Supporting Information
of
Total Synthesis of Thromboxane B_2 via a Key Bicyclic Enal Intermediate

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General Information

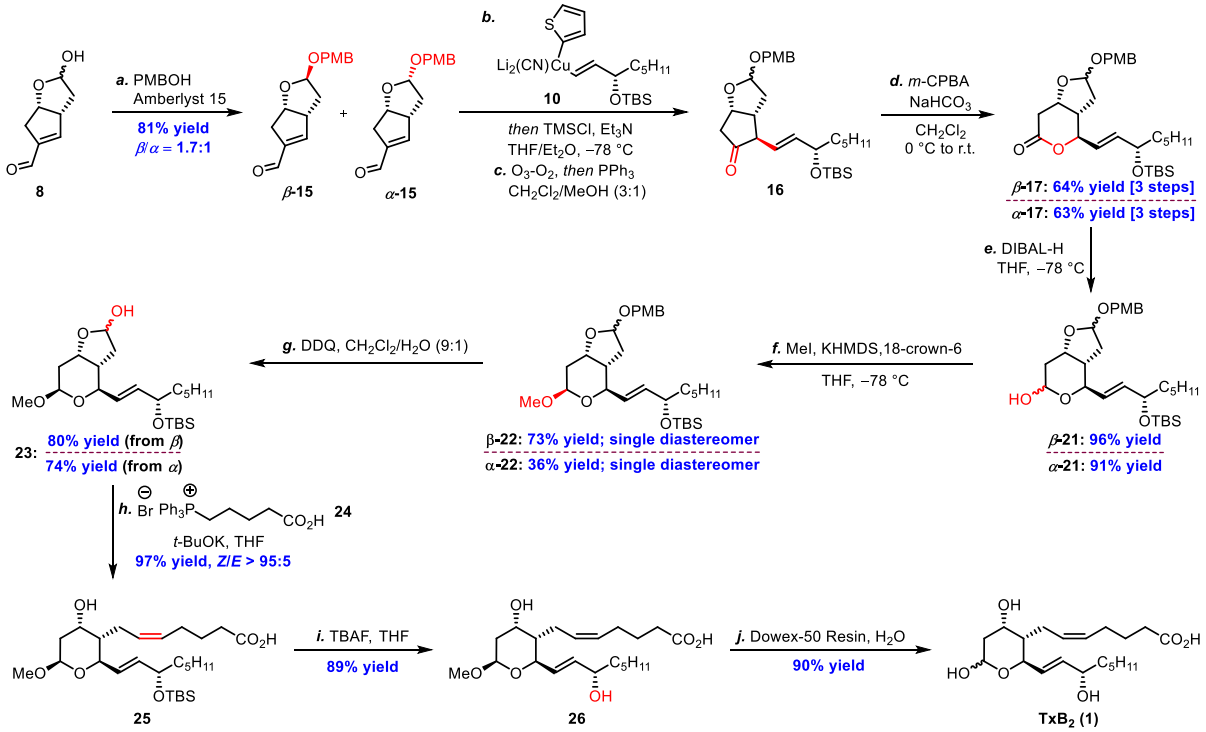
Solvents and Reagents. Generally, reactions were carried out using reagent grade solvents and without air excluded. Reactions requiring anhydrous solvents and an inert atmosphere were carried out under a nitrogen atmosphere using standard manifold techniques. All solvents were commercially supplied or obtained from a purification column composed of activated alumina.[1] All chemicals were purchased from Acros, Aldrich, Alfa Aesar, Fluka, Lancaster or Merck and used as received unless otherwise stated. Triethylamine and trimethylsilyl chloride were distilled over CaH_2 under reduced pressure prior to use. *n*-BuLi and *tert*-BuLi were purchased from Acros and were titrated against *N*-benzylbenzamide using the procedure of Chong *et al.*[2]

Chromatography. Flash column chromatography (FCC) was carried out using Sigma-Aldrich silica gel (60 Å, 230 – 400 mesh, 40 – 63 μm) or using Biotage Isolera™ One with Biotage® SNAP/SNAP Ultra Cartridges. All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F254 fluorescent treated silica gel, which was visualized under UV light or by staining with aqueous basic potassium permanganate or an ethanolic and acidic solution of *p*-anisaldehyde.

Spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on Jeol ECS 400, Bruker Nano 400, Varian VNMRS500 and Bruker Avance III HD 500 Cryo spectrometers. Chemical shift (δ value) are referenced relative to the residual protiated solvent and are reported in parts per million (ppm), and coupling constants (*J* value) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: chemical shift, multiplicity (s = singlet, br.s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, h = heptet, m = multiplet, dd = doublet of doublets, etc.), coupling constants and assignment. NMR assignments are made according to spin systems, using two-dimensional NMR spectroscopy (COSY, HSQC and HMBC etc.) to assist the assignment. High resolution mass spectra (HRMS) were recorded on a on a Bruker micrOTOF instrument by Electrospray Ionisation (ESI). Infra-red (IR) spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer as a thin film. Only selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Melting points were recorded in degrees Celsius (°C), using a Kofler hot-stage microscope apparatus and are reported uncorrected. Optical rotation ($[\alpha]_D^T$) was measured on a Bellingham and Stanley Ltd. ADP220 polarimeter and is quoted in (° mL)(g $dm)^{-1}$. Chiral supercritical fluid chromatography (SFC) was performed using a Daicel Chiralpak® IA column (4.6 × 250 mm × 5μm) using a Waters TharSFC system and monitored by Diode Array Detector (DAD).

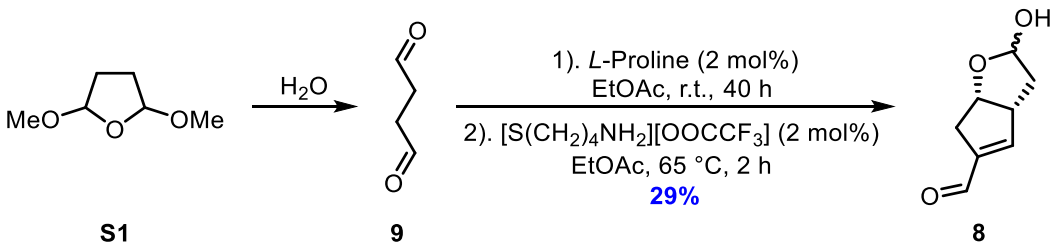
Naming of Compounds. Compound names are generated by ChemDraw 11.0 software (PerkinElmer), following IUPAC nomenclature.

Experimental Procedures



Scheme S1. Complete synthetic scheme for the synthesis of thromboxane B_2. *Reagents and conditions:* (a) PMBOH (2 eq.), Amberlyst 15 (cat.), $MgSO_4$ (2.5 eq.), CH_2Cl_2, 0 °C to r.t., 24 h; then MnO_2 (6 eq.), r.t., 12 h, 81% yield, 1.7:1 β/α. (b) Cuprate **10** (1.2 eq.), THF/Et_2O, −78 °C; then TMSCl (5 eq.), Et_3N (6 eq.), −78 °C to −20 °C. (c) O_3-O_2, CH_2Cl_2/MeOH (*v*/*v*, 3:1), −78 °C; then PPh_3 (1.5 eq.). (d) *m*-CPBA (2.5 eq.), $NaHCO_3$ (2.7 eq.), CH_2Cl_2, 0 °C to r.t., 36 h, 64% yield for *β*, 63% yield for *α*, 3 steps. (e) DIBAL-H (3.0 eq.), THF, −78 °C, 3 h, 96% yield for *β*, 91% yield for *α*. (f) MeI (3 eq.), KHMDS (1.1 eq.), 18-Crown-6 (1.1 eq.), THF, −78 °C, 18 h, single diastereomer, 73% yield for *β*, 36% yield for *α*. (g) DDQ (1.5 eq.), CH_2Cl_2/H_2O (*v*/*v*, 9:1), 0 °C to r.t., 6 h, 80% yield for *β*, 74% yield for *α*. (h) (4-carboxybutyl)triphenyl-phosphonium bromide (4 eq.), *t*-BuOK (8 eq.), THF, 0 °C to r.t., 2 h, 97% yield with *Z*/*E* > 95:5. (i) TBAF (2 eq.), THF, 0 °C to r.t.,12 h, 89% yield. (j) Dowex-50 Resin, H_2O, r.t., 16 h, 90% yield. PMB, *p*-methoxybenzyl. TBS, *tert*-butyldimethylsilyl. TMS, trimethylsilyl. *m*-CPBA, *m*-chloroperoxybenzoic acid. DIBAL-H, diisobutylaluminum hydride. HMDS, bis(trimethylsilyl)amide. DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. TBAF, tetrabutylammonium fluoride.

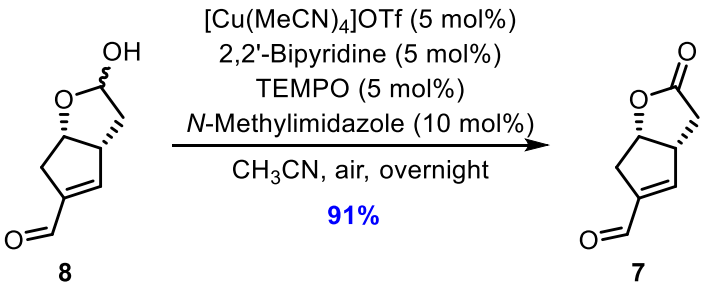
Synthesis of the key bicyclic enals 8 from 2,5-dimethoxytetrahydrofuran



Lactol **8** was prepared from freshly distilled succinaldehyde (**9**) according to the literature, and afforded the product as a light brown solid whose analytical data was consistent with the data reported in the literature.[3] The enantiomeric excess was determined by SFC analysis of

(3a*R*,6a*S*)-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-5-carbaldehyde generated from simple oxidation of enal **8**.

(3a*R*,6a*S*)-2-Oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-5-carbaldehyde (7)



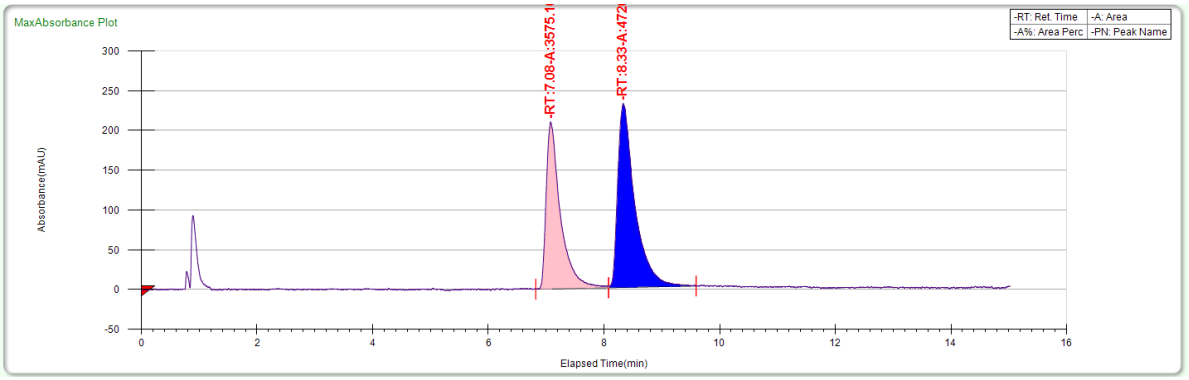
8 **7**

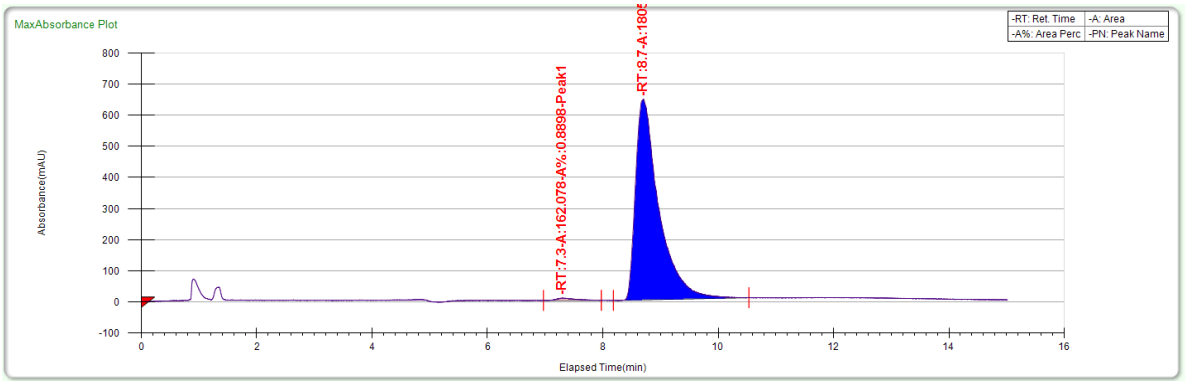
To a solution of lactol **8** (13.0 g, 84.3 mmol, 1.0 eq.) in acetonitrile (420 mL) were added tetrakisacetonitrile copper (I) triflate (1.59 g, 4.22 mmol, 5 mol %), 2,2'-bipyridine (658 mg, 4.22 mmol, 5 mol %), TEMPO (658 mg, 4.22 mmol, 5 mol %) and *N*-methylimidazole (671 µL, 8.44 mmol, 10 mol %). The reaction mixture was stirred at r.t. overnight and then filtered through a silica plug, washed with EtOAc. The filtrate was concentrated, and the crude mixture was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 50:50 to 30:70) to give the lactone **7** as a white solid (11.67 g, 76.71 mmol, 91%, 99:1 er).

Analytical data was consistent with data reported in the literature.[4]

The enantiomeric excess was determined by SFC analysis:

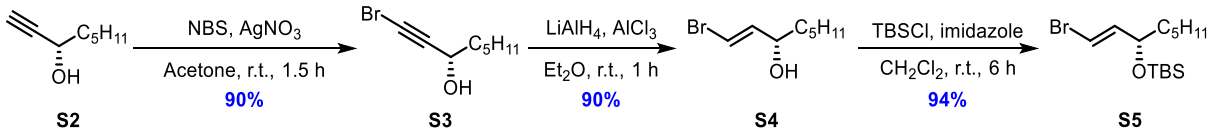
Chrial SFC Conditions: Chiralpak® IA column; 125 bar, 40 °C, flow rate 4 mL/min, CO_2/*i*-PrOH = 95:5; retention time: t_{minor} = 7.3 min, t_{major} = 8.7 min; er = 99:1.



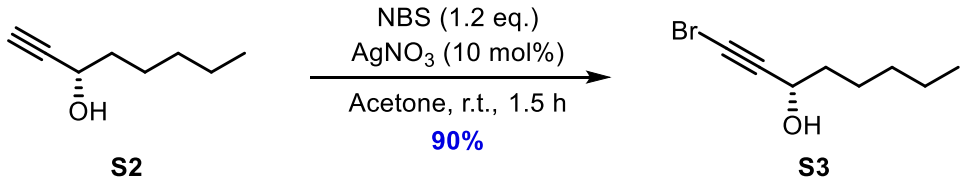


Synthesis of side chains

Synthesis of (*S*,*E*)-((1-bromooct-1-en-3-yl)oxy)(*tert*-butyl)dimethylsilane (S5) from S2



(*S*)-1-Bromooct-1-yn-3-ol (S3)



To a stirring solution of **S2** (3.8 g, 30.0 mmol, 1.0 eq.) in acetone (150 mL) was added NBS (6.4 g, 36.0 mmol, 1.2 eq.) and $AgNO_3$ (510 mg, 3.0 mmol, 10 mol %) sequentially. The reaction mixture was stirred at r.t. for 1.5 h before it was poured over H_2O (160 mL) and extracted with EtOAc (3 × 160 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 19:1 to 9:1) to give alcohol **S3** (5.5 g, 27.0 mmol, 90%) as a clear, colorless oil.

R_f = 0.46 (Hexanes/EtOAc = 9:1)

IR (thin film) ν_{max} /cm^{-1}: 3357, 2958, 2933, 2860, 1462, 1390, 1250, 1224, 1055, 895, 757.

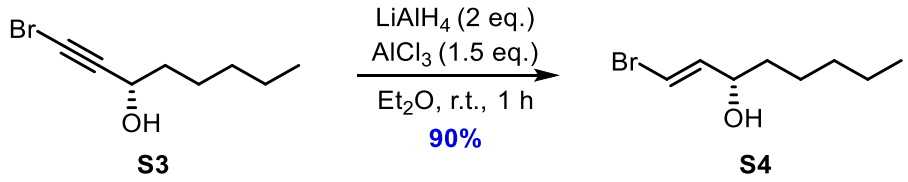
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.39 (t, J = 6.6 Hz, 1H), 1.73 – 1.67 (m, 3H), 1.49 – 1.39 (m, 2H), 1.38 – 1.27 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 81.4, 63.4, 45.1, 37.8, 31.5, 24.8, 22.7, 14.1.

$[\alpha]_D^{25}$ = +3.0 (*c* 1.00, $CHCl_3$).

Analytical data is consistent with data reported in the literature.[5]

(*S*,*E*)-1-Bromooct-1-en-3-ol (S4)



S3 **S4**

To a solution of $LiAlH_4$ (1.5 g, 40.0 mmol, 2.0 eq.) in dry Et_2O (75 mL), $AlCl_3$ (4.0 g, 30.0 mmol, 1.5 eq.) was carefully added portion-wise. A solution of **S3** (4.1 g, 20.0 mmol, 1.0 eq.) in dry Et_2O (14.5 mL) was added dropwise to the above mixture, and the resulting reaction mixture was stirred at r.t. for 1 h. Following cooling to 0 °C, H_2O (1.5 mL) was carefully added dropwise followed by aqueous NaOH solution (0.5 M, 1.5 mL) and then a further portion of H_2O (4.6 mL). The mixture was stirred at r.t. for 30 min, $MgSO_4$ (20.5 g) was added and the mixture was stirred for a further 15 min prior to sinter filtration, washing with Et_2O (3 × 80 mL). The filtrate was concentrated *in vacuo* to afford pure **S4** (3.7 g, 17.9 mmol, 90%) as a clear, colorless oil.

$\boldsymbol{R_f}$ = 0.46 (Hexanes/EtOAc = 9:1)

IR (thin film) $\boldsymbol{\nu_{max}}$ /cm^{-1}: 3358, 2956, 2929, 2858, 1620, 1465, 1379, 1266, 1028, 937, 791, 724.

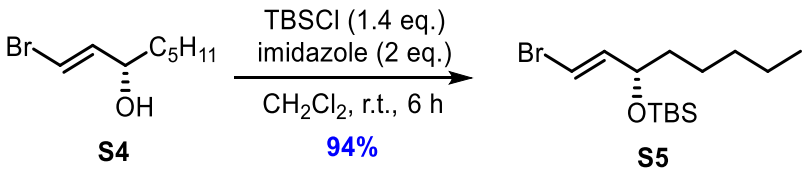
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.32 (dd, *J* = 13.6, 0.9 Hz, 1H), 6.23 (dd, *J* = 13.6, 6.5 Hz, 1H), 4.11 (qd, *J* = 6.9, 0.8 Hz, 1H), 1.72 (br.s, 1H), 1.54 – 1.48 (m, 2H), 1.35 – 1.27 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 140.6, 107.1, 72.8, 37.0, 31.8, 25.0, 22.7, 14.1.

$\boldsymbol{[\alpha]_D^{25}}$ = +4.0 (*c* 1.00, $CHCl_3$) [lit.[5] $\boldsymbol{[\alpha]_D^{23}}$ = +5.0 (*c* 2.00, $CHCl_3$)]

Analytical data is consistent with data reported in the literature.[5,6]

(*S*,*E*)-((1-Bromooct-1-en-3-yl)oxy)(*tert*-butyl)dimethylsilane (S5)



S4 **S5**

Imidazole (2.4 g, 35.8 mmol, 2.0 eq.) and TBSCl (3.8 g, 25.1 mmol, 1.4 eq.) were sequentially added to a stirring solution of **S4** (3.7 g, 17.9 mmol, 1.0 eq.) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was stirred at r.t. for 6 h before it was poured over aqueous HCl (0.5 M, 80 mL) and extracted with Et_2O (3 × 80 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column

chromatography on silica gel (Hexanes) to give pure **S5** as a clear, colorless oil (5.4 g, 16.8 mmol, 94%).

R_f = 0.52 (Hexanes)

IR (thin film) ν_{max}/cm^{-1}: 2955, 2929, 2857, 1624, 1470, 1360, 1255, 1089, 936, 835, 715, 706.

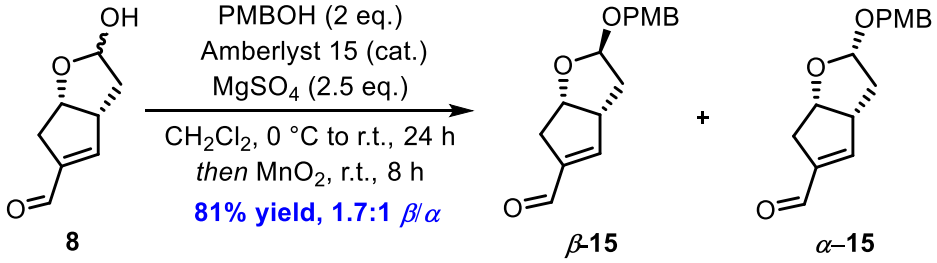
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.22 – 6.14 (m, 2H), 4.09 (tdd, *J* = 6.2, 4.0, 0.9 Hz, 1H), 1.52–1.41 (m, 2H), 1.35 – 1.23 (m, 6H), 0.90 – 0.87 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 141.2, 105.6, 73.3, 37.9, 31.9, 26.0, 24.7, 22.5, 18.3, 14.2, -4.4, -4.7.

$[\alpha]_D^{24}$ = −14.0 (*c* 1.00, $CHCl_3$) [lit.[7] **$[\alpha]_D^{22}$** = –19.9 (*c*. 1.00, $CHCl_3$)]

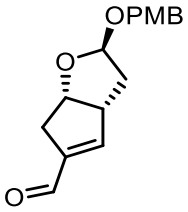
Analytical data is consistent with data reported in the literature.[7]

Synthesis of the enals 15



To an oven-dried flask, enal **8** (11.9 g, 77.5 mmol, 1.0 eq.), amberlyst 15 (2.4 g) and $MgSO_4$ (23.3 g, 194 mmol, 2.5 eq., dried under *vacuum* at 400 °C) were dissolved in CH_2Cl_2 (77.5 mL) at 0 °C under N_2 atmosphere. Then, a solution of 4-methoxybenzyl alcohol (21.4 g, 155 mmol, 2 eq.) in dry CH_2Cl_2 (77.5 mL) was added to the above mixture at the same temperature, and the resulting reaction mixture was stirred at r.t. After 24 h, MnO_2 (26.9 g, 310 mmol, 4.0 eq.) was added, and the reaction was stirred at r.t. overnight. The reaction mixture was filtered through Celite® and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica gel (Toluene/Et_2O = 10:1 to 1:1) to give pure *β*-**15** (major) and *α*-**15** (minor) (17.2 g, 62.8 mmol, 81%, 1.7:1 β/α) as white amorphous solids.

(2*R*,3a*R*,6a*S*)-2-((4-Methoxybenzyl)oxy)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-5-carbaldehyde (*β*-15)



β-**15**

R_f = 0.49 (Toluene/Et_2O = 7:3)

IR (thin film) ν_{max}/cm^{-1}: 2932, 2834, 1680, 1613, 1513, 1464, 1302, 1247, 1172, 1093, 1029, 978, 822, 706.

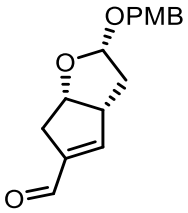
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 9.78 (s, 1H), 7.29 – 7.26 (m, 2H), 6.91 – 6.86 (m, 2H), 6.65 (q, *J* = 2.0 Hz, 1H), 5.23 (d, *J* = 5.1 Hz, 1H), 4.86 (dt, *J* = 6.9, 3.8 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 3.69 – 3.60 (m, 1H), 2.80 – 2.74 (m, 2H), 2.31 (ddd, *J* = 13.3, 10.1, 1.1 Hz, 1H), 1.91 (dt, *J* = 13.3, 5.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 190.1, 159.4, 152.6, 144.7, 130.0, 129.8, 114.0, 102.9, 80.6, 68.6, 55.4, 49.5, 37.4, 35.3.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{18}NaO_4$ 297.1097; Found 297.1097.

$[\alpha]_D^{22}$ = –134.5 (*c* 1.05, $CHCl_3$)

(2*S*,3a*R*,6a*S*)-2-((4-Methoxybenzyl)oxy)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-5-carbaldehyde (*α*-15)



α–**15**

R_f = 0.38 (Toluene/Et_2O = 7:3)

IR (thin film) ν_{max}/cm^{-1}: 2945, 2910, 2835, 1677, 1613, 1585, 1513, 1464, 1359, 1301, 1247, 1159, 1078, 1030, 948, 822, 708.

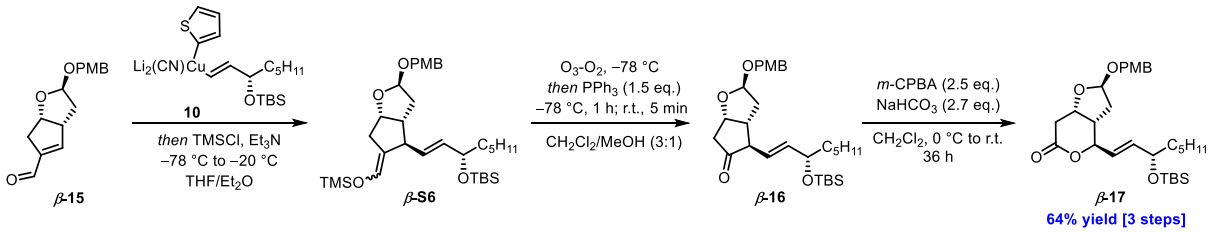
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 9.76 (s, 1H), 7.11 – 7.08 (m, 2H), 6.83 – 6.80 (m, 2H), 6.74 (q, *J* = 2.0 Hz, 1H), 5.20 (d, *J* = 4.8 Hz, 1H), 4.96 (dt, *J* = 6.5, 4.1 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 3.78 (s, 3H), 3.56 (ddt, *J* = 9.4, 6.3, 1.7 Hz, 1H), 2.83 (dd, *J* = 3.2, 1.7 Hz, 2H), 2.22 – 2.16 (m, 1H), 2.14 – 2.10 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 190.1, 159.3, 153.4, 144.6, 130.0, 129.7, 113.9, 103.0, 82.8, 68.7, 55.4, 49.9, 38.0, 37.3.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{18}NaO_4$ 297.1097; Found 297.1108.

$[\alpha]_D^{23}$ = –36.0 (*c* 1.00, $CHCl_3$)

(2*R*,3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-((4-methoxybenzyl)oxy)hexahydro-6*H*-furo[3,2-*c*]pyran-6-one (*β*-17)



To a solution of **S5** (3.5 g, 10.8 mmol, 1.2 eq.) in Et_2O (43.2 mL) stirring at –78 °C, *t*-BuLi (1.7 M in pentane, 12.7 mL, 21.6 mmol, 2.4 eq.) was added dropwise and the resulting pale yellow solution was stirred at –78 °C for 2 h prior to warming to –40 °C to stir for a further 2 h before cooling back to –78 °C.

A separate solution of thiophene (866 µL, 909 mg, 10.8 mmol, 1.2 eq.) in THF (43.2 mL) was prepared and cooled to –40 °C and *n*-BuLi (1.6 M in hexanes, 6.8 mL, 10.8 mmol, 1.2 eq.) was added dropwise. The resulting colorless/very pale yellow, clear solution was stirred at –40 °C for 45 min before cooling to –78 °C whereupon CuCN (967 mg, 10.8 mmol, 1.2 eq.) was added in a single portion and the solution was warmed to r.t. The formed thienyl cuprate solution was then added to the above vinyl lithium solution at –78 °C and THF (43.2 mL) was added (used for washing the flask). The bright yellow reaction mixture was warmed to –20 °C to facilitate the formation of cuprate **10**. The reaction mixture was stirred at –20 °C for 1 h before cooling back to –78 °C.

A solution of *β*-**15** (2.5 g, 9.0 mmol, 1.0 eq.) in THF (43.2 mL) was prepared and added to the solution of cuprate **10** at –78 °C to give a bright orange reaction mixture. The reaction mixture was stirred at –78 °C for 1 h before the sequential addition of TMSCl (5.7 mL, 4.9 g, 45.0 mmol, 5.0 eq.) and Et_3N (7.5 mL, 5.5 g, 54.0 mmol, 6.0 eq.). The reaction mixture was warmed to –20 °C to stir for 20 min before quenching by addition of saturated aqueous NH_4Cl solution (80 mL) and warming to r.t.. The aqueous phase was extracted with EtOAc (3 × 80 mL), the organic phases were then combined, washed further with saturated aqueous $Na_2S_2O_3$ solution (80 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude *β*-**S6** as a brown oil, which was used directly in the next step.

In a round-bottom flask, a solution of crude *β*-**S6** in CH_2Cl_2/MeOH (72 mL, 3:1 *v/v*) was cooled to –78 °C and a stream of O_3-O_2 (g) was bubbled through the reaction solution. The reaction

progress was carefully monitored by TLC (Hexanes/EtOAc = 6:1) until a small amount of *β*-**S6** remained (~7.0 min). The reaction mixture was then purged of O_3 (g) by bubbling N_2 (g) through the solution for 20 min followed by the addition of freshly ground PPh_3 (3.5 g, 13.5 mmol, 1.5 eq.). The reaction was stirred at –78 °C for 1 h before the dry ice/acetone bath was removed and the reaction was allowed to warm to r.t., at which point it was stirred for a further 5 min. The reaction mixture was then poured over saturated brine solution (80 mL) and extracted with EtOAc (3 × 80 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude *β*-**16** as a brown oil, which was used directly in the next step.

In a round-bottom flask, a solution of crude *β*-**16** in dry CH_2Cl_2 (90 mL) was cooled to 0 °C. Then, *m*-CPBA (77% purity, 5.0 g, 22.5 mmol, 2.5 eq.) and $NaHCO_3$ (2.0 g, 24.3 mmol, 2.7 eq.) were added to the above mixture at 0 °C under N_2 atmosphere, and the mixture was stirred for 36 h at r.t. The reaction mixture was diluted with EtOAc and poured over water (80 mL) and extracted with EtOAc (3 × 80 mL). The organic phases were combined, washed with 5% $Na_2S_2O_3$ solution (60 mL), 5% Na_2CO_3 solution (60 mL), saturated brine solution (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 10:1 to 4:1) to give pure *β*-**17** (3.0 g, 5.8 mmol, 64%) as a white amorphous solid.

Mp 37 – 41 °C

$\boldsymbol{R_f}$ = 0.32 (Hexanes/EtOAc = 4:1)

IR (thin film) $\boldsymbol{\nu_{max}}$/cm^{-1}: 2953, 2929, 2858, 1752, 1613, 1514, 1453, 1353, 1302, 1248, 1173, 1152, 1090, 1029, 873, 836, 775.

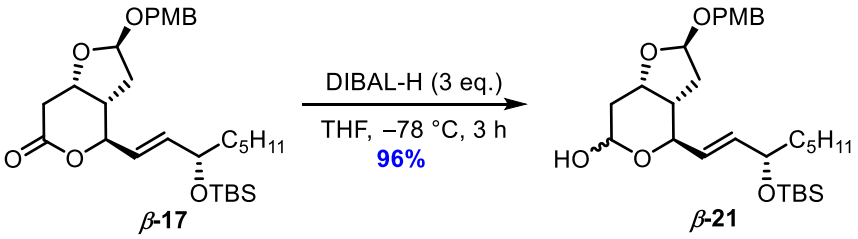
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.28 – 7.21 (m, 2H), 6.91 – 6.82 (m, 2H), 5.80 (ddd, *J* = 15.5, 5.4, 1.1 Hz, 1H), 5.61 (ddd, *J* = 15.5, 6.8, 1.4 Hz, 1H), 5.25 (d, *J* = 4.7 Hz, 1H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.55 – 4.45 (m, 2H), 4.40 (d, *J* = 11.3 Hz, 1H), 4.15 – 4.09 (m, 1H), 3.80 (s, 3H), 3.02 (dd, *J* = 15.4, 6.8 Hz, 1H), 2.63 (ddd, *J* = 15.9, 8.4, 2.5 Hz, 2H), 2.10 (dd, *J* = 13.5, 9.1 Hz, 1H), 1.73 (ddd, *J* = 13.5, 6.9, 5.0 Hz, 1H), 1.50 – 1.39 (m, 2H), 1.33 – 1.21 (m, 6H), 1.01 – 0.67 (m, 12H), 0.04 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 170.6, 159.5, 139.2, 129.8, 129.8, 129.7, 124.4, 114.0, 102.6, 80.8, 72.6, 72.2, 68.7, 55.4, 41.0, 38.1, 35.6, 35.5, 31.9, 26.0, 24.8, 22.7, 14.1, -4.3, -4.7.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{29}H_{46}NaO_6Si$ 541.2955; Found 541.2950.

$[\alpha]_D^{24}$ = –24.3 (*c* 1.00, $CHCl_3$)

(2*R*,3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-((4-methoxybenzyl)oxy)hexahydro-4*H*-furo[3,2-*c*]pyran-6-ol (*β*-17)



To a solution of *β*-**17** (622.6 mg, 1.20 mmol, 1.0 eq.) in dry THF (12.0 mL) at –78 °C under N_2 atmosphere, diisobutylaluminium hydride (1.0 M in hexanes, 3.6 mL, 3.6 mmol, 3.0 eq.) was added dropwisely. The reaction mixture was stirred at –78 °C for 3 h and quenched by addition of saturated potassium sodium tartrate solution (12.0 mL). The reaction mixture was warmed to r.t., and stirred for 30 min at r.t.. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 9:1 to 3:1) to give pure *β*-**21** (1.2:1 epimers, 602.0 mg, 1.16 mmol, 96%) as a colorless oil.

R_f = 0.26 (Hexanes/EtOAc = 3:1)

IR (thin film) ν_{max}/cm^{-1}: 3381, 2956, 2930, 2857, 1612, 1514, 1463, 1361, 1333, 1300, 1249, 1172, 1081, 1059, 1053, 1037, 1004, 974, 835, 774.

^{1}H NMR (400 MHz, $CDCl_3$) *Epimer a*: δ_H = 7.39 – 7.19 (m, 2H), 6.92 – 6.79 (m, 2H), 5.74 – 5.61 (m, 1H), 5.56 – 5.46 (m, 1H), 5.27 (t, *J* = 4.6 Hz, 1H), 5.24 (d, *J* = 5.8 Hz, 1H), 4.73 – 4.59 (m, 1H), 4.44 – 4.37 (m, 1H), 4.32 (q, *J* = 3.8 Hz, 1H), 4.09 – 4.03 (m, 1H), 4.00 (dd, *J* = 10.6, 6.9 Hz, 1H), 3.77 (s, 3H), 3.60 (dd, *J* = 10.4, 6.9 Hz, 1H), 2.23 (dt, *J* = 14.3, 2.6 Hz, 1H), 2.15 – 2.04 (m, 1H), 2.03 – 1.85 (m, 2H), 1.71 (ddd, *J* = 14.0, 9.4, 4.2 Hz, 1H), 1.49 – 1.37 (m, 2H), 1.30 – 1.16 (m, 6H), 0.93 – 0.79 (m, 12H), 0.00 (s, 3H), -0.03 (s, 3H); *Epimer b*: δ_H = 7.39 – 7.19 (m, 2H), 6.92 – 6.79 (m, 2H), 5.74 – 5.61 (m, 1H), 5.56 – 5.46 (m, 1H), 5.18 (dd, *J* = 5.8, 3.2 Hz, 1H), 5.01 (d, *J* = 9.3 Hz, 1H), 4.73 – 4.59 (m, 1H), 4.44 – 4.37 (m, 1H), 4.36 (td, *J* = 4.1, 2.6 Hz, 1H), 4.15 (d, *J* = 8.8 Hz, 1H), 4.09 – 4.03 (m, 1H), 3.77 (s, 3H), 3.01 (s, 1H), 2.15 – 2.04 (m, 1H), 2.03 – 1.85 (m, 3H), 1.81 (dd, *J* = 13.9, 5.9 Hz, 1H), 1.49 – 1.37 (m, 2H), 1.30 – 1.16 (m, 6H), 0.93 – 0.79 (m, 12H), 0.00 (s, 3H), -0.03 (s, 3H).

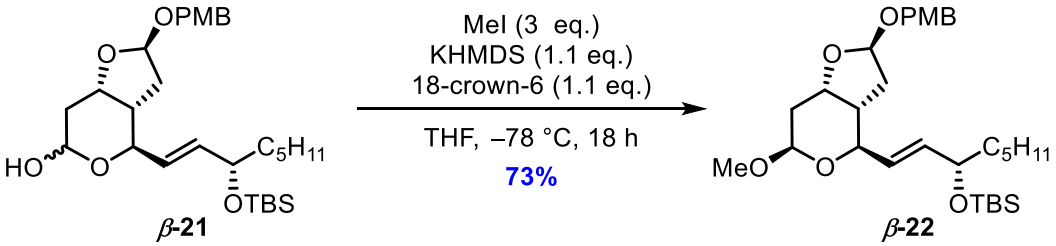
^{13}C NMR (100 MHz, $CDCl_3$) *Epimer a* and *b*: δ_C = 159.4, 159.4, 137.1, 137.1, 130.2, 129.9, 129.7, 129.6, 127.3, 127.0, 114.0, 113.9, 102.4, 102.2, 92.8, 91.3, 77.1, 74.8, 73.4, 72.7, 72.7,

69.7, 69.4, 68.6, 55.4, 40.9, 40.9, 38.4, 36.7, 35.9, 34.0, 31.9, 31.7, 31.1, 26.0, 25.1, 22.8, 22.8, 18.4, 14.3, 14.2, -4.1, -4.7.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{29}H_{48}NaO_6Si$ 543.3112; Found 543.3117.

$[\alpha]_D^{23}$ = –56.67 (*c* 1.00, $CHCl_3$)

***tert*-Butyl(((*S*,*E*)-1-((2*R*,3a*S*,4*R*,6*R*,7a*S*)-6-methoxy-2-((4-methoxybenzyl)oxy)hexahydro-4*H*-furo[3,2-*c*]pyran-4-yl)oct-1-en-3-yl)oxy)dimethylsilane (*β*-22)**



In an oven-dried Schlenk tube, KHMDS (1.0 M in THF, 1.2 mL, 1.16 mmol, 1.1 eq.) was added to a solution of lactol *β*-**21** (546.8 mg, 1.05 mmol, 1.0 eq.) in dry THF (6.2 mL) at –78 °C under N_2 atmosphere, and the reaction mixture was stirred at this temperature for 40 min. Then a solution of 18-crown-6 (306.6 mg, 1.16 mmol, 1.1 eq.) in dry THF (2.1 mL) was added slowly to the above mixture at –78 °C. After stirring for 40 min at –78 °C, methyl iodide (196 µL, 447.1 mg, 3.15 mmol, 3.0 eq.) was added and the reaction mixture was stirred at –78 °C for 18 h. The mixture was quenched by the addition of water (15 mL), and the aqueous phase was extracted with EtOAc (3 × 15 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 15:1 to 9:1) to give pure *β*-**22** (410.2 mg, 0.767 mmol, 73%) as a colorless oil.

R_f = 0.23 (Hexanes/EtOAc = 9:1)

IR (thin film) ν_{max}/cm^{-1}: 2955, 2930, 2856, 1613, 1514, 1463, 1360, 1302, 1249, 1205, 1139, 1085, 1059, 1036, 1005, 969, 835, 775.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.27 (dd, *J* = 6.8, 1.9 Hz, 2H), 6.95 – 6.81 (m, 2H), 5.67 (ddd, *J* = 15.4, 6.1, 0.8 Hz, 1H), 5.54 (ddd, *J* = 15.4, 7.0, 1.1 Hz, 1H), 5.22 (dd, *J* = 5.8, 3.2 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.62 (dd, *J* = 9.2, 2.4 Hz, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.38 (td, *J* = 4.2, 2.7 Hz, 1H), 4.08 (q, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, *J* = 10.5, 6.9 Hz, 1H), 3.48 (s, 3H), 2.17 (dt, *J* = 14.3, 2.6 Hz, 1H), 2.06 – 1.99 (m, 1H), 1.93 (ddd, *J* = 14.1, 7.3, 3.3

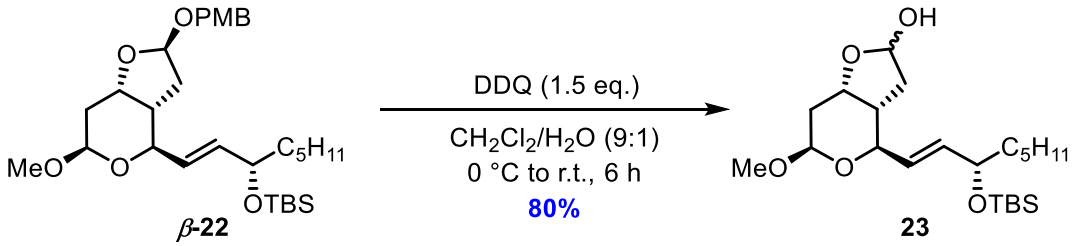
Hz, 1H), 1.88 – 1.75 (m, 2H), 1.51 – 1.40 (m, 2H), 1.34 – 1.23 (m, 6H), 0.93 – 0.82 (m, 12H), 0.04 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 159.4, 137.1, 130.2, 129.6, 127.5, 113.9, 102.3, 99.6, 76.9, 74.8, 73.0, 69.4, 56.3, 55.4, 41.2, 38.3, 35.9, 32.7, 31.9, 26.1, 25.1, 22.8, 18.4, 14.2, -4.1, -4.6.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{30}H_{50}NaO_6Si$ 557.3269; Found 557.3247.

$[\alpha]_D^{24}$ = –72.30 (*c* 1.00, $CHCl_3$)

(3a*S*,4*R*,6*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-6-methoxyhexahydro-4*H*-furo[3,2-*c*]pyran-2-ol (23, from *β*-22)



In a round-bottom flask, a solution of *β*-**22** (320.9 mg, 0.60 mmol, 1.0 eq.) in degassed (N_2) CH_2Cl_2/H_2O (40.0 mL, 9:1 *v/v*) was cooled to 0 °C. Then, fresh recrystalized DDQ (177.1 mg, 0.78 mmol, 1.3 eq.) was added in one portion at 0 °C under N_2 atmosphere. After the reaction mixture was stirred for 3 h at r.t., DDQ (27.2 mg, 0.12 mmol, 0.2 eq.) was added and the mixture was stirred for another 3 h at r.t.. After completion of the reaction, the mixture was poured over saturated $NaHCO_3$ solution (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 10:1 to 3:1) to give pure **23** (3.3:1 epimers, 200 mg, 0.48 mmol, 80%) as a pale-yellow oil.

R_f = 0.17 (Hexanes/EtOAc = 3:1)

IR (thin film) ν_{max}/cm^{-1}: 3428, 2955, 2929, 2856, 1612, 1463, 1395, 1361, 1252, 1204, 1138, 1095, 1055, 1012, 970, 836, 811, 775.

^{1}H NMR (400 MHz, $CDCl_3$) *Epimer a*: δ_H = 5.78 – 5.64 (m, 1H), 5.64 – 5.51 (m, 2H), 4.58 (dd, *J* = 9.3, 2.4 Hz, 1H), 4.48 (td, *J* = 4.2, 2.7 Hz, 1H), 4.17 – 4.02 (m, 1H), 3.59 (dd, *J* = 10.6, 6.9 Hz, 1H), 3.47 (s, 3H), 2.86 (s, 1H), 2.17 – 2.01 (m, 2H), 1.97 – 1.80 (m, 2H), 1.79 – 1.67 (m, 1H), 1.52 – 1.39 (m, 2H), 1.36 – 1.17 (m, 6H), 1.01 – 0.73 (m, 12H), 0.05 (s, 3H), 0.02 (s, 3H); *Epimer b*: δ_H = 5.78 – 5.64 (m, 1H), 5.64 – 5.51 (m, 1H), 5.47 (dd, *J* = 6.0, 2.8 Hz, 1H),

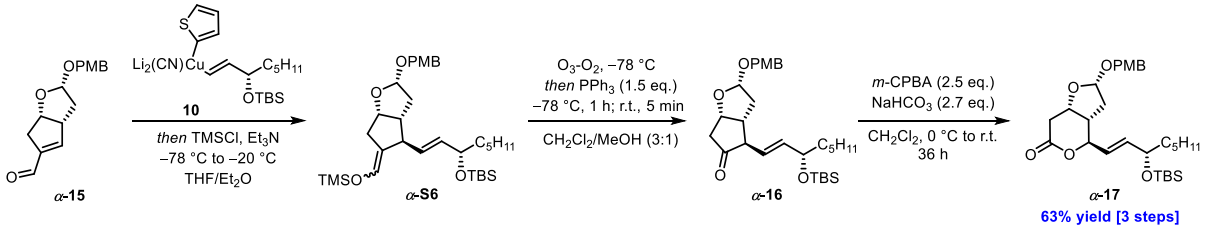
4.68 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.31 – 4.20 (m, 2H), 4.17 – 4.02 (m, 1H), 3.49 (s, 3H), 3.13 (s, 1H), 2.17 – 2.01 (m, 2H), 1.97 – 1.80 (m, 2H), 1.79 – 1.67 (m, 1H), 1.52 – 1.39 (m, 2H), 1.36 – 1.17 (m, 6H), 1.01 – 0.73 (m, 12H), 0.05 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) *Epimer a* and *b*: δ_C = 137.2, 137.1, 127.8, 127.4, 99.5, 99.3, 98.5, 97.8, 76.7, 76.3, 75.1, 73.0, 73.0, 56.3, 56.3, 41.6, 40.5, 38.3, 38.3, 36.9, 36.5, 33.7, 32.8, 31.9, 31.9, 26.1, 26.1, 25.1, 25.1, 22.8, 22.8, 18.4, 14.3, 14.2, -4.1, -4.1, -4.6, -4.6.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{22}H_{42}NaO_5Si$ 437.2694; Found 437.2709.

$[\alpha]_D^{24}$ = –52.24 (*c* 0.49, $CHCl_3$)

(2*S*,3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-((4-methoxybenzyl)oxy)hexahydro-6*H*-furo[3,2-*c*]pyran-6-one (*α*-15)



To a solution of **S5** (3.5 g, 10.8 mmol, 1.2 eq.) in Et_2O (43.2 mL) stirring at –78 °C, *t*-BuLi (1.7 M in pentane, 12.7 mL, 21.6 mmol, 2.4 eq.) was added dropwise and the resulting pale yellow solution was stirred at –78 °C for 2 h prior to warming to –40 °C to stir for a further 2 h before cooling back to –78 °C.

A separate solution of thiophene (866 µL, 909 mg, 10.8 mmol, 1.2 eq.) in THF (43.2 mL) was prepared and cooled to –40 °C and *n*-BuLi (1.6 M in hexanes, 6.8 mL, 10.8 mmol, 1.2 eq.) was added dropwise. The resulting colorless/very pale yellow, clear solution was stirred at –40 °C for 45 min before cooling to –78 °C whereupon CuCN (967 mg, 10.8 mmol, 1.2 eq.) was added in a single portion and the solution was warmed to r.t. The formed thienyl cuprate solution was then added to the above vinyl lithium solution at –78 °C and THF (43.2 mL) was added (used for washing the flask). The bright yellow reaction mixture was warmed to –20 °C to facilitate the formation of cuprate **10**. The reaction mixture was stirred at –20 °C for 1 h before cooling back to –78 °C.

A solution of *α*-**15** (2.5 g, 9.0 mmol, 1.0 eq.) in THF (43.2 mL) was prepared and added to the solution of cuprate **10** at –78 °C to give a bright orange reaction mixture. The reaction mixture was stirred at –78 °C for 1 h before the sequential addition of TMSCl (5.7 mL, 4.9 g, 45.0 mmol, 5.0 eq.) and Et_3N (7.5 mL, 5.5 g, 54.0 mmol, 6.0 eq.). The reaction mixture was warmed to –20 °C to stir for 20 min before quenching by addition of saturated aqueous NH_4Cl solution

(80 mL) and warming to r.t.. The aqueous phase was extracted with EtOAc (3 × 80 mL), the organic phases were then combined, washed further with saturated aqueous $Na_2S_2O_3$ solution (80 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude *α*-**S6** as a brown oil, which was used directly in the next step.

In a round-bottom flask, a solution of crude *α*-**S6** in CH_2Cl_2/MeOH (72 mL, 3:1 *v/v*) was cooled to –78 °C and a stream of O_3-O_2 (g) was bubbled through the reaction solution. The reaction progress was carefully monitored by TLC (Hexanes/EtOAc = 6:1) until a small amount of *α*-**S6** remained (~7.0 min). The reaction mixture was then purged of O_3 (g) by bubbling N_2 (g) through the solution for 20 min followed by the addition of freshly ground PPh_3 (3.5 g, 13.5 mmol, 1.5 eq.). The reaction was stirred at –78 °C for 1 h before the dry ice/acetone bath was removed and the reaction was allowed to warm to r.t., at which point it was stirred for a further 5 min. The reaction mixture was then poured over saturated brine solution (80 mL) and extracted with EtOAc (3 × 80 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude *α*-**16** as a brown oil, which was used directly in the next step.

In a round-bottom flask, a solution of crude *α*-**16** in dry CH_2Cl_2 (90 mL) was cooled to 0 °C. Then, *m*-CPBA (77% purity, 5.0 g, 22.5 mmol, 2.5 eq.) and $NaHCO_3$ (2.0 g, 24.3 mmol, 2.7 eq.) were added to the above mixture at 0 °C under N_2 atmosphere, and the mixture was stirred for 36 h at r.t. The reaction mixture was diluted with EtOAc and poured over saturated brine solution (80 mL) and extracted with EtOAc (3 × 80 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc =10:1 to 4:1) to give pure *α*-**17** (2.95 g, 5.7 mmol, 63%) as a colorless oil.

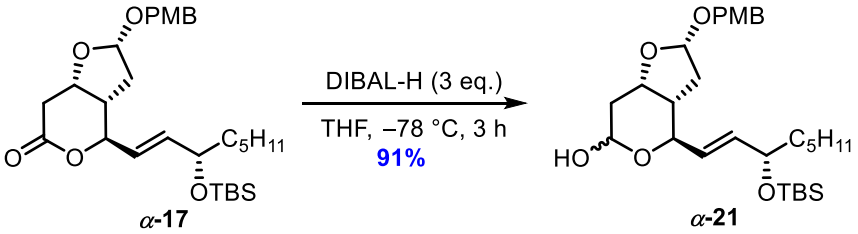
$\boldsymbol{R_f}$ = 0.31 (Hexanes/EtOAc = 4:1)

IR (thin film) $\boldsymbol{\nu_{max}}$/cm^{-1}: 2954, 2930, 2857, 1754, 1613, 1514, 1463, 1348, 1301, 1248, 1082, 1029, 970, 835, 775.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.25 – 7.19 (m, 2H), 6.96 – 6.81 (m, 2H), 5.84 (ddd, *J* = 15.4, 5.5, 0.9 Hz, 1H), 5.61 (ddd, *J* = 15.5, 7.4, 1.3 Hz, 1H), 5.21 (d, *J* = 4.9 Hz, 1H), 4.92 (dd, *J* = 10.7, 7.4 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.57 (td, *J* = 8.9, 6.9 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.18 – 4.07 (m, 1H), 3.81 (s, 3H), 3.05 (dd, *J* = 14.5, 6.9 Hz, 1H), 2.73 (dd, *J* = 14.5, 9.3 Hz, 1H), 2.48 (tdd, *J* = 10.1, 8.4, 1.3 Hz, 1H), 2.15 (ddd, *J* = 13.7, 10.1, 5.0 Hz, 1H), 1.95 – 1.83 (m, 1H), 1.53 – 1.40 (m, 2H), 1.37 – 1.22 (m, 6H), 0.94 – 0.83 (m, 12H), 0.05 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 171.1, 159.5, 139.7, 129.6, 129.5, 124.7, 114.1, 103.8, 80.6, 75.7, 72.4, 69.0, 55.4, 42.5, 38.1, 37.9, 35.5, 31.9, 26.0, 24.9, 22.7, 18.4, 14.2, -4.2, -4.7.
HRMS (ESI) m/z: $[M+ NH_4]^+$ Calcd. for $C_{29}H_{50}NO_6Si$ 536.3136; Found 536.3129.
$[\alpha]_D^{25}$ = +106.3 (*c* 1.00, $CHCl_3$)

(2*S*,3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-((4-methoxybenzyl)oxy)hexahydro-4*H*-furo[3,2-*c*]pyran-6-ol (*α*-21)



To a solution of *α*-**17** (259.4 mg, 0.50 mmol, 1.0 eq.) in dry THF (5.0 mL) at –78 °C under N_2 atmosphere, diisobutylaluminium hydride (1.0 M in hexanes, 1.5 mL, 1.5 mmol, 3.0 eq.) was added dropwisely. The reaction mixture was stirred at –78 °C for 3 h and quenched by addition of saturated potassium sodium tartrate solution (5.0 mL). The reaction mixture was warmed to r.t., and stirred for 30 min at r.t.. The aqueous phase was extracted with EtOAc (3 × 5 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 9:1 to 3:1) to give pure *α*-**21** (1.4:1 epimers, 235.9 mg, 0.45 mmol, 91%) as a colorless oil.

***R*$_f$** = 0.28 (Hexanes/EtOAc = 3:1)
IR (thin film) ν_{max}/cm^{-1}: 3418, 2955, 2931, 2858, 1614, 1514, 1463, 1359, 1302, 1249, 1173, 1110, 1058, 1033, 978, 835, 775.

^{1}H NMR (400 MHz, $CDCl_3$) *Epimer a*: δ_H = 7.30 – 7.19 (m, 2H), 6.92 – 6.78 (m, 2H), 5.80 – 5.66 (m, 1H), 5.63 – 5.47 (m, 1H), 5.20 – 5.09 (m, 1H), 5.04 (ddd, *J* = 9.1, 5.2, 2.3 Hz, 1H), 4.77 – 4.66 (m, 1H), 4.48 – 4.31 (m, 2H), 4.27 (td, *J* = 4.4, 2.9 Hz, 1H), 4.12 – 4.00 (m, 2H), 3.77 (s, 3H), 2.28 – 1.95 (m, 3H), 1.94 – 1.87 (m, 1H), 1.83 – 1.70 (m, 1H), 1.51 – 1.38 (m, 2H), 1.35 – 1.18 (m, 6H), 0.87 (d, *J* = 6.9 Hz, 12H), 0.03 (s, 3H), 0.01 (s, 3H); *Epimer b*: δ_H = 7.30 – 7.19 (m, 2H), 6.92 – 6.78 (m, 2H), 5.80 – 5.66 (m, 1H), 5.63 – 5.47 (m, 1H), 5.24 (dt, *J* = 9.0, 3.5 Hz, 1H), 5.20 – 5.09 (m, 1H), 4.77 – 4.66 (m, 1H), 4.63 (dd, *J* = 10.5, 6.9 Hz, 1H), 4.48 – 4.31 (m, 2H), 4.20 (q, *J* = 4.5 Hz, 1H), 4.12 – 4.00 (m, 1H), 3.77 (s, 3H), 2.28 – 1.95

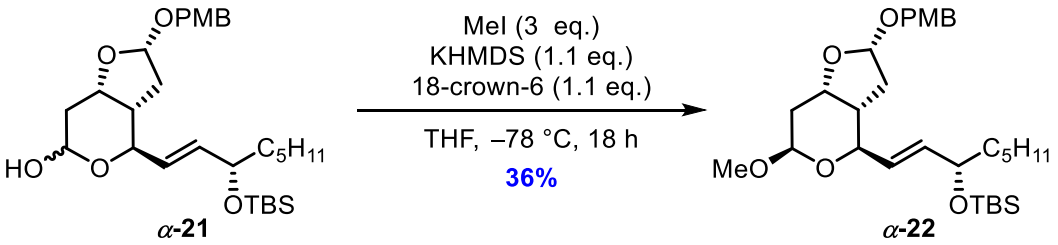
(m, 3H), 1.83 – 1.70 (m, 2H), 1.51 – 1.38 (m, 2H), 1.35 – 1.18 (m, 6H), 0.87 (d, *J* = 6.9 Hz, 12H), 0.03 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *Epimer a* and *b*: δ_C = 159.3, 159.1, 136.8, 136.78, 130.1, 129.6, 129.5, 129.2, 127.7, 127.5, 113.9, 113.8, 103.7, 102.8, 92.6, 91.4, 77.9, 76.1, 76.0, 72.7, 72.7, 70.2, 69.1, 68.4, 55.2, 40.2, 40.0, 38.2, 36.2, 35.6, 34.9, 32.4, 31.8, 25.9, 25.0, 22.6, 18.3, 14.1, -4.2, -4.8, -4.8.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{29}H_{48}NaO_6Si$ 543.3112; Found 543.3122.

$[\alpha]_D^{24}$ = +54.83 (*c* 2.00, $CHCl_3$)

tert-Butyl(((*S*,*E*)-1-((2*S*,3a*S*,4*R*,6*R*,7a*S*)-6-methoxy-2-((4-methoxybenzyl)oxy)hexahydro-4*H*-furo[3,2-*c*]pyran-4-yl)oct-1-en-3-yl)oxy)dimethylsilane (*α*-22)



In an oven-dried Schlenk tube, KHMDS (1.0 M in THF, 0.32 mL, 0.317 mmol, 1.1 eq.) was added to a solution of lactol *α*-**21** (150.0 mg, 0.288 mmol, 1.0 eq.) in dry THF (1.7 mL) at –78 °C under N_2 atmosphere, and the reaction mixture was stirred at this temperature for 40 min. Then a solution of 18-crown-6 (83.8 mg, 0.317 mmol, 1.1 eq.) in dry THF (0.6 mL) was added slowly to the above mixture at –78 °C. After stirring for 40 min at –78 °C, methyl iodide (54 µL, 122.6 mg, 0.864 mmol, 3.0 eq.) was added and the reaction mixture was stirred at –78 °C for 20 h. The mixture was quenched by the addition of water (5 mL), and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 15:1 to 8:1) to give pure *α*-**22** (55.5 mg, 0.104 mmol, 36%) as a colorless oil.

***R*$_f$** = 0.24 (Hexanes/EtOAc = 8:1)

IR (thin film) ν_{max}/cm^{-1}: 2954, 2929, 2857, 1614, 1514, 1463, 1361, 1301, 1249, 1207, 1173, 1136, 1054, 1034, 967, 835, 775.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.27 – 7.22 (m, 2H), 6.97 – 6.75 (m, 2H), 5.67 (ddd, *J* = 15.4, 6.1, 0.8 Hz, 1H), 5.52 (ddd, *J* = 15.4, 7.0, 1.0 Hz, 1H), 5.11 (dd, *J* = 6.1, 1.0 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.57 (dd, *J* = 8.8, 2.3 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.30 – 4.20

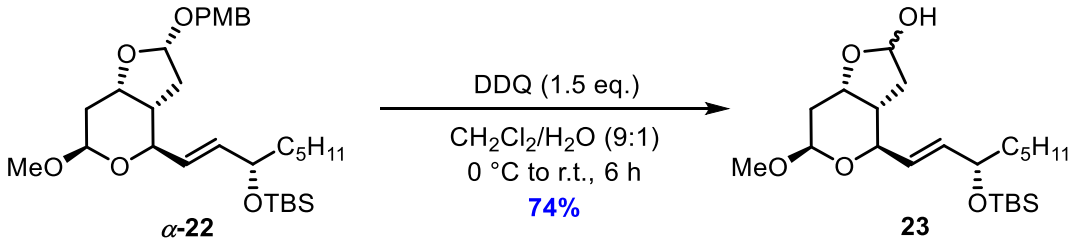
(m, 2H), 4.11 – 4.03 (m, 1H), 3.78 (s, 3H), 3.44 (s, 3H), 2.12 (dt, *J* = 14.2, 2.7 Hz, 1H), 2.05 (ddd, *J* = 13.7, 7.5, 6.2 Hz, 1H), 1.90 (ddd, *J* = 10.5, 7.3, 4.9 Hz, 1H), 1.81 – 1.68 (m, 2H), 1.52 – 1.38 (m, 2H), 1.34 – 1.20 (m, 6H), 0.89 – 0.80 (m, 12H), 0.02 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 159.2, 136.8, 130.4, 129.3, 128.0, 113.9, 103.1, 99.4, 77.8, 75.9, 73.1, 69.4, 56.2, 55.4, 40.3, 38.2, 35.7, 33.9, 31.9, 26.1, 25.1, 22.8, 18.4, 14.2, -4.1, -4.6.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{30}H_{50}NaO_6Si$ 557.3269; Found 557.3287.

$[\alpha]_D^{24}$ = +55.02 (*c* 0.83, $CHCl_3$)

(3a*S*,4*R*,6*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-6-methoxyhexahydro-4*H*-furo[3,2-*c*]pyran-2-ol (23, from *α*-22)



In a round-bottom flask, a solution of *α*-**22** (27.0 mg, 50.5 µmol, 1.0 eq.) in degassed (N_2) CH_2Cl_2/H_2O (3.4 mL, 9:1 *v*/*v*) was cooled to 0 °C. Then, fresh recrystalized DDQ (14.9 mg, 65.7 µmol, 1.3 eq.) was added in one portion at 0 °C under N_2 atmosphere. After the reaction mixture was stirred for 3 h at r.t., DDQ (2.3 mg, 10.1 µmol, 0.2 eq.) was added and the mixture was stirred for another 3 h at r.t.. After completion of the reaction, the mixture was poured over saturated $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 10:1 to 3:1) to give pure **23** (3.2:1 epimers, 15.5 mg, 37.4 µmol, 74%) as a pale-yellow oil.

***R*$_f$** = 0.17 (Hexanes/EtOAc = 3:1)

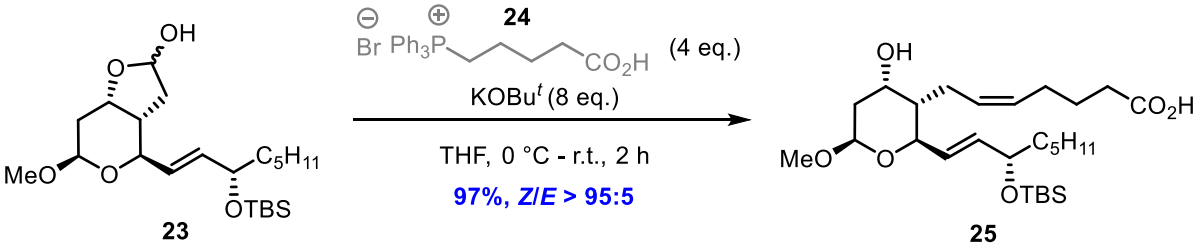
^{1}H NMR (400 MHz, $CDCl_3$) *Epimer a*: δ_H = 5.78 – 5.64 (m, 1H), 5.64 – 5.51 (m, 2H), 4.58 (dd, *J* = 9.3, 2.4 Hz, 1H), 4.48 (td, *J* = 4.2, 2.7 Hz, 1H), 4.16 – 4.03 (m, 1H), 3.59 (dd, *J* = 10.6, 6.9 Hz, 1H), 3.47 (s, 3H), 2.76 (d, *J* = 3.2 Hz, 3H), 2.19 – 2.01 (m, 2H), 1.99 – 1.81 (m, 2H), 1.80 – 1.68 (m, 1H), 1.54 – 1.40 (m, 2H), 1.35 – 1.23 (m, 6H), 0.95 – 0.84 (m, 12H), 0.05 (s, 3H), 0.03 (s, 3H); *Epimer b*: δ_H = 5.78 – 5.64 (m, 1H), 5.64 – 5.51 (m, 1H), 5.47 (dd, *J* = 5.7, 3.4 Hz, 1H), 4.69 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.30 – 4.19 (m, 2H), 4.15 – 4.03 (m, 1H), 3.49 (s,

3H), 3.00 (d, *J* = 3.4 Hz, 1H), 2.19 – 2.01 (m, 2H), 1.99 – 1.81 (m, 2H), 1.80 – 1.68 (m, 1H), 1.54 – 1.40 (m, 2H), 1.35 – 1.23 (m, 6H), 0.95 – 0.84 (m, 12H), 0.05 (s, 3H), 0.03 (s, 3H).

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{22}H_{42}NaO_5Si$ 437.2694; Found 437.2707.

$[\alpha]_D^{24}$ = –52.02 (*c* 0.62, $CHCl_3$)

(*Z*)-7-((2*R*,3*S*,4*S*,6*R*)-2-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-4-hydroxy-6-methoxytetrahydro-2*H*-pyran-3-yl)hept-5-enoic acid (25)



KOBu^t (1.0 M in THF, 3.4 mL, 3.36 mmol, 8.0 eq.) was added to a stirring suspension of (4-carboxybutyl)triphenylphosphonium bromide (744.8 mg, 1.68 mmol, 4.0 eq.) in THF (8.4 mL) at 0 °C under N_2 atmosphere. The resulting orange suspension was stirred at 0 °C for 1 h. Lactol **23** (174.2 mg, 0.42 mmol, 1.0 eq.) was added as a solution in THF (2.8 mL) to the orange suspension and the reaction was stirred at 0 °C for 2 h. The reaction mixture was quenched by addition of water (10 mL), adjusted to pH 3.0 by addition of 0.1 N aqueous HCl in ice bath, and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product (*Z*/*E* > 95:5) was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 10:1 with 1% AcOH to Hexanes/EtOAc = 2:1 with 1% AcOH) to give pure **25** (203.7 mg, 0.41 mmol, 97%) as a colorless oil.

***R*$_f$** = 0.27 (Hexanes/EtOAc = 2:1 with 1% AcOH)

IR (thin film) ν_{max}/cm^{-1}: 3480, 2954, 2929, 2856, 1709, 1452, 1394, 1360, 1251, 1199, 1137, 1087, 1059, 1031, 969, 889, 835, 775.

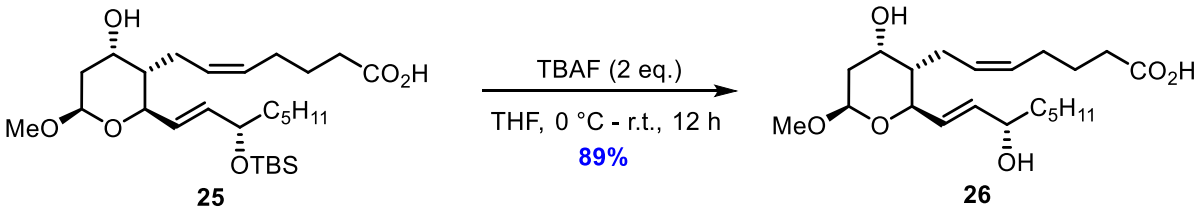
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.68 (dd, *J* = 15.4, 6.3 Hz, 1H), 5.55 (ddd, *J* = 15.4, 7.8, 0.9 Hz, 1H), 5.45 – 5.31 (m, 2H), 4.74 (dd, *J* = 9.7, 2.1 Hz, 1H), 4.20 – 4.06 (m, 2H), 4.03 (dd, *J* = 10.3, 7.8 Hz, 1H), 3.47 (s, 3H), 2.35 (td, *J* = 7.2, 3.2 Hz, 2H), 2.16 (dt, *J* = 14.2, 7.1 Hz, 1H), 2.12 – 1.83 (m, 4H), 1.75 – 1.56 (m, 3H), 1.56 – 1.39 (m, 3H), 1.37 – 1.18 (m, 6H), 0.88 (s, 12H), 0.05 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 178.9, 137.9, 130.6, 128.3, 128.3, 98.9, 75.6, 73.2, 66.3, 56.3, 44.8, 39.4, 38.2, 33.3, 31.9, 26.6, 26.1, 25.1, 24.8, 24.7, 22.7, 18.4, 14.1, -4.1, -4.6.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{27}H_{50}NaO_6Si$ 521.3269; Found 521.3251.

$[\alpha]_D^{24}$ = +1.33 (*c* 1.00, $CHCl_3$)

(*Z*)-7-((2*R*,3*S*,4*S*,6*R*)-4-Hydroxy-2-((*S*,*E*)-3-hydroxyoct-1-en-1-yl)-6-methoxytetrahydro-2*H*-pyran-3-yl)hept-5-enoic acid (26)



To a solution of **25** (43.0 mg, 86.2 µmol, 1.0 eq.) in dry THF (0.86 mL) at 0 °C under N_2 atmosphere, TBAF (1.0 M in THF, 170 µL, 172 µmol, 2.0 eq.) was added dropwisely and the resulting reaction mixture was stirred for 10 min at 0 °C. Then, the mixture was warmed to r.t. and stirred for another 12 h. The mixture was poured over brine and extracted with EtOAc (3 × 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 10:1 with 1% AcOH to Hexanes/EtOAc = 1:2 with 1% AcOH) to give pure **26** (29.4 mg, 76.5 µmol, 89%) as a colorless oil.

***R*f** = 0.39 (Hexanes/EtOAc = 1:2 with 1% AcOH)

IR (thin film) ν_{max}/cm^{-1}: 3418, 2954, 2925, 2855, 1709, 1550, 1449, 1395, 1378, 1346, 1242, 1197, 1136, 1087, 1059, 1027, 971, 912, 886, 713.

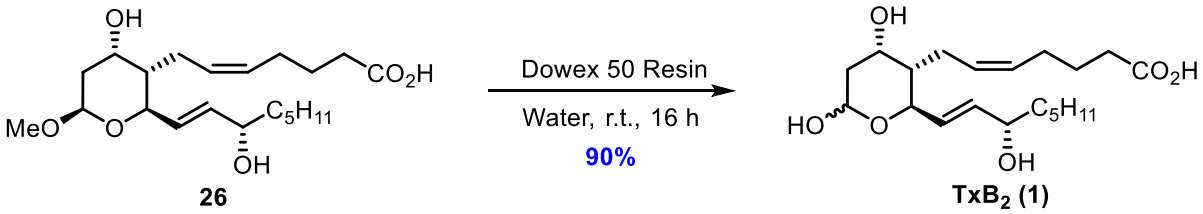
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.79 (dd, *J* = 15.6, 5.7 Hz, 1H), 5.69 (ddd, *J* = 15.6, 7.3, 1.0 Hz, 1H), 5.49 – 5.36 (m, 2H), 4.76 (dd, *J* = 9.8, 2.1 Hz, 1H), 4.74 (br. s, 2H), 4.21 – 4.14 (m, 2H), 4.06 (dd, *J* = 10.3, 7.3 Hz, 1H), 3.48 (s, 3H), 2.33 (dd, *J* = 7.3, 6.1 Hz, 2H), 2.18 – 2.07 (m, 2H), 2.06 – 1.90 (m, 3H), 1.75 – 1.58 (m, 3H), 1.58 – 1.48 (m, 2H), 1.48 – 1.37 (m, 2H), 1.34 – 1.24 (m, 5H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 177.5, 136.4, 130.8, 129.2, 127.8, 99.1, 75.3, 72.4, 66.0, 56.5, 45.2, 39.3, 36.9, 32.9, 31.8, 26.5, 25.2, 24.6, 24.4, 22.7, 14.1.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{21}H_{36}NaO_6$ 407.2404; Found 407.2400.

$[\alpha]_D^{25}$ = +20.00 (*c* 0.70, $CHCl_3$)

(*Z*)-7-((2*R*,3*S*,4*S*)-4,6-Dihydroxy-2-((*S*,*E*)-3-hydroxyoct-1-en-1-yl)tetrahydro-2*H*-pyran-3-yl)hept-5-enoic acid (TxB$_2$,1)



Thromboxane B_2 methyl glycoside **26** (30.0 mg, 78.0 μmol, 1.0 eq.), Dowex 50 resin (2.1 g) and water (6.5 mL) were combined. The suspension was stirred overnight to completely hydrolyze the methyl glycoside. The reaction mixture was filtered through a medium porosity frit to remove the resin, and the resin was washed sequentially with DCM (3 × 3.0 mL) and EtOAc (3 × 3.0 mL). The mixture was concentrated *in vacuo*, and dried overnight under high vacuum to give thromboxane B_2 (26 mg, 70.2 μmol, 90% yield) as a colorless solid.

We have tried several deuterated solvents (CD_3OD, $CDCl_3$, CD_2Cl_2, 6D-DMSO, and D-8 toluene), but we found that the natural product (TxB_2) was difficult to characterize by NMR because it had a tendency to aggregate. This observation matched with previous report by Steven D. Burke (ref.: Org. Lett. ***2007****, 9, 5353–5356). In his paper he stated: "Esterification of the carboxylic acid with trimethylsilyldiazomethane (****23b****) intersected the methyl ester of TXB_2 methyl glycoside previously synthesized by Hanessian to provide an intermediate for direct spectroscopic comparison. We also subjected methyl glycoside* ***23a*** *to hydrolysis with DOWEX-50 resin in water to provide thromboxane B_2 (****5****). In our hands, the natural product was difficult to characterize by NMR because it has a tendency to aggregate in deuterated chloroform. However, high resolution mass spectrometry did confirm methyl glycoside hydrolysis. As further confirmation of the synthesis of TXB_2, we derivatized the natural product to the triacetate of the methyl ester (****23c****). This derivative matched published data in terms of both HRMS and ^1H NMR." Burke did not provide NMR data for the final compound, TxB_2. Indeed, no NMR data has been reported of TxB_2 over the last few decades due to this nature. However, the final compound (TxB_2) was confirmed by high resolution mass spectrometry, mp. and $[\alpha]_D$ which all matched the literature, confirming its purity. For comparison, we have included the ^1H NMR of our sample with that of a commercial sample from Cayman in this SI (See below).*

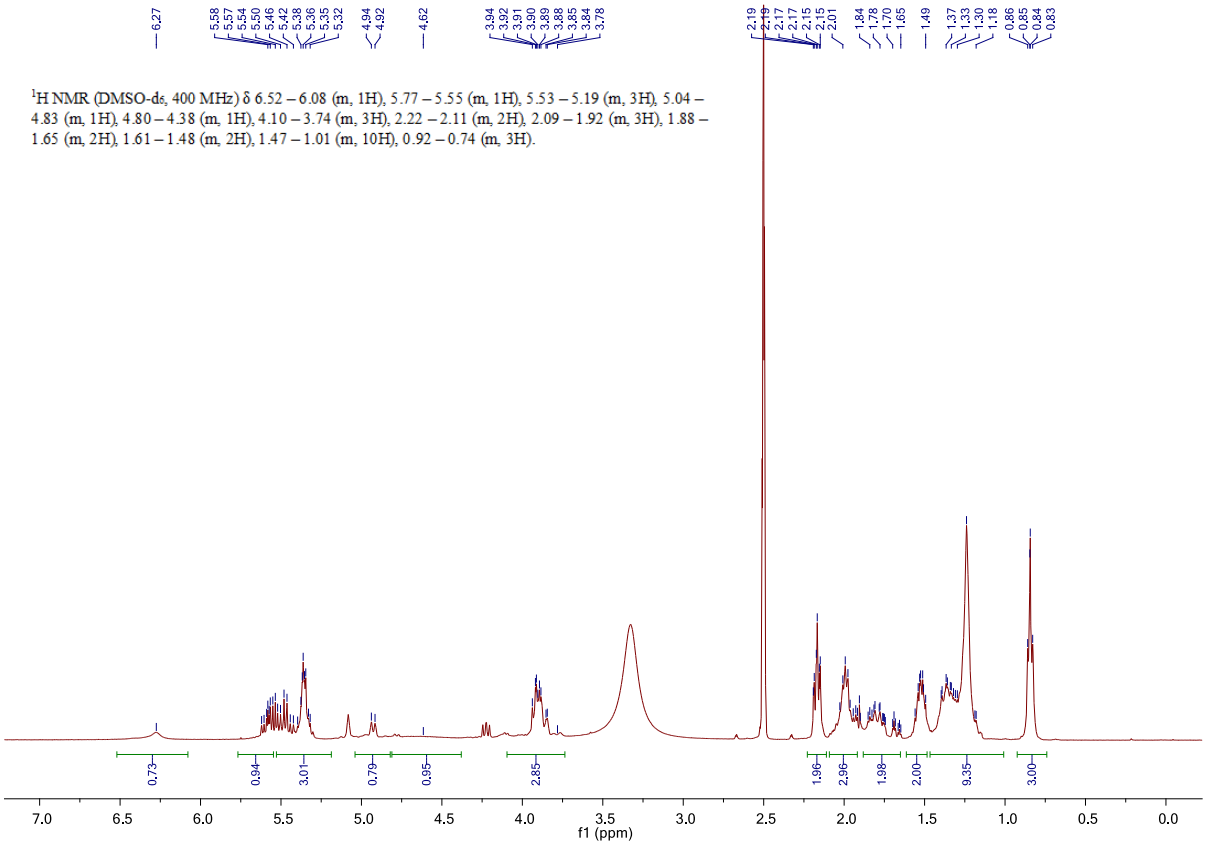
Mp 91 – 94 °C

$\boldsymbol{R_f}$ = 0.21 (Hexanes/EtOAc = 1:3 with 1% AcOH)

IR (thin film) $\boldsymbol{\nu_{max}}$/cm^{-1}: 3430, 2955, 2926, 2856, 1707, 1550, 1449, 1396, 1379, 1348, 1248, 1197, 1087, 1059, 1027, 974, 887, 716.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{20}H_{34}NaO_6$ 393.2248; Found 393.2246.

$[\alpha]_D^{24}$ = +57.10 (*c* 1.0, EtOH)



^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 6.52 – 6.08 (m, 1H), 5.77 – 5.55 (m, 1H), 5.53 – 5.19 (m, 3H), 5.04 – 4.83 (m, 1H), 4.80 – 4.38 (m, 1H), 4.10 – 3.74 (m, 3H), 2.22 – 2.11 (m, 2H), 2.09 – 1.92 (m, 3H), 1.88 – 1.65 (m, 2H), 1.61 – 1.48 (m, 2H), 1.47 – 1.01 (m, 10H), 0.92 – 0.74 (m, 3H).

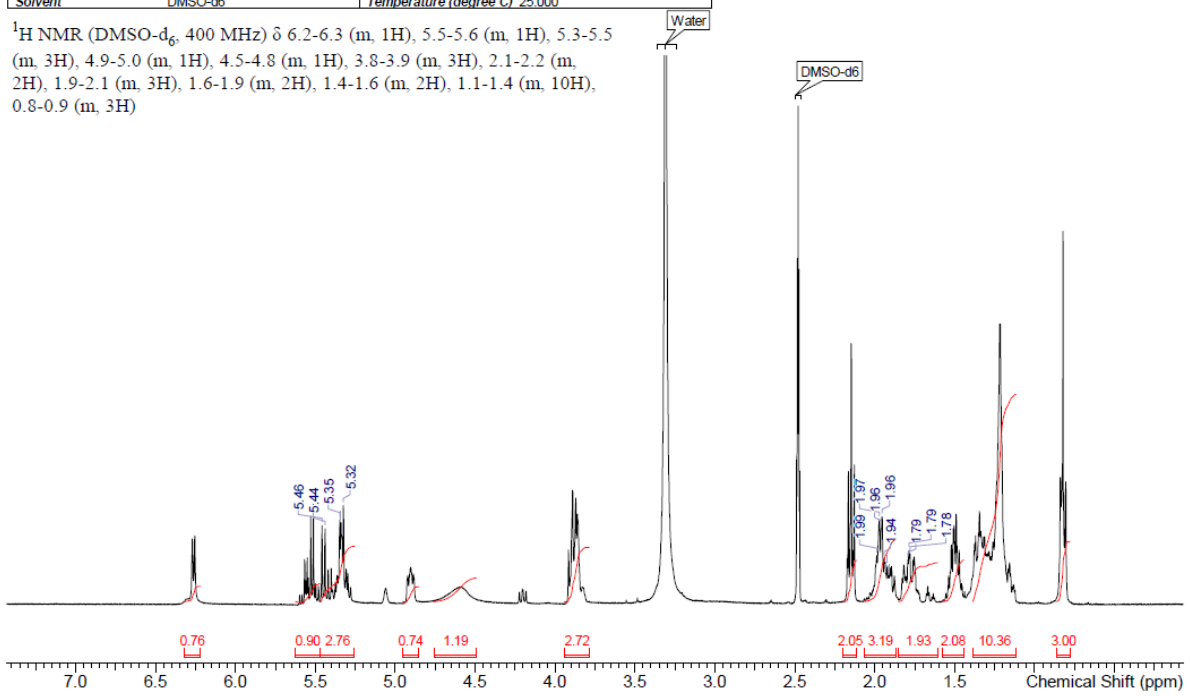
Thromboxane B2

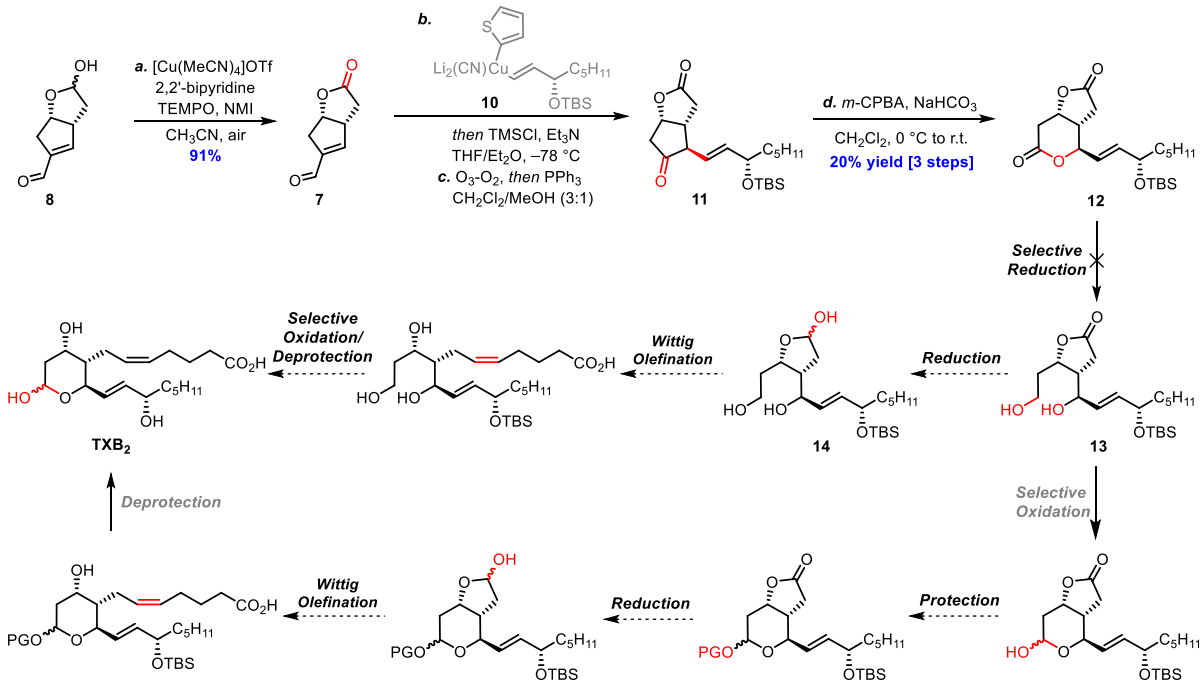
Item #19030

Batch #0456533

Date	Apr 27 2018				
File Name	\\sulfur\private\nmrdata_2018\SMC-19030-0456533_20180427_\SMC-19030-0456533_20180427_01\SMC-19030-0456533_20180427_001.fid\fid				
Frequency (MHz)	399.9680	*Nucleus*	1H	*Number of Transients*	32
Solvent	DMSO-d6	*Temperature (degree C)*	25.000		

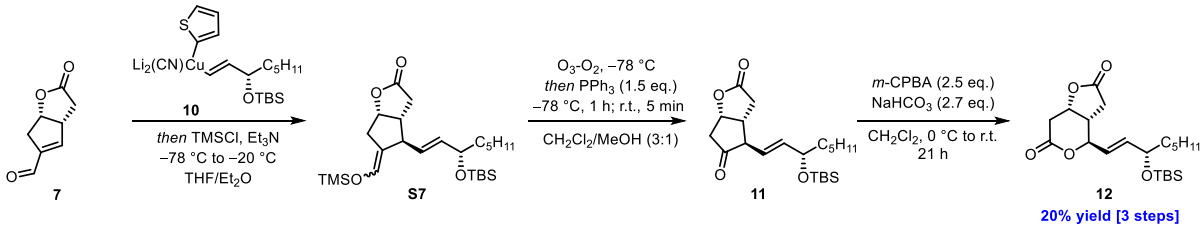
^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 6.2-6.3 (m, 1H), 5.5-5.6 (m, 1H), 5.3-5.5 (m, 3H), 4.9-5.0 (m, 1H), 4.5-4.8 (m, 1H), 3.8-3.9 (m, 3H), 2.1-2.2 (m, 2H), 1.9-2.1 (m, 3H), 1.6-1.9 (m, 2H), 1.4-1.6 (m, 2H), 1.1-1.4 (m, 10H), 0.8-0.9 (m, 3H)





Scheme S2. Possible routes and attempts to thromboxane B_2 via the formation of dilactone 12. *Reagents and conditions:* (a) [Cu(MeCN)$_4$]OTf (5 mol %), 2'-Bipyridine (5 mol %), TEMPO (5 mol %), NMI (10 mol %), CH_3CN, Air, r.t., overnight, 91% yield. (b) Cuprate **10** (1.2 eq.), THF/Et_2O, −78 °C; then TMSCl (5 eq.), Et_3N (6 eq.), −78 °C to −20 °C. (c) O_3-O_2, CH_2Cl_2/MeOH (*v*/*v*, 3:1), −78 °C; then PPh_3 (1.5 eq.). (d) *m*-CPBA (2.5 eq.), $NaHCO_3$ (2.7 eq.), CH_2Cl_2, 0 °C to r.t., 36 h, 20% yield, 3 steps. TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy. NMI, *N*-methylimidazole. TBS, *tert*-butyldimethylsilyl. TMS, trimethylsilyl. *m*-CPBA, *m*-chloroperoxybenzoic acid. DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

(3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)tetrahydro-4*H*-furo[3,2-*c*]pyran-2,6-dione (12)



To a solution of **S5** (772.0 mg, 2.4 mmol, 1.2 eq.) in Et_2O (9.6 mL) stirring at –78 °C, *t*-BuLi (1.7 M in pentane, 2.8 mL, 4.8 mmol, 2.4 eq.) was added dropwise and the resulting pale yellow solution was stirred at –78 °C for 2 h prior to warming to –40 °C to stir for a further 2 h before cooling back to –78 °C.

A separate solution of thiophene (192 µL, 202.4 mg, 2.4 mmol, 1.2 eq.) in THF (9.6 mL) was prepared and cooled to –40 °C and *n*-BuLi (1.6 M in hexanes, 1.5 mL, 2.4 mmol, 1.2 eq.) was added dropwise. The resulting colorless/very pale yellow, clear solution was stirred at –40 °C for 45 min before cooling to –78 °C whereupon CuCN (215.2 mg, 2.4 mmol, 1.2 eq.) was

added in a single portion and the solution was warmed to r.t. The formed thienyl cuprate solution was then added to the above vinyl lithium solution at –78 °C and THF (9.6 mL) was added (used for washing the flask). The bright yellow reaction mixture was warmed to –20 °C to facilitate the formation of cuprate **10**. The reaction mixture was stirred at –20 °C for 1 h before cooling back to –78 °C.

A solution of **7** (304.3 mg, 2.0 mmol, 1.0 eq.) in THF (9.6 mL) was prepared and added to the solution of cuprate **10** at –78 °C to give a bright orange reaction mixture. The reaction mixture was stirred at –78 °C for 1 h before the sequential addition of TMSCl (1.3 mL, 1.09 g, 10.0 mmol, 5.0 eq.) and NEt_3 (1.7 mL, 1.22 g, 12.0 mmol, 6.0 eq.). The reaction mixture was warmed to –20 °C to stir for 20 min before quenching by addition of saturated aqueous NH_4Cl solution (24 mL) and warming to r.t.. The aqueous phase was extracted with EtOAc (3 × 24 mL), the organic phases were then combined, washed further with saturated aqueous $Na_2S_2O_3$ solution (24 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude **S7** as a brown oil, which was used directly in the next step.

In a round-bottom flask, a solution of crude **S7** in CH_2Cl_2/MeOH (16 mL, 3:1 *v/v*) was cooled to –78 °C and a stream of O_3-O_2 (g) was bubbled through the reaction solution. The reaction progress was carefully monitored by TLC (Hexanes/EtOAc = 6:1) until a small amount of **S7** remained (~6.0 min). The reaction mixture was then purged of O_3 (g) by bubbling N_2 (g) through the solution for 20 min followed by the addition of freshly ground PPh_3 (786.9 mg, 3.0 mmol, 1.5 eq.). The reaction was stirred at –78 °C for 1 h before the dry ice/acetone bath was removed and the reaction was allowed to warm to r.t., at which point it was stirred for a further 5 min. The reaction mixture was then poured over saturated brine solution (24 mL) and extracted with EtOAc (3 × 24 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude **11** as a brown oil, which was used directly in the next step.

In a round-bottom flask, a solution of crude **11** in dry CH_2Cl_2 (20 mL) was cooled to 0 °C. Then, *m*-CPBA (77% purity, 1.12 g, 5.0 mmol, 2.5 eq.) and $NaHCO_3$ (453.7 mg, 5.4 mmol, 2.7 eq.) were added to the above mixture at 0 °C under N_2 atmosphere, and the mixture was stirred for 21 h at r.t. The reaction mixture was diluted with EtOAc and poured over water (24 mL) and extracted with EtOAc (3 × 24 mL). The organic phases were combined, washed with 5% $Na_2S_2O_3$ solution (18 mL), 5% Na_2CO_3 solution (18 mL), saturated brine solution (18 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 10:1 to 2:1) to give pure **12** (158.6 g, 0.4 mmol, 20%) as a colorless oil.

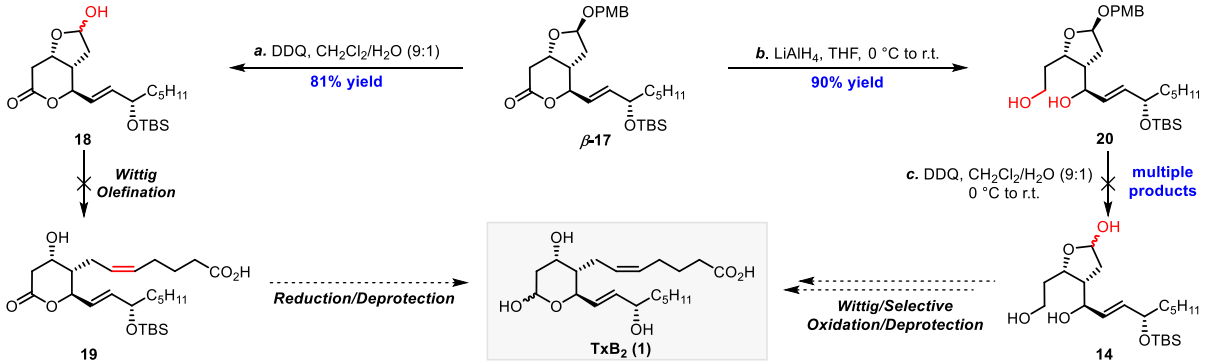
***R*f** = 0.38 (Hexanes/EtOAc = 2:1)

IR (thin film) ν_{max}/cm^{-1}: 2955, 2929, 2857, 1760, 1617, 1463, 1364, 1250, 1170, 1078, 967, 834, 775.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.93 (dd, *J* = 15.4, 5.0 Hz, 1H), 5.62 (ddd, *J* = 15.4, 7.4, 1.4 Hz, 1H), 4.95 (q, *J* = 7.4 Hz, 1H), 4.71 – 4.53 (m, 1H), 4.17 (q, *J* = 5.7, 5.2 Hz, 1H), 3.24 (dd, *J* = 15.7, 7.3 Hz, 1H), 2.90 – 2.66 (m, 3H), 2.38 (dd, *J* = 18.0, 2.1 Hz, 1H), 1.54 – 1.44 (m, 2H), 1.35 – 1.24 (m, 6H), 0.97 – 0.83 (m, 12H), 0.06 (s, 3H), 0.02 (s, 3H).

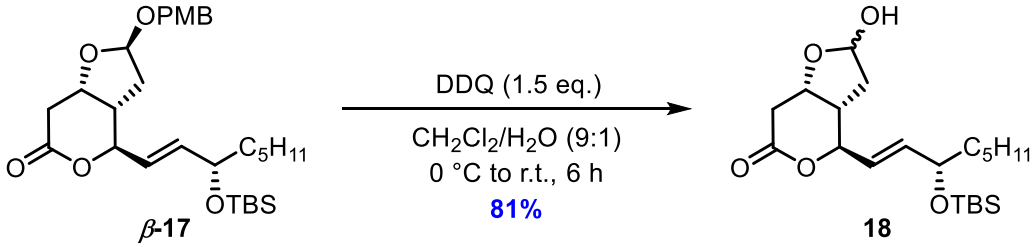
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 173.95, 167.97, 141.59, 122.61, 79.04, 74.07, 71.79, 38.56, 37.85, 35.39, 31.75, 30.41, 25.84, 24.73, 22.59, 18.21, 14.02, -4.41, -4.80.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{21}H_{36}NaO_5Si$ 419.2225; Found 419.2230.



Scheme S3. Additional attempts to thromboxane B$_2$ from ketone *β*-17. *Reagents and conditions:* (a) DDQ (1.5 eq.), CH_2Cl_2/H_2O (*v*/*v*, 9:1), 0 °C to r.t., 6 h, 81% yield. (b) $LiAlH_4$ (1.2 eq.), THF, 0 °C to r.t., 6 h, 90% yield. (c) DDQ (1.5 eq.), CH_2Cl_2/H_2O (*v*/*v*, 9:1), 0 °C to r.t., 6 h, messy. PMB, *p*-methoxybenzyl. TBS, *tert*-butyldimethylsilyl. DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

(3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-hydroxyhexahydro-6*H*-furo[3,2-*c*]pyran-6-one (18)



In a round-bottom flask, a solution of ***β*-17** (555.1 mg, 1.07 mmol, 1.0 eq.) in degassed (N_2) CH_2Cl_2/H_2O (42.8 mL, 9:1 *v*/*v*) was cooled to 0 °C. Then, fresh recrystalized DDQ (315.8 mg, 1.39 mmol, 1.3 eq.) was added in one portion at 0 °C under N_2 atmosphere. After the reaction mixture was stirred for 3 h at r.t., DDQ (48.6 mg, 0.21 mmol, 0.2 eq.) was added and the mixture was stirred for another 3 h at r.t.. After completion of the reaction, the mixture was

poured over saturated $NaHCO_3$ solution (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 9:1 to 7:3) to give pure **18** (1.6:1 epimers, 345.5 mg, 0.87 mmol, 81%) as a pale-yellow oil.

$\boldsymbol{R_f}$ = 0.31 (Hexanes/EtOAc = 7:3)

IR (thin film) $\boldsymbol{\nu_{max}}$/cm^{-1}: 3419, 2954, 2929, 2857, 1748, 1471, 1463, 1359, 1251, 1145, 1082, 1014, 971, 861, 835, 809, 775.

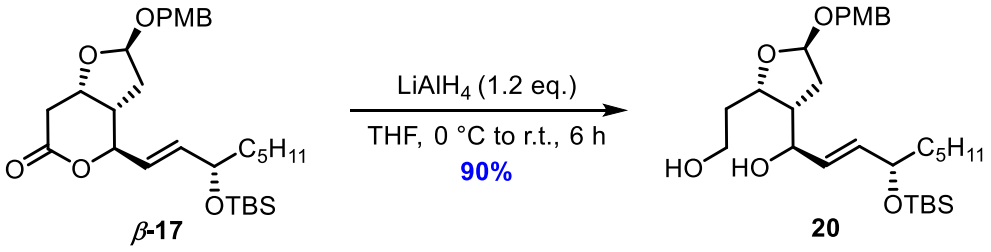
^{1}H NMR (400 MHz, $CDCl_3$) *Epimer a*: δ_H = 5.97 – 5.79 (m, 1H), 5.74 – 5.46 (m, 2H), 4.65 (q, *J* = 7.5 Hz, 1H), 4.61 – 4.46 (m, 1H), 4.23 – 4.07 (m, 1H), 3.11 – 2.94 (m, 1H), 2.91 – 2.75 (m, 1H), 2.68 (qd, *J* = 8.8, 7.0 Hz, 1H), 2.59 (dd, *J* = 15.4, 7.5 Hz, 1H), 2.20 – 2.04 (m, 1H), 1.76 (dt, *J* = 12.8, 6.1 Hz, 1H), 1.55 – 1.42 (m, 2H), 1.36 – 1.22 (m, 6H), 0.98 – 0.78 (m, 12H), 0.04 (s, 2H), 0.01 (s, 2H); *Epimer b*: δ_H = 5.97 – 5.79 (m, 1H), 5.74 – 5.46 (m, 2H), 5.01 (dd, *J* = 10.7, 7.5 Hz, 1H), 4.61 – 4.46 (m, 1H), 4.23 – 4.07 (m, 1H), 3.11 – 2.94 (m, 2H), 2.91 – 2.75 (m, 1H), 2.48 (tdd, *J* = 10.1, 8.3, 1.5 Hz, 1H), 2.20 – 2.04 (m, 1H), 1.87 (d, *J* = 13.7 Hz, 1H), 1.55 – 1.42 (m, 2H), 1.36 – 1.22 (m, 6H), 0.98 – 0.78 (m, 12H), 0.05 (s, 2H), 0.02 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) *Epimer a* and *b*: δ_C = 171.2, 170.6, 139.9, 139.3, 124.6, 124.4, 99.5, 98.4, 80.8, 80.7, 75.7, 72.9, 72.3, 72.3, 42.6, 40.8, 38.4, 38.1, 38.1, 36.2, 35.9, 35.5, 31.9, 26.0, 25.9, 25.0, 24.9, 22.7, 22.7, 18.4, 18.3, 14.2, -4.2, -4.2, -4.7, -4.7.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{21}H_{38}NaO_5Si$ 421.2380; Found 421.2370.

$[\alpha]_D^{23}$ = –42.44 (*c* 1.00, $CHCl_3$)

(1*R*,4*S*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-((2*S*,3*R*,5*R*)-2-(2-hydroxyethyl)-5-((4-methoxybenzyl)oxy)tetrahydrofuran-3-yl)non-2-en-1-ol (20)



To a solution of *β*-**17** (51.9 mg, 0.10 mmol, 1.0 eq.) in dry THF (2.0 mL) at 0 °C under N_2 atmosphere, $LiAlH_4$ (1.0 M in THF, 0.12 mL, 0.12 mmol, 1.2 eq.) was added dropwisely. After stirring at this temperature for 5 min, the reaction mixture was warmed to r.t. and stirred for

another 6 h. The reaction was quenched by addition of $Na_2SO_4 \cdot 10H_2O$ and 10% NaOH solution. The above mixture was stirred at r.t. for 10 min before $MgSO_4$ (*s*) was added and stirred for a further 5 min prior to sinter filtration. After washing with EtOAc (3 × 5 mL), the filtrate was concentrated in *vacuo* and purified by flash column chromatography on silica gel (Hexanes/EtOAc = 2:1 to 1:1) to give pure **20** (47.0 mg, 0.09 mmol, 90%) as a colorless oil.

$\boldsymbol{R_f}$ = 0.12 (Hexanes/EtOAc = 1:1)

IR (thin film) $\boldsymbol{\nu_{max}}$/cm^{-1}: 3405, 2955, 2931, 2854, 1740, 1491, 1461, 1360, 1250, 1135, 1062, 1011, 863, 809, 776.

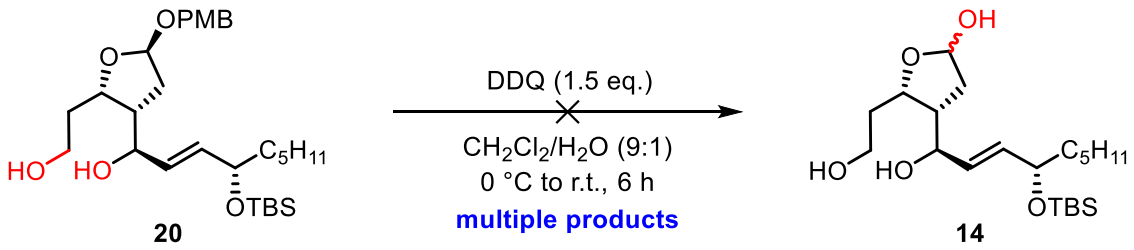
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.26 – 7.22 (m, 2H), 6.93 – 6.83 (m, 2H), 5.65 (dd, *J* = 15.4, 5.6 Hz, 1H), 5.57 (ddd, *J* = 15.4, 7.1, 0.8 Hz, 1H), 5.14 (dd, *J* = 5.2, 1.1 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.45 (td, *J* = 7.3, 3.6 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.11 – 4.02 (m, 2H), 3.92 – 3.85 (m, 2H), 3.80 (s, 3H), 2.80 (br. s, 1H), 2.65 – 2.57 (m, 1H), 2.08 – 2.01 (m, 1H), 1.87 – 1.76 (m, 2H), 1.73 – 1.66 (m, 1H), 1.56 – 1.36 (m, 3H), 1.31 – 1.23 (m, 6H), 0.89 (s, 12H), 0.04 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 159.3, 136.7, 130.8, 130.3, 129.6, 113.9, 101.8, 80.8, 72.8, 72.7, 68.8, 62.5, 55.4, 45.9, 38.3, 35.7, 32.6, 31.9, 26.0, 25.0, 22.7, 18.4, 14.2, -4.1, -4.6.

HRMS (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{29}H_{50}NaO_6Si$ 545.3269; Found 545.3271.

$[\alpha]_D^{22}$ = –32.34 (*c* 1.00, $CHCl_3$)

Attempt to 14 from 20



In a small round-bottom flask, a solution of **20** (8.4 mg, 16.0 µmol, 1.0 eq.) in degassed (N_2) CH_2Cl_2/H_2O (0.64 mL, 9:1 *v/v*) was cooled to 0 °C. Then, fresh recrystalized DDQ (4.7 mg, 20.8 µmol, 1.3 eq.) was added in one portion at 0 °C under N_2 atmosphere. After the reaction mixture was stirred for 3 h at r.t., DDQ (0.7 mg, 3.2 µmol, 0.2 eq.) was added and the mixture was stirred for another 3 h at r.t.. *Upon completion, the reaction was monitored by TLC, and the result showed that deprotection of the PMB group of **20** was not clean.* The mixture was poured over saturated $NaHCO_3$ solution (1 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and

concentrated *in vacuo*. *Then the reaction mixture was monitored by crude* ^{1}H *NMR, and the result showed that deprotection of the PMB group of* ***20*** *gave multiple products.*

Notes and References

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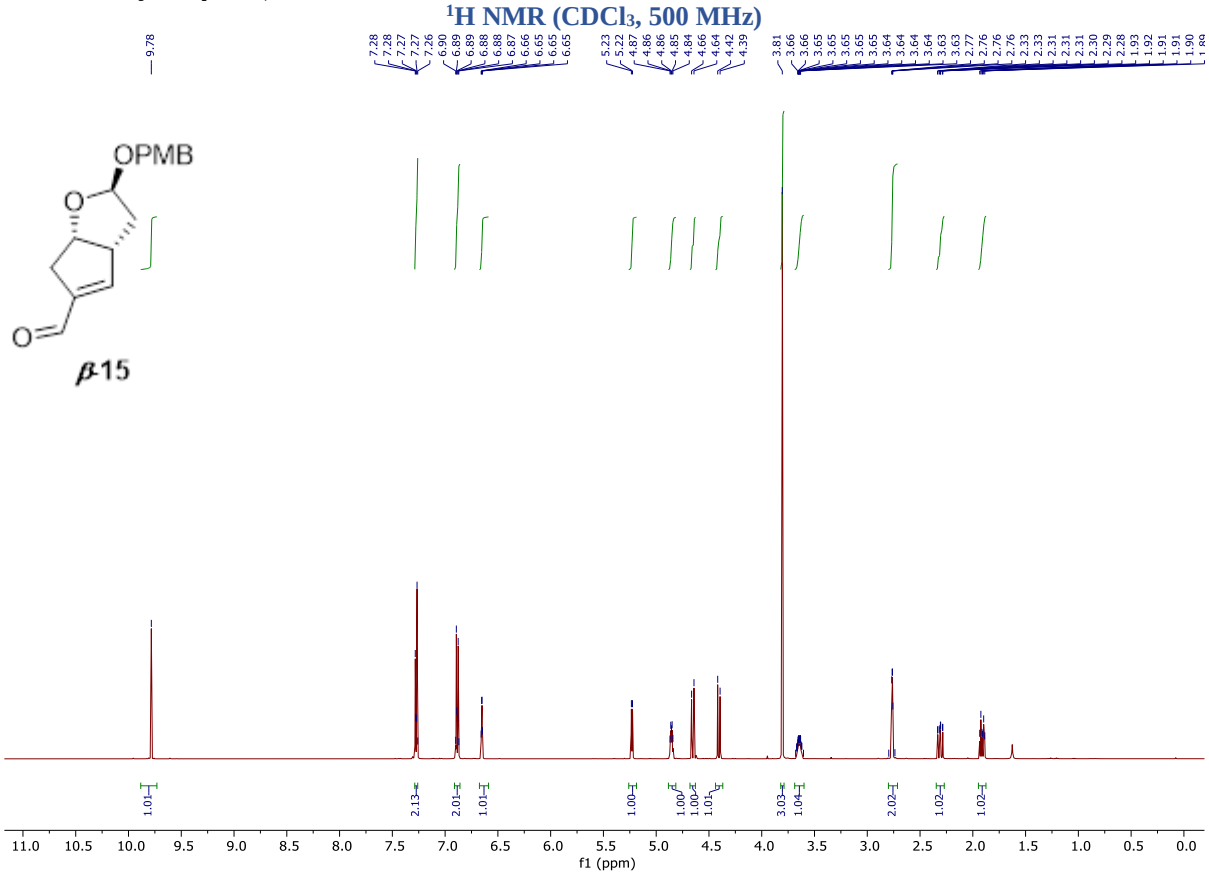
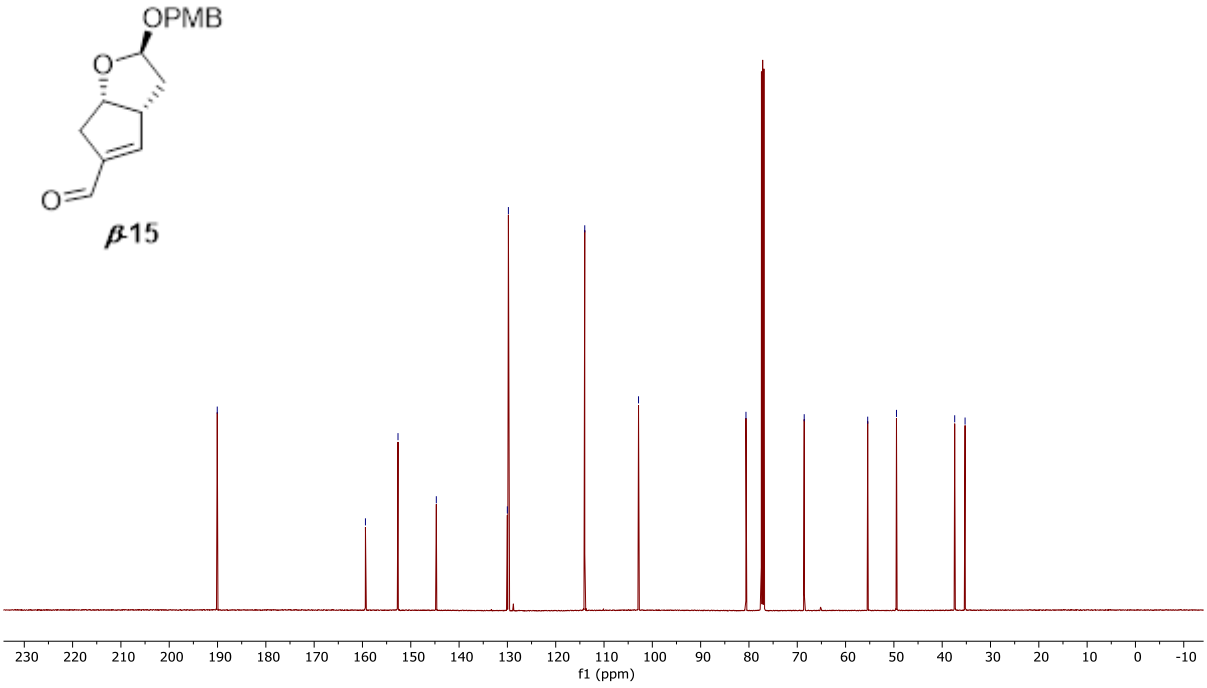
NMR Spectra for the Products

(2*R*,3a*R*,6a*S*)-2-((4-Methoxybenzyl)oxy)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-5-carbaldehyde (*β*-15)

^{1}H NMR ($CDCl_3$, 500 MHz)

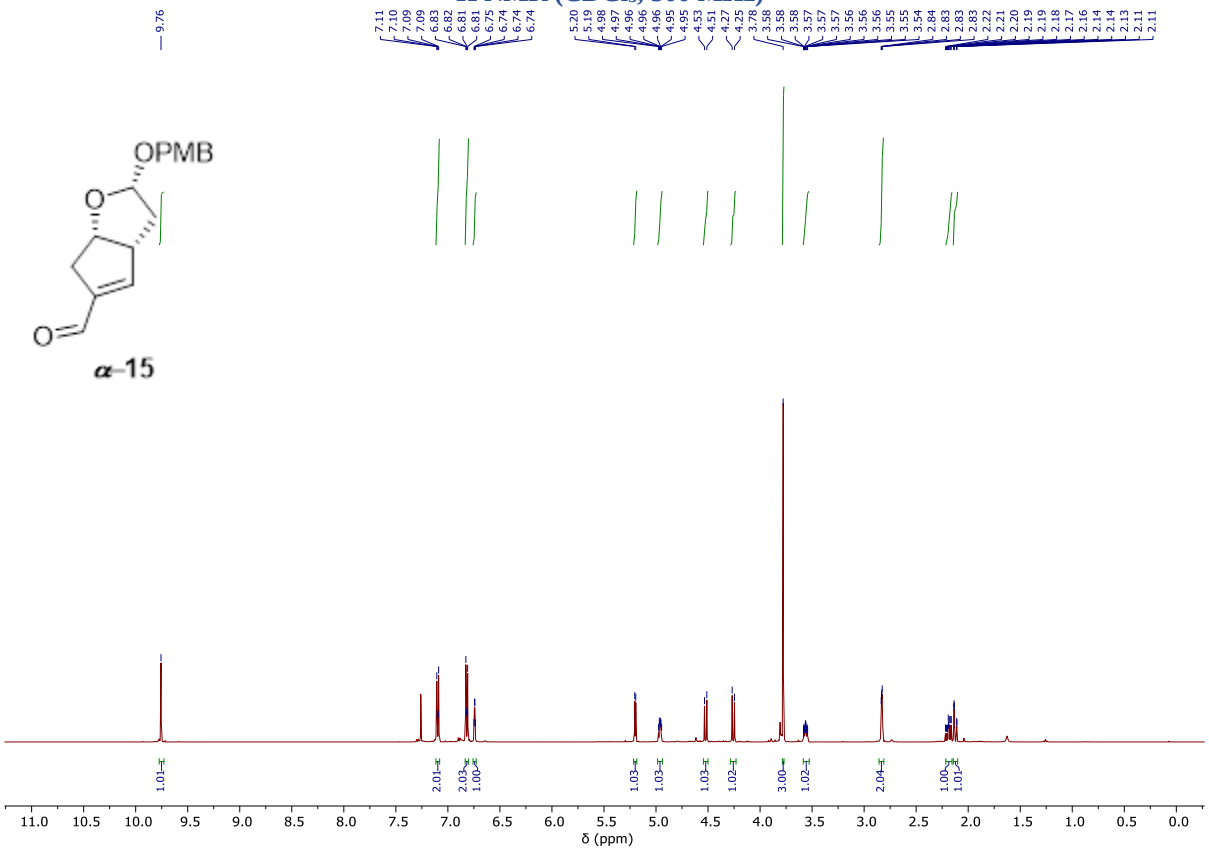


^{13}C NMR ($CDCl_3$, 125 MHz)

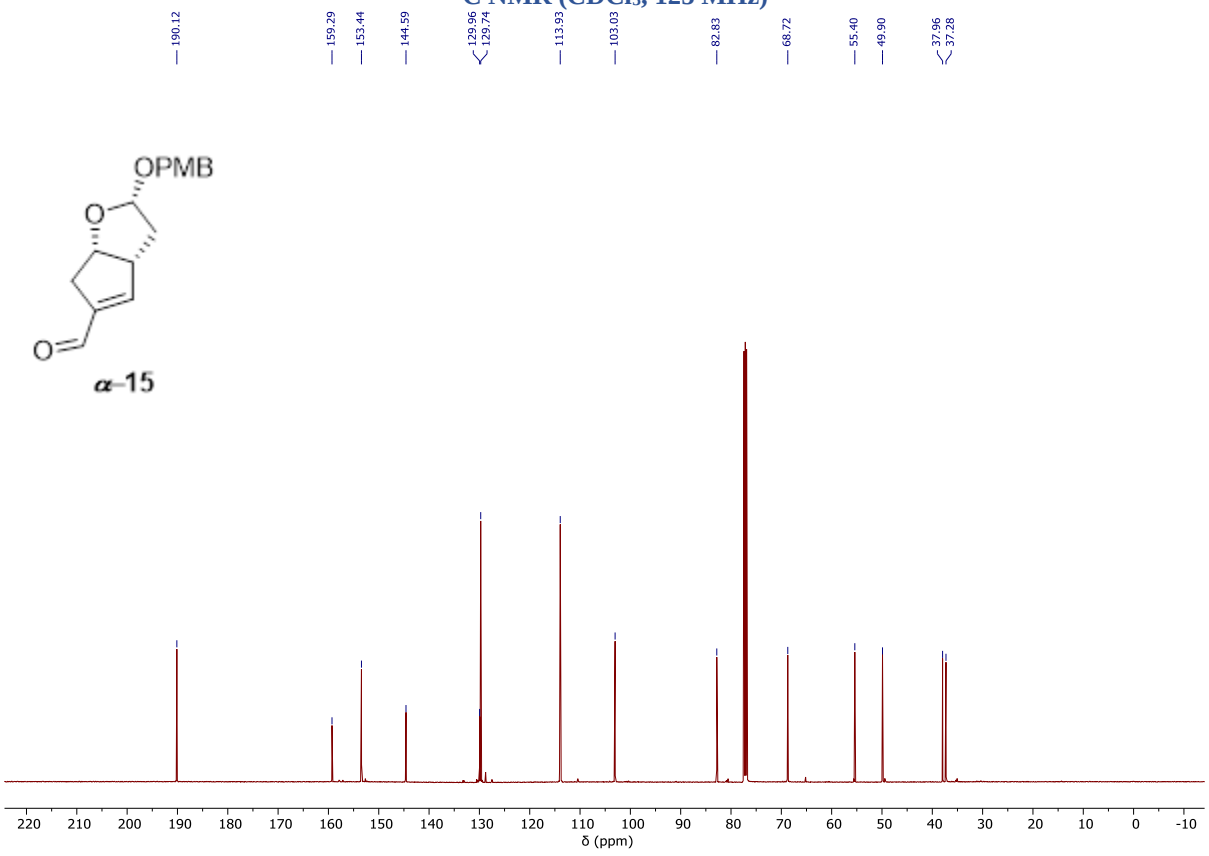


(2*S*,3a*R*,6a*S*)-2-((4-methoxybenzyl)oxy)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-5-carbaldehyde (*α*-15)

^{1}H NMR ($CDCl_3$, 500 MHz)

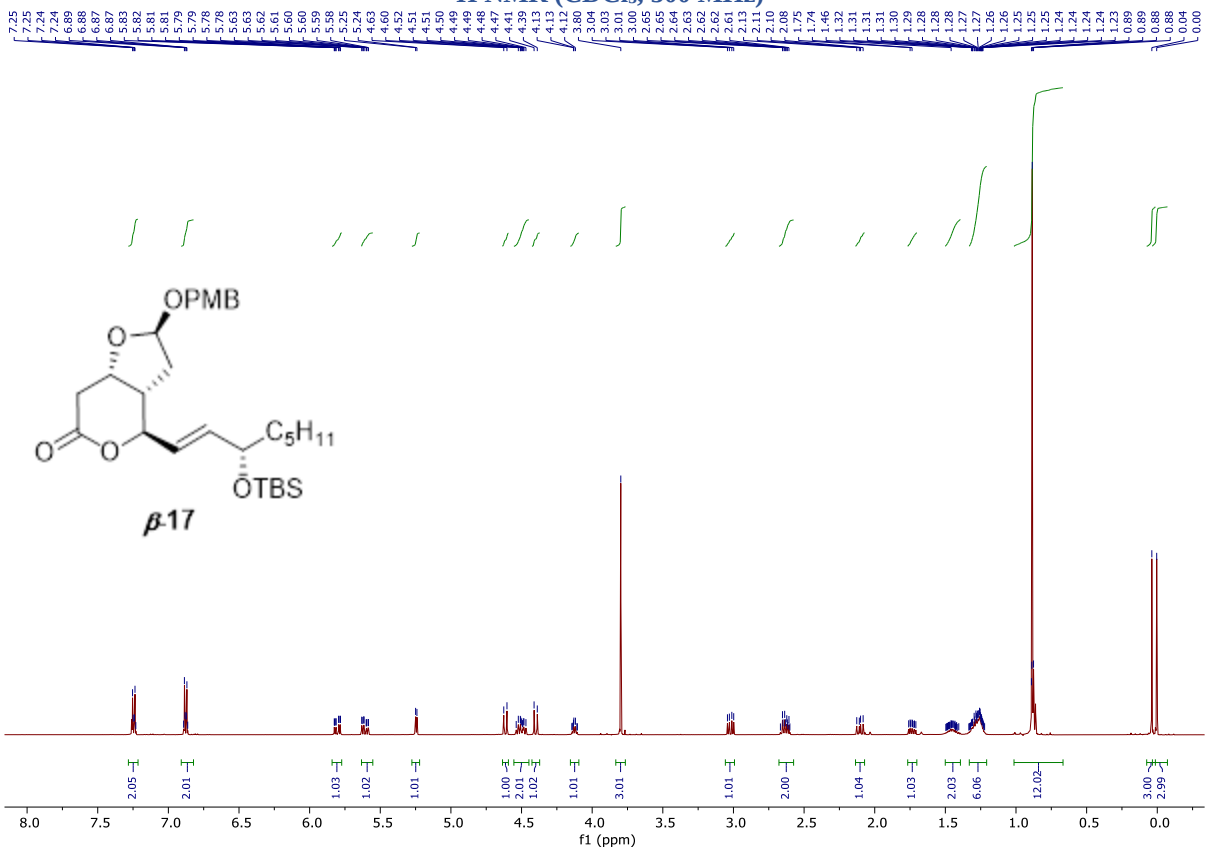


^{13}C NMR ($CDCl_3$, 125 MHz)

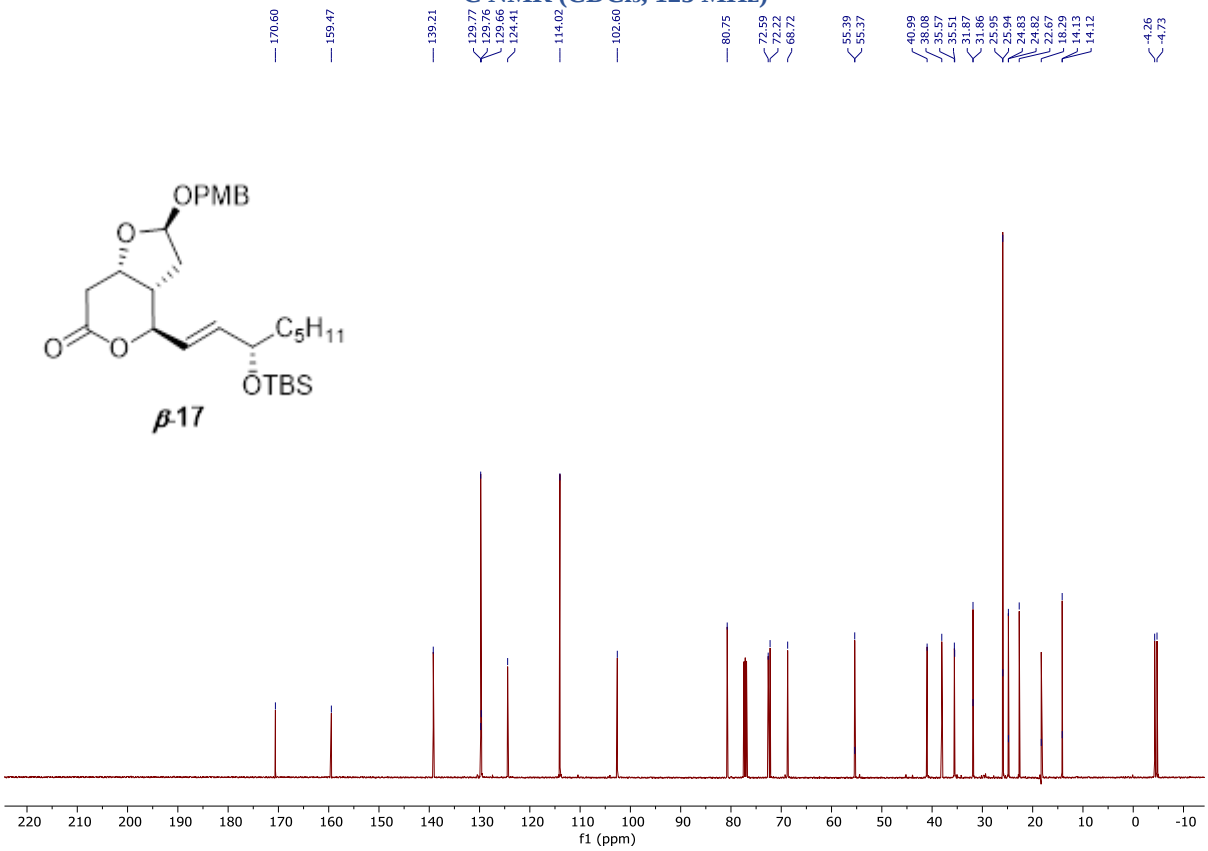


(2*R*,3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-((4-methoxybenzyl)oxy)hexahydro-6*H*-furo[3,2-*c*]pyran-6-one (*β*-17)

^{1}H NMR ($CDCl_3$, 500 MHz)

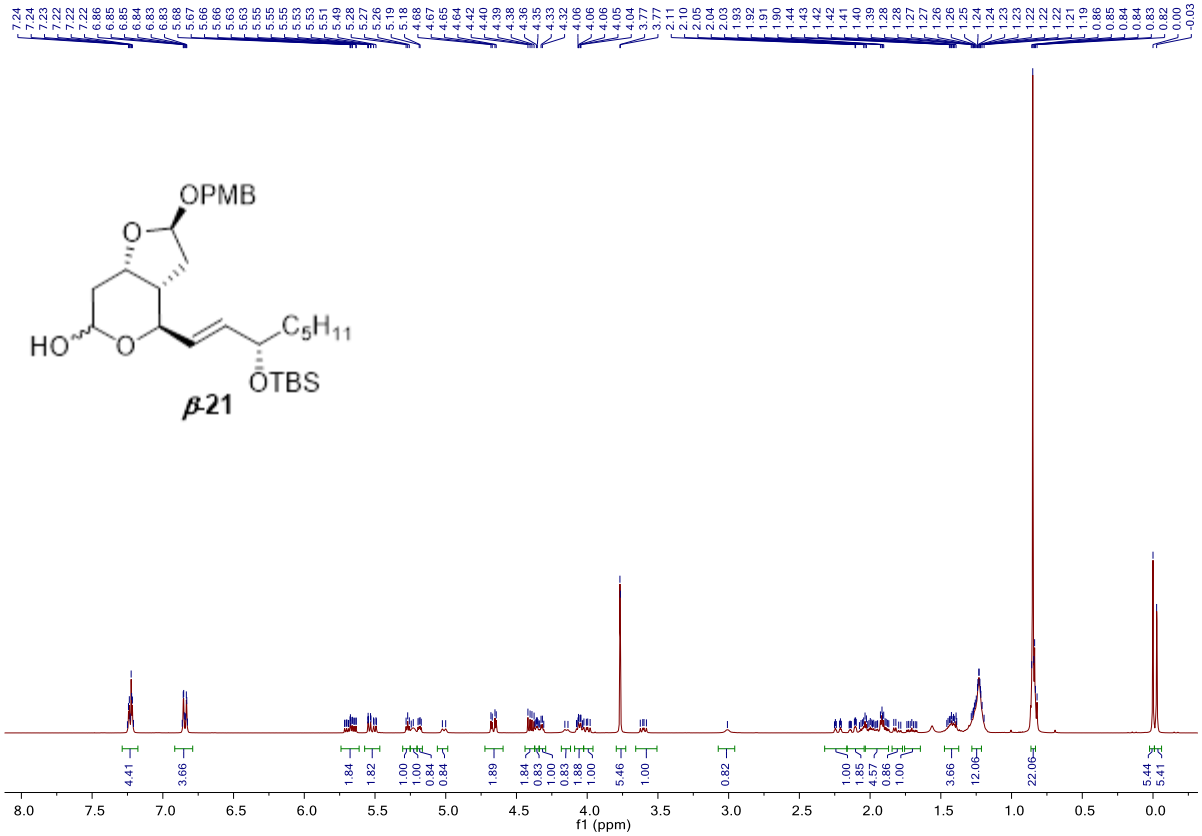


^{13}C NMR ($CDCl_3$, 125 MHz)

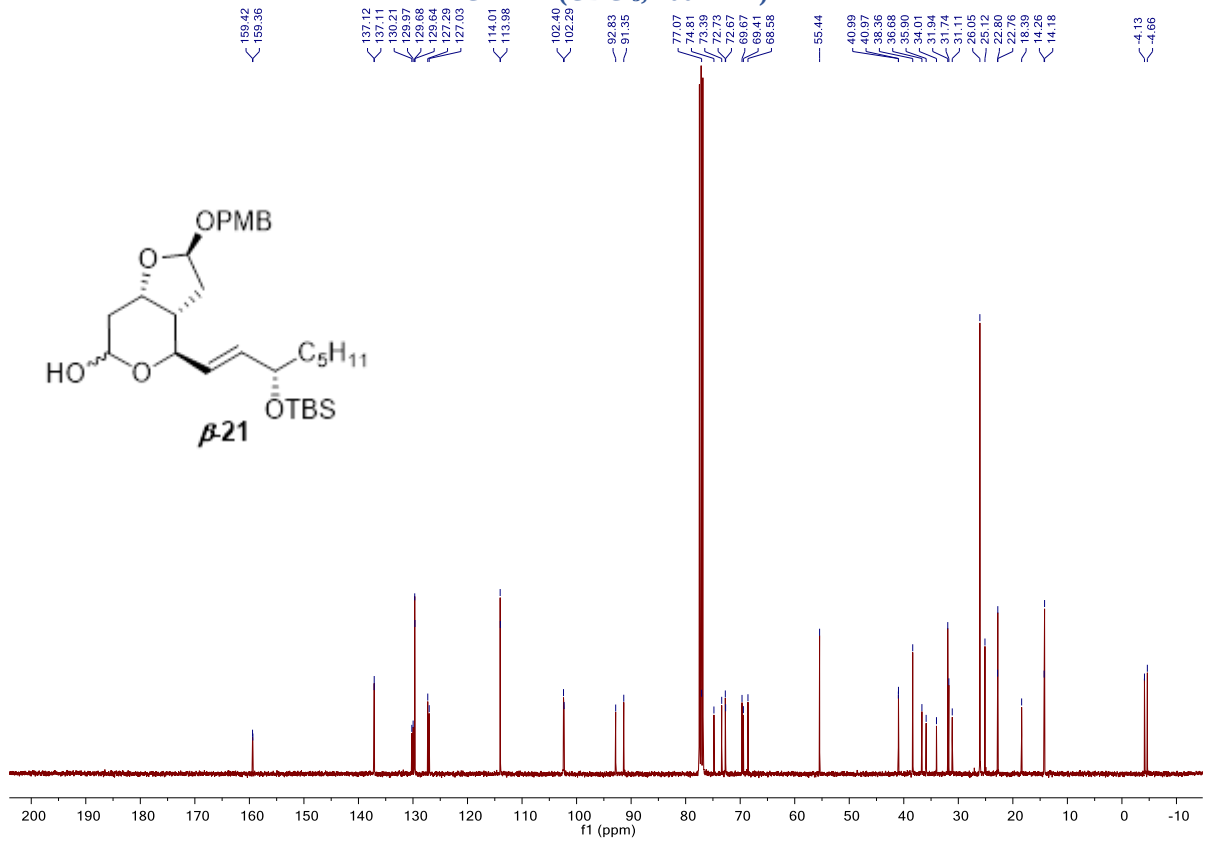


(2*R*,3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-((4-methoxybenzyl)oxy)hexahydro-4*H*-furo[3,2-*c*]pyran-6-ol (*β*-21)

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

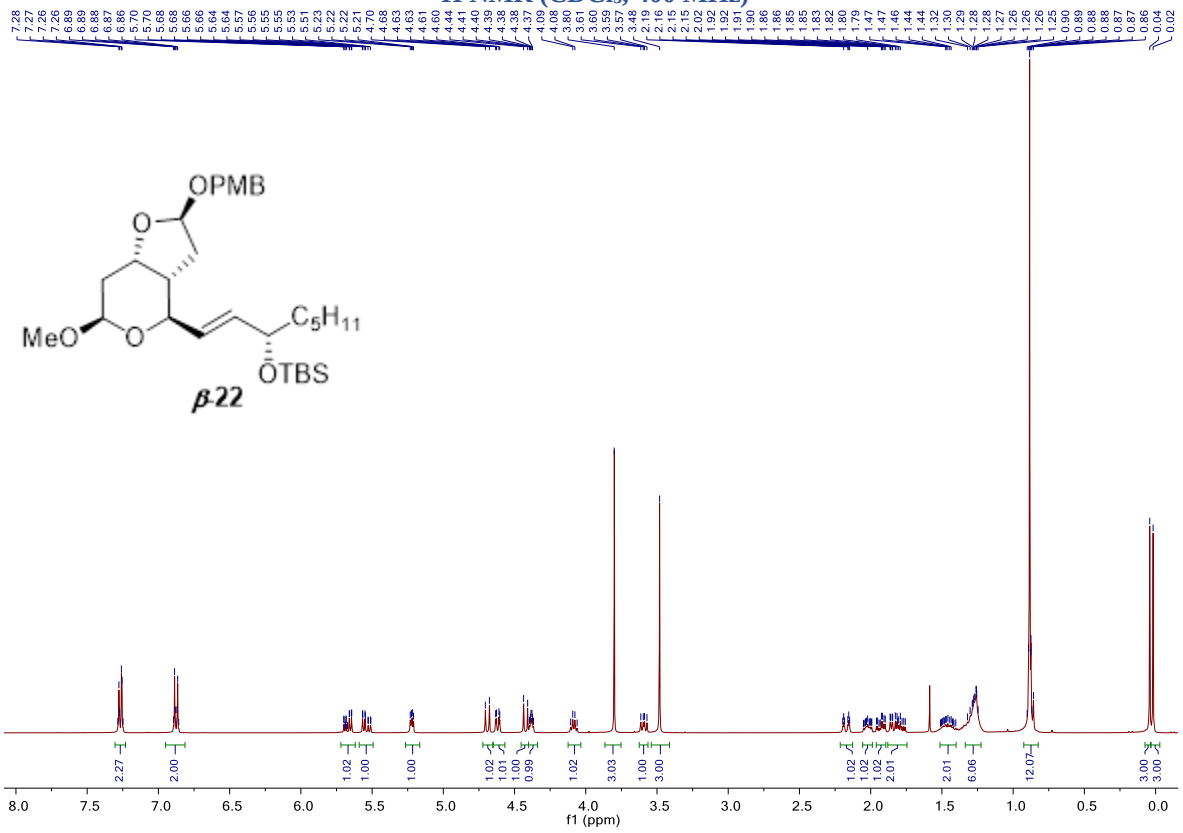


^{13}C NMR ($CDCl_3$, 100 MHz)

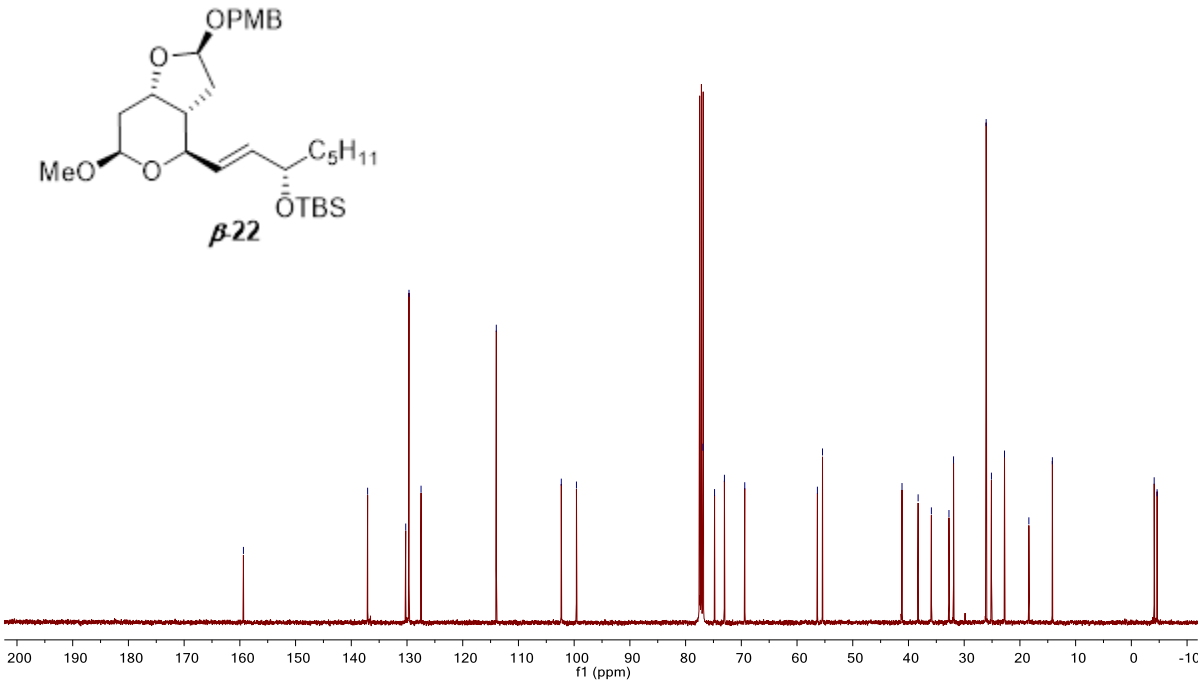


***tert*-Butyl(((*S*,*E*)-1-((2*R*,3a*S*,4*R*,6*R*,7a*S*)-6-methoxy-2-((4-methoxybenzyl)oxy)hexahydro-4*H*-furo[3,2-*c*]pyran-4-yl)oct-1-en-3-yl)oxy)dimethylsilane (*β*-22)**

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

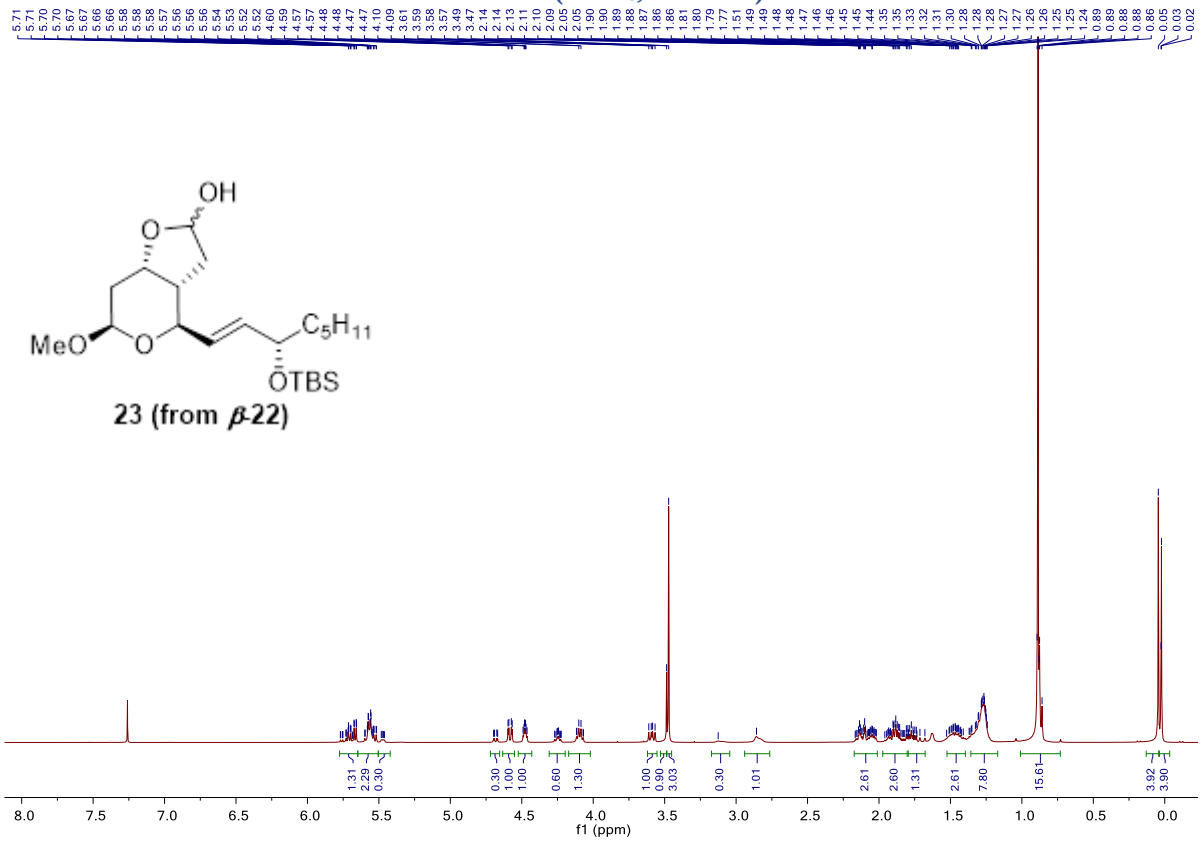


^{13}C NMR ($CDCl_3$, 100 MHz)

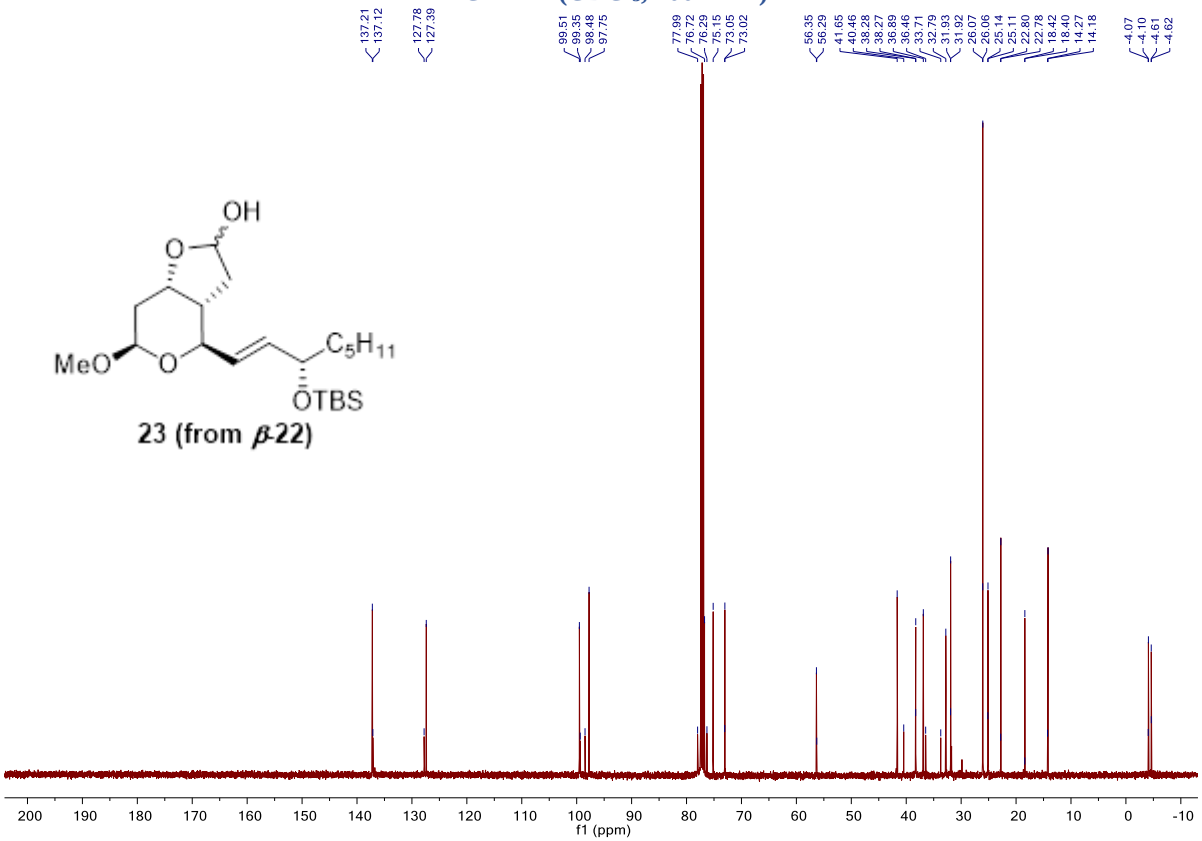


(3a*S*,4*R*,6*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-6-methoxyhexahydro-4*H*-furo[3,2-*c*]pyran-2-ol (23, from *β*-22)

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

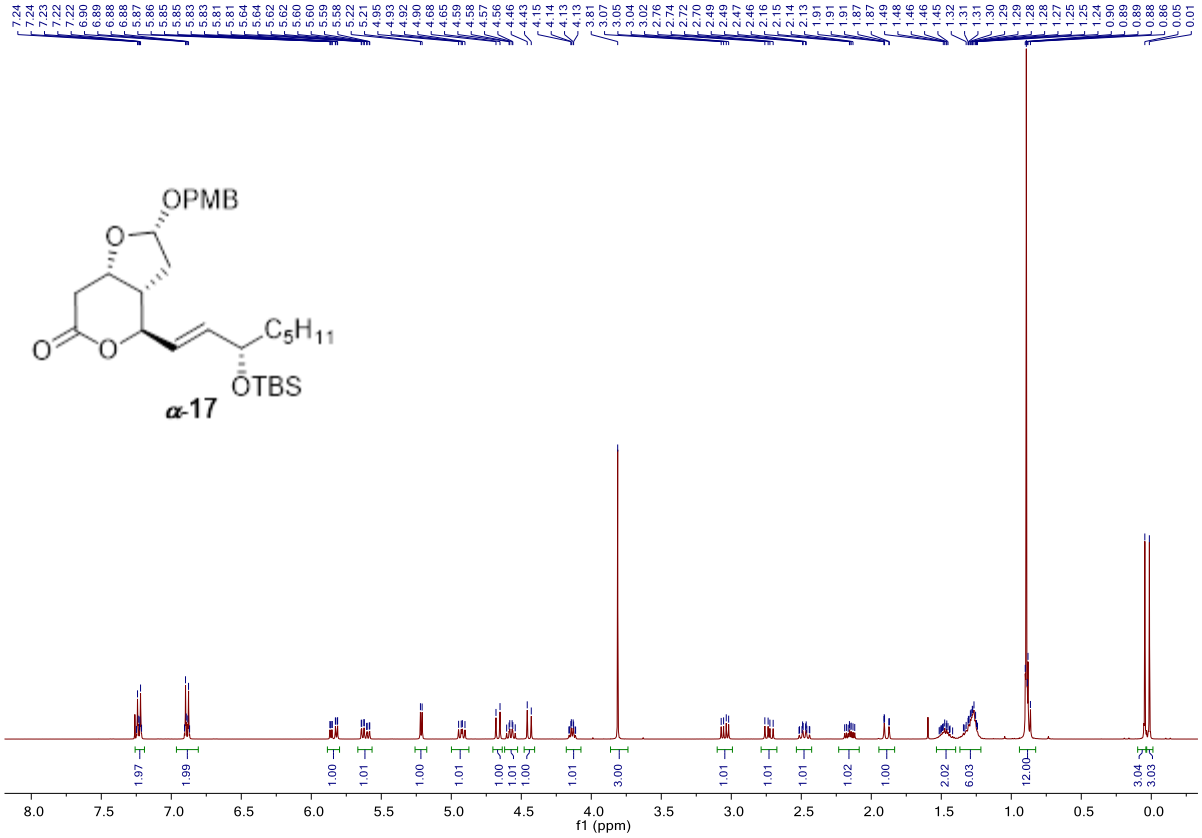


^{13}C NMR ($CDCl_3$, 100 MHz)

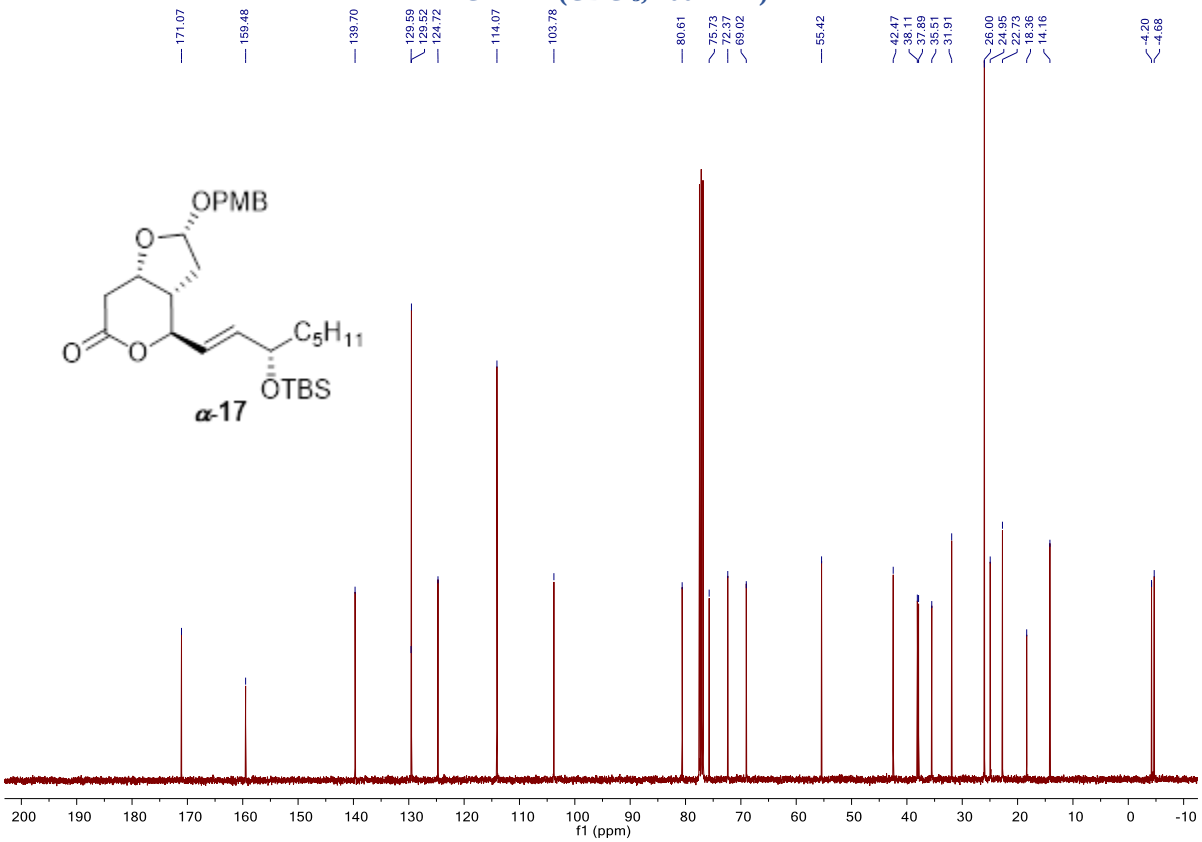


(2*S*,3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-((4-methoxybenzyl)oxy)hexahydro-6*H*-furo[3,2-*c*]pyran-6-one (*α*-17)

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

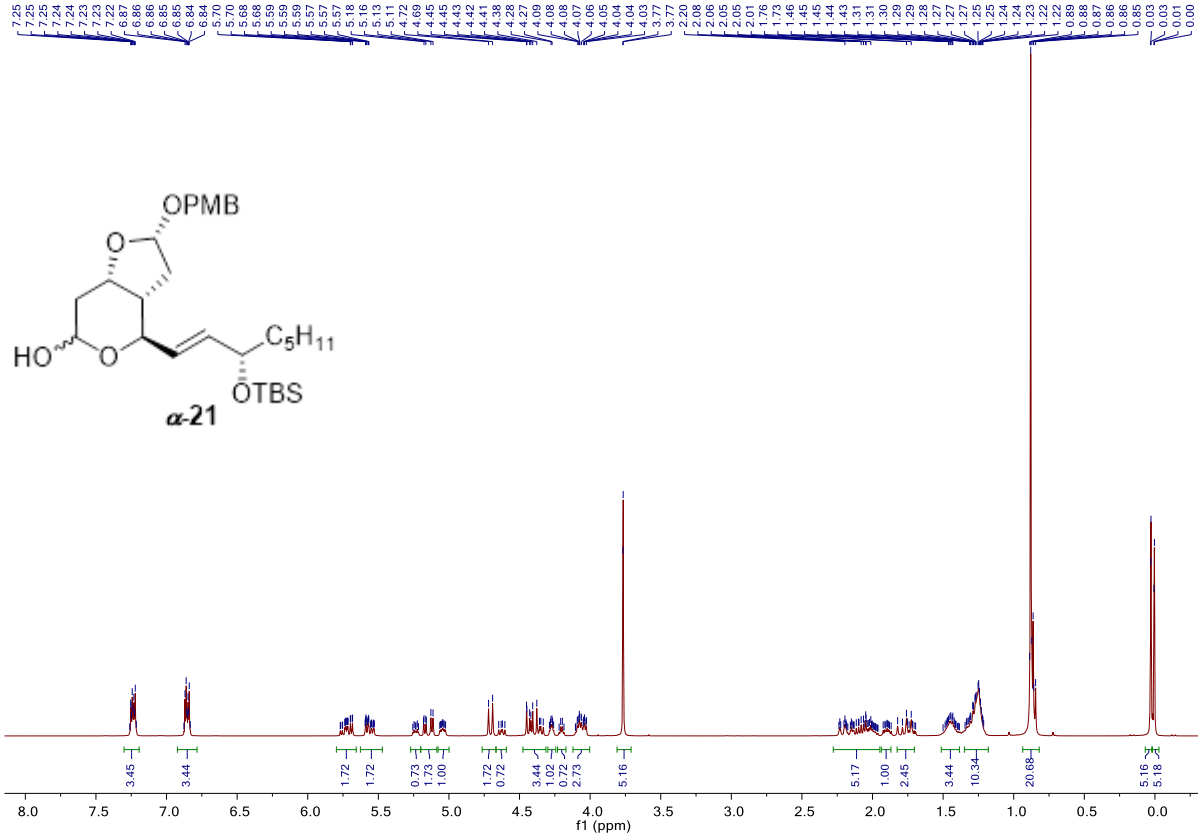


^{13}C NMR ($CDCl_3$, 100 MHz)

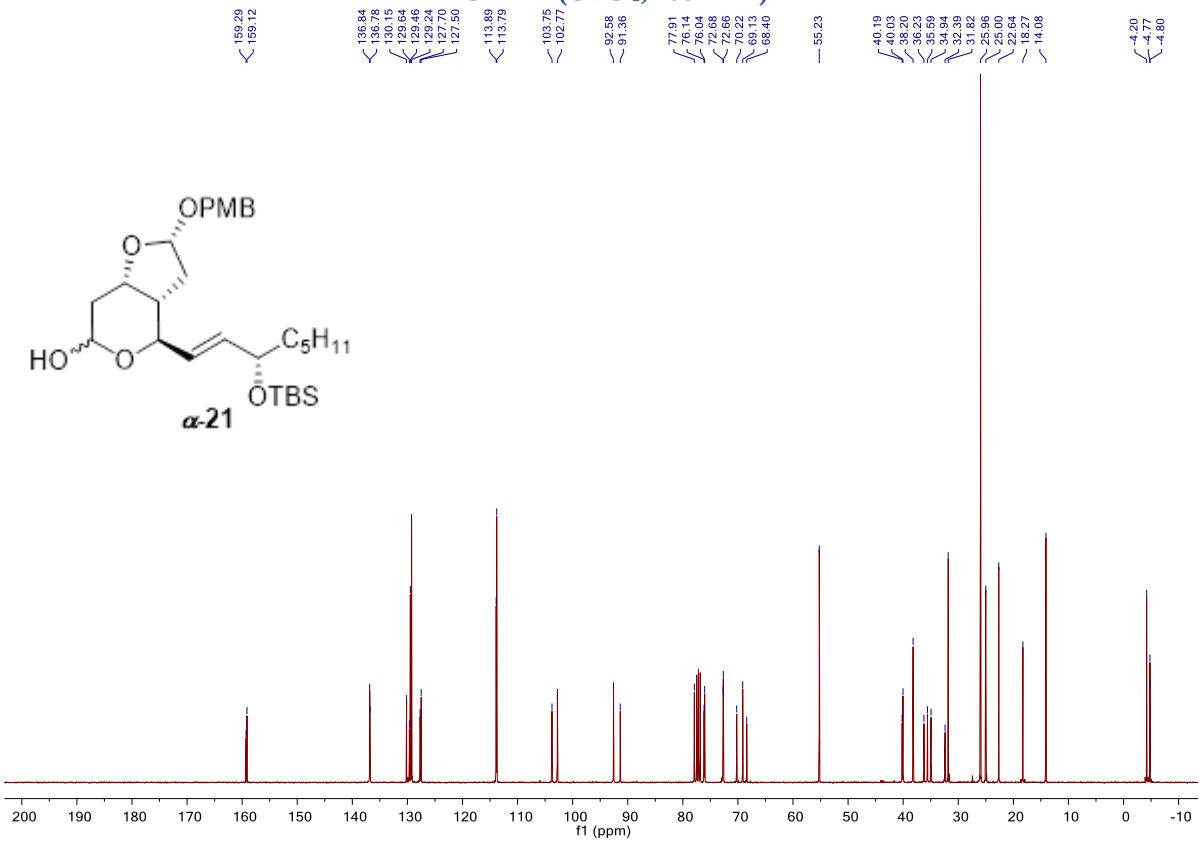


(2*S*,3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-((4-methoxybenzyl)oxy)hexahydro-4*H*-furo[3,2-*c*]pyran-6-ol (*α*-21)

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

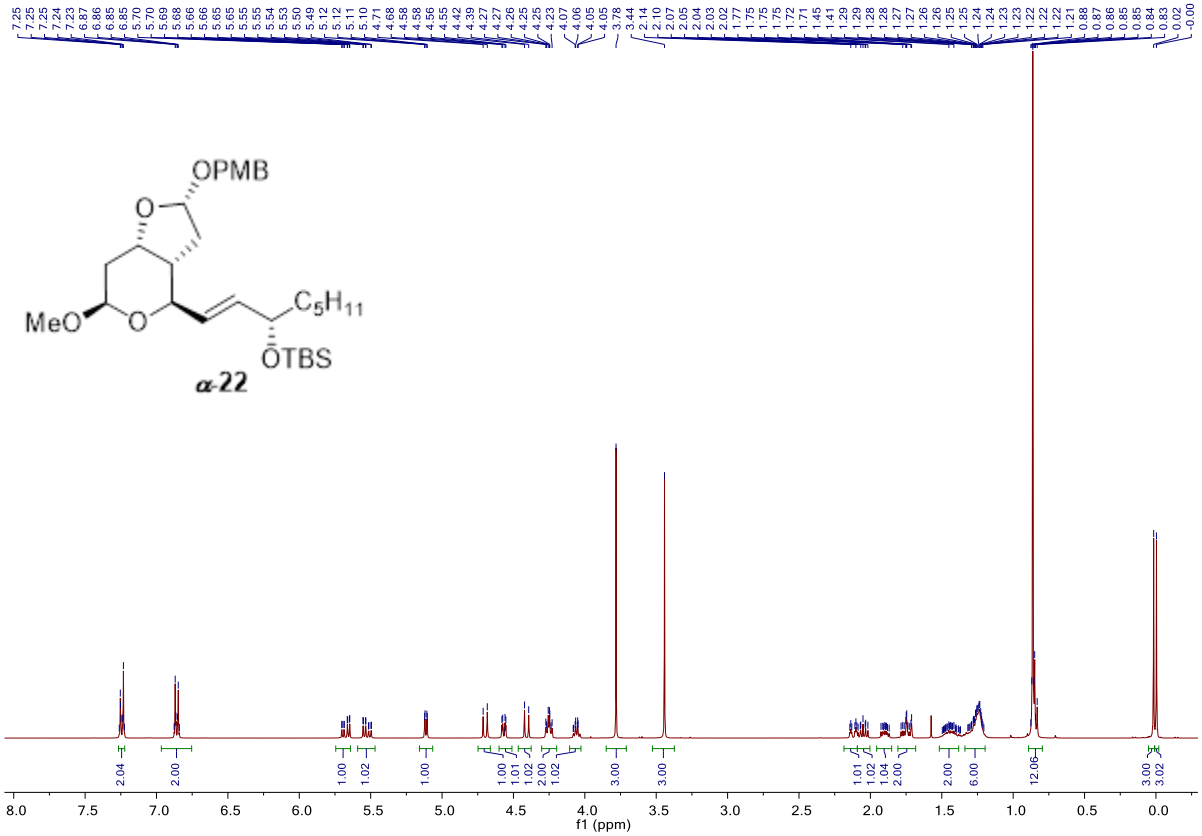


^{13}C NMR ($CDCl_3$, 100 MHz)

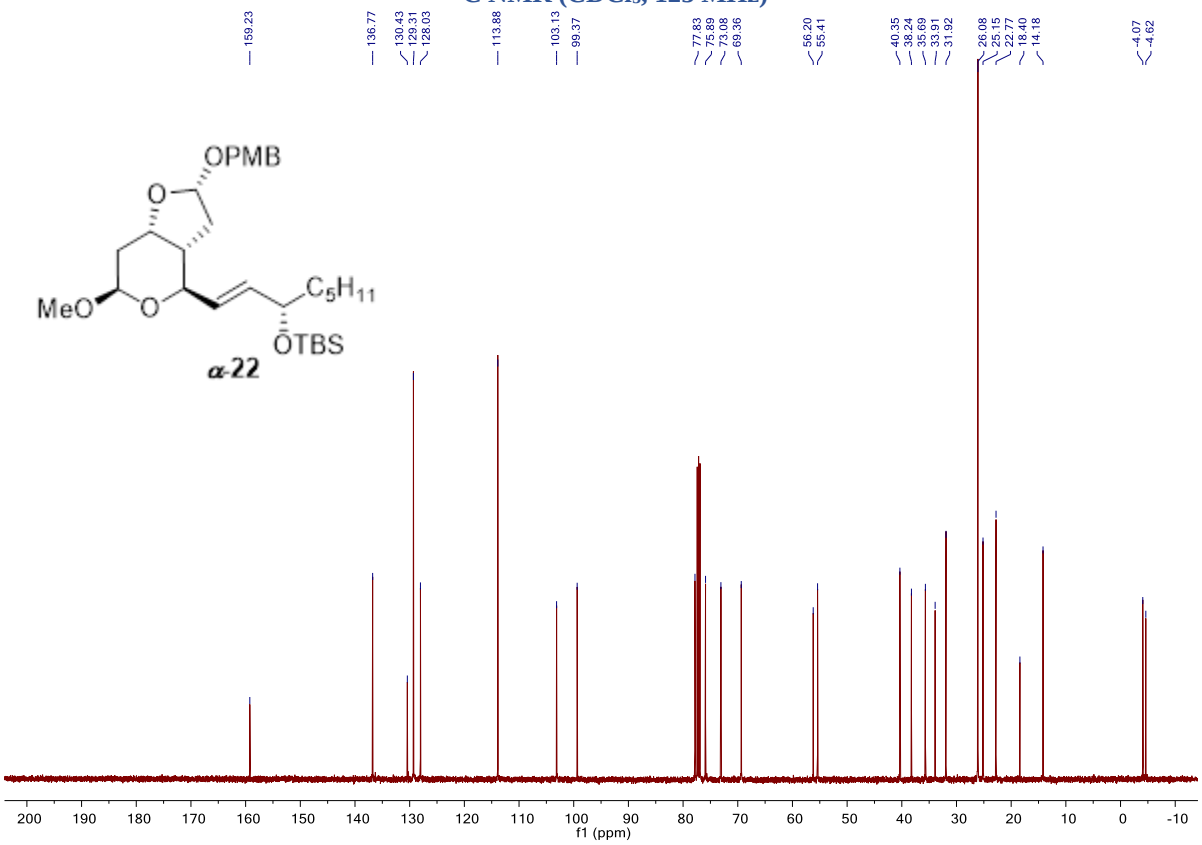


***tert*-Butyl(((*S*,*E*)-1-((2*S*,3a*S*,4*R*,6*R*,7a*S*)-6-methoxy-2-((4-methoxybenzyl)oxy)hexahydro-4*H*-furo[3,2-*c*]pyran-4-yl)oct-1-en-3-yl)oxy)dimethylsilane (*α*-22)**

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

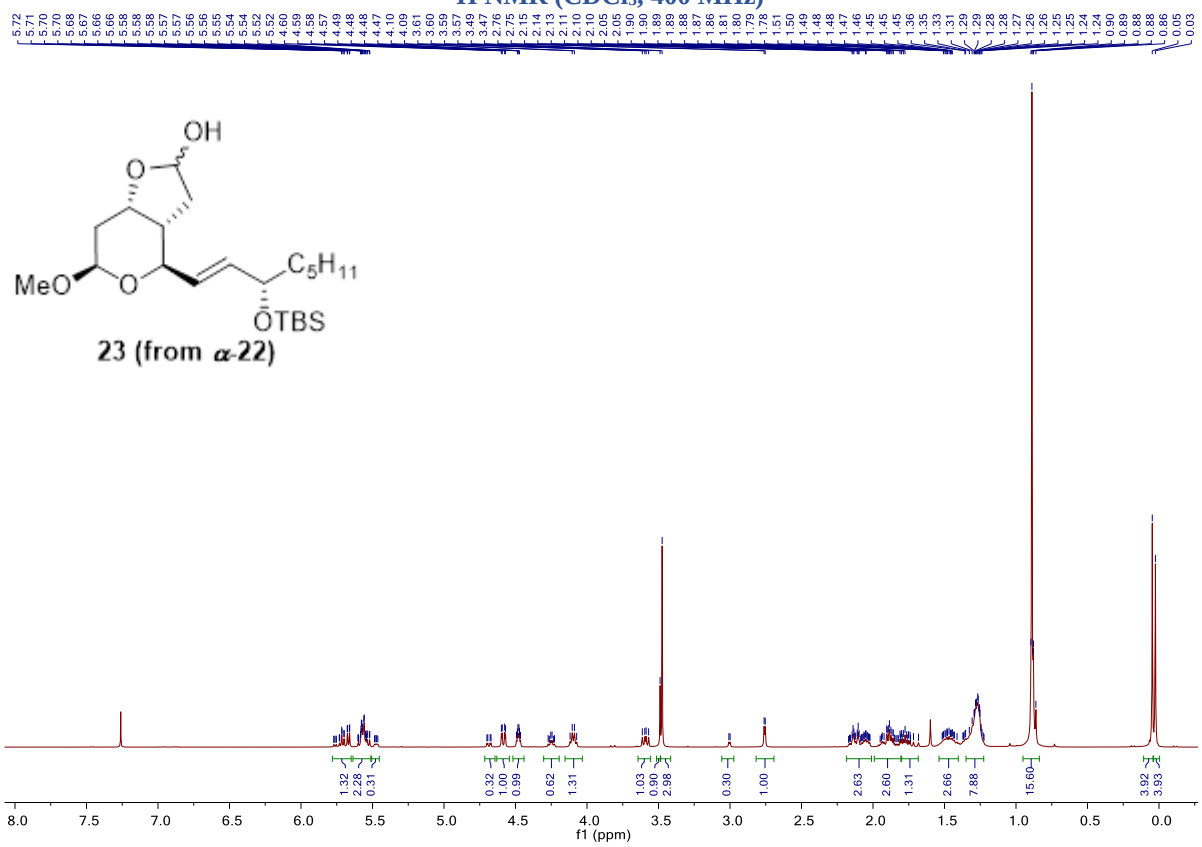


^{13}C NMR ($CDCl_3$, 125 MHz)



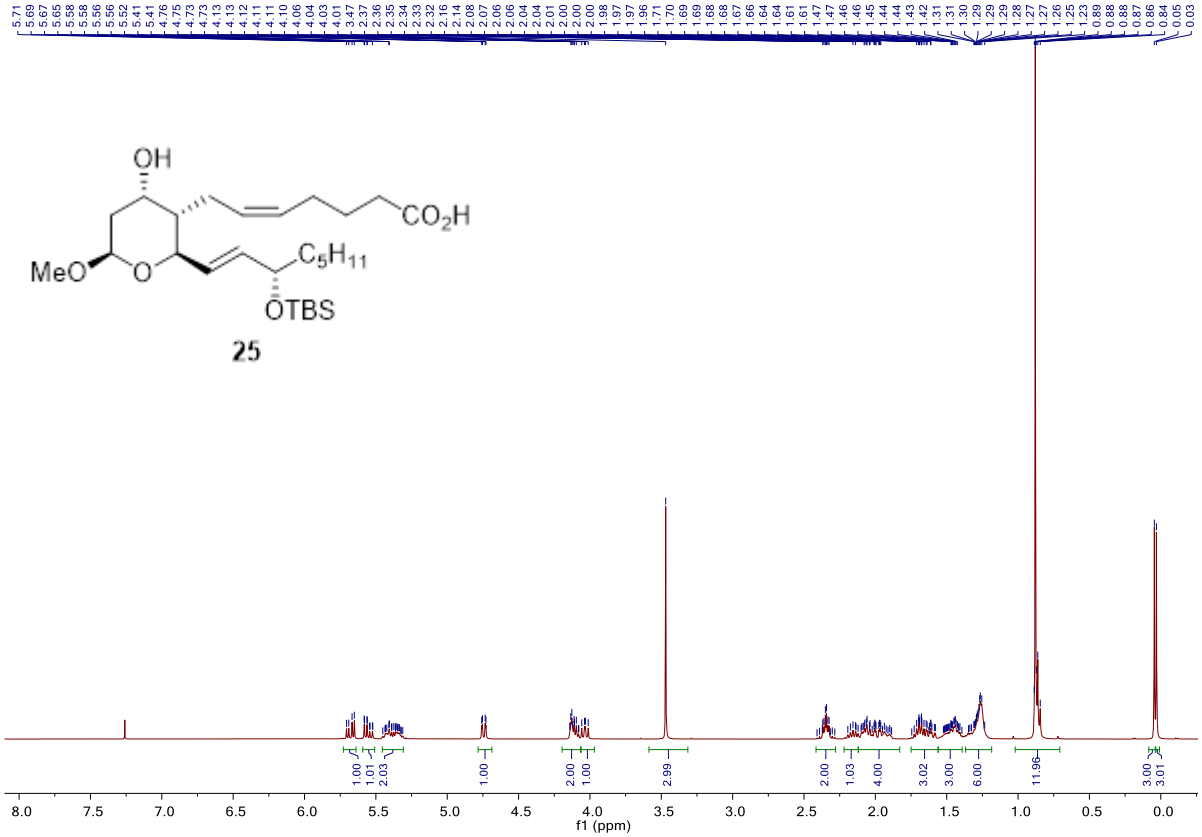
(3a*S*,4*R*,6*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-6-methoxyhexahydro-4*H*-furo[3,2-*c*]pyran-2-ol (23, from *α*-22)

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

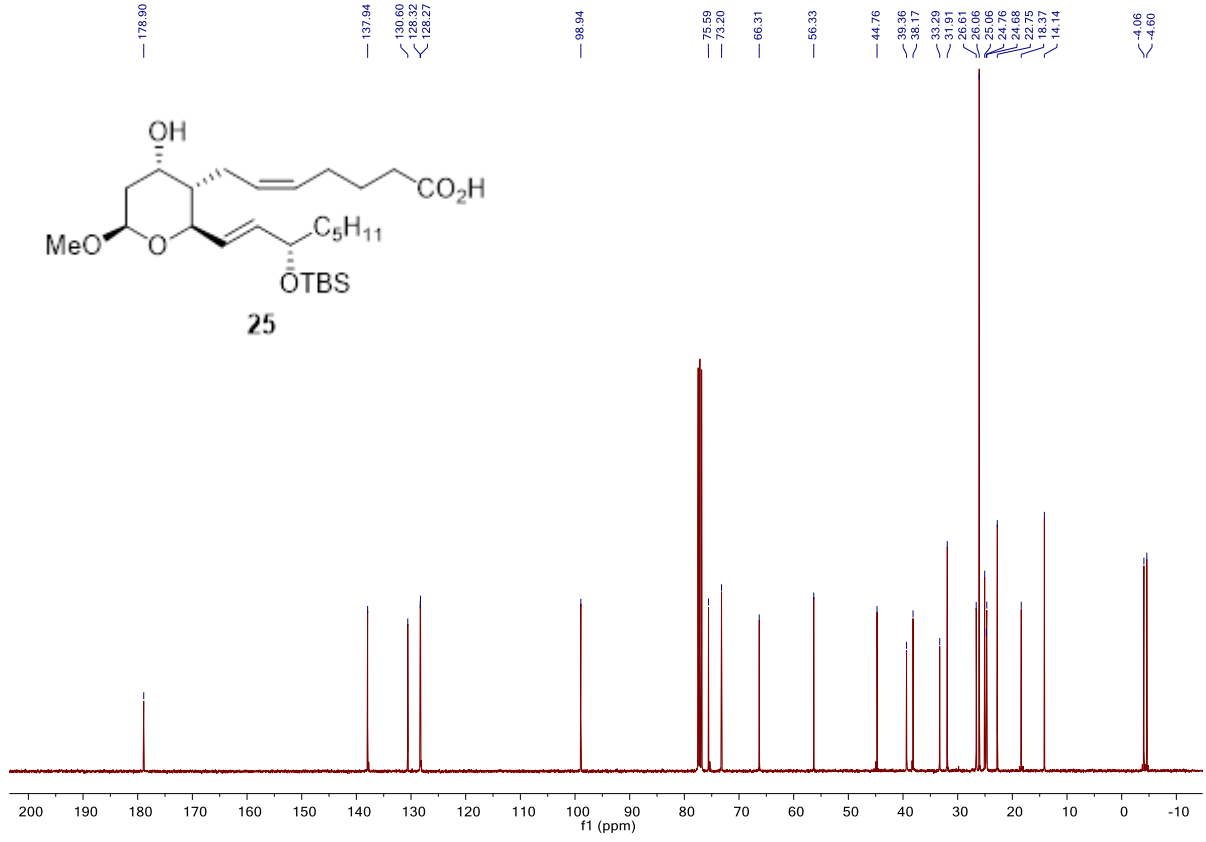


(*Z*)-7-((2*R*,3*S*,4*S*,6*R*)-2-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-4-hydroxy-6-methoxytetrahydro-2*H*-pyran-3-yl)hept-5-enoic acid (25)

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

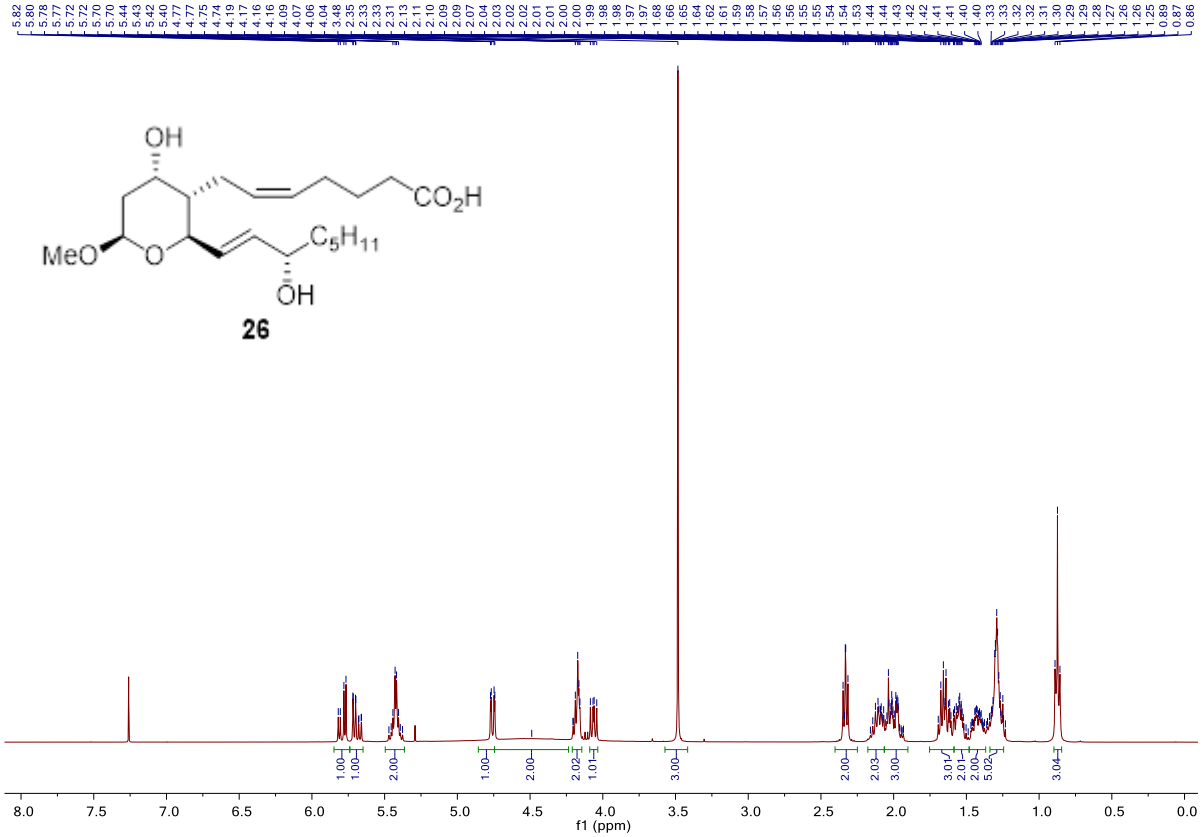


^{13}C NMR ($CDCl_3$, 100 MHz)

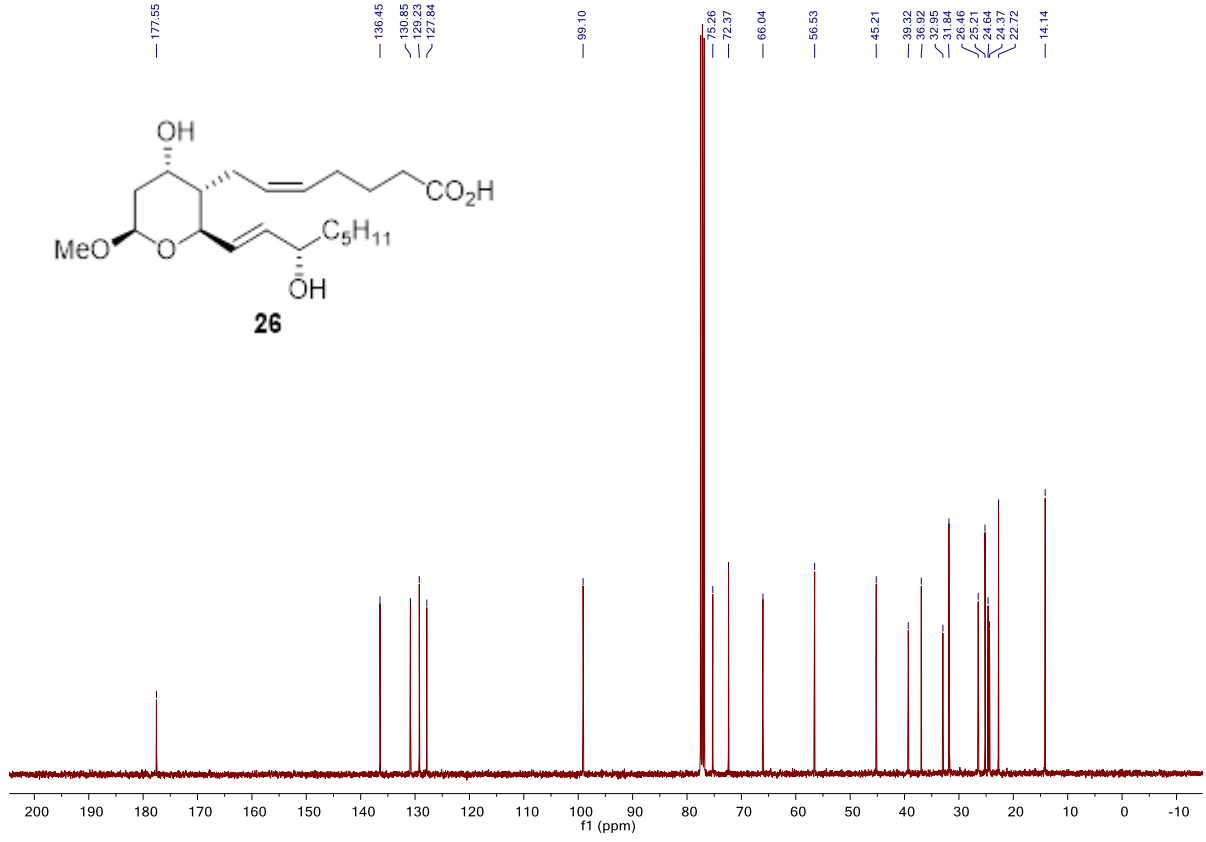


(*Z*)-7-((2*R*,3*S*,4*S*,6*R*)-4-Hydroxy-2-((*S*,*E*)-3-hydroxyoct-1-en-1-yl)-6-methoxytetrahydro-2*H*-pyran-3-yl)hept-5-enoic acid (26)

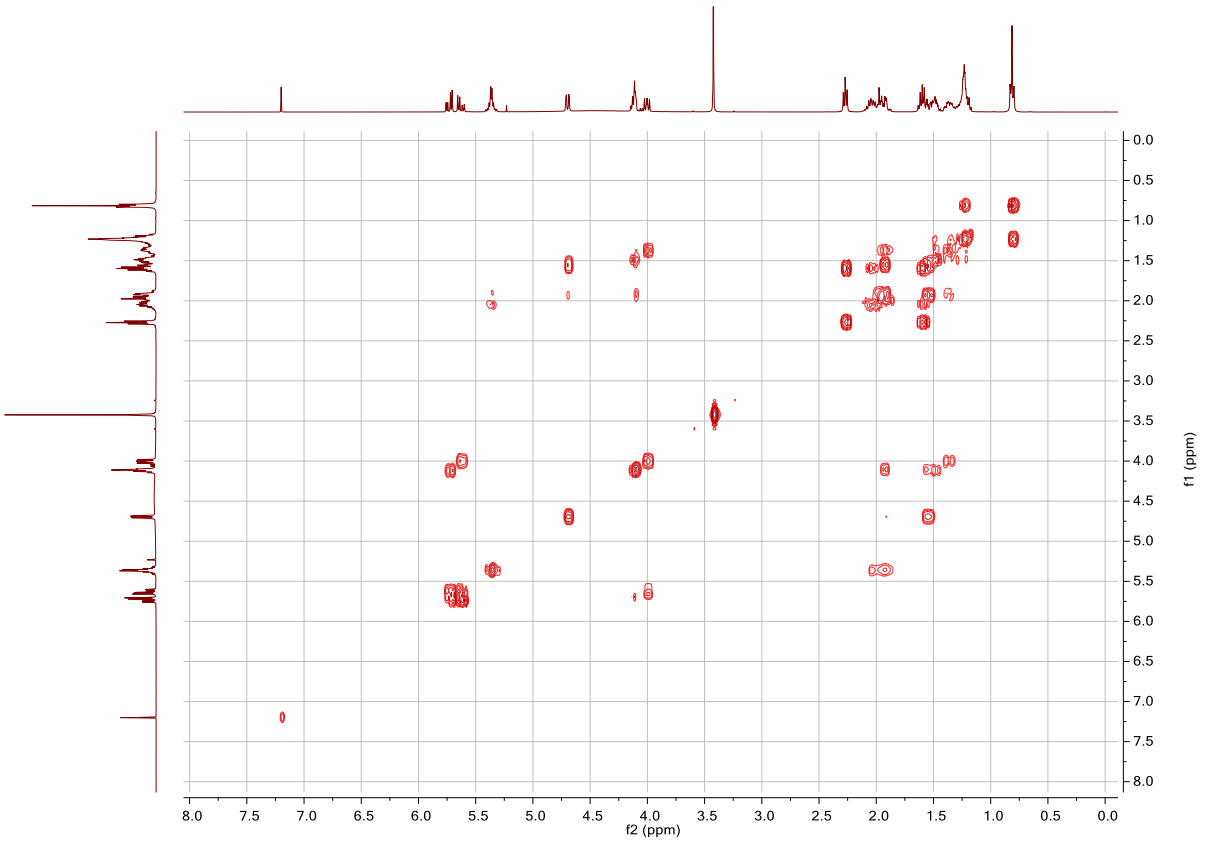
^{1}H NMR ($CDCl_3$, 400 MHz)



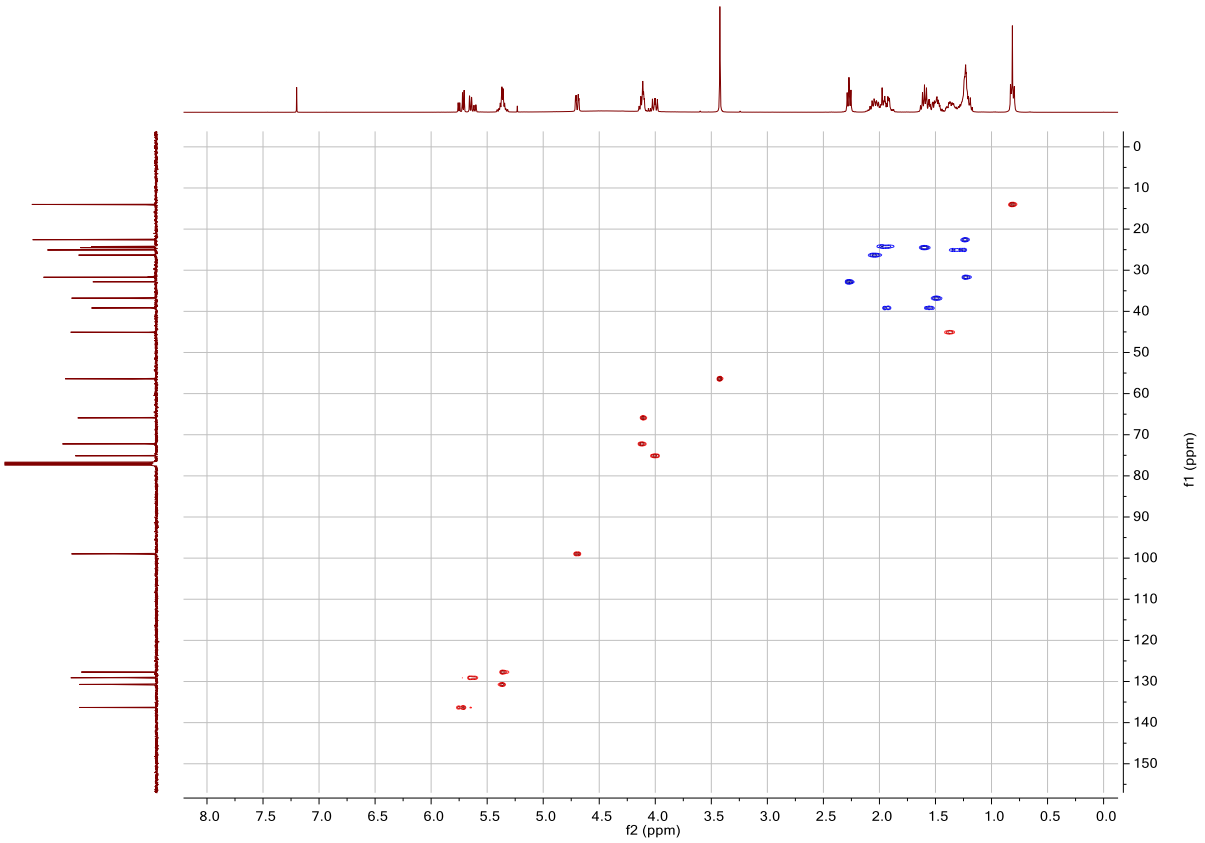
^{13}C NMR ($CDCl_3$, 100 MHz)



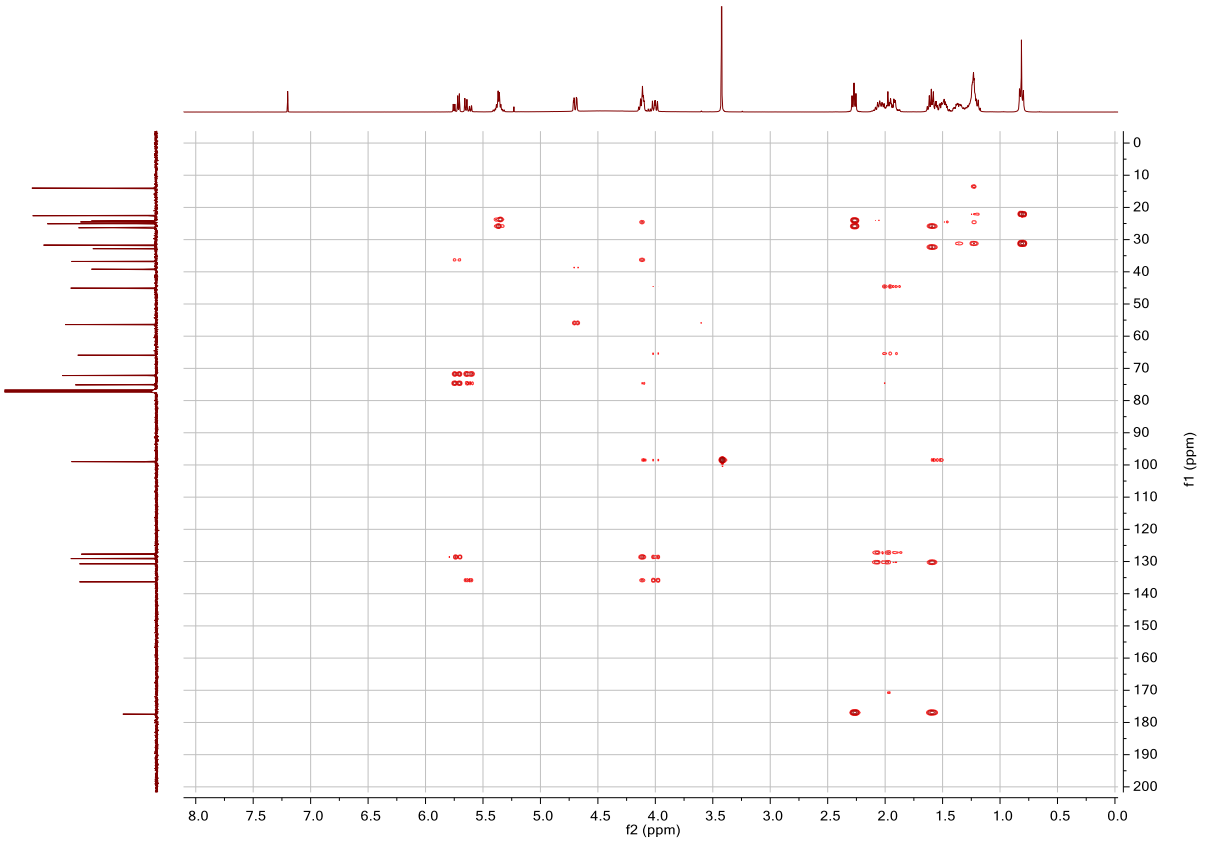
COSY Spectrum ($CDCl_3$, 400 MHz/400 MHz) of 26



HSQC Spectrum ($CDCl_3$, 400 MHz/100 MHz) of 26

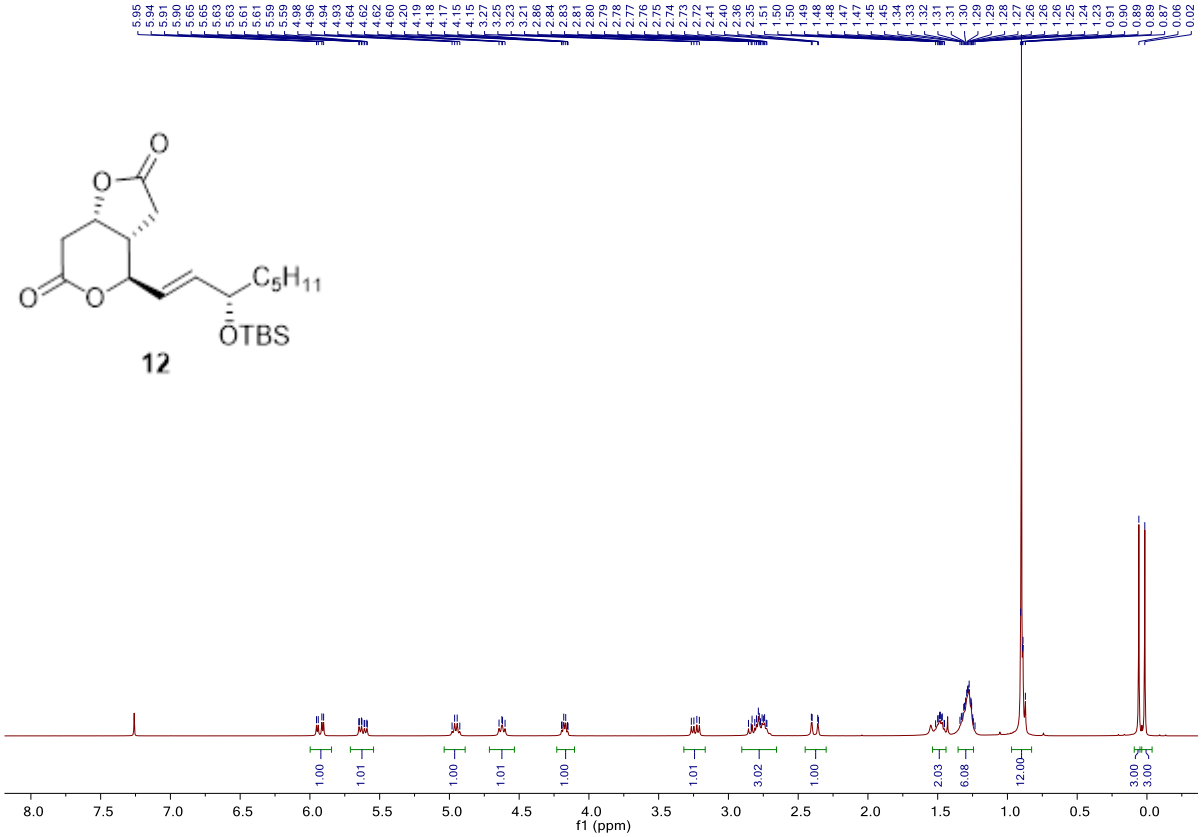


HMBC Spectrum ($CDCl_3$, 400 MHz/100 MHz) of 26

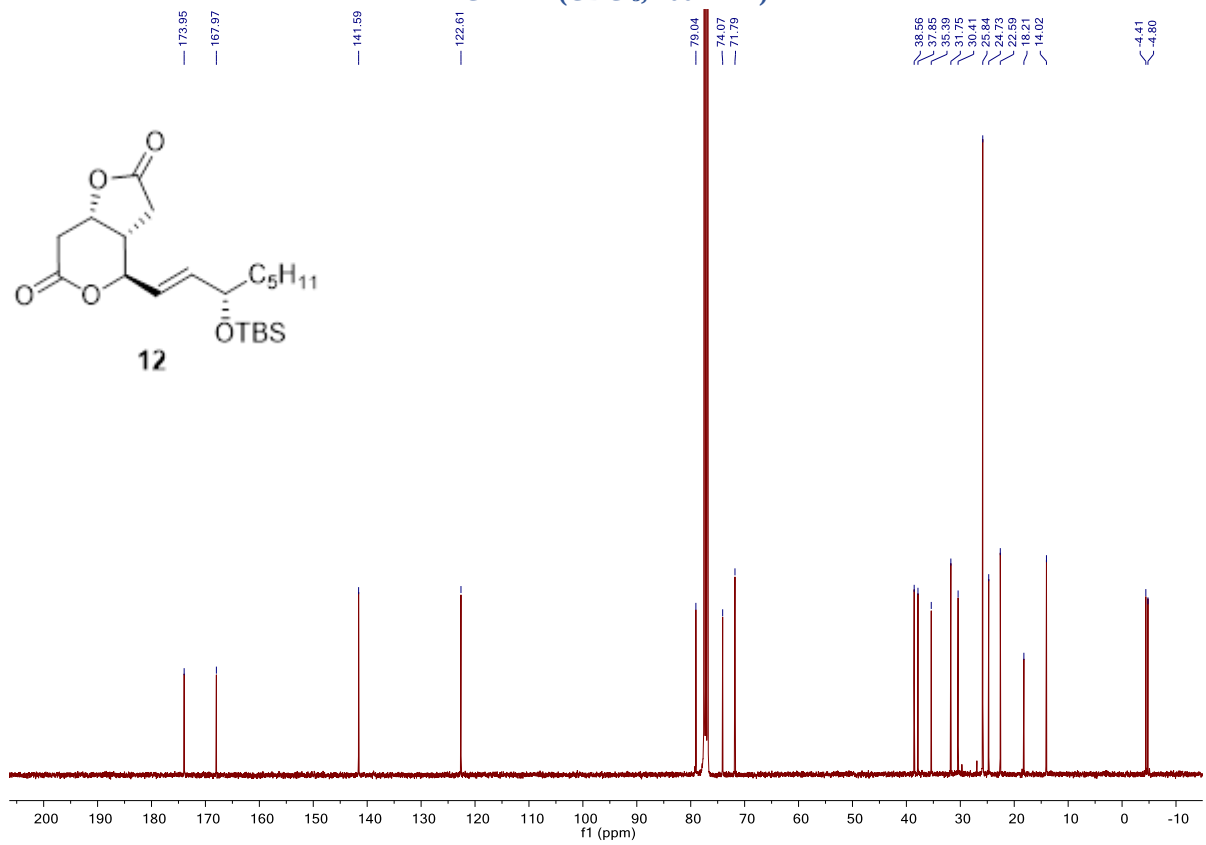


(3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)tetrahydro-4*H*-furo[3,2-*c*]pyran-2,6-dione (12)

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

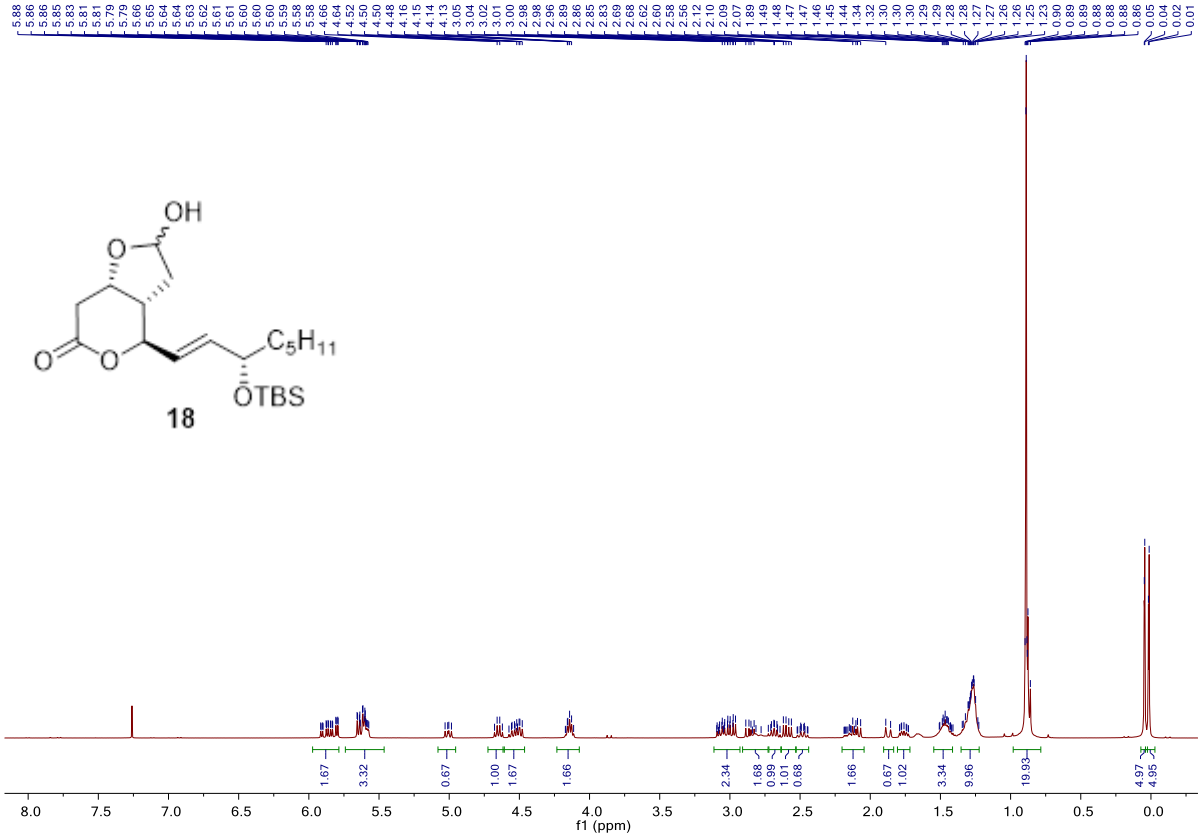


^{13}C NMR ($CDCl_3$, 100 MHz)

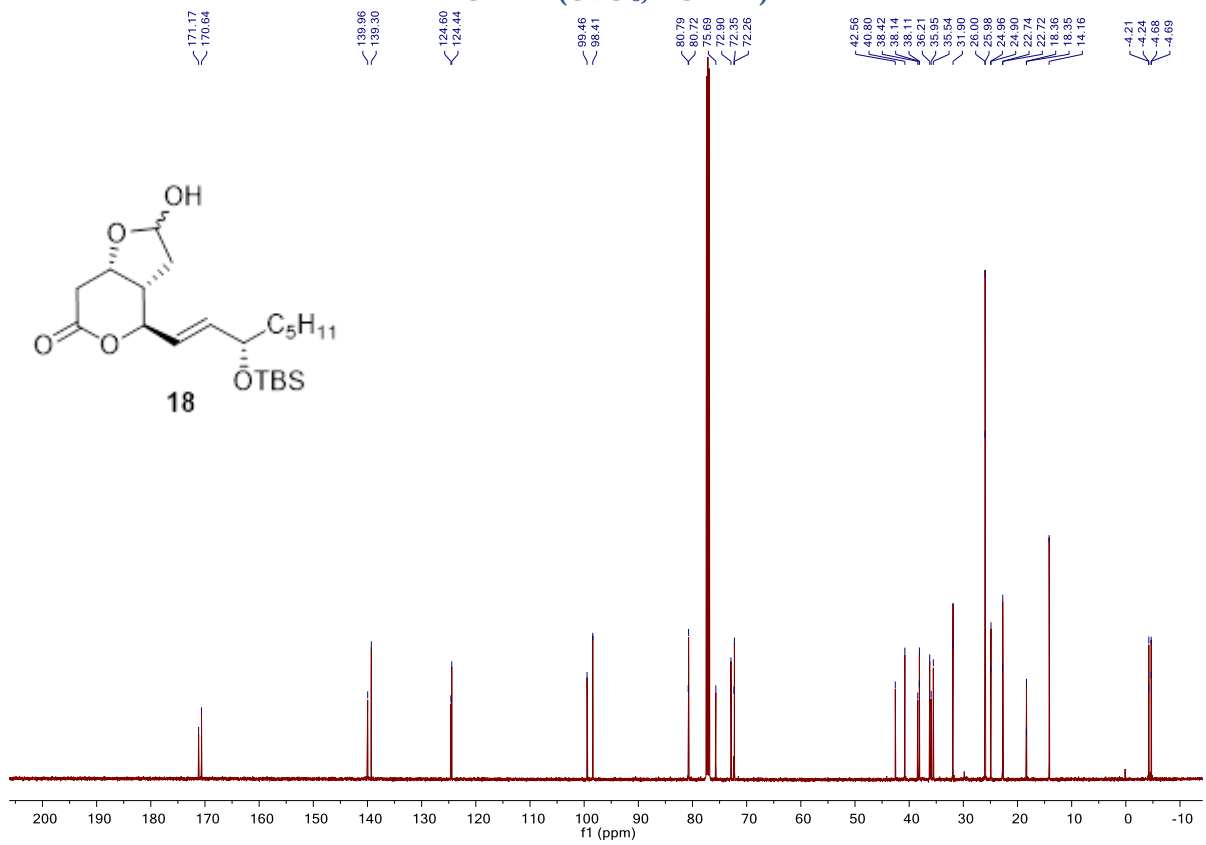


(3a*S*,4*R*,7a*S*)-4-((*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-1-yl)-2-hydroxyhexahydro-6*H*-furo[3,2-*c*]pyran-6-one (18)

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

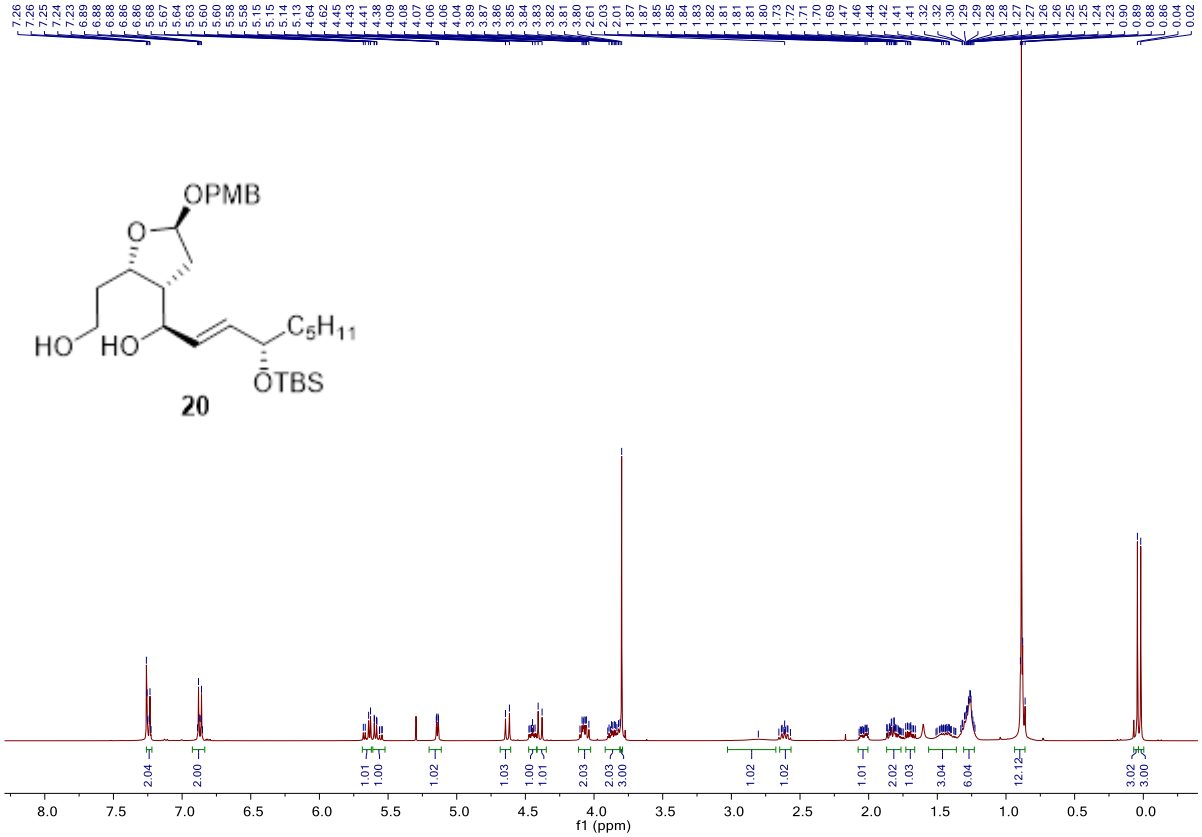


^{13}C NMR ($CDCl_3$, 125 MHz)



(1*R*,4*S*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-((2*S*,3*R*,5*R*)-2-(2-hydroxyethyl)-5-((4-methoxybenzyl)oxy)tetrahydrofuran-3-yl)non-2-en-1-ol (20)

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



^{13}C NMR ($CDCl_3$, 125 MHz)