Supporting information

A Short Synthesis of (+)-Brefeldin C via Enantioselective Radical Hydroalkynylation

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1. General information

1.1. Techniques

All reactions requiring anhydrous conditions were performed in heat-gun, oven or flame dried glassware under an argon atmosphere. An ice bath was used to obtain a temperature of 0 °C. To obtain a temperature of –78 °C, a bath of acetone was cooled with dry ice. To obtain temperatures of –40 °C and –15 °C, a bath of isopropanol or acetonitrile was cooled to the desired temperature using dry ice. Silica gel 60 Å (40–63 µm) from Silicycle was used for flash column chromatography. Thin layer chromatography (TLC) was performed on Silicycle silica gel 60 F254 plates, visualization under UV light (254 nm) and/or by dipping in a solution of (NH4)2MoO4 (15.0 g), Ce(SO4)2 (0.5 g), H2O (90 mL), conc. H2SO4 (10 mL); or KMnO4 (3 g), K2CO3 (20 g) and NaOH 5% (3 mL) in H2O (300 mL) and subsequent heating. Anhydrous sodium sulfate was used as drying reagent.

1.2. Materials

Commercial reagents were used without further purification unless otherwise stated. Dry solvents for reactions were filtered over columns of dried alumina under a positive pressure of argon. Solvents for extractions (Et_2O, *n*-pentane, CH_2Cl_2, EtOAc) and flash column chromatography were of technical grade and distilled prior to use. Commercial dry DMF was used without further purification.

1.3. Instrumentation

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance IIIHD-300 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C at rt (24-25°C) unless otherwise stated. Some ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance IIIHD-400 or a Bruker Avance II-400 spectrometer (^1H: 400 MHz; ^{13}C: 75 MHz). Chemical shifts (δ) are reported in parts per million (ppm) using the residual solvent or $Si(CH_3)_4$ (δ = 0.00 for ^1H NMR spectra) as an internal standard. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), and br (broad). Coupling constant (*J*) is reported in Hz. In ^{13}C-NMR spectra, the peak positions are reported on one decimal unless the difference in chemical shift between two signals is small and required two decimals.Infrared spectra were recorded on a Jasco FT-IR-460 plus spectrometer equipped with a Specac MKII Golden Gate Single Reflection Diamond ATR system and are reported in wave numbers (cm^{-1}). At maximum, the ten most prominent peaks are reported.

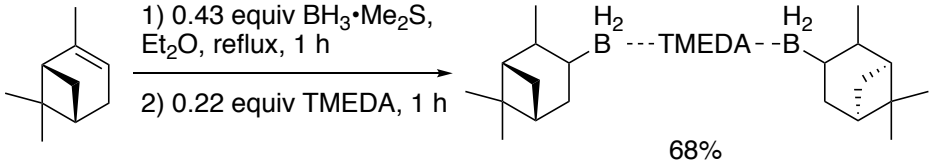
Low resolution mass spectra were recorded on a Waters Micromass Autospec Q mass spectrometer in EI mode at 70 eV or were taken from GC-MS analyses performed on a Finnigan Trace GC-MS (quadrupole mass analyzer using EI mode at 70 eV) fitted with a Macherey-Nagel Optima delta-3-0.25 µm capillary column (20 m, 0.25 mm); gas carrier: He 1.4 mL/min; injector: 220 °C split mode.

HRMS analyses and accurate mass determinations were performed on a Thermo Scientific LTQ Orbitrap XL mass spectrometer using ESI mode (positive ion mode). Melting points were measured on a Büchi B-545 apparatus and are corrected. Syringe filters with polytetrafluoroethylene membrane were used with a pore size of 0.45µm from Machery-Nagel (CHROMAFIL®Xtra PTFE 0.45).

2. Synthesis

2.1. Preparation of reagents

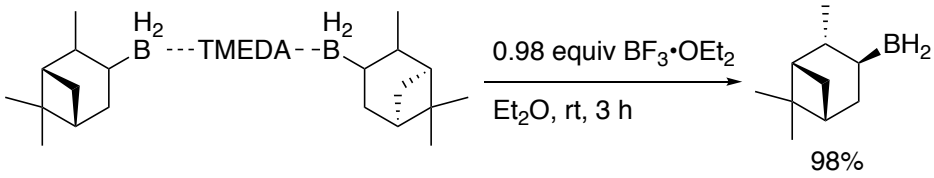
(+)-Isopinocampheylborane-TMEDA complex



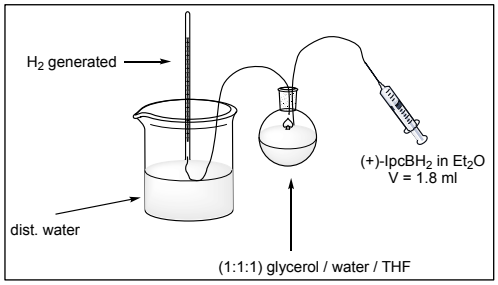
Borane-dimethylsulfide (15.0 mL, 150 mmol) was dissolved in dry Et_2O (85 mL) and (+)-α-pinene (54.8 mL, 345 mmol) was added dropwise in such a rate that the reaction mixture refluxed gently. The mixture was refluxed for 1 h. TMEDA (11.3 mL, 75 mmol) was added to the reaction mixture and the mixture was refluxed for 1 h. Seedlings of TMEDA·2BH_2Ipc were added, so that the product started to crystallize. A thick white suspension was formed which was then stored in the freezer overnight. The suspension was filtered and washed with pentane. The crude product was dried under high vacuum which afforded the title compound (21.2 g, 68%).

Colorless crystals; $[\alpha]_D^{23}$ = +67.6 (c = 9.3, THF) (lit.[1] $[\alpha]_D^{23}$ = +69.03 (c = 9.33, THF)); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.31 – 3.06 (m, 4H), 2.63 (s, 6H), 2.59 (s, 6H), 2.20 (ddt, J = 8.2, 6.1, 3.1 Hz, 2H), 2.12 – 2.04 (m, 2H), 1.85 (td, J = 5.9, 3.4 Hz, 4H), 1.73 (td, J = 5.8, 2.0 Hz, 2H), 1.61 – 1.53 (m, 2H), 1.16 (s, 6H), 1.09 (s, 6H), 1.00 (d, J = 7.0 Hz, 6H), 0.78 (d, J = 8.9 Hz, 2H), 0.66 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 57.4, 51.1, 51.0, 48.8, 43.1, 42.4, 39.1, 38.2, 34.3, 28.6, 25.8, 23.0, 22.8; ^{11}B-NMR (96 MHz, $CDCl_3$): δ 1.2 (s). Physical and spectral data are in accordance with literature data.[1,2]

(+)-Monoisopinocampheylborane



To a suspension of TMEDA·2BH_2Ipc (10.41 g, 25 mmol) in dry Et_2O (34 mL) was dropwise added BF_3·Et_2O (6.2 mL, 49.0 mmol). The mixture was stirred at rt for 3 h. By using a thick needle, the suspension was then transferred to a filter chamber under Argon atmosphere. The solid TMEDA·2BF_3 complex was washed with dry Et_2O until a total volume of 62 mL of the filtrate containing (+)-IpcBH_2 (49 mmol, 98%) was obtained.



Colorless transparent solution; $[\alpha]_D^{23}$ = +52.9 (c=11.6, Et_2O) (lit.[3] $[\alpha]_D^{23}$ = +39.93 (c=11.6, Et_2O)); ^{11}B-NMR (96 MHz, $CDCl_3$): δ 22.6 (s). Physical and spectral data are in accordance with literature data.[3,2] The concentration of the solution was determined by hydrolysis of (+)-IpcBH_2 in a 1:1:1 mixture of water/THF/ethylene glycol (30 mL) and subsequent gas-

volumetric analysis using the setup depicted below:

Note: To generate stable values of H_2, it is recommended to perform a blank injection of Et_2O (1.8 mL) prior to injecting (+)-$IpcBH_2$ solution.

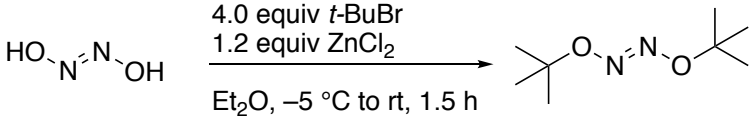
Volume of (+)-$IpcBH_2$ solution in Et_2O, V_{IpcBH_2}:	1.8 mL
V_{H_2}; measurement 1:	75.8 mL
V_{H_2}; measurement 2:	75.8 mL
V_{H_2}; measurement 3:	75.8 mL
Average volume H_2 formed:	75.8 mL
Standard atmospheric pressure, p:	1013 mbar
Ambient pressure, p_a:	955 mbar
Vapor pressure of water at 296 K, p_v:	28 mbar
Temperature, $t_{0°C}$:	273 K
Temperature, $t_{24°C}$:	297 K

$$n(H_2) = \frac{(p_a - p_v) \times t_{0°C} \times (V_{H_2} - V_{IpcBH_2})}{p \times t_{24°C} \times 22.4 \times V_{IpcBH_2}}$$

$$n(H_2) = \frac{(955\ mbar - 28\ mbar) \times 273\ K \times (75.8\ ml - 1.8\ ml)}{1013\ mbar \times 297\ K \times 22.4\ \frac{L}{mol} \times 1.8\ ml} = 1.540\ mol$$

$$n\big((+)IpcBH_2\big) = 0.770\ \frac{mol}{L}$$

Di-*tert*-butylhyponitrite (DTBHN)

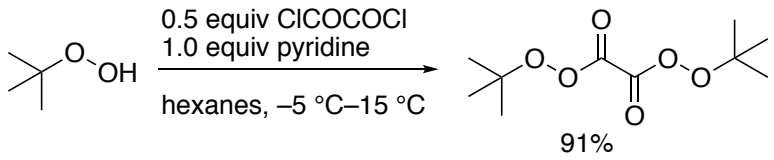


52%

Under high vacuum, sodium *trans*-hyponitrite hydrate was dried for 3 days to a constant weight. The dry sodium *trans*-hyponitrite (5.37 g, 50.7 mmol) was added to *tert*-butyl bromide (45.5 mL, 405 mmol) followed by the addition of dry Et_2O (25 mL). The mixture was cooled to −5 °C. A suspension of $ZnCl_2$ (2 M in Et_2O, 30.4 mL, 60.8 mmol) was cannulated to the reaction mixture at 0 °C. The suspension was allowed to stir at rt for 1.5 h and was then filtered. The filtrate was extracted with water (100 mL) and the aqueous layer was extracted with Et_2O (50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated at rt. Recrystallisation from pentane afforded di-*tert*-butylhyponitrite (4.56 g, 52%).

Colorless crystals; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 81.2, 27.8. Physical and spectral data are in accordance with literature data.[4,5]

Di-*tert*-butyl peroxyoxalate (DTBPO)

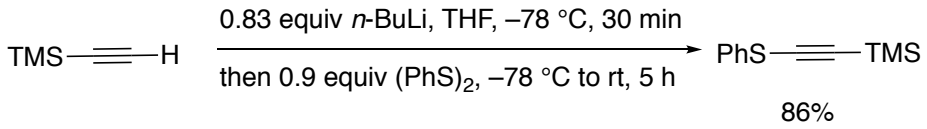


DTBPO is sensitive to heat and shock and therefore a potent explosive. This compound should only be handled with extreme care and appropriate safety precautions (small scale, avoid scratching, use of a blast shield and cut protection gloves).

A solution of freshly opened oxalyl chloride (0.86 mL, 10.0 mmol) in dry hexane (10 mL) was added to a stirred solution of pyridine (1.61 mL, 20.0 mmol) and *tert*-butyl hydroperoxide (3.64 mL, 5.5 mol/L in decane, 20.0 mmol) in dry hexane (20 mL) at −5 °C. The mixture was allowed to warm up to 15 °C, filtered and washed with pentane. The filtrate was cooled to −78 °C and the liquid was removed with a syringe. The solid residue was diluted with pentane (20 mL), cooled to −78 °C, and decantated. This process was repeated twice. The residue was crystallized from pentane at −25 °C overnight. The liquid was removed with a needle and the crystals were dried under high vacuum at 0 °C which afforded di-*tert*-butyl peroxyoxalate (2.14 g, 91%).

Colorless crystals; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 18H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 154.3 (very weak signal), 85.9, 26.1. Physical and spectral data are in accordance with literature data.[6]

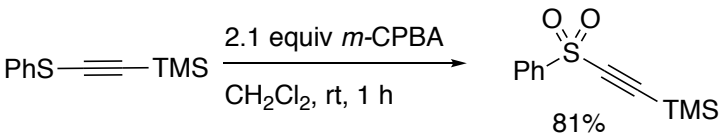
Trimethyl(2-phenylsulfanylethynyl)silane



Ethynyl(trimethyl)silane (12.2 mL, 88.0 mmol) in dry THF (80 mL) was cooled to –78 °C. *n*-BuLi (2.5 M in hexane, 29.0 mL, 72.5 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min. Diphenyldisulfide (17.5 g, 80.2 mmol) in dry THF (40 mL) was added at –78 °C. After being stirred at –78 °C for 30 min, the reaction mixture was allowed to warm up to rt and stirred for 5 h. The reaction mixture was cooled to 0 °C and dist. water (40 mL) and Et_2O (80 mL) were added. The mixture was washed with a solution of NaOH (0.1 M in H_2O, 3x 40 mL) and dist. water (3 x 10 mL). The organic phase was dried over Na_2SO_4 and concentrated. FC (heptanes) afforded trimethyl(2-phenylsulfanylethynyl)silane (14.3 g, 86%).

Yellowish liquid; R_f 0.58 (heptanes); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45 – 7.37 (m, 2H), 7.33 (ddd, J = 7.9, 5.8, 1.9 Hz, 2H), 7.25 – 7.18 (m, 1H), 0.25 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 132.4, 129.3, 126.6, 126.2, 106.4, 90.2, 0.0. Physical and spectral data are in accordance with literature data.[7,8]

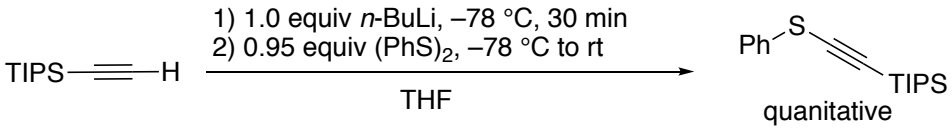
Trimethyl((phenylsulfonyl)ethynyl)silane



To a stirred solution of trimethyl(2-phenylsulfanylethynyl)silane (14.3 mL, 69.3 mmol) in CH_2Cl_2 (80 mL) was added dropwise a solution of *m*-CPBA (77.0%, 32.6 g, 145 mmol) in CH_2Cl_2 (400 mL). After being stirred at rt for 1 h, the reaction mixture was cooled to 0 °C and a sat. $NaHCO_3$ solution (300 mL) was added. The reaction mixture was stirred at rt for 15 min and was extracted with CH_2Cl_2 (50 mL), once more washed with a cold sat. aq. $NaHCO_3$ solution (100 mL), and washed with dist. water (2 x 100 mL). The organic phase was dried over Na_2SO_4 and concentrated. The product was repeatedly precipitated from Et_2O at –25 °C, filtered off and dried under high vacuum affording trimethyl((phenylsulfonyl)ethynyl)silane (13.5 g, 81%).

White solid; R_f 0.70 (heptanes); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 2H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.63 – 7.53 (m, 2H), 0.22 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 141.9, 134.8, 129.9, 128.0, 102.7, 98.6, -0.6. Physical and spectral data are in accordance with literature data.[7]

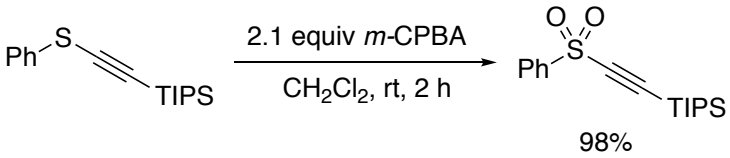
Trimethyl(2-phenylsulfanylethynyl)silane



(Triisopropylsilyl)acetylene (30 mL, 134 mmol) was dissolved in dry THF (100 mL) and the solution was cooled to –78 °C. *n*-BuLi (2.5 M in hexane, 50.6 mL, 126 mmol) was added dropwise and the mixture was stirred for 30 min at this temperature. Diphenyldisulfide (27.6 g, 126 mmol) in dry THF (44 mL) was slowly added at –78 °C. After being stirred at –78 °C for 30 min, the reaction mixture was allowed to warm up to rt and stirred overnight. The reaction mixture was cooled to 0 °C, stirred for further 10 min and subsequently treated with dist. water (60 mL). The reaction mixture was diluted with Et_2O (50 mL). The phases were separated and the aqueous phase was extracted twice with Et_2O (50 mL). The combined organic phase was washed with aq. NaOH (0.1 M, 2 x 100 mL), dist. water (3 x 50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, concentrated and the obtained oil was dried under high vacuum. Trimethyl(2-phenylsulfanylethynyl)silane was obtained after FC (heptanes) (36 g, quantitative).

Yellowish oil; R_f 0.75 (heptanes); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.45 – 7.37 (m, 2H), 7.33 (ddd, *J* = 7.9, 5.8, 1.9 Hz, 2H), 7.25 – 7.18 (m, 1H), 0.25 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 132.4, 129.3, 126.6, 126.2, 106.4, 90.2, 0.0. Physical and spectral data are in accordance with literature data.[9,8,10]

Triisopropyl((phenylsulfonyl)ethynyl)silane



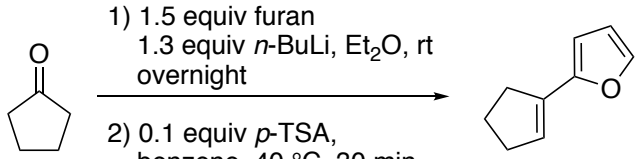
To a stirred solution of the crude trimethyl(2-phenylsulfanylethynyl)silane in dry CH_2Cl_2 was added drop wise a solution of *m*-CPBA (77%, 60 g, 265 mmol) in dry CH_2Cl_2 at rt over 2 h using a dropping funnel. The white suspension was stirred for 2 h until complete consumption of the thioether. The reaction was cooled to 0 °C and transferred into a beaker flask. Sat. $NaHCO_3$ (250 ml) was added and the mixture was

stirred vigorously for 20 min at rt to give a white suspension. The organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were washed with sat. $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated. FC (Et_2O/pentane 1:9) afforded triisopropyl((phenylsulfonyl)ethynyl)silane (39.8 g, 98%).

Colorless, viscous oil; R_f 0.63 (Et_2O/pentane 1:9); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.06 – 7.95 (m, 2H), 7.67 (d, J = 7.4 Hz, 1H), 7.63 – 7.53 (m, 2H), 0.22 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 141.9, 134.8, 129.9, 128.0, 102.7, 98.6, -0.6. Physical and spectral data are in accordance with literature data.[10]

2.2. Enantioselective hydroboration

2-(Cyclopent-1-en-1-yl)furan (1)

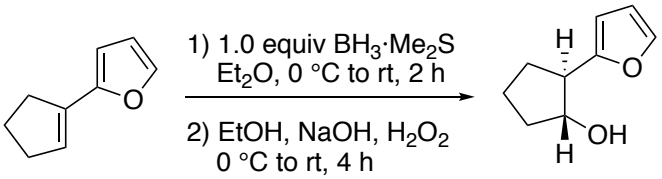


1 67%

To a solution of freshly distilled furan (25.0 mL, 344 mmol) in dry Et_2O (250 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 120 mL, 300 mmol) at 0 °C. After being stirred at 0 °C for 1 h, a white suspension was observed to which freshly distilled cyclopentanone (20.0 mL, 225 mmol) in dry Et_2O (100 mL) was added at 0 °C. The mixture was stirred at this temperature for 1 h, then allowed to warm to rt and stirred overnight. The mixture was treated with dist. water (30 mL) and was then filtered over Celite®, dried over Na_2SO_4, and concentrated. The crude 1-(furan-2-yl)cyclopentane-1-ol[11] was dissolved in dry benzene (400 mL) and *p*-toluenesulfonic acid (4.3 g, 22.5 mmol) was added at rt. The mixture was stirred at 40 °C for 30 min. The mixture was diluted with water (100 mL) and the organic layer was separated. The benzene layer was concentrated and the residue was re-dissolved in EtOAc. The above aqueous layer was extracted with EtOAc (3 x 100ml). All combined organic layers were washed twice with sat. aq. $NaHCO_3$, dried over Na_2SO_4 and concentrated in vacuo. The residue was filtered through a pad of silica which was then thoroughly washed with pentane. The filtrate was concentrated in vacuo. Distillation (50 °C, 2 mbar) afforded **1** (20.3 g, 67%).

Colorless liquid; R_f 0.61 (pentane); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J = 1.5 Hz, 1H), 6.37 (dd, J = 3.3, 1.8 Hz, 1H), 6.17 (d, J = 3.3 Hz, 1H), 6.11 – 6.07 (m, 1H), 2.67 – 2.48 (m, 4H), 2.05 – 1.94 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 152.7, 141.6, 133.0, 125.0, 111.1, 106.0, 33.3, 32.6, 23.4. Physical and spectral data are in accordance with literature data.[2]

(±)-*trans*-2-(2-Furanyl)cyclopentanol

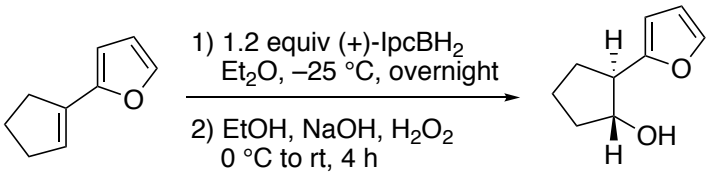


63%

To a solution of 2-(cyclopent-1-en-1-yl)furan (134 mg, 1.0 mmol) in dry Et_2O (2 mL) was added dropwise BH_3·DMS (0.10 mL, 1.0 mmol) at 0 °C. The reaction was allowed to warm to rt and stirred for 2 h. The reaction mixture was cooled to 0 °C and treated with EtOH (2 mL), a solution of aq. NaOH (3 M, 2 mL), and a solution of H_2O_2 (30% in H_2O, 2 mL). The reaction mixture was allowed to stir at rt for 4 h. The mixture was diluted with dist. water (20 mL) and extracted with Et_2O (20 and 10 mL). The organic layers were washed with dist. water (2 x 10 mL), dried over Na_2SO_4, and concentrated. FC (pentane/Et_2O 6:4) afforded *trans*-2-(2-furanyl)cyclopentanol (96 mg, 63%).

Colorless liquid; R_f 0.30 (pentane/Et_2O 6:4); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.33 (d, J = 1.2 Hz, 1H), 6.29 (dd, J = 3.1, 1.9 Hz, 1H), 6.05 (d, J = 3.2 Hz, 1H), 4.24 (q, J = 6.5 Hz, 1H), 2.99 (q, J = 7.9 Hz, 1H), 2.22 – 1.97 (m, 3H), 1.92 – 1.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 141.3, 110.1, 104.5, 78.1, 47.5, 33.8, 28.8, 21.7. Physical and spectral data are in accordance with literature data.[2]

(1*R*,2*R*)-2-(Furan-2-yl)cyclopentan-1-ol

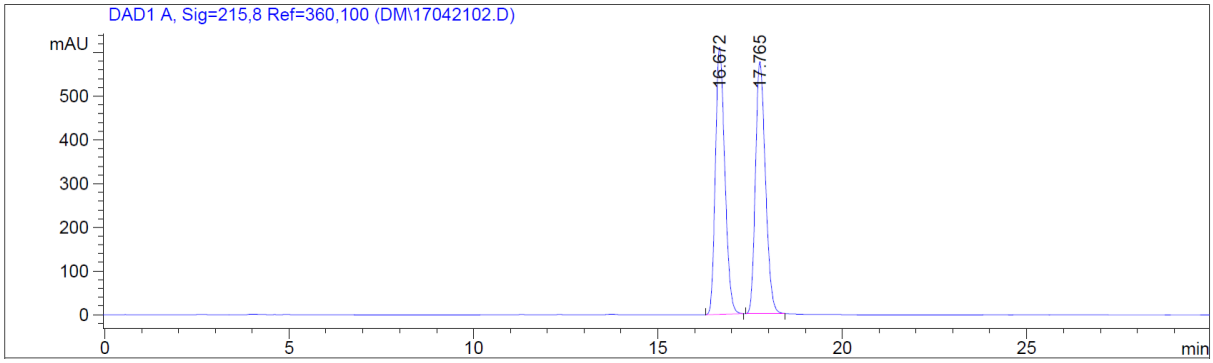


92%

To a solution of (+)-$IpcBH_2$ (0.77 M Et_2O, 1.2 mmol) was added the 2-(cyclopent-1-en-1-yl)furan (134 mg, 1.0 mmol) at −78 °C. The mixture was stored in the freezer at −25 °C overnight. The reaction was treated with EtOH (2 mL) at −25 °C and allowed to warm up to 0 °C. Then, aq. NaOH (3 M, 2 mL) and H_2O_2 (30% in H_2O, 2 mL) were added. The mixture was stirred at rt for 4 h, diluted with water (20 mL), and extracted with Et_2O (20/10 mL). The organic layers were washed with water (2 x 10 mL), dried over Na_2SO_4, and concentrated. FC (CH_2Cl_2/Et_2O 92:8) afforded the title compound (140 mg, 92%).

Colorless liquid; R_f 0.55 (CH_2Cl_2/Et_2O 92:8); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.40–7.28 (m, 1H), 6.29 (dd, J = 3.2, 1.9 Hz, 1H), 6.05 (d, J = 3.2 Hz, 1H), 4.24 (q, J = 6.5 Hz, 1H), 2.99 (dd, J = 14.9, 7.9 Hz, 1H), 2.21–1.97 (m, 2H), 2.04 (s, 1H), 1.90–1.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 141,3, 110.1, 104.5, 78.1, 47.5, 33.8, 28.8, 21.7 Er 94:6. Physical and spectral data are in accordance with literature data.[2,12]

HPLC trace of (±)-*trans*-2-(2-furyl)cyclopentanol (CHIRALPAK IC-3; hexane/iPrOH 98:2; 1 mL min^{-1}, λ = 210 nm)

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Signal 1: DAD1 A, Sig=215,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]    [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  16.672 BB    0.2775 1.08664e4   611.00970  50.0635
   2  17.765 BB    0.2932 1.08388e4   576.80896  49.9365
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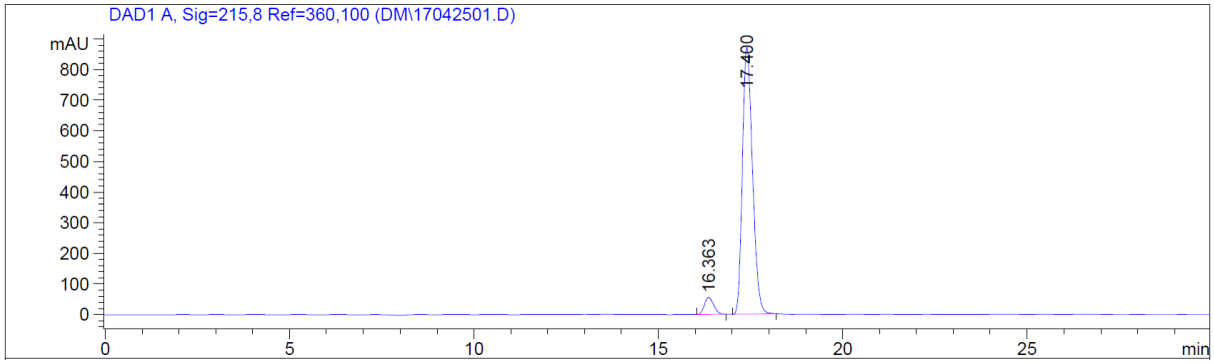
HPLC trace of (1*R*,2*R*)-2-(furan-2-yl)cyclopentan-1-ol (CHIRALPAK IC-3; hexane/iPrOH 98:2; 1 mL min^{-1}, λ = 210 nm)



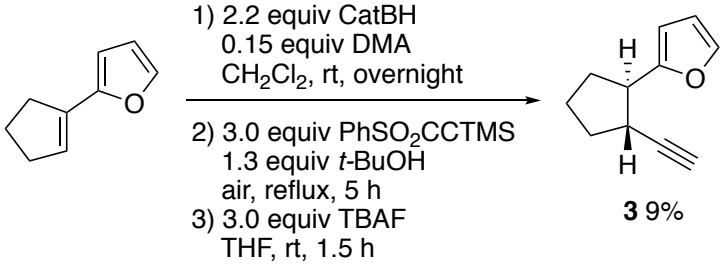

```
Signal 1: DAD1 A, Sig=215,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]    [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  16.363 BB    0.2705  966.49951   55.69291   5.5057
   2  17.400 BB    0.2963 1.65881e4   870.70294  94.4943

Totals :                  1.75546e4   926.39585
```

2.3. Enantioselective hydroalkynylation

(±)-*trans*-2-(2-Ethynylcyclopentyl)furan (3)[13]



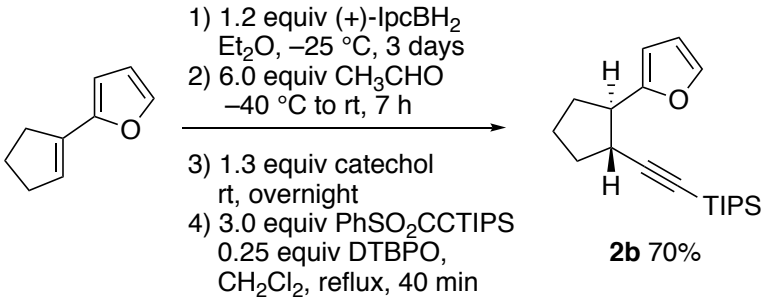
3 9%

To a solution of 2-(cyclopenten-1-yl)furan (134 mg, 1.00 mmol) and dry N,N-dimethylacetamide (DMA) (14 µL, 0.15 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise catecholborane (235 µL, 2.2 mmol) at 0 °C.

The reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was treated with *t*BuOH (0.124 mL, 1.3 mmol) at 0 °C and stirred at rt for 15 min. Then, 2-(benzenesulfonyl)ethynyl-trimethylsilane (713 mg, 3.0 mmol) was added portionwise. The solution was heated to reflux and DTBHN (8 mg, 0.46 mmol) was added every hour. After being stirred for a total of 3 h (three additions of initiator) t pentane (20 mL) was added and the mixture was washed with water (3 x 10 mL). The organic phases were dried over Na_2SO_4 and concentrated. FC (pentane) afforded the unstable TMS-protected alkyne (*unstable*; 30 mg, 13%) which was rapidly dissolved in dry THF (2 mL) and treated with TBAF (1M in THF, 0.4 mL, 1.38 mmol). After stirring for 1.5 h, the reaction mixture was diluted with pentane (30 mL) and washed with water (3 x 20 mL). The solution was dried by passing through a pad of Na_2SO_4 and concentrated. FC (pentane) afforded (±)-**3** (15 mg, 9%) as a single diastereomer.

Colorless liquid; R_f 0.52 (pentane); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.33 (dd, J = 1.7, 0.7 Hz, 1H), 6.29 (dd, J = 3.1, 1.9 Hz, 1H), 6.11 (d, J = 3.2 Hz, 1H), 3.15 (d, J = 8.2 Hz, 1H), 2.78 (s, 1H), 2.20 – 2.05 (m, 3H), 1.79 (tt, J = 6.0, 3.4 Hz, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 156.9, 141.2, 110.0, 104.6, 87.2, 68.8, 46.1, 36.0, 33.4, 31.2, 24.0; IR (cm^{-1}): 3312, 2942, 2865, 1463, 1260, 1010, 883, 798, 728, 676. Physical and spectral data are in accordance with literature data.[13]

(((1*R*,2*R*)-2-(Furan-2-yl)cyclopentyl)ethynyl)triisopropylsilane (2b)



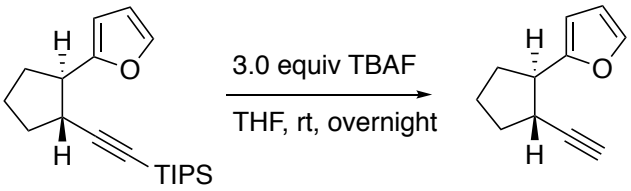
To a stirred solution of (+)-$IpcBH_2$ (0.77 M in Et_2O, 6.0 mmol) at –78 °C was added 2-(cyclopenten-1-yl)furan (671mg, 5.0 mmol). After 30 min, the mixture was stored in the freezer at –25°C for 3 nights. The mixture was cooled to –40 °C and acetaldehyde (1.7 mL, 30.0 mmol) was added dropwise. The cooling bath was exchanged with an ice bath after 20 min and the reaction mixture was stirred at this temperature for 30 min and then allowed to warm up to rt. After stirring at rt for 8 h, the reaction mixture was cooled to 0 °C before catechol (720 mg, 6.5 mmol) was added and the solution was stirred at rt overnight. The volatiles were carefully removed under vacuum and to the residues were quickly added dry CH_2Cl_2 (19 mL), triisopropyl((phenylsulfonyl)ethynyl)silane (4.8 g, 15.0 mmol) and a solution of DTBPO (290 mg, 1.25 mmo) in dry CH_2Cl_2 (3 mL). The reaction mixture was immediately put in a preheated oil bath at 60 °C for 40 min. After cooling, the reaction mixture was diluted with pentane (20 mL) and dist. water (20 mL). The mixture was extracted with pentane (3 x 20 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. FC (pentane) afforded **2b** (1.11 g, 70%) as a single *trans* diastereomer.

Note: Enantioselective hydroboration can be performed equally well in one night. The radical reaction however appears to be scale-dependent. 10 mmol scale: 38%; 5 mmol: 70%; 0.7 mmol: 85%

Colorless liquid; R_f 0.74 (heptanes/EtOAc 5:5); $[\alpha]_D^{23}$ = –127.5 (c = 1, $CHCl_3$); ^{1}H-NMR (300 MHz,

$CDCl_3$): δ 7.30 (dd, J = 1.8, 0.8 Hz, 1H), 6.27 (dd, J = 3.1, 1.9 Hz, 1H), 6.08 (d, J = 3.2 Hz, 1H), 3.13 (s, 1H), 2.80 (s, 1H), 2.16 – 2.05 (m, 2H), 1.80 (dd, J = 3.9, 2.3 Hz, 4H), 1.03 (s, 21H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 157.2, 141.0, 111.8, 109.9, 104.6, 80.5, 46.7, 37.5, 33.6, 30.9, 23.9, 18.6, 18.5, 11.3; IR (cm^{-1}): 2941, 2891, 2864, 2166, 1506, 1463, 1383, 1236, 1150, 1071, 1010, 918, 882, 796, 727, 673; HRMS calc. for $C_{20}H_{33}O_3Si$ $[M+H]^+$: 317.2301, found: 317.2300; Er determined after conversion to **3** (see below)

2-((1*R*,2*R*)-2-Ethynylcyclopentyl)furan (3)

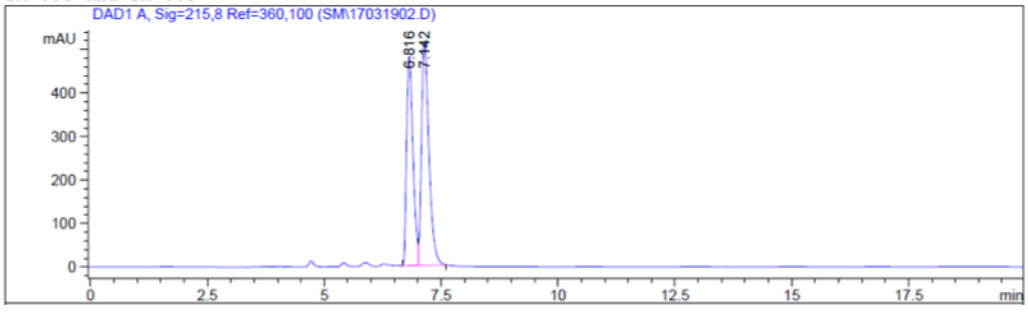


2b **3** quant.

To a solution of (1*R*,2*R*)-**2b** (316 mg, 1.0 mmol) in dry THF (2.5 mL) was added TBAF (1M in THF, 3 mL) and the mixture was stirred at rt overnight. Water (10 mL) was added and the mixture was extracted with pentane (3 x 10 mL). The organic phase was washed with dist. water (3 x 30 mL), dried over Na_2SO_4, and concentrated. FC (pentane) afforded (1*R*,2*R*)-**3** (160 mg, quantitative).

Colorless liquid; R_f 0.28 (heptanes); er 95:5; $[\alpha]_D^{23}$ = –11.3 (c = 1, THF); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.33 (dd, J = 1.7, 0.7 Hz, 1H), 6.29 (dd, J = 3.1, 1.9 Hz, 1H), 6.11 (d, J = 3.2 Hz, 1H), 3.15 (d, J = 8.2 Hz, 1H), 2.78 (s, 1H), 2.20 – 2.05 (m, 3H), 1.79 (tt, J = 6.0, 3.4 Hz, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 156.9, 141.2, 110.0, 104.6, 87.2, 68.8, 46.1, 36.0, 33.4, 31.2, 24.0.

HPLC trace of *trans*-(±)-3 (CHIRALPAK IC-3; hexane; 1 mL min^{-1}, λ = 210 nm).

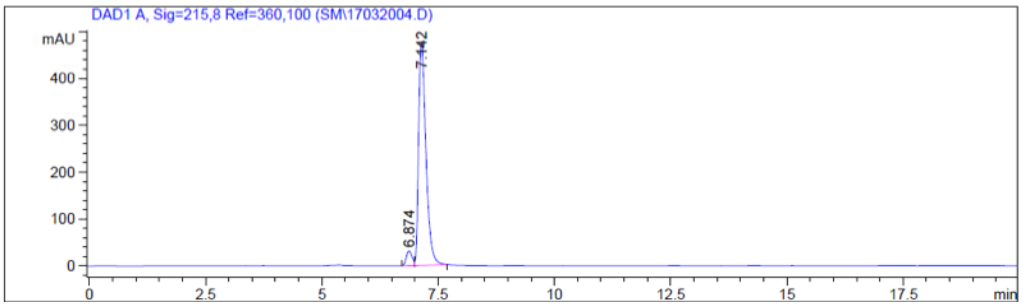



```
Signal 1: DAD1 A, Sig=215,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.816 BV    0.1467 4582.18115  482.85602  44.5268
   2   7.142 VB    0.1693 5708.65186  515.14417  55.4732

Totals :                 1.02908e4   998.00018
```

HPLC trace of enantiomerically enriched (1*R*,2*R*)-**3** (CHIRALPAK IC-3; hexane; 1 mL min^{-1}, λ = 210 nm)

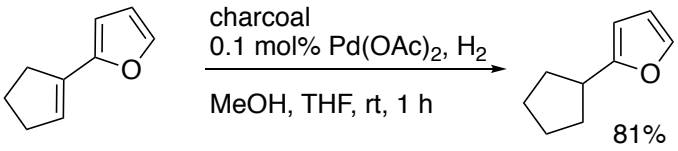


Signal 1: DAD1 A, Sig=215,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.874	BV	0.1349	268.07962	30.98556	4.8955
2	7.142	VB	0.1655	5208.01270	476.55481	95.1045
Totals :				5476.09232	507.54037	

2.4. Model study for the oxidative furan opening

2-Cyclopentylfuran

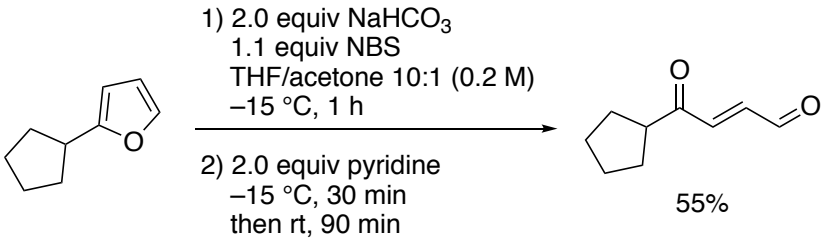


The procedure was adapted from literature.[14]

To a stirred suspension of active charcoal (25.6 mg) and 2-(cyclopent-1-en-1-yl)furan (1.5 g, 11.2 mmol) in dry MeOH was added a $Pd(OAc)_2$ solution (1 mL, 0.011 mmol) prepared in advance by dissolving $Pd(OAc)_2$ (25.6 mg, 0.112 mmol) in dry THF (10 mL) under inert atmosphere. The suspension was stirred for 10 min and then a balloon of H_2 was mounted. Via a small needle, H_2 was continuously bubbled through the mixture for 1 h. The mixture was filtered through a pad of Celite®, washed with pentane and concentrated. FC (pentane) afforded 2-cyclopentylfuran (1.23 g, 81%).

Colorless liquid; R_f 0.78 (pentane); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 1H), 6.26 (dd, J = 3.0, 1.9 Hz, 1H), 5.97 (d, J = 3.1 Hz, 1H), 3.07 (s, 1H), 2.00 (dd, J = 7.3, 4.7 Hz, 2H), 1.78 – 1.58 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 160.1, 140.6, 109.9, 103.1, 38.7, 31.8, 25.2. Physical and spectral data are in accordance with literature data.[15]

(*E*)-4-Cyclopentyl-4-oxobut-2-enal



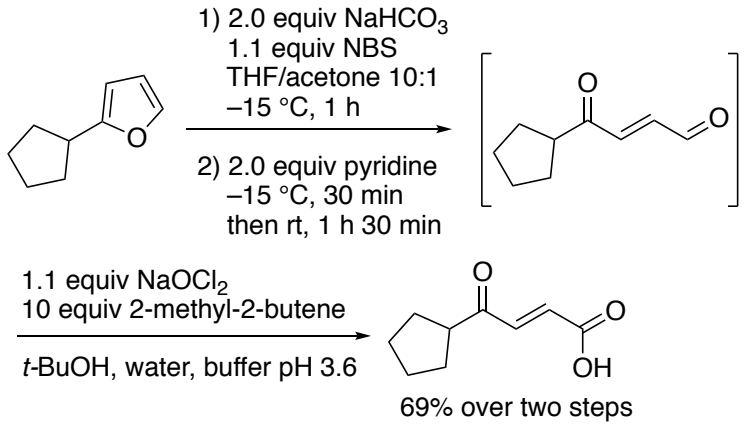
The procedure was adapted from literature.[16]

To a suspension of 2-cyclopentylfuran (100 mg, 0.73 mmol) and $NaHCO_3$ (123 mg, 1.47 mmol) in 3.8 mL

of solvent (acetone/water 10:1) was added NBS (144 mg, 0.81 mmol) at –15 °C. The yellow suspension was stirred for 1 h before addition of pyridine (0.12 mL, 1.54 mmol). The mixture was stirred for 30 min, warmed up to rt and then stirred for 1.5 h. The mixture was then directly loaded on column without workup or concentration. FC (heptanes/EtOAc 7:3) afforded (*E*)-4-cyclopentyl-4-oxobut-2-enal (0.4 mmol, 55%).
Note: The compound is sensitive to acid and thermally labile (partial decomposition occurs already during ^{13}C-NMR measurement). The nature (acidity) of the used silica gel is important.
Yellow oil; R_f 0.74 (heptanes/EtOAc 5:5); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.78 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 16.2 Hz, 1H), 6.86 (d, J = 7.2 Hz, 1H), 3.27 – 3.14 (m, 1H), 1.94 – 1.77 (m, 4H), 1.75 – 1.60 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 202.0, 193.4, 144.9, 137.6, 50.0, 29.0, 26.2; IR (cm^{-1}): 2956, 2923, 2870, 2853, 1694, 1452, 1118, 981, 908, 730; HRMS calc. for $C_9H_{13}O_2$ $[M+H]^+$: 153.0910, found: 153.0908.

(*E*)-4-Cyclopentyl-4-oxobut-2-enoic acid

Procedure 1

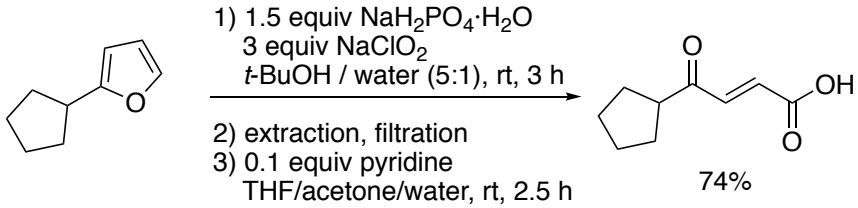


69% over two steps

The procedure was adapted from literature.[16]

To a mixture of crude (*E*)-4-cyclopentyl-4-oxobut-2-enal (65 mg, 0.43 mmol), 2-methyl-2-butene (0.45 mL, 4.27 mmol), *t*BuOH (0.96 mL) and a pH 3.6 phosphate buffer (0.48 mL) [prepared in advance of by dissolving $Na_2HPO_4 \cdot H_2O$ (1.73 g) and citric acid monohydrate in H_2O (Milli-Q water, 98.6 g)] was added a solution of $NaClO_2$ (53.1 mg, 0.47 mmol) in H_2O (Milli-Q water, 0.14 mL). The mixture was stirred at rt for 2 h. The liquids were removed under high vacuum and the residue was dissolved in EtOAc and brine was added. The clear phases were separated and the aqueous phase was acidified to pH 4 with a few drops of aq. HCl. The now turbid suspension was extracted 3 x with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated. FC (heptanes/EtOAc/formic acid 60:40:1) afforded (*E*)-4-cyclopentyl-4-oxobut-2-enoic acid (50 mg, 69% over two steps).
White solid; R_f 0.42 (heptanes/EtOAc/formic acid 60:40:1); m.p. 104-107 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.22 (d, J = 15.9 Hz, 1H), 6.71 (d, J = 15.9 Hz, 1H), 3.14 (ddd, J = 15.7, 8.4, 7.2 Hz, 1H), 1.92 – 1.76 (m, 4H), 1.72 – 1.60 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 201.4, 170.3, 140.9, 129.6, 50.4, 28.7, 26.1; IR (cm^{-1}): 3064, 2963, 2869, 1683, 1661, 1429, 1278, 1195, 1009, 642; HRMS: calc. for $C_9H_{13}O_3$ $[M+H]^+$: 169.0865; found 169.0856.

Procedure 2

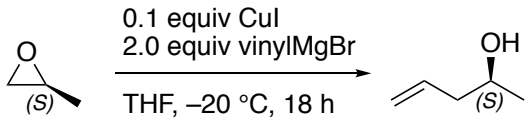


The procedure was adapted from literature.[17]

To a stirred solution of 2-cyclopentylfuran (140 mg, 1.03 mmol) in a solution of *t*BuOH/H_2O (5:1, 5 mL) was added $NaH_2PO_4 \cdot H_2O$ (207 mg, 1.50 mmol) and $NaClO_2$ (80%, 340 mg, 3.09 mmol) at rt. The reaction mixture was stirred for 3 h and the reaction mixture was extracted with Et_2O (3 x 10 mL), washed with brine (2 x 15 mL), dried over Na_2SO_4 and concentrated. The crude product was dissolved in THF/acetone/H_2O (5:4:1, 4 mL) and dry pyridine (10 µl, 0.12 mmol) was added at rt. The reaction mixture was stirred for 2.5 h and the reaction mixture was extracted with Et_2O (3 x 10 mL), washed with aq. $NaHSO_4$ (5%, 20 mL) and water (20 mL). The organic layers were dried over Na_2SO_4 and concentrated. MPLC (pentane/Et_2O 6:3 to 0:10) afforded (*E*)-4-cyclopentyl-4-oxobut-2-enoic acid (129 mg, 74%).

2.5. Synthesis of (+)-brefeldin C

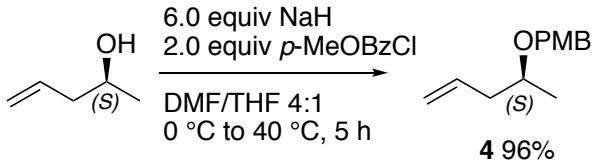
(*S*)-Pent-4-en-2-ol



CuI (5.34 g, 28 mmol) was added to a round bottomed flask and dried by heating under vacuum. Dry THF (108 mL) was added and the solution was cooled to –20 °C using a cryostat under constant stirring. Vinylmagnesium bromide (1 M in THF, 542 mL, 542 mmol) was added *via* cannula over 1 h. *S*-(–)-propylene oxide (19 mL, 271 mmol) dissolved in dry THF (10 mL) was added in portions of 1 mL over 3 h. *Note: delayed exothermic behavior*. The reaction mixture was stirred at –20 °C for 18 h, allowed to warm up to rt and was transferred to a sat. aq. NH_4Cl solution (250 mL) *via* cannula. The phases were separated and the blue aqueous phase was extracted 3 x with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. Distillation (70 °C, 150 mbar) afforded (*S*)-pent-4-en-2-ol (12.5 g, 55%).

Colorless crystals; R_f 0.28 (Et_2O/pentane 2:8); $[\alpha]_D^{23}$ = +4.0 (c = 1, $CHCl_3$) (lit.[18] $[\alpha]_D^{23}$ = +10.86 (c = 3.2, Et_2O)); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.89 – 5.73 (m, 1H), 5.14 (dhept, *J* = 4.2, 1.0 Hz, 1H), 5.09 (dt, *J* = 2.1, 1.1 Hz, 1H), 3.90 – 3.77 (m, 1H), 2.30 – 2.10 (m, 2H), 1.78 (d, *J* = 6.9 Hz, 1H), 1.19 (dd, *J* = 6.2, 0.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 36.2, 119.4, 68.3, 45.1, 24.1. Physical and spectral data are in accordance with literature data.[18]

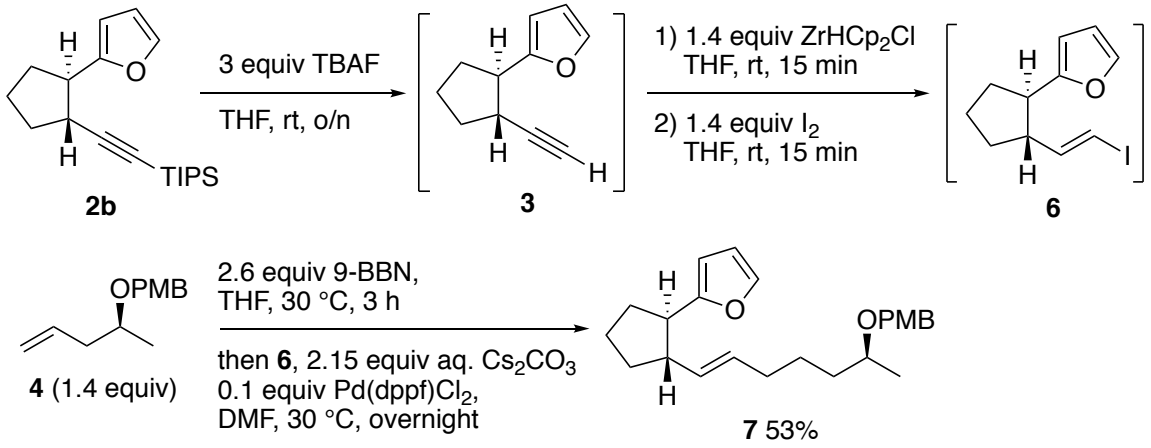
(*S*)-1-Methoxy-4-((pent-4-en-2-yloxy)methyl)benzene (4)



To a stirred suspension of NaH (60 % in mineral oil, 4.75 g, 124 mmol) in dry DMF (100 mL) was added dropwise a solution of (*S*)-pent-4-en-2-ol (1.78 g, 20.7 mmol) and *p*-methoxybenzoyl chloride (5.8 mL, 41.3 mmol) in dry THF (20 mL) at 0 °C. The suspension was stirred at 40 °C for 5 h. The reaction mixture was cooled to 0 °C and sat. aq. NH_4Cl (30 mL) was slowly added. The mixture extracted with Et_2O (3 x 100 mL) and the combined organic phases were washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated. FC (heptanes/EtOAc 95:5) afforded **4** (4.07 g, 96%).

Colorless liquid; R_f 0.21 (heptanes/EtOAc 95:5); $[\alpha]_D^{23}$ = +8.7 (c = 1, $CHCl_3$) (lit.[19] $[\alpha]_D^{20}$ = +10.1 (c = 1, MeOH)); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.27 (d, J = 8.3 Hz, 2H), 6.90 – 6.82 (m, 2H), 5.83 (d, J = 7.1 Hz, 1H), 5.12 – 5.01 (m, 2H), 4.46 (q, J = 11.4 Hz, 2H), 3.80 (s, 3H), 3.56 (dd, J = 12.2, 6.1 Hz, 1H), 2.43 – 2.15 (m, 2H), 1.18 (d, J = 6.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.1, 135.1, 131.1, 129.1, 116.8, 113.8, 74.1, 70.0, 55.3, 40.9, 19.5. Physical and spectral data are in accordance with literature data.[19]

2-((1*R*,2*S*)-2-((*S*,*E*)-6-((4-methoxybenzyl)oxy)hept-1-en-1-yl)cyclopentyl)furan (7)



Preparation of **3**

To a solution of **2b** (636 mg, 2.0 mmol) in dry THF (5 mL) was added TBAF (1M in THF, 5 mL, 6 mmol) and the mixture was stirred at rt overnight. Water (10 mL) was added and the mixture was extracted with pentane (3 x 10 mL). The organic phase was washed with dist. water (3 x 30 mL), dried over Na_2SO_4, and concentrated to afford the crude terminal alkyne **3**.

Preparation of **6**

The crude **3** was dissolved in dry THF (20 mL) and added to a solution of Schwartz' reagent (1.14 g, 4.4 mmol) in dry THF (12 mL). After stirring for 15 min at rt, a solution of I_2 (1.12 g, 4.4 mmol) in dry THF (5.9 mL) was added to the bright yellow mixture, which results in a sharp change of colour to black. After 15 min of stirring at rt, the reaction was treated with water (10 mL). The reaction mixture was extracted with Et_2O (3 x 50 mL), washed several times with 10% aq. $Na_2S_2O_3$ until the solution became colorless.

The organic phase was dried over Na_2SO_4 and quickly concentrated. The crude iodide **6** was only rapidly purified by FC (pentane; R_f 0.43) and then dissolved in dry DMF (24 mL) for the next step.

Preparation of 5

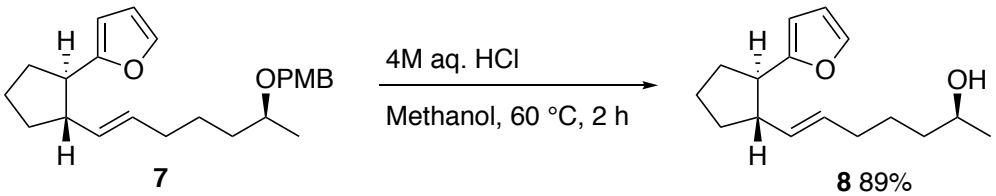
A stirred solution of (*S*)-**4** (920 mg, 4.2 mmol) in dry THF (22 mL) was treated with a solution of 9-BBN (0.5 M in THF, 16.4 mL, 8.2 mmol) and kept at 30 °C for 3 h. This crude solution of **5** was used as it stands for the next step.

Preparation of 7

A degassed 3 M solution of Cs_2CO_3 (2.2 g, 6.8 mmol) in water (2.2 mL) was added to the solution of **5** (see above) followed by the crude vinyl iodide **6** solution (see above) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (260 mg, 0.32 mmol). The dark solution was stirred overnight at 30 °C and treated with a sat. aq. NH_4Cl (20 mL). The mixture was extracted with Et_2O (3 x 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. FC (pentane/Et_2O 95:5) afforded **7** (623 mg, 53%).

Colorless oil; R_f 0.35 (pentane / Et_2O 95:5); $[\alpha]_D^{23}$ = –8.2 (c = 0.4, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.22 – 7.16 (m, 3H), 6.83 – 6.74 (m, 2H), 6.18 (dd, J = 3.1, 1.9 Hz, 1H), 5.90 (d, J = 3.1 Hz, 1H), 5.36 – 5.18 (m, 2H), 4.34 (d, J = 20.6 Hz, 2H), 3.72 (s, 3H), 3.44 – 3.33 (m, 1H), 2.68 (q, J = 8.8 Hz, 1H), 2.53 – 2.38 (m, 1H), 2.05 – 1.93 (m, 1H), 1.92 – 1.79 (m, 3H), 1.78 – 1.59 (m, 3H), 1.51 – 1.17 (m, 5H), 1.08 (d, J = 6.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.1, 140.8, 133.3, 131.4, 130.1, 129.3, 113.8, 110.0, 104.1, 74.5, 70.0, 55.4, 48.9, 45.5, 36.0, 33.1, 32.6, 31.9, 25.5, 23.9, 19.8; IR (cm^{-1}): 2934, 2862, 1612, 1587, 1512, 1454, 1372, 1337, 1301, 1245, 1172, 1133, 1110, 1070, 1036, 1009, 965, 909, 884, 821, 728, 648; HRMS calc. for $C_{24}H_{33}O_3$ $[M+H]^+$: 369.2424, found: 369.2427.

(*S*,*E*)-7-((1*S*,2*R*)-2-(Furan-2-yl)cyclopentyl)hept-6-en-2-ol (8)



7 **8** 89%

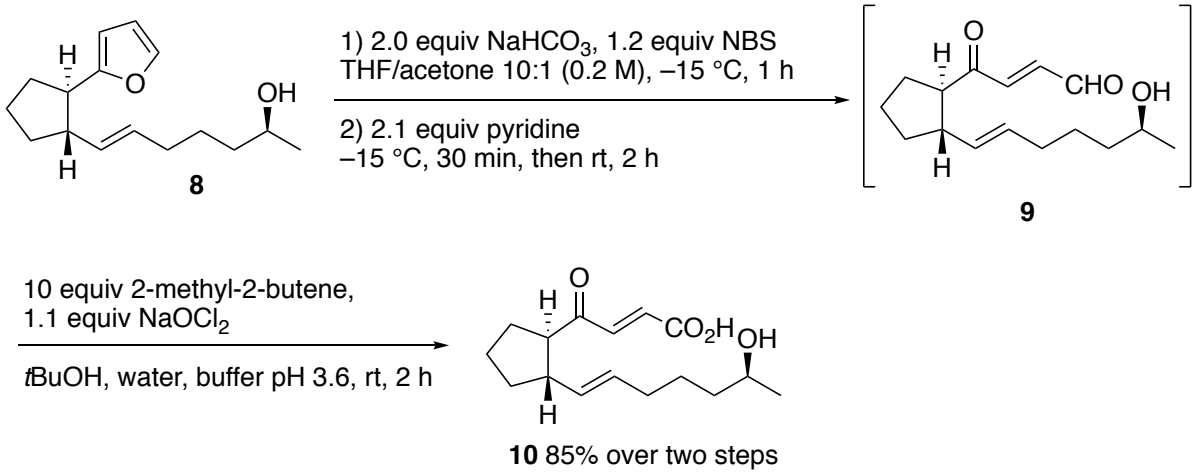
To a solution of **7** (100 mg, 0.27 mmol) in MeOH (7 mL) was added aq. HCl (4 M, 5 mL) at rt. The white suspension was stirred at 60 °C for 2 h (the reaction mixture turned dark) and sat. aq. $NaHCO_3$ was added until the pH was neutral. The mixture was extracted with CH_2Cl_2 and the organic phase was dried over Na_2SO_4, filtered and concentrated. FC (heptanes/EtOAc 8:2) afforded **8** (60 mg, 89%).

Note: Yield is generally lower on larger scale. It is recommended to split a larger batch up for parallel deprotection.

Colorless oil; R_f 0.22 (heptanes/EtOAc 8:2); $[\alpha]_D^{23}$ = –67.4 (c = 1, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.26 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.98 (dt, *J* = 3.2, 0.8 Hz, 1H), 5.45 – 5.27 (m, 2H), 3.76 (q, *J* = 5.8 Hz, 1H), 2.76 (q, *J* = 8.8 Hz, 1H), 2.53 (tt, *J* = 9.7, 6.9 Hz, 1H), 2.11 – 1.88 (m, 4H), 1.75 (dddd, *J* = 16.3, 10.3, 8.0, 3.9 Hz, 3H), 1.53 – 1.21 (m, 6H), 1.16 (d, *J* = 6.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 158.7, 140.8, 133.6, 129.9, 110.0, 104.1, 68.2, 49.0, 45.6, 38.8, 38.8, 33.1, 32.5, 32.0, 25.7, 25.7, 23.9, 23.6, 23.6 IR (cm^{-1}): 3341, 2929, 2871, 1595, 1506, 1452, 1373, 1009, 964, 726; HRMS calc.

for $C_{16}H_{25}O_2$ $[M+H]^+$: 249.1849, found: 249.1844

(*E*)-4-((1*R*,2*S*)-2-((*S*,*E*)-6-Hydroxyhept-1-en-1-yl)cyclopentyl)-4-oxobut-2-enoic acid (10)



To a stirred solution of $NaHCO_3$ (20 mg, 0.24 mmol) and **8** (30 mg, 0.12 mmol) in acetone/water (10:1, 0.63 mL) at –15 °C was added NBS (26 mg, 0.15 mmol). The yellow solution was stirred at this temperature for 1 h. Then, pyridine (21 µL, 0.25 mmol) was added, the mixture was stirred for 30 min and allowed to warm up to rt and the orange solution was stirred for 2 h. The reaction mixture was directly loaded on a silica gel column without workup nor concentration. Rapid purification by FC (heptanes/EtOAc 5:5) afforded the intermediate enal **9** as yellowish oil which was used without further purification in the next step.

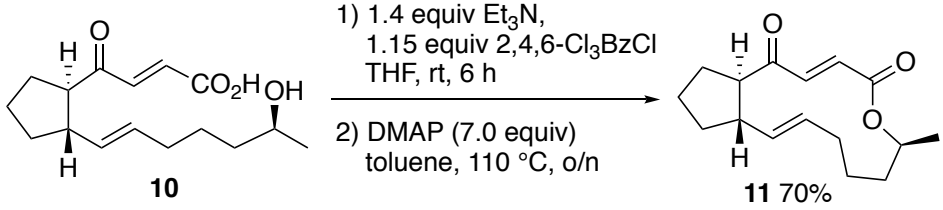
Note: The compound is very sensitive to acid.[20] Partial decomposition was observed in presence of silica gel.

To a mixture of crude **9** (33 mg), 2-methyl-2-butene (0.13 mL, 1.25 mmol), *t*BuOH (0.28 mL) and the phosphate buffer (0.14 mL) was added a solution of $NaClO_2$ (15.5 mg, 0.14 mmol) in Milli-Q water (40 µL). The mixture was stirred at rt for 2 h. The liquids were removed under high vacuum and the residue was dissolved in EtOAc and brine. The clear phases were separated and the aq. phase was acidified to pH 4 with a few drops of aq. HCl. The turbid suspension was extracted 3 x with EtOAc. The combined organic phase was dried over Na_2SO_4, filtered and concentrated. FC (heptanes/EtOAc/formic acid 50:50:1) afforded **10** (29 mg, 85% over two steps).

Note: It is recommended to use the crude acid directly for the lactonization step without purification by column.

Yellow sticky residue; R_f 0.36 (heptanes/EtOAc/formic acid 50:50:1); $[\alpha]_D^{23}$ = –20.7 (c = 1 $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.19 (d, J = 15.8 Hz, 1H), 6.66 (d, J = 15.8 Hz, 1H), 5.49 – 5.34 (m, 2H), 3.90 – 3.75 (m, 1H), 2.89 (td, J = 8.8, 7.2 Hz, 1H), 2.55 (p, J = 8.9 Hz, 1H), 2.03 (ddt, J = 11.4, 7.8, 4.5 Hz, 3H), 1.91 (tdd, J = 13.5, 8.6, 5.2 Hz, 2H), 1.86 – 1.55 (m, 4H), 1.54 – 1.31 (m, 6H), 1.18 (d, J = 6.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 201.32, 168.51, 141.12, 133.46, 131.29, 129.85, 77.48, 77.16, 76.84, 68.71, 57.07, 48.31, 38.49, 34.86, 32.41, 28.19, 25.77, 25.27, 23.02; IR (cm^{-1}): 3429, 2922, 2856, 1679, 1406, 1288, 1212, 1091, 996, 968; HRMS calc. for $C_{16}H_{23}O_4$ $[M–H^+]^–$: 279.1602, found: 279.1610

4-Dehydro-brefeldin C (11)

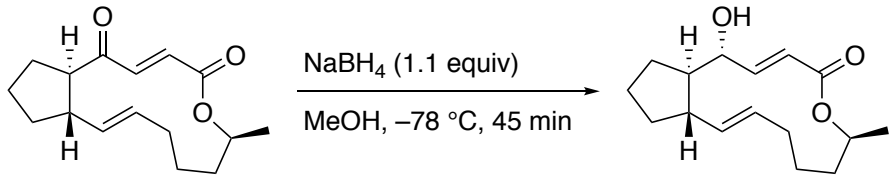


To a solution of **10** (62mg, 0.22 mmol) in dry THF (12.8 mL) were added dropwise Et_3N (43 µL, 0.31 mmol) and 2,4,6-trichlorobenzoyl chloride (40 µL, 0.26 mmol). After 8 h of stirring at rt, the reaction mixture was diluted with dry toluene (28.5 mL). This solution was transferred slowly via cannula to a refluxing solution of DMAP (190 mg, 1.55 mmol) in dry toluene (28.5 mL). The cannula was rinsed with dry toluene (5 mL). The mixture was heated under reflux overnight. The reaction mixture was cooled down to rt and filtered through 1 cm of Celite®. The Celite® cake was thoroughly washed with dry toluene. The clear orange filtrate was concentrated affording a brown slurry. FC (pentane/Et_2O 9:1) afforded **11** (40.5 mg, 70%).

Colorless residue; R_f 0.34 (pentane/Et_2O 9:1); $[\alpha]_D^{23}$ = +3.0 (c = 0.22 $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 15.9 Hz, 1H), 6.41 (d, J = 15.9 Hz, 1H), 5.90 (ddd, J = 15.0, 10.8, 4.1 Hz, 1H), 5.46 (ddd, J = 15.0, 9.4, 1.5 Hz, 1H), 4.67 (dqd, J = 10.3, 6.1, 2.5 Hz, 1H), 2.66 – 2.45 (m, 2H), 2.27 – 2.09 (m, 2H), 2.06 – 1.39 (m, 12H), 1.33 (d, J = 6.2 Hz, 3H), 1.29 – 1.11 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 201.3, 166.4, 140.7, 135.9, 132.9, 128.14, 73.7, 58.3, 48.7, 35.3, 34.4, 32.5, 25.9, 25.3, 20.5; IR (cm^{-1}): 2956, 2925, 2855, 1720, 1455, 1378, 1267, 1119, 1073, 1039; HRMS calc. for $C_{16}H_{23}O_3$ $[M+H]^+$: 263.1642, found: 263.1649. Physical and spectral data are in accordance with literature data.[21]

(+)-Brefeldin C

The procedure was adapted from literature.[22]

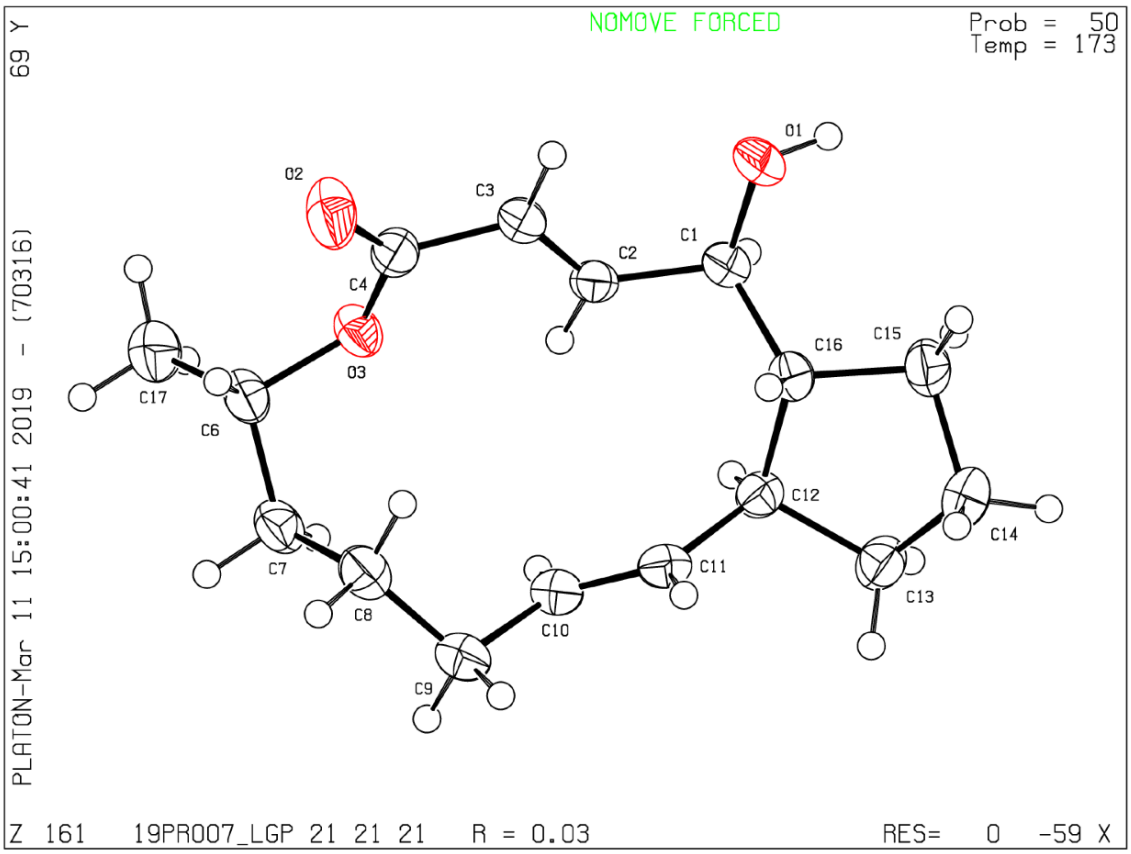


To a solution of **11** (15 mg, 0.06 mmol) in MeOH (2 mL) at –78 °C was added $NaBH_4$ (3 mg, 0.06 mmol). The mixture was stirred at –78 °C for 45 min. After warming up to rt, a sat. aq. $NaHCO_3$ solution (4 mL) was added. The white suspension was extracted with CH_2Cl_2 (3 x 10 mL) and the organic phases were dried over Na_2SO_4, filtered and concentrated. FC (heptanes/EtOAc 7:3) afforded (+)-brefeldin C (13 mg, 90%).

White solid; R_f 0.38 (heptanes/EtOAc 7:3); m.p. 155–162 °C (lit.[23] m.p. 160–161 °C); $[\alpha]_D^{23}$ = +23.9 (c = 0.42 $CHCl_3$) (lit. $[\alpha]_D^{23}$ = +121 (c = 0.07, MeOH)[19] and $[\alpha]_D^{23}$ = +119.8 (c = 1, $CHCl_3$)[24]); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.37 (dd, J = 15.7, 3.1 Hz, 1H), 5.90 (dd, J = 15.7, 2.0 Hz, 1H), 5.72 (ddd, J = 15.0, 10.2, 4.7 Hz, 1H), 5.19 (dd, J = 15.2, 9.5 Hz, 1H), 4.86 (dqd, J = 11.0, 6.3, 1.8 Hz, 1H), 4.09 (dt, J = 9.6, 2.5 Hz,

1H), 2.25 (p, *J* = 8.7 Hz, 1H), 2.01 (tdd, *J* = 13.0, 6.1, 3.3 Hz, 2H), 1.91 – 1.78 (m, 2H), 1.78 – 1.32 (m, 9H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.00 – 0.89 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.4, 152.0, 136.5, 130.5, 117.5, 76.2, 71.8, 54.2, 47.1, 35.3, 34.3, 32.1, 32.0, 26.9, 25.4, 21.0; IR (cm^{-1}): 3435, 2954, 2922, 2848, 1686, 1641, 1447, 1266, 1118, 978; HRMS calc. for $C_{16}H_{24}O_3$ $[M+H]^+$: 265.1798, found: 265.1806. Physical and spectral data are in accordance with literature data, except for the amplitude of the optical rotation. The structure of (+)-brefeldin C synthesized by us was confirmed by single crystal X-ray crystallography. Suitable crystals were obtained upon evaporation of a solution of (+)-brefeldin C in heptanes/EtOAc under vacuum.

3. X-Ray crystal structure report of (+)-brefeldin C[25]



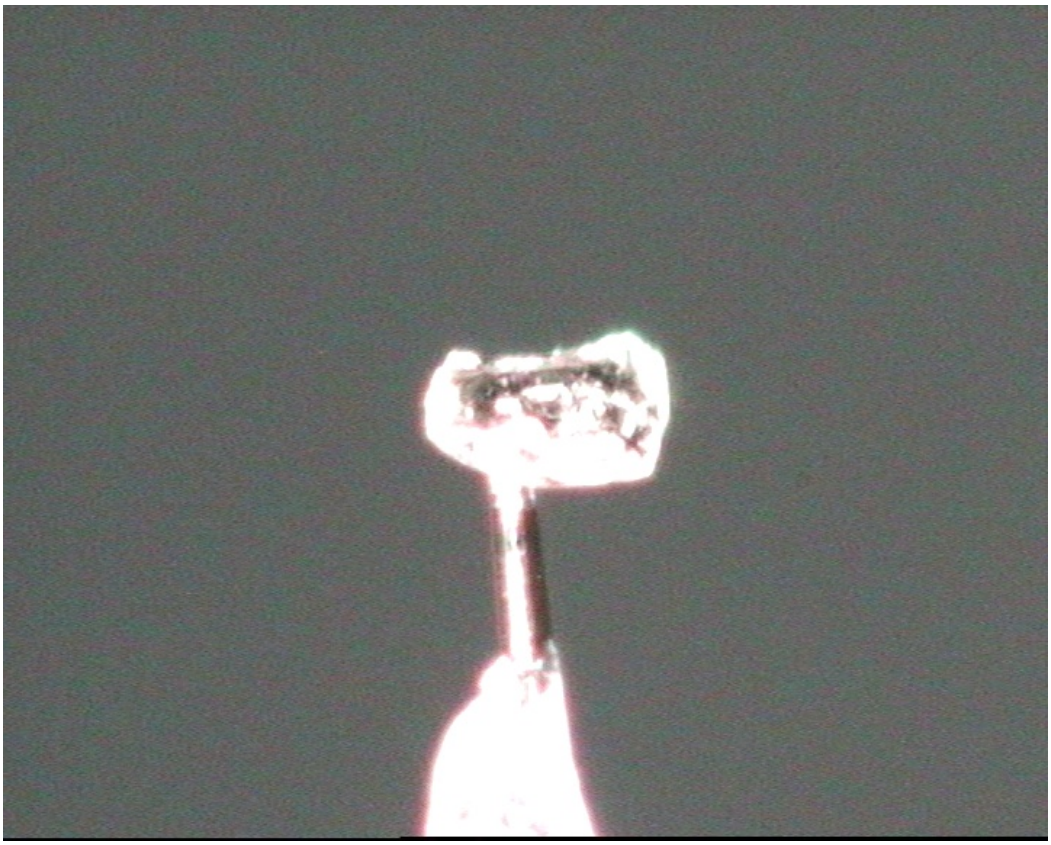
Crystal-Structure Determination. A crystal of $C_{16}H_{24}O_3$ was mounted in air at ambient conditions. All measurements were made on a *RIGAKU Synergy S* area-detector diffractometer[26] using mirror optics monochromated Cu *Kα* radiation (λ = 1.54184 Å).[27] The unit cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of the setting angles of reflections in the range 9.988° < 2θ < 144.482°. A total of 562 frames were collected using ω scans, with 0.05 seconds exposure time, a rotation angle of 0.5° per frame, a crystal-detector distance of 31.0 mm, at T = 173(2) K.

Data reduction was performed using the *CrysAlisPro* program.[26] The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method using SCALE3

ABSPACK in *CrysAlisPro* was applied.[26] Data collection and refinement parameters are given in *Table 1.*

The structure was solved by direct methods using *SHELXT*,[28] which revealed the positions of all non-hydrogen atoms of the title compound. All non-hydrogen atoms were refined anisotropically. H-atoms were assigned in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2Ueq of its parent atom (1.5Ueq for methyl groups).

Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. The weighting scheme was based on counting statistics and included a factor to downweight the intense reflections. All calculations were performed using the *SHELXL-2014/7*[28] program in OLEX2.[29]



A single crystal of the compound mounted on a glass fiber.

4. References

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[25] CCDC 1937167 Contain the Supplementary Crystallographic Data for This Paper. These Data Are Provided Free of Charge by The Cambridge Crystallographic Data Centre.

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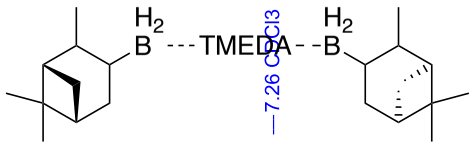
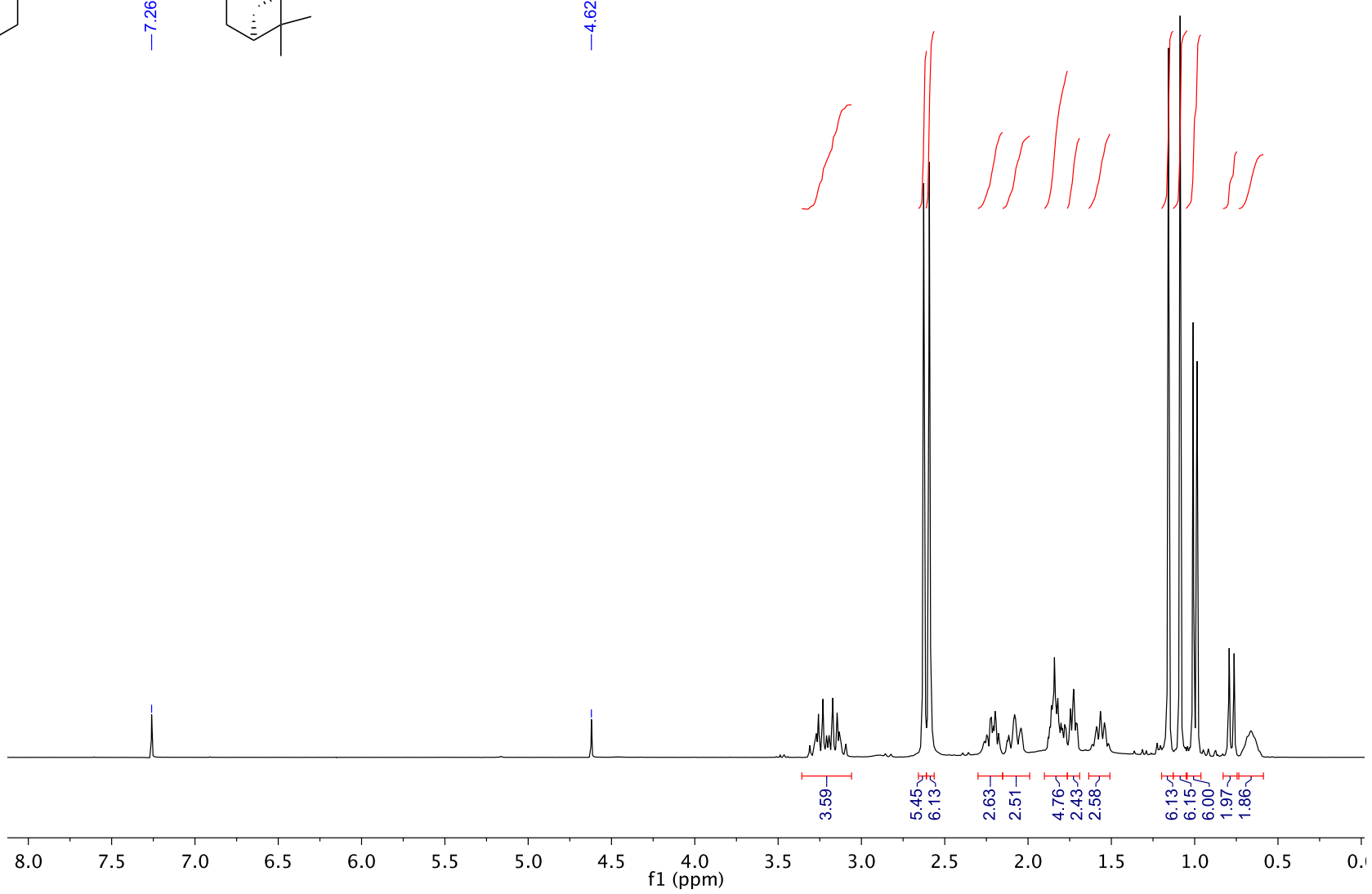
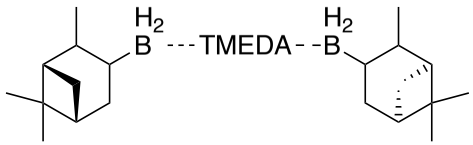
5. Spectra

^{1}H NMR (300 MHz, $CDCl_3$)
(+)IpcBH$_2$ TMEDA complex

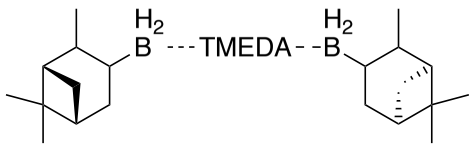




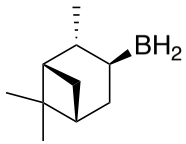
^{13}C NMR (75 MHz, $CDCl_3$)
(+)IpcBH_2 TMEDA complex



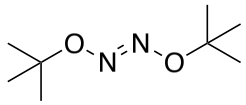
^{11}B NMR (96 MHz, $CDCl_3$)
(+)IpcBH$_2$ TMEDA complex



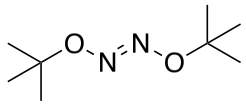
^{11}B NMR (96 MHz, $CDCl_3$)
(+)IpcBH$_2$



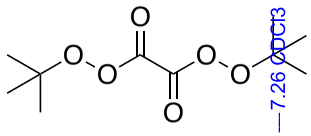
^{1}H NMR (300 MHz, $CDCl_3$)
Di-*tert*-butylhyponitrite (DTBHN)

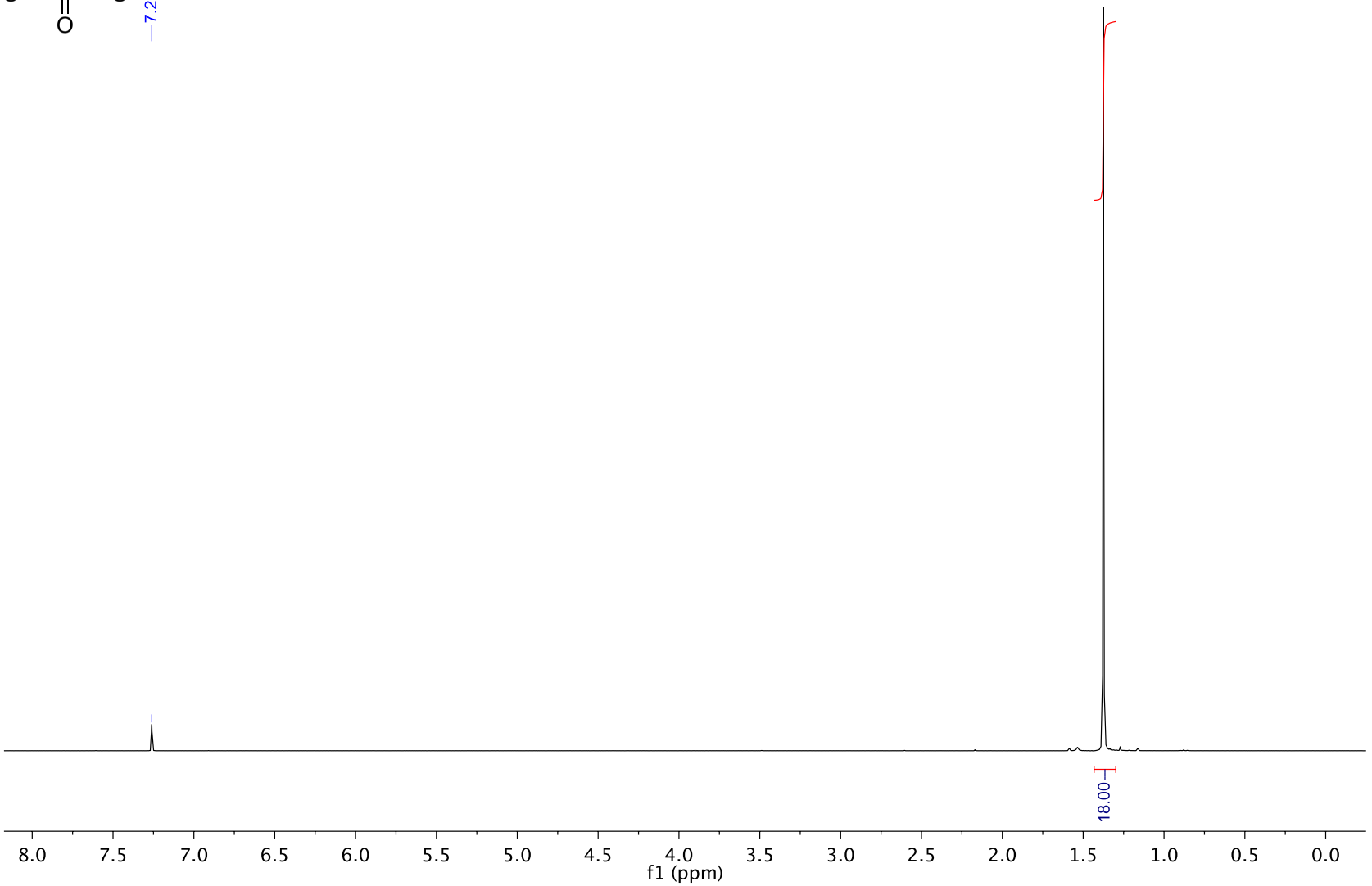


^{13}C NMR (75 MHz, $CDCl_3$)
Di-*tert*-butylhyponitrite (DTBHN)

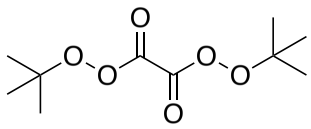


^{1}H NMR (300 MHz, $CDCl_3$)
Di-*tert*-butyl peroxyoxalate (DTBPO)

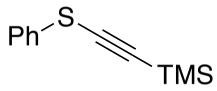




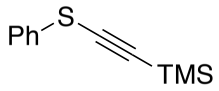
^{13}C NMR (75 MHz, $CDCl_3$)
Di-*tert*-butyl peroxyoxalate (DTBPO)



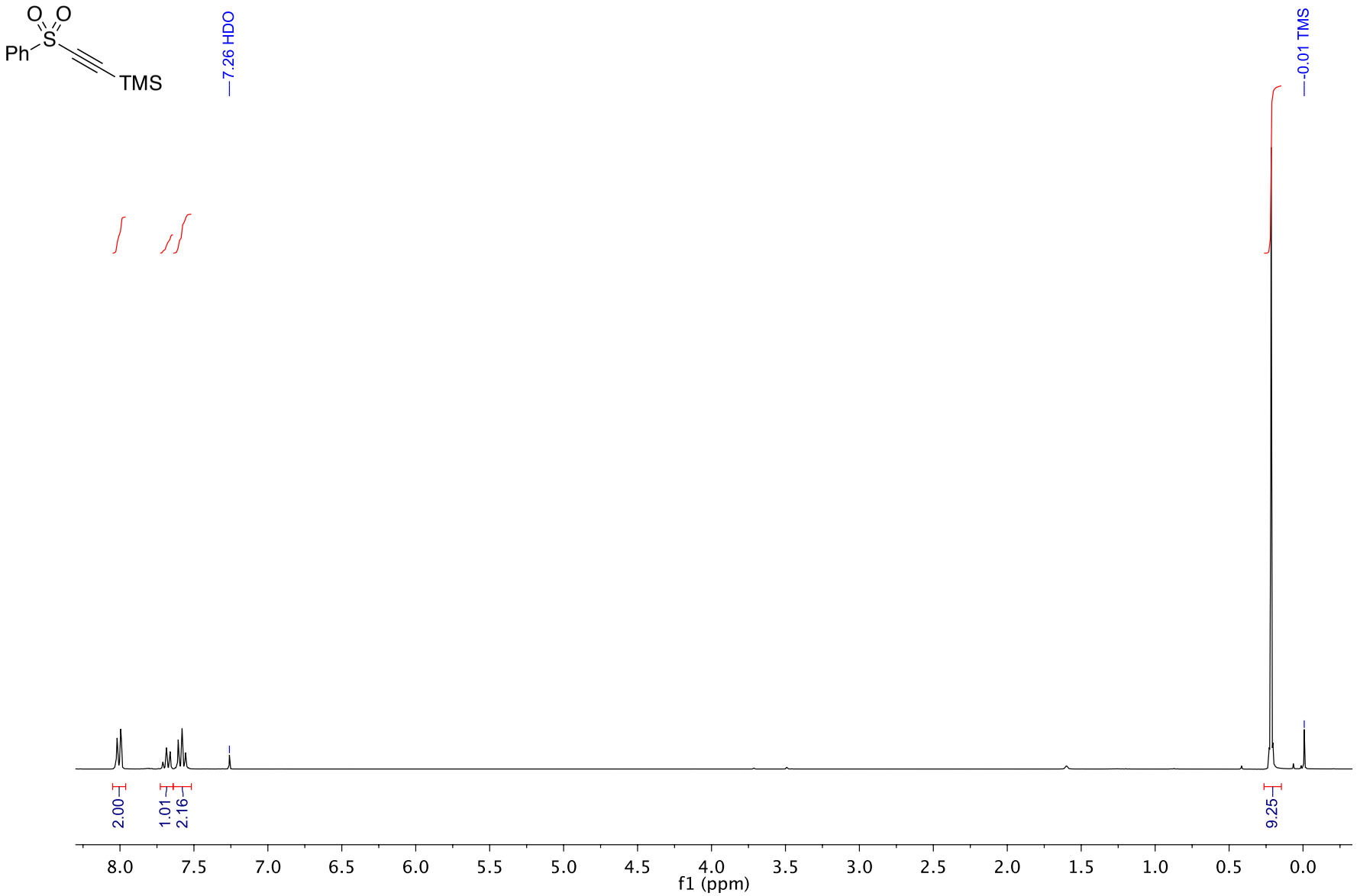
^{1}H NMR (300 MHz, $CDCl_3$)
Trimethyl(2-phenylsulfanylethynyl)silane



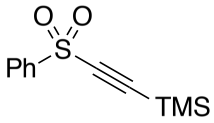
^{13}C NMR (75 MHz, $CDCl_3$)
Trimethyl(2-phenylsulfanylethynyl)silane



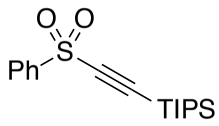
^{1}H NMR (300 MHz, $CDCl_3$)
Trimethyl((phenylsulfonyl)ethynyl)silane



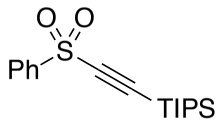
^{13}C NMR (75 MHz, $CDCl_3$)
Trimethyl((phenylsulfonyl)ethynyl)silane



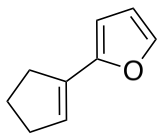
^{1}H NMR (300 MHz, $CDCl_3$)
Triisopropyl((phenylsulfonyl)ethynyl)silane

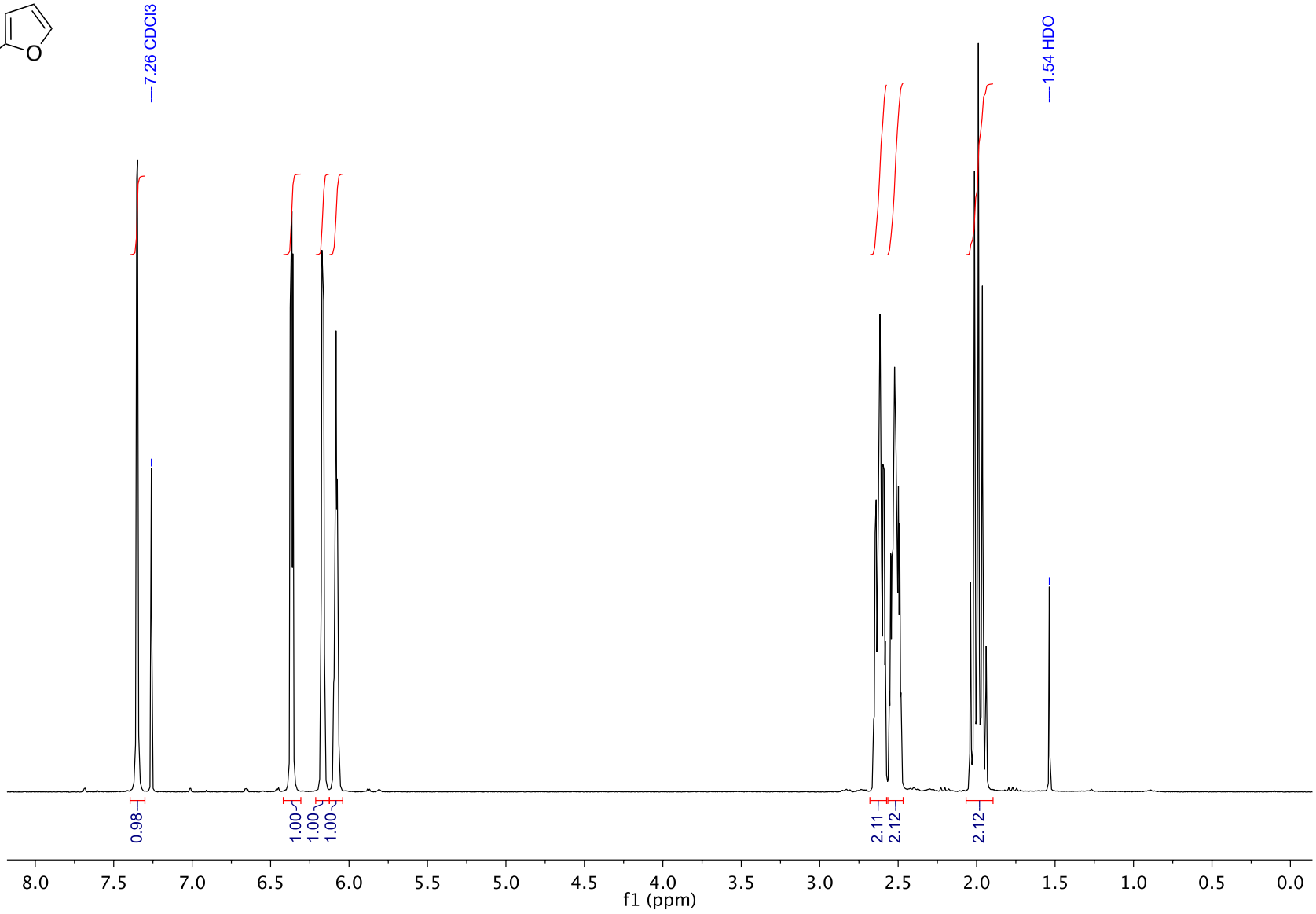


^{13}C NMR (75 MHz, $CDCl_3$)
Triisopropyl((phenylsulfonyl)ethynyl)silane

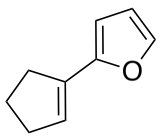


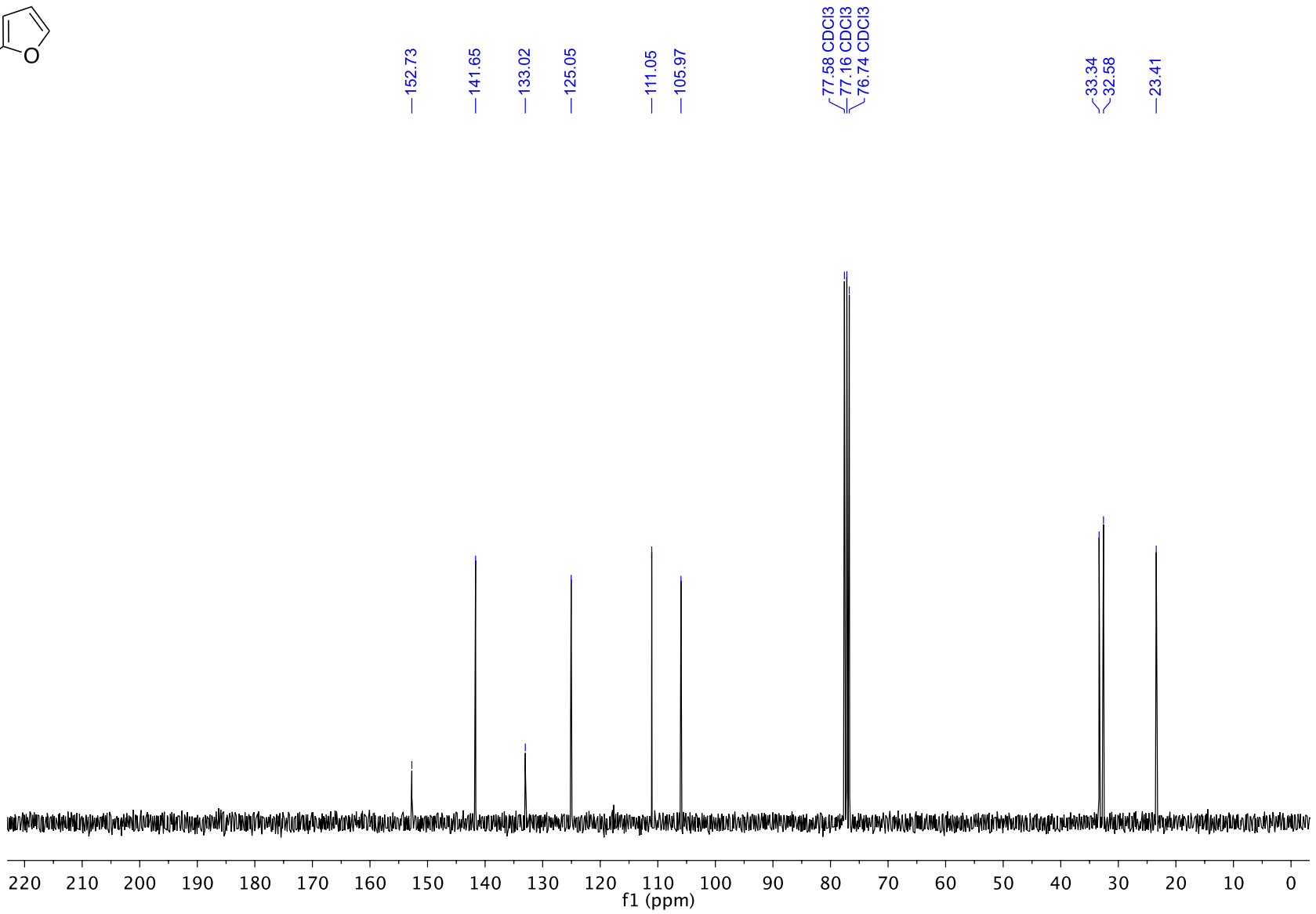
^{1}H NMR (300 MHz, $CDCl_3$)
2-(Cyclopent-1-en-1-yl)furan (**1**)



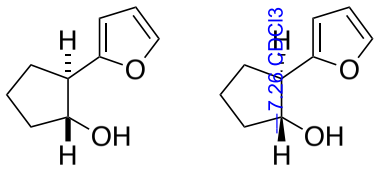


^{13}C NMR (75 MHz, $CDCl_3$)
2-(Cyclopent-1-en-1-yl)furan (**1**)



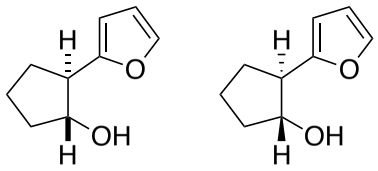


^{1}H NMR (300 MHz, $CDCl_3$)
trans-2-(2-furyl)cyclopentanol / (1*R*,2*R*)-2-(Furan-2-yl)cyclopentan-1-ol



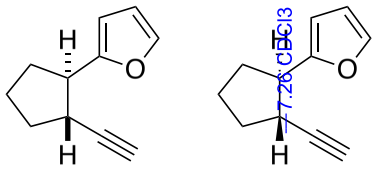
^{13}C NMR (75 MHz, $CDCl_3$)

trans-2-(2-furyl)cyclopentanol / (1*R*,2*R*)-2-(Furan-2-yl)cyclopentan-1-ol



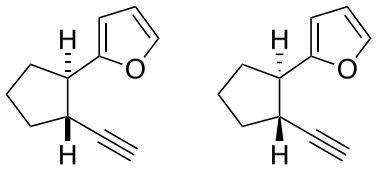
^{1}H NMR (300 MHz, $CDCl_3$)

trans-2-(2-ethynylcyclopentyl)furan / 2-((1*R*,2*R*)-2-ethynylcyclopentyl)furan (**3**)

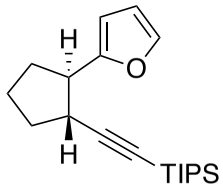


^{13}C NMR (75 MHz, $CDCl_3$)

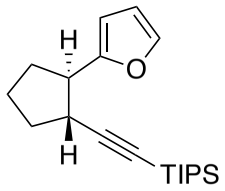
trans-2-(2-ethynylcyclopentyl)furan / 2-((1*R*,2*R*)-2-ethynylcyclopentyl)furan (**3**)



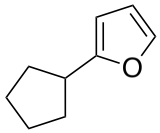
^{1}H NMR (300 MHz, $CDCl_3$)
(((1*R*,2*R*)-2-(furan-2-yl)cyclopentyl)ethynyl)triisopropylsilane (**2b**)

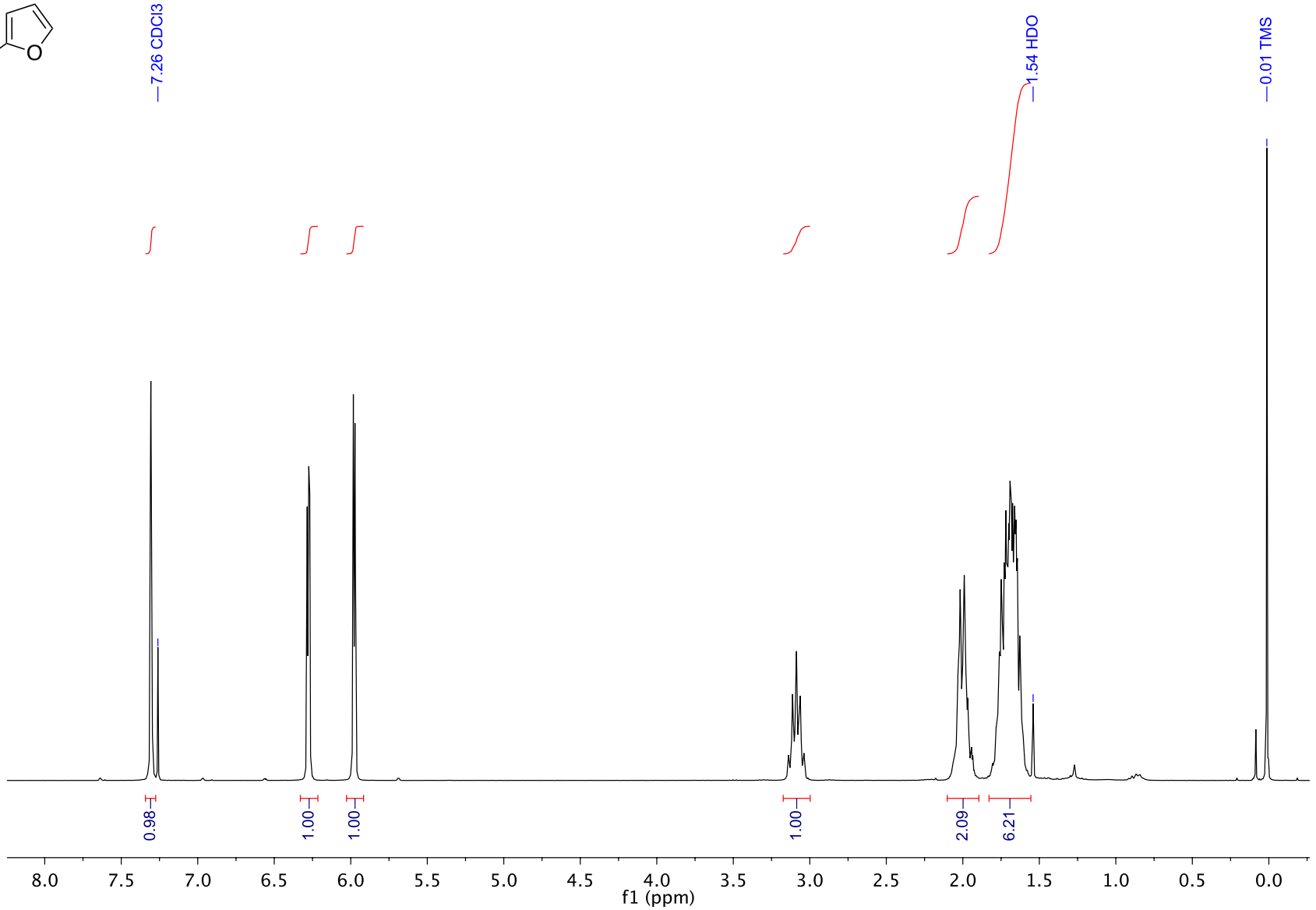


^{13}C NMR (75 MHz, $CDCl_3$)
(((1*R*,2*R*)-2-(furan-2-yl)cyclopentyl)ethynyl)triisopropylsilane (**2b**)

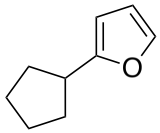


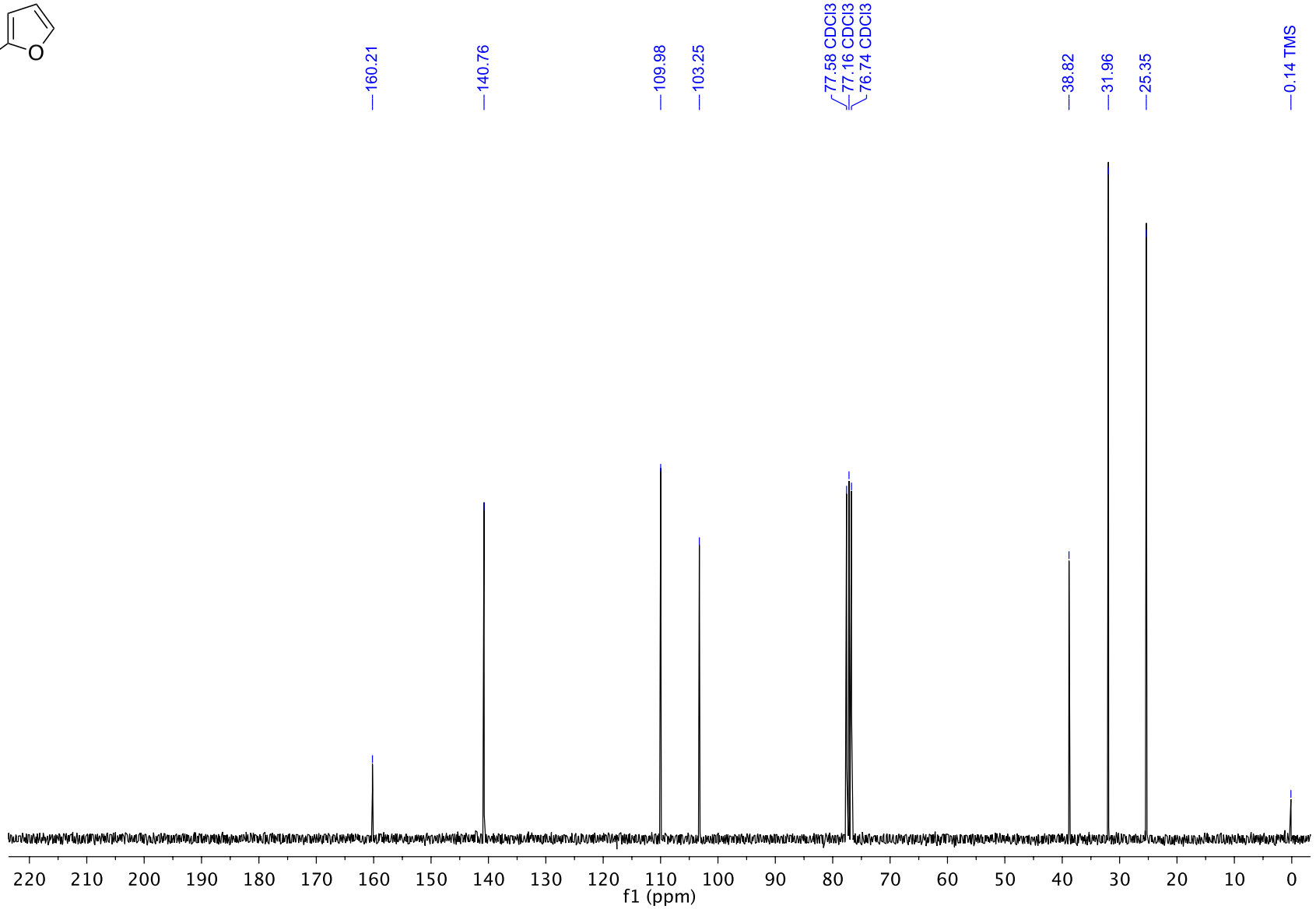
^{1}H NMR (300 MHz, $CDCl_3$)
2-cyclopentylfuran



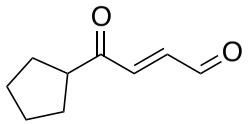


^{13}C NMR (75 MHz, $CDCl_3$)
2-cyclopentylfuran

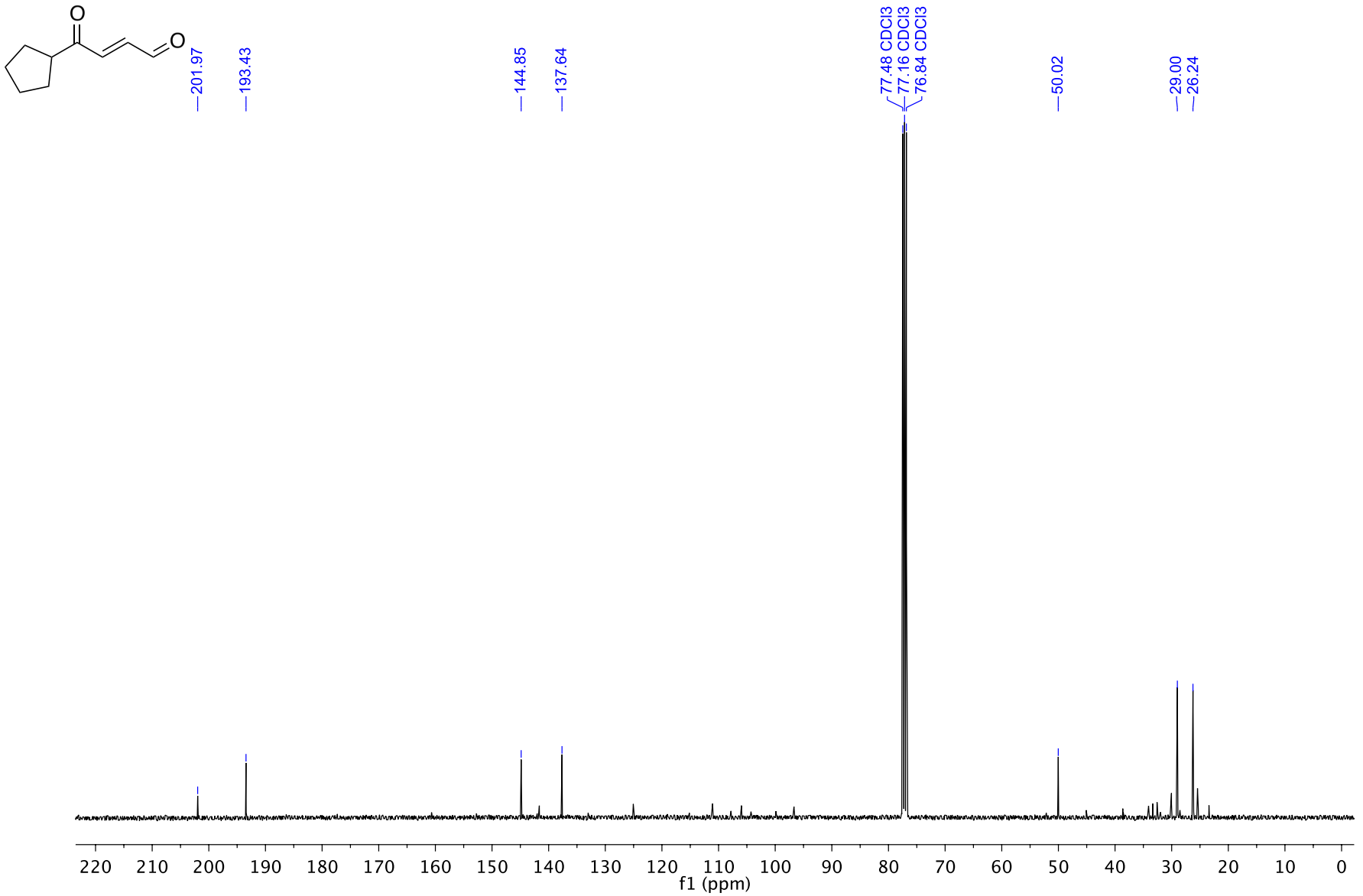




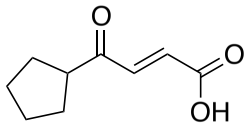
^{1}H NMR (300 MHz, $CDCl_3$)
(*E*)-4-cyclopentyl-4-oxobut-2-enal



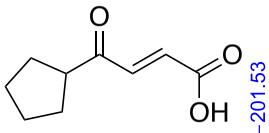
^{13}C NMR (75 MHz, $CDCl_3$)
(*E*)-4-cyclopentyl-4-oxobut-2-enal (*partial decomposition during time of measurement)*



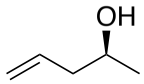
^{1}H NMR (300 MHz, $CDCl_3$)
(*E*)-4-cyclopentyl-4-oxobut-2-enoic acid

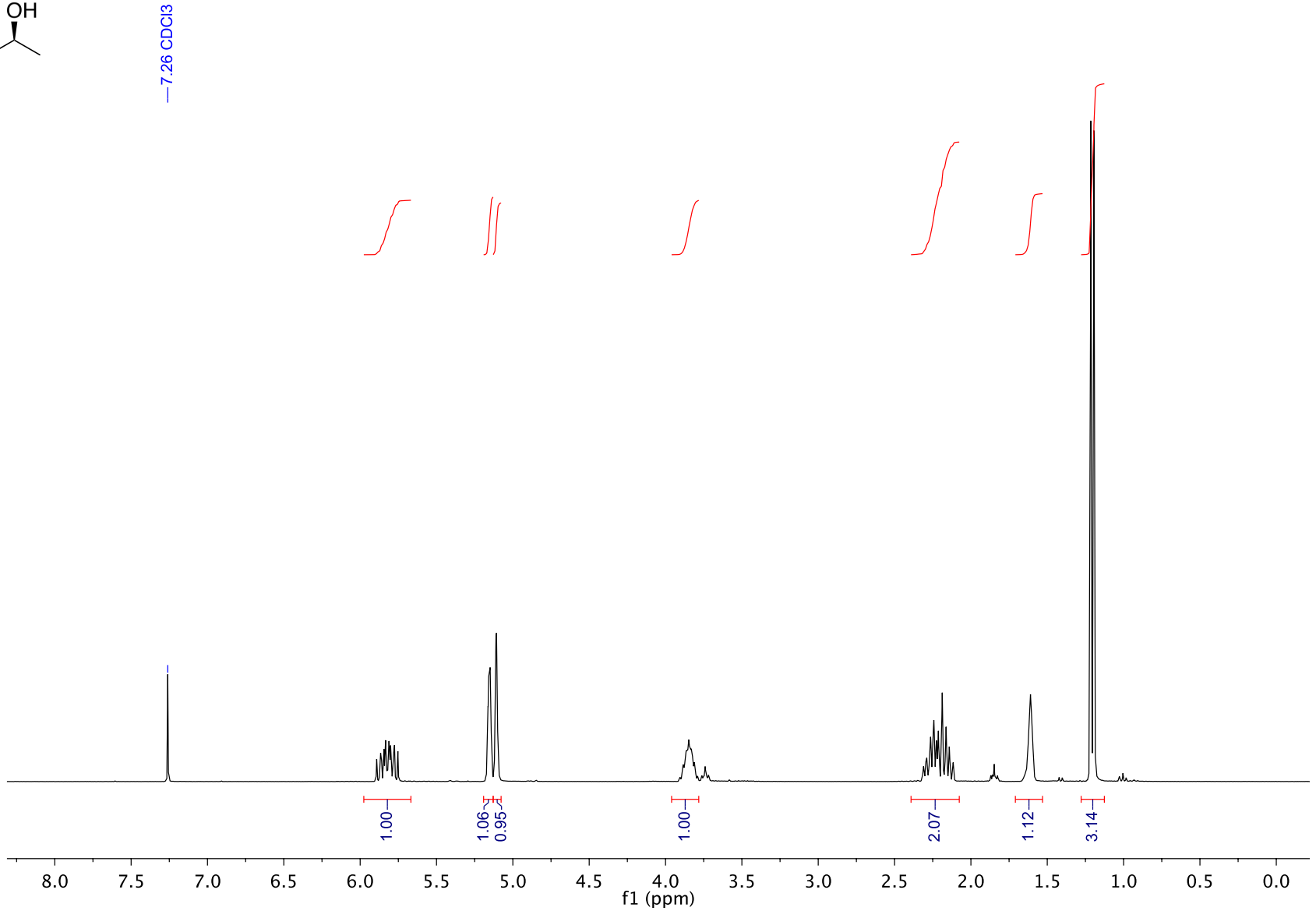


^{13}C NMR (75 MHz, $CDCl_3$)
(*E*)-4-cyclopentyl-4-oxobut-2-enoic acid

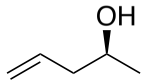


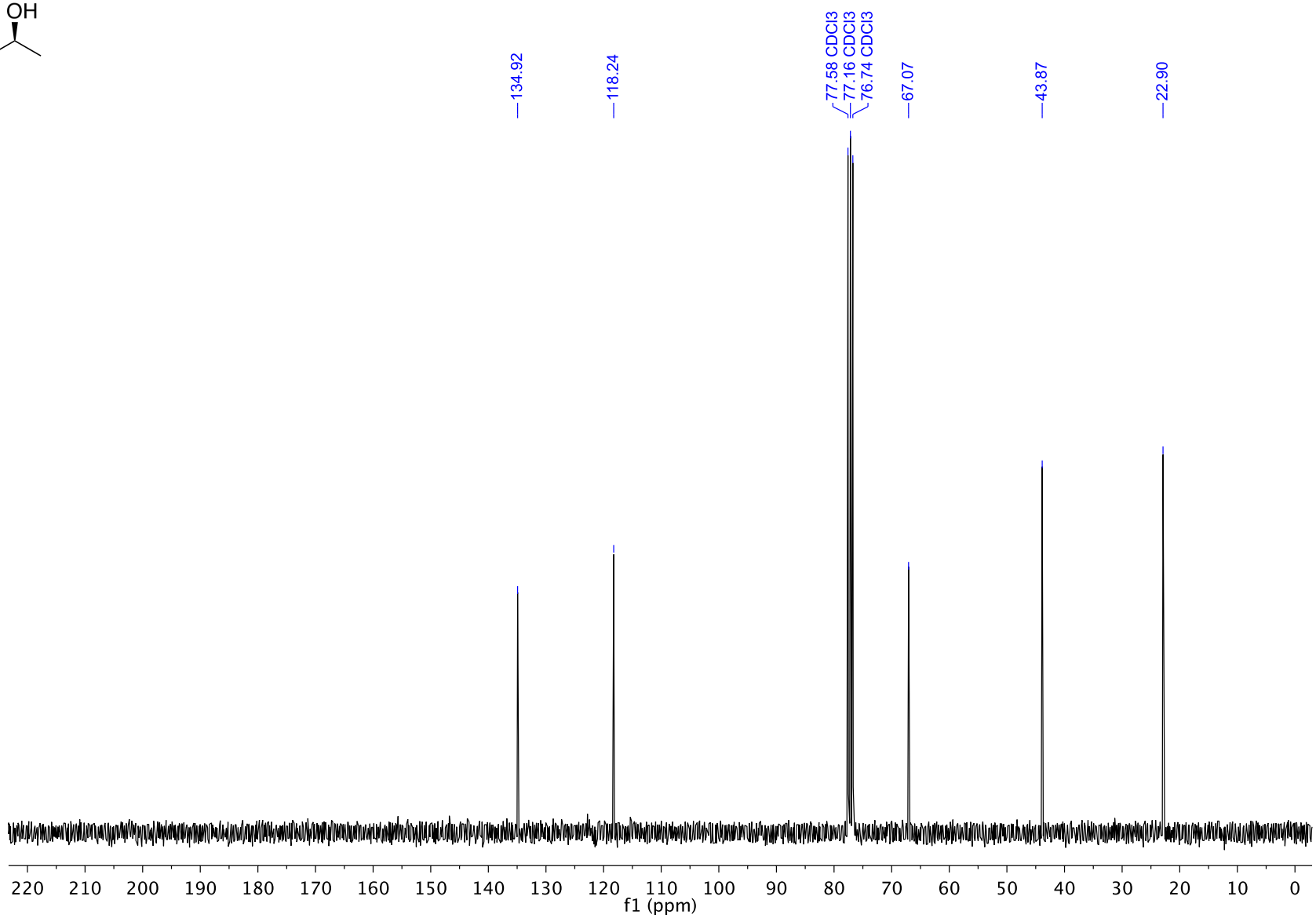
^{1}H NMR (300 MHz, $CDCl_3$)
(*S*)-pent-4-en-2-ol



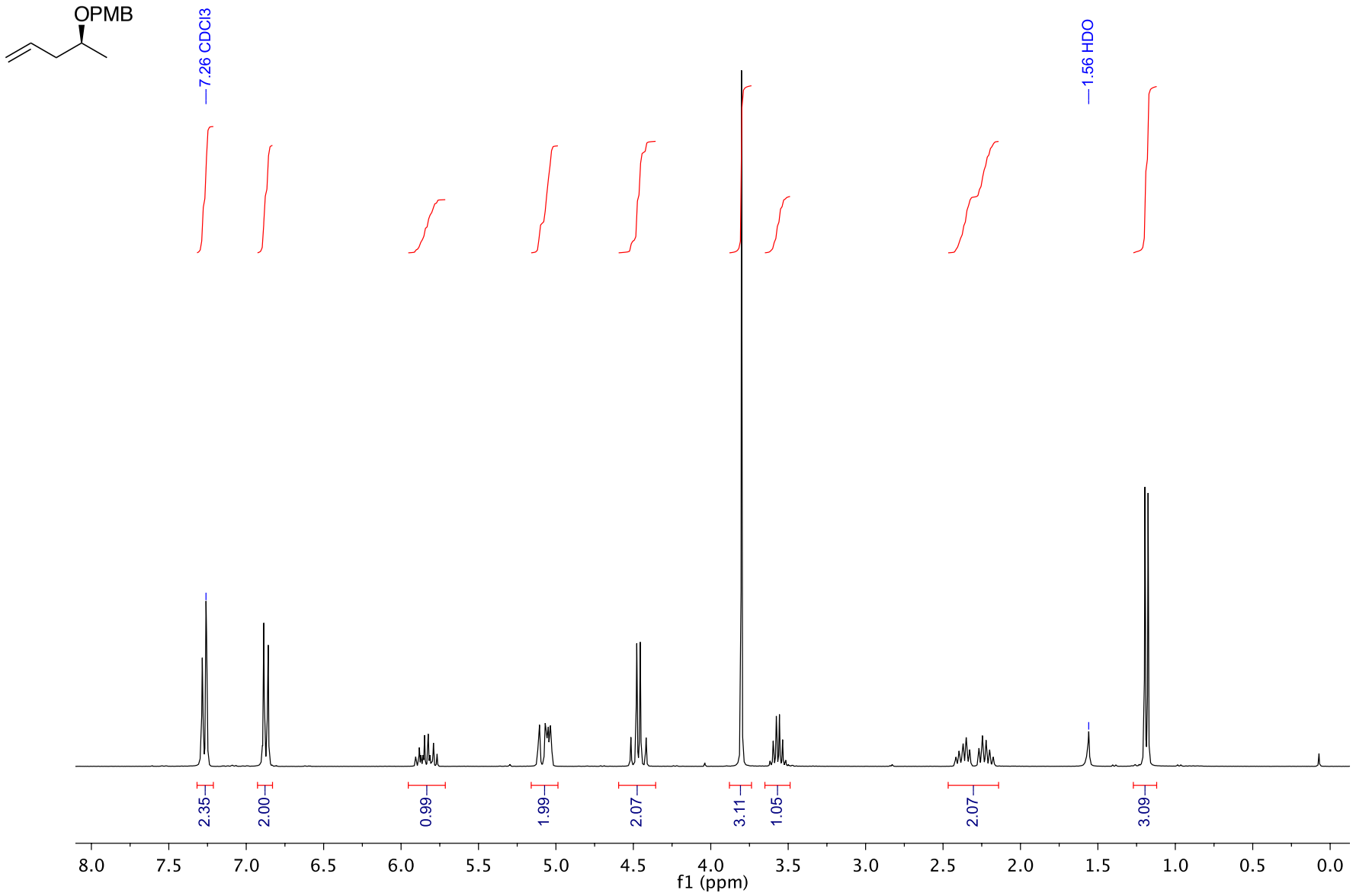


^{13}C NMR (75 MHz, $CDCl_3$)
(*S*)-pent-4-en-2-ol

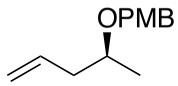


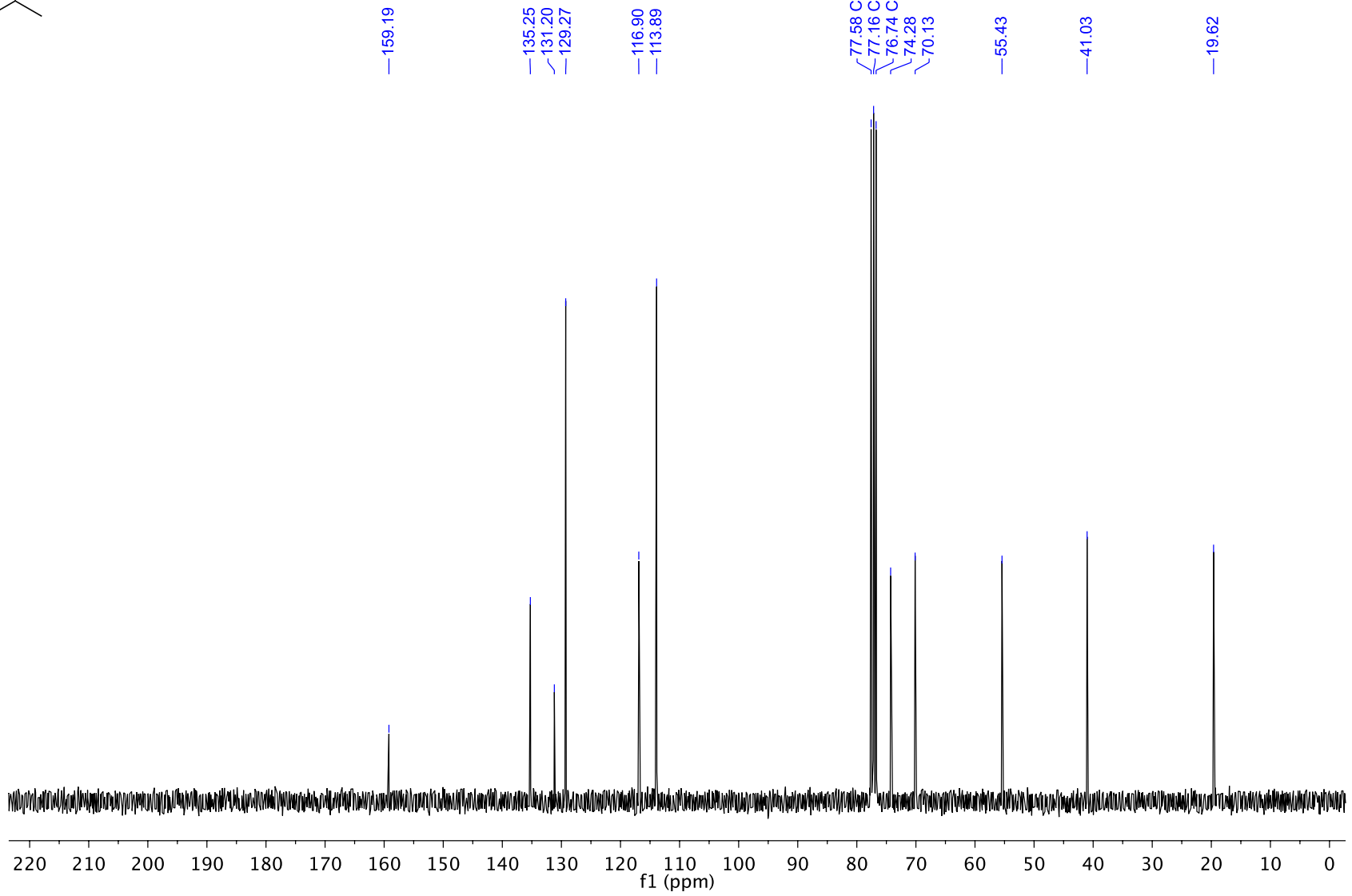


^{1}H NMR (300 MHz, $CDCl_3$)
(*S*)-1-methoxy-4-((pent-4-en-2-yloxy)methyl)benzene (**4**)

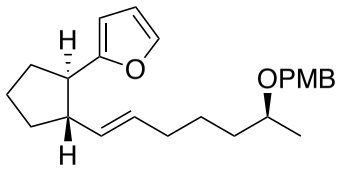


^{13}C NMR (75 MHz, $CDCl_3$)
(*S*)-1-methoxy-4-((pent-4-en-2-yloxy)methyl)benzene (**4**)

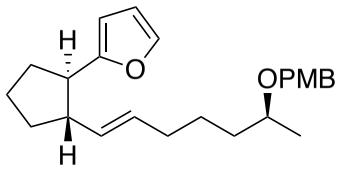




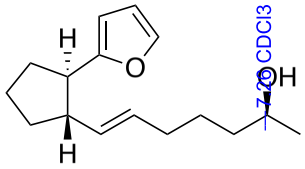
^{1}H NMR (300 MHz, $CDCl_3$)
2-((1*R*,2*S*)-2-((*S*,*E*)-6-((4-methoxybenzyl)oxy)hept-1-en-1-yl)cyclopentyl)furan (**7**)



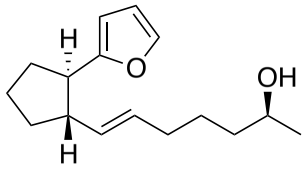
^{13}C NMR (75 MHz, $CDCl_3$)
2-((1*R*,2*S*)-2-((*S*,*E*)-6-((4-methoxybenzyl)oxy)hept-1-en-1-yl)cyclopentyl)furan (**7**)



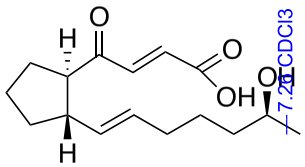
^{1}H NMR (300 MHz, $CDCl_3$)
(*S*,*E*)-7-((1*S*,2*R*)-2-(furan-2-yl)cyclopentyl)hept-6-en-2-ol (**8**)

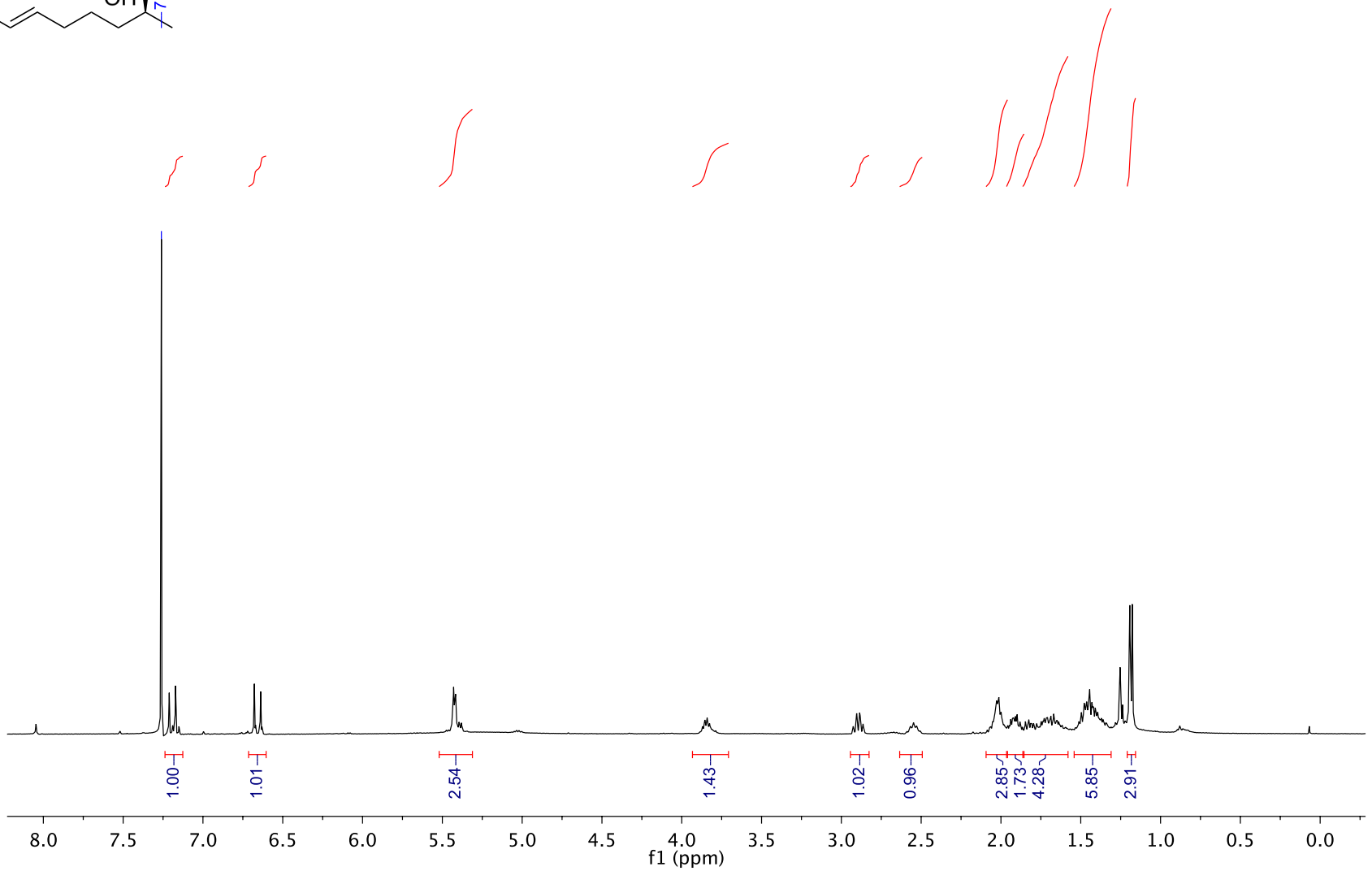


^{13}C NMR (75 MHz, $CDCl_3$)
(*S*,*E*)-7-((1*S*,2*R*)-2-(furan-2-yl)cyclopentyl)hept-6-en-2-ol (**8**)

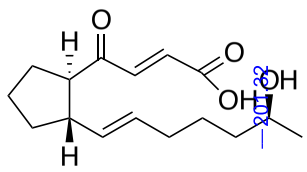


^{1}H NMR (300 MHz, $CDCl_3$)
(*E*)-4-((1*R*,2*S*)-2-((*S*,*E*)-6-hydroxyhept-1-en-1-yl)cyclopentyl)-4-oxobut-2-enoic acid (**10**)

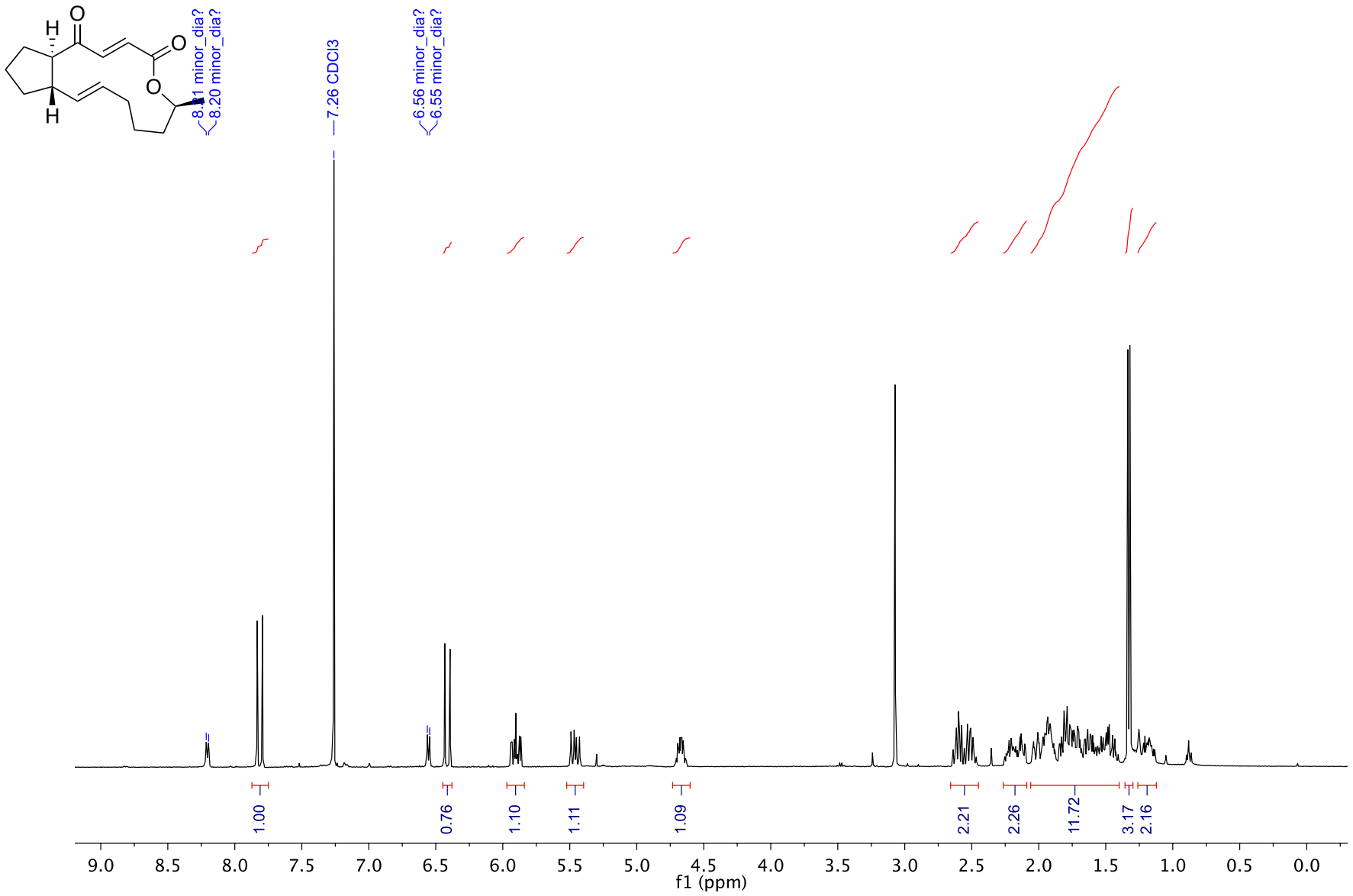




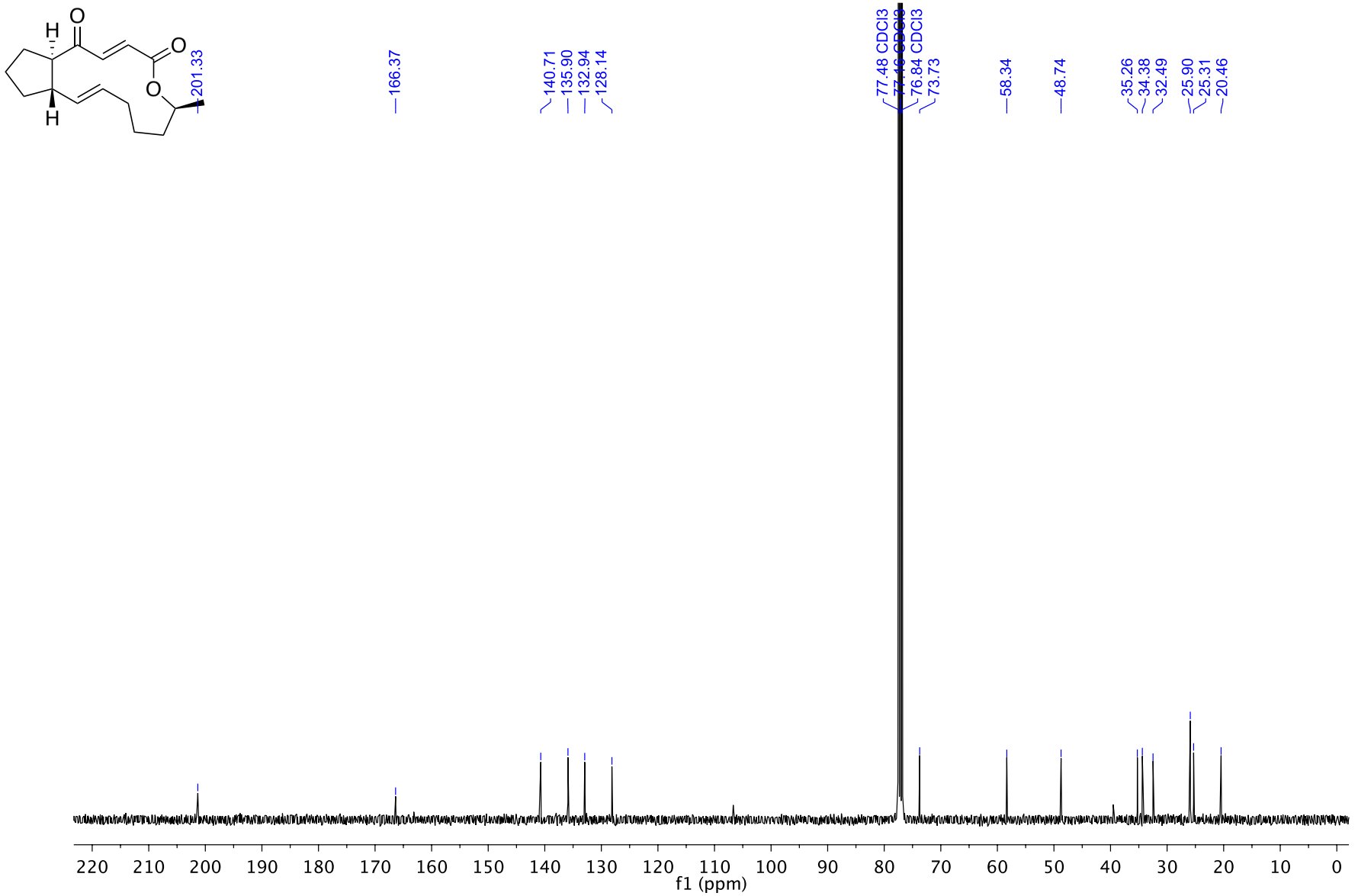
^{13}C NMR (75 MHz, $CDCl_3$)
(*E*)-4-((1*R*,2*S*)-2-((*S*,*E*)-6-hydroxyhept-1-en-1-yl)cyclopentyl)-4-oxobut-2-enoic acid (**10**)



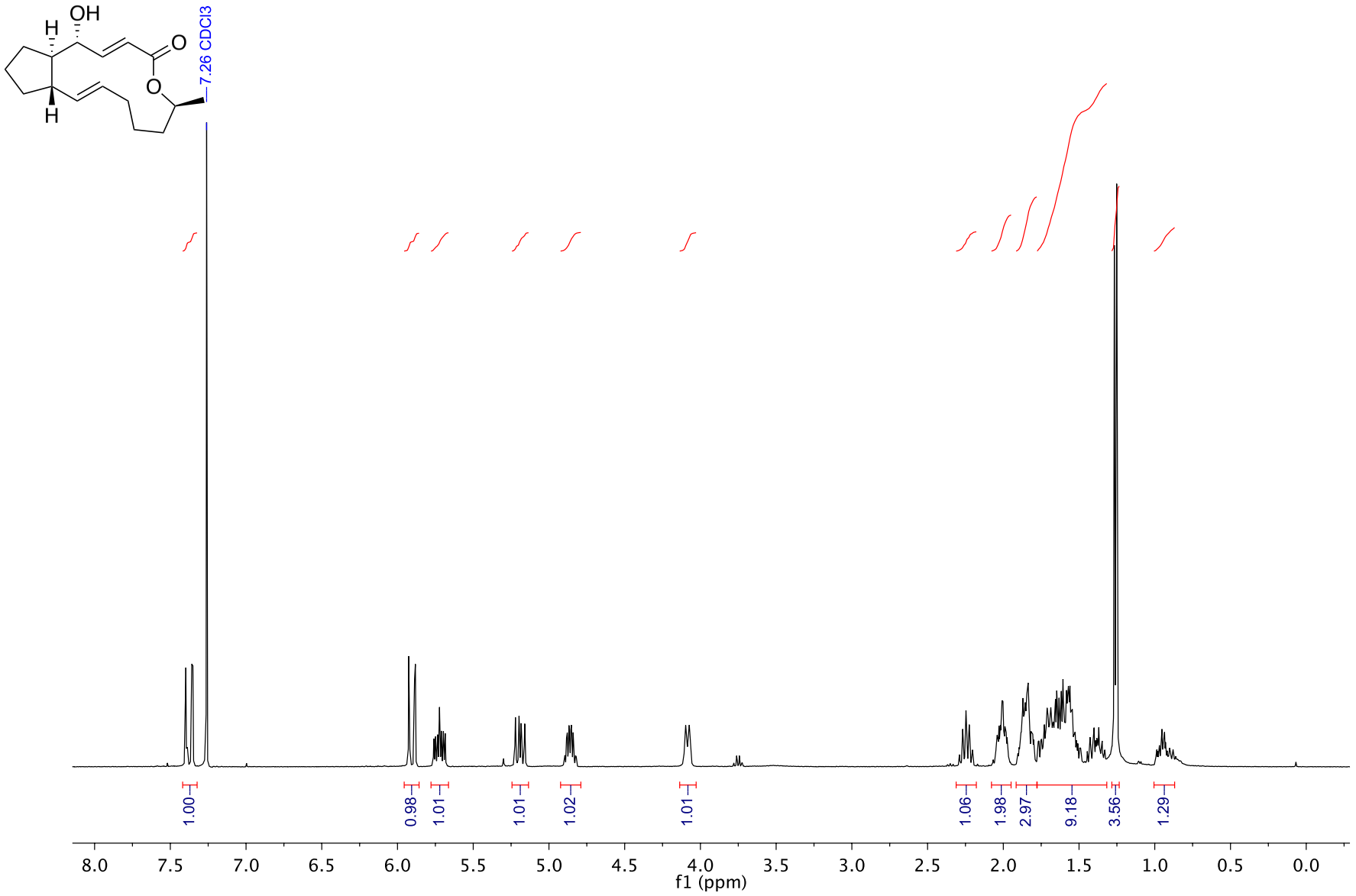
^{1}H NMR (300 MHz, $CDCl_3$)
4-dehydro-brefeldin C (**11**)



^{13}C NMR (75 MHz, $CDCl_3$)
4-dehydro-Brefeldin C (**11**)



^{1}H NMR (300 MHz, $CDCl_3$)
(+)-brefeldin C



^{13}C NMR (75 MHz, $CDCl_3$)
(+)-brefeldin C