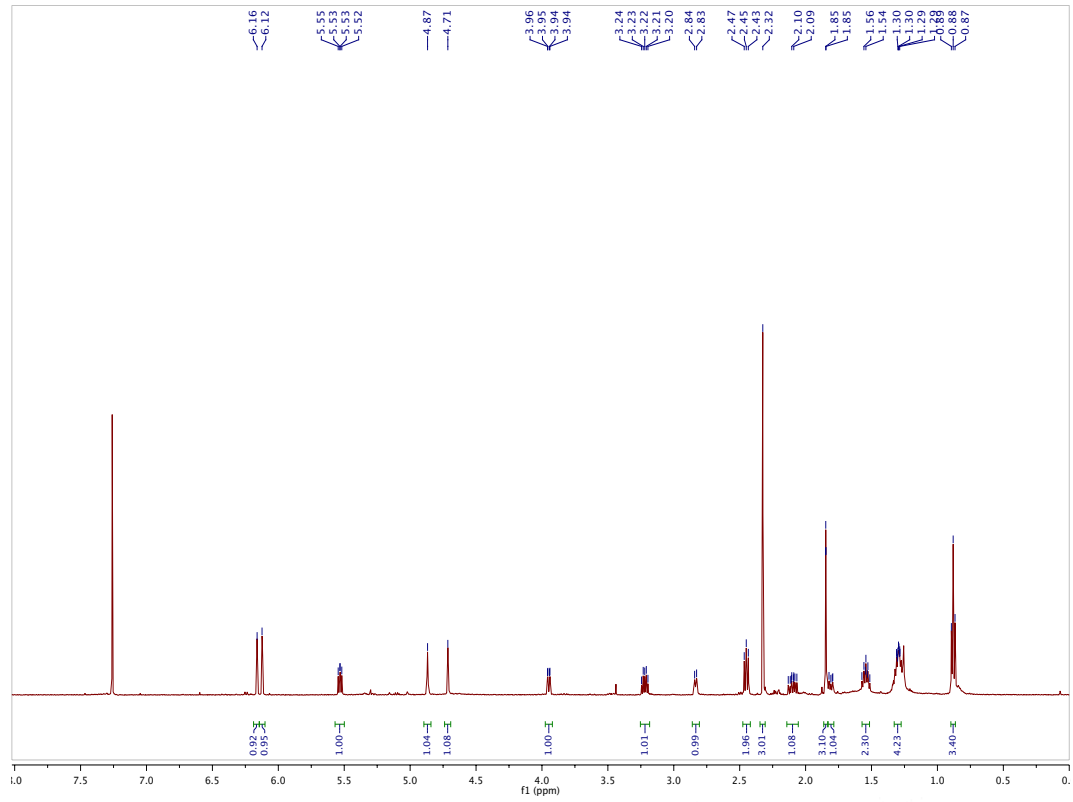
$^{1}$H NMR

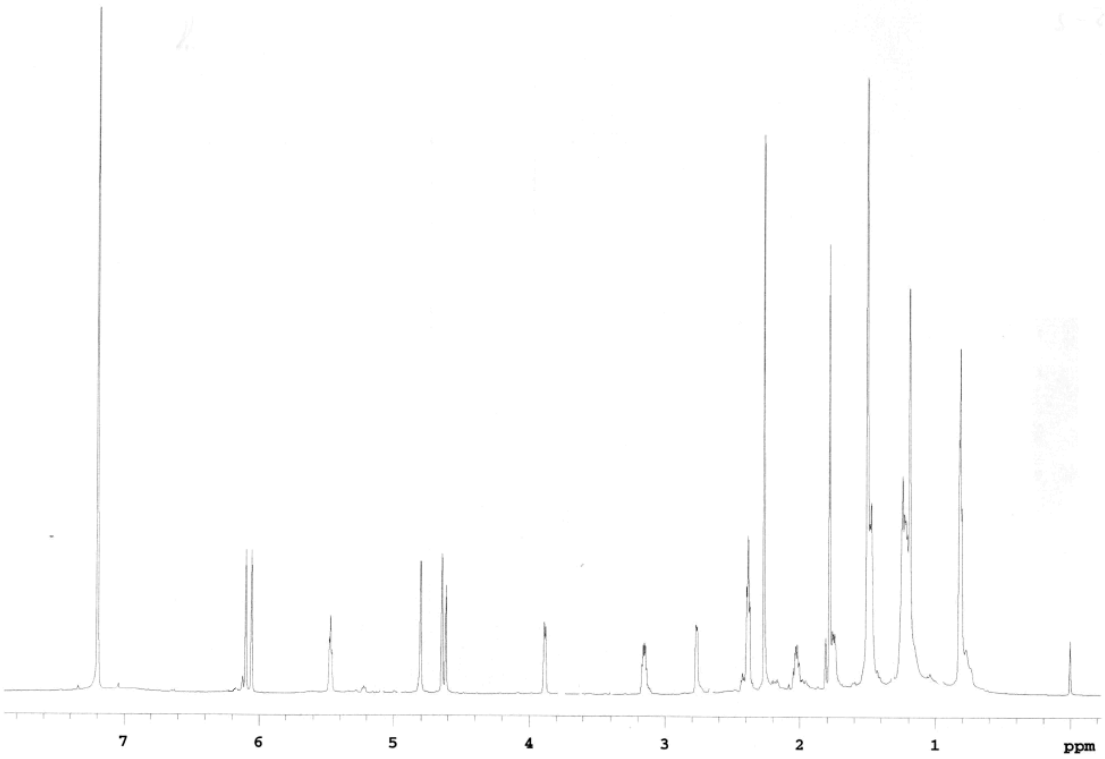



$^{13}$C NMR



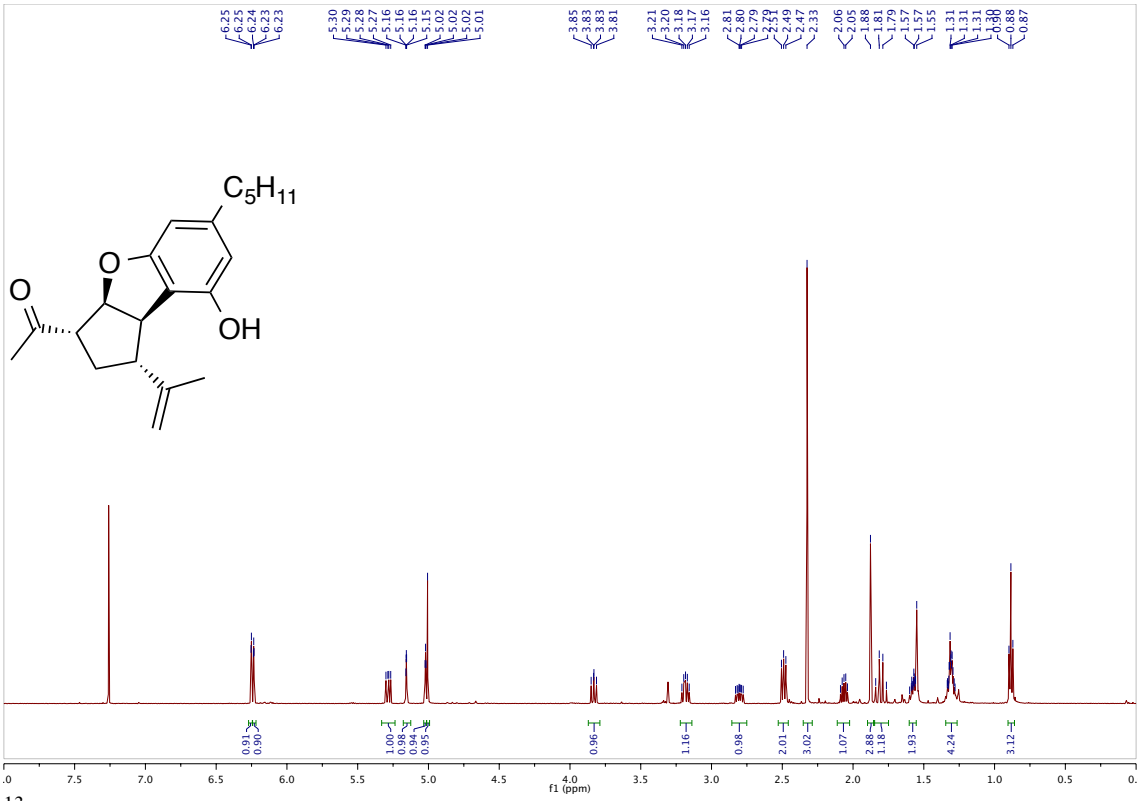
$^{1}$H NMR comparative of Anhydrocannabimovone **6** and previously reported (*Eur. J. Org. Chem.* **2010**, 2067)



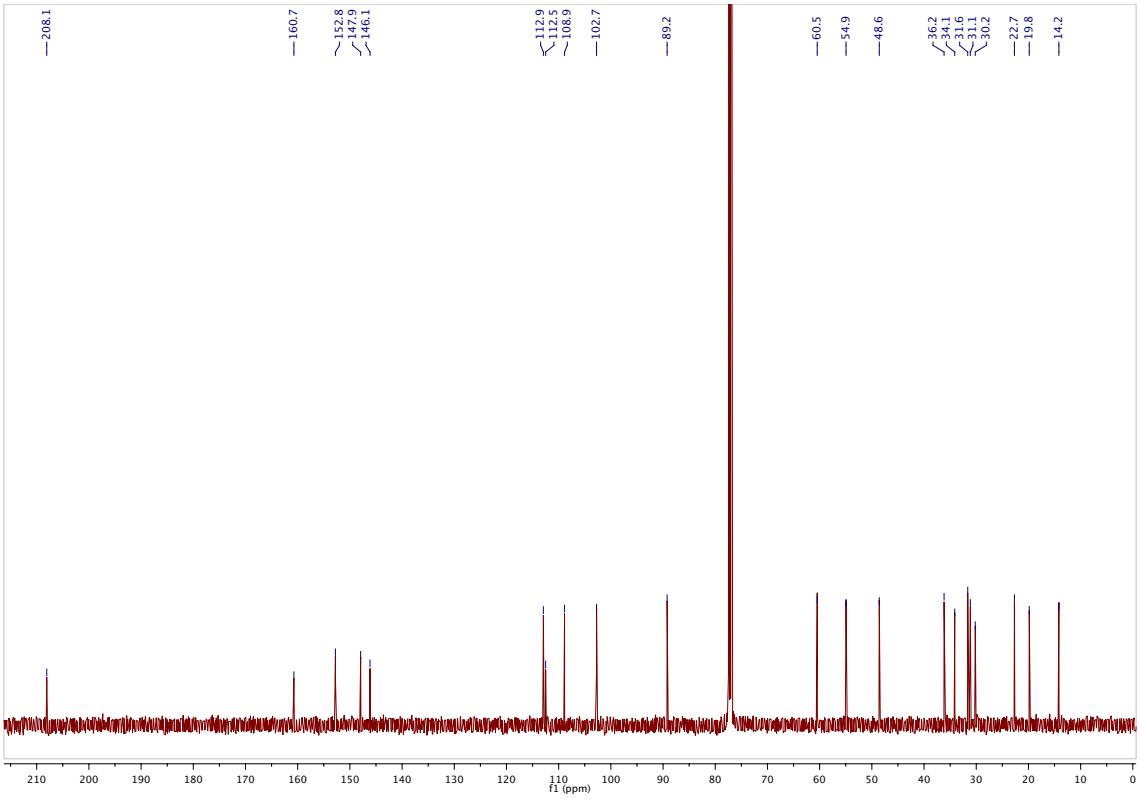



**Anhydrocannabimovone (6´´)**

$^{1}$H NMR

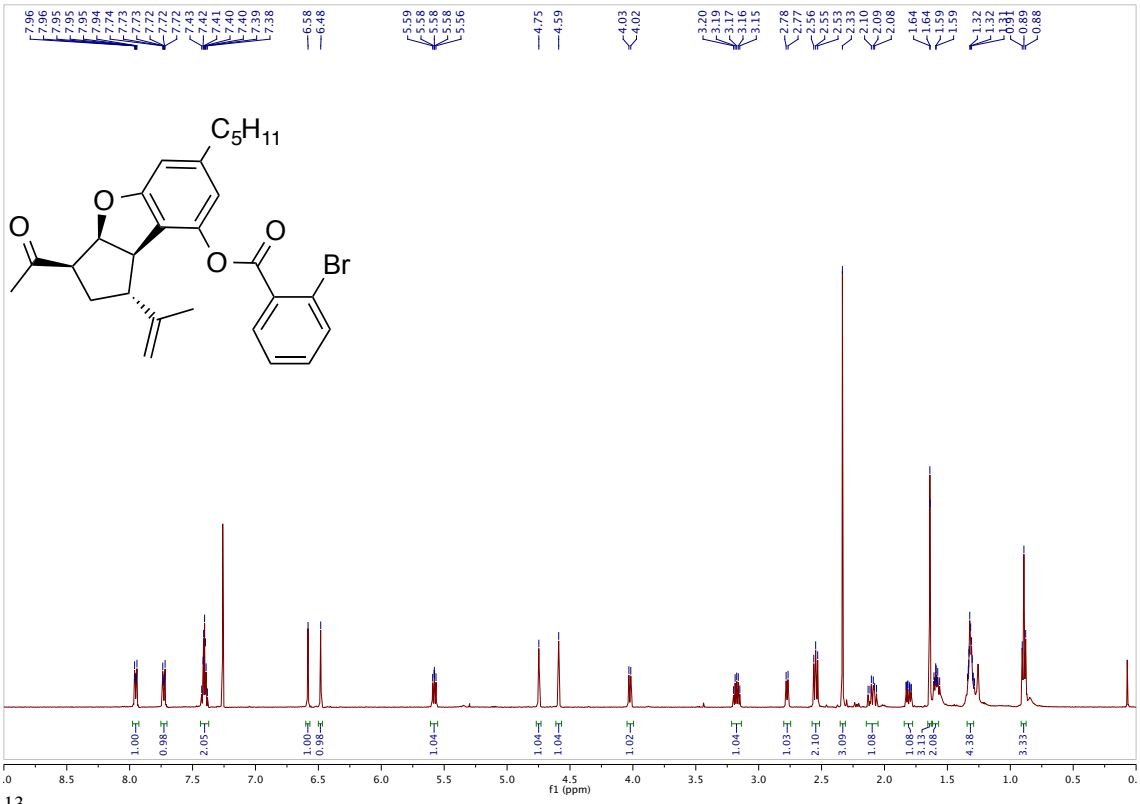



$^{13}$C NMR

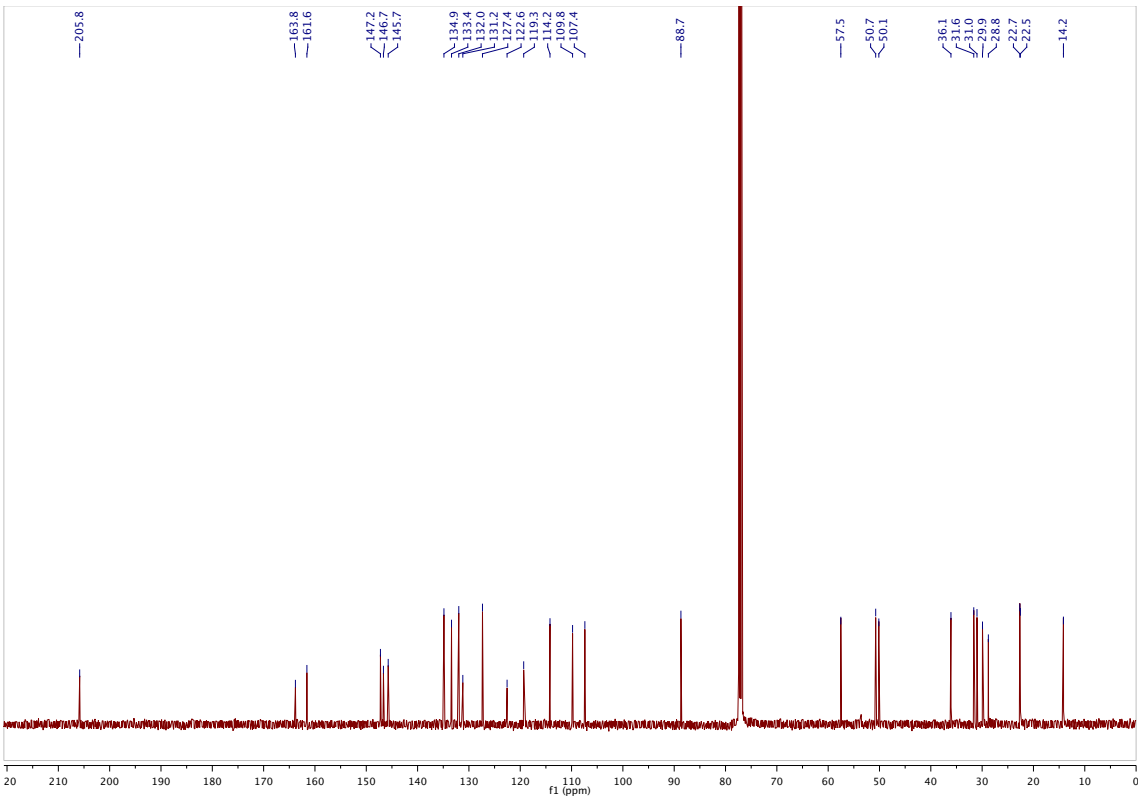


**(1*R*,3*R*,3a*S*,8b*R*)-3-acetyl-6-pentyl-1-(prop-1-en-2-yl)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-8-yl 2-bromobenzoate (23)**

$^{1}$H NMR

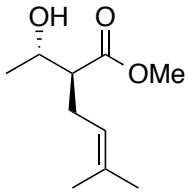


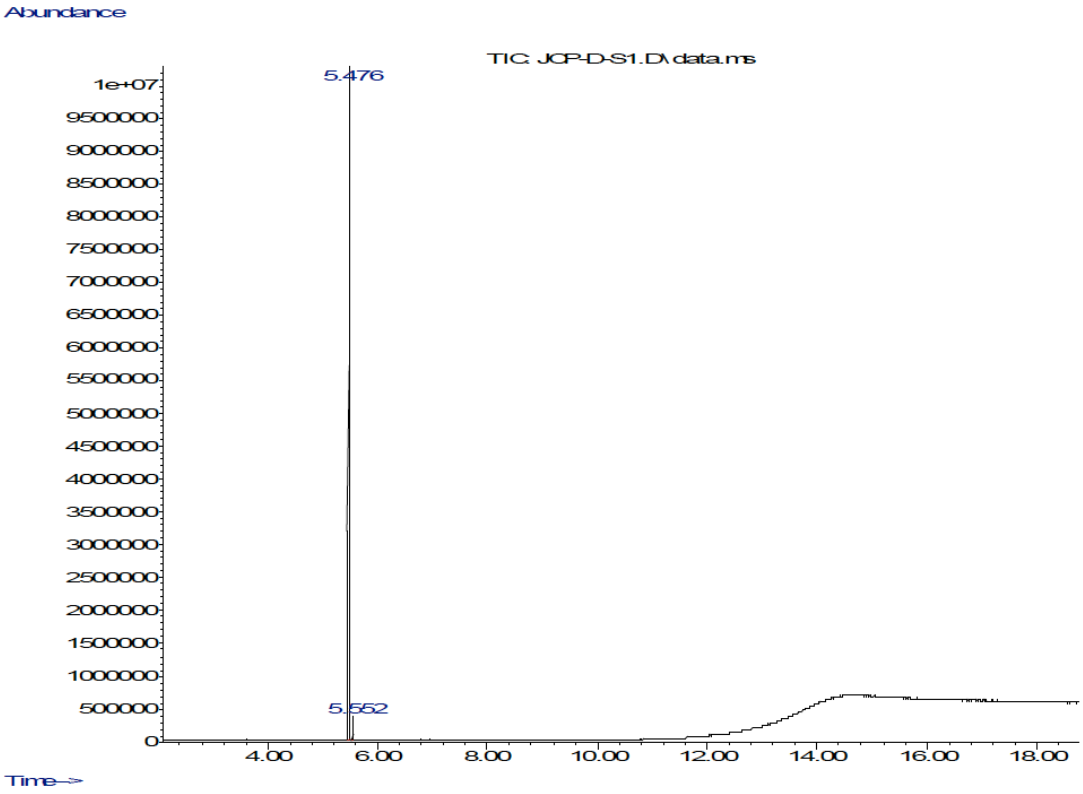

$^{13}$C NMR



## GC analysis of 10

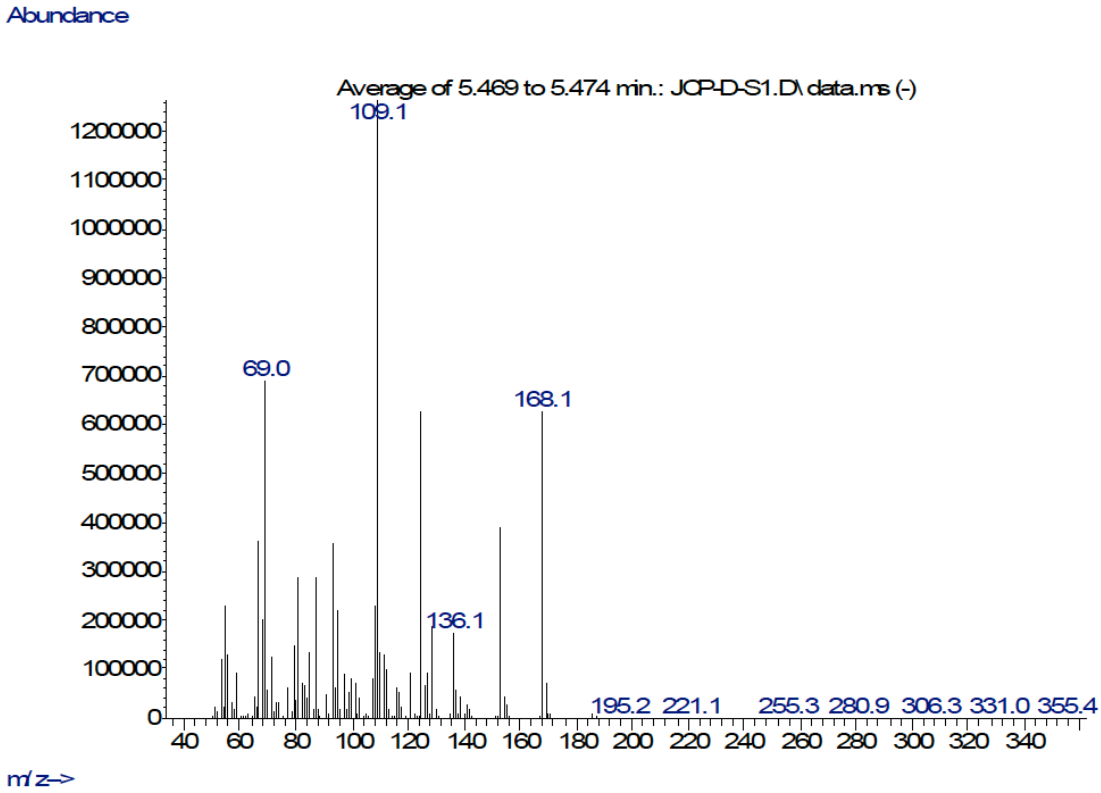
**HP5-MS 30mx0.25mm, 0.25µm**
**Tinj/Aux 280ºC**
**Flow 1.5mL/min**
**split 50:1 (1µL)**
**50ºC-325ºC(5)/20 ºCmin-1**

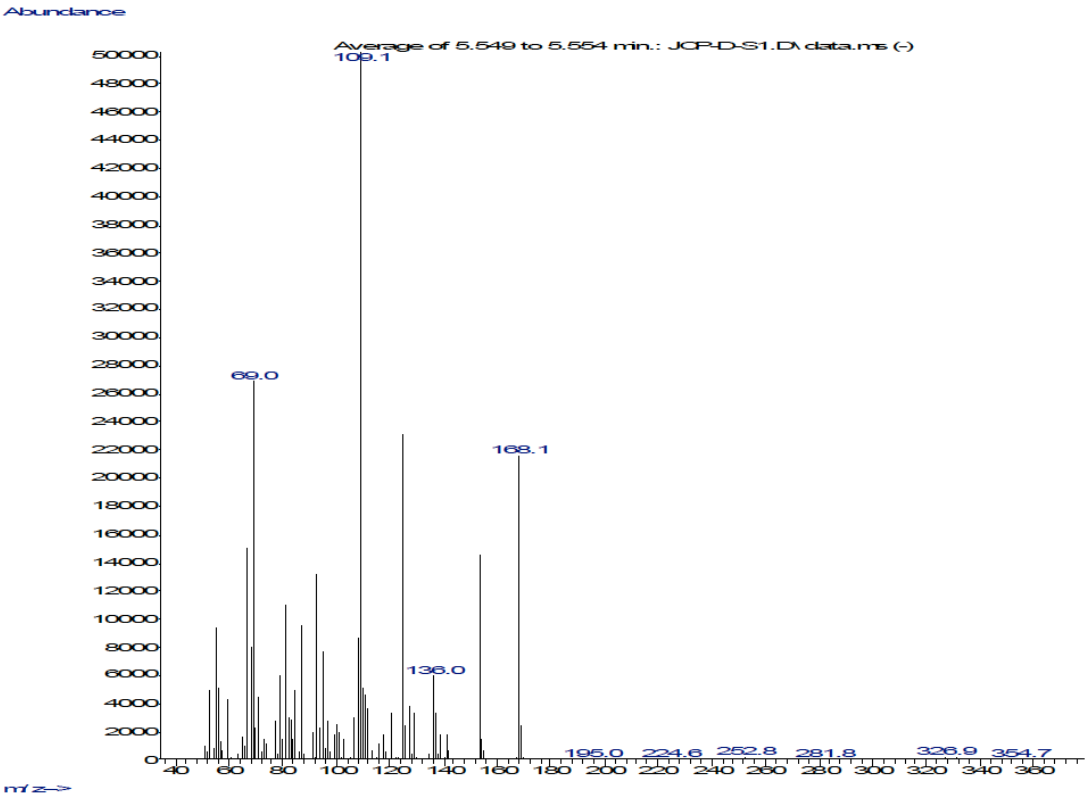



| peak # | R.T. min | first scan | max scan | last scan | PK TY | peak height | corr. area | corr. % max. | % of total |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 5.476 | 587 | 593 | 597 | M | 10295089 | 135341216 | 100.00% | 97.757% |
| 2 | 5.552 | 604 | 607 | 609 | M | 377193 | 3104755 | 2.29% | 2.243% |

**Sum of corrected areas: 138445971**


Abundance
Average of 5.469 to 5.474 min.: JCP-D-S1.D\ data.ms (-)
109.1
69.0
168.1
136.1
195.2 221.1 255.3 280.9 306.3 331.0 355.4
m/z-->


Abundance
Average of 5.549 to 5.554 min.: JCP-D-S1.D\ data.ms (-)
109.1
69.0
168.1
136.0
195.0 224.6 252.8 281.8 326.9 354.7
m/z-->