# Synthesis and biological profiling of parthenolide ether analogs

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## Electronic Supplementary Information (ESI)

## Table of content

# 1 Enantiopure parthenolide ether analogs

The racemic parthenolide derivatives **6** and **7** were separated into their enantiomeris by means of preparative chiral-phase HPLC. After separation, their stereochemistry was tentatively assigned based on a comparison with the natural products (+)-costunolide (**3**) and its 1(10)*Z* isomer **SI-1** (Figure S1).[S1] These ten-membered germacranolides possess the same *trans* configured αMγB as well as the endocyclic double bond in (*E*) or (*Z*) configuration, makes the relationship to **6** and **7** reasonably close for an assignment by the sign of specific optical rotations.

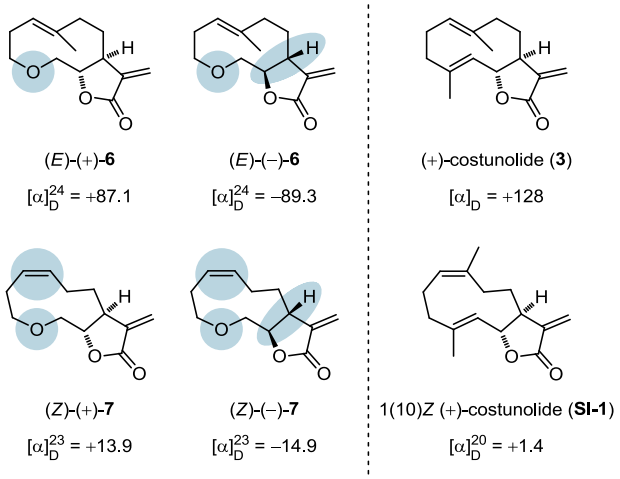



**Figure S1.** Structures of the pure enantiomers of the parthenolide ether analogs. Deviations from natural parthenolide's structure are marked. Stereochemical assignment based on the specific optical rotation of two related natural products.

With the exception of positive control PTL, all derivatives tested did not significantly affect the tubulin detyrosination level of axon tips. In addition, the mentioned compounds were screened in the context of growth rate acceleration of sensory nerves. Also here, varying concentrations of the compounds in between $0.5 \leq c \leq 50$ nM had no significant effect, with the exception of natural PTL (see main text and Figure S2).

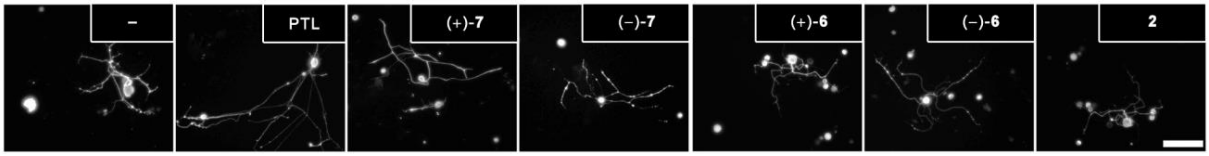



**Figure S2.** Representative pictures of dissociated sensory DRG neurons treated with DMSO (–), parthenolide (PTL), and parthenolide derivatives (–)-**6**, (+)-**6**, (–)-**7**, (–)-**7** and **2** stained with βIII-tubulin two days after culturing. Scale bar: 200 µm.

# 2 General information

## 2.1 Instrumentation

**NMR** spectra were recorded on one of the following Bruker machines: Avance I (250 MHz, probe: BBO), Fourier (300 MHz, probe: Dual $^{1}H/^{13}C$), Avance I (400 MHz, probe: BBO), Avance II [400 MHz, probes: BBFO, BBO (+ATM)], Avance III HD [500 MHz, probe: BBO (Prodigy)] or Avance III [600 MHz, probes: TCPI (+ATM), PAQXI (+ATM), BBO (+ATM)]. $^{1}H,^{13}C$ ASAP-HSQC and Multiplicity-edited ASAP-HSQC (denoted as HSQC/DEPT) spectra were recorded as described by Luy and co-workers.[S2] Chemical shifts ($\delta$) are expressed in parts per million (ppm) with respect to the solvent signal ($^{13}C$ NMR, $\delta$: $C_6D_6$ 128.06), the residual nondeuterated solvent signal ($^{1}H$ NMR, $\delta$: $C_6D_5H$ 7.16).[S3] Signals were assigned on the basis of 2D NMR experiments.

**RP-HPLC** analyses were conducted on a Shimadzu system fitted with a Macherey-Nagel EC 125/4 Nucleodur C18 Gravity column (5 µm, 125 × 10 mm ID). Linear MeCN/$H_2O$ gradients were employed at 1 ml/min flow rate. **Chiral-phase HPLC** analyses and separations were conducted on a Shimadzu system with an analytical Phenomenex Lux i-Amylose-1 column (5 µm, 250 × 4.6 mm ID) with guard cartridge, eluting with isocratic *n*-hexane/EtOH mixtures (see experimental procedures for details) at 1 ml/min flow rate.

High resolution mass spectra (**HRMS**) were recorded on one of the following machines: Bruker Maxis Impact (QTOF) in ESI mode, Thermo Scientific Q Exactive Plus (Orbitrap) in ESI or APCI mode or Thermo Q Exactive GC (Orbitrap) in EI mode.

**FT-IR** spectra were recorded on a Shimadzu IRAffinity-1 machine in ATR mode. The following notations indicate the intensity of the absorption bands: *s* = strong, *m* = medium, *w* = weak.

**Optical rotations** were recorded with a Jasco P-2000 polarimeter at 589 nm. The path length of the cuvette was $d$ = 10 mm. Specific rotations ($[\alpha]$) are expressed in deg × ml × $g^{-1}$ × $dm^{-1}$, but reported without the unit. Corresponding concentrations ($c$) are given in g/(100 ml).

## 2.2 Methods and materials (Chemistry)

Unless otherwise stated, all reactions and storage of anhydrous reagents/solvents were carried out using standard Schlenk techniques under a positive pressure of anhydrous $N_2$ or Ar. Analytical thin layer chromatography (**TLC**) was performed on silica gel 60 $F_{254}$ on aluminum sheets. Substances were detected by UV quenching (254 nm) or staining ($KMnO_4$ in aq. $K_2CO_3$ solution). **Silica gel** 60 with a mean particle size of 40–63 μm (standard conditions) or 15–40 μm (denoted) was used for flash column chromatography (approx. 0.3–0.5 bar positive pressure).[S4]

Reagents available from commercial sources were used without further purification, with the following exceptions: Anhydrous amines (**$Et_3N$**, **pyridine**, **2,6-lutidine**) were obtained by distillation from $CaH_2$. Anhydrous **PhMe** was obtained from a solvent purification system (HPLC grade solvents, activated $Al_2O_3$, $N_2$ atmosphere), prior to use. Anhydrous **$CH_2Cl_2$** was obtained by distillation from $CaH_2$. Anhydrous **$Et_2O$** and **THF** were obtained by distilling peroxide free (KOH) and pre-dried ($CaCl_2$) material from purple Na/benzophenone. **MeOH**, **DMF** and **MeCN** (HPLC grade) were dehydrated by treatment with 3 Å molecular sieves (min. 48 h).[S5] Anhydrous **HMPA** was obtained by distillation from $CaH_2$ under vacuum, followed by storage with activated 3 Å molecular sieves. **$C_6D_6$** was stored with activated 3 Å molecular sieves. **$CDCl_3$** was dehydrated by passing through a short plug of anhydrous, activated basic alumina directly before use.

Commercial, brown ***p*-benzoquinone** was dissolved in $CH_2Cl_2$ and washed with water. The organic layer was concentrated *in vacuo* and the residue was dissolved in boiling EtOH. Slow cooling to rt and then to –25 °C initiated crystallization. The yellow needles obtained after 15 h were collected, washed with cold EtOH (–25 °C) and hexanes (3×) and dried *in vacuo* (~1 mbar). **Methanesulfonyl chloride** was distilled from $P_2O_5$ under vacuum. **MeI** was dehydrated by passing through a short plug of anhydrous, activated basic alumina under $N_2$ atmosphere directly before use. **LiBr** was dried under vacuum ($10^{-2}$–$10^{-3}$ mbar) by slowly heating (+20°C/h) the solid to 160 °C and keeping it at this temperature for 5 h. Stock solutions in THF were prepared by stirring the anhydrous salt in anhydrous solvent, together with activated 3 Å molecular sieves for 1 h. **CuCN** was dried under vacuum ($10^{-2}$–$10^{-3}$ mbar) by heating the solid to 150 °C for 16 h.

**pH 7 phosphate buffer** (0.5 M) was prepared by dissolving $Na_3PO_4 \times 12H_2O$ (58.8 g, 144 mmol), $NaH_2PO_4$ (42.7 g, 356 mmol) and $NaN_3$ (113 mg, 1.74 mmol) in 900 ml water and filling up to a total volume of 1 l. **$Na_2EDTA$ solution** (0.5 M, pH 8) was prepared by suspending $Na_2EDTA \times 3H_2O$ (186 g, 0.5 mol) in 900 ml water and slowly adding NaOH

pellets until dissolution was complete and pH 8 was reached. It was filled up to a total volume of 1 l.

The concentration of *n*- and *t*-BuLi solutions was determined by threefold titration using 4-biphenyl acetic acid in anhydrous THF at room temperature.[S6]

The following substances were prepared according to the published procedures: α,β-epoxy aldehydes (±)-**SI-2**[S7] and (±)-**SI-3a,b**,[S8] Homoallyloxy acetaldehyde **SI-4**,[S9] Boronates (*Z*)-**15a,** (*Z*)-**15b**, and (*Z*)-**15c**,[S7] boronate (2*Z*)-**SI-5a,b**,[S10] homoallyl alcohol (±)-**SI-6**,[S7] Vinyl iodide (*E*)-**18**,[S11] lithium naphthalenide ($LiC_{10}H_8$),[S12] dihydroparthenolide (**2**).[S13]

## 2.3 Methods and materials (biology)

Cultures were prepared as described previously.[S14] DRG neurons were harvested from adult C57BL/6j mice as described previously.[S14] Isolated DRGs (T8–L6) were incubated in 0.25% trypsin/EDTA (GE Healthcare, Chalfont St Giles, UK) and 0.3% collagenase type IA (Sigma) in DMEM (Life Technologies, Carlsbad, US-CA) at 37 °C and 5% $CO_2$ for 45 min and mechanically dissociated. Cells were resuspended in DMEM containing 10% fetal bovine serum (GE Healthcare) and penicillin/streptomycin (500 U/ml; Merck Millipore, Billerica, US-MA) and cultured at 37 °C and 5% $CO_2$ on poly-D-lysine (PDL, 0.1 mg/ml, molecular weight <300,000 kDa; Sigma) and laminin (20 µg/ml; Sigma)-coated plates (Sarstedt, Germany). Cells were either treated with vehicle (DMSO), 1 nM (–)-parthenolide (Sigma-Aldrich, USA, MO), 0.5–50 nM (–)-**6**, 0.5–50 nM (+)-**6**, 0.5–50 nM (–)-**7**, 0.5–50 nM (–)-**7** or 0.5–50 nM **2**.

Axonal growth was determined 48 h upon incubation by fixation in 4% PFA (Sigma) and immunocytochemical staining with antibodies against βIII-tubulin (1:2,000; Covance, Princeton, US-NJ). Imaging and quantification of total axon length and neuron numbers per well were automatically performed with the Olympus VS120 microscope system (BD, Franklin Lakes, US-NJ) and ImageJ NeuriteTracer plugin, avoiding experimenter-induced quantification bias. Average axon length per neuron and neuron counts per experimental group were normalized to control groups. Data represent means ± SEM of 3 replicate wells per experiment and two independent experiments. Significances of intergroup differences were evaluated using either one- or two-way analysis of variance (ANOVA) followed by the Holm-Sidak *post hoc* test.

Microtubule detyrosination in axon tips was evaluated two days in culture using antibodies against βIII-tubulin (1:2,000; Covance) and detyrosinated tubulin (1:2,000; Millipore) as described previously.[S14] Axon tips were defined as the last 15 μm of βIII-tubulin positive neurite extensions and determined positive with a gray value above 30 after background subtraction. Data represent means ± SEM of three replicate wells with 20 tips per well from at least two independent experiments. Significances of intergroup differences were evaluated using either one-way analysis of variance (ANOVA) followed by Holm-Sidak *post hoc* test.

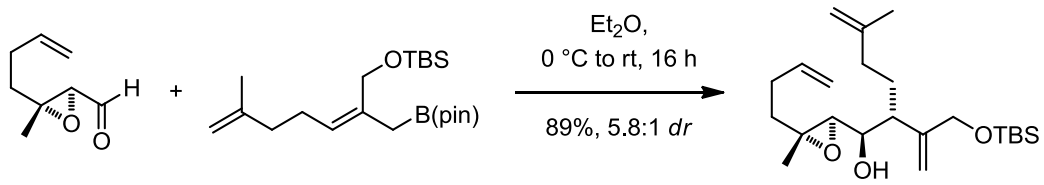
## 2.4 Abbreviations

αMγB = α-*exo*-methylene γ-butyrolactone, ASAP = Acceleration by Sharing Adjacent Polarization,[S15] Ar = aryl, brsm = (yield) based on recovered starting material, DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, DMF = dimethyl-formamide, DQF = double quantum filtered, dr = diastereomeric ratio, DRG = dorsal root ganglion, ee = enantiomeric excess, KHMDS = potassium hexamethyldisilazide, $LiC_{10}H_8$ = lithium naphthalenide, Ms = methanesulfonyl, MTBE = methyl *tert*-butyl ether, n.s. = not significant, *p*-BQ = *p*-benzoquinone, PE = petroleum ether (bp. 35–70 °C), pin = pinacolate [2,3-dimethylbutane-2,3-bis(olate)], PMB = *p*-methoxy benzyl, PTL = parthenolide, PS = phase sensitive, py = pyridine, rt = room temperature (20–25 °C), sat. = saturated, SEM = standard error mean, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TCP = tubulin carboxypeptidase, TEMPO = 2,2,6,6-tetra-methyl-piperidine-1-oxyl, THF = tetrahydrofuran, tub = tubulin.

# 3 Experimental

## 3.1 Preparation of RCM precursors for parthenolide synthesis studies

**(1*R**,2*R**)-1-[(2*R**,3*R**)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl]-2-{3-[(*tert*-butyldimethylsilyl)oxy)prop-1-en-2-yl}-5-methylhex-5-en-1-ol [(±)-12a]**




(±)-**SI-2** (*Z*)-**15a** (±)-**12a**

α,β-Epoxy aldehyde (±)-**SI-2** (56 mg, 0.41 mmol, 1.1 equiv.) was added to a stirred solution of boronate (*Z*)-**15a** (140 mg, 0.37 mmol, 1.0 equiv.) in anhydrous $Et_2O$ (1.3 ml) at 0 °C. The solution was allowed to reach rt within 2 h. After 14 h at rt (TLC control: PE/$Et_2O$ 7:1) the mixture was directly subjected to column chromatography (PE/MTBE 12:1, 2 × 20 cm) to obtain the homoallylic alcohol (±)-**12a** (110 mg, 0.28 mmol, 76 %) as a colorless oil. A second isomer was detected by HPLC–MS (5.8:1 dr major:minor), but not isolated.

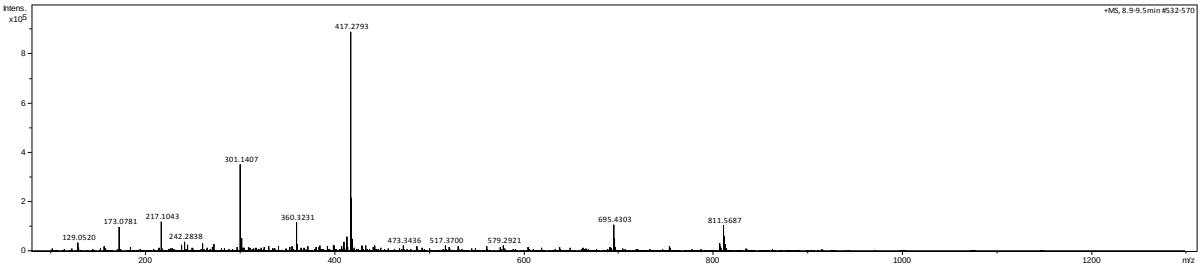
**TLC:** $R_f$ = 0.27 (PE/MTBE 15:1).

**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 5.78 (*ddt*, 1H, $^3J_{H,H}$ = 16.8, 10.2, 6.6 Hz, C(H)═), 5.23 (*s*, 1H, ═C(H)H'), 5.11 (*d*, 1H, $^4J_{H,H}$ = 1.7 Hz, ═C(H)H'), 5.03–4.92 (*m*, 2H, ═$CH_2$), 4.85–4.80 (*m*, 2H, ═$CH_2$), 4.12 (*dd*, 1H, $^{3,4}J_{H,H}$ = 12.3, 0.7 Hz, C(H)H'OSi), 3.98 (*d*, 1H, $^3J_{H,H}$ = 12.3 Hz, C(H)H'OSi), 3.51 (*ddd*, 1H, $^3J_{H,H}$ = 8.4, 6.2, 6.1 Hz, C(H)OH), 3.23 (*d*, 1H, $^3J_{H,H}$ = 6.1 Hz, C(H)OH), 2.78 (*d*, 1H, $^3J_{H,H}$ = 8.4 Hz, C(O)C(H), epoxide), 2.57–2.49 (*m*, 1H, C(H)C(R)═$CH_2$), 2.18–2.08 (*m*, 2H, $CH_2$), 2.06–1.92 (*m*, 3H, $CH_2$ + C(H)H'), 1.82–1.73 (*m*, 1H, C(H)H'), 1.71–1.59 (*m*, 4H, $CH_3$ + C(H)H'), 1.56–1.44 (*m*, 1H, C(H)H'), 1.33 (*s*, 3H, $CH_3$), 0.94 (*s*, 9H, $SiC(CH_3)_3$), 0.05–0.03 (*m*, 6H, $Si(CH_3)_2$).

**$^{13}$C{$^1$H} NMR** (101 MHz, $C_6D_6$): $\delta$ = 147.2 ($R_2C$═), 145.6 ($R_2C$═), 138.5 (C(H)═), 116.9 (═$CH_2$), 114.8 (═$CH_2$), 110.7 (═$CH_2$), 72.8 (C(H)OH), 65.9 ($CH_2OSi$), 64.9 (C(O)C(H), epoxide), 60.2 (C(O)C(H), epoxide), 50.1 (C(H)C(R)═$CH_2$), 38.4 ($CH_2$), 35.9 ($CH_2$), 29.9 ($CH_2$), 28.1 ($CH_2$), 26.0 ($SiC(CH_3)_3$), 22.5 ($CH_3$), 18.5 ($SiC(CH_3)_3$), 17.2 ($CH_3$), –5.4 ($Si(CH_3)CH_3$), –5.4 ($Si(CH_3)CH_3$),

**IR** (ATR): $\tilde{\nu}$ = 3068 (*w*), 2941 (*m*), 2832 (*m*), 2360 (*w*), 1533 (*w*), 1521 (*w*), 1449 (*m*), 1371 (*m*), 1304 (*m*), 1245 (*m*), 1062 (*m*), 1055 (*m*), 921 (*s*), 828 (*m*), 770 (*s*), 660 (*m*) $cm^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{23}H_{42}O_3Si$ [M+Na]$^+$ 417.2795; observed 417.2793.

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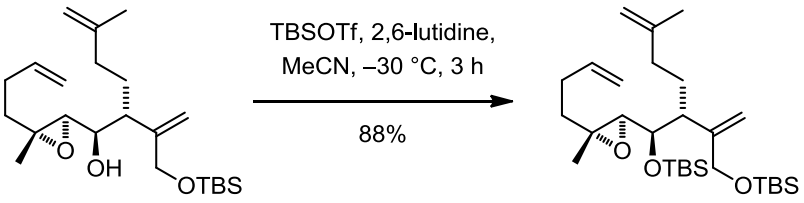
**(5*R**,6*R**)-5-[(2*R**,3*R**)-3-(but-3-en-1-yl)-3-methyloxiran-2-yl]-2,2,3,3,10,10,11,11-octamethyl-6-(3-methylbut-3-en-1-yl)-7-methylene-4,9-dioxa-3,10-disiladodecane [(±)-12b]**




(±)-**12a** (±)-**12b**

TBSOTf (0.04 ml, 50.2 mg, 0.19 mmol, 1.1 equiv.) was added to a stirred solution of 2,6-lutidine (0.06 ml, 56.2 mg, 0.52 mmol, 3.0 equiv.) in anhydrous MeCN (1.9 ml) at –30 °C. After 10 min a solution of alcohol (±)-**12a** (69 mg, 0.17 mmol, 1.0 equiv.) in anhydrous MeCN (1.5 ml) was added dropwise and the solution was allowed to stir for 3 h at this temperature (TLC control: PE/MTBE 2:1). The solution was added to a stirred sat. $NaHCO_3$ solution (10 ml) at 0 °C and extracted with MTBE (10 ml). The combined organic layers were washed consecutively with sat. $CuSO_4$ solution (3 × 5 ml), $Na_2EDTA$ solution (2 × 10 ml, 0.2 M, pH 8), and brine (2 × 10 ml). The organic extract was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography of the residue (PE/MTBE 50:1, 2 × 18 cm) provided TBS ether (±)-**12b** (76 mg, 0.15 mmol, 88%) as a colorless oil.

**TLC:** $R_f$ = 0.41 (PE/MTBE 40:1).

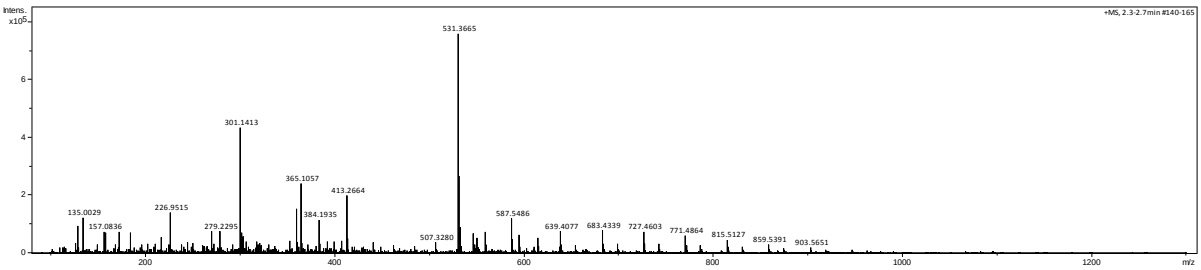
**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 5.76–5.62 (*m*, 2H, ═C(H)H' + C(H)═), 5.44 (*d*, 1H, $^2J_{H,H}$ = 2.1 Hz, ═C(H)H'), 5.00–4.89 (*m*, 2H, ═$CH_2$), 4.83 (*s*, 1H, ═C(H)H'), 4.80 (*s*, 1H, ═C(H)H'), 4.53–4.39 (*m*, 2H, $CH_2$OSi), 3.60 (*dd*, 1H, $^3J_{H,H}$ = 8.1, 3.0 Hz, C(H)OSi), 2.80 (*d*, 1H, $^3J_{H,H}$ = 8.1 Hz, C(O)C(H), epoxide), 2.45–2.37 (*m*, 1H, C(H)C(R)═$CH_2$), 2.18–1.85 (*m*, 5H, 2 × $CH_2$ + C(H)H'), 1.73–1.61 (*m*, 4H, $CH_3$ + C(H)H'), 1.58–1.37 (*m*, 2H, $CH_2$), 1.13 (*s*,

3H, $CH_3$), 1.01 (*s*, 9H, $SiC(CH_3)_3$), 0.96 (*s*, 9H, $SiC(CH_3)_3$), 0.15– 0.13 (*m*, 6H, $Si(CH_3)_2$), 0.05 (*s*, 3H, $Si(C\underline{H}_3)(CH_3)$'), –0.01 (*s*, 3H, $Si(CH_3)(C\underline{H}_3)$').

**$^{13}C\{^1H\}$ NMR** (75 MHz, $C_6D_6$): $\delta$ = 147.6 ($R_2C$═), 145.9 ($R_2C$═), 138.4 (C(H)═), 114.8 (═$CH_2$), 112.0 (═$CH_2$), 110.3 (═$CH_2$), 72.3 (C(H)OSi), 65.8 ($CH_2OSi$), 64.4 (C(O)<u>C</u>(H), epoxide), 61.1 (<u>C</u>(O)C(H), epoxide), 46.7 (<u>C</u>(H)C(R)═$CH_2$), 37.8 ($CH_2$), 35.9 ($CH_2$), 30.1 ($CH_2$), 29.5 ($CH_2$), 26.2 ($SiC(\underline{C}H_3)_3$), 26.1 ($SiC(\underline{C}H_3)_3$), 22.7 ($CH_3$), 18.7 ($Si\underline{C}(CH_3)_3$), 18.4 ($Si\underline{C}(CH_3)_3$), 17.5 ($CH_3$), –3.8 ($Si(CH_3)_2$), –4.5 ($Si(\underline{C}H_3)CH_3$), –5.1 ($Si(CH_3)\underline{C}H_3$).

**IR** (ATR): $\tilde{\nu}$ = 3076 (*w*), 2930 (*m*), 2856 (*m*), 2325 (*w*), 2192 (*w*), 2024 (*w*), 1783 (*w*), 1644 (*m*), 1459 (*m*), 1385 (*m*), 1253 (*m*), 1099 (*m*), 1005 (*m*), 834 (*s*), 773 (*s*), 670 (*m*) $cm^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{29}H_{56}O_3Si_2$ $[M+Na]^+$ 531.3660; observed 531.3665.

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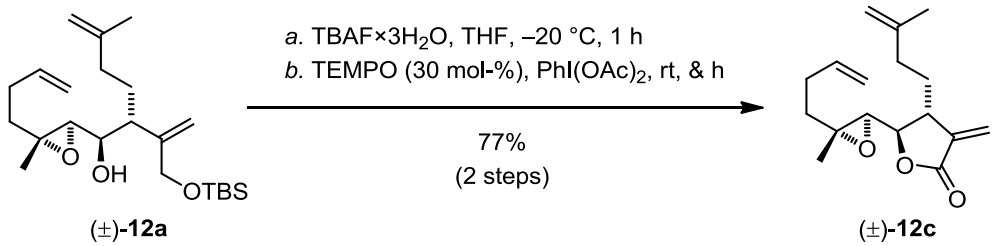
**(4*R**,5*R**)-5-[(2*R**,3*R**)-3-(but-3-en-1-yl)-3-methyloxiran-2-yl]-4-(3-methylbut-3-en-1-yl)-3-methylenedihydrofuran-2(*3H*)-one [(±)-12c]**




(±)-**12a** (±)-**12c**

To a stirred solution of mono TBS protected diol (±)-**12a** (87.0 mg, 0.22 mmol, 1.0 equiv.) in anhydrous THF (2.2 ml) at –20 °C was added a TBAF×$3H_2O$ solution (0.22 ml, 0.22 mmol, 1.0 equiv., 1.0 M in THF). The solution was kept at this temperature for 1 h (TLC control: PE/MTBE, 2:1) and then added to a mixture of sat. $NH_4Cl$ solution (10 ml) and MTBE (10 ml). The organic layer was separated, washed with sat. $NH_4Cl$ solution (2 × 10 ml) and brine (2 × 10 ml), dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography of the residue (PE/MTBE 1:1, 2 × 15 cm) delivered diol (±)-**SI-7** as colorless oil which was directly taken to the next step.

To a stirred solution of diol (±)-**SI-7** in anhydrous $CH_2Cl_2$ (2.2 ml) at 0 °C was added $PhI(OAc)_2$ (209 mg, 0.65 mmol, 3.0 equiv.) followed by TEMPO (9.7 mg, 65.3 µmol, 0.3 equiv.). After 6 h at this temperature (TLC control: PE/MTBE 2:1) sat. $NaHCO_3$ solution (10 ml) was added, followed by a $Na_2SO_3$ solution (10 ml) and MTBE (20 ml) and the biphasic mixture was stirred for 30 min. The organic layer was separated and washed with brine (20 ml). The organic extract was dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography of the residue (PE/MTBE 9:1, 2 × 20 cm) delivered lactone (±)-**12c** (47.0 mg, 0.17 mmol, 77% over 2 steps) as slightly yellow oil.

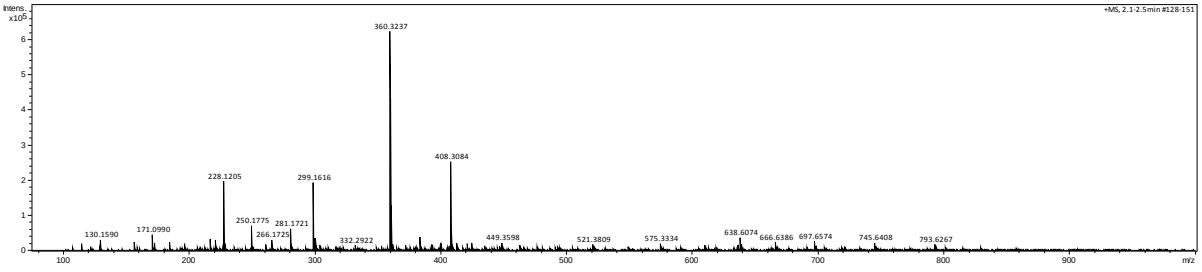
**TLC:** $R_f$ = 0.30 (PE/MTBE 9:1).

**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 6.20 (*d*, 1H, $^2J_{H,H}$ = 2.7 Hz, C(O)C═C(H)H'), 5.74–5.59 (*m*, 1H, C(H)═), 5.04 (*d*, 1H, $^2J_{H,H}$ = 2.7 Hz, C(O)C═C(H)H'), 5.00–4.96 (*m*, 1H, ═C(H)H'), 4.94 (*s*, 1H, ═C(H)H'), 4.79–4.73 (*m*, 2H, ═$CH_2$), 3.62 (*dd*, 1H, $^3J_{H,H}$ = 8.7, 4.5 Hz, C(H)OCO), 2.63 (*dtt*, 1H, $^3J_{H,H}$ = 8.7, 5.4, 2.5 Hz, C(H)C═$CH_2$), 2.35 (*d*, 1H, $^3J_{H,H}$ = 8.7 Hz, C(O)C(H), epoxide), 1.99–1.86 (*m*, 4H, 2 × $CH_2$), 1.56 (*s*, 3H, $CH_3$), 1.50–1.24 (*m*, 4H, 2 × $CH_2$), 1.09 (*s*, 3H, $CH_3$).

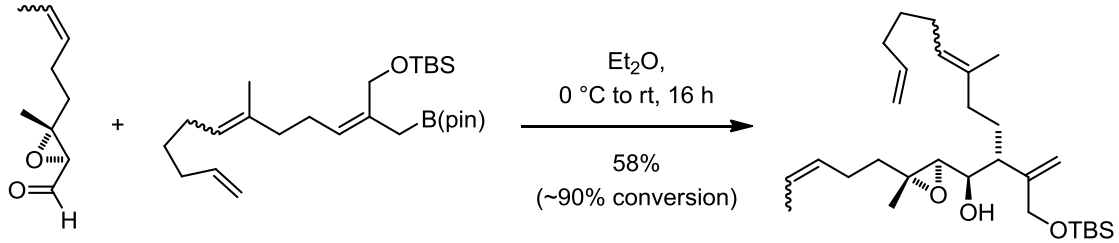
**$^{13}$C{$^1$H} NMR** (101 MHz, $C_6D_6$): $\delta$ = 169.1 ($CO_2$), 144.5 ($R_2C$═), 139.0 ($R_2C$═), 137.8 (C(H)═), 122.1 (C(O)C═$CH_2$), 115.2 (═$CH_2$), 111.1 (═$CH_2$), 80.4 (C(H)OCO), 63.0 (C(O)C(H), epoxide), 61.7 (C(O)C(H), epoxide), 43.4 (C(H)C═$CH_2$), 37.4 ($CH_2$), 34.4 ($CH_2$), 31.9 ($CH_2$), 29.4 ($CH_2$), 22.5 ($CH_3$), 16.8 ($CH_3$).

**IR** (ATR): $\tilde{\nu}$ = 3076 (*w*), 2930 (*w*), 2388 (*w*), 2047 (*w*), 1891 (*w*), 1768 (*s*), 1644 (*w*), 1449 (*w*), 1386 (*w*), 1263 (*m*), 1098 (*m*), 995 (*m*), 912 (*m*), 814 (*m*), 765 (*m*), 627 (*w*) cm$^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{17}H_{24}O_3$ $[M+Na]^+$ 299.1618; observed 299.1616.



**(1*R**,2*R**,*EZ*)-2-(3-((*tert*-Butyldimethylsilyl)oxy]prop-1-en-2-yl}-5-methyl-1-{(2*R**,3*R**)-3-methyl-3-[(*ZE*)-pent-3-en-1-yl]oxiran-2-yl}undeca-5,10-dien-1-ol [(±)-SI-8a,b,c,d]**




(±)-**SI-3a,b** (*Z*/*E* ~ 3:1) (2*Z*)-**SI-5a,b** (*E*/*Z* ~ 6:1) (±)-**SI-8a,b,c,d** (18:6:3:1)

α,β-Epoxy aldehyde (±)-**SI-3a,b** (315 mg, 2.04 mmol, 1.0 equiv., *Z*/*E* ~ 3:1) was added to a stirred solution of boronate (2*Z*)-**SI-5a,b** (875 mg, 1.95 mmol, 1.0 equiv., *E*/*Z* ~ 6:1) in anhydrous $Et_2O$ (3.0 ml) at 0 °C. The solution was allowed to reach rt within 4 h. After 24 h (TLC control: PE/MTBE 8:1) pH 7 buffer (20 ml) was added and the mixture was stirred for 10 min. The organic layer was separated and washed with brine (20 ml), dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. Column chromatography of the residue (PE/MTBE 8:1, 5 × 20 cm) delivered homoallyl alcohol (±)-**SI-8a,b,c,d** (545 mg, 1.14 mmol, 58%) as a colorless oil and inseparable mixture of 4 diastereomers (18:6:3:1 ratio, GC–MS).

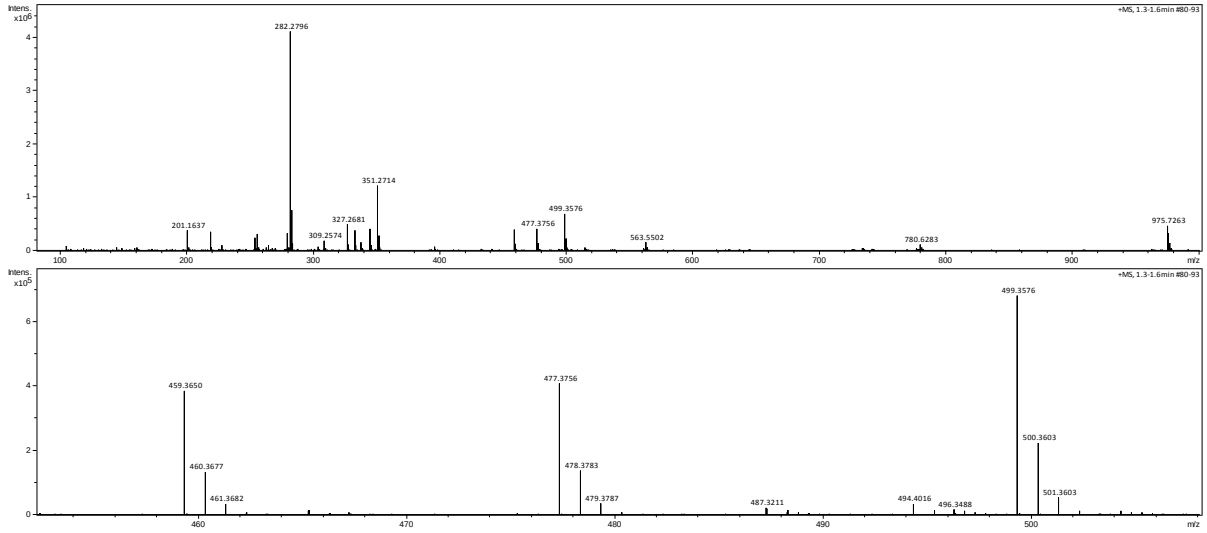
**TLC:** $R_f$ = 0.42 (PE/MTBE 8:1).

**$^1$H NMR** (300 MHz, $C_6D_6$, mixture of isomers): $\delta$ = 5.85–5.69 (*m*, 1H, C(H)═), 5.47–5.33 (*m*, 2H, 2 × C(H)═), 5.26–5.19 (*m*, 2H, ═C(H)H' + C(H)═), 5.13 (*s*, 1H, ═C(H)H'), 5.07–4.95 (*m*, 2H, ═$CH_2$), 4.18–4.10 (*m*, 1H, C(H)H'OSi), 4.05–3.96 (*m*, 1H, C(H)H'OSi), 3.51 (*ddd*, 1H, $^3J_{H,H}$ = 8.3, 6.3, 6.1 Hz, C(H)OH), 3.25–3.16 (*m*, 1H, OH), 2.82–2.76 (*m*, 1H, HC(O)C, epoxide), 2.58–2.49 (*m*, 1H, HCC═$CH_2$), 2.21–1.93 (*m*, 8H, 4 × $CH_2$), 1.84–1.68 (*m*, 2H, $CH_2$), 1.67–1.60 (*m*, 1H, C(H)H'), 1.58–1.54 (*m*, 3H, $CH_3$), 1.52–1.43 (*m*, 4H, C(H)H' + $CH_3$), 1.43–1.36 (*m*, 2H, $CH_2$), 1.36–1.32 (*m*, 3H, $CH_3$), 0.92 (*s*, 9H, SiC($CH_3$)$_3$), 0.03 (*s*, 6H, Si($CH_3$)$_2$).

**$^{13}$C{$^1$H} NMR** (75 MHz, $C_6D_6$, major diastereomer): $\delta$ = 147.4 ($R_2C$═), 139.1 (C(H)═), 135.2 ($R_2C$═), 130.3 (C(H)═), 125.2 (C(H)═), 124.3 (C(H)═), 116.8 (═$CH_2$), 114.7 (═$CH_2$), 72.8 (C(H)OH), 65.9 ($CH_2$OSi), 65.0 (HC(O)C, epoxide), 60.4 (HC(O)C, epoxide), 50.1 (HCC═$CH_2$), 38.9 ($CH_2$), 37.9 ($CH_2$), 33.8 ($CH_2$), 29.5 ($CH_2$), 28.6 ($CH_2$), 27.8 ($CH_2$), 26.1 (SiC($CH_3$)$_3$), 23.2 ($CH_2$), 18.5 (SiC($CH_3$)$_3$), 17.3 ($CH_3$), 16.1 ($CH_3$), 12.8 ($CH_3$), –5.3 (Si($CH_3$)($CH_3$)'), –5.4 (Si($CH_3$)($CH_3$)'),

**IR** (ATR): $\tilde{\nu}$ = 3404 (*w*), 2929 (*m*), 2857 (*m*), 2325 (*w*), 2207 (*w*), 2135 (*w*), 2040 (*w*), 1958 (*w*), 1778 (*w*), 1641 (*w*), 1455 (*m*), 1384 (*m*), 1253 (*m*), 1044 (*m*), 908 (*m*), 835 (*s*), 776 (*s*), 677 (*m*) $cm^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{29}H_{52}O_3Si$ $[M+H]^+$ 477.3758; observed 477.3756.

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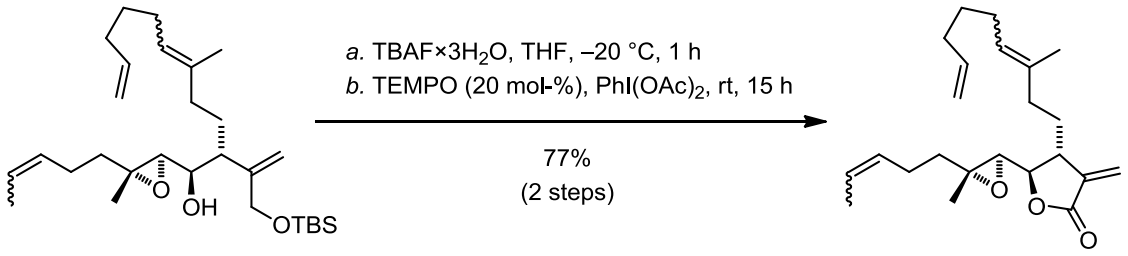
**(4*R**,5*R**)-5-[(2*R**,3*R**)-3-methyl-3-(pent-3-en-1-yl)oxiran-2-yl]-3-methylene-4-(3-methylnona-3,8-dien-1-yl)dihydrofuran-2(*3H*)-one [(±)-12d]**




(±)-**7a,b,c,d**
(18:6:3:1)

(±)-**12d**

To a stirred solution of mono TBS protected diol (±)-**SI-8a,b,c,d** (486 mg, 1.02 mmol, 1.0 equiv.) in anhydrous THF (10.0 ml) at –20 °C was added a TBAF×$3H_2O$ solution (1.1 ml, 1.1 mmol, 1.1 equiv., 1.0 M in THF). After 1 h at this temperature (TLC control: PE/MTBE 1:1) the solution was diluted with MTBE (40 ml) and added to a sat. $NH_4Cl$ solution (20 ml). Then, the organic layer was separated and washed with brine (3 × 20 ml), dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography of the residue (PE/MTBE 1:1, 2 × 18 cm) delivered diol (±)-**SI-9a,b,c,d** as colorless oil, which was used directly in the following step.

To a stirred solution of the crude diol (±)-**SI-9a,b,c,d** in anhydrous $CH_2Cl_2$ (9 ml) at rt was added $PhI(OAc)_2$ (860 mg, 2.67 mmol, 3.0 equiv.) followed by TEMPO (28.2 mg, 0.18 mmol, 0.2 equiv.). After 15 h at this temperature (TLC control: PE/$Et_2O$, 7:1) sat. $Na_2S_2O_3$ solution (5 ml) and water (5 ml) were added, and the biphasic mixture was stirred for 30 min. The organic layer was separated and washed with sat. $Na_2S_2O_3$ solution (3 × 10 ml) and brine (10 ml). The organic extract was dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography of the residue (PE/$Et_2O$ 7:1, 2 × 17 cm) delivered an inseparable mixture of lactone (±)-**12d** and co-eluted TEMPO. The latter was removed by sublimation at rt under vacuum ($10^{-2}$–$10^{-3}$ mbar, 24 h) to give rise to the lactone (±)-**12d** (47.0 mg, 0.17 mmol, 77%) as a slightly yellow oil and inseparable mixture of four diastereomers (18:6:3:1).

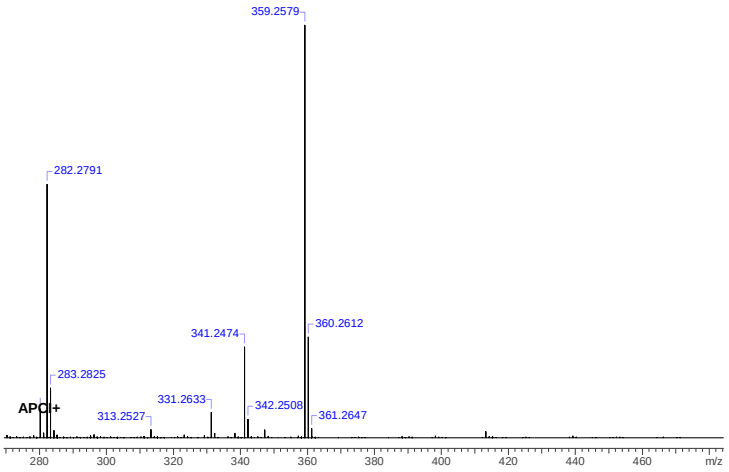
**TLC:** $R_f$ = 0.38 (PE/$Et_2O$ 7:1)

**$^1$H NMR** (300 MHz, $C_6D_6$, mixture of isomers): $\delta$ = 6.19 (*d*, 1H, $^2J_{H,H}$ = 2.6 Hz, =C(H)H'), 5.76 (*ddt*, 1H, $^3J_{H,H}$ = 16.9, 10.2, 6.7 Hz, C(H)=), 5.50–5.39 (*m*, 1H, C(H)=), 5.36–5.26 (*m*, 1H, C(H)=), 5.18 (*t*, 1H, $^3J_{H,H}$ = 6.7 Hz, C(H)=), 5.08–4.95 (*m*, 3H, =C(H)H' + =C$H_2$), 3.67 (*dd*, 1H, $^3J_{H,H}$ = 8.6, 4.4 Hz, HCOC=O), 2.71–2.56 (*m*, 1H, HCC=$CH_2$), 2.44–2.38 (*m*, 1H, HC(O)C, epoxide), 2.07–1.84 (*m*, 8H, 4 × $CH_2$), 1.51–1.21 (*m*, 12H, 3 × $CH_2$ + 2 × $CH_3$), 1.15–1.11 (*m*, 3H, $CH_3$).

**$^{13}$C{$^1$H} NMR** (75 MHz, $C_6D_6$, major diastereomer assigned): $\delta$ = 169.1 (C=O), 139.1 (OC(O)C=), 139.0 (C(H)=), 134.1 ($R_2$C=), 129.6 (C(H)=), 125.9 (C(H)=), 124.8 (C(H)=), 122.0 (=$CH_2$), 114.8 (=$CH_2$), 80.5 (HCOC=O), 63.1 (HC(O)C, epoxide), 61.8 (HC(O)C, epoxide), 43.5 (HCC=$CH_2$), 38.1 ($CH_2$), 36.5 ($CH_2$), 33.7 ($CH_2$), 32.5 ($CH_2$), 29.4 ($CH_2$), 27.7 ($CH_2$), 22.8 ($CH_2$), 16.9 ($CH_3$), 16.0 ($CH_3$), 12.8 ($CH_3$).

**IR** (ATR): $\tilde{\nu}$ = 2925 (*m*), 2857 (*m*), 1771 (*s*), 1640 (*w*), 1449 (*m*), 1386 (*m*), 1264 (*m*), 1101 (*m*), 997 (*m*), 909 (*m*), 813 (*m*), 766 (*m*), 691 (*m*) $cm^{-1}$.

**HRMS** (APCI, Orbitrap): m/z calc'd for $C_{23}H_{34}O_3$ $[M+H]^+$ 359.2581; observed 359.2580.

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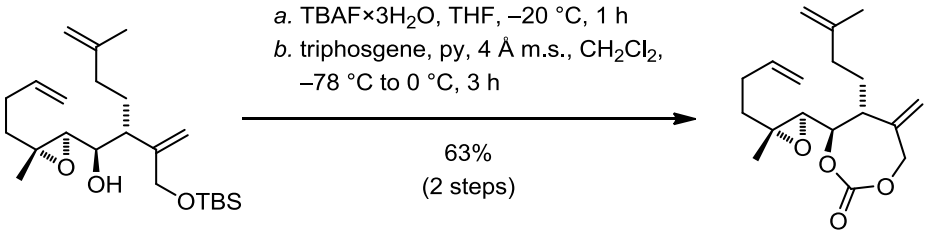
**(4*R**,5*R**)-4-[(2*R**,3*R**)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl]-5-(3-methylbut-3-en-1-yl)-6-methylene-1,3-dioxepan-2-one [(±)-12e]**




(±)-**12a** (±)-**12e**

According to the procedure described for the synthesis of lactone (±)-**12c**, 25 mg (63.3 µmol) of homoallyl alcohol (±)-**12a** was treated with TBAF×3$H_2O$ to obtain diol (±)-**SI-7**, which was processed further.

Diol (±)-**SI-7** was dissolved in anhydrous $CH_2Cl_2$ (0.8 ml) with stirring. Powdered, activated 4 Å molecular sieve (18 mg) was added and the suspension was cooled to –78 °C. Then, anhydrous pyridine (43.0 µl, 42.2 mg, 0.53 mmol, 10.0 equiv.) was added, followed by a solution of triphosgene (23.8 mg, 80.1 µmol, 1.5 equiv.) in anhydrous $CH_2Cl_2$ (0.4 ml). The reaction mixture was allowed to warm to 0 °C within 3 h (TLC control: PE/MTBE 6:1) and kept at this temperature for additional 15 min. pH 7 phosphate buffer (1.0 ml) was added and stirring was continued for 30 min. Next, the suspension was filtered through a plug of Celite ($CH_2Cl_2$, d × h = 1 × 2 cm) and the filtrate was diluted with $CH_2Cl_2$ to a final volume of 20 ml, followed by sequential washing with sat. $NaHCO_3$ solution (2 × 10 ml) and brine (20 ml). The organic extract was dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography of the residue (PE/MTBE 3:1, 1 × 15 cm) delivered carbonate (±)-**12e** (12.2 mg, 39.8 µmol, 63% over 2 steps) as colorless oil.

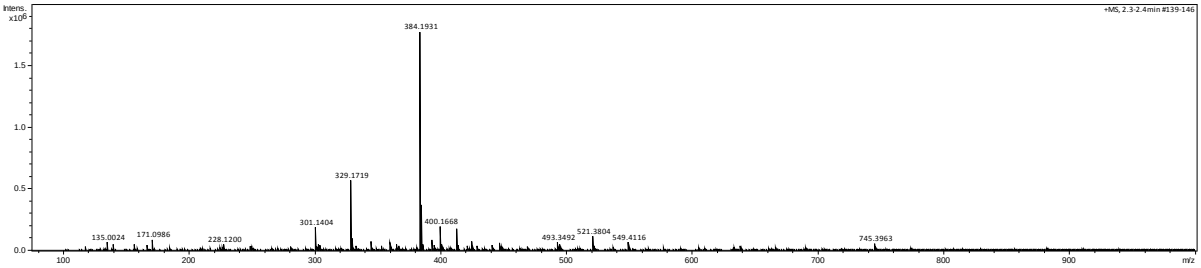
**TLC:** $R_f$ = 0.48 (PE/MTBE 3:1).

**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 5.68 (*ddt*, 1H, $^3J_{H,H}$ = 16.9, 10.3, 6.5 Hz, C(H)═), 5.02–4.91 (*m*, 2H, ═$CH_2$), 4.82–4.68 (*m*, 4H, 2 × ═$CH_2$), 4.03 (*d*, 1H, $^2J_{H,H}$ = 12.1 Hz, C(H)H'OSi), 3.85 (*dd*, 1H, J = 8.3, 5.7 Hz, C(H)OC═O), 3.78 (*dd*, 1H, $^{2,4}J_{H,H}$ = 11.9, 0.7 Hz, C(H)H'OSi), 2.84 (*d*, 1H, $^3J_{H,H}$ = 8.3 Hz, C(O)CH, epoxide), 2.47–2.38 (*m*, 1H, C(H)C(R)═$CH_2$), 2.11–1.97 (*m*, 2H, $CH_2$), 1.75–1.44 (*m*, 7H, 2 × $CH_2$ + $CH_3$), 1.42–1.23 (*m*, 5H, $CH_2$ + $CH_3$).

**$^{13}$C{$^1$H} NMR** (75 MHz, $C_6D_6$): $\delta$ = 151.9 ($O_2C$═O), 144.5 ($R_2C$═), 140.1 ($R_2C$═), 137.9 (C(H)═), 122.3 (═$CH_2$), 115.1 (═$CH_2$), 111.2 (═$CH_2$), 81.1 (C(H)OC═O), 70.2 ($CH_2O$), 61.3 (C(O)CH, epoxide), 61.1 (C(O)CH, epoxide), 48.2 (C(H)C(R)═$CH_2$), 37.7 ($CH_2$), 35.0 ($CH_2$), 29.4 ($CH_2$), 27.3 ($CH_2$), 22.4 ($CH_3$), 17.0 ($CH_3$).

**IR** (ATR): $\tilde{\nu}$ = 3485 (*w*), 3078 (*w*), 2928 (*m*), 2859 (*m*), 2362 (*w*), 2328 (*w*), 1762 (*s*), 1646 (*m*), 1511 (*w*), 1453 (*m*), 1385 (*m*), 1312 (*m*), 1259 (*m*), 1167 (*s*), 1060 (*s*), 994 (*m*), 914 (*s*), 805 (*m*), 737 (*m*), 702 (*m*), 637 (*m*) $cm^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{18}H_{26}O_4$ $[M+Na]^+$ 329.1723; observed 329.1719.

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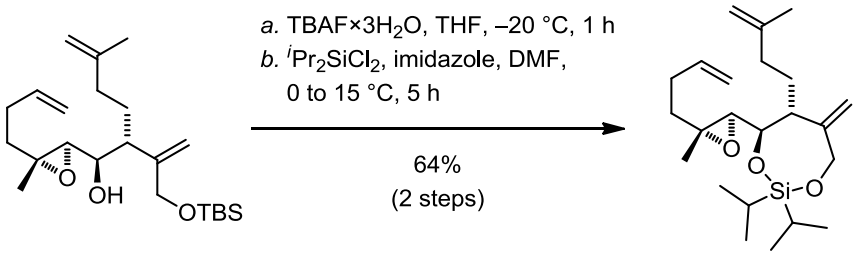
**(4*R**,5*R**)-4-[(2*R**,3*R**)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl]-2,2-diisopropyl-5-(3-methylbut-3-en-1-yl)-6-methylene-1,3,2-dioxasilepane [(±)-12f]**




(±)-**12a** (±)-**12f**

According to the procedure described for the synthesis of lactone (±)-**12c**, 25 mg (63.3 µmol) of homoallyl alcohol (±)-**12a** was treated with TBAF×3$H_2O$ to obtain diol (±)-**SI-7**, which was processed further.

Diol (±)-**SI-7** was dissolved in anhydrous DMF (0.6 ml) with stirring and cooled to 0 °C. Imidazole (14.6 mg, 0.21 mmol, 4.0 equiv.) was added, followed by $^{i}Pr_2SiCl_2$ (11.6 µl, 11.9 mg, 64.1 µmol, 1.2 equiv.). The solution was allowed to reach 15 °C within 2 h and kept at this temperature for additional 3 h (TLC control: PE/MTBE 6:1). The reaction mixture was again cooled to 0 °C, pH 7 phosphate buffer (5 ml) and MTBE (5 ml) were added and stirring was continued for 30 min at 0 °C. The organic layer was separated, sequentially washed with sat. $NH_4Cl$ solution (3 × 10 ml) and brine (10 ml), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography of the residue (PE/MTBE 20:1, 1 × 30 cm) delivered cyclic dialkoxysilane (±)-**12f** (18.0 mg, 40.7 µmol, 76%) as colorless oil.

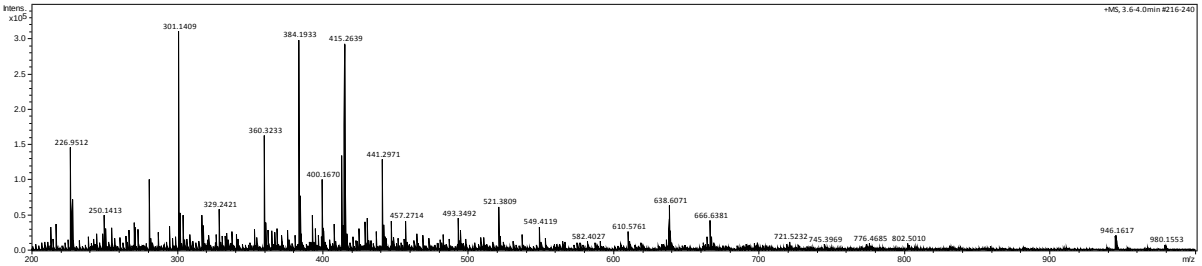
**TLC:** $R_f$ = 0.53 (PE/MTBE 15:1).

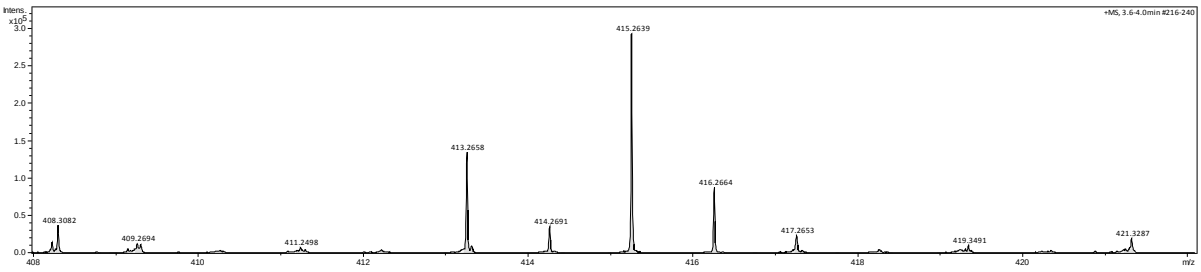
**$^{1}$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 5.76 (*ddt*, 1H, $^{3}J_{H,H}$ = 16.8, 10.2, 6.6 Hz, C(H)═), 5.05–4.92 (*m*, 4H, 2 × ═$CH_2$), 4.84–4.77 (*m*, 2H, ═$CH_2$), 4.37 (*d*, 1H, $^{3}J_{H,H}$ = 12.1 Hz, C(H)H'OSi), 4.18 (*d*, 1H, $^{3}J_{H,H}$ = 12.2 Hz, C(H)H'OSi), 3.67 (*dd*, 1H, $^{3}J_{H,H}$ = 8.5, 6.7 Hz, C(H)OSi), 2.89 (*d*, 1H, $^{3}J_{H,H}$ = 8.6 Hz, C(O)CH, epoxide), 2.67 (*ddd*, 1H, $^{3}J_{H,H}$ = 10.7, 6.6, 3.8 Hz, C(H)C(R)═$CH_2$), 2.20–2.11 (*m*, 2H, $CH_2$), 2.09–1.99 (*m*, 1H, C(H)H'), 1.97–1.83 (*m*, 2H, $CH_2$), 1.80–1.68 (*m*, 1H, C(H)H'), 1.65 (*s*, 3H, $CH_3$), 1.60–1.54 (*m*, 2H, $CH_2$), 1.30 (*s*, 3H, $CH_3$), 1.18–1.12 (*m*, 12H, 2 × HC($CH_3$)$_2$), 1.12–1.01 (*m*, 2H, 2 × HC($CH_3$)$_2$).

**$^{13}$C{$^{1}$H} NMR** (75 MHz, $C_6D_6$): $\delta$ = 147.5 ($R_2C$═), 145.4 ($R_2C$═), 138.3 (C(H)═), 117.7 (═$CH_2$), 114.9 (═$CH_2$), 110.8 (═$CH_2$), 77.2 (C(H)OSi), 68.3 ($CH_2OSi$), 65.1 (C(O)CH, epoxide), 60.2 (C(O)CH, epoxide), 51.2 (C(H)C(R)═$CH_2$), 38.2 ($CH_2$), 35.7 ($CH_2$), 29.7 ($CH_2$), 27.9 ($CH_2$), 22.5 ($CH_3$), 17.8 ($CH_3$), 17.7 (C($CH_3$)($CH_3$)'), 17.6 (C($CH_3$)($CH_3$)'), 17.1 (C($CH_3$)$_2$), 14.1 (HC($CH_3$)$_2$), 13.6 (HC($CH_3$)$_2$).

**IR** (ATR): $\tilde{\nu}$ = 3076 (*w*), 2925 (*s*), 2863 (*s*), 2364 (*w*), 2329 (*w*), 1828 (*w*), 1736 (*m*), 1645 (*m*), 1510 (*w*), 1462 (*m*), 1382 (*m*), 1253 (*m*), 1090 (*s*), 993 (*m*), 913 (*s*), 885 (*s*), 770 (*m*), 693 (*m*) cm$^{-1}$.

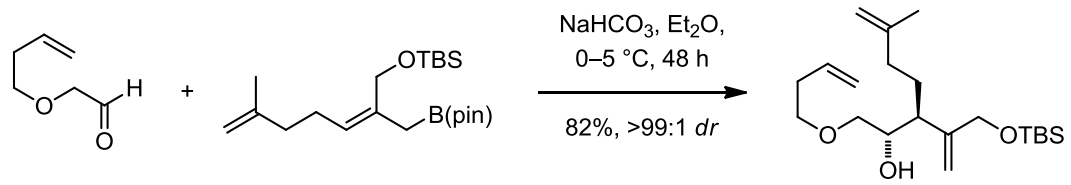
**HRMS** (ESI, TOF): *m/z* calc'd for $C_{23}H_{40}O_3Si$ [M+Na]$^{+}$ 415.2639; observed 415.2639.






## 3.2 Syntheses of parthenolide ether analogs

**(2*R**,3*R**)-1-(But-3-en-1-yloxy)-3-{3-[(*tert*-butyldimethylsilyl)oxy]prop-1-en-2-yl}-6-methylhept-6-en-2-ol [(±)-SI-10]**




**SI-4** (*Z*)-**15a** (±)-**SI-10**

Homoallyloxy acetaldehyde **SI-4** (571 mg, 5.0 mmol, 2.5 equiv.) was added to a stirred suspension of boronate (*Z*)-**15a** (761 mg, 2.0 mmol, 1.0 equiv.) and $NaHCO_3$ (8.4 mg, 0.1 mmol, 0.05 equiv.) in anhydrous $Et_2O$ (20 ml) at 0 °C. After 48 h at 0–5 °C (TLC control: PE/$Et_2O$, 7:1) the mixture was directly subjected to column chromatography (PE/$Et_2O$ 3:1, 3 × 15 cm) to obtain the homoallyl alcohol (±)-**SI-10** (601 mg, 1.63 mmol, 82%) as a colorless oil.

**TLC:** $R_f$ = 0.34 (PE/$Et_2O$ 3:1).

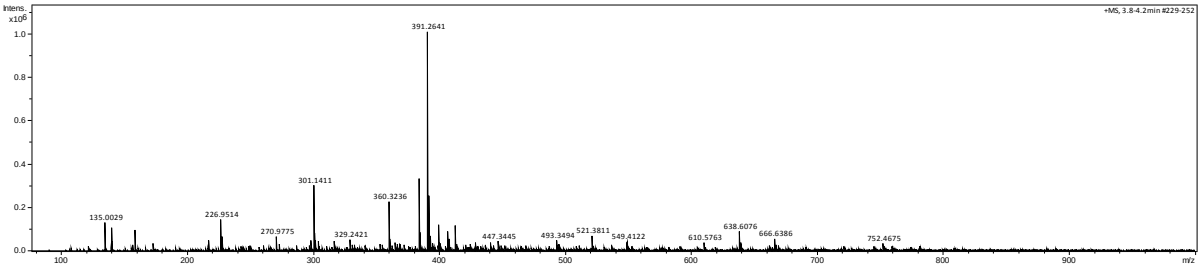
**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 5.76 (*ddt*, 1H, $^3J_{H,H}$ = 17.0, 10.3, 6.7 Hz, C(H)═), 5.39–5.37 (*m*, 1H, ═C(H)H'), 5.08–4.97 (*m*, 3H, ═C(H)H' + ═$CH_2$), 4.82 (*s*, 2H, ═$CH_2$), 4.27 (*d*, 1H, $^3J_{H,H}$ = 13.9 Hz, C(H)H'OSi), 4.11 (*d*, 1H, $^3J_{H,H}$ = 13.9 Hz, C(H)H'OSi), 3.86–3.76 (*m*, 1H, C(H)OH), 3.35 (*d*, 2H, $^3J_{H,H}$ = 5.8 Hz, $CH_2O$), 3.32–3.21 (*m*, 2H, $CH_2O$), 2.80 (*d*, 1H, $^3J_{H,H}$ = 4.6 Hz, OH), 2.38–2.29 (*m*, 1H, C(H)C(R)═$CH_2$), 2.22 (*d*, 1H, $^3J_{H,H}$ = 6.7 Hz, C(H)H'), 2.18 (*d*, 1H, $^3J_{H,H}$ = 6.2 Hz, C(H)H'), 2.11–1.93 (*m*, 2H, $CH_2$), 1.81–1.71 (*m*, 2H, $CH_2$), 1.66 (*s*, 3H, $CH_3$), 0.98 (*s*, 9H, $SiC(CH_3)_3$), 0.08 (*s*, 6H, $Si(CH_3)_2$).

**$^{13}$C{$^1$H} NMR** (101 MHz, $C_6D_6$): $\delta$ = 148.1 ($R_2C$═), 145.8 ($R_2C$═), 135.7 (C(H)═), 116.4 (═$CH_2$), 113.4 (═$CH_2$), 110.5 (═$CH_2$), 74.0 (C(H)OH), 72.6 ($CH_2O$), 70.7 ($CH_2O$), 65.6

($CH_2O$), 46.7 ($\underline{C}(H)C(R)=CH_2$), 36.0 ($CH_2$), 34.7 ($CH_2$), 28.5 ($CH_2$), 26.1 ($SiC(\underline{C}H_3)_3$), 22.6 ($CH_3$), 18.6 ($Si\underline{C}(CH_3)_3$), –5.2 ($Si(\underline{C}H_3)(CH_3)$'), –5.3 ($Si(CH_3)(\underline{C}H_3)$').

**IR** (ATR): $\tilde{\nu}$ = 3840 (*w*), 3488 (*w*), 3412 (*w*), 3102 (*m*), 2842 (*m*), 2620 (*m*), 2333 (*w*), 1638 (*w*), 1478 (*w*), 1307 (*m*), 1355 (*w*), 1240(*m*), 1148 (*s*), 985 (*m*), 886 (*s*), 752 (*s*), 659 (*m*) $cm^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{21}H_{40}O_3Si\,[M+Na]^+$ 391.2639; observed 391.2641.

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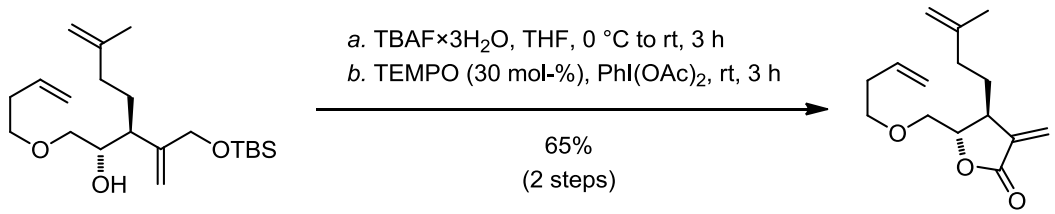
**(4*S**,5*S**)-5-[(But-3-en-1-yloxy)methyl]-4-(3-methylbut-3-en-1-yl)-3-methylenedihydrofuran-2(*3H*)-one [(±)-8]**




(±)-**SI-10** (±)-**8**

To a stirred solution of homoallyl alcohol (±)-**SI-10** (0.50 g, 1.36 mmol, 1.0 equiv.) in anhydrous THF (14 ml) at 0 °C was added a TBAF×$3H_2O$ solution (1.50 ml, 1.50 mmol, 1.1 equiv., 1.0 M in THF). The solution was allowed to reach rt within 30 min. After 4 h at rt (TLC control: PE/$Et_2O$, 2:1) the solution was diluted with $Et_2O$ (50 ml) and added to a sat. $NH_4Cl$ solution (30 ml). The organic layer was separated and washed with sat. $NH_4Cl$ solution (2 × 15 ml) and brine (30 ml), dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The residue was filtered through a plug of silica gel ($Et_2O$/PE 3:2, d × h = 4 × 4 cm) to obtain diol (±)-**SI-11** as colorless oil which was directly processed further.

To a stirred solution of the crude diol (±)-**SI-11** in anhydrous $CH_2Cl_2$ (20 ml) at rt was added $PhI(OAc)_2$ (1.25 g, 3.89 mmol, 3.0 equiv.) followed by TEMPO (41.0 mg, 0.26 mmol, 0.2 equiv.). After 10 h at rt (TLC control: PE/$Et_2O$ 1:1) a sat. NaHCO3 solution (10 ml), followed by a $Na_2SO_3$ solution (10 ml) was added and the biphasic mixture was stirred for

30 min. The organic layer was separated and washed with brine (20 ml). The organic extract was dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography of the residue (PE→PE/MTBE 6:1, 2 × 20 cm) delivered the lactone (±)-**8** (218 mg, 0.87 mmol, 65% over 2 steps) as a colorless oil.

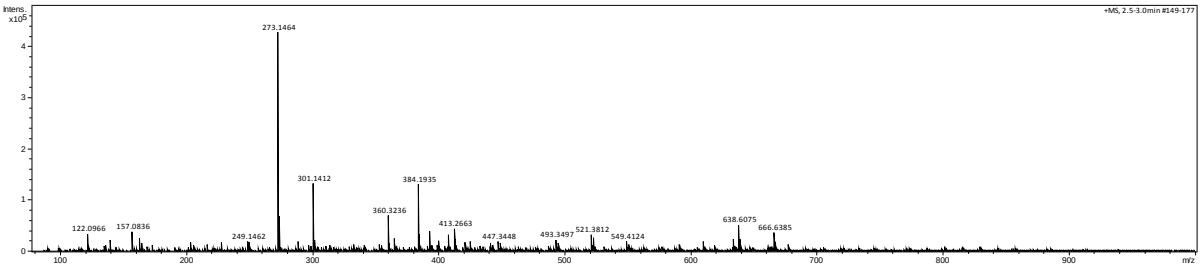
**TLC:** $R_f$ = 0.39 (PE/$Et_2O$ 2:1).

**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 6.19 (*d*, 1H, $^4J_{H,H}$ = 2.5 Hz, =C(H)H'), 5.79–5.62 (*m*, 1H, C(H)=), 5.10–4.95 (*m*, 3H, =C(H)H' + $=CH_2$), 4.74 (*d*, 1H, $^4J_{H,H}$ = 0.5 Hz, =C(H)H'), 4.64 (*s*, 1H, =C(H)H'), 3.87 (*dt*, 1H, $^3J_{H,H}$ = 4.1, 4.0 Hz, C(H)OC(O)), 3.23–3.03 (*m*, 4H, 2 × $CH_2O$), 2.63–2.51 (*m*, 1H, C(H)C(R)=$CH_2$), 2.14 (*dt*, 1H, $^{3,4}J_{H,H}$ = 6.7, 1.3 Hz, C(H)H'), 2.09 (*dt*, 1H, $^{3,4}J_{H,H}$ = 6.7, 1.3 Hz, C(H)H'), 1.75 (*t*, 2H, $^3J_{H,H}$ = 7.9 Hz, $CH_2$), 1.53 (*s*, 3H, $CH_3$), 1.38–1.25 (*m*, 2H, $CH_2$).

**$^{13}$C{$^1$H} NMR** (75 MHz, $C_6D_6$): $\delta$ = 169.5 (OC=O), 144.6 ($R_2C$=), 140.0 ($R_2C$=), 135.4 (C(H)=), 121.1 ($=CH_2$), 116.5 ($=CH_2$), 111.0 ($=CH_2$), 81.0 (C(H)O), 72.1 ($CH_2O$), 71.1 ($CH_2O$), 40.6 (C(H)C(R)=$CH_2$), 34.4 ($CH_2$), 34.3 ($CH_2$), 32.5 ($CH_2$), 22.4 ($CH_3$).

**IR** (ATR): $\tilde{\nu}$ = 3844 (*w*), 3749 (*w*), 3655 (*w*), 3053(*w*), 2867 (*m*), 2411 (*w*), 1775 (*s*), 1652 (*m*), 1529 (*w*), 1422 (*m*), 1339 (*w*), 1276 (*s*), 1129 (*s*), 1011 (*m*), 981 (*m*), 915 (*s*), 826 (*m*), 779 (*s*), 633 (*m*), 621(*w*) $cm^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{15}H_{22}O_3$ $[M+Na]^+$ 273.1461; observed 273.1464.

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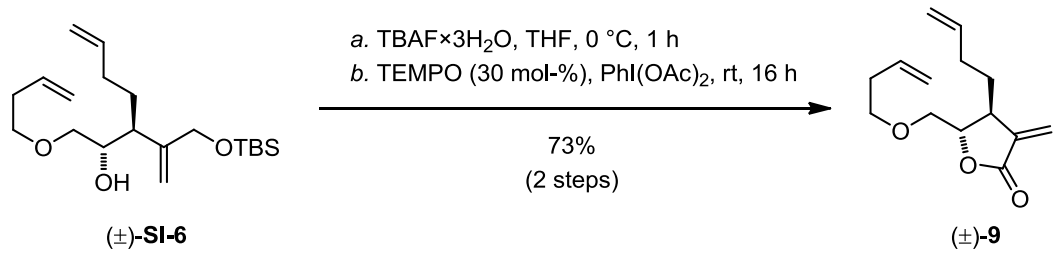
**(4*S**,5*S**)-4-(But-3-en-1-yl)-5-[(but-3-en-1-yloxy)methyl]-3-methylenedihydrofuran-2(*3H*)-one [(±)-9]**




(±)-**SI-6** (±)-**9**

To a stirred solution of homoallyl alcohol (±)-**SI-6** (93.0 mg, 0.26 mmol, 1.0 equiv.) in anhydrous THF (2.6 ml) at 0 °C was added a TBAF×3$H_2O$ solution (0.27 ml, 0.27 mmol, 1.02 equiv., 1.0 M in THF). The solution was allowed to reach rt within 30 min. After 1 h at rt (TLC control: PE/$Et_2O$ 1:1) the solution was diluted with $Et_2O$ (15 ml) and added to a sat. $NH_4Cl$ solution (15 ml). The organic layer was separated, washed with sat. $NH_4Cl$ solution (2 × 15 ml) and brine (30 ml), dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. After column chromatography of the residue ($Et_2O$/PE 3:2, 2 × 20 cm) the diol (±)-**SI-12** was obtained as a colorless oil, which still contained impurities. The material was used like this in the following step.

To a stirred solution of the crude diol (±)-**SI-12** in anhydrous $CH_2Cl_2$ (2.5 ml) at 0 °C was added $PhI(OAc)_2$ (251 mg, 0.78 mmol, 3.0 equiv.) followed by TEMPO (7.80 mg, 0.05 mmol, 0.2 equiv.). After 3 h the cooling bath was removed and the solution was stirred for further 16 h at rt (TLC control: PE/$Et_2O$ 1:1). Then sat. $Na_2S_2O_3$ solution (3 ml) was added and the biphasic mixture was stirred for 30 min. The organic layer was separated and washed with brine (3 ml). The organic extract was dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*. Column chromatography of the residue (PE→PE/MTBE 6:1, 2 × 20 cm) delivered the butyrolactone (±)-**9** (46 mg, 0.19 mmol, 73% over 2 steps) as a colorless oil.

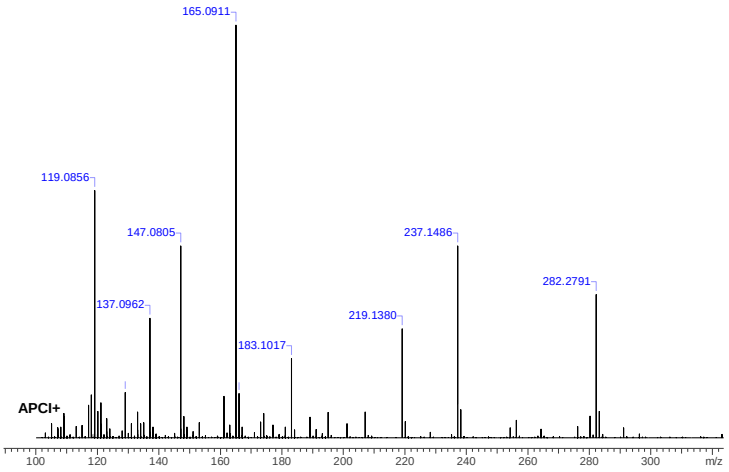
**TLC:** $R_f$ = 0.31 (PE/MTBE 6:1).

**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 6.18 (*d*, 1H, $^4J_{H,H}$ = 2.5 Hz, =C(H)H'), 5.78–5.63 (*m*, 1H, C(H)=), 5.55 (*ddt*, 1H, $^3J_{H,H}$ = 16.9, 10.4, 6.6 Hz, C(H)=), 5.04–4.85 (*m*, 5H, =C(H)H' + 2 × $=CH_2$), 3.81 (*dt*, 1H, $^3J_{H,H}$ = 4.1, 4.1 Hz, C(H)OC(O)), 3.16 (*t*, 2H, $^3J_{H,H}$ = 6.6 Hz, $CH_2O$), 3.10 (*dd*, 1H, $^{2,3}J_{H,H}$ = 10.5, 4.4 Hz, C(H)H'O), 3.04 (*dd*, 1H, $^{2,3}J_{H,H}$ = 10.5, 4.2 Hz, C(H)H'O), 2.58–2.49 (*m*, 1H, C(H)C(R)=$CH_2$), 2.11 (*dt*, 2H, $^3J_{H,H}$ = 6.7, 6.1 Hz, $CH_2$), 1.78–1.69 (*m*, 2H, $CH_2$), 1.27–1.08 (*m*, 2H, $CH_2$).

**$^{13}$C{$^1$H} NMR** (75 MHz, $C_6D_6$): $\delta$ = 169.3 (OC=O), 139.9 (OC(O)C=), 137.7 (C(H)=), 135.3 ($R_2C$=), 121.1 (=$CH_2$), 116.5 (=$CH_2$), 115.5 (=$CH_2$), 80.8 (C(H)OC=O), 72.0 ($CH_2O$), 71.1 ($CH_2O$), 40.4 (C(H)C(R)=$CH_2$), 34.4 ($CH_2$), 33.7 ($CH_2$), 30.5 ($CH_2$).

**IR** (ATR): $\tilde{\nu}$ = 3902 (*w*), 3839 (*w*), 3736 (*w*), 3650 (*w*), 3567 (*w*), 3077 (*w*), 2922 (*w*), 2861 (*w*), 2362 (*w*), 1762 (*s*), 1641 (*m*), 1542 (*w*), 1407 (*w*), 1363 (*w*), 1266 (*s*), 1116 (*s*), 1047 (*m*), 993 (*m*), 912 (*s*), 815 (*m*), 750 (*s*), 634 (*m*) $cm^{-1}$.

**HRMS** (APCI, Orbitrap): *m/z* calc'd for $C_{14}H_{20}O_3$ $[M+H]^+$ 237.1485; observed 237.1486.

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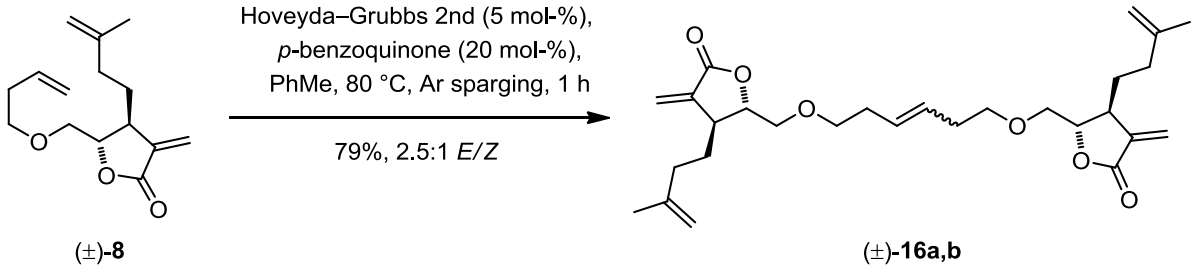
**(4*S**,4'*S**,5*S**,5'*S**)-5,5'-{[Hex-3-ene-1,6-diylbis(oxy)]bis(methylene)}bis[4-(3-methylbut-3-en-1-yl)-3-methylenedihydrofuran-2(*3H*)-one] [(±)-16a,b].**




(±)-**8** (±)-**16a,b**

Anhydrous toluene used for the reaction was deoxygenated by sparging with anhydrous Ar for 1 h under stirring at rt.

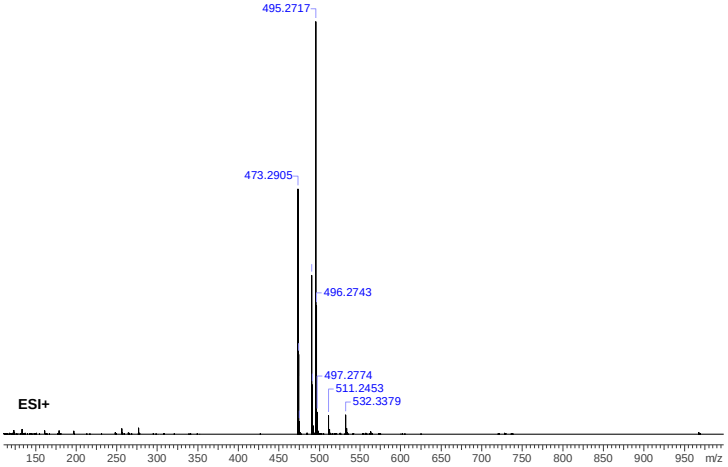
Diene (±)-**8** (16.5 mg, 64.1 µmol, 1.0 equiv.) and recrystallized *p*-benzoquinone (2.2 mg, 20.4 µmol, 0.3 equiv.) were dissolved in anhydrous PhMe (20 ml). The yellow solution was heated up to 80 °C under stirring and sparged with anhydrous Ar for 10 min. Then, a solution of Hoveyda–Grubbs 2$^{nd}$ generation catalyst (2.5 mg, 3.99 µmol, 0.06 equiv.) in anhydrous PhMe (1.0 ml) was added dropwise to the solution within 30 min using a syringe pump (0.033 ml/min), maintaining continuous Ar sparging of the reaction mixture. After additional 6 h (TLC control: PE/MTBE 2:1) the green solution was cooled to 0 °C, kept at this temperature for 10 min and aq. $H_2O_2$ (4.0 ml, 15*w*-%) was added under vigorous stirring. The biphasic mixture was warmed to rt after 15 min and kept at this temperature for further 30 min. Brine (20 ml) was added and the organic layer was separated, sequentially washed with sat. $Na_2SO_3$ solution (20 ml) and brine (20 ml), followed by drying with $MgSO_4$, filtration and removal of the volatiles *in vacuo*. After column chromatography of the residue (PE/MTBE 2:1→1:1, 2 × 25 cm) the dimer (±)-**16a,b** (12.0 mg, 25.4 µmol, 79%) was obtained as a slightly green oil and inseparable mixture of isomers (2.5:1).

**TLC:** $R_f$ = 0.28 (PE/MTBE 2:1).

**$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ = 6.20 (*s*, 1H, =C(H)H'), 5.51–5.38 (*m*, 1H, C(H)=), 5.12–5.03 (*m*, 1H, =C(H)H'), 4.76 (*s*, 1H, =C(H)H'), 4.65 (*s*, 1H, =C(H)H'), 3.89 (*dt*, 1H, $^3J_{H,H}$ = 7.9, 4.0 Hz, C(H)OC(O)), 3.33–3.10 (*m*, 4H, 2 × $CH_2O$), 2.64–2.53 (*m*, 1H, C(H)C(R)=$CH_2$), 2.26–2.12 (*m*, 2H, $CH_2$), 1.76 (*t*, 2H, $^3J_{H,H}$ = 7.9 Hz, $CH_2$), 1.53 (*s*, 3H, $CH_3$), 1.43–1.22 (*m*, 2H, $CH_2$).

**$^{13}$C{$^1$H} NMR** (75 MHz, $C_6D_6$): $\delta$ = 169.5 (OC=O), 144.6 ($R_2C$=), 140.1 ($R_2C$=), 128.8 (C(H)=), 121.0 (=$CH_2$), 111.0 (=$CH_2$), 81.1 (C(H)O), 72.1 ($CH_2O$), 71.6 ($CH_2O$), 40.6 (C(H)C(R)=$CH_2$), 34.3 ($CH_2$), 33.4 ($CH_2$), 32.6 ($CH_2$), 22.4 ($CH_3$).

**HRMS** (ESI, Orbitrap): *m/z* calc'd for $C_{28}H_{40}O_6$ $[M+H]^+$ 473.2898; observed 473.2905; $[M+Na]^+$ 495.2717; observed 495.2717; $[M+K]^+$ 511.2456; observed 511.2453.

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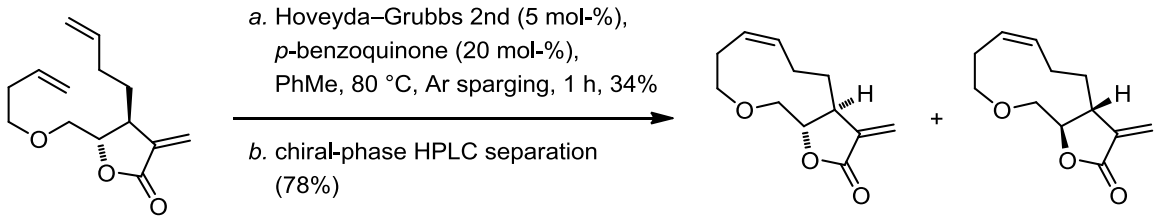
**(3a*S*,11a*S*,*Z*)-3-Methylene-3,3a,4,5,8,9,11,11a-octahydro-2H-furo[2,3-c]oxecin-2-one [(+)-7] and (3a*R*,11a*R*,*Z*) isomer [(–)-7].**




(±)-**9** (+)-(*Z*)-**7** (–)-(*Z*)-**7**

Anhydrous toluene used for the reaction was deoxygenated by sparging with anhydrous Ar for 1 h under stirring at rt.

Diene (±)-**9** (20.0 mg, 84.6 µmol, 1.0 equiv.) and recrystallized *p*-benzoquinone (1.83 mg, 16.9 µmol, 0.2 equiv.) were dissolved in anhydrous PhMe (50 ml). The yellow

solution was heated up to 80 °C under stirring and sparged with anhydrous Ar for 10 min. Then, a solution of Hoveyda–Grubbs 2nd generation catalyst (2.65 mg, 4.23 μmol, 0.05 quiv.) in anhydrous PhMe (5.0 ml) was added dropwise to the solution within 1 h using a syringe pump (0.083 ml/min), maintaining continuous Ar sparging of the reaction mixture. After additional 10 min (TLC control: PE/MTBE 2:1) the green solution was cooled to 0 °C, kept at this temperature for 10 min and aq. $H_2O_2$ (4.0 ml, 15*w*-%) was added under vigorous stirring. The biphasic mixture was warmed to rt after 15 min and kept at this temperature for further 45 min. Then, brine (40 ml) was added and the organic layer was separated, sequentially washed with sat. $Na_2SO_3$ solution (40 ml) and brine (40 ml), followed by drying with $MgSO_4$, filtration and removal of the volatiles *in vacuo*. After column chromatography of the residue (PE/MTBE 2:1→1:1, 2 × 25 cm) the parthenolide analog (±)-(*Z*)-**7** (6.0 mg, 28.8 μmol, 34%) was obtained as a colorless oil. Separation of the enantiomers was achieved by chiral-phase HPLC (78% recovery, see below).

**TLC:** $R_f$ = 0.36 (PE/MTBE 2:1).

$[\alpha]_D^{23}$ = +13.9 (*c* = 1.0, THF, >99% *ee*) for (*S*,*S*)-(*Z*)-**7**.

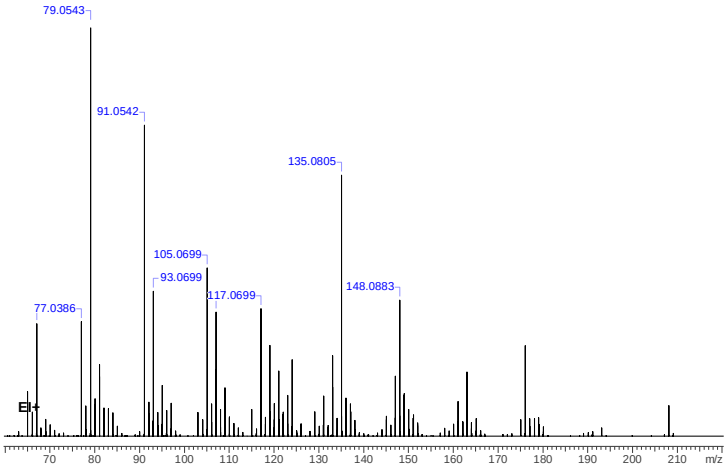
$[\alpha]_D^{23}$ = –14.9 (*c* = 1.0, THF, >99% *ee*) for (*R*,*R*)-(*Z*)-**7**.

**$^1$H NMR** (600 MHz, $C_6D_6$): $\delta$ = 6.16 (*d*, 1H, $^4J_{H,H}$ = 3.2 Hz, ═C(H)H’), 5.34–5.26 (*m*, 1H, C(H)═), 5.16 (*ddd*, 1H, $^3J_{H,H}$ = 11.0, 5.0, 4.9 Hz, C(H)═), 4.94 (*d*, 1H, $^4J_{H,H}$ = 2.8 Hz, ═C(H)H’), 3.75 (*td*, 1H, $^3J_{H,H}$ = 6.4, 4.3 Hz, C(H)OC(O)), 3.27 (*dd*, 1H, $^{2,3}J_{H,H}$ = 11.2, 4.1 Hz, C(H)H’O), 3.13–3.03 (*m*, 3H, C(H)H’O + $CH_2O$), 2.99–2.90 (*m*, 1H, C(H)C(R)═$CH_2$), 2.15–2.01 (*m*, 2H, $CH_2$), 1.77–1.68 (*m*, 1H, C(H)H’), 1.44–1.39 (*m*, 1H, C(H)H’), 1.36–1.29 (*m*, 1H, C(H)H’), 1.08–1.02 (*m*, 1H, C(H)H’).

**$^{13}$C{$^1$H} NMR** (75 MHz, $C_6D_6$): $\delta$ = 169.2 (OC═O), 140.8 (OC(O)C═), 131.6 (2C, 2 × C(H)═), 120.1 (═$CH_2$), 81.1 (C(H)OC═O), 70.4 ($CH_2O$), 70.2 ($CH_2O$), 39.5 (C(H)C(R)═$CH_2$), 31.7 ($CH_2$), 27.4 ($CH_2$), 24.8 ($CH_2$).

**IR** (ATR): $\tilde{\nu}$ = 3650 (*w*), 3567 (*w*), 3099 (*w*), 2921 (*m*), 2859 (*m*), 2362 (*m*), 1762 (*m*), 1473 (*m*), 1404 (*w*), 1363 (*w*), 1264 (*m*), 1151 (*m*), 1033 (*s*), 935 (*m*), 816 (*w*), 750 (*m*), 669 (*w*) $cm^{-1}$.

**HRMS** (GC–EI, Orbitrap): *m/z* calc’d for $C_{12}H_{16}O_3$ $[M]^{\bullet+}$ 208.1094; observed 208.1093.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93.0699
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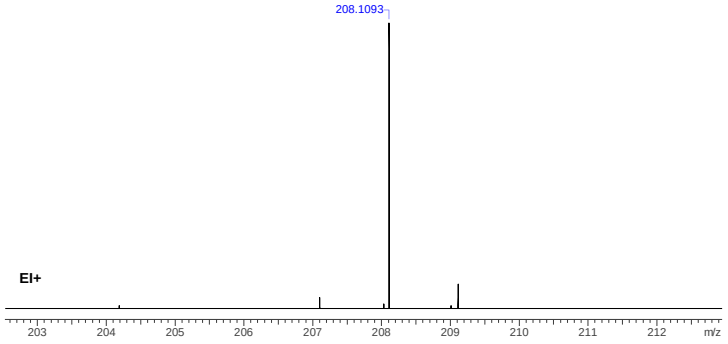
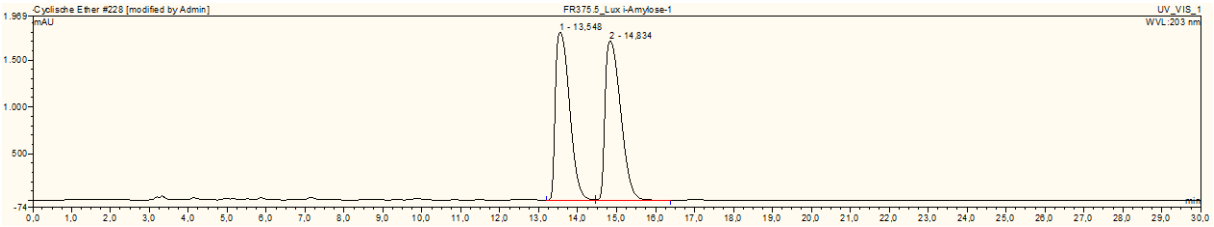
130
140
150
160
170
180
190
200
210
m/z


208.1093
EI+
203
204
205
206
207
208
209
210
211
212
m/z

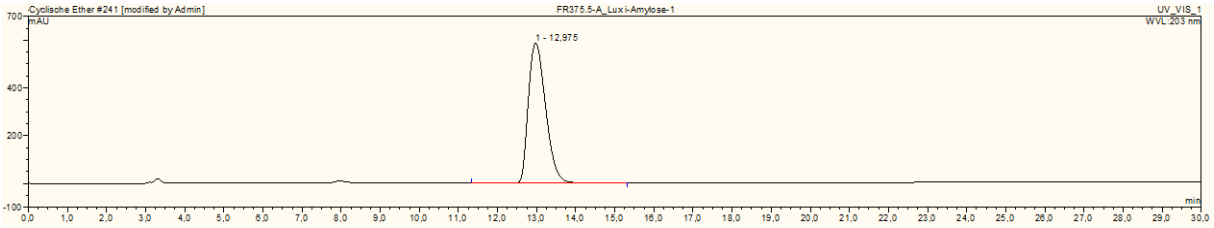
**Chiral-phase HPLC** [Phenomenex Lux i-Amylose-1 column (5 µm, 250 × 4.6 mm ID) with guard cartridge, *n*-Hexan/EtOH, 90:10, 1 ml/min, 25 °C, 220 nm]:

**a.** (±)-(*Z*)-**7**

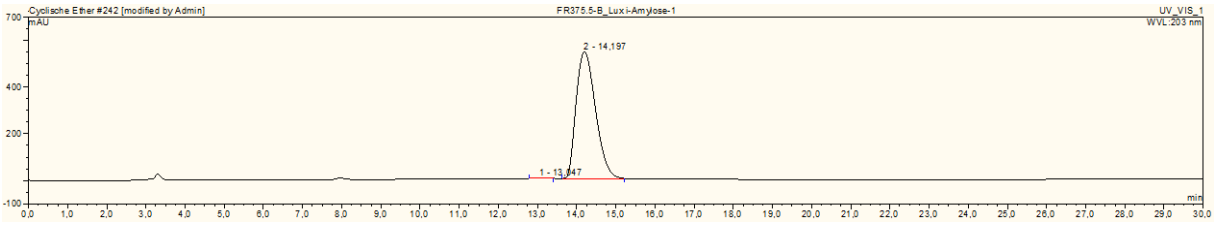



| No. | Ret. time / min | Area / mAU×min | Height / mAU | Rel. area / % | Resolution |
|---|---|---|---|---|---|
| 1 | 13.5 | 754.6 | 1794 | 49.0 | 1.80 |
| 2 | 14.8 | 785.1 | 1701 | 51.0 | – |

**b.** (*S*,*S*)-(+)-(*Z*)-**7,** >99% ee after preparative chiral-phase HPLC.

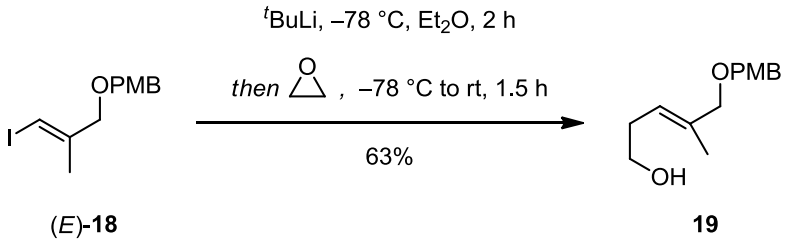



**c.** (*R*,*R*)-(–)-(*Z*)-**7,** 99.5% ee after preparative chiral-phase HPLC.




| No. | Ret. time / min | Area / mAU×min | Height / mAU | Rel. area / % | Resolution |
|---|---|---|---|---|---|
| 1 | 13.0 | 1.10 | 3.08 | 0.35 | 1.48 |
| 2 | 14.2 | 311.7 | 544.2 | 99.65 | – |

**(*E*)-5-[(4-Methoxybenzyl)oxy]-4-methylpent-3-en-1-ol (19)**




Vinyl iodide (*E*)-**18** (2.07 g, 6.51 mmol, 1.0 equiv.) was added as a solution in anhydrous $Et_2O$ (10 ml) within 10 min to a stirred solution of $^t$BuLi (7.21 ml, 13.7 mmol, 2.1 equiv., 1.9 M in pentane) in anhydrous $Et_2O$ (40 ml) at –78 °C. After 2 h (TLC control: PE/MTBE 2:1) ethylene oxide solution (3.38 ml, 8.46 mmol, 1.3 equiv., 2.5 M in THF with added 3 Å molecular sieve) was added and the mixture was allowed to reach rt within 1.5 h (TLC control: PE/MTBE 2:1). The mixture was added to sat. $NH_4Cl$ solution (100 ml) and extracted with $Et_2O$ (100 ml). The organic layer was separated, washed with sat. $NaHCO_3$ solution (100 ml) and brine (100 ml), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography of the residue (PE/MTBE, 1:1, 5 ×18 cm) provided homoallyl alcohol **19** (973 mg, 4.12 mmol, 63%) as colorless oil.

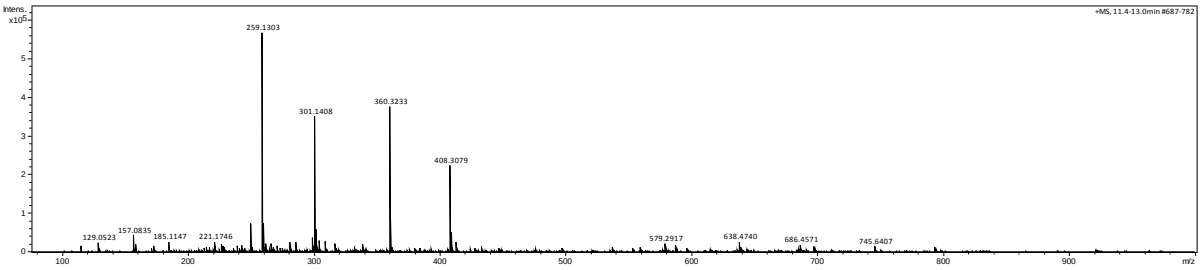
**TLC:** $R_f$ = 0.27 (MTBE/PE 3:2).

**$^1$H NMR** (400 MHz, $C_6D_6$): $\delta$ = 7.29–7.22 (*m*, 2H, CH, Ar), 6.87–6.75 (*m*, 2H, CH, Ar), 5.43 (*td*, 1H, $^{3,4}J_{H,H}$ = 7.3, 1.1 Hz, C(H)═), 4.33 (*s*, 2H, $CH_2O$), 3.81 (*s*, 2H, $CH_2O$), 3.40 (*t*, 2H, $^3J_{H,H}$ = 6.6 Hz, $CH_2O$), 3.31 (s, 3H, $OCH_3$), 2.14 (*td*, 2H, $^3J_{H,H}$ = 6.9, 6.8 Hz, $CH_2$), 1.63 (*s*, 3H, $CH_3$), 1.34 (*br s*, 1H, OH).

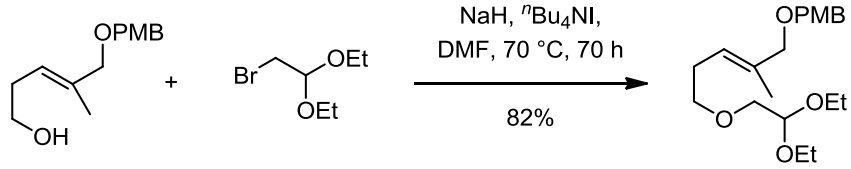
**$^{13}$C{$^1$H} NMR** (101 MHz, $C_6D_6$): $\delta$ = 159.7 ($C_{quart}O$), 135.1 ($R_2C$═), 131.3 ($C_{quart}$, Ar), 129.5 (CH, Ar), 124.0 (C(H)═), 114.1 (CH, Ar), 75.9 ($OCH_2$), 71.6 ($OCH_2$), 62.2 ($OCH_2$), 54.8 ($OCH_3$), 31.7 ($CH_2$), 14.2 ($CH_3$).

**IR** (ATR): $\tilde{\nu}$ = 2855 (*m*), 2207 (*w*), 2049 (*w*), 2002 (*w*), 1885 (*w*), 1611 (*m*), 1512 (*s*), 1444 (*m*), 1351 (*m*), 1302 (*m*), 1245 (*s*), 1173 (*m*), 1033 (*s*), 819 (*s*), 755 (*m*), 614 (*m*) cm$^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{14}H_{20}O_3$ [M+Na]$^+$ 259.1305; observed 259.1303.



**(*E*)-2-{{5-[(4''-Methoxybenzyl)oxy]-4'-methylpent-3'-en-1'-yl}oxy}acetaldehyde diethyl-acetal [SI-13]**




**19** **SI-14** **SI-13**

Alcohol **19** (973 mg, 4.12 mmol, 1.0 equiv.), $^{n}Bu_4NI$ (152 mg, 0.41 mmol, 0.1 equiv.) and bromoacetaldehyde diethyl acetal (**SI-14,** 2.03 g, 10.3 mmol, 2.5 equiv.) were dissolved in anhydrous DMF with stirring (14 ml) and cooled to 0 °C. NaH (329 mg, 8.23 mmol, 2.0 equiv., ~60*w*-% in mineral oil) was added and the mixture was allowed to reach first rt within 30 min and was then heated to 70 °C. After 70 h the light yellow suspension was cooled to rt (TLC control: PE/MTBE 2:1) and treated with pH 7 phosphate buffer (40 ml). The mixture was extracted with $Et_2O$ (40 ml) and the extract was washed with sat. $NaHCO_3$ solution (40 ml) and brine (40 ml), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography of the residue (PE/MTBE 3:1 + 0.2% $Me_2NEt$, 5 × 15 cm) provided acetal **SI-13** (1.19 g, 3.38 mmol, 82%) as colorless oil.

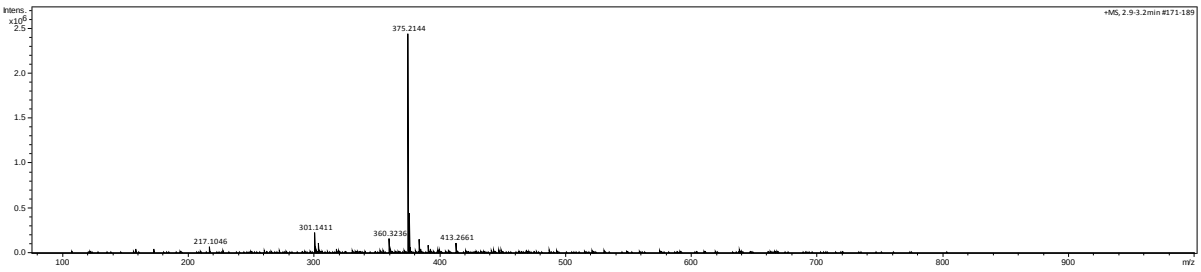
**TLC:** $R_f$ = 0.51 (MTBE/PE 2:1).

**$^{1}$H NMR** (400 MHz, $C_6D_6$): $\delta$ = 7.27 (*d*, 2H, $^{3}J_{H,H}$ = 8.5 Hz, CH, Ar), 6.81 (*d*, 2H, $^{3}J_{H,H}$ = 8.5 Hz, CH, Ar), 5.54 *t*, 1H, $^{3,4}J_{H,H}$ = 6.8 Hz, C(H)═), 4.68 (*t*, 1H, $^{3}J_{H,H}$ = 5.2 Hz, $HC(OEt)_2$), 4.34 (*s*, 2H, $CH_2O$), 3.84 (*s*, 2H, $CH_2O$), 3.64–3.55 (*m*, 4H, 2 × $CH_2O$), 3.47–3.40 (*m*, 2H, $CH_2O$), 3.37 (*t*, 2H, $^{3}J_{H,H}$ = 6.8 Hz, $CH_2O$), 3.31 (*s*, 3H, $OCH_3$), 2.31 (*dt*, 2H, $^{3}J_{H,H}$ = 6.9, 6.8 Hz, $CH_2$), 1.64 (*s*, 3H, $CH_3$), 1.12 (*t*, 6H, $^{3}J_{H,H}$ = 7.0 Hz, $CH_3$).

**$^{13}$C{$^{1}$H} NMR** (101 MHz, $C_6D_6$): $\delta$ = 159.7 ($OCH_3$), 134.5 ($R_2C$═), 131.4 ($C_{quart}$, Ar), 129.5 (CH, Ar), 124.2 (C(H)═), 114.1 (CH, Ar), 101.8 ($HC(OEt)_2$), 75.9 ($CH_2O$), 72.4 ($CH_2O$), 71.4 ($CH_2O$), 71.2 ($CH_2O$), 62.1 ($CH_2O$), 54.8 ($OCH_3$), 28.9 ($CH_2$), 15.7 ($CH_3$), 14.1 ($CH_3$).

**IR** (ATR): $\tilde{\nu}$ = 2974 (*w*), 2863 (*m*), 2188 (*w*), 2064 (*w*), 1885 (*w*), 1736 (*w*), 1612 (*m*), 1512 (*m*), 1444 (*m*), 1372 (*m*), 1302 (*m*), 1245 (*s*), 1064 (*s*), 819 (*m*), 755 (*m*), 615 (*m*) $cm^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{20}H_{32}O_5$ $[M+Na]^+$ 375.2142; observed 375.2144.

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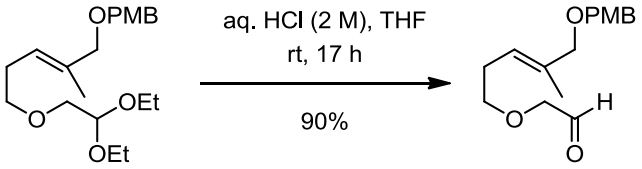
**(*E*)-2-{{5-[(4''-Methoxybenzyl)oxy]-4'-methylpent-3'-en-1'-yl}oxy}acetaldehyde (20)**




**SI-13** **20**

Acetal **SI-13** (1.19 g, 3.38 mmol, 1.0 equiv.) was dissolved in THF (25.0 ml) open to air, followed by the addition of an aq. HCl solution (8.50 ml, 16.9 mmol, 5.0 equiv., 2.0 M). The reaction mixture was stirred at rt for 17 h (TLC control: PE/MTBE 3:2) whereupon sat. $NaHCO_3$ solution (50 ml) and MTBE (70 ml) were added. After an additional stirring time of 10 min the organic layer was separated and washed with brine (30 ml), dried with $MgSO_4$, filtered, and the solvent was removed *in vacuo*. After column chromatography of the residue (MTBE/PE 2:1, 5 × 15 cm) the obtained oil was dissolved in $Et_2O$ (20 ml), which was then removed *in vacuo*. The aldehyde **20** (846 mg, 3.04 mmol, 90%) was obtained as colorless oil.

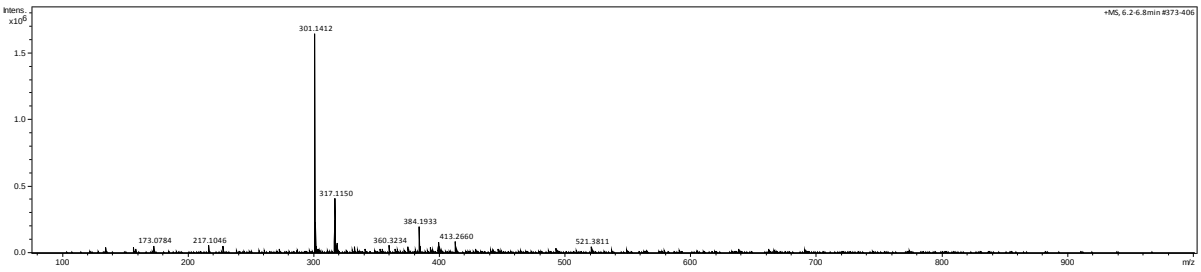
**TLC:** $R_f$ = 0.35 (MTBE/PE 2:1).

**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 9.30 (*t*, 1H, $^3J_{H,H}$ = 0.9 Hz, CHO), 7.32–7.21 (*m*, 2H, CH, Ar), 6.88–6.76 (*m*, 2H, CH, Ar), 5.47 (*tq*, 1H, $^{3,4}J_{H,H}$ = 7.1, 1.3 Hz, C(H)═), 4.34 (*s*, 2H, $CH_2O$), 3.82 (*s*, 2H, $CH_2O$), 3.40 (*d*, 2H, $^3J_{H,H}$ = 0.9 Hz, O$\underline{CH_2}$CHO), 3.31 (*s*, 3H, $OCH_3$), 3.12 (*t*, $^3J_{H,H}$ = 6.8 Hz, $CH_2C\underline{H_2}O$), 2.21 (*dtd*, 2H, $^{3,3,5}J_{H,H}$ = 6.9, 6.8, 0.6 Hz, $C\underline{H_2}CH_2O$), 1.62 (*s*, 3H, $CH_3$).

**$^{13}$C{$^1$H} NMR** (75 MHz, $C_6D_6$): $\delta$ = 200.0 (CHO), 159.7 ($\underline{C}OCH_3$), 134.9 ($R_2C$═), 131.3 ($OCH_2\underline{C}$, Ar), 129.5 (CH, Ar), 123.3 (C(H)═), 114.1 (CH, Ar), 76.2 ($CH_2O$), 75.7 ($CH_2O$), 71.6 ($CH_2O$), 71.3 ($CH_2O$), 54.8 ($OCH_3$), 28.6 ($CH_2$), 14.1 ($CH_3$).

**IR** (ATR): $\tilde{\nu}$ = 2855 (*w*), 2194 (*w*), 2056 (*w*), 2002 (*w*), 1886 (*w*), 1735 (*m*), 1612 (*m*), 1512 (*s*), 1444 (*m*), 1352 (*m*), 1302 (*m*), 1244 (*s*), 1032 (*s*), 818 (*s*), 756 (*m*), 614 (*m*) $cm^{-1}$.

**HRMS** (ESI, TOF): m/z calc'd for $C_{16}H_{22}O_4$ $[M+Na]^+$ 301.1410; observed 301.1412.

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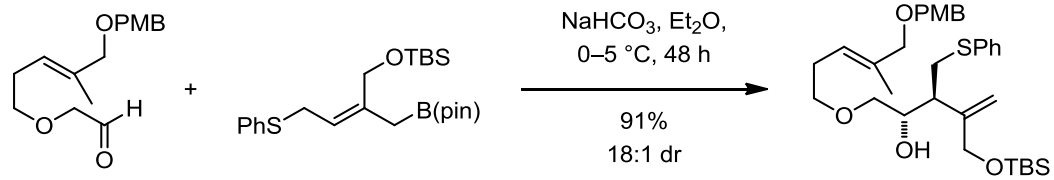
**(2S*,3*S**,*E*)-1-{{5'-[(4''-methoxybenzyl)oxy]-4'-methylpent-3'-en-1'-yl}oxy}-3-[(phenylthio)methyl]-4-{[(tert-butyldimethylsilyl)oxy]methyl}pent-4-en-2-ol [(±)-21]**




**20** (*Z*)-**15c** (±)-**21**

Boronate (*Z*)-**15c** (426 mg, 0.98 mmol, 1.00 equiv.) was added to a stirred solution of aldehyde **20** (274 mg, 0.98 mmol, 1.30 equiv.) and $NaHCO_3$ (4.12 mg, 50.0 μmol, 0.05 equiv.) in anhydrous $Et_2O$ (7.0 ml) at 0 °C. After 48 h at 0–5 °C (TLC control: PE/MTBE 3:1) sat. $NaHCO_3$ solution (30 ml) and $Et_2O$ (20 ml) were added and the biphasic mixture was stirred for 10 min. Then the organic layer was separated and washed with brine (30 ml). The organic extract was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography of the residue (PE/MTBE 3:1, 5 × 35 cm) provided the isomerically pure homoallyl alcohol (±)-**21** (491 mg, 0.84 mmol, 86%) as colorless oil. A minor isomer was detected by HPLC–MS (18:1 dr major:minor), but not isolated.

**TLC:** $R_f$ = 0.32 (PE/MTBE 3:1).

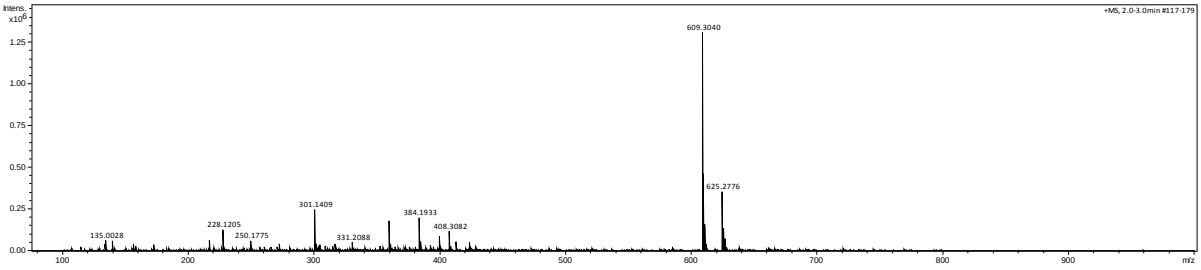
**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 7.36–7.24 (*m*, 4H, CH, Ar), 7.07–6.99 (*m*, 2H, CH, Ar), 6.94–6.88 (*m*, 1H, CH, Ar), 6.84–6.80 (*m*, 2H, CH, Ar), 5.49 (*td*, 1H, $^{3,4}J_{H,H}$ = 7.1, 1.1 Hz, C(H)═), 5.36 (*d*, 1H, $^4J_{H,H}$ = 1.5 Hz, ═C(H)H'), 5.10 (*s*, 1H, ═C(H)H'), 4.35 (*s*, 2H, $CH_2O$), 4.27 (*d*, 1H, $^2J_{H,H}$ = 13.6 Hz, C(H)H'OSi), 4.12–4.03 (*m*, 2H, C(H)H'OSi + C(H)OH), 3.84 (*s*, 2H, $CH_2O$), 3.42–3.13 (*m*, 9H, $CH_2S$ + 2 × $CH_2O$ + $OCH_3$), 2.72 (*ddd*, 1H, $^3J_{H,H}$ = 8.4, 6.9, 4.3 Hz, C(H)C(R)═$CH_2$), 2.26 (*d*, 1H, $^3J_{H,H}$ = 6.8 Hz, C(H)H'), 2.22 (*d*, 1H, $^3J_{H,H}$ = 6.8 Hz, C(H)H'), 1.65 (*s*, 3H, $CH_3$), 0.95 (*s*, 9H, $SiC(CH_3)_3$), 0.05 (*s*, 6H, $Si(CH_3)_2$).

**$^{13}$C{$^1$H} NMR** (75 MHz, $C_6D_6$): $\delta$ = 159.7 ($COCH_3$), 146.8 ($R_2C$═), 137.6 ($R_2C$═), 134.7 ($C_{quart}$, Ar), 131.3 ($C_{quart}$, Ar), 129.5 (CH, Ar), 129.2 (CH, Ar), 129.2 (CH, Ar), 125.9 (CH,

Ar), 123.9 (C(H)═), 115.3 (═$CH_2$), 114.1 (CH, Ar), 75.8 ($CH_2O$), 73.8 ($CH_2O$), 71.6 ($CH_2O$), 71.2 (C(H)OH), 70.9 ($CH_2O$), 65.7 ($CH_2OSi$), 54.8 ($OCH_3$), 46.3 ($\underline{C}$(H)C(R)═$CH_2$), 35.0 ($CH_2S$), 28.8 ($CH_2$), 26.1 (SiC($\underline{C}H_3)_3$), 18.5 (Si$\underline{C}(CH_3)_3$), 14.2 ($CH_3$), –5.3 (Si($\underline{C}H_3$)($CH_3$)'), –5.3 (Si($CH_3$)($\underline{C}H_3$)').

**IR** (ATR): $\tilde{\nu}$ = 3855 (*w*), 3737 (*w*), 3675 (*w*), 3650 (*w*), 3567 (*w*), 2929 (*m*), 2856 (*m*), 1699 (*w*), 1649 (*w*), 1613 (*m*), 1584 (*w*), 1513 (*m*), 1460 (*m*), 1391 (*m*), 1362 (*m*), 1252 (*s*), 1174 (*m*), 1086 (*s*), 1036 (*s*), 904 (*m*), 835 (*s*), 747 (*s*), 691 (*m*), 614 (*m*) $cm^{-1}$.

**HRMS** (ESI, TOF): m/z calc'd for $C_{33}H_{50}O_5SSi$ $[M+Na]^+$ 609.3040; observed 609.3040.

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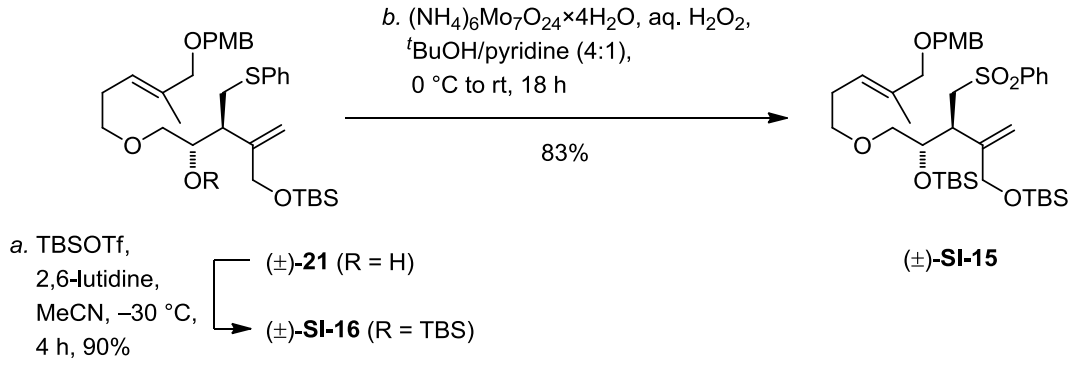
**(2*S**,3*S**,*E*)-2-[(*tert*-butyldimethylsilyl)oxy]-3-[(phenylsulfonyl)methyl]-4-{[(*tert*-butyldimethylsilyl)oxy]methyl}pent-4-en-1-yl-5'-[(4'''-methoxybenzyl)oxy]-4'-methyl-pent-3'-en-1-ylether [(±)-SI-15]**




TBSOTf (0.18 ml, 206 mg, 0.78 mmol, 1.0 equiv.) was added to a stirred solution of 2,6-lutidine (0.27 ml, 250 mg, 2.33 mmol, 3.0 equiv.) in anhydrous MeCN (4.0 ml) at –30 °C. After 10 min a solution of alcohol (±)-**21** (456 mg, 0.78 mmol, 1.0 equiv.) in anhydrous MeCN (2.0 ml) was added dropwise and the solution was allowed to stir for 3 h at this temperature (TLC control: PE/MTBE 3:1). The solution was added to a stirred sat. $NaHCO_3$ solution (30 ml) at 0 °C and extracted with MTBE (30 ml). The combined organic layers were washed with pH 7 phosphate buffer (30 ml) and brine (40 ml). The organic extract was dried with $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography of the residue

(PE/$Et_2O$ 9:1, 5 × 5 cm) provided crude TBS ether (±)-**SI-16** (492 mg, 0.70 mmol, 90%) as a colorless oil, which was processed further.

**TLC:** $R_f$ = 0.48 (PE/$Et_2O$ 9:1).

TBS ether (±)-**SI-16** was dissolved in $^t$BuOH (4.5 ml) and pyridine (1.5 ml) open to air and cooled to 0 °C. $(NH_4)_6Mo_7O_{24}\times4H_2O$ (519 mg, 0.42 mmol, 0.6 equiv.) was added in one portion, followed by aq. $H_2O_2$ (0.90 ml, ~30*w*-%). The suspension was allowed to warm to rt within 6 h. After additional 12 h (TLC control: PE/$Et_2O$ 2:1) a mixture of sat. $Na_2SO_3$ solution (5.0 ml) and sat. $NaHCO_3$ solution (20 ml) was added slowly to the yellow suspension at 0 °C. $Et_2O$ (30 ml) was added and the biphasic mixture was stirred for 10 min. The organic layer was separated and washed with pH 7 phosphate buffer (3 × 20 ml) and brine (30 ml). The organic extract was dried with $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography of the residue (PE/$Et_2O$ 2:1, 4 × 25 cm) provided the sulfone (±)-**SI-15** (428 mg, 0.58 mmol, 83%) as a colorless oil.

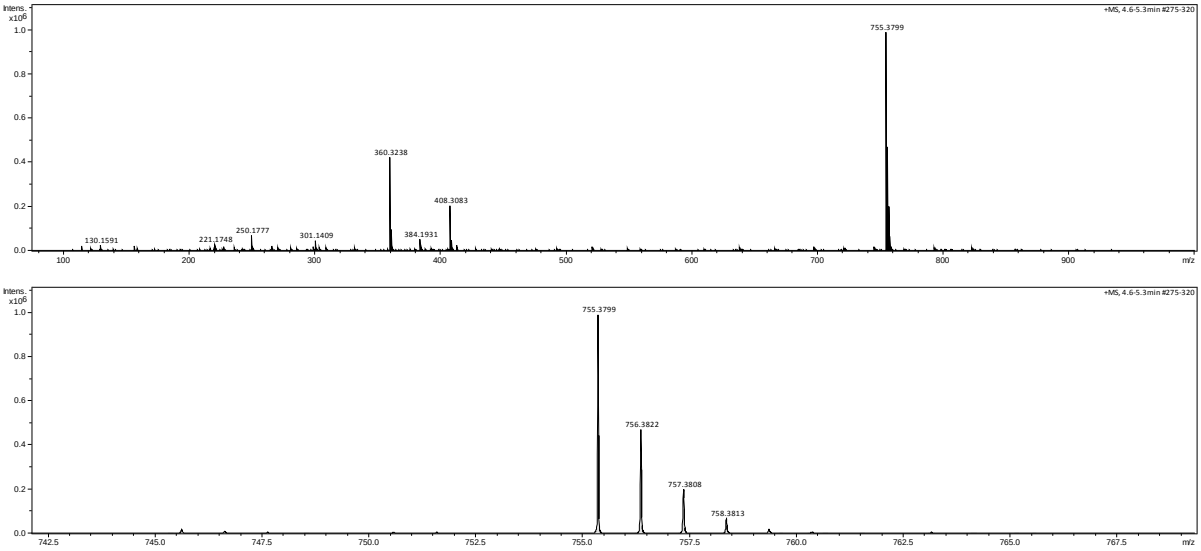
**TLC:** $R_f$ = 0.40 (PE/$Et_2O$ 2:1).

**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 7.90–7.80 (*m*, 2H, CH, Ar), 7.34–7.25 (*m*, 2H, CH, Ar), 6.98–6.88 (*m*, 3H, CH, Ar), 6.88–6.78 (*m*, 2H, CH, Ar), 5.53 (*t*, 1H, $^3J_{H,H}$ = 6.6 Hz, C(H)═), 5.42 (*d*, 1H, $^4J_{H,H}$ = 1.7 Hz, ═C(H)H'), 5.10 (*s*, 1H, ═C(H)H'), 4.51–4.43 (*m*, 1H, C(H)OSi), 4.38 (*s*, 2H, $CH_2O$), 4.31 (*d*, $^2J_{H,H}$ = 14.9 Hz, C(H)H'OSi), 4.11 (*d*, $^2J_{H,H}$ = 14.9 Hz, C(H)H'OSi), 3.89 (*s*, 2H, $CH_2O$), 3.73 (*dd*, 1H, $^{2,3}J_{H,H}$ = 15.6, 8.8 Hz, C(H)H'$SO_2$), 3.34–3.18 (*m*, 9H, C(H)H'$SO_2$ + 2 × $CH_2O$ + $OCH_3$ + C(H)C(R)═$CH_2$), 2.29 (*td*, 2H, $^3J_{H,H}$ = 6.9, 6.8 Hz, $CH_2$), 1.69 (*s*, 3H, $CH_3$), 0.98 (*s*, 18H, 2 × $SiC(CH_3)_3$), 0.24 (*s*, 3H, Si($CH_3$)($CH_3$)'), 0.18 (*s*, 3H, Si($CH_3$)($CH_3$)'), 0.11–0.08 (*m*, 6H, Si($CH_3$)($CH_3$)').

**$^{13}$C{$^1$H} NMR** (75 MHz, $C_6D_6$): $\delta$ = 159.2 ($COCH_3$), 146.0 ($R_2C$═), 140.6 ($C_{quart}$, Ar), 134.2 ($R_2C$═), 132.7 (CH, Ar), 130.9 ($C_{quart}$, Ar), 129.0 (CH, Ar), 128.7 (CH, Ar), 127.9 (CH, Ar), 123.3 (C(H)═), 113.6 (CH, Ar), 112.8 (═$CH_2$), 75.4 ($CH_2O$), 73.2 ($CH_2O$), 72.0 (C(H)OSi), 71.1 ($CH_2O$), 70.5 ($CH_2O$), 64.9 ($CH_2OSi$), 56.7 ($CH_2SO_2$), 54.3 ($OCH_3$), 41.4 (C(H)C(R)═$CH_2$), 28.3 ($CH_2$), 25.8 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), 13.7 ($CH_3$), –4.7 ($Si(CH_3)_2$), –5.2 (Si($CH_3$)($CH_3$)'), –5.7 (Si($CH_3$)($CH_3$)').

**IR** (ATR): $\tilde{\nu}$ = 3902 (*w*), 3854 (*w*), 3737 (*w*), 3712 (*w*), 3675 (*w*), 3650 (*w*), 3567 (*w*), 2930 (*m*), 2856 (*m*), 1699 (*w*), 1650 (*w*), 1614 (*w*), 1513 (*m*), 1462 (*m*), 1400 (*w*), 1362 (*w*), 1306 (*m*), 1253 (*s*), 1087 (*s*), 967 (*w*), 940 (*w*), 910 (*w*), 836 (*s*), 750 (*s*), 688 (*m*) $cm^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{39}H_{64}O_7SSi_2$ $[M+Na]^+$ 755.3803; observed 755.3799.

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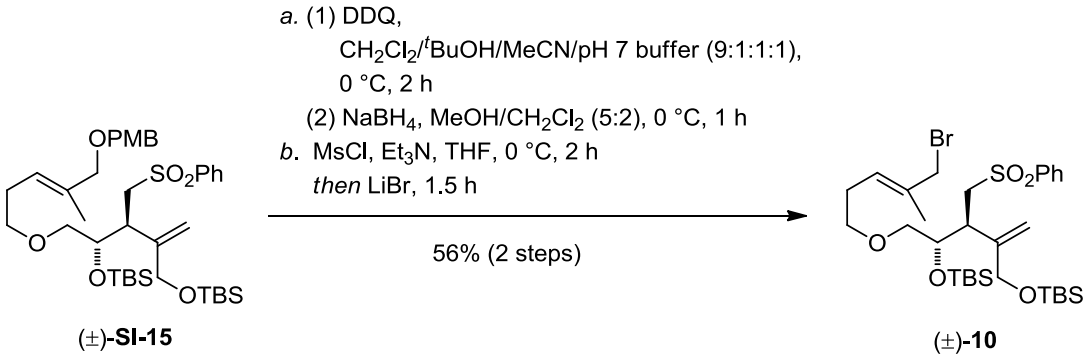
**(2*S**,3*S**,*E*)-2-[(*tert*-butyldimethylsilyl)oxy]-3-[(phenylsulfonyl)methyl]-4-{[(*tert*-butyldimethylsilyl)oxy]methyl}pent-4-en-1-yl-5'-bromo-4'-methyl-pent-3'-en-1-ylether [(±)-10]**




(±)-**SI-15** (±)-**10**

To a stirred solution of PMB ether (±)-**SI-15** (405 mg, 0.55 mmol, 1.0 equiv.) in a mixture of $CH_2Cl_2$ (4.5 ml), $^t$BuOH (0.5 ml), MeCN (0.5 ml) and pH 7 phosphate buffer (0.5 ml, 0.5 M) was added DDQ (251 mg, 1.10 mmol, 2.0 equiv.) in six portions, every 2 min at 0 °C. After 1 h another equivalent of DDQ was added, which was repeated after 2 h (TLC control: PE/MTBE 2:1). After 3 h at 0 °C the mixture was filtered. Sat. $NaHCO_3$ solution (20 ml) was added and the mixture was stirred until all solids dissolved and the solution had turned red (~20 min). More sat. $NaHCO_3$ solution (40 ml) was added and the mixture was extracted with

MTBE/PE (2:1, 60 ml). The organic layer was washed with sat. $NaHCO_3$ solution (60 ml) and brine (60 ml), dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residual oil was taken up in anhydrous MeOH/$CH_2Cl_2$ (5:2, 7 ml) and cooled to 0 °C. $NaBH_4$ (52.0 mg, 1.38 mmol, 2.5 equiv.) was added under stirring and the mixture was kept at this temperature for 1 h (TLC control: PE/EtOAc 2:1) followed by addition of sat. $NH_4Cl$ solution (15 ml) and $CH_2Cl_2$ (20 ml). The organic layer was separated, washed with sat. $NaHCO_3$ solution (20 ml) and brine (20 ml), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography of the residue (MTBE/PE 3:2, 4 × 30 cm) provided the allyl alcohol (±)-**SI-17** (242 mg, 0.39 mmol, 71%) as a colorless oil, which was processed further.

**TLC:** $R_f$ = 0.42 (PE/MTBE 1:1).

To a stirred solution of anhydrous $Et_3N$ (70.7 µl, 51.3 mg, 0.51 mmol, 1.30 equiv.) in anhydrous THF (2.0 ml) at 0 °C was added MsCl (30.2 µl, 44.7 mg, 0.39 mmol, 1.0 equiv.). After 5 min a solution of allyl alcohol (±)-**SI-17** (242 mg, 0.39 mmol, 1.0 equiv.) in anhydrous THF (1.0 ml) was added and the suspension was stirred for 1 h. Then anhydrous LiBr (339 mg, 3.90 mmol, 10.0 equiv.) in anhydrous THF (1.96 ml; stored as 2.0 M stock solution with 4 Å molecular sieves) was added at 0 °C and the mixture was stirred for another 2 h (TLC control: PE/EtOAc 3:1). pH 7 phosphate buffer (10 ml, 0.5 M) was added and the mixture was extracted with MTBE (20 ml). The extract was washed with brine (2 × 20 ml), dried with $MgSO_4$, and filtered. Toluene (1.0 ml) was added and the solution was concentrated *in vacuo*. Column chromatography of the residue (PE/MTBE 8:1→6:1→4:1, 3 × 20 cm) provided the allyl bromide (±)-**10** (209 mg, 0.31 mmol, 79%) as a colorless oil, which was stored at –25 °C.

**TLC:** $R_f$ = 0.32 (PE/MTBE 6:1).

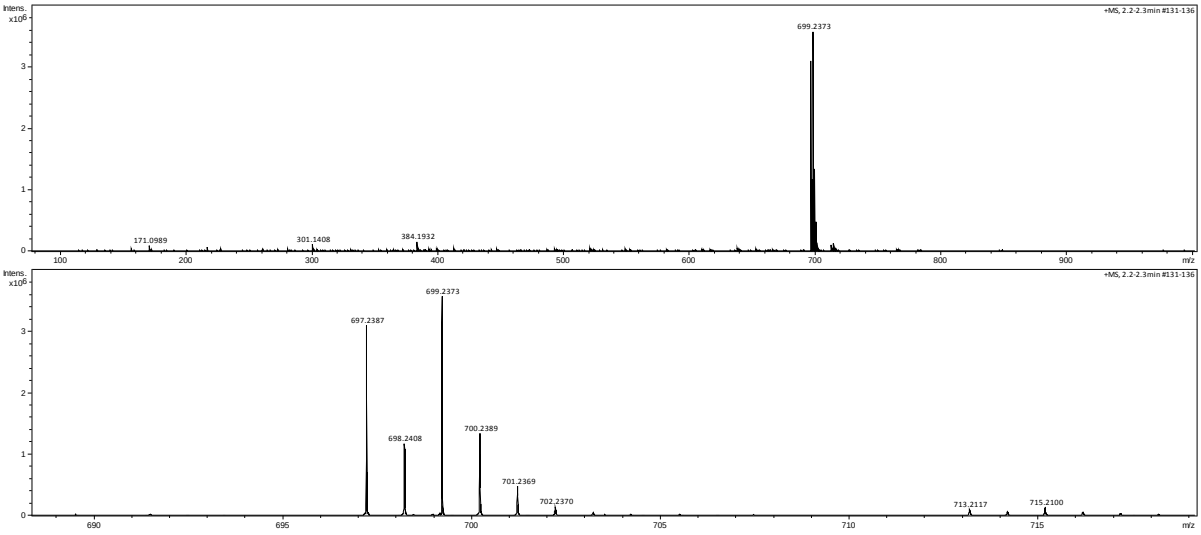
**$^1$H NMR** (300 MHz, $C_6D_6$): $\delta$ = 7.87–7.82 (*m*, 2H, CH, Ar), 6.99–6.89 (*m*, 3H, CH, Ar), 5.42 (*d*, 1H, $^4J_{H,H}$ = 1.8 Hz, ═C(H)H'), 5.36 (*t*, 1H, $^3J_{H,H}$ = 7.0 Hz, C(H)═), 5.09 (*d*, 1H, $^4J_{H,H}$ = 1.5 Hz, ═C(H)H'), 4.49–4.43 (*m*, 1H, C(H)OSi), 4.30 (*dt*, 1H, $^{2,4}J_{H,H}$ = 14.9, 1.9 Hz, C(H)H'OSi), 4.09 (*d*, 1H, $^2J_{H,H}$ = 14.8 Hz, C(H)H'OSi), 3.73–3.64 (*m*, 3H, $CH_2Br$ + C(H)H'$SO_2$), 3.29–3.21 (*m*, 4H, 2 × $CH_2O$), 3.16–3.02 (*m*, 2H, C(H)C(R)═$CH_2$ + C(H)H'$SO_2$), 2.08 (*d*, 1H, $^3J_{H,H}$ = 6.8 Hz, C(H)H'), 2.03 (*d*, 1H, $^3J_{H,H}$ = 6.7 Hz, C(H)H'), 1.60

(*d*, 3H, $^4J_{H,H}$ = 1.0 Hz, $CH_3$), 0.98 (*s*, 18H, 2 × $SiC(CH_3)_3$), 0.24 (*s*, 3H, $Si(C\underline{H}_3)(CH_3)$'), 0.16 (*s*, 3H, $Si(CH_3)(C\underline{H}_3)$'), 0.11–0.08 (*m*, 6H, $Si(CH_3)(CH_3)$').

**$^{13}C\{^1H\}$ NMR** (75 MHz, $C_6D_6$): $\delta$ = 146.5 ($R_2C$═), 141.1 ($C_{quart}$, Ar), 133.9 ($R_2C$═), 133.2 (CH, Ar), 129.2 (CH, Ar), 128.3 (CH, Ar), 127.9 (C(H)═), 113.3 (═$CH_2$), 73.7 ($CH_2O$), 72.4 ($CH_2O$), 70.3 (C(H)OSi), 65.4 ($CH_2O$), 57.1 ($CH_2SO_2$), 41.8 ($\underline{C}$(H)C(R)═$CH_2$), 41.1 ($CH_2$), 29.2 ($CH_2$), 26.2 ($SiC(\underline{C}H_3)_3$), 26.1 ($SiC(\underline{C}H_3)_3$), 18.5 ($Si\underline{C}(CH_3)_3$), 18.5 ($Si\underline{C}(CH_3)_3$), 14.7 ($CH_3$), –4.2 ($Si(\underline{C}H_3)(CH_3)$'), –4.7 ($Si(CH_3)(\underline{C}H_3)$'), –5.2 ($Si(CH_3)_2$).

**IR** (ATR): $\tilde{\nu}$ = 2953 (*m*), 2930 (*m*), 2888 (*m*), 2857 (*m*), 1470 (*m*), 1391 (*w*), 1362 (*w*), 1307 (*m*), 1254 (*m*), 1209 (*w*), 1146 (*m*), 1086 (*s*), 1006 (*m*), 967 (*m*), 939 (*m*), 909 (*m*), 835 (*s*), 776 (*s*), 751 (*s*), 720 (*m*), 689 (*m*) $cm^{-1}$.

**HRMS** (ESI, TOF): *m/z* calc'd for $C_{31}H_{55}BrO_5SSi_2$ $[M+Na]^+$ 697.2384; observed 697.2387.

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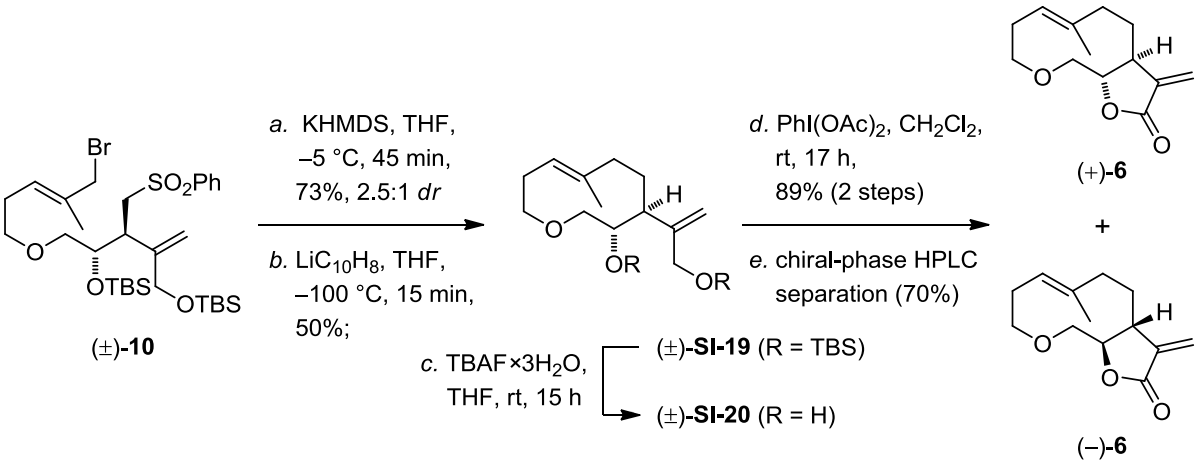
**(3a*S*,11a*S*,*E*)-6-Methyl-3-methylene-3,3a,4,5,8,9,11,11a-octahydro-2*H*-furo[2,3-c]oxecin-2-one [(+)-6] and (3a*R*,11a*R*,*E*) isomer (–)-6**



To a stirred solution of a KHMDS solution (0.41 ml, 0.41 mmol, 4.0 equiv., 1.0 M in THF) in anhydrous THF (25 ml) at –5 °C was added a solution of sulfone (±)-**10** (70.0 mg, 0.10 mmol, 1.0 equiv.) in anhydrous THF (5.0 ml) within 30 min using a syringe pump (0.166 ml/min). After another 15 min (TLC control: PE/MTBE 4:1) sat. $NH_4Cl$ solution (30 ml) was added, followed by $Et_2O$ (90 ml). The organic layer was separated, washed with sat. $NaHCO_3$ solution (90 ml) and brine (90 ml), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. After column chromatography of the residue (PE/MTBE, 4:1, 2 × 30 cm) the inseparable diastereomeric sulfones (±)-**SI-18a** and (±)-**SI-18b** were obtained as colorless glass, which was processed further. Yield in total: 92 mg, 0.15 mmol, 73%, ~2.5:1 dr.

**TLC:** $R_f$ = 0.36 (PE/MTBE 4:1).

The sulfones (±)-**SI-18a** and (±)-**SI-18b** (42 mg, 70.6 μmol, 1.0 equiv.) were dissolved in anhydrous THF (1.0 ml) and cooled to –100 °C. A solution of lithium naphthalenide in anhydrous THF (0.2 ml, 0.12 mmol, 1.7 equiv., 0.60 M in THF) was added dropwise until a dark green color persisted. After 15 min at –100 °C (TLC control: PE/MTBE 6:1) a 4:1 mixture of EtOH and AcOH (1 ml) was added. The cooling bath was removed and the mixture was added to pH 7 phosphate buffer (20 ml) and $Et_2O$ (20 ml). After 10 min of vigorous stirring, the organic layer was collected and washed with sat. $NaHCO_3$ solution (20 ml) and brine (20 ml). The organic extract was dried with $MgSO_4$, filtered, and all volatiles were removed *in vacuo*. Column chromatography of the residue ($SiO_2$ 15–40 μm, PE/MTBE 40:1, 2 × 25 cm) delivered cyclic ether (±)-**SI-19** (16.0 mg, 35.2 μmol, 50%) as colorless oil, which was taken further to the next step.

**TLC:** $R_f$ = 0.36 (PE/MTBE 40:1).

The material such obtained was dissolved in anhydrous THF (0.4 ml) at rt under stirring, followed by addition of a TBAF×$3H_2O$ solution (70.4 μl, 70.4 μmol, 2.0 equiv.). The reaction mixture was stirred for 15 h at rt (TLC control: PE/MTBE 40:1) and then added to a stirred mixture of pH 7 phosphate buffer (10 ml) and MTBE (10 ml). After 10 min, the organic layer was collected, washed sequentially with sat. $NaHCO_3$ (10 ml) and brine (3 × 5 ml), dried with $MgSO_4$, filtered through a plug of silica gel (MTBE, d × h = 3 × 4 cm), and concentrated *in vacuo*. The residual oil containing diol (±)-**SI-20** was dissolved in anhydrous $CH_2Cl_2$ (0.5 ml) and TEMPO (1.60 mg, 10.5 μmol, 0.3 equiv.) was added at rt with stirring, followed by

$PhI(OAc)_2$ (33.8 mg, 105 μmol, 3.0 equiv.). After 17 h (TLC control, MTBE) the mixture was diluted with PE (0.5 ml) and directly subjected to column chromatography (PE/EtOAc 3:1, 2 × 20 cm). Parthenolide analog (±)-**6** (7.0 mg, 31.5 μmol, 89% over 2 steps) was obtained as colorless oil. Separation of the enantiomers was achieved by chiral-phase HPLC (70% recovery, see below).

**TLC:** $R_f$ = 0.30 (PE/EtOAc 3:1).

$[\alpha]_D^{23}$ = +87.1 (*c* = 1.0, THF, >99% *ee*) for (*S*,*S*)-**6**.

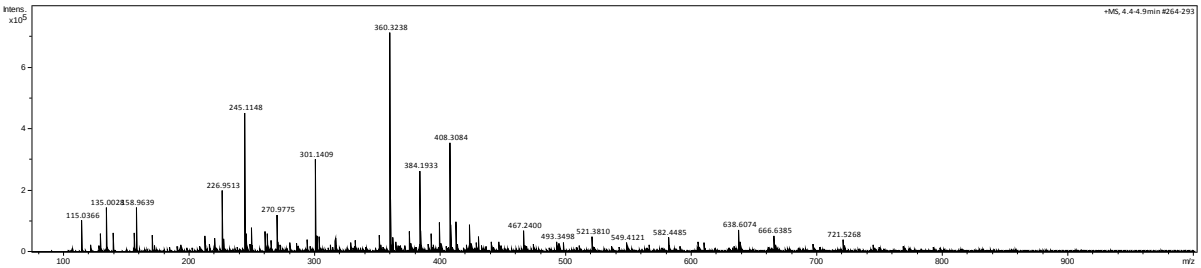
$[\alpha]_D^{23}$ = –89.3 (*c* = 1.0, THF, >99% *ee*) for (*R*,*R*)-**6**.

**$^1$H NMR** (400 MHz, $CDCl_3$, +**50 °C**): $\delta$ = 6.25 (*d*, 1H, $^4J_{H,H}$ = 2.2 Hz, =C(H)H'), 5.63 (*d*, 1H, $^4J_{H,H}$ = 1.9 Hz, =C(H)H'), 5.35 (*br s*, 1H, C(H)=), 4.28 (*br s*, 1H, C(H)OC=O), 3.87–3.74 (m, 1H, C(H)H'O), 3.67 (*d*, 1H, $^3J_{H,H}$ = 12.2 Hz, C(H)H'O), 3.57–3.44 (*m*, 1H, C(H)H'O), 3.42–3.29 (*m*, 1H, C(H)H'O), 2.92 (*d*, 1H, $^3J_{H,H}$ = 10.8 Hz, C(H)C(R)=$CH_2$), 2.41–2.13 (*m*, 3H, $CH_2$ + C(H)H'), 1.97–1.83 (*m*, 1H, C(H)H'), 1.82–1.67 (*m*, 4H, $CH_3$ + C(H)H'), 1.58–1.46 (*m*, 1H, C(H)H').

**$^{13}$C{$^1$H} NMR** (101 MHz, $CDCl_3$, **–30 °C**, extracted from ASAP–HSQC–DEPT; mixture of rotamers, only main isomer assigned): $\delta$ = 125.2 (C(H)=), 124.1 (=$CH_2$), 82.7 (C(H)O), 73.8 ($CH_2O$), 70.5 ($CH_2O$), 43.1 (C(H)C(R)=$CH_2$), 40.2 ($CH_2$), 34.9 ($CH_2$), 28.3 ($CH_2$), 16.1 ($CH_3$); three signals missing.[1]

**IR** (ATR): $\tilde{\nu}$ = 3749 (*w*), 3650 (*w*), 3567 (*w*), 2923 (*m*), 2863 (*m*), 2362 (*m*), 1759 (*s*), 1659 (*m*), 1450 (*m*), 1401 (*w*), 1267 (*s*), 1107 (*m*), 1042 (*s*), 943 (*m*), 817 (*m*), 751 (*m*), 670 (*w*), 626 (*w*) $cm^{-1}$.

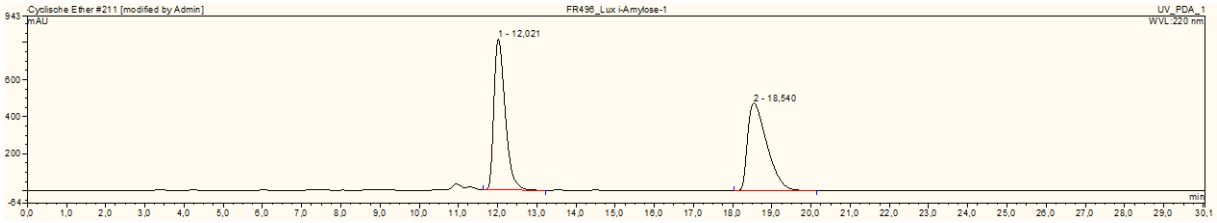
**HRMS** (ESI, TOF): m/z calc'd for $C_{13}H_{18}O_3$ $[M+Na]^+$ 245.1148; observed 245.1148.




[1] Slow conformational isomerism of **6** rendered the recording of standard $^{13}C\{^1H\}$ NMR spectra meaningless, even at elevated or lowered temperatures. However, by using an ASAP–HSQC–DEPT experiment[S15] at –30 °C, ten out of 13 carbon resonances were detected. The signals for three quaternary carbons remained obscure, inherent to the method.

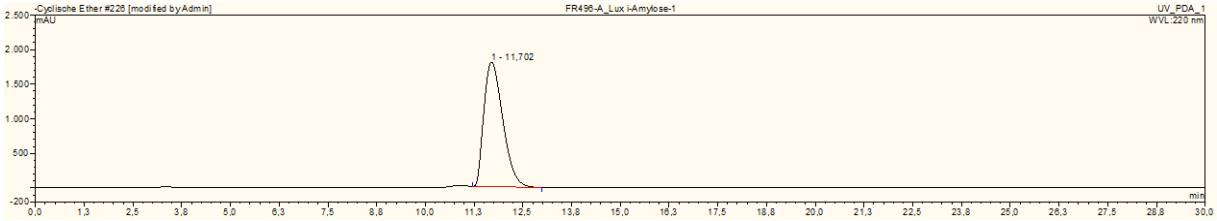
**Chiral-phase HPLC** [Phenomenex Lux i-Amylose-1 column (5 µm, 250 × 4.6 mm ID) with guard cartridge, *n*-Hexan/EtOH, 90:10, 1 ml/min, 25 °C, 220 nm]:

**a.** (±)-**6**

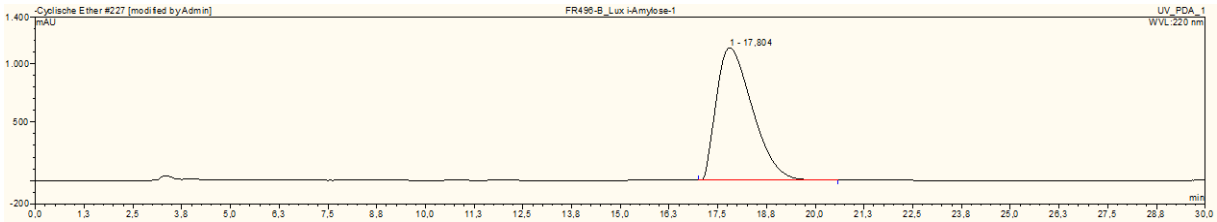



| No. | Ret. time / min | Area / mAU×min | Height / mAU | Rel. area / % | Resolution |
|---|---|---|---|---|---|
| 1 | 12.0 | 270.4 | 813.1 | 50.1 | 9.18 |
| 2 | 18.5 | 268.9 | 471.7 | 49.9 | – |

**b.** (*S*,*S*)-(+)-**6,** >99% *ee* after preparative chiral-phase HPLC.




**c.** (*R*,*R*)-(–)-**6,** >99% *ee* after preparative chiral-phase HPLC.



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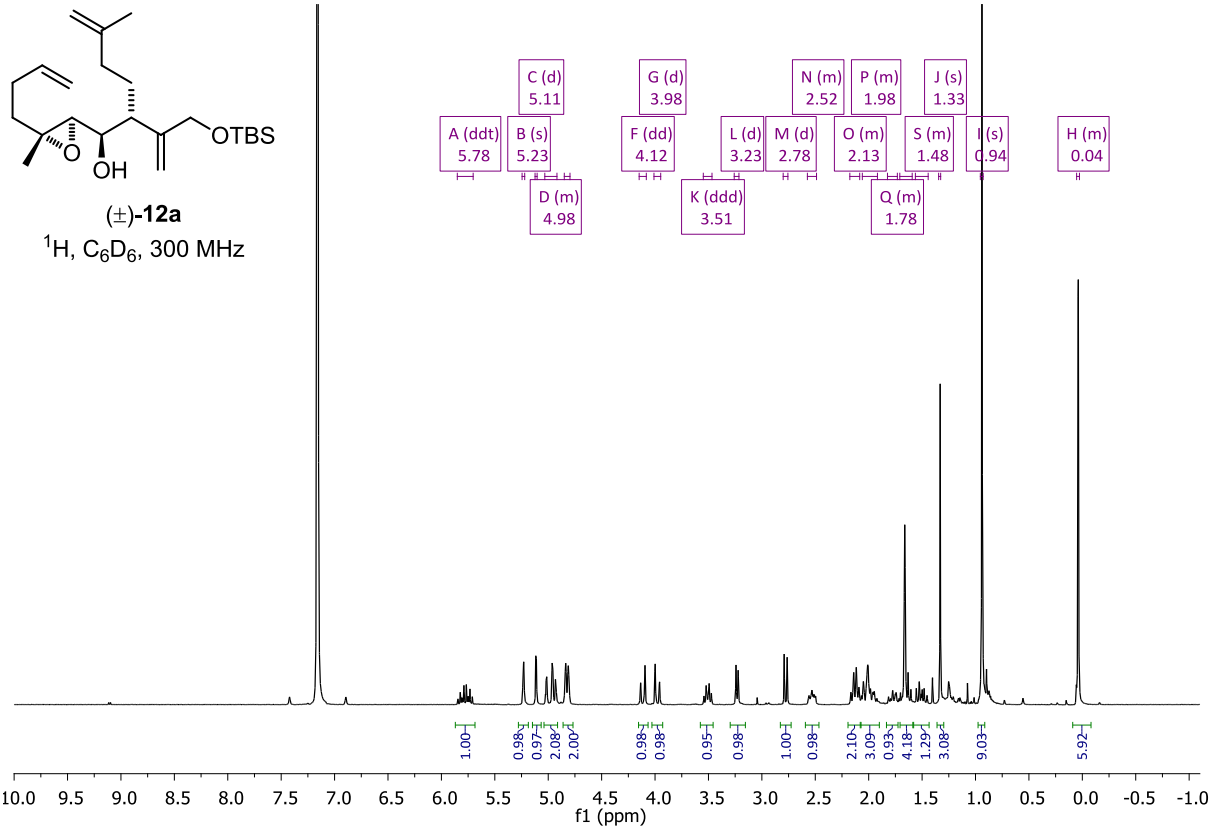
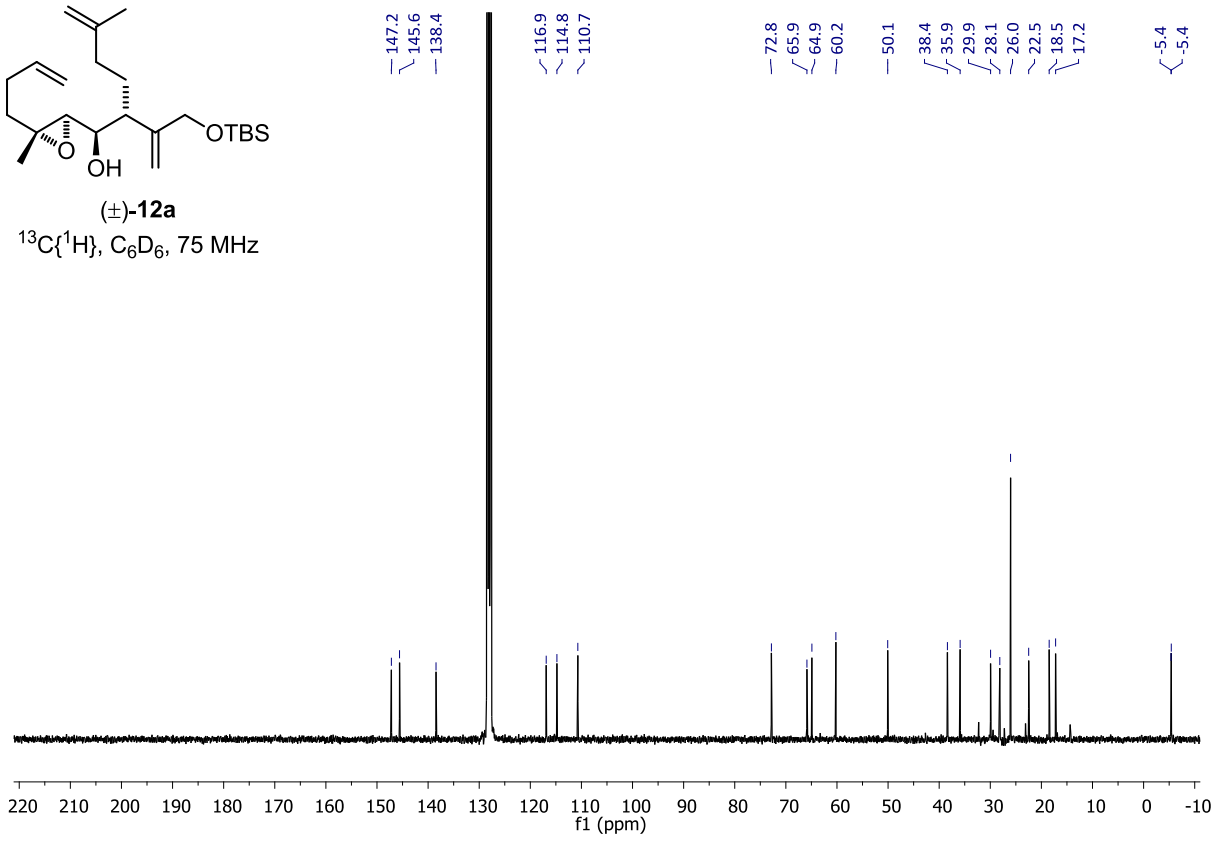
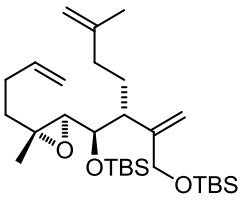
# 5 NMR spectra of new compounds



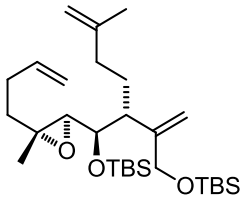






(±)-**12b**

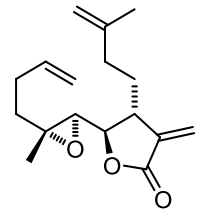
$^{1}H$, $C_6D_6$, 300 MHz




(±)-**12b**

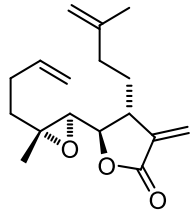
$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz



(±)-**12c**

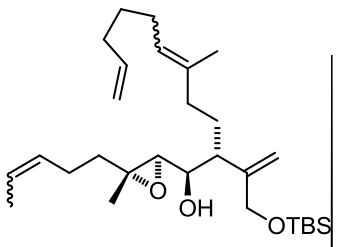
$^{1}$H, $C_6D_6$, 300 MHz



(±)-**12c**

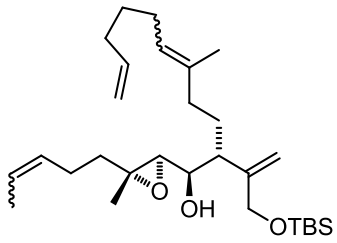
$^{13}$C{$^{1}$H}, $C_6D_6$, 75 MHz




(±)-**SI-8a,b,c,d**

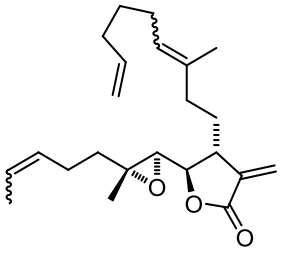
$^{1}H$, $C_6D_6$, 300 MHz



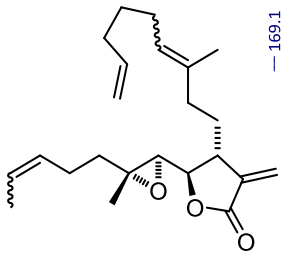

(±)-**SI-8a,b,c,d**

$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz

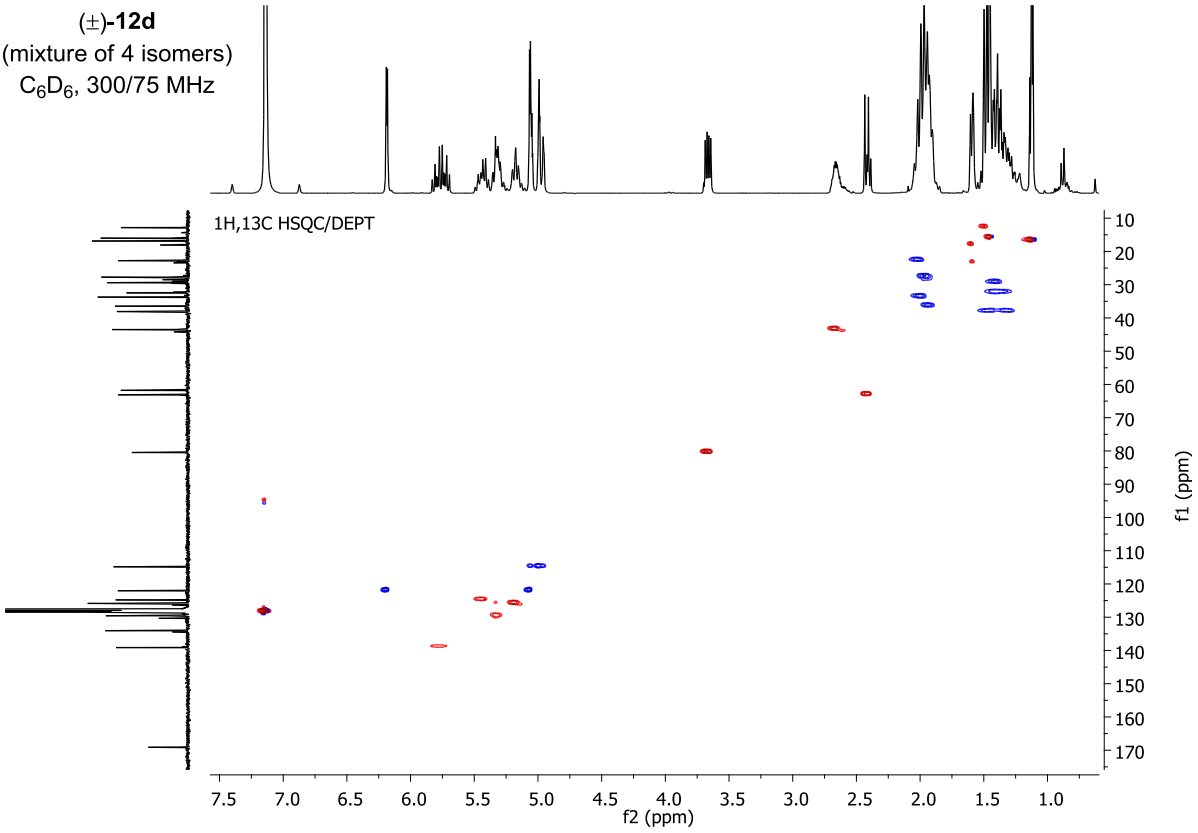


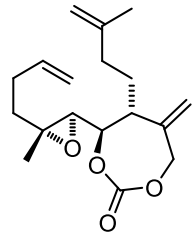
(±)-**12d**
(mixture of 4 isomers)
$^{1}H$, $C_6D_6$, 300 MHz



(±)-**12d**
(mixture of 4 isomers)
$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz

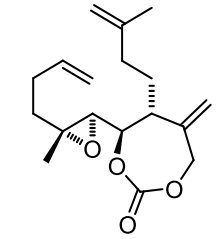

(±)-12d
(mixture of 4 isomers)
C6D6, 300/75 MHz
1H,13C HSQC/DEPT
f2 (ppm)
f1 (ppm)



(±)-**12e**

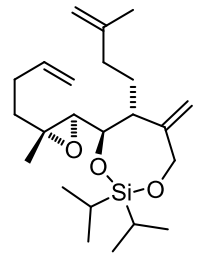
$^{1}H$, $C_6D_6$, 300 MHz



(±)-**12e**

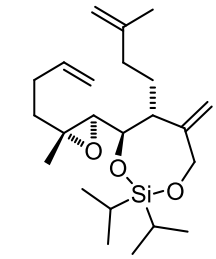
$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz



(±)-**12f**

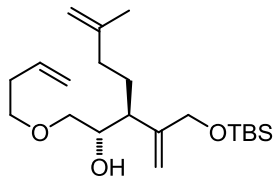
$^{1}H$, $C_6D_6$, 300 MHz



(±)-**12f**

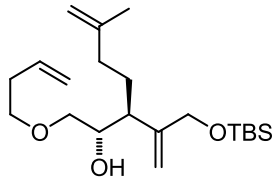
$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz




(±)-**SI-10**

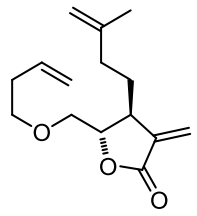
$^{1}$H, $C_6D_6$, 300 MHz




(±)-**SI-10**

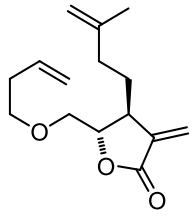
$^{13}$C{$^{1}$H}, $C_6D_6$, 101 MHz



(±)-**8**

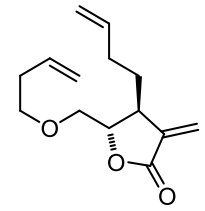
$^{1}H$, $C_6D_6$, 300 MHz



(±)-**8**

$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz

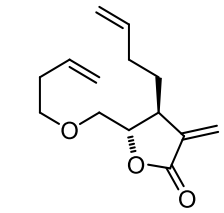


(±)-**9**

$^{1}H$, $C_6D_6$, 300 MHz

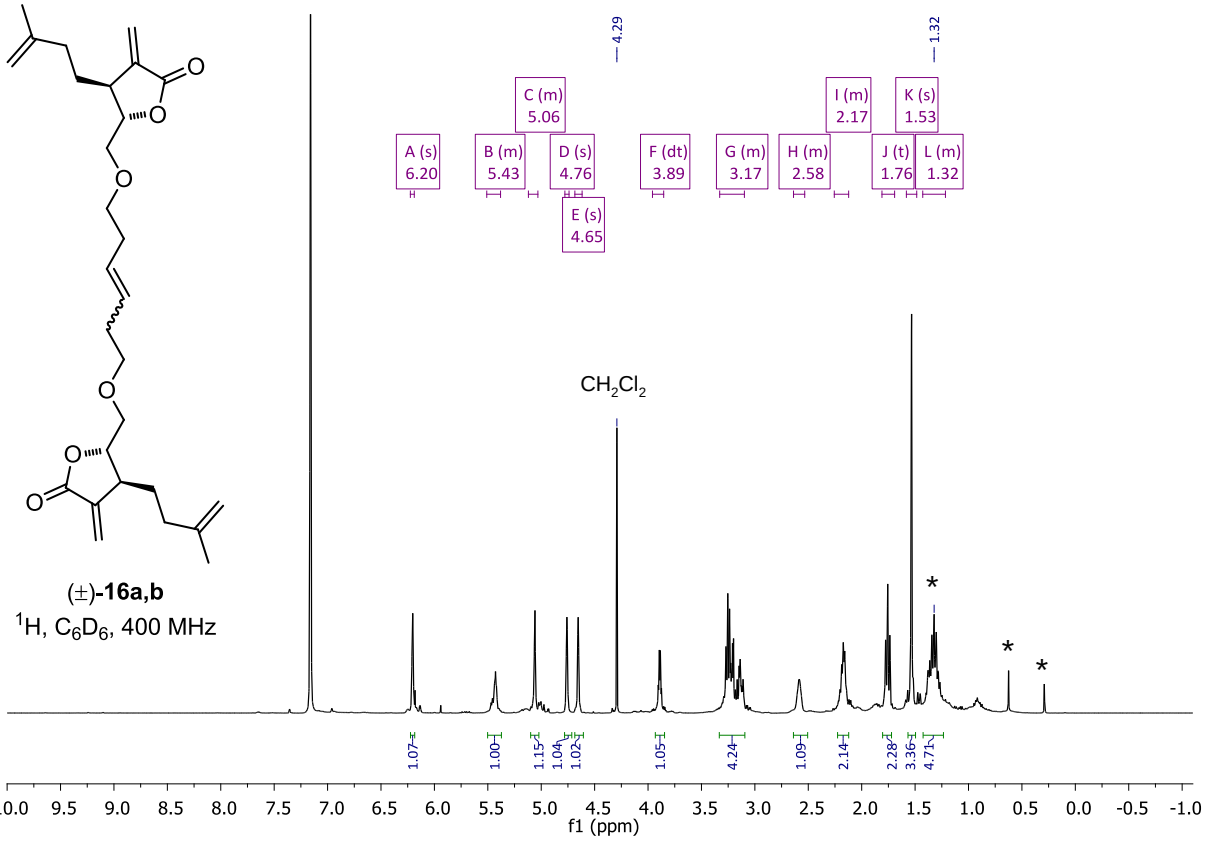



* = impurity

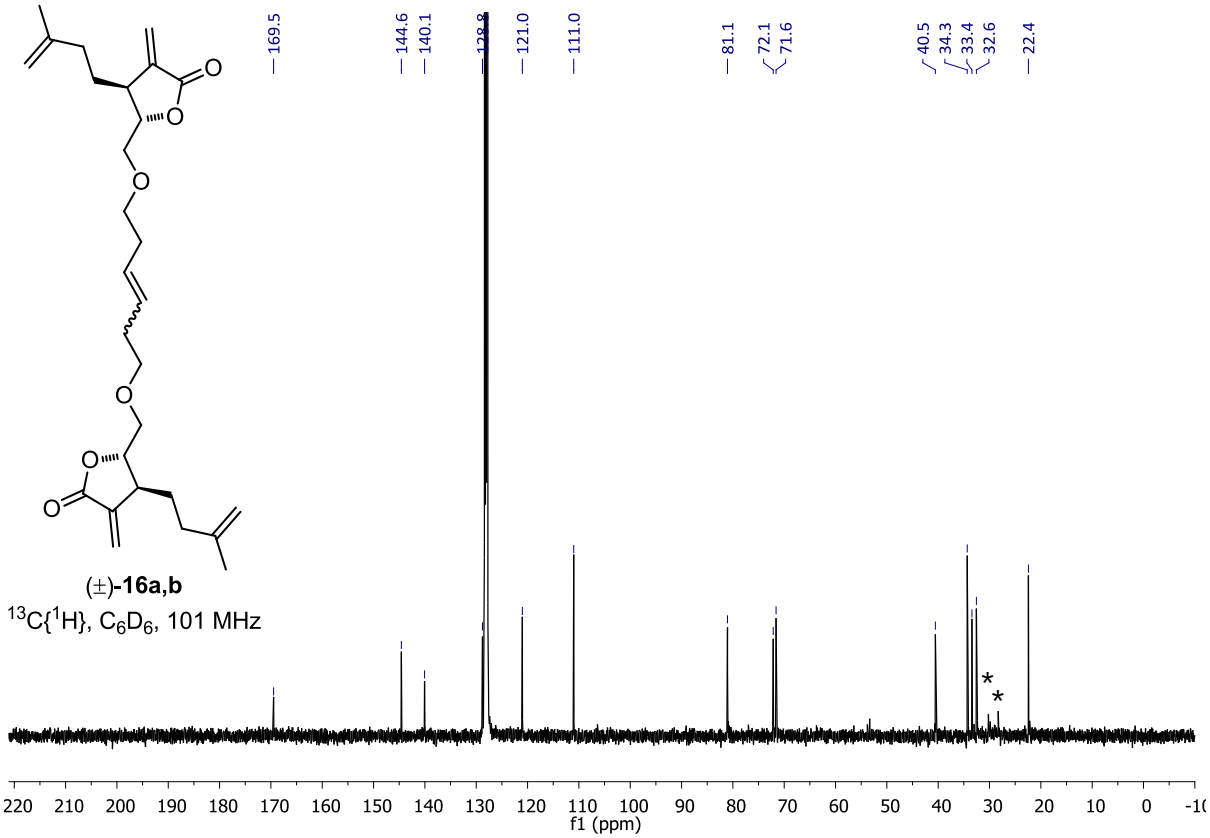


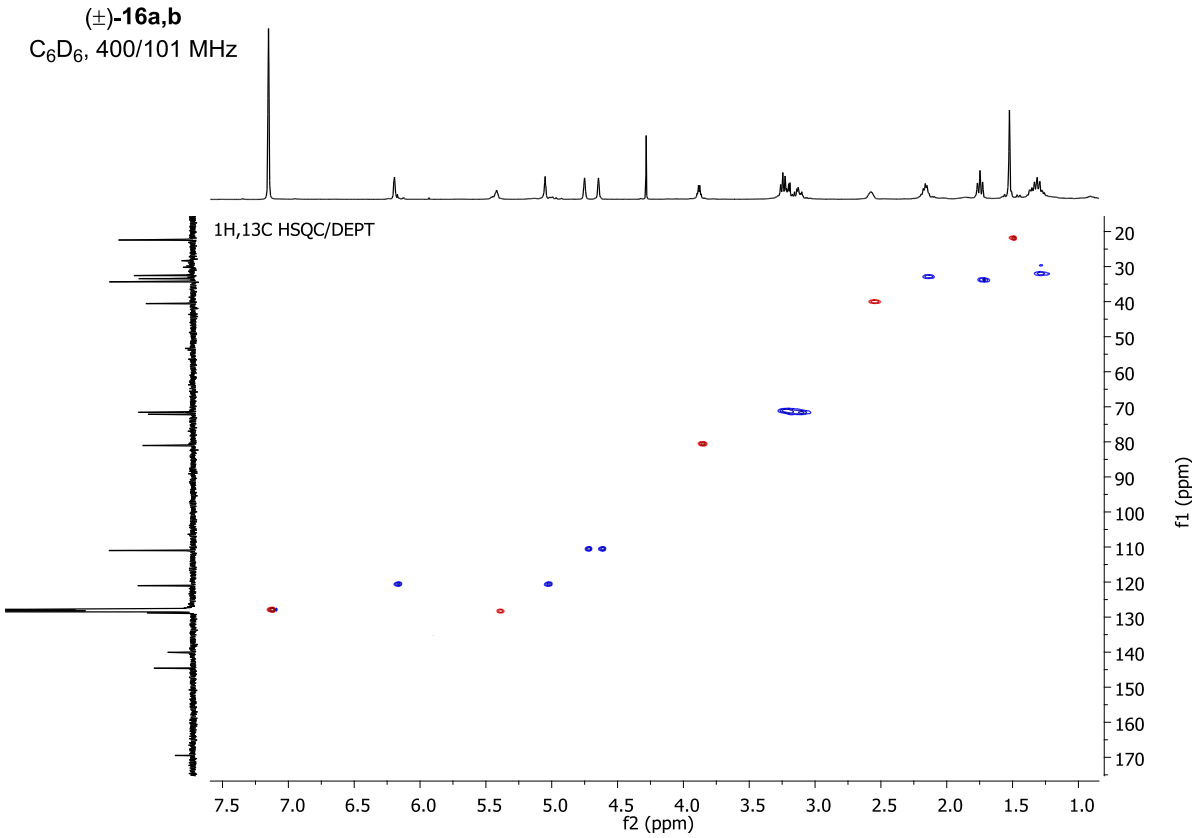
(±)-**9**

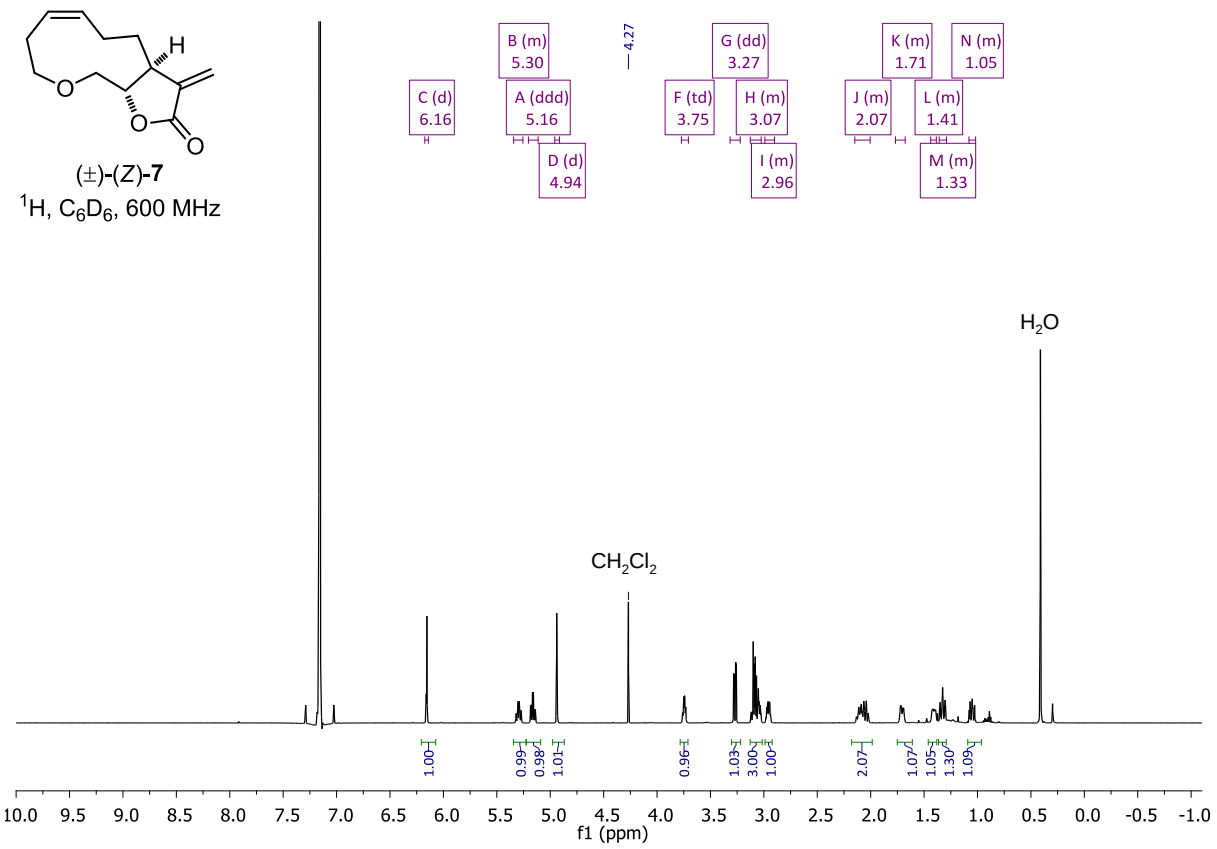
$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz

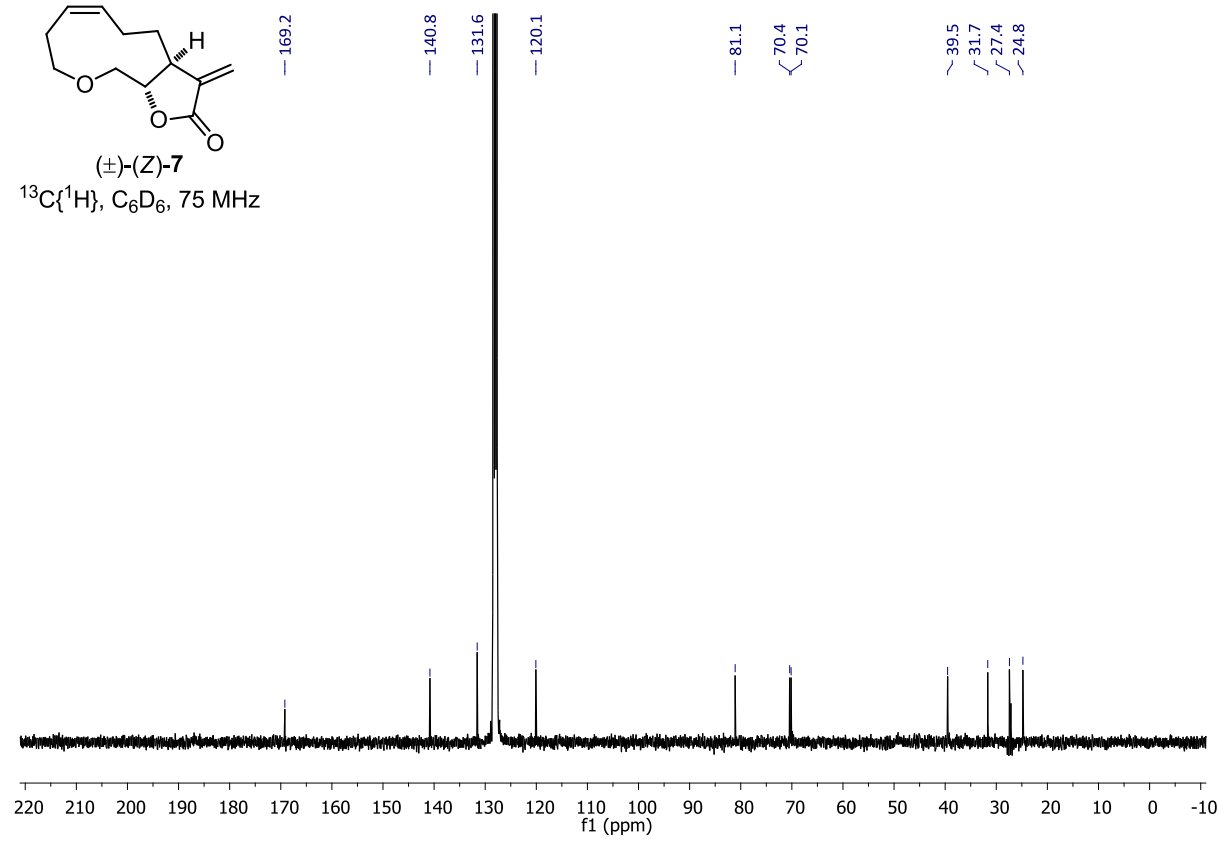

(±)-16a,b
1H, C6D6, 400 MHz
A (s) 6.20
B (m) 5.43
C (m) 5.06
D (s) 4.76
E (s) 4.65
F (dt) 3.89
G (m) 3.17
H (m) 2.58
I (m) 2.17
J (t) 1.76
K (s) 1.53
L (m) 1.32
4.29
1.32
CH2Cl2
*
f1 (ppm)

* = impurity

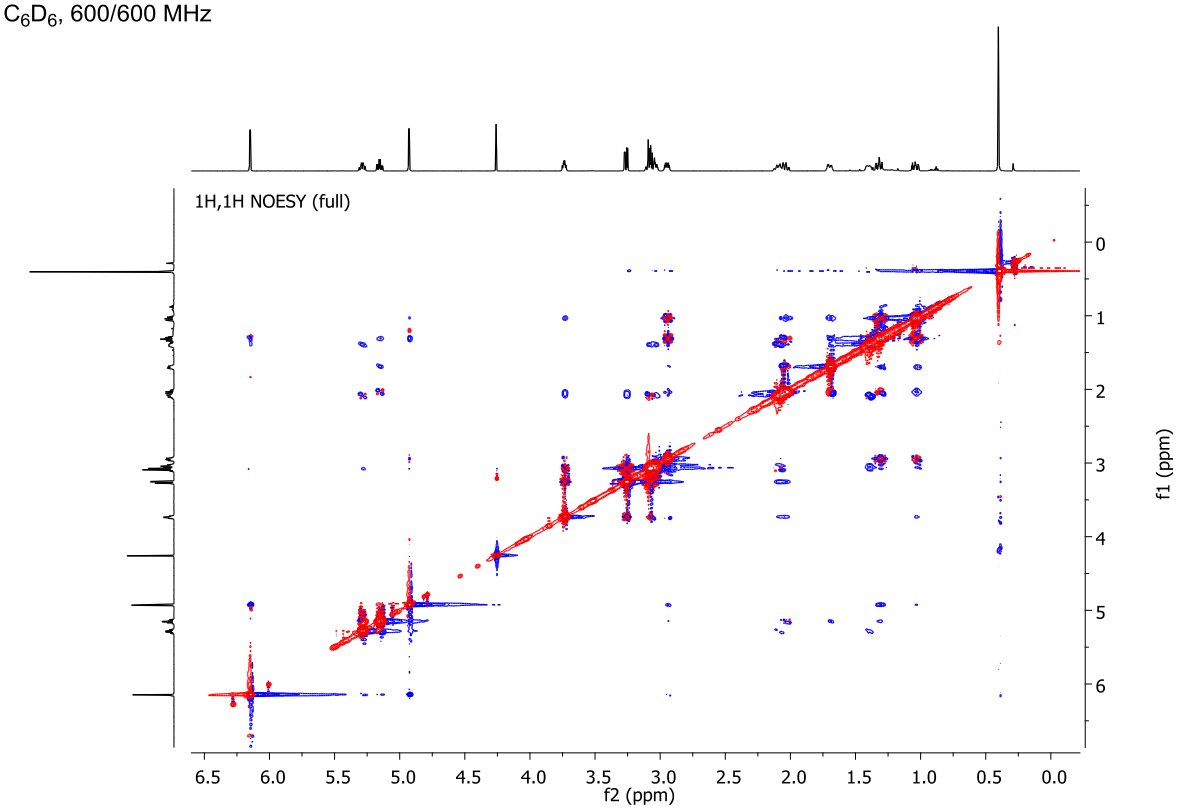

(±)-16a,b
13C{1H}, C6D6, 101 MHz
169.5
144.6
140.1
128.8
121.0
111.0
81.1
72.1
71.6
40.5
34.3
33.4
32.6
22.4
*
f1 (ppm)


(±)-16a,b
C6D6, 400/101 MHz
1H,13C HSQC/DEPT
f2 (ppm)
f1 (ppm)

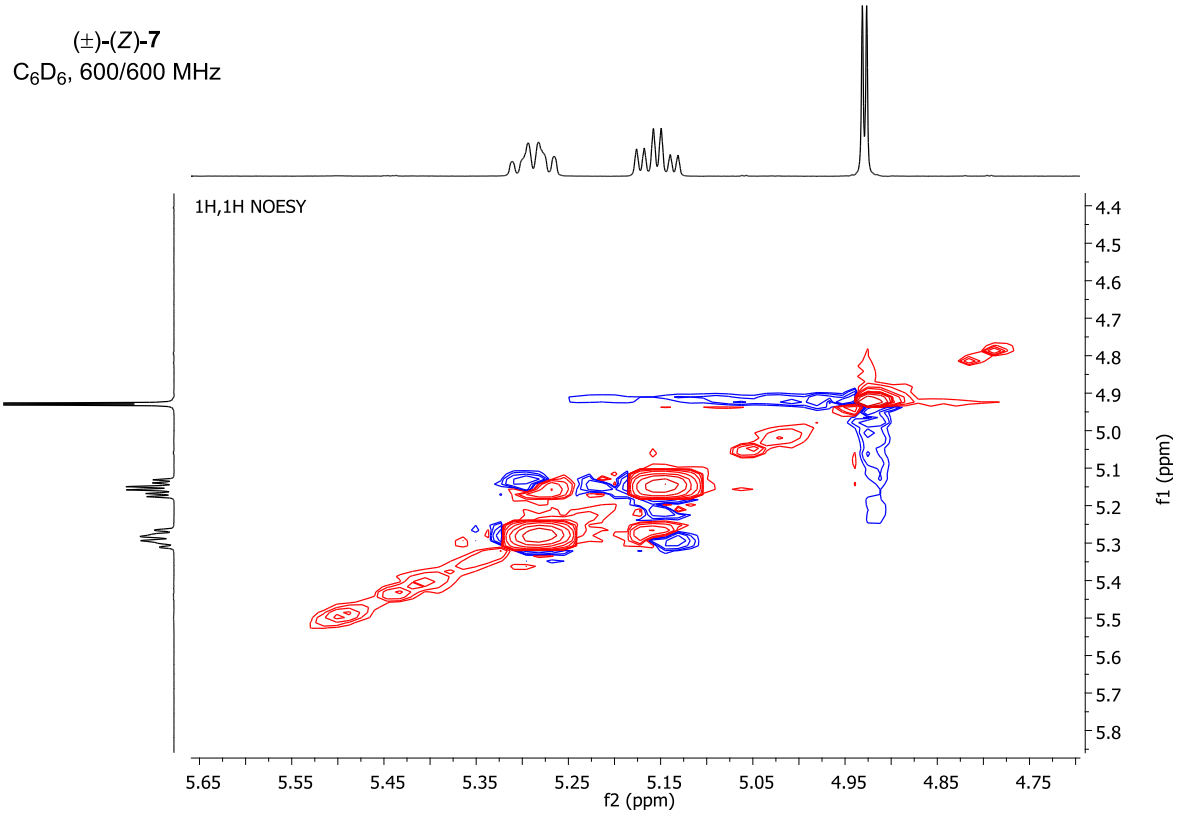

(±)-(Z)-7
1H, C6D6, 600 MHz
C (d) 6.16
B (m) 5.30
A (ddd) 5.16
D (d) 4.94
4.27
F (td) 3.75
G (dd) 3.27
H (m) 3.07
I (m) 2.96
J (m) 2.07
K (m) 1.71
L (m) 1.41
M (m) 1.33
N (m) 1.05
H2O
CH2Cl2
1.00 0.99 0.98 1.01 0.96 1.03 3.00 1.00 2.07 1.07 1.05 1.30 1.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

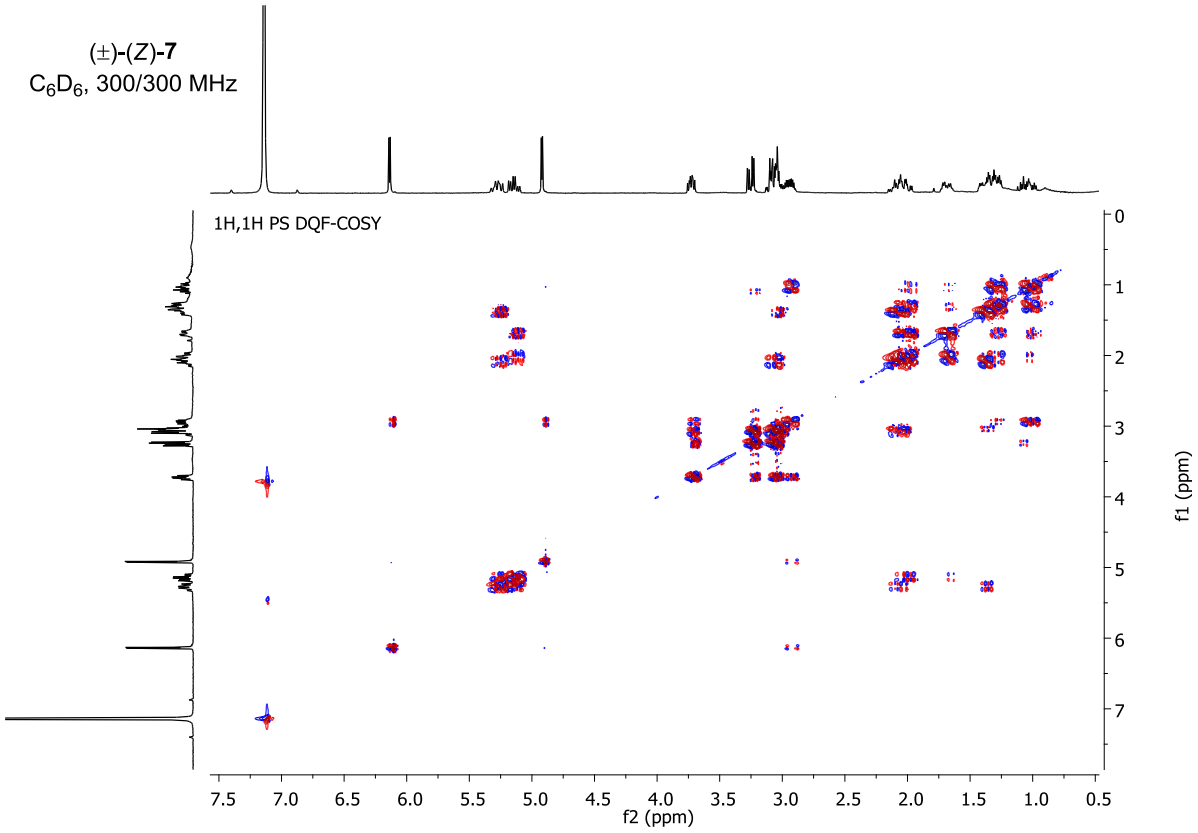

(±)-(Z)-7
13C{1H}, C6D6, 75 MHz
169.2
140.8
131.6
120.1
81.1
70.4
70.1
39.5
31.7
27.4
24.8
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

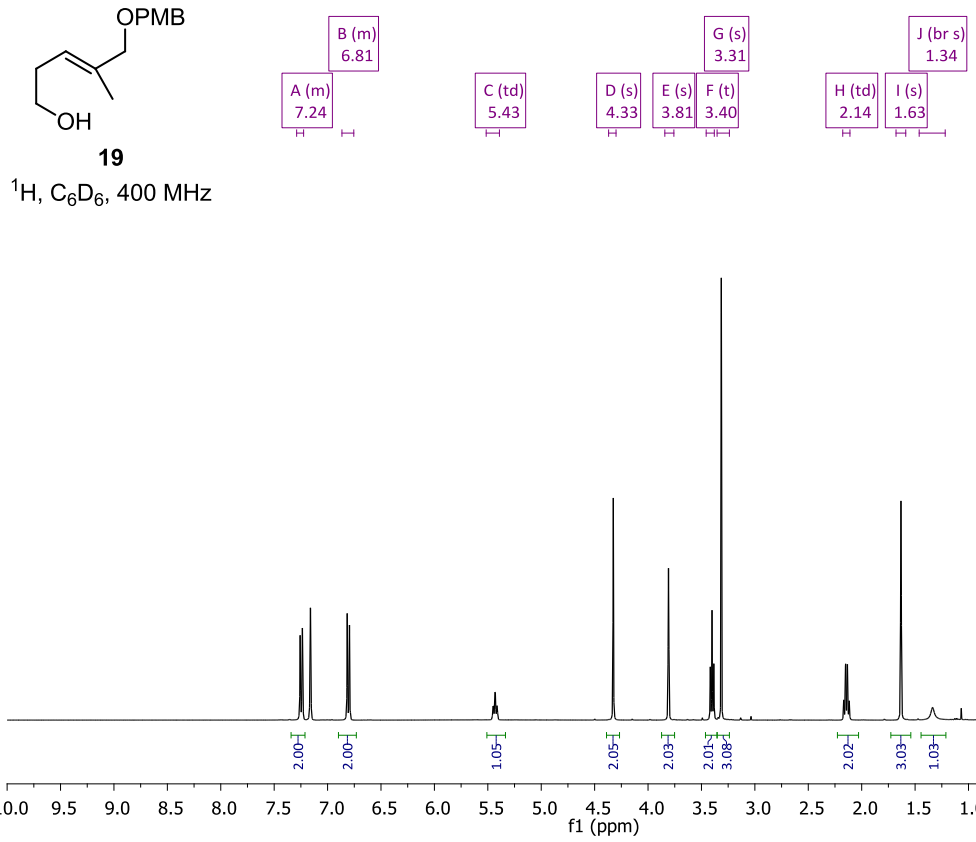
(±)-(*Z*)-**7**
$C_6D_6$, 600/600 MHz



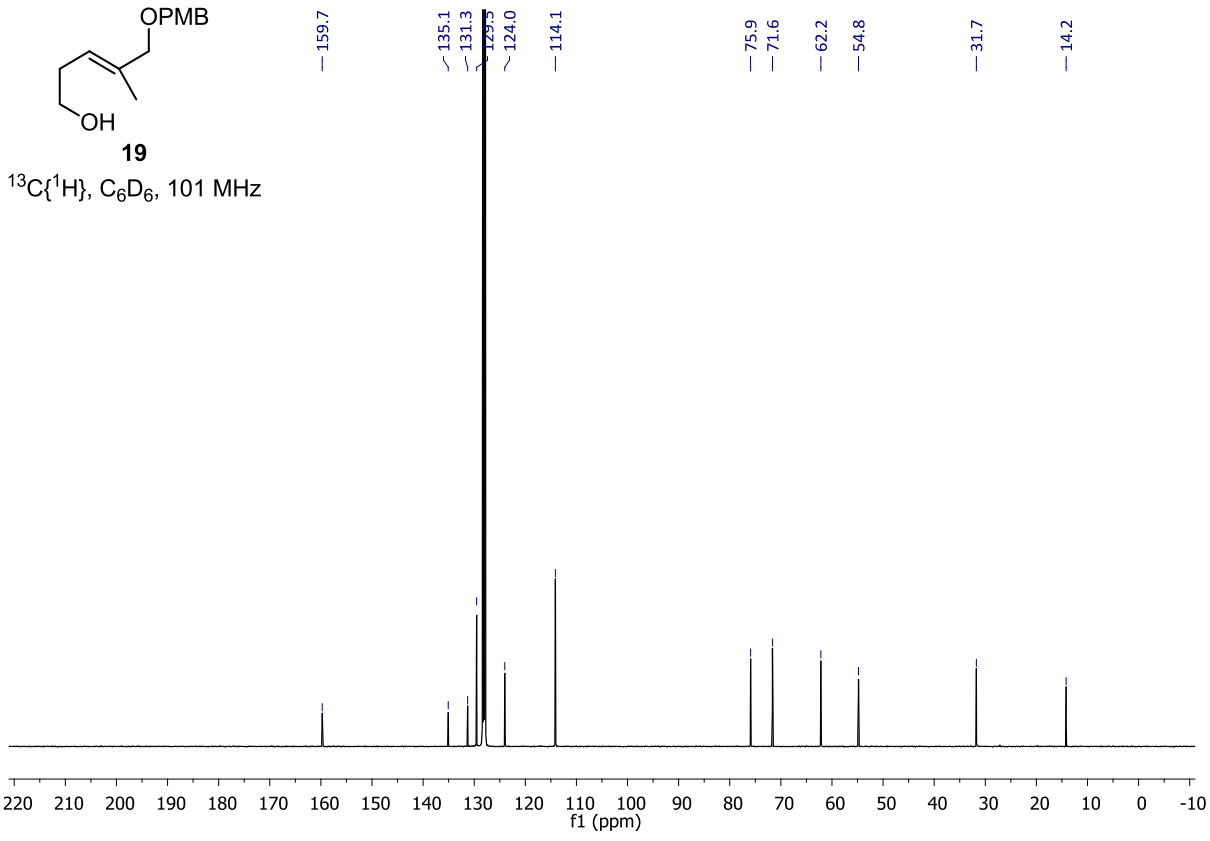

(±)-(*Z*)-**7**
$C_6D_6$, 600/600 MHz




(±)-(Z)-7
C6D6, 300/300 MHz
1H,1H PS DQF-COSY
f2 (ppm)
f1 (ppm)



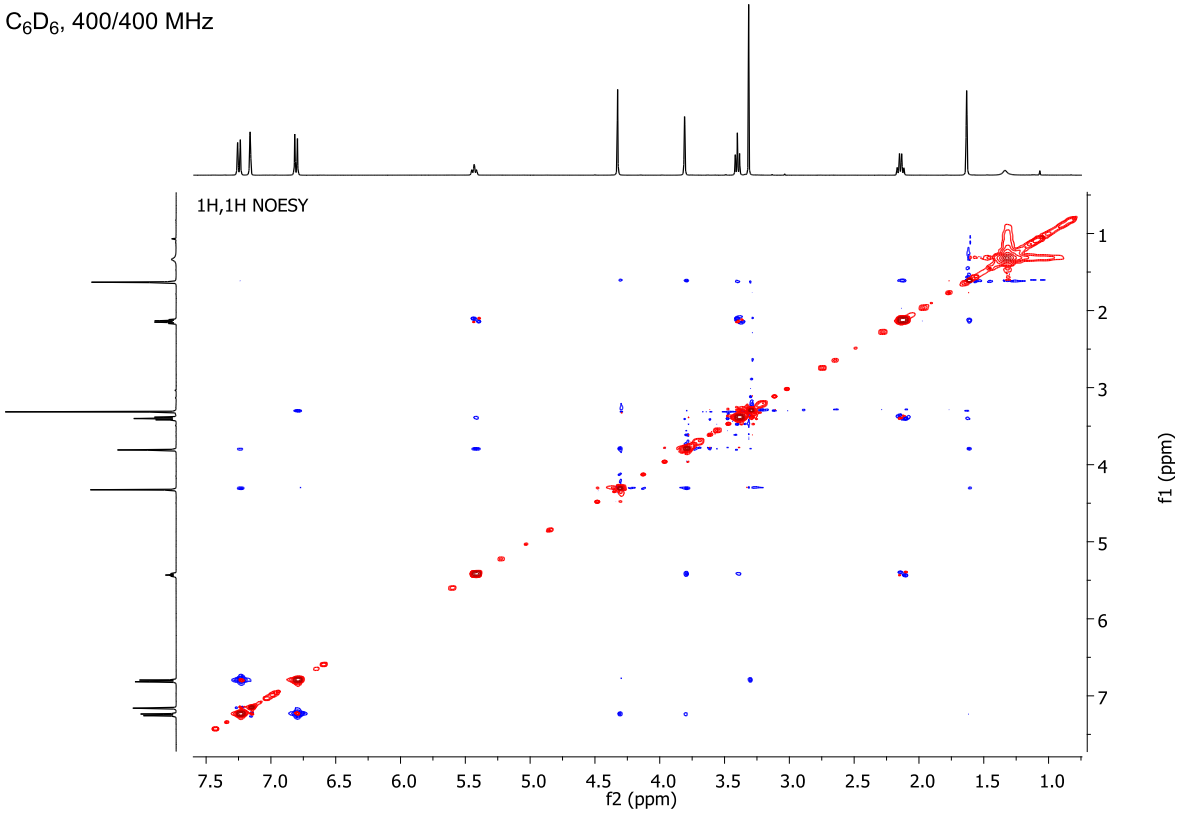

$^{1}H$, $C_6D_6$, 400 MHz

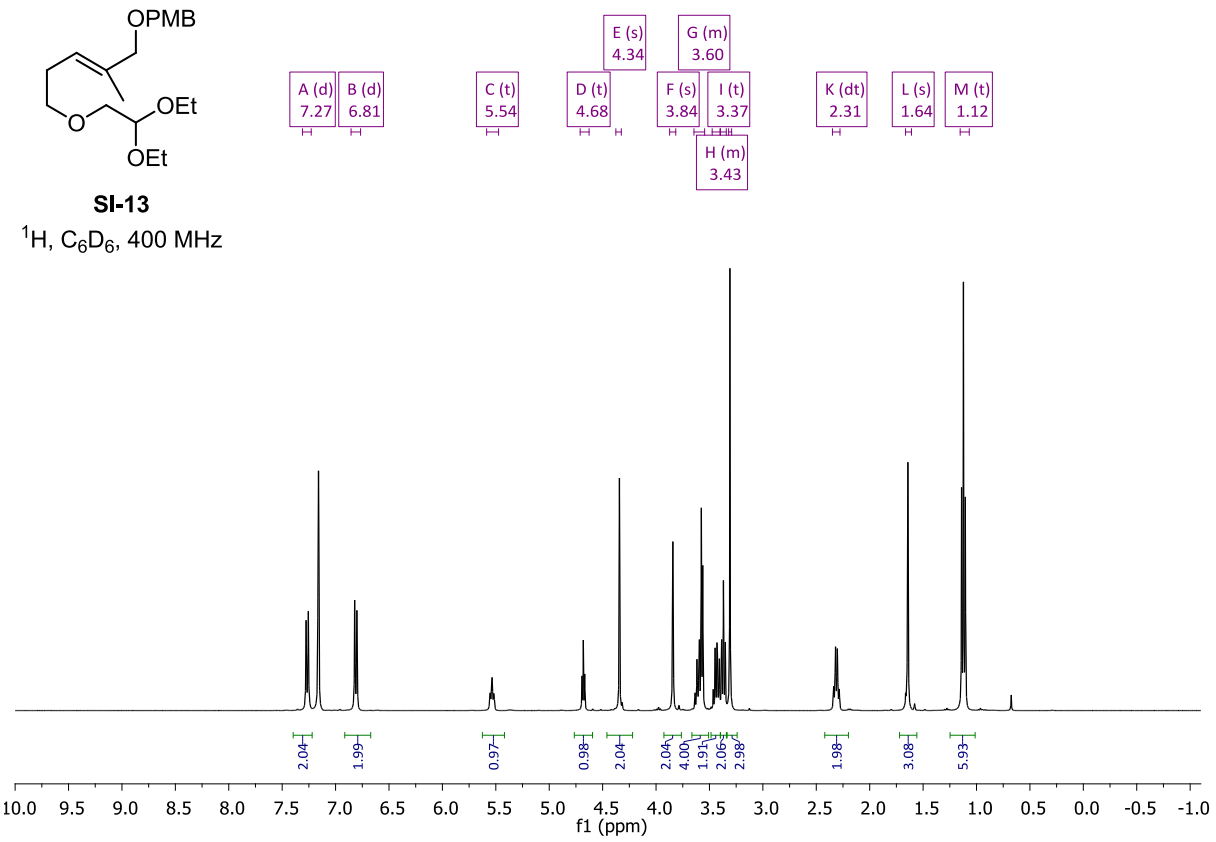



$^{13}C\{^{1}H\}$, $C_6D_6$, 101 MHz

**19**

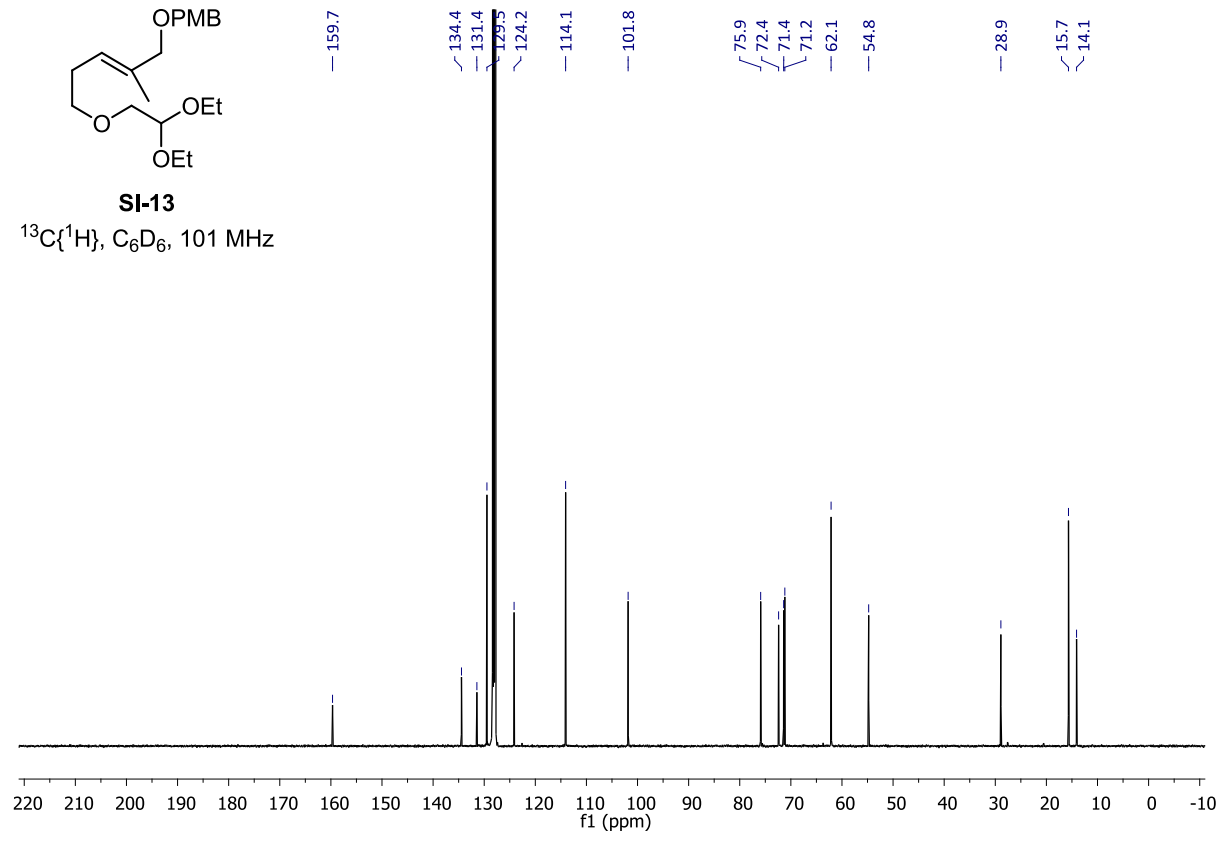
$C_6D_6$, 400/400 MHz





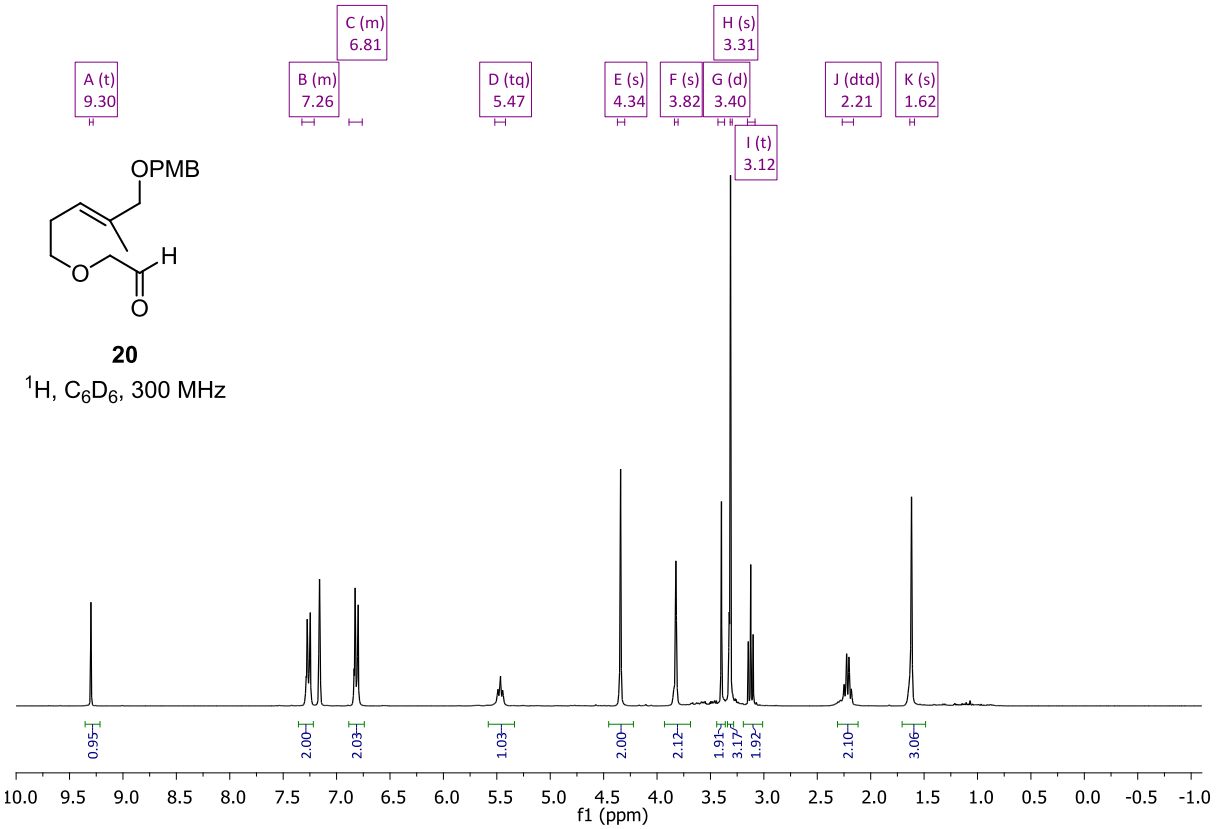

**SI-13**

$^{1}H$, $C_6D_6$, 400 MHz



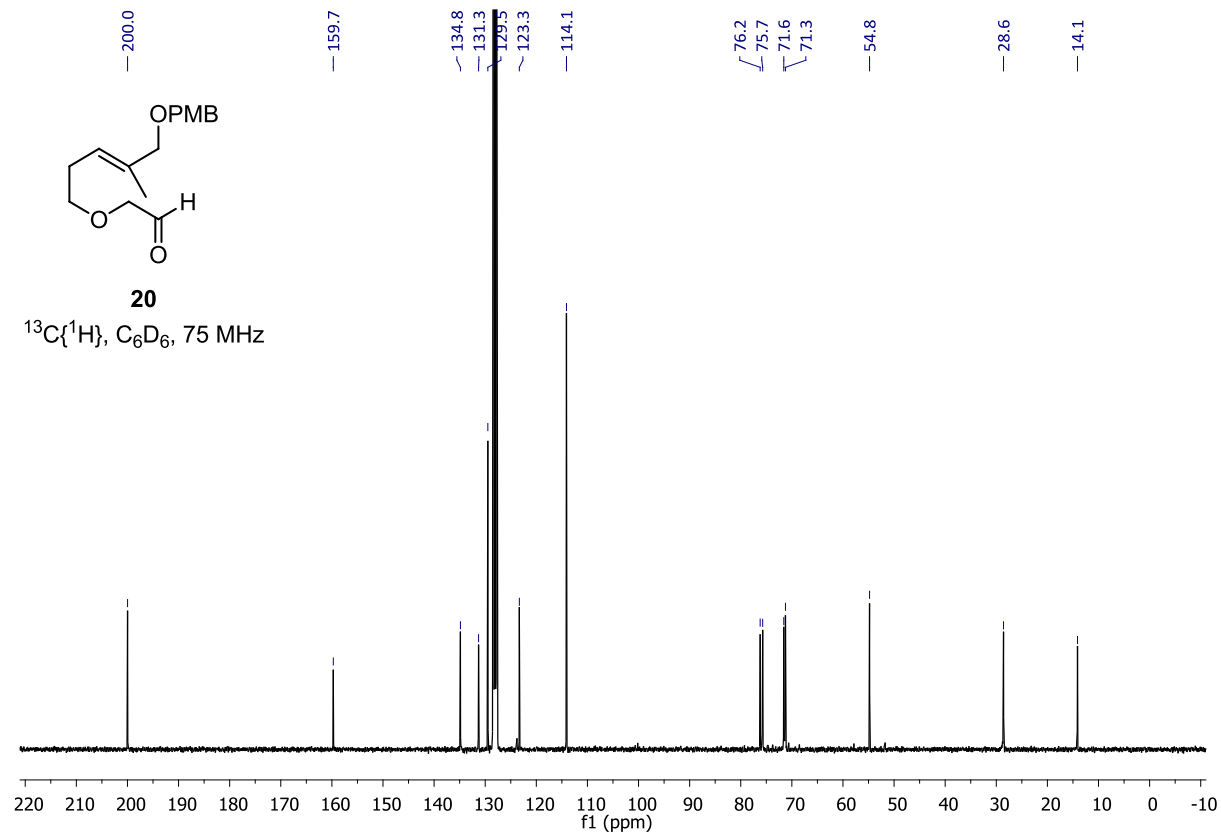

**SI-13**

$^{13}C\{^{1}H\}$, $C_6D_6$, 101 MHz



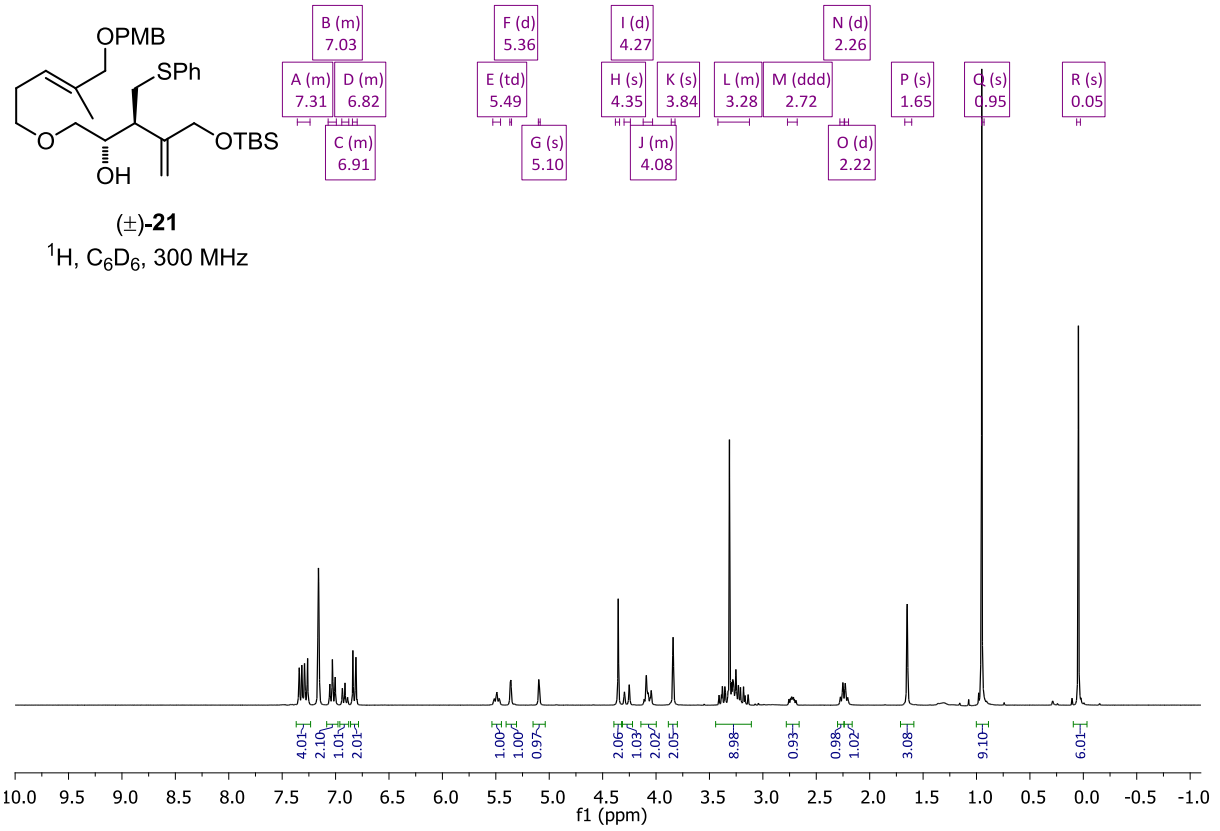

**20**

$^{1}H$, $C_6D_6$, 300 MHz



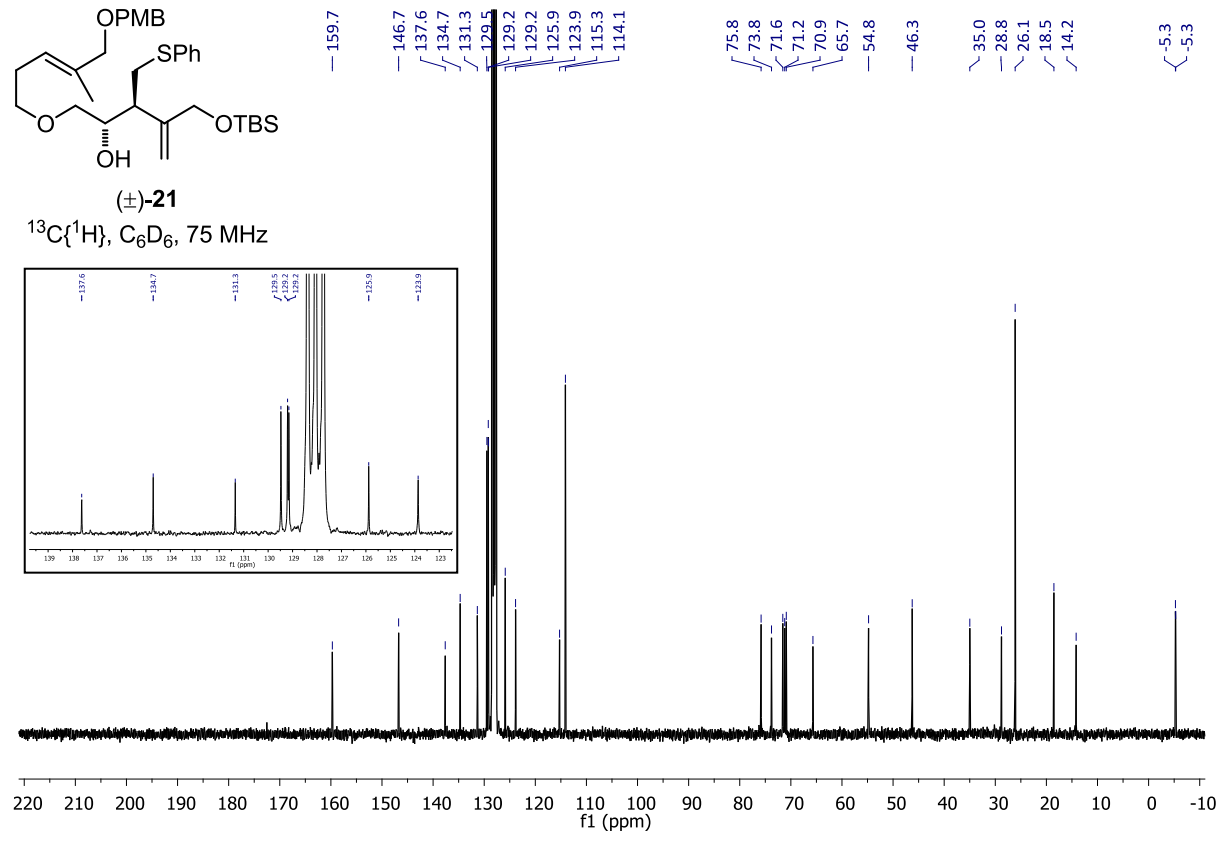

**20**

$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz



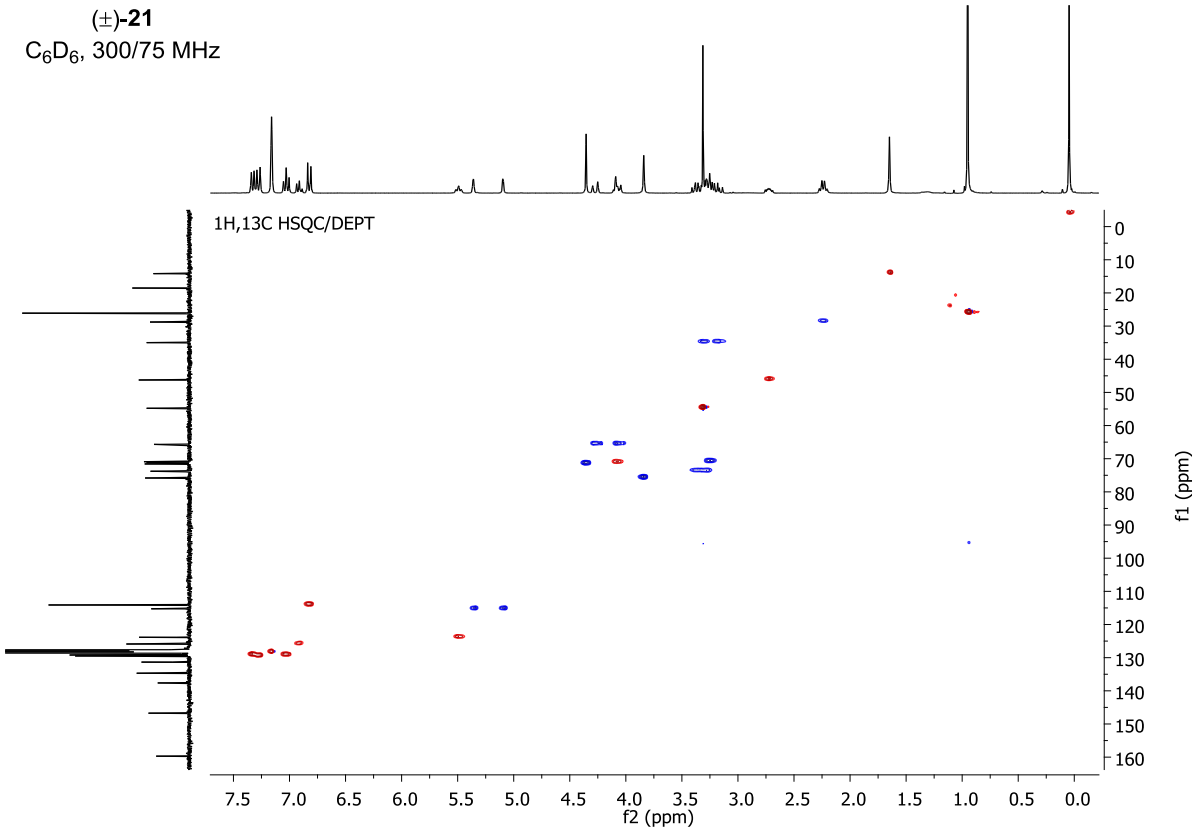

(±)-**21**

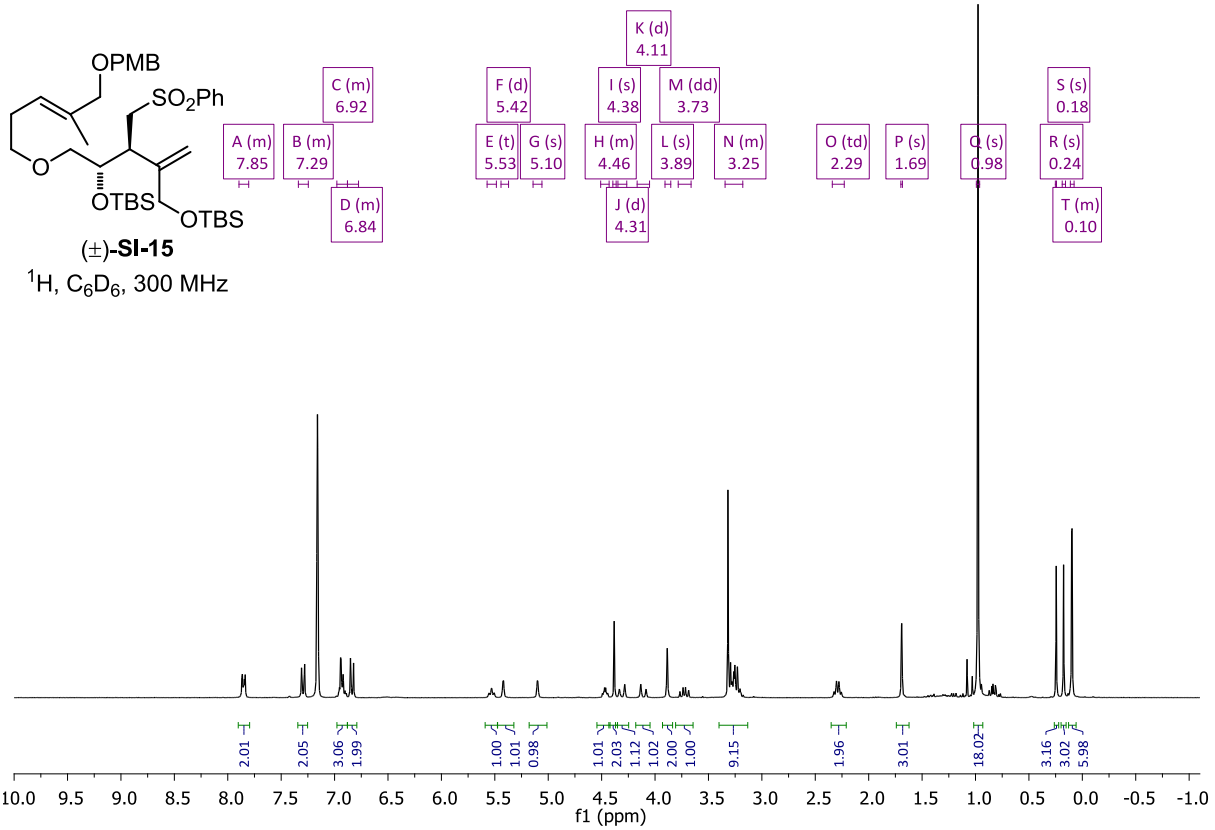
$^{1}H$, $C_6D_6$, 300 MHz




(±)-**21**

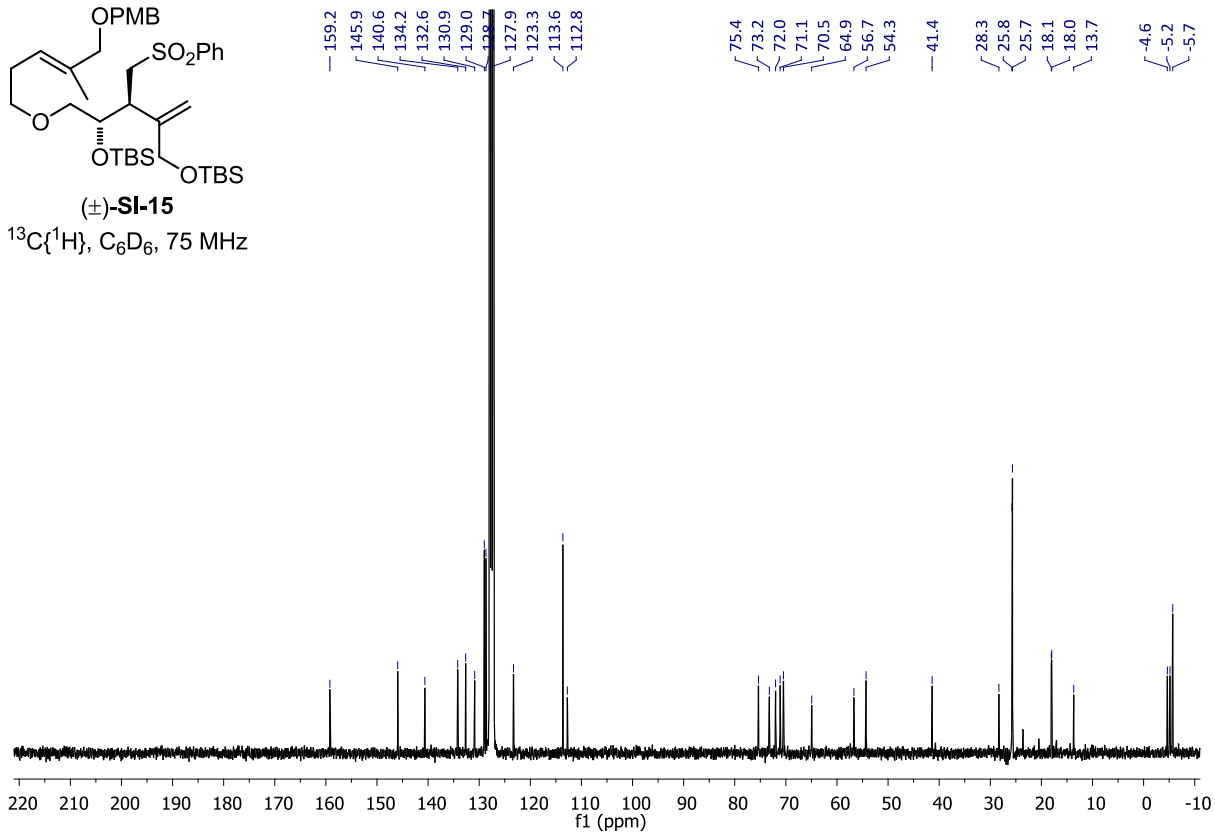
$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz


(±)-21
C6D6, 300/75 MHz
1H,13C HSQC/DEPT
f2 (ppm)
f1 (ppm)



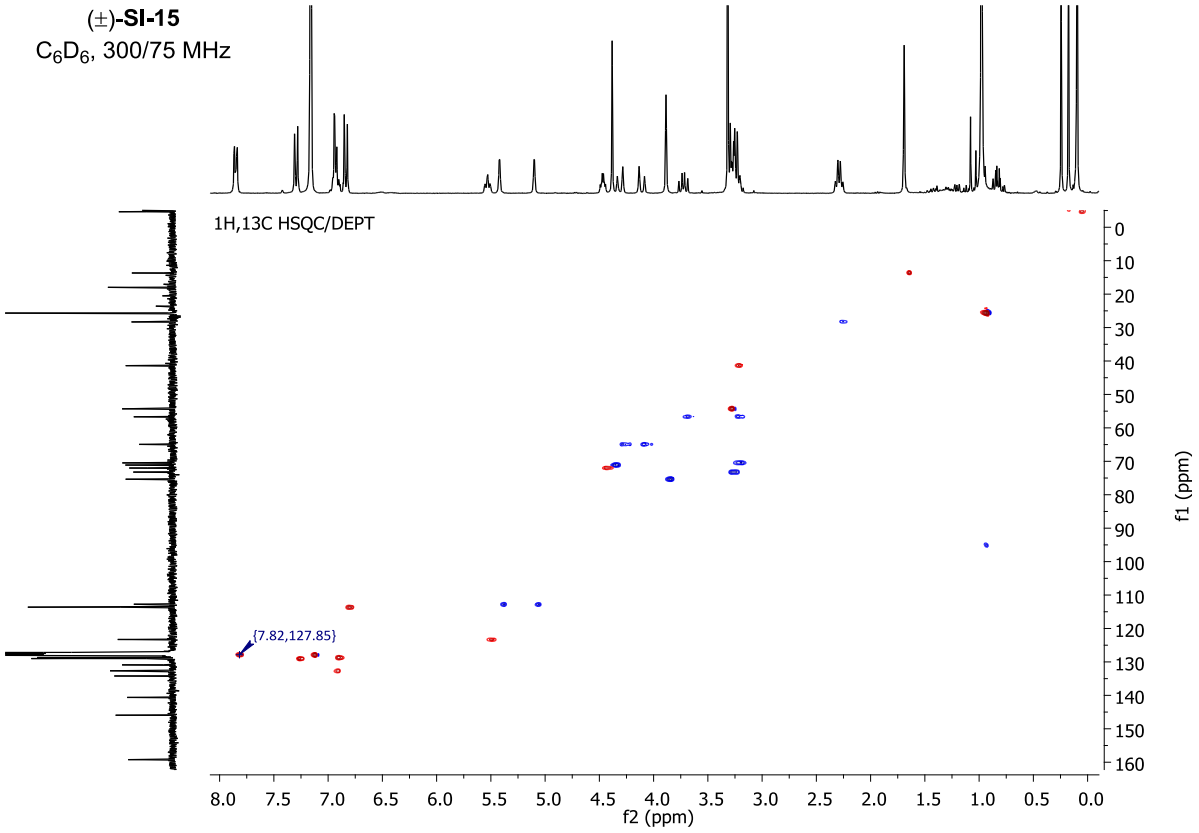

(±)-**SI-15**

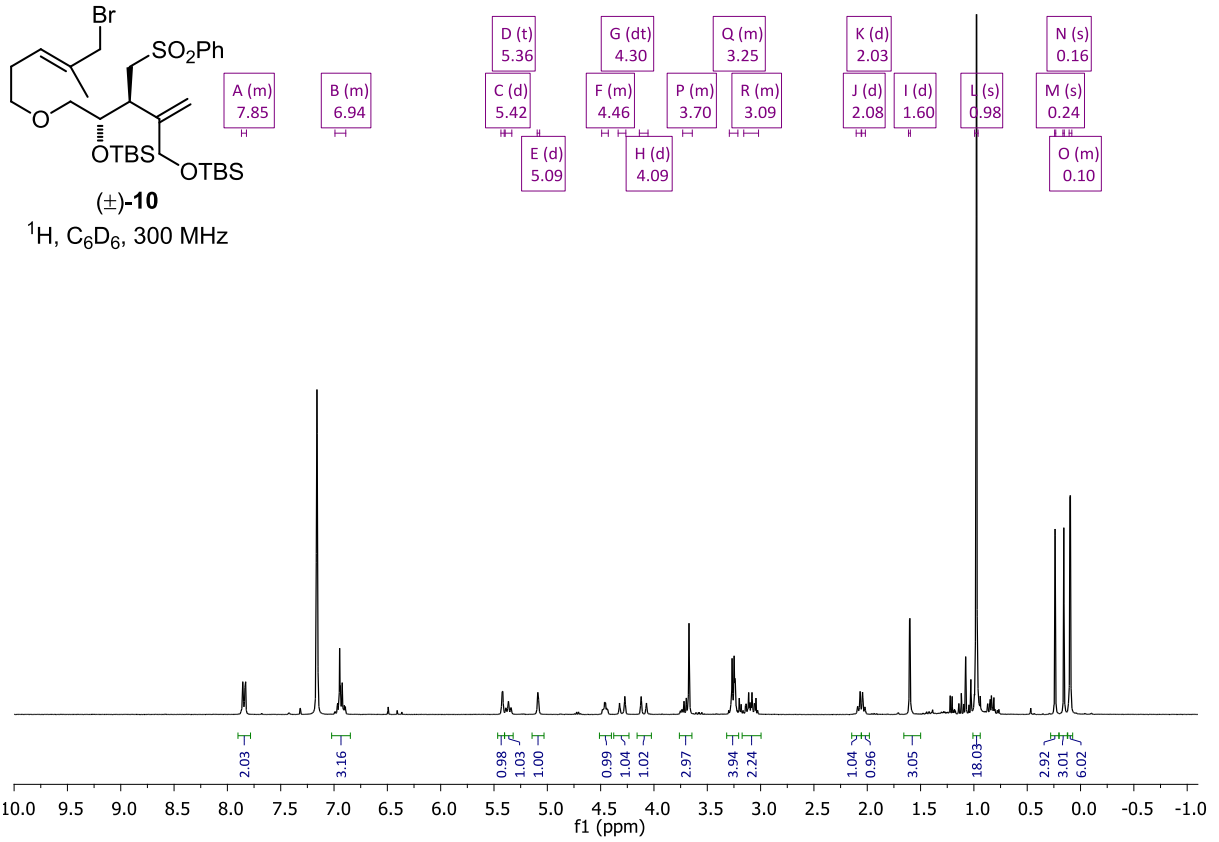
$^{1}H$, $C_6D_6$, 300 MHz




(±)-**SI-15**

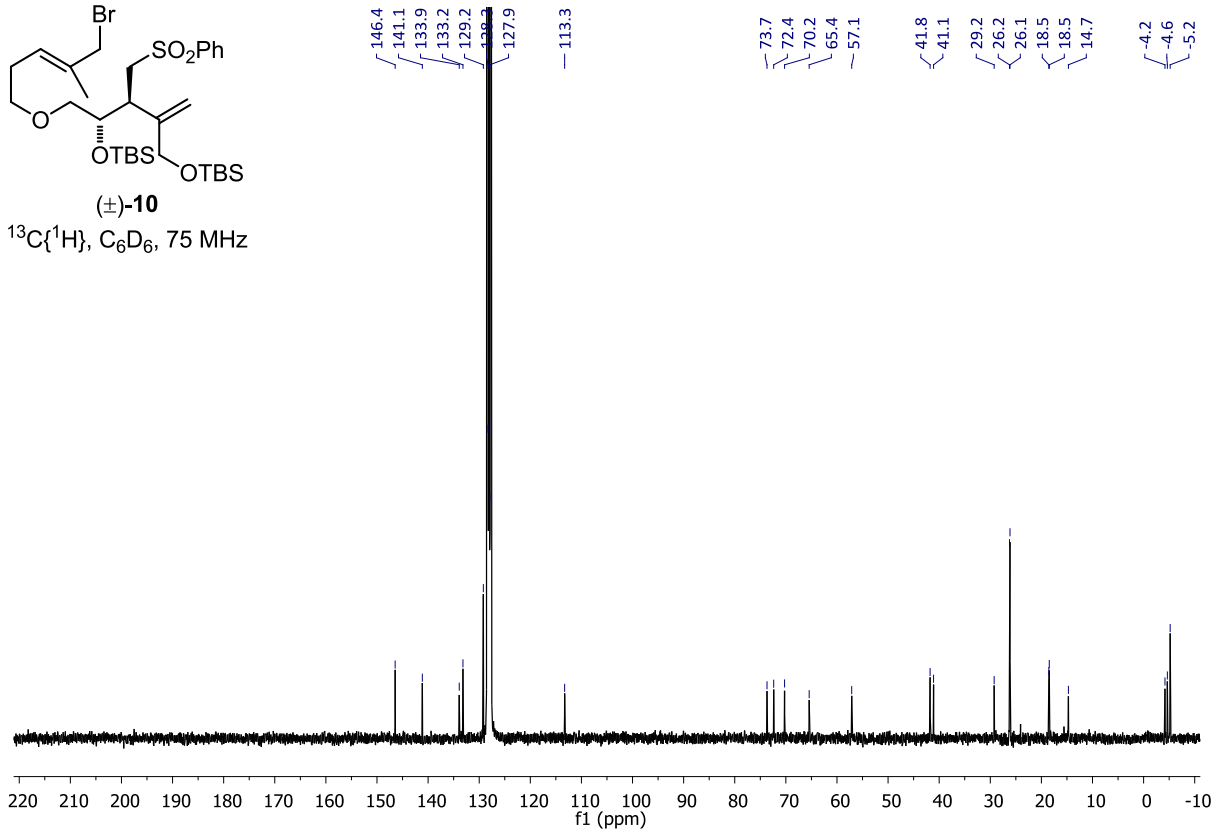
$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz


(±)-SI-15
C6D6, 300/75 MHz
1H,13C HSQC/DEPT
{7.82,127.85}
f2 (ppm)
f1 (ppm)



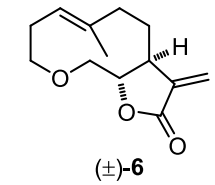

(±)-**10**

$^{1}H$, $C_6D_6$, 300 MHz




(±)-**10**

$^{13}C\{^{1}H\}$, $C_6D_6$, 75 MHz



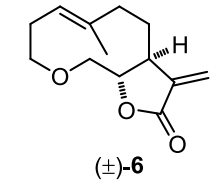
(±)-**6**

$^1$H, $CDCl_3$, 400 MHz,

50 °C



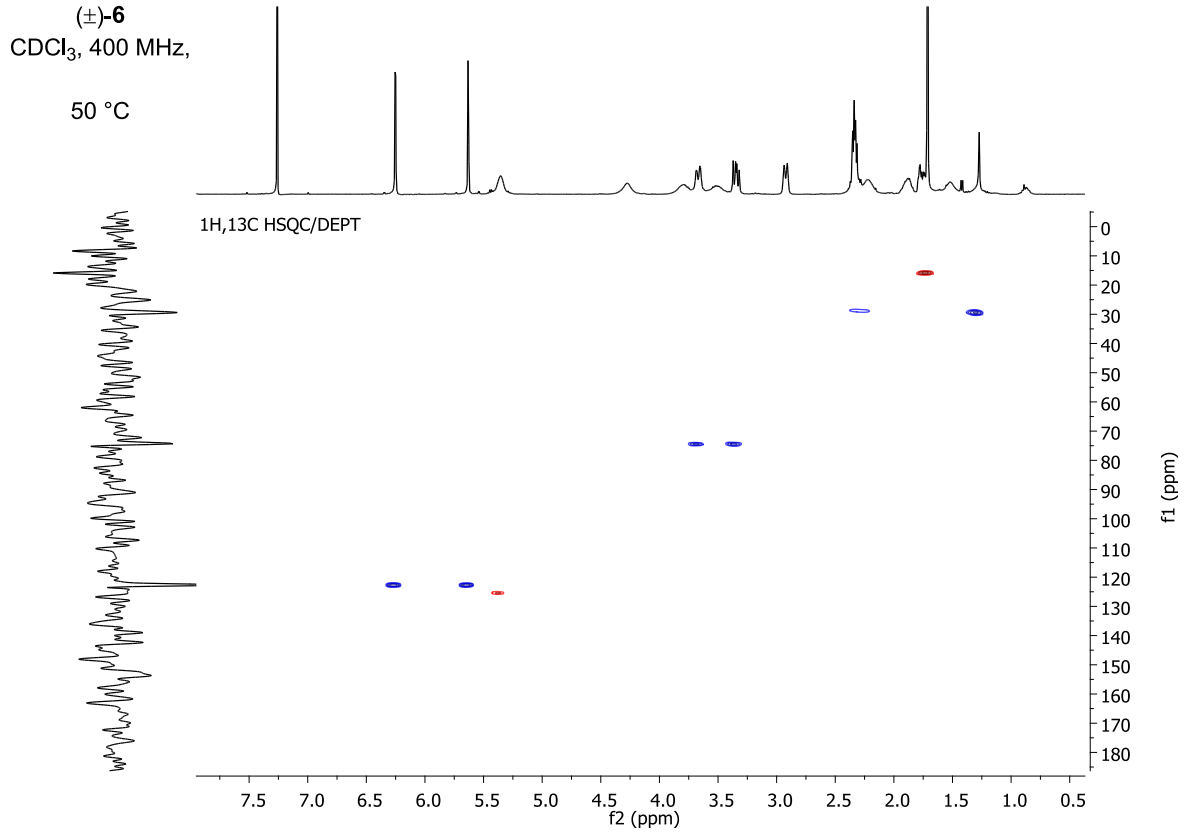

* = impurity

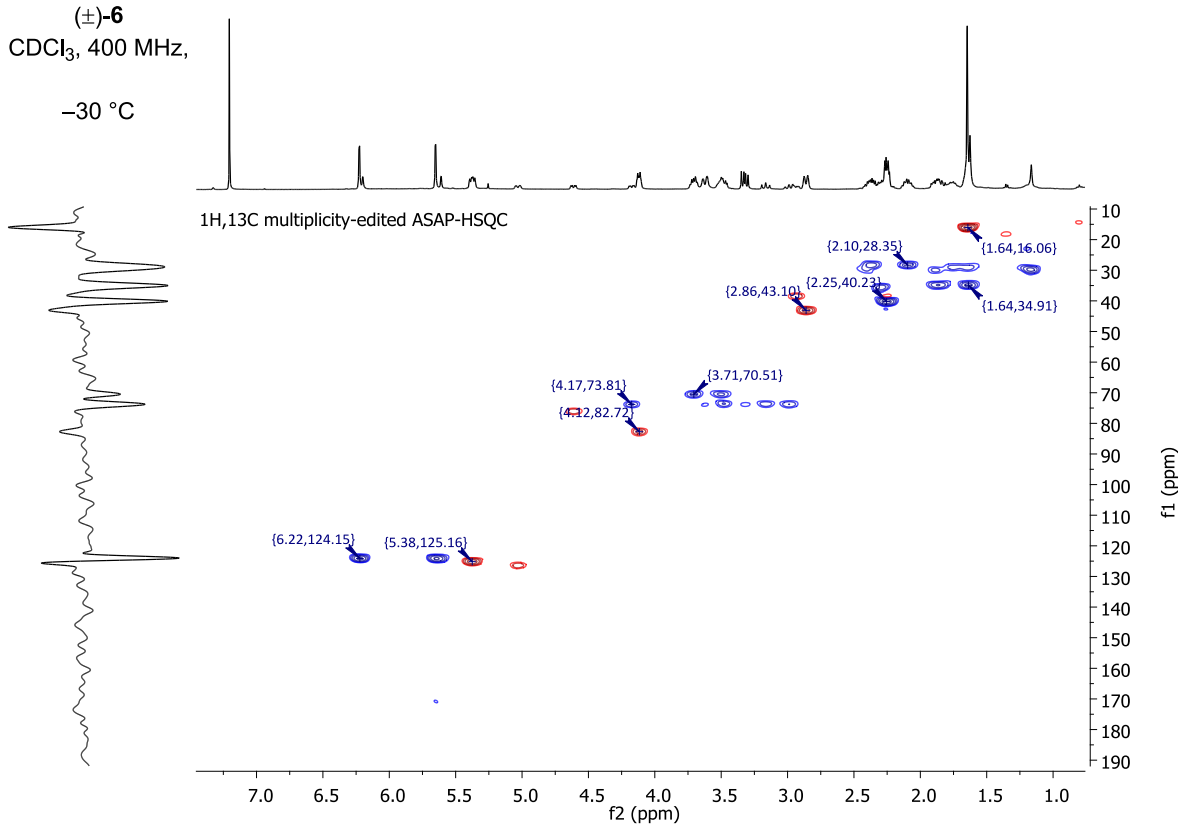


(±)-**6**

$^1$H, $CDCl_3$, 400 MHz,

–30 °C




The 1D projection of the 2D spectrum is displayed in the f1 dimension