Supporting Information

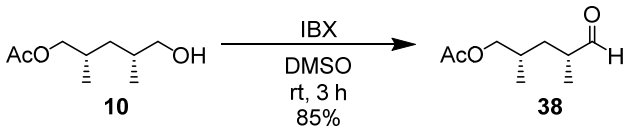
Total synthesis of verucopeptin, an inhibitor of hypoxia-inducible factor 1 (HIF-1)

Nobuaki Takahashi [a], Hideaki Hayashi [a], Viktors Poznaks [a], Hideaki Kakeya *[a]

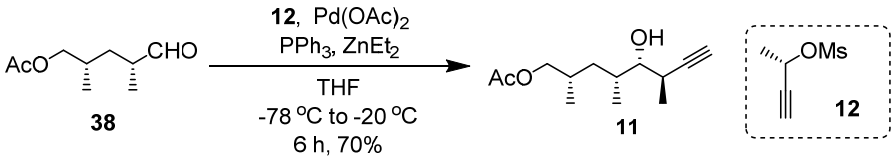
[a]Department of System Chemotherapy and Molecular Sciences, Division of Bioinformatics and Chemical Genomics, Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan.

Table of Contents

General. IR: recorded on a JASCO FT/IR-4100 spectrophotometer. ^{1}H and ^{13}C NMR spectra: recorded on JEOL NMR spectrometers at 500 MHz (^{1}H NMR) and at 125 MHz (^{13}C NMR) or Bruker Avance I at 150 MHz (^{13}C NMR). J values are given in Hz. Multiplicities are given as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. ESI-MS: recorded on LC-IT-TOF MS (Shimadzu) mass spectrometers. Optical rotation: measured with a JASCO P-2200 polarimeter. TLC: precoated silica gel 60 F254 plates (Merck, 0.25 mm thick). Column chromatography: Silica Gel 60N [KANTO, 40-50 μm (for flash column chromatography)]. High performance liquid chromatography (HPLC): performed using a Prominence CBM-20A (Shimadzu) system equipped with a Prominence SPD-20A UV/VIS detector (Shimadzu).

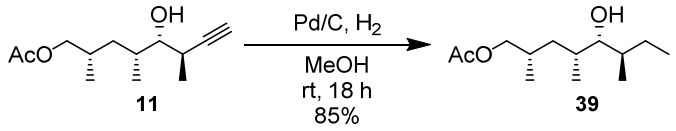


Aldehyde 38: To a stirred solution of **10** (1.25 g, 7.27 mmol) in dry DMSO (20.0 mL) was added IBX (4.20 g, 15.00 mmol) under N_2 atmosphere and the mixture was stirred at room temperature. After stirring for 3 hours, the reaction was quenched by adding a mixture of sat. $Na_2S_2O_3$ aq and sat. $NaHCO_3$ aq (1:1). The whole mixture was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 30:70) to afford 1.05 g (85%) of **38** as a colorless oil; $[\alpha]_D^{20}$ –12.3 (*c* 0.98, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2969, 1771 (CO), 1731, 1053; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 9.59 (1H, s), 3.92 (2H, dd, *J* = 10.5, 5.5), 2.48 (1H, m), 2.06 (3H, s), 1.92-1.80 (2H, overlapped), 1.18 (1H, dddd, *J* = 6.0, 6.0, 6.0, 6.0), 1.12 (3h, d, *J* = 6.5), 0.96 (3H, d, *J* = 6.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 204.6, 171.1, 68.8, 43.9, 34.5, 30.2, 20.9, 17.2, 14.2; HR-ESI-MS calcd for $C_9H_{17}O_3$ $[M+H]^+$: 173.1178, found: 173.1178.

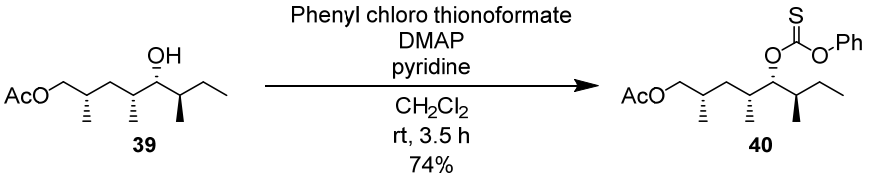


Propargylalcohol 11: A round-bottomed flask was charged with $Pd(OAc)_2$ (14.8 mg, 0.066 mmol) and PPh_3 (17.8 mg, 0.068 mmol). The flask was fitted with a rubber septum, evacuated and then backfilled with N_2, and Freshly degassed dry THF (5.0 mL) was added to the flask. After the flask was cooled to -78 °C, mesylate **12** (132.9 mg, 0.898 mmol) and aldehyde **38** (117.7 mg, 0.692 mmol) were added followed by dropwise addition of diethylzinc (1.9 mL, 1 M in toluene, 1.9 mmol). The solution was then warmed to -20 °C. After stirring for 6 h, the reaction was quenched with 1*N* HCl aq., and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 20:80) to afford 109.9 mg (70%) of **11** as a pale yellow oil; $[\alpha]_D^{20}$ +12.5 (*c* 0.50, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2972, 2932, 1733 (CO), 1461, 1397, 1372, 1245, 1043, 981; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 3.96 (1H, dd, *J* = 11.0, 5.0), 3.85 (1H, dd, *J* = 11.0, 5.0), 3.21 (1H, dd, *J* = 6.5, 5.5), 2.66 (1H, dq, *J* = 6.5, 2.0), 2.13 (1H, d, *J* = 2.5), 2.05 (3H, s), 1.92 (1H, m), 1.80 (1H, br-s), 1.73 (1H, m), 1.50 (1H, m),

1.19 (3H, d, *J* = 7.5), 1.08 (1H, m), 0.95 (3H, d, *J* = 8.0), 0.93 (3H, s, *J* = 8.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 171.2, 85.7, 71.0, 68.9, 37.6, 32.9, 30.7, 29.8, 20.9, 17.9, 17.6, 14.2, 13.9 HR-ESI-MS calcd for $C_{13}H_{23}O_3$ $[M+H]^+$: 227.1647, found: 227.1670.

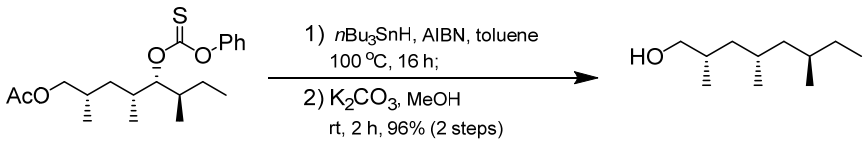


Acetate 39: To a stirred solution of compound **11** (940. 0 mg, 4.16 mmol) in MeOH (40.0 mL) was added Pd/C (10%, 94.0 mg) and the mixture was stirred at room temperature under H_2 atmosphere for 18 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (ethyl acetate /*n*-haxane = 20:80) to afford 813.5 mg (85%) of acetate **39** as a colorless oil; $[\alpha]_D^{20}$ +1.3 (*c* 0.40, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2969, 1736 (CO), 1246, 1039; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.96 (1H, dd, *J* = 11.0, 6.0), 3.86 (1H, dd, *J* = 10.5, 6.5), 3.15 (1H, dd, *J* = 8.5, 3.0), 2.06 (3H, s), 1.89 (dq, *J* = 6.5, 2.0), 1.78 (1H, m), 1.72 (1H, m), 1.50 (br-s), 1.47 (1H, m), 1.17-1.06 (2H, overlapped), 0.94 (3H, d, *J* = 5.5), 0.91 (3H, d, *J* = 7.5), 0.85 (3H, d, *J* = 7.0), 0.82 (3H, d, *J* = 7.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 171.2, 77.6, 69.4, 38.1, 37.6, 31.6, 29.7, 25.1, 17.6, 15.1, 12.9, 11.0; HR-ESI-MS calcd for $C_{13}H_{27}O_3$ $[M+H]^+$: 231.1960, found: 231.1944.



Carbonothioate 40: To a stirred solution of compound **39** (24.5 mg, 0.064 mmol) in dry CH_2Cl_2 (0.25 mL) and dry pyridine (0.25 mL) were added Phenyl Chlorothionoformate (43.2 μL, 0.32 mmol) and DMAP (7.8 mg, 6.4 μmol) under N_2 atmosphere and the mixture was stirred at room temperature. After stirring for 3.5 hours, the reaction was quenched with 1*N* HCl aq., and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 3:97) to afford 28.3 mg (74%) of **40** as a yellow oil; $[\alpha]_D^{20}$ -6.00 (*c* 0.11, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2972, 1740 (CO), 1287, 1232, 1192; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.40 (2H, m), 7.28 (1H, m), 7.09

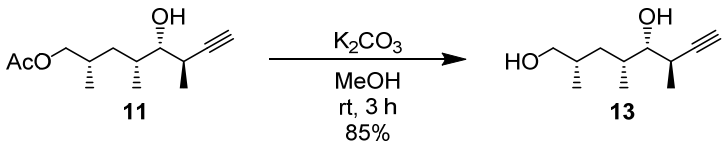
(2H, d, *J* = 7.5), 5.27 (1H, dd, *J* = 8.0, 3.0), 3.91 (2H, m), 2.10-2.00 (1H, overlapped), 2.05 (3H, s), 1.88 (1H, m), 1.63-1.50 (3H, overlapped), 1.18 (1H, m), 1.08 (1H, m), 0.97 (3H, dd, *J* = 7.0, 7.0), 0.96 (3H, d, *J* = 7.0), 0.94 (3H, d, *J* = 7.0), 0.92 (3H, d, *J* = 7.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 195.9, 171.3, 153.4, 129.6, 129.4, 126.4, 122.0, 120.9, 91.6, 69.0, 37.6, 36.6, 31.9, 29.9, 29.7, 24.8, 21.0, 17.6, 15.2, 14.2, 11.4; HR-ESI-MS calcd for $C_{20}H_{31}O_4S$ $[M+H]^+$: 367.1943, found: 367.1955.



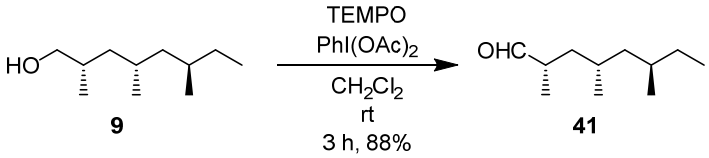
40 **9**

Alcohol 9: To a stirred solution of **40** (913.0 mg, 2.54 mmol) in toluene (32.0 mL) were added AIBN (26.8 mg, 0.163 mol) and *n*Bu_3SnH (1.40 mL, 5.20 mmol). After stirring for 16 h at 100 °C, the reaction was quenched with sat. KF aq. and the mixture were extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a crude product that was subjected to the next reaction without further purification.

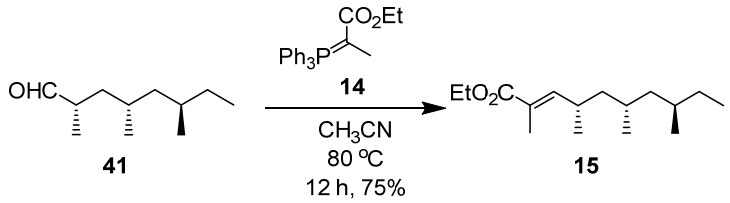
To a stirred solution of the above crude product in MeOH (40.0 mL) was added K_2CO_3 (699.5 mg, 5.07 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction was quenched with sat. NH_4Cl aq. and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 10:90) to afford 421.8 mg (96%, 2 steps) of **9** as a colorless oil; $[\alpha]_D^{20}$ -37.6 (*c* 0.33, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2959, 2914, 2874, 1461, 1382, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.51 (1H, dd, *J* = 10.4, 5.2), 3.38 (1H, dd, *J* = 10.4, 7.2), 1.72 (1H, m), 1.58 (1H, m), 1.37 (2H, m), 1.25 (2H, m), 1.18-0.96 (4H, overlapped), 0.91 (3H, d, *J* = 6.4), 0.86 (3H, d, *J* = 7.6), 0.85 (3H, d, *J* = 7.2), 0.82 (3H, dd, *J* = 7.2, 5.6); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 68.5, 43.9, 41.9, 33.0, 31.7, 30.6, 27.4, 20.3, 18.8, 17.1, 11.5; HR-ESI-MS calcd for $C_{11}H_{25}O$ $[M+H]^+$: 173.1905, found: 173.1915.



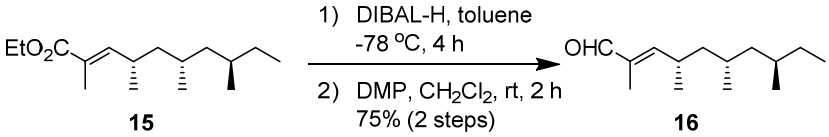
Diol 13: To a stirred solution of **11** (23.4 mg, 0.104 mmol) in MeOH (1.0 mL) was added K_2CO_3 (43.0 mg, 0.312 mmol) at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched with sat. NH_4Cl aq. and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 30:70) to afford 16.2 mg (85%) of **13** as a colorless oil; $[\alpha]_D^{20}$ +5.7 (*c* 0.68, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2965, 2918, 2877, 1453, 1375, 1033, 983, 637; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 3.51 (1H, dd, *J* = 10.5, 5.5), 3.45 (1H, dd, *J* = 10.5, 6.0), 3.27 (1H, t, *J* = 5.5), 2.68 (1H, dddd, *J* = 13.0, 7.0, 7.0, 2.0), 2.15 (1H, d, *J* = 2.0), 1.98 (1H, br-s), 1.74 (3H, m), 1.55 (1H, ddd, *J* = 14.0, 7.0, 7.0), 1.20 (3H, d, *J* = 7.0), 0.94 (3H, d, *J* = 6.5), 0.93 (3H, d, *J* = 6.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 85.9, 76.8, 70.9, 67.8, 37.2, 33.0, 32.8, 30.6, 17.6, 17.5, 14.3; HR-ESI-MS calcd for $C_{11}H_{21}O_2$ $[M+H]^+$: 185.1542, found: 185.1535.



Aldehyde 41: To a stirred solution of alcohol **9** (18.0 mg, 0.105 mmol) in CH_2Cl_2 (1.0 mL) were added $PhI(OAc)_2$ (50.4 mg, 0.156 mmol), and TEMPO (0.82 mg, 5.3 μmol) at 0 °C under N_2 atmosphere. After stirring for 3 h at room temperature, the reaction was quenched with sat. $NaHCO_3$ aq., and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 5:95) to afford 16.7 mg (88%) of **41** as a pale yellow oil; $[\alpha]_D^{20}$ +15.9 (*c* 0.39, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2968, 1741 (CO), 1211; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 9.59 (1H, s), 2.44 (1H, dq, *J* = 7.0, 2.5), 1.67 (1H, dq, *J* = 13.5, 7.0), 1.56 (1H, m), 1.41 (1H, m), 1.32-1.21 (2H, overlapped), 1.15 (2H, m), 1.08 (3H, d, *J* = 8.0), 1.08-1.04 (2H, overlapped), 0.87 (3H, d, *J* = 8.0), 0.85 (3H, d, *J* = 8.0), 0.82 (3H, d, *J* = 8.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 205.6, 44.1, 40.0, 39.0, 31.6, 30.4, 27.7, 19.7, 18.8, 14.0, 11.4; HR-ESI-MS calcd for $C_{11}H_{23}O$ $[M+H]^+$: 171.1749, found: 171.1769.



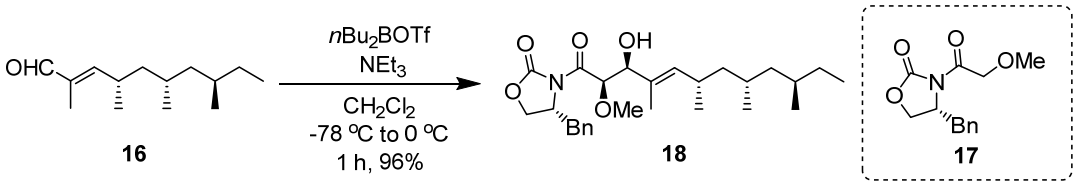
Unsaturated ester 15: To a stirred solution of aldehyde **41** (153.0 mg, 0.900 mmol) in CH_3CN (10.0 mL) was added ethyl 2-(triphenylphosphoranylidene)propionate (**14**, 650.0 mg, 1.796 mmol) at room temperature under N_2 atmosphere. After stirring for 12 h at 80 °C, the reaction mixture was evaporated and purified by silica gel open column chromatography (ethyl acetate/*n*-hexane = 95:5) to afford 171.4 mg (75%) of **15** as a pale yellow oil; $[\alpha]_D^{20}$ +7.2 (*c* 0.24, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2966, 2915, 2873, 1716 (CO), 1213, 1208, 1153, 1105, 771; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.51 (1H, d, *J* = 10.4), 4.18 (2H, m), 2.62 (1H, m), 1.85 (3H, d, *J* = 1.2), 1.56 (1H, s), 1.38 (2H, m), 1.29 (3H, dd, *J* = 7.0, 7.0), 1.29-1.27 (2H, overlapped), 1.19-1.02 (3H, overlapped), 0.97 (3H, d, *J* = 6.4), 0.85 (3H, dd, *J* = 7.2, 7.2), 0.82-0.76 (6H, overlapped) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 168.5, 148.3, 126.1, 60.3, 45.2, 44.8, 31.6, 30.8, 30.2, 28.0, 20.4, 19.6, 19.0, 14.3, 12.5, 11.4; HR-ESI-MS calcd for $C_{16}H_{30}NaO$ $[M+Na]^+$: 277.2143, found: 277.2130.



Unsaturated aldehyde 16: To a stirred solution of **15** (114.4 mg, 0.50 mmol) in dry toluene (5.0 mL) was added DIBAL-H (1.0 M in toluene, 1.5 mL, 1.5 mmol) at –78 °C under N_2 atmosphere. After stirring for 4 h, the reaction was quenched with sat. Rochelle salt aq. and then the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a crude product that was subjected to the next reaction without further purification.

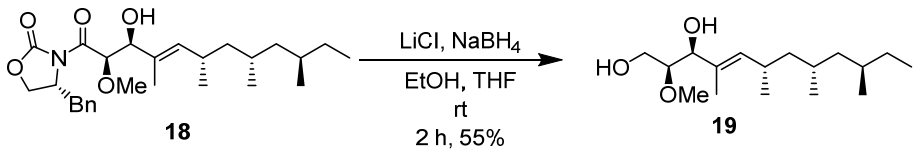
To a stirred solution of the above crude product in dry CH_2Cl_2 (11.0 mL) was added DMP (424.3 mg, 1.0 mmol) at 0 °C under N_2 atmosphere. After stirring for 2 h at room temperature, the reaction was quenched with sat. $NaHCO_3$ aq./sat. $Na_2S_2O_3$ aq. (1:1) and then the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 10:90) to afford 78.8 mg (75%, 2 steps) of **16** as a colorless oil; $[\alpha]_D^{20}$ -11.4 (*c* 0.18,

$CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2963, 2922, 2877, 1690 (CO), 1644, 1461, 1380, 1283, 672; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 9.39 (1H, s), 6.23 (1H, d, *J* = 9.6), 2.82 (1H, m), 1.77 (3H, s), 1.44-1.18 (5H, m), 1.15-0.98 (3H, overlapped), 1.05 (3H, d, *J* = 6.4), 0.86 (3H, dd, *J* = 7.2, 7.2), 0.82 (3H, d, *J* = 6.4), 0.79 (3H, d, *J* = 6.4); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 195.7, 160.9, 137.8, 45.1, 44.8, 31.6, 31.2, 30.2, 28.1, 20.3, 19.4, 19.0, 11.4, 9.3; HR-ESI-MS calcd for $C_{14}H_{27}O$ $[M+H]^+$: 211.2062, found: 211.2057.



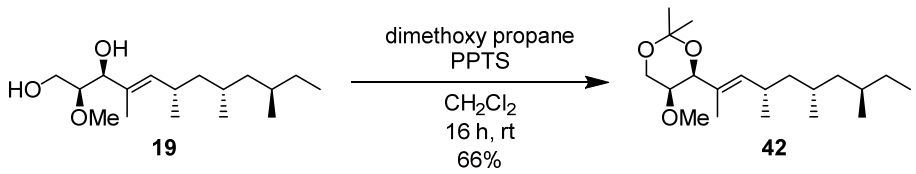
16 18 17

Aldol product 18: To a stirred solution of oxazoridinone **17** (69.3 mg, 0.278 mmol) in dry CH_2Cl_2 (0.7 mL) were added *n*Bu_2BOTf (1.0 M in CH_2Cl_2, 0.35 mL, 0.350 mmol) and NEt_3 (48.5 μL, 0.348 mmol) at 0 °C under N_2 atmosphere. After 1 h, the reaction mixture was cooled to -78 °C and **16** (48.7 mg, 0.232 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise and stirred at -78 °C for 1 h. The reaction was then warmed up to 0 °C and stirred for 1 h. MeOH/ pH 7.4 PBS buffer (2:1, 730 μL) and MeOH/30% H_2O_2 (2:1, 300 μL) were added and the whole reaction mixture was stirred at room temperature. After 12 h, the whole mixture was extracted three times with ethyl acetate and then the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 20:80) to afford 102.2 mg (96%) of **18** as a colorless oil; $[\alpha]_D^{20}$ -8.7 (*c* 0.49, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2956, 2922, 2872, 2837, 1779 (CO), 1706 (CO), 1456, 1382, 1352, 1293, 1212, 1194, 1126, 1109, 1071, 1051, 966, 763, 752, 704; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.34 (2H, dd, *J* = 8.0, 6.5), 7.29 (1H, dd, *J* = 7.0, 7.0), 7.23 (2H, d, *J* = 7.0), 5.19 (2H, dd, *J* = 4.0, 3.5), 4.67 (1H, m), 4.26 (1H, br-s), 4.21 (2H, m), 3.46 (3H, s), 3.39 (1H, dd, *J* = 11.5, 3.0), 3.84 (1H, dd, *J* = 13.0, 9.5), 2.61 (1H, m), 2.53 (1H, m), 1.72 (3H, s), 1.47 (1H, m), 1.38 (1H, m), 1.30-1.18 (2H, overlapped), 1.14 (4H, overlapped), 0.86 (3H, d, *J* = 8.0), 0.85 (3H, d, *J* = 8.0, 7.5), 0.80 (3H, d, *J* = 6.5), 0.78 (3H, d, *J* = 6.5); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 171.2, 153.2, 135.0, 134.1, 131.1, 129.4, 129.0, 127.5, 80.5, 76.6, 58.8, 55.8, 45.8, 45.0, 37.8, 31.6, 29.7, 27.8, 19.3, 19.1, 12.7, 11.4; HR-ESI-MS calcd for $C_{16}H_{30}NaO$ $[M+Na]^+$: 482.2882, found: 482.2887.



18 19

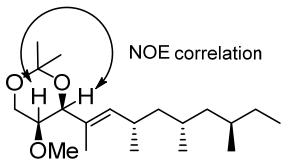
Diol 19: To a stirred solution of aldol product **18** (55.0 mg, 0.21 mmol) in THF (1.0 mL) were added $NaBH_4$ (30.7 mg, 0.808 mmol) and LiCl (33.8 mg, 0.805 mmol) at 0 °C. After 1 h, EtOH (1.0 mL) was added dropwise and stirred at room temperature for 2 h. The reaction was quenched with H_2O and the layers were separated. The aqueous layer was extracted two times with $CHCl_3$ and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 45:55) to afford 18.0 mg (55%) of **19** as a pale yellow oil; $[\alpha]_D^{20}$ -2.1 (*c* 0.30, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2959, 2924, 2871, 2842, 1119, 1055, 1014, 775, 671, 647; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.25 (1H, d, *J* = 10.0), 4.02 (1h d, *J* = 7.5), 3.72 (1H, dd, *J* = 12.0, 4.0), 3.53 (1H, dd, *J* = 12.0, 4.0), 3.52 (3H, s), 3.27 (1H, m), 2.52 (1H, m), 1.67 (3H, d, *J* = 1.5), 1.45 (1H, m), 1.38 (1H, m), 1.25 (2H, m), 1.14-0.98 (4H, overlapped), 0.90 (3H, d, *J* = 7.0), 0.85 (3H, dd, *J* = 7.5, 7.5), 0.80 (3H, d, *J* = 4.0), 0.79 (3H, d, *J* = 4.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 135.8, 131.9, 82.8, 77.1, 60.9, 58.8, 45.7, 44.8, 31.6, 30.2, 29.5, 27.8, 21.1, 19.5, 19.0, 12.2, 11.4; HR-ESI-MS calcd for $C_{17}H_{35}O_3$ $[M+Na]^+$:287.2586, found: 287.2595.



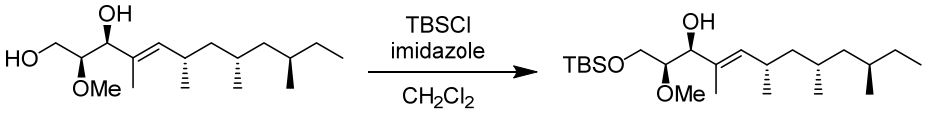
19 42

Acetal 42: To a stirred solution of diol **19** (13.0 mg, 0.046 mmol) in CH_2Cl_2 (1.0 mL) were added dimethoxypropane (17.0 μL, 0.139 mmol) and PPTS (11.5 mg, 0.046 mmol) at 0 °C. After stirring for 16 h at room temperature, the reaction was quenched with sat. NH_4Cl aq. and then the whole mixture were extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 10:90) to afford 9.5 mg (66%) of **42** as a colorless oil; $[\alpha]_D^{20}$ +19.3 (*c* 0.45, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2960, 2924, 2871, 2841, 1456, 1376, 1276, 1195, 1096, 864, 772, 761; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.25 (1H, d, *J* = 9.0), 4.22 (1H, s), 4.02-3.92 (2H, overlapped), 3.35 (3H, s), 3.06 (1H, d, *J* = 1.5), 2.53 (1H, m), 1.70 (3H, s), 1.51 (1H, m), 1.47 (3H, s), 1.46 (3H, s), 1.39 (1H, m), 1.25 (2H, m), 1.10 (1H, m), 1.02 (3H, dd, *J* = 7.0, 7.0), 0.92 (3H, d, *J* = 7.0), 0.85 (3H, dd, *J* = 7.5, 7.0), 0.81 (3H, d, *J* =

6.5), 0.80 (3H, d, *J* = 7.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 132.6, 130.5, 98.6, 75.0, 74.8, 62.1, 57.9, 46.0, 44.7, 31.7, 30.4, 29.3, 29.2, 27.7, 21.2, 19.8, 19.0, 18.9, 13.5, 11.5; HR-ESI-MS calcd for $C_{20}H_{39}O_3$ $[M+H]^+$: 327.2899, found: 327.2878.

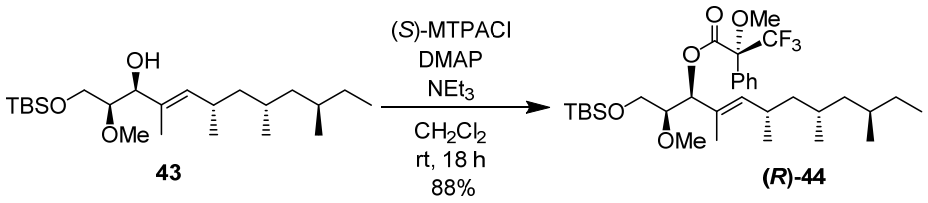


42

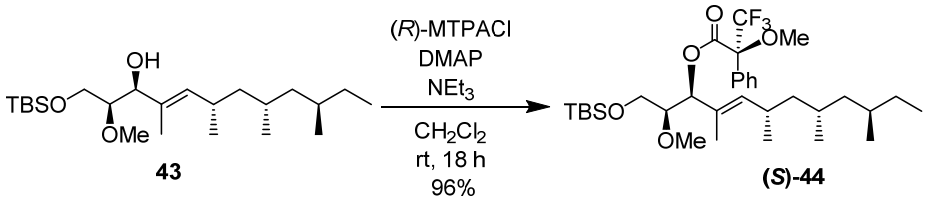


19 **43**

Mono-TBS-protected compound 43: To a stirred solution of diol **19** (49.6 mg, 0.183 mmol) in CH_2Cl_2 (2.0 mL) were added TBSCl (32.8 mg, 0.217 mmol), and imidazole (18.7 mg, 0.275 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction was quenched with H_2O, and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 5:95) to afford 59.3 mg (81%) of **43** as a pale yellow oil; $[\alpha]_D^{20}$ +2.9 (*c* 0.20, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2955, 2927, 2858, 1455, 1255, 1125, 1087, 1007, 836, 773, 670; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 5.20 (1H, d, *J* = 9.5), 3.93 (1H, d, *J* = 7.0), 3.71 (1H, dd, *J* = 11.0, 3.5), 3.57 (1H, dd, 11.0, 3.5), 3.50 (3H, s), 3.22 (1H, m), 2.52 (1H, m), 1.66 (3H, d, *J* = 10.0), 1.48 (1H, m), 1.38 (1H, m), 1.25 (2H, m), 1.14-0.98 (4H, overlapped), 0.90 (9H, s), 0.88 (3H, overlapped), 0.85 (3H, dd, *J* = 7.5, 7.5), 0.80 (3H, d, *J* = 6.5), 0.78 (3H, d, *J* = 6.0), 0.05 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 135.0, 132.1, 83.0, 76.1, 62.7, 59.2, 45.8, 44.9, 31.6, 30.2, 29.5, 27.8, 25.9, 21.2, 19.5, 19.1, 18.2, 12.4, 11.4, -5.5; HR-ESI-MS calcd for $C_{23}H_{48}NaO_3Si$ $[M+Na]^+$: 423.3270, found: 423.3265.

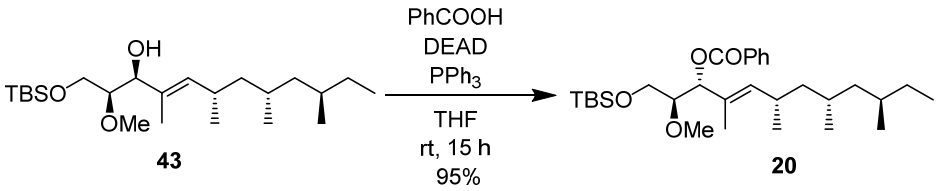


(*R*)-MTPA ester 44: To a stirred solution of alcohol **43** (4.8 mg, 0.012 mmol) in dry CH_2Cl_2 (1.0 mL) were added (*S*)-MTPACl (60.0 μL, 0.321 mmol), NEt_3 (61.2 μL, 0.440 mmol), and DMAP (cat. amount) at 0 °C under N_2 atmosphere. After stired for 18 h at room temperature, the reaction was quenched with H_2O, and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 5:95) to afford 6.5 mg (88%) of **(*R*)-44** as a colorless oil; $[\alpha]_D^{20}$ -3.2 (*c* 1.08, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2956, 2927, 2857, 1748 (CO), 1256, 1187, 1171, 1017, 839, 773; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.53 (2H, m), 7.41-7.34 (3H, overlapped), 5.41 (1H, d, *J* = 9.0), 5.36 (1H, d, *J* = 10.0), 3.62 (1H, dd, *J* = 11.0, 3.0), 3.54 (3H, s), 3.48 (1H, dd, *J* = 10.5, 5.5), 3.32 (1H, m), 3.24 (3H, s), 2.50 (1H, m), 1.69 (3H, s), 1.48-1.33 (2H, overlapped), 1.28-1.18 (2H, overlapped), 1.10-0.96 (3H, overlapped), 0.89 (3H, d, *J* = 4.5), 0.88 (9H, s), 0.84 (3H, dd, *J* = 7.5, 7.5), 0.77 (3H, d, *J* = 3.5), 0.76 (3H, d, *J* = 3.5), 0.07 (6H, s) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 165.4, 139.4, 132.7, 129.6, 129.3, 128.5, 128.4, 127.6, 127.3, 82.1, 81.6, 65.5, 59.1, 55.3, 45.5, 45.0, 31.6, 30.3, 29.6, 27.9, 25.9, 20.6, 19.4, 18.9, 18.1, 14.0, 12.7, 11.4, -5.5; HR-ESI-MS calcd for $C_{33}H_{55}F_3NaO_5Si[M+Na]^+$: 639.3669, found: 639.3664.

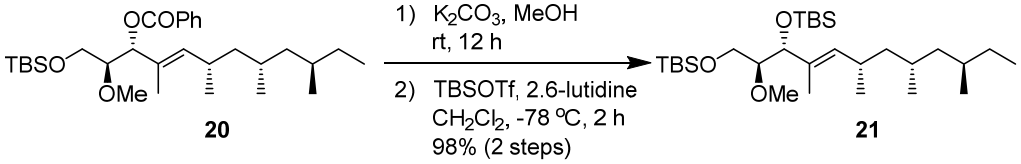


(*S*)-MTPA ester 44: To a stirred solution of alcohol **43** (4.0 mg, 0.010 mmol) in dry CH_2Cl_2 (1.0 mL) were added (*R*)-MTPACl (60.0 μL, 0.321 mmol), NEt_3 (62.5 μL, 0.449 mmol), and DMAP (cat. amount) at 0 °C under N_2 atmosphere. After stired for 18 h at room temperature, the reaction was quenched with H_2O, and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane

= 5:95) to afford 5.9 mg (96%) of **(*S*)-44** as a colorless oil; $[\alpha]_D^{20}$ +8.2 (*c* 1.07, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2955, 2928, 2858, 1749 (CO), 1259, 1188, 1170, 1017, 837, 776; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.53 (2H, m), 7.40-7.32 (3H, overlapped), 5.34 (1H, d, *J* = 9.5), 5.32 (1H, d, *J* = 9.5), 3.68 (1H, dd, *J* = 11.0, 3.0), 3.58 (3H, s), 3.50 (1H, dd, *J* = 11.0, 5.0), 3.43 (3H, s), 3.40 (1H, m), 2.48 (1H, m), 1.56 (3H, s), 1.42 (1H, m), 1.30-1.18 (3H, overlapped), 1.15-0.96 (3H, overlapped), 0.89 (9H, s), 0.87 (3H, dd, *J* = 9.5, 3.5), 0.84 (3H, d, *J* = 7.5), 0.81 (3H, d, *J* = 7.5), 0.79 (3H, d, *J* = 6.5), 0.05 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm:165.5, 139.5, 132.4, 129.4, 128.2, 127.9, 127.5, 82.1, 81.7, 62.1, 58.8, 55.4, 45.6, 45.0, 31.6, 30.2, 29.6, 27.9, 25.9, 20.9, 19.3, 18.9, 18.2, 12.3, 11.4, -5.5;HR-ESI-MS calcd for $C_{33}H_{55}F_3NaO_5Si[M+Na]^+$: 639.3669, found: 639.3656.

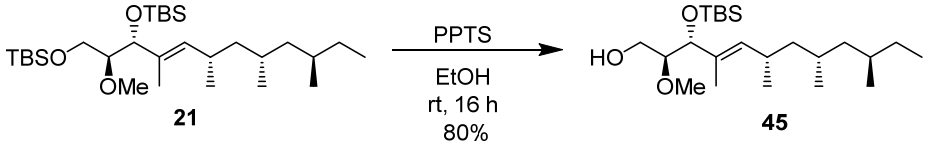


Phenyl ester 20: To a stirred solution of **43** (7.1 mg, 0.018 mmol), PhCOOH (8.8 mg, 0.072 mmol) and PPh_3 (18.9 mg, 0.072 mmol) in THF (0.5 mL) was added DEAD (2.2 M in toluene, 32.3 μL, 0.072 mmol) under N_2 atmosphere at 0 °C. After stirring for 15 h at room temperature, the reaction was quenched with H_2O, and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 2:98) to afford 8.6 mg (95%) of **20** as a pale yellow oil; $[\alpha]_D^{20}$ -2.3 (*c* 0.08, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2956, 2928, 2855, 1725 (CO), 1270, 1111, 956, 838, 776, 712; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 8.03 (2H, d, *J* = 7.0), 7.56 (1H, dd, *J* = 7.5, 7.0), 7.44 (2H, dd, *J* = 8.0, 7.5), 5.41 (1H, d, *J* = 5.5), 5.26 (1H, d, *J* = 9.5), 3.79 (1H, dd, *J* = 10.5, 3.0), 3.70 (1H, dd, *J* = 11.0, 7.0), 3.54 (1H, m), 3.49 (3H, s), 2.52 (1H, m), 1.78 (3H, d, *J* = 1.0), 1.38 (1H, m), 1.32 (1H, m), 1.18 (2H, m), 1.06-0.98 (3H, overlapped), 0.94 (1H, m), 0.92 (3H, d, *J* = 7.0), 0.89 (9H, s), 0.80 (3H, dd, *J* = 7.5, 7.5), 0.76 (3H, d, *J* =6.5), 0.72 (3H, d, *J* = 6.5), 0.04 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 165.1, 136.1, 132.8, 130.6, 129.5, 129.3, 128.3, 83.0, 78.0, 63.2, 59.3, 45.8, 45.0, 31.6, 30.2, 29.6, 27.8, 25.9, 21.3, 19.3, 19.0, 18.3, 13.9, 11.3, -5.3; HR-ESI-MS calcd for $C_{30}H_{52}NaO_4Si$ $[M+Na]^+$: 527.3533, found: 527.3516.



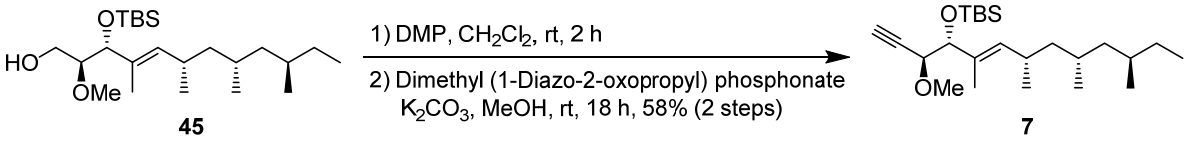
Di-TBS-protected compound 21: To a stirred solution of **20** (159.1 mg, 0.316 mmol) in MeOH (3.0 mL) was added K_2CO_3 (128.3 mg, 0.930 mmol) at 0 °C. After stirring for 16 h at room temperature, the reaction was quenched with sat. NH_4Cl aq. and the mixture were extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a crude product that was subjected to the next reaction without further purification.

To a stirred solution of the above crude product in dry CH_2Cl_2 (3.0 mL) were added 2.6-litidine (0.11 mL, 0.954 mmol), and TBSOTf (0.15 mL, 0,632 mmol) at -78 °C under N_2 atmosphere. After stirring for 2 h, the reaction was quenched with sat. NH_4Cl aq. and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 2:98) to afford 159.2 mg (98%, 2 steps) of **21** as a colorless oil; $[\alpha]_D^{20}$ -13.2 (*c* 0.75, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2955, 2927, 2857, 1461, 1251, 1135, 1091, 1064, 835, 775, 668; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.06 (1H, d, *J* = 9.5), 3.90 (1H, d, *J* = 6.5), 3.84 (1H, dd, *J* = 11.5, 1.0), 3.58 (1H, dd, *J* = 10.5, 6.5), 3.39 (3H, s), 3.17 (1H, dt, *J* = 7.0, 2.5), 2.51 (1H, m), 1.66-1.58 (1H, overlapped), 1.63 (3H, d, *J* = 1.0), 1.48 (1H, m), 1.37 (1H, m), 1.29-0.94 (4H, overlapped), 0.92-0.85 (1H, overlapped), 0.91 (3H, d, *J* = 8.0), 0.90 (9H, s), 0.87 (9H, s), 0.86 (3H, dd, *J* = 7.5, 7.5), 0.79 (3H, d, *J* = 9.5), 0.78 (3H, d, *J* = 9.5), 0.05 (6H, s), 0.02 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 134.9, 133.0, 83.9, 78.0, 63.9, 59.1, 46.1, 45.1, 31.6, 30.4, 29.5, 27.8, 25.9, 25.8, 21.3, 19.1, 19.0, 18.3, 18.1, 12.0, 11.4, -4.5, -5.2, -5.29, -5.31; HR-ESI-MS calcd for $C_{29}H_{62}NaO_3Si_2$ $[M+Na]^+$: 537.4135, found: 537.4131.



Alcohol 45: To a stirred solution of **21** (25.0 mg, 0.048 mmol) in EtOH (0.56 mL) was added PPTS (1.2 mg, 4.78 μmol) at 0 °C. After stirring for 16 h at room temperature, the reaction mixture was evaporated and the residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 5:95) to afford 15.4 mg (80%) of **45** as a

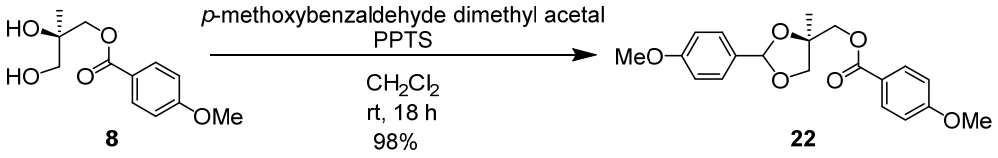
colorless oil; $[\alpha]_D^{20}$ -21.5 (*c* 0.23, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2957, 2926, 2862, 1059, 1033, 1009, 836, 773, 670, 654; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.16 (1H, d, *J* = 9.5), 4.00 (1H, d, *J* = 6.5), 3.75 (1H, dd, *J* = 11.5, 4.5), 3.64 (1H, dd, *J* = 11.0, 5.0), 3.38 (3H, s), 3.18 (1H, dt, *J* = 6.0, 5.5), 2.52 (1H, m), 1.64 (3H, d, *J* = 1.0), 1.46 (1H, m), 1.37 (1H, m), 1.26-0.94 (5H, overlapped), 0.91 (3H, d, *J* = 7.0), 0.88-0.85 (1H, overlapped), 0.88 (9H, s), 0.85 (3H, dd, *J* = 7.5, 7.5), 0.79 (3H, d, *J* = 7.0), 0.78 (3H, d, *J* = 6.5), 0.06 (3H, s), 0.00 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 135.3, 132.6, 82.0, 78.9, 61.7, 58.3, 46.0, 45.1, 31.6, 30.4, 29.5, 27.9, 25.8, 21.2, 19.04, 18.97, 18.1, 12.2, 11.4, -4.5, -5.3; HR-ESI-MS calcd for $C_{23}H_{48}NaO_3Si$ $[M+Na]^+$: 423.3270, found: 423.3262.



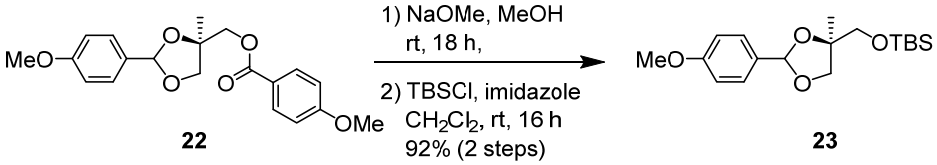
Alkyne 7: To a stirred solution of **45** (30.0 mg, 0.075 mmol) in CH_2Cl_2 (1.0 mL) was added DMP (63.6 mg, 0.15 mmol) at 0 °C under N_2 atmosphere. After stirring for 2 h at room temperature, the reaction was quenched with sat. $NaHCO_3$ aq. / sat. $NaHCO_3$ aq. (1:1) and the mixture was extracted three times with CHCl3. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a crude product that was subjed to the next reaction without further purification.

To a stirred solution of $MeCOCN_2PO(OMe)_2$ (43.2 mg, 0.225 mmol) in dry MeOH (0.8 mL) was added K_2CO_3 (50.4 mg, 0.156 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred at room temperature. After stirring for 10 min, the reaction mixture was cooled to 0 °C and the above crude aldehyde in dry MeOH (0.5 mL) was added dropwise. After stirring for 18 h at room temperature, the reaction mixture was quenched with sat. NH_4Cl aq. and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 1:99) to afford 17.0 mg (58% in 2 steps) of **7** as a colorless oil; $[\alpha]_D^{20}$ +4.8 (*c* 0.20, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2963, 1057, 774, 669, 652; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 5.09 (1H, d, *J* = 9.5), 4.02 (1H, d, *J* = 7.5), 3.86 (1H, dd, *J* = 11.5, 4.5), 3.35 (3H, s), 2.52 (1H, m), 1.59 (3H, d, *J* = 1.0), 1.47 (1H, m), 1.37 (1H, m), 1.28-0.94 (5H, overlapped), 0.90 (3H, d, *J* = 6.5), 0.89-0.83 (1H, overlapped), 0.88 (9H, s), 0.85 (3H, dd, *J* = 7.5, 7.5), 0.79 (3H, d, *J* = 6.5), 0.77 (3H, d, *J* = 7.0), 0.08 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.1, 132.3, 82.2, 80.2, 73.9, 73.4, 56.6, 46.0, 45.2, 31.7, 30.4, 29.6, 27.7, 25.8, 21.2, 18.99, 18.97, 18.2,

11.4, 11.0, -4.6, -4.9; HR-ESI-MS calcd for $C_{24}H_{46}NaO_2Si$ [M+Na]$^+$: 417.3165, found: 417.3145.

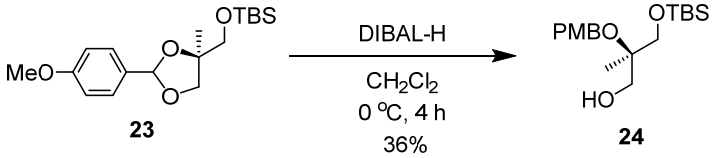


Acetal 22: To a stirred solution of known diol **8** (1.50 g, 6.25 mmol) and *p*-methoxy-benzaldehyde dimethyl acetal (4.74 mL, 28.12 mmol) in dichloromethane (50.0 mL) was added PPTS (156.8 mg, 0.625 mmol) at 0 °C. After stirring for 18 h at room temperature, the reaction was quenched with sat. $NaHCO_3$ aq., and the layers were separated. The aqueous layer was extracted three times with chloroform and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 30:70) to afford 2.19 g (98%) of **22** as a colorless oil; $[\alpha]_D^{20}$ +64.6 (*c* 1.08, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2972, 2838, 1716 (CO), 1606, 1510, 1457, 1394, 1316, 1253, 1169, 1102, 1073, 1031, 980, 848, 831, 770; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 8.03 (0.8H, d, *J* = 8.5), 8.00 (1.2H, d, *J* = 8.5), 7.44 (0.8H, d, *J* = 3.0), 7.43 (1.2H, d, *J* = 2.5), 6.95-6.86 (4H, overlapped), 5.95 (0.4H, s), 5.89 (0.6H, s), 4.40 (1.2H, m), 4.29 (0.8H, m), 4.07 (0.4H, d, *J* = 8.5), 3.95 (0.6H, d, *J* = 8.5), 3.86 (1.2H, s), 3.81 (1.2H, s), 3.79 (1.8H, s), 1.52 (1.2H, s), 1.50 (1.8H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 166.1, 163.7, 163.6, 160.62, 160.59, 131.9, 131.8, 129.9, 129.4, 128.3, 128.2, 122.3, 113.84, 113.76, 104.6, 103.8, 79.8, 79.5, 73.6, 73.1, 68.3, 67.7, 55.6, 55.41, 55.39, 23.2, 21.6; HR-ESI-MS calcd for $C_{20}H_{22}NaO_6$[M+Na]$^+$: 381.1314, found: 381.1313.

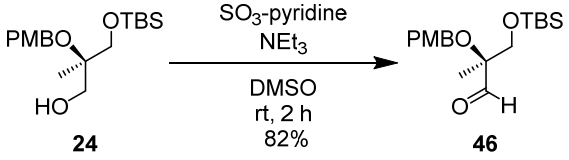


***O*-silylated compound 23**: To a stirred solution of **22** (1.52 g, 4.24 mmol) in MeOH (30.0 mL) was added NaOMe (687.0 mg, 12.72 mmol) at 0 °C. After stirring for 18 h at room temperature, the reaction was quenched with sat. NH_4Cl aq. and the mixture were extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a crude product that was subjected to the next reaction without further purification.

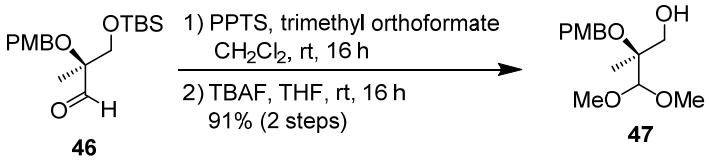
To a stirred solution of the above crude alcohol in dichloromethane (80.0 mL) were added imidazole (910.7 mg, 13.4 mmol) and TBSCl (1.50 g, 13.8 mmol) at 0 °C. After stirring for 16 h at room temperature, the reaction was quenched with sat. $NaHCO_3$ aq., and the layers were separated. The aqueous layer was extracted three times with Chloroform and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 5:95) to afford 2.08 g (92%, 2 steps) of **23** as a pale yellow oil; $[\alpha]_D^{20}$ +5.7 (*c* 0.38, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2954, 2931, 2856, 1615, 1586, 1520, 1469, 1390, 1302, 1249, 1170, 1100, 1074, 1035, 980, 834, 777, 670; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.41 (1H, d, *J* = 9.0), 7.41 (1H, d, *J* = 8.5), 6.90 (1H, d, *J* = 9.0), 6.89 (1H, d, *J* = 8.5), 5.87 (0.5H, s), 5.83 (0.5H, s), 4.21 (0.5H, d, *J* = 8.0), 4.08 (0.5H, d, *J* = 8.0), 3.84-3.78 (0.5H, overlapped), 3.81 (3H, s), 3.72 (0.5H, d, *J* = 10.5), 3.63 (1H, *J* = 9.0), 3.59 (0.5H, d, *J* = 10.0), 3.49 (0.5H, d, *J* = 8.5), 1.38 (3H, s), 0.92 (4.5H, s), 0.90 (4.5H, s), 0.068 (3H, s), 0.065 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 160.4, 160.3, 130.2, 129.8, 128.1, 128.0, 113.71, 113.67, 104.4, 103.2, 80.95, 80.94, 73.4, 72.8, 67.8, 67.4, 55.3, 25.85, 25.82, 22.8, 21.5, 18.24, 18.21; HR-ESI-MS calcd for $C_{18}H_{30}O_4Si$ $[M+H]^+$: 339.1992, found: 339.1961.



Alcohol 24: To a stirred solution of **23** (2.40 g, 7.1 mmol) in dichloromethane (40.0 mL) was added DIBAL-H (28.4 mL, 1.0 M in toluene, 28.4 mmol) at 0 °C. After stirring for 4 h, the reaction was quenched with sat. Rochelle salt aq., and then stirred vigorously for 16 h. After the layers were separated, the aqueous layer was extracted three times with Chloroform and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 10:90) to afford 869.1 mg (36%) of **24** as a colorless oil; $[\alpha]_D^{20}$ -4.3 (*c* 0.38, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2954, 2927, 2856, 1613, 1585, 1514, 1462, 1363, 1301, 1248, 1172, 1097, 1038, 891, 837, 775, 669; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.26 (2H, d, *J* = 8.5), 6.87 (2H, d, *J* = 8.5), 4.48 (2H, s), 3.80 (3H, s), 3.73 (1H, d, *J* = 10.0), 3.63 (1H, d, 7.0), 3.59 (1H, d, *J* = 10.5), 1.23 (3H, s), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 159.0, 131.2, 129.0, 113.8, 77.4, 66.9, 66.1, 64.2, 55.3, 25.8, 18.1, 17.5; HR-ESI-MS calcd for $C_{18}H_{32}NaO_4Si$ $[M+Na]^+$: 363.1968, found: 363.1916.



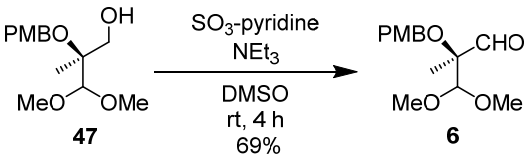
Aldehyde 46: To a stirred solution of alcohol **24** (781.2 mg, 2.30 mmol) in DMSO (12.5 mL) were added NEt_3 (1.05 mL, 10.4 mmol) and SO_3-pyridine complex (1.14 g, 7.17 mmol) at room temperature. After stirring for 2 h at the same temperature, the reaction was quenched with sat. NH_4Cl aq. and the layers were separated. The aqueous layer was extracted two times with Ethyl Acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 5:95) to afford 636.8 mg (82%) of **46** as a pale yellow oil; $[\alpha]_D^{20}$ -2.5 (*c* 0.38, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2998, 2936, 2836, 1736 (CO), 1612, 1514, 1454, 1378, 1303, 1247, 1174, 1137, 1105, 1082, 1035, 824; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 9.67 (1H, s), 7.29 (2H, d, *J* = 8.5), 6.88 (2H, d, *J* = 9.0), 4.53 (1H, d, *J* = 10.5), 4.42 (1H, d, *J* = 10.5), 3.86 (1H, d, *J* = 11.0), 3.80 (3H, s), 3.73 (1H, d, *J* = 10.5), 1.33 (3H, s), 0.88 (9H, s), 0.04 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 159.2, 130.4, 129.3, 113.8, 82.7, 66.3, 66.1, 55.3, 25.7, 18.1, 15.8; HR-ESI-MS calcd for $C_{18}H_{30}NaO_4Si$ $[M+Na]^+$: 361.1889, found: 361.1854.



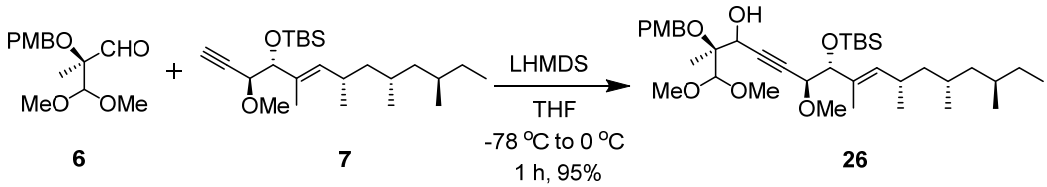
Alcohol 47: To a stirred solution of aldehyde **46** (618.5 mg, 1.83 mmol) in dry CH_2Cl_2 (20.0 mL) was added trimethyl orthoformate (0.80 mL, 7.32 mmol) and PPTS (45.9 mg, 0.183 mmol) at 0 °C. After stirring for 16 h at room temperature, the reaction was quenched with sat. $NaHCO_3$ aq. and then the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a crude product that was subjected to the next reaction without further purification.

To a stirred solution of the above crude product in dry THF (20.0 mL) was added TBAF (1.0 mM, 5.5 mL, 5.5 mmol) at 0 °C under N_2 atmosphere. After stirring for 16 h at room temperature, the reaction was quenched with H_2O and then the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash

column chromatography (ethyl acetate/*n*-hexane = 40:60) to afford 450.9 mg (91%, 2 steps) of **47** as a colorless oil; $[\alpha]_D^{20}$ -2.4 (*c* 0.38, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2936, 2836, 1739, 1514, 1244, 1184, 1134, 1078, 1031, 773, 669, 650; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.27 (2H, d, *J* = 8.5), 6.87 (2H, d, *J* = 8.5), 4.55-4.51 (2H, overlapped), 4.27 (1H, s), 3.80 (3H, s), 3.65 (2H, m), 3.55 (3H, s), 3.54 (3H, s), 2.50 (1H, dd, *J* = 6.5, 6.5), 1.22 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 158.9, 131.3, 128.8, 113.7, 109.8, 79.4, 65.1, 64.3, 58.1, 55.2, 14.7; HR-ESI-MS calcd for $C_{14}H_{22}NaO_5$ $[M+Na]^+$: 293.1365, found: 293.1322.

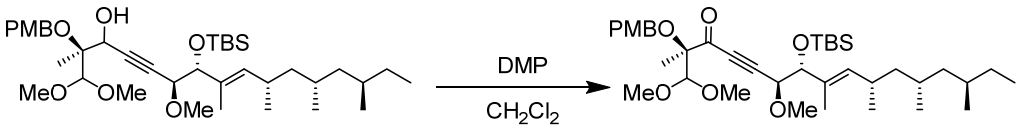


Aldehyde 6: To a stirred solution of alcohol **47** (220.0 mg, 0.815 mmol) in DMSO (2.0 mL) were added NEt_3 (0.37 mL, 2.69 mmol) and SO_3-Pyridine complex (393.8 mg, 2.47 mmol) at room temperature. After stirring for 4 h at the same temperature, the reaction was quenched with sat. NH_4Cl aq. and the layers were separated. The aqueous layer was extracted two times with Ethyl Acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 10:90) to afford 150.5 mg (69%) of **6** as a colorless oil; $[\alpha]_D^{20}$ +8.7 (*c* 0.43, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2996, 2937, 2835, 1736 (CO), 1613, 1513, 1458, 1383, 1301, 1248, 1177, 1139, 1106, 1079, 1030, 820; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 9.61 (1H, s), 7.29 (2H, d, *J* = 8.5), 6.87 (2H, d, *J* = 9.0), 4.53 (1H, d, *J* = 11.0), 4.39 (1H, d, *J* = 11.0), 4.37 (1H, s), 3.80 (3H, s), 3.53 (3H, s), 3.49 (3H, s), 1.39 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 202.0, 159.1, 130.4, 129.0, 113.7, 107.9, 84.5, 66.3, 58.1, 57.4, 55.2, 13.2; HR-ESI-MS calcd for $C_{14}H_{20}NaO_5$ $[M+Na]^+$: 291.1208, found: 291.1159.



Alcohol 26: To a stirred solution of alkyne **7** (22.0 mg, 0.056 mmol) in dry THF (0.6 mL) was added LHMDS (1.04 M in hexane, 0.21 mL, 0.218 mmol) at -78 °C under N_2 atmosphere. After stirring for 30 min at 0 °C, the reaction mixture was cooled to -78 °C

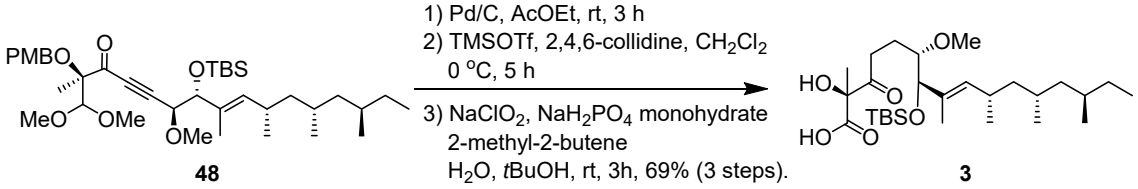
and aldehyde **6** (60.0 mg, 0.224 mmol) in dry THF (0.6 mL) was added dropwise. After stirring for 1 h at 0 °C, the reaction was quenched with sat. NH_4Cl aq. and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 15:85) to afford 35.4 mg (95%) of **26** as a colorless oil; $[\alpha]_D^{20}$ -68.2 (*c* 0.10, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2955, 2926, 1515, 1458, 1378, 1249, 1107, 1078, 1036, 838, 775 ; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.29－7.26 (2H, overlapped), 6.87-6.84 (2H, overlapped), 5.13-5.08 (1H, overlapped), 4.72-4.60 (2H, overlapped), 4.54 (0.4H, s), 4.46 (1H, d, *J* = 8.0), 4.42 (0.6H, s), 4.04 (1H, d, *J* = 7.0), 3.96-3.93 (1H, overlapped), 3.80 (1.8H, s), 3.79 (1.2H, s), 3.58 (1.2H, s), 3.57 (1.8H, s), 3.54 (1.2H, s), 3.52 (1.8H, s), 3.33 (1.8H, s), 3.32 (1.2H, s), 2.98-2.93 (1H, overlapped), 2.51 (1H, m), 1.60-1.39 (3H, overlapped), 1.47 (1H, m), 1.40 (4H, overlapped), 1.25 (1H, m), 1.11 (1H, m), 1.04 (2H, m), 0.97 (1H, m), 0.90 (3H, overlapped), 0.87 (6H, s), 0.86 (3H, s), 0.84 (2H, d, *J* = 7.5), 0.79 (3H, d, *J* = 7.0), 0.78-0.76 (3H, overlapped), 0.07 (3H, s), 0.01 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 158.91, 158.86, 135.7, 135.6, 132.5, 132.4, 131.4, 129.0, 128.9, 113.6, 109.3, 108.8, 84.8, 84.2, 84.1, 80.6, 80.4, 80.2, 80.1, 73.8, 73.7, 66.9, 66.5, 65.8, 65.6, 58.9, 58.2, 57.6, 56.4, 56.2, 55.2, 46.1, 46.06, 45.1, 31.6, 30.4, 30.36, 29.5, 27.8, 25.8, 21.3, 19.1, 18.9, 18.2, 14.0, 13.7, 11.4, 11.37, 11.2, -4.7, -4.78, -4.83; HR-ESI-MS calcd for $C_{38}H_{66}NaO_7Si$ $[M+Na]^+$: 685.4476, found: 685.4447.



26 **48**

Ketone 48: To a stirred solution of alcohol **26** (33.0 mg, 0.050 mmol) in CH_2Cl_2 (1.0 mL) was added DMP (52.8 mg, 0.125 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction was quenched with sat. $NaHCO_3$ aq./sat. $Na_2S_2O_3$ aq. (1:1) and then the whole mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 10:90) to afford 31.7 mg (quant) of **48** as a colorless oil; $[\alpha]_D^{20}$ +35.6 (*c* 0.75, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2955, 2926, 2854, 2207, 1682 (CO), 1612, 1517, 1459, 1378, 1247, 1140, 1111, 1087, 1036, 987, 836, 778; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.29 (2H, d, *J* = 8.8), 6.87 (2H, d, *J* = 9.6), 5.13 (1H, d, *J* = 10.0), 4.60 (1H, s), 4.46 (1H, d, *J* = 11.2), 4.33 (1H, d, *J* = 11.2), 4.08 (1H, d, *J* = 7.6), 4.04 (1H, d, *J* = 7.6), 3.80 (3H, s), 3.58 (3H,

s), 3.46 (3H, s), 3.33 (3H, s), 2.50 (1H, m), 1.57 (3H, s), 1.46 (3H, s), 1.37 (1H, m), 1.30-0.96 (4H, overlapped), 0.91 (3H, d, *J* = 6.4), 0.88-0.82 (12H, overlapped), 0.80 (3H, d, *J* = 6.4), 0.77 (3H, d, *J* = 6.4), 0.06 (3H, s), 0.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 187.2, 159.0, 136.5, 131.8, 130.5, 129.0, 113.6, 107.4, 93.0, 86.2, 84.0, 79.7, 73.8, 66.1, 58.9, 57.1, 56.8, 55.2, 46.0, 45.1, 31.6, 30.4, 29.6, 27.8, 25.7, 21.2, 19.0, 18.9, 18.1, 13.1, 11.4, 11.1, -4.7, -5.0; HR-ESI-MS calcd for $C_{38}H_{64}NaO_7Si$ $[M+Na]^+$: 683.4319, found: 683.4328.

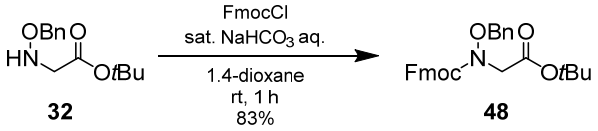


Carboxylic acid 3: To a stirred solution of ketone **48** (17.5 mg, 0.027 mmol) in AcOEt (1.0 mL) was added Pd/C (10%, 15.0 mg) and the mixture was stirred at room temperature under H_2 atmosphere for 3 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give a crude product that was subjected to the next reaction without further purification.

To a stirred solution of the above crude product in dry CH_2Cl_2 (1.0 mL) were added 2,4,6-collidine (71.4 μL, 0.540 mmol), and TMSOTf (121.8 μL, 0.675 mmol) at 0 °C under N_2 atmosphere. After stirring for 5 h, the reaction was quenched with sat. NH_4Cl aq. and the mixture were extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a crude product that was subjected to the next reaction without further purification.

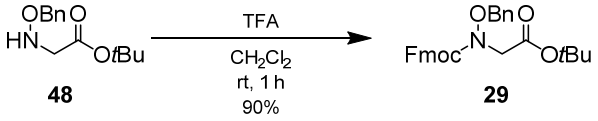
To a stirred solution of the above crude product and 2-methyl-2-butene (16.2 μL, 0.153 mmol) in *t*BuOH (0.8 mL) at 0°C was added a solution of $NaClO_2$ (6.3 mg, 0.070 mmol) and NaH_2PO_4 monohydrate (3.2 mg, 0.027 mmol) in H_2O (0.2 mL). After stirring for 3 h at room temperature, the reaction was quenched with sat. NH_4Cl aq. and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 20:80) to afford 9.5 mg (69% in 3 steps) of carboxylic acid **3** as a colorless oil; $[\alpha]_D^{20}$ -8.2 (*c* 0.25, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2955, 2925, 2856, 1711 (COOH), 1463, 1255, 840, 774; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm:5.14 (1H, d, *J* = 10.0), 3.90 (1H, d, *J* = 5.0), 3.36 (3H, s), 3.17 (1H, m), 2.49-2.45 (3H, overlapped), 1.82 (1H, m), 1.73 (1H, m), 1.62 (3H, d, *J* = 1.5), 1.55 (1H, m), 1.45 (1H, m), 1.37 (1H, m), 1.25

(3H, s), 1.25-1.20 (1H, overlapped), 1.19 (1H, m), 1.12 (1H, m), 1.05 (1H, m), 0.98 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 177.1, 135.1, 132.8, 82.6, 79.2, 58.5, 46.1, 45.0, 31.6, 30.41, 30.38, 29.7, 29.5, 27.9, 25.8, 25.4, 22.7, 21.2, 19.1, 18.9, 18.1, 14.1, 12.5, 11.4, -4.5, -5.2; HR-ESI-MS calcd for $C_{28}H_{54}NaO_6Si$ $[M+Na]^+$: 537.3587, found: 537.3580.



32 **48**

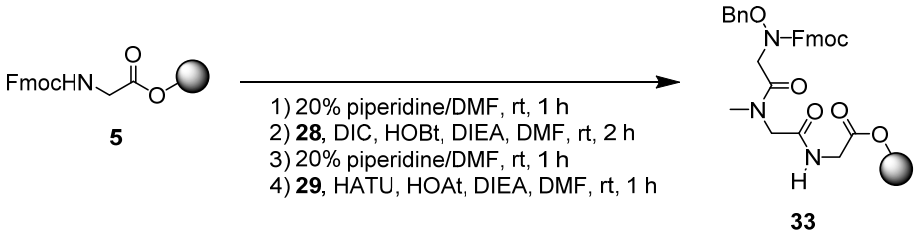
Hydroxyl glycine **48**: To a stirred solution of compound **32** (1.45 g, 6.10 mmol) in 1.4-dioxane (20.0 mL) and sat. $NaHCO_3$ aq. (20.0 mL) was added FmocCl (1.74 g, 6.72 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was diluted with AcOEt and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 15:85) to afford 2.33 g (83%) of **48** as a white solid; IR (ATR) ν_{max} cm^{-1}: 2980, 1746 (CO), 1715 (CO), 1453, 1416, 1369, 1340, 1253, 1229, 1156, 1095, 996, 760, 742; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.76 (2H, d, *J* = 8.0), 7.65 (2H, d, *J* = 7.5), 7.40 (2H, dd, *J* = 7.5, 7.5), 7.37-7.29 (7H, overlapped), 4.84 (2H, s), 4.56 (2H, d, *J* = 7.0), 4.29 (1H, dd, *J* = 7.0, 6.5), 4.00 (2H, s), 1.45 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 167.1, 157.6, 143.5, 141.1, 135.2, 129.2, 128.3, 128.2, 127.6, 126.9, 125.0, 119.8, 82.0, 77.2, 67.8, 52.9, 46.9, 27.8; HR-ESI-MS calcd for $C_{28}H_{29}NNaO_5$ $[M+Na]^+$: 482.1943, found: 482.1962.



48 **29**

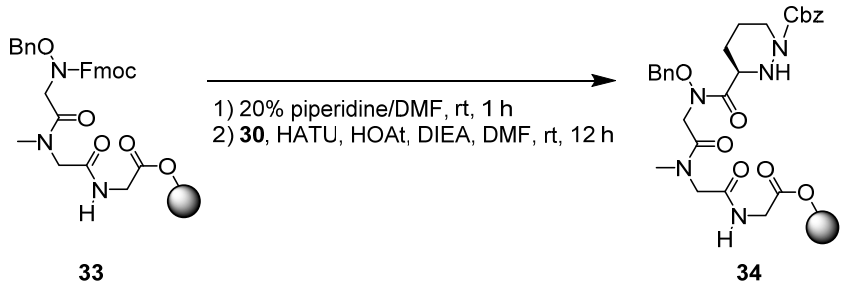
Fmoc hydroxyl glycine **29**: To a stirred solution of compound **48** (343.3 mg, 0.748 mmol) in CH_2Cl_2 (3.4 mL) was added TFA (3.4 mL) at 0 °C. After stirring for 1 h at room temperature, the volatile substances were evaporated and the remained TFA was removed by co-evaporation with toluene to afford 271.3 mg (90%) of Fmoc hydroxyl glycine **29** as a white solid; IR (ATR) ν_{max} cm^{-1}: 1731 (CO), 1714 (CO), 1454, 1418, 1340, 1255, 1102, 759, 741; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.74 (2H, d, *J* = 7.0), 7.63 (2H, d, *J* = 7.5), 7.39 (2H, dd, *J* = 7.5, 7.0), 7.34-7.25 (7H, overlapped), 4.78 (2H, s), 4.61 (2H, d, *J* = 6.5), 4.28 (1H, dd, *J* = 6.5, 6.0), 4.06 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 173.8, 157.7, 143.5, 141.3, 135.0, 129.5, 128.7, 128.5, 127.8, 127.1, 125.0, 120.0, 77.5, 68.0, 51.9, 47.1; HR-ESI-MS calcd for $C_{24}H_{21}NNaO_5$ $[M+Na]^+$: 426.1317, found:

426.1313.



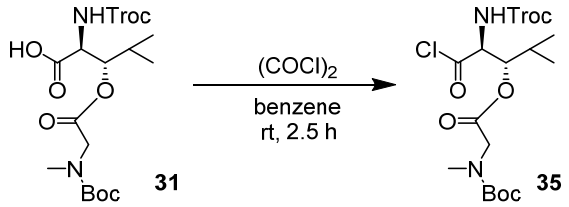
Tripeptide 33: The solid-phase peptide synthesis was started from Fmoc glycine loaded resin **5**. 20% piperidine in DMF was added to the reaction tube containing resin **5** (0.80 mmol/g, 145.0 mg, 0.116 mmol) and the mixture was shaken for 1 h at room temperature. The resin was washed with DMF three times. In another flask, Fmoc-sarcosine **28** (110.0 mg, 0.354 mmol) was activated with DIC (55.0 μL, 0.355 mmol), HOBt (48.0 mg, 0.355 mmol), DIEA (61.7 μL, 0.355 mmol) in DMF and resultant mixture was transferred to the above reaction tube. After shaken for 2 h, the resin was washed with DMF three times.

Introduction of hydloxyglycine **29** was conducted in the same manner. 20% piperidine in DMF was added to the reaction tube containing resin and the mixture was shaken for 1 h at room temperature. The resin was washed with DMF three times. In another flask, **29** (143.1 mg, 0.355 mmol) was activated with HATU (134.9 mg, 0.355 mmol), HOAt (47.9 mg, 0.355 mmol), DIEA (123.4 μL, 0.710 mmol) in DMF and resultant mixture was transferred to the above reaction tube. After shaken for 1 h, the resin was washed with DMF three times.

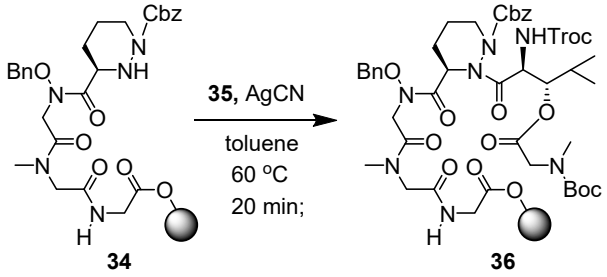


Tetrapeptide 34: 20% piperidine in DMF was added to the reaction tube containing the above resin **33** (0.116 mmol) and the mixture was shaken for 1 h at room temperature. The resin was washed with DMF three times. In another flask, piperazic acid **30** (93.7 mg, 0.355 mmol) was activated with HATU (134.9 mg, 0.355 mmol), HOAt (47.9 mg, 0.355 mmol), DIEA (123.4 μL, 0.710 mmol) in DMF and resultant mixture was

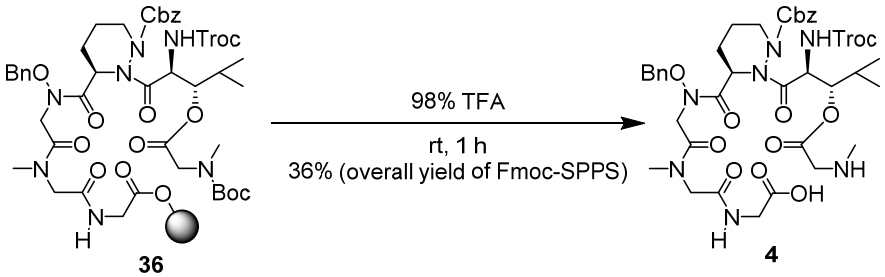
transferred to the above reaction tube. After shaken for 12 h, the resin was washed with DMF three times.



Acid chloride 35: To a stirred solution of dipeptide **31** (68.2 mg, 0.139 mmol) in benzene (0.50 mL) was added $(COCl)_2$ (0.42 mL, 4.90 mmol) at room temperature. After stirring for 2.5 h at the same temperature, the volatile substances were evaporated and the remained $(COCl)_2$ was removed by co-evaporation with benzene to afford acid chloride **35** as a white amorphous.

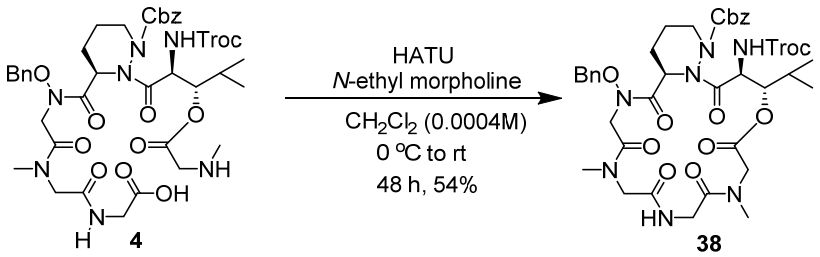


Hexapeptide 36: To the reaction tube containing resin **34** (0.116 mmol) and AgCN (23.3 mg, 0.174 mmol) was added dry toluene (0.9 mL) and shaken for 5 min. The solution of the above dipeptide **35** (0.139 mmol) in toluene (0.6 mL) was added to the whole mixture via cannula and coupling reaction was conducted at 60 °C for 20 min. After washing the reaction tube with DMF for 5 times, CH_2Cl_2 was added and the floating resin was collected. (The resultant silver salt sank to the bottom of the reaction tube.)



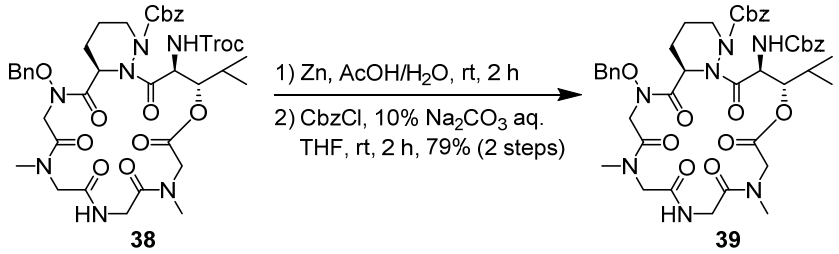
Liner peptide 4: To the resin-bound peptide **36** was added 98% aqueous TFA (2.0 mL). After being stirred for 1 h, the reaction mixture was filtered, and washed with CH_2Cl_2

three times. The filtrate was concentrated to give the crude product. The residue was purified by reversed-phase HPLC (column: Cosmosil AR-II 20 × 250 mm, eluent A: MeCN + 0.1% TFA, eluent B: H_2O + 0.1% TFA, A/B = 55/45, flow rate: 8.0 mL/min, detection: UV 220 nm) to give **4** (Rt = 31.3 min, 24.0 mg, 36% from resin **5**) as a white amorphous ; $[\alpha]_D^{20}$ -4.0 (*c* 0.10, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 1732, 1716, 1698, 1683, 1669, 1653, 1634, 1614, 1558, 1540, 1416; ^1H NMR (500 MHz, CD_3OD, 40 °C, as a mixture of conformational isomers) δ ppm: 7.58-7.20 (10H, overlapped), 6.88-6.20 (0.5H, m), 5.90 (0.5H, m), 5.45 (0.5H, m), 5.36-5.02 (4H, overlapped), 5.01-4.70 (4H, overlapped), 4.53 (1H, m), 4.24-3.74 (7H, overlapped), 3.08 (1H, s), 2.95 (2H, m), 2.76 (2H, m), 2.60 (2H, m), 2.15 (1H, m), 1.86 (1H, m), 1.55 (1H, m), 1.30 (3H, m), 1.02 (3H, d, J = 7.5), 1.00-0.90 (5H, overlapped); ^{13}C NMR (125 MHz, CD_3OD, 40 °C, as a mixture of conformational isomers) δ ppm: 176.2, 175.0, 173.4, 173.0, 172.8, 172.8, 172.1, 171.9, 171.7, 171.1, 171.0, 170.7, 170.6, 169.3, 167.4, 165.0, 164.9, 157.6, 156.84, 156.76, 156.5, 156.39, 156.35, 156.2, 156.1, 156.0, 137.6, 137.1, 136.9, 136.0, 135.9, 135.8, 131.0, 130.9, 130.7, 130.6, 130.1, 129.8, 129.7, 129.6, 129.5, 129.2, 128.6, 97.0, 95.4, 80.6, 79.4, 79.2, 78.9, 78.7, 78.3, 75.8, 75.7, 75.4, 70.2, 69.4, 58.3, 57.8, 52.8, 52.7, 52.0, 50.8, 50.1, 49.7, 47.5, 46.3, 41.9, 41.8, 41.7, 36.3, 36.1, 35.9, 35.7, 33.9, 33.8, 33.7, 33.6, 30.3, 30.2, 29.7, 29.6, 26.5, 26.3, 26.1, 20.3, 19.82, 19.77, 19.7, 18.7, 18.3, 17.4, 16.1, 15.9; HR-ESI-MS calcd for $C_{39}H_{51}Cl_3N_7O_{13}$ $[M+H]^+$: 930.2610, found: 930.2604.



Cyclic peptide 38: To a stirred solution of HATU (391.7 mg, 1.03 mmol) in dry CH_2Cl_2 (200.0 mL) at 0 °C under N_2 was added a mixture of **4** (95.7 mg, 0.103 mmol) and *N*-ethylmorpholine (175.6 μL, 1.39 mmol) in dry CH_2Cl_2 (50.0 mL) using syringe pump over a 6 h. After the addition was completed, the reaction mixture was allowed to warm up to rt and the whole mixture was stirred for 48 h. The solvent was then removed in vacuo, and the residue was diluted with EtOAc. The solution was washed successively with 1N HCl aq., sat.$NaHCO_3$ aq. and brine. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel flash column chromatography

(MeOH/$CHCl_3$ = 10:90) to afford 51.1 mg (54%) of **38** as a yellow solid; $[\alpha]_D^{20}$ -2.5 (*c* 0.10, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 1748, 1736, 1697, 1684, 1670, 1654, 1635, 1626; ^1H NMR (500 MHz, $CDCl_3$, as a mixture of conformational isomers) δ ppm: 7.51-7.13 (10H, overlapped), 7.00 (1H, m), 7.65 (0.3H, m), 6.18 (0.3H, m), 5.94 (0.3H, m), 5.62 (0.4H, d, *J* = 6.5), 5.30-4.60 (10H, overlapped), 4.52 (0.5H, m), 4.42-4.25 (2H, overlapped), 4.18-3.69 (4H, overlapped), 3.32 (0.3H, d, *J* = 17.5), 3.29 (0.3H, d, *J* = 17.5), 3.17-3.07 (3H, overlapped), 3.07 (2H, s), 2.92 (2H, s), 2.85 (1H, s), 2.62 (0.7H, m), 2.48 (0.3H, m), 2.30 (0.8H, m), 1.96-1.38 (4H, overlapped), 1.02 (1.2H, d, *J* = 6.0), 0.98-0.90 (3.6H, overlapped), 0.88 (1.2H, d, *J* = 6.5); ^{13}C NMR (125 MHz, $CDCl_3$, as a mixture of conformational isomers) δ ppm: 171.9, 171.4, 170.7, 169.7, 169.6, 168.7, 168.6, 168.3, 168.1, 167.8, 167.3, 166.6, 155.8, 155.4, 155.3, 154.0, 153.9, 153.6, 151.7, 150.5, 135.7, 132.3, 132.5, 131.0, 130.0, 129.5, 129.0, 128.8, 128.5, 128.4, 128.32, 128.27, 128.1, 95.8, 95.4, 95.3, 95.0, 79.5, 77.8, 77.5, 76.2, 74.8, 74.7, 74.2, 69.4, 69.0, 53.9, 53.4, 52.3, 51.9, 51.8, 51.0, 50.9, 50.2, 50.1, 49.7, 49.5, 49.1, 47.9, 47.6, 47.5, 47.0, 43.0, 40.4, 40.2, 37.5, 36.4, 35.2, 29.0, 28.8, 28.5, 25.2, 25.0, 20.3, 19.3, 19.1, 18.0, 16.5, 16.3; HR-ESI-MS calcd for $C_{39}H_{48}Cl_3N_7NaO_{12}$ $[M+Na]^+$: 934.2324, found: 934.2292.

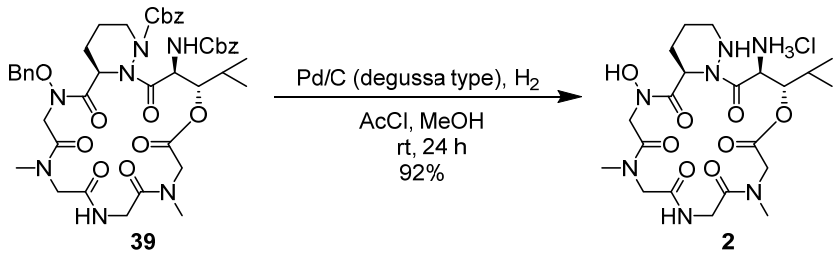


38 **39**

Cyclic peptide 39: To a stirred solution of **38** (12.3 mg, 13.5 μmol) in AcOH/H_2O (9:1, 0.6 mL) at was added Zn powder (158.8 mg, 2.44 mmol). After stirring for 2 h at room temperature, the reaction mixture was diluted with THF and filtered through Celite. The filtrate was then concentrated in vacuo, and the resulting residue co-evaporated with toluene to remove the excess acetic acid.

To a stirred solution of the above crude in CH_2Cl_2 (1.0 mL) and 10% $NaHCO_3$ aq. (1.0 mL) was added CbzCl (5.7 μL, 40.4 μmol) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was diluted with EtOAc, washed with brine. The organic layer was dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography (MeOH/$CHCl_3$ = 10:90) to afford 9.3 mg (79%, 2 steps) of **39** as a yellow solid; $[\alpha]_D^{20}$ +5.9 (*c* 0.25, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 1749, 1733, 1718, 1671, 1664, 1655, 1649, 1637; ^1H NMR (600 MHz, $CDCl_3$, as a mixture of

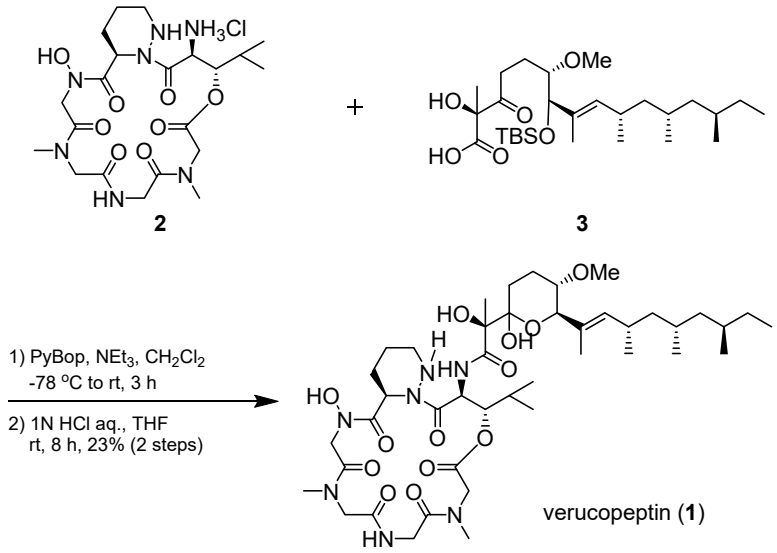
conformational isomers) δ ppm: 7.52-7.20 (15H, overlapped), 7.18 (1H, m), 7.10 (1H, m), 6.98 (1H, m), 6.62 (1H, d, *J* = 9.6), 5.87 (1H, br-s), 5.63 (1H, d, *J* = 4.2), 5.26-5.10 (m), 5.07 (m), 4.95 (1H, m), 4.89 (m), 4.72 (m), 4.59 (1H, m), 4.52 (1H, m), 4.29 (2H, m), 4.08 (1H, m), 3.98 (m), 3.82 (1H, m), 3.28 (1H, m), 3.10 (m), 3.06 (1H, m), 2.92 (m), 2.89 (m), 2.73 (2H, s), 2.62 (2H, m), 2.48 (1H, m), 2.28 (1H, m), 1.98 (1H, m), 1.83 (m), 1.58 (m), 1.30 (1H, m), 1.26 (m), 0.99 (3H, d, *J* = 6.0), 0.94 (m), 0.87 (3H, d, *J* = 6.6), 0.84 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 177.1, 172.4, 170.7, 169.8, 169.3, 168.7, 168.6, 168.4, 168.3, 168.1, 168.0, 167.9, 166.6, 155.8, 155.33, 155.26, 137.5, 136.5, 136.0, 135.8, 135.4, 131.1, 131.0, 130.1, 129.7, 129.0, 128.8, 128.7, 128.5, 128.4, 128.33, 128.26, 128.2, 128.10, 128.08, 127.8, 127.3, 79.9, 77.9, 77.5, 76.1, 69.3, 68.9, 68.8, 67.0, 66.0, 65.6, 53.9, 53.3, 52.4, 51.9, 51.8, 50.8, 50.0, 49.5, 49.3, 47.7, 47.6, 46.9, 43.0, 40.5, 40.3, 40.2, 37.1, 36.4, 36.3, 35.0, 31.9, 29.7, 29.6, 29.0, 28.7, 28.4, 26.0, 25.7, 25.2, 24.9, 22.7, 20.4, 20.3, 19.2, 18.5, 18.2, 16.6, 16.1, 14.1, ; HR-ESI-MS calcd for $C_{44}H_{53}N_7NaO_{12}$ $[M+Na]^+$: 894.3650, found: 894.3597.



Depsipeptide core 2: The solution of 0.01 M HCl in dry MeOH was prepared by addition of AcCl (7.2 μL) to dry MeOH (10.0 mL) at 0 °C and stirred for 10 min.

To a stirred solution of compound **39** (14.7 mg, 16.8 μmol) in 0.01M HCl in MeOH (1.6 mL) was added Pd/C (10%, Degussa type, 20.8 mg) and the mixture was stirred at room temperature under H_2 atmosphere for 24 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to afford 8.5 mg (92%) of depsipeptide **2** as a white soid; $[\alpha]_D^{20}$ -75.4 (*c* 0.24, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 2922, 2849, 1716, 1698, 1684, 1670, 1653, 1647, 1636, 1033; ^{1}H NMR (600 MHz, CD_3OD) δ ppm: 5.37 (1H, d, *J* = 15.0), 5.26 (1H, s), 5.12 (1H, d, *J* = 4.8), 5.08 (1H, d, *J* = 8.4), 5.01 (1H, d, *J* = 17.4), 4.45 (1H, d, *J* = 17.4), 4.00 (1H, d, *J* = 17.4), 3.89 (1H, dd, *J* = 18.6, 18.0), 3.81 (1H, d, *J* = 15.6), 3.76 (1H, d, *J* = 18.0), 3.34 (3H, s), 3.15 (3H, s), 3.10 (1H, m), 2.87 (3H, s), 2.73 (1H, dd, *J* = 11.4, 11.4), 2.18 (1H, d, *J* = 13.2), 2.00 (1H, m), 1.84 (1H, br-s), 1.62 (1H, d, *J* = 12.0), 1.55 (1H, m) 1.27 (1H, s), 1.16 (3H, d, *J* = 6.0), 0.91 (3H, d, *J* = 5.4); ^{13}C NMR (150 MHz, CD_3OD) δ ppm: 173.6, 172.4, 171.9, 169.9, 169.3, 169.1, 147.4, 78.4, 53.4, 52.7, 52.6, 52.3, 51.4, 50.6, 49.9, 47.6, 42.8, 37.4, 34.9,

30.7, 30.4, 24.2, 21.8, 19.3, 19.2; HR-ESI-MS calcd for $C_{21}H_{35}N_7NaO_8$ $[M+Na]^+$: 536.2445, found: 536.2448.

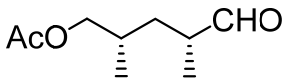


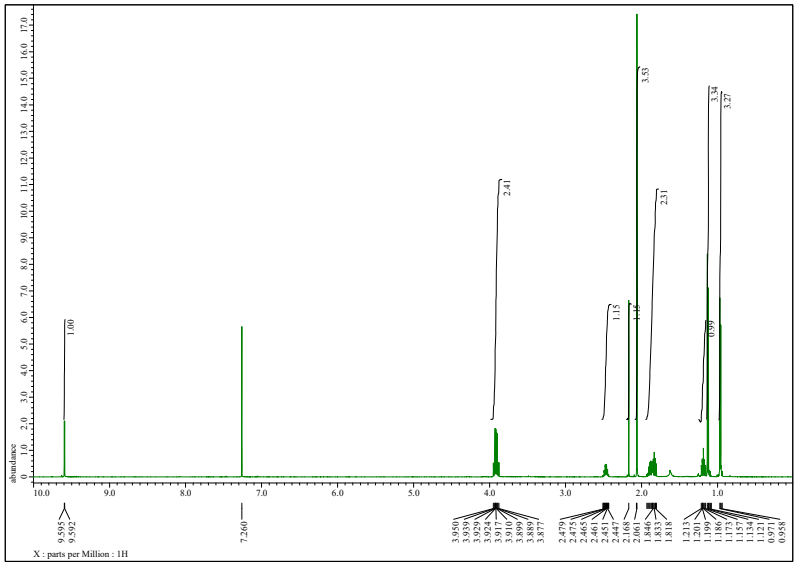
verucopeptin (**1**): To a stirred solution of depsipeptide core **2** (5.5 mg, 10.7 μmol) in dry CH_2Cl_2 (0.3 mL) was added NEt_3 (3.0 μL, 21.5 μmol) at -78 °C under N_2 atmosphere. In another flask, carboxylic acid **3** (3.0 mg, 5.8 μmol) was activated with PyBop (6.0 mg, 11.6 μmol) and NEt_3 (1.9 μL, 13.9 μmol) in dry CH_2Cl_2 (0.3 mL) and resultant mixture was transferred to the above reaction mixture. After stirring for 3 h at room temperature, the reaction was quenched with H_2O and the layers were separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was subjected to the next reaction without further purification.

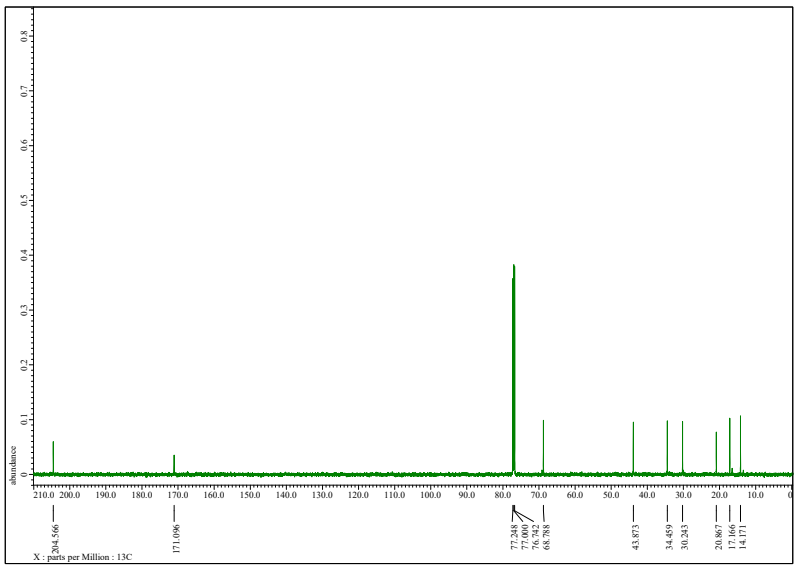
To a stirred solution of the above crude product in THF (0.30 mL) was added 1N HCl aq. (0.30 mL) at 0 °C. After stirring for 8 h at room temperature, the reaction mixture was evaporated and the residue was purified by silica gel flash column chromatography (Methanol/$CHCl_3$ = 10:90) to afford 1.2 mg (23%, 2 steps) of verucopeptin (**1**) as a white solid; $[\alpha]_D^{20}$ -89.5 (*c* 0.13, $CHCl_3$); IR (ATR) ν_{max} cm^{-1}: 3354, 2954, 1632, 1405, 1242, 753; ^1H NMR (600 MHz, $CDCl_3$) δ ppm: 9.14 (1H, br-s), 7.35 (1H, d, *J* = 9.0), 7.25 (1H, d, overlapped), 6.09 (1H, d, *J* = 9.6), 5.92 (1H, br-s), 5.31 (1H, d, *J* = 7.2), 5.26 (1H, d, *J* = 15.6), 5.17 (1H, d, *J* = 9.6), 5.04 (1H, dd, *J* = 16.8, 6.6), 4.88 (1H, d, *J* = 13.2), 4.78 (1H, d, *J* = 10.2), 4.64 (1H, d, *J* = 16.8), 4.11 (1H, m), 4.10 (1H, m), 3.88 (1H, d, *J* = 15.0), 3.65 (1H, d, *J* = 17.4), 3.60 (1H, d, *J* = 16.8), 3.49 (1H, s), 3.44 (1H, m), 3.28 (3H, s), 3.11 (3H, s), 3.08 (overlapped), 3.04 (1H, m), 2.91 (3H, s), 2.65 (1H, m), 2.55 (1H, m), 2.17 (1H, m), 2.03 (1H, m), 1.83 (m), 1.73 (m), 1.65 (3H, s), 1.59 (m), 1.50 (m), 1.46 (m),

1.40 (3H, s), 1.37 (m), 1.28 (m), 1.20 (m), 1.12 (m), 1.06 (3H, d, J = 6.0), 1.02 (m), 0.97 (3H, d, J = 6.0), 0.89-0.83 (12H, overlapped), 0.82-0.75 (9H, overlapped); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 176.2, 171.9, 171.3, 170.9, 170.2, 167.1, 166.9, 137.0, 130.0, 98.4, 80.0, 79.9, 77.6, 75.7, 56.8, 52.4, 51.7, 51.3, 48.5, 46.9, 46.5, 46.2, 45.0, 42.4, 36.7, 34.7, 31.7, 30.4, 29.7, 27.8, 27.2, 24.1, 23.9, 21.3, 20.6, 19.5, 19.2, 19.0, 18.3, 14.1, 11.4; HR-ESI-MS calcd for $C_{43}H_{73}N_7NaO_{13}$ $[M+Na]^+$: 918.5164, found: 918.5153.

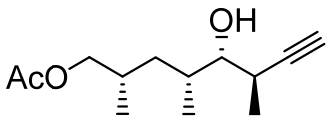
Compound 38

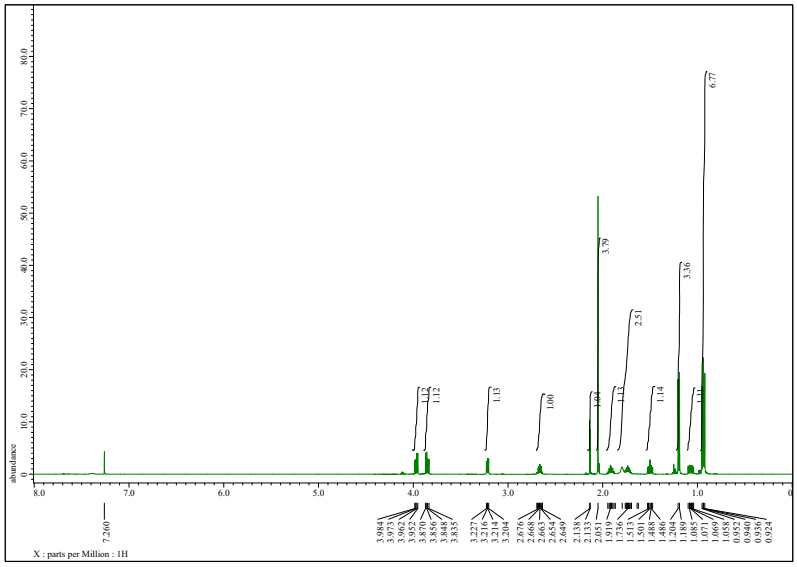

AcO
CHO

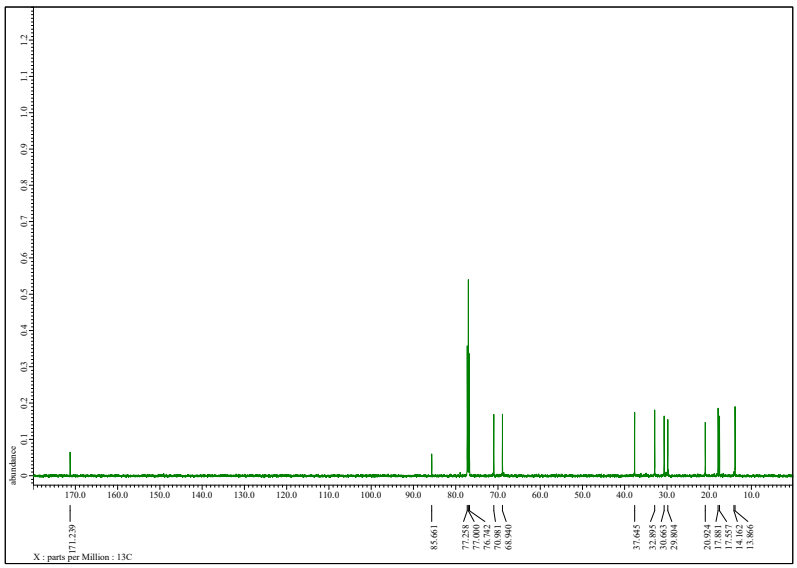

abundance
X : parts per Million : 1H


abundance
X : parts per Million : 13C

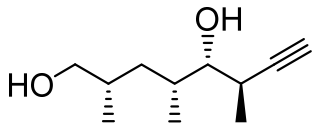
Compound 11

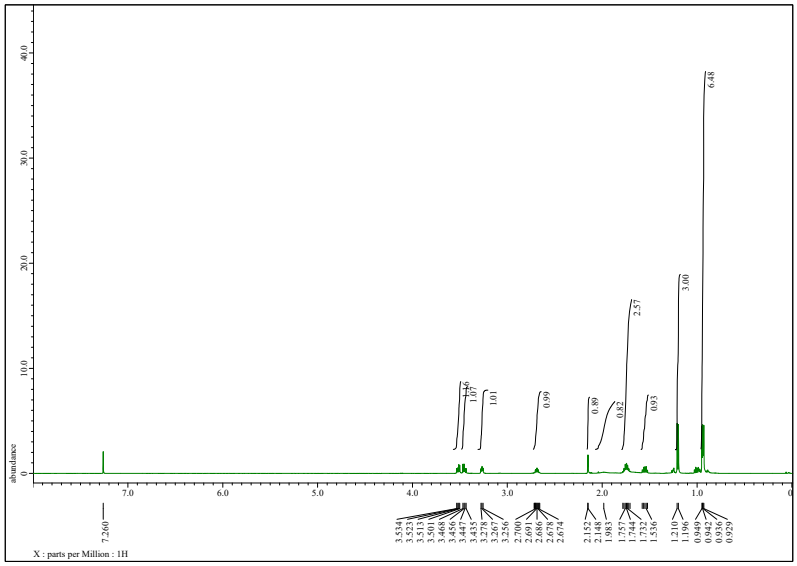

OH
AcO

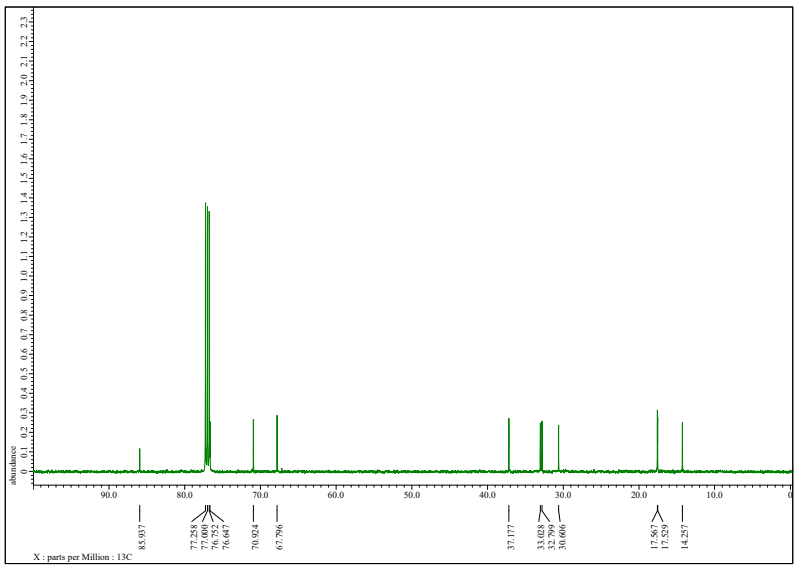

abundance
X : parts per Million : 1H


abundance
X : parts per Million : 13C

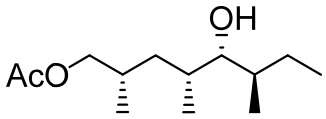
Compound 13

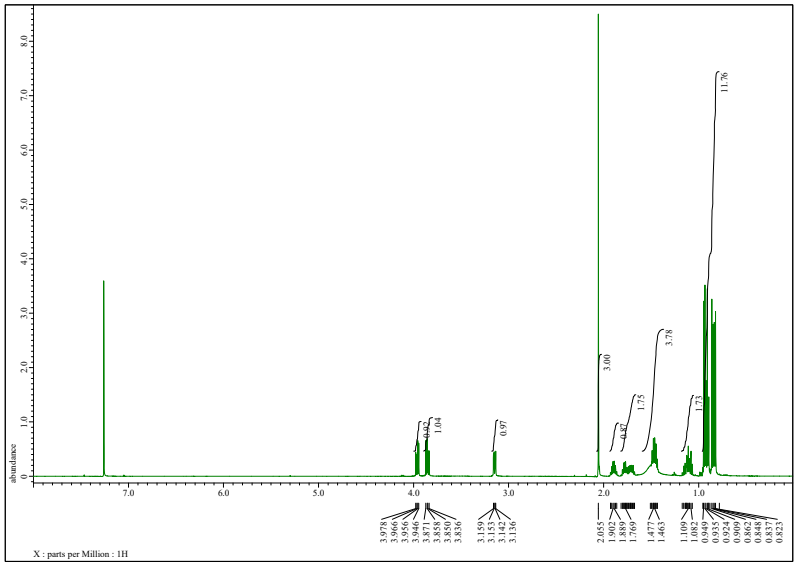

OH
HO

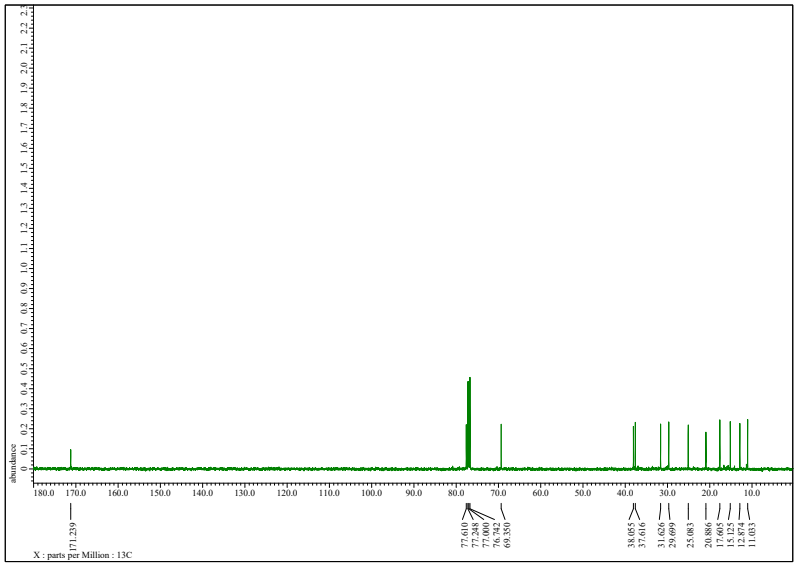

6.48
3.00
2.57
1.01
0.99
0.89
0.82
0.93
abundance
7.260
X : parts per Million : 1H


abundance
85.937
77.258
77.000
76.752
76.647
70.924
67.796
37.177
33.028
32.799
30.666
17.567
17.529
14.257
X : parts per Million : 13C

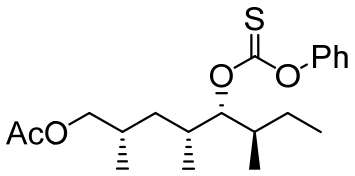
Compound 39

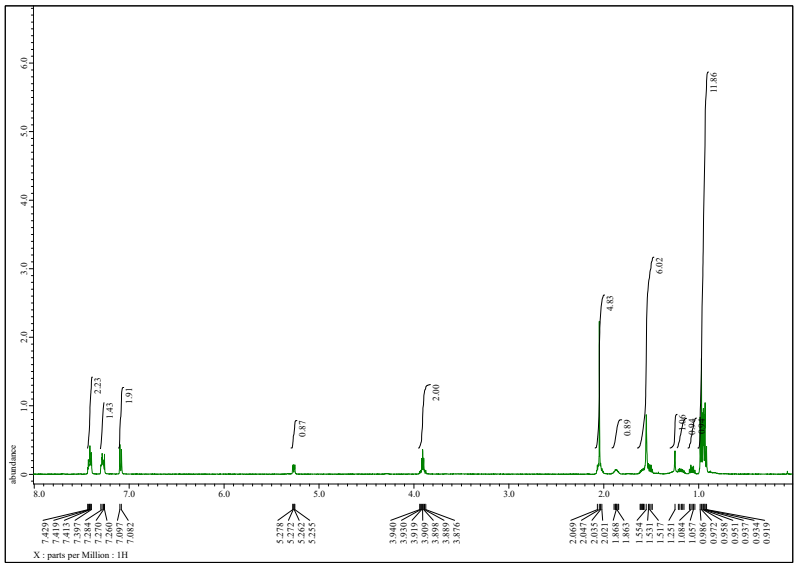

OH
AcO

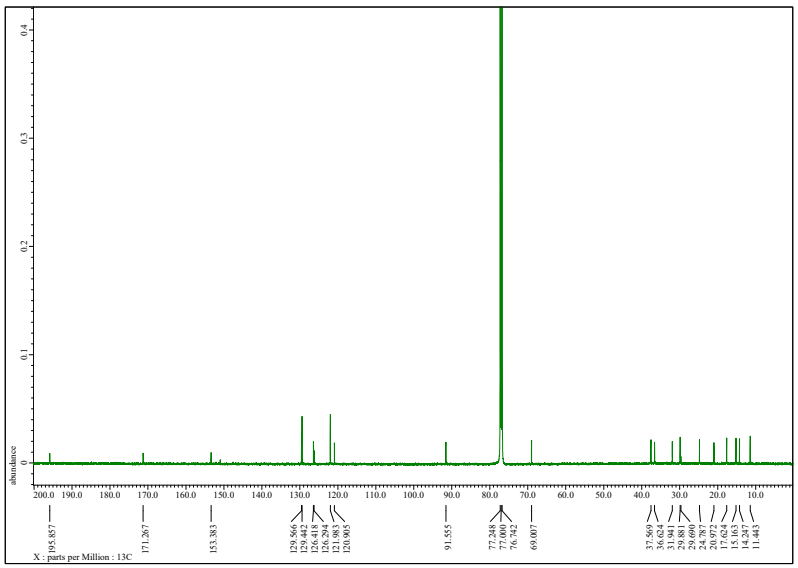

abundance
X : parts per Million : 1H


abundance
X : parts per Million : 13C

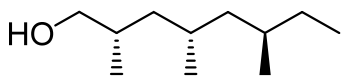
Compound 40

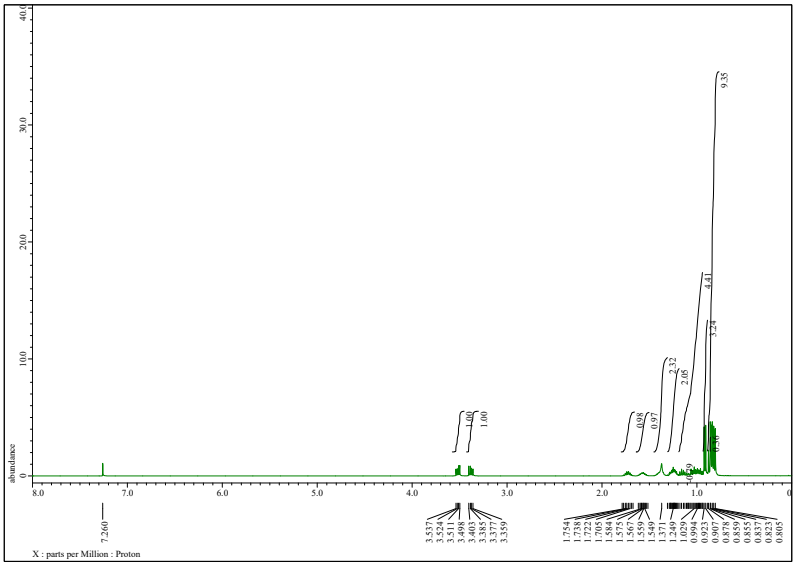

S
O
O
Ph
AcO

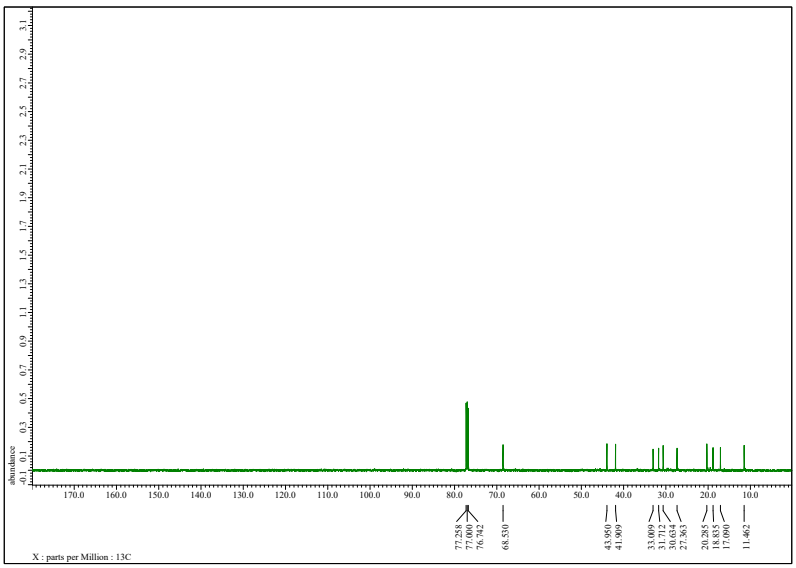

11.86
6.02
4.83
2.23
1.91
1.43
2.00
0.87
0.89
abundance
X : parts per Million : 1H


abundance
X : parts per Million : 13C

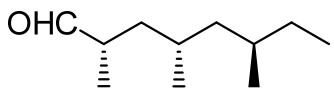
Compound 9

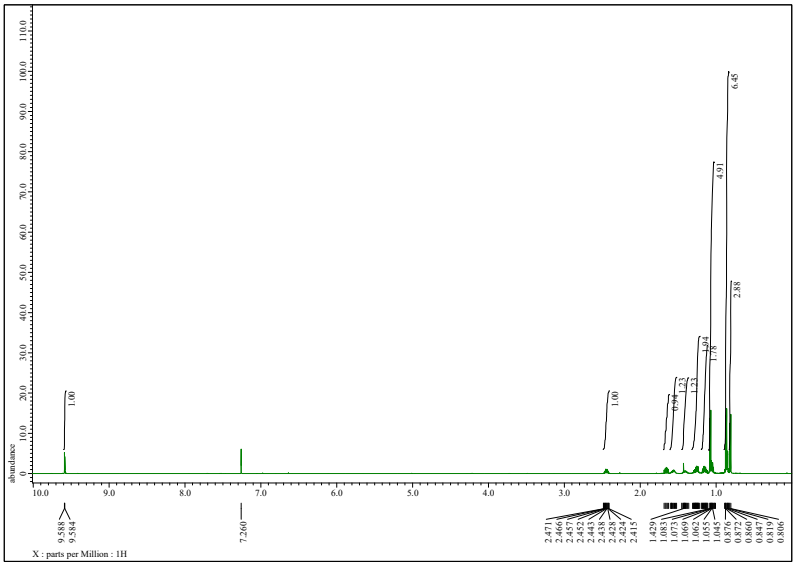

HO

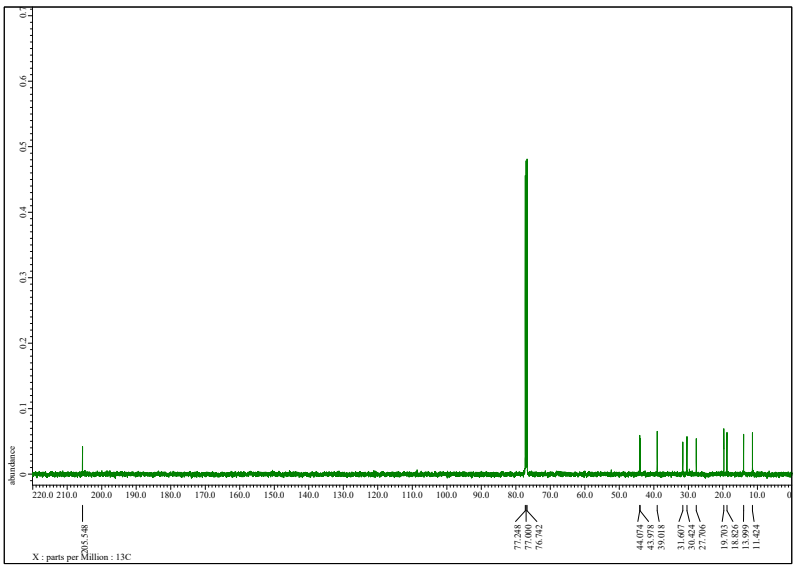

9.35
4.41
3.24
2.32
2.05
1.00
1.00
0.98
0.97
0.68
2.260
3.537
3.524
3.511
3.498
3.403
3.385
3.377
3.359
1.754
1.738
1.722
1.707
1.584
1.575
1.567
1.559
1.540
1.371
1.249
1.024
0.994
0.923
0.901
0.876
0.859
0.855
0.833
0.825
0.805
abundance
X : parts per Million : Proton


77.258
77.000
76.742
68.530
43.950
41.909
33.009
31.712
30.414
29.363
20.285
18.835
17.000
11.462
abundance
X : parts per Million : 13C

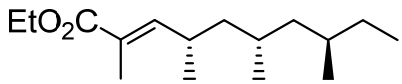
Compound 41

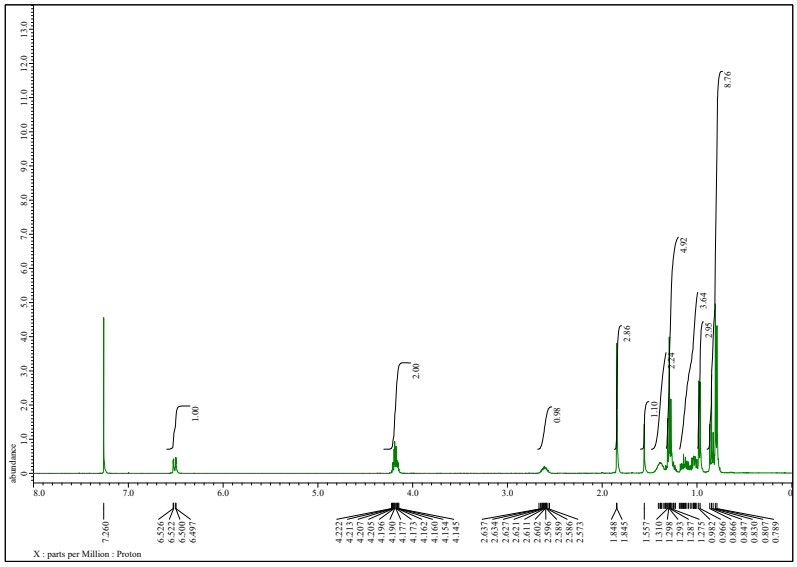

OHC

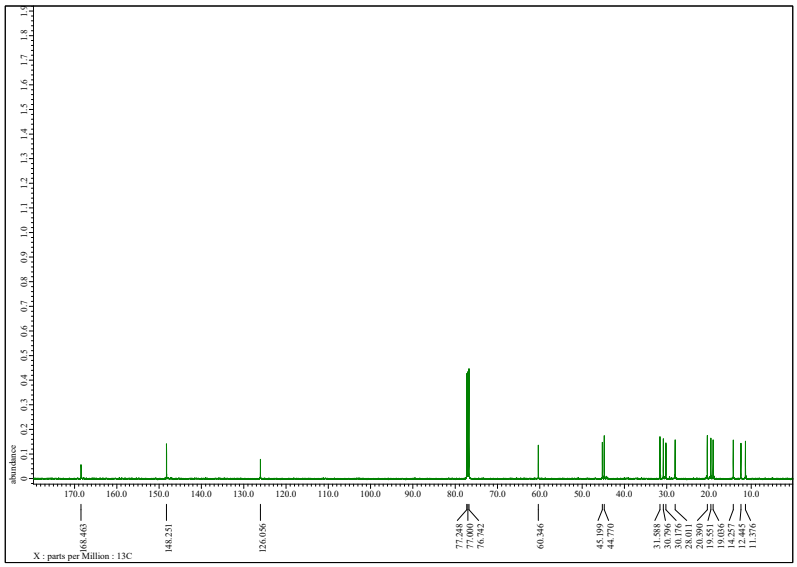

abundance
X : parts per Million : 1H


abundance
X : parts per Million : 13C

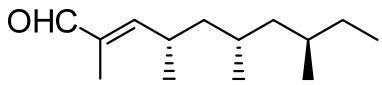
Compound 15

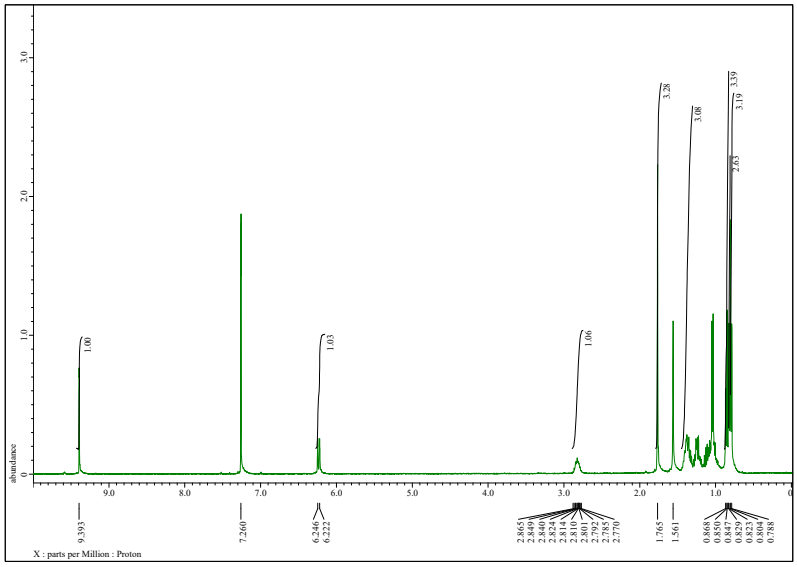

EtO2C

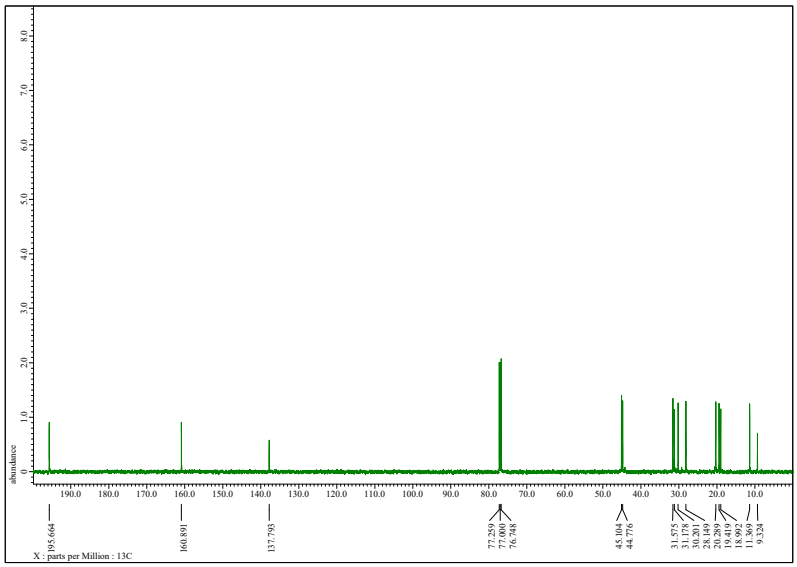

abundance
X : parts per Million : Proton


abundance
X : parts per Million : 13C

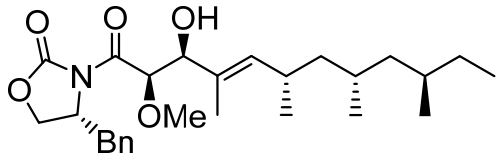
Compound 16

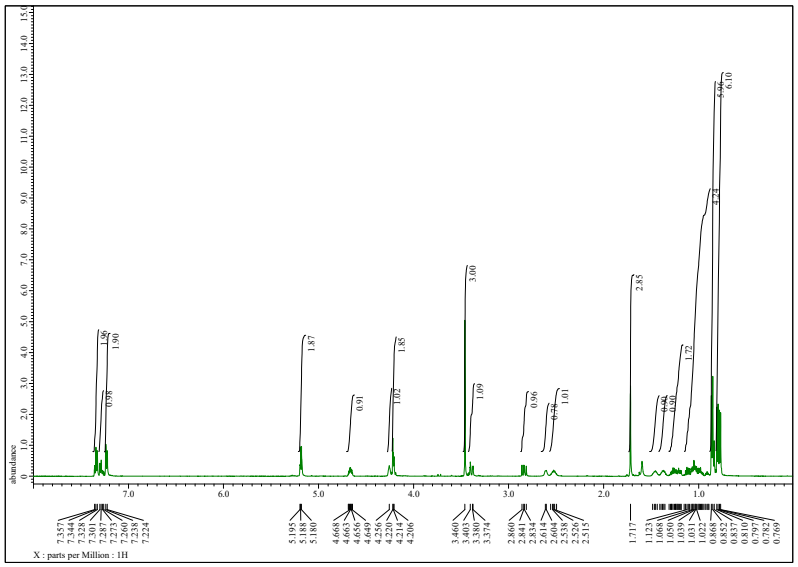

OHC

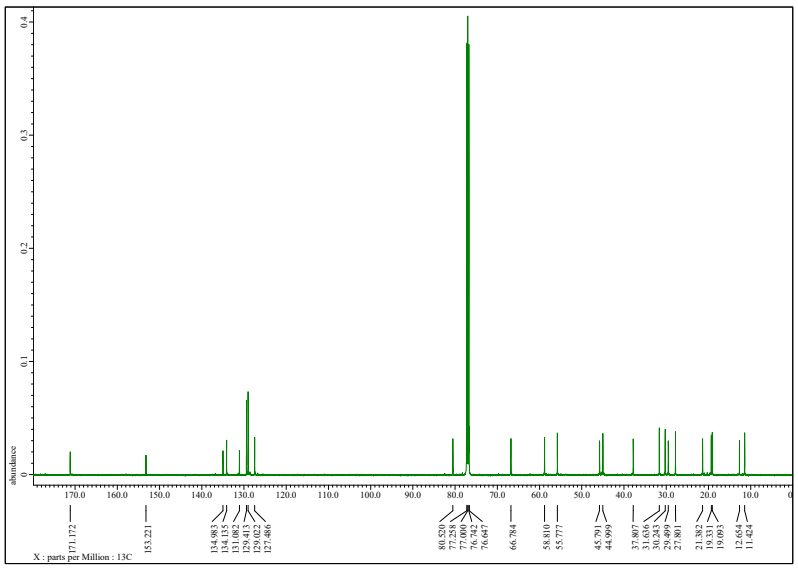

abundance
1.00
1.03
1.06
3.28
3.08
3.39
3.19
2.63
9.393
7.260
6.246
6.222
2.865
2.848
2.840
2.824
2.818
2.810
2.801
2.792
2.782
2.770
1.765
1.561
0.868
0.859
0.847
0.829
0.825
0.804
0.788
X : parts per Million : Proton


abundance
195.664
160.891
137.793
77.258
77.000
76.748
45.104
44.770
31.575
31.375
30.201
28.149
20.289
19.643
18.992
11.369
9.324
X : parts per Million : 13C

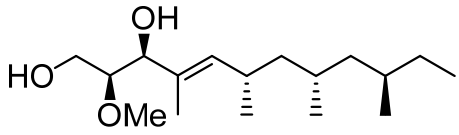
Compound 18

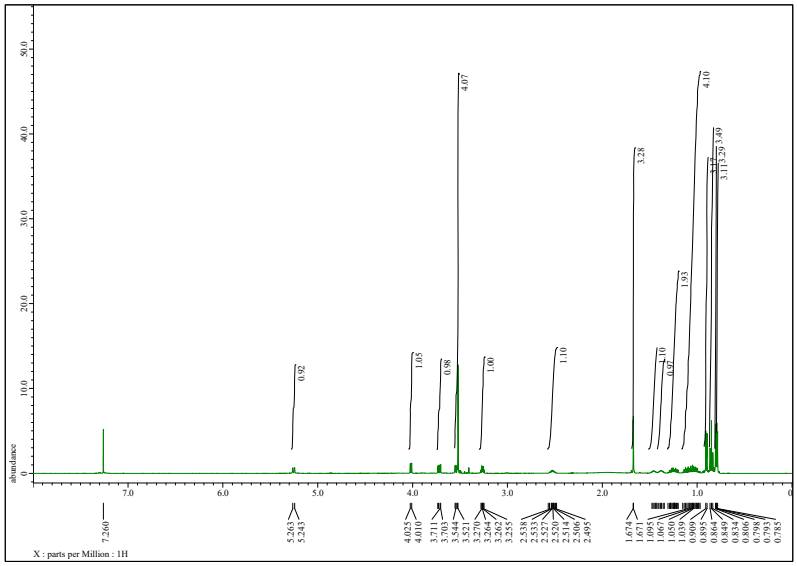


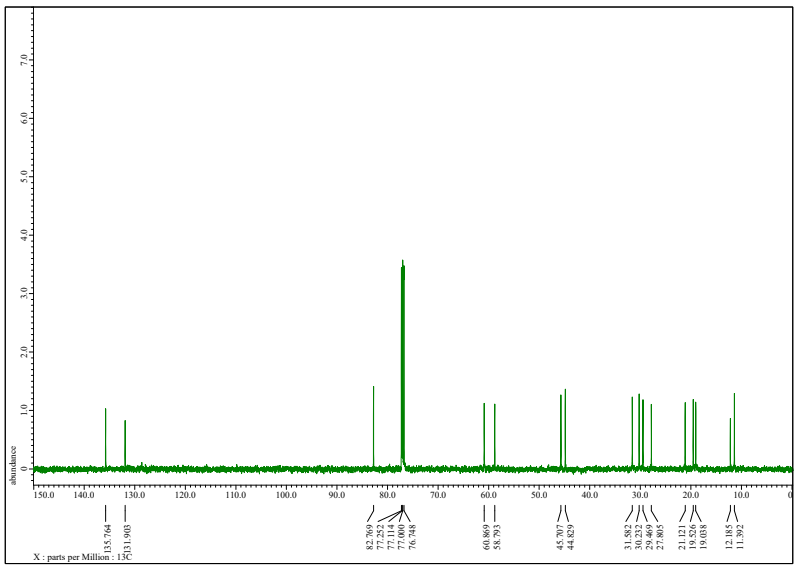




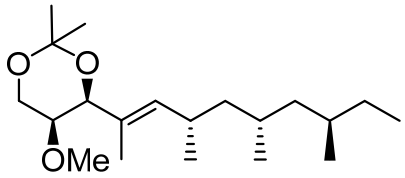
Compound 19

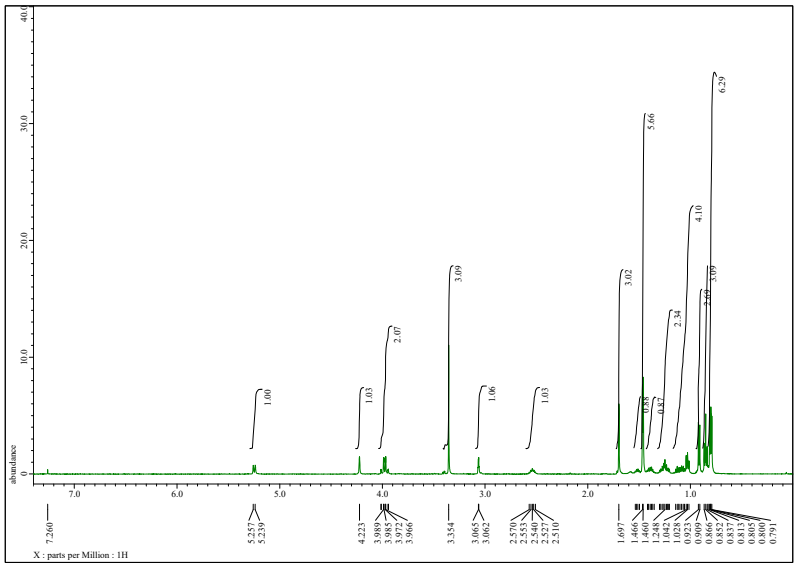


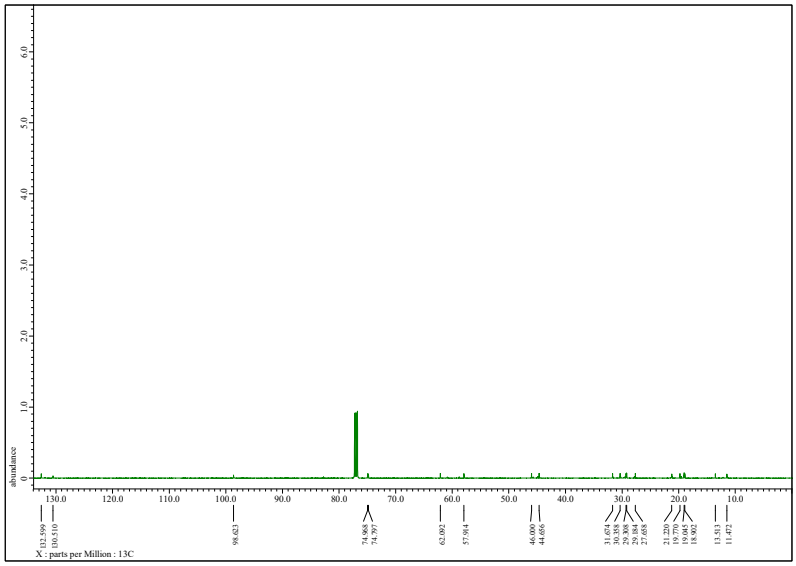




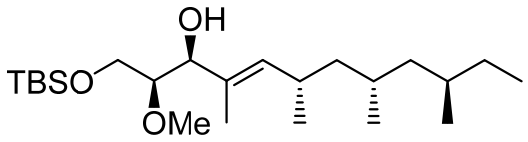
Compound 42

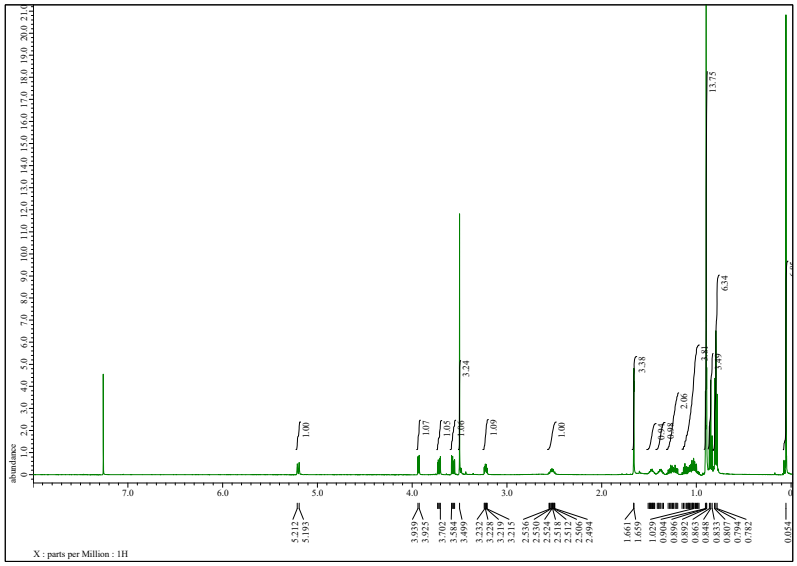

O
O
OMe

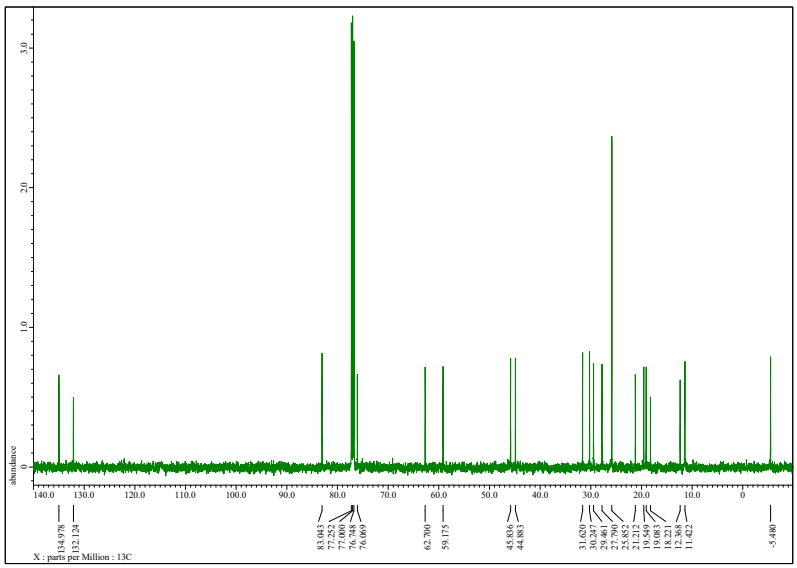

abundance
X : parts per Million : 1H


abundance
X : parts per Million : 13C

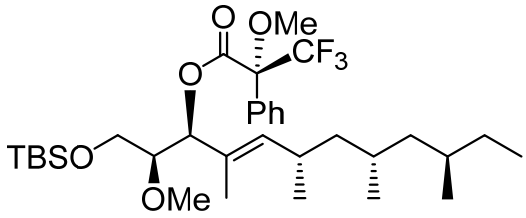
Compound 43

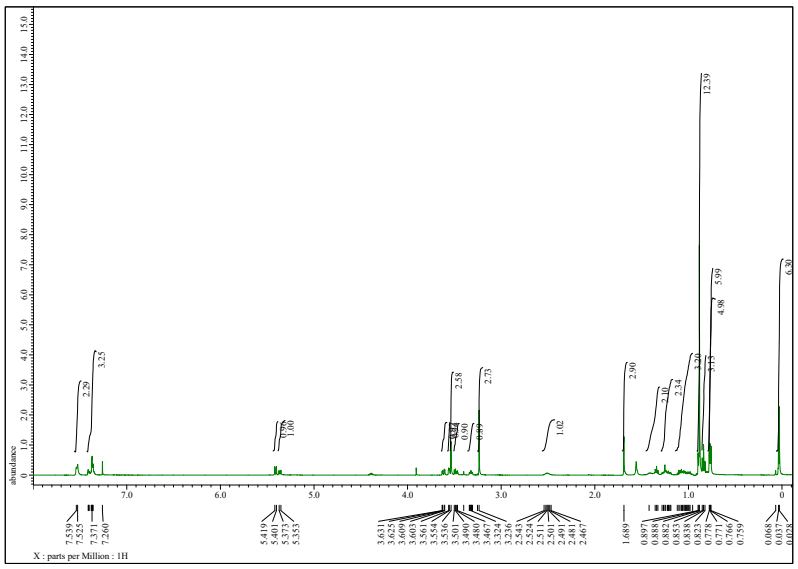


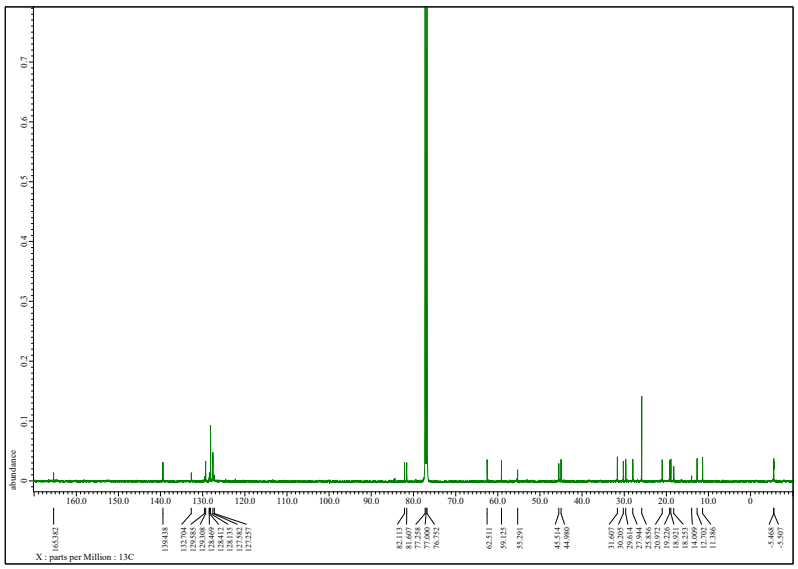




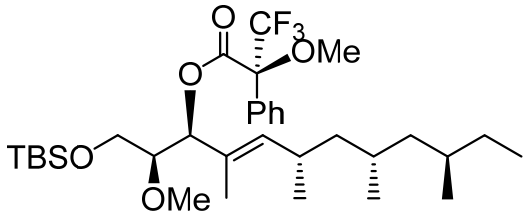
Compound (*R*)-44

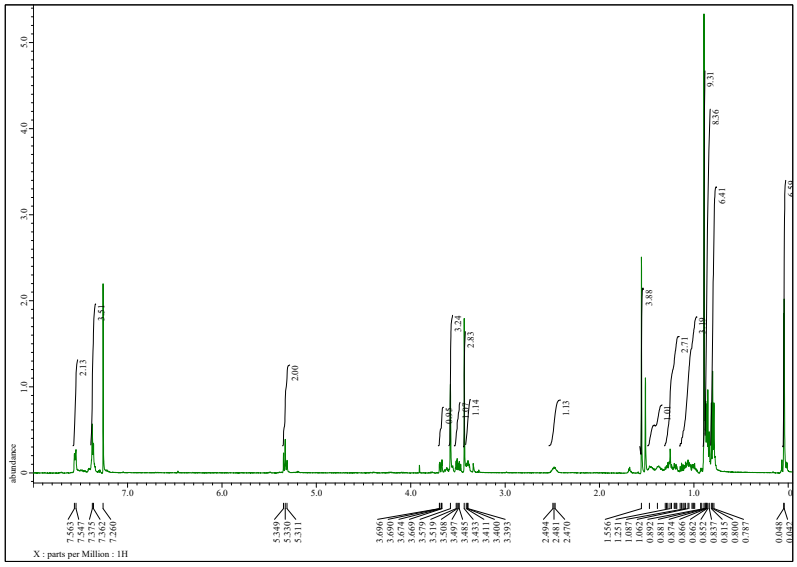


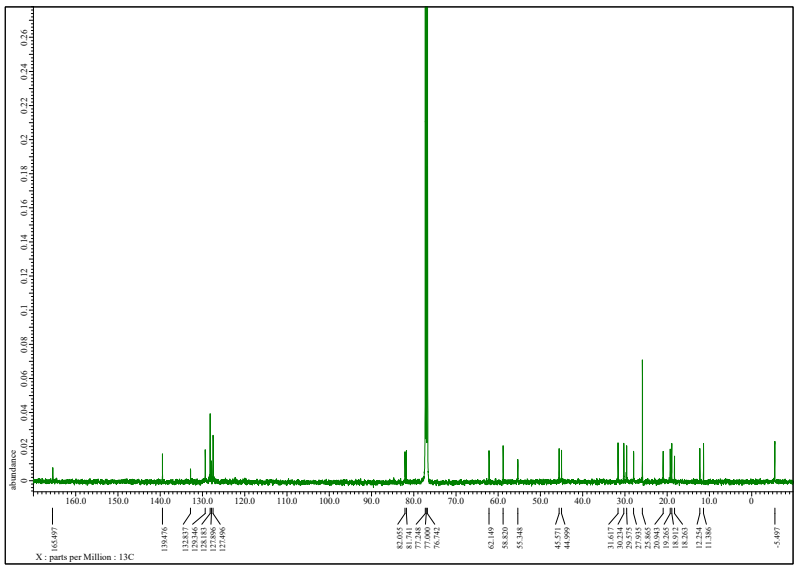




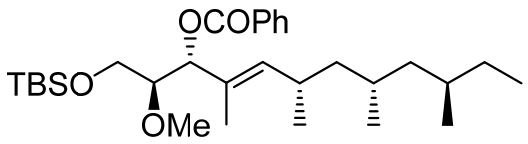
Compound (*S*)-44

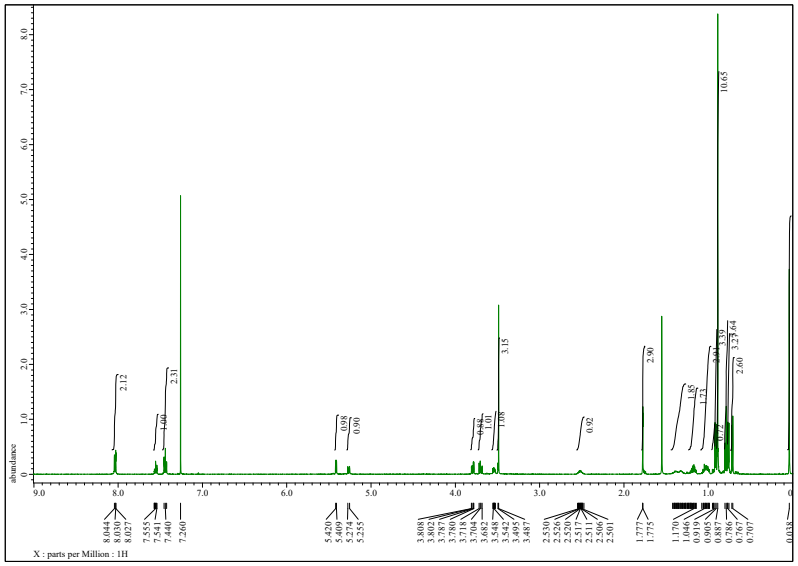


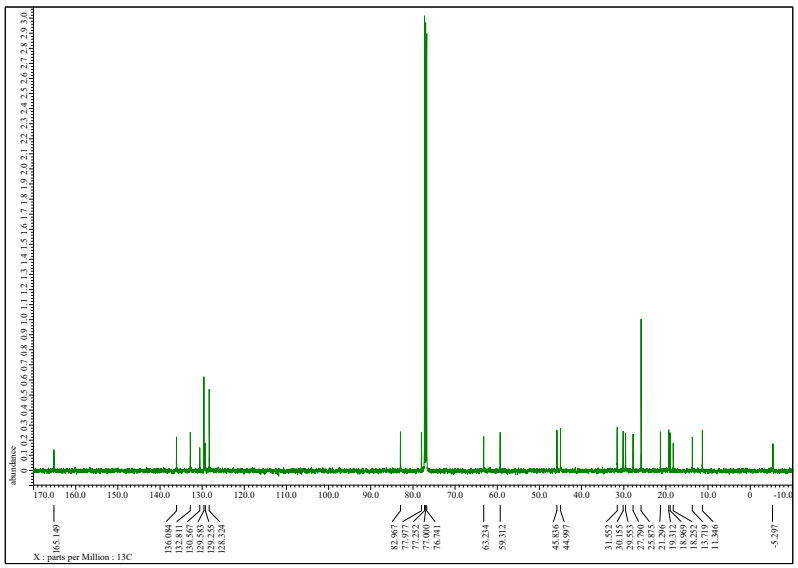




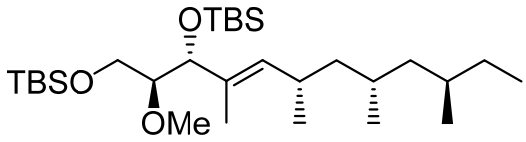
Compound 20

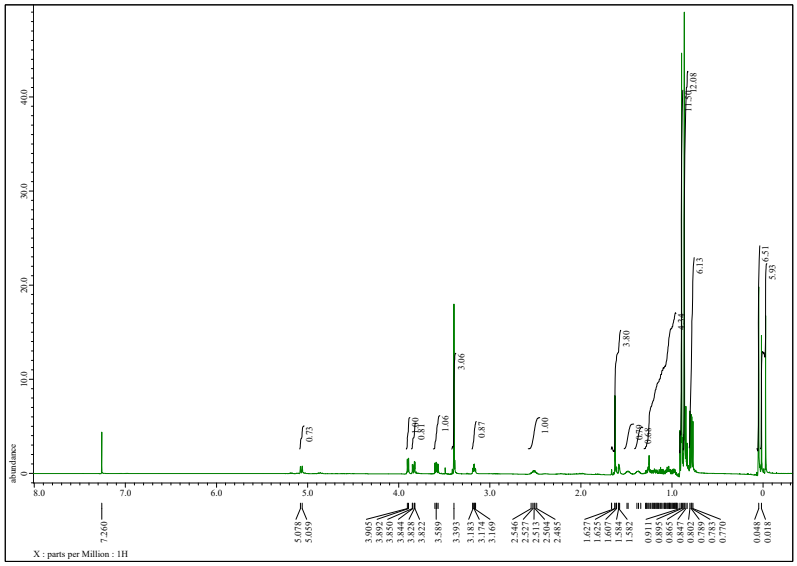


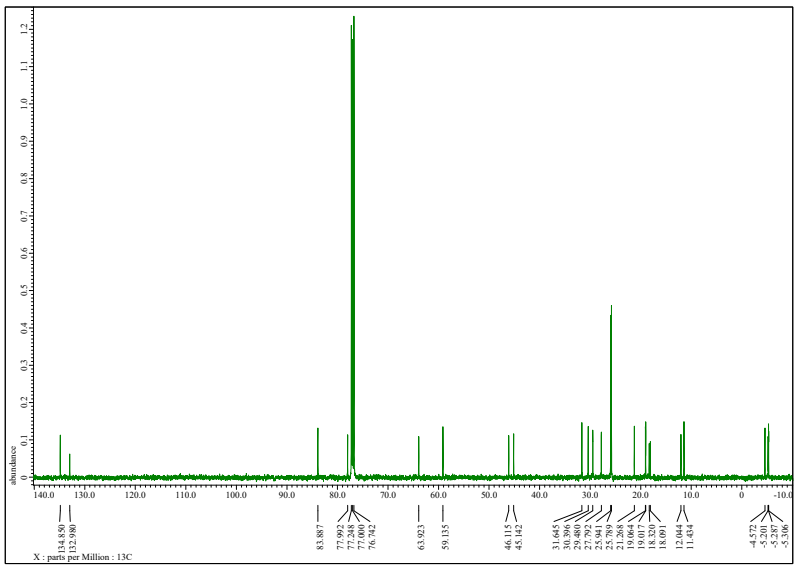




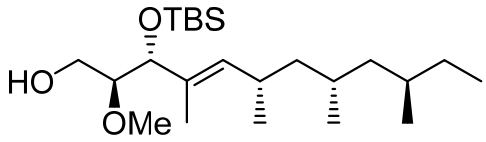
Compound 21

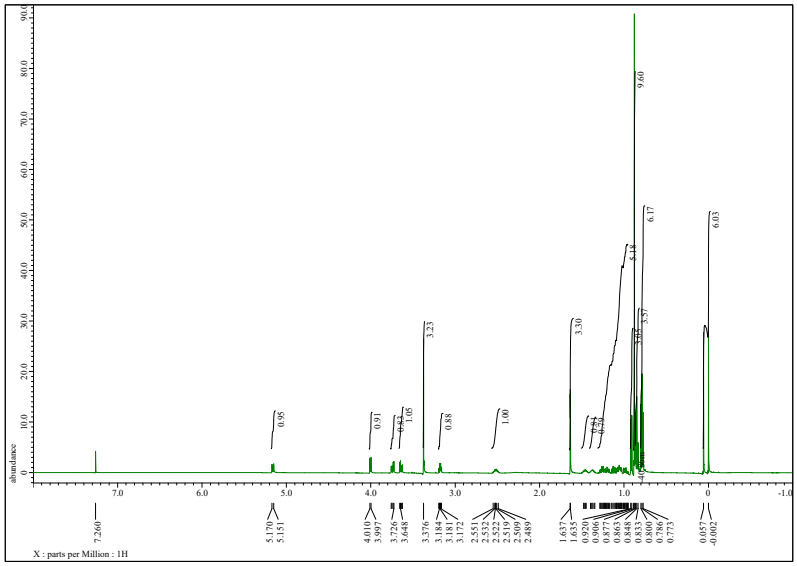


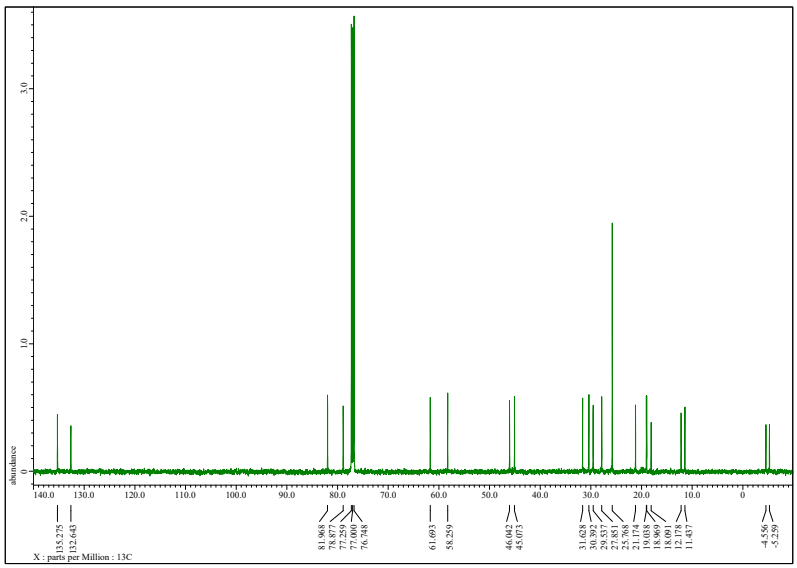




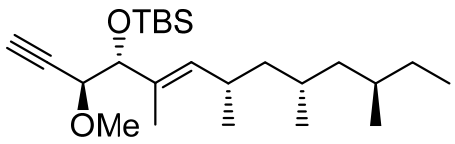
Compound 45

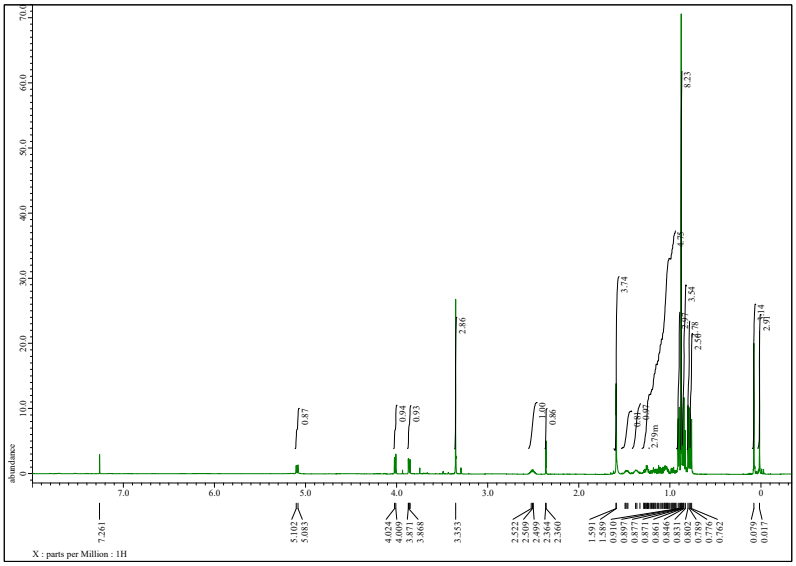


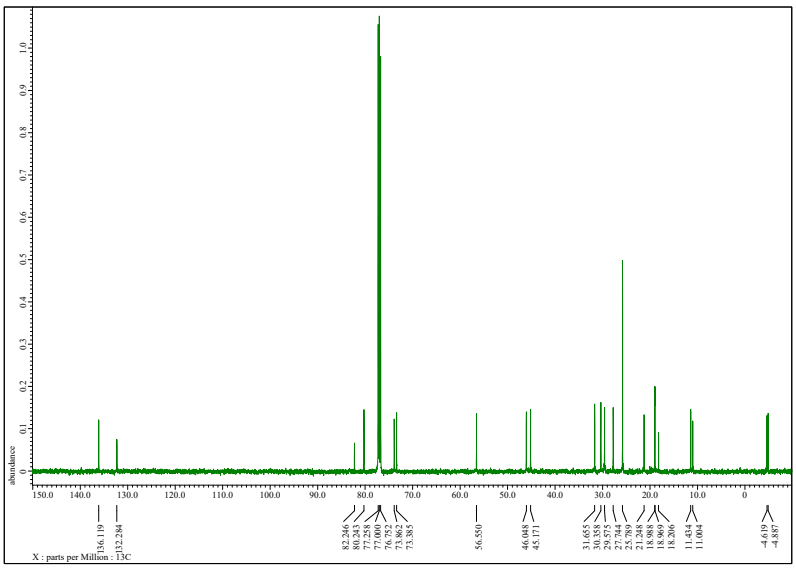




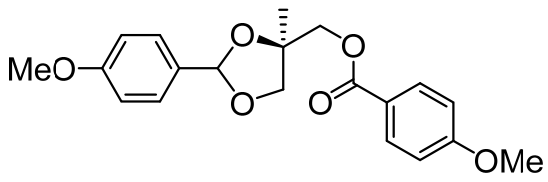
Compound 7

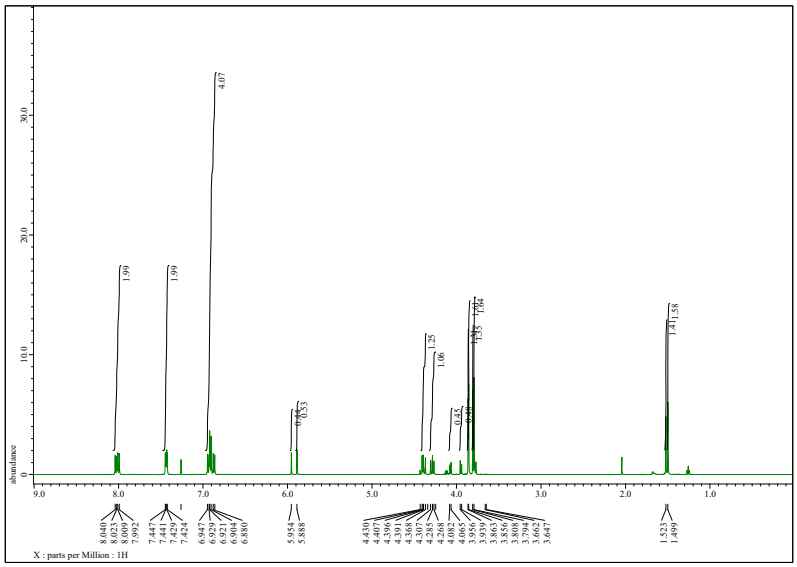


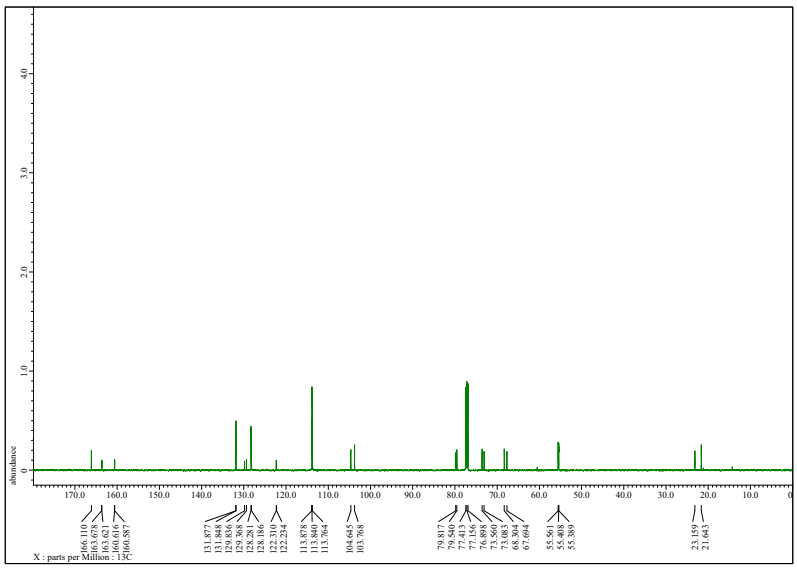




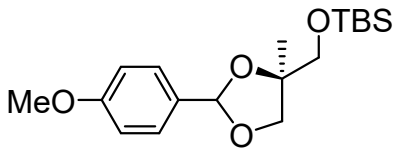
Compound 22

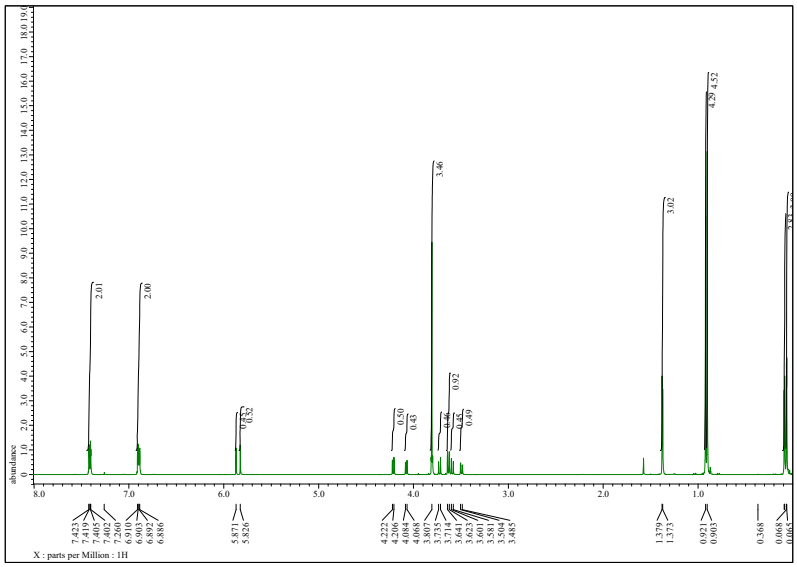


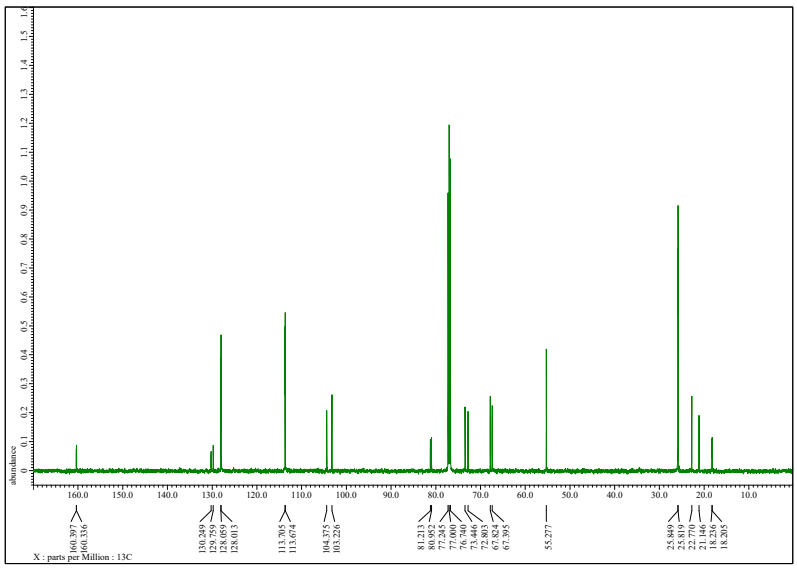




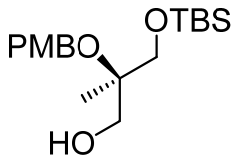
Compound 23

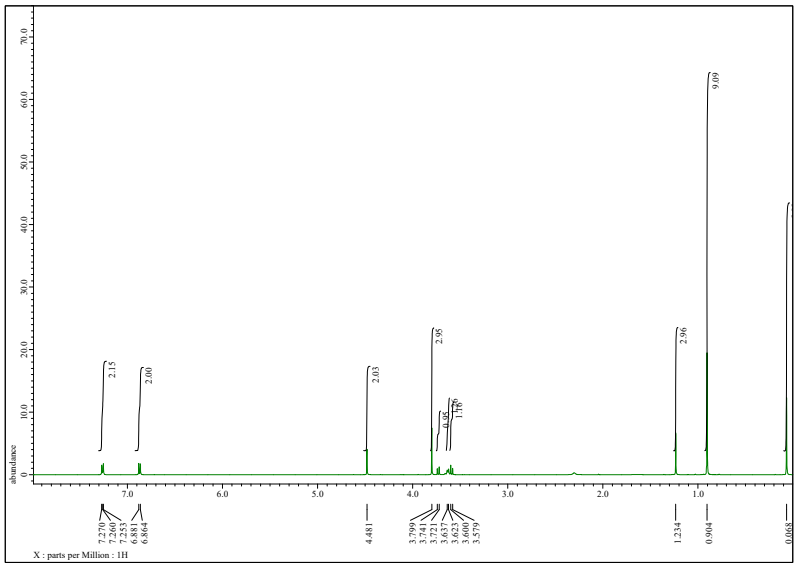


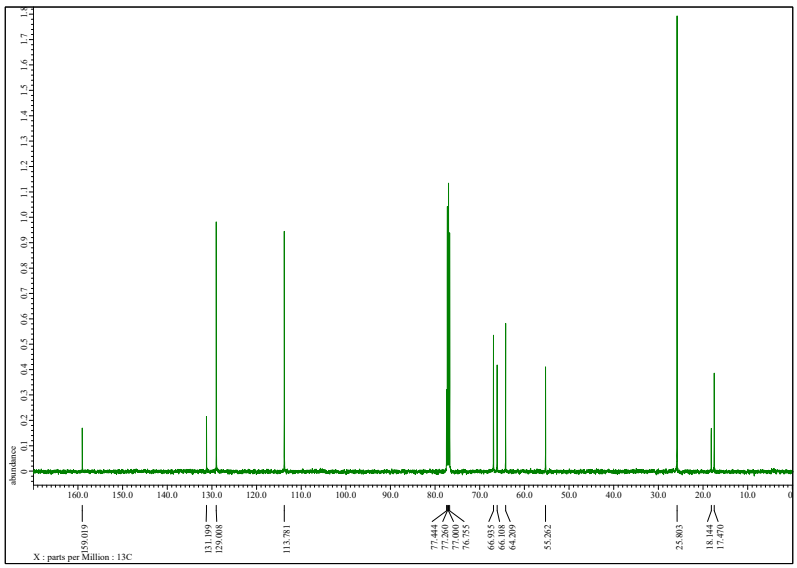




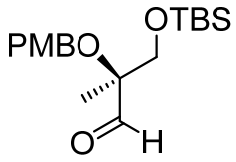
Compound 24

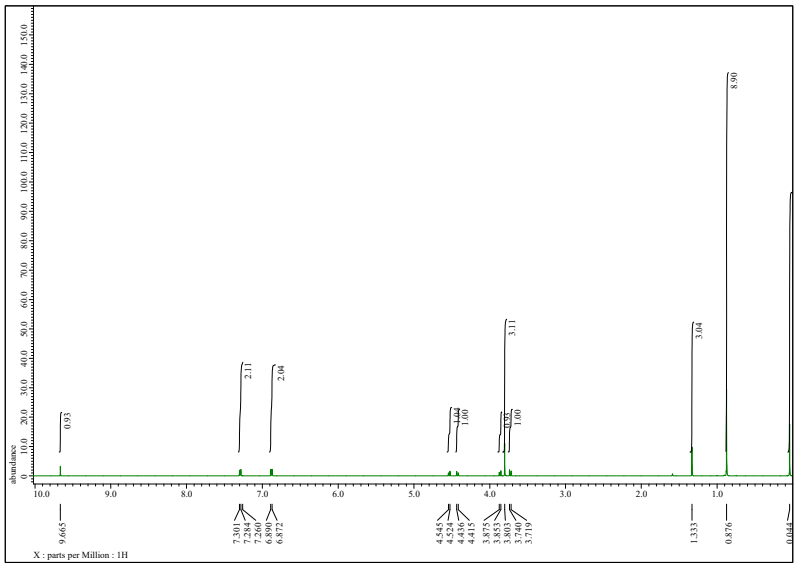

OTBS
PMBO
HO

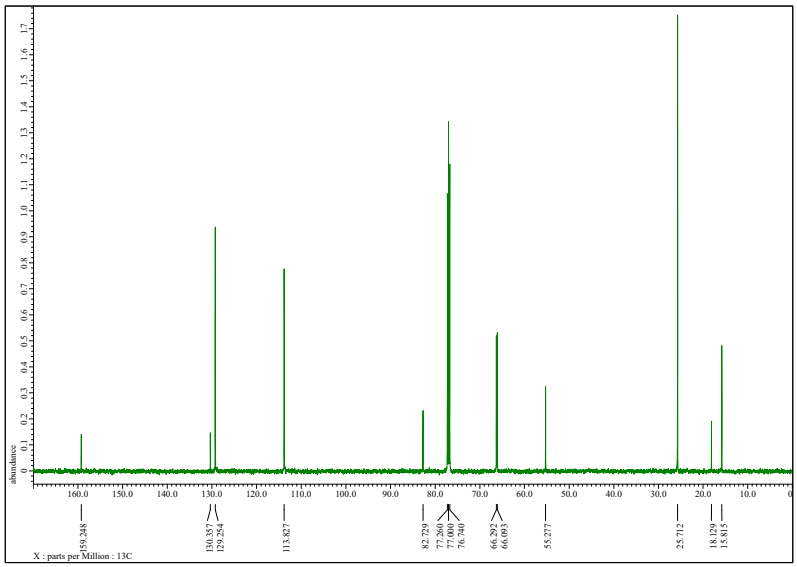

abundance
2.13
2.00
2.03
2.95
0.95
1.06
2.96
9.09
7.270
7.260
7.255
6.881
6.864
4.481
3.799
3.741
3.732
3.637
3.623
3.600
3.579
1.234
0.904
0.088
X : parts per Million : 1H


abundance
159.019
131.199
129.008
113.781
77.444
77.260
77.000
76.755
66.938
66.108
64.209
55.262
25.803
18.144
17.470
X : parts per Million : 13C

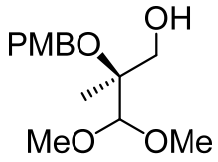
Compound 46

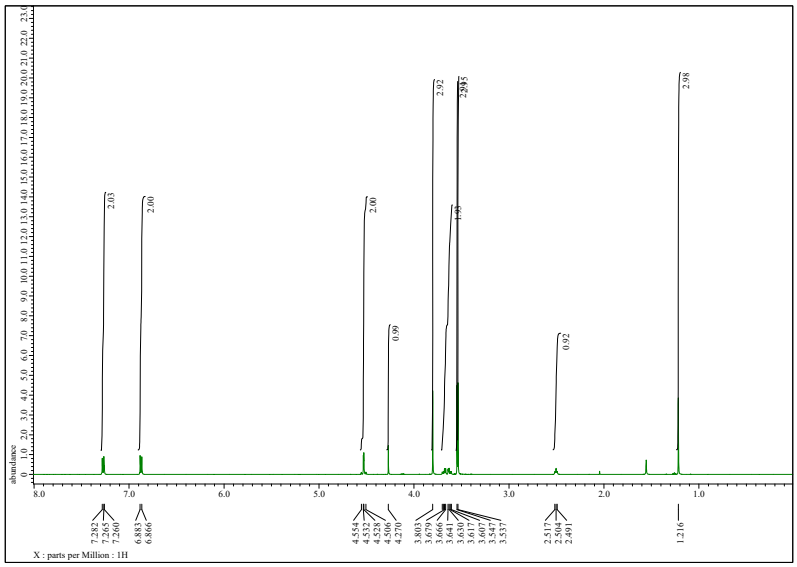


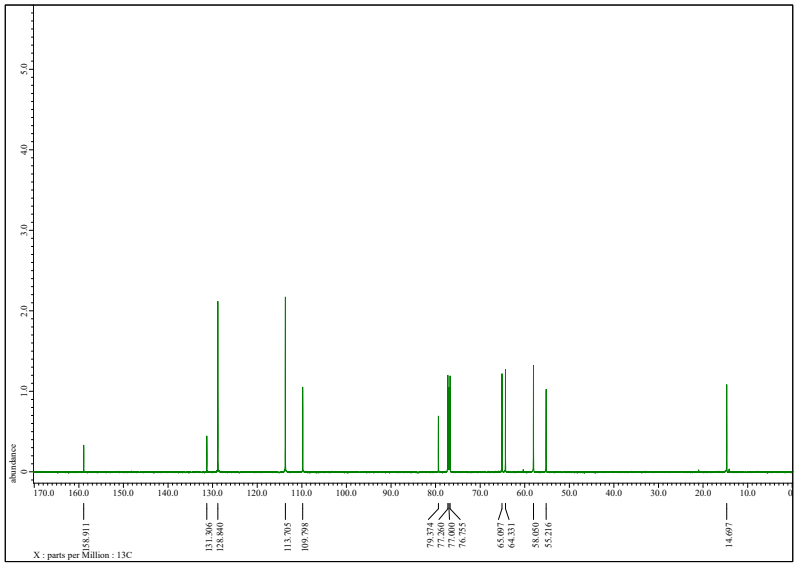




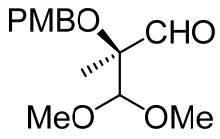
Compound 47

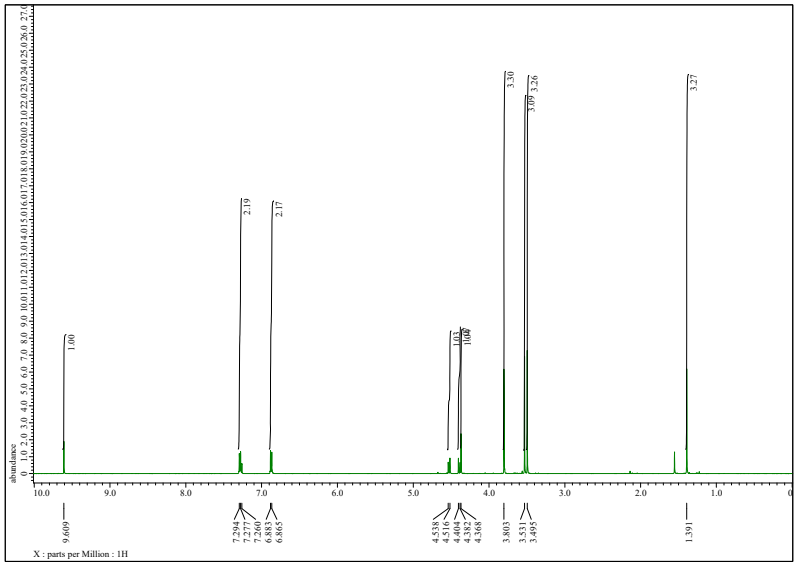

PMBO
OH
MeO
OMe

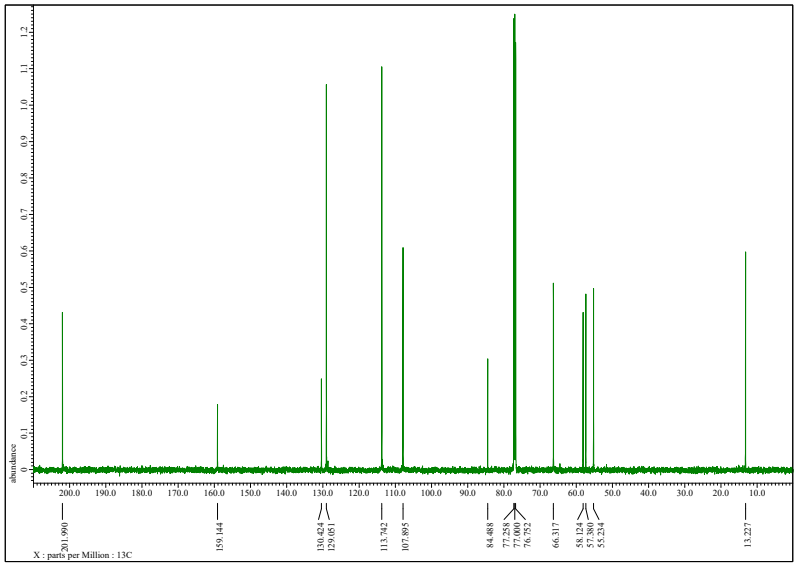

2.03
2.00
2.00
0.99
2.92
2.94
2.95
1.00
0.92
2.98
abundance
X : parts per Million : 1H


158.911
131.306
128.840
113.705
109.798
79.374
77.260
77.000
76.755
65.097
64.331
58.050
55.216
14.697
abundance
X : parts per Million : 13C

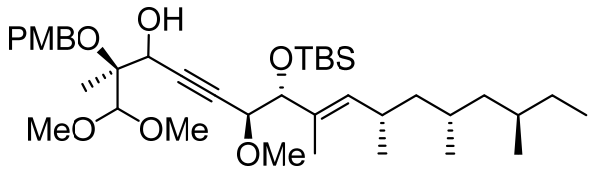
Compound 6

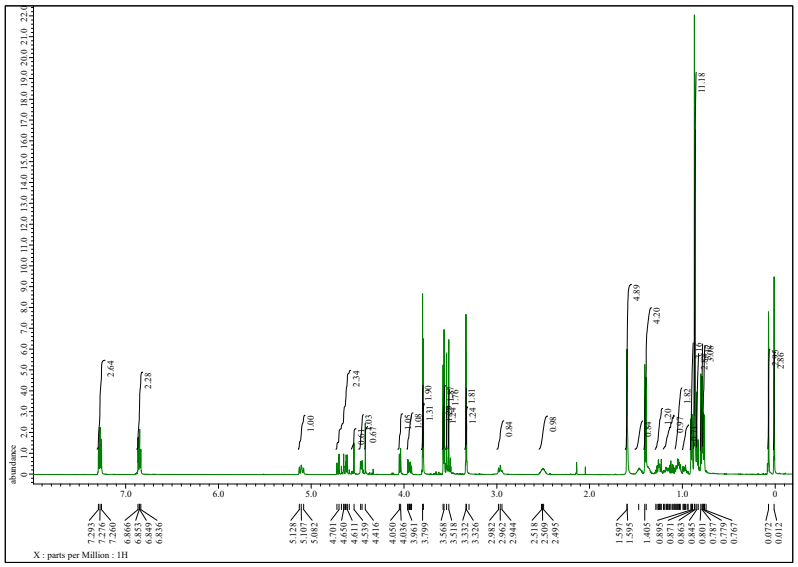

PMBO
CHO
MeO
OMe

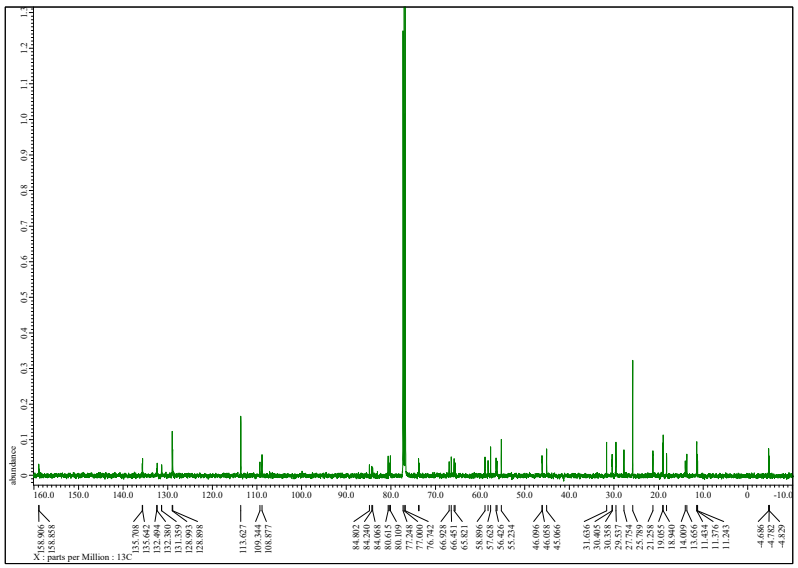

1.00
2.19
2.17
1.03
1.02
3.30
3.09
3.26
3.27
9.609
7.294
7.277
7.260
6.885
6.865
4.538
4.516
4.404
4.382
4.368
3.803
3.531
3.495
1.391
X : parts per Million : 1H


201.990
159.144
130.424
129.051
113.742
107.895
84.488
77.258
77.000
76.752
66.317
58.128
57.388
57.234
13.227
X : parts per Million : 13C

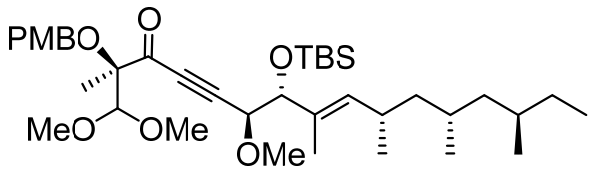
Compound 26

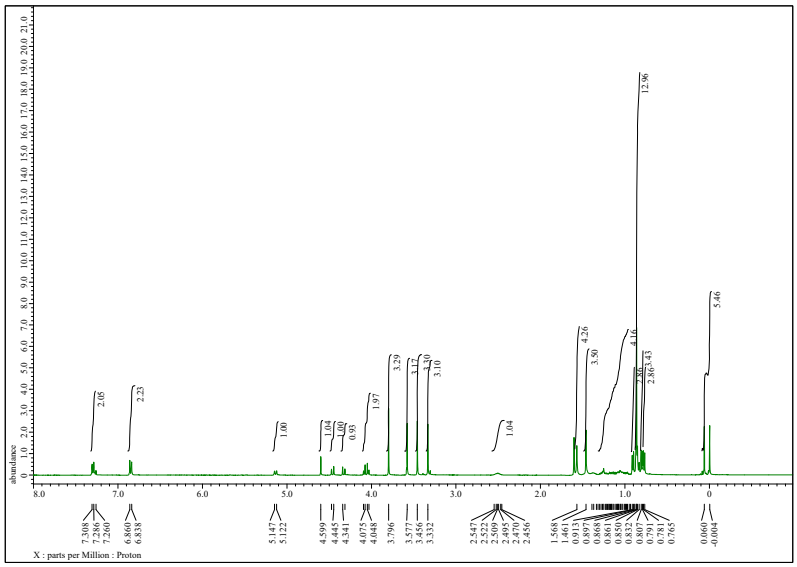


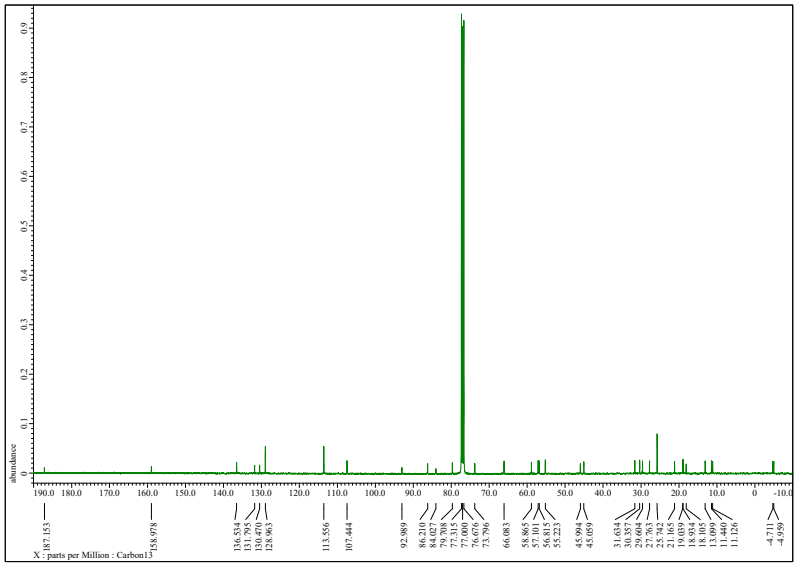




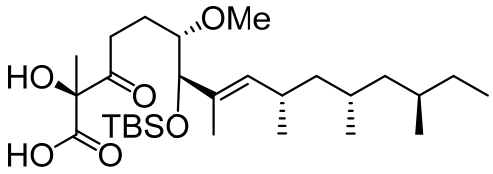
Compound 48

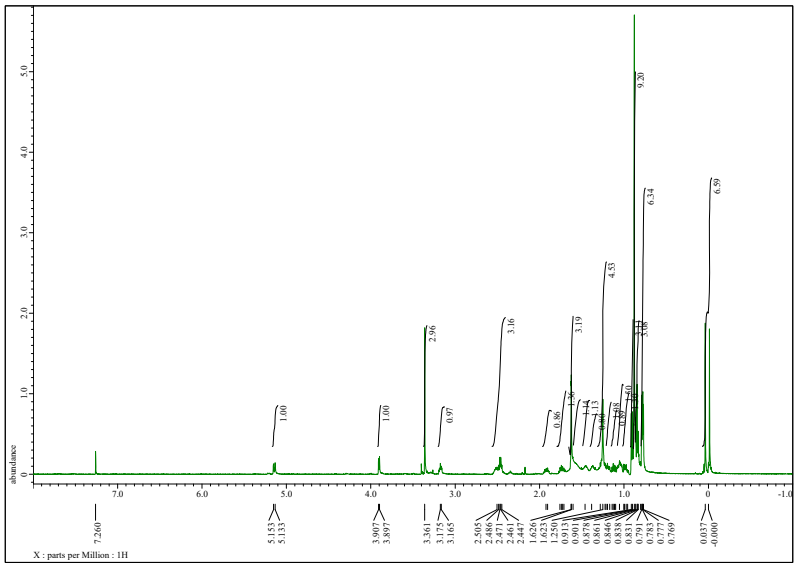


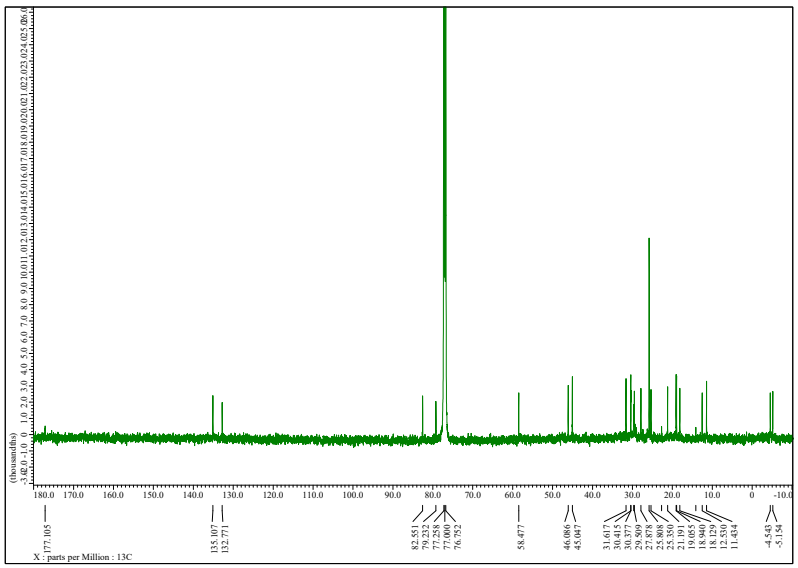




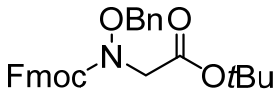
Compound 3

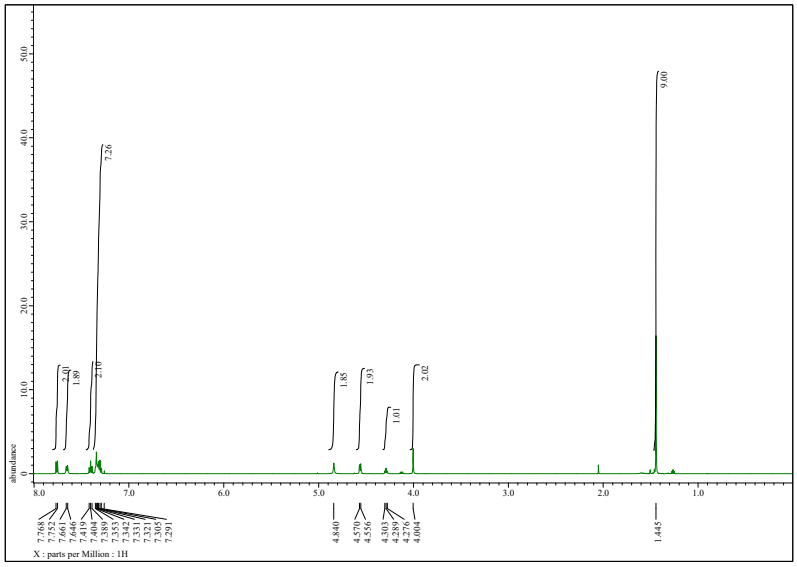

OMe
HO
O
TBSO
HO
O

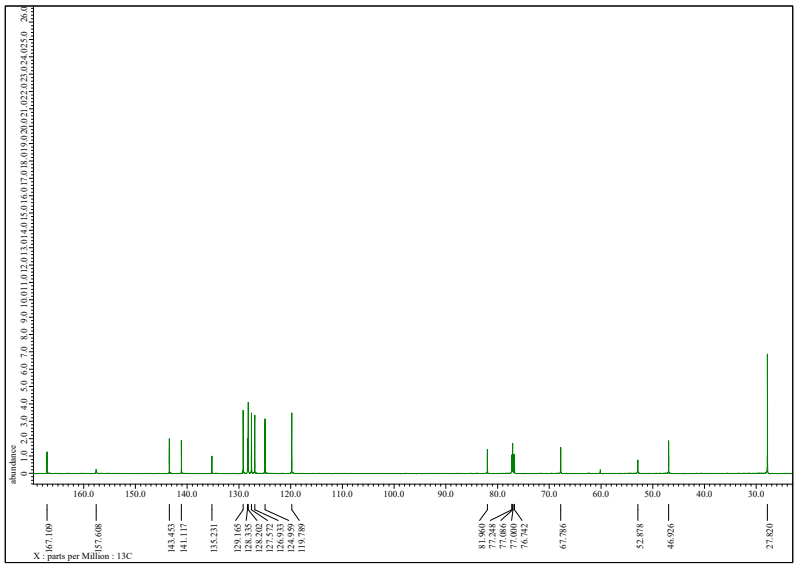

abundance
X : parts per Million : 1H


(thousands)
X : parts per Million : 13C

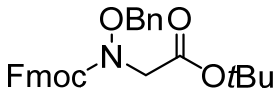
Compound 48

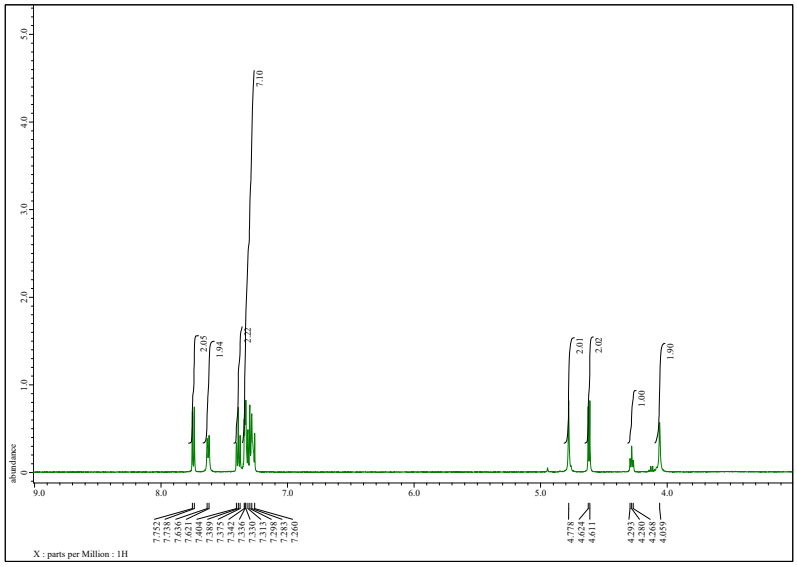

OBn
O
N
Fmoc
OtBu

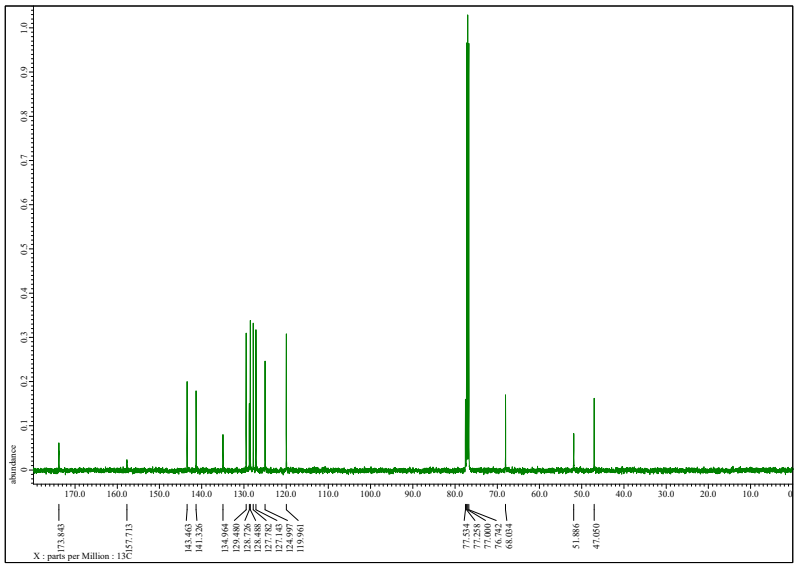

abundance
X : parts per Million : 1H


abundance
X : parts per Million : 13C

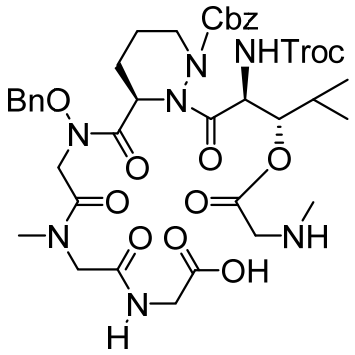
Compound 29

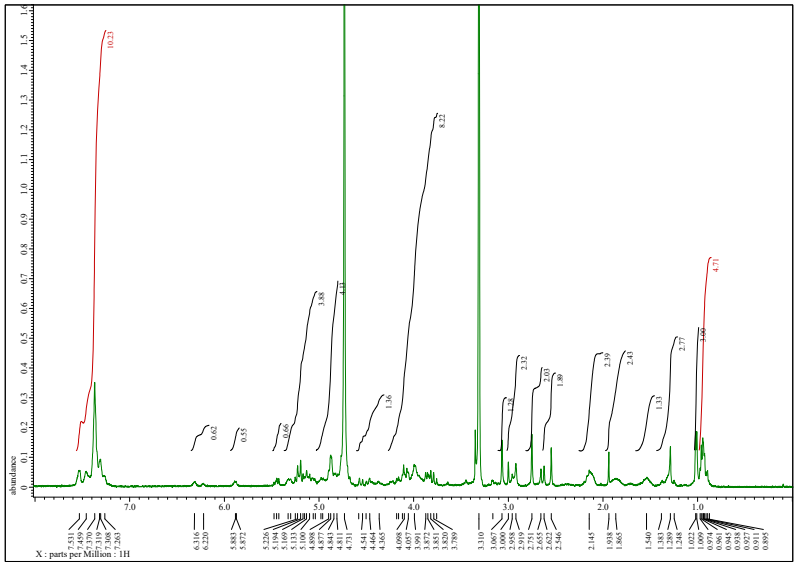

OBn
O
N
Fmoc
O*t*Bu

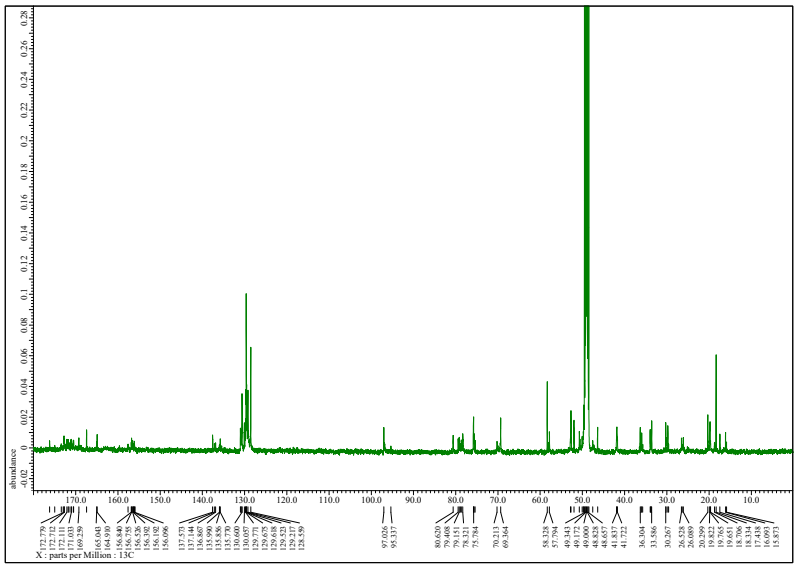

7.10
2.05
1.94
2.23
2.01
2.02
1.00
1.90
abundance
X : parts per Million : 1H


abundance
X : parts per Million : 13C

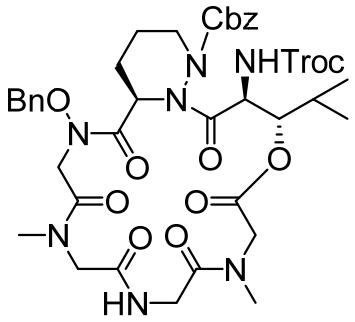
Compound 4

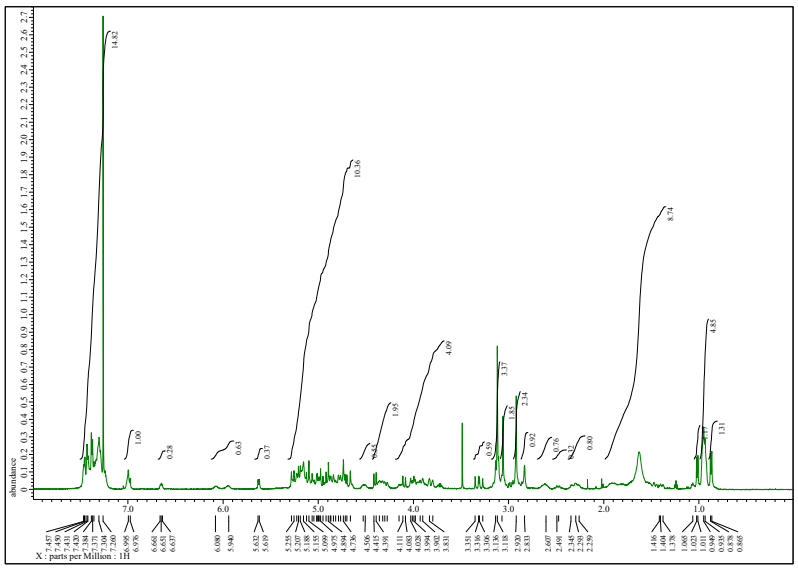


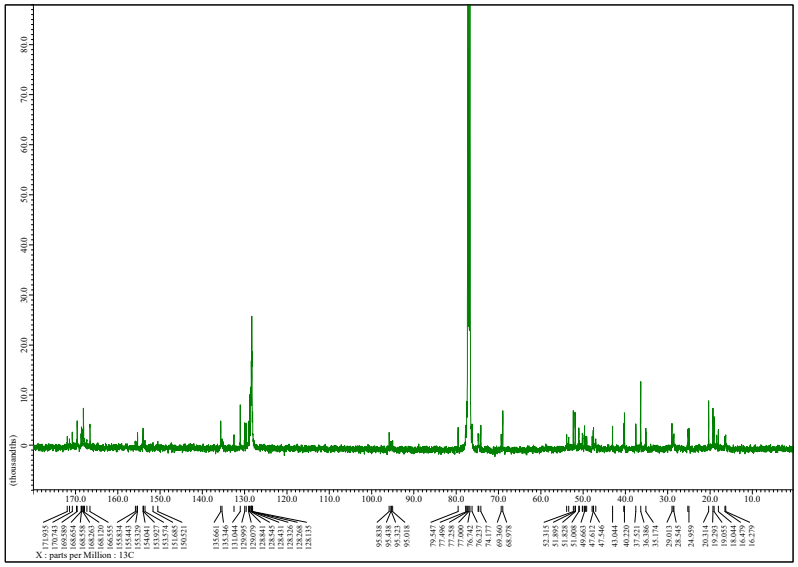




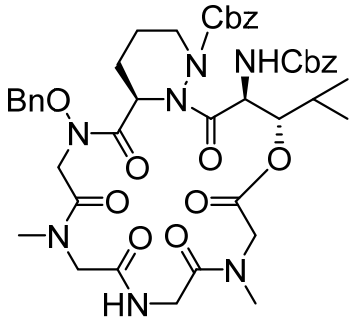
Compound 37

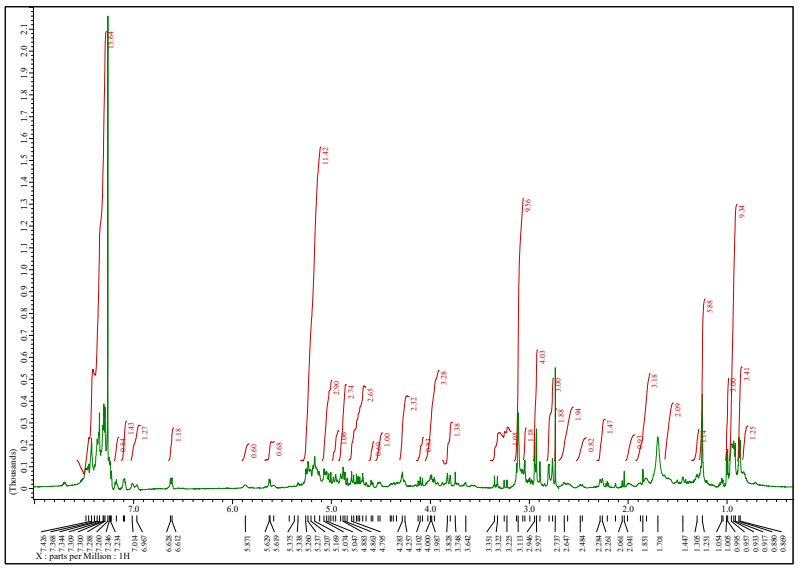


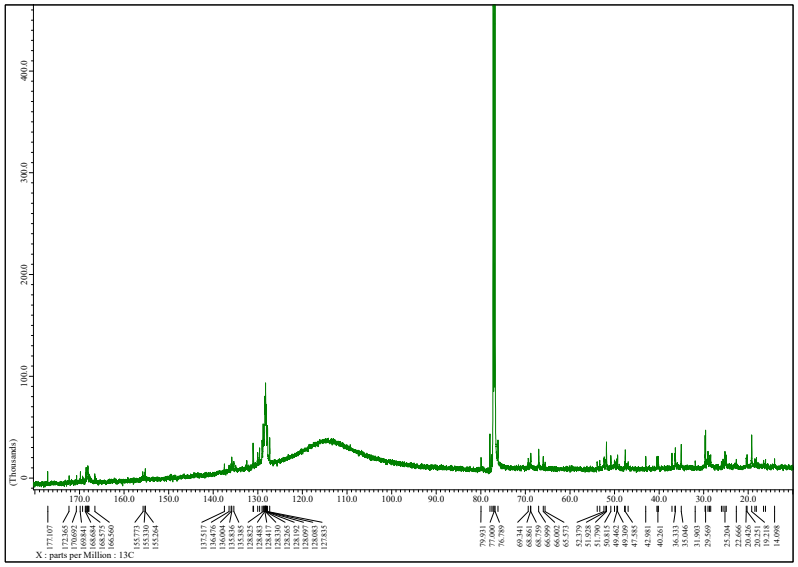




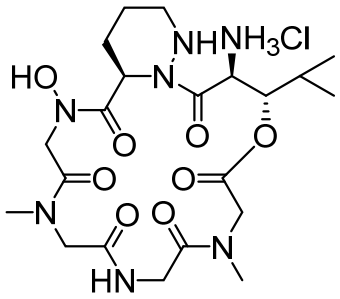
Compound 38

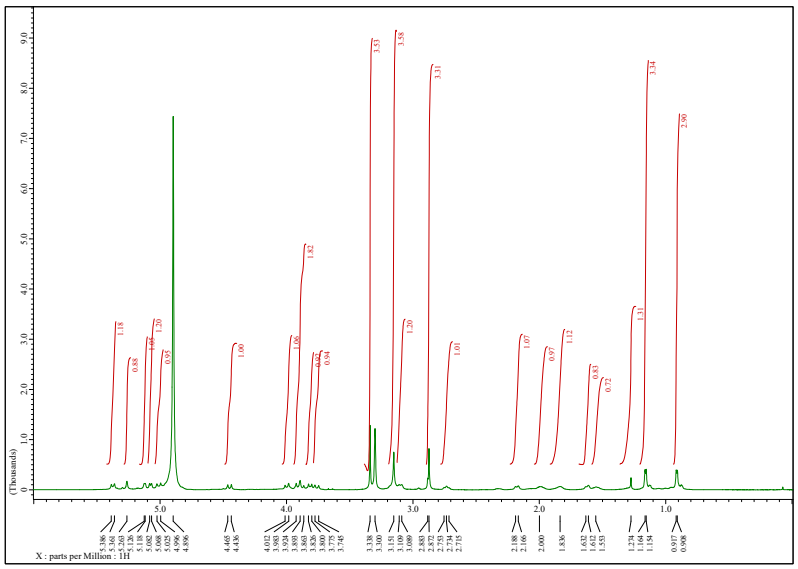


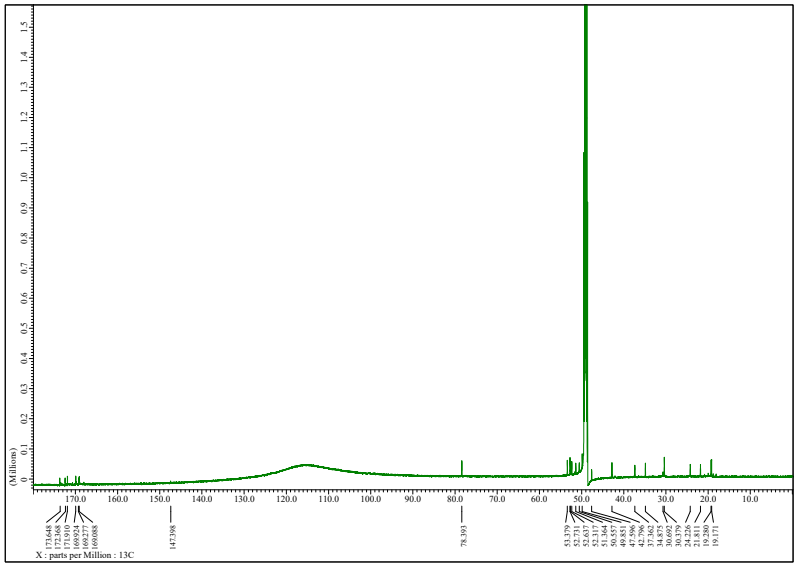




Compound 2







verucopeptin (**1**)