Evaluating Transition-Metal Catalyzed Transformations for the Synthesis of Laulimalide

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Supporting Information

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General: All reactions were run under an atmosphere of nitrogen unless otherwise indicated. Anhydrous solvents were transferred via oven-dried syringe or cannula. Flasks were flame-dried under vacuum and cooled under a stream of nitrogen or argon. Tetrahydrofuran (THF), and dimethoxyethane (DME), benzene, pyridine, diisopropylamine, triethylamine, diisopropylethylamine, and dimethylsulfoxide, acetonitrile, hexane, toluene, diethyl ether, and dichloromethane were purified with a Solv-Tek solvent purification system by passing through a column of activated alumina. Acetone was distilled from calcium sulfate. Methanol was distilled from magnesium methoxide.

Where indicted, solvents are degassed via freezing in liquid nitrogen and thawing under high vacuum. The above cycle is repeated three times, unless otherwise indicated.

Analytical thin layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (DC-Fertigplatten Krieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still. Solvents for chromatography are listed as volume:volume ratios.

Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. High resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Regional Center of the University of California-San Francisco on a Kratos MS-90 mass spectrometer with an ionizing current of 98 A and an ionizing voltage of 79 eV and reported as m/e (relative intensity). Accurate masses are reported for the molecular ion (M^+) or a suitable fragment ion. Low resolution CI mass spectral data was obtained using an AX-505H mass spectrometer (JEOL, USA, Inc.).

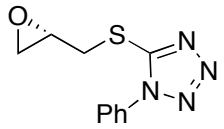
Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Varian UI-600 (600 MHz), UI-500 (500 MHz) or Varian MERC-400 (400 MHz). Chemical shifts are reported in delta (δ) units, part per million (ppm) downfield from tetramethylsilane (TMS) relative to the singlet at 7.27 ppm for deuterochloroform. Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet.

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Varian UI-600 (150 MHz), Varian UI-500 (125 MHz) or Varian MERC-400 (100 MHz). Chemical shifts are reported in delta (δ) units, part per million (ppm) relative to the center line of the triplet at 77.0 ppm for deuterochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

Optical rotation data was obtained with a Jasco DIP-360 digital polarimeter at the sodium D line (589 nm) in the solvent and concentration indicated.

I- Synthesis of the dihydropyran side chain

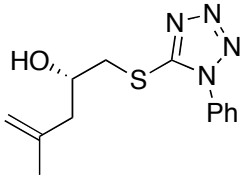
(*S*)-5-(oxiran-2-ylmethylthio)-1-phenyl-1*H*-tetrazole:



To a solution of (*R*)-glycidol **11** (1.00 g, 13.5 mmol) in THF (65 mL) were successively added triphenylphosphine (4.25 g, 16.2 mmol) and 1-phenyl-1H-tetrazole-5-thiol (2.89 mg, 16.2 mmol). The mixture was cooled to 0 ºC and diethylazodicarboxylate (2.77 mL, 17.6 mmol) was added dropwise. The resulting yellow solution was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel (petroleum ether/EtOAc : 80/20) to yield 2.59 g (82%) of the titled epoxysulfide as a colorless oil which crystallized upon cooling to give white crystals.

mp = 48-49 ºC; **$[\alpha]_D^{25}$** = + 47.7 (*c* 1.0, $CHCl_3$); **R*f*** = 0.42 (petroleum ether/EtOAc : 2/1); **IR (neat):** ν 3062, 2995, 2992, 1751, 1735, 1596, 1500, 1412, 1389, 1244, 1090, 1015 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.61-7.55 (m, 5H), 3.76 (dd, *J* = 13.9, 4.7 Hz, 1H), 3.45 (m, 1H), 3.36 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.92 (m, 1H), 2.76 (dd, *J* = 4.7, 2.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 153.5, 133.3, 130.2, 129.8 (2C), 123.7 (2C), 50.0, 47.8, 35.4; **HRMS** (EI): Calcd. for $C_{10}H_{10}N_4OS$ [M^+]: 234.0575, found 234.0575.

(*S*)-4-Methyl-1-(1-phenyl-1*H*-tetrazol-5-ylthio)pent-4-en-2-ol (12):

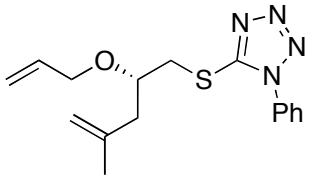


To a suspension of CuI (81 mg, 0.426 mmol) in THF (2 mL) at -30 °C was added isopropenylmagnesium bromide (0.5 M in THF, 6.4 mL, 3.2 mmol) dropwise. The resulting orange thick mixture was stirred at this temperature for 5 min. A solution of the previously obtained epoxide (500 mg, 2.13 mmol) in THF (4 mL) was then added dropwise. After the addition was complete, the mixture was allowed to warm to 0 °C and was stirred at this temperature for 4 hours. The resulting dark mixture was poured into a saturated aqueous solution of NH_4Cl and was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash

column chromatography on silica gel (petroleum ether/EtOAc : 85/15 to 70/30) furnished 586 mg (99%) of homoallylic alcohol **12** as a colorless oil.

$[\alpha]_D^{25}$ = +40.1 (*c* 1.38, $CHCl_3$); **R*f*** = 0.5 (petroleum ether/EtOAc : 70/30); **IR (neat)** : ν 3414, 30.73, 29.72, 29.35, 1647, 1596, 1499, 1411, 1243, 1078, 896, 691 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60-7.50 (m, 5H), 4.89 (m, 1H), 4.81 (m, 1H), 4.20 (m, 1H), 3.68 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.33 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.91 (d, *J* = 3.6 Hz, OH), 2.40-2.28 (m, 2H), 1.77 (br s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 154.9, 141.8, 133.8, 130.5, 130.1 (2), 124.1 (2), 114.5, 68.1, 45.1, 40.0, 22.7.

(*S*)-5-[2-(Allyloxy)-4-methylpent-4-enylthio]-1-phenyl-1*H*-tetrazole (13):



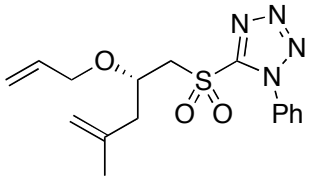
13

To a solution of alcohol **12** (2.25 g, 1.38 mmol) in THF (6 mL) was added diethylzinc (1.0 M in hexanes, 5.3 mL, 5.29 mmol) dropwise. The resulting solution was stirred at rt for 1 hour. Meanwhile, $Pd(OAc)_2$ (92 mg, 0.407 mmol) and triphenylphosphine (534 mg, 2.04 mmol) were inserted in a separate flask. The flask was purged with argon and THF (12 mL) was added. The mixture was vigorously stirred for 10 min to give a yellow suspension, whereupon allylacetate (2.6 mL, 24.42 mmol) was added in a single portion and the resulting mixture was stirred for an additional 10 min. The zinc alkoxide solution previously obtained was added to the preformed η^3-π-allyl complex *via* cannula and the resulting orange reaction mixture was stirred at rt for 48 hours. The solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc : 95/5) to give 1.76 g (62%) of ether **13**, along with 410 mg of recovered starting material (corrected yield of **13** = 76% brsm).

$[\alpha]_D^{25}$ = +15.1 (*c* 1.57, $CHCl_3$); **R*f*** = 0.8 (petroleum ether/EtOAc : 70/30); **IR (neat)** : ν 3075, 2977, 2936, 2861, 1732, 1646, 1596, 1500, 1412, 1387, 1242, 762, 690 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60-7.50 (m, 5H), 5.85 (m, 1H), 5.24 (m, 1H), 5.13 (m, 1H), 4.81 (m, 2H), 4.07 (br d, *J* = 5.6 Hz, 2H), 3.91 (ddd, *J* = 11.2, 6.4, 4.8 Hz, 1H), 23.68 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.45 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.42 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.29 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.77 (br s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 154.7, 141.7, 134.7, 133.9, 130.3, 130.0 (2), 124.1

(2), 117.6, 114.1, 75.5, 70.8, 42.3, 37.6, 23.1; **HRMS** (ESI): Calcd. for $C_{16}H_{20}N_4ONaS$ [M + Na]$^+$: 339.1256, found: 339.1258.

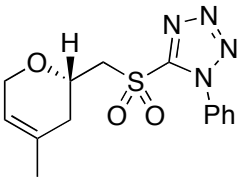
(*S*)-5-[2-(Allyloxy)-4-methylpent-4-enylsulfonyl]-1-phenyl-1*H*-tetrazole:



To a solution of sulfide **13** (1.71 g, 5.40 mmol) in ethanol (50 mL) at 0 °C was added a solution of the oxidant made from $Mo_7O_{24}(NH_4)_6$-$4H_2O$ (1.00 g, 0.811 mmol) in H_2O_2 (30% in H_2O, 5 mL). The cold bath was removed and the resulting mixture was stirred for 18 hours. The reaction being incomplete, a solution of $Mo_7O_{24}(NH_4)_6$-$4H_2O$ (1.00 mg, 0.811 mmol) in H_2O_2 (30% in H_2O, 5 mL) was added and the mixture was stirred for 18 more hours at rt. The reaction mixture was then diluted with EtOAc, and the organic phase was sequentially washed with water, brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc: 95/5 to 80/20) furnished 1.57 g (83%) of the title sulfone as a colorless oil.

R*f* = 0.9 (petroleum ether/EtOAc : 80/20); **IR (neat)** : ν 3077, 2977, 2921, 2219, 1729, 1646, 1596, 1498, 1460, 1425, 1344, 1152, 1086, 1013, 924, 764, 690 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.66-7.56 (m, 5H), 5.61 (ddt, *J* = 16.8, 10.4, 6.0 Hz, 1H), 5.10 (m, 1H), 5.05 (br q_{app}, *J* = 1.6 Hz, 1H), 4.86 (br t, *J* = 1.6 Hz, 1H), 4.73 (m, 1H), 4.16 (m, 1H), 3.95 (ddt, *J* = 15.6, 12.0, 1.6 Hz, 1H), 3.79 (ddt, *J* = 12.0, 6.0, 1.2 Hz, 1H), 3.70 (dd, *J* = 15.2, 8.8 Hz, 1H), 3.62 (dd, *J* = 15.2, 3.2 Hz, 1H), 2.42 (br d, *J* = 13.6, 4.4 Hz, 1H), 2.19 (ddd, *J* = 14.0, 8.0, 0.8 Hz, 1H), 1.72 (br s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 154.5, 140.5, 133.6, 133.3, 131.7, 129.8 (2), 126.0 (2), 118.1, 115.4, 72.2, 70.6, 60.0, 41.6, 23.0; **HRMS** (ESI): Calcd. for $C_{16}H_{20}N_4O_3NaS$ [M + Na]$^+$: 371.1154, found: 371.1156

(*S*)-5-[(4-Methyl-3,6-dihydro-2*H*-pyran-2-yl)methylsulfonyl]-1-phenyl-1*H*-tetrazole (6):



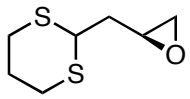
6

To a solution of the previously obtained diene (1.06 g, 3.04 mmol), azeotroped 3 times with toluene, in CH_2Cl_2 (200 mL) was added second generation Grubbs' catalyst **G2** (78 mg, 0.091 mmol) at rt. After stirring for 3 hours, the mixture was concentrated under reduced pressure and the crude residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc : 90/10) to yield 929 mg (95%) of the title compound **6** as a brown solid.

$[\alpha]_D^{25}$ = – 62.9 (*c* 1.37, $CHCl_3$); **R*f* =** 0.70 (petroleum ether/EtOAc : 80/20); **IR (neat)**: ν 3066, 2921, 2853, 1680, 1594, 1497, 1450, 1383, 1345, 1255, 1151, 1121 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ **7**.66-7.56 (m, 5H), 5.36 (m, 1H), 4.16 (m, 1H), 3.95-3.91 (m, 2H), 3.75 (dd, *J* = 15.2, 9.2 Hz, 1H), 3.64 (dd, *J* = 15.2, 2.8 Hz, 1H), 2.10-2.00 (m, 1H), 1.95-1.87 (m, 1H) 1.67 (br s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 154.3, 133.3, 131.7, 130.4, 129.8 (2), 126.0 (2), 119.6, 68.3, 65.9, 61.0, 34.5, 23.0; **HRMS** (ESI): Calcd. for $C_{14}H_{16}N_4O_3NaS$ $[M + Na]^+$: 343.0841, found: 343.0840.

II- Synthesis of the northern fragment 5

(*S*)-2-[(1,3-Dithian-2-yl)methyl]oxirane (14):

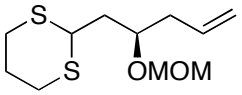


14

To a solution of 1,3-dithiane (2.8 g 23.2 mmol) in THF (30 mL) at -10 ºC was added *n*-BuLi (2.5M in Hexanes, 9.5 L, 23.8 mmol) dropwise. The solution was stirred at -10 ºC for 2 hours, and then cooled to -78 ºC. A solution of (*S*)-glycidyl tosylate in THF (8 mL) was then added *via* cannula and the solution was maintained at -78 ºC for 4 hours. The solution was allowed to warm slowly to rt over 2 hours, and was hydrolyzed by adding a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with Et_2O (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 95/5) gave 2.63 g (68%) of the title compound **14** as a colorless oil. The spectroscopic data matched those reported in the literature.[1]

(*R*)-2-[2-(Methoxymethoxy)pent-4-enyl]-1,3-dithiane

[1] Jin, H.; Taylor, R. E. *Org. Lett.* **2005**, *7*, 1303–1305.

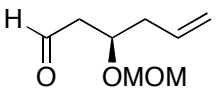


To a stirred suspension of CuI (420 mg, 2.2 mmol) in THF (70 mL) was added vinylmagnesium bromide (1.0M in THF, 22.05 mL, 22.05 mmol) dropwise at -50 ºC and the mixture was stirred for 30 min. A solution of epoxide **14** (2.6 g, 14.7 mmol) in THF (10 mL) was then added *via* cannula. The resulting mixture was stirred at -40 ºC for 40 min, and was then warmed up to -10 ºC. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous layer was extracted with Et_2O (x3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 95/5) furnished 2.86 g (95%) of the desired homoallylic alcohol as a colorless oil.

To a stirred solution of the previously obtained alcohol (2.00 g, 9.79 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added diisopropylethylamine (7.19 mL, 44.0 mmol). After 10 min, chloromethyl methylether (2.23 mL, 29.36 mmol) was added dropwise *via* syringe and the reaction mixture was stirred overnight at rt. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ and the aqueous phase was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 95/5) furnished 2.36 g (97%) of the title compound as a colorless oil.

$[\alpha]_D^{25}$ = – 24.5 (*c* 2.18, $CHCl_3$); **R*f* =** 0.70 (petroleum ether/EtOAc : 90/10); **IR (neat)**: ν 2935, 2897, 1640, 1424, 1370, 1276, 1148, 1099, 1038, 916, 771 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.78 (ddt, *J* = 16.8, 10.0, 7.2 Hz, 1H), 5.11-5.04 (m, 2H), 4.68 (s, 2H), 4.15 (dd, *J* = 8.8, 5.5 Hz, 1H), 3.90 (m, 1H), 3.38 (s, 3H), 2.91-2.77 (m, 4H), 2.35-2.29 (m, 2H), 2.09 (m, 1H), 1.95-1.79 (m, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 134.1, 118.1, 96.2, 73.9, 56.0, 43.9, 40.5, 39.5, 30.6, 30.2, 26.2.

(*R*)-3-(Methoxymethoxy)hex-5-enal (15):

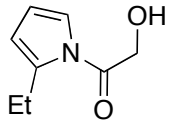


15

To a solution of the previously obtained dithiane (2.50 g, 10.08 mmol) in a $MeCN/H_2O$ mixture (9:1, 135 mL) were successively added MeI (6.27 mL, 100.8 mmol) and $CaCO_3$ (5.04 g,

50.38 mmol). The mixture was heated at 45 °C for 4 hours, then allowed to cool down to rt and finally concentrated under reduced pressure to remove the bulk of CH_3CN. The resulting mixture was then extracted with Et_2O (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by flash chromatography on silica gel (petroleum ether/EtOAc : 98/2) furnished 1.36 g (85%) of the desired aldehyde **15** as a colorless oil. The spectroscopic data matched those reported in the literature for its enantiomer.[2] {$[\alpha]_D^{25}$ = – 42.8 (*c* 1.96, $CHCl_3$); Lit[2] $[\alpha]_D^{25}$ = + 38.9 (*c* 1.00, $CHCl_3$) for its enantiomer}.

1-(2-Ethyl-1*H*-pyrrol-1-yl)-2-hydroxyethanone (16):



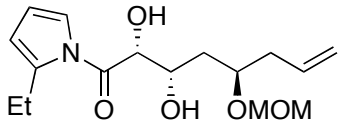
16

To a solution of ethyl pyrrole (500 mg, 5.25 mmol) in THF (11 mL) at 0 ºC was added *n*-BuLi (2.5M in hexanes, 2.10 mL, 5.25 mmol) dropwise. The brown solution was stirred at 0 ºC for 15 min at which time it was cannulated into a solution of benzyloxyacetyl chloride (777 µL, 5.00 mmol) in THF (3 mL) at 0 ºC. The solution was allowed to warm to room temperature and was stirred overnight. The resulting brown solution was poured into water and extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. Purification of the residue by flash column chromatography (petroleum ether/EtOAc : 99/1) provided 929 mg (76%) of 2-(benzyloxy)-1-(2-ethyl-1*H*-pyrrol-1-yl)ethanone as a red oil. This oil (929 mg, 3.83 mmol) was subsequently dissolved in CH_2Cl_2 (30 mL) and cooled to -78 ºC. BCl_3 (11.5 mL, 11.5 mmol, 1.0M in heptane) was added dropwise, and the resulting solution was stirred at -78 ºC for 1 h. The reaction mixture was hydrolyzed by adding methanol (2 mL) and the solution was allowed to warm to room temperature. The mixture was diluted with EtOAc and the resulting solution was washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 90/10) provided 405 mg (69%) of the title compound **16** as a red-orange oil, which solidified to a tan solid.

[2] Nicolaou, K. C.; Lim, Y. H.; Piper, J. L.; Papageorgiou, C. D. *J. Am. Chem. Soc.* **2007**, *129*, 4001–4013.

mp = 48-49 ºC; **R*f*** = 0.30 (petroleum ether/EtOAc : 5/1); **IR (neat):** ν 3416, 3148, 3100, 2969, 2921, 2873, 1726, 1506, 1416, 1286, 1087; **^{1}H NMR (400 MHz, $CHCl_3$):** δ 6.87 (d, *J* = 1.4 Hz, 1H), 6.23 (t, *J* = 1.4 Hz, 3H), 6.06 (d, *J* = 1.4 Hz, 1H), 4.65 (d, *J* = 4.3 Hz, 2H), 3.24 (s, 1H), 2.95 (q, *J* = 7.3 Hz, 2H), 1.25 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR (100 MHz, $CHCl_3$):** δ 171.5, 139.6, 117.4, 113.2, 111.0, 61.6, 22.6, 12.7.

(2*R*,3*S*,5*R*)-1-(2-ethyl-1*H*-pyrrol-1-yl)-2,3-dihydroxy-5-(methoxymethoxy)oct-7-en-1-one (17):



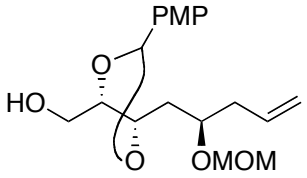
17

(*R*,*R*)-Prophenol ligand (30 mg, 0.047 mmol) was placed under argon and THF (500 µL) was added. Diethylzinc (1.0 M in hexanes, 95 µL, 0.095 mmol) was added dropwise at rt and the reaction mixture was stirred for 20 min to give the dinuclear zinc catalyst as a yellow solution. Separately, powdered molecular sieves (4Å, 50 mg) were placed into a flame-dried flask followed by acyl pyrrole **16** (63 mg, 0.411 mmol) and the flask was placed under argon. Aldehyde **15** (50 mg, 0.316 mmol) in THF (500 µL) was then added to the acyl pyrrole/molecular sieves mixture in one portion. The resulting mixture was stirred vigorously and the catalyst was added dropwise *via* syringe. After stirring at rt for 12 hours, the reaction mixture was hydrolyzed by adding a 1M aqueous solution of HCl (2 mL) and the mixture was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (petroleum ether/EtOAc : 90/10 to 70/30) provided 1,2-diol **17** as a mixture of two inseparable diastereoisomers (52.1 mg, 53%) in an 10:1 ratio as determined by the ratio of the NMR peaks at δ 6.97 and 7.06 ppm (brown solid).

mp = 54 °C; **$[\alpha]_D^{25}$** = –25.7 (*c* 0.75, $CHCl_3$); **R*f*** = 0.20 (petroleum ether/EtOAc : 80/20); **IR (neat)** : ν 3375, 2928, 1726, 1641, 1502, 1450, 1420, 1377, 1322, 1252, 1147, 1125, 1094, 1040, 914, 872, 813, 704 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.97 (dd, *J* = 3.6, 1.6 Hz, 1H), 6.20 (t, *J* = 3.6 Hz, 1H), 6.04 (m, 1H), 5.76 (ddt, *J* = 16.8, 10.4, 7.2 Hz, 1H), 5.12-5.06 (m, 2H), 4.66 (dd, *J* = 7.6, 1.6 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.23 (m, 1H), 3.85 (m, 1H), 3.69 (d, *J* = 7.6 Hz, OH), 3.27 (s, 3H), 2.97-2.90 (m, 2H+OH), 2.41-2.27 (m, 2H), 1.97 (ddd, *J* = 14.8, 10.8, 2.8 Hz, 1H), 1.70 (ddd, *J* = 14.8, 9.6, 2.8 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 172.5, 140.1, 134.1, 119.1, 118.2, 112.9, 111.4, 96.8, 75.3, 74.0, 69.4,

56.0, 39.8, 38.5, 22.8, 13.1; **HRMS** (ESI): Calcd. for $C_{16}H_{25}NO_5Na$ [M + Na]$^+$: 334.1620, found: 334.1630.

{(5*S*)-5-[(*R*)-2-(Methoxymethoxy)pent-4-enyl]]-2-(4-methoxyphenyl)-1,3-dioxolan-4-yl}methanol:



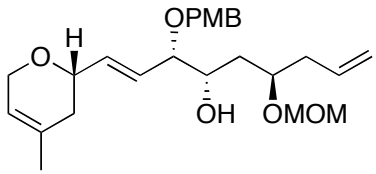
To a solution of diol **17** (52.0 mg, 0.167 mmol) in CH_2Cl_2 (3 mL) was added *p*-anisaldehyde dimethylacetal (34 μL, 0.200 mmol) followed by camphor-10-sulfonic acid (4 mg, 0.0167 mmol) at rt. After stirring for 1 h, triethylamine (50 μL) was added and the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 95/5) furnished 58 mg (81%) of the desired PMP-acetal as a 3.5:1 mixture of diastereoisomers and as a colorless oil.

To a slurry of sodium borohydride (8 mg, 0.219 mmol) in THF (2 mL) was added a solution of the previously obtained acyl pyrrole (47 mg, 0.110 mmol) in THF (2 mL) at 0 ºC. The reaction mixture was stirred at this temperature for 4 hours and then warmed to rt overnight. A saturated aqueous solution potassium carbonate was then added and the aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 60/40) furnished 32 mg (86%) of the title compound as a 3:1 mixture of diasteroisomers (colorless oil).

Analysis for the major diastereoisomer:

R*f* = 0.25 (petroleum ether/EtOAc : 60/40); **IR (neat)** : ν 3461, 2921, 1728, 1640, 1615, 1516, 1439, 1382, 1304, 1250, 1153, 1099, 1036, 918, 831 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 (m, 2H), 6.90 (m, 2H), 5.87 (s, 1H), 5.81 (m, 1H), 5.12-5.07 (m, 2H), 4.71 (m_{systAB}, 2H), 4.18 (ddd, *J* = 11.2, 7.6, 4.0 Hz, 1H), 3.96-3.85 (m, 2H), 3.81 (s, 3H), 3.80 (br s, 1H), 3.73 (br m, 1H), 3.39 (s, 3H), 2.37 (m, 2H), 2.17 (br s, OH), 1.88-1.75 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 160.7, 134.2, 130.0, 128.3 (2C), 118.0, 114.0 (2C), 103.7, 96.3, 82.0, 75.9, 74.6, 62.3, 55.9, 55.6, 39.9, 38.2; **HRMS** (ESI): Calcd. for $C_{18}H_{26}O_6Na$ [M + Na]$^+$: 361.1627, found: 361.1627.

(3*S*,4*S*,6*R*,*E*)-3-(4-Methoxybenzyloxy)-6-(methoxymethoxy)-1-[(*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl]nona-1,8-dien-4-ol (18):



18

To a solution of the previously obtained alcohol (20 mg, 0.059 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added Dess-Martin periodinane (50 mg, 0.118 mmol) in one portion. The cold bath was removed and the solution was stirred for 3 hours at rt. The reaction mixture was poured into a 1/1 mixture of a saturated aqueous solution of $NaHCO_3$ and a saturated aqueous solution of sodium thiosulfate and Et_2O (5 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude aldehyde **7** (18 mg, colorless oil) was used in the next step without further purification.

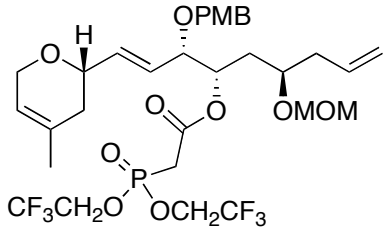
To a solution of sulfone **6** (25 mg, 0.0767 mmol) in a DMF/HMPA mixture (3/1, 665 µL) was added a freshly prepared solution of LiHMDS (89 µL, 1.0M in THF) at -35 °C. This was immediately followed by the addition of the previously obtained aldehyde in a DMF/HMPA mixture (3/1, 665 µL) dropwise *via* syringe. The reaction mixture was allowed to warm slowly to rt and was stirred for 12 hours. Water and Et_2O were added, and the layers were separated. The aqueous phase was extracted with Et_2O (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 95/5 to 90/10) furnished 16.2 mg (64%, 2 steps) of the desired (*E*)-configured alkene as a colorless oil.

To a solution of the previously obtained PMP-acetal (101 mg, 0.235 mmol) in CH_2Cl_2 (10 mL) was added DIBAL-H (1.0M in hexanes, 704 µL, 0.704 mmol) dropwise at -78 C. After stirring for 5 min at this temperature, the cold bath was replaced by an ice bath. After stirring at 0 °C for 30 min, some more DIBAL-H (1.0M in hexanes, 704 µL, 0.704 mmol) was added and the mixture was stirred for 2.5 h. More DIBAL-H (1.0M in hexanes, 704 µL, 0.704 mmol) was again added and the mixture was stirred for further 2 h. The reaction mixture was hydrolyzed by adding a saturated aqueous solution of Rochelle's salt. The mixture was diluted with Et_2O and was stirred at rt for 1 h. The aqueous phase was extracted with Et_2O (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 80/20) furnished 62 mg (61%) of the desired alcohol **18** along with 21 mg (21%) of its regioisomer.

$[\alpha]_D^{25}$ = –27.9 (*c* 1.48, $CHCl_3$); **R*f*** = 0.25 (petroleum ether/EtOAc : 70/30); **IR (neat)** : 3467, 2924, 1612, 1513, 1442, 1379, 1301, 1248, 1101, 1036, 974, 915, 821 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.23 (m, 2H), 6.87 (m, 2H), 5.83 (dd, *J* = 16.0, 5.2 Hz, 1H), 5.79 (m, 1H), 5.61 (ddd, *J* = 16.0, 8.0, 1.2 Hz, 1H), 5.44 (br s, 1H), 5.10-5.03 (m, 2H), 4.68 (s, 2H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.27 (d, *J* = 11.6 Hz, 1H), 4.20 (br s, 2H), 4.08 (m, 1H), 3.92 (m, 1H), 3.80 (s, 3H), 3.76 (m, 1H), 3.59 (t_{app}, *J* = 7.2 Hz, 1H), 3.37 (s, 3H), 2.80 (br s, OH), 2.39-2.24 (m, 2H), 2.10 (m, 1H), 1.95 (m, 1H), 1.72 (s, 3H), 1.60-1.46 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.5, 136.6, 134.7, 131.5, 130.3, 129.8 (2C), 127.6, 119.9, 117.6, 114.1 (2C), 96.5, 83.5, 74.2, 73.4, 70.3, 70.1, 65.8, 55.9, 55.5, 40.1, 38.0, 35.9, 23.2; **HRMS** (ESI): Calcd. for $C_{25}H_{36}O_6Na$ $[M + Na]^+$: 455.2410, found: 455.2398.

(3*S*,4*S*,6*R*,*E*)-3-(4-Methoxybenzyloxy)-6-(methoxymethoxy)-1-[(*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl]nona-1,8-dien-4-yl-2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (5):



5

Alcohol **18** (65 mg, 0.150 mmol) and 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetic acid[3] (105 mg, 0.346 mmol) were azeotroped together three times with toluene in a round bottom flask. THF (15 mL) was added and *i*Pr_2NEt (120 µL, 0.690 mmol) followed by 2,4,6-trichlorobenzoylchloride (68 µL, 0.435 mmol) were then sequentially added at rt. The resulting mixture was stirred for 10 min at rt. The solvent was removed *in vacuo* and the residue was dissolved in benzene (15 mL). DMAP (126 mg, 1.035 mmol) was added in one portion at rt and the resulting white suspension was stirred for 2 hours. The mixture was then diluted with EtOAc and the resulting solution was successively washed with a saturated aqueous solution of sodium bicarbonate, a 1M solution of $KHSO_4$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash

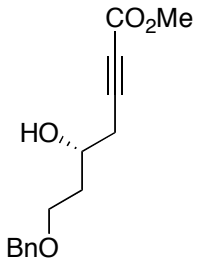
[3] Prepared by enzymatic reduction of the corresponding commercially available methyl ester according to: Sano, S.; Takemoto, Y.; Nagao, Y. ARKIVOC **2003**, *8*, 93–101.

chromatography on silica gel (petroleum ether/EtOAc : 80/20) provided 107 mg (99%) of the title compound **5** as a colorless oil.

$[\alpha]_D^{25}$ = –22.7 (*c* 1.06, $CHCl_3$); **R*f*** = 0.25 (petroleum ether/EtOAc : 80/20); **IR (neat)** : 3076, 2931, 2852, 1741, 1641, 1613, 1514, 1445, 1421, 1383, 1301, 1268, 1174, 1101, 1071, 1037, 964, 917, 888, 845, 783 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.20 (m, 2H), 6.85 (m, 2H), 5.83 (dd, *J* = 15.5, 5.5 Hz, 1H), 5.75 (m, 1H), 5.59 (ddd, *J* = 15.5, 7.5, 1.0 Hz, 1H), 5.43 (br s, 1H), 5.24 (ddd, *J* = 10.5, 5.0, 2.5 Hz, 1H), 5.10-5.05 (m, 2H), 4.64 (d, *J* = 7.0 Hz, 1H), 4.56 (d, *J* = 7.0 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.48-4.38 (m, 4H), 4.27 (d, *J* = 11.5 Hz, 1H), 4.18 (br s, 2H), 4.06 (m, 1H), 3.84 (dd, *J* = 7.0, 5.5 Hz, 1H), 3.80 (s, 3H), 3.57 (m, 1H), 3.34 (s, 3H), 3.18-3.06 (m, 2H), 2.37-2.24 (m, 2H), 2.05 (m, 1H), 1,90 (m, 1H), 1.77 (ddd, *J* = 14.5, 10.0, 2.5 Hz, 1H), 1.71 (s, 3H), 1.68 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 164.4 (d, $^2J_{PC}$ = 4.0 Hz), 159.5, 136.3, 134.1, 131.5, 130.1, 129.8 (2C), 126.5, 119.9, 118.1, 114.0 (2C), 96.6, 79.5, 74.1, 73.9, 73.4, 70.4, 65.9, 63.4-62.2 (m, 2C), 56.1, 55.5, 39.9, 35.9, 35.4, 34.2 (d, $^1J_{PC}$ = 143.9 Hz), 23.2, CF_3-signals missing (2C); **HRMS** (ESI): Calcd. for $C_{31}H_{41}O_{10}NaPF_6$ $[M + Na]^+$: 741.2224. Found: 741.2239.

III- Synthesis of the southern fragment 8

(*R*)-Methyl 7-(benzyloxy)-5-hydroxyhept-2-ynoate (20):



20

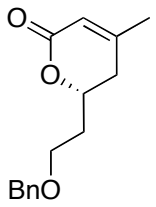
To a solution of methyl propiolate (1.57 g, 18.67 mmol) in THF (25 ml) at –78 °C was added *n*-butyllithium (1.59 M in hexanes, 11.74 ml, 18.67 mmol). After stirring for 20 min, BF_3•OEt_2 (2.37 mL, 18.67 mmol) was slowly added, followed by a solution of epoxide **19**[4] (1.11 g, 6.22 mmol) in dry THF (15 ml). The resulting deep red solution was stirred at –78 °C for 1 h, after which time the reaction mixture was hydrolyzed by adding a saturated aqueous solution of NH_4Cl. The mixture was allowed to warm to rt and the aqueous layer was extracted with EtOAc

[4] Prepared from D-aspartic acid according to: Frick, J. A.; Klassen, J. B.; Bathe, A.; Abramson, J. M.; Rapoport, H. *Synthesis* **1992**, 621.

(x3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (petroleum ether/Et_2O : 1/1) furnished 1.51 g (93%) of alcohol **20** as a reddish yellow oil.

$[\alpha]_D^{25}$ = –14.2 (*c* = 1.52, $CHCl_3$); **R*f*** = 0.8 (petroleum ether/EtOAc : 5/1); **IR (neat):** ν 3442, 2952, 2239, 1714, 1436, 1260, 1076 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.32-7.29 (m, 5H), 4.52 (s, 2H), 4.06-4.03 (m, 1H), 3.74 (s, 3H), 3.72-3.62 (m, 2H), 3.36 (d, *J* = 3.4 Hz, 1H), 2.57 (dd, *J* = 17.1, 5.9 Hz, 1H), 2.50 (dd, *J* = 17.1, 6.3 Hz), 1.91-1.84 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 153.9, 137.6, 128.4, 137.8, 127.6, 86.1, 74.4, 73.3, 69.1, 68.4, 52.6, 35.2, 27.1; **HRMS** (ESI): Calcd. for $C_{15}H_{18}O_4$ [M^+]: 262.1205, found: 262.1202.

(*R*)-6-[2-(Benzyloxy)ethyl]-4-methyl-5,6-dihydro-2*H*-pyran-2-one (21):

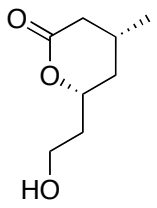


21

In a flame-dried flask were introduced freshly purified CuI (14.4 g, 75.4 mmol) and THF (200 mL), and the mixture was cooled to –78 °C. A solution of methyllithium (1.6 M in Et_2O, 88.8 ml, 141.6 mmol) was then added slowly and the mixture was subsequently warmed to 0 °C and stirred at this temperature for 10 min. The reaction mixture was cooled again to –78 °C, and a solution of alcohol **20** (6.2 g, 23.6 mmol) in dry THF (200 ml) was added dropwise. After stirring at –78 °C for 1 h, the reaction was quenched by adding a saturated aqueous solution of NH_4Cl and the resulting mixture was allowed to warm to rt. The biphasic mixture was filtered through a pad of Celite®, and the layers were separated. The aqueous layer was extracted with EtOAc (x2), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue then was dissolved in benzene (200 mL), acetic acid (0.5 mL) was added and the solution was stirred under gentle reflux overnight. The reaction mixture was then allowed to cool to rt, EtOAc (200 mL) was added and the resulting solution was filtered through a pad of $NaHCO_3$ and Celite®. The filtrated was concentrated under reduced pressure and the residue was purified by flash column chromatography (petroleum ether/EtOAc : 80/20) to give 5.45 g (94%) of lactone **21** as a light yellow oil.

$[\alpha]_D^{25}$ = +77.43 (*c* 1.1, CH_2Cl_2); **R*f*** = 0.15 (petroleum ether/EtOAc : 2/1); **IR (neat):** ν 2865, 1716, 1392, 1249, 1099 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37-7.29 (m, 5H), 5.80-5.79 (m, 1H), 4.63-4.59 (m, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 3.75-3.61 (m, 2H), 2.36 (ddq, *J* = 17.8, 11.9, 1.1 Hz, 1H), 2.20 (dd, *J* = 17.8, 3.7 Hz, 1H), 2.11-2.02 (m, 1H), 1.98-1.90 (m, 1H), 1.96 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.2, 157.2, 138.1, 128.4, 127.7, 116.4, 74.5, 73.1, 65.6, 35.0, 34.7, 22.9; **HRMS** (ESI): Calcd for $C_{15}H_{18}O_3$: 246.1256 [M^+], found: 246.1256.

(4*R*,6*R*)-6-(2-Hydroxyethyl)-4-methyl-tetrahydro-2*H*-pyran-2-one (22):

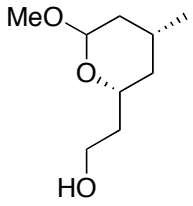


22

To a solution of unsaturated lactone **21** (4.16 g, 16.9 mmol) in EtOAc (100 mL) was added $Pd(OH)_2$ (1.80 g) and the flask was flushed with hydrogen gas several times. After stirring under hydrogen gas (under a balloon pressure) at rt overnight, the reaction mixture was filtered through a pad of Celite®, and the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography (100% EtOAc) furnished 2.59 g (97%) of the saturated lactone **22** as a clear colorless oil and as a single diastereoisomer.

$[\alpha]_D^{25}$ = –38.2 (*c* 1.06, CH_2Cl_2); **R*f*** = 0.26 (petroleum ether/EtOAc : 5/1); **IR (neat):** ν 3424, 2956, 1727, 1250, 1087, 1057 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.52 (dddd, *J* = 11.7, 7.8, 4.6, 2.9 Hz, 1H), 3.88 (ddd, *J* = 10.8, 7.5, 5.2 Hz, 1H), 3.81 ($quint_{app}$, *J* = 5.5 Hz, 1H), 2.74-2.65 (s, 1H), 2.13-1.82 (m, 1H), 1.04 (d, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.3, 78.2, 58.7, 38.5, 38.0, 37.2, 26.7, 21.6; **Elemental Analysis:** Calcd for $C_{15}H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.56; H, 8.86.

2-[(2*R*,4*R*)-6-Methoxy-4-methyltetrahydro-2*H*-pyran-2-yl]ethanol (23):

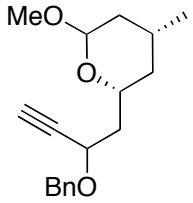


23

To a solution of lactone **22** (3.50 g, 22.1 mmol) in CH_2Cl_2 (260 mL) at -78 ºC was added DIBAL-H (1M in toluene, 48.7 mL, 48.6 mmol) dropwise over 1 h using a syringe pump. Upon completion of the addition, the reaction was stirred for another hour at -78 ºC. MeOH (8.75 mL) was then added and the reaction was allowed to warm to room temperature. Water (8.75 mL) and Celite® were subsequently added and the mixture was stirred for 15 min at rt. The reaction mixture was filtered and concentrated *in vacuo*. The resulting crude residue was dissolved in dry methanol (260 mL), a catalytic amount of Dowex 50W x 8 was added (20 mg) and the reaction was stirred for 12 h at rt. The reaction mixture was filtered and concentrated to yield 3.81 g (99%) of acetal **23** as a colorless oil.

R*f* = 0.34-0.41 (petroleum ether/EtOAc : 50/50); **IR (neat):** ν 3442, 2926, 1443, 1392, 1126, 1057, 992 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** (mixture of diastereomers): δ 4.75 (d, *J* = 3.4 Hz, 0.68H), 4.33 (dd, *J* = 9.6, 2.1 Hz, 0.32H), 3.94 (dddd, *J* = 11.6, 8.7, 3.8, 2.1 Hz, 0.68H), 3.82-3.76 (m, 2H), 3.63 (dddd, *J* = 11.1, 8.7, 3.8, 2.1 Hz, 0.32H), 3.48 (s, 0.96H), 3.62 (s, 2.04H), 2.83 (br s, 2.04H), 2.62 (br s, 0.32H), 2.01-1.65 (m, 4H), 1.60-1.53 (m, 1H), 1.08-1.98 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 0.96H), 0.89 (d, *J* = 6.6 Hz, 2.04H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 103.0, 98.5, 74.6, 69.0, 61.3, 60.7, 56.1, 54.5, 39.8, 39.5, 39.8, 38.0, 37.8, 37.7, 28.9, 24.2, 22.0, 21.7; HRMS (ESI): Calcd for $C_9H_{18}O_3$ [M^+]: 174.1256, found: 147.1258.

(2*R*,4*R*)-2-[2-(Benzyloxy)but-3-ynyl]-6-methoxy-4-methyltetrahydro-2*H*-pyran (24):



24

To a solution of alcohol **23** (2.40 g, 13.77 mmol) in CH_2Cl_2 (24 mL) at -15 °C was added KBr (161 mg, 1.38 mmol) dissolved in H_2O (2.4 mL). TEMPO (108 mg, 0.689 mmol) was then added, followed by sodium hypochlorite (1.6M in H_2O, 11.2 mL, 17.90 mmol) and solid $NaHCO_3$

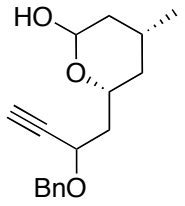
(347 mg, 4.13 mmol). The resulting mixture was stirred at -15 °C for 10 min, and the reaction was then allowed to warm to rt. After stirring at rt for 10 min, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 2.31 g (97%) of the desired aldehyde as a light yellow oil, which was used in the next step without further purification.

To a solution of the obtained aldehyde (2.31 g, 13.42 mmol) in THF (120 ml) at –78 °C was added a solution of ethynylmagnesium bromide (0.52 M in THF, 53 mL, 27.54 mmol) dropwise *via* a syringe. The reaction mixture was allowed to warm slowly to rt over 12 hours and was then hydrolyzed by adding a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with EtOAc (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by flash chromatography on silica gel (petroleum ether/EtOAc : 80/20) provided 2.05 g (77%) of the desired propargylic alcohol as a mixture of four diastereoisomers.

To a suspension of sodium hydride (60% in mineral oil, 990 mg, 24.82 mmol) in DMF (25 ml) at 0 °C was added a solution of the previously obtained propargylic alcohol (2.46 g, 12.41 mmol) in DMF (50 mL) slowly *via* syringe. After stirring for 20 min, benzyl bromide (2.97 ml, 24.82 mmol) was added dropwise and the resulting mixture was stirred for 2 hours at 0 °C. The reaction mixture was then diluted with Et_2O and was hydrolyzed by adding a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with Et_2O (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 98/2 to 95/5) furnished 3.45 g (96%) of benzyl ether **24** as a mixture of four diastereoisomers. The diastereomeric ratio was 0.44 : 0.21 : 0.19 : 0.16 as determined by ^{1}H NMR integration of the acetylenic proton signals.

R*f* = 0.40-0.55 (petroleum ether/EtOAc : 90/10); **IR (neat):** ν 3290, 2926, 1455, 1172, 1073, 1056 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38-7.27 (m, 5H), 4.84-4.79 (m, 1H), 4.70 (d, *J* = 3.2 Hz, 0.62H), 4.56-4.36 (m, 2H), 4.27 (dd, *J* = 9.7, 2.0 Hz, 0.2H), 4.17 (dd, *J* = 9.6, 2.0 Hz, 0.16H), 4.04 -3.57 (m, 1H), 3.44 (s, 0.51H), 3.35 (s, 1.19H), 3.28 (s, 0.43H), 3.21 (s, 0.56H), 2.51 (d, *J* = 2.1 Hz, 0.44H), 2.49 (d, *J* = 2.0 Hz, 0.19H), 2.47 (d, *J* = 2.1 Hz, 0.21H), 2.45 (d, *J* = 2.0 Hz, 0.16H), 2.17-1.49 (m, 5H), 1.25-0.85 (m, 5H); **Elemental Analysis:** Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.75; H, 8.14.

(4*R*,6*R*)-6-[2-(Benzyloxy)but-3-ynyl]-4-methyl-tetrahydro-2*H*-pyran-2-ol (25):

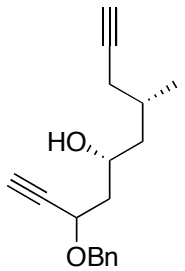


25

To a solution of acetal **24** (3.97 g, 0.042 mmol) in acetic acid (70 mL) in a Schlenk flask was added a solution of sulfuric acid (1M in H_2O, 25 mL) and the mixture was stirred at 80 °C for 3 hours. The reaction mixture was allowed to cool down to rt and was diluted with CH_2Cl_2. The resulting solution was washed several times with a saturated aqueous solution of $NaHCO_3$ until complete neutralization. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 90/10) furnished 3.09 g (82%) of hemiacetal **25** as a mixture of four diastereoisomers. The diastereomeric ratio was 0.34 : 0.30 : 0.20 : 0.16 as judged by ^{1}H NMR integration of the acetylenic proton signals.

R*f* = 0.25 (petroleum ether/EtOAc : 80/20); **IR(neat):** ν 3418, 3290, 2926, 1455, 1072, 974, 737, 699 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.27 (m, 5H), 5.28 (br d, *J* = 2.9 Hz, 0.20H), 5.12 (br d, *J* = 2.7 Hz, 0.16H), 4.82-4.77 (m, 1H), 4.43 (br d, *J* = 9.6 Hz, 0.34H), 4.53-4.46 (m, 1.30H), 4.39-4.27 (m, 1H), 4.23 (dddd, *J* = 11.3, 9.0, 4.0, 2.0 Hz, 0.30H), 4.11-4.05 (m, 0.16H), 3.69 (dddd, *J* = 11.0, 8.9, 4.1, 2.1 Hz, 0.34H), 3.59 (dddd, *J* = 11.6, 9.8, 3.1, 2.0 Hz, 0.20H), 2.50 (d, *J* = 2.1 Hz, 0.30H), 2.49 (d, *J* = 2.0 Hz, 0.34H), 2.44 (d, *J* = 2.0 Hz, 0.16H), 2.43 (d, *J* = 2.1 Hz, 0.20H), 2.15-0.77 (m, 10H); **HRMS (ESI):** Calcd for $C_{17}H_{22}O_3Na$ $[M + Na]^+$: 297.1237, found: 297.1230.

(5*R*,7*S*)-3-(Benzyloxy)-7-methyldeca-1,9-diyn-5-ol (10) :

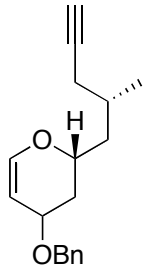


10

A mixture of hemiketal **25** (781 mg, 2.85 mmol), potassium carbonate (3.94 g, 28.48 mmol) and methanol (28 ml) was placed in a round bottom flask, and was warmed to 60 °C. Neat dimethyl-1-diazo-2-oxopropylphosphonate (5.5 g, 28.48 mmol) was then slowly added over a period of 24 hours using a syringe pump. The reaction mixture was allowed to cool to rt, diluted with ethyl acetate and hydrolyzed by adding water. The aqueous layer was extracted with EtOAc (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 90/10) furnished 438 mg (57%) of diyne **10** as a mixture of two diastereoisomers (dr = 0.55 : 0.45) along with 136 mg (17%) of recovered starting material **255** (yield = 69% brsm)

R*f* = 0.40 (petroleum ether/EtOAc : 5/1); **IR (neat)**: ν 3487, 3296, 2925, 1724, 1414, 1279, 1072 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.32 (m, 5H), 4.69 (AXq, *J* = 11.4 Hz, Δν = 133.9 Hz, 0.55H), 4.67 (AXq, *J* = 11.6 Hz, Δν =135.1 Hz, 0.45H), 4.41-4.32 (m, 1H), 4.15-4.13 (m, 0.45H), 3.96-3.91 (m, 0.55H), 2.55-2.54 (m, 1H), 2.19-2.14 (m, 2H), 2.03-1.84 (m, 3H), 1.29-1.21 (m, 3H), 1.03 (d, *J* = 6.6 Hz, 1.35 H), 1.02 (d, *J* = 6.1 Hz, 1.65 H); **Elemental Analysis:** Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.97; H, 8.34.

(2*R*)-4-(Benzyloxy)-2-[(*S*)-2-methylpent-4-ynyl]-3,4-dihydro-2*H*-pyran (9):

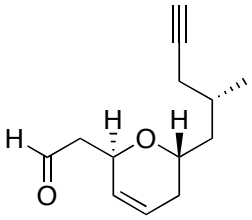


9

To a solution of diyne **10** (438 mg, 1.62 mmol) in degassed DMF (15 ml) in a Schlenk flask was added a mixture of $[Rh(COD)Cl]_2$ (64 mg, 0.081 mmol) and the bidentate phosphine ligand $[m\text{-}F(C_6H_6)]_2PCH_2CH_2P[m\text{-}F(C_6H_6)]_2$ (142 mg, 0.324 mmol). The Schlenk flask was then purged with argon, closed and was immersed in a preheated oil bath (85 °C). After 5 hours, the reaction mixture was allowed to cool down to rt, diluted with diethyl ether and subsequently hydrolyzed with water. The aqueous layer was extracted with ether (x3), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude residue by flash chromatography on deactivated silica gel (petroleum ether/EtOAc : 99/1) furnished 243 mg (55%) of dihydropyran **9** as a colorless oil.

R*f* = 0.67 (petroleum ether/EtOAc : 10/1); **IR (neat)**: ν 3301, 2926, 1640, 1243, 1081 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37-7.27 (m, 5H), 6.54 (d, *J* = 6.1 Hz, 0.9H), 6.39 (d, *J* = 6.3 Hz, 0.1H), 4.99 (ddd, *J* = 6.1, 5.3, 2.0 Hz, 0.9H), 4.86 (dt, *J* = 6.3, 1.9 Hz, 0.1H), 4.76 (ABq, *J* = 11.7, Δν = 41.8 Hz, 0.2H), 4.57 (ABq, *J* = 11.9, Δν = 31.3 Hz, 1.8H), 4.09-4.02 (m, 1H), 3.85 (deformed ddd, *J* = 5.3, 4.1, 1.8 Hz, 1.8H), 2.22 (ddd, *J* = 16.6. 6.1. 2.7 Hz, 0.9H), 2.16 (ddd, *J* = 16.6, 6.3, 2.7 Hz, 0.9H), 2.07-2.00 (m, 1H), 1.98(t, *J* = 2.7 Hz, 0.9H), 1.95 (ddd, *J* = 14.3, 3.7, 1.8 Hz, 0.9H), 1.79 (ddd, *J* = 14.0, 9.8, 4.7 Hz, 0.9H), 1.58 (ddd, *J* = 14.3, 12.0, 4.1 Hz, 0.9H), 1.36 (ddd, *J* = 14.0, 9.5, 3.5 Hz, 0.9H), 1.05 (d, *J* = 6.6 Hz, 2.7H), 1.02 (d, *J* = 6.7 Hz, 0.3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 147.3, 138.8, 128.4, 127.7, 127.6, 127.5, 100.2, 82.9, 69.4, 69.4, 66.4, 41.3, 34.8, 28.6, 26.5, 18.9; **HRMS** (ESI): Calcd. for $C_{11}H_{15}O_2$ [M – $PhCH_2$]: 179.1072, found: 179.1071.

2-{(2*R*,6*R*)-6-[(*S*)-2-Methylpent-4-ynyl]-5,6-dihydro-2*H*-pyran-2-yl}acetaldehyde (8):



8

To a solution of dihydropyrane **9** (64 mg, 0.237 mmol) and *tert*-butyldimethyl(vinyloxy)silane[5] (75 mg, 0.473 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added Montmorillonite K-10 (70 mg) in one portion. The cold bath was removed and the resulting slurry was stirred for 45 min at rt. The reaction mixture was then filtered over cotton and the resulting crude residue was purified by flash chromatography on silica gel (PE/EtOAc : 95/5 to 90/10) to provide 40 mg (82%) of the title aldehyde **8** as a colorless oil.

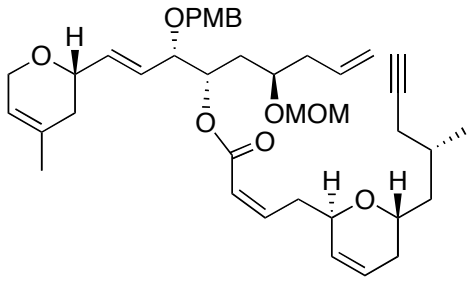
R*f* = 0.20 (petroleum ether/EtOAc : 90/10); **IR (neat)** : ν 3294, 3034, 2959, 2924, 2727, 1725, 1459, 1431, 13.91, 1260, 1214, 1179, 1096, 804, 701 cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 9.81 (dd, *J* = 3.6, 1.8 Hz, 1H), 5.88 (ddt, *J* = 10.2, 14.8, 2.4 Hz, 1H), 5.69 (m, 1H), 4.79 (br m, 1H), 3.75 (m, 1H), 2.74 (ddd, *J* = 16.2, 9.0, 3.6 Hz, 1H), 2.54 (ddd, *J* = 16.2, 4.8, 1.8 Hz, 1H), 2.17 (ddd, *J* = 16.8, 6.0, 3.0 Hz, 1H), 2.12 (ddd, *J* = 16.8, 6.6, 3.0 Hz, 1H), 2.03 (m, 1H), 1.98-1.87 (m, 2H), 1.96 (t, *J* = 3.0 Hz, 1H), 1.72 (ddd, *J* = 14.4, 10.2, 4.2 Hz, 1H), 1.28 (ddd, *J* = 14.4, 9.6, 3.6 Hz, 1H), 0.99 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.6, 125.4, 123.2, 80.6,

[5] Prepared according to: Srisiri, W.; Buyle Padias, A.; Hall, H. K. *J. Org. Chem.* **1994**, *59*, 5424–5435.

67.1, 65.4, 63.4, 45.6, 38.8, 28.5, 28.4, 26.0, 24.2; **HRMS** (ESI): Calcd. for $C_{13}H_{18}O_2Na$ [M + Na]$^+$: 229.1207, found: 229.1204.

IV- Completion of the synthesis of laulimalide and a potent analogue

(*Z*)-{(3*S*,4*S*,6*R*,*E*)-3-(4-Methoxybenzyloxy)-6-(methoxymethoxy)-1-[(*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl]nona-1,8-dien-4-yl}-4-{(2*R*,6*R*)-6-[(*S*)-2-methylpent-4-ynyl]-5,6-dihydro-2*H*-pyran-2-yl}but-2-enoate (4):



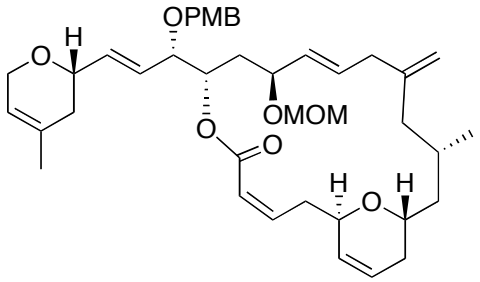
4

To a mixture of phosphonate **5** (146 mg, 0.204 mmol) and 18-crown-6 (247 mg, 0.934 mmol) in THF (7 mL) at -78 °C was added KHMDS (0.35 M in THF). After 45 min at this temperature, a solution of aldehyde **8** (35 mg, 0.1698 mmol) in THF (3.5 mL) was added dropwise and the mixture was stirred for 25 min. The reaction mixture was hydrolyzed by adding a saturated aqueous solution of ammonium chloride. Ethyl acetate was added and the layers were separated. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. ^{1}H NMR spectroscopy of the crude residue indicated the quantitative formation of the desired alkene as a 1/5 mixture of *E*/*Z* geometric isomers. Purification of the crude residue by flash chromatography on silica gel (petroleum ether/EtOAc : 95/5 to 80/20) furnished 56 mg (50%) of the desired *Z*-isomer **4** along with 14 mg (12%) of the undesired *E*-isomer (combined yield = 62%). Excess phosphonate **5** was entirely recovered.

$[\alpha]_D^{25}$ = – 73.3 (*c* 1.18, $CHCl_3$); **R*f*** = 0.45 (petroleum ether/EtOAc : 80/20); **IR (neat)** : ν 3294, 3032, 2927, 1717, 1643, 1613, 1514, 1439, 1380, 1364, 1300, 1248, 1212, 1168, 1093, 1037, 918, 819 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.21 (m, 2H), 6.84 (m, 2H), 6.42 (ddd, *J* = 11.5, 7.5, 6.5 Hz, 1H), 5.88 (dt, *J* = 11.5, 2.0 Hz, 1H), 5.81 (m, 1H), 5.76 (m, 1H), 5.67 (m, 1H), 5.59 (ddd, *J* = 16.0, 7.0, 1.8 Hz, 1H), 5.42 (br m, 1H), 5.24 (ddd, *J* = 10.0, 5.0, 2.5 Hz, 1H), 5.09-5.04 (m, 2H), 4.64 (d, *J* = 7.0 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 4.27 (br m, 1H), 4.18 (m, 2H), 4.05 (m, 1H), 3.87 (m, 1H), 3.80-3.74 (m, 1H), 3.79

(s, 3H), 3.55 (m, 1H), 3.34 (s, 3H), 2.97 (dddd, *J* = 16.5, 8.0, 4.5, 2.0 Hz, 1H), 2.88 (dddd, *J* = 16.0, 9.5, 6.5, 2.0 Hz, 1H), 2.33-2.28 (m, 2H), 2.21 (ddd, *J* = 16.5, 5.5, 2.5 Hz, 1H), 2.12 (ddd, *J* = 17.0, 7.0, 3.0 Hz, 1H), 2.07-1.85 (m, 5H), 1.96 (t, *J* = 3.5 Hz, 1H), 1.78-1.66 (m, 3H), 1.70 (s, 3H), 1.31-1.21 (m, 2H), 0.98 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 165.9, 159.3, 147.5, 135.4, 134.4, 131.5, 130.5, 129.7, 129.2 (2C), 127.1, 124.9, 121.0, 119.9, 117.8, 113.9 (2C), 96.7, 83.4, 79.5, 74.4, 73.6, 72.3, 71.2, 70.5, 69.6, 65.8, 65.6, 56.0, 55.5, 41.7, 40.1, 35.9, 35.6, 33.8, 31.4, 28.8, 26.8, 23.2, 19.1; **HRMS** (ESI): Calcd. for $C_{40}H_{54}O_8Na$ $[M + Na]^+$: 685.3716, found: 685.3715.

(1*R*,3*Z*,7*S*,9*S*,10*E*,15*S*,17*R*)-7-{(*S*,*E*)-1-(4-Methoxybenzyloxy)-3-[(*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl]allyl}-9-(methoxymethoxy)-15-methyl-13-methylene-6,21-dioxabicyclo[15.3.1]henicosa-3,10,19-trien-5-one (26):



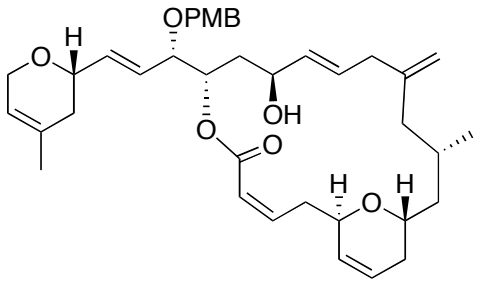
26

To a solution of enyne **4** (103 mg, 0.157 mmol) in freshly distilled acetone (160 mL) at 50 °C was added $CpRu(CH_3CN)_3PF_6$ (3.4 mg, 7.85 μmol) in one portion. The resulting light brown solution was stirred at this temperature for 15 min, at which time TLC indicated complete consumption of the starting material. The mixture was filtered over a short plug of silica gel to remove the Ru-catalyst and was concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 80/20) furnished 103 mg (99%) of the title 1,4-diene **26** as a colorless oil.

$[\alpha]_D^{25}$ = – 145 (*c* 2.56, $CHCl_3$); **R*f* =** 0.2 (petroleum ether/EtOAc : 80/20); **IR (neat)** : ν 2925, 1717, 1641, 1613, 1513, 1460, 1378, 1248, 1172, 1092, 1034, 975, 919, 820 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.22 (m, 2H), 6.84 (m, 2H), 6.28 (ddd, *J* = 11.5, 9.5, 5.5 Hz, 1H), 5.88-5.80 (m, 3H), 5.69 (m, 1H), 5.61 (ddd, *J* = 16.0, 7.0, 1.5 Hz, 1H), 5.58 (dd, *J* = 14.5, 7.0 Hz, 1H), 5.42 (br m, 1H), 5.31 (br dd, *J* = 15.5, 8.5 Hz, 1H), 5.17 (ddd, *J* = 9.5, 5.0, 2.5 Hz, 1H), 4.80 (br s, 1H), 4.69 (br s, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 7.0 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 4.30 (br m, 1H), 4.17 (m, 2H), 4.04 (m, 1H), 3.90 (m, 1H), 3.79 (s, 3H), 3.75 (br m, 1H), 3.42 (m, 1H), 3.32 (s, 3H), 2.81 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.68 (dd, *J* = 15.0,

7.0, 1H), 2.35 (m, 1H), 2.13 (m, 1H), 2.09-1.98 (m, 3H), 1.92-1.72 (m, 6H), 1.70 (s, 3H), 1.49 (dt, *J* = 14.0, 7.0 Hz, 1H), 1.19 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 165.7, 159.3, 146.5 (2C), 135.8, 133.2, 131.6, 130.8, 130.5, 129.6 (2C), 129.0, 126.8, 125.2, 122.4, 120.0, 113.9 (2C), 113.3, 93.3, 79.5, 74.9, 73.6, 72.8, 71.7, 70.5, 67.1, 65.8, 55.7, 55.5, 43.5, 43.2, 40.3, 36.2, 35.9, 34.7, 31.5, 28.8, 23.2, 20.7; **HRMS** (ESI): Calcd. for $C_{40}H_{54}O_8Na$ [M + Na]$^+$: 685.3716, found: 685.3720.

(1*R*,3*Z*,7*S*,9*S*,10*E*,15*S*,17*R*)-9-Hydroxy-7-{(*S*,*E*)-1-(4-methoxybenzyloxy)-3-[(*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl]allyl}-15-methyl-13-methylene-6,21-dioxabicyclo[15.3.1]henicosa-3,10,19-trien-5-one (3):



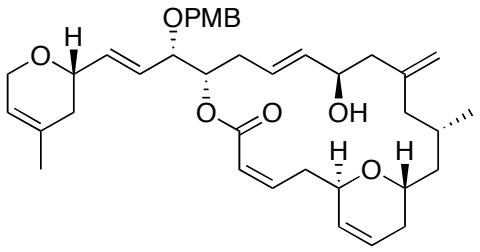
3

A solution of MOM-protected macrolactone **26** (103 mg, 0.156 mmol) in *tert*-BuOH (6.5 mL) was placed in a reaction vial containing a stir bar and PPTS (508 mg, 2.02 mmol) was added in one portion. The tube was sealed and subsequently immersed in a 85 °C oil bath. After stirring for 8 hours at this temperature, the reaction mixture was then allowed to cool to rt and was subsequently poured into water. The aqueous layer was extracted with EtOAc (x3) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc : 80/20 to 70/30) provided 63.6 mg (66%) of allylic alcohol **3** as a colorless oil.

$[\alpha]_D^{25}$ = –118 (*c* 1.14, $CHCl_3$); **R*f* =** 0.25 (petroleum ether/EtOAc : 70/30); **IR (neat)** : ν 3445, 3031, 2956, 2921, 2835, 1714, 1642, 1613, 1513, 1422, 1380, 1300, 1247, 1175, 1085, 1035, 973, 892, 819 cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.22 (m, 2H), 6.85 (m, 2H), 6.29 (ddd, *J* = 11.4, 9.5, 5.4 Hz, 1H), 5.88-5.81 (m, 3H), 5.69 (m, 1H), 5.65-5.55 (m, 2H), 5.50 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.42 (br m, 1H), 5.15 ($quint_{app}$, *J* = 3.6 Hz, 1H), 4.81 (br s, 1H), 4.70 (br s, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.34 (d, *J* = 11.4 Hz, 1H), 4.28 (br m, 1H), 4.18 (m, 2H), 4.14 (m, 1H), 4.06 (m, 1H), 3.95 (t_{app}, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 3.75 (br m, 1H), 3.42 (dt, *J* = 15.0, 9.0 Hz, 1H), 2.79 (dd, *J* = 15.0, 7.2 Hz, 1H), 2.67 (dd, *J* = 15.0, 7.2 Hz, 1H), 2.36 (m, 1H), 2.12-1.96 (m, 4H+OH), 1.92-1.72 (m, 5H), 1.70 (s, 3H), 1.53 (dt, *J* = 13.6, 6.0 Hz, 1H), 1.16 (dt, *J* = 13.8, 6.6 Hz, 1H),

0.86 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.8, 159.4, 146.7, 146.5, 135.9, 133.7, 131.5, 130.4, 130.3, 129.6 (2C), 128.9, 126.6, 125.1, 122.0, 119.9, 114.0 (2C), 113.1, 79.3, 73.5, 72.6, 72.2, 71.3, 70.6, 67.0, 65.8, 55.5, 43.6, 43.1, 40.2, 37.9, 35.9, 34.6, 31.4, 28.4, 23.2, 20.6; **HRMS** (ESI): Calcd. for $C_{38}H_{50}O_7Na$ $[M + Na]^+$: 641.3454, found: 641.3458.

(1*R*,3*Z*,7*S*,9*E*,11*R*,15*S*,17*R*)-11-Hydroxy-7-{(*S*,*E*)-1-(4-methoxybenzyloxy)-3-[(*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl]allyl}-15-methyl-13-methylene-6,21-dioxabicyclo[15.3.1]henicosa-3,9,19-trien-5-one (2):



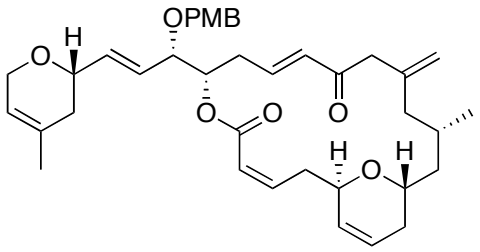
2

In the glove box, $O_3ReOSiPh_3$ (16.5 mg, 0.032 mmol, 1.0 equiv) was inserted into a flame-dried round bottom flask. Out of the glove box, Et_2O (2.5 mL) was added under argon. The flask was cooled to -50 °C and the solution was stirred at this temperature for 10 min. A solution of the allylic alcohol **3** (19.8 mg, 0.032 mmol, 1.0 equiv) in Et_2O (2.5 mL) was then added dropwise and the mixture was stirred for 5 min. The reaction mixture was quenched by successively adding silica gel and Et_3N (200 μL) and was allowed to warm to rt. After removal of the solvents *in vacuo*, the crude was analyzed by ^{1}H NMR which indicated the presence of the desired rearranged product **2** along with the starting material **3** in a 1:4 ratio in favor of the rearranged product **2**. Purification of the residue by flash chromatography on silica gel (Hexanes/EtOAc : 90/10 to 85/15) furnished the desired compound **2** (15.4 mg, 78%) as a colorless oil. Moreover, 3.9 mg of the starting material **3** could be recovered (yield = 97% brsm).

$[\alpha]_D^{25}$ = –85 (*c* 0.46, $CHCl_3$); **R*f* =** 0.2 (petroleum ether/EtOAc : 80/20); **IR (neat)** : ν 3439, 2958, 2921, 2854, 1718, 1644, 1613, 1513, 1421, 1381, 1297, 1250, 1213, 1169, 1085, 1036, 971, 811, 756 cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.21 (m, 2H), 6.86 (m, 2H), 6.31 (td, *J* = 10.8, 4.8 Hz, 1H), 5.88 (br d, *J* = 12.0 Hz, 1H), 5.85 (dd, *J* = 15.6, 5.4 Hz, 1H), 5.85-5.79 (m, 1H), 5.70 (m, 1H), 5.63-5.54 (m, 2H), 5.49 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.43 (br s, 1H), 5.09 (ddd, *J* = 7.8, 3.6, 2.4 Hz, 1H), 4.86 (s, 1H), 4.84 (s, 1H), 4.59 (d, *J* = 11.4 Hz, 2H), 4.31 (d, *J* = 12.0 Hz, 1H), 4.20 (br s, 2H), 4.15 (m, 1H), 4.12-4.06 (m, 2H), 3.83 (t_{app}, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 3.78 (sept, *J* = 4.2 Hz, 1H), 3.71 (m, 1H), 2.31 (m, 1H), 2.27-2.14 (m, 4H), 2.11-2.01 (m, 3H), 1.95-1.83 (m,

3H), 1.79-1.72 (m, 2H), 1.71 (s, 3H), 1.67 (ddd, *J* = 12.0, 7.8, 3.6 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.6, 159.4, 147.6, 144.6, 136.1, 135.9, 131.5, 130.4, 129.6 (2C), 128.6, 127.9, 126.7, 125.0, 121.7, 119.9, 115.8, 113.9 (2C), 79.5, 73.5, 72.9, 71.8, 70.3, 70.2, 67.8, 65.8, 55.5, 43.9, 40.7, 36.0, 34.3, 34.0, 31.6, 28.5, 23.2, 21.2; **HRMS** (ESI): Calcd. for $C_{38}H_{50}O_7Na$ $[M + Na]^+$: 641.3454, found: 641.3461.

(1*R*,3*Z*,7*S*,9*E*,15*S*,17*R*)-7-{(*S*,*E*)-1-(4-Methoxybenzyloxy)-3-[(*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl]allyl}-15-methyl-13-methylene-6,21-dioxabicyclo[15.3.1]henicosa-3,9,19-triene-5,11-dione:

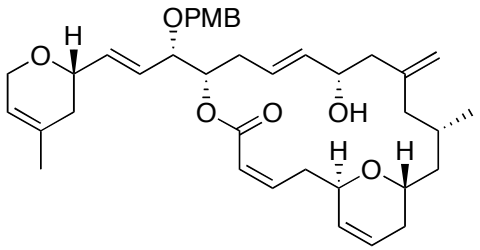


To a solution of allylic alcohol **2** (10.1 mg, 0.0163 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C was added Dess-Martin periodinane (14 mg, 0.0327 mmol, 2.0 equiv) in one portion. The resulting mixture was stirred for 2 hours at rt. The reaction mixture was poured into a 1/1 mixture of a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium thiosulfate and Et_2O (2 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (Hexanes/EtOAc : 80/20) furnished the desired title enone (9.6 mg, 96%) as a colorless oil.

$[\alpha]_D^{25}$ = –71 (*c* 0.84, $CHCl_3$); **R*f* =** 0.5 (petroleum ether/EtOAc 70:30); **IR (neat)** : ν 3032, 2921, 1719, 1671, 1640, 1614, 1513, 1421, 1380, 1248, 1212, 1168, 1087, 1035, 976, 896, 818 cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.22 (m, 2H), 6.86 (m, 2H), 6.72 (ddd, *J* = 16.2, 7.8, 6.6 Hz, 1H), 6.37 (ddd, *J* = 11.4, 10.2, 4.8 Hz, 1H), 6.09 (d, *J* = 16.2 Hz, 1H), 6.88-6.83 (m, 3H), 5.69 (m, 1H), 5.63 (ddd, *J* = 15.6, 7.2, 1.2 Hz, 1H), 5.43 (br s, 1H), 4.90 (s, 1H), 4.82 (s, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 4.26 (m, 1H), 4.20 (m, 2H), 4.08 (m, 1H), 3.92 (t_{app}, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.72 (m, 1H), 3.55 (dt, *J* = 15.6, 10.2 Hz, 1H), 3.25 (d, *J* = 15.6 Hz, 1H), 3.11 (d, *J* = 15.0 Hz, 1H), 2.54-2.44 (m, 2H), 2.34 (m, 1H), 2.09-2.00 (m, 3H), 1.95-1.86 (m, 2H), 1.78 (dd, J = 13.8, 10.2 Hz, 1H), 1.71 (s, 3H), 1.49 (ddd, *J* = 14.4, 8.4, 5.4 Hz, 1H), 1.19 (ddd, *J* = 14.4, 8.4, 2.0 Hz, 1H), 0.83 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.4,

165.6, 159.4, 148.8, 143.4, 142.1, 136.2, 132.1, 131.4, 130.2, 129.6 (2C), 128.8, 126.2, 125.4, 120.9, 119.9, 116.1, 114.0 (2C), 79.2, 73.4, 72.8, 72.3, 70.5, 66.6, 65.8, 55.5, 46.5, 44.7, 43.7, 35.9, 34.3, 33.6, 31.8, 28.1, 23.2, 19.9; **HRMS** (ESI): Calcd. for $C_{38}H_{48}O_7Na$ $[M + Na]^+$: 639.3298, found: 639.3316.

(1*R*,3*Z*,7*S*,9*E*,11*S*,15*S*,17*R*)-11-Hydroxy-7-{(*S*,*E*)-1-(4-methoxybenzyloxy)-3-[(*S*)-4-methyl-3,6-dihydro-2*H*-pyran-2-yl]allyl}-15-methyl-13-methylene-6,21-dioxabicyclo[15.3.1]henicosa-3,9,19-trien-5-one:

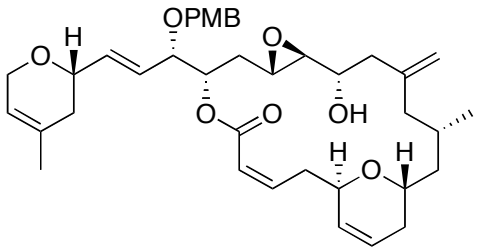


To a solution of the previously obtained α,β-unsaturated ketone (7.5 mg, 0.0122 mmol, 1.0 equiv) in THF (1.5 mL) were successively added (*R*)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 61 µL, 0.0609 mmol, 5.0 equiv) followed by BH_3•THF (1.0 M in THF, 43 µL, 0.0426 mmol, 3.5 equiv) slowly *via* syringe at 0 °C. The reaction mixture was stirred for 5 min at this temperature, and was hydrolyzed by adding H_2O (1.5 mL). The resulting mixture was warmed to rt, Et_2O was added and the organic phase was washed with a 1.0 M aqueous solution of HCl. The aqueous phase was extracted with Et_2O (3x) and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. ^{1}H NMR of the crude residue indicated the presence of only one diastereoisomer. Purification of the residue by flash column chromatography on silica gel (Hexanes/EtOAc : 85/15) furnished the titled allylic alcohol (7.3 mg, 97%) as a colorless oil.

$[\alpha]_D^{25}$ = – 105 (*c* 0.59, $CHCl_3$); **R*f* =** 0.2 (petroleum ether/EtOAc 80:20); **IR (neat)**: 3433, 2924, 2854, 1720, 1644, 1612, 1513, 1450, 1379, 1248, 1166, 1087, 1037, 974, 815 ν cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.21 (m, 2H), 6.85 (m, 2H), 6.32 (ddd, *J* = 11.4, 9.6, 5.4 Hz, 1H), 5.90 (d, *J* = 11.4 Hz, 1H), 5.84 (dd, *J* = 15.6, 5.4 Hz, 1H), 5.84-5.80 (m, 1H), 5.70 (m, 1H), 5.63-5.58 (m, 3H), 5.42 (br s, 1H), 5.07 (ddd, *J* = 10.2, 5.4, 3.0 Hz, 1H), 4.84 (s, 2H), 5.59 (d, *J* = 12.0 Hz, 1H), 4.31 (d, *J* = 11.4 Hz, 1H), 4.19 (br s, 2H), 4.18-4.10 (m, 2H), 4.07 (m, 1H), 3.89-3.83 (m, 2H), 3.80 (s, 3H), 3.53 (m, 1H), 2.35-2.18 (m, 5H), 2.15 (dd, *J* = 13.2, 4.2 Hz, 1H), 2.11 (dd, *J* = 14.4, 9.6 Hz, 1H), 2.07-2.01 (m, 1H), 1.90 (br d, *J* = 16.8 Hz, 1H), 1.85-1.71 (m, 3H), 1.70 (s, 3H), 1.64 (ddd, *J* = 13.8, 8.4, 4.8 Hz, 1H), 1.35-1.26 (m, 1H), 1.12 (ddd, *J* = 12.0, 7.8, 4.2 Hz, 1H),

0.85 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 165.6, 159.4, 146.9, 145.1, 135.8, 135.3, 131.5, 130.4, 129.7 (2C), 128.6, 127.2, 126.7, 124.9, 121.9, 119.9, 114.6, 114.0 (2C), 79.5, 74.1, 73.5, 71.4, 70.3, 70.0, 67.8, 65.9, 55.5, 45.0, 43.5, 42.4, 36.0, 34.5, 33.6, 31.1, 28.4, 23.2, 19.9; **HRMS** (ESI): Calcd. for $C_{38}H_{50}O_7Na$ $[M + Na]^+$: 641.3454, found: 641.3464.

Epoxide 27:



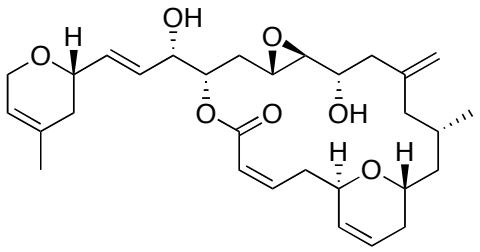
27

To a suspension of flame-dried 4 Å MS (85 mg) in CH_2Cl_2 (1.5 mL) at -20 °C were sequentially added (+)-diethyl-L-tartrate (18 μL, 0.0860 mmol) and Ti(O*i*Pr)$_4$ (21 μL, 0.0725 mmol). The resulting mixture was stirred for 15 min at this temperature and *tert*-butylhydroperoxide (5.5M in dodecane, 25 μL, 0.140 mmol) was then added dropwise. The mixture was stirred another 15 min and a solution of the previously obtained allylic alcohol (7.0 mg, 0.0113 mmol) in CH_2Cl_2 (3 mL) was subsequently added dropwise. After stirring for 1 hour at -20 °C, the reaction mixture was hydrolyzed by adding a mixture of a 4 N solution of sodium hydroxide (1.5 mL) and brine (1.5 mL). The resulting mixture was stirred at 0 °C for 1 hour, and EtOAc was added. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (Hexanes/EtOAc 80:20) yielded 6.4 mg (88%) of the title epoxide **27** as a colorless oil.

$[\alpha]_D^{25}$ = −141 (*c* 0.41, $CHCl_3$); **R*f*** = 0.25 (petroleum ether/EtOAc 80:20); **IR (neat)**: ν 3452, 2918, 1720, 1643, 1612, 1513, 1421, 1378, 1300, 1247, 1213, 1171, 1115, 1084, 1033, 977, 891, 814 cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.21 (m, 2H), 6.86 (m, 2H), 6.42 (dt, *J* = 10.8, 3.6Hz, 1H), 5.89 (br d, *J* = 11.4 Hz, 1H), 5.84 (dd, *J* = 15.6, 5.4 Hz, 1H), 5.83 (m, 1H), 5.68 (m, 1H), 5.59 (dd, *J* = 15.6, 6.6 Hz, 1H), 5.43 (br s, 1H), 5.21 (dd, *J* = 10.8, 4.8 Hz, 1H), 4.85 (s, 1H), 4.83 (s, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 4.32-4.28 (m, 1H), 4.19 (br s, 2H), 4.06 (m, 2H), 3.88 (t_{app}, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.79-3.75 (m, 1H+OH), 3.03 (m, 1H), 2.87 (m, 1H), 2.37 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 2.11-1.86 (m, 8H), 1.77 (dd,

J = 13.2, 10.2 Hz, 1H), 1.71 (s, 3H), 1.47-1.40 (m, 2H), 1.35-1.30 (m, 1H), 0.82 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 166.1, 159.4, 150.3, 145.2, 136.0, 131.5, 130.2, 129.7 (2C), 128.8, 126.3, 125.4, 121.0, 120.0, 114.0 (2C), 112.6, 79.3, 73.4, 71.1, 70.6, 68.1, 66.7, 65.9, 60.8, 55.5, 52.4, 45.9, 43.7, 37.3, 35.9, 33.9, 33.3, 31.9, 30.0, 23.2, 21.1; **HRMS** (ESI): Calcd. for $C_{38}H_{50}O_8Na$ $[M + Na]^+$: 657.3403, found: 657.3411.

Laulimalide (1):



1

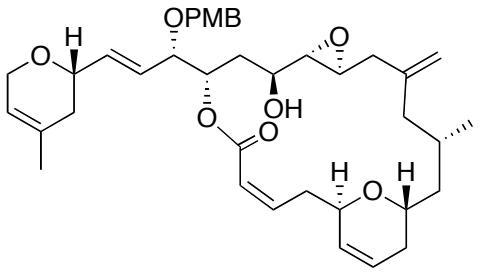
To a solution of the previously obtained PMB-ether **27** (5.4 mg, 8.52 μmol) in CH_2Cl_2 (1.5 mL), pH7 buffer (75 μL) and tert-BuOH (75 μL) was added DDQ (5.8 mg, 25.56 μmol) in one portion. The resulting green mixture was stirred at rt for 30 min. Another portion of DDQ (5.8 mg, 25.56 μmol) was added. After stirring for one hour, some more DDQ (5.8 mg, 25.56 μmol) was added and the mixture was stirred for another hour. The resulting orange suspension was then washed with a saturated aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (Hexanes/EtOAc : 80/20 to 50/50) furnished 3.9 mg (89%) of laulimalide (**1**) as a colorless oil. The analytical and spectroscopic data perfectly matched those reported in the literature.[6]

$[\alpha]_D^{25}$ = −193 (*c* 0.15, $CHCl_3$); **R*f*** = 0.2 (PE/EtOAc 50:50); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.44 (ddd, *J* = 11.4, 9.6, 3.6 Hz, 1H), 3.91 (m, 1H), 5.88 (ddd, *J* = 15.6, 6.4, 1.2 Hz, 1H), 5.86-5.82 (m, 1H), 5.75 (ddd, *J* = 15.6, 6.0, 1.2 Hz, 1H), 5.69 (m, 1H), 5.42 (br s, 1H), 5.16 (ddd, *J* = 11.4, 5.4, 1.8 Hz, 1H), 4.86 (s, 1H), 4.85 (s, 1H), 4.31 (m, 1H), 4.22 (q_{app}, *J* = 5.4 Hz, 1H), 4.20-4.16 (m, 2H), 4.08 (m, 1H), 4.03 (m, 1H), 3.79-3.69 (m, 2H), 3.07 (m, 1H), 2.90 (t, J = 2.4 Hz, 1H), 2.40-2.35 (m, 2H), 2.40-2.35 (m, 2H), 2.22 (m, 1H), 2.12 (br d, *J* = 15.6 Hz, 1H), 2.05-1.84 (m, 6H), 1.78 (dd, *J* = 13.2, 10.2 Hz, 1H), 1.70 (s, 3H), 1.49 (ddd, J = 14.4, 11.4, 9.6 Hz, 1H), 1.45 (m, 1H), 1.33 (ddd, J = 14.4, 4.2, 3.0 Hz, 1H), 0.83 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (125 MHz,**

[6] See references (1) and (3) in the manuscript.

$CDCl_3$): δ 166.0, 150.4, 144.8, 133.9, 131.2, 128.7, 128.5, 125.2, 120.5, 119.7, 112.5, 73.5, 73.1 (2C), 72.2, 67.9, 66.5, 65.6, 60.6, 52.0, 45.5, 43.4, 37.0, 35.6, 33.7, 33.4, 31.6, 29.5, 22.9, 20.7; **HRMS** (ESI): Calcd. for $C_{30}H_{42}O_7Na$ $[M + Na]^+$: 537.2828, found: 537.2825.

Epoxide 28:



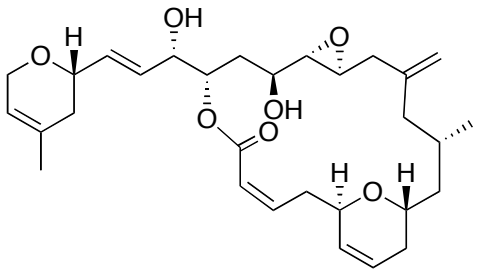
28

To a suspension of flame-dried 4 Å MS (100 mg) in CH_2Cl_2 (2 mL) at -20 °C were sequentially added (+)-diethyl-L-tartrate (28 μL, 0.134 mmol) and $Ti(OiPr)_4$ (34 μL, 0.113 mmol). The resulting mixture was stirred for 15 min at this temperature and *tert*-butylhydroperoxide (5.5M in dodecane, 40 μL, 0.218 mmol) was then added dropwise. The mixture was stirred another 15 min and a solution of allylic alcohol **3** (10.9 mg, 0.0176 mmol) in CH_2Cl_2 (4 mL) was subsequently added dropwise. After stirring for 1 hour at -20 °C, the reaction mixture was hydrolyzed by adding a mixture of a 4 N solution of sodium hydroxide (2 mL) and brine (2 mL). The resulting mixture was stirred at 0 °C for 1 hour, and EtOAc was added. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (Hexanes/EtOAc : 80/20); yielded 9.6 mg (86%) of epoxide **28** as a colorless oil.

$[\alpha]_D^{25}$ = –78.3 (*c* 0.49, $CHCl_3$); **R*f* =** 0.20 (petroleum ether/EtOAc : 70/30); **IR (neat)** : ν 3435, 2922, 1715, 1643, 1612, 1513, 1445, 1379, 1247, 1213, 1172, 1086, 1034, 974, 896, 821 cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.22 (m, 2H), 6.85 (m, 2H), 6.34 (ddd, *J* = 11.4, 9.6, 6.6 Hz, 1H), 5.91 (d, *J* = 12.0 Hz, 1H), 5.85 (dd, *J* = 15.6, 5.4 Hz, 1H), 5.83 (m, 1H), 5.67 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.64 (ddd, *J* = 15.6, 7.2, 0.6 Hz, 1H), 5.43 (br s, 1H), 5.24 ($quint_{app}$, *J* = 4.8 Hz, 1H), 4.91 (br s, 1H), 4.79 (br s, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.33 (d, *J* = 11.4 Hz, 1H), 4.24 (br m, 1H), 4.19 (br s, 2H), 4.06 (m, 1H), 3.93 (t_{app}, *J* = 6.0 Hz, 1H), 3.88 (m, 1H), 3.84 (m, 1H), 3.80 (s, 3H), 3.41 (dt, *J* = 13.8, 8.4 Hz, 1H), 2.99 (td, *J* = 6.0, 1.8 Hz, 1H), 2.87 (t, *J* = 2.4 Hz, 1H), 2.38 (m, 1H), 2.30-2.28 (m, 2H), 2.21-2.17 (m, 2H), 2.06 (m, 1H), 1.98 (ddd, *J* = 15.0, 6.0, 4.2

Hz, 1H), 1.92-1.72 (m, 5H), 1.71 (s, 3H), 1.68 (m, 1H), 1.57 (br s, OH), 1.11 (ddd, *J* = 13.8, 7.8, 6.0 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.9, 159.5, 147.2, 144.0, 136.1, 131.5, 130.2, 129.6 (2C), 128.8, 126.5, 124.8, 122.0, 119.9, 114.5, 114.0 (2C), 79.4, 73.5, 71.9, 71.5, 70.7, 67.5, 67.4, 65.9, 60.6, 55.5, 54.6, 44.7, 42.5, 38.4, 35.9, 34.7, 33.9, 31.1, 27.8, 23.2, 20.3; **HRMS** (ESI): Calcd. for $C_{38}H_{50}O_8Na$ [M + Na]$^+$: 657.3403, found: 657.3388.

Laulimalide analogue 29:

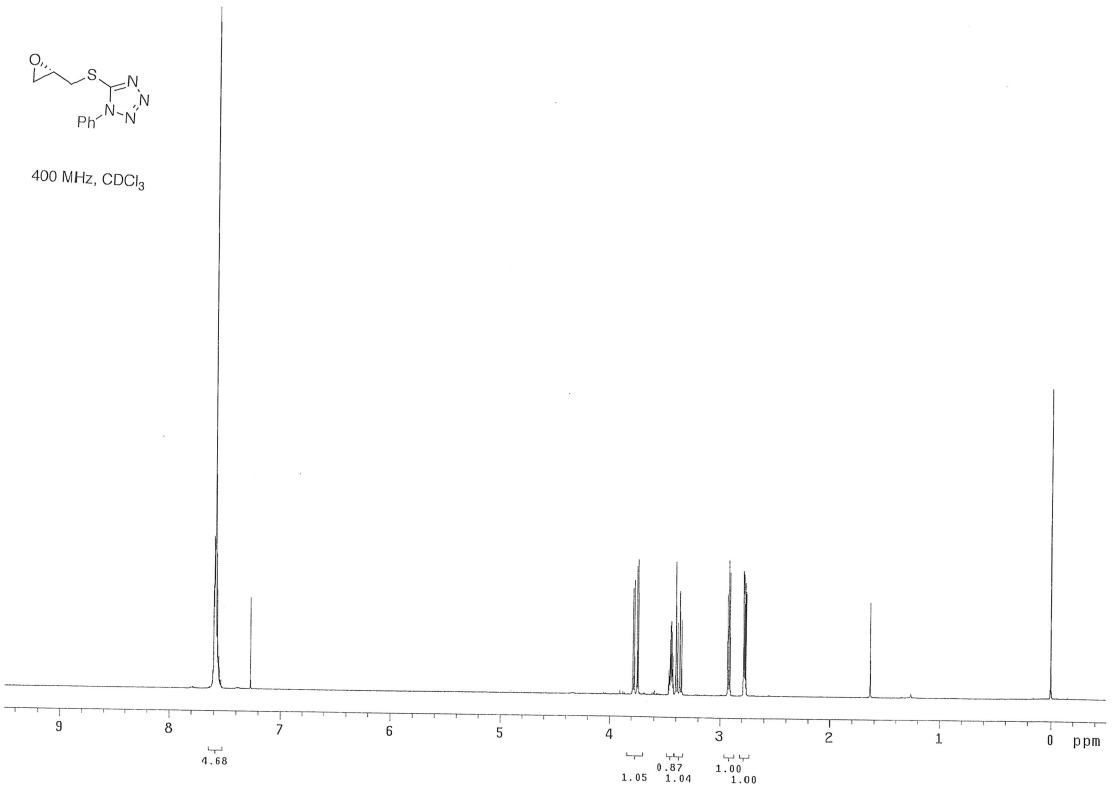


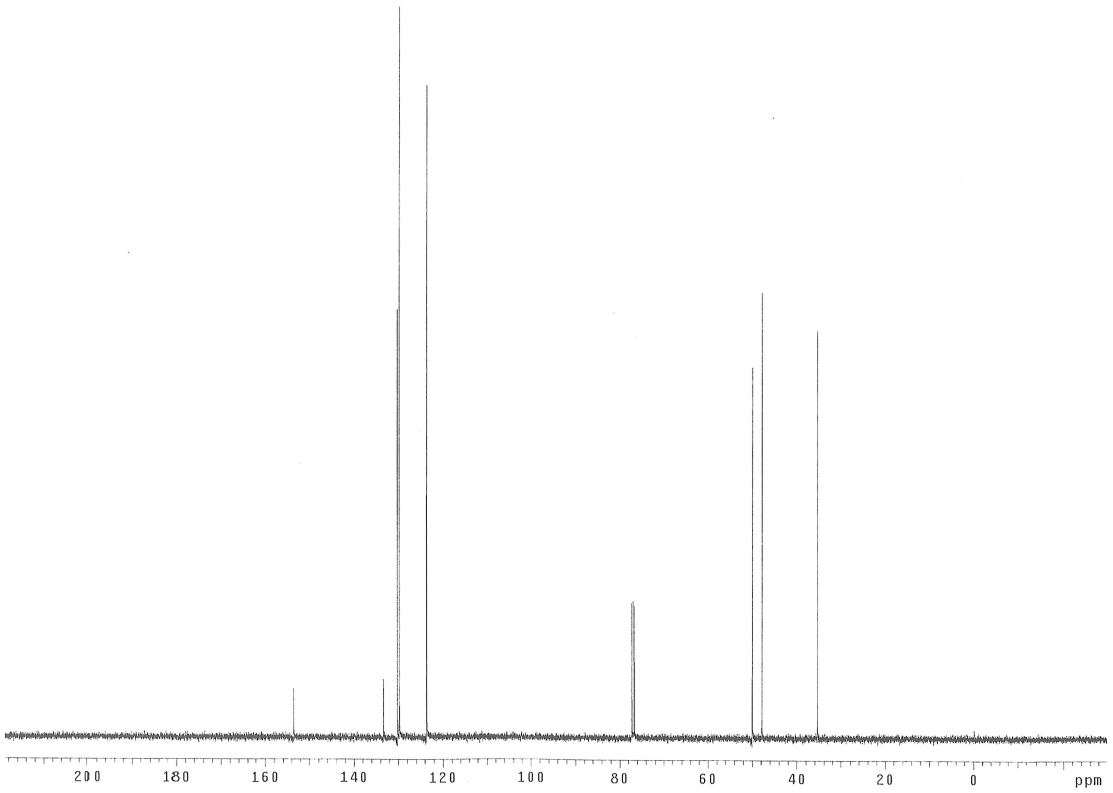
29

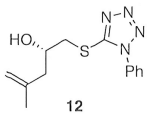
To a solution of epoxide **28** (5.0 mg, 7.89 μmol) in CH_2Cl_2 (1.5 mL) and pH7 buffer (75 μL) was added DDQ (5.3 mg, 23.66 μmol) in one portion. The resulting green mixture was stirred at rt for 3 hours. The resulting orange suspension was then washed with a saturated aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (Hexanes/EtOAc : 80/20 to 50/50) furnished 2.9 mg (71%) of the laulimalide analogue **29** as a colorless oil.

$[\alpha]_D^{25}$ = – 86 (*c* 0.21, $CHCl_3$); **R*f*** = 0.2 (petroleum ether/EtOAc 50:50); **IR (neat)**: ν 3397, 2921, 2852, 1714, 1644, 1417, 1381, 1264, 1214, 1171, 1086, 1035, 975 cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.34 (ddd, *J* = 11.4, 9.9, 6.0 Hz, 1H), 5.93 (d, *J* = 11.4 Hz, 1H), 5.89 (ddd, *J* = 15.6, 5.4, 1.2 Hz, 1H), 5.87-5.82 (m, 1H), 5.79 (ddd, *J* = 15.6, 5.4, 1.2 Hz, 1H), 5.70 (m, 1H), 5.41 (br s, 1H); 5.11 (m, 1H); 4.92 (s, 1H); 4.81 (s, 1H); 4.33 (m, 1H), 4.28 (m, 1H); 4.18 (br s, 2H), 4.05 (dt, *J* = 9.8, 4.7 Hz, 1H), 3.98 (br s, 1H), 3.79 (m, 1H), 3.44 (m, 1H), 3.00 (m, 1H); 2.91 (t, *J* = 2.6 Hz, 1H); 2.48 (br s, 1H, OH); 2.44-2.38 (m, 2H); 2.32 (br s, 1H, OH), 2.24-2.12 (m, 3H), 2.08-1.94 (m, 3H), 1.92-1.85 (m, 2H), 1.79 (m, 1H), 1.75-1.69 (m, 1H), 1.70 (s, 3H), 1.65 (m, 1H), 1.18 (m, 1H), 0.88 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 166.2, 147.3, 143.5, 133.8, 131.5, 129.2, 128.8, 124.9, 121.9, 119.9, 115.0, 73.9, 73.5, 73.0, 71.9, 67.4, 66.9, 65.8, 60.9, 54.3, 44.5, 43.2, 38.4, 35.9, 34.6, 33.9, 31.2, 27.8, 23.2, 20.3; **HRMS** (ESI): Calcd. for $C_{30}H_{42}O_7Na$ [M + Na]$^+$: 537.2828, found: 537.2843.

V- ^{1}H and ^{13}C spectra

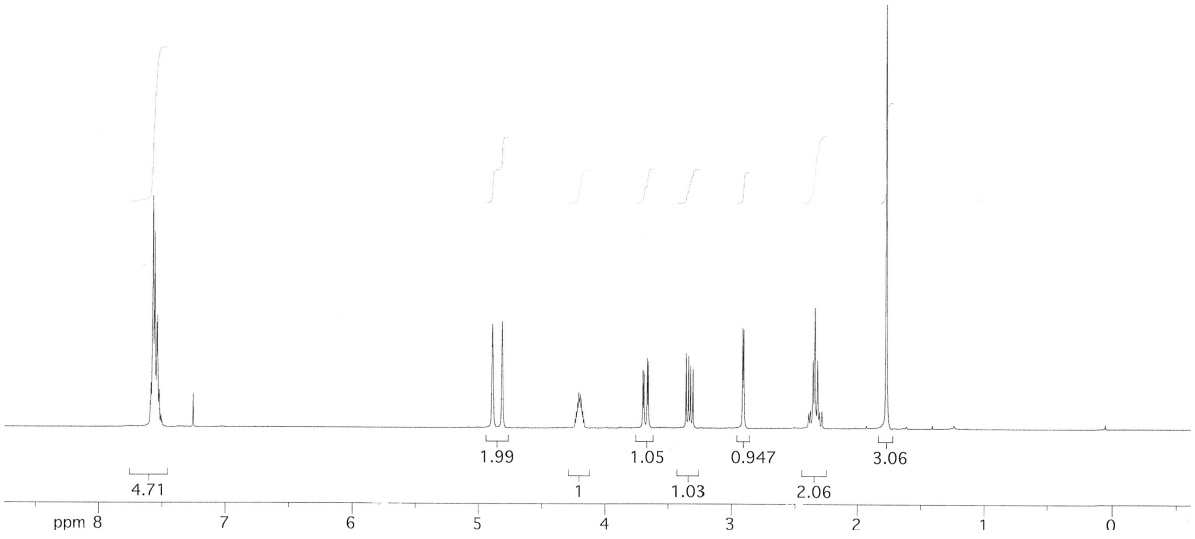

400 MHz, CDCl3
9
8
7
6
5
4
3
2
1
0 ppm
4.68
1.05
0.87
1.04
1.00
1.00

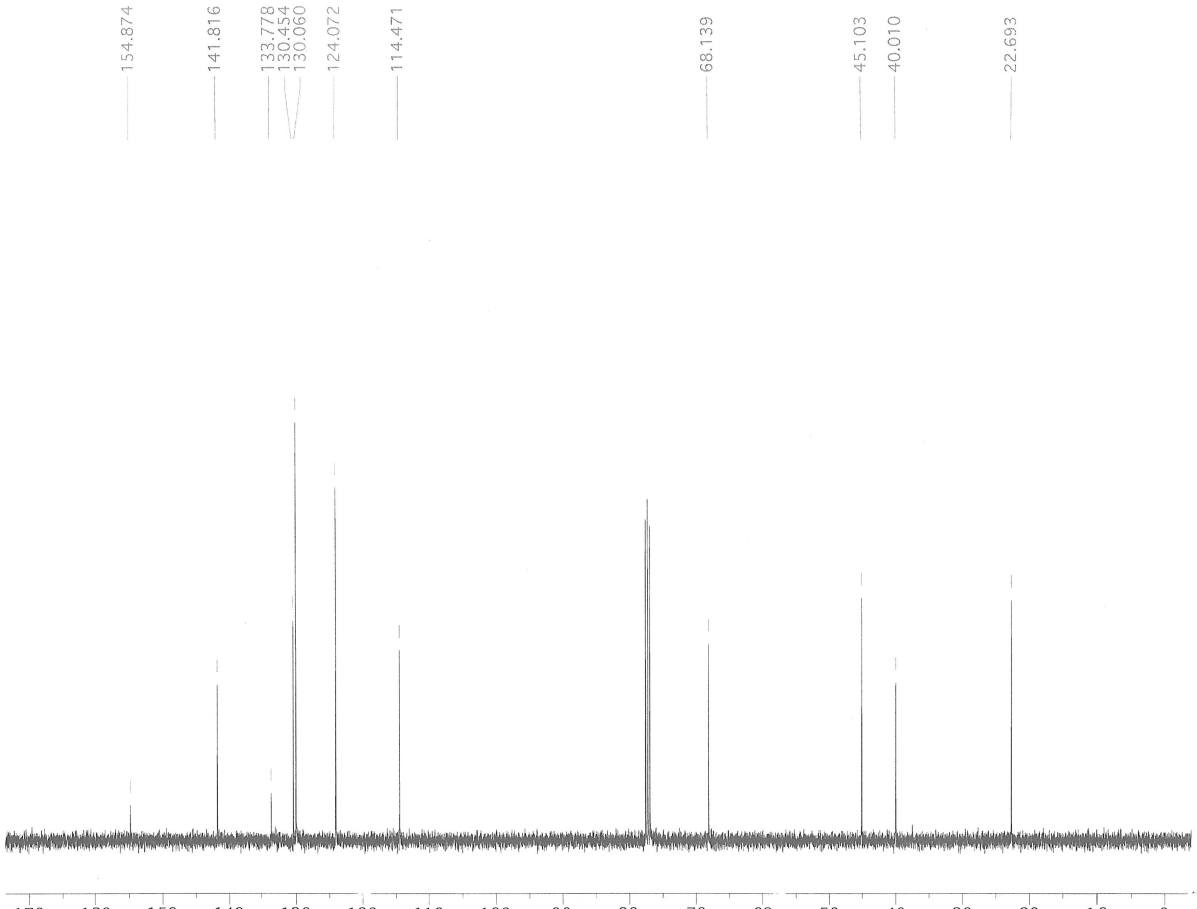

200
180
160
140
120
100
80
60
40
20
0
ppm

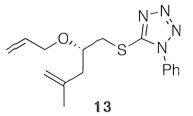


12

400 MHz, $CDCl_3$

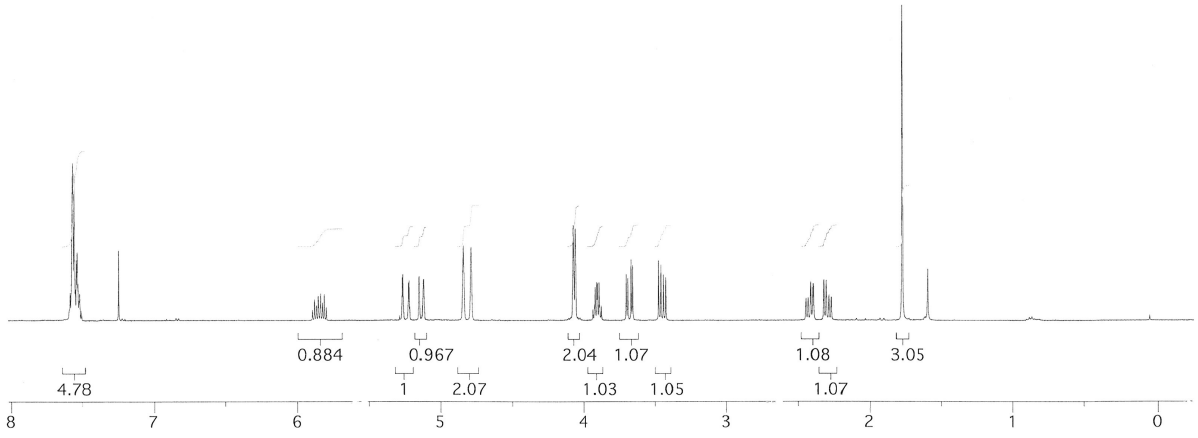


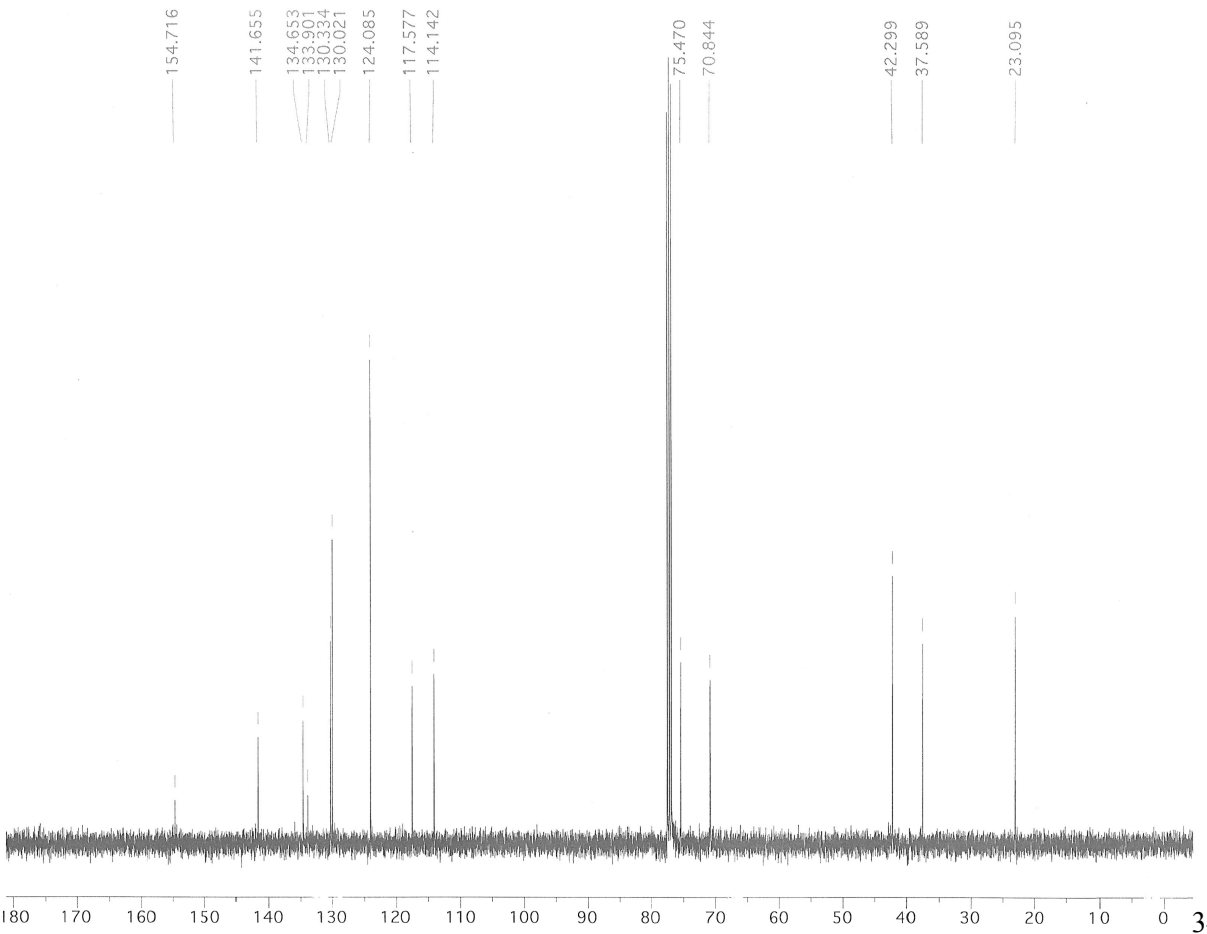


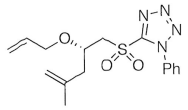


13

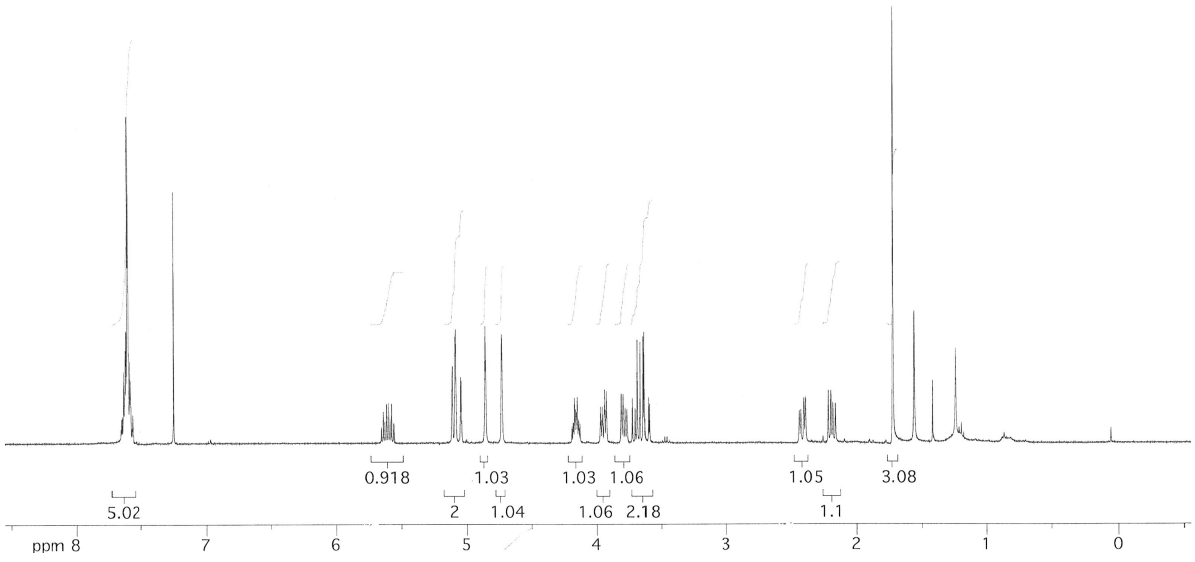
400 MHz, $CDCl_3$

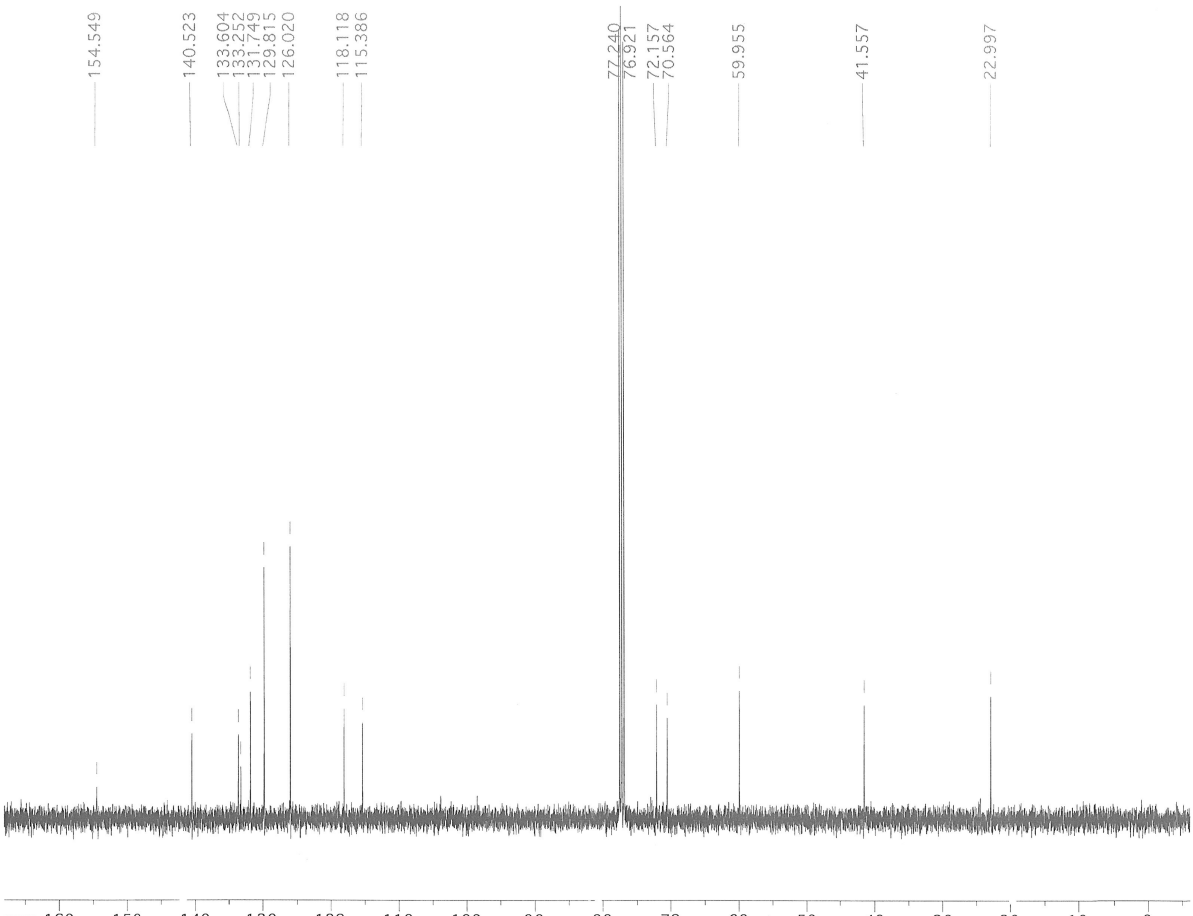


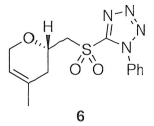




400 MHz, $CDCl_3$

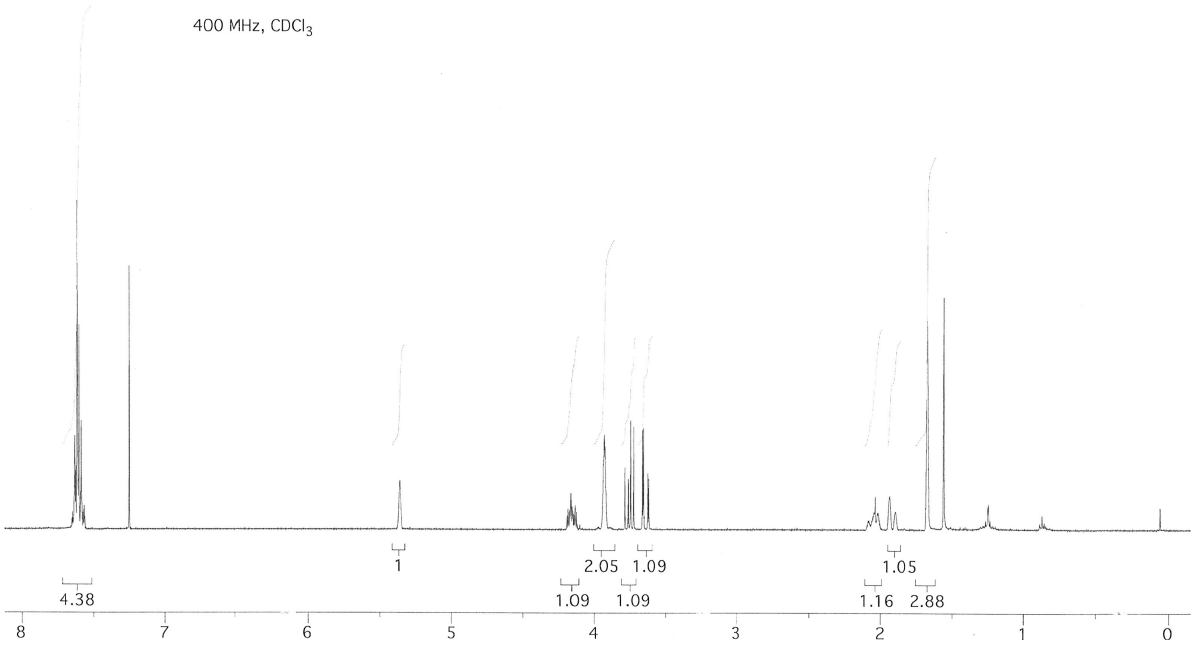


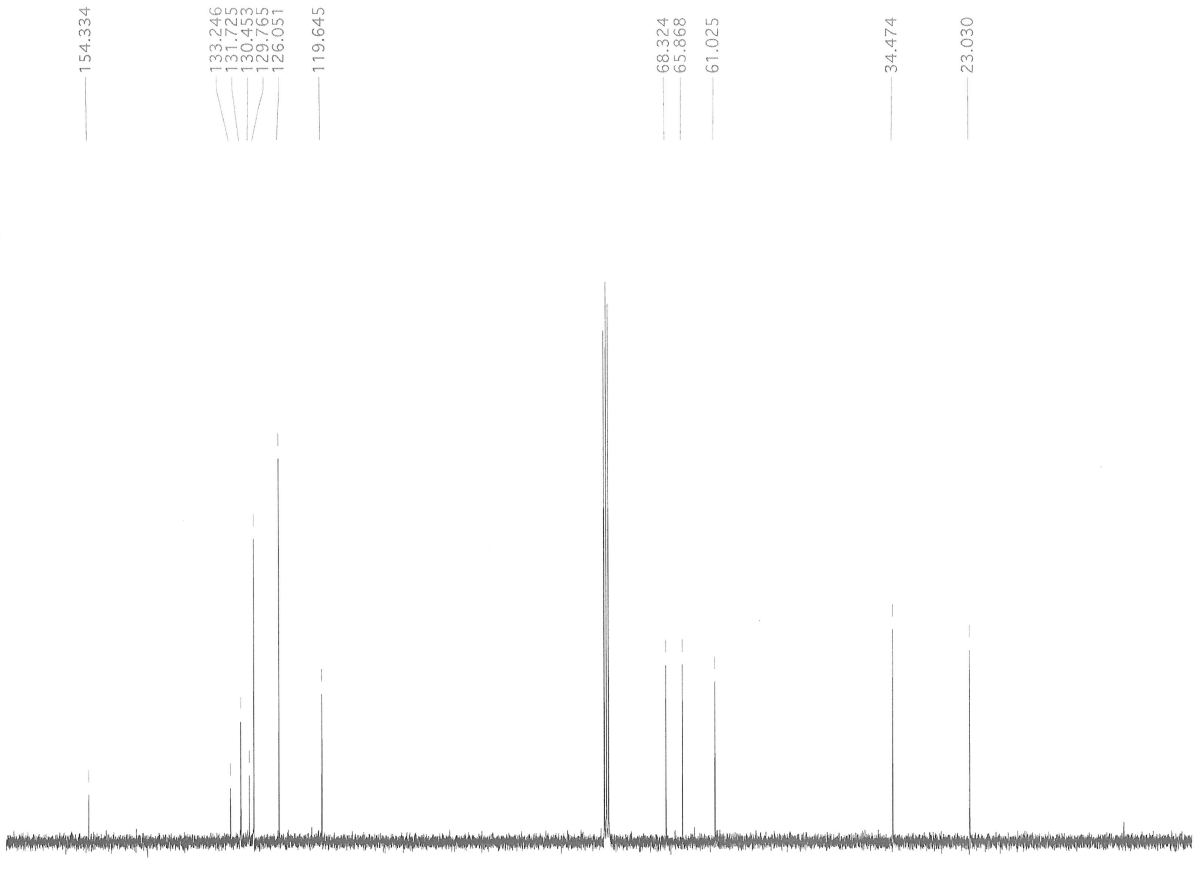


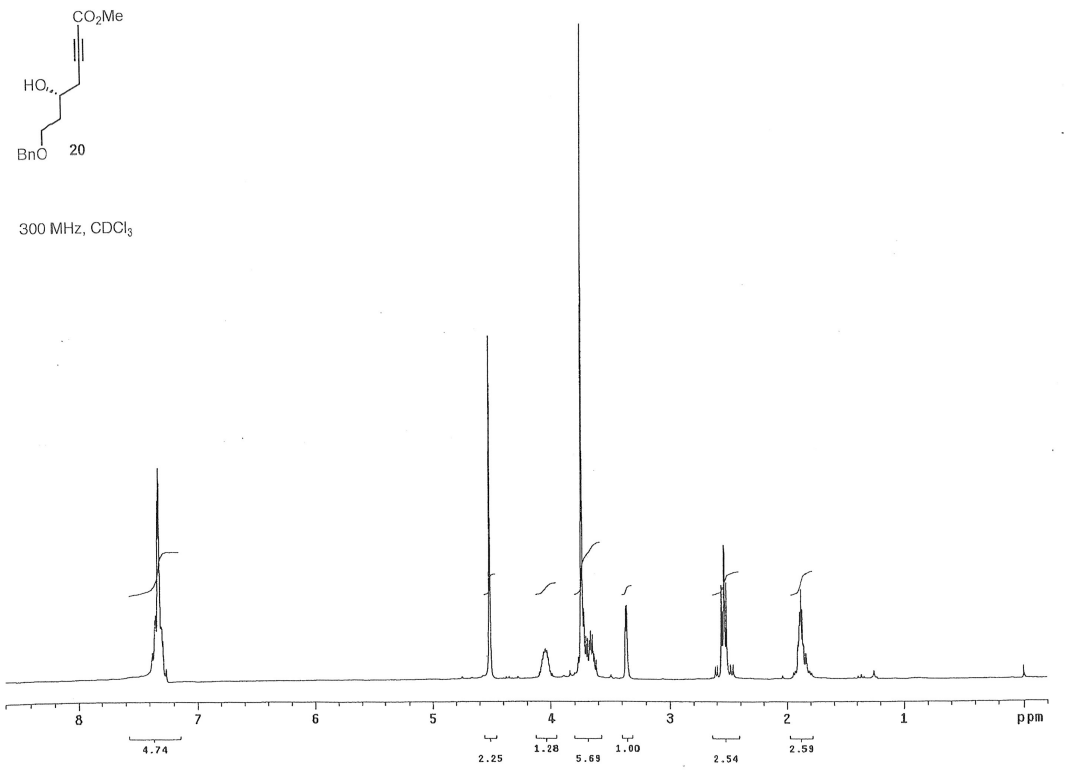


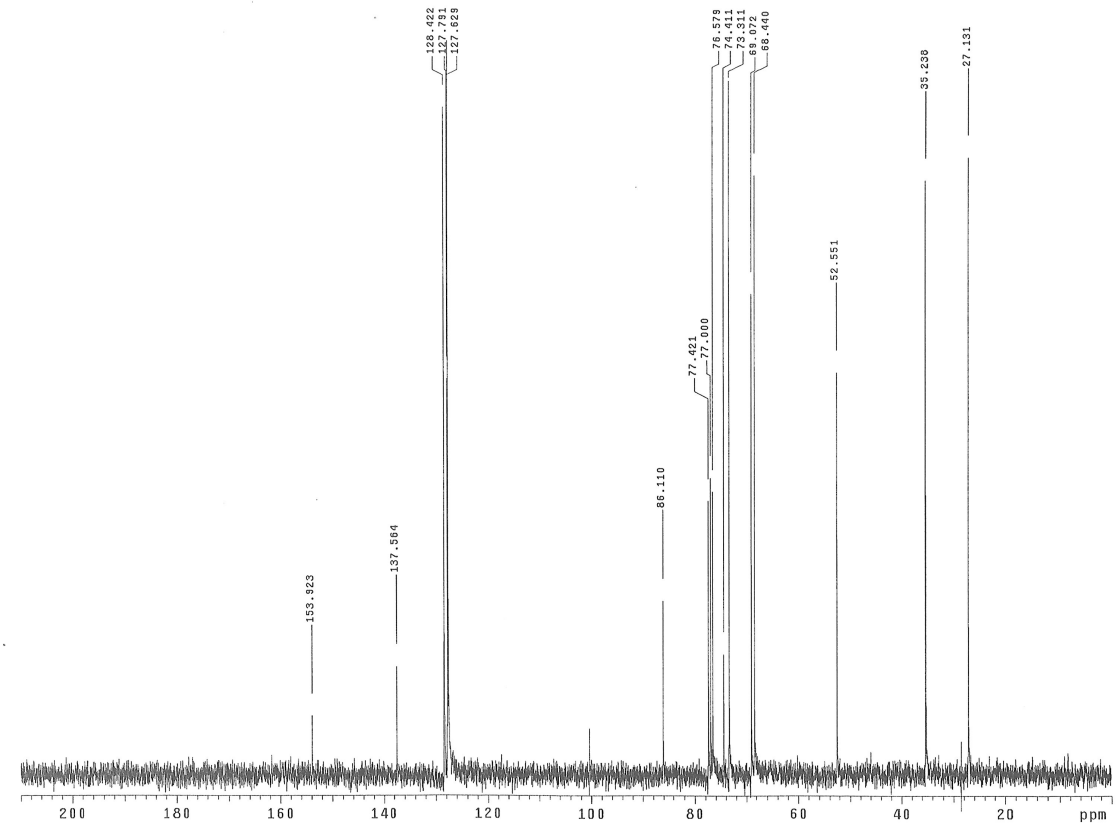
6

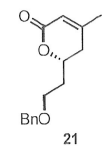
400 MHz, $CDCl_3$





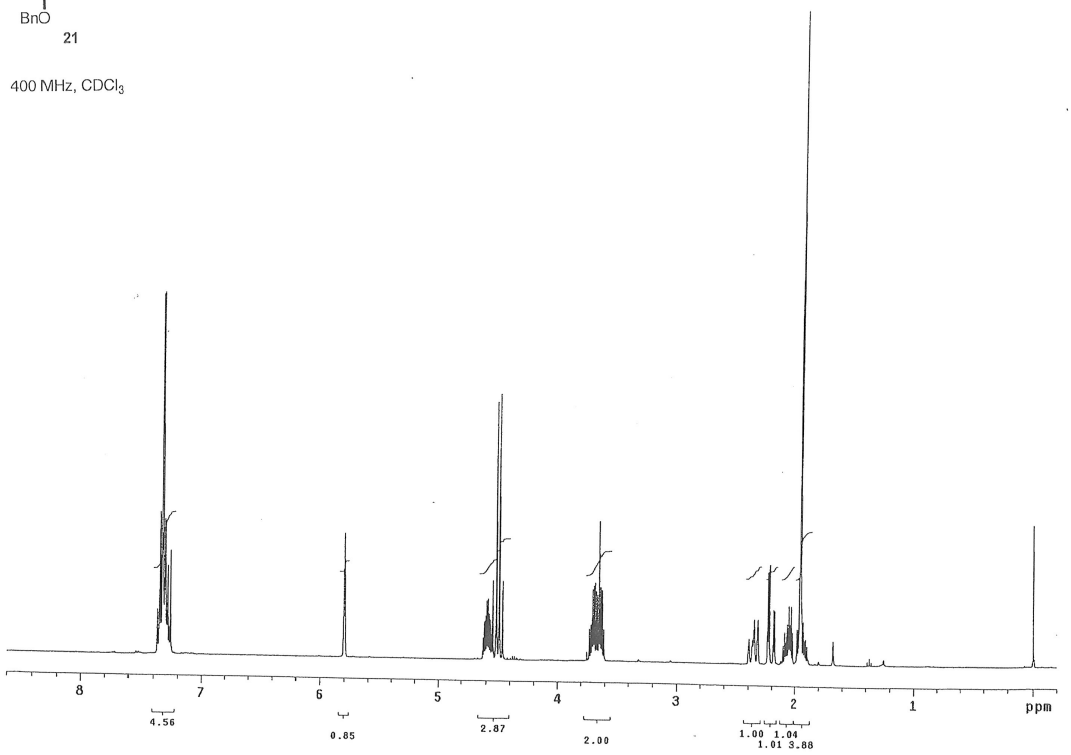

CO2Me
HO
BnO
20
300 MHz, CDCl3
8
7
6
5
4
3
2
1
ppm
4.74
2.25
1.28
5.69
1.00
2.54
2.58

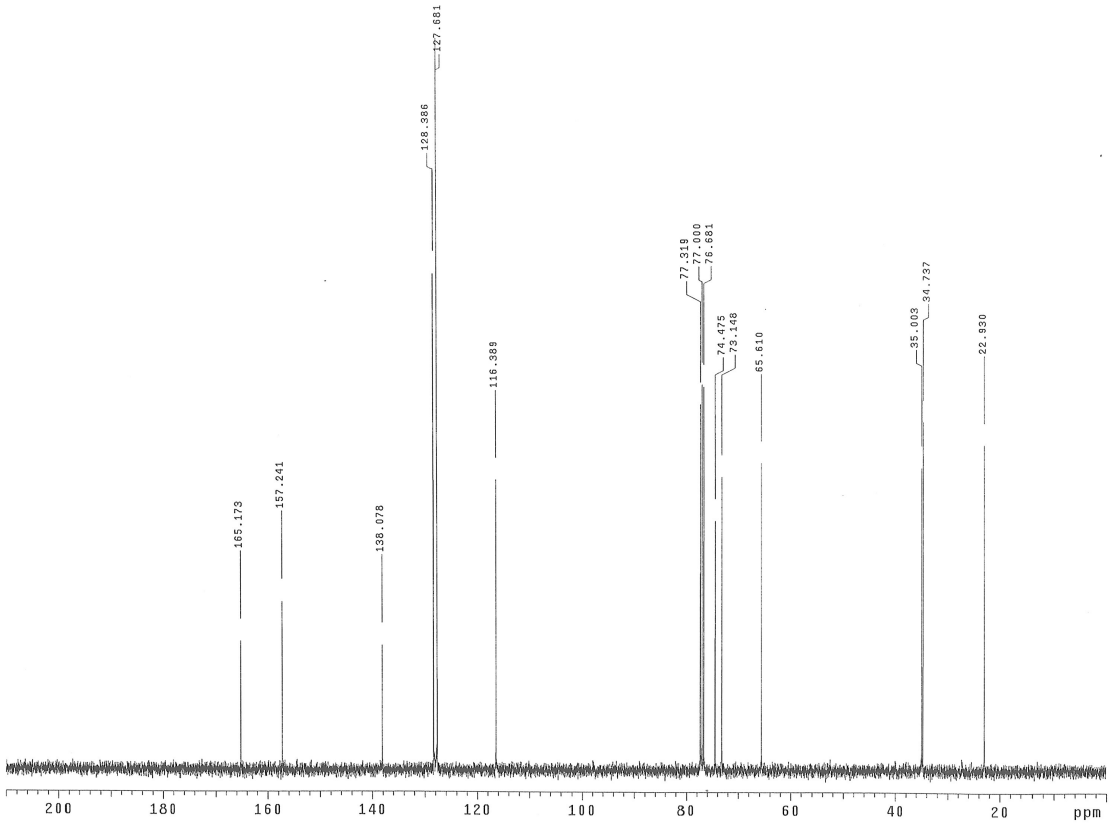

128.422
127.791
127.629
76.579
74.411
73.311
69.072
68.440
35.238
27.131
52.551
77.421
77.000
86.110
137.564
153.923
200
180
160
140
120
100
80
60
40
20
ppm

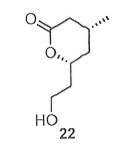


21

400 MHz, $CDCl_3$

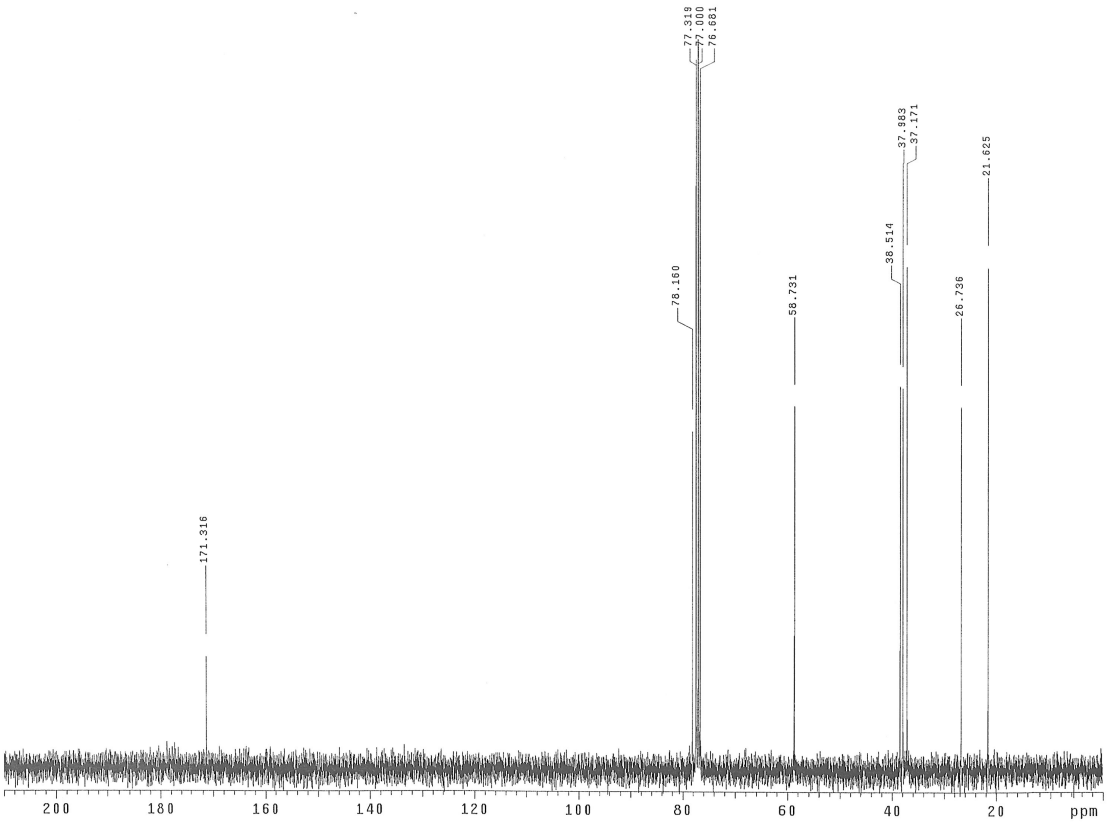


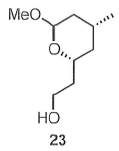




22

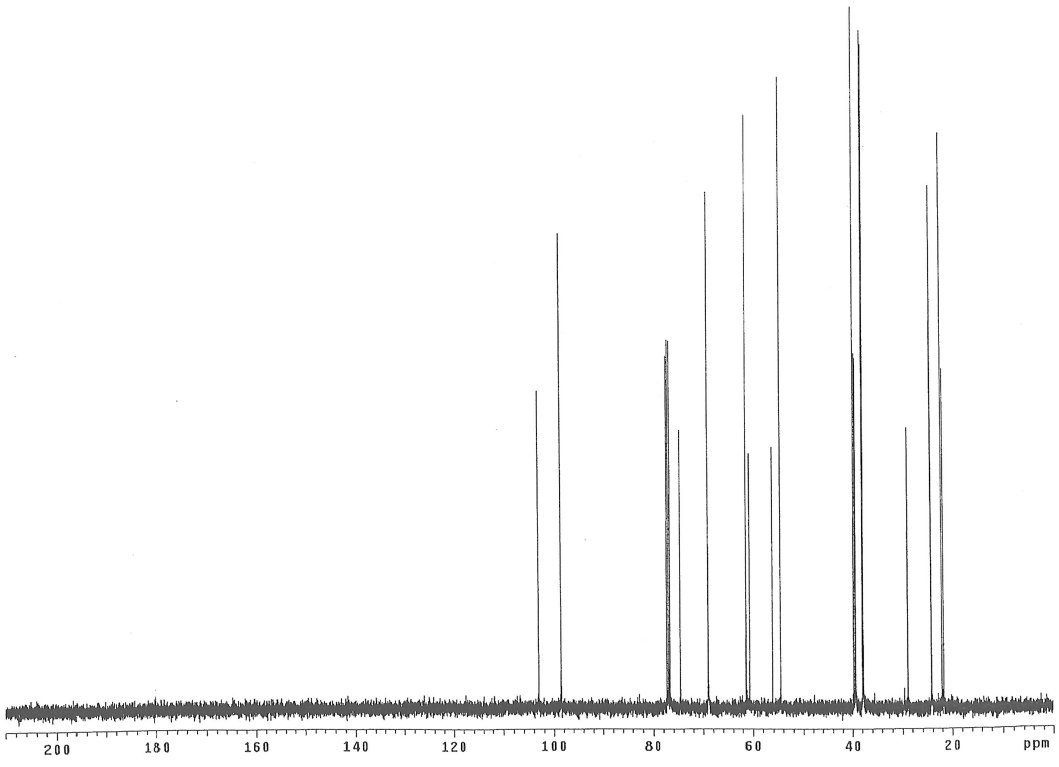
400 MHz, $CDCl_3$

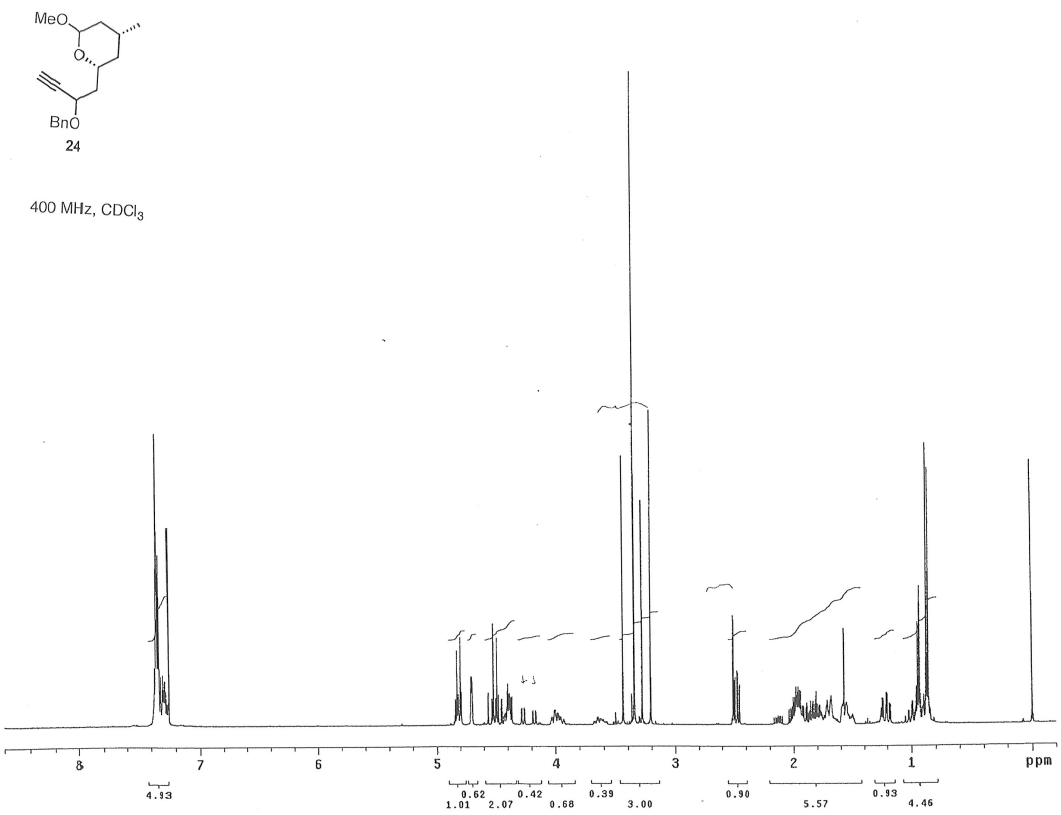


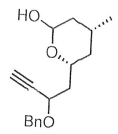


23

400 MHz, $CDCl_3$

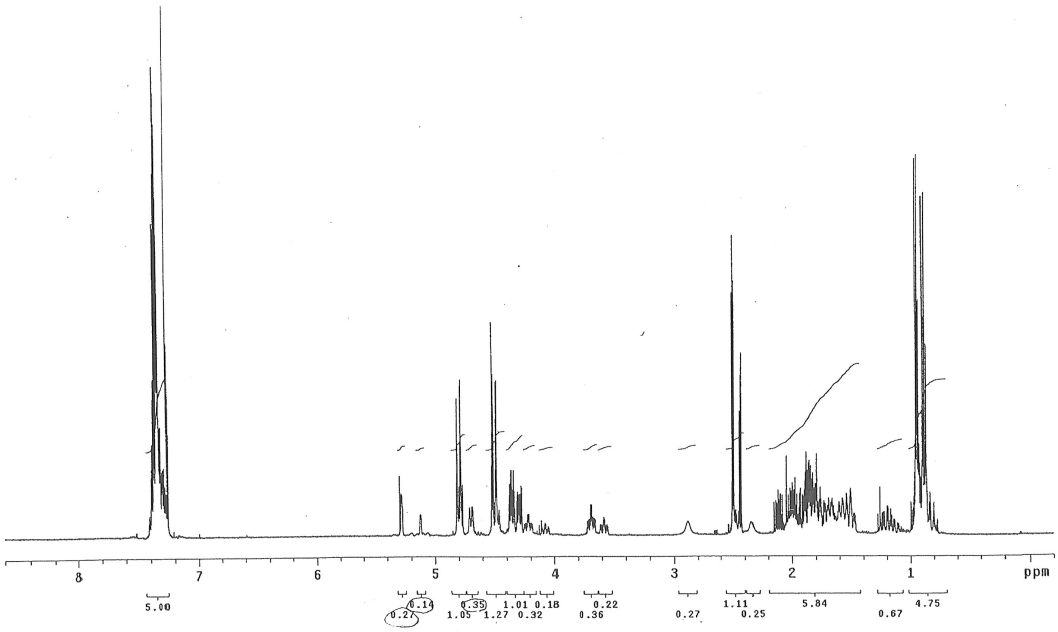


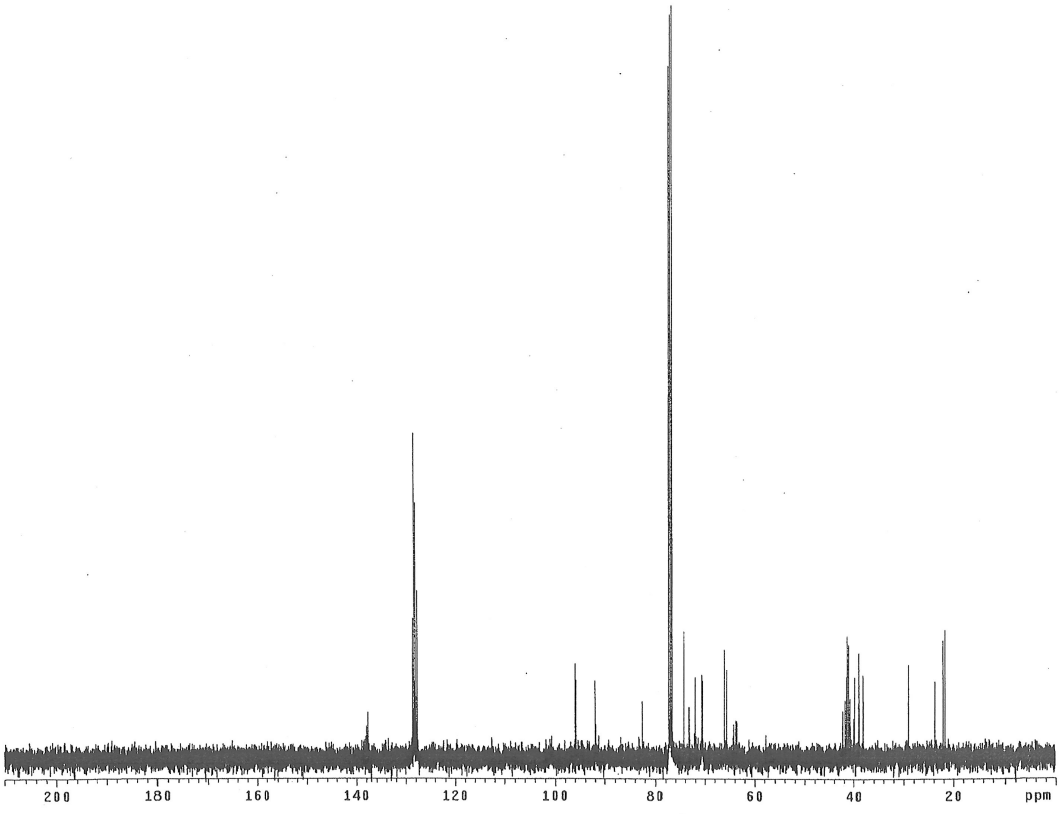

MeO
O
BnO
24
400 MHz, CDCl3
8
7
6
5
4
3
2
1
ppm
4.93
1.01
0.62
2.07
0.42
0.68
0.39
3.00
0.90
5.57
0.93
4.46

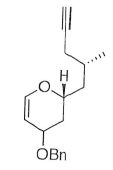


25

400 MHz, $CDCl_3$

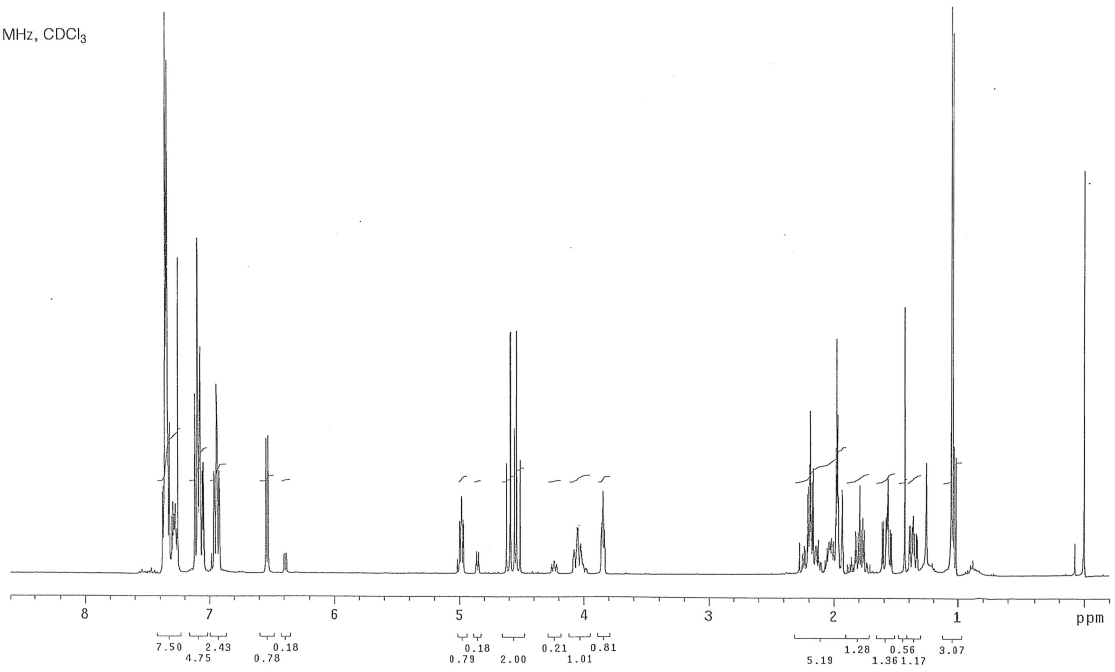


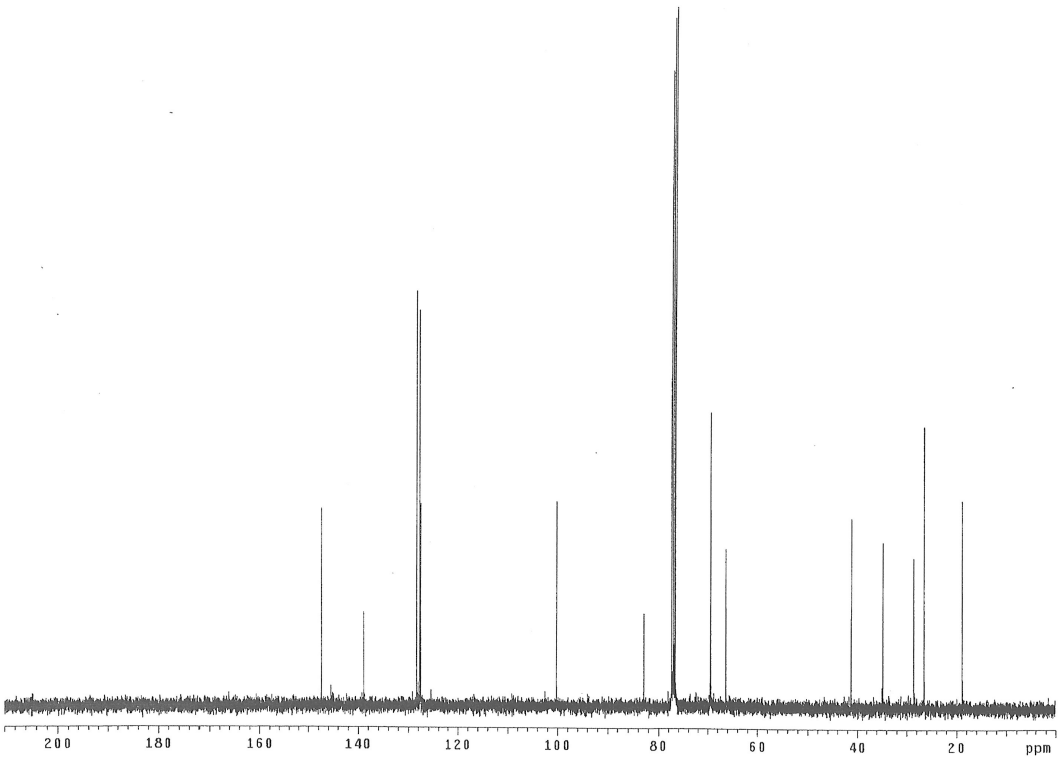


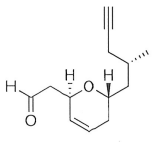


9

400 MHz, $CDCl_3$

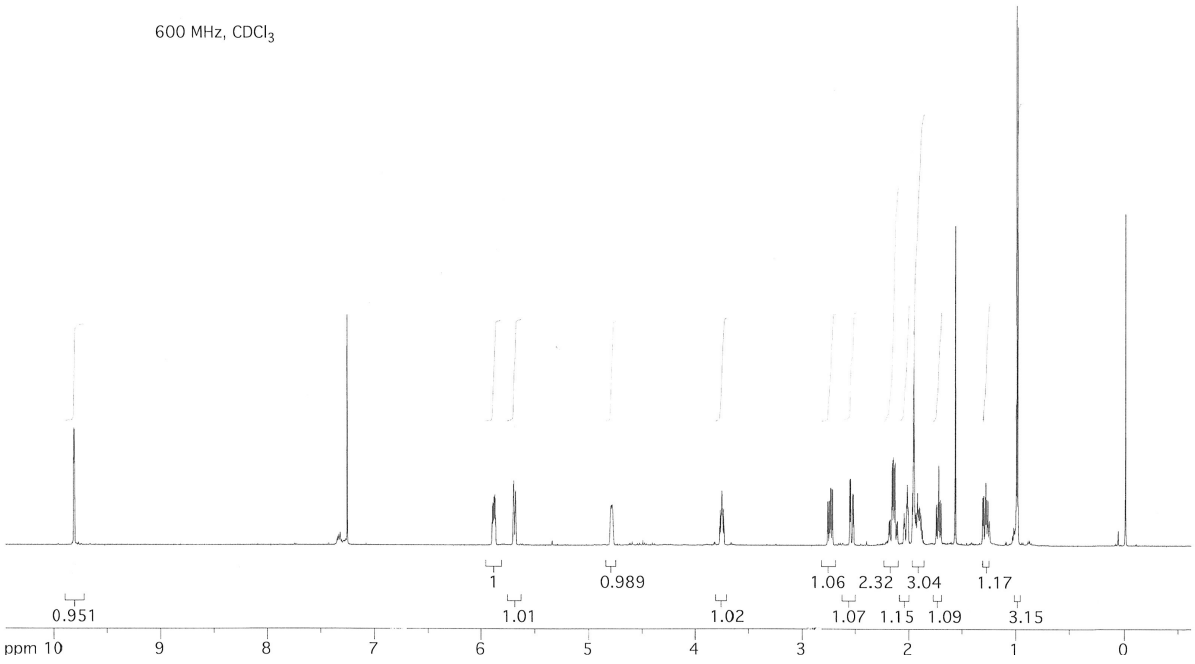


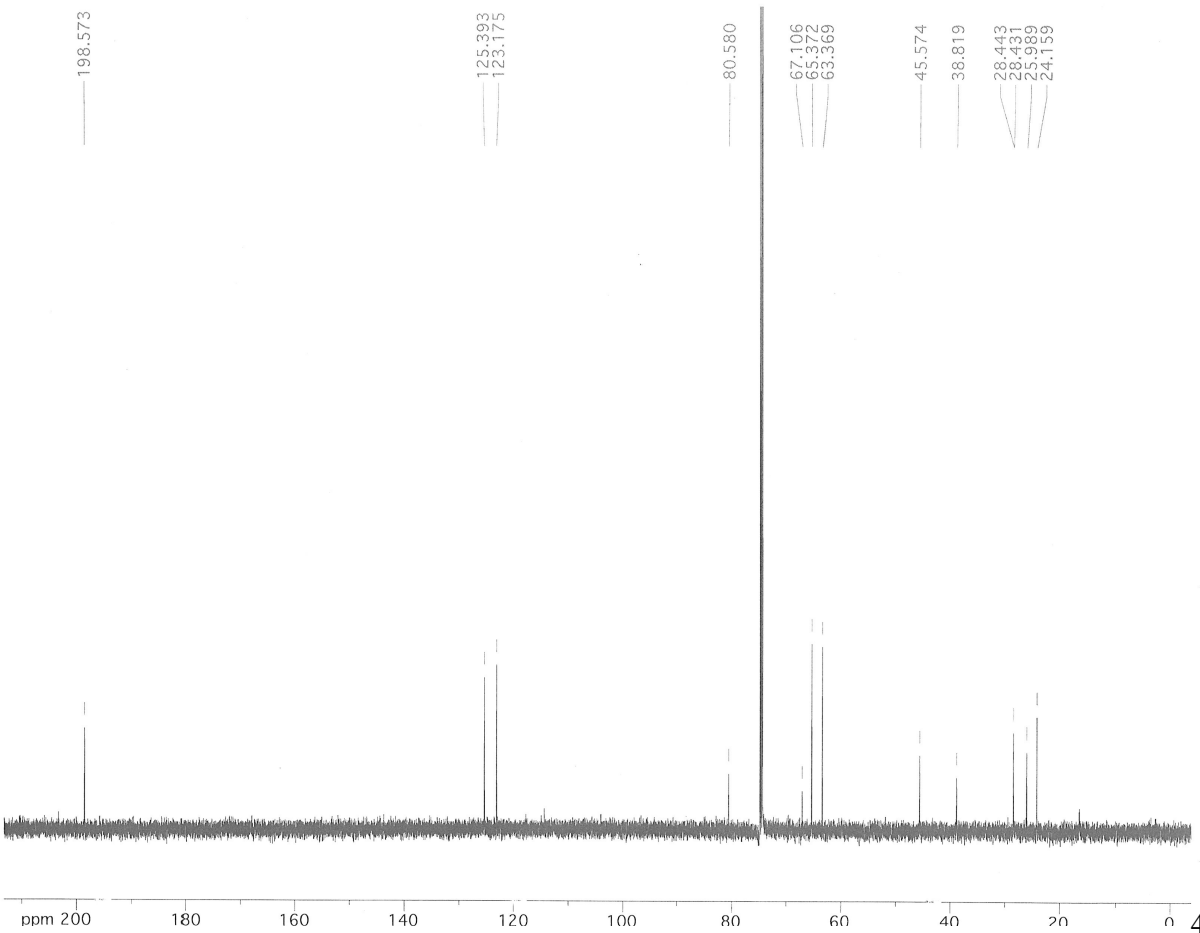


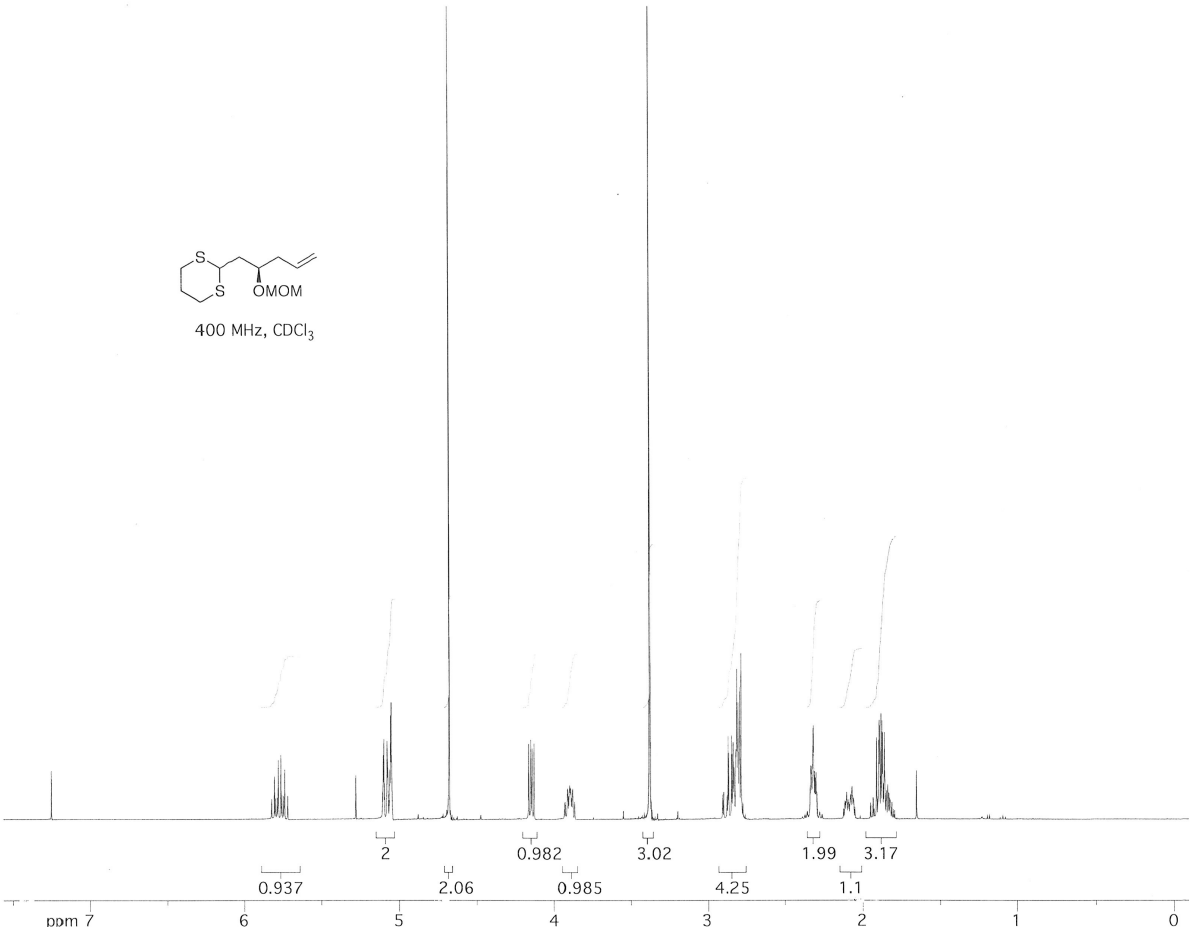


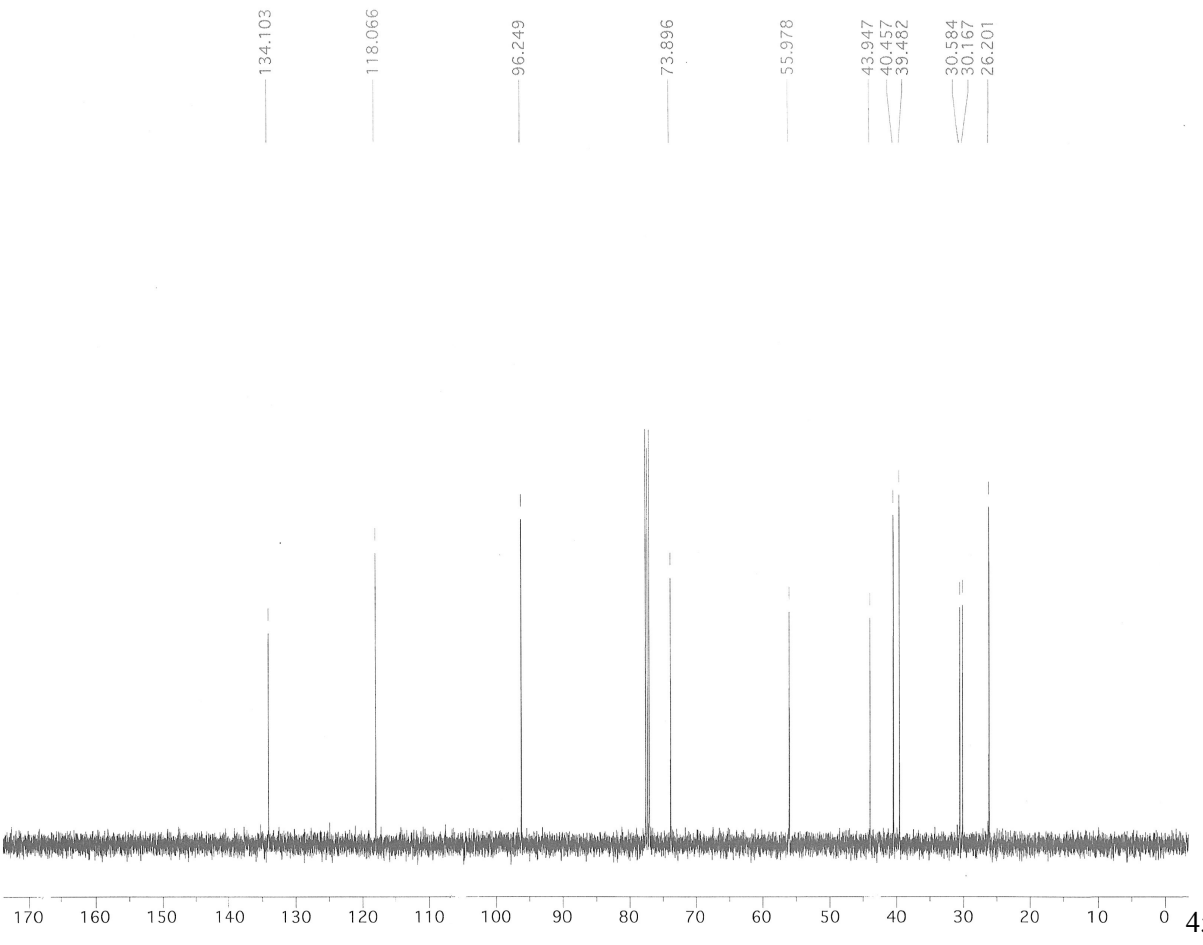
8

600 MHz, $CDCl_3$






S
S
OMOM
400 MHz, CDCl3
2
0.982
3.02
1.99
3.17
0.937
2.06
0.985
4.25
1.1
ppm 7
6
5
4
3
2
1
0


134.103
118.066
96.249
73.896
55.978
43.947
40.457
39.482
30.584
30.167
26.201
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150
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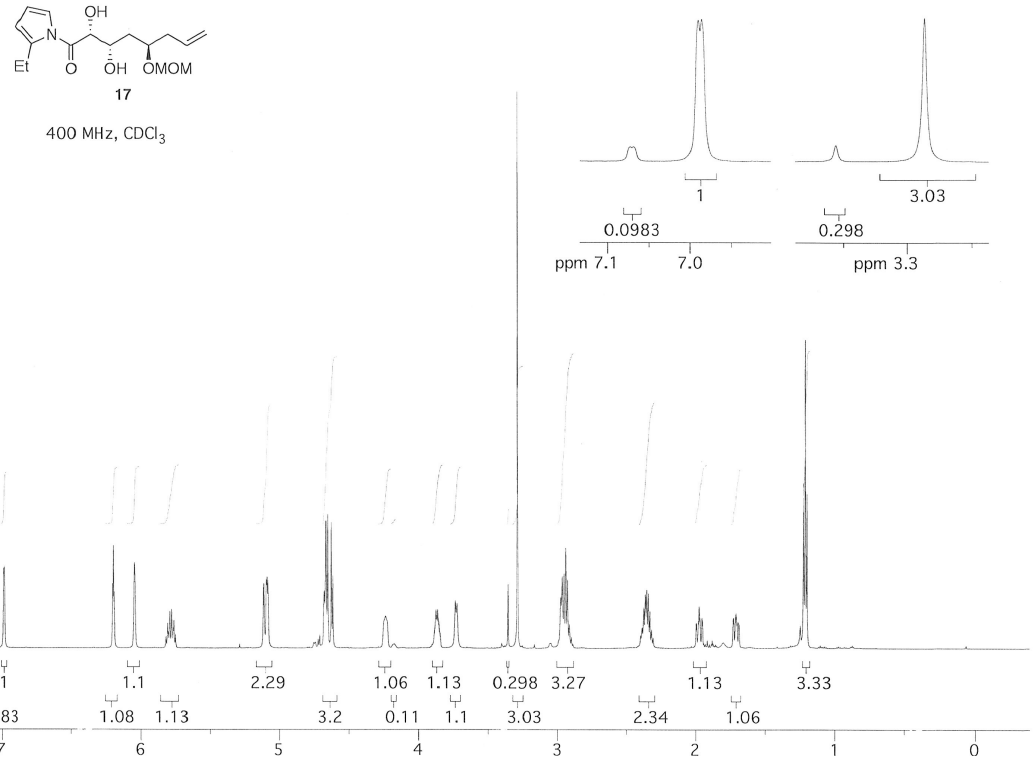
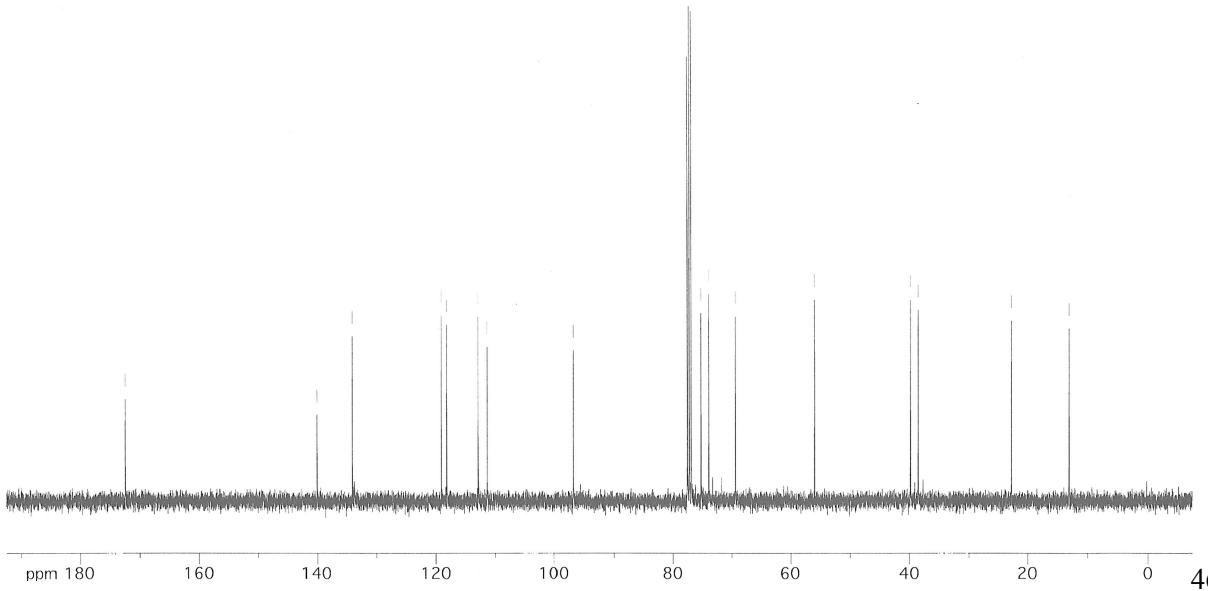
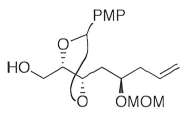
90
80
70
60
50
40
30
20
10
0


OH
N
Et
O
OH
OMOM
17
400 MHz, CDCl3
1
3.03
0.0983
0.298
ppm 7.1
7.0
ppm 3.3
1
1.1
2.29
1.06
1.13
0.298
3.27
1.13
3.33
0.0983
1.08
1.13
3.2
0.11
1.1
3.03
2.34
1.06
8
7
6
5
4
3
2
1
0

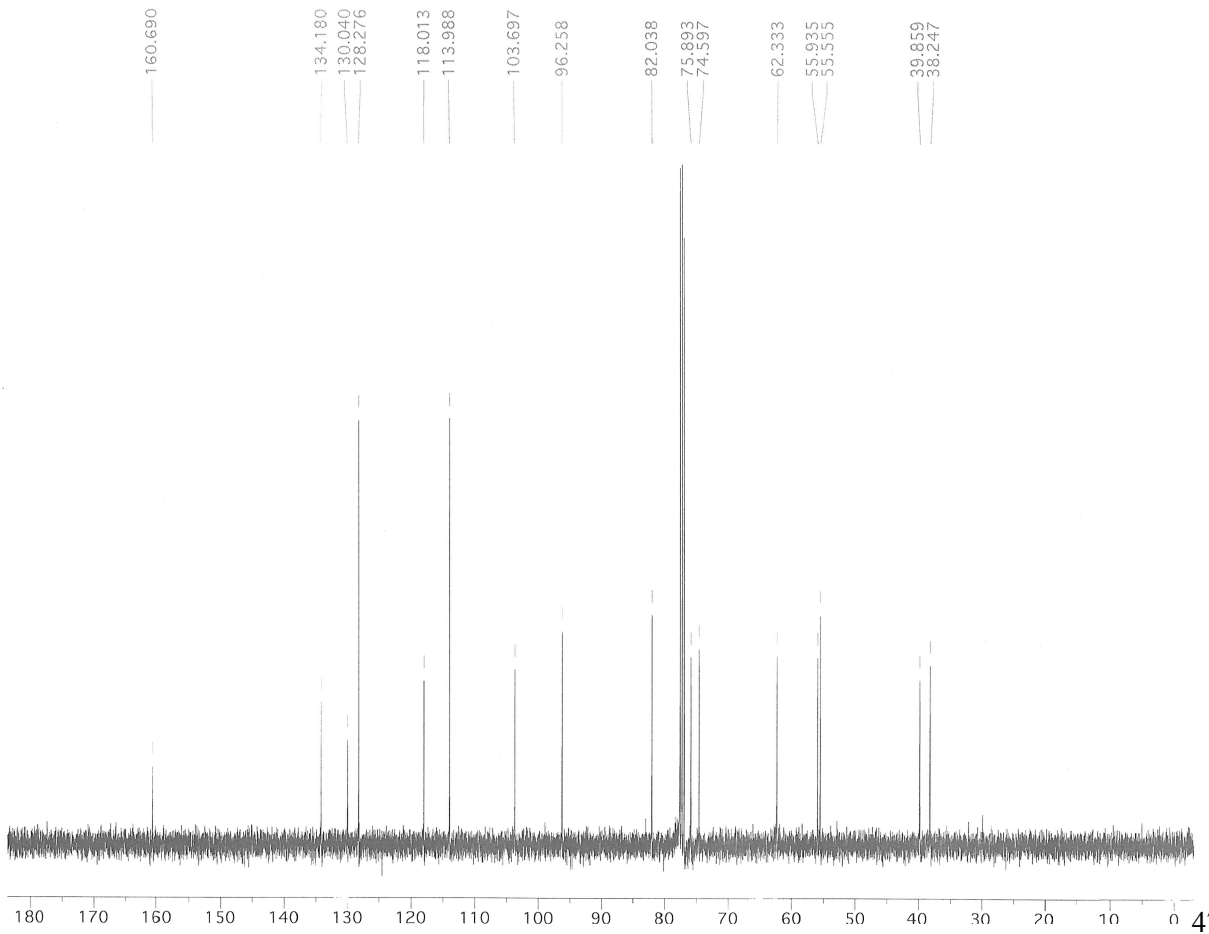

172.473
140.099
134.124
119.077
118.222
112.910
111.364
96.789
75.273
73.964
69.426
56.002
39.809
38.524
22.814
13.112

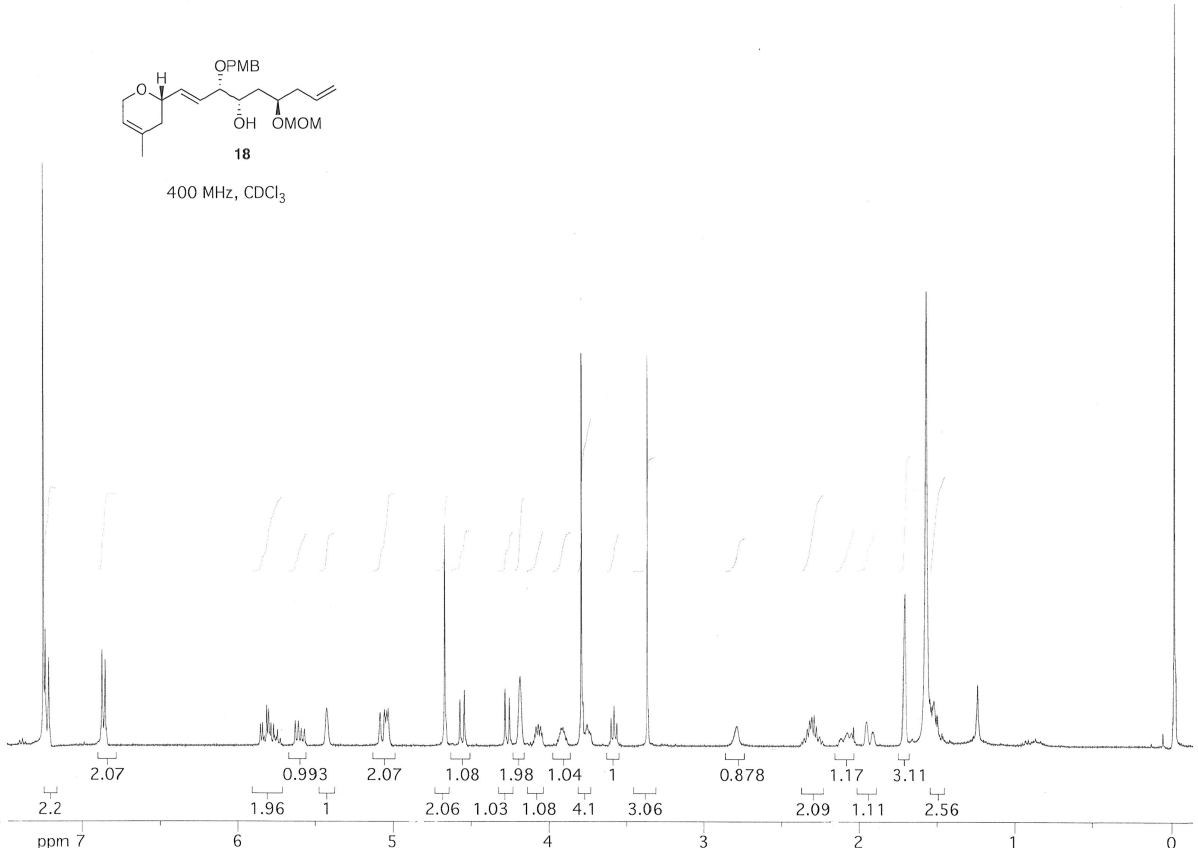

ppm 180
160
140
120
100
80
60
40
20
0

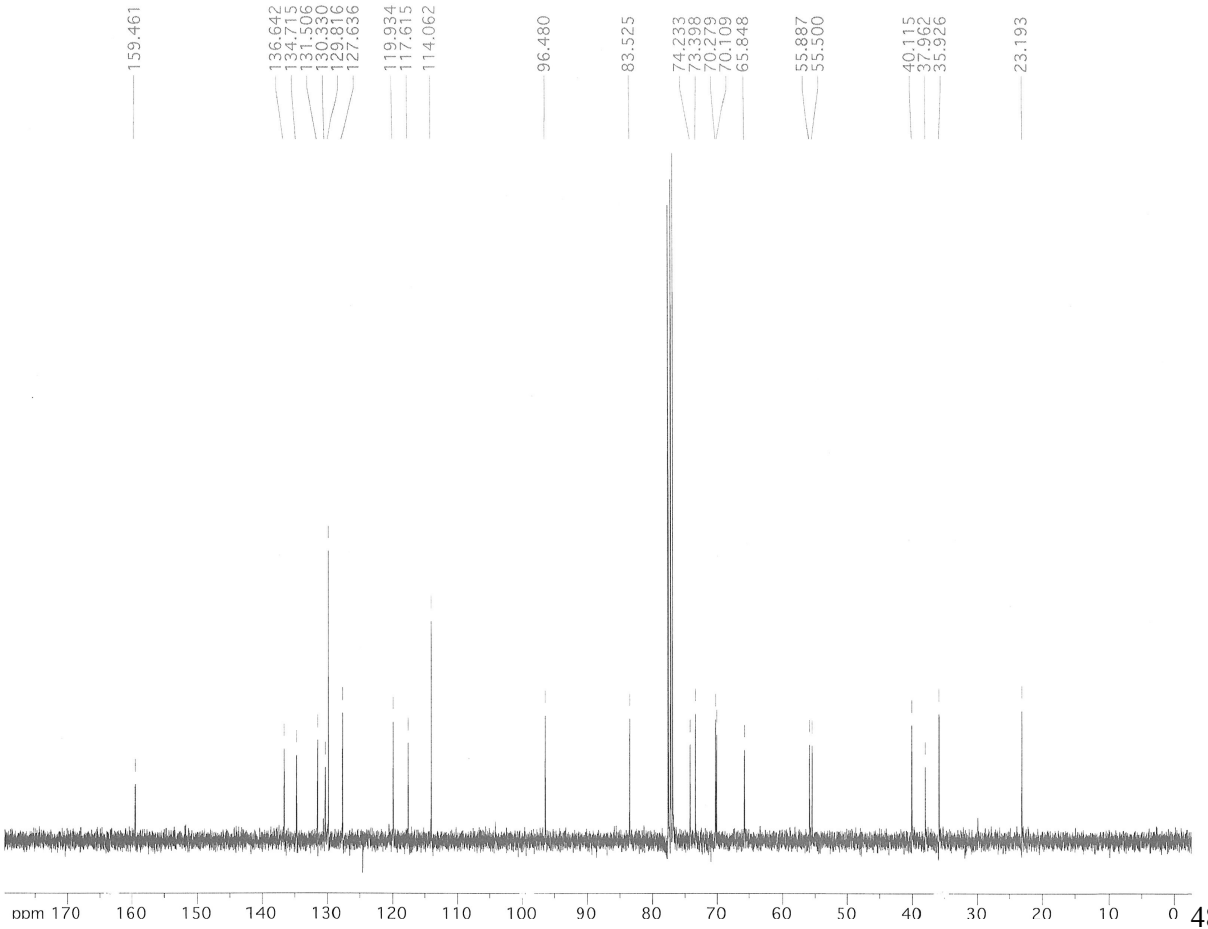


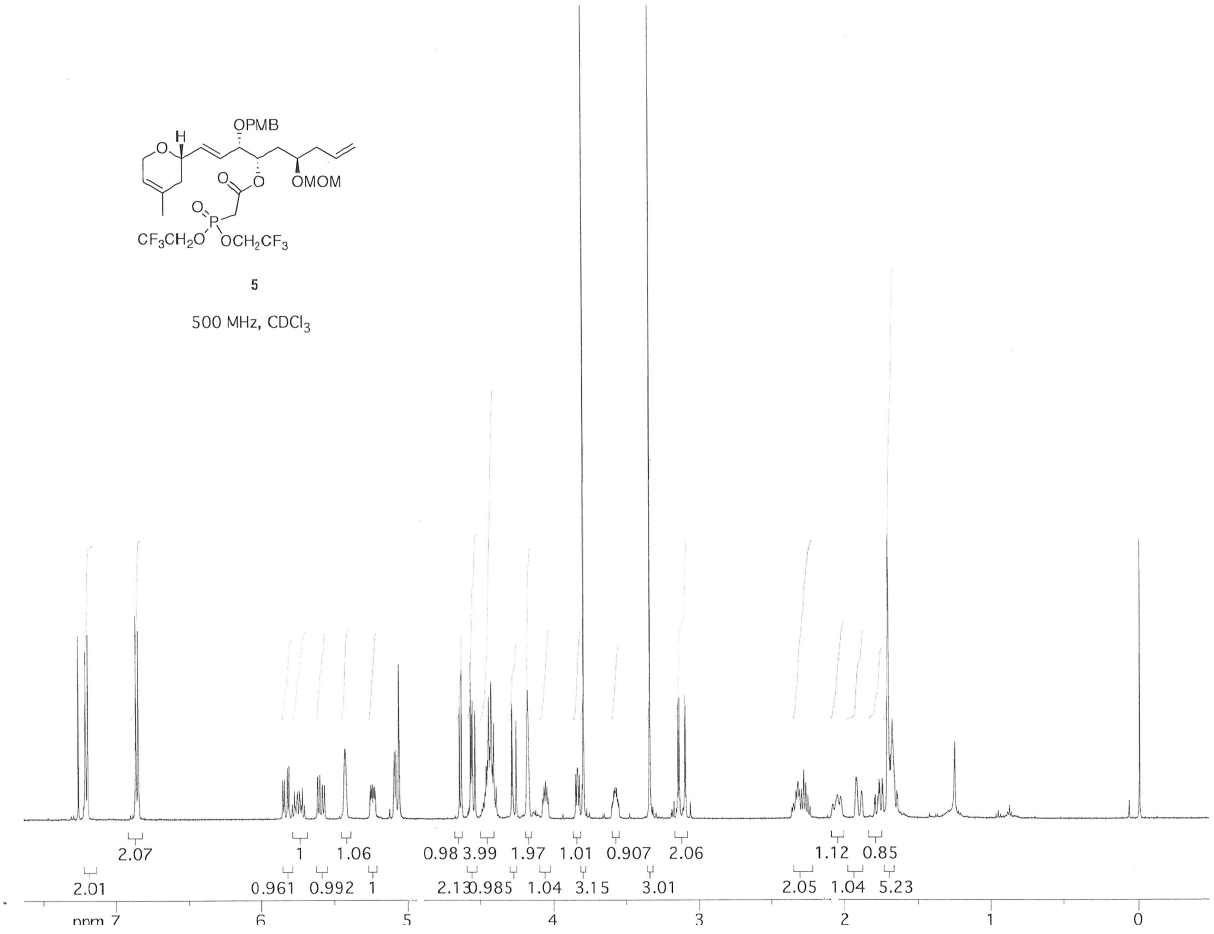
(major diastereoisomer)

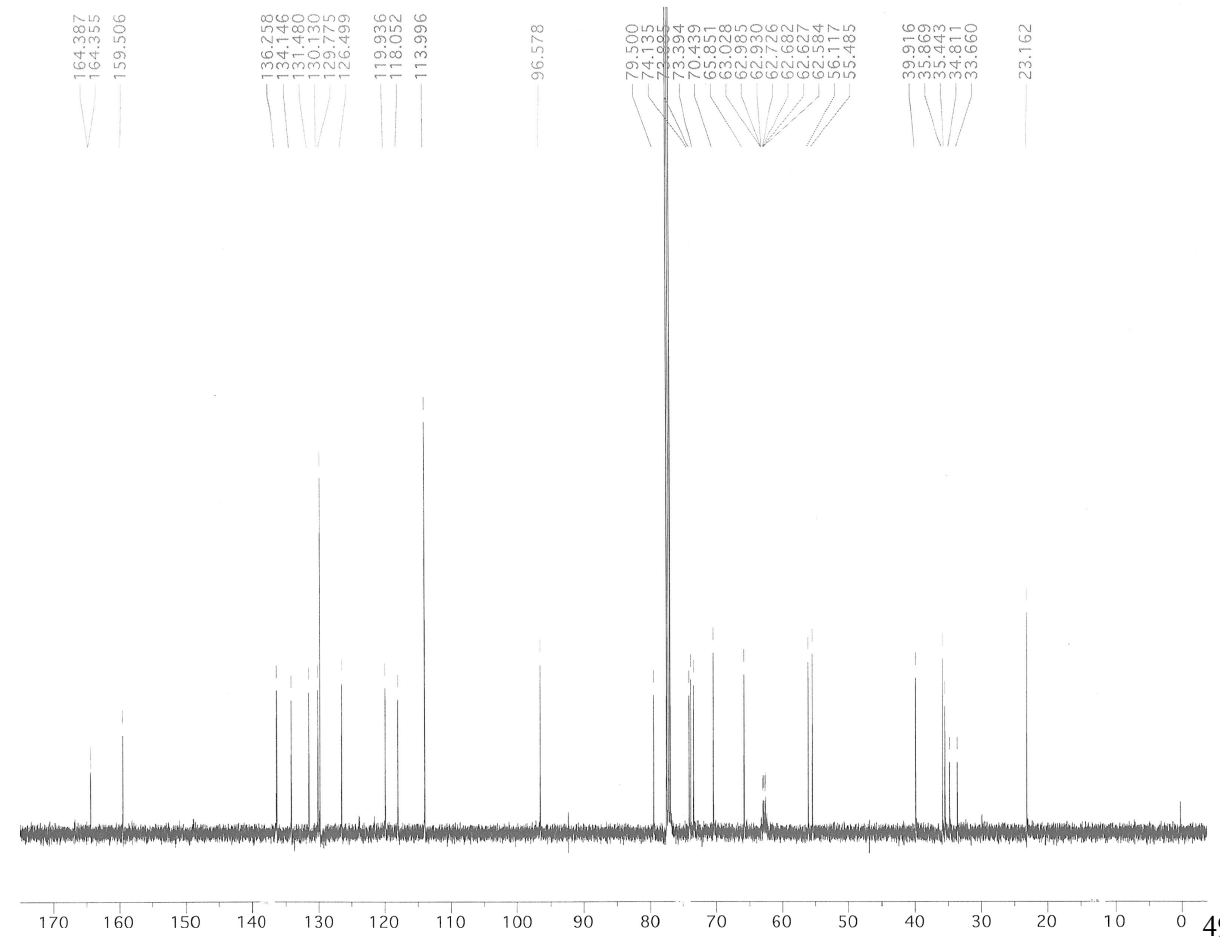
400 MHz, $CDCl_3$

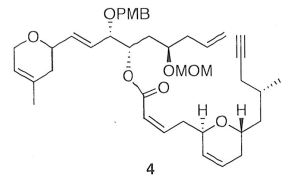



OPMB
H
O
OH
OMOM
18
400 MHz, CDCl3
2.07
0.993
2.07
1.08
1.98
1.04
1
0.878
1.17
3.11
2.2
1.96
1
2.06
1.03
1.08
4.1
3.06
2.09
1.11
2.56
ppm 7
6
5
4
3
2
1
0


159.461
136.642
134.715
131.506
130.330
129.816
127.636
119.934
117.615
114.062
96.480
83.525
74.233
73.398
70.279
70.109
65.848
55.887
55.500
40.115
37.962
35.926
23.193
ppm 170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

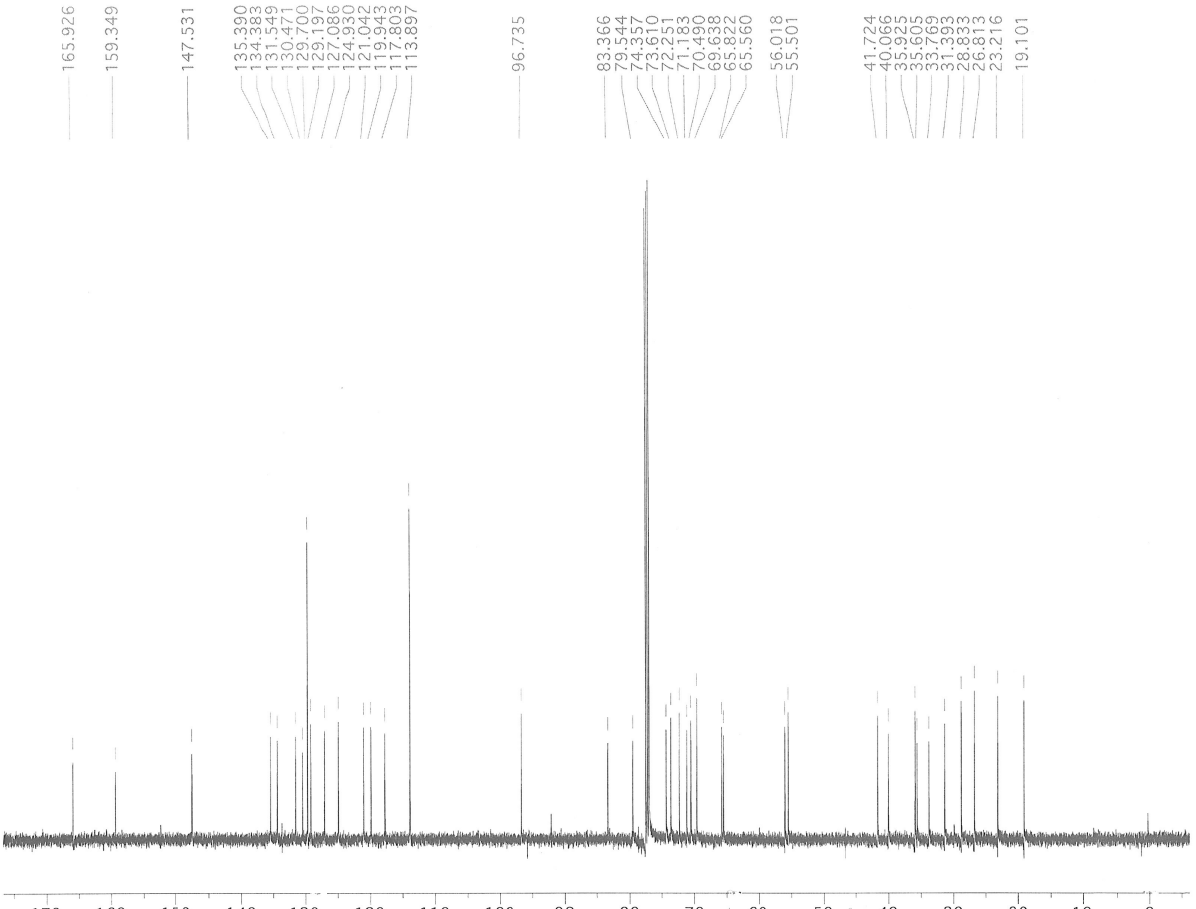

OPMB
H
O
O
O
OMOM
O
P
O
CF3CH2O
OCH2CF3
5
500 MHz, CDCl3
2.07
1
1.06
0.98
3.99
1.97
1.01
0.907
2.06
1.12
0.85
2.01
0.961
0.992
1
2.13
0.985
1.04
3.15
3.01
2.05
1.04
5.23
ppm 7
6
5
4
3
2
1
0

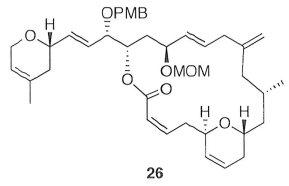

164.387
164.355
159.506
136.258
134.146
131.480
130.130
129.775
126.499
119.936
118.052
113.996
96.578
79.500
74.135
73.394
70.439
65.851
63.028
62.985
62.930
62.726
62.682
62.627
62.584
56.117
55.485
39.916
35.869
35.443
34.811
33.660
23.162
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



4

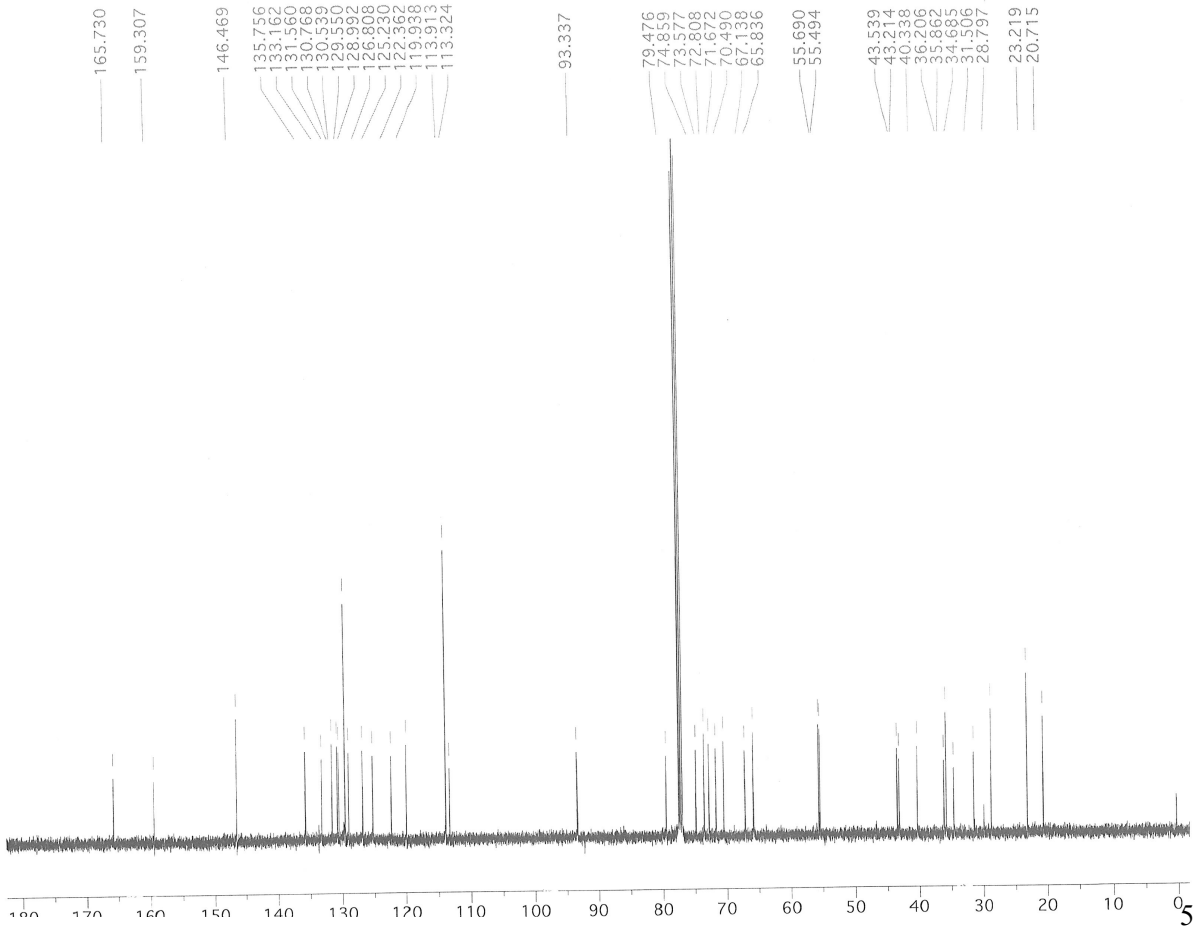
600 MHz, $CDCl_3$

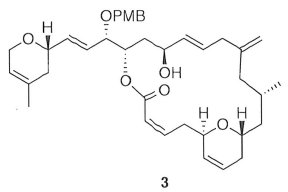




26

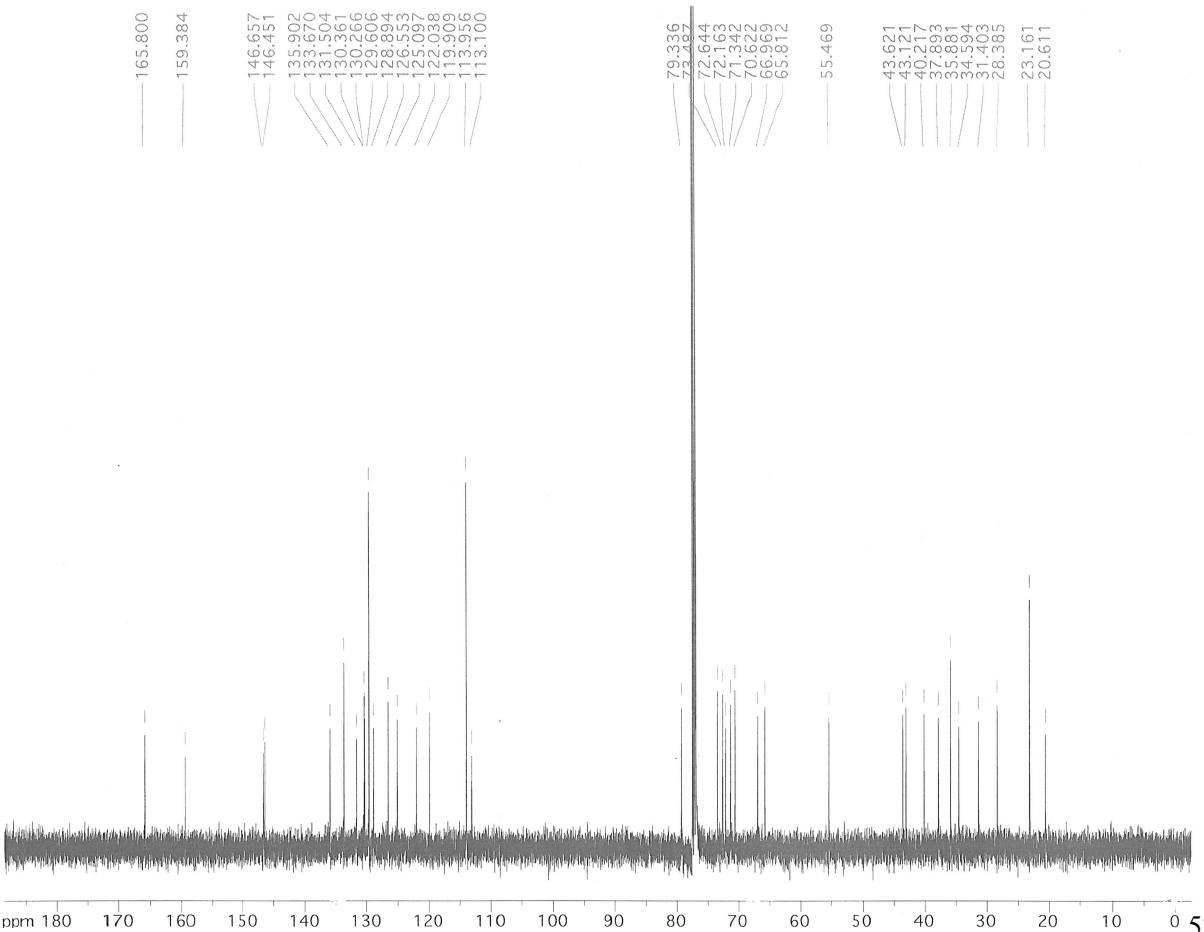
500 MHz, $CDCl_3$

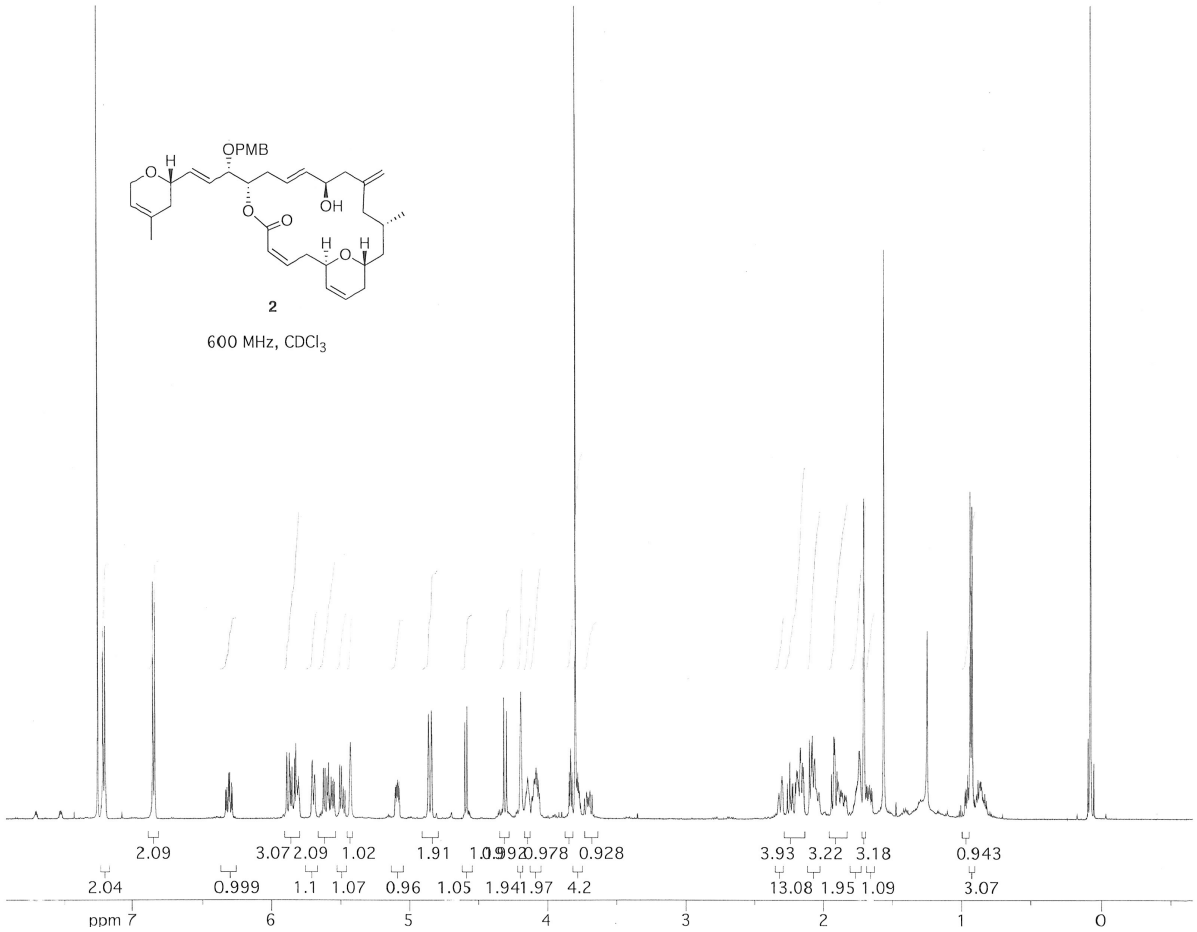


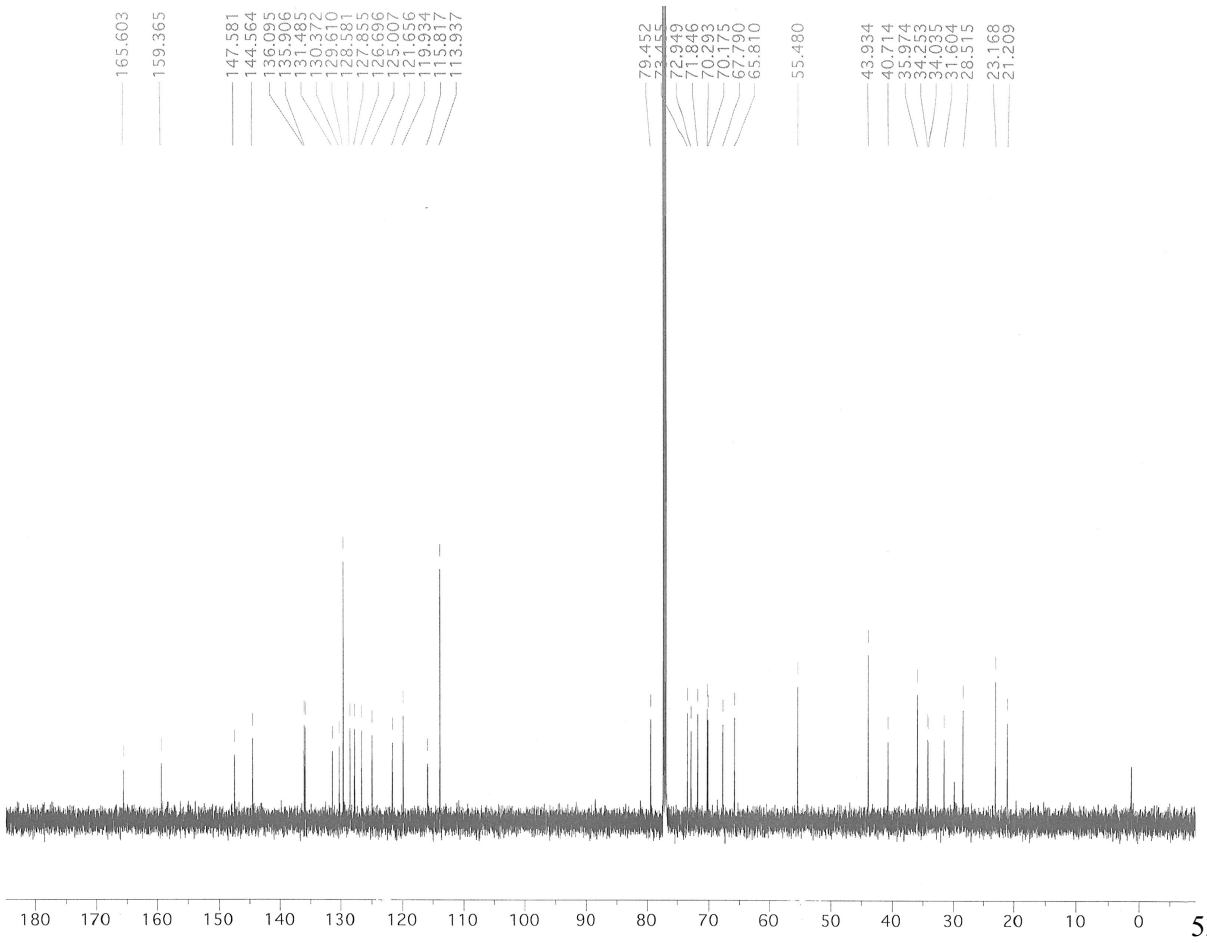


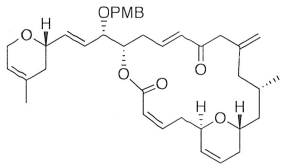
3

600 MHz, $CDCl_3$

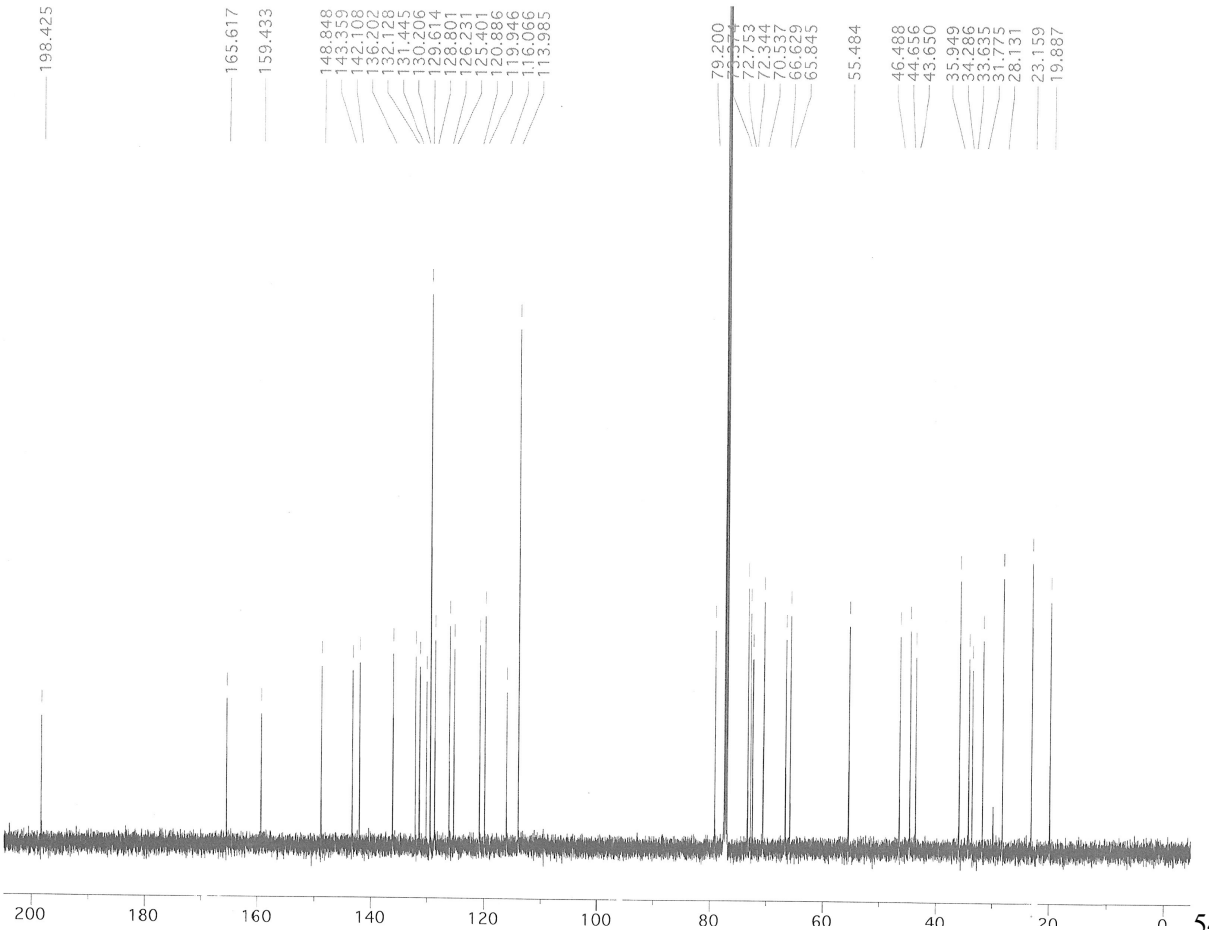


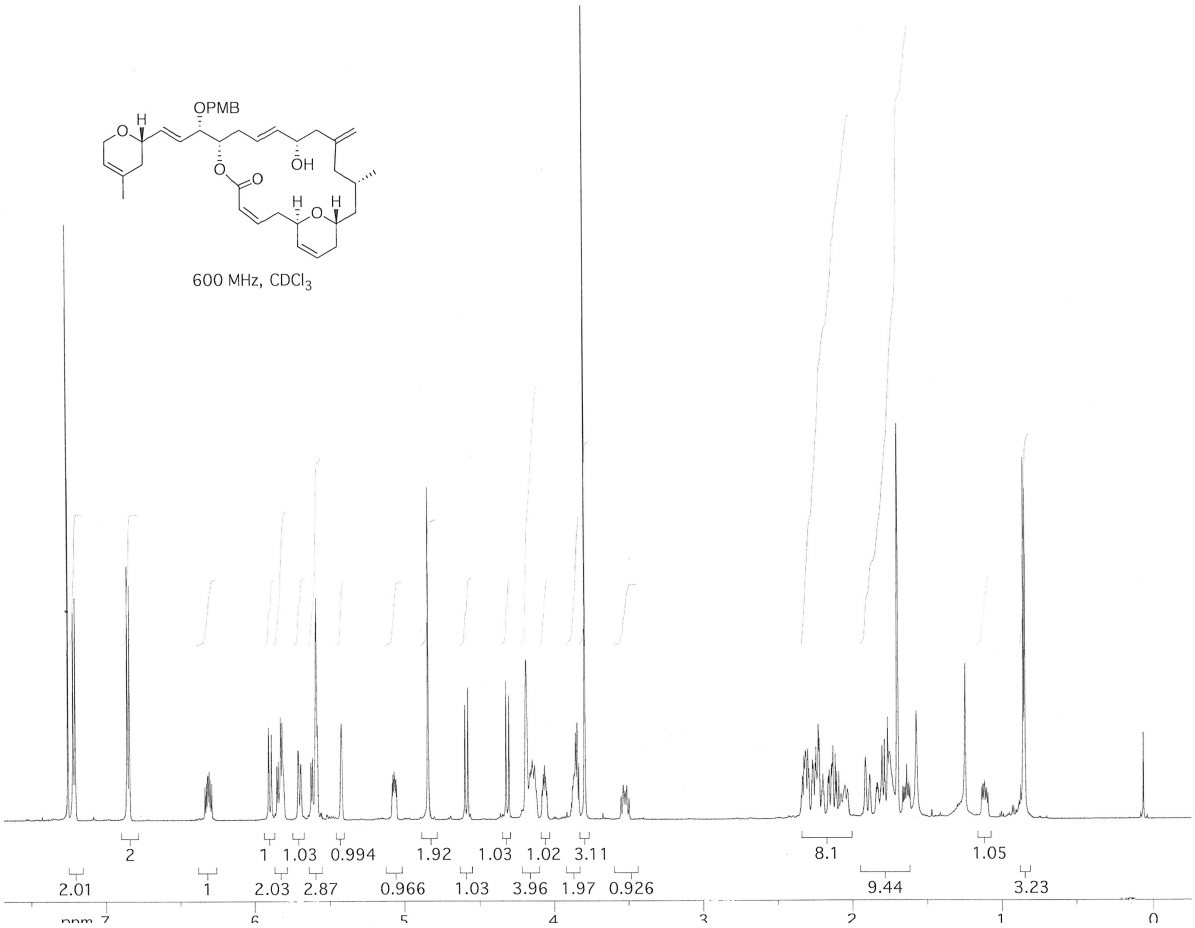

OPMB
H
O
OH
O
O
H
O
H
2
600 MHz, CDCl3
2.09
3.07
2.09
1.02
1.91
0.978
0.928
3.93
3.22
3.18
0.943
2.04
0.999
1.1
1.07
0.96
1.05
1.94
1.97
4.2
13.08
1.95
1.09
3.07
ppm
7
6
5
4
3
2
1
0

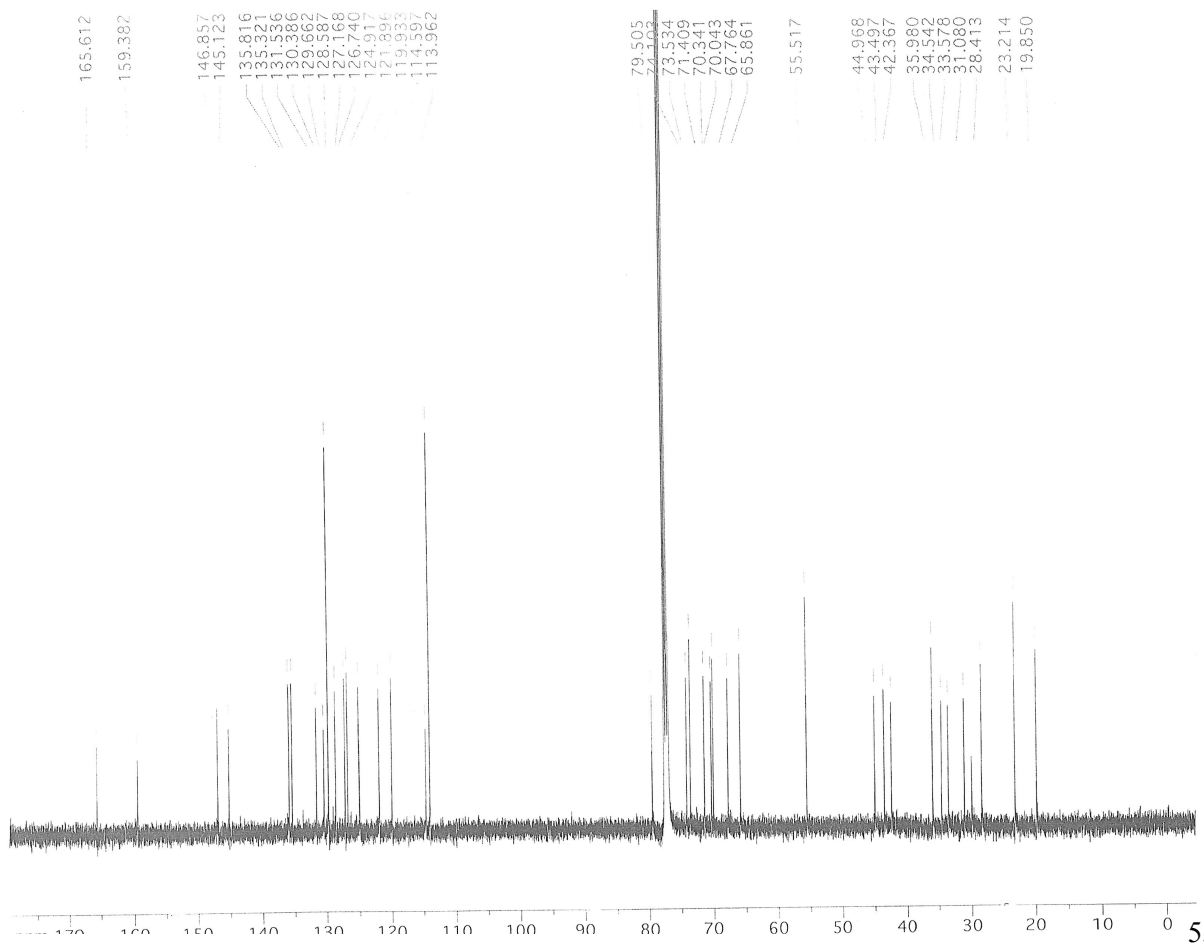

165.603
159.365
147.581
144.564
136.085
135.906
131.485
130.372
129.610
128.581
127.855
126.696
125.007
121.656
119.934
115.817
113.937
79.452
72.949
71.846
70.293
70.175
67.790
65.810
55.480
43.934
40.714
35.974
34.253
34.035
31.604
28.515
23.168
21.209
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

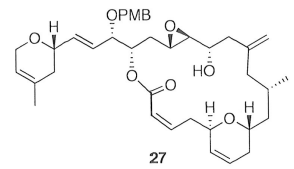


600 MHz, $CDCl_3$



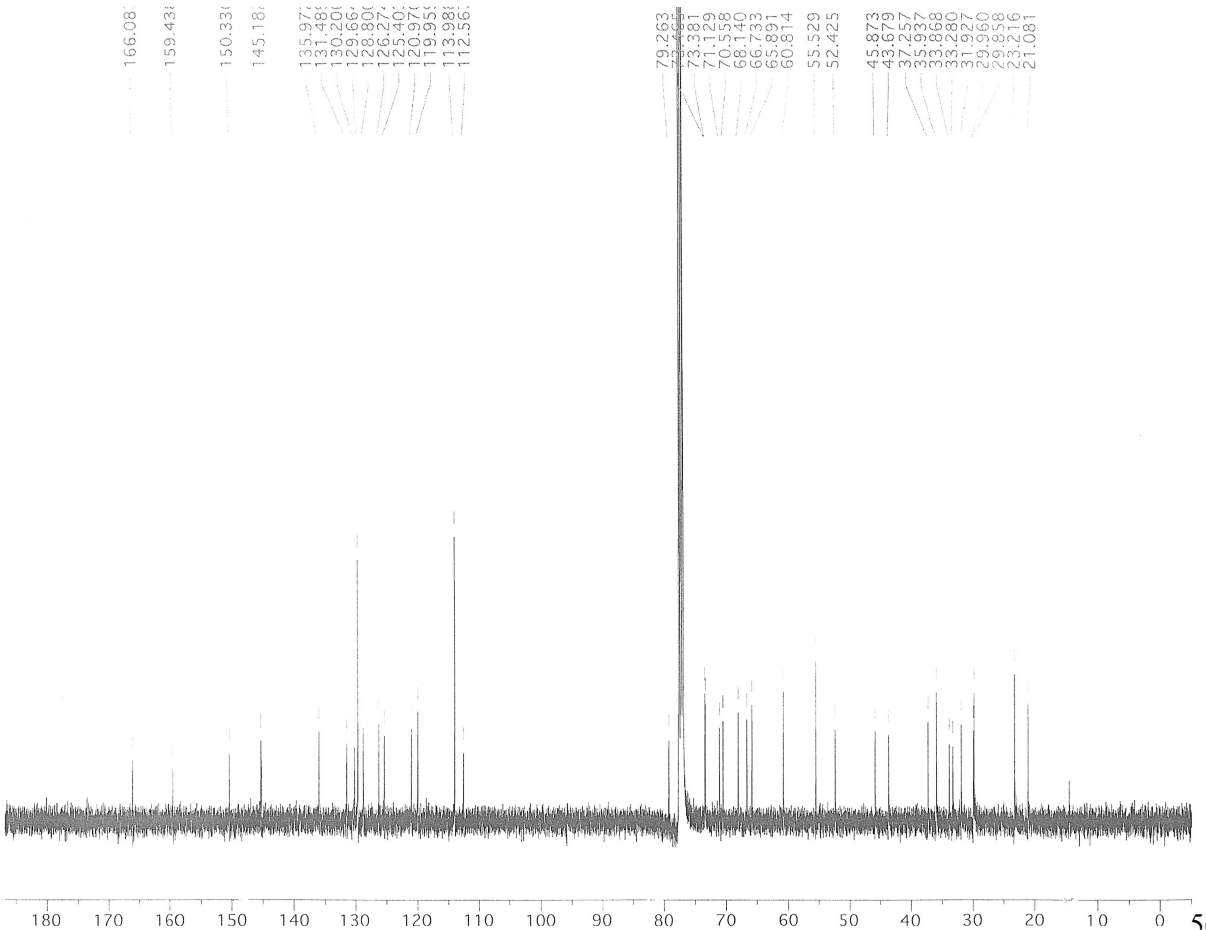

OPMB
H
O
OH
O
O
H
H
O
600 MHz, CDCl3
2
1
1.03
0.994
1.92
1.03
1.02
3.11
8.1
1.05
2.01
1
2.03
2.87
0.966
1.03
3.96
1.97
0.926
9.44
3.23
ppm

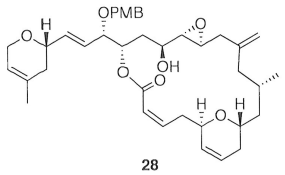

165.612
159.382
146.857
145.123
135.816
135.321
131.536
130.386
129.662
128.587
127.168
126.740
124.917
121.896
119.933
114.597
113.962
79.505
74.103
73.534
71.409
70.341
70.043
67.764
65.861
55.517
44.968
43.497
42.367
35.980
34.542
33.578
31.080
28.413
23.214
19.850
ppm



27

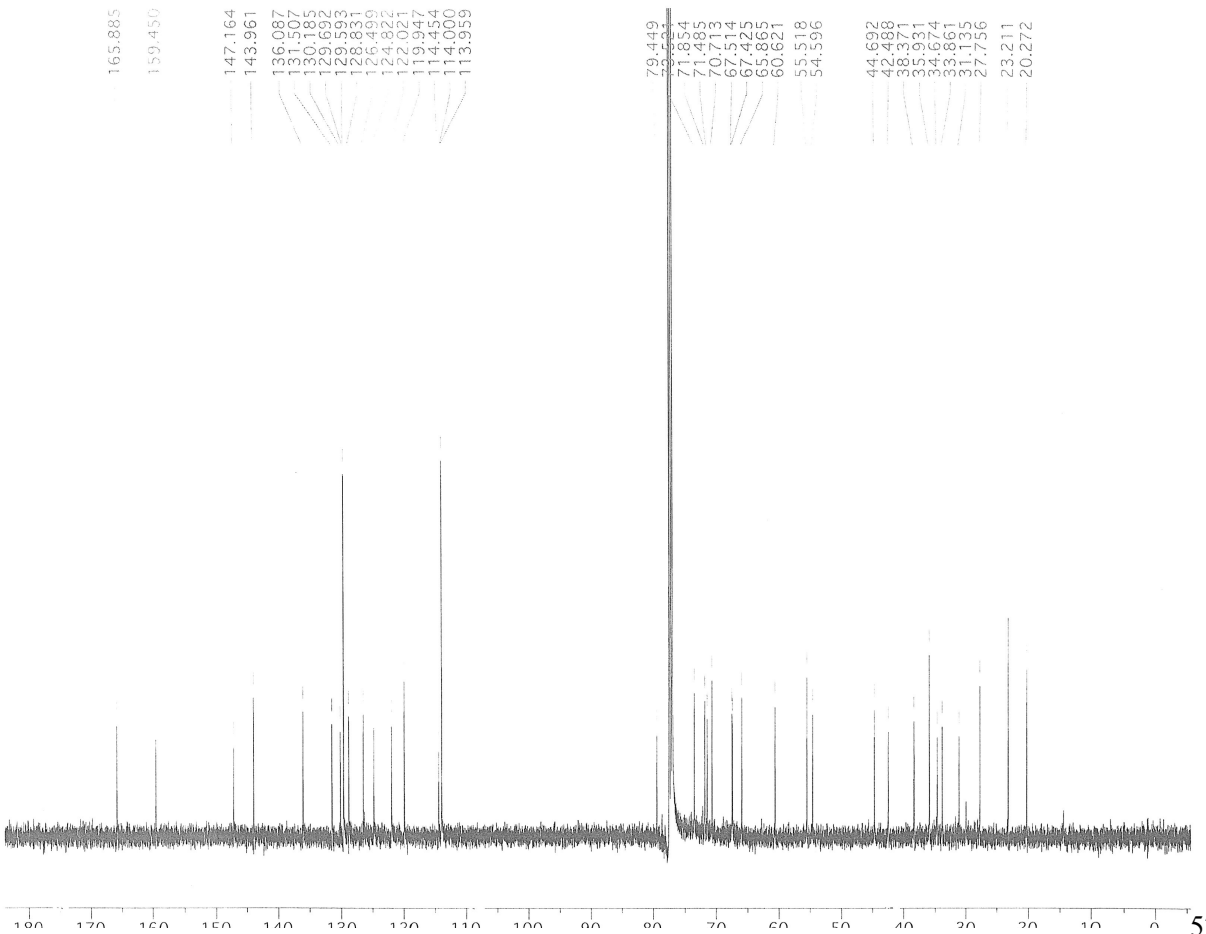
600 MHz, $CDCl_3$

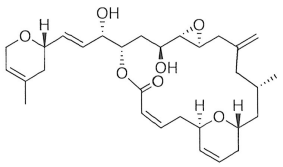




28

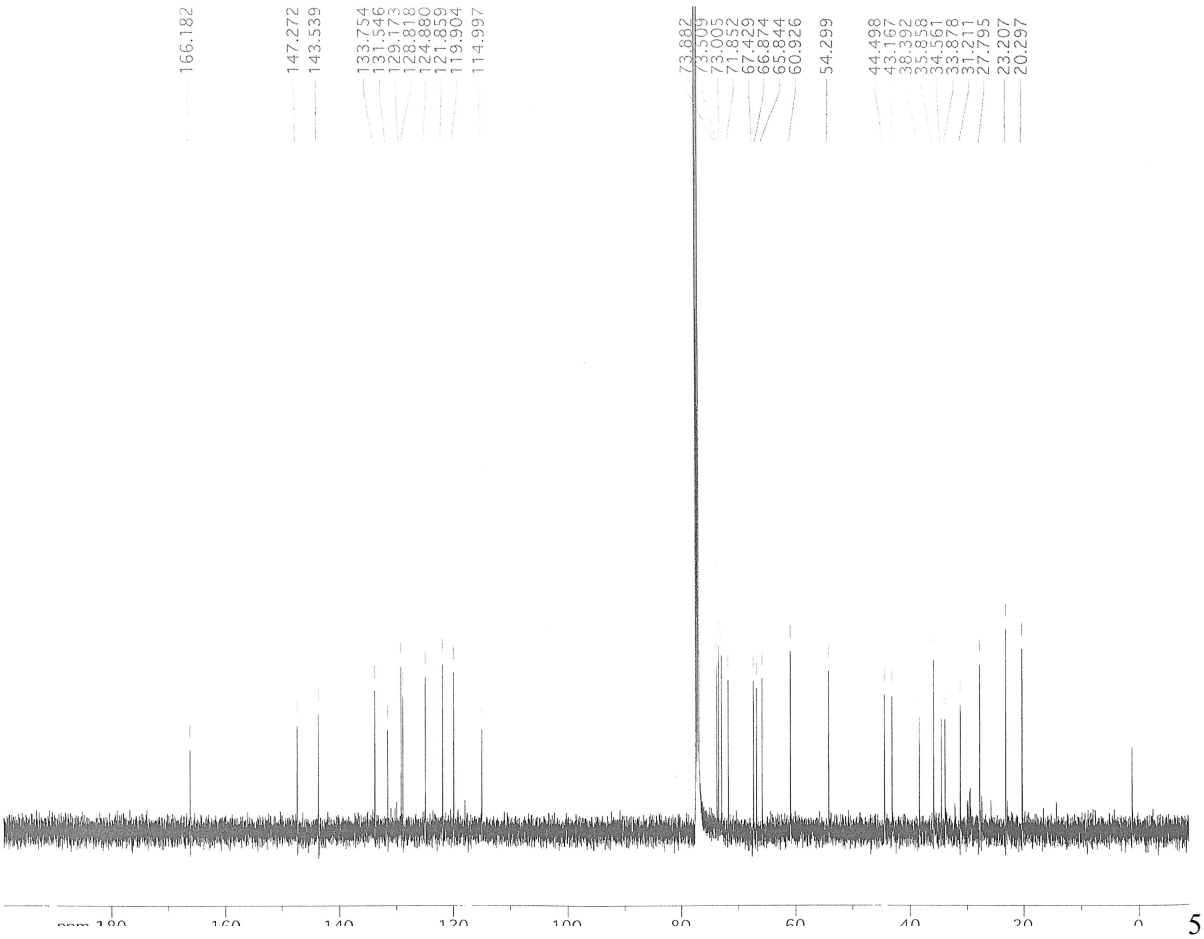
600 MHz, $CDCl_3$

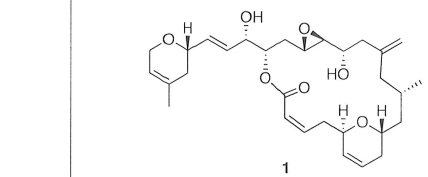




Laulimalide Analogue **29**

600 MHz, $CDCl_3$

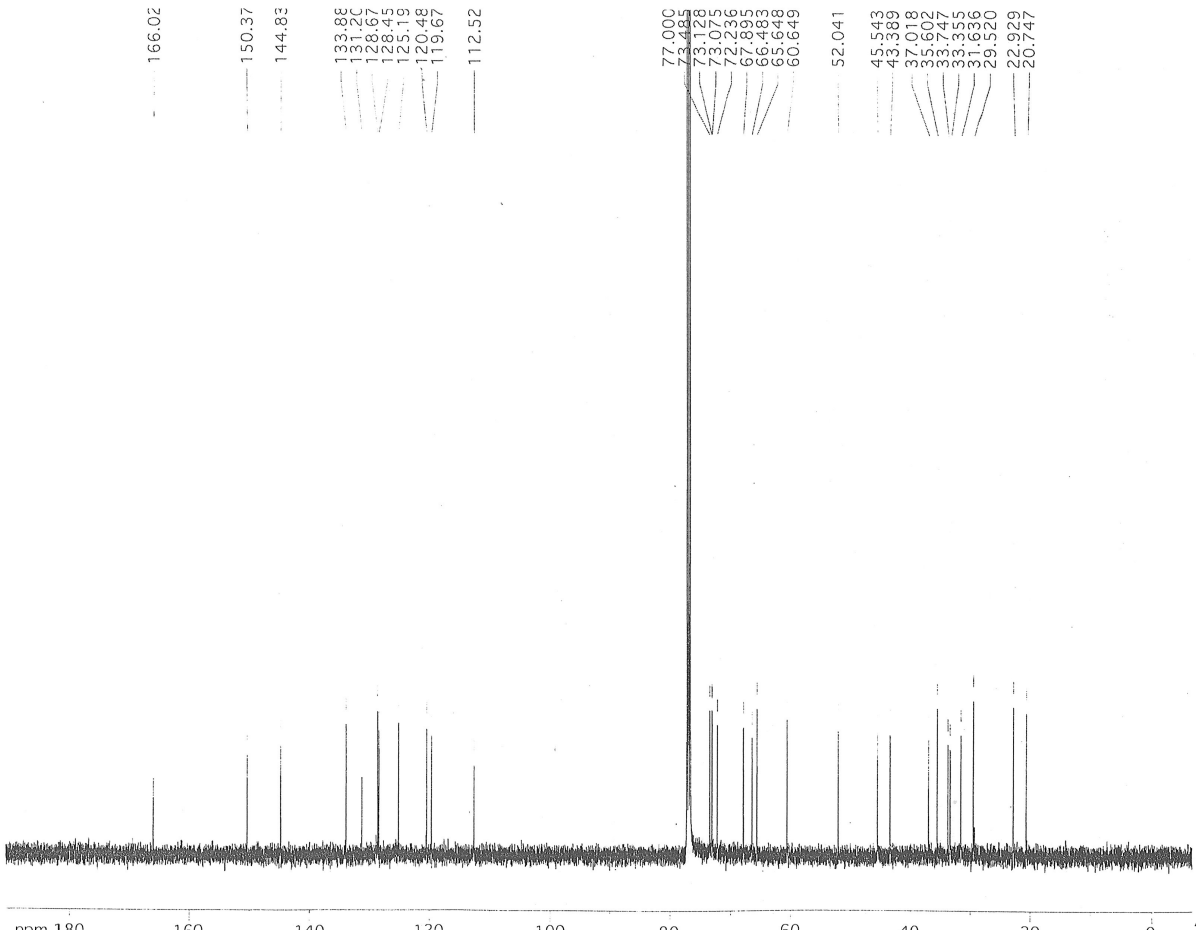


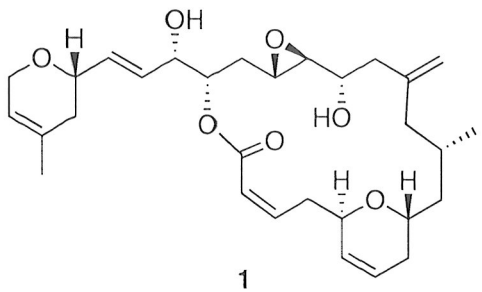


1

Laulimalide

600 MHz, $CDCl_3$





1

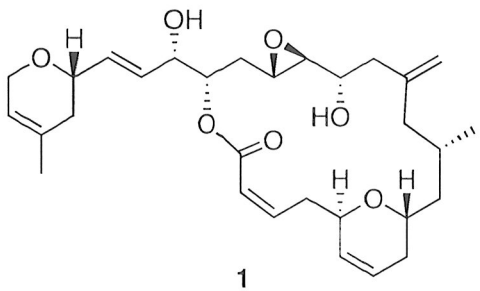
Natural

P. Crews, Santa Cruz

Laulimalide

Varian 600 MHz, $CDCl_3$

60



1

Synthetic

DA-5-410

ppm 7 6 5 4 3 2 1 0