Supporting information

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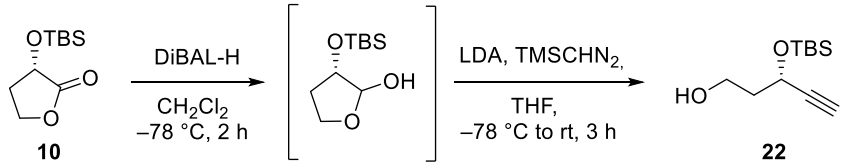
General information

All commercially available reagents and solvents were used in the form they were supplied without any further purification. The stated yields are based on isolated material. Thin layer chromatography was performed on silica gel 60 F_{254} aluminum-backed plates fabricated by Merck. Flash column chromatography was performed on silica gel 60 (40 - 63 µm) fabricated by Merck. NMR spectra were recorded on a Bruker AVII 400 or a Bruker AVIII HD 400 spectrometer at 400 MHz for ^{1}H NMR and at 101 MHz for ^{13}C NMR. Coupling constants (*J*) are reported in hertz and chemical shifts are reported in parts per million (δ) relative to the central residual protium solvent resonance in ^{1}H NMR ($CDCl_3$ = δ 7.27, MeOD-d_4 = δ 3.31) and the central carbon solvent resonance in ^{13}C NMR ($CDCl_3$ = δ 77.00 ppm, MeOD-d_4 = δ 49.00). Mass spectra were recorded at 70 eV on Micromass Prospec Q or Micromass QTOF 2 W spectrometer using ESI as the method of ionization. High resolution mass spectra were recorded at 70 eV on Micromass Prospec Q or Micromass QTOF 2W spectrometer using ESI as the method of ionization. Optical rotations were measured using a 0.7 mL cell with a 1.0 dm path length on an Anton Paar MCP 100 polarimeter. HPLC-analyses were performed using a C_{18} stationary phase (Eclipse XDB-C18, 4.6 x 250 mm, particle size 5 µm, from Agilent Technologies), applying the conditions stated. The UV/Vis spectrum was recorded using an Agilent Technologies Cary 8485 UV-VIS spectrophotometer using quartz cuvettes.

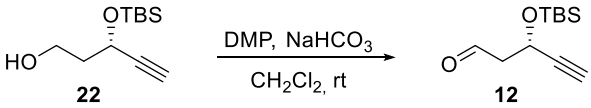
Experimental Details

(*S*)-3-((*Tert*-butyldimethylsilyl)oxy)pent-4-yn-1-ol (22)



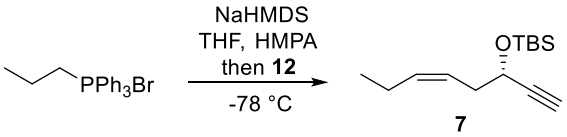
To a solution of TBS-lactone **10** (1.50 g, 6.90 mmol, 1.00 eq.) in CH_2Cl_2 (75 mL) was added DIBAl-H (1.0 M in CH_2Cl_2, 8.30 mL, 8.30 mmol, 1.20 eq.) at –78 °C. The reaction mixture was stirred for 2 h at this temperature and then quenched by addition of MeOH (10 mL). The solution was poured into a saturated aq. solution of Rochelle salt (100 mL) and vigorously stirred for 3 h at rt. The layers were separated and the aq. layer was extracted (CH_2Cl_2, 3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to yield the crude lactol. Next, to a solution of LDA (1.0 M in Hex/THF, 16.6 mL, 16.6 mmol, 2.40 eq.) in THF (18 mL) was added $TMSCHN_2$ (2 M in Et_2O, 4.14 mL, 8.28 mmol, 1.2 eq.) at –78 °C and the reaction mixture was stirred for 30 min at the same temperature. The crude lactol in THF (20 mL) was carefully added and stirring was continued for 2 h. The reaction was warmed to rt, stirred for 30 min and then quenched by careful addition of a saturated aq. solution of NH_4Cl (15 mL). The layers were separated and the aqueous layer was extracted (Et_2O, 3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. Alcohol **22** (832 mg, 3.88 mmol, 46%) was obtained after purification by column chromatography (heptane/EtOAc 80/20) as a colorless oil. $\mathbf{R_f}$ (hexanes/EtOAc 8:2, $KMnO_4$ stain) = 0.21; $\mathbf{[\alpha]_D^{20}}$ = -55 (c = 0.11, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.61 (ddd, *J* = 7.0, 5.1, 2.1 Hz, 1H), 3.89 (ddd, *J* = 11.8, 7.6, 4.2 Hz, 1H), 3.75 (ddd, *J* = 10.9, 6.1, 4.5 Hz, 1H), 2.47 (bs, 1H), 2.42 (d, *J* = 2.1 Hz, 1H), 2.02 – 1.82 (m, 2H), 0.88 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 84.8, 73.2, 61.8, 59.8, 40.2, 25.8 (3C), 18.2, -4.5, -5.1.

(*S*)-3-((*Tert*-butyldimethylsilyl)oxy)pent-4-ynal (12)



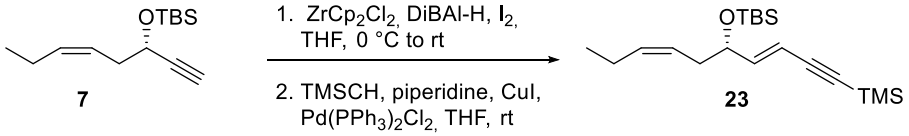
To a solution of alcohol **22** (1.55 g, 7.21 mmol, 1.0 eq.) in CH_2Cl_2 (230 mL) was added DMP (3.67 g, 8.66 mmol, 1.2 eq.) and $NaHCO_3$ (3.45 g, 41.1 mmol, 5.7 eq.) at rt. The reaction mixture was stirred for 1 h and quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (80 mL). The layers were separated and the aqueous layer was extracted (CH_2Cl_2, 3 x 50 mL). The combined organic layers were washed dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. The residue was filtered through a plug of silica (heptane/EtOAc 80/20), concentrated and aldehyde **12** was used without further purification in the next step. $\mathbf{R_f}$ (hexanes/EtOAc 95:5, $KMnO_4$ stain) = 0.17.

(*S*,*Z*)-T*ert*-butyldimethyl(oct-5-en-1-yn-3-yloxy)silane (7)



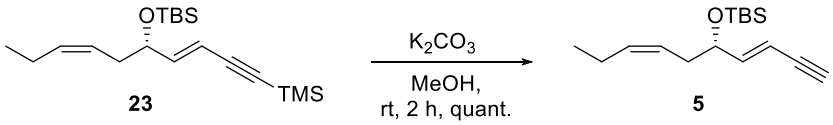
To a solution of propyltriphenylphosphonium bromide (2.78 g, 7.48 mmol, 1.05 eq.) in THF (65 mL) was added HMPA (10.0 mL, 57.7 mmol, 8.00 eq.) and NaHMDS (0.6 M in toluene, 12.5 mL, 7.48 mmol, 1.05 eq.) at –78 °C. The reaction mixture was warmed to rt and stirred for 10 min. Aldehyde **12** in dry THF (20 mL) was added, the reaction was allowed to warm to rt overnight and stirred for 20 h. The reaction was quenched by addition of a phosphate buffer solution (pH = 7.0, 50 mL) and Et_2O (50 mL) was added. The phases were separated and the aqueous layer was extracted (Et_2O, 3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. Alkene **7** (887 mg, 3.72 mmol, 52% over two steps) was obtained after purification by column chromatography (1% EtOAc in heptane) as a yellow oil. **R_f** (2% EtOAc in Hep) = 0.40; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.57 – 5.37 (m, 2H), 4.34 (td, *J* = 6.6, 2.1 Hz, 1H), 2.46 – 2.41 (m, 2H), 2.38 (d, *J* = 2.1 Hz, 1H), 2.12 – 2.02 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 134.6, 123.7, 85.54, 72.21, 62.95, 36.63, 25.92, 20.93, 18.41, 14.38, -4.49, -4.89 ppm; **HRMS (ESI):** calculated $C_{14}H_{26}NaOSi$: 261.1651, found: 261.1645; **$[\alpha]_D^{20}$:** -24.1 (c = 1.0, MeOH).

***Tert*-butyldimethyl(((*S*,3*E*,7*Z*)-1-(trimethylsilyl)deca-3,7-dien-1-yn-5-yl)oxy)silane (23)**



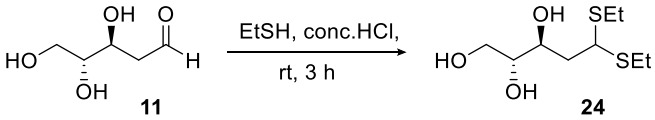
To a suspension of bis(cyclopentadienyl)zirconium(IV) dichloride (1.20 g, 4.09 mmol, 1.10 eq.) in THF (9.2 mL) was added D*i*BAl-H (1.0 M in THF, 4.10 mL, 4.09 mmol, 1.10 eq.) at 0 °C and it was stirred for 30 min. A solution of alkene **7** (887 mg, 3.72 mmol, 1.00 eq.) in THF (1.8 mL) was added at 0 °C, the suspension was allowed to warm to rt and stirred for 60 min. A solution of iodine (614 mg, 4.84 mmol, 1.30 eq.) in THF (5.5 mL) was added at rt to the yellow solution and stirring was continued for further 40 min. TMS-acetylene (0.74 mL, 5.21 mmol, 1.40 eq.), piperidine (0.74 mL, 7.44 mmol, 2.00 eq.), copper(I) iodide (70.8 mg, 372 µmol, 10 mol%) and bis(triphenylphosphine) palladium(II) dichloride (104 mg, 149 µmol, 4 mol%) were added successively and the reaction mixture was stirred for 3 h at rt. The solvent was evaporated and the residue was filtered through silica (heptane/EtOAc 80/20). TMS-alkyne **23** (670 mg, 1.99 mmol, 54% over two steps) was obtained as a yellow oil after purification by column chromatography (0.5% Et_2O in heptane). **R_f** (1% Et_2O in Hep) = 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.22 (dd, *J* = 15.9, 5.0 Hz, 1H), 5.72 (dd, *J* = 15.8, 1.7 Hz, 1H), 5.54 – 5.29 (m, 2H), 4.24 – 4.15 (m, 1H), 2.36 – 2.20 (m, 2H), 2.11 – 1.98 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H), 0.92 (s, 9H), 0.21 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.2, 134.0, 124.0, 108.7, 103.7, 94.42, 72.32, 35.79, 25.85, 20.75, 18.21, 14.12, -0.03, -4.61, -4.81 ppm; **HRMS (ESI):** calculated $C_{19}H_{36}NaO_3Si_2$: 359.2202, found: 359.2196; **$[\alpha]_D^{20}$:** -8.1 (c = 1.0, MeOH).

***Tert*-butyl(((*S*,3*E*,7*Z*)-deca-3,7-dien-1-yn-5-yl)oxy)dimethylsilane (5)**



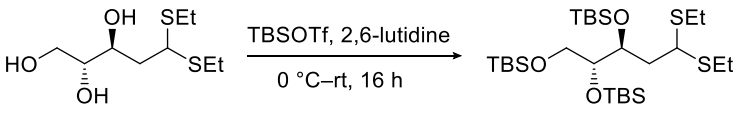
To a solution of TMS-alkyne **23** (670 mg, 1.99 mmol, 1.00 eq.) in MeOH (13 mL) was added K_2CO_3 (330 mg, 2.34 mmol, 1.20 eq.) at rt. The reaction mixture was stirred for 2 h and quenched by addition of a saturated aqueous solution of NH_4Cl (20 mL) and EtOAC (20 mL). The layers were separated and the aqueous layer was extracted (EtOAc, 3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. Alkyne **5** (524 mg, 1.98 mmol, quant.) was obtained after purification by column chromatography (heptane/EtOAc 95/5) as an orange oil. $\mathbf{R_f}$ (heptane/EtOAc 95/5) = 0.62; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.25 (dd, *J* = 15.9, 5.0 Hz, 1H), 5.71 – 5.61 (m, 1H), 5.54 – 5.26 (m, 2H), 4.24 – 4.14 (m, 1H), 2.86 (d, *J* = 2.3 Hz, 1H), 2.34 – 2.17 (m, 2H), 2.09 – 1.97 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.90 (d, *J* = 1.0 Hz, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 148.2, 134.3, 124.0, 107.8, 82.25, 77.16, 72.41, 35.88, 25.98, 20.88, 18.37, 14.29, -4.50, -4.66 ppm; **HRMS (ESI):** calculated $C_{164}H_{28}NaOSi$: 287.1807, found: 287.1807; $\mathbf{[\alpha]_D^{20}}$**:** +8.0 (c = 1.0, MeOH).

(2*R*,3*S*)-5,5-*Bis*(ethylthio)pentane-1,2,3-triol (24)



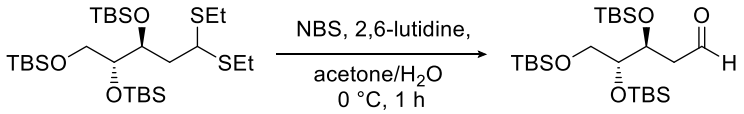
To a solution of 2-deoxy-D-ribose (**11**) (5.00 g, 37.3 mmol, 1.00 eq.) in conc. HCl (6.5 mL) was added ethanethiol (6.5 mL, 89.5 mmol, 2.40 eq.) and the reaction mixture was stirred for 3 h at rt. The solution was neutralized with an aqueous solution of K_2CO_3 (30 mL) and extracted (CH_2Cl_2, 3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Thioacetal **24** (6.33 g, 26.3 mmol, 71%) was obtained as a yellow oil after purification by column chromatography (5% MeOH in CH_2Cl_2). $\mathbf{R_f}$ (10% MeOH in CH_2Cl_2) = 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.12 – 4.00 (m, 2H), 3.82 – 3.71 (m, 2H), 3.65 – 3.59 (m, 1H), 3.49 (br s, 3H), 2.78 – 2.52 (m, 4H), 2.02 – 1.94 (m, 2H), 1.31 – 1.22 (m, 6H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 74.33, 71.38, 63.44, 48.48, 38.98, 24.50, 23.96, 14.63, 14.57 ppm; **HRMS (ESI):** calculated $C_9H_{20}NaO_3S_2$: 263.0752, found: 263.0746; $\mathbf{[\alpha]_D^{20}}$**:** –19.2 (c = 1.0, MeOH).

(5*S*,6*R*)-5-(2,2-*Bis*(ethylthio)ethyl)-6-((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (14)



To a solution of thioacetal **24** (3.16 g, 13.2 mmol, 1.00 eq.) in CH_2Cl_2 (60 mL) was added 2,6-lutidine (12.1 mL, 105 mmol, 8.00 eq.) and TBSOTf (12.1 mL, 52.7 mmol, 4.0 eq.) at 0 °C. The reaction was warmed to rt, stirred for 16 h and was then quenched by addition of a saturated aqueous solution of NH_4Cl (40 mL). The layers were separated and the aqueous layer was extracted (CH_2Cl_2, 3 x 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. TBS-triol **14** (7.43 g, 12.7 mmol, 97%) was obtained after purification by column chromatography (heptane /EtOAc 95/5) as a colorless oil. **R_f** (heptane /EtOAc 95/5) = 0.57; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.17 (ddd, *J* = 9.5, 2.6, 1.4 Hz, 1H), 3.93 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.69 (ddd, *J* = 7.2, 5.8, 1.4 Hz, 1H), 3.54 – 3.41 (m, 2H), 2.72 – 2.51 (m, 4H), 2.11 – 2.02 (m, 1H), 1.78 (ddd, *J* = 14.7, 11.0, 2.6 Hz, 1H), 1.28 – 1.20 (m, 6H), 0.94 – 0.85 (m, 27H), 0.14 – -0.05 (m, 18H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 77.78, 72.20, 64.53, 48.17, 39.01, 26.20, 26.12, 26.10, 24.61, 23.20, 18.44, 18.38, 18.32, -3.45, -4.35, -4.37, -4.65, -5.26, -5.30 ppm; **HRMS (ESI):** calculated $C_{27}H_{62}NaO_3S_2Si_3$: 605.3346, found: 605.3338; **$[\alpha]_D^{20}$:** –8.9 (c = 1.0, MeOH).

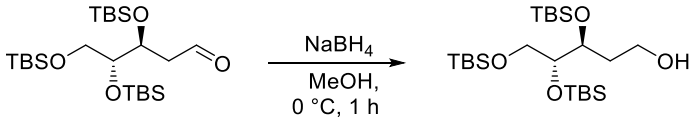
(3*S*,4*R*)-3,4,5-*Tris*((*tert*-butyldimethylsilyl)oxy)pentanal (15)



14 **15**

To a solution of TBS-triol **14** (6.01 g, 10.3 mmol, 1.00 eq.) in a solvent mixture of acetone/water (70 mL/24 mL) was added 2,6-lutidine (9.5 mL, 82.4 mmol, 8.00 eq.) and NBS (14.7 g, 82.4 mmol, 8.00 eq.) at 0 °C. The reaction mixture was stirred for 1 h and quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (50 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer was extracted (Et_2O, 3 x 50 mL). The combined organic layers were washed with HCl (1.0 M 20 mL), $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Aldehyde **15** (4.91 g, 10.3 mmol, quant.) was obtained after purification by column chromatography (1 % EtOAc in heptane) as a colorless oil. **R_f** (heptane /EtOAc 95/5) = 0.40; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.85 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.35 (td, *J* = 5.1, 2.3 Hz, 1H), 3.80 – 3.74 (m, 1H), 3.53 – 3.37 (m, 2H), 2.66 – 2.42 (m, 2H), 0.93 – 0.84 (m, 27H), 0.15 – 0.00 (m, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 202.5, 77.19, 69.62, 64.41, 45.70, 25.88, 25.83, 18.11, -4.30, -4.61, -4.90, -4.94, -5.50 ppm; **HRMS (ESI):** calculated $C_{23}H_{52}NaO_4Si_3$: 499.3071, found: 499.3065; **$[\alpha]_D^{20}$:** –5.9 (c = 1.0, MeOH).

(3*S*,4*R*)-3,4,5-*Tris*((*tert*-butyldimethylsilyl)oxy)pentan-1-ol (25)

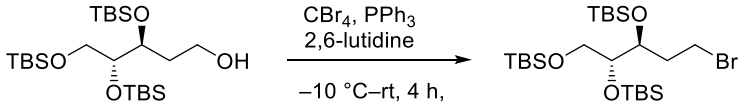


15 **25**

To a solution of aldehyde **15** (3.53 g, 7.41 mmol, 1.00 eq.) in MeOH (35 mL) was added $NaBH_4$ (420 mg, 11.1 mmol, 1.50 eq.) at 0 °C and the reaction was stirred for 2 h. The reaction was quenched by addition of brine and EtOAc was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Alcohol **25**

(3.00 g, 6.28 mmol, 85%) was obtained after purification by column chromatography (heptane/EtOAc 95/5 → 90/10) as a colorless oil. R_f (Hep/EtOAc 80/20) = 0.39; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.03 (ddd, *J* = 5.7, 4.8, 2.6 Hz, 1H), 3.83 – 3.75 (m, 2H), 3.71 – 3.62 (m, 1H), 3.59 – 3.45 (m, 2H), 1.92 – 1.69 (m, 2H), 0.93 – 0.86 (m, 27H), 0.13 – 0.05 (m, 18H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 77.37, 71.80, 64.82, 59.15, 34.28, 26.18, 26.08, 26.05, 18.41, 18.38, 18.30, -4.02, -4.40, -4.44, -4.75, -5.22, -5.31 ppm; **HRMS (ESI):** calculated $C_{23}H_{54}NaO_4Si_3$: 501.3228, found: 501.3222; **$[\alpha]_D^{20}$:** –12.7 (c = 1.0, MeOH).

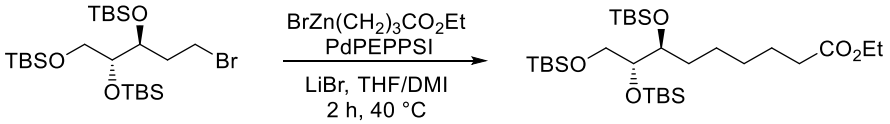
(5*S*,6*R*)-5-(2-Bromoethyl)-6-((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (8)



25 **8**

To a solution of alcohol **25** (2.50 g, 5.21 mmol, 1.00 eq.) in CH_2Cl_2 (100 mL) was added CBr_4 (2.60 g, 7.85 mmol, 1.50 eq.), then 2,6–lutidine (0.60 mL, 5.21 mmol, 1.00 eq.) was added at –10 °C. A solution of PPh_3 (2.06 g, 7.85 mmol, 1.50 eq.) in CH_2Cl_2 (30 mL) was added over 15 min and the resulting reaction mixture was stirred for 4 h, warmed to rt and stirred for another hour. The solvent was evaporated and the remaining residue was filtered through a plug of silica (Hep/EtOAc 80/20). Bromide **8** (2.34 g, 4.32 mmol, 83%) was obtained after purification by column chromatography (0.5% EtOAc in Hep) as a colorless oil. R_f (2.5% EtOAc in Hep) = 0.44; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.97 (dt, *J* = 8.1, 2.8 Hz, 1H), 3.70 (ddd, *J* = 7.3, 5.7, 2.1 Hz, 1H), 3.58 – 3.42 (m, 4H), 2.21 – 2.10 (m, 1H), 1.99 – 1.89 (m, 1H), 0.92 – 0.87 (m, 27H), 0.11 – 0.04 (m, 18H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$)) δ = 77.35, 72.16, 64.65, 35.71, 31.41, 26.15, 26.11, 26.07, 18.42, 18.35, 18.30, -3.78, -4.33, -4.43, -4.64, -5.26, -5.29 ppm; **HRMS (ESI):** calculated $C_{23}H_{53}BrNaO_3Si_3$: 563.2384, found: 563.2377; **$[\alpha]_D^{20}$:** –26.9 (c = 1.0, MeOH).

Ethyl (7*S*,8*R*)-7,8,9-*tris*((*tert*-butyldimethylsilyl)oxy)nonanoate (16)

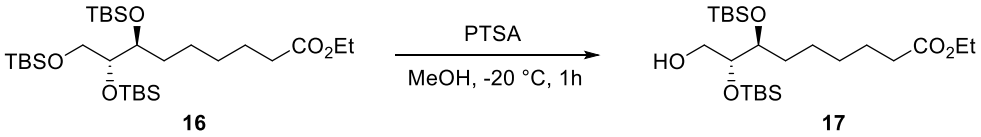


8 **16**

To a solution of Pd-PEPPSI^{TM}-IPr (351 mg, 0.517 mmol, 16 mol%) in DMI (7 mL) was added LiBr (0.5 M in THF, 21.4 mL, 10.7 mmol, 3.30 eq.) at rt, followed by the addition of 4-Ethoxy-4-oxobutylzinc bromide (0.5 M in THF, 10.3 mL, 5.17 mmol, 1.60 eq.) and a solution of bromide **8** (1.75 g, 3.23 mmol, 1.00 eq.) in DMI (8.75 mL). The reaction mixture was stirred for 2 h at 40 °C, quenched by addition of an aqueous solution of Na_2EDTA (0.5 M, 60 mL) and diluted with Et_2O (40 mL). The layers were separated and the aqueous layer was extracted (Et_2O, 3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Ester **16** (1.00 g, 1.74 mmol, 54%) was obtained after purification by column chromatography (1 % EtOAc in heptane) as a colorless oil. R_f (2.5% EtOAc in heptane) = 0.17; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.12 (q, *J* = 7.1 Hz, 2H), 3.72 – 3.67 (m, 1H), 3.66 – 3.58 (m, 2H), 3.49 – 3.42 (m, 1H), 2.28 (t, *J* = 7.6

Hz, 2H), 1.67 – 1.49 (m, 3H), 1.47 – 1.35 (m, 2H), 1.35 – 1.22 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.90 – 0.86 (m, 27H), 0.08 – 0.01 (m, 18H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 174.0, 77.32, 74.21, 65.25, 60.30, 34.55, 32.51, 29.67, 26.18, 26.16, 26.13, 25.31, 25.22, 18.52, 18.40, 18.31, 14.41, -3.95, -4.11, -4.49, -5.17, -5.26 ppm; **HRMS (ESI):** calculated $C_{29}H_{64}NaO_5Si_3$: 599.3959, found: 599.3954; **$[\alpha]_D^{20}$:** –11.0 (c = 0.5, MeOH).

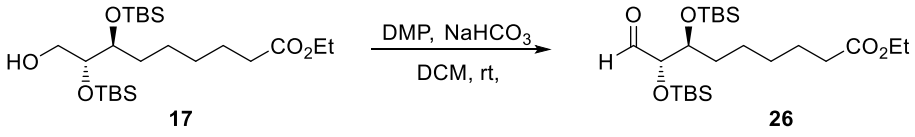
Ethyl (7*S*,8*R*)-7,8-*bis*((*tert*-butyldimethylsilyl)oxy)-9-hydroxynonanoate (17)



16 **17**

To a solution of ester **16** (991 mg, 1.72 mmol, 1.00 eq.) in MeOH (20 mL) was added PTSA (327 mg, 1.72 mmol, 1.0 eq.) at –20 °C and it was stirred for one hour at the same temperature. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (40 mL) and diluted with EtOAc (20 mL). The layers were separated and the aqueous layer was extracted (EtOAc, 3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Alcohol **17** (452 mg, 0.976 mmol, 57%, (81% brsm)) was obtained after purification by column chromatography (heptane /EtOAc 95/5) as a colorless oil and unreacted starting material was isolated again. **R_f** (Hep/EtOAc 90/10) = 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.12 (q, *J* = 7.1 Hz, 2H), 3.76 – 3.65 (m, 2H), 3.63 – 3.56 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.99 (br s, 1H), 1.67 – 1.57 (m, 2H), 1.57 – 1.43 (m, 2H), 1.41 – 1.27 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.10 – 0.08 (m, 9H), 0.06 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 173.9, 74.85, 74.56, 64.04, 60.33, 34.47, 33.84, 29.58, 26.05, 26.03, 25.14, 24.41, 18.28, 18.25, 14.39, -4.27, -4.33, -4.38 ppm; **HRMS (ESI):** calculated $C_{23}H_{50}NaO_5Si_2$: 485.3094, found: 485.3089; **$[\alpha]_D^{20}$:** –1.9 (c = 1.0, MeOH).

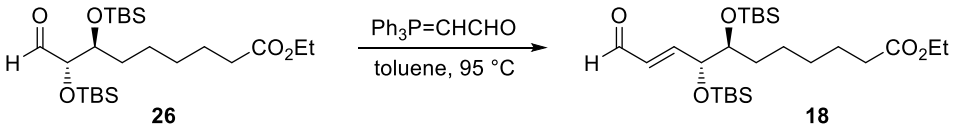
Ethyl (7*S*,8*S*)-7,8-*bis*((*tert*-butyldimethylsilyl)oxy)-9-oxononanoate (26)



17 **26**

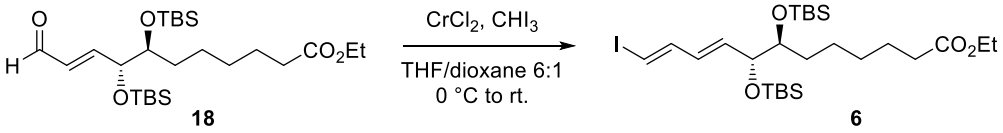
To a solution of alcohol **17** (445 mg, 0.962 mmol, 1.00 eq.) in CH_2Cl_2 (25 mL) was added $NaHCO_3$ (460 mg, 5.48 mmol, 5.7 eq.) and DMP (897 mg, 2.12 mmol, 2.2 eq.) at rt. The reaction mixture was stirred overnight and quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (10 mL). The layers were separated and the aqueous layer was extracted (CH_2Cl_2, 3 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. Aldehyde **26** (443 mg, 0.962 mmol, quant.) was obtained after purification by column chromatography (Hep/EtOAc 90/10) as a colorless oil. **R_f** (Hep/EtOAc 90/10) = 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 1.2 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.90 – 3.79 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.67 – 1.45 (m, 4H), 1.39 – 1.28 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.10 – 0.05 (m, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.9, 173.8, 81.0, 75.6, 60.4, 34.4, 33.6, 29.4, 26.0 (3C), 26.0 (3C), 25.0, 24.9, 18.4, 18.3, 14.4, -4.3, -4.5 (2C), -4.7. **HRMS (ESI):** calculated $C_{23}H_{48}NaO_5Si_2$: 483.2938, found: 483.2932; **$[\alpha]_D^{25}$:** +12.7 (c = 0.83, MeOH).

Ethyl (7*S*,8*R*,*E*)-7,8-*bis*((*tert*-butyldimethylsilyl)oxy)-11-oxoundec-9-enoate (18)



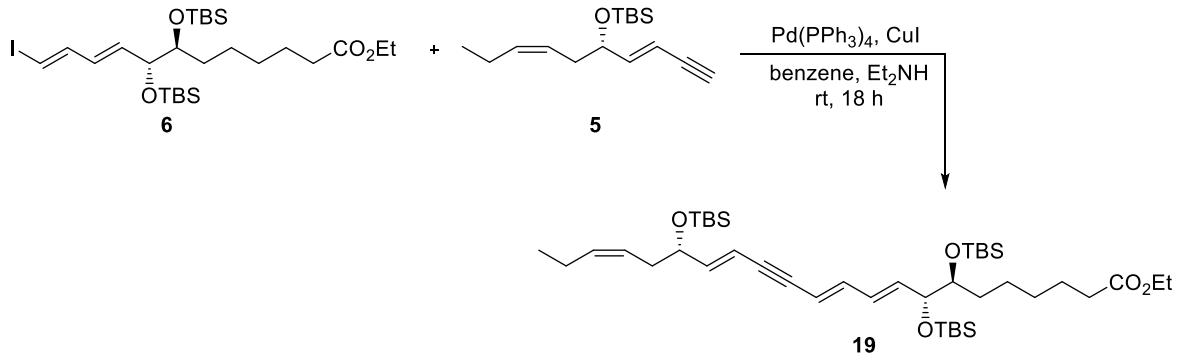
To a solutuion of aldehyde **26** (443 mg, 0.962 mmol, 1.00 equiv.) in toluene (20 mL) was added (triphenyl-phosphoranylidene)acetaldehyde (293 mg, 0.962 mmol, 1.00 eq.). The reaction mixture was warmed to 95 °C and stirred for 6 h. Then another equivalent of (triphenyl-phosphoranylidene)acetaldehyde (293 mg, 0.962 mmol, 1.00 eq.) was added and the solution was stirred overnight at 95 °C. After cooling to rt the solvent was evaporated and aldehyde **18** (271 mg, 0.558 mmol, 58% (91% brsm)) was obtained as a colorless oil after purification by column chromatography (heptane/Et_2O 90/10) and unreacted starting material was reisolated. **R_f** (heptane/EtOAc 80/20) = 0.46; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.57 (d, *J* = 8.0 Hz, 1H), 6.86 (dd, *J* = 15.7, 5.3 Hz, 1H), 6.24 (ddd, *J* = 15.7, 8.0, 1.4 Hz, 1H), 4.26 (ddd, *J* = 5.5, 4.3, 1.5 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.66 (dt, *J* = 6.5, 4.3 Hz, 1H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.68 – 1.26 (m, 8H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 193.6, 173.8, 158.2, 132.4, 76.51, 75.65, 60.36, 34.43, 33.79, 29.49, 26.05, 26.02, 25.08, 24.83, 18.38, 18.30, 14.40, -3.91, -4.25, -4.37, -4.61 ppm; **HRMS (ESI):** calculated $C_{25}H_{50}NaO_5Si_2$: 509.3094, found: 509.3089; **$[\alpha]_D^{20}$:** +4.8 (c = 1.0, MeOH).

Ethyl (7*S*,8*R*,9*E*,11*E*)-7,8-*bis*((*tert*-butyldimethylsilyl)oxy)-12-iodododeca-9,11-dienoate (6)



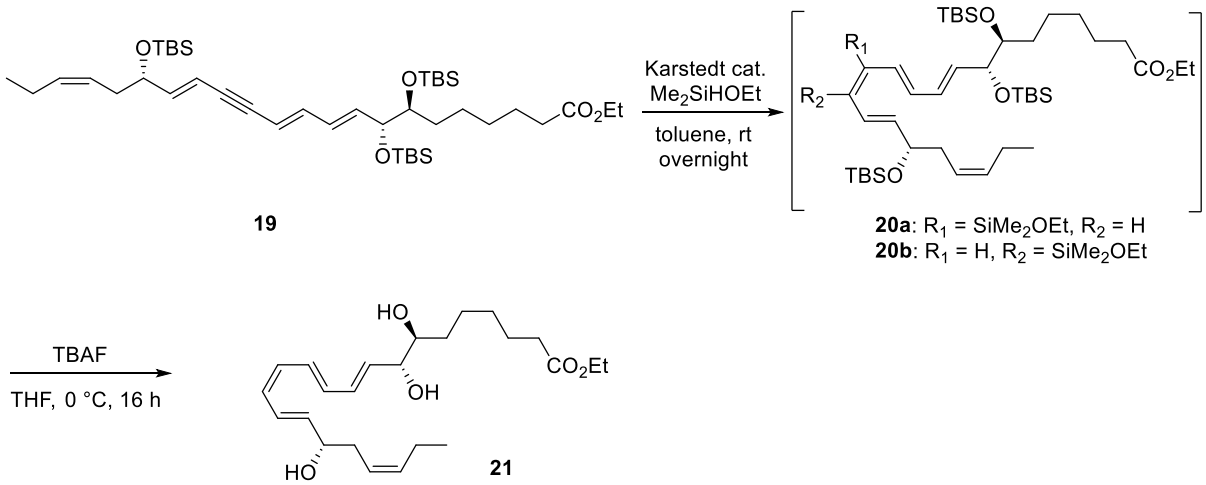
To a suspension of $CrCl_2$ (1.99 g, 16.2 mmol, 30 eq.) in a mixture of dioxane/THF (27 mL, 6/1) was added a solution of aldehyde **18** (263 mg, 0.542 mmol, 1.0 eq.) in dioxane/THF (18 mL, 6/1) and CHI_3 (1.71 g, 4.32 mmol, 8.0 eq.) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, afterwards it was warmed to rt and stirring was continued for further 60 min. The reaction was diluted with EtOAc (50 mL) and quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (30 mL) and a saturated aqueous solution of NH_4Cl (20 mL). The layers were separated and the aqueous layer was extracted (EtOAc, 3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Vinyliodide **6** (258 mg, 0.423 mmol, 78%, *E*/*Z* 16.7:1) was obtained as a colorless oil after purification by column chromatography (1 % EtOAc in heptane). **R_f** (2.5% EtOAc in heptane) = 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.01 (dd, *J* = 14.4, 10.7 Hz, 1H), 6.28 (d, *J* = 14.4 Hz, 1H), 6.04 (dd, *J* = 15.4, 10.7 Hz, 1H), 5.68 (dd, *J* = 15.4, 6.9 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.99 – 3.88 (m, 1H), 3.59 – 3.51 (m, 1H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.68 – 1.54 (m, 5H), 1.52 – 1.27 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 174.0, 145.0, 135.9, 131.0, 78.68, 77.16, 76.53, 76.26, 60.33, 34.50, 33.47, 29.60, 26.15, 26.11, 26.08, 25.15, 24.75, 18.39, 18.32, 14.41, -3.87, -3.96, -4.36, -4.56 ppm; **HRMS (ESI):** calculated $C_{26}H_{51}INaO_5Si_2$: 633.2268, found: 633.2263; **$[\alpha]_D^{20}$:** –1.6 (c = 1.0, MeOH).

Ethyl (7*S*,8*R*,9*E*,11*E*,15*E*,17*S*,19*Z*)-7,8,17-*tris*((*tert*-butyldimethylsilyl)oxy)docosa-9,11,15,19-tetraen-13-ynoate (19)



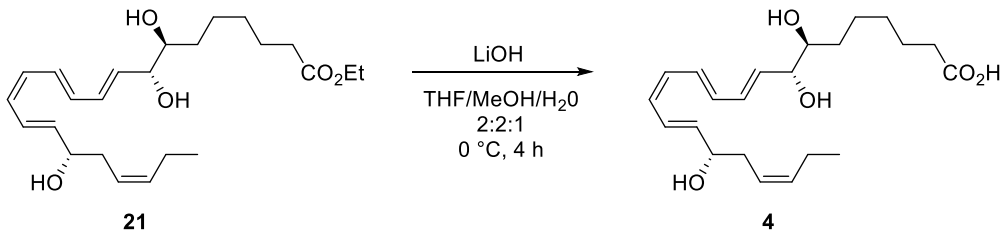
To a solution of vinyliodide **6** (232 mg, 0.380 mmol, 1.00 eq.) in Et_2NH (1.6 mL) and benzene (0.65 mL) was added $Pd(PPh_3)_4$ (13.1 mg, 11.4 µmol, 3 mol%) at rt and the reaction mixture was stirred for 30 min in the dark. CuI (3.60 mg, 18.9 µmol, 5 mol%) and a solution of alkyne **5** (100 mg, 0.380 mmol, 1.00 eq.) in Et_2NH (0.3 mL) were added and the solution was stirred for 18 h before it was quenched by addition of a saturated aqueous solution of NH_4Cl (15 mL). It was diluted with Et_2O (15 mL), the layers were separated and the aqueous layer was extracted (Et_2O, 2 x 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Alkyne **19** (241 mg, 0.323 mmol, 85%) was obtained as a colorless oil after purification by column chromatography (1.0 % EtOAc in heptane). $\mathbf{R_f}$ (heptane/EtOAc 95/5) = 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.56 (dd, *J* = 15.5, 10.8 Hz, 1H), 6.22 – 6.08 (m, 1H), 5.84 – 5.64 (m, 1H), 5.51 – 5.27 (m, 1H), 4.22 – 4.16 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.00 – 3.93 (m, 1H), 3.58 – 3.51 (m, 1H), 2.34 – 2.18 (m, 4H), 2.08 – 1.98 (m, 2H), 1.67 – 1.57 (m, 2H), 1.52 – 1.29 (m, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.91 – 0.83 (m, 27H), 0.06 – -0.02 (m, 18H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 174.0, 146.0, 141.1, 137.7, 134.1, 130.8, 124.2, 111.0, 109.1, 90.65, 89.40, 77.36, 77.16, 76.70, 76.30, 72.74, 60.32, 36.06, 34.52, 33.53, 29.63, 26.11, 26.08, 26.00, 25.17, 24.60, 20.90, 18.39, 18.31, 14.41, 14.31, -3.85, -3.91, -4.33, -4.43, -4.57, -4.65 ppm; **HRMS (ESI):** calculated $C_{42}H_{78}NaO_5Si_3$: 769.5055, found: 769.5049; **$[\alpha]_D^{20}$:** –12.2 (c = 1.0, MeOH).

RvD1 $_{n\text{-}3\ DPA}$ ethyl ester (21)



To a stirred solution of alkyne **19** (150 mg, 0.200 mmol, 1.00 equiv.) in toluene (1.60 mL) were sequentially added dimethylethoxysilane (166 mg, 0.160 mmol. 8.00 equiv.) and Karsted catalyst (46.0 μL, 2 wt% in xylene, 0,004 mmol, 2 mol%) at rt. The reaction mixture was stirred at that temperature overnight before it was filtered through a small silica plug. The solvent was removed *in vacuo* and the remaining residue was dissolved in THF (1.75 mL). TBAF (1.0 M in THF, 1.61 mL, 1.61 mmol, 8.00 equiv.) was added at -78 °C and stirred overnight at the same temperature. MeOH (2 mL) and water (0.1 mL) were added and the solution was stirred for another 30 min. Phosphate buffer (pH = 7.0, 3.0 mL) and EtOAc (10 mL) were added. The phases were separated and the organic phase was washed with water (2 x 10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. RvD1 $_{n\text{-}3\ DPA}$ ethyl ester (**21**) (63.0 mg, 0.150 mmol, 78% over two steps) was obtained after purification by column chromatography (hexane/EtOAc 50:50) as a colorless oil. **R_f** (heptane/EtOAc 50/50) = 0.15; **^{1}H NMR** (400 MHz, Methanol-d_4) δ = 6.81 – 6.69 (m, 2H), 6.44 – 6.25 (m, 2H), 6.06 – 5.96 (m, 2H), 5.85 (dd, *J* = 14.9, 6.9 Hz, 1H), 5.75 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.53 - 5.45 (m, 1H), 5.43 – 5.34 (m, 1H), 4.21 – 4.08 (m, 3H), 4.02 – 3.96 (m, 1H), 3.53 -3.48 (m, 1H), 2.38 – 2.25 (m, 4H), 2.12 – 2.01 (m, 2H), 1.70 – 1.51 (m, 4H), 1.43 – 1.31 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (101 MHz, MeOD) δ 175.6, 138.3, 134.8, 134.7, 134.5, 133.3, 130.5, 130.2, 129.1, 126.6, 125.4, 76.8, 75.6, 73.1, 61.4, 36.2, 35.1, 33.6, 30.2, 26.6, 26.0, 21.7, 14.6, 14.5. **HRMS (ESI):** calculated $C_{24}H_{38}NaO_5$: 429.2611, found: 429.2612; **HPLC:** Eclipse XDB-C18, MeOH/H_2O 75:25, 1.0 mL/min): t_r = 10.28 min. **UV:** (MeOH) λ_{max} 288, 301, 315 nm. **$[\alpha]_D^{25}$:** +11.0 (c = 0.10, MeOH).

RvD1 $_{n\text{-}3\ DPA}$ (4)



21 **4**

To a solution of ethyl ester **21** (10 mg, 0.025 mmol, 1.0 equiv.) in THF/MeOH/H_2O (2/2/1, 3.5 mL), solid LiOH (21 mg, 0.86 mmol, 35 equiv.) was added at 0 °C. The mixture was stirred at 0 °C for 4 h. The solution was acidified with aq. sat. NaH_2PO_4 (4 mL) before EtOAc (4 mL) was added. The layers were separated and the water phase was extracted with EtOAc (2 x 4 mL). The combined organic layer was dried (Na_2SO_4) before being concentrated *in vacuo.* RvD1 $_{n\text{-}3\ DPA}$ (**4**) (8.8 mg, 0.24 mmol, 93%) was obtained after purification by column chromatography (5% MeOH in CH_2Cl_2) as a colorless oil. $\mathbf{R_f}$ (5% MeOH in CH_2Cl_2) = 0.12. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 6.75 (dd, *J* = 14.8, 10.4 Hz, 2H), 6.34 (ddd, *J* = 38.6, 14.6, 10.8 Hz, 2H), 6.08 – 5.94 (m, 2H), 5.85 (dd, *J* = 14.9, 6.9 Hz, 1H), 5.74 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.54 – 5.43 (m, 1H), 5.44 – 5.32 (m, 1H), 4.21 – 4.12 (m, 1H), 4.02 – 3.93 (m, 1H), 3.54 – 3.46 (m, 1H), 2.40 – 2.22 (m, 4H), 2.14 – 2.02 (m, 2H), 1.69 – 1.51 (m, 4H), 1.45 – 1.32 (m, 4H), 0.97 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (101 MHz, MeOD) δ 178.1, 138.2, 134.8, 134.7, 134.5, 133.3, 130.5, 130.2, 129.1, 126.6, 125.5, 76.8, 75.7, 73.1, 36.2, 35.3, 33.7, 30.3, 26.6, 26.2, 21.7, 14.5. **HRMS (ESI):** calculated $C_{22}H_{34}NaO_5$: 401.2298, found: 401.2299; **UV:** (MeOH) λ_{max} 288, 301, 315 nm; $\mathbf{[\alpha]_D^{25}}$**:** +13.1 (c = 0.84, MeOH).

^{1}H NMR and ^{13}C NMR Spectra of compounds

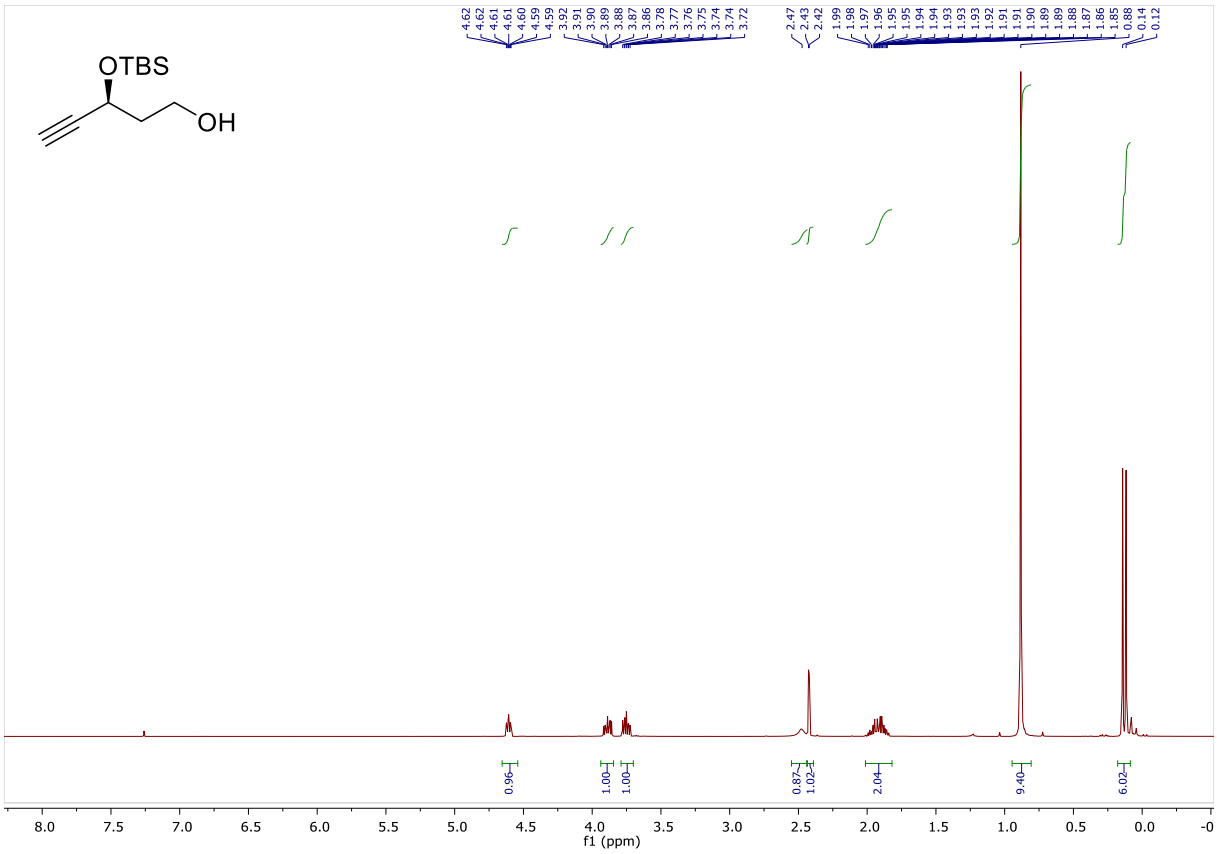


Figure S-1 ^{1}H-NMR spectrum of compound **22**.

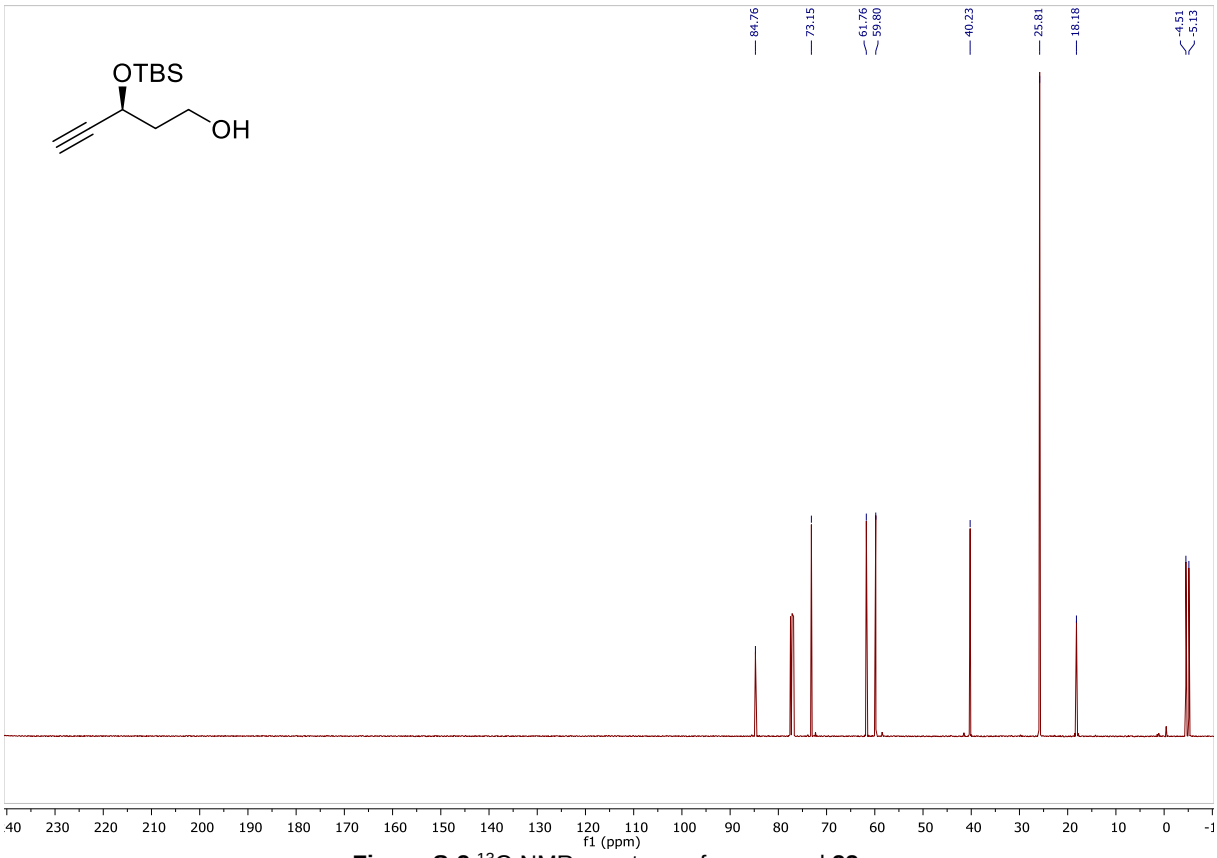


Figure S-2 ^{13}C-NMR spectrum of compound **22.**

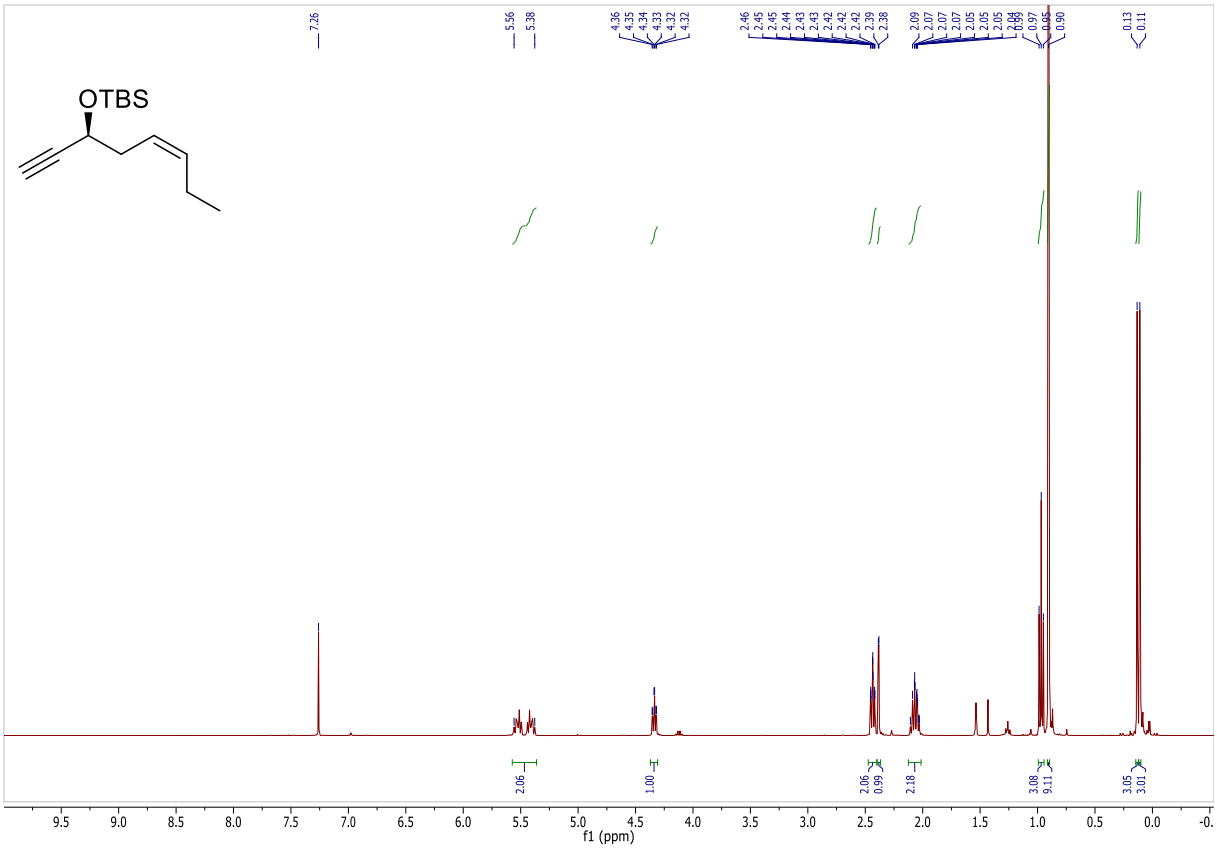


Figure S-3 ^{1}H-NMR spectrum of compound **7**.

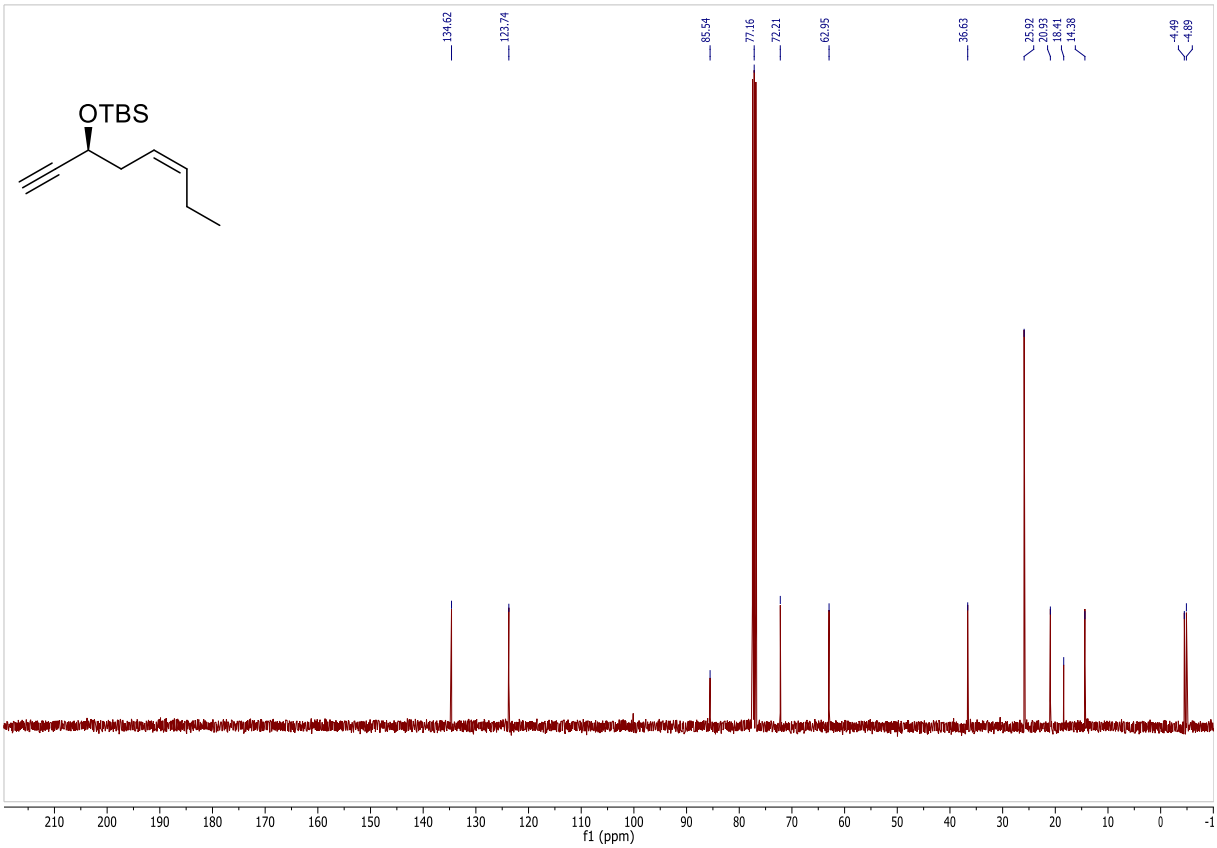


Figure S-4 ^{13}C-NMR spectrum of compound **7**.

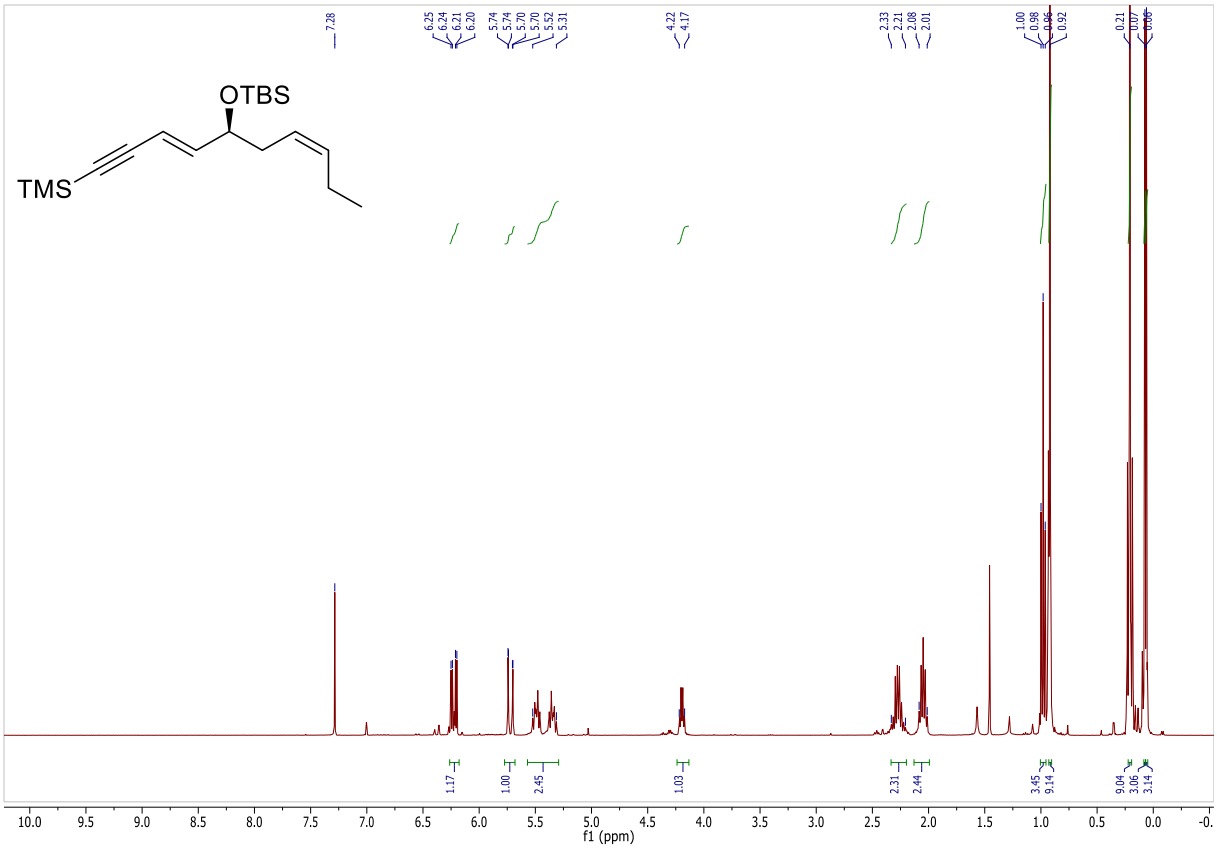


Figure S-5 ^{1}H-NMR spectrum of compound **23**.

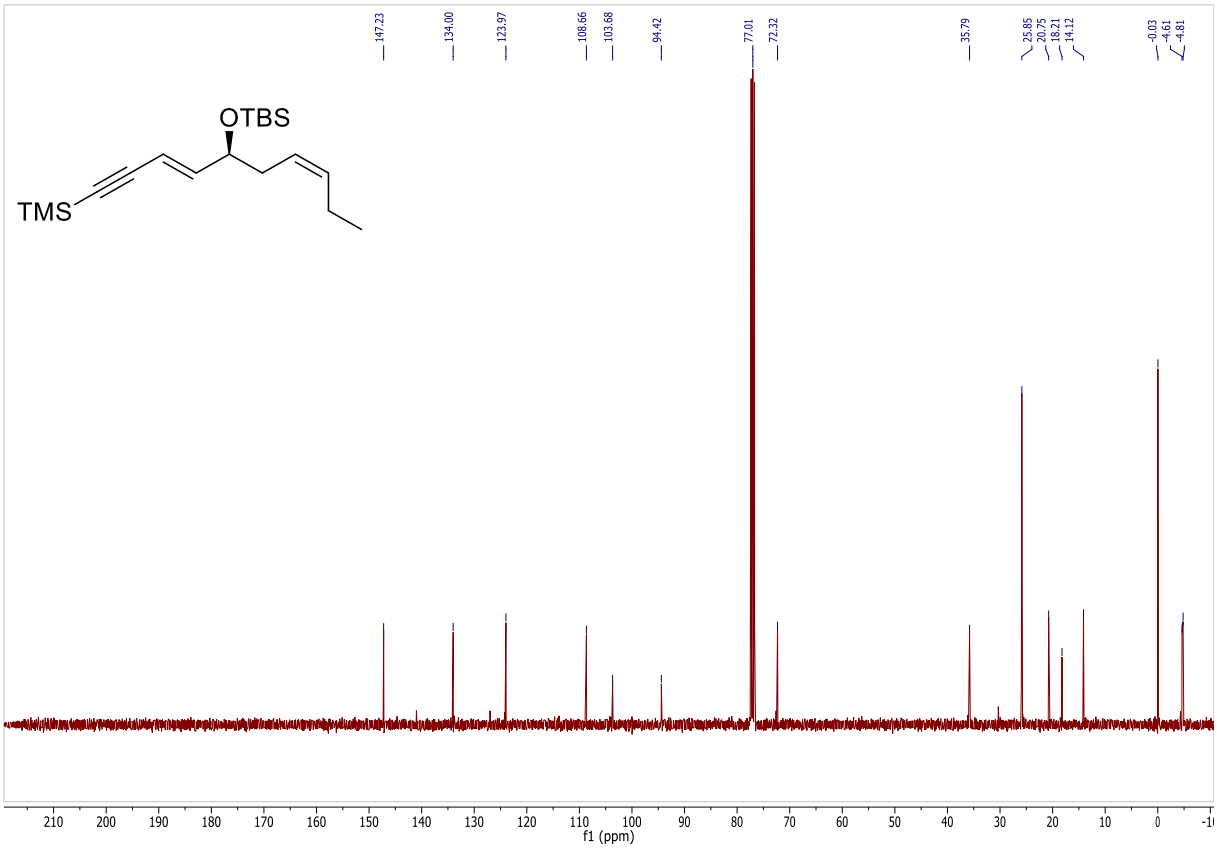


Figure S-6 ^{13}C-NMR spectrum of compound **23**.

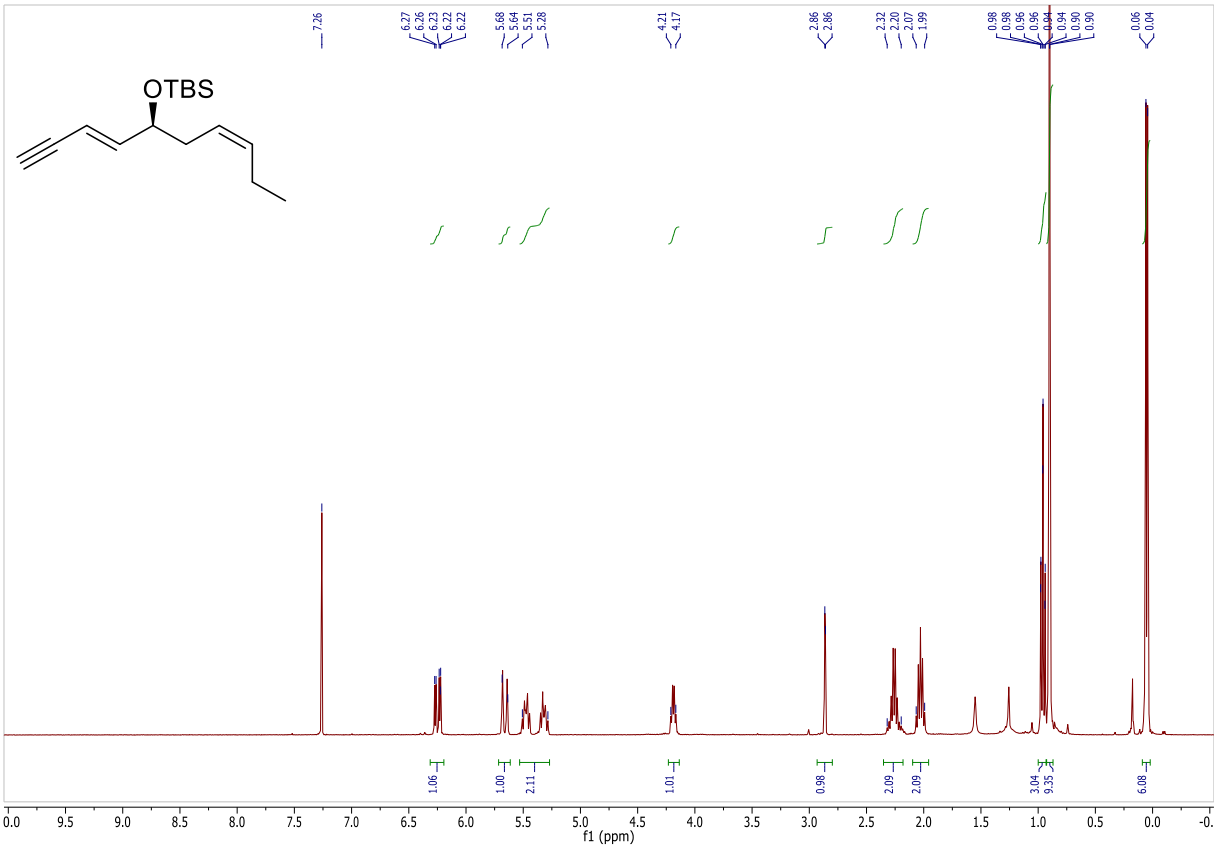


Figure S-7 ^{1}H-NMR spectrum of compound **5**.

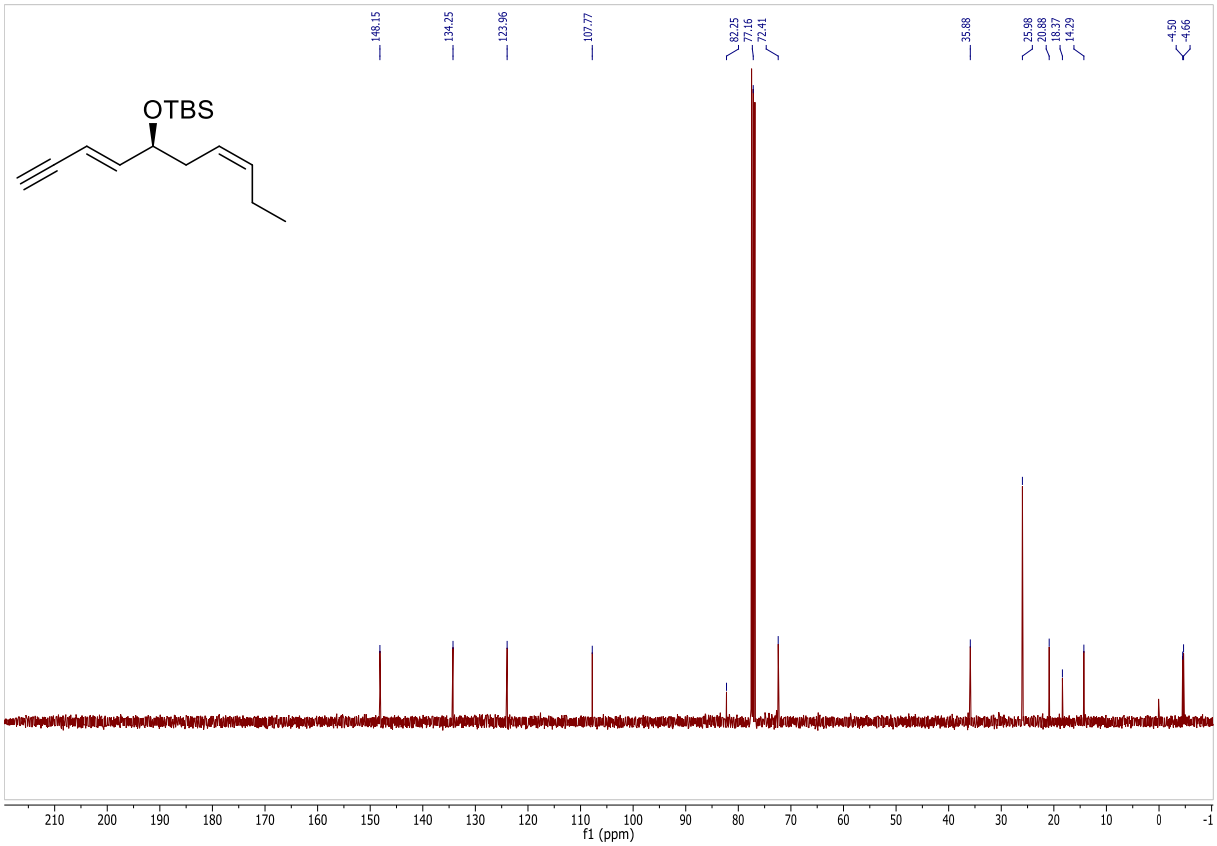


Figure S-8 ^{13}C-NMR spectrum of compound **5**.

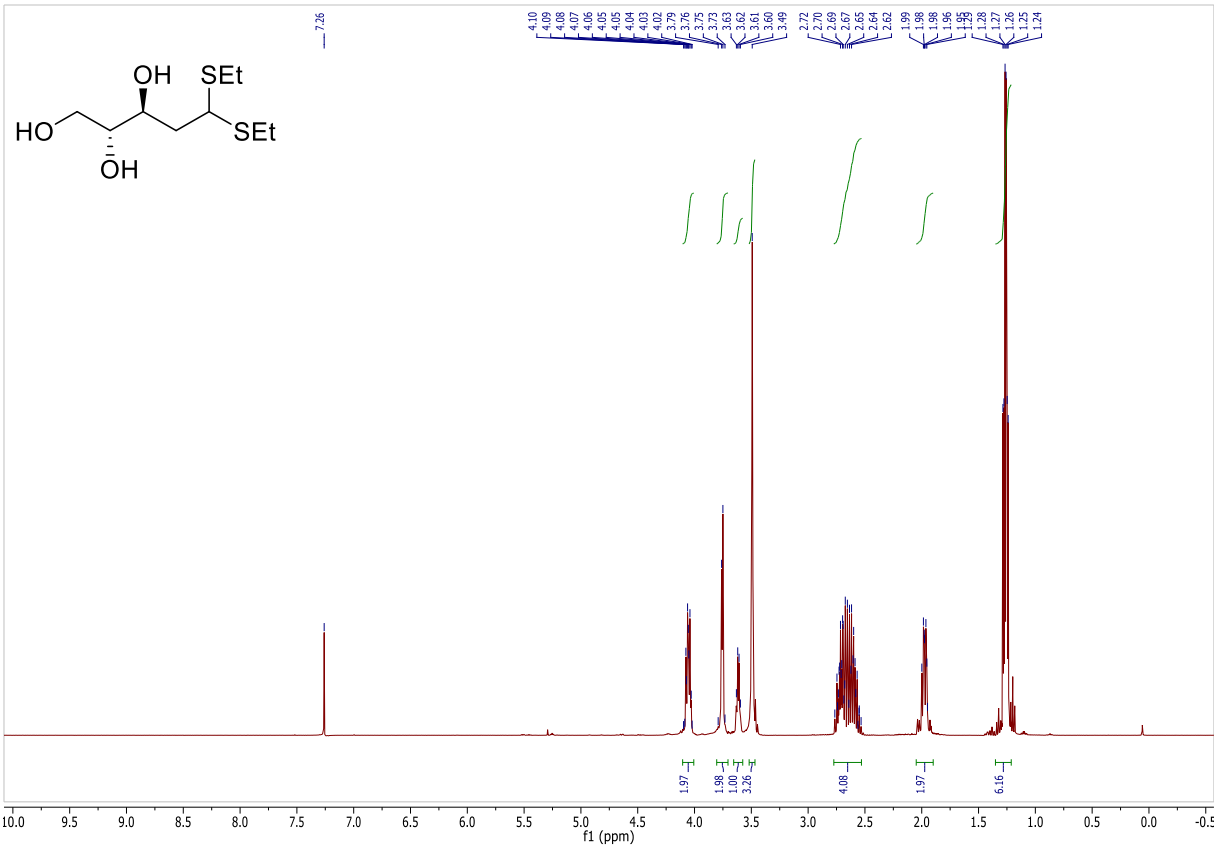


Figure S-9 ^{1}H-NMR spectrum of compound **24**.

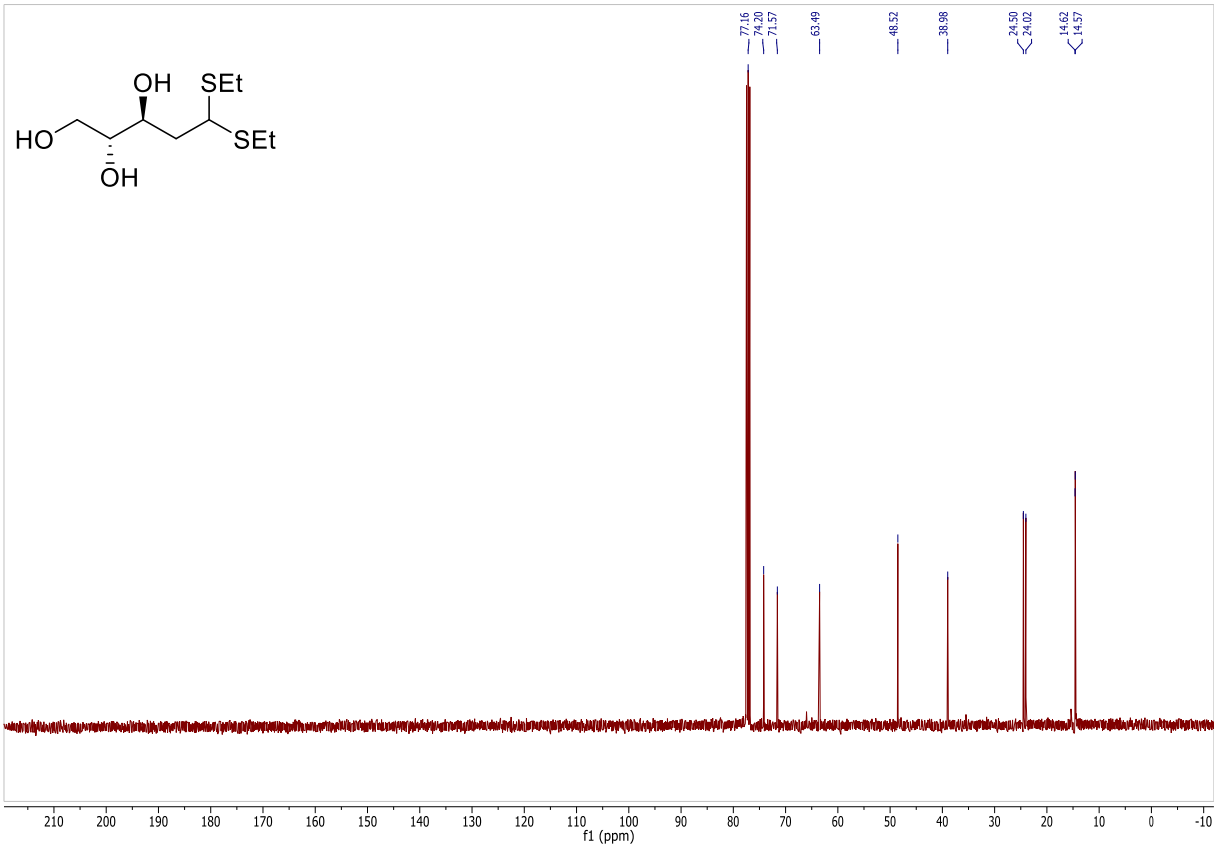


Figure S-10 ^{13}C-NMR spectrum of compound **24**.

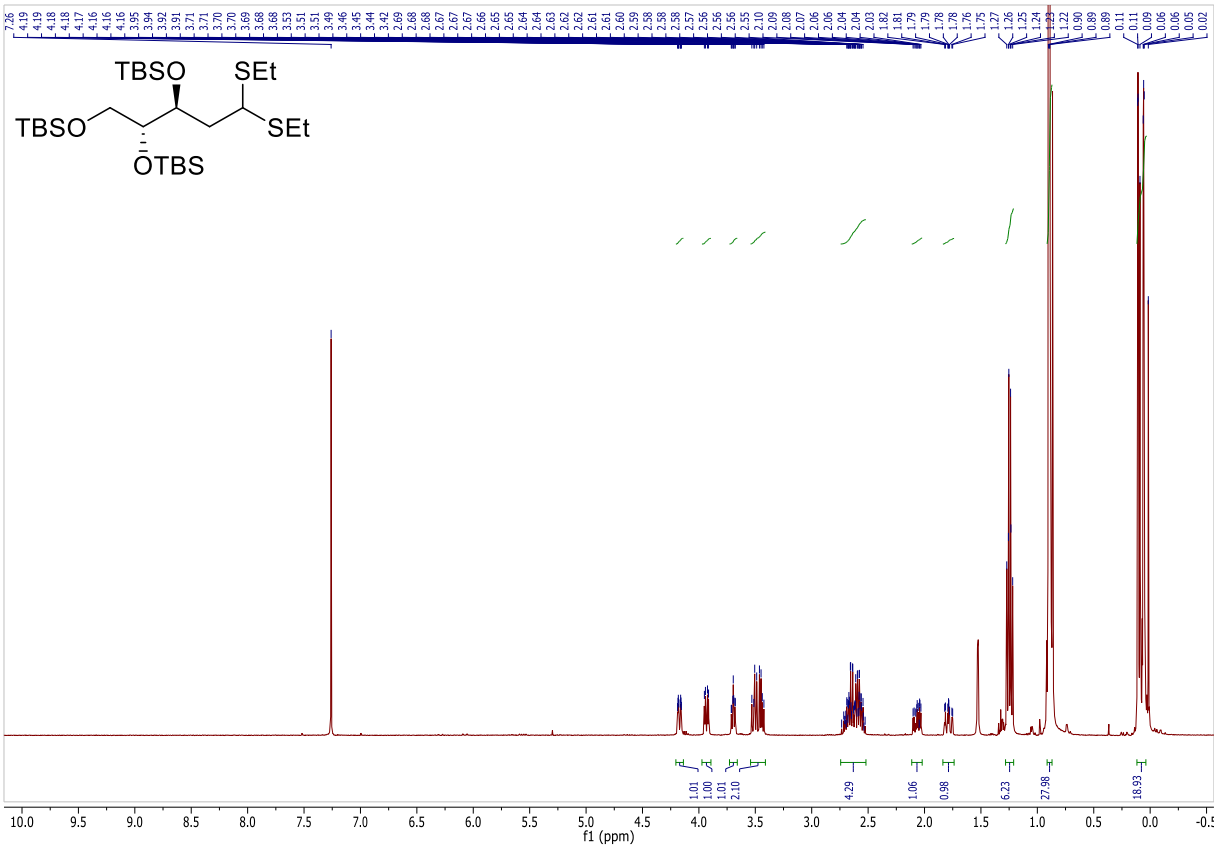


Figure S-11 ^{1}H-NMR spectrum of compound **14**.

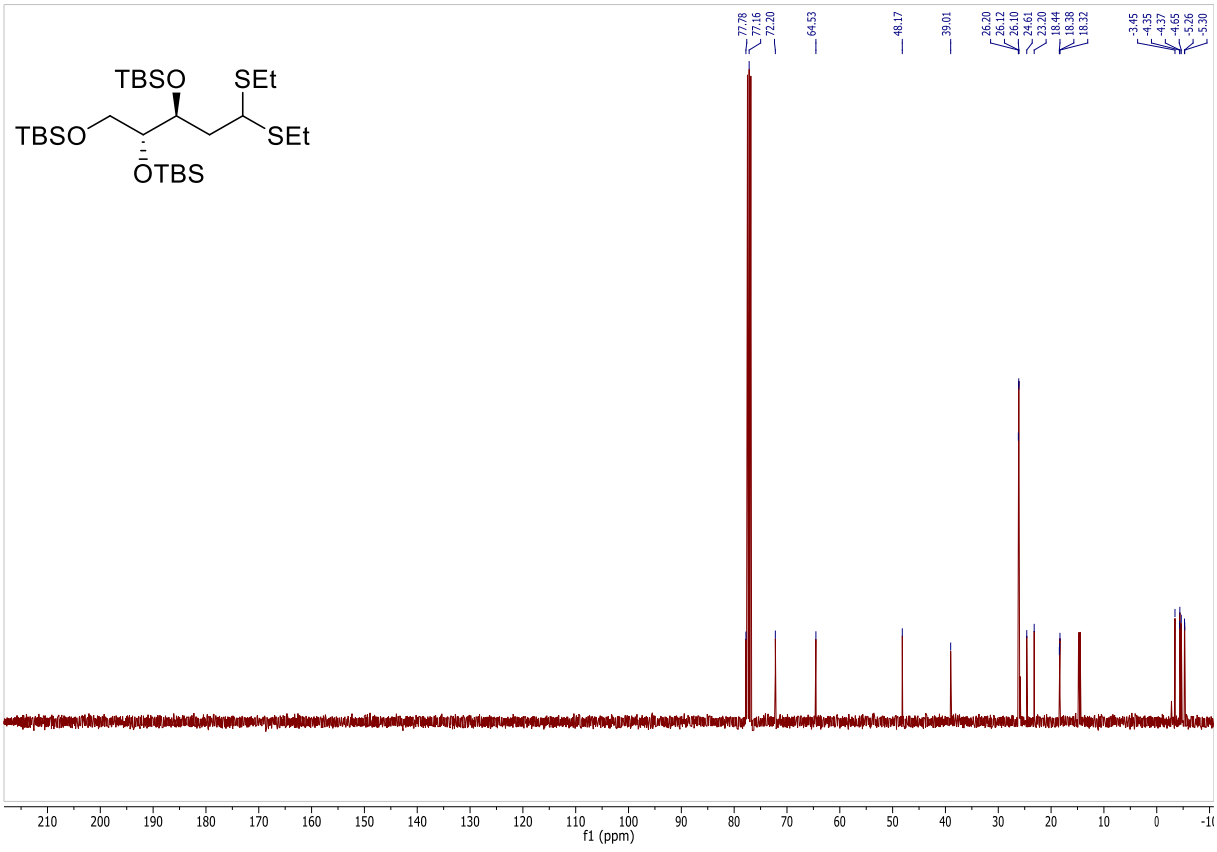


Figure S-12 ^{13}C-NMR spectrum of compound **14**.

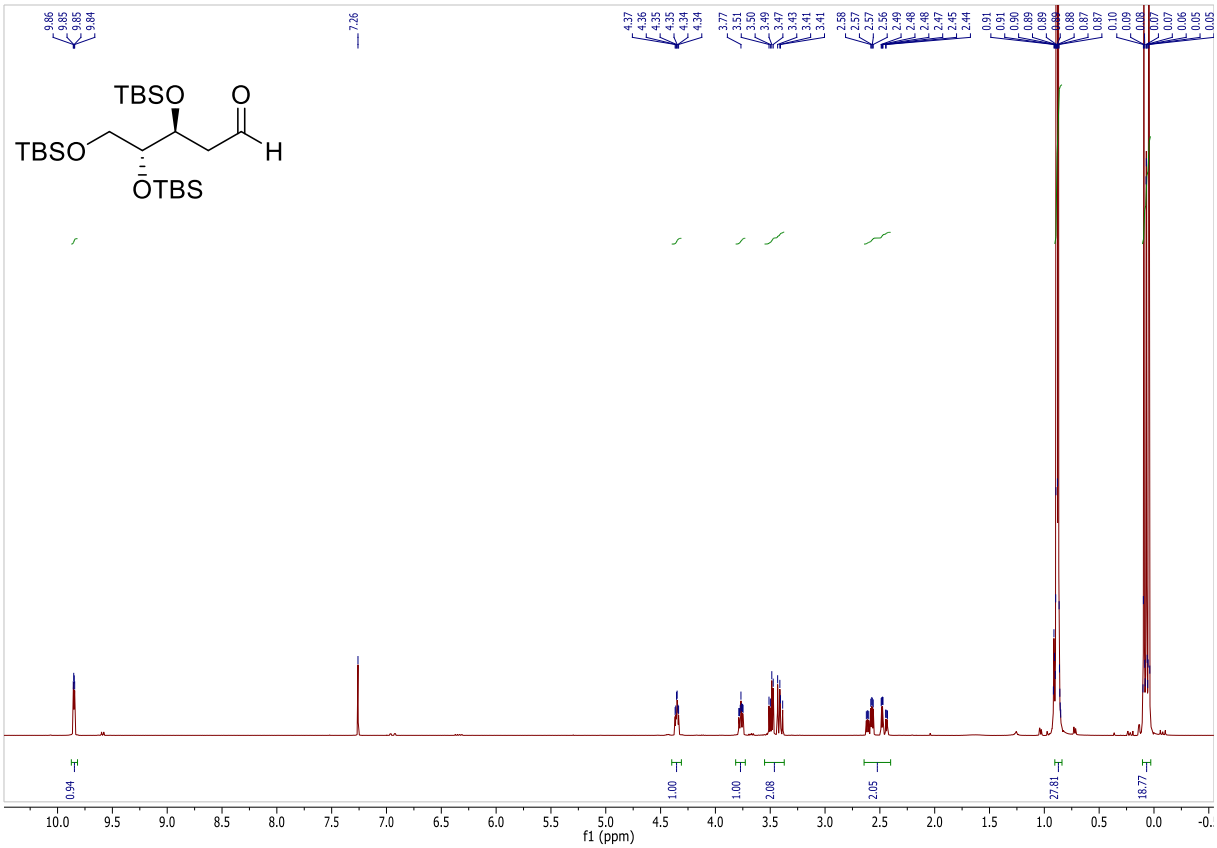


Figure S-13 ^{1}H-NMR spectrum of compound **15**.

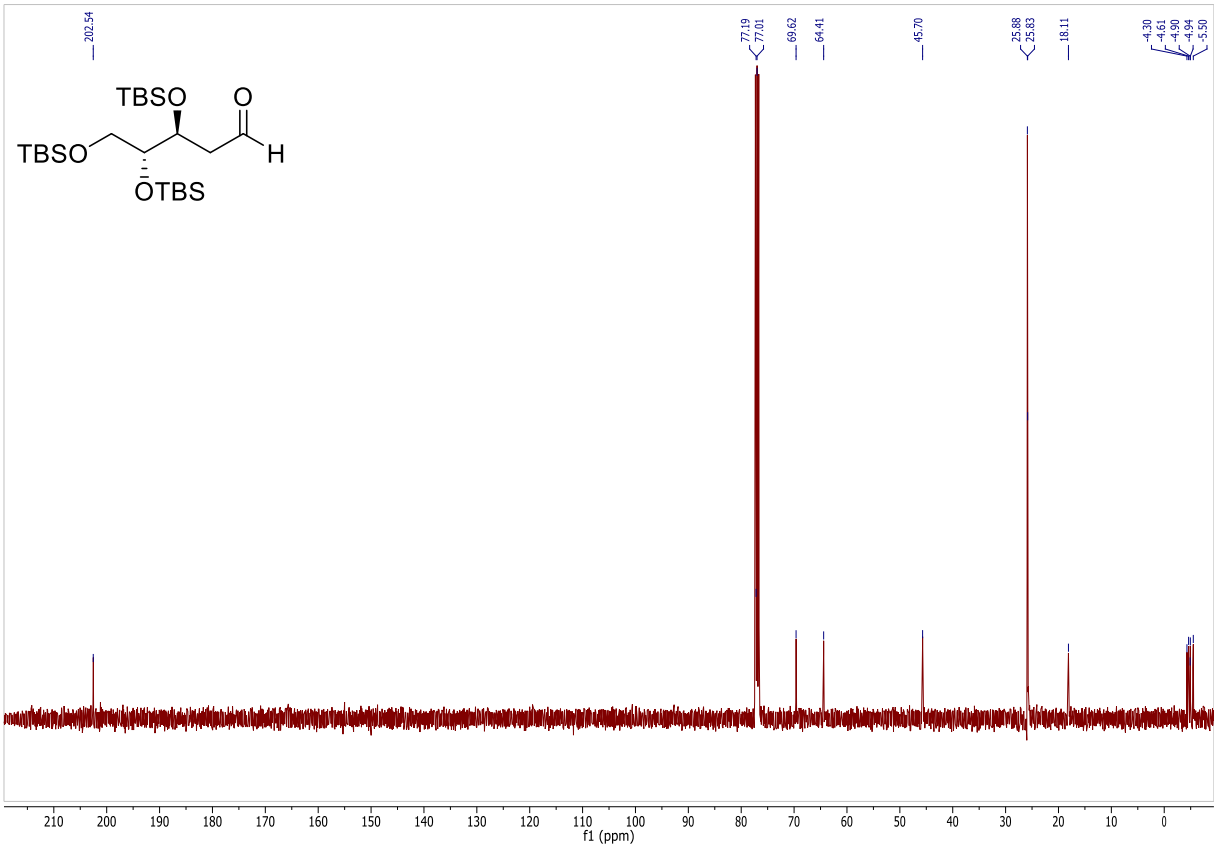


Figure S-14 ^{13}C-NMR spectrum of compound **15**.

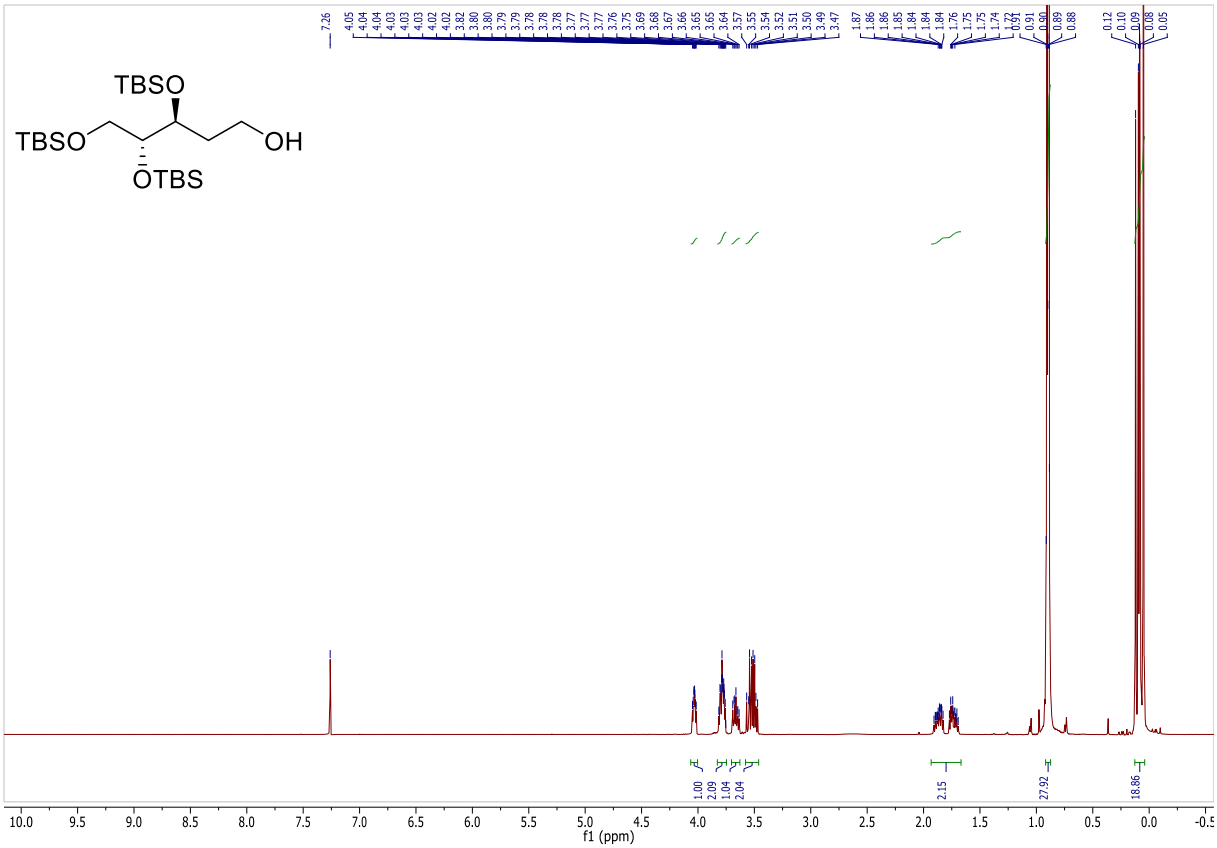


Figure S-15 ^{1}H-NMR spectrum of compound **25**.

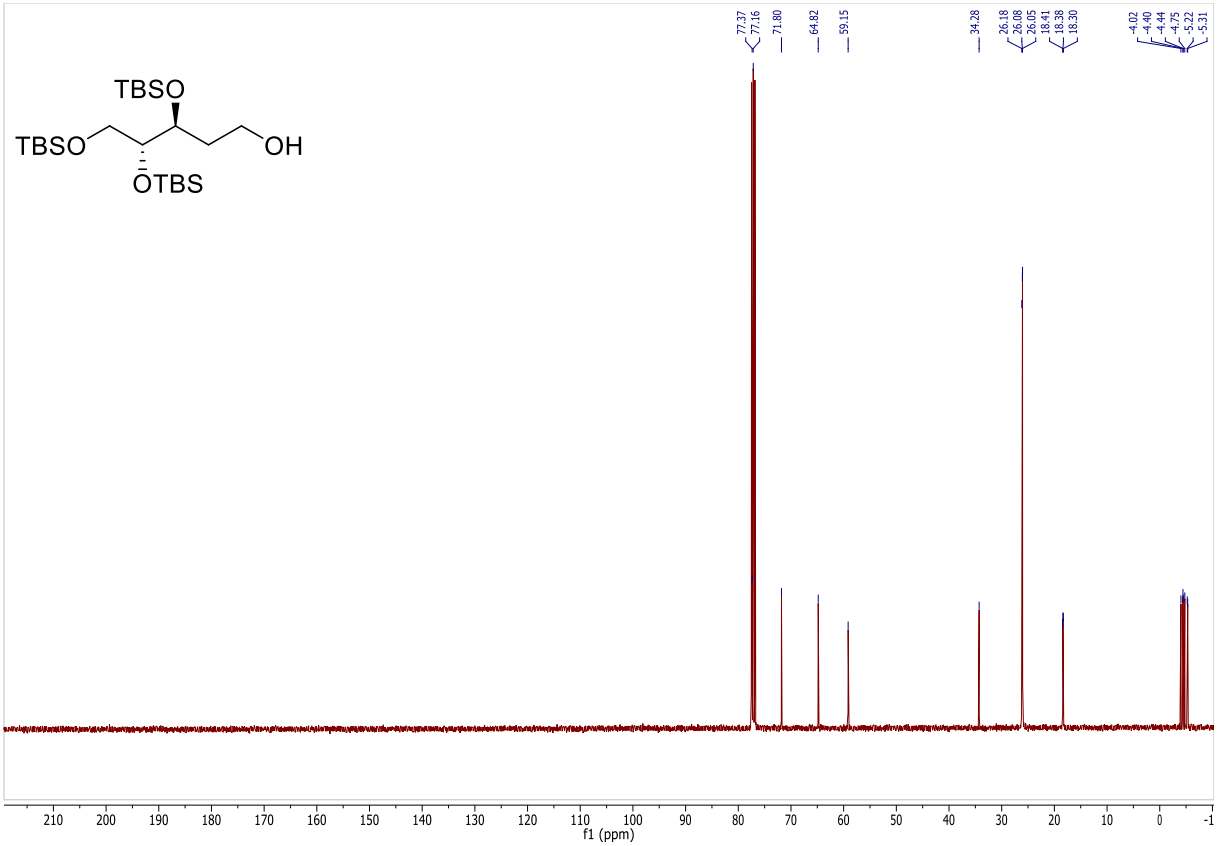


Figure S-16 ^{13}C-NMR spectrum of compound **25**.

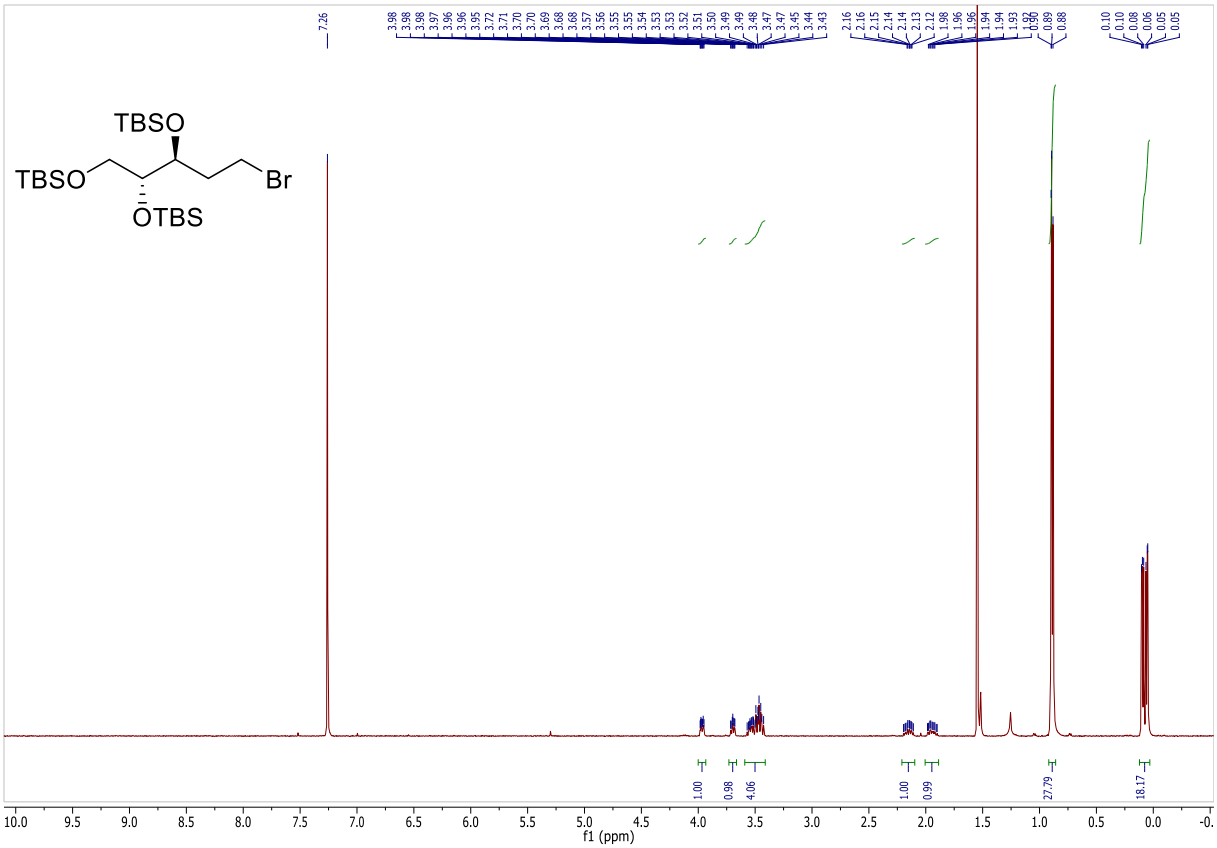


Figure S-17 ^{1}H-NMR spectrum of compound **8**.

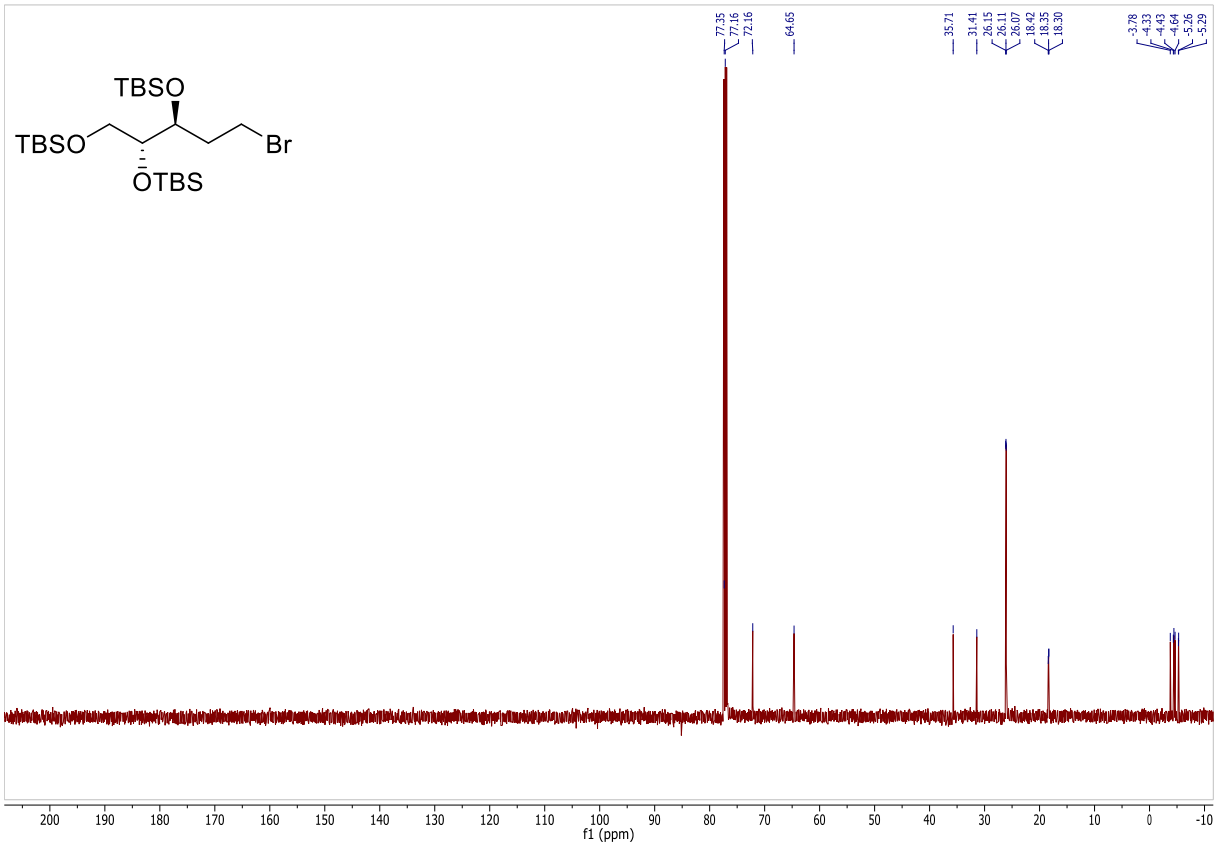


Figure S-18 ^{13}C-NMR spectrum of compound **8**.

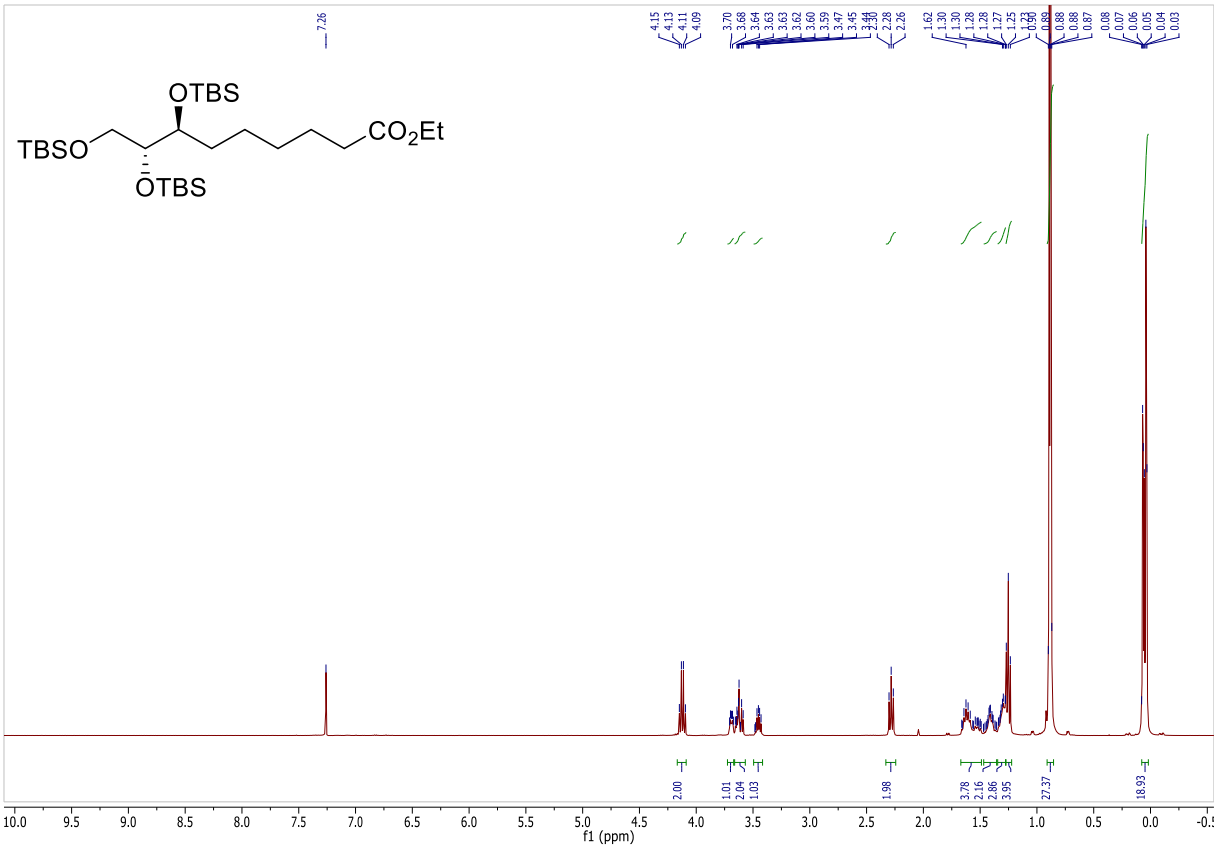


Figure S-19 ^{1}H-NMR spectrum of compound **16**.

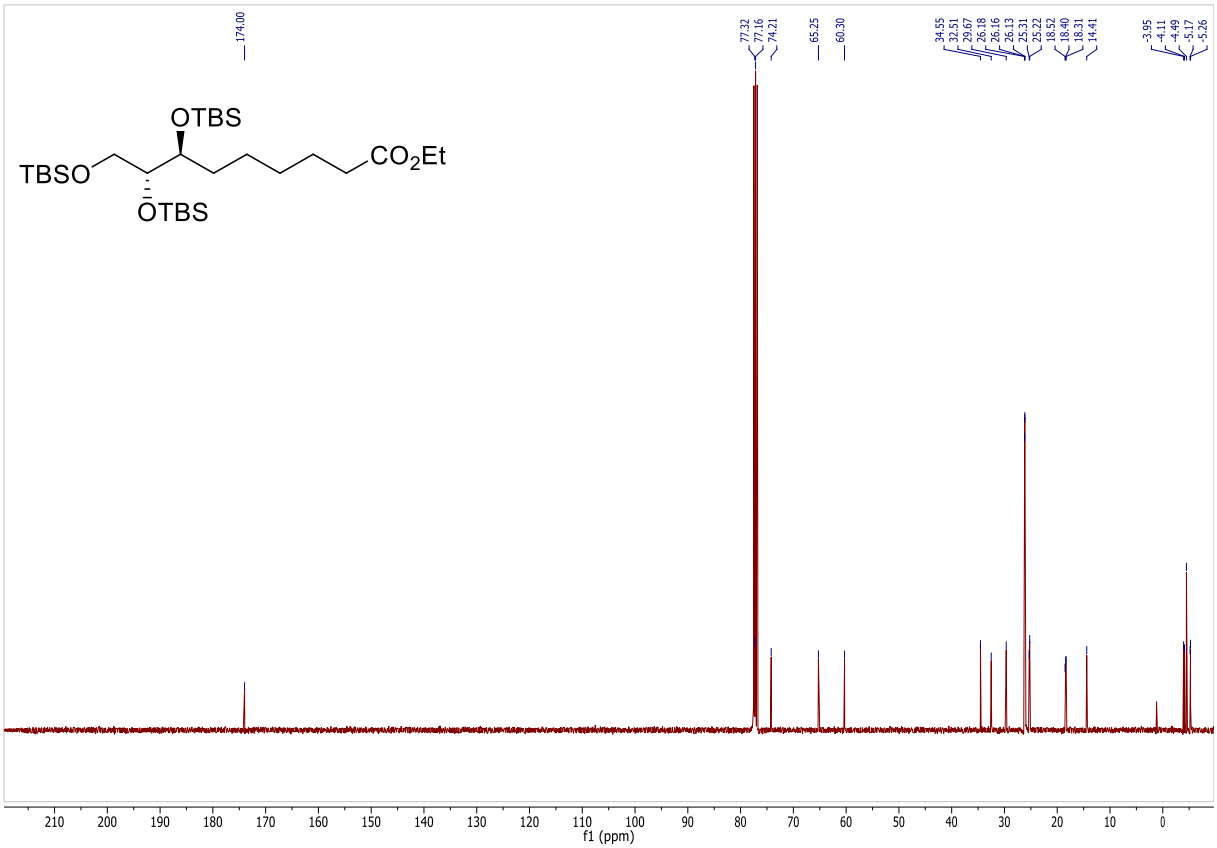


Figure S-20 ^{13}C-NMR spectrum of compound **16**.

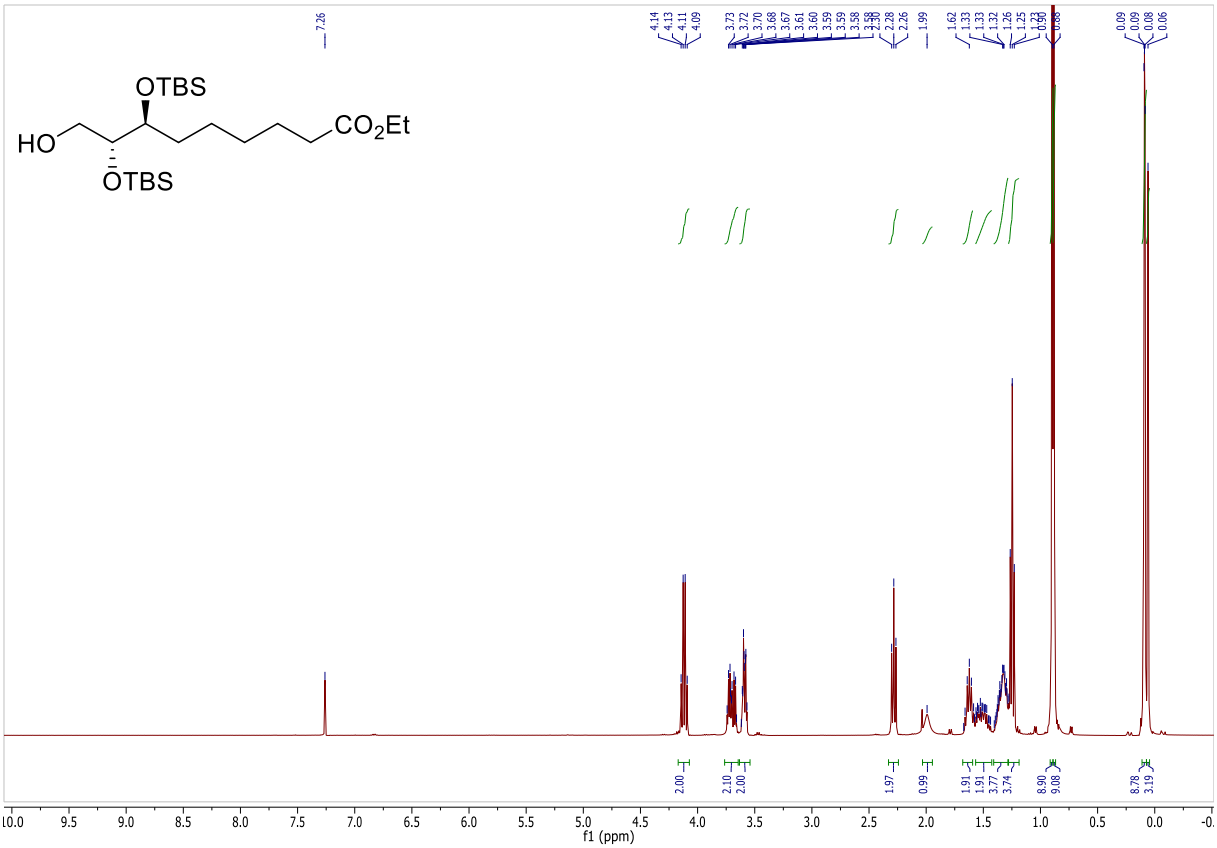


Figure S-21 ^{1}H-NMR spectrum of compound **17**.

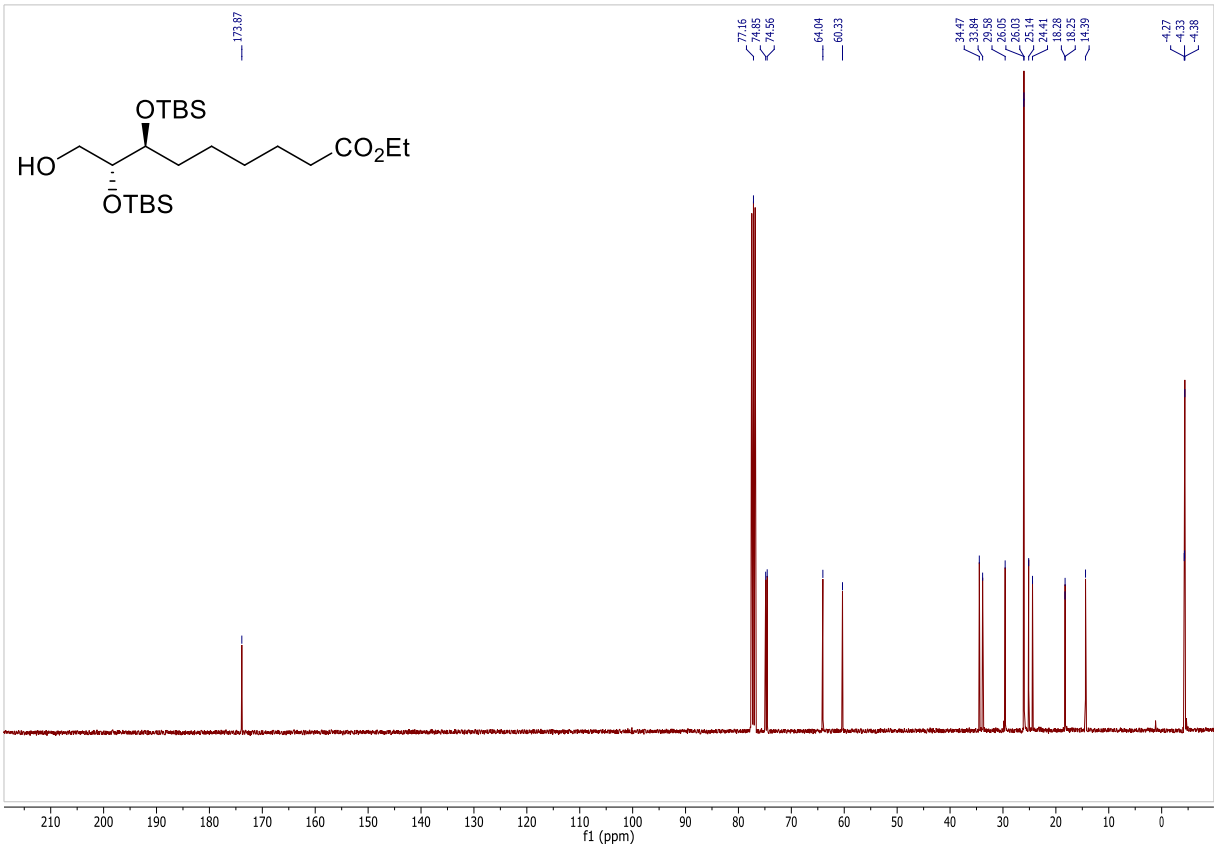


Figure S-22 ^{13}C-NMR spectrum of compound **17**.

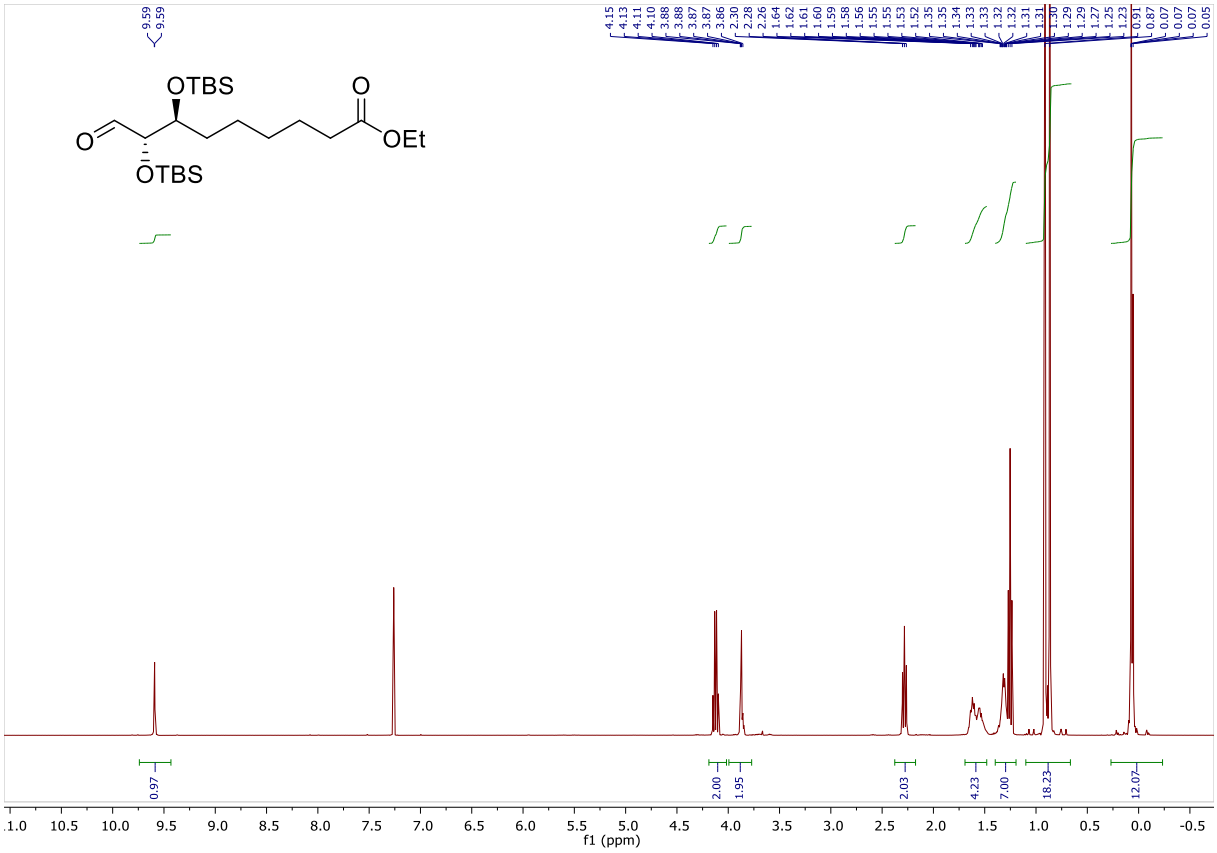


Figure S-23 ^{1}H-NMR spectrum of compound **26**.

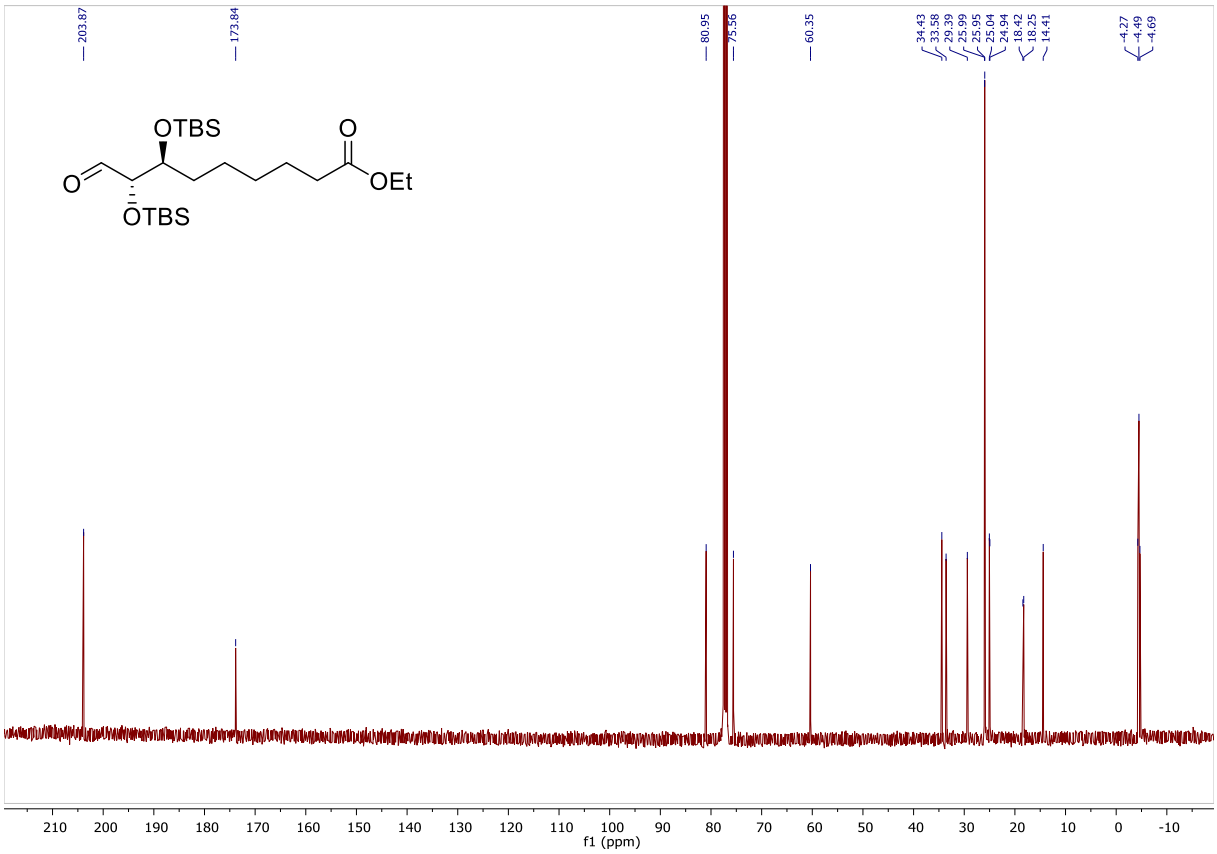


Figure S-24 ^{13}C-NMR spectrum of compound **26**.

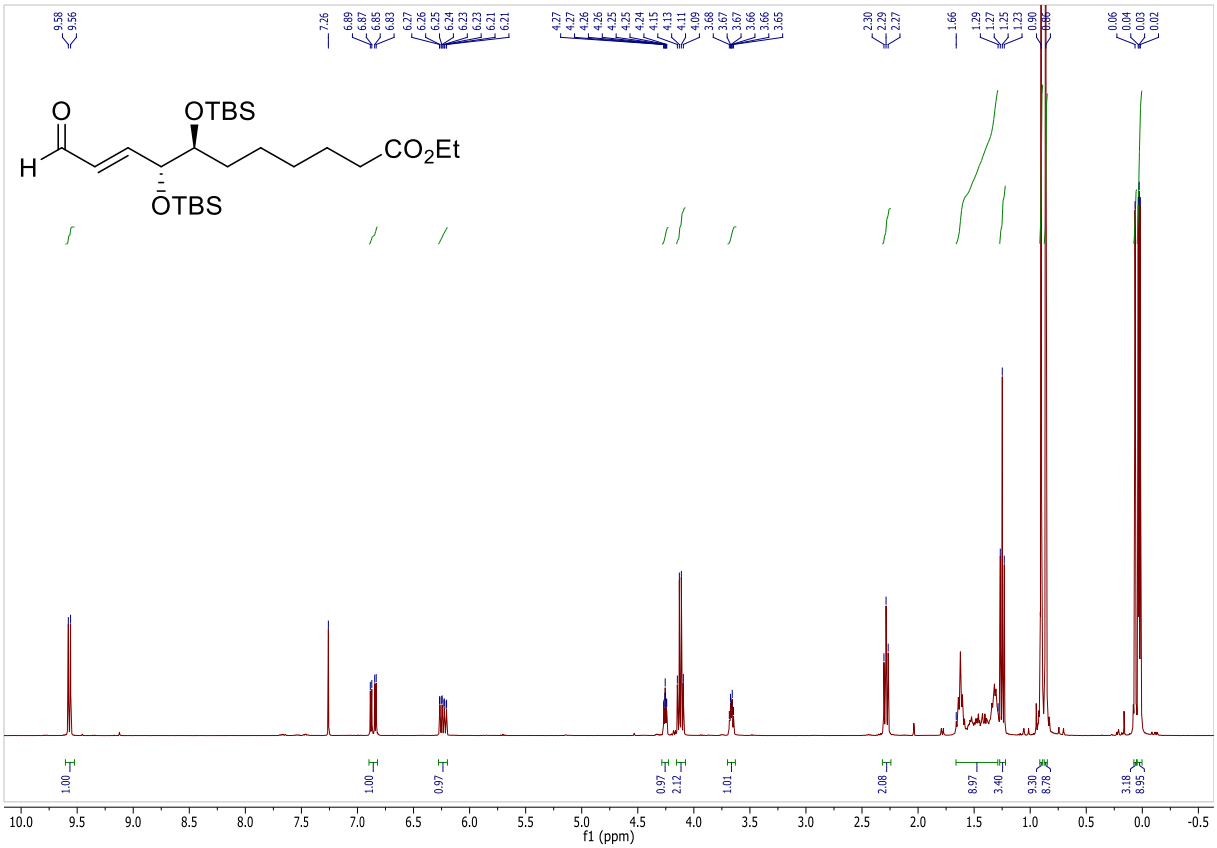


Figure S-25 ^{1}H-NMR spectrum of compound **18**.

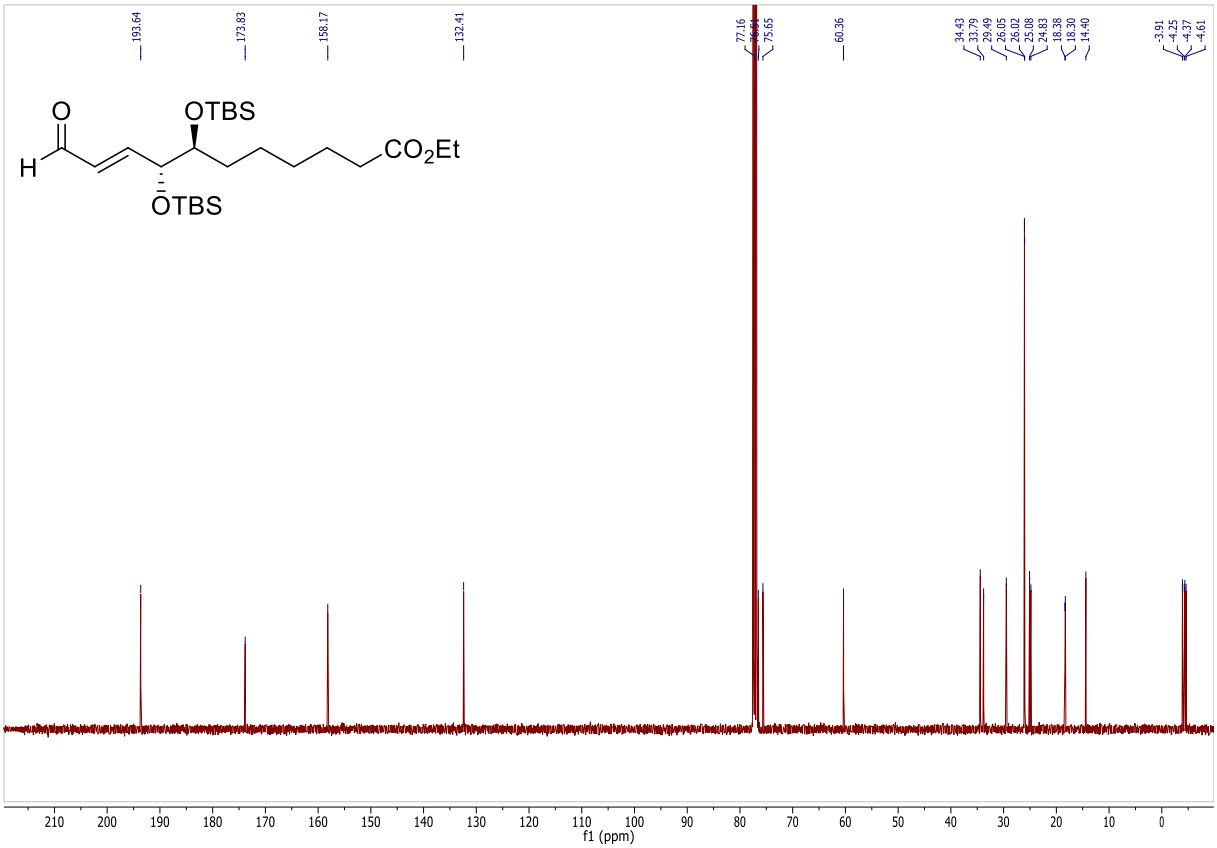


Figure S-26 ^{13}C-NMR spectrum of compound **18**.

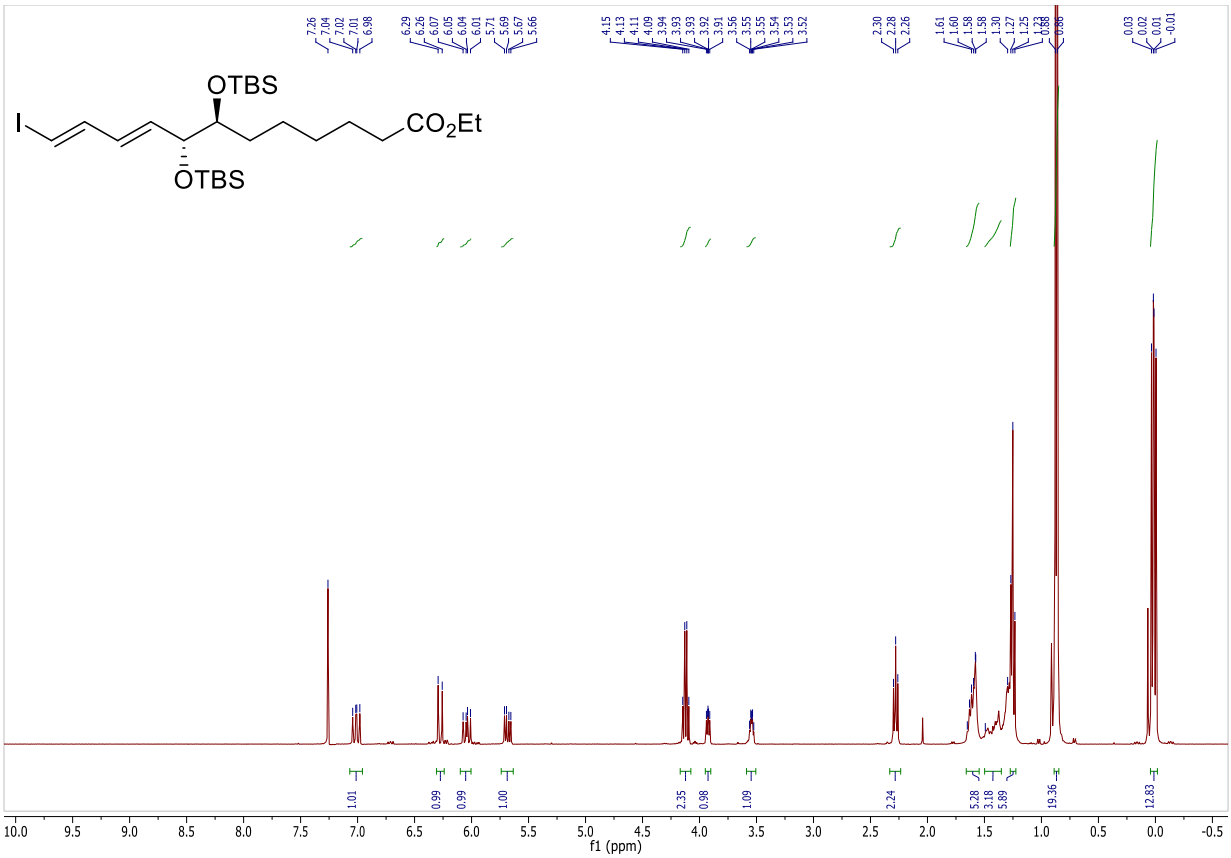


Figure S-27 ^{1}H-NMR spectrum of compound **6**.

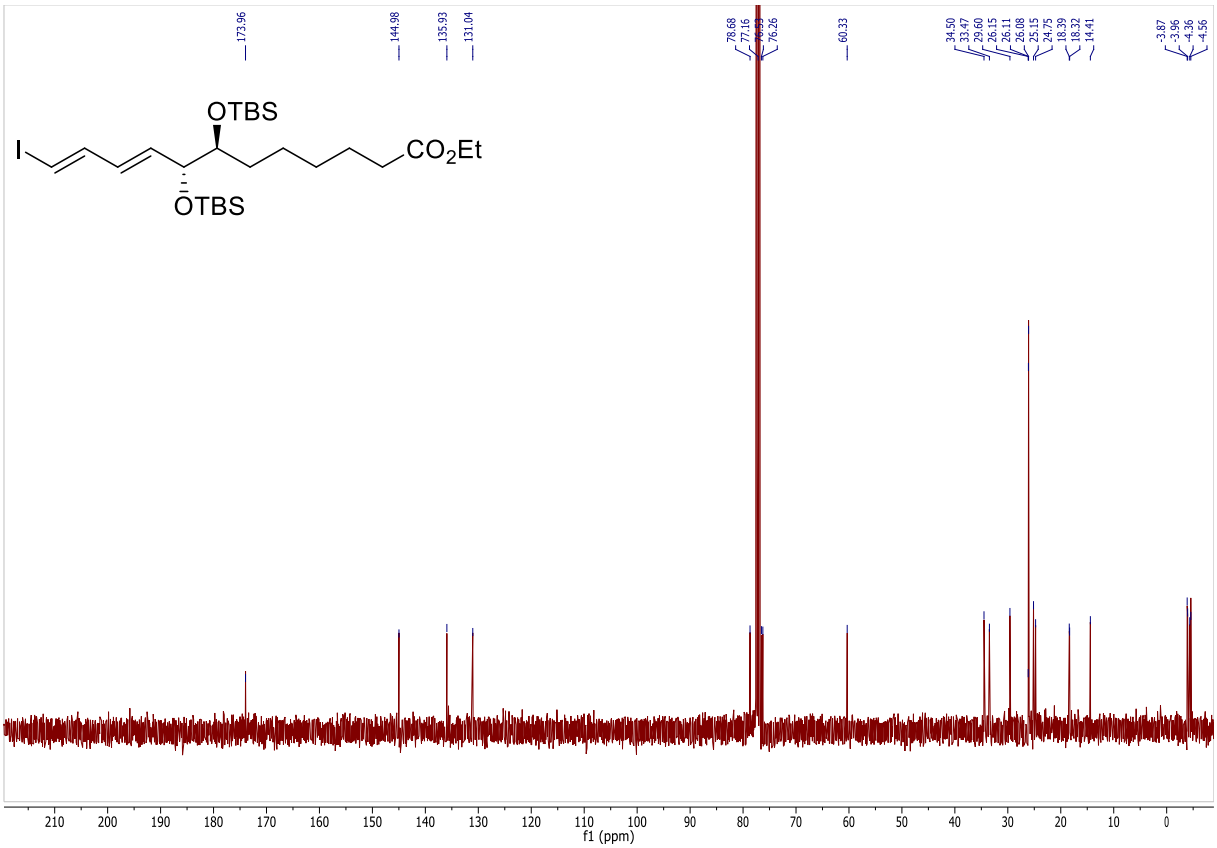


Figure S-28 ^{13}C-NMR spectrum of compound **6**.

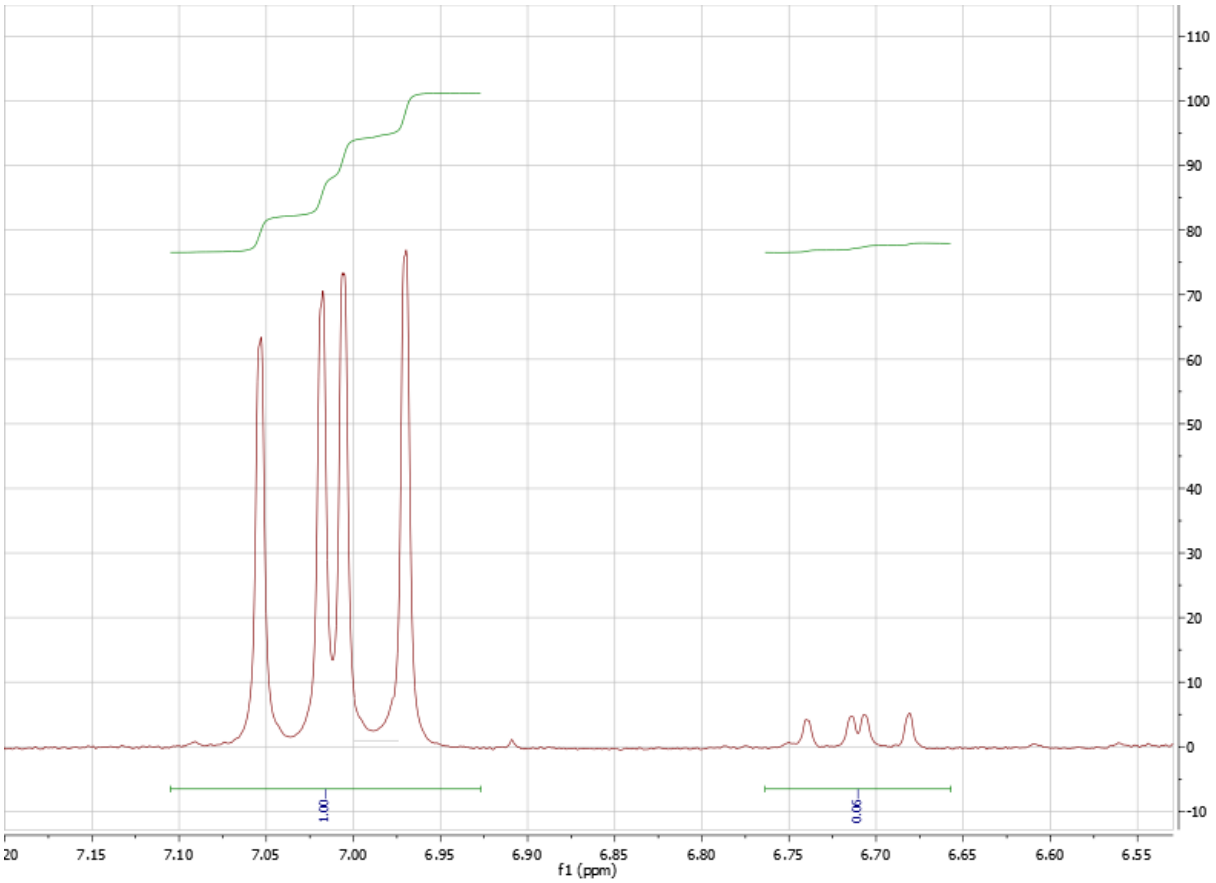


Figure S-29 Expansion of ^{1}H-NMR spectrum of compound **6**.

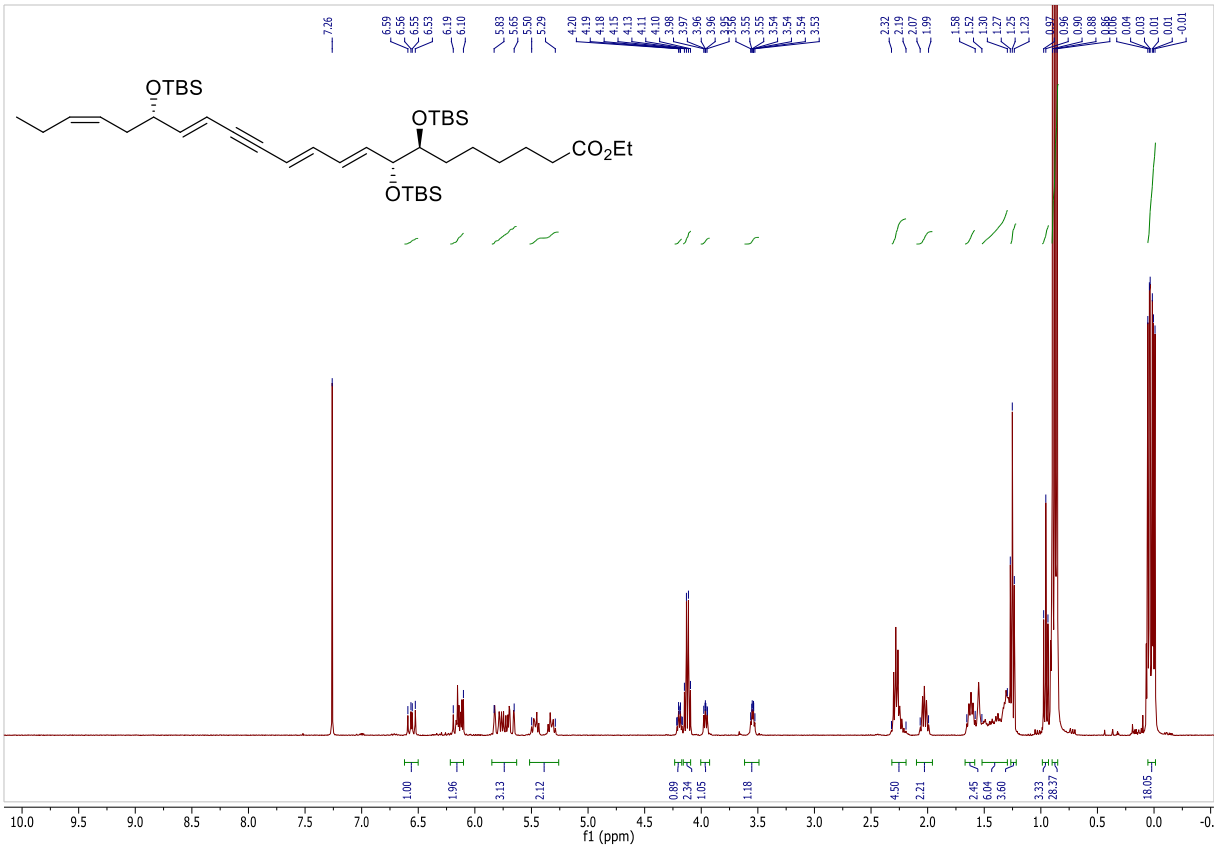


Figure S-30 ^{1}H-NMR spectrum of compound **19**.

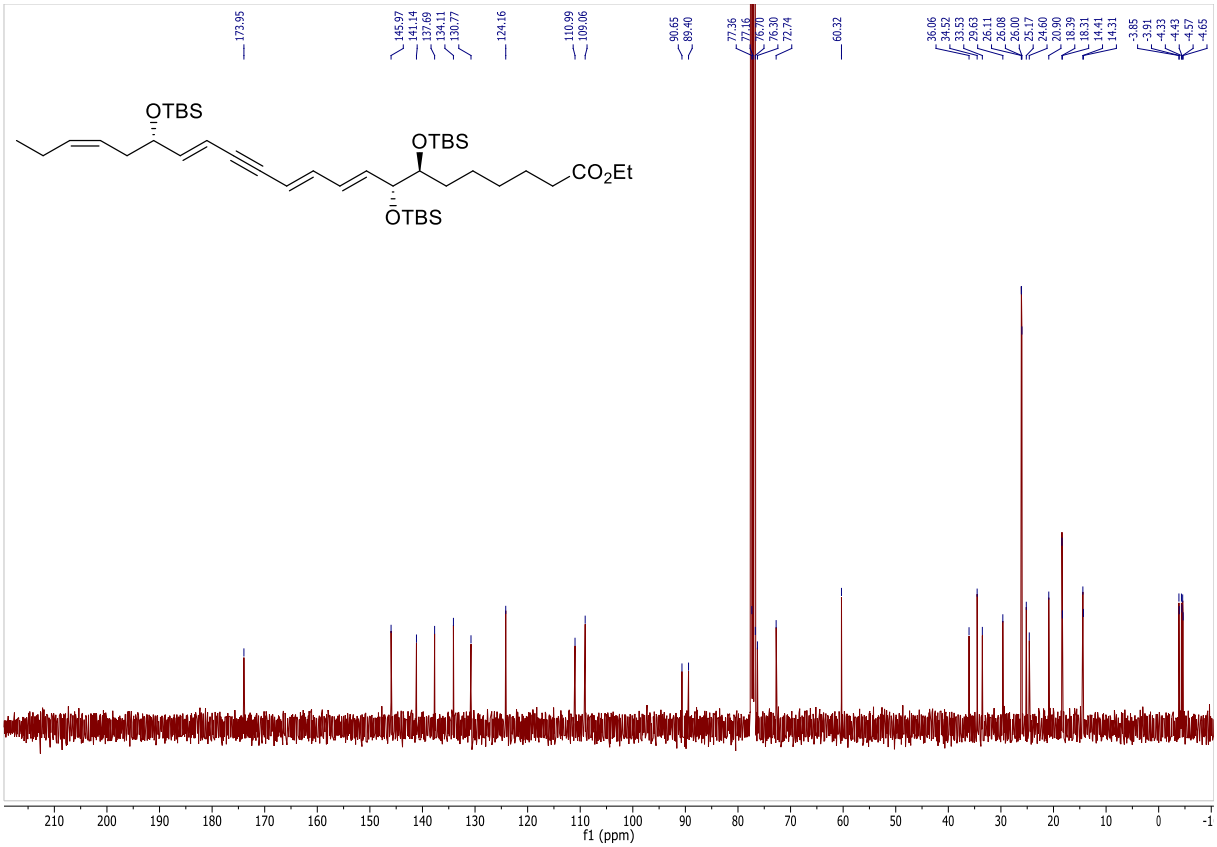


Figure S-31 ^{13}C-NMR spectrum of compound **19**.

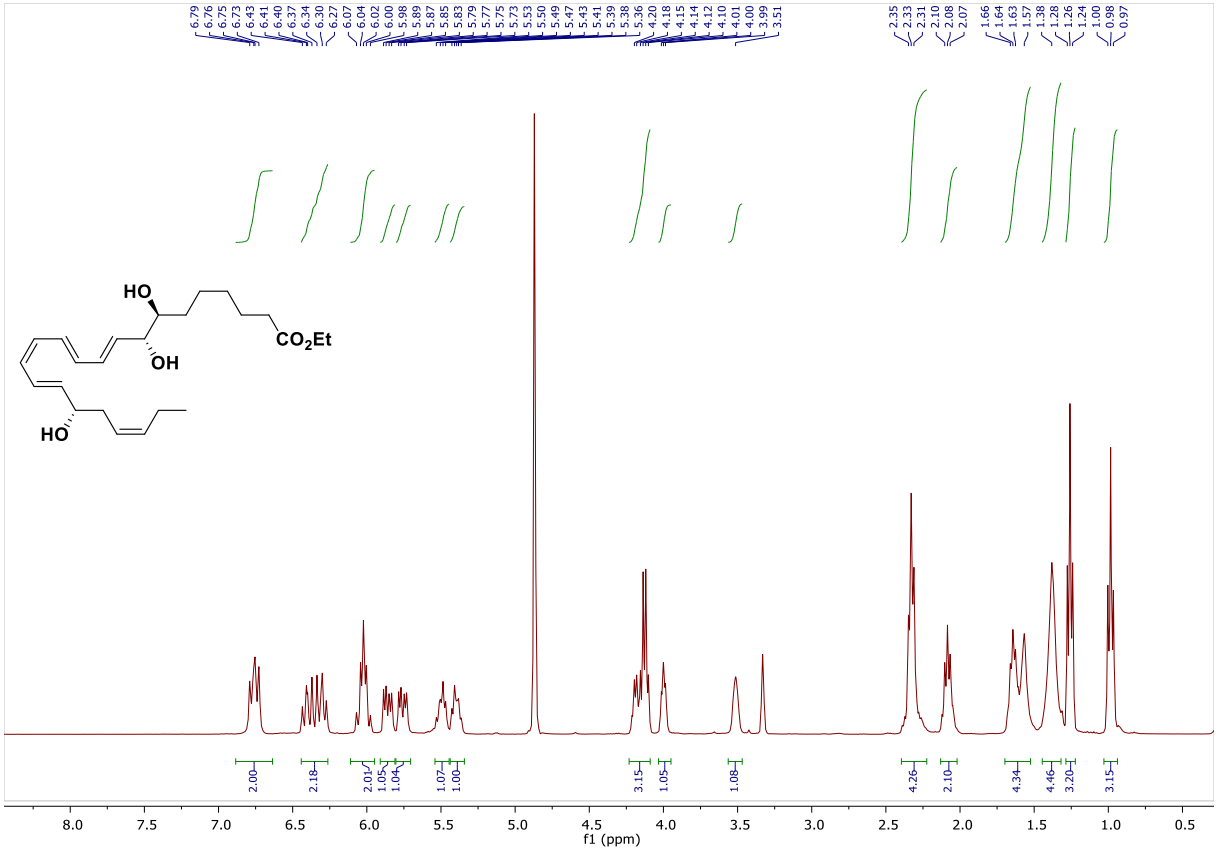


Figure S-32 ^{1}H-NMR spectrum of compound RvD1 $_{n\text{-}3\ DPA}$ ethyl ester (**21**).

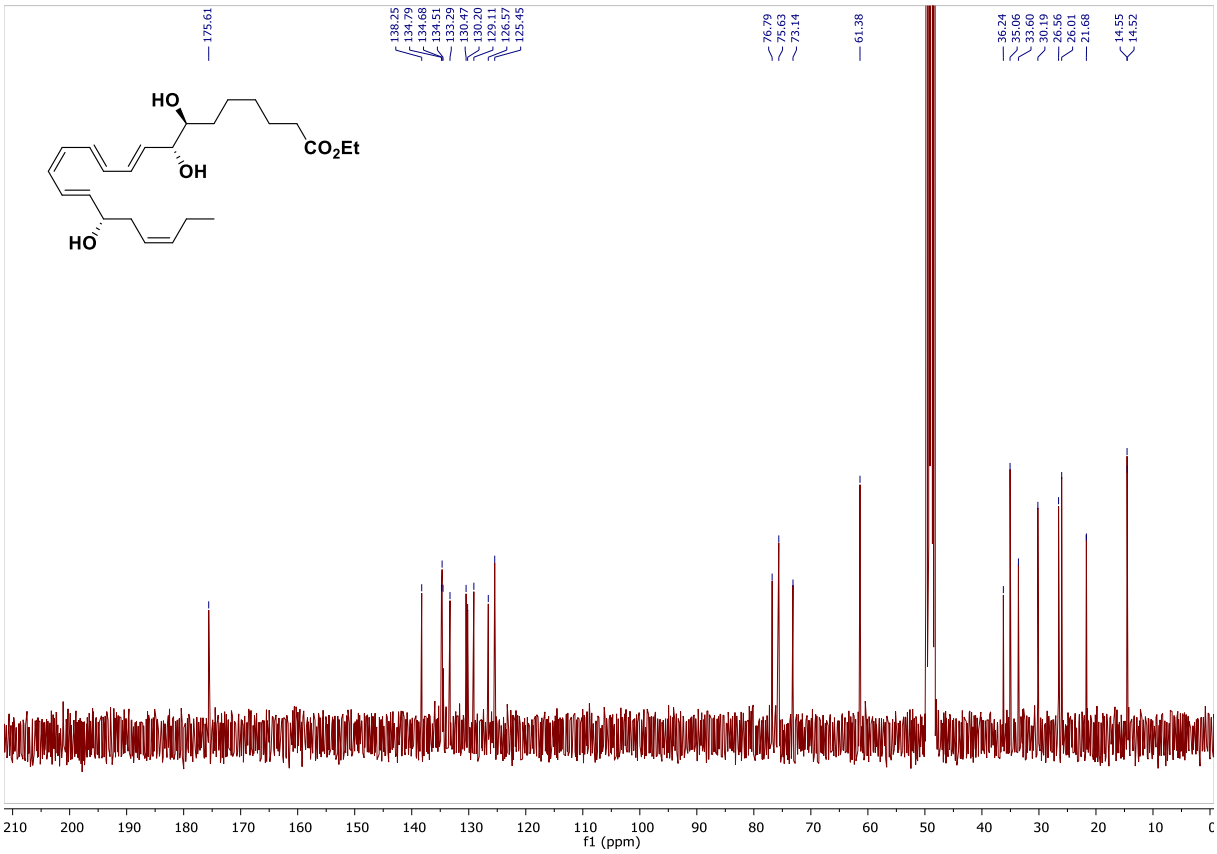


Figure S-33 ^{13}C-NMR spectrum of compound RvD1 $_{n\text{-}3\ DPA}$ ethyl ester (**21**).

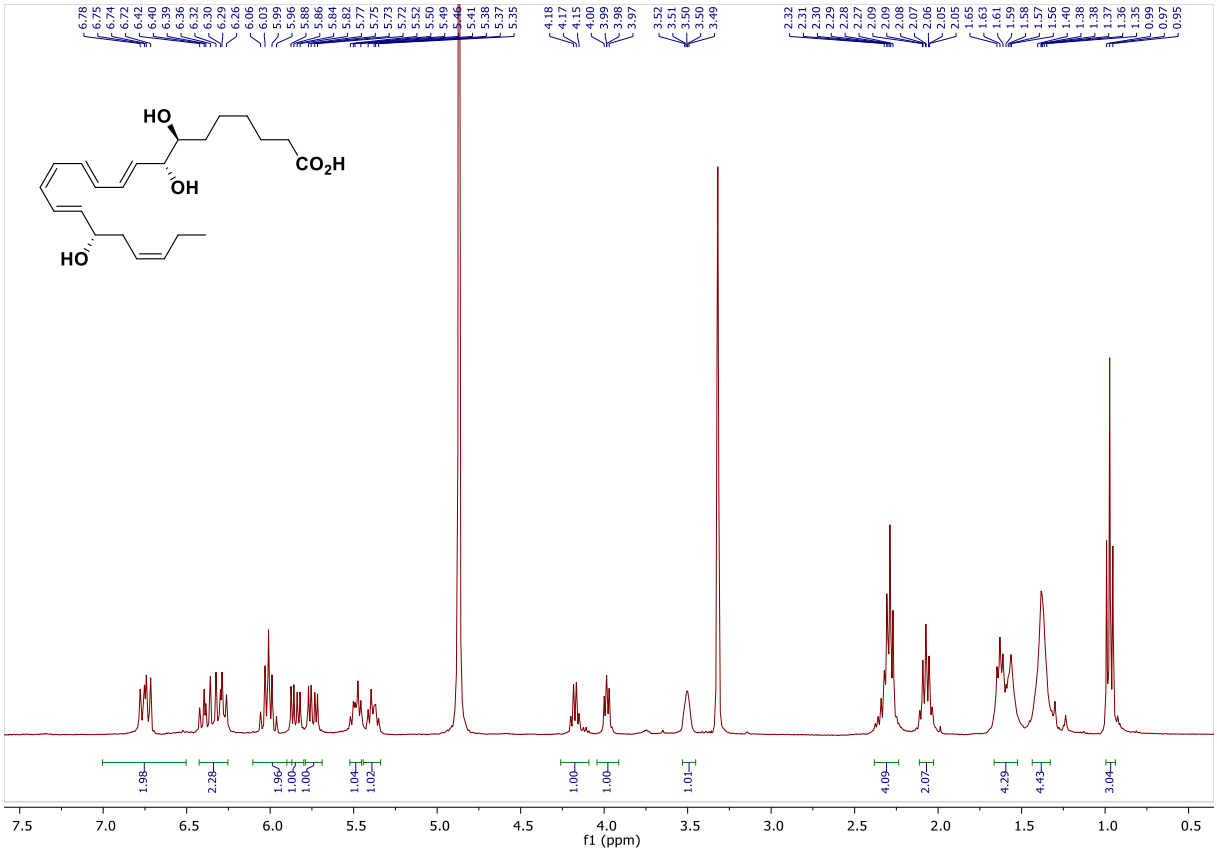


Figure S-34 ^{1}H-NMR spectrum of compound RvD1 $_{n\text{-}3\ DPA}$ (**4**).

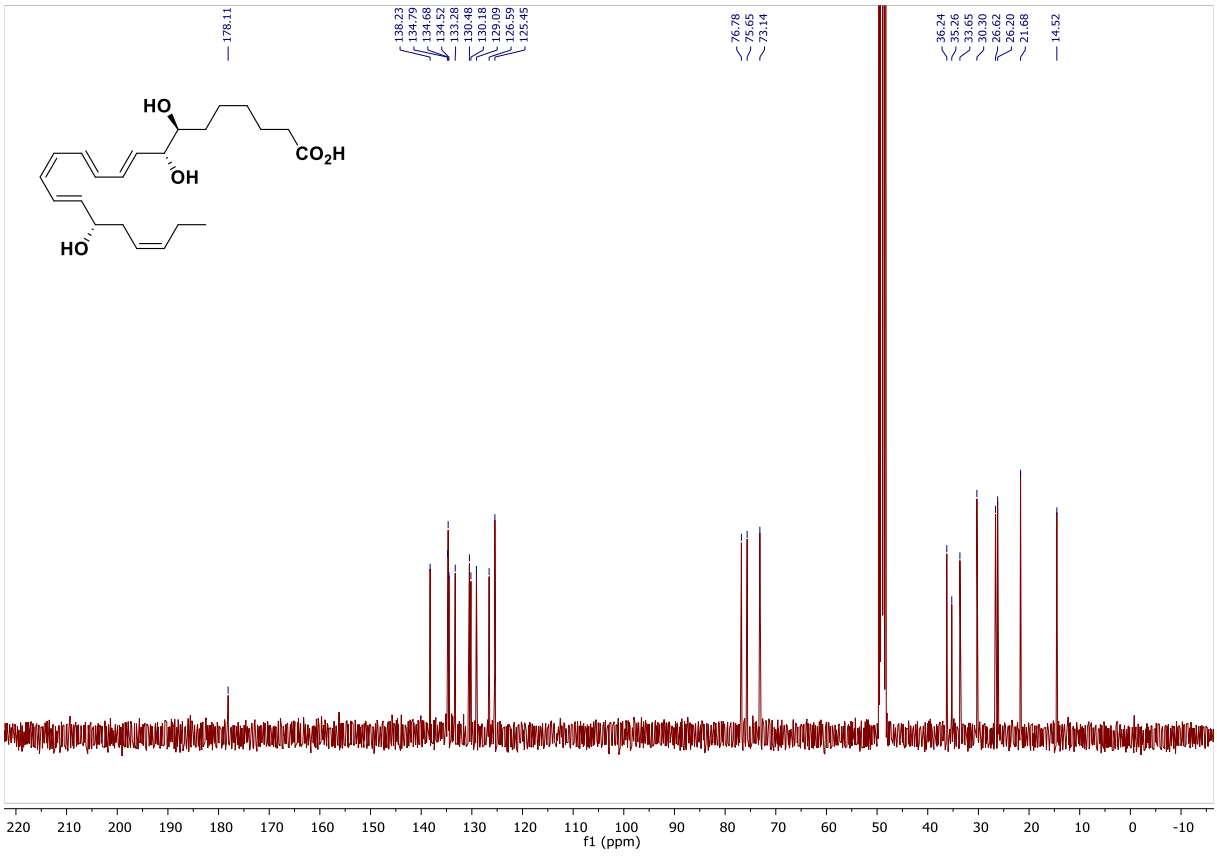


Figure S-35 ^{1}H-NMR spectrum of compound RvD1 $_{n\text{-}3\ DPA}$ (**4**).

HPLC chromatograms

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    Acq. Instrument  : Instrument 1                    Location : Vial 1
    Injection Date   : 25.09.2017 10:16:53
                                                     Inj Volume : 5 µl
    Acq. Method      : D:\METHODS\Jorn\AD-H.m
    Last changed     : 25.09.2017 10:28:05  by JORN
    Analysis Method  : D:\METHODS\Jorn\AD-H.m
    Last changed     : 25.09.2017 10:31:29  by JORN
    Sample Info      :
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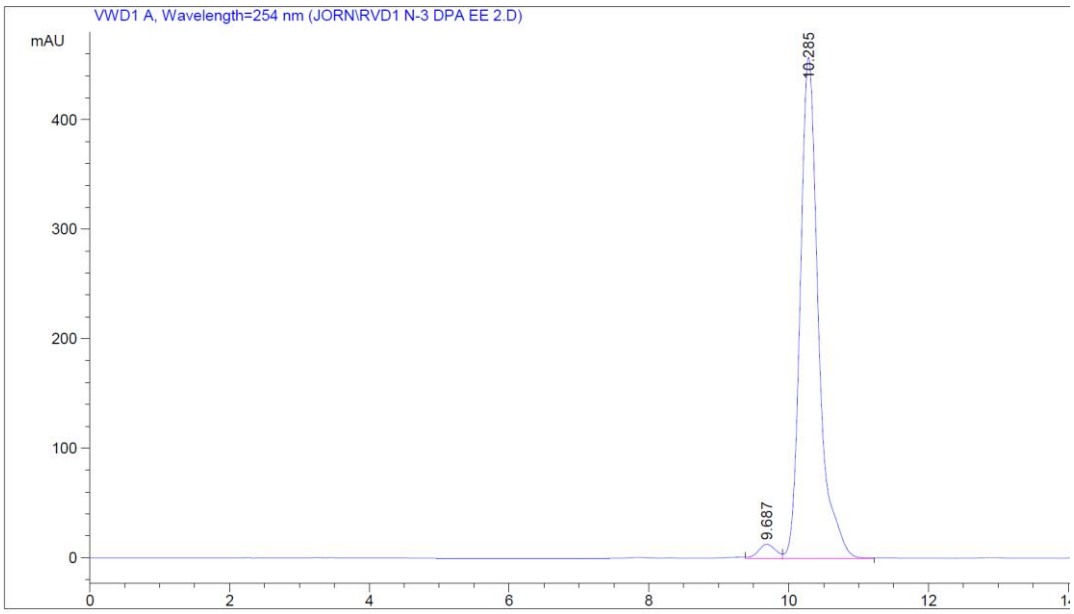


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    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Sample Amount         :      1.00000  [ng/ul]   (not used in calc.)
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=254 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]  mAU   *s   [mAU   ]      %
    ----|-------|----|-------|----------|----------|--------|
       1   9.687 VV    0.2631  219.80016   12.88292   2.5972
       2  10.285 VB    0.2743 8243.23633  457.45389  97.4028

    Totals :                  8463.03648  470.33680


    ======================================================================
                              *** End of Report ***



Instrument 1 25.09.2017 10:34:44  JORN                          Page   1 of 1
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Figure S-36 HPLC chromatogram of RvD1 $_{n\text{-}3\ DPA}$ ethyl ester (**21**).

UV-Vis chromatograms

Spectrum/Peak Report Date 9/25/2017 Time 14:25:04 Page 1 of 1

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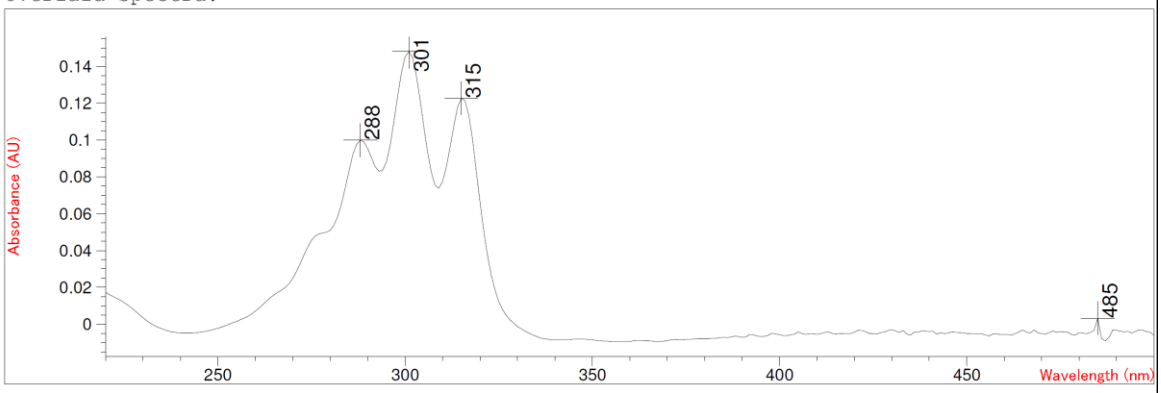

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1		315.0	0.12262	1		485.0	3.3121E-3

Report generated by : Hamid Signature: .....

*** End Spectrum/Peak Report ***

Figure S-37 UV-Vis chromatogram of RvD1 $_{n\text{-}3\ DPA}$ ethyl ester (**21**).

Spectrum/Peak Report Date 9/13/2017 Time 11:01:18 Page 1 of 1

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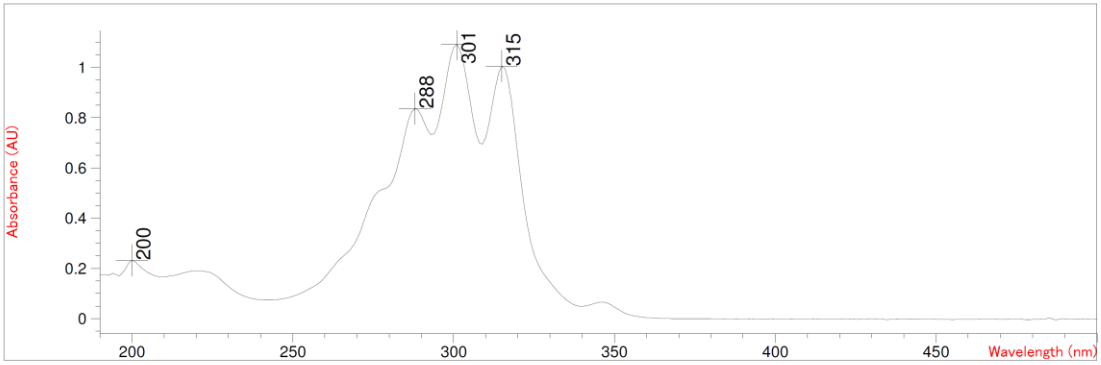

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1		315.0	1.00550	1		200.0	0.23256

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Figure S-38 UV-Vis chromatogram of RvD1 $_{n\text{-}3\ DPA}$ (**21**).

Matching experiments

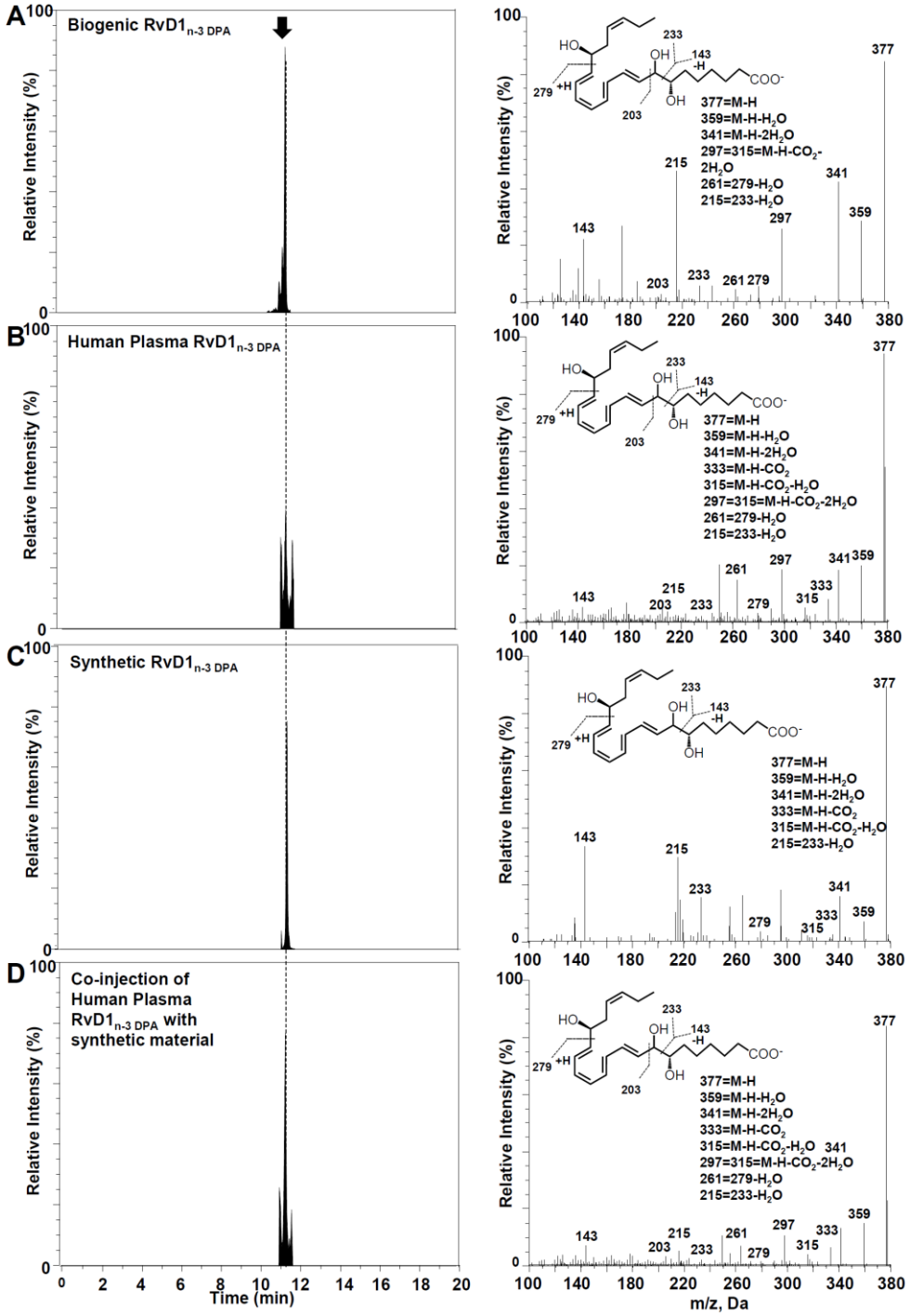

Figure S-39 Matching synthetic material of RvD1 $_{n\text{-}3\ DPA}$ (**4**) with authentic **4** produced in human plasma. (A) RvD1$_{n\text{-}3\ DPA}$ obtained *via* biogenic enzymatic synthesis (B) Endogenous RvD1$_{n\text{-}3\ DPA}$ from human plasma. Products were extracted *via* and mediators RvD1$_{n\text{-}3\ DPA}$ identified using lipid mediator profiling (C) synthetic material (D) co-injection of human plasma with synthetic material (left panels). Multiple reaction monitoring chromatograms for m/z 377>143. (right panels) MS/MS spectra for product under peak with T_R 11.3 min. Results are representative of n = 3 distinct experiments.

Lipid Mediator Metabololipidomics.

Matching of synthetic **4** with endogenous products was conducted as previously reported (PMID: 23438748).[1] Briefly, biological samples were subject to C18 solid-phase extraction. Prior to sample extraction, d_4-RvD2 (500 pg) was added. Extracted samples were analyzed using QTrap 6500+ (ABSciex) MS system, coupled with a Shimadzu SIL-20AC HT autosampler and LC-20AD LC pumps. Agilent C18 Poroshell column (150 mm × 4.6 mm × 2.7 µm) was used to profile lipid mediators. The gradient was initiated at 20:80:0.01 (vol/vol/vol) methanol/water/acetic acid for 0.2 mins this was ramped to 50:50:0.01 (vol/vol/vol) over 12 seconds, maintained for 2 minutes, then ramped to 80:20:0.01 (vol/vol/vol) over 9 minutes, and maintained for 3.5 minutes. The ratio was then ramped to 98:2:0.01 (vol/vol/vol) for 5.5 minutes. The flow rate was kept at 0.5 mL/minute throughout.

Mediator identity was established using multiple reaction monitoring (MRM) using signature parent ion (Q1) and characteristic daughter ion (Q3) pairs to match retention time of the biological material to synthetic **4**. An Enhanced Product Ion scan of a minimum of six diagnostic ions were used to confirm the identity, in accord with published criteria.[1]

Biogenic synthesis

$RvD1_{n3\ DPA}$ was produced using soybean-LOX and potato ALOX5 as detailed earlier.[2] Briefly, 17S-HpDPA was prepared from n-3 DPA (15 µM) incubated with 100 U/ml isolated soybean-LOX (Borate buffer, 4 ^{o}C, pH = 9.2). 17S-HpDHA was isolated using RP-HPLC. This was then incubated with potato ALOX5 (4 ^{o}C, 0.1 M phosphate buffer, pH = 6.3, 0.03% Tween 20) for 1 h.

Evaluations of efferocytosis and phagocytosis bioactions

***E. coli* peritonitis**

Healthy 6-11-week-old male C57/Black6 Wildtype mice (Charles River) were used in the reported studies. The experiments strictly adhered to UK Home Office regulations (Guidance on the Operation of Animals, Scientific Procedures Act, 1986) and Laboratory Animal Science Association (LASA) Guidelines (Guiding Principles on Good Practice for Animal Welfare and Ethical Review Bodies, 3rd Edition, 2015). Animals were kept on a 12 h light dark cycle, with lights turned on at 7:00 h and lights turned off at 19:00 h under specific pathogen free housing and had access to food and water *ad libitum*. Sample size was based on the statistical analysis of previous experiments and no mice were excluded. Animals were randomly assigned to control and experimental groups. The investigators were not blinded to group assignments. Mice were administered *E. coli* $1x10^5$ (CFU/mouse) via intraperitoneal injection together with either $RvD1_{n\text{-}3\ DPA}$ (**4**) (50ng/mouse) or vehicle. Cells were then collected after 4 h, leukocyte numbers were enumerated using light microscopy and flow cytometry and neutrophil phagocytosis was determined using flow cytometry as detailed below.

Flow cytometry

Peritoneal cells were centrifuged and then incubated with anti CD16/C32 for 30 min at 4 ^{o}C, then with anti-mouse Ly6G (Clone 1A8, Biolegend) for 30 min at 4 ^{o}C. Cells were then washed using cold PBS containing 0.1% BSA and then incubated with Foxp3 / Transcription Factor Staining Buffer Set (eBiosciences) for 30 min at 4 ^{o}C. Cells were then incubated with a FITC labelled anti-*E. Coli* antibody (GenTex) for 40 min at 4 ^{o}C, then washed and the staining was analysed using BD Fortessa and FlowJo Software (TreeStar Inc).

Human macrophage phagocytosis and efferocytosis

Human macrophages were prepared from peripheral blood mononuclear cells as previously described.[1] Human macrophages were then incubated with either RvD1n-3 DPA (0.1 or 1nM) or PBS containing 0.01% ethanol for 15 minutes at 37 ^{o}C these were then incubated with fluorescently labelled E. coli or fluorescently labelled apoptotic cells prepared according to literature[3] for 45 min at 37 ^{o}C. Cells were washed with PBS and extracellular fluorescence was quenched using trypan blue (1:15 in PBS). Fluorescence was then measured using a FLUOstar Omega microplate reader (BMG Labtech).

Ligand receptor interactions experiments

Activation of human ALX and GPR32: comparison of RvD1, RvD1$_{n\text{-}3\ DPA}$ and RvD1$_{n\text{-}3\ DPA}$ ethyl ester

Ligand receptor interactions were monitored using the PathHunter® β-Arrestin cell–based assays (Eurofins DiscoverX Corporation, Fremont, CA, USA) and carried out with HEK-ALX or CHO-GPR32 cells essentially as described earlier.[4] Cells (2x10^4 cells) were plated onto 96-well plates 24 h prior to experiments. Test compounds at indicated concentrations were incubated with cells for 1 h at 37 °C and receptor activation was determined by measuring chemiluminescence using the PathHunter detection kit (Eurofins DiscoverX Corporation, Fremont, CA, USA). Results are expressed as % increase of chemiluminescence above vehicle control; mean from 3 independent experiments and 4 replicates in each experiment.

References

1. J. Dalli, J. W. Winkler, R. A. Colas, H. Arnardottir, C. Y. Cheng, N. Chiang, N. A. Petasis, C. N. Serhan, *Chem. Biol*. **2013**, *20*, 188.
2. J. Dalli, R. A. Colas, C. N. Serhan, *Sci. Rep*. **2013**, *3*, 1940.
3. K. D. F. Pistorius, P. R. S. de Souza, K. G. Primdahl, R. A.Colas, A. Vik, T. V. Hansen, J. Dalli, *Cell Chem. Biol.*, **2018**, *25*, 749.
4. S. Krishnamoorthy, A. Recchiuti, N. Chiang, S. Yacoubian, C. H. Lee, R. Yang, N. A. Petasis, C. N. Serhan, *Proc. Natl. Acad. Sci. USA*, **2010**, *107*, 1660.