Supporting information for

Synthesis of Alfaprostol and $PGF_{2\alpha}$ Through 1,4-Addition of an Alkyne to an Enal Intermediate as the Key Step

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Contents

1. General Information

In general, reactions were carried out using reagent grade solvents and without the exclusion of air. For reactions which used anhydrous solvents and an inert atmosphere, this is mentioned in the experimental section for this reaction. Under these circumstances tetrahydrofuran and dichloromethane were obtained from a purification column composed of activated alumina[1] and reactions were carried out under nitrogen using standard manifold techniques.

Generally, chemicals were purchased from commercial sources (Acros, Aldrich, Alfa Aesar, Fluka, Lancaster or Merck) and used without further purification unless stated otherwise. Et_3N was distilled over CaH_2 under reduced pressure prior to use. CuI·0.75DMS was prepared from commercially available CuI according to a procedure from House *et al*.[2] Solutions of *n*-BuLi were titrated against *N*-benzylbenzamide using the procedure of Chong *et al*.[3] Molecular sieves were activated prior to use by microwave irradiation in a reaction microwave. TMSI was purchased from Sigma Aldrich and the compound was transferred from an ampoule to a Young's tube, containing copper turnings, in a glove box. The tube with the TMSI was covered with aluminium foil and stored in the freezer.

Flash column chromatography was either performed manually using glass columns with Sigma-Aldrich, 60 Å, 40 – 63 μm silica gel or using a Biotage® Isolera™ one system with either Biotage® Flash Silica, Biotage® ZIP® Sphere (60 μm), Biotage® ZIP KP-Sil or Biotage® SNAP Ultra (HP-Sphere™ 25 μm) pre-packed columns, using reagent grade solvents. All thin layer chromatography was performed on aluminium backed plates pre-coated with silica gel (Merck, Silica Gel 60 F_{254}). Compounds were visualized under UV light and/or by dipping the plates in solutions of potassium permanganate or *p*-anisaldehyde followed by heating.

NMR spectra were recorded on Varian 500 MHz, Varian 400 MHz, JEOL 400 MHz or Bruker 400 MHz spectrometers and signals are reported relative to the residual signal of the undeuterated solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, etc.) and integration.

Mass spectra were recorded by the University of Bristol Spectrometry Services Laboratory using electron impact (EI), electrospray (ESI), or chemical (CI) ionization techniques. IR data was obtained on either a PerkinElmer Spectrum One or PerkinElmer Spectrum Two FT-IR-spectrometer with only selected peaks being reported. Chiral HPLC was performed using a Daicel Chiralpack IA column (4.6 × 250 mm × 5 μm) fitted with the respective guard

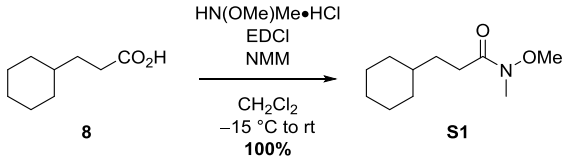
(4 × 10 mm) and monitored by DAD (Diode Array Detector). Optical rotations were obtained on a Bellingham and Stanley Ltd. ADP 220 polarimeter. Melting points were determined using a Kopfler hot stage apparatus and are uncorrected.

Enal **6** was synthesised according to our previously reported literature procedures.[4-5] – the major diastereomer of **6** was used in this report to simplify NMR analysis of subsequent intermediates. Alkyne **4** was synthesised according to the literature procedure from the corresponding commercially available unprotected alcohol, and all spectroscopic data were in agreement.[4]

2. Experimental procedures

2.1 Synthesis of Alfaprostol

3-Cyclohexyl-*N*-methoxy-*N*-methylpropanamide (S1):



3-cyclohexylpropionic acid (3.00 g, 19.2 mmol, 1.0 eq.) was added to a flame dried Schlenk flask under N_2-atmosphere and dissolved in CH_2Cl_2 (100 mL). The solution was cooled to −15 °C and *N*,*O*-dimethylhydroxylamine·HCl (2.06 g, 21.1 mmol, 1.1 eq.), *N*-methylmorpholine (2.32 mL, 21.1 mmol, 1.1 eq.) and EDCl (4.05 g, 21.1 mmol, 1.1 eq.) were added in sequence. The reaction was stirred at room temperature for 2 h, before it was quenched by the addition of a saturated NH_4Cl solution. The mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution (50 mL), dried over $MgSO_4$, filtered and concentrated in vaccum. The crude product was purified by flash column chromatography (SiO_2, pentane → pentane/Et_2O (85:15)) to yield the weinreb amide **S1** (3.83 g, 19.2 mmol, quantitative yield) as a colourless oil.

$\boldsymbol{R_f}$ = 0.25 (pentane/Et_2O 9:1).

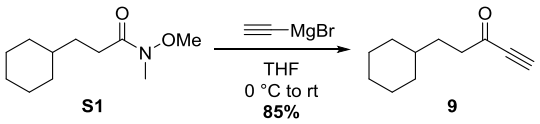
$\boldsymbol{\nu_{max}}$ (film): 2923, 2851, 1668, 1449, 1385, 1178, 999, 730 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.68 (s, 3H, OCH_3), 3.17 (s, 3H, NCH_3), 2.42 (t, *J* = 8.0 Hz, 2H, CH_2), 1.73–1.60 (m, 5H, 2 × CH_2 + C*H*H), 1.53 (dd, *J* = 16.0, 6.8 Hz, 2H, CH_2), 1.27–1.11 (m, 4H, CH_2 + C*H*H + CH), 0.96–0.86 (m, 2H, CH_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 175.4 (C=O), 61.3 (OCH_3), 37.6 (CH), 33.3 (2 × CH_2), 32.2 (NCH_3, CH_2), 29.6 (CH_2), 26.7 (CH_2), 26.4 (2 × CH_2).

HRMS (ESI) calcd. for $C_{11}H_{22}NO_2$ $[M+Na]^+$ 200.1643, found 200.1645.

5-Cyclohexylpent-1-yn-3-one (9):



To a solution of weinreb amide **S1** (3.60 g, 18.1 mmol, 1.0 eq.) in anhydrous THF (50 mL) in a flame dried Schlenk flask under N_2-atmosphere at 0 °C was added a solution of ethynylmagnesium bromide (0.5 M in THF, 72.4 mL, 36.2 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature for 1.5 h, before it was quenched by the addition of a saturated NH_4Cl solution (50 mL). The mixture was diluted with H_2O (40 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was further purified by flash column chromatography (SiO_2, pentane → pentane/Et_2O (9:1)) to yield ketone **9** (2.52 g, 15.3 mmol, 85%) as a yellowish oil.

$\boldsymbol{R_f}$ = 0.83 (pentane/Et_2O 9:1).

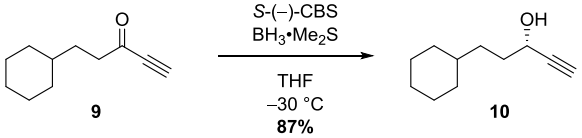
$\boldsymbol{\nu_{max}}$ (film): 3256, 2922, 2851, 2092, 2678, 1449, 1406, 1366, 1261, 1210, 1107, 1071, 1027 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.19 (s, 1H, C≡CH), 2.60 (t, *J* = 7.6 Hz, 2H, CH_2), 1.75–1.62 (m, 5H, 2 × CH_2 + C*H*H), 1.58 (dd, *J* = 8.3, 7.1 Hz, 2H, CH_2), 1.28–1.10 (m, 4H, CH_2 + C*H*H + CH), 0.96–0.85 (m, 2H, CH_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 187.8 (C=O), 81.5 (*C*≡CH), 78.2 (C≡*C*H), 43.1 (CH_2), 37.0 (CH), 33.0 (2 × CH_2), 31.1 (CH_2), 26.5 (CH_2), 26.2 (2 × CH_2).

HRMS (ESI) calcd. for $C_{11}H_{16}NaO$ $[M+Na]^+$ 187.1092, found 187.1093.

(*S*)-5-Cyclohexylpent-1-yn-3-ol (10):



A solution of ketone **9** (2.00 g, 12.2 mmol, 1.0 eq.) in anhydrous THF (40 mL) was dried over 4 Å molecular sieves for 1.5 h before being added to a solution of (*S*)-(−)-2-Methyl-CBS-oxazaborolidine (1 M in toluene, 24.4 mL, 24.4 mmol, 2.0 eq.) in a flame dried Schlenk flask under N_2-atmosphere. The mixture was cooled to −30 °C and a solution $BH_3{\cdot}SMe_2$ (2 M in THF, 30.5 mL, 61.0 mmol, 2.0 eq.) was added dropwise *via* the wall of the flask. The reaction was stirred for 2 h at −30 °C before it was quenched by the careful addition of methanol (20 mL).

The mixture was diluted with ether (100 mL) and washed with saturated solutions of NH_4Cl (2 × 50 mL), NaHCO3 (2 × 50 mL) and NaCl (2 × 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vaccuum to give the crude product which was purified by flash column chromatography (SiO_2, pentane → pentane/Et_2O (8:2)) to yield the alcohol **10** (1.77 g, 10.7 mmol, 87%) as a colourless oil.

$\boldsymbol{R_f}$ = 0.31 (pentane/Et_2O 9:1).

$\boldsymbol{\nu_{max}}$ (film): 3309 (broad), 2920, 2850, 1448, 1335, 1262, 1054, 1023, 959, 890 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.34 (ddd, *J* = 4.4, 3.7, 2.1 Hz, 1H, C*H*OH), 2.46 (d, *J* = 2.1 Hz, 1H, C≡CH), 1.77–1.64 (m, 7H, 3 × CH_2 + C*H*H), 1.39–1.30 (m, 2H, CH_2), 1.28–1.13 (m, 4H, CH_2 + CH*H* + CH), 0.97–0.85 (m, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 85.2 (*C*≡CH), 73.0 (C≡*C*H), 62.8 (CHOH), 37.5 (CH), 35.3 (CH_2), 33.5 (CH_2), 33.4 (CH_2), 32.7 (CH_2), 26.8 (CH_2), 26.5 (2 × CH_2).

HRMS (ESI) calcd. for $C_{11}H_{18}NaO$ $[M+Na]^+$ 189.1252, found 189.1250.

$[\alpha]_D^{22}$ = −4.00 (c 0.86, $CHCl_3$).

The enantiomeric ratio was determined by HPLC analysis of the benzoyl derivative.

HPLC (IA Column ChiralPak with guard, 100% hexane, rt, 1.0 mL/min)

major = 21.3 min, minor = 17.5 min (97:3 er)

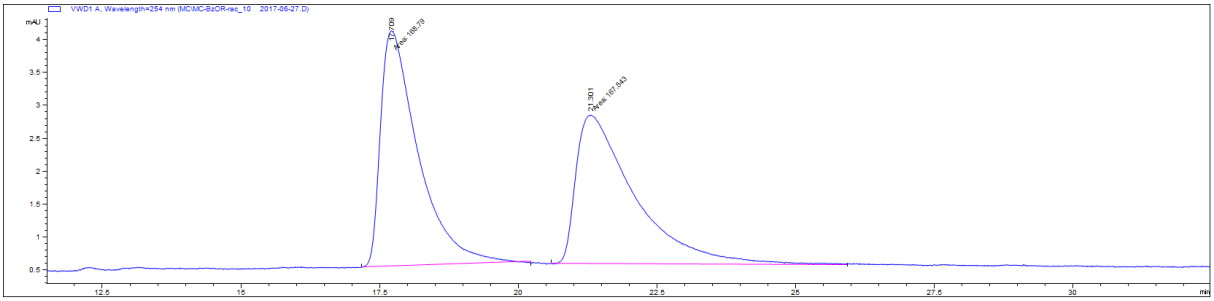


Figure 1: HPLC chromatogram of *rac*-**10**

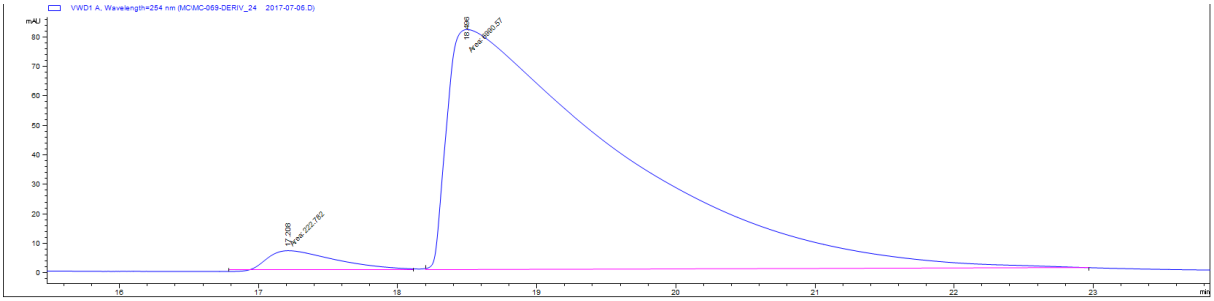
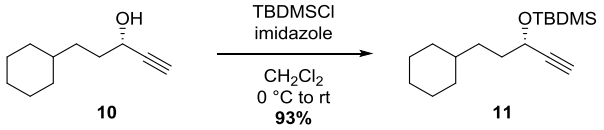


Figure 2: HPLC chromatogram of **10**

(*S*)-*tert*-Butyl((5-cyclohexylpent-1-yn-3-yl)oxy)dimethylsilane (11):



A solution of alcohol **10** (1.77 g, 10.7 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (80 mL) was added to a flame dried Schlenk flask under nitrogen atmosphere. The solution was cooled to 0 °C and TBDMSCl (1.93 g, 12.8 mmol, 1.2 eq.) and imidazole (1.09 g, 16.1 mmol, 1.5 eq.) were added. The mixture was stirred at room temperature overnight, before it was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified using flash column chromatography (SiO_2, pentane) to yield the protected alcohol **11** (2.77 g, 9.87 mmol, 93%) as a colourless oil.

$\boldsymbol{R_f}$ = 0.73 (pentane).

$\boldsymbol{\nu_{max}}$ (film): 3312, 2925, 2853, 1472, 1463, 1389, 1361, 1340, 1251, 1087, 1005, 967, 930, 834, 776, 652, 626 cm^{-1}.

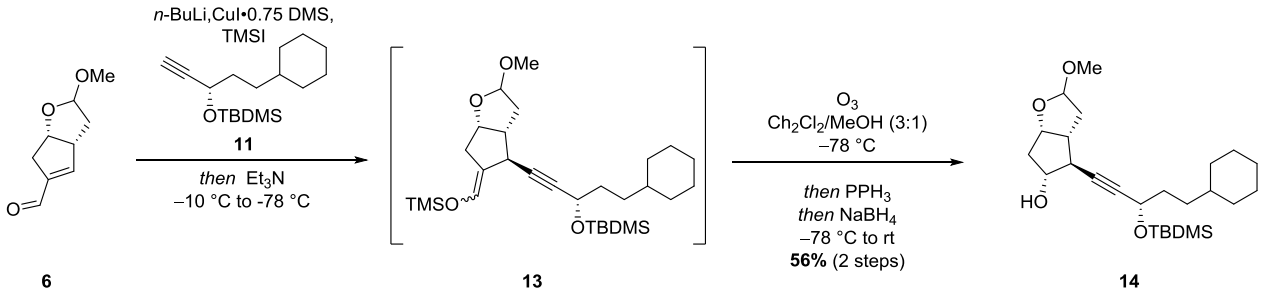
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.31 (td, *J* = 6.5, 2.1 Hz, 1H, C*H*OTBDMS), 2.37 (d, *J* = 2.1 Hz, 1H, C≡CH), 1.75–1.61 (m, 7H, 3 × CH_2, C*H*H), 1.33–1.12 (m, 6H, 2 × CH_2, C*H*H, CH), 0.95–0.83 (m, 11H, CH_2, 3 × CH_3), 0.13 (s, 3H, CH_3), 0.11 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 86.0 (*C*≡CH), 72.0 (C≡*C*H), 63.3 (*C*HOTBDMS), 37.5 (CH), 36.2 (CH_2), 33.5 (2 × CH_2), 32.9 (CH_2), 26.8 (CH_2), 26.5 (2 × CH_2), 26.0 (3 × CH_3), 18.4 (C), −4.4 (CH_3), −4.9 (CH_3).

HRMS (ESI) calcd. for $C_{17}H_{33}OSi$ $[M+H]^+$ 281.2296, found 281.2295.

$[\alpha]_D^{22}$ = −32.0 (c 1.1, $CHCl_3$).

(3a*R*,4*S*,5*R*,6a*S*)-4-((*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-cyclohexylpent-1-yn-1-yl)-2-methoxyhexahydro-2*H*-cyclopenta[*b*]furan-5-ol (14):



A solution of protected alcohol **11** (1.25 g, 4.46 mmol, 1.5 eq.) in anhydrous THF (12 mL) was added to a flame dried Schlenk flask under N_2-atmosphere. The solution was cooled to −10 °C and *n*-butyllithium (1.6 M in hexane, 2.79 mL, 4.46 mmol, 1.5 eq.) was added dropwise. After stirring for 20 min, CuI·0.75DMS (1.16 g, 4.90 mmol, 1.65 eq.) was added in one portion and the mixture was stirred for an additional 45 min. The solution was cooled to −78 °C and TMSI (650 µL, 4.46 mmol, 1.5 eq.) was added. After 5 min, enal **6**[6] (500 mg, 2.97 mmol, 1.0 eq.) in anhydrous THF (3 mL) was added dropwise *via* the wall of the flask. After the addition was completed the mixture was stirred for an additional 1.5 h at −78 °C, before Et_3N (1.86 mL, 13.4 mmol, 4.5 eq.) was added. Stirring was continued for 1 h at room temperature, before Et_2O (30 mL) was added. The mixture was transferred to a separation funnel and washed with saturated solutions of $Na_2S_2O_3$ (50 mL), $NaHCO_3$ (50 mL) and NaCl (50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the crude silyl enol ether **13**, which was used directly in the next step.

The crude silyl enol ether **13** was dissolved in a mixture of CH_2Cl_2 and MeOH (3:1, 30 mL) and cooled to −78 °C. A stream of ozone was bubbled through the stirred solution. The reaction progress was monitored periodically by TLC to judge completion of the reaction. After completion (ca. 15 min), the mixture was flushed with a stream of N_2 to remove excess O_3. Afterwards triphenylphosphine (2.33 g, 8.91 mmol, 3.0 eq.) was added at −78 °C and the mixture was stirred for 1 h at −78 °C. $NaBH_4$ (333 mg, 8.91 mmol, 3.0 eq.) was added and the mixture was stirred 2 h at −78 °C and 1 h at room temperature. The mixture was poured into a separation funnel filled with brine (50 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (SiO_2, petroleum ether → petroleum ether/EtOAc (3:1)) to yield the alcohol **14** (725 mg, 1.66 mmol, 56% over 2 steps) as a white solide.

Mp 42 °C

R_f = 0.39 (petroleum ether/EtOAc 8:2)

ν_{max} (film): 3452 (broad), 2924, 2853, 1472, 1448, 1361, 1340, 1251, 1204, 1093, 1074, 1046, 1004, 970, 834, 776, 717, 668 cm^{-1}.

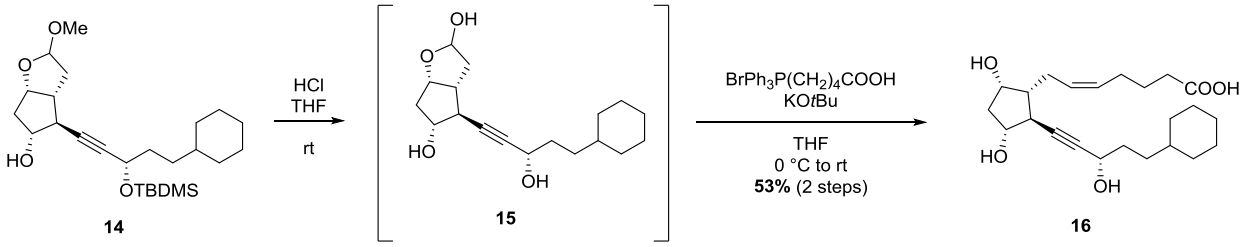
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.08 (d, *J* = 5.0 Hz, 1H, C*H*OOCH$_3$), 4.61 (td, *J* = 6.8, 1.5 Hz, 1H, CH), 4.27 (td, *J* = 6.5, 1.9 Hz, 1H, C*H*OTBDMS), 4.18 (d, *J* = 9.6 Hz, 1H, C*H*OH), 3.31 (s, 3H, OCH$_3$), 2.81 (ddd, *J* = 11.7, 10.1, 5.2 Hz, 1H, CH), 2.63 (t, *J* = 4.2 Hz, 1H, CH), 2.39 (d, *J* = 6.8 Hz, 1H, OH), 2.31–2.28 (m, 1H, CH*H*), 2.27–2.22 (m, 1H, CH*H*), 2.06 (dt, *J* = 13.7, 5.3 Hz, 1H, C*H*H), 2.02–1.96 (m, 1H, C*H*H), 1.70–1.58 (m, 7H, 3 × CH$_2$ + C*H*H), 1.29–1.15 (m, 6H, 2 × CH$_2$, CH*H* + CH), 0.89 (s, 11H, 3 × CH$_3$ + CH$_2$), 0.09 (s, 3H, CH$_3$), 0.08 (s, 3H, CH$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 106.2 (*C*HOOCH$_3$), 85.0 (C≡C), 84.6 (C≡C), 82.8 (*C*H), 80.2 (CHOH), 63.6 (*C*HOTBDMS), 54.6 (OCH$_3$), 48.0 (CH), 46.7 (CH), 40.5 (CH$_2$), 39.4 (CH$_2$), 37.5 (CH), 36.4 (CH$_2$), 33.6 (2 × CH$_2$), 33.2 (CH$_2$), 26.8 (CH$_2$), 26.5 (2 × CH$_2$), 26.0 (3 × CH$_3$), 18.4 (C), −4.3 (CH$_3$), −4.7 (CH$_3$).

HRMS (ESI) calcd. for $C_{25}H_{44}NaO_4Si$ $[M+Na]^+$ 459.2903, found 459.2901.

$[\alpha]_D^{22}$ = −76.0 (c 1.1, $CHCl_3$)

(*Z*)-7-((1*R*,2*S*,3*R*,5*S*)-2-((*S*)-5-Cyclohexyl-3-hydroxypent-1-yn-1-yl)-3,5-dihydroxycyclopentyl)hept-5-enoic acid (16):



Alcohol **14** (200 mg, 458 µmol, 1.0 eq.) was dissolved in 1.5% aqueous HCl/THF (3:2, 5 mL) and stirred at room temperature for 16 h. The reaction mixture was neutralized with 2 M NaOH and extracted with CH_2Cl_2 (5 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give triol **15** and a silanol by-product as a clear yellowish oil, which was directly used in the next step without further purification.

(4-Carboxybutyl)(triphenyl)phosphonium bromide (1.22 g, 2.75 mmol, 6.0 eq.) was added to a flame dried Schlenk flask under N_2-atmosphere. Anhydrous THF (8 mL) was added and the resulting suspension was cooled to 0 °C before KO*t*-Bu (1 M in THF, 5.50 mL, 5.50 mmol, 12.0 eq.) was added. The orange mixture was stirred at 0 °C for 40 min, before the crude triol

15 in anhydrous THF (3 mL) was added dropwise. After the complete addition, the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with H_2O (3 mL) and washed with Et_2O (2 × 5 mL) to remove triphenylphosphine oxide. The aqueous phase was acidified with 1 M HCl (~ 2 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was triturated with EtOAc/heptane (1:1, 5 mL) and the resulting solid was washed with EtOAc (5 × 3 mL). The filtrate was concentrated and purified by flash column chromatography (SiO_2, petroleum ether/EtOAc/AcOH 19:80:1) to give carboxylic acid **16** (95 mg, 243 µmol, 53% over 2 steps) as a colourless oil.

$\boldsymbol{R_f}$ = 0.29 (petroleum ether/EtOAc/AcOH 19:80:1)

$\boldsymbol{\nu_{max}}$ (film): 3340 (broad), 2921, 2850, 1708, 1448, 1260, 1051, 926 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 5.52 (dd, *J* = 10.4, 7.5 Hz, 1H, C=CH), 5.38 (dd, *J* = 10.6, 7.5 Hz, 1H, C=CH), 5.67–4.84 (brs, 4H, COOH, 3 × OH), 4.34 (t, *J* = 6.6 Hz, 1H, C*H*OH), 4.20 (s, 1H, C*H*OH), 4.16 (s, 1H, C*H*OH), 2.63 (dd, *J* = 10.7, 5.2 Hz, 1H, CH), 2.43–2.31 (m, 3H, CH_2 + CH*H*), 2.30–2.22 (m, 2H, C*H*H + C*H*H), 2.16 (q, *J* = 7.4 Hz, 2H, CH_2), 1.78 (dd, *J* = 14.8, 3.2 Hz, 1H, CH*H*), 1.74–1.56 (m, 10H, 4 × CH_2, CH + CH*H*), 1.31–1.16 (m, 6H, 4 × CH_2 + CH + *CH*H), 0.88 (ddd, *J* = 14.0, 10.4, 8.4 Hz, 2H, CH_2).

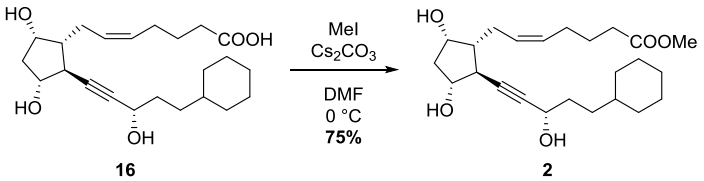
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 177.8 (*C*O_2H), 130.0 (*C*=C), 128.9 (C=*C*), 86.4 (*C*≡C), 83.6 (C≡*C*), 78.6 (CHOH), 72.6 (CHOH), 63.0 (CHOH), 52.1 (CH), 43.9 (CH), 42.8 (CH_2), 37.5 (CH), 35.4 (CH_2), 33.5 (CH_2), 33.5 (CH_2), 33.1 (CH_2), 33.1 (CH_2), 26.8 (CH_2), 26.5 (2 × CH_2), 26.4 (CH_2), 25.8 (CH_2), 24.6 (CH_2).

HRMS (ESI) calcd. for $C_{23}H_{36}NaO_5$ $[M+Na]^+$ 415.2454, found 415.2455

$[\alpha]_D^{23}$ = 28.0 (c 1.0, $CHCl_3$)

$[\alpha]_D^{23}$ = 24.0 (c 1.0, EtOH) (lit.,[7] $[\alpha]_D^{25}$ 24.0 (EtOH))

Methyl (*Z*)-7-((1*R*,2*S*,3*R*,5*S*)-2-((*S*)-5-cyclohexyl-3-hydroxypent-1-yn-1-yl)-3,5-dihydroxycyclopentyl)hept-5-enoate, Alfaprostol (2):



16 2

Carboxylic acid **16** (30.0 mg, 76.4 µmol, 1.0 eq.) was dissolved in DMF (0.5 mL) and cooled to 0 °C. Cs_2CO_3 (37.8 mg, 115 µmol, 1.5 eq.) and MeI (9.51 µL, 153 µmol, 2.0 eq.) were added and the suspension was stirred for 3 h at 0 °C, before the reaction mixture was poured into

3% citric acid solution (5 mL) and extracted with TBME (4 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure, to give the crude product, which was further purified by flash column chromatography (SiO_2, petroleum ether/EtOAc (50:50 → 0:100)) to yield Alfaprostol **2**. This was taken up in TBME (10 mL) and washed with a saturated solution of $NaHCO_3$ (2 × 5 mL) to remove remaining citric acid. The organic phase was dried over $MgSO_4$, filtered and evaporated to yield Alfaprostol **2** as a clear colourless oil (23 mg, 57.6 μmol, 75%).

$\boldsymbol{R_f}$ = 0.35 (petroleum ether/EtOAc 20:80)

$\boldsymbol{\nu_{max}}$ (film): 3352 (broad), 2922, 2851, 1738, 1447, 1317, 1224, 1169, 1052, 926 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.54–5.45 (m, 1H, C=CH), 5.45–5.36 (m, 1H, C=CH), 4.33 (brs, 1H, C*H*OH), 4.26–4.16 (m, 2H, 2 × C*H*OH), 3.67 (s, 3H, OC*H*$_3$), 2.85–2.73 (brs, 1H, OH), 2.62 (ddd, *J* = 10.4, 4.4, 1.7 Hz, 1H, CH), 2.34 (m, 4H, 2 × CH_2), 2.21–2.18 (m, 1H, CH*H*), 2.17–2.11 (m, 2H, CH_2), 1.87–1.77 (m, 2H, C*H*H + CH), 1.74–1.62 (m, 9H, 4 × CH_2 + CH*H*), 1.33–1.15 (m, 6H, 2 × CH_2 + C*H*H + CH), 0.94–0.85 (m, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 174.6 (*C*O_2Me), 130.2 (C=C), 128.8 (C=C), 86.3 (C≡C), 84.0 (C≡C), 79.3 (CHOH), 73.3 (CHOH), 63.1 (CHOH), 52.6 (CH), 51.8 (O*C*H_3), 44.5 (CH), 42.9 (CH_2), 37.6 (CH), 35.7 (CH_2), 33.5 (CH_2), 33.5 (2 × CH_2), 33.0 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.5 (2 × CH_2), 26.3 (CH_2), 24.9 (CH_2).

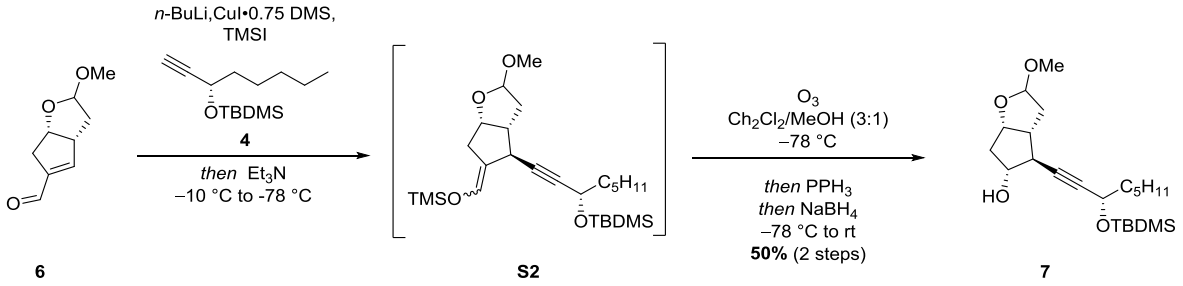
HRMS (ESI) calcd. for $C_{24}H_{38}NaO_5$ $[M+Na]^+$ 4292625, found 429.2611

$[\alpha]_D^{25}$ = 36.0 (c 1.0, $CHCl_3$)

$[\alpha]_D^{23}$ = 22.0 (c 1.0, EtOH)

2.2 Synthesis of $PGF_{2\alpha}$:

(3a*R*,4*S*,5*R*,6a*S*)-4-((*S*)-3-((*tert*-Butyldimethylsilyl)oxy)oct-1-yn-1-yl)-2-methoxy-hexahydro-2*H*-cyclopenta[*b*]furan-5-ol (18):



A solution of protected alcohol **4** (1.07 g, 4.46 mmol, 1.5 eq.) in anhydrous THF (12 mL) was added to a flame dried Schlenk flask under N_2-atmosphere. The solution was cooled to −10 °C and *n*-butyllithium (1.6 M in hexane, 2.79 mL, 4.46 mmol, 1.5 eq.) was added dropwise. After stirring for 20 min, CuI·0.75DMS (1.16 g, 4.90 mmol, 1.65 eq.) was added in one portion and the mixture was stirred for an additional 45 min. The solution was cooled to −78 °C and TMSI (650 µL, 4.46 mmol, 1.5 eq.) was added. After 5 min, enal **6** (500 mg, 2.97 mmol, 1.0 eq.) in anhydrous THF (3 mL) was added dropwise *via* the wall of the flask. After the addition was completed the mixture was stirred for an additional 1.5 h at −78 °C, before Et_3N (1.86 mL, 13.4 mmol, 4.5 eq.) was added. Stirring was continued for 1 h at room temperature, before Et_2O (30 mL) was added. The mixture was transferred to a separation funnel and washed with saturated solutions of $Na_2S_2O_3$ (50 mL), $NaHCO_3$ (50 mL) and NaCl (50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the crude silyl enol ether **S2**, which was used directly in the next step.

The crude silyl enol ether **S2** was dissolved in a mixture of CH_2Cl_2 and MeOH (3:1, 30 mL) and cooled to −78 °C. A stream of ozone was bubbled through the stirred solution. The reaction progress was monitored periodically by TLC to judge completion of the reaction. After completion, the mixture was flushed with a stream of N_2 to remove excess O_3. Afterwards triphenylphosphine (2.33 g, 8.91 mmol, 3.0 eq.) was added at −78 °C and the mixture was stirred for 1 h at −78 °C. $NaBH_4$ (333 mg, 8.91 mmol, 3.0 eq.) was added and the mixture was stirred 2 h at −78 °C and 1 h at room temperature. The mixture was over brine (50 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (SiO_2, petroleum ether → petroleum ether/EtOAc (7:3)) to yield the alcohol **7** (590 mg, 149 mmol, 50% over 2 steps) as a colourless oil.

R_f = 0.31 (petroleum ether/EtOAc 80:20)

ν_{max} (film): 2953, 2929, 2857, 1463, 1341, 1252, 1090,1047, 1004, 837, 777 cm^{-1}.

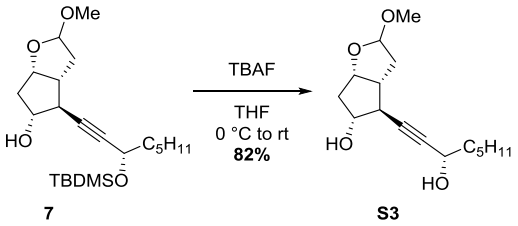
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.08 (d, *J* = 5.0 Hz, 1H, C*H*OOCH$_3$), 4.61 (td, *J* = 6.2, 1.6 Hz, 1H, C*H*OC), 4.30 (td, *J* = 6.6, 1.9 Hz, 1H, C*H*OTBDMS), 4.23–4.15 (m, 1H, C*H*OH), 3.31 (s, 3H, OC*H*$_3$), 2.86–2.75 (m, 1H, CH), 2.63 (t, *J* = 4.3 Hz, 1H, CH), 2.40 (d, *J* = 6.7 Hz, 1H, OH), 2.33–2.21 (m, 2H, CH*H* + CH*H*), 2.06 (dt, *J* = 13.7, 5.3 Hz, 1H, C*H*H), 1.99 (dt, *J* = 14.6, 2.0, Hz, 1H, C*H*H), 1.70–1.58 (m, 2H, CH_2), 1.46–1.23 (m, 6H, 3 × CH_2), 0.91–0.88 (m, 12H, 4 × CH_3), 0.10 (s, 3H, CH_3), 0.08 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 106.2 (*C*HOOCH$_3$), 85.0 (C≡C), 84.6 (C≡C), 82.8 (*C*HOC), 80.2 (CHOH), 63.3 (*C*HOTBDMS), 54.6 (O*C*H$_3$), 48.1 (CH), 46.7 (CH), 40.5 (CH_2), 39.4 (CH_2), 39.0 (CH_2), 31.6 (CH_2), 26.0 (3 × CH_3), 25.2 (CH_2), 22.7 (CH_2), 18.4 (C), 14.2 (CH_3), −4.3 (CH_3), −4.8 (CH_3).

HRMS (ESI) calcd. for $C_{22}H_{40}NaO_4Si$ $[M+Na]^+$ 419.2588, found 419.2588.

$[\alpha]_D^{23}$ = −133 (c 2.0, $CHCl_3$)

(3a*R*,4*S*,5*R*,6a*S*)-4-((*S*)-3-Hydroxyoct-1-yn-1-yl)-2-methoxyhexahydro-2*H*-cyclopenta[*b*]furan-5-ol (S3):



7 S3

A solution of alcohol **7** (500 mg, 1.26 mmol, 1.0 eq.) in anhydrous THF was added to a flame dried Schlenk flask under N_2-atmosphere and cooled to 0 °C. A solution of tetra-*n*-butylammonium fluoride (1 M in THF, 2.52 mL, 2.52 mmol, 2.0 eq.) was added dropwise. The resulting red solution was stirred at room temperature for 1 h, before it was poured over brine (20 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was further purified by flash column chromatography (SiO_2, petroleum ether/EtOAc (8:2 → 3:7)) to give diol **S3** (292 mg, 1.03 mmol, 82%) as a clear yellowish oil.

R_f = 0.83 (petroleum ether/EtOAc 30:70)

ν_{max} (film): 3399 (broad), 2932, 2859, 1448, 1340, 1204, 1103, 1045, 915 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.09 (d, *J* = 5.1 Hz, 1H, C*H*OOCH$_3$), 4.61 (td, *J* = 6.3, 1.9 Hz, 1H, C*H*OC), 4.34 (s, 1H, C*H*OH), 4.20 (s, 1H, C*H*OH), 3.31 (s, 3H, OC*H*$_3$), 2.84–

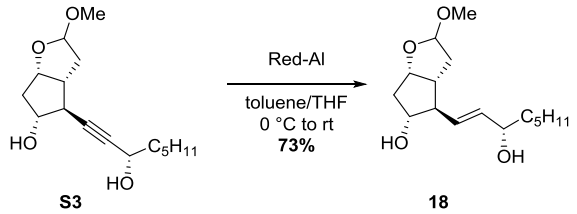
2.77 (m, 1H, CH), 2.66–2.61 (m, 1H, CH), 2.46 (d, *J* = 6.8 Hz, 1H, OH), 2.32–2.23 (m, 2H, CH*H* + CH*H*), 2.07 (dt, *J* = 13.7, 5.2 Hz, 1H, C*H*H), 1.99 (td, *J* = 14.6, 2.1 Hz, 1H, C*H*H), 1.75–1.70 (brs, 1H, OH), 1.65 (tt, *J* = 8.4, 6.6 Hz, 2H, CH_2), 1.48–1.38 (m, 2H, CH_2), 1.35–1.28 (m, 4H, 2 ×), 0.90 (t, *J* = 6.8 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 106.2 (*C*HOOCH$_3$), 85.8 (C≡C), 84.1 (C≡C), 82.6 (*C*HOC), 80.2 (CHOH), 62.8 (CHOH), 54.7(OCH$_3$), 48.1 (CH), 46.6 (CH), 40.4 (CH_2), 39.4 (CH_2), 38.2 (CH_2), 31.6 (CH_2), 25.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

HRMS (ESI) calcd. for $C_{16}H_{26}NaO_4$ $[M+Na]^+$ 305.1734, found 305.1723.

$[\alpha]_D^{23}$ = −99.0 (c 1.5, $CHCl_3$)

(3a*R*,4*R*,5*R*,6a*S*)-4-((*S*,*E*)-3-Hydroxyoct-1-en-1-yl)-2-methoxyhexahydro-2*H*-cyclopenta[*b*]furan-5-ol (18):



Anhydrous THF (2 mL) and Red-Al (60% in toluene, 288 µL, 885 µmol, 5.0 eq.) were added into a flame dried Schlenk flask under N_2-atmosphere and the resulting solution was cooled to 0 °C. A solution of diol **S3** (50 mg, 177 µmol, 1.0 eq.) in anhydrous THF (1 mL) was added dropwise. The mixture was stirred for 5 min at 0 °C, before being stirred at room temperature for 16 h. The reaction was quenched with H_2O (2 mL), followed by a saturated solution of NH_4Cl (1 mL) and extracted with Et_2O (4 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was further purified by flash column chromatography (SiO_2, petroleum ether/EtOAc (1:1 → 0:100)) yielding diol **18** (36.8 mg, 129 µmol, 73%) as a colourless oil.

R_f = 0.39 (petroleum ether/EtOAc 30:70)

ν_{max} (film): 3370 (broad), 2927, 2858, 1447, 1341, 1261, 1098, 1044, 1003, 973, 922, 836, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.54 (dd, *J* = 15.4, 6.6 Hz, 1H, C=CH), 5.46 (dd, *J* = 15.4, 7.8 Hz, 1H, C=CH), 5.11 (dd, *J* = 5.3, 1.3 Hz, 1H, C*H*OOCH$_3$), 4.46 (td, *J* = 6.7, 3.5 Hz, 1H, C*H*OC), 4.04 (q, *J* = 6.5 Hz, 1H, C*H*OH), 3.87 (q, *J* = 7.4 Hz, 1H, C*H*OH), 3.31 (s, 3H, OC*H*$_3$), 2.43–2.34 (m, 2H, CH*H*+CH), 2.18 (q, *J* = 7.9 Hz, 1H, CH), 2.07 (ddd, *J* = 8.9, 4.7, 1.4 Hz,

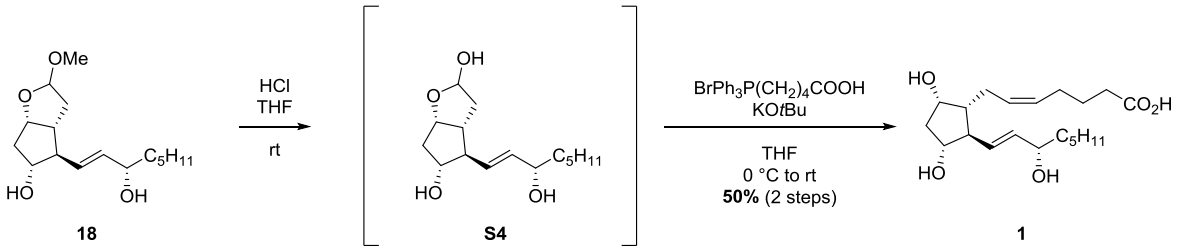
1H, CH*H*), 1.93 (dt, *J* = 13.6, 0.2 Hz, 1H, C*H*H), 1.83–1.76 (m, 1H, C*H*H), 1.57–1.44 (m, 2H, CH_2), 1.33–1.25 (m, 6H, 3 × CH_2), 0.87 (t, *J* = 6.9 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 135.4 (C=C), 131.9 (C=C), 106.7 (*C*H$OOCH_3$), 80.6 (*C*HOC), 78.5 (CHOH), 73.1 (CHOH), 57.8 (CH), 54.7 (OCH_3), 45.7 (CH), 39.7 (CH_2), 38.9 (CH_2), 37.4 (CH_2), 31.8 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 14.2 (CH_3).

HRMS (ESI) calcd. for $C_{16}H_{28}NaO_4$ $[M+Na]^+$ 307.1893, found 307.1880.

$[\alpha]_D^{24}$ = 47.0 (c 0.67, $CHCl_3$)

(*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-((*S*,*E*)-3-hydroxyoct-1-en-1-yl)cyclopentyl)hept-5-enoic acid, $PGF_{2\alpha}$ (1):



Alcohol **18** (40.0 mg, 141 µmol, 1.0 eq.) was dissolved in 1.5% aqueous HCl/THF (3:2, 2 mL) and stirred at room temperature for 16 h. The reaction mixture was neutralized with 2 M NaOH and extracted with CH_2Cl_2 (5 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give triol **S4** and silanol by-product as a clear yellowish oil, which was directly used in the next step without further purification.

(4-Carboxybutyl)(triphenyl)phosphonium bromide (375 mg, 846 µmol, 6.0 eq.) was added to a flame dried Schlenk flask under N_2-atmosphere. Anhydrous THF (2 mL) was added and the resulting suspension was cooled to 0 °C before KO*t*-Bu (1 M in THF, 1.69 mL, 1.69 mmol, 12.0 eq.) was added. The orange mixture was stirred at 0 °C for 40 min, before the crude triol **S4** in anhydrous THF (1 mL) was added dropwise. After the complete addition, the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with H_2O (3 mL) and washed with Et_2O (2 × 5 mL) to remove triphenylphosphine oxide. The aqueous phase was acidified with 1 M HCl (~ 2 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was triturated with EtOAc/heptane (1:1, 5 mL) and the resulting solid was washed with EtOAc (5 × 3 mL). The filtrate was concentrated and purified by flash column chromatography (SiO_2, petroleum ether/EtOAc/AcOH 35:60:5) to give $PGF_{2\alpha}$ **1** (24.8 mg, 70.0 µmol, 50% over 2 steps) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 5.55 (dd, *J* = 15.3, 7.0 Hz, 1H, C=CH), 5.50–5.40 (m, 2H, 2 × C=CH), 5.34 (dt, *J* = 10.8, 7.3 Hz, 1H, C=CH), 5.01 (brs, 1H, CO_2H), 4.15 (t, *J* = 4.7 Hz, 1H, C*H*OH), 4.07 (q, *J* = 6.8 Hz, 1H, C*H*OH), 3.93 (s, 1H, C*H*OH), 2.32 (t, *J* = 6.6 Hz, 3H, CH+CH_2), 2.27–2.18 (m, 2H, CH_2), 2.17–2.05 (m, 3H, CH+CH_2), 1.74 (dd, *J* = 15.7, 3.2 Hz, 1H, CH), 1.66 (p, *J* = 7.2 Hz, 2H, CH_2), 1.62–1.55 (m, 1H, CH), 1.49–1.43 (m, 2H, 2 × CH), 1.32–1.26 (m, 6H, 3 × CH_2), 0.87 (t, *J* = 6.6 Hz, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 177.9 (CO_2H), 135.2 (C=CH), 132.9 (C=CH), 129.8 (C=CH), 129.3 (C=CH), 77.8 (CHOH), 73.3 (CHOH), 72.7 (CHOH), 55.4 (CH), 50.4 (CH), 42.9 (CH_2), 37.1 (CH_2), 33.4 (CH_2), 31.9 (CH_2), 26.5 (CH_2), 25.4 (CH_2), 25.4 (CH_2), 24.7 (CH_2), 22.8 (CH_2), 14.2 (CH_3).

$[\alpha]_D^{23}$ = 24.0 (c 1.00, THF) (lit.,[8] $[\alpha]_D^{25}$ 23.8 (synthetic material) (c 1.0 THF)) (lit.,[8] $[\alpha]_D^{25}$ 23.5 (natural material) (c 1.0 THF))

3. References

[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

[2] House O. H.; Chia-Yeh Chu; Wilkins J. M.; Umen M. J. *J. Org. Chem.* **1975**, *40*, 1460-1469.

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[4] Coulthard, G.; Erb, W.; Aggarwal, V. K. *Nature* **2012,** *489*, 278.

[5] Prevost, S.; Thai, K.; Schützenmeister, N.; Coulthard, G.; Erb, W.; Aggarwal, V. K. *Org. Lett.* **2015**, *17*, 504.

[6] The major diastereomer of **6** was used in this study to simplify NMR analysis of subsequent intermediates.

[7] Gandolfi, C.; Pellegata, R.; Ceserjani, R.; Usardi, M. M. US Patent Application, **1977**, No.4035415.

[8] Corey E. J.; Schaaf T.; Huber W.; Koelliker U.; Winshenker N. *J. Am. Chem. Soc.* **1970**, *92*, 397-398.

4. ^{1}H and ^{13}C spectra

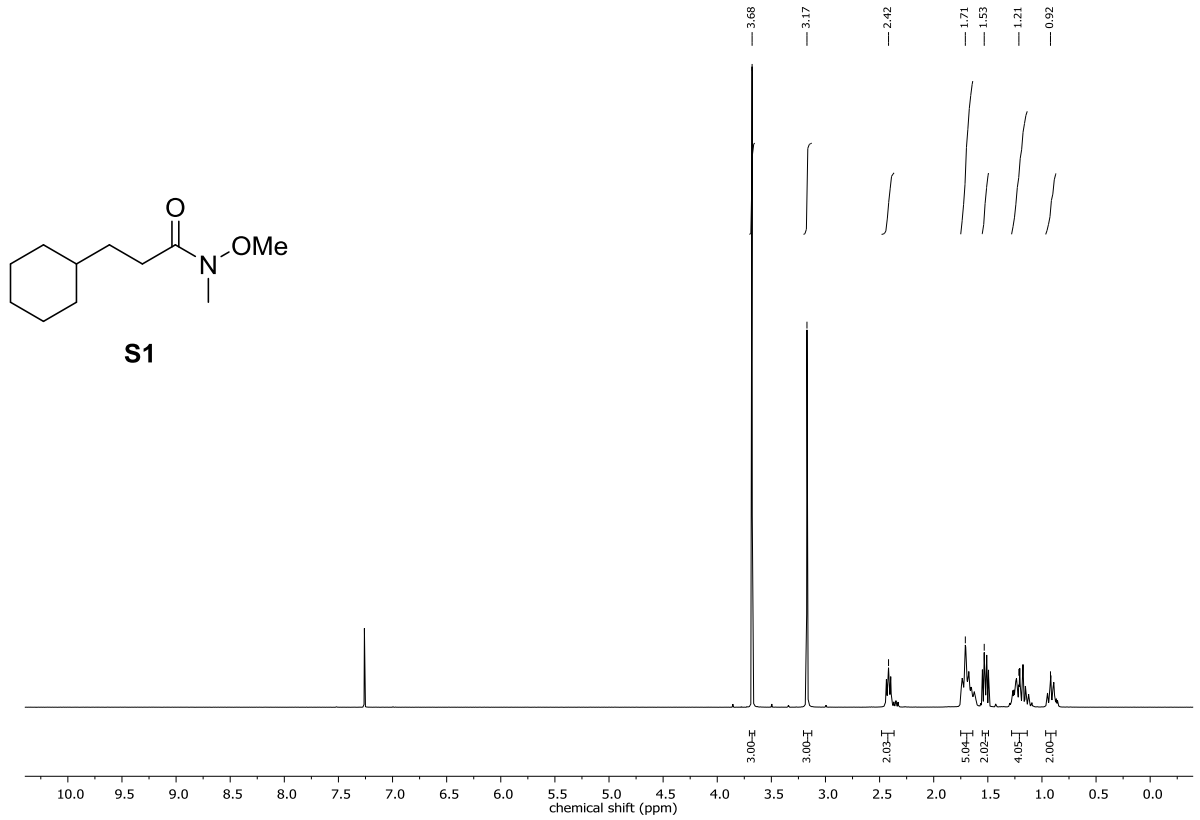

Figure 3: ^{1}H-NMR Spectrum of weinreb amide **S1** in $CDCl_3$ at 400 MHz

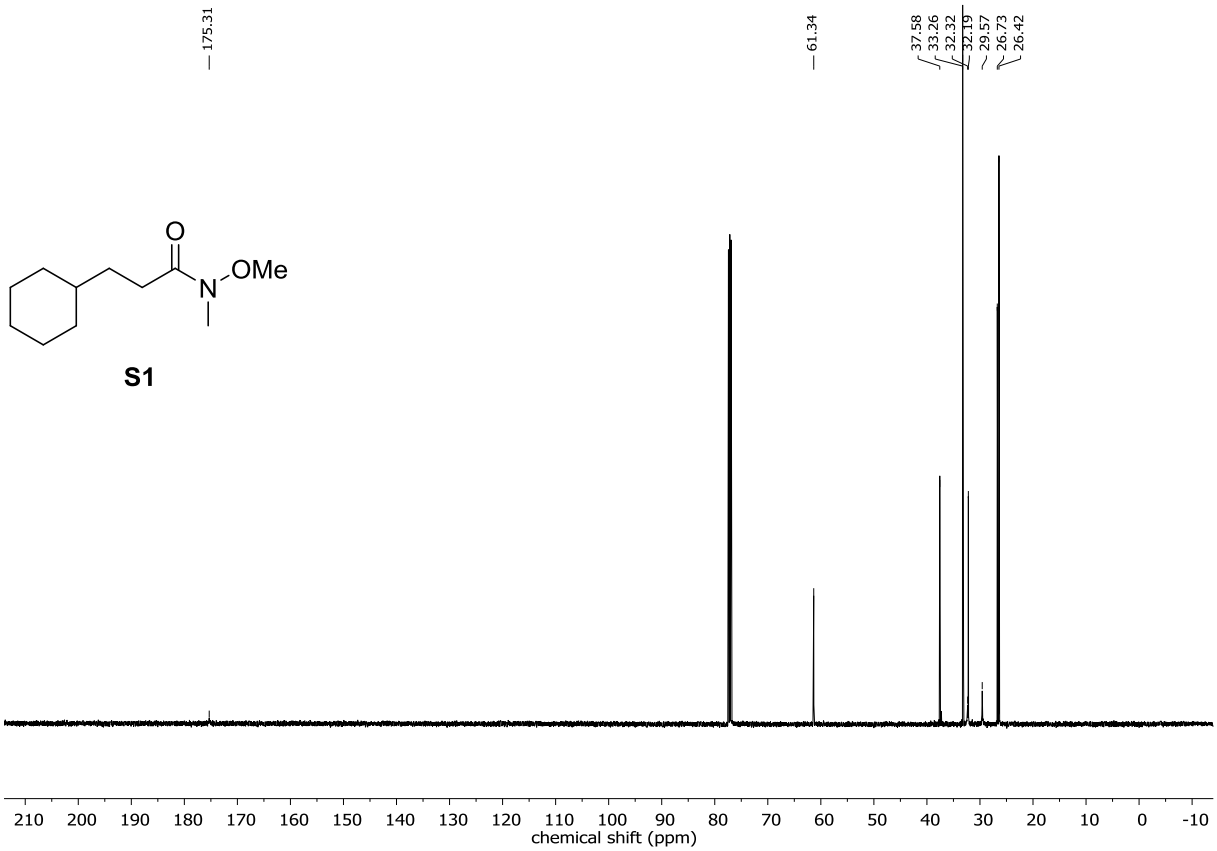

Figure 4: ^{13}C-NMR Spectrum of weinreb amide **S1** in $CDCl_3$ at 126 MHz

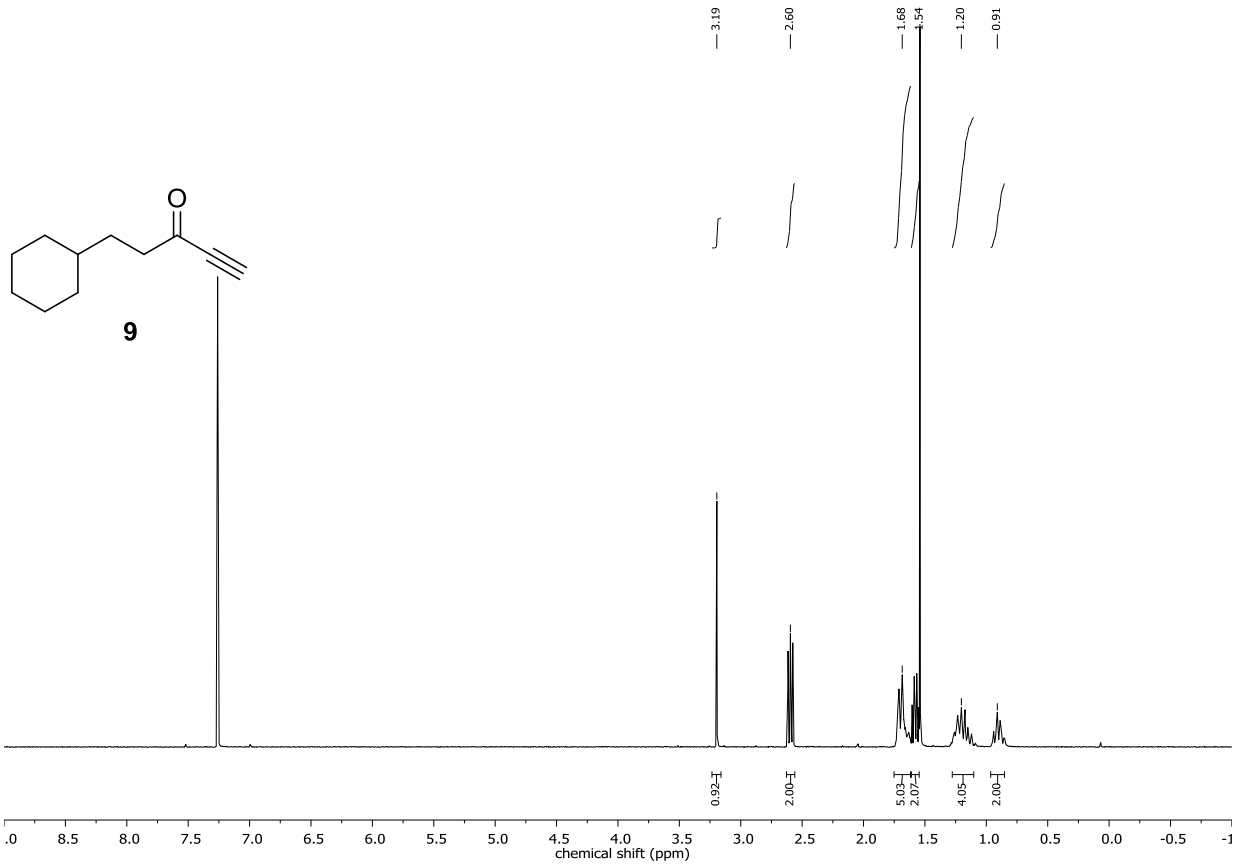

Figure 5: ^{1}H-NMR Spectrum of ketone **9** in $CDCl_3$ at 400 MHz

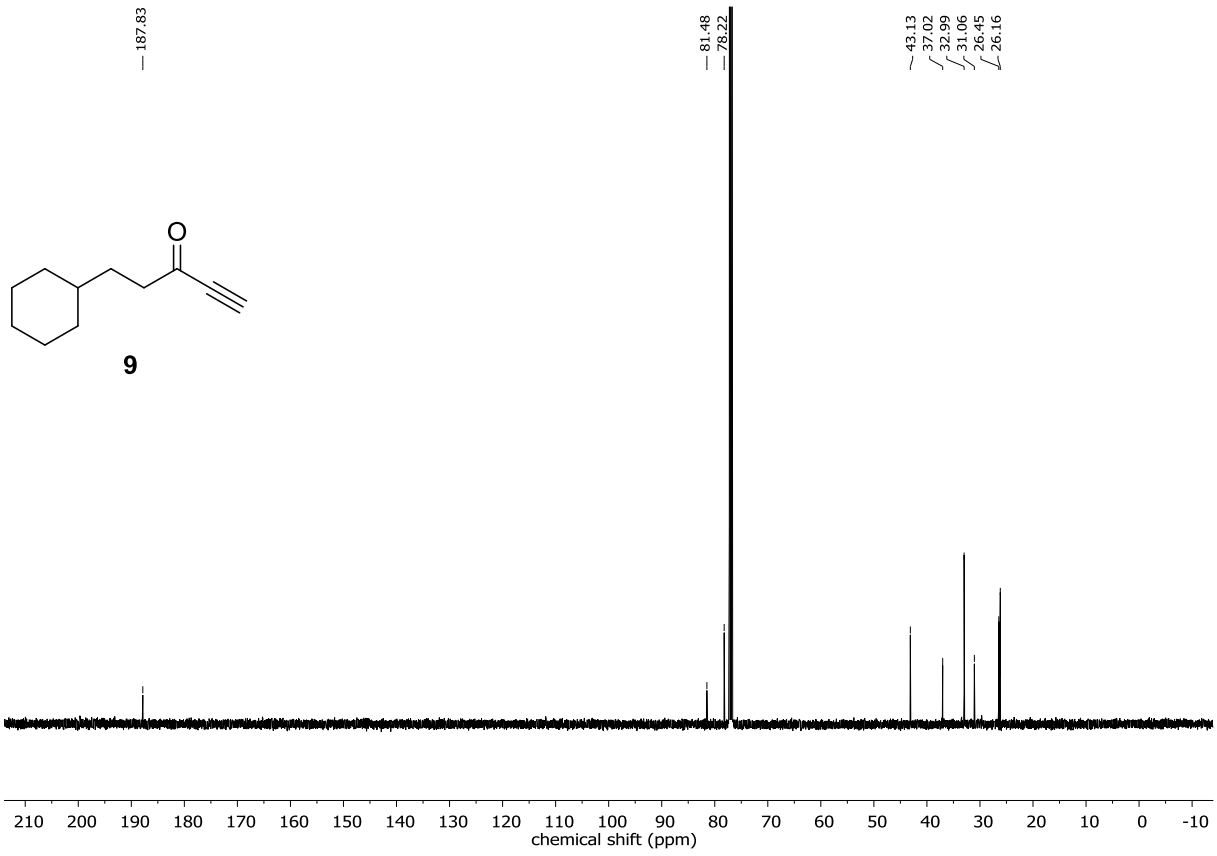

Figure 6: ^{13}C-NMR Spectrum of ketone **9** in $CDCl_3$ at 126 MHz

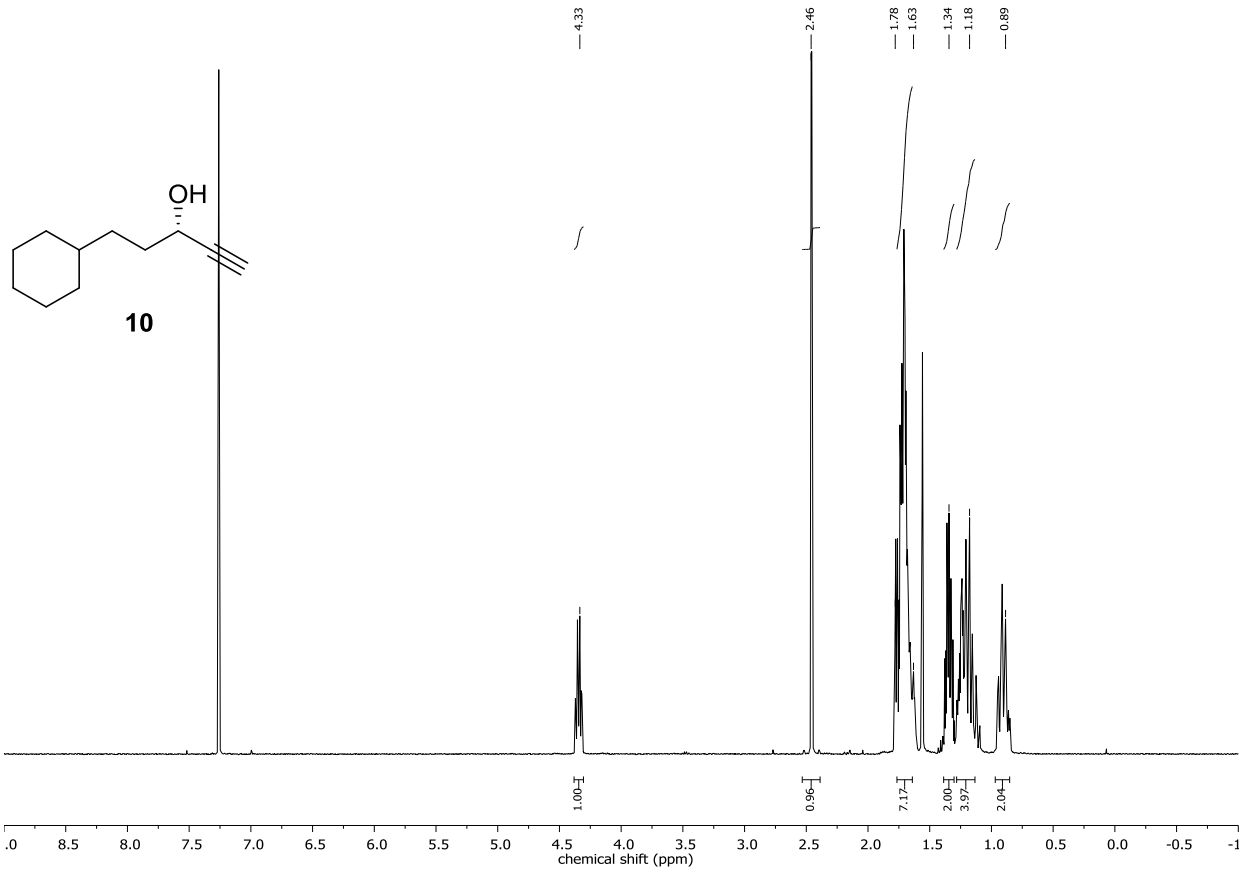

Figure 7: ^{1}H-NMR Spectrum of alcohol **10** in $CDCl_3$ at 400 MHz

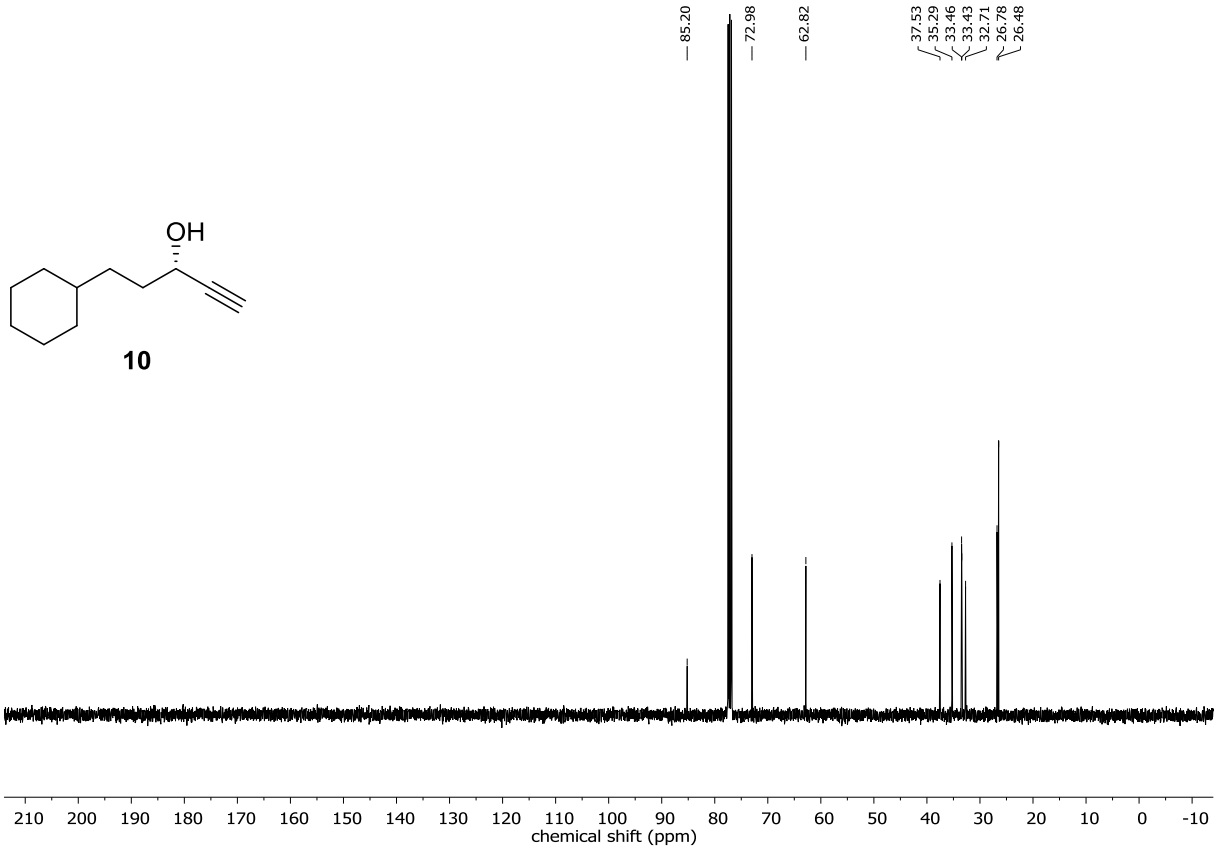

Figure 8: ^{13}C-NMR Spectrum of alcohol **10** in $CDCl_3$ at 101 MHz

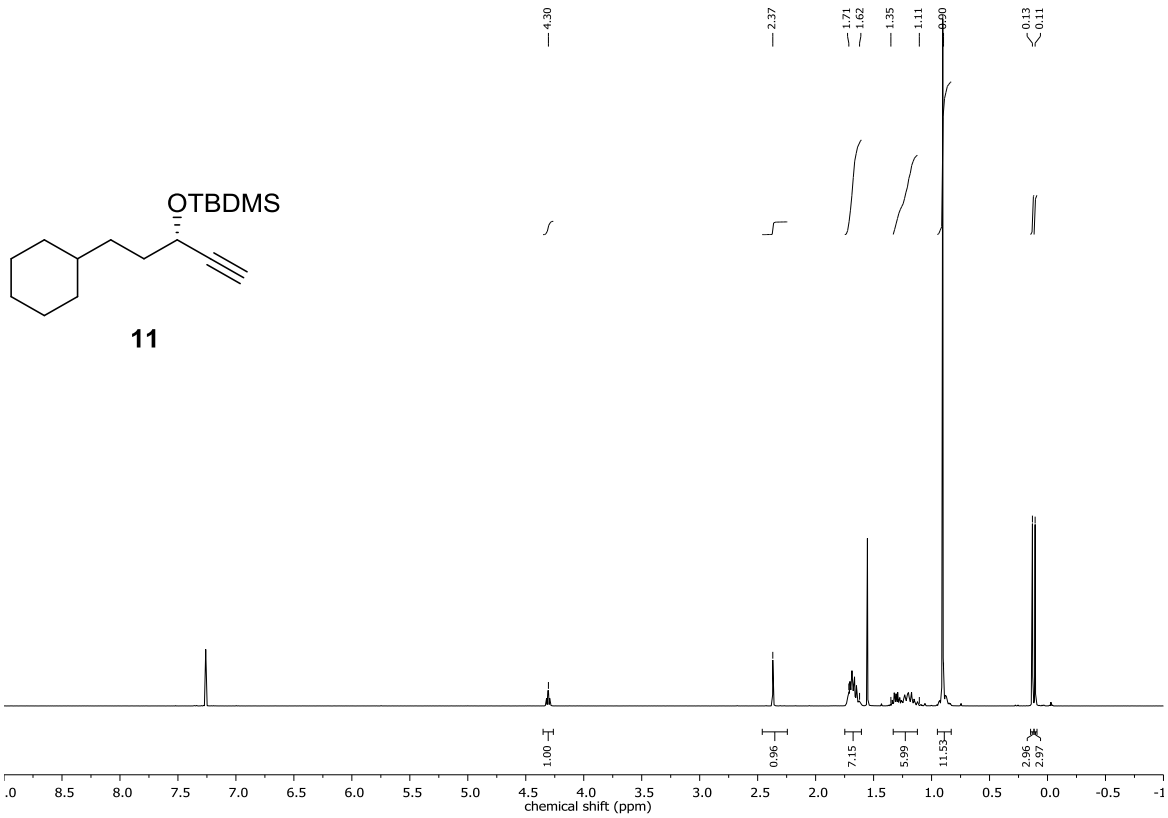

Figure 9: ^{1}H-NMR Spectrum of protected alcohol **11** in $CDCl_3$ at 400 MHz

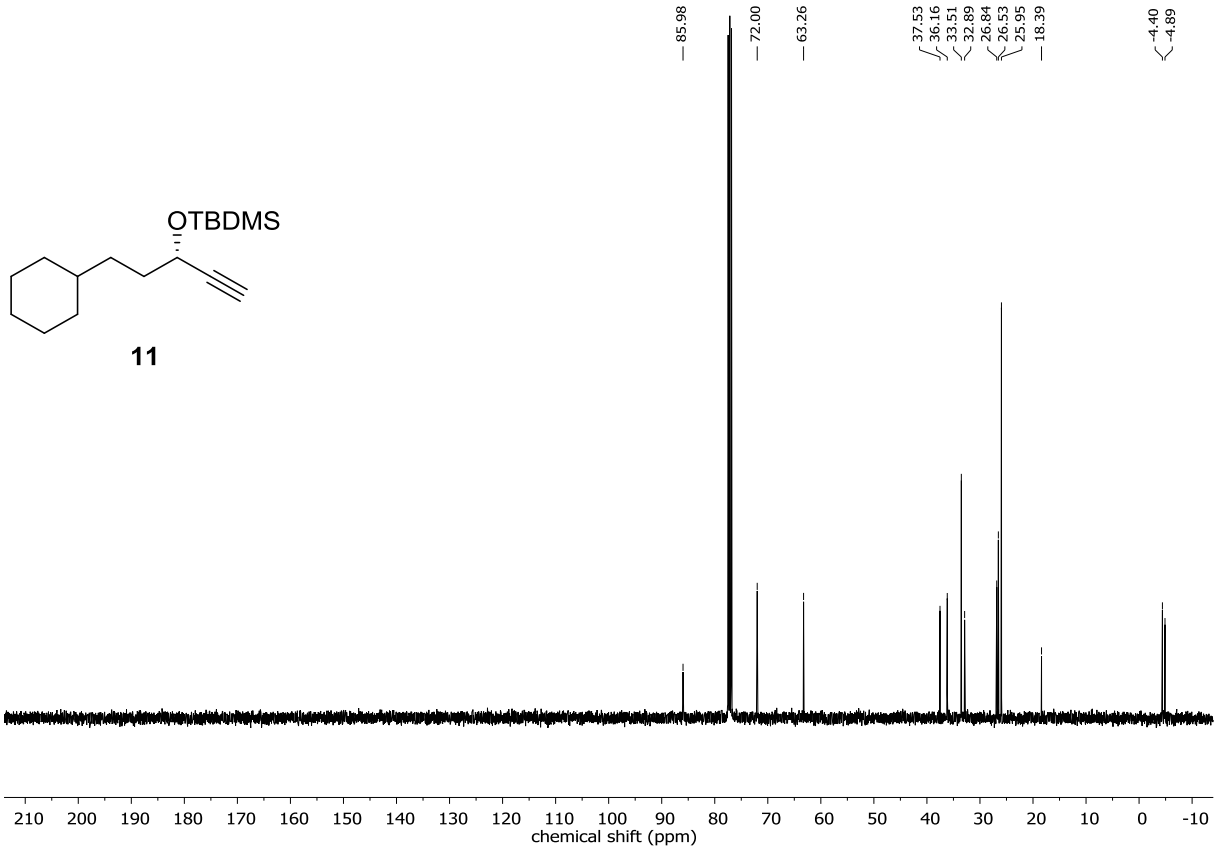

Figure 10: ^{13}C-NMR Spectrum of protected alcohol **11** in $CDCl_3$ at 101 MHz

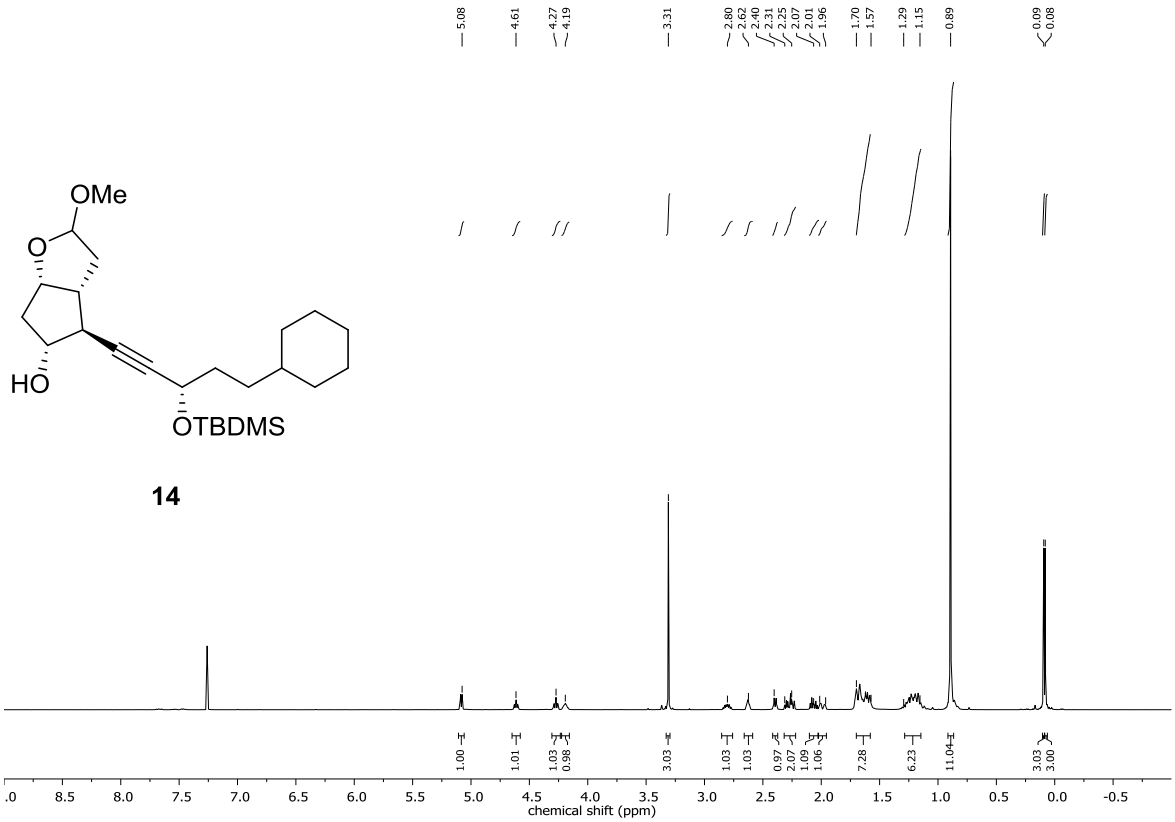

Figure 11: ^{1}H-NMR Spectrum of alcohol **14** in $CDCl_3$ at 400 MHz

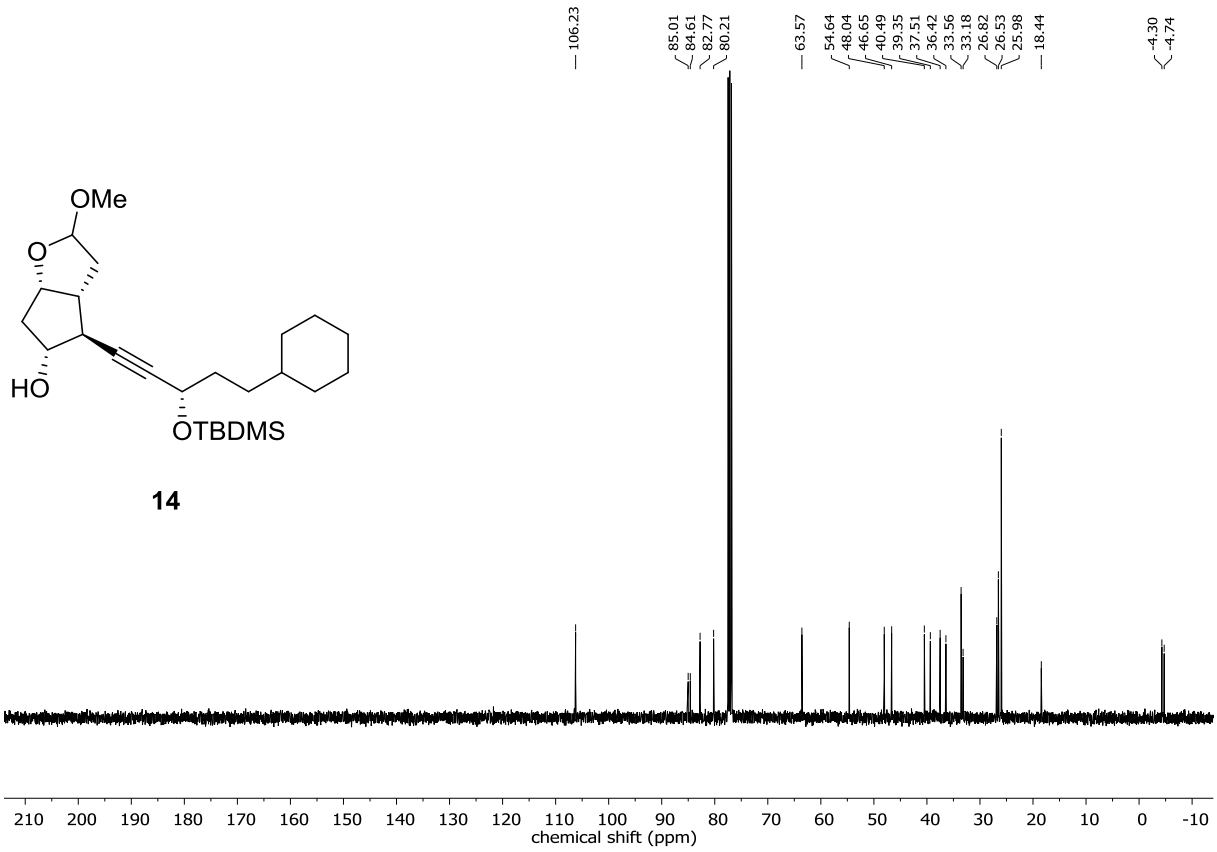

Figure 12: ^{13}C-NMR Spectrum of alcohol **14** in $CDCl_3$ at 101 MHz

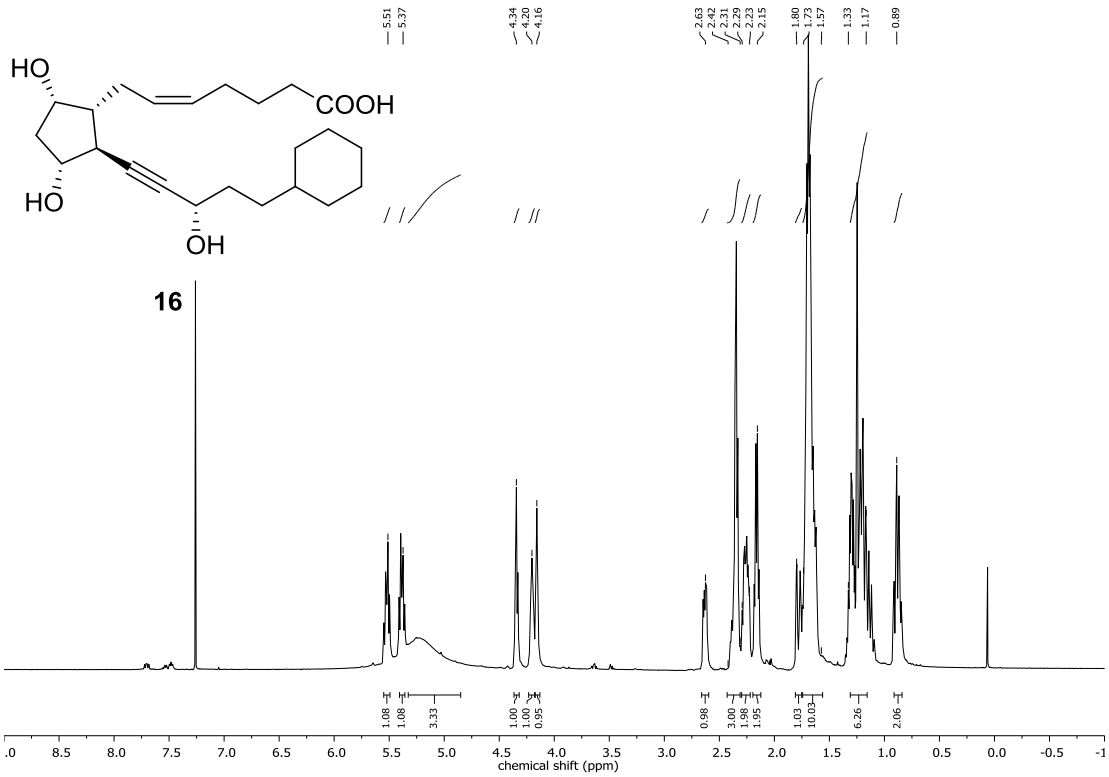

Figure 13: ^{1}H-NMR Spectrum of carboxylic acid **16** in $CDCl_3$ at 500 MHz

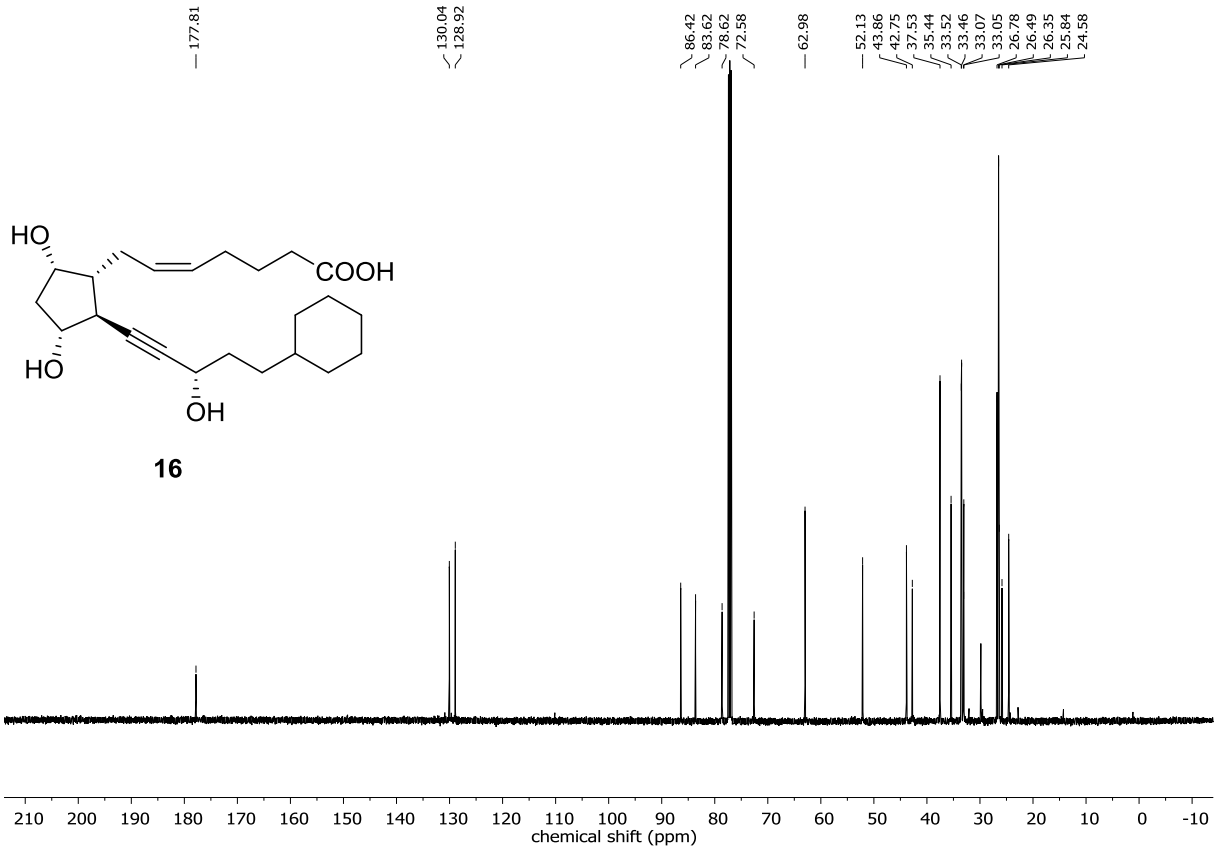

Figure 14: ^{13}C-NMR Spectrum of carboxylic acid **16** in $CDCl_3$ at 126 MHz

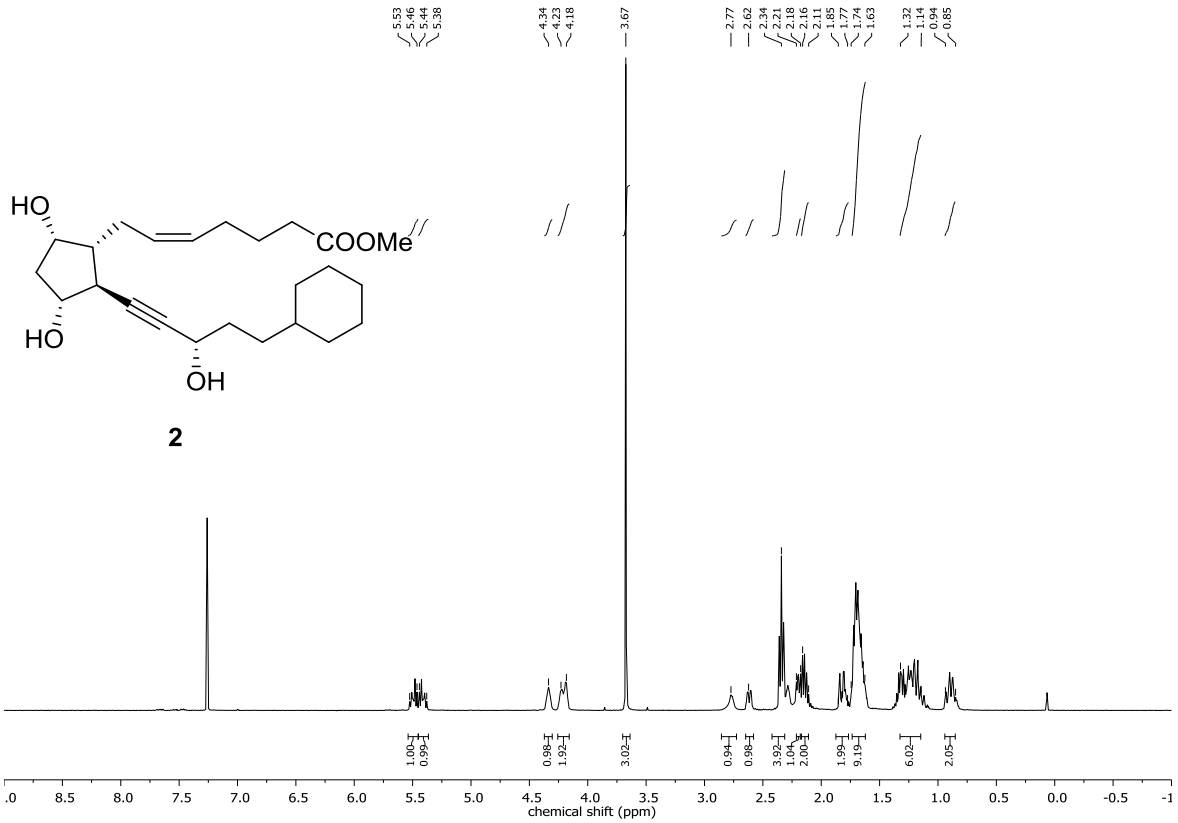

Figure 15: ^{1}H-NMR Spectrum of Alfaprostol **2** in $CDCl_3$ at 400 MHz

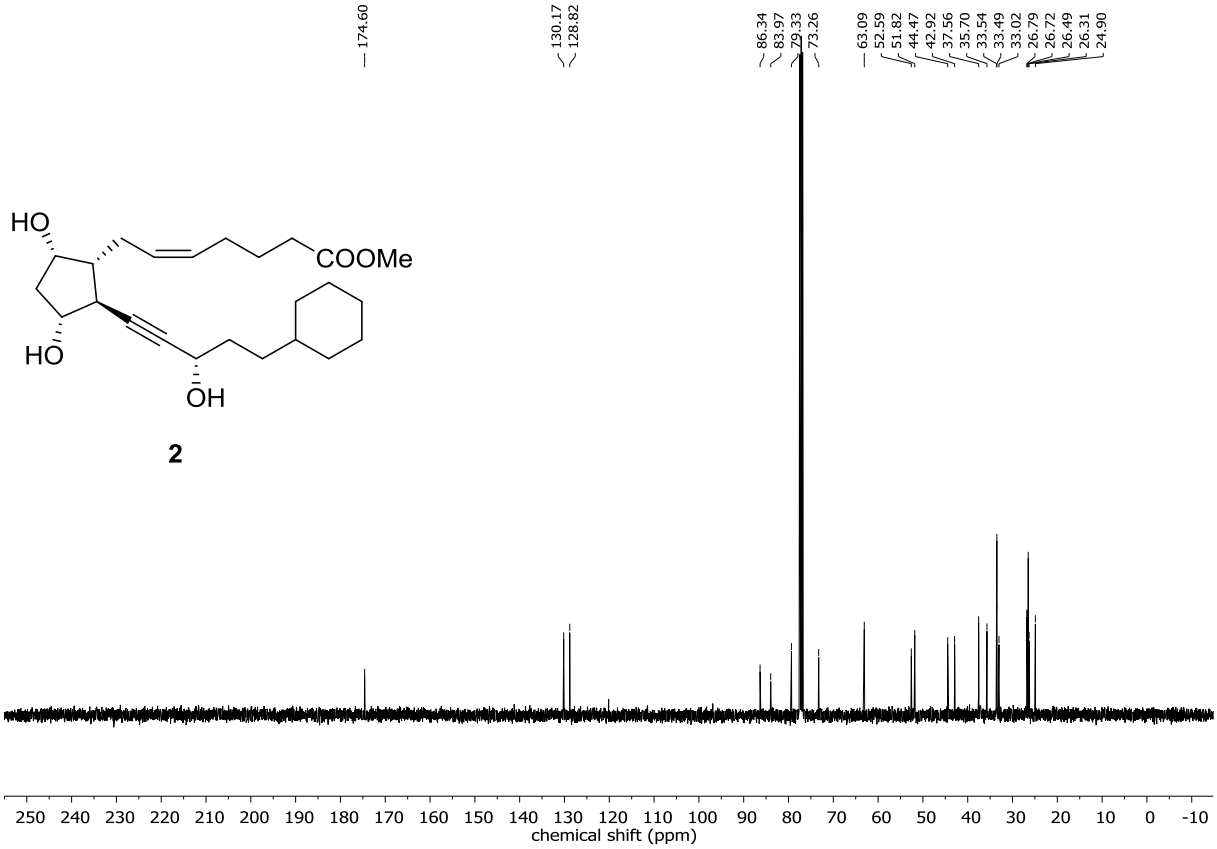

Figure 16: ^{13}C-NMR Spectrum of Alfaprostol **2** in $CDCl_3$ at 101 MHz

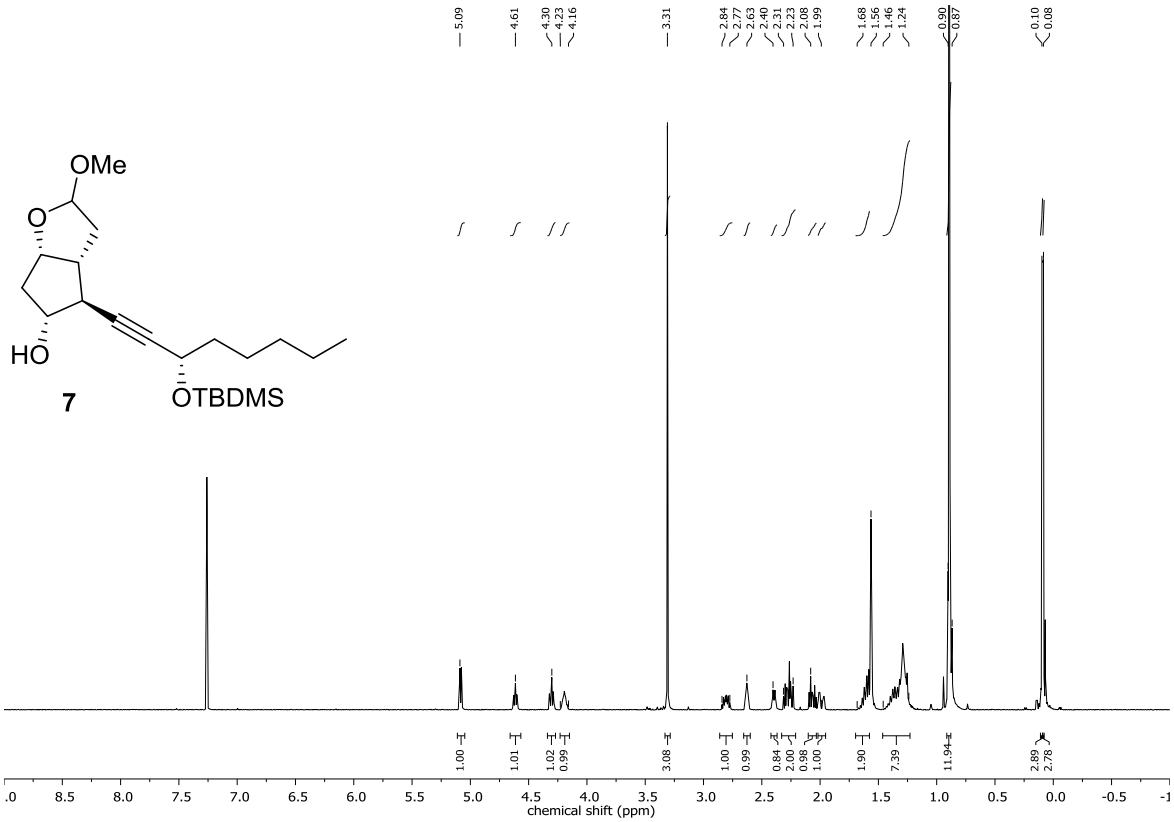

Figure 17: ^{1}H-NMR Spectrum of alcohol **7** in $CDCl_3$ at 400 MHz

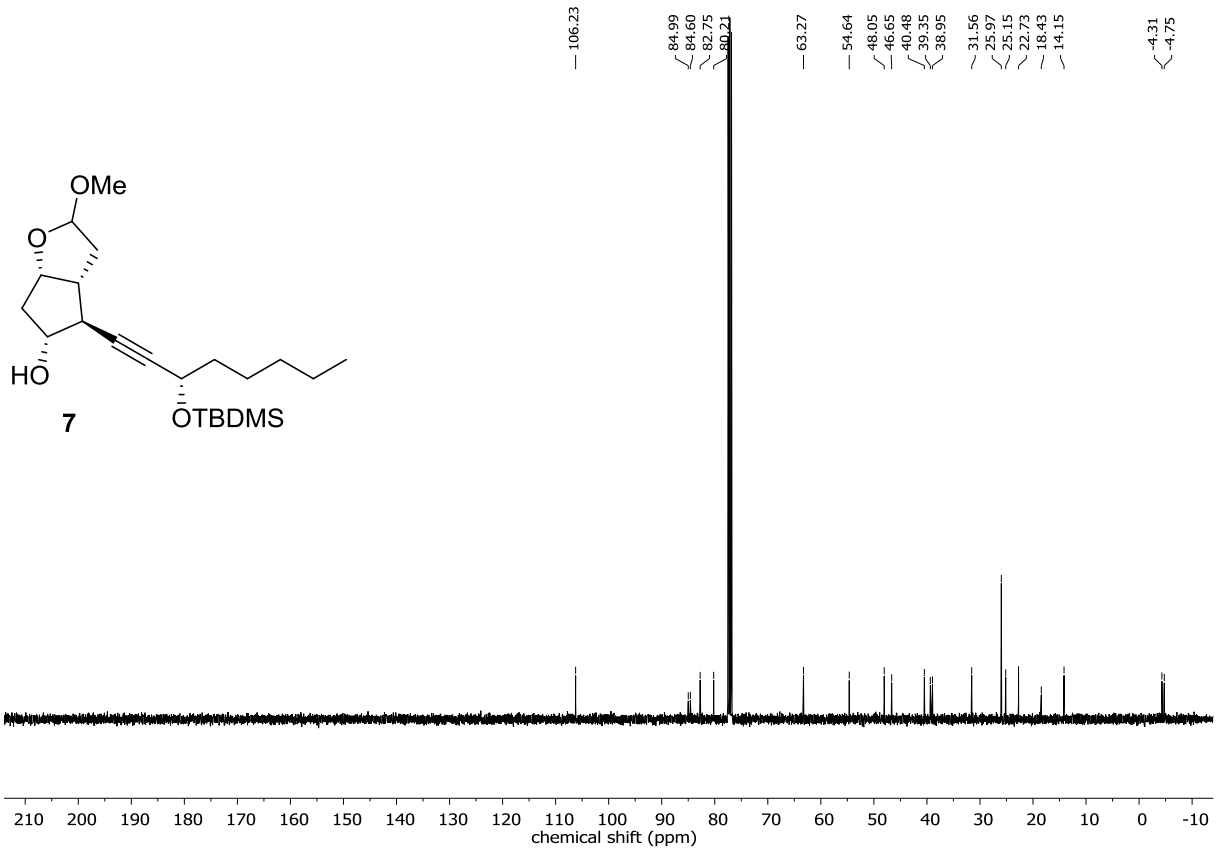

Figure 18: ^{13}C-NMR Spectrum of alcohol **7** in $CDCl_3$ at 101 MHz

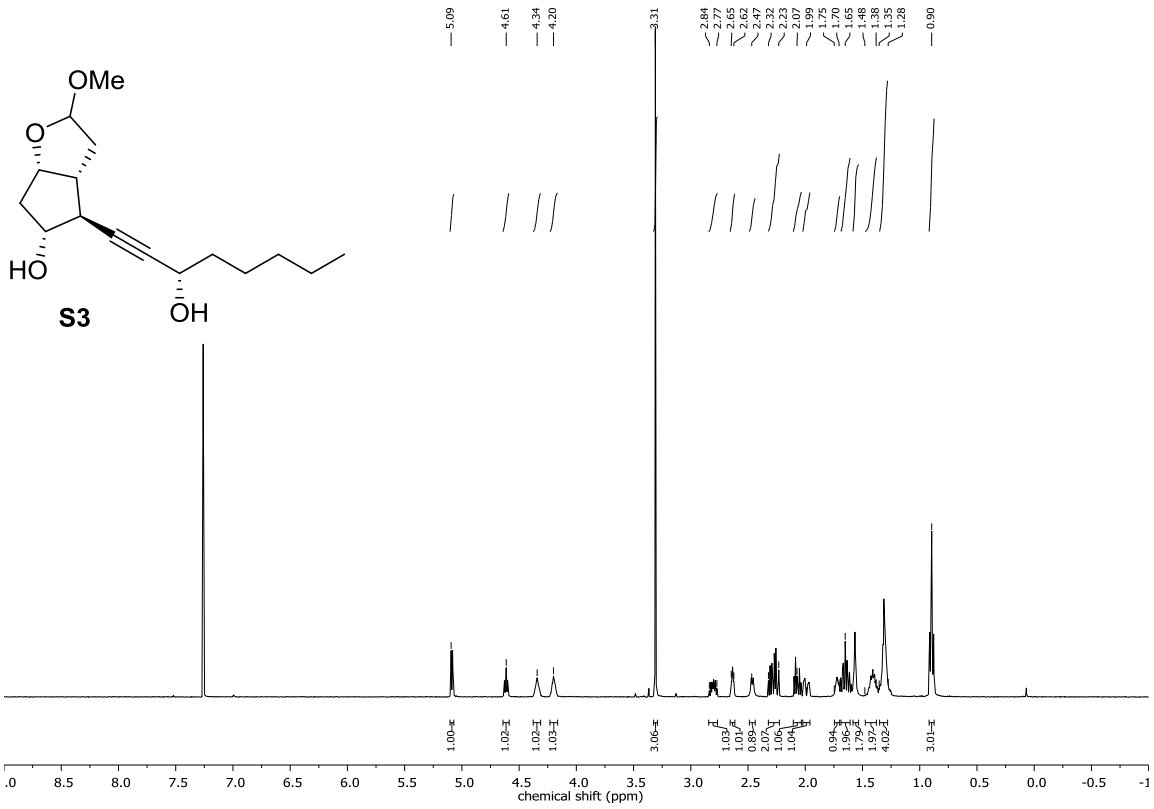

Figure 19: ^{1}H-NMR Spectrum of diol **S3** in $CDCl_3$ at 400 MHz

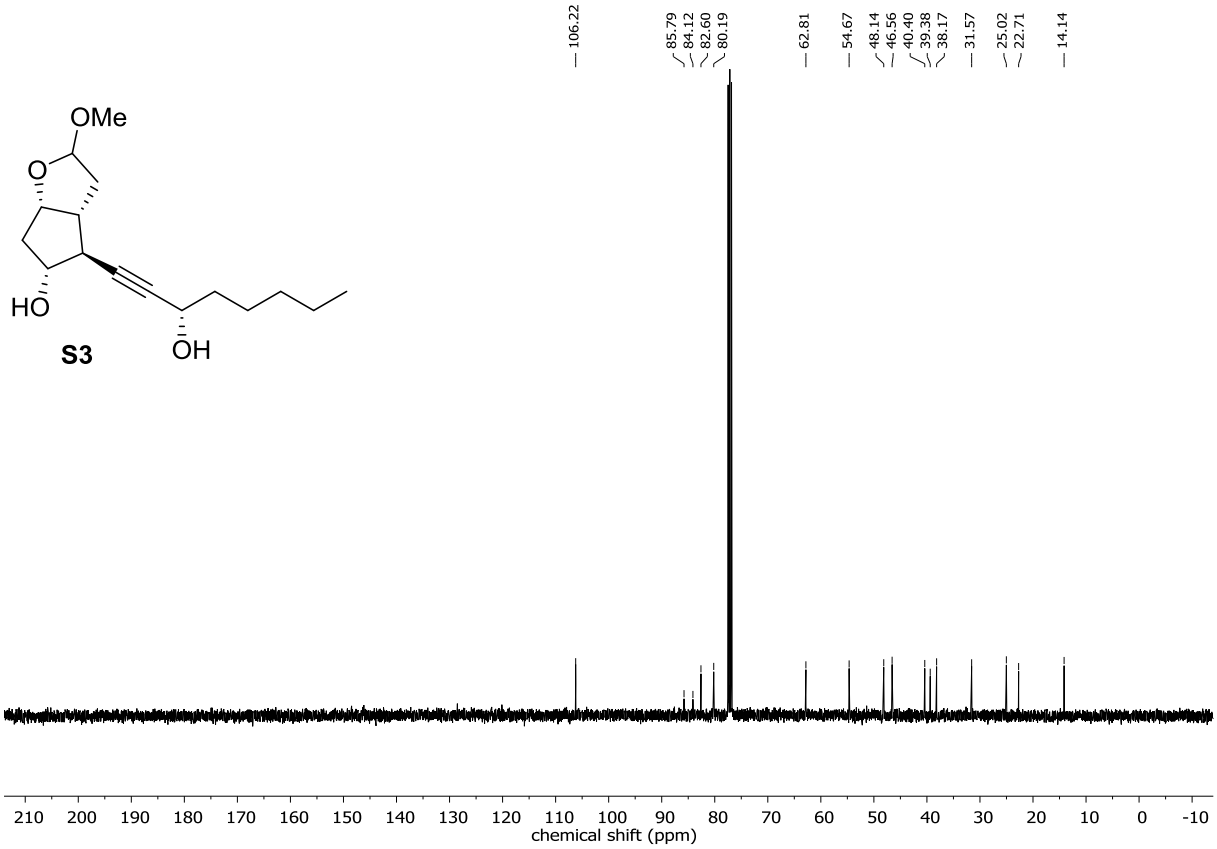

Figure 20: ^{13}C-NMR Spectrum of diol **S3** in $CDCl_3$ at 101 MHz

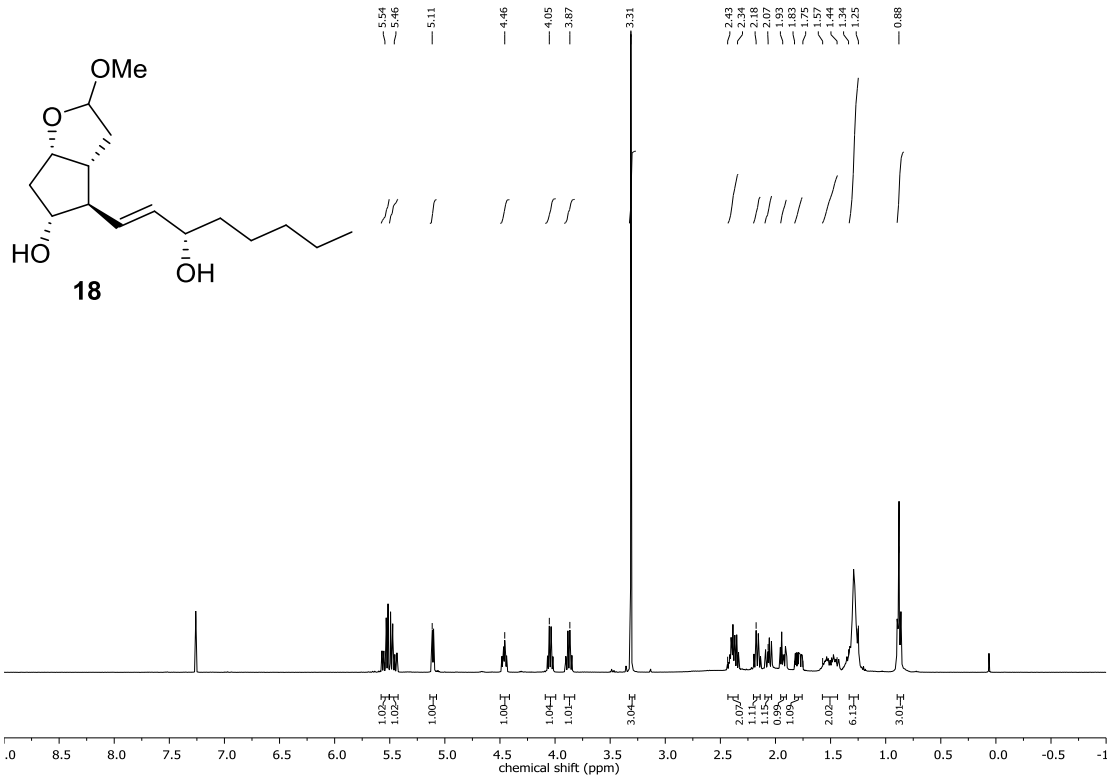

Figure 21: ^{1}H-NMR Spectrum of diol **18** in $CDCl_3$ at 400 MHz

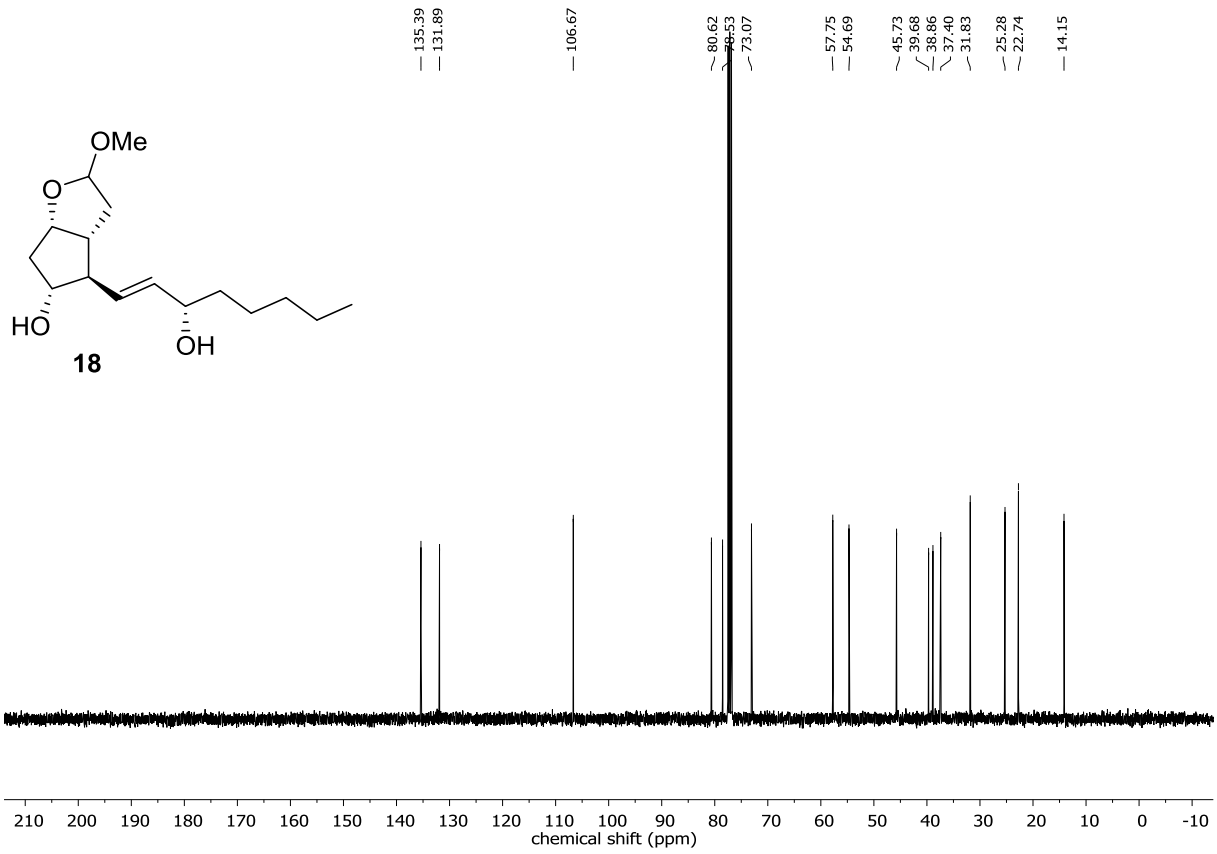

Figure 22: ^{13}C-NMR Spectrum of diol **18** in $CDCl_3$ at 101 MHz

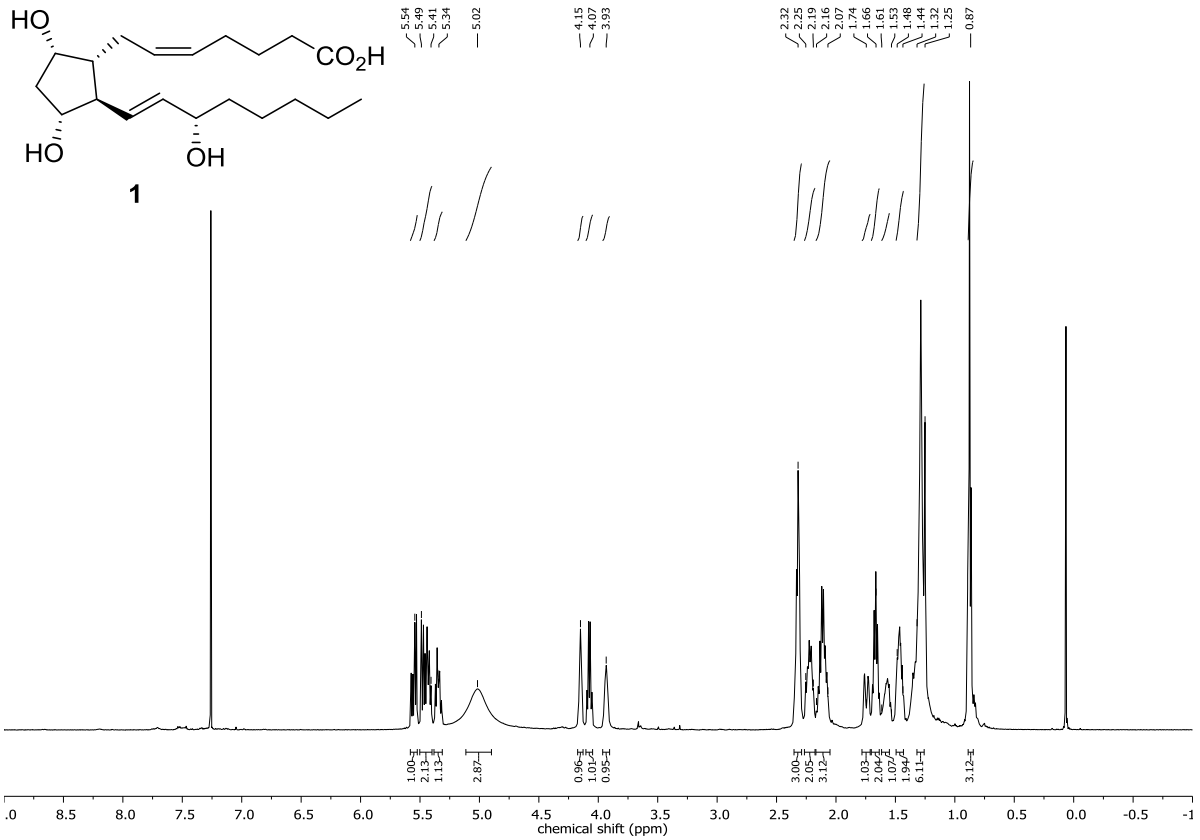

Figure 23: ^{1}H-NMR Spectrum of $PGF_{2\alpha}$ **1** in $CDCl_3$ at 500 MHz

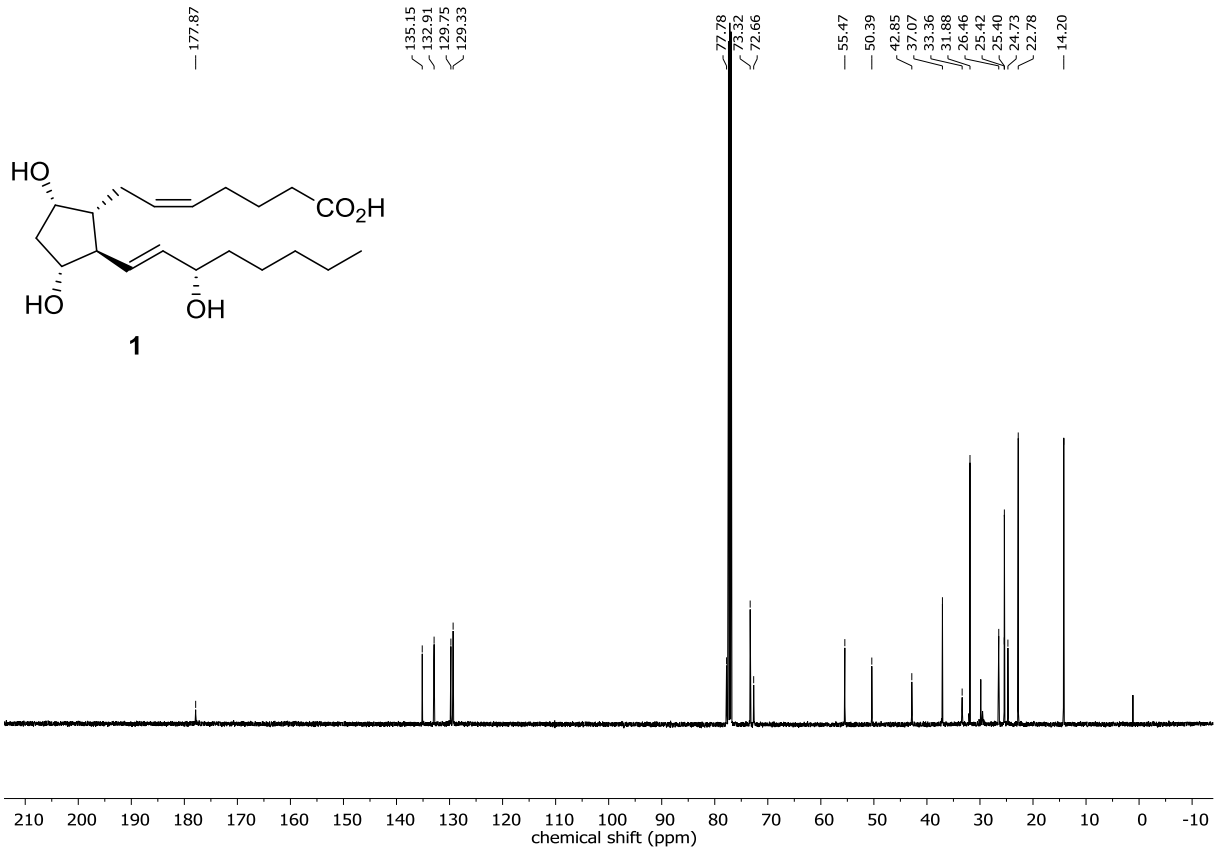

Figure 24: ^{13}C-NMR Spectrum of $PGF_{2\alpha}$ **1** in $CDCl_3$ at 101 MHz.