Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Total Synthesis of Applanatumol A

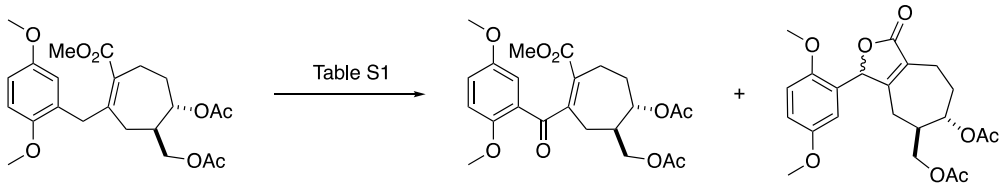
Kyohei Uchida, Yuichiro Kawamoto, Toyoharu Kobayashi, and Hisanaka Ito*

School of Life Sciences, Tokyo University of Pharmacy and Life Sciences
1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan.
itohisa@toyaku.ac.jp

General

All reactions involving air- and moisture-sensitive reagents were carried out using standard syringe-septum cap techniques. Unless otherwise noted, all solvents and reagents were obtained from commercial suppliers and used without further purification. Routines monitoring of reactions were carried out Merck silica gel 60 F254 TLC plates. Column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 60–230 μm) with the solvents indicated. ^{1}H and ^{13}C NMR spectra were measured with a JASCO EZC 400S (400 MHz) spectrometer. Chemical shifts were expressed in ppm using $CHCl_3$ (7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR) in $CDCl_3$ and $(CH_3)_2O$ (2.05 ppm for ^{1}H NMR, 29.8 and 206.2 ppm for ^{13}C NMR) in $(CD_3)_2O$ as internal standard. Infrared spectral measurements were carried out with a JASCO FT/IR-4700 and only noteworthy absorptions were listed. HRMS spectra measured on a Micromass LCT spectrometer.

Table S1. Investigation of oxidation of benzylic position.

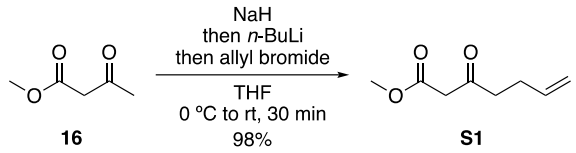


25 **23** **26**

entry	reagents	solv.	temp.	results (**23**:**26**)
1	AIBN, NHPI, O_2	CH_3CN	80	decomp.
2	DDQ	acetone/H_2O	rt	no reaction
3	SeO_2	1,2-DCE	70	1:4
4	SeO_2	toluene	90	1:10
5	SeO_2	wet-dioxane	80	1:5
6	SeO_2	dry-dioxane	80	1.7:1
7	SeO_2, MnO_2, MS 4A	dry-dioxane	100	2:1
8	SeO_2, IBX	dry-dioxane	100	1.5:1

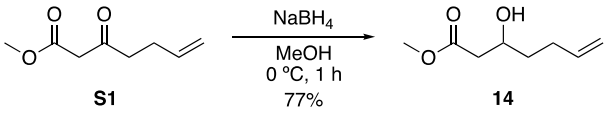
Experimental procedure

methyl 3-oxohept-6-enoate (**S1**)



To a stirred solution of methyl malonate (**16**) (5.00 g, 43.0 mmol, 1.0 eq.) in THF (50 mL) was added NaH (2.25 g, 51.6 mmol, 1.2 eq.) at 0 ºC under Ar, and reaction mixture was stirred for 30 min. To this mixture was added dropwise *n*-butyl lithium (1.58 M in *n*-hexane, 32.6 mL, 51.6 mmol, 1.2 eq.) at same temperature. Then, to this mixture was added allyl bromide (4.50 mL, 51.6 mmol, 1.2 eq.) at 0 ºC, and the mixture was stirred for 30 min at room temperature. The reaction mixture was quenched with sat. NH_4Cl aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 3:1) to afford **S1** (6.60 g, 98%) as yellow oil. IR (neat) 3423, 3079, 2955, 1748, 1717, 1642, 1437, 1321, 1270, 1078, 999, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (2H, dt, J = 15.6, 7.6 Hz), 2.62 (2H, 7.2, t, J = 7.2 Hz), 3.43 (3H, s), 3.70 (3H, s), 4.96 (1H, dt, J = 10.8, 1.2 Hz), 5.76 (1H, ddt, J = 17.2, 10.8, 7.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 27.5, 41.9, 48.9, 52.2, 115.5, 136.4, 167.5, 201.8; HRMS (ESI–TOF) Calcd for $C_8H_{12}O_3Na$ $[M+Na]^+$ 179.0682. Found 179.0682.

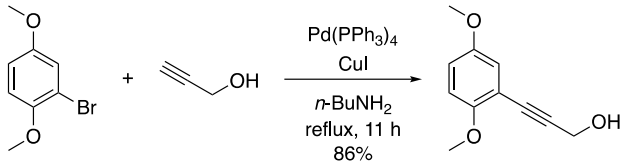
methyl (*S*)-3-hydroxyhept-6-enoate (**14**)



To a stirred solution of compound **S1** (4.84 g, 30.6 mmol, 1.0 eq.) in MeOH (90 mL) was added $NaBH_4$ (1.70 g, 45.9 mmol, 1.5 eq.) at –40 ºC and reaction mixture was stirred for 1 h. The reaction mixture was quenched with sat. NH_4Cl aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 3:1) to afford **14** (3.73 g, 77%) as yellow oil. IR (neat) 3415, 3077, 2929, 1737, 1641, 1438, 1294, 1168, 1082,

996, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45-1.64 (2H, m), 2.06-2.24 (2H, m), 2.40 (1H, dd, *J* = 16.4, 8.4 Hz), 2.48 (1H, dd, *J* = 16.4, 3.6 Hz), 2.80 (1H, brs), 3.68 (3H, s), 4.00 (1H, ddt, *J* = 8.8, 4.4, 3.2 Hz), 4.94 (1H, dt, *J* = 10.4, 3.2 Hz), 5.01 (1H, dt, *J* = 16.0, 3.6 Hz), 5.79 (1H, ddt, *J* = 16.8, 10.4, 6.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 29.6, 35.4, 41.0, 51.6, 67.3, 114.9, 137.9, 173.2; HRMS (ESI–TOF) Calcd for $C_8H_{14}O_3Na$ $[M+Na]^+$ 181.0841. Found 181.0839.

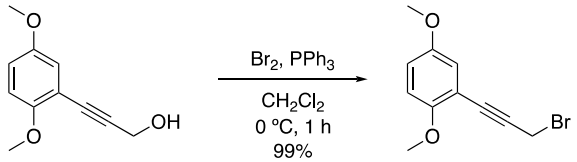
3-(2,5-dimethoxyphenyl)prop-2-yn-1-ol (**S3**)



17 **S2** **S3**

2-bromo-1,4-dimethoxybenzene (**17**) (5.00 g, 23.0 mmol, 1.0 eq.) in *n*-butylamine (40 mL) was placed in a flame-dried round-bottomed flask under an argon atmosphere. A mixture of propargyl alcohol (**S2**) (2.00 mL, 34.5 mmol, 1.5 eq.) in *n*-butylamine (40 mL) and $Pd(PPh_3)_4$ (1.32 g, 1.15 mmol, 0.05 eq.) was added, with the optional addition of CuI (131 mg, 0.690 mmol, 0.03 eq.) where appropriate. The mixture was heated for 11 h at reflux temperature and poured into H_2O. The product was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexanes, 1:1) to afford **S3** (3.79 g, 86%) as white solid. mp 67-68 ºC, IR (KBr) 2230, 3396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.66 (1H, t, *J* = 6.0 Hz), 3.72 (3H, s), 3.81 (3H, s), 4.52 (2H, d, *J* =6.0 Hz), 6.77 (1H, d, *J* =9.2 Hz), 6.82 (1H, dd, *J* = 9.2, 3.2 Hz), 6.93 (1H, d, *J* = 3.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 51.5, 55.6, 56.2, 81.5, 91.4, 111.7, 112.0, 115.7, 118.2, 153.0, 154.2; HRMS (ESI–TOF) Calcd for $C_{11}H_{12}O_3Na$ $[M+Na]^+$ 215.0684. Found 215.0681.

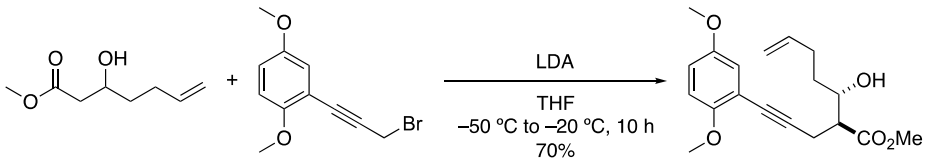
2-(3-bromoprop-1-yn-1-yl)-1,4-dimethoxybenzene (**15**)



S3 **15**

To a stirred solution of PPh_3 (5.37 g, 20.5 mmol, 1.2 eq.) in CH_2Cl_2 (50 mL) was added dropwise Br_2 (1.05 mL, 20.5 mmol, 1.2 eq.) at 0 ºC under Ar, and reaction mixture was stirred for 30 min. To this mixture was added dropwise a solution of compound **S3** (3.28 g, 17.0 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL), and the mixture was stirred for 1 h at 0 ºC. The reaction mixture was concentrated in vacuo, and filtered through short pad of silica, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 10:1) to afford **15** (4.29 g, 99%) as an off-white solid. mp 47-48 ºC, IR (KBr) 2205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75, (3H, s), 3.83 (3H, s), 4.21 (2H, s), 6.79 (1H, d, J = 8.8 Hz), 6.85 (1H, dd, J = 8.8, 3.2 Hz), 6.95 (1H, d, J = 2.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.6, 55.7, 56.3, 83.0, 88.0, 111.5, 111.9, 116.4, 118.2, 153.0, 154.7); HRMS (ESI–TOF) Calcd for $C_{11}H_{11}BrO_2Na$ $[M+Na]^+$ 276.9840. Found 276.9835.

methyl (2*S**,3*S**)-2-(3-(2,5-dimethoxyphenyl)prop-2-yn-1-yl)-3-hydroxyhept-6-enoate (**13**)

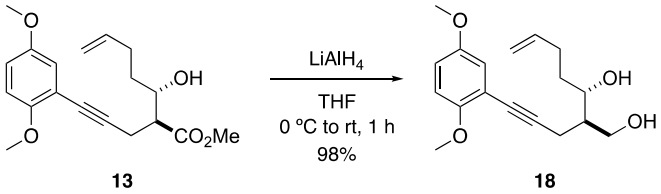


14 **15** **13**

To a stirred solution of diisopropylamine (10.0 ml, 71.3 mmol, 2.4 eq.) in THF (50 mL) was added dropwise *n*-butyl lithium (1.56 M in *n*-hexane, 45.7 mL, 71.3 mmol, 2.4 eq.) at 0 ºC under Ar, and reaction mixture was stirred for 20 min. To this mixture was added dropwise a solution of compound **14** (4.70 g, 29.7 mmol, 1.0 eq.) in THF (5 mL) at –50 ºC, and the mixture was stirred for 1 h at 0 ºC. Then, to this mixture was added dropwise a solution of compound **15** (9.00 g, 35.6 mmol, 1.2 eq.) in THF (10 mL) at –50 ºC, and the mixture was stirred for 10 h at –20 ºC. The reaction mixture was quenched with sat. NH_4Cl aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 3:1 to 2:1) to afford **13** (6.68 g, 70%) as yellow oil. IR (neat) 3519,2948, 2834, 1732, 1605, 1500, 1439, 1269, 1232, 1208, 1170, 1045, 915, 808, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (2H, dt, J = 14.4, 7.2 Hz), 2.14-2.75 (2H, m), 2.79-2.91 (3H, m), 3.74 (3H, s), 3.75 (3H, s), 3.81 (3H, s), 4.00 (1H, dt, J = 4.0, 6.4 Hz), 4.97 (1H, d, J = 9.2 Hz), 5.06 (1H, d, J = 16.0 Hz), 5.83 (1H, ddt, J = 16.8, 10.0, 6.8 Hz), 6.76 (1H, d, J = 9.2 Hz), 6.81 (1H, dd, J = 9.2, 2.8 Hz), 6.89 (1H, d, 2.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 19.8, 30. 1, 34.2, 49.5, 51.9, 55.7, 56.2, 70.9, 77.3, 90.5, 111.7, 115.0,

115.0, 115.0, 118.2, 138.0, 153.1, 154.4, 174.0); HRMS (ESI–TOF) Calcd for $C_{19}H_{24}O_5Na$ $[M+Na]^+$ 355.1521. Found 355.1514.

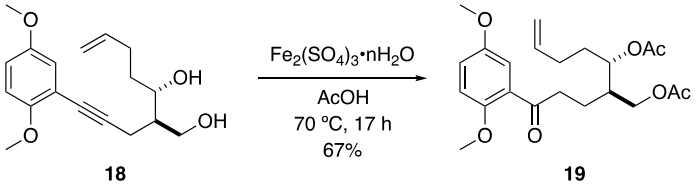
(2*R**,3*S**)-2-(3-(2,5-dimethoxyphenyl)prop-2-yn-1-yl)hept-6-ene-1,3-diol (**18**)



13 **18**

To a stirred solution of $LiAlH_4$ (689 mg, 18.6 mmol, 1.5 eq.) in THF (30 mL) was added solution of compound **13** (4.00 g, 12.4 mmol, 1.0 eq.) in THF at 0 ºC and reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with sat. Rochell's salt aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 1:1) to afford **18** (3.59 g, 98%) as yellow oil. mp 62-63 ºC, IR (KBr) 3819, 3700, 3130, 3049, 2276, 2143, 1943, 1791, 1687, 1559, 1159, 799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62-1.78 (2H, m), 1.87-1.89 (1H, m), 2.13-2.22 (1H, m), 2.25-2.34 (1H, m), 2.40 (2H, brs), 2.66 (1H, dd, *J* = 16.8, 6.4 Hz), 2.71 (1H, dd, *J* = 16.4, 6.0 Hz), 3.75 (3H, s), 3.81 (3H, s), 3.93 (1H, dd, *J* = 11.6, 4.8 Hz), 3.93-3.99 (1H, m), 4.03 (1H, dd, *J* = 11.2, 4.4 Hz), 4.98 (1H, d, *J* = 10.4 Hz), 5.07 (1H, d, *J* = 17.6 Hz), 5.86 (1H, ddt, *J* = 17.2, 10.0, 6.8 Hz), 6.77 (1H, d, *J* = 8.8 Hz), 6.80 (1H, dd, *J* = 8.8, 2.8 Hz), 6.9 (1H, d, *J* = 2.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.1, 30.2, 34.4, 43.9, 55.7, 56.1, 63.4, 73.6, 78.3, 92.3, 111.5,113.0,114.8, 114.8, 115.0, 117.9, 138.3, 153.1, 154.3; HRMS (ESI–TOF) Calcd for $C_{18}H_{24}O_4Na$ $[M+Na]^+$ 327.1572. Found 327.1566.

(2*R**,3*S**)-2-(3-(2,5-dimethoxyphenyl)-3-oxopropyl)hept-6-ene-1,3-diyl diacetate (**19**)

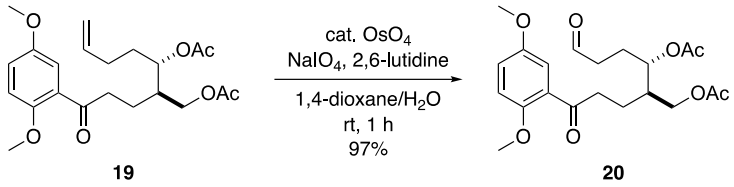


18 **19**

To a stirred solution of compound **18** (547 mg, 1.80 mmol, 1.0 eq.) in AcOH (9 mL) was added

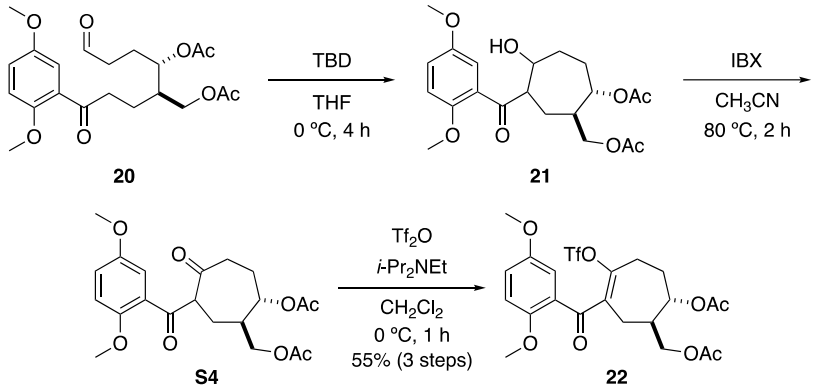
$Fe_2(SO_4)_3 \cdot nH_2O$ (360 mg, 0.900 mmol, 0.5 eq.) at room temperature and reaction mixture was stirred for 17 h at 70 ºC. The reaction mixture was filtered through Celite, and concentrated in vacuo, and washed with sat. $NaHCO_3$ aq., then, extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 2:1) to afford **19** (487 mg, 67%) as yellow oil. IR (neat) 2942, 1737, 1673, 1582, 1495, 1412, 1370, 1228, 1165, 1110, 1043, 915, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64-1.79 (3H, m), 1.97-2.10 (3H, m), 2.03 (3H, s), 2.04 (3H, s), 3.06 (2H, td, *J* = 8.0, 3.2 Hz), 3.39-3.43 (2H, m), 3.79 (3H, s), 3.86 (3H, s), 4.12 (1H, dd, *J* = 11.6, 5.6 Hz), 4.96 (1H, d, *J* = 10.0 Hz), 5.01 (1H, d, *J* = 17.2 Hz), 5.01-5.07 (1H, m), 5.78 (1H, ddt, *J* = 17.2, 10.8, 6.8 Hz), 6.90 (1H, d, *J* = 8.4 Hz), 7.01 (1H, dd, *J* = 8.4, 3.2 Hz), 7.23 (1H, d, *J* = 3.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.9, 21.0, 22.3, 26.4, 29.7, 30.5, 40.3, 41.0, 55.8, 56.0, 63.6, 70.5, 113.0, 113.8, 119.9, 128.2, 137.5, 153.0, 153.4, 170.6, 171.1, 201.4; HRMS (ESI–TOF) Calcd for $C_{22}H_{30}O_7Na$ $[M+Na]^+$ 429.1889. Found 429.1884.

(2*R**,3*S**)-2-(3-(2,5-dimethoxyphenyl)-3-oxopropyl)-6-oxohexane-1,3-diyl diacetate (**20**)



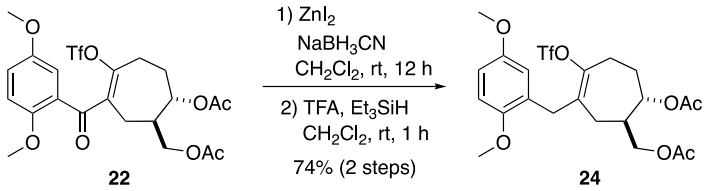
To a solution of **19** (140 mg, 0.320 mmol, 1.0 eq.) in 1,4-dioxane (2.4 mL) and H_2O (0.8 mL) was added 2,6-lutidine (73.0 μL, 0.640 mmol, 2.0 eq.) and $NaIO_4$ (273 mg, 1.28 mmol, 4.0 eq.) and 4% OsO_4 aqueous solution (100 μL, 0.0160 mmol, 0.05 eq.) at room temperature, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. $Na_2S_2O_3$ aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 1:1) to afford **20** (127 mg, 97%) as yellow oil. IR (neat). 2942, 2836, 1736, 1672, 1582, 1495, 1412, 1227, 1165, 1042, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.66-1.75 (1H, m), 1.78-1.88 (1H, m), 1.90-2.07 (3H, m), 2.03 (3H, s), 2.04 (3H, s), 2.50 (2H, t, *J* = 8.4 Hz), 3.08 (2H, t, *J* = 7.2 Hz), 3.79 (3H, s), 3.87 (3H, s), 4.11 (2H, d, *J* = 5.2 Hz), 5.00-5.06 (1H, m), 6.90 (1H, d, *J* = 9.2 Hz), 7.02 (1H, dd, *J* = 8.4, 3.2 Hz), 7.23 (1H, d, *J* = 3.2 Hz), 9.76 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.9, 20.9, 22.1, 23.8, 40.1, 40.4, 40.8, 55.8, 56.0, 63.2, 73.0, 113.0, 113.8, 120.0, 128.1, 153.0, 153.4, 170.6, 171.0, 201.1, 201.2; HRMS (ESI–TOF) Calcd for $C_{21}H_{28}O_8Na$ $[M+Na]^+$ 431.1682. Found 431.1674.

((1*R**,7*S**)-7-acetoxy-3-(2,5-dimethoxybenzoyl)-4-(((trifluoromethyl)sulfonyl)oxy)cyclohept-3-en-1-yl)methyl acetate (**22**)



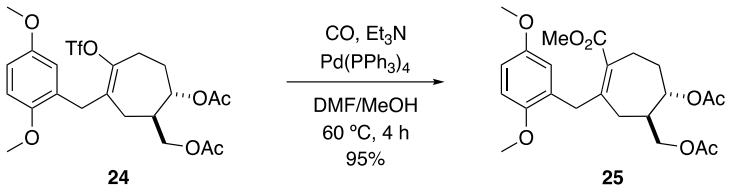
To a stirred solution of compound **20** (362 mg, 0.880 mmol, 1.0 eq.) in THF (18 mL) was added TBD (37.0 mg, 0.260 mmol, 0.3 eq.) at 0 ºC and reaction mixture was stirred for 4 h at same temperature. The reaction mixture was quenched with sat. NH_4Cl aqueous solution, and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo afford the crude **21** as a diastereomer mixture. To a stirred solution of the crude **21** in CH_3CN (10 mL) was added IBX (490 mg, 1.76 mmol, 2.0 eq.) at room temperature, and the mixture was stirred for 2 h at 80 ºC. The reaction mixture was filtered through Celite and concentrated in vacuo afford the crude **S4**. To a stirred solution of the crude **S4** in CH_2Cl_2 (1 mL) was added *i*Pr_2NEt (0.490 mL, 2.64 mmol, 3.0 eq.) and Tf_2O (0.230 mL, 1.32 mmol, 1.5 eq.) at 0 ºC under Ar atmosphere, and the mixture was stirred for 1 h at same temperature. The reaction mixture was quenched with sat. NH_4Cl aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 2:1) to afford **22** (262 mg, 55% in 3 steps) as pale yellow oil. IR (neat) 2923, 2852, 1739, 1651, 1496, 1416, 1225, 1139, 1040, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.01 (3H, s), 2.03-2.08 (2H, m), 2.09 (3H, s), 2.15-2.24 (1H, m), 2.32-2.39 (1H, m), 2.43-2.55 (2H, m), 2.86 (1H, dd, *J* = 19.2, 10.8 Hz), 3.77 (1H, d, *J* = 4.8 Hz), 3.79 (3H, s), 3.84 (3H, s), 4.04 (1H, d, *J* = 4.8 Hz), 4.98 (1H, ddd, *J* = 14.0, 8.8, 4.8 Hz), 6.89 (1H, d, *J* = 9.2 Hz), 7.09 (1H, dd, *J* = 9.2, 3.2 Hz), 7.25 (1H, d, *J* = 2.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.7, 21.2, 27.1, 27.3, 28.6, 40.4, 55.8, 56.1, 64.9, 72.4, 112.9, 112.9, 114.4, 121.9, 126.1, 135.1, 146.8, 153.3, 153.7, 170.2, 170.8, 192.7; HRMS (ESI–TOF) Calcd for $C_{22}H_{25}O_{10}F_3NaS$ $[M+Na]^+$ 561.1018. Found 561.1019.

((1*R**,7*S**)-7-acetoxy-3-(2,5-dimethoxybenzyl)-4-(((trifluoromethyl)sulfonyl)oxy)cyclohept-3-en-1-yl)methyl acetate (**24**)



To a stirred solution of compound **22** (75.0 mg, 0.140 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) was added ZnI_2 (137 mg, 0.420 mmol, 3.0 eq.) and $NaBH_3CN$ (66.0 mg, 1.05 mmol, 7.5 eq.) at room temperature and reaction mixture was stirred for 12 h. The reaction mixture was filtered through Celite, and concentrated in vacuo. The less polar side product was removed by short silica filter (hexanes-AcOEt, 1:1). The mixture of desired product **24** and benzylic alcohol intermediate was used directly in the next step. To a stirred solution of **24** and alcohol in CH_2Cl_2 (2 mL) was added TFA (2.5 mL) and Et_3SiH (66.0 μL, 0.420 mmol, 3.0 eq.). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with sat. $NaHCO_3$ aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 2:1) to afford **24** (54.0 mg, 74% in two steps) as pale yellow oil. IR (neat) 2936, 1739, 1501, 1409, 1366, 1221, 1140, 1025, 981, 888, 607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ1.78-1.85 (1H, m), 1.87-1.92 (1H, m), 1.95 (3H, s), 2.01-2.07 (2H, m), 2.03 (3H, s), 2.18 (1H, d, *J* = 15.6 Hz), 2.48 (1H, dd, *J* = 16.4, 8.8 Hz), 2.72 (1H, dd, *J* = 17.2, 10.0 Hz), 3.47 (1H, d, *J* = 15.2 Hz), 3.58 (1H, d, *J* = 15.2 Hz), 3.75 (3H, s), 3.77 (3H, s), 3.84 (2H, t, *J* = 6.0 Hz), 4.83 (1H, ddd, *J* = 9.2, 6.4, 3.6 Hz), 6.68 (1H, d, *J* = 2.8 Hz), 6.74 (1H, dd, *J* = 8.8, 3.2 Hz), 6.78 (1H, d, *J* = 8.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.6, 21.1, 27.0, 28.6, 29.0, 32.2, 40.1, 55.6, 55.8, 64.8, 73.1, 111.4,112.0, 116.6, 126.3, 131.4, 145.6, 151.9, 153.4, 170.1, 170.8, 190.0; HRMS (ESI–TOF) Calcd for $C_{22}H_{27}O_9F_3NaS$ $[M+Na]^+$ 547.1226. Found 547.1226.

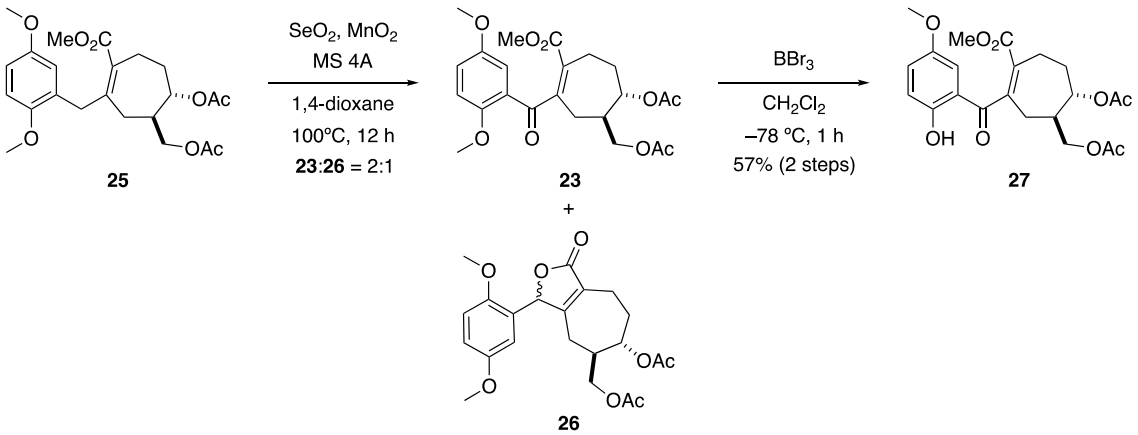
Methyl (4*R**,5*S**)-5-acetoxy-4-(acetoxymethyl)-2-(2,5-dimethoxybenzyl)cyclohept-1-ene-1-carboxylate (**25**)



24 **25**

To a solution of **24** (100 mg, 0.190 mmol, 1.0 eq.) in DMF (2 mL) and MeOH (1 mL) was added Et_3N (0.130 mL, 0.950 mmol, 5.0 eq.) and $Pd(PPh_3)_4$ (22.0 mg, 0.0190 mmol, 0.1 eq.) at room temperature. CO was bubbled through the solution and the reaction mixture was stirred for 4 h under a CO atmosphere at 60 ºC. The reaction mixture was quenched with sat. NH_4Cl aqueous solution and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 2:1) to afford **25** (78.0 mg, 95%) as yellow oil. IR (neat). 2926, 2852, 1737, 1499, 1463, 1375, 1236, 1100, 1233 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45-1.51 (1H, m), 1.98 (3H, s), 2.00 (3H, s), 2.03-2.09 (2H, m), 2.17-2.22 (2H, m), 2.30 (1H, dd, *J* = 15.6, 11.2 Hz), 2.66 (1H, dd, *J* = 16.0, 8.8 Hz), 3.58 (1H, d, *J* = 14.8 Hz), 3.75 (9H, s), 3.73-3.75 (1H, m), 3.84 (1H, d, *J* = 10.0 Hz), 3.91 (1H, dd, *J* = 11.2, 5.6 Hz), 4.82 (1H, td, *J* = 9.6, 4.0 Hz), 6.71 (1H, dd, *J* = 8.8, 2.8 Hz), 6.76-6.89 (2H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.7, 21.1, 24.7, 29.7, 31.0, 35.2, 39.9, 51.5, 55.6, 55.6, 65.1, 74.7, 111.2, 111.3, 116.8, 127.8, 131.5, 148.6, 151.9, 153.4, 169.7, 170.0, 171.0; HRMS (ESI–TOF) $C_{23}H_{30}O_8Na$ $[M+Na]^+$ 457.1838. Found 457.1834.

methyl (4*R**,5*S**)-5-acetoxy-4-(acetoxymethyl)-2-(2-hydroxy-5-methoxybenzoyl)cyclohept-1-ene-1-carboxylate (**27**)



25 **23** **26** **27**

To a stirred solution of compound **25** (7.00 mg, 0.0160 mmol, 1.0 eq.) in dry-1,4-dioxane (0.3 mL) was added SeO_2 (18.0 mg, 0.150 mmol, 9.5 eq.), MnO_2 (80% activated, 35.0 mg, 0.400 mmol,

19.8 eq.) and 4A MS, then reaction mixture was stirred for 12 h at 100 ºC. The reaction mixture was filtered through Celite and concentrated in vacuo. The resulting residue was purified by short pad of silica to afford **23** and **26** as inseparable products. To a stirred solution of mixtures of **23** and **26** in CH_2Cl_2 (0.3 mL) was added BBr_3 (85.0 μL, 0.0850 mmol, 5.2 eq.) at –78 ºC and reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with H_2O and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 2:1 to 1:1) to afford **27** (4.00 mg, 57% in 2 steps) as yellow oil.

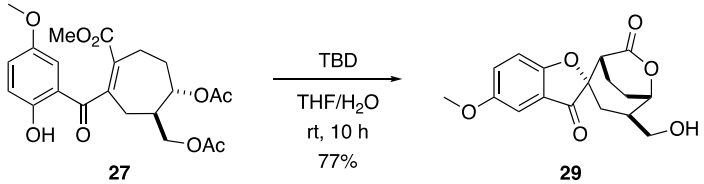
Data for **27**

IR (neat) 2950, 2839, 1730, 1641, 1634, 1613, 1485, 1367, 1282, 1244, 1034, 831, 774, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80-0.89 (1H, m), 1.70-1.79 (1H, m), 1.98 (3H, s), 2.09 (3H, s), 2.09-2.15 (1H, m), 2.20-2.26 (1H, m), 2.48-2.59 (2H, m), 2.90 (1H, dd, *J* = 17.2, 10.4 Hz), 3.52 (3H, s), 3.75 (3H, s), 4.02 (1H, dd, *J* = 11.2, 4.0 Hz), 4.11 (1H, dd, *J* = 10.8, 6.0 Hz), 5.01 (1H, td, *J* = 8.8, 3.6 Hz), 6.80 (1H, d, *J* = 3.2 Hz), 6.97 (1H, d, *J* = 9.2 Hz), 7.11 (1H, dd, *J* = 8.8, 3.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.6, 21.1, 22.5, 29.5, 30.7, 39.9, 52.2, 55.8, 64.5, 73.6, 113.8, 117.4, 119.2, 123.3, 134.2, 148.5, 151.8, 156.7, 166.2, 170.0, 170.7, 203.2; HRMS (ESI–TOF) $C_{22}H_{26}O_9Na$ $[M+Na]^+$ 457.1475. Found 457.1471.

Data for **26** (diastereomeric mixtures)

IR (neat) 3816, 3709, 2923, 2410, 2323, 1735, 1504, 1456, 1366, 1237, 1025, 785, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (2H, m, overlapped), 1.91 (3H, s), 1.97-2.01 (1H, m), 2.04-2.08 (3H, m), 2.14-2.35 (2H, m), 2.43-2.63 (2H, m), 3.74 (3H, s), 3.83 (3H, s), 3.79-3.83 (1H, m), 3.83-3.97 (1H, m), 5.04-5.29 (1H, m), 6.14 (1H, s), 6.57 (1H, s), 6.86-7.00 (2H, m) ; ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.4, 21.1, 25.6, 29.7, 29.7, 39.8, 55.8, 56.2, 60.3, 64.7, 73.1, 78.6, 112.4, 112.4, 115.1, 128.2, 128.2, 144.9, 151.6, 158.9, 170.0, 174.4; HRMS (ESI–TOF) $C_{22}H_{26}O_8Na$ $[M+Na]^+$ 441.1525. Found 441.1522.

(1'*R**,2*S**,4'*R**,5'*S**)-4'-(hydroxymethyl)-5-methoxy-3*H*-6'-oxaspiro[benzofuran-2,2'-bicyclo[3.2.2]nonane]-3,7'-dione (**29**)

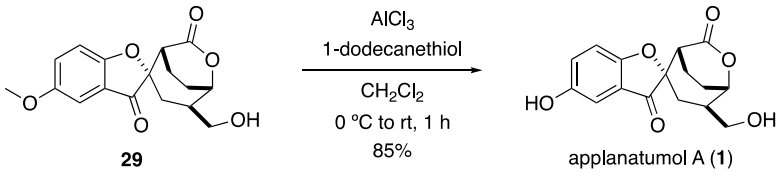


27 **29**

To a stirred solution of compound **27** (3.70 mg, 0.00850 mmol, 1.0 eq.) in THF (0.2 mL) and H_2O

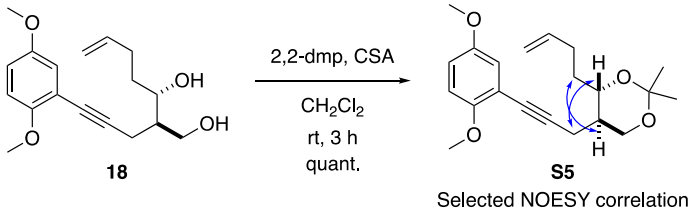
(20 μL) was added TBD (4.00 mg, 0.0280 mmol, 3.3 eq.) at room temperature and reaction mixture was stirred for 10 h. The reaction mixture was quenched with sat. NH_4Cl aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 1:1) to afford **29** (2.10 mg, 77%) as pale yellow oil. IR (neat) 2924, 2854, 1712, 1489, 1277, 1227, 1180, 1097, 1070, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (1H, dd, *J* = 14.8, 4.4 Hz), 1.91-1.98 (1H, m), 2.03-2.09 (1H, m), 2.16-2.25 (1H, m), 2.26-2.38 (1H, m), 2.57-2.66 (2H, m), 2.87 (1H, d, *J* = 5.6 Hz), 3.53 (1H, dd, *J* = 10.4, 7.2 Hz), 3.66 (1H, dd, *J* = 10.8, 4.8 Hz), 3.80 (3H, s), 4.85 (1H, d, *J* = 6.4 Hz), 7.00 (1H, d, *J* = 2.8 Hz), 7.05 (1H, d, *J* = 8.8 Hz), 7.27 (1H, d, *J* = 2.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.7, 29.7, 31.2, 42.6, 44.0, 56.0, 64.5, 77.0, 86.6, 104.4, 114.9, 118.9, 128.9, 155.5, 170.4, 192.9, 201.9; HRMS (ESI–TOF) Calcd for $C_{17}H_{18}O_6Na$ $[M+Na]^+$ 341.1001. Found 341.0998.

(1'*R**,2*S**,4'*R**,5'*S**)-5-hydroxy-4'-(hydroxymethyl)-3*H*-6'-oxaspiro[benzofuran-2,2'-bicyclo[3.2.2]nonane]-3,7'-dione (**1**)

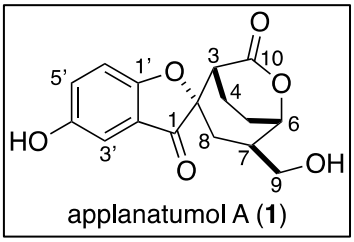


To a stirred solution of compound **29** (4.00 mg, 0.0125 mmol, 1.0 eq.) in CH_2Cl_2 (0.3 mL) was added $AlCl_3$ (17.0 mg, 0.120 mmol, 10 eq.) and 1-dodecanethiol (15.0 μL, 0.0590 mmol, 4.7 eq.) at 0 ºC and reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with H_2O and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by preparative TLC (hexane-AcOEt, 1:1) to afford applanatumol A (**1**) (3.30 mg, 85%) as pale yellow solid. IR (neat) 2921, 2856, 2338, 1704, 1484, 1383, 1297, 1248, 1015, 807 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2O$) δ 1.66 (1H, dd, *J* = 14.4, 4.0), 1.89-1.98 (1H, m), 2.07 (1H, overlap), 2.12-2.17 (2H, m), 2.41-2.49 (1H, m), 2.52-2.60 (1H, m), 2.75 (1H, d, *J* = 6.0 Hz), 3.49 (1H, t, *J* = 8.0 Hz), 3.59 (1H, dd, *J* = 10.8, 5.2 Hz), 4.02-4.07 (1H, m), 4.79 (1H, t, *J* = 3.6 Hz), 6.97 (1H, d, *J* = 2.8 Hz), 7.06 (1H, d, *J* = 9.2 Hz), 7.29 (1H, dd, *J* = 8.8, 2.8 Hz); ^{13}C NMR (400 MHz, $(CD_3)_2O$) δ 17.8, 19.9, 30.0, 43.9,44.8, 64.0, 77.9, 87.5, 108.3, 115.1, 119.8, 128.4, 153.7, 165.6, 170.1, 202.4; HRMS (ESI–TOF) Calcd for $C_{16}H_{16}O_6Na$ $[M+Na]^+$ 327.0845. Found 327.0844.

(2*R**,3*S**)-2-(3-(2,5-dimethoxyphenyl)prop-2-yn-1-yl)hept-6-ene-1,3-diol (**S5**)

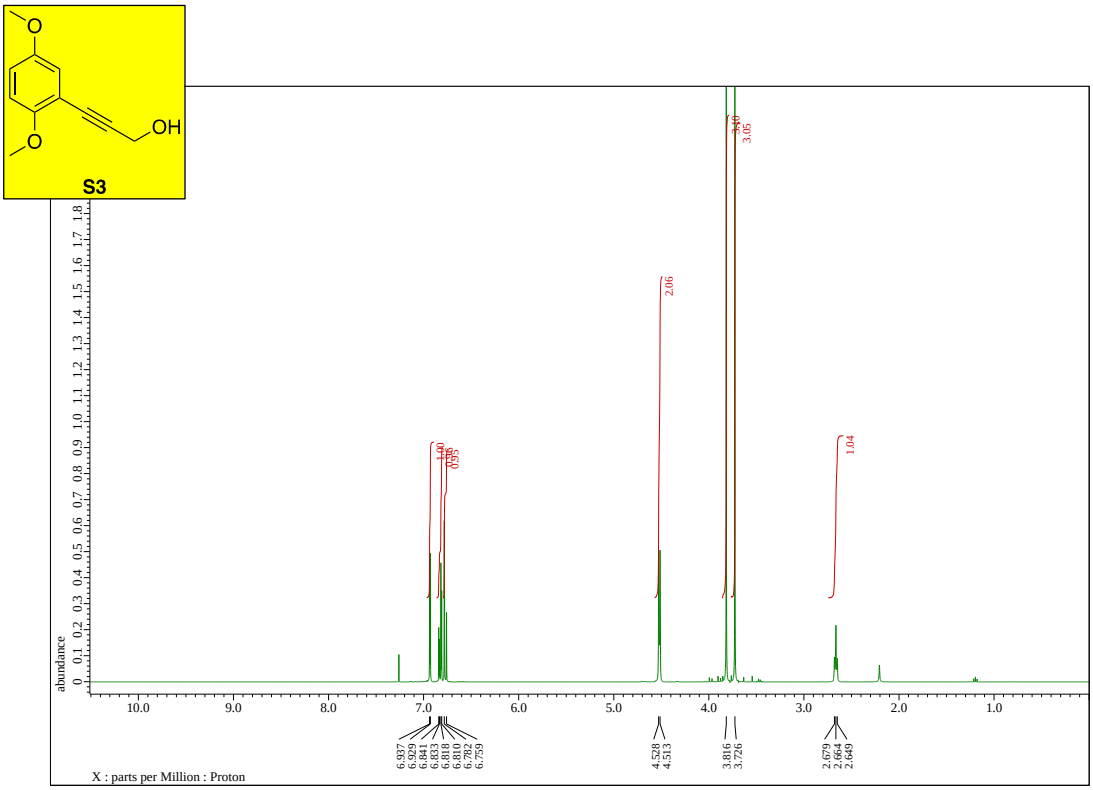


To a solution of **18** (24.0 mg, 0.0790 mmol, 1.0 eq.) in CH_2Cl_2 (0.4 mL) was added CSA (1.80 mg, 0.00780 mmol, 0.1 eq.) and 2,2-dmp (2.00 mL, 0.0110 mmol, 1.4 eq.) at room temperature and the mixture was stirred for 3 h. The reaction mixture was quenched with $NaHCO_3$ aqueous solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane-AcOEt, 4:1) to afford **S5** (27.0 mg, 99%) as yellow oil. IR (neat) 3074, 2992, 2938, 2834, 1640, 1604, 1499, 1463, 1380, 1267, 1232, 1170, 1047, 914, 875, 805, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, s), 1.46 (3H, s), 1.48-1.53 (1H, m), 1.72-1.89 (2H, m), 2.06-2.15 (1H, m), 2.21-2.28 (1H, m), 2.41 (2H, d, *J* = 6.4 Hz), 3.74 (3H, s), 3.80 (3H, s), 3.87 (1H, td, *J* = 10.4, 2.8 Hz), 3.91 (2H, d, *J* = 8.0 Hz), 4.93 (1H, d, *J* = 10.4 Hz), 5.26 (1H, d, *J* = 15.2 Hz), 5.81 (1H, ddt, *J* = 16.8, 10.0, 6.8 Hz), 6.75-6.79 (2H, m), 6.88 (1H, d, *J* = 2.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.8, 19.4, 29.0, 29.4, 32.1, 37.7, 55.7, 56.2, 63.7, 71.3, 78.7, 90.2, 98.2, 111.7, 113.1, 114.6, 114.9, 118.2, 138.4, 153.1, 154.4; HRMS (ESI–TOF) Calcd for $C_{21}H_{28}O_4Na$ $[M+Na]^+$ 367.1885. Found 367.1882.



applanatumol A (**1**)

	synthetic product			isolated product	
No.	δ_H	δc	No.	δ_H	δc
1'		165.6	1'		165.7
2'		119.8	2'		119.9
3'	6.97 (d, 2.8)	108.3	3'	6.98 (d, 2.7)	108.3
4'		153.7	4'		153.7
5'	7.29 (dd, 8.8, 2.8)	128.4	5'	7.29 (dd, 8.9, 2.7)	128.4
6'	7.06 (d, 9.2)	115.1	6'	7.06 (d, 8.9)	115.2
1		202.4	1		202.5
2		87.5	2		87.6
3	2.75 (d, 6.0)	44.8	3	2.76 (dd, 6.0, 2.6)	44.9
4a	2.52-2.60 (m)	17.8	4a	2.56 (m)	17.9
4b	1.89-1.98 (m)		4b	1.92 (m)	
5	2.12-2.17 (m)	19.9	5	2.15 (m)	20.1
6	4.79 (t, 3.6)	77.9	6	4.79 (t-like, 5.9)	78.0
7	2.41-2.49 (m)	43.9	7	2.45 (m)	43.9
8a	2.07 (overlap)	30.0	8a	2.07 (overlap)	30.1
8b	1.66 (dd, 14.4, 4.0)		8b	1.66 (dd, 15.0, 4.1)	
9a	3.59 (dd, 10.8, 5.2)	64.0	9a	3.58 (dd, 11.0, 5.2)	64.0
9b	3.49 (t, 8.0)		9b	3.48 (dd, 11.0, 8.0)	
10		170.1	10		170.3
4'-OH			4'-OH	8.67 (s)	
9-OH	4.02-4.07 (m)		9-OH	4.04 (s)	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O
OH
S3
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6.841
6.833
6.818
6.810
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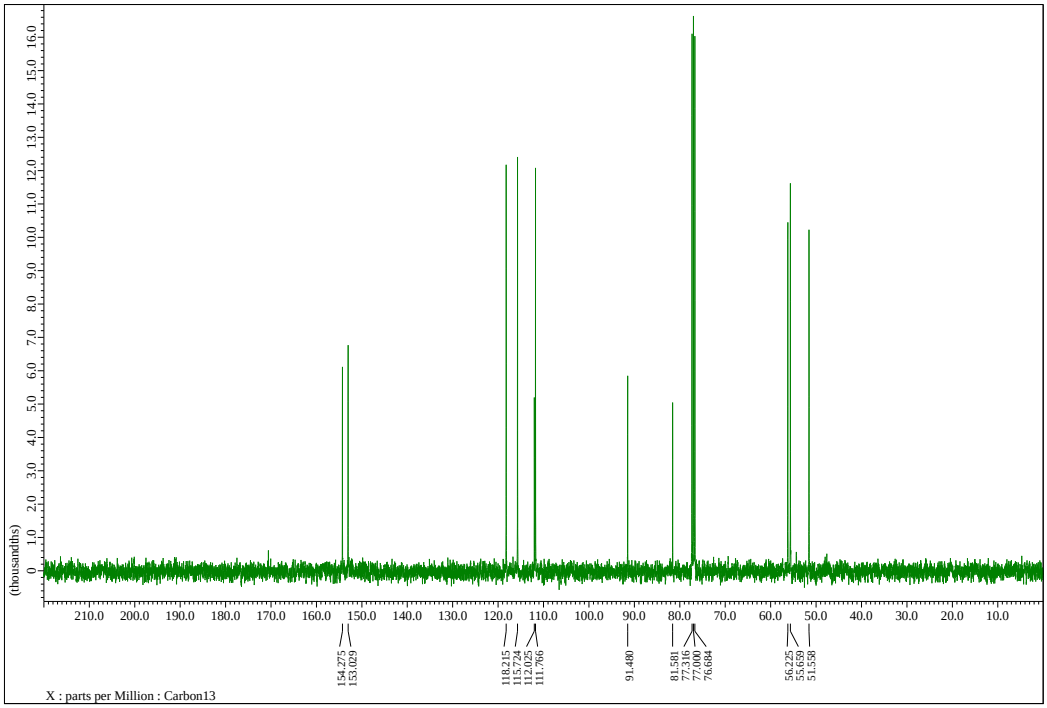
2.679
2.664
2.649
2.06
3.05
1.04


(thousandths)
X : parts per Million : Carbon13
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153.029
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115.724
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111.766
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77.000
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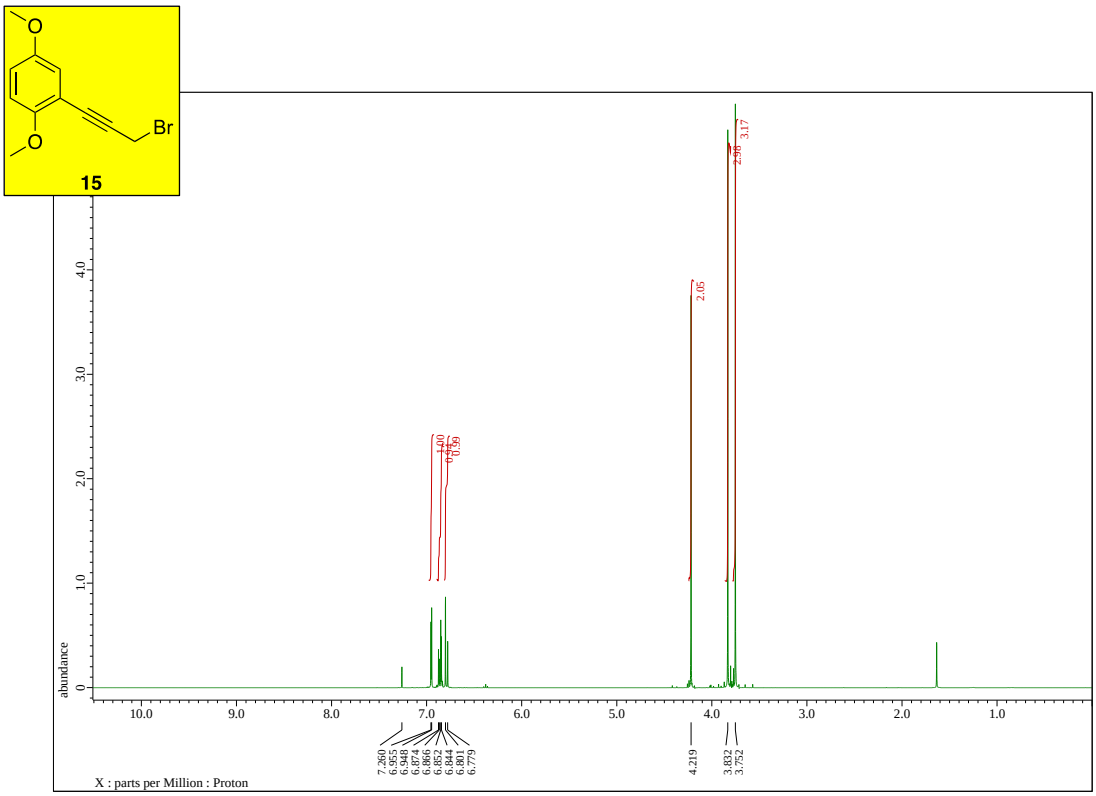
55.659
51.558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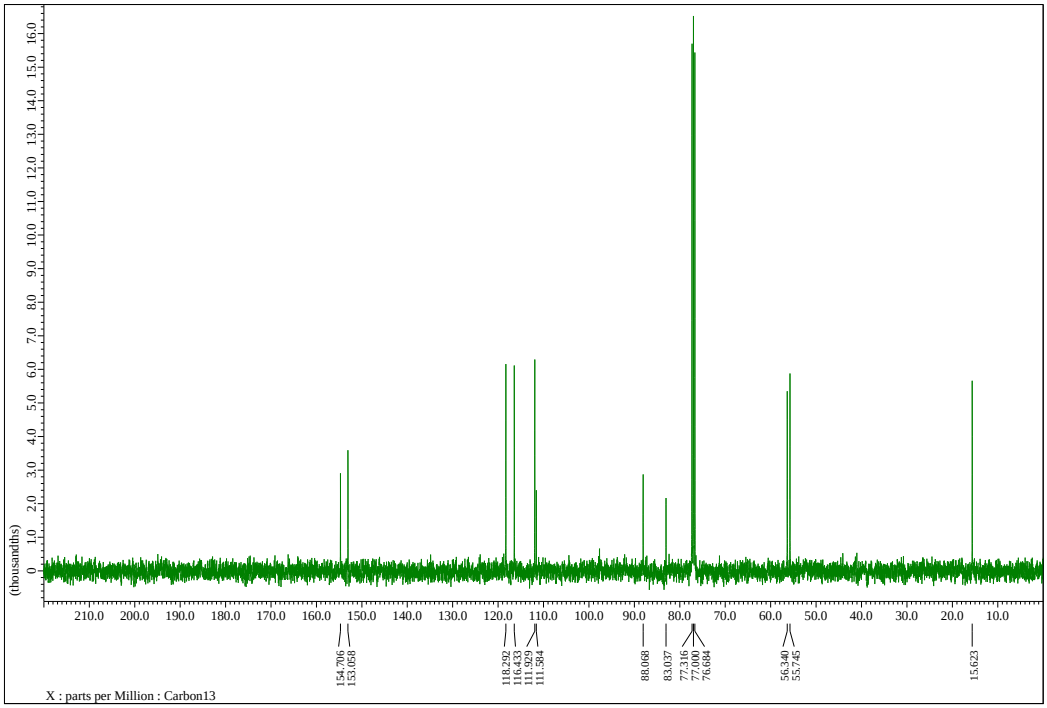
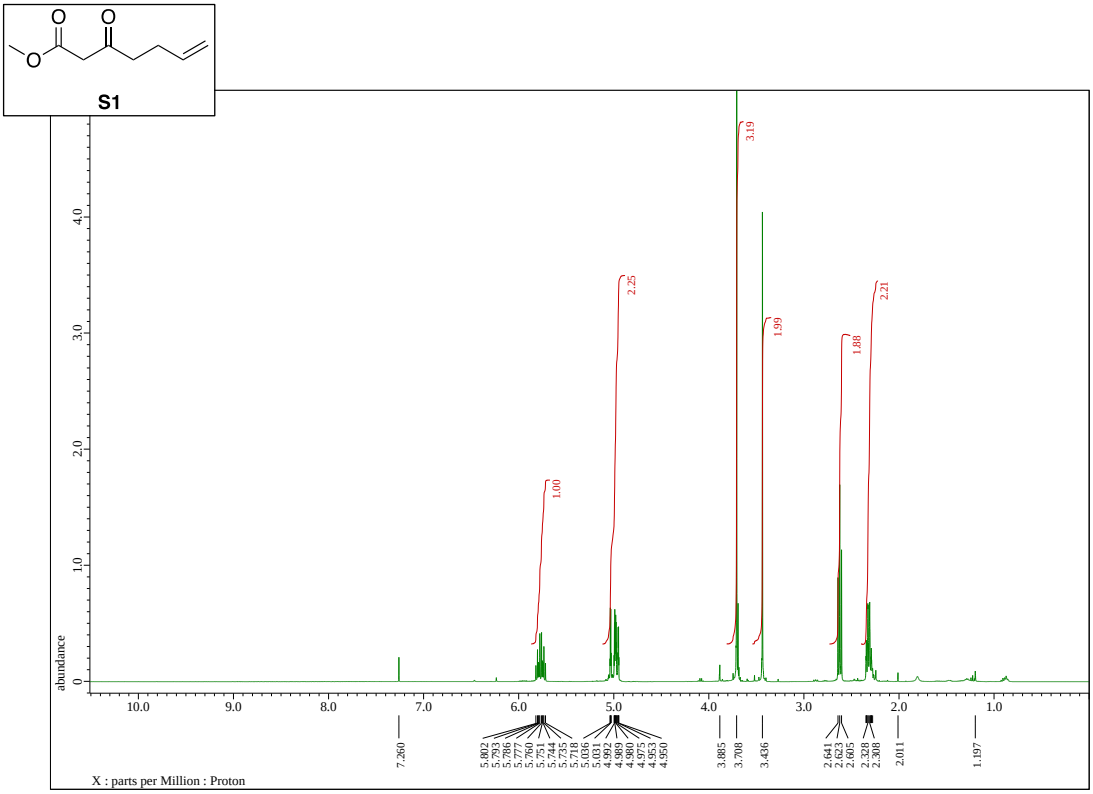
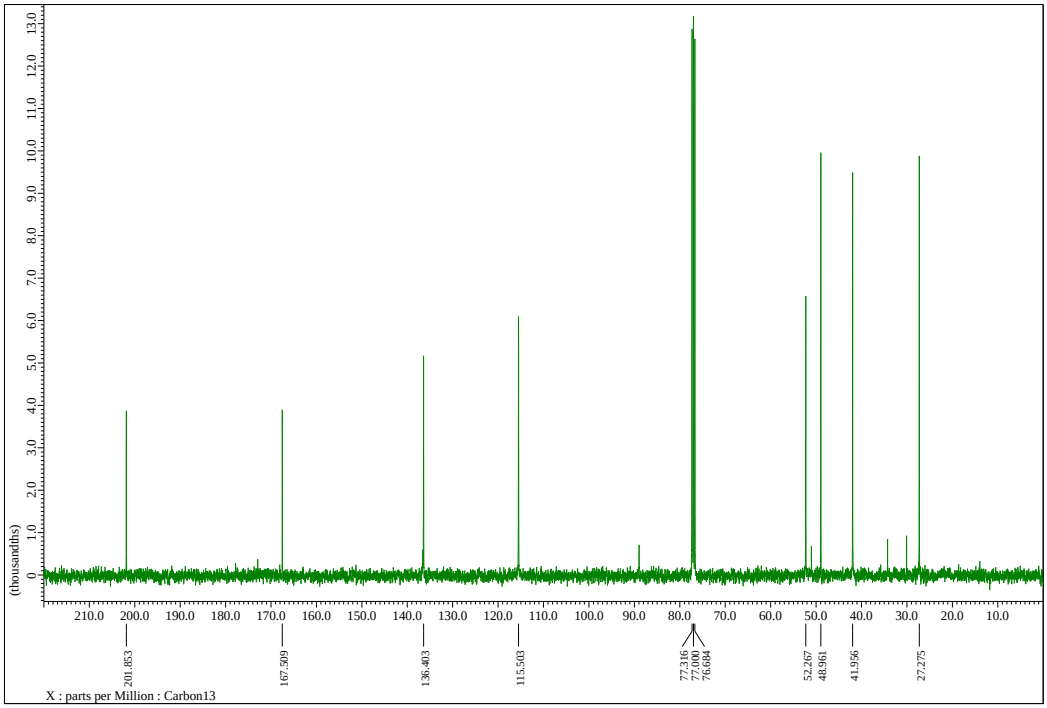
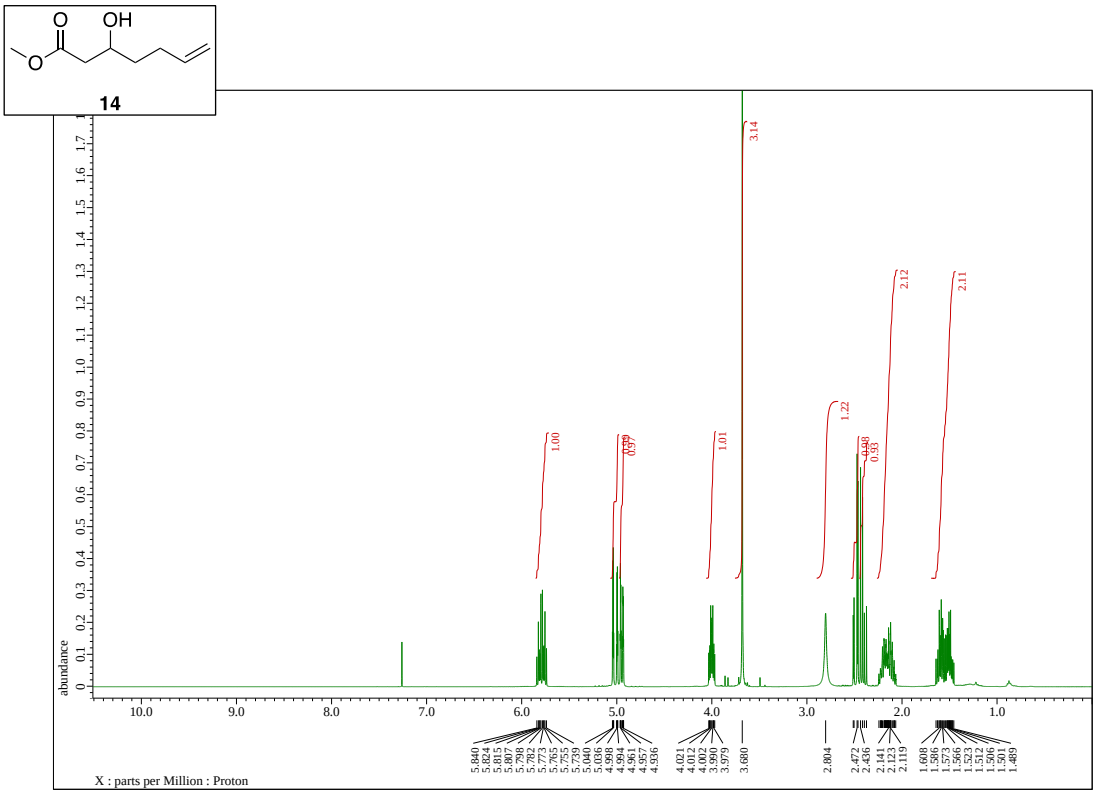
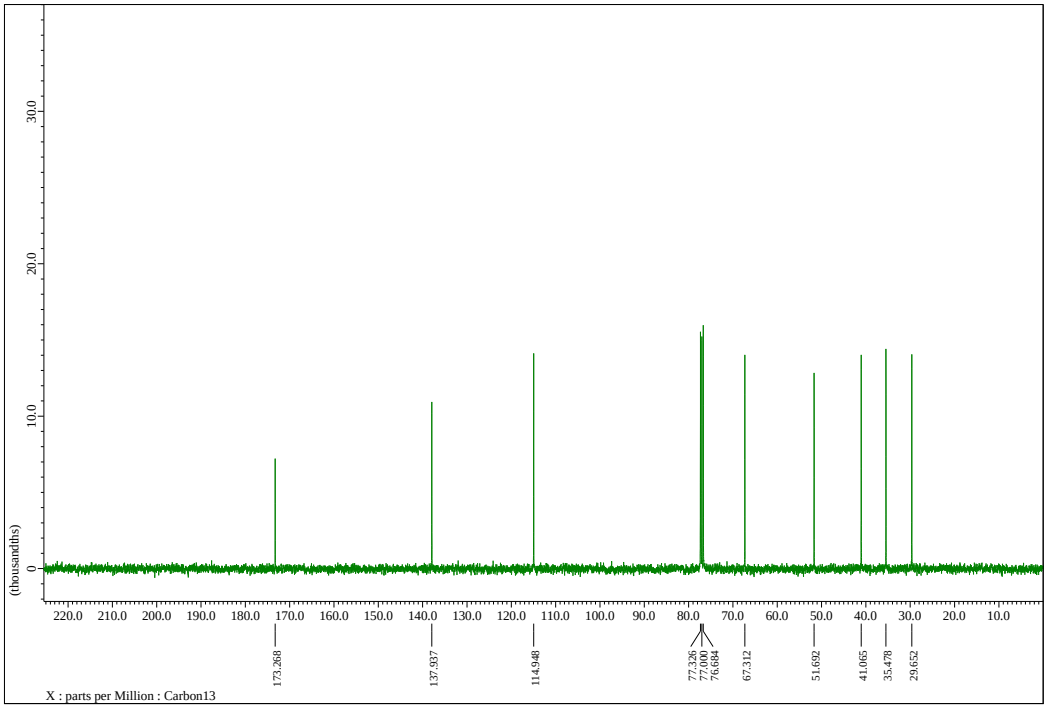
O
Br
15
abundance
X : parts per Million : Proton

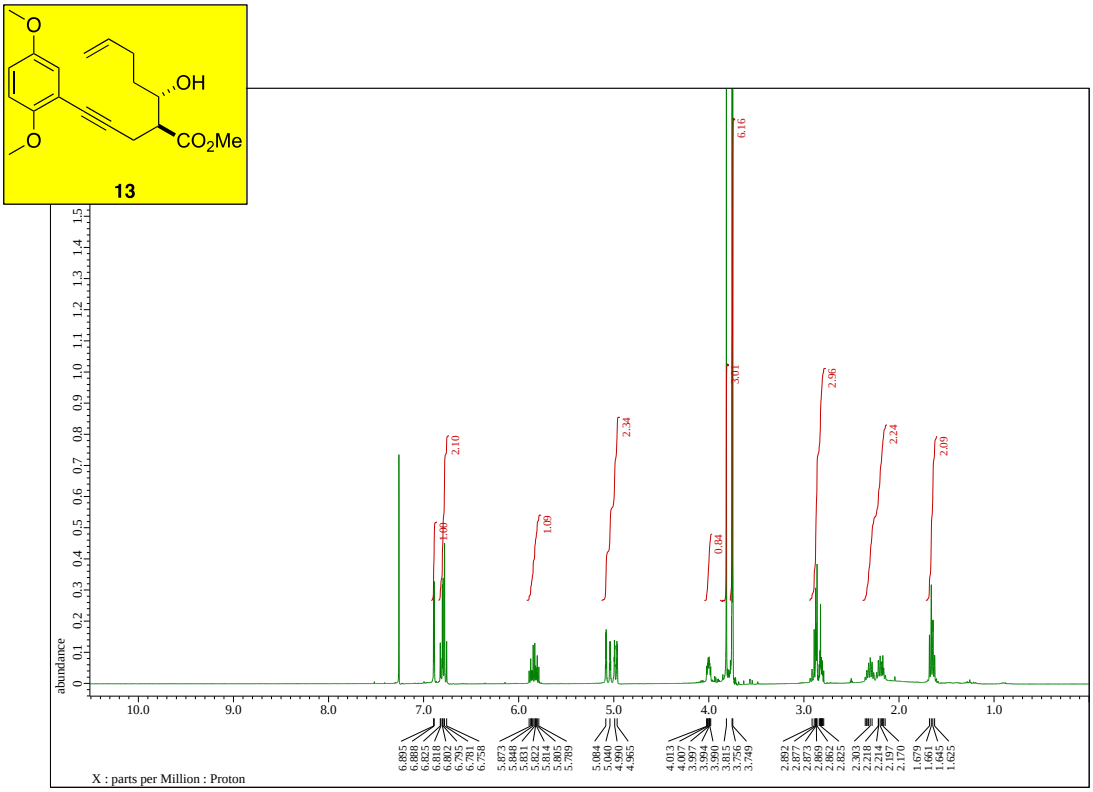

(thousandths)
X : parts per Million : Carbon13

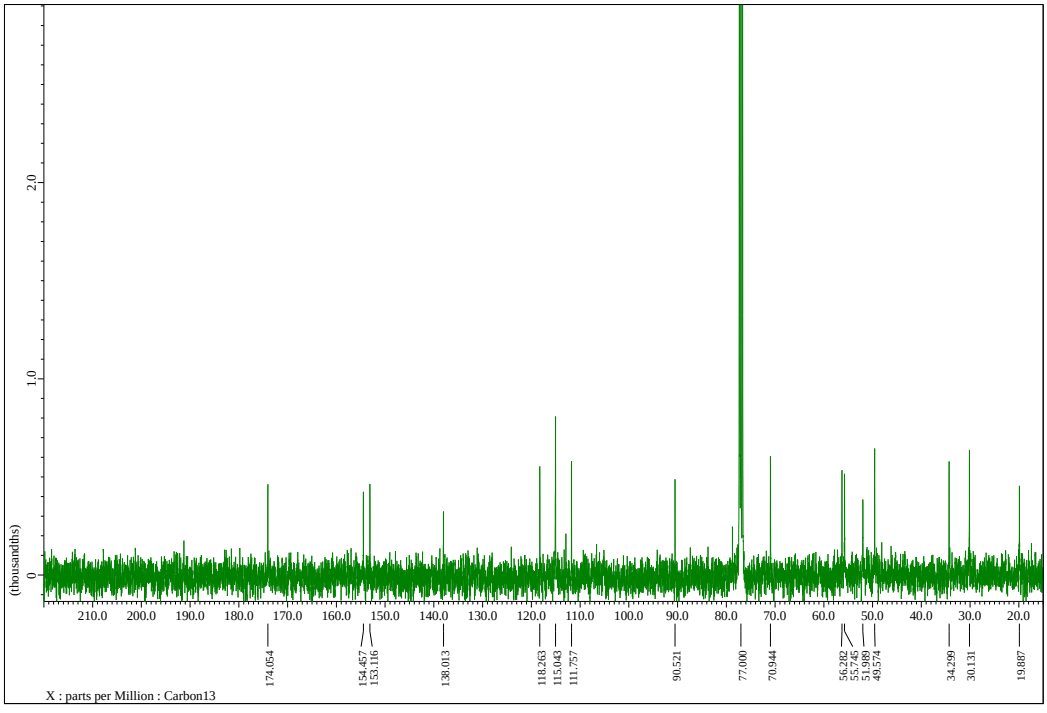

S1
abundance
X : parts per Million : Proton

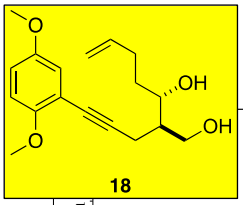

(thousandths)
X : parts per Million : Carbon13

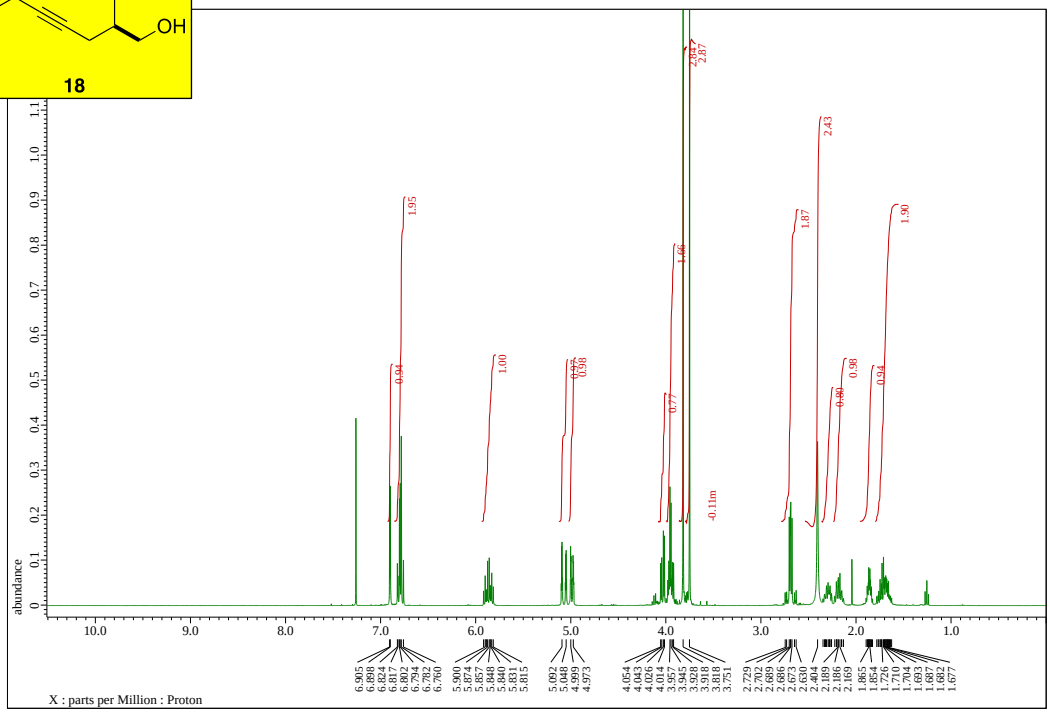

O
OH
O
14
abundance
X : parts per Million : Proton

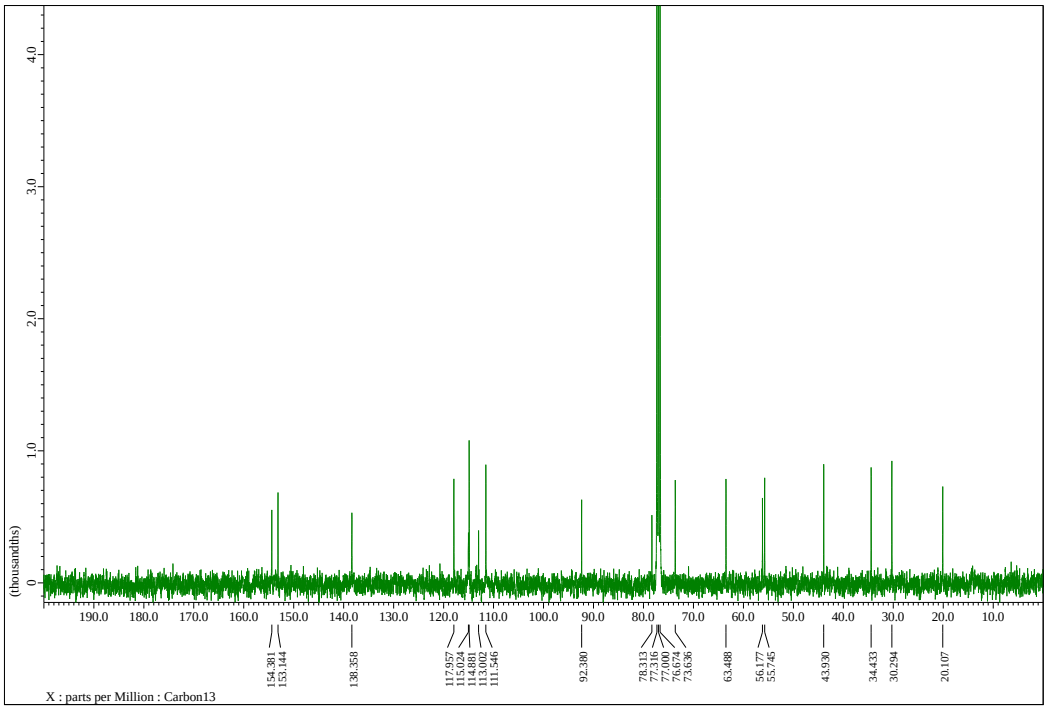

(thousandths)
X : parts per Million : Carbon13

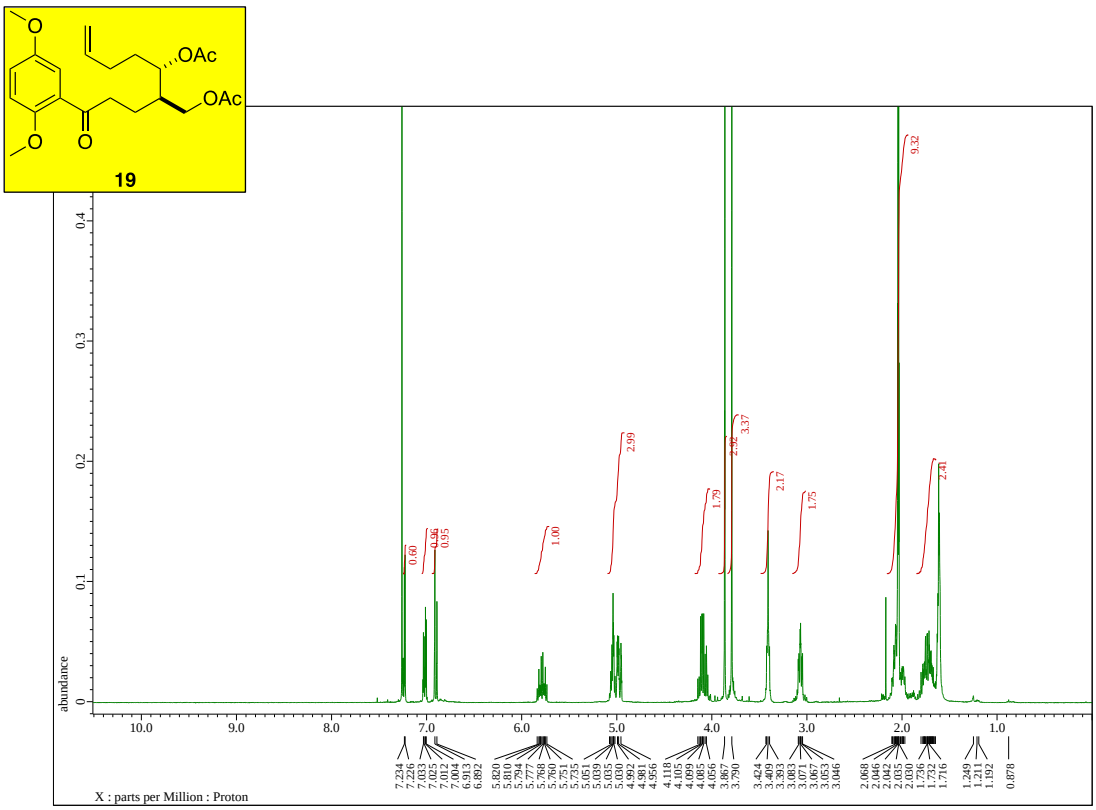

O
OH
O
CO2Me
13
abundance
X : parts per Million : Proton

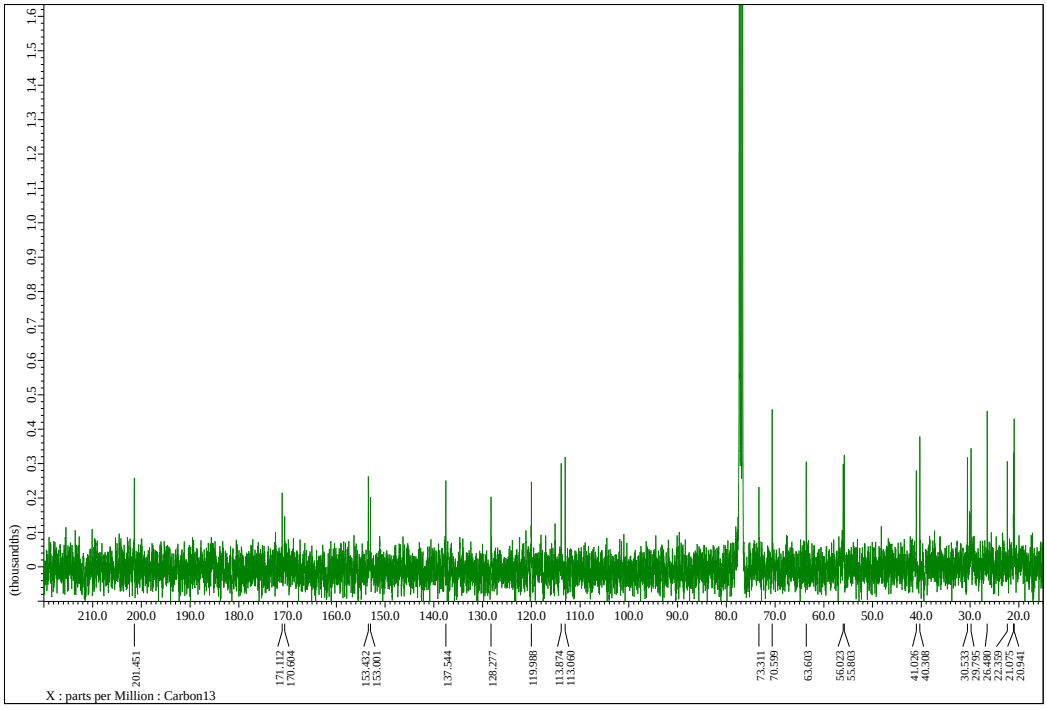

(thousandths)
X : parts per Million : Carbon13

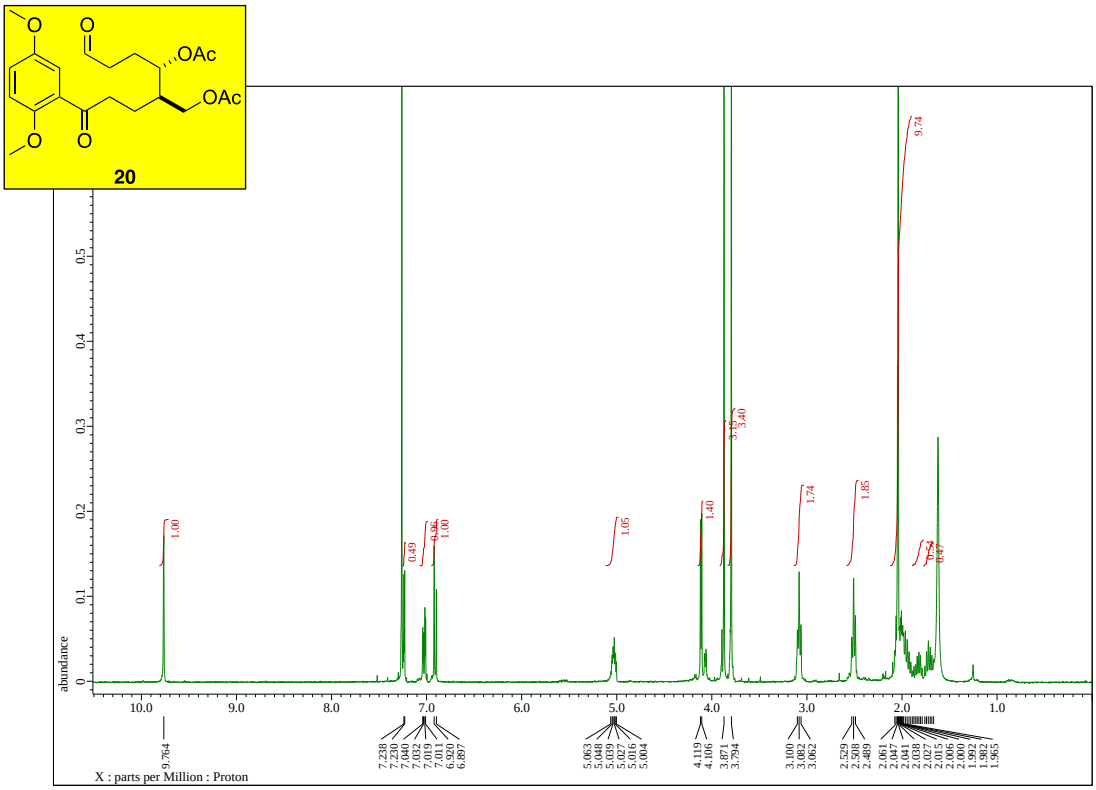

O
OH
OH
O
18

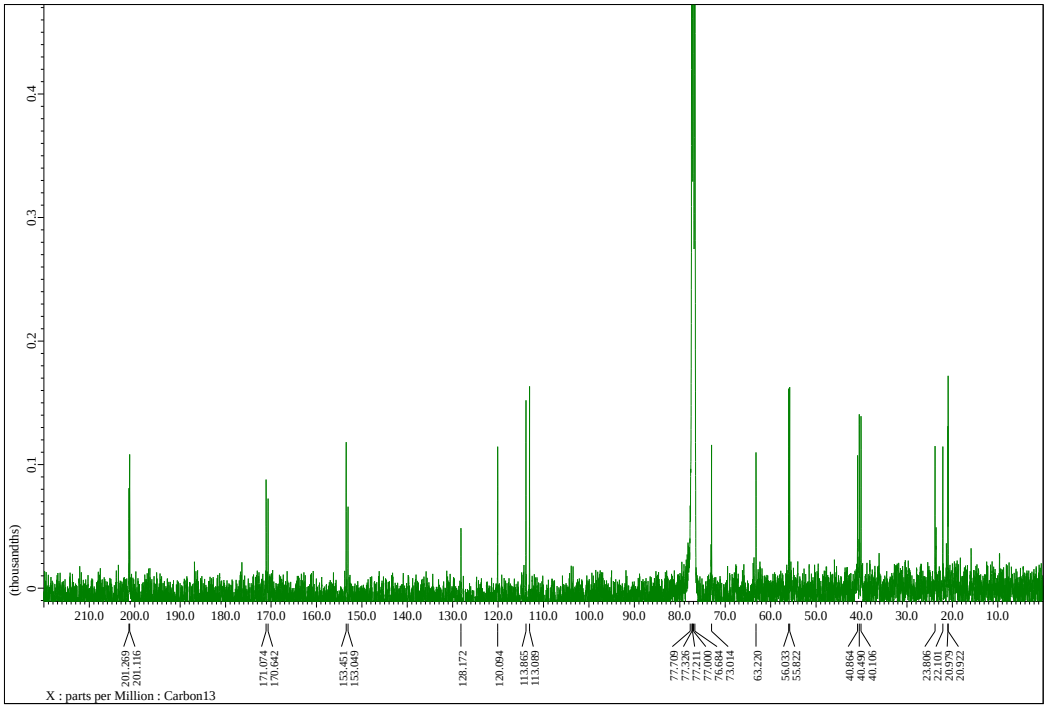

abundance
X : parts per Million : Proton

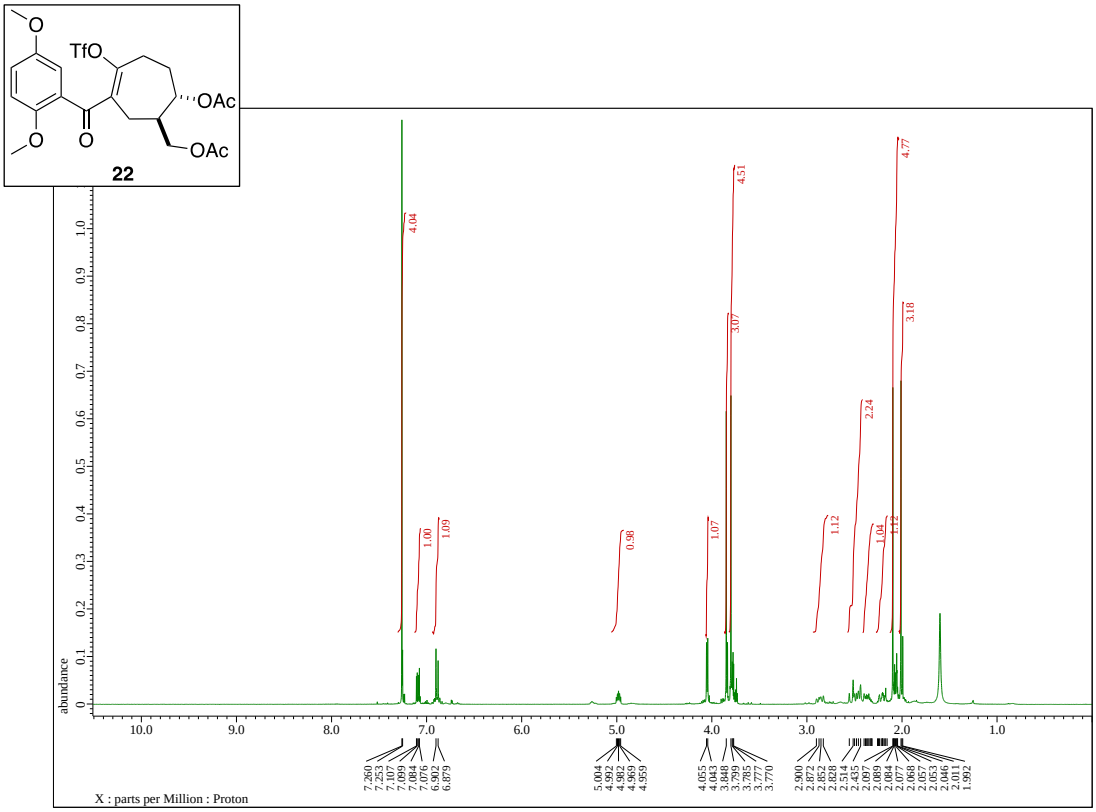

(thousandths)
X : parts per Million : Carbon13

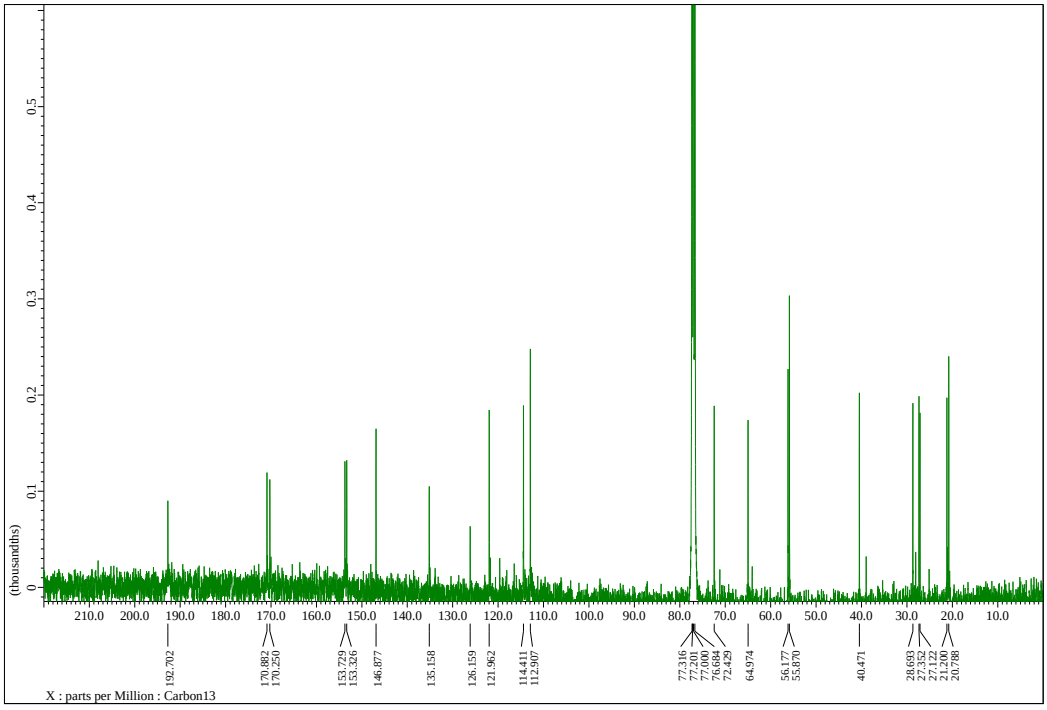

OAc
OAc
O
O
O
19
abundance
X : parts per Million : Proton

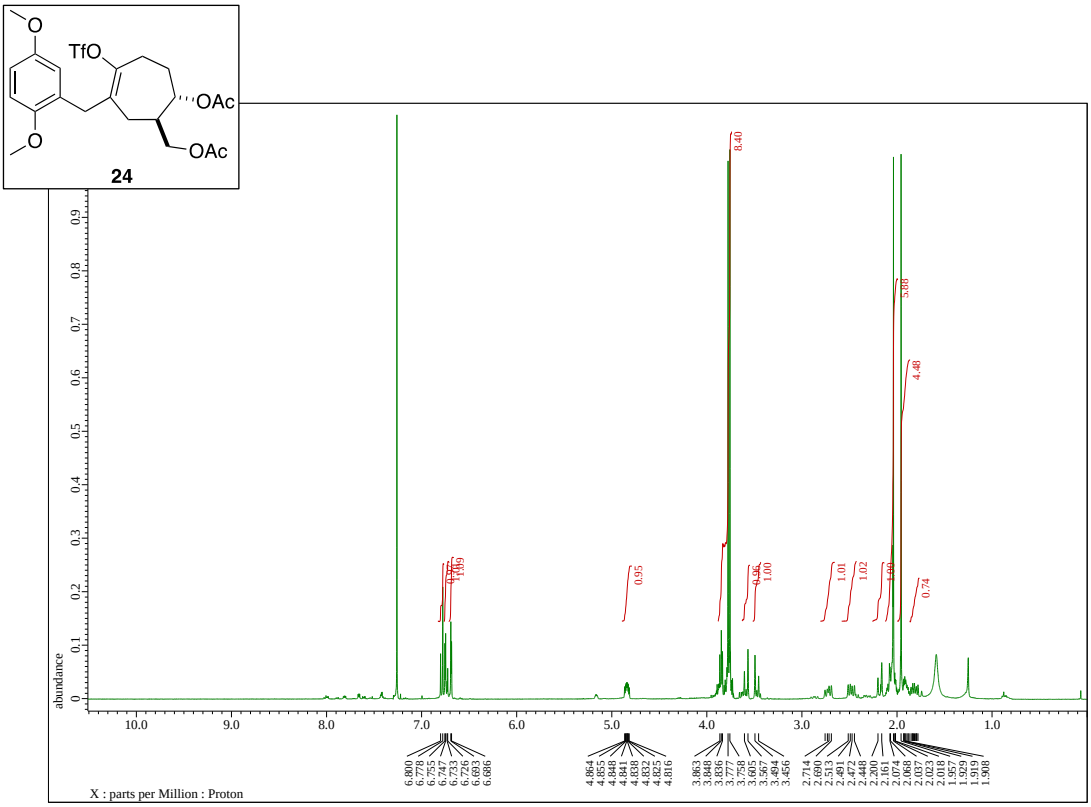

(thousandths)
X : parts per Million : Carbon13

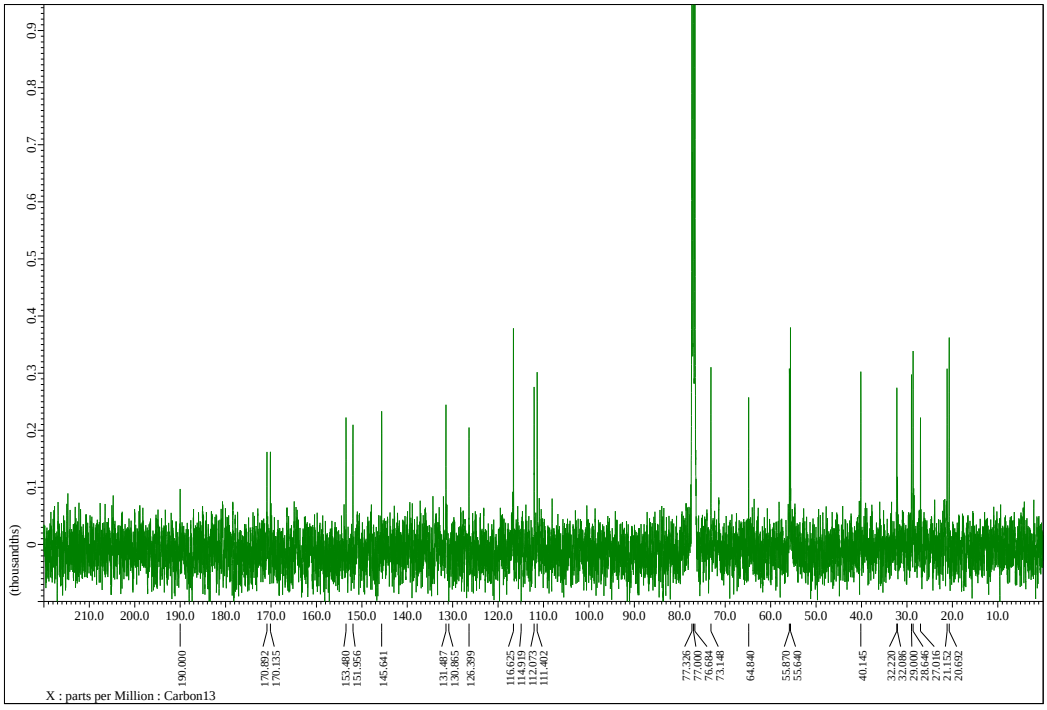

20
abundance
X : parts per Million : Proton

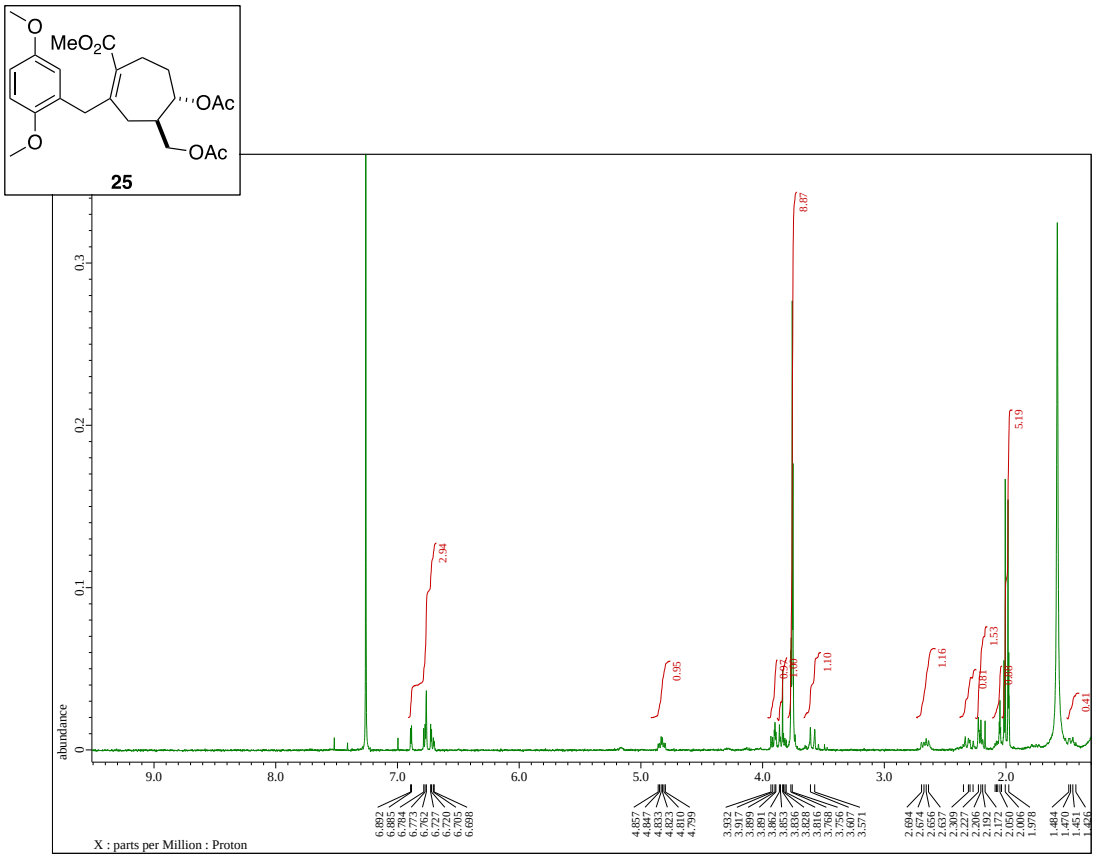

(thousandths)
X : parts per Million : Carbon13

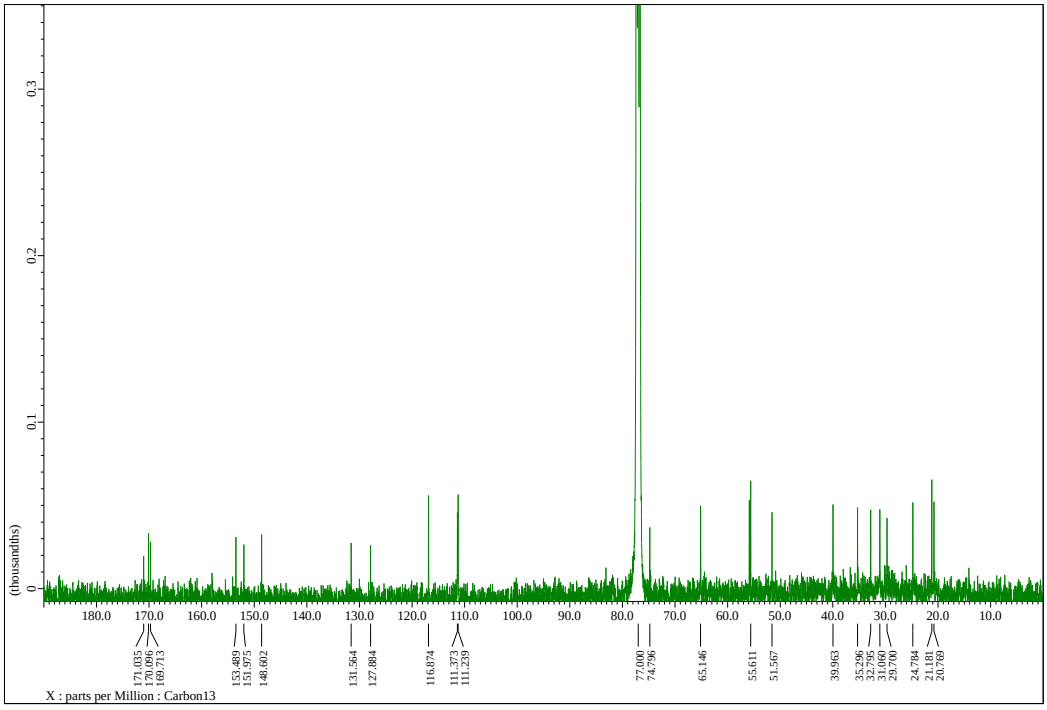

TfO
OAc
OAc
O
O
O
22
abundance
X : parts per Million : Proton

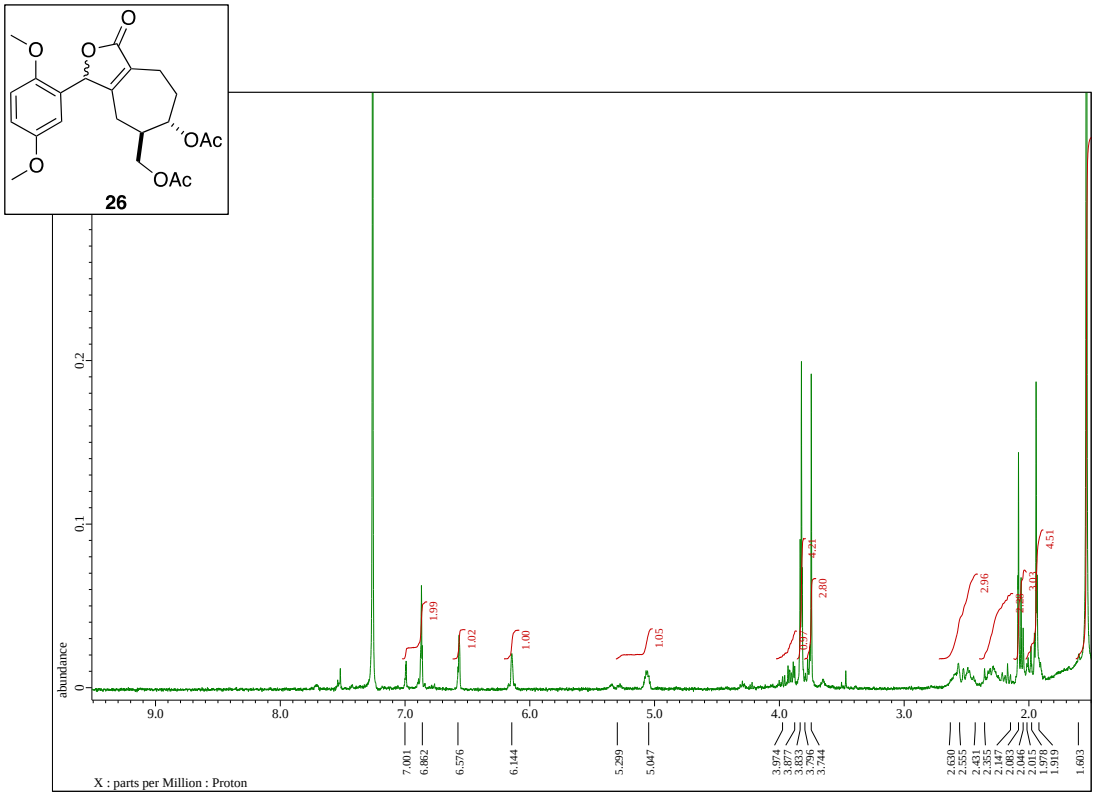

(thousandths)
X : parts per Million : Carbon13

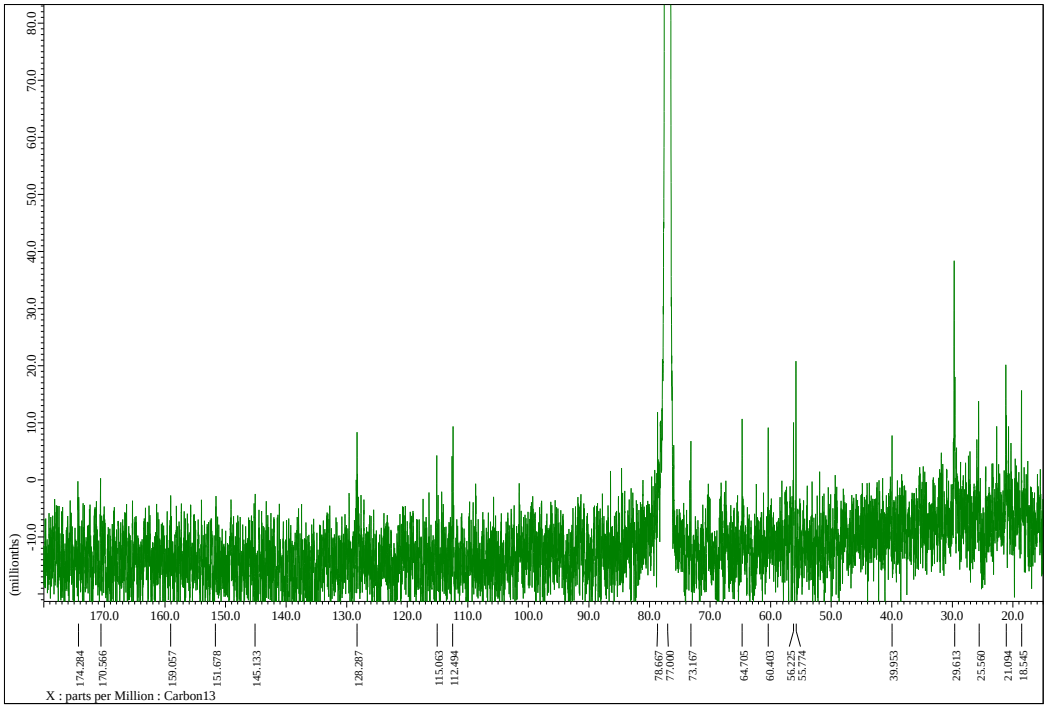

O
TfO
OAc
OAc
O
24
abundance
X : parts per Million : Proton

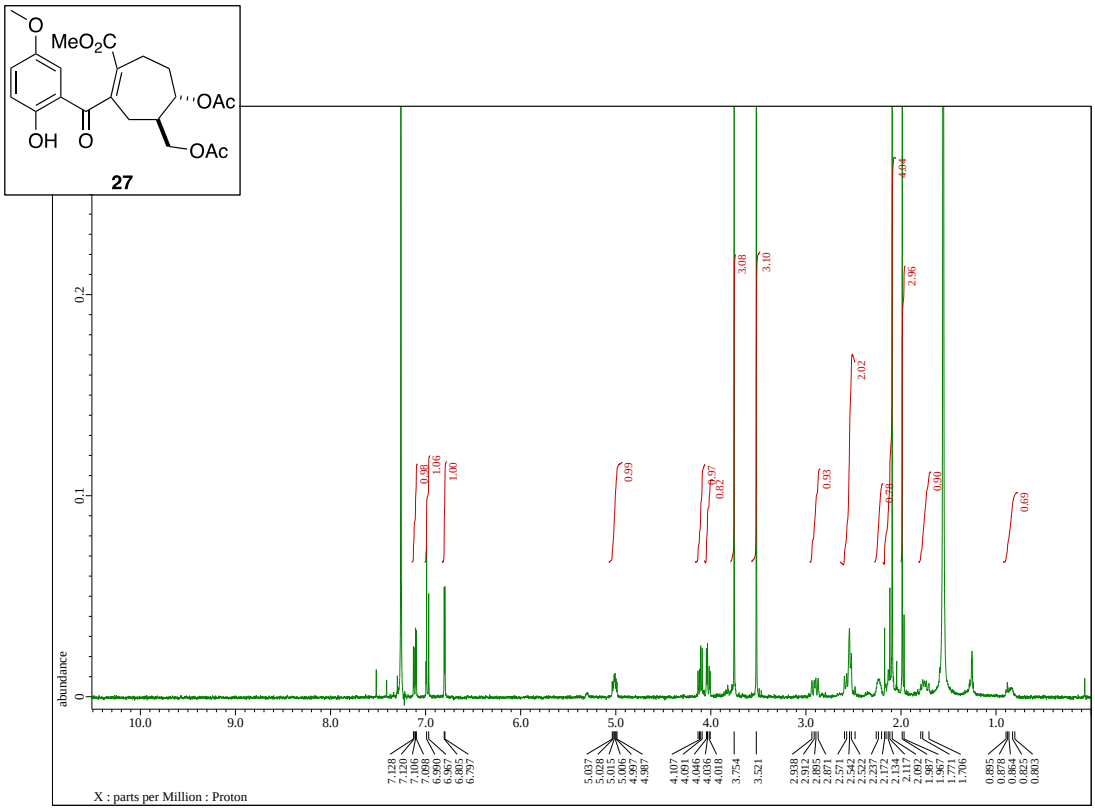

(thousandths)
X : parts per Million : Carbon13

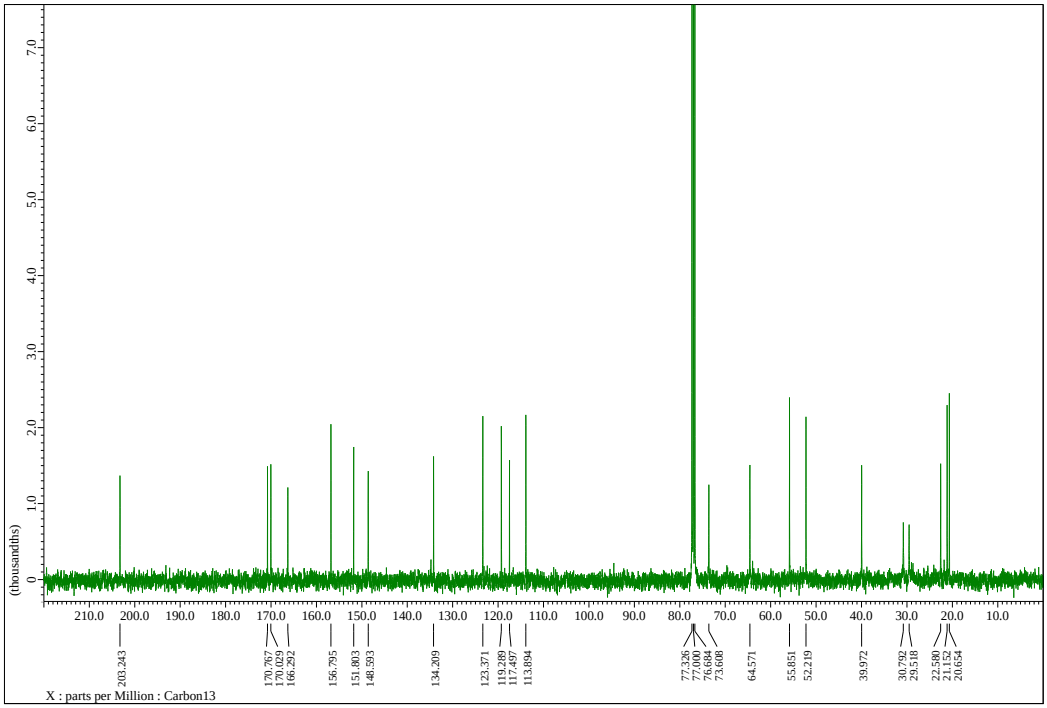

MeO2C
OAc
OAc
25
abundance
X : parts per Million : Proton

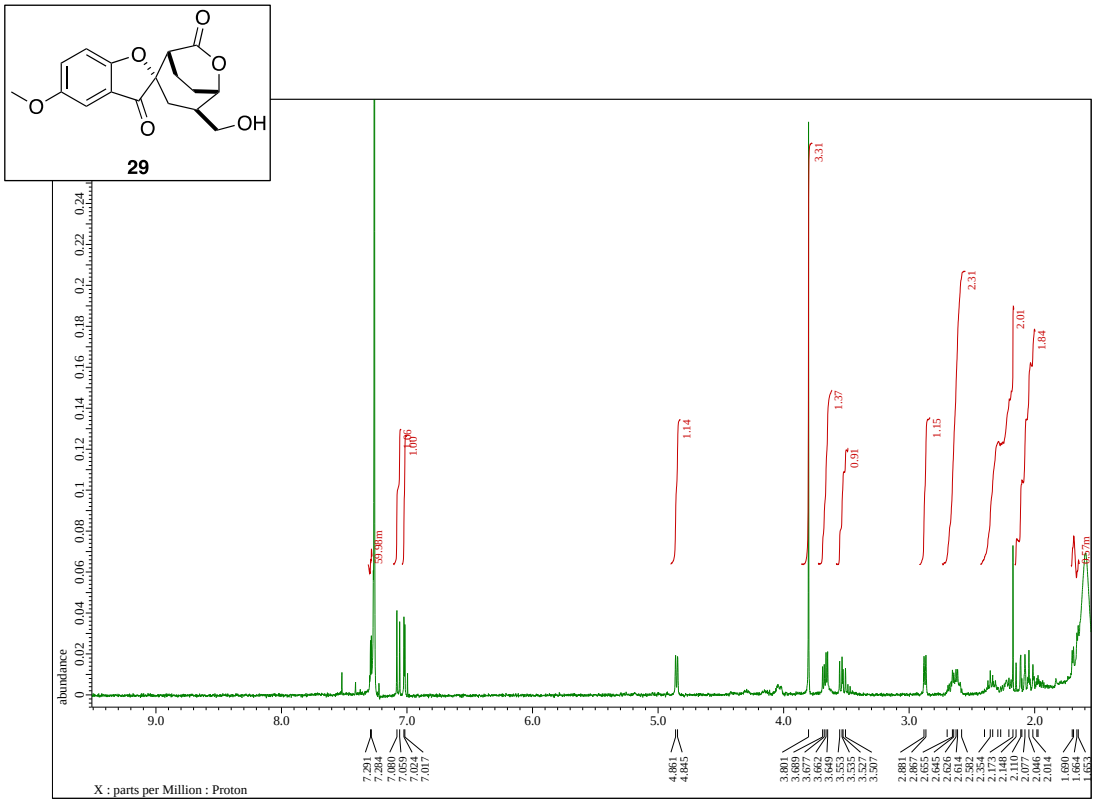

(thousandths)
X : parts per Million : Carbon13

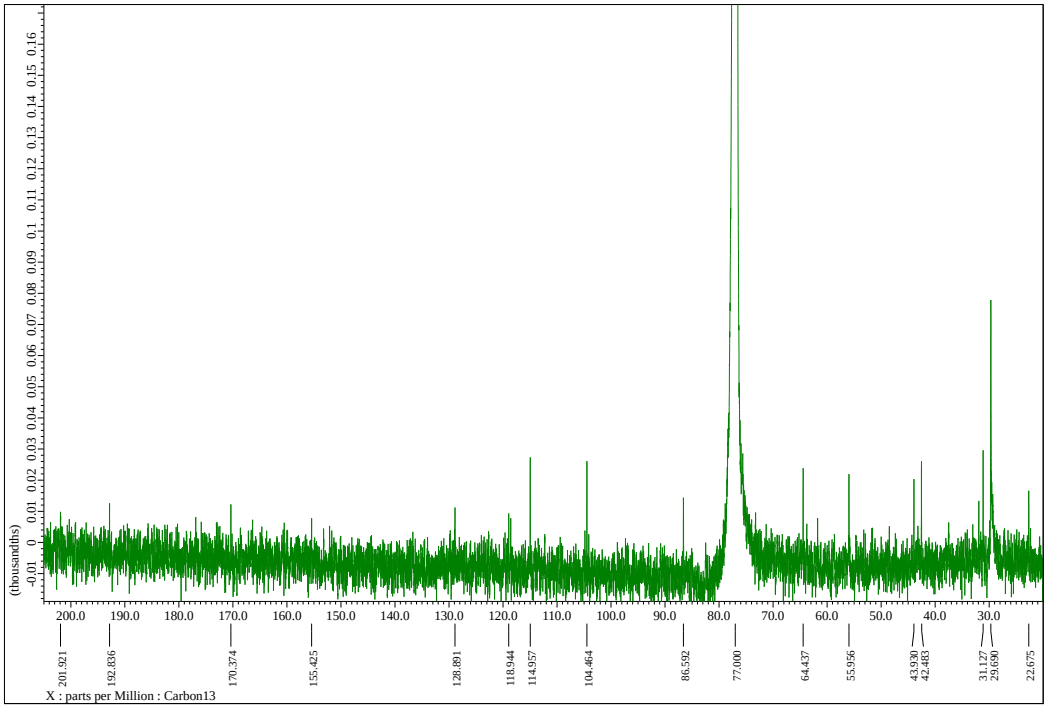

O
O
O
OAc
OAc
O
O
26
abundance
0
0.1
0.2
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.99
1.02
1.00
1.05
4.21
2.80
2.96
3.03
4.51
7.001
6.862
6.576
6.144
5.299
5.047
3.974
3.877
3.823
3.796
3.744
2.630
2.555
2.431
2.355
2.147
2.083
2.046
2.015
1.978
1.919
1.603
X : parts per Million : Proton


(millionths)
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
174.284
170.566
159.057
151.678
145.133
128.287
115.063
112.494
78.667
77.000
73.167
64.705
60.403
56.225
55.774
39.953
29.613
25.560
21.094
18.545
X : parts per Million : Carbon13

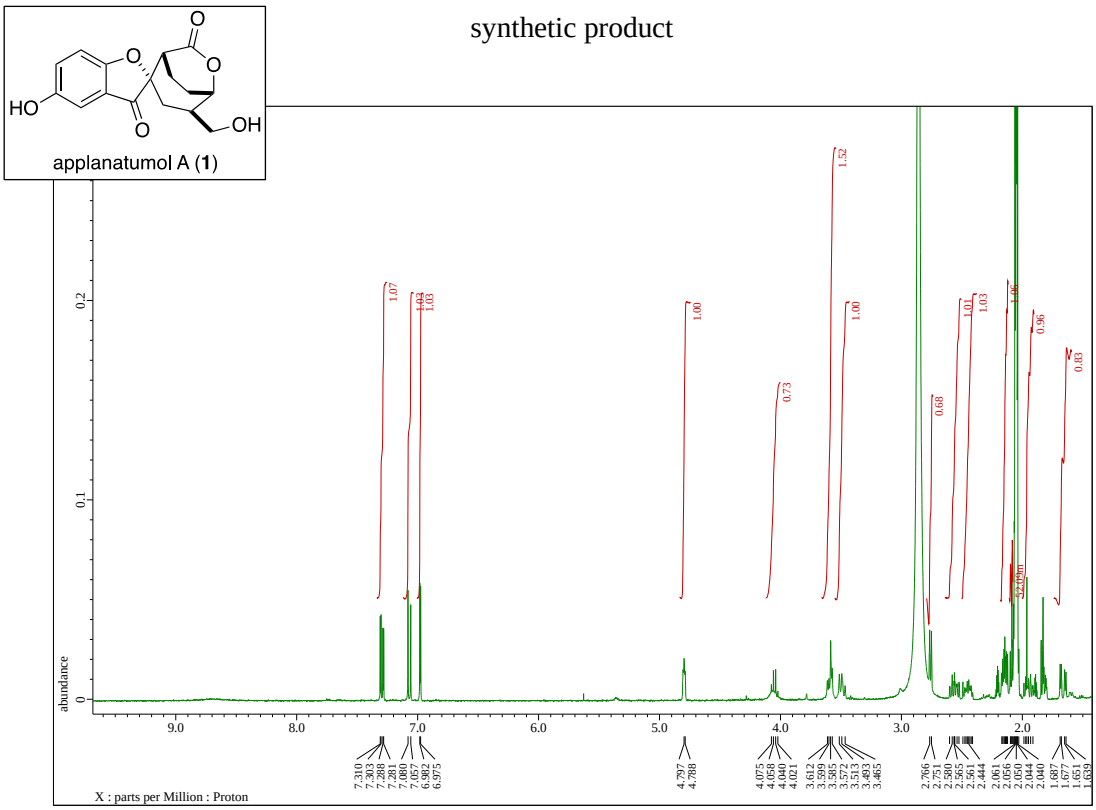

MeO2C
OAc
OAc
OH
O
O
27
abundance
X : parts per Million : Proton


(thousandths)
X : parts per Million : Carbon13

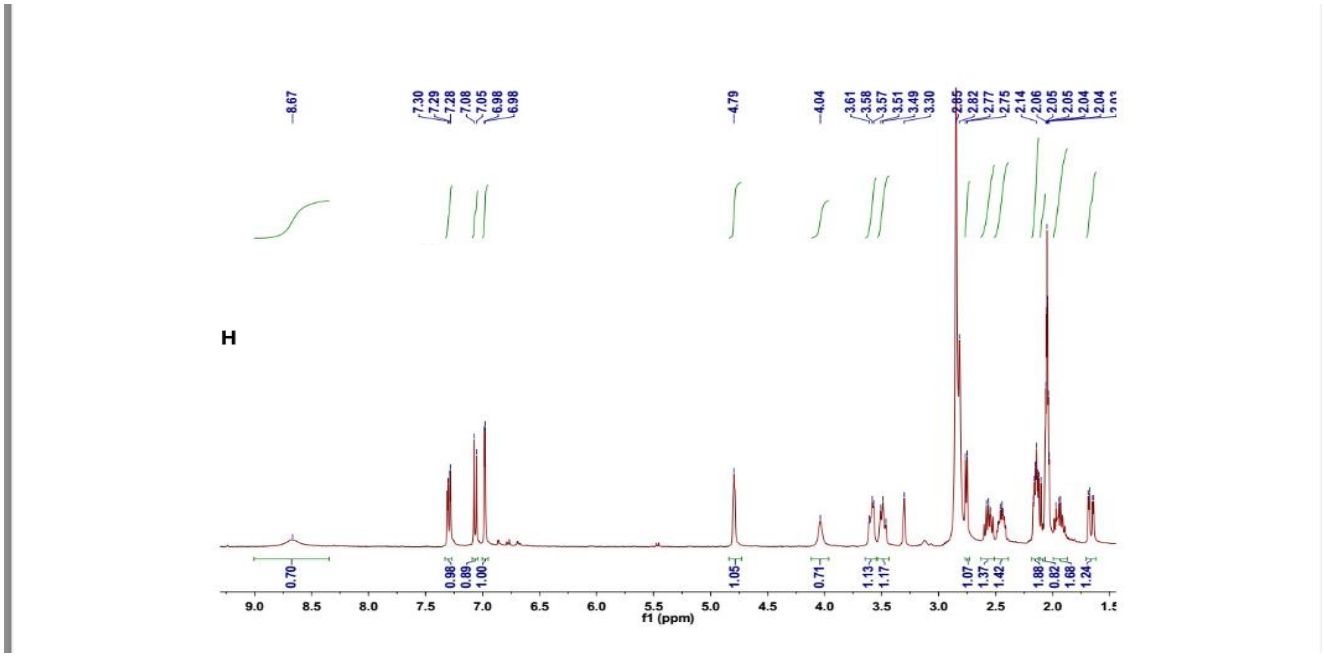

29
abundance
X : parts per Million : Proton


(thousandths)
X : parts per Million : Carbon13

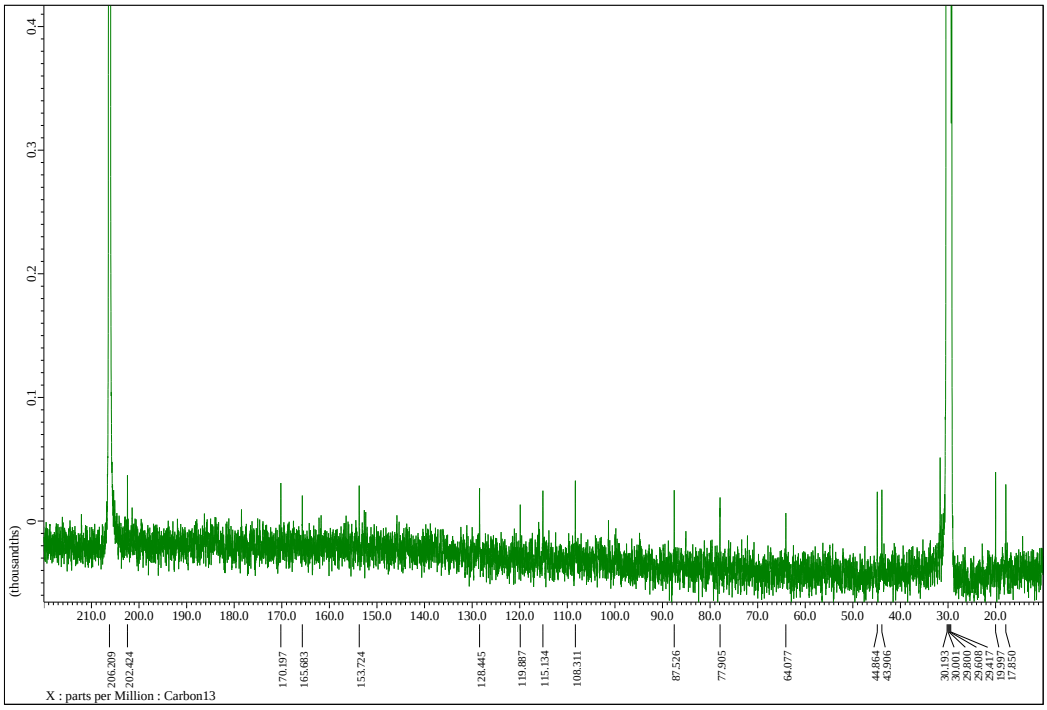
synthetic product



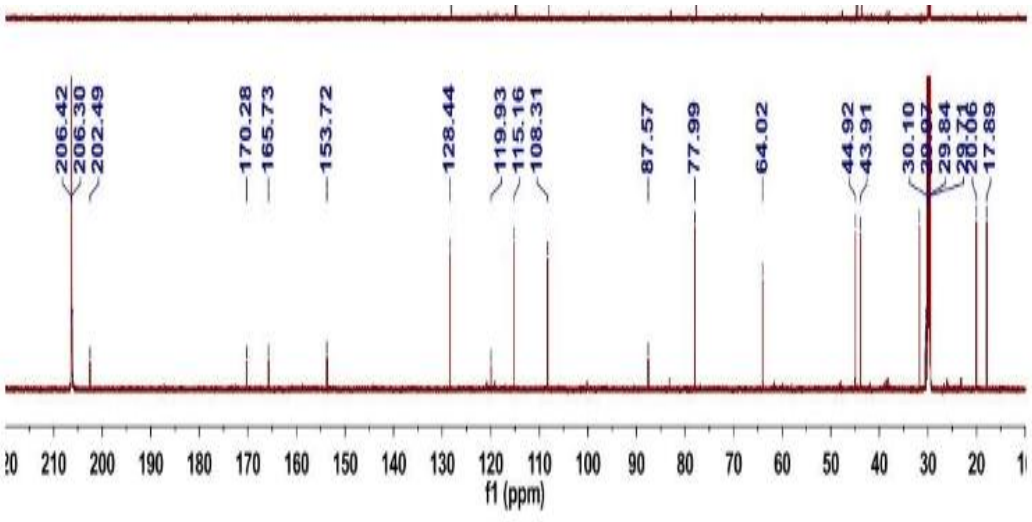
isolated product

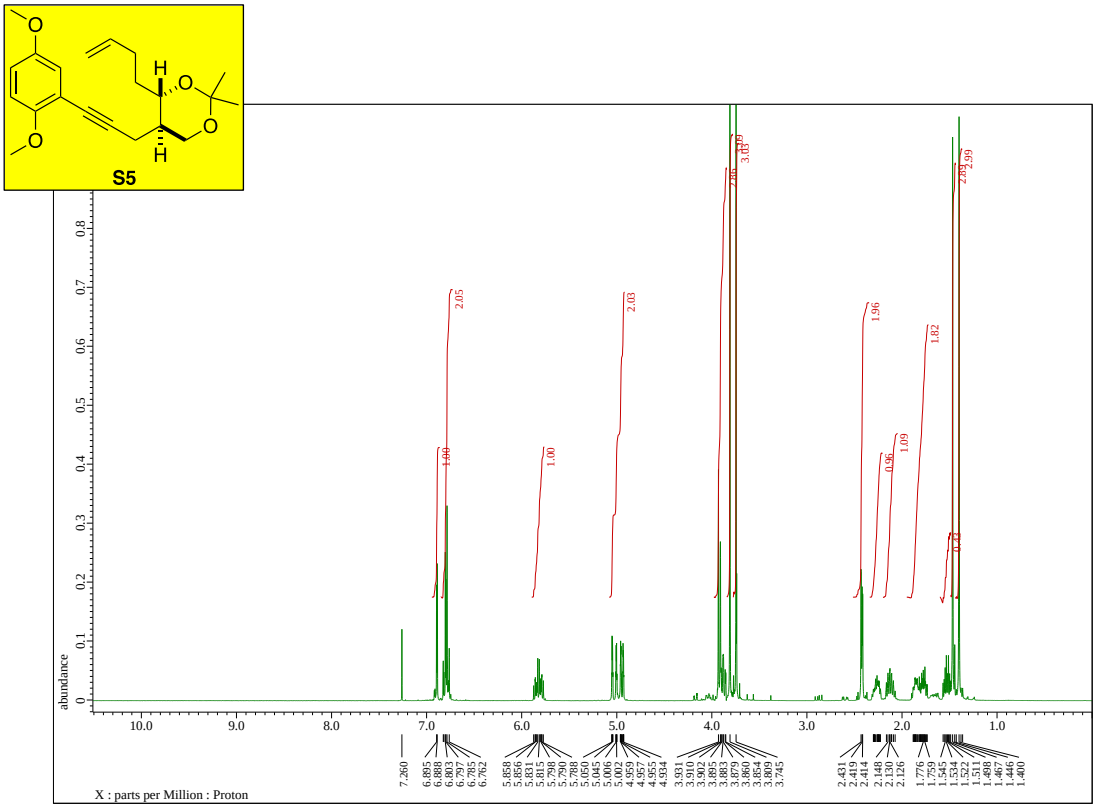


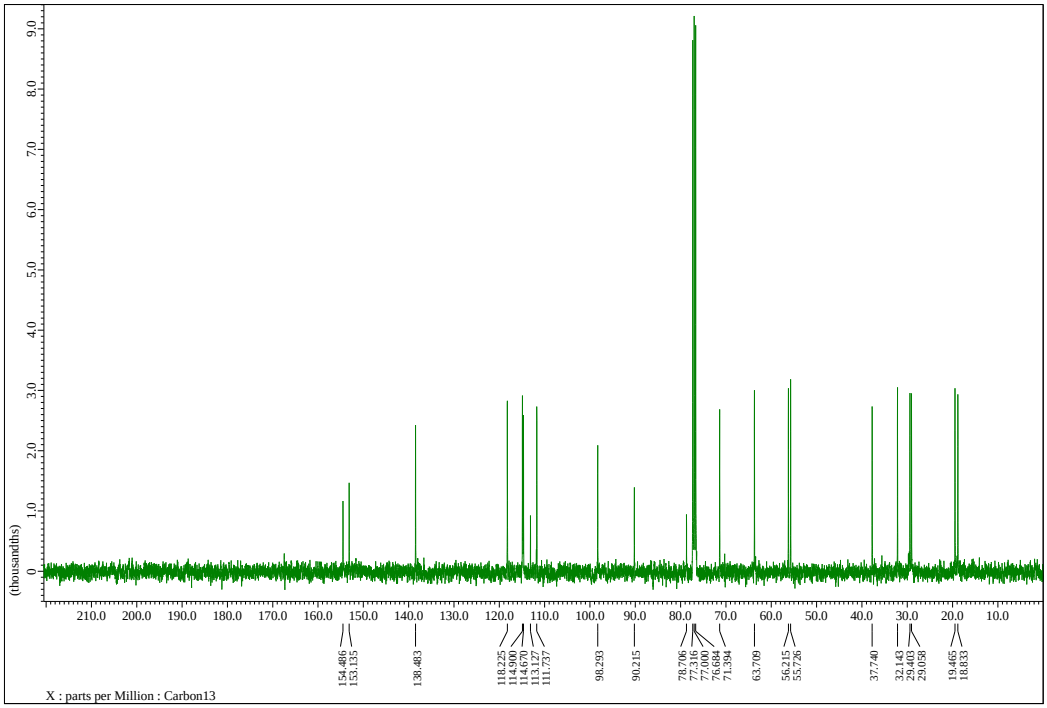
synthetic product



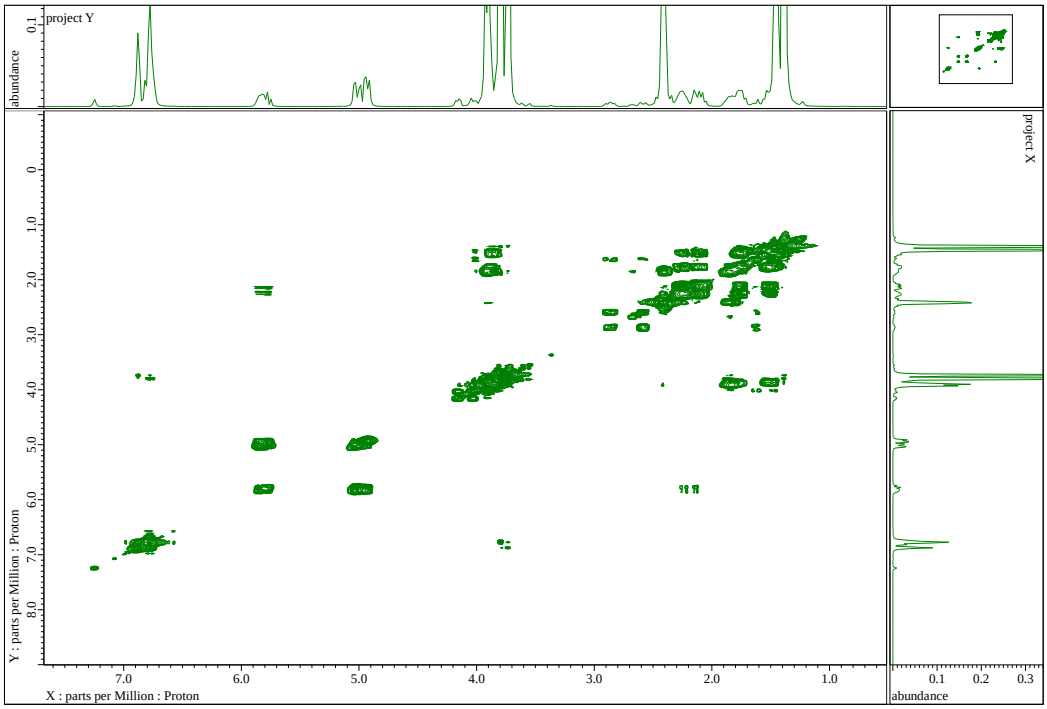
isolated product




S5
abundance
X : parts per Million : Proton


(thousandths)
X : parts per Million : Carbon13

COSY spectra of compound **S5**.



NOESY spectra of compound **S5**.