Supplementary Information

Stereo Flexible Synthesis of the C8-C23 Fragment of Antarlides, Androgen Receptor Antagonists

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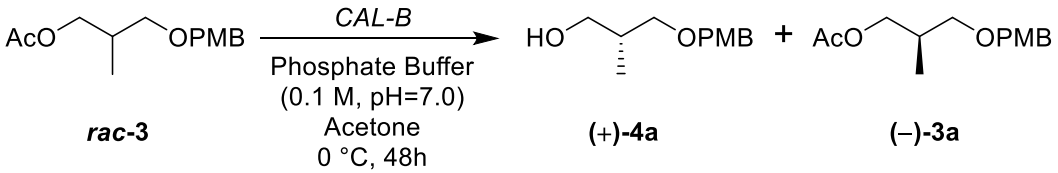
Contents

1. General Information:

Unless otherwise noted, all reactions were carried out in flame-dried or oven-dried glassware under a nitrogen atmosphere with magnetic stirring. Commercially available solvents and reagents were used as received without further purification. All solvents were reagent grade or HPLC grade. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone, and dichloromethane (CH_2Cl_2) was distilled from calcium hydride under a nitrogen atmosphere. Reactions were monitored by thin-layer chromatography (TLC) silica gel glass plates (60 F_{254}). TLC plates were visualized under UV light at 254 nm and *p*-Anisaldehyde stain. Column chromatography was carried out using silica gel (60-120 mesh & 100-200 mesh) packed in glass columns. The ^{1}H NMR and spectra were recorded at 400 and 500 MHz, ^{13}C NMR and spectra were recorded at 101 and 126 MHz. ^{1}H and ^{13}C NMR Chemical shifts were calibrated to tetra-methylsilane as an external reference. Data are reported as follows: chemical shift, multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, brs = broad singlet, app = apparent), coupling constants (*J*) in Hertz (Hz), integration. Purities of the final compounds were determined by high-performance liquid chromatography (HPLC) and were greater than 95% unless otherwise noted. Specific Optical rotations were recorded on an Anton Paar Polarimeter at 589 nm and reported as follows: $[\alpha]^{20}_D$, concentration (*c* in g/100 mL), and solvent. Infrared spectra were recorded on a Bruker Alpha spectrophotometer. HRMS were obtained on an Agilent Q-TOF mass spectrometer with ESI resource (analyzer type: TOF).

2. Experimental Procedures and Analytical Data:

2.1. The procedure for enzymatic hydrolysis:

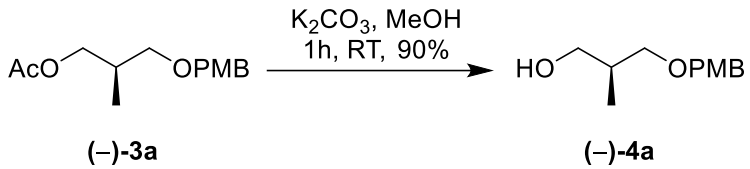


***rac*-3** **(+)-4a** **(–)-3a**

The reaction closely followed a previously reported method with slight modifications.[1] In a reaction vessel equipped with a mechanical stirrer, introduced ***rac*-3** (111.0 g, 440 mmol), which was dissolved in a mixture of acetone (880 mL) and 0.1 M phosphate buffer (pH 7.0, 2:3 ratio, 2.2 L). After being stirred at 0 °C for 10 minutes, the immobilized form of *Candida antarctica* lipase B (CAL-B, 2.3 g) was added, and the reaction mixture was stirred for 48 hours while maintaining the same temperature. Subsequently, the enzyme was filtered off and washed with EtOAc. The aqueous and organic layers were separated and the aqueous layer was further extracted with EtOAc (2 x 1.0 L). The combined organic layers were evaporated, and the

resulting crude mixture was separated by column chromatography using ethyl acetate–hexanes in a gradient from 0:1 to 1:1 as an eluent, resulting in the enantiomerically enriched deacetylated product **(+)-4a** (yield: 31.0 g; 33.8%, >95% ee, see **Figure S1&S2**) and unreacted material (67.0 g).

The unreacted material again reacted with *CAL*-B enzyme using the same reaction procedure described above, ultimately producing compound **(–)-3a** (48.0 g, 43.0%) with >99% *ee* and **(+)-4a** (yield: 7.0 g; 12.8%, >95% ee). The chiral purity of **(–)-3a** was analyzed after deacetylation using a catalytic amount of K_2CO_3 in methanol (see **Figure S3**).

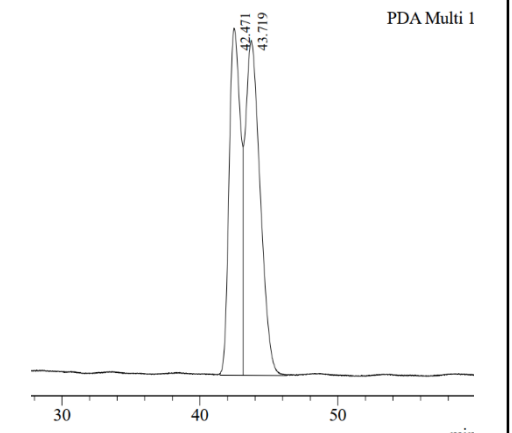


The enantiomeric excess was determined by chiral stationary phase HPLC using a Daicel Chiralpak OD-H column (250 x 4.6 mm) (hexane/2-propanol = 98:02, flow rate 0.7 mL/min, λ = 220 nm), for **(+)-4a**: t_R = 42.17 min (minor), t_R = 43.07 min (major) (**Figure S1 & S2**) and for **(–)-4a**: t_R = 41.34 min (major) (**Figure S3**).

For **(+)-4a**: $[\alpha]^{20}_D$ = –2.4˚ (*c* = 0.67 in EtOH) [Reported[1] $[\alpha]^{20}_D$ = –2.8˚ (c = 0.67 in EtOH)]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.65 – 3.56 (m, 2H), 3.55 – 3.48 (m, 1H), 3.39 (t, *J* = 8.6 Hz, 1H), 2.10 – 2.00 (m, 1H), 0.87 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 130.2, 129.3, 113.9, 75.1, 73.1, 67.8, 55.3, 35.6, 13.6; **IR** (neat): 2923, 2862, 1612, 1515, 1462, 1366, 1249, 1091, 1036 and 822 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{12}H_{18}O_3Na$ $[M+Na]^+$ 233.1148; found: 233.1148. *See NMR spectra*

For **(–)-3a**: $[\alpha]^{22}_D$ = –7.6˚ (*c* = 0.08 in EtOH) [Reported[1] $[\alpha]^{22}_D$ = –5.0˚ (c = 0.8 in EtOH)]



1 PDA Multi 1 / 220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

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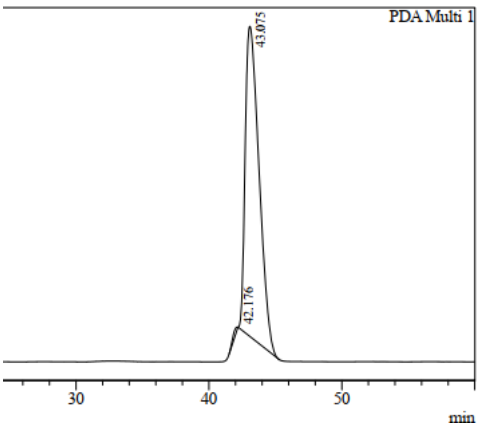
1	42.479	38649349	661875	44.458
2	43.715	48285179	638973	55.542
Total		86934528	1300847	100.000

Figure S1: HPLC report of ***rac*-4.**



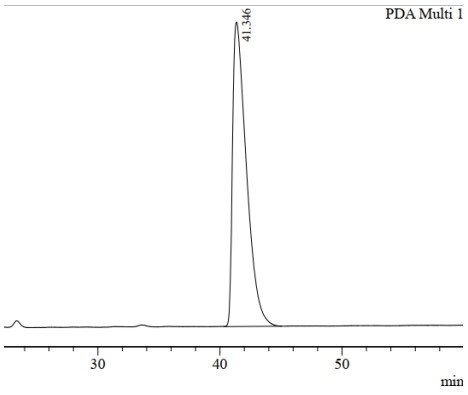
1 PDA Multi 1 / 220nm 4nm

PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	42.176	562571	1422	0.740
2	43.075	75463097	1047558	99.260
Total		76025668	1048981	100.000

Figure S2: HPLC report of **(+)-4a**.



1 PDA Multi 1 / 220nm 4nm

PeakTable

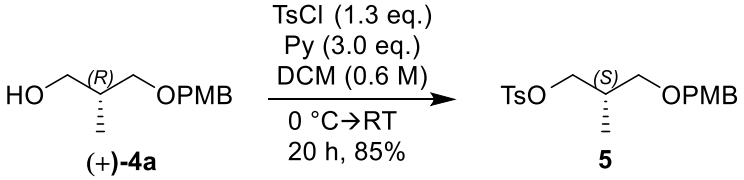
PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	41.347	169056207	1870390	100.000
Total		169056207	1870390	100.000

Figure S3: HPLC report of **(–)-4a**.

2.2. Synthesis of key aldehyde (+)-7 from (+)-4a:

(*S*)-3-((4-Methoxybenzyl)oxy)-2-methylpropyl 4-methylbenzenesulfonate (5):

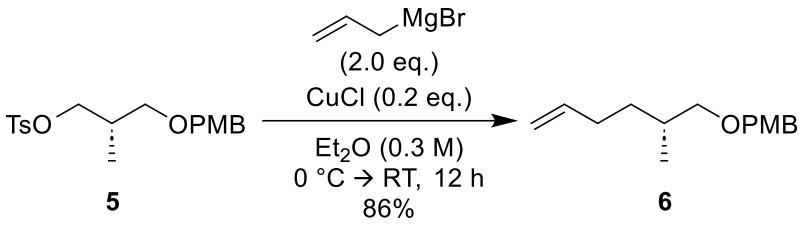


(+)-4a **5**

In a 1 L two neck round bottom flask, (*R*)-3-((4-Methoxybenzyl)oxy)-2-methylpropan-1-ol **(+)-4a** (35.0 g, 166.7 mmol, 1.0 eq) was dissolved in dry dichloromethane (300.0 mL) and cooled to 0 ˚C. Subsequently, pyridine (40.0 mL, 500.0 mmol, 3.0 eq.) was added. After a 15-

minute interval, *p*-toluenesulfonyl chloride (41.3 g, 217.0 mmol, 1.3 eq.) was slowly introduced, and the mixture was stirred at room temperature for 20 hours. Following the reaction's completion, confirmed by TLC, the reaction mixture was neutralized with 1N aqueous hydrochloric acid and subsequently extracted with DCM (2 x 400 mL). The organic layer was separated, washed with a brine solution (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash chromatography on silica gel using a gradient of 0-10% ethyl acetate in hexanes as the eluent, resulted compound **5** (51.5 g, 85% yield) as a colorless liquid. R_f = 0.4 (ethyl acetate/hexane 1:9); $[\alpha]^{20}_D$ = +5.2˚ (*c* = 0.5 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.33 (s, 2H), 4.12 – 3.83 (m, 2H), 3.80 (s, 3H), 3.45 – 3.17 (m, 2H), 2.42 (s, 3H), 2.15 – 2.04 (m, 1H), 0.92 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.2, 144.7, 133.1, 130.4, 129.9, 129.2, 128.0, 113.8, 72.8, 72.4, 70.9, 55.4, 33.8, 21.7, 13.7; **IR** (neat): 2929, 2861, 1736, 1612, 1515, 1463, 1364, 1251, 1099, 973, and 761 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{19}H_{24}O_5SNa$ $[M+Na]^+$ 387.1237; found: 387.1234. *See NMR spectra*

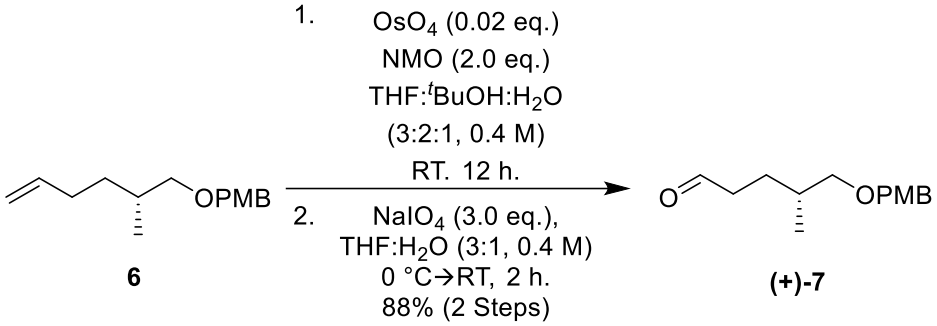
(*R*)-1-Methoxy-4-(((2-methylhex-5-en-1-yl)oxy)methyl)benzene (6):



In a 1 L two-neck round bottom flask, allyl magnesium bromide (1.0 M solution in Et_2O, 137.0 mL, 137.0 mmol, 2.0 eq.) was introduced into a suspension of CuCl (1.36 g, 1.37 mmol, 0.2 eq.) in Et_2O (150 mL) at 0 ˚C. After being stirred for 10 minutes, a solution of compound **5** (25.0 g, 68.6 mmol, 1.0 eq.) in Et_2O (50.0 mL) was added at 0 ˚C. The resulting mixture was stirred for 12 hours at room temperature, then quenched with a saturated aq. NH_4Cl (100 mL), and extracted the compound with diethyl ether (2 x 400 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (elution with hexane) to obtain alkene **6** (13.8 g, 86%); R_f = 0.8 (ethyl acetate/hexane 5:95); $[\alpha]^{20}_D$ = –4.7˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.86 – 5.73 (m, 1H), 5.11 – 4.85 (m, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.29 (dd, *J* = 9.1, 6.1 Hz, 1H), 3.22 (dd, *J* = 9.1, 6.6 Hz, 1H), 2.23 – 1.93 (m, 2H), 1.84 – 1.70 (m, 1H), 1.62 – 1.41 (m, 1H), 1.27 – 1.13 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.2, 139.2, 131.0, 129.2, 114.3, 113.8, 75.6, 72.7, 55.4, 33.1, 33.0, 31.3, 17.1; **IR** (neat): 2927, 2857, 1615,

1516, 1461, 1250, 1096, 1038, 824 and 760 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{15}H_{22}O_2Na$ $[M+Na]^+$ 257.1512; found: 257.1511. *See NMR spectra*

(*R*)-5-((4-Methoxybenzyl)oxy)-4-methylpentanal [(+)-7]:



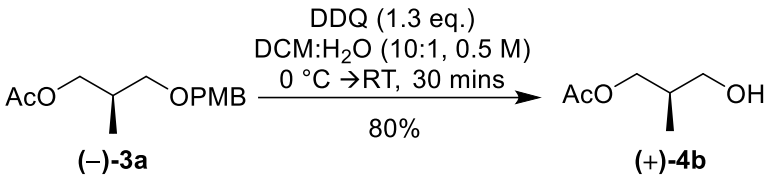
6 **(+)-7**

Alkene **6** (13.8 g, 59.0 mmol, 1.0 eq.) was charged in a 1 L RB flask and dissolved in THF (90 mL). Subsequently, ^{t}BuOH (45 mL), water (15 mL), NMO (13.8 g, 118.0 mmol, 2.0 eq.), and OsO_4 (0.016 M in toluene, 73.0 mL, 1.18 mmol, 0.02 eq.) were added simultaneously at room temperature. The resulting mixture was stirred for 16 h at the same temperature, then quenched with $Na_2S_2O_3$•$5H_2O$ (30.0 g) and water (200 mL). Stirring was continued for an additional 2 h. The organic layer was extracted with EtOAc (2 x 300 mL), washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to obtain the corresponding crude diol.

The above crude reaction mixture was dissolved in THF:H_2O (3:1, 160 mL) and at 0 °C, $NaIO_4$ (37.0 g, 177.0 mmol, 3.0 eq.) was added portion-wise to the solution. After complete addition, the reaction mixture was stirred at room temperature for 1 hour. Upon completion, as indicated by TLC, the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 300 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash chromatography on silica gel, eluting with 0-10% ethyl acetate in hexanes, yielding aldehyde compound **(+)-7** (12.3 g, 88% yield) as a yellow oil. R_f = 0.5 (ethyl acetate/hexane 1:9); $[\alpha]^{20}_D$ = +2.6° (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.8 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.41 (s, 2H), 3.79 (s, 3H), 3.31 – 3.23 (m, 2H), 2.51 – 2.36 (m, 2H), 1.85 – 1.74 (m, 2H), 1.54 – 1.43 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.8, 159.2, 130.7, 129.2, 113.8, 75.1, 72.8, 55.3, 41.6, 33.1, 26.0, 17.0; **IR** (neat): 2952, 2860, 1725, 1613, 1515, 1250, 1094, 1036, 826 and 761 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{14}H_{21}O_3$ $[M+H]^+$ 237.1485; found: 237.1483. *See NMR spectra*

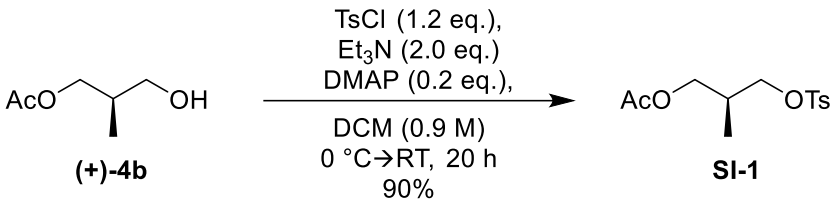
2.3. Synthesis of key aldehyde (+)-7 from (–)-3a:

(*R*)-3-Hydroxy-2-methylpropyl acetate [(+)-4b]:



Added 30.0 grams of (*R*)-3-((4-Methoxybenzyl)oxy)-2-methylpropyl acetate **(–)-3a** (119.0 mmol, 1.0 eq.) to a 500 mL RB flask and dissolved it in a mixture of solvents DCM:H_2O (10:1, 250 mL). Cooled the resulting solution to 0 °C and added 35.0 grams of DDQ (154.0 mmol, 1.3 eq.) portion-wise. Stirred the mixture at room temperature for 30 minutes while monitoring the reaction's progress using TLC. Once the reaction was complete, quenched the mixture with 100 mL of aqueous $NaHCO_3$, extracted it with DCM (2 x 500 mL), dried it using Na_2SO_4, filtered, and concentrated it under reduced pressure. Purified the crude residue through flash chromatography on silica gel using a gradient of 0-20% ethyl acetate in hexanes. This process yielded compound **(+)-4b** (12.6 grams, 80% yield) as a yellow oil. R_f = 0.3 (ethyl acetate/hexane 2:8); $[\alpha]^{20}_D$ = +10.3˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.06 (qd, *J* = 11.1, 5.8 Hz, 2H), 3.51 (qd, *J* = 11.1, 5.9 Hz, 2H), 2.06 (s, 3H), 2.03 – 1.92 (m, 1H), 0.94 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.8, 66.3, 64.6, 35.5, 21.0, 13.6; **IR** (neat): 2967, 1735, 1382,1259, 1024 and 762 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_6H_{12}O_3Na$ $[M+Na]^+$ 155.0679; found: 155.0678. *See NMR spectra*

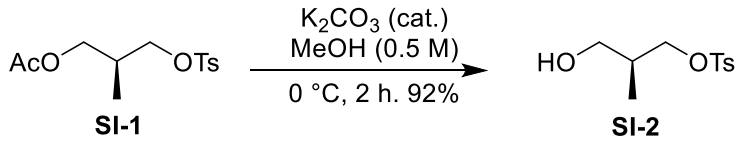
(*S*)-2-Methyl-3-(tosyloxy)propyl acetate (SI-1):



In a dry round-bottom flask, 12.0 grams of alcohol **(+)-4b** (90.8 mmol, 1.0 eq.) was added and dissolved in 100 mL of DCM. The reaction mixture was cooled to 0 °C, and simultaneously, 25.0 mL of triethylamine (180.0 mmol, 2.0 eq.) and 2.2 grams of DMAP (18.0 mmol, 0.2 eq.) were introduced. After 30 minutes at 0 °C, *p*-toluenesulfonyl chloride (21.0 g, 109.0 mmol, 1.2 eq.) was added in portions and stirred at room temperature for 20 hours. Once the reaction was complete, as indicated by TLC, the reaction mixture was quenched with aq. NH_4Cl (100 mL) and extracted with DCM (2 x 200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue underwent purification by flash chromatography on silica gel, eluting with a gradient of 0-10% ethyl acetate in hexanes,

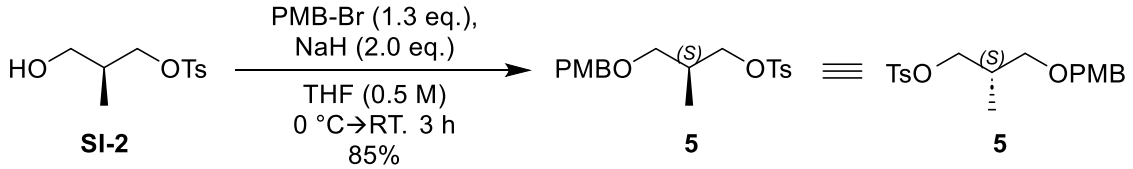
yielding compound **SI-1** (23.5 g, 90% yield) as a colorless oil. R_f = 0.6 (ethyl acetate/hexane 1:9); **[α]$^{20}_D$** = +4.6˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.04 – 3.82 (m, 4H), 2.44 (s, 3H), 2.24 – 2.06 (m, 1H), 1.96 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.8, 145.0, 132.9, 130.0, 128.0, 71.4, 65.0, 32.7, 21.7, 20.8, 13.5; **IR** (neat): 2972, 1743, 1367, 1246, 1183, 978, 829 and 671 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{13}H_{19}O_5S$ $[M+H]^+$ 287.0948; found: 287.0947. *See NMR spectra*

(*S*)-3-Hydroxy-2-methylpropyl 4-methylbenzenesulfonate (SI-2):



The 500 mL RB flask was charged with (*S*)-2-Methyl-3-(tosyloxy)propyl acetate **SI-1** (21.0 g, 73.4 mmol, 1.0 eq.) and was dissolved in dry methanol (150 mL). The resulting mixture was cooled to 0 °C, and a catalytic amount of K_2CO_3 was added under a nitrogen atmosphere. Stirring was continued for 2 hours at the same temperature. After the reaction was complete, as indicated by TLC, the solvent was evaporated under reduced pressure at below 25 °C. The crude residue was purified by flash chromatography on silica gel, eluting with 0-10% ethyl acetate in hexanes, yielding compound **SI-2** (16.5 g, 92% yield) as a colorless oil. R_f = 0.5 (ethyl acetate/hexane 2:8); **[α]$^{20}_D$** = +18.4˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.01 (dd, *J* = 5.7, 1.9 Hz, 2H), 3.54 (ddd, *J* = 17.6, 11.0, 5.8 Hz, 2H), 2.45 (s, 3H), 2.05 – 1.94 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.0, 132.9, 130.0, 128.0, 72.1, 63.7, 35.6, 21.7, 13.2; **IR** (neat): 2928, 1359, 1181, 1042, 971, 830 and 671 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{11}H_{17}O_4S$ $[M+H]^+$ 245.0842; found: 245.0841. *See NMR spectra*

(*S*)-3-((4-Methoxybenzyl)oxy)-2-methylpropyl 4-methylbenzenesulfonate (5):

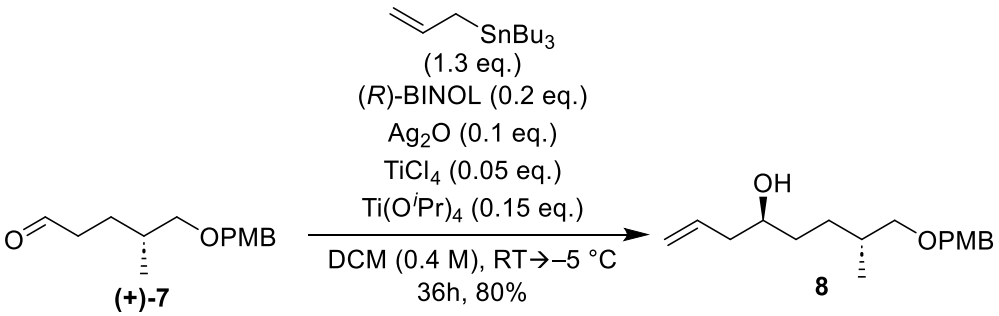


In a 500 mL round-bottom flask (RB), **SI-2** (12.7 g, 52.0 mmol, 1.0 eq.) was charged and dissolved in THF (150 mL). The resulting mixture was cooled to 0 °C, then NaH (25.0 g, 104.0 mmol, 2.0 eq.) was added in portion-wise. After stirring for 30 mins at 0 ˚C, PMB-Br (9.0 mL, 67.6 mmol, 1.3 eq. freshly prepared from PMB-OH) in THF solution was added slowly using

an additional funnel at 0 ˚C over 1 h and after completing the addition, the resulting mixture was stride at RT for 2 h. Upon completion of the reaction, the mixture was quenched with water (100 mL) at 0 °C and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude residue was purified by flash chromatography on silica gel eluting with 0-10% ethyl acetate in hexanes to afford compound **5** (32.1 g, 85% yield) as a colorless oil; R_f = 0.5 (ethyl acetate/hexane 2:8); $[\alpha]^{20}_D$ = +5.8˚ (*c* = 0.5 in $CHCl_3$) [Specific rotation for same fragment synthesized from **(+)-4a** $[\alpha]^{20}_D$ = +5.2˚ (*c* = 0.5 in $CHCl_3$)]; The other spectroscopic data is compared to that of the previously synthesized compound **5** (see page **S-4**). *See NMR spectra*

2.4. Synthesis of Julia-Kocienski olefination partner fragment-19:

(4*S*,7*R*)-8-((4-Methoxybenzyl)oxy)-7-methyloct-1-en-4-ol (8):

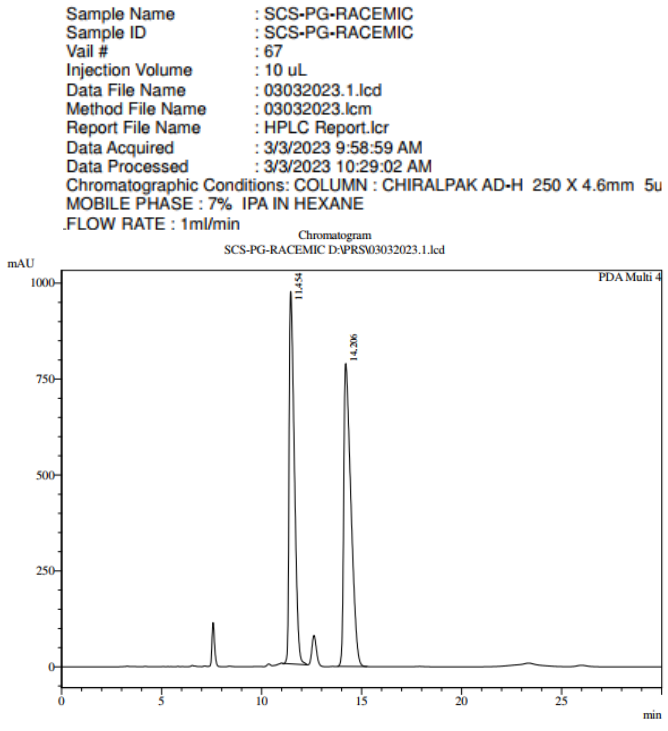


Under a nitrogen atmosphere, a 500 mL reaction flask was charged with 4.3 mL of $TiCl_4$ (4.24 mmol, 0.05 eq.) dissolved in 100 mL of DCM. The solution was cooled to 0 °C, and then 3.9 mL of $Ti(O^iPr)_4$ (12.7 mmol, 0.15 eq.) was added. The mixture was then warmed to room temperature and stirred for 1 hour. Ag_2O (2.0 g, 8.5 mmol, 0.1 eq.) was added at room temperature and the mixture was stirred for 5 h in the dark. At this point, a solution of (*R*)-BINOL (4.9 g, 17.0 mmol, 0.2 eq.) in 150 mL of DCM was added to the reaction mixture, and stirring was continued for an additional 2 hours. The mixture was cooled to -15 °C, and a DCM (50 mL) solution of aldehyde **(+)-7** (20.0 g, 85.0 mmol, 1.0 eq.) and allyl tributyltin (34.3 mL, 110 mmol, 1.3 eq.) were sequentially added. The mixture was allowed to warm to –5 °C and stirred for 24 hours. Following TLC confirmation, the reaction mixture was quenched with saturated aq. $NaHCO_3$, and extracted with DCM (2 x 400 mL). The organic extracts were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (using EtOAc/Hexane 1:9) resulted in the isolation of compound **8** as a colorless oil (18.8 g, 80% yield, 95:5 *dr*. & major isomer enantiomeric ratio (*er*): 94.7:5.3); R_f = 0.5 (ethyl acetate/hexane 2:8); $[\alpha]^{20}_D$ = –0.4˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.90 – 5.75 (m, 1H), 5.17 – 5.12 (m, 1H), 5.12 – 5.09 (m, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.65 – 3.56 (m, 1H), 3.33 – 3.19 (m, 2H), 2.34 – 2.24 (m,

1H), 2.19 – 2.07 (m, 1H), 1.82 – 1.71 (m, 2H), 1.54 – 1.47 (m, 1H), 1.46 – 1.40 (m, 1H), 1.23 – 1.11 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 135.0, 130.9, 129.3, 118.2, 113.8, 75.5, 72.8, 71.1, 55.4, 41.9, 34.2, 33.6, 29.7, 17.3; **IR** (neat): 2959, 2895, 1469, 1375, 1253, 1094 and 761 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{17}H_{26}O_3Na$ $[M+Na]^+$ 301.1774; found: 301.1771. *See NMR spectra*

HPLC Report of compound 8.

The enantiomeric ratio (*er.*) was determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H column (250 x 4.6 mm) (hexane/2-propanol = 93:07, flow rate 1.0 mL/min, λ = 280 nm), t_R = 11.6 min (minor), t_R = 14.1 min (major).



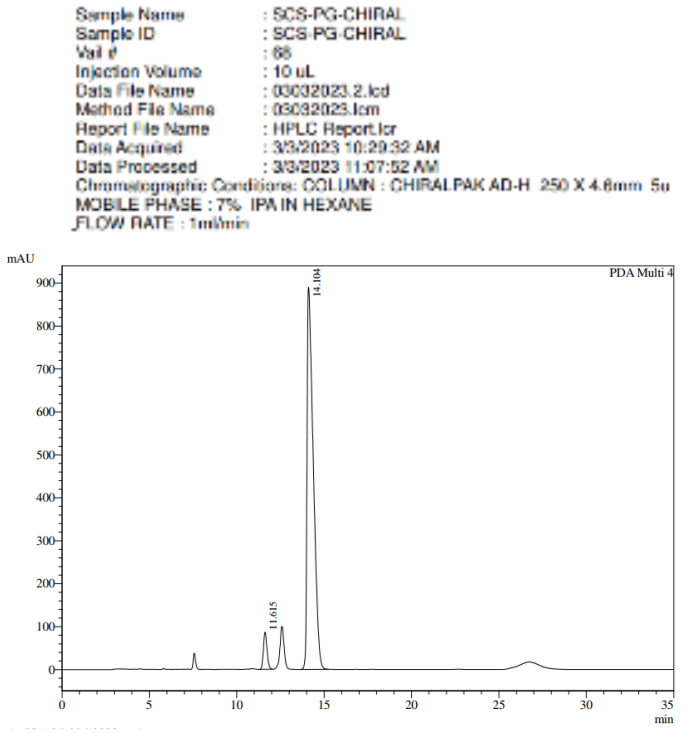
1 PDA Multi 4 / 280nm 4nm

PeakTable

PDA Ch4 280nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.454	17722209	971098	47.349	55.143
2	14.206	19706423	789969	52.651	44.857
Total		37428632	1761067	100.000	100.000

Figure S4: HPLC report of diastereomeric **8**



1 PDA Multi 4 / 280nm 4nm

PeakTable

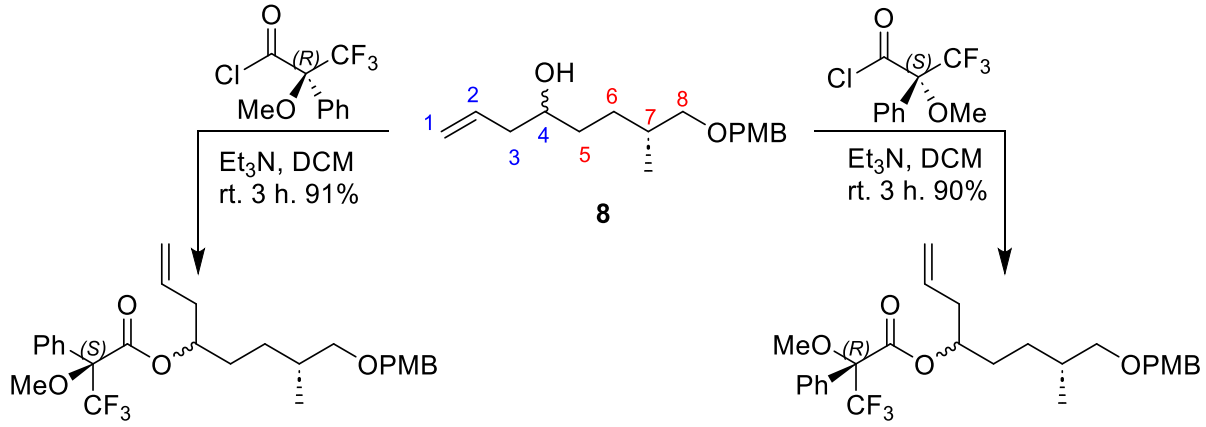
PDA Ch4 280nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.615	1245992	86358	5.346	8.844
2	14.104	22062921	890073	94.654	91.156
Total		23308912	976431	100.000	100.000

Figure S5: HPLC report of Chiral **8**

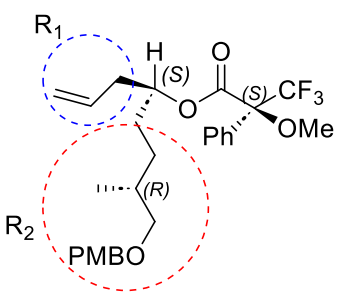
Mosher ester analysis on compound 8:

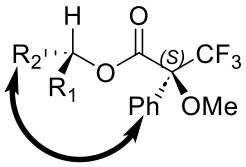
Figure-S6: $\Delta\delta$ (= δ_S - δ_R) data for the *S*- and *R*-MTPA- Mosher ester's **SI-3** and **SI-4**



	δ *S* ester (ppm)	δ *R* ester (ppm)	$\Delta\delta^{SR}$ (= δ_S - δ_R) (ppm)
1	5.11, 5.07	5.02, 4.98	0.02, 0.01
2	5.74	5.61	0.06
3	2.40	2.33	0.07
4	5.11	5.12	-0.01
5	1.51	1.63	-0.12
6	1.25, 0.94	1.51, 1.14	-0.26, -0.2
7	1.57	1.72	-0.15
8	3.07	3.22	-0.15

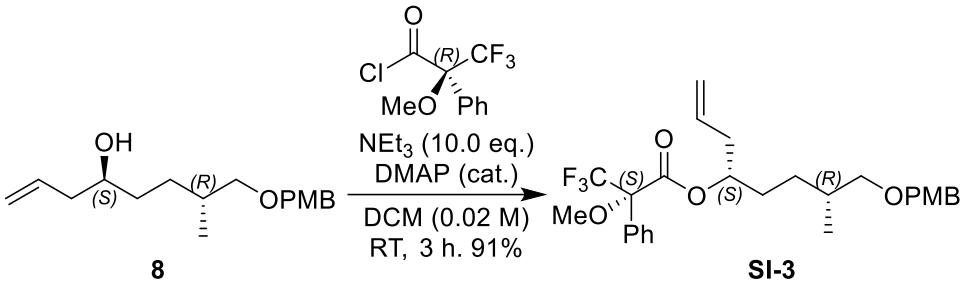
Precisely, protons that have positive $\Delta\delta_{SR}$ values reside within R_1 and the protons with negative values belong to R_2. According to this allylic side chain resides within R_1 (due to its positive $\Delta\delta_{SR}$ values) and the linear saturated fragment belongs to R_2 *i.e.* on the opposite side of that plane (**Figure-S6**).





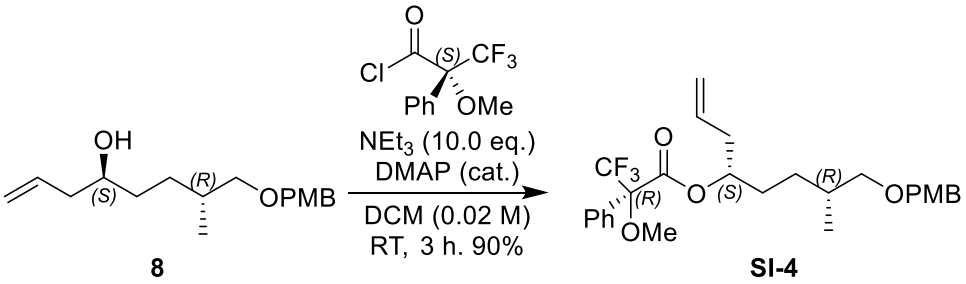
Phenyl group shielding effect results upfield chemical shift for the protons belong to R_2

(4*S*,7*R*)-8-((4-Methoxybenzyl)oxy)-7-methyloct-1-en-4-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-3):



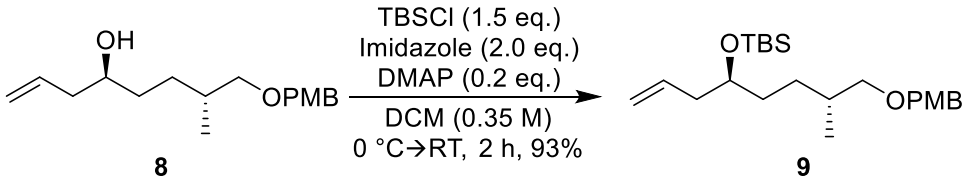
The flame-dried RB flask was charged with 2˚ alcohol **8** (10.0 mg, 0.036 mmol, 1.0 eq.) and dissolved in DCM (2.0 mL). To this solution, triethylamine (51.0 µL, 0.36 mmol, 10.0 eq.) and a catalytic amount of DMAP were added. Subsequently, (*R*)-(–)-MTPA-Cl (10.5 µL, 0.054 mmol, 1.5 eq.) was introduced, and the reaction mixture was stirred for 3 hours at room temperature. After completion, the reaction mixture was quenched with a saturated aq. NH_4Cl solution and extracted with DCM (2 x 5 mL). The organic extracts were then dried over Na_2SO_4. Upon solvent evaporation, purification of the residue by column chromatography on silica gel (ethyl acetate/hexane 1:9) yielded compound **SI-3** as a yellow oil (16.3 mg, 91% yield); R_f = 0.7 (ethyl acetate/hexane 1:9) $\mathbf{[\alpha]^{20}_D}$ = –23.6˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.43 – 7.33 (m, 3H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.78 – 5.67 (m, 1H), 5.20 – 5.10 (m, 2H), 5.09 (s, 1H), 4.39 (s, 2H), 3.81 (s, 3H), 3.56 (d, *J* = 1.0 Hz, 3H), 3.23 – 3.13 (m, 2H), 2.46 – 2.38 (m, 2H), 1.70 – 1.54 (m, 3H), 1.41 – 1.25 (m, 1H), 1.08 – 0.98 (m, 1H), 0.85 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.3, 159.2, 133.3, 132.6, 130.8, 129.6, 129.2, 128.4, 127.5, 123.5 (q, *J* = 286.8 Hz), 118.5, 113.8, 84.6 (q, *J* = 27.3 Hz), 76.8, 75.3, 72.7, 55.7, 55.3, 38.3, 33.3, 30.8, 28.9, 17.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –71.27; **IR** (neat): 2951, 2859, 1748, 1258, 1179, 1111 and 764 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{27}H_{33}O_5F_3Na$ $[M+Na]^+$ 517.2172; found: 517.2168. *See NMR spectra*

(4*S*,7*R*)-8-((4-Methoxybenzyl)oxy)-7-methyloct-1-en-4 (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-4):



The flame-dried RB flask was charged 2˚ alcohol **8** (10.0 mg, 0.036 mmol, 1.0 eq.) and dissolved in DCM (2.0 mL). To this mixture triethylamine (51.0 µL, 0.36 mmol, 10.0 eq.) and a catalytic amount of DMAP were added. Subsequently, (*S*)-(+)-MTPA-Cl (10.5 µL, 0.054 mmol, 1.5 eq.) was introduced, and the reaction mixture was stirred for 3 hours at room temperature. Upon completion, the reaction mixture was quenched with a saturated aq. NH_4Cl solution and extracted with DCM (2 x 5 mL). The organic extracts were then dried over Na_2SO_4. After evaporating the solvents, purification of the residue by column chromatography on silica gel (ethyl acetate/hexane 1:9) afforded compound **SI-4** as a yellow oil (16.0 mg, 90% yield); R_f = 0.7 (ethyl acetate/hexane 1:9); **[α]$^{20}_D$** = +10.0˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 2H), 7.41 – 7.35 (m, 3H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.71 – 5.55 (m, 1H), 5.19 – 5.07 (m, 1H), 5.06 – 5.01 (m, 1H), 4.99 (s, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.53 (d, *J* = 1.1 Hz, 3H), 3.23 (d, *J* = 6.2 Hz, 2H), 2.36 – 2.32 (m, 2H), 1.80 – 1.58 (m, 3H), 1.56 – 1.48 (m, 1H), 1.21 – 1.09 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.3, 158.2, 131.9, 131.5, 129.8, 128.6, 128.3, 127.4, 126.6, 122.5 (q, *J* = 289.7 Hz), 117.5, 112.9, 83.7 (q, *J* = 27.6 Hz), 75.9, 74.3, 71.8, 54.6, 54.4, 37.0, 32.4, 29.8, 28.3, 16.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ –71.28; **IR** (neat): 2951, 2859, 1748, 1258, 1179, 1111 and 764 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{27}H_{33}O_5F_3Na$ $[M+Na]^+$ 517.2172; found: 517.2169. *See NMR spectra*

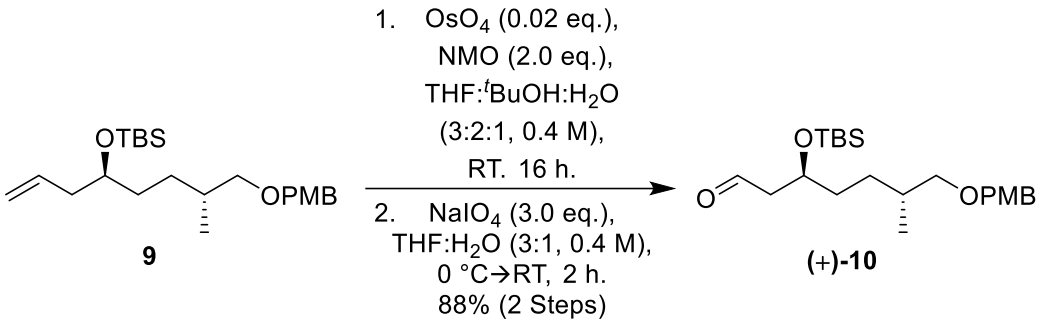
***tert*-Butyl(((4*S*,7*R*)-8-((4-methoxybenzyl)oxy)-7-methyloct-1-en-4-yl)oxy)dimethylsilane (9):**



The flame-dried RB flask was charged with 2˚ Alcohol **8** (10.0 g, 36.0 mmol, 1.0 eq.) and dissolved in 100 mL of DCM. The mixture was cooled to 0 ˚C, and then Imidazole (5.0 g, 73.5 mmol, 2.0 eq.) and DMAP (0.9 g, 7.3 mmol, 0.2 eq.) were added simultaneously. After 10 mins, TBS-Cl (8.3 g, 55.0 mmol, 1.5 eq.) was introduced, and stirred the reaction mixture at room temperature for 2 h. Upon completion, the reaction mixture was quenched with water, and the compound was extracted with DCM (2 x 200 mL). The organic extracts were combined and dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (EtOAc/Hexane 0-5%) yielded compound **9** as a greenish oil (13.0 g, 93% yield); R_f = 0.8 (ethyl acetate/hexane 5:95); **[α]$^{20}_D$** = –7.5˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.86 – 5.74 (m, 1H), 5.07 – 5.02 (m, 1H), 5.01 (s, 1H), 4.43 (dd, *J* = 11.6, 13.6 Hz, 2H), 3.81 (s, 3H), 3.73 –

3.61 (m, 1H), 3.29 (dd, *J* = 9.1, 6.1 Hz, 1H), 3.21 (dd, *J* = 9.0, 6.7 Hz, 1H), 2.30 – 2.14 (m, 2H), 1.78 – 1.67 (m, 1H), 1.57 – 1.33 (m, 3H), 1.14 – 1.02 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.045 (s, 3H), 0.042 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 135.6, 131.0, 129.2, 116.7, 113.8, 75.8, 72.8, 72.3, 55.4, 41.9, 34.2, 33.7, 29.4, 26.1, 18.3, 17.4, -4.2, -4.3; **IR** (neat): 2945, 2860, 1515, 1464, 1252, 1094, 835 and 771 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{23}H_{40}O_3SiNa$ $[M+Na]^+$ 415.2639; found: 415.2636. *See NMR spectra*

(3*S*,6*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-6-methylheptanal [(+)-10]:

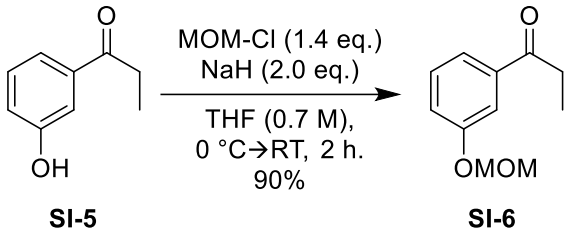


Alkene **9** (13.0 g, 33.0 mmol, 1.0 eq.) was charged into a round-bottom flask, dissolved in THF (90 mL) and treated with ^{t}BuOH (45 mL), water (15 mL), NMO (7.76 g, 66.0 mmol, 2.0 eq.), and OsO_4 (0.016 M in toluene, 100 mL, 1.65 mmol, 0.02 eq.) sequentially. After being stirred for 16 h at room temperature, the reaction mixture was quenched with saturated aq. $Na_2S_2O_3$•$5H_2O$ (100 mL) and diluted with EtOAc (100 mL). Stirring was continued for an additional 2 h. The layers were separated and the organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a corresponding crude diol.

The above crude diol was taken into THF:H_2O (3:1, 160 mL) and at 0 ˚C, $NaIO_4$ (21.5 g, 99 mmol, 3.0 eq.) was added. the reaction mixture was warmed to RT and stirred for 1 h. After complete consumption of diol, the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel eluting with 0-10% ethyl acetate in hexanes to afford compound **(+)-10** (11.4 g, 88% yield) as a yellow oil. R_f = 0.5 (ethyl acetate/hexane 1:9); **$[\alpha]^{20}_D$** = +5.2˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.75 (t, *J* = 2.5 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.37 (s, 2H), 4.11 (dd, *J* = 7.3, 4.2 Hz, 1H), 3.75 (s, 3H), 3.25 – 3.14 (m, 2H), 2.45 (dd, *J* = 5.7, 2.5 Hz, 2H), 1.76 – 1.63 (m, 1H), 1.58 – 1.40 (m, 3H), 1.12 – 0.97 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.82 (s, 9H), 0.01 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.5, 159.2, 130.9, 129.3, 113.9, 75.5, 72.8, 68.6, 55.4, 50.8, 35.2, 33.6, 29.2, 25.9, 18.1, 17.2, -4.2, -4.6; **IR** (neat):

2945, 2860, 2760, 1515, 1464, 1252, 1094, 835 and 771cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{22}H_{38}O_4SiNa$ $[M+Na]^+$ 417.2432; found: 417.2431. *See NMR spectra*

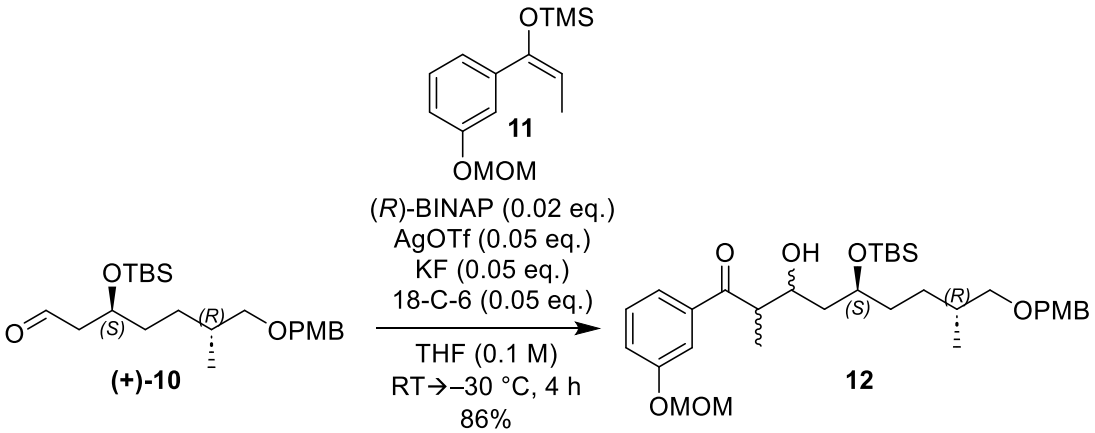
1-(3-(Methoxymethoxy)phenyl)propan-1-one (SI-6):



SI-5 **SI-6**

A flame-dried round-bottom flask was charged with 1-(3-hydroxyphenyl)propan-1-one **SI-5** (5.0 g, 33.0 mmol, 1.0 eq.) and dissolved in THF (50 mL). The mixture was cooled to 0 °C, and NaH (60%, 1.6 g, 66.0 mmol, 2.0 eq.) was added portion-wise. After being stirred for 30 minutes at 0 °C, MOM-Cl (3.6 mL, 47.0 mmol, 1.4 eq.) was added dropwise. The resulting mixture was stirred for 2 h at room temperature, and then the mixture was quenched with ice and diluted with EtOAc. The layers were separated, and the aqueous layer was further extracted with EtOAc (2 x 150 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel, eluting with 0-10% ethyl acetate in hexanes to afford compound **SI-6** (5.8 g, 90% yield) as a red oil. R_f = 0.5 (ethyl acetate/hexane 1:9); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H), 7.36 (t, J = 7.9 Hz, 1H), 7.22 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 5.21 (s, 2H), 3.48 (s, 3H), 2.98 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.5, 157.5, 138.5, 129.7, 121.7, 121.0, 115.6, 94.5, 56.2, 32.0, 8.4; **IR** (neat): 3065, 2976, 1681, 1571, 1451, 1311, 1228, 1099 and 950 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0831; found: 217.0828. *See NMR spectra*

(5*S*,8*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-9-((4-methoxybenzyl)oxy)-2,8-dimethyl-1-phenylnonan-1-one (12):

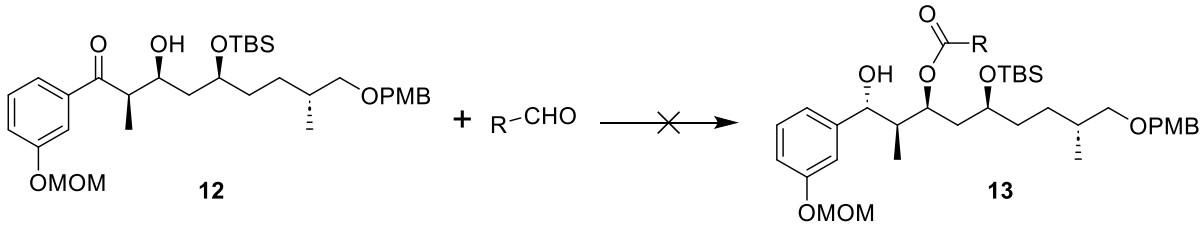


Optimization Table:

Sl. no	Reaction condition	Yield	Comments
1.	$TiCl_4$, DIPEA, DCM, -78 °C, 2h	83%	dr. 1:1
2.	(*R*)- BINAP, AgOTf, KF, 18-Crown -6-ether, THF, rt. to - 78 °C, 12h	33%	dr. 4:1 SM not fully consumed
3.	(*R*)- BINAP, AgOTf, KF, 18-Crown -6-ether, THF, rt. to - 30 °C, 4h	86%	dr. 4:1 SM fully consumed
4.	(*R*)- T-BINAP, AgOTf, KF, 18-Crown -6-ether, THF, rt. to - 30 °C, 12h	64%	dr. 4:1 SM not fully consumed
5.	(*R*)- T-BINAP, AgOTf, KF, 18-Crown -6-ether, THF, 0 °C, 12h	89%	dr. 1:1

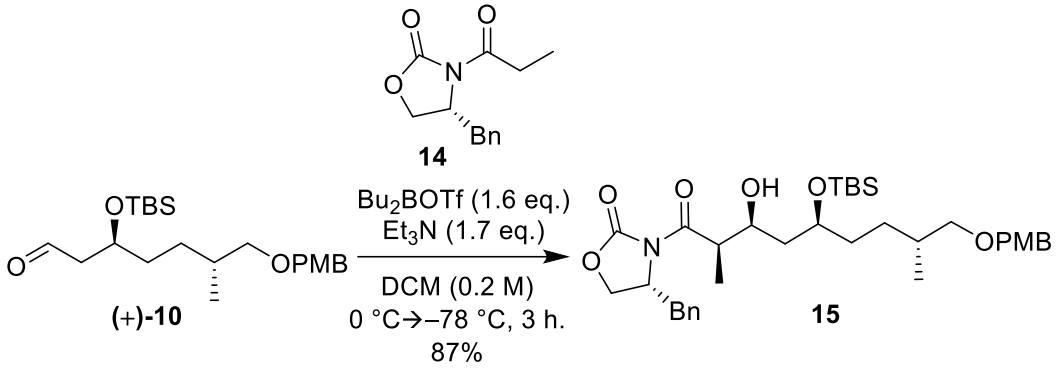
A flame-dried 50 mL round-bottom was charged with AgOTf (16.0 mg, 0.063 mmol, 0.05 eq.), (*R*)-BINAP (16.0 mg, 0.025 mmol, 0.02 eq.), KF (3.7 mg, 0.063 mmol, 0.05 eq.), and 18-Crown-6-ether (17.0 mg, 0.063 mmol, 0.05 eq.) and dissolved the mixture in dry THF (5 mL). This resultant mixture was shielded from light and stirred for 20 minutes at room temperature. Subsequently, the reaction mixture was cooled down to –30 ˚C, aldehyde **(+)-10** (0.5 g, 1.27 mmol, 1.0 eq.) in THF (3 mL) followed by TMS enolate **11** (prepared in situ using the reported procedure)[2] in THF (2 mL) was added. The resulting mixture was stirred for 4 hours at -30 °C, then quenched with water. After filtration through a celite pad, the compound was extracted with EtOAc (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel eluting with 0-15% ethyl acetate in hexanes to afford compound **12** (640 mg, 86% yield, *dr* = 4:1) as a colorless oil. R_f = 0.5 (ethyl acetate/hexane 2:8); $[\alpha]^{20}_D$ = +10.0˚ (*c* = 0.2 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$, inseparable diastereomeric mixture) (major isomer) δ 7.64 – 7.54 (m, 2H), 7.41 – 7.33 (m, 1H), 7.28 – 7.21 (m, 3H), 6.90 – 6.83 (m, 2H), 5.21 (s, 2H), 4.46 – 4.37 (m, 2H), 4.32 – 4.20 (m, 1H), 3.99 – 3.88 (m, 1H), 3.79 (s, 3H), 3.57– 3.50 (m, 1H), 3.49 (s, 3H), 3.32 – 3.15 (m, 2H), 1.78 – 1.58 (m, 3H), 1.58 – 1.39 (m, 3H), 1.27 (d, *J* = 7.08 Hz, 3H), 1.14 – 1.01 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.91 – 0.84 (m, 9H), 0.12 – 0.03 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$, inseparable diastereomeric mixture) (major isomer) δ 204.4, 159.2, 157.7, 138.0, 130.9, 129.8, 129.3, 122.1, 121.3, 116.0, 113.8, 94.6, 75.8, 72.8, 71.2, 69.0, 56.3, 55.4, 46.7, 39.7, 34.1, 33.7, 29.3, 26.0, 18.1, 17.2, 12.9, -4.37, -4.63; **IR** (neat): 2942, 2861, 1861, 1597, 1464, 1253, 1087, 834 and 767 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{33}H_{53}O_7Si$ $[M+H]^+$ 589.3555; found: 589.3549. *See NMR spectra*

Summarising Table for conversion of 13 from 12:



Sl. No	Reaction Conditions	Aldehyde	Remark
1.	SmI_2, THF, -20 °C	CH_3CHO	0 % conversion, complete SM recovered
2.	SmI_2, THF, 0 °C	CH_3CHO	0 % conversion, complete SM recovered
3.	SmI_2, THF, -20 °C	Propionaldehyde	0 % conversion, complete SM recovered
4.	SmI_2, THF, -20 °C	Benzaldehyde	0 % conversion, complete SM recovered
5.	$Sc(OTf)_3$, THF, -20 °C	CH_3CHO	0 % conversion, complete SM recovered
6.	$Zr[OC(CH_3)_3]_4$, THF, 0 °C	CH_3CHO	0 % conversion, complete SM recovered

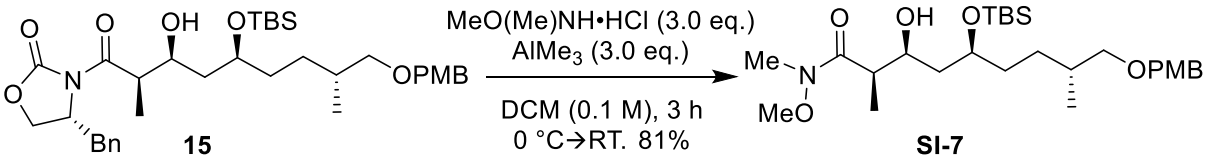
(*R*)-4-Benzyl-3-((2*R*,3*S*,5*S*,8*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-9-((4-methoxybenzyl)oxy)-2,8-dimethylnonanoyl)oxazolidin-2-one (15):



In a round-bottom flask, compound **14**[3] (5.0 g, 21.4 mmol, 1.0 equiv.) was dissolved in dry DCM (50 mL) and chilled to 0 °C. Bu_2BOTf (1.0 M in DCM, 34.3 mL, 34.3 mmol, 1.6 equiv.) was subsequently added dropwise, leading to the formation of a brown reaction mixture. Triethylamine (5.2 mL, 36.5 mmol, 1.7 equiv.) was added dropwise. After stirring for 45 minutes, the reaction mixture was cooled down to −78 °C, and aldehyde **(+)-10** (11.0 g, 27.9 mmol, 1.3 equiv.) in DCM (60 mL) was added slowly over a period of 30 minutes. The reaction mixture was then allowed to stir at -78 °C for 3 hours and at 0 °C for 1 hour before phosphate

buffer (pH=7) and MeOH (1:1) were added simultaneously. The mixture was again cooled down to -10 °C, then 30% solution of H_2O_2 was added, and the solution was stirred at 0 °C for 30 minutes. After treating the reaction mixture with aq. $Na_2S_2O_3$, the organic compound was extracted with diethyl ether (2 x 200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Finally, the crude residue was purified by flash chromatography on silica gel eluting with 10-15% ethyl acetate in hexanes to afford compound **15** (11.7 g, 87% yield, single diastereomer) as a colorless oil. R_f = 0.3 (ethyl acetate/hexane 2:8); $[\alpha]^{20}_D$ = –20.5˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.30 – 7.23 (m, 3H), 7.23 – 7.19 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.74 – 4.64 (m, 1H), 4.42 (s, 2H), 4.20 – 4.13 (m, 2H), 4.12 – 4.04 (m, 1H), 4.01 – 3.85 (m, 1H), 3.79 (s, 3H), 3.79 – 3.74 (m, 1H), 3.40 (s, 1H), 3.32 – 3.19 (m, 3H), 2.77 (dd, *J* = 13.4, 9.6 Hz, 1H), 1.78 – 1.54 (m, 4H), 1.51 – 1.40 (m, 2H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.19 – 1.09 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.08 (d, *J* = 2.6 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.5, 159.2, 153.2, 135.3, 130.9, 129.5, 129.2, 129.0, 127.5, 113.8, 75.6, 72.8, 72.4, 70.7, 66.2, 55.44, 55.36, 43.0, 40.3, 37.9, 35.0, 33.7, 28.7, 26.0, 18.1, 17.31, 11.3, -4.0, -4.5; **IR** (neat): 2941, 2861, 1785, 1702, 1383, 1249, 1097, 835 and 766 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{35}H_{54}NO_7Si$ $[M+H]^+$ 628.3664; found: 628.3659. *See NMR spectra*

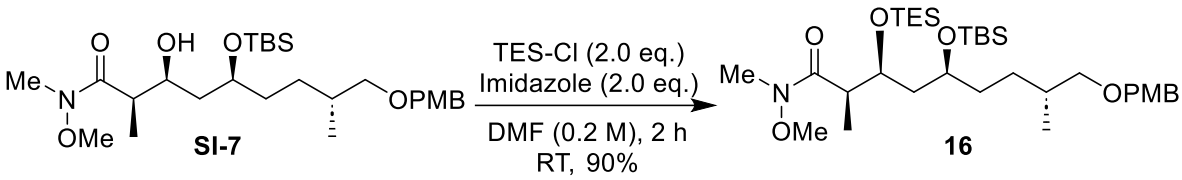
(2*R*,3*S*,5*S*,8*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-*N*-methoxy-9-((4-methoxybenzyl)oxy)-*N*,2,8-trimethylnonanamide (SI-7):



A flame-dried 250 mL round-bottom was charged with *N*,*O*-Dimethylhydroxylamine hydrochloride (2.3 g, 24.0 mmol, 3.0 eq.) and dissolved it in 30 mL of dry DCM. The mixture was cooled to 0 °C and under nitrogen atmosphere trimethylaluminium (2.0 M in toluene, 12.0 mL, 24.0 mmol, 3.0 eq.) was added dropwise. After stirring at the same temperature for 1 h, the reaction mixture was then cooled to -20 °C, and oxazolidinone **15** (5.0 g, 8.0 mmol, 1.0 eq.) in DCM (50 mL) was added dropwise. After 10 minutes, the reaction mixture was allowed to warm to room temperature and stirred for 3 h. Upon completion, the reaction mixture was cooled down to 0 °C and quenched with a 0.5 M aqueous sodium potassium tartrate solution, stirring at RT for 2 h. The reaction mixture was then diluted with DCM, layers were separated and the aqueous layer was further extracted with DCM (2 x 100 mL). Combined DCM layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel, eluting with 15-25% ethyl acetate in

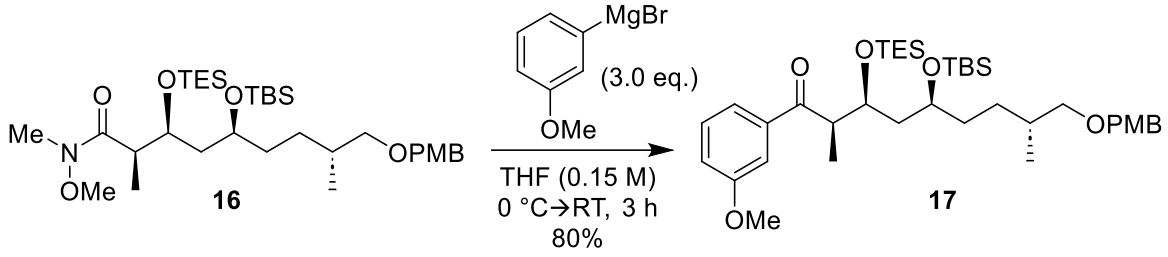
hexanes, to yield compound **SI-7** (3.25 g, 81% yield) as a yellow oil. R_f = 0.1 (ethyl acetate/hexane 2:8); **[α]$^{20}_{D}$** = +4.0˚ (*c* = 0.5 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.49 – 4.32 (m, 2H), 4.00 – 3.93 (m, 1H), 3.92 – 3.84 (m, 2H), 3.79 (s, 3H), 3.67 (s, 3H), 3.27 (dd, *J* = 9.1, 6.1 Hz, 1H), 3.20 (dd, *J* = 9.1, 6.6 Hz, 1H), 3.17 (s, 3H), 2.92 (s, brs, 1H), 1.74 – 1.60 (m, 2H), 1.60 – 1.50 (m, 2H), 1.50 – 1.38 (m, 2H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.16 – 1.06 (m, 1H), 0.90 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.8, 159.1, 130.9, 129.2, 113.8, 75.7, 72.7, 71.9, 70.3, 61.6, 55.3, 40.5, 39.9, 34.5, 33.7, 32.0, 28.9, 26.0, 18.1, 17.3, 11.6, -4.1, -4.4; **IR** (neat): 2942, 2861, 1643, 1465, 1252, 1088, 834 and 761 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{27}H_{50}NO_6Si$ $[M+H]^+$ 512.3402; found: 512.3397. *See NMR spectra*

(2*R*,3*S*,5*S*,8*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-9-((4-methoxybenzyl)oxy)-*N*,2,8-trimethyl-3-((triethylsilyl)oxy)nonanamide) (16):



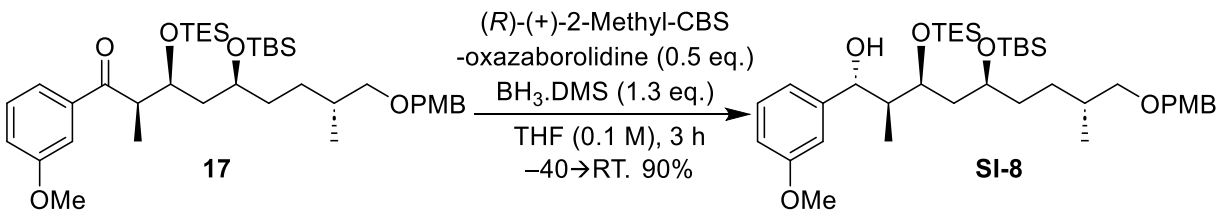
In a 100 mL round-bottom flask, a solution of 2° alcohol **SI-7** (5.0 g, 9.8 mmol, 1.0 eq.) in DMF (50 mL) was treated with imidazole (1.33 g, 19.6 mmol, 2.0 eq.) followed by the TES-Cl (3.5 mL, 19.6 mmol, 2.0 eq.) at room temperature. The mixture was allowed to stir for 2 hours. Upon completion of the starting material, the reaction mixture was quenched with water (50 mL), and the aqueous phase was extracted with EtOAc (2 x 200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel, eluting with 5-15% ethyl acetate in hexanes, to afford compound **16** (5.5 g, 90% yield) as a colorless oil; R_f = 0.5 (ethyl acetate/hexane 2:8); **[α]$^{20}_{D}$** = –11.0˚ (*c* = 0.5 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.47 – 4.26 (m, 2H), 4.02 – 3.85 (m, 1H), 3.74 (s, 3H), 3.71 – 3.63 (m, 1H), 3.60 (s, 3H), 3.25 (dd, *J* = 9.0, 5.9 Hz, 1H), 3.14 (dd, *J* = 9.0, 7.0 Hz, 1H), 3.10 (s, 3H), 2.94 – 2.81 (m, 1H), 1.73 – 1.42 (m, 5H), 1.34 – 1.18 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.05 – 0.95 (m, 1H), 0.94 – 0.89 (m, 9H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.81 (s, 9H), 0.62 – 0.51 (m, 6H), -0.01 (s, 3H), -0.02 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.1, 159.1, 131.1, 129.2, 113.8, 75.9, 72.7, 71.3, 70.0, 61.4, 55.4, 44.3, 42.3, 34.2, 33.8, 32.3, 29.4, 26.1, 18.2, 17.4, 13.8, 7.2, 5.4, -4.1, -4.4; **IR** (neat): 2948, 2870, 1668, 1465, 1252, 1098, 837 and 764 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{33}H_{64}NO_6Si_2$ $[M+H]^+$ 626.4267; found: 626.4263. *See NMR spectra*

(2*R*,3*S*,5*S*,8*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-9-((4-methoxybenzyl)oxy)-1-(3-methoxyphenyl)-2,8-dimethyl-3-((triethylsilyl)oxy)nonan-1-one (17).



Weinreb amide **16** (5.0 g, 8.0 mmol, 1.0 equiv.) was dissolved in 50 mL of dry THF. Following this, 3-methoxyphenyl magnesium bromide (1M in THF, 24 mL, 24.0 mmol, 3.0 equiv.) was added dropwise to the solution at 0 °C. After 20 minutes, the reaction mixture was allowed to warm to room temperature and stirring was continued for 3 hours. Upon completion, the reaction mixture was quenched with an aqueous NH_4Cl solution, and the compound was extracted with EtOAc (2 x 200 mL). The organic extracts were then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel, eluting with 0-5% ethyl acetate in hexanes, to yield compound **17** (4.3g, 80% yield) as a colorless oil. R_f = 0.5 (ethyl acetate/hexane 1:9); $[\alpha]^{20}_D$ = –11.3˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 1H), 7.48 – 7.42 (m, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.09 – 7.03 (m, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.45 – 4.35 (m, 2H), 4.16 (q, *J* = 5.9 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.76 – 3.69 (m, 1H), 3.65 – 3.54 (m, 1H), 3.25 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.17 (dd, *J* = 9.0, 6.8 Hz, 1H), 1.73 – 1.50 (m, 4H), 1.50 – 1.41 (m, 1H), 1.38 – 1.29 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.07 – 0.95 (m, 1H), 0.92 – 0.86 (m, 12H), 0.84 (s, 9H), 0.57 – 0.48 (m, 6H), -0.00 (s, 3H), -0.01 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.0, 160.0, 159.2, 138.7, 131.0, 129.6, 129.2, 121.1, 119.4, 113.8, 112.8, 75.8, 72.8, 70.9, 70.1, 55.5, 55.4, 47.2, 43.6, 34.4, 33.8, 29.3, 26.0, 18.2, 17.3, 12.7, 7.1, 5.4, -4.1, -4.3; **IR** (neat): 2948, 2870, 1602, 1465, 1254, 1090, 1044, 834 and 759 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{38}H_{65}O_6Si_2$ $[M+H]^+$ 673.4319; found: 673.4315. *See NMR spectra*

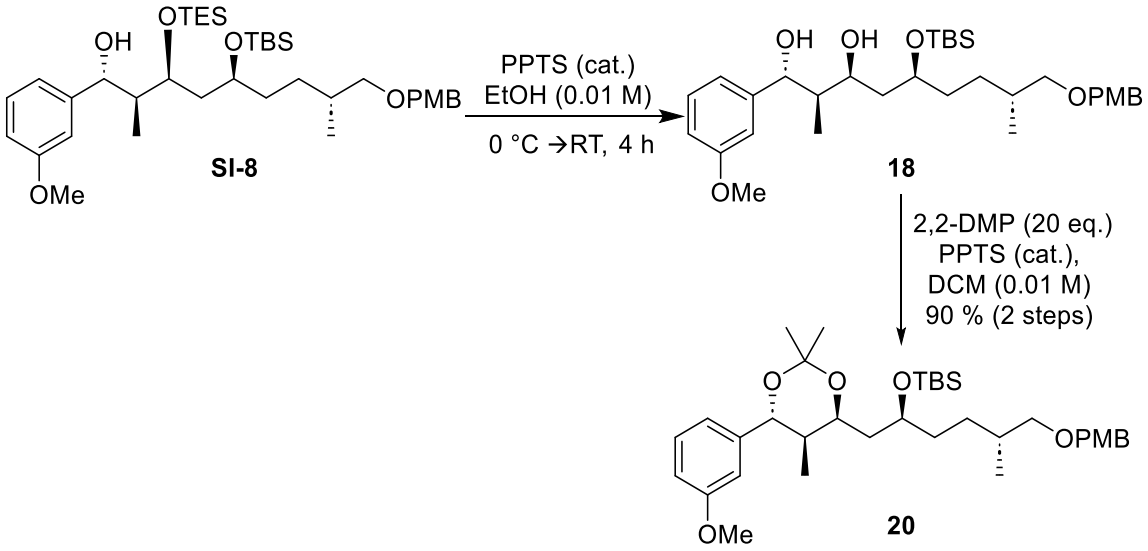
(1*R*,2*S*,3*S*,5*S*,8*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-9-((4-methoxybenzyl)oxy)-1-(3-methoxyphenyl)-2,8-dimethyl-3-((triethylsilyl)oxy)nonan-1-ol (SI-8):



A flame-dried round-bottom flask was charged with (*R*)-Me-CBS catalyst (3.0 mL, 3.0 mmol, 0.5 eq.) dissolved in dry THF (30 mL). The resulting mixture was cooled to –40 ˚C, and

BH_3.DMS (7.7 mL, 7.7 mmol, 1.3 eq.) was added dropwise. After being stirred for 30 minutes at –40 ˚C, ketone **17** (4.0 g, 5.9 mmol, 1.0 eq.) in THF (30 mL) was added dropwise and stirring was continued for 1 hour. Subsequently, the reaction mixture was warmed to room temperature, and stirred for 2 hours. Upon completion, the reaction mixture was cooled to 0 ˚C and quenched by adding MeOH (20 mL) dropwise. The resulting mixture was then concentrated under reduced pressure, and the crude residue was purified by flash chromatography on silica gel eluting with 0-10% ethyl acetate in hexanes, yielding compound **SI-8** (3.6 g, 90% yield, single diastereomer) as a colorless oil. R_f = 0.4 (ethyl acetate/hexane 1:9); $[\alpha]^{20}_D$ = –2.4˚ (*c* = 0.5 in $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 3H), 6.93 – 6.89 (m, 2H), 6.89 – 6.84 (m, 2H), 6.80 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 4.57 (dd, *J* = 9.2, 1.6 Hz, 1H), 4.49 (s, 1H), 4.46 – 4.37 (m, 2H), 4.06 – 3.99 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.29 (dd, *J* = 9.0, 6.1 Hz, 1H), 3.23 (dd, *J* = 9.0, 6.7 Hz, 1H), 2.04 – 1.93 (m, 1H), 1.92 – 1.80 (m, 1H), 1.81 – 1.68 (m, 2H), 1.62 – 1.54 (m, 2H), 1.40 – 1.30 (m, 1H), 1.19 – 1.06 (m, 1H), 1.06 – 0.99 (m, 9H), 0.95 – 0.91 (m, 4H), 0.92 – 0.86 (m, 9H), 0.74 – 0.66 (m, 6H), 0.62 (d, *J* = 7.1 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.7, 159.2, 145.8, 131.0, 129.23, 129.19, 119.6, 113.8, 113.1, 112.5, 77.7, 75.8, 73.9, 72.8, 69.8, 55.4, 55.3, 44.7, 39.7, 34.1, 33.9, 29.3, 26.1, 18.2, 17.4, 13.5, 7.1, 5.3, -4.2, -4.3; **IR** (neat): 2949, 2870, 1465, 1254, 1217, 1090, 1044, 834 and 759 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{38}H_{67}O_6Si_2$ $[M+H]^+$ 675.4471; found: 675.4465. *See NMR spectra*

***tert*-Butyl(((2*S*,5*R*)-6-((4-methoxybenzyl)oxy)-1-((4*S*,5*R*,6*R*)-6-(3-methoxyphenyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-methylhexan-2-yl)oxy)dimethylsilane (20):**

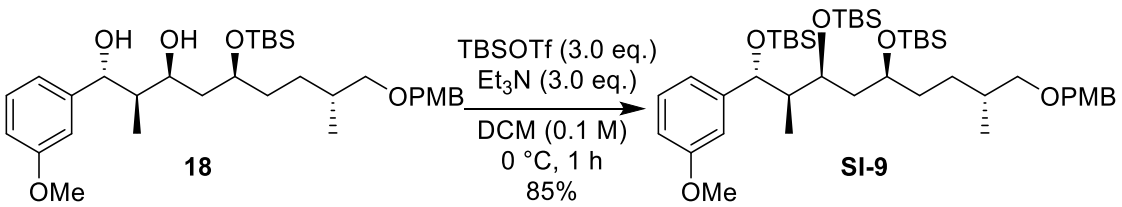


To a solution of alcohol **SI-8** (15.0 mg, 0.02 mmol, 1 eq.) in EtOH (2.0 mL) at 0 °C was added PPTS (1.0 mg, 0.004 mmol, 0.20 equiv.). The reaction mixture was slowly warmed to RT and

stirred for 4 h, then concentrated to dryness to afford crude **18** which was directly used in next step without further purification.

The above crude diol **18** was dissolved in 2.0 mL of DCM, and then 2,2-DMP (54.0 µl, 0.44 mmol, 20.0 eq.) was added. Subsequently, a catalytic amount of PPTS was introduced, and the mixture was stirred at room temperature for 1 hour. After completion, the reaction mixture was quenched with aq. $NaHCO_3$ and compound was extracted with DCM (2 x 5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel eluting with 0-5% ethyl acetate in hexanes to afford compound **20** (12.0 mg, 90% yield) as a colorless oil. R_f = 0.3 (ethyl acetate/hexane 1:9); $[\alpha]^{20}_D$ = +23.4˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 3H), 7.0 – 6.92 (m, 2H), 6.91 – 6.85 (m, 2H), 6.84 – 6.80 (m, 1H), 4.48 – 4.38 (m, 2H), 4.30 – 4.22 (m, 1H), 4.19 (d, *J* = 8.3 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.76 – 3.70 (m, 1H), 3.30 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.22 (dd, *J* = 9.0, 6.7 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.78 – 1.62 (m, 2H), 1.61 – 1.45 (m, 4H), 1.41 (s, 6H), 1.18 – 1.06 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.06 (d, *J* = 3.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9, 159.2, 143.7, 131.0, 129.6, 129.2, 119.6, 113.9, 113.3, 112.7, 101.2, 77.8, 75.8, 72.8, 69.9, 65.9, 55.4, 55.36, 41.9, 38.1, 34.6, 33.8, 29.4, 26.1, 25.0, 24.1, 18.2, 17.4, 11.8, -4.2, -4.3; **IR** (neat): 2944, 2860, 1606, 1464, 1222, 1087, 1044, 834 and 760 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{35}H_{56}O_6SiNa$ $[M+Na]^+$ 623.3738; found: 623.3735. *See NMR spectra*

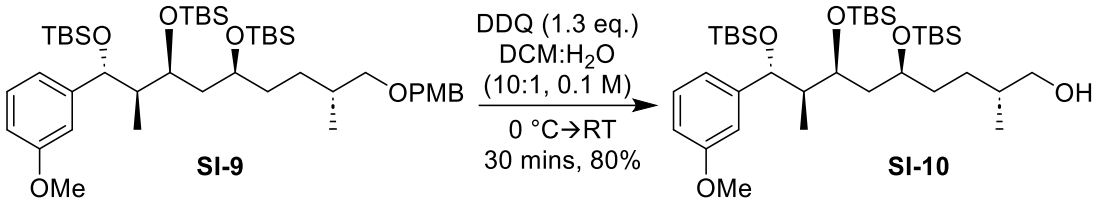
(5*R*,6*R*,7*S*,9*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-9-((*R*)-4-((4-methoxybenzyl)oxy)-3-methylbutyl)-5-(3-methoxyphenyl)-2,2,3,3,6,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disilatridecane (SI-9):



To a solution of crude alcohol **18** (3.5 g, 6.25 mmol, 1.0 eq.) and triethylamine (2.2 mL, 15.6 mmol, 3.0 eq.) in dichloromethane (30 mL) at 0 °C was added TBSOTf (3.6 mL, 15.6 mmol, 3.0 eq.) dropwise. The reaction mixture was stirred at 0 °C for 1 h, then quenched with saturated aq. $NaHCO_3$. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel eluting with 0-10% ethyl acetate in hexanes to afford compound **SI-9** (4.0 g, 85% yield) as a colorless

oil; R_f = 0.6 (ethyl acetate/hexane 1:9); **[α]$^{20}_D$** = +11.6˚ (*c* = 0.5 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H), 7.21 – 7.14 (m, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.82 – 6.75 (m, 3H), 4.47 – 4.41 (m, 3H), 4.39 – 4.33 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.76 – 3.69 (m, 1H), 3.31 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.21 (dd, *J* = 9.0, 7.0 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.78 – 1.69 (m, 2H), 1.67 – 1.58 (m, 2H), 1.55 – 1.50 (m, 1H), 1.44 – 1.32 (m, 1H), 1.12 – 1.1 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.83 (s, 9H), 0.47 (d, *J* = 7.0 Hz, 3H), 0.13 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H), -0.39 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5, 159.2, 146.1, 131.1, 129.2, 129.0, 120.5, 113.8, 113.2, 112.8, 77.4, 75.9, 72.8, 70.3, 69.0, 55.4, 55.3, 46.5, 43.6, 34.2, 33.8, 29.7, 26.3, 26.2, 26.1, 18.5, 18.3, 18.2, 17.4, 10.0, -3.1, -3.4, -3.9, -4.0, -4.28, -4.33; **IR** (neat): 2949, 2863, 1608, 1468, 1256, 1083, 1044, 839 and 769 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{44}H_{84}NO_6Si_3$ $[M+NH_4]^+$ 806.5606; found: 806.5602. *See NMR spectra*

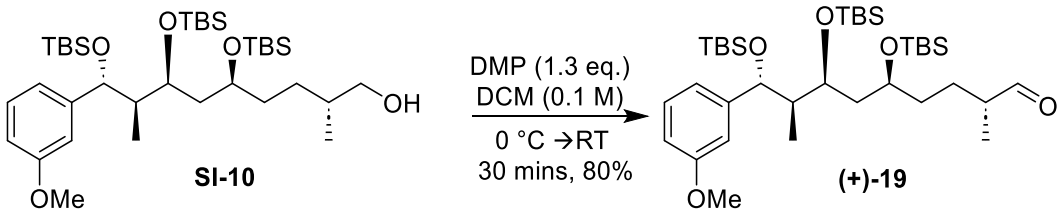
(2*R*,5*S*,7*S*,8*R*,9*R*)-5,7,9-*tris*((*tert*-Butyldimethylsilyl)oxy)-9-(3-methoxyphenyl)-2,8-dimethylnonan-1-ol (SI-10):



A 250-mL round-bottomed flask was charged with **SI-9** (3.9 mmol, 1.0 eq.), DCM (30 mL), and water (3.0 mL). The flask was cooled to 0 °C and DDQ (1.12 g, 4.9 mmol, 1.3 eq.) was added as a single portion. The resulting mixture was rapidly stirred for 30 minutes at RT, and then the reaction was quenched by addition of sat. aq. $NaHCO_3$ (75 mL). The mixture was diluted with DCM and H_2O. The layers were separated, and the aqueous phase was extracted with DCM (2 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and then concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel, using a gradient of 0-10% ethyl acetate in hexanes as the eluent. This process yielded compound **SI-10** (2.1 g, 80% yield) as a yellow oil. R_f = 0.3 (ethyl acetate/hexane 1:9); **[α]$^{20}_D$** = +15.3˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.0 Hz, 1H), 6.85 – 6.74 (m, 3H), 4.43 (d, *J* = 9.0 Hz, 1H), 4.36 – 4.31 (m, 1H), 3.80 (s, 3H), 3.78 – 3.70 (m, 1H), 3.53 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.42 (dd, *J* = 10.5, 6.7 Hz, 1H), 2.03 – 1.88 (m, 1H), 1.79 – 1.68 (m, 1H), 1.67 – 1.59 (m, 3H), 1.54 – 1.47 (m, 1H), 1.44 – 1.35 (m, 1H), 1.33 (br, s, 1H), 1.14 – 1.02 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.83 (s, 9H), 0.46 (d, *J* = 7.8 Hz, 3H), 0.13 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H), -0.40 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5, 146.0, 129.0, 120.5, 113.2, 112.8, 77.4, 70.3, 69.0,

68.5, 55.3, 46.6, 43.7, 36.14, 34.07, 29.0, 26.3, 26.15, 26.10, 18.5, 18.3, 18.2, 16.9, 10.1, -3.1, -3.4, -3.9, -4.0, -4.30, -4.35; **IR** (neat): 3021, 2951, 1468, 1215, 1046, 747 and 699 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{36}H_{72}O_5Si_3Na$ $[M+Na]^+$ 691.4596; found: 691.4589. *See NMR spectra*

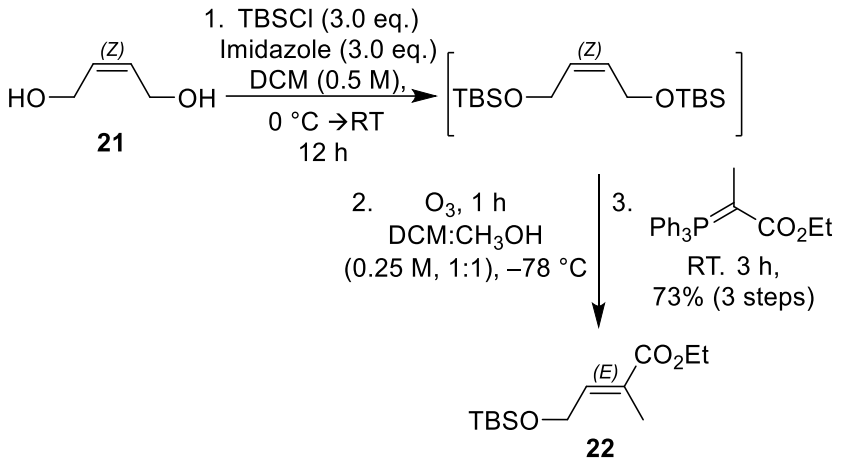
(2*R*,5*S*,7*S*,8*R*,9*R*)-5,7,9-*tris*((*tert*-Butyldimethylsilyl)oxy)-9-(3-methoxyphenyl)-2,8-dimethylnonanal (+)-19:



To a solution of 1˚ alcohol **SI-10** (1.0 g, 1.5 mmol, 1.0 eq.) in DCM (10 mL) at 0 ˚C, Dess-Martin periodinane (0.950 g, 2.25 mmol, 1.5 eq.) was added and stirred at room temperature for 30 minutes. After completion, the reaction mixture was quenched with a saturated sodium thiosulfate solution and stirred for an additional hour. The organic phase was extracted with DCM (2 x 50 mL), dried over Na_2SO_4, and the solvents were evaporated at below 30 °C. Compound **(+)-19** was obtained as a colorless oil (0.85 g, 85% crude yield) and used directly in the next step without further purification (<u>see **S-31**</u>); R_f = 0.5 (ethyl acetate/hexane 1:9); **^{1}H NMR** (400 MHz, $CDCl_3$, Crude NMR) δ 9.63 (d, J = 1.8 Hz, 1H), 7.23 – 7.13 (m, 1H), 6.88 – 6.64 (m, 3H), 4.43 (d, J = 9.0 Hz, 1H), 4.36 – 4.22 (m, 1H), 4.17 – 4.12 (m, 1H), 3.80 (s, 3H), 2.33 – 2.25 (m, 2H), 2.1 – 1.97 (m, 1H), 1.95 – 1.90 (m, 1H), 1.89 – 1.81 (m, 1H), 1.79 – 1.70 (m, 1H), 1.64 – 1.56 (m, 2H), 1.10 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.83 (s, 9H), 0.48 (d, J = 7.0 Hz, 3H), 0.13 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.00 (s, 3H), -0.41 (s, 3H). *See NMR spectra*

2.5. Synthesis of Julia-Kocienski olefination partner fragment-28:

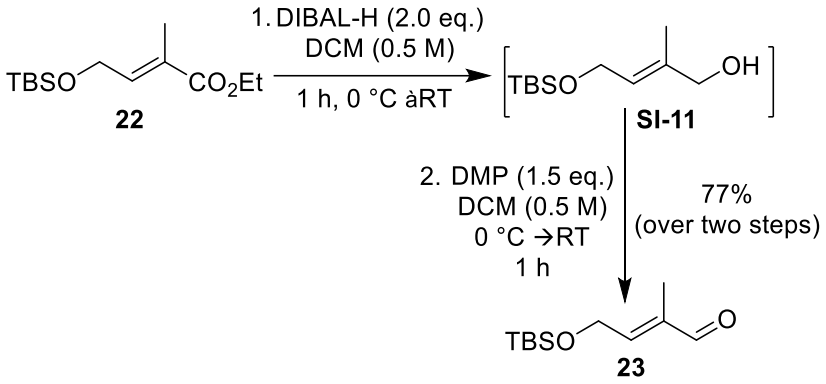
Ethyl (*E*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylbut-2-enoate (22):



In a round-bottom flask charged with *cis*-1,4-butene diol **21** (10.0 g, 113.0 mmol, 1.0 eq.) and dissolved in DCM (200 mL) at 0 ˚C, followed by imidazole (23.0 g, 341.0 mmol, 3.0 eq.) was added. The resulting mixture was stirred for 10 minutes, and then TBS-Cl (51.0 g, 341.0 mmol, 3.0 eq.) was introduced at 0 ˚C. The reaction mixture was warmed to room temperature and stirred for 12 hours. Upon completion, the reaction mixture was quenched with water, and the layers were separated. The aqueous phase was further extracted with DCM (2 x 300 mL). Combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure.

The crude residue taken into DCM:MeOH (1:1, 300 mL) was cooled to –78 °C. Ozone was slowly bubbled through the solution until it turned blue solution. Then the reaction mixture was purged with N_2 and charged with triphenylphosphine (23.0 g, 87.0 mmol, 1.1 eq.) and stirring was continued at room temperature for 30 minutes. Subsequently, (1-Carbethoxyethylidene)triphenylphosphorane (31.5 g, 87.0 mmol, 1.1 eq.) was added to the above crude solution at room temperature and allowed to stir for 3 hours. Then, the solvent was evaporated and concentrated under reduced pressure. Most of the triphenylphosphine oxide was removed by hexane trituration and the obtained crude residue was purified by flash chromatography on silica gel eluting in hexanes to afford compound **22** (21.5 g, 73% yield) as a colorless oil. R_f = 0.5 (ethyl acetate/hexane 1:9**)**; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.77 (td, J = 5.6, 1.2 Hz, 1H), 4.41 – 4.28 (m, 2H), 4.19 (q, J = 7.1 Hz, 2H), 1.81 (d, J = 1.0 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 141.4, 127.5, 60.8, 60.7, 26.0, 18.5, 14.4, 12.8, -5.1; **IR** (neat): 2953, 2866, 1720, 1468, 1378, 1255, 1134, 1065, 844 and 774 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{13}H_{27}O_3Si$ $[M+H]^+$ 259.1724; found: 259.1721. *See NMR spectra*

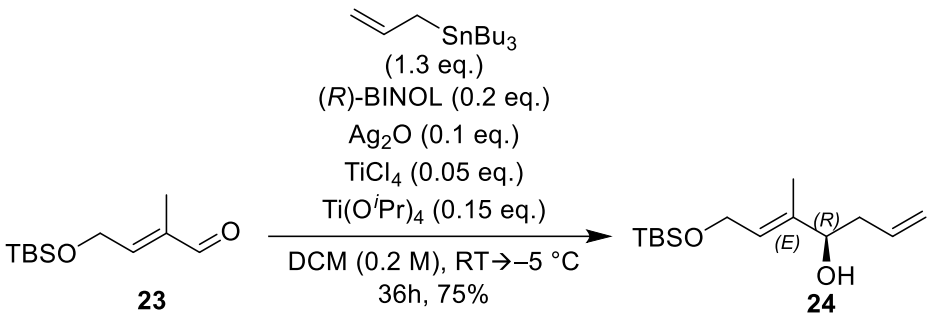
(*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylbut-2-enal (23):



To a solution of compound **22** (15.0 g, 58.0 mmol, 1.0 eq.) in DCM (150 mL) at 0 °C was added a solution of DIBAL-H in toluene (116.0 mL, 1.0 M, 116.0 mmol, 2.0 eq.) dropwise for 15 minutes. The reaction mixture was slowly warmed to room temperature and stirred for 1 h. After completion, the reaction mixture was cooled to 0 °C and quenched with sat. aq. Rochelle's salt. The biphasic mixture was stirred vigorously at RT for 2 h, and then the layers were separated. The aqueous phase was further extracted with DCM (2 x 250 mL), and combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was utilized in the next step without further purification; **^{1}H NMR** (400 MHz, $CDCl_3$, crude **SI-11**) δ 5.52 – 5.44 (m, 1H), 4.15 (dd, J = 6.3, 0.8 Hz, 2H), 3.91 (s, 2H), 1.57 (s, 3H), 0.82 (s, 9H), -0.01 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$, crude **SI-11**) δ 136.3, 125.2, 68.3, 60.0, 26.1, 18.5, 13.9, -5.0. *See NMR spectra*

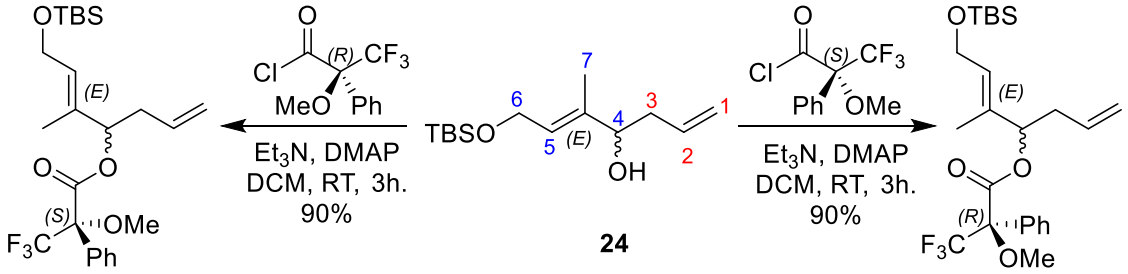
The above crude alcohol **SI-11** (12.0 g, 55.6 mmol, 1.0 equiv.) was dissolved in dichloromethane (DCM, 100 mL) followed by Dess Martin periodinane (35.0 g, 83.4 mmol, 1.5 equiv.) was added at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was quenched with a saturated sodium thiosulfate solution and stirred for an additional 1 hour. The organic compounds were then extracted with DCM (2 x 250 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to purification by flash chromatography on silica gel, eluting with ethyl acetate: hexanes (0-10%), yielding aldehyde compound **23** (9.6 g, 77% yield) as a yellow oil; R_f = 0.5 (ethyl acetate/hexane 1:9); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 6.50 (ddd, J = 6.7, 4.1, 1.3 Hz, 1H), 4.48 (ddd, J = 5.3, 2.2, 1.0 Hz, 2H), 1.71 (dd, J = 2.4, 1.1 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.7, 153.2, 137.8, 60.6, 25.9, 18.4, 9.5, -5.2; **IR** (neat): 2950, 2863, 1696, 1468, 1259, 1117, 1068, 839 and 777 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{11}H_{22}O_2SiNa$ $[M+Na]^+$ 237.1281; found: 237.1284. *See NMR spectra*

(*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-methylhepta-1,5-dien-4-ol (24):



Under a nitrogen atmosphere, a 500 mL reaction flask was charged with 1.85 mL of $TiCl_4$ (1.85 mmol, 0.05 eq.) dissolved in 80 mL of DCM. The solution was cooled to 0 °C, and then 1.7 mL of $Ti(O^iPr)_4$ (5.6 mmol, 0.15 eq.) was added. The mixture was then warmed to room temperature and stirred for 1 hour. Ag_2O (0.86 g, 3.7 mmol, 0.1 eq.) was added at room temperature and the mixture was stirred for 5 h in the dark. At this point, a solution of (*R*)-BINOL (1.72 g, 7.4 mmol, 0.2 eq.) in 100 mL of DCM was added to the reaction mixture, and stirring was continued for an additional 2 hours. The mixture was cooled to -15°C, and a DCM (50 mL) solution of aldehyde **23** (8.0 g, 37.0 mmol, 1.0 eq.) and allyl tributyltin (15.0 mL, 48.1 mmol, 1.3 eq.) were sequentially added. The mixture was allowed to warm to –5 °C and stirred for 24 hours. Following TLC confirmation, the reaction mixture was quenched with saturated aq. $NaHCO_3$, and extracted with DCM (2 x 200 mL). The organic extracts were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (using EtOAc/Hexane 1:9) resulted in the isolation of compound **24** as a colorless oil (7.1 g, 75% yield, the enantiomeric ratio was determined to be 94:6, after TBDPS protection, see **S-28**); R_f = 0.3 (ethyl acetate/hexane 1:9); $[\alpha]^{20}_D$ = +9.4˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.87 – 5.66 (m, 1H), 5.66 – 5.51 (m, 1H), 5.23 – 5.06 (m, 2H), 4.23 (d, *J* = 6.0 Hz, 2H), 4.09 – 3.97 (m, 1H), 2.44 – 2.21 (m, 2H), 1.62 (d, *J* = 0.9 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.7, 134.8, 126.3, 117.9, 76.0, 60.1, 39.8, 26.1, 18.5, 12.2, -5.0; **IR** (neat): 2943, 2863, 1466, 1386, 1258, 1063, 840 and 765 cm^{-1}; **HRMS** (SI-TOF): calculated for $C_{14}H_{28}O_2SiNa$ $[M+Na]^+$ 279.1751; found: 279.1748. *See NMR spectra*

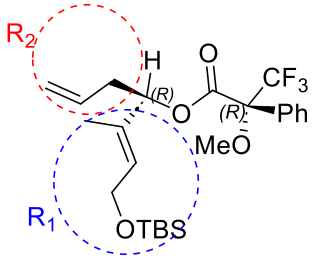
Mosher ester analysis on compound 24:

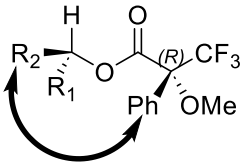


$\Delta\delta$ (= δ_R - δ_S) data for the S- and R-MTPA- Mosher ester's **SI-12** and **SI-13** (**Figure-S9**)

	δ *R* ester (ppm)	δ *S* ester (ppm)	$\Delta\delta^{RS}$ (= δ_R - δ_S) (ppm)
1	5.03, 5.00	5.12, 5.09	-0.09, -0.9
2	5.60	5.71	-0.11
3	2.42	2.47	-0.05
4	5.46	5.43	0.03
5	5.70	5.63	0.07
6	4.23	4.19	0.05
7	1.64	1.49	0.15

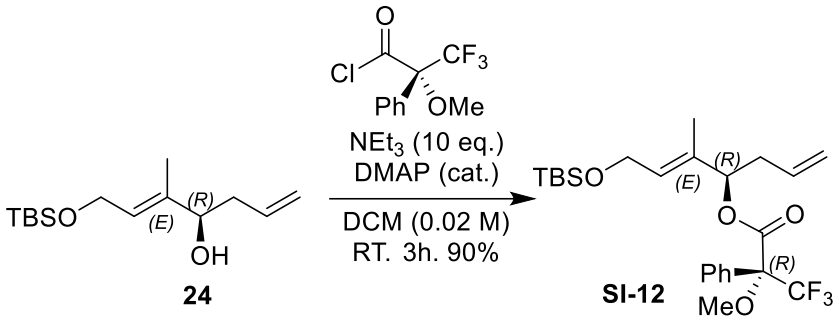
Precisely, protons that have positive $\Delta\delta_{RS}$ values reside within R_1 and the protons with negative values belong to R_2. According to this allylic side chain resides within R_2 (due to its negative $\Delta\delta_{RS}$ values) and the -OTBS fragment belongs to R_1 *i.e* on the opposite side of that plane (Figure- S9).





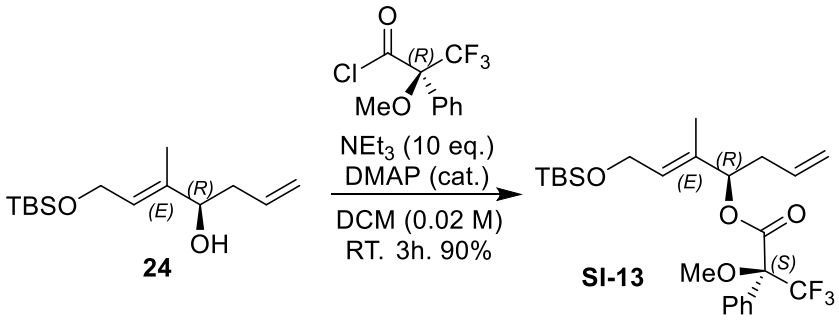
Phenyl group shielding effect results upfield chemical shift for the protons belong to R_2

(*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-methylhepta-1,5-dien-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-12):



SI-12 was synthesized by following the procedure described on page **S-11** and resulted in 90% yield; R_f = 0.6 (ethyl acetate/hexane 1:9); **[α]$^{20}_{D}$** = +39.3˚ (*c* = 1.0 in $CHCl_3$).; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 2H), 7.42 – 7.34 (m, 3H), 5.70 (dt, *J* = 5.6, 4.8 Hz, 1H), 5.61 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.46 (dd, *J* = 7.7, 6.1 Hz, 1H), 5.11 – 4.97 (m, 2H), 4.31 – 4.15 (m, 2H), 3.52 (d, *J* = 1.1 Hz, 3H), 2.60 – 2.31 (m, 2H), 1.64 (d, *J* = 1.1 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.8, 132.8, 132.54, 132.52, 130.5, 129.6, 128.4, 127.6, 123.5 (q, *J* = 288.4 Hz), 118.4, 84.7 (q, *J* = 27.7 Hz), 80.7, 59.8, 55.5, 37.2, 26.0, 18.4, 12.4, -5.0, -5.0.; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -71.38; **IR** (neat): 2945, 2861, 1751, 1465, 1259, 1180, 1114, 1081, 839, 772 and 721 cm^{-1}. *See NMR spectra*

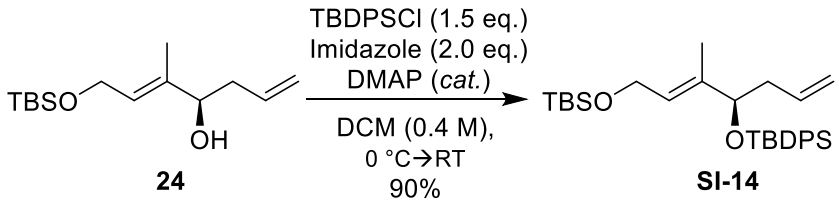
(*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-methylhepta-1,5-dien-4-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-13):



SI-13 was synthesized by following the procedure described on page **S-11** and resulted in 90% yield; R_f = 0.6 (ethyl acetate/hexane 1:9); **[α]$^{20}_{D}$** = –31.0˚ (*c* = 1.0 in $CHCl_3$).; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.38 (dt, *J* = 3.2, 2.3 Hz, 3H), 5.79 – 5.66 (m, 1H), 5.63 (t, *J* = 5.9 Hz, 1H), 5.43 (dd, *J* = 8.0, 5.8 Hz, 1H), 5.17 – 5.06 (m, 2H), 4.20 (dd, *J* = 8.3, 3.1 Hz, 2H), 3.55 (d, *J* = 1.1 Hz, 3H), 2.46 (dtt, *J* = 14.5, 4.5, 2.6 Hz, 2H), 1.49 (d, *J* = 0.9 Hz, 3H), 0.90 (s, 9H), 0.06 (d, *J* = 1.5 Hz, 6H).; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.8, 133.1, 132.53, 132.48, 130.3, 129.6, 128.4, 127.5, 123.5 (q, *J* = 288.5 Hz), 118.4, 84.6 (q, *J* = 27.6 Hz), 80.8, 59.8, 55.7, 37.2, 26.0, 18.4, 12.1, -5.01, -5.04.; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -71.47.; **IR**

(neat): 2945, 2861, 1751, 1465, 1259, 1180, 1114, 1081, 839, 772 and 721 cm^{-1}. *See NMR spectra*

(*R*,*E*)-5-Allyl-2,2,6,10,10,11,11-heptamethyl-3,3-diphenyl-4,9-dioxa-3,10-disiladodec-6-ene (SI-14) :

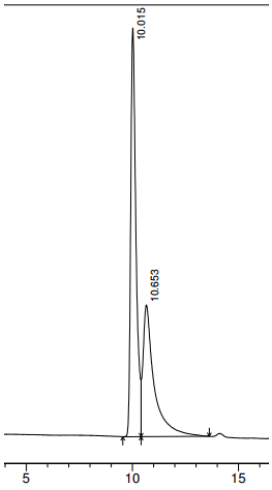


24 **SI-14**

The flame-dried RB flask was charged with 2˚ Alcohol **24** (5.0 g, 19.5 mmol, 1.0 eq.) and dissolved in 50 mL of DCM. The mixture was cooled to 0 ˚C, and then Imidazole (2.7 g, 39.0 mmol, 2.0 eq.) and DMAP (0.237 g, 1.95 mmol, 0.1 eq.) were added simultaneously. After 10 mins, TBDPS-Cl (7.5 mL, 29.0 mmol, 1.5 eq.) was introduced and stirred the reaction mixture at room temperature for 2 h. Upon completion, the reaction mixture was quenched with water, and the compound was extracted with DCM (2 x 100 mL). The organic extracts were combined and dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (EtOAc/Hexane 0-5%) yielded compound **SI-14** as a greenish oil (8.7 g, 90% yield); R_f = 0.8 (ethyl acetate/hexane 5:95); $[\alpha]^{20}_D$ = +9.2˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.61 (m, 4H), 7.46 – 7.30 (m, 6H), 5.67 – 5.46 (m, 1H), 5.41 – 5.14 (m, 1H), 5.07 – 4.77 (m, 2H), 4.18 – 4.02 (m, 3H), 2.28 – 2.20 (m, 2H), 1.57 (s, 3H), 1.07 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.7, 136.14, 136.08, 134.9, 134.6, 134.1, 129.65, 129.62, 127.6, 127.5, 126.9, 116.6, 78.4, 60.0, 40.7, 27.2, 26.1, 19.5, 18.5, 11.8, -5.0; **IR** (neat): 2945, 2862, 1471, 1257, 1108, 1081, 840, 770 and 704 cm^{-1}; **HRMS** (ESI-TOF) calculated for $C_{30}H_{50}NO_2Si_2$ $[M+NH_4]^+$ 512.3375; found: 512.3373. *See NMR spectra*

HPLC report of compound SI-14.

Acquired by : Manjula
Sample Name : SCS-MCR-49-RAC
Sample ID : SCS-MCR-49-RAC
Tray# : 1
Vail # : 87
Injection Volume : 2 uL
Data File Name : 28042022.9.lcd
Method File Name : 28042022.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 4/28/2022 3:24:53 PM
Data Processed : 4/28/2022 3:55:03 PM
COLUMN: EUROCEL-02 250 X 4.6mm 5u
MOBILE PHASE: 0.5% IPA IN HEXANE
FLOW RATE : 0.3ml/min

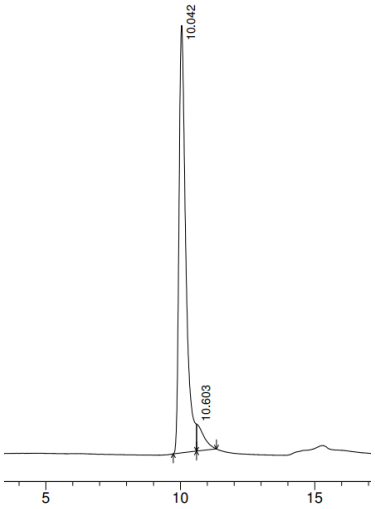


PDA Ch1 210nm 1nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.015	8304765	475212	59.616	75.624
2	10.653	5625551	153173	40.384	24.376
Total		13930316	628385	100.000	100.000

Figure S7: HPLC report of Racemic **SI-14**

Acquired by : Manjula
Sample Name : SCS-MCR-2398-CHIRAL
Sample ID : SCS-MCR-2398-CHIRAL
Tray# : 1
Vail # : 85
Injection Volume : 2 uL
Data File Name : 28042022.12.lcd
Method File Name : 28042022.lcm
Batch File Name :
Report File Name : Default.lcr
Data Acquired : 4/28/2022 4:45:35 PM
Data Processed : 4/28/2022 5:21:36 PM
COLUMN: EUROCEL-02 250 X 4.6mm 5u
MOBILE PHASE: 0.5% IPA IN HEXANE
FLOW RATE : 0.3ml/min

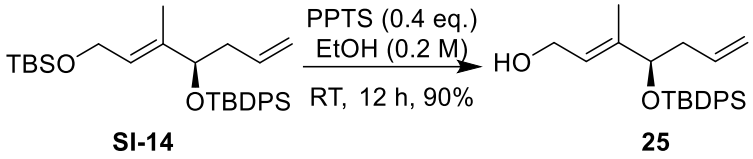


PDA Ch1 210nm 1nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.042	11436700	647536	93.858	94.065
2	10.603	748383	40853	6.142	5.935
Total		12185083	688389	100.000	100.000

Figure S8: HPLC report of Chiral **SI-14**

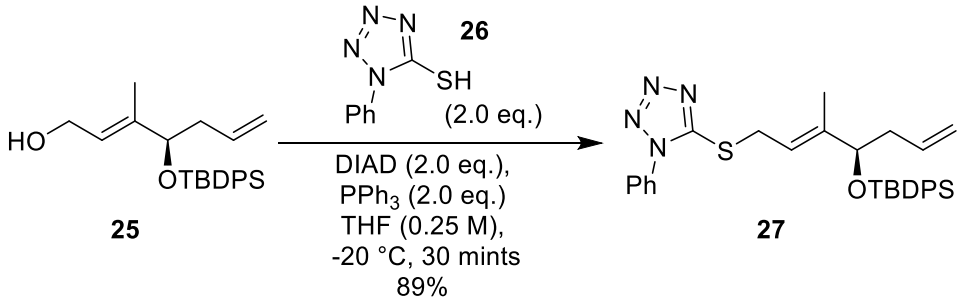
(*R*,*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylhepta-2,6-dien-1-ol (25):



SI-14 **25**

In a round-bottom flask, compound **SI-14** (8.0 g, 16.2 mmol, 1.0 eq.) was dissolved in ethanol (80 mL) at room temperature. PPTS (1.65 g, 6.5 mmol, 0.4 eq.) was added, and the mixture was stirred overnight. Upon completion of the reaction, ethanol was evaporated, and the residue was diluted with MTBE. Aqueous $NaHCO_3$ was then added. Organic phase was extracted with MTBE (2 x 150 mL), dried over Na_2SO_4, evaporation of solvents and purification of the residue by column chromatography on silica gel (EtOAc/Hexane 1:9) gave compound **25** as a colorless oil (5.5 g, 90% yield); R_f = 0.2 (ethyl acetate/hexane 1:9); $[\alpha]^{20}_D$ = –5.9˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 – 7.60 (m, 4H), 7.51 – 7.32 (m, 6H), 5.77 – 5.53 (m, 1H), 5.34 – 5.13 (m, 1H), 4.99 – 4.96 (m, 1H), 4.95 – 4.92 (m, 1H), 4.13 (t, *J* = 6.5 Hz, 1H), 4.00 – 3.92 (m, 2H), 2.43 – 2.22 (m, 2H), 1.59 (s, 3H), 1.09 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.6, 136.15, 136.08, 134.7, 134.4, 134.2, 129.72, 129.66, 127.6, 127.5, 125.4, 116.8, 78.3, 58.9, 40.7, 27.2, 19.5, 11.6; **IR** (neat): 3358, 3067, 2935, 2861, 1470, 1430, 1107, 1003, 756 and 703 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{24}H_{36}NO_2Si$ $[M+NH_4]^+$ 398.2515; found: 398.2512. *See NMR spectra*

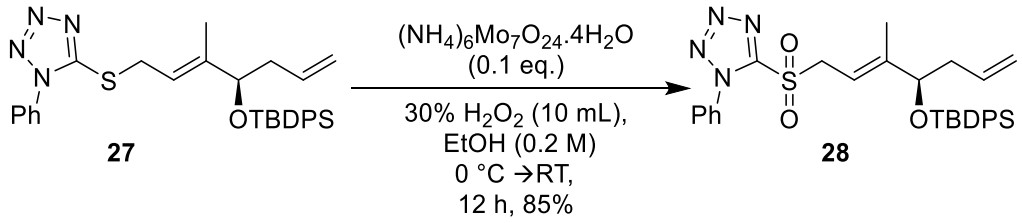
(*R*,*E*)-5-((4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylhepta-2,6-dien-1-yl)thio)-1-phenyl-1*H*-tetrazole (27):



A flame-dried 100 mL round-bottom flask was charged with 6.0 grams (15.8 mmol, 1.0 eq.) of 1˚ alcohol **25** and dissolved in dry tetrahydrofuran (60 mL). To this solution, triphenylphosphine (8.3 g, 31.6 mmol, 2.0 eq.) and PTSH **26** (5.6 g, 31.6 mmol, 2.0 eq.) were added simultaneously. The mixture was cooled to -20 ˚C, subsequently, DIAD (6.21 mL, 31.6 mmol, 2.0 eq.) was added dropwise, and the reaction was allowed to stir for 30 mints at that temperature. After completion, the reaction mixture was quenched with aqueous sodium bicarbonate, and the organic phase was extracted with ethyl acetate (2 x 150 mL). The

combined organic extracts were dried over Na_2SO_4, followed by solvent evaporation. The obtained crude residue was subjected to purification by column chromatography on silica gel (ethyl acetate/hexane 1:9), resulting in the isolation of compound **27** as a colorless oil (7.6 g, 89% yield); R_f = 0.5 (ethyl acetate/hexane 1:9); $[\alpha]^{20}_D$ = +34.7˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 2H), 7.61 – 7.48 (m, 7H), 7.43 – 7.38 (m, 1H), 7.37 – 7.30 (m, 3H), 7.30 – 7.23 (m, 2H), 5.60 – 5.42 (m, 1H), 5.37 (t, *J* = 7.9 Hz, 1H), 4.90 – 4.86 (m, 1H), 4.86 – 4.82 (m, 1H), 4.07 (t, *J* = 6.3 Hz, 1H), 3.96 (qd, *J* = 12.6, 8.0 Hz, 2H), 2.32 – 2.20 (m, 2H), 1.69 (s, 3H), 1.03 (s, 9H);**^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.3, 143.6, 136.0, 135.99, 134.2, 134.1, 133.9, 130.2, 129.9, 129.8, 129.7, 127.6, 127.5, 123.9, 118.6, 117.0, 77.7, 40.5, 31.0, 27.1, 19.5, 12.1; **IR** (neat): 3067, 2931, 2860, 1561, 1500, 1422, 1104, 1073, 760 and 701 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{31}H_{36}N_4OSSiNa$ $[M+Na]^+$ 563.2277; found: 563.2274. *See NMR spectra*

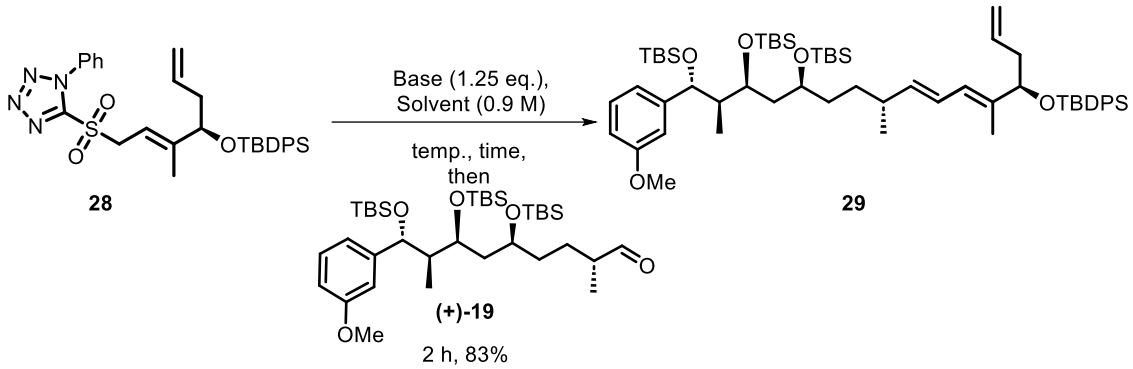
(*R*,*E*)-5-((4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylhepta-2,6-dien-1-yl)sulfonyl)-1-phenyl-1H-tetrazole (28):



To a solution of tetrazole compound **27** (5.0 g, 9.26 mmol, 1.0 eq.) in ethanol (50 mL) at 0 ˚C, ammonium molybdate (1.14 g, 0.9 mmol, 0.1 eq.) and 30% H_2O_2 (10 mL) were added dropwise. The mixture was slowly warmed to room temperature and allowed to stir for 12 hours. After completion, the reaction was quenched by the dropwise addition of a saturated sodium thiosulfate solution at 0 ˚C. Ethanol was removed, and the organic phase was extracted with EtOAc, followed by drying over Na_2SO_4, evaporation of solvents and purification of the residue by column chromatography on silica gel (EtOAc/Hexane 1:9) gave compound **28** as a colorless gel (4.5 g, 85% yield); R_f = 0.5 (ethyl acetate/hexane 1:9); $[\alpha]^{20}_D$ = +24.9˚ (*c* = 1.0 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.61 (m, 4H), 7.61 – 7.51 (m, 5H), 7.45 – 7.33 (m, 4H), 7.33 – 7.27 (m, 2H), 5.50 – 5.38 (m, 1H), 5.38 – 5.32 (m, 1H), 4.86 – 4.75 (m, 2H), 4.36 (qd, *J* = 14.5, 7.8 Hz, 2H), 4.12 (t, *J* = 6.0 Hz, 1H), 2.23 – 2.15 (m, 2H), 1.72 (s, 3H), 1.02 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5, 150.1, 135.9, 134.0, 133.6, 133.5, 133.2, 131.5, 129.9, 129.8, 127.7, 127.7, 125.1, 117.4, 108.7, 77.4, 55.6, 40.2, 27.1, 19.4, 13.2; **IR** (neat): 3067, 2933, 2860, 1497, 1428, 1156, 1107, 762 and 702 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{31}H_{40}N_5O_3SSi$ $[M+NH_4]^+$ 590.2621; found: 590.2621. *See NMR spectra*

2.6 Synthesis of C8-C23 fragment of Antarlides:

(*5R,6E,8E,10R,13S,15S,16R,17R*)-5-Allyl-13-((*tert*-butyldimethylsilyl)oxy)-17-(3-methoxyphenyl)-2,2,6,10,16,19,19,20,20-nonamethyl-3,3-diphenyl-15-((triethylsilyl)oxy)-4,18-dioxa-3,19-disilahenicosa-6,8-diene (29):



Optimization table of Julia-Kocienski olefination:

S.No	Base (1.25 eq.)	Solvent	Temperature	Time	29 Yield (*E*/*Z*)
1	KHMDS	THF	0 °C	2 h	60 (2:1 *E*/*Z*)
2	KHMDS	THF	–78→0 °C	2 h	85% (3:1 *E*/*Z*)
3	KHMDS	THF	–78 °C	2 h	83% (6:1 *E*/*Z*)
4	KHMDS	DME	–78 °C	12 h	70% (4:1 *E*/*Z*)
5	LiHMDS	THF	0 °C→RT	24 h	<15% conversion

The sulphone **28** (0.5 g, 0.88 mmol, 1.0 eq.) was taken into flame-dried 50 mL round-bottom flask and dissolved in dry THF (5.0 mL). The resulting mixture was cooled to −78 ˚C, was added KHDMS (1M in THF, 1.1 mL, 1.1 mmol, 1.25 eq.) dropwise. After being stirred for 15 minutes, the crude aldehyde **(+)-19** (0.79 g, 1.18 mmol, 1.3 eq. see S-22) in THF (5 mL) was added dropwise to the reaction mixture and stirring was continued for 2 hours at -78 °C. the reaction was monitored by TLC, After completion of starting material **28**, the reaction mixture was quenched with saturated aq.NH_4Cl and extracted the compound with EtOAc (2 x 25 mL), dried over Na_2SO_4, evaporation of solvents and purification of the residue by column chromatography on silica gel (Hexane) gave compound **29** as a colourless oil (0.74 g, 83% yield); R_f = 0.7 (ethyl acetate/hexane 1:9); $[\alpha]^{20}_D$ = +61.75˚ (*c* = 0.4 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$, 6:1 E/Z, major stereoisomer) δ 7.73 – 7.65 (m, 2H), 7.65 – 7.58 (m, 2H), 7.42 – 7.30 (m, 6H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.86 – 6.72 (m, 3H), 6.16 – 6.01 (m, 2H), 5.65 – 5.49 (m, 1H), 5.19 (t, *J* = 10 Hz, 1H), 4.91 – 4.83 (m, 2H), 4.47 (d, *J* = 9.0 Hz, 1H), 4.36 (t, *J* = 6.4 Hz, 1H), 4.12 (t, *J* = 6.1 Hz, 1H), 3.79 (s, 3H), 3.76 – 3.69 (m, 1H), 2.57 – 2.34 (m, 1H), 2.31 – 2.20 (m, 2H), 2.04 – 1.90 (m, 1H), 1.79 – 1.66 (m, 2H), 1.65 (s, 3H), 1.53 – 1.37 (m, 2H),

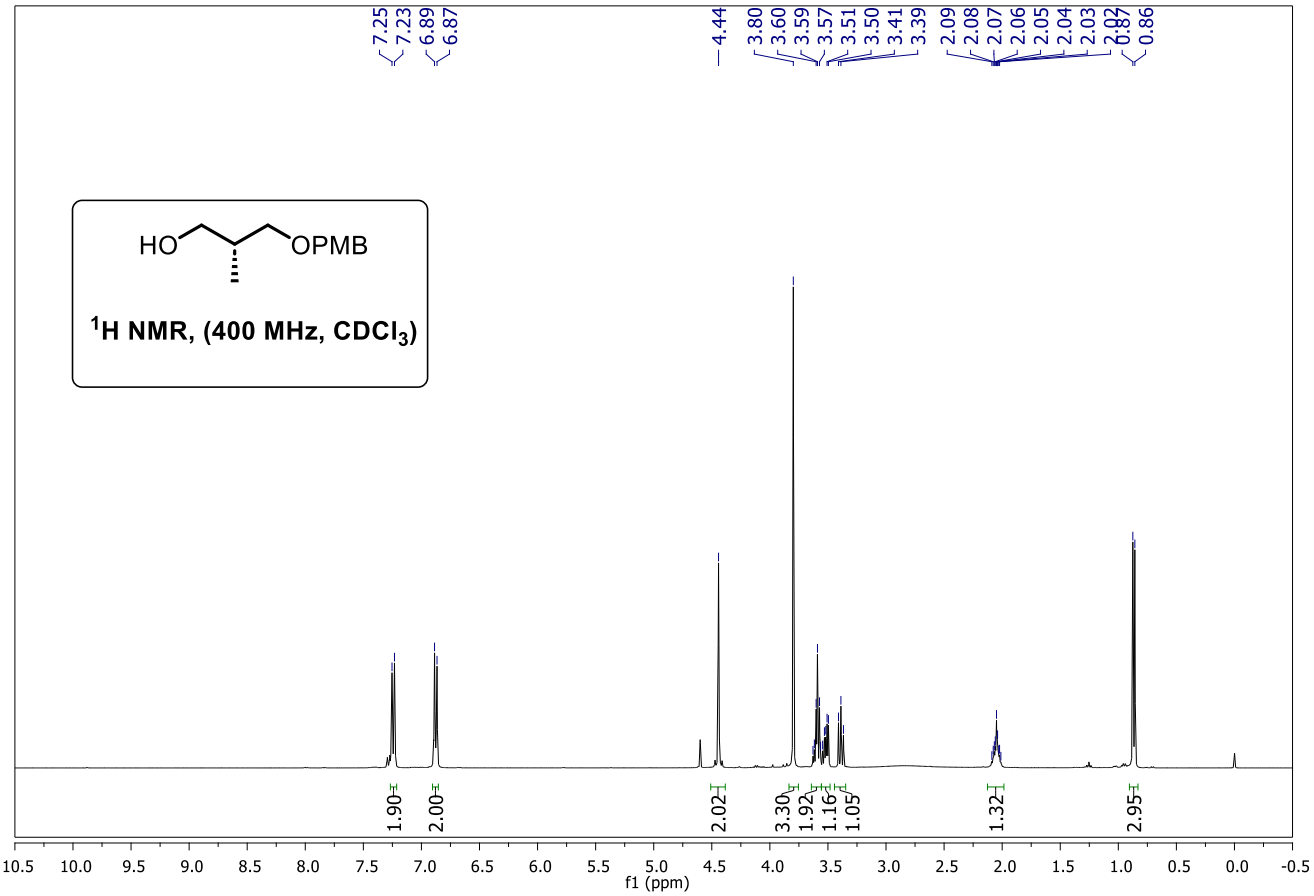
1.36 – 1.23 (m, 2H), 1.06 (s, 9H), 0.95 – 0.87 (m, 21H), 0.82 (s, 9H), 0.49 (d, *J* = 7.0 Hz, 3H), 0.14 (s, 3H), 0.1 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H), –0.37 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$, 6:1 E/Z, major stereoisomer) δ 159.5 (C), 146.2 (C), 138.5 (C), 138.0 (CH), 136.1 (4 x CH), 134.8 (CH), 134.6 (C), 134.1 (C), 129.7 (CH), 129.6 (CH), 129.0 (CH), 127.55 (2 x CH), 127.50 (2 x CH), 123.0 (CH), 121.0 (CH), 120.5 (CH), 116.6 (CH_2), 113.3 (CH), 112.7 (CH), 78.4 (CH), 77.3 (CH), 70.2 (CH), 69.1 (CH), 55.2 (CH_3), 46.1 (CH), 43.2 (CH_2), 40.9 (CH_2), 34.7 (CH_2), 33.0 (CH_2), 32.2 (CH), 27.2 (3 x CH_3), 26.3 (3 x CH_3), 26.19 (3 x CH_3), 26.18 (3 x CH_3), 21.4 (CH_3), 19.6 (C), 18.5 (C), 18.3 (C), 18.2 (C), 12.6 (CH_3), 10.0 (CH_3), -3.0 (CH_3), -3.5 (CH_3), -3.9 (CH_3), -4.0 (CH_3), -4.1 (CH_3), -4.2 (CH_3); **IR** (neat): 2939, 2861, 1468, 1258, 1063, 839, 770 and 704 cm^{-1}; **HRMS** (ESI-TOF): calculated for $C_{60}H_{104}NO_5Si_4$ $[M+NH_4]^+$ 1030.6986; found: 1030.6984. *See NMR spectra*

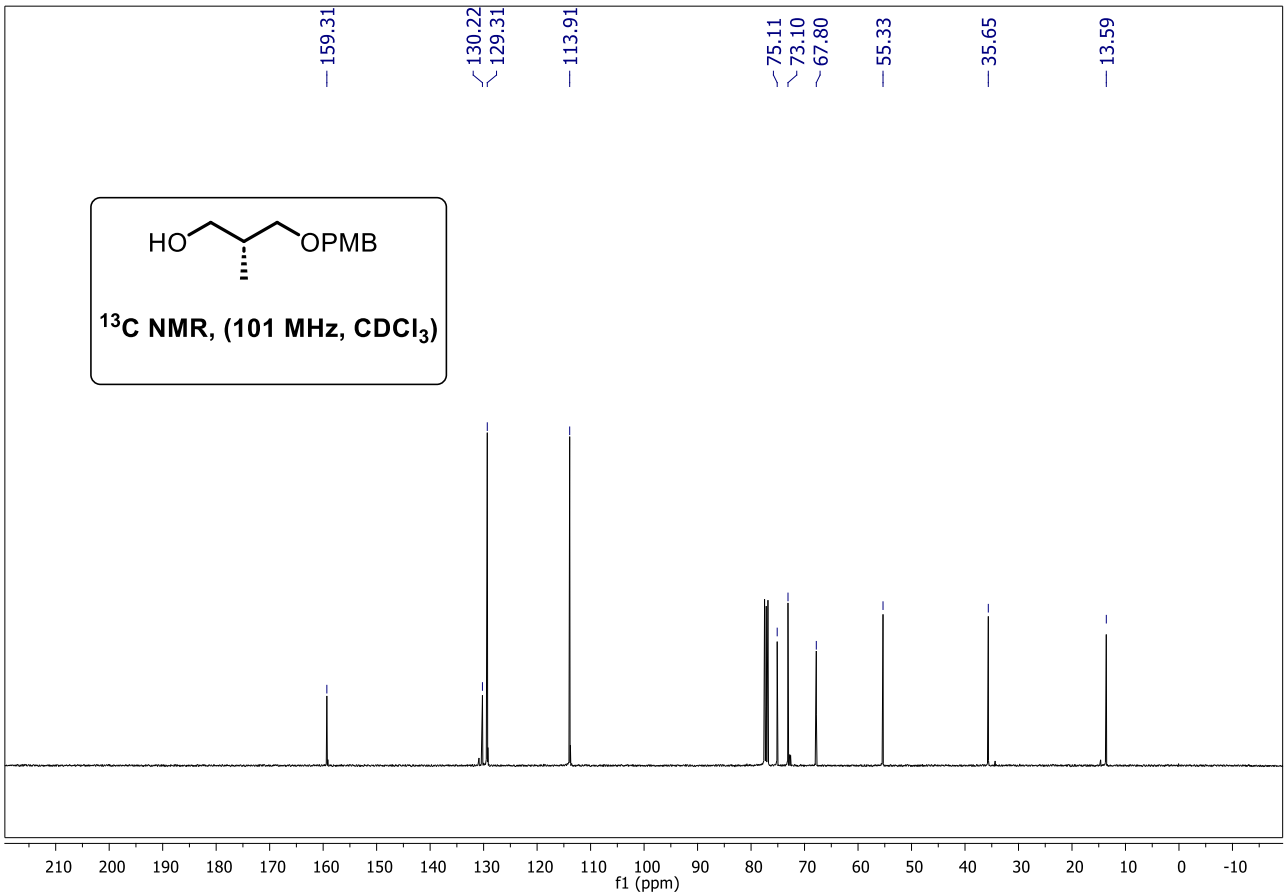
3. References:

1. T. Akeboshi, Y. Ohtsuka, T. Ishihara and T. Sugai, *Adv. Synth. Catal.* 2001, **343**, 6–7.
2. M. E. Casao, G. Licini and M. Orlandi, *J. Am. Chem. Soc*. 2021, **143**, 3289–3294.
3. A. D. Fotiadou and A. L. Zografos, *Org. Lett*. 2011, **13**, 4592–4595.

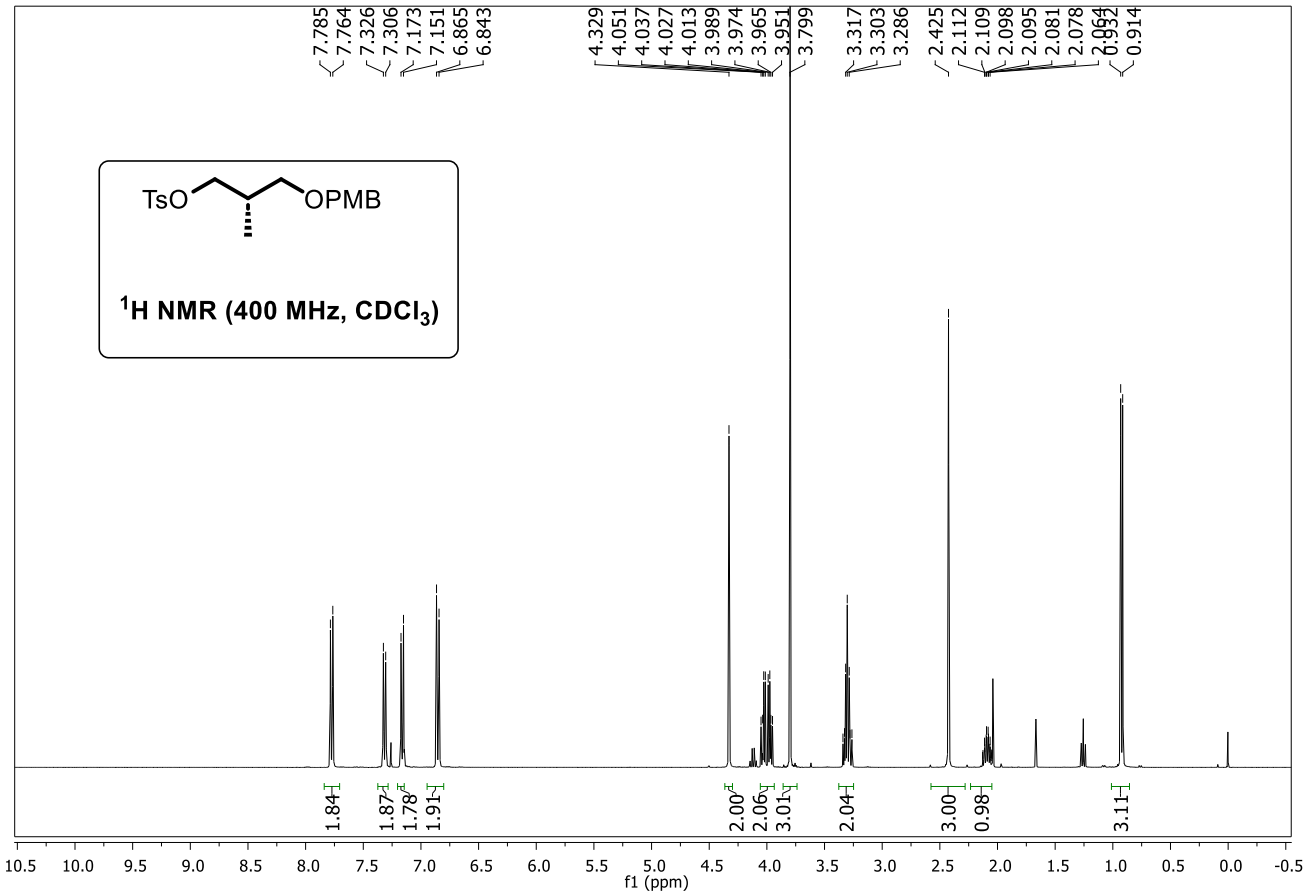
4. ^{1}H NMR, ^{13}C NMR & ^{19}F NMR Spectra for New Compounds:

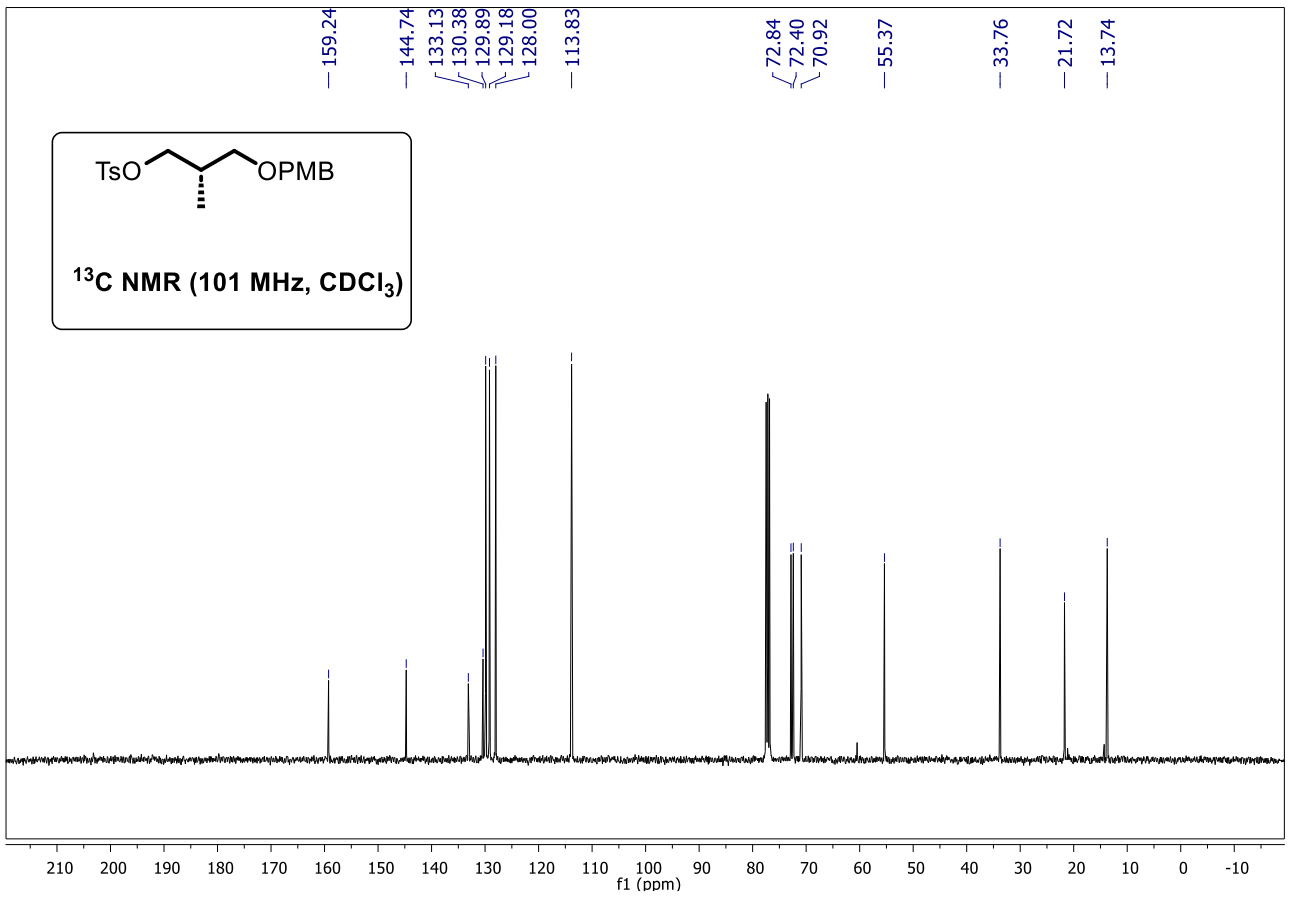
(*R*)-3-((4-Methoxybenzyl)oxy)-2-methylpropan-1-ol [(+)4a]: *See procedure*



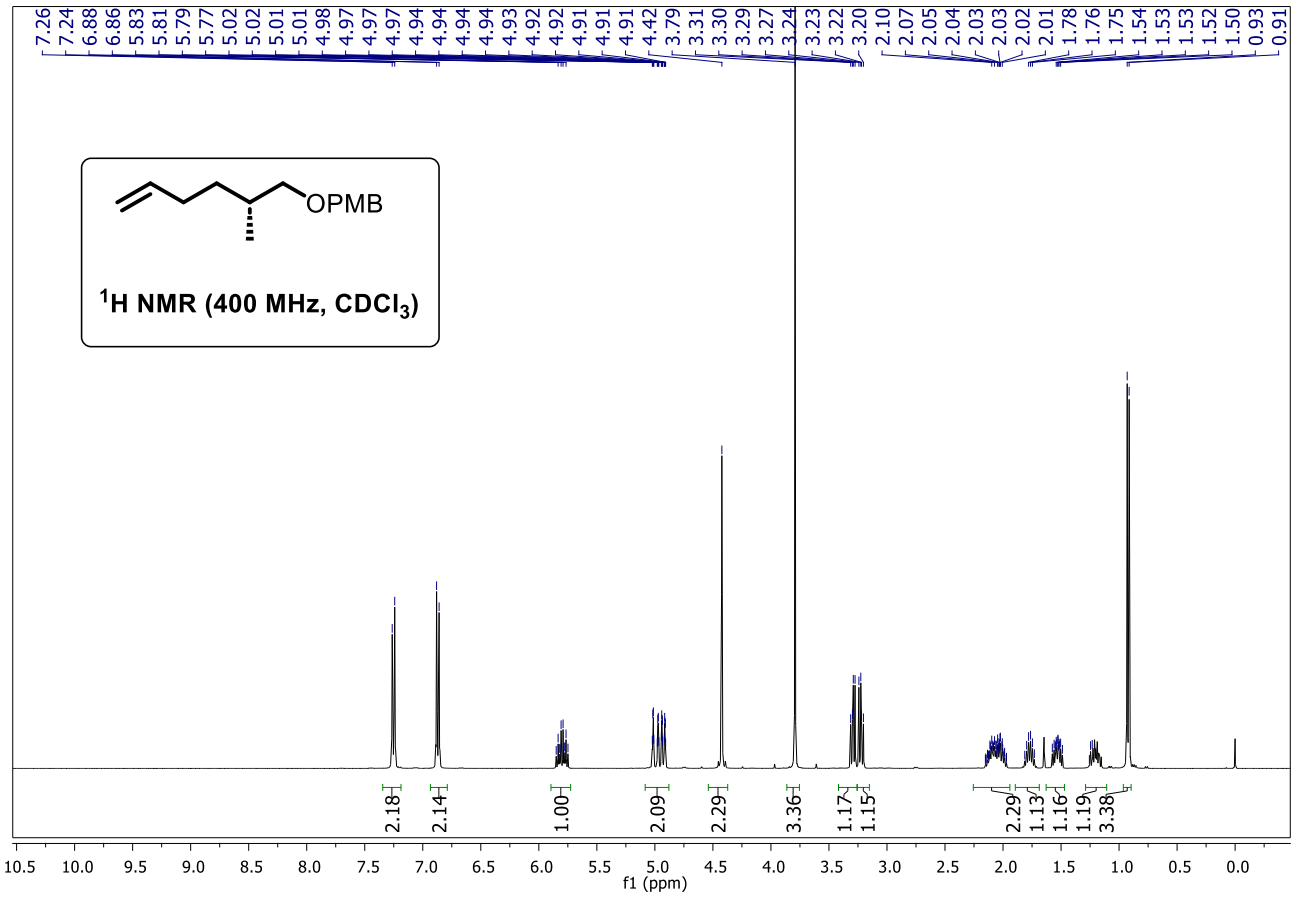


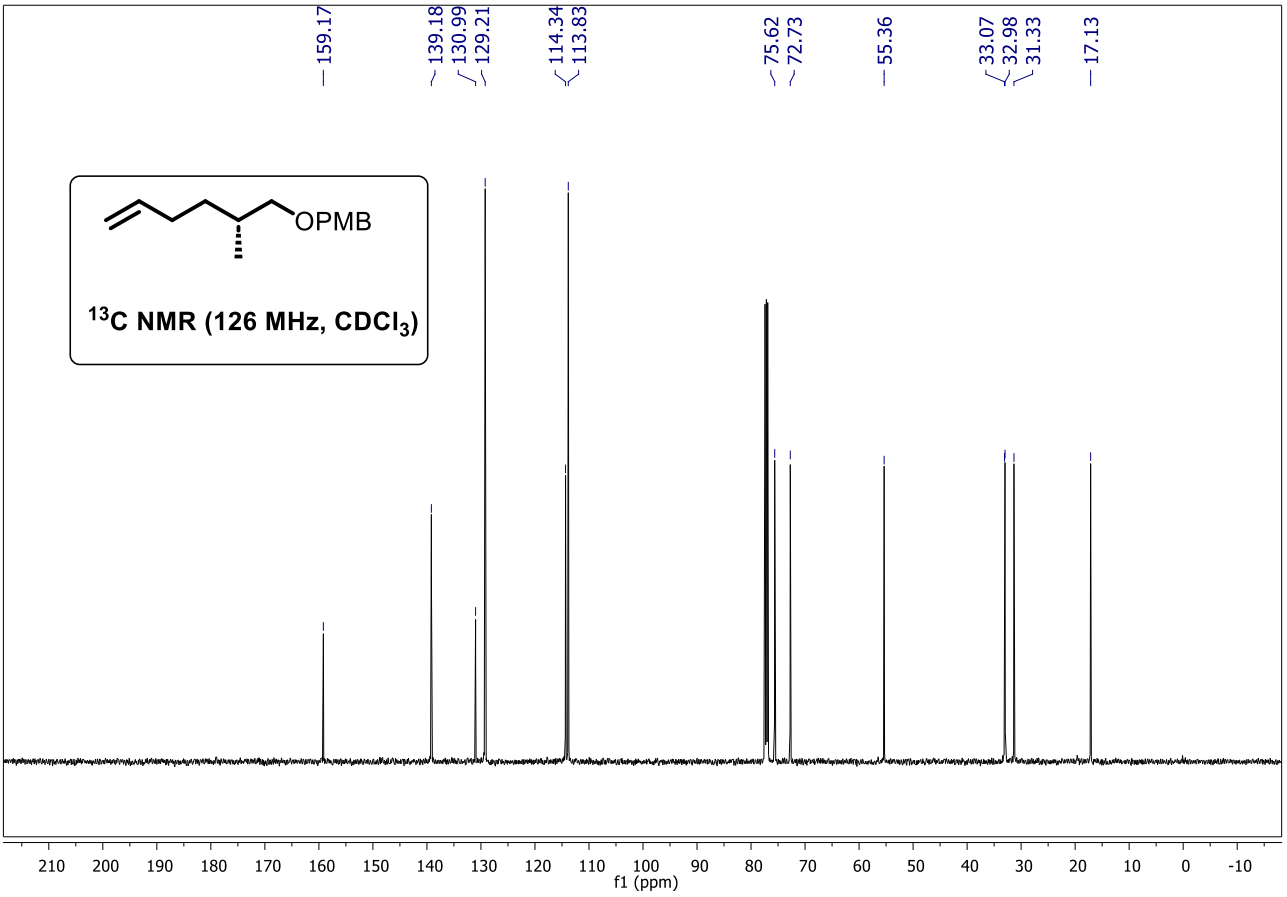
(*S*)-3-((4-Methoxybenzyl)oxy)-2-methylpropyl 4-methylbenzenesulfonate (5): *Procedure*



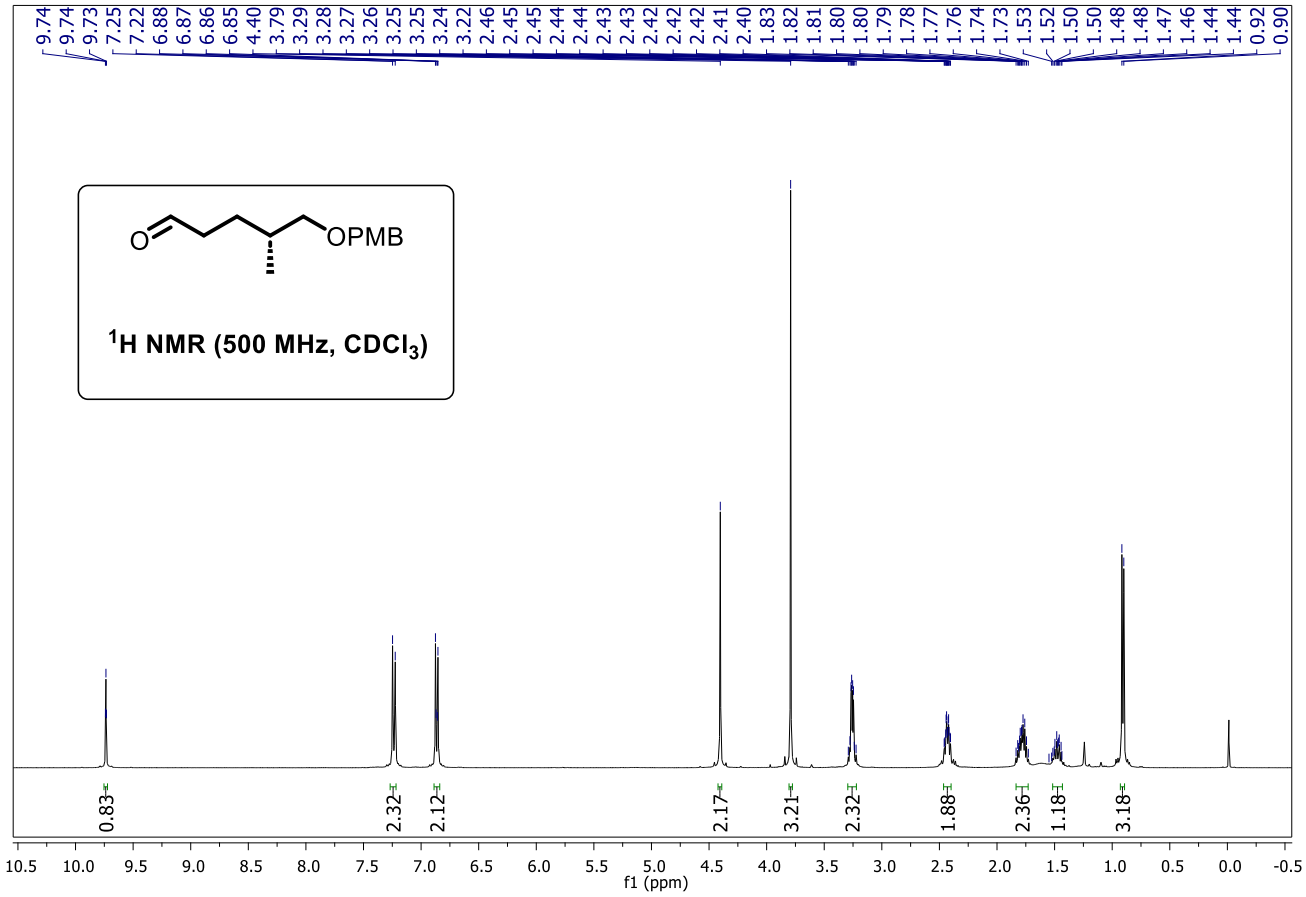


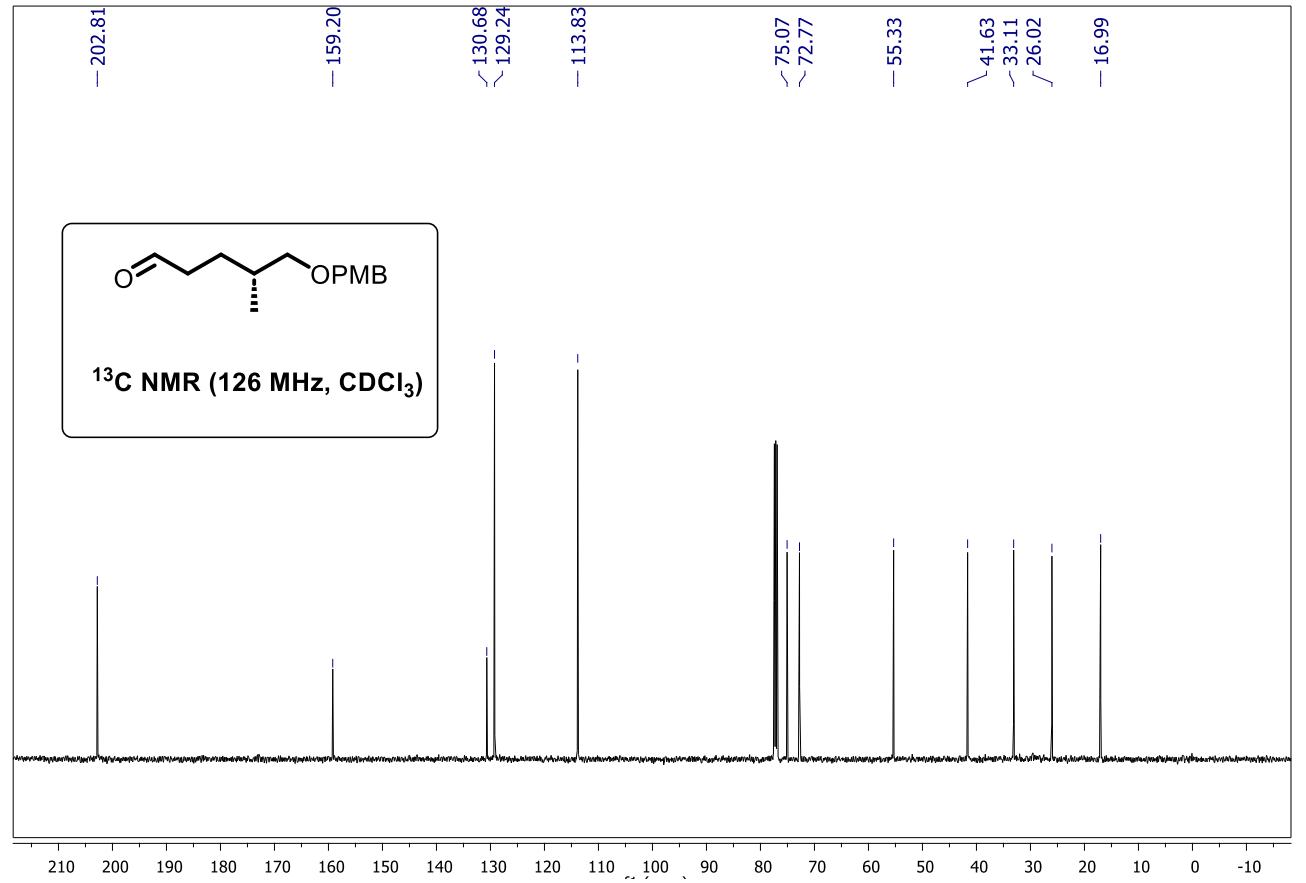
(*R*)-1-Methoxy-4-(((2-methylhex-5-en-1-yl)oxy)methyl)benzene (6): *See procedure*



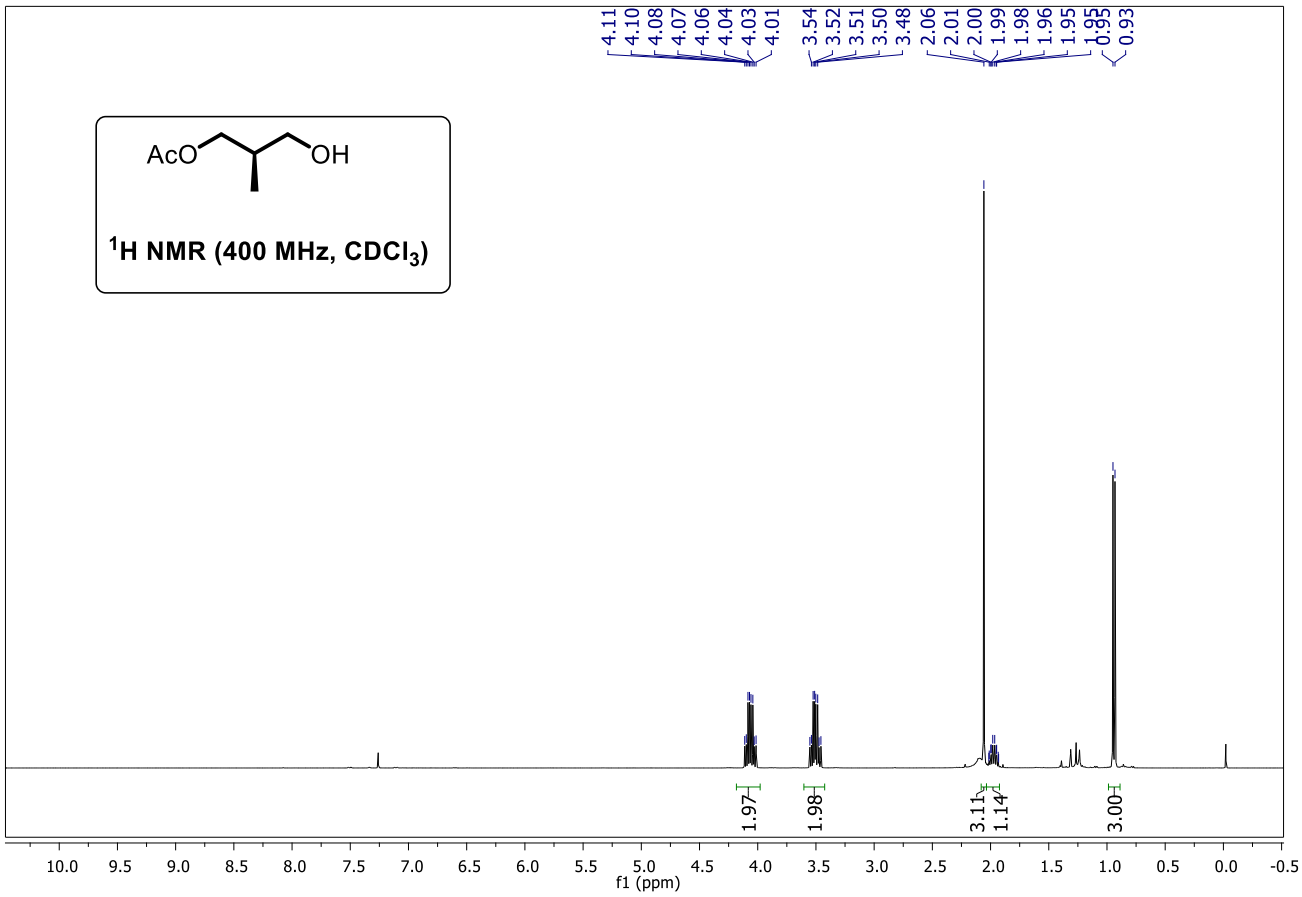


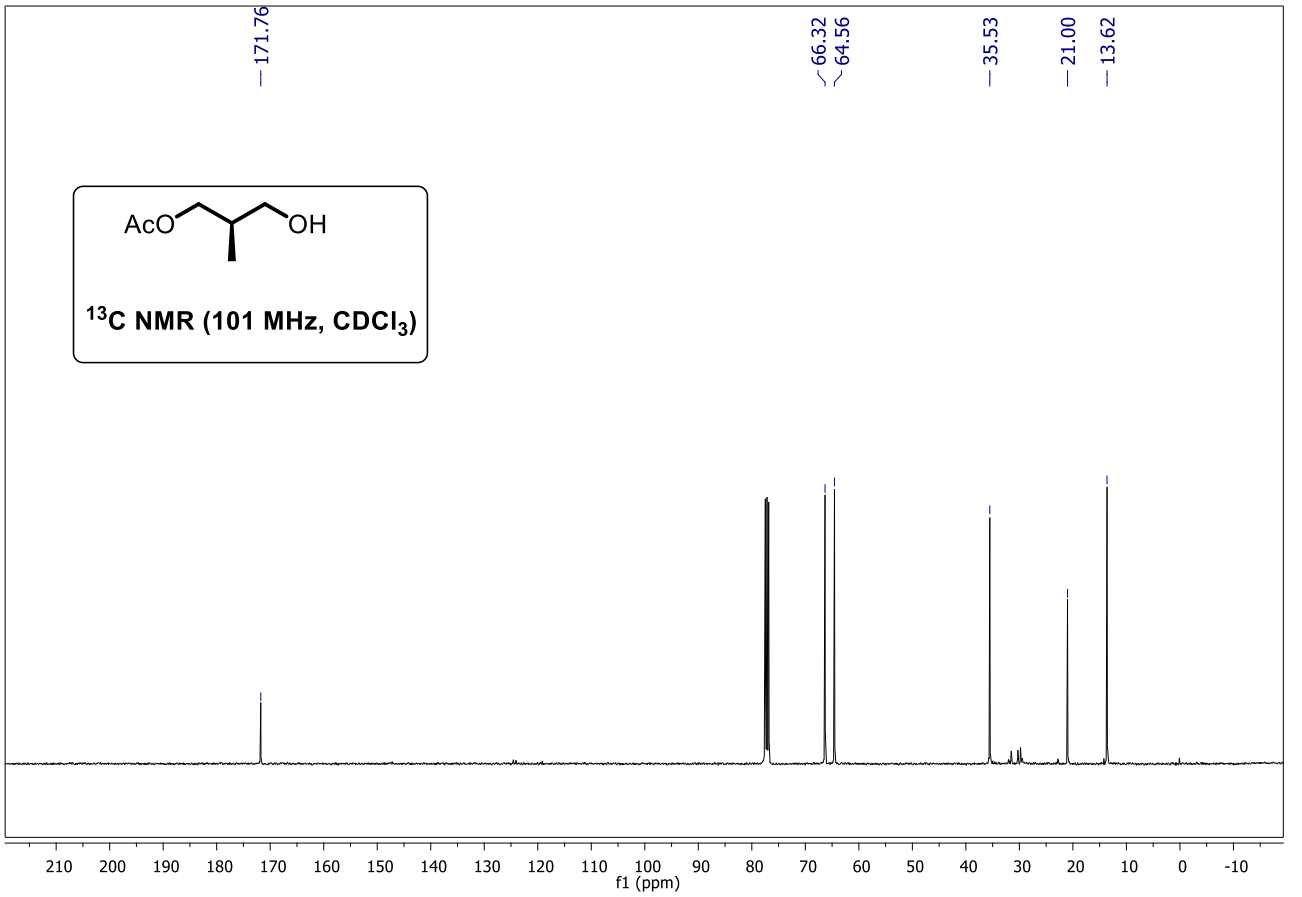
(*R*)-5-((4-Methoxybenzyl)oxy)-4-methylpentanal [(+)-7]: *See procedure*



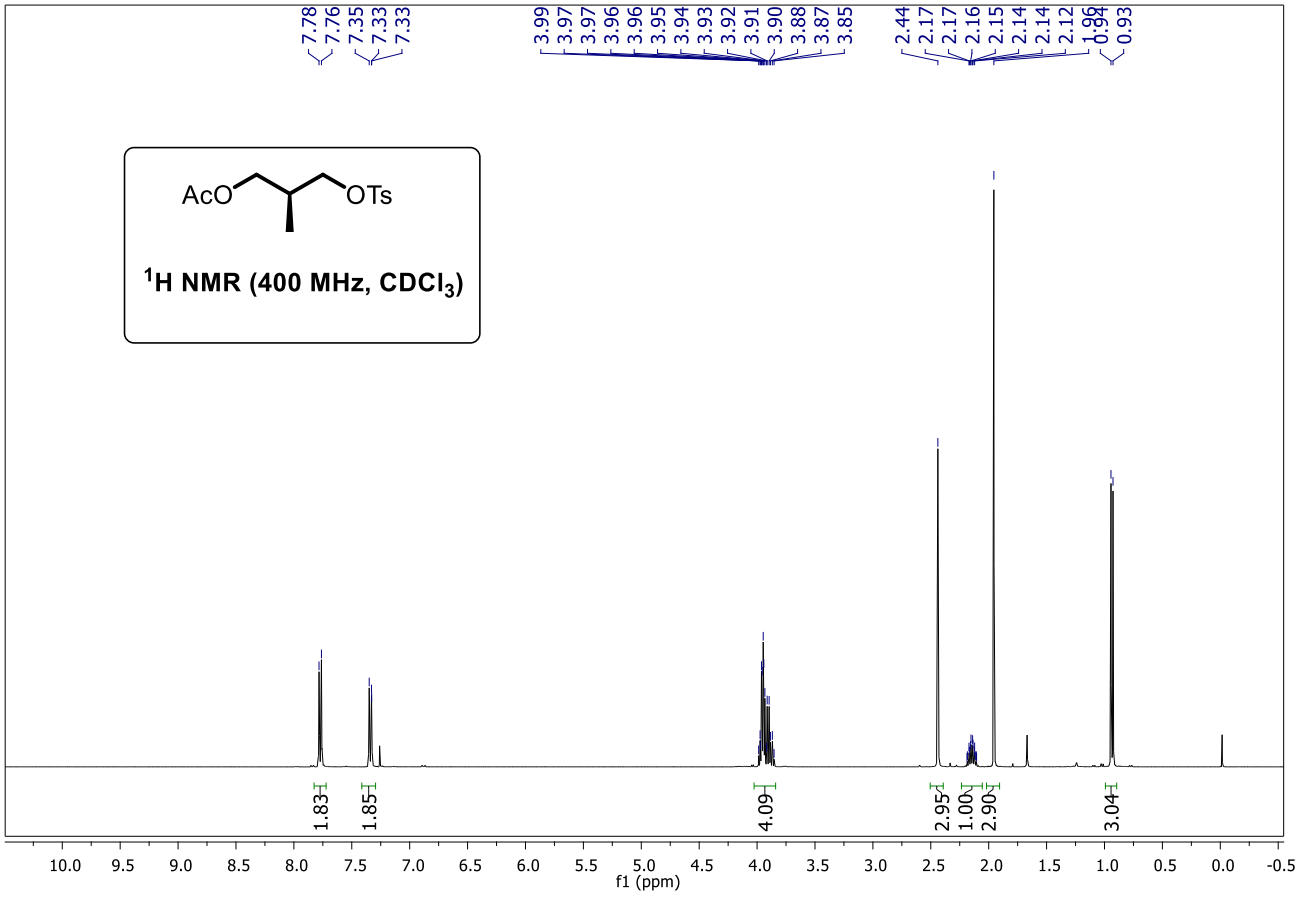


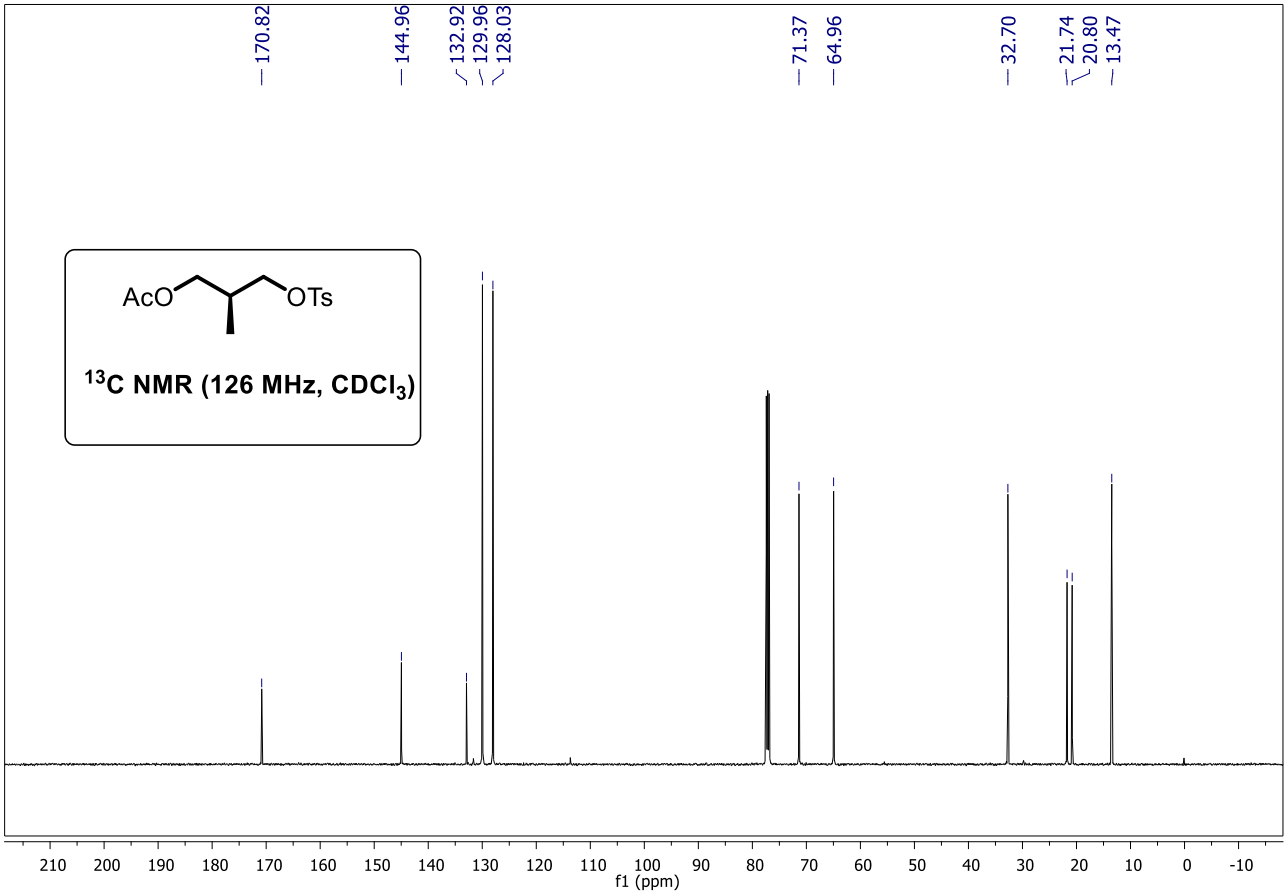
(*R*)-3-Hydroxy-2-methylpropyl acetate [(+)-4b]: *See procedure*



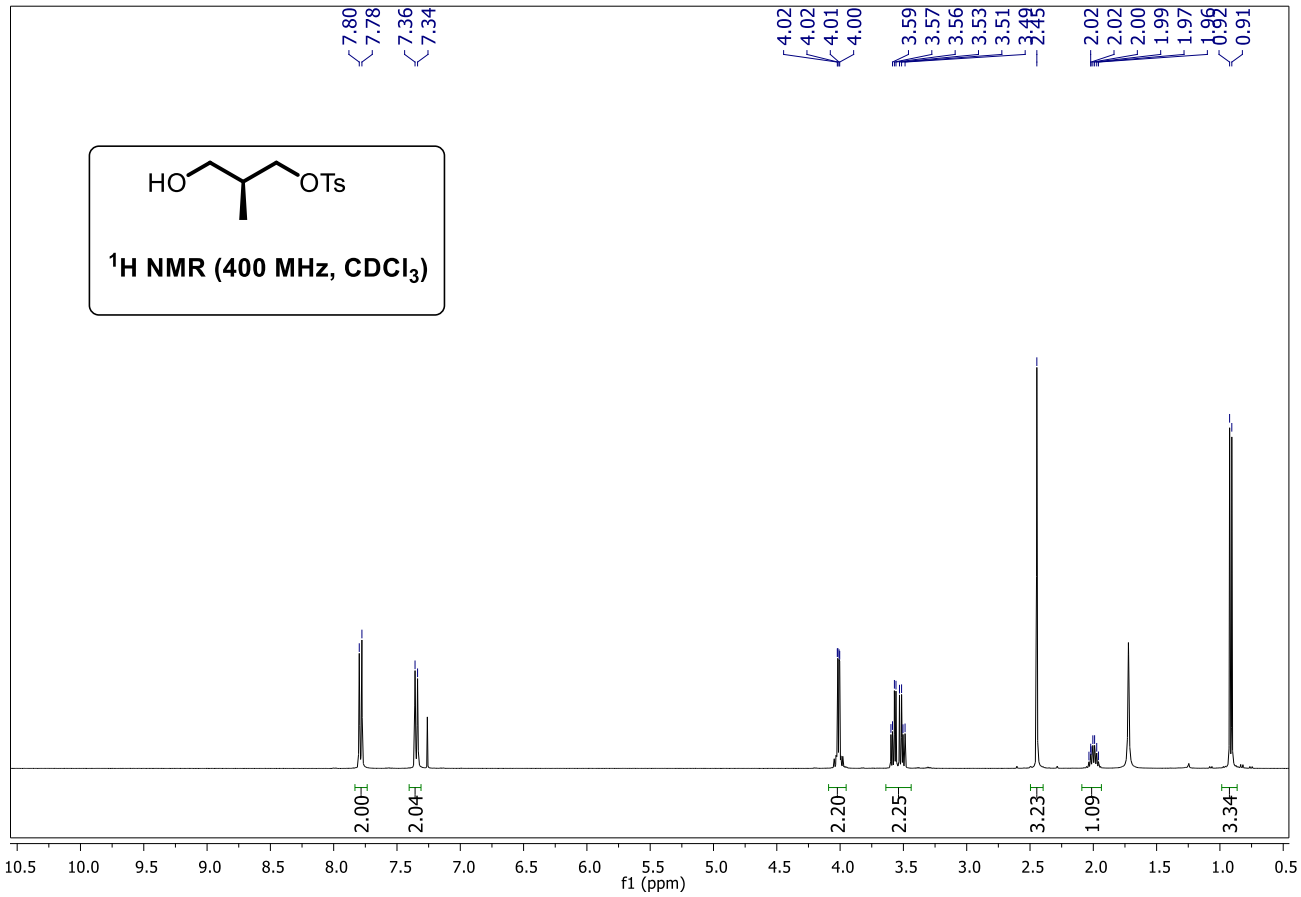


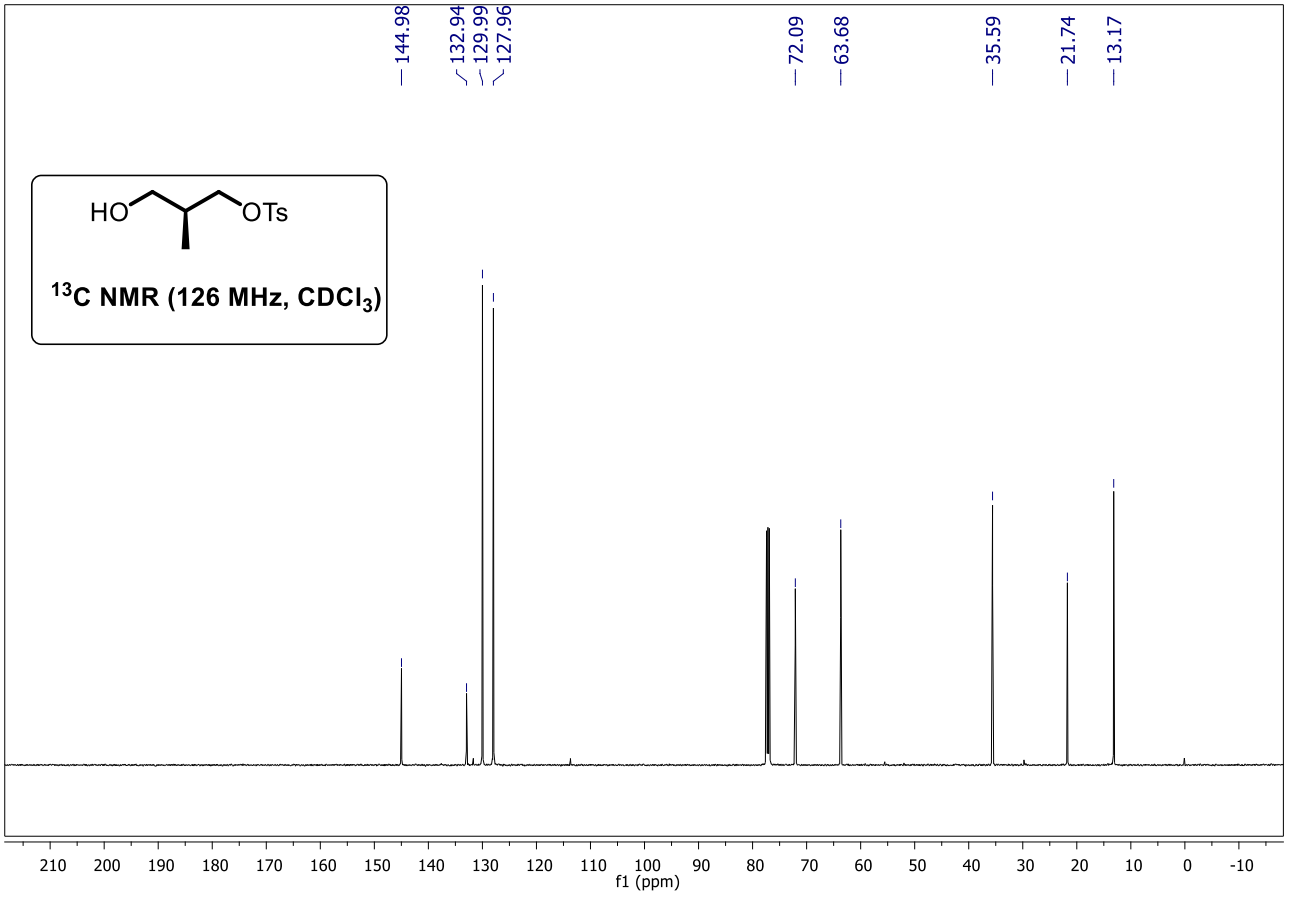
(*S*)-2-Methyl-3-(tosyloxy)propyl acetate (SI-1): *See procedure*



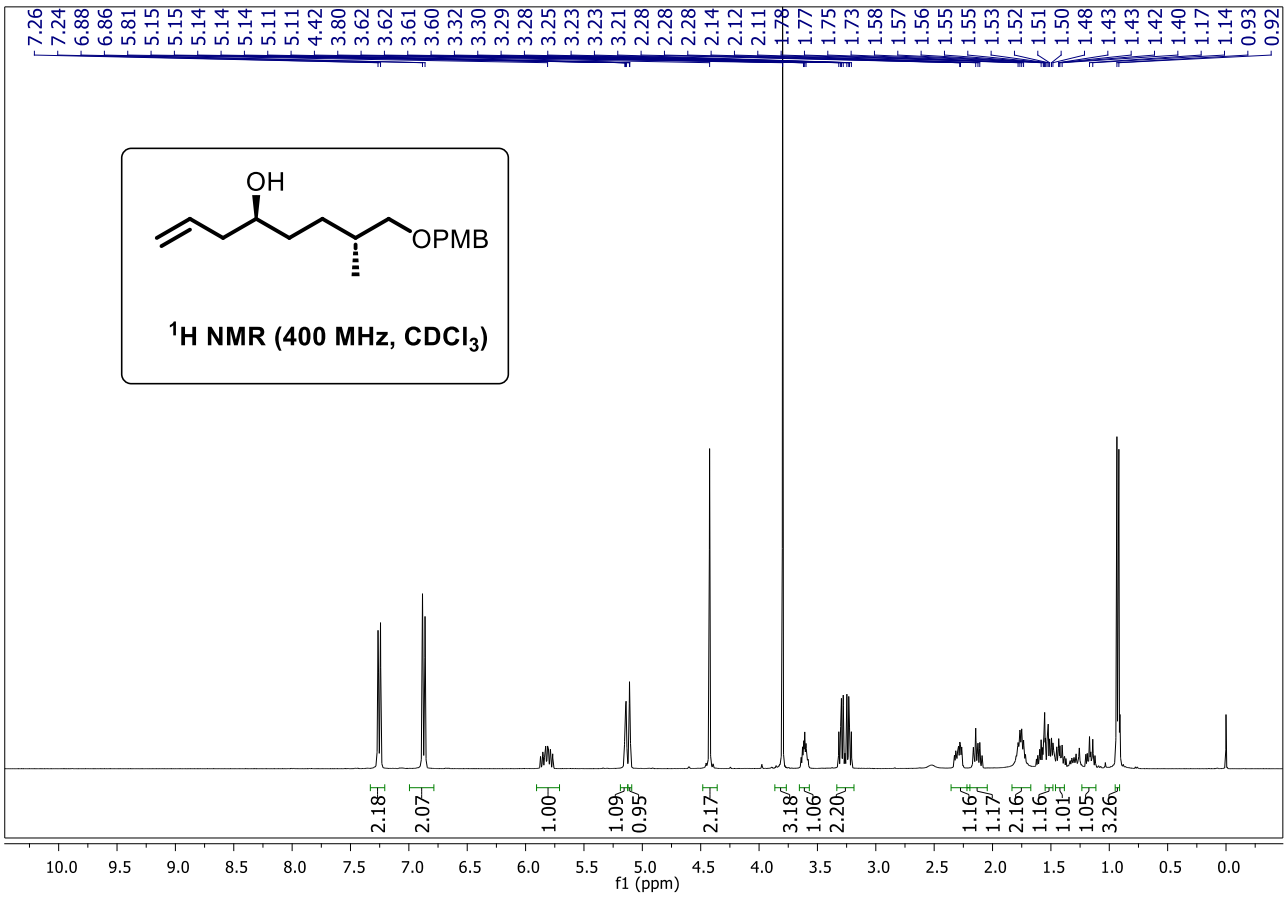


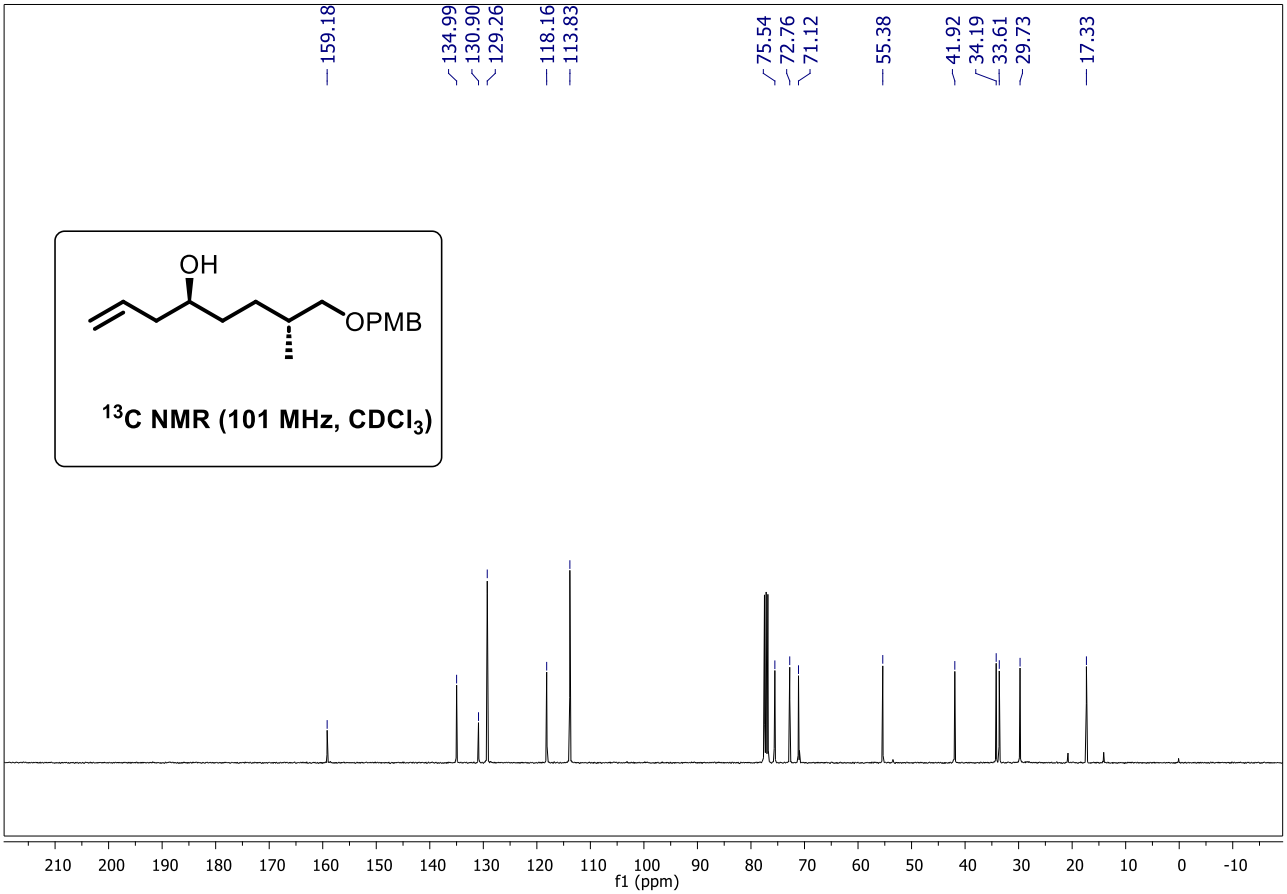
(*S*)-3-Hydroxy-2-methylpropyl 4-methylbenzenesulfonate (SI-2): *See procedure*



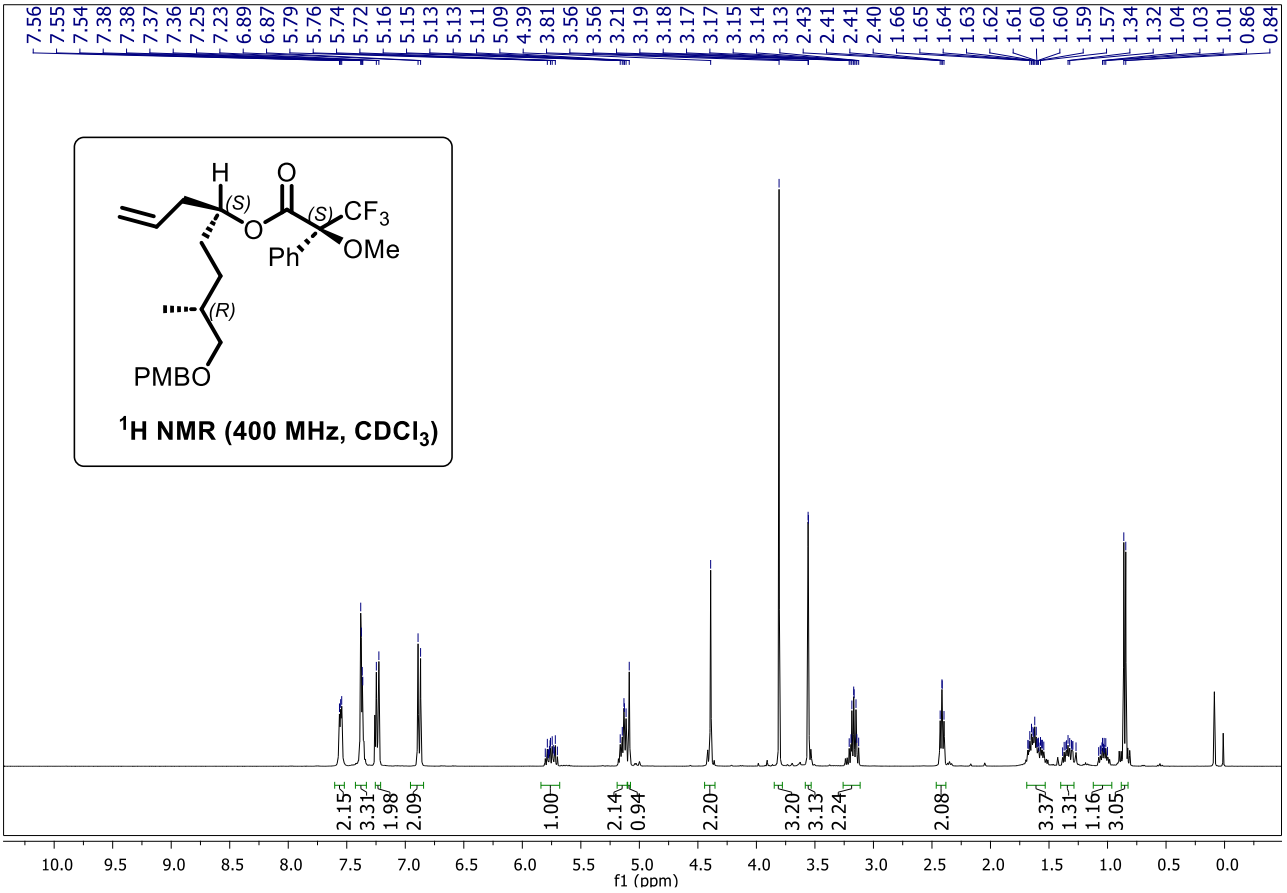


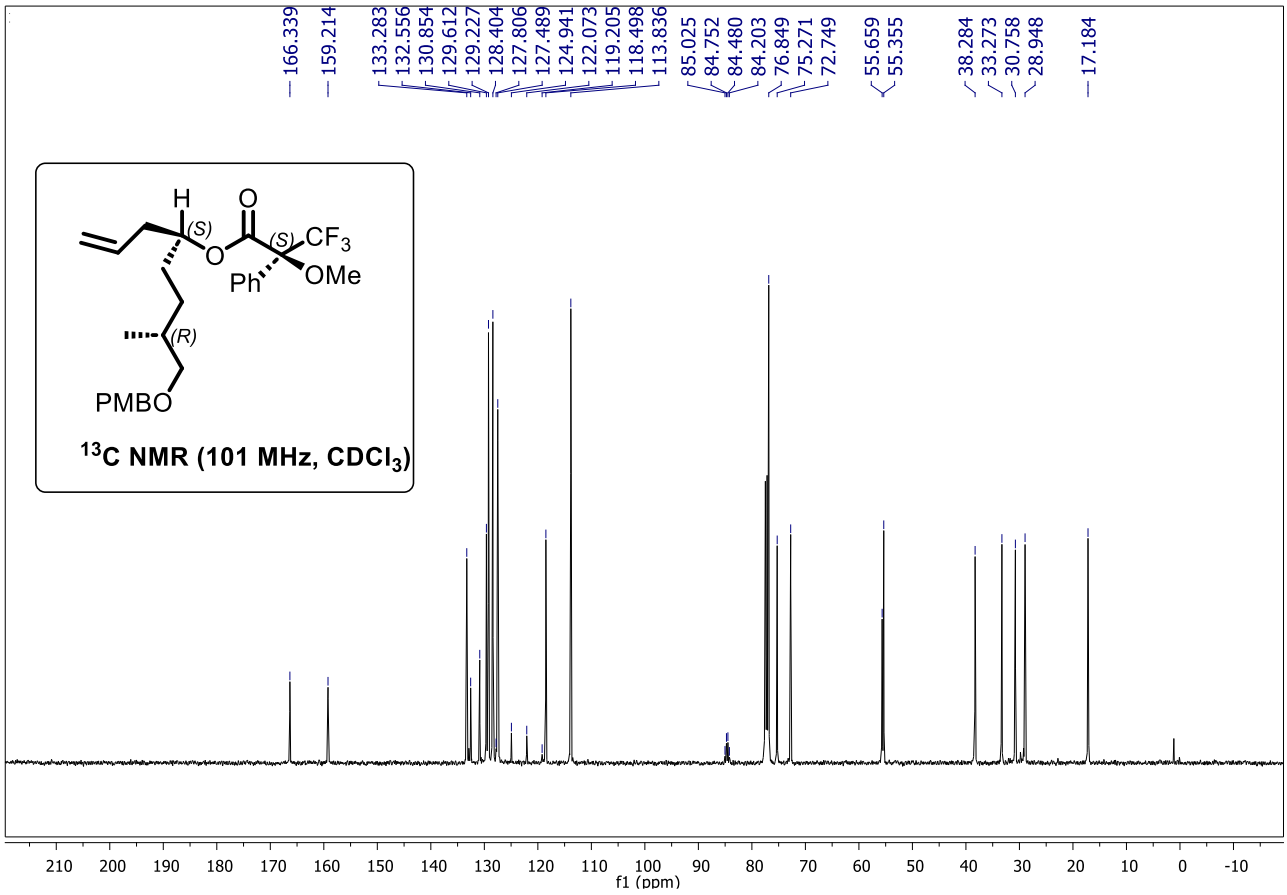
(4*S*,7*R*)-8-((4-Methoxybenzyl)oxy)-7-methyloct-1-en-4-ol (8): *See procedure*

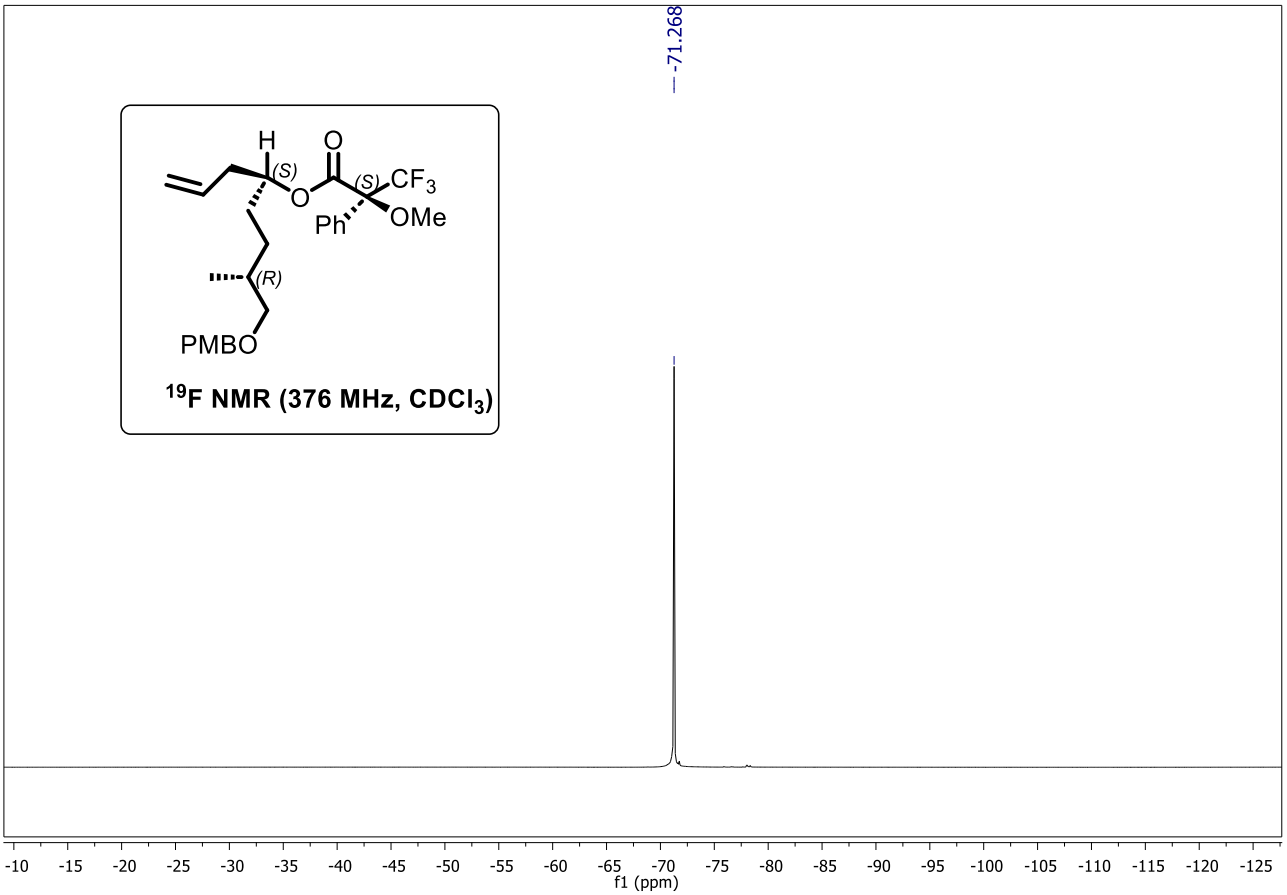




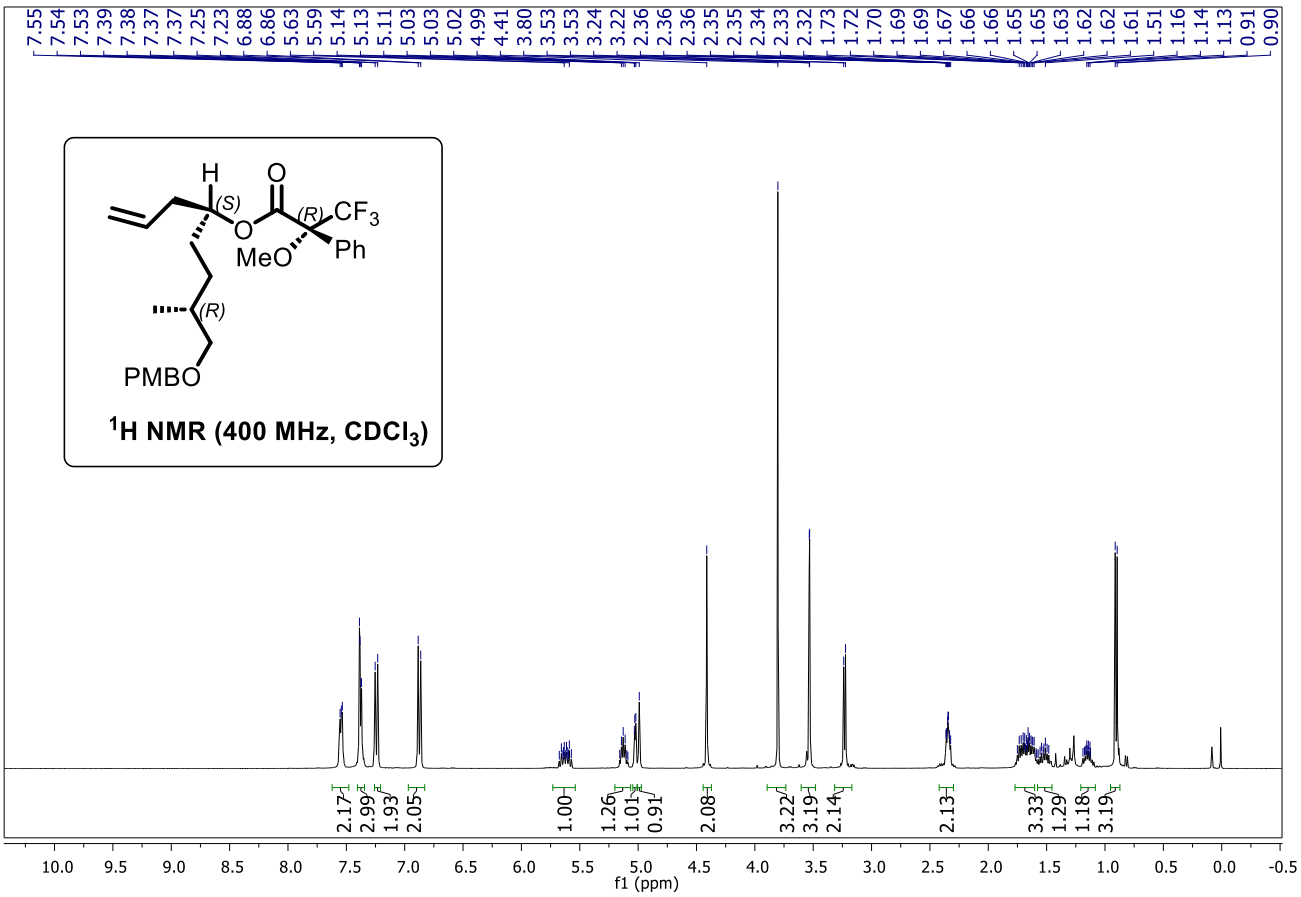
(4*S*,7*R*)-8-((4-Methoxybenzyl)oxy)-7-methyloct-1-en-4-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-3): *See procedure*

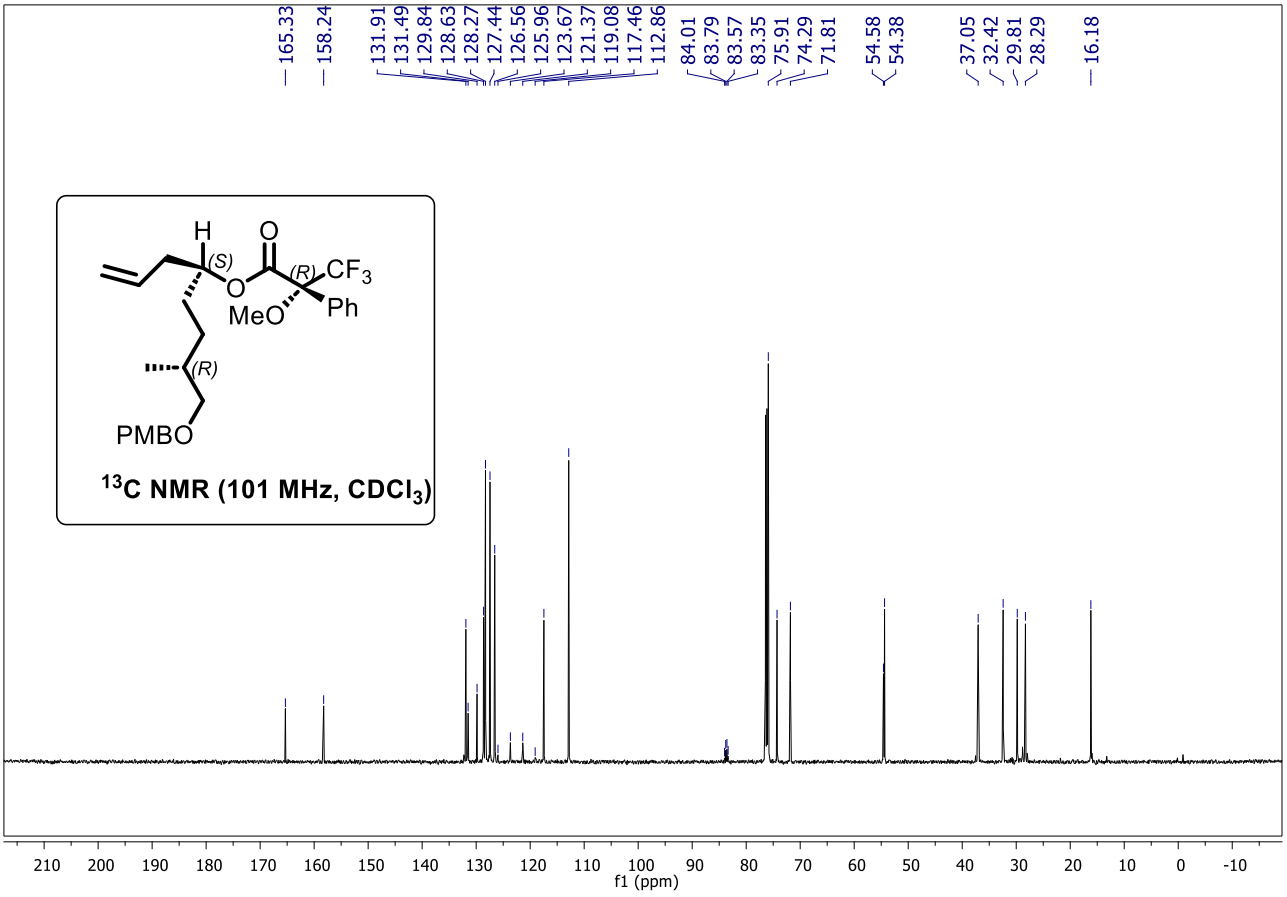






(4*S*,7*R*)-8-((4-Methoxybenzyl)oxy)-7-methyloct-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-4): *See procedure*

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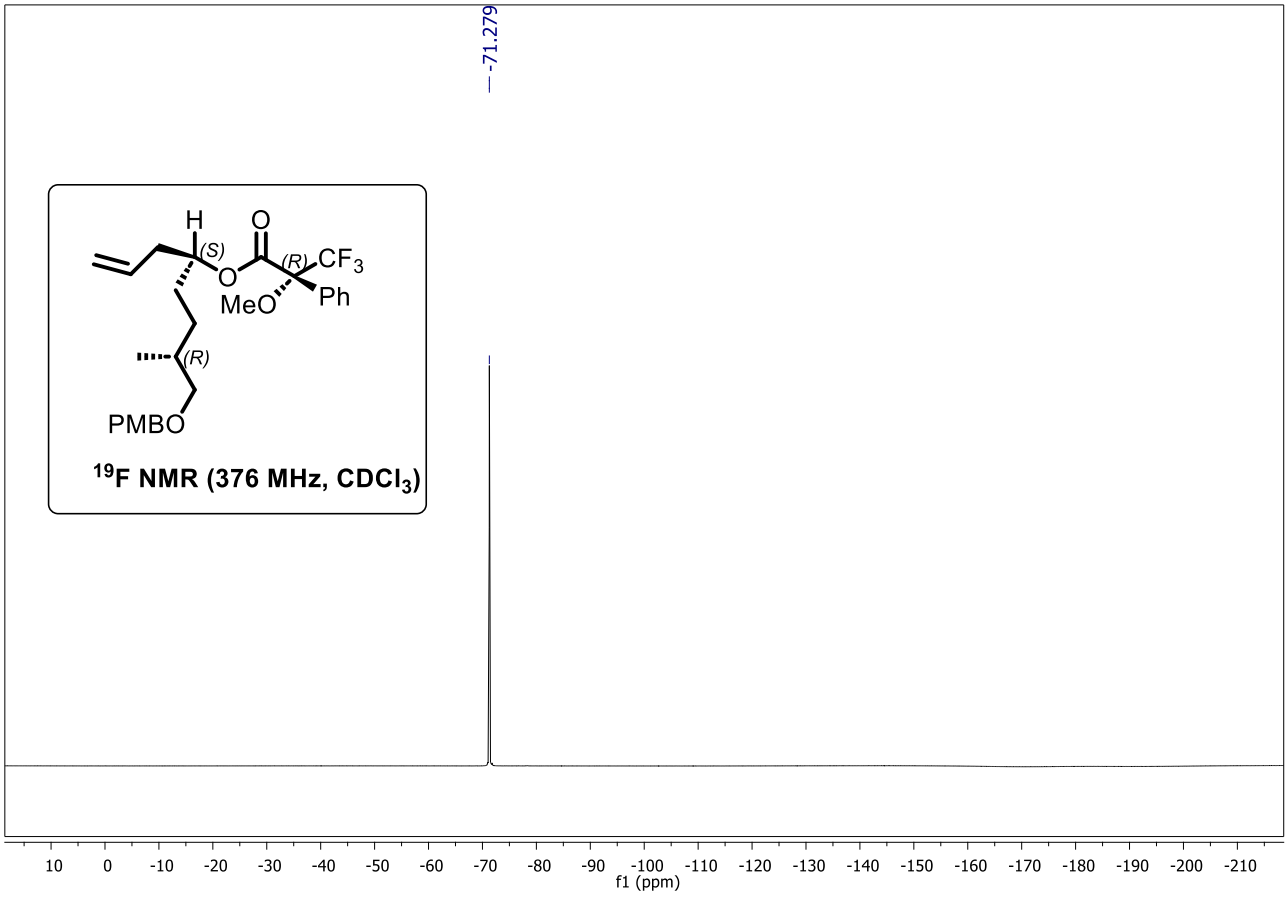
75.91
74.29
71.81
54.58
54.38
37.05
32.42
29.81
28.29
16.18
H
O
(S)
O
(R)
CF3
MeO
Ph
(R)
PMBO
13C NMR (101 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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CF3
MeO
Ph
(R)
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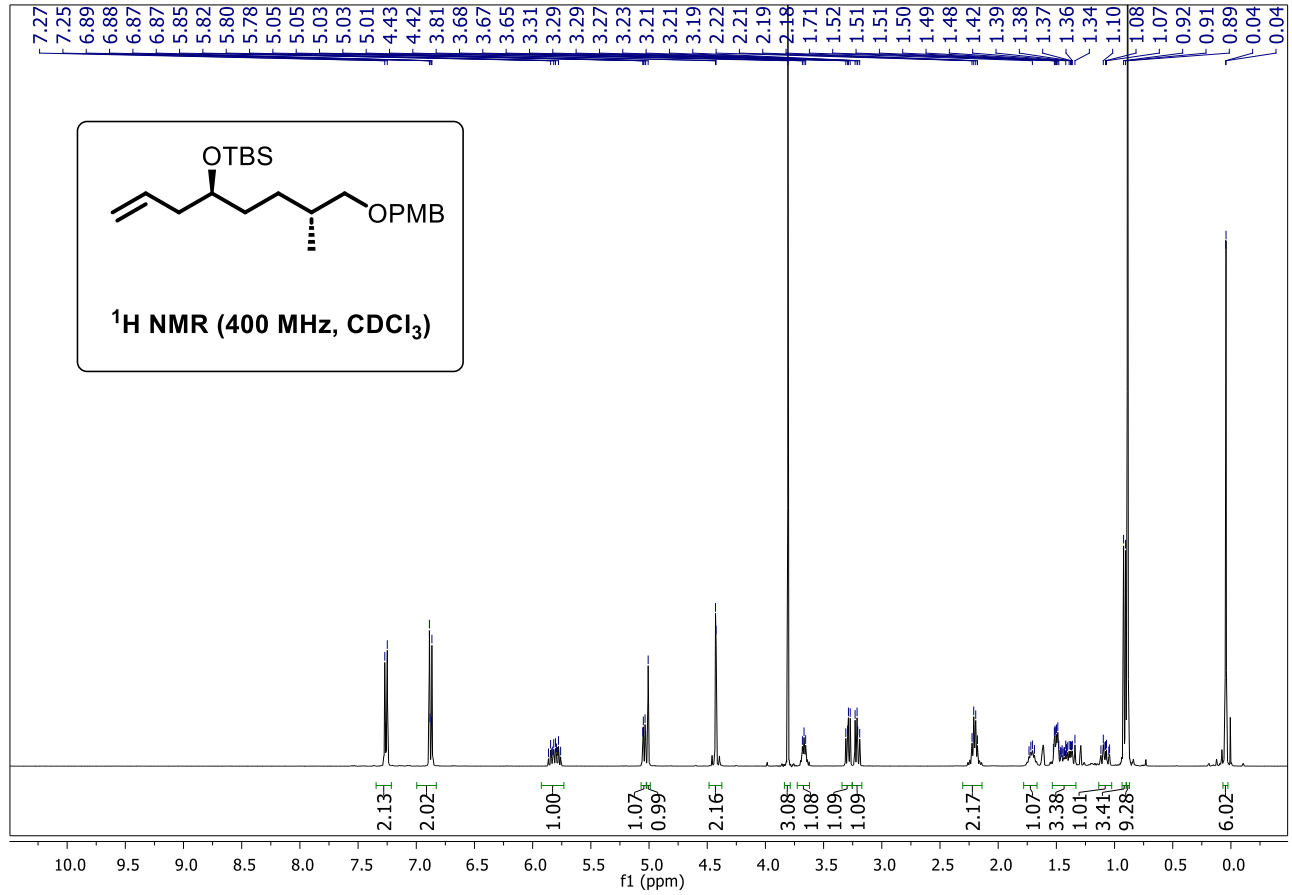
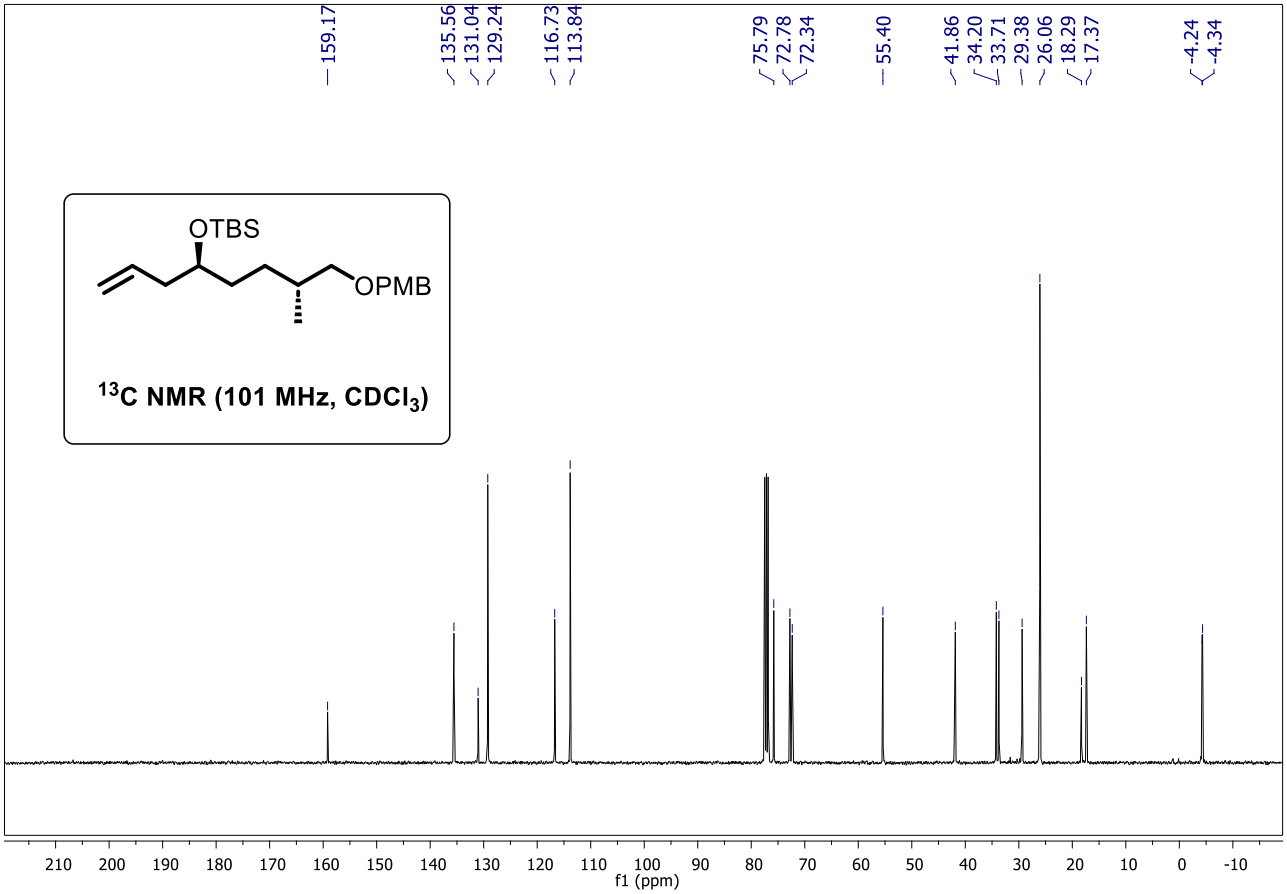
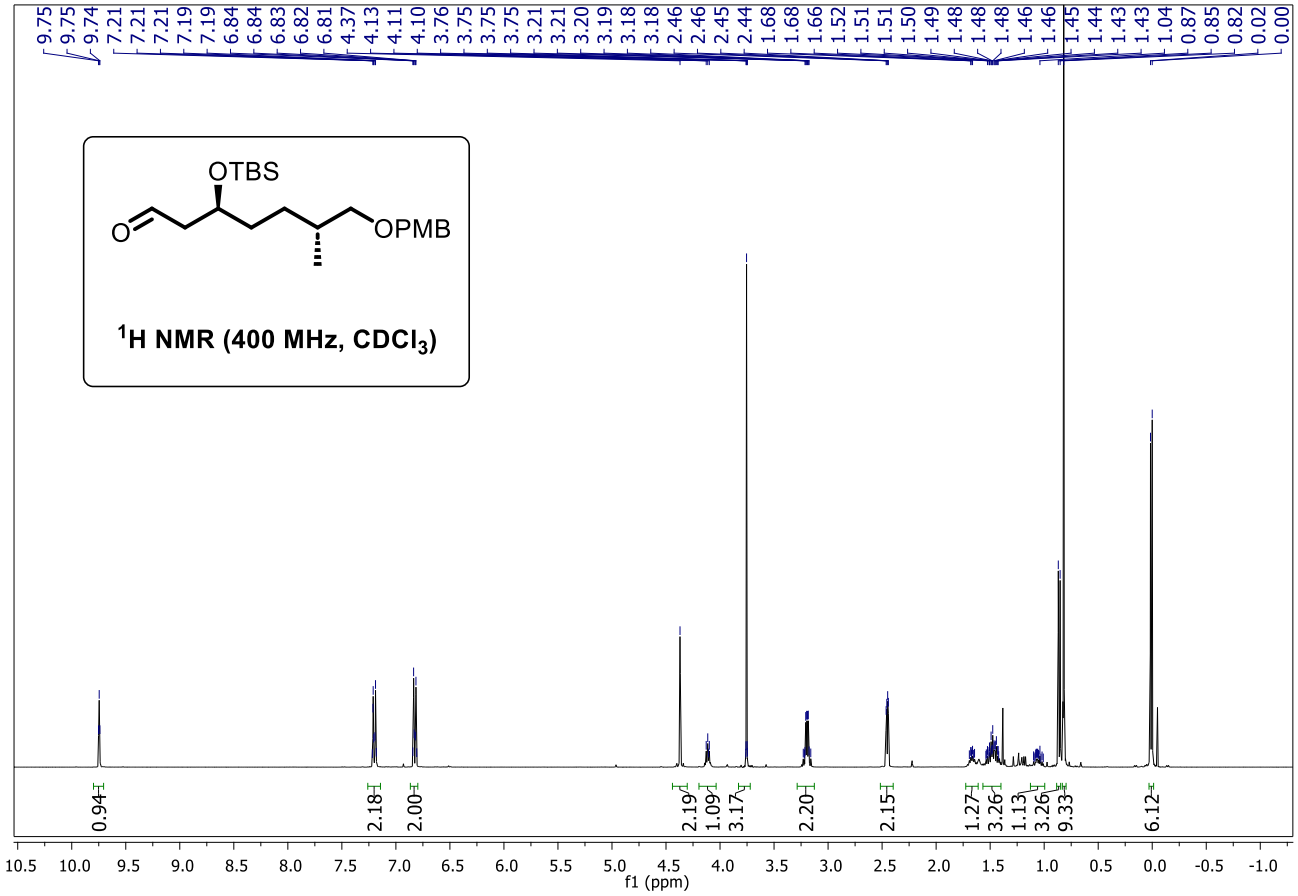
19F NMR (376 MHz, CDCl3)
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

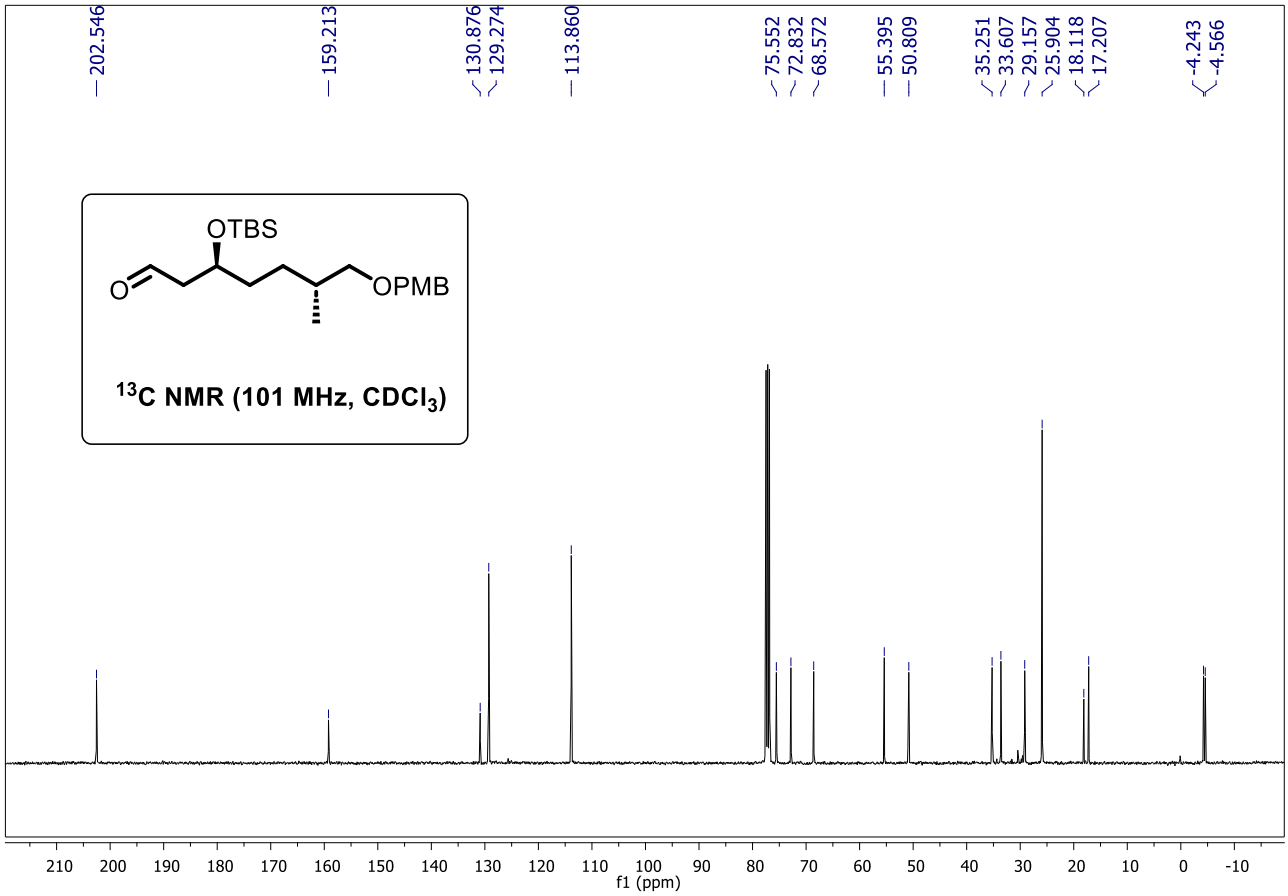
***tert*-Butyl(((4*S*,7*R*)-8-((4-methoxybenzyl)oxy)-7-methyloct-1-en-4-yl)oxy)dimethylsilane (9):**
See procedure



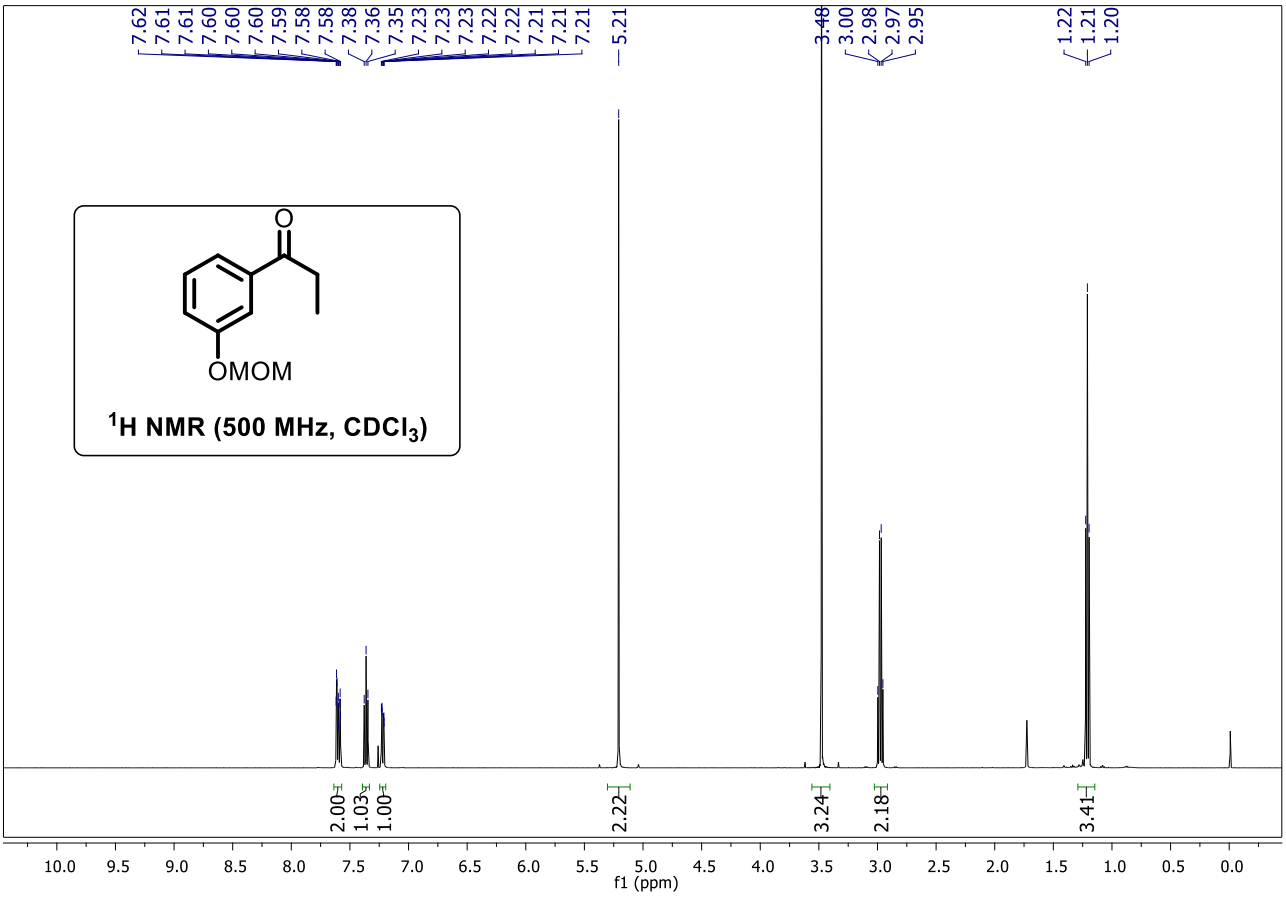


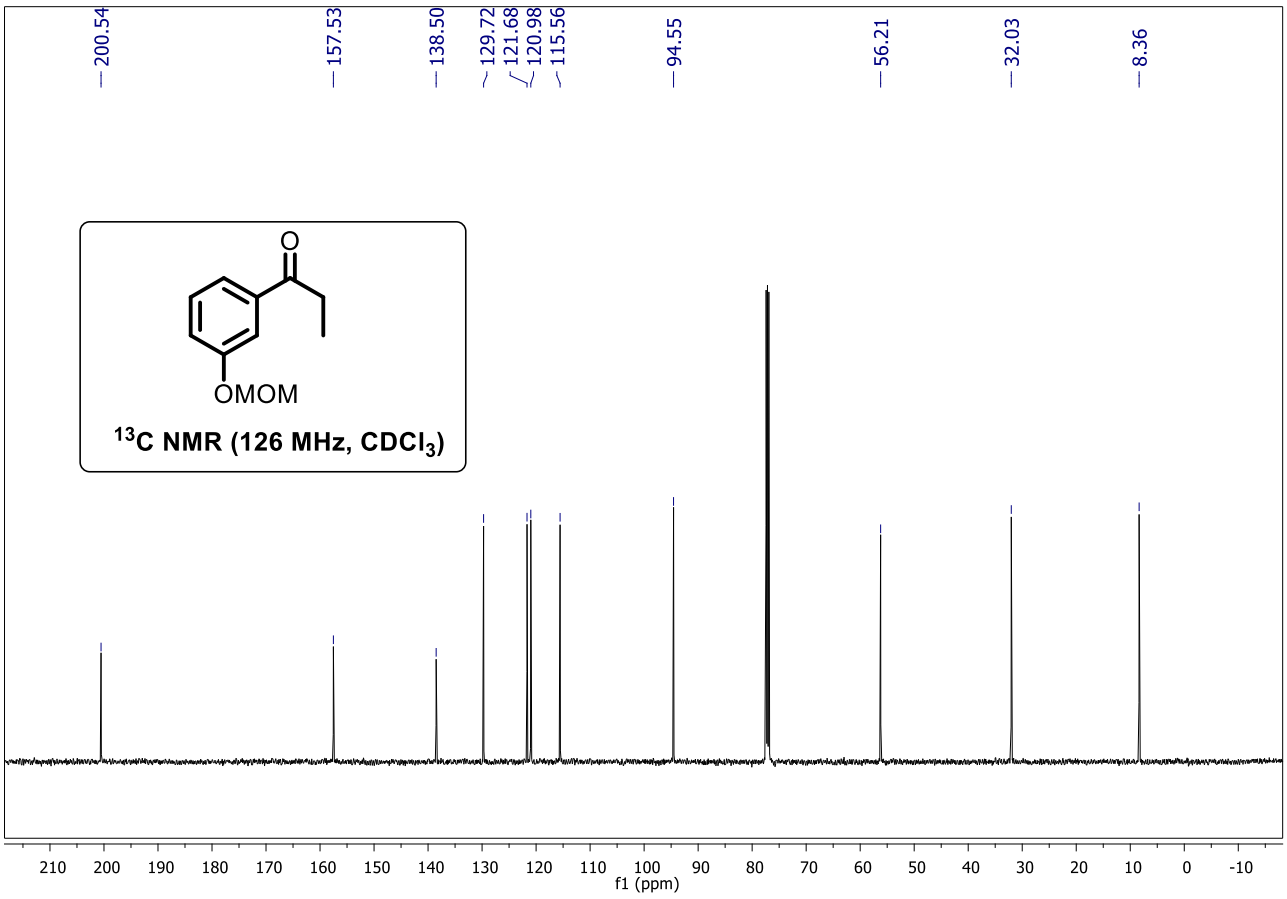
(3*S*,6*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-6-methylheptanal [(+)-10]: *See procedure*



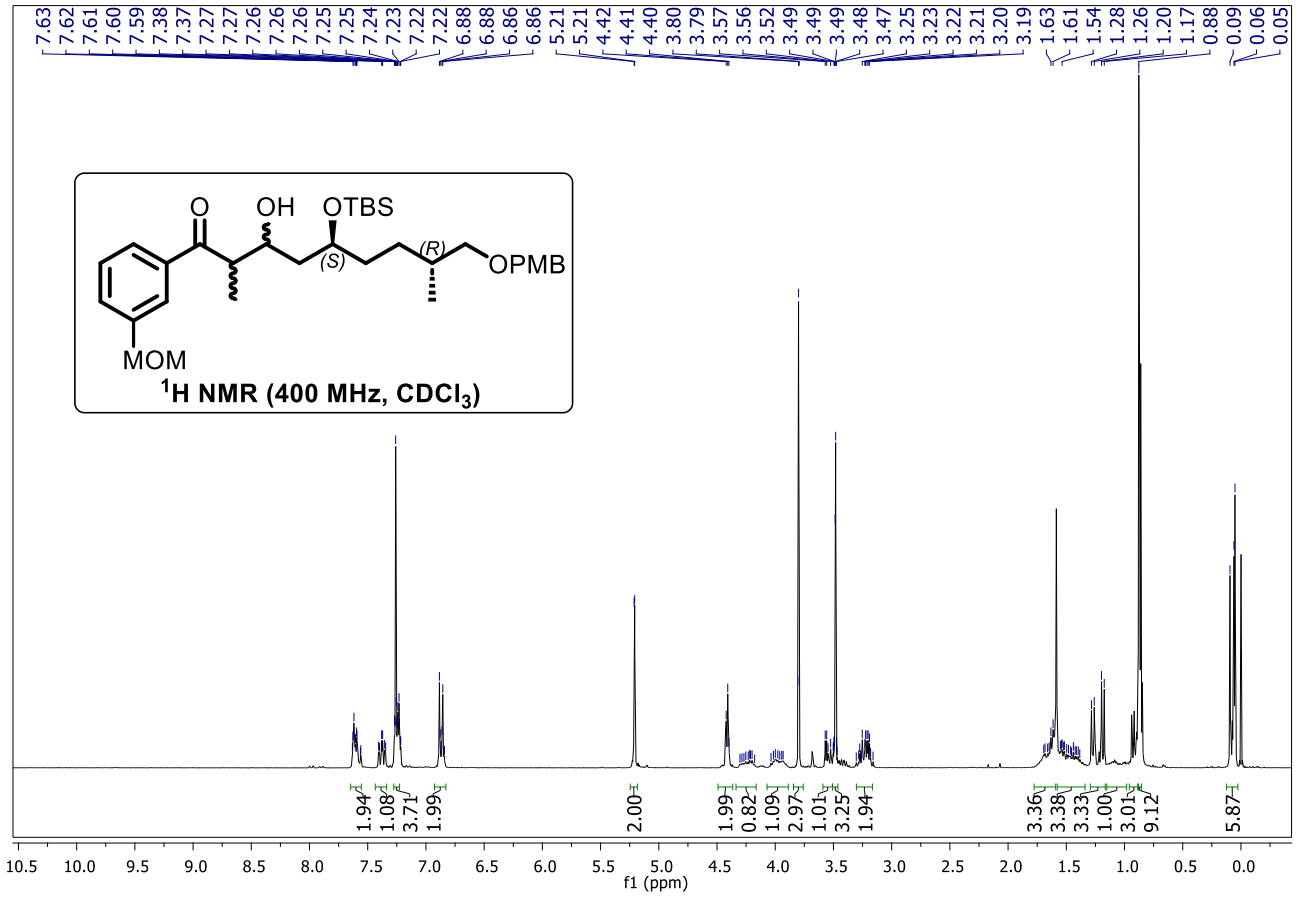


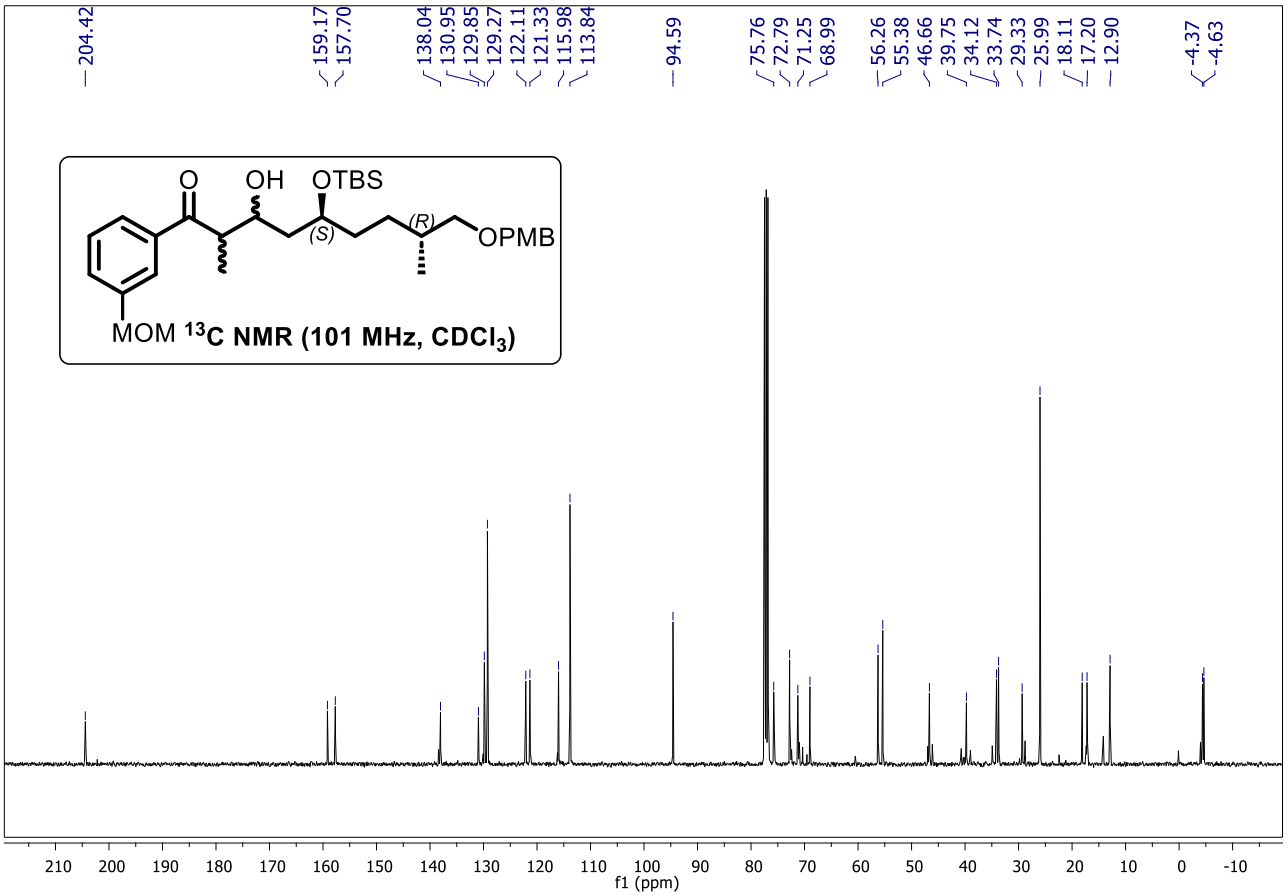
1-(3-(Methoxymethoxy)phenyl)propan-1-one (SI-6): *See procedure*



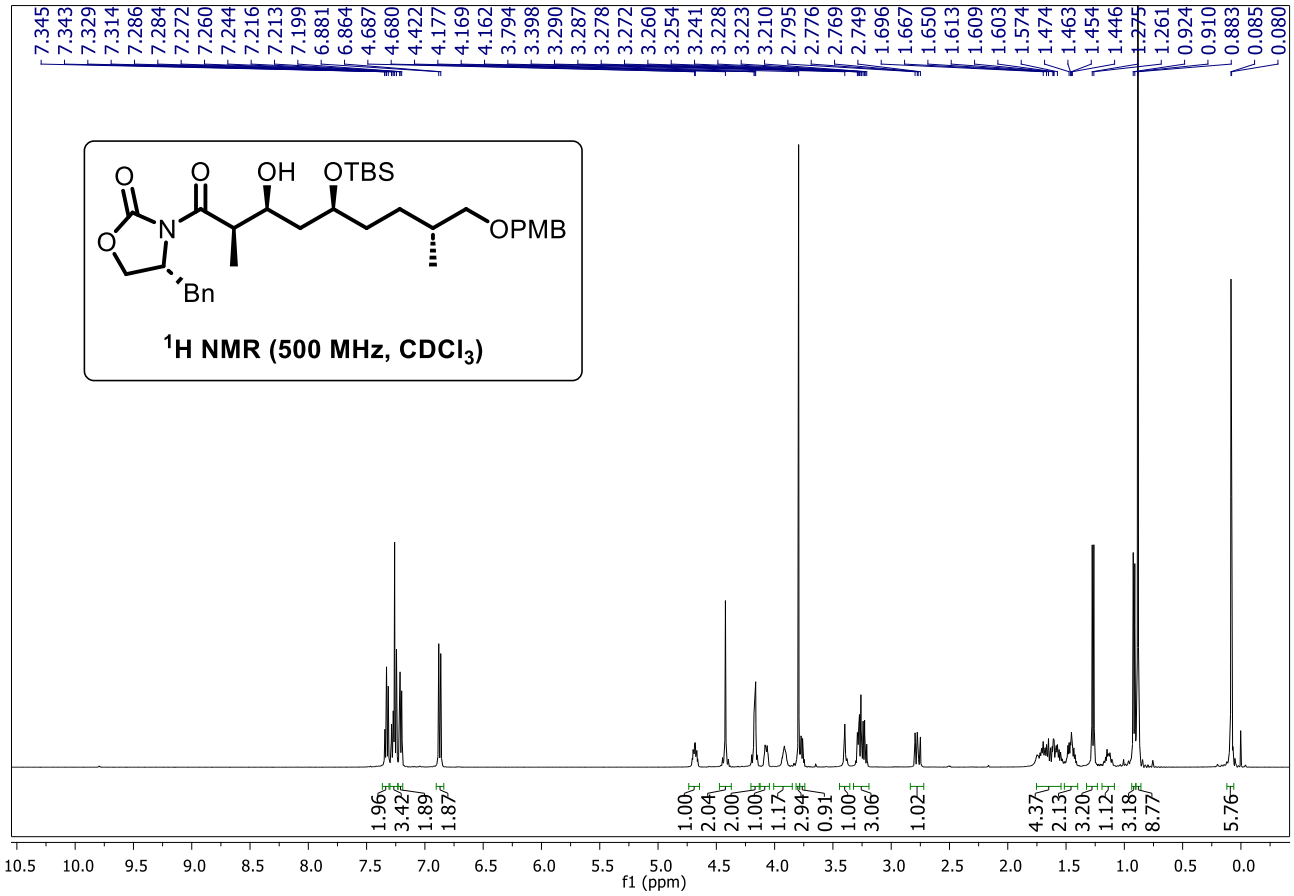


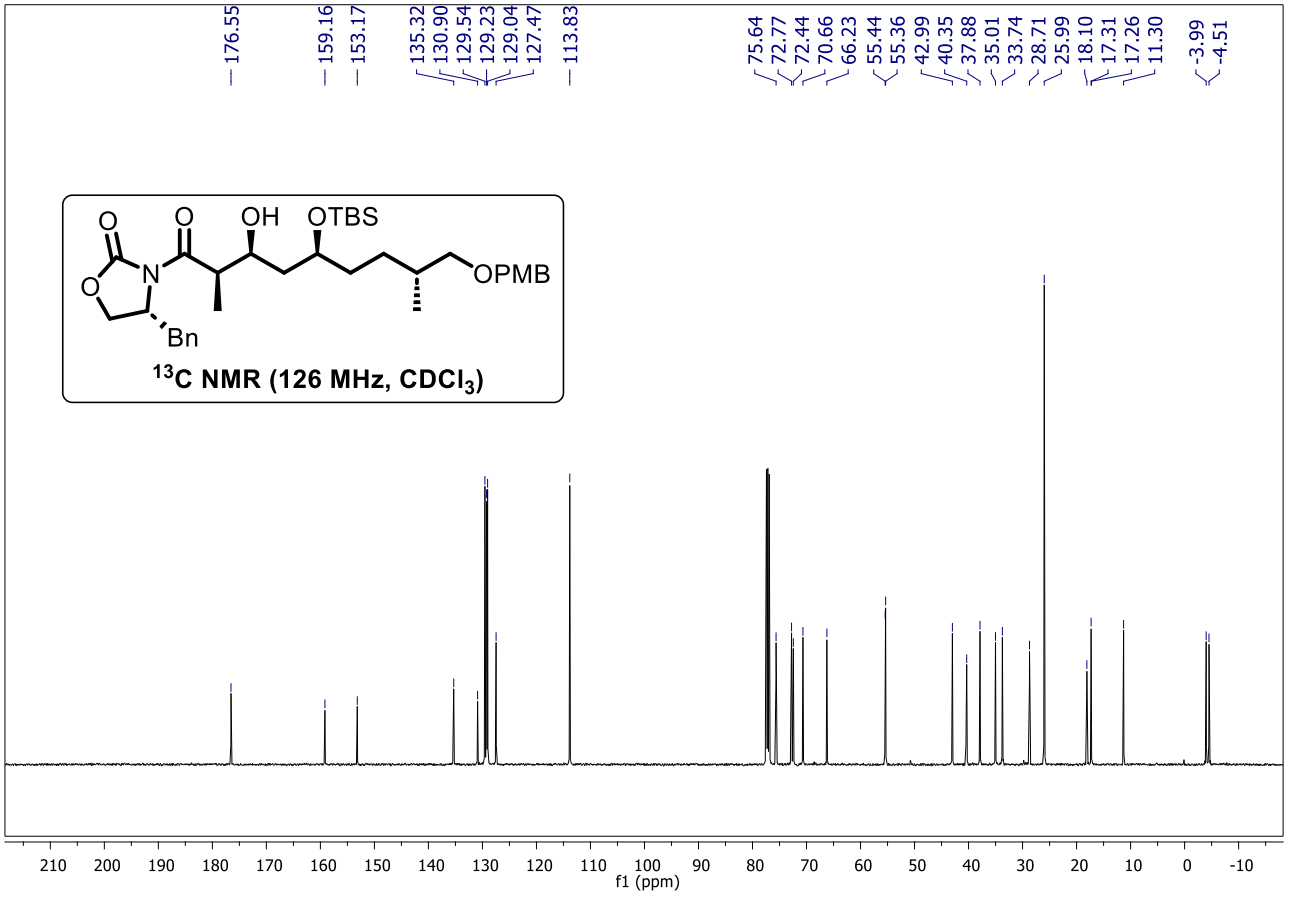
(5*S*,8*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-9-((4-methoxybenzyl)oxy)-2,8-dimethyl-1-phenylnonan-1-one (12): *See procedure*



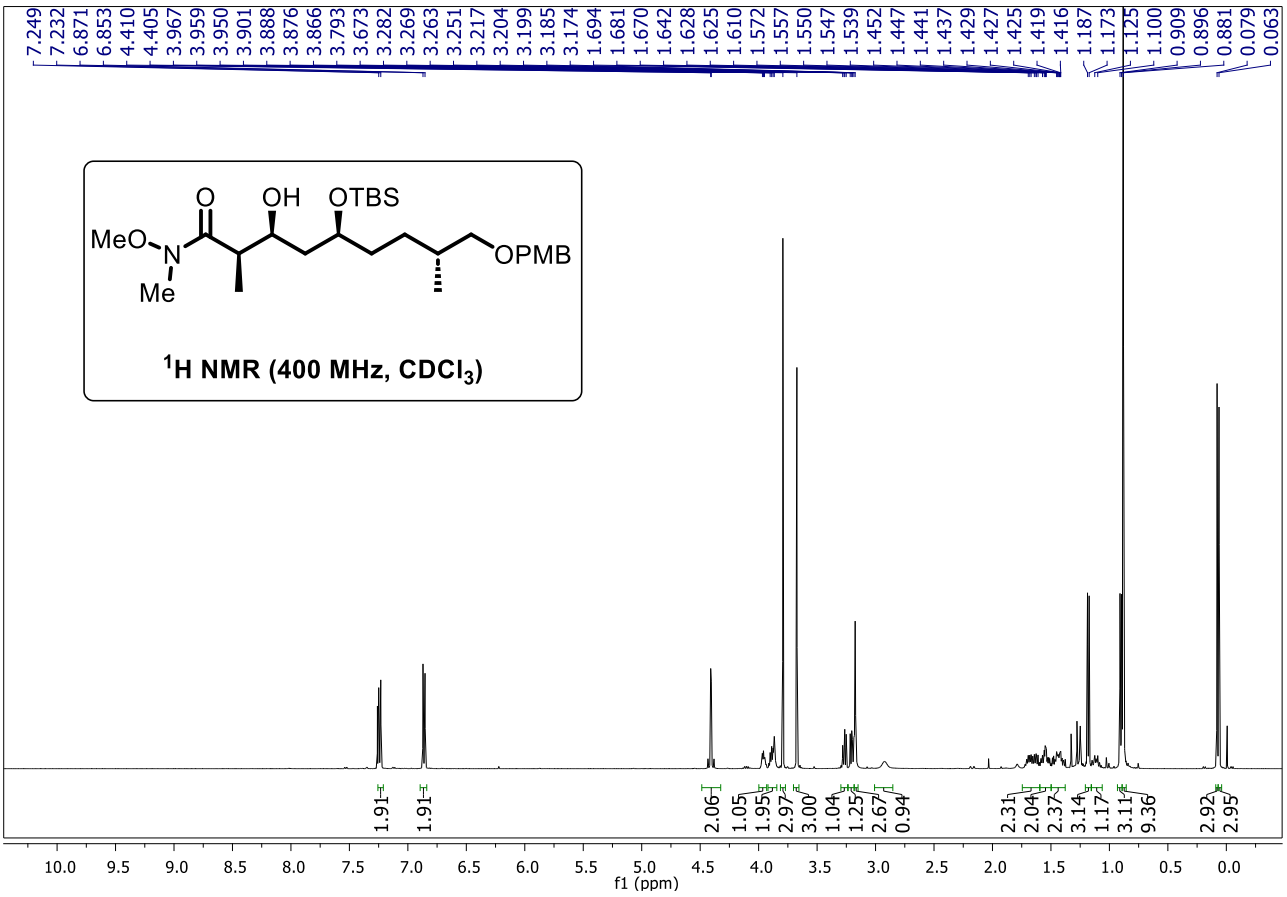


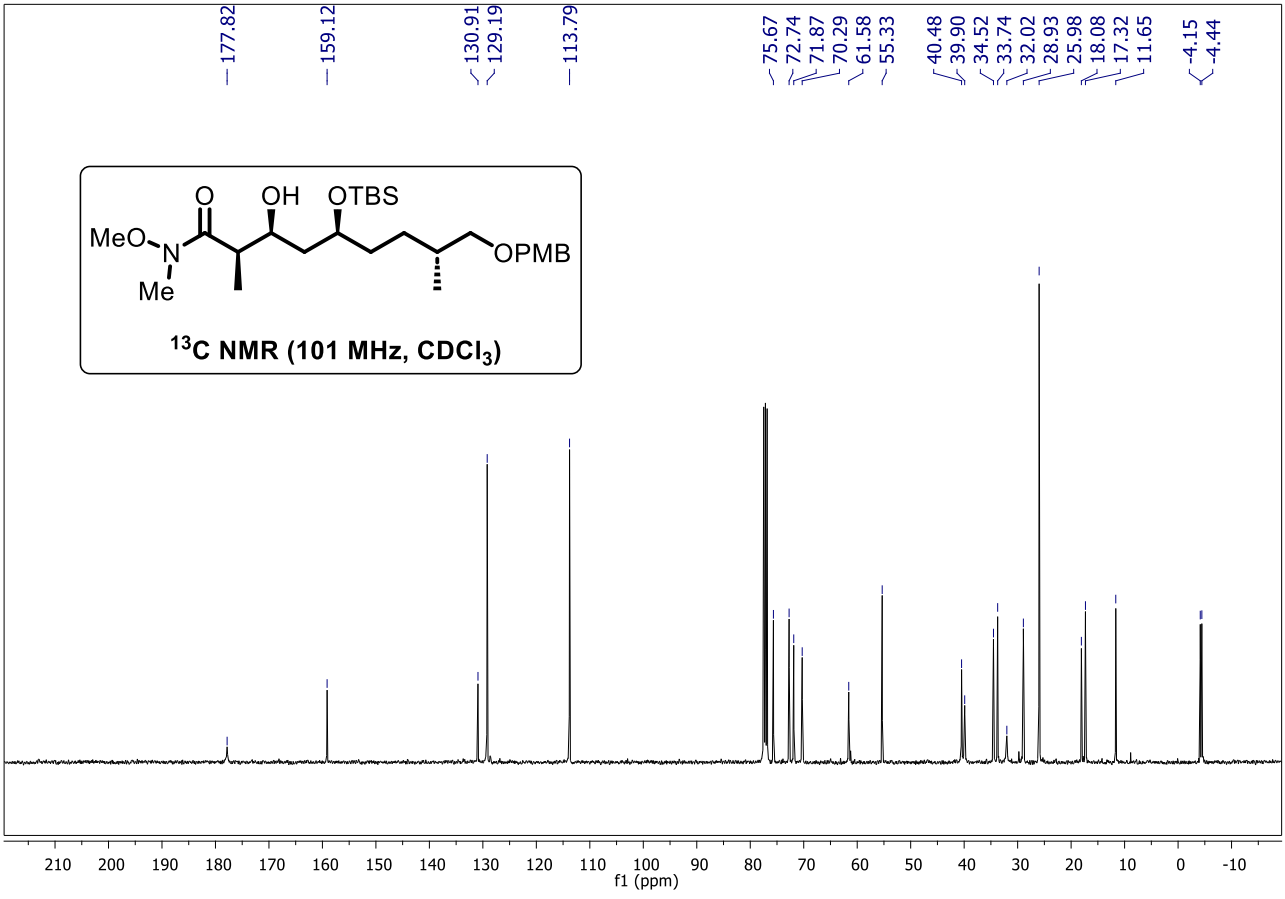
(*R*)-4-Benzyl-3-((2*R*,3*S*,5*S*,8*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-9-((4-methoxybenzyl)oxy)-2,8-dimethylnonanoyl)oxazolidin-2-one (15): *See procedure*



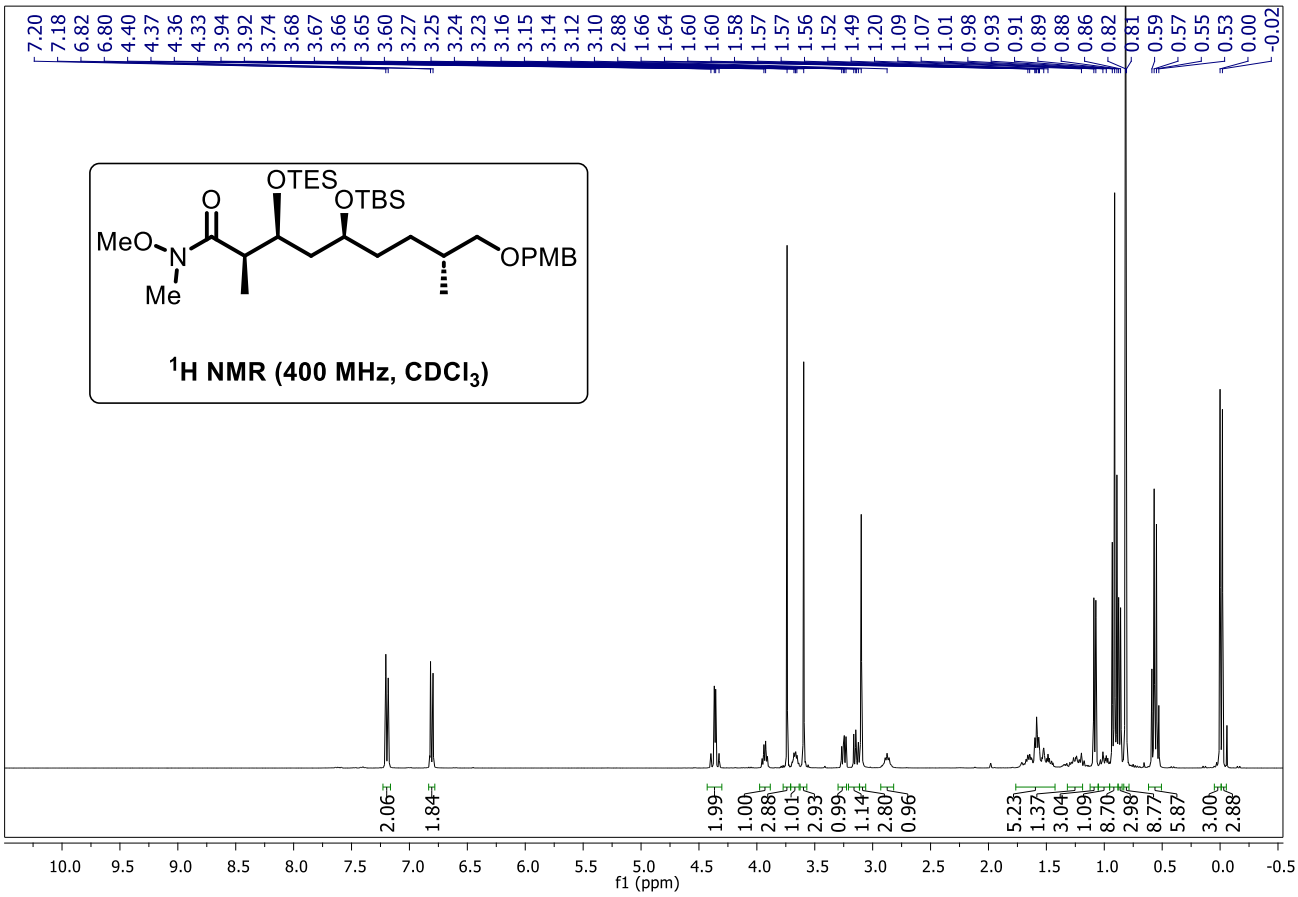


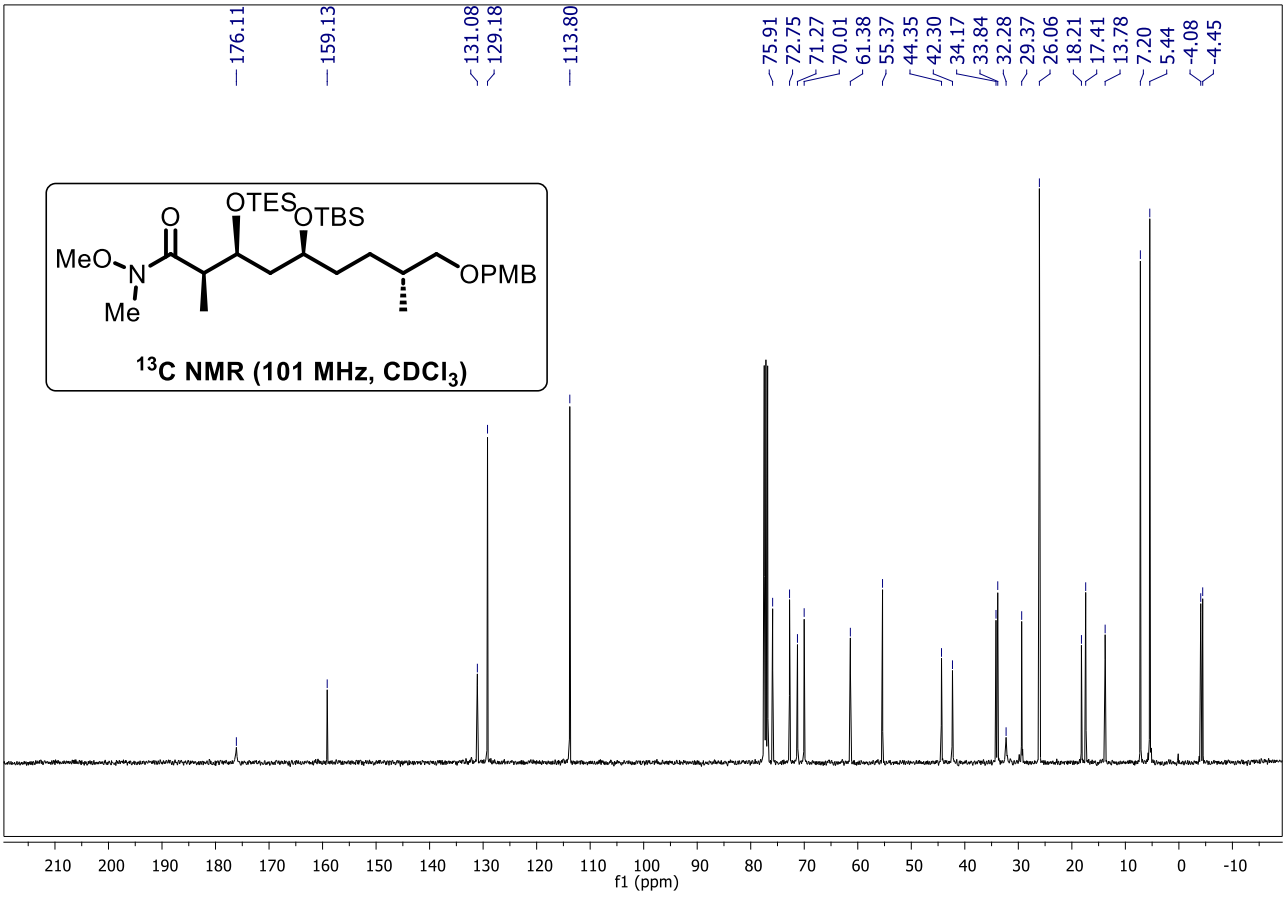
(2*R*,3*S*,5*S*,8*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-N-methoxy-9-((4-methoxybenzyl)oxy)-N,2,8-trimethylnonanamide (SI-7): *See procedure*



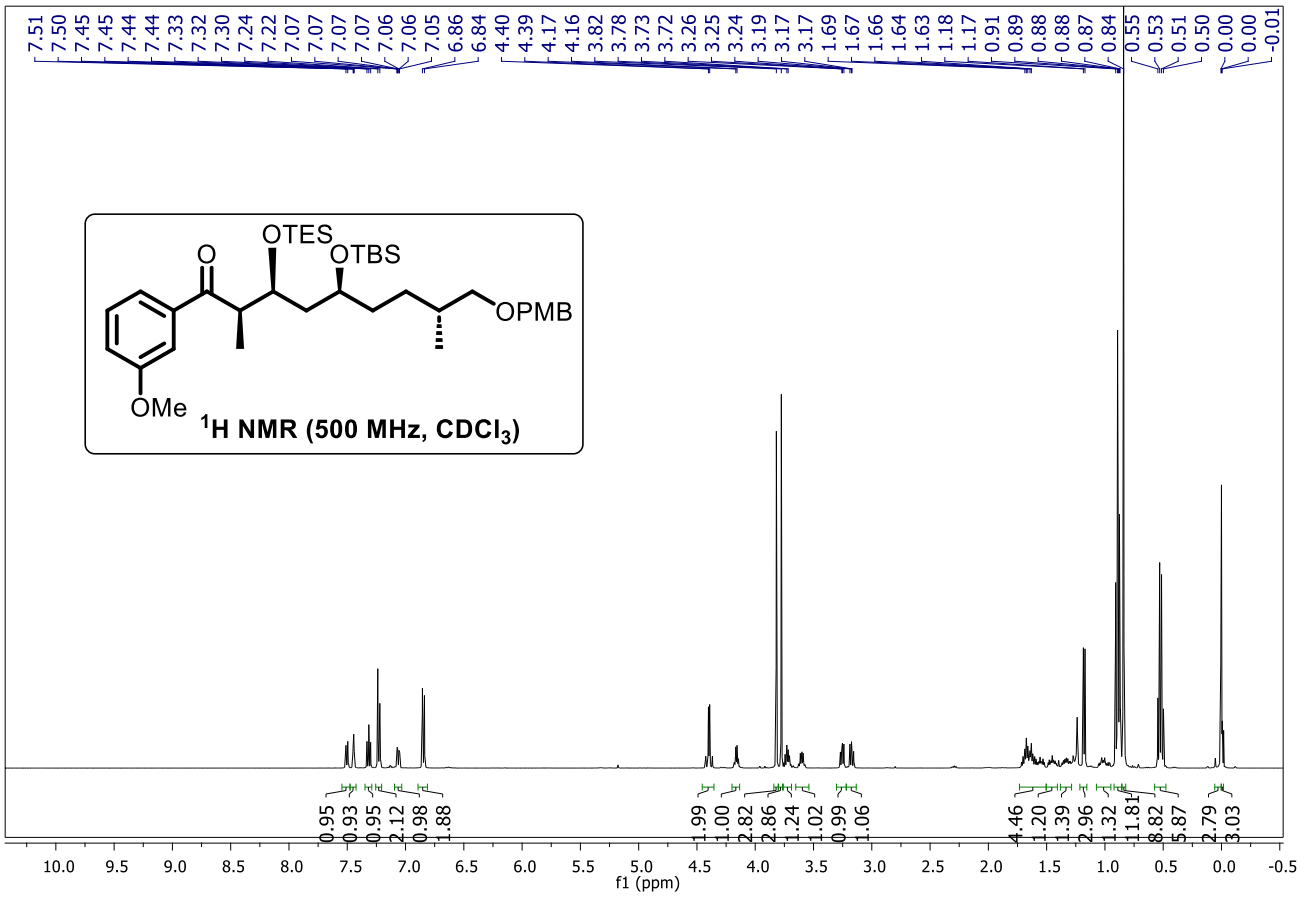


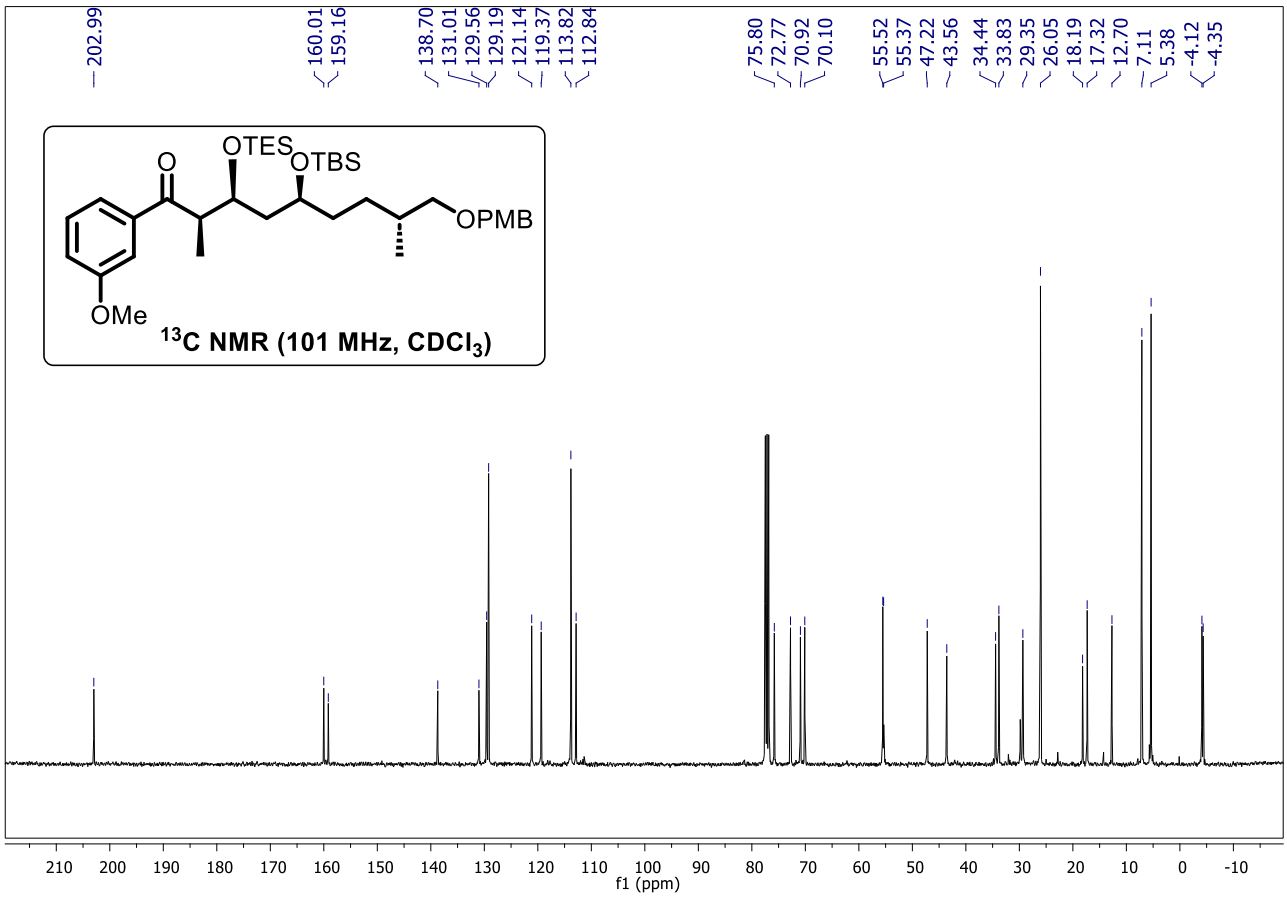
(2*R*,3*S*,5*S*,8*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-9-((4-methoxybenzyl)oxy)-*N*,2,8-trimethyl-3-((triethylsilyl)oxy)nonanamide) (16): *See procedure*



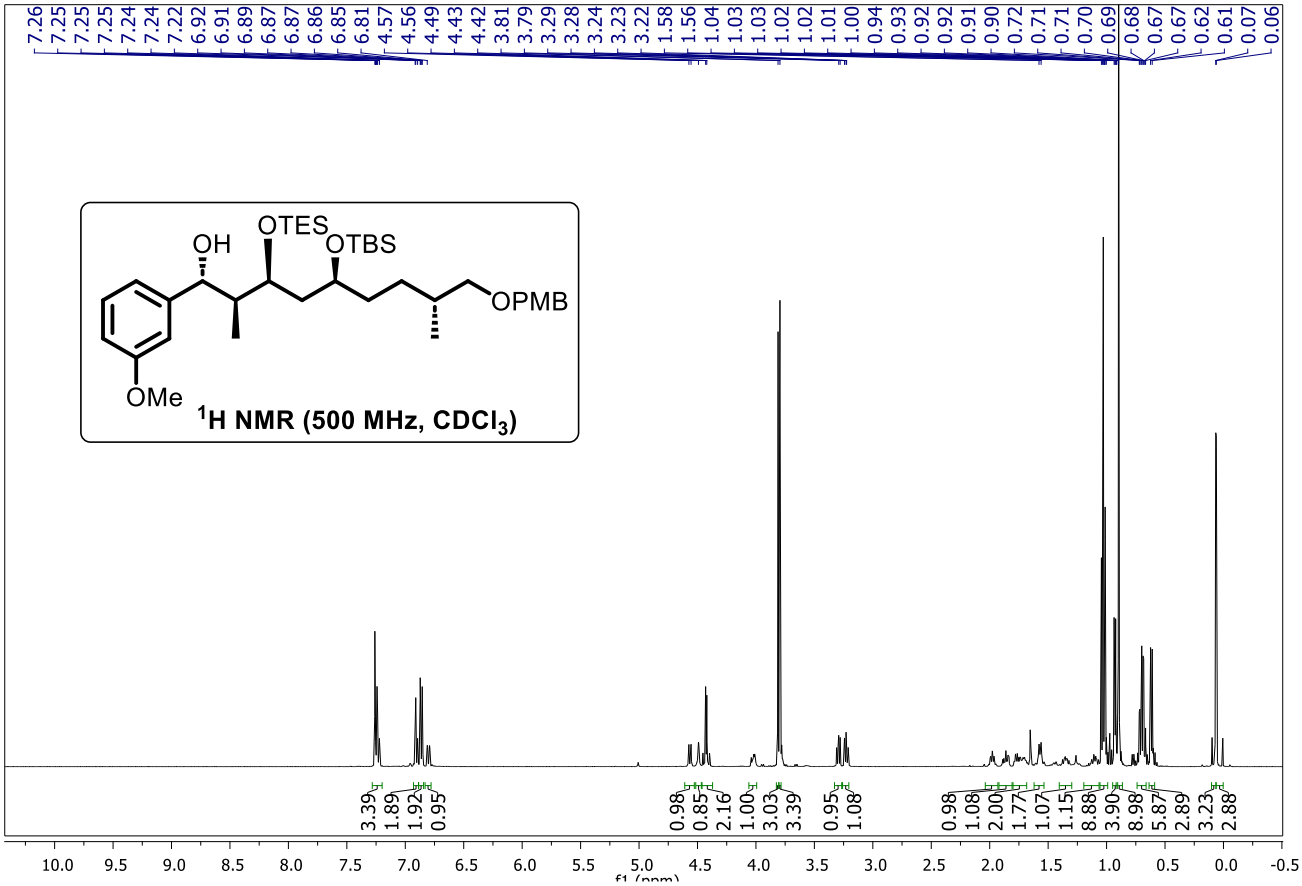


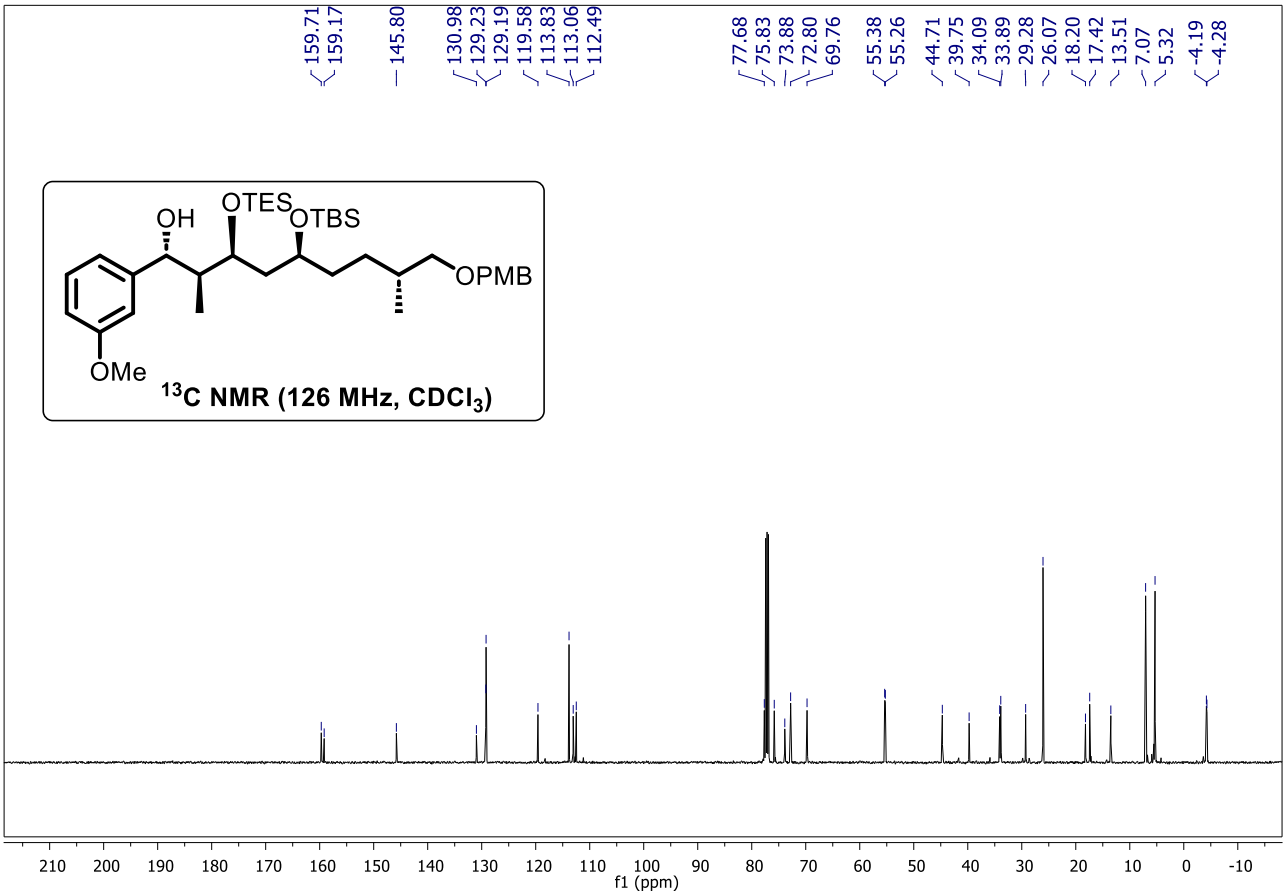
(2*R*,3*S*,5*S*,8*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-9-((4-methoxybenzyl)oxy)-1-(3-methoxyphenyl)-2,8-dimethyl-3-((triethylsilyl)oxy)nonan-1-one (17): *See procedure*



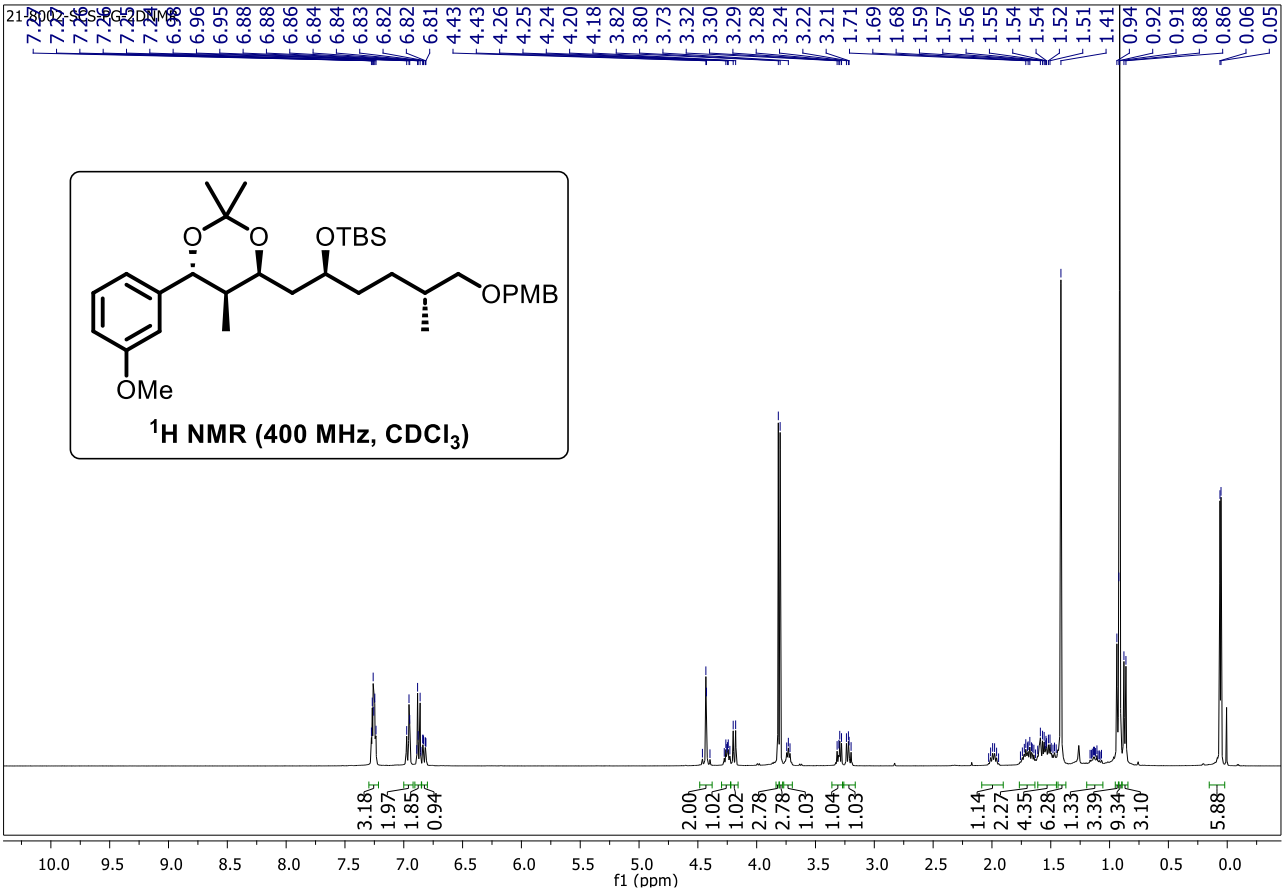


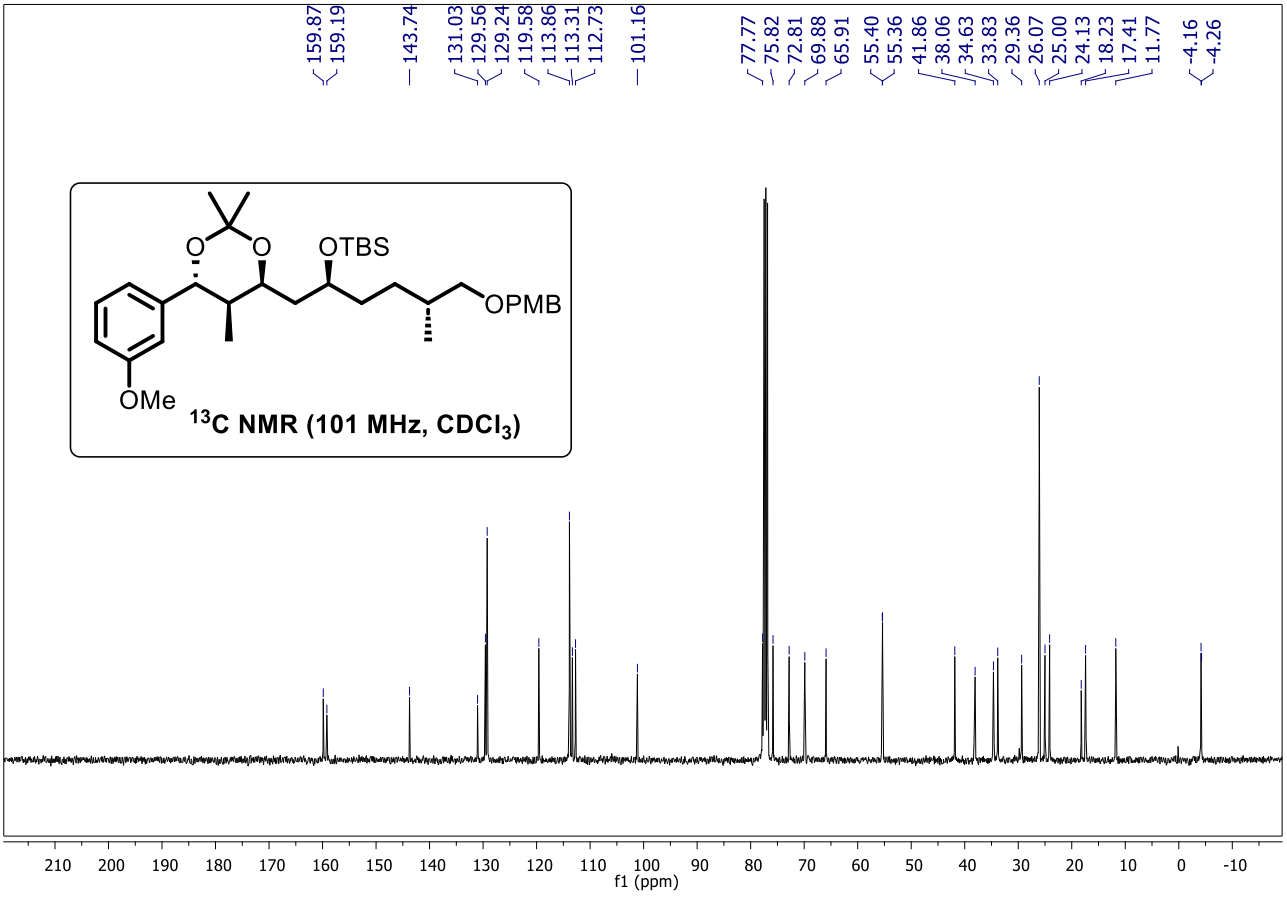
(1*R*,2*S*,3*S*,5*S*,8*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-9-((4-methoxybenzyl)oxy)-1-(3-methoxyphenyl)-2,8-dimethyl-3-((triethylsilyl)oxy)nonan-1-ol (SI-8): *See procedure*



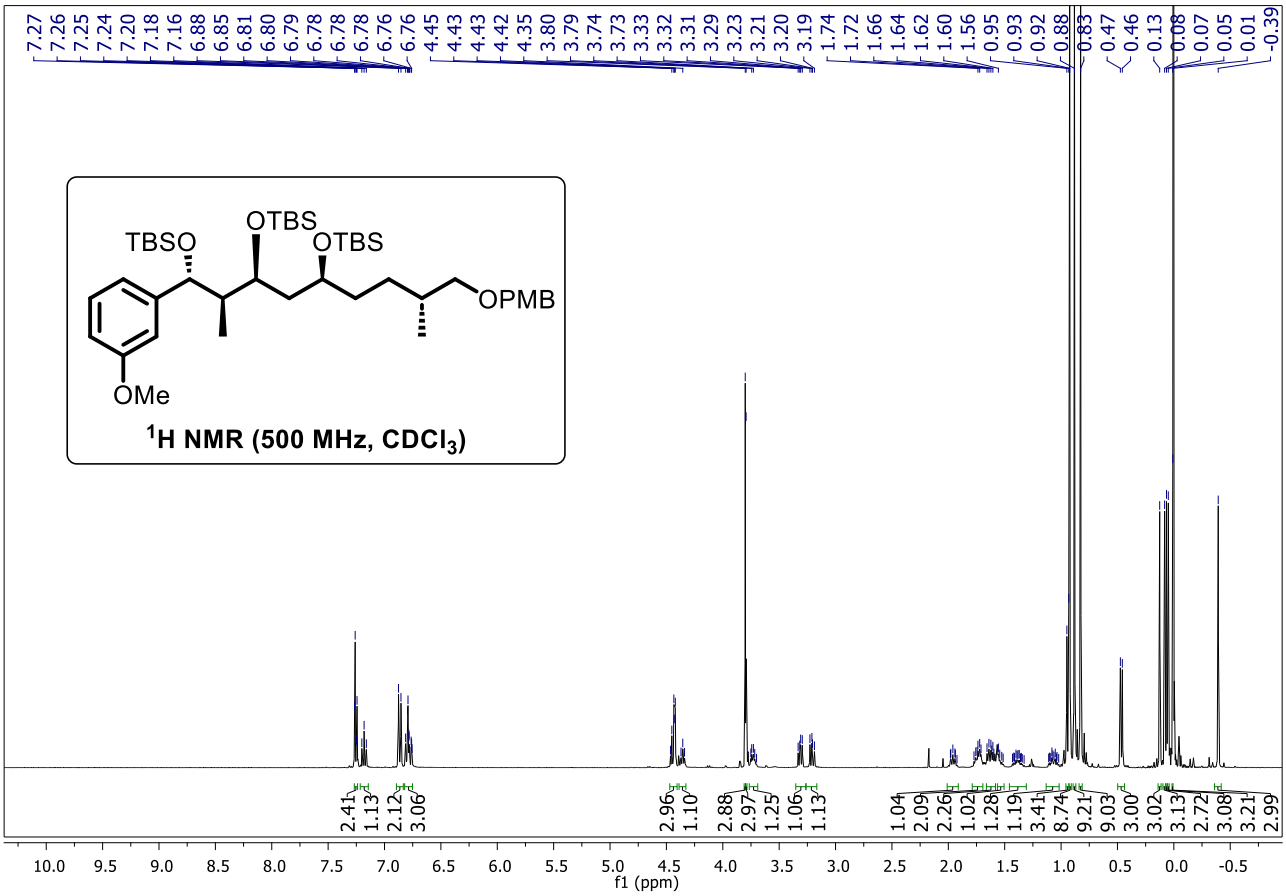


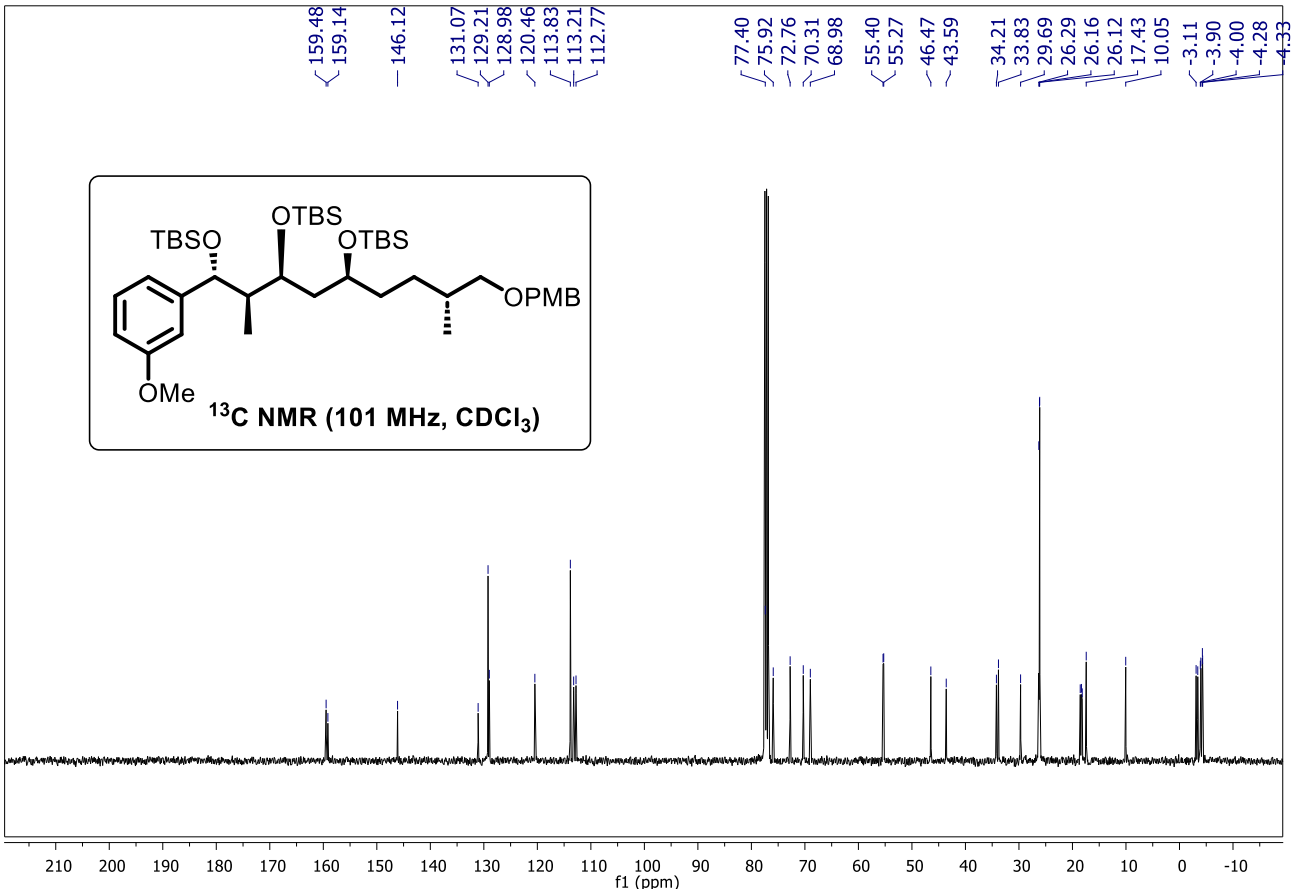
***tert*-Butyl(((2*S*,5*R*)-6-((4-methoxybenzyl)oxy)-1-((4*S*,5*R*,6*R*)-6-(3-methoxyphenyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-methylhexan-2-yl)oxy)dimethylsilane (20):** *See procedure*



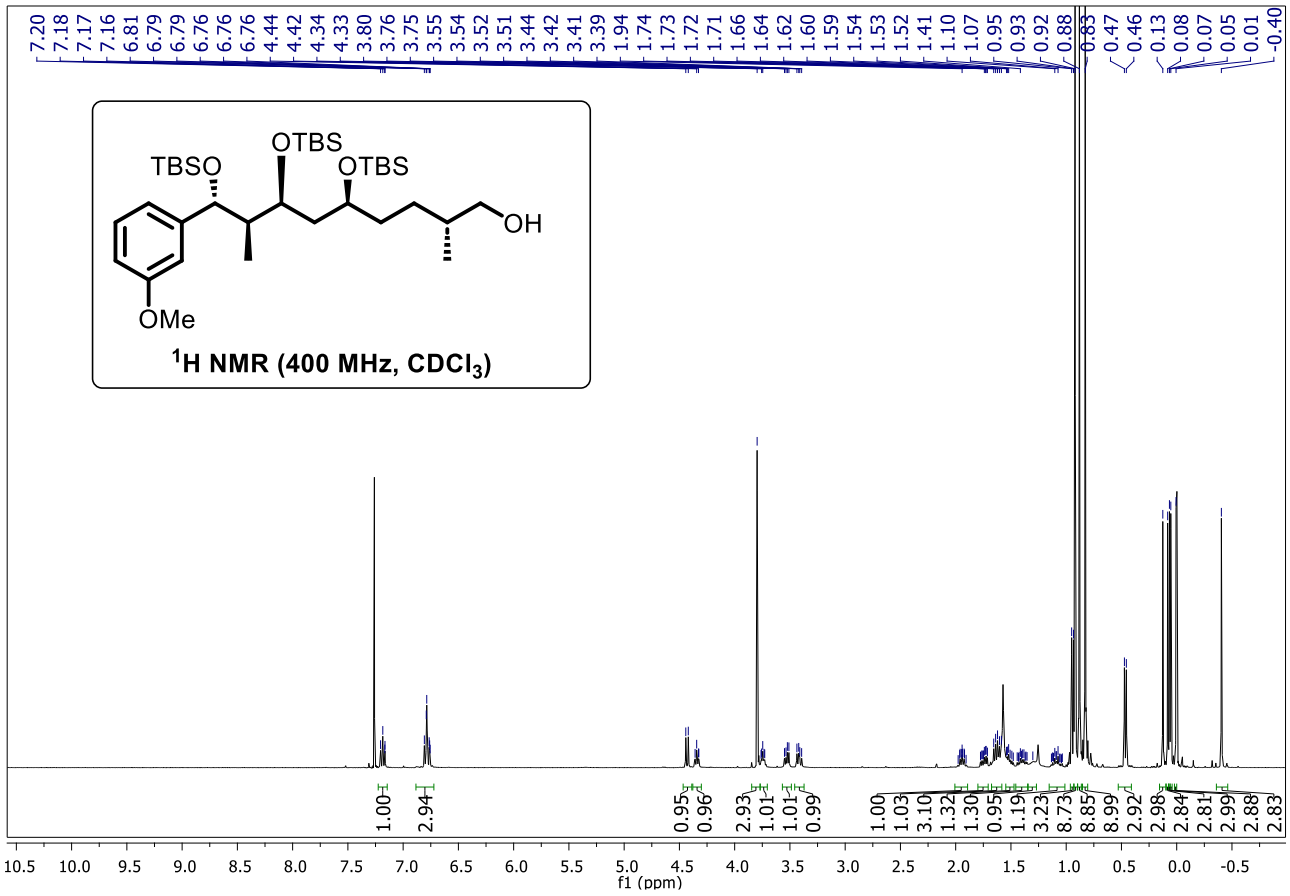


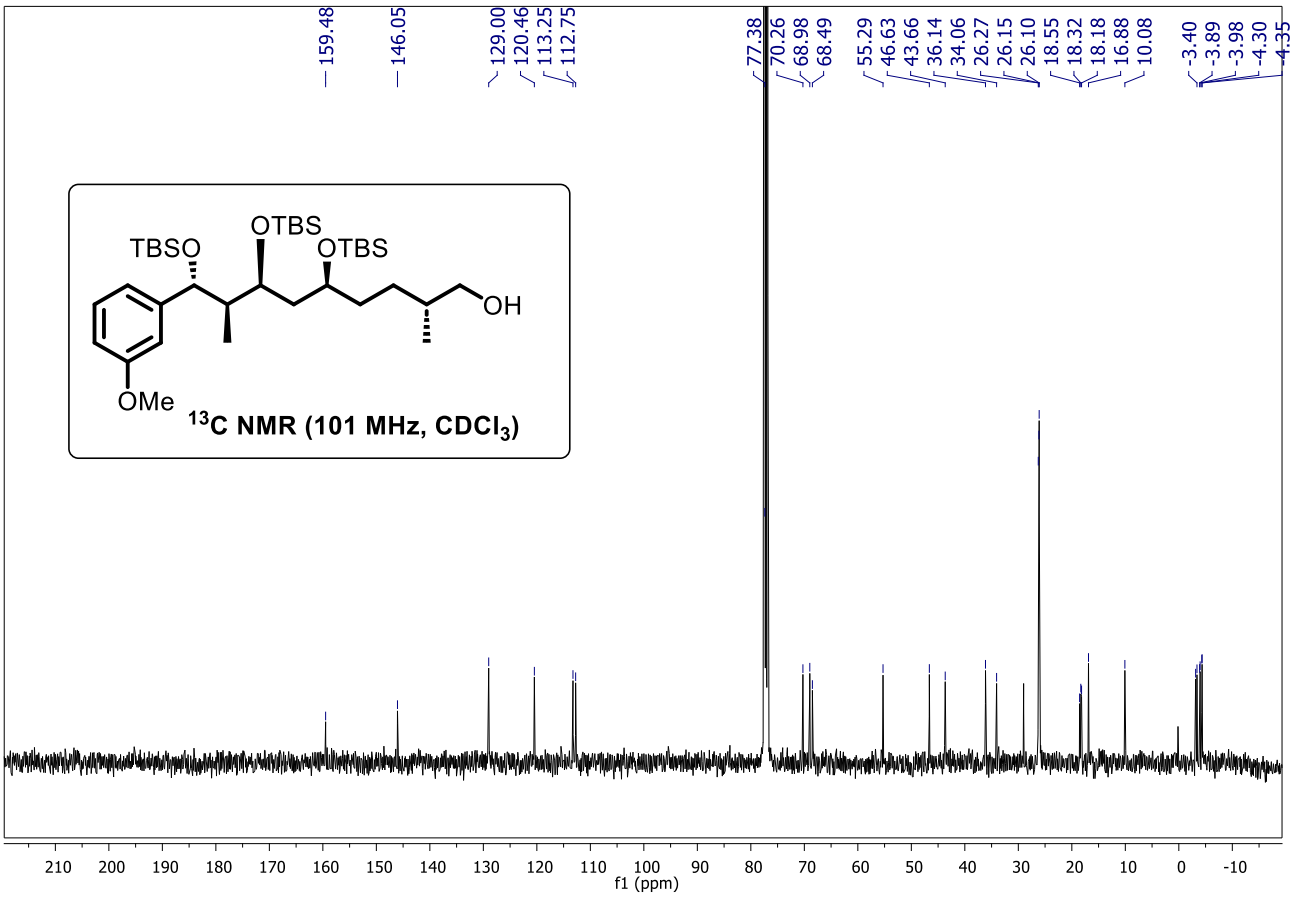
(5*R*,6*R*,7*S*,9*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-9-((*R*)-4-((4-methoxybenzyl)oxy)-3-methylbutyl)-5-(3-methoxyphenyl)-2,2,3,3,6,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disilatridecane (SI-9): *See procedure*



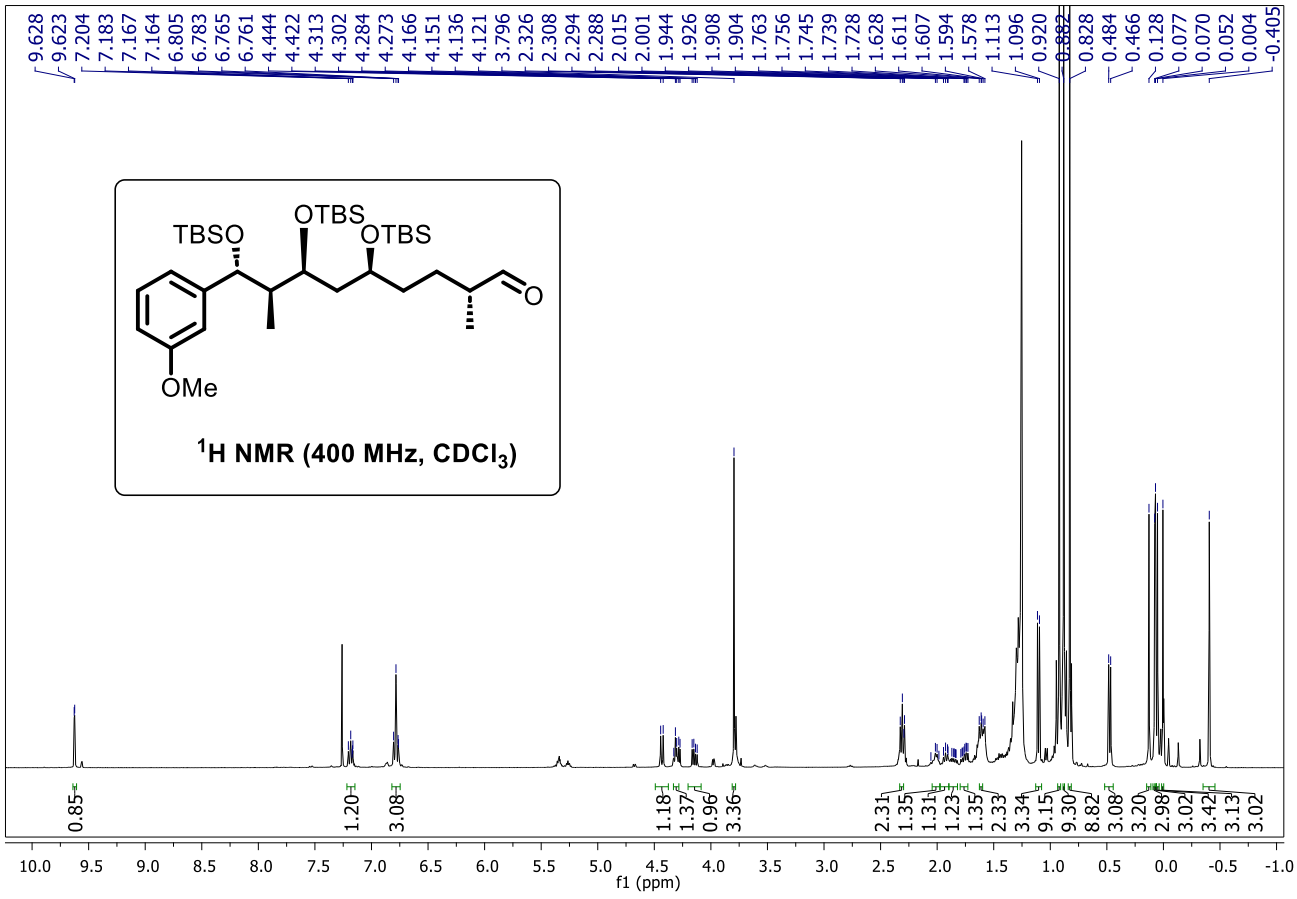


(2*R*,5*S*,7*S*,8*R*,9*R*)-5,7,9-*tris*((*tert*-Butyldimethylsilyl)oxy)-9-(3-methoxyphenyl)-2,8-dimethylnonan-1-ol (SI-10): *See procedure*

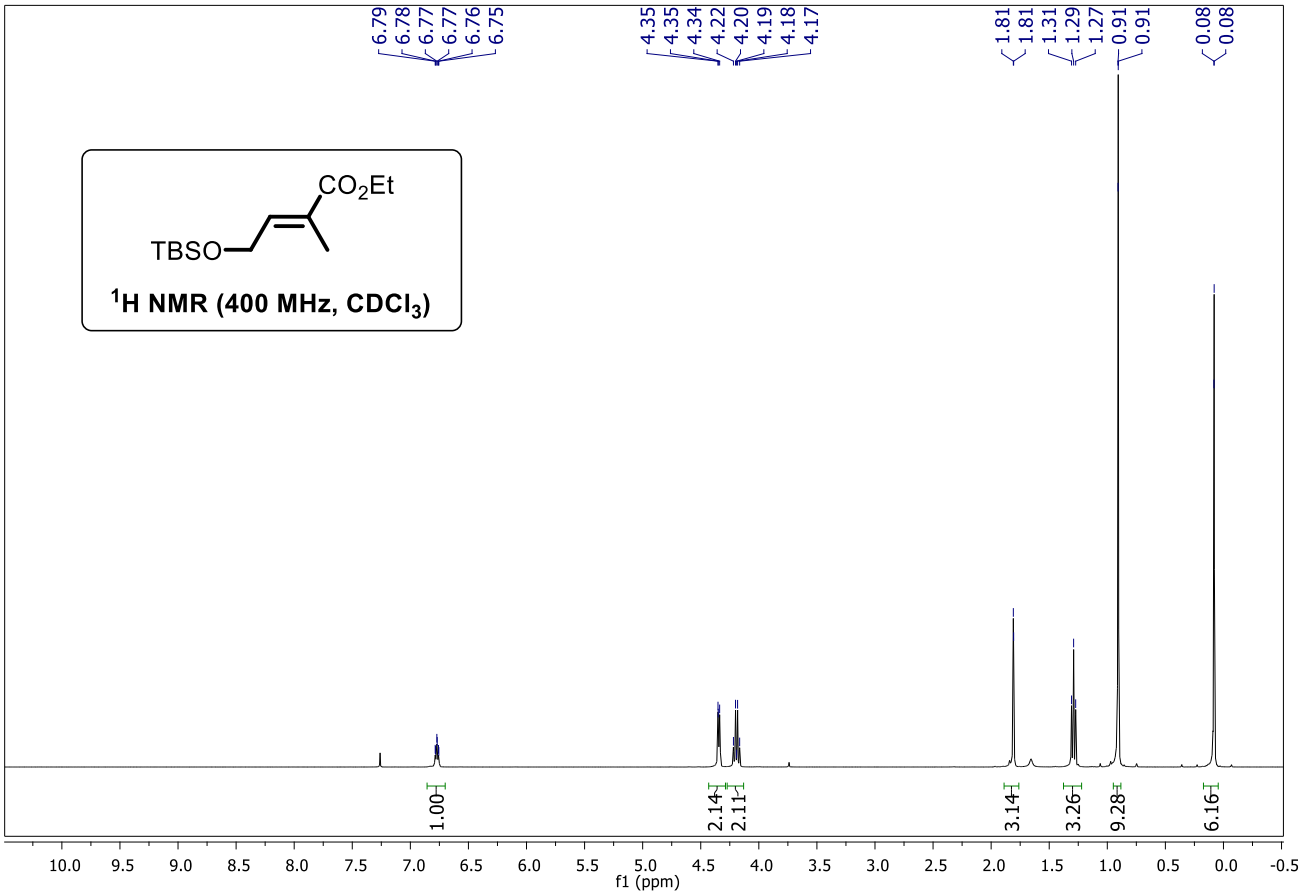


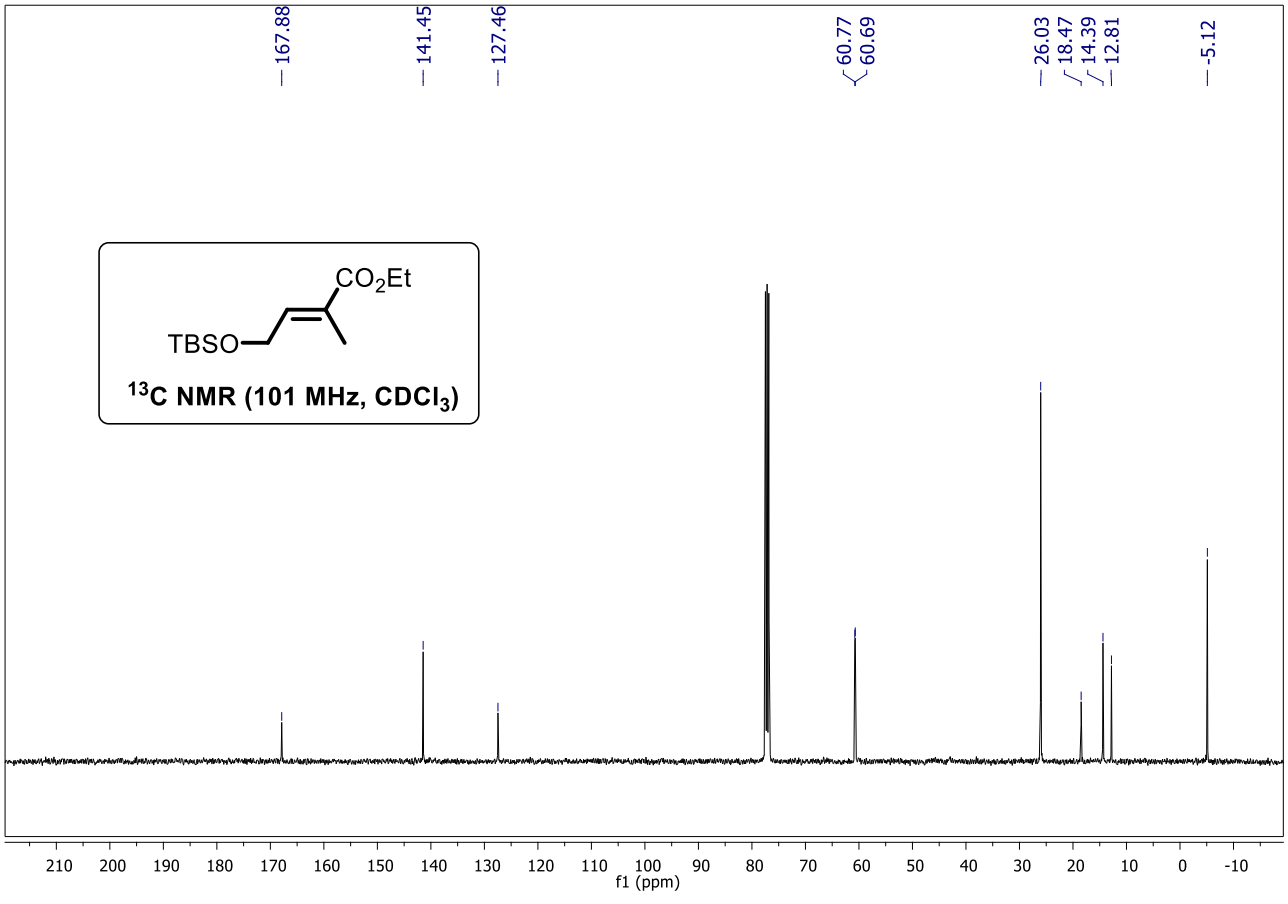


(2*R*,5*S*,7*S*,8*R*,9*R*)-5,7,9-*tris*((*tert*-butyldimethylsilyl)oxy)-9-(3-methoxyphenyl)-2,8-dimethylnonanal [(+)-19]: *See procedure*

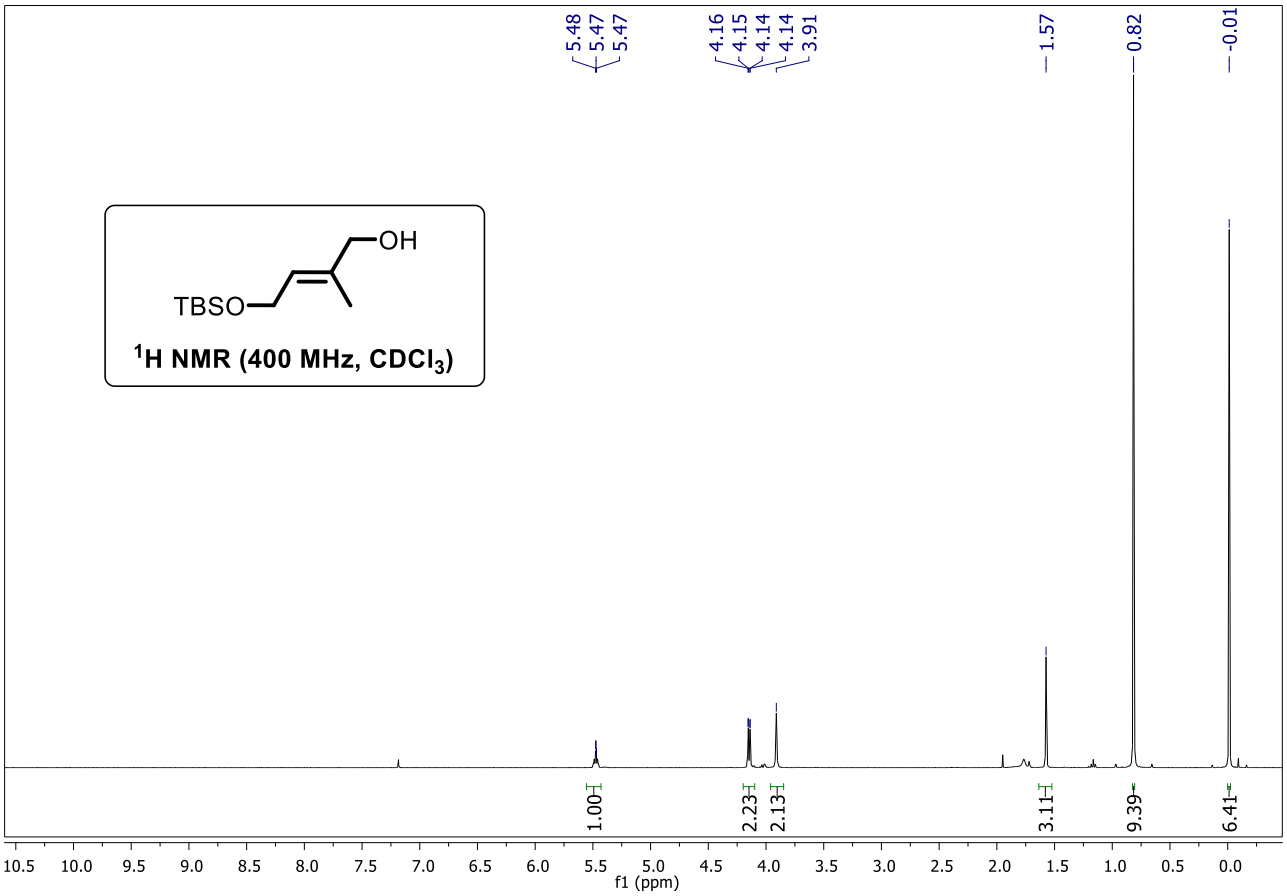


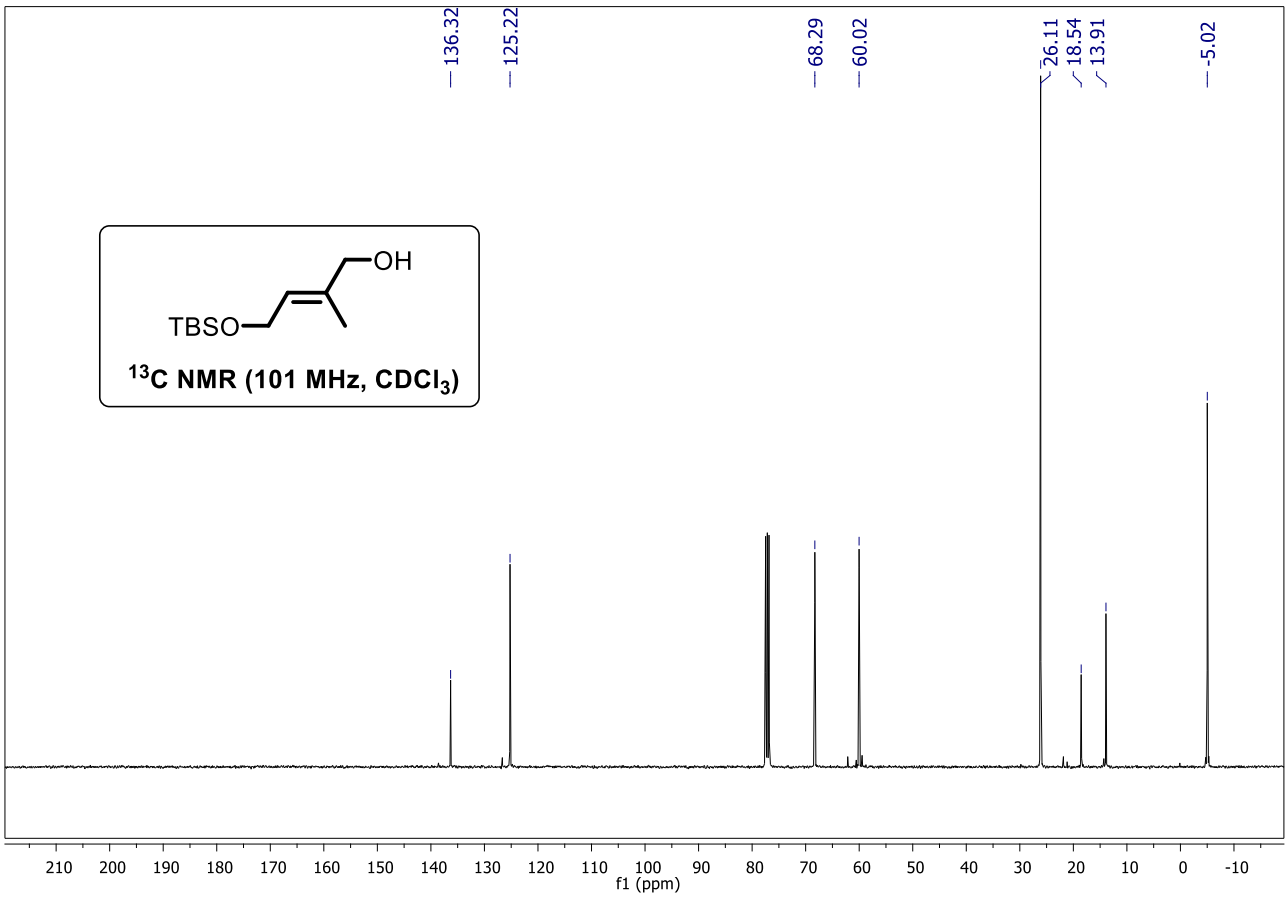
Ethyl (*E*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylbut-2-enoate (22): *See procedure*



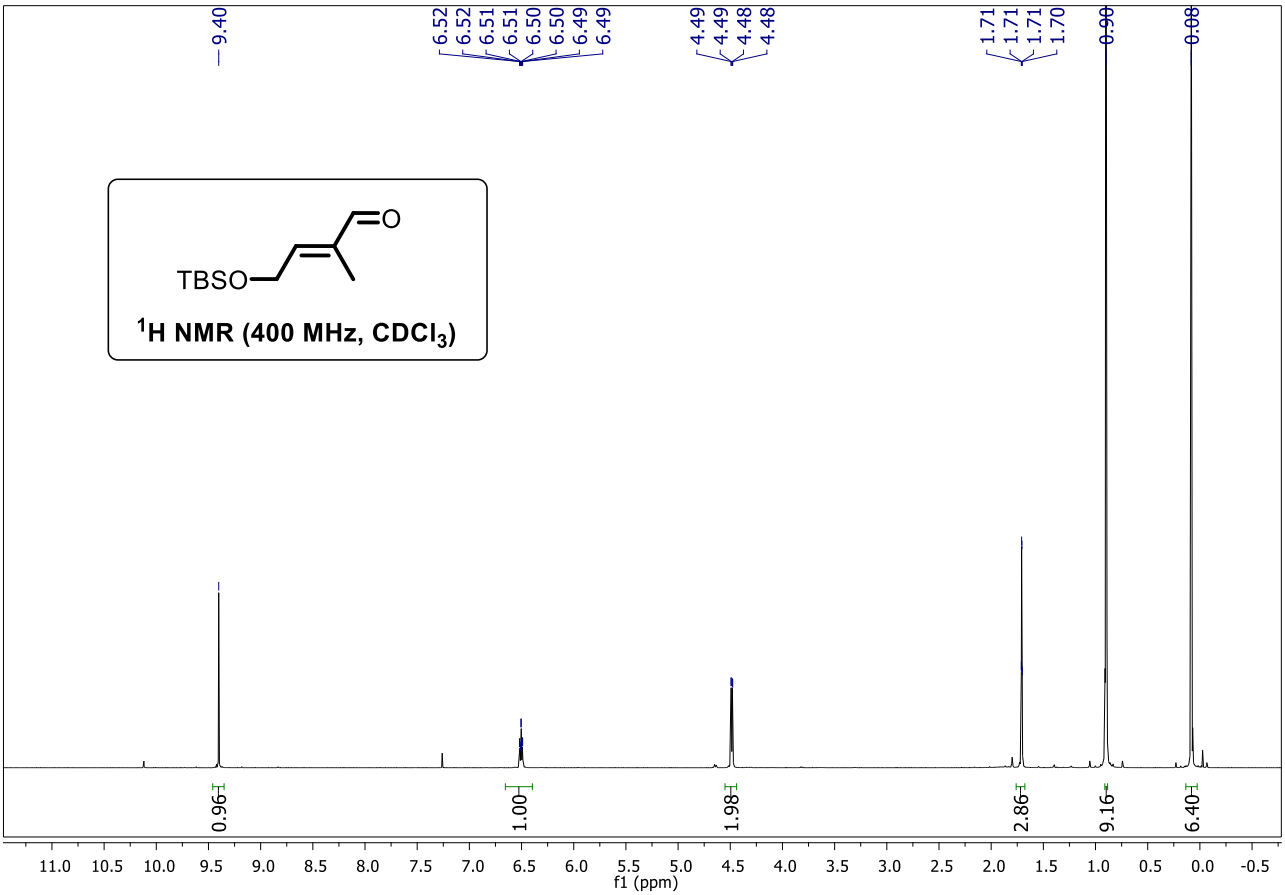


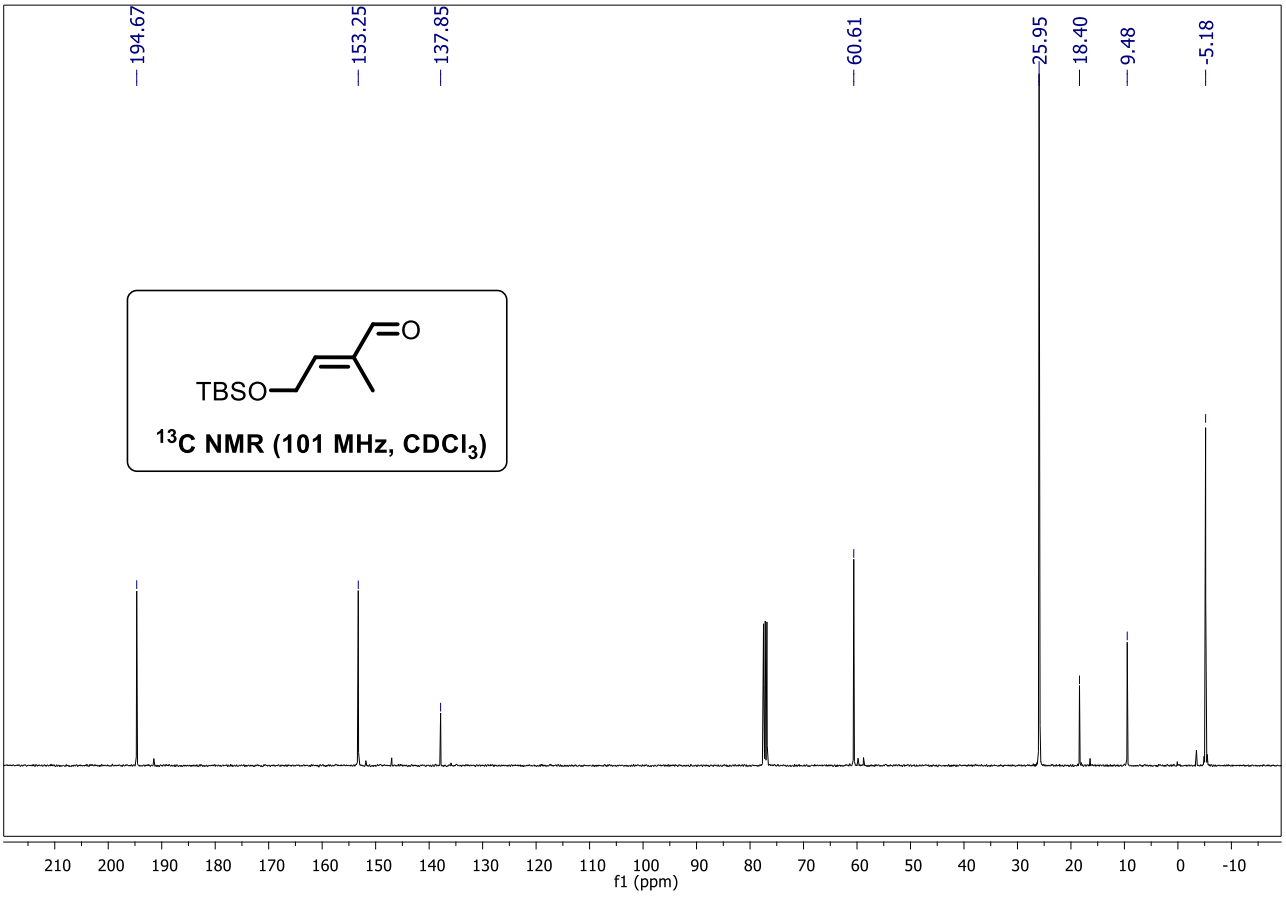
(*E*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylbut-2-en-1-ol (SI-11): *See procedure*



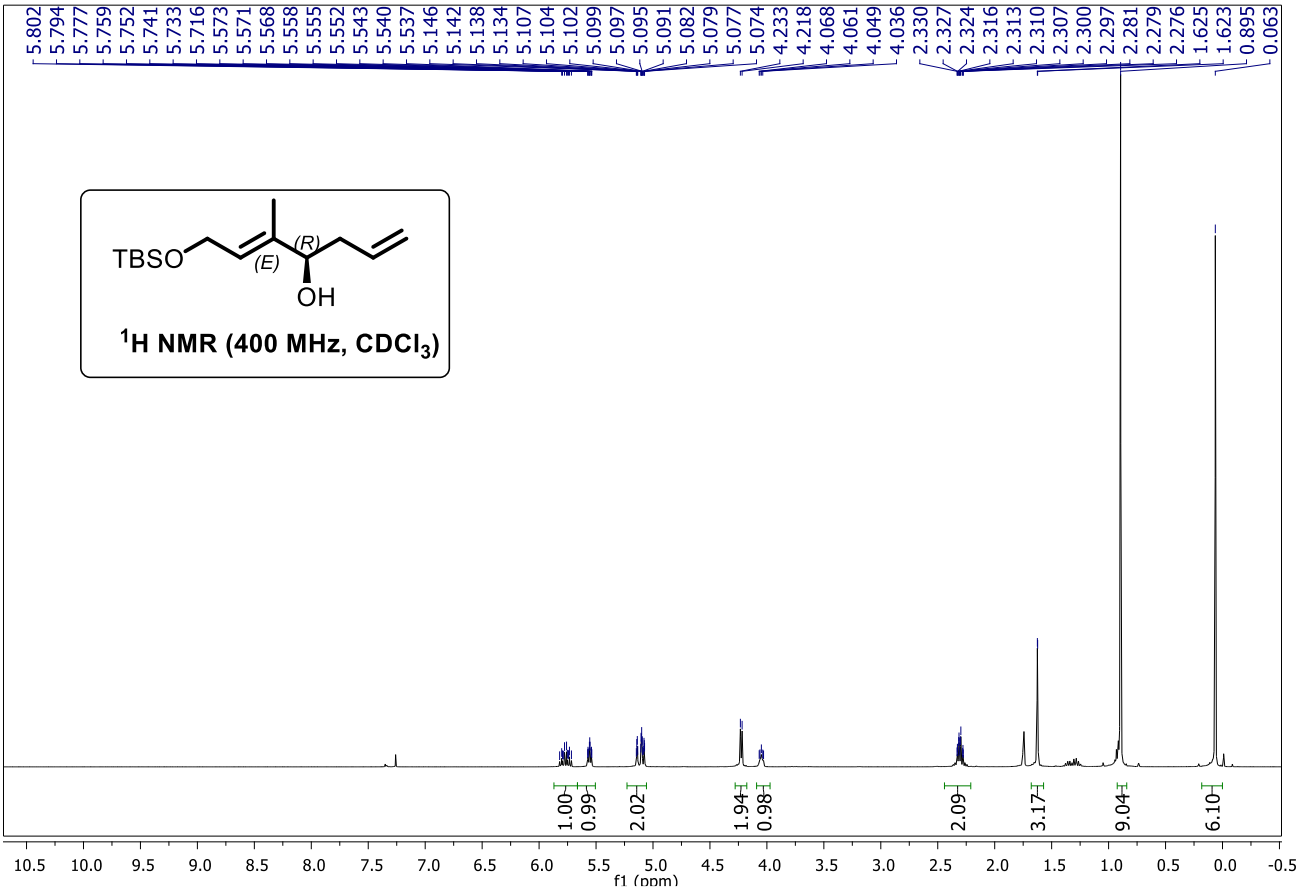


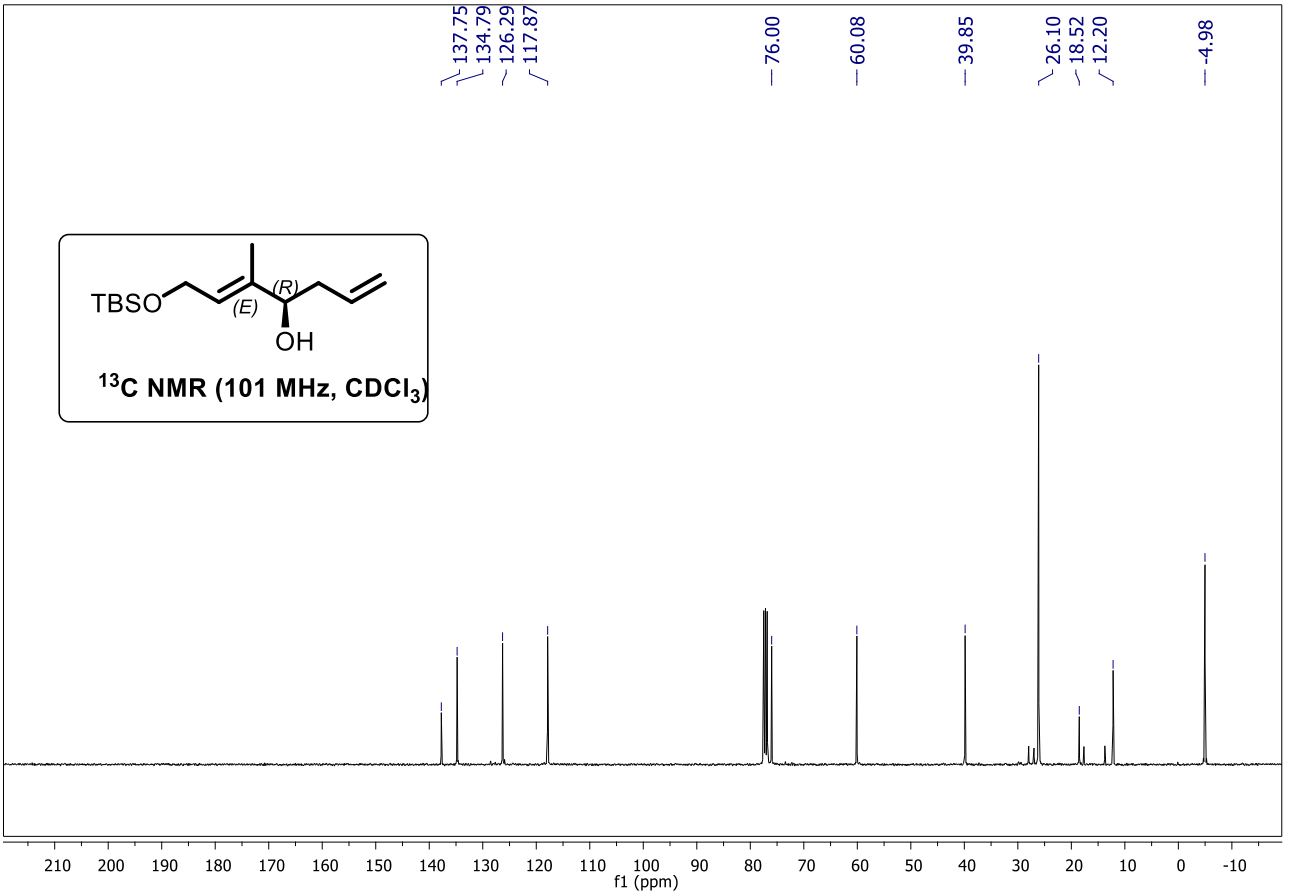
(*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylbut-2-enal (23): *See procedure*



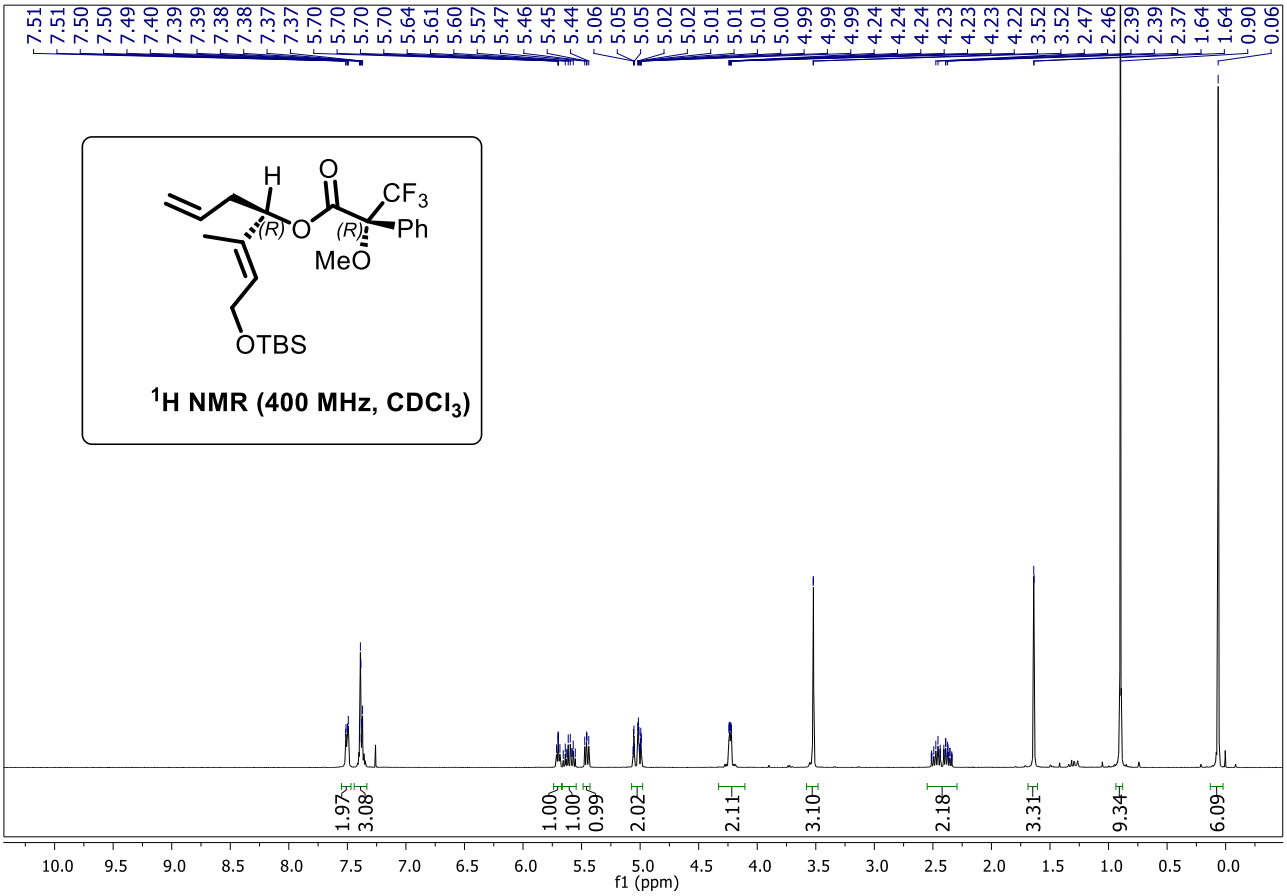


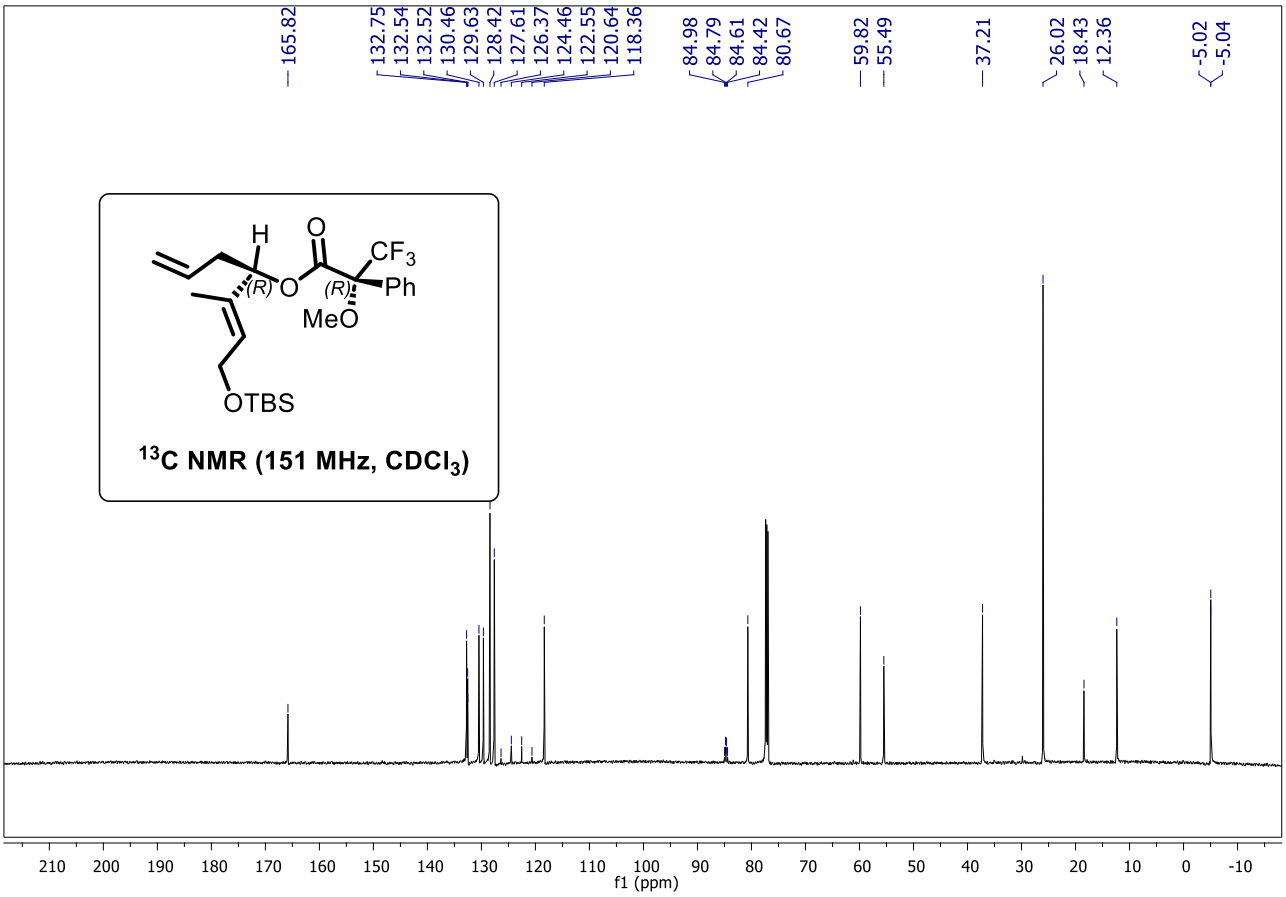
(*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-methylhepta-1,5-dien-4-ol (24): *See procedure*

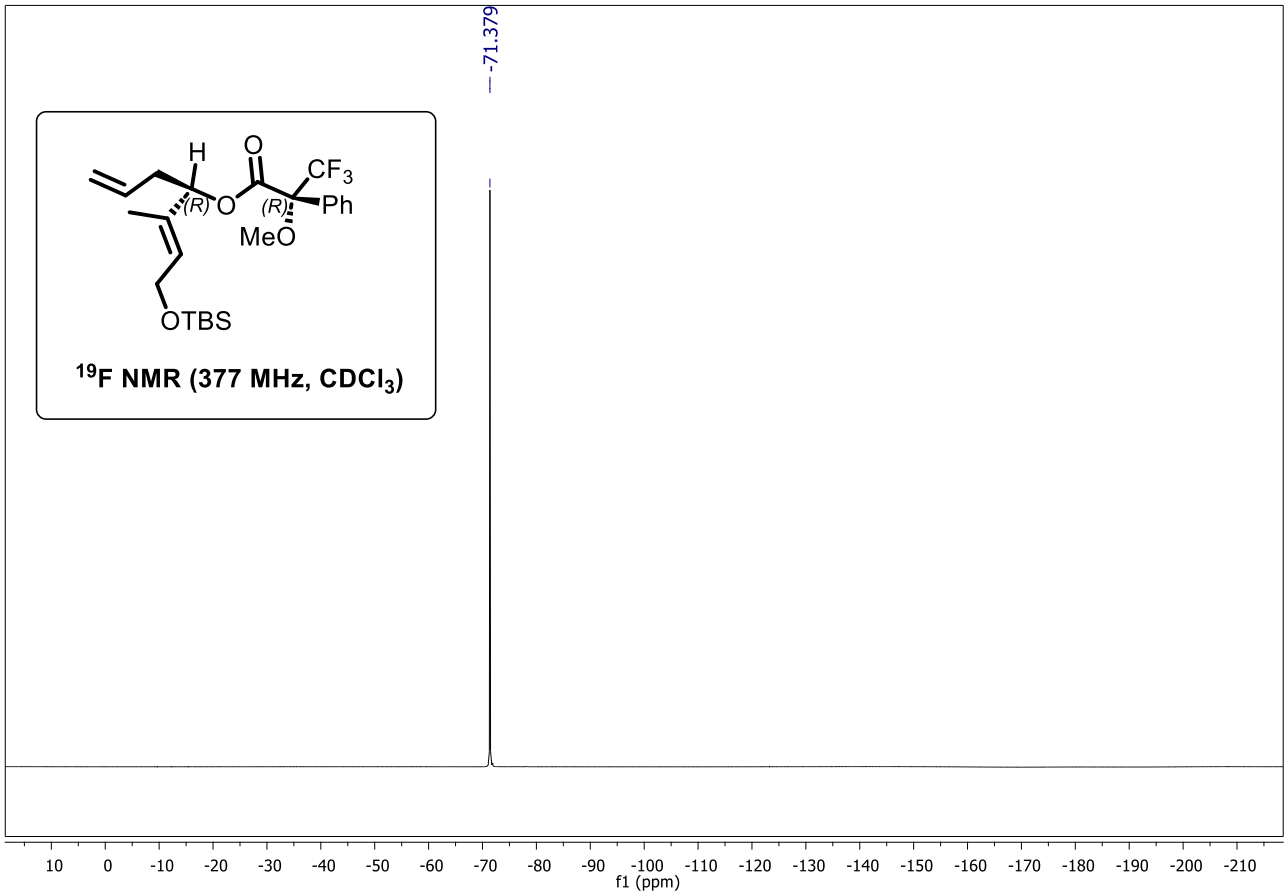




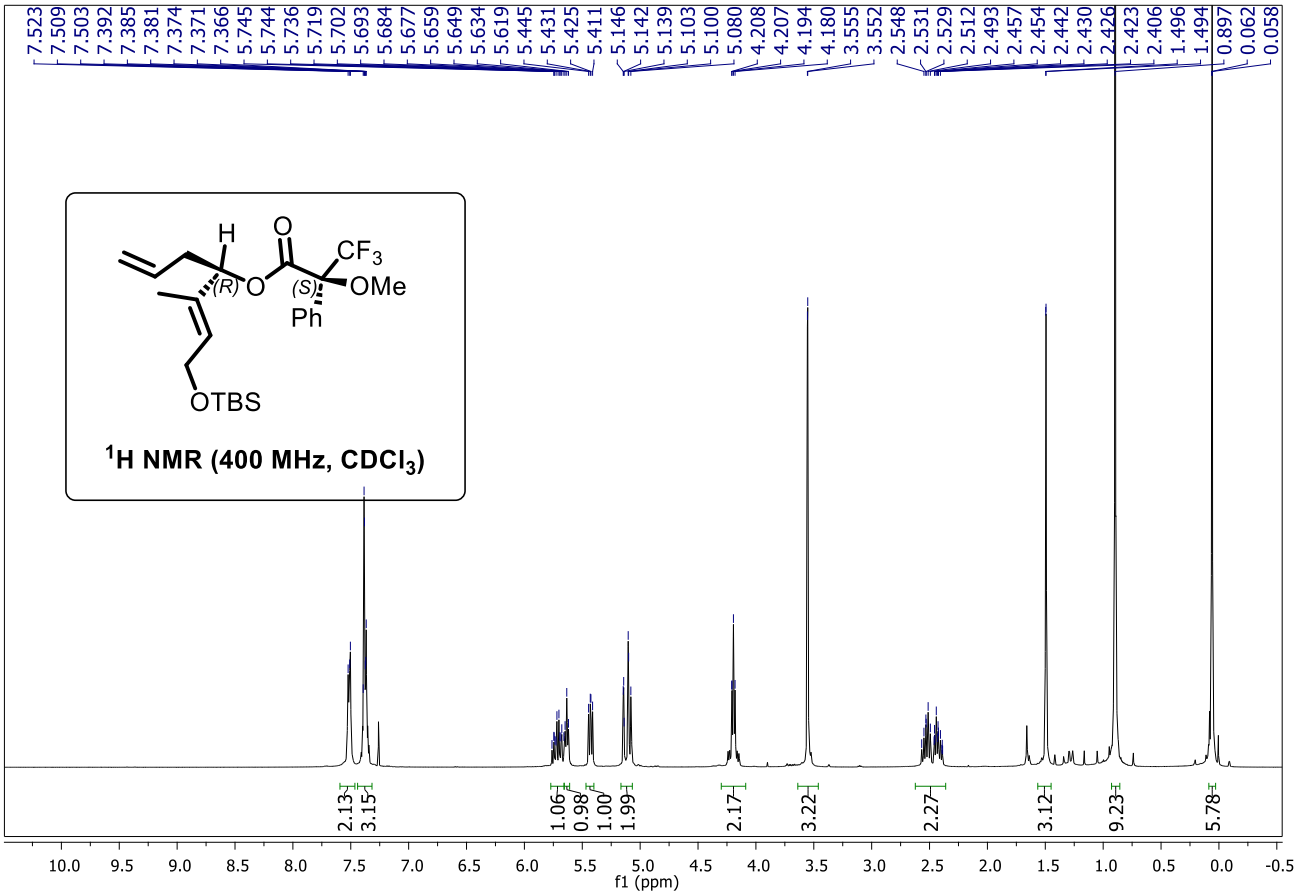
(*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-methylhepta-1,5-dien-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-12): *See procedure*

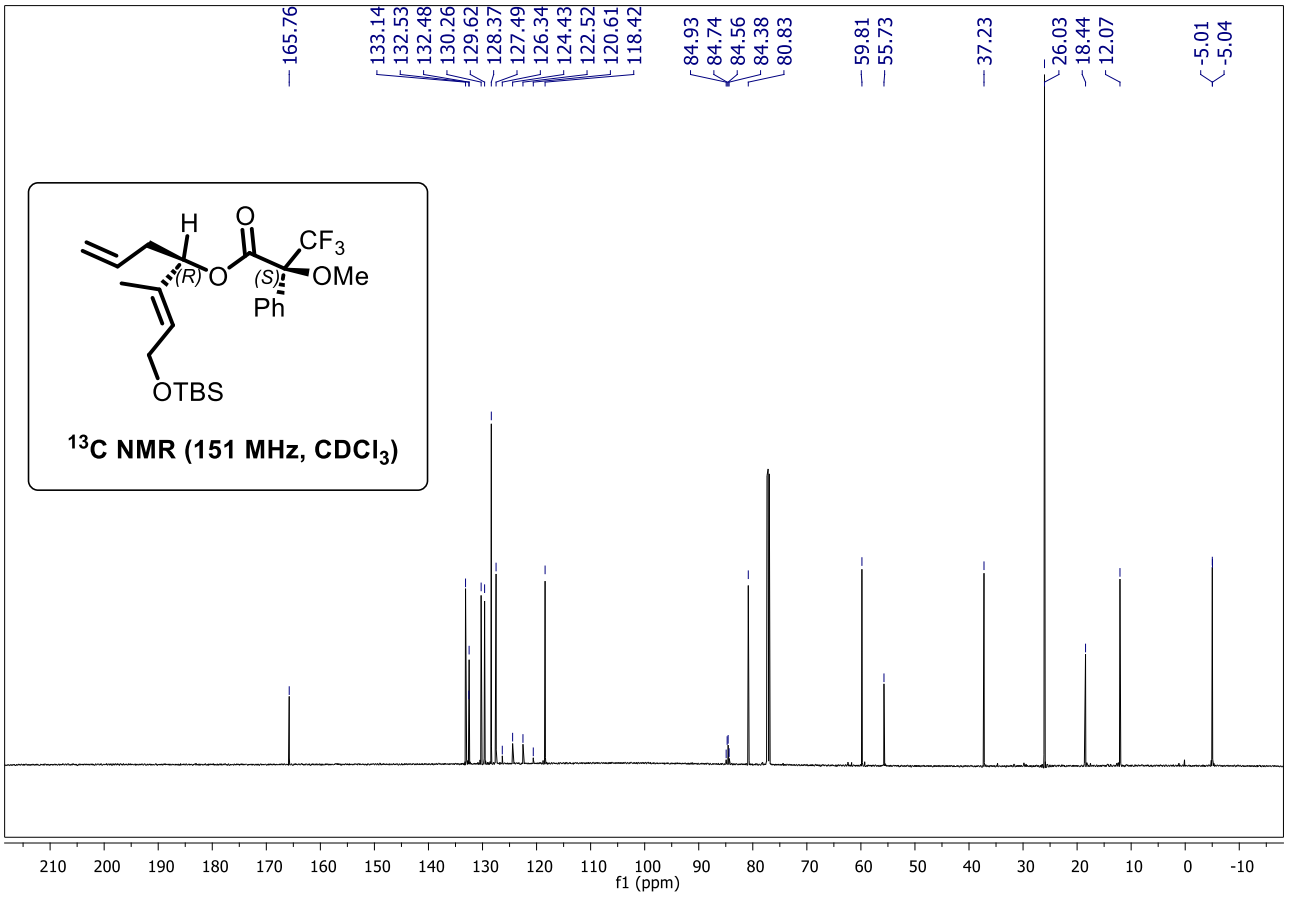






(*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-methylhepta-1,5-dien-4-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (SI-13): *See procedure*

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(R)
O
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OMe
Ph
OTBS
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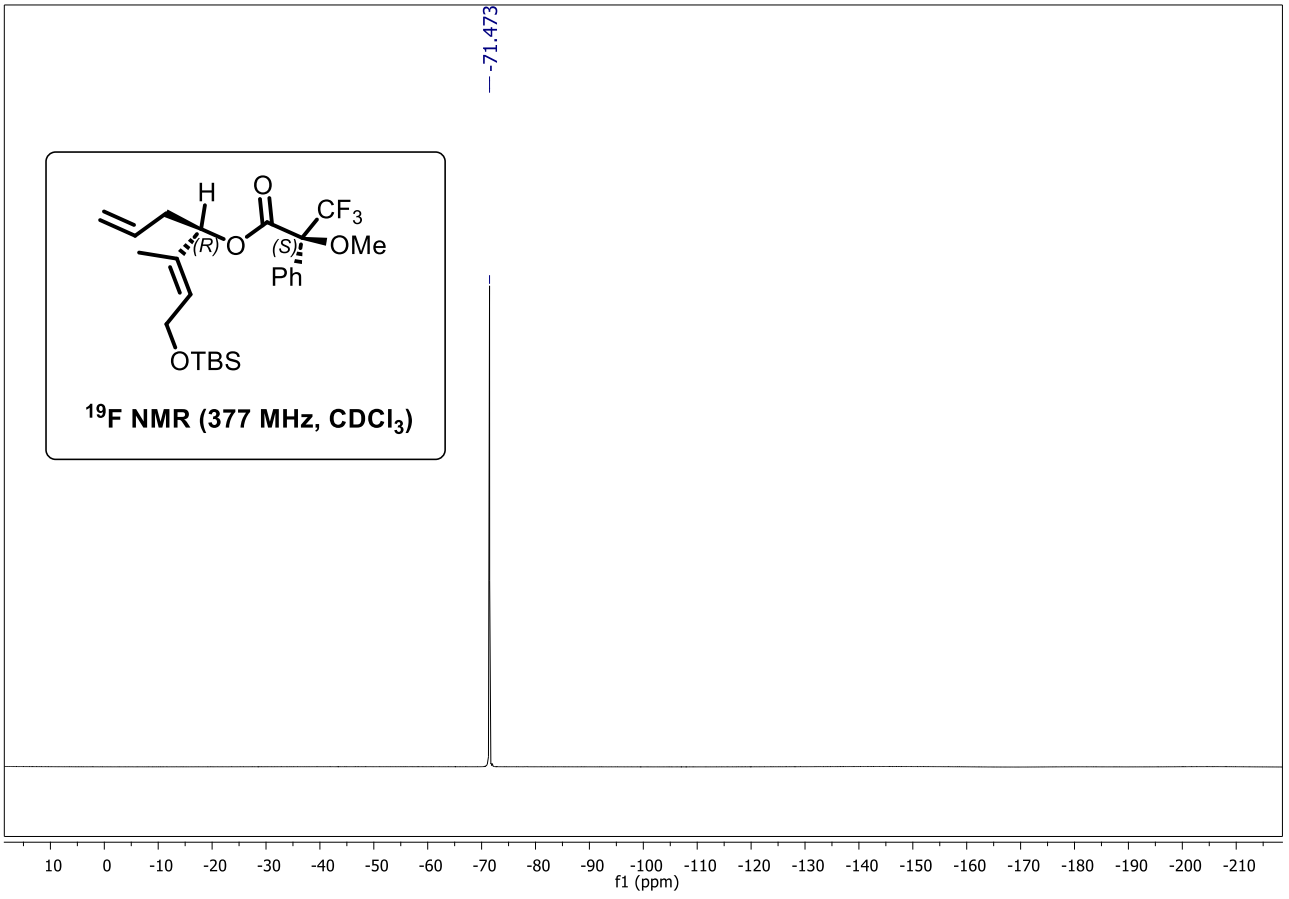
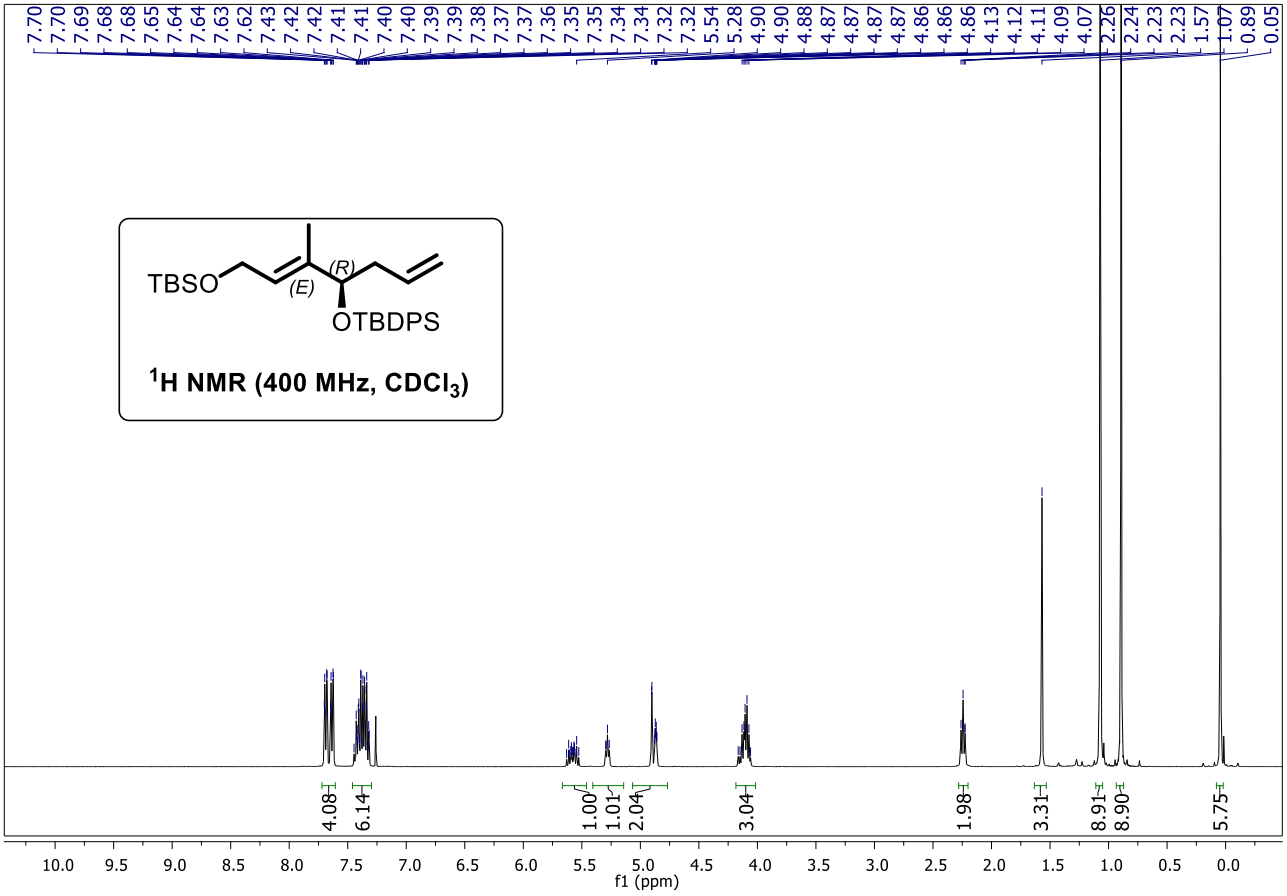
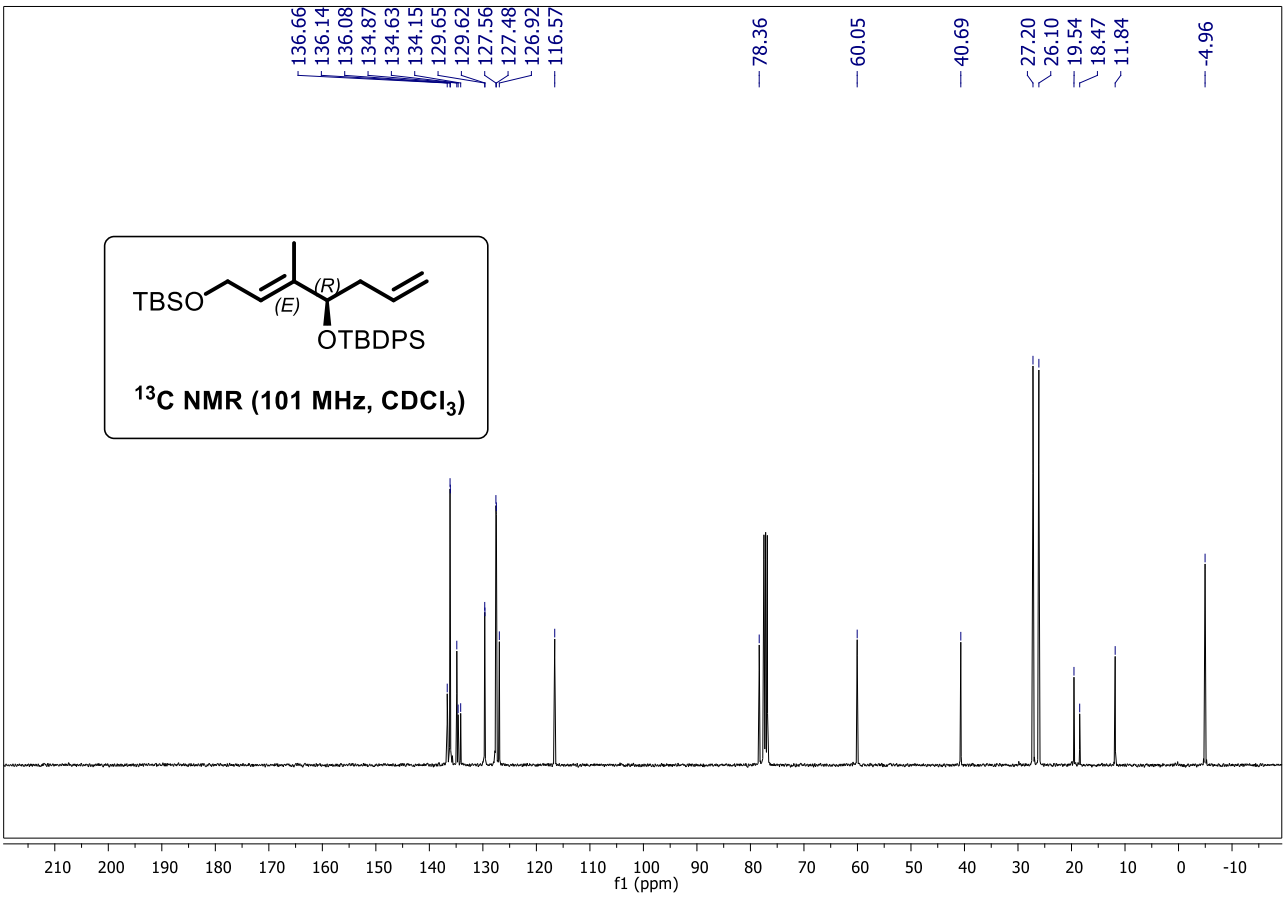
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

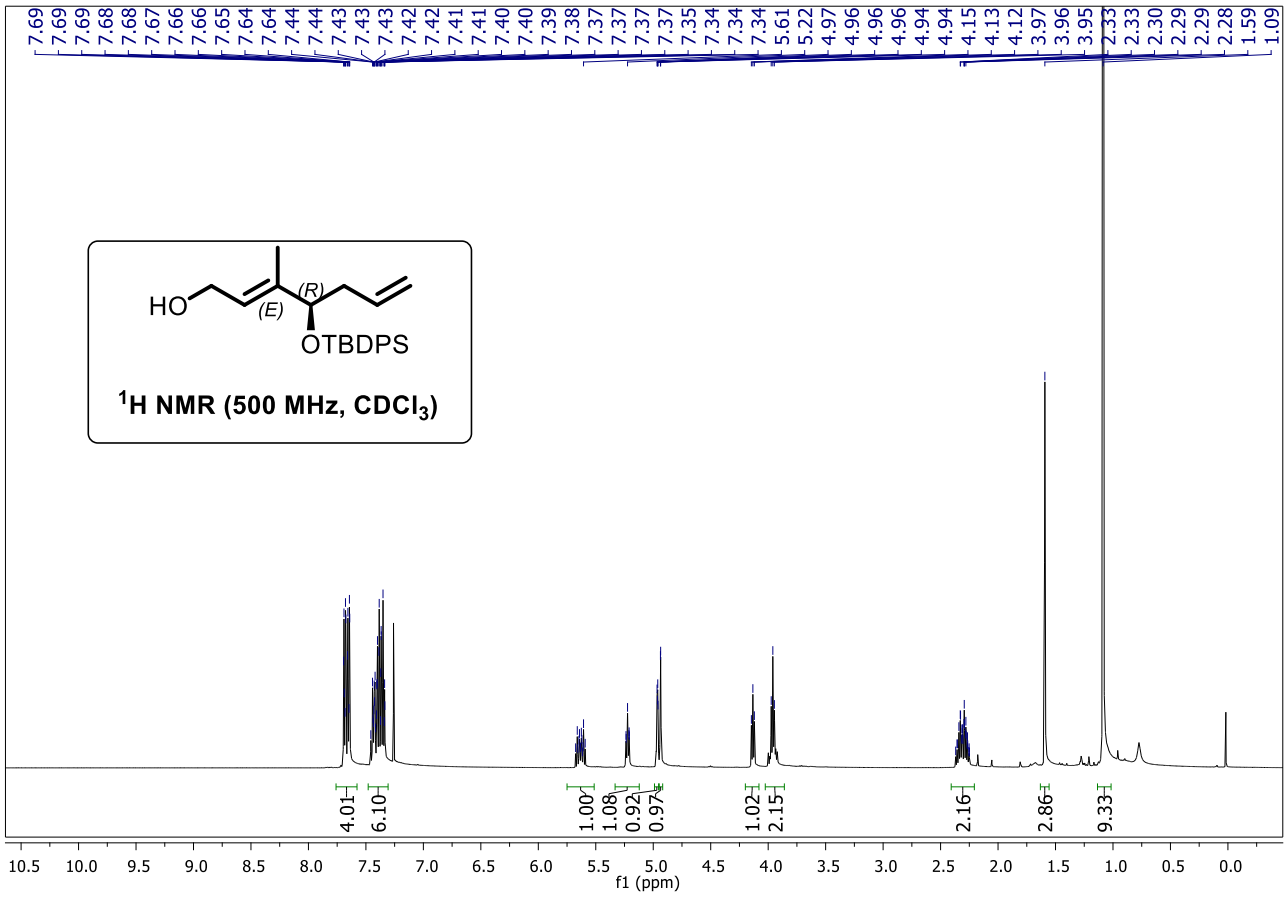

-71.473
H
O
CF3
(R)
O
(S)
OMe
Ph
OTBS
19F NMR (377 MHz, CDCl3)
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

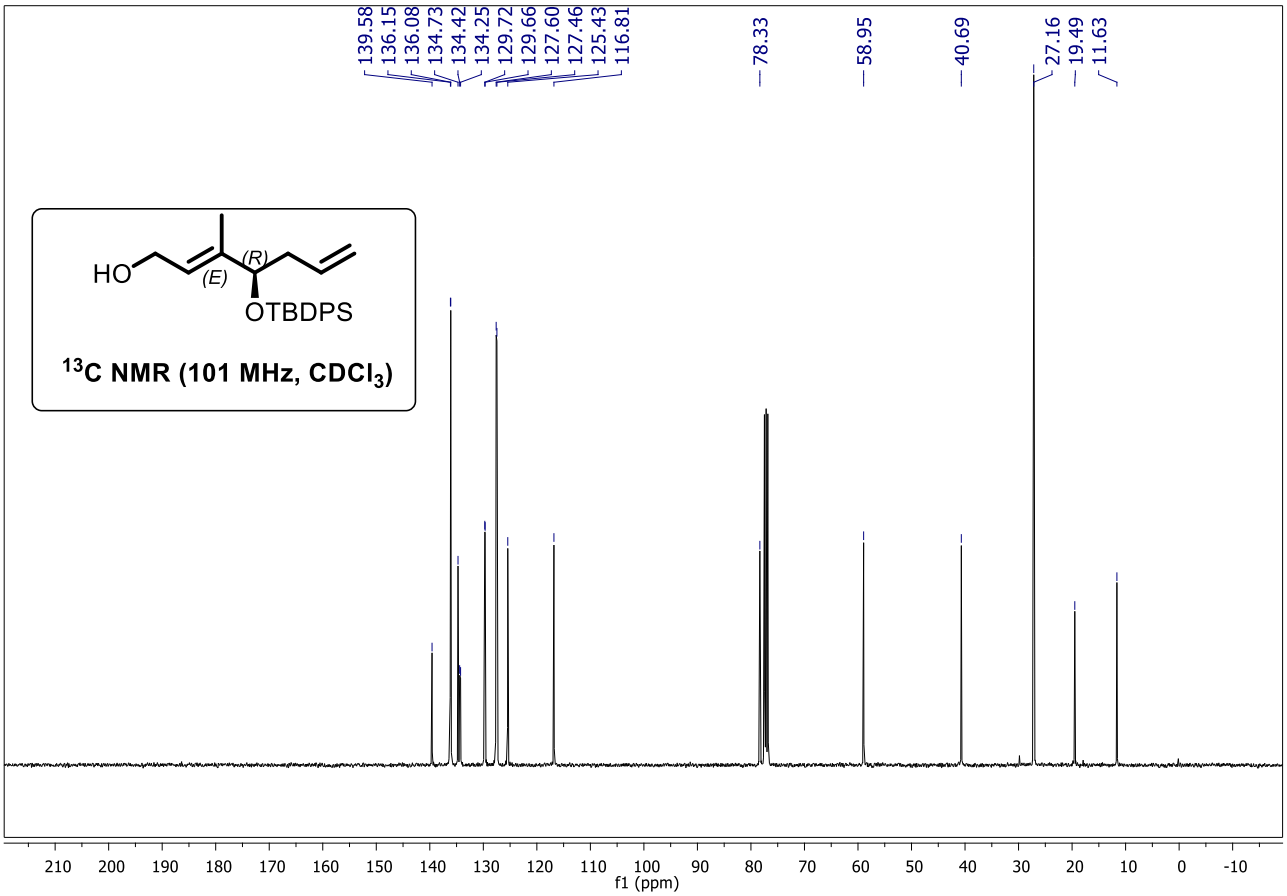
(*R*,*E*)-5-*allyl*-2,2,6,10,10,11,11-heptamethyl-3,3-diphenyl-4,9-dioxa-3,10-disiladodec-6-ene (SI-14): *See procedure*



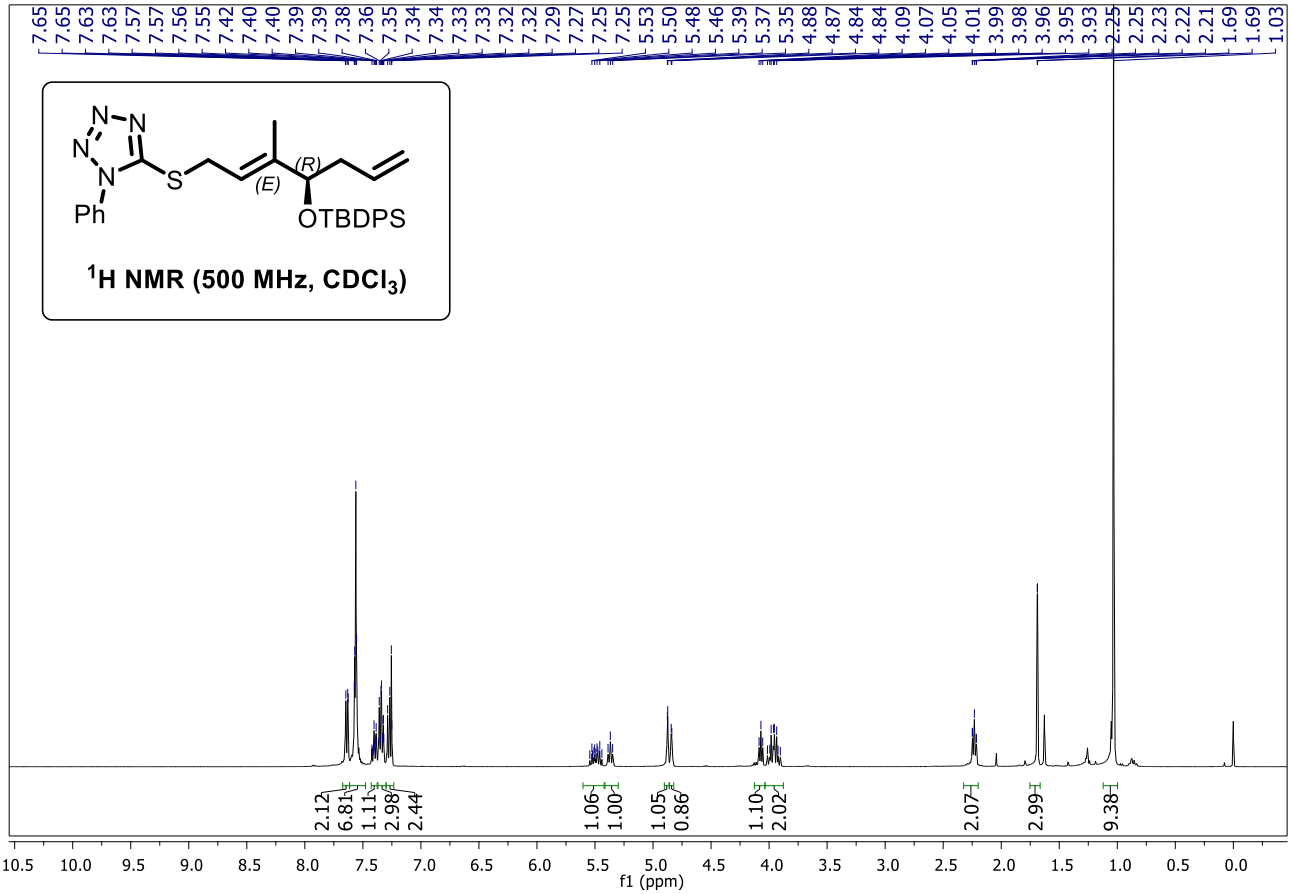


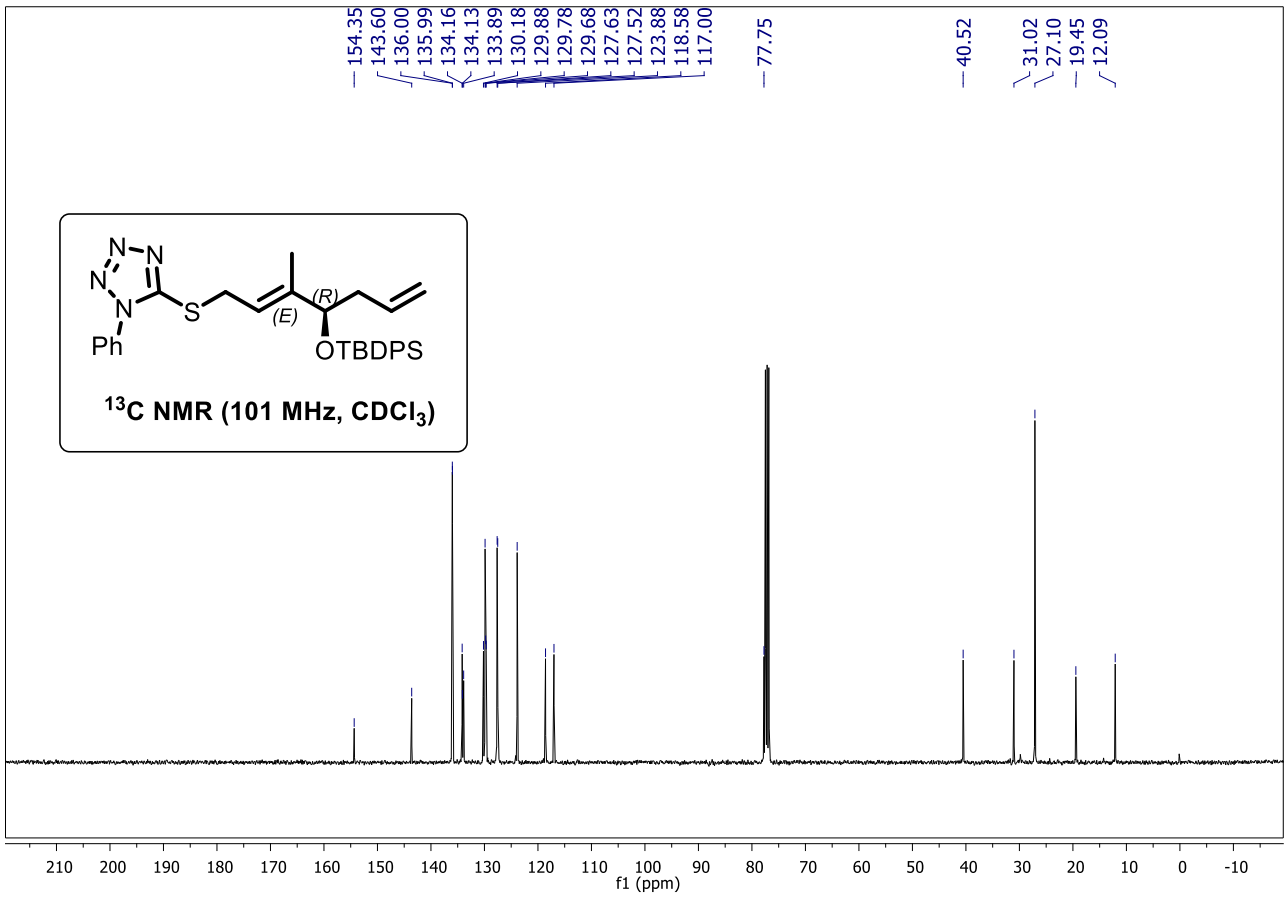
(*R*,*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylhepta-2,6-dien-1-ol (25): *See procedure*



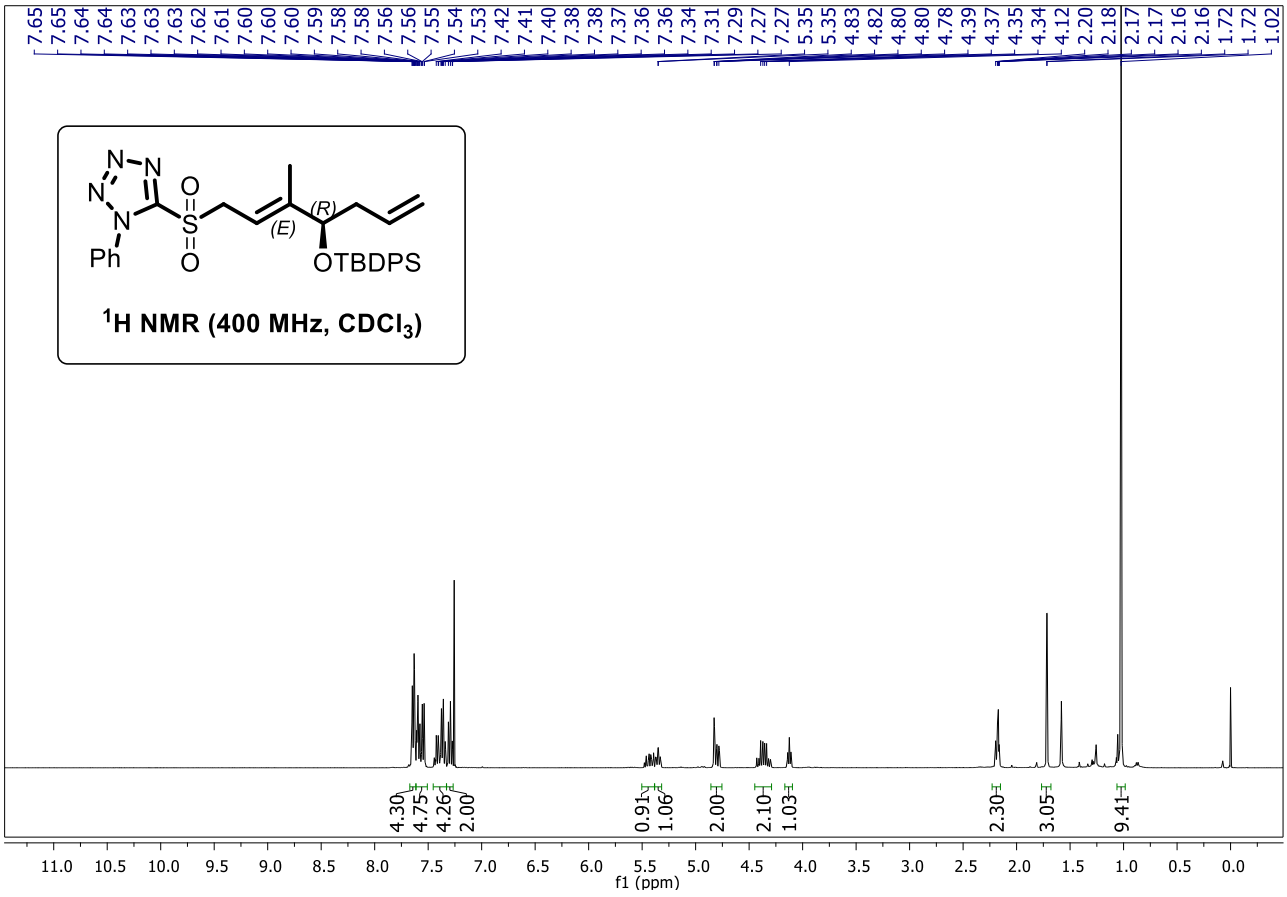


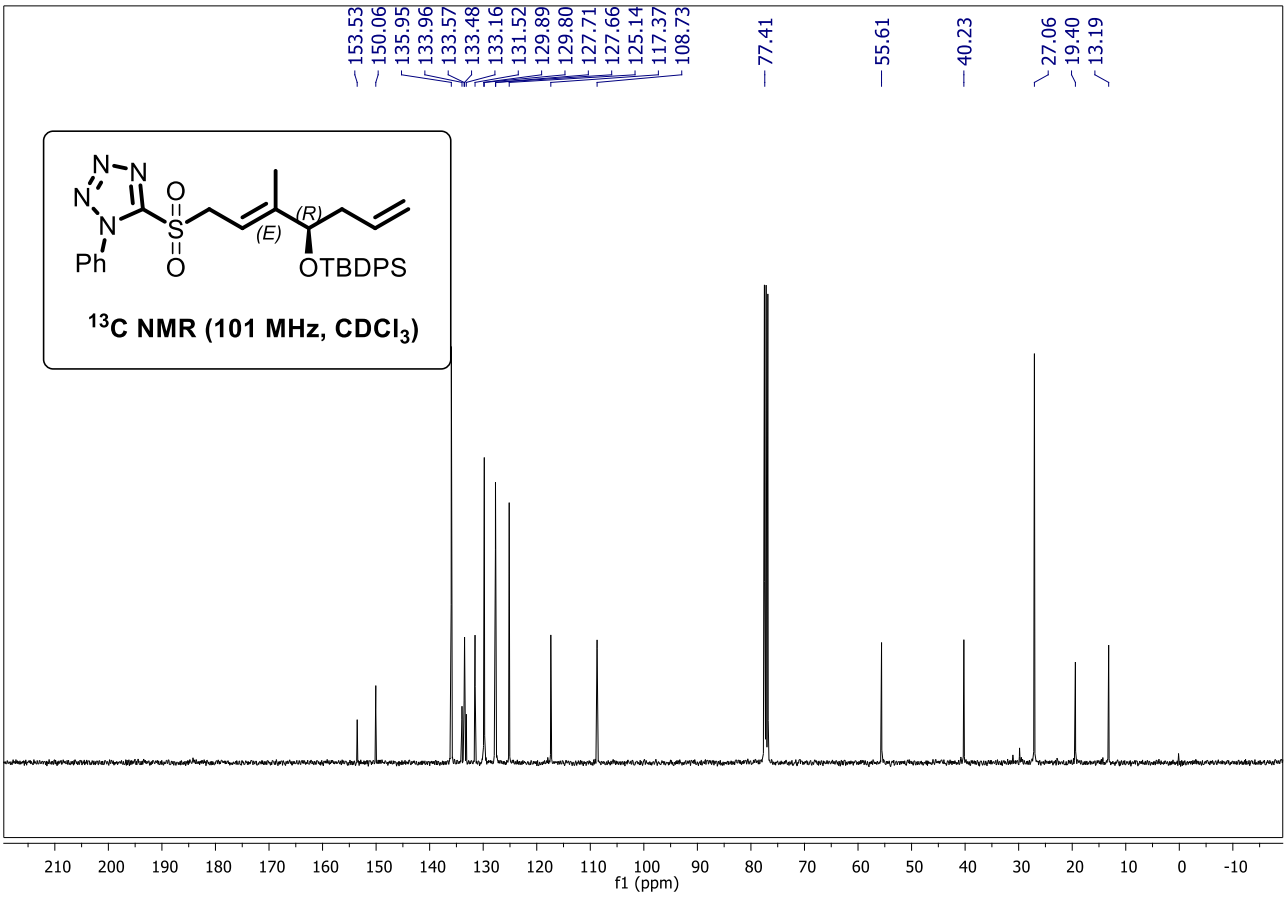
(*R*,*E*)-5-((4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylhepta-2,6-dien-1-yl)thio)-1-phenyl-1H-tetrazole (27): *See procedure*





(*R*,*E*)-5-((4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylhepta-2,6-dien-1-yl)sulfonyl)-1-phenyl-1H-tetrazole (28): *See procedure*





(*5R,6E,8E,10R,13S,15S,16R,17R*)-5-Allyl-13-((*tert*-butyldimethylsilyl)oxy)-17-(3-methoxyphenyl)-2,2,6,10,16,19,19,20,20-nonamethyl-3,3-diphenyl-15-((triethylsilyl)oxy)-4,18-dioxa-3,19-disilahenicosa-6,8-diene (29): *See procedure*