Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Total synthesis and biological evaluation of (-)-atrop-abyssomicin C

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1 General experimental

All chromatographic separations[1] were performed on Silica, 10-18, 60 Å, ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents.[2] NMR spectra were recorded on a Varian Gemini 200 (^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz), and on Bruker Avance III 500 (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz), in deuterated chloroform if not otherwise stated. Chemical shifts are expressed in ppm (δ) using tetramethylsilane as internal standard, coupling constants (*J*) are in Hz. IR spectra were recorded on a Nicolet 6700 FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on Agilent technologies 6210 TOF LC/MS instrument (LC: series 1200) or LTQ Orbitrap XL hybrid FTMS (Thermo Scientific). Microanalyses were performed at the Vario EL III instrument CHNOS Elementar Analyzer, Elementar Analysensysteme GmbH, Hanau-Germany. Optical rotation was measured on Rudolph Research Analytical AUTOPOL IV Automatic Polarimeter. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

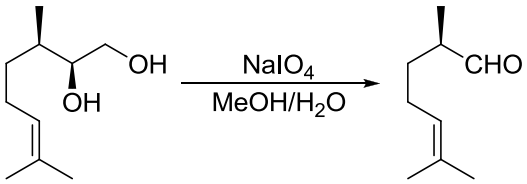
X-ray crystal structure determination

A single colorless crystal was selected and glued on glass fiber. Diffraction data were collected on an Oxford Diffraction KM4 four-circle goniometer equipped with Sapphire CCD detector. The crystal to

detector distance was 45.0 mm and a graphite monochromated MoKα (λ = 0.71073 Å) X-radiation was employed in the measurements. The frame widths of 1° in ω, with 19 and 27 s were used to acquire each frame. More than a hemisphere of three-dimensional data was collected in all measurements. The data were reduced using the Oxford Diffraction program CrysAlisPro. A semiempirical absorption-correction based upon the intensities of equivalent reflections was applied, and the data were corrected for Lorentz, polarization, and background effects. Scattering curves for neutral atoms, together with anomalous-dispersion corrections, were taken from *International Tablesfor X-ray Crystallography*.[3] The structures were solved by direct methods,[4] and the figures were drawn using MERCURY.[5] Refinements were based on *F*2 values and done by full-matrix least-squares[6] with all non-H atoms anisotropic. The positions of all non H-atoms were located by direct methods. The positions of hydrogen atoms were found from the inspection of the difference Fourier maps. The final refinement included atomic positional and displacement parameters for all non-H atoms. The non-H atoms were refined anisotropically. However, at the final stage of the refinement, H atoms belonging to molecules were positioned geometrically (O−H = 0.82 and C−H = 0.93-0.97 Å) and refined using a riding model with fixed isotropic displacement parameters.

2 Experimental procedures

2.1 (*R*)-2,6-dimethylhept-5-enal ((*R*)-norcitronellal) (5)[7]

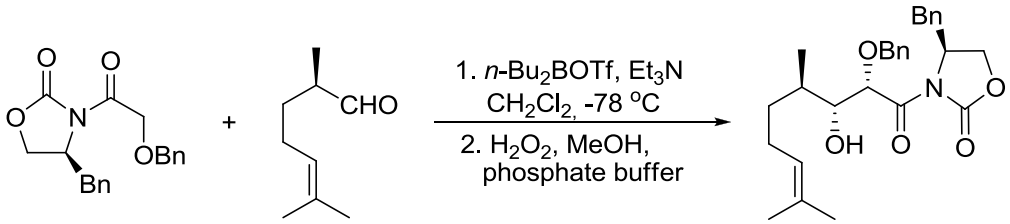


5

Aqueous solution of sodium periodate (4.35 g of $NaIO_4$ in 50 mL of distilled water; 20.3 mol; 3.5 eq) was added dropwise to the methanolic solution of (2*S*,3*R*)-3,7-dimethyloct-6-en-1,2-diol (1 g of the diol in 45 mL of methanol; 5.8 mmol). The resulting milky white suspension was stirred at room temperature for 30 minutes, before it was partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane (3 x 40 mL) and the combined organic extract was dried over $MgSO_4$. The extract was concentrated under reduced pressure (300 mmHg, 25 °C), the residue filtered through a short pad of silica, and eluted with dichloromethane. Removal of solvent at rotovap afforded 660 mg (80%) of (*R*)-2,6-dimethylhept-5-enal **5**, as a colorless liquid with a pleasant odor.

Spectral data identical to those reported in the literature.[8]

2.2 (S)-4-benzyl-3-((2*S*,3*R*,4*R*)-2-(benzyloxy)-3-hydroxy-4,8-dimethylnon-7-enoyl)oxazolidin-2-one (8)

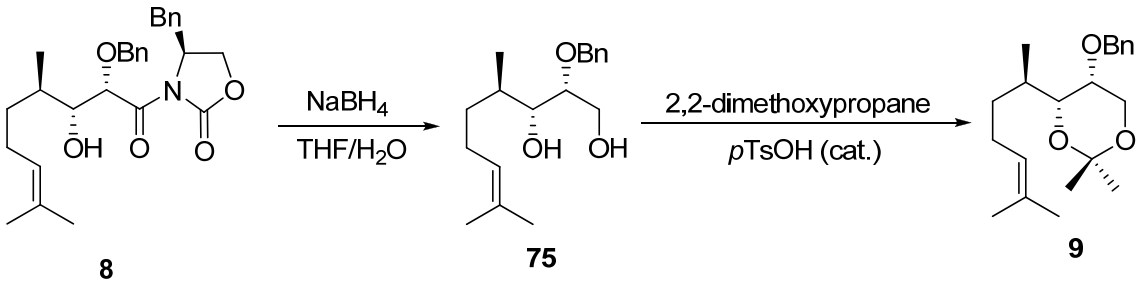


7 **5** **8**

Triethylamine (6 mL; 43 mmol; 1.40 eq) was added to a cold (-78 °C) solution of (*S*)-4-benzyl-3-(2-(benzyloxy)acetyl)-oxazolidin-2-one **7** (10.34 g; 31.8 mmol; 1.04 eq) in dry dichloromethane (130 mL), under an argon atmosphere, followed by a dropwise addition (10 min) of di-*n*-butylboron trifluoromethanesulfonate (9.3 mL; 37 mmol; 1.2 eq). The mixture was allowed to reach 0 °C during one hour, stirred continuously for 15 minutes, and then cooled again to -78 °C. A solution of (*R*)-norcitronellal **5** (4.3 g; 30.7 mmol; 1 eq) in dry dichloromethane (20 mL) was added dropwise into the reaction mixture, and stirring was continued for 10 minutes at -78 °C. The mixture was allowed to reach 0 °C during 1.5 h and stirring continued for 4 h at that temperature. After cooling to -25 °C, the reaction was carefully quenched by simultaneous addition of phosphate buffer (140 mL) and methanol (400 mL), keeping the temperature below -15 °C. A mixture of methanol and 30% hydrogen peroxide (2:1; 280 mL) was then added while maintaining the same temperature, and stirring continued for 1 h at 0 °C. The reaction mixture was extracted with dichloromethane (3x300 mL), the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by MPL chromatography (eluent: toluene : ethyl acetate = 5 : 1) afforded 10.92 g (77%) of aldol **8**, as a very viscous, colorless oil, which was preceded by unreacted starting oxazolidinone **7** (1.84 g). The yield based on the recovered starting oxazolidinone was 90%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19-7.49 (m, 10H), 5.33 (d, J=1.7, 1H), 5.06-5.15 (m, 1H), 4.78 (d, J=11.4, 1H), 4.66-4.76 (m, 1H), 4.48 (d, J=11.4, 1H), 4.19-4.32 (m, 2H), 3.56 (dt, J_1=1.7, J_2=10.3, 1H), 3.36 (dd, J_1=3.3, J_2=13.3, 1H), 2.83 (dd, J_1=9.6, J_2=13.3, 1H), 2.03-2.16 (m, 2H), 1.86-2.00 (m, 1H), 1.71-1.85 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.11-1.25 (m, 1H), 0.90 (d, J=6.7, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 153.3, 137.1, 135.1, 131.3, 129.4, 129.0, 128.5, 128.46, 128.2, 127.5, 124.7, 78.2, 76.6, 72.8, 67.1, 55.8, 37.8, 36.3, 32.7, 25.7, 25.2, 17.7, 15.2.
IR (film): cm^{-1} 3507, 2918, 1777, 1708, 1386, 1210, 1110, 698.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{28}H_{35}NO_5Na$: 488.2413; found: 488.2390.
$[\alpha]_D^{20}$ +20.5 (*c* 0.8, $CHCl_3$).
***R*$_f$**=0.27 (toluene : ethyl acetate = 5 : 1).

2.3 (4*R*,5*R*)-5-(benzyloxy)-2,2-dimethyl-4-((*R*)-6-methylhept-5-en-2-yl)-1,3-dioxane (9)

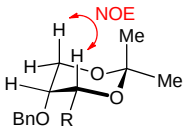


8 **75** **9**

A) Compound **75** (Reductive elimination of the oxazolidinone chiral auxillary with sodium borhydride): Sodium borohydride (15 mg; 0.4 mmol; 5 eq) was added to a solution of aldol **8** (37 mg; 0.08 mmol) in tetrahydrofuran/water mixture (5:2; 1.4 mL) and the mixture was stirred 75 minutes at room temperature, before the excess of the reducing agent was destroyed by careful addition of saturated ammonium chloride solution (2 mL). The mixture was extracted with ethyl acetate (2x20 mL), the organic layer was rinsed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture of the diol **75** and oxazolidinone was used in next step without purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.39 (m, 5H), 5.10 (t, *J*=2.8, 1H), 4.74 (d, *J*=11.5, 1H), 4.60 (d, *J*=11.5, 1H), 3.91 (dd, J_1=4.5, J_2=12, 1H), 3.72 (dd, J_1=4.5, J_2=12, 1H), 3.57 (dd, J_1=4.5, J_2=8, 1H), 3.42-3.44 (m, 1H), 2.20-2.35 (bs, 2H), 2.05-2.18 (m, 1H), 1.89-1.96 (m, 1H), 1.67-1.73 (m, 1H), 1.69 (s, 3H), 1.58-1.64 (m, 1H), 1.61 (s, 3H), 1.18-1.24 (m, 1H), 0.89 (d, *J*=7, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 131.5, 128.6, 128.0, 127.9, 124.6, 78.5, 76.8, 72.5, 62.6, 35.2, 31.7, 25.7, 25.3, 17.7, 16.1.
IR (film): cm^{-1} 3399, 2964, 2921, 2879, 1454, 1054.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{18}H_{28}O_3Na$: 315.1931; found: 315.1925.
$[\alpha]_D^{20}$ +3.6 (*c* 0.3, $CHCl_3$).
***R*$_f$**=0.26 (petroleum ether : ethyl acetate = 2 : 1).

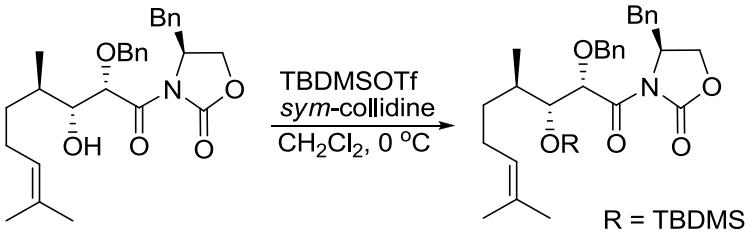
B) Compound **9**: The crude mixture of diol **75** and the oxazolidinone obtained in the previous step, was redissolved in 2,2-dimethoxypropane (0.8 mL), *p*TsOH (one crystal) was added and stirring was continued for 1 h at room temperature. The reaction mixture was diluted with dichloromethane (25 mL), washed with saturated sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1) afforded 17 mg (64%) of compound **9**, as a colorless oil.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.38 (m, 5H), 5.10-5.14 (m, 1H), 4.76 (d, *J*=12, 1H), 4.46 (d, *J*=12, 1H), 4.09 (dd, J_1=2, J_2=12.5, 1H), 3.85 (dd, J_1=2, J_2=12=3, 1H), 3.42 (dd, J_1=1.5, J_2=9.5, 1H), 3.26 (dd, J_1=2, J_2=4, 1H), 1.86-2.06 (m, 3H), 1.68 (s, 3H), 1.63-1.71 (m, 1H), 1.60 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.04-1.11 (m, 1H), 0.71 (d, *J*=7, 3H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2, 130.9, 128.3, 128.1, 127.7, 125.1, 98.7, 75.6, 70.6, 69.7, 61.5, 32.4, 32.3, 29.1, 25.7, 24.8, 18.9, 17.5, 14.3.

IR (film): cm^{-1} 2965, 2924, 2858, 1377, 1200, 1090.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{21}H_{32}O_3Na$: 355.2249; found: 355.2254.
$[\alpha]_D^{20}$ -14.3 (*c* 0.3, $CHCl_3$).
***R*$_f$**=0.41 (petroleum ether : ethyl acetate = 7 : 1).

2.4 (*S*)-4-benzyl-3-((2*S*,3*R*,4*R*)-2-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnon-7-enoyl)oxazolidin-2-one (10)

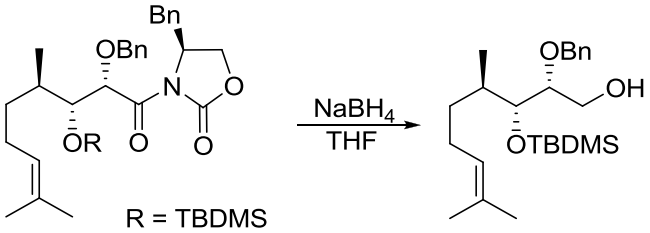


8 **10**

Freshly distilled *sym*-collidine (6.4 mL; 48.3 mmol; 2.5 eq) was added to a cold (0 °C) solution of (*S*)-4-benzyl-3-((2*S*,3*R*,4*R*)-2-(benzyloxy)-3-hydroxy-4,8-dimethylnon-7-enoyl)oxazolidin-2-one **8** (9.0 g; 19.33 mmol) in dry dichloromethane (32 mL), under an argon atmosphere. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (6.7 mL; 29 mmol; 1.5 eq) was then added dropwise and the reaction mixture was stirred at room temperature for 15 minutes. The reaction was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (eluent: petroleum ether : ethyl acetate = 7 : 3) afforded 11.02 g (99%) of compound **10**, as a colorless, viscous oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.16-7.45 (m, 10H), 5.32 (d, *J*=5.4, 1H), 5.05 (t, *J*=7.1, 1H), 4.66 (ABq, *J*=3.2, 2H), 4.44-4.58 (m, 1H), 4.06-4.18 (m, 2H), 3.99 (dd, J_1=3.6, J_2=5.4, 1H), 3.16 (dd, J_1=3.0, J_2=13.5, 1H), 2.50 (dd, J_1=10.3, J_2=13.5, 1H), 1.73-2.18 (m, 2H), 1.66 (s, 3H), 1.60 (s, 3H), 1.40-1.58 (m, 2H), 1.06-1.26 (m, 1H), 1.00 (d, *J*=6.7, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8, 152.8, 137.9, 135.3, 131.3, 129.4, 129.0, 128.4, 128.2, 127.8, 127.3, 124.5, 79.6, 77.5, 73.3, 66.3, 55.9, 37.3, 36.2, 31.3, 26.0, 25.9, 25.7, 18.3, 17.6, 16.6, -4.2, -4.5.
IR (film): cm^{-1} 2958, 2930, 1784, 1706, 1384, 1210, 1110.
Elemental analysis: calcd. for $C_{34}H_{49}NO_5Si$: C 70.43%, H 8.52%, N 2.42%; found: C 70.79%, H 8.67%, N 2.45%.
$[\alpha]_D^{20}$ +50.3 (*c* 1.1, EtOAc).
***R*$_f$**=0.65 (petroleum ether : ethyl acetate = 3 : 1).

2.5 (2*R*,3*R*,4*R*)-2-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnon-7-en-1-ol (11)

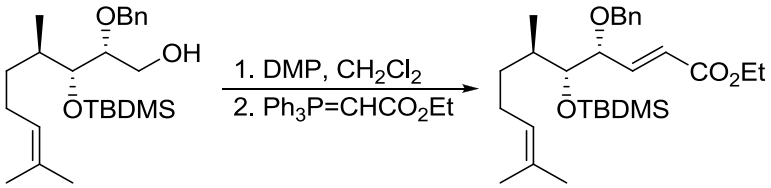


10 **11**

A solution of sodium borohydride (1.63 g; 43.1 mmol; 4.2 eq) in distilled water (21 mL) was added dropwise into a cold (0 °C) solution of (*S*)-4-benzyl-3-((2*S*,3*R*,4*R*)-2-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnon-7-enoyl)oxazolidin-2-one **10** (5.94 g; 10.24 mmol) in tetrahydrofuran (115 mL). The reaction mixture was stirred at room temperature for 20 h and the excess of borohydride was decomposed by slow addition of saturated ammonium chloride solution. Tetrahydrofuran was removed under reduced pressure, and the reaction mixture partitioned between ethyl acetate (400 mL) and water (100 mL). The aqueous layer was additionally extracted with ethyl acetate (3x 100 mL), combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated at rotovap. Purification by dry-flash chromatography (eluent: petroleum ether : ethyl acetate = 9 : 1) afforded 3.59 g (86%) of the title compound **11**, as a colorless, viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.38 (m, 5H), 5.08 (t, *J*=7.2, 1H), 4.69 (d, *J*=12.1, 1H), 4.56 (d, *J*=12.1, 1H), 3.77 (ddd, J_1=4.2, J_2=6.4, J_3=11.5, 1H),3.66 (dd, J_1=4.7, J_2=5.6, 1H), 3.62 (dd, J_1=5.8, J_2=11.5, 1H), 3.53 (ddd, J_1=4.2, J_2=5.6, J_3=9.8, 1H),1.98-2.10 (m, 2H), 1.84-1.93 (m, 1H), 1.68 (s, 3H), 1.63-1.70 (m, 1H), 1.60 (s, 3H), 1.44-1.53 (m, 1H), 1.10-1.20 (m, 1H), 0.99 (d, *J*=6.9, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 131.4, 128.4, 127.7, 127.6, 124.7, 82.4, 76.1, 72.6, 61.7, 35.1, 32.0, 26.0, 25.7, 25.6, 18.2, 17.6, 17.0, -4.1, -4.5.
IR (film): cm^{-1} 3459, 2957, 2930, 2858, 1464, 1253, 1085, 1043, 838, 776.
Elemental analysis: calcd. for $C_{24}H_{42}O_3Si$: C 70.88%, H 10.41%; found: C 71.03%, H 10.16%.
$[\alpha]_D^{20}$ +8.5 (*c* 0.9, EtOAc).
***R*$_f$**=0.30 (toluene : ethyl acetate = 94 : 6).

2.6 (4*R*,5*R*,6*R*,*E*)-ethyl-4-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-6,10-dimethylundeca-2,9-dienoate (12)



11 **12**

Dess-Martin's periodinane (5.5 g; 12.97 mmol; 1.5 eq) was added to a solution of (2*R*,3*R*,4*R*)-2-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnon-7-en-1-ol **11** (3.59 g; 8.83 mmol) in dry dichloromethane (110 mL) and the mixture was stirred at room temperature for 2.5 h. Solid (ethoxycarbonylmethylene)triphenylphosphorane (9.23 g; 26.5 mmol; 3 eq) was added and stirring was continued for additional 20 h. The reaction mixture was concentrated under reduced pressure and triturated with petroleum ether. The clear solution was decanted from the sticky solid, and dissolved in a minimal amount of dichloromethane. Triphenyphosphine oxide was separated again by the addition of petroleum ether, the obtained clear extract was combined with the first extract and the trituration process repeated two more times. The organic solution was successively washed with 10% sodium thiosulfate, saturated sodium bicarbonate and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by dry-flash chromatography (eluent: petroleum ether : toluene = 2 : 1) afforded 3.45 g (82 %) of (4*R*,5*R*,6*R*,*E*)-ethyl-4-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-6,10-dimethylundeca-2,9-dienoate **12**, as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18-7.41 (m, 5H), 6.91 (dd, J_1=6.4, J_2=15.8, 1H), 6.06 (dd, J_1=1.2, J_2=15.8, 1H), 5.05 (t, J=6.7, 1H), 4.58 (d, J=11.8, 1H), 4.39 (d, J=11.8, 1H), 4.22 (q, J=7.1, 2H), 3.97 (dt, J_1=1.2, J_2=6.3, 1H), 3.59 (dd, J_1=3.5, J_2=6.3, 1H), 1.73-2.14 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.31 (t, J=7.1, 3H), 1.03-1.68 (m, 3H), 0.95 (d, J=6.8, 3H), 0.88 (s, 9H), 0.03 (s, 3H), -0.04 (s, 3H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 166.1, 145.5, 138.1, 131.4, 128.2, 127.6, 127.5, 124.7, 122.8, 81.7, 78.6, 71.2, 60.4, 35.2, 31.0, 26.0, 25.6, 25.5, 18.3, 17.6, 17.1, 14.2, -4.1, -4.8.
IR (film): cm^{-1} 2958, 2931, 2859, 1724, 1460, 1301, 1256, 1170, 1095, 1041, 838.
Elemental analysis: calcd. for $C_{28}H_{46}O_4Si$: C 70.84%, H 9.77%; found: C 71.08%, H 9.55%.
$[\alpha]_D^{20}$ +12.3 (*c* 1.1, EtOAc).
***R*$_f$**=0.22 (petroleum ether : toluene = 1 : 1).

2.7 (4*R*,5*R*,6*R*,*E*)-4-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-6,10-dimethylundeca-2,9-dien-1-ol (13)

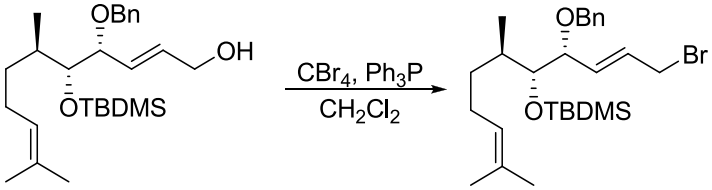
12 **13**

Di*iso*butylaluminum hydride (20 mL of 1.5 M solution in toluene; 30 mmol; 2.6 eq) was added dropwise to a cold (-40 °C) solution of (4*R*,5*R*,6*R*,*E*)-ethyl-4-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-6,10-dimethylundeca-2,9-dienoate **12** (5.48 g; 11.55 mmol) in dry diethyl ether (165 mL), under an argon atmosphere. Stirring was continued for 15 minutes and the reaction was quenched with saturated potassium sodium tartrate (50 mL). The resulting biphasic mixture was vigorously stirred for 2 h, until all the initially formed gel has redissolved. The organic layer was separated and the aqueous layer was additionally extracted with ether (4x100 mL). The combined organic extracts were dried over $MgSO_4$,

and concentrated under reduced pressure. Purification by dry-flash chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1) afforded 4.85 g (85%) of alcohol **13**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.33 (m, 5H), 5.83 (dtt, J_1=0.7, J_2=5.5, J_3=15.7, 1H), 5.59 (qt, J_1=1.5, J_2=15.7, 1H), 5.07 (t, J=7.2, 1H), 4.55 (d, J=12, 1H), 4.38 (d, J=12, 1H), 4.15 (bs, 2H), 3.80 (t, J=7.2, 1H), 3.54 (dd, J_1=3.1, J_2=6.7, 1H), 1.97-2.07 (m, 1H), 1.79-1.88 (m, 1H), 1.67 (s, 3H), 1.59-1.65 (m, 1H), 1.58 (s, 3H), 1.37-1.46 (m, 1H), 1.32 (bs, 1H, OH), 1.14-1.24 (m, 1H), 0.94 (d, J=6.7, 3H), 0.87 (s, 9H), 0.02 (s, 3H), -0.03 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 132.7, 131.2, 129.1, 128.1, 127.6, 127.2, 124.9, 83.0, 79.2, 70.4, 63.1, 35.0, 30.5, 26.1, 25.7, 25.6, 18.4, 17.6, 17.3, -3.8, -4.8.
IR (film): cm^{-1} 2957, 2929, 2860, 1711, 1112.
Elemental analysis: calcd. for $C_{26}H_{44}O_3Si$: C 72.17%, H 10.25%; found: C 71.95%, H 10.56%.
$[\alpha]_D^{20}$ +10.6 (*c* 1.0, EtOAc).
***R*$_f$**=0.39 (petroleum ether : ethyl acetate = 3 : 1).

2.8 ((4*R*,5*R*,6*R*,*E*)-4-(benzyloxy)-1-bromo-6,10-dimethylundeca-2,9-dien-5-yloxy)(*tert*-butyl)dimethylsilane (14)



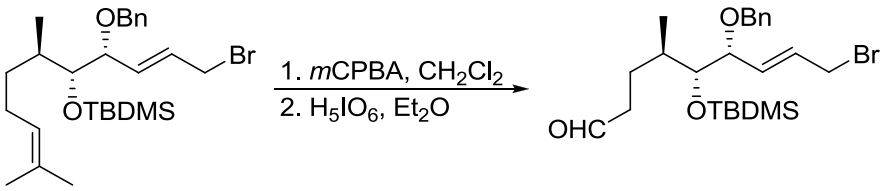
13 **14**

Triphenylphosphine (3.23 g; 12.3 mmol; 1.1 eq) and carbon tetrabromide (5.92 g; 17.8 mmol; 1.6 eq) were added to a cold (0 °C) solution of (4*R*,5*R*,6*R*,*E*)-4-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-6,10-dimethylundeca-2,9-dien-1-ol **13** (4.84 g; 11.2 mmol) in dry dichloromethane (62 mL). The reaction mixture was stirred for 15 minutes under an argon atmosphere, and concentrated under reduced pressure. The residue was triturated with petroleum ether and the solution was filtered from the precipitated solid. The solid was redissolved in a minimal volume of dichloromethane and the trituration process was repeated three more times. Silica (25 g) was added to the combined filtrates and the mixture was evaporated to dryness. The solid was loaded on a dry-flash column and eluted (eluent: petroleum ether : ethyl acetate = 98 : 2) to give 5.27 g (95%) of bromide **14**, as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21-7.38 (m, 5H), 5.82-6.02 (m, 1H), 5.67 (dd, J_1=7.5, J_2=15.4, 1H), 5.08 (t, J=6.8, 1H), 4.57 (d, J=12.2, 1H), 4.36 (d, J=12.2, 1H), 3.98 (d, J=7.6, 2H), 3.81 (t, J=7.5), 3.53 (dd, J_1=3.0, J_2=7.5), 1.74-2.15 (m, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.04-1.55 (m, 3H), 0.95 (d, J=6.8, 3H), 0.88 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H).
^{13}C NMR (50 MHz, $CDCl_3$) δ138.5, 133.0, 131.2, 129.5, 128.2, 127.8, 127.3, 124.9, 82.2, 79.1, 70.4, 35.2, 32.0, 30.5, 26.1, 25.7, 25.6, 18.4, 17.7, 17.3, -3.8, -4.8.
IR (film): cm^{-1} 2957, 2930, 2858, 1461, 1252, 1100, 1045, 839.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{26}H_{43}BrO_2SiNa$: 517.2108; found: 517.2115.

Elemental analysis: calcd. for $C_{26}H_{43}BrO_2Si$: C 63.01%, H 8.75%; found: C 62.87%, H 8.99%.
$[\alpha]_D^{20}$ +11.9 (*c* 3.6, EtOAc).
R_f=0.75 (petroleum ether : ethyl acetate = 9 : 1).

2.9 (4*R*,5*R*,6*R*,*E*)-6-(benzyloxy)-9-bromo-5-(*tert*-butyldimethylsilyloxy)-4-methylnon-7-enal (15)

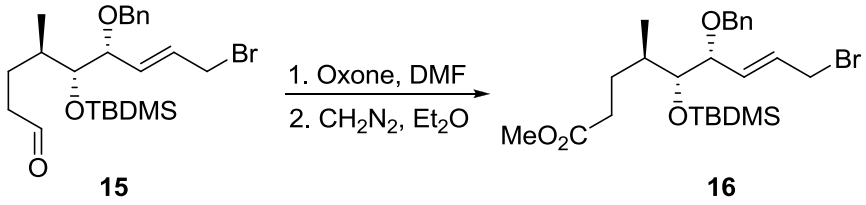


14 **15**

Solid *m*CPBA (0.726 g 77% *m*CPBA; 3.24 mmol; 1.3 eq) was added in several portions to the ice cold solution of ((4*R*,5*R*,6*R*,*E*)-4-(benzyloxy)-1-bromo-6,10-dimethylundeca-2,9-dien-5-yloxy)(*tert*-butyl) dimethylsilane **14** (1.235 g; 2.49 mmol) in dichloromethane (36 mL). After all the starting material was epoxidized (15 min), the reaction mixture was diluted with dichloromethane (200 mL), and washed successively with 10% sodium thiosulfate, saturated sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$ and solvent evaporated, to yield the crude epoxide. Saturated solution of periodic acid in diethyl ether (630 mg H_5IO_6/150 mL diethyl ether; 2.76 mmol; 1.1 eq) was added to the ethereal solution (20 mL) of the crude epoxide, causing the mixture to become milky white. After 15 minutes the fragmentation was complete and the mixture was washed with 10% sodium thiosulfate, saturated sodium bicarbonate and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, to afford 1.13 g of the crude aldehyde **15**, which was used directly in the next step, without purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9,76 (t, *J*=1.8, 1H), 7.28-7.36 (m, 5H), 5.97 (dt, J_1=7.4, J_2=15.6, 1H), 5.71 (dd, J_1=7.4, J_2=15.6, 1H), 4.58 (d, *J*=11.9, 1H), 4.36 (d, *J*=11.9, 1H), 3.99 (d, *J*=7.4, 2H), 3.84 (t, *J*=7.1, 1H), 3.58 (dd, J_1=3.0, J_2=6.5, 1H), 2.23-2.60 (m, 2H), 1.70-1.90 (m, 1H), 1.51-1.69 (m, 1H), 1.34-1.51 (m, 1H), 0.95 (d, *J*=6.7, 3H), 0.88 (s, 9H), 0.03 (s, 3H), -0.02 (s, 3H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 203.0, 138.3, 132.6, 129.8, 128.2, 127.8, 127.5, 82.1, 78.7, 70.6, 41.9, 34.9, 31.9, 26.0, 22.7, 17.4, -3.9, -4.8 (one carbon resonance was not observed under the recording conditions).
R_f=0.60 (petroleum ether : ethyl acetate = 4 : 1).

2.10 (4*R*,5*R*,6*R*,*E*)-methyl 6-(benzyloxy)-9-bromo-5-(*tert*-butyldimethylsilyloxy)-4-methylnon-7-enoate (16)

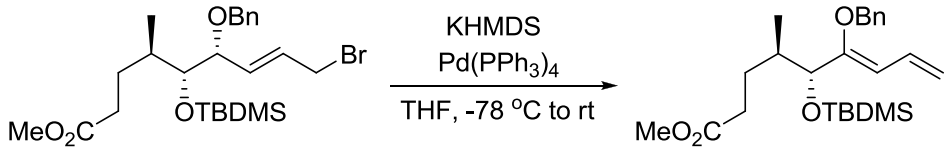


15 **16**

To a solution of crude aldehyde **15** (32 mg; 0.068 mmol) in dry DMF (1.2 mL) was added finely powdered Oxone® (63 mg; 0.1 mmol; 1.5 eq) and the resulted heterogeneous mixture was stirred 1.5 h at room temperature, under an argon atmosphere. The mixture was diluted with diethyl ether (50 mL) and the organic extract was washed with 0.5 M hydrochloric acid. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, to afford the corresponding acid. The crude acid was dissolved in diethyl ether (1.5 mL), the solution was cooled to 0 °C and treated with a cold solution of diazomethane in ether, until yellow color persists. After additional 30 minutes of stirring, the reaction mixture was concentrated at rotovap. Purification of the residue by dry-flash chromatography (petroleum ether : ethyl acetate = 97 : 3) afforded 25.4 mg (75%) of methyl ester **16**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.34 (m, 5H), 5.92-5.98 (m, 1H), 5.71 (dd, J_1=7.5, J_2=15.5, 1H), 4.56 (d, J=11.5, 1H), 4.36 (d, J=11.5, 1H), 3.95-4.01 (m, 2H), 3.83 (t, J=7, 1H), 3.66 (s, 3H), 3.54 (dd, J_1=3, J_2=6.5, 1H), 2.33-2.39 (m, 1H), 2.18-2.24 (m, 1H), 1.76-1.82 (m, 1H), 1.58-1.62 (m, 1H), 1.40-1.48 (m, 1H), 0.94 (d, J=7, 3H), 0.87 (s, 9H), 0.02 (s, 3H). -0.03 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 138.4, 132.7, 129.7, 128.2, 127.7, 127.4, 82.1, 78.8, 70.6, 51.4, 35.1, 32.0, 31.9, 26.1, 25.9, 18.4, 17.2, -3.9, -4.8.
IR (film): cm^{-1} 2955, 2931, 2885, 2857, 1739, 1103, 836.
HRMS (m/z) $[M+NH_4]^+$ calcd. for $C_{24}H_{43}BrNO_4Si$: 516.2139; found: 516.2132.
$[\alpha]_D^{20}$ +15.5 (*c* 0.95, $CHCl_3$).
***R*$_f$**=0.28 (petroleum ether : ethyl acetate = 94 : 6).

2.11 (4*R*,5*R*,*Z*)-methyl 6-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4-methylnona-6,8-dienoate (17)



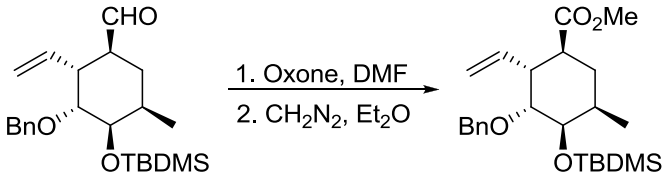
16 **17**

A solution of KHMDS in dry THF (82 µL; c=0.8 M; 0.066 mmol; 1.3 eq) was added to a cold (-78 °C) solution of bromide **16** (25 mg; 0.05 mmol) in dry tetrahydrofuran (3.2 mL), under an argon atmosphere. The temperature of the mixture was allowed to reach -50 °C during 30 minutes, when a solution of *tetrakis*(triphenylphosphine)palladium(0) (2.9 mg; 5 mol% in 200 µL of dry THF) was added. Stirring was continued for 1 h at room temperature and the mixture was evaporated to dryness under reduced

pressure. The residue was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 94 : 6) to yield 18.3 mg (87%) of diene **17**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.41 (m, 5H), 6.70 (dt, J_1=10, J_2=18, 1H), 5.67 (dd, J_1=0.5, J_2=10, 1H), 5.13 (dd, J_1=2, J_2=18, 1H), 4.97 (dd, J_1=2, J_2=10, 1H), 4.93 (d, J=11.5, 1H), 4.89 (d, J=11.5, 1H), 3.92 (d, J=5, 1H), 3.64 (s, 3H), 2.33-2.39 (m, 1H), 2.20-2.26 (m, 1H), 1.88-1.95 (m, 1H), 1.79-1.84 (m, 1H), 1.37-1.44 (m, 1H), 0.92 (s, 9H), 0.90 (d, J=7, 3H), 0.04 (s, 3H), 0.00 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 156.7, 137.8, 130.6, 128.4, 127.8, 115.0, 114.0, 76.9, 74.0, 51.4, 36.7, 32.2, 26.2, 25.9, 18.2, 16.4, -4.4, -5.1.
IR (film): cm^{-1} 2955, 2931, 2858, 1740, 1255, 838.
HRMS (m/z) $[M+NH_4]^+$ calcd. for $C_{24}H_{42}NO_4Si$: 436.2878; found: 436.2862.
$[\alpha]_D^{20}$ +32.5 (*c* 1.0, $CHCl_3$).
***R*$_f$**=0.48 (petroleum ether : ethyl acetate = 9 : 1).

2.12 (1*S*,2*R*,3*R*,4*R*,5*R*)-methyl 3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-2-vinylcyclohexanecarboxylate (18)

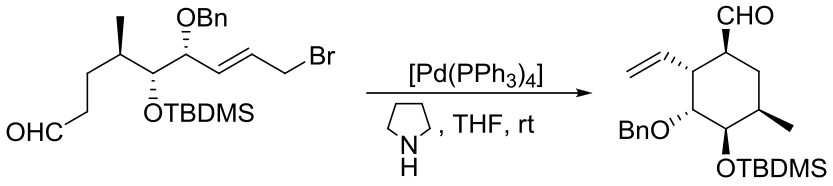


19 **18**

Finely powdered Oxone® (2.9 g; 4.72 mmol; 4 eq) was added in one portion to a solution of aldehyde **19** (458 mg; 1.18 mmol) in dry DMF (23 mL), and the resulted suspension was stirred at room temperature for 18 h. The reaction mixture was diluted with 1M hydrochloric acid (10 mL) and extracted with diethyl ether. The organic extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude acid was dissolved in diethyl ether (15 mL), the solution was cooled to 0 °C and treated with a cold solution of diazomethane in ether, until yellow color persisted. After additional 15 minutes of stirring, the reaction mixture was concentrated at rotavap. Purification of the residue by dry-flash (petroleum ether : ethyl acetate = 97 : 3) afforded 320 mg (65%) of methyl ester **18**, as a colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26-7,38 (m, 5H), 5.81-6.00 (m, 1H), 4.98-5.11 (m, 2H), 4.52 (s, 2H), 3.69 (t, J=2.7, 1H), 3.62 (s, 3H), 3.42 (dd, J_1=1.7, J_2=3.3, 1H), 2.71-2.82 (m, 2H), 1.92-2.01 (m, 1H), 1.45-1.71 (m, 2H), 0.93 (s, 9H), 0.88 (d, J=7.0, 3H), 0.00 (s, 3H), -0.02 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 138.7, 138.6, 128.2, 127.5, 127.4, 116.2, 81.6, 72.9, 70.8, 51.2, 43.2, 42.8, 30.4, 30.1, 25.8, 25.7, 18.0, -4.7, -4.9.
IR (film): cm^{-1} 2951, 2861, 1739, 1461, 1363, 1256, 1153, 1078.
Elemental analysis: calcd. for $C_{24}H_{38}O_4Si$: C 68.86%, H 9.15%; found: C 69.24%, H 9.31%.
$[\alpha]_D^{20}$ +39.5 (*c* 0.56, EtOAc).
***R*$_f$**= 0.72 (petroleum ether : ethyl acetate = 5 : 1).

2.13 (2*R*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-2-vinylcyclohexanecarbaldehyde (19)



15 **19**

A) Compound **19** (Cyclization of bromide **15**): A freshly distilled pyrrolidine (244 μL; 2.9 mmol; 1.2 eq) was added to a solution of crude (4*R*,5*R*,6*R*,*E*)-6-(benzyloxy)-9-bromo-5-(*tert*-butyldimethylsilyloxy)-4-methylnon-7-enal **15** from the previous step (1.13 g; ca. 2.4 mmol) in dry tetrahydrofuran (160 mL), followed by the addition of *tetrakis*(triphenylphosphine)palladium(0) (278 mg; 0.24 mmol; 10 mol%), under an argon atmosphere. The reaction mixture was stirred 2 h, when TLC indicated the full consumption of the starting material. Silica (8 g) was added and the mixture was evaporated to dryness under reduced pressure. The solid thus obtained was loaded on a dry-flash chromatography column and eluted (eluent: petroleum ether : ethyl acetate = 95 : 5) to give 0.775 g (83% over 3 steps, from **14**) of product **19**, as a colorless oil (*trans*/*cis* = 5 : 1).

B) Compound **19** (Cyclization of acetate **21**): A solution of triphenylphosphine (1.2 mg; 2.6 μmol; 20 mol%) and palladium acetate (0.25 mg; 1.1 μmol; 5 mol%) in dry DMSO (50 μL) was stirred 15 minutes at room temperature, producing a yellowish suspension. A solution of allylic acetate **21** (10.2 mg; 0.023 mmol) in dry DMSO (20 μL) was added to the resulted suspension, followed by the addition of pyrrolidine (0.8 μL; 9.2 μmol; 40 mol%) 10 minutes later. The reaction mixture was stirred overnight at room temperature, and then partitioned between dichloromethane and water. The organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (petroleum ether : ethyl acetate = 95 : 5) afforded 3.8 mg (43%) of product **19**, as a colorless oil (*trans*/*cis* = 5 : 1).

Spectral data for the mixture of diastereoisomers (assignation of peaks in ^{1}H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Major diastereoisomer (**19**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, *J*=3.1, 1H), 7.23-7.37 (m, 5H), 5.91-6.00 (m, 1H), 5.09-5.15 (m, 2H), 4.55 (s, 2H), 3.68 (dd, J_1=2.2, J_2=3.7, 1H), 3.43 (dd, J_1=2.5, J_2=3.7, 1H), 2.63-2.76 (m, 2H), 1.96-2.05 (m, 1H), 1.38-1.51 (m, 2H), 0.92 (d, *J*=6.7, 3H), 0.91 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1, 138.5, 138.4, 128.3, 127.7, 127.5, 117.0, 81.8, 73.0, 70.9, 48.6, 41.1, 29.6, 26.9, 25.8, 18.1, 18.0 -4.7, -4.9.

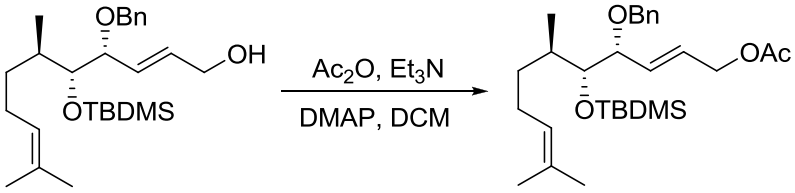
Minor diastereoisomer (**23**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.23-7.37 (m, 5H), 6.20-6.30 (m, 1H), 5.16-5.26 (m, 2H), 4.59 (d, *J*=12.0, 1H), 4.53 (d, *J*=12.0, 1H), 3.72 (t, *J*=3.6, 1H), 3.49 (dd, J_1=2.2, J_2=3.6, 1H), 2.99-3.05 (m, 1H), 2.36-2.41 (m, 1H), 1.96-2.04 (m, 1H) 1.91 (dt, J_1=3.0, J_2=13.3, 1H), 1.45-1.51 (m, 1H), 0.90 (s, 9H), 0.89 (d, *J*=6.8, 3H), 0.025 (s, 3H), -0.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 138.3, 137.8, 128.3, 137.6, 127.2, 116.7, 80.9,72.4, 70.7, 49.8, 41.6, 29.6, 26.9, 25.8, 18.1, 18.0, -4.6, -4.9.

IR (film): cm^{-1} 2933, 2862, 1725, 1255, 1073, 1040, 837.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{23}H_{36}O_3SiNa$: 389.2506; found: 389.2497.
Elemental analysis: calcd. for $C_{23}H_{36}O_3Si$: C 71.08%, H 9.34%; found: C 71.08%, H 9.49%.
$[\alpha]_D^{20}$ +42.0 (*c* 0.2, EtOAc).
***R*$_f$**=0.73 (petroleum ether : ethyl acetate = 4 : 1).

2.14 (4*R*,5*R*,6*R*,*E*)-4-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-6,10-dimethylundeca-2,9-dienyl acetate (20)

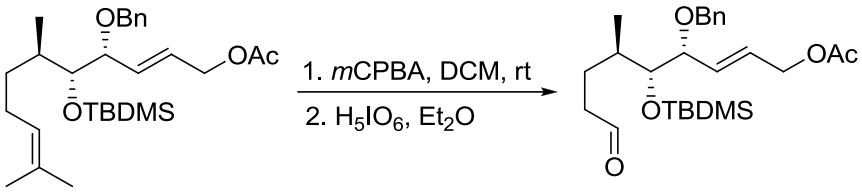


13 **20**

A catalytic amount of 4-dimethylaminopyridine was added to a solution of allylic alcohol **13** (15.6 mg; 0.036 mmol), acetic anhydride (7 μL; 0.072 mmol; 2 eq) and triethylamine (10 μL; 0.072 mmol; 2 eq) in dry dichloromethane (0.4 mL). After 5 minutes of stirring at room temperature, the volatiles were removed under reduced pressure. The residue was purified by column chromatography (eluent: toluene : ethyl acetate = 99 : 1), to afford the title compound **20** (14.2 mg; 91%), as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.35 (m, 5H), 5.77 (dt, J_1=6, J_2=15.5, 1H), 5.66 (dd, J_1=7.5, J_2=15.5, 1H), 5.05 (t, *J*=6.5, 1H), 4.58 (d, *J*=11, 2H), 4.55 (d, *J*=12, 1H), 4.34 (d, *J*=12, 1H), 3.80 (t, *J*=7, 1H), 3.53 (dd, J_1=3, J_2=6.5, 1H), 2.07 (s, 3H), 1.96-2.08 (m, 1H), 1.79-1.87 (m, 1H), 1.68 (s, 3H), 1.59 (s, 3H), 1.37-1.43 (m, 1H), 1.13-1.22 (m, 1H), 0.94 (d, *J*=7, 3H), 0.87 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 138.7, 132.0, 131.2, 128.1, 127.7, 127.6, 127.5, 127.2, 124.9, 82.7, 79.1, 70.4, 64.3, 35.2, 30.6, 26.1, 25.7, 20.9, 18.4, 17.6, 17.3, -3.8, -4.7.
IR (film): cm^{-1} 2957, 2930, 2857, 1745, 1231, 1095, 836.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{28}H_{46}O_4SiNa$: 497.3058; found: 497.3042.
$[\alpha]_D^{20}$ +13.8 (*c* 0.9 $CHCl_3$).
***R*$_f$**=0.66 (petroleum ether : ethyl acetate = 9 : 1).

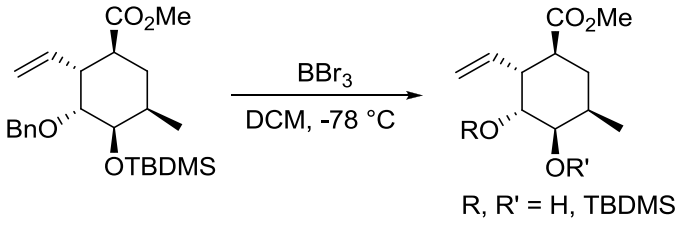
2.15 (4*R*,5*R*,6*R*,*E*)-4-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-6-methyl-9-oxonon-2-enyl acetate (21)



20 **21**

Solid *m*CPBA (9.6 mg 77% *m*CPBA; 0.038 mmol; 1.3 eq) was added in several portions to a cold (-10 °C) solution of compound **20** (14 mg; 0.0295 mmol) in dichloromethane (0.6 mL). After all the starting material was consumed (30 min), the reaction mixture was diluted with dichloromethane (20 mL), and washed successively with 10% sodium thiosulfate, saturated sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$ and solvent was evaporated, to yield the crude epoxide. Saturated solution of periodic acid in diethyl ether (7.5 mg H_5IO_6/3 mL diethyl ether; 0.0324 mmol; 1.1 eq) was added to the ethereal solution (0.6 mL) of the crude epoxide, causing the mixture to become milky white. After 15 minutes the fragmentation was complete and the mixture was washed with 10% sodium thiosulfate, saturated sodium bicarbonate and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, to afford 12.7 mg (96%) of the crude aldehyde **21**, which was used directly in the next step, without purification.

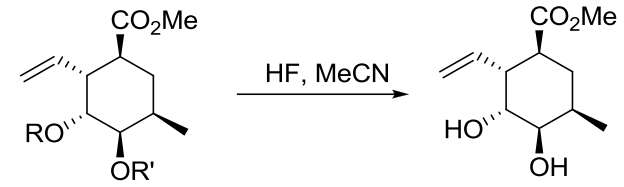
2.16 (1*S*,2*R*,3*R*,4*R*,5*R*)-methyl 4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-5-methyl-2-vinylcyclohexanecarboxylate and (1*S*,2*R*,3*R*,4*R*,5*R*)-methyl 3-(*tert*-butyldimethylsilyloxy)-4-hydroxy-5-methyl-2-vinylcyclohexanecarboxylate (24)



18 **24**

Boron-tribromide (30 µL; 0.315 mmol; 4 eq) was added dropwise to a cold (-78 °C) solution of methyl ester **18** (33 mg; 0.079 mmol) in dry dichloromethane (1.6 mL), under an argon atmosphere. The mixture was stirred for 30 minutes at that temperature, then quenched with saturated sodium bicarbonate solution (2 mL). After allowing to reach room temperature, the mixture was partitioned between ethyl acetate and brine. The organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography (petroleum ether : ethyl acetate = 5 : 1) afforded 23 mg (85%) of debenzylated products **24** (a mixture of silyl-ether regioisomers), as a colorless oil. The product was used in the next deprotection step, without prior separation of regioisomers.

2.17 (1S,2R,3R,4R,5R)-methyl 3,4-dihydroxy-5-methyl-2-vinylcyclohexanecarboxylate (25)



R, R' = H, TBDMS

24 **25**

A solution of concentrated hydrofluoric acid (120 µL), acetonitrile (730 µL) and the mixture of regioisomers **24** from the previous step (23 mg; 0.070 mmol) was stirred at room temperature for 4 days, in a polyethylene vessel. The mixture was partitioned between ethyl acetate and saturated sodium bicarbonate, the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The crude product was purified by dry-flash chromatography (petroleum ether : ethyl acetate = 1 : 1), affording 14.3 mg (91%) of diol **25**, as a white solid. The product was recrystallized from *n*-hexane/ethyl acetate, yielding well defined needle-like colorless crystals, suitable for X-ray analysis.

mp 89 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84-5.90 (m, 1H), 5.16-5.20 (m, 2H), 3.84 (bs, 1H), 3.78 (t, *J*=2.8, 1H), 3.63 (s, 3H), 2.77-2.80 (m, 2H), 2.00-2.05 (m, 1H), 1.77 (bs, 1H), 1.69 (bs, 1H), 1.58-1.62 (m, 2H), 1.00 (d, *J*=7.0, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 137.8, 117.7, 72.9, 72.4, 51.7, 41.9, 41.7, 30.6, 29.4, 17.3.

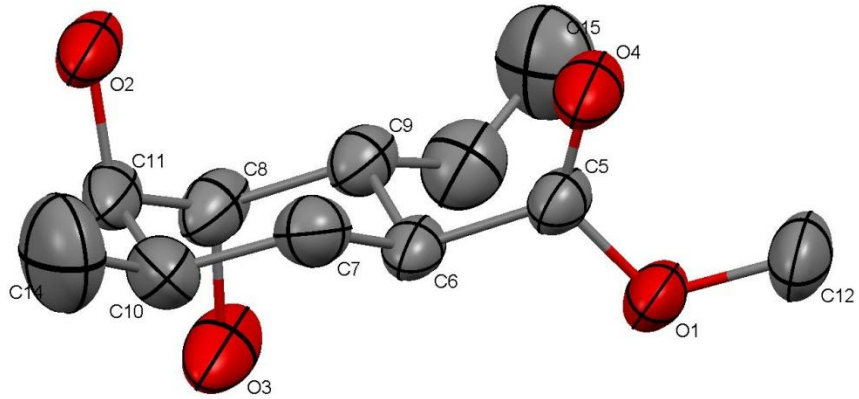
IR (film): cm^{-1} 3456, 2955, 2925, 1715, 1284, 1159, 991.

HRMS (m/z) $[M+Na]^+$ calcd. for $C_{11}H_{18}NaO_4$: 237.1097; found: 237.1090.

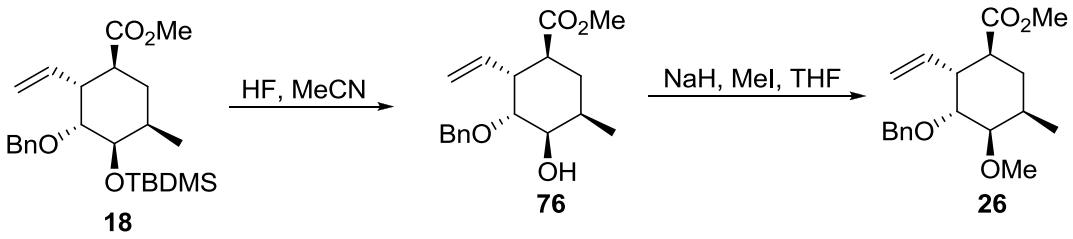
$[\alpha]_D^{20}$ +42.5 (*c* 0.2, $CHCl_3$).

***R*$_f$**=0.30 (petroleum ether : ethyl acetate = 1 : 1)

ORTEP diagram for diol 25



2.18 (1*S*,2*R*,3*R*,4*R*,5*R*)-methyl 3-(benzyloxy)-4-methoxy-5-methyl-2-vinylcyclohexanecarboxylate (26)



A) Compound **76** (deprotection of compound **18**): A solution of concentrated hydrofluoric acid (250 µL), acetonitrile (900 µL) and compound **18** (30 mg; 0.072 mmol) was stirred for 4 days at 40 °C, in a polyethylene vessel. The mixture was partitioned between ethyl acetate and saturated sodium bicarbonate, the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The crude product was purified by dry-flash chromatography (petroleum ether : ethyl acetate = 4 : 1), affording 19.5 mg (90%) of alcohol **76**, as a colorless oil.

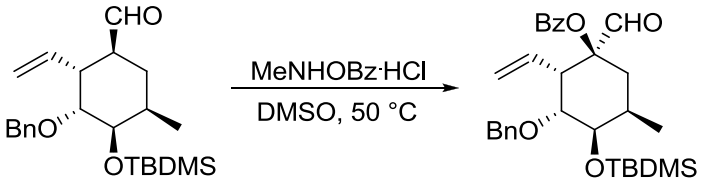
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5H), 5.88-5.95 (m, 1H), 5.11 (ddd, J_1=0.5, J_2=2, J_3=17.5, 1H), 5.03 (dd, J_1=2, J_2=10, 1H), 4.57 (d, *J*=12, 1H), 4.52 (d, *J*=12, 1H) 3.80 (t, *J*=2.5, 1H), 3.61 (s, 3H), 3.57 (t, *J*=3, 1H), 2.76-2.82 (m, 1H), 2.67-2.72 (m, 1H), 2.00-2.06 (m, 1H), 1.54-1.63 (m, 3H), 0.98 (d, *J*=7, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 138.5, 137.9, 128.3, 127.5, 127.3, 116.7, 80.9, 72.9, 70.3, 51.3, 43.3, 42.7, 30.0, 29.6, 17.3,
IR (film): cm^{-1} 3529, 3073, 2961, 1744, 1461, 1288.
HRMS (m/z) $[M+NH_4]^+$ calcd. for $C_{18}H_{28}O_4N$: 322.2013; found: 322.2014.
$[\alpha]_D^{20}$ +69.3 (*c* 1.0, $CHCl_3$).
***R*$_f$**=0.25 (petroleum ether : ethyl acetate = 4 : 1).

B) Compound **26** (Methylation of compound **75**): Sodium hydride (0.7 mg; 0.027 mmol; 2 eq) was added to a solution of alcohol **76** (4.2 mg; 0.0138 mmol) in dry THF (0.3 mL), under an argon atmosphere. Methyl iodide (17 µL; 0.27 mmol; 20 eq) was added after 10 minutes, and stirring was continued for 3 days at room temperature. The mixture was partitioned between diethyl ether and saturated ammonium chloride solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent: petroleum ether : ethyl acetate = 95 : 5), afforded 2.8 mg (64%) of methylether **26**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.38 (m, 5H), 5.88-5.95 (m, 1H), 5.10 (ddd, J_1=1, J_2=2, J_3=17.5, 1H), 5.03 (ddd, J_1=0.5, J_2=2.5, J_3=10.5, 1H), 4.54 (d, *J*=1, 2H), 3.64 (t, *J*=3, 1H), 3.60 (s, 3H), 3.35 (s, 3H), 3.15 (t, *J*=3, 1H), 2.72-2.77 (m, 1H), 2.59-2.63 (m, 1H), 1.95-2.00 (m, 1H), 1.50-1.59 (m, 2H), 0.98 (d, *J*=7, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 138.5, 138.2, 128.3, 127.6, 127.4, 116.5, 79.8, 77.6, 72.9, 58.7, 51.2, 43.4, 43.1, 30.9, 29.7, 17.5.
IR (film): cm^{-1} 2927, 2871, 1736, 1156, 1095.

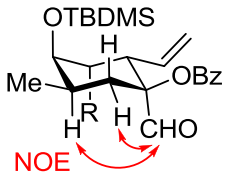
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{19}H_{26}O_4Na$: 319.1904; found: 319.1888.
$[\alpha]_D^{20}$ +72.6 (*c* 0.3, $CHCl_3$).
R_f=0.43 (petroleum ether : ethyl acetate = 9 : 1).

2.19 (1*S*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-1-formyl-5-methyl-2-vinylcyclohexyl benzoate (27)



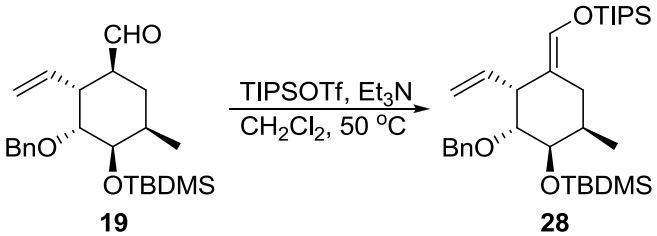
19 **27**

N-Methyl-*O*-benzoylhydroxylamine hydrochloride (2.2 mg; 11.6 μmol; 1.5 eq) was added to a solution of aldehyde **19** (3 mg; 7.7 μmol) in dry DMSO (100 μL), and the mixture was stirred for 5 days at 50 °C, under an argon atmosphere. The mixture was purified by preparative thin layer chromatography (eluent: PhMe : EtOAc = 9 : 1), to afford 1.3 mg (33%) of the title compound **27**, as a colorless film.



^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.96-8.00 (m, 2H), 7.51-7.55 (m, 1H), 7.40-7.43 (m, 2H), 7.26-7.37 (m, 5H), 6.18 (dt, J_1=9.9, J_2=17.0, 1H), 5.29 (dd, J_1=2.0, J_2=17.0, 1H), 5.23 (dd, J_1=2.0, J_2=9.5, 1H), 4.58 (d, *J*=12.1, 1H), 4.53 (d, *J*=12.1, 1H), 3.69 (t, *J*=3.0, 1H), 3.57 (dd, J_1=2.4, J_2=3.3, 1H), 3.17 (dd, J_1=2.0, J_2=9.5, 1H), 2.70 (dd, J_1=3.7, J_2=12.9, 1H), 2.38-2.47 (m, 1H), 1.70 (t, *J*=12.9, 1H), 0.96 (d, *J*=6.9, 3H), 0.91 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H).
HRMS (m/z) $[M+H]^+$ calcd. for $C_{30}H_{41}O_5Si$: 509.2718; found: 590.2719.
R_f=0.80 (petroleum ether : ethyl acetate = 4 : 1).

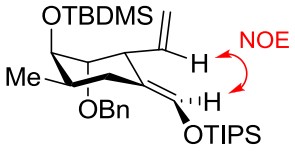
2.20 ((*E*)-((2*R*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-2-vinylcyclohexylidene)methoxy)tri*iso*propylsilane (28)



19 **28**

Tri*iso*propylsilyl trifluoromethanesulfonate (1.85 mL; 6.95 mmol; 4 eq) was added to a solution of (2*R*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-2-vinylcyclohexanecarbaldehyde **19** (0.675 g; 1.74 mmol) and triethylamine (4.3 mL; 10.42 mmol; 6 eq) in dry dichloromethane (4.3 mL). The mixture was stirred under argon at 50 °C for one hour, then diluted with petroleum ether (100 mL) and washed with 10% sodium thiosulfate, saturated sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by dry flash

chromatography (eluent: petroleum ether : ethyl acetate = 97 : 3), followed by additional drying at high vacuum (30 °C, 0.1 mmHg, to remove the residues of tri*iso*propylsilanol) afforded 0.935 g (99%) of silylenolether **28**, as a colorless oil.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.34 (m, 5H), 6.05-6.13 (m, 2H), 5.06-5.15 (m, 2H), 4.55 (s, 2H), 3.74 (dd, J_1=2.7, J_2=4.9, 1H), 3.38 (dd, J_1=3.6, J_2=4.9, 1H), 3.14 (bd, J=7.7, 1H), 2.51 (dd, J_1=4.1,J_2=13.2, 1H), 1.90-1.97 (m, 1H), 1.82-1.90 (m, 1H), 1.10-1.19 (m, 3H), 1.08 (d, J=6.3, 18H), 0.89-0.91 (m, 12H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 137.6, 134.4, 128.1, 127.3, 127.2, 118.4, 116.1, 82.4, 72.4, 72.1, 44.1, 32.1, 26.4, 25.8, 18.1, 17.8, 17.7, 12.0, -4.5, -4.9.

IR (film): cm^{-1} 2953, 2892, 2865, 1464, 1106, 1073, 834.

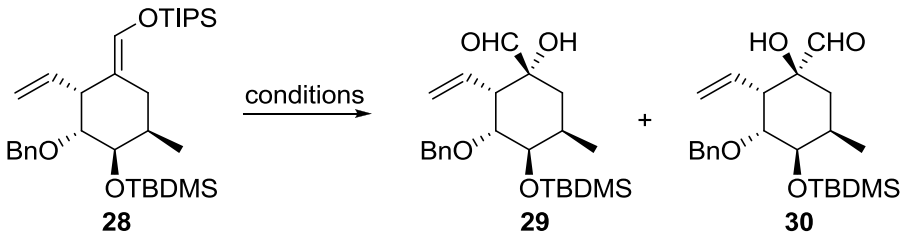
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{32}H_{56}O_3Si_2Na$: 567.3660; found: 567.3662.

Elemental analysis: calcd. for $C_{32}H_{56}O_3Si_2$: C 70.53%, H 10.36%; found: C 70.14%, H 10.57%.

$[\alpha]_D^{20}$ +19.0 (*c* 0.2, EtOAc).

***R*$_f$**=0.83 (petroleum ether : ethyl acetate = 98 : 2).

2.21 (1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-1-hydroxy-5-methyl-2-vinylcyclohexanecarbaldehyde (29) and (1*S*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-1-hydroxy-5-methyl-2-vinylcyclohexanecarbaldehyde (30)



A) Sharpless asymmetric dihydroxylation: To a solution of silylenolether **28** (177 mg; 0.325 mmol) in *tert*-butanol/water mixture (1:1.4; 2.4 mL) was added $(DHQD)_2PHAL$ (25 mg; 10 mol%), $K_3[Fe(CN)_6]$ (214 mg; 0.65 mmol; 2 eq), potassium carbonate (135 mg; 0.975 mmol; 3 eq) and potassium osmate dihydrate (18 mg; 15 mol%). The mixture was stirred for 48 h at 4 °C and saturated sodium sulfite solution (1 mL) was added. After additional 24 h of stirring, the mixture was partitioned between ethyl acetate (50 mL) and water (15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by dry flash chromatography (eluent: petroleum ether : ethyl acetate = 96 : 4), afforded 68 mg of the unreacted starting compound **28**, followed by 76 mg (58% or 94% based on recovered starting material) of product **30**, as a colorless oil.

If equivalent amount of $(DHQ)_2PHAL$ was used instead of $(DHQD)_2PHAL$, the same stereoisomer was isolated in 39% yield.

B) Epoxidation with *m*CPBA: Solid *m*CPBA (77%; 14.7 mg; 0.085 mmol; 2.5 eq) was added to a cold (-30 °C) solution of silylenolether **28** (20 mg; 0.034 mmol) in dichloromethane (2 mL). After 1.5 h of stirring, HF-pyridine complex (50 μL) was added and stirring was continued for one hour at room temperature. Silica (100 mg) was added to the mixture, all volatiles were removed on rotovap and the residue was

purified by column chromatography (eluent: petroleum ether : ethyl acetate = 9 : 1), affording 11.7 mg (85%) of the diastereoisomeric mixture of **29** and **30** (**29** : **30** = 1.5 : 1), as a colorless oil.

C) Epoxidation with MMPP: Magnesium monoperoxyphthalate (80%; 23 mg; 34 μmol; 1 eq) was added to a solution of silylenolether **28** (20 mg; 34 μmol) in ethanol (3 mL). After 3 h of stirring, HF-pyridine complex (50 μL) was added and stirring was continued for one hour at room temperature. Silica (100 mg) was added to the mixture, all volatiles were removed on rotovap and the residue was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 9 : 1), to afford 6.3 mg (46%) of the mixture of diastereoisomers **29** and **30** (**29** : **30** = 1 : 4), as a colorless oil.

D) Epoxidation with DMDO: A freshly prepared[9] solution of dimethyldioxirane (0.75 mL) was added dropwise to a solution of silylenolether **28** (20 mg; 0.034 mmol) in dry dichloromethane (1.2 mL), during 10 minutes. Epoxide HF-pyridine complex (100 μL) was added to this solution and stirring was continued for 2 h at room temperature. Silica (100 mg) was added to the mixture, all volatiles were removed on rotovap and the residue was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 9 : 1), to afford 11.3 mg (82%) of product **30**, as a colorless oil.

E) Epoxidation with a modified Davis' oxaziridine: Solution of silylenolether **28** (3.4 mg; 5.8 mmol) and 2-benzenesulphonyl-3-(*p*-nitrophenyl)oxaziridine (70% purity; 2.8 mg; 1.1 eq) in chloroform (0.2 mL) was stirred for 3 h at 65 °C. The reaction mixture was cooled to room temperature, HF-pyridine complex (50 μL) was added and stirring was continued for an additional hour. The reaction mixture was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 9 : 1), to afford 2.0 mg (86%) of product **30**, as a colorless oil.

Spectral data for isomer **29**

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.33-7.39 (m, 5H), 6.06-6.14 (m, 1H), 5.14-5.16 (m, 1H), 5.09-5.13 (m, 1H), 4.59 (s, 2H), 4.38 (s, 1H), 3.74 (t, *J*=2.5, 1H), 3.57 (t, *J*=3, 1H), 2.80 (dd, J_1=2.5, J_2=9, 1H), 2.18-2.23 (m, 1H), 1.66 (t, *J*=13, 1H), 1.34 (dd, J_1=4, J_2=13, 1H), 0.93 (d, *J*=7, 3H), 0.89 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 137.2, 134.4, 128.6, 128.2, 127.9, 118.8, 83.8, 80.2, 73.8, 70.4, 43.1, 34.9, 25.7, 25.5, 18.0, 17.7, -4.7, -4.9.

IR (film): cm^{-1} 3509, 2955, 2931, 2858, 1737, 1255, 1068, 1023.

HRMS (m/z) $[M+Na]^+$ calcd. for $C_{23}H_{36}O_4SiNa$: 427.2275; found: 427.2282.

$[\alpha]_D^{20}$ +36.6 (*c* 1.0, $CHCl_3$).

***R*$_f$**=0.31 (petroleum ether : ethyl acetate = 9 : 1).

Spectral data for isomer **30**

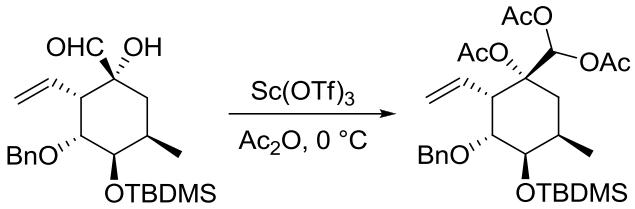
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.26-7.44 (m, 5H), 5.72 (dt, J_1=10, J_2=17, 1H), 5.25 (ddd, J_1=0.5, J_2=2, J_3=17, 1H), 5.22 (dd, J_1=2, J_2=10, 1H), 4.61 (d, *J*=3, 2H), 3.80 (t, *J*=3, 1H), 3.64 (t, *J*=3, 1H), 3.58 (s, 1H), 2.85 (dd, J_1=3, J_2=10, 1H), 2.36-2.41 (m, 1H), 1.86 (t, *J*=13.5, 1H), 1.58 (dd, J_1=3.5, J_2=13.5, 1H), 0.98 (d, *J*=6.5, 3H), 0.94 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 137.9, 133.5, 128.5, 127.9, 127.5, 112.0, 82.7, 78.2, 73.4, 70.0, 50.6, 35.7, 28.9, 25.8, 18.2, 18.0, -4.6, -4.9.

IR (film): cm^{-1} 3514, 2955, 2931, 2858, 1714, 1254, 1066.

HRMS (m/z) $[M+Na]^+$ calcd. for $C_{23}H_{36}O_4SiNa$: 427.2275; found: 427.2263.
$[\alpha]_D^{20}$ +55.8 (*c* 0.65, $CHCl_3$).
***R*$_f$**=0.21 (petroleum ether : ethyl acetate = 94 : 6).

2.22 ((1*R*,2*S*,3*R*,4*R*,5*R*)-1-acetoxy-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-2-vinylcyclohexyl)methylene diacetate (32)

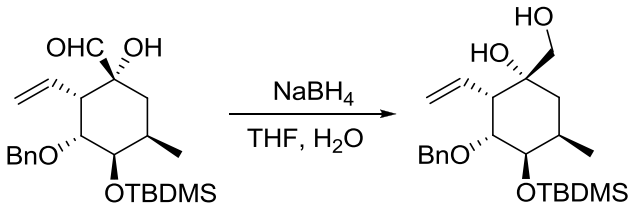


29 **32**

A pinch of scandium triflate was added to a cold (0 °C) solution of hydroxyaldehyde **29** (3.3 mg; 8.2 μmol) in acetic anhydride (150 μL), under an argon atmosphere. After 3 h of stirring, the solution was diluted with dichloromethane (15 mL) and washed with saturated sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by dry flash chromatography (eluent: petroleum ether : ethyl acetate = 9 : 1), afforded 3.4 mg (76%) of product **32**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.35 (m, 5H), 6.99 (s, 1H), 6.31-6.39 (m, 1H), 5.14 (dd, J_1=1.0, J_2=10.0, 1H), 5.00 (ddd, J_1=0.5, J_2=2.0, J_3=17.0, 1H), 4.53 (d, *J*=11.5, 1H), 4.46 (d, *J*=11.5, 1H), 3.72 (bt, *J*=2.5, 1H), 3,41 (t, *J*=3.5, 1H), 2.73 (dd, J_1= 3.0, J_2= 7.0, 1H), 2.70 (t, *J*=2.5, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 1.84 (s, 3H), 1.69 (dd, J_1=1.0, J_2=13.0, 1H), 0.92 (s, 9H), 0.90 (d, *J*=3.0, 3H), 0.04 (s, 3H), 0.03 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 168.6, 168.1, 138.8, 136.3, 128.2, 127.5, 127.3, 117.2, 88.8, 84.6, 84.5, 73.5, 70.7, 44.6, 27.4, 26.6, 25.7, 22.2, 20.8, 20.6, 18.0, 17.8, -4.7, -4.8.
IR (film): cm^{-1} 2955, 2931, 2857, 1771, 1741, 1247, 1223, 1200, 1084, 1038, 1012.
HRMS (m/z) $[M+NH_4]^+$ calcd. for $C_{29}H_{48}O_8NSi$: 566.3144; found: 566.3143.
$[\alpha]_D^{20}$ -6.2 (*c* 0.1, $CHCl_3$).
***R*$_f$**=0.51 (petroleum ether : ethyl acetate = 4 : 1).

2.23 (1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-1-(hydroxymethyl)-5-methyl-2-vinylcyclohexanol (34)

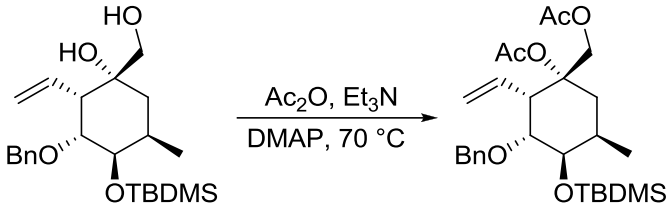


29 **34**

Sodium borohydride (11.2 mg; 0.30 mmol; 2 eq) was added to a solution of hydroxyaldehyde **29** (60 mg; 0.15 mmol) in tetrahydrofuran/water mixture (5:1; 4.2 mL) and the stirring was continued for 30 minutes at room temperature. The mixture was partitioned between ethyl acetate and water, and the organic layer was washed with brine. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by dry flash chromatography (eluent: petroleum ether : ethyl acetate = 2 : 1), to give 60.2 mg (100%) of diol **34**, as a colorless, viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.34 (m, 5H), 6.24 (dt, J_1=10, J_2=17, 1H), 5.16 (dd, J_1=2, J_2=10, 1H), 5.11 (ddd, J_1=0.5, J_2=2, J_3=17, 1H), 4.58 (d, J=12, 1H), 4.55 (d, J=12, 1H), 4.20 (s, 1H), 3.72 (t, J=3, 1H), 3.53 (t, J=3, 1H), 3.47-3.49 (m, 1H), 3.29 (dd, J_1=6.5, J_2=10.5, 1H), 2.48 (dd, J_1=2.5, J_2=9.5, 1H), 2.14-2.19 (m, 1H), 1.79 (bs, 1H), 1.56 (dd, J_1=3.5, J_2=13, 1H), 1.48 (t, J=13, 1H), 0.93 (d, J=6.5, 3H), 0.88 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 136.7, 128.5, 128.1, 127.8, 117.2, 85.7, 73.7, 73.6, 70.7, 69.4, 44.0, 36.6, 26.4, 25.7, 18.0, 17.9, -4.7, -4.9.
IR (film): cm^{-1} 3480, 2954, 2929, 2858, 1254, 1065, 1024.
HRMS (m/z) $[M+K]^+$ calcd. for $C_{23}H_{38}O_4KSi$: 445.2171; found: 445.2184.
$[\alpha]_D^{20}$ +42.8 (*c* 0.6, $CHCl_3$).
***R*$_f$**=0.29 (petroleum ether : ethyl acetate = 3 : 1).

2.24 ((1*R*,2*S*,3*R*,4*R*,5*R*)-1-acetoxy-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-2-vinylcyclohexyl)methyl acetate (35)



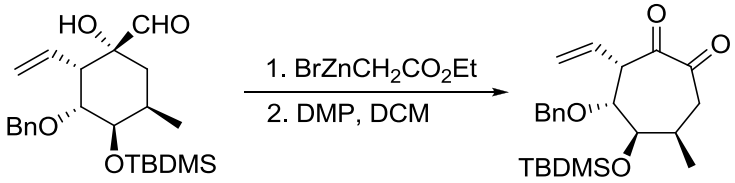
34 **35**

Acetic anhydride (60 μL; 0.619 mmol; 24 eq) and 4-dimethylaminopyridine (9.5 mg; 0.078 mmol; 3 eq) were added to a solution of diol **34** (10.5 mg; 0.026 mmol) in dry triethylamine (300 μL) and the mixture was stirred for 4 days at 70 °C, under an argon atmosphere. The mixture was partitioned between dichloromethane and 5% hydrochloric acid, the organic layer was washed with saturated sodium bicarbonate solution and brine. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent: petroleum ether : ethyl acetate = 9 : 1) afforded 6.3 mg (50%) of diacetate **35**, as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.35 (m, 5H), 6.23 (dt, J_1=10, J_2=17, 1H), 5.12 (dd, J_1=2.5, J_2=10.5, 1H), 5.05 (dd, J_1=1.5, J_2=17, 1H), 4.61 (d, J=11, 1H), 4.56 (d, J=12, 1H), 4.49 (d, J=12, 1H), 4.08 (d, J=10.5, 1H), 3.73 (s, 1H), 3.42 (t, J=3.5, 1H), 2.65 (dd, J_1=3.5, J_2=9.5, 1H), 2.37 (dd, J_1=2.5, J_2=14, 1H), 2.10-2.15 (m, 1H), 2.01 (s, 3H), 1.95 (s, 3H), 1.63 (dd, J_1=13, J_2=14.5, 1H), 0.92 (s, 9H), 0.89 (d, J=7, 3H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 170.2, 139.0, 136.2, 128.1, 127.3, 126.9, 117.4, 84.0, 82.7, 73.2, 70.8, 65.5, 45.2, 30.6, 26.5, 25.7, 22.1, 20.8, 18.0, 17.9, -4.7, -4.8.
IR (film): cm^{-1} 2956, 2931, 2858, 1741, 1248, 1223, 1076, 1035.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{27}H_{42}O_6SiNa$: 513.2643; found: 513.2622.
$[\alpha]_D^{20}$ +3.7 (*c* 0.4, $CHCl_3$).
***R*$_f$**=0.65 (petroleum ether : ethyl acetate = 4 : 1).

2.25 (3*S*,4*R*,5*R*,6*R*)-4-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-6-methyl-3-vinylcycloheptane-1,2-dione (36)

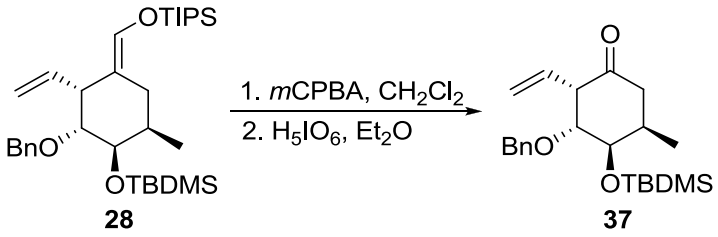


29 **36**

Ethyl bromoacetate (7.7 μL; 0.069 mmol; 5 eq) and zinc powder (3.6 mg; 0.055 mmol; 4 eq) were added to a solution of hydroxyaldehyde **29** (5.6 mg; 0.014 mmol) in benzene/diethyl ether mixture (1:1; 0.6 mL). A small crystal of iodine was added and the mixture was heated to 70 °C. After 1 h of stirring at that temperature, the mixture was diluted with ethyl acetate and washed with brine. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was redissolved in dry dichloromethane (400 μL) and treated with Dess-Martin's periodinane (11.1 mg; 0.026 mmol; 3 eq). After the oxidation was complete (2.5 h), silica (100 mg) was added to the mixture and volatiles were evaporated under reduced pressure. Purification of the residue by column chromatography (eluent: petroleum ether : ethyl acetate = 9 : 1) afforded 2.7 mg (49%) of the title compound **36**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.33 (m, 5 H), 6.28-6.45 (m, 1H), 5.24-5.30 (m, 1H), 5.09-5.13 (m, 1H), 4.62 (d, *J*=12.0, 1H), 4.43 (d, *J*=12.0, 1H), 4.12 (dd, J_1=0.5, J_2=8.5, 1H), 3.78-3.79 (m, 1H), 3.70-3.71 (m, 1H), 3.07 (dd, J_1=12.0, J_2=2.0, 1H), 2.34-2.41 (m, 1H), 2.27 (dd, J_1=1.0, J_2=12.0, 1H), 1.03 (d, *J*=7.0, 3H), 0.93 (s, 9H), 0.05 (s, 3H), -0.01 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 198.1, 196.1, 137.2, 134.4, 128.5, 128.1, 127.9, 118.0, 84.7, 73.4, 73.0, 53.1, 41.4, 31.8, 25.8, 20.6, 18.0, -4.1, -4.9.
IR (film): cm^{-1} 2955, 2929, 2856, 1716, 1253, 1075.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{23}H_{35}O_4Si$: 403.2299; found: 403.2286.
$[\alpha]_D^{20}$ +25.7 (*c* 0.4, $CHCl_3$).
***R*$_f$**=0.62 (petroleum ether : ethyl acetate = 4 : 1).

2.26 (2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-2-vinylcyclohexanone (37)

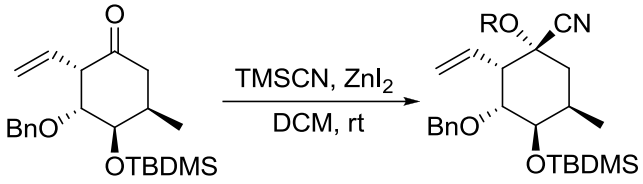


28 **37**

Solid *m*CPBA (427 mg 77% *m*CPBA; 1.89 mmol; 1.1 eq) was added to a solution of ((*E*)-((2*R*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-2-vinylcyclohexylidene)methoxy)tri*iso*propylsilane **28** (0.938 g; 1.72 mmol) in dry dichloromethane (25 mL), and the resulting mixture was stirred at room temperature for 15 minutes, when TLC indicated the full consumption of the starting material. A saturated ethereal solution of periodic acid (470 mg H_5IO_6 in 130 mL diethyl ether; 2.06 mmol; 1.2 eq) was added and stirring was continued for 2 h. The milky white suspension was diluted with diethyl ether (100 mL) and washed successively with 10% sodium thiosulfate, sodium bicarbonate and brine. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by dry flash chromatography (eluent: petroleum ether : ethyl acetate = 94 : 6) afforded 560 mg (87%) of cyclohexanone **37**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.38 (m, 5H), 6.24 (ddd, J_1=8.9, J_2=10.3, J_3=17.6, 1H) 5.23 (dd, J_1=10.4, J_2=1.6, 1H), 5.07 (d, J=17.5, 1H), 4.57 (d, J=12.0, 1H), 4.49 (d, J=12.0, 1H), 3.79 (t, J=3.5, 1H), 3.72 (bd, J=2.8, 1H), 3.47 (dd, J_1=3.2, J_2=8.8, 1H), 2.30-2.50 (m, 2H), 2.14 (dd, J_1=2.7, J_2=12.2, 1H), 0.97 (d, J=6.4, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 138.0, 133.9, 128.4, 127.8, 127.7, 117.9, 86.1, 73.1, 70.9, 53.7, 44.0, 33.1, 25.8, 18.0, 17.9, -4.6, -4.8.
IR (film): cm^{-1} 2955, 2930, 2886, 2858, 1719, 1254, 1064, 836.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{22}H_{35}O_3Si$: 375.2350; found 375.2352.
Elemental analysis: calcd. for $C_{22}H_{34}O_3Si$: C 70.54%, H 9.15%; found: C 70.50%, H 9.03%.
$[\alpha]_D^{20}$ +24.0 (*c* 0.2, EtOAc).
***R*$_f$**=0.40 (petroleum ether : ethyl acetate = 95 : 5).

2.27 (1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-1-(trimethylsilyloxy)-2-vinylcyclohexanecarbonitrile (38) and (1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-1-hydroxy-5-methyl-2-vinylcyclohexanecarbonitrile (39)



37

38 R=TMS

39 R=H

Zinc iodide (7 mg; 0.022 mmol; 6 mol%) and a freshly distilled trimethylsilyl cyanide (50 μL; 0.400 mmol; 3 eq) were added to a solution of ketone **37** (50 mg; 0.133 mmol) in dry dichloromethane (2 mL). After 15 minutes, silica (300 mg) was added and the mixture was evaporated to dryness. The residue was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 97 : 3), to afford 33.6 mg (54%) of TMS-protected cyanohydrin **38** and 19.6 mg (36%) of free cyanohydrin **39**, as colorless oils.

Spectral data for TMS-protected cyanohydrin **38**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5H), 6.21 (dt, J_1=9.5, J_2=17.5, 1H), 5.26-5.31 (m, 2H), 4.54 (d, J=12, 1H), 4.50 (d, J=12, 1H), 3.71 (bs, 1H), 3.42 (t, J=3.5, 1H), 2.52 (dd, J_1=3.5, J_2=9.5, 1H), 2.22-2.32 (m, 1H), 2.01 (t, J=13.5, 1H), 1.79 (dd, J_1=2.5, J_2=13.5, 1H), 0.91 (s, 9H), 0.90 (d, J=6.5, 3H), 0.22 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 135.0, 128.1, 127.2, 126.7, 121.8, 118.9, 82.1, 73.1, 71.9, 70.8, 48.3, 39.6, 25.7, 18.0, 17.5, 1.6, 1.1, -4.6, -4.8.

IR (film): cm^{-1} 2956, 2931, 2860, 1255, 1114, 1064, 842.

HRMS (m/z) $[M+K]^+$ calcd. for $C_{26}H_{43}NO_3Si_2K$: 512.2413; found: 512.2416.

$[\alpha]_D^{20}$ +12.1 (*c* 1.0, $CHCl_3$).

***R*$_f$**=0.62 (petroleum ether : ethyl acetate = 95 : 5).

Spectral data for cyanohydrin **39**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5H), 6.19-6.26 (m, 1H), 5.35-3.39 (m, 2H), 4.59 (d, J=11.5, 1H), 4.56 (d, J=11.5, 1H), 4.51 (s, 1H), 3.69 (bs, 1H), 3.60 (t, J=3, 1H), 2.73 (dd, J_1=2.5, J_2=9, 1H), 2.15-2.20 (m, 1H), 1.96 (dd, J_1=4, J_2=13.5, 1H), 1.89 (t, J=13.5, 1H), 0.93 (d, J=7, 3H), 0.88 (s, 9H), 0.00 (s, 3H), -0.05 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 133.2, 128.7, 128.5, 128.0, 120.7, 120.1, 82.9, 74.1, 72.0, 70.0, 45.1, 39.8, 25.7, 25.4, 17.9, 17.2, -4.7, -4.9.

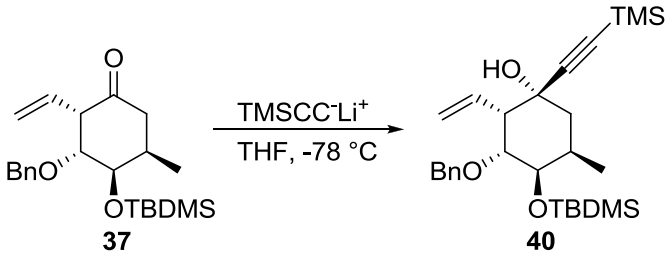
IR (film): cm^{-1} 3455, 2955, 2930, 2858, 1758, 1462, 1255, 1059, 843.

HRMS (m/z) $[M+H]^+$ calcd. for $C_{23}H_{36}NO_3Si$: 402.2459; found: 402.2461.

$[\alpha]_D^{20}$ +10.4 (*c* 1.0, $CHCl_3$).

***R*$_f$**=0.22 (petroleum ether : ethyl acetate = 95 : 5).

2.28 (1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-1-(trimethylsilyl)ethynyl)-2-vinylcyclohexanol (40)

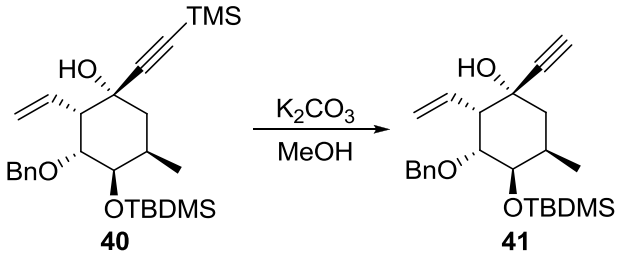


37 **40**

A solution of *n*-butyl lithium in hexanes (1.5 M; 110 µL; 0.16 mmol; 3 eq) was added dropwise to a cold (-78 °C) solution of trimethylsilylacetylene (25 µL; 0.16 mmol; 3 eq) in dry tetrahydrofuran (1 mL), under an argon atmosphere. After 45 minutes of stirring at that temperature, a solution of ketone **37** (20 mg; 0.053 mmol; 1 eq) in dry THF (1 mL) was added. Stirring was continued for 20 minutes at -78 °C, followed by 15 minutes at room temperature. The reaction mixture was partitioned between water and diethyl ether and the organic layer was washed with brine. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 96 : 4), to afford 21 mg (83%) of product **40**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.35 (m, 5H), 6.23-6.31 (m, 1H), 5.24-5.26 (m, 1H), 5.17-5.21 (m, 1H), 4.57 (s, 2H), 4.33 (s, 1H), 3.71 (t, *J*=2.5, 1H), 3.60 (t, *J*=3.5, 1H), 2.58 (dd, J_1=2.5, J_2=9, 1H), 2.10-2.18 (m, 1H), 1.82 (dd, J_1=4, J_2=13, 1H), 1.77 (t, *J*=13, 1H), 0.90 (d, *J*=7, 3H), 0.89 (s, 9H), 0.14 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 135.4, 128.5, 128.1, 127.8, 17.8, 108.6, 87.2, 83.5, 73.8, 71.0, 70.5, 46.8, 41.8, 26.1, 25.8, 18.0, 17.5, -0.02, -4.65. -4.86.
IR (film): cm^{-1} 3494, 2956, 2930, 1252, 1059, 841.
HRMS (m/z) $[M+K]^+$ calcd. for $C_{27}H_{44}O_3Si_2K$: 511.2461; found: 511.2451.
$[\alpha]_D^{20}$ +148 (*c* 0.1, $CHCl_3$).
***R*$_f$**=0.15 (petroleum ether : ethyl acetate = 96 : 4).

2.29 (1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-1-ethynyl-5-methyl-2-vinylcyclohexanol (41)



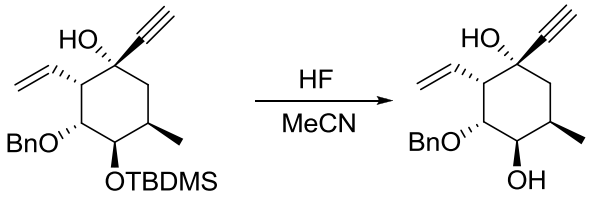
40 **41**

A finely powdered potassium carbonate (29 mg; 0.21 mmol; 5 eq) was added to a solution of TMS-alkyne **40** (20 mg; 0.042 mmol) in methanol (2.8 mL) and the resulted yellow suspension was stirred for

1 h at room temperature. After the reaction was complete, the most of methanol was evaporated and the residue was partitioned between 1M HCl and ether. The organic extract was washed with brine and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 94 : 6), to give 15 mg (88%) of alcohol **41**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.33 (m, 5H), 6.27-6.25 (m, 1H), 5.22-5.29 (m, 2H), 4.57 (d, *J*=2, 2H), 4.35 (s, 1H), 3.69 (t, *J*=2.5, 1H), 3.59 (t, *J*=2.5, 1H), 2.63 (dd, J_1=2.5, J_2=9, 1H), 2.40 (s, 1H), 2.13-2.18 (m, 1H), 1.86 (dd, J_1=4, J_2=13, 1H), 1.80 (t, *J*=13, 1H), 0.91 (d, *J*=7, 3H), 0.88 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 135.6, 128.5, 128.2, 127.8, 118.0, 86.9, 83.7, 73.9, 71.0, 70.5, 46.6, 41.9, 26.0, 25.7, 18.0, 17.5, -4.7, -4.9.
IR (film): cm^{-1} 2954, 2929, 2858, 1253, 1056, 840.
HRMS (m/z) $[M+K]^+$ calcd. for $C_{24}H_{36}O_3K$: 439.2065; found: 439.2051.
$[\alpha]_D^{20}$ +12.7 (*c* 1.0, $CHCl_3$).
***R*$_f$**=0.31 (petroleum ether : ethyl acetate = 9 : 1).

2.30 (1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-1-ethynyl-5-methyl-2-vinylcyclohexane-1,4-diol (42)

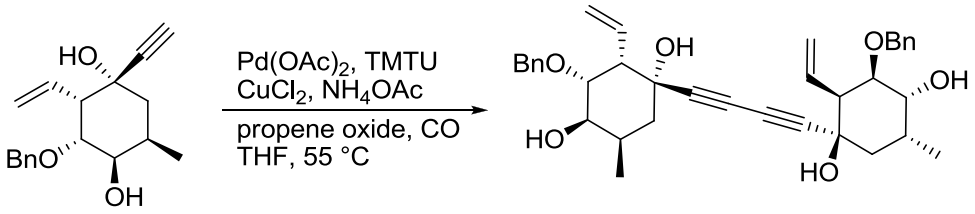


41 **42**

A solution of compound **41** (10 mg; 0.025 mmol), acetonitrile (0.5 mL) and 50% hydrofluoric acid (80 μL) in a polyethylene flask was heated to 50 °C over 4 days. The mixture was cooled to room temperature and partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate solution and brine and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1), to afford 4.5 mg (63%) of diol **42**, as a colorless, viscous film.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.40 (m, 5H), 6.25-6.34 (m, 1H), 5.27-5.33 (m, 2H), 4.59 (q, *J*=11.3, 2H), 4.33 (s, 1H), 3.86 (bs, 1H), 3.78 (t, *J*=3.2, 1H), 2.66 (dd, J_1=2.4, J_2=8.6, 1H), 2.41 (s, 1H), 2.18-2.29 (m, 1H), 1.93 (dd, J_1=3.8, J_2=13.7, 1H), 1.82 (t, *J*=13.7, 1H), 1.01 (d, *J*=7.0, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 135.1, 128.7, 128.3, 127.9, 118.6, 86.8, 83.3, 74.1, 71.5, 70.6, 70.0, 46.6, 41.7, 25.8, 17.0.
IR (film): cm^{-1} 3439, 3300, 2923, 1406, 1062, 1029, 995.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{18}H_{22}O_3Na$: 309.1461; found: 309.1463.
$[\alpha]_D^{20}$ +32.0 (*c* 0.2, $CHCl_3$).
***R*$_f$**=0.44 (petroleum ether : ethyl acetate = 2 : 1).

2.31 (1*R*,1'*R*,2*S*,2'*S*,3*R*,3'*R*,4*R*,4'*R*,5*R*,5'*R*)-1,1'-(buta-1,3-diyne-1,4-diyl)bis(3-(benzyloxy)-5-methyl-2-vinylcyclohexane-1,4-diol) (43)

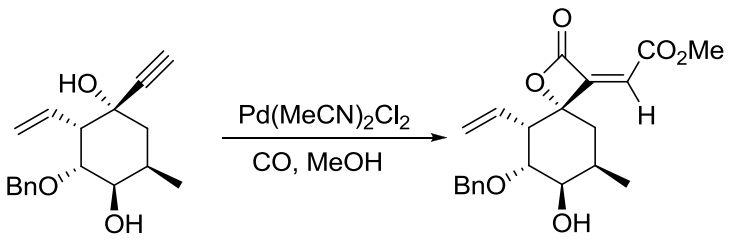


42 **43**

A suspension of palladium acetate (0.12 mg; 0.5 μmol; 10 mol%), anhydrous copper(II) chloride (1.8 mg; 13.1 μmol; 2.5 eq), ammonium acetate (0.4 mg; 5.2 μmol; 1 eq) and propylene oxide (1.8 μL; 26.2 μmol; 5 eq) in dry THF (350 μL) was stirred for 30 minutes at room temperature. The atmosphere in the flask was replaced with carbon monoxide and a solution of alkyne **42** (1.5 mg; 5.2 μmol; 1 eq) in dry THF (300 μL) was added. The reaction mixture was stirred for 40 h at 50 °C and then evaporated to dryness. The crude product was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 1 : 1), to give 0.7 mg (50%) of compound **43**, as a colorless film.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.35 (m, 5H), 6.18-6.25 (m, 1H), 5.26-5.30 (m, 2H), 4.57 (q, *J*=11, 2H), 4.27 (s, 1H), 3.82 (bs, 1H), 3.76 (bt, *J*=3.0, 1H), 2.63 (dd, J_1=2.5, J_2=9.0, 1H), 2.18-2.22 (m, 1H), 1.88 (dd, J_1=3.5, J_2=14, 1H), 1.78 (t, *J*=14, 1H), 1.46 (d, *J*=3, 1H), 0.98 (d, *J*=7.0, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 134.5, 128.5, 128.2, 127.7, 118.9, 83.0, 81.5, 74.0, 71.1, 70.0, 67.9, 46.3, 41.3, 25.6, 16.7.
IR (film): cm^{-1} 3441, 2925, 1406, 1063, 994.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{36}H_{42}O_6Na$: 593.2873; found: 593.2863.
R_f=0.17 (petroleum ether : ethyl acetate = 2 : 1).

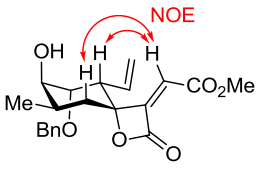
2.32 (*Z*)-methyl 2-((4*R*,5*S*,6*R*,7*R*,8*R*)-6-(benzyloxy)-7-hydroxy-8-methyl-2-oxo-5-vinyl-1-oxaspiro[3.5]nonan-3-ylidene)acetate (44)



42 **44**

To a solution of alkyne **42** (1.0 mg; 3.5 μmol) in dry methanol (0.4 mL), *bis*(acetonitril)palladium(II) chloride (0.9 mg; 3.5 μmol; 1 eq) was added and atmosphere in the flask was replaced with carbon monoxide. The solution was heated at 55 °C for 30 minutes, then cooled to room temperature and

evaporated to dryness. The crude product was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 2 : 1), to give 1.0 mg (77%) of β-lactone **44**, as a colorless film.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.34 (m, 5H), 6.04-6.10 (m, 1H), 5.81 (s, 1H), 5.21 (dd, J_1=1.5, J_2=10, 1H), 5.13 (dd, J_1=1.0, J_2=17, 1H), 4.59 (s, 2H), 3.83 (bs, 1H), 3.82 (s, 3H), 3.65 (t, J=3.5, 1H), 2.76 (dd, J_1=3.5, J_2=9.5, 1H), 2.35-2.37 (m, 1H), 1.89 (t, J=14.5, 1H), 1.80 (dd, J_1=4, J_2=14.5, 1H), 1.48-1.70 (m, 1H), 1.00 (d, J=7.3, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 158.7, 155.0, 138.2, 132.7, 128.3, 127.6, 127.5, 120.9, 118.8, 85.8, 81.3, 73.1, 70.0, 52.4, 44.7, 35.9, 26.5, 17.0.

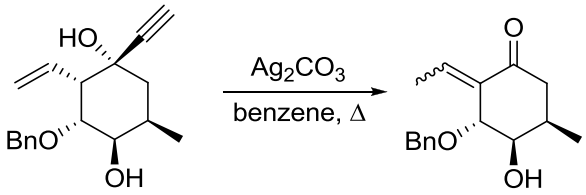
IR (film): cm^{-1} 3460, 2924, 1819, 1730, 1115.

HRMS (m/z) $[M+H]^+$ calcd. for $C_{21}H_{25}O_6$: 373.1646; found: 373.1635.

$[\alpha]_D^{20}$ +12.1 (*c* 0.1, $CHCl_3$).

***R*$_f$**= 0.20 (petroleum ether : ethyl acetate = 2 : 1).

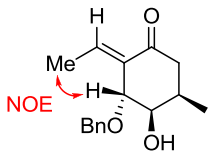
2.33 (3*R*,4*R*,5*R*)-3-(benzyloxy)-2-ethylidene-4-hydroxy-5-methylcyclohexanone (45)



42 **45**

Silver carbonate (6.1 mg; 0.022 mmol; 1 eq) was added to a solution of alkyne **42** (6.3 mg; 0.022 mmol) in dry benzene (600 μL) and the suspension was stirred for 18 h at 80 °C. The black suspension was evaporated to dryness and the residue was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1), to give 1.2 mg (23%) of *E*-isomer of **45** and 1.0 mg (16%) of *Z*-isomer of **45**.

Spectral data for E-isomer **45**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.39 (m, 5H), 6.93 (q, J=7.0, 1H), 4.56 (d, J=4.0, 1H), 4.54 (d, J=12.3, 1H), 4.38 (d, J=12.3, 1H), 4.06 (bs, 1H), 2.57-2.63 (m, 1H), 2.40 (dd, J_1=4.5, J_2=17.0, 1H), 2.30 (dd, J_1=12.3, J_2=4.5, 1H), 1.84 (d, J=7.5, 3H), 1.08 (d, J=7.0, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 140.7, 138.0, 135.0, 128.4, 127.8, 127.5, 74.5, 71.5, 69.8, 42.1, 29.3, 17.3, 13.9.

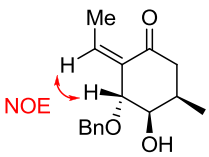
IR (film): cm^{-1} 3442, 2928, 1690, 1258, 833.

HRMS (m/z) $[M+Na]^+$ calcd. for $C_{16}H_{20}O_3Na$: 283.1305; found: 283.1298.

$[\alpha]_D^{20}$ +17.2 (*c* 0.1, $CHCl_3$).

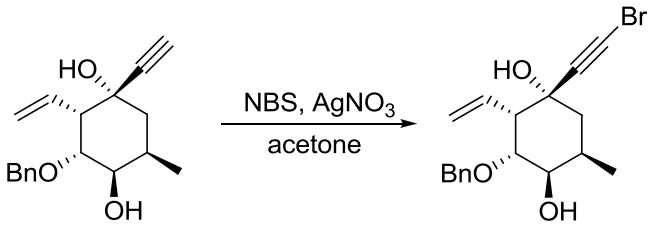
***R*$_f$**=0.23 (petroleum ether : ethyl acetate = 3 : 1).

Spectral data for Z-isomer **45**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.35 (m, 5H), 5.94 (q, *J*=7.0, 1H), 4.57 (d, *J*=12.1, 1H), 4.29 (d, *J*=12.1, 1H), 4.00, (d, *J*=4.1, 1H), 3.95 (bs, 1H), 2.56-2.60 (m, 1H), 2.35-2.37 (m, 2H), 1.99 (d, *J*=7.3, 3H), 1.60 (d, *J*=5.0, 1H), 1.07 (d, *J*=6.9, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 139.3, 137.8, 134.6, 128.3, 127.7, 127.6, 83.9, 72.3, 69.1, 44.6, 30.8, 16.9, 15.2.
IR (film): cm^{-1} 3444, 2932, 1686, 1257, 840.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{16}H_{20}O_3Na$: 283.1305; found: 283.1302.
$[\alpha]_D^{20}$ +13.6 (*c* 0.1, $CHCl_3$).
***R*$_f$**=0.14 (petroleum ether : ethyl acetate = 3 : 1).

2.34 (1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-1-(bromoethynyl)-5-methyl-2-vinylcyclohexane-1,4-diol (46)

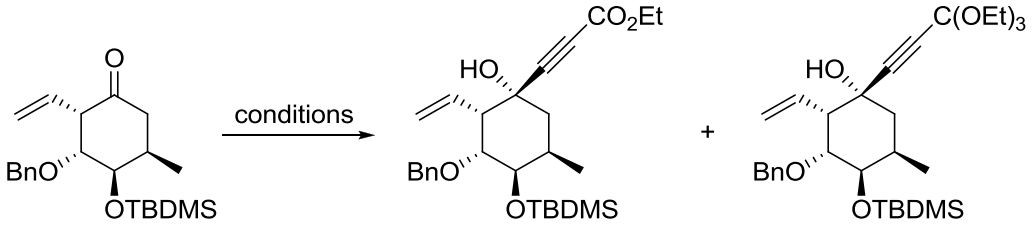


42 **46**

A finely powdered silver nitrate (1.8 mg; 10.8 μmol; 1 eq) was added to solution of alkyne **42** (3.1 mg; 10.8 μmol) in acetone (0.5 mL), and after 10 minutes the mixture was treated with a freshly recrystallized *N*-bromosuccinimide (1.8 mg; 10.8 μmol; 1 eq). The mixture was stirred for 15 minutes at room temperature and evaporated to dryness. The crude product was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1), to give 3.3 mg (85 %) of bromoalkyne **46**, as a colorless film.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5H), 6.22-6.30 (m, 1H), 5.27-5.31 (m, 2H), 4.58 (ABq, *J*=10.2, 2H), 4.30 (s, 1H), 3.84 (bs, 1H), 3.77 (t, *J*=3.4, 1H), 2.65 (dd, J_1=2.6, J_2=8.6, 1H), 2.17-2.25 (m, 1H), 1.91 (dd, J_1=4.1, J_2=13.8, 1H), 1.80 (t, *J*=13.8, 1H), 1.48 (d, *J*=3.1, 1H), 1.00 (d, *J*=7.0, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 134.7, 128.5, 128.2, 127.7, 118.6, 83.0, 82.7, 73.9, 71.7, 69.7, 46.4, 43.7, 41.5, 25.6, 16.7.
IR (film): cm^{-1} 3442, 2924, 1407, 1063, 994.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{18}H_{21}BrO_3Na$: 387.0566; found: 387.0583.
$[\alpha]_D^{20}$ +43.0 (*c* 0.3, $CHCl_3$).
***R*$_f$**=0.67 (petroleum ether : ethyl acetate = 2 : 1).

2.35 Ethyl 3-(1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-1-hydroxy-5-methyl-2-vinylcyclohexyl)propiolate (48) and (1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-1-(3,3,3-triethoxyprop-1-ynyl)-2-vinylcyclohexanol (50)



37 **48** **50**

A) Reaction with 3,3,3-triethoxyprop-1-yne: *n*-Butyl lithium (1.5 M in hexanes; 4.1 mL; 6.12 mmol; 3.5 eq) was added to the cold (-30 °C) solution of di*iso*propylamine (865 µL; 6.12 mmol; 3.5 eq) in dry toluene (30 mL). After 30 minutes of stirring, the resulting solution of LDA was cooled to -78 °C and 3,3,3-triethoxyprop-1-yn (1.204 g; 6.99 mmol; 4 eq) was added dropwise. The stirring was continued for additional 30 minutes and the solution of (2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-2-vinylcyclohexanone **37** (655 mg; 1.748 mmol) in dry toluene (60 mL) was added dropwise. After 20 minutes the reaction was allowed to warm up to 0 °C during one hour and the reaction was quenched with brine (20 mL). The product was extracted with ethyl acetate, the organic layer dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by dry flash chromatography (gradient elution: petroleum ether : ethyl acetate, from 95 : 2 to 9 : 1), to give 782 mg of the mixture of compounds **48** and **50**, which was used as such in the following transformation (i. e. experiment 2.36).

B) Reaction with ethyl propiolate: *n*-Butyl lithium (1.36 M in hexanes; 28 µL; 1.5 eq) was added to the cold (-78 °C) solution of ethyl propiolate (3.4 µL; 0.033 mmol; 1.3 eq) in dry THF (0.8 mL). After 60 minutes of stirring, a solution of ketone **37** (9.6 mg; 0.026 mmol) in dry THF (0.2 mL) was added dropwise. The mixture was allowed to reach room temperature during 60 minutes and the reaction was quenched by the addition of saturated ammonium chloride solution. The mixture was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 9 : 1), to give 4 mg (33%) of the product **48**, as a colorless oil.

Spectral data for **48**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.36 (m, 5H), 6.22-6.29 (m, 1H), 5.25-5.31 (m, 2H), 4.57 (d, *J*=1.5, 2H), 4.44 (s, 1H), 4.20 (q, *J*=7.5, 2H), 3.70 (t, *J*=3, 1H), 3.60 (t, *J*=3, 1H), 2.66 (dd, J_1=2, J_2=8.5, 1H), 2.15-2.18 (m, 1H), 1.78-1.88 (m, 2H), 1.28 (t, *J*=7.5, 3H), 0.91 (d, *J*=7, 3H), 0.88 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 137.0, 134.6, 128.6, 128.3, 127.9, 118.7, 89.4, 83.6, 75.2, 74.0, 70.8, 70.4, 61.9, 46.0, 41.0, 25.8, 18.0, 17.4, 14.0, -4.7, -4.9.

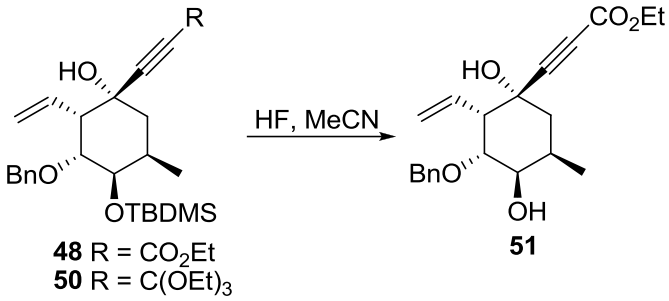
IR (film): cm^{-1} 3474, 2955, 2930, 1712, 1247, 1062.

HRMS (m/z) $[M+NH_4]^+$ calcd. for $C_{27}H_{44}NO_5Si$: 490.2983; found: 490.2976.

$[\alpha]_D^{20}$ +13.0 (*c* 1.0, $CHCl_3$).

***R*$_f$**=0.27 (petroleum ether : ethyl acetate = 9 : 1).

2.36 Ethyl 3-(1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-1,4-dihydroxy-5-methyl-2-vinylcyclohexyl)propiolate (51)



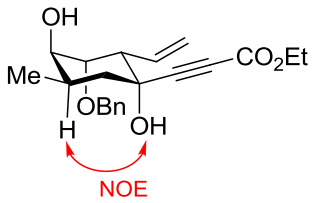
48 R = CO_2Et
50 R = $C(OEt)_3$

51

The mixture of propiolate **48** and the corresponding orthoester **50** (782 mg), from the previous step, was dissolved in acetonitrile (5 mL) in a polyethylene flask, and 50% hydrofluoric acid (2.1 mL) was added dropwise to the solution. The mixture was stirred at 60 °C for 9 h, and then partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 5 : 2) to give 473 mg (75% from **37**) of diol **51**, as a colorless solid.

mp 80 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.34 (m, 5H), 6.19-6.27 (ddd, J_1=1.5, J_2= 8.5, J_3=10.1, 1H), 5.30-5.34 (m, 2H), 4.61 (d, *J*=11.5, 1H), 4.55 (d, *J*=11.5, 1H), 4.39 (s, 1H), 4.19 (q, *J*=7.5, 2H), 3.86 (bs, 1H), 3.78 (t, *J*=2.9, 1H), 2.72 (dd, *J*=2.5, *J*=9.2, 1H), 2.19-2.25 (m, 1H), 1.93 (dd, *J*=4.1, *J*=13.5, 1H), 1.85 (t, *J*=13.5, 1H), 1.73 (bs, 1H), 1.28 (t, *J*=7.5, 3H), 1.00 (d, *J*=7.0, 3H).



^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 137.0, 134.1, 128.5, 128.2, 127.7, 119.1, 89.2, 82.9, 75.3, 74.0, 70.8, 69.5, 61.9, 45.8, 40.7, 25.4, 16.7, 13.9.

IR (film): cm^{-1} 3453, 2961, 2238, 1710, 1248, 1068, 1028.

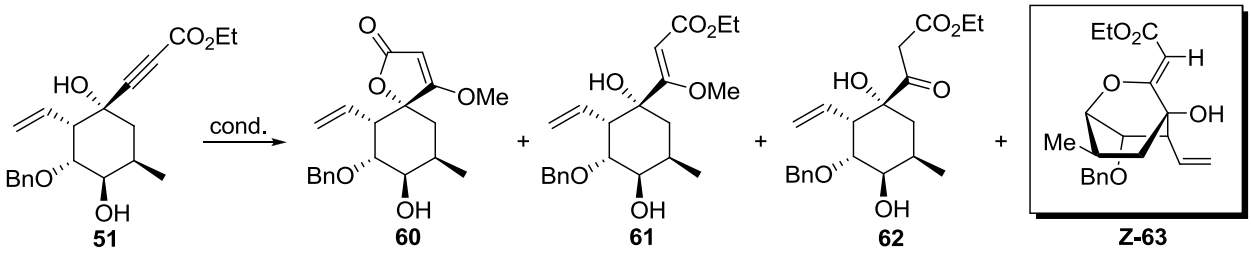
HRMS (m/z) $[M+NH_4]^+$ calcd. for $C_{21}H_{30}NO_5$: 376.2118; found: 376.2119.

Elemental analysis: calcd. for $C_{21}H_{26}O_5$: C 70.37%, H 7.31%; found: C 70.67%, H 7.48%.

$[\alpha]_D^{20}$ +49.8 (*c* 0.4, EtOAc).

***R*$_f$**=0.39 (petroleum ether : ethyl acetate = 2 : 1).

2.37 (*Z*)-ethyl 2-((1*R*,4*R*,5*S*,6*R*,7*R*)-6-(benzyloxy)-4-hydroxy-7-methyl-5-vinyl-2-oxabicyclo[2.2.2]octan-3-ylidene)acetate (Z-63)



A) Reaction in methanol as a solvent: A solution of (triphenylphosphine)gold(I)*bis*(trifluoromethane sulfonyl) imidate (1.1 mg; 10 mol%) and ethyl 3-((1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-1,4-dihydroxy-5-methyl-2-vinylcyclohexyl)propiolate **51** (5.2 mg; 14.5 µmol) in dry methanol (1 mL) was stirred for 4 h at 60 °C. Methanol was removed on rotovap and the residue was purified by column chromatography (gradient elution: petroleum ether : ethyl acetate, from 3 : 1 to 1 : 1), affording 1.1 mg (21%) of methyl tetronate **60**, followed by an inseparable mixture (3.1 mg) of **61** (7%), **62** (14%) and **Z-63** (38%).

B) Reaction in 2-propanol as a solvent: A solution of (triphenylphosphine)gold(I) *bis*(trifluoromethanesulfonyl)imidate (2.1 mg; 10 mol%) and ethyl 3-((1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-1,4-dihydroxy-5-methyl-2-vinylcyclohexyl)propiolate **51** (10 mg; 27.9 µmol) in dry 2-propanol (1 mL) was stirred for 1.5 h at 70 °C. 2-Propanol was removed on rotovap and the residue was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1), affording 8.5 mg (85%) of an inseparable mixture of **62** (25%) and **Z-63** (60%).

Spectral data for compound (extracted from NMR spectrum of the mixture produced by protocol A) **61**

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27-7.36 (m, 5H), 6.01-6.09 (m, 1H), 5.67 (s, 1H), 5.12-5.17 (m, 2H), 4.62 (d, *J*=11.0, 1H), 4.55 (d, *J*=11.0, 1H), 4.09-4.17 (m, 2H), 3.92 (s, 3H), 3.88 (bs, 1H), 3.81 (t, *J*=3.2, 1H), 2.88 (dd, J_1=2.6, J_2=9.1, 1H), 2.20-2.30 (m, 1H), 1.93 (t, *J*=13.1, 1H), 1.37 (dd, J_1=3.7, J_2=13.1, 1H), 1.25 (t, *J*=7.1, 3H), 1.00 (d, *J*=7.0, 3H).

HRMS (m/z) $[M+H]^+$ calcd. for $C_{22}H_{31}O_6$: 391.2115; found: 391.2115.

Spectral data for β-ketoester **62**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.36 (m, 5H), 6.06 (dt, J_1=9.8, J_2=19.6, 1H), 5.11-5.17 (m, 2H), 4.62 (d, *J*=11.6, 1H), 4.53 (d, *J*=11.6, 1H), 4.45 (s, 1H), 4.13-4.19 (m, 2H), 3.9 (bs, 1H), 3.75 (t, *J*=3.2, 1H), 3.70 (d, *J*=16.4, 1H), 3.38 (d, *J*=16.4, 1H), 2.84 (dd, J_1=2.4, J_2=9.5, 1H), 2.21-2.24 (m, 1H), 1.79 (t, *J*=13.5, 1H), 1.52-1.55 (m, 1H), 1.20-1.28 (m, 1H), 1.25 (t, *J*=7.2, 3H), 1.01 (d, *J*=6.9, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 167.9, 137.1, 133.6, 128.6. 128.2, 127.8, 119.5, 83.3, 82.9, 73.9, 69.6, 61.0, 46.3, 44.2, 37.0, 25.5, 17.0, 14.1.

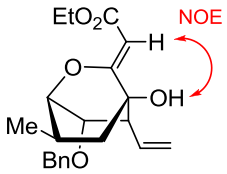
IR (film): cm^{-1} 3474, 2959, 2922, 1741, 1712, 1313, 1256, 1088, 1063, 1030.

HRMS (m/z) $[M+K]^+$ calcd. for $C_{21}H_{28}O_6K$: 415.1517; found: 415.1518.

$[\alpha]_D^{20}$ +53.0 (*c* 0.2, $CHCl_3$).

***R*$_f$**= 0.26 (petroleum ether : ethyl acetate = 3 : 1).

Spectral data for bicyclic ether **Z-63**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.36 (m, 5H), 6.11 (dt, J_1=10.2, J_2=17.0, 1H), 5.44 (dd, J_1=1.9, J_2=10.1, 1H), 5.33 (dd, J_1=1.9, J_2=17.0, 1H), 5.27 (s, 1H), 4.60 (d, J=12.0, 1H), 4.42 (d, J=12.0, 1H), 4.23 (dd, J_1=1.0, J_2=4.1, 1H), 4.09-4.18 (m, 2H), 4.07 (dd, J_1=4.1, J_2=9.8, 1H), 2.58 (dt, J_1=1,8, J_2=9.9, 1H), 2.50-2.57 (m, 1H), 2.19 (dd, J_1=11.1, J_2=12.9, 1H), 1.94 (bs, 1H), 1.25 (t, J=7.1, 3H), 1.11 (ddd, J_1=2.1, J_2=4.9, J_3=12.9, 1H), 1.08 (J=6.7, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 165.9, 137.6, 131.9, 128.4, 127.9, 127.5, 122.4, 86.8, 76.9, 73.6, 72.4, 69.9, 59.1, 49.2, 35.7, 26.1, 19.4, 14.4.

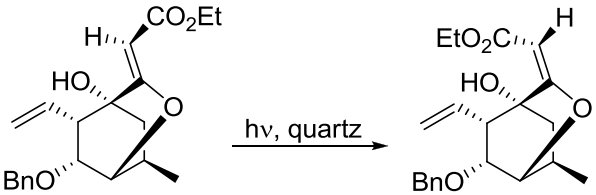
HRMS (m/z) $[M+H]^+$ calcd. for $C_{21}H_{28}O_5$: 359.1858; found: 359.1860.

IR (film): cm^{-1} 3426, 2966, 2928, 1692, 1643, 1185, 1080, 999.

$[\alpha]_D^{20}$ +28.0 (*c* 0.1, $CHCl_3$).

***R*$_f$**=0.34 (petroleum ether : ethyl acetate = 3 : 1).

2.38 (*E*)-ethyl 2-((1*R*,4*R*,5*S*,6*R*,7*R*)-6-(benzyloxy)-4-hydroxy-7-methyl-5-vinyl-2-oxabicyclo[2.2.2]octan-3-ylidene)acetate (E-63)



Z-63 **E-63**

A quartz test tube, containing a solution of bicyclic enolether **Z-63** (3.5 mg; 9.8 μmol) in dry *n*-hexane (3 mL), was irradiated with UV light from a low pressure mercury lamp (6W), under an argon atmosphere. After 6 minutes of the irradiation, a photochemical equilibrium was reached and the mixture was evaporated to dryness. The significantly less polar *E*-isomer (1.0 mg) was separated from the *Z*-isomer (2.2 mg) by column chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1). The isolated starting material was subjected to the second photochemical cycle, to afford additional 0.7 mg of *E*-isomer. The overall yield of **E-63** was 50% (71% based on the recovered starting material).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.27-7.36 (m, 5H), 6.05 (dt, J_1=10.1, J_2=17.0, 1H), 5.39 (dd, J_1=2.0, J_2=10.1, 1H), 5.35 (ddd, J_1=0.6, J_2=2.1, J_3=17.0, 1H), 5.32 (s, 1H), 4.65 (d, J=11.7, 1H), 4.39 (d, J=11.7, 1H), 4.14 (q, J=7.1, 2H), 4.02 (dd, J_1=0.6, J_2=3.9, 1H), 3.88 (dd, J_1=3.8, J_2=9.6, 1H), 2.76 (dt, J_1=1.8, J_2=9.8, 1H), 2.46-2.55 (m, 1H), 2.35 (dd, J_1=10.9, J_2=13.2, 1H), 1.27 (t, J=7.1, 3H), 1.21 (ddd, J_1=1.7, J_2=5.6, J_3=13.2, 1H), 1.04 (d, J=7.2, 3H).

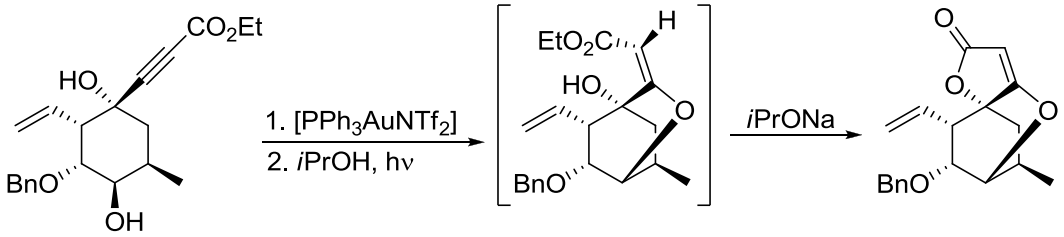
^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.9, 170.4, 137.8, 131.6, 128.4, 127.8, 127.6, 121.3, 92.9, 77.7, 74.0, 72.5, 72.3, 60.9, 49.7, 36.1, 22.6, 19.5, 14.2.

IR (film): cm^{-1} 3421, 2967, 2942, 1652, 1082.

HRMS (m/z) $[M+Na]^+$ calcd. for $C_{21}H_{28}O_6Na$: 381.1672; found: 381.1669.

$[\alpha]_D^{20}$ +21.5 (*c* 0.1, $CHCl_3$).
***R*$_f$**=0.76 (petroleum ether : ethyl acetate = 2 : 1).

2.39 (5*R*,6*R*,7*aR*,8*S*,9*R*)-8-vinyl-6,7-dihydro-9-(benzyloxy)-6-methyl-5H-5,7a-ethano-2H-furo[3,2-b]pyran-2-one (47)



51 **E-63** **47**

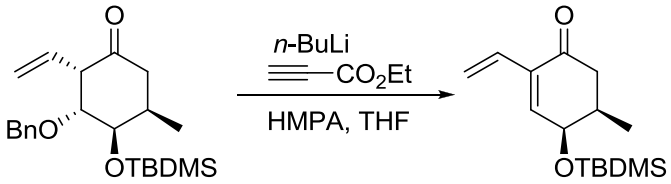
A) Base promoted cyclization of **E-63**: A catalytic amount of sodium hydride was added to a solution of bicyclic enolether **E-63** (1.4 mg; 3.9 μmol) in dry THF (0.5 mL), under an argon atmosphere. The reaction mixture was stirred for 30 minutes at room temperature, diluted with diethyl ether and the organic layer was washed with brine. The organic extract was dried over anhydrous $MgSO_4$, evaporated under reduced pressure and purified by column chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1), to afford 1.2 mg (85%) of the pure product **47**, as a white solid.

B) Three step one-pot sequence: A solution of (triphenylphosphine)gold(I)-*bis*(trifluoromethanesulfonyl) imidate (10mg; 10 mol%) and ethyl 3-((1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-1,4-dihydroxy-5-methyl-2-vinylcyclohexyl)propiolate **51** (50 mg; 0.14 mmol) in dry 2-propanol (5 mL) was heated at 70 °C, under an argon atmosphere. After 150 minutes TLC indicated the complete conversion of the starting material to a single intermediate (bicyclic *Z*-enolether **Z-63**). The yellowish-brown solution was transferred to the quartz test tube, diluted with 2-propanol (4.5 mL), the solution of sodium 2-propoxide (prepared from 0.7 mg of sodium hydride and 0.5 mL of 2-propanol; 20 mol%) was added, and the reaction mixture irradiated with UV light from a low pressure mercury lamp (6W). After two hours of irradiation, the mixture was concentrated to 2 mL and partitioned between ethyl acetate and brine, the organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 4 : 1) to afford 26.2 mg (60%) of product **47**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.39 (m, 5H), 6.07-6.14 (m, 1H), 5.38-5.42 (m, 2H), 4.94 (s, 1H), 4.65 (d, *J*=11.5, 1H), 4.42 (d, *J*=11.5, 1H), 4.28 (dd, J_1=1.5, J_2=3.4, 1H), 4.03 (dd, J_1=3.4, J_2=9.5, 1H), 2.74 (dd, J_1=11.1, J_2=12.5, 1H), 2.59-2.64 (m, 2H), 1.10 (d, *J*=7.5, 3H), 1.00 (ddd, J_1=2.5, J_2=5.2, J_3=7.1, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 183.8, 172.8, 137.1, 129.6, 128.5, 128.1, 127.6, 122.2, 84.6, 80.7, 79.3, 73.1, 72.8, 46.0, 31.7, 25.4, 19.1.
IR (film): cm^{-1} 2967, 1765, 1650, 1083, 912.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{19}H_{21}O_4$: 313.1434; found: 313.1430.
Elemental analysis: calcd. for $C_{19}H_{20}O_4$: C 73.06%, H 6.45%; found: C 72.65%, H 6.72%.
$[\alpha]_D^{20}$ +11.1 (*c* 1.0, EtOAc).

R_f=0.42 (petroleum ether : ethyl acetate = 3 : 1).

2.40 (4*R*,5*R*)-4-(*tert*-butyldimethylsilyloxy)-5-methyl-2-vinylcyclohex-2-enone (49)

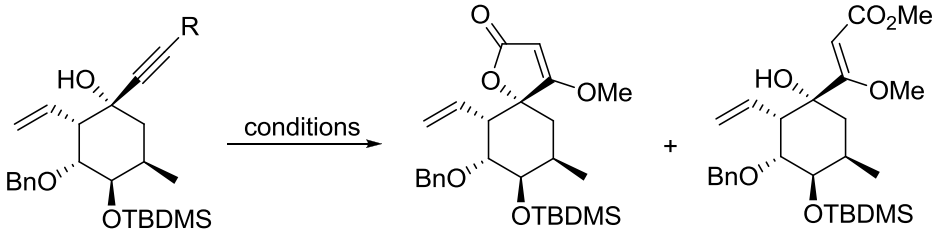


37 **49**

n-Butyl lithium (1.5 M in hexanes; 50 μL; 0.08 mmol; 3 eq) was added dropwise to a cold (-90 °C) solution of ethyl propiolate (8.1 μL; 0.08 mmol; 3 eq) in dry THF (0.5 mL). After 15 minutes, HMPA (37 μL; 0.214 mmol; 6 eq) was added and stirring was continued for additional 15 minutes. A solution of ketone **37** (10 mg; 0.0267 mmol) in dry THF (0.2 mL) was added to the resulting mixture, which was allowed to reach -60 °C over 1 h. The reaction was quenched by the addition of saturated ammonium chloride (1 mL) and the product was extracted with dichloromethane. The organic extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent: petroleum ether : ethyl acetate = 95 : 5) gave 3.7 mg (52%) of diene **49**, as a colorless film.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.77 (d, *J*=3.8, 1H), 6.55 (dd, J_1=11.2, J_2=17.4, 1H), 5.73 (d, *J*=17.4), 5.26 (d, *J*=11.2, 1H), 4.51 (t, *J*=4.0, 1H), 2.31-2.65 (m, 3H), 1.04 (d, *J*=6.8, 3H), 0.95 (s, 9H), 0.15 (s, 6H).
HRMS (m/z) $[M+H]^+$ calcd. for $C_{15}H_{27}O_2Si$: 267.1775; found: 267.1778.
R_f=0.48 (petroleum ether : ethyl acetate = 95 : 5).

2.41 (*Z*)-methyl 3-((1*R*,2*S*,3R,4*R*,5*R*)-3-(benzyloxy)-4-(tert-butyldimethylsilyloxy)-1-hydroxy-5-methyl-2-vinylcyclohexyl)-3-methoxyacrylate (52) and (5R,6S,7R,8R,9R)-7-(benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-4-methoxy-9-methyl-6-vinyl-1-oxaspiro[4.5]dec-3-en-2-one (53)



48 R=CO_2Et
50 R=C(OEt)$_3$
53 **52**

A) Magnesium methoxide catalyzed cyclization of **48**: Methanolic solution of magnesium methoxide (100 μL; 8.6 μmol; 2 eq) was added to a solution of propiolate **48** (2.7 mg; 5.7 μmol) in dry methanol (100 μL), under an argon atmosphere. The solution was stirred for 4 h at 55 °C, evaporated to dryness

and purified by column chromatography (gradient elution from petroleum ether : ethyl acetate = 95 : 5 to 8 : 2), to give 1.0 mg (36%) of product **52** and 0.8 mg (29%) of methyl tetronate **53**, as a colorless oils.
B) Cyclization of **50** catalyzed by mercury modified nafion resin: Finely powdered nafion resin modified with mercury (22.6 mg) was added to a solution of **50** (104 mg; 0.19 mmol) in methanol (6.3 mL) and water (17 µL; 0.95 mmol; 5 eq). After 2 days of stirring at room temperature, the resin was removed by filtration and the solution was evaporated to dryness. Purification of the residue by column chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1) afforded 78 mg (90%) of tetronate **53**, as a colorless oil.

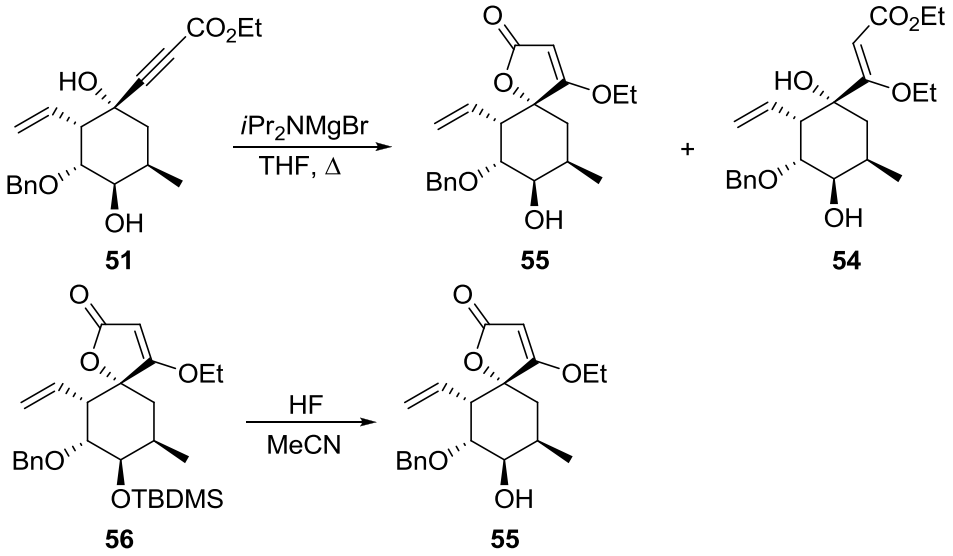
Spectral data for compound **52**

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27-7.37 (m, 5H), 6.02-6.09 (m, 1H), 5.70 (s, 1H), 5.07-5.13 (m, 2H), 4.56 (s, 2H), 4.46 (s, 1H), 3.90 (s, 3H), 3.71 (t, *J*=2.4, 1H), 3.66 (s, 3H), 3.60 (t, *J*=3.1, 1H), 2.95 (dd, J_1=2.6, J_2=9.2, 1H), 2.12-2.21 (m, 1H), 1.99 (t, *J*=12.8, 1H), 1.28 (dd, J_1=3.9, J_2=12.8, 1H), 0.90 (s, 9H), 0.90 (d, *J*=7.6, 3H), 0.01 (s, 3H), -0.04 (s, 3H).
HRMS (m/z) $[M+H]^+$ calcd. for $C_{27}H_{43}O_6Si$: 491.2823; found: 491.2227.
R_f=0.75 (petroleum ether : ethyl acetate = 3 : 1).

Spectral data for methyl tetronate **53**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.37 (m, 5H), 6.02-6.09 (m, 1H), 5.70 (s, 1H), 5.07-5.13 (m, 2H), 4.56 (s, 2H), 4.46 (s, 1H), 3.90 (s, 3H), 3.71 (t, *J*=2.4, 1H), 3.66 (s, 3H), 3.60 (t, *J*=3.1, 1H), 2.95 (dd, J_1=2.6, J_2=9.2, 1H), 2.12-2.21 (m, 1H), 1.99 (t, *J*=12.8, 1H), 1.28 (dd, J_1=3.9, J_2=12.8, 1H), 0.90 (s, 9H), 0.90 (d, *J*=7.6, 3H), 0.01 (s, 3H), -0.04 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 184.3, 172.4, 138.7, 134.0, 128.2, 127.5, 127.4, 118.1, 88.7, 85.5, 81.3, 73.1, 71.0, 59.2, 43.3, 34.9, 26.8, 25.7, 18.0, 17.7, -4.7, -5.0.
IR (film): cm^{-1} 2954, 2930, 1756, 1637, 1065.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{26}H_{39}O_5Si$: 459.2567; found: 459.2576.
$[\alpha]_D^{20}$ -13.4 (*c* 1.0, $CHCl_3$).
R_f=0.44 (petroleum ether : ethyl acetate = 2 : 1).

2.42 (*Z*)-ethyl 3-((1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-1,4-dihydroxy-5-methyl-2-vinylcyclohexyl)-3-ethoxyacrylate (54) and (5*R*,6*S*,7*R*,8*R*,9*R*)-7-(benzyloxy)-4-ethoxy-8-hydroxy-9-methyl-6-vinyl-1-oxaspiro[4.5]dec-3-en-2-one (55)



A) Base promoted cyclization of compound **51**: A solution (THF) of bromomagnesium di*iso*propylamide (c=0.3 mM; 190 μL; 0.056 mmol; 10 eq) was added to a solution of compound **51** (2 mg; 5.6 μmol) in dry THF (150 μL), under an argon atmosphere. The mixture was heated for 3 h at 55 °C and then evaporated to dryness. The product was purified by column chromatography (eluent: petroleum ether : ethyl acetate = 2:1), to give 0.6 mg (36%) of product **54** and 0.4 mg (29%) of methyl tetronate **55**, as colorless oils.

B) Compound **55** (deprotection of TBDMS-ether **56**): A solution of silyl ether **56** (30 mg; 0.0635 mmol) in acetonitrile (1 mL) and 50% hydrofluoric acid (250 μL) was heated to 40 °C over 7 days, in a polyethylene flask. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate and brine. The organic layer was dried over anhydrous $MgSO_4$, evaporated under reduced pressure and purified by dry flash chromatography (eluent: petroleum ether : ethyl acetate = 1 : 1), to give 20.6 mg (91%) of the pure product **55**, as a white solid.

Spectral data for compound **54**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.36 (m, 5H), 6.01-6.08 (m, 1H), 4.93-5.09 (m, 2H), 5.66 (s, 1H), 5.13-5.18 (m, 2H), 4.62 (d, *J*=11.5, 1H), 4.55 (d, *J*=11.5, 1H), 4.52 (s, 1H), 4.41 (dq, J_1=7.8, J_2=11.0, 1H), 4.05-4.15 (m, 2H), 3.99 (dq, J_1=7.8, J_2=11.0, 1H), 3.88 (bs, 1H), 3.81 (t, *J*=3.3, 1H), 2.90 (dd, J_1=2.6, J_2=8.6, 1H), 2.22-2.30 (m, 1H), 1.97 (t, *J*=15.4, 1H), 1.38 (dd, J_1=3.7, J_2=15.4, 1H), 1.28 (t, *J*=7.5, 3H), 7.4, (t, *J*=7.5, 3H), 1.01 (d, *J*=7.0, 3H).

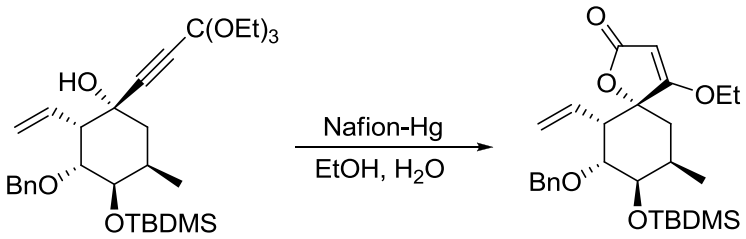
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{23}H_{32}O_6Na$: 427.2091; found: 427.2088.

Spectral data for compound **55**

mp 178 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.37 (m, 5H), 5.89 (dt, J_1=9.5, J_2=17.5, 1H), 4.93-5.09 (m, 2H), 4.58 (s, 1H), 4.58 (ABq, J=2.0, 2H), 3.92-4.07 (m, 2H), 3.82 (bs, 1H), 3.61 (bs, 1H), 2.77 (dd, J_1=3.1, J_2=9.4, 1H), 2.41-2.51 (m, 1H), 1.96 (t, J=13.3, 1H), 1.76 (bs, 1H), 1.37 (t, J=6.8, 3H), 1.34-1.38 (m, 1H), 0.97 (d, J=7.0 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 183.2, 172.7, 138.7, 133.6, 128.2, 127.3, 127.2, 118.5, 88.6, 85.3, 81.1, 73.0, 70.3, 68.3, 43.3, 34.7, 26.5, 17.2, 14.0.
IR (film): cm^{-1} 3538, 2923, 1727, 1626, 1324, 1201, 1033, 802.
HRMS (m/z) $[M+NH_4]^+$ calcd. for $C_{21}H_{30}NO_5$: 376.2118; found: 376.2115.
$[\alpha]_D^{20}$ +10.5 (*c* 0.2, $CHCl_3$).
***R*$_f$**=0.38 (petroleum ether : ethyl acetate = 1 : 1).

2.43 (5*R*,6*S*,7*R*,8*R*,9*R*)-7-(benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-4-ethoxy-9-methyl-6-vinyl-1-oxaspiro[4.5]dec-3-en-2-one (56)

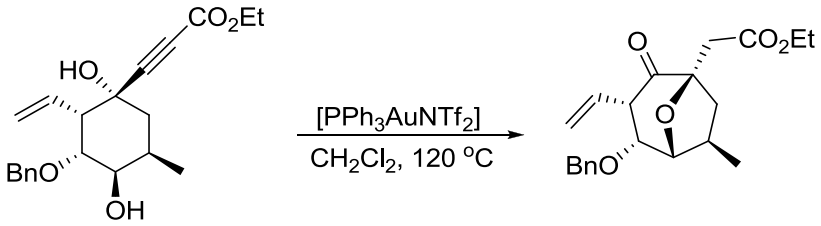


50 **56**

Finely powdered nafion resin modified with mercury (20 mg) was added to a solution of **50** (44 mg; 0.08 mmol) in dry ethanol (2.5 mL) and water (7.2 µL; 0.40 mmol; 5 eq). After 2 days of stirring at room temperature, the resin was removed by filtration and the solution evaporated to dryness. Purification of the residue by column chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1) afforded 31 mg (82%) of tetronate **56**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.37 (m, 5H), 5.90 (dt, J_1=10.0, J_2=17.5, 1H), 4.98-5.04 (m, 2H), 4.92 (s, 1H), 4.61 (d, J=12.5, 1H), 4.52 (d, J=12.5, 1H), 4.03 (dq, J_1=7.1, J_2=9.8, 1H), 3.94 (dq, J_1=7.1, J_2=9.8, 1H), 3.65 (bs, 1H), 3.43 (t, J=3.5, 1H), 2.77 (dd, J_1=3.5, J_2=9.5, 1H), 2.39-2.41 (m, 1H), 1.97 (t, J=13.5, 1H), 1.37 (t, J=7.1, 3H), 1.29 (dd, J_1=3.5, J_2=13.5, 1H), 0.89 (s, 9H), 0.87 (d, J=6.5, 3H), -0.02 (s, 3H), -0.07 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 183.3, 172.8, 138.7, 134.0, 128.2, 127.5, 127.4, 118.1, 89.5, 85.4, 81.3, 73.1, 71.0, 68.1, 43.3, 35.0, 26.7, 25.6, 17.9, 17.8, 13.9, -4.7, -5.0.
IR (film): cm^{-1} 2955, 2930, 2857, 1757, 1634, 1067.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{27}H_{40}O_5Na$: 495.2537; found: 495.2524.
$[\alpha]_D^{20}$ -6.3 (*c* 0.2, $CHCl_3$).
***R*$_f$**=0.30 (petroleum ether : ethyl acetate = 3 : 1).

2.44 Ethyl 2-((1*R*,3*S*,4*R*,5*R*,6*R*)-4-(benzyloxy)-6-methyl-2-oxo-3-vinyl-8-oxabicyclo[3.2.1]octan-1-yl)acetate (58)

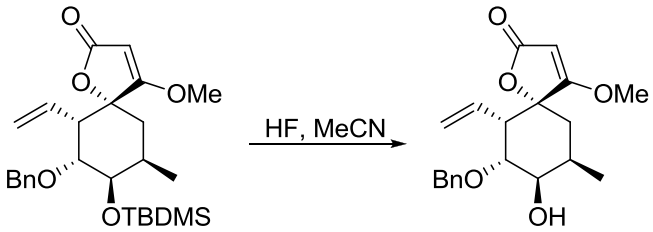


51 **58**

A solution of (triphenylphosphine)gold(I) *bis*(trifluoromethanesulfonyl)imidate (0.7 mg; 10 mol%) and ethyl 3-((1*R*,2*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-1,4-dihydroxy-5-methyl-2-vinylcyclohexyl)propiolate **51** (3.5 mg; 7 µmol) in dichloromethane (1.5 mL) was heated overnight to 120 °C in a sealed ampoule. After cooling to room temperature, the solvent was removed on rotovap. Purification of the residue by column chromatography (petroleum ether : ethyl acetate = 4 : 1), afforded 2.7 mg (77%) of the title compound **58**, as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.36 (m, 5H), 5.67 (dt, J_1=10.0, J_2=17.0, 1H), 5.23-5.28 (m, 2H), 4.65 (d, *J*=12.2, 1H), 4.45 (d, *J*=12.2, 1H), 4.37 (dd, J_1=6.8, J_2=8.8, 1H), 4.31 (d, *J*=6.8, 1H), 4.11-4.16 (m, 2H), 3.05 (d, *J*=16.2, 1H), 2.96 (t, *J*=9.5, 1H), 2.78 (dd, J_1=8.1, J_2= 17.5, 1H), 2.56-2.62 (m, 1H), 2.46 (d, *J*=16.2, 1H), 2.25 (ddd, J_1=1.5, J_2=3.2, J_3=17.5, 1H), 1.24 (s, 9H) 1.23 (t, *J*=9.5, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 169.9, 137.8, 130.5, 128.4, 127.7, 127.2, 120.8, 88.1, 81.8, 79.4, 73.2, 60.6, 54.5, 42.6, 37.7, 28.9, 20.8, 14.1.
HRMS (m/z) $[M+K]^+$ calcd. for $C_{21}H_{26}KO_5$: 397.1412; found: 397.1404.
IR (film): cm^{-1} 2962, 2931, 1721, 1116, 1027.
$[\alpha]_D^{20}$ +46.0 (*c* 0.2, $CHCl_3$).
***R*$_f$**=0.45 (petroleum ether : ethyl acetate = 3 : 1).

2.45 (5*R*,6*S*,7*R*,8*R*,9*R*)-7-(Benzyloxy)-8-hydroxy-4-methoxy-9-methyl-6-vinyl-1-oxaspiro[4.5]dec-3-en-2-one (60)



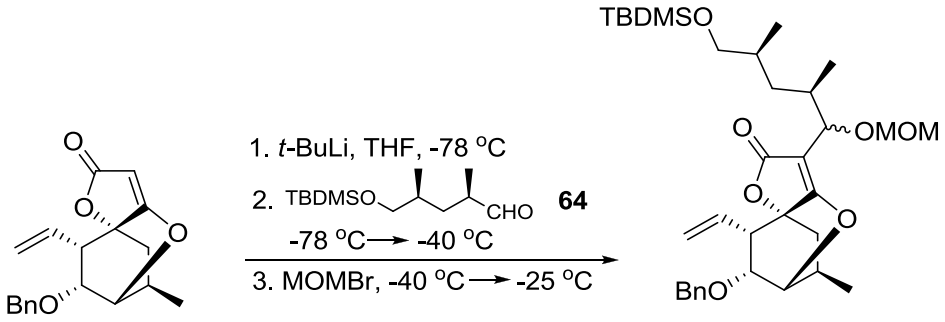
53 **60**

A solution of silyl ether **53** (110 mg; 0.24 mmol) in acetonitrile (4 mL) and 50% hydrofluoric acid (1 mL) was heated to 50 °C over 55 h, in a polyethylene flask. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate and brine. The organic layer was dried over anhydrous $MgSO_4$, evaporated under reduced pressure and purified by dry flash chromatography

(eluent: petroleum ether : ethyl acetate = 1 : 1), to afford 69 mg (84%) of the pure product **60**, as a white solid.

mp 164 °C
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.37 (m, 4H), 7.23-7.27 (m, 1H), 5.89 (ddd, J_1=0.5, J_2=9.5, J_3=20, 1H), 5.03-5.09 (m, 2H), 4.97 (s, 1H), 4.58 (d, *J*=1, 2H), 3.82 (bs, 1H), 3.80 (s, 3H), 3.61 (t, *J*=3.5, 1H), 2.76 (dd, J_1=3.5, J_2=9.5, 1H), 2.42-2.50 (m, 1H), 1.96 (t, *J*=13.5, 1H), 1.68 (bs, 1H), 1.37 (dd, J_1=3.0, J_2=13.5, 1H), 0.97 (d, *J*=7.0, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 172.4, 138.6, 133.6, 128.2, 127.3, 127.2, 118.5, 88.8, 85.3, 80.9, 73.0, 70.3, 59.1, 43.2, 34.7, 26.5, 17.2.
IR (film): cm^{-1} 3445, 2875, 1728, 1632, 1356, 1204, 954.
HRMS (m/z) $[M+NH_4]^+$ calcd. for $C_{20}H_{28}NO_5$: 362.1962; found: 362.1958.
$[\alpha]_D^{20}$ +20.8 (*c* 0.59, ethyl acetate).
***R*$_f$**=0.31 (petroleum ether : ethyl acetate = 1 : 1).

2.46 (5*R*,6*R*,7*aS*,8*R*,9*R*)-9-benzyloxy-3-[(2*R*,4*S*)-5-(*tert*-butyldimethylsilyloxy)-1-(methoxymethoxy)-2,4-dimethylpentyl]-6,7-dihydro-9-methyl-7-vinyl-5H-5,7a-ethano-2H-furo[3.2-b]pyran-2-one (65)



47 **65**

tert-Butyl lithium solution (0.4 mL; 1.5 M in pentane; 0.6 mmol; 1.3 eq) was added dropwise to a cold (-78 °C) solution of compound **47** (145 mg; 0.464 mmol) and a small crystal of 2,2'-bipyridine in dry tetrahydrofuran (10 mL), under an argon atmosphere. The red reaction mixture was stirred at that temperature for 45 minutes, and the solution of (2*R*,4*S*)-5-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-pentanal **64** (170 mg; 0.696 mmol; 1.5 eq) in dry THF (3.5 mL) was added dropwise to the mixture. Stirring was continued for 10 minutes at -78 °C and then for 40 minutes at -40 °C, before methoxymethylbromide (76 µL; 0.928 mmol; 1.5 eq) was added to the reaction mixture and the temperature was allowed to reach -25 °C. The reaction mixture was stirred for one hour at that temperature, then quenched by the addition of water (5 mL), the product was extracted with ethyl acetate, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent: petroleum ether : ethyl acetate = 5 : 1) afforded 125 mg (44%; mixture of 2 inseparable isomers in a ratio 1 : 1.8) of compound **65,** as a colorless oil, followed by 64.2 mg of the unreacted starting compound **47** (the yield calculated on the basis on the recovered starting material **47** was 79%).

Spectral data for the mixture of diastereoisomers (assignation of peaks in ^{1}H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Major diastereoisomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.40 (m, 5H), 6.05-6.14 (m, 1H), 5.36-5.43 (m, 2H), 4.65 (d, *J*=11.7, 1H), 4.59 (d, *J*=6.7, 1H), 4.56 (d, *J*=6.7, 1H), 4.41 (d, *J*=11.7, 1H), 4.29-4.31 (m, 1H), 4.27 (d, *J*=5.5, 1H), 3.97 (dd, J_1=3.6, J_2=9.7, 1H), 3.51 (dd, J_1=5.2, J_2=9.8, 1H), 3.34 (s, 3H), 3.27 (dd, J_1=7.2, J_2=9.8, 1H), 2.72-2.80 (m, 1H), 2.52-2.64 (m, 2H), 1.98-2.07 (m, 1H), 1.65-1.85 (m, 1H), 1.43-1.50 (m, 1H), 1.11 (d, *J*=7.4, 3H), 0.99 (d, *J*=6.0, 3H), 0.92-0.99 (m, 2H) 0.92 (d, *J*=6.6, 3H), 0.88 (s, 9H), 0.01 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 172.0, 137.1, 129.7, 128.5, 128.1, 127.6, 122.2, 96.6, 95.2, 80.5, 77.7, 73.8, 73.2, 72.8, 68.2, 55.8, 46.4, 36.9, 34.6, 33.1, 32.0, 25.9, 25.2, 19.3, 18.3, 17.9, 15.8, -5.4.

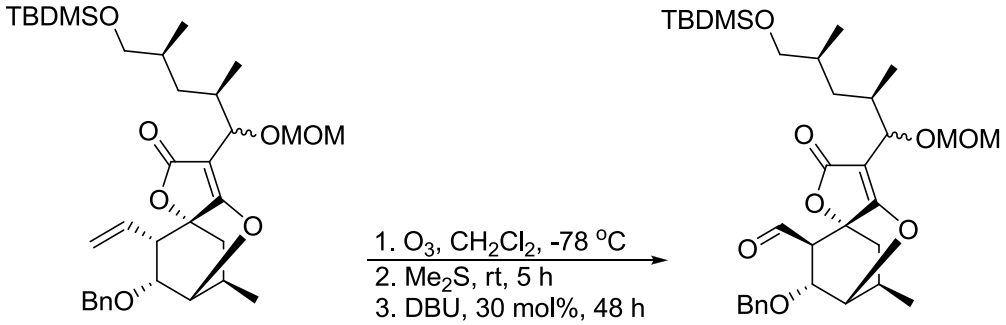
Minor diastereoisomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.40 (m, 5H), 6.05-6.14 (m, 1H), 5.36-5.43 (m, 2H), 4.66 (d, *J*=11.6, 1H), 4.62 (d, *J*=6.7, 1H), 4.57 (d, *J*=6.7, 1H), 4.42 (d, *J*=11.8, 1H), 4.29-4.31 (m, 1H), 4.20 (d, *J*=6.6, 1H), 4.01 (dd, J_1=3.6, J_2=9.7, 1H), 3.54 (dd, J_1=4.7, J_2=9.8, 1H), 3.36 (s, 3H), 3.27 (dd, J_1=7.2, J_2=9.8, 1H), 2.72-2.80 (m, 1H), 2.52-2.64 (m, 2H), 2.08-2.16 (m, 1H), 1.65-1.85 (m, 1H), 1.54-1.62 (m, 1H), 1.07 (d, *J*=7.2, 3H), 0.92-0.99 (m, 2H), 0.92 (d, *J*=6.6, 3H), 0.91 (d, *J*=6.6, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4, 171.9, 137.1, 129.6, 128.5, 128.1, 127.6, 122.2, 96.0, 94.7, 80.5, 77.6, 74.2, 73.4, 72.9, 67.9, 55.7, 46.4, 36.9, 34.6, 33.2, 32.1, 25.9, 25.87, 19.2, 18.6, 17.9, 16.5, -5.4.

IR (film): cm^{-1} 2957, 2930, 2884, 2856, 1755, 1684, 1459, 1100, 1036, 920.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{34}H_{52}O_7SiNa$: 623.3374; found: 623.3345.
$R_{f1,2}$=0.48 (petroleum ether : ethyl acetate = 4 : 1).

2.47 (5*R*,6*R*,7a*R*,8*R*,9*R*)-6-benzyloxy-3-[(2*R*,4*S*)-5-(*tert*-butyldimethylsilyloxy)-1-(methoxymethoxy)-2,4-dimethylpentyl]-6,7-dihydro-9-methyl-7-formyl-5H-5,7a-ethano-2H-furo[3.2-b]pyran-2-one (66)



65 **66**

A stream of oxygen enriched with ozone was bubbled through the cold (-78 °C) solution of alkene **65** (124 mg; 0.2065 mmol) in dry dichloromethane (12 mL) for 12 minutes, when the reaction mixture turned light blue. The excess ozone was removed by bubbling argon gas, followed by the addition of dimethyl sulfide (0.2 mL). The mixture was stirred at room temperature for 5 h, when DBU (6.2 µL; 20 mol%) was added and stirring was continued for 24 h. Another portion of DBU (3.1 µL; 10 mol%) was then added, and after additional 24 h of stirring the isomerization was complete (the progress of the reaction was followed by ^{1}H NMR spectroscopy). The solvent was removed under reduced pressure and the residue purified by column chromatography (petroleum ether : ethyl acetete = 2 : 1) to give 100 mg (81%) of aldehyde **66** as a colorless oil.

Spectral data for the mixture of diastereoisomers (assignation of peaks in ^{1}H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Major diastereoisomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, *J*=0.6, 1H), 7.26-7.38 (m, 5H), 4.46-4.57 (m, 4H), 4.34-4.40 (m, 2H), 4.22 (d, *J*=5.3, 1H), 3.49 (dd, J_1=4.6, J_2=9.7, 1H), 3.34 (s, 3H), 3.26 (dd, J_1=6.4, J_2=9.7, 1H), 3.15 (d, *J*=4.0, 1H), 2.72 (dd, J_1=3.8, J_2=11.5, 1H), 2.57-2.68 (m, 1H), 1.94-2.02 (m, 1H), 1.67-1.79 (m, 1H), 1.42 (ddd, J_1=6.0, J_2=7.2, J_3=13.6, 1H), 1.15-1.21 (m, 1H), 1.12 (d, *J*=7.4, 3H), 0.96 (d, *J*=6.7, 3H), 0.91 (d, *J*=6.5, 3H), 0.87-0.92 (m, 1H), 0.88 (s, 9H), 0.02 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 175.3, 170.8, 136.7, 128.6, 128.4, 127.9, 98.4, 95.0, 79.6, 76.8, 73.2, 72.3, 71.7, 68.2, 56.0, 55.9, 38.2, 36.8, 34.5, 33.0, 25.9, 25.5, 19.0, 18.3, 17.7, 15.7, -5.4.

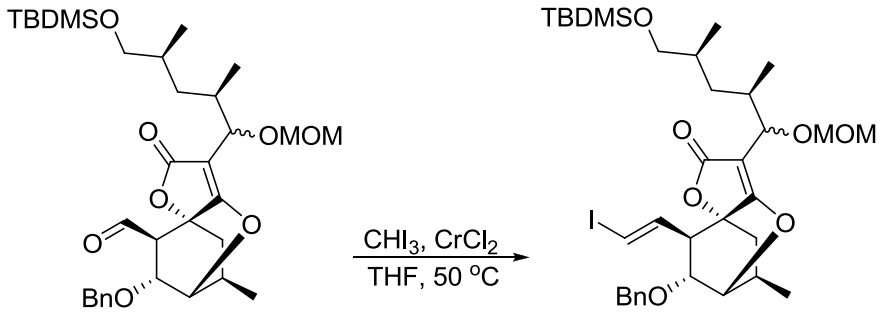
Minor diastereoisomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, *J*=0.6, 1H), 7.26-7.38 (m, 5H), 4.46-4.57 (m, 4H), 4.34-4.40 (m, 2H), 4.14 (d, *J*=7.0, 1H), 3.53 (dd, J_1=4.7, J_2=9.7, 1H), 3.35 (s, 3H), 3.27 (dd, J_1=6.5, J_2=9.7, 1H), 3.14 (d, *J*=4.0, 1H), 2.75 (dd, J_1=3.6, J_2=11.2, 1H), 2.57-2.68 (m, 1H), 2.02-2.12 (m, 1H), 1.67-1.79 (m, 1H), 1.51 (ddd, J_1=4.3, J_2=8.6, J_3=13.2, 1H), 1.15-1.21 (m, 1H), 1.08 (d, *J*=7.1, 3H), 0.92 (d, *J*=6.5, 3H), 0.87-0.92 (m, 1H), 0.89 (s, 9H), 0.84 (d, *J*=6.8, 3H), 0.03 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 176.0, 170.8, 136.7, 128.6, 128.4, 127.9, 97.7, 94.6, 79.6, 76.7, 73.9, 72.3, 71.7, 67.9, 55.9, 55.8, 38.4, 37.1, 34.5, 33.1, 25.9, 25.6, 18.9, 18.5, 17.7, 16.0, -5.4.

IR (film): cm^{-1} 2955, 2930, 2884, 2856, 1761, 1725, 1682, 1250, 1091, 1034, 838.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{33}H_{50}O_8SiNa$: 625.3167; found: 625.3151.
R_f=0.32-0.44 (petroleum ether : ethyl acetate = 3 : 1).

2.48 (5*R*,6*R*,7*aR*,8*R*,9*R*)-6-benzyloxy-6,7-dihydro-7-(*E*-2-iodovinyl)-3-[(2*R*,4*S*)-5-(*tert*-butyldimethylsilyloxy)-1-(methoxymethoxy)-2,4-dimethylpentyl]-9-methyl-5H-5,7a-ethano-2H-furo-[3.2-b]pyran-2-one (67)



Commercial chromium(II) chloride (340 mg; 2.77 mmol; 24 eq; 99.9% purity) was suspended in dry tetrahydrofuran (1.5 mL), in a glovebox, under an argon atmosphere. A solution of aldehyde **66** (67 mg; 0.111 mmol) and iodoform (362 mg; 8 eq) in dry THF (4 mL + 2 x 1.5 mL to rinse) was added dropwise to the greenish suspension and the mixture was stirred for 10 minutes at room temperature, followed by additional 15 minutes at 50 °C. The reaction mixture was partitioned between ethyl acetate and brine, the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (gradient elution: petroleum ether : ethyl acetate = 9 : 1 → 2 : 1), afforded 49 mg (61%) of the title compound **67** as a colorless oil, followed by 6.7 mg (10%) of the desilylated product **77**. The overall yield in the Takai olefination was 71%.

Spectral data for the mixture of diastereoisomers (assignation of peaks in ^{1}H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Major diastereoisomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 6.30 (dd, J_1=0.7, J_2=14.6, 1H), 6.10 (dd, J_1=9.0, J_2=14.6, 1H), 4.51-4.64 (m, 4H), 4.32 (d, *J*=3.7, 1H), 4.24 (d, *J*=5.7, 1H), 3.71 (t, *J*=3.8, 1H), 3.52 (dd, J_1=5.4, J_2=9.8, 1H), 3.35 (s, 3H), 3.24-3.31 (m, 1H), 2.76-2.81 (m, 1H), 2.54-2.65 (m, 2H), 1.98-2.19 (m, 1H), 1.68-1.84 (m, 1H), 1.38-1.47 (m, 1H), 1.13-1.20 (m, 1H), 1.11 (d, *J*=6.8, 3H), 0.99 (d, *J*=6.5, 3H), 0.92 (d, *J*=6.8, 3H), 0.88 (s, 9H), 0.02 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 171.5, 140.2, 136.7, 128.7, 128.4, 127.8, 99.0, 95.7, 80.9, 79.7, 77.4, 76.3, 74.2, 72.1, 68.2, 55.9, 51.9, 37.5, 37.0, 34.5, 33.0, 25.9, 25.3, 19.0, 18.3, 18.0, 15.9, -5.4.

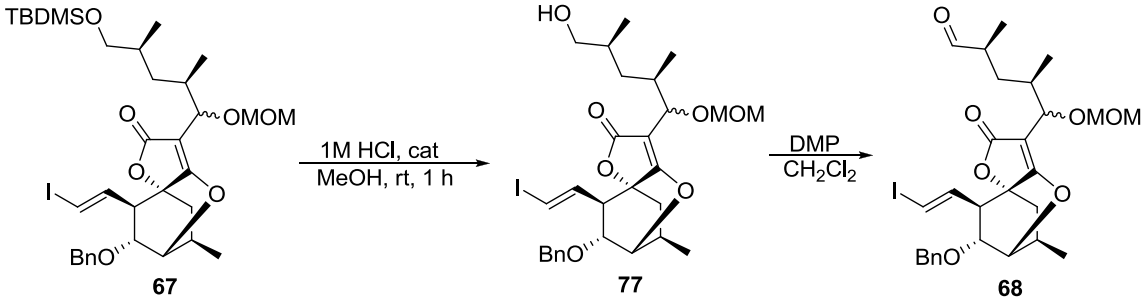
Minor diastereoisomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 6.30 (dd, J_1=0.9, J_2=14.6), 6.13 (dd, J_1=8.9, J_2=14.7, 1H), 4.51-4.64 (m, 4H), 4.32 (d, *J*=3.7, 1H), 4.18 (d, *J*=7.3, 1H), 3.82 (t, *J*=3.8, 1H), 3.57 (dd, J_1=4.9, J_2=10.0, 1H), 3.37 (s, 3H), 3.24-3.31 (m, 1H), 2.76-2.81 (m, 1H), 2.54-2.65 (m, 2H), 1.98-2.19 (m, 1H), 1.68-1.84 (m, 1H), 1.54-1.61 (m, 1H), 1.13-1.20 (m, 1H), 1.06 (d, *J*=6.8, 3H), 0.92 (d, *J*=6.8, 3H), 0.89 (s, 9H) 0.88 (d, *J*=5.9, 3H), 0.039 (s, 3H), 0.036 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 171.4, 140.3, 136.8, 128.7, 127.84, 127.81, 98.1, 94.7, 81.0, 79.7, 77.4, 76.2, 74.2, 72.1, 68.0, 55.8, 51.7, 37.6, 37.0, 34.9, 33.1, 25.9, 25.4, 18.9, 18.6, 18.3, 16.2, -5.3.

IR (film): cm^{-1} 2955, 2930, 2883, 2857, 1756, 1682, 1492, 1090, 1035.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{34}H_{51}O_7ISiNa$: 749.2341; found: 749.2349.
R_{f1}=0.43, R_{f2}=0.50 (petroleum ether : ethyl acetate = 4 : 1).

2.49 (5*R*,6*R*,7a*R*,8*R*,9*R*)-6-benzyloxy-6,7-dihydro-7-(*E*-2-iodovinyl)-3-[(2*R*,4*S*)-1-(methoxymethoxy)-2,4-dimethyl-5-oxopentyl]-9-methyl-5H-5,7a-ethano-2H-furo-[3.2-b]pyran-2-one (68)



A) Compound 77 (deprotection of **67**): A solution of **67** (62 mg; 0.085 mmol) and 1M hydrochloric acid (40 µL) in methanol (5 mL) was stirred at room temperature for 1 h. The solution was evaporated to dryness and filtered through a short pad of silica (eluent: petroleum ether : ethyl acetate = 1 : 1), to yield 48.6 mg (94%) of the alcohol **77**, as a colorless oil.

Spectral data for the mixture of diastereoisomers **77** *(assignation of peaks in ^{1}H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):*

Major diastereoisomer
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 6.31 (dd, J_1=0.7, J_2=14.4, 1H), 6.10 (dd, J_1=9.1, J_2=14.5, 1H), 4.51-4.63 (m, 4H), 4.33 (d, *J*=3.2, 1H), 4.20 (d, *J*=6.8, 1H), 3.72 (t, *J*=4.0, 1H), 3.48-3.55 (m, 1H), 3.42-3.48 (m, 1H), 3.36 (s, 3H), 2.76-2.81 (m, 1H), 2.55-2.66 (m, 2H), 2.04-2.18 (m, 1H), 1.74-1.83 (m, 1H), 1.65-1.74 (bs, 1H), 1.58-1.65 (m, 1H), 1.41-1.49 (m, 1H), 1.13-1.21 (m, 1H), 1.11 (d, *J*=6.7, 3H), 1.01 (d, *J*=6.8, 3H), 0.98 (d, *J*=6.7, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 171.6, 140.1, 136.7, 128.7, 128.4, 127.8, 98.6, 95.9, 81.0, 79.8, 77.4, 76.3, 74.1, 72.1, 67.4, 56.0, 51.8, 37.4, 36.6, 34.2, 32.9, 25.3, 19.0, 18.1, 16.2.

Minor diastereoisomer
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 6.31 (dd, J_1=0.7, J_2=14.5, 1H), 6.15 (dd, J_1=8.8, J_2=14.5, 1H), 4.51-4.63 (m, 4H), 4.33 (d, *J*=3.2, 1H), 4.25 (d, *J*=6.6, 1H), 3.77 (t, *J*=3.9, 1H), 3.48-3.55 (m, 1H), 3.42-3.48 (m, 1H), 3.38 (s, 3H), 2.76-2.81 (m, 1H), 2.55-2.66 (m, 2H), 2.04-2.18 (m, 1H), 1.74-1.83 (m, 1H), 1.65-1.74 (bs), 1.58-1.65 (m, 1H), 1.41-1.49 (m, 1H), 1.13-1.21 (m, 1H), 1.06 (d, *J*=6.7, 3H), 0.98 (d, *J*=6.9, 3H), 0.92 (d, *J*=6.9, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 171.6, 140.2, 136.7, 128.7, 128.4, 127.8, 97.9, 94.7, 81.1, 79.7, 77.4, 76.3, 74.1, 72.0, 67.3, 55.9, 51.6, 37.6, 36.6, 34.9, 33.3, 25.3, 19.0, 18.2, 16.8.

IR (film): cm^{-1} 3489, 2959, 2929, 2878, 1754, 1680, 1456, 1409, 1075, 1033, 915.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{28}H_{37}O_7ISiNa$: 635.1476; found: 635.1468.
R_{f1}=0.56, R_{f2}=0.65 (petroleum ether : ethyl acetate = 1 : 1).

B) Compound **68** (oxidation of **77**): Dess Martin's periodinane (76 mg; 0.180 mmol; 2 eq) was added to the solution of alcohol **77** (55 mg; 0.09 mmol) in dry dichloromethane (5 mL), and the resulting suspension was stirred at room temperature for 15 minutes. The reaction mixture was diluted with ethyl acetate and water, the organic layer was washed successively with 5% sodium thiosulfate, sodium bicarbonate and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent: petroleum ether : ethyl acetate = 2 : 1) afforded 48 mg (88%) of the title aldehyde **68** as a colorless oil.

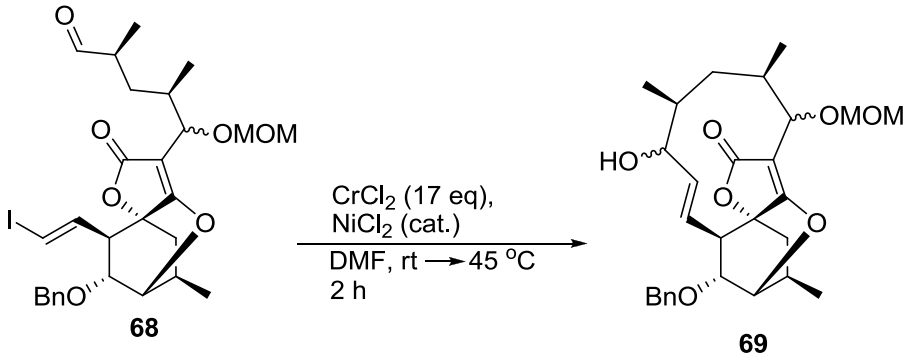
Spectral data for the mixture of diastereoisomers (assignation of peaks in ^{1}H NMR and ^{13}C NMR spectra is based on the detailed analysis of COSY, HSQC, HMBC and NOESY NMR spectra of the mixture):

Major diastereoisomer
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (d, *J*=2.5, 1H), 7.26-7.40 (m, 5H), 6.31 (dd, J_1=0.8, J_2=14.6, 1H), 6.10 (dd, J_1=8.9, J_2=14.6, 1H), 4.52-4.64 (m, 4H), 4.35 (d, *J*=3.7, 1H), 4.25 (d, *J*=6.1, 1H), 3.73 (t, *J*=3.9, 1H), 3.35 (s, 3H), 2.77-2.83 (m, 1H), 2.48-2.68 (m, 3H), 2.01-2.12 (m, 2H), 1.85-1.92 (m, 1H), 1.15-1.22 (m, 2H), 1.13 (d, *J*=7.1, 6H), 0.99 (d, *J*=6.8, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 175.8, 171.5, 140.1, 136.7, 128.6, 128.4, 127.8, 98.3, 95.5, 81.0, 79.9, 77.2, 76.4, 73.6, 72.0, 56.0, 51.7, 43.8, 37.4, 34.5, 33.8, 25.3, 19.0, 15.7, 14.2.

Minor diastereoisomer
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (d, *J*=2.5, 1H), 7.26-7.40 (m, 5H), 6.30 (dd, J_1=0.8, J_2=14.6, 1H), 6.14 (dd, J_1=8.6, J_2=14.6, 1H), 4.52-4.64 (m, 4H), 4.35 (d, *J*=3.7, 1H), 4.24 (d, *J*=6.8, 1H), 3.79 (t, *J*=3.8, 1H), 3.38 (s, 3H), 2.77-2.83 (m, 1H), 2.48-2.68 (m, 3H), 2.01-2.12 (m, 2H), 1.15-1.22 (m, 2H), 1.11 (d, *J*=7.0, 3H), 1.06 (d, *J*=6.5, 3H), 0.90 (d, *J*=6.5, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1, 176.1, 171.5, 140.2, 136.6, 128.6, 127.83, 127.81, 97.7, 94.6, 81.0, 79.8, 77.2, 76.4, 73.7, 72.1, 55.9, 51.5, 44.1, 37.5, 34.9, 34.3, 25.3, 18.9, 16.1, 14.5.

IR (film): cm^{-1} 2960, 2923, 2877, 1755, 1721, 1680, 1456, 1409, 1075, 1031, 914.
HRMS (m/z) $[M+NH_4]^+$ calcd. for $C_{28}H_{39}O_7NISi$: 628.1766; found: 628.1763.
R_{f1}=0.52, R_{f2}=0.58 (petroleum ether : ethyl acetate = 2 : 1).

2.50 (5*R*,7*S*,9*E*,10a*R*,11*R*,12*R*,13*R*,14a*R*)-11-(benzyloxy)-5,6,7,8,11,12,13,14-octahydro-8-hydroxy-4-(methoxymethoxy)-5,7,13-trimethyl-12,14a,3-(epoxymethyno)-2H-1-benzoxacyclododecin-2-2(4H,10aH)-one (69)

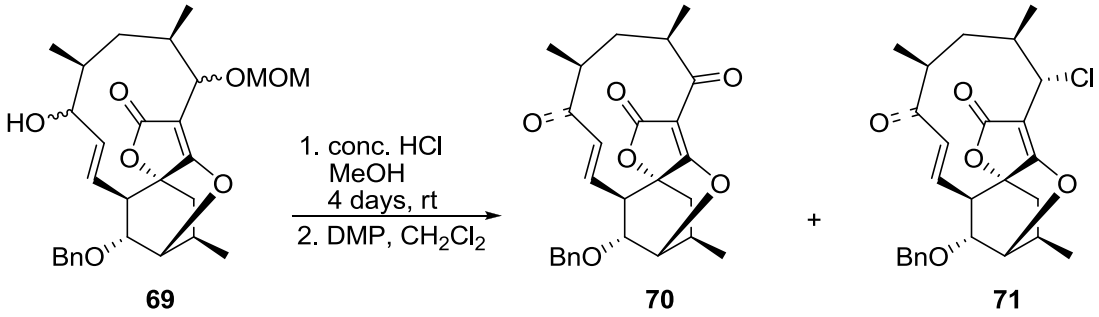


68 **69**

Commercial chromium(II) chloride (167 mg; 1.36 mmol; 17 eq; 99.9% purity) and anhydrous nickel(II) chloride (cat. amount) were suspended in a freshly distilled dry DMF (3 mL), in a glovebox, under an argon atmosphere. The solution of **68** (48 mg; 0.0786 mmol) in DMF (11 mL) was added dropwise to the suspension, and the mixture was stirred at room temperature for 90 minutes. After additional stirring at 45 °C for 15 minutes, the mixture was partitioned between diethyl ether and diluted hydrochloric acid (1M). The etheral layer was washed with diluted hydrochloric acid (1 M), brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (gradient elution: petroleum ether : ethyl acetate = 3 : 1 → 1 : 1) afforded 34 mg (90%) of the title compound **69** as a mixture of four diastereoisomers. Additionally, 3.4 mg of the unreacted starting material was isolated; therefore, the yield based on the recovered starting material was 96%.

IR (film): cm^{-1} 3479, 2955, 2929, 2873, 1751, 1680, 1092, 1025.
HRMS (m/z) $[M+Na]^+$ calcd. for $C_{28}H_{36}NaO_7$: 507.2353; found: 507.2352.
R_{f1}=0.61, R_{f2}=0.71 (petroleum ether : ethyl acetate = 1 : 1).

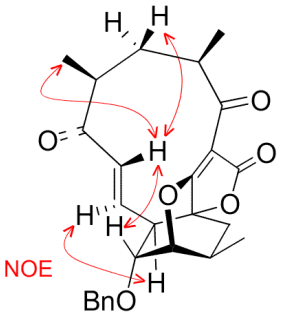
2.51 (5*R*,7*S*,9*E*,10a*R*,11*R*,12*R*,13*R*,14a*R*)-11-(benzyloxy)-6,7,11,12,13,14-hexahydro-5,7,13-trimethyl-12,14a,3-(epoxymethyno)-2H-1-benzoxacyclododecin-2,4,8(5H,10aH)-trione (70) and (3*S*,5*R*,7*S*,9*E*,10a*R*,11*R*,12*R*,13*R*,14a*R*)-4-chloro-11-(benzyloxy)-6,7,11,12,13,14-hexahydro-5,7,13-trimethyl-12,14a,3-(epoxymethyno)-2H-1-benzoxacyclododecin-2,8(5H,10aH)-dione (71)



69 **70** **71**

A solution of compound **69** (3.5 mg; 7.22 µmol) and concentrated hydrochloric acid (15 µL) in methanol (0.2 mL) was stirred at room temperature for 4 days and then evaporated under reduced pressure. The residue was dissolved in dry dichloromethane (0.8 mL) and Dess Martin's periodinane (30.6 mg; 0.722 µmol; 10 eq) was added. The mixture was stirred for 3 h at room temperature, then partitioned between diethyl ether and water. The organic layer was washed with 10% sodium thiosulfate, sodium bicarbonate and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1) afforded 0.5 mg (14%) of chloro-derivative **71**, followed by 2.4 mg (78%) of the compound **70**, as colorless oils.

Spectral data for compound **70**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.38 (m, 5H), 6.70 (dd, J_1= 5.9, J_2=16.4, 1H), 6.15 (d, J=16.4, 1H), 4.61 (d, J=11.3, 1H), 4.56 (dd, J_1=1.5, J_2=4.2, 1H), 4.43 (d, J=11.3, 1H), 4.01 (dd, J_1=3.0, J_2=4.1, 1H), 3.21 (ddd, J_1=0.8, J_2=2.9, J_3=6.0, 1H), 2.71-2.82 (m, 2H), 2.67 (dd, J_1=1.2, J_2=11.2, 1H), 2.58-2.66 (m, 1H), 1.75 (ddd, J_1=3.1, J_2=11.4, J_3=15.9, 1H), 1.51 (dd, J_1=3.0, J_2=12.5, 1H), 1.46 (ddd, J_1=4.0, J_2=4.6, J_3=15.9, 1H), 1.16-1.19 (m, 6H), 1.11 (d, J=7.1, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 199.3, 177.5, 169.0, 138.1, 136.2, 128.7, 128.6, 128.5, 128.0, 106.5, 81.3, 79.5, 73.6, 71.9, 47.9, 47.6, 42.9, 38.7, 33.4, 25.5, 18.6, 18.1, 17.2.

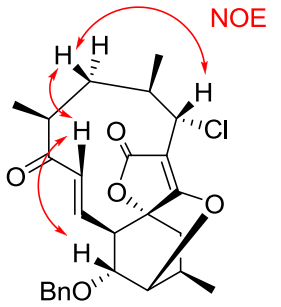
IR (film): cm^{-1} 2965, 2929, 2873, 1759, 1693, 1647, 1456, 1088, 960.

HRMS (m/z) $[M+K]^+$ calcd. for $C_{26}H_{28}KO_6$: 475.1517; found: 475.1517.

$[\alpha]_D^{20}$ -81.8 (*c* 0.5, $CHCl_3$).

***R*$_f$**=0.40 (petroleum ether : ethyl acetate = 2 : 1).

Spectral data for chloro-derivative **71**



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.40 (m, 5H), 6.38 (dd, J_1=4.1, J_2=17.0, 1H), 6.16 (dd, J_1=1.3, J_2=17.0, 1H), 4.64 (d, J=11.9, 1H), 4.50 (dd, J_1=1.7, J_2=4.5, 1H), 4.46 (d, J=11.9, 1H), 4.23 (d, J=11.1, 1H), 4.14 (dd, J_1=2.1, J_2=4.5, 1H), 3.07-3.10 (m, 1H), 2.70-2.78 (m, 2H), 2.66 (dd, J_1=11.0, J_2=12.4, 1H), 2.50-2.58 (m, 1H), 1.98-2.09 (m, 1H), 1.40-1.47 (m, 2H), 1.18 (d, J=6.7, 3H), 1.12 (d, J=7.2, 3H), 1.09-1.19 (m, 1H), 1.09 (d, J=6.8, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 2-03.5, 173.1, 169.6, 137.3, 136.5, 130.4, 128.7, 128.5, 127.8, 101.0, 80.7, 78.6, 72.3, 71.7, 55.8, 47.8, 46.1, 40.7, 38.1, 34.3, 25.5, 21.5, 18.5, 16.1.

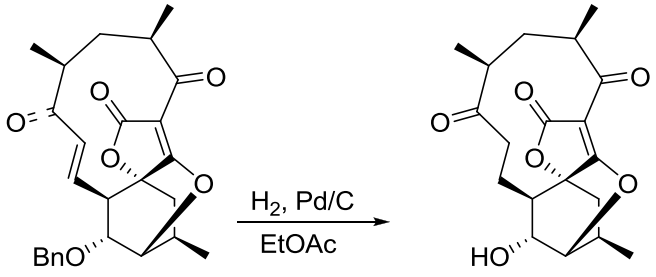
IR (film): cm^{-1} 2926, 1764, 1682, 1455, 1406, 1068.

HRMS (m/z) $[M+Na]^+$ calcd. for $C_{26}H_{29}ClO_5Na$: 479.1596; found: 479.1598.

$[\alpha]_D^{20}$ -37.0 (*c* 0.1, $CHCl_3$).

***R*$_f$**= 0.41 (petroleum ether : ethyl acetate = 3 : 1).

2.52 Abyssomicin H

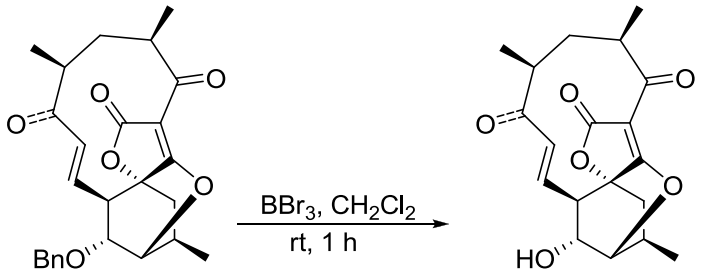


70

A suspension of compound **70** (1.35 mg; 3.09 µmol) and palladium on carbon (1 mg, 5% Pd/C) in ethyl acetate (500 µL) was vigorously stirred overnight under a hydrogen atmosphere (4 atm). The catalyst was removed by filtration through a short pad of celite, and the solvent was removed under reduced pressure. Purification by dry-flash chromatography (eluent: petroleum ether : ethyl acetete = 2 : 3) afforded abyssomicin H (0.8 mg, 74%), as a white amorphous solid.

^{1}H NMR (500 MHz, MeOD-d_4) δ 4.55 (dd, J_1=1.1, J_2=3.8, 1H), 4.46 (dd, J_1=3.8, J_2=5.2, 1H), 3.31-3.37 (m, 1H), 2.78 (ddd, J_1=3.3, J_2=11.1, J_3=18.8, 1H), 2.73 (ddd, J_1=2.1, J_2=7.2, J_3=10.7, 1H), 2.63-2.70 (m, 2H), 2.60 (dd, J_1=11.1, J_2=12.0, 1H), 2.22-2.26 (m, 1H), 2.14-2.22 (m, 1H), 1.89-1.99 (m, 2H) 1.44 (ddd, J_1=2.1, J_2=3.0, J_3=14.6, 1H), 1.13 (dd, J_1=4.2, J_2=12.0, 1H), 1.11 (d, J=7.1, 3H), 1.08 (d, J=6.8, 3H), 1.05 (d, J=7.2, 3H). ^{1}H NMR spectrum for this compound has been reported, with chemical shifts identical to these presented in this manuscript.[10] However, as no coupling constants were listed in the literature report, we provide the full listing of the ^{1}H NMR spectrum here.
***R*$_f$**=0.24 (petroleum ether : ethyl acetate = 1 : 1).

2.53 atrop-Abyssomicin C (**AA**)

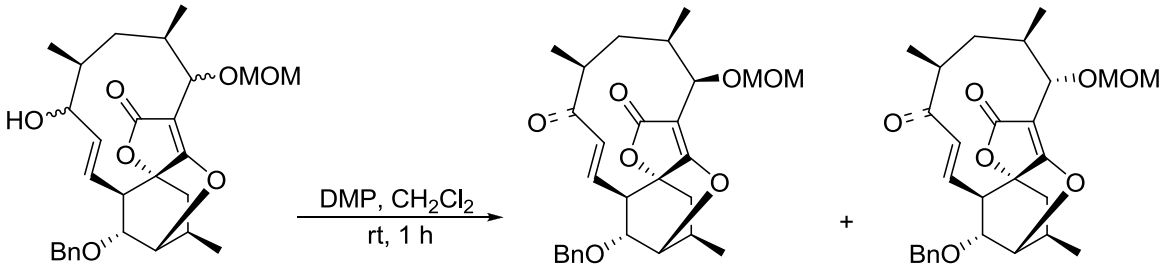


70

A solution of boron(III) bromide (15 µL; 0.155 mmol; 15 eq) in dry dichloromethane (300 µL) was added dropwise to a cold (0 °C) solution of compound **70** (4.5 mg; 10.3 µmol) in dry dichloromethane (2 mL), under an argon atmosphere. The reaction mixture was stirred at room temperature for one hour and then partitioned between diethyl ether and saturated sodium bicarbonate solution. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (gradient elution: petroleum ether : ethyl acetate = 7 : 3 → 1 : 2) afforded 2.9 mg (81%) of atrop-abyssomicin C (2.9 mg; 81%), as a white amorphous solid.

^{1}H NMR (500 MHz, MeOD-d_4) δ 6.65 (dd, J_1=5.8, J_2=16.5, 1H), 6.52 (d, J=16.5, 1H), 4.63 (dd, J_1=1.4, J_2=4.3, 1H), 4.41 (dd, J_1=3.1, J_2=4.3, 1H), 3.19 (ddd, J_1=0.7, J_2=2.9, J_3=5.7, 1H), 2.78-2.83 (m, 1H), 2.70 (dd, J_1=10.7, J_2=12.6, 1H), 2.62-2.66 (m, 1H), 2.54 (ddq, J_1=3.6, J_2=7.1, J_3=14.3, 1H), 1.88 (ddd, J_1=2.5, J_2=12.2, J_3=15.7, 1H), 1.43-1.48 (m, 2H), 1.16 (d, J=7.0, 3H), 1.15 (d, J=7.0, 3H), 1.12 (d, J=6.7, 3H).
^{13}C NMR (125 MHz, MeOD-d_4) δ 204.3, 201.3, 180.2, 171.6, 141.0, 129.8, 107.0, 85.2, 81.9, 67.7, 51.3, 49.8, 44.3, 39.4, 34.5, 26.4, 18.9, 18.2, 17.1.
HRMS (m/z) $[M+NH_4]^+$ calcd. for $C_{19}H_{26}NO_6$: 364.1755; found: 364.1754.
$[\alpha]_D^{20}$ -72.7 (*c* 0.17, MeOH).[11]
***R*$_f$**=0.32 (petroleum ether : ethyl acetate = 1 : 2).

2.54 (4*S*,5*R*,7*S*,9*E*,10a*R*,11*R*,12*R*,13*R*,14a*R*)-11-(benzyloxy)-5,6,7,11,12,13,14-pentahydro-4-(methoxymethoxy)-5,7,13-trimethyl-12,14a,3-(epoxymethyno)-2H-1-benzoxacyclododecin-2,8(5H,10aH)-dione (72) and (4*R*,5*R*,7*S*,9*E*,10a*R*,11*R*,12*R*,13*R*,14a*R*)-11-(benzyloxy)-5,6,7,11,12,13,14-pentahydro-4-(methoxymethoxy)-5,7,13-trimethyl-12,14a,3-(epoxymethyno)-2H-1-benzoxacyclododecin-2,8(5H,10aH)-dione (73)



69 **72** **73**

Freshly prepared DMP (9.2 mg; 21.7 μmol; 3 eq) was added to a solution of **69** (3.5 mg; 7.2 μmol) in dry dichloromethane (350 μL) and the resulted suspension was stirred for 60 minutes at room temperature. The reaction mixture was partitioned between diethyl ether and 10% sodium thiosulfate solution and the organic extract was washed with saturated sodium bicarbonate solution and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative HPLC afforded 1.7 mg (49%) of **72** and 1.2 mg (34%) of **73,** as colorless oils.

Spectral data for derivative **72**

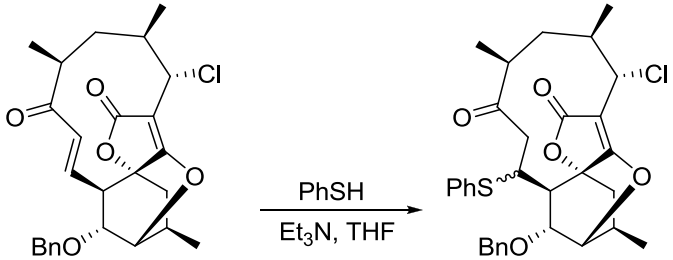
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.38 (m, 5H), 6.56 (dd, J_1=1, J_2=17, 1H), 6.46 (d, J=17, 1H), 4.66 (d, J=6.5, 1H), 4.62 (d, J=12, 1H), 4.60 (d, J=6.5, 1H), 4.48 (dd, J_1=3.5, J_2=4.5, 1H), 4.43 (d, J=12, 1H), 4.30 (s, 1H), 4.19 (dd, J_1=1.5, J_2=4.5, 1H), 3.39 (s, 3H), 3.10 (dd, J_1=2, J_2=5, 1H), 2.62-2.73 (m, 2H), 2.36-2.44 (m, 1H), 1.99 (dd, J_1=12.5, J_2=15, 1H), 1.36 (dd, J_1=1.5, J_2=12, 1H), 1.29-1.32 (m, 1H), 1.19 (dd, J_1=2.5, J_2=8, 1H), 1.15 (d, J=7, 3H), 1.11 (d, J=6.5, 3H), 1.07 (d, J=7, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 172.4, 171.2, 137.8, 136.5, 129.6, 128.6, 128.4, 127.9, 101.5, 94.8, 79.9, 79.4, 75.8, 72.7, 71.6, 55.8, 47.9, 46.8, 37.4, 36.0, 34.8, 25.3, 19.9, 18.4, 18.2.
IR (film): cm^{-1} 2958, 2926, 1750, 1685, 1456, 1033, 913.

HRMS (m/z) $[M+H]^+$ calcd. for $C_{28}H_{35}O_7$: 483.2377; found: 483.2378.
$[\alpha]_D^{20}$ +7.0 (*c* 0.1, $CHCl_3$).
***R*$_f$**=0.48 (petroleum ether : ethyl acetate = 2 : 1).

Spectral data for derivative **73**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5H), 6.42 (dd, J_1=4, J_2=17, 1H), 6.21 (dd, J_1=1, J_2=17, 1H), 4.63 (d, *J*=11.5, 1H), 4.59 (d, *J*=7, 1H), 4.56 (d, *J*=7, 1H), 4.49 (dd, J_1=1.5, J_2=4.5, 1H), 4.46 (d, *J*=11.5, 1H), 4.16 (dd, J_1=1.5, J_2=4.5, 1H), 3.88 (d, *J*=10.5, 1H), 3.34 (s, 3H), 3.08-3.09 (m, 1H), 2.65-2.72 (m, 2H), 2.49-2.56 (m, 1H), 1.86-1.91 (m, 1H), 1.42 (ddd, J_1=2.5, J_2=7.5, J_3=15, 1H), 1.37 (dd, J_1=1, J_2=11.5, 1H), 1.10 (d, *J*=6.5, 9H), 1.04 (dt, J_1=5.5, J_2=15, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8, 175.6. 170.4, 137.4, 136.6, 130.3, 128.7, 128.4, 127.8, 100.0, 94.9, 80.2, 78.6, 72.5, 72.4, 71.6, 55.7, 47.8, 46.1, 39.4, 36.4, 34.9, 25.6, 19.6, 18.5, 16.5.
IR (film): cm^{-1} 2929, 2874, 1766, 1683, 1455, 1407, 1095, 1025, 734.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{28}H_{34}O_7$: 483.2377; found: 483.2365.
$[\alpha]_D^{20}$ -65.0 (*c* 0.1, $CHCl_3$).
***R*$_f$**=0.35 (petroleum ether : ethyl acetate = 2 : 1).

2.55 (3*S*,5*R*,7*S*,9*E*,10a*R*,11*R*,12*R*,13*R*,14a*R*)-4-chloro-11-(benzyloxy)-6,7,9,10,11,12,13,14-octahydro-5,7,13-trimethyl-10-(phenylthio)-12,14a,3-(epoxymethyno)-2H-1-benzoxacyclododecin-2,8(5H,10aH)-dione (74) (addition of thiophenol to chloro-derivative 71)



71 **74**

A mixture of chloro-derivative **71** (1.1 mg; 2.41 μmol), thiophenol (0.5 μL; 4.82 μmol; 2 eq) and triethylamine (0.65 μL; 4.82 μmol; 2 eq) in dry THF (1 mL) was stirred for 2 h at room temperature, under an argon atmosphere. All volatiles were evaporated on rotovap and the mixture was purified by HPLC to give two isomers of products **74** (diastereoisomer 1: 0.34 mg; 25% and diastereoisomer 2: 0.29 mg; 22%).

Spectral data for diastereoisomer **1**
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.41 (m, 10H), 4.88 (d, *J*=11.4, 1H), 4.67 (d, *J*=11.4, 1H), 4.39 (dd, J_1=1.5, J_2=4.1, 1H), 4.27 (d, *J*=11.7, 1H), 4.16-4.20 (m, 1H), 4.01 (t, *J*=3.8, 1H), 2.77 (dd, J_1=4.7, J_2=18.1, 1H), 2.58-2.69 (m, 1H), 2.55 (dd, J_1=2.2, J_2=3.4, 1H), 2.42-2.52 (m, 2H), 2.30-2.38 (m, 1H), 2.23 (dd, J_1=4.8, J_2=18.1,

1H), 1.27-1.37 (m, 2H), 1.19 (d, *J*=6.8, 3H), 1.10 (dd, J_1=3.5, J_2=12.7, 1H), 1.02 (d, *J*=7.3, 3H), 0.99 (d, *J*=6.8, 3H), 0.88-0.92 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 174.3, 169.3, 137.3, 133.4, 131.6, 129.2, 128.6, 128.3, 128.0, 127.6, 99.0, 80.7, 74.5, 72.5, 56.0, 49.1, 46.5, 41.0, 38.7, 38.4, 36.9, 36.7, 29.7, 25.7, 22.1, 18.7, 17.7.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{32}H_{36}ClO_5Si$: 567.1966; found: 567.1977.
***R*$_f$**=0.44 (petroleum ether : ethyl acetate = 3 : 1).

Spectral data for diastereoisomer **2**
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.55 (m, 2H), 7.31-7.41 (m, 8H), 4.80 (d, *J*=11.3, 1H), 4.58 (d, *J*=11.3, 1H), 4.41 (dd, J_1=1.2, J_2=4.1, 1H), 4.11 (d, *J*=11.2, 1H), 4.00 (t, *J*=3.7, 1H), 3.74-3.77 (m, 1H), 2.86 (dd, J_1=2.6, J_2=3.7, 1H), 2.73 (dd, J_1=4.7, J_2=18.0, 1H), 2.64-2.71 (m, 1H), 2.60 (t, *J*=11.9, 1H), 2.40-2.46 (m, 1H), 2.27-2.33 (m, 2H), 1.26-1.39 (m, 4H), 1.17 (d, *J*=6.9, 3H), 1.14-1.18 (m, 1H), 1.04 (d, *J*=7.2, 3H), 0.96 (d, *J*=6.9, 3H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 174.2, 169.2, 137.1, 135.8, 129.3, 129.1, 128.7, 128.3, 128.1, 127.9, 99.0, 80.6, 74.3, 72.6, 56.0, 48.9, 46.3, 40.9, 39.8, 38.3, 36.7, 31.9, 29.4, 25.7, 22.7, 18.7, 17.7.
HRMS (m/z) $[M+H]^+$ calcd. for $C_{32}H_{36}ClO_5Si$: 567.1966; found: 567.1975.
***R*$_f$**=0.42 (petroleum ether : ethyl acetate = 3 : 1).

3 Biological test

3.1. Antibacterial activity

The agar plate diffusion assay, and the determination of MIC values were performed according to the literature procedure.[12] The determination of MIC was modified, with respect to the literature procedure, in that Mueller Hinton broth was used.

3.2. Cytotoxicity assay

Reagents: RPMI-1640 medium was purchased from PAA The Cell Culture Company (Linz, Austria), Fetal calf serum (FCS), 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), gentamicin sulfate salt, penicillin, streptomycin, glutamine, β-mercaptoethanol, phytohemagglutinin (PHA), dimethyl sulfoxide (DMSO) and Histopaque were purchased from the Sigma Chemical Co. (St. Louis, MO, USA), 0.22 µm Millipore Ultrafree-MC centrifugal devices were purchased from Merck Millipore (Billerica, Massachusetts, US).

Cell culture. Human cervix adenocarcinoma cells (HeLa), were grown in RPMI-1640 medium supplemented with 10% fetal calf serum (FCS), 1% glutamine (200 mM), 1% penicillin (10000 IU mL^{-1}) and 1% streptomycin (10 mg mL^{-1}). The cells were grown at 37 °C in a 6.0 % CO_2 humidified air atmosphere. Peripheral blood mononuclear cells (PBMC) were separated from whole heparinized blood of healthy volunteer. Blood was diluted with phosphate buffered saline (PBS) (1:1) and layered on Histopaque solution. After centrifugation, interface cells were collected and washed three times with PBS. After counting, cells were resuspended in nutrient medium. Nutrient medium was RPMI-1640 medium, supplemented with 10% fetal calf serum (FCS), 1% glutamine (200 mM), 1% β-mercaptoethanol (5 µM), 1% penicillin (10000 IU mL^{-1}), 1% streptomycin (10 mg mL^{-1}) and with 0,5% phytohemagglutinin (PHA) (1 mg mL^{-1}). The cells were grown at 37°C in a humidified atmosphere with 6% CO_2.

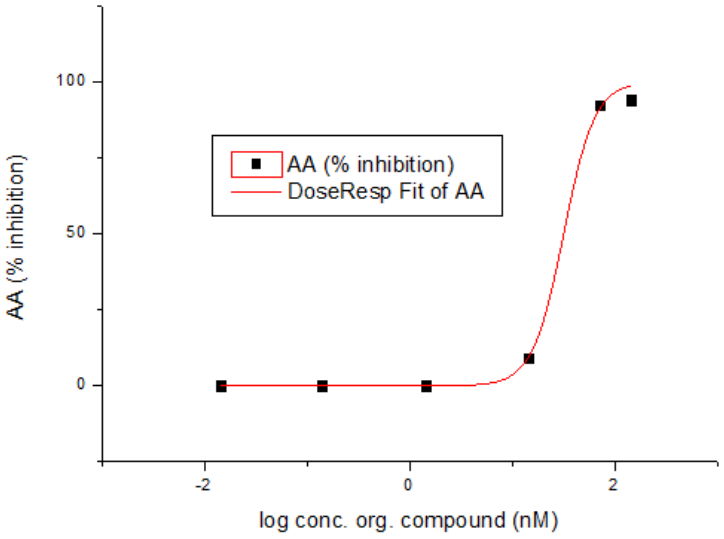
Determination of target cell survival. HeLa cells were seeded (10 000 cells per well) into 96-well microtiter plates and 24 h later, after the cell adherence, six different concentrations of investigated compounds were added to the wells. Final concentrations were in the range from 0,0144 nM to 144 nM for HeLa cells and PBMCs. Only nutrient medium was added to the cells in the control wells. All experiments were done in triplicate. Nutrient medium void of cells was used as blank. PBMC were seeded (200,000 cells per well) into nutrient medium in 96-well microtiter plates and 2 h later, investigated compounds were added to the wells, in triplicates, to six final concentrations, except to the control wells where a nutrient medium only was added to the cells. Nutrient medium void of cells was used as blank. Cell survival was determined by MTT test according to the method of Mosmann[13] and modified by Ohno and Abe,[14] 24 and 72 h after the drug addition to HeLa cells and PBMCs, respectively. Briefly, 20 µL of MTT solution (5 mg/mL in PBS) were added to each well and incubated for 4 h at 37 °C in humidified atmosphere with 6% CO_2. After the incubation, medium was carefully removed and 200 µL of DMSO were added to dissolve the formazan complexes; absorbance was read at 492 nm. The *IC*50 value which represents drug concentration that diminishes 50% of viable cells was assessed from the graph of cell survival *vs.* concentration of the investigated compound.

Results of the determination of cytotoxicity of compounds AA, 70, 71, 72 and 73 on HeLa cells

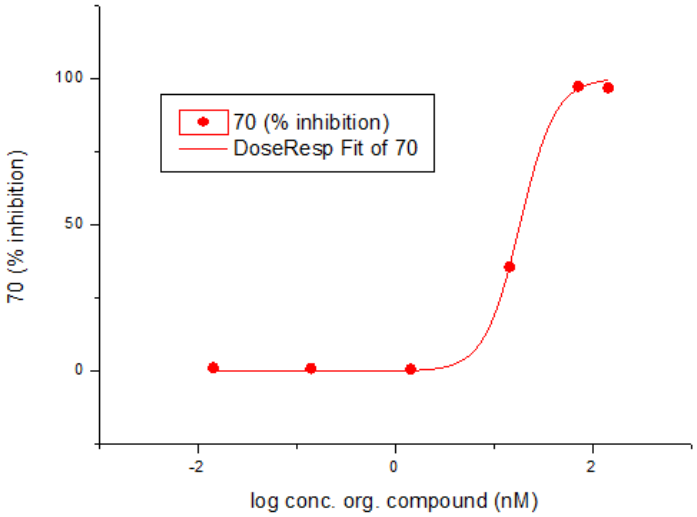
Summary

	A1		A2		LOGx0		p		EC50	EC90	EC20	EC80
	Value	Error	Value	Error	Value	Error	Value	Error	Value			
AA	0	0	100	0	1,50206	0,09585	2,86969	0,77617	31,77294	68,32546	19,60006	51,50595
70	0	0	100	0	1,26434	0,07524	2,42309	1,31156	18,37991	45,51519	10,3723	32,56955
71	0	0	100	0	1,26594	0,09452	2,82635	2,21285	18,44777	40,1391	11,29606	30,12734
72	0	0	100	0	1,2647	0,07076	2,166	0,93847	18,39483	50,72847	9,6992	34,88636
73	0	0	100	0	1,02937	0,10958	1,08865	0,2533	10,69975	80,52095	2,99462	38,23013

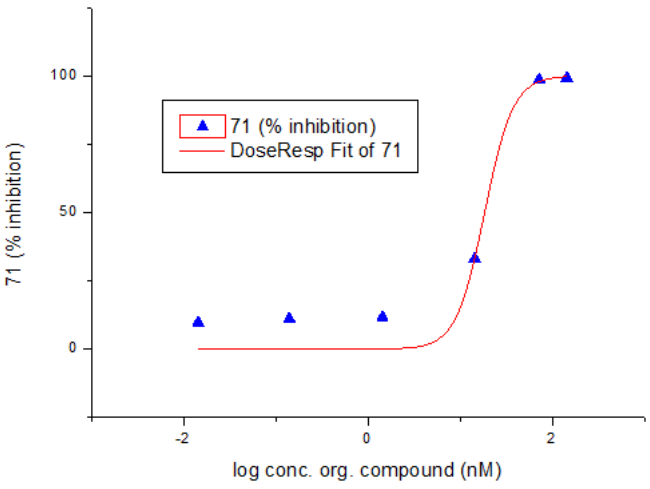
Compound: AA (atrop-abyssomicin C) IC_{50} = 31.77 nM; IC_{90} = 68.32 nM



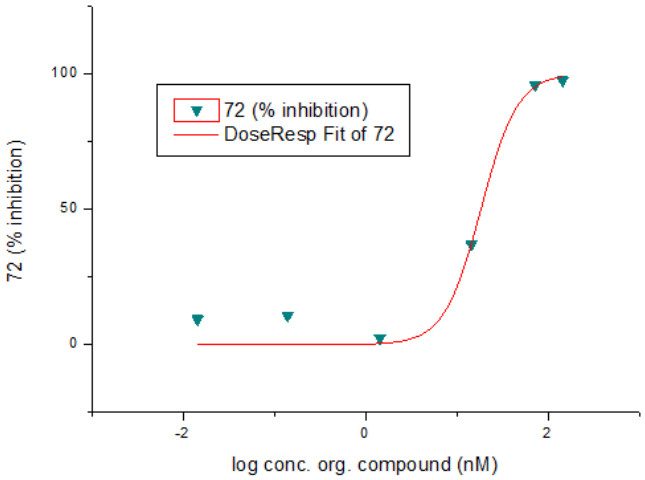
Compound: 70 IC_{50} = 18.38 nM; IC_{90} = 45.51 nM



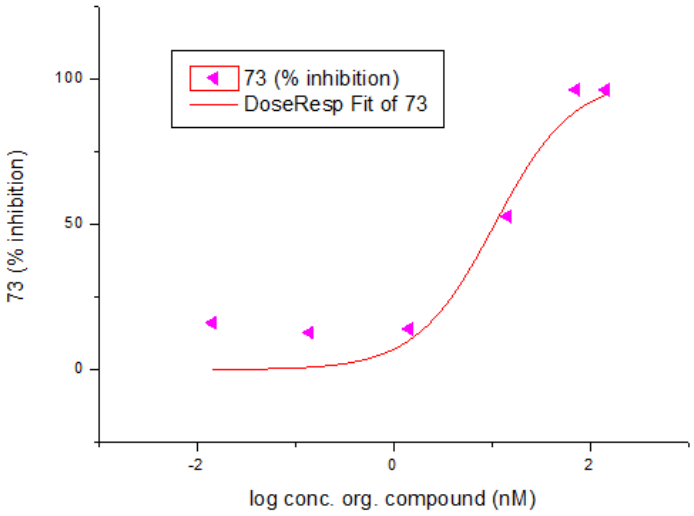
Compound: 71 IC_{50} = 18.45 nM; IC_{90} = 40.14 nM



Compound: 72 IC_{50} = 18.39 nM; IC_{90} = 50.73 nM



Compound: 73 IC_{50} = 10.7 nM; IC_{90} = 80.52 nM

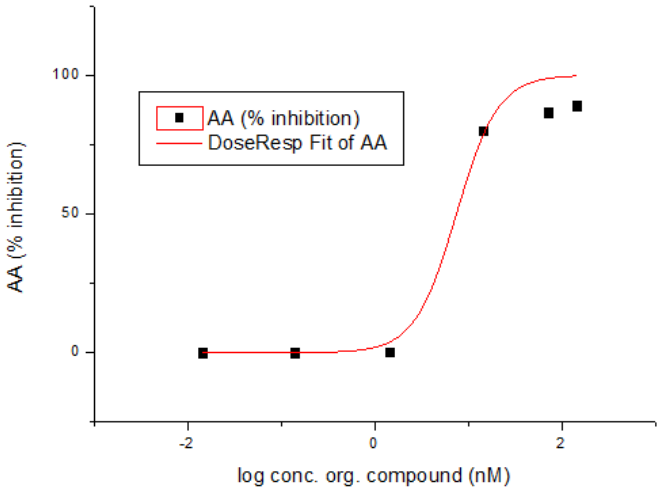


Results of the determination of cytotoxicity of compounds AA, 70, 71, 72 and 73 on Peripheral blood mononuclear cells (PBMC)

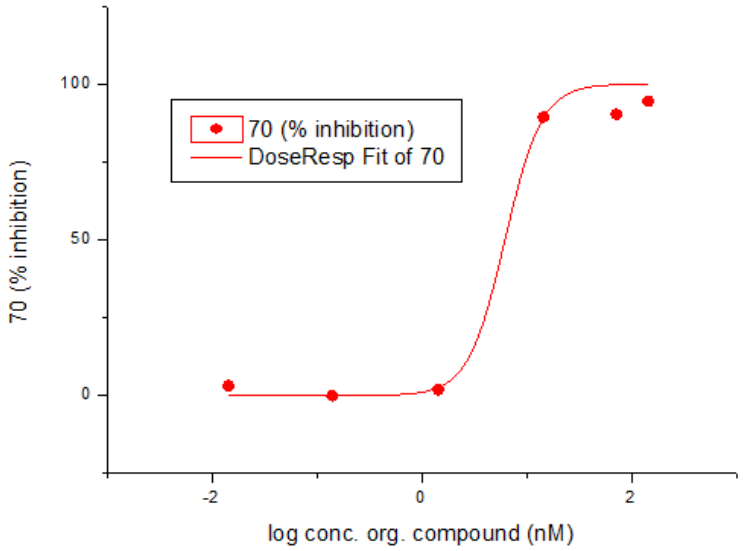
Summary

	A1		A2		LOGx0		p		EC50	EC90	EC20	EC80
	Value	Error	Value	Error	Value	Error	Value	Error	Value			
AA	0	0	100	0	0,87372	0,13469	1,95738	0,81497	7,47687	22,97364	3,68244	15,18114
70	0	0	100	0	0,7934	0,19287	2,47956	1,23306	6,21446	15,07465	3,55299	10,86958
71	0	0	100	0	0,78981	0,14499	2,11424	0,75281	6,16324	17,42406	3,19922	11,87335
72	0	0	100	0	0,7054	0,10906	1,28486	0,26605	5,07459	28,0597	1,72513	14,9273
73	0	0	100	0	0,69995	0,14523	2,21661	0,65957	5,01128	13,50347	2,68124	9,36617

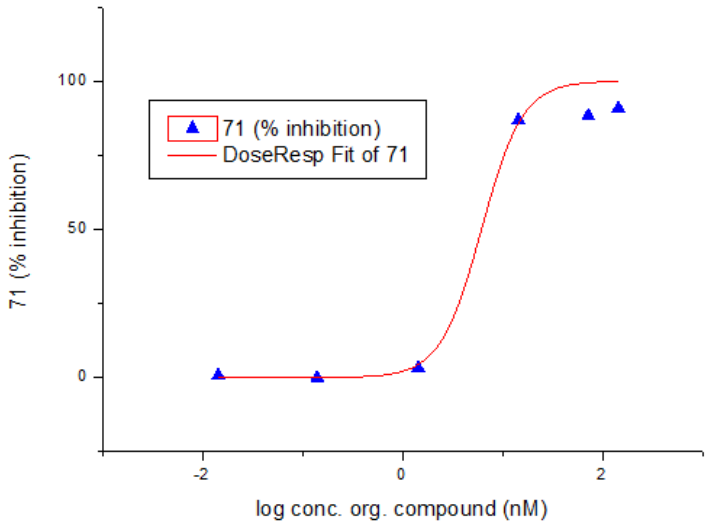
Compound: AA (atrop-abyssomicin C) IC_{50} = 7.48 nM; IC_{90} = 22.97 nM



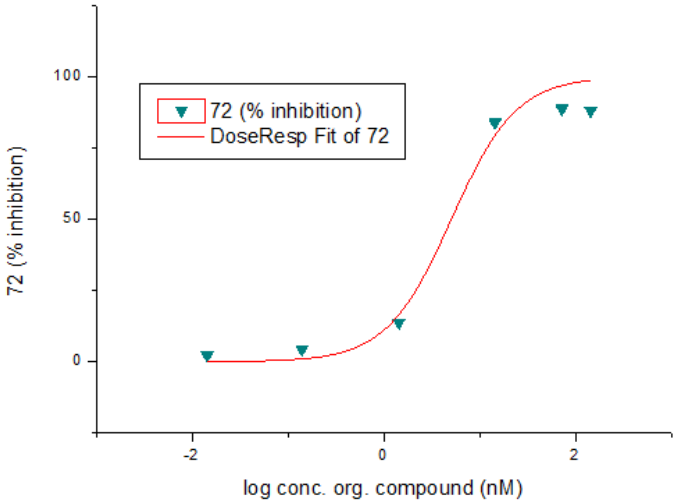
Compound: 70 IC_{50} = 6.21 nM; IC_{90} = 15.07 nM



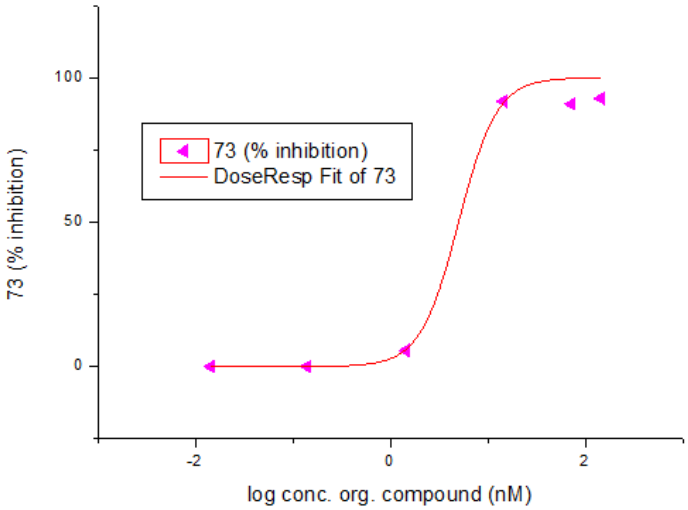
Compound: 71 IC_{50} = 6.16 nM; IC_{90} = 17.42 nM



Compound: 72 IC_{50} = 5.07 nM; IC_{90} = 28.06 nM



Compound: 70 IC_{50} = 5.01 nM; IC_{90} = 13.50 nM



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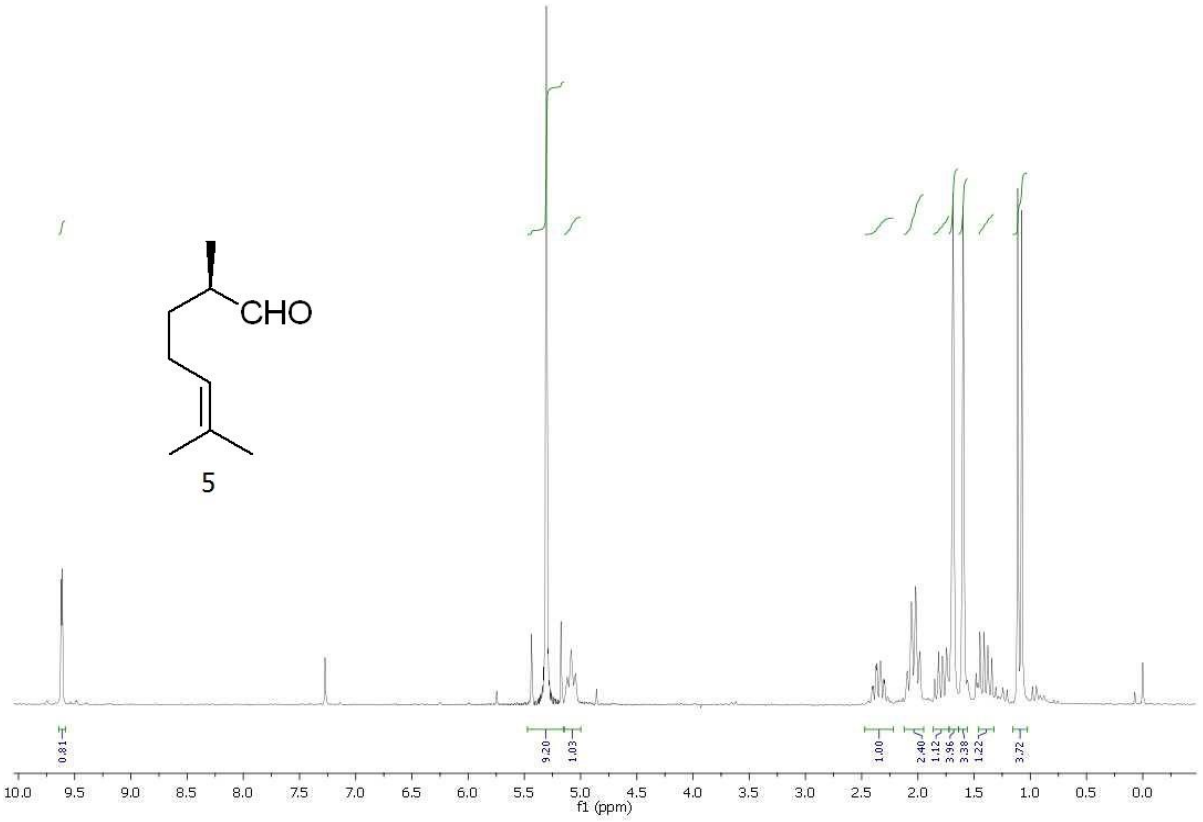
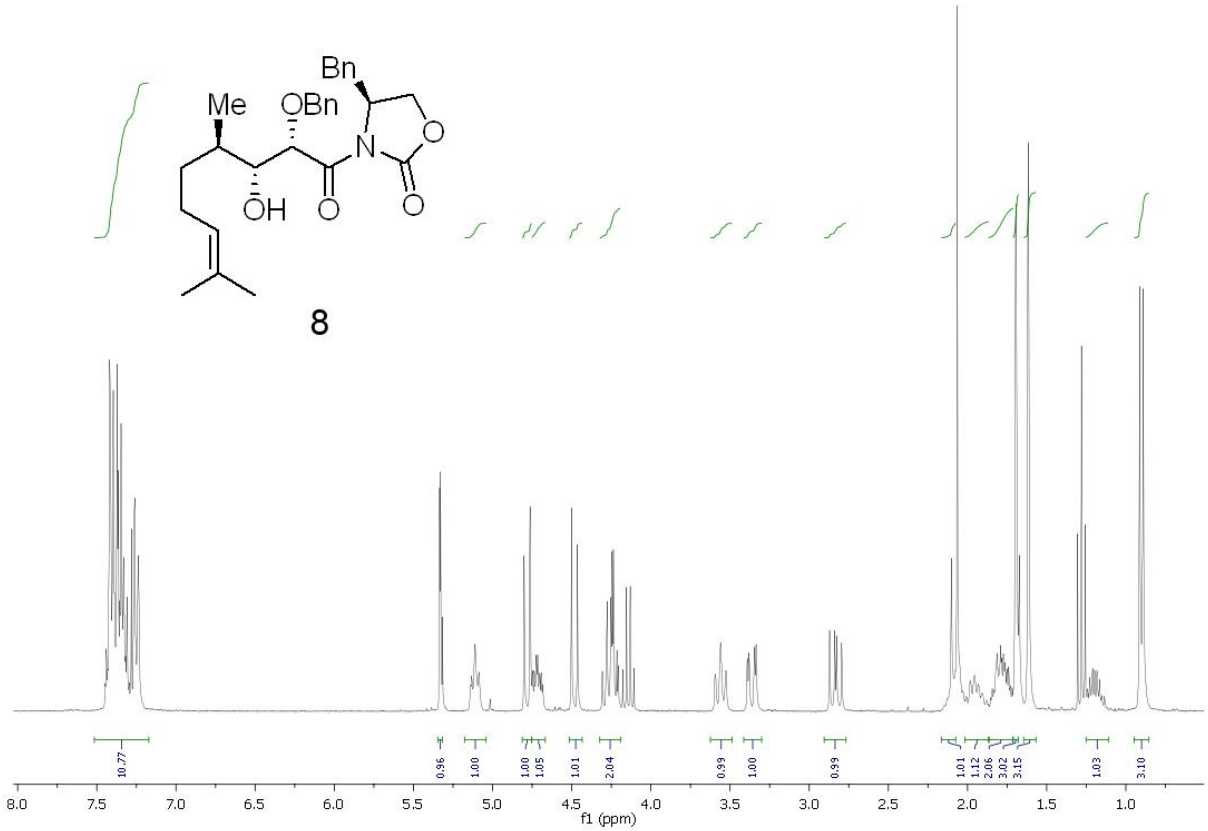
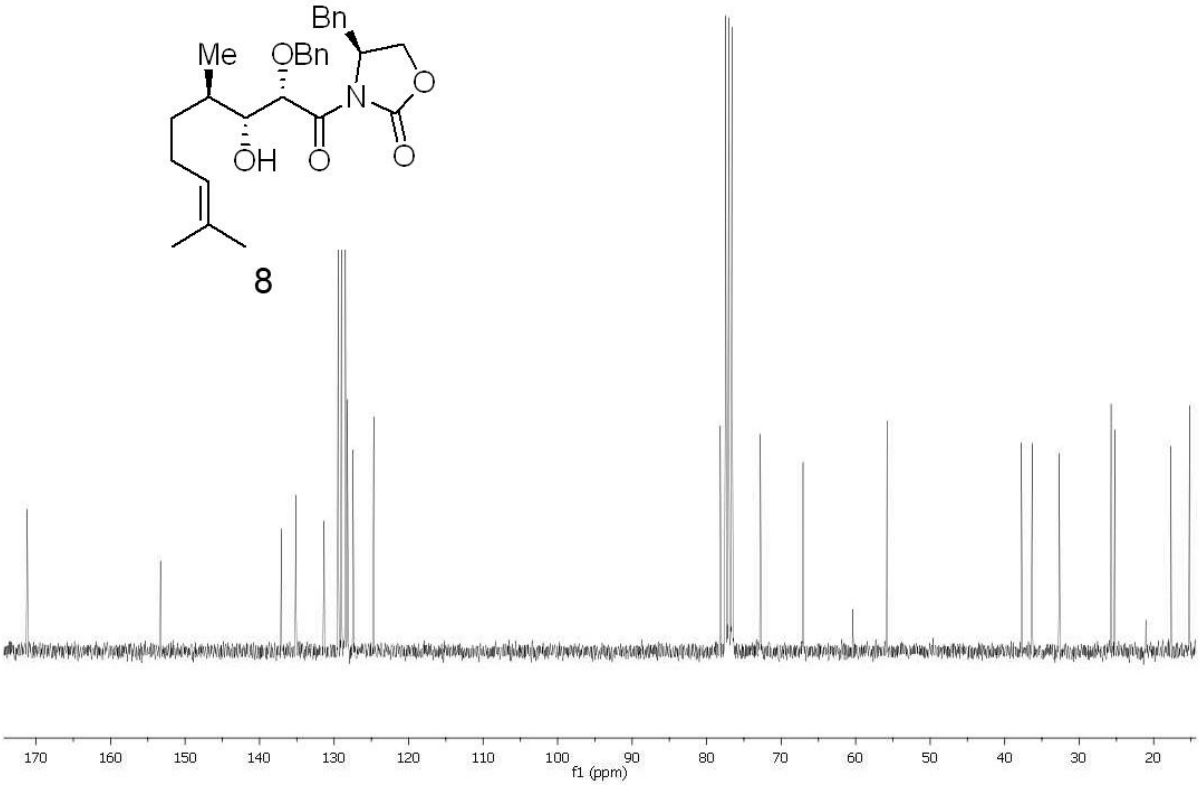
5. Copies of spectra







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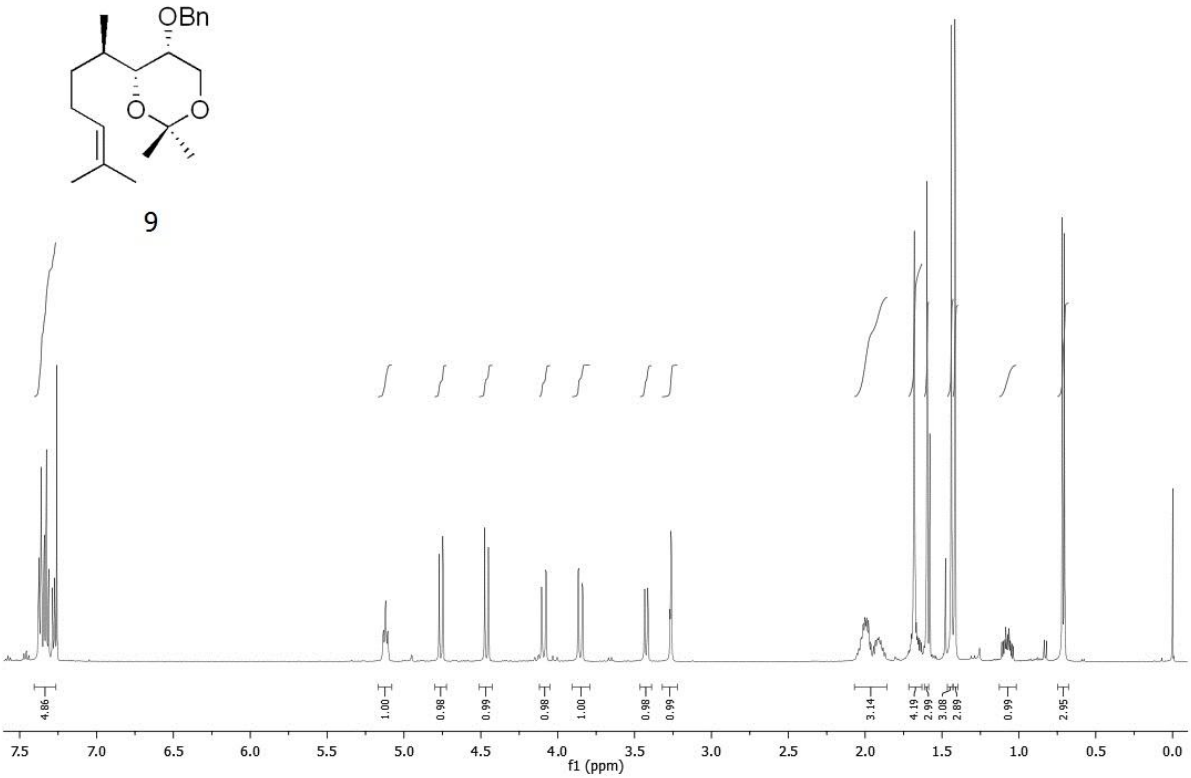

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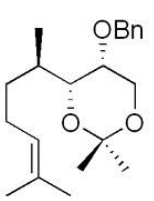

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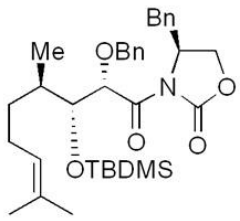

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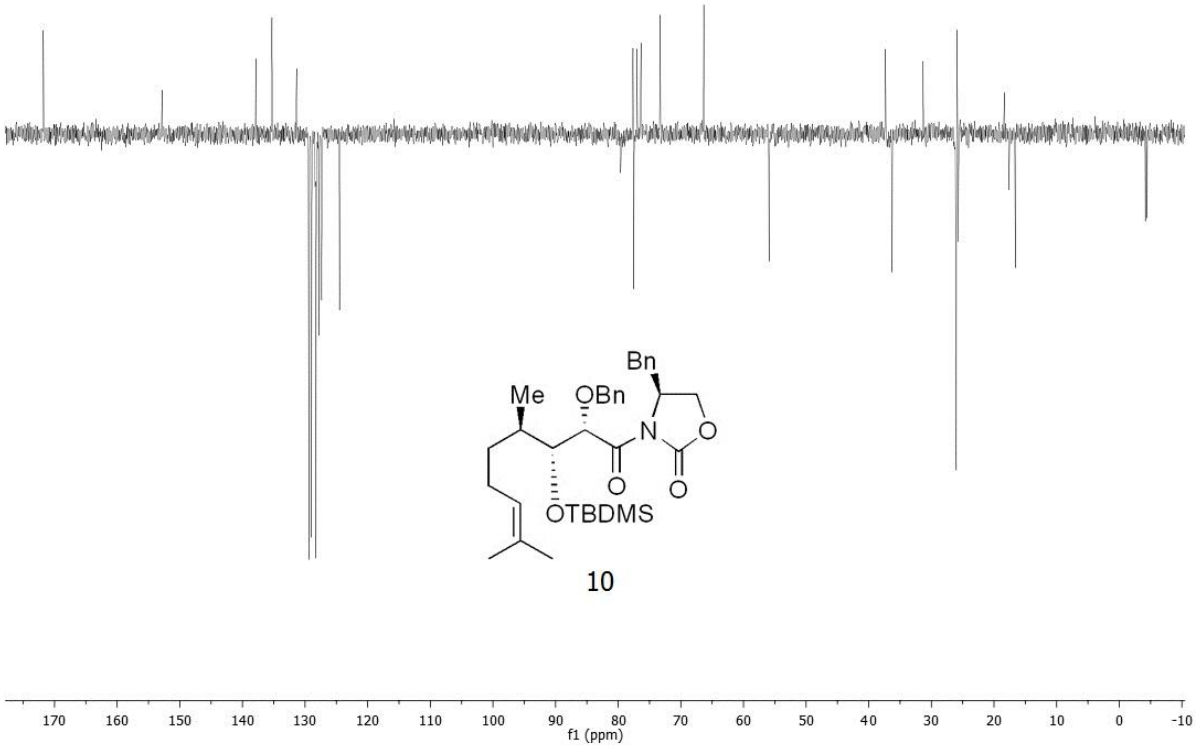

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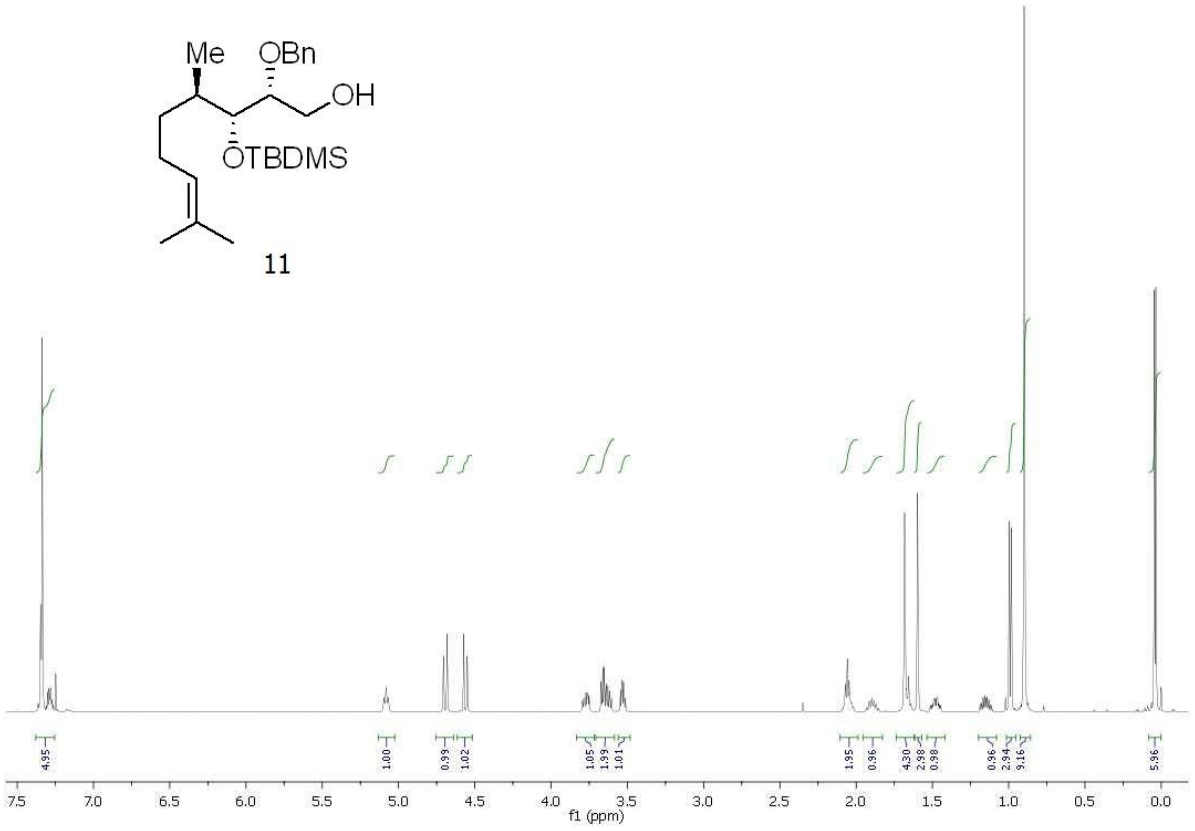

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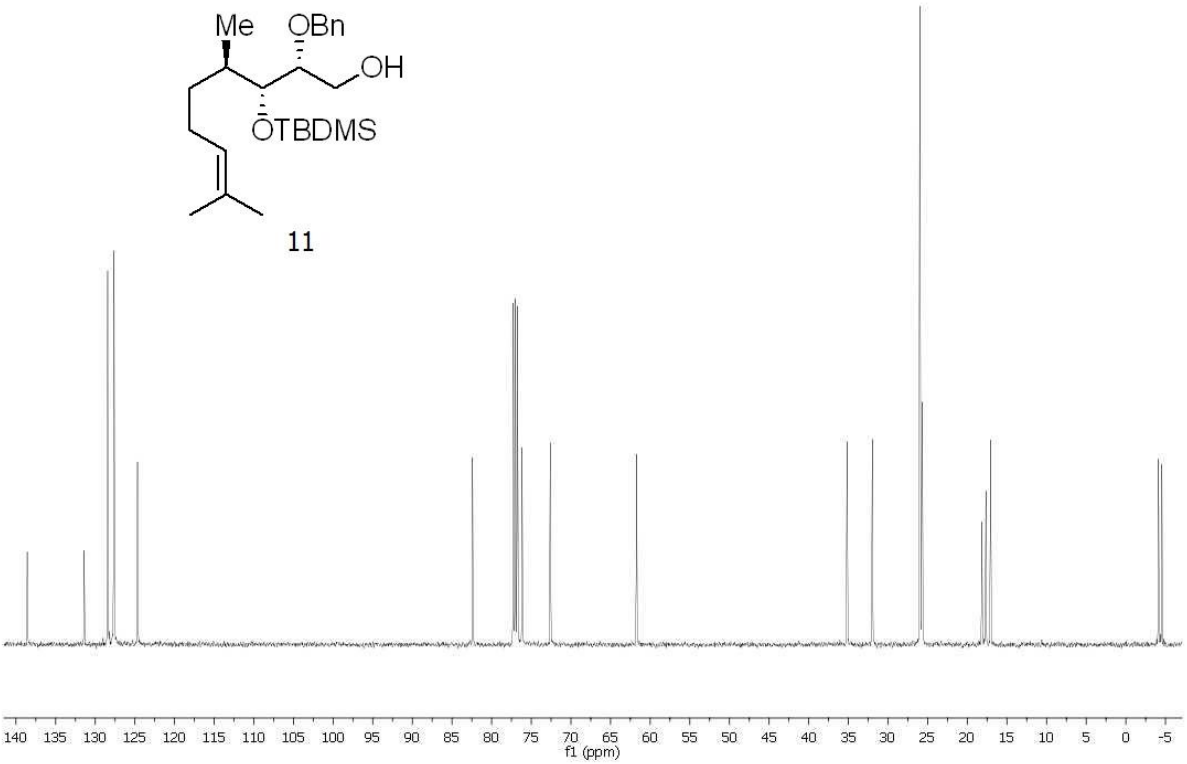

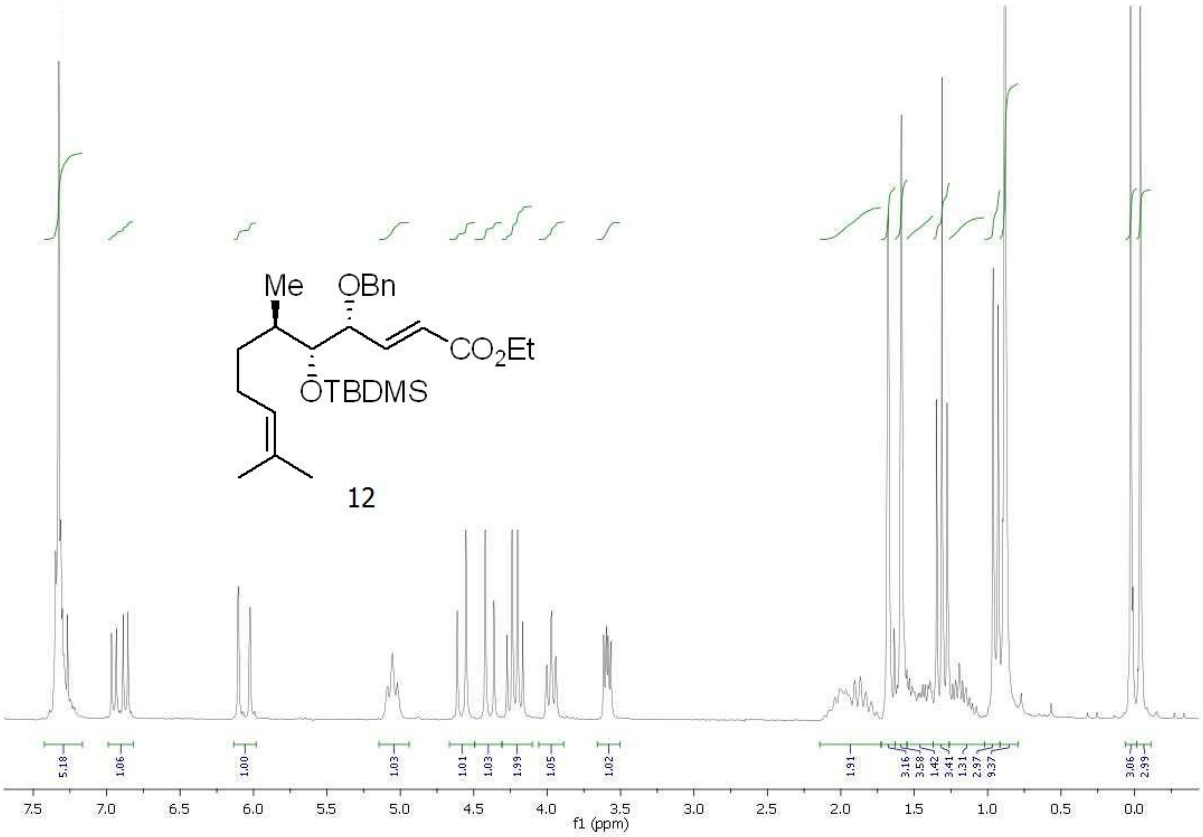

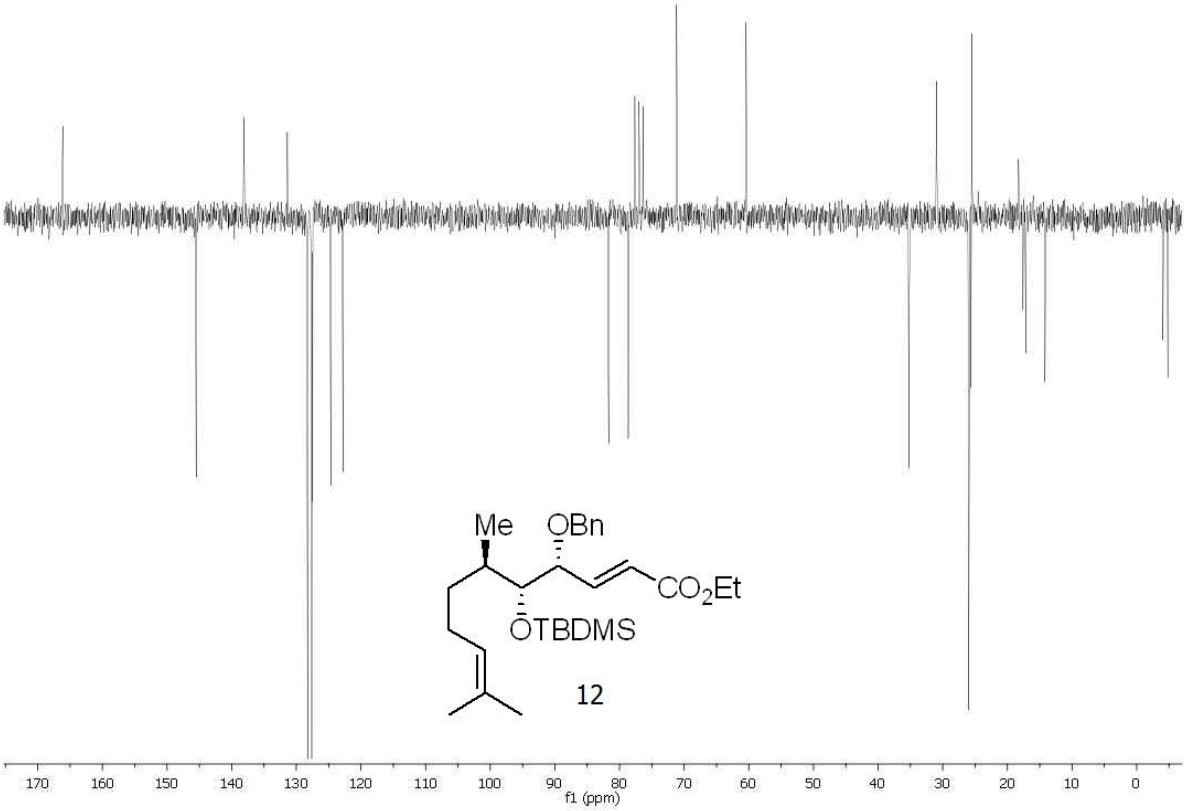

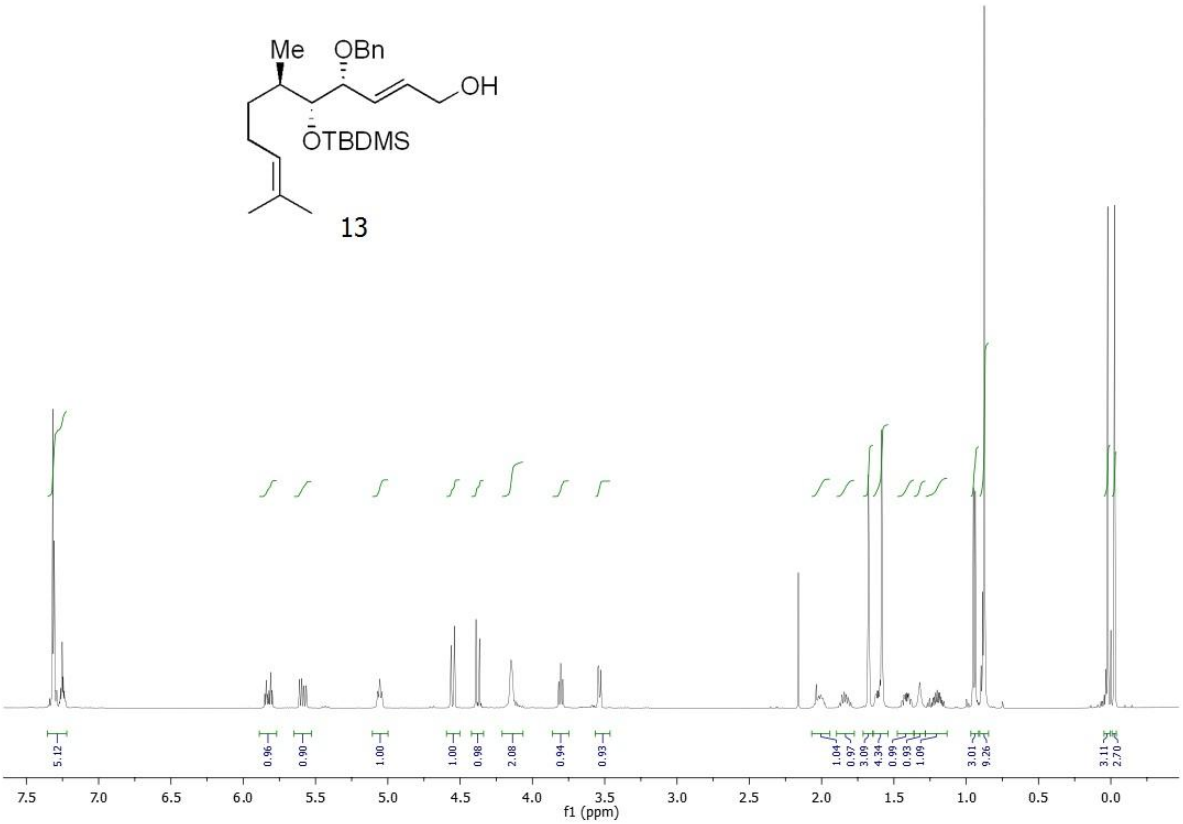

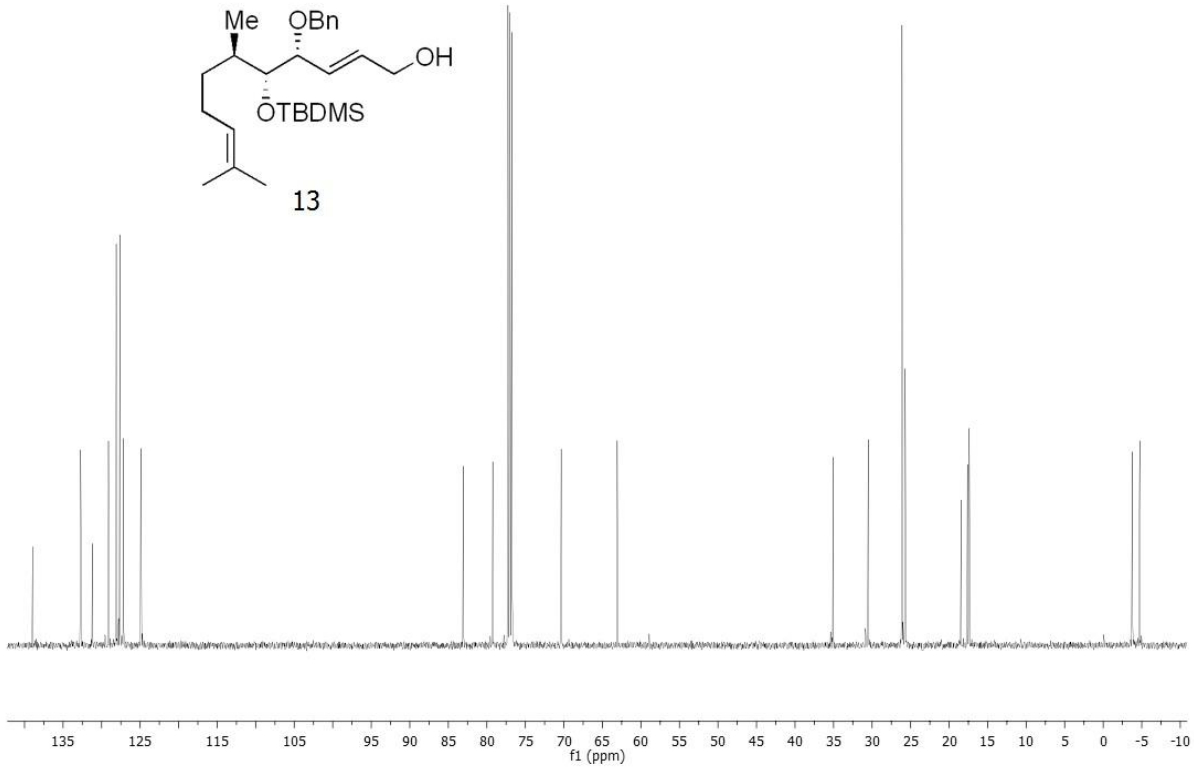

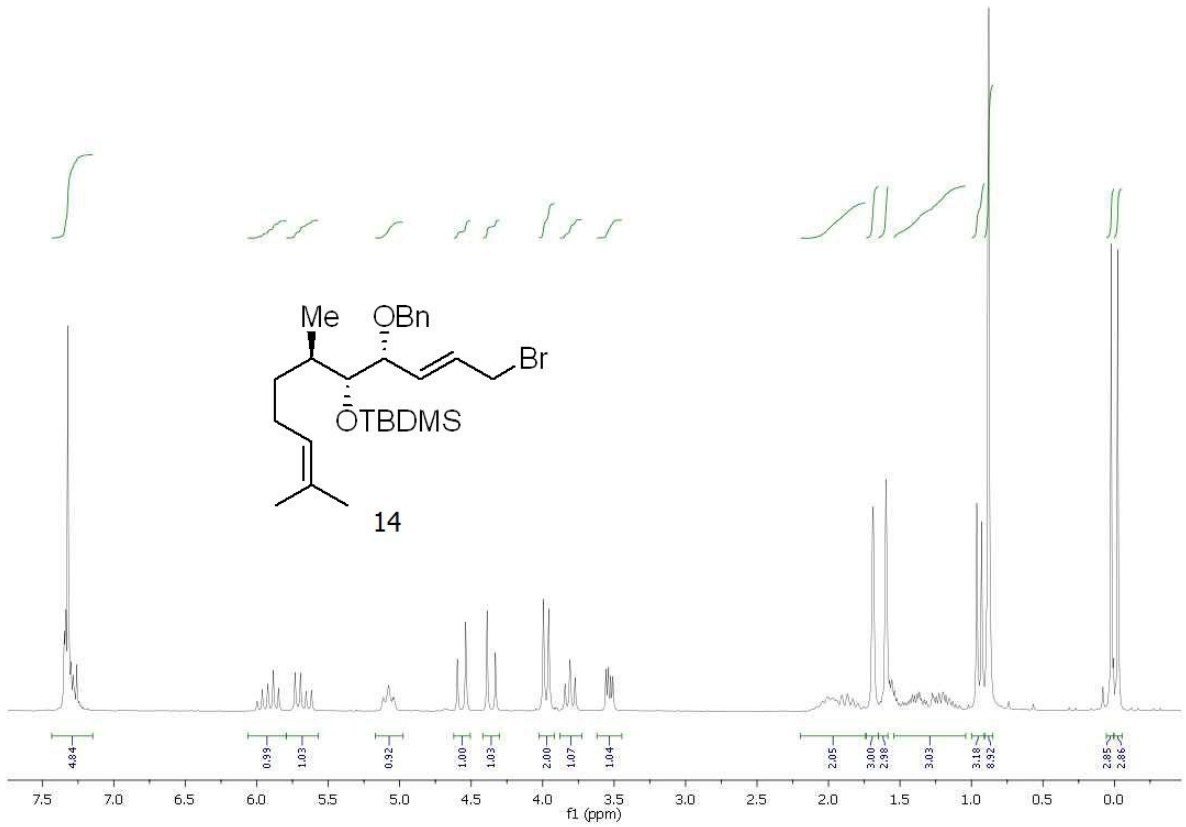

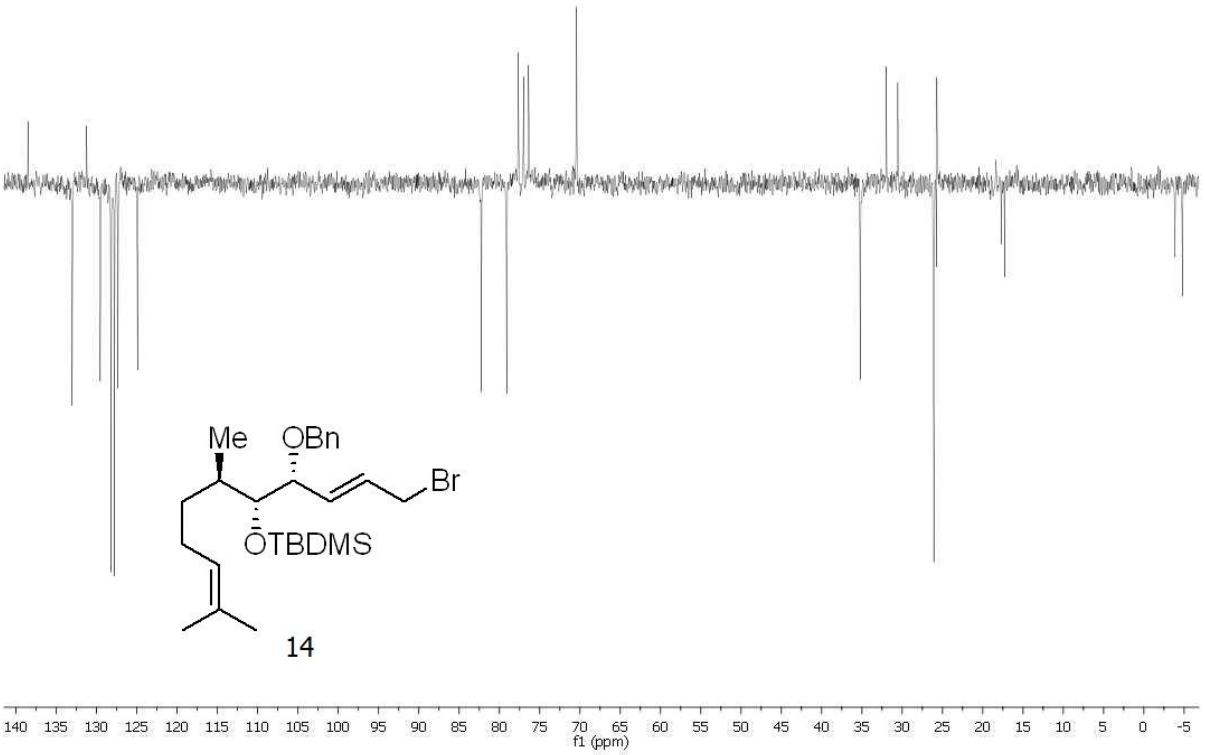

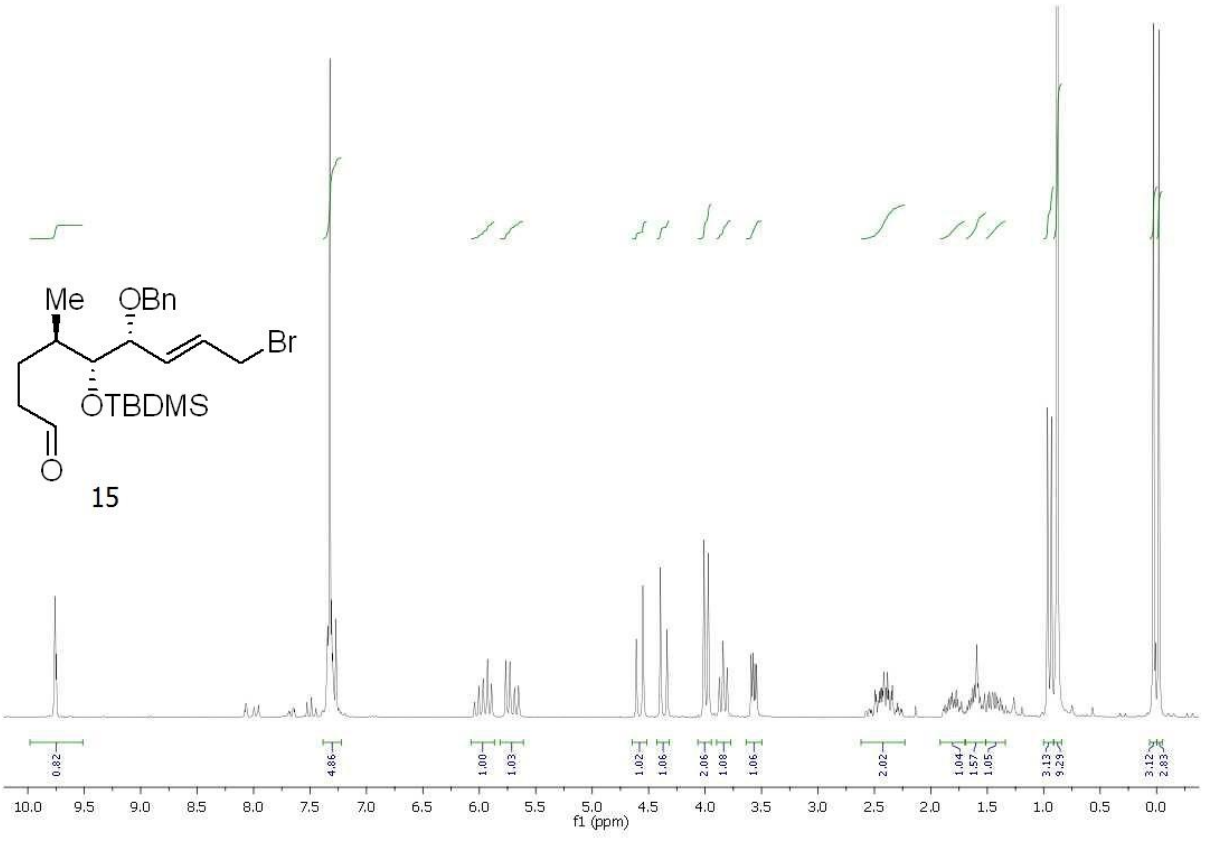

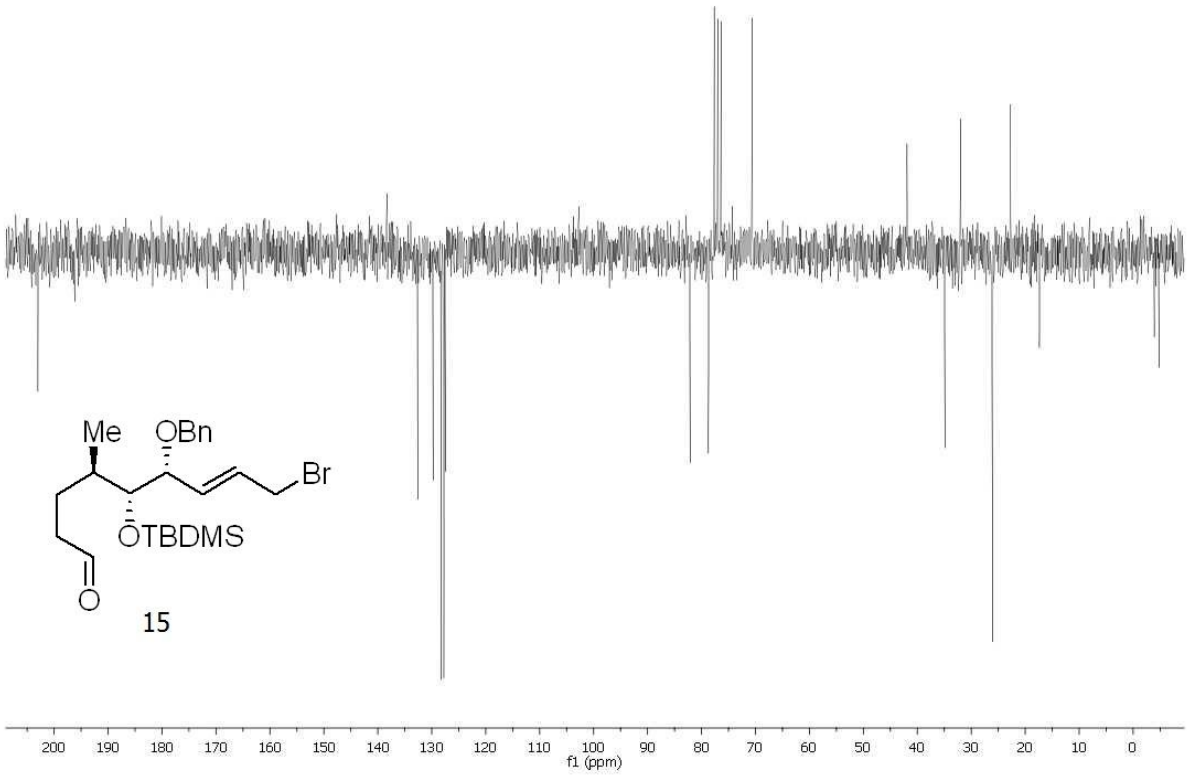

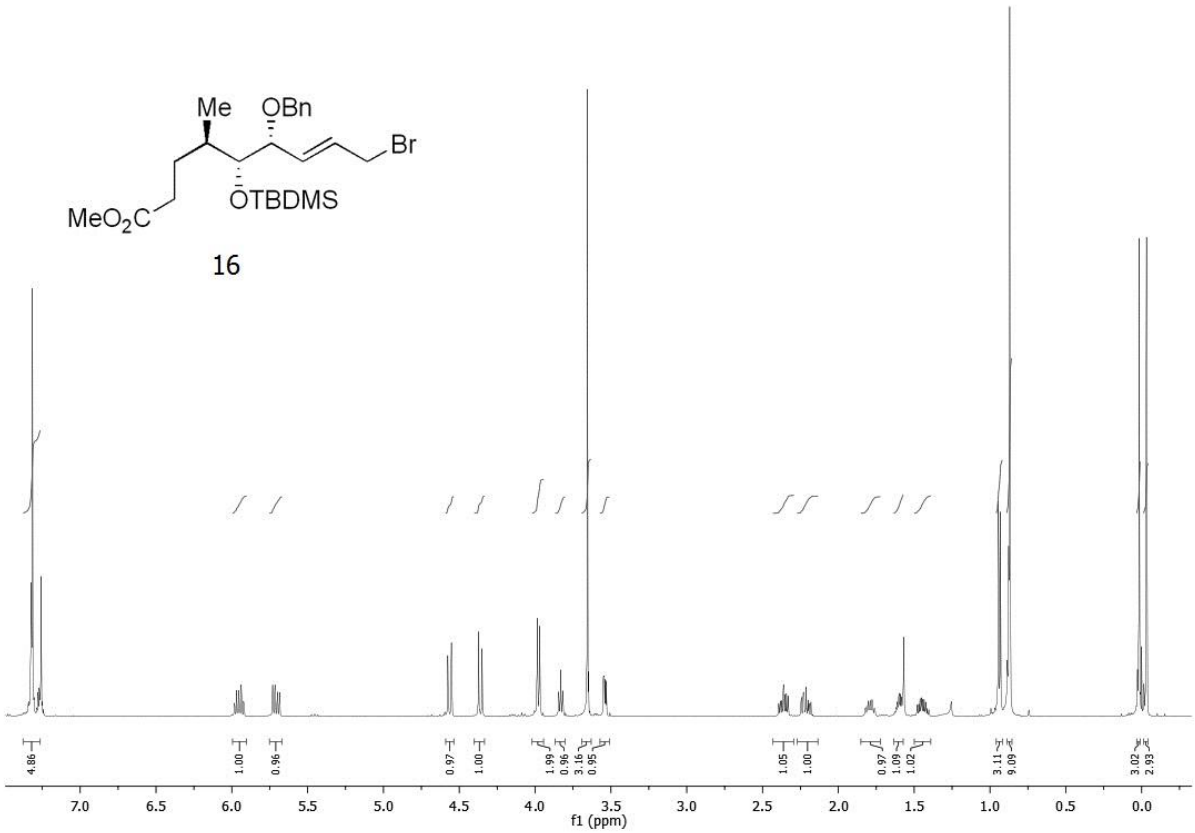

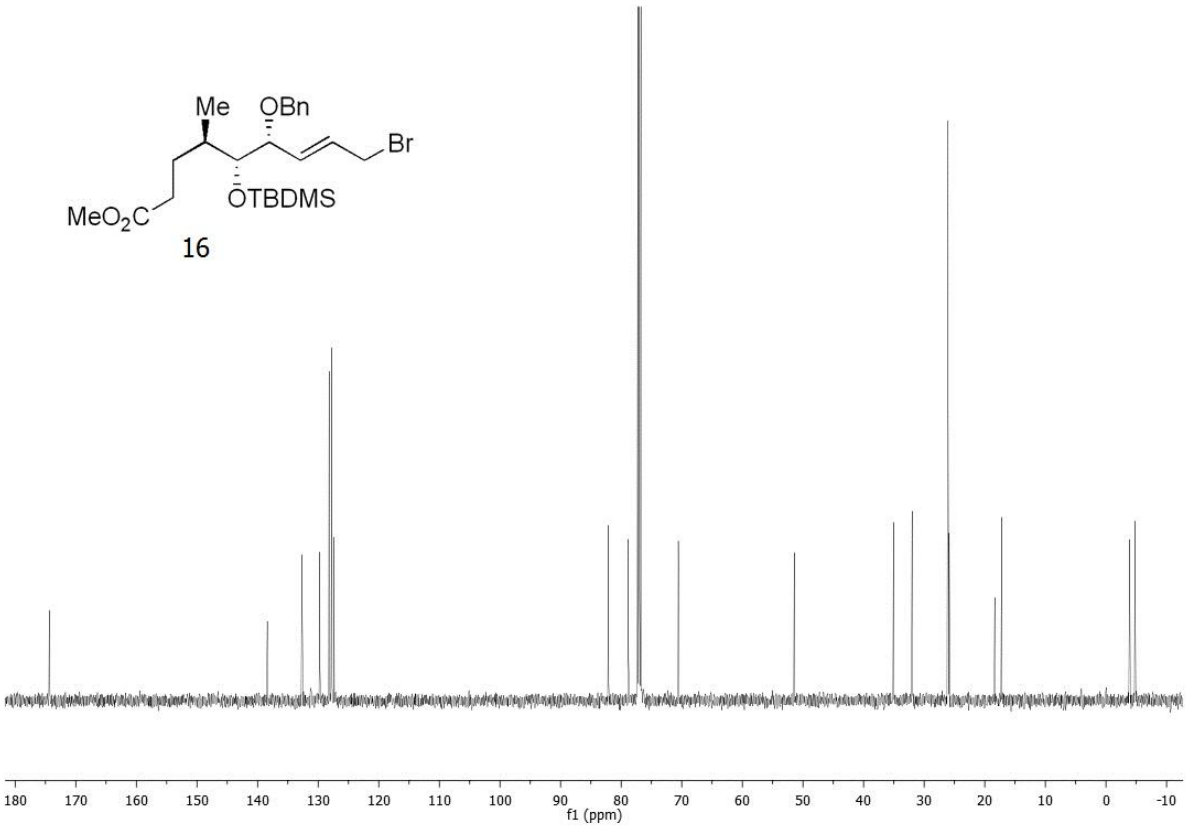

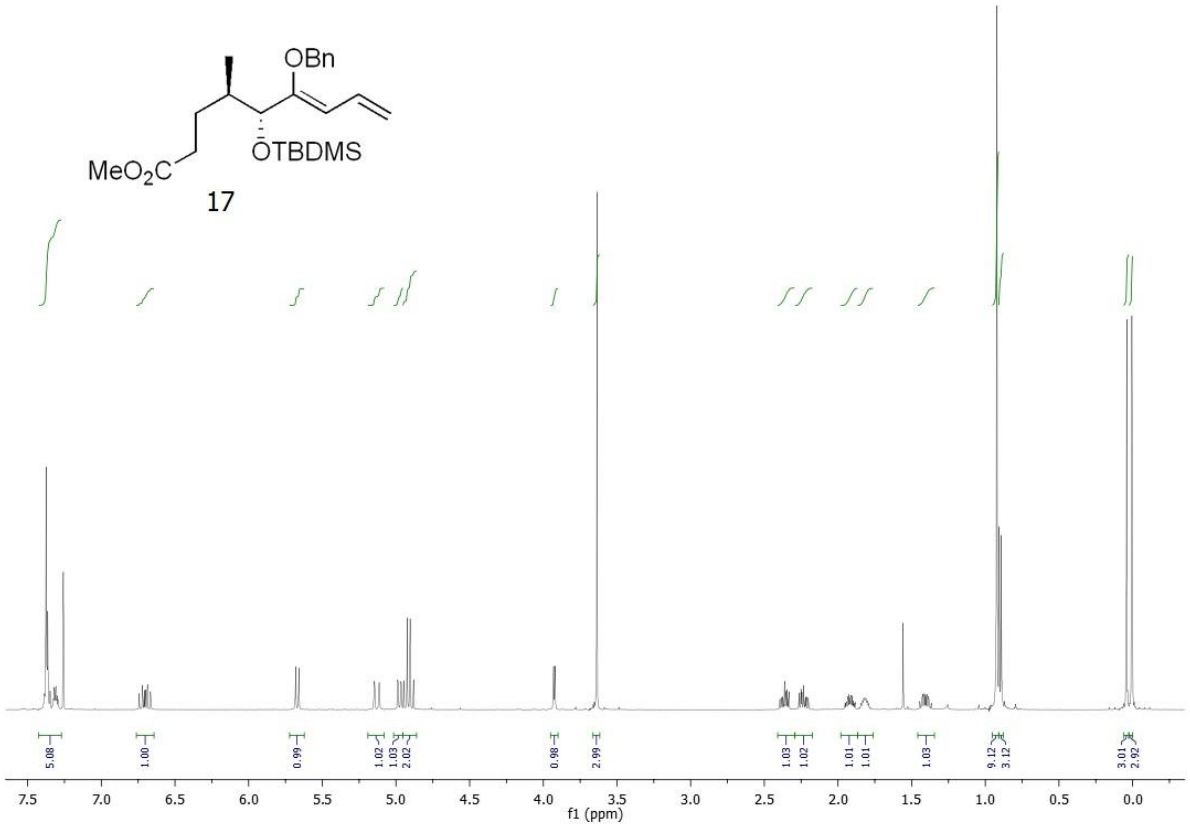

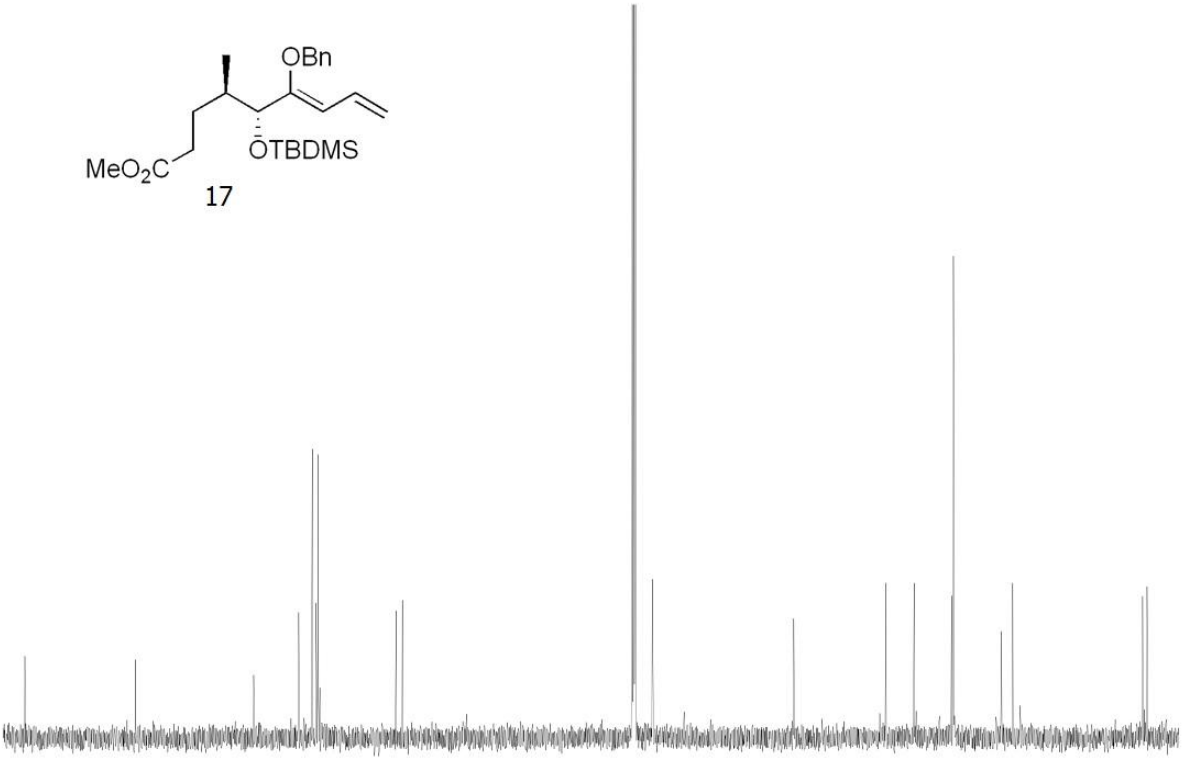

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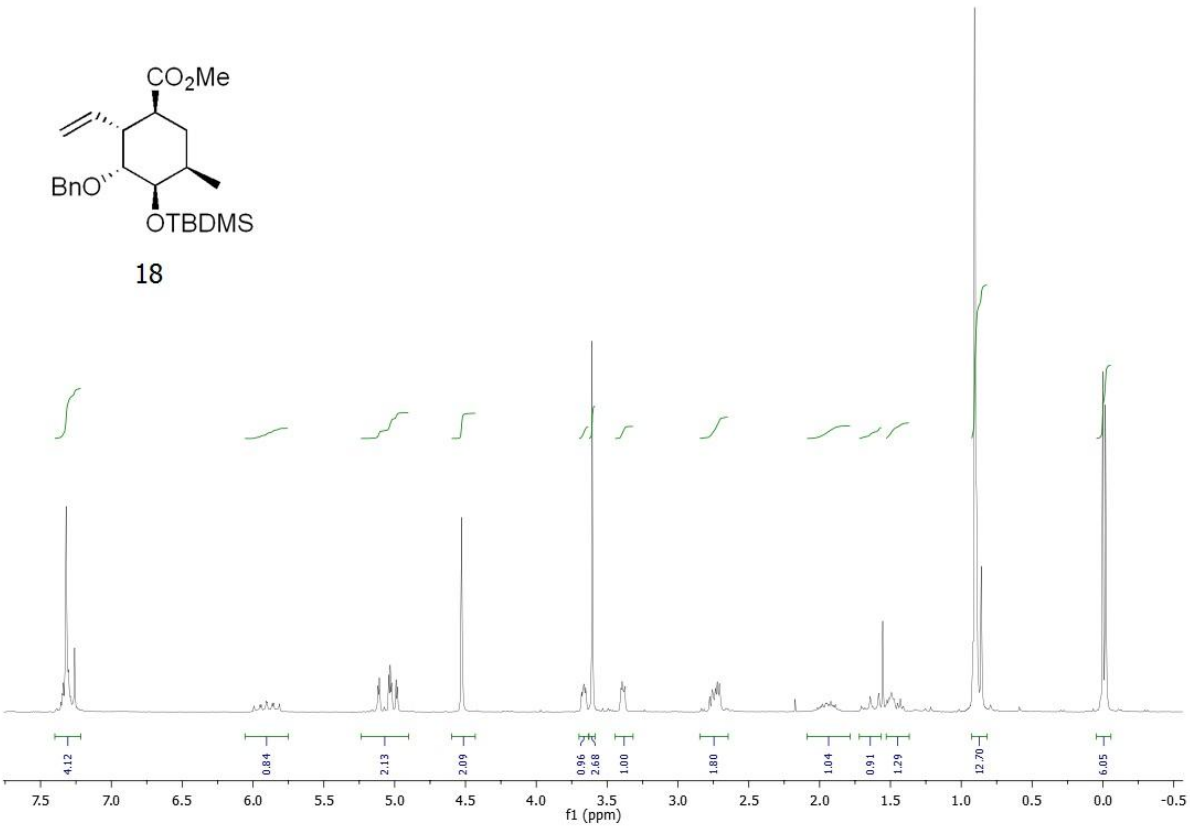

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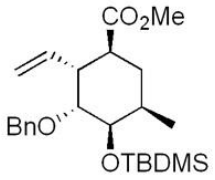

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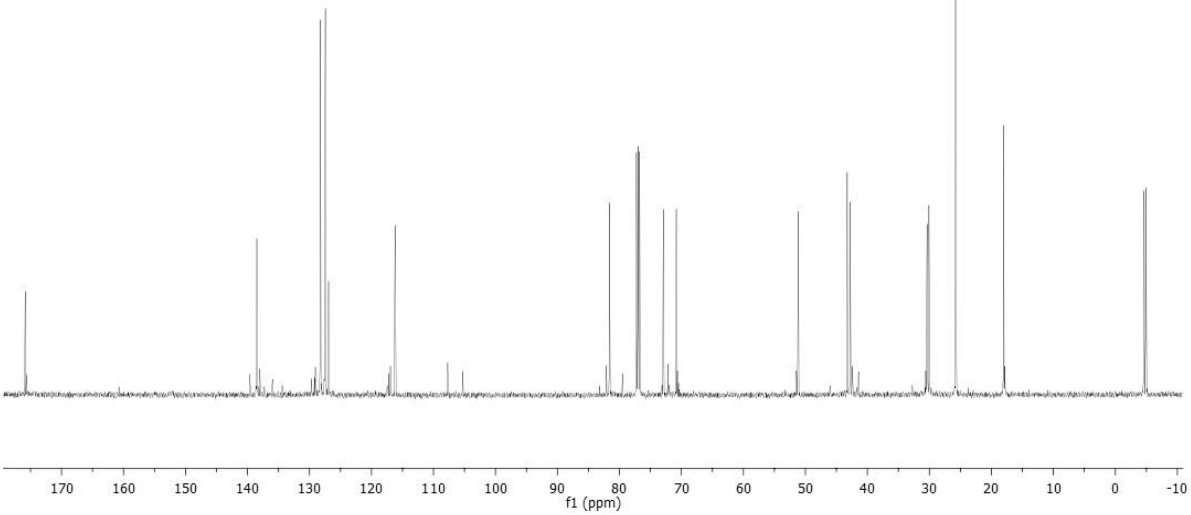

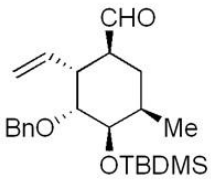

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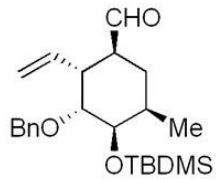

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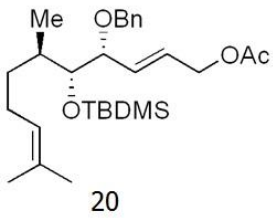

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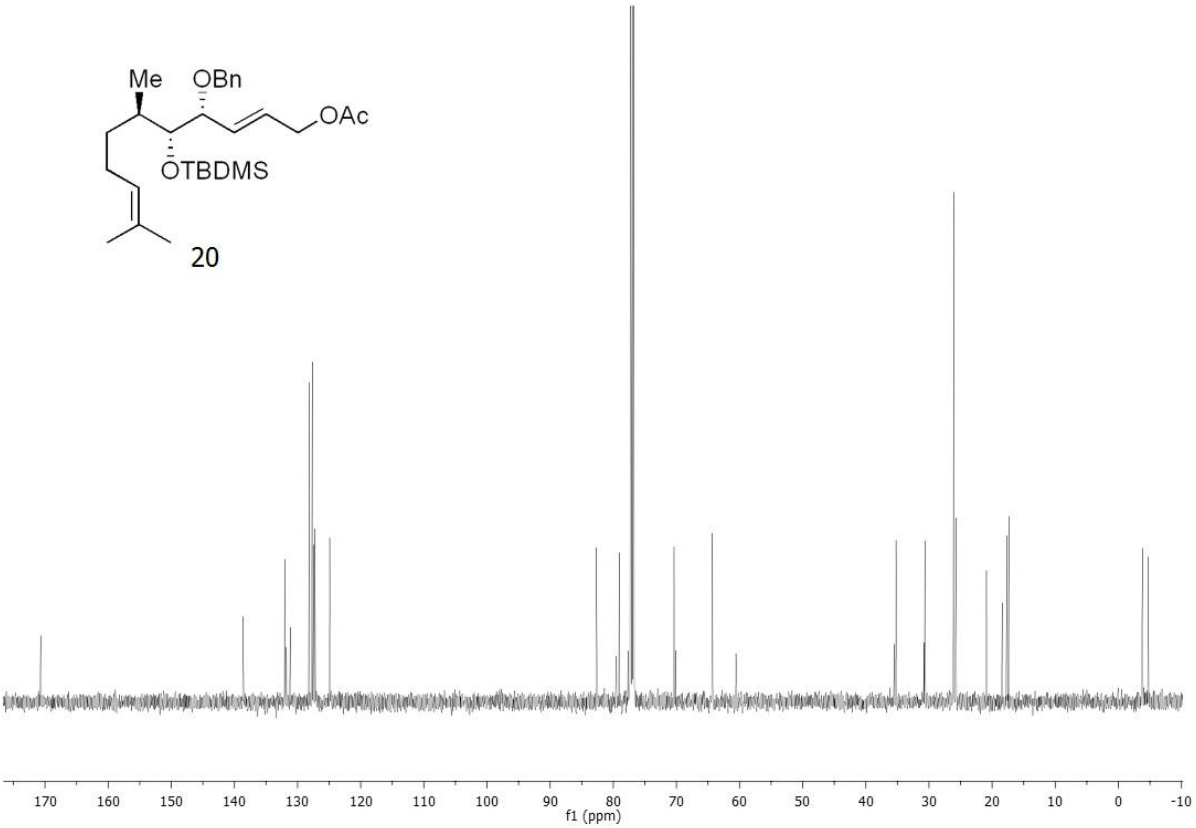

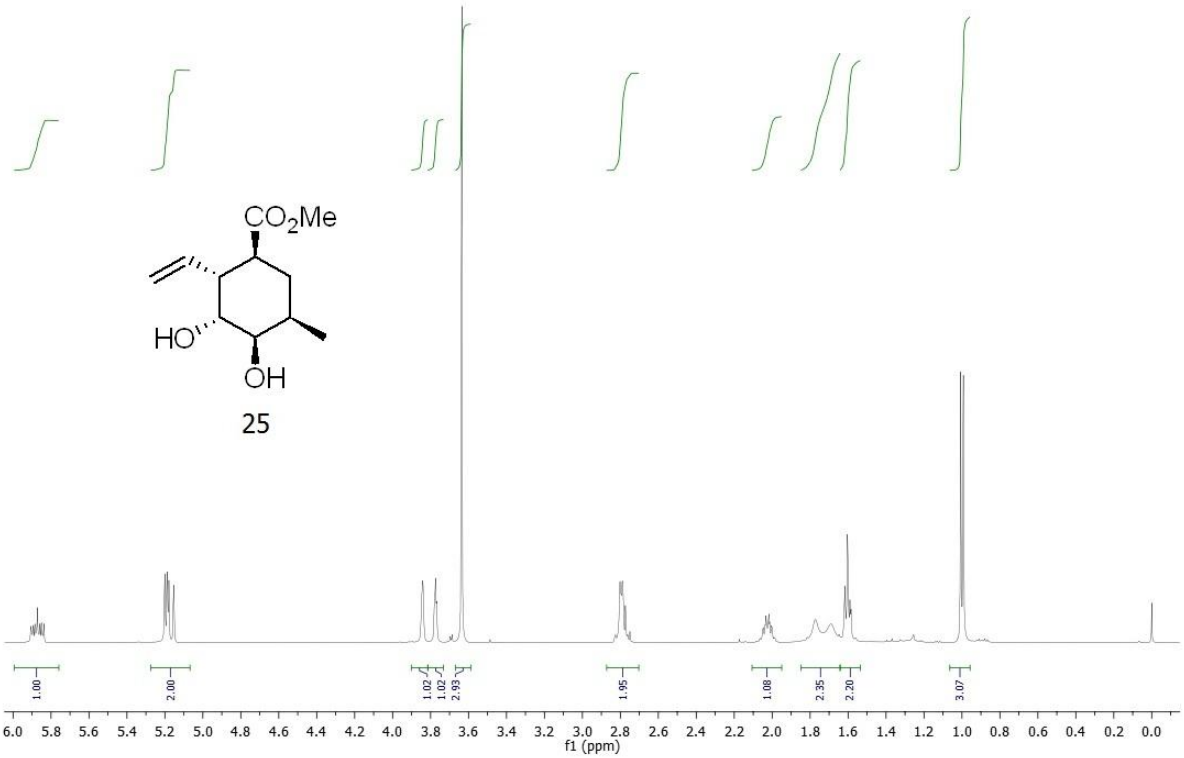

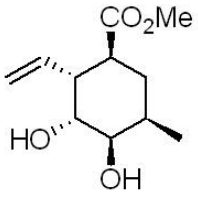

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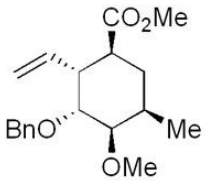

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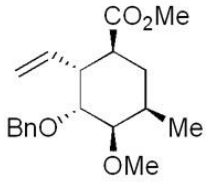

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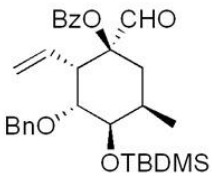

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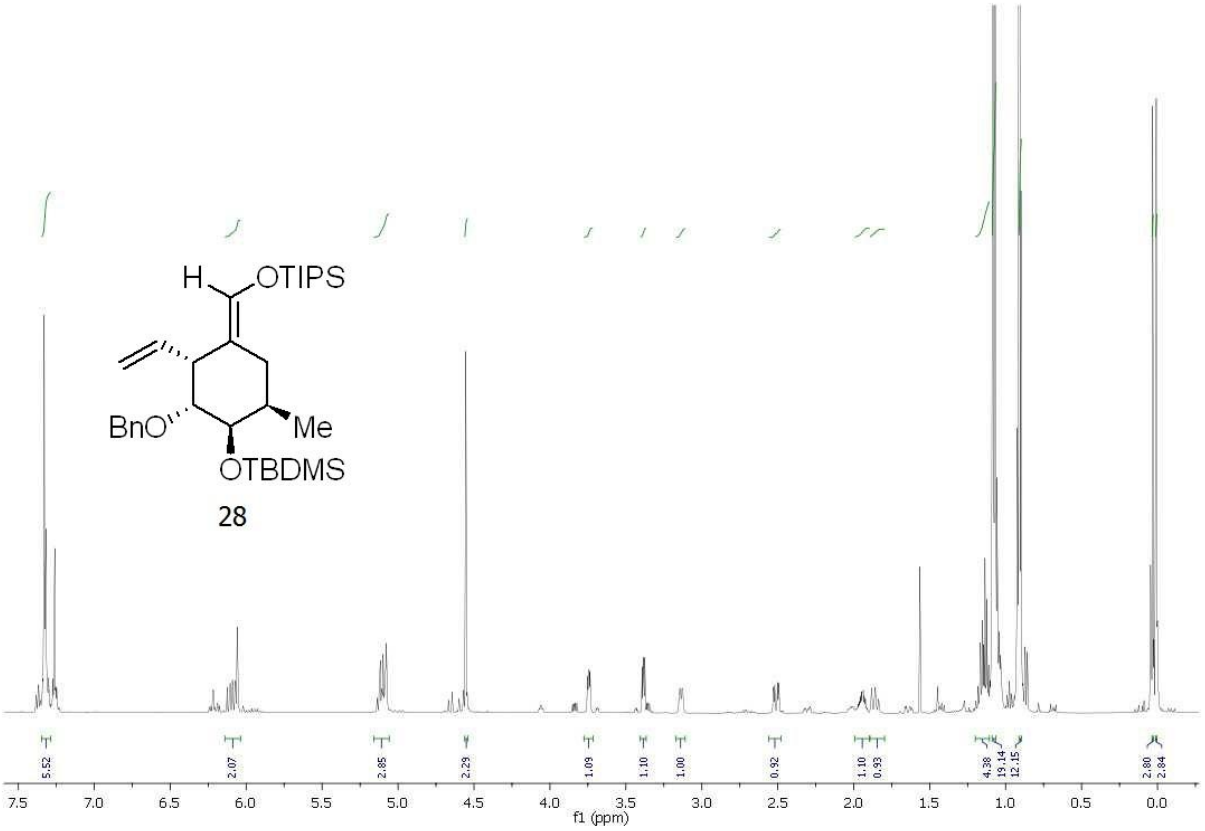

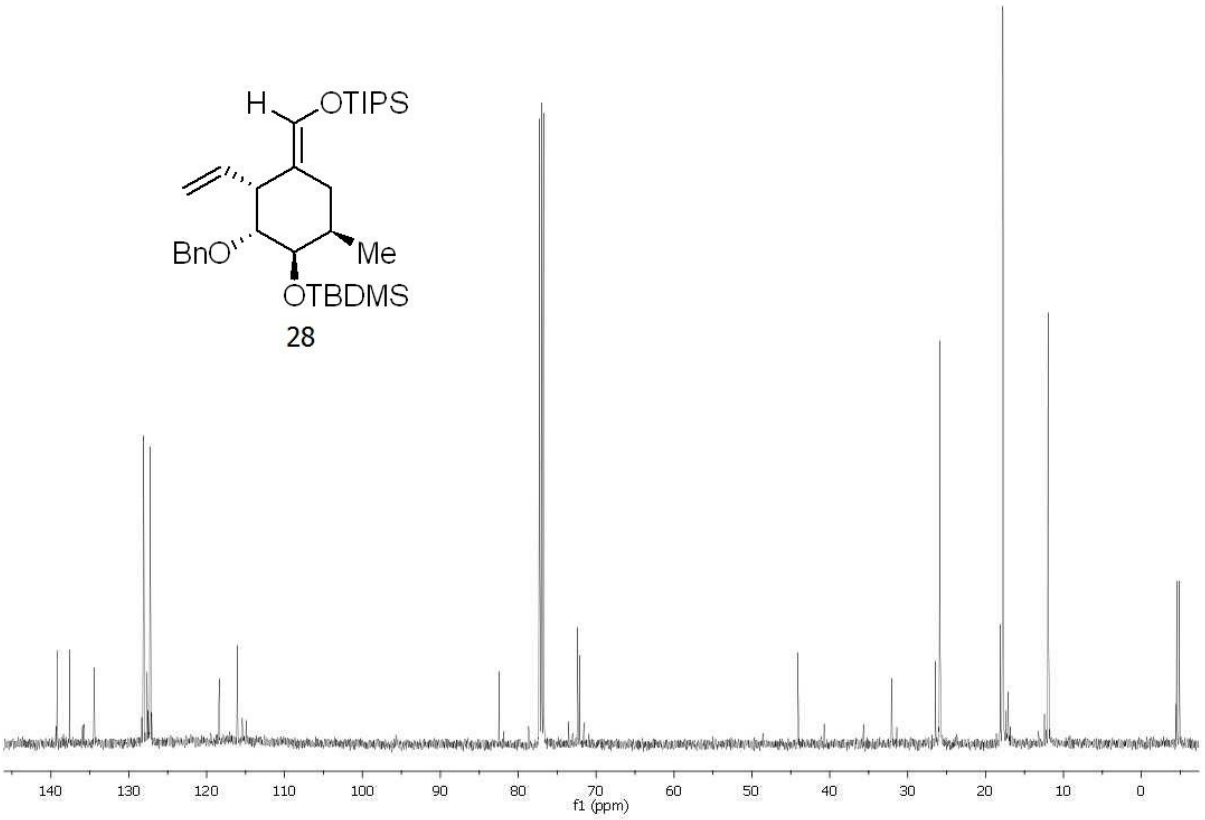

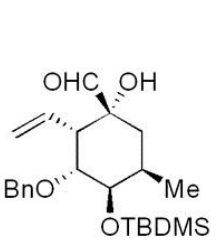

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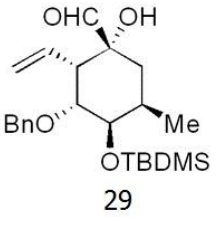

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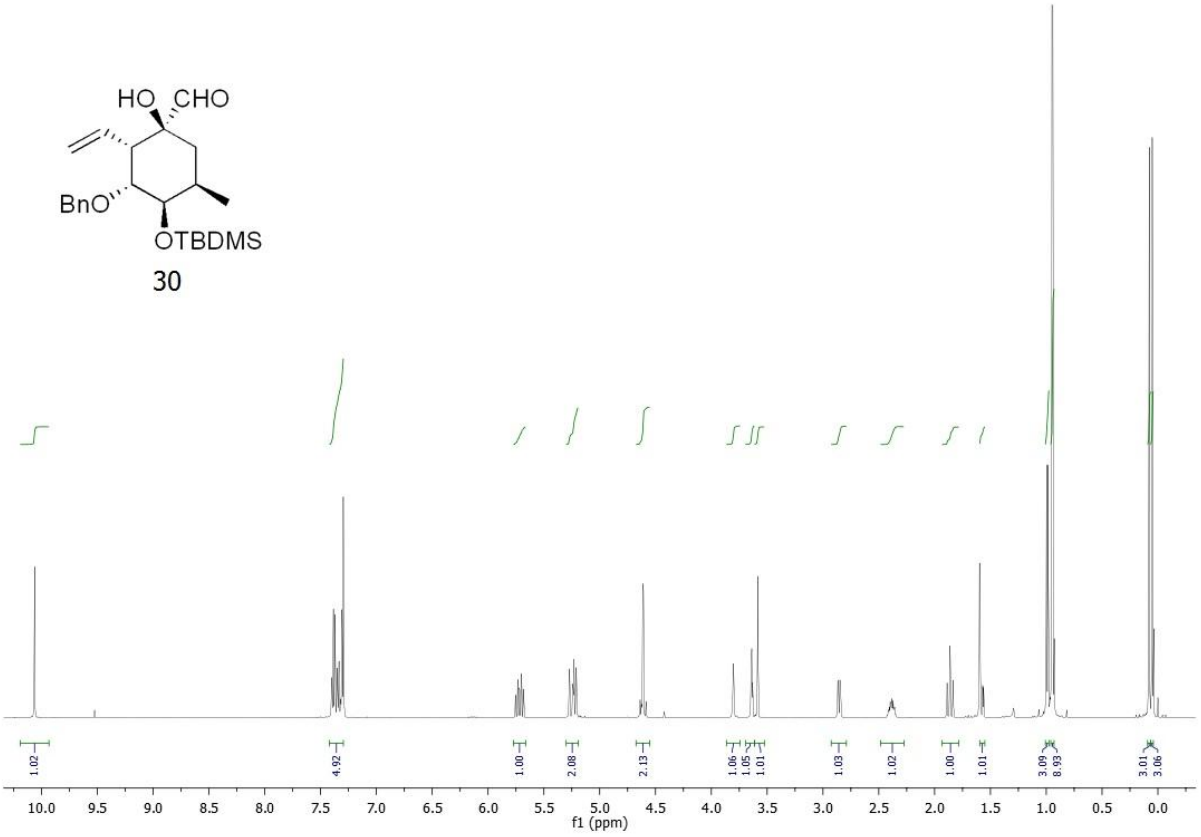

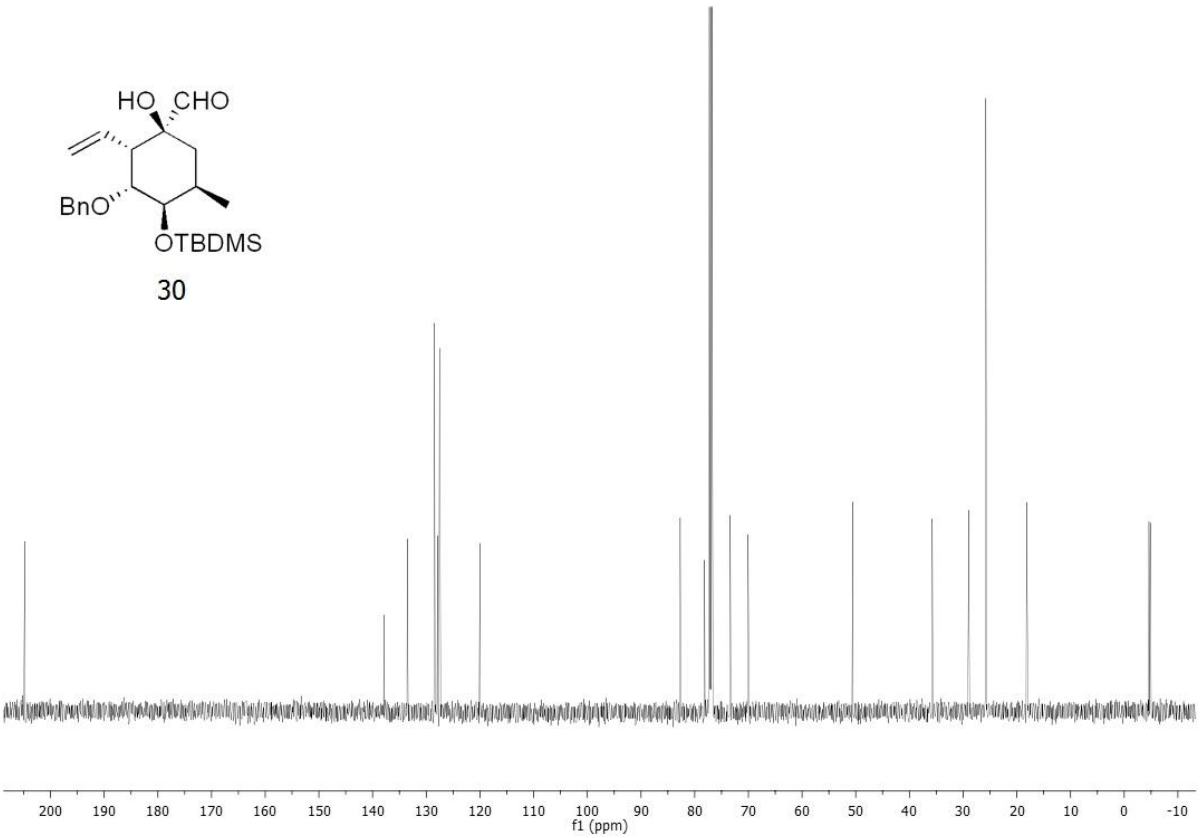

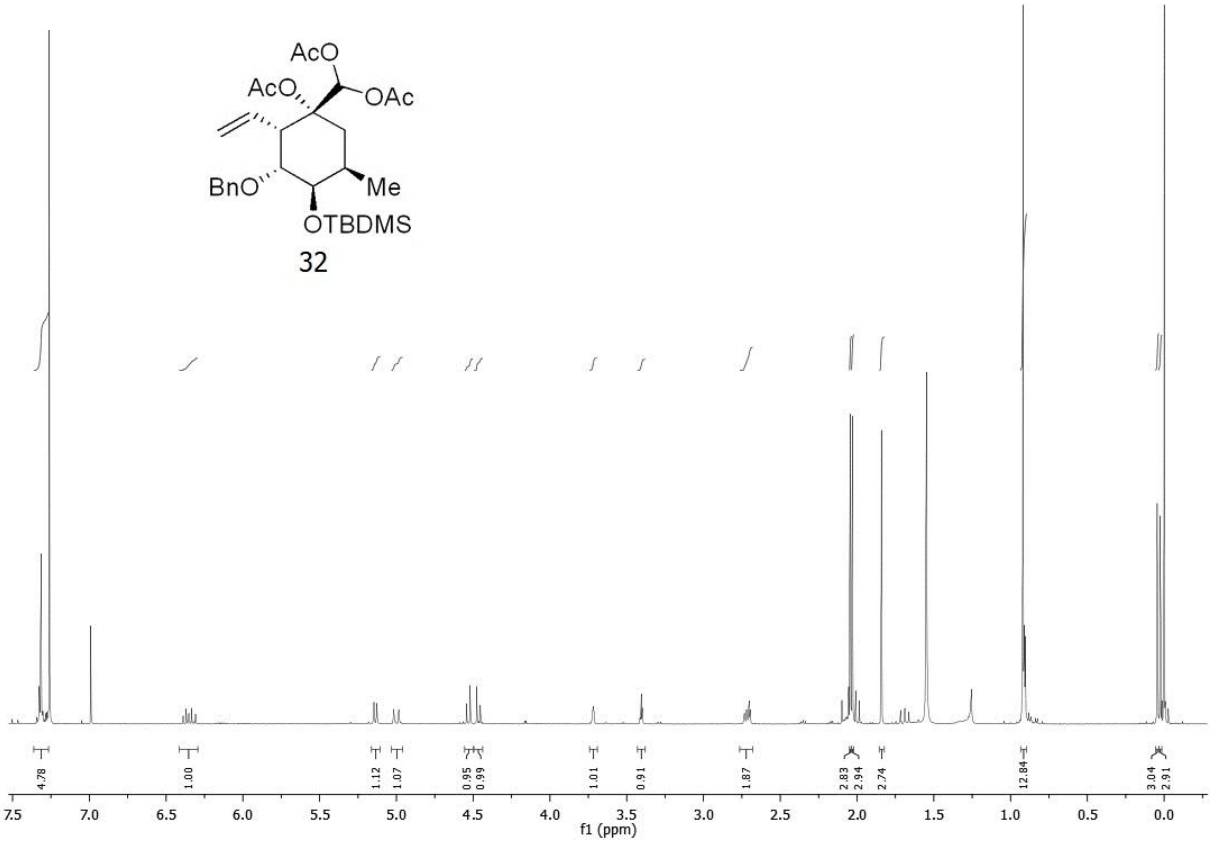

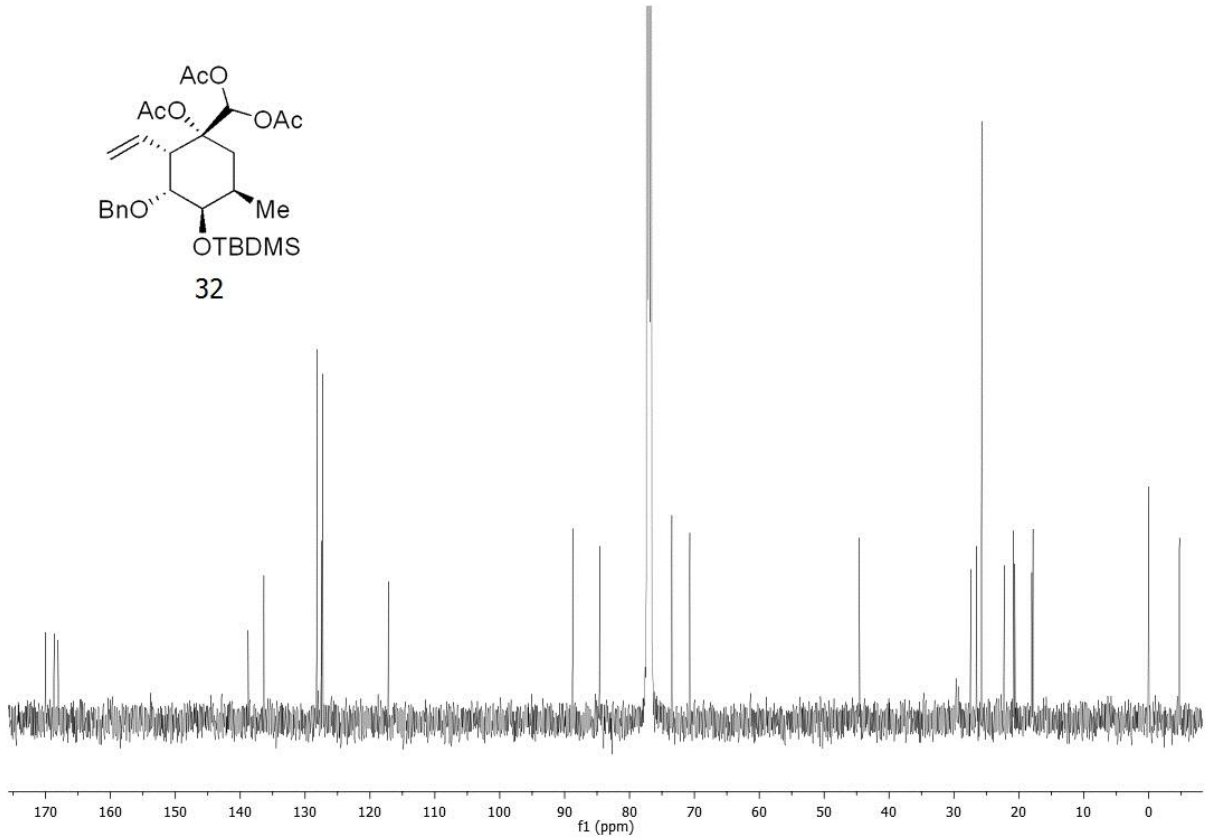

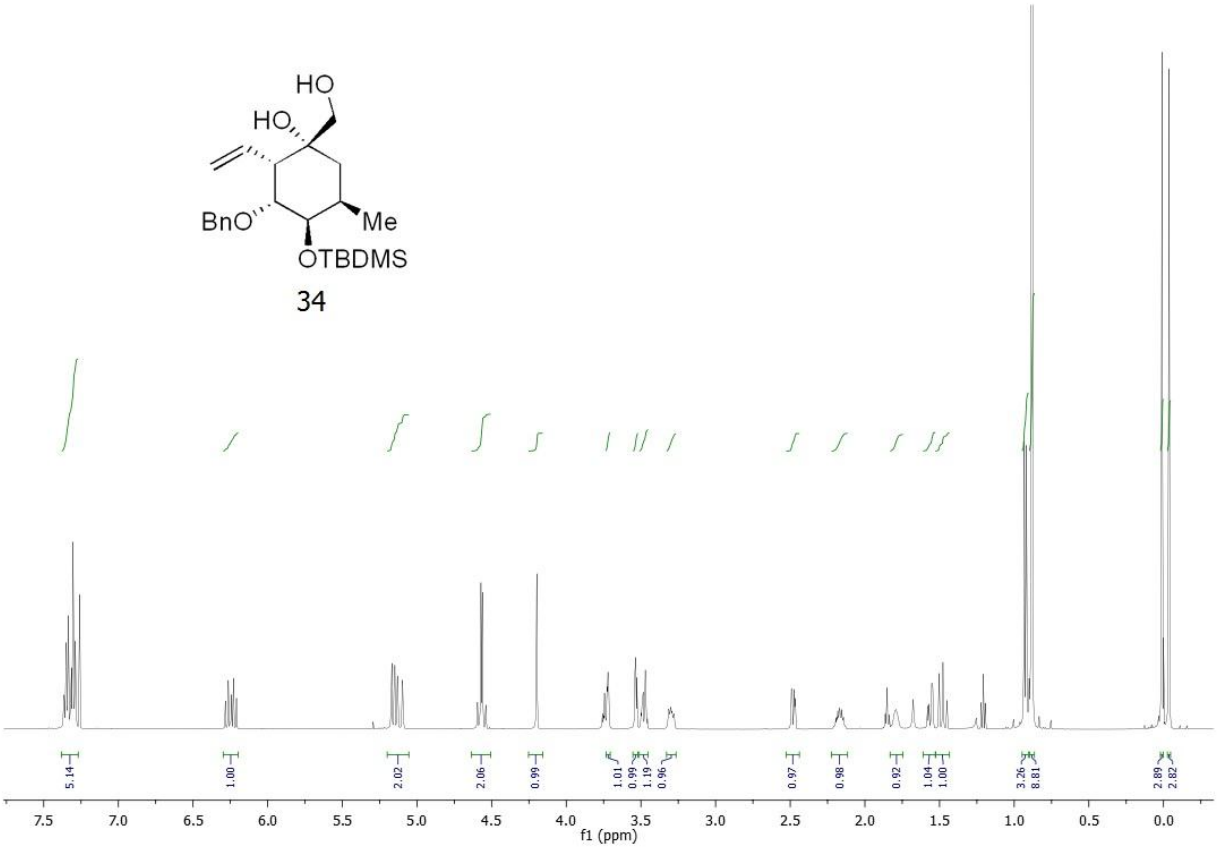

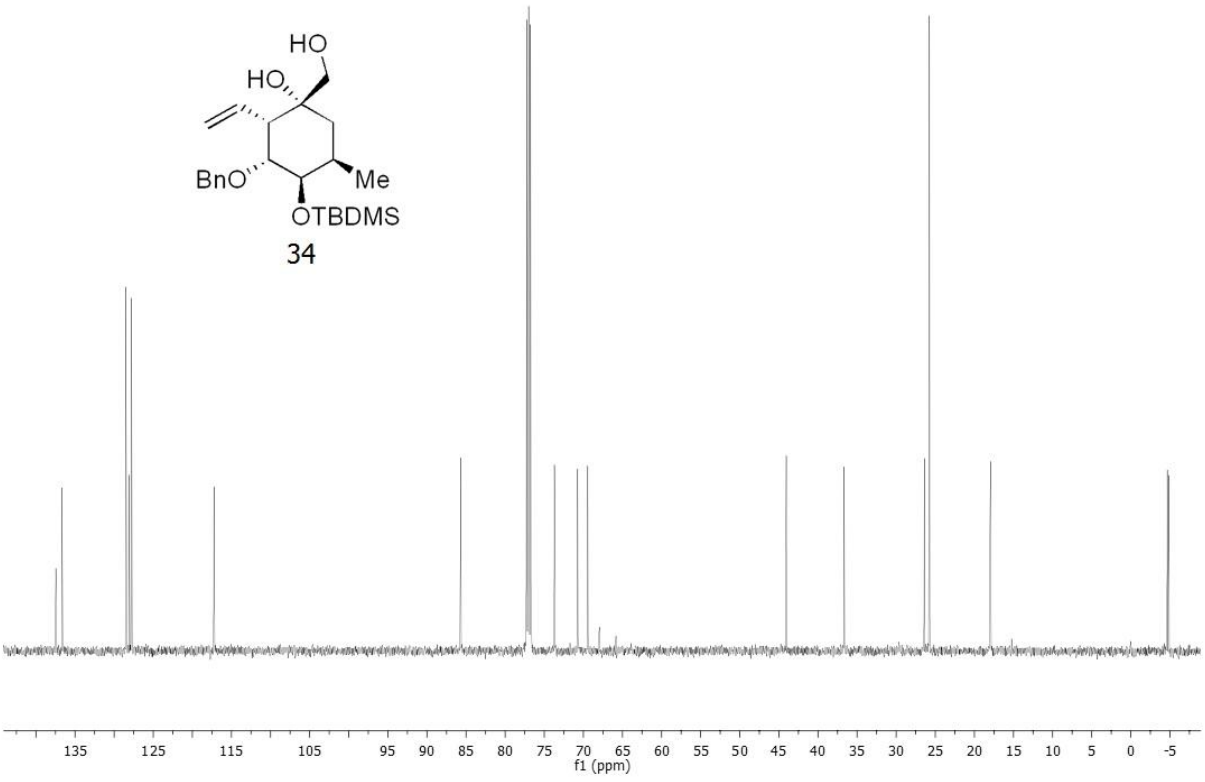

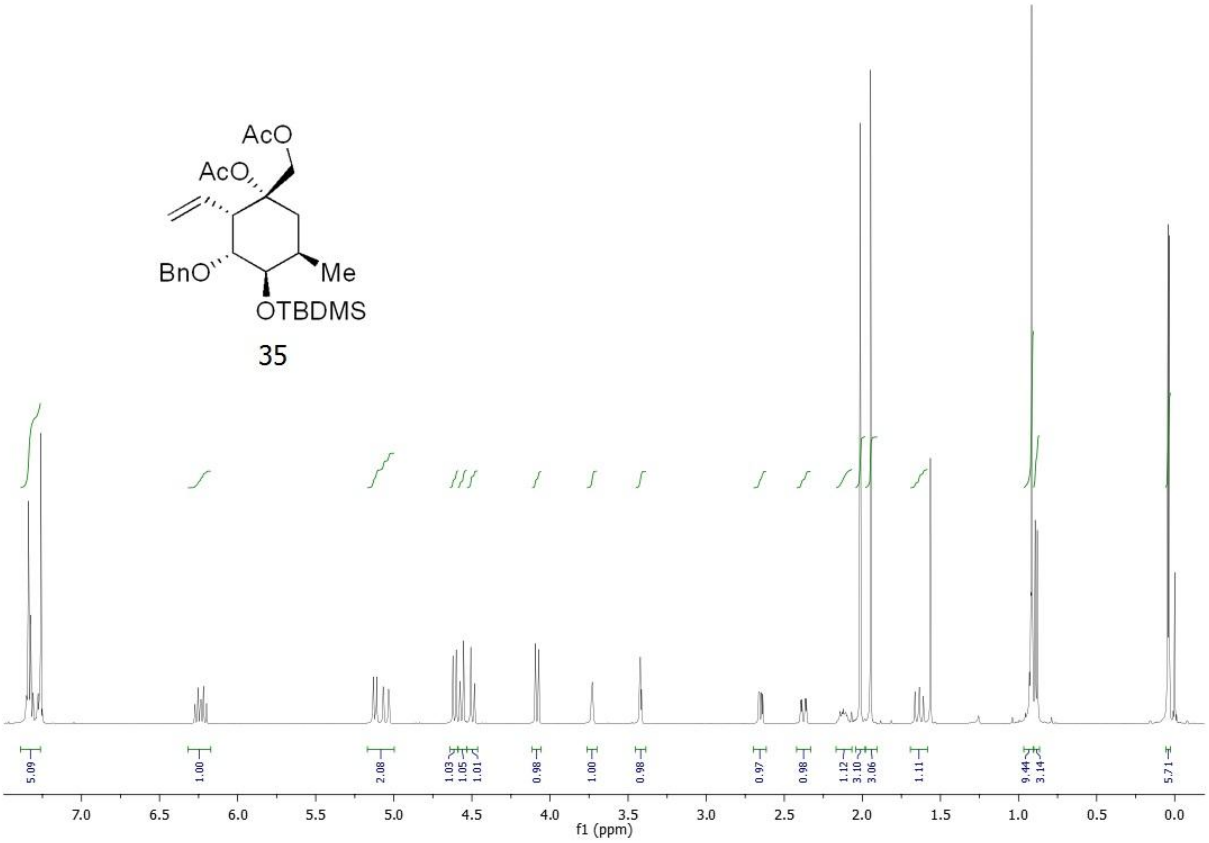

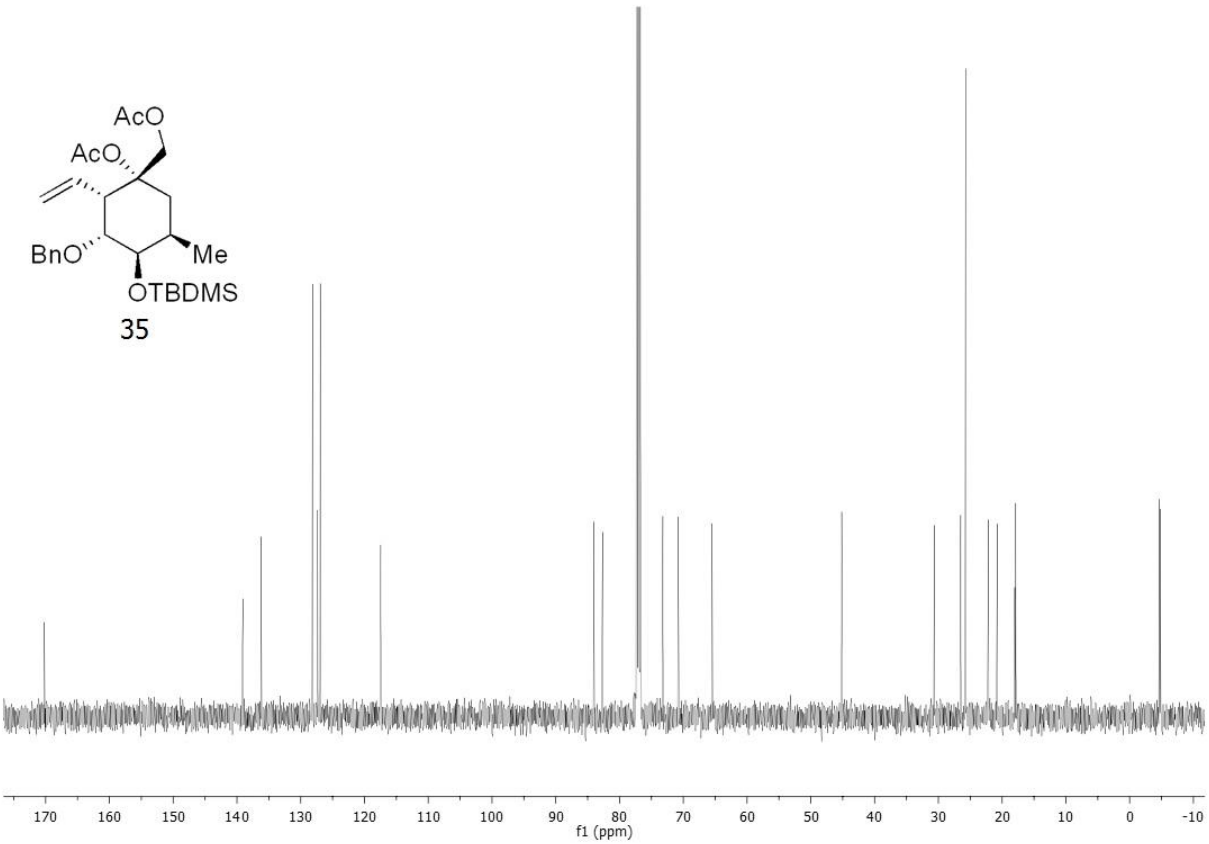

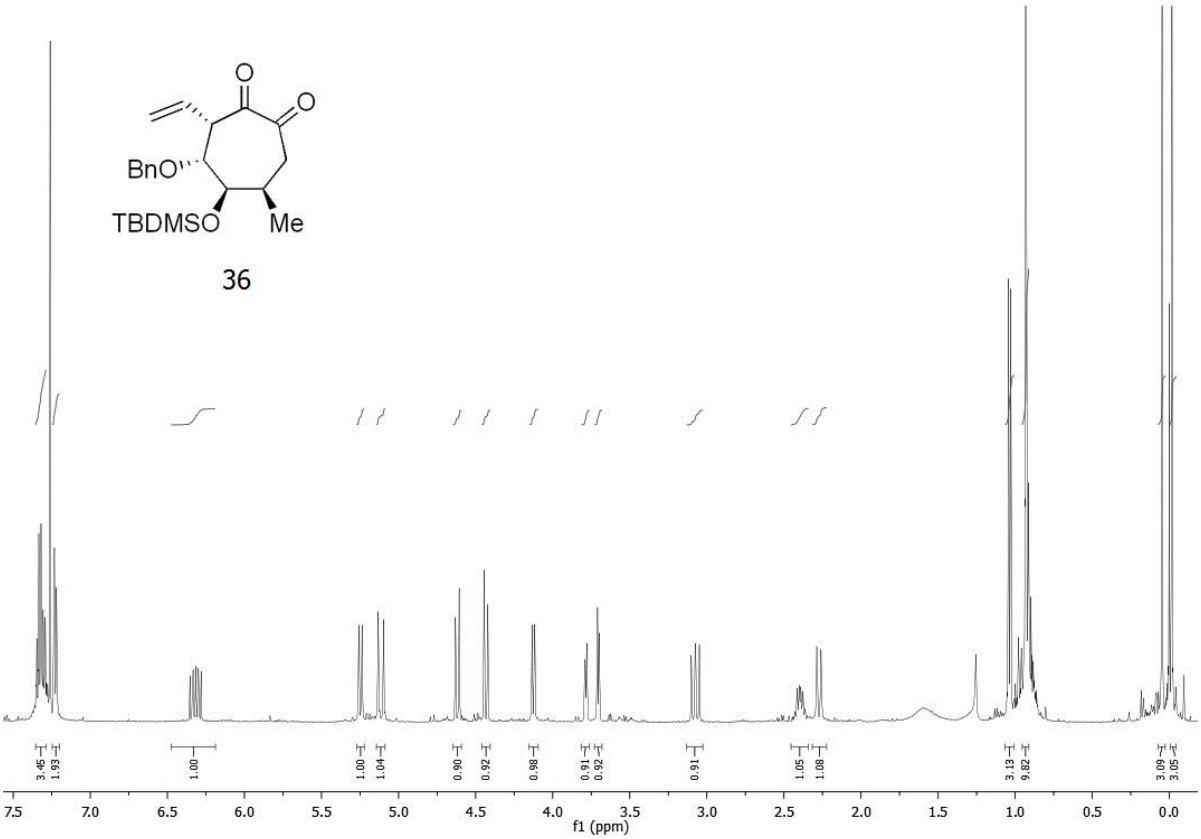

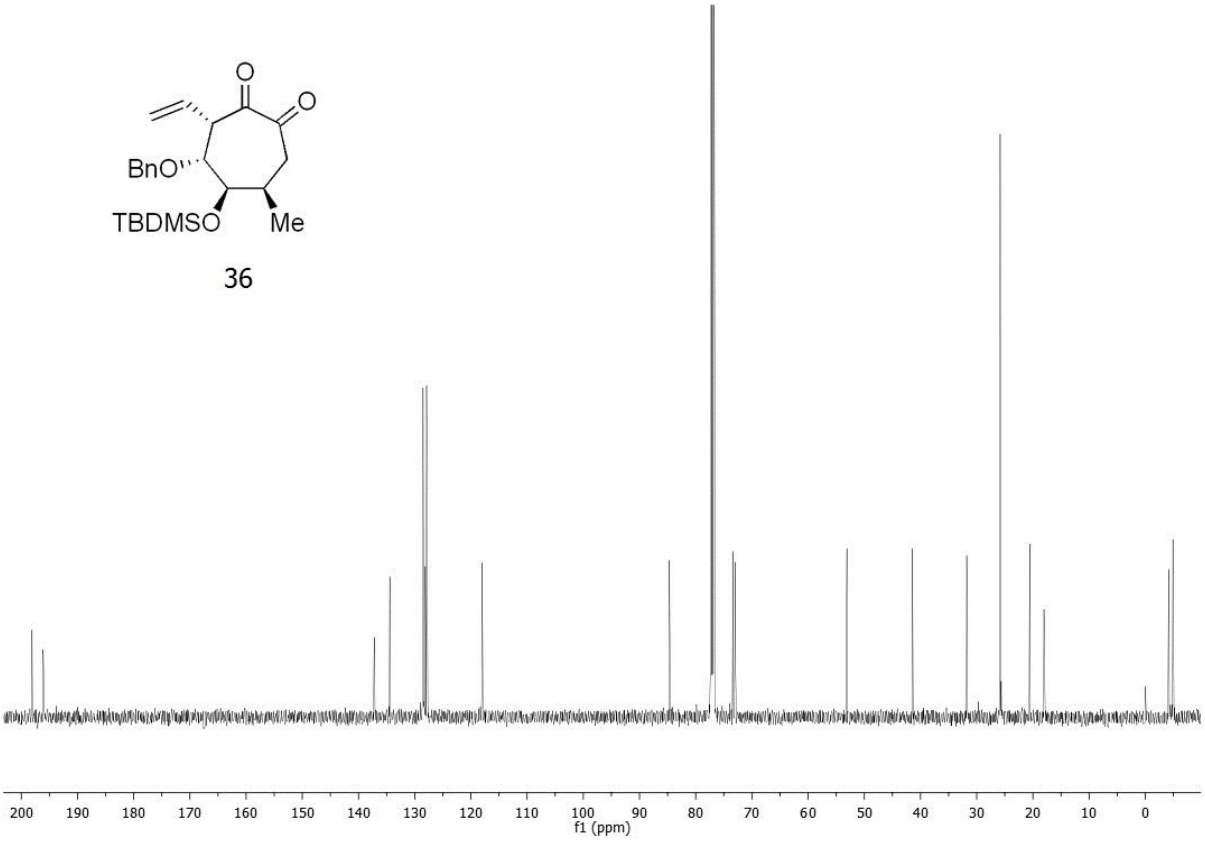

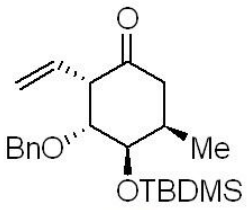

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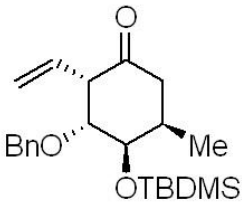

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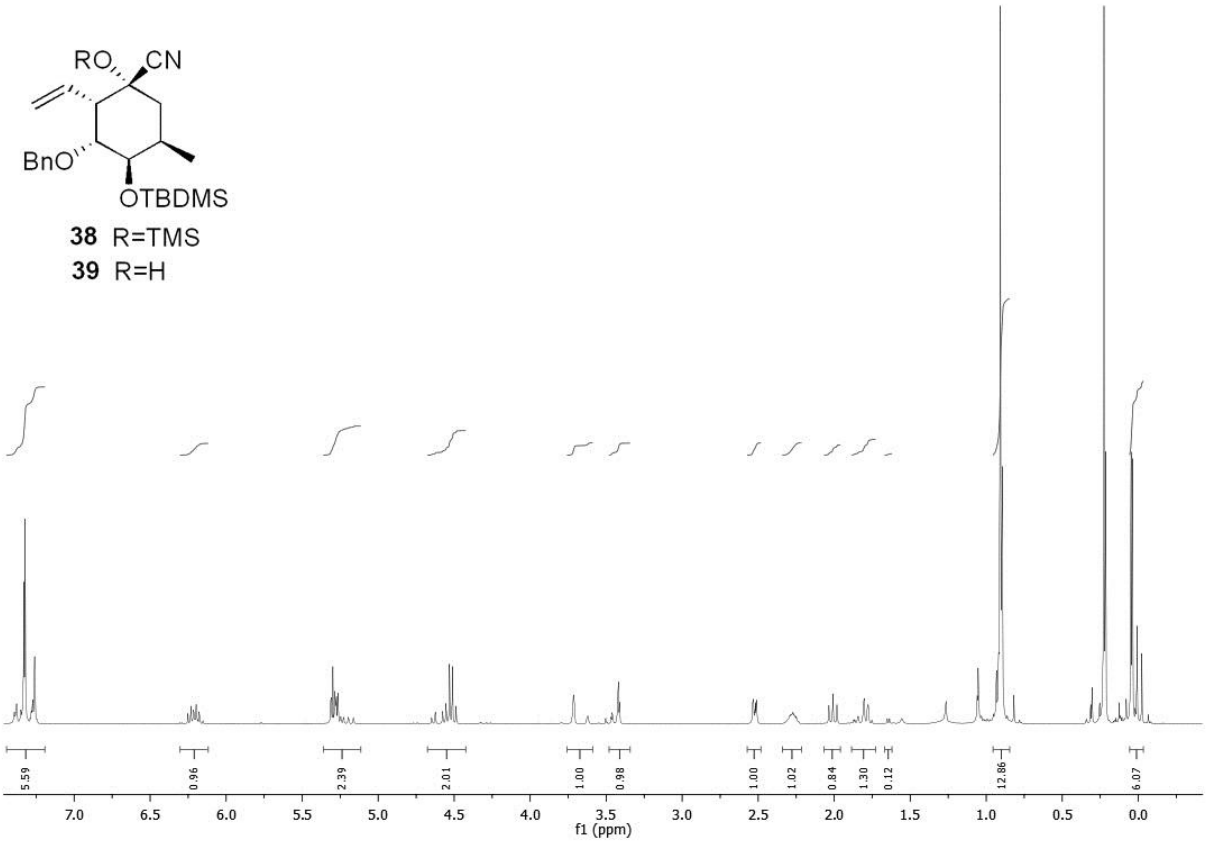

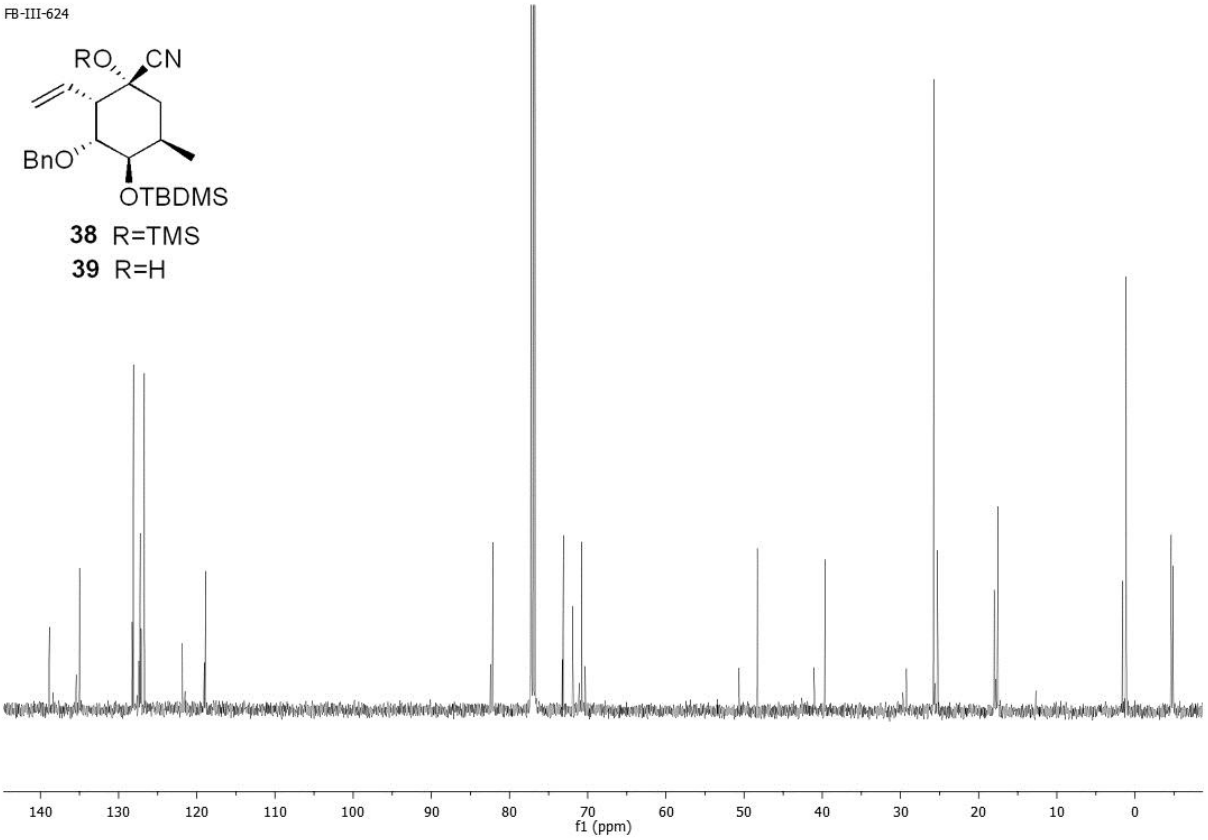

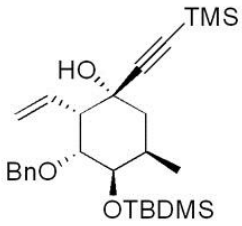

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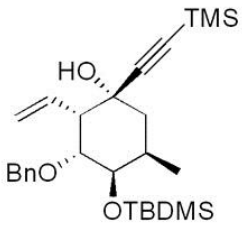

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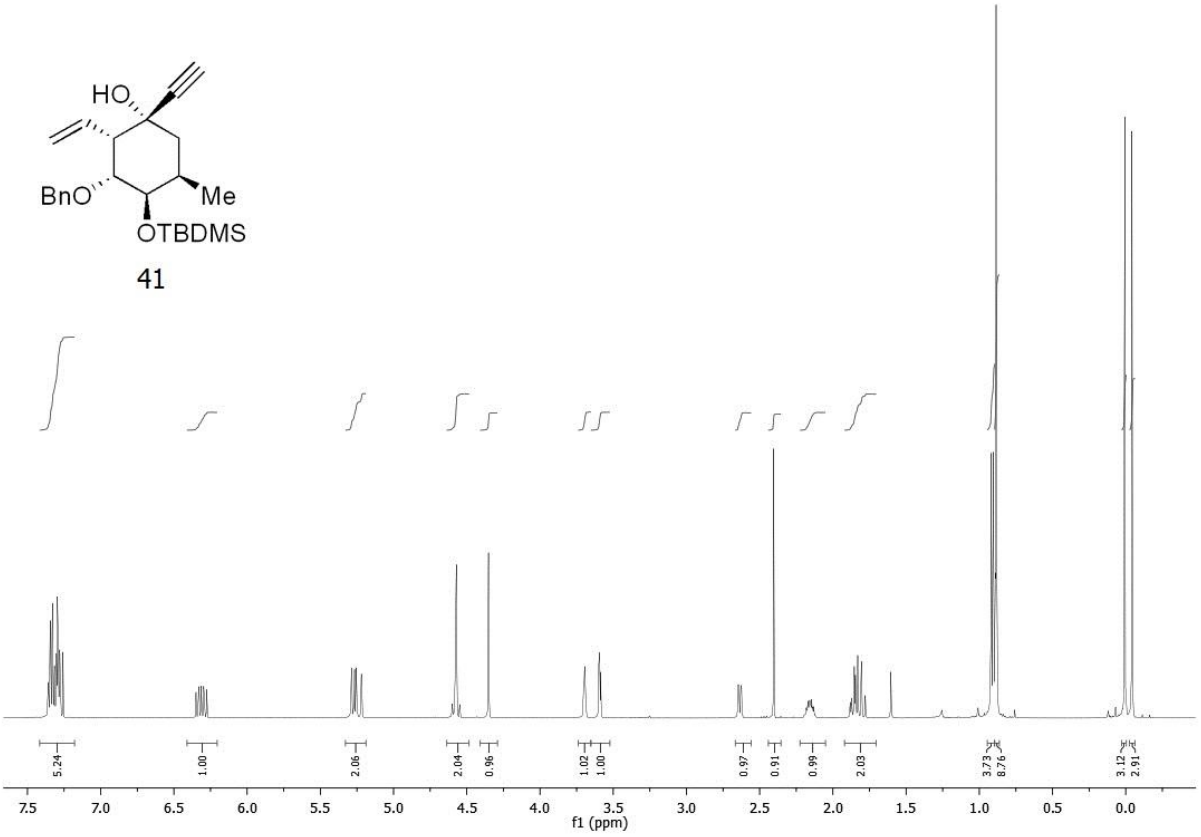

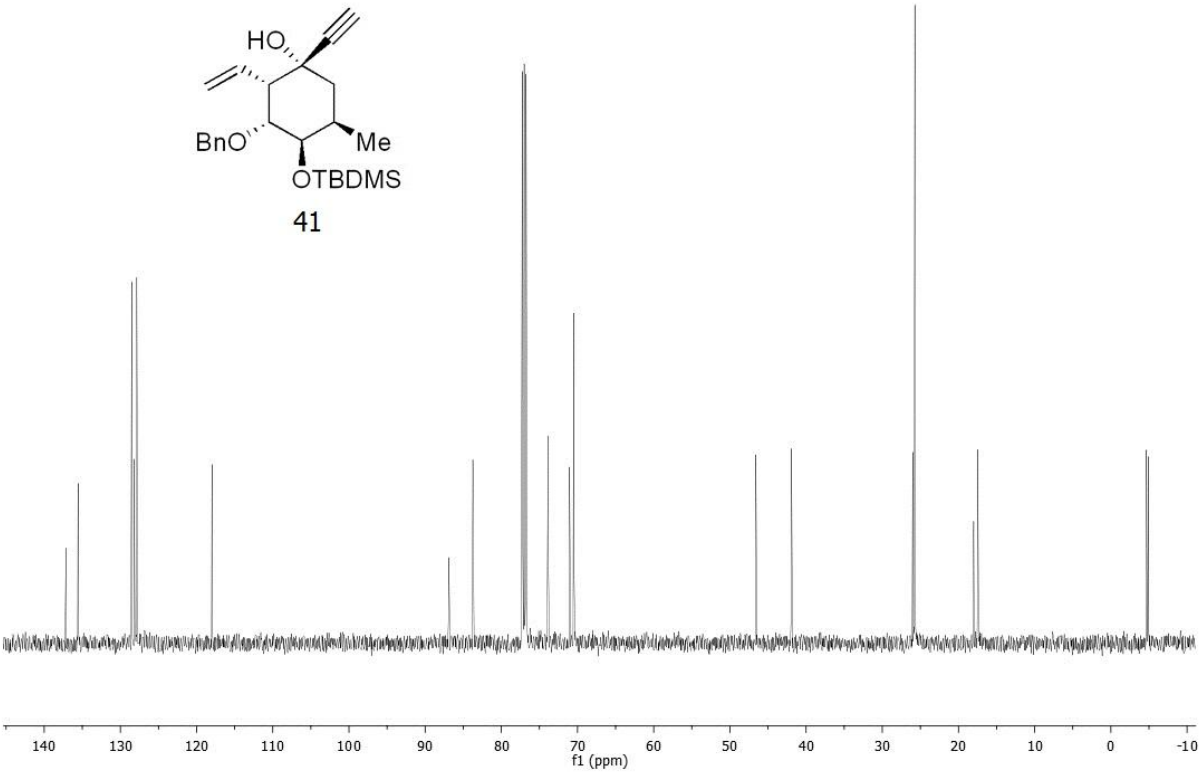

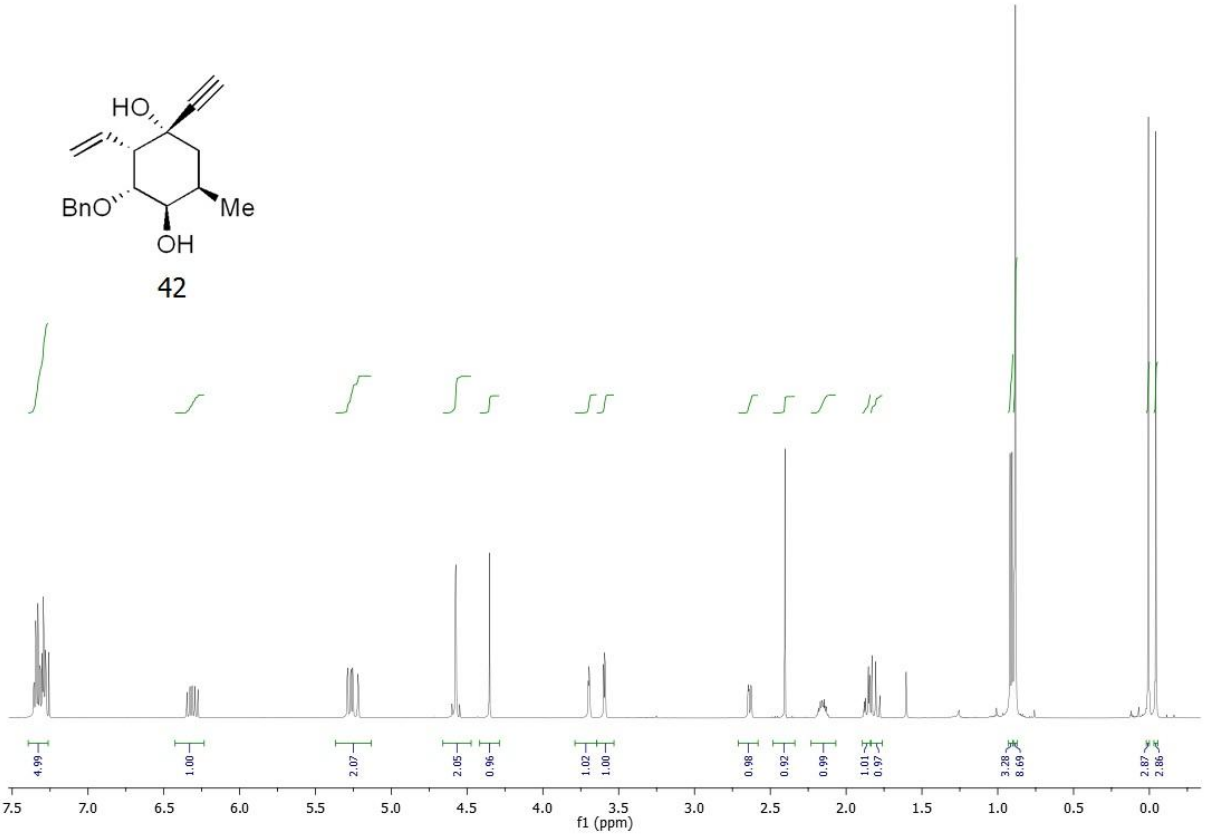

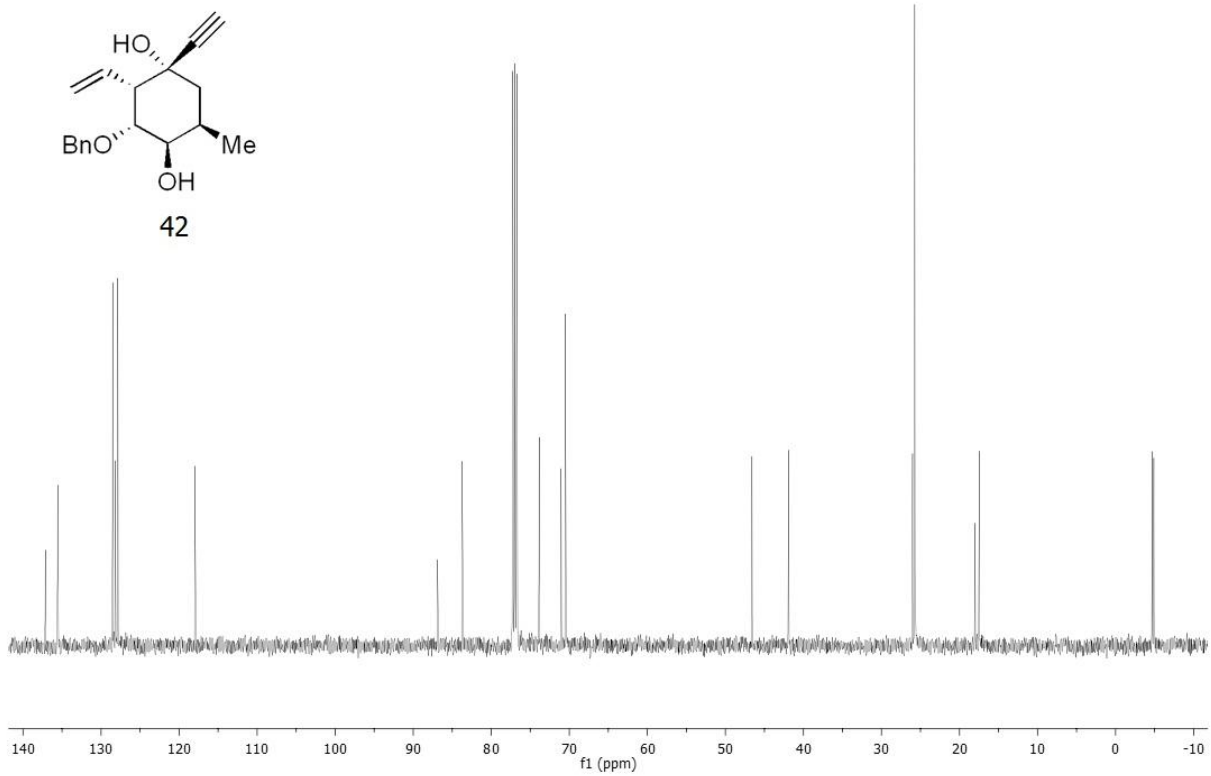

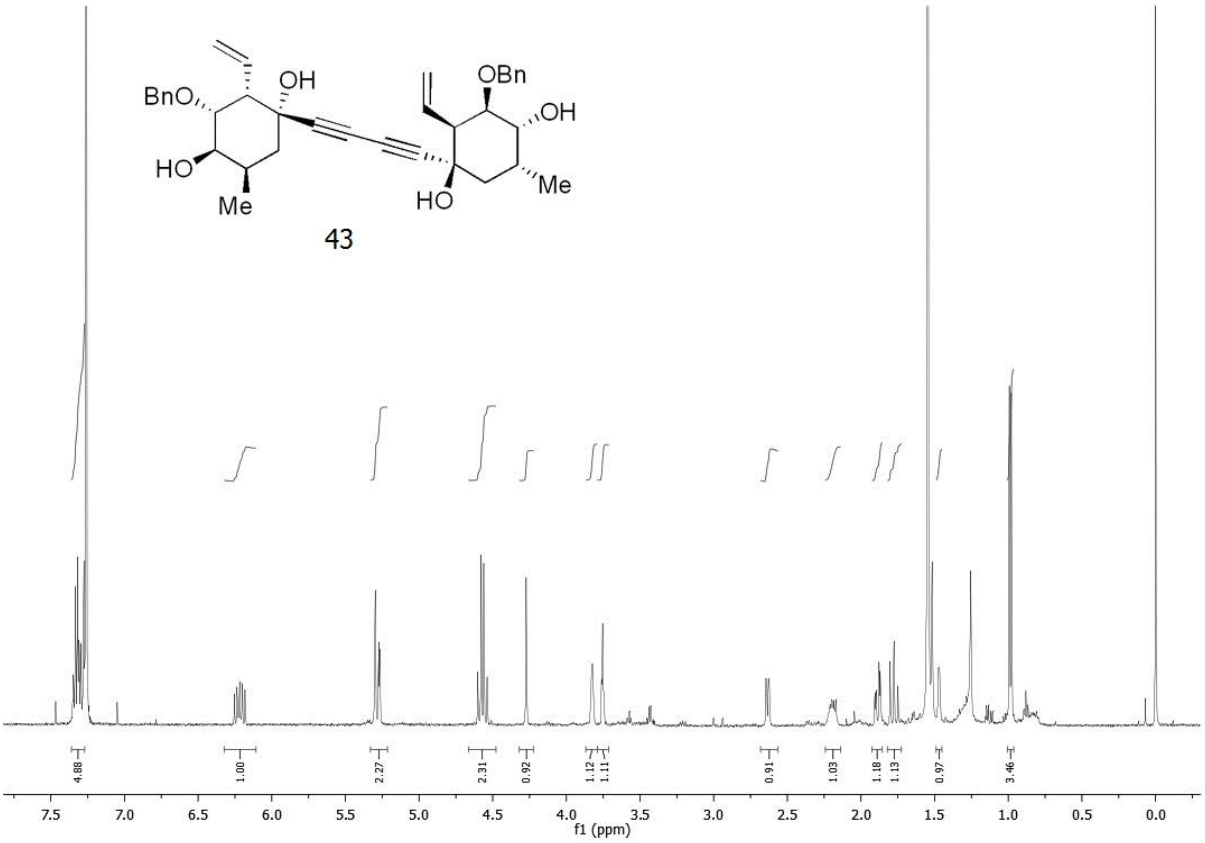

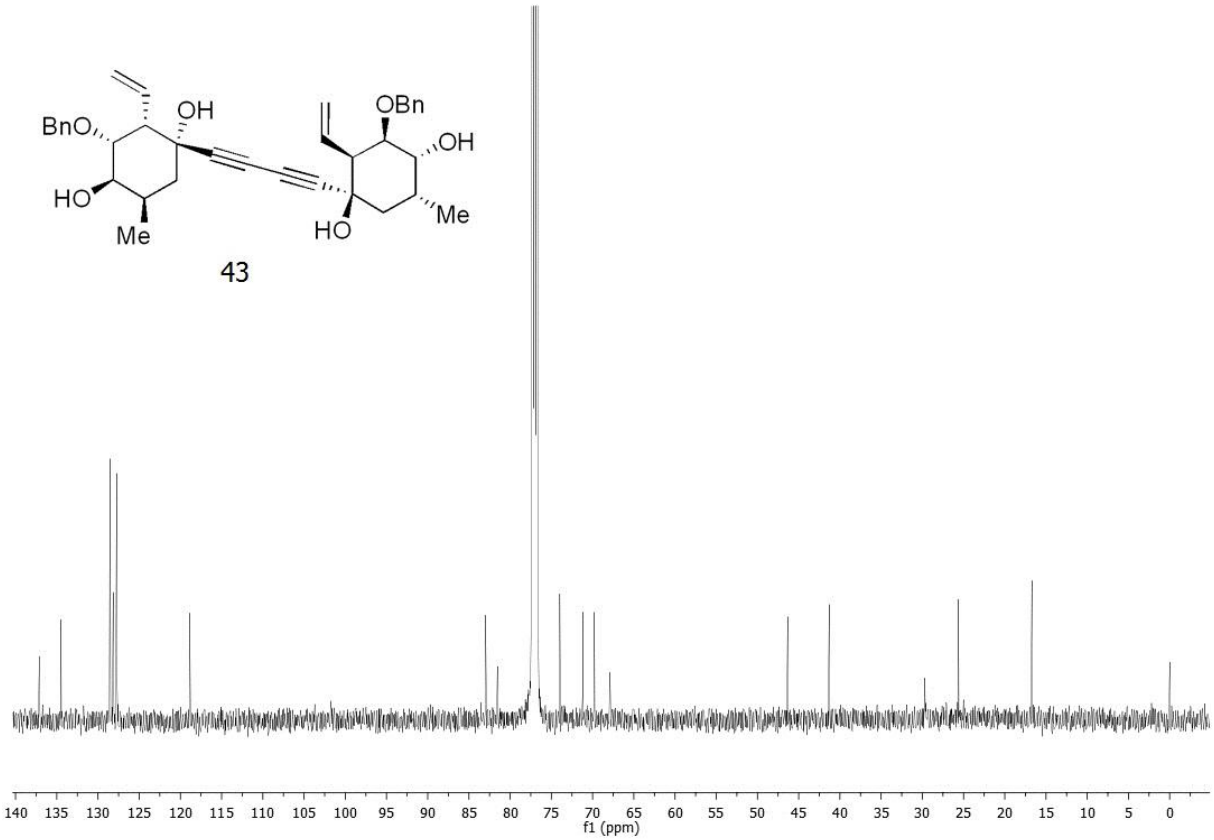

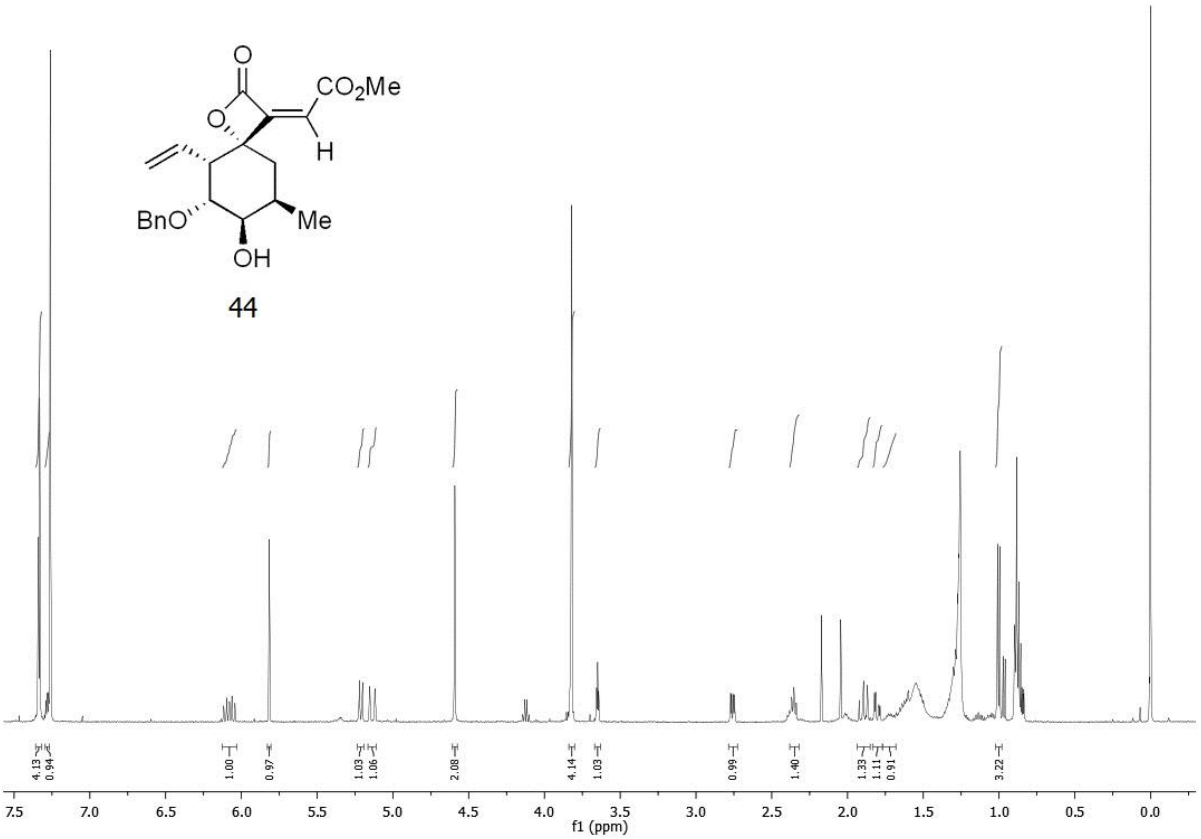

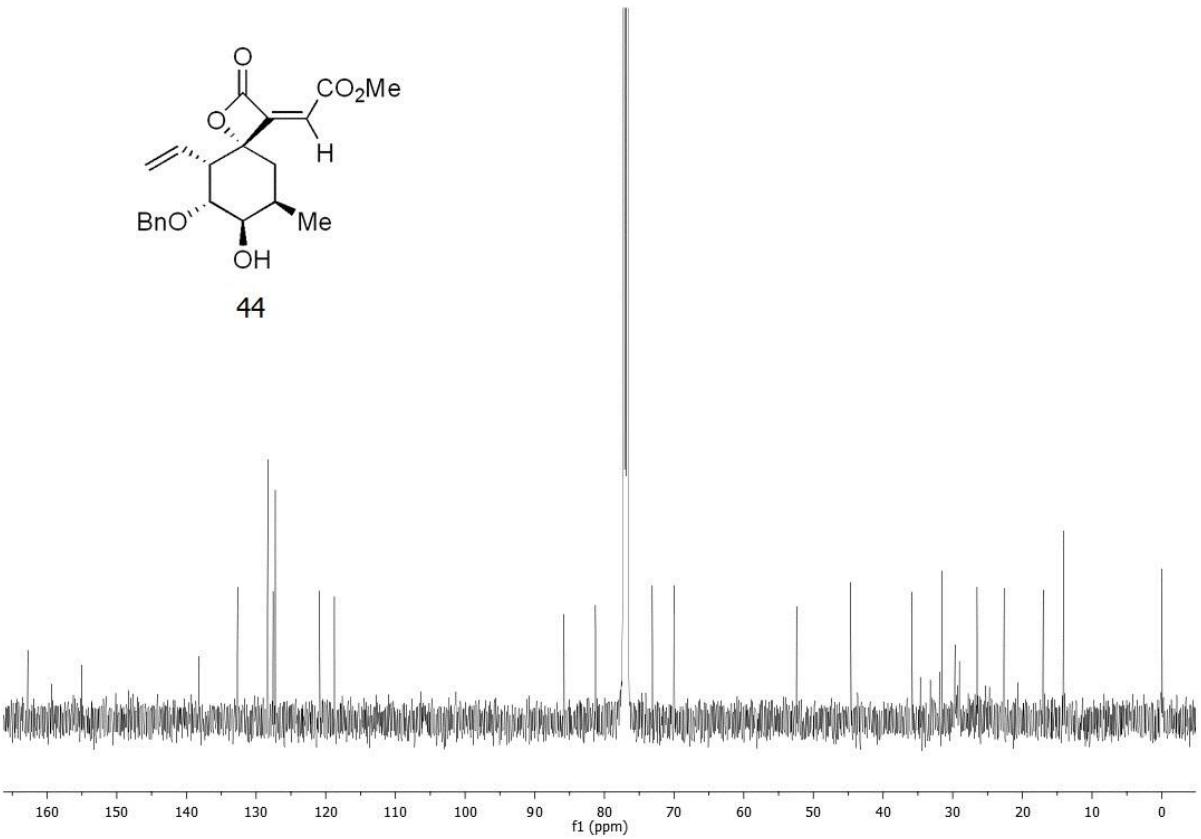

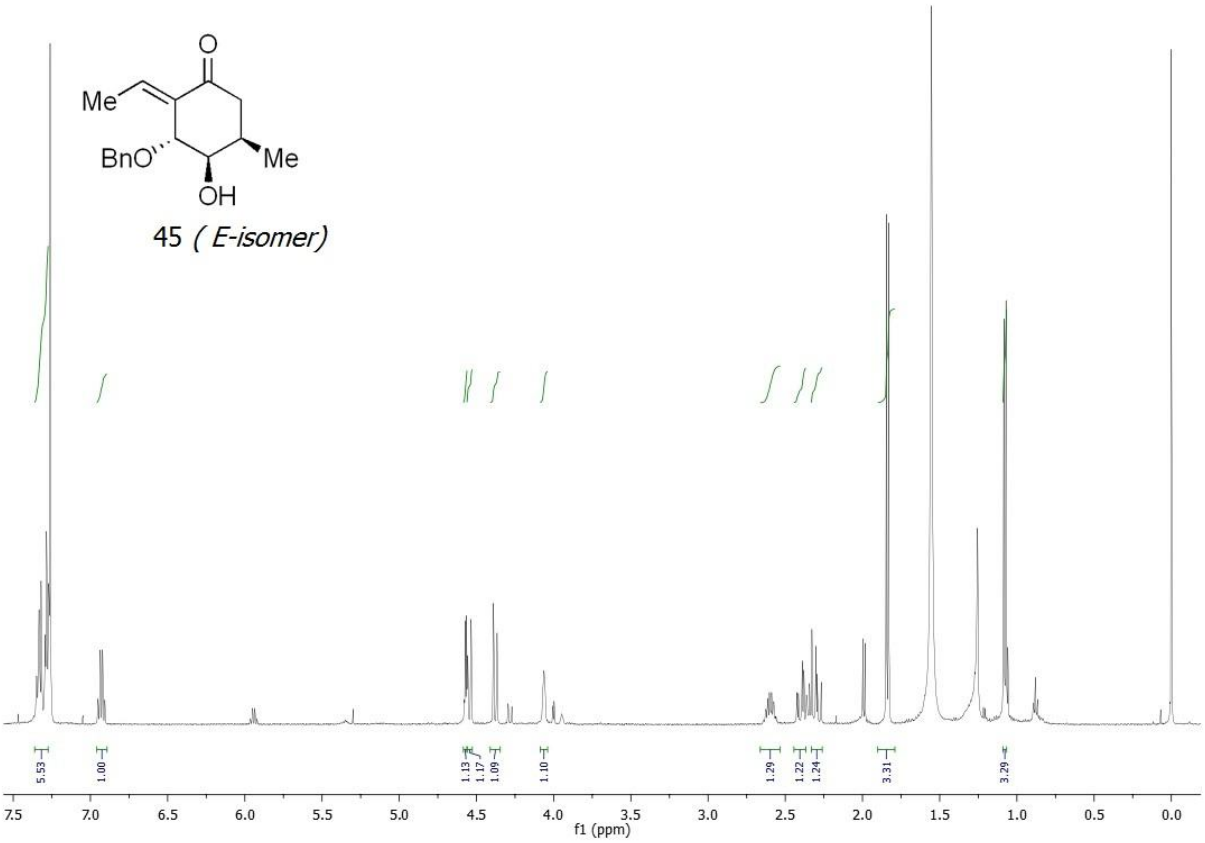

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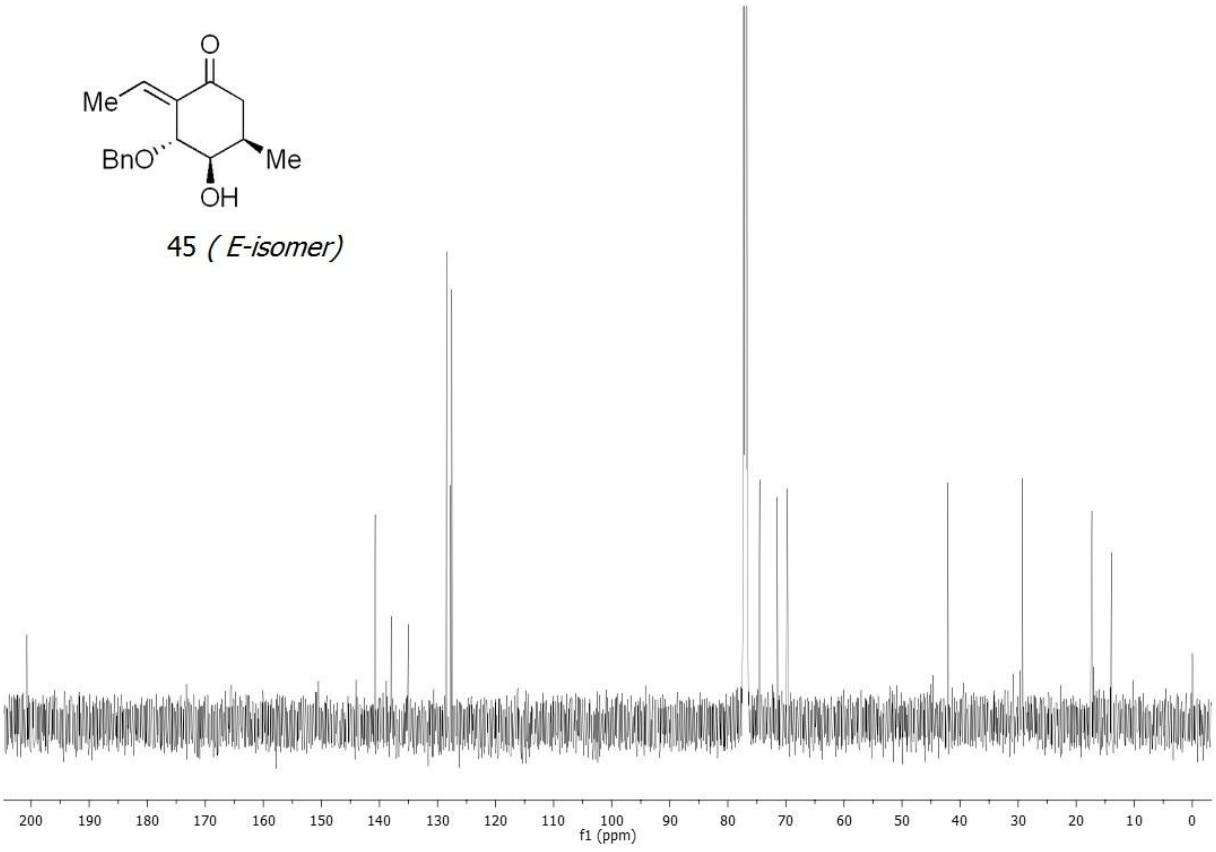

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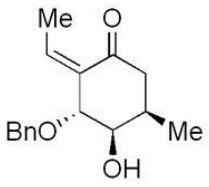

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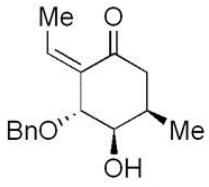

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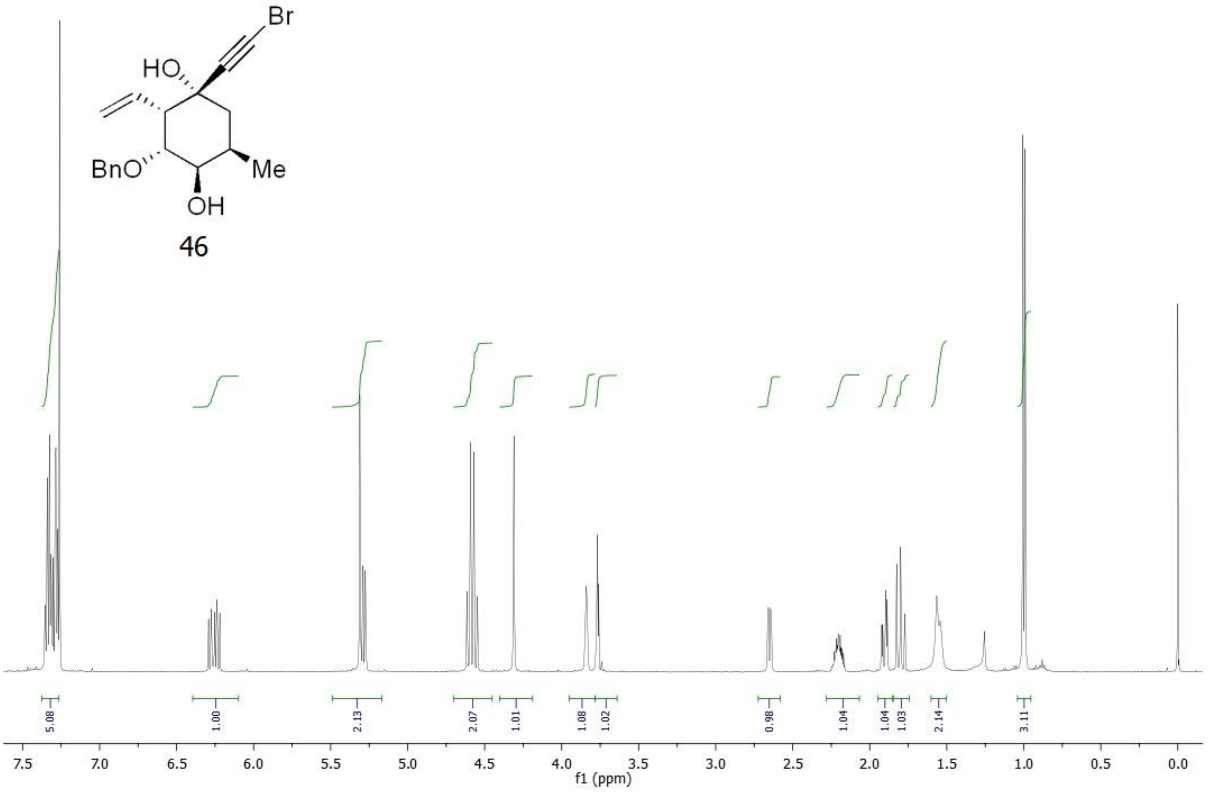

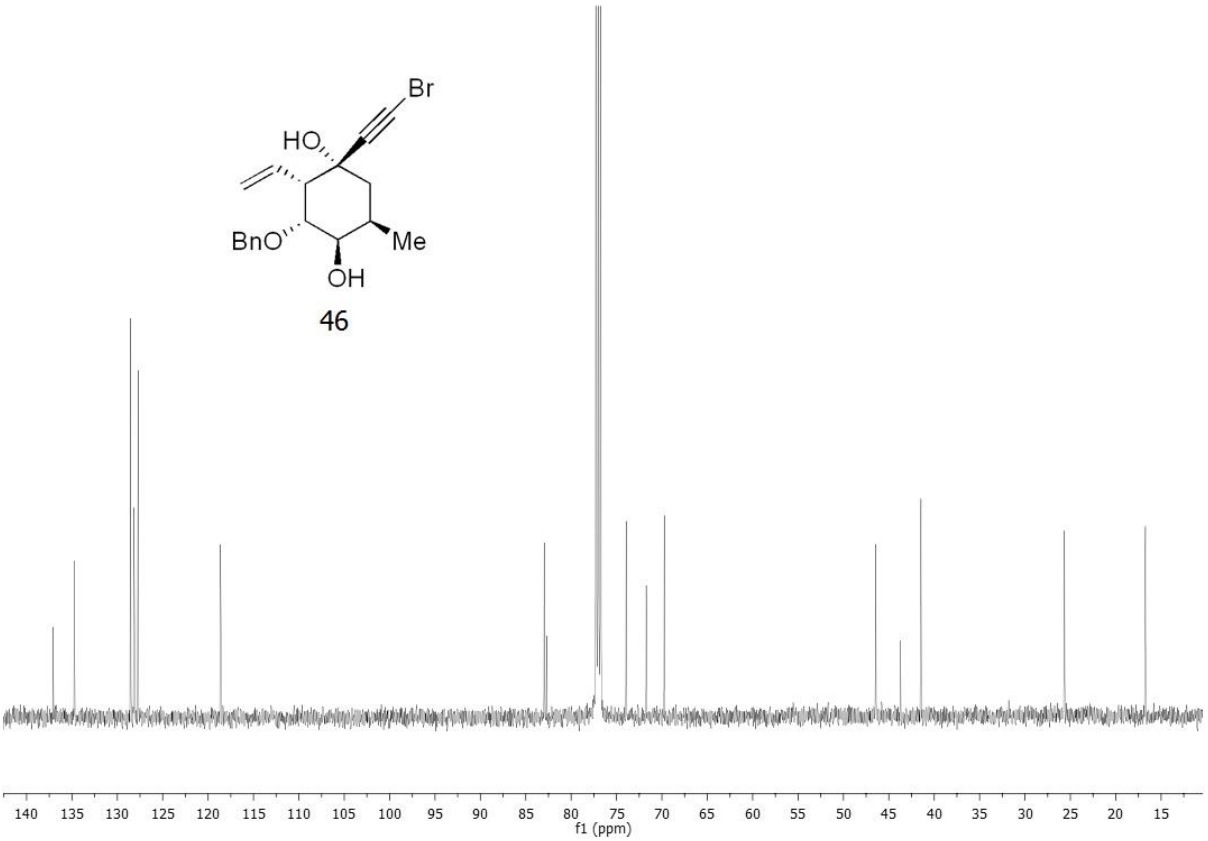

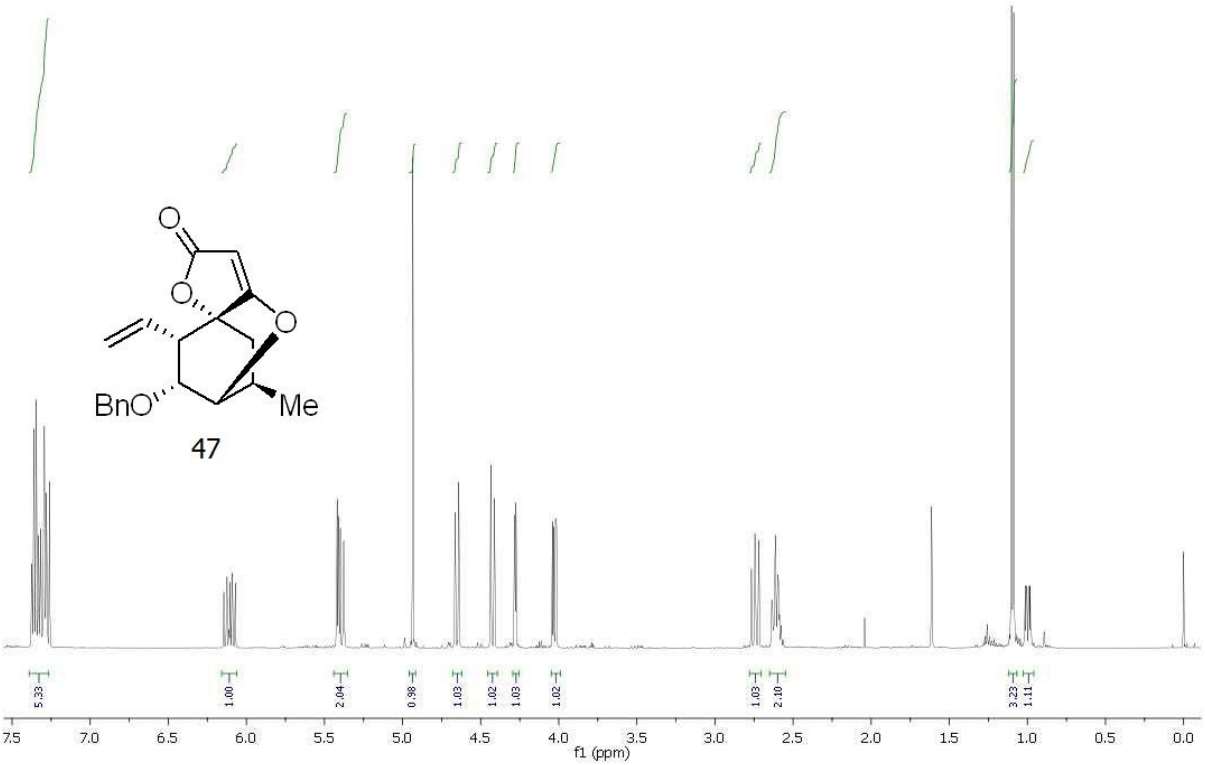

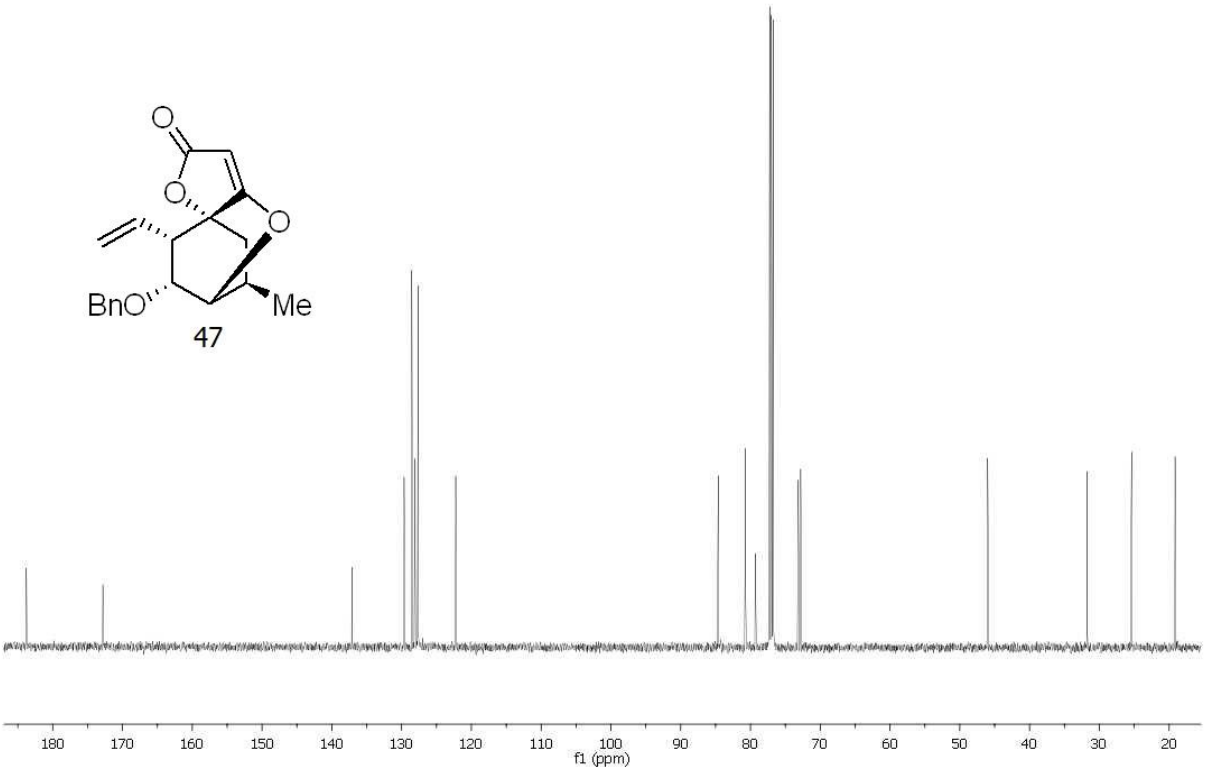

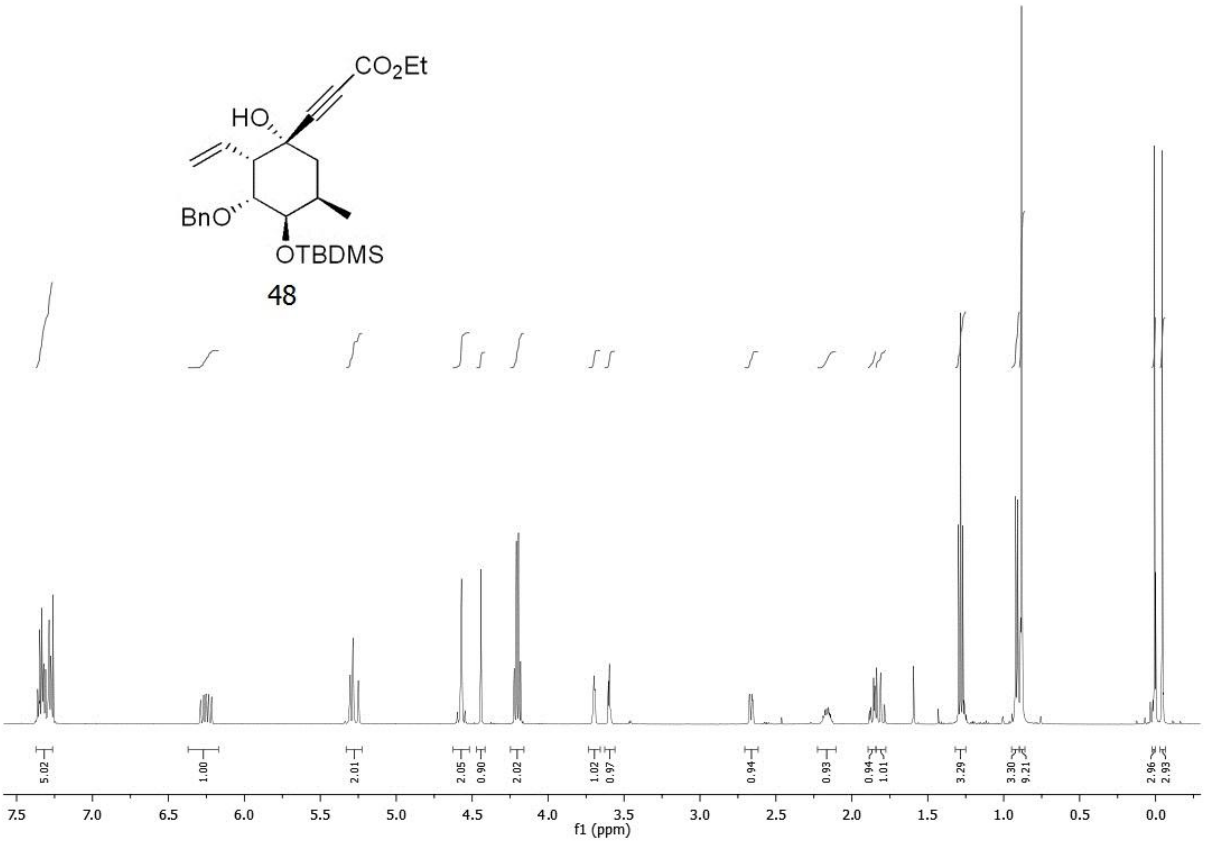

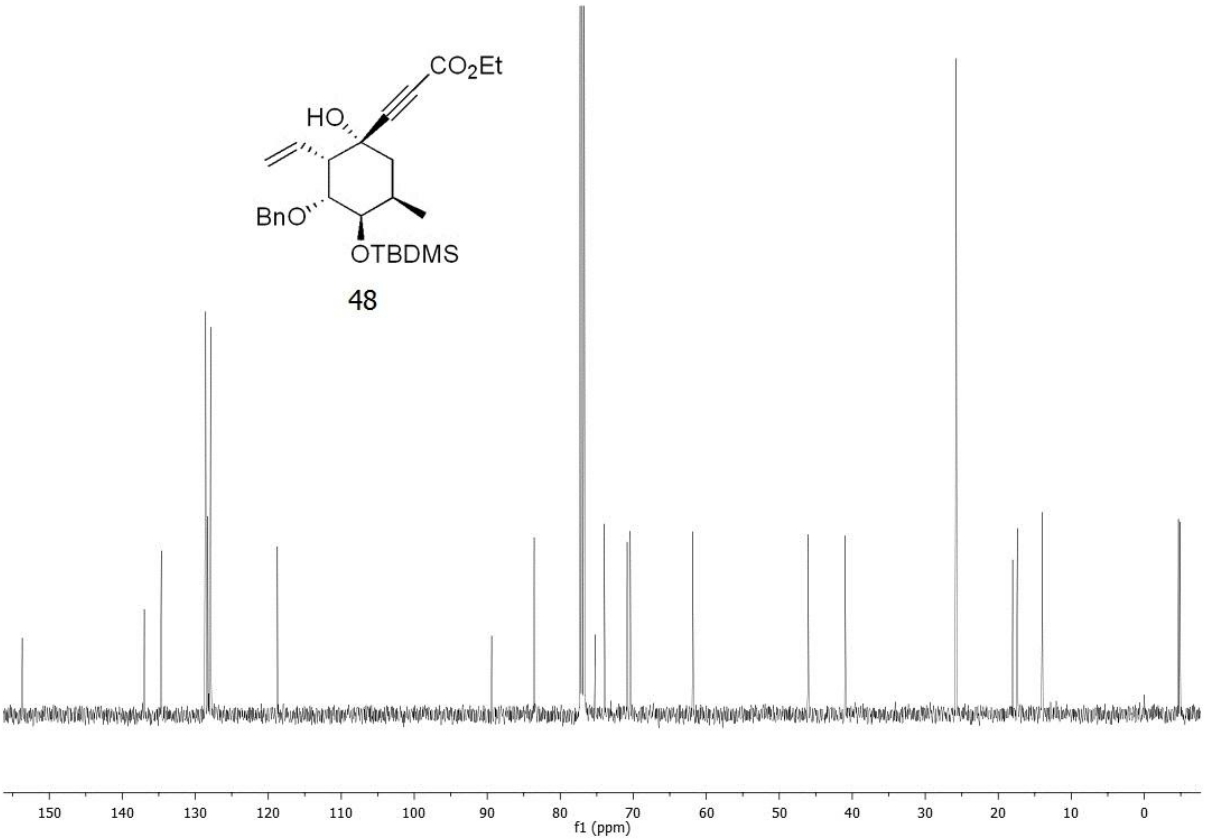

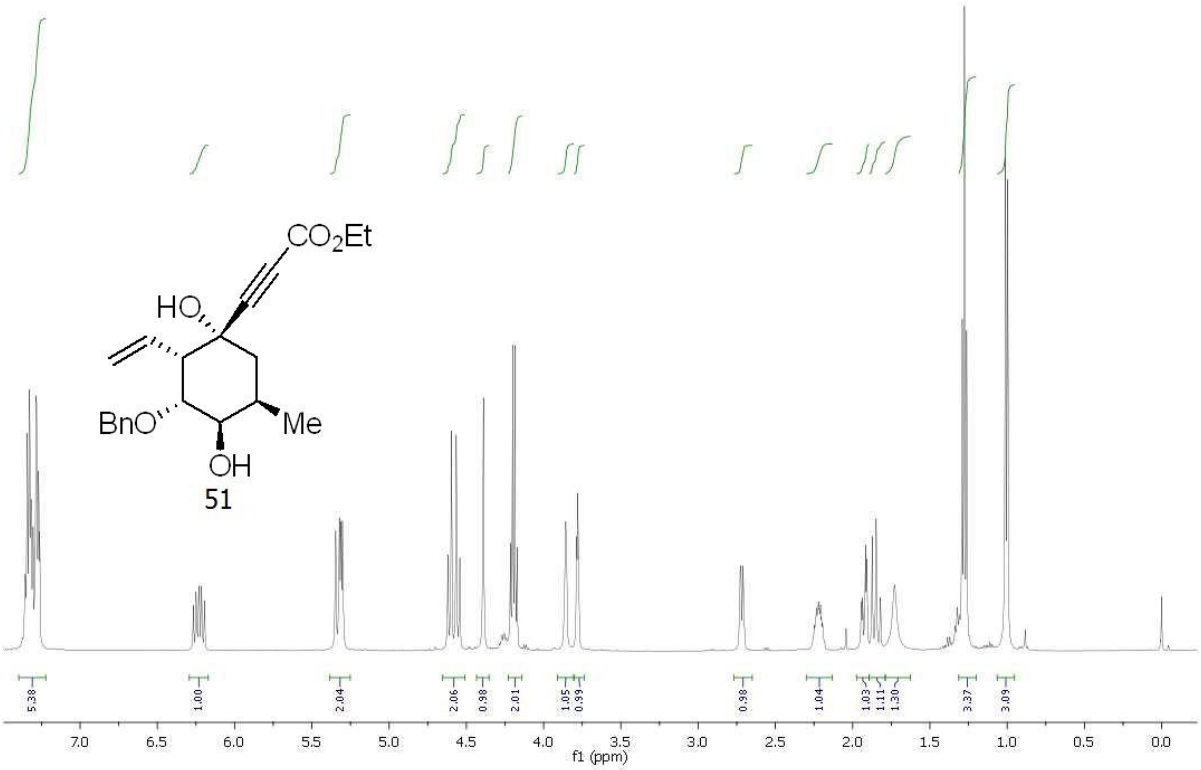

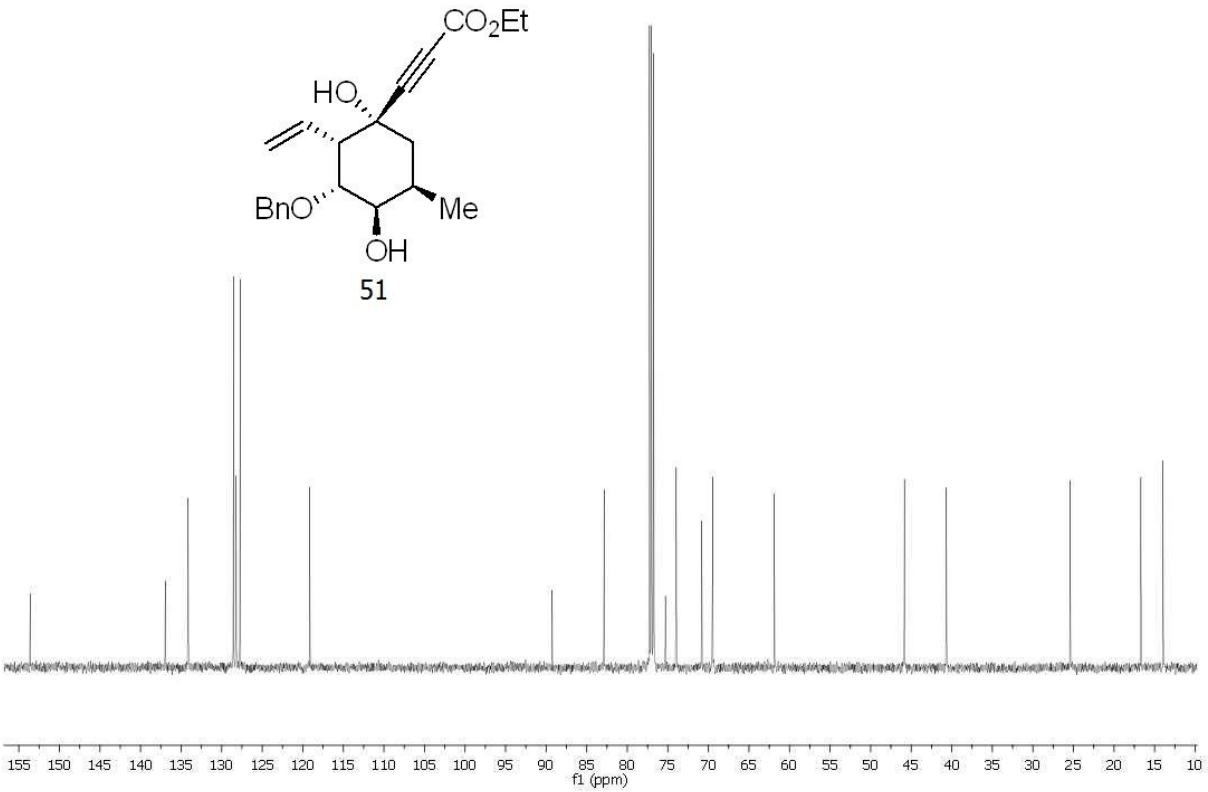

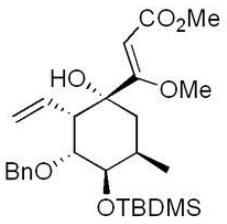

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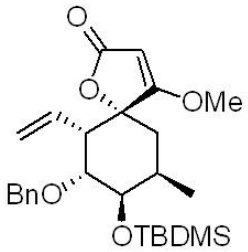

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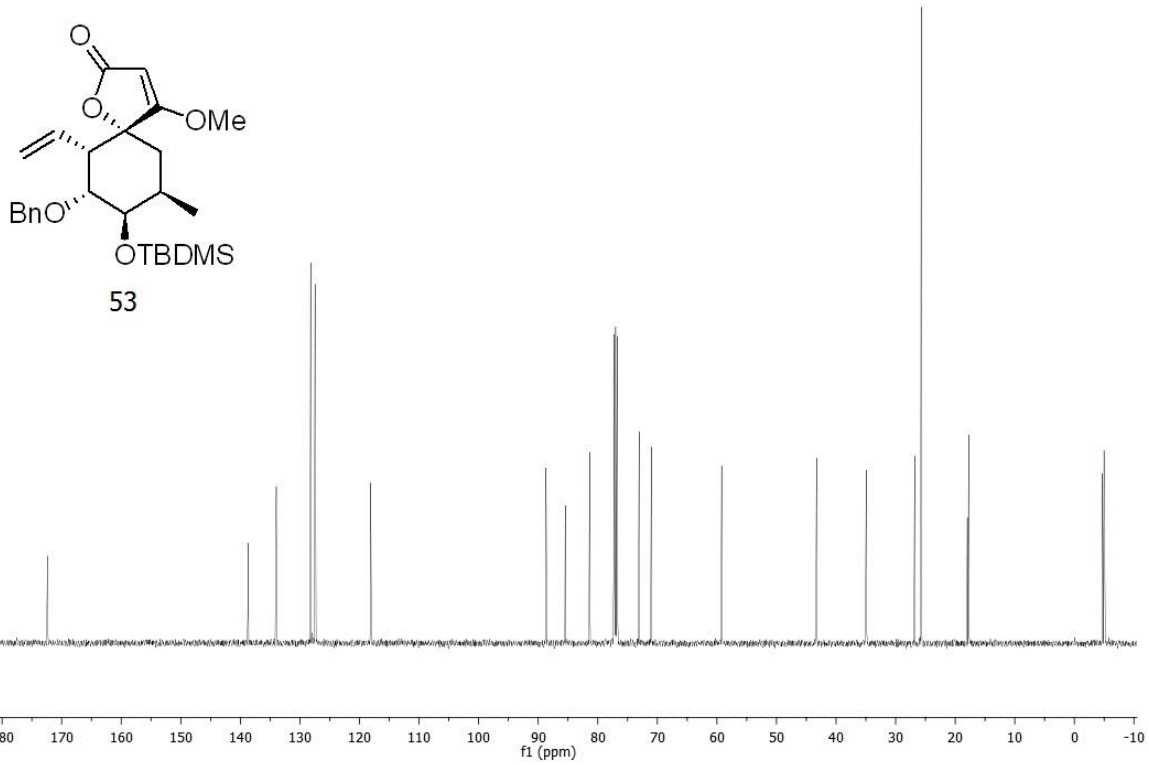

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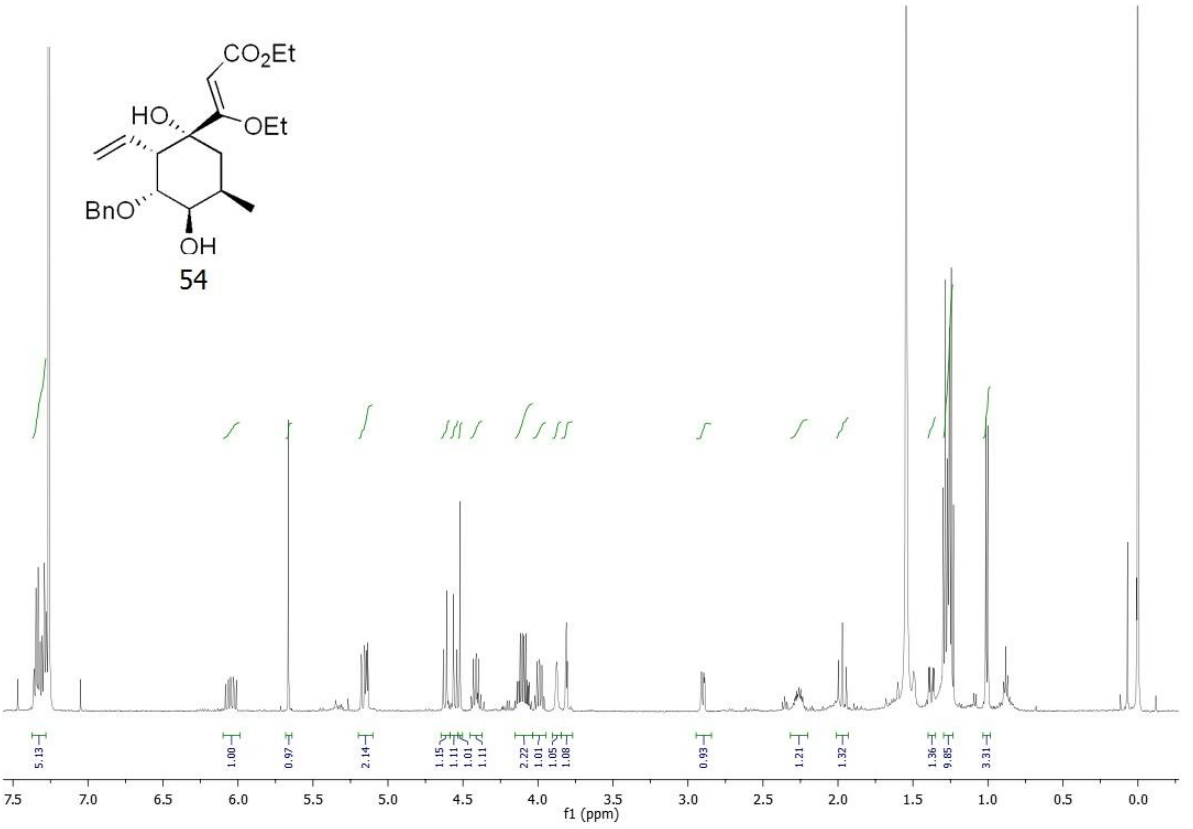

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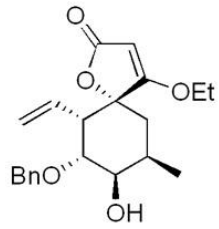

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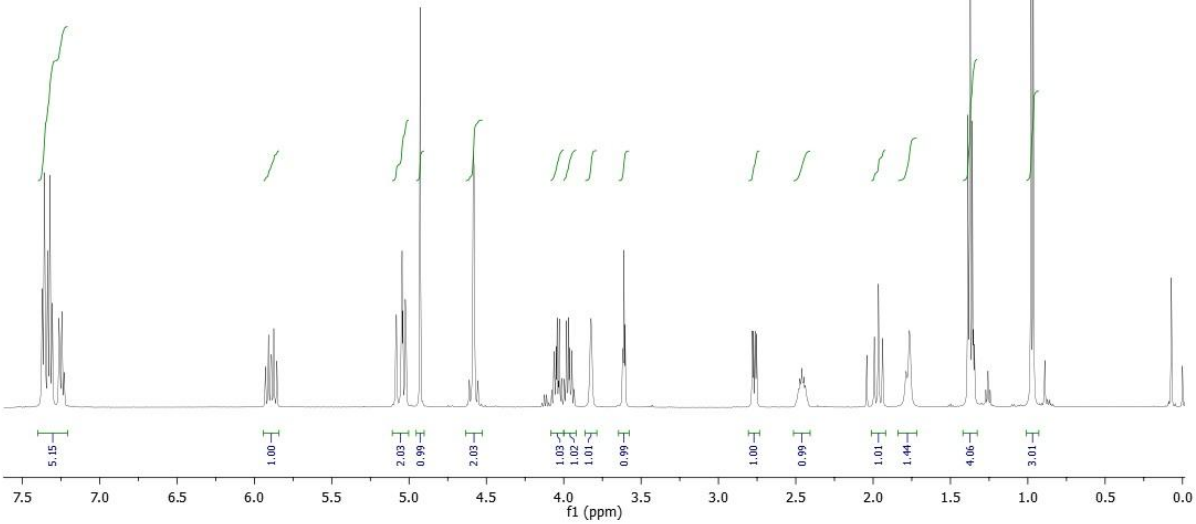

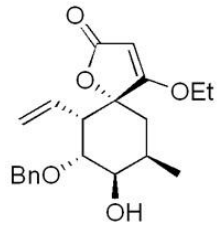

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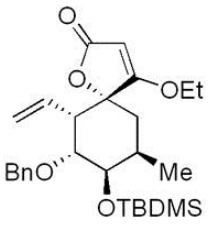

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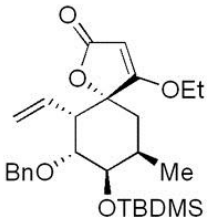

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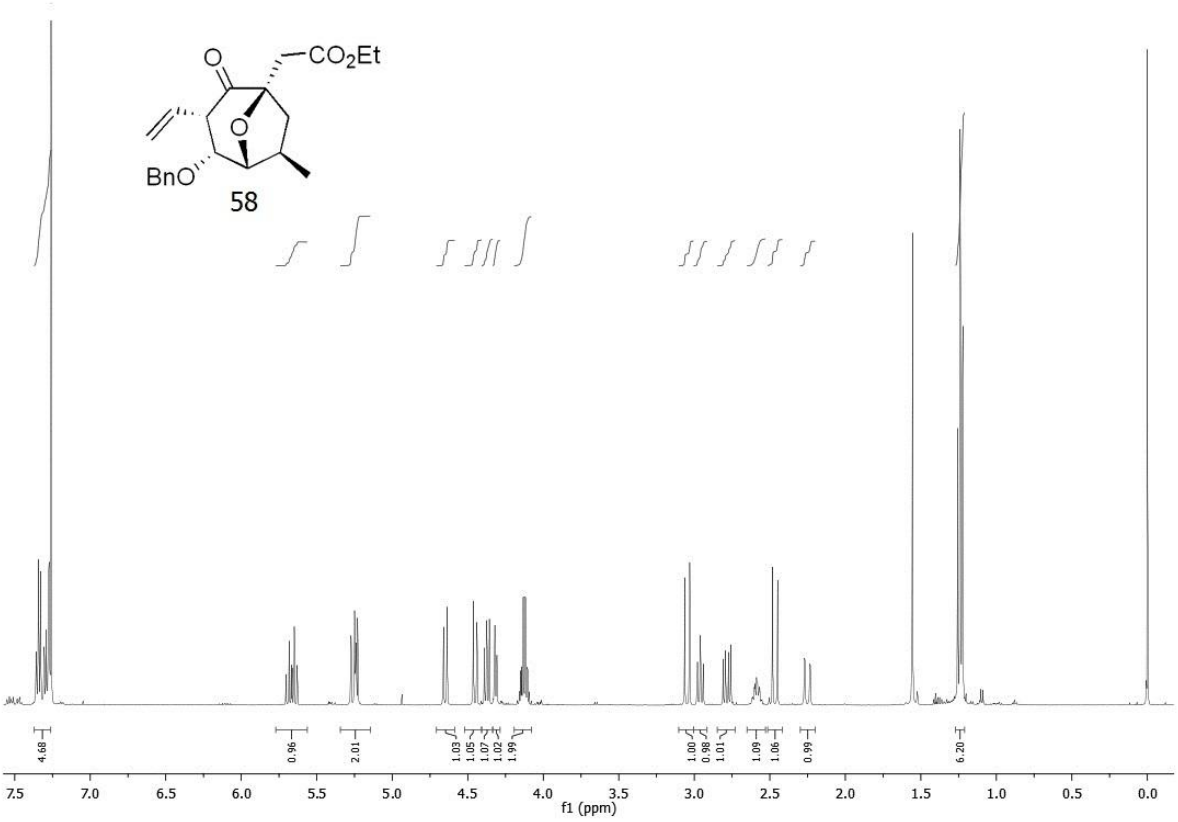

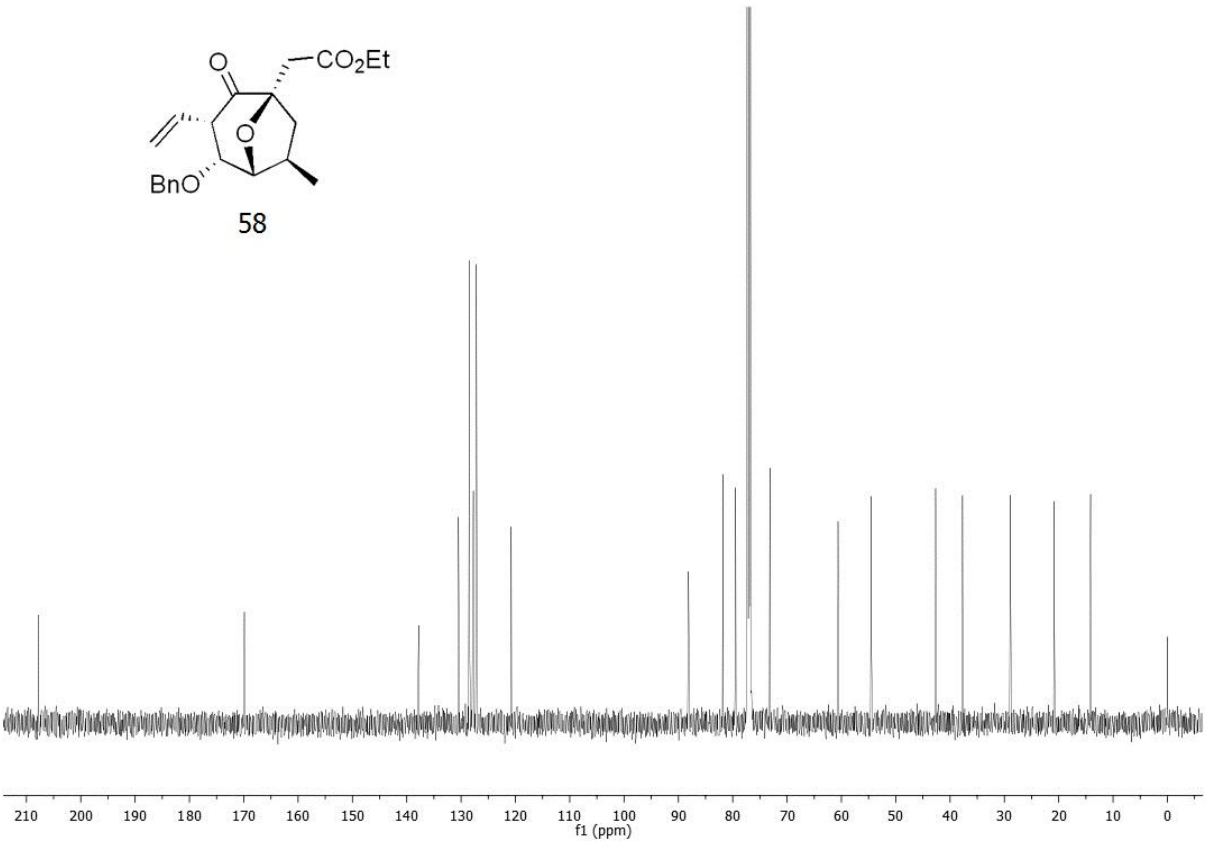

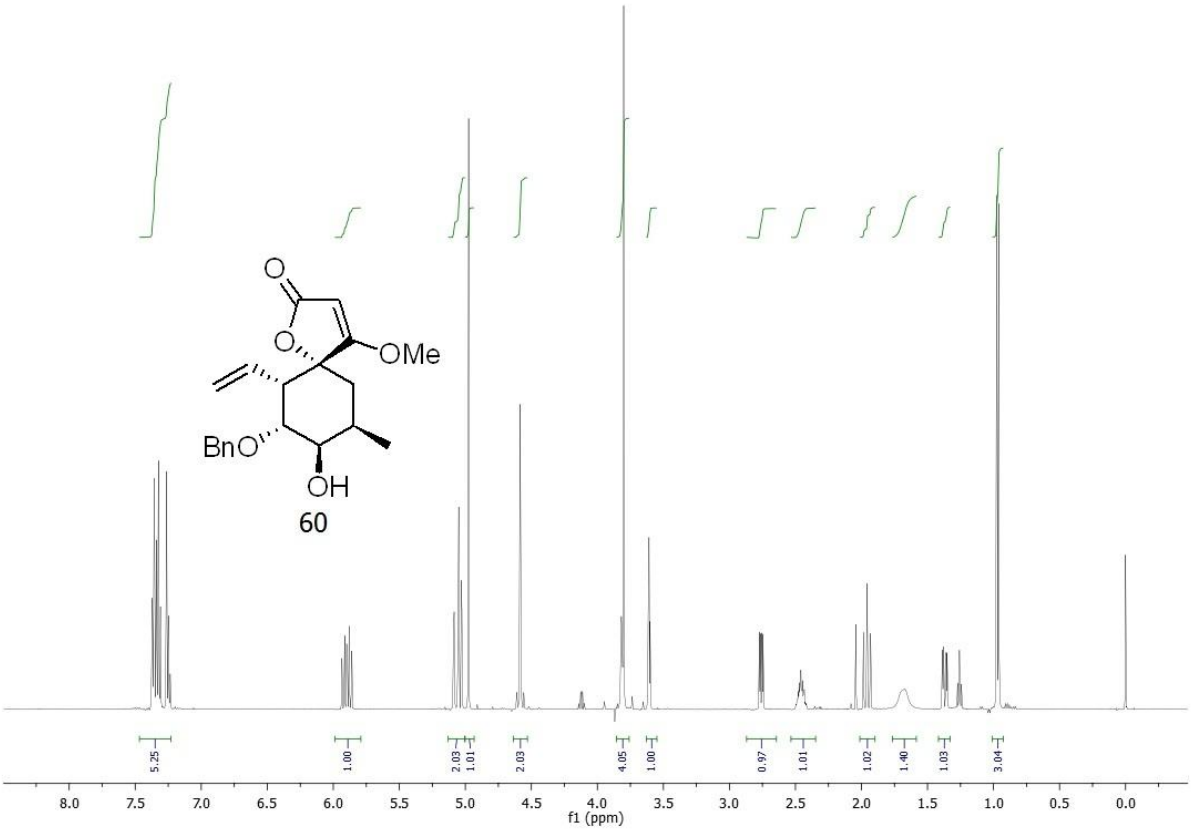

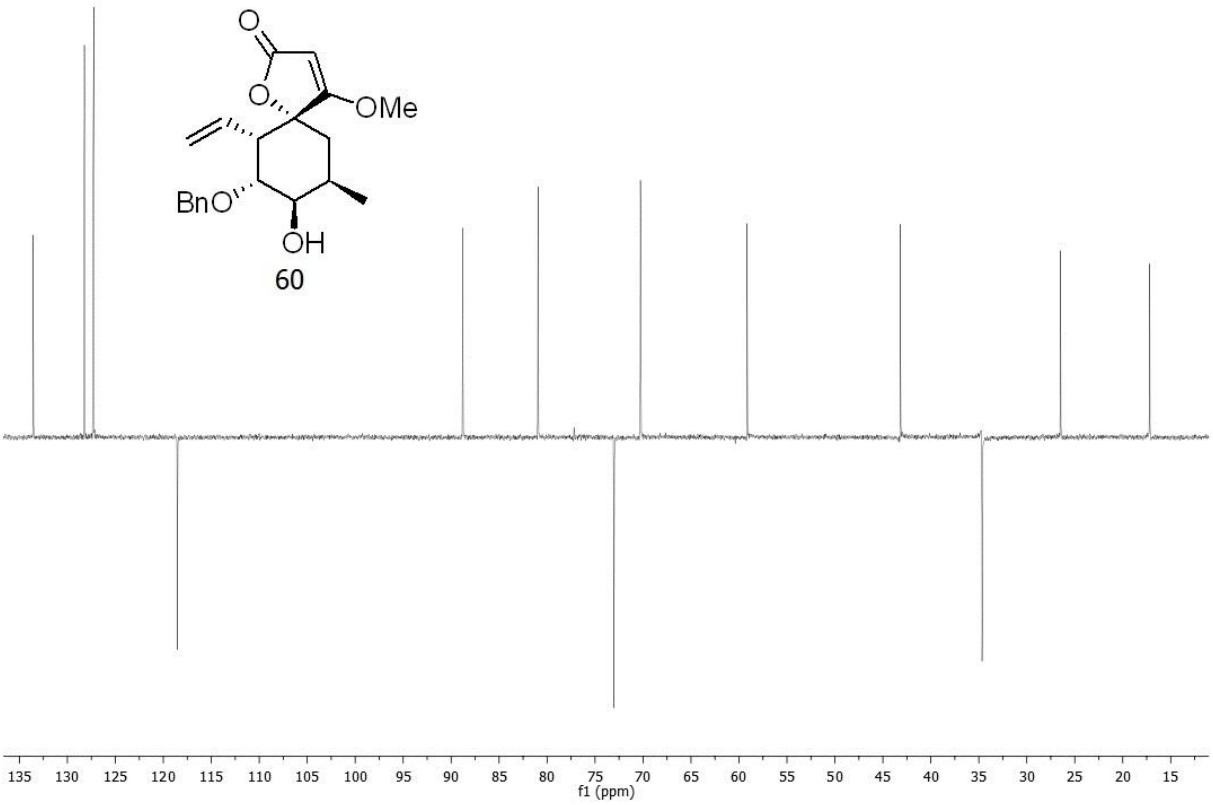

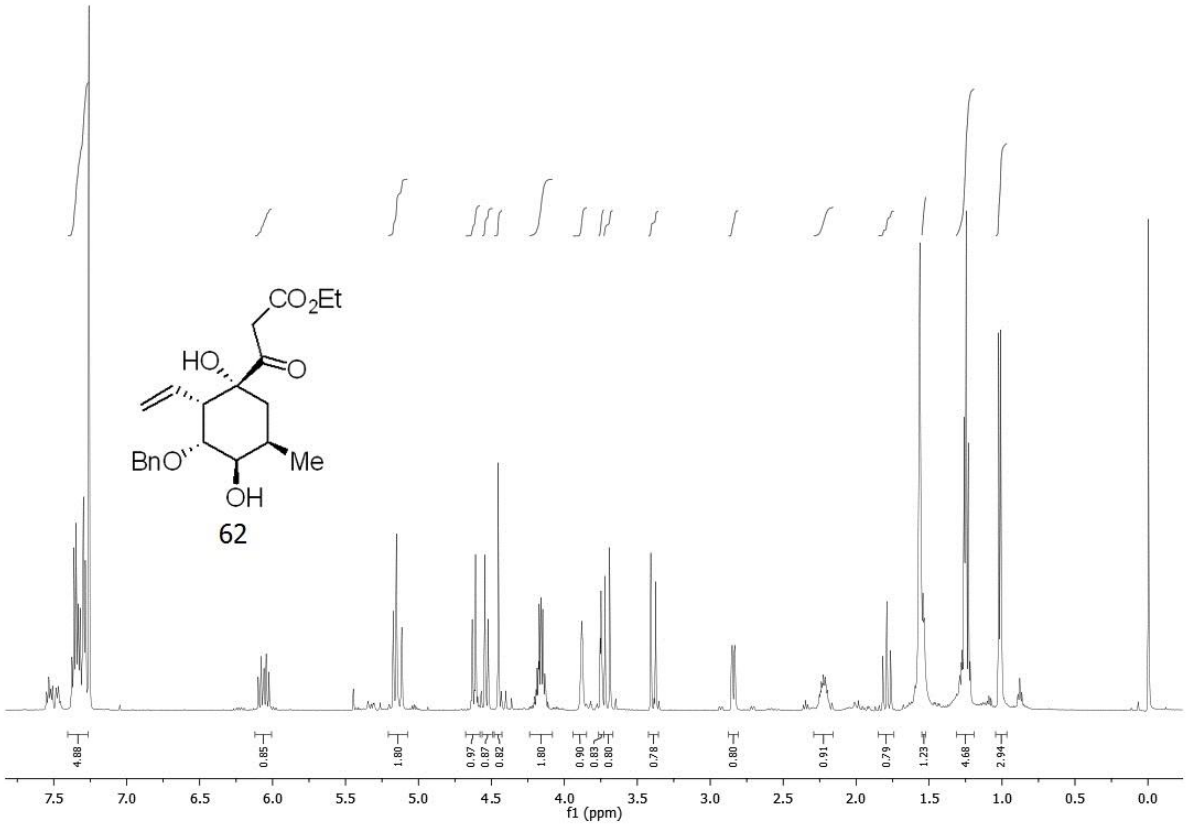

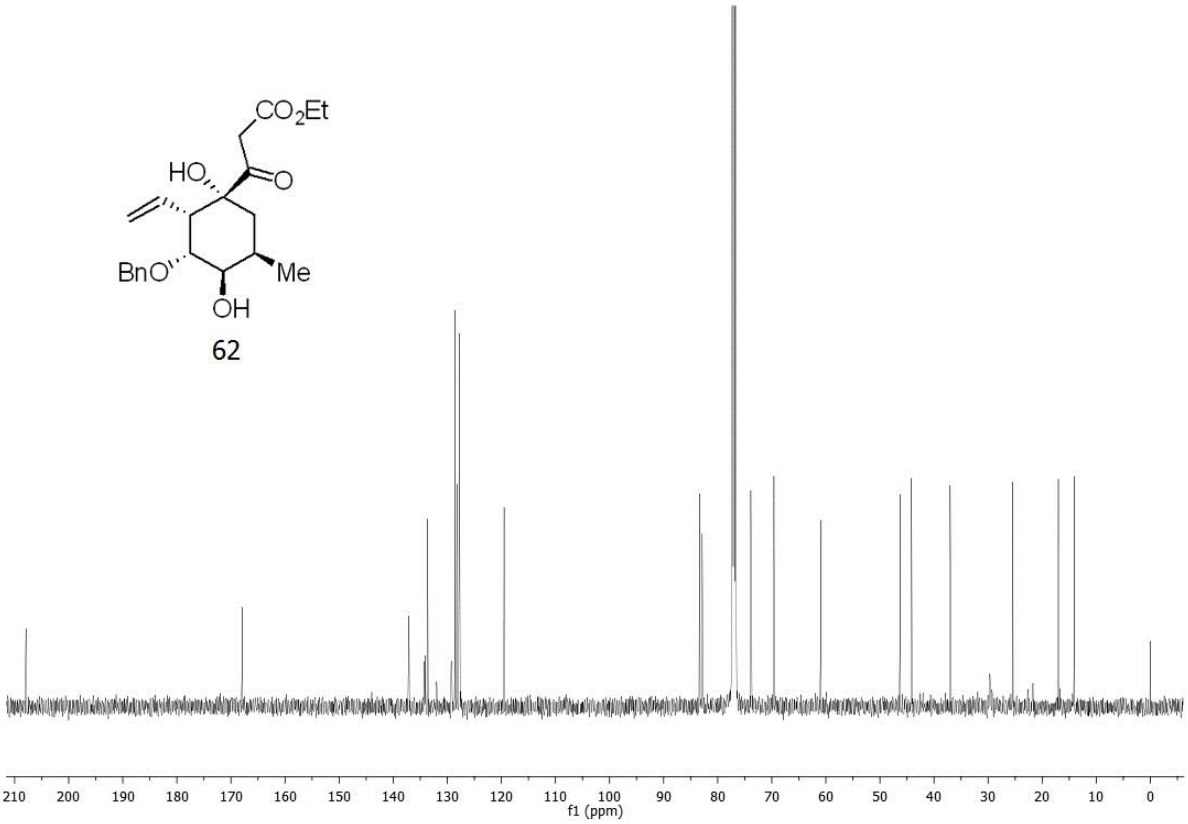

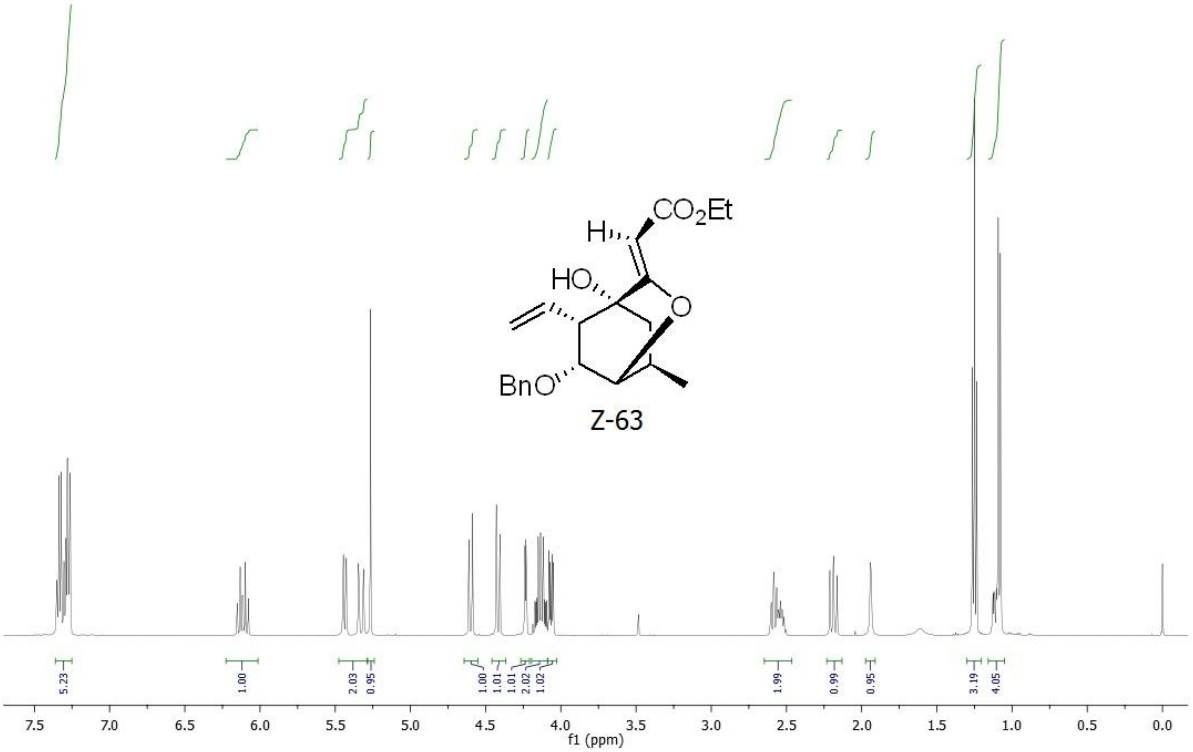

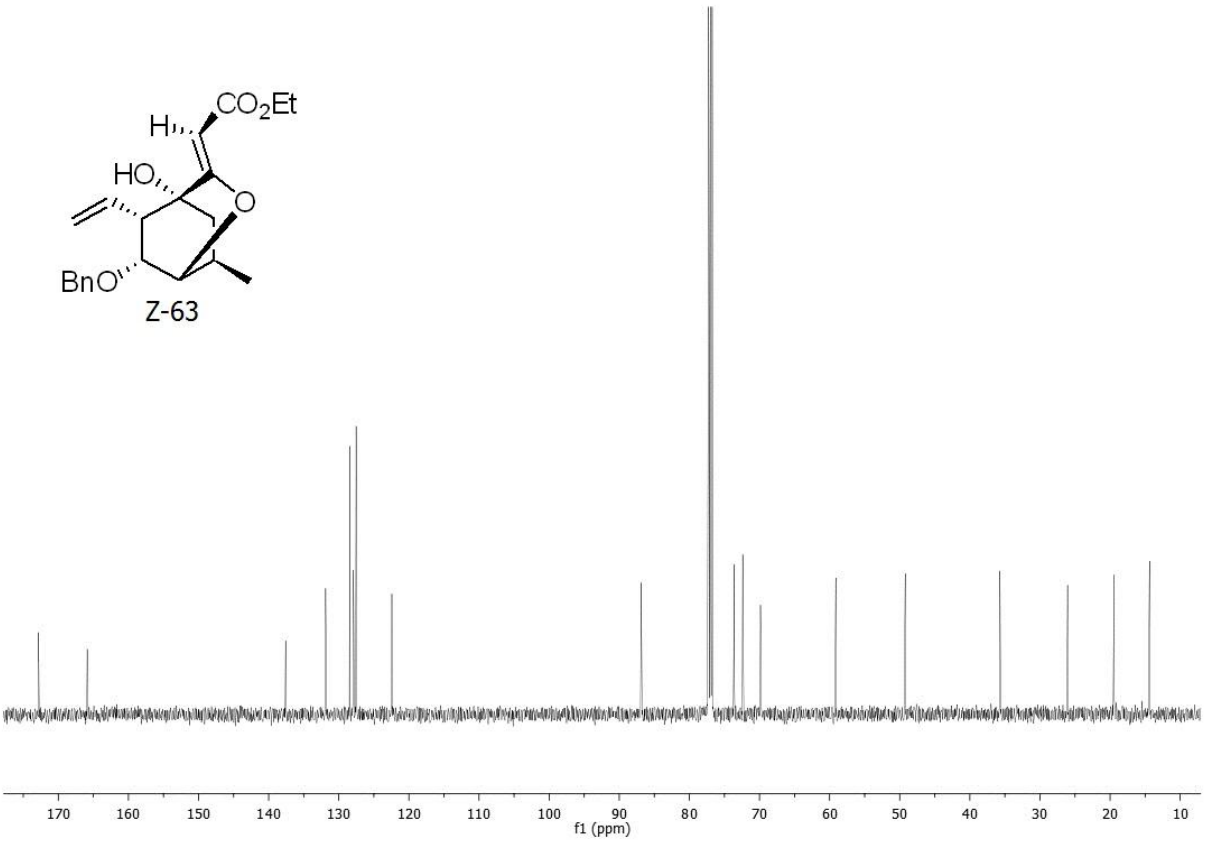

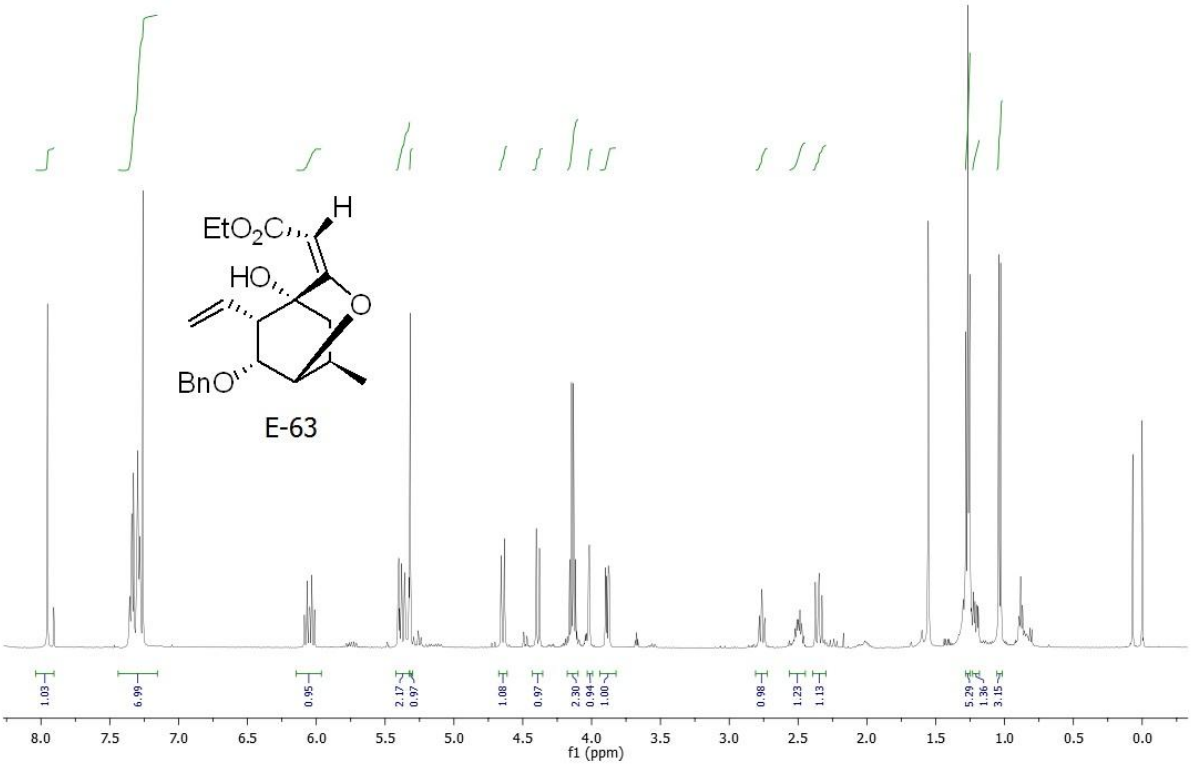

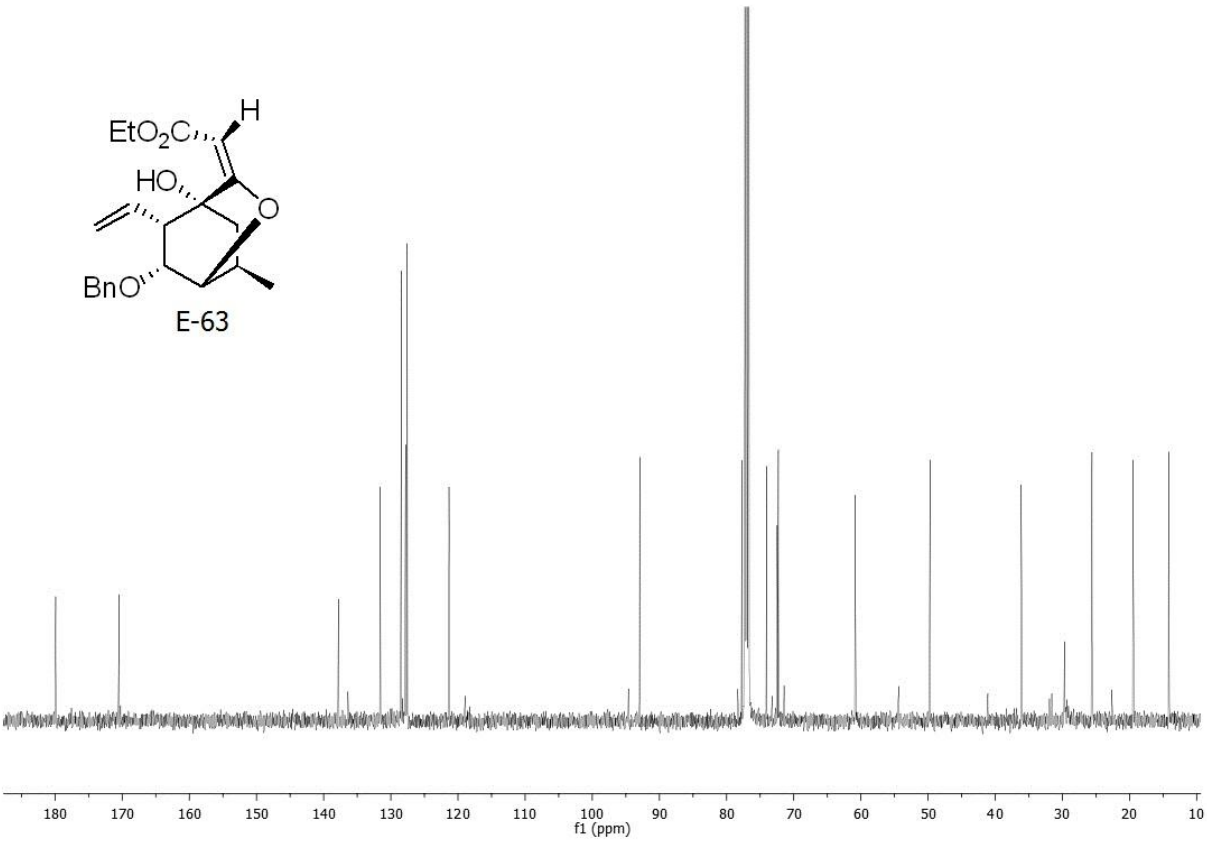

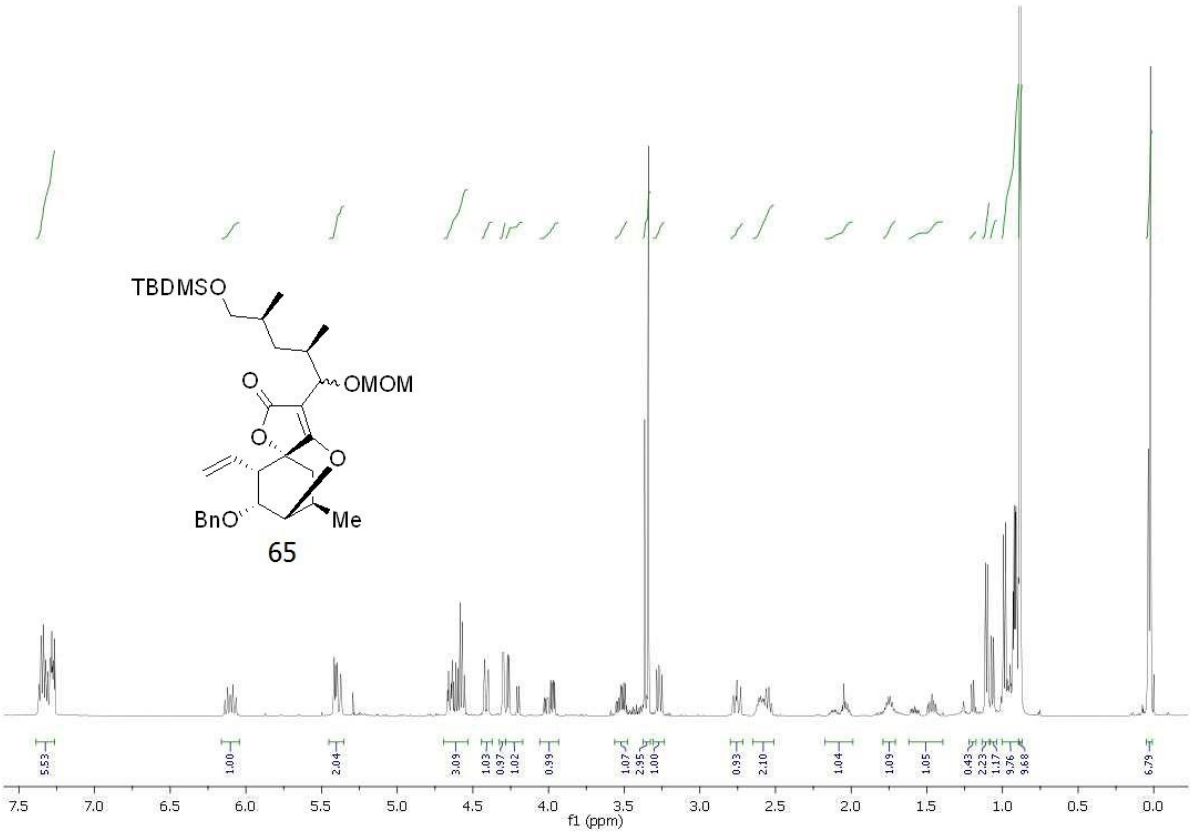

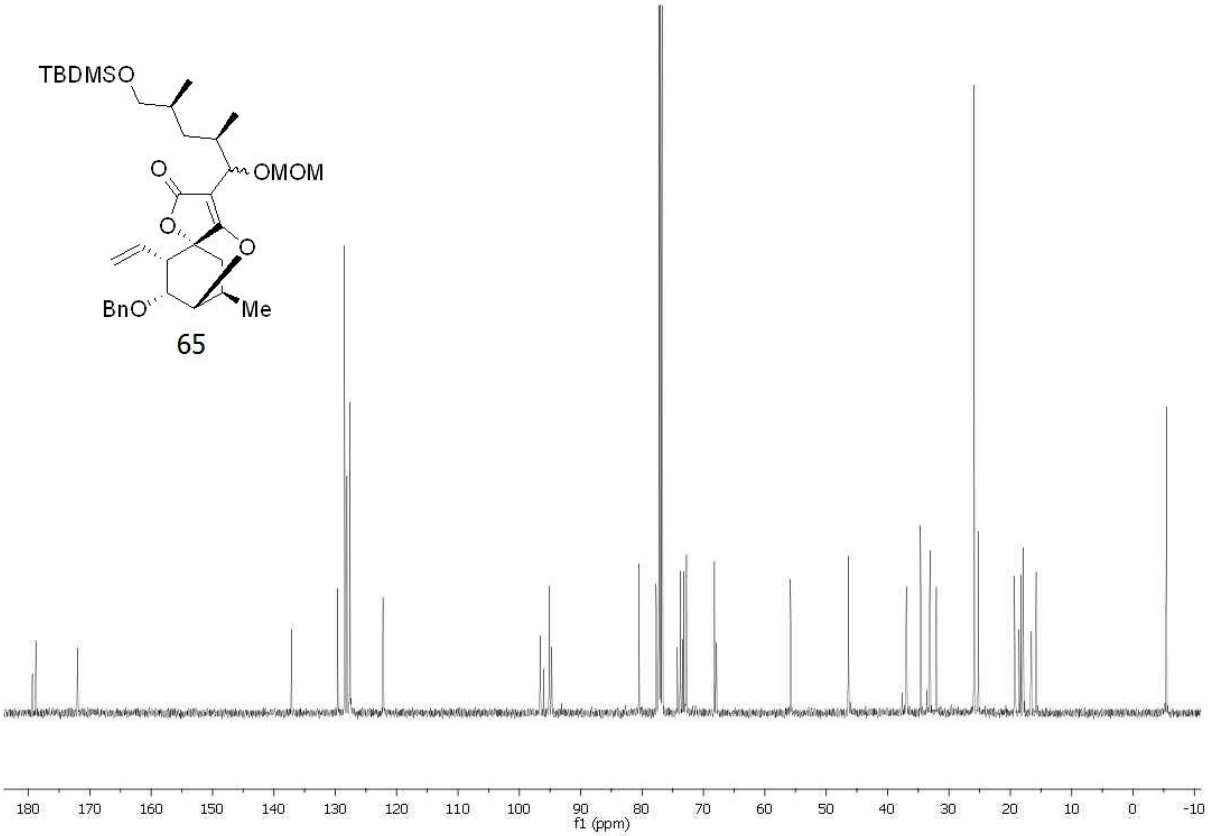

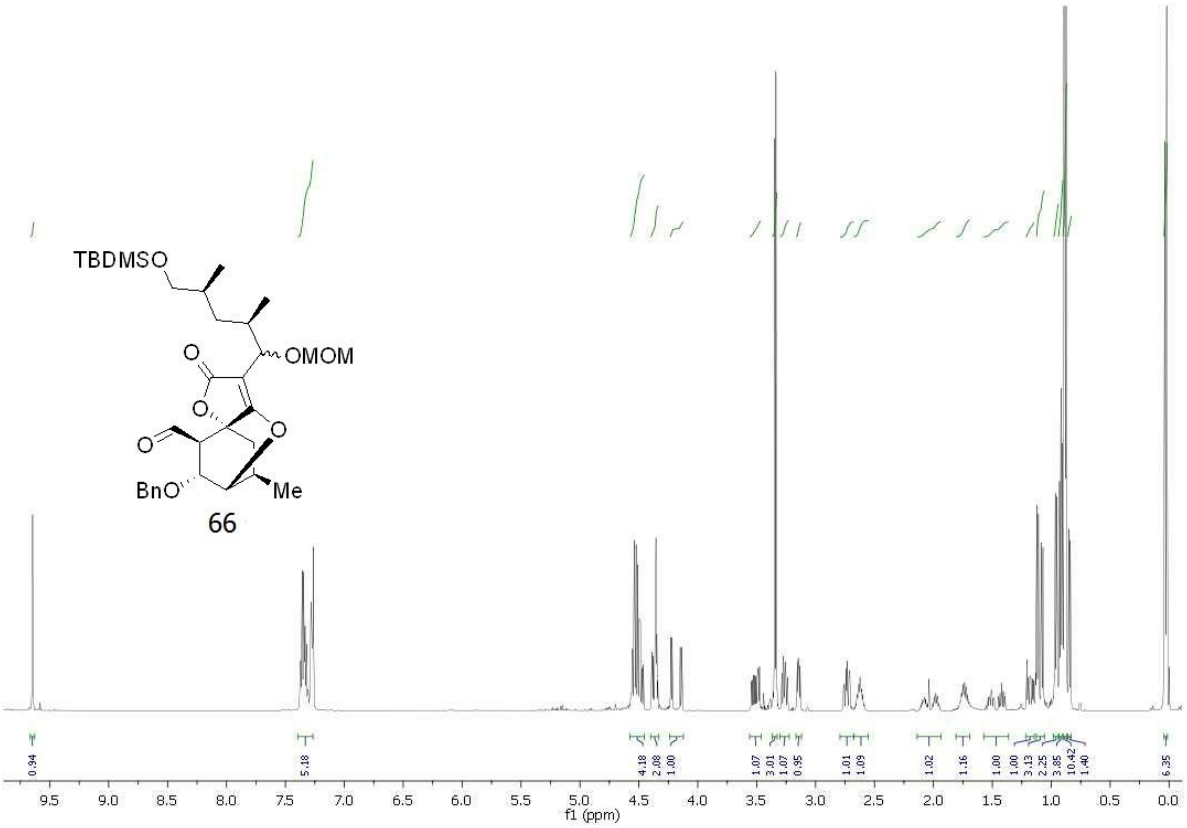

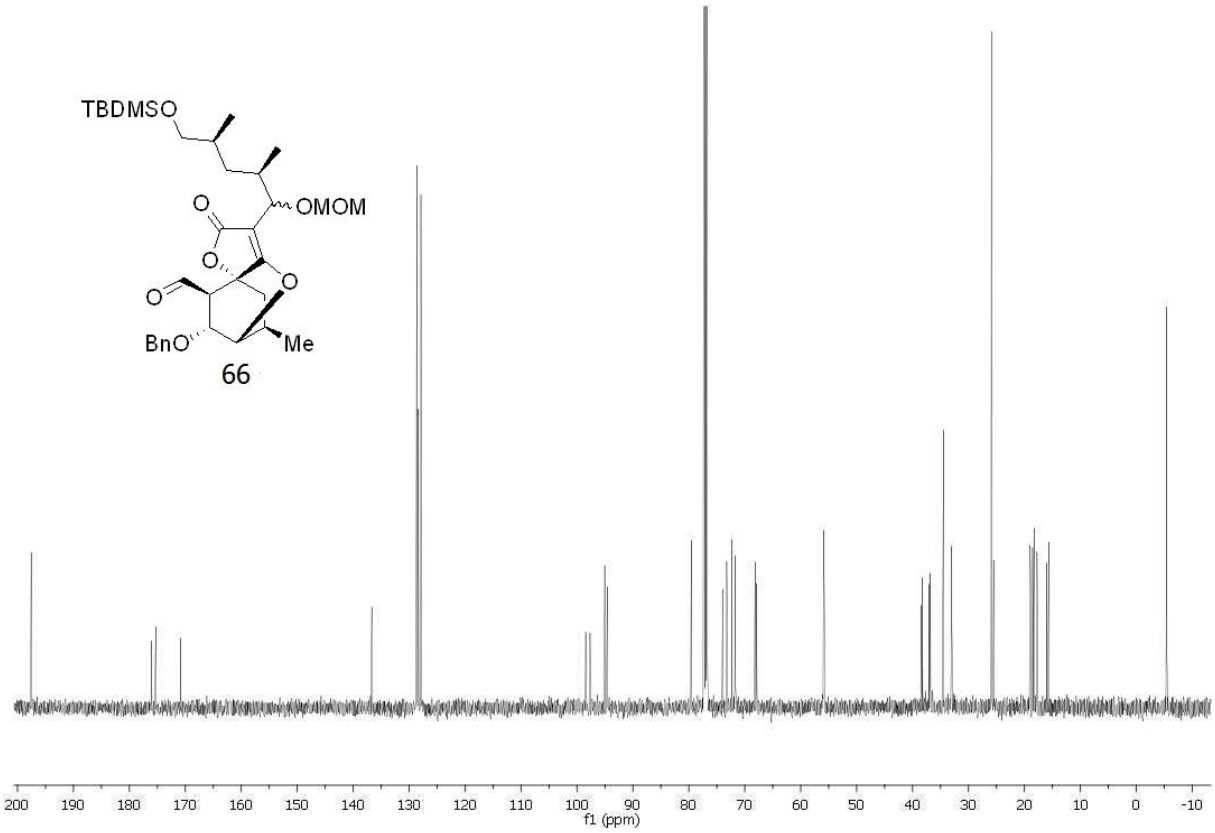

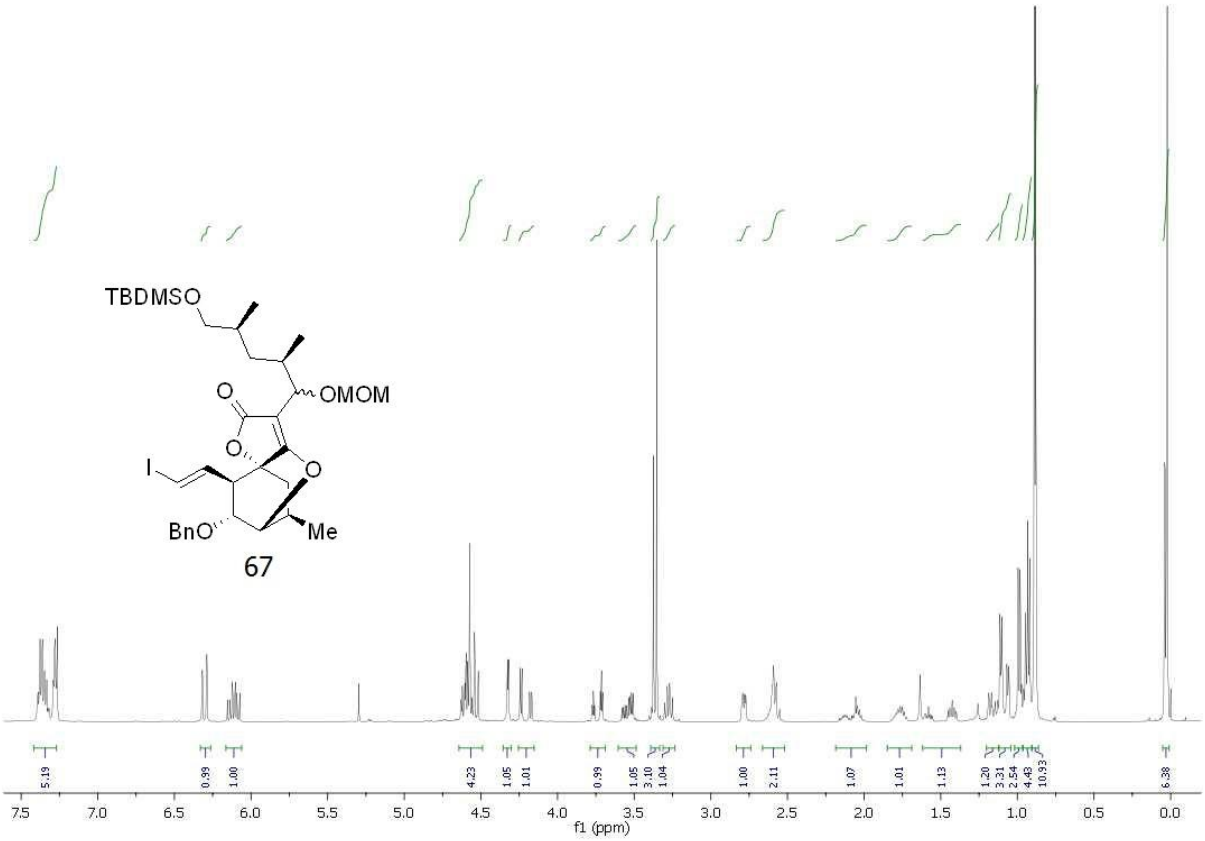

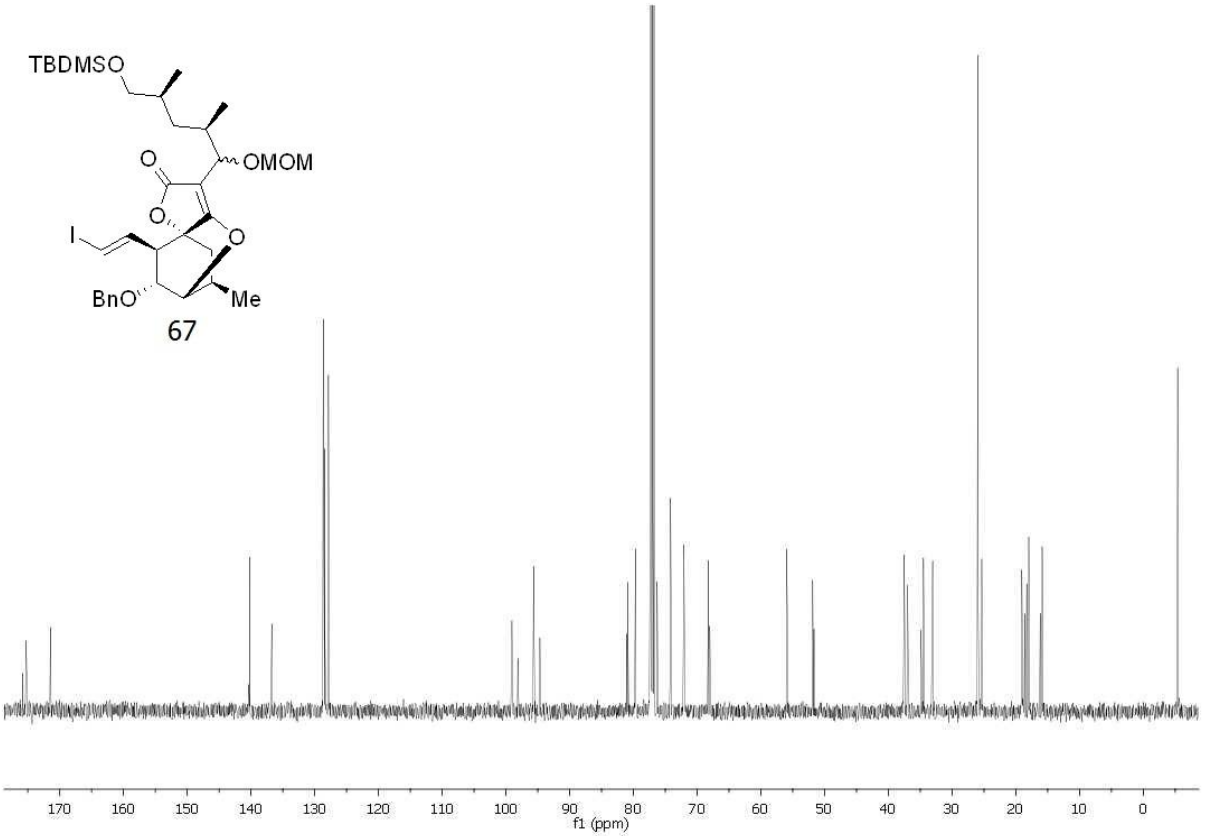

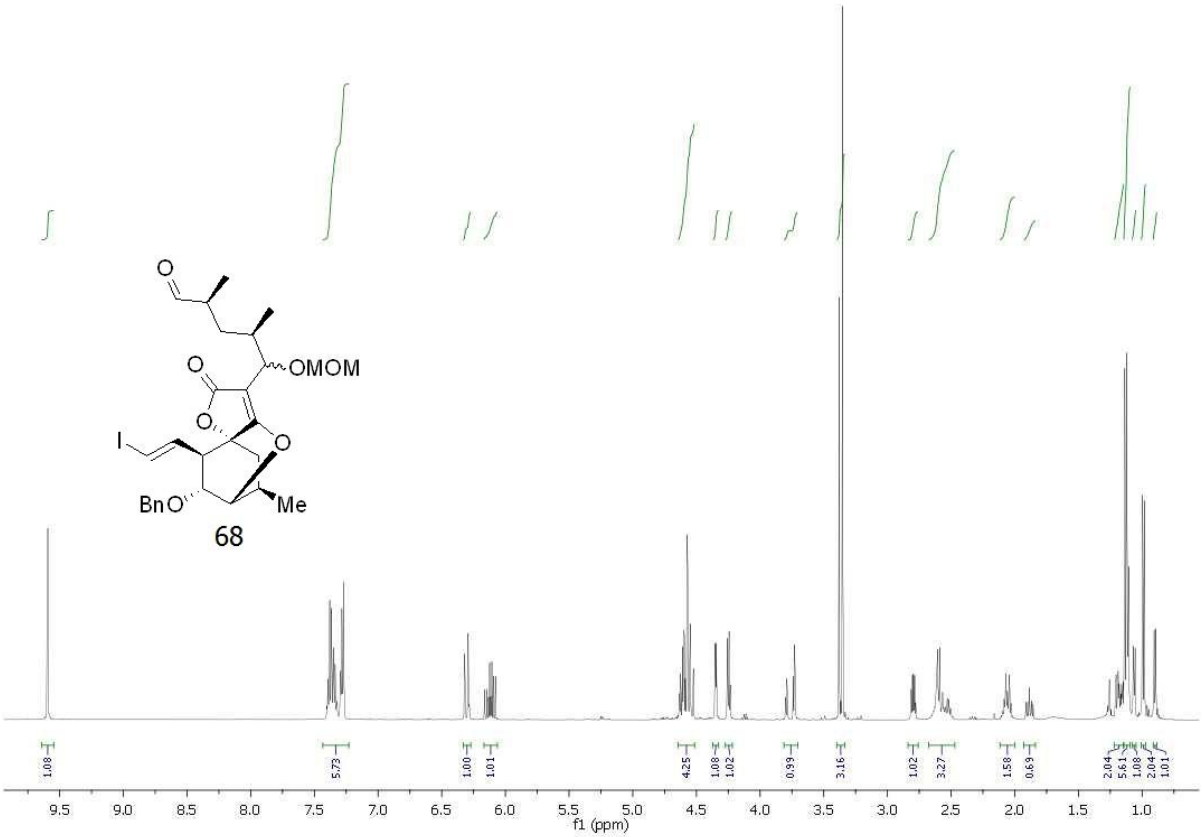

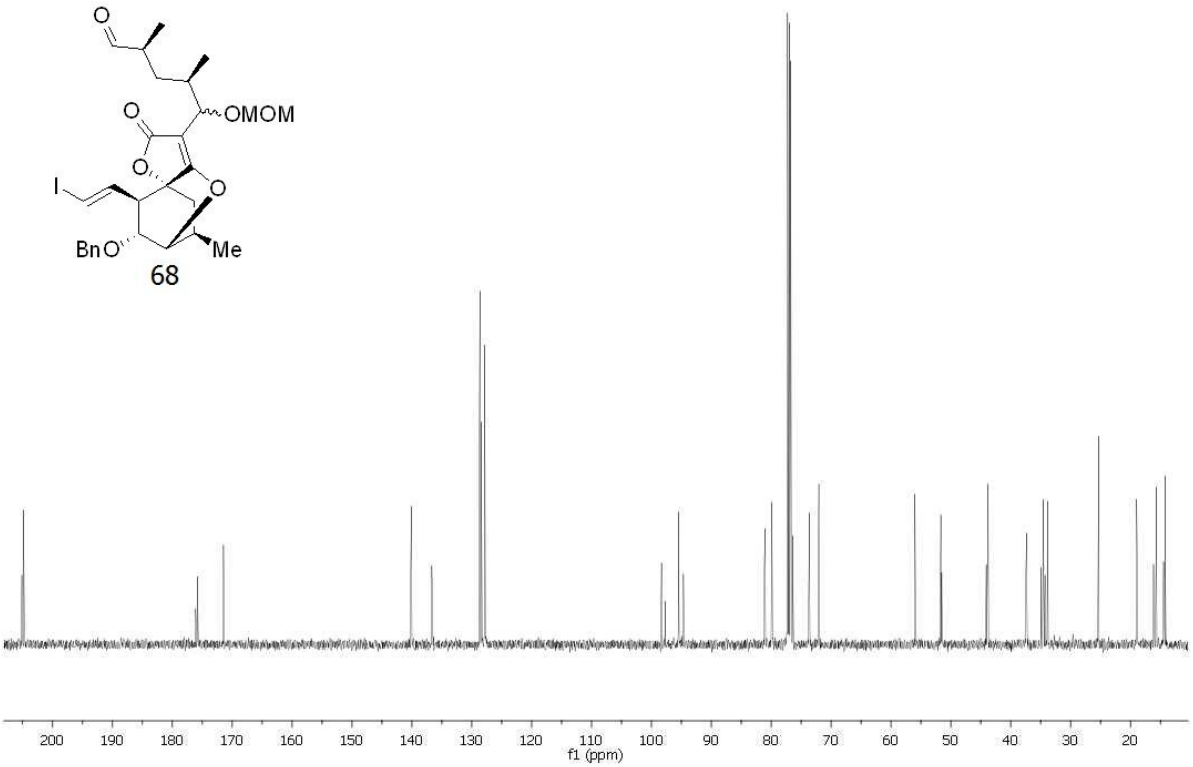

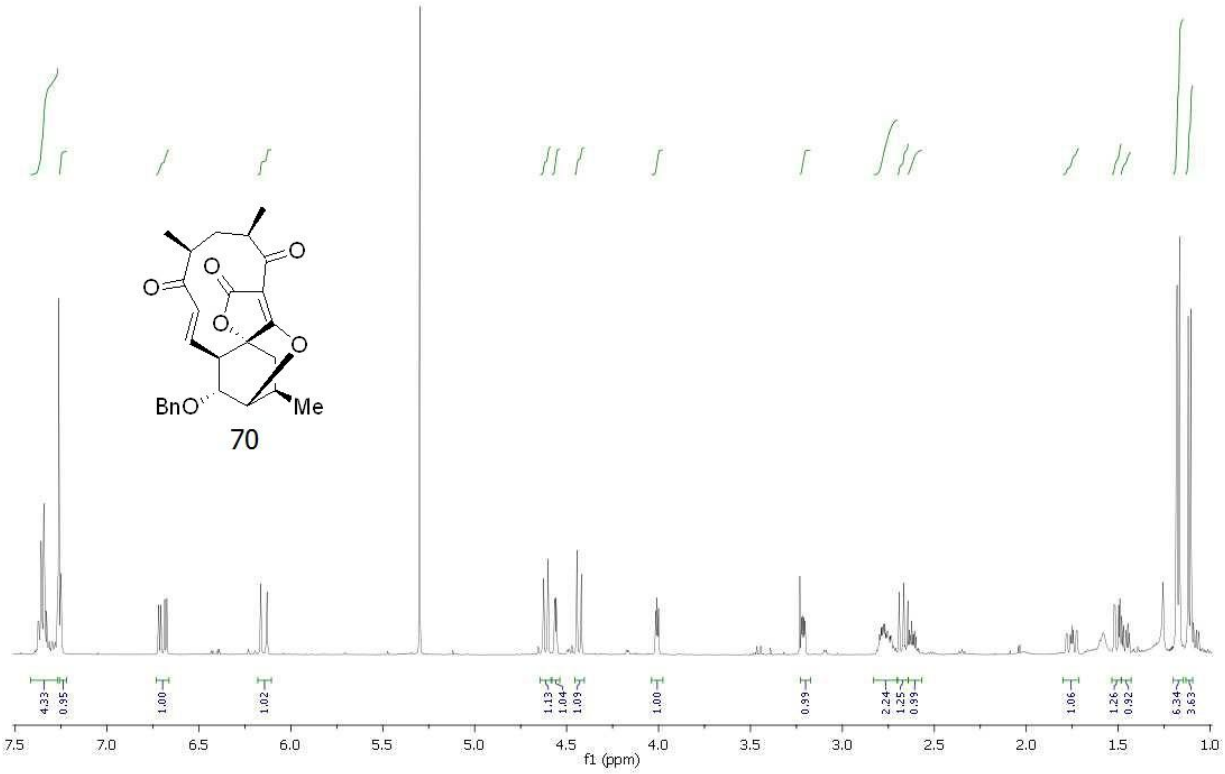

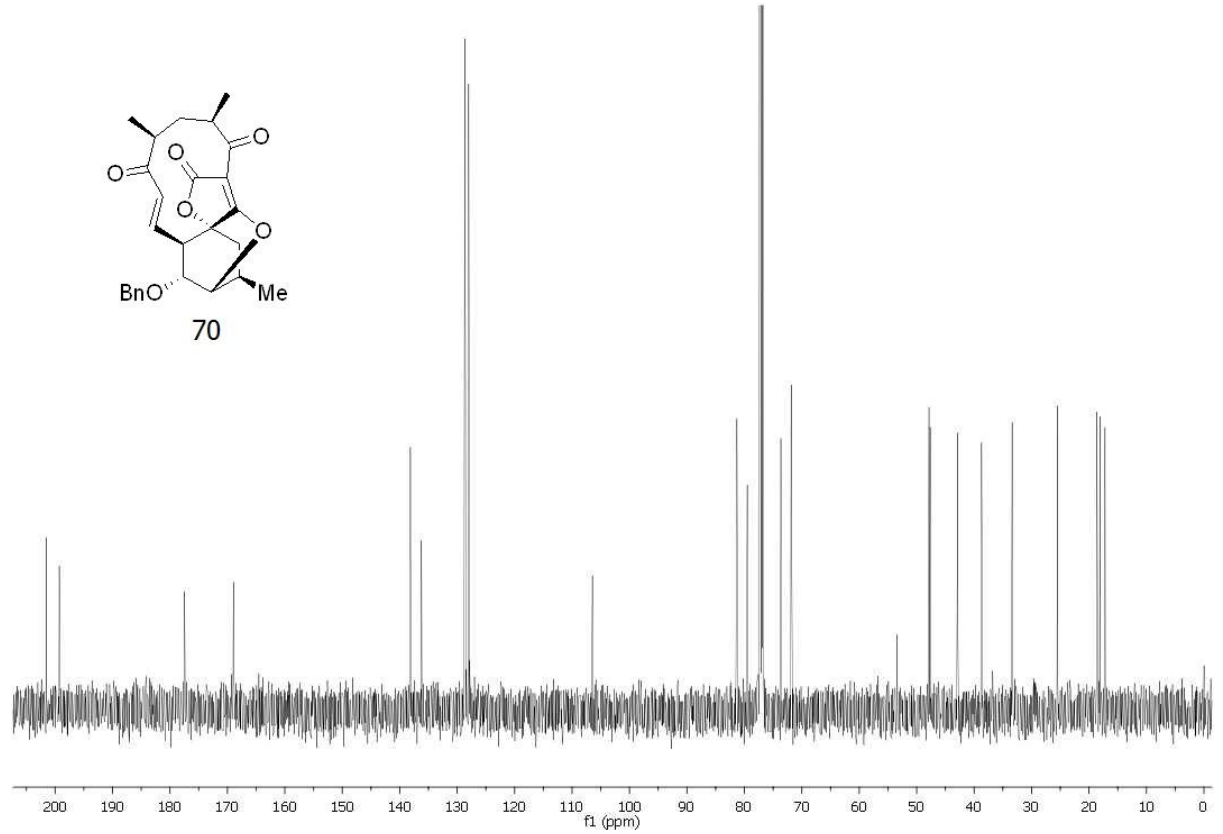

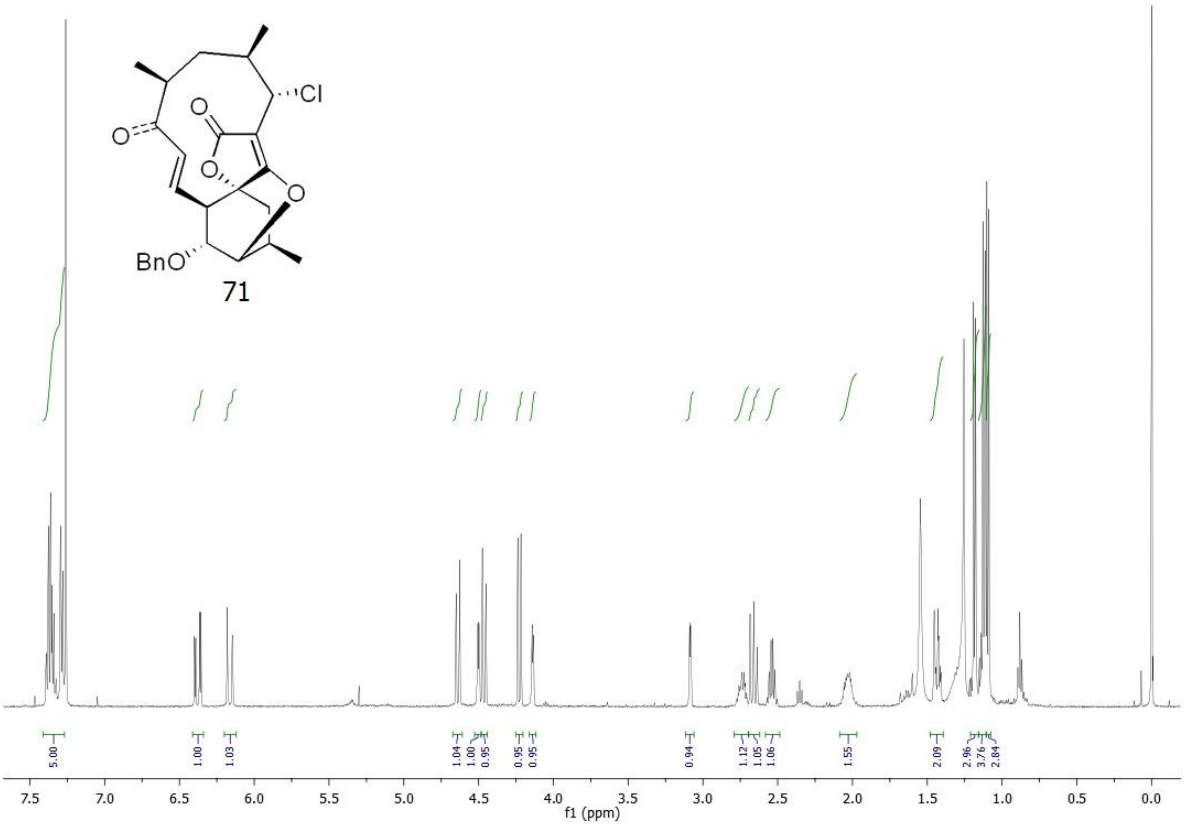

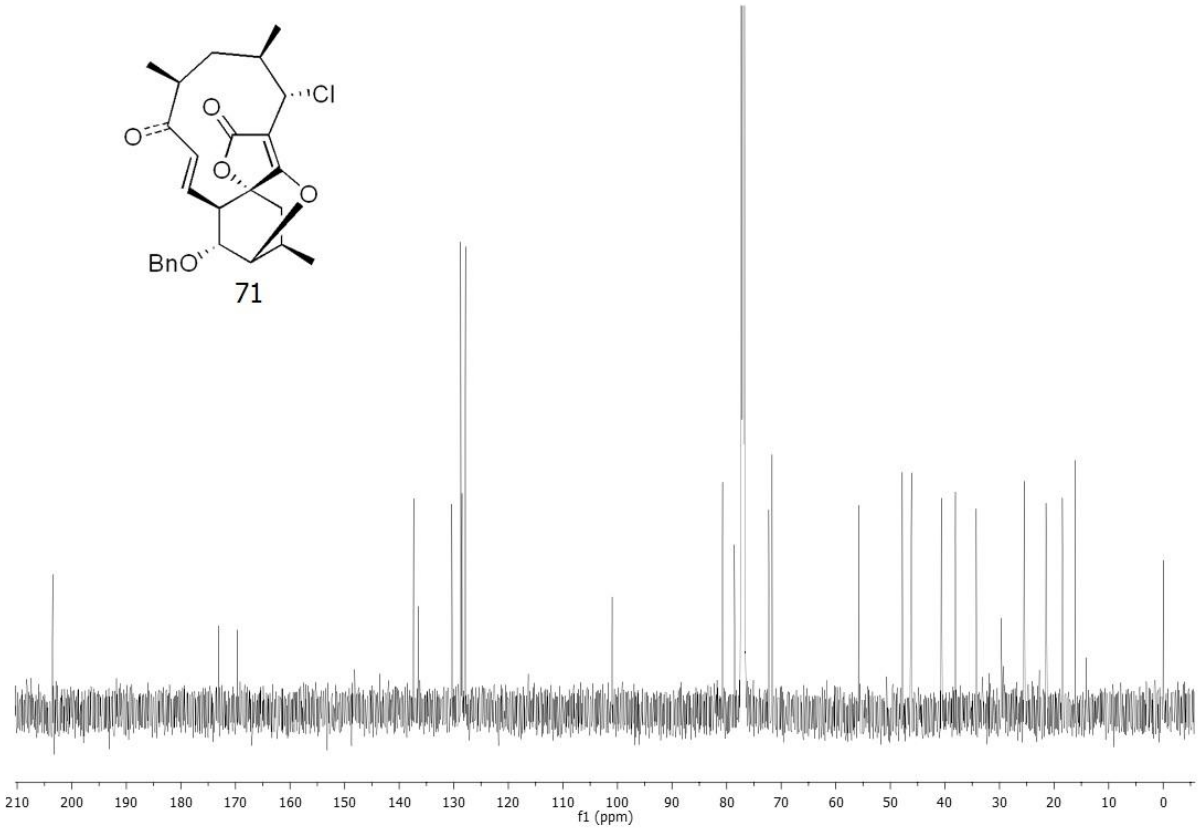

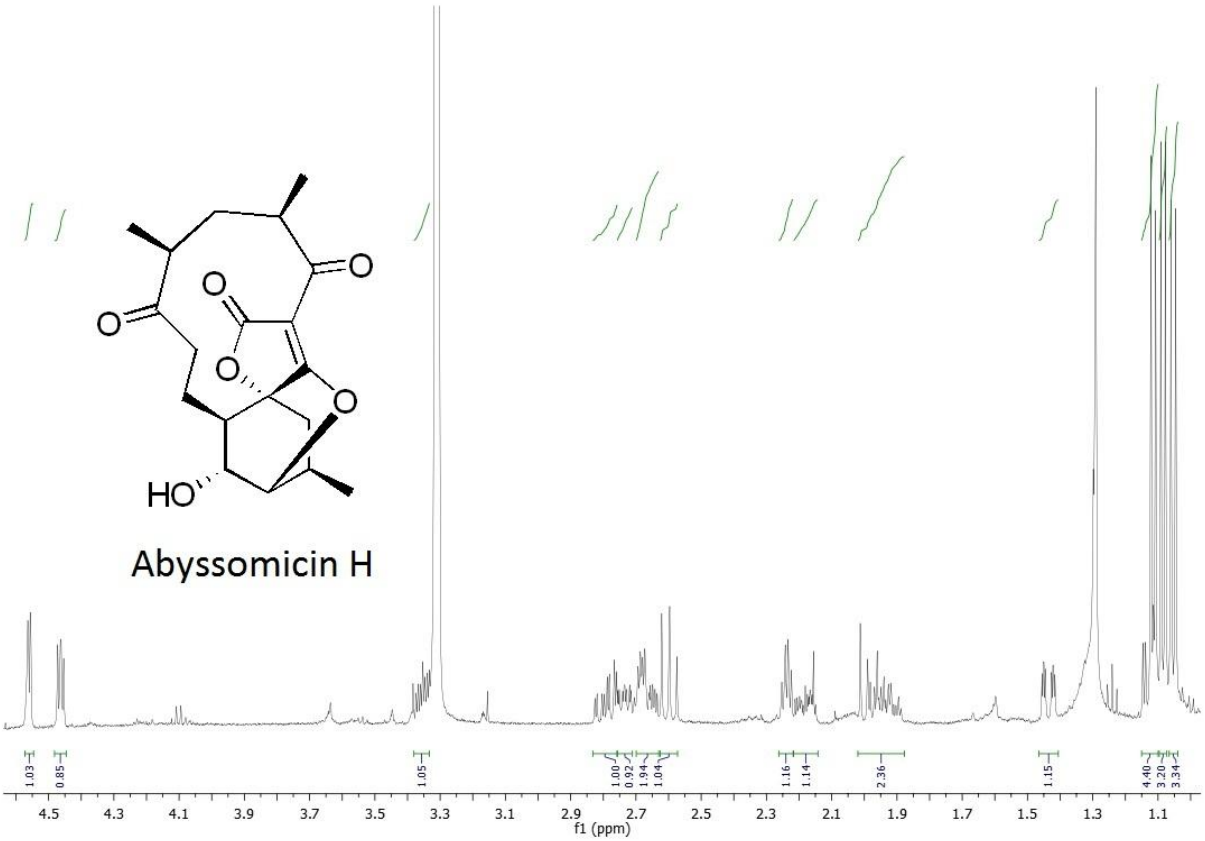

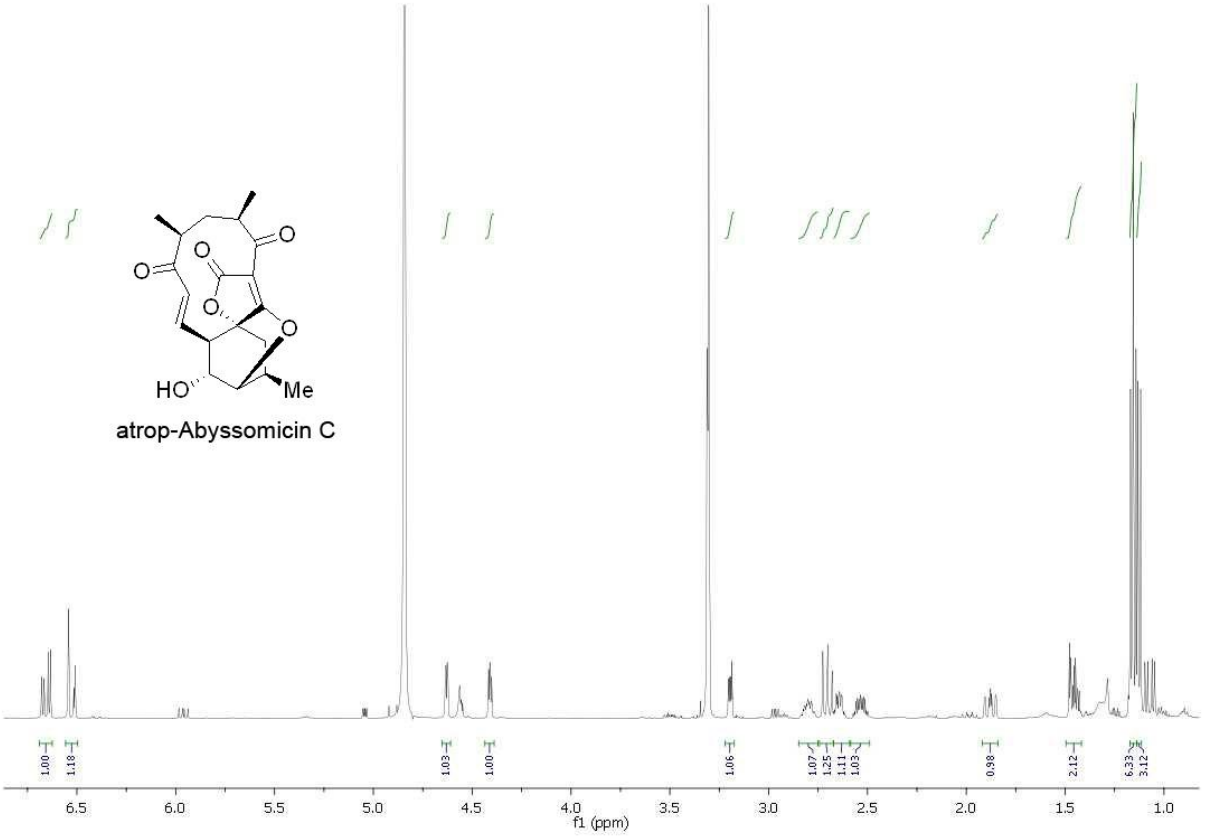

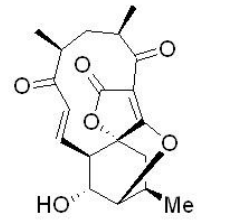

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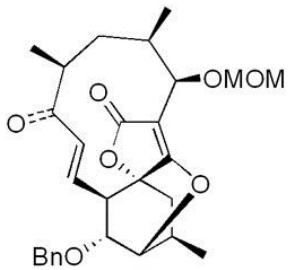

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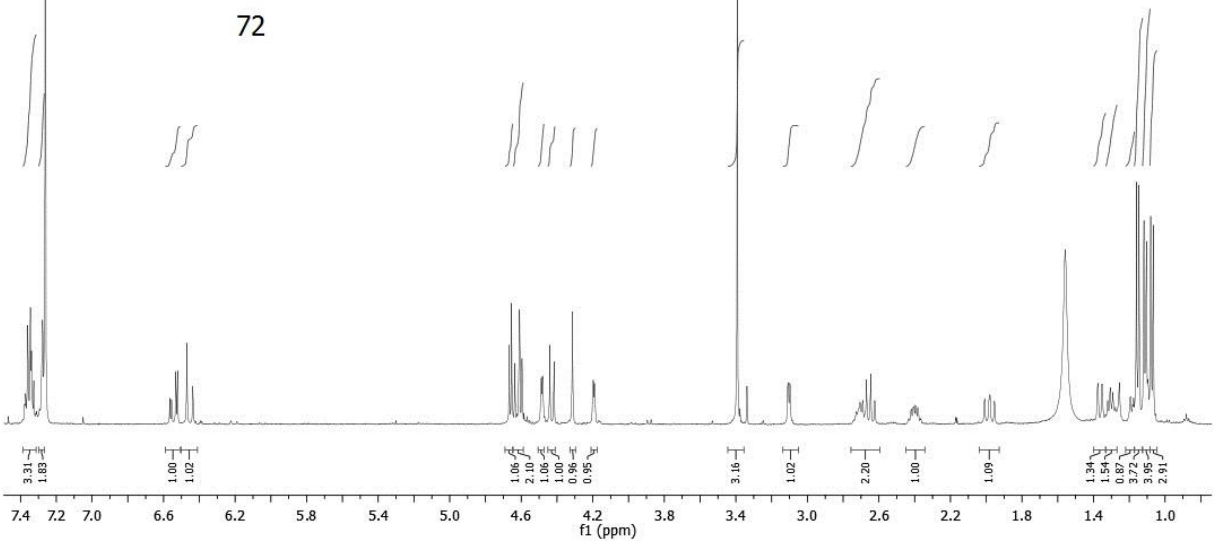

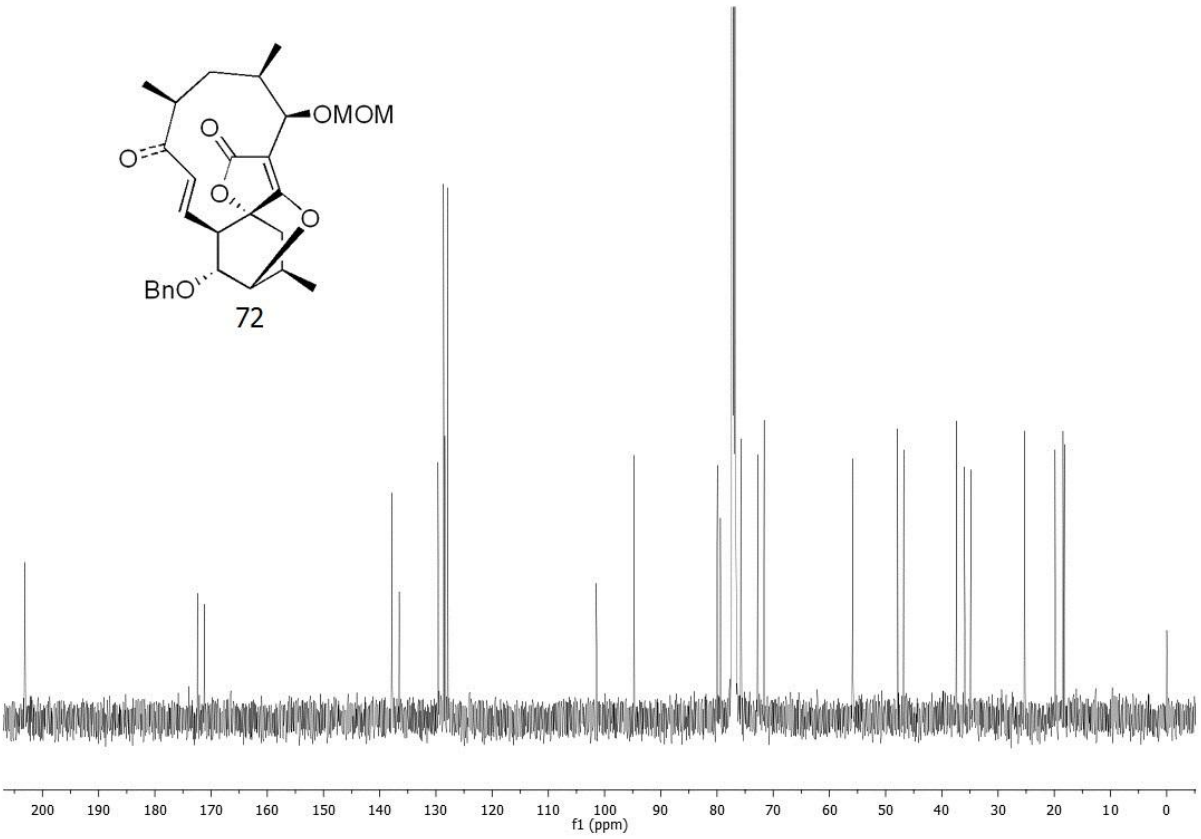

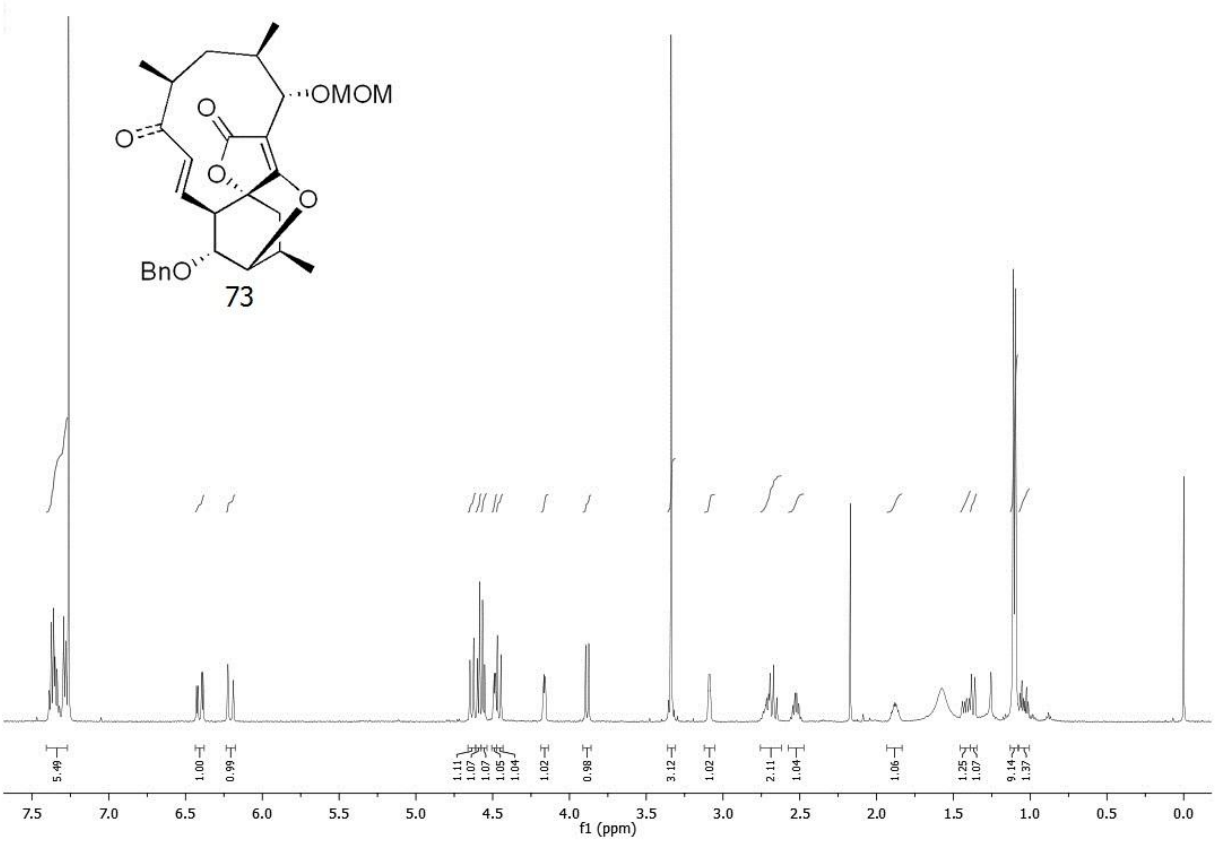

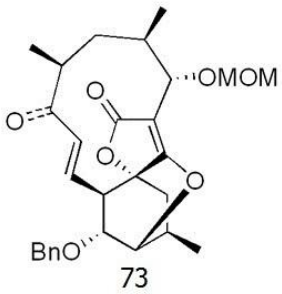

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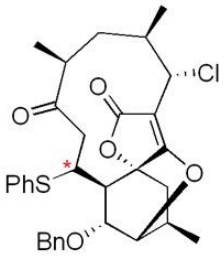
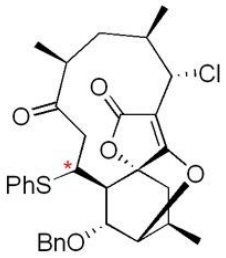
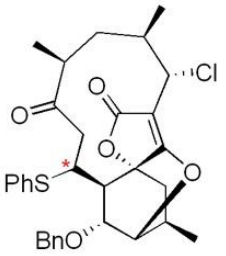


74 *(diastereoisomer 1)*



74 (diastereoisomer 1)



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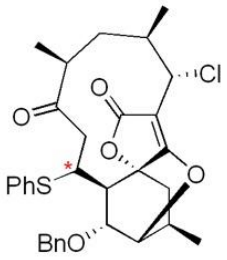
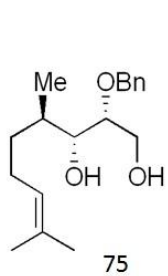


74 (diastereoisomer 2)



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