Total Synthesis and in Vitro Anti-tumor-Promoting Activities of Racemic Acetophenone Monomers from *Acronychia trifoliolata*

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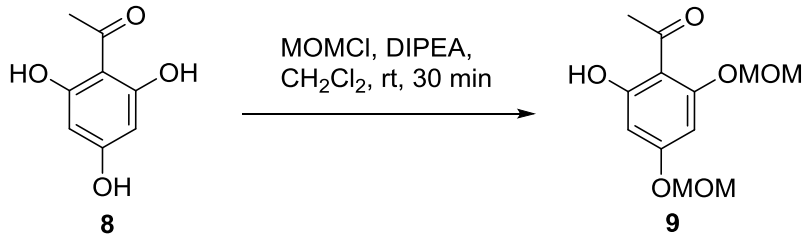
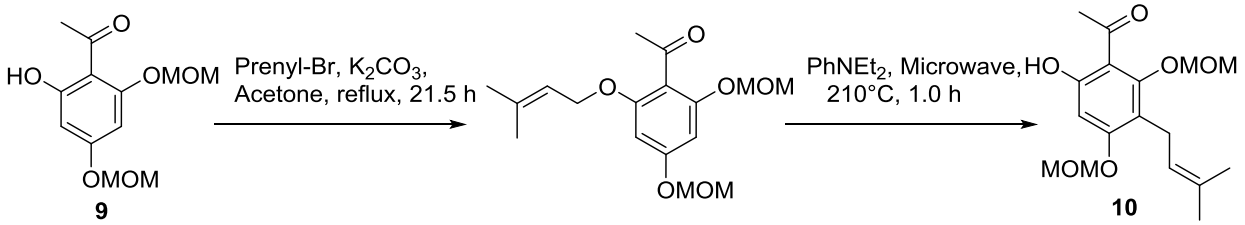
Preparations of 9–13 and 18



8 **9**

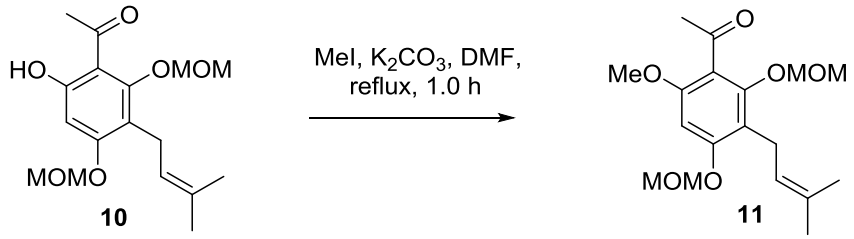
A solution of **8** (500.2 mg, 3.0 mmol) in CH_2Cl_2 (15 mL) was cooled to 0°C, and DIPEA (1.45 mL, 8.3 mmol) was slowly added. After 20 min, MOMCl (0.54 mL, 7.1 mmol) was added dropwise. The mixture was maintained at 0°C for 20 min, then brought room temperature. The reaction was quenched with water (20.0 mL), and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified with column chromatography on silica gel to obtain **9** (422.9 mg, 1.65 mmol, 73% brsm). ^{1}H-NMR (600 MHz, $CDCl_3$, δ): 13.73 (s, 1H, 2-O*H*), 6.27 (d, *J* = 2.4 Hz, 1H, 3-*H*), 6.25 (d, *J* = 2.4 Hz, 1H, 5-*H*), 5.26 (s, 2H, OCH_2OCH_3), 5.17 (s, 2H, OCH_2OCH_3), 3.52 (s, 3H, 6-OCH_2OCH_3), 3.47 (s, 3H, 4-OCH_2OCH_3), 2.66 (s, 3H, 1-COCH_3). The spectra of this product matched those of the known compound.[1]



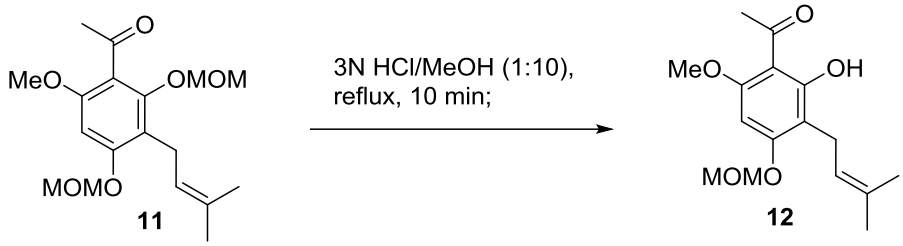
9 **10**

1-[2,4-Bis(methoxymethoxy)-6-(3-methylbut-2-enyloxy)phenyl]ethanone. To a solution of **9** (234.2 mg, 0.91 mmol) and K_2CO_3 (503.2 mg, 3.64 mmol) in acetone (10 mL) was added prenylbromide (0.16 mL, 1.36 mmol) and refluxed for 21.5 h under N_2. The mixture was cooled to room temperature, filtered with EtOAc, and concentrated *in vacuo*. The residue was chromatographed on silica gel with EtOAc–hexane (1:2) to afford *O*-prenyl compound (272.4 mg, 92%) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (d, 1H, *J* = 1.6 Hz), 6.31 (d, 1H, *J* = 2.0 Hz), 5.42–5.38 (m, 1H), 5.15 (s, 2H), 5.13 (s, 2H), 4.49 (d, 2H, *J* = 6.4 Hz), 3.48 (s, 3H), 3.46 (s, 3H), 2.47(s, 3H), 1.76 (s, 3H), 1.71 (s, 3H). The spectra of this product matched those of the known compound.[1]

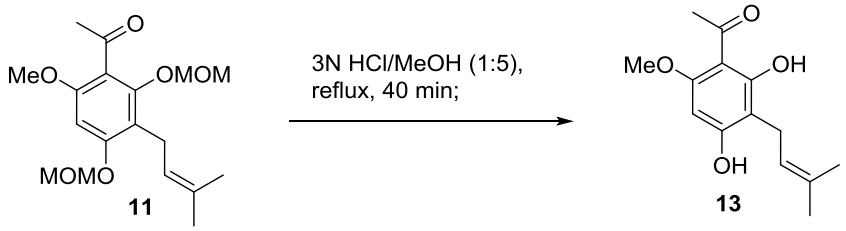
1-(6-Hydroxy-2,4-bis(methoxymethoxy)-3-(3-methylbut-2-enyl)phenyl)ethanone (10). A solution of 1-[2,4-bis(methoxymethoxy)-6-(3-methylbut-2-enyloxy)phenyl]ethanone (84.9 mg, 0.26 mmol) in *N*,*N*-diethylaniline (0.5 mL) in a vessel suited for microwave irradiation and irradiated at 210 °C for 1.0 h. The mixture was washed with aqueous 10% HCl, water, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel with EtOAc–hexane (1:20) to afford the target **10** (67.2 mg, 79%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.9 (1H, s), 6.47 (1H, s), 5.22 (2H, s), 5.16–5.14 (1H, m), 4.96 (2H, s), 3.52 (3H, s), 3.46 (3H, s), 3.31 (2H, d, *J* = 7.2 Hz), 2.70 (3H, s), 1.76 (3H, s), 1.71 (3H, s). The spectra of this product matched those of the known compound.[1]



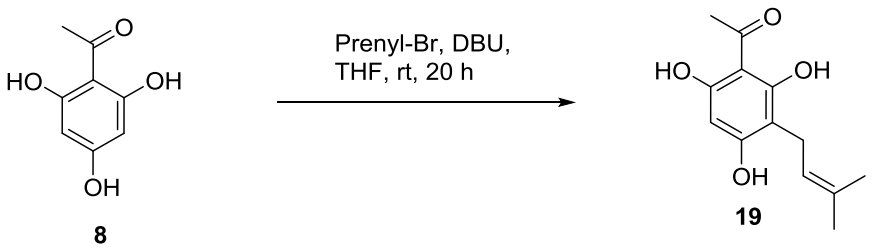
1-(6-Methoxy-2,4-bis(methoxymethoxy)-3-(3-methylbut-2-enyl)phenyl)ethanone (11). To a solution of **10** (96.4 mg, 0.30 mmol) in anhydrous DMF (6.0 mL) were added K_2CO_3 (205 mg, 1.48 mmol) and Iodomethane (0.05 mL, 0.75 mmol). The mixture was refluxed for 1.0 h under N_2. The mixture was cooled to room temperature, quenched with water (10 mL) and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel with EtOAc–hexane (1:5) to afford the target compound **11** (96.5 mg, 96%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (1H, s), 5.20 (2H, s), 5.15–5.12 (1H, m), 4.90 (2H, s), 3.80 (3H, s), 3.49 (3H, s), 3.47 (3H, s), 3.30 (2H, d, J = 6.4 Hz), 2.50 (3H, s), 1.74 (3H, s), 1.65 (3H, s). The spectra of this product matched those of the known compound.[1]



1-(2-Hydroxy-6-methoxy-4-(methoxymethoxy)-3-(3-methylbut-2-enyl)phenyl)ethanone (**12**). To a solution of **11** (88.8 mg, 0.26 mmol) in anhydrous MeOH (6.0 mL) was added 3N HCl (0.6 mL) and refluxed for 10 min under N_2. The mixture was cooled to room temperature, quenched with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel with EtOAc–hexane (1:6) to afford the target **12** (71.2 mg, 92%) as pale yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 14.0 (1H, s), 6.19 (1H, s), 5.25 (2H, s), 5.20–5.18 (1H, m), 3.86 (3H, s), 3.48 (3H, s), 3.29 (2H, d, J = 6.6 Hz), 2.61 (3H, s), 1.78 (3H, s), 1.66 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.6, 163.7, 161.4, 160.9, 131.3, 122.7, 110.6, 106.6, 93.9, 88.5, 56.2, 55.4, 33.2, 25.8, 21.5, 17.8; HRMS (FAB) *m/z* 295.1541 $[M + H]^+$ (calcd for $C_{16}H_{23}O_5$, 295.1545). The spectra of this product matched those of the known compound.[2]



1-[2,4-Dihydroxy-6-methoxy-3-(3-methylbut-2-enyl)phenyl]ethanone (13). To a solution of **11** (95.4 mg, 0.28 mmol) in anhydrous MeOH 5.5 mL was added 3N HCl (1.1 mL) and refluxed for 40 min under N_2. The mixture was cooled to room temperature, quenched with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel with EtOAc–hexane (1:6) to afford the target **13** (51.8 mg, 73%) as colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.4 (1H, s), 6.14 (1H, s), 5.90 (1H, s), 5.30–5.26 (1H, m), 3.84 (3H, s), 3.37 (2H, d, *J* = 7.6 Hz), 2.61 (3H, s), 1.82 (3H, s), 1.77 (3H, s). The spectra of this product matched those of the known compound. [2]



8 **19**

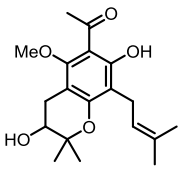
2,4,6-Trihydroxy-3-prenylacetophenone (**19**). To a solution of **8** (106.4 mg, 0.63 mmol) in anhydrous THF (4.0 mL) were added DBU (0.08 mL, 0.54 mmol) and prenylbromide (0.07 mL, 0.60 mmol). The whole was stirred at room temperature for 18 h under N_2. After addition of saturated NH_4Cl water (15.0 mL), the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel with EtOAc–hexane (1:4) to afford **19** (84.6 mg, 57%) as pale yellow oil. ^{1}H NMR (600 MHz, DMSO) δ 14.0 (1H, s), 10.5 (1H, s), 10.3 (1H, s), 5.95 (1H, s), 5.07–5.05 (1H, m), 3.03 (2H, d, *J* = 6.6 Hz), 2.50 (3H, s), 1.63 (3H, s), 1.55 (3H, s). The spectra of this product matched those of the known compound. [3]

Spectrum Data of 31

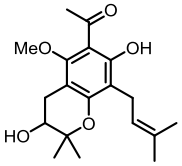
1-[4-(*tert*-Butyldimethylsilyloxy)-2-(2-hydroxypropan-2-yl)-6-methoxy-5-(3-methylbut-2-enyl)-2,3-dihydrobenzofuran-7-yl]ethanone (31). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12–5.09 (1H, m), 4.62 (1H, t, *J* = 8.8 Hz), 3.68 (3H, s), 3.23 (2H, d, *J* = 6.0 Hz), 3.11–3.00 (2H, m), 2.57 (3H, s), 1.71 (3H, s), 1.67 (3H, s), 1.35 (3H, s), 1.22 (3H, s), 1.01 (9H, s), 0.22 (3H, s), 0.21 (3H, s).

References

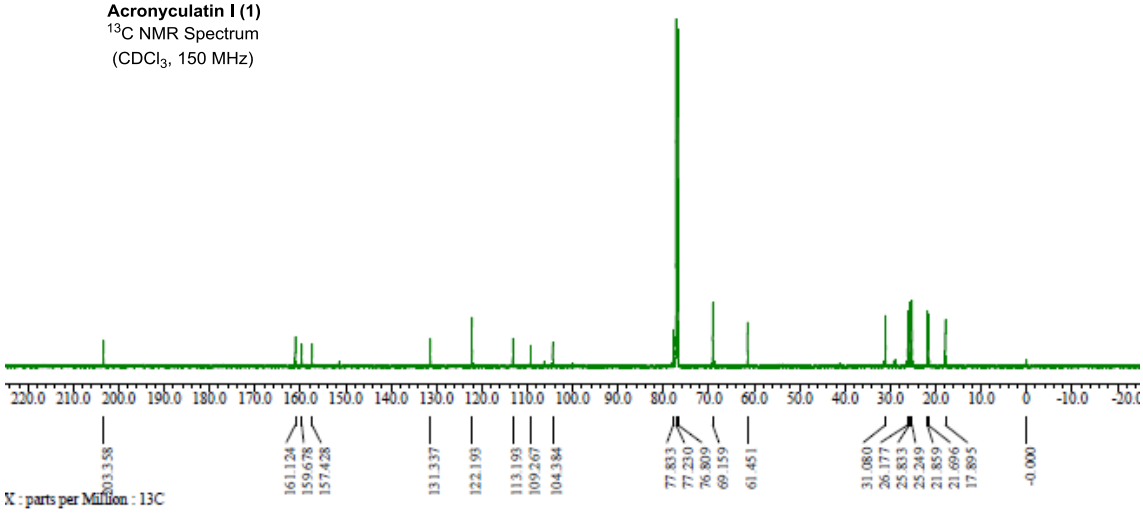
(1) Khupse, R. S.; Erhardt, P. W. *J. Nat. Prod.*, **2007**, *70*, 1507–1509.
(2) Tan, W. F.; Li, W. D.; Li, Y. L. *Synth. Comm.* **2002**, *32*, 1077–1083.
(3) Lee, Y. R.; Li, X.; Kim, J. H. *J. Org. Chem.*., **2008**, *73*, 4313–4316.

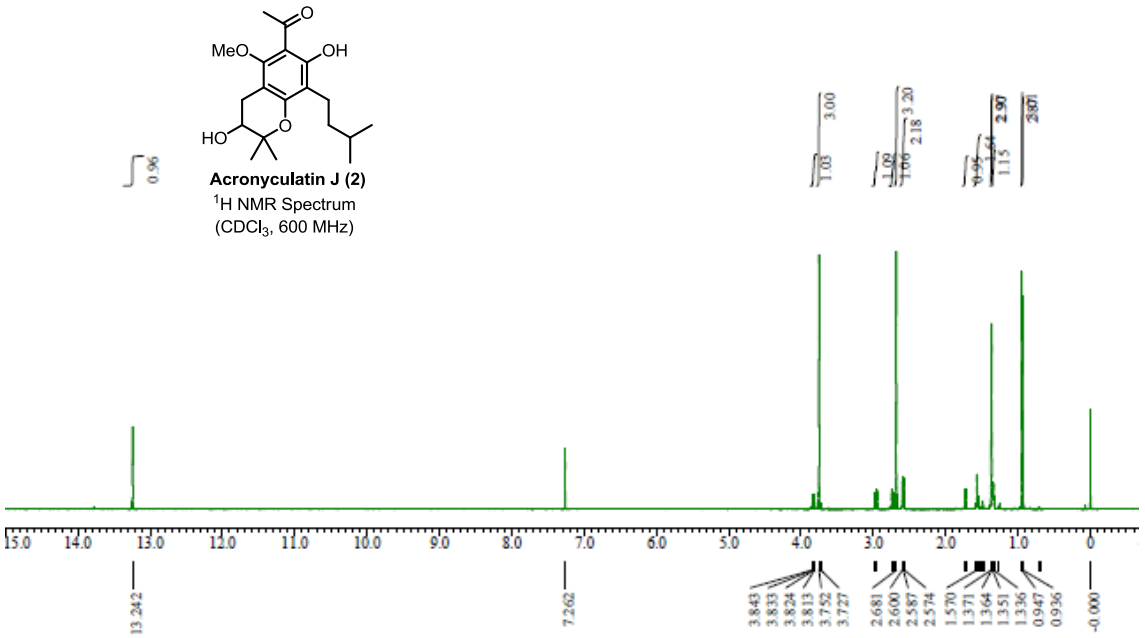


Acronyculatin I (1)
^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)



Acronyculatin I (1)
^{13}C NMR Spectrum
($CDCl_3$, 150 MHz)

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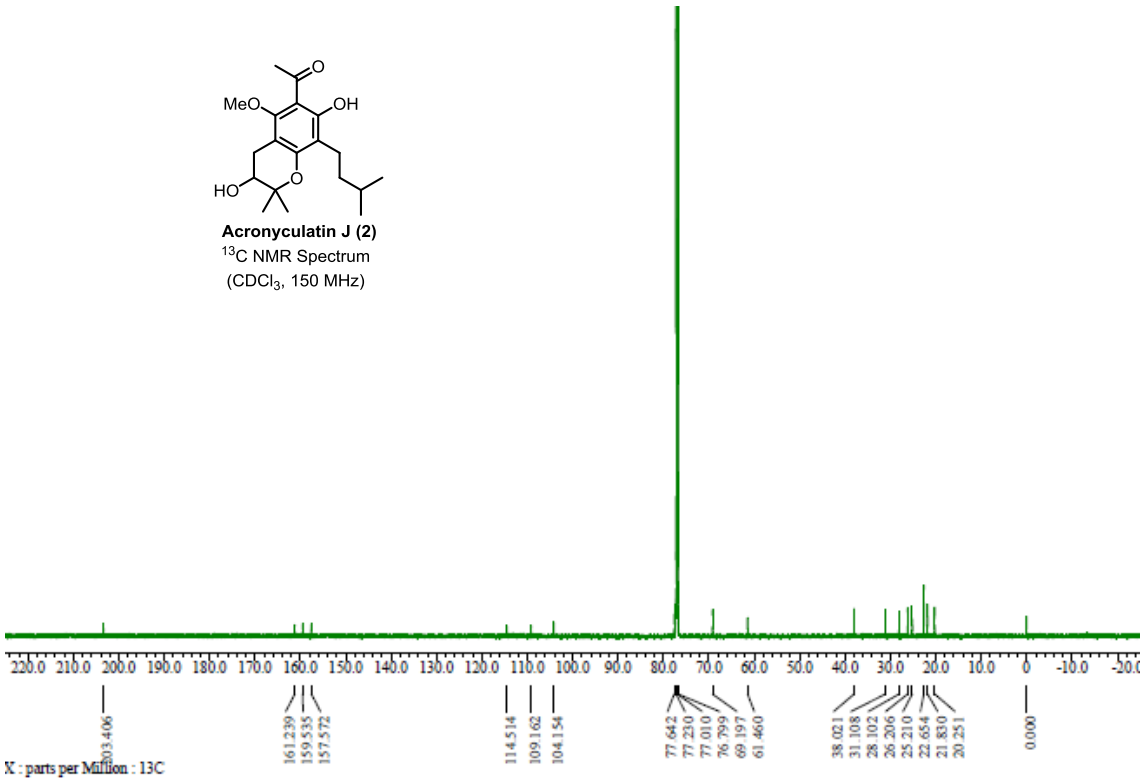
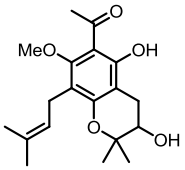
HO
O
Acronyculatin J (2)
^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)

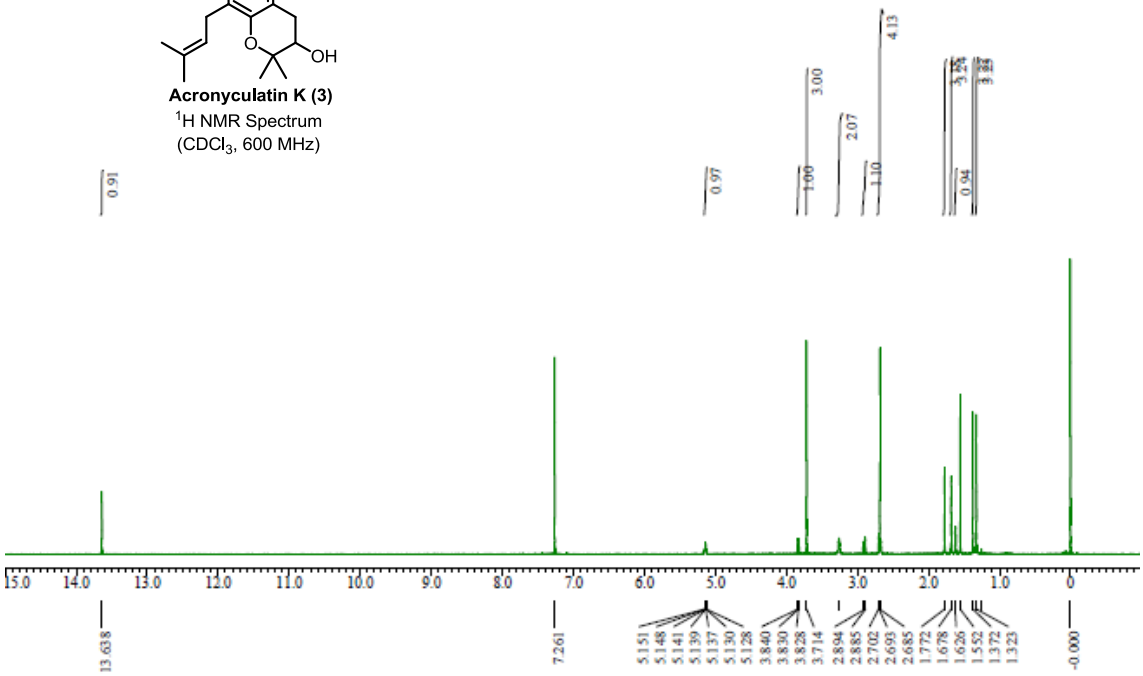

MeO
OH
HO
O
Acronyculatin J (2)
^{13}C NMR Spectrum
($CDCl_3$, 150 MHz)
X : parts per Million : 13C

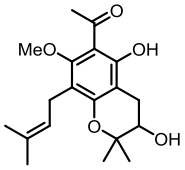


Acronyculatin K (3)

^{1}H NMR Spectrum

($CDCl_3$, 600 MHz)

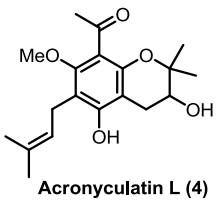




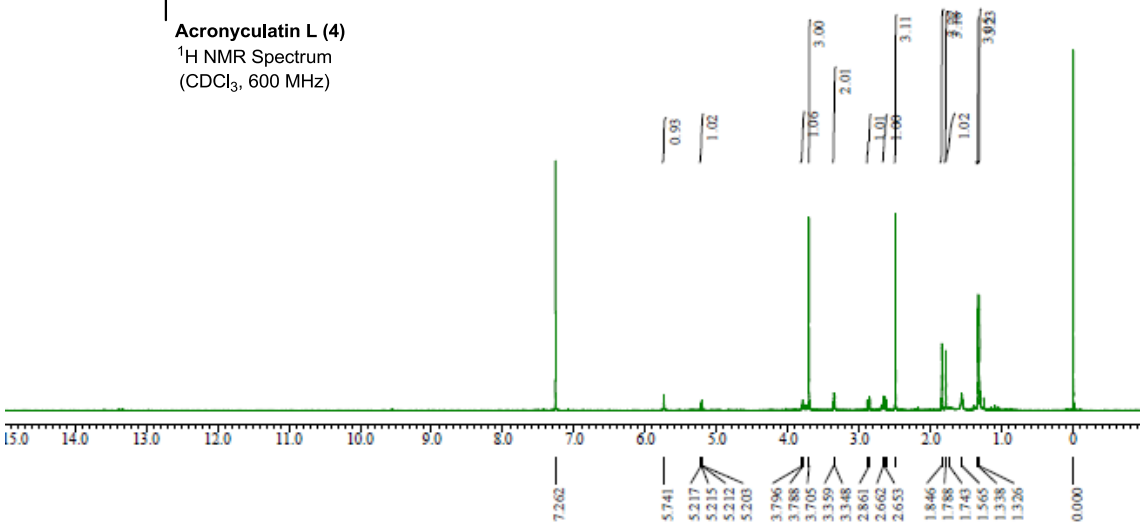
Acronyculatin K (3)

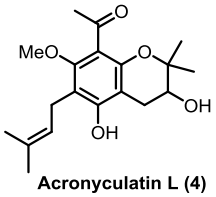
^{13}C NMR Spectrum

($CDCl_3$, 150 MHz)



Acronyculatin L (4)
^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)





Acronyculatin L (4)
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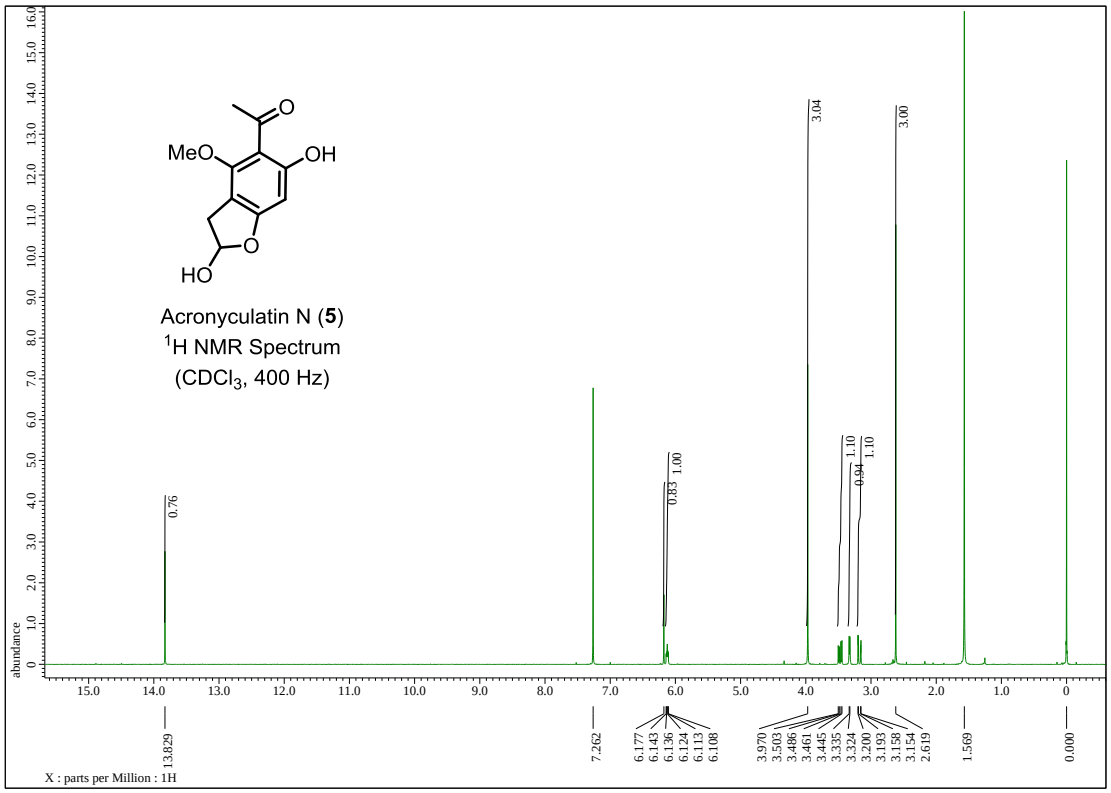
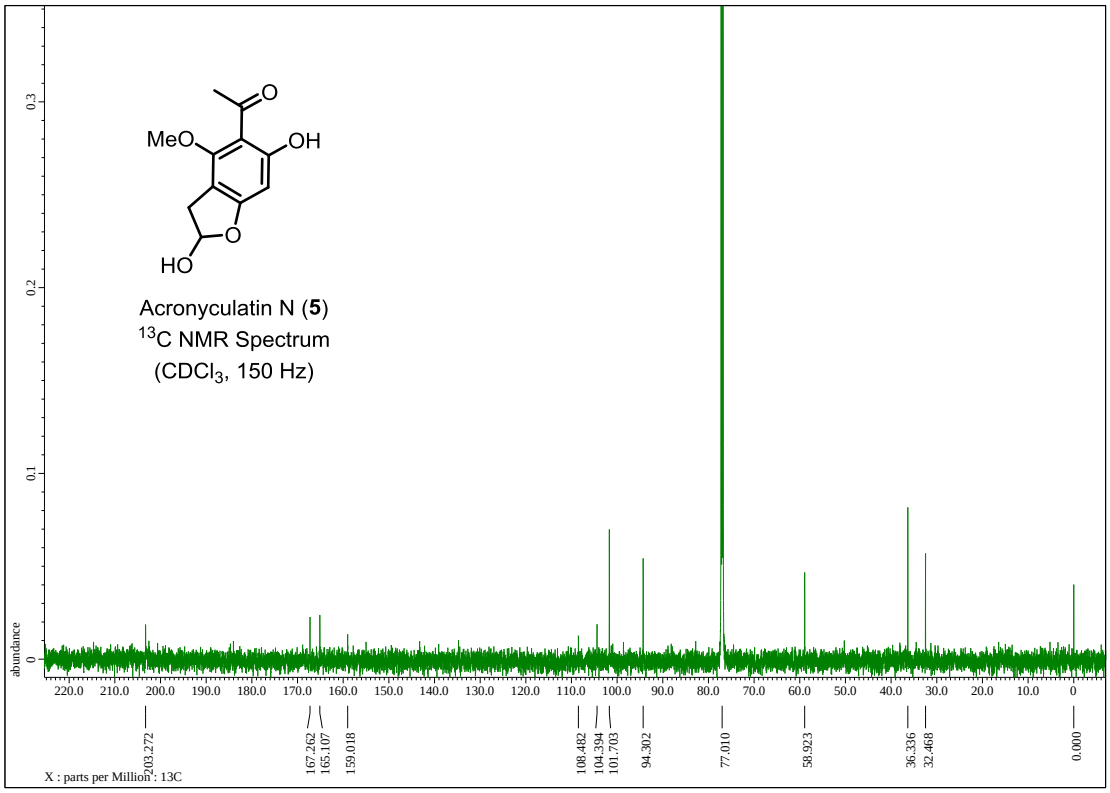

MeO
OH
O
HO
Acronyculatin N (5)
1H NMR Spectrum
(CDCl3, 400 Hz)
abundance
X : parts per Million : 1H


MeO
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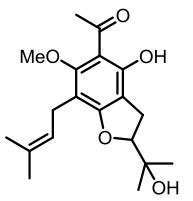
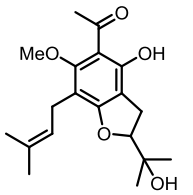
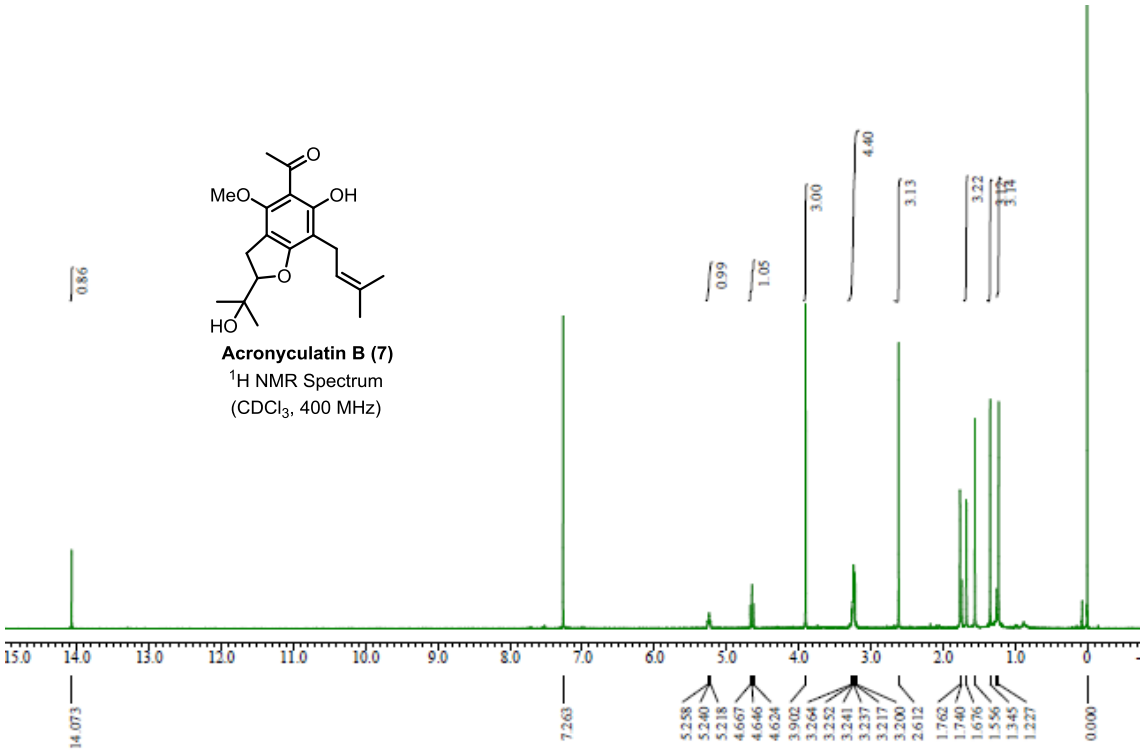
O
HO
Acronyculatin N (5)
13C NMR Spectrum
(CDCl3, 150 Hz)
abundance
X : parts per Million : 13C



Acronyculatin O (6)
^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)



Acronyculatin O (6)
^{13}C NMR Spectrum
($CDCl_3$, 150 MHz)



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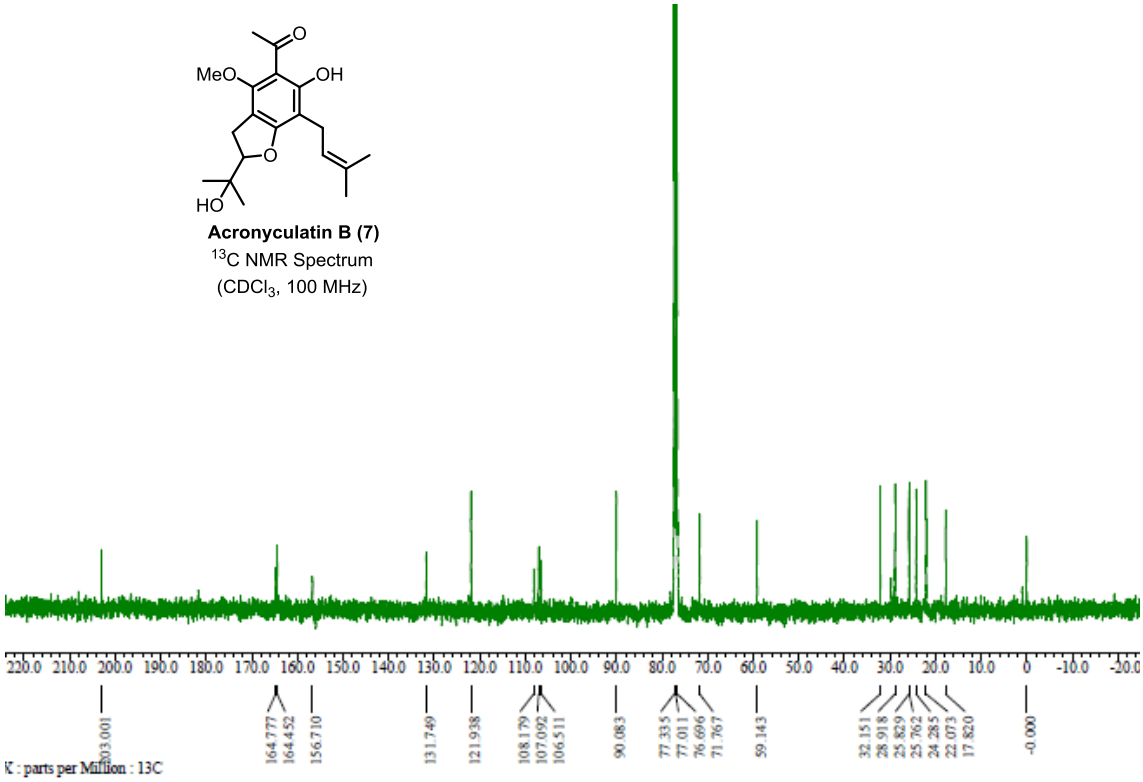
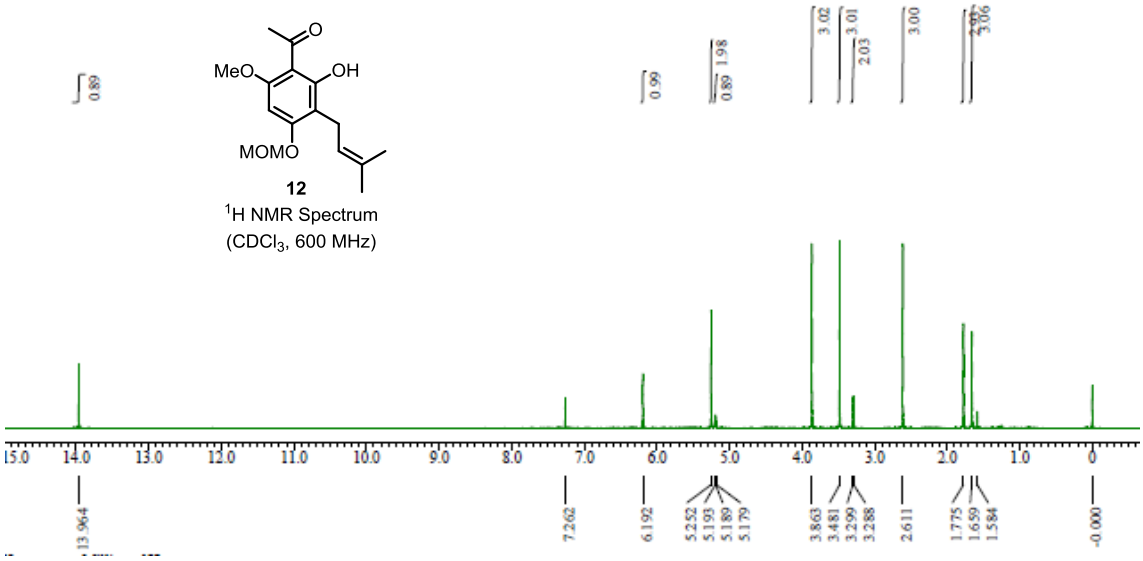
($CDCl_3$, 400 MHz)



Acronyculatin B (7)
^{13}C NMR Spectrum
($CDCl_3$, 100 MHz)


MeO
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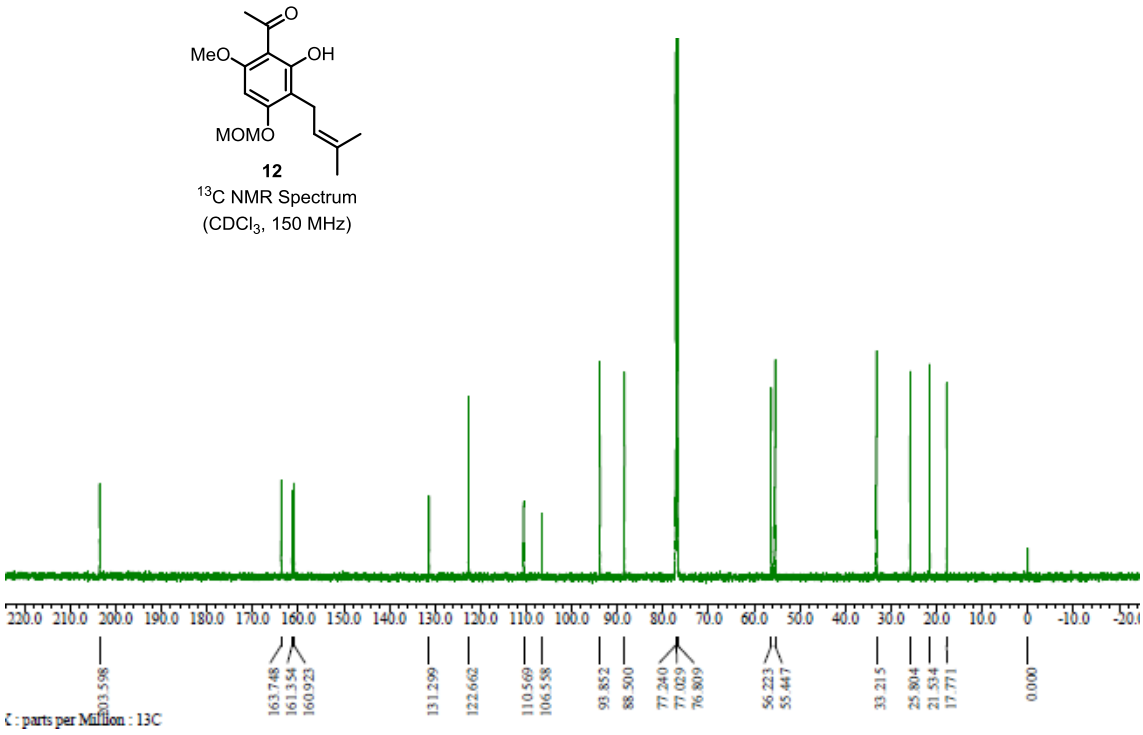
MOMO
O
12
1H NMR Spectrum
(CDCl3, 600 MHz)


MeO
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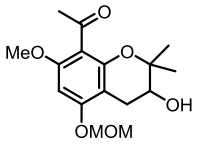
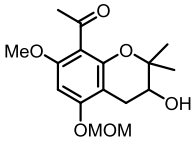
MOMO
O
12
13C NMR Spectrum
(CDCl3, 150 MHz)
C : parts per Million : 13C



14

^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)



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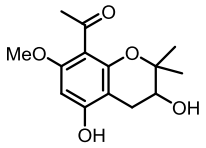
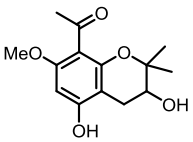
^{13}C NMR Spectrum
($CDCl_3$, 150 MHz)



1-(3,5-dihydroxy-7-methoxy-2,2-dimethylchroman-8-yl)ethan-1-one

^{1}H NMR Spectrum

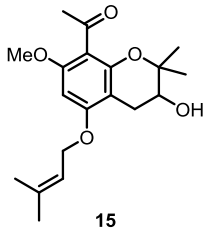
($CDCl_3$, 600 MHz)



1-(3,5-dihydroxy-7-methoxy-2,2-dimethylchroman-8-yl)ethan-1-one

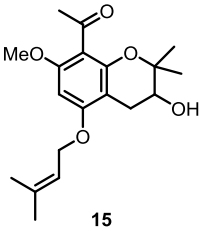
^{13}C NMR Spectrum

(Acetone-d_6, 150 MHz)



15

^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)



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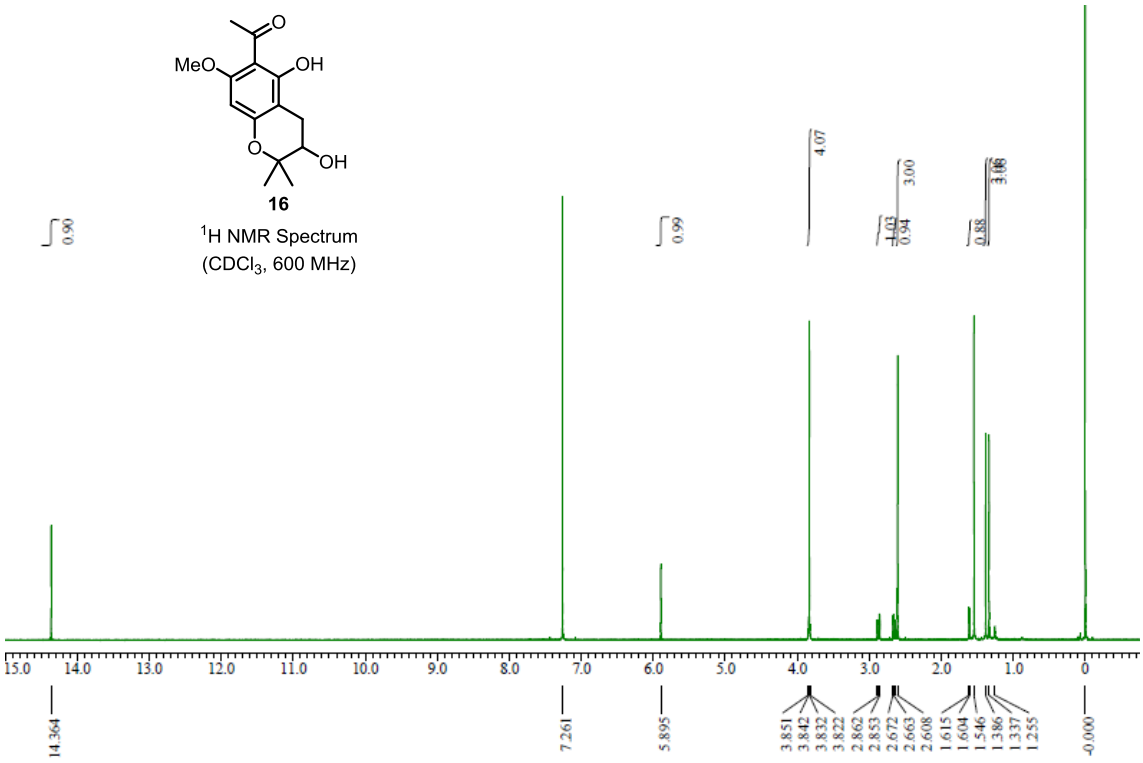
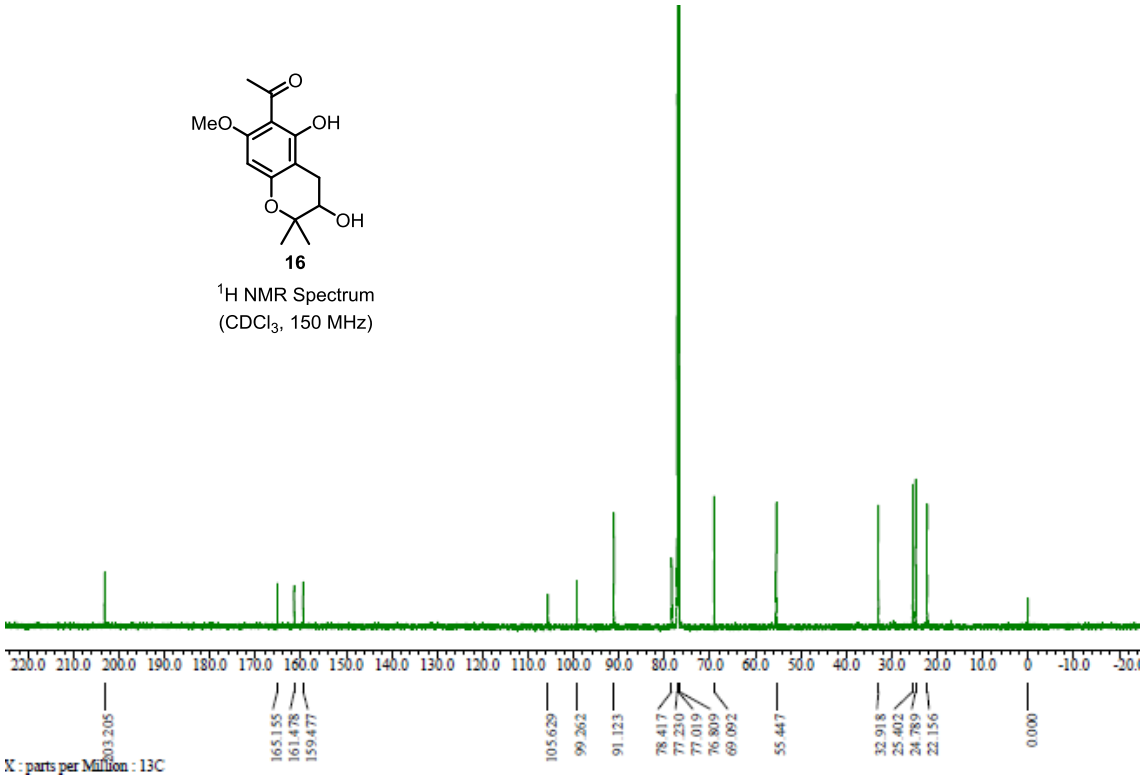
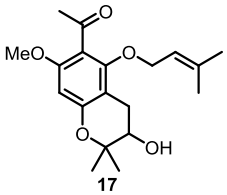


^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)

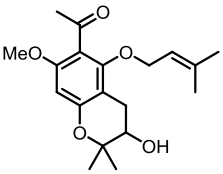


^{1}H NMR Spectrum
($CDCl_3$, 150 MHz)



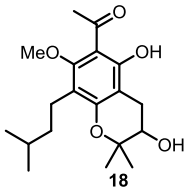
17

^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)



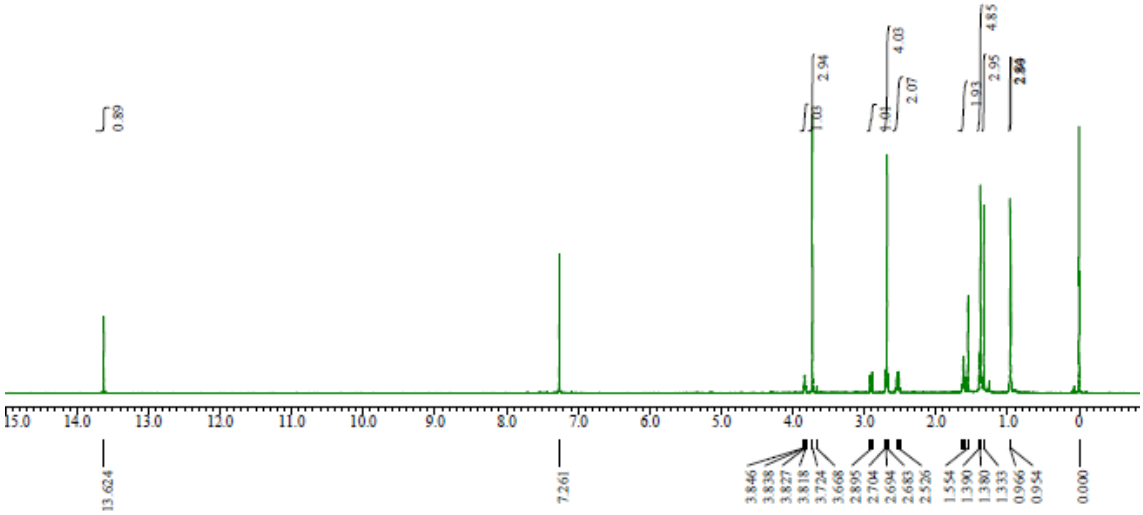
17

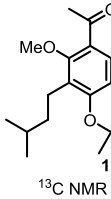
^{13}C NMR Spectrum
($CDCl_3$, 150 MHz)



18

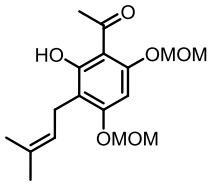
^{1}H NMR Spectrum
($CDCl_3$, 400 MHz)





18

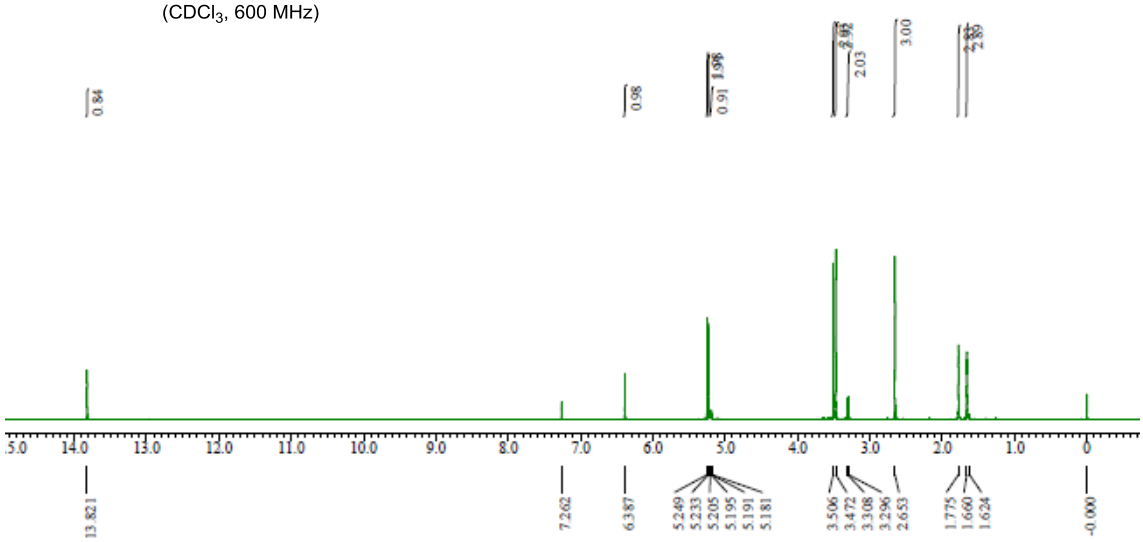
^{13}C NMR Spectrum
($CDCl_3$, 100 MHz)

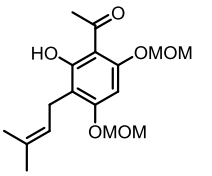


1-[2-hydroxy-4,6-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl]ethan-1-one

^{1}H NMR Spectrum

($CDCl_3$, 600 MHz)

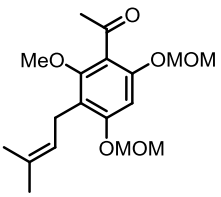




1-[2-hydroxy-4,6-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl]ethan-1-one

^{13}C NMR Spectrum

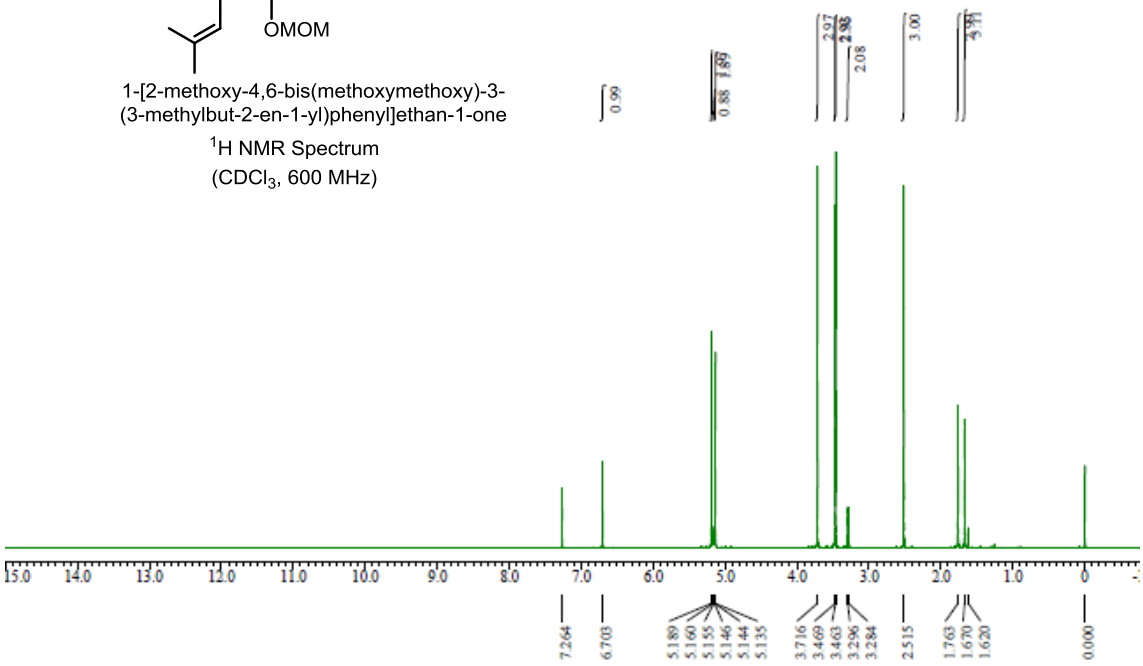
($CDCl_3$, 150 MHz)

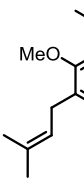


1-[2-methoxy-4,6-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl]ethan-1-one

^{1}H NMR Spectrum

($CDCl_3$, 600 MHz)

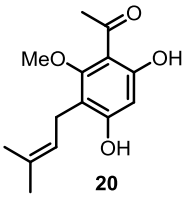




1-[2-methoxy-4,6-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl]ethan-1-one

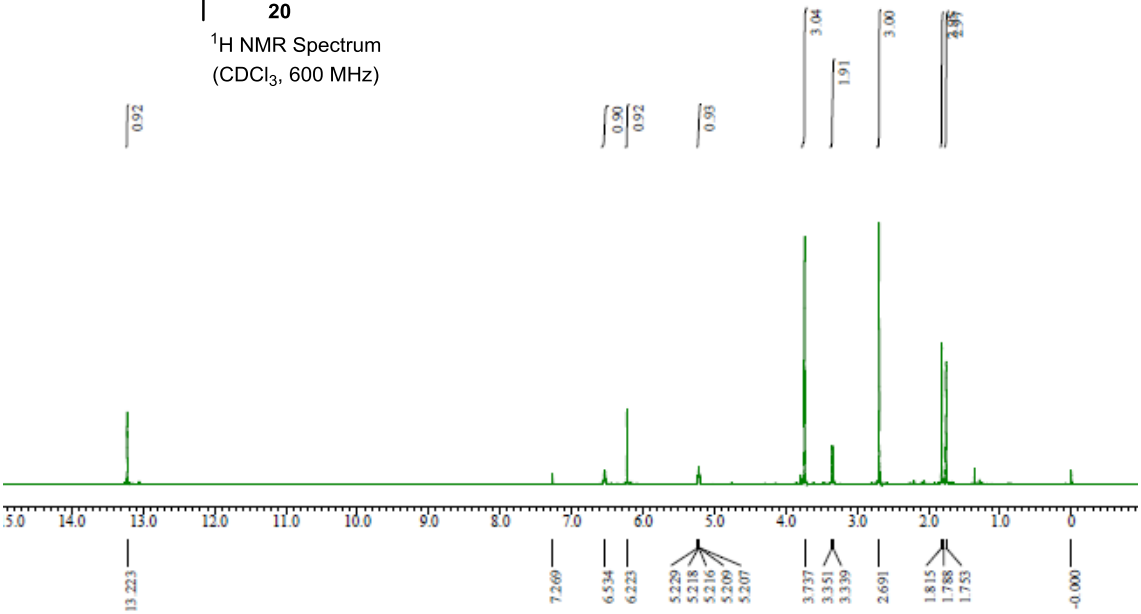
^{13}C NMR Spectrum

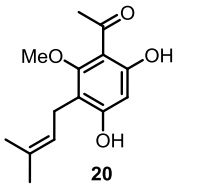
($CDCl_3$, 150 MHz)



20

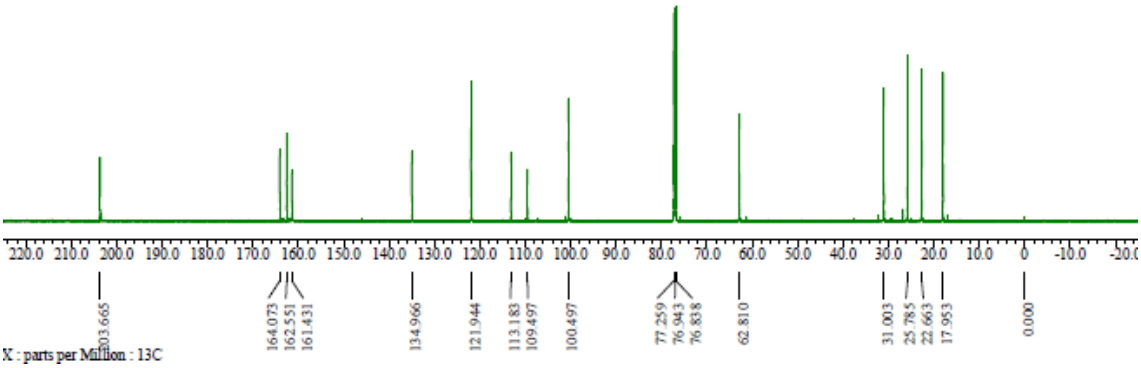
^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)

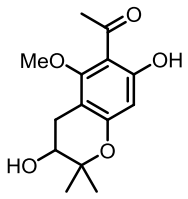




20

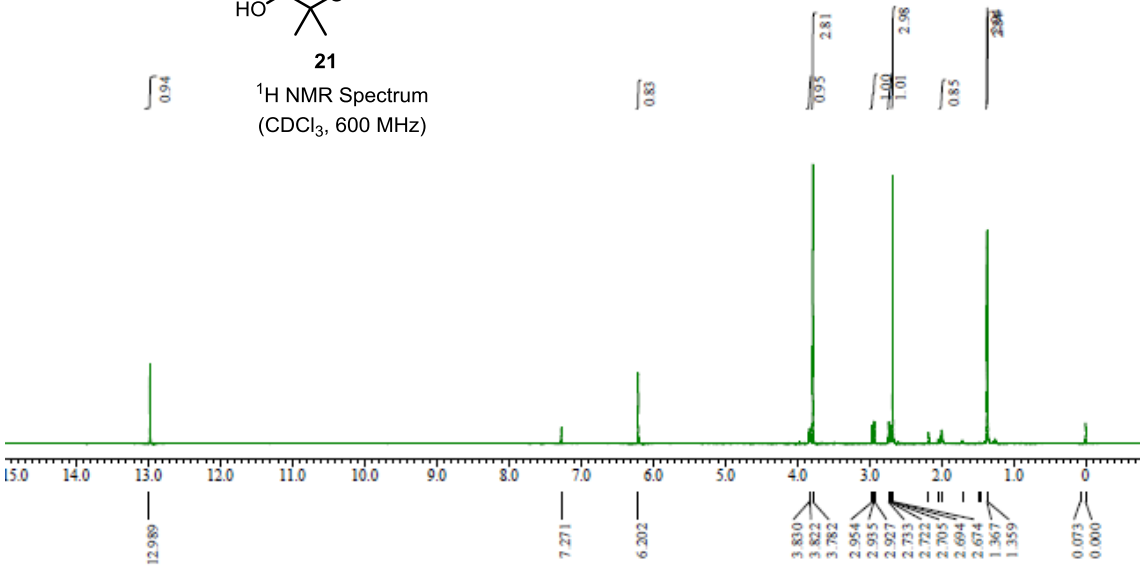
^{13}C NMR Spectrum
($CDCl_3$, 150 MHz)

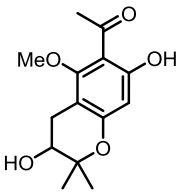




21

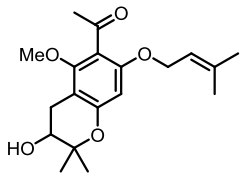
^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)





21

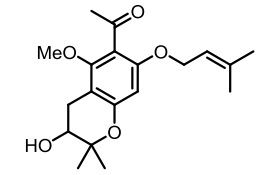
^{13}C NMR Spectrum
($CDCl_3$, 150 MHz)



1-{3-hydroxy-5-methoxy-2,2-dimethyl-7-[(3-methylbut-2-en-1-yl)oxy]chroman-6-yl}ethan-1-one

^{1}H NMR Spectrum

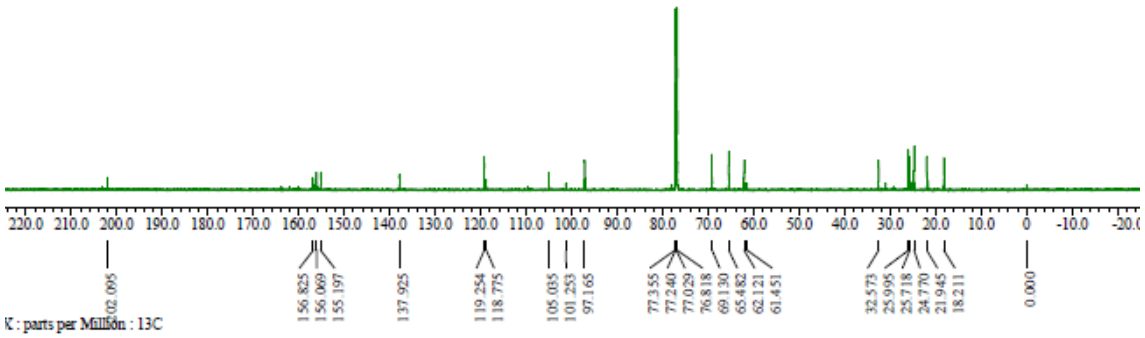
($CDCl_3$, 600 MHz)

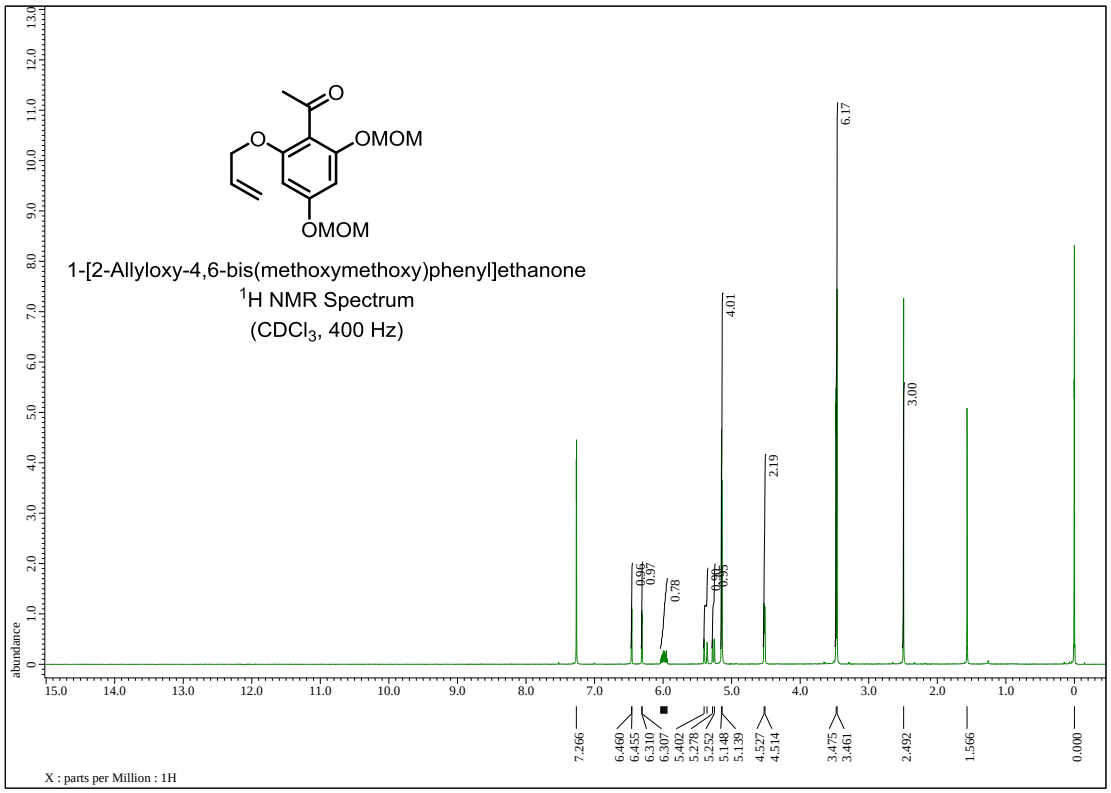


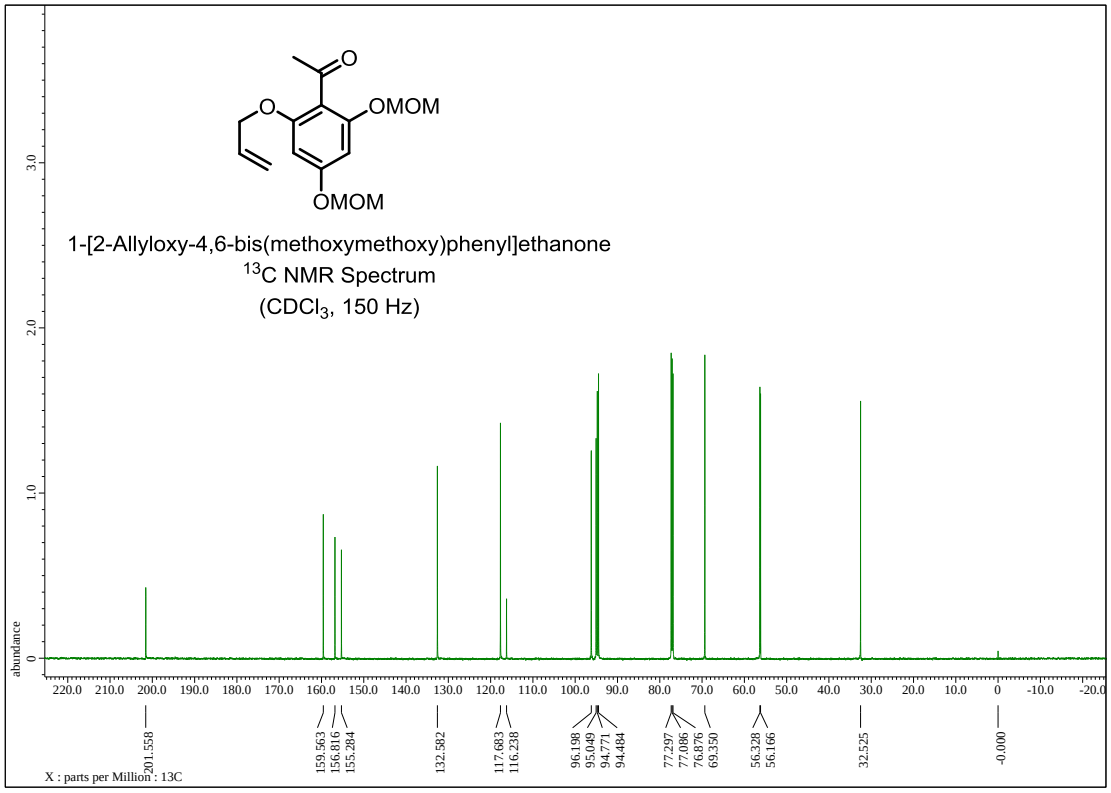
1-{3-hydroxy-5-methoxy-2,2-dimethyl-7-[(3-methylbut-2-en-1-yl)oxy]chroman-6-yl}ethan-1-one

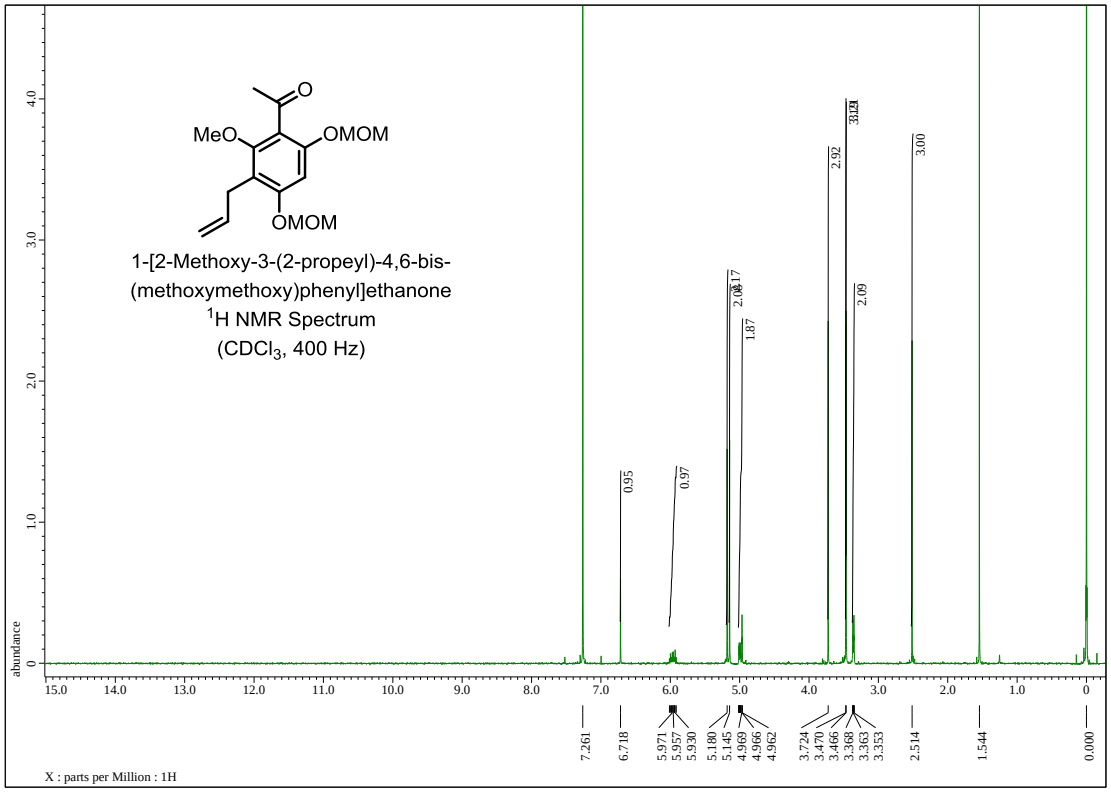
^{13}C NMR Spectrum

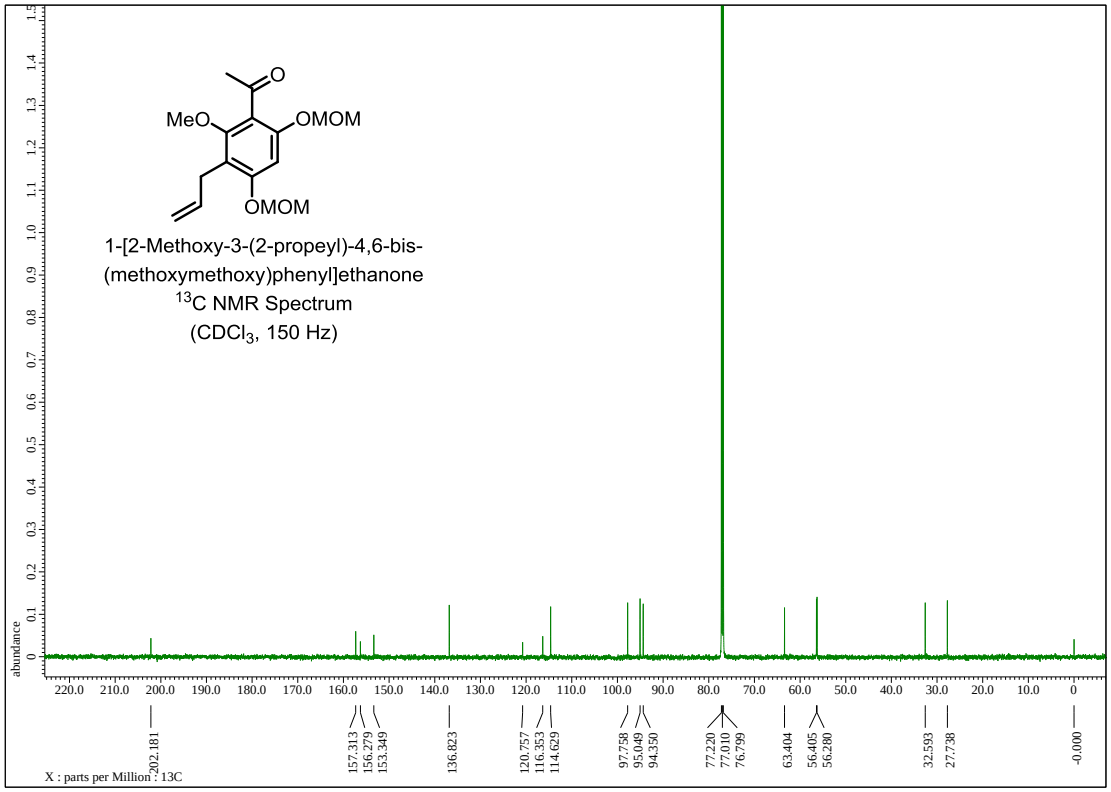
($CDCl_3$, 150 MHz)

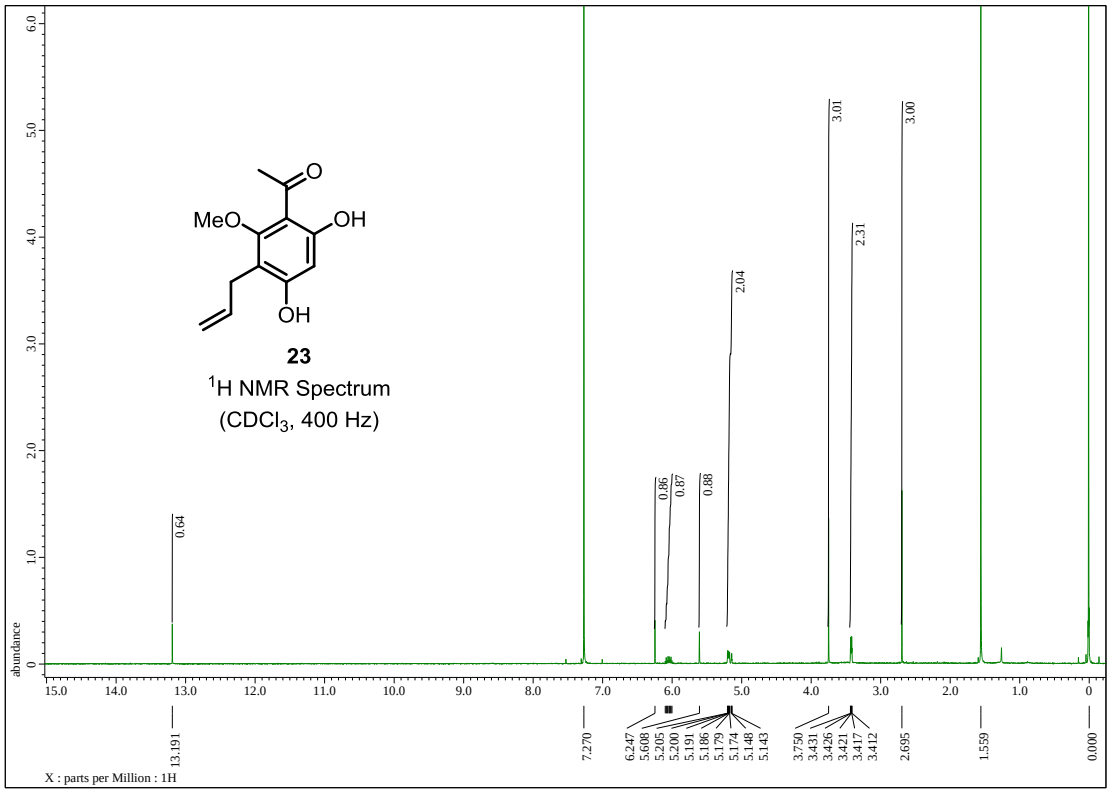


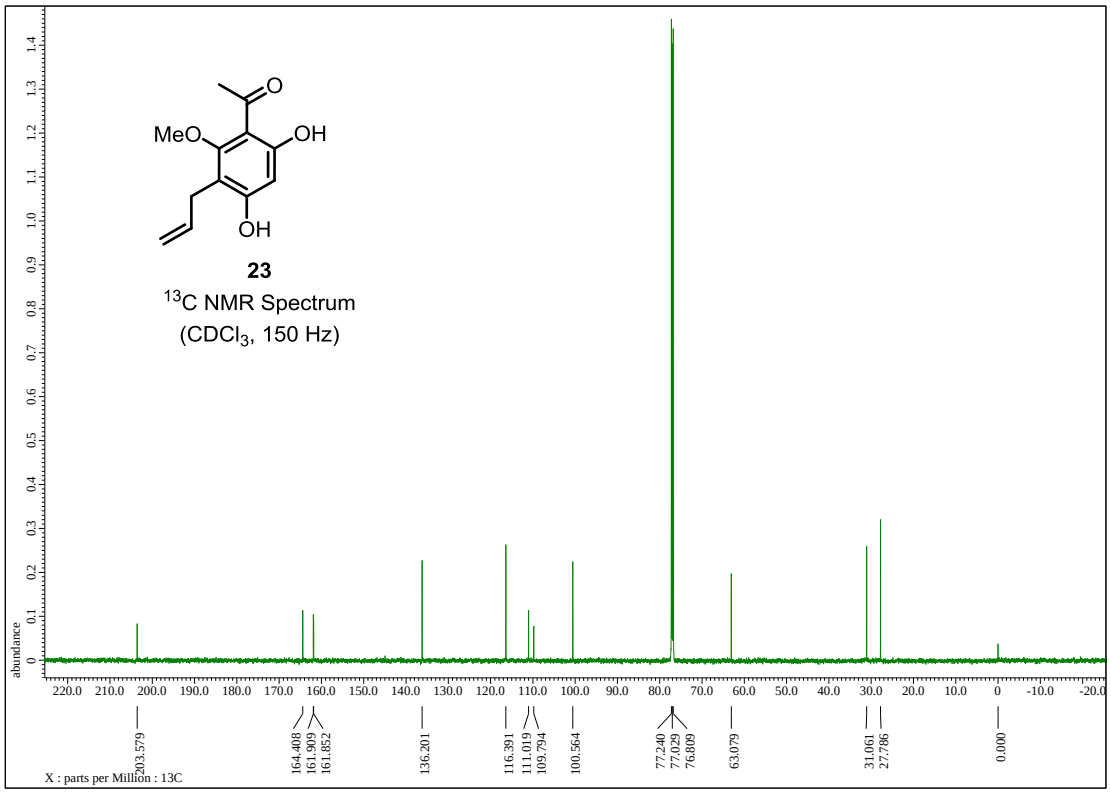

O
OMOM
O
OMOM
1-[2-Allyloxy-4,6-bis(methoxymethoxy)phenyl]ethanone
1H NMR Spectrum
(CDCl3, 400 Hz)
abundance
X : parts per Million : 1H

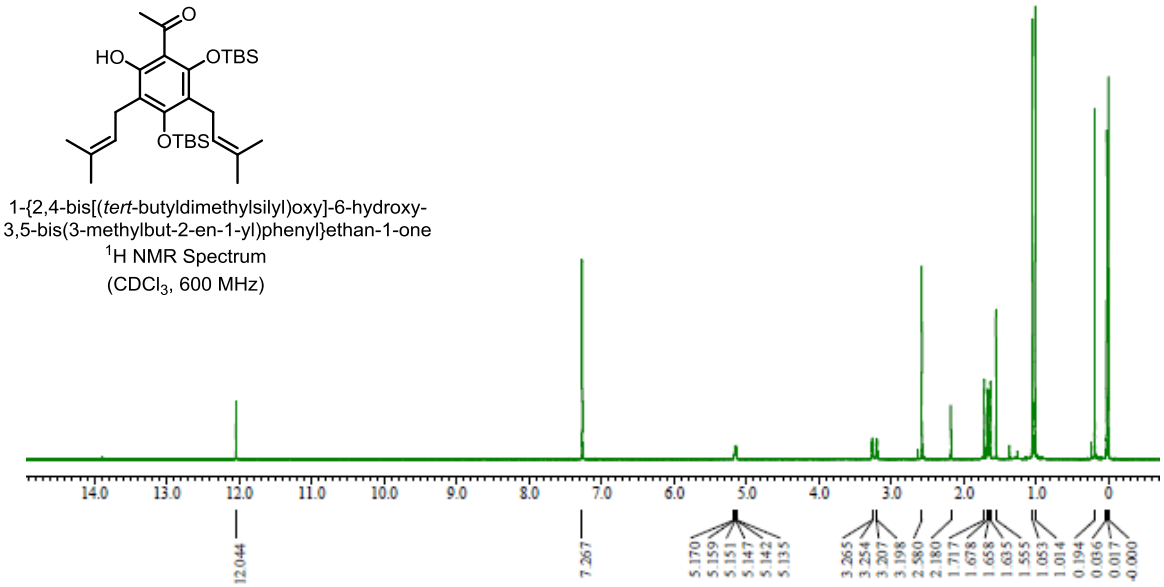

O
OMOM
O
OMOM
1-[2-Allyloxy-4,6-bis(methoxymethoxy)phenyl]ethanone
13C NMR Spectrum
(CDCl3, 150 Hz)
abundance
X : parts per Million : 13C


MeO
OMOM
OMOM
1-[2-Methoxy-3-(2-propeyl)-4,6-bis-
(methoxymethoxy)phenyl]ethanone
1H NMR Spectrum
(CDCl3, 400 Hz)
abundance
X : parts per Million : 1H
7.261
6.718
5.971
5.957
5.930
5.180
5.145
4.969
4.966
4.962
3.724
3.470
3.466
3.368
3.363
3.353
2.514
1.544
0.000


MeO
OMOM
OMOM
1-[2-Methoxy-3-(2-propeyl)-4,6-bis-
(methoxymethoxy)phenyl]ethanone
13C NMR Spectrum
(CDCl3, 150 Hz)
abundance
X : parts per Million : 13C
202.181
157.313
156.279
153.349
136.823
120.757
116.353
114.629
97.758
95.049
94.350
77.220
77.010
76.799
63.404
56.405
56.280
32.593
27.738
-0.000


MeO
OH
OH
O
23
1H NMR Spectrum
(CDCl3, 400 Hz)
abundance
X : parts per Million : 1H

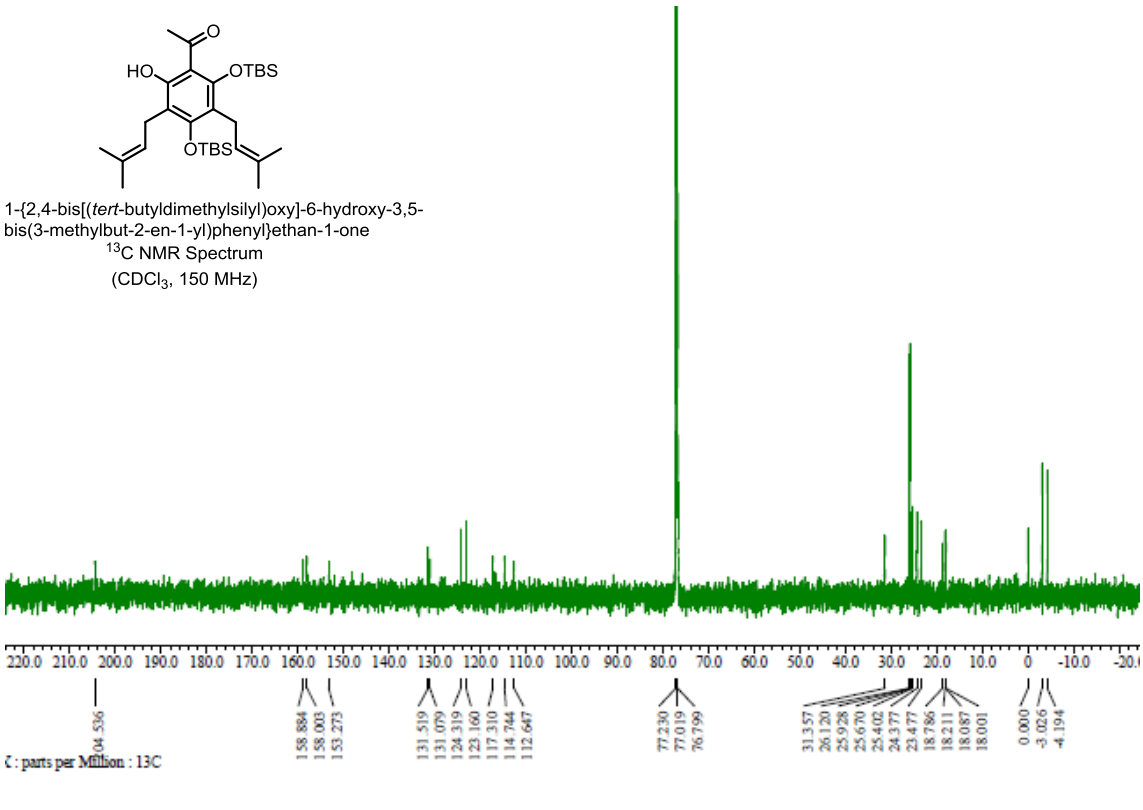

MeO
OH
OH
O
23
13C NMR Spectrum
(CDCl3, 150 Hz)
abundance
X : parts per Million : 13C



1-{2,4-bis[(*tert*-butyldimethylsilyl)oxy]-6-hydroxy-3,5-bis(3-methylbut-2-en-1-yl)phenyl}ethan-1-one

^{1}H NMR Spectrum

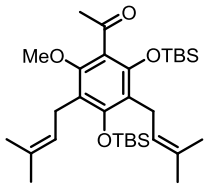
($CDCl_3$, 600 MHz)



1-{2,4-bis[(*tert*-butyldimethylsilyl)oxy]-6-hydroxy-3,5-bis(3-methylbut-2-en-1-yl)phenyl}ethan-1-one

^{13}C NMR Spectrum

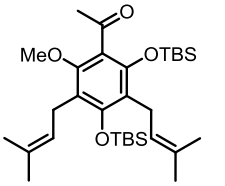
($CDCl_3$, 150 MHz)



1-{2,4-bis[(*tert*-butyldimethylsilyl)oxy]-6-methoxy-3,5-bis(3-methylbut-2-en-1-yl)phenyl}ethan-1-one

^{1}H NMR Spectrum

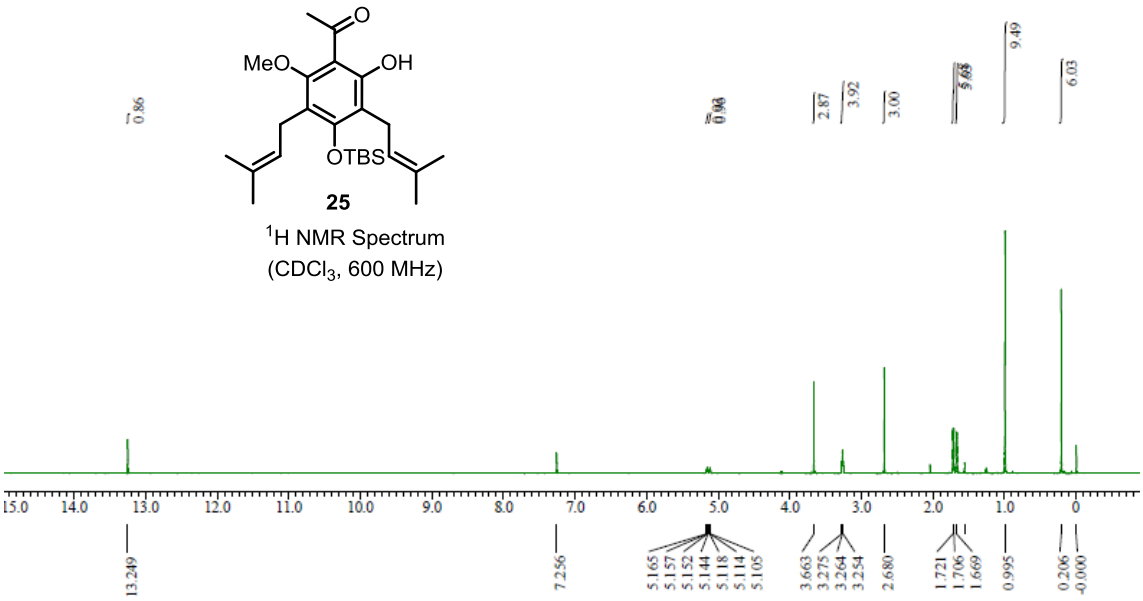
($CDCl_3$, 600 MHz)



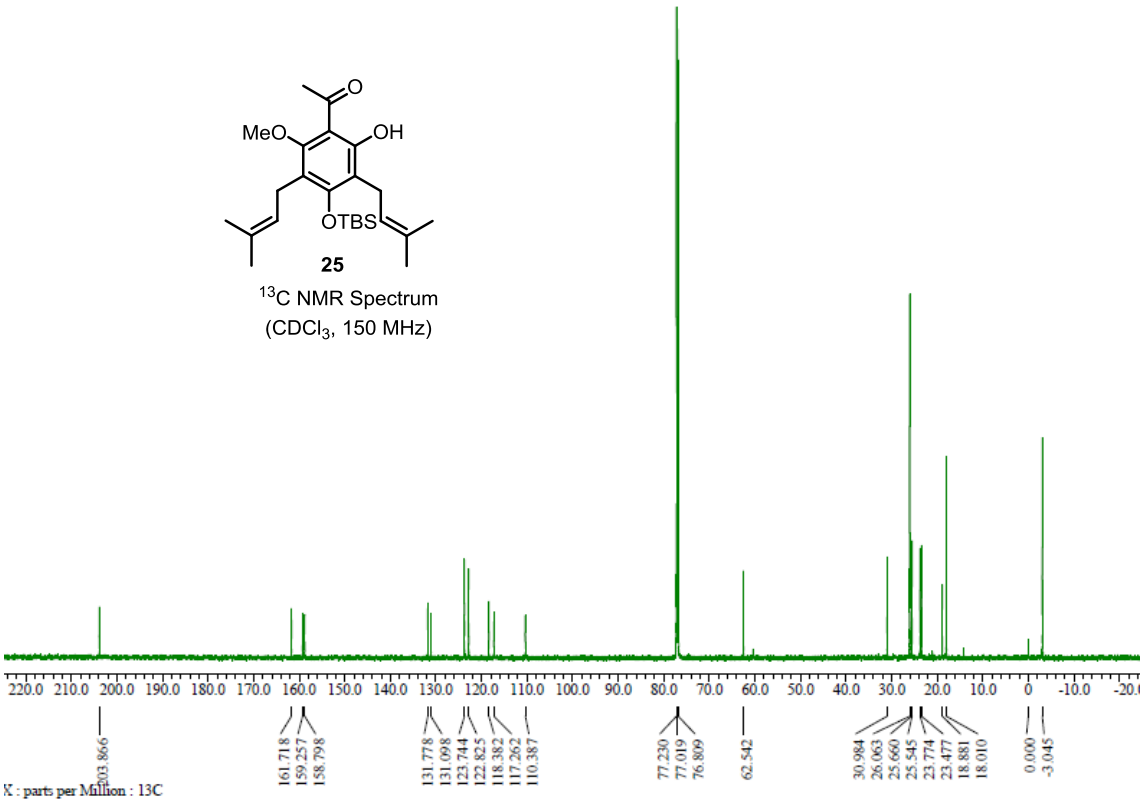
1-{2,4-bis[(*tert*-butyldimethylsilyl)oxy]-6-methoxy-3,5-bis(3-methylbut-2-en-1-yl)phenyl}ethan-1-one

^{13}C NMR Spectrum

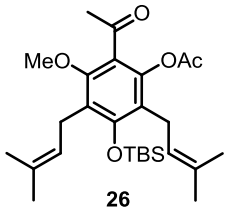
($CDCl_3$, 150 MHz)



^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)

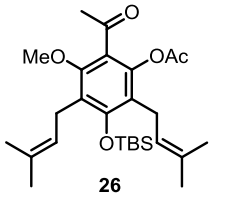


^{13}C NMR Spectrum
($CDCl_3$, 150 MHz)



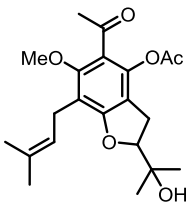
26

^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)



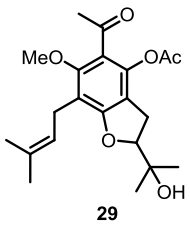
26

^{13}C NMR Spectrum
($CDCl_3$, 100 MHz)



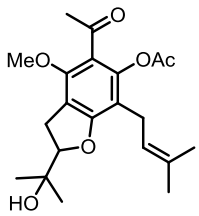
29

^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)



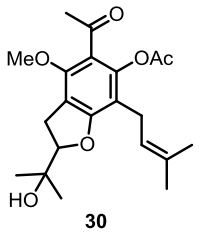
29

^{13}C NMR Spectrum
($CDCl_3$, 100 MHz)



30

^{1}H NMR Spectrum
($CDCl_3$, 600 MHz)

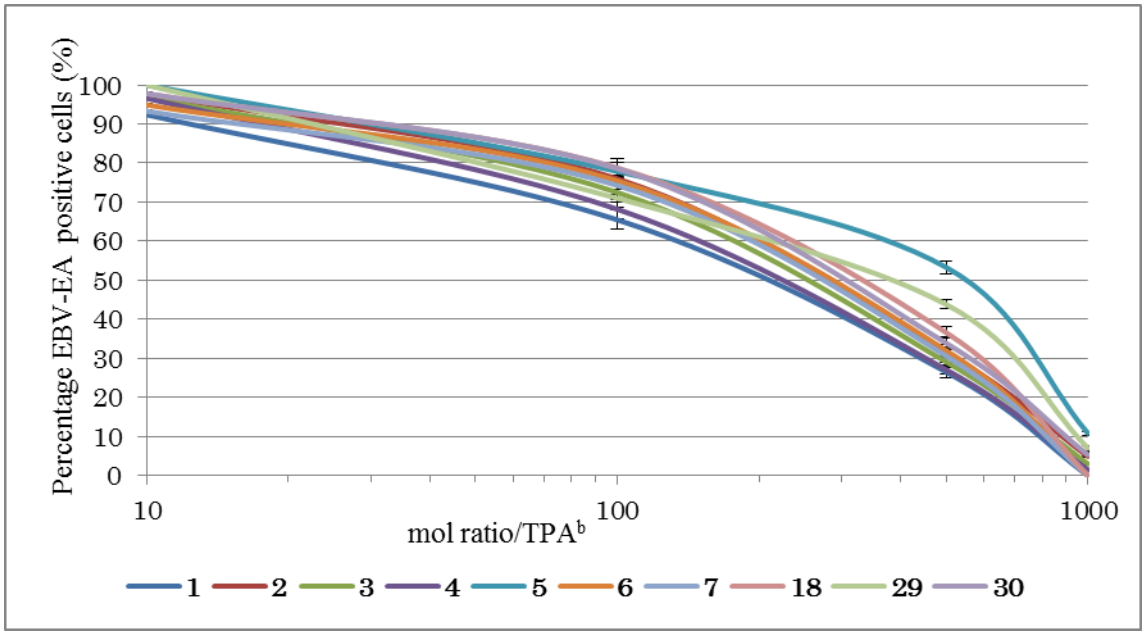


30

^{13}C NMR Spectrum
($CDCl_3$, 100 MHz)

Assay Curve for Table 3.

Relative Ratio[a] of EBV-EA Activation with Respect to Positive Control (100%)



[a]Values represent percentages relative to the positive control value (100%). [b]TPA concentration is 20 ng/mL (32 pmol/mL).