An asymmetric Suzuki-Miyaura approach to prostaglandins: Synthesis of Tafluprost

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Supplementary Information

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Experimental procedures

1.1 General Methods

Procedures using oxygen and/or moisture-sensitive materials were performed with anhydrous solvents (*vide infra*) under an atmosphere of anhydrous argon in flame-dried flasks, using standard Schlenk techniques. Heating was performed using DrySyn heating blocks. Analytical thin-layer chromatography was performed on precoated glass-backed plates (Silica Gel 60 F254; Merck), and visualised using a combination of UV light (254 nm) and CAM solution or aqueous basic potassium permanganate stain. Flash column chromatography was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), Merck 60 Å silica gel, VWR (40-63 μm) silica gel and Sigma Aldrich silica gel.

Nuclear magnetic resonance (NMR) spectroscopy measurements were carried out at room temperature. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, COSY, HSQC, HMBC and NOESY experiments were carried out using Bruker AVG-400 (400/100 MHz), AVH-400 (400/100 MHz), AVX-500 (500/125 MHz) or AVC-500 (500/125 MHz) spectrometers. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak with corresponding coupling constants (*J*) in Hertz (Hz) and multiplicities (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet and combinations of these and app.: apparent multiplicities). Assignment follows HSQC, COSY or/and HMBC spectra, chemical shift and coupling constant analysis.

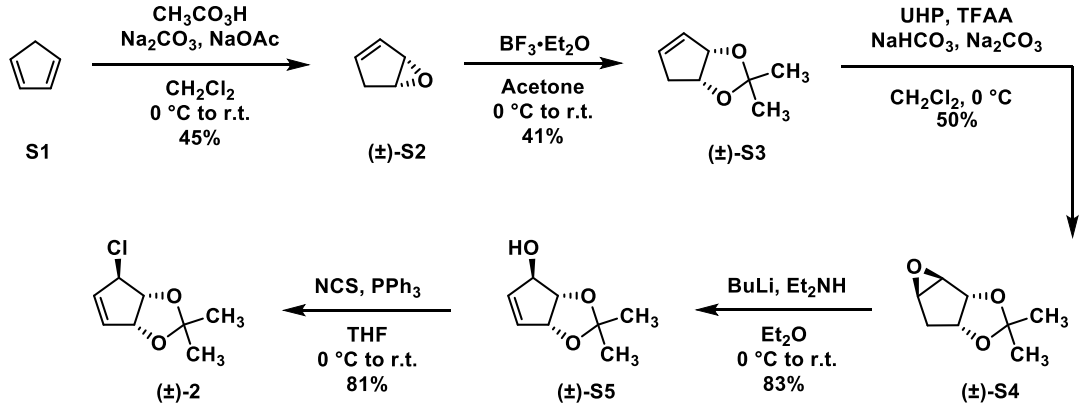
Infrared (IR, neat or thin film) spectroscopy was carried out on a Bruker Tensor 27 FT–IR spectrometer within internal calibration range of 4000 – 600 cm^{-1}. The samples are reported as absorption maxima in cm^{-1} with corresponding relative intensities described as br (broad), s (strong), m (medium), and w (weak).

Chiral SFC (supercritical fluid chromatography) separations were conducted on a Waters Acquity UPC2 system using Waters Empower software. Chiralpak® columns (150×3 mm, particle size 3 μm) were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn).

High Resolution Mass spectra were carried out by internal service at the University of Oxford. Electron spray ionisation (ESI^{+}) were recorded on a Thermo Exactive with an orbitrap ion analyser.

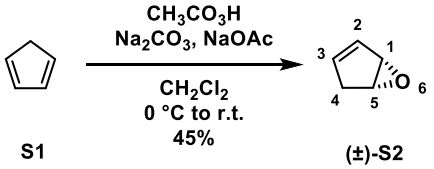
Commercially available reagents and ligands were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, Fluorochem and Strem Chemicals and unless otherwise stated were used without further purification. $[Rh(cod)OH]_2$ was synthesized according to a literature procedure[1] Dry solvents were collected fresh from an mBraun SPS–800 solvent purification system after having passed through anhydrous alumina columns. Deuterated solvents were purchased from Sigma Aldrich.

1.2 Procedures for the Synthesis of Allyl Chloride (±)-2



Scheme S1: Overview for the synthesis of allyl chloride **(±)-2**.

***rac*-6-oxabicyclo[3.1.0]hex-2-ene ((±)-S2)**



Epoxide **(±)-S2** was prepared according to a procedure by M. E. Jung *et al*.[2]

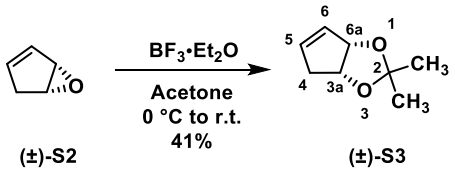
Cyclopentadiene (15 mL, 210 mmol, 1.1 equiv.) was added to a suspension of Na_2CO_3 (49.7 g, 470 mmol, 2.47 equiv.) and NaOAc (950 mg, 11.5 mmol, 0.06 equiv.) in CH_2Cl_2 (235 mL). Peracetic acid (40 wt% in acetic acid, 32 mL, 190 mmol, 1.0 equiv.) was added dropwise at 0 °C. The reaction mixture was then allowed to reach r.t. and was stirred for further 3 h. The mixture was filtered under reduced pressure, washed with CH_2Cl_2, and concentrated under reduced pressure (15 °C, 250 mbar). Vacuum distillation (25 mbar, 60 °C) afforded the desired product **(±)-S2** as a colorless oil in a mixture with CH_2Cl_2 (estimated yield: 6.50 g, 45%).

The spectroscopic data are in agreement with the literature.[2,3]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.14 (dtd, *J* = 5.6, 2.2, 1.1 Hz, 1H, C(2)-H), 5.98 (dp, *J* = 6.3, 2.1 Hz, 1H, C(3)-H), 3.91 (td, *J* = 3.3, 2.2 Hz, 1H, C(5)-H), 3.81 (dtd, *J* = 2.9, 1.9, 1.1 Hz, 1H, C(1)-H), 2.63 (dq, *J* = 19.1, 2.1 Hz, 1H, C(4)-H_2), 2.38 (ddt, *J* = 19.1, 3.5, 2.1 Hz, 1H, C(4)-H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 138.0 (C(3)), 131.4 (C(2)), 59.3 (C(1)), 57.0 (C(5)), 35.7 (C(4)).

***rac*-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxole ((±)-S3)**



Acetal **(±)-S3** was prepared according to a procedure by B. M. Trost *et al*.[4]

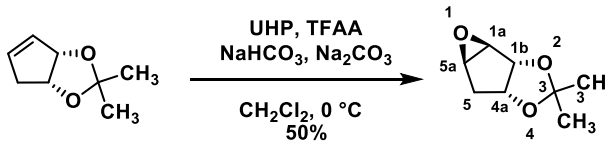
$BF_3{\cdot}Et_2O$ (0.98 mL, 7.9 mmol, 0.10 equiv.) was added dropwise to a solution of epoxide **(±)-S2** (6.50 g, 79.2 mmol, 1.00 equiv.) in dry acetone (49 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and was stirred for 6 h. The reaction mixture was then concentrated under reduced pressure (35 °C, 300 mbar), dissolved in Et_2O (150 mL), washed with an aq. sat. sol. of $NaHCO_3$ (2 x 25 mL) and an aq. sat. sol. of NH_4Cl (2 x 25 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by gradient flash column chromatography (Et_2O/pentane = 2.5% to 10%) afforded acetonide **(±)-S3** as a colorless oil (4.62 g, 41%).

The spectroscopic data are in agreement with the literature.[3,4]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.86 – 5.80 (m, 1H, C(5)-H), 5.77 (dq, *J* = 5.8, 1.9 Hz, 1H, C(6)-H), 5.10 (d, *J* = 6.0 Hz, 1H, C(6a)-H), 4.76 (td, *J* = 5.8, 1.5 Hz, 1H, C(3a)-H), 2.64 – 2.45 (m, 2H, C(4)-H_2), 1.41 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 132.6 (C(5)), 130.8 (C(6)), 109.8 (C(2)), 85.6 (C(6a)), 77.9 (C(3a)), 38.9 (C(4)), 27.5 (CH_3), 25.7 (CH_3).

***rac-(trans)*-3,3-dimethyltetrahydro-5H-oxireno[2',3':3,4]cyclopenta[1,2-d][1,3]dioxole ((±)-S4)**



(±)-S3 (±)-S4

Epoxide **(±)-S4** was prepared according to a procedure by B. M. Trost *et al*.[4]

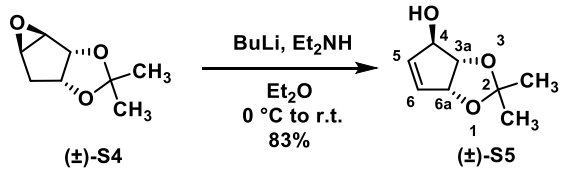
Alkene **(±)-S3** (4.55 g, 32.5 mmol, 1 equiv.) and urea hydrogen peroxide (UHP) (15.3 g, 162 mmol, 5.00 equiv.) were added to a suspension of $NaHCO_3$ (2.73 g, 32.5 mmol, 1.00 equiv.) and Na_2CO_3 (10.32 g, 97.7 mmol, 3.00 equiv.) in CH_2Cl_2 (330 mL) at 0 °C. A solution of trifluoroacetic anhydride (TFAA) (11 mL, 81 mmol, 2.5 equiv.) in CH_2Cl_2 (150 mL) was then added dropwise and the resulting mixture was stirred for 3 h at 0 °C. The reaction mixture was then washed with an aq. sat. sol. of $NaHCO_3$ (3 x 50 mL), an aq. sat. sol. of $Na_2S_2O_3$ (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by gradient flash column chromatography (Et_2O/pentane = 10% to 25%) afforded epoxide **(±)-S4** as a colorless oil (2.55 g, 50%).

The spectroscopic data are in agreement with the literature.[3,4]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.55 (d, J = 5.5 Hz, 1H, C(1b)-H), 4.52 (tdd, J = 5.6, 1.9, 0.9 Hz, 1H, C(4a)-H), 3.60 – 3.54 (m, 2H, C(1a)-H and C(5a)-H), 2.27 (dd, J = 15.4, 6.0 Hz, 1H, C(5)-H_2), 1.94 (dt, J = 15.4, 2.0 Hz, 1H, C(5)-H_2), 1.45 (s, 3H, CH_3), 1.29 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 112.0 (C(3)), 81.5 (C(4a)), 80.2 (C(1b)), 59.2 (C(1a) or C(5a)), 59.0 (C(1a) or C(5a)), 35.8 (C(5)), 27.4 (CH_3), 24.9 (CH_3).

***rac-(trans)*-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-4-ol ((±)-S5)**



Allylic alcohol **(±)-S5** was prepared according to a procedure by B. M. Trost *et al*.[4]

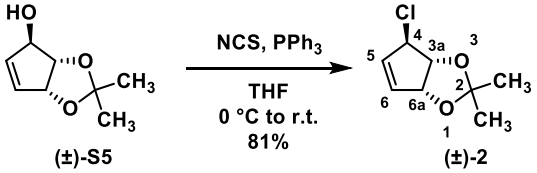
n-butyl lithium (2.5 M in hexane, 13 mL, 32 mmol, 2.0 equiv.) was added dropwise to a solution of diethylamine (3.5 mL, 34 mmol, 2.1 equiv.) in Et_2O (18 mL) at 0 °C. After stirring for 30 min, a solution of epoxide **(±)-S4** (2.50 g, 16.0 mmol, 1.00 equiv.) in Et_2O (18 mL) was added dropwise and the reaction mixture was allowed to reach r.t.. After 2 h, the reaction mixture was diluted with Et_2O (30 mL) and washed with an aq. sat. sol. of NH_4Cl (3 x 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by gradient flash column chromatography (ethyl acetate/pentane = 10% to 50%) afforded alcohol **(±)-S5** as a colorless oil (2.08 g, 83%).

The spectroscopic data are in agreement with the literature.[3,4]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.02 (dt, *J* = 5.8, 1.5 Hz, 1H, C(6)-H), 5.90 (ddt, *J* = 5.8, 2.1, 0.9 Hz, 1H, C(5)-H), 5.28 (dtd, *J* = 5.7, 1.7, 0.9 Hz, 1H, C(6a)-H), 4.78 (d, *J* = 5.0 Hz, 1H, C(4)-H), 4.51 (d, *J* = 5.6 Hz, 1H, C(3a)-H), 2.20 (m, 1H, OH), 1.39 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 135.7 (C(6)), 134.8 (C(5)), 111.9 (C(2)), 86.1 (C(3a)), 84.4 (C(6a)), 81.1 (C(4)), 27.4 (CH_3), 25.8 (CH_3).

***rac-(trans)*-4-chloro-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxole ((±)-2)**



Allylic alcohol **(±)-2** was prepared according to a procedure by F. W. Goetzke *et al*.[3]

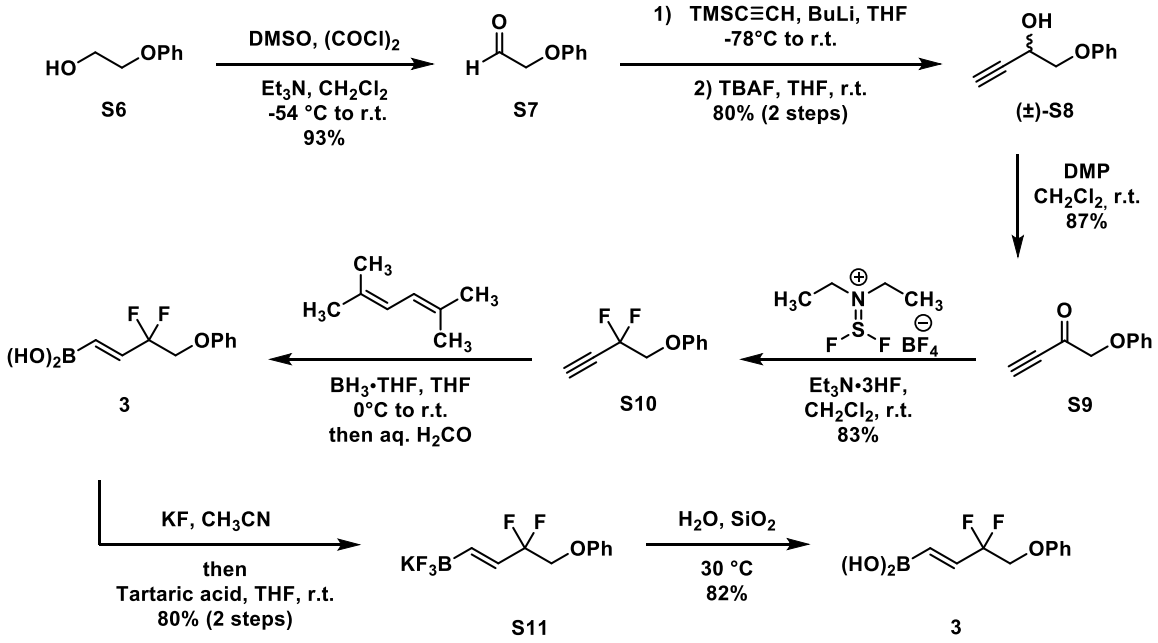
Triphenylphosphine (5.04 g, 19.2 mmol, 1.50 equiv.) and *N*-chlorosuccinimide (NCS) (2.74 g, 20.5 mmol, 1.60 equiv.) were added to a solution of alcohol **(±)-S5** (2.00 g, 12.8 mmol, 1.00 equiv.) in THF (20 mL) at 0 °C. After 1 h, the reaction mixture was allowed to reach r.t. and was stirred for additional 1 h. The reaction mixture was then filtered through a pad of Celite and concentrated under reduced pressure. Purification by gradient flash column chromatography (CH_2Cl_2/pentane = 0% to 50%) afforded allyl chloride **(±)-2** as a colorless oil (1.81 g, 81%).

The spectroscopic data are in agreement with the literature.[3]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.01 (ddt, *J* = 5.7, 1.7, 0.7 Hz, 1H, C(6)-H), 5.91 (ddt, *J* = 5.6, 2.3, 0.9 Hz, 1H, C(5)-H), 5.32 (dq, *J* = 5.6, 1.4 Hz, 1H, C(6a)-H), 4.81 (ddt, *J* = 2.4, 1.5, 0.7 Hz, 1H, C(4)-H), 4.79 (dd, *J* = 5.5, 0.8 Hz, 1H, C(3a)-H), 1.38 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

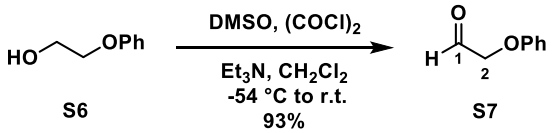
^{13}C NMR (101 MHz, $CDCl_3$) δ: 135.7 (C(6)), 133.6 (C(5)), 112.3 (C(2)), 86.1 (C(3a)), 84.4 (C(6a)), 65.1 (C(4)), 27.6 (CH_3), 26.3 (CH_3).

1.3 Procedures for the Synthesis of Boronic Acid 3



Scheme S2: Overview for the synthesis of boronic acid **3**.

2-phenoxyacetaldehyde (S7)



Aldehyde **S7** was prepared according to a procedure by D. R. Dragoli *et al*.[5]

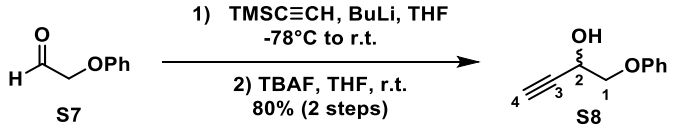
A solution of DMSO (11 mL, 160 mmol, 2.2 equiv.) in CH_2Cl_2 (36 mL) was added dropwise over 30 min to a solution of oxalyl chloride (6.7 ml, 80 mmol, 1.1 equiv.) in CH_2Cl_2 (290 mL) at -54 °C. After 10 min, a solution of 2-phenoxyethanol (10.0 g, 72.4 mmol, 1.00 equiv.) in CH_2Cl_2 (70 mL) was added dropwise over 30 min and the reaction mixture was stirred with mechanical stirrer for additional 60 min. Triethylamine (40 mL, 290 mmol, 4.0 equiv.) was then added dropwise over 20 min. After 60 min, water (320 mL) was added and the reaction mixture was allowed to reach r.t.. The organic phase was separated and the aq. phase extracted with CH_2Cl_2 (4 x 50 mL). The combined organic phases were washed with 1 M aq. HCl (5 x 50 mL), brine (2 x 60 mL), an aq. sat. sol. of $NaHCO_3$ (3 x 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldehyde **S7** was obtained as a pale yellow oil (9.17 g, 93%) and used in the next step without further purification.

The spectroscopic data are in agreement with the literature.[6]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.87 (t, J = 1.1 Hz, 1H, C(1)-H), 7.36 – 7.26 (m, 2H, C_{meta}-H), 7.06 – 7.00 (m, 1H, C_{para}-H), 6.94 – 6.87 (m, 2H, C_{ortho}-H), 4.57 (d, J = 1.1 Hz, 2H, C(2)-H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 199.6 (C(1)), 157.8 (C_q), 129.9 (C_{meta}), 122.1 (C_{para}), 114.7 (C_{ortho}), 72.8 (C(2)).

***rac*-1-phenoxybut-3-yn-2-ol ((±)-S8)**



Alcohol **(±)-S8** was prepared according to a procedure by E. J. Corey *et al*.[7]

n-butyl lithium (2.5 M in hexane, 22 mL, 55 mmol, 1.5 equiv.) was added to a solution of ethynyltrimethylsilane (10 mL, 73 mmol, 2.0 equiv.) in THF (220 mL) at -78 °C. After stirring for 30 min, a solution of aldehyde **S7** (5.00 g, 36.7 mmol, 1.00 equiv.) in THF (30 mL) was added dropwise over 15 min. After 30 min, the reaction mixture was allowed reach r.t. and stirred at this temperature for 30 min. The reaction mixture was then quenched with an aq. sat. sol. of NH_4Cl (150 mL) and extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure.

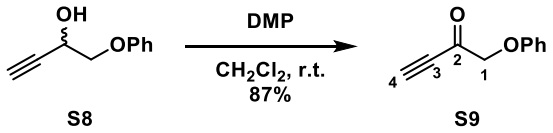
The residue was dissolved in THF (150 mL) and a solution of tetrabutylammonium fluoride (TBAF) (1 M in THF, 38 ml, 37 mmol, 1.0 equiv.) was added dropwise at 0 °C. The resulting orange solution was stirred for 20 min at r.t. and then poured onto an aq. sat. sol. of $NaHCO_3$. The aq. phase was extracted with Et_2O (3 x 100 mL), the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by gradient flash column chromatography (ethyl acetate/hexane = 5% to 35%) afforded alcohol **(±)-S8** as a colorless solid (4.75 g, 80%, over 2 steps).

The spectroscopic data are in agreement with the literature.[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 – 7.26 (m, 2H, C_{meta}-H), 7.00 (tt, *J* = 7.3, 1.1 Hz, 1H, C_{para}-H), 6.97 – 6.90 (m, 2H, C_{ortho}-H), 4.77 (dddd, *J* = 7.4, 5.7, 3.6, 2.2 Hz, 1H, C(1)-H), 4.16 (dd, *J* = 9.6, 3.7 Hz, 1H, C(1)-H_2), 4.09 (dd, *J* = 9.6, 7.0 Hz, 1H, C(1)-H_2), 2.71 (d, *J* = 5.4 Hz, 1H, OH), 2.54 (d, *J* = 2.3 Hz, 1H, C(4)-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.2 (C_q), 129.7 (C_{meta}), 121.7 (C_{para}), 114.9 (C_{ortho}), 81.2 (C(4)), 74.5 (C(5)), 71.4 (C(2)), 61.4 (C(1)).

1-phenoxybut-3-yn-2-one (S9)



S8 S9

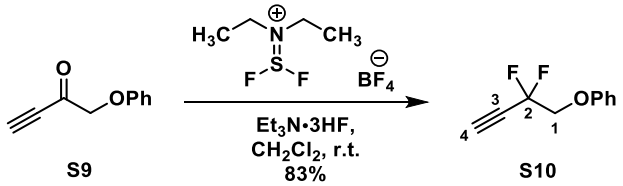
Dess-Martin periodinane (DMP) (21.9 g, 51.6 mmol, 1.20 equiv.) was added to a solution of alcohol **(±)-S8** (6.97 g, 43.0 mmol, 1.00 equiv.) in CH_2Cl_2 (200 mL) and the resulting solution was stirred for 50 min at r.t. The reaction mixture was then poured onto an aq. sat. sol. of $NaHCO_3$ (200 mL) and the aq. phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The colorless residue was passed through a short plug of silica (6 cm) and eluted with 15% mixture of ethyl acetate in hexane. The purified product **S9** was obtained as a colourless crystalline solid (5.99 g, 87%, >98% purity) contaminated with orange residue (product of decomposition on silica).

The spectroscopic data are in agreement with the literature.[8]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 – 7.27 (m, 2H, C_{meta}-H), 7.05 – 6.99 (m, 1H, C_{para}-H), 6.93 – 6.87 (m, 2H, C_{ortho}-H), 4.75 (s, 2H, C(1)-H_2), 3.39 (s, 1H, C(4)-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 182.7 (C(2)), 157.6 (C_q), 129.7 (C_{meta}), 122.1 (C_{para}), 114.8 (C_{ortho}), 82.4 (C(4)), 79.1 (C(3)), 73.5 (C(1)).

((2,2-difluorobut-3-yn-1-yl)oxy)benzene (S10)



Compound **S10** was prepared according to a procedure by J.-F. Syu *et al*.[9]

Triethylamine trihydrofluoride (12 mL, 74 mmol, 2.0 equiv.) was added to a suspension of XtalFluor-E (12.7 g, 55.3 mmol, 1.50 equiv.) in CH_2Cl_2 (13 mL) at r.t. After complete dissolution of solid reagent, a solution of ketone **S9** (5.90 g, 36.8 mmol, 1.00 equiv.) in CH_2Cl_2 (30 mL) was added and the resulting mixture was stirred for 18 h. The reaction mixture was then poured onto an aq. sat. sol. of $NaHCO_3$ (150 mL) and was extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure (30 °C, 50 mbar). Purification by gradient flash column chromatography (ethyl acetate/pentane = 2% to 6%) afforded alkyne **S10** as a pale yellow oil (5.57 g, 83%).

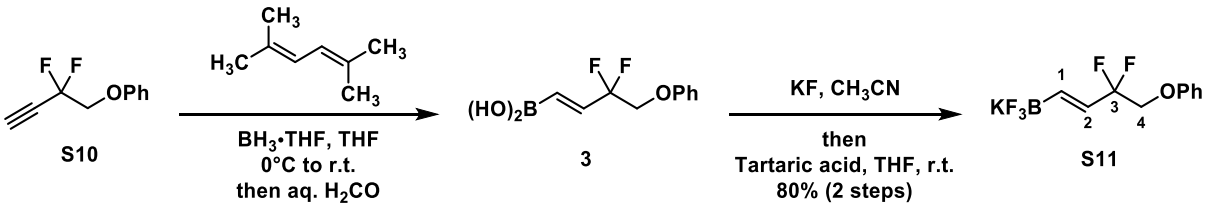
The spectroscopic data are in agreement with the literature.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 – 7.28 (m, 2H, C_{meta}-H), 7.07 – 7.01 (m, 1H, C_{para}-H), 6.99 – 6.94 (m, 2H, C_{ortho}-H), 4.30 (t, J = 11.3 Hz, 2H, C(1)-H_2), 2.86 (t, J = 5.1 Hz, 1H, C(4)-H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.0 (C_q), 129.8 (C_{meta}), 122.3 (C_{para}), 115.2 (C_{ortho}), 111.0 (C(2)), 77.2 (C(4)), 74.8 (C(3)), 70.3 (C(1)). (Peak reported at 77.1 ppm overlaps with solvent peak).

^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -93.34.

Potassium (*E*)-(3,3-Difluoro-4-phenoxybut-1-en-1-yl)- trifluoroborate (S11)



Compound **S11** was prepared according to a procedure by J.-F. Syu *et al.*[9]

A solution of borane tetrahydrofuran complex (1 M in THF, 61 mL, 61 mmol, 2.5 equiv.) was added to a solution of 2,5-dimethylhexa-2,4-diene (20 mL, 130 mmol, 5.5 equiv.) in THF (11 mL) at 0 °C. After stirring for 3 h, a solution of alkyne **S10** (4.44 g, 24.4 mmol, 1.00 equiv.) in THF (24 mL) was added dropwise and the reaction mixture was stirred overnight at r.t. The reaction mixture was then carefully quenched by addition of water (9.3 mL) (evolution of gas observed) at 0 °C. After stirring for 90 min at r.t., 37% aq. sol. of formaldehyde (22 mL) was added (slightly exothermic reaction, exothermicity compensate by water bath) and the resulting mixture was stirred overnight at r.t.

The reaction mixture was then poured onto brine (40 mL), and the aq. phase was extracted with ethyl acetate (4 x 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to provide crude boronic acid **3** together with (*E*)-2,2,5-trimethylhex-3-en-1-ol as a pale yellow oil (25.4 g).

A solution of potassium fluoride (5.14 g, 88.5 mmol, 3.63 equiv.) in water (7.6 mL) was added to a solution of above prepared boronic acid **3** in CH_3CN (100 mL). The resulting mixture was vigorously stirred until dissolution was achieved (1 h). A solution of L-(+)-tartaric acid (6.84 g, 45.6 mmol, 1.87 equiv.) in THF (35 mL) was then added dropwise over 20 min (formation of a white precipitate). After stirring for 30 min, the solids were filtered off and washed with CH_3CN (50 mL). The collected solution was concentrated under reduced pressure and the obtained residue was suspended in Et_2O (20 mL). After stirring for 1 h, the solid product was filtered off and washed with hexane to provide trifluoroborate **S11** as a pale yellow solid (4.83 g, 68%).

Note: The trifluoroborate **S11** is partially soluble in (*E*)-2,2,5-trimethylhex-3-en-1-ol formed as a by-product in the hydroboration step. Therefore, an additional portion of trifluoroborate can be isolated from the solution obtained during the last filtration by removal of volatiles on rotavap and evaporation of the side product on kugelrohr, followed by precipitation of compound **S11** with hexane (0.85 g, 12%; combined yield: 80%).

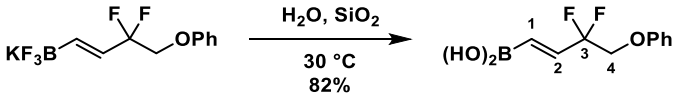
The spectroscopic data are in agreement with the literature.[9]

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ: 7.37 – 7.20 (m, 2H, C_{meta}-H), 7.07 – 6.88 (m, 3H, C_{ortho}-H and C_{para}-H), 6.08 (dq, *J* = 18.3, 3.1 Hz, 1H, C(1)-H), 5.74 (dt, *J* = 18.2, 11.4 Hz, 1H, C(2)-H), 4.24 (t, *J* = 13.2 Hz, 2H, C(4)-H_2).

^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ: 157.9 (C_q), 129.6 (C_{meta}), 126.1 (tq, *J* = 24.6, 3.9 Hz, C(2)), 121.2 (C_{para}), 119.7 (t, *J* = 238.6 Hz, C(3)), 114.7 (C_{ortho}), 68.6 (t, *J* = 31.3 Hz, C(4)). (The C−B signal was not observed due to quadrupolar relaxation.)

^{19}F NMR (471 MHz, $(CD_3)_2SO$, ^{1}H decoupled) δ: -101.32, -139.42.

(*E*)-(3,3-difluoro-4-phenoxybut-1-en-1-yl)boronic acid (3)



S11 3

Compound **3** was prepared according to a procedure by J.-F. Syu *et al*.[9]

A suspension of trifluorobotonate **S11** (4.75 g, 16.4 mmol, 1.00 equiv.) and silica gel (984 mg, 16.4 mmol, 1.00 equiv.) in water (16 mL) were stirred at 30 °C overnight. The solids were collected by vacuum filtration (pore size S4) and washed with water (5 mL). The solid was extracted several times with CH_3CN. The collected solution was concentrated under reduced pressure and the obtained pale yellow product was triturated with pentane (3 x 5 mL) to afford boronic acid **3** as a white solid (3.05 g, 82%).

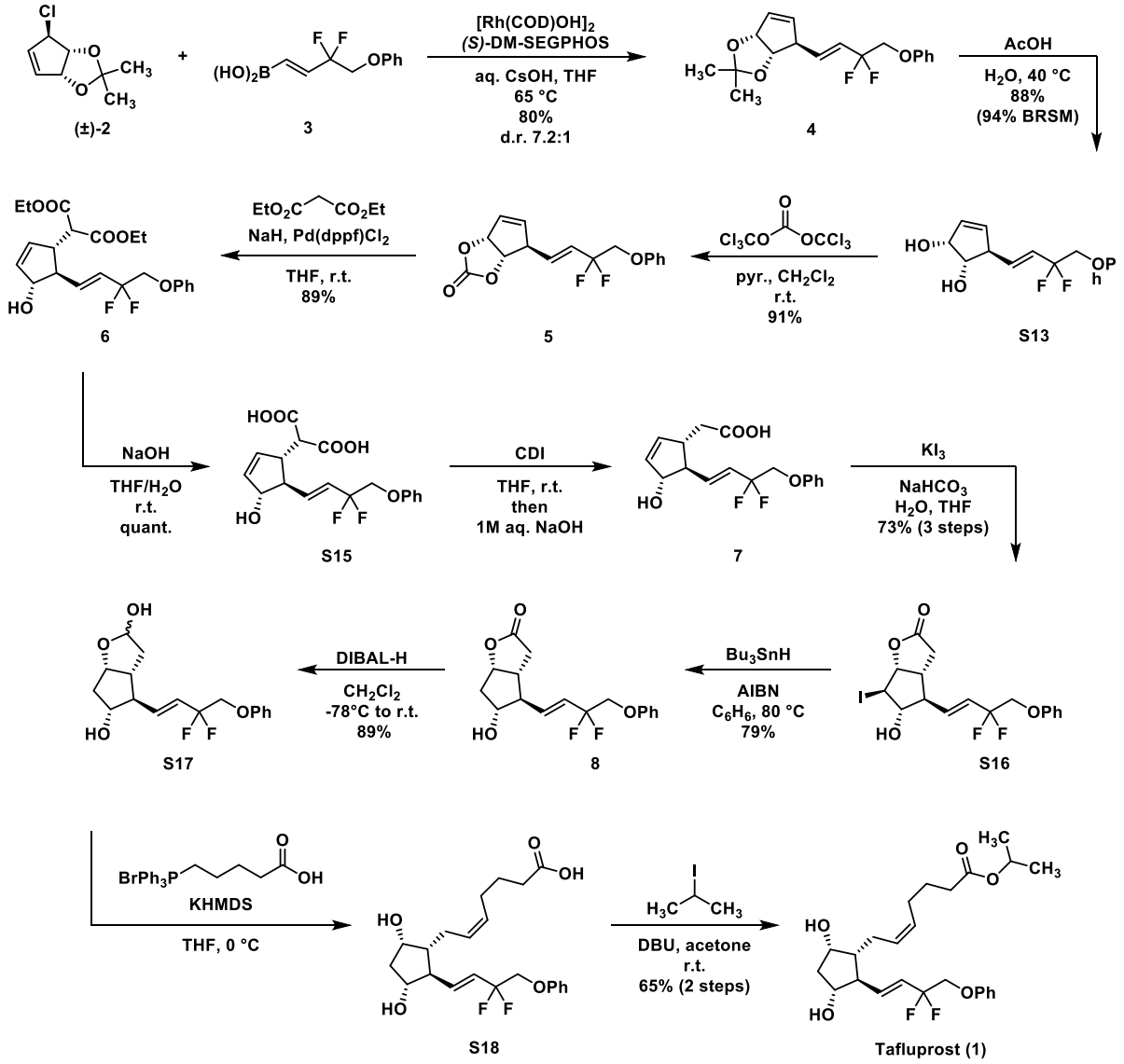
The spectroscopic data are in agreement with the literature.[9]

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ: 8.12 (s, 2H, OH), 7.37 – 7.26 (m, 2H, C_{meta}-H), 7.05 – 6.94 (m, 3H, C_{ortho}-H and C_{para}-H), 6.56 (dt, *J* = 18.3, 11.1 Hz, 1H, C(1)-H), 6.07 (dt, *J* = 18.3, 2.4 Hz, 1H, C(2)-H), 4.37 (t, *J* = 12.9 Hz, 2H, C(4)-H_2).

^{13}C NMR (126 MHz, $(CD_3)_2SO$, ^{19}F decoupled) δ: 157.6 (C_q), 138.2 (C(2)), 129.6 (C_{meta}), 121.5 (C_{para}), 118.8 (C(3)), 114.8 (C_{ortho}), 68.2 (C(4)). (The C−B signal was not observed due to quadrupolar relaxation.)

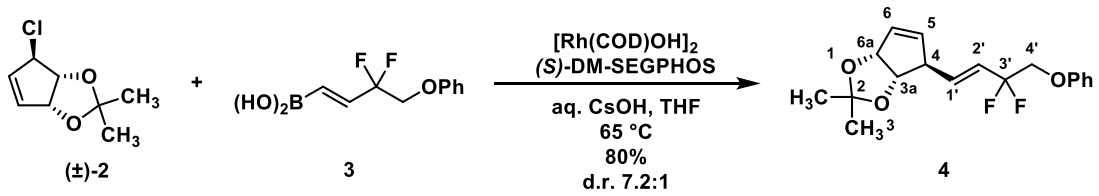
^{19}F NMR (471 MHz, $(CD_3)_2SO$, ^{1}H decoupled) δ: -103.99.

1.4 Procedures for the Synthesis of Tafluprost



Scheme S3: Overview for the synthesis of Tafluprost (**1**).

(3a*S*,4*S*,6a*R*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxole (4)



Compound **4** was prepared adopting a procedure by F. W. Goetzke *et al*.[3]

An aq. sol. of CsOH (50 wt%, 330 µL, 1.9 mmol, 1.0 equiv.) was added to a solution of *(S)*-DM-SEGPHOS (82.4 mg, 114 µmol, 6.0 mol %) and [Rh(cod)OH]$_2$ (21.7 mg, 47.5 µmol, 2.5 mol%) in THF (3.3 mL) and the resulting mixture was stirred at 65 °C for 30 min. Then, a solution of boronic acid **3** (650 mg, 2.85 mmol, 1.50 equiv.) and allyl chloride **(±)-2** (300 µL, 1.9 mmol, 1.0 equiv.) in THF (3.3 mL) was added, the flask was rinsed with THF (0.9 mL). The resulting solution was stirred at 65 °C for 4 h. The unpurified reaction mixture showed a d.r. of 7.2:1. The reaction mixture was then diluted with Et_2O, loaded on silica and the crude product purified by flash column chromatography (ethyl acetate/hexane = 0% to 8%). The product **4** was obtained as a colorless oil (490 mg, 80%, 90% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 – 7.27 (m, 2H, C_{meta}-H), 7.01 (tt, *J* = 7.4, 1.1 Hz, 1H, C_{para}-H), 6.94 – 6.87 (m, 2H, C_{ortho}-H), 6.21 (ddt, *J* = 15.9, 7.6, 2.5 Hz, 1H, C(1')-H), 5.92 (dt, *J* = 5.8, 1.8 Hz, 1H, C(6)-H), 5.80 – 5.69 (m, 2H, C(2')-H and C(5)-H), 5.16 (dq, *J* = 5.7, 1.4 Hz, 1H, C(6a)-H), 4.46 (d, *J* = 5.7 Hz, 1H, C(3a)-H), 4.18 (t, *J* = 11.5 Hz, 2H, C(4')-H_2), 3.54 (d, *J* = 6.6 Hz, 1H, C(4)-H), 1.43 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.1 (Cq), 137.3 (t, *J* = 8.9 Hz, C(1')), 133.8 (C(5)), 132.9 (C(6)), 129.8 (C_{meta}), 123.8 (t, J = 25.1 Hz, C(2')), 122.0 (C_{para}), 118.3 (t, *J* = 240.3 Hz, C(3')), 114.9 (C_{ortho}), 110.6 (C(2)), 85.0 (C(6a)), 83.1 (C(3a)), 69.6 (t, *J* = 35.1 Hz, C(4')), 53.8 (C(4)), 27.5 (CH_3), 25.8 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.69 (d, *J* = 257.7 Hz), -103.46 (d, *J* = 257.9 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 2987 (w), 1599 (w), 1496 (m), 1287 (m), 1210 (m), 1160 (m), 1050 (s), 754 (m).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{20}O_3F_2Na$ 345.1273; Found 345.1273.

SFC Chiralpak® IF; 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 95.0:5.0 er (major enantiomer t_R = 1.66 min; minor enantiomer t_R = 1.76 min).

$[\alpha]^{25}_D$= –131.8 (c=0.5, $CHCl_3$).

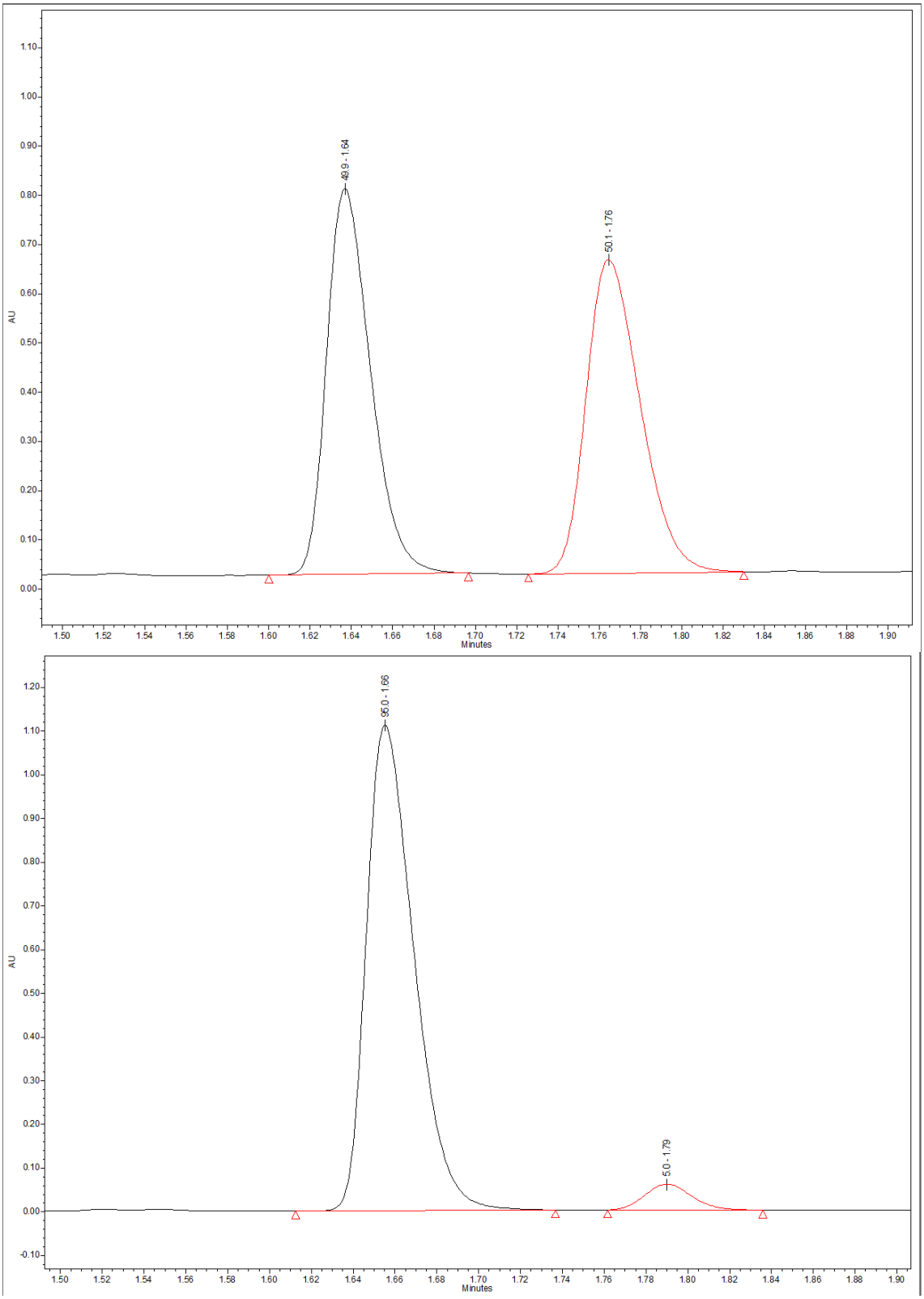
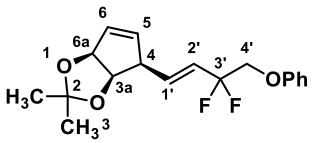


Figure S1: SFC traces of the racemic **(±)-4** (top) and enantioenriched (–)-**4** (bottom).

(3a*S*,4*R*,6a*R*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxole (S12)



S12

Compound **S12** was isolated as a by-product of the above describe coupling reaction between allylchloride **(±)-2** and boronic acid **3** as a colorless oil (61 mg, 10%). The *ee* of the minor diastereomer was not determined.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.26 (m, 2H, C_{meta}-H), 7.04 – 6.97 (m, 1H, C_{para}-H), 6.97 – 6.88 (m, 2H, C_{ortho}-H), 6.32 (ddt, *J* = 16.0, 8.2, 2.5 Hz, 1H, C(1‘)-H), 5.90 (dt, *J* = 5.8, 2.2 Hz, 1H, C(6)-H), 5.82 (dtd, *J* = 15.9, 11.1, 1.1 Hz, 1H, C(2‘)-H), 5.71 – 5.66 (m, 1H, C(5)-H), 5.13 (d, *J* = 5.6 Hz, 1H, C(6a)-H), 4.77 (t, *J* = 5.8 Hz, 1H, C(3a)-H), 4.21 (t, *J* = 11.6 Hz, 2H, C(4‘)-H_2), 3.44 – 3.37 (m, 1H, C(4)-H), 1.36 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

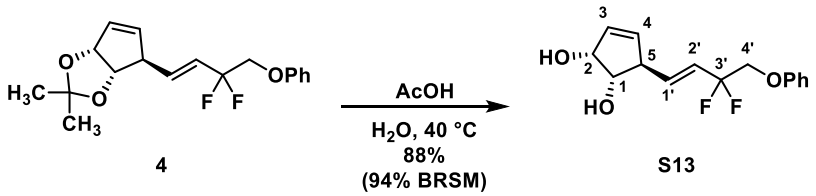
^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.2 (C_q), 135.2 (t, *J* = 9.1 Hz, C(1‘)), 134.3 (C(5)), 132.3 (C(6)), 129.7 (C_{meta}), 124.0 (t, *J* = 25.3 Hz, C(2‘)), 121.9 (C_{para}), 118.4 (t, *J* = 240.2 Hz, C(3‘)), 115.0 (C_{meta}), 111.1 (C(2)), 85.6 (C(6a)), 79.5 (C(3a)), 69.8 (t, *J* = 34.6 Hz, C(4‘)), 50.2 (C(4)), 27.4 (CH_3), 26.2 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.93, -102.95.

FT-IR ($CHCl_3$ film) cm^{-1}: 2987 (w), 1599 (w), 1497 (m), 1249 (m), 1161 (m), 1059 (vs), 755 (m).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{20}O_3F_2Na$ 345.1273; Found 345.1273.

(1*S*,2*R*,5*S*)-5-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)cyclopent-3-ene-1,2-diol (S13)



4 S13

Diol **S13** was prepared adopting procedure by F. W. Goetzke *et al*.[3]

A solution of acetonide **4** (764 mg) in AcOH (5.2 mL) and water (2.3 mL) was stirred for 19 h at 40 °C. The reaction mixture was then concentrated under reduced pressure. Purification by gradient flash chromatography (ethyl acetate/hexane = 50% to 60%) afforded diol **S13** as a white solid (588 mg, 88%, 94% brsm).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.26 (m, 2H, C_{meta}-H), 7.01 (tt, *J* = 7.3, 1.1 Hz, 1H, C_{para}-H), 6.95 – 6.89 (m, 2H, C_{ortho}-H), 6.25 (ddt, *J* = 15.8, 7.6, 2.5 Hz, 1H, C(1‘)-H), 5.96 (dt, *J* = 6.1, 2.2 Hz, 1H, C(3)-H), 5.89 (dd, *J* = 6.1, 2.0 Hz, 1H, C(4)-H), 5.81 (dtd, *J* = 15.9, 11.2, 1.3 Hz, 1H, C(2‘)-H), 4.64 – 4.58 (m, 1H, C(2)-H), 4.19 (t, *J* = 11.6 Hz, 2H, C(4‘)-H_2), 3.97 (q, *J* = 5.6 Hz, 1H, C(1)-H), 3.38 (m, 1H, C(5)-H), 2.70 (d, *J* = 7.1 Hz, 1H, OH), 2.15 (d, *J* = 6.2 Hz, 1H, OH).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.1 (C_q), 137.1 (t, *J* = 8.9 Hz, C(1’)), 136.1 (C(4)), 132.7 (C(3)), 129.8 (C_{meta}), 123.7 (t, *J* = 25.1 Hz, C(2‘)), 122.0 (C_{para}), 118.3 (t, *J* = 240.3 Hz, C(3‘)), 115.0 (C_{ortho}), 76.9 (C(1)), 75.0 (C(2)), 69.6 (t, *J* = 34.8 Hz, C(4‘)), 53.7 (C(5)).

^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.66 (d, *J* = 257.2 Hz), -103.38 (d, *J* = 256.5 Hz).

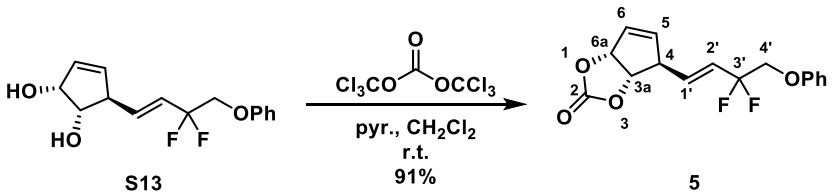
FT-IR ($CHCl_3$ film) cm^{-1}: 3360 (br. m), 1599 (m), 1496 (s), 1248 (s), 1163 (m), 1065 (s), 754 (s).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{16}O_3F_2Na$ 305.0960; Found 305.0961.

m.p. 45 – 48 °C.

$[\alpha]^{25}_D$= –152.9 (c=0.5, $CHCl_3$).

(3a*S*,4*S*,6a*R*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-3a,6a-dihydro-4H-cyclopenta[d][1,3]-dioxol-2-one (5)



A solution of triphosgene (399 mg, 1.34 mmol, 1.10 equiv.) in CH_2Cl_2 (4.0 mL) was added to a solution of diol **S13** (353 mg, 1.21 mmol, 1.00 equiv.) and pyridine (590 µL, 7.3 mmol, 6.0 equiv.) in CH_2Cl_2 (7.5 mL) at r.t. After stirring for 20 min, the reaction mixture was directly loaded onto silica and purification by gradient flash chromatography (ethyl acetate/hexane = 10% to 25%) afforded the product **5** as a colorless oil (352 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 – 7.26 (m, 2H, C_{meta}-H), 7.02 (tt, *J* = 7.3, 1.1 Hz, 1H, C_{para}-H), 6.96 – 6.86 (m, 2H, C_{ortho}-H), 6.20 (ddt, *J* = 15.9, 7.3, 2.4 Hz, 1H, C(1')-H), 6.14 – 6.07 (m, 1H, C(5)-H), 6.03 (dt, *J* = 5.8, 1.8 Hz, 1H, C(6)-H), 5.78 (dtd, *J* = 15.9, 11.0, 1.4 Hz, 1H, C(2')-H), 5.59 (dtd, *J* = 6.6, 1.6, 0.9 Hz, 1H, C(6a)-H), 4.87 (dt, *J* = 6.5, 0.9 Hz, 1H, C(3a)-H), 4.19 (t, *J* = 11.3 Hz, 2H, C(4')-H), 3.84 – 3.76 (m, 1H, C(4)-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.8 (C_q), 154.1 (C(2)), 137.8 (C(5)), 134.4 (t, *J* = 8.9 Hz, C(1')), 129.8 (C_{meta}), 129.5 (C(6)), 125.8 (t, *J* = 25.4 Hz, C(2')), 122.2 (C_{para}), 118.0 (t, *J* = 240.8 Hz, C(3')), 114.9 (C_{ortho}), 84.6 (C(6a)), 82.1 (t, *J* = 2.1 Hz, C(3a)), 69.4 (t, *J* = 35.3 Hz, C(4')), 53.2 (C(4)).

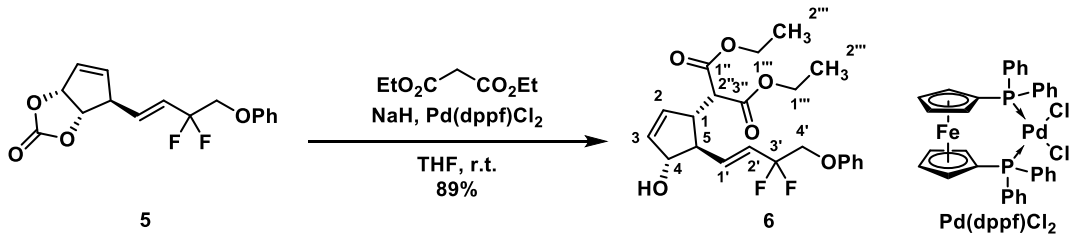
^{19}F NMR (376 MHz, $CDCl_3$, ^{1}H decoupled) δ: -103.19 (d, *J* = 259.7 Hz), -103.97 (d, *J* = 259.2 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 1791 (s), 1598 (w), 1495 (m), 1248 (m), 1157 (s), 1047 (s), 7570 (s).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{14}O_4F_2Na$ 331.0752; Found 331.0574.

$[\alpha]^{25}_D$= –170.7 (c=0.5, $CHCl_3$).

Diethyl 2-((1*S*,4*R*,5*R*)-5-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-4-hydroxycyclopent-2-en-1-yl)malonate (6)



Compound **6** was prepared adopting procedure by H. L. Sebahar *et al*.[10]

A solution of malonate enolate, prepared by addition of diethyl malonate (480 µL, 3.2 mmol, 3.5 equiv.) to mixture of NaH (60% in mineral oil, washed with pentane; 109 mg, 2.72 mmol, 3.00 equiv.) in THF (3.0 mL), was added to a solution of carbonate **5** (280 mg, 0.908 mmol, 1.00 equiv.) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium ($Pd(dppf)Cl_2$) (19.9 mg, 27.3 µmol, 0.03 equiv.) in THF (10 mL) at r.t.. After stirring for 1 h, the reaction mixture was poured onto an aq. sat. sol. of NH_4Cl (30 mL) and was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. Purification by gradient flash column chromatography (ethyl acetate/hexane = 10% to 40%) afforded **6** as a colorless oil (342 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 – 7.25 (m, 2H, C_{meta}-H), 7.04 – 6.96 (m, 1H, C_{para}-H), 6.96 – 6.88 (m, 2H, C_{ortho}-H), 6.17 (ddt, *J* = 15.7, 9.3, 2.5 Hz, 1H, C(1‘)-H), 5.92 – 5.84 (m, 2H, C(2)-H and C(3)-H), 5.88 – 5.74 (m, 1H, C(2‘)-H), 4.53 (dt, *J* = 5.4, 2.8 Hz, 1H, C(4)-H), 4.29 – 4.07 (m, 6H, C(4‘)-H_2 and C(1‘‘‘)-H_2), 3.47 (d, *J* = 6.7 Hz, 1H, C(2‘‘)-H), 3.13 – 3.04 (m, 1H, C(1)-H), 2.66 (dddd, *J* = 7.9, 5.3, 4.1, 1.1 Hz, 1H, C(5)-H), 2.44 (d, *J* = 8.4 Hz, 1H, OH), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.4 (C(1‘‘)), 168.2 (C(3‘‘)), 158.1 (C_q), 138.2 (t, *J* = 9.0 Hz, C(1‘)), 134.5 (C(2)), 133.5 (C(3)), 129.7 (C_{meta}), 123.7 (t, *J* = 25.1 Hz, C(2‘)), 122.0 (C_{para}), 118.2 (t, *J* = 239.0 Hz, C(3‘)), 115.0 (C_{ortho}), 82.4 (C(4)), 69.6 (t, *J* = 34.8 Hz, C(4’)), 61.8 (C(1‘‘‘)), 61.7 (C(1‘‘‘)), 55.0 (C(2‘‘)), 54.3 (C(5)), 49.6 (C(1)), 14.2 (C(2‘‘‘)), 14.1 (C(2‘‘‘)).

^{19}F NMR (376 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.03 (d, *J* = 257.0 Hz), -103.78 (d, *J* = 257.1 Hz).

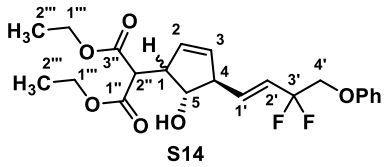
FT-IR ($CHCl_3$ film) cm^{-1}: 3509 (br, w), 1729 (s), 1599 (w), 1496 (w), 1249 (s), 1177 (s), 1159 (s), 1033 (m), 756 (m).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{26}O_6F_2Na$ 447.1590; Found 447.1588.

$[\alpha]^{25}_D$= +20.3 (c=0.5, $CHCl_3$).

Diethyl 2-((4*S*,5*S*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-5-hydroxycyclopent-2-en-1-yl)malonate (S14)

Compound **S14** was isolated as a by-product of allylic substitution reaction between carbonate **5** and malonate anion as a colorless oil (33.4 mg, 9%).



S14

^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ: 7.36 – 7.28 (m, 2H, C_{meta}-H), 7.04 – 6.96 (m, 3H, C_{ortho}-H and C_{para}-H), 6.30 (ddt, *J* = 16.0, 7.3, 2.5 Hz, 1H, C(1‘)-H), 5.88 (dtd, *J* = 16.0, 11.2, 1.4 Hz, 1H, C(2‘)-H), 5.75 (dt, *J* = 6.1, 2.2 Hz, 1H, C(3)-H), 5.67 (dt, *J* = 6.1, 2.1 Hz, 1H, C(2)-H), 4.33 (t, *J* = 12.3 Hz, 2H, C(4‘)-H_2), 4.17 (m, 4H, C(1‘‘‘)-H_2), 4.04 (q, *J* = 6.0 Hz, 1H, C(5)-H), 3.47 (d, *J* = 7.9 Hz, 1H, C(2‘‘)-H), 3.37 – 3.29 (m, 1H, C(4)-H), 3.20 (ddq, *J* = 8.2, 6.3, 2.2 Hz, 1H, C(1)-H), 1.23 (t, *J* = 7.0 Hz, 3H, CH_3), 1.22 (t, *J* = 7.0 Hz, 3H, CH_3).

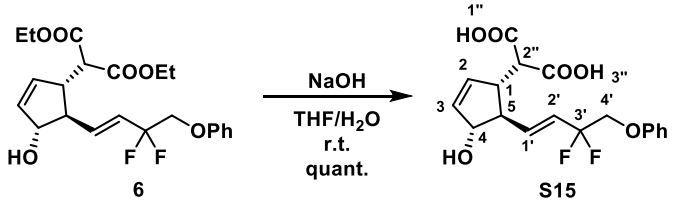
^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ: 168.5 (C(3‘‘)), 168.1 (C(1‘‘)), 158.3 (C_q), 138.7 (t, *J* = 9.0 Hz, C(1‘)), 131.4 (C(3)), 131.1 (C(2)), 129.6 (C_{meta}), 123.0 (t, *J* = 25.2 Hz, C(2‘)), 121.5 (C_{para}), 118.8 (t, *J* = 239.1 Hz, C(3‘)), 114.8 (C_{ortho}), 80.8 (t, *J* = 1.9 Hz, C(5)), 69.1 (t, *J* = 33.3 Hz, C(4‘)), 61.1 (C(1‘‘‘)), 61.0 (C(1‘‘‘)), 55.6 (C(4)), 54.4 (C(2‘‘)), 53.2 (C(1)), 13.6 (C(2‘‘‘)), 13.5 (C(2‘‘‘)).

^{19}F NMR (377 MHz, $(CD_3)_2CO$) δ: -102.76 (d, *J* = 255.9 Hz), -103.47 (d, *J* = 256.8 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3511 (br, w), 1725 (s), 1599 (w), 1496 (w), 1247 (s), 1160 (s), 1041 (m), 755 (m).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{26}O_6F_2Na$ 447.1590; Found 447.1585.

2-((1*S*,4*R*,5*R*)-5-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-4-hydroxycyclopent-2-en-1-yl)malonic acid (S15)



An aq. sol. of NaOH (1 M, 14 mL, 14 mmol, 16 equiv.) was added to a solution of ester **6** (378 mg, 890 µmol, 1.00 equiv.) in THF (10 mL) at r.t.. After stirring for 24 h, the reaction mixture was acidified with 1 M aq. solution of HCl (60 mL) and extracted with ethyl acetate (3 x 60 mL). The combined organic phases were washed with brine (60 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product **S15** was obtained as a pale yellow oil (343 mg, >95%) and was used in the next step without further purification.

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ: 11.30 (br s, 2H, COOH), 7.35 – 7.26 (m, 2H, C_{meta}-H), 7.05 – 6.94 (m, 3H, C_{ortho}-H and C_{para}-H), 6.34 (ddt, *J* = 15.8, 8.9, 2.6 Hz, 1H, C(1‘)-H), 5.96 – 5.80 (m, 3H, C(2‘)-H, C(2)-H and C(3)-H), 4.61 (dq, *J* = 5.2, 1.7 Hz, 1H, C(4)-H), 4.33 (t, *J* = 12.7 Hz, 2H, C(4‘)-H_2), 3.42 (d, *J* = 7.8 Hz, 1H, C(2‘‘)-H), 3.15 – 3.05 (m, 1H, C(1)-H), 2.62 (dddd, *J* = 7.8, 6.7, 5.2, 1.2 Hz, 1H, C(5)-H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ: 169.9 (C(1‘‘)), 169.6 (C(3‘‘)), 159.3 (C_q), 139.6 (t, *J* = 9.2 Hz, C(1‘)), 135.8 (C(2)), 133.5 (C(3)), 130.4 (C_{meta}), 124.4 (t, *J* = 25.1 Hz, C(2‘)), 122.4 (C_{para}), 119.6 (t, *J* = 238.2 Hz, C(3‘)), 115.8 (C_{ortho}), 82.0 (C(4)), 67.0 (t, *J* = 32.2 Hz, C(4‘)), 56.0 (C(5)), 55.9 (C(2‘‘)), 49.6 (C(1)).

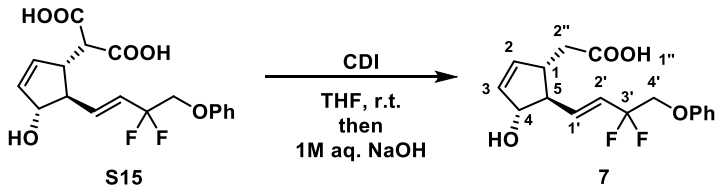
^{19}F NMR (377 MHz, $(CD_3)_2CO$, ^{1}H decoupled) δ: -103.33 (d, *J* = 252.4 Hz), -104.22 (d, *J* = 252.4 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 2918 (br. w), 1714(s), 1599 (m), 1495 (m), 1248 (s), 1164 (m), 1054 (m), 756 (s).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{18}O_6F_2Na$ 391.0964; Found 391.0963.

$[\alpha]^{25}_D$= +14.8 (c=0.5, $CHCl_3$).

2-((1*S*,4*R*,5*R*)-5-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-4-hydroxycyclopent-2-en-1-yl)acetic acid (7)



Compound **7** was prepared adopting procedure by D. Lafrance *et al*.[11]

1,1'-Carbonyldiimidazole (CDI) (402 mg, 2.23 mmol, 2.50 equiv.) was added to a solution of acid **S15** (333 mg, 864 µmol, 1.00 equiv.) in THF (18 mL) at r.t.. After stirring the mixture for 3 h, an aq. sol. of 1 M NaOH (7.8 mL, 7.8 mmol, 8.7 equiv.) was added and the reaction mixture stirred for 20 h. The reaction mixture was then acidified with aq. 1 M HCl (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product **7** was obtained as a pale yellow oil (305 mg, >95%) and used in the next step without further purification.

NOTE: The reaction can be monitored by TLC using 80% THF/hexane +1% AcOH.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 – 7.24 (m, 2H, C_{meta}-H), 7.04 – 6.97 (m, 1H, C_{para}-H), 6.97 – 6.88 (m, 2H, C_{ortho}-H), 6.23 (ddt, *J* = 15.7, 9.1, 2.4 Hz, 1H, C(1‘)-H), 5.93 – 5.77 (m, 3H, C(2‘)-H, C(2)-H and C(3)-H), 4.61 (dq, *J* = 5.5, 1.7 Hz, 1H, C(4)-H), 4.19 (t, *J* = 11.6 Hz, 2H, C(4‘)-H_2), 2.81 (dtd, *J* = 8.2, 6.3, 1.9 Hz, 1H, C(1)-H), 2.47 (dd, *J* = 15.8, 6.1 Hz, 1H, C(2‘‘)-H), 2.40 (dd, *J* = 15.8, 8.0 Hz, 1H, C(2‘‘)-H), 2.38 – 2.30 (m, 1H, C(5)-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6 (C(1‘‘)), 158.1 (C_q), 137.6 (t, *J* = 9.0 Hz, C(1’)), 135.2 (C(2)), 133.6 (C(3)), 129.8 (C_{meta}), 124.5 (t, *J* = 25.0 Hz, C(2‘)), 122.0 (C_{para}), 118.2 (t, *J* = 240.6 Hz, C(3‘)), 115.0 (C_{ortho}), 82.0 (C(4)), 69.5 (t, *J* = 34.6 Hz, C(4‘)), 57.7 (C(5)), 45.9 (C(1)), 38.4 (C(2‘‘)).

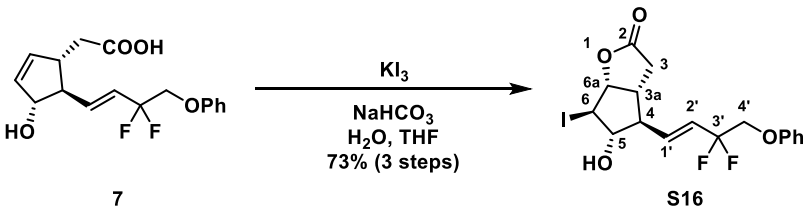
^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.50 (d, *J* = 256.8 Hz), -103.31 (d, *J* = 256.5 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 2927 (br. w.), 1710 (s), 1599(m), 1496 (m), 1248 (s), 1161 (s), 1054 (s), 754 (s).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{18}O_4F_2Na$ 347.1065; Found 347.1065.

$[\alpha]^{25}_D$= –2.5 (c=0.5, $CHCl_3$).

(3a*R*,4*R*,5*S*,6*R*,6a*R*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-5-hydroxy-6-iodohexahydro-2H-cyclopenta[b]furan-2-one (S16)



7 S16

Compound **S16** was prepared adopting procedure by K. Yagi *et al*.[12]

A solution of $NaHCO_3$ (676 mg, 8.04 mmol, 10.0 equiv.) in H_2O (5.7 mL) and solution of KI (801 mg, 4.83 mmol, 6.00 equiv.) and I_2 (408 mg, 1.61 mmol, 2.00 equiv.) in H_2O (5.7 mL) were added to a solution of acid **7** (289 mg, 804 µmol, 1.00 equiv.) in THF (3.2 mL) at r.t.. After stirring the mixture for 24 h in the dark, the reaction mixture was poured onto an aq. sat. sol. of $Na_2S_2O_3$ (30 mL) and was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by gradient flash column chromatography (ethyl acetate/hexane = 10% to 40%) **S16** as a colorless oil (266 mg, 73% over 3 steps).

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ: 7.37 – 7.27 (m, 2H, C_{meta}-H), 7.04 – 6.95 (m, 3H, C_{ortho}-H and C_{para}-H), 6.30 (ddt, *J* = 15.8, 7.8, 2.5 Hz, 1H, C(1‘)-H), 6.03 (dtd, *J* = 15.8, 11.2, 1.1 Hz, 1H, C(2‘)-H), 5.15 – 5.05 (m, 1H, C(6a)-H), 5.05 – 4.99 (m, 1H, OH), 4.34 (t, *J* = 12.4 Hz, 2H, C(4‘)-H_2), 4.18 – 4.08 (m, 1H, C(5)-H), 4.12 – 4.04 (m, 1H, C(6)-H), 3.01 (tdd, *J* = 10.2, 8.4, 3.1 Hz, 1H, C(3a)-H), 2.82 (dd, *J* = 18.2, 10.1 Hz, 1H, C(3)-H), 2.54 – 2.46 (m, 1H, C(4)-H), 2.42 (dd, *J* = 18.2, 3.1 Hz, 1H, C(3)-H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ: 175.8 (C(2)), 159.2 (C_q), 137.0 (t, *J* = 9.2 Hz, C(1‘)), 130.4 (C_{meta}), 126.0 (t, *J* = 25.1 Hz, C(2‘)), 122.5 (C_{para}), 119.4 (t, *J* = 239.5 Hz, C(3‘)), 115.7 (C_{ortho}), 89.9 (C(6a)), 83.6 (C(5)), 70.0 (t, *J* = 33.0 Hz, C(4‘)), 53.9 (C(4)), 41.3 (C(3a)), 33.7 (C(6)), 33.6 (C(3)).

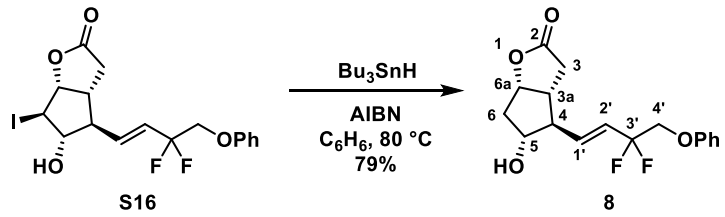
^{19}F NMR (376 MHz, $(CD_3)_2CO$, ^{1}H decoupled) δ: -103.62 (d, *J* = 254.3 Hz), -104.34 (d, *J* = 253.3 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3422.4 (br. w), 1760(s), 1598 (m), 1494 (m), 1247 (s), 1161 (s), 1052 (s), 973 (s), 756 (s).

HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_{17}H_{16}O_4F_2I$ 449.0067; Found 449.0066.

$[\alpha]^{25}_D$= +15.6 (c=0.5, $CHCl_3$).

(3a*R*,4*R*,5*R*,6a*S*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-5-hydroxyhexahydro-2H-cyclopenta[b]furan-2-one (8)



Compound **8** was prepared adopting procedure by K. Yagi *et al*.[12]

Tributyltinhydride (100 µL, 390 µmol, 3.0 equiv.) and azobisisobutyronitrile (AIBN) (2.1 mg, 13µmol, 0.10 equiv.) were added to solution of iodolactone **S16** (58.2 mg, 129 µmol, 1.00 equiv.) in benzene (2.6 mL). The resulting mixture was stirred at 80 °C. After 1 h, the reaction mixture was cooled down to room temperature, solid KF (85 mg) was added and the resulting mixture was stirred for additional 1 h. The reaction mixture was then loaded on silica and the crude product purified by gradient flash column chromatography (ethyl acetate/hexane = 0% to 70%, stationary phase K_2CO_3/silica = 1:9). The product **8** was obtained as a colorless oil (33.1 mg, 79%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ: 7.37 – 7.24 (m, 2H, C_{meta}-H), 7.06 – 6.93 (m, 3H, C_{ortho}-H and C_{para}-H), 6.23 (ddt, *J* = 15.9, 7.9, 2.5 Hz, 1H, C(1‘)-H), 5.97 (dtd, *J* = 15.9, 11.1, 1.1 Hz, 1H, C(2‘)-H), 4.94 (td, *J* = 7.0, 3.1 Hz, 1H, C(6a)-H), 4.33 (t, *J* = 12.4 Hz, 2H, C(4‘)-H_2), 4.25 (d, *J* = 5.0 Hz, 1H, OH), 4.09 (qd, *J* = 7.1, 5.1 Hz, 1H, C(5)-H), 2.82 – 2.71 (m, 2H, C(3a)-H and C(3)-H), 2.54 – 2.42 (m, 2H, C(4)-H and C(6)-H), 2.42 – 2.30 (m, 1H, C(3)-H), 1.84 (ddd, *J* = 14.5, 7.2, 3.2 Hz, 1H, C(6)-H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ: 176.8 (C(2)), 159.2 (C_q), 138.3 (t, *J* = 9.1 Hz, C(1‘)), 130.4 (C_{meta}), 125.1 (t, *J* = 25.0 Hz, C(2‘)), 122.4 (C_{para}), 119.5 (t, *J* = 239.5 Hz, C(3‘)), 115.7 (C_{ortho}), 83.0 (C(6a)), 76.9 (C(5)), 69.9 (t, *J* = 33.1 Hz, C(4‘)), 56.5 (C(4)), 42.8 (C(3a)), 41.2 (C(6)), 34.6 (C(3)).

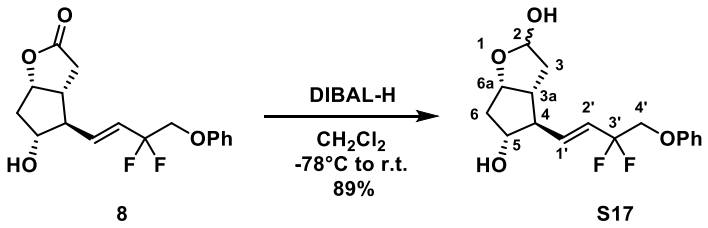
^{19}F NMR (377 MHz, $(CD_3)_2CO$, decoupled) δ: -103.41 (d, *J* = 253.7 Hz), -104.17 (d, *J* = 253.0 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3431 (br. w), 2932 (w), 1760 (s), 1598 (m), 1494 (m), 1247 (s), 1161 (s), 1079 (s), 1025 (s), 973 (s), 973 (m), 756 (s), 692 (s).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{18}O_4F_2Na$ 347.1065; Found 347.1065.

$[\alpha]^{25}_D$= –1.9 (c=0.5, $CHCl_3$).

(3a*R*,4*R*,5*R*,6a*S*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)hexahydro-2H-cyclopenta[b]furan-2,5-diol (S17)



Compound **S16** was prepared adopting procedure by S. Prevost *et al*.[13]

A solution of diisobutylaluminium hydride (DIBAL-H) (1 M in CH_2Cl_2, 580 µL, 580 µmol, 2.2 equiv.) was added to a solution of **8** (85.0 mg, 262 µmol, 1.00 equiv.) in CH_2Cl_2 (5.4 mL) at -78 °C. After stirring for 1 h, the reaction mixture was allowed to warm to r.t., quenched with an aq. sat. sol. of potassium sodium tartrate (10 mL), and was stirred for additional 1 h. The reaction mixture was then extracted with CH_2Cl_2 (4 x 15 mL), the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate/hexane = 70%) afforded **S16** as colorless oil (76.4 mg, 89%) as an inseparable mixture of two diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 – 7.27 (m, 4H, C_{meta}-H and C‘$_{meta}$-H), 7.01 (ddt, *J* = 8.4, 7.2, 1.2 Hz, 2H, C_{para}-H and C‘$_{para}$-H), 6.95 – 6.88 (m, 4H, C_{ortho}-H and C_{ortho}-H), 6.15 – 6.04 (m, C(1‘)-H and C‘(1‘)-H), 5.88 – 5.74 (m, 2H, C(2‘)-H and C‘(2‘)-H), 5.67 (d, *J* = 5.0 Hz, 1H, C(2)-H), 5.58 (d, *J* = 5.5 Hz, 1H, C‘(2)-H), 4.69 (dt, *J* = 6.7, 3.3 Hz, 1H, C(6a)-H), 4.64 (td, *J* = 7.1, 3.4 Hz, 1H, C‘(6a)-H), 4.19 (t, *J* = 11.4 Hz, 4H, C(4‘)-H_2 and C‘(4‘)-H_2), 4.01 – 3.93 (m, 2H, C(5)-H and C‘(5)-H), 2.89 (q, *J* = 6.9 Hz, 1H, C‘(4)-H), 2.80 (s, 1H, C(2)-OH), 2.56 (dtd, *J* = 8.9, 7.2, 4.5 Hz, 1H, C(3a)-H), 2.49 (dtd, *J* = 8.5, 7.1, 1.3 Hz, 1H, C‘(3a)-H), 2.40 – 2.31 (m, 3H, C(4)-H, C(6)-H and C‘(6)-H), 2.24 (ddd, *J* = 13.8, 9.7, 5.6 Hz, 1H, C‘(3)-H), 2.14 (ddd, *J* = 13.6, 9.0, 1.6 Hz, 1H, C(3)-H), 2.09 (ddd, *J* = 14.2, 6.1, 3.5 Hz, 1H, C‘(6)-H), 2.06 – 1.97 (m, 2H, C(3)-H and C‘(3)-H), 1.85 (ddd, *J* = 14.2, 6.8, 3.1 Hz, 1H, C(6)-H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.9 (C‘$_q$), 157.9 (C_q), 138.4 (t, *J* = 8.8 Hz, C‘(1‘)), 137.7 (t, *J* = 8.8 Hz, C(1‘)), 129.79 (C_{meta}), 129.77(C‘$_{meta}$), 124.0 (t, *J* = 24.9 Hz, C(2‘)), 123.5 (t, *J* = 24.8 Hz, C‘(2‘)), 122.01 (C_{para}), 121.98 (C‘$_{para}$), 118.26 (t, *J* = 240.4 Hz, C‘(3‘)), 118.20 (t, *J* = 240.5 Hz, C(3‘)), 114.8 (C_{ortho} and C‘$_{ortho}$), 101.1 (C‘(2)), 100.0 (C(2)), 84.5 (C‘(6a)), 81.3 (C(6a)), 78.4 (C(5) and C‘(5)), 69.4 (t, *J* = 35.3 Hz, C(4‘) and C;(4‘)), 57.2 (C(4)), 57.0 (C‘(4)), 46.6 (C‘(3a)), 45.6 (C(3a)), 42.8 (C‘(6)), 39.8 (C(6) or C(3)), 39.7 (C(6) or C(3)), 39.3 (C‘(3)).

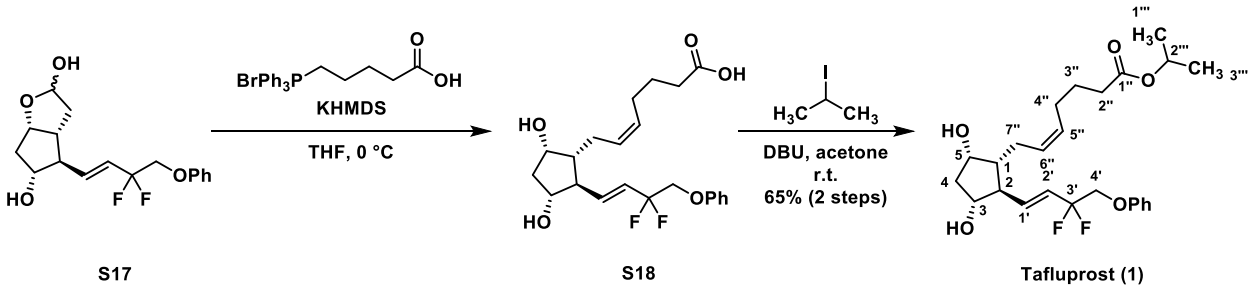
^{19}F NMR (471 MHz, $CDCl_3$) δ: -102.44 (d, *J* = 256.8 Hz), -102.82 (d, *J* = 257.8 Hz), -102.87 (d, *J* = 256.5 Hz), -103.28 (d, *J* = 256.5 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3372 (br. w), 1496 (m), 1294 (m), 1060 (m).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}O_4F_2Na$ 349.1222; Found 349.1223.

$[\alpha]^{25}_D$= –10.4 (c=0.5, $CHCl_3$).

Isopropyl (*Z*)-7-((1*R*,2*R*,3*R*,5*S*)-2-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-3,5-dihydroxycyclopen-tyl)hept-5-enoate (Tafluprost (1))



Compound **1** was prepared adopting procedure by Y. Zhao *et al*.[14]

A solution of potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M in toluene, 490 µL, 250 µmol, 8.0 equiv.) was added to a suspension of (4-Carboxybutyl)triphenylphosphonium bromide (54.2 mg, 123 µmol, 4.00 equiv.) in THF (350 µL) at 0 °C (intensively orange solution). After stirring for 15 min, a solution of hemiacetal **S17** (10 mg, 30.6 µmol, 1.00 equiv.) in THF (300 µL) was added and the resulting solution was stirred for 2 h at 0 °C. H_2O (0.5 mL) was added, the reaction mixture was acidified with aq. 1 M HCl, and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product **S18** was passed through plug of silica (ethyl acetate/acetic acid = 99%) and used directly in the next step without any further purification.

Crude **S18** was dissolved in acetone (400 µL) and DBU (28 µL, 180 µmol, 6.0 equiv.). 2-iodopropane (18 µL, 180 µmol, 6.0 equiv.) was added to the mixture and the resulting solution was stirred for 22 h at r.t. The reaction mixture was then directly loaded on silica and purified by gradient flash column chromatography (ethyl acetate/hexane = 30% to 70%). Tafluprost **(1)** was obtained as a colorless oil (9.0 mg, 65%, 90% brsm)

The spectroscopic data are in agreement with the literature.[15,16,17]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.26 (m, 2H, C_{meta}-H), 7.00 (tt, *J* = 7.3, 1.1 Hz, 1H, C_{para}-H), 6.95 – 6.88 (m, 2H, C_{ortho}-H), 6.10 (ddt, *J* = 15.8, 9.1, 2.5 Hz, 1H, C(1‘)-H), 5.80 (dt, *J* = 15.7, 11.3 Hz, 1H, C(2‘)-H), 5.44 – 5.32 (m, 2H, C(6‘‘)-H and C(5‘‘)-H), 4.99 (h, *J* = 6.3 Hz, 1H, C(2‘‘‘)-H), 4.25 – 4.16 (m, 3H, C(4‘)-H_2 and C(5)-H), 4.06 – 3.99 (m, 1H, C(3)-H), 2.47 (td, *J* = 9.7, 4.0 Hz, 1H, C(2)-H), 2.42 (d, *J* = 7.2 Hz, 1H, C(3)-OH), 2.38 – 2.29 (m, 1H, C(7‘‘)-H), 2.26 (td, *J* = 7.2, 2.4 Hz, 2H, C(2‘‘)-H_2), 2.19 – 1.96 (m, 4H, C(4)-H, C(7‘‘)-H and C(4‘‘)-H_2), 1.85 (d, *J* = 14.6 Hz, 1H, C(4)-H), 1.73 – 1.63 (m, 2H, C(3‘‘)-H_2), 1.61 (m, 1H, C(1)-H), 1.22 (d, *J* = 6.3 Hz, 6H, C(1‘‘‘)-H_3 and C(3‘‘‘)-H_3). (One exchanging proton of OH not visible.)

^{13}C NMR (126 MHz, $CDCl_3$) δ: 173.6 (C(1‘‘)), 158.1 (C_q), 138.8 (t, *J* = 8.8 Hz, C(1‘)), 130.3 (C(6‘‘)), 129.8 (C_{meta}), 128.8 (C(5‘‘)), 123.7 (t, *J* = 24.9 Hz, C(2‘)), 122.0 (C_{para}), 118.3 (t, *J* = 240.3 Hz, C(3‘)), 114.9 (C_{ortho}), 78.2 (C(3)), 73.5 (C(5)), 69.6 (t, *J* = 35.0 Hz, C(4‘)), 67.8 (C(2‘‘‘)), 56.0 (C(2)), 50.7 (C(1)), 43.1 (C(4)), 34.1 (C(2‘‘)), 26.8 (C(4‘‘)), 25.9 (C(7‘‘)), 25.0 (C(3‘‘)), 21.99 (C(1‘‘‘)), 21.97 (C(3‘‘‘)).

^{19}F NMR (470 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.46 (d, *J* = 255.7 Hz), -103.21 (d, *J* = 255.6 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3395 (br. w), 2933 (w), 1725 (s), 1599 (m), 1497(s), 1249 (s), 1108 (s), 755 (s).

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{34}O_5F_2Na$ 475.2267; Found 475.2264.

$[\alpha]^{25}_D$= +22.4 (c=0.5, $CHCl_3$), lit **$[\alpha]^{25}_D$**= +21.6 (c=1.0, $CHCl_3$).[17]

TABLE S1: Comparison of ^{1}H and ^{13}C NMR data of the synthetized Tafluprost with literature.

Reported ^{1}H NMR (600 MHz, $CDCl_3$)[16]	Reported ^{1}H NMR (unknown frequency, $CDCl_3$)[15]	Measured ^{1}H NMR (500 MHz, $CDCl_3$)	Reported ^{13}C NMR (150 MHz, $CDCl_3$)[16]	Measured ^{13}C NMR (126 MHz, $CDCl_3$)
1.22 (d, 6H)	1.22 (d, *J* = 6.2 Hz, 3H) and 1.22 (d, *J* = 6.2 Hz, 3H)	1.22 (d, *J* = 6.3 Hz, 6H)	21.8 (2s)	21.99 and 21.97
1.61 (m, 1H)	1.58 – 1.63 (m, 1H)	1.61 (m, 1H)	24.8	25.0
1.67 (m, 2H)	1.63 – 1.69 (m, 2H)	1.63 – 1.73 (m, 2H)	25.7	25.9
1.85 (m, 1H)	1.84 (d, *J* = 14,7 Hz, 1H)	1.85 (d, *J* = 14.6 Hz, 1H)	26.6	26.8
2.06 (m, 1H)	2.02 – 2.08 (m, 1H)	1.96 – 2.19 (m, 4H)	34.0	34.1
2.09 – 2.16 (m, 3H)	2.10 – 2.16 (m, 3H)		42.9	43.1
	2.25 (t, *J* = 7.3 Hz, 1H)	2.26 (td, *J* = 7.2, 2.4 Hz, 2H)	50.5	50.7
	2.26 (t, *J* = 7.1 Hz, 1H)		55.7	56.0
	2.30 – 2.35 (m, 1H)	2.29 – 2.38 (m, 1H)	67.7	67.8
[a]	2.46 – 2.49 (m, 2H)	2.42 (d, *J* = 7.2 Hz, 1H)	69.5 (*J* = 34.9 Hz)	69.6 (t, *J* = 35.0 Hz)
2.47 (m, 1H)		2.47 (td, *J* = 9.7, 4.0 Hz, 1H)	73.3	73.5
[b]	2.61–2.63 (m, 1H)	[b]	77.9	78.2
4.02 (m, 1H)	4.02 – 4.03 (m, 1H)	3.99 – 4.06 (m, 1H)	114.8	114.9
4.17 – 4.22 (m, 2H)[c]	4.18 – 4.21 (m, 3H)	4.16 – 4.25 (m, 3H)	118.2 (*J* = 240.0 Hz)	118.3 (t, *J* = 240.3 Hz)
5.00 (sept, *J* = 6.30 Hz, 1H)	5.00 (heptet, *J* = 6.2 Hz, 1H)	4.99 (h, *J* = 6.3 Hz, 1H)	121.8	122.0
5.33 – 5.42 (m, 2H)	5.35 – 5.42 (m, 2H),	5.32 – 5.44 (m, 2H)	123.6 (*J* = 25.0 Hz)	123.7 (t, *J* = 24.9 Hz)
5.80 (m, 1H)	5.80 (dt, *J* = 15.8, 11.2 Hz, 1H)	5.80 (dt, *J* = 15.7, 11.3 Hz, 1H)	128.6	128.8
6.10 (m, 1H)	6.10 (dd, *J* = 15.8, 8.8 Hz, 1H)	6.10 (ddt, *J* = 15.8, 9.1, 2.5 Hz, 1H)	129.6	129.8
6.92 (m, 2H)	6.91 (d, *J* = 8.8 Hz, 2H)	6.88 – 6.95 (m, 2H)	130.1	130.3
7.00 (m, 1H)	7.00 (t, *J* = 7.3 Hz, 1H)	7.00 (tt, *J* = 7.3, 1.1 Hz, 1H)	138.6 (*J* = 8.8 Hz)	138.8 (t, *J* = 8.8 Hz)
7.30 (m, 2H)	7.30 (dd, *J* = 8.8, 7.3 Hz, 2H)	7.26 – 7.34 (m, 2H)	157.9	158.1
			173.5	173.6

[a] Exchanging OH visible. [b] Exchanging OH not visible. [c] One proton not reported.

TABLE S2: Comparison of ^{19}F NMR data of the synthetized Tafluprost with literature.

Reported ^{19}F NMR (470 MHz, $CDCl_3$)[16]	Reported ^{19}F NMR (unknown frequency, $CDCl_3$)[15]	Measured ^{19}F NMR (470 MHz, $CDCl_3$)
−102.6 ($^{2}J_{F\text{-}F}$ = 255.8 Hz)	−102.8 ($^{2}J_{F\text{-}F}$ = 255.6 Hz)	-102.5 (d, *J* = 255.7 Hz)
−103.1 ($^{2}J_{F\text{-}F}$ = 255.8 Hz)	−103.6 ($^{2}J_{F\text{-}F}$ = 255.6 Hz)	-103.2 (d, *J* = 255.6 Hz)

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NMR spectra

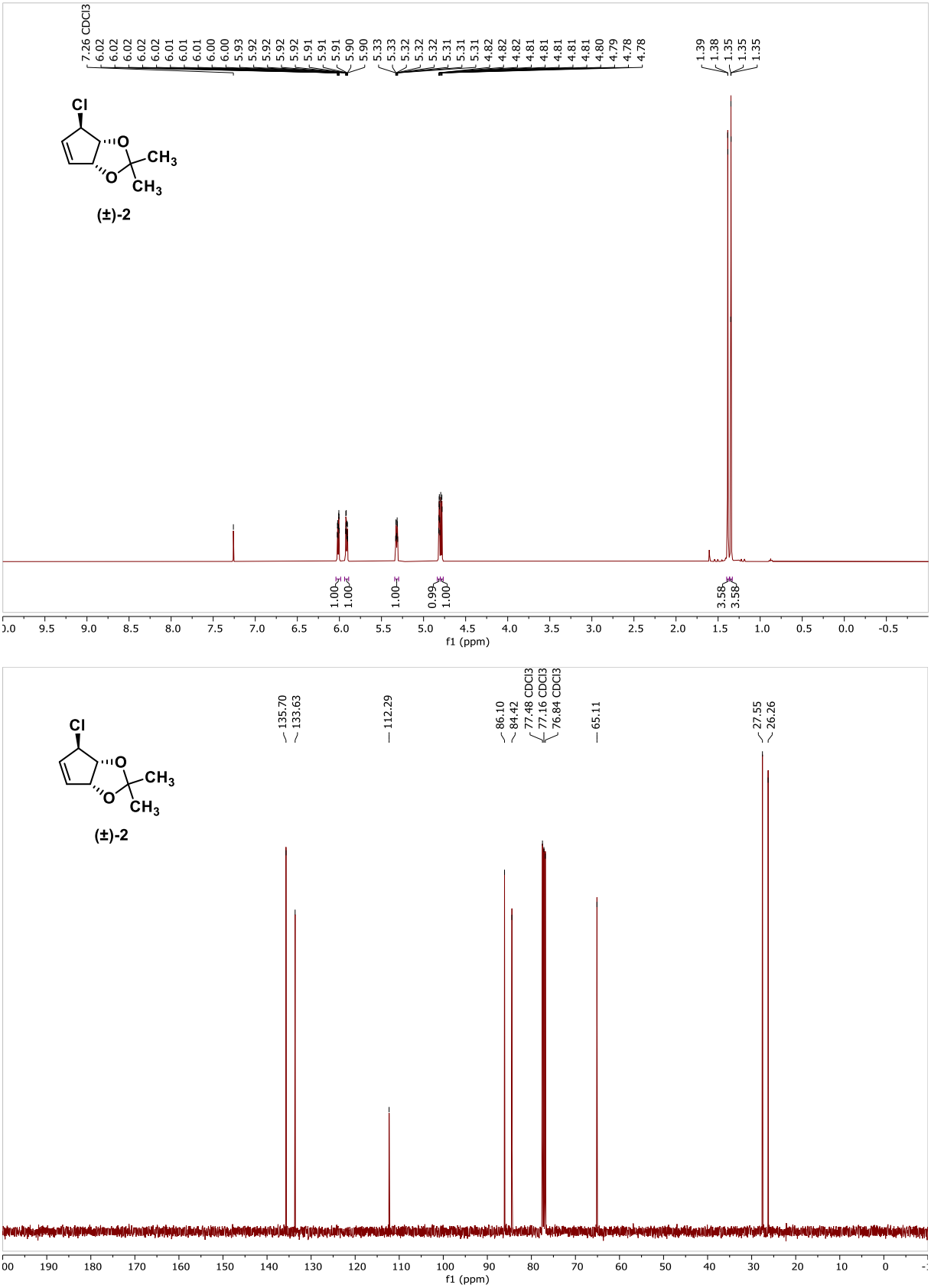

Figure S2: ^{1}H NMR (400 MHz, $CDCl_3$, top) and ^{13}C NMR (100 MHz, $CDCl_3$, bottom) of compound **(±)-2**.

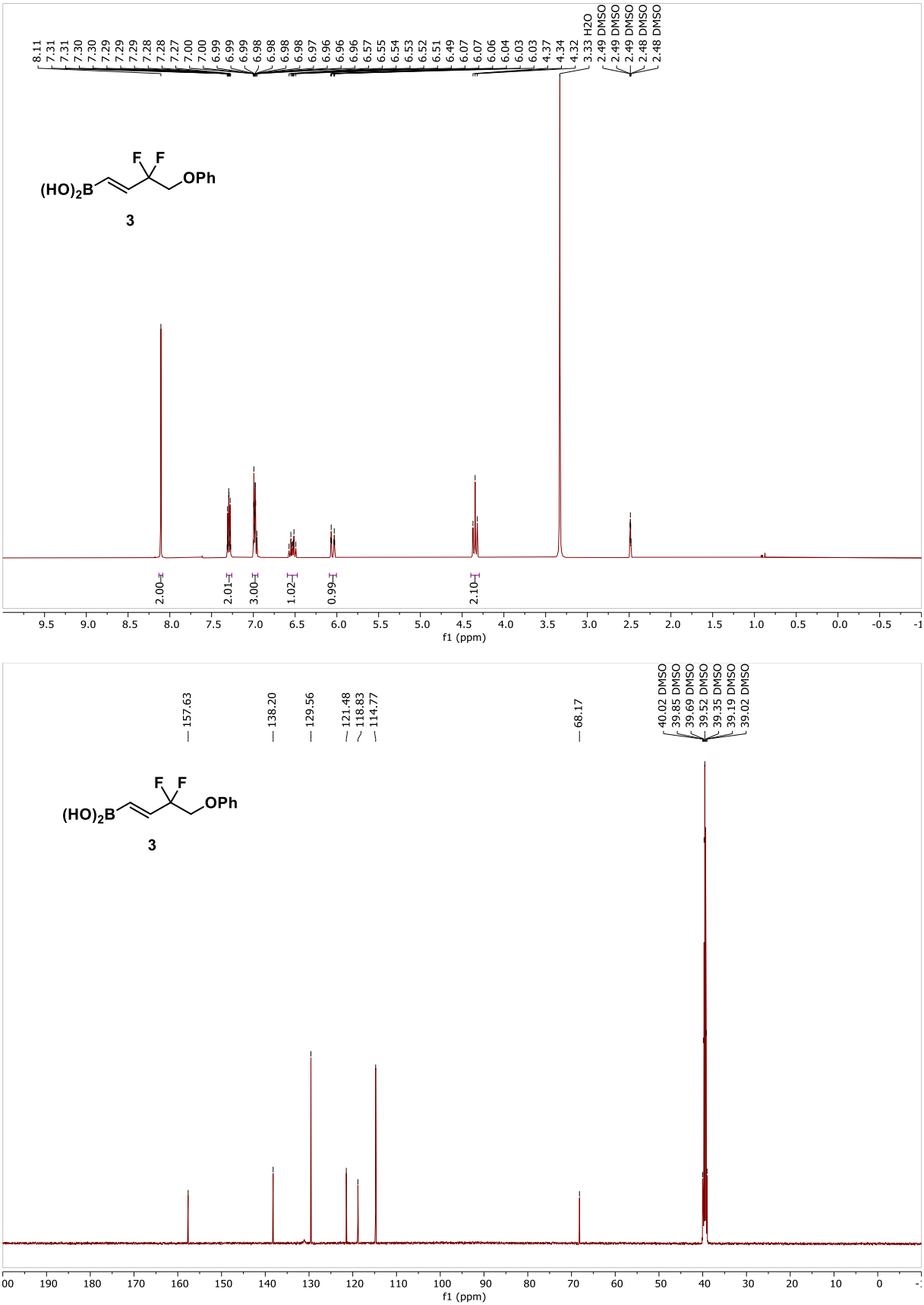

Figure S3: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, top) and ^{13}C NMR (126 MHz, $(CD_3)_2SO$, bottom) of compound **3**.

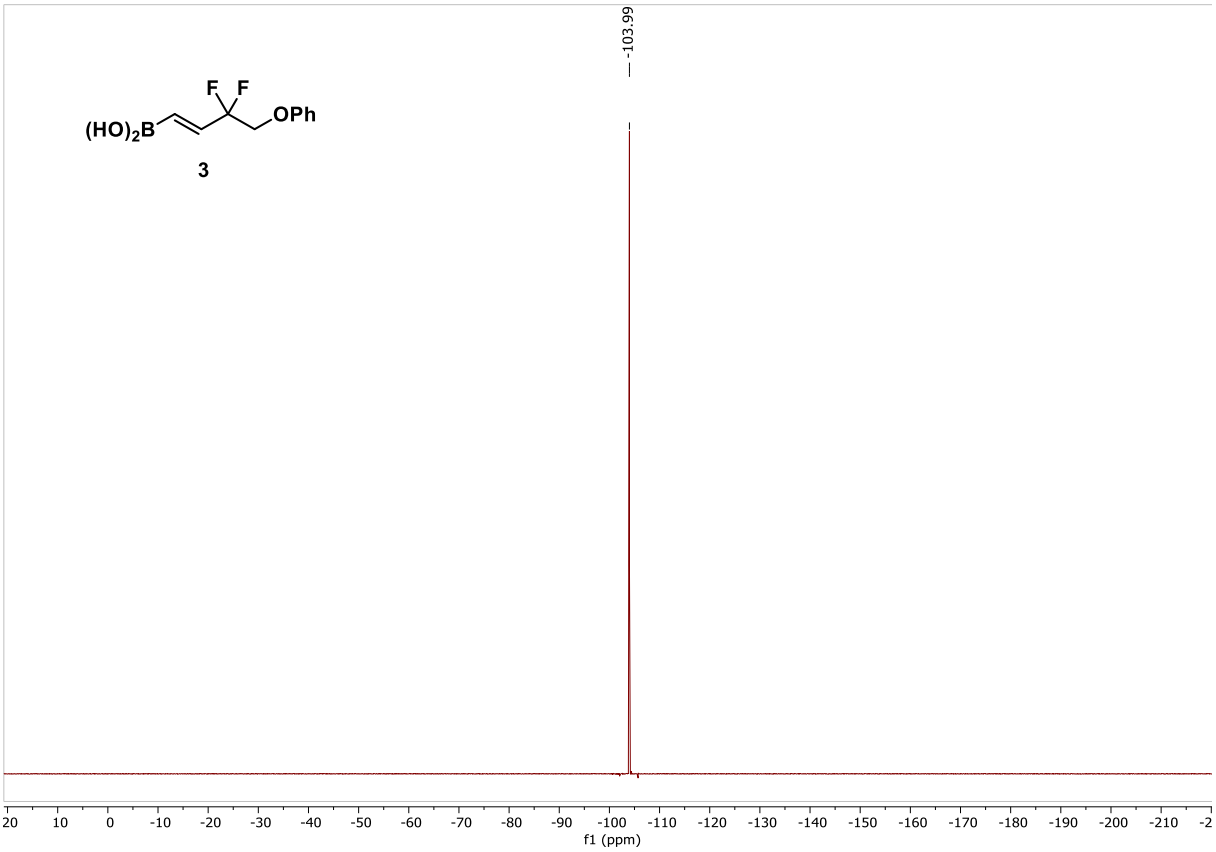

Figure S4: ^{19}F NMR (471 MHz, $(CD_3)_2SO$, ^{1}H decoupled) of compound **3**.

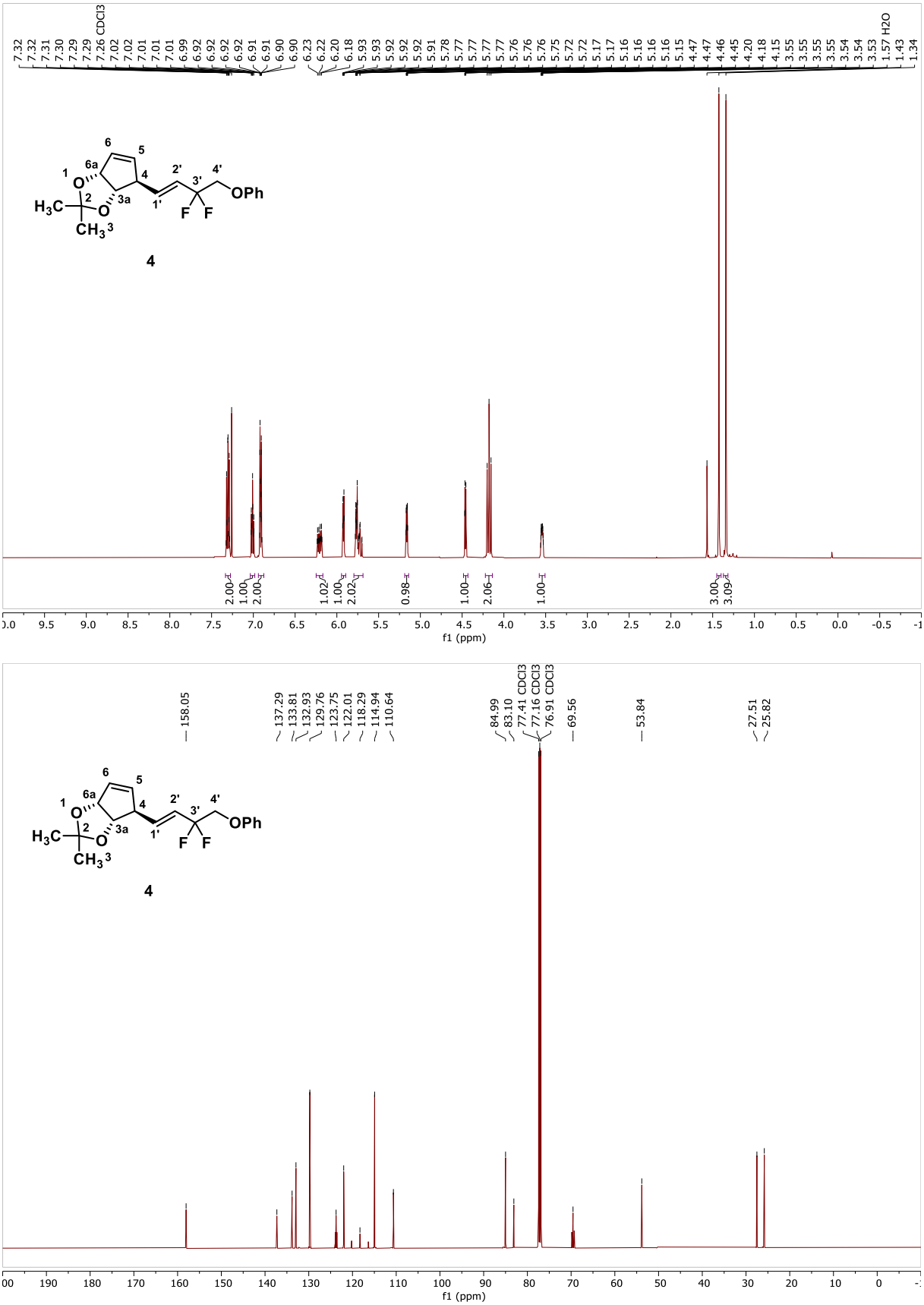

Figure S5: ^{1}H NMR (500 MHz, $CDCl_3$, top) and ^{13}C NMR (126 MHz, $CDCl_3$, bottom) of compound **4**.

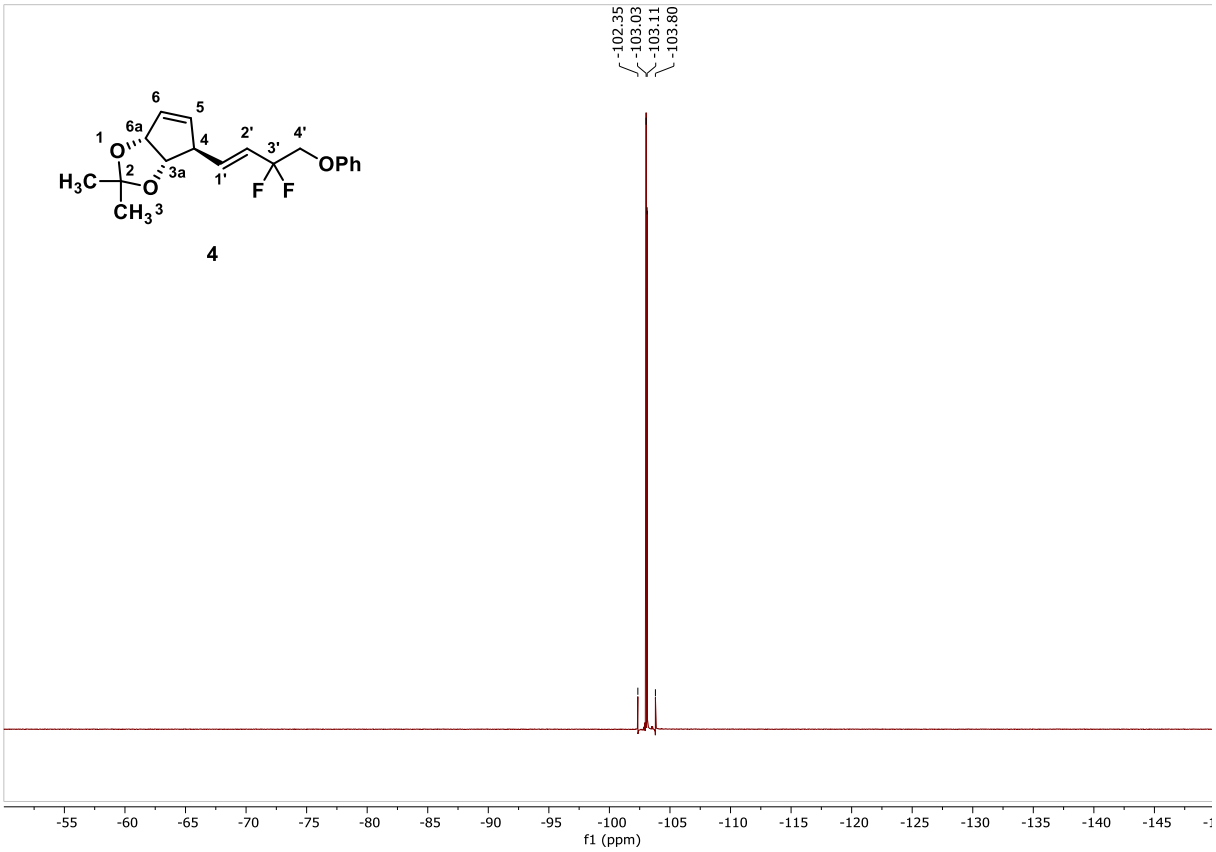

Figure S6: ^{19}F NMR (471 MHz, $CDCl_3$, ^{1}H decoupled) of compound **4**.

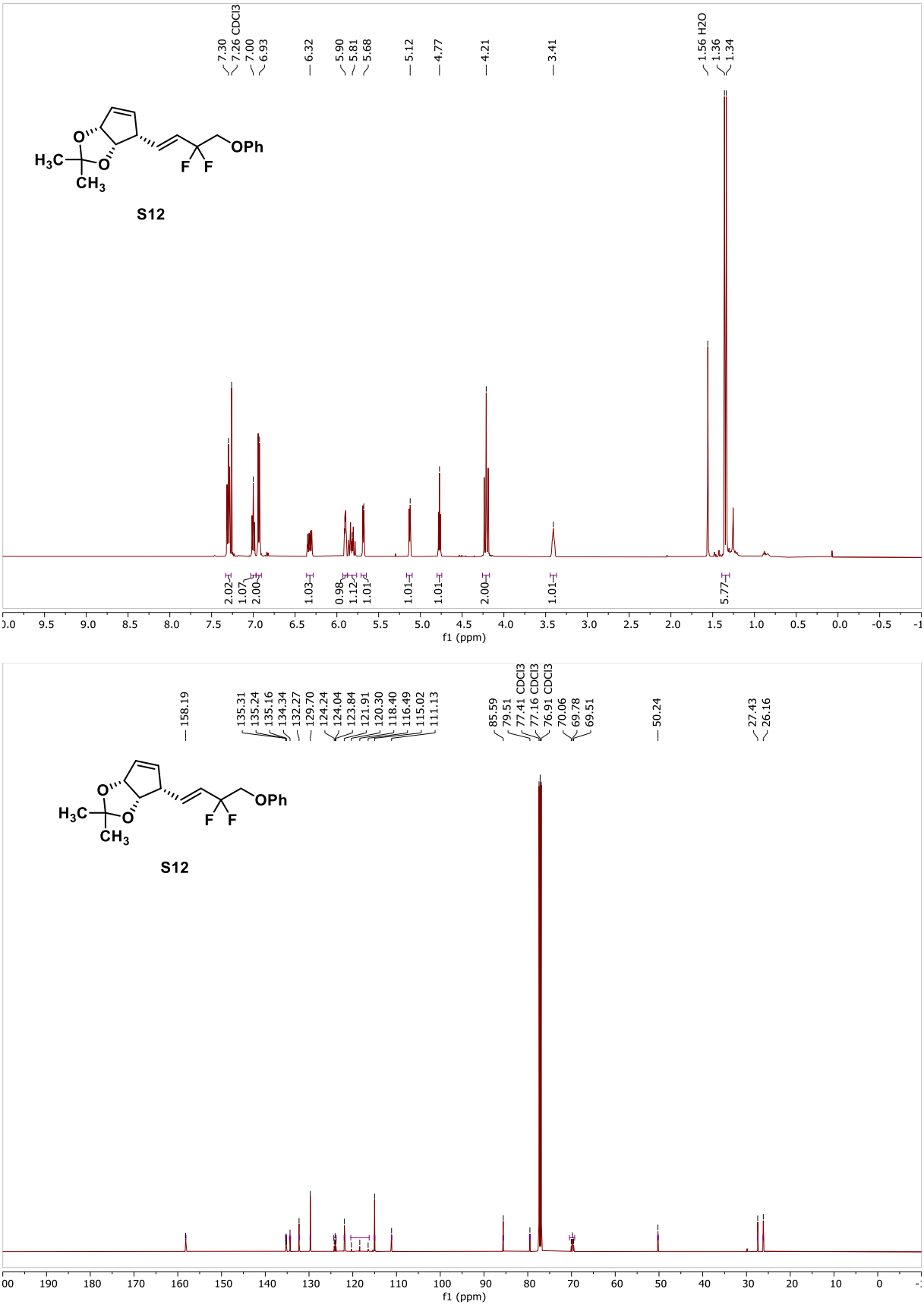

Figure S7: ^{1}H NMR (500 MHz, $CDCl_3$, top) and ^{13}C NMR (126 MHz, $CDCl_3$, bottom) of compound **S12**.

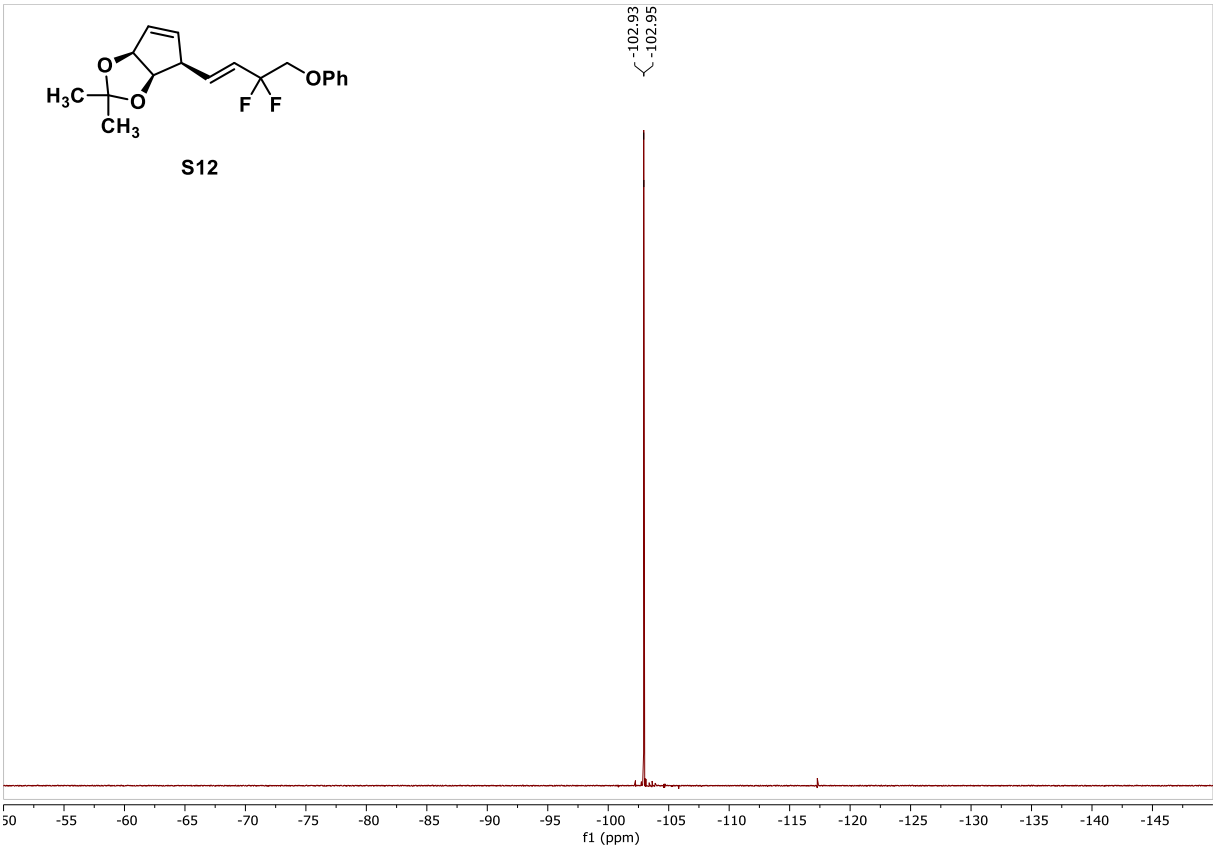

Figure S8: ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) of compound **S12**.

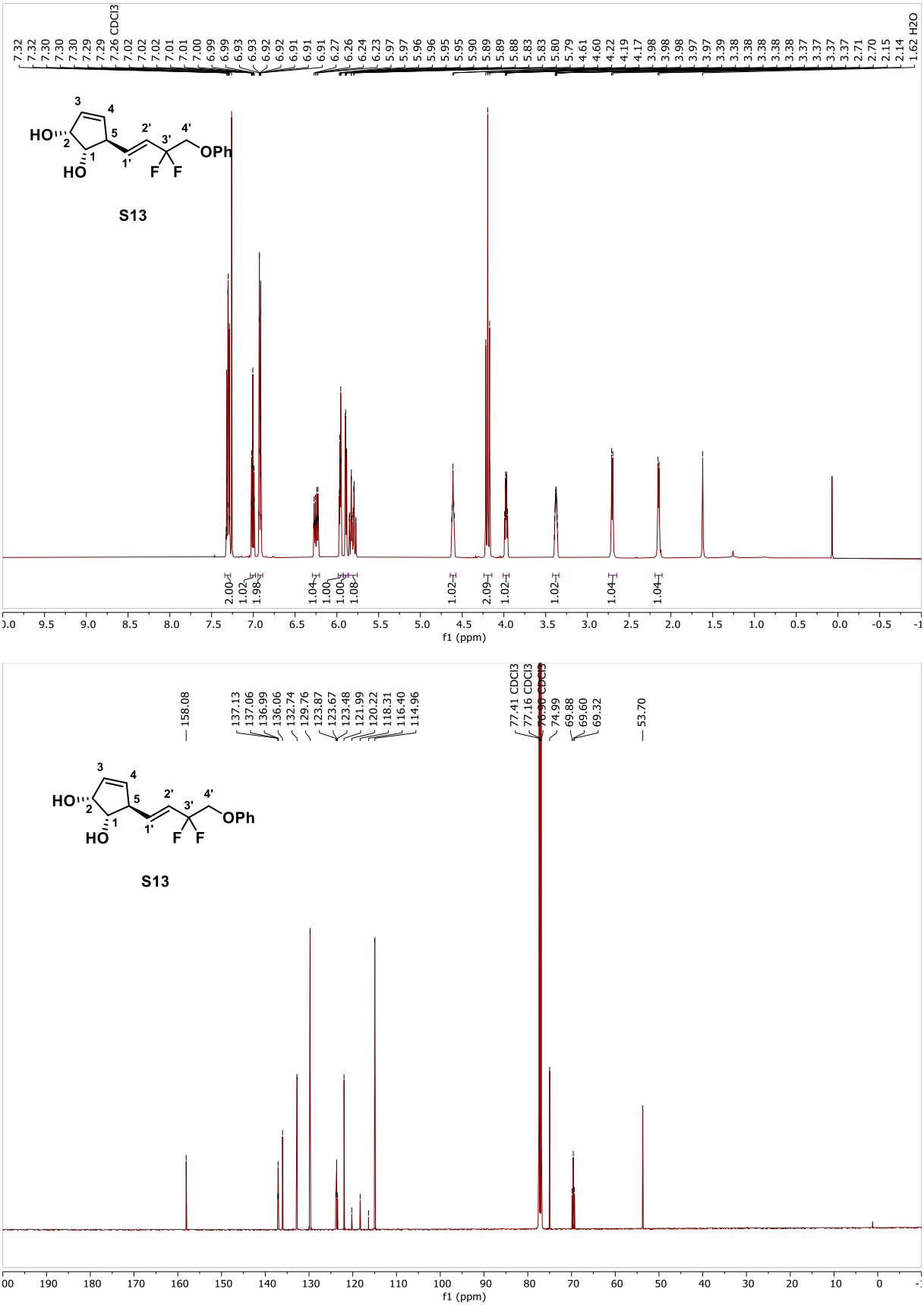

Figure S9: ^{1}H NMR (500 MHz, $CDCl_3$, top) and ^{13}C NMR (126 MHz, $CDCl_3$, bottom) of compound **S13**.

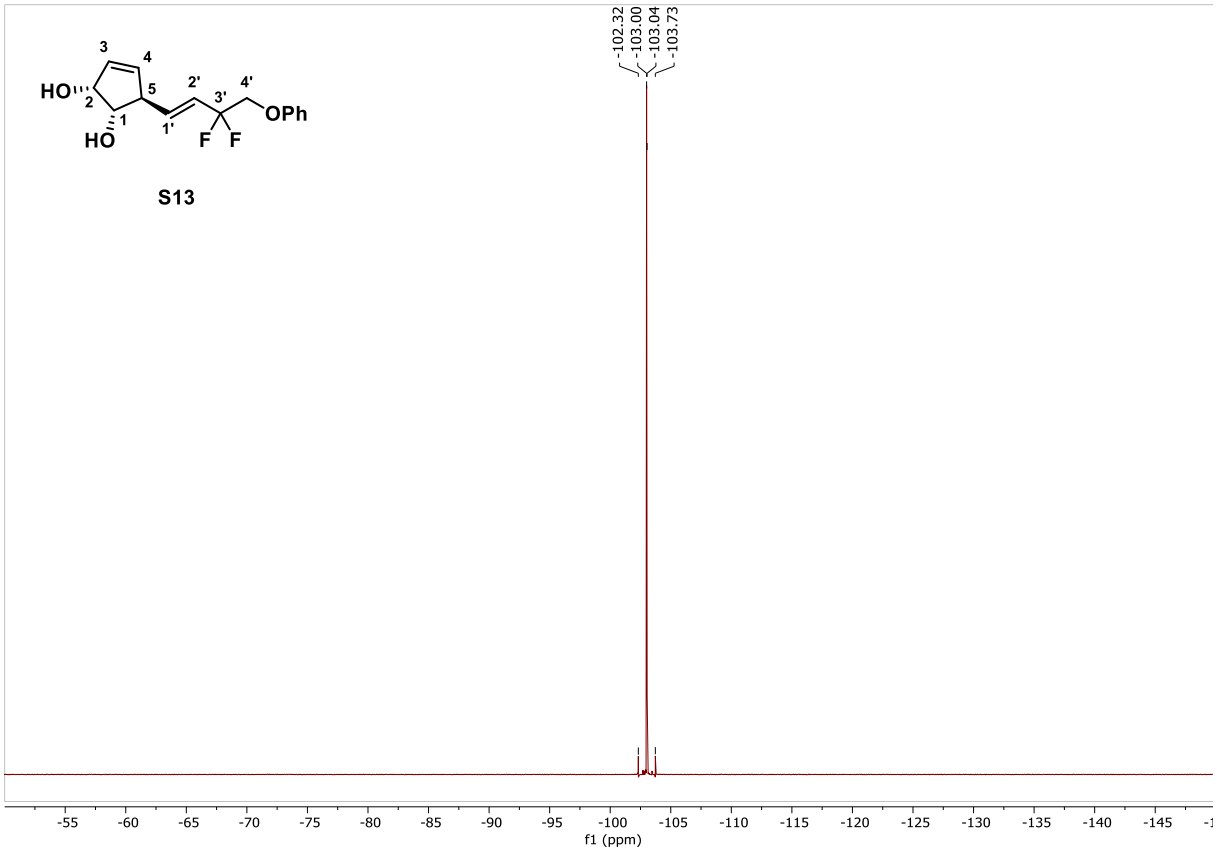

Figure S10: ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) of compound **S13**.

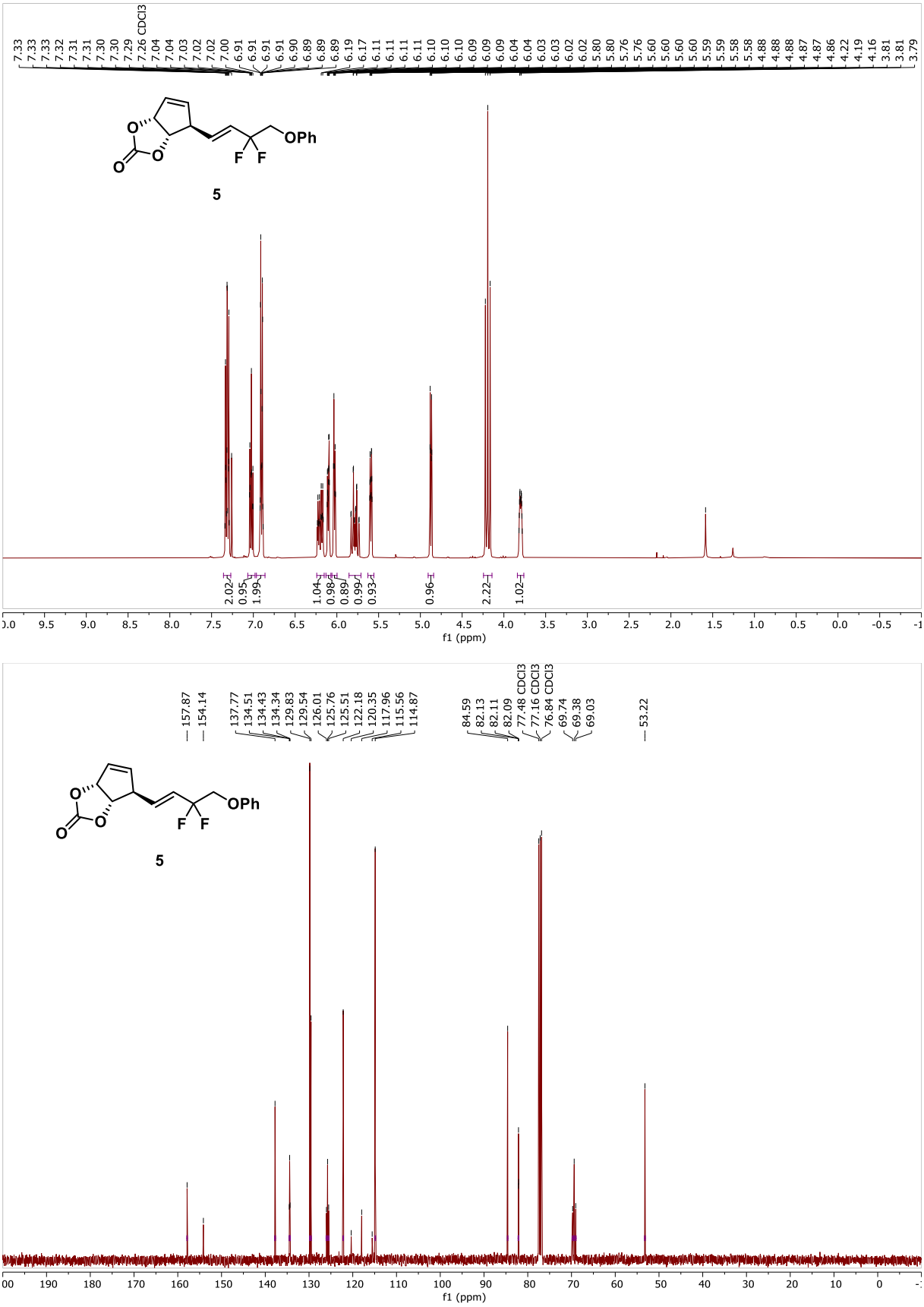

Figure S11: ^{1}H NMR (400 MHz, $CDCl_3$, top) and ^{13}C NMR (101 MHz, $CDCl_3$, bottom) of compound **5**.

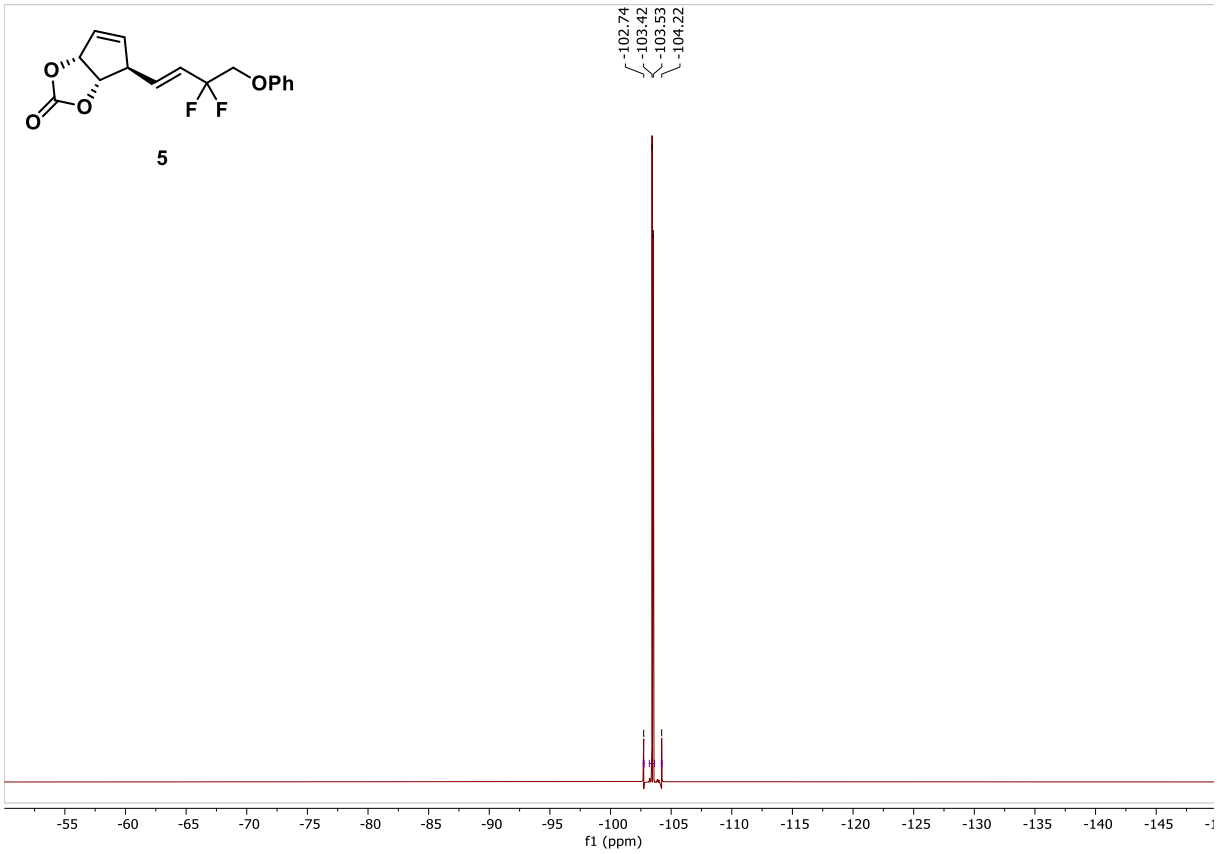

Figure S12: ^{17}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) of compound **5**.

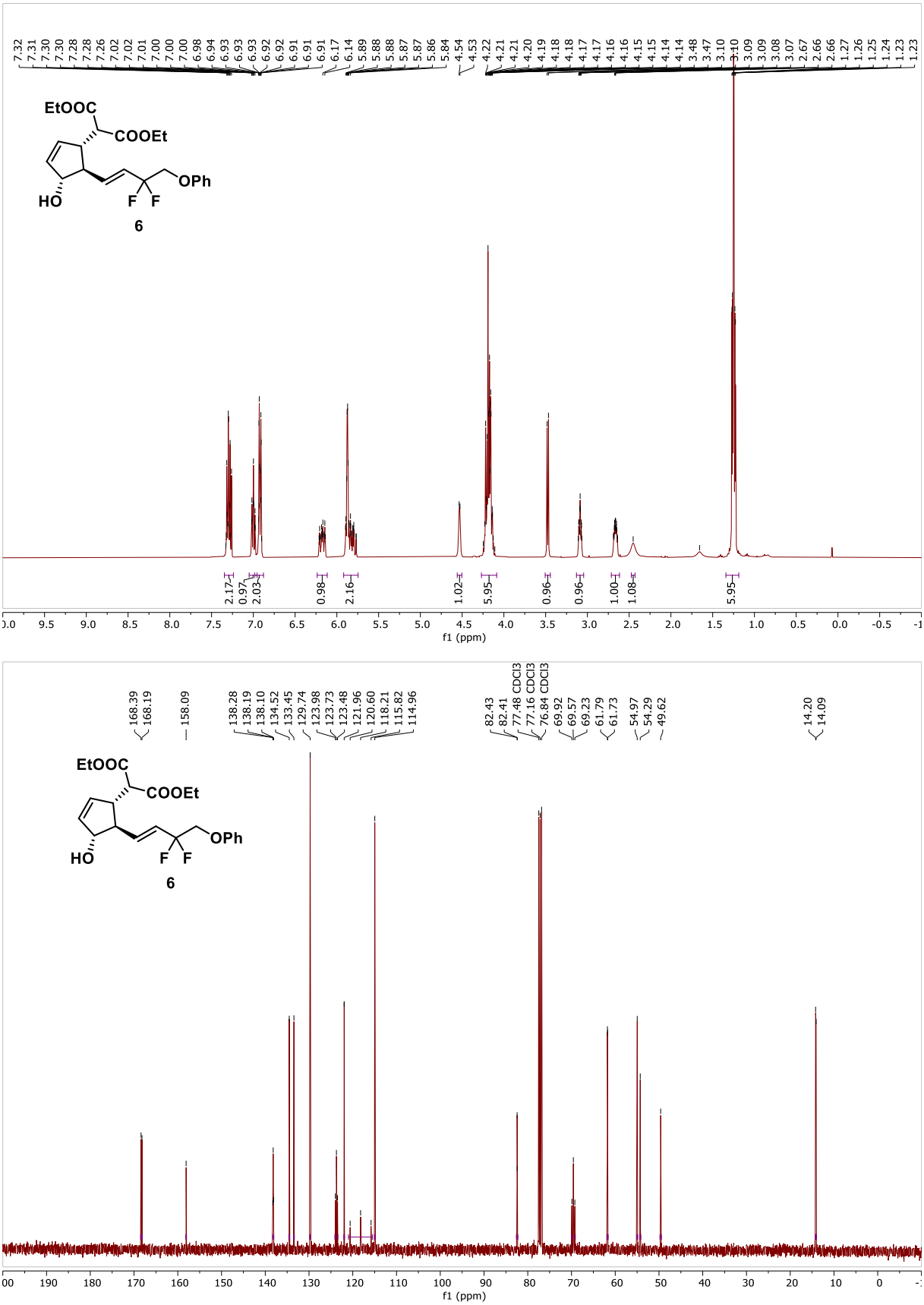

Figure S13: ^{1}H NMR (400 MHz, $CDCl_3$, top) and ^{13}C NMR (101 MHz, $CDCl_3$, bottom) of compound **6**.

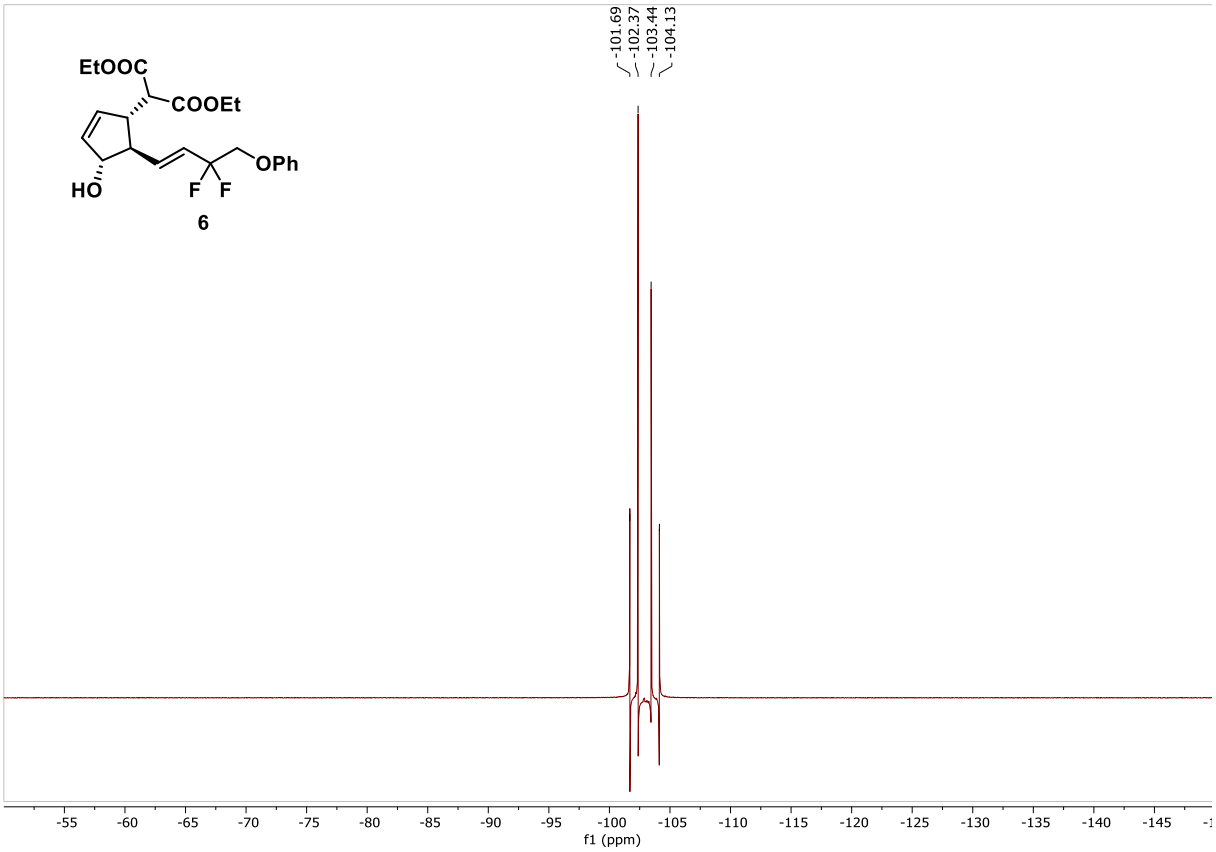

Figure S14: ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) of compound **6**.

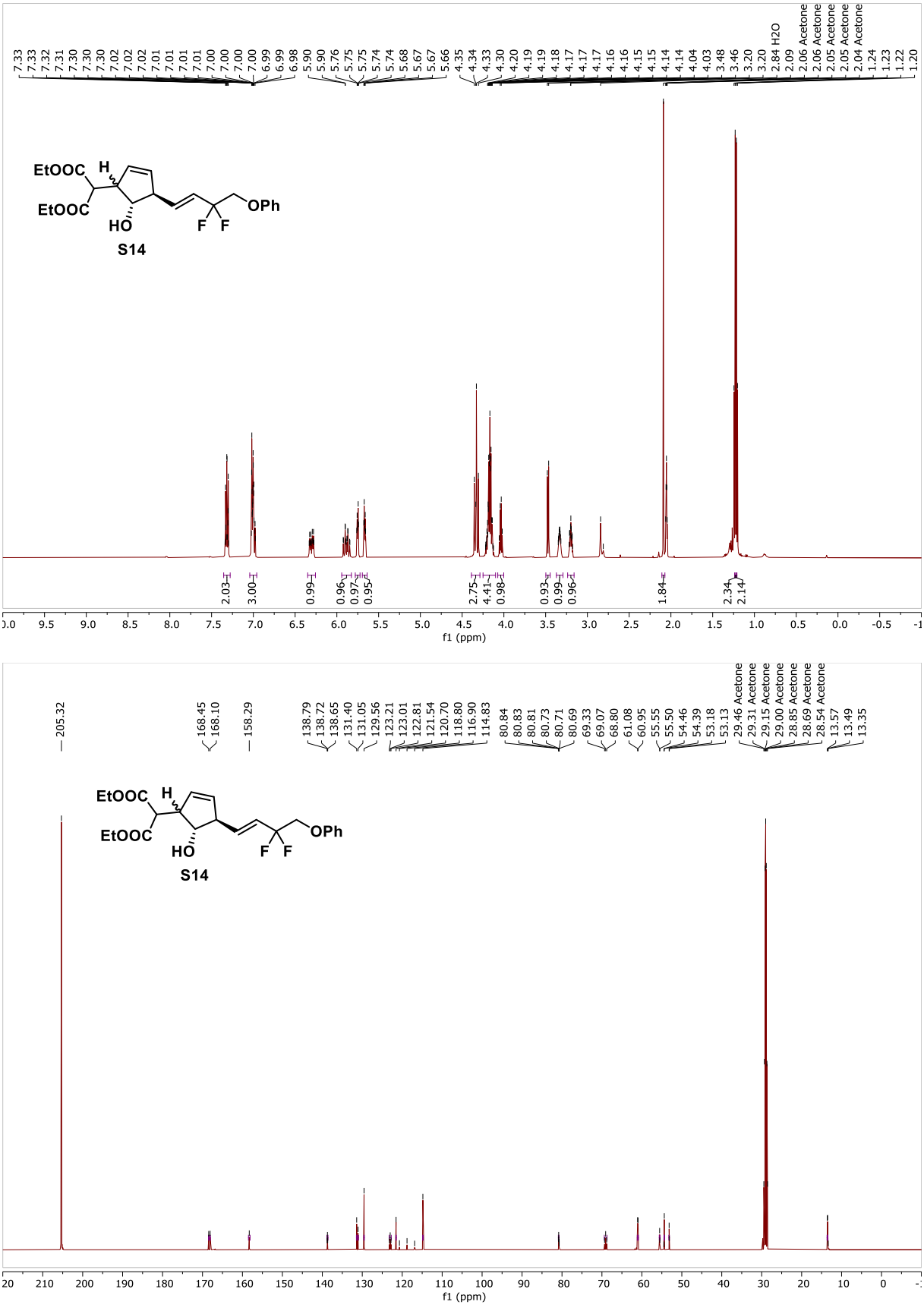

Figure S15: ^{1}H NMR (500 MHz, $(CD_3)_2CO$, top) and ^{13}C NMR (126 MHz, $(CD_3)_2CO$, bottom) of compound **S14**.

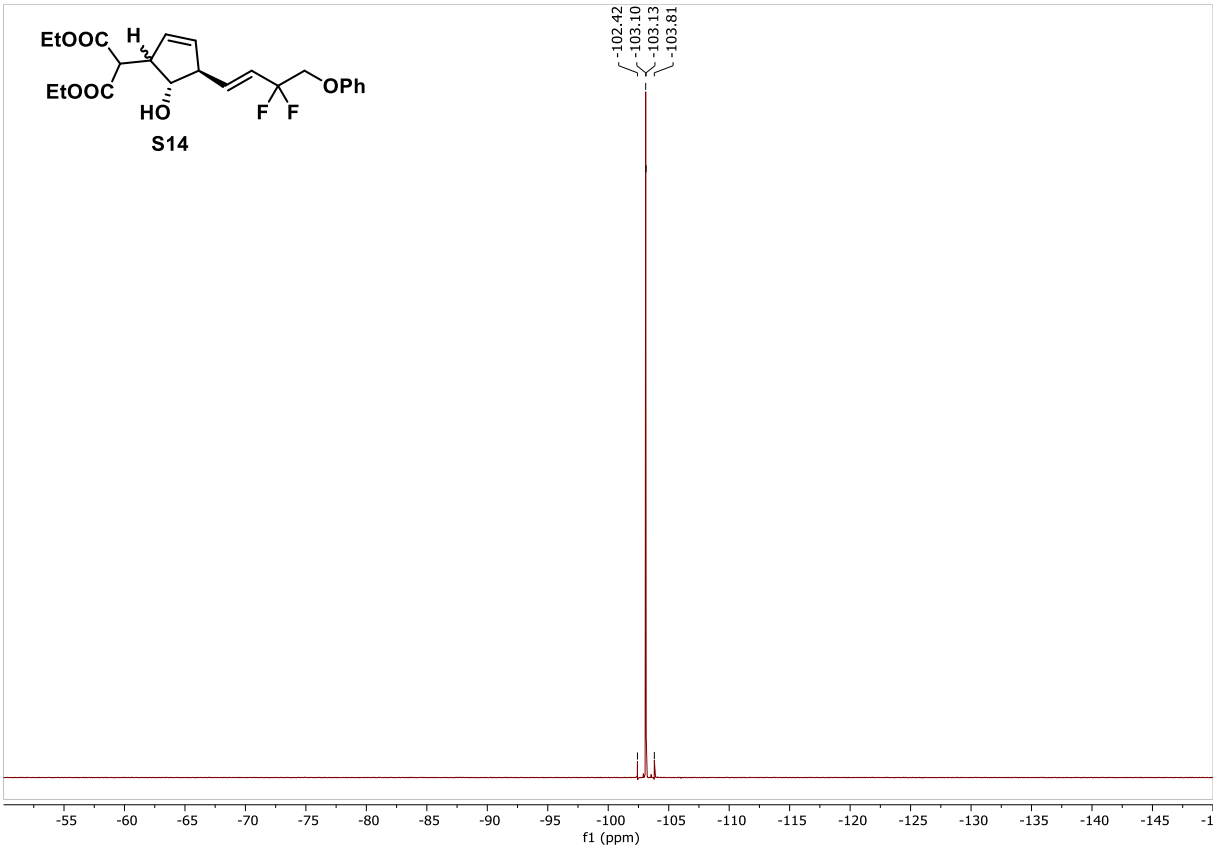

Figure S16: ^{1}H NMR (377 MHz, $(CD_3)_2CO$, ^{1}H decoupled) of compound **S14**.

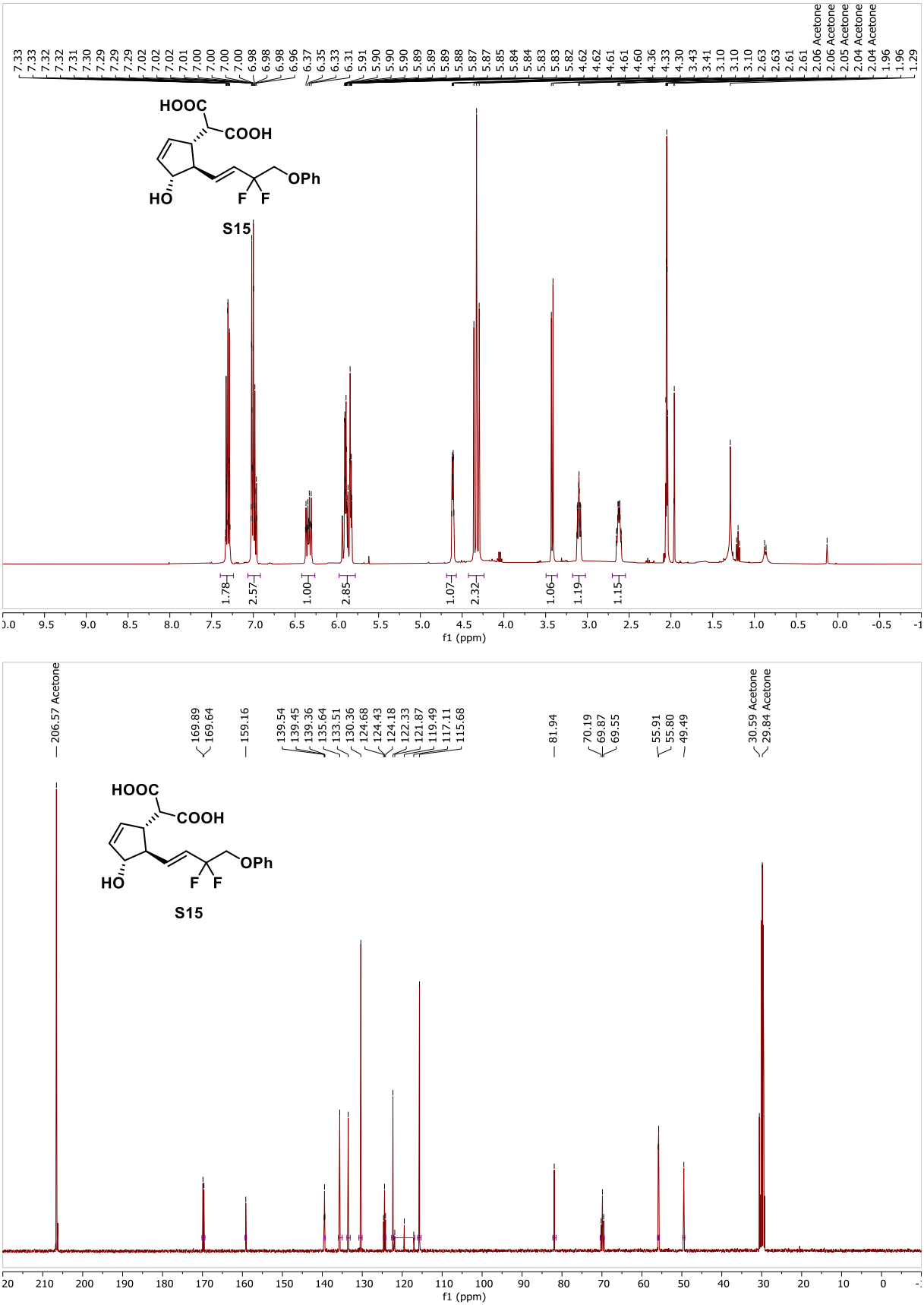

Figure S17: ^{1}H NMR (400 MHz, $(CD_3)_2CO$, top) and ^{13}C NMR (101 MHz, $(CD_3)_2CO$, bottom) of compound **S15**.

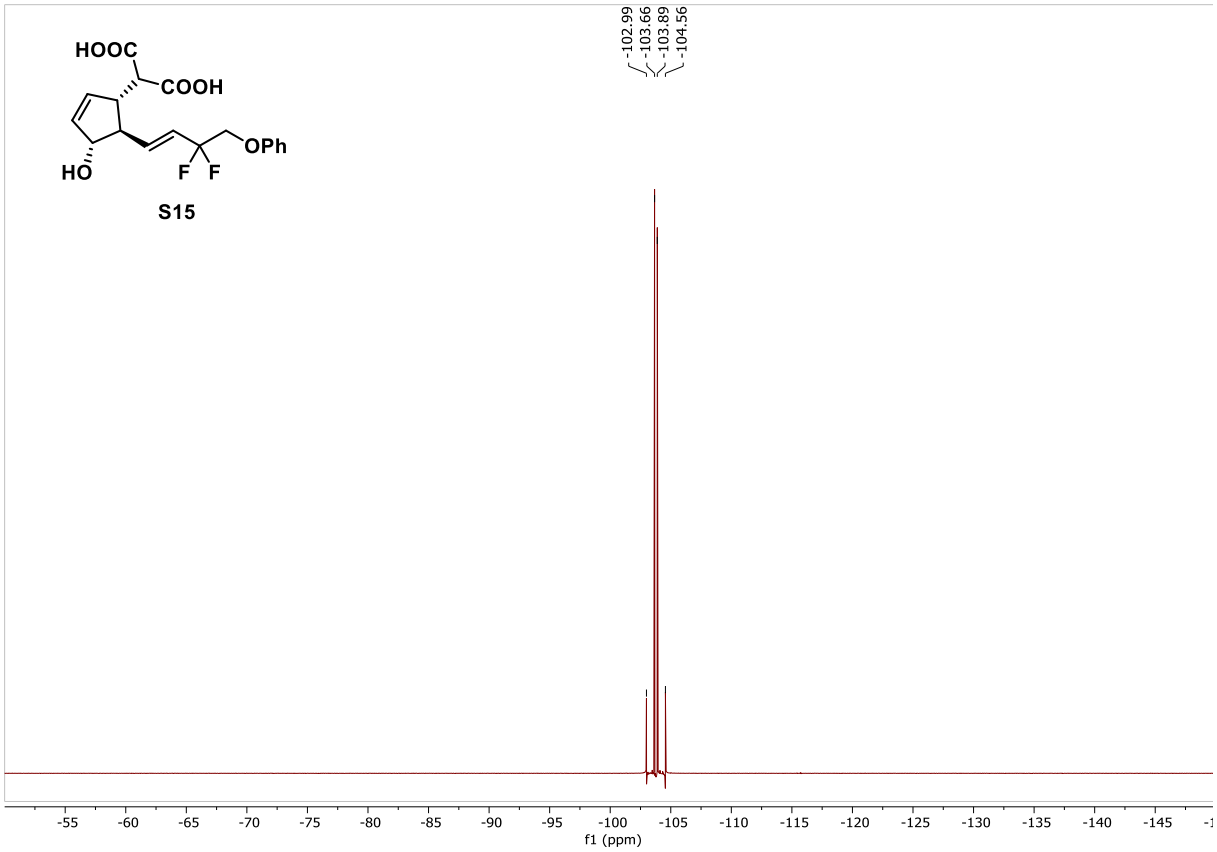

Figure S18: ^{19}F NMR (377 MHz, $(CD_3)_2CO$, ^{1}H decoupled) of compound **S15**.

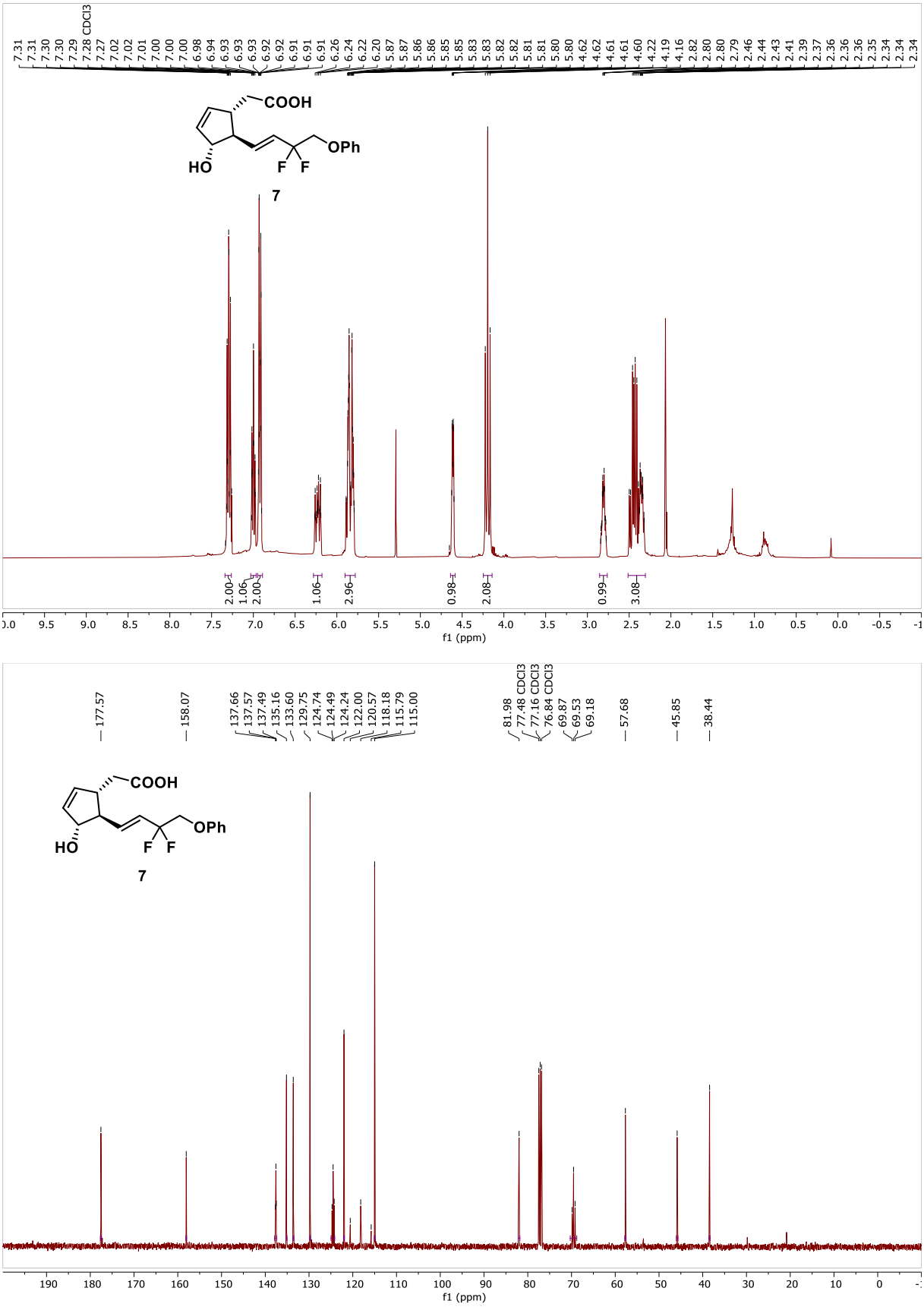

Figure S19: ^{1}H NMR (400 MHz, $CDCl_3$, top) and ^{13}C NMR (101 MHz, $CDCl_3$, bottom) of compound **7**.

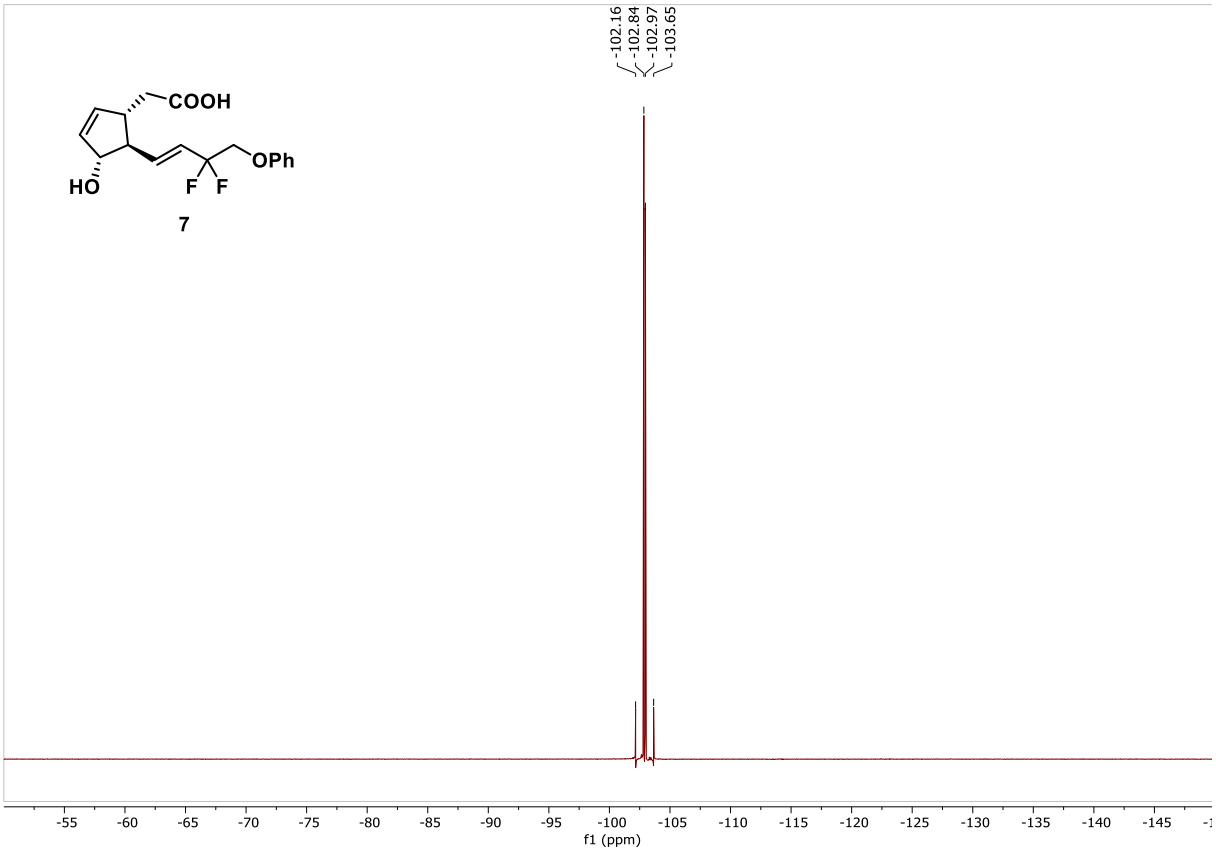

Figure S20: ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) of compound **7**.

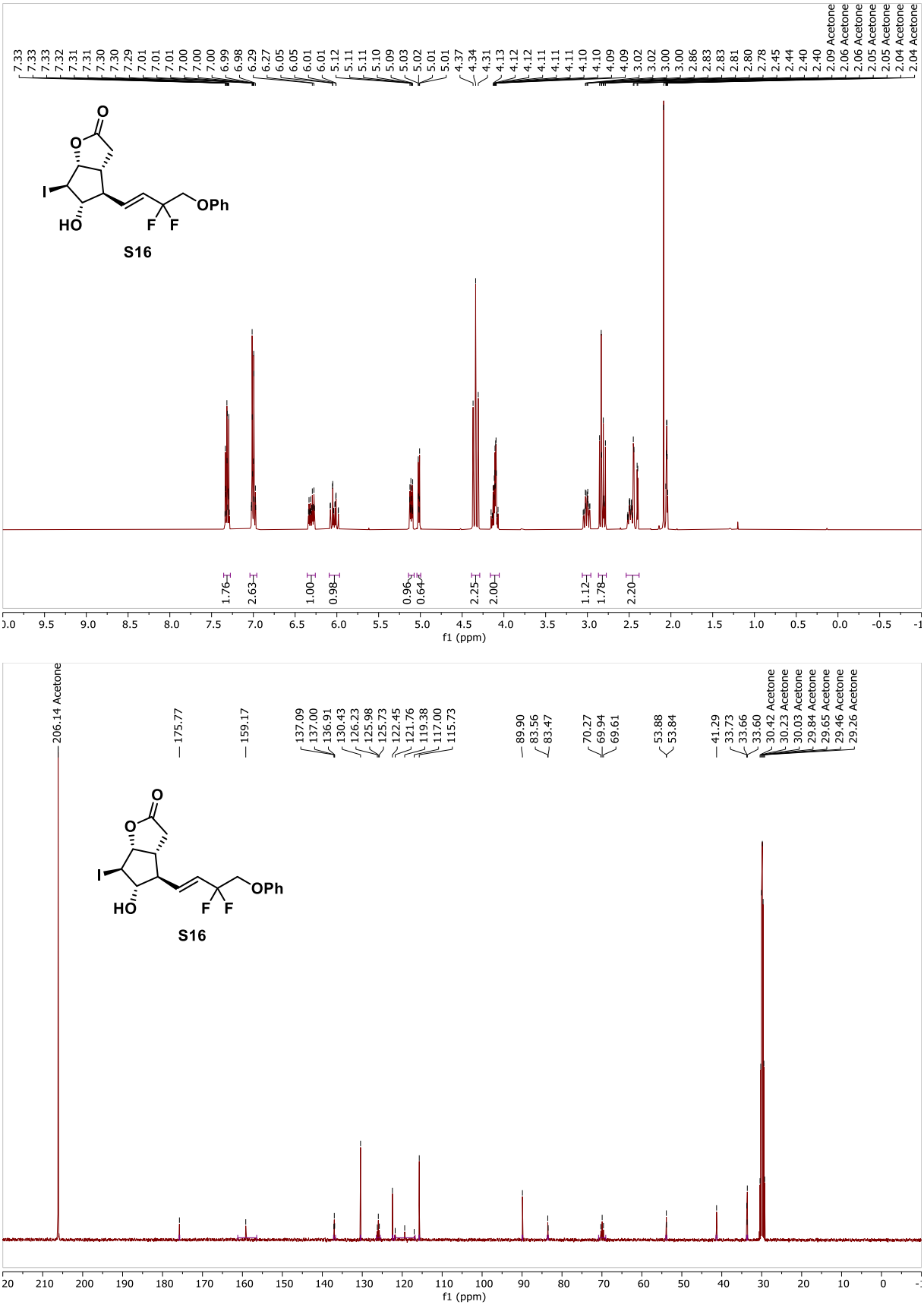

Figure S21: ^{1}H NMR (400 MHz, $(CD_3)_2CO$, top) and ^{13}C NMR (101 MHz, $(CD_3)_2CO$, bottom) of compound **S16**.

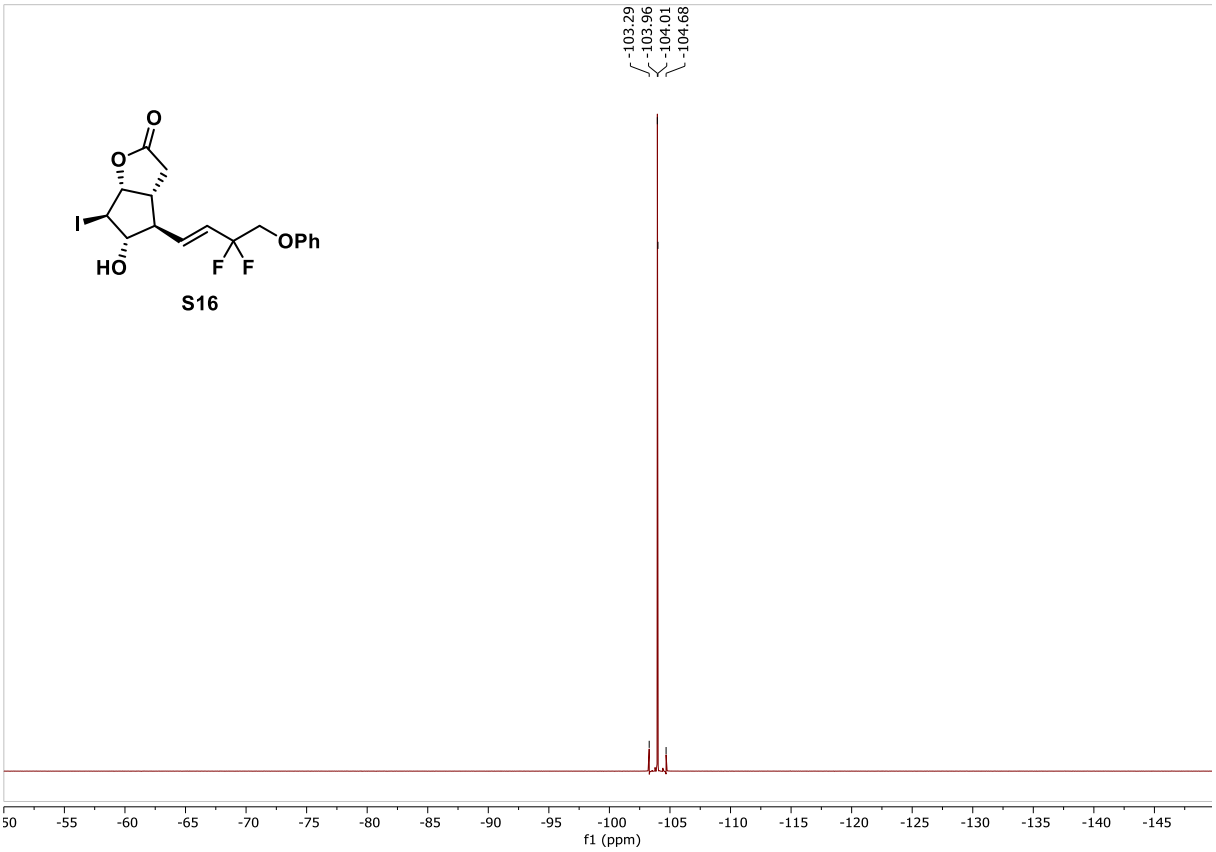

Figure S22: ^{19}F NMR (377 MHz, $(CD_3)_2CO$, ^{1}H decoupled) of compound **S16**.

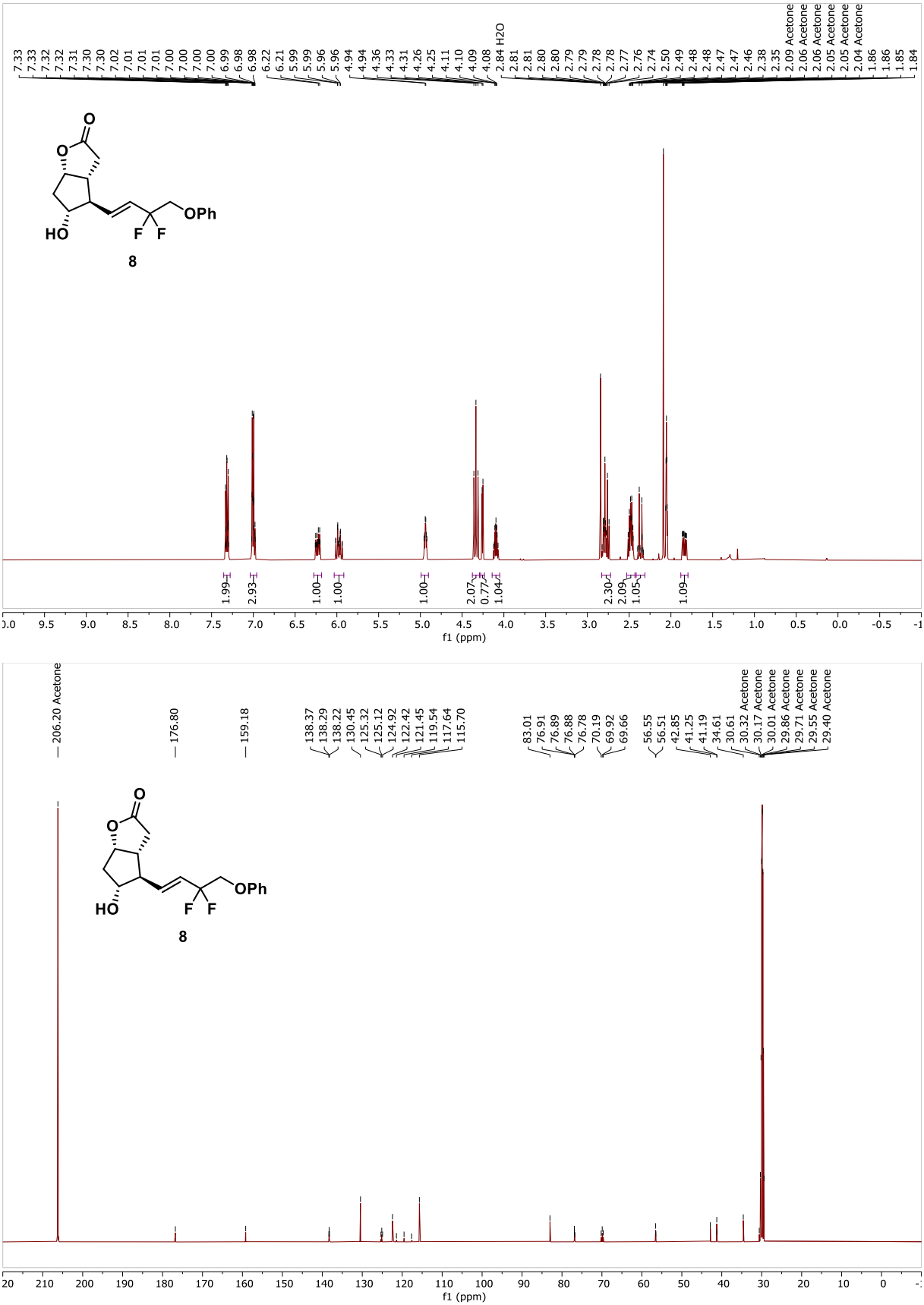

Figure S23: ^{1}H NMR (400 MHz, $(CD_3)_2CO$, top) and ^{13}C NMR (101 MHz, $(CD_3)_2CO$, bottom) of compound **8**.

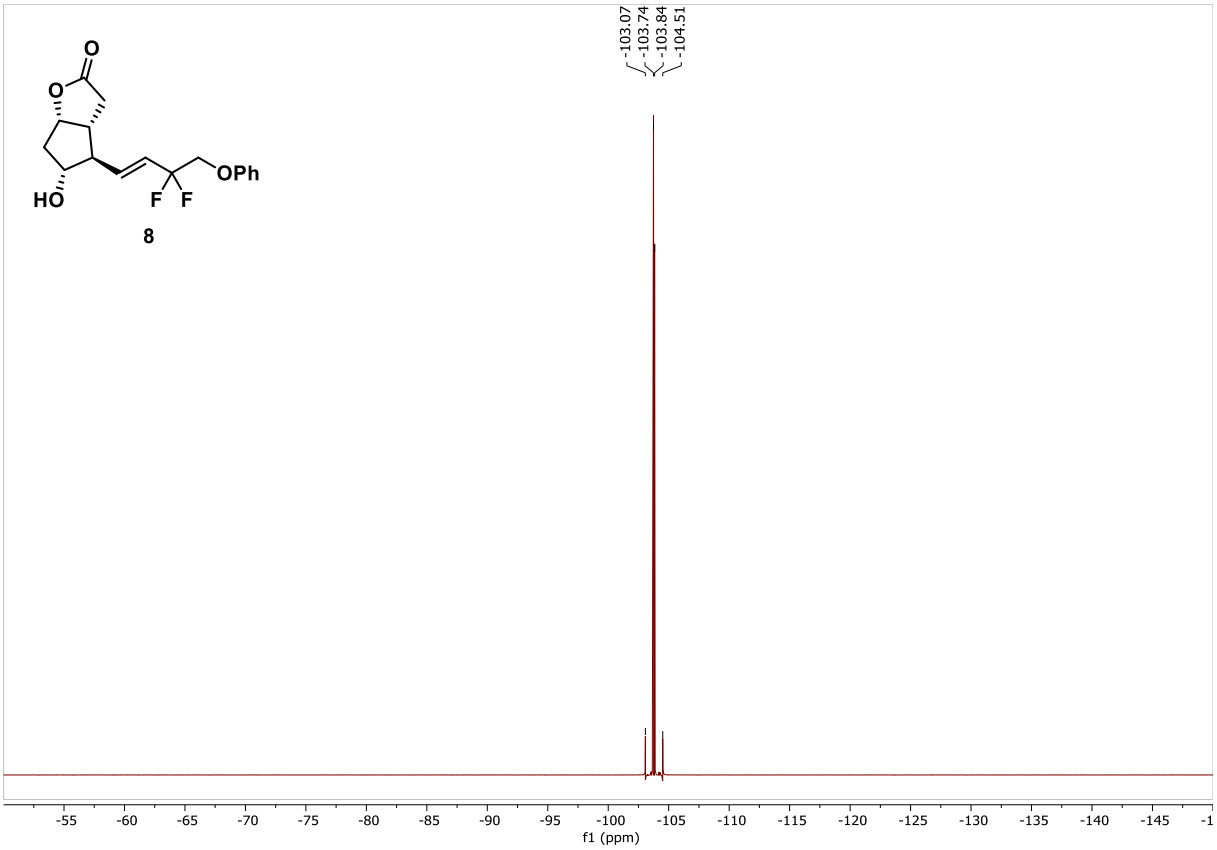

Figure S24: ^{19}F NMR (377 MHz, $(CD_3)_2CO$, ^{1}H decoupled) of compound **8**.

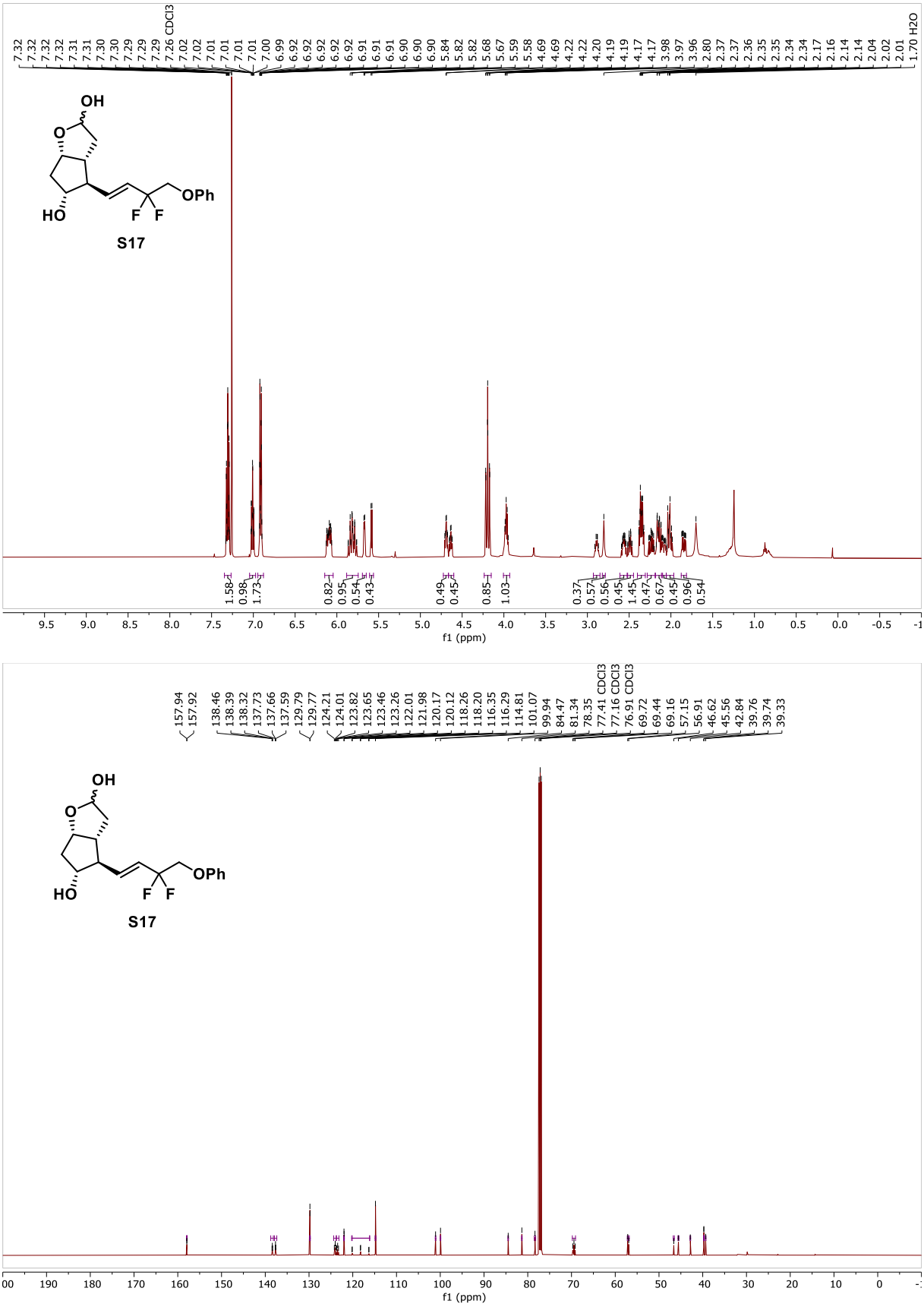

Figure S25: ^{1}H NMR (500 MHz, $CDCl_3$, top) and ^{13}C NMR (126 MHz, $CDCl_3$, bottom) of compound **S17**.

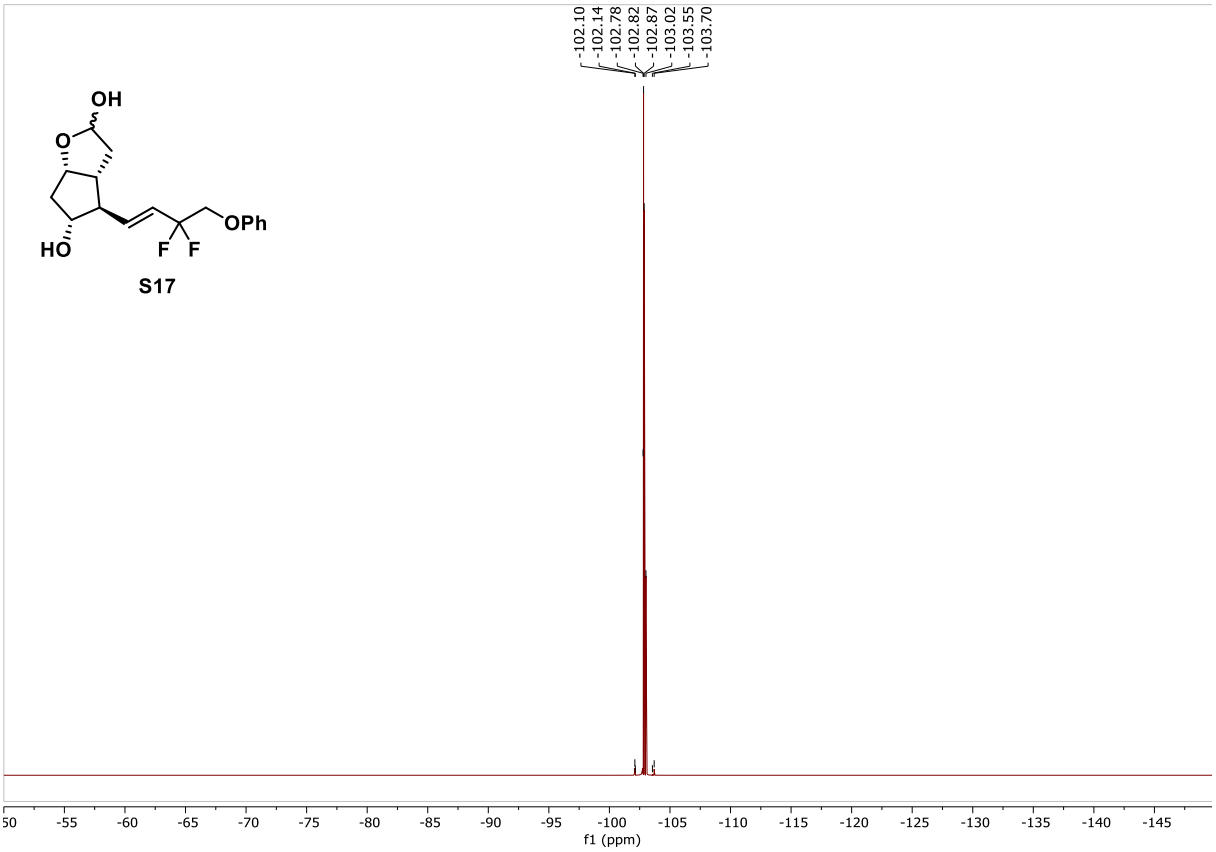

Figure S26: ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) of compound **S17**.

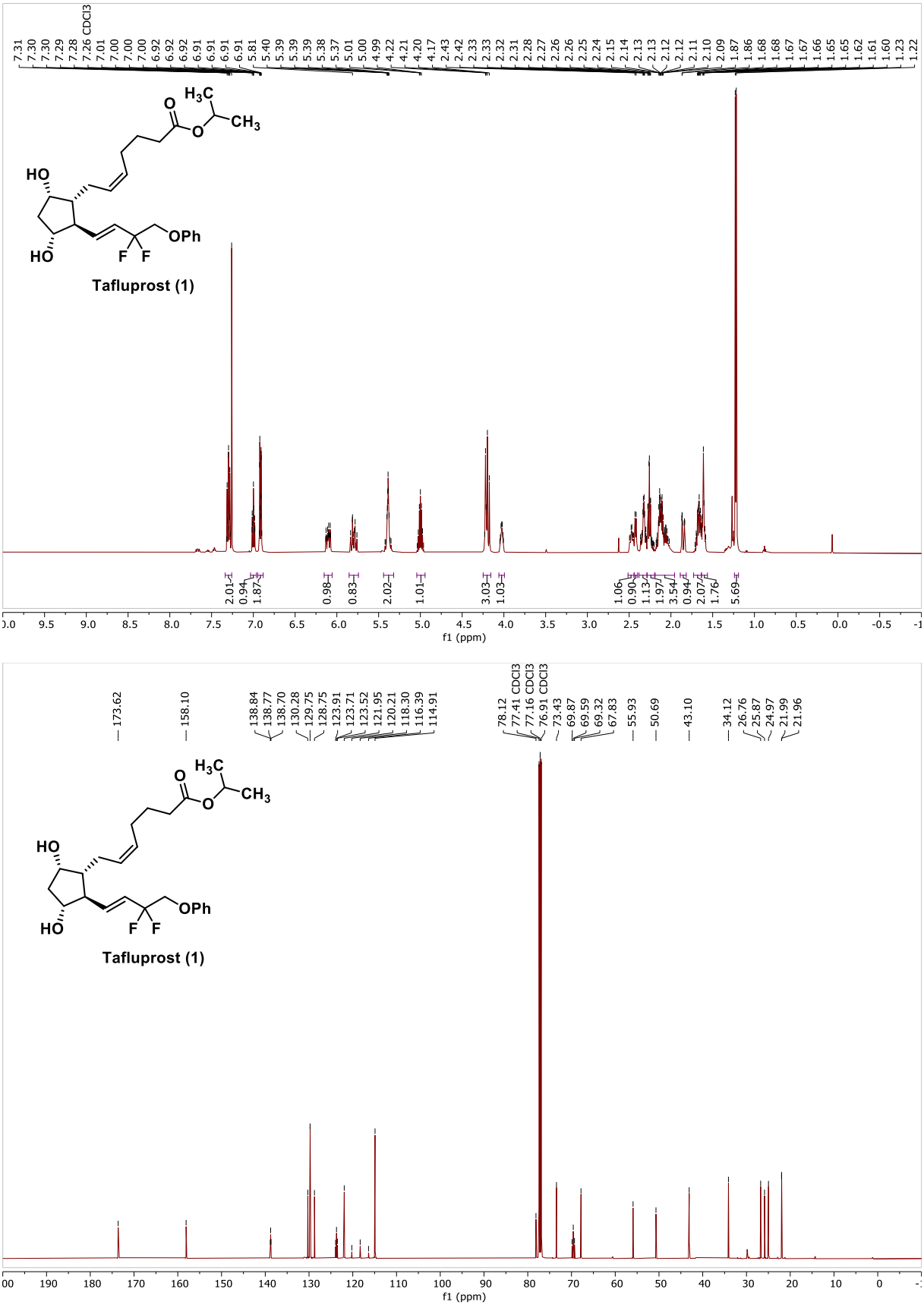

Figure S27: ^{1}H NMR (500 MHz, $CDCl_3$, top) and ^{13}C NMR (126 MHz, $CDCl_3$, bottom) of **Tafluprost (1)**.

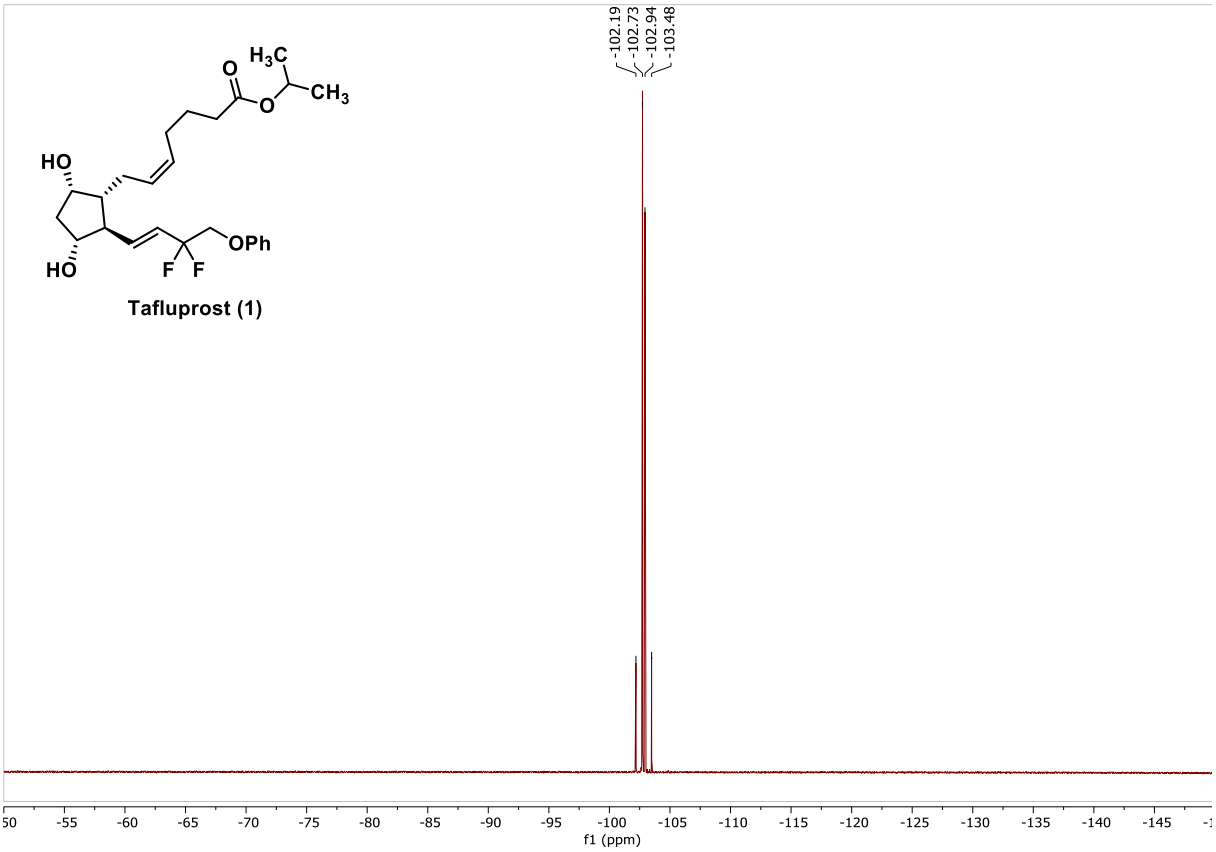

Figure S28: ^{19}F NMR (470 MHz, $CDCl_3$, ^{1}H decoupled) of **Tafluprost (1)**.