

## Single-Position Ligand Modifications Tune CB<sub>2</sub>R Activity by Targeting the Toggle Switch

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# SUPPORTING INFORMATION

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## **TR-FRET CB<sub>1</sub> and CB<sub>2</sub>R Binding Assays**

### **General**

Human embryonic kidney 293TR cells were obtained from ThermoFisher Scientific. Unless otherwise stated, culture media, chemicals and ligands were purchased from Sigma-Aldrich. SR-144,528, and HU-308 were obtained from Tocris Bioscience (Bristol, United Kingdom). All ligands were dissolved in 100% DMSO (Sigma-Aldrich, 276855) and stored as aliquots at  $-20^{\circ}\text{C}$  until required.

### **Cell culture**

SNAP-tagged human CB<sub>1</sub> and CB<sub>2</sub> HEK293-TR cells were maintained in a humidified environment at  $37^{\circ}\text{C}$  and 5% CO<sub>2</sub> in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (FBS) containing blasticidin (5  $\mu\text{g}/\text{mL}$ ; Invitrogen) and Zeocin (20  $\mu\text{g}/\text{mL}$ ; Invitrogen). For receptor-inducible expression, cells were seeded into t175 cm<sup>2</sup> flasks, grown to 70% confluence and DMEM containing 1  $\mu\text{g}/\text{mL}$  tetracycline added. 48h later cells were labelled with SNAP-Lumi4-Tb (CisBio) and membranes prepared as described in detail below.

### **Terbium labeling of SNAP-tagged CB<sub>1</sub> and CB<sub>2</sub>R HEK293-TR cells**

Cell culture medium was removed from the t175 cm<sup>2</sup> flasks containing confluent adherent CB<sub>1</sub> and CB<sub>2</sub>R HEK293-TR cells. Cells were washed 1 $\times$  in PBS (GIBCO Carlsbad, CA) followed by 1 $\times$  Tag-lite labeling medium (LABMED, CisBio) to remove the excess cell culture media, then ten millilitre of LABMED containing 100 nM of SNAP-Lumi4-Tb was added to the flask and incubated for 1 h at  $37^{\circ}\text{C}$  under 5% CO<sub>2</sub>. Cells were washed 1 $\times$  in PBS (GIBCO Carlsbad, CA) to remove the excess of SNAP-Lumi4-Tb then detached using 5 mL of GIBCO enzyme-free Hank's-based cell dissociation buffer (GIBCO, Carlsbad, CA) and collected in a vial containing 5 mL of DMEM (Sigma-Aldrich) supplemented with 10% fetal calf serum. Cells were pelleted by centrifugation (5 min at 1500 rpm) and the pellets were frozen to  $-80^{\circ}\text{C}$ . To prepare membranes, homogenization steps were conducted at  $4^{\circ}\text{C}$  (to avoid receptor degradation). Following homogenization in ice cold buffer 10 mM HEPES containing 10 mM EDTA pH 7.4, an initial centrifugation was performed at 1200 g for 3 min to remove the nuclear fraction. Subsequent centrifugation steps were then performed as described by Borrega-Roman et al. <sup>1</sup>

### **Fluorescent ligand binding assays**

All fluorescent ligand binding experiments were conducted in white 384-well Optiplate plates, in assay binding buffer, consisting of Hanks Balanced Salt Solution (HBSS), 5 mM HEPES, 0.5% BSA, 0.02% pluronic F-127 pH 7.4 and 100  $\mu\text{M}$  GppNHp at room temperature.

### **Saturation binding assays to determine D77 equilibrium affinity**

To determine equilibrium affinity values, at least six different concentrations of fluorescent ligand were used. Increasing concentrations of fluorescent ligand were incubated with human CB<sub>2</sub>R HEK293-TR cell membranes (1  $\mu\text{g}$  per well) in assay binding buffer (final assay volume, 50  $\mu\text{L}$ ). Nonspecific binding

was determined as the amount of HTRF signal detected in the presence of rimonabant (1  $\mu\text{M}$ ) or SR-144,528 (1  $\mu\text{M}$ ) in the case of human CB<sub>1</sub>R and CB<sub>2</sub>R, respectively, and was subtracted from total binding, to calculate specific binding, meaning that  $t = 0$  was always equal to zero. The degree of fluorescent ligand bound to the receptor was assessed by TR-FRET detection. Saturation analysis was performed at equilibrium, by simultaneously fitting total and non-specific (NSB) binding data (Eq. 1) allowing the determination of fluorescent ligand binding affinity.

## **Competition binding TR-FRET assays**

To determine the affinity of CB<sub>1</sub>R and CB<sub>2</sub>R-specific ligands, we used a competition binding assay. This approach involves the simultaneous addition of both fluorescent ligand and competitor to the CB<sub>1</sub> and CB<sub>2</sub>R membrane preparations. Binding experiments were conducted in white 384-well Optiplate plates, in assay binding buffer, Hanks Balanced Salt Solution (HBSS), 5mM HEPES, 0.5% BSA, 0.02% pluronic F-127 pH 7.4, and 100  $\mu\text{M}$  GppNHp. HEK293 cell membranes containing the human CB<sub>1</sub>R and CB<sub>2</sub>R (1  $\mu\text{g}$  per well) were added to wells containing increasing concentrations of unlabelled ligands, and a fixed concentration of the fluorescent ligand D77 (700 nM), a concentration approximately 2-3x its  $K_d$  in 50  $\mu\text{L}$  of assay buffer in a 384-well plate incubated at room temperature with orbital mixing. The degree of fluorescent ligand bound to the receptor was assessed at multiple time points by HTRF detection.

The equilibrium affinity of D77 plus those of unlabeled compounds were determined following an incubation period of 3h. Nonspecific binding was determined as the amount of HTRF signal detected in the presence of (rimonabant, 1  $\mu\text{M}$ ) or (SR-144,528, 1  $\mu\text{M}$ ) in the case of human CB<sub>1</sub>R and CB<sub>2</sub>R respectively, and was subtracted from total binding, to calculate specific binding. Data were normalized to the specific binding of the tracer D77 in the absence of test compounds, which was set as 100% (maximum binding).  $\text{IC}_{50}$  and  $K_i$  values obtained from competition binding assays were determined by fitting the data to a four-parameter logistic Hill equation (Eq. 2) and applying the Cheng and Prusoff correction.

## **In vitro functional assays**

### **Homogeneous Time Resolved Fluorescence (HTRF) assays**

The HTRF cAMP assay was performed as previously described.<sup>2</sup> Briefly, CHO cells stably overexpressing the CB<sub>2</sub> receptor were cultured in Ham's F12 medium supplemented with 10% fetal bovine serum, 100 U/mL penicillin, 100  $\mu\text{g}/\text{mL}$  streptomycin, and 400  $\mu\text{g}/\text{mL}$  Geneticin Selective Antibiotic (G418 Sulfate). For compound testing, cells were harvested using Cell Dissociation Buffer and resuspended in F-12K medium at a density of  $0.4 \times 10^6$  cells/mL. Subsequently, 5  $\mu\text{L}$  of cell suspension (2000 cells/well) was dispensed into 384-well low-volume plates. The cells were then stimulated with test compounds diluted in Stimulation Buffer (2.5  $\mu\text{L}/\text{well}$ ) for 15 min at room

temperature, followed by the addition of 2.5  $\mu\text{L}$  of 25  $\mu\text{M}$  forskolin. After an additional 15 min incubation, the reactions were terminated by adding 5  $\mu\text{L}$ /well of cAMP-d2 conjugate working solution, followed by 5  $\mu\text{L}$ /well of anti-cAMP cryptate working solution. Following a 1 h incubation at room temperature, time-resolved fluorescence resonance energy transfer was measured using a PerkinElmer EnVision plate reader (excitation: 620 nm; emission: 665 nm). Data were analyzed by plotting the HTRF ratio ((Signal 665 nm/Signal 620 nm)  $\times$  104) against compound concentrations using Prism 8.1 (GraphPad Software).

### **Mini-G<sub>i</sub> and $\beta$ -arrestin recruitment assays**

HEK293TR SNAP-CB<sub>2</sub>R-nLuc cells expressing either a fluorescently labelled (Venus) mG<sub>i</sub> or  $\beta$ -arrestin protein were maintained in a humidified environment at 37 °C and 5% CO<sub>2</sub> in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (FBS) containing blasticidin (5  $\mu\text{g}/\text{mL}$ ; Invitrogen), Zeocin (20  $\mu\text{g}/\text{mL}$ ; Invitrogen) and G418 (0.2mg/mL; Invitrogen) and used to assess either compound stimulated mG<sub>i</sub> or  $\beta$ -arrestin recruitment to the human CB<sub>2</sub>R. Cultured cells were harvested upon reaching 70% confluency and plated at a seeding density of 50,000 cells per well. The cells were grown for 48h until they reached confluency and then stimulated with 1  $\mu\text{g}/\text{mL}$  tetracycline for a further 48h to induce CB<sub>2</sub>R expression. Cell culture media was then aspirated from the wells and the cells were washed with assay buffer, 100  $\mu\text{L}/\text{well}$  HBSS containing 0.5% BSA and 5 mM HEPES. Following the wash, assay buffer containing 10  $\mu\text{M}$  furimazine, 99  $\mu\text{L}/\text{well}$  was added to the wells. The plate was then incubated at 37°C for 15 minutes to allow the nanoLuc substrate furimazine to enter the cells. Three BRET cycles of 1-minute intervals were performed to assess basal BRET levels, following which 1  $\mu\text{L}$  of each compound, diluted in DMSO was added to the assay plate, which was read at 1-minute intervals for 30 minutes.

Compounds included serial dilutions of the synthetic CB<sub>2</sub>R agonists CP-55,950, HU-308 and the novel HU-308-based agonists. DMSO (1% final) served as the vehicle control and 1  $\mu\text{M}$  CP-55,950 was the positive control to which all responses were normalised.

### **G<sub>i</sub>CASE assay**

The development of the membrane-based G<sub>i</sub>-CASE biosensor assay for profiling compounds at cannabinoid receptors has been described previously in the publication by Scott-Dennis et al.<sup>3</sup> The assay buffer used to profile compounds in the CB<sub>2</sub>R G<sub>i</sub>-CASE system consisted of HBSS containing 0.02% pluronic F127, 0.5% BSA and 5 mM HEPES. The reference compounds CP-55,950, HU-308, SR-144,528 and the test compounds were initially diluted in DMSO in a 96-well polypropylene plate. CB<sub>2</sub>R membranes containing the G<sub>i</sub>-CASE biosensor were thawed and added into assay buffer containing 50  $\mu\text{M}$  furimazine. Membranes (49.5  $\mu\text{L}$ ) were added to a white 384 well Optiplat<sup>TM</sup> (PerkinElmer) at a final concentration of 5  $\mu\text{g}/\text{well}$ . After 5 cycles (each of 1 min duration) 0.5  $\mu\text{L}$  of reference and test compound serial dilutions were then added to the plate, the total assay volume was 50  $\mu\text{L}$ . The assay plates were read using a BMG Pherastar FSX reader at 28 °C.<sup>4</sup> The duration of data collection on the

PERAstar FSX using the BRET1 plus module (535-30LP/475-30BP), was 60 minutes at 1-minute intervals (60 cycles).

## Signal detection and data analysis

For fluorescent ligand-binding assays signal detection was performed on a Pherastar FSX (BMG Labtech, Offenburg, Germany). The terbium donor was always excited with four laser flashes at a wavelength of 337 nm. TR-FRET signals were collected at both 520 nm (acceptor) and 620 nm (donor surrogate), when using the green NBD fluorescent ligand D77. TR-FRET ratios were obtained by dividing the acceptor signal by the donor signal and multiplying this value by 10,000.

Steady state CB<sub>1</sub>R and CB<sub>2</sub>R saturation binding data were analysed using GraphPad Prism 10.0 by non-linear regression according to a one-site equation by globally fitting total and NSB. Individual estimates for the fluorescent ligand dissociation constant ( $K_d$ ) were calculated using the following equations where L is the fluorescent ligand concentration:

$$\begin{aligned} \text{Total binding} &= \text{Specific} + \text{NSB} = (\text{Bmax} * [\text{L}] / (\text{Kd} + [\text{L}]) + \text{slope} * [\text{L}] + \text{Background} \\ \text{NSB} &= \text{slope} * [\text{L}] + \text{Background} \end{aligned} \quad (\text{Eq. 1})$$

Fitting the total and NSB data sets globally (simultaneously), sharing the value of slope, provides one best-fit value for both the  $K_d$  and the  $B_{\text{max}}$ .

Steady state CB<sub>1</sub>R and CB<sub>2</sub>R competition displacement binding data were fitted to sigmoidal (variable slope) curves using a four-parameter logistic equation:

$$Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{1 + 10^{(\log \text{IC}_{50} - X) * \text{Hillslope}}} \quad (\text{Eq. 2})$$

Where, Bottom and Top are the plateaus of the agonist and inverse agonist curves. LogIC<sub>50</sub> is the concentration of competitor that gives a half-maximal effect, and the Hillslope is the unitless slope factor or Hillslope. IC<sub>50</sub> values obtained from the inhibition curves were converted to  $K_i$  values using the method of Cheng and Prusoff.<sup>5</sup>

For *in-vitro* CB<sub>2</sub>R functional assays signal detection was performed on a Pherastar FSX (BMG Labtech, Offenburg, Germany). The raw data from all experiments were converted to the ratio of BRET 1 (535-30LP/475-30BP). The data were then transferred to GraphPad PRISM 10. Characterisation of agonist CB<sub>2</sub>R responses was achieved by selecting the concentration-response data from membranes at fixed time points which produced maximal responses to the ligands under test.

The selected data was normalized and expressed as the change in the BRET signal relative to the addition of vehicle. The graphs were plotted from the normalized data using sigmoidal dose-response (variable slope) or four-parameter logistic equation:

$$Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{1 + 10^{(\log \text{EC}_{50} - X) * \text{Hillslope}}} \quad (\text{Eq 3})$$

Where, Bottom and Top are the plateaus of the agonist and inverse agonist curves. LogEC<sub>50</sub> is the concentration of agonist/inverse agonist that gives a half-maximal effect and the HillSlope is the unitless slope factor or Hill slope.

To determine the relative effectiveness of the compounds to activate the different signaling pathways, the difference between the log(E<sub>max</sub>/EC<sub>50</sub>) values was calculated. Analysis was performed as described previously<sup>6,7</sup> to determine Δlog(E<sub>max</sub>/EC<sub>50</sub>) allowing the calculation of bias factors:

$$\Delta \log \left( \frac{E_{max}}{EC_{50}} \right) = \log \left( \frac{E_{maxL1}}{EC_{50L1}} \right) - \log \left( \frac{E_{maxL2}}{EC_{50L2}} \right) \quad (\text{Eq.4})$$

Where ligand 2 (L2) is the reference compound and ligand 1 (L1) is the test compound. Δlog(E<sub>max</sub>/EC<sub>50</sub>) values were determined using CP-55,940 as the reference agonist.

Using the estimates of agonist activity Δlog(E<sub>max</sub>/EC<sub>50</sub>) for test and reference agonist, pathway log bias was calculated as follows:

$$\Delta \Delta \log \left( \frac{E_{max}}{EC_{50}} \right) = \Delta \log \left( \frac{E_{max}}{EC_{50}} \right) P1 - \Delta \log \left( \frac{E_{max}}{EC_{50}} \right) P2 \quad (\text{Eq.5})$$

Where pathway 1 (P1) is mG<sub>s</sub> dependent recruitment and pathway 2 (P2) is β-arrestin2 recruitment. Bias factors were calculated by taking the antilog of the ΔΔlog(E<sub>max</sub>/EC<sub>50</sub>).

Statistical analysis of the obtained data was performed using a two-tailed Welch t-test using Prism 10.4 (GraphPad Software). The data is tabulated below (Table S1 ).

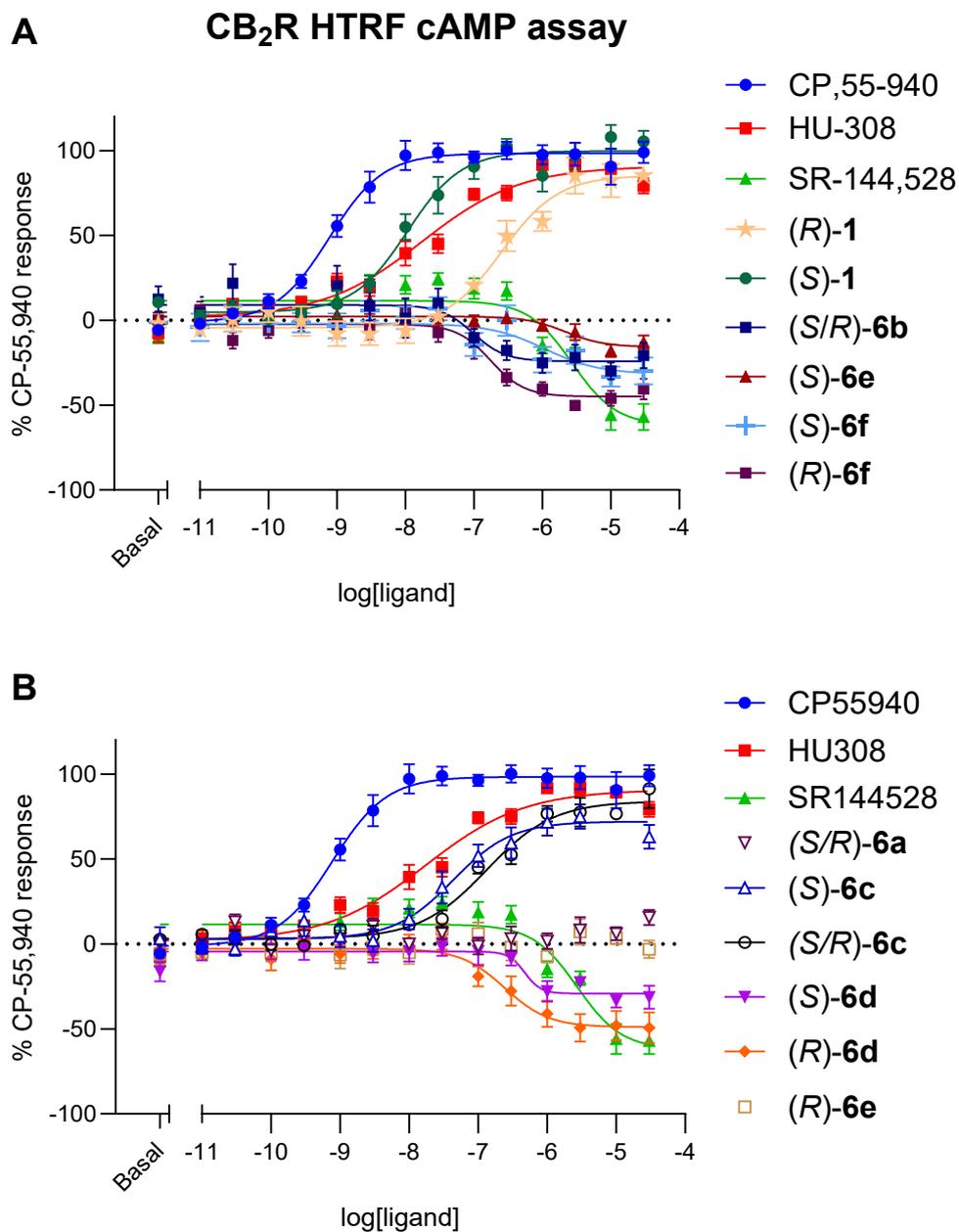
**Table S1.** Results of statistical analysis of calculated bias factors

Ligand	C(2')-R	Log Bias Factor ± SEM (BF)	N	p-value
(S)-1	CF <sub>3</sub>	0.62 ± 0.21 (4.2)	7	0.032*
(S)-6c	Et	0.65 ± 0.28 (4.5)	8	0.064+
(S/R)-6c	Et	0.68 ± 0.20(4.7)	6	0.020*
HU-308	-	0.45± 0.15 (2.8)	7	0.050*
CP55940	-	0 ± 0.14 (1)	8	n/a

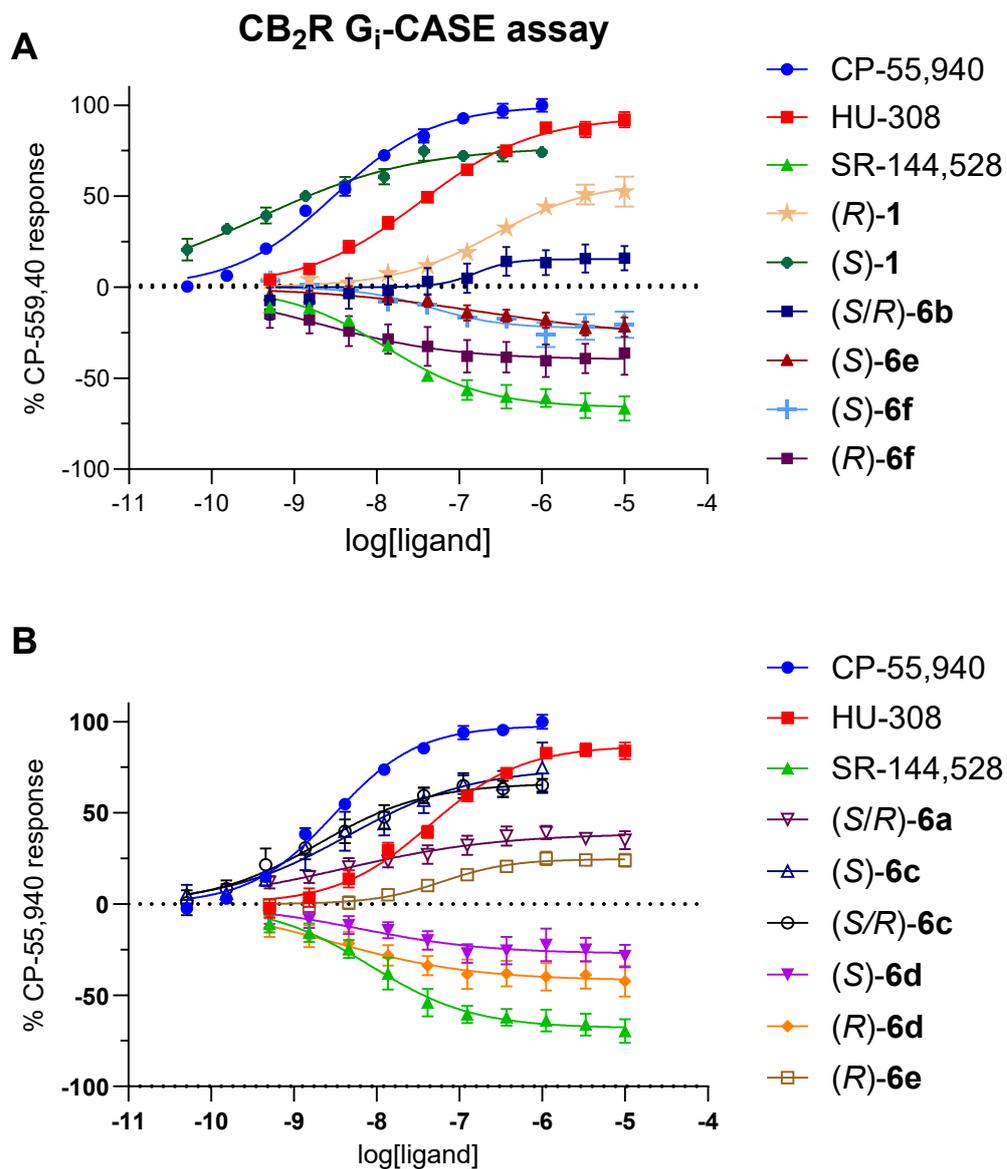
\*Significance at the 5% level; +significance at the 10% level.

**Note:** (S)-6c did not cross the significance threshold for significance at the 5% level, however, as p ((S)-6c) < 0.1 we attribute a trend towards bias for this compound.

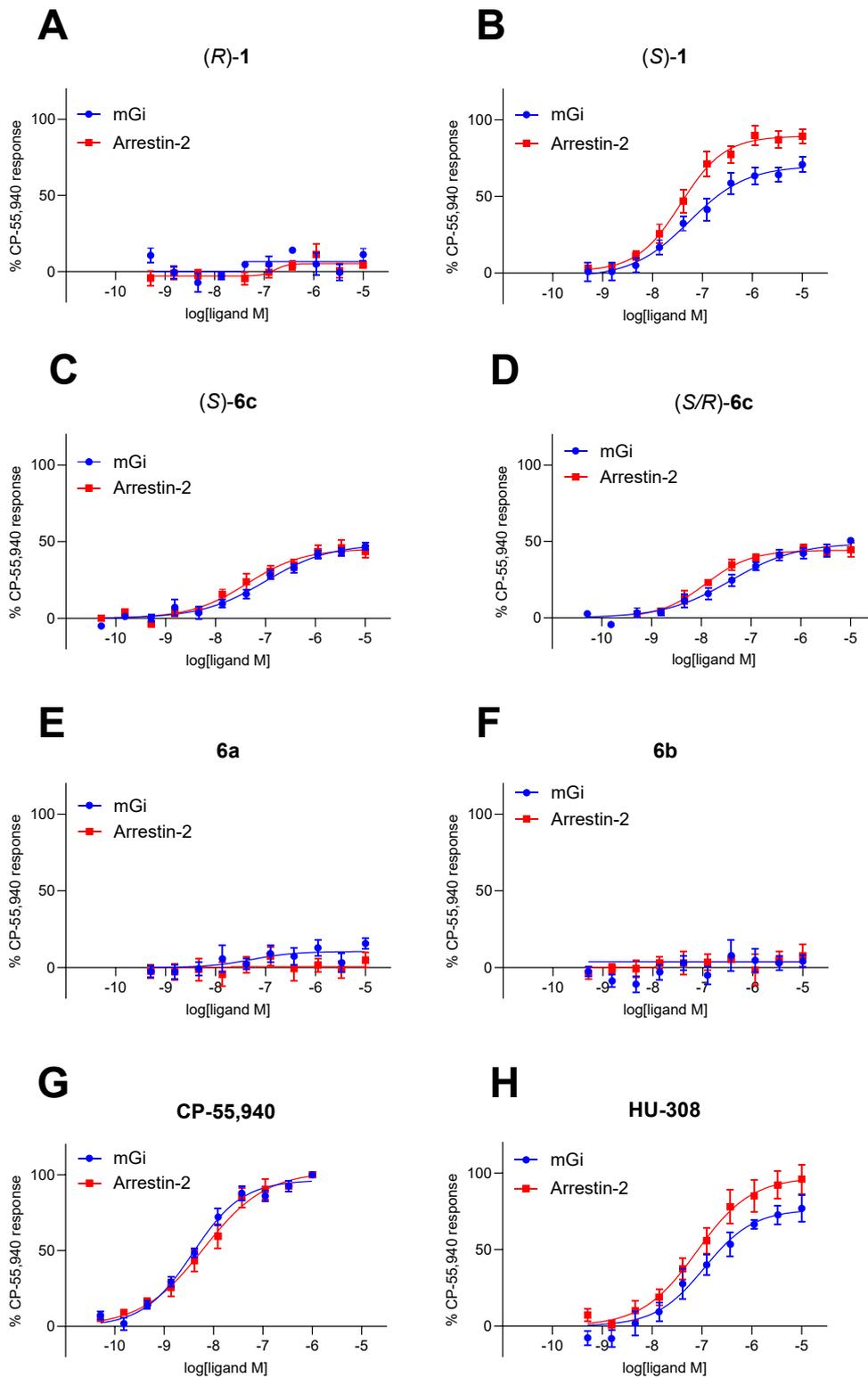
## Supplementary figures for in vitro assays



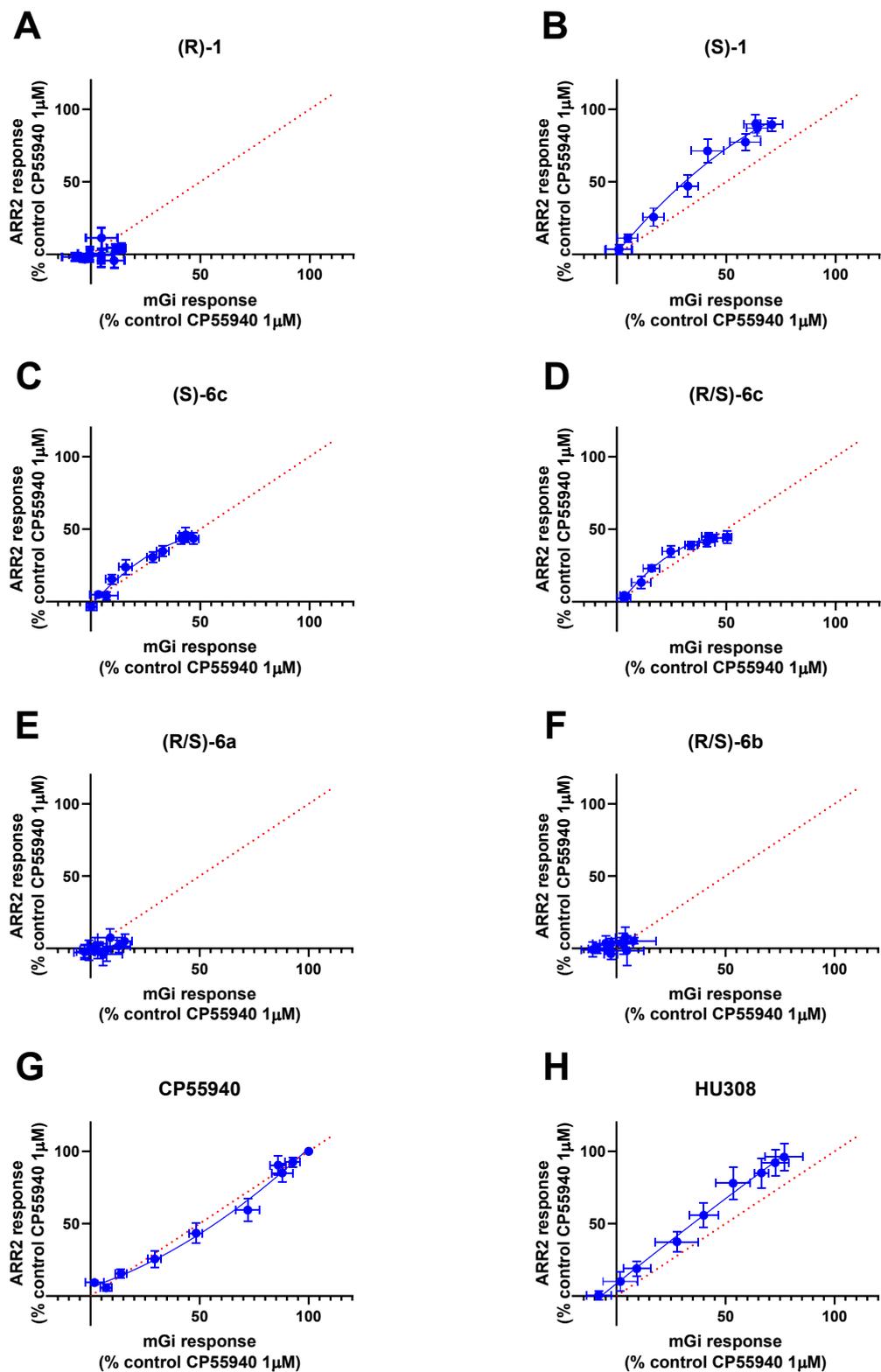
**Figure S1.** Visualized data from HTRF cAMP assay using hCB<sub>2</sub>R-CHO cells. Comparable spectrum of response to G<sub>i</sub>-CASE assay: (A) corresponds to Figure S2 A and (B) corresponds to Figure S2 B. Data were normalized to agonist CP-55,940 response (100%) and basal level (0%). Data shown as a mean,  $N = 3-4$  ( $\pm$ SD).



**Figure S2.** Visualized data from G<sub>i</sub>-CASE assay using membrane preparations from hCB<sub>2</sub>R-HEK293 T-REx cells. Comparable spectrum of response to HTRF cAMP assay: (A) corresponds to Figure S1 A and (B) corresponds to Figure S1 B. Data were normalized to agonist CP-55,940 response (100%) and basal level (0%). Data shown as a mean,  $N = 3-4(\pm SD)$ .



**Figure S3-1.** Visualized data were obtained in a mini-G<sub>i</sub> BRET and  $\beta$ -arrestin BRET assay using hCB<sub>2</sub>R-HEK293 T-Rex cells. Data were normalized to agonist CP-55,940 response (100%) and basal level (0%). Data shown as a mean, N = 6–8 ( $\pm$ SD).



**Figure S3-2.** Qualitative bias plots for BRET-based CB<sub>2</sub>R mGi and β-arrestin2 recruitment assay responses at equimolar concentrations. CB<sub>2</sub>R mGi (x-axis) and β-arrestin2 responses (y-axis) for the CB<sub>2</sub>R agonists **(A)** (R)-1, **(B)** (S)-1, **(C)** (S)-6c, **(D)** (R/S)-6c, **(E)** (R/S)-6a, **(F)** (R/S)-6b, **(G)** CP55940, and **(H)** HU308 plotted at equimolar concentrations. The BRET ratios obtained were normalized using the pathway balanced ligand CP55940 as the reference agonist (100% response). Data shown are the mean ± SEM from 3 or more experiments. A centered second-order polynomial fit of these response values in the respective assays is shown.

# Molecular Modeling and Molecular Dynamics Simulations

## Molecular docking

*Protein Preparation.* The crystal structures of the human CB<sub>2</sub> receptor were obtained from the Protein Data Bank. For docking of agonists, the active-state structure in complex with HU-308 (PDB ID: 8GUS)<sup>8</sup> was used, whereas the inactive-state structure in complex with AM10257 (PDB ID: 5ZTY)<sup>9</sup> was used for docking of inverse agonists and antagonists. Protein preparation was performed in MOE<sup>10</sup> v.2019.0102 (Chemical Computing Group, Montreal, Canada) using the QuickPrep module with the following settings: Preserve Sequence and Neutralize enabled, Use Protonate 3D for Protonation = True, Allow ASN/GLN/HIS "Flips" in Protonate3D = True, and Delete Water Molecules Farther than 4.5 Å from Ligand or Receptor = True. The receptor was tethered (Strength = 10, Buffer = 0.25) and atoms farther than 8 Å from the ligand were fixed. Hydrogens close to the ligand were not fixed. Energy minimization was performed to a root mean square (RMS) gradient of 0.1 kcal/mol/Å, with Retain QuickPrep Minimization Restraints enabled.

*Ligand Docking.* All ligands were docked using static docking, i.e., without modeling induced fit effects. Docking was carried out using GOLD<sup>11</sup> v.5.2.2 integrated into MOE v.2019.0102 with the following parameters: Efficiency = default, Score efficiency = 100, Early Termination (Number = 3, RMS = 1.5), GOLD scoring, and 30 poses per compound. No receptor flexibility was allowed during the docking procedure.

*Pose Minimization and Selection.* The top 10 docking poses of each compound were energy-minimized within the rigid binding site using MOE: We selected the top-ranked pose per ligand by GOLDScore and report the corresponding Gold.PLP.PLP value in parentheses. For the inactive CB<sub>2</sub>R structure (PDB 5ZTY), the best poses gave: p-F-phenyl 121.01 (−82.35), n-propyl 140.06 (−102.55), and phenyl 119.24 (−79.38). For the active CB<sub>2</sub>R structure (PDB 8GUS), the best poses were: ethyl 143.05 (−106.71), CF<sub>3</sub> 133.42 (−110.71), and HU-308 140.61 (−102.75). These poses correspond to Fig. 2A–F and show no obvious steric clashes.

We emphasize that docking scores are most useful within a ligand to compare alternative poses and diagnose unfavorable contacts/clashes; they should not be used to compare different ligands to each other or to infer relative binding affinities across chemotypes or receptor states

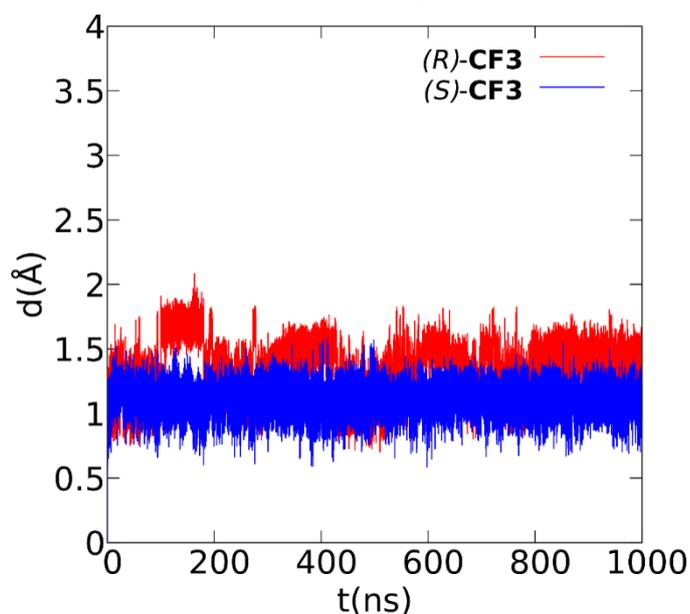
## Molecular dynamics: computational methods

Ligands were built with UCSF Chimera 1.17<sup>12</sup> followed by initial energy minimization (EM) at the molecular mechanics level, using AM1-BC charges. The molecules were then fully optimized using the GAMESS program<sup>13</sup> at the Hartree–Fock level with the STO-3G basis set and subjected to HF/6-

31G\*/STO-3G single-point calculations to derive the partial atomic charges using the RESP procedure.<sup>14, 15</sup> The complexes were completed by addition of all hydrogen atoms, and they underwent energy minimization (EM) and then molecular dynamics (MD) simulations with Amber20 pmemd.cuda module,<sup>16</sup> using the 14SB version of the AMBER force field for the protein, gaff2 for the ligand and lipid 14 force field parameter for the lipid. The inactivating mutations present in the PDB entry 5ZTY were back-mutated to wild type residues before MD simulations. The energy-minimized complexes were embedded in a pre-equilibrated palmitoyl-oleoyl-phosphatidyl-choline (POPC) lipid bilayer and solvated in an aqueous medium using the charmmgui web-interface (<http://www.charmm-gui.org>). Potassium and chloride ions were added to ensure electric neutrality and 0.15 M ionic strength. The systems underwent EM and MD simulations following a previously-published.<sup>17</sup> Production runs were carried out at least for 1  $\mu$ s. Python scripts ante-MMPBSA.py and MMPBSA.py were used to compute MM/PB(GB)SA, selecting the GBn model (igb=5).<sup>18</sup> 1000 frames were taken evenly from the last 500 ns of MD trajectories. A LCPO algorithm<sup>19</sup> was used to estimate solvent accessible area. The Cpptraj module and the UCSF Chimera 1.17 program were used to perform MD analysis and to draw the figures, respectively.

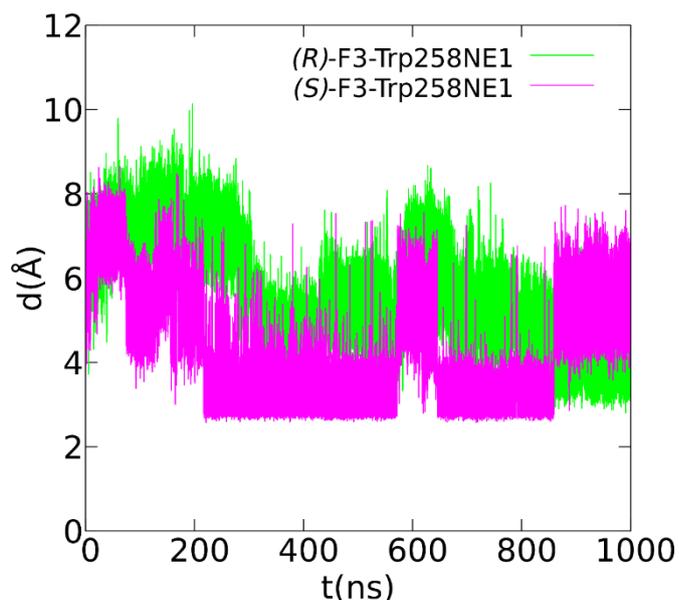
#### Molecular Dynamics simulations on (*S*)-1 and (*R*)-1 epimers

To rationalize at molecular level the experimentally observed differences at CB<sub>2</sub>R in terms of both binding affinity and functional profile (agonist vs antagonist) between (*S*)-1 and (*R*)-1 comparative study based on molecular dynamics (MD) in membrane environment was carried out, using the respective docking complexes as starting point. The X-ray structure of CB<sub>2</sub>R in the inactive form (PDB:5ZTY) was selected for the study. The rmsd (root mean square deviation) plots of the ligands after best fit of protein backbone showed that both binding poses were stable over 1  $\mu$ s (Figure S1).



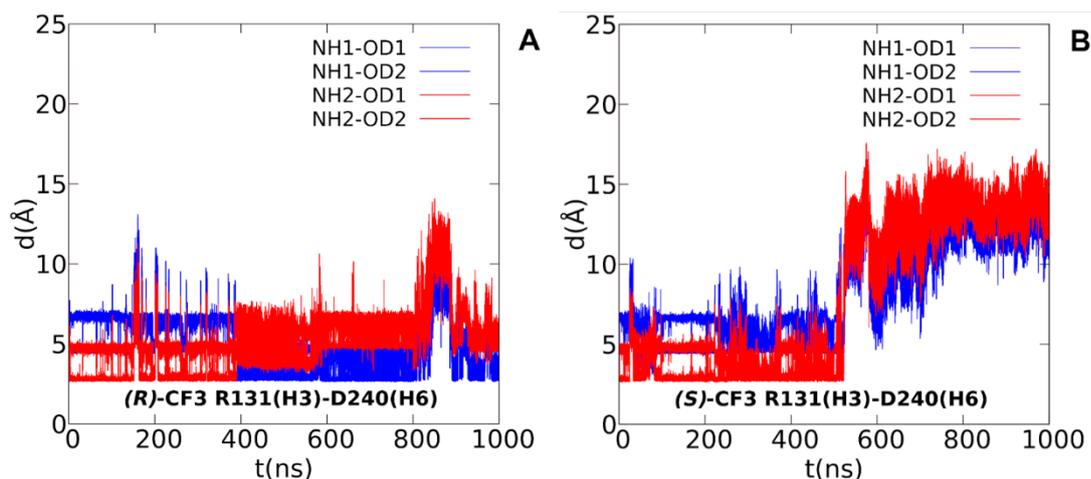
**Figure S4.** Ligand atom root-mean-square deviation (rmsd) plot calculated for CB<sub>2</sub>R with the ligand complexes, after best fit of the protein backbone atoms (except the flexible N-terminus and ICL3 loop) over 1  $\mu$ s of MD. The rmsd plot was smoothed with a five-point window running average.

Both the epimers adopt the canonical L-shaped conformation in the orthosteric binding site, with the terminal end of the dimethyl-heptyl chain hosted in a cleft formed by aromatic and polar residues such as Phe183<sup>ECL2</sup>, Tyr190<sup>5.39</sup>, Trp194<sup>5.43</sup> and Thr114<sup>3.33</sup>. The resorcinol moiety is sandwiched between Phe183<sup>ECL2</sup> and Phe87<sup>2.57</sup> while the bicyclo heptene ring is surrounded by aromatic residues (Phe183<sup>ECL2</sup>, Phe91<sup>2.61</sup> and Phe94<sup>2.64</sup>). Both compounds are involved in an H-bond between the hydroxyl group on the bicyclic moiety with His95<sup>2.65</sup> (occurrence 29% and 32% for (*S*)-**1** and (*R*)-**1**, respectively). However, looking at the pattern of interactions engaged by the CF<sub>3</sub> group within the binding site, a clear difference emerges between the two ligands. Only the (*S*)-epimer was able to form a close contact interaction with the indole NE1 atom of the Trp258<sup>6.48</sup> sidechain, which in turn promotes a reorientation of the Trp258<sup>6.48</sup> sidechain, as shown in Figure 1 in the article. This interaction is also mirrored by the shorter distance between the fluorine atoms and the Trp258<sup>6.48</sup>NE1 atom in the CB<sub>2</sub>R/(*S*)-**1** complex in comparison to the CB<sub>2</sub>R/(*R*)-**1** one over the simulated period (Figure S2). The average F-NE1 minimum distance for the (*S*)-epimer over the whole MD trajectory is 4.28 ± 0.0019 Å. The distance is ≤3.5 Å in 50.07% of MD frames. For the (*R*)-epimer the distance is 5.62 ± 0.0017 Å with 0.98% of MD frames showing a distance of ≤3.5 Å.



**Figure S5.** Minimum distance plot between the ligand fluorine atoms (Fx, x=1-3) of the (*R*)- and the (*S*)-epimers and the Trp238 NE1 atom calculated over 1 μs of MD. The plot was smoothed with a five-point window running average.

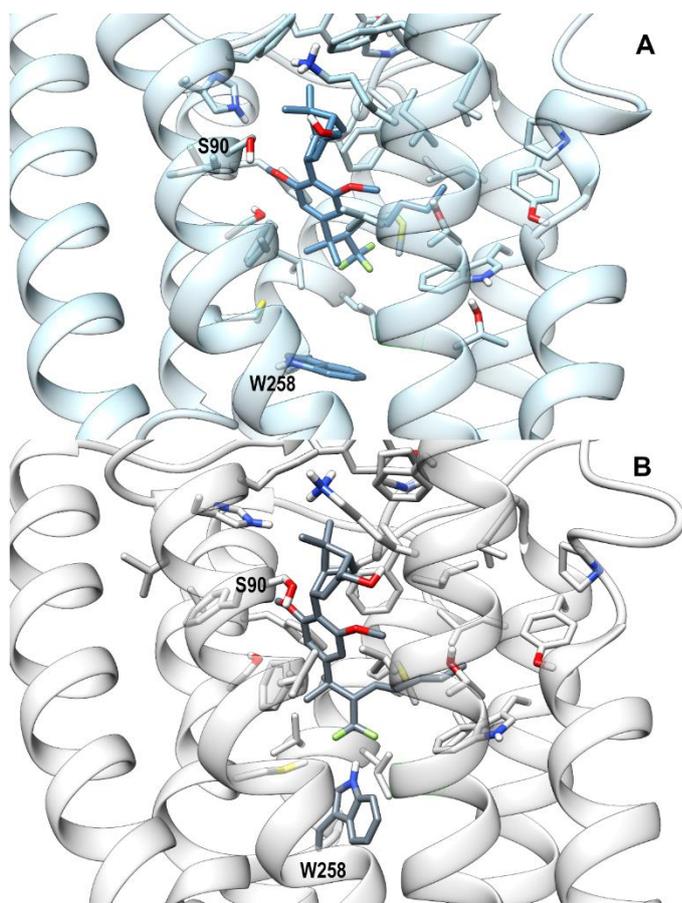
Only in the CB<sub>2</sub>R/(*S*)-**1** complex a breakage of the ionic lock between Arg131<sup>3.50</sup> and Asp240<sup>6.30</sup> is observed, suggestive of a conformational switch toward the CB<sub>2</sub>R activated form (see Figure S3).



**Figure S6.** Distance plot between the guanidine nitrogen atoms of R131<sup>3,50</sup> and the carboxylate oxygen atoms of Asp240<sup>6,30</sup> in the CB<sub>2</sub>R/(*R*)-1 (A) and CB<sub>2</sub>R/(*S*)-1 (B) complexes over 1  $\mu$ s of MD simulation. Distance plot was smoothed with a five-point window running average.

The difference in free energy of binding ( $\Delta\Delta G$ ) between the two epimers, obtained performing molecular mechanics/Poisson-Boltzmann (Generalized Born) surface area (MM/PB(GB)SA) calculations, shows that the (*S*)-epimer is more stable by 3.55 kcal mol<sup>-1</sup> (MM/GBSA) and 3.53 kcal mol<sup>-1</sup> (MM/PBSA) than the (*R*)-epimer ( $-63.00 \pm 0.46$  kcal mol<sup>-1</sup> versus  $-59.45 \pm 0.52$  (MM/GBSA) and  $-7.81 \pm 0.68$  kcal mol<sup>-1</sup> versus  $-4.28 \pm 0.64$  kcal mol<sup>-1</sup> (MM/PBSA), respectively).

To further assess the propensity of the *S*-epimer to engage in interaction with Trp258<sup>6,48</sup>, additional MD simulations on CB<sub>2</sub>R complexes were carried out using a different starting docking pose, with the bicyclic moiety rotated by  $\sim 180^\circ$  and the hydroxyl group oriented toward Ser90<sup>2,60</sup> instead of His95<sup>2,65</sup>. Also in this case the occurrence of a close contact interaction was observed in the CB<sub>2</sub>R/(*S*)-1 complex alone (Figure S4), with the relative arrangement of the resorcinol and the alkyl chain conserved in respect to the ligand poses already described for both the epimers.



**Figure S7.** Representative frames from MD of CB2R in complex with (*S*)-**1** and (*R*)-**1** starting from the pose with the hydroxyl group pointing toward Ser90. (*R*)-**1** (panel A) is colored in steel blue, (*S*)-**1** in slate gray (panel B). A stick representation is used for heavy atoms of the ligand and for protein sidechains within 5 Å of the ligand. Protein backbone atoms are represented as ribbons colored in light blue (A) gray (B) according to the sidechains, using half-transparency. Hydrogen, nitrogen, oxygen, and sulfur atoms are painted white, blue, red, and yellow, respectively. A green wire representation is adopted for H-bonds.

# General Synthetic Methods

## Procedure

Unless otherwise noted, all reactions were carried out under nitrogen atmosphere.

## Chemicals

All chemicals and solvents were purchased from commercial suppliers and were used without further purification. DMF, DMSO, THF, Et<sub>2</sub>O, MeCN, toluene, benzene and CH<sub>2</sub>Cl<sub>2</sub> were dried using 4 Å molecular sieves or using an LC Technology Solutions solvent purification system (SP-1) under an atmosphere of dry nitrogen. Deuterated solvents were purchased from Cambridge Isotopic Laboratories. Pyridine and *i*-Pr<sub>2</sub>NEt were distilled from KOH under an atmosphere of dry nitrogen. Et<sub>3</sub>N was distilled from CaH<sub>2</sub> under an atmosphere of dry nitrogen.

## Chromatography

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F<sub>254</sub> TLC glass plates. Purification of reaction products was carried out by flash column chromatography (FCC) using Sigma Aldrich silica 230-400 mesh particle size, 60 Å under 0.3–0.5 bar overpressure or Büchi Pure Chromatography System C-805 Flash with FlashPure silica cartridges.

## Nuclear Magnetic Resonance Spectroscopy

NMR spectra were acquired on Bruker AVIII HD 600 MHz, 500 MHz and 400 MHz spectrometers operating at the denoted spectrometer frequency given in MHz for the specified nucleus. <sup>1</sup>H NMR spectra are reported with the solvent resonance as the reference (CDCl<sub>3</sub> at 7.26 ppm). Peaks are reported as (s = singlet, bs = broad singlet, d = doublet, bt = broad triplet, t = triplet, q = quartet, m = multiplet or unresolved, coupling constant(s) in Hz, integral). <sup>13</sup>C NMR spectra were recorded with <sup>1</sup>H-decoupling and are reported in ppm with the solvent resonance as the reference (CDCl<sub>3</sub> at 77.16 ppm). Service measurements were performed by the NMR service team of the Laboratorium für Organische Chemie at ETH Zürich.

## High-Resolution Mass Spectrometry

High-resolution mass spectrometric data were obtained at ETH Zürich mass spectrometry service on Bruker Daltonics maXis ESI-QTOF, Thermo Q Exactive EI-Trace 1310 Analyser or a Bruker Daltonics maXis II ESI-QTOF spectrometers and are reported as (*m/z*).

## Infrared Spectroscopy

Infrared (IR) spectra were measured neat on a Perkin-Elmer UATR Two FT-IR Spectrometer and the band maxima are reported in wavenumbers (cm<sup>-1</sup>).

## Optical Rotation

Optical rotations ( $[\alpha]_D^{25}$ ) were determined using a Jasco P-2000 Polarimeter (10 cm, 1.5 mL cell).

## X-ray Diffraction

Single crystalline samples were measured on a Rigaku Oxford Diffraction XtaLAB Synergy-R kappa diffractometer equipped with a Rigaku HyPix Arc150 HPAD detector and using microfocus rotating anode Cu-K $\alpha$  radiation with mirror optics ( $\lambda = 1.54178 \text{ \AA}$ ).

All measurements were carried out at 100K using an Oxford Cryosystems Cryostream 1000+ sample cryostat. Data were integrated using CrysAlisPro and corrected for absorption effects using a combination of empirical (ABSPACK) and numerical corrections.<sup>20</sup> The structures were solved using SHELXT<sup>21</sup> and refined by full-matrix least-squares analysis (SHELXL),<sup>22, 23</sup> using the program package OLEX2.<sup>24</sup> All non-hydrogen atoms were refined anisotropically and hydrogen atoms were constrained to ideal geometries and refined with fixed isotropic displacement parameters (in terms of a riding model). CCDC2450722 contains the supplementary crystallographic data for this paper, including structure factors and refinement instructions. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)-336-033; e-mail: deposit@ccdc.cam.ac.uk), or via <https://www.ccdc.cam.ac.uk/structures>.

The X-ray diffraction was measured and analyzed by Dr. Nils Trapp and Mr. Michael Solar.

## Semi-preparative SFC

The separations were performed using a Prep-SFC-100 semi preparative system with columns (20  $\times$  250 mm, 5  $\mu$ m) supplied by Daicel, Chiral Technology and 90 mL/min flow of solvent A (CO<sub>2</sub>) and co-solvent B, specified by one of the methods below:

**Method 1.** Column: Chiralpak IC, B = 25% *i*-PrOH

**Method 2.** Column: Chiralcel IK, B = 15% MeOH

**Method 3.** Column: Chiralcel IK, B = 16% MeOH

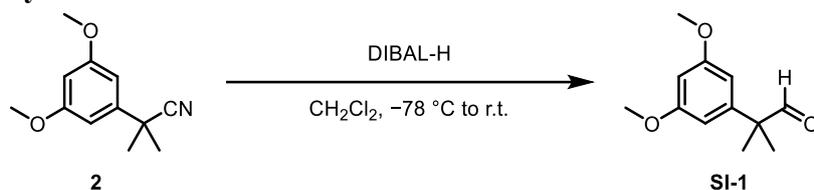
**Method 4.** Column: Chiralpak IK, B = 18% *i*-PrOH

**Method 5.** Column: Chiralcel OD-H, B = 20% (EtOH:*n*-heptane, 1:1)

**Method 6.** Column: Chiralpak AD-H, B = 10% (MeOH:EtOH:*i*-PrOH, 1:1:1)

## Synthesis

### Synthesis of SI-1

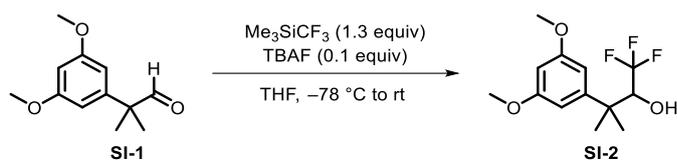


To a solution of **2** (5.00 g, 24.4 mmol, 1.00 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (85.0 mL) at  $-78\text{ }^\circ\text{C}$  under argon atmosphere was added dropwise DIBAL-H (1.00 M solution in  $\text{CH}_2\text{Cl}_2$ , 60.9 mL, 60.9 mmol, 2.50 equiv). The reaction mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 1 h and subsequently quenched by dropwise addition of Rochelle salt (as a 10% solution in water). The resulting mixture was allowed to warm to ambient temperature, stirred vigorously for 40 min, and then diluted with EtOAc. The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. Purification by filtration through a silica plug, eluting with 10 % EtOAc in *n*-hexane afforded the product (4.89 g, 23.5 mmol, 96% yield) as a colorless oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 9.46 (s, 1H), 6.41 – 6.40 (m, 2H), 6.39 – 6.38 (m, 1H), 3.79 (s, 6H), 1.43 (s, 6H) ppm.

Data in accordance with that reported in the literature.<sup>25</sup>

## Synthesis of SI-2



To a solution of **SI-1** (2.00 g, 9.60 mmol, 1.0 equiv) in anhydrous THF (16.0 mL) at  $-78^\circ\text{C}$  was added  $\text{Me}_3\text{SiCF}_3$  (1.85 mL, 12.5 mmol, 1.3 equiv) followed by a solution of TBAF (1.0 M in THF, 960  $\mu\text{L}$ , 960  $\mu\text{mol}$ , 0.1 equiv). The mixture was allowed to warm up to rt and stirred overnight. Additional  $\text{Me}_3\text{SiCF}_3$  (710  $\mu\text{L}$ , 4.80 mmol, 0.5 equiv) and a solution of TBAF (1.0 M in THF, 960  $\mu\text{L}$ , 960  $\mu\text{mol}$ , 0.1 equiv) were added dropwise and stirred for 1 h to bring the reaction to completion. The mixture was quenched with water (25 mL), extracted with  $\text{Et}_2\text{O}$  ( $3 \times 25$  mL) and the organic extracts concentrated under reduced pressure. The unpurified mixture was dissolved in THF (10 mL) and aq. 1 M HCl (10 mL) and refluxed for 1 h. The mixture was cooled down to rt extracted with  $\text{Et}_2\text{O}$  ( $3 \times 25$  mL), combined organic extracts dried with  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The material was purified by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 30%  $\text{Et}_2\text{O}$  in hexanes) to yield the product (2.50 g, 8.98 mmol, 94%) as a colorless liquid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.55 (d,  $J = 2.2$  Hz, 2H), 6.37 (t,  $J = 2.2$  Hz, 1H), 4.06 (td,  $J = 7.5, 5.6$  Hz, 1H), 3.80 (s, 6H), 2.28 (d,  $J = 5.6$  Hz, 1H), 1.49 – 1.42 (m, 6H).

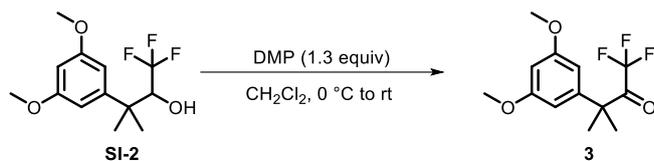
$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  160.9, 148.0, 125.4 (q,  $J = 284.4$  Hz), 105.4, 98.0, 77.1 (q,  $J = 28.1$  Hz), 55.4, 41.2, 24.8 (q,  $J = 2.4$  Hz), 23.7 (q,  $J = 2.0$  Hz).

$^{19}\text{F NMR}$  (377 MHz,  $\text{CDCl}_3$ )  $\delta$  -71.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3472, 2942, 2841, 1597, 1458, 1425, 1270, 1156.

**HRMS (ESI)**:  $m/z = 279.1204$  [ $\text{M}+\text{H}$ ] $^+$  (calc. for  $\text{C}_{13}\text{H}_{18}\text{F}_3\text{O}_3$   $m/z = 279.1203$ )

### Synthesis of 3



To a solution of **SI-2** (2.70 g, 9.70 mmol, 1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (29.0 mL) at  $0\text{ }^\circ\text{C}$  was added DMP (5.35 g, 12.6 mmol, 1.3 equiv) in one portion. The mixture was allowed to warm up to rt and stirred for 2 h. The mixture was concentrated under reduced pressure and the residue triturated with pentane (50 mL). The white solid was filtered off and the filter cake was washed with pentane ( $2 \times 50$  mL). The organic washings were concentrated under reduced pressure and the residue was purified by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 15%  $\text{Et}_2\text{O}$  in hexanes) to afford the product (2.10 g, 7.60 mmol, 78%) as a colorless liquid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.39 (t,  $J = 2.2$  Hz, 1H), 6.34 (d,  $J = 2.2$  Hz, 2H), 3.78 (s, 6H), 1.58 (q,  $J = 0.8$  Hz, 6H).

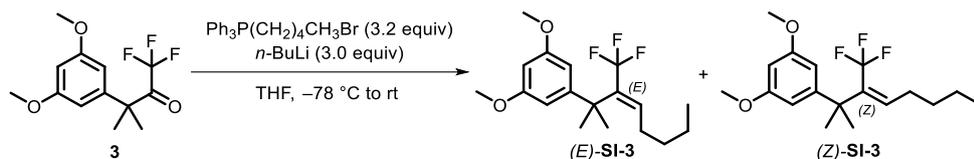
$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  193.8 (q,  $J = 31.2$  Hz), 161.4, 142.7, 116.2 (q,  $J = 295.1$  Hz), 104.3, 99.1, 55.4, 50.2, 24.7 (q,  $J = 1.4$  Hz).

$^{19}\text{F NMR}$  (377 MHz,  $\text{CDCl}_3$ )  $\delta$  -71.0.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2941, 2841, 1745, 1596, 1458, 1426, 1371, 1341, 1299, 1261, 1203.

**HRMS (ESI)**:  $m/z = 277.1047$   $[\text{M}+\text{H}]^+$  (calc. for  $\text{C}_{13}\text{H}_{16}\text{F}_3\text{O}_3$   $m/z = 277.1046$ ).

## Synthesis of (*E*)-SI-3 & (*Z*)-SI-3



To a suspension of pentyltriphenylphosphonium bromide (1.92 g, 4.63 mmol, 3.2 equiv) at  $-78\text{ }^\circ\text{C}$  in dry THF (40 mL) was added dropwise  $n\text{-BuLi}$  (1.6 M in hexane, 2.71 mL, 4.34 mmol, 3.0 equiv). The solution was stirred for 10 min at  $-78\text{ }^\circ\text{C}$ , allowed to warm up to ambient temperature, and stirred for additional 30 min. Subsequently, **3** (400 mg, 1.45 mmol, 1.0 equiv) was dissolved in dry THF (1 mL) and added dropwise to the mixture at  $0\text{ }^\circ\text{C}$ . The mixture was stirred overnight at rt, quenched with aq. sat.  $\text{NH}_4\text{Cl}$  solution (25 mL), diluted with  $\text{Et}_2\text{O}$  (25 mL) and the phases were separated. The aqueous phase was extracted with  $\text{Et}_2\text{O}$  ( $2 \times 25\text{ mL}$ ). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 10%  $\text{Et}_2\text{O}$  in hexanes) to yield separable (*E*)-SI-3 (210 mg, 636  $\mu\text{mol}$ , 44%) and (*Z*)-SI-3 (145 mg, 438  $\mu\text{mol}$ , 30%) isomers, respectively, as light yellow liquids.

**Note:** For the purposes of synthetic ease, the (*E*)- and (*Z*)-isomers do not need to be separated before subjection to the subsequent hydrogenation step.

### (*E*)-3.55

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.48 (d,  $J = 2.2\text{ Hz}$ , 2H), 6.30 (t,  $J = 2.2\text{ Hz}$ , 1H), 6.14 (tq,  $J = 7.6, 2.0\text{ Hz}$ , 1H), 3.78 (s, 6H), 1.64 – 1.57 (m, 2H), 1.51 (q,  $J = 1.2\text{ Hz}$ , 6H), 1.13 – 0.98 (m, 4H), 0.70 (t,  $J = 7.1\text{ Hz}$ , 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  160.8, 153.5, 138.18 (q,  $J = 7.7\text{ Hz}$ ), 135.30 (q,  $J = 24.4\text{ Hz}$ ), 125.17 (q,  $J = 274.4\text{ Hz}$ ), 104.5, 97.2, 55.4, 41.8, 30.5, 29.91 (q,  $J = 1.9\text{ Hz}$ ), 28.3, 22.4, 13.9.

$^{19}\text{F NMR}$  (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -60.9.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2958, 2931, 2874, 2838, 1649, 1596, 1457, 1423, 1290.

**HRMS (ESI):**  $m/z = 331.1882$  [ $\text{M}+\text{H}$ ] $^+$  (calc. for  $\text{C}_{18}\text{H}_{26}\text{F}_3\text{O}_2$   $m/z = 331.1879$ ).

### (*Z*)-3.55

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.43 (d,  $J = 2.2\text{ Hz}$ , 2H), 6.32 (t,  $J = 2.2\text{ Hz}$ , 1H), 6.04 (t,  $J = 7.7\text{ Hz}$ , 1H), 3.78 (s, 6H), 2.41 – 2.33 (m, 2H), 1.53 – 1.48 (m, 2H), 1.47 (s, 6H), 1.45 – 1.36 (m, 2H), 0.96 (t,  $J = 7.2\text{ Hz}$ , 3H).

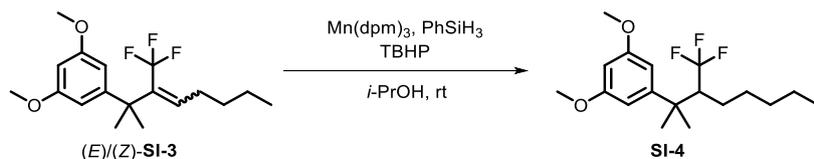
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  160.8, 150.7, 137.4 (q,  $J = 25.2\text{ Hz}$ ), 137.0 (q,  $J = 3.5\text{ Hz}$ ), 124.9 (q,  $J = 279.4\text{ Hz}$ ), 104.1, 97.4, 55.3, 43.1, 31.8, 29.6, 28.5, 22.5, 14.0.

$^{19}\text{F NMR}$  (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -53.9.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2959, 2933, 2874, 2838, 1652, 1596, 1457, 1424, 1204.

**HRMS (ESI):**  $m/z = 331.1881$  [ $\text{M}+\text{H}$ ] $^+$  (calc. for  $\text{C}_{18}\text{H}_{26}\text{F}_3\text{O}_2$   $m/z = 331.1879$ ).

## Synthesis of SI-4



To a solution of **SI-3** (1.20 g, 3.63 mmol, 1.0 equiv) in *i*-PrOH (70 mL) was added phenylsilane (1.22 g, 1.39 mL, 11.3 mmol, 3.1 equiv) and *t*-BuOOH (2.64 mL, 14.5 mmol, 5.5 M in water, 4.0 equiv), and the solution was degassed by bubbling Ar under vigorous stirring for 15 minutes. Then,  $\text{Mn(dpm)}_3$  (659 mg, 1.09 mmol, 0.300 equiv) was added in one portion, and the dark reaction mixture was degassed by bubbling Ar for another 5 min. The reaction mixture turned pale brown after 5 min, light yellow after 20 min. The mixture was stirred for 20 h and return of a dark brown color of the solution indicated reductant consumption. Sat. aq  $\text{NaHCO}_3$  and  $\text{Na}_2\text{SO}_5$  (50:50 v/v%) were added, and the heterogeneous brown mixture was diluted with  $\text{CH}_2\text{Cl}_2$ . The phases were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 50$  mL). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. Filtration over a plug of silica (10%  $\text{Et}_2\text{O}$  in hexane) afforded a brown oil, which displayed incomplete reaction (as judged by NMR) and was re-subjected to the exact same conditions for a second cycle of hydrogenation. The residue was then purified by flash column chromatography ( $\text{SiO}_2$ , dry load on celite, 1 to 1.5%  $\text{Et}_2\text{O}$  in hexane), affording the product (1.00 g, 3.01 mmol, 83% yield) as a colorless oil.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.49 (d,  $J = 2.2$  Hz, 2H), 6.34 (t,  $J = 2.2$  Hz, 1H), 3.80 (s, 6H), 2.37 (qdd,  $J = 10.3, 7.7, 2.7$  Hz, 1H), 1.54 – 1.43 (m, 1H), 1.41 (d,  $J = 2.0$  Hz, 3H), 1.35 (s, 3H), 1.29 – 1.20 (m, 1H), 1.18 – 0.97 (m, 6H), 0.78 (t,  $J = 7.2$  Hz, 3H).

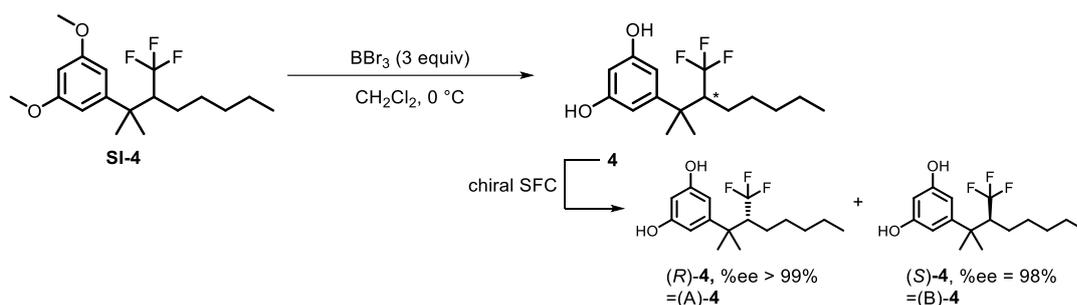
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  160.7, 151.5, 129.07 (q,  $J = 283.3$  Hz), 105.0, 97.4, 55.4, 52.50 (q,  $J = 22.1$  Hz), 40.4, 31.7, 29.4, 28.33 (q,  $J = 2.5$  Hz), 26.26 (q,  $J = 2.4$  Hz), 23.80 (q,  $J = 1.8$  Hz), 22.3, 14.0.

$^{19}\text{F NMR}$  (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.1.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2957, 2873, 1597, 1458, 1206, 1156.

**HRMS (ESI)**:  $m/z = 333.2033$  [ $\text{M}+\text{H}$ ] $^+$  (calc. for  $\text{C}_{18}\text{H}_{28}\text{F}_3\text{O}_2$   $m/z = 333.2036$ ).

## Synthesis of (+)-(R)-4/(A)-4 & (-)-(S)-4/(B)-4



To a solution of **SI-4** (100 mg, 301  $\mu\text{mol}$ , 1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (3.0 mL) at 0  $^\circ\text{C}$  was added  $\text{BBr}_3$  (86  $\mu\text{L}$ , 903  $\mu\text{mol}$ , 3.0 equiv) dropwise and the solution was stirred at 0  $^\circ\text{C}$  for 2 h. The mixture was carefully quenched with aq. sat.  $\text{NaHCO}_3$  (5 mL) and diluted with  $\text{Et}_2\text{O}$  (10 mL). The layers were separated and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  ( $2 \times 10$  mL). Combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 30%  $\text{EtOAc}$  in hexanes) afforded the product as a light red oil (91 mg, 299  $\mu\text{mol}$ , 99%).

The racemate **4** was resolved by chiral SFC Method 4 to afford enantiomers (+)-(R)-**4** (38 mg, 138  $\mu\text{mol}$ , 42%, %ee > 99%) and (-)-(S)-**4** (115 mg, 38%, %ee = 98%). Please refer to the following section for the stereochemical assignment. Prefixes (A)- and (B)- denote the elution sequence on the chiral column and were used for identification before the assignment of configuration (Scheme S1 and Scheme S2).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.42 (d,  $J = 2.2$  Hz, 2H), 6.23 (t,  $J = 2.2$  Hz, 1H), 5.51 (bs, 2H, phenol OHs), 2.30 (qdd,  $J = 10.2, 7.5, 2.6$  Hz, 1H), 1.51 – 0.96 (m, 8H), 1.34 (q,  $J = 1.9$  Hz, 3H), 1.28 (s, 3H), 0.79 (t,  $J = 7.1$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  156.4, 152.6, 128.93 (q,  $J = 283.4$  Hz), 106.3, 100.8, 52.52 (q,  $J = 22.1$  Hz), 40.1, 31.7, 29.4, 27.6, 26.20 (q,  $J = 2.4$  Hz), 24.3, 22.3, 14.0.

$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.1.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3349, 2957, 2928, 2872, 1598, 1459, 1256, 1148.

**HRMS (ESI)**:  $m/z = 305.1721$  [ $\text{M}+\text{H}$ ] $^+$  (calc. for  $\text{C}_{16}\text{H}_{24}\text{F}_3\text{O}_2$   $m/z = 305.1723$ ).

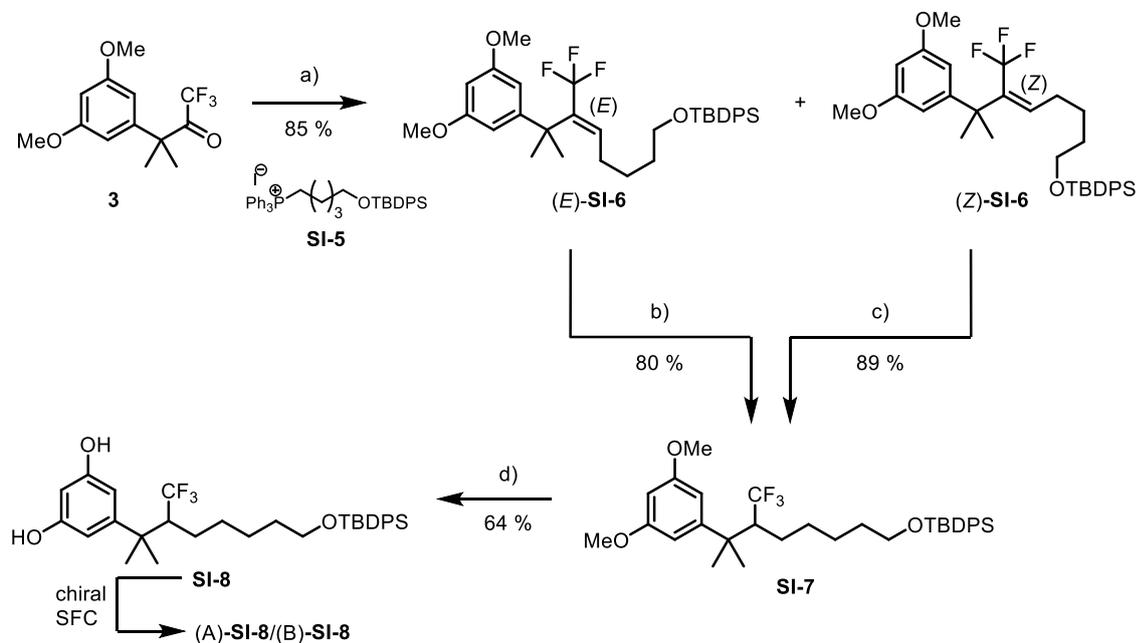
(R)-**4**  $[\alpha]_{\text{D}}^{25} = +17.570 \pm 0.110$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

(S)-**4**  $[\alpha]_{\text{D}}^{25} = -16.414 \pm 0.153$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## X-Ray Crystallographic Studies for the Stereochemical Assignment of (+)-(R)-4/(-)-(S)-4

Derivatizable Sidechain Synthesis:

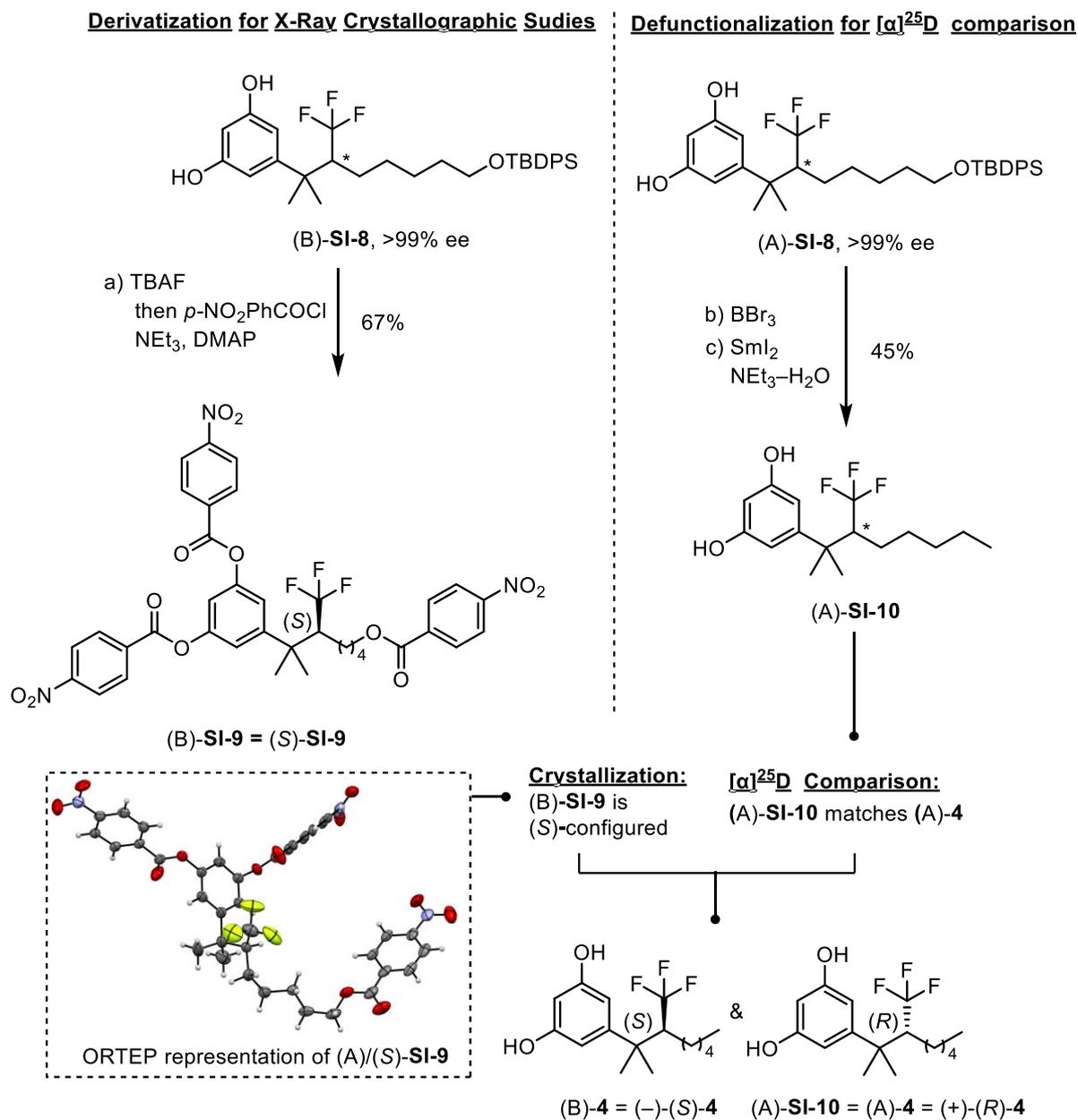
**Scheme S1.** Synthesis of (A)-SI-8/(B)-SI-8 from intermediates **3** and **SI-5**.<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) **3**, *n*-BuLi, -78 °C to r.t. to 0 °C to r.t., 85 %; (b) Mn(dpm)<sub>3</sub>, PhSiH<sub>3</sub>, TBHP, <sup>t</sup>PrOH, r.t., 24 h, 80 % after 3 cycles; (c) Mn(dpm)<sub>3</sub>, PhSiH<sub>3</sub>, TBHP, <sup>t</sup>PrOH, r.t., 24 h, 89 %; (d) BCl<sub>3</sub>, TBAI, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h, 64 %.

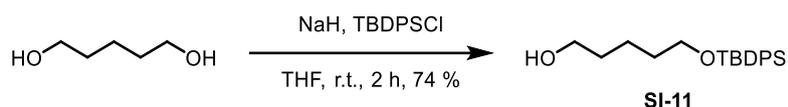
Synthesis of Derivative (B)-SI-9 Suitable for Crystallization/X-Ray Crystallographic Analysis & Defunctionalization of (A)-SI-8 for Optical Rotation Comparison with Enantiomerically Enriched (A)-4. As before, prefixes (A)- and (B)- denote elution sequence and were used as identifiers before assignment:

**Scheme S2.** Synthesis of (B)-SI-9 for crystallization and compound (A)-SI-10 for comparison to authentic material.<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) TBAF, THF, rt, then *p*-NO<sub>2</sub>PhCOCl, NEt<sub>3</sub>, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, (b) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt, 67% (c) SmI<sub>2</sub>, H<sub>2</sub>O-NEt<sub>3</sub>, rt, 45%, steps.

## Synthesis of SI-11

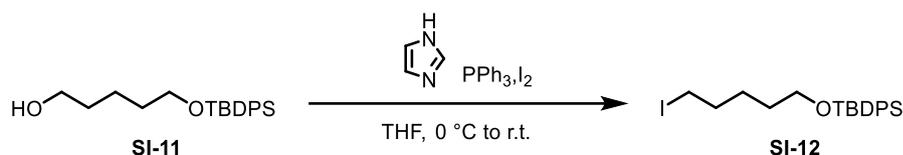


To a suspension of sodium hydride (60% in mineral oil, 1.15 g, 28.8 mmol, 1.0 equiv) in anhydrous THF (60.0 mL) was added pentane-1,5-diol (3.00 g, 3.02 mL, 28.8 mmol, 1.0 equiv) and the mixture was allowed to stir at room temperature for 1 h. Then, TBDPSCI (7.92 g, 7.49 mL, 28.8 mmol, 1.0 equiv) was added under vigorous stirring, and the reaction mixture was further stirred for 1 h. The reaction mixture was quenched by addition of saturated aqueous NaHCO<sub>3</sub> solution, the phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>, 30 % EtOAc in *n*-hexane) afforded the product (7.40 g, 21.6 mmol, 75 %) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.69 – 7.65 (m, 4H), 7.45 – 7.36 (m, 6H), 3.68 (t, J = 6.4 Hz, 2H), 3.65 – 3.59 (m, 2H), 1.66 – 1.49 (m, 4H), 1.49 – 1.38 (m, 2H), 1.27 (s, 1H), 1.06 (s, 9H) ppm.

Data in accordance with that reported in the literature:<sup>26</sup>

## Synthesis of SI-12



To a solution of alcohol **SI-11** (4.00 g, 11.7 mmol, 1.0 equiv), triphenylphosphine (4.59 g, 17.5 mmol, 1.5 equiv), and imidazole (1.19 g, 0.969 mL, 17.5 mmol, 1.5 equiv) in anhydrous THF (78.0 mL) at 0 °C was added molecular iodine (4.45 g, 17.5 mmol, 1.5 equiv) in one portion. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 h. Then, the reaction mixture was diluted with Et<sub>2</sub>O, washed with aqueous 10 % Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. Purification by trituration in *n*-hexane afforded the product (5.25 g, 11.6 mmol, 99 %) as a pale-yellow oil.

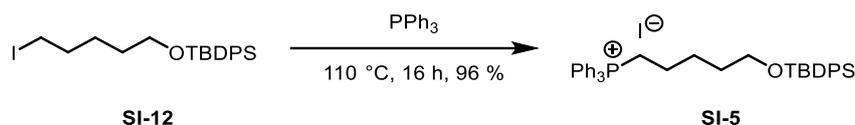
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.69 – 7.64 (m, 4H), 7.45 – 7.35 (m, 6H), 3.66 (t, J = 6.2 Hz, 2H), 3.16 (t, J = 7.0 Hz, 2H), 1.81 (p, J = 7.1 Hz, 2H), 1.61 – 1.54 (m, 2H), 1.52 – 1.44 (m, 2H), 1.05 (s, 9H) ppm.

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 135.7, 134.1, 129.7, 127.8, 63.7, 33.4, 32.4, 31.6, 27.0, 19.4, 7.2 ppm.

IR (neat, ν<sub>max</sub>/cm<sup>-1</sup>) 3070, 2931, 2857, 1472, 1428, 1390, 1361, 1213, 1172, 1111, 998, 823, 740, 701, 614, 541, 505, 493.

ESI-HRMS m/z calcd for C<sub>21</sub>H<sub>29</sub>INaOSi [M+Na]<sup>+</sup> 475.0925; found 475.0925.

## Synthesis of SI-5



Triphenylphosphine (3.35 g, 12.8 mmol, 1.1 equiv) was added to neat **SI-12** (5.25 g, 11.6 mmol, 1.0 equiv), and the reaction mixture was stirred at 110 °C for 1 h. Then, the reaction mixture was allowed to cool to ambient temperature, at which point it developed a gum-like consistency. Et<sub>2</sub>O was added, and the semi-solid mixture was ultrasonicated for 10 min, facilitating solidification. Subsequently, the mixture was filtered, the residue was washed with Et<sub>2</sub>O, and dried under reduced pressure to give the product (7.95 g, 11.1 mmol, 96 %) as a colorless solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.85 – 7.75 (m, 9H), 7.71 – 7.65 (m, 6H), 7.61 – 7.57 (m, 4H), 7.41 – 7.30 (m, 6H), 3.76 – 3.67 (m, 2H), 3.61 (t, J = 6.3 Hz, 2H), 1.78 – 1.64 (m, 2H), 1.62 – 1.52 (m, 4H), 0.98 (s, 9H) ppm.

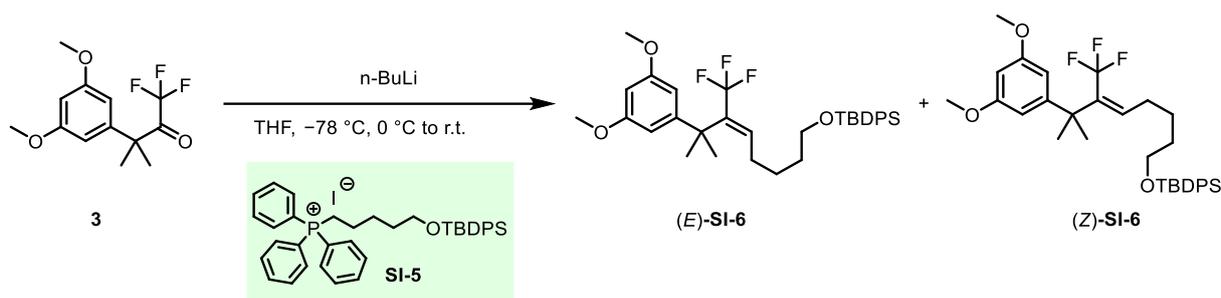
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 135.6, 135.2, 135.2, 133.9, 133.8, 130.7, 130.6, 129.7, 127.8, 118.8, 118.0, 63.5, 32.0, 27.1, 27.0, 23.6, 23.1, 22.6, 19.3 ppm.

<sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>) δ = 24.4 ppm.

IR (neat, ν<sub>max</sub>/cm<sup>-1</sup>) 2930, 2857, 1587, 1472, 1438, 1111, 996, 824, 742, 723, 705, 689, 614, 532, 498.

ESI-HRMS m/z calcd for C<sub>39</sub>H<sub>44</sub>OPSi [M]<sup>+</sup> 587.2894; found 587.2888.

## Synthesis of (*E*)-SI-6/(*Z*)-SI-6



To a suspension of **3** (3.10 g, 4.34 mmol, 1.2 equiv) in anhydrous THF (36.0 mL) at  $-78\text{ }^{\circ}\text{C}$  was added dropwise butyllithium (.60 mL, 4.16 mmol, 1.6 M in *n*-hexane, 1.15 equiv). The solution was stirred for 10 min at  $-78\text{ }^{\circ}\text{C}$ , allowed to warm to ambient temperature, and stirred for additional 30 min. Then, the reaction mixture was cooled to  $0\text{ }^{\circ}\text{C}$ , and a solution of ketone **3** (1.00 g, 3.62 mmol, 1.0 equiv) in anhydrous THF (2.00 mL) was added dropwise. The reaction mixture was allowed to reach ambient temperature and stirred for further 2 h. Subsequently, the reaction mixture was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  solution, diluted with  $\text{Et}_2\text{O}$ , the phases were separated, and the aqueous phase was extracted with  $\text{Et}_2\text{O}$ . Combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ , eluting with 1–2 %  $\text{Et}_2\text{O}$  in *n*-hexane) afforded the two diastereomers as colourless oils and a mixed fraction. The mixed fraction was further purified by flash column chromatography ( $\text{SiO}_2$ , eluting with 1 %  $\text{Et}_2\text{O}$  and 10 %  $\text{CH}_2\text{Cl}_2$  in *n*-hexane), affording the products (*E*)-SI-6 (1.10 g, 1.93 mmol, 53 %) and (*Z*)-SI-6 (655 mg, 1.15 mmol, 32 %), after merging fractions.

### (*E*)-SI-6

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.66 – 7.58 (m, 4H), 7.46 – 7.32 (m, 6H), 6.45 (d,  $J$  = 2.3 Hz, 2H), 6.26 (t,  $J$  = 2.2 Hz, 1H), 6.12 (td,  $J$  = 7.5, 2.0 Hz, 1H), 3.73 (s, 6H), 3.48 (t,  $J$  = 6.2 Hz, 2H), 1.63 – 1.57 (m, 2H), 1.50 (bs, 6H), 1.30 – 1.13 (m, 4H), 1.02 (s, 9H) ppm.

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 160.8, 153.4, 138.0, 135.7, 134.1, 129.7, 127.7, 104.5, 97.2, 63.6, 55.4, 41.8, 32.2, 29.9, 28.3, 27.0, 24.7, 19.3 ppm.

$^{19}\text{F NMR}$  (377 MHz,  $\text{CDCl}_3$ )  $\delta$  =  $-60.9$  ppm.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ) 3072, 2934, 2859, 1648, 1597, 1459, 1427, 1390, 1300, 1206, 1193, 1169, 1156, 1107, 1067, 938, 824, 741, 702, 689, 614, 505.

**ESI-HRMS**  $m/z$  calcd for  $\text{C}_{34}\text{H}_{43}\text{F}_3\text{NaO}_3\text{Si}$  [ $\text{M}+\text{Na}$ ] $^+$  607.2826; found 607.2818.

**(Z)-SI-6**

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.70 – 7.65 (m, 4H), 7.45 – 7.36 (m, 6H), 6.41 (d,  $J$  = 2.2 Hz, 2H), 6.30 (t,  $J$  = 2.2 Hz, 1H), 6.00 (t,  $J$  = 7.7 Hz, 1H), 3.76 (s, 6H), 3.70 (t,  $J$  = 6.0 Hz, 2H), 2.40 – 2.29 (m, 2H), 1.67 – 1.56 (m, 4H), 1.45 (s, 6H), 1.06 (s, 9H) ppm.

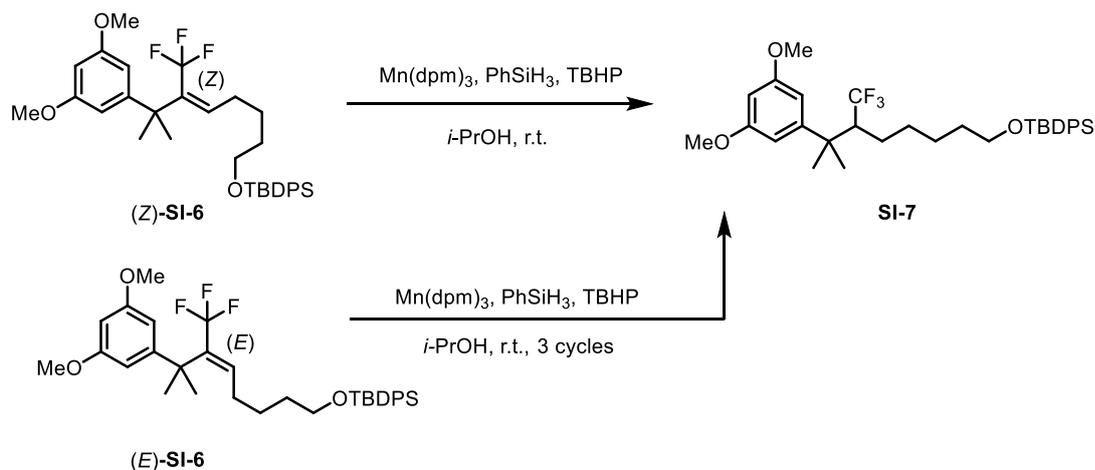
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 160.8, 150.6, 136.7, 135.7, 134.2, 129.7, 127.8, 126.3, 104.1, 97.4, 63.7, 55.3, 43.1, 32.3, 29.6, 28.5, 27.0, 25.9, 19.4 ppm.

**<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>)  $\delta$  = –53.9 ppm.

**IR** (neat,  $\nu_{\text{max}}$ /cm<sup>-1</sup>) 3072, 2999, 2934, 2859, 1652, 1596, 1459, 1427, 1389, 1377, 1362, 1339, 1311, 1291, 1251, 1203, 1156, 1110, 1067, 1006, 938, 824, 741, 702, 614, 505.

**ESI-HRMS**  $m/z$  calcd for C<sub>34</sub>H<sub>43</sub>F<sub>3</sub>NaO<sub>3</sub>Si [M+Na]<sup>+</sup> 607.2826; found 607.2830.

## Synthesis of SI-7



To a solution of (*Z*)-**SI-6** (630 mg, 1.08 mmol, 1.0 equiv) was added phenyl silane (361 mg, 412  $\mu$ L, 3.34 mmol, 3.1 equiv) and 2-hydroperoxy-2-methylpropane (388 mg, 784  $\mu$ L, 4.31 mmol, 5.5 M, 4.0 equiv), and the solution was degassed by bubbling Ar under vigorous stirring for 15 minutes. Then, Mn(dpm)<sub>3</sub> (195 mg, 323  $\mu$ mol, 0.3 equiv) was added in one portion, and the dark reaction mixture was degassed by bubbling Ar for another 5 min. The solution turned pale brown after 5 min, light yellow after 35 min. The mixture was stirred for 24 h and return of a dark brown color of the solution indicated reaction completion. Saturated aqueous NaHCO<sub>3</sub> solution and Na<sub>2</sub>SO<sub>5</sub> were added, and the heterogeneous brown mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>. The phases were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>, dry load on celite, eluting with 2.5% EtOAc in hexane) afforded the product (563 mg, 959  $\mu$ mol, 89% yield) as a colorless oil.

(*E*)-**SI-6** (20.0 mg, 34.2  $\mu$ mol, 1.00 equiv) was treated analogously, however, the reaction conditions proceeded sluggishly and the material was re-subjected to the hydrogenation conditions 3 times for full conversion. Final purification afforded the product (16.0 mg, 27.3  $\mu$ mol, 80% yield)

**Note:** For ease of preparation, only the reaction employing (*Z*)-**SI-6** was scaled up to preparatively useful quantities.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.67 – 7.60 (m, 4H), 7.46 – 7.33 (m, 6H), 6.50 – 6.44 (m, 2H), 6.31 (t, *J* = 2.2 Hz, 1H), 3.77 (s, 6H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.35 (ddd, *J* = 12.9, 6.5, 2.6 Hz, 1H), 1.39 (q, *J* = 2.4, 2.0 Hz, 4H), 1.37 (s, 2H), 1.33 (s, 3H), 1.22 – 1.09 (m, 1H), 1.03 (d, *J* = 0.8 Hz, 9H) ppm.

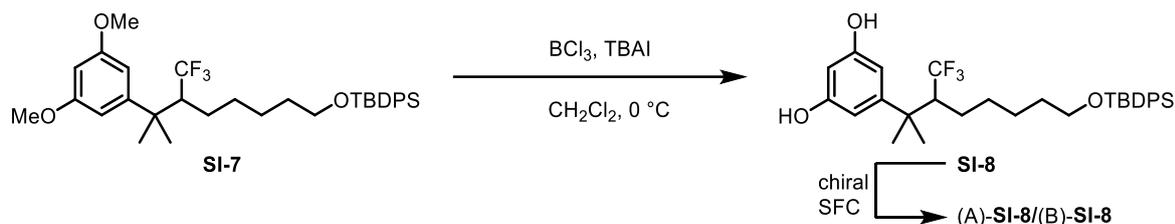
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 160.7, 151.5, 135.7, 134.3, 130.4, 129.6, 127.7, 105.0, 97.3, 77.2, 63.9, 55.4, 52.6, 52.4, 40.4, 32.2, 29.6, 28.2, 27.0, 26.3, 25.7, 24.0, 19.3 ppm.

<sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$  = –62.0 ppm.

IR (neat,  $\nu_{\max}$ /cm<sup>-1</sup>) 2933, 1596, 1457, 1427, 1205, 1156, 1105, 1068, 1053, 824, 740, 701, 614, 504, 489.

ESI-HRMS *m/z* calcd for C<sub>34</sub>H<sub>45</sub>F<sub>3</sub>NaO<sub>3</sub>Si [M+Na]<sup>+</sup> 609.2982; found 609.297

## Synthesis of SI-8



The starting material and TBAI were dried by azeotropic distillation two times with benzene. To a solution of **SI-7** (271 mg, 462  $\mu\text{mol}$ , 1.00 equiv) and tetrabutylammonium iodide (426 mg, 1.15 mmol, 2.50 equiv) in  $\text{CH}_2\text{Cl}_2$  (14.9 mL) at  $0\text{ }^\circ\text{C}$  was dropwise added trichloro borane (1.00 M in  $\text{CH}_2\text{Cl}_2$ , 162 mg, 1.39 mL, 1.39 mmol, 3.00 equiv). The solution adopted a faint yellow color, and the color deepened over the course of the reaction. The reaction mixture was stirred for 1 h at  $0\text{ }^\circ\text{C}$  until full consumption of the starting material was observed. Saturated aqueous  $\text{NaHCO}_3$  solution was carefully added to the reaction mixture, the phases were separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ , eluting with 20 %–25% EtOAc in *n*-hexane) afforded the product (164 mg, 294  $\mu\text{mol}$ , 64% yield) as a transparent liquid.

Combined material from two batches of the racemate (335 mg, 600  $\mu\text{mol}$ ) was resolved by chiral SFC Method 6 to afford enantiomers (A)-**SI-8** (107 mg, 191  $\mu\text{mol}$ , 32%, %ee > 99%) and (B)-**SI-8** (115 mg, 206  $\mu\text{mol}$ , 34%, %ee > 99%)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.69 – 7.62 (m, 4H), 7.46 – 7.33 (m, 6H), 6.35 (d,  $J$  = 2.2 Hz, 2H), 6.11 (t,  $J$  = 2.2 Hz, 1H), 4.65 (s, 2H), 3.55 (t,  $J$  = 6.5 Hz, 2H), 2.29 (tt,  $J$  = 10.2, 7.5 Hz, 1H), 1.59 (s, 1H), 1.51 – 1.40 (m, 1H), 1.37 (dd,  $J$  = 4.4, 2.3 Hz, 4H), 1.30 (s, 3H), 1.15 (h,  $J$  = 6.8 Hz, 2H), 1.04 (s, 12H) ppm.

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 156.6, 152.3, 135.8, 135.7, 134.3, 134.3, 129.7, 127.8, 106.1, 100.8, 77.2, 63.9, 52.5, 52.3, 52.1, 40.1, 32.1, 29.3, 28.1, 27.0, 26.1, 25.5, 23.9, 19.4 ppm.

$^{19}\text{F NMR}$  (377 MHz,  $\text{CDCl}_3$ )  $\delta$  = -62.1 ppm.

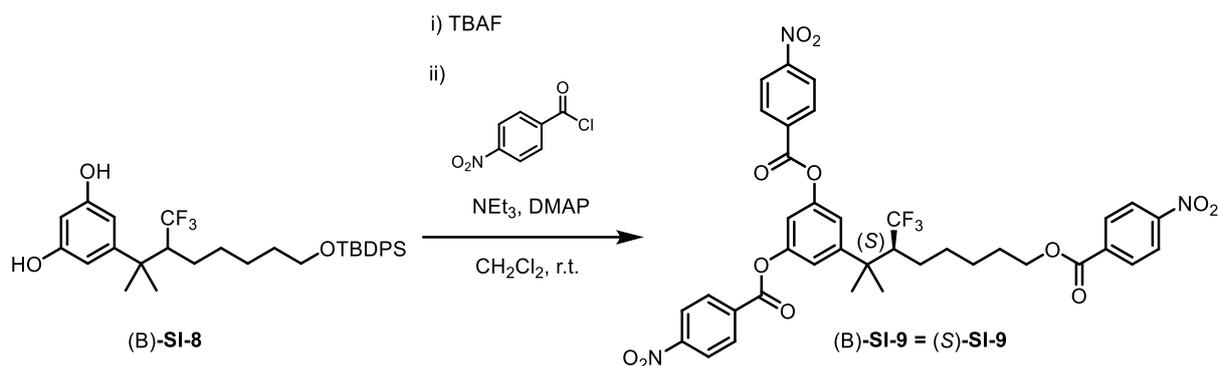
**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ) 3341, 2934, 2860, 1601, 1472, 1429, 1330, 1251, 1147, 1111, 998, 823, 740, 702, 505.

**ESI-HRMS**  $m/z$  calcd for  $\text{C}_{32}\text{H}_{41}\text{F}_3\text{NaO}_3\text{S}$  [ $\text{M}+\text{Na}$ ] $^+$  581.2669; found 581.2666

(A)-**4** [ $\alpha$ ] $^{25}_{\text{D}}$  = +8.257  $\pm$  0.229 ( $c$  = 1.0,  $\text{CHCl}_3$ ).

(B)-**4** [ $\alpha$ ] $^{25}_{\text{D}}$  = -8.556  $\pm$  0.114 ( $c$  = 1.0,  $\text{CHCl}_3$ ).

## Synthesis of (B)/(S)-SI-9



To a solution of (B)-SI-8 (57.6 mg, 103  $\mu$ mol, 1.00 equiv) in THF (1.0 mL) was added TBAF (309  $\mu$ L, 309  $\mu$ mol, 1 M in THF, 3.0 equiv) and the reaction was allowed to stir for 5 h. Then, sat. aq. NH<sub>4</sub>Cl was added and the mixture was diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The obtained brown residue was employed immediately in the subsequent reaction (quant. yield assumed).

To a solution of unpurified deprotection product, N,N-diethylethanamine (73.0 mg, 101  $\mu$ L, 721  $\mu$ mol, 7.0 equiv) and N,N-dimethylpyridin-4-amine (2.52 mg, 20.6  $\mu$ mol, 0.2 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.51 mL) was added in one portion solid 4-nitrobenzoyl chloride (95.6 mg, 515  $\mu$ mol, 5.0 equiv). The yellow reaction mixture was allowed to stir for 14 h before being loaded directly onto a silica column. Purification by flash column chromatography (SiO<sub>2</sub>, 15 – 20% EtOAc in *n*-hexane) afforded the product (49.0 mg, 63.8  $\mu$ mol, 62% yield) as an off-white solid.

Crystallization by slow evaporation (1 week) from 20% CH<sub>2</sub>Cl<sub>2</sub> in MeOH afforded a mother liquor containing needle crystals suitable for X-Ray crystallographic studies (see appended data). Deposition number: CCDC2450722

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.37 (s, 8H), 8.26 – 8.22 (m, 2H), 8.18 – 8.14 (m, 2H), 7.19 (d, J = 2.1 Hz, 2H), 7.10 (t, J = 2.0 Hz, 1H), 4.29 (t, J = 6.7 Hz, 2H), 2.47 – 2.33 (m, 1H), 1.68 (p, J = 7.0 Hz, 2H), 1.63 – 1.57 (m, 1H), 1.50 (bs, 3H), 1.44 (s, 3H), 1.36 (d, J = 7.2 Hz, 1H), 1.34 – 1.27 (m, 5H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  164.83, 163.10, 152.17, 151.23, 151.01, 150.61, 135.94, 134.58, 131.49, 130.77, 128.64 (d, J = 283.4 Hz), 123.98, 123.63, 117.57, 113.49, 65.91, 52.75 (d, J = 22.7 Hz), 40.63, 29.85, 28.25, 27.92, 26.32, 25.86, 23.97.

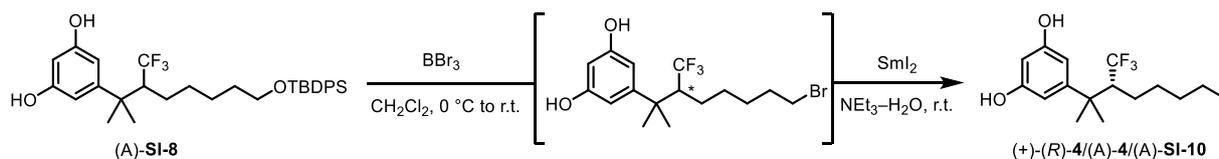
<sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$  -62.22.

IR (neat,  $\nu_{\max}$ /cm<sup>-1</sup>) 3112, 2924, 2854, 1746, 1723, 1608, 1528, 1466, 1433, 1410, 1349, 1320, 1257, 1128, 1104, 1078, 1014, 962, 872, 856, 839, 779, 715.

ESI-HRMS  $m/z$  calcd for C<sub>37</sub>H<sub>32</sub>F<sub>3</sub>N<sub>3</sub>NaO<sub>12</sub> [M+Na]<sup>+</sup> 790.1830; found 790.1835

$[\alpha]_{\text{D}}^{25} = -2.964 \pm 0.392$  (c = 0.89, CHCl<sub>3</sub>).

## Independent Synthesis of (+)-(R)-4/(A)-4/(A)-SI-10



To a solution of (A)-SI-8 (22.3 mg, 39.9  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (2.70 mL) at 0  $^\circ\text{C}$  was dropwise added  $\text{BBr}_3$  (132  $\mu\text{L}$ , 132  $\mu\text{mol}$ , 1 M in  $\text{CH}_2\text{Cl}_2$ , 3.3 equiv), and the resulting light orange solution was allowed to stir at ambient temperature for 1 h. Then, sat. aq.  $\text{NaHCO}_3$  was added, the phases were separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Filtration over a plug of silica (30% EtOAc in *n*-hexane) afforded the unpurified alkyl bromide as a pink gum and was employed immediately in the subsequent reaction (quant. yield assumed).

**Note:** Due to observed instability of the compound upon prolonged exposure to silica and/or air, the material was directly employed in the next step.

To a solution of the unpurified alkyl bromide in dry THF (0.2 ml) was added  $\text{NEt}_3$  (156  $\mu\text{L}$ , 1.12 mmol, 28.0 equiv) and water (25.2 mg, 25.2  $\mu\text{L}$ , 1.40 mmol, 35.0 equiv) and the mixture was thoroughly degassed via freeze-pump-thaw procedure (3x), and back-filled with argon, before a solution of  $\text{SmI}_2$  (2.79 mL, 279  $\mu\text{mol}$ , 0.100M, 7.00 equiv) was added dropwise. The ink-blue solution was allowed to stir for 12 h before diluting the reaction mixture with 1M aq. HCl and EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ , 20 – 25% EtOAc in hexane) afforded the product (6.40 mg, 21.0  $\mu\text{mol}$ , 53% yield) as a colorless gum.

**Note:** The product (A)-SI-10  $^1\text{H}$  NMR spectrum (shifts and coupling constants) as well as its  $[\alpha]^{25}_{\text{D}}$  (value and sign) matched the data of separately accessed/authentic (A)-4, hence allowing for the unambiguous stereochemical assignment of (A)-4 as (+)-(R)-4. Slight deviations are attributed to concentration effects, as data on (A)-SI-10 was obtained with less material.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.39 (d,  $J$  = 2.2 Hz, 2H), 6.20 (t,  $J$  = 2.2 Hz, 1H), 4.73 (bs, 2H, phenol OHs), 2.38 – 2.25 (m, 1H), 1.51 – 0.97 (m, 8H) 1.37 (q,  $J$  = 2.0 Hz, 3H), 1.31 (s, 3H), , 0.79 (t,  $J$  = 7.1 Hz, 3H).

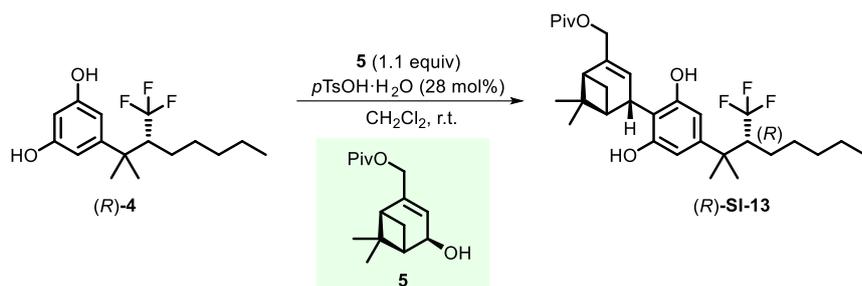
$[\alpha]^{25}_{\text{D}}$  = +11.864  $\pm$  0.429 ( $c$  = 0.58,  $\text{CHCl}_3$ ).

### Comparison to authentic (A)-4:

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.42 (d,  $J$  = 2.2 Hz, 2H), 6.23 (t,  $J$  = 2.2 Hz, 1H), 5.51 (bs, 2H, phenol OHs), 2.30 (qdd,  $J$  = 10.2, 7.5, 2.6 Hz, 1H), 1.51 – 0.96 (m, 8H), 1.34 (q,  $J$  = 1.9 Hz, 3H), 1.28 (s, 3H), 0.79 (t,  $J$  = 7.1 Hz, 3H).

(R)-4  $[\alpha]^{25}_{\text{D}}$  = +17.570  $\pm$  0.110 ( $c$  = 1.0,  $\text{CHCl}_3$ ).

## Synthesis of (*R*)-SI-13



To a solution of (+)-(*R*)-4 (17.9 mg, 58.8  $\mu$ mol, 1.0 equiv) and **5** (16.3 mg, 64.7  $\mu$ mol, 1.1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2.3 mL) was added *p*TsOH·H<sub>2</sub>O (3.1 mg, 16.4  $\mu$ mol, 0.28 equiv) and the solution was stirred for 30 min. The reaction was stopped by addition on sat. aq. NaHCO<sub>3</sub> (4 mL) and diluted with Et<sub>2</sub>O (5 mL). The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O (3  $\times$  5 mL). Combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 0 – 15% EtOAc in hexanes) afforded the product as a colourless foam (23.3 mg, 74%).

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.34 (s, 2H), 5.99 (dt, *J* = 3.0, 1.5 Hz, 1H), 5.68 (bs, 2H), 4.64 (ddd, *J* = 13.5, 2.1, 1.4 Hz, 1H), 4.51 (ddd, *J* = 13.6, 2.4, 1.6 Hz, 1H), 4.04 – 3.97 (m, 1H), 2.36 (dt, *J* = 9.7, 5.6 Hz, 1H), 2.33 – 2.22 (m, 3H), 1.47 (d, *J* = 9.7 Hz, 1H), 1.45 – 1.38 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.32 – 1.20 (m, 2H), 1.28 (s, 3H), 1.23 (s, 9H), 1.14 – 1.00 (m, 5H), 0.98 (s, 3H), 0.76 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  178.7, 155.2, 149.8, 149.3, 129.1 (q, *J* = 283.3 Hz), 120.1, 112.5, 106.7, 66.6, 52.4 (q, *J* = 22.1 Hz), 47.5, 44.2, 41.1, 39.8, 39.1, 37.9, 31.6, 29.4, 28.1, 28.1, 27.4, 26.1, 26.0, 23.6, 22.2, 20.9, 14.0.

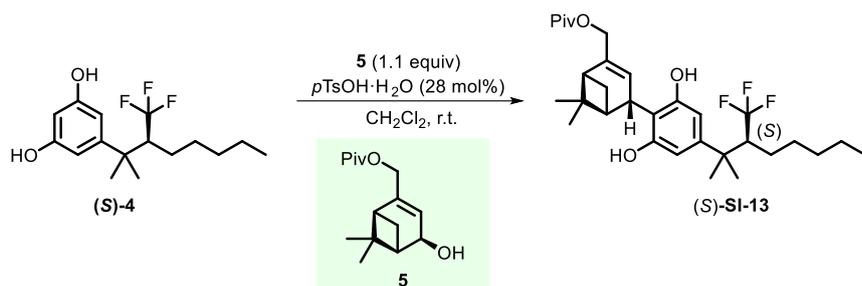
**<sup>19</sup>F NMR** (471 MHz, CDCl<sub>3</sub>)  $\delta$  -62.2.

**IR** (neat,  $\nu_{\text{max}}$ /cm<sup>-1</sup>): 3445, 2942, 2872, 1707, 1626, 1578, 1481, 1254, 1149.

**HRMS (ESI):** *m/z* = 561.3147 [M+Na]<sup>+</sup> (calc. for C<sub>31</sub>H<sub>45</sub>F<sub>3</sub>NaO<sub>4</sub> *m/z* = 561.3162).

**$[\alpha]_{\text{D}}^{25}$**  = +62.961  $\pm$  0.119 (*c* = 1.0, CHCl<sub>3</sub>).

## Synthesis of (S)-SI-13



To a solution of (–)-(S)-**4** (16.6 mg, 54.5 μmol, 1.0 equiv) and **5** (15.1 mg, 60.0 μmol, 1.1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2.3 mL) was added *p*TsOH·H<sub>2</sub>O (2.9 mg, 15.2 μmol, 0.28 equiv) and the solution was stirred for 30 min. The reaction was stopped by addition on sat. aq. NaHCO<sub>3</sub> (4 mL) and diluted with Et<sub>2</sub>O (5 mL). The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O (3 × 5 mL). Combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 0 – 15% EtOAc in hexanes) afforded the product as a faint yellow foam (23.0 mg, 78%).

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 6.34 (s, 2H), 6.00 (dt, *J* = 3.1, 1.6 Hz, 1H), 5.76 (bs, 2H), 4.64 (ddd, *J* = 13.5, 2.0, 1.4 Hz, 1H), 4.51 (ddd, *J* = 13.5, 2.3, 1.5 Hz, 1H), 4.02 – 3.98 (m, 1H), 2.36 (dt, *J* = 9.7, 5.6 Hz, 1H), 2.33 – 2.22 (m, 3H), 1.46 (d, *J* = 9.7 Hz, 1H), 1.45 – 1.38 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.33 – 1.19 (m, 2H), 1.28 (s, 3H), 1.23 (s, 9H), 1.16 – 0.96 (m, 5H), 0.98 (s, 3H), 0.76 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 178.7, 155.2, 149.8, 149.3, 129.1 (q, *J* = 283.5 Hz), 120.1, 112.4, 106.7, 66.6, 52.5 (q, *J* = 22.2 Hz), 47.5, 44.2, 41.1, 39.8, 39.1, 37.9, 31.6, 29.4, 28.1, 28.1, 27.4, 26.1, 26.0, 23.6, 22.2, 20.9, 14.0.

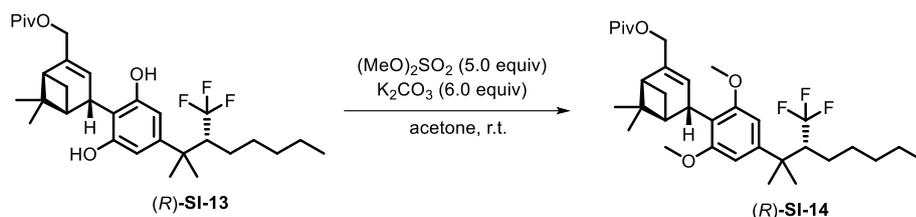
**<sup>19</sup>F NMR** (471 MHz, CDCl<sub>3</sub>) δ -62.2.

**IR** (neat,  $\nu_{\max}$ /cm<sup>-1</sup>): 3446, 2942, 2872, 1707, 1626, 1578, 1481, 1254, 1149.

**HRMS (ESI):** *m/z* = 561.3154 [M+Na]<sup>+</sup> (calc. for C<sub>31</sub>H<sub>45</sub>F<sub>3</sub>NaO<sub>4</sub> *m/z* = 561.3162).

**[α]<sub>D</sub><sup>25</sup>** = +38.128 ± 0.330 (*c* = 1.0, CHCl<sub>3</sub>).

## Synthesis of (*R*)-SI-14



To a solution of (*R*)-SI-13 (23.3 mg, 43.2  $\mu$ mol, 1.0 equiv) in acetone (0.5 mL) was added (MeO)<sub>2</sub>SO<sub>2</sub> (20.5  $\mu$ L, 0.216 mmol, 5.0 equiv) and K<sub>2</sub>CO<sub>3</sub> (35.9 mg, 0.260 mmol, 6.0 equiv) and the light purple suspension was stirred overnight at rt. The reaction mixture was filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 0 – 10% Et<sub>2</sub>O in hexanes) afforded the product as a light red wax (23.1 mg, 94%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.47 (s, 2H), 5.76 (dt, *J* = 2.9, 1.5 Hz, 1H), 4.61 – 4.54 (m, 1H), 4.51 (ddd, *J* = 12.2, 1.7, 1.2 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.74 (s, 6H), 2.31 (dddd, *J* = 20.6, 10.3, 7.4, 2.5 Hz, 1H), 2.20 – 2.10 (m, 2H), 2.02 (tt, *J* = 5.8, 1.9 Hz, 1H), 1.73 – 1.66 (m, 1H), 1.50 – 1.41 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.34 – 1.18 (m, 2H), 1.29 (s, 3H), 1.21 (s, 9H), 1.12 – 0.88 (m, 5H), 0.97 (s, 3H), 0.74 (t, *J* = 7.1 Hz, 3H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  178.6, 158.6, 148.1, 137.5, 129.1 (q, *J* = 283.3 Hz), 126.1, 118.7, 103.1, 67.6, 56.0, 52.7 (q, *J* = 22.1 Hz), 47.6, 44.0, 41.1, 40.5, 39.0, 37.7, 31.5, 30.5, 29.4, 28.8, 27.6, 27.4, 26.4, 26.2, 22.2, 21.2, 14.0.

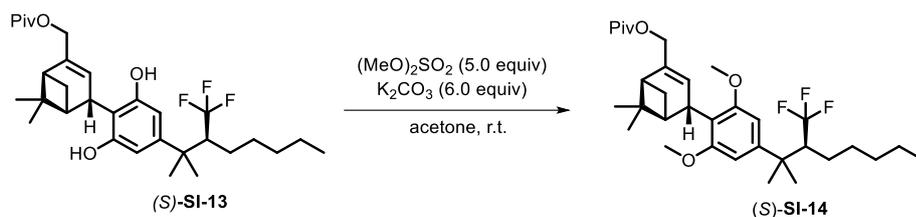
<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>)  $\delta$  -62.1.

IR (neat,  $\nu_{\max}$ /cm<sup>-1</sup>): 2957, 2932, 2870, 1727, 1605, 1575, 1461, 1412, 1150.

HRMS (ESI): *m/z* = 589.3470 [M+Na]<sup>+</sup> (calc. for C<sub>33</sub>H<sub>49</sub>F<sub>3</sub>NaO<sub>4</sub> *m/z* = 589.3475).

$[\alpha]_D^{25} = +73.052 \pm 0.280$  (*c* = 1.0, CHCl<sub>3</sub>).

## Synthesis of (S)-SI-14



To a solution of (S)-SI-13 (23.0 mg, 42.7  $\mu\text{mol}$ , 1.0 equiv) in acetone (0.5 mL) was added  $(\text{MeO})_2\text{SO}_2$  (20.2  $\mu\text{L}$ , 0.214 mmol, 5.0 equiv) and  $\text{K}_2\text{CO}_3$  (35.4 mg, 0.256 mmol, 6.0 equiv) and the light purple suspension was stirred overnight at rt. The reaction mixture was filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 10%  $\text{Et}_2\text{O}$  in hexanes) afforded the product as a light red wax (23.5 mg, 97%).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.47 (s, 2H), 5.88 – 5.64 (m, 1H), 4.61 – 4.55 (m, 1H), 4.51 (ddd,  $J = 12.2, 1.7, 1.3$  Hz, 1H), 4.02 – 3.95 (m, 1H), 3.74 (s, 6H), 2.31 (dddd,  $J = 20.4, 10.1, 7.2, 2.5$  Hz, 1H), 2.19 – 2.11 (m, 2H), 2.06 – 1.96 (m, 1H), 1.73 – 1.64 (m, 1H), 1.49 – 1.41 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.35 – 1.19 (m, 2H), 1.29 (s, 3H), 1.21 (s, 9H), 1.12 – 0.86 (m, 5H), 0.97 (s, 3H), 0.74 (t,  $J = 7.1$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  178.6, 158.6, 148.1, 137.5, 129.1 (q,  $J = 283.3$  Hz), 126.2, 118.7, 103.1, 67.6, 56.0, 52.7 (q,  $J = 22.1$  Hz), 47.5, 43.9, 41.0, 40.5, 39.0, 37.7, 30.5, 29.4, 28.8, 27.6, 27.4, 26.4, 26.2, 23.3, 22.1, 21.2, 14.0.

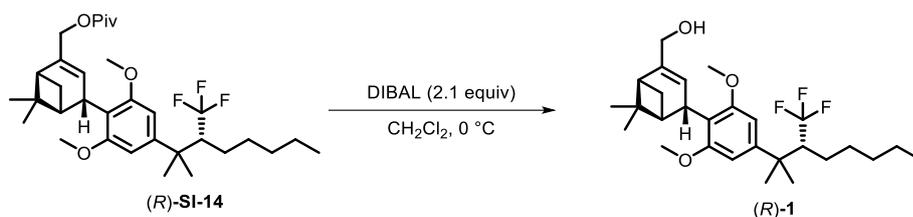
$^{19}\text{F NMR}$  (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.1.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2956, 2932, 2870, 1727, 1605, 1575, 1461, 1412, 1149.

**HRMS (ESI)**:  $m/z = 589.3460$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{33}\text{H}_{49}\text{F}_3\text{NaO}_4$   $m/z = 589.3475$ ).

$[\alpha]_{\text{D}}^{25} = +58.259 \pm 0.119$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (*R*)-1



Solution of (*R*)-SI-14 (26.1 mg, 46.0  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.4 mL) was cooled to 0  $^\circ\text{C}$  and DIBAL (1.0 M in hexanes, 97  $\mu\text{L}$ , 96.7  $\mu\text{mol}$ , 2.1 equiv) was added dropwise. The mixture was stirred at 0  $^\circ\text{C}$  for 15 min. and subsequently quenched with sat. aq. Rochelle's salt (4 mL) and diluted with  $\text{Et}_2\text{O}$  (5 mL). The mixture was vigorously stirred at rt until the phases cleanly separated. The phases were separated and the aqueous phase extracted with  $\text{Et}_2\text{O}$  ( $2 \times 5$  mL). Combined organic fractions were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 5 – 20%  $\text{EtOAc}$  in hexanes) afforded the product as a clear oil (18.3 mg, 82%).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.47 (s, 2H), 5.69 (dt,  $J = 2.8, 1.4$  Hz, 1H), 4.07 (ddd,  $J = 1.9, 1.3, 0.6$  Hz, 2H), 4.03 – 3.98 (m, 1H), 3.75 (s, 6H), 2.31 (qdd,  $J = 10.3, 7.4, 2.6$  Hz, 1H), 2.25 – 2.16 (m, 2H), 2.04 (tt,  $J = 5.8, 1.9$  Hz, 1H), 1.69 (d,  $J = 8.3$  Hz, 1H), 1.50 – 1.41 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.34 – 1.16 (m, 2H), 1.31 (s, 3H), 1.12 – 0.89 (m, 5H), 0.97 (s, 3H), 0.74 (t,  $J = 7.1$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  158.6, 148.1, 142.2, 129.1 (q,  $J = 283.4$  Hz), 123.6, 118.8, 103.2, 66.8, 56.1, 52.7 (q,  $J = 22.2$  Hz), 47.6, 44.0, 41.0, 40.5, 37.6, 31.6, 29.4, 28.8, 28.0, 26.4, 26.3, 23.3, 22.2, 21.2, 14.0.

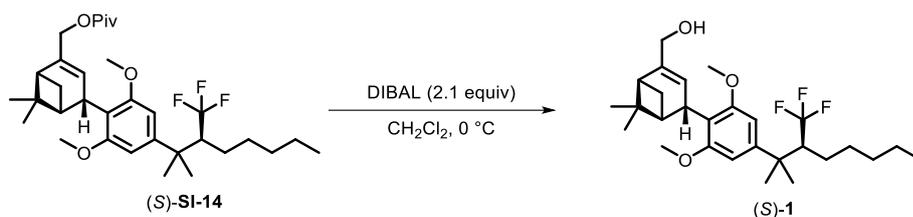
$^{19}\text{F NMR}$  (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.1.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3373, 2929, 2866, 1605, 1574, 1460, 1412, 1239, 1119.

**HRMS (ESI)**:  $m/z = 505.2903$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{28}\text{H}_{41}\text{F}_3\text{NaO}_3$   $m/z = 505.2900$ ).

$[\alpha]_{\text{D}}^{25} = +97.242 \pm 0.182$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (S)-1



Solution of (S)-SI-14 (24.0 mg, 42.3  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.4 mL) was cooled to 0  $^\circ\text{C}$  and DIBAL (1.0 M in hexanes, 89  $\mu\text{L}$ , 88.9  $\mu\text{mol}$ , 2.1 equiv) was added dropwise. The mixture was stirred at 0  $^\circ\text{C}$  for 15 min. and subsequently quenched with sat. aq. Rochelle's salt (4 mL) and diluted with  $\text{Et}_2\text{O}$  (5 mL). The mixture was vigorously stirred at rt until the phases cleanly separated. The phases were separated and the aqueous phase extracted with  $\text{Et}_2\text{O}$  ( $2 \times 5$  mL). Combined organic fractions were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 5 – 20%  $\text{EtOAc}$  in hexanes) afforded the product as a clear oil (16.6 mg, 81%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.47 (s, 2H), 5.69 (dt,  $J = 2.8, 1.4$  Hz, 1H), 4.11 – 4.04 (m, 2H), 4.04 – 3.96 (m, 1H), 3.75 (s, 6H), 2.32 (qdd,  $J = 10.2, 7.4, 2.5$  Hz, 1H), 2.25 – 2.16 (m, 2H), 2.04 (tt,  $J = 5.9, 1.9$  Hz, 1H), 1.68 (d,  $J = 8.2$  Hz, 1H), 1.51 – 1.45 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.34 – 1.16 (m, 2H), 1.31 (s, 3H), 1.12 – 0.87 (m, 5H), 0.97 (s, 3H), 0.74 (t,  $J = 7.0$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  158.7, 148.1, 142.2, 129.1 (d,  $J = 283.3$  Hz), 123.6, 118.8, 103.2, 66.8, 56.0, 52.7 (q,  $J = 22.0$  Hz), 47.6, 44.0, 41.0, 40.5, 37.6, 31.6, 29.4, 28.8, 28.0, 26.4, 26.2, 23.3, 22.2, 21.2, 14.0.

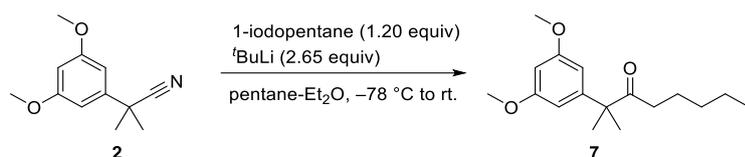
$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.1.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3371, 2929, 2866, 1605, 1574, 1459, 1412, 1239, 1119.

**HRMS (ESI)**:  $m/z = 505.2902$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{28}\text{H}_{41}\text{F}_3\text{NaO}_3$   $m/z = 505.2900$ ).

$[\alpha]_{\text{D}}^{25} = +78.198 \pm 0.132$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of 7



A solution of 1-iodopentane (3.82 mL, 29.2 mmol, 1.20 equiv) in 3:2 pentane-Et<sub>2</sub>O (300 mL) was cooled to -78 °C under argon atmosphere and *t*-BuLi (1.7 M in pentane, 38.0 mL, 64.6 mmol, 2.65 equiv) was added dropwise. The solution was stirred at -78 °C for 5 min following addition, and then the mixture was allowed to reach rt. and was left standing for 1 h. The reaction mixture was cooled back to -78 °C, and a solution of **2** (5.00 g, 24.4 mmol, 1.00 equiv) in pentane (10 mL) was added in one portion. The mixture was stirred for 5 min. at -78 °C, allowed to warm up to rt. and stirred for 1.5 h. The reaction was quenched by addition of aq. HCl (0.5 M, 50 mL). The organic solvents were removed under reduced pressure, THF (150 mL) and aq. HCl (0.5 M, 100 mL) were added and the mixture stirred vigorously overnight at rt. The mixture was diluted with EtOAc (150 mL), layers were separated, and the aqueous phase was extracted with EtOAc (2 × 150 mL). Combined organic extracts were washed with 5% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (150 mL), followed by brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 0 – 15% Et<sub>2</sub>O in hexanes) afforded the product as a light-yellow liquid (6.10 g, 90%).

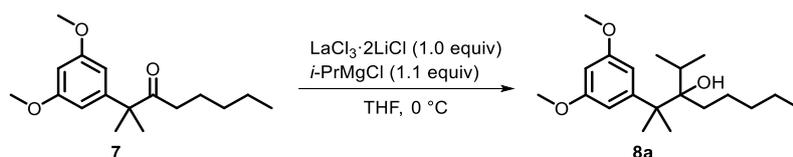
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.36 (d, J = 2.2 Hz, 2H), 6.33 (t, J = 2.2 Hz, 1H), 3.75 (s, 6H), 2.20 (t, J = 7.4 Hz, 2H), 1.50 – 1.43 (m, 2H), 1.42 (s, 6H), 1.23 – 1.02 (m, 4H), 0.79 (t, J = 7.2 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 213.0, 161.1, 146.7, 104.6, 98.3, 55.3, 52.4, 37.2, 31.4, 25.1, 24.1, 22.5, 13.9.

IR (neat, ν<sub>max</sub>/cm<sup>-1</sup>): 2956, 2932, 2872, 1708, 1594, 1456, 1423, 1205, 1155.

HRMS (ESI): *m/z* = 279.1955 [M+H]<sup>+</sup> (calc. for C<sub>17</sub>H<sub>27</sub>O<sub>3</sub> *m/z* = 279.1955).

## Synthesis of 8a



To a solution of  $\text{LaCl}_3 \cdot 2\text{LiCl}$  (0.6 M in THF, 6.00 mL, 3.59 mmol, 1.0 equiv) was added 7 (1.00 g, 3.59 mmol, 1.0 equiv) in dry THF (3.3 mL) and the resulting mixture was stirred at rt. for 1 h. The reaction mixture was cooled to  $0^\circ\text{C}$  and a solution of  $i\text{-PrMgCl}$  (1.4 M in THF, 2.82 mL, 3.95 mmol, 1.1 equiv) was added dropwise and the mixture was allowed to stir at the same temperature for 2.5 h. The mixture was quenched with sat.  $\text{NH}_4\text{Cl}$  solution (10 mL) and  $\text{H}_2\text{O}$  (10 mL) and diluted with  $\text{Et}_2\text{O}$  (10 mL). The layers were separated and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL). Combined organic extracts were dried with  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography ( $\text{SiO}_2$ ; 0 – 15%  $\text{EtOAc}$  in hexanes) to afford the product as a colourless oil (820 mg, 71%).

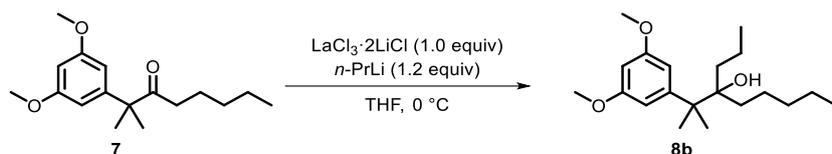
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.65 (d,  $J = 2.3$  Hz, 2H), 6.34 (t,  $J = 2.2$  Hz, 1H), 3.78 (s, 6H), 2.07 (hept,  $J = 7.0$  Hz, 1H), 1.62 (ddd,  $J = 13.9, 11.2, 4.9$  Hz, 1H), 1.50 – 1.38 (m, 1H), 1.43 (s, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.35 – 1.12 (m, 6H), 0.90 – 0.79 (m, 9H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  160.2, 150.5, 107.2, 97.4, 78.4, 55.3, 47.9, 33.7, 33.4, 33.2, 26.1, 25.3, 24.7, 22.8, 20.5, 20.2, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3573, 2955, 1594, 1457, 1421, 1204, 1155, 1052.

**HRMS (ESI):**  $m/z = 345.2398$   $[\text{M}+\text{Na}]^+$  (calc. for  $\text{C}_{20}\text{H}_{34}\text{NaO}_3$   $m/z = 345.2400$ ).

## Synthesis of 8b



### Preparation of *n*-PrLi:

To a solution of 1-iodopropane (414  $\mu$ L, 4.25 mmol, 1.20 equiv) in dry 3:2 pentane-Et<sub>2</sub>O (42 mL) at  $-78$  °C was added *t*-BuLi (1.7 M in pentane, 5.52 mL, 9.38 mmol, 2.65 equiv) dropwise. The solution was stirred at  $-78$  °C for 5 min following addition, and then the mixture was allowed to reach rt and was left standing for 1 h.

To a solution of LaCl<sub>3</sub>·2LiCl (0.6 M in THF, 5.90 mL, 3.54 mmol, 1.00 equiv) was added 7 (985 mg, 3.54 mmol, 1.00 equiv) in dry THF (3 mL) and the resulting mixture was stirred at rt for 1 h. The reaction mixture was cooled to 0 °C and the previously prepared solution of *n*-PrLi was added dropwise. The mixture was stirred for 30 min. at 0 °C and then was quenched with sat. NH<sub>4</sub>Cl solution (15 mL) and H<sub>2</sub>O (15 mL). The mixture was diluted with Et<sub>2</sub>O (15 mL), the phases were separated and the aqueous phase was extracted with Et<sub>2</sub>O (3  $\times$  15 mL). Combined organic extracts were dried with MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO<sub>2</sub>; 0 – 15% EtOAc in hexanes) to afford the product as a colourless oil (1.13 g, 99%).

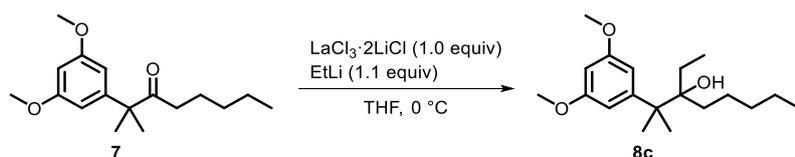
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.62 (d, *J* = 2.2 Hz, 2H), 6.35 (t, *J* = 2.2 Hz, 1H), 3.79 (s, 6H), 1.56 – 1.40 (m, 4H), 1.37 (s, 6H), 1.31 – 1.24 (m, 8H), 1.24 (s, 1H), 0.85 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  160.2, 149.8, 107.1, 97.5, 77.1, 55.4, 46.8, 38.1, 35.6, 33.1, 24.9, 24.6, 22.8, 18.2, 15.2, 14.2.

IR (neat,  $\nu_{\max}$ /cm<sup>-1</sup>): 3572, 2957, 2871, 1595, 1457, 1421, 1205, 1156, 1054.

HRMS (ESI):  $m/z$  = 245.2405 [M+Na]<sup>+</sup> (calc. for C<sub>20</sub>H<sub>34</sub>NaO<sub>3</sub>  $m/z$  = 345.2400).

## Synthesis of 8c



To a solution of  $\text{LaCl}_3 \cdot 2\text{LiCl}$  (0.6 M in THF, 5.57 mL, 3.34 mmol, 1.0 equiv) was added 7 (930 mg, 3.34 mmol, 1.0 equiv) in dry THF (3.0 mL) and the resulting mixture was stirred at rt for 1 h. The reaction mixture was cooled to  $0\text{ }^\circ\text{C}$  and a solution of  $\text{EtLi}$  (0.3 M in benzene:cyclohexane, 12.2 mL, 3.68 mmol, 1.1 equiv) was added dropwise and the mixture was allowed to stir at the same temperature for 1.5 h. The mixture was quenched with sat.  $\text{NH}_4\text{Cl}$  solution (10 mL) and  $\text{H}_2\text{O}$  (10 mL) and diluted with  $\text{Et}_2\text{O}$  (10 mL). The layers were separated and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL). The combined organic extracts were dried with  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography ( $\text{SiO}_2$ ; 0 – 15%  $\text{EtOAc}$  in hexanes) to afford the product as a colourless oil (932 mg, 99%).

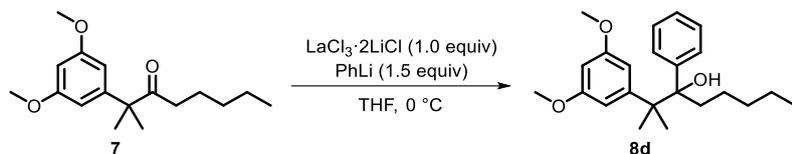
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.62 (d,  $J = 2.3$  Hz, 2H), 6.34 (t,  $J = 2.2$  Hz, 1H), 3.76 (s, 6H), 1.60 – 1.41 (m, 4H), 1.38 (s, 6H), 1.30 (s, 1H), 1.29 – 1.15 (m, 6H), 0.85 (t,  $J = 6.8$  Hz, 3H), 0.81 (t,  $J = 7.4$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  160.1, 149.7, 107.0, 97.3, 77.0, 55.1, 46.7, 34.9, 33.0, 27.8, 24.8, 24.8, 24.5, 22.6, 14.1, 9.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3568, 2954, 2872, 1594, 1456, 1421, 1204, 1154, 1021.

**HRMS (ESI)**:  $m/z = 331.2244$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{19}\text{H}_{32}\text{NaO}_3$   $m/z = 331.2244$ ).

## Synthesis of 8d



To a solution of  $\text{LaCl}_3 \cdot 2\text{LiCl}$  (0.6 M in THF, 6.29 mL, 3.77 mmol, 1.0 equiv) was added 7 (1.05 g, 3.77 mmol, 1.0 equiv) in dry THF (3.0 mL) and the resulting mixture was stirred at rt. for 1 h. The reaction mixture was cooled to  $0^\circ\text{C}$  and  $\text{PhLi}$  (1.8 M in dibutyl ether, 3.14 mL, 5.66 mmol, 1.5 equiv) was added dropwise. The mixture was stirred for 30 min. at  $0^\circ\text{C}$  and then was quenched with aq. sat.  $\text{NH}_4\text{Cl}$  solution (15 mL) and  $\text{H}_2\text{O}$  (15 mL). The aqueous phase was diluted with  $\text{Et}_2\text{O}$  (20 mL), the phases were separated and the aqueous phase extracted with  $\text{Et}_2\text{O}$  ( $3 \times 30$  mL). Combined organic extracts were dried with  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography ( $\text{SiO}_2$ ; 0 – 15%  $\text{EtOAc}$  in hexanes) to afford the product as a light yellow oil (1.33 g, 99%).

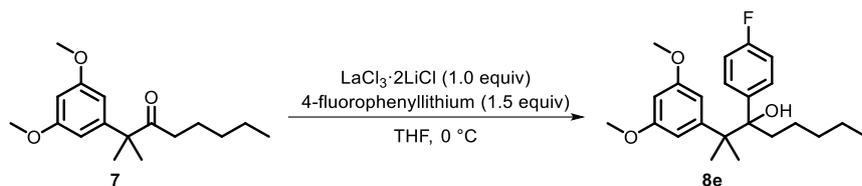
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.20 (m, 5H), 6.46 (d,  $J = 2.3$  Hz, 2H), 6.37 (t,  $J = 2.2$  Hz, 1H), 3.75 (s, 6H), 2.21 (ddd,  $J = 14.0, 11.6, 4.2$  Hz, 1H), 1.81 (s, 1H), 1.60 (ddd,  $J = 13.0, 11.6, 3.6$  Hz, 1H), 1.39 (s, 3H), 1.27 (s, 3H), 1.24 – 1.09 (m, 4H), 0.94 – 0.84 (m, 2H), 0.83 – 0.77 (m, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  160.0, 148.4, 142.5, 128.0, 127.0, 126.4, 107.5, 98.0, 80.5, 55.3, 46.7, 35.7, 32.6, 25.1, 24.8, 23.8, 22.8, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3552, 2954, 2870, 1595, 1457, 1205, 1155.

**HRMS (ESI)**:  $m/z = 379.2241$  [ $\text{M} + \text{Na}$ ] $^+$  (calc. for  $\text{C}_{23}\text{H}_{32}\text{NaO}_3$   $m/z = 379.2244$ ).

## Synthesis of 8e



### Preparation of 4-fluorophenyllithium:

To a solution of 4-fluoroiodobenzene (853  $\mu$ L, 7.40 mmol, 2.0 equiv) in dry Et<sub>2</sub>O (8.0 mL) was added at  $-78$  °C *n*-BuLi (1.6 M in hexane, 3.47 mL, 5.55 mmol, 1.5 equiv) dropwise and the solution was stirred at  $-78$  °C for 30 min.

To a solution of LaCl<sub>3</sub>·2LiCl (0.6 M in THF, 6.17 mL, 3.70 mmol, 1.0 equiv) was added 7 (1.03 g, 3.70 mmol, 1.0 equiv) in dry THF (3.0 mL) and the resulting mixture was stirred at rt. for 1 h. The reaction mixture was cooled to 0 °C and the previously prepared solution of 4-fluorophenyllithium was added dropwise. The mixture was stirred for 30 min. at 0 °C and then was quenched with aq. sat. NH<sub>4</sub>Cl solution (15 mL) and H<sub>2</sub>O (15 mL). The aqueous phase was diluted with Et<sub>2</sub>O (15 mL), the phases were separated and the aqueous phase extracted with Et<sub>2</sub>O (3  $\times$  15 mL). Combined organic extracts were dried with MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO<sub>2</sub>; 0 – 15% EtOAc in hexanes) to afford the product as a colourless oil (1.36 g, 98%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.19 (bs, 2H), 6.94 (t,  $J$  = 8.8 Hz, 2H), 6.44 (d,  $J$  = 2.0 Hz, 2H), 6.36 (t,  $J$  = 2.2 Hz, 1H), 3.75 (s, 6H), 2.21 – 2.09 (m, 1H), 1.79 (s, 1H), 1.58 (ddd,  $J$  = 15.1, 11.7, 3.5 Hz, 1H), 1.35 (s, 3H), 1.24 (s, 3H), 1.21 – 1.04 (m, 4H), 0.92 – 0.74 (m, 2H), 0.79 (t,  $J$  = 6.9 Hz, 3H).

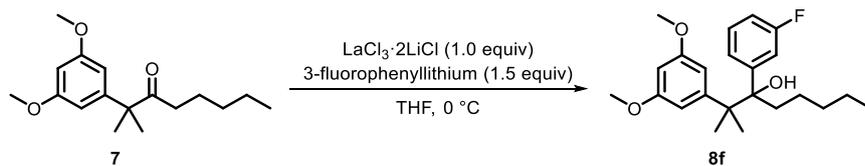
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  161.64 (d,  $J$  = 244.7 Hz), 160.1, 148.2, 138.14 (d,  $J$  = 3.1 Hz), 129.54 (d,  $J$  = 7.8 Hz), 113.69 (d,  $J$  = 20.9 Hz), 107.5, 97.9, 80.3, 55.3, 46.7, 35.8, 32.5, 24.9, 24.8, 23.8, 22.7, 14.1.

<sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$  -117.8.

IR (neat,  $\nu_{\text{max}}$ /cm<sup>-1</sup>): 3559, 2955, 2872, 1595, 1508, 1457, 1421, 1205, 1156, 1054.

HRMS (ESI):  $m/z$  = 397.2156 [M+Na]<sup>+</sup> (calc. for C<sub>23</sub>H<sub>31</sub>FN<sub>3</sub>O<sub>3</sub>  $m/z$  = 397.2149).

## Synthesis of 8f



### Preparation of 3-fluorophenyllithium:

To a solution of 3-fluoroiodobenzene (861  $\mu\text{L}$ , 7.33 mmol, 2.0 equiv) in dry  $\text{Et}_2\text{O}$  (8.0 mL) was added at  $-78\text{ }^\circ\text{C}$   $n\text{-BuLi}$  (1.6 M in hexane, 3.43 mL, 5.50 mmol, 1.5 equiv) dropwise and the solution was stirred at  $-78\text{ }^\circ\text{C}$  for 30 min.

To a solution of  $\text{LaCl}_3 \cdot 2\text{LiCl}$  (0.6 M in THF, 6.11 mL, 3.66 mmol, 1.0 equiv) was added 7 (1.02 g, 3.66 mmol, 1.0 equiv) in dry THF (3.0 mL) and the resulting mixture was stirred at rt for 1 h. The reaction mixture was cooled to  $0\text{ }^\circ\text{C}$  and the previously prepared solution of 3-fluorophenyllithium was added dropwise. The mixture was stirred for 30 min. at  $0\text{ }^\circ\text{C}$  and then quenched with aq. sat.  $\text{NH}_4\text{Cl}$  solution (15 mL) and  $\text{H}_2\text{O}$  (15 mL). The mixture was diluted with  $\text{Et}_2\text{O}$  (15 mL), the phases were separated and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 15\text{ mL}$ ). Combined organic extracts were dried with  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography ( $\text{SiO}_2$ ; 0 – 15%  $\text{EtOAc}$  in hexanes) to afford the product as a colourless oil (1.26 g, 99%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 – 7.20 (m, 1H), 7.11 – 6.99 (m, 2H), 6.98 – 6.91 (m, 1H), 6.51 (d,  $J = 2.3\text{ Hz}$ , 2H), 6.41 (t,  $J = 2.2\text{ Hz}$ , 1H), 3.78 (s, 6H), 2.27 – 2.14 (m, 1H), 1.88 (s, 1H), 1.70 – 1.56 (m, 1H), 1.41 (s, 3H), 1.29 (s, 3H), 1.20 (d,  $J = 4.2\text{ Hz}$ , 4H), 0.94 – 0.77 (m, 2H), 0.82 (t,  $J = 6.8\text{ Hz}$ , 3H).

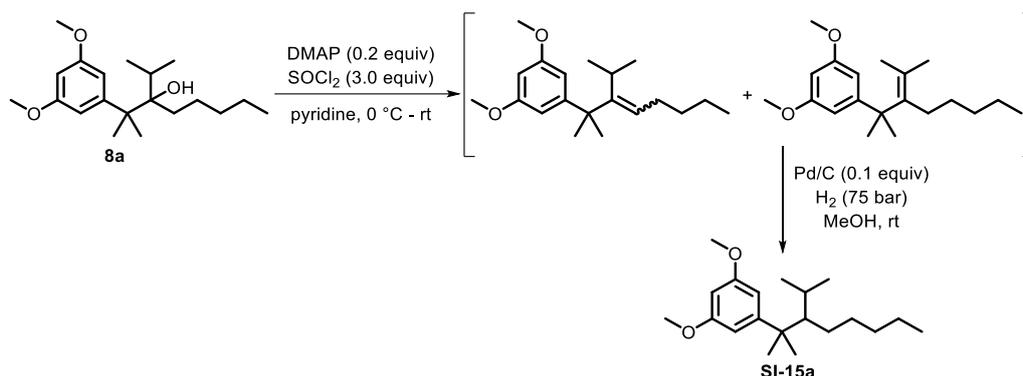
$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  162.33 (d,  $J = 243.6\text{ Hz}$ ), 160.1, 148.0, 145.58 (d,  $J = 6.6\text{ Hz}$ ), 128.15 (d,  $J = 8.0\text{ Hz}$ ), 123.54 (d,  $J = 2.7\text{ Hz}$ ), 115.22 (d,  $J = 22.4\text{ Hz}$ ), 113.11 (d,  $J = 21.1\text{ Hz}$ ), 107.5, 98.0, 80.3, 55.3, 46.6, 35.8, 32.5, 25.0, 24.7, 23.7, 22.7, 14.1.

$^{19}\text{F NMR}$  (377 MHz,  $\text{CDCl}_3$ )  $\delta$  -114.5.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3554, 2955, 2871, 1594, 1457, 1422, 1205, 1156, 1059.

**HRMS (ESI):**  $m/z = 397.2144$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{23}\text{H}_{31}\text{FNaO}_3$   $m/z = 397.2149$ ).

## Synthesis of SI-15a



To a solution of **8a** (550 mg, 1.71 mmol, 1.0 equiv) in dry pyridine (6.0 mL) was added DMAP (41.7 mg, 341  $\mu$ mol, 0.2 equiv). The mixture was cooled to 0 °C, SOCl<sub>2</sub> (373  $\mu$ L, 5.12 mmol, 3.0 equiv) was added dropwise and the solution was allowed to warm up to rt. and stirred for 30 min. The reaction was quenched by addition of aq. 1 M HCl (30 mL) and diluted with EtOAc (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (50 mL). Combined organic phases were washed with 0.5 M HCl (2  $\times$  20 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The unpurified material was dissolved in dry MeOH (3.0 mL), Pd (10 wt% on C, 182 mg, 171  $\mu$ mol, 0.1 equiv) was added and the resulting mixture was stirred in an autoclave at rt for 48 h under 75 bar H<sub>2</sub> pressure. Then the reaction mixture was filtered through Celite, evaporated under reduced pressure, and the residue was purified by flash column chromatography (SiO<sub>2</sub>; 0 – 10% EtOAc in hexanes) to afford the product as a colourless oil (425 mg, 81%).

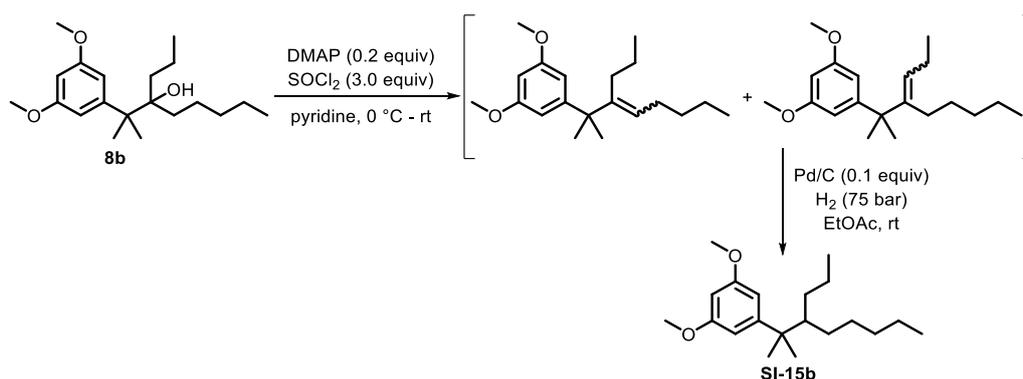
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.52 (d, *J* = 2.2 Hz, 2H), 6.31 (t, *J* = 2.2 Hz, 1H), 3.80 (s, 6H), 1.76 – 1.63 (m, 1H), 1.56 (ddd, *J* = 7.2, 3.9, 1.5 Hz, 1H), 1.34 – 1.21 (m, 8H), 1.25 (s, 3H), 1.21 (s, 3H), 0.90 – 0.80 (m, 9H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  160.4, 154.0, 105.1, 96.6, 55.3, 53.5, 43.1, 32.7, 31.4, 27.8, 27.8, 26.3, 26.3, 24.9, 22.7, 18.6, 14.2.

**IR** (neat,  $\nu_{\text{max}}$ /cm<sup>-1</sup>): 2955, 2872, 1595, 1456, 1421, 1205, 1155, 1055.

**GC-MS (EI)**: *m/z* = 306.2557 [M]<sup>+</sup> (calc. for C<sub>20</sub>H<sub>34</sub>O<sub>2</sub> *m/z* = 306.2553).

## Synthesis of SI-15b



To a solution of **8b** (840 mg, 2.61 mmol, 1.0 equiv) in dry pyridine (6.5 mL) was added DMAP (63.6 mg, 521  $\mu\text{mol}$ , 0.2 equiv). The mixture was cooled to 0 °C,  $\text{SOCl}_2$  (570  $\mu\text{L}$ , 7.81 mmol, 3.0 equiv) was added dropwise and the solution was allowed to warm up to rt. and stirred for 30 min. The reaction was quenched by addition of aq. 1 M HCl (30 mL) and diluted with EtOAc (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (50 mL). Combined organic phases were washed with 0.5 M HCl (2  $\times$  20 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The unpurified material was dissolved in dry EtOAc (7.0 mL), Pd (10 wt% on C, 278 mg, 261  $\mu\text{mol}$ , 0.1 equiv) was added and the resulting mixture was stirred in an autoclave at rt for 24 h under 75 bar hydrogen pressure. Then the reaction mixture was filtered through Celite and the residue was purified by flash column chromatography ( $\text{SiO}_2$ ; 0 – 10% EtOAc in hexanes) to afford the product as a colourless oil (790 mg, 99%).

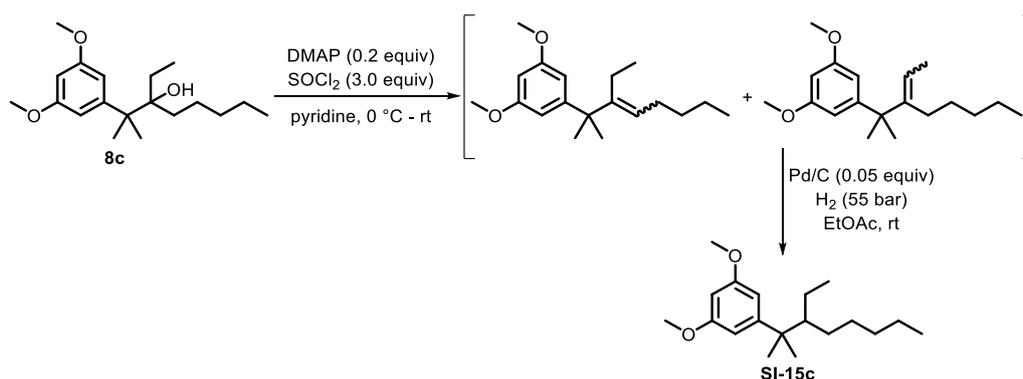
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.56 (d,  $J = 2.3$  Hz, 2H), 6.34 (t,  $J = 2.2$  Hz, 1H), 3.81 (s, 6H), 1.51 (tt,  $J = 7.4, 2.6$  Hz, 1H), 1.47 – 1.18 (m, 10H), 1.25 (s, 6H), 1.14 – 1.03 (m, 2H), 0.96 – 0.78 (m, 6H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  160.4, 153.5, 105.2, 96.6, 55.1, 48.7, 41.9, 34.5, 32.5, 32.0, 29.8, 25.6, 25.4, 23.1, 22.6, 14.7, 14.1.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2956, 2931, 2871, 1595, 1456, 1421, 1205, 1155, 1055.

**GC-MS (EI)**:  $m/z = 306.2552$   $[\text{M}]^+$  (calc. for  $\text{C}_{20}\text{H}_{34}\text{O}_2$   $m/z = 306.2553$ ).

## Synthesis of SI-15c



To a solution of **8c** (932 mg, 3.02 mmol, 1.0 equiv) in dry pyridine (12.0 mL) was added DMAP (73.8 mg, 604  $\mu\text{mol}$ , 0.2 equiv). The mixture was cooled to 0 °C,  $\text{SOCl}_2$  (661  $\mu\text{L}$ , 9.07 mmol, 3.0 equiv) was added dropwise and the solution was allowed to warm up to rt. and stirred for 30 min. The reaction was quenched by addition of aq. 1 M HCl (30 mL) and diluted with EtOAc (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (50 mL). Combined organic phases were washed with 0.5 M HCl (2  $\times$  20 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The unpurified material was dissolved in dry EtOAc (6.0 mL), Pd (10 wt% on C, 161 mg, 151  $\mu\text{mol}$ , 0.05 equiv) was added and the resulting mixture was stirred in an autoclave at rt for 16 h under 55 bar  $\text{H}_2$  pressure. Then the reaction mixture was filtered through Celite, evaporated under reduced pressure, and the residue was purified by flash column chromatography ( $\text{SiO}_2$ ; 0 – 10% EtOAc in hexanes) to afford the product as a colourless oil (830 mg, 94%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.54 (d,  $J = 2.2$  Hz, 2H), 6.32 (t,  $J = 2.2$  Hz, 1H), 3.81 (s, 6H), 1.47 – 1.00 (m, 11H), 1.23 (s, 6H), 0.86 (t,  $J = 7.2$ , 3H), 0.86 (t,  $J = 6.2$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  160.4, 153.7, 105.2, 96.6, 55.3, 50.9, 42.1, 32.5, 31.5, 30.0, 25.9, 25.3, 24.6, 22.7, 14.6, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2957, 2932, 2872, 1595, 1457, 1421, 1205, 1155, 1055.

**HRMS (ESI)**:  $m/z = 315.2294$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{19}\text{H}_{32}\text{NaO}_2$   $m/z = 315.2295$ ).

## Synthesis of 9a



To a solution of **SI-15a** (230 mg, 751  $\mu\text{mol}$ , 1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (7.5 mL) at 0  $^\circ\text{C}$  was added  $\text{BBr}_3$  (1.0 M in  $\text{CH}_2\text{Cl}_2$ , 2.25 mL, 2.25 mmol, 3.0 equiv) dropwise and the green solution was stirred at 0  $^\circ\text{C}$  for 5.5 h. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (15 mL) and carefully quenched with aq. sat.  $\text{NaHCO}_3$  (15 mL). The layers were separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  mL). Combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 40% EtOAc in hexanes) afforded the product as a golden oil (220 mg, 96%).

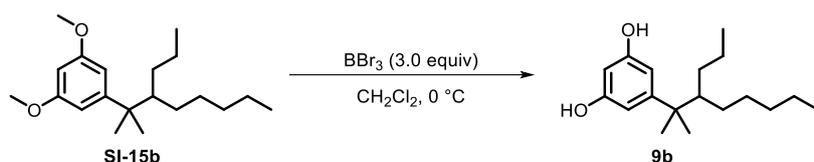
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.45 (d,  $J = 2.2$  Hz, 2H), 6.20 (t,  $J = 2.2$  Hz, 1H), 5.78 (bs, 2H), 1.65 (heptd,  $J = 7.0, 1.3$  Hz, 1H), 1.48 (ddd,  $J = 7.2, 4.0, 1.5$  Hz, 1H), 1.33 – 1.09 (m, 8H), 1.16 (s, 3H), 1.13 (s, 3H), 0.86 (t,  $J = 7.0$  Hz, 3H), 0.83 – 0.75 (m, 6H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  156.0, 155.2, 106.5, 100.1, 53.4, 40.8, 32.7, 31.4, 27.8, 27.8, 26.3, 26.2, 24.7, 22.7, 18.6, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3330, 2958, 2872, 1597, 1469, 1325, 1152, 991.

**HRMS (ESI)**:  $m/z = 279.2319$   $[\text{M}+\text{H}]^+$  (calc. for  $\text{C}_{18}\text{H}_{31}\text{O}_2$   $m/z = 279.2319$ ).

## Synthesis of 9b



To a solution of **SI-15b** (890 mg, 2.90 mmol, 1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (30 mL) at  $0\text{ }^\circ\text{C}$  was added  $\text{BBr}_3$  (827  $\mu\text{L}$ , 8.71 mmol, 3.0 equiv) dropwise and the green solution was stirred at  $0\text{ }^\circ\text{C}$  for 4 h. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (30 mL) and carefully quenched with aq. sat.  $\text{NaHCO}_3$  (30 mL). The layers were separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 50\text{ mL}$ ). Combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 40%  $\text{EtOAc}$  in hexanes) afforded the product as a golden oil (800 mg, 99%).

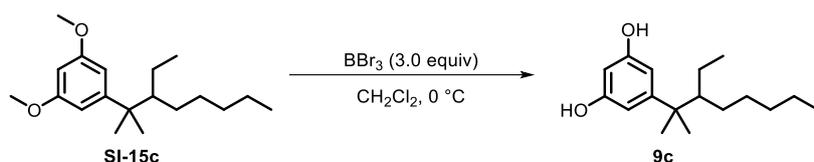
**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.59 (bs, 2H), 6.49 (d,  $J = 2.2\text{ Hz}$ , 2H), 6.23 (t,  $J = 2.1\text{ Hz}$ , 1H), 1.43 – 1.35 (m, 1H), 1.34 – 1.16 (m, 10H), 1.12 (d,  $J = 2.0\text{ Hz}$ , 6H), 1.04 – 0.92 (m, 2H), 0.84 (t,  $J = 7.1\text{ Hz}$ , 3H), 0.78 (t,  $J = 6.9\text{ Hz}$ , 3H).

**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.8, 155.0, 106.8, 100.2, 48.6, 41.8, 34.4, 32.5, 31.9, 29.7, 25.6, 25.2, 23.1, 22.7, 14.7, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3324, 2957, 2930, 2871, 1596, 1466, 1325, 1151, 992.

**HRMS (ESI)**:  $m/z = 279.2318$  [ $\text{M}+\text{H}$ ] $^+$  (calc. for  $\text{C}_{18}\text{H}_{31}\text{O}_2$   $m/z = 279.2319$ ).

## Synthesis of 9c



To a solution of **SI-15c** (890 mg, 3.04 mmol, 1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (30 mL) at 0 °C was added  $\text{BBr}_3$  (866  $\mu\text{L}$ , 9.13 mmol, 3.0 equiv) dropwise and the green solution was stirred at 0 °C for 3 h. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (30 mL) and carefully quenched with aq. sat.  $\text{NaHCO}_3$  (30 mL). The layers were separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 50$  mL). Combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 40% EtOAc in hexanes) afforded the product as a golden oil (777 mg, 97%).

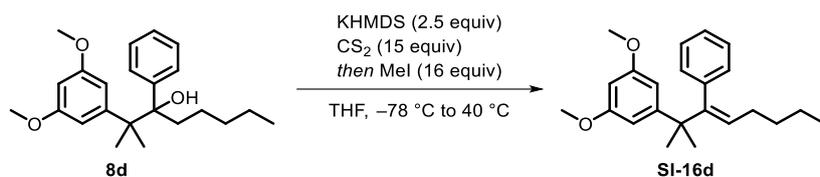
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.43 (d,  $J = 2.2$  Hz, 2H), 6.19 (t,  $J = 2.2$  Hz, 1H), 5.38 (bs, 2H), 1.37 – 1.10 (m, 9H), 1.15 (s, 3H), 1.14 (s, 3H), 1.07 – 0.95 (m, 2H), 0.84 (t,  $J = 7.1$  Hz, 3H), 0.80 (t,  $J = 7.3$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  156.1, 154.8, 106.5, 100.0, 50.8, 41.9, 32.6, 31.4, 30.0, 25.9, 25.1, 24.6, 22.7, 14.5, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3322, 2959, 2931, 2873, 1596, 1465, 1325, 1150, 991.

**HRMS (ESI)**:  $m/z = 265.2164$   $[\text{M}+\text{H}]^+$  (calc. for  $\text{C}_{17}\text{H}_{29}\text{O}_2$   $m/z = 264.2162$ ).

## Synthesis of SI-16d



To a solution of **8d** (2.65 g, 7.43 mmol, 1.0 equiv) in anhydrous THF (48 mL) at  $-78\text{ }^{\circ}\text{C}$  was added KHMDS (1.0 M in THF, 18.6 mL, 18.6 mmol, 2.5 equiv) and CS<sub>2</sub> (6.71 mL, 112 mmol, 15 equiv). The yellow solution was stirred at  $-78\text{ }^{\circ}\text{C}$  for 10 min, the cooling bath was removed and the mixture stirred for another 30 min. MeI (7.40 mL, 119 mmol, 16 equiv) was added and the mixture was first stirred at ambient temperature for 1 h, and then at  $40\text{ }^{\circ}\text{C}$  overnight. The mixture was diluted with Et<sub>2</sub>O (50 mL) and aq. sat. NaHCO<sub>3</sub> (50 mL) was added. The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O ( $2 \times 50\text{ mL}$ ). Combined organic extracts were washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 0.5% Et<sub>2</sub>O in pentanes) afforded the product as an amber orange liquid (2.35 g, 93%).

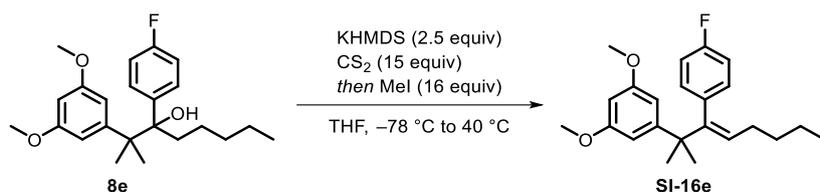
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.19 – 7.11 (m, 3H), 6.75 – 6.64 (m, 2H), 6.55 (d,  $J = 2.3\text{ Hz}$ , 2H), 6.35 (t,  $J = 2.3\text{ Hz}$ , 1H), 5.71 (t,  $J = 7.2\text{ Hz}$ , 1H), 3.79 (s, 6H), 1.78 (q,  $J = 7.1\text{ Hz}$ , 2H), 1.40 (s, 6H), 1.36 – 1.18 (m, 4H), 0.83 (t,  $J = 7.2\text{ Hz}$ , 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  160.4, 151.2, 148.5, 140.5, 129.7, 127.4, 126.5, 126.1, 105.7, 97.4, 55.3, 44.2, 32.3, 29.1, 29.0, 22.4, 14.1.

IR (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2956, 2872, 1595, 1456, 1423, 1204, 1153.

HRMS (ESI):  $m/z = 339.2315$  [M+H]<sup>+</sup> (calc. for C<sub>23</sub>H<sub>31</sub>O<sub>2</sub>  $m/z = 339.2319$ ).

## Synthesis of SI-16e



To a solution of **8e** (1.32 g, 3.53 mmol, 1.0 equiv) in anhydrous THF (22 mL) at  $-78\text{ }^{\circ}\text{C}$  was added KHMDS (0.5 M in toluene, 17.6 mL, 8.81 mmol, 2.5 equiv) and CS<sub>2</sub> (3.20 mL, 52.9 mmol, 15 equiv). The yellow solution was stirred at  $-78\text{ }^{\circ}\text{C}$  for 10 min, the cooling bath was removed and the mixture stirred for another 30 min. MeI (3.51 mL, 56.4 mmol, 16 equiv) was added and the mixture was first stirred at ambient temperature for 1 h, and then at  $40\text{ }^{\circ}\text{C}$  overnight. The mixture was diluted with Et<sub>2</sub>O (25 mL) and aq. sat. NaHCO<sub>3</sub> (25 mL) was added. The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O (2 × 25 mL). Combined organic extracts were washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; 0 – 1.5% Et<sub>2</sub>O in hexanes) afforded the product as an amber orange liquid (1.25 g, 99%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.87 – 6.77 (m, 2H), 6.63 – 6.57 (m, 2H), 6.49 (d,  $J = 2.3$  Hz, 2H), 6.32 (t,  $J = 2.3$  Hz, 1H), 5.72 (t,  $J = 7.3$  Hz, 1H), 3.77 (s, 6H), 1.79 – 1.68 (m, 2H), 1.36 (s, 6H), 1.31 – 1.19 (m, 4H), 0.80 (t,  $J = 7.1$  Hz, 3H).

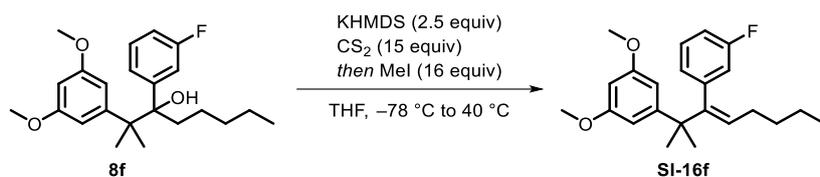
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  161.5 (d,  $J = 244.1$  Hz), 160.5, 150.8, 147.5, 136.2 (d,  $J = 3.4$  Hz), 131.2 (d,  $J = 7.6$  Hz), 126.9, 114.3 (d,  $J = 20.9$  Hz), 105.7, 97.4, 55.4, 44.2, 32.2, 29.0, 28.9, 22.4, 14.1.

<sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$  -117.2.

IR (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2958, 2933, 2867, 1600, 1508, 1458, 1422, 1205, 1155, 1059.

HRMS (ESI):  $m/z = 379.2043$  [M+Na]<sup>+</sup> (calc. for C<sub>23</sub>H<sub>29</sub>FNaO<sub>2</sub>  $m/z = 379.2044$ ).

## Synthesis of SI-16f



To a solution of **8f** (1.40 g, 3.74 mmol, 1.0 equiv) in anhydrous THF (24 mL) at  $-78\text{ }^{\circ}\text{C}$  was added KHMDS (0.5 M in toluene, 18.7 mL, 9.35 mmol, 2.5 equiv) and CS<sub>2</sub> (3.39 mL, 56.1 mmol, 15 equiv). The yellow solution was stirred at  $-78\text{ }^{\circ}\text{C}$  for 10 min, the cooling bath was removed and the mixture stirred for another 30 min. MeI (3.72 mL, 59.8 mmol, 16 equiv) was added and the mixture was first stirred at ambient temperature for 1 h, and then at  $40\text{ }^{\circ}\text{C}$  overnight. The mixture was diluted with Et<sub>2</sub>O (25 mL) and aq. sat. NaHCO<sub>3</sub> (25 mL) was added. The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O (2 × 25 mL). Combined organic extracts were washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; 0 – 1.2% Et<sub>2</sub>O in hexanes) afforded the product as an amber orange liquid (1.09 g, 82%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.10 (ddd,  $J = 8.4, 7.6, 6.1$  Hz, 1H), 6.89 – 6.82 (m, 1H), 6.52 (d,  $J = 2.3$  Hz, 2H), 6.50 – 6.46 (m, 1H), 6.41 (ddd,  $J = 10.2, 2.7, 1.5$  Hz, 1H), 6.35 (t,  $J = 2.2$  Hz, 1H), 5.73 (t,  $J = 7.3$  Hz, 1H), 3.79 (s, 6H), 1.82 – 1.73 (m, 2H), 1.39 (s, 6H), 1.37 – 1.20 (m, 4H), 0.83 (t,  $J = 7.2$  Hz, 3H).

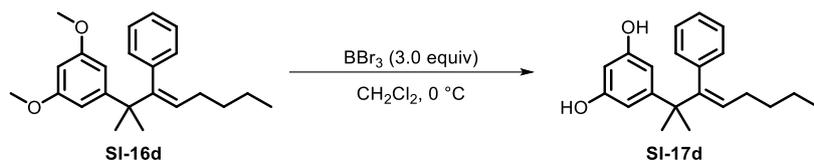
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  162.2 (d,  $J = 244.9$  Hz), 160.5, 150.7, 147.4 (d,  $J = 1.6$  Hz), 142.8 (d,  $J = 7.5$  Hz), 128.7 (d,  $J = 8.4$  Hz), 127.0, 125.57 (d,  $J = 2.8$  Hz), 116.6 (d,  $J = 20.8$  Hz), 113.0 (d,  $J = 20.9$  Hz), 105.6, 97.5, 55.3, 44.1, 32.2, 29.0, 29.0, 22.4, 14.0.

<sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$  -114.6.

IR (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2957, 2933, 2873, 1598, 1458, 1423, 1205, 1155, 1058.

HRMS (ESI):  $m/z = 379.2041$  [M+Na]<sup>+</sup> (calc. for C<sub>23</sub>H<sub>29</sub>FNaO<sub>2</sub>  $m/z = 379.2044$ ).

## Synthesis of SI-17d



To a solution of **SI-16d** (1.70 g, 5.02 mmol, 1.0 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (48 mL) at 0 °C was added BBr<sub>3</sub> (1.43 mL, 15.1 mmol, 3.0 equiv) dropwise and the green solution was stirred at 0 °C for 3 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and carefully quenched with aq. sat. NaHCO<sub>3</sub> (50 mL). The layers were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 100 mL). Combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 0 – 30% EtOAc in hexanes) afforded the product as a golden oil (1.54 g, 99%).

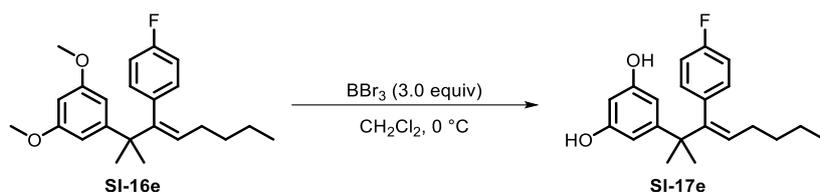
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.18 – 7.09 (m, 3H), 6.73 – 6.63 (m, 2H), 6.40 (d, J = 2.3 Hz, 2H), 6.19 (t, J = 2.2 Hz, 1H), 5.66 (t, J = 7.3 Hz, 1H), 4.87 (s, 2H), 1.72 (q, J = 7.2 Hz, 2H), 1.33 (s, 6H), 1.32 – 1.16 (m, 4H), 0.81 (t, J = 7.1 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 156.2, 152.1, 148.2, 140.5, 129.8, 127.4, 126.6, 126.2, 107.2, 100.4, 43.9, 32.3, 29.0, 28.9, 22.5, 14.1.

**IR** (neat,  $\nu_{\max}$ /cm<sup>-1</sup>): 3337, 3054, 2960, 2928, 2872, 1598, 1492, 1465, 1439, 1322, 1149.

**HRMS (ESI)**:  $m/z = 311.2013$  [M+H]<sup>+</sup> (calc. for C<sub>21</sub>H<sub>27</sub>O<sub>2</sub>  $m/z = 311.2006$ ).

## Synthesis of SI-17e



To a solution of **SI-16e** (1.25 g, 3.51 mmol, 1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (30 mL) at  $0\text{ }^\circ\text{C}$  was added  $\text{BBr}_3$  (1.0 M in  $\text{CH}_2\text{Cl}_2$ , 10.5 mL, 10.5 mmol, 3.0 equiv) dropwise and the green solution was stirred at  $0\text{ }^\circ\text{C}$  for 5.5 h. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (25 mL) and carefully quenched with aq. sat.  $\text{NaHCO}_3$  (25 mL). The layers were separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 30$  mL). Combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 50% EtOAc in hexanes) afforded the product as a golden oil (1.14 g, 99%).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.86 – 6.78 (m, 2H), 6.64 – 6.57 (m, 2H), 6.38 (d,  $J = 2.2$  Hz, 2H), 6.20 (t,  $J = 2.2$  Hz, 1H), 5.68 (t,  $J = 7.2$  Hz, 1H), 5.19 (bs, 2H), 1.75 – 1.65 (m, 2H), 1.32 (s, 6H), 1.29 – 1.17 (m, 4H), 0.81 (t,  $J = 7.2$  Hz, 3H).

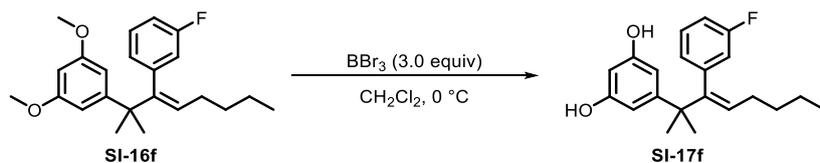
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  161.5 (d,  $J = 244.2$  Hz), 156.3, 151.8, 147.2, 136.1 (d,  $J = 3.5$  Hz), 131.2 (d,  $J = 7.6$  Hz), 127.0, 114.3 (d,  $J = 20.8$  Hz), 107.1, 100.5, 43.9, 32.2, 29.0, 28.8, 22.5, 14.1.

**$^{19}\text{F}$  NMR** (377 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.0.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3311, 2961, 2929, 2872, 1599, 1507, 1466, 1324, 1220, 1153, 993, 835.

**HRMS (ESI)**:  $m/z = 351.1729$   $[\text{M}+\text{Na}]^+$  (calc. for  $\text{C}_{21}\text{H}_{25}\text{FNaO}_2$   $m/z = 351.1731$ ).

## Synthesis of SI-17f



To a solution of **SI-16f** (1.01 g, 2.83 mmol, 1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (25 mL) at  $0\text{ }^\circ\text{C}$  was added  $\text{BBr}_3$  (1.0 M in  $\text{CH}_2\text{Cl}_2$ , 8.50 mL, 8.50 mmol, 3.0 equiv) dropwise and the green solution was stirred at  $0\text{ }^\circ\text{C}$  for 5.5 h. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (25 mL) and carefully quenched with aq. sat.  $\text{NaHCO}_3$  (25 mL). The layers were separated and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 30$  mL). Combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 50% EtOAc in hexanes) afforded the product as a golden oil (920 mg, 99%).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.08 (dd,  $J = 8.0, 6.1$  Hz, 1H), 6.83 (ddd,  $J = 8.5, 2.6, 1.0$  Hz, 1H), 6.46 (dd,  $J = 7.6, 1.2$  Hz, 1H), 6.40 (d,  $J = 2.1$  Hz, 2H), 6.39 (dd,  $J = 2.7, 1.7$  Hz, 1H), 6.20 (t,  $J = 2.2$  Hz, 1H), 5.67 (t,  $J = 7.3$  Hz, 1H), 5.27 (bs, 2H), 1.75 – 1.68 (m, 2H), 1.31 (s, 6H), 1.29 – 1.17 (m, 4H), 0.81 (t,  $J = 7.1$  Hz, 3H).

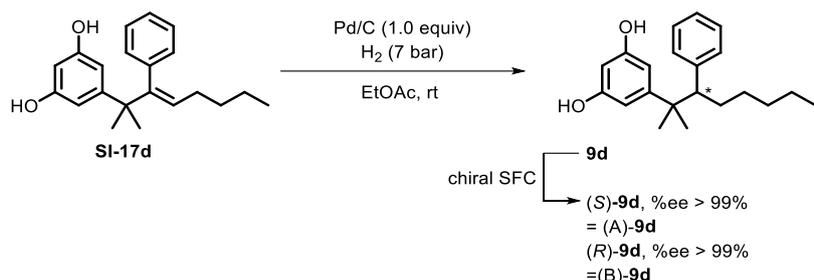
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  162.2 (d,  $J = 244.7$  Hz), 156.2, 151.8, 147.1 (d,  $J = 1.7$  Hz), 142.7 (d,  $J = 7.5$  Hz), 128.8 (d,  $J = 8.4$  Hz), 127.1, 125.6 (d,  $J = 2.7$  Hz), 116.6 (d,  $J = 20.8$  Hz), 113.1 (d,  $J = 20.9$  Hz), 107.1, 100.6, 43.8, 32.1, 29.0, 28.8, 22.4, 14.1.

**$^{19}\text{F}$  NMR** (377 MHz,  $\text{CDCl}_3$ )  $\delta$  -114.3.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3341, 2961, 2930, 2872, 1599, 1580, 1466, 1434, 1423, 1324, 1151, 993.

**HRMS (ESI)**:  $m/z = 351.1732$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{21}\text{H}_{25}\text{FNaO}_2$   $m/z = 351.1731$ ).

## Synthesis of (-)-(S)-9d/(A)-9d and (+)-(R)-9d/(B)-9d



To a solution of **SI-17d** (1.00 g, 3.22 mmol, 1.0 equiv) in EtOAc (27 mL) was added Pd (10 wt% on C, 3.43 g, 3.22 mmol, 1.0 equiv) and the mixture was stirred overnight in an autoclave under 7 bar H<sub>2</sub> pressure. The suspension was filtered over a pad of Celite and concentrated under reduced pressure to afford the product as a pink foam (960 mg, 95% yield).

The racemate was resolved by chiral SFC Method 1 to afford (-)-(S)-**9d** (430 mg, 43%, %ee >99%) and (+)-(R)-**9d** (420 mg, 42%, %ee >99%).

**Note:** vide infra for stereochemical assignment

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.28 – 7.14 (m, 3H), 7.11 – 7.03 (m, 2H), 6.39 (d, J = 2.2 Hz, 2H), 6.20 (t, J = 2.2 Hz, 1H), 4.69 (bs, 2H), 2.73 (dd, J = 12.1, 2.9 Hz, 1H), 1.61 (dddd, J = 13.3, 12.1, 9.7, 4.7 Hz, 1H), 1.38 (dddd, J = 13.1, 9.6, 6.5, 2.9 Hz, 1H), 1.22 (s, 3H), 1.18 – 1.01 (m, 4H), 1.07 (s, 3H), 1.00 – 0.79 (m, 2H), 0.74 (t, J = 6.6 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 156.2, 153.3, 141.8, 130.2, 127.5, 126.2, 106.8, 100.2, 57.1, 41.6, 31.9, 29.4, 29.1, 28.1, 23.5, 22.6, 14.2.

**IR** (neat, ν<sub>max</sub>/cm<sup>-1</sup>): 3340, 2956, 2931, 2870, 1599, 1496, 1467, 1328, 1151, 992, 704.

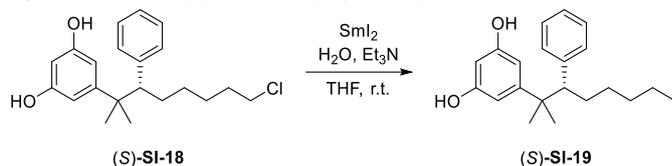
**GC-MS (EI):** m/z = 312.2084 [M]<sup>+</sup> (calc. for C<sub>21</sub>H<sub>28</sub>O<sub>2</sub> m/z = 312.2084).

(-)-(S)-**9d** [α]<sup>25</sup><sub>D</sub> = -38.557 ± 0.179 (c = 1.0, CHCl<sub>3</sub>).

(+)-(R)-**9d** [α]<sup>25</sup><sub>D</sub> = +38.058 ± 0.691 (c = 1.0, CHCl<sub>3</sub>).

## Derivatization studies for the stereochemical assignment of (*S*)-**9** and (*R*)-**9**

### Synthesis of (*S*)-**SI-19**/**(A)**-**9**/**(S)**-**9**



**Note:** The stereochemistry of (*S*)-**SI-18** was unambiguously assigned by X-Ray crystallographic analysis of a derivative in our previous work.<sup>2</sup> Herein, we defunctionalized (*S*)-**SI-18** to (*S*)-**SI-19** to compare optical rotations with authentic (**A**)-**9d** and thereby assign the C(2') configuration as (*S*) in (–)-(**S**)-**9** (see Note).

To a solution of (*S*)-**SI-18** (11.4 mg, 32.9  $\mu\text{mol}$ , 1.00 equiv) in dry THF (0.2 ml) was added dry triethylamine (128  $\mu\text{L}$ , 920  $\mu\text{mol}$ , 28.0 equiv) and water (20.7  $\mu\text{L}$ , 1.15 mmol, 35.0 equiv). The mixture was thoroughly degassed via freeze-pump-thaw procedure (3x) and back-filled with argon before a solution of  $\text{SmI}_2$  (2.30 mL, 230  $\mu\text{mol}$ , 0.1 M in THF, 7.00 equiv) was added dropwise. The ink-blue solution was allowed to stir for 12 h before diluting the reaction mixture with 1M aq HCl and EtOAc. The phases were separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ , 20 – 30% EtOAc in *n*-hexane) afforded **XX** (6.00 mg, 19.2  $\mu\text{mol}$ , 58% yield) as a colorless gum.

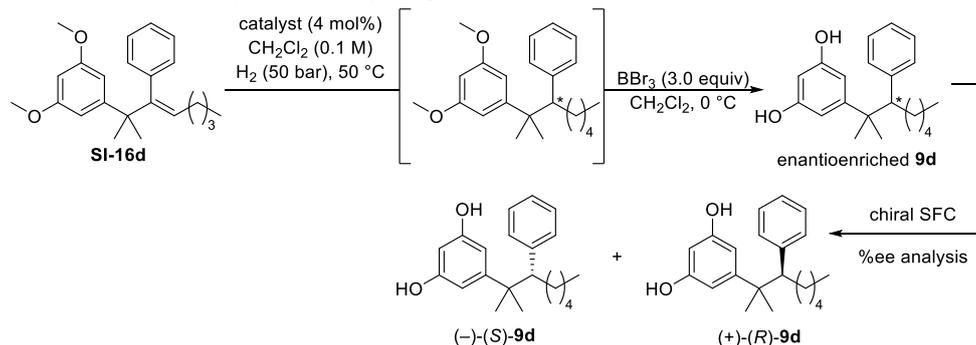
**Note:** The  $^1\text{H}$  NMR spectra and the  $[\alpha]^{25}_{\text{D}}$  of (*S*)-**SI-19** matched (**A**)-**9d**, therefore allowing for the assignment of (*S*)-**SI-19**/**(A)**-**9d** as (*S*)-**9d**.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 – 7.16 (m, 3H), 7.09 – 7.05 (m, 2H), 6.39 (d,  $J = 2.2$  Hz, 1H), 6.19 (t,  $J = 2.2$  Hz, 1H), 4.64 (bs, 2H), 2.72 (dd,  $J = 12.2, 2.9$  Hz, 1H), 1.65 – 1.59 (m, 1H), 1.37 (dddd,  $J = 13.2, 9.7, 6.4, 2.9$  Hz, 1H), 1.22 (s, 3H), 1.17 – 1.01 (m, 4H), 1.07 (s, 3H), 0.99 – 0.79 (m, 2H), 0.74 (t,  $J = 6.8$  Hz, 3zH).

$[\alpha]^{25}_{\text{D}} = -39.250 \pm 1.204$  ( $\text{CHCl}_3$ ,  $c=0.2$ )

## Asymmetric Hydrogenation Study

**Scheme S3.** Workflow for asymmetric hydrogenation and ee determination



### General Procedure:

Catalyst (2.4  $\mu\text{mol}$ , 4 mol%) was weighed into a 5 mL glass vial equipped with a stirring bar and **SI-16d** (20.0 mg, 59.1  $\mu\text{mol}$ ) in  $\text{CH}_2\text{Cl}_2$  (667  $\mu\text{L}$ ) was added. The vial was placed in a 350 mL parallel autoclave and pressurized with argon (6 bar). The autoclave was connected to a  $\text{H}_2$  line, flushed three times with  $\text{H}_2$  ( $5 \times 20$  bar) and sealed under  $\text{H}_2$  (50 bar). The autoclave was placed in a pre-heated metal block and stirred at 50  $^\circ\text{C}$  for 16 h. The pressure was released, and the solvent was removed under reduced pressure. The unpurified product was analyzed by LCMS. If reduction product was observed, the unpurified residue was treated with  $\text{BBr}_3$  in analogy to the synthesis of **SI-17e** and analyzed by chiral SFC Method 1.

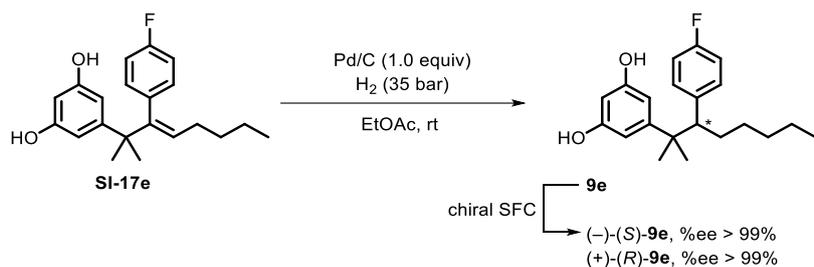
**Note:** See SFC chromatograms for Table S2 entries 1 and 11

**Table S2.** Screening of  $[\text{Ir}(\text{L}_2)(\text{cod})]\text{BAr}^{\text{F}_4}$  complexes.

Entry	Catalyst	Conversion/ %	ee/ %
1	$[\text{Ir}((S)\text{-DTB-MeOBIPHEP})(\text{cod})]\text{BAr}^{\text{F}_4}$	78	80
2	$[\text{Ir}((S,S)\text{-Cy-UBAPHOX})(\text{cod})]\text{BAr}^{\text{F}_4}$	<1	N.A.
3	$[\text{Ir}(\text{Trifer SL-F131-2})(\text{cod})]\text{BAr}^{\text{F}_4}$	<1	N.A.
4	$[\text{Ir}((S,S)\text{-Ph-Bn-SIPHOX})(\text{cod})]\text{BAr}^{\text{F}_4}$	<1	N.A.
5	$[\text{Ir}((S)\text{-Ph}_2\text{PCH}_2\text{CMe}_2\text{-ox-}t\text{-Bu})(\text{cod})]\text{BAr}^{\text{F}_4}$	<1	N.A.
6	$[\text{Ir}((S)\text{-}t\text{-Bu}_2\text{PCH}_2\text{-ox-Ph})(\text{cod})]\text{BAr}^{\text{F}_4}$	25	25
7	$[\text{Ir}((S)\text{-Cy}_2\text{PCH}_2\text{-4-ox-Ph})(\text{cod})]\text{BAr}^{\text{F}_4}$	75	11
8	(S)-Burgess' catalyst	<1	N.A.
9	$[\text{Ir}((R)\text{-IPr-DHCCP-Ph})(\text{cod})]\text{BAr}^{\text{F}_4}$	<1	N.A.
10	$[\text{Ir}((R)\text{-Ph}_2\text{PO-THQ-Ph})(\text{cod})]\text{BAr}^{\text{F}_4}$	<1	N.A.
11 <sup>‡</sup>	$[\text{Ir}((S)\text{-Cy}_2\text{PCH}_2\text{-ox-DTB})(\text{cod})]\text{BAr}^{\text{F}_4}$	97	32
12	$[\text{Ir}((S)\text{-}t\text{-Bu}_2\text{PO-DHCPP-Ph})(\text{cod})]\text{BAr}^{\text{F}_4}$	<1	N.A.
13	$[\text{Ir}((R)\text{-}^o\text{Tol}_2\text{POCMe}_2\text{-ox-}t\text{-Bu})(\text{cod})]\text{BAr}^{\text{F}_4}$	50	-8

<sup>‡</sup>The catalyst and substrate were analyzed by the quadrant model outlined by Andersson and Church<sup>28</sup> and suggests that the catalyst yields the (S)-enantiomer of **9a** preferentially. Combined with the chiral SFC analysis, the enriched product thus has the (S)- configuration at C(2').

## Synthesis of (-)-(S)-9e & (+)-(R)-9e



To a solution of **SI-17e** (800 mg, 2.44 mmol, 1.0 equiv) in EtOAc (20 mL) was added Pd (10 wt% on C, 2.59 g, 2.44 mmol, 1.0 equiv) and the mixture was stirred for 48 h at rt in an autoclave under 35 bar H<sub>2</sub> pressure. The suspension was filtered over a pad of Celite and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 20 – 30% EtOAc in hexanes) afforded the product as a golden foam (550 mg, 68% yield). The racemate was resolved by chiral SFC Method 2. to afford (-)-(S)-**9e** (170 mg, 21%, %ee >99%) and (+)-(R)-**9e** (160 mg, 20%, %ee >99%).

**Note:** Based on the close structural similarity to (*S*)-**9d** and (*R*)-**9d**, the compounds (-)-**9e** and (+)-**9e** are assigned by analogy based on optical rotation and SFC retention (the (-)-isomer elutes first under comparable conditions, see SFC methods 1 and 2) time as (-)-(S)-**9e** and (+)-(R)-**9e**.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.02 – 6.95 (m, 2H), 6.95 – 6.88 (m, 2H), 6.36 (d, *J* = 2.2 Hz, 2H), 6.21 (t, *J* = 2.2 Hz, 1H), 5.03 (bs, 2H), 2.71 (dd, *J* = 12.1, 3.0 Hz, 1H), 1.62 – 1.50 (m, 1H), 1.47 – 1.37 (m, 1H), 1.20 (s, 3H), 1.15 – 1.01 (m, 4H), 1.07 (s, 3H), 0.96 – 0.83 (m, 2H), 0.75 (t, *J* = 6.7 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 161.5 (d, *J* = 243.7 Hz), 156.2, 153.0, 137.4 (d, *J* = 3.2 Hz), 131.3 (d, *J* = 7.6 Hz), 114.3 (d, *J* = 20.8 Hz), 106.8, 100.3, 56.4, 41.6, 31.8, 29.5, 28.6, 28.0, 23.8, 22.6, 14.1.

**<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>) δ -117.4.

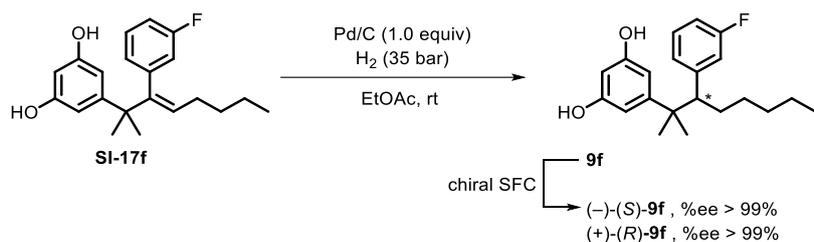
**IR** (neat,  $\nu_{\max}$ /cm<sup>-1</sup>): 3345, 2961, 2932, 2863, 1600, 1509, 1225, 1157, 993, 842.

**HRMS (ESI)**: 353.1889 [M+Na]<sup>+</sup> (calc. for C<sub>21</sub>H<sub>27</sub>FNaO<sub>2</sub> *m/z* = 353.1887).

(-)-(S)-**9e** [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -40.068 ± 0.134 (c = 1.0, CHCl<sub>3</sub>).

(+)-(R)-**9e** [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +40.982 ± 0.175 (c = 1.0, CHCl<sub>3</sub>).

## Synthesis of (-)-(S)-9f & (+)-(R)-9f



To a solution of **SI-17f** (850 mg, 2.59 mmol, 1.0 equiv) in EtOAc (25 mL) was added Pd (10 wt% on C, 2.75 g, 2.59 mmol, 1.0 equiv) and the mixture was stirred for 48 h at rt in an autoclave under 35 bar H<sub>2</sub> pressure. The suspension was filtered over a pad of Celite and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 20 – 30% EtOAc in hexanes) afforded the product as a golden foam (560 mg, 65% yield). The racemate was resolved by chiral SFC Method 3. to afford (-)-(S)-**9f** (200 mg, 23%, %ee >99%) and (+)-(R)-**9f** (190 mg, 22%, %ee >99%).

**Note:** Based on the close structural similarity to (*S*)-**9d** and (*R*)-**9d**, the compounds (-)-**9f** and (+)-**9f** are assigned by analogy based on optical rotation and SFC retention (the (-)-isomer elutes first under comparable conditions, see SFC methods 2 and 4) time as (-)-(S)-**9f** and (+)-(R)-**9f**.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.21 – 7.11 (m, 1H), 6.92 – 6.74 (m, 3H), 6.43 (d, *J* = 2.2 Hz, 2H), 6.26 (t, *J* = 2.1 Hz, 1H), 6.08 (bs, 2H), 2.73 (dd, *J* = 12.1, 2.8 Hz, 1H), 1.61 – 1.49 (m, 1H), 1.48 – 1.34 (m, 1H), 1.21 (s, 3H), 1.15 – 1.00 (m, 4H), 1.05 (s, 3H), 0.95 – 0.84 (m, 2H), 0.74 (t, *J* = 6.9 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 162.5 (d, *J* = 243.9 Hz), 156.1, 153.1, 144.7 (d, *J* = 6.7 Hz), 128.8 (d, *J* = 8.3 Hz), 126.0 (d, *J* = 1.2 Hz), 116.6 (d, *J* = 20.8 Hz), 113.0 (d, *J* = 21.0 Hz), 106.9, 100.5, 56.9, 41.5, 31.8, 29.4, 28.7, 28.0, 23.6, 22.5, 14.1.

**<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>) δ -114.4.

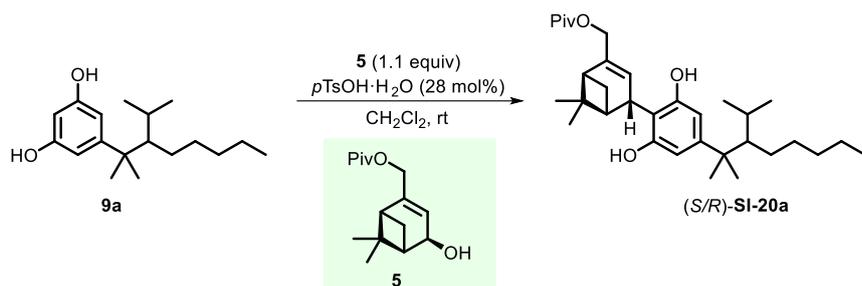
**IR** (neat,  $\nu_{\text{max}}$ /cm<sup>-1</sup>): 3342, 2960, 2933, 2862, 1595, 1486, 1466, 1445, 1326, 1150, 992, 704.

**HRMS (ESI)**: 353.1882 [M+Na]<sup>+</sup> (calc. for C<sub>21</sub>H<sub>27</sub>FNaO<sub>2</sub> *m/z* = 353.1887).

**(-)-(S)-9f** [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -40.385 ± 0.408 (c = 1.0, CHCl<sub>3</sub>).

**(+)-(R)-9f** [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +42.357 ± 0.102 (c = 1.0, CHCl<sub>3</sub>).

## Synthesis of (*S/R*)-SI-20a



To a solution of **9a** (50.1 mg, 180  $\mu$ mol, 1.0 equiv) and **5** (49.9 mg, 198  $\mu$ mol, 1.1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (7.0 mL) was added *p*TsOH·H<sub>2</sub>O (9.6 mg, 50.4  $\mu$ mol, 0.28 equiv), and the mixture was stirred for 1 h at rt. The reaction was quenched by addition of sat. aq. NaHCO<sub>3</sub> (3 mL) and diluted with Et<sub>2</sub>O (3 mL). The phases were separated, and the aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  3 mL). Combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; 2 – 8% EtOAc in hexanes) afforded the product as a colourless foam (58.6 mg, 64%).

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.35 (s, 2H), 6.02 (m, 1H), 5.90 – 5.47 (bs, 2H), 4.68 – 4.59 (m, 1H), 4.55 – 4.47 (m, 1H), 4.05 – 3.99 (m, 1H), 2.42 – 2.33 (m, 1H), 2.32 – 2.27 (m, 2H), 1.71 (dhept,  $J$  = 7.0, 1.7 Hz, 1H), 1.49 (d,  $J$  = 1.6 Hz, 1H), 1.48 – 1.43 (m, 1H), 1.34 (s, 3H), 1.30 – 1.05 (m, 8H), 1.23 (s, 9H), 1.18 (s, 3H), 1.14 (s, 3H), 0.98 (s, 3H), 0.85 (t,  $J$  = 5.2 Hz, 3H), 0.84 (d,  $J$  = 7.2 Hz, 3H), 0.78 (dd,  $J$  = 6.9, 1.2 Hz, 3H).

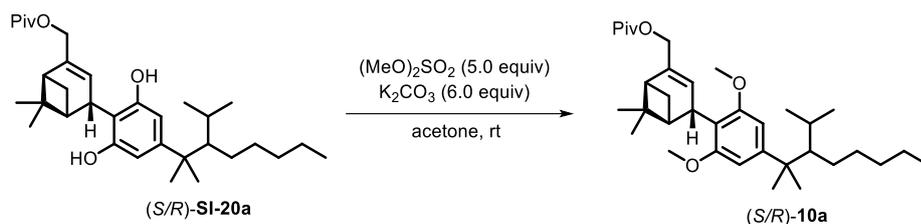
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  178.7, 154.9, 151.9, 149.4, 120.6, 111.5, 106.9, 66.6, 53.4, 47.5, 44.3, 42.4, 41.0, 39.1, 37.9, 32.6, 31.4, 28.2, 28.1, 27.7, 27.4, 27.4, 26.2, 26.0, 25.0, 22.7, 20.9, 18.6, 14.2.

**IR** (neat,  $\nu_{\text{max}}$ /cm<sup>-1</sup>): 3457, 2956, 2871, 1707, 1625, 1575, 1480, 1429, 1366, 1283, 1233, 1162, 1027, 837.

**HRMS (ESI):**  $m/z$  = 535.3749 [M+Na]<sup>+</sup> (calc. for C<sub>33</sub>H<sub>52</sub>NaO<sub>4</sub>  $m/z$  = 535.3758).

**$[\alpha]_{\text{D}}^{25}$**  = +63.340  $\pm$  0.159 ( $c$  = 1.0, CHCl<sub>3</sub>).

## Synthesis of (*S/R*)-10a



To a suspension of (*S/R*)-**SI-20a** (48.1 mg, 93.8  $\mu\text{mol}$ , 1.0 equiv) and  $\text{K}_2\text{CO}_3$  (77.8 mg, 563  $\mu\text{mol}$ , 6.0 equiv) in acetone (1.0 mL) was added  $(\text{MeO})_2\text{SO}_2$  (45  $\mu\text{L}$ , 469  $\mu\text{mol}$ , 5.0 equiv). The resulting purple suspension was stirred for 20 h at rt. The reaction was quenched by addition of sat. aq.  $\text{NaHCO}_3$  (3 mL). The phases were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 3$  mL). Combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 0 – 15%  $\text{Et}_2\text{O}$  in hexanes) afforded the product as a pale pink oil (38.2 mg, 75%).

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.49 (m, 2H), 5.82 – 5.75 (m, 1H), 4.61 – 4.55 (m, 1H), 4.54 – 4.47 (m, 1H), 4.02 – 3.98 (m, 1H), 3.74 (s, 6H), 2.21 – 2.12 (m, 2H), 2.08 – 2.01 (m, 1H), 1.77 – 1.65 (m, 2H), 1.55 – 1.48 (m, 1H), 1.36 – 1.05 (m, 8H), 1.30 (s, 3H), 1.25 (s, 3H), 1.21 (s, 9H), 1.20 (s, 3H), 0.98 (s, 3H), 0.86 (dd,  $J = 7.1, 1.1$  Hz, 3H), 0.85 (t,  $J = 7.2$  Hz, 3H), 0.80 (d,  $J = 6.9$  Hz, 3H).

**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.6, 158.4, 150.7, 137.3, 126.6, 117.7, 103.3, 67.7, 55.9, 53.7, 47.5, 44.0, 43.1, 41.0, 39.0, 37.7, 32.7, 31.4, 27.8, 27.7, 27.6, 27.5, 26.5, 26.3, 25.2, 25.1, 22.7, 21.2, 18.6, 14.2.

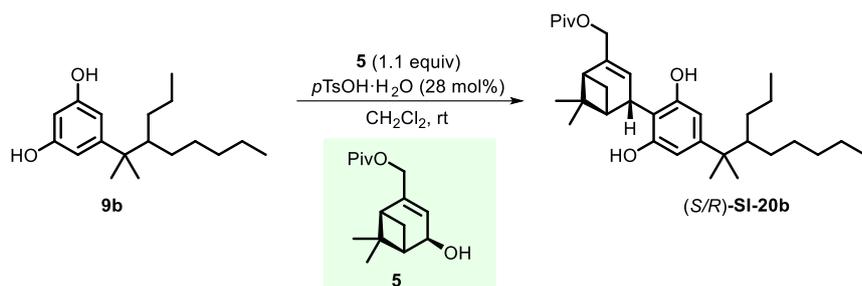
**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2946, 2870, 1728, 1605, 1572, 1461, 1410, 1365, 1280, 1239, 1151, 1122, 832.

**HRMS (ESI)**:  $m/z = 563.4057$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{35}\text{H}_{56}\text{NaO}_4$   $m/z = 563.4071$ ).

**$[\alpha]_D^{25}$**  =  $+89.637 \pm 0.233$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).



## Synthesis of (*S/R*)-SI-20b



To a solution of (*S/R*)-**9b** (50.6 mg, 182  $\mu\text{mol}$ , 1.0 equiv) and **5** (60.0 mg, 236  $\mu\text{mol}$ , 1.3 equiv) in  $\text{CH}_2\text{Cl}_2$  (7.0 mL), was added  $p\text{TsOH}\cdot\text{H}_2\text{O}$  (9.7 mg, 50.8  $\mu\text{mol}$ , 0.28 equiv) and the mixture was stirred for 30 min at rt. The reaction was quenched by addition of sat. aq.  $\text{NaHCO}_3$  (3 mL). The phases were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 5$  mL). Combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 0 – 10%  $\text{EtOAc}$  in hexanes) afforded the product as a white foam (82.2 mg, 88%).

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.35 (s, 2H), 6.04 – 5.99 (m, 1H), 5.90 – 5.51 (bs, 2H), 4.67 – 4.59 (m, 1H), 4.55 – 4.47 (m, 1H), 4.04 – 3.99 (m, 1H), 2.40 – 2.33 (m, 1H), 2.32 – 2.27 (m, 2H), 1.49 (d,  $J = 9.7$  Hz, 1H), 1.35 – 0.91 (m, 12H), 1.34 (s, 3H), 1.23 (s, 9H), 1.14 (s, 3H), 1.13 (s, 3H), 0.98 (s, 3H), 0.84 – 0.80 (m, 1H), 0.82 (t,  $J = 7.0$  Hz, 3H), 0.80 (t,  $J = 7.0$  Hz, 3H).

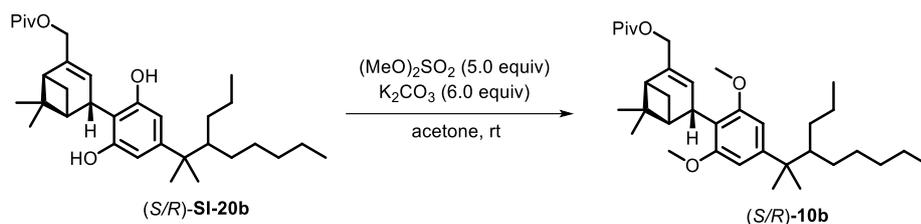
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.7, 154.9, 151.5, 149.4, 120.6, 111.5, 107.0, 66.6, 48.7, 47.5, 44.3, 41.4, 41.1, 39.1, 37.9, 34.4, 32.5, 31.9, 29.8, 28.1, 27.4, 26.0, 25.7, 25.1, 23.1, 22.7, 20.9, 14.8, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3458, 2956, 2929, 2870, 1730, 1708, 1625, 1574, 1479, 1462, 1429, 1366, 1282, 1232, 1159, 1026, 837, 757.

**HRMS (ESI):**  $m/z = 535.375$  [ $\text{M}+\text{Na}$ ]<sup>+</sup> (calc. for  $\text{C}_{33}\text{H}_{52}\text{NaO}_4$   $m/z = 535.3758$ ).

**$[\alpha]_{\text{D}}^{25}$**  =  $+53.675 \pm 0.246$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (*S/R*)-10b



To a suspension of (*S/R*)-SI-20b (82.2 mg, 160  $\mu\text{mol}$ , 1.0 equiv) and  $\text{K}_2\text{CO}_3$  (133 mg, 962  $\mu\text{mol}$ , 6.0 equiv) in acetone (1.6 mL) was added  $(\text{MeO})_2\text{SO}_2$  (76  $\mu\text{L}$ , 80.2  $\mu\text{mol}$ , 5.0 equiv) and the mixture was stirred for 19 h at rt. The suspension was filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 0 – 15%  $\text{Et}_2\text{O}$  in hexanes) afforded the product as a pale pink oil (86.0 mg, 99%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.49 (s, 2H), 5.81 – 5.76 (m, 1H), 4.62 – 4.55 (m, 1H), 4.54 – 4.48 (m, 1H), 4.03 – 3.98 (m, 1H), 3.74 (s, 6H), 2.20 – 2.13 (m, 2H), 2.08 – 2.01 (m, 1H), 1.75 – 1.68 (m, 1H), 1.46 – 0.97 (m, 12H), 1.30 (s, 3H), 1.22 (s, 12H), 1.21 (s, 3H), 0.98 (s, 3H), 0.85 – 0.80 (m, 1H), 0.82 (t,  $J = 7.1$  Hz, 3H), 0.82 (t,  $J = 7.0$  Hz, 3H).

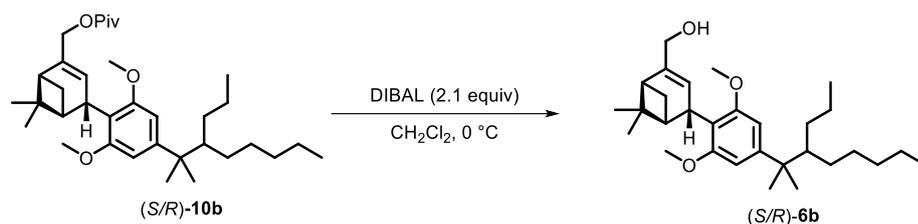
$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.7, 158.4, 150.4, 137.3, 126.6, 117.7, 103.5, 67.7, 56.0, 48.9, 47.6, 44.0, 42.0, 41.0, 39.0, 37.7, 34.6, 32.5, 32.1, 29.9, 27.7, 27.5, 26.5, 26.0, 25.4, 23.1, 22.7, 21.2, 14.8, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2955, 2928, 2868, 1728, 1605, 1572, 1461, 1410, 1280, 1239, 1151, 1123.

**HRMS (ESI)**:  $m/z = 563.4056$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{35}\text{H}_{56}\text{NaO}_4$   $m/z = 563.4071$ ).

$[\alpha]_{\text{D}}^{25} = +65.594 \pm 0.383$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (*S/R*)-6b



A solution of (*S/R*)-**10b** (86.0 mg, 159  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (1.6 mL) was cooled to 0  $^\circ\text{C}$  and DIBAL (1.0 M in hexanes, 334  $\mu\text{L}$ , 334  $\mu\text{mol}$ , 2.1 equiv) was added dropwise. The mixture was stirred at 0  $^\circ\text{C}$  for 20 min, subsequently diluted with  $\text{CH}_2\text{Cl}_2$  (2 mL) and quenched with sat. aq. Rochelle's salt (5 mL). The mixture was stirred vigorously at rt until the phases cleanly separated. The layers were separated, and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  ( $5 \times 3$  mL). Combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 10 – 20%  $\text{EtOAc}$  in hexanes) afforded the product (61.6 mg, 85%) as a pale pink oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.50 (s, 2H), 5.73 – 5.69 (m, 1H), 4.08 (s, 2H), 4.03 – 3.98 (m, 1H), 3.74 (s, 6H), 2.26 – 2.17 (m, 2H), 2.09 – 2.03 (m, 1H), 1.71 (d,  $J = 7.9$  Hz, 1H), 1.47 – 1.39 (m, 1H), 1.38 – 0.99 (m, 11 H), 1.31 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 0.97 (s, 3H), 0.87 – 0.83 (m, 1H), 0.83 (t,  $J = 7.0$  Hz, 3H), 0.82 (t,  $J = 7.1$  Hz, 3H).

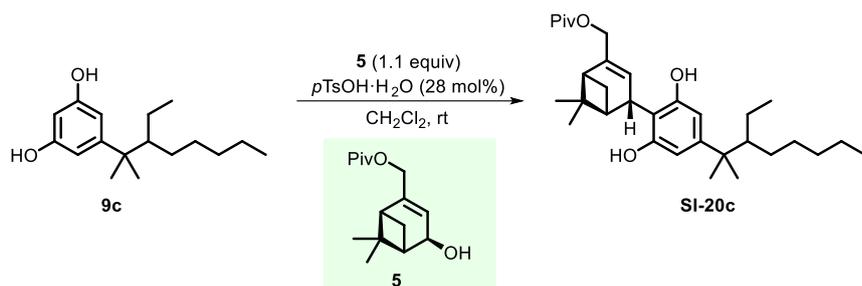
$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  158.4, 150.3, 142.0, 123.9, 117.8, 103.5, 66.8, 56.0, 48.8, 47.6, 43.9, 42.0, 41.0, 37.6, 34.6, 32.5, 32.0, 29.9, 28.0, 26.4, 25.9, 25.4, 23.1, 22.6, 21.2, 14.8, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3368, 2954, 2930, 2868, 1605, 1571, 1463, 1409, 1238, 1121, 831.

**HRMS (ESI)**:  $m/z = 495.3234$  [ $\text{M}+\text{K}$ ] $^+$  (calc. for  $\text{C}_{30}\text{H}_{48}\text{KO}_3$   $m/z = 495.3235$ ).

$[\alpha]_{\text{D}}^{25} = +92.576 \pm 0.103$  ( $c = 1.0$ ,  $\text{CDCl}_3$ ).

## Synthesis of (*S/R*)-SI-20c



To a solution of **9c** (52.0 mg, 197  $\mu$ mol, 1.0 equiv) and **5** (54.6 mg, 216  $\mu$ mol, 1.1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (6.7 mL) was added *p*TsOH·H<sub>2</sub>O (10.5 mg, 55.0  $\mu$ mol, 0.28 equiv) and the solution was stirred for 30 min. The reaction was stopped by addition on sat. aq. NaHCO<sub>3</sub> (5 mL) and diluted with Et<sub>2</sub>O (10 mL). The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O (3  $\times$  10 mL). Combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 0 – 20% EtOAc in hexanes) afforded the product as a colourless foam (72.0 mg, 73%).

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.35 (s, 2H), 6.01 (dt, *J* = 3.1, 1.7 Hz, 1H), 5.63 (bs, 2H), 4.63 (ddd, *J* = 13.5, 2.0, 1.2 Hz, 1H), 4.51 (ddd, *J* = 13.5, 2.4, 1.6 Hz, 1H), 4.07 – 3.94 (m, 1H), 2.40 – 2.33 (m, 1H), 2.32 – 2.27 (m, 2H), 1.49 (d, *J* = 9.6 Hz, 1H), 1.42 – 0.79 (m, 11H), 1.34 (s, 3H), 1.23 (s, 9H), 1.15 (s, 3H), 1.14 (s, 3H), 0.98 (s, 3H), 0.83 (t, *J* = 6.8 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H).

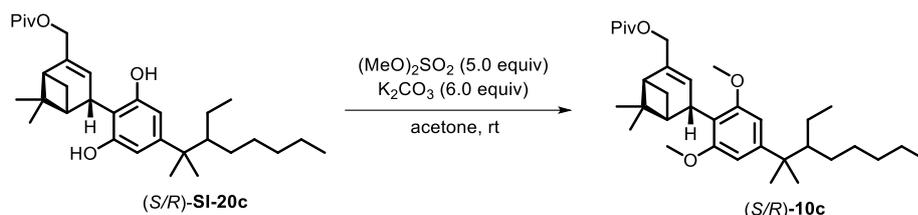
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  178.6, 154.9, 151.6, 149.5, 120.5, 111.5, 107.0, 66.6, 50.8, 47.5, 44.3, 41.5, 41.1, 39.1, 37.9, 32.5, 31.3, 30.0, 28.2, 27.4, 26.0, 25.7, 25.2, 24.6, 22.7, 20.9, 14.5, 14.2.

**IR** (neat,  $\nu_{\text{max}}$ /cm<sup>-1</sup>): 3453, 2958, 2931, 2872, 1730, 1708, 1625, 1575, 1480, 1157.

**HRMS (ESI):** *m/z* = 521.3596 [M+Na]<sup>+</sup> (calc. for C<sub>32</sub>H<sub>50</sub>NaO<sub>4</sub> *m/z* = 521.3601).

**$[\alpha]_{\text{D}}^{25}$**  = +53.699  $\pm$  0.155 (*c* = 1.0, CHCl<sub>3</sub>).

## Synthesis of (*S/R*)-10c



To a solution of (*S/R*)-**SI-20c** (43.0 mg, 86.2  $\mu\text{mol}$ , 1.0 equiv) in acetone (0.9 mL) was added  $(\text{MeO})_2\text{SO}_2$  (40.9  $\mu\text{L}$ , 431  $\mu\text{mol}$ , 5.0 equiv) and  $\text{K}_2\text{CO}_3$  (71.5 mg, 517  $\mu\text{mol}$ , 6.0 equiv) and the light purple suspension was stirred overnight at rt. The reaction mixture was filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 5%  $\text{Et}_2\text{O}$  in hexanes) afforded the product as a light red wax (40.0 mg, 88%).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.49 (s, 2H), 5.78 (dt,  $J = 2.8, 1.4$  Hz, 1H), 4.60 – 4.56 (m, 1H), 4.52 – 4.49 (m, 1H), 4.02 – 3.98 (m, 1H), 3.73 (s, 6H), 2.22 – 2.11 (m, 2H), 2.11 – 1.99 (m, 1H), 1.77 – 1.66 (m, 1H), 1.44 – 1.00 (m, 11H), 1.29 (s, 3H), 1.22 (s, 3H), 1.21 (s, 9H), 1.21 (s, 3H), 0.97 (s, 3H), 0.84 (t,  $J = 7.3$  Hz, 3H), 0.83 (t,  $J = 7.1$  Hz, 3H).

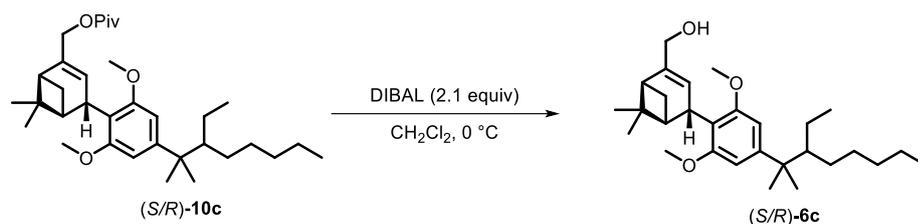
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  178.6, 158.4, 150.4, 137.3, 126.6, 117.7, 103.5, 67.7, 56.0, 51.1, 47.5, 44.0, 42.1, 41.0, 39.0, 37.7, 32.5, 31.5, 30.0, 27.7, 27.5, 26.5, 25.7, 25.7, 24.7, 22.7, 21.2, 14.6, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2957, 2930, 2871, 1728, 1605, 1573, 1461, 1410, 1151.

**HRMS (ESI)**:  $m/z = 549.3917$   $[\text{M}+\text{Na}]^+$  (calc. for  $\text{C}_{34}\text{H}_{54}\text{NaO}_4$   $m/z = 549.3914$ ).

$[\alpha]_{\text{D}}^{25} = +67.051 \pm 0.163$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (*S/R*)-6c



A solution of (*S/R*)-10c (20.0 mg, 37.9  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.3 mL) was cooled to 0  $^\circ\text{C}$  and DIBAL (1.0 M in hexanes, 80  $\mu\text{L}$ , 79.7  $\mu\text{mol}$ , 2.1 equiv) was added dropwise. The mixture was stirred at 0  $^\circ\text{C}$  for 15 min. and subsequently quenched with sat. aq. Rochelle's salt (4 mL) and diluted with  $\text{Et}_2\text{O}$  (5 mL). The mixture was vigorously stirred at rt. until the phases cleanly separated. The phases were separated and the aqueous phase extracted with  $\text{Et}_2\text{O}$  ( $3 \times 5$  mL). Combined organic fractions were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 5 – 20%  $\text{EtOAc}$  in hexanes) afforded the product as a clear wax (15.0 mg, 89%).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.50 (s, 2H), 5.71 (dt,  $J = 2.8, 1.4$  Hz, 1H), 4.08 – 4.06 (m, 2H), 4.01 – 3.99 (m, 1H), 3.74 (s, 6H), 2.25 – 2.17 (m, 2H), 2.06 (tt,  $J = 5.8, 1.8$  Hz, 1H), 1.71 (d,  $J = 8.1$  Hz, 1H), 1.45 – 0.98 (m, 11H), 1.31 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 0.97 (s, 3H), 0.84 (t,  $J = 7.4$  Hz, 3H), 0.83 (t,  $J = 7.1$  Hz, 3H).

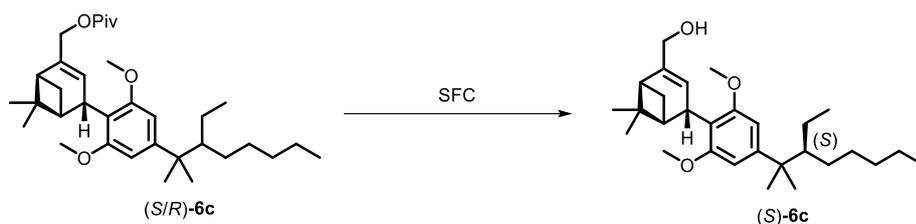
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  158.4, 150.4, 142.0, 124.0, 117.7, 103.5, 66.8, 56.0, 51.1, 47.6, 44.0, 42.1, 41.0, 37.6, 32.5, 31.5, 30.0, 28.0, 26.4, 25.7, 25.6, 24.7, 22.7, 21.2, 14.6, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3375, 2956, 2929, 2868, 1605, 1572, 1463, 1410, 1239, 1122.

**HRMS (ESI)**:  $m/z = 460.3778$  [ $\text{M}+\text{NH}_4$ ] $^+$  (calc. for  $\text{C}_{29}\text{H}_{50}\text{NO}_3$   $m/z = 460.3785$ ).

$[\alpha]_{\text{D}}^{25} = +88.454 \pm 0.171$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (*S*)-**6c**

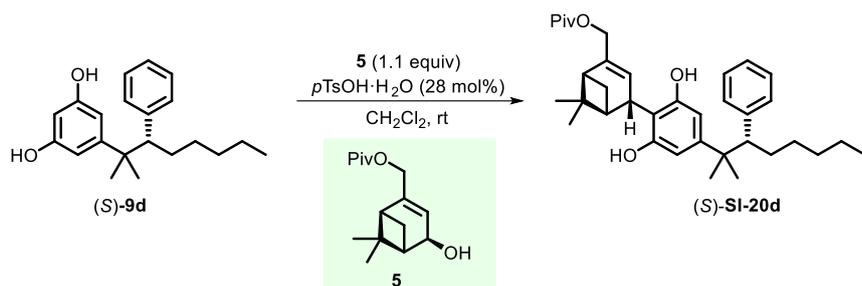


The C(2') diastereomeric mixture of (*S/R*)-**6c** was purified by chiral SFC Method 5 to yield the diastereomer (*S*)-**6c** (4.5 mg, 27%, ee > 99%).

**Note:** Based on the structural similarity to (*R*)-**1** ( $[\alpha]_{\text{D}}^{25} = +97.242 \pm 0.182$ ) and (*S*)-**1** ( $[\alpha]_{\text{D}}^{25} = +58.259 \pm 0.119$ ), and taking into account the optical rotation of the C(2') diastereomeric mixture **6c** ( $[\alpha]_{\text{D}}^{25} = +88.454 \pm 0.171$ ), the compound is tentatively assigned as (*S*)-**6c**.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are homogenous and indistinguishable from the C(2') epimeric mixture.

$[\alpha]_{\text{D}}^{25} = +54.405 \pm 0.207$  ( $c = 0.45$ ,  $\text{CHCl}_3$ ).

## Synthesis of (S)-SI-20d



To a solution of resorcinol (*S*)-**9d** (17.6 mg, 56.3 μmol, 1.0 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1.4 mL) was added *p*TsOH·H<sub>2</sub>O (3.0 mg, 15.7 μmol, 0.28 equiv) and a solution of **5** (15.6 mg, 61.9 μmol, 1.1 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.7 mL). The reaction was stirred at ambient temperature for 30 min. The reaction was quenched by addition of sat. aq. NaHCO<sub>3</sub> (2 mL). The phases were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL) and EtOAc (3 × 15 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>, 5 – 10 % EtOAc in hexanes) afforded the product (23.5 mg, 76 %) as a light-yellow foam.

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.25 – 7.14 (m, 3H), 7.12 – 7.05 (m, 2H), 6.36 (s, 2H), 6.04 (dt, *J* = 3.1, 1.5 Hz, 1H), 5.69 (s, 2H), 4.65 (dt, *J* = 13.3, 1.6 Hz, 1H), 4.53 (dt, *J* = 13.5, 1.9 Hz, 1H), 4.03 (s, 1H), 2.72 (dd, *J* = 12.1, 2.9 Hz, 1H), 2.43 – 2.35 (m, 1H), 2.35 – 2.28 (m, 2H), 1.68 – 1.54 (m, 1H), 1.51 (d, *J* = 9.6 Hz, 1H), 1.41 – 1.33 (m, 1H), 1.36 (s, 3H), 1.24 (s, 9H), 1.19 (s, 3H), 1.13 – 1.00 (m, 4H), 1.02 (s, 3H), 1.00 (s, 3H), 0.98 – 0.82 (m, 2H), 0.74 (t, *J* = 6.5 Hz, 3H).

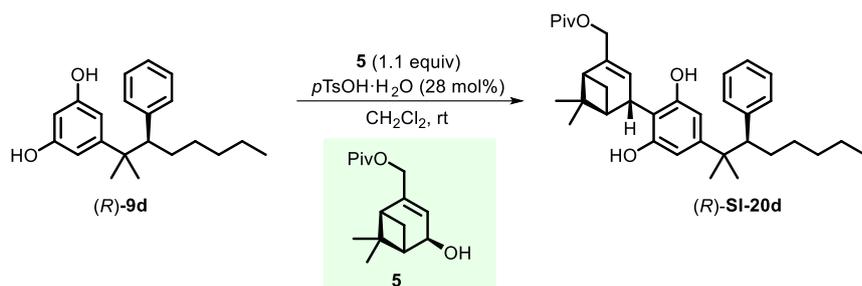
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 178.7, 154.9, 150.4, 149.5, 142.0, 130.2, 127.5, 126.1, 120.5, 111.8, 107.3, 66.6, 56.9, 47.5, 44.3, 41.2, 41.1, 39.1, 37.9, 31.8, 29.4, 29.3, 28.2, 28.0, 27.4, 26.0, 22.8, 22.5, 20.9, 14.2.

IR (neat,  $\nu_{\max}$ /cm<sup>-1</sup>): 3455, 2957, 2932, 2871, 1728, 1707, 1625, 1575, 1479, 1465, 1452, 1429, 1367, 1283, 1230, 1163, 1040, 1029, 748, 704.

HRMS (ESI): *m/z* = 569.3603 [M+Na]<sup>+</sup> (calc. for C<sub>36</sub>H<sub>50</sub>NaO<sub>4</sub> *m/z* = 569.3601).

[ $\alpha$ ]<sub>D</sub><sup>25</sup> = +19.921 ± 0.144 (*c* = 1.0, CHCl<sub>3</sub>).

## Synthesis of (*R*)-SI-20d



To a solution of resorcinol (*R*)-**9d** (18.3 mg, 58.5 μmol, 1.0 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1.7 mL) was added *p*TsOH·H<sub>2</sub>O (3.1 mg, 16.4 μmol, 0.28 equiv) and a solution of **5** (16.3 mg, 64.4 μmol, 1.1 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). The reaction was stirred at ambient temperature for 30 min. The reaction was quenched by addition of sat. aq. NaHCO<sub>3</sub> (2 mL). The phases were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL) and EtOAc (3 × 15 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>, 5 – 10% EtOAc in hexanes) afforded the product (24.3 mg, 76%) as a light-yellow foam.

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.25 – 7.14 (m, 3H), 7.10 – 6.98 (m, 2H), 6.36 (s, 2H), 6.04 (dt, *J* = 3.3, 1.6 Hz, 1H), 5.68 (bs, 2H), 4.65 (dt, *J* = 13.3, 1.7 Hz, 1H), 4.52 (dt, *J* = 13.5, 2.0 Hz, 1H), 4.08 – 3.97 (m, 1H), 2.71 (dd, *J* = 12.1, 2.9 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.34 – 2.28 (m, 2H), 1.69 – 1.56 (m, 1H), 1.52 (d, *J* = 9.7 Hz, 1H), 1.44 – 1.33 (m, 1H), 1.36 (s, 3H), 1.24 (s, 9H), 1.19 (s, 3H), 1.16 – 1.00 (m, 4H), 1.03 (s, 3H), 0.99 (s, 3H), 0.96 – 0.82 (m, 2H), 0.74 (t, *J* = 6.5 Hz, 3H).

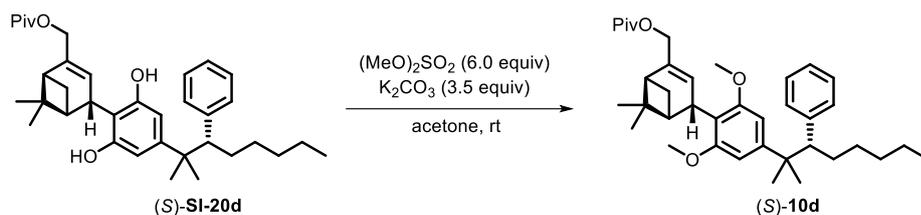
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 178.7, 154.9, 150.3, 149.6, 142.0, 130.2, 127.5, 126.1, 120.5, 111.8, 107.3, 66.6, 57.0, 47.5, 44.3, 41.2, 41.1, 39.1, 37.9, 31.9, 29.4, 29.4, 28.2, 28.0, 27.4, 26.0, 22.9, 22.5, 20.9, 14.2.

IR (neat,  $\nu_{\text{max}}$ /cm<sup>-1</sup>): 3459, 2957, 2932, 2871, 1729, 1707, 1625, 1575, 1480, 1465, 1452, 1429, 1367, 1326, 1283, 1230, 1163, 1029, 759, 704.

HRMS (ESI): *m/z* = 569.3592 [M+Na]<sup>+</sup> (calc. for C<sub>36</sub>H<sub>50</sub>NaO<sub>4</sub> *m/z* = 569.3601).

[ $\alpha$ ]<sub>D</sub><sup>25</sup> = +82.985 ± 0.109 (*c* = 1.0, CHCl<sub>3</sub>).

## Synthesis of (S)-10d



To a solution of (S)-SI-20d (23.5 mg, 42.9  $\mu$ mol, 1.0 equiv) in acetone (0.5 mL) was added (MeO)<sub>2</sub>SO<sub>2</sub> (12.2  $\mu$ L, 129  $\mu$ mol, 3.0 equiv) and K<sub>2</sub>CO<sub>3</sub> (20.8 mg, 0.150 mmol, 3.5 equiv) and the light red suspension was stirred overnight at rt. Subsequently, (MeO)<sub>2</sub>SO<sub>2</sub> (12.2  $\mu$ L, 0.129 mmol, 3.0 equiv) was added and the solution stirred for 2h at rt. The reaction mixture was diluted with Et<sub>2</sub>O (5 mL) and water (5 mL). The layers were separated and the aqueous layer extracted with Et<sub>2</sub>O (2  $\times$  5 mL). Combined organic fractions were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 0 to 5% Et<sub>2</sub>O in hexanes) afforded the product as a light red wax (21.8 g, 88%).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.25 – 7.15 (m, 3H), 7.07 – 6.98 (m, 2H), 6.42 (s, 2H), 5.79 (dt,  $J$  = 2.7, 1.4 Hz, 1H), 4.65 – 4.55 (m, 1H), 4.55 – 4.46 (m, 1H), 4.05 – 3.97 (m, 1H), 3.69 (s, 6H), 2.72 (dd,  $J$  = 12.1, 2.9 Hz, 1H), 2.21 – 2.13 (m, 2H), 2.09 – 2.02 (m, 1H), 1.73 (d,  $J$  = 7.8 Hz, 1H), 1.61 (dddd,  $J$  = 13.5, 11.9, 9.5, 4.6 Hz, 1H), 1.50 – 1.40 (m, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 1.22 (s, 9H), 1.14 (s, 3H), 1.13 – 1.02 (m, 4H), 0.98 (s, 3H), 0.97 – 0.84 (m, 2H), 0.75 (t,  $J$  = 7.0 Hz, 3H).

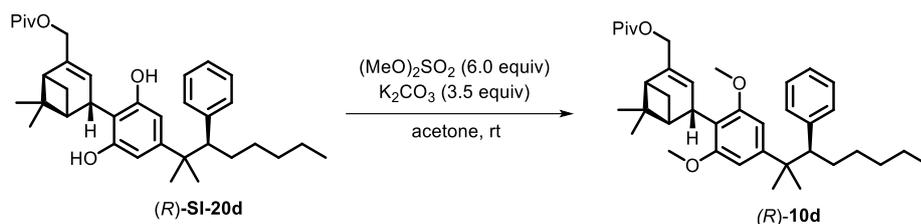
**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  178.6, 158.3, 148.7, 142.0, 137.4, 130.2, 127.4, 126.5, 126.1, 118.0, 104.0, 67.6, 57.3, 56.0, 47.6, 44.0, 41.8, 41.0, 39.0, 37.7, 31.9, 29.3, 28.8, 28.1, 27.7, 27.5, 26.5, 24.1, 22.6, 21.2, 14.2.

**IR** (neat,  $\nu_{\text{max}}$ /cm<sup>-1</sup>): 2932, 2870, 1727, 1604, 1573, 1453, 1411, 1151, 1122.

**HRMS (ESI)**:  $m/z$  = 597.3915 [M+Na]<sup>+</sup> (calc. for C<sub>38</sub>H<sub>54</sub>NaO<sub>4</sub>  $m/z$  = 597.3914).

**$[\alpha]_{\text{D}}^{25}$**  = +38.804  $\pm$  0.225 ( $c$  = 1.0, CHCl<sub>3</sub>).

## Synthesis of (*R*)-10d



To a solution of (*R*)-SI-20 (24.3 mg, 44.4  $\mu$ mol, 1.0 equiv) in acetone (0.5 mL) was added (MeO)<sub>2</sub>SO<sub>2</sub> (12.6  $\mu$ L, 0.133 mmol, 3.0 equiv) and K<sub>2</sub>CO<sub>3</sub> (21.5 mg, 0.155 mmol, 3.5 equiv) and the light red suspension was stirred overnight at rt. Subsequently, (MeO)<sub>2</sub>SO<sub>2</sub> (12.6  $\mu$ L, 0.133 mmol, 3.0 equiv) was added and the solution stirred for 2 h at rt. The reaction mixture was diluted with Et<sub>2</sub>O (5 mL) and water (5 mL). The layers were separated and the aqueous layer extracted with Et<sub>2</sub>O (2  $\times$  5 mL). Combined organic fractions were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 0 – 5% Et<sub>2</sub>O in hexanes) afforded the product as a light red wax (23.4 g, 92%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.25 – 7.15 (m, 3H), 7.06 – 6.99 (m, 2H), 6.42 (s, 2H), 5.80 (dt, *J* = 2.8, 1.4 Hz, 1H), 4.61 – 4.56 (m, 1H), 4.54 – 4.49 (m, 1H), 4.03 – 3.98 (m, 1H), 3.69 (s, 6H), 2.72 (dd, *J* = 12.0, 2.9 Hz, 1H), 2.23 – 2.13 (m, 2H), 2.06 (ddt, *J* = 5.4, 3.6, 1.8 Hz, 1H), 1.75 – 1.54 (m, 2H), 1.51 – 1.39 (m, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 1.22 (s, 9H), 1.15 (s, 3H), 1.12 – 1.03 (m, 4H), 0.99 (s, 3H), 0.96 – 0.83 (m, 2H), 0.75 (t, *J* = 6.9 Hz, 3H).

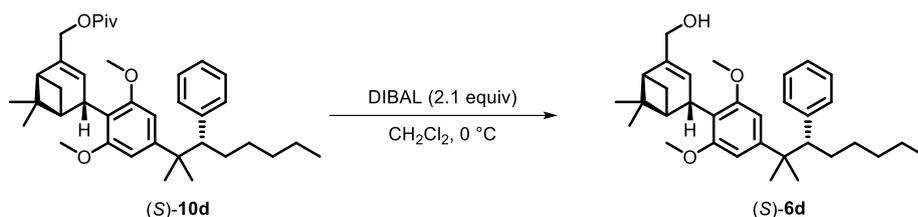
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  178.6, 158.2, 148.7, 142.0, 137.3, 130.2, 127.4, 126.6, 126.1, 118.0, 103.9, 67.7, 57.3, 55.9, 47.6, 44.0, 41.8, 41.1, 39.1, 37.7, 31.9, 29.4, 28.9, 28.1, 27.7, 27.5, 26.5, 24.1, 22.6, 21.2, 14.2.

IR (neat,  $\nu_{\max}$ /cm<sup>-1</sup>): 2931, 2869, 1727, 1604, 1573, 1452, 1411, 1151, 1122.

HRMS (ESI): *m/z* = 597.3911 [M+Na]<sup>+</sup> (calc. for C<sub>38</sub>H<sub>54</sub>NaO<sub>4</sub> *m/z* = 597.3914).

[ $\alpha$ ]<sub>D</sub><sup>25</sup> = +86.208  $\pm$  0.243 (*c* = 1.0, CHCl<sub>3</sub>).

## Synthesis of (S)-6d



Solution of (S)-**10d** (22.0 mg, 38.2  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.4 mL) was cooled to 0  $^\circ\text{C}$  and DIBAL (1.0 M in hexanes, 81  $\mu\text{L}$ , 80.7  $\mu\text{mol}$ , 2.1 equiv) was added dropwise. The mixture was stirred at 0  $^\circ\text{C}$  for 15 min. and subsequently quenched with sat. aq. Rochelle's salt (4 mL) and diluted with  $\text{Et}_2\text{O}$  (5 mL). The mixture was vigorously stirred at rt. until the phases cleanly separated. The phases were separated and the aqueous phase extracted with  $\text{Et}_2\text{O}$  ( $2 \times 5$  mL). Combined organic fractions were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 10 – 15%  $\text{EtOAc}$  in hexanes) afforded the product as a white foam (16.0 mg, 85%).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 – 7.14 (m, 3H), 7.08 – 6.96 (m, 2H), 6.43 (s, 2H), 5.76 – 5.68 (m, 1H), 4.08 (s, 2H), 4.05 – 3.98 (m, 1H), 3.70 (s, 6H), 2.73 (dd,  $J = 12.0, 2.9$  Hz, 1H), 2.28 – 2.18 (m, 2H), 2.11 – 2.00 (m, 1H), 1.78 – 1.69 (m, 1H), 1.68 – 1.54 (m, 1H), 1.52 – 1.39 (m, 1H), 1.32 (s, 3H), 1.27 (s, 3H), 1.15 (s, 3H), 1.13 – 1.02 (m, 4H), 0.98 (s, 3H), 0.96 – 0.81 (m, 2H), 0.75 (t,  $J = 6.8$  Hz, 3H).

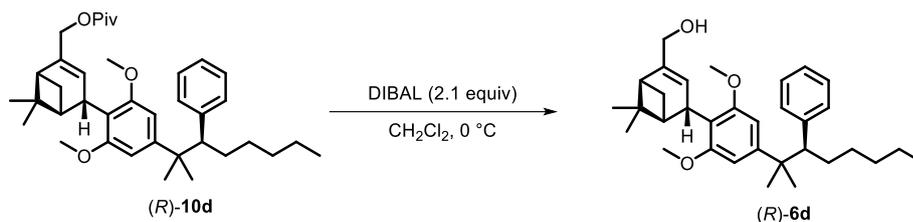
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  158.3, 148.7, 142.1, 142.0, 130.2, 127.4, 126.1, 123.9, 118.1, 104.0, 66.8, 57.3, 56.0, 47.6, 44.0, 41.8, 41.0, 37.6, 31.9, 29.4, 28.9, 28.1, 28.0, 26.4, 24.1, 22.6, 21.2, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3398, 2931, 2866, 1604, 1573, 1410, 1122.

**HRMS (ESI)**:  $m/z = 513.3335$  [ $\text{M} + \text{Na}$ ] $^+$  (calc. for  $\text{C}_{33}\text{H}_{46}\text{NaO}_3$   $m/z = 513.3339$ ).

$[\alpha]_{\text{D}}^{25} = +57.735 \pm 0.424$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (*R*)-6d



Solution of (*R*)-10d (23.4 mg, 40.7  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.4 mL) was cooled to 0  $^\circ\text{C}$  and DIBAL (1.0 M in hexanes, 86  $\mu\text{L}$ , 85.4  $\mu\text{mol}$ , 2.1 equiv) was added dropwise. The mixture was stirred at 0  $^\circ\text{C}$  for 15 min. and subsequently quenched with sat. aq. Rochelle's salt (4 mL) and diluted with  $\text{Et}_2\text{O}$  (5 mL). The mixture was vigorously stirred at rt. until the phases cleanly separated. The phases were separated and the aqueous phase extracted with  $\text{Et}_2\text{O}$  ( $2 \times 5$  mL). Combined organic fractions were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 10 – 15%  $\text{EtOAc}$  in hexanes) afforded the product as a white foam (17.3 mg, 87%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 – 7.13 (m, 3H), 7.06 – 6.99 (m, 2H), 6.43 (s, 2H), 5.79 – 5.68 (m, 1H), 4.08 (s, 2H), 4.03 – 4.00 (m, 1H), 3.70 (s, 6H), 2.73 (dd,  $J = 12.1, 2.9$  Hz, 1H), 2.28 – 2.18 (m, 2H), 2.10 – 2.05 (m, 1H), 1.76 – 1.67 (m, 1H), 1.67 – 1.54 (m, 1H), 1.50 – 1.39 (m, 1H), 1.32 (s, 3H), 1.27 (s, 3H), 1.15 (s, 3H), 1.13 – 1.03 (m, 4H), 0.98 (s, 3H), 0.96 – 0.84 (m, 2H), 0.75 (t,  $J = 6.7$  Hz, 3H).

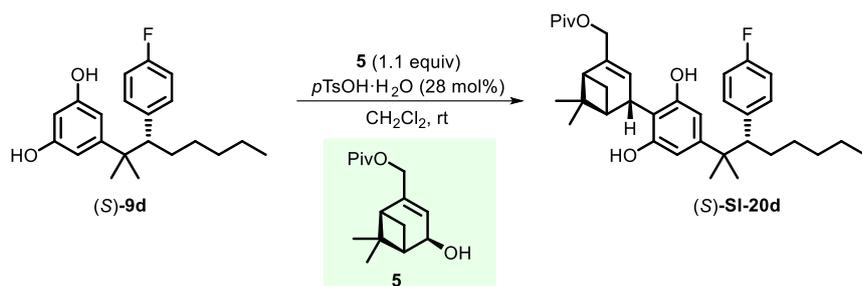
$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  158.3, 148.7, 142.0, 142.0, 130.2, 127.4, 126.1, 123.9, 118.0, 104.0, 66.8, 57.3, 56.0, 47.6, 44.0, 41.8, 41.0, 37.6, 31.9, 29.4, 28.9, 28.1, 28.0, 26.4, 24.1, 22.6, 21.2, 14.2.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3369, 2931, 2867, 1604, 1573, 1410, 1122.

**HRMS (ESI)**:  $m/z = 513.3335$  [ $\text{M} + \text{Na}$ ] $^+$  (calc. for  $\text{C}_{33}\text{H}_{46}\text{NaO}_3$   $m/z = 513.3339$ ).

$[\alpha]_{\text{D}}^{25} = +123.317 \pm 0.334$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (S)-SI-20e



To a solution of (S)-**9d** (24.0 mg, 72.6  $\mu$ mol, 1.0 equiv) and **5** (20.2 mg, 79.8  $\mu$ mol, 1.1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added *p*TsOH·H<sub>2</sub>O (3.8 mg, 20.3  $\mu$ mol, 0.28 equiv) and the solution was stirred for 30 min. The reaction was stopped by addition of sat. aq. NaHCO<sub>3</sub> (3 mL) and diluted with Et<sub>2</sub>O (5 mL). The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O (3  $\times$  5 mL). Combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; using 0 – 10% EtOAc in hexanes) afforded the product as a white foam (32.3 mg, 79%).

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.04 – 6.94 (m, 2H), 6.94 – 6.87 (m, 2H), 6.31 (s, 2H), 6.03 (dt, *J* = 3.1, 1.6 Hz, 1H), 5.69 (bs, 2H), 4.65 (dt, *J* = 13.4, 1.5 Hz, 1H), 4.52 (ddd, *J* = 13.5, 2.4, 1.6 Hz, 1H), 4.05 – 4.00 (m, 1H), 2.69 (dd, *J* = 12.0, 3.0 Hz, 1H), 2.39 (dt, *J* = 9.6, 5.6 Hz, 1H), 2.35 – 2.24 (m, 2H), 1.59 – 1.48 (m, 1H), 1.50 (d, *J* = 9.7 Hz, 1H), 1.47 – 1.38 (m, 1H), 1.35 (s, 3H), 1.24 (s, 9H), 1.17 (s, 3H), 1.15 – 1.05 (m, 4H), 1.03 (s, 3H), 0.99 (s, 3H), 0.94 – 0.83 (m, 2H), 0.75 (t, *J* = 6.7 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  178.7, 161.5 (d, *J* = 243.6 Hz), 154.9, 149.8, 149.6, 137.6 (d, *J* = 3.2 Hz), 131.3 (d, *J* = 7.5 Hz), 120.4, 114.2 (d, *J* = 20.8 Hz), 111.9, 107.3, 66.6, 56.3, 47.5, 44.3, 41.2, 41.1, 39.1, 37.9, 31.8, 29.5, 28.9, 28.2, 28.0, 27.4, 26.0, 23.4, 22.6, 20.9, 14.1.

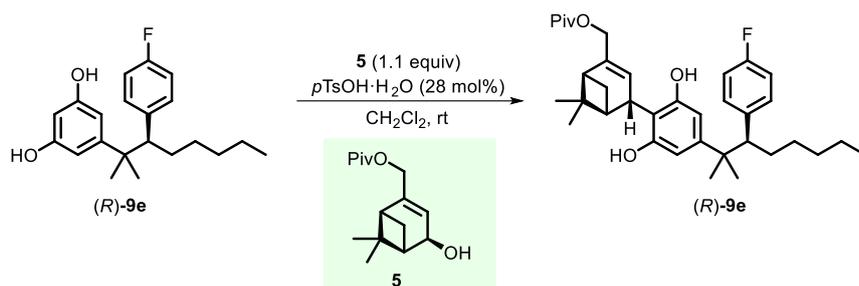
**<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>)  $\delta$  -117.6.

**IR** (neat,  $\nu_{\text{max}}$ /cm<sup>-1</sup>): 3453, 2956, 2928, 2871, 2857, 1729, 1707, 1625, 1575, 1509, 1225, 1160.

**HRMS (ESI):** *m/z* = 587.3509 [M+Na]<sup>+</sup> (calc. for C<sub>36</sub>H<sub>49</sub>FNaO<sub>4</sub> *m/z* = 587.3507).

**$[\alpha]_{\text{D}}^{25}$**  = +28.542  $\pm$  0.383 (*c* = 1.0, CHCl<sub>3</sub>).

## Synthesis of (*R*)-SI-20e



To a solution of (*R*)-**9e** (26.6 mg, 80.5  $\mu$ mol, 1.0 equiv) and **5** (22.4 mg, 88.5  $\mu$ mol, 1.1 equiv) in  $\text{CH}_2\text{Cl}_2$  (3.3 mL) was added *p*TsOH· $\text{H}_2\text{O}$  (4.3 mg, 22.5  $\mu$ mol, 0.28 equiv) and the solution was stirred for 30 min. The reaction was stopped by addition of sat. aq.  $\text{NaHCO}_3$  (3 mL) and diluted with  $\text{Et}_2\text{O}$  (5 mL). The layers were separated and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3  $\times$  5 mL). Combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; using 0 – 10%  $\text{EtOAc}$  in hexanes) afforded the product as a white foam (38.5 mg, 85%).

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.03 – 6.96 (m, 2H), 6.96 – 6.87 (m, 2H), 6.32 (s, 2H), 6.03 (dt,  $J = 3.1, 1.5$  Hz, 1H), 5.70 (bs, 2H), 4.65 (ddd,  $J = 13.5, 2.0, 1.4$  Hz, 1H), 4.52 (ddd,  $J = 13.5, 2.4, 1.6$  Hz, 1H), 4.09 – 3.96 (m, 1H), 2.69 (dd,  $J = 12.1, 3.0$  Hz, 1H), 2.39 (dt,  $J = 9.7, 5.6$  Hz, 1H), 2.35 – 2.25 (m, 2H), 1.58 – 1.48 (m, 1H), 1.50 (d,  $J = 9.8$  Hz, 1H), 1.45 – 1.38 (m, 1H), 1.35 (s, 3H), 1.24 (s, 9H), 1.17 (s, 3H), 1.14 – 1.05 (m, 4H), 1.02 (s, 3H), 0.99 (s, 3H), 0.95 – 0.81 (m, 2H), 0.74 (t,  $J = 6.6$  Hz, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  178.7, 161.5 (d,  $J = 243.6$  Hz), 154.9, 149.9, 149.6, 137.6 (d,  $J = 3.2$  Hz), 131.3 (d,  $J = 7.5$  Hz), 120.4, 114.3 (d,  $J = 20.8$  Hz), 111.9, 107.3, 66.6, 56.2, 47.5, 44.3, 41.2, 41.1, 39.1, 37.9, 31.8, 29.4, 28.8, 28.2, 28.0, 27.4, 26.0, 23.2, 22.6, 20.9, 14.1.

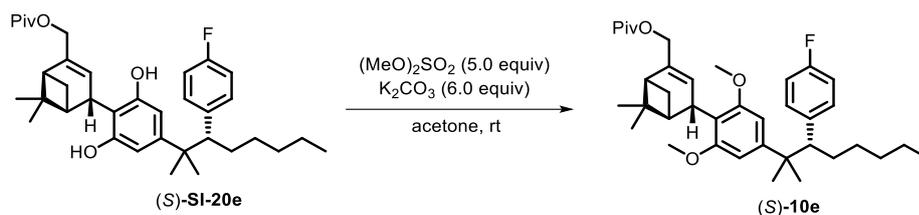
$^{19}\text{F NMR}$  (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.6.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3453, 2956, 2929, 2871, 1728, 1707, 1625, 1575, 1509, 1225, 1160.

**HRMS (ESI):**  $m/z = 587.3495$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{36}\text{H}_{49}\text{FNaO}_4$   $m/z = 587.3507$ ).

$[\alpha]_{\text{D}}^{25} = +77.406 \pm 0.191$  ( $c = 1.0, \text{CHCl}_3$ ).

## Synthesis of (S)-10e



To a suspension of (S)-SI-20e (32.3 mg, 57.1  $\mu\text{mol}$ , 1.0 equiv) and  $\text{K}_2\text{CO}_3$  (47.4 mg, 343  $\mu\text{mol}$ , 6.0 equiv) in acetone (1.0 mL) was added  $(\text{MeO})_2\text{SO}_2$  (27.1  $\mu\text{L}$ , 286  $\mu\text{mol}$ , 5.0 equiv) and the solution was stirred at rt overnight. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (5 mL), filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 0 – 5% EtOAc in hexanes) afforded the product as a white foam (28.9 mg, 85%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.00 – 6.80 (m, 4H), 6.39 (s, 2H), 5.78 (dt,  $J = 2.8, 1.4$  Hz, 1H), 4.62 – 4.55 (m, 1H), 4.54 – 4.48 (m, 1H), 4.01 (s, 1H), 3.69 (s, 6H), 2.71 (dd,  $J = 11.6, 3.4$  Hz, 1H), 2.18 (dd,  $J = 7.2, 5.6$  Hz, 2H), 2.05 (td,  $J = 6.0, 2.9$  Hz, 1H), 1.72 (d,  $J = 7.4$  Hz, 1H), 1.63 – 1.45 (m, 2H), 1.31 (s, 3H), 1.26 (s, 3H), 1.22 (s, 9H), 1.15 (s, 3H), 1.14 – 1.02 (m, 4H), 0.98 (s, 3H), 0.94 – 0.81 (m, 2H), 0.76 (t,  $J = 6.8$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.6, 161.5 (d,  $J = 243.7$  Hz), 158.3, 148.3, 137.6 (d,  $J = 3.3$  Hz), 137.4, 131.3 (d,  $J = 7.5$  Hz), 126.4, 118.1, 114.2 (d,  $J = 20.8$  Hz), 103.9, 67.6, 56.6, 55.9, 47.6, 44.0, 41.8, 41.1, 39.0, 37.7, 31.8, 29.5, 28.4, 28.0, 27.7, 27.5, 26.5, 24.4, 22.6, 21.2, 14.1.

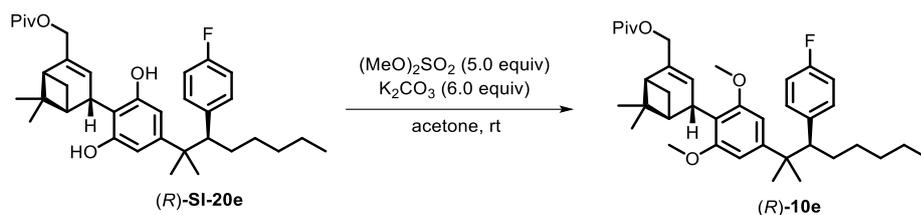
$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.6.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2955, 2930, 2869, 1726, 1658, 1604, 1572, 1508, 1479, 1462, 1410, 1381, 1365, 1339, 1280, 1239, 1224, 1152, 11122, 1032, 1015, 957, 938, 907, 841, 770, 742, 702, 670, 546.

**HRMS (ESI):**  $m/z = 615.3808$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{38}\text{H}_{53}\text{FNaO}_4$   $m/z = 615.3820$ ).

$[\alpha]_{\text{D}}^{25} = +50.994 \pm 0.086$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (*R*)-10e



To a suspension of diol (*R*)-SI-20e (38.5 mg, 68.1  $\mu\text{mol}$ , 1.0 equiv) and  $\text{K}_2\text{CO}_3$  (56.5 mg, 409  $\mu\text{mol}$ , 6.0 equiv) in acetone (1.0 mL) was added  $(\text{MeO})_2\text{SO}_2$  (32.3  $\mu\text{L}$ , 341  $\mu\text{mol}$ , 5.0 equiv) and the solution was stirred at rt overnight. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (5 mL), filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 0 – 5% EtOAc in hexanes) afforded the product as a white foam (35.5 mg, 88%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.99 – 6.85 (m, 4H), 6.39 (s, 2H), 5.79 (dt,  $J = 2.9, 1.4$  Hz, 1H), 4.62 – 4.56 (m, 1H), 4.55 – 4.48 (m, 1H), 4.01 (s, 1H), 3.69 (s, 6H), 2.71 (dd,  $J = 11.7, 3.4$  Hz, 1H), 2.22 – 2.14 (m, 2H), 2.10 – 2.02 (m, 1H), 1.70 (d,  $J = 7.8$  Hz, 1H), 1.63 – 1.45 (m, 2H), 1.31 (s, 3H), 1.26 (s, 3H), 1.22 (s, 9H), 1.15 (s, 3H), 1.14 – 1.02 (m, 4H), 0.99 (s, 3H), 0.94 – 0.81 (m, 2H), 0.76 (t,  $J = 6.8$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.6, 161.5 (d,  $J = 243.7$  Hz), 158.3, 148.3, 137.6 (d,  $J = 3.2$  Hz), 137.4, 131.3 (d,  $J = 7.3$  Hz), 126.5, 118.1, 114.2 (d,  $J = 20.8$  Hz), 103.9, 67.6, 56.6, 55.9, 47.6, 44.0, 41.8, 41.1, 39.0, 37.7, 31.8, 29.5, 28.4, 28.0, 27.7, 27.5, 26.5, 24.4, 22.6, 21.2, 14.1.

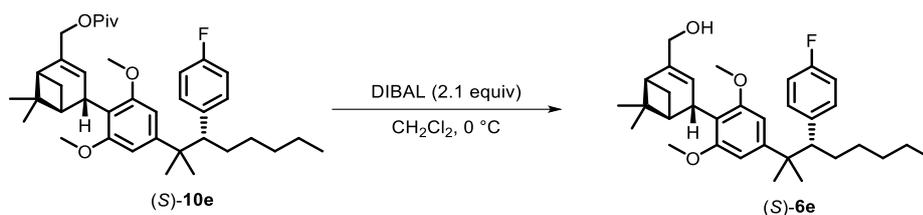
$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.6.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2931, 2869, 1726, 1658, 1604, 1572, 1508, 1479, 14623, 1410, 1397, 1381, 1364, 1339, 1280, 1239, 1224, 1151, 1121, 1042, 1031, 1015, 957, 938, 907, 841, 769, 757, 702, 562, 547, 525.

**HRMS (ESI):**  $m/z = 615.3818$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{38}\text{H}_{53}\text{FNaO}_4$   $m/z = 615.3820$ ).

$[\alpha]_{\text{D}}^{25} = +96.771 \pm 0.079$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (S)-6e



To a solution of (S)-10e (28.9 mg, 48.7  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.55 mL) was added DIBAL (102  $\mu\text{L}$ , 102  $\mu\text{mol}$ , 2.1 equiv) at 0  $^\circ\text{C}$ . After stirring the reaction for 15 minutes at 0  $^\circ\text{C}$ , sat. aq.  $\text{NH}_4\text{Cl}$  (3 mL) was added, the layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 5$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 5 – 20% EtOAc in hexanes) afforded the product as a colorless oil (21.3 mg, 86%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.02 – 6.84 (m, 4H), 6.39 (s, 2H), 5.71 (dt,  $J = 3.0, 1.4$  Hz, 1H), 4.08 (s, 2H), 4.01 (t,  $J = 2.3$  Hz, 1H), 3.69 (s, 6H), 2.71 (dd,  $J = 11.5, 3.5$  Hz, 1H), 2.27 – 2.17 (m, 2H), 2.10 – 2.03 (m, 1H), 1.72 (d,  $J = 6.9$  Hz, 1H), 1.62 – 1.45 (m, 2H), 1.32 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H), 1.13 – 1.01 (m, 4H), 0.98 (s, 3H), 0.94 – 0.82 (m, 2H), 0.76 (t,  $J = 6.6$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  161.5 (d,  $J = 243.7$  Hz), 158.3, 148.3, 142.1, 137.6 (d,  $J = 3.3$  Hz), 131.3 (d,  $J = 7.5$  Hz), 123.8, 118.2, 114.2 (d,  $J = 20.8$  Hz), 104.0, 66.8, 56.6, 56.0, 47.6, 44.0, 41.8, 41.0, 37.6, 31.8, 29.5, 28.4, 28.0, 28.0, 26.4, 24.4, 22.6, 21.2, 14.1.

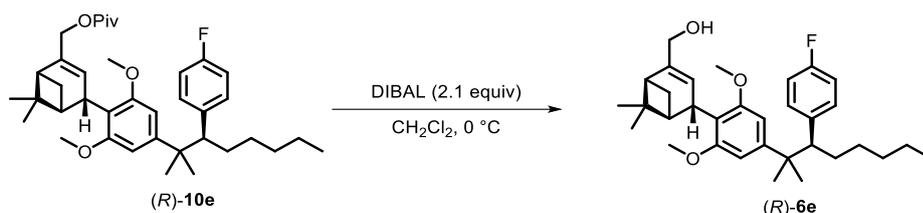
$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.6.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3378, 2928, 2863, 1655, 1604, 1572, 1508, 1461, 1410, 1380, 1364, 1340, 1301, 1238, 1224, 1184, 1160, 1120, 1049, 1014, 986, 908, 840, 743, 701, 669, 563, 547, 525.

**HRMS (ESI)**:  $m/z = 531.3238$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{33}\text{H}_{45}\text{FNaO}_3$   $m/z = 531.3245$ ).

$[\alpha]_{\text{D}}^{25} = +43.736 \pm 0.139$  ( $c = 1.0$ ,  $\text{CDCl}_3$ ).

## Synthesis of (*R*)-6e



To a solution of (*R*)-10e (35.5 mg, 59.8  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.55 mL) was added DIBAL (126  $\mu\text{L}$ , 126  $\mu\text{mol}$ , 2.1 equiv) at 0  $^\circ\text{C}$ . After stirring the reaction for 15 minutes at 0  $^\circ\text{C}$ , sat. aq.  $\text{NH}_4\text{Cl}$  (3 mL) was added, the layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 5$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 5 – 20% EtOAc in hexanes) afforded the product as a colorless oil (29.1 mg, 96%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.98 – 6.83 (m, 4H), 6.39 (s, 2H), 5.72 (dt,  $J = 2.9, 1.4$  Hz, 1H), 4.08 (s, 2H), 4.01 (s, 1H), 3.70 (s, 6H), 2.71 (dd,  $J = 11.7, 3.3$  Hz, 1H), 2.26 – 2.18 (m, 2H), 2.11 – 2.05 (m, 1H), 1.70 (d,  $J = 7.6$  Hz, 1H), 1.63 – 1.45 (m, 2H), 1.32 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H), 1.14 – 1.02 (m, 4H), 0.98 (s, 3H), 0.94 – 0.80 (m, 2H), 0.76 (t,  $J = 6.7$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  161.5 (d,  $J = 243.7$  Hz), 158.3, 148.3, 142.1, 137.6 (d,  $J = 3.2$  Hz), 131.3 (d,  $J = 7.5$  Hz), 123.7, 118.2, 114.2 (d,  $J = 20.8$  Hz), 103.9, 66.8, 56.6, 56.0, 47.6, 44.0, 41.8, 41.0, 37.6, 31.8, 29.5, 28.4, 28.0, 28.0, 26.4, 24.4, 22.6, 21.2, 14.1.

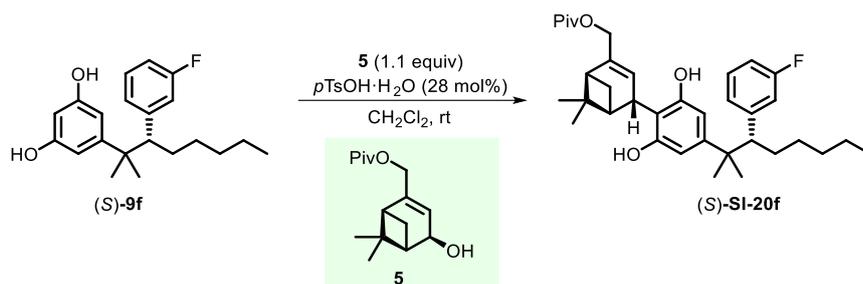
$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -117.6.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3379, 2929, 2864, 1655, 1604, 1572, 1508, 1462, 1410, 1381, 1364, 1340, 1301, 1238, 1224, 1184, 1160, 1120, 1049, 1014, 986, 908, 841, 742, 701, 670, 563, 525.

**HRMS (ESI)**:  $m/z = 531.3248$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{33}\text{H}_{45}\text{FNaO}_3$   $m/z = 531.3245$ ).

$[\alpha]_{\text{D}}^{25} = +109.233 \pm 0.100$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (S)-SI-20f



To a solution of resorcinol (S)-9f and *p*TsOH·H<sub>2</sub>O (4.1 mg, 21.6 μmol, 0.28 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added **5** (21.4 mg, 84.8 μmol, 1.1 equiv) and the solution was stirred at rt for 30 minutes. The reaction was stopped by addition of sat. aq. NaHCO<sub>3</sub> (3 mL), the layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O (3 × 5 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; 5 – 15% EtOAc in hexanes) afforded the product as a colourless foam (33.6 mg, 77%).

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.17 (td, *J* = 8.0, 6.2 Hz, 1H), 6.91 – 6.82 (m, 2H), 6.75 (dt, *J* = 10.4, 2.1 Hz, 1H), 6.33 (s, 2H), 6.03 (dt, *J* = 3.2, 1.6 Hz, 1H), 5.72 (bs, 2H), 4.65 (dt, *J* = 13.5, 1.7 Hz, 1H), 4.52 (dt, *J* = 13.5, 2.0 Hz, 1H), 4.06 – 4.01 (m, 1H), 2.71 (dd, *J* = 12.0, 2.9 Hz, 1H), 2.39 (dt, *J* = 9.7, 5.6 Hz, 1H), 2.35 – 2.28 (m, 2H), 1.62 – 1.53 (m, 1H), 1.51 (d, *J* = 9.7 Hz, 1H), 1.45 – 1.38 (m, 1H), 1.35 (s, 3H), 1.24 (s, 9H), 1.20 (s, 3H), 1.16 – 1.05 (m, 4H), 1.04 (s, 3H), 0.99 (s, 3H), 0.96 – 0.82 (m, 2H), 0.75 (t, *J* = 6.7 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 178.7, 162.5 (d, *J* = 244.0 Hz), 155.0, 149.8, 149.6, 145.0 (d, *J* = 6.7 Hz), 128.7 (d, *J* = 8.3 Hz), 126.0, 120.4, 116.6 (d, *J* = 20.8 Hz), 113.0 (d, *J* = 21.0 Hz), 112.0, 107.3, 66.6, 56.9, 47.5, 44.3, 41.2, 41.1, 39.1, 37.9, 31.8, 29.4, 28.9, 28.1, 28.0, 27.4, 26.0, 23.3, 22.5, 20.9, 14.1.

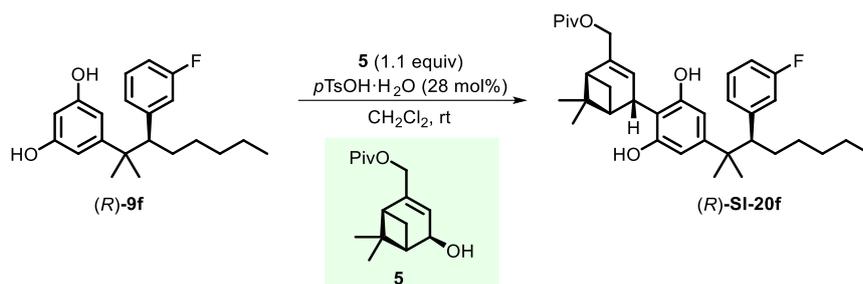
**<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ -114.7.

**IR** (neat,  $\nu_{\max}$ /cm<sup>-1</sup>): 3451, 2956, 2931, 2870, 1728, 1707, 1624, 1613, 1586, 1577, 1510, 1480, 1464, 1445, 1429, 1398, 1384, 1366, 1328, 1283, 1230, 1159, 1111, 1073, 1040, 1027, 963, 935, 916, 876, 783., 758, 724, 700, 672, 587, 569, 545, 521.

**HRMS (ESI):** *m/z* = 587.3499 [M+Na]<sup>+</sup> (calc. for C<sub>36</sub>H<sub>49</sub>FNaO<sub>4</sub> *m/z* = 587.3507).

**[α]<sup>25</sup><sub>D</sub>** = +14.014 ± 0.249 (c = 1.0, CHCl<sub>3</sub>).

## Synthesis of (*R*)-SI-20f



To a solution of resorcinol (*R*)-**9f** (25.5 mg, 77.1  $\mu$ mol, 1.0 equiv) and *p*TsOH·H<sub>2</sub>O (4.1 mg, 21.6  $\mu$ mol, 0.28 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added **5** (21.4 mg, 84.8  $\mu$ mol, 1.1 equiv) and the solution was stirred at rt for 30 minutes. The reaction was stopped by addition of sat. aq. NaHCO<sub>3</sub> (3 mL), the layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  5 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>; 5 – 15% EtOAc in hexanes) afforded the product as a colourless foam (31.6 mg, 73%).

**Note:** Allylic alcohol **5** was prepared according to our previously published procedure.<sup>27</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.23 – 7.14 (m, 1H), 6.94 – 6.82 (m, 2H), 6.76 (ddd, *J* = 10.7, 2.6, 1.6 Hz, 1H), 6.33 (s, 2H), 6.03 (dt, *J* = 3.2, 1.6 Hz, 1H), 5.73 (bs, 2H), 4.68 – 4.61 (m, 1H), 4.52 (ddd, *J* = 13.5, 2.3, 1.6 Hz, 1H), 4.03 (s, 1H), 2.71 (dd, *J* = 12.0, 2.9 Hz, 1H), 2.43 – 2.35 (m, 1H), 2.33 – 2.29 (m, 2H), 1.61 – 1.52 (m, 1H), 1.50 (d, *J* = 9.7 Hz, 1H), 1.45 – 1.37 (m, 1H), 1.35 (s, 3H), 1.24 (s, 9H), 1.20 (s, 3H), 1.19 – 1.05 (m, 4H), 1.04 (s, 3H), 0.99 (s, 3H), 0.96 – 0.80 (m, 2H), 0.75 (t, *J* = 6.6 Hz, 3H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  178.7, 162.5 (d, *J* = 244.1 Hz), 155.0, 149.9, 149.6, 145.0 (d, *J* = 6.7 Hz), 128.7 (d, *J* = 8.2 Hz), 126.0, 120.4, 116.6 (d, *J* = 20.7 Hz), 113.0 (d, *J* = 21.0 Hz), 112.0, 107.2, 66.6, 56.9, 47.5, 44.3, 41.2, 41.1, 39.1, 37.9, 31.8, 29.4, 28.9, 28.2, 28.0, 27.4, 26.0, 23.2, 22.5, 20.9, 14.1.

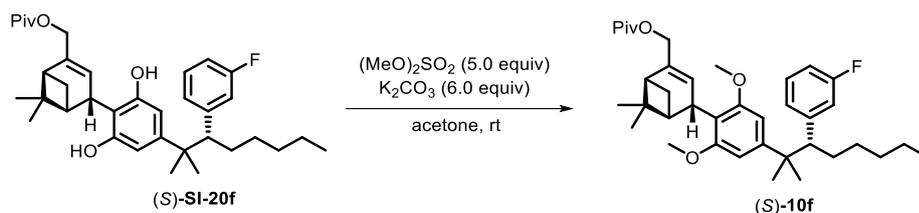
<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -114.7.

IR (neat,  $\nu_{\max}$ /cm<sup>-1</sup>): 3449, 2956, 2930, 2870, 1726, 1707, 1625, 1613, 1586, 1577, 1480, 1464, 1445, 1428, 1398, 1384, 1366, 1337, 1326, 1283, 1229, 1157, 1111, 1073, 1040, 1028, 962, 935, 916, 876, 783, 756, 724, 700, 668, 587, 569, 545, 521.

HRMS (ESI): *m/z* = 587.3498 [M+Na]<sup>+</sup> (calc. for C<sub>36</sub>H<sub>49</sub>FNaO<sub>4</sub> *m/z* = 587.3507).

$[\alpha]_{\text{D}}^{25} = +69.607 \pm 0.141$  (*c* = 1.0, CHCl<sub>3</sub>).

## Synthesis of (S)-10f



To a suspension of (S)-SI-20f (33.6 mg, 59.4  $\mu\text{mol}$ , 1.0 equiv) and  $\text{K}_2\text{CO}_3$  (49.3 mg, 357  $\mu\text{mol}$ , 6.0 equiv) in acetone (0.7 mL) was added  $(\text{MeO})_2\text{SO}_2$  (28.2  $\mu\text{L}$ , 298  $\mu\text{mol}$ , 5.0 equiv) and the solution was stirred at rt overnight. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (5 mL), filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 0 – 5% EtOAc in hexanes) afforded the product as a white foam (28.3 mg, 80%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21 – 7.12 (m, 1H), 6.91 – 6.84 (m, 1H), 6.79 (d,  $J = 7.7$  Hz, 1H), 6.75 – 6.66 (m, 1H), 6.40 (s, 2H), 5.78 (dt,  $J = 2.8, 1.4$  Hz, 1H), 4.61 – 4.55 (m, 1H), 4.55 – 4.48 (m, 1H), 4.01 (s, 1H), 3.69 (s, 6H), 2.72 (dd,  $J = 11.8, 3.2$  Hz, 1H), 2.23 – 2.14 (m, 2H), 2.08 – 2.02 (m, 1H), 1.72 (d,  $J = 7.6$  Hz, 1H), 1.62 – 1.44 (m, 2H), 1.30 (s, 3H), 1.28 (s, 3H), 1.22 (s, 9H), 1.16 (s, 3H), 1.15 – 1.03 (m, 4H), 0.98 (s, 3H), 0.94 – 0.84 (m, 2H), 0.76 (t,  $J = 6.8$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.6, 162.5 (d,  $J = 244.1$  Hz), 158.3, 148.3, 145.0 (d,  $J = 6.7$  Hz), 137.4, 128.6 (d,  $J = 8.3$  Hz), 126.4, 126.0, 118.2, 116.6 (d,  $J = 21.2$  Hz), 112.9 (d,  $J = 21.0$  Hz), 103.9, 67.6, 57.2, 56.0, 47.6, 44.0, 41.8, 41.1, 39.0, 37.7, 31.8, 29.4, 28.5, 28.0, 27.7, 27.5, 26.5, 24.3, 22.6, 21.2, 14.1.

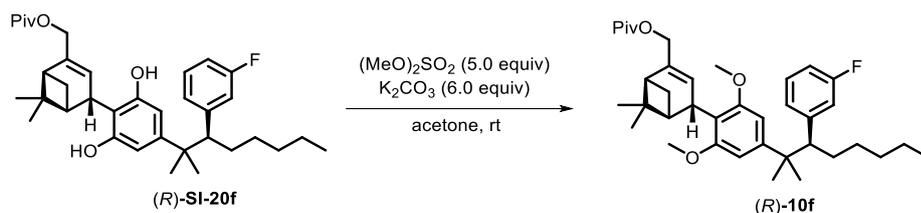
$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -114.8.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2955, 2930, 2869, 1726, 1656, 1604, 1586, 1573, 1480, 1455, 1410, 1397, 1382, 1365, 1338, 1280, 1239, 1149, 1120, 1032, 957, 928, 904, 871, 852, 832, 782, 724, 699, 585, 520.

**HRMS (ESI):**  $m/z = 615.3806$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{38}\text{H}_{53}\text{FNaO}_4$   $m/z = 615.3820$ ).

$[\alpha]_{\text{D}}^{25} = +25.224 \pm 0.173$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (*R*)-10f



To a suspension of diol (*R*)-SI-20f (31.6 mg, 55.9  $\mu\text{mol}$ , 1.0 equiv) and  $\text{K}_2\text{CO}_3$  (46.4 mg, 336  $\mu\text{mol}$ , 6.0 equiv) in acetone (0.7 mL) was added  $(\text{MeO})_2\text{SO}_2$  (26.5  $\mu\text{L}$ , 280  $\mu\text{mol}$ , 5.0 equiv) and the solution was stirred at rt overnight. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (5 mL), filtered and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 0 – 5% EtOAc in hexanes) afforded the product as a white foam (30.2 mg, 91%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.20 – 7.12 (m, 1H), 6.91 – 6.83 (m, 1H), 6.80 (d,  $J = 7.9$  Hz, 1H), 6.71 (d,  $J = 10.5$  Hz, 1H), 6.41 (s, 2H), 5.79 (s, 1H), 4.61 – 4.55 (m, 1H), 4.55 – 4.48 (m, 1H), 4.01 (s, 1H), 3.70 (s, 6H), 2.72 (dd,  $J = 11.7, 3.2$  Hz, 1H), 2.23 – 2.13 (m, 2H), 2.09 – 2.01 (m, 1H), 1.70 (d,  $J = 7.5$  Hz, 1H), 1.63 – 1.43 (m, 2H), 1.31 (s, 3H), 1.28 (s, 3H), 1.22 (s, 9H), 1.17 (s, 3H), 1.15 – 1.04 (m, 4H), 0.98 (s, 3H), 0.94 – 0.85 (m, 2H), 0.76 (t,  $J = 6.4$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.6, 162.5 (d,  $J = 244.1$  Hz), 158.3, 148.2, 145.0 (d,  $J = 6.8$  Hz), 137.4, 128.7 (d,  $J = 8.2$  Hz), 126.4, 126.0, 118.2, 116.6 (d,  $J = 20.0$  Hz), 112.9 (d,  $J = 21.0$  Hz), 103.9, 67.6, 57.2, 55.9, 47.6, 44.0, 41.8, 41.1, 39.0, 37.7, 31.8, 29.4, 28.6, 28.0, 27.7, 27.5, 26.5, 24.3, 22.6, 21.2, 14.1.

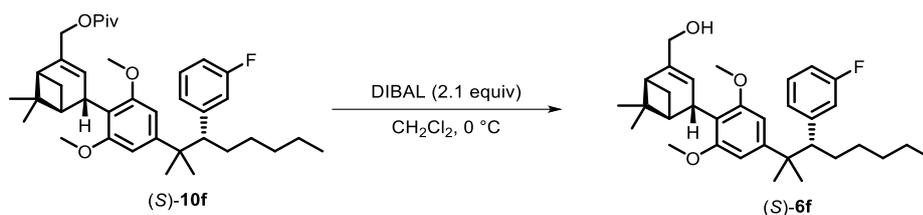
$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -114.8.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 2955, 2930, 2869, 1725, 1657, 1635, 1604, 1586, 1573, 1508, 1480, 1463, 1450, 1410, 1382, 1365, 1337, 1281, 1260, 1239, 1150, 1120, 1031, 957, 928, 904, 871, 832, 782, 756, 669, 654, 584, 521.

**HRMS (ESI)**:  $m/z = 615.3804$  [ $\text{M}+\text{Na}$ ] $^+$  (calc. for  $\text{C}_{38}\text{H}_{53}\text{FNaO}_4$   $m/z = 615.3820$ ).

$[\alpha]_{\text{D}}^{25} = +73.779 \pm 0.081$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (S)-6f



To a solution of (S)-10f (30.2 mg, 50.1  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.55 mL) was added DIBAL (107  $\mu\text{L}$ , 107  $\mu\text{mol}$ , 2.1 equiv) at 0  $^\circ\text{C}$ . After stirring the reaction for 15 minutes at 0  $^\circ\text{C}$ , sat. aq.  $\text{NH}_4\text{Cl}$  (3 mL) was added, the layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 5$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 5 – 20% EtOAc in hexanes) afforded the product as a colourless oil (21.8 mg, 84%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.22 – 7.10 (m, 1H), 6.93 – 6.83 (m, 1H), 6.79 (d,  $J = 7.7$  Hz, 1H), 6.71 (d,  $J = 10.5$  Hz, 1H), 6.41 (s, 2H), 5.71 (dt,  $J = 2.7, 1.4$  Hz, 1H), 4.08 (s, 2H), 4.03 – 3.99 (m, 1H), 3.70 (s, 6H), 2.72 (dd,  $J = 11.7, 3.2$  Hz, 1H), 2.26 – 2.19 (m, 2H), 2.09 – 2.05 (m, 1H), 1.72 (d,  $J = 7.9$  Hz, 1H), 1.65 – 1.41 (m, 2H), 1.32 (s, 3H), 1.28 (s, 3H), 1.16 (s, 3H), 1.14 – 1.02 (m, 4H), 0.98 (s, 3H), 0.96 – 0.82 (m, 2H), 0.76 (t,  $J = 6.9$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  162.4 (d,  $J = 244.1$  Hz), 158.2, 148.1, 144.8 (d,  $J = 6.7$  Hz), 142.0, 128.5 (d,  $J = 8.2$  Hz), 125.9, 123.6, 118.2, 116.5 (d,  $J = 21.1$  Hz), 112.8 (d,  $J = 21.0$  Hz), 103.8, 66.7, 57.1, 55.9, 47.5, 43.8, 41.6, 40.9, 37.5, 31.7, 29.3, 28.4, 27.8, 27.8, 26.3, 24.2, 22.4, 21.1, 14.0.

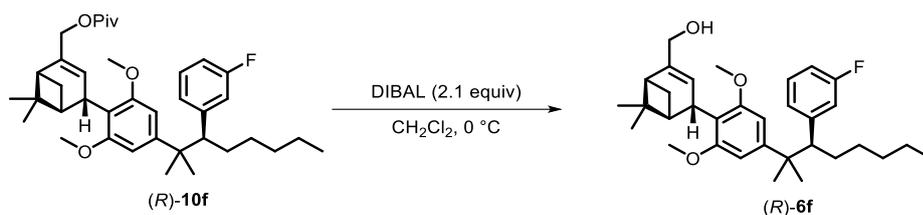
$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -114.8.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3381, 2928, 2862, 1656, 1605, 1586, 1572, 1487, 1463, 1449, 1410, 1380, 1364, 1340, 1302, 1238, 1184, 1160, 1119, 1049, 986, 927, 871, 832, 782, 724, 699, 671, 654, 578.

**HRMS (ESI)**:  $m/z = 531.3245$  [ $\text{M} + \text{Na}$ ] $^+$  (calc. for  $\text{C}_{33}\text{H}_{45}\text{FNaO}_3$   $m/z = 531.3245$ ).

$[\alpha]_{\text{D}}^{25} = +55.004 \pm 0.309$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

## Synthesis of (*R*)-6f



To a solution of (*R*)-**10f** (27.3 mg, 46.0  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.55 mL) was added DIBAL (97.0  $\mu\text{L}$ , 97.0  $\mu\text{mol}$ , 2.1 equiv) at 0  $^\circ\text{C}$ . After stirring the reaction for 15 minutes at 0  $^\circ\text{C}$ , sat. aq.  $\text{NH}_4\text{Cl}$  (3 mL) was added, the layers were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 5$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ ; 5 – 20% EtOAc in hexanes) afforded the product as a colourless oil (21.5 mg, 92%).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 – 7.13 (m, 1H), 6.91 – 6.83 (m, 1H), 6.79 (d,  $J = 7.7$  Hz, 1H), 6.71 (d,  $J = 10.2$  Hz, 1H), 6.41 (s, 2H), 5.72 (dt,  $J = 2.8, 1.4$  Hz, 1H), 4.08 (d,  $J = 4.4$  Hz, 2H), 4.03 – 3.96 (m, 1H), 3.70 (s, 6H), 2.72 (dd,  $J = 11.8, 3.2$  Hz, 1H), 2.27 – 2.18 (m, 2H), 2.11 – 2.05 (m, 1H), 1.70 (d,  $J = 7.7$  Hz, 1H), 1.61 – 1.40 (m, 2H), 1.32 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3H), 1.15 – 1.02 (m, 4H), 0.98 (s, 3H), 0.96 – 0.81 (m, 2H), 0.76 (t,  $J = 6.5$  Hz, 3H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  162.5 (d,  $J = 244.1$  Hz), 158.3, 148.2, 145.0 (d,  $J = 6.7$  Hz), 142.1, 128.7 (d,  $J = 8.3$  Hz), 126.0, 123.7, 118.3, 116.6 (d,  $J = 21.2$  Hz), 112.9 (d,  $J = 21.0$  Hz), 103.9, 66.8, 57.2, 56.0, 47.6, 44.0, 41.8, 41.0, 37.6, 31.8, 29.4, 28.6, 28.0, 28.0, 26.4, 24.3, 22.6, 21.2, 14.1.

$^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -114.8.

**IR** (neat,  $\nu_{\text{max}}/\text{cm}^{-1}$ ): 3373, 2927, 2862, 1661, 1604, 1586, 1572, 1508, 1487, 1463, 1450, 1410, 1380, 1364, 1341, 1302, 1239, 1183, 1160, 1119, 1072, 1049, 987, 927, 871, 832, 782, 724, 699, 671, 578, 522.

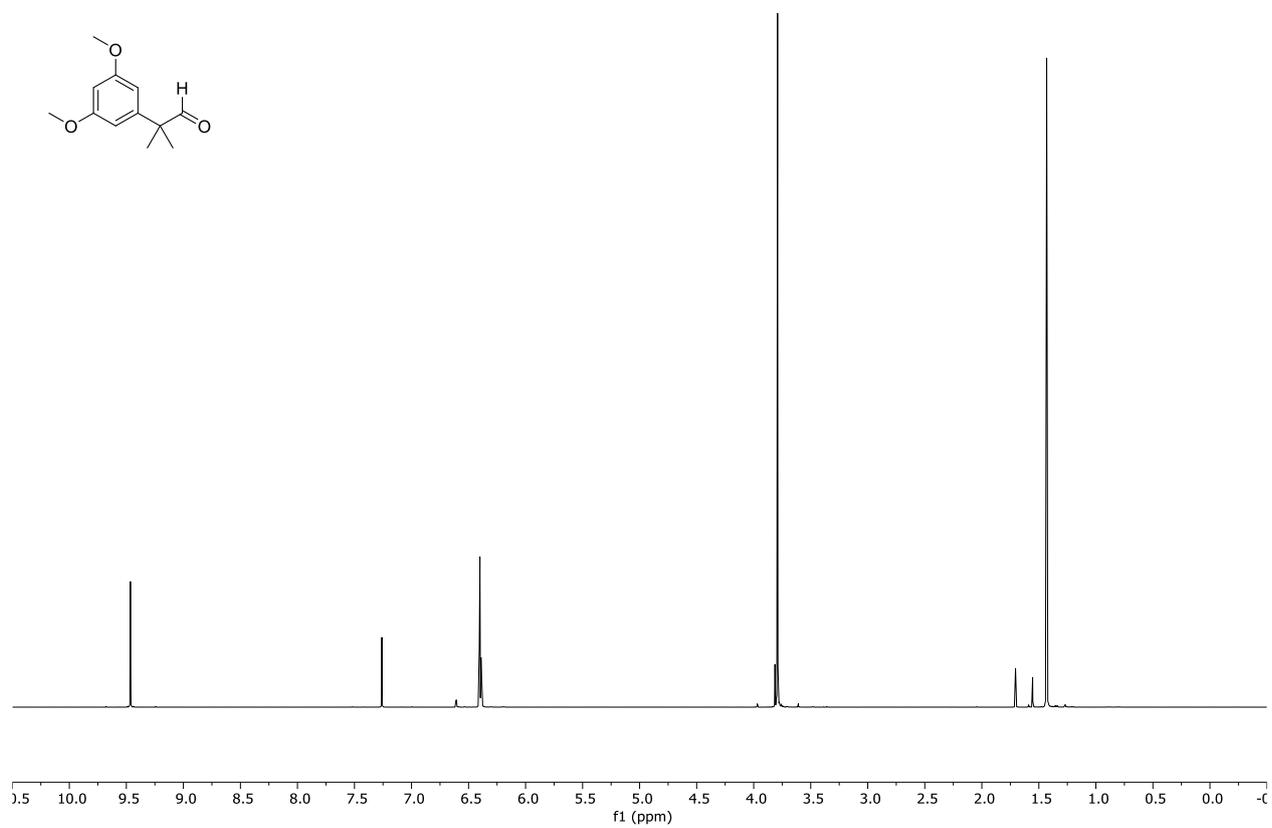
**HRMS (ESI)**:  $m/z = 531.3245$  [ $\text{M} + \text{Na}$ ] $^+$  (calc. for  $\text{C}_{33}\text{H}_{45}\text{FNaO}_3$   $m/z = 531.3245$ ).

$[\alpha]_{\text{D}}^{25} = +107.650 \pm 0.171$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

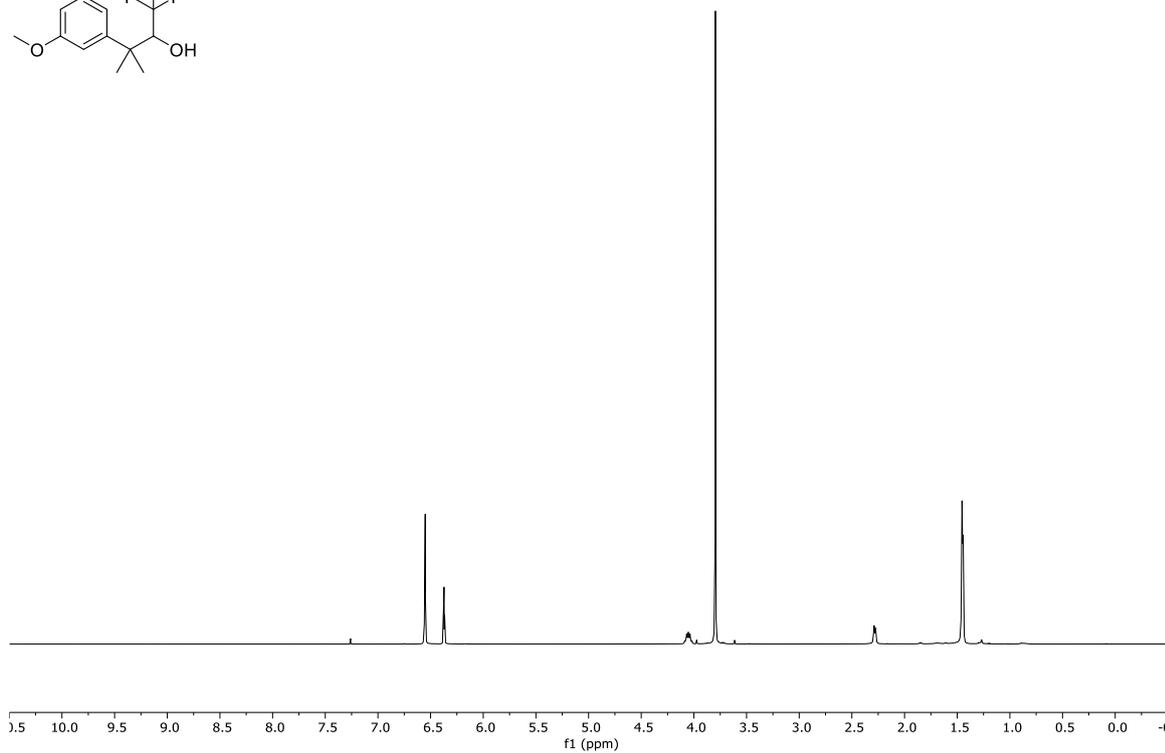
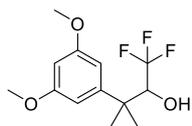


## NMR Spectra

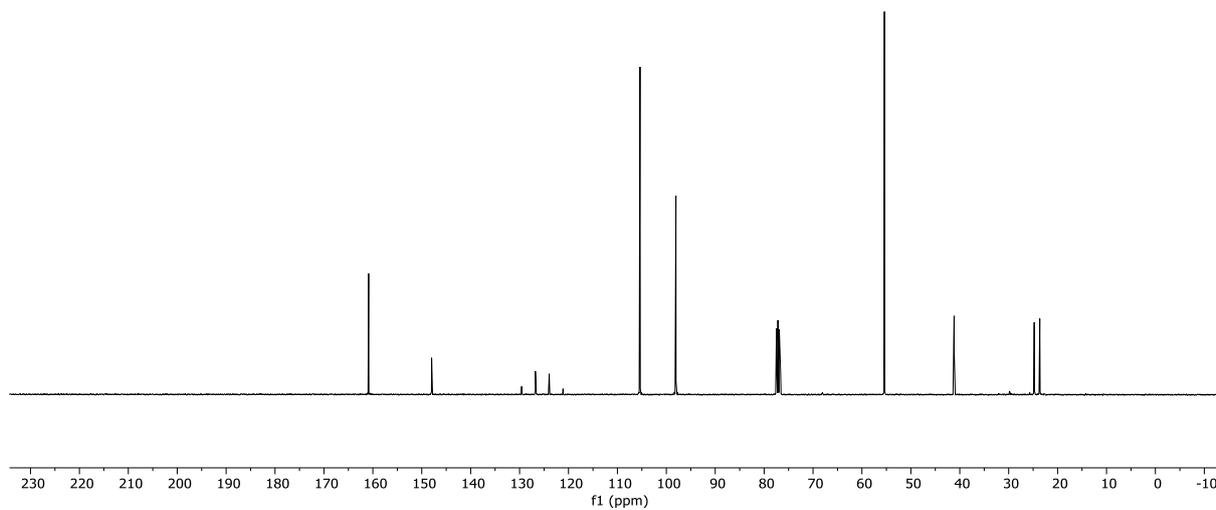
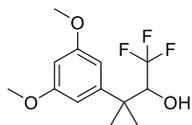
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of **SI-3**.



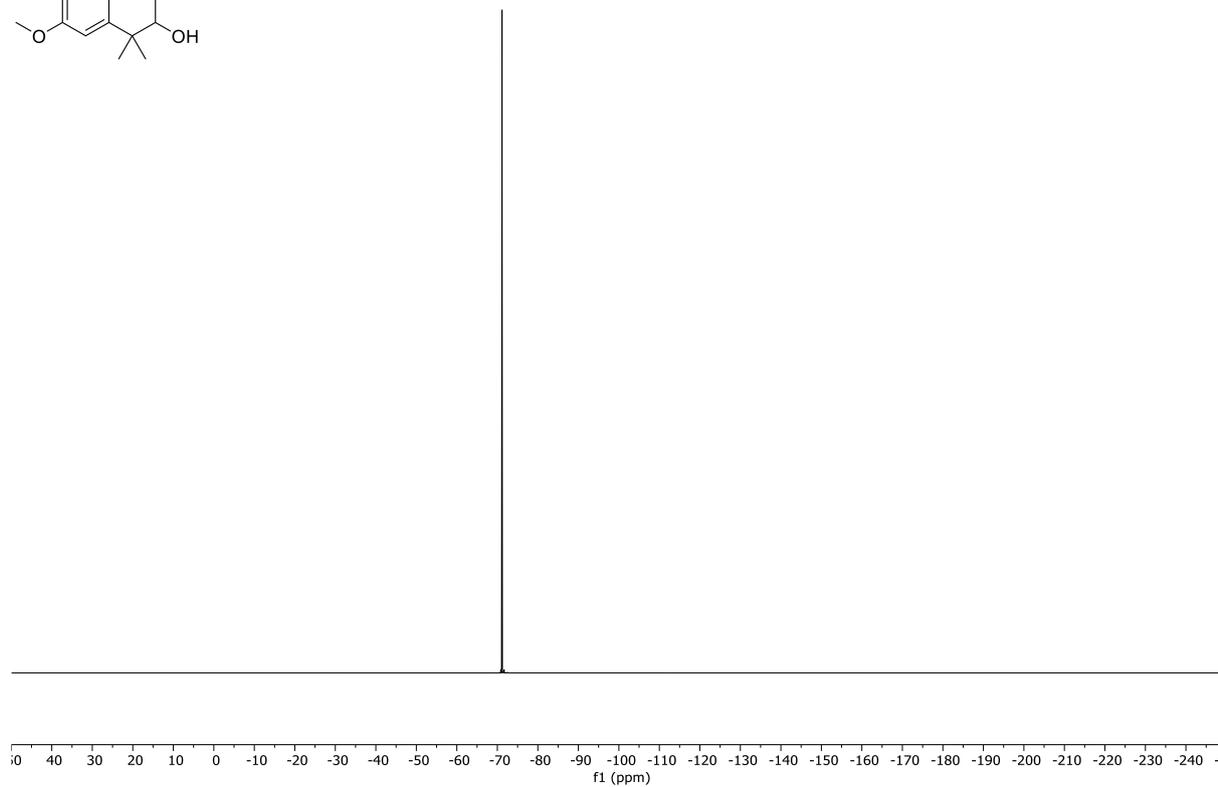
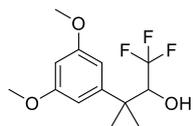
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **SI-2**



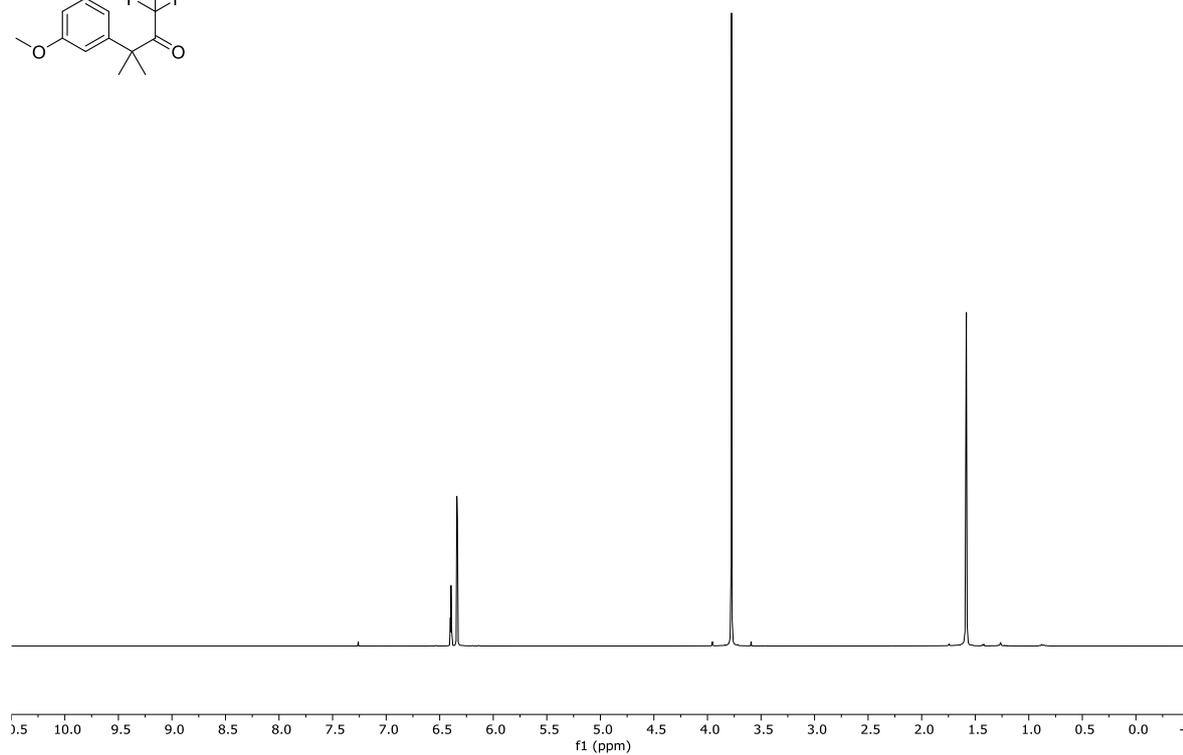
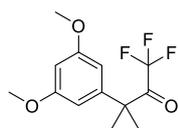
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **SI-2**



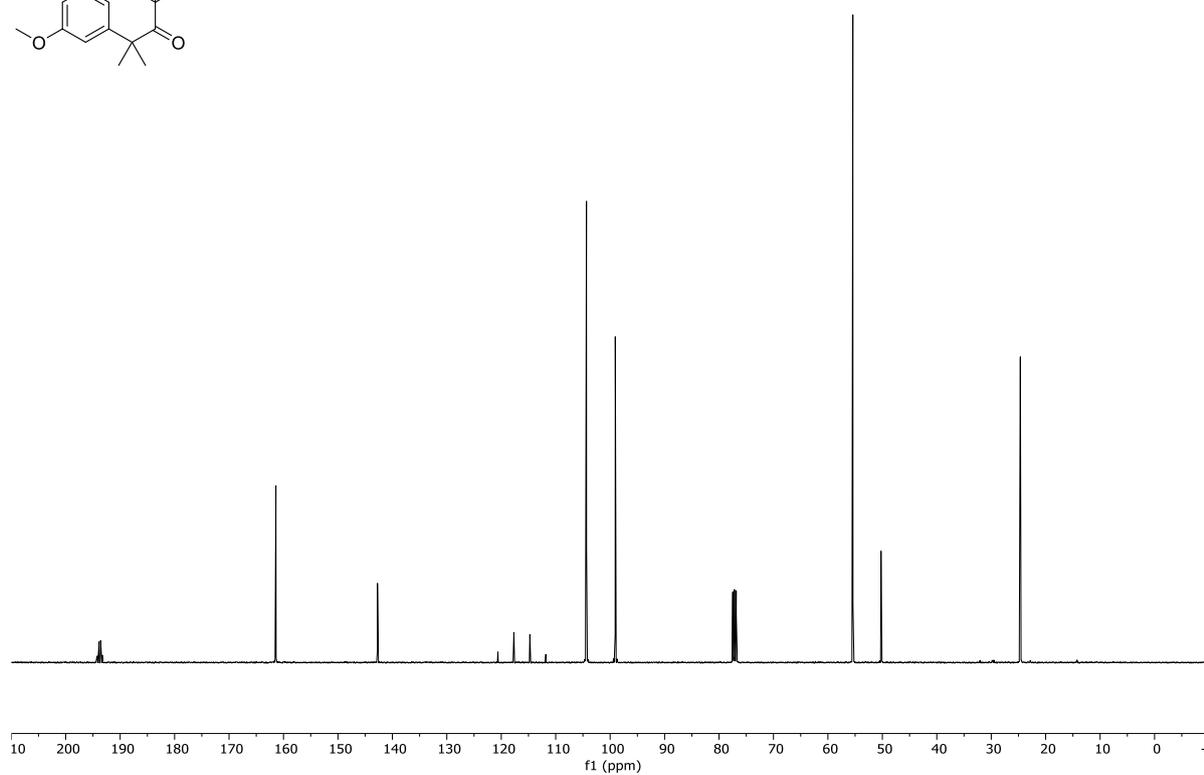
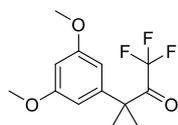
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of **SI-2**



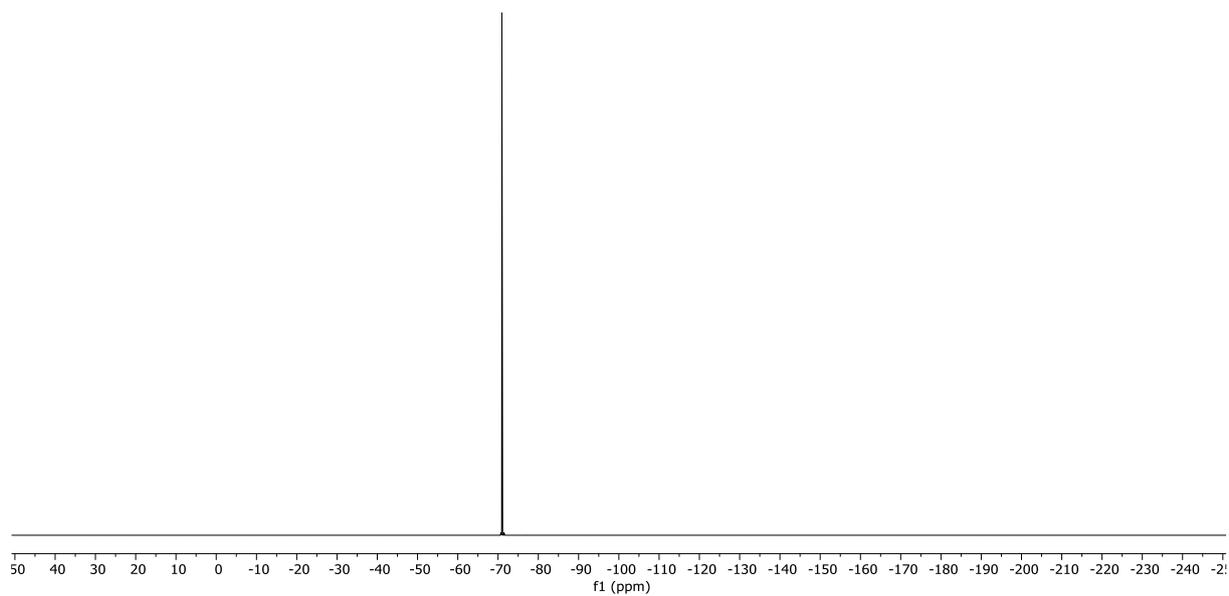
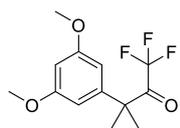
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **3**



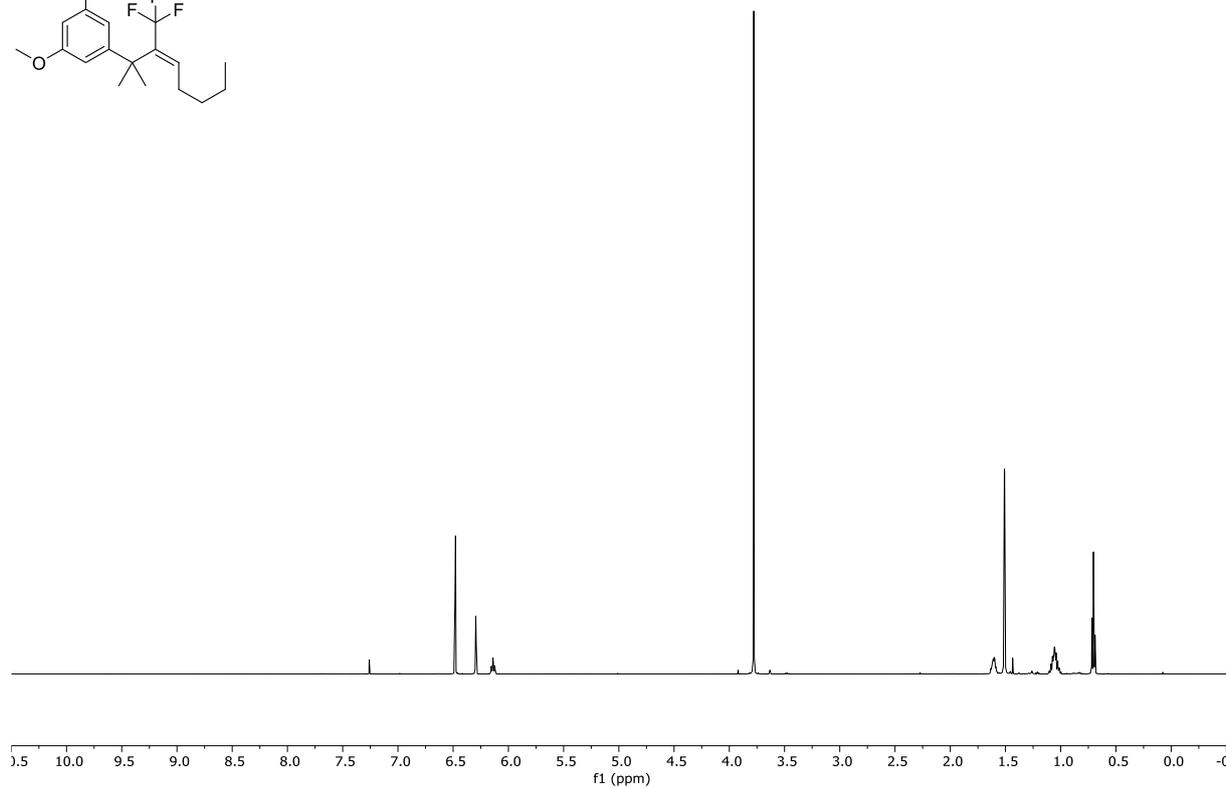
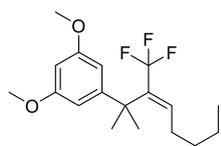
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **3**



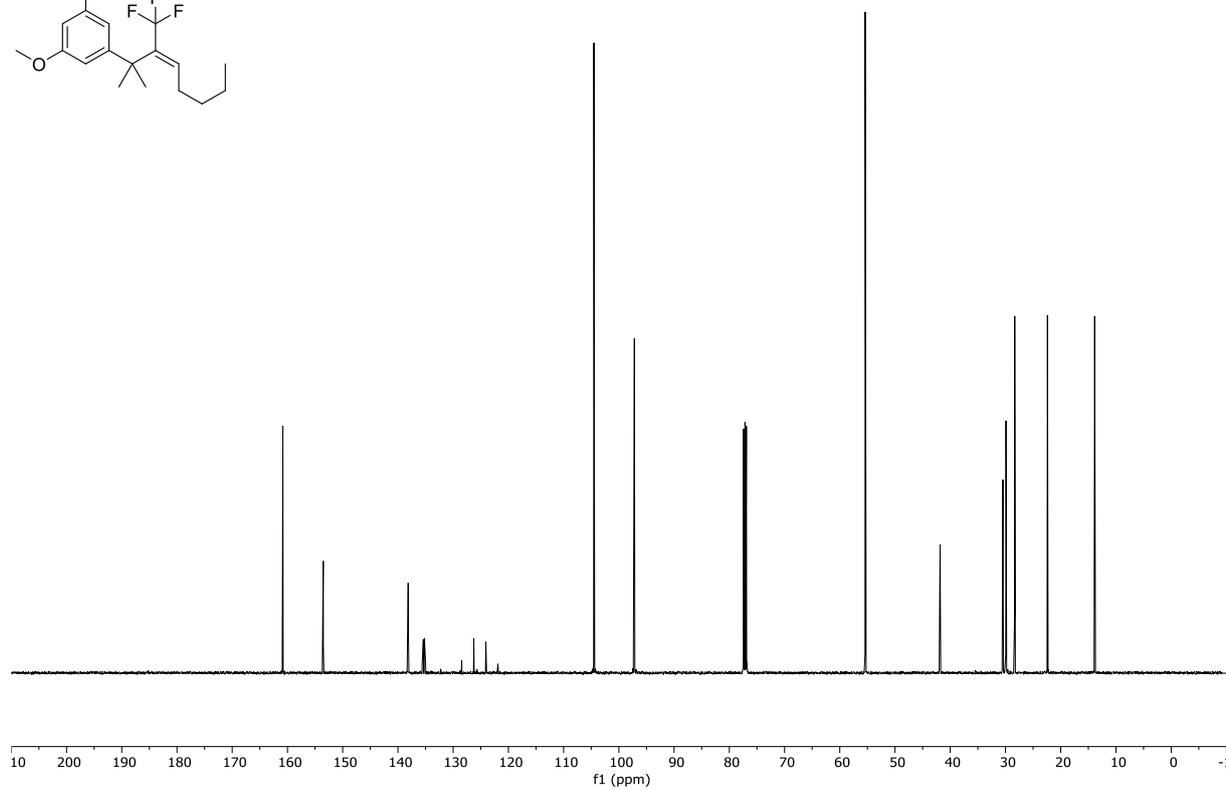
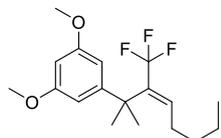
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of **3**



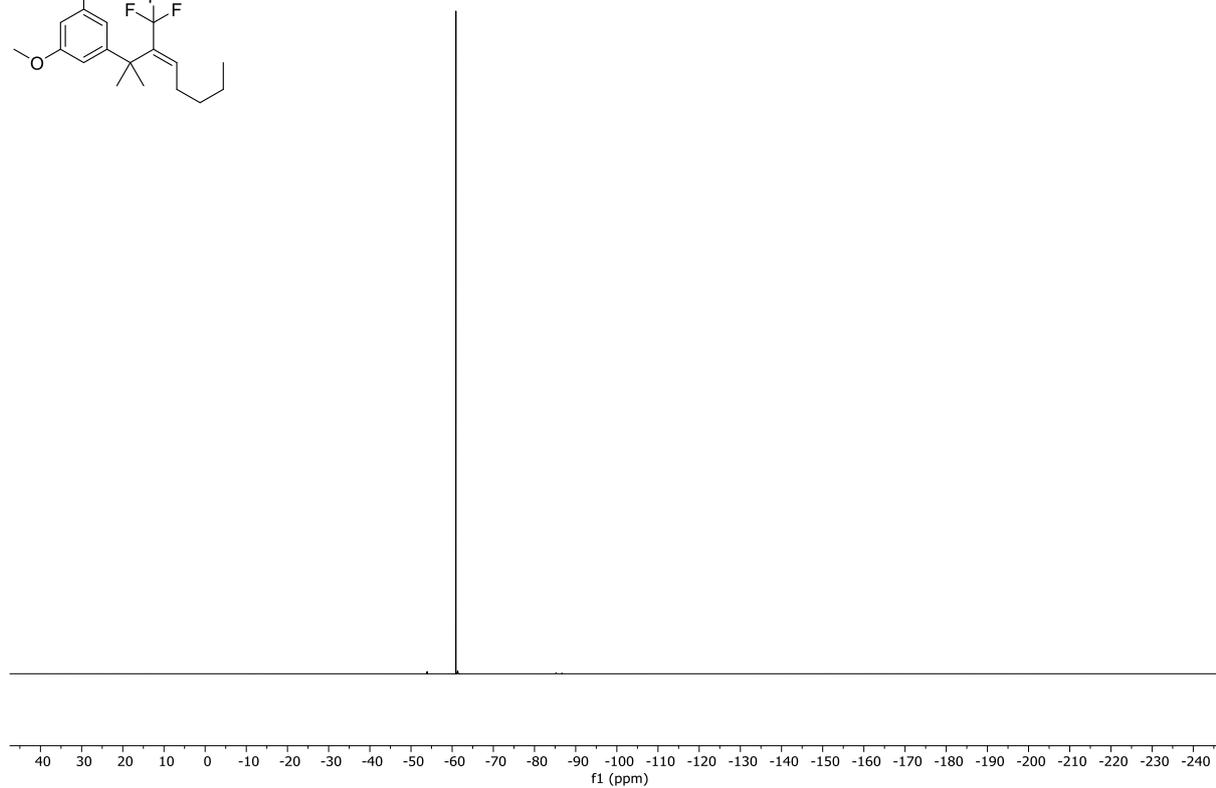
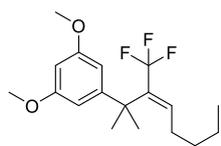
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (*E*)-SI-3



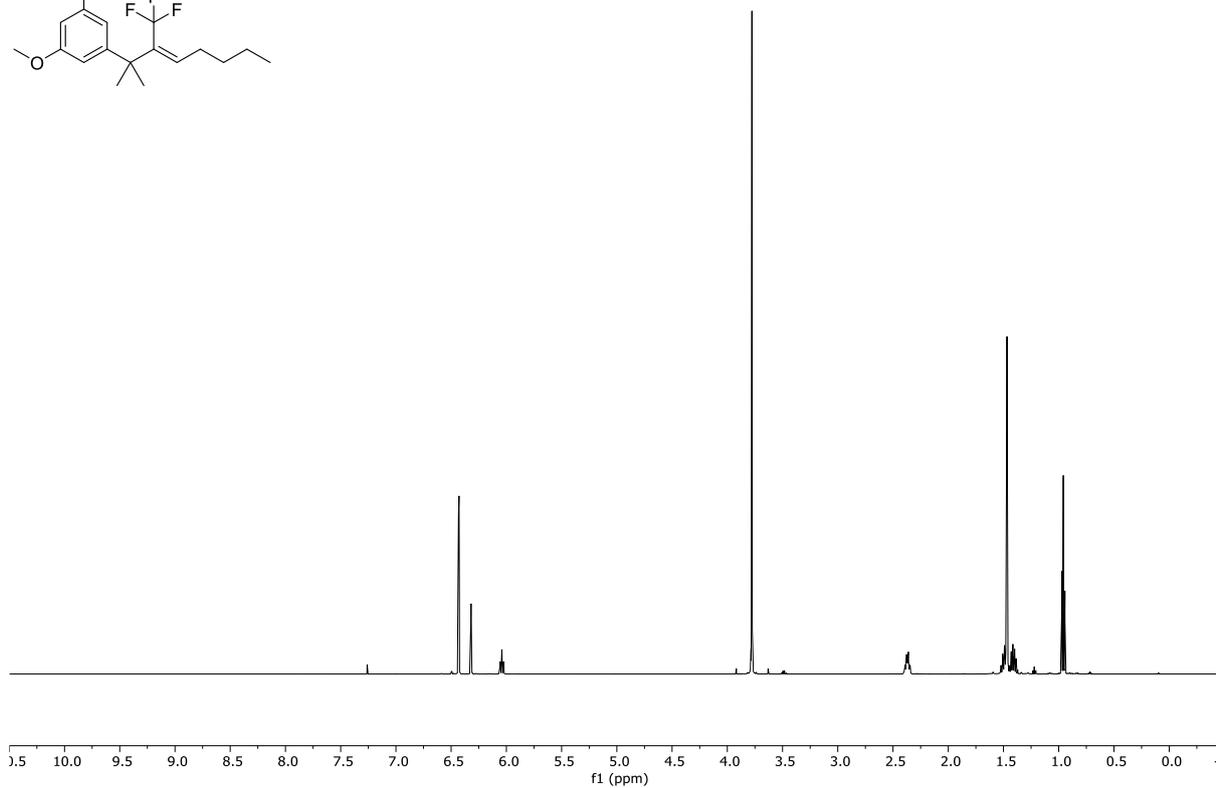
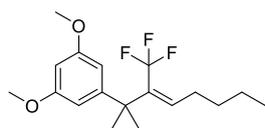
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) of (*E*)-SI-3



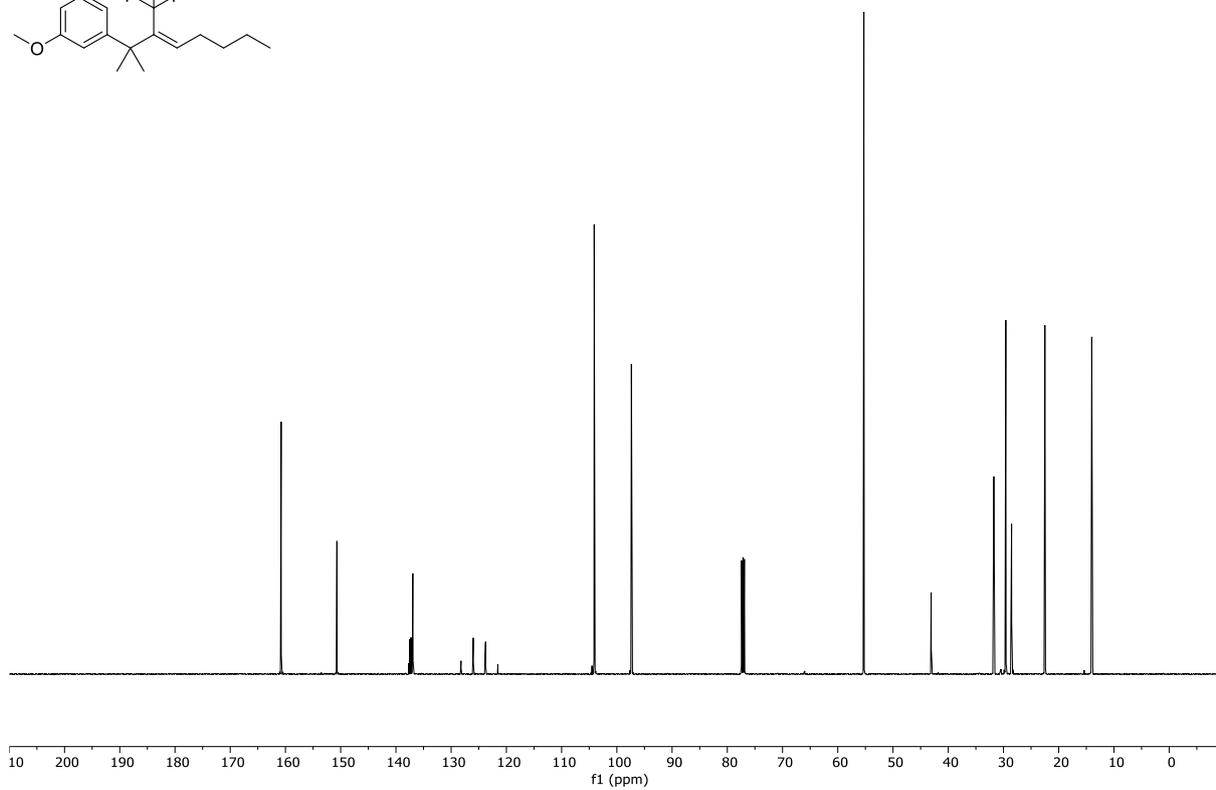
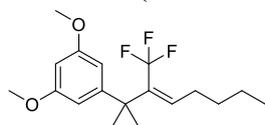
$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ) of (*E*)-SI-3



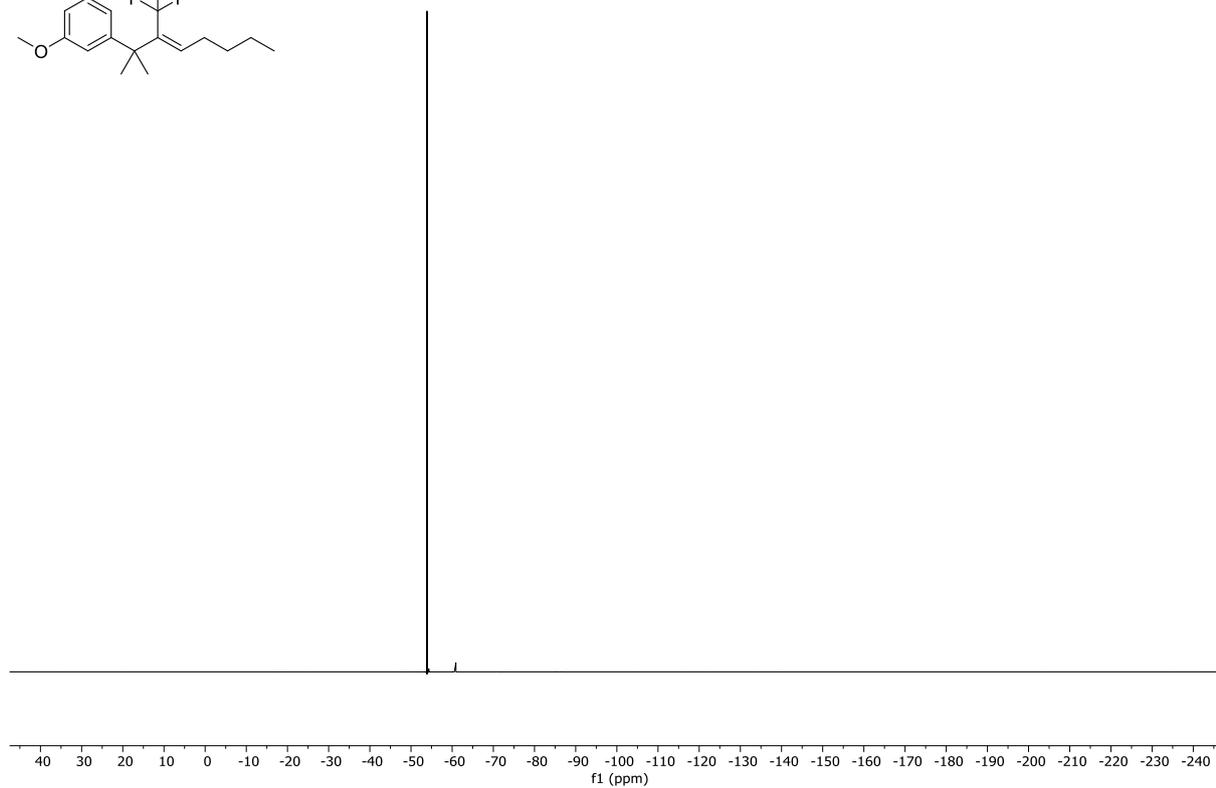
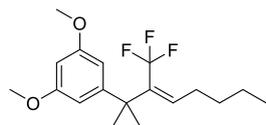
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (*Z*)-SI-3



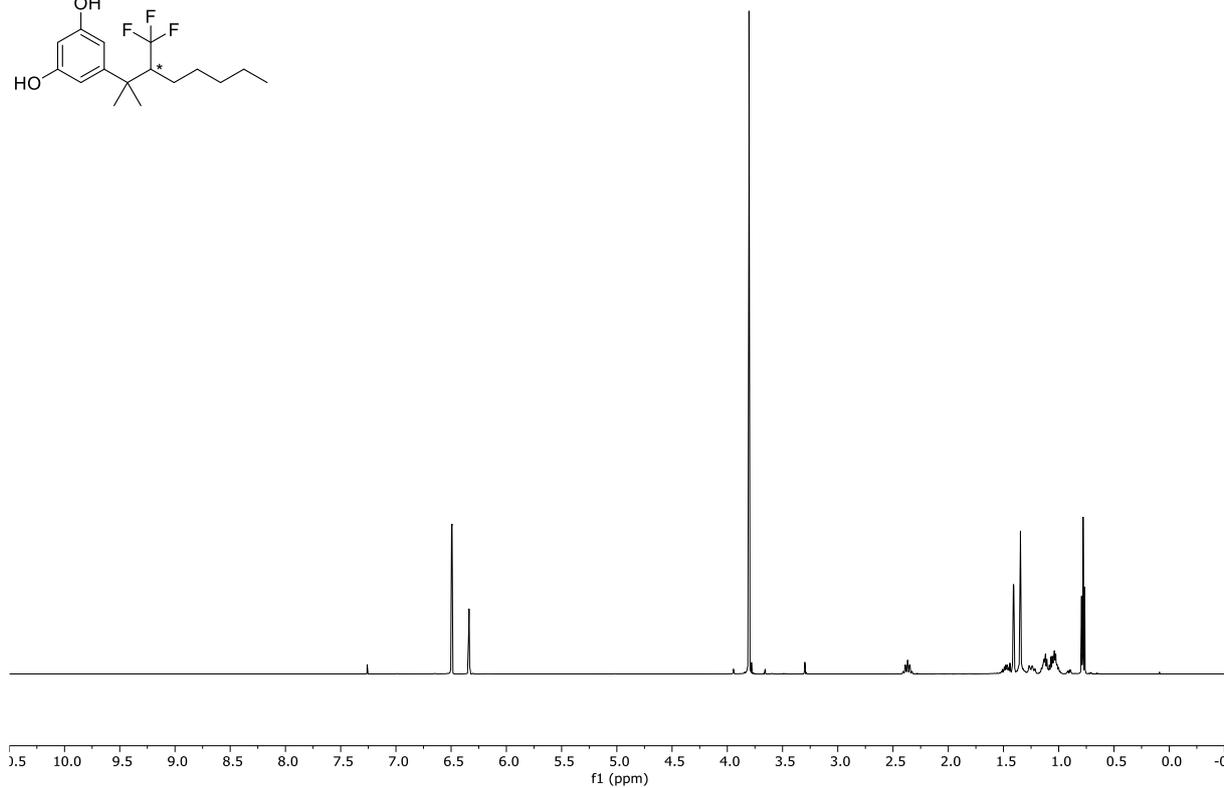
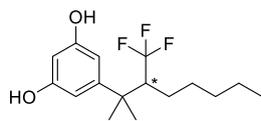
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) of (*Z*)-SI-3



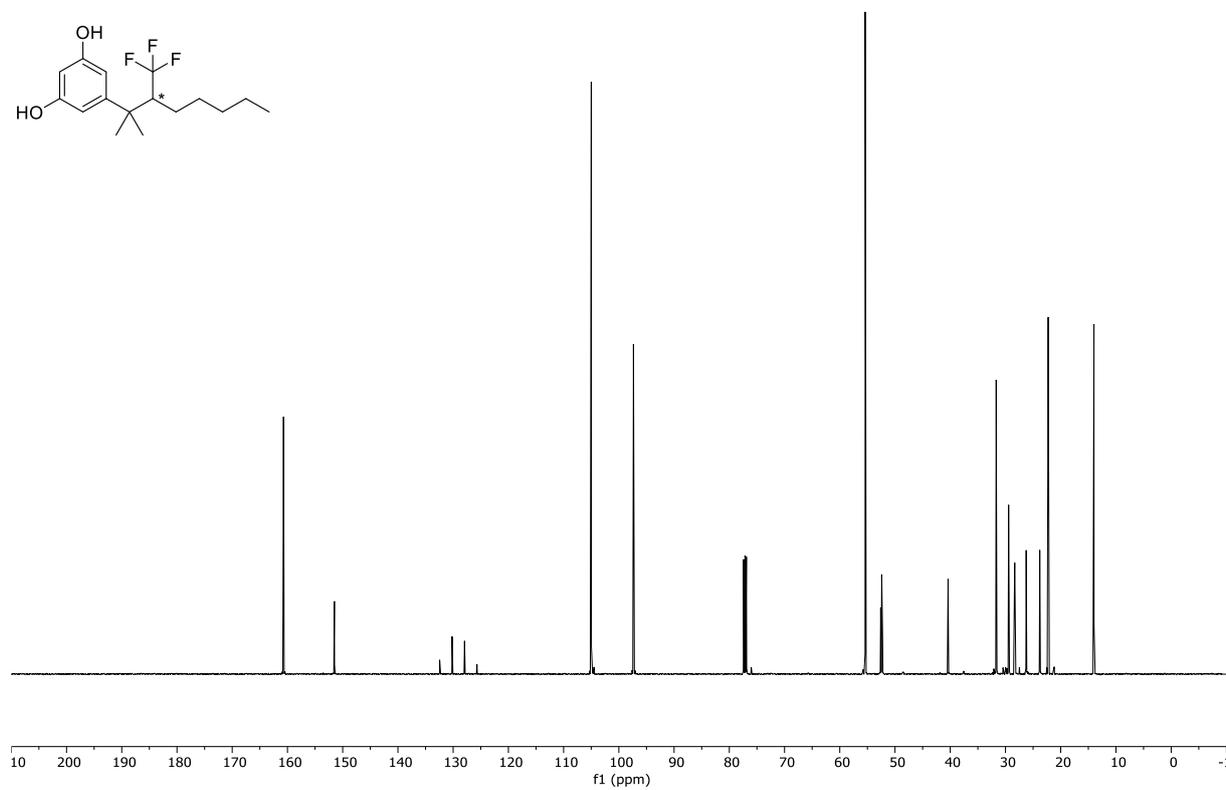
$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ) of **(Z)-SI-3**



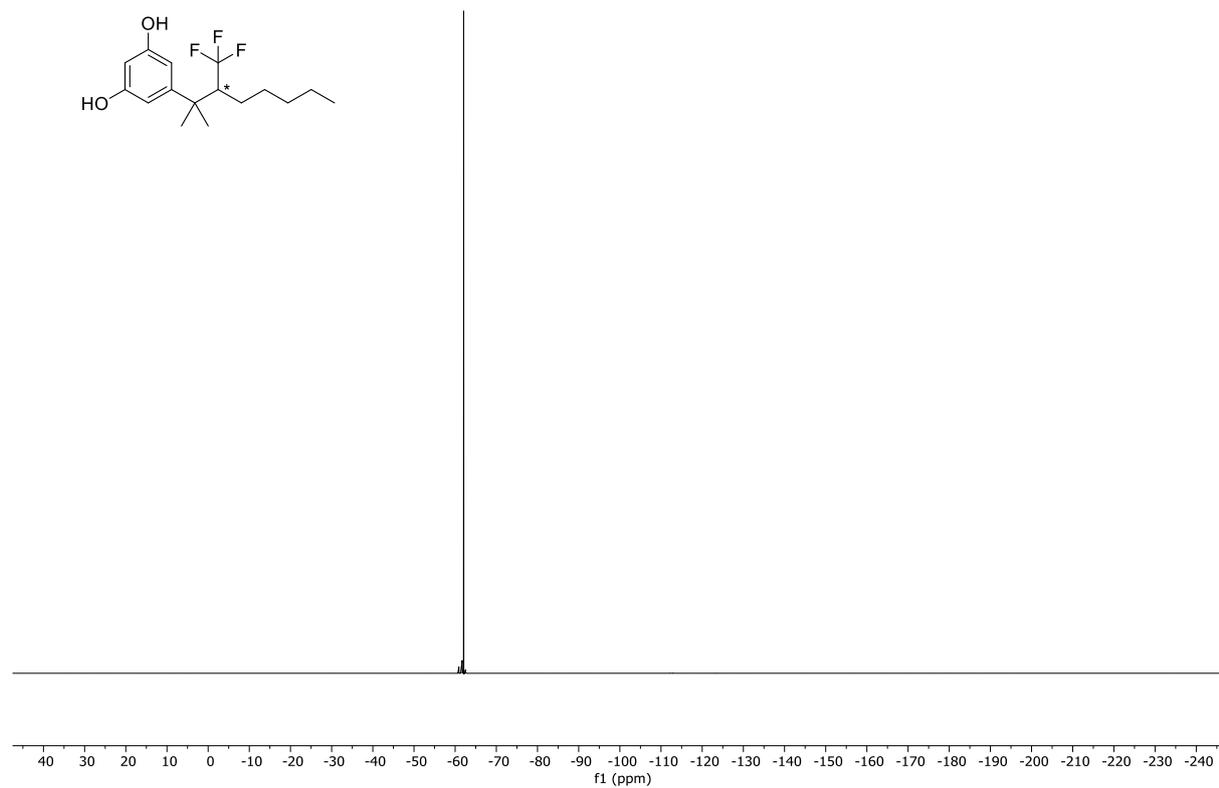
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (+)-(*R*)-4 & (-)-(*S*)-4



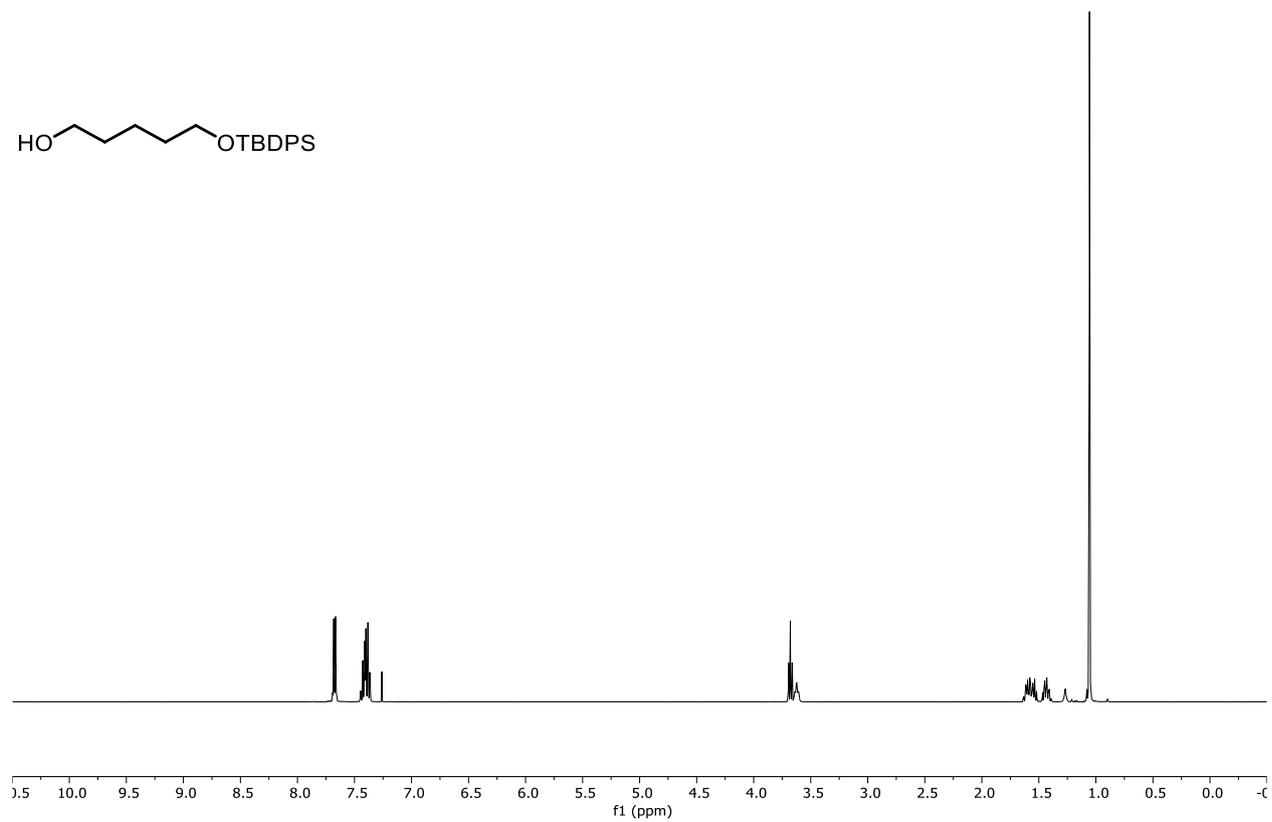
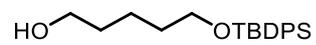
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) of (+)-(*R*)-4 & (-)-(*S*)-4



$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ) of (+)-(*R*)-**4** & (-)-(*S*)-**4**

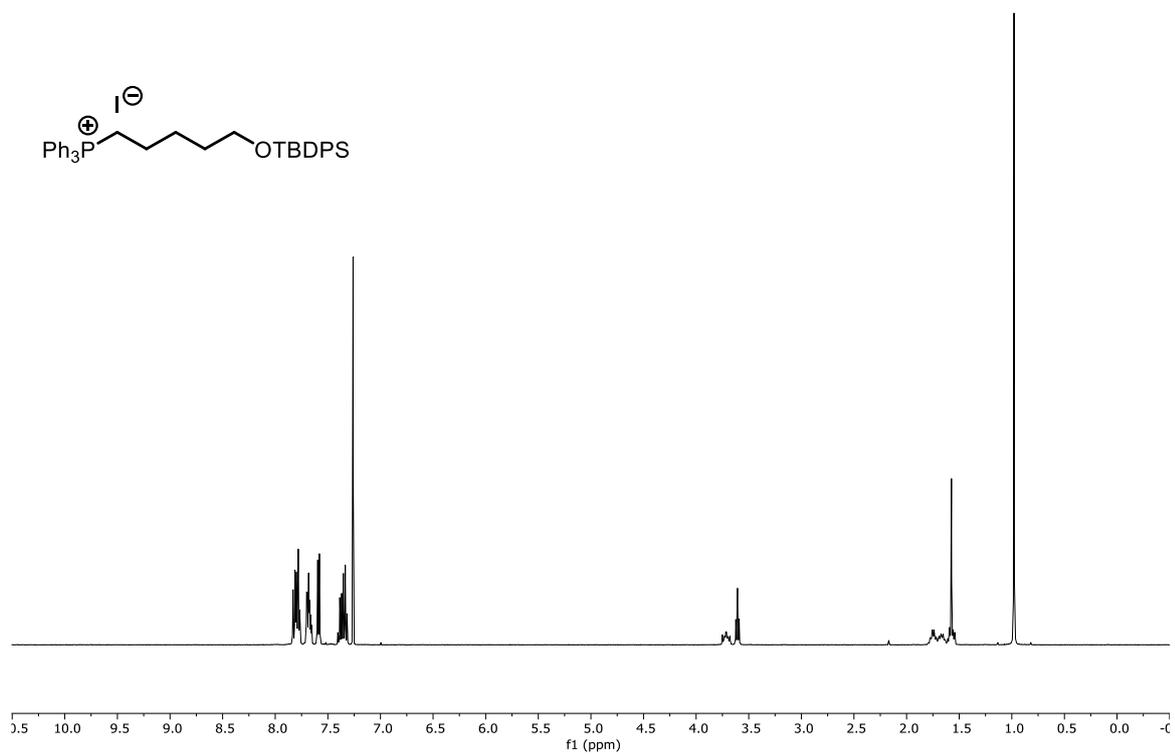


$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of **SI-11**

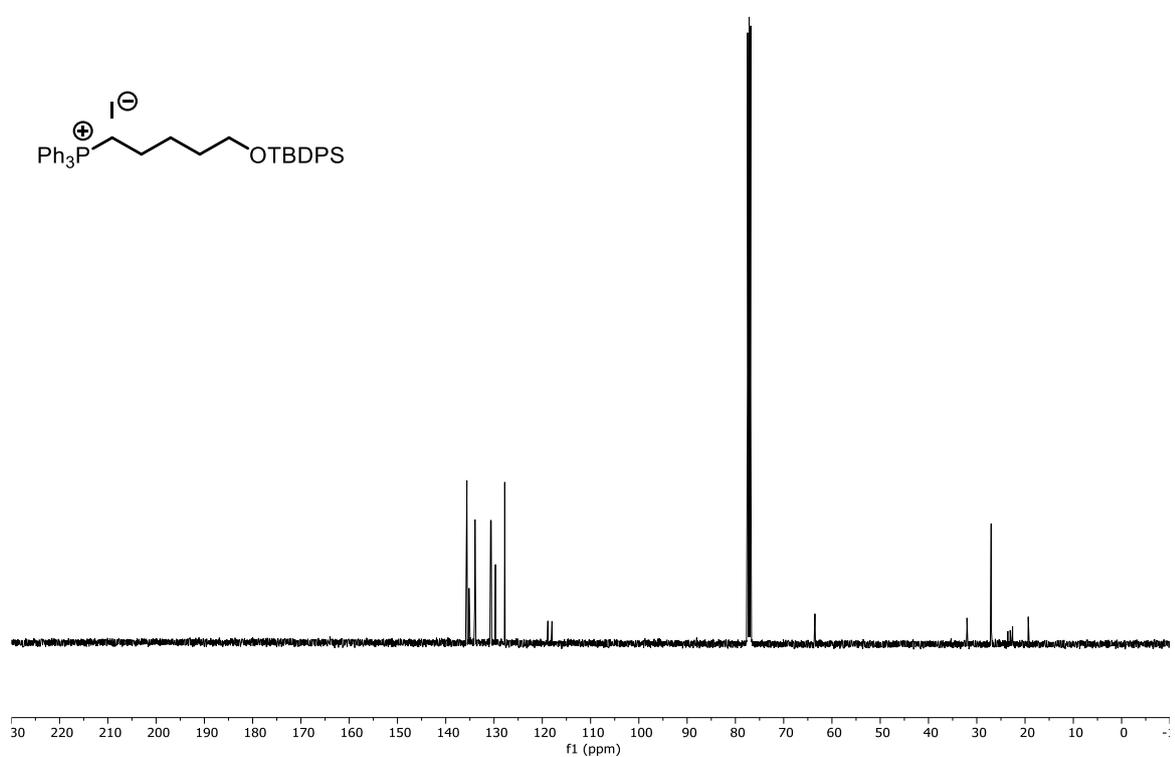




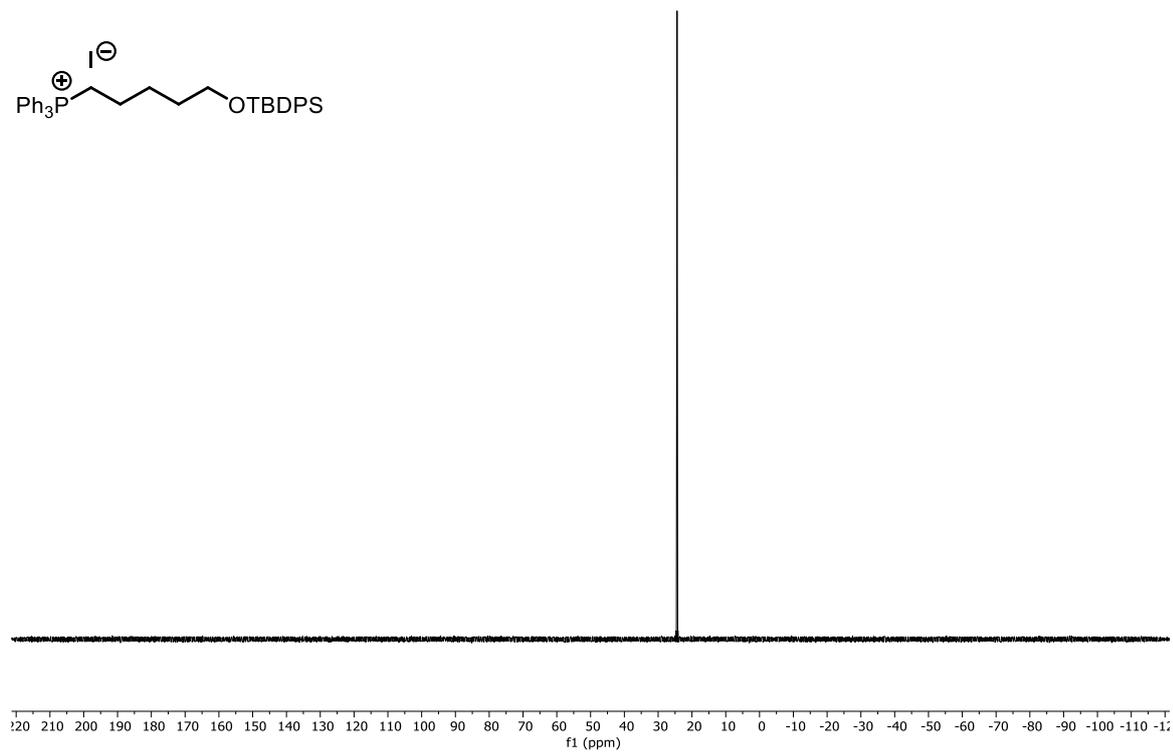
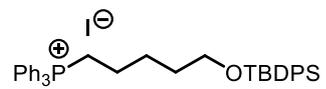
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of **SI-5**



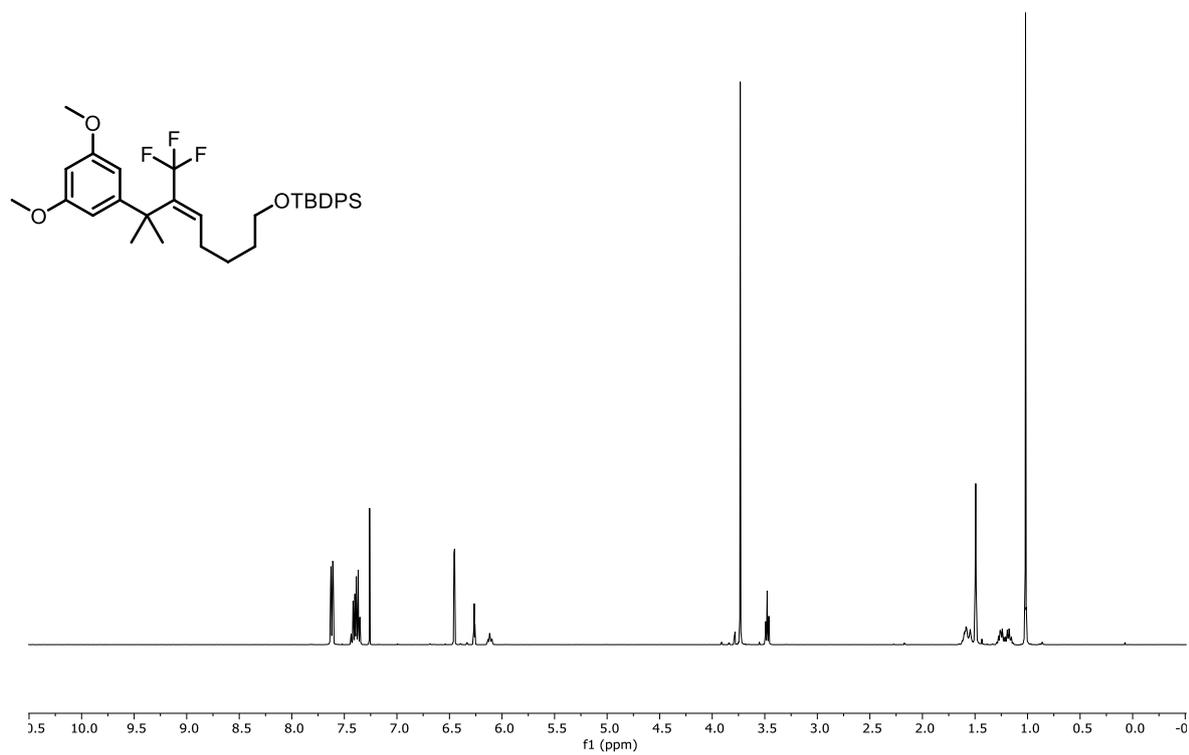
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of **SI-5**



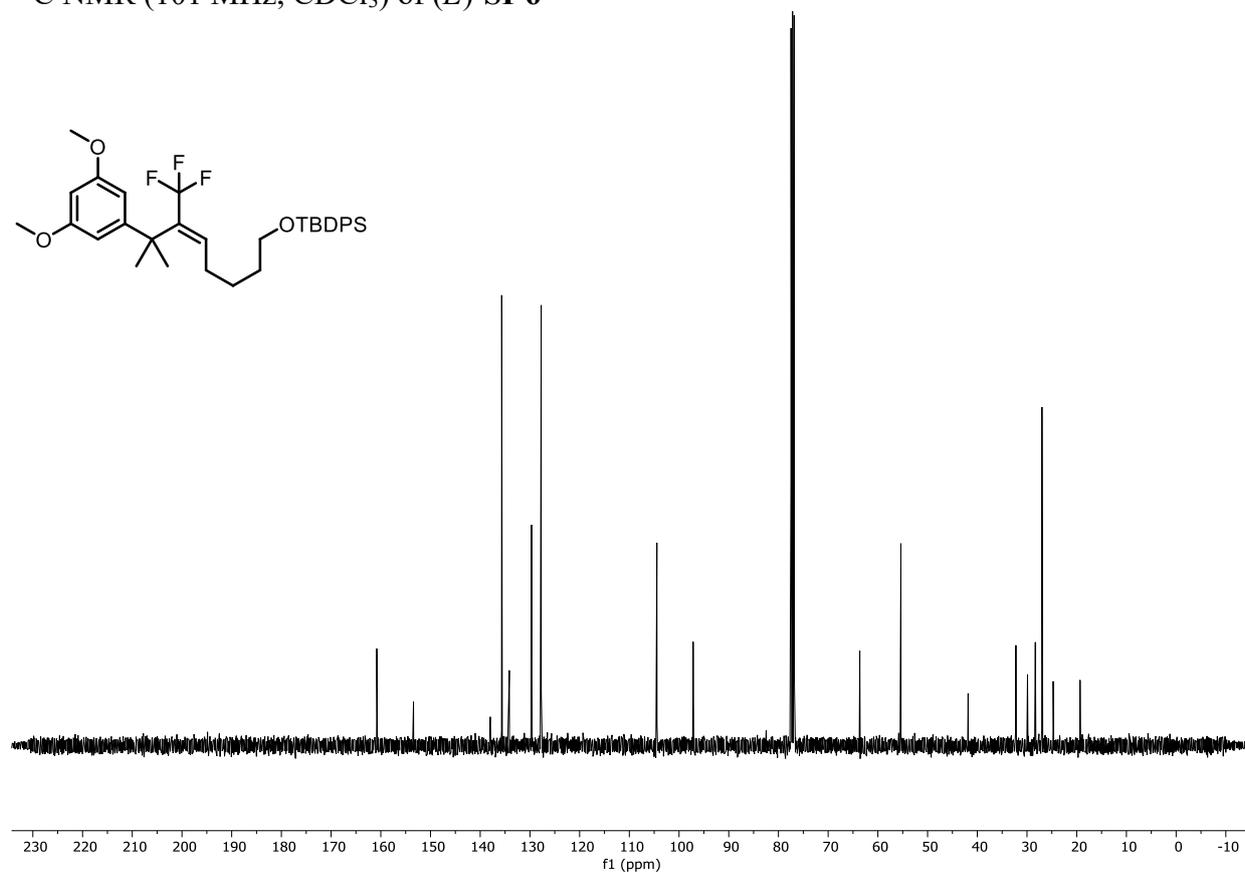
$^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ) of **SI-5**



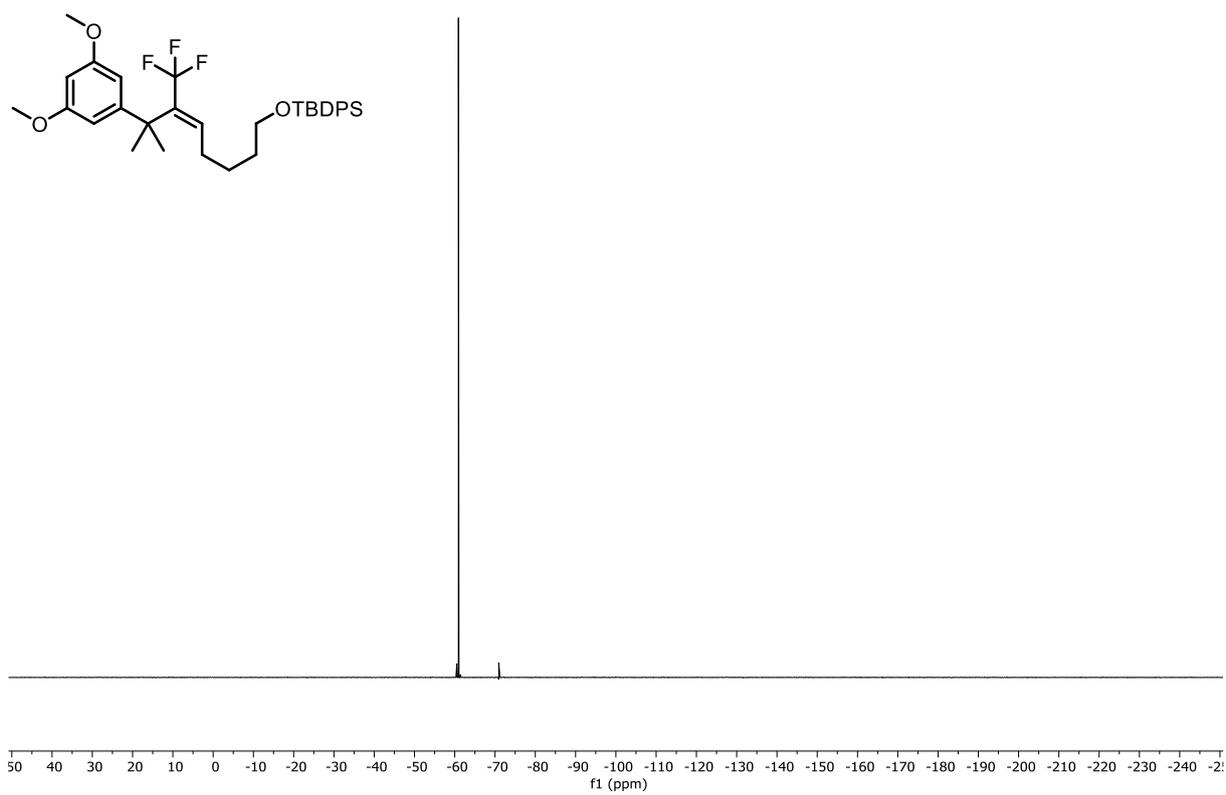
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*E*)-SI-6



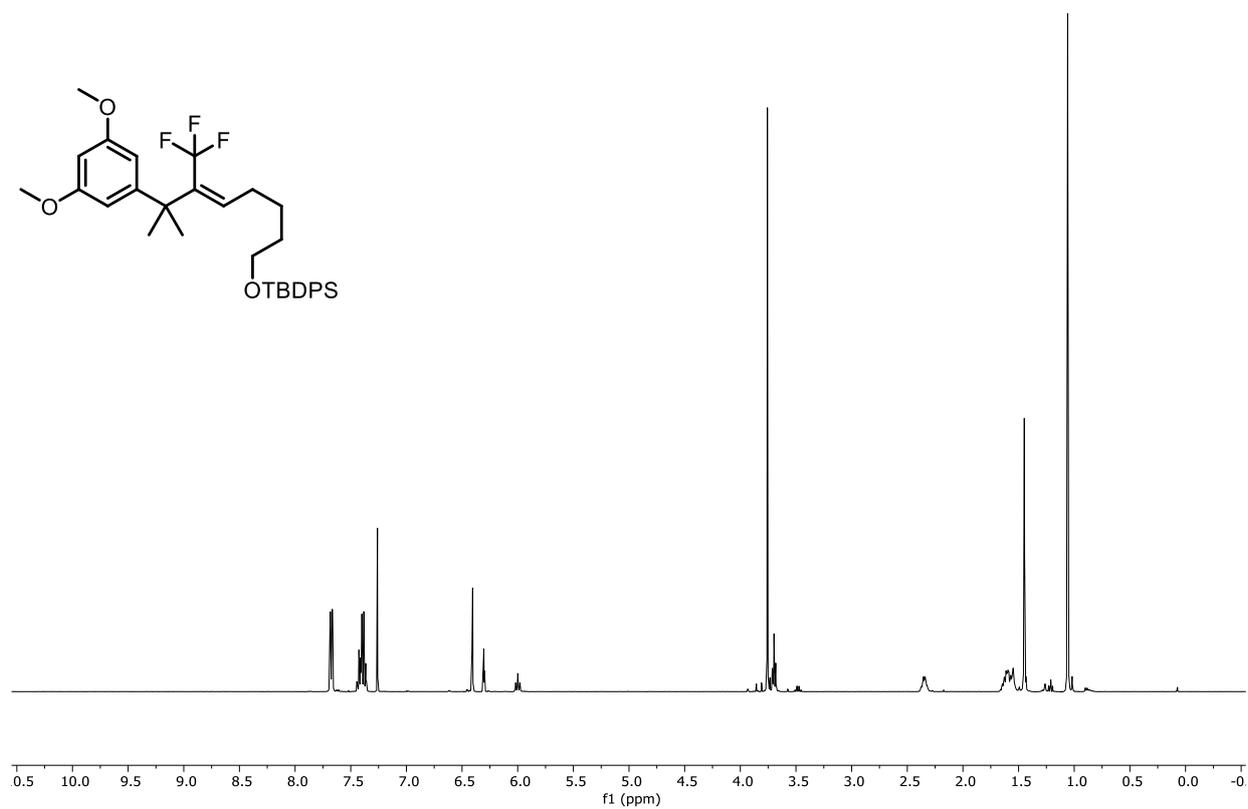
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*E*)-SI-6



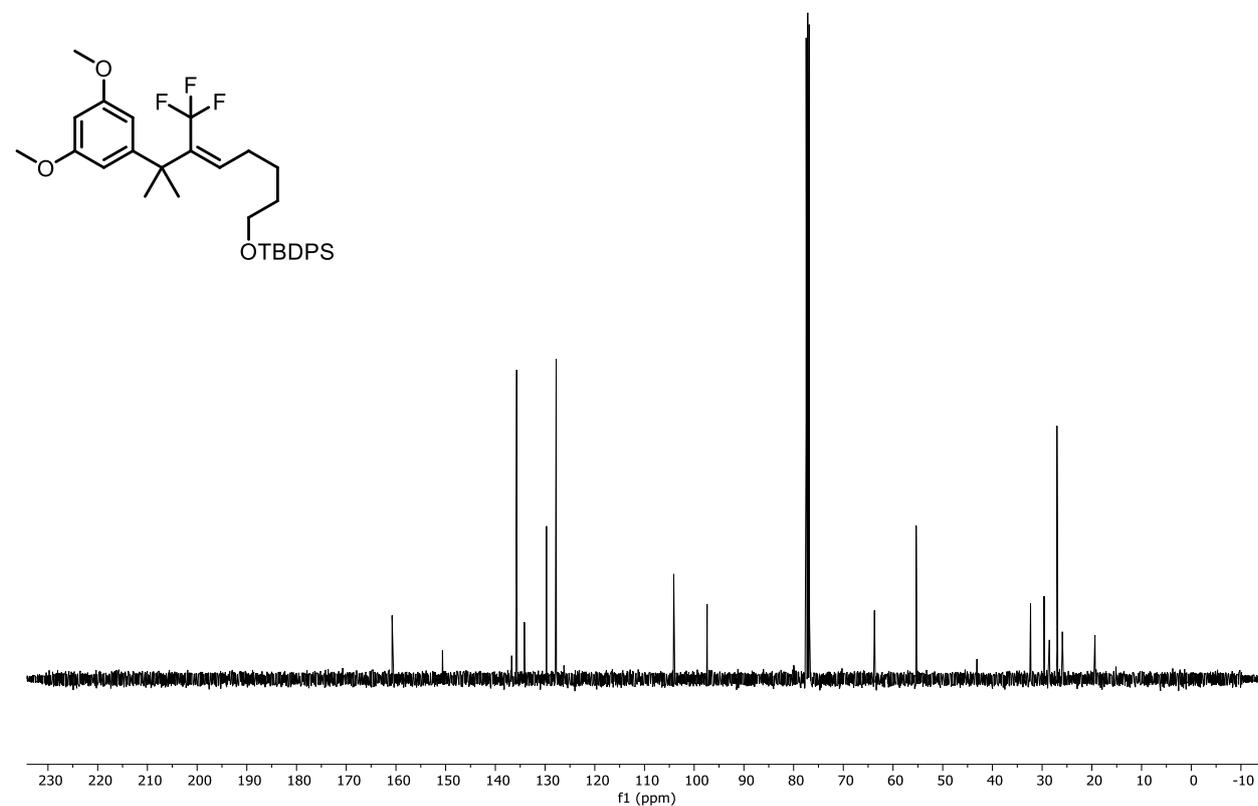
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of (*E*)-**SI-6**



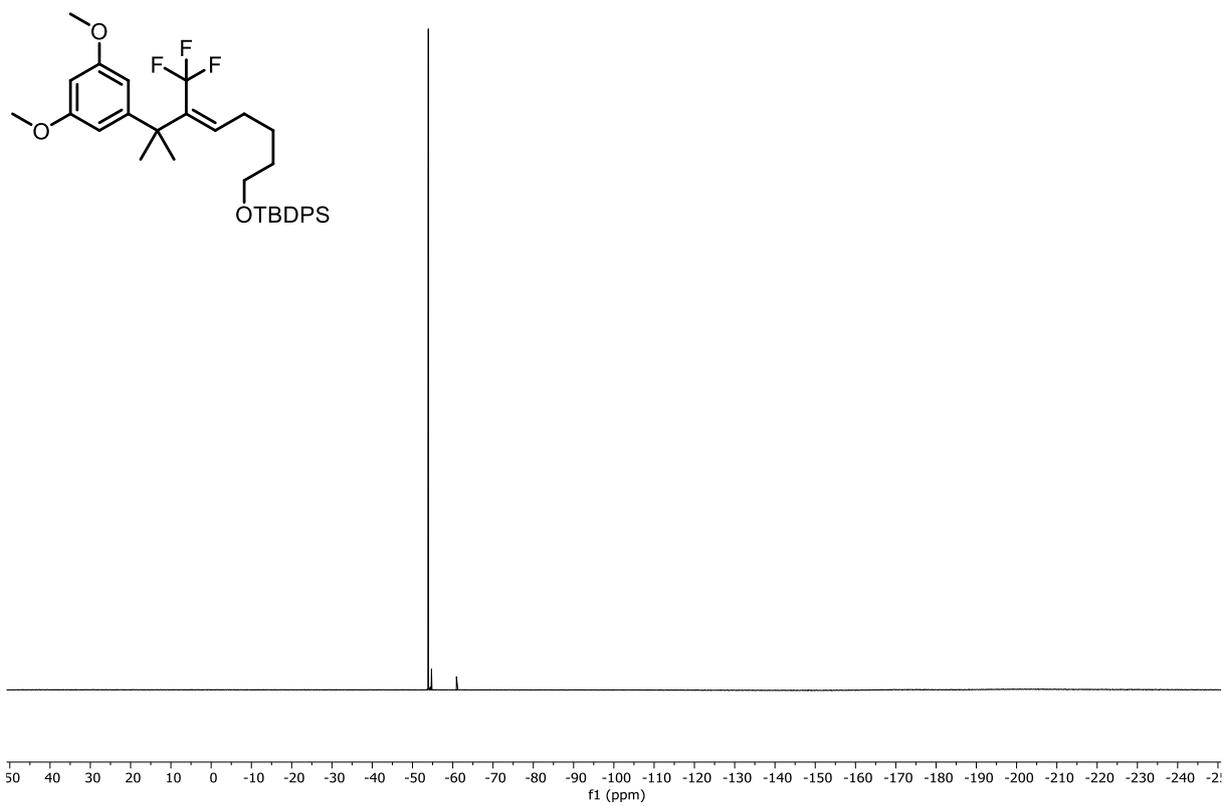
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of (Z)-SI-6



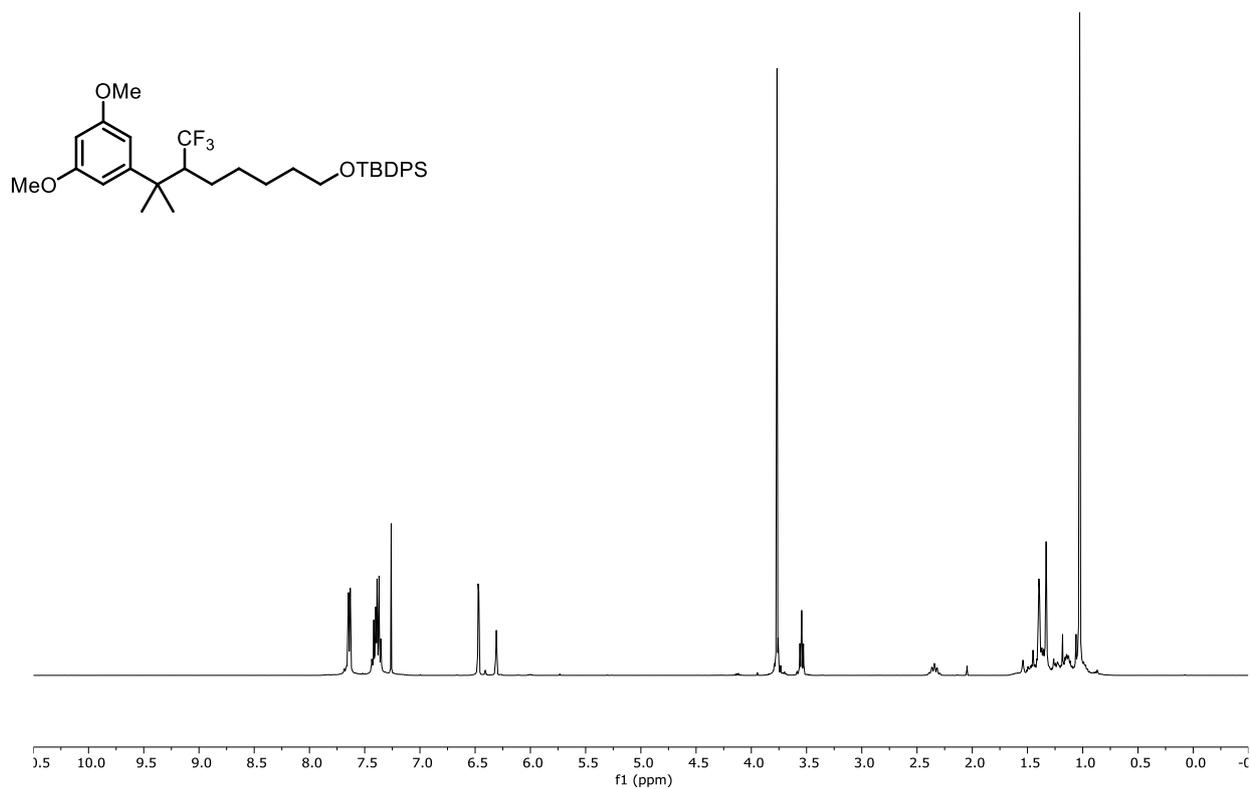
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of (Z)-SI-6



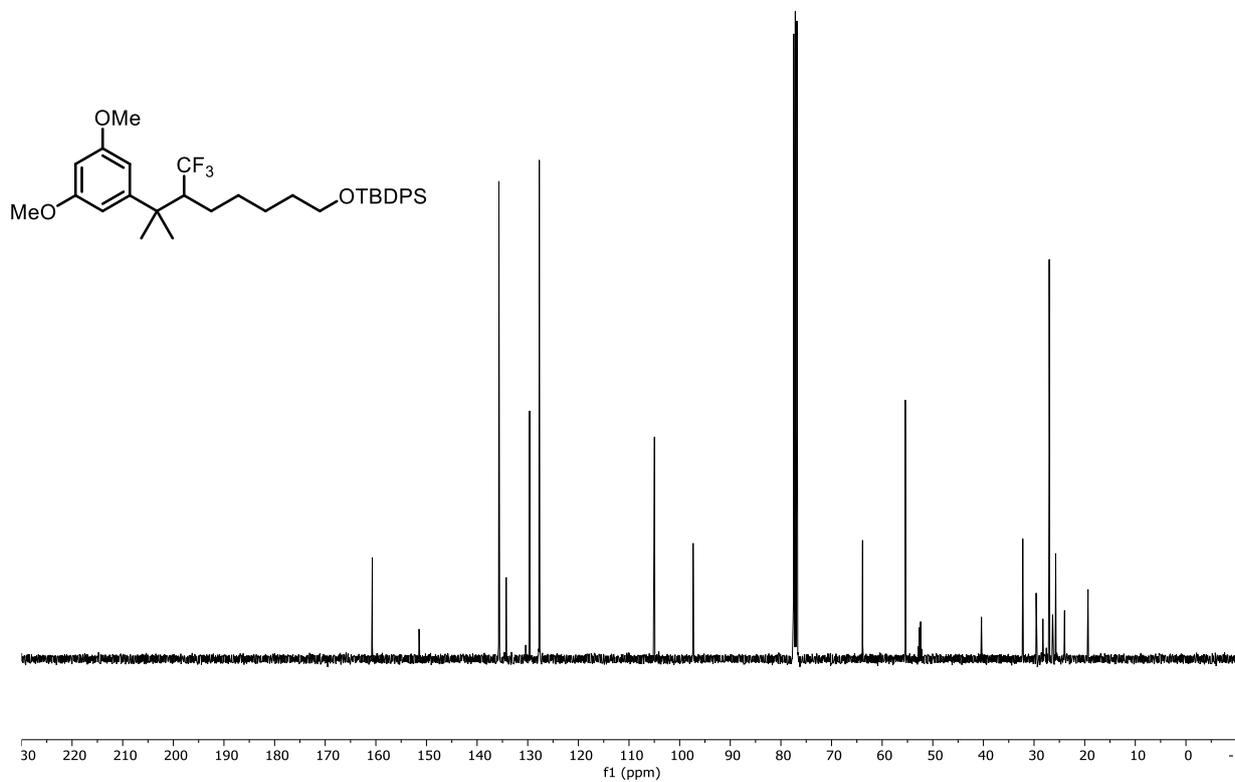
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of (Z)-SI-6



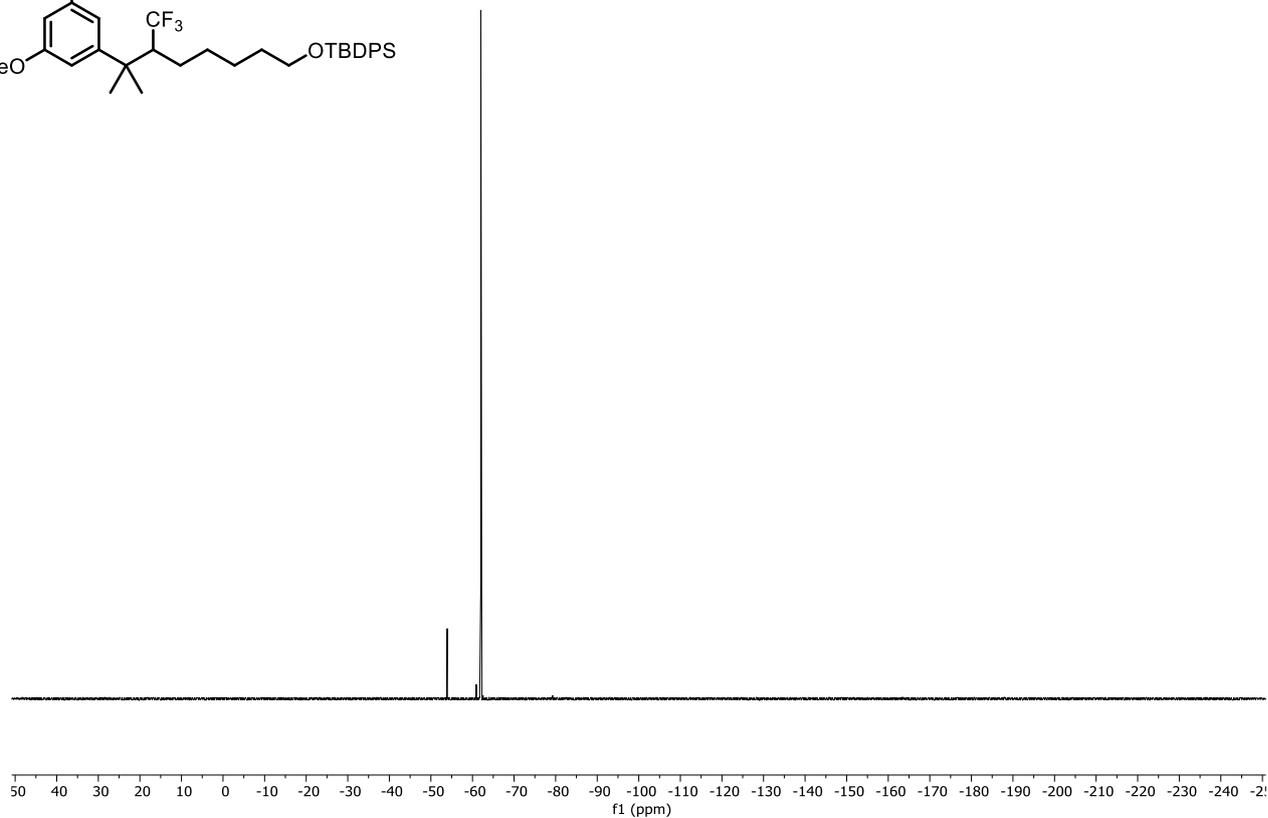
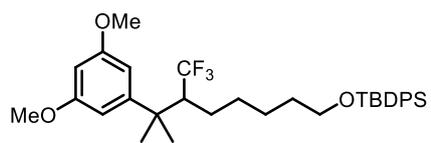
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of **SI-7**



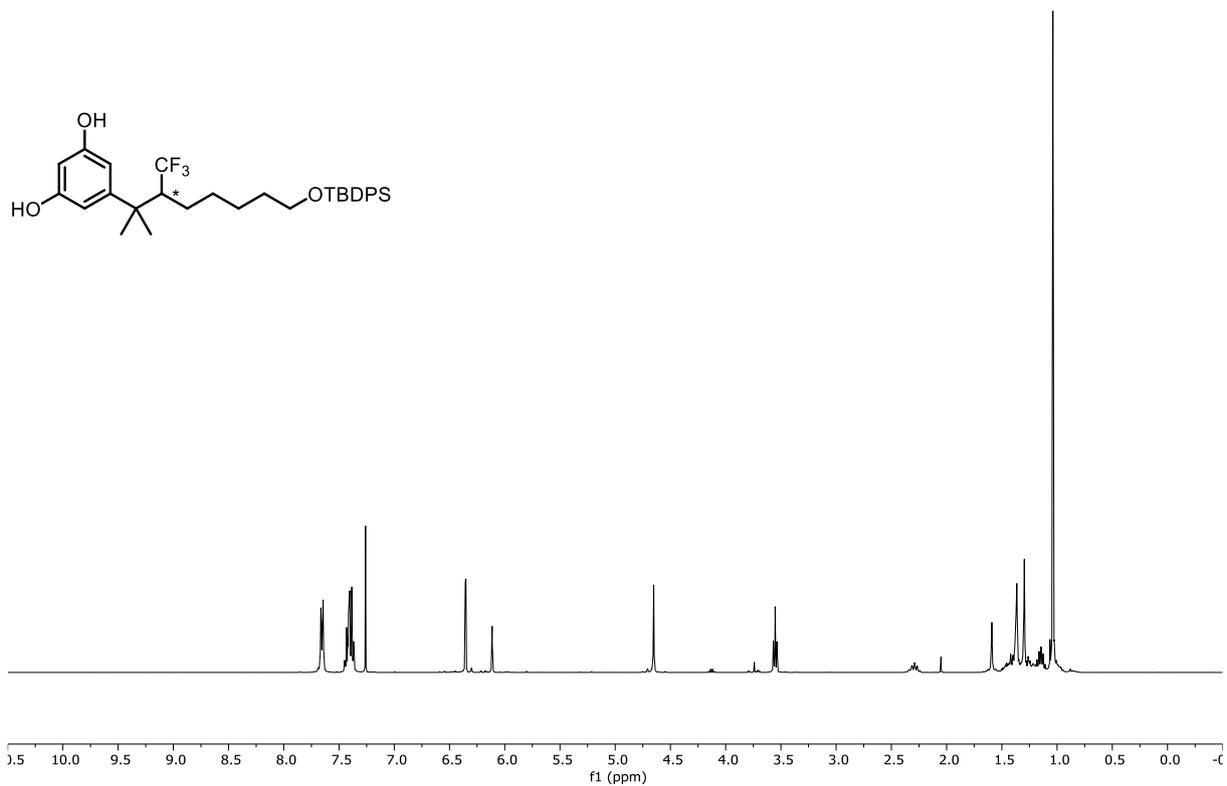
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of **SI-7**



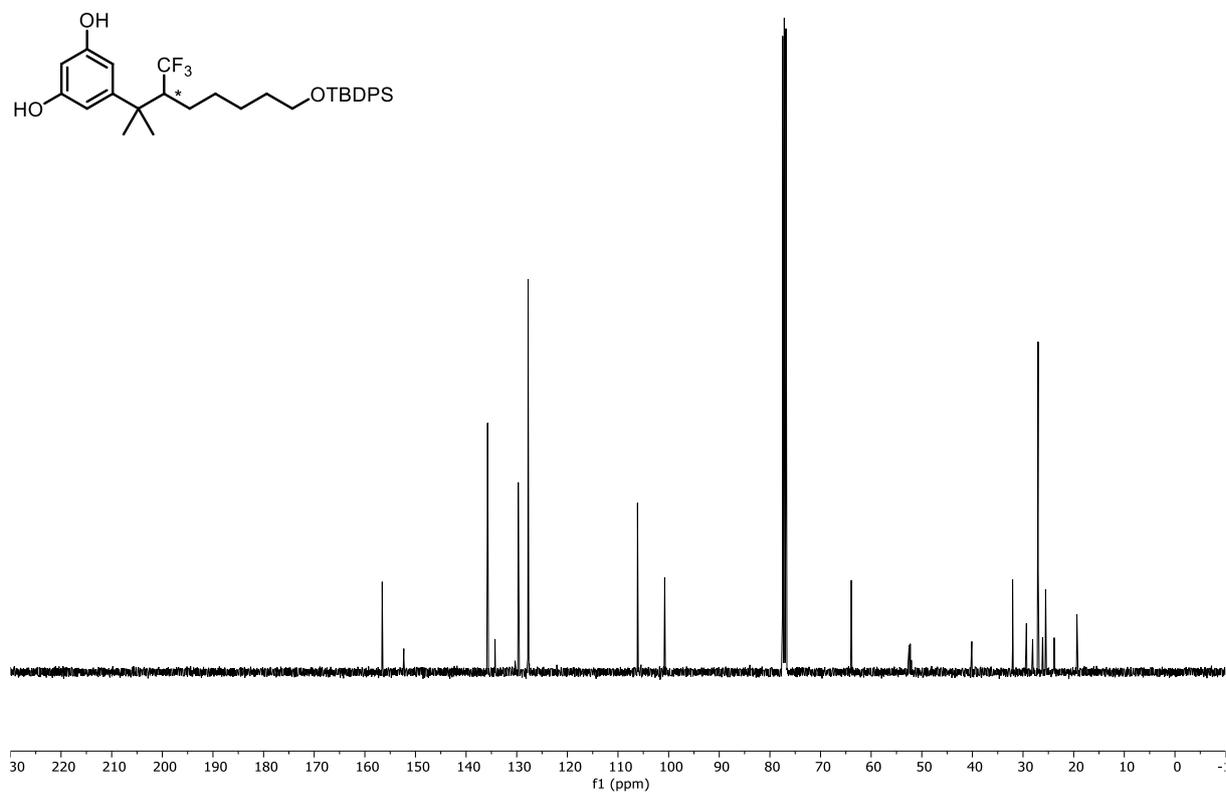
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of **SI-7**



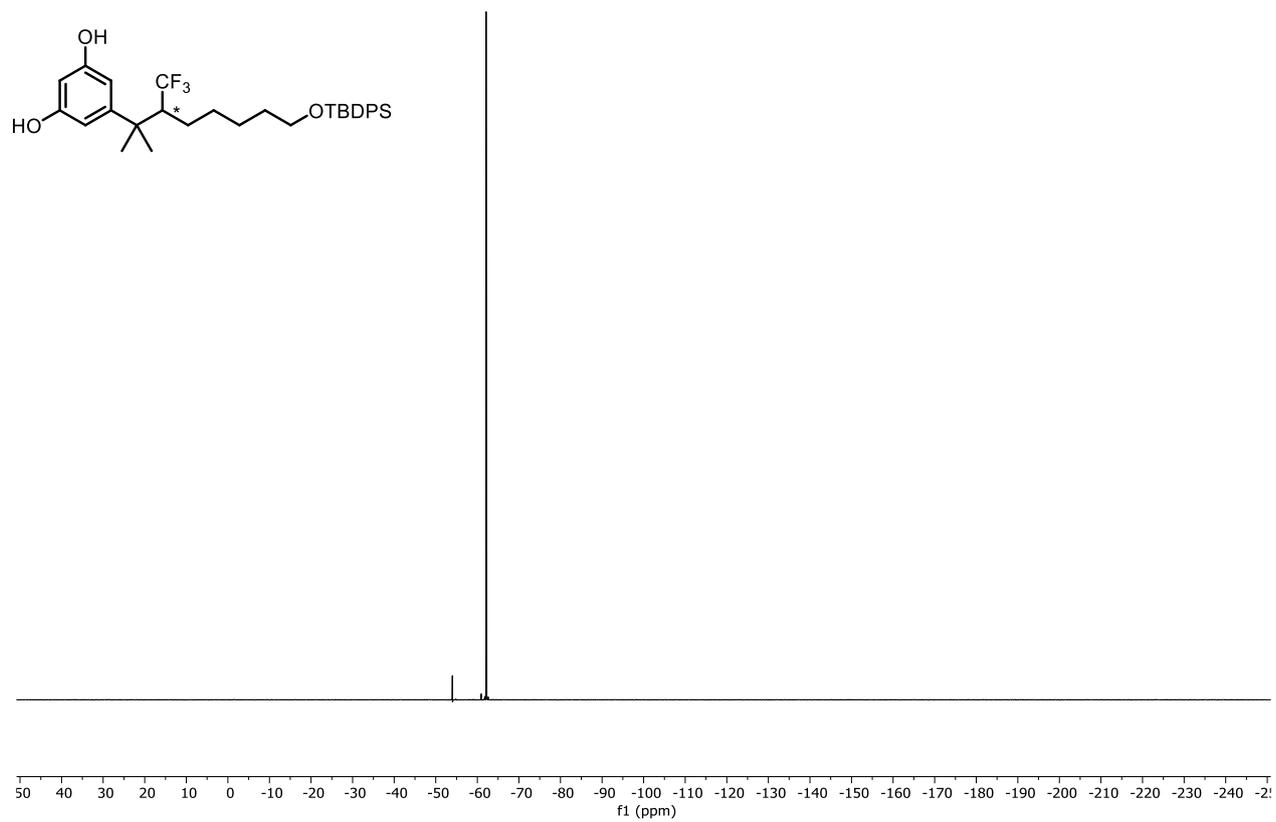
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (A)-SI-8 & (B)-SI-8



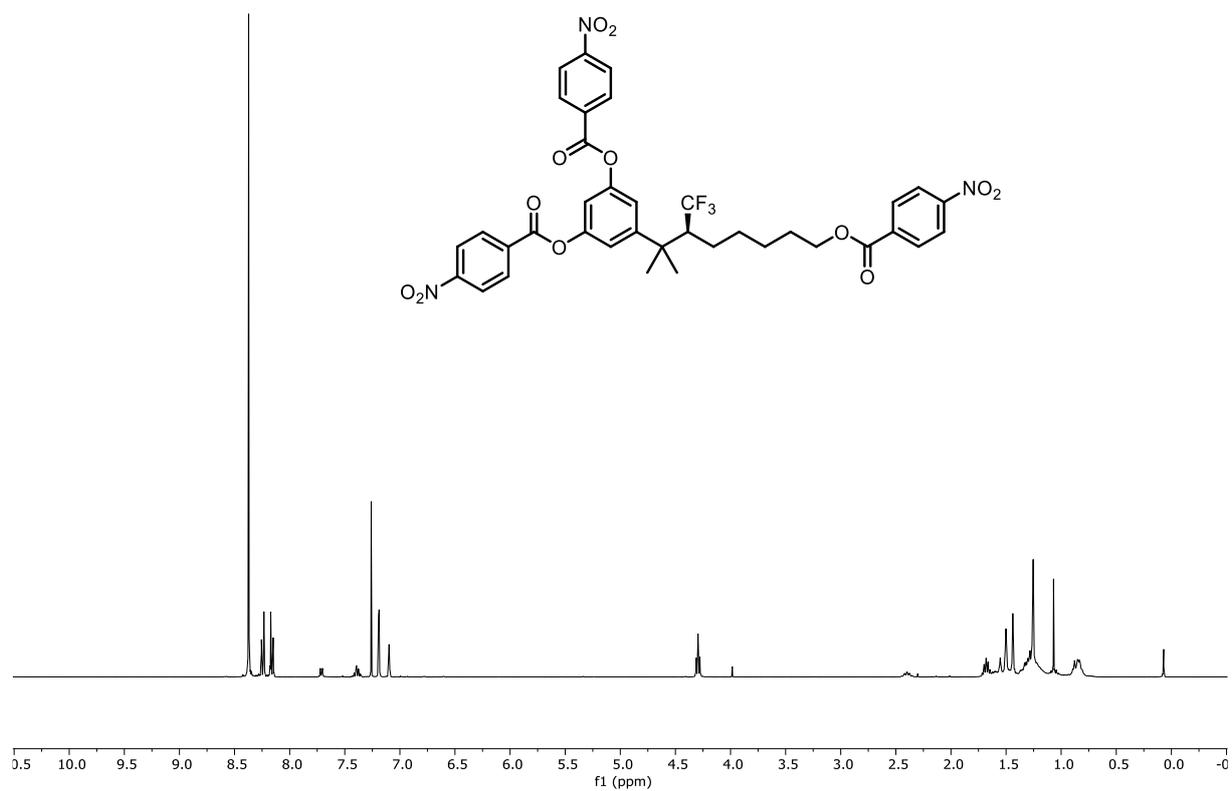
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (A)-SI-8 & (B)-SI-8



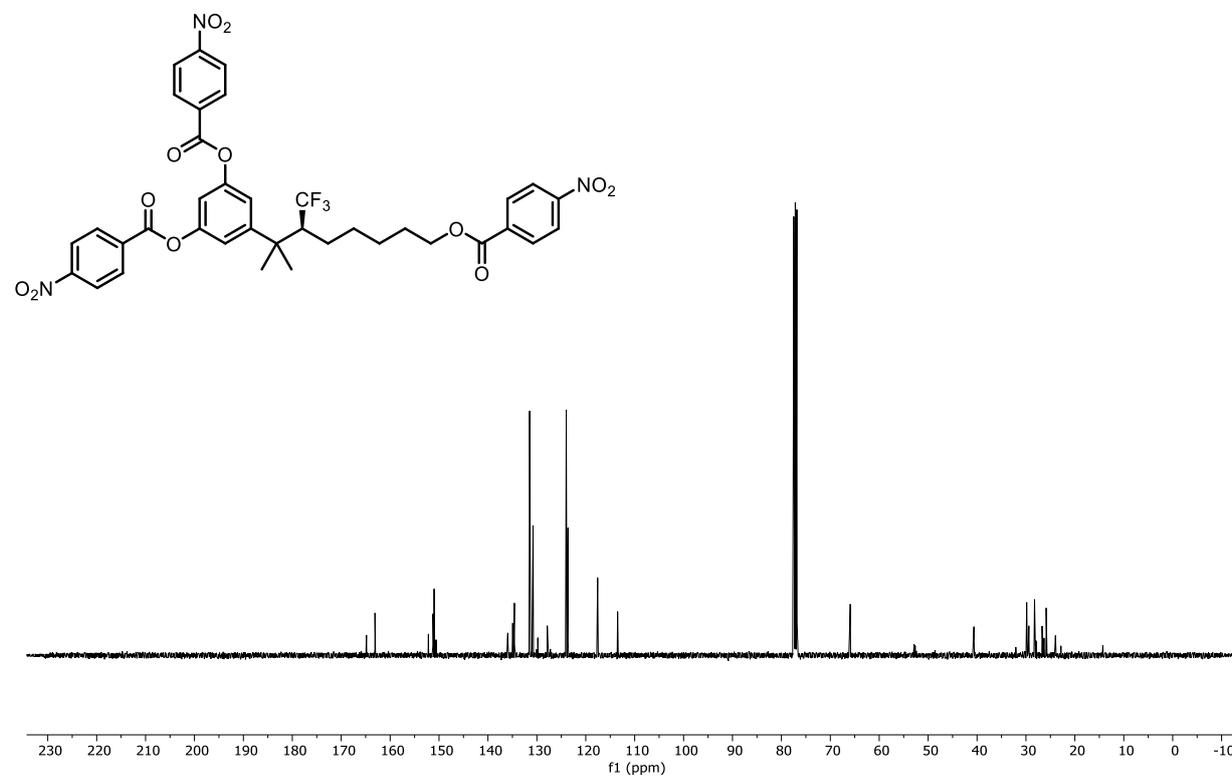
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of (A)-**SI-8** & (B)-**SI-8**



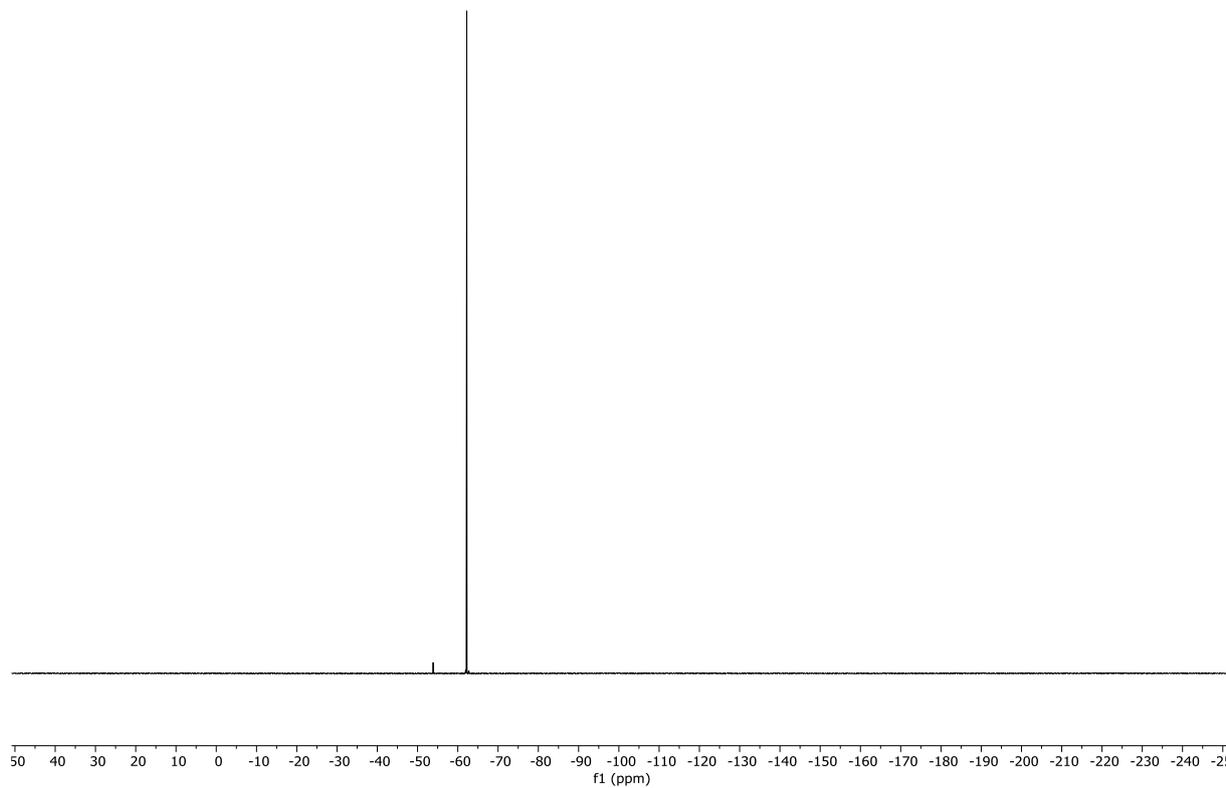
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (B)/(S)-SI-9



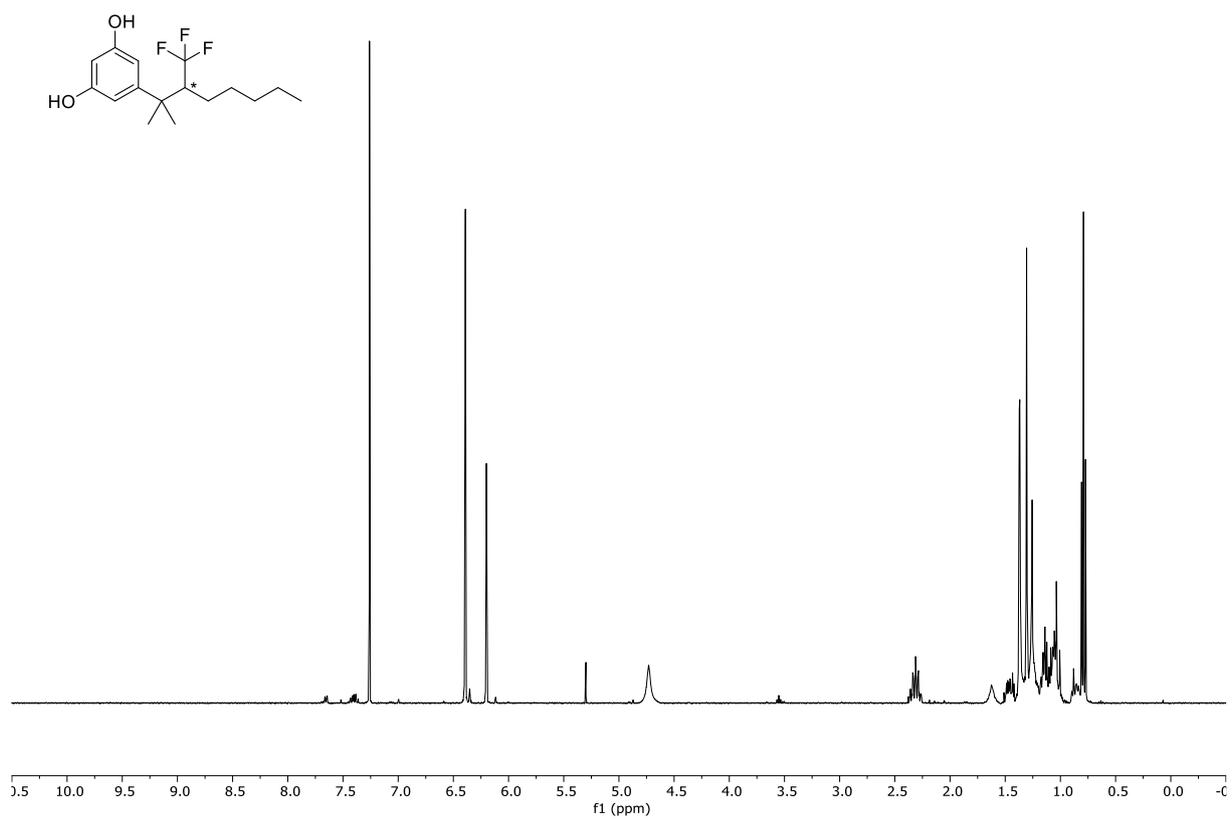
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (B)/(S)-SI-9



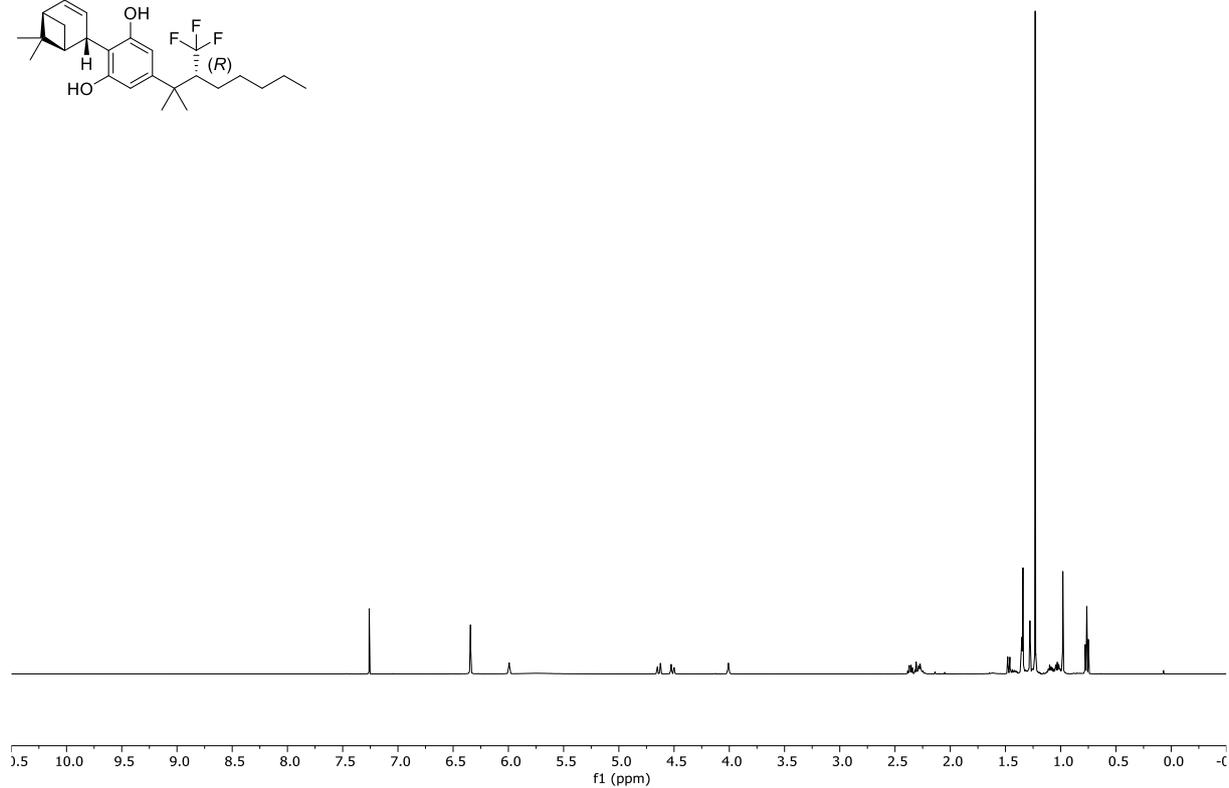
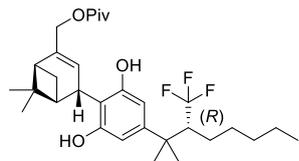
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of (B)/(S)-**SI-9**



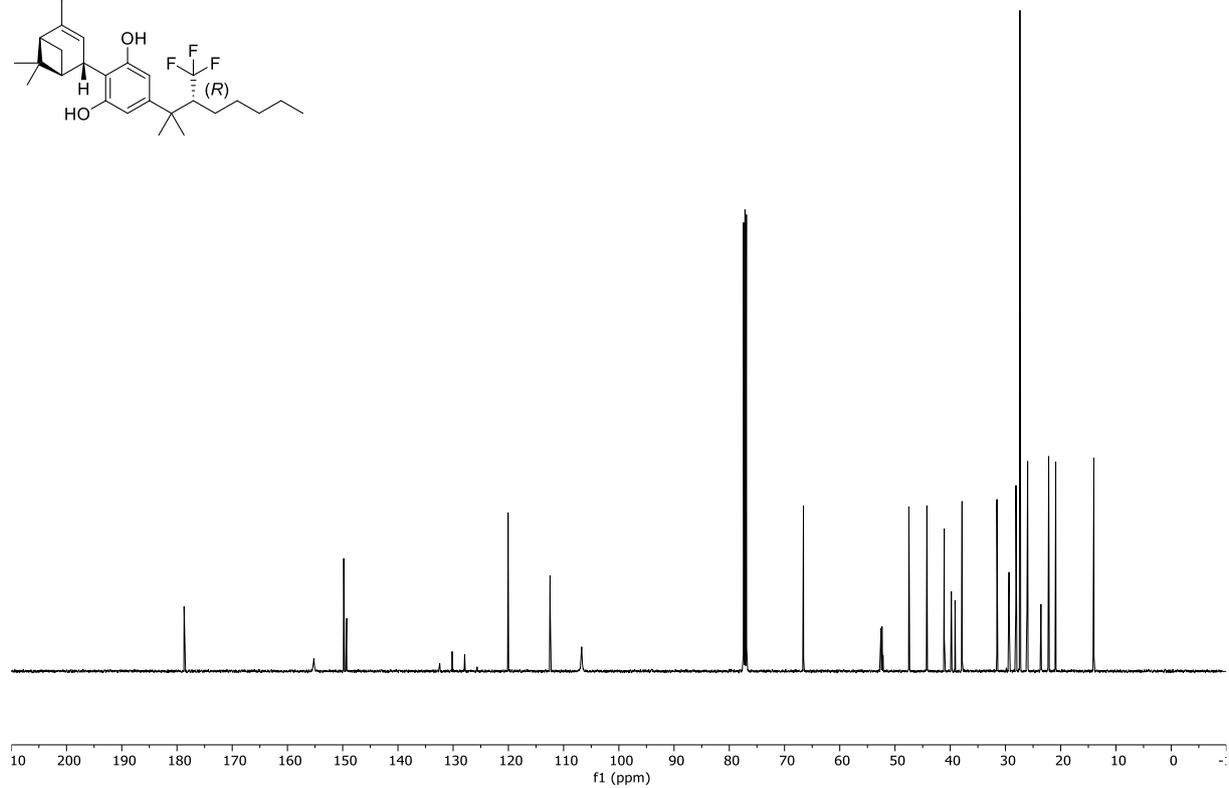
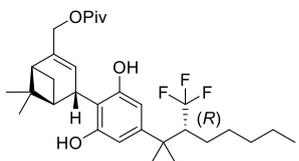
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (A)-**SI-10** for comparison to (A)-**4** = (+)-(*R*)-**4**



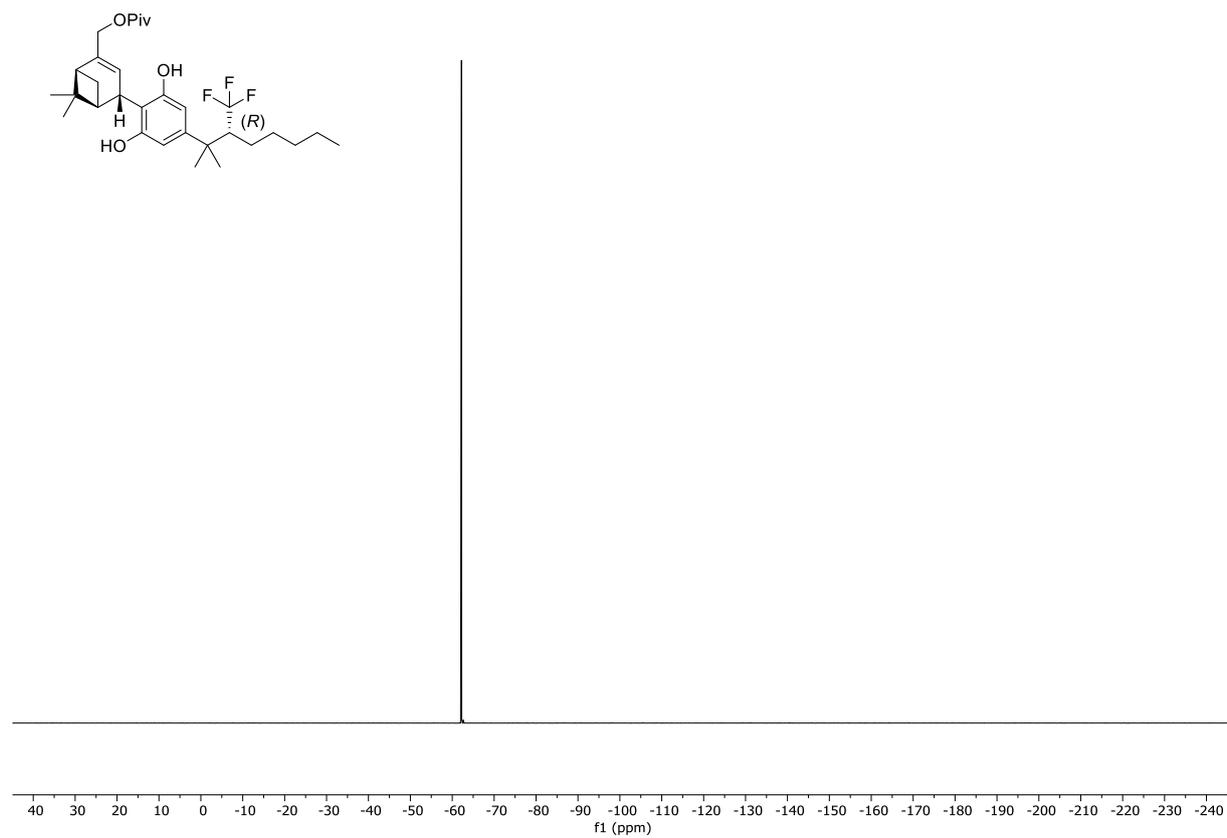
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (*R*)-SI-13



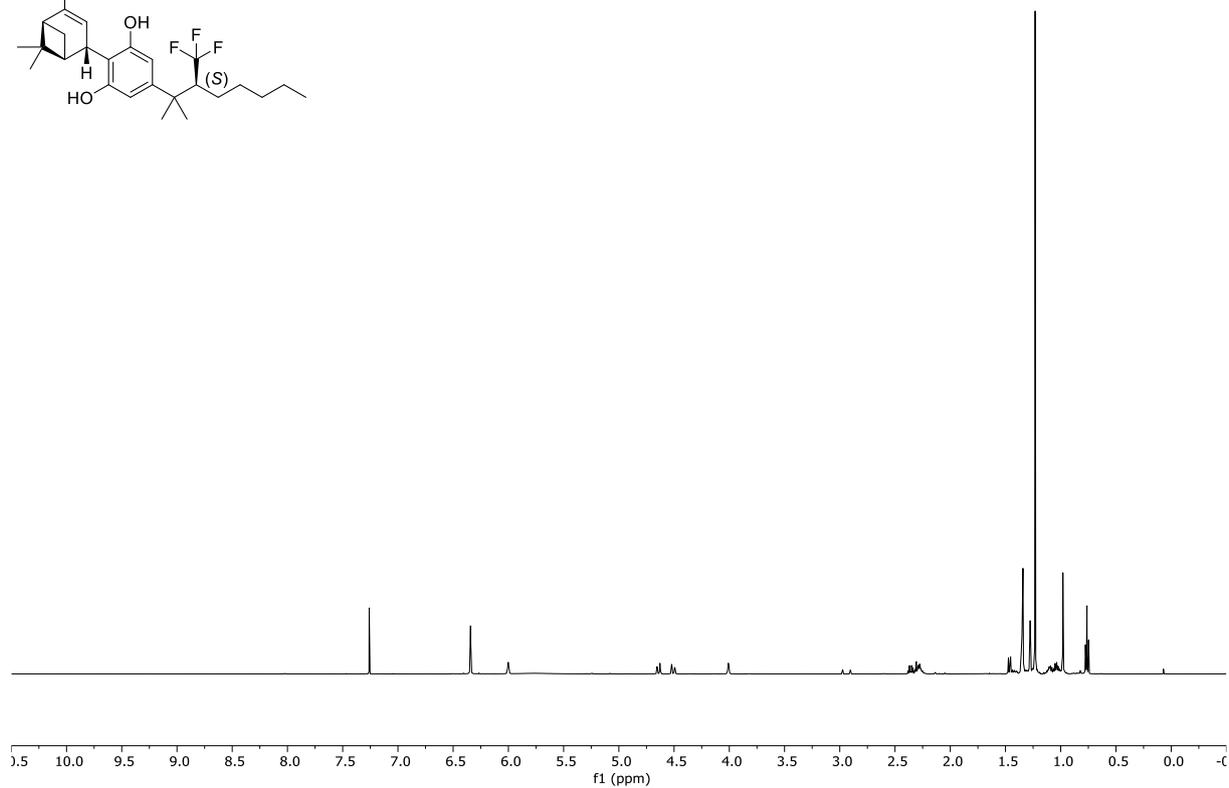
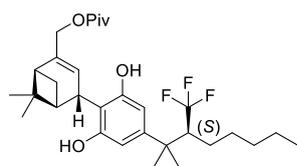
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) of (*R*)-SI-13



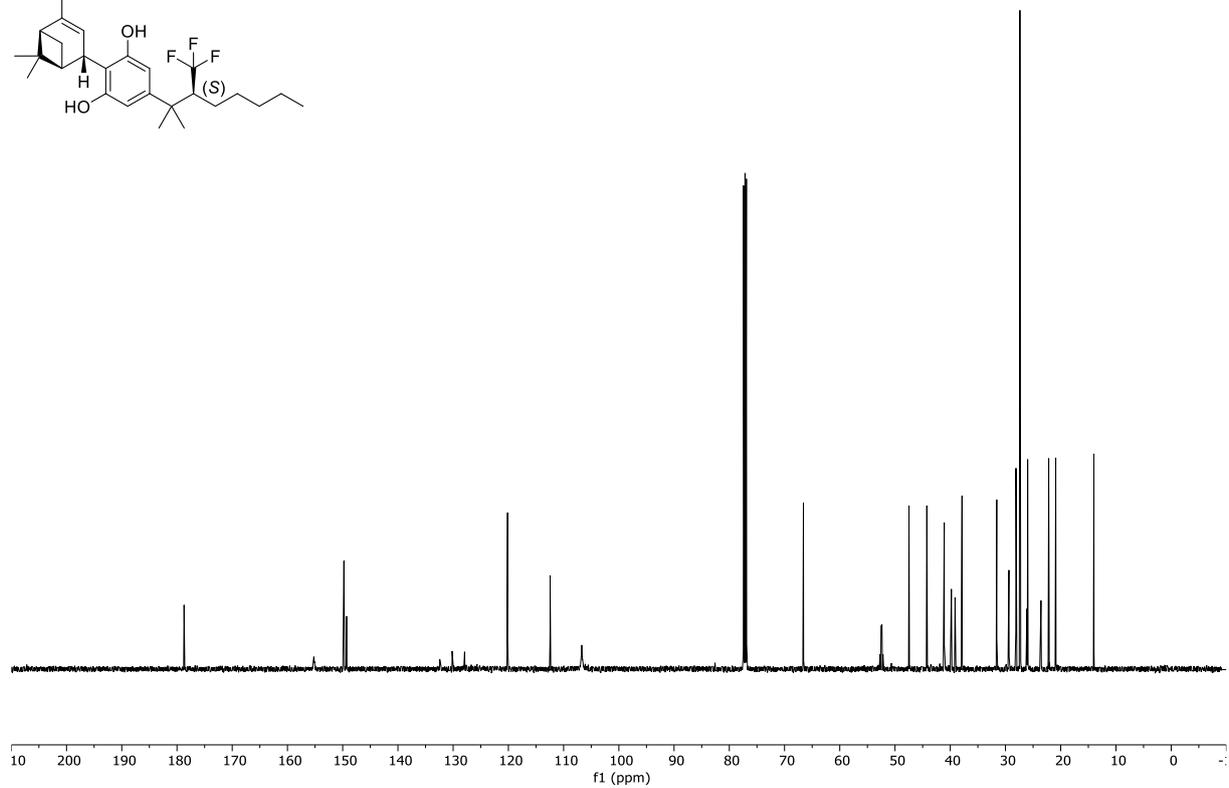
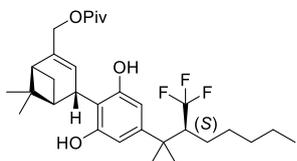
$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ) of (*R*)-**SI-13**



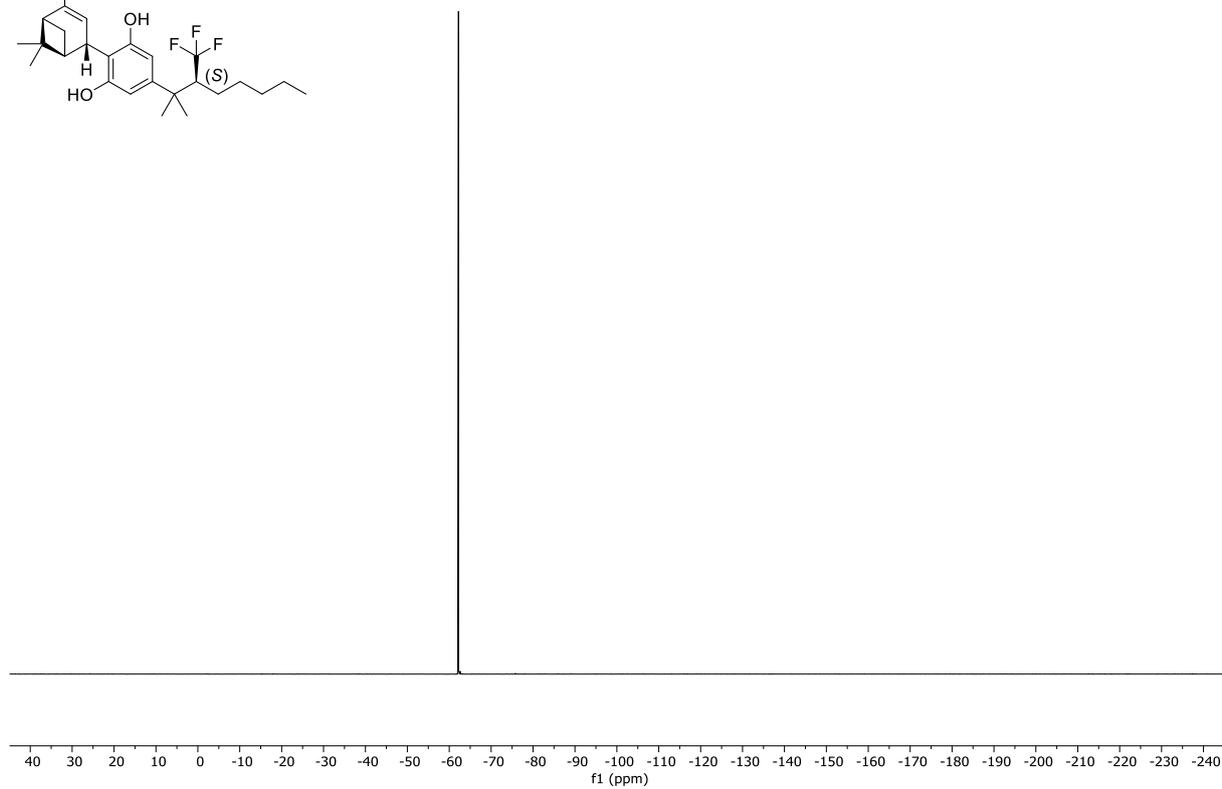
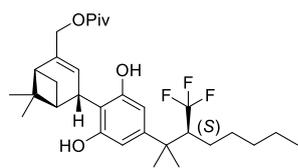
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (*S*)-**SI-13**



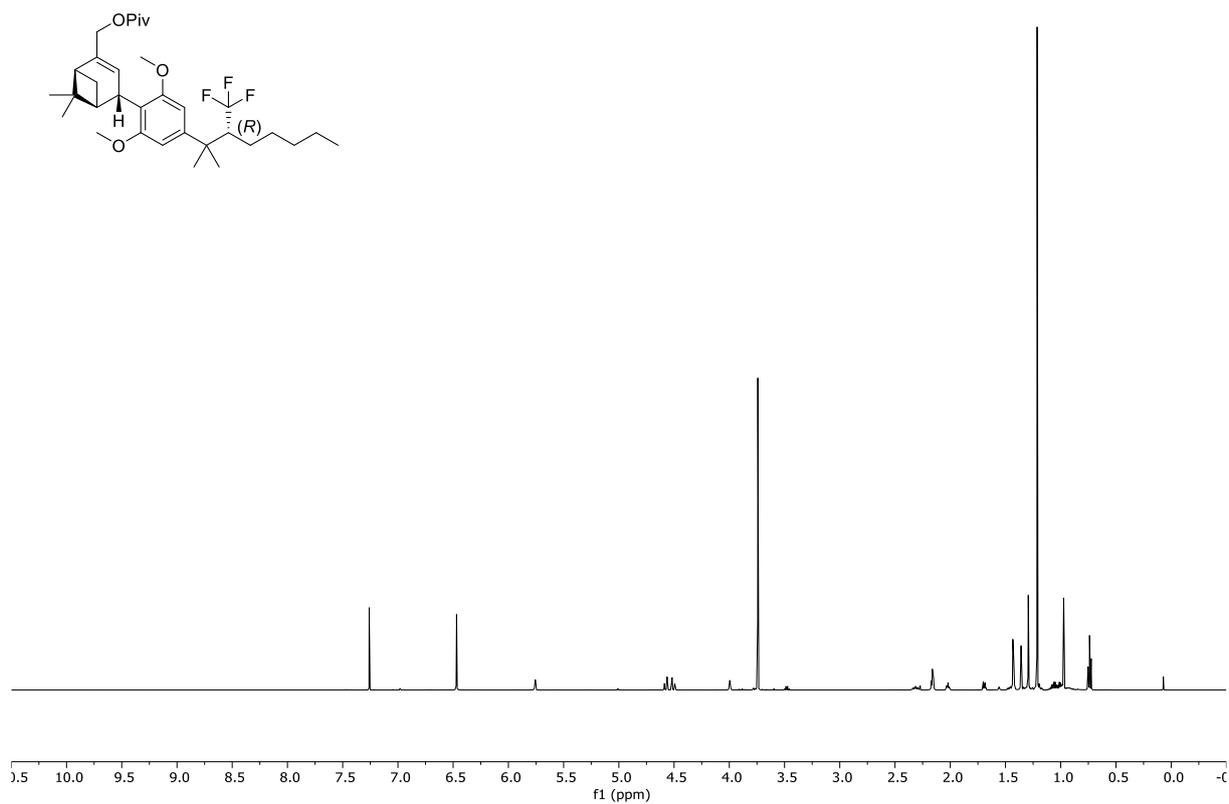
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) of (*S*)-**SI-13**



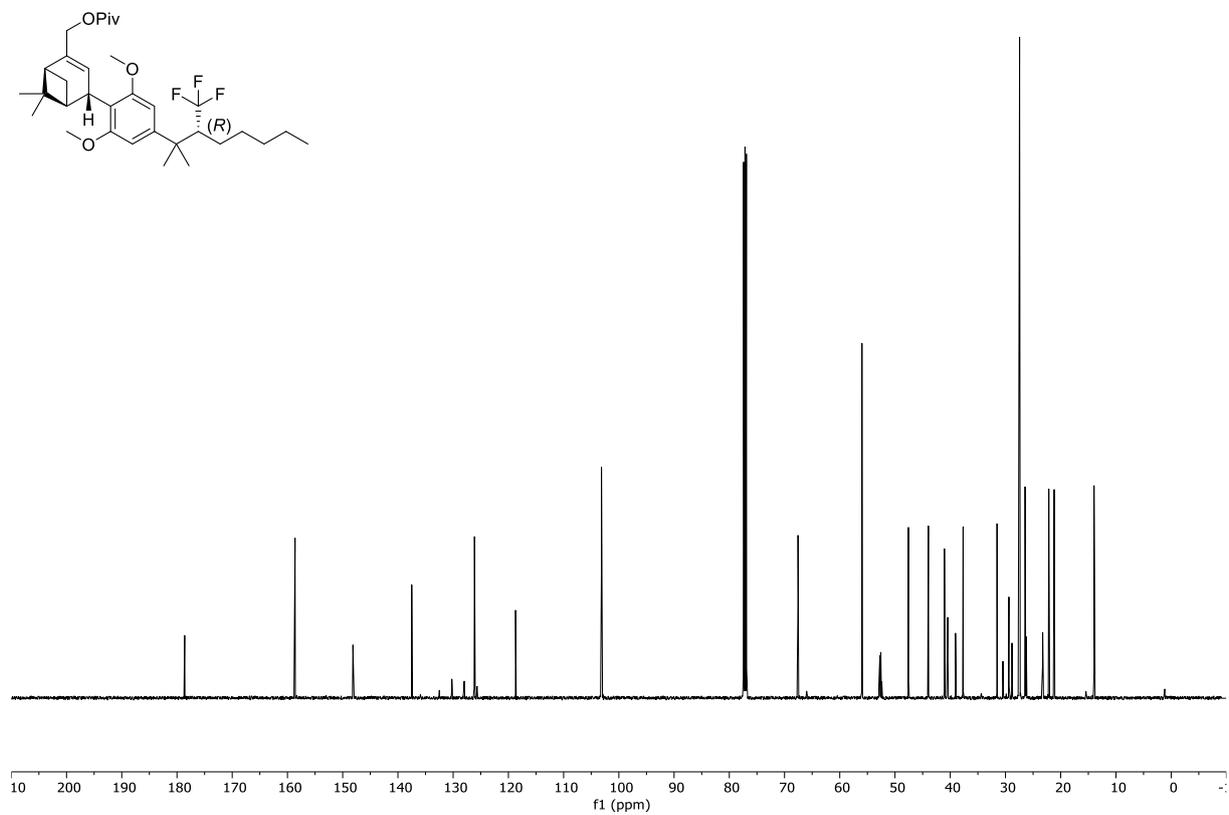
$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ) of (*S*)-**SI-13**



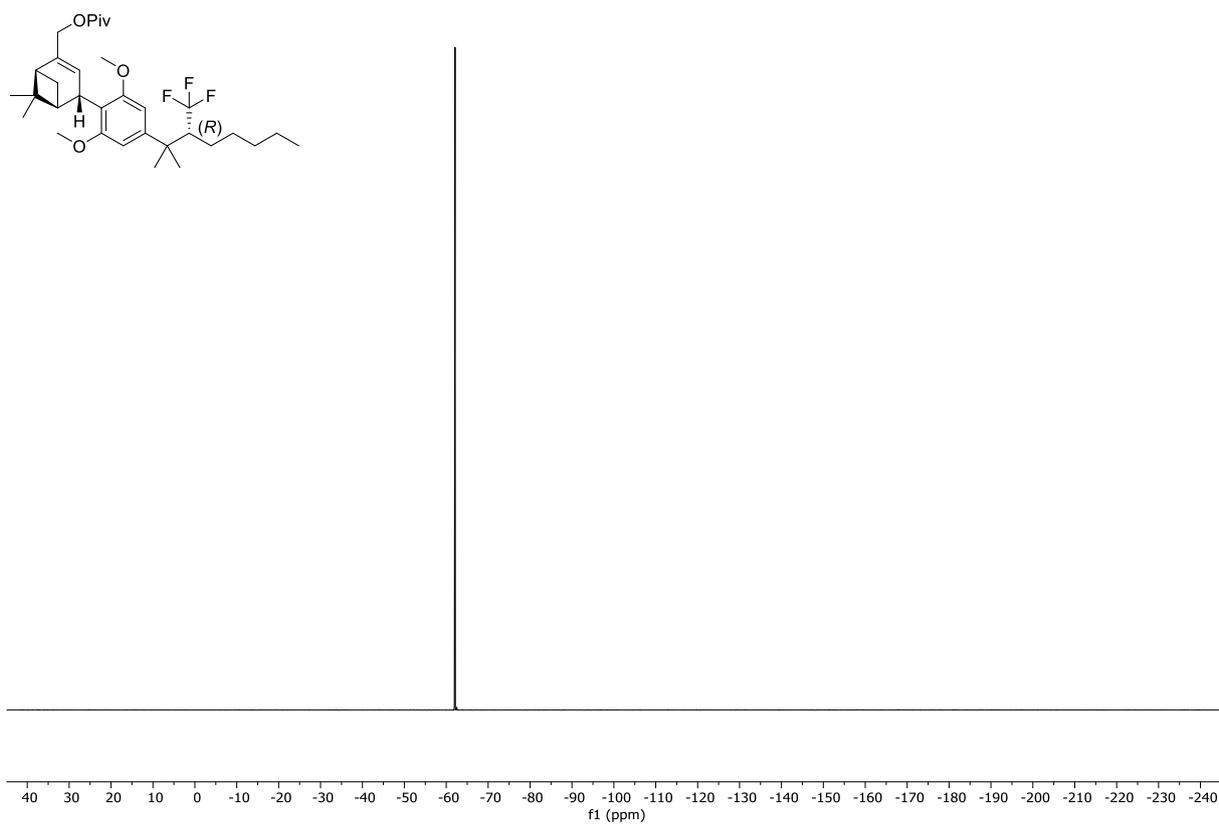
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (*R*)-SI-14



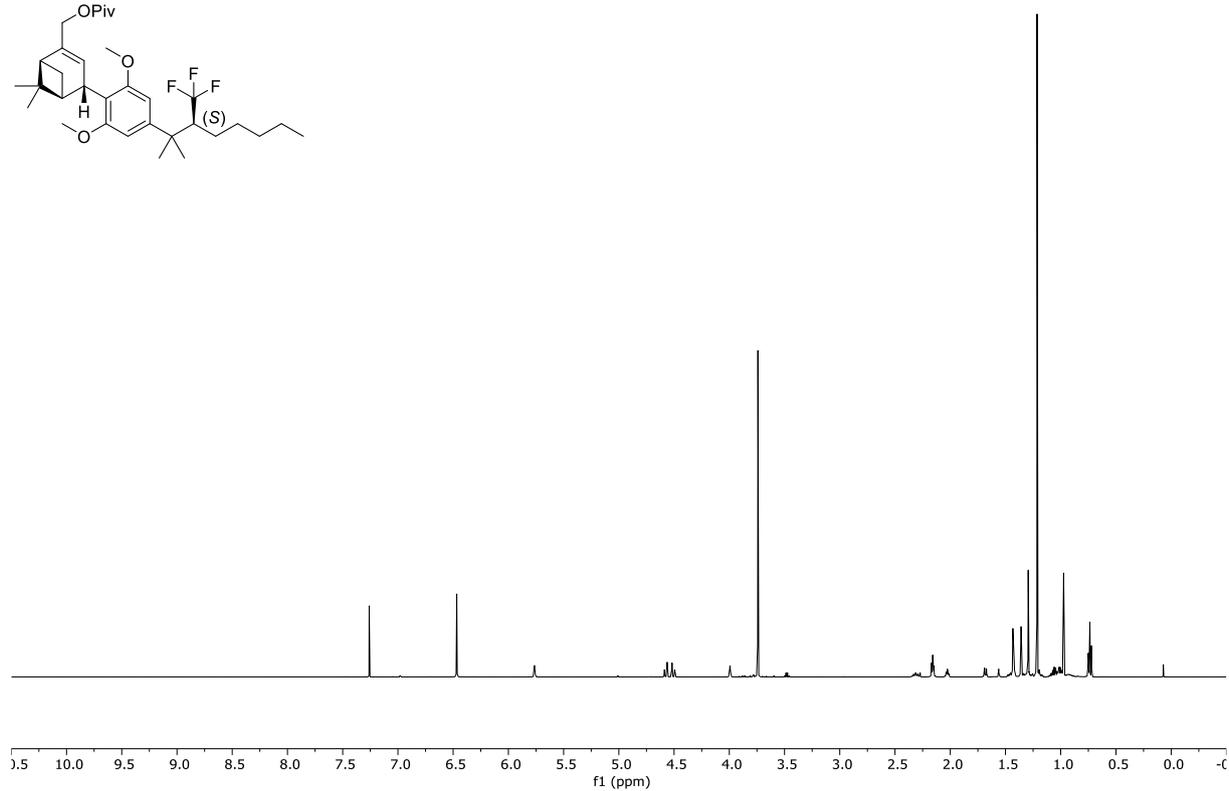
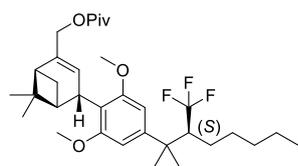
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) of (*R*)-SI-14



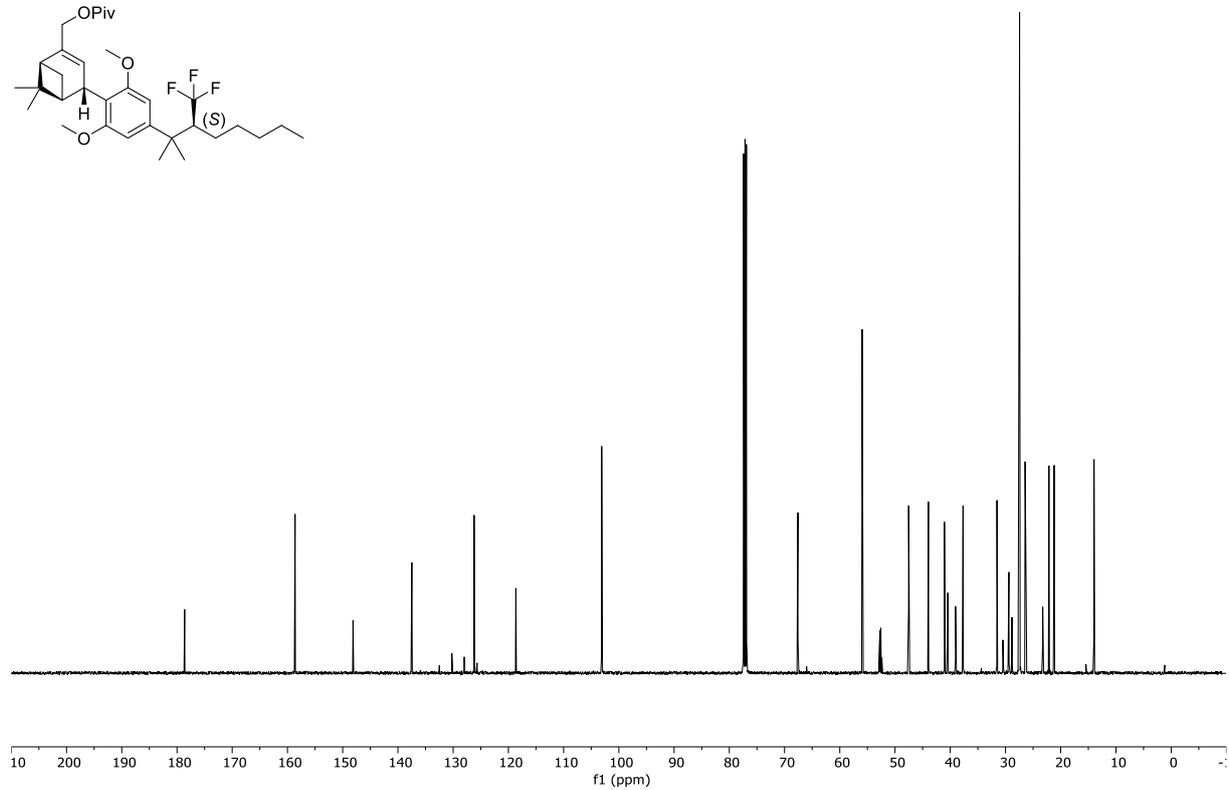
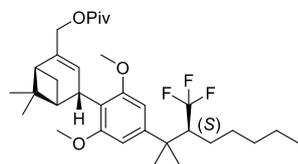
$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ) of (*R*)-**SI-14**



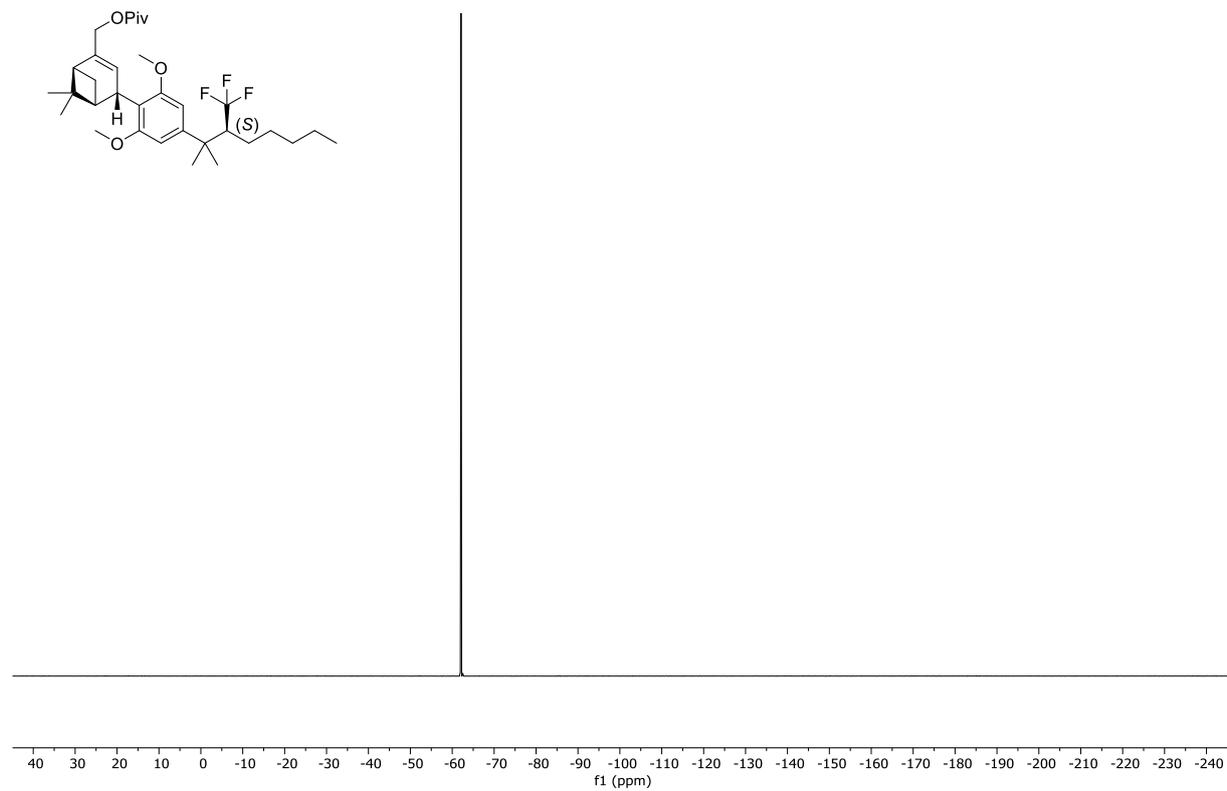
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (*S*)-**SI-14**



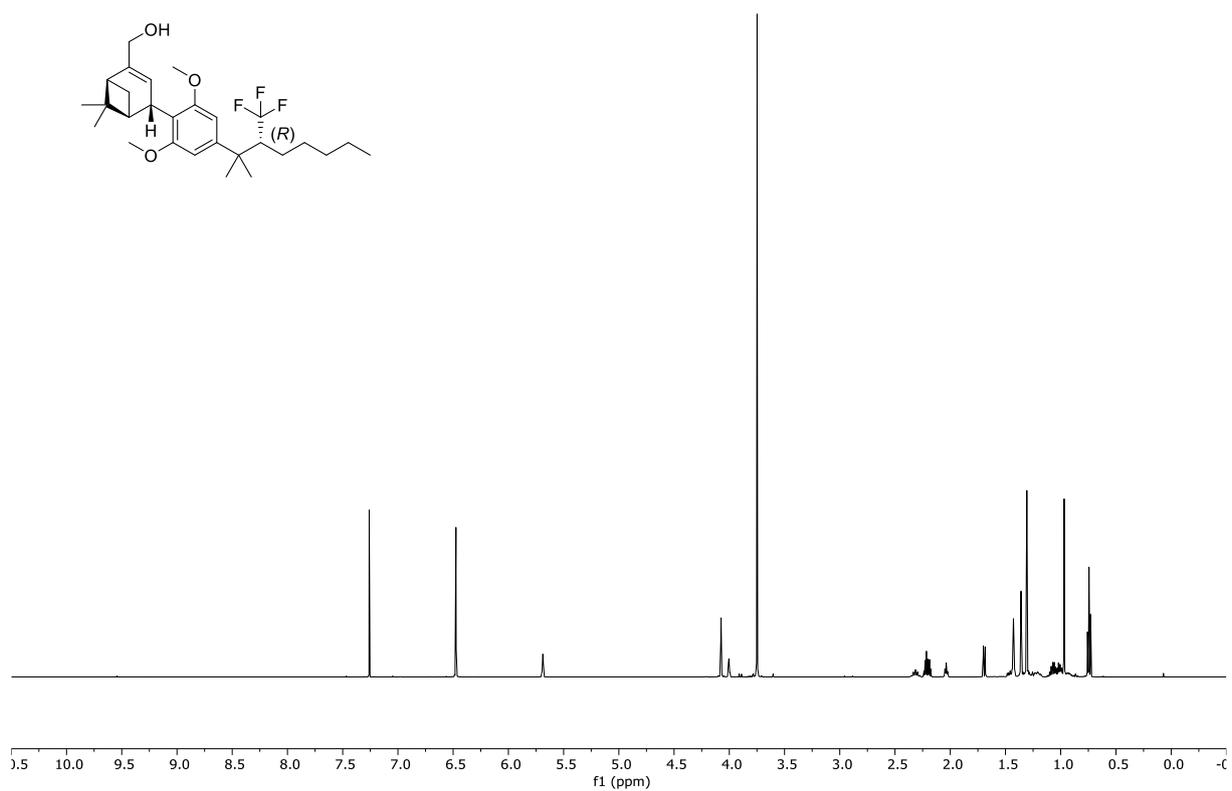
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) of (*S*)-**SI-14**



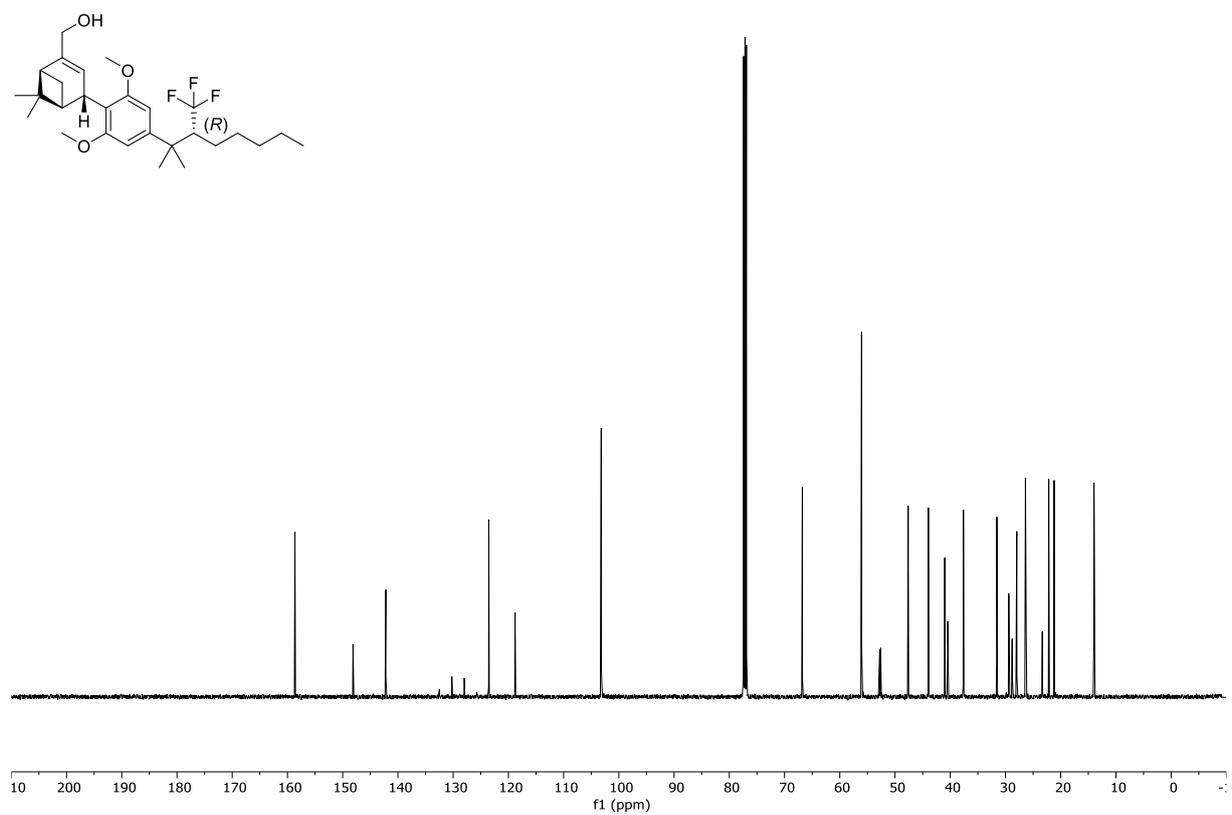
$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ) of (*S*)-SI-14



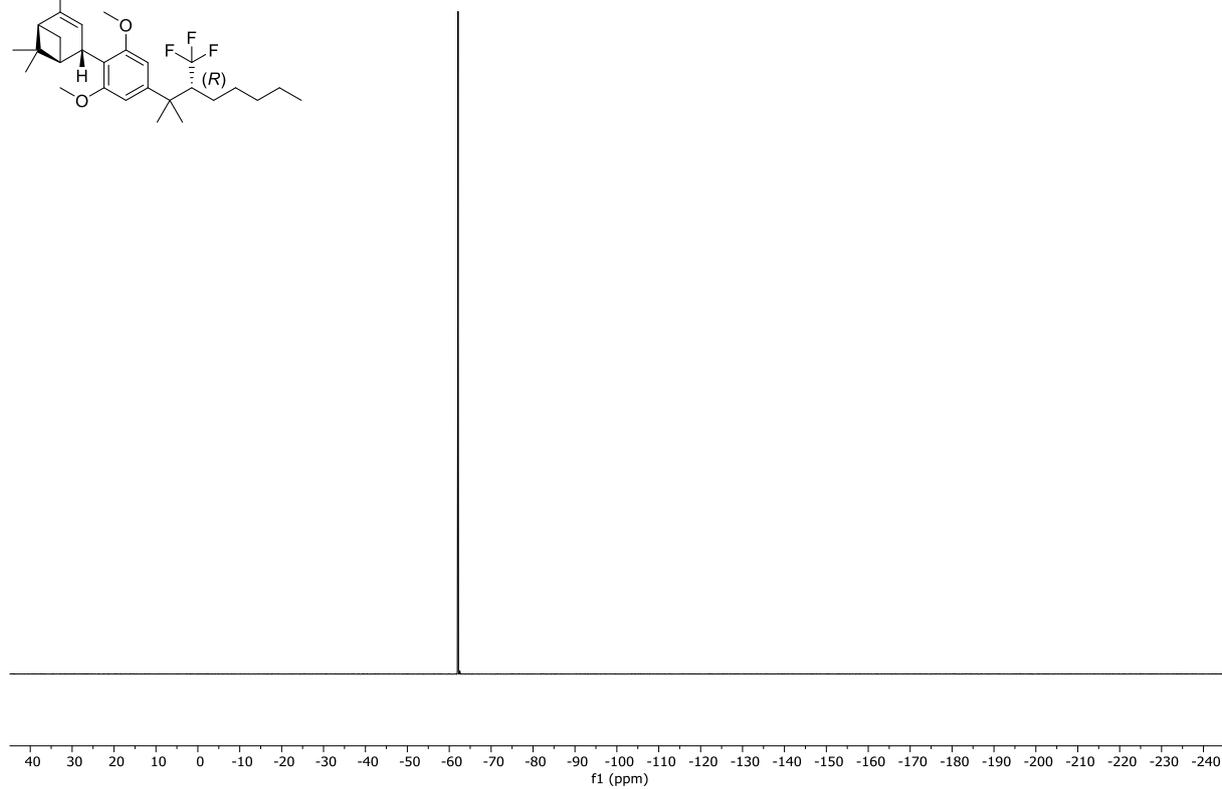
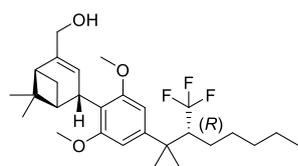
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (*R*)-**1**



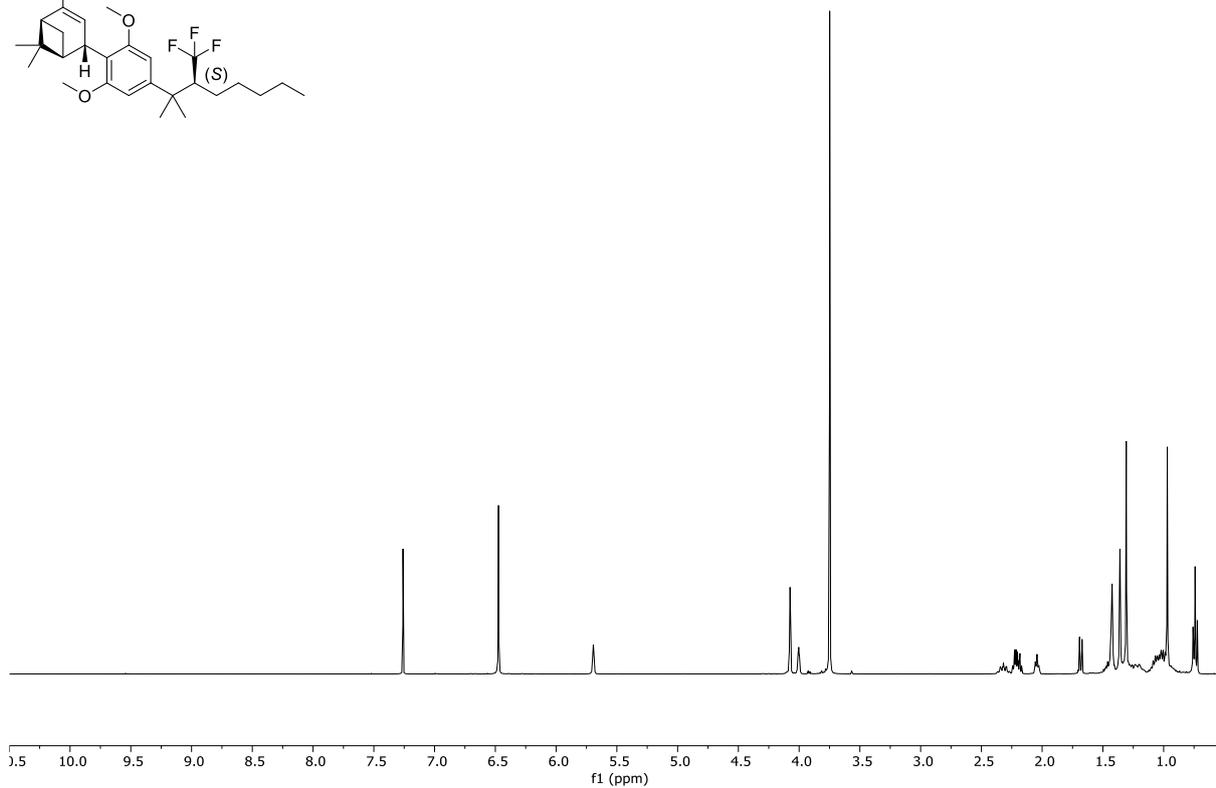
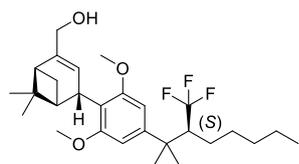
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) of (*R*)-**1**



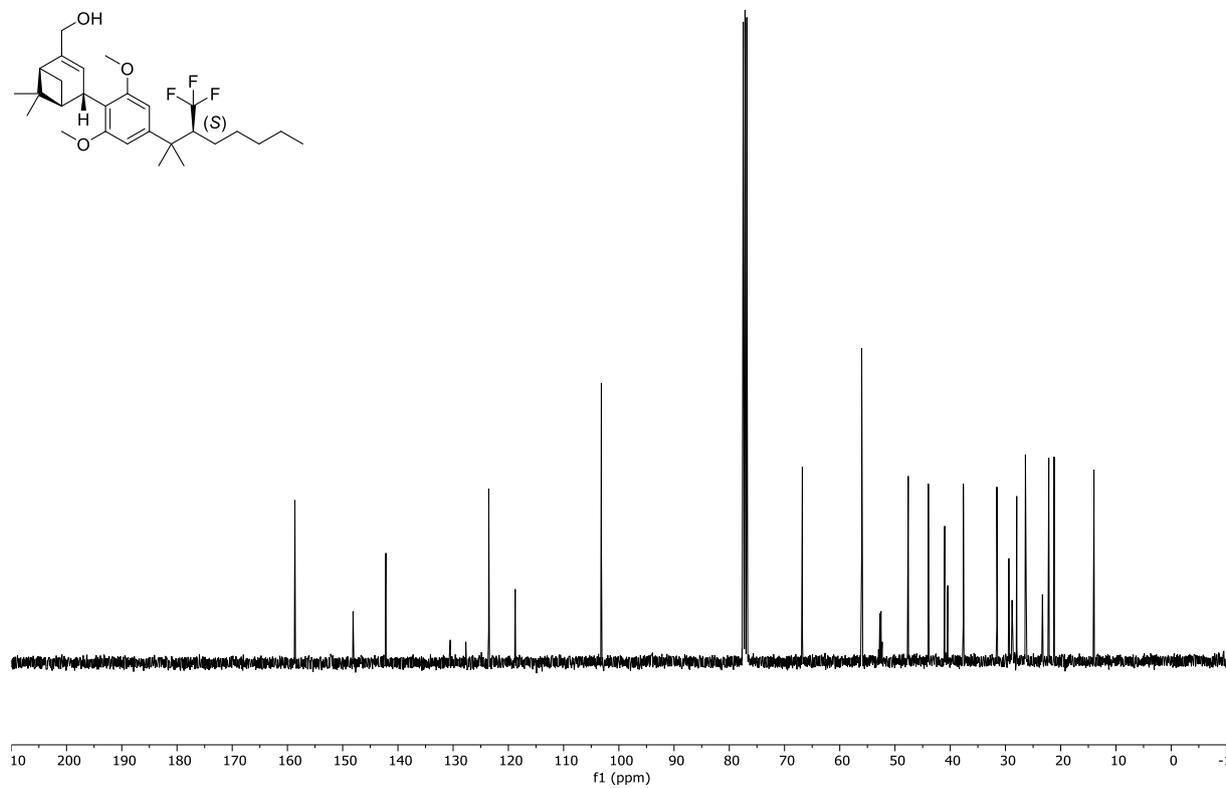
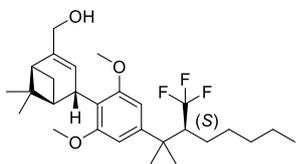
$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ) of (*R*)-**1**



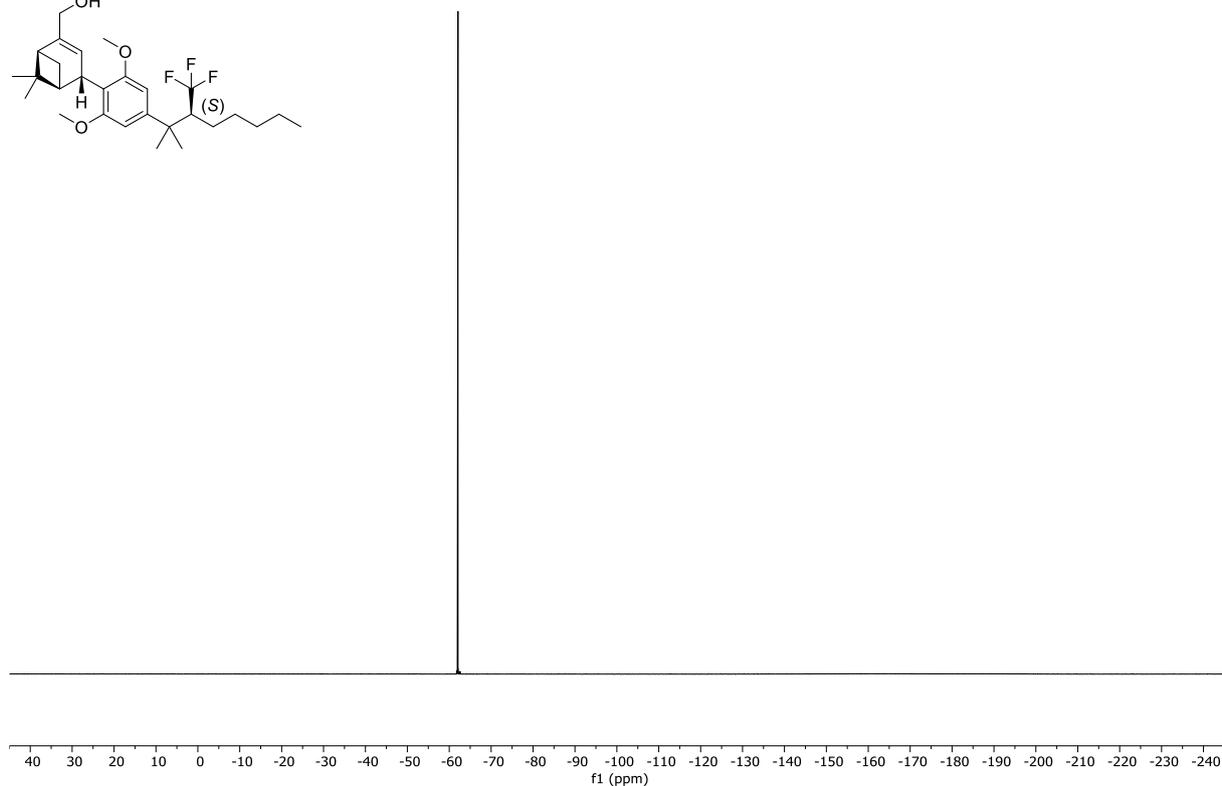
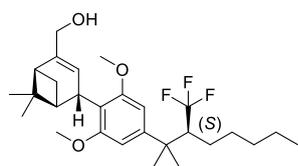
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S*)-1



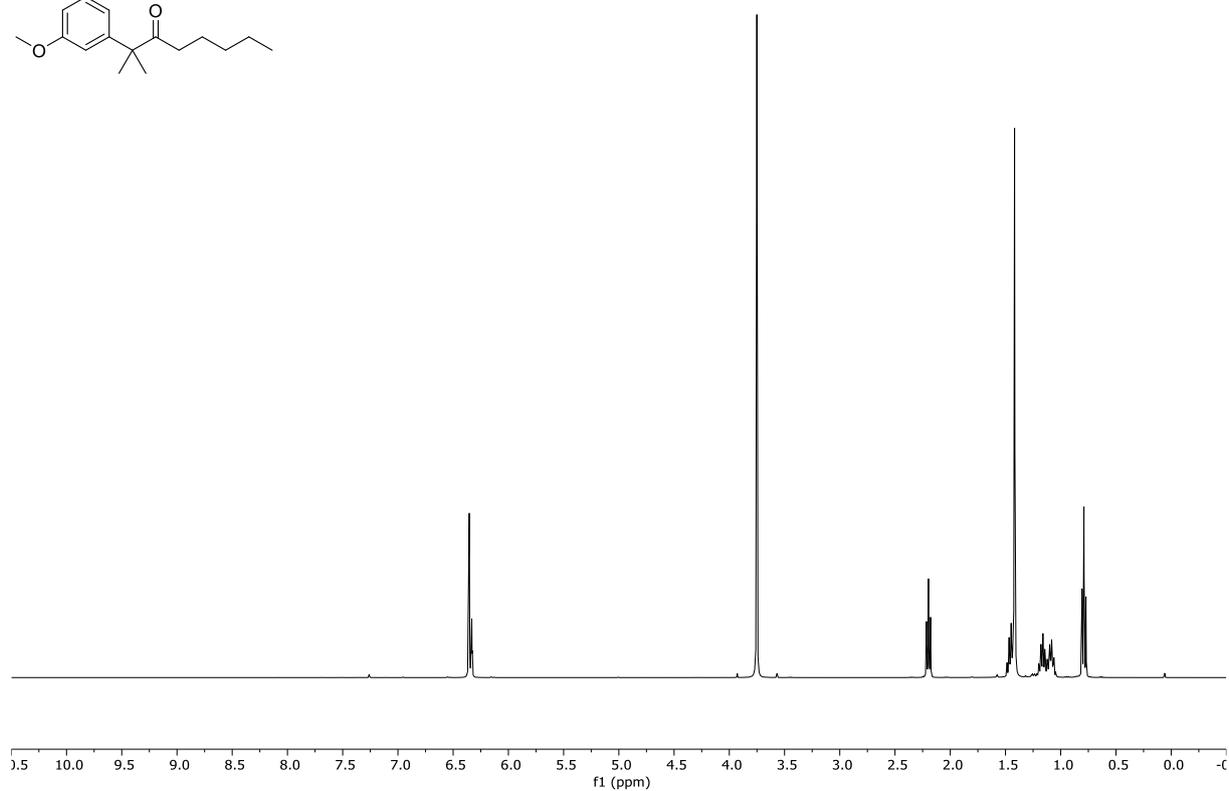
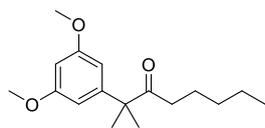
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S*)-1



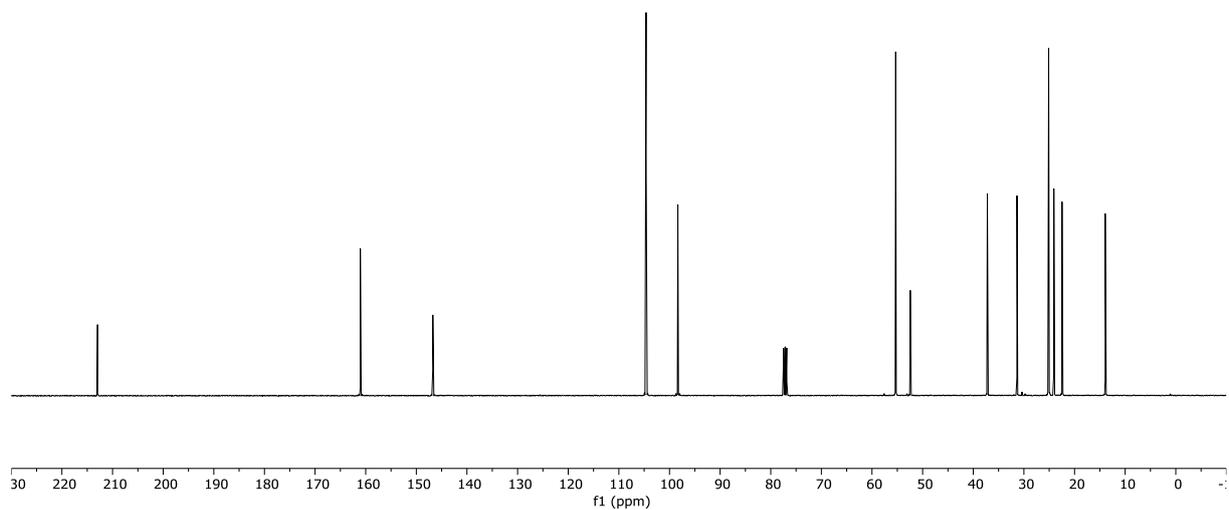
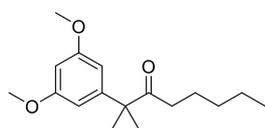
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of (*S*)-**1**



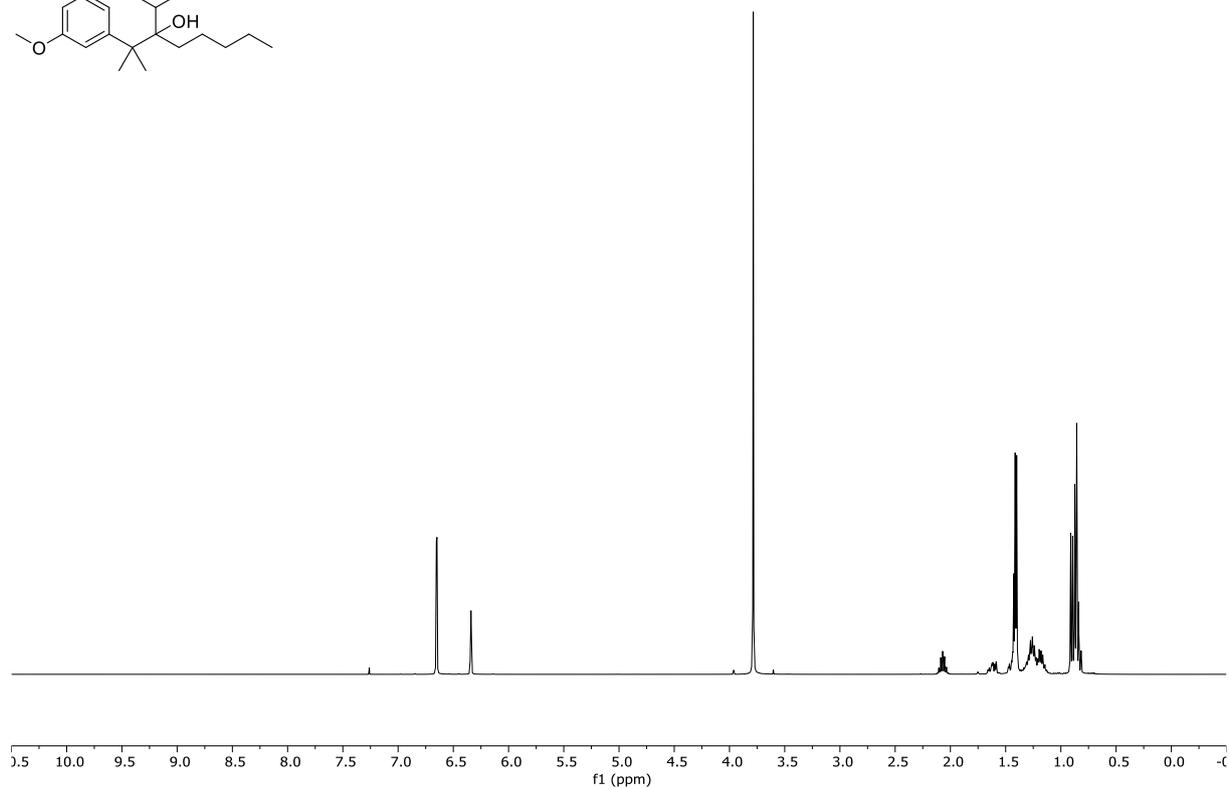
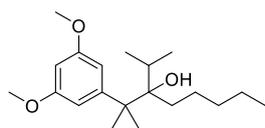
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of **7**



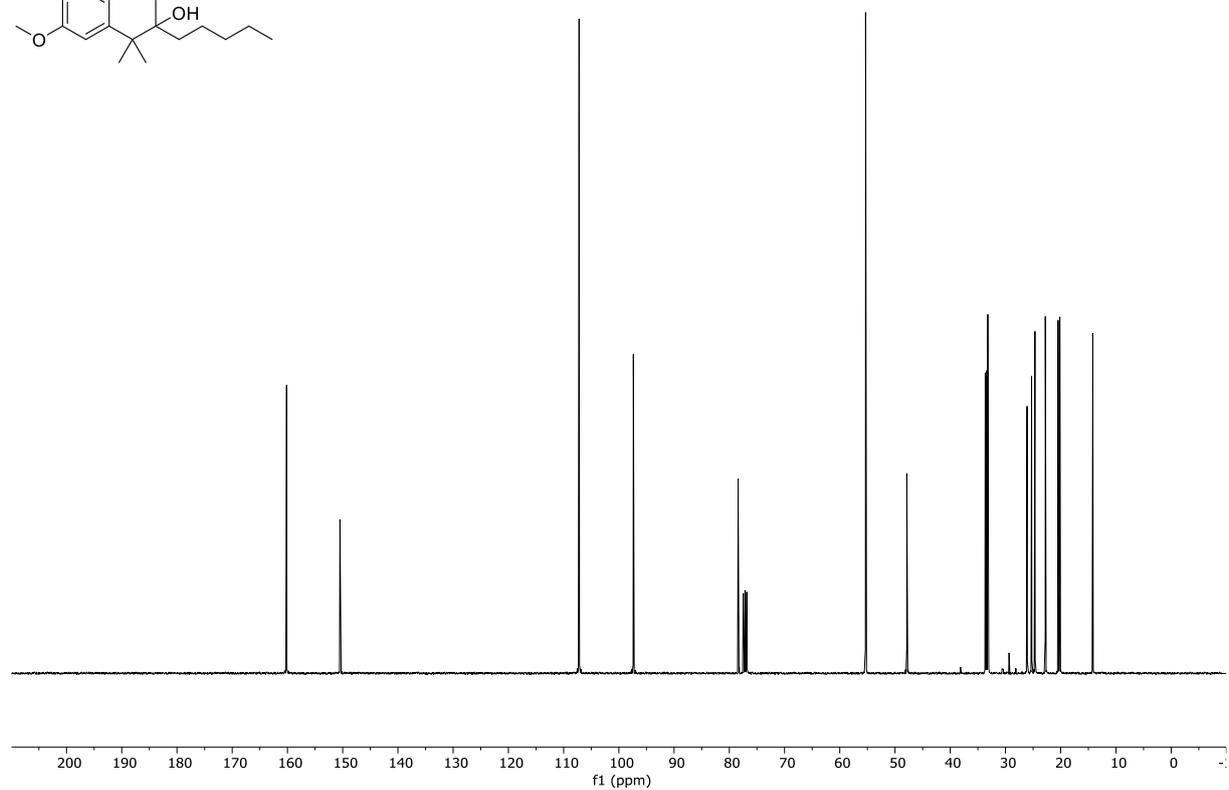
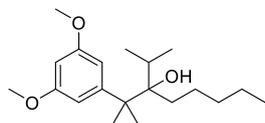
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of **7**



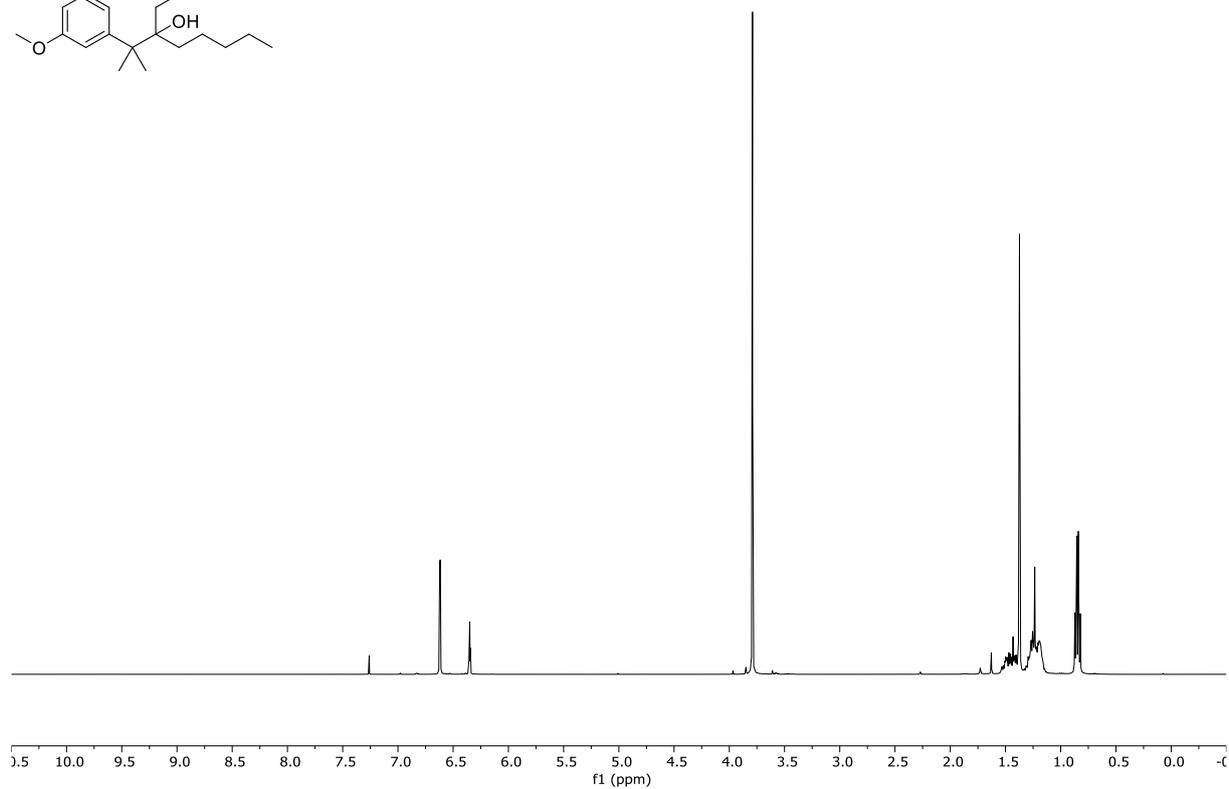
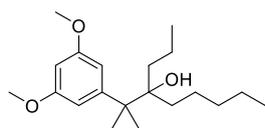
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **8a**



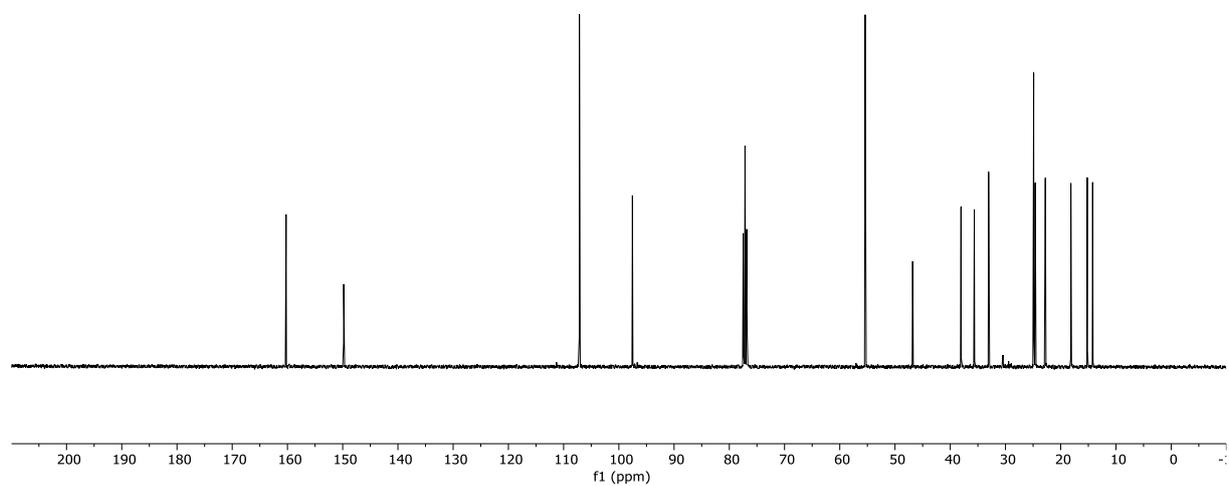
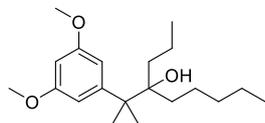
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **8a**



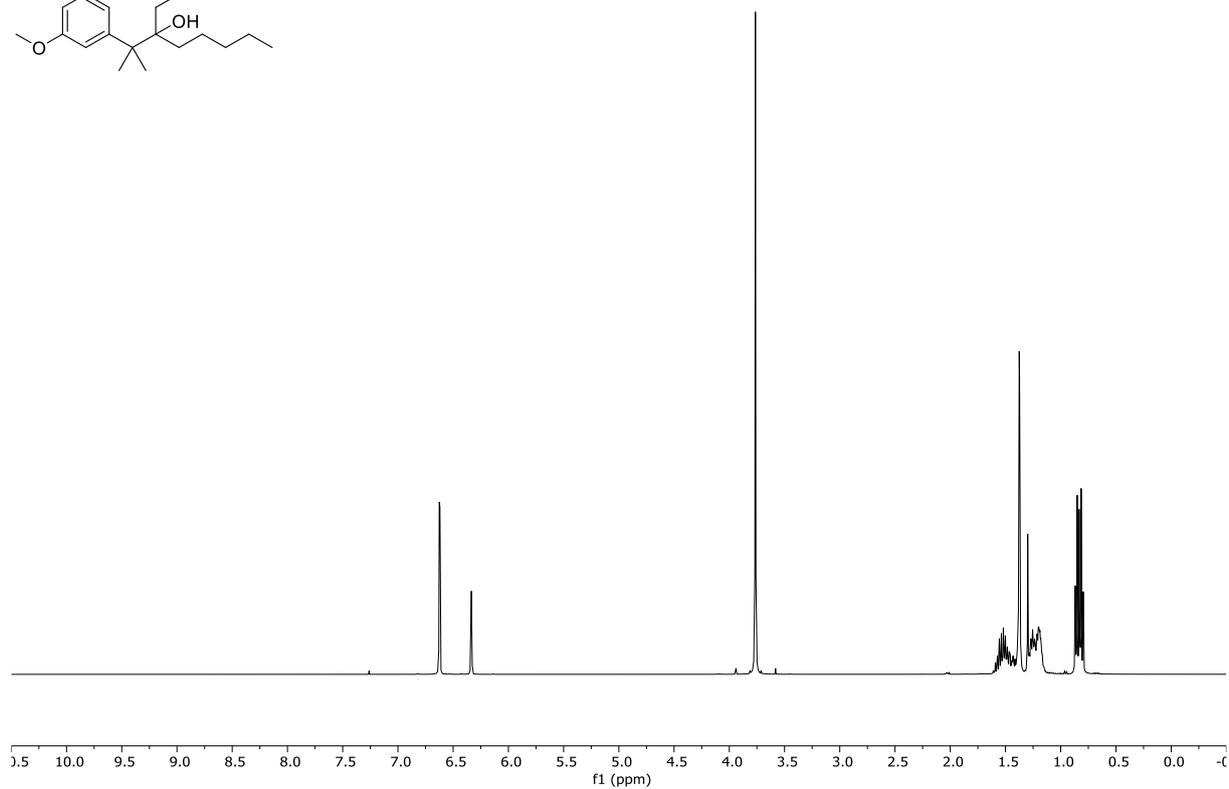
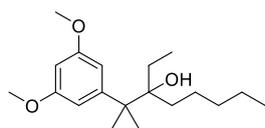
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **8b**



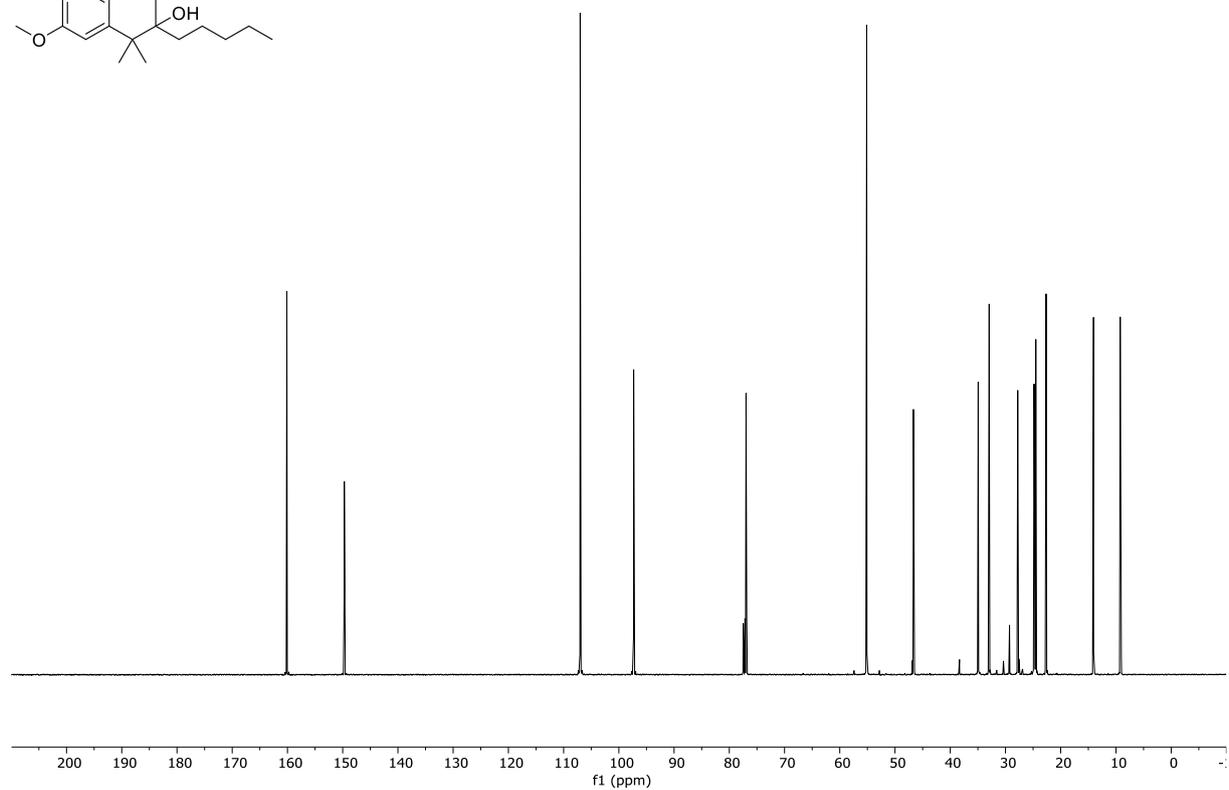
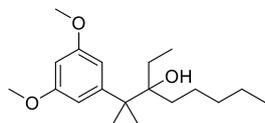
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **8b**



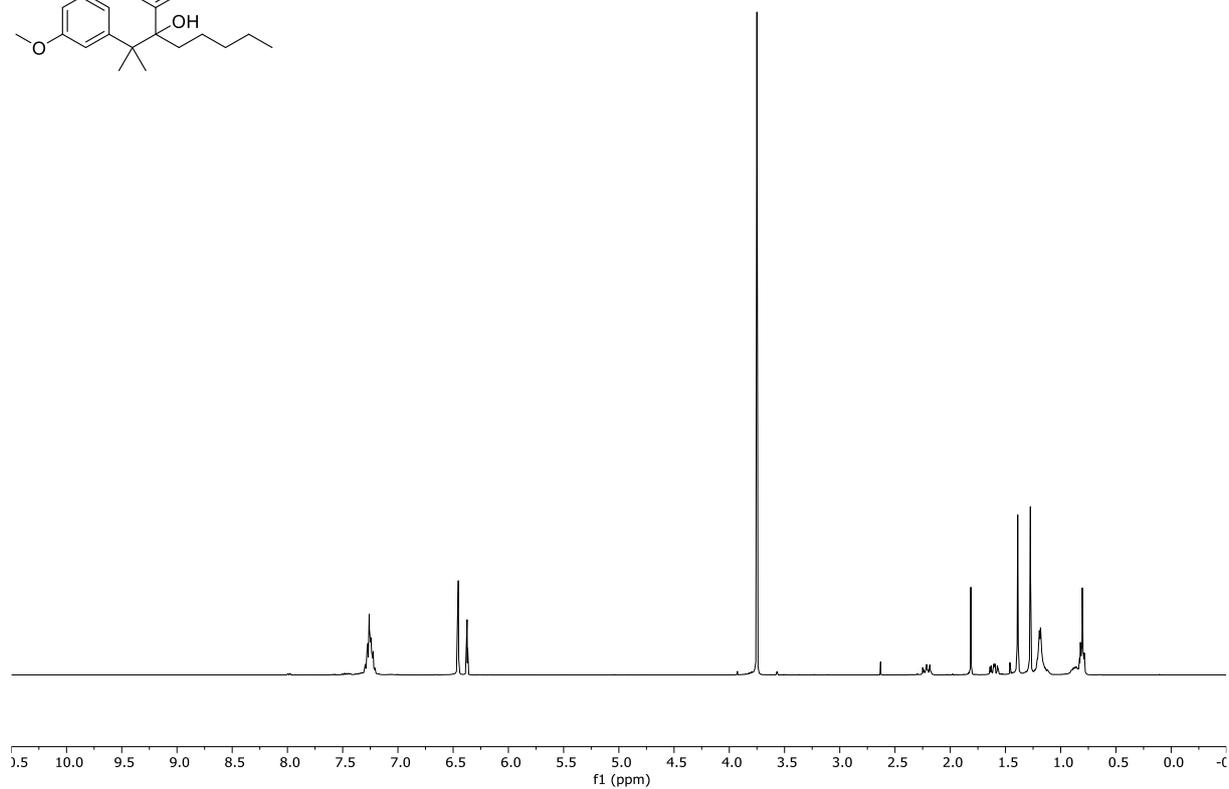
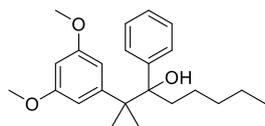
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **8c**



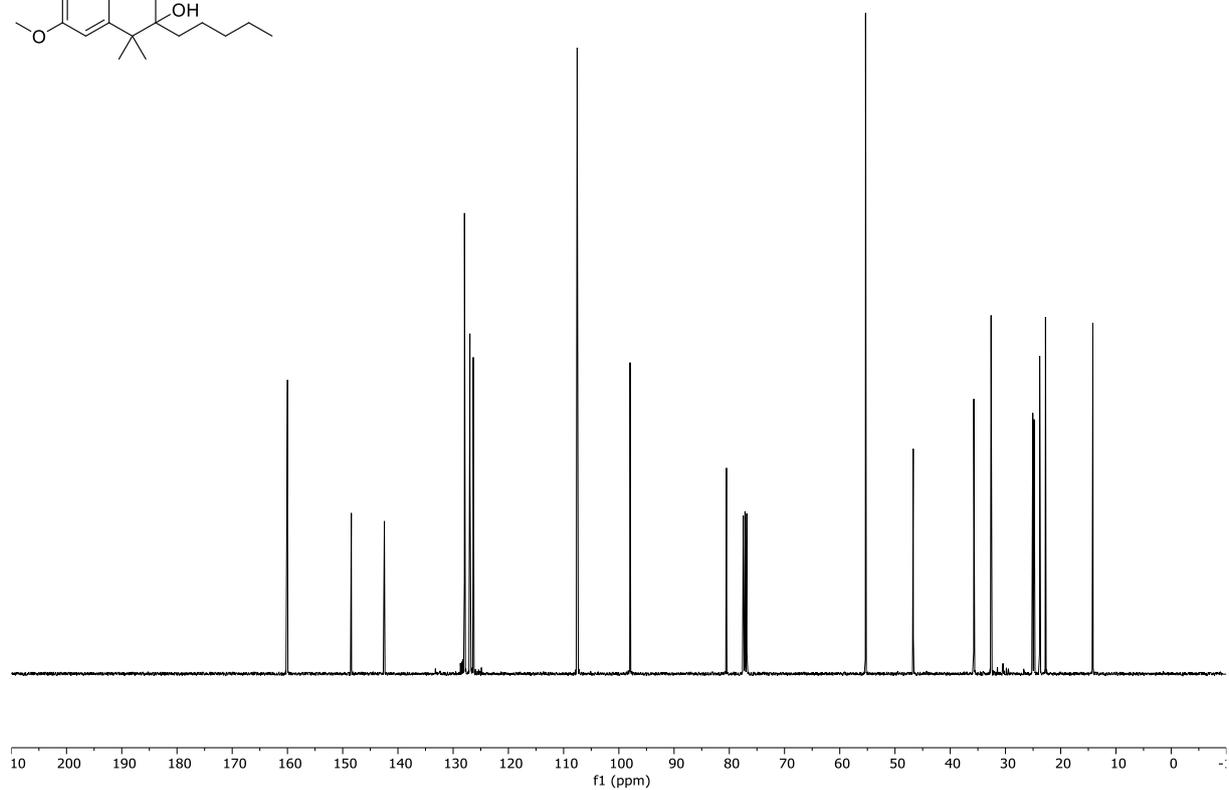
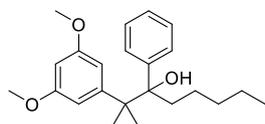
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **8c**



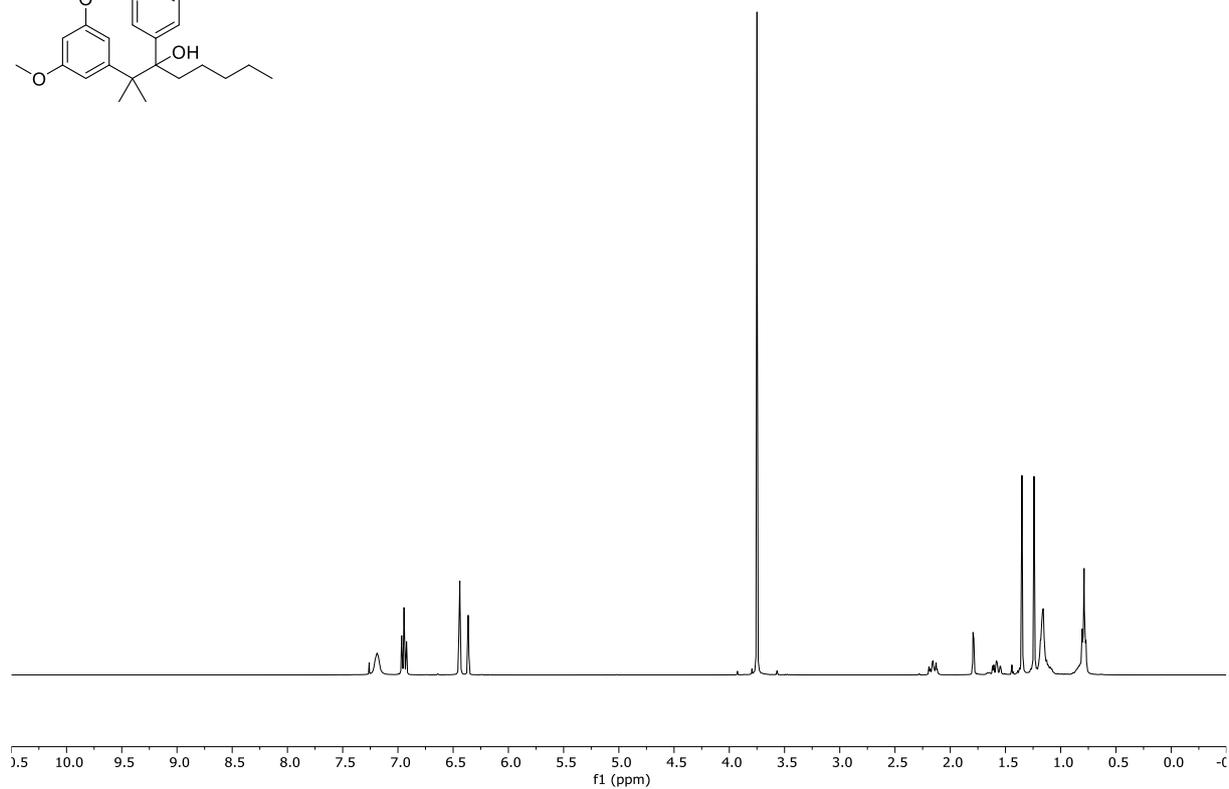
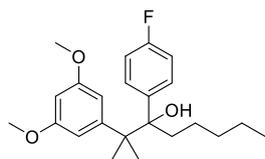
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **8d**



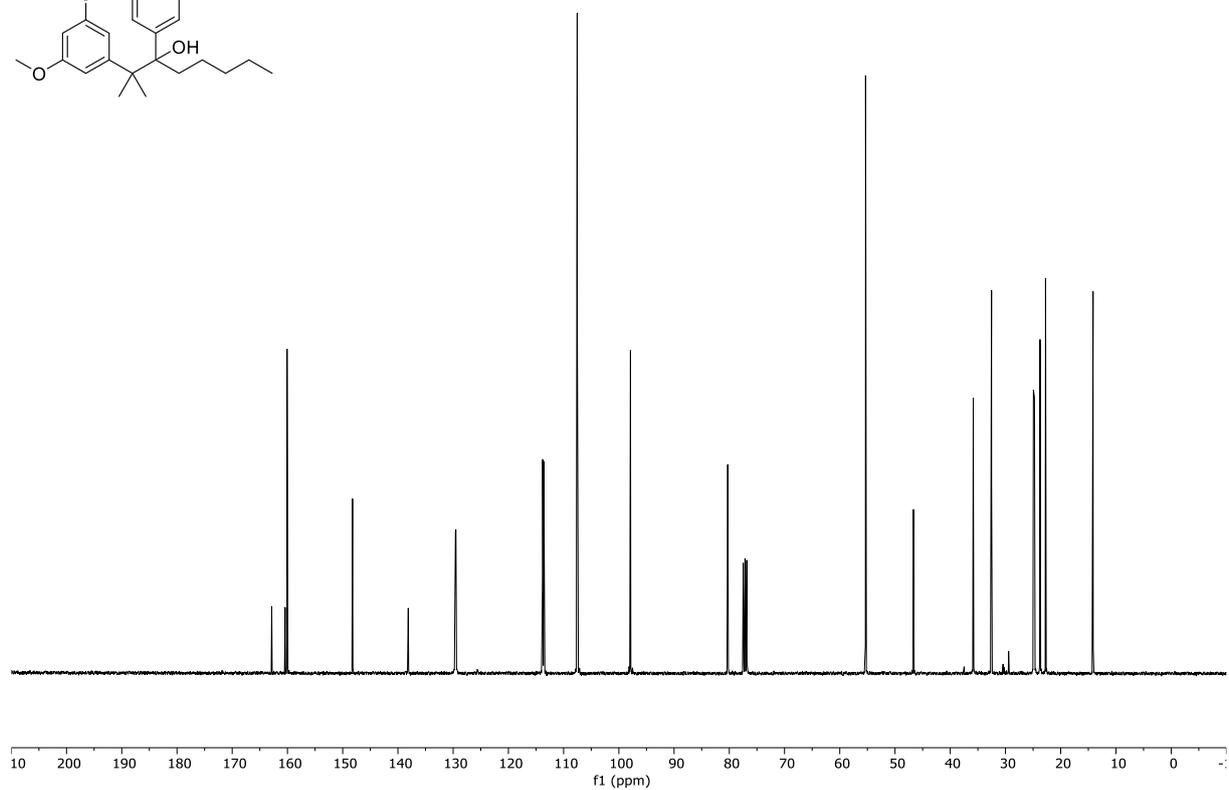
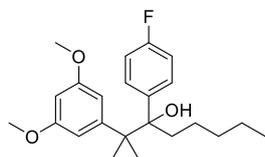
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **8d**



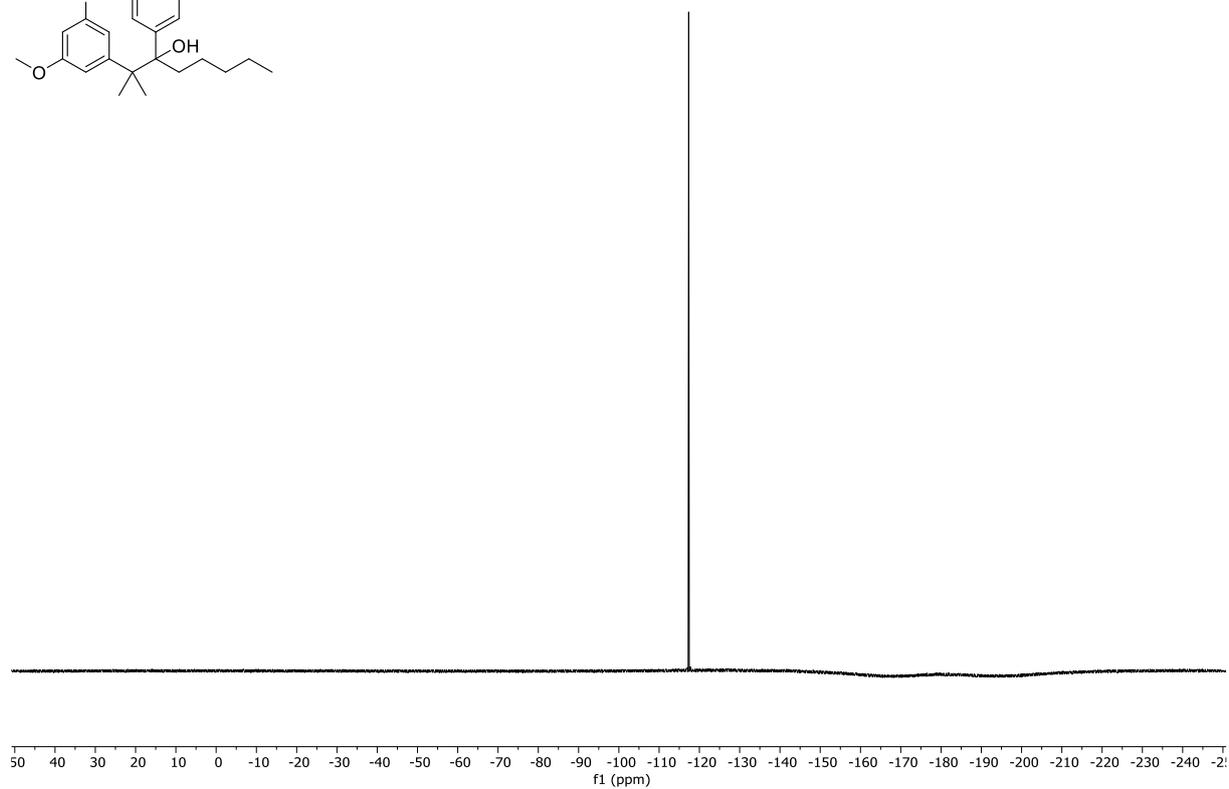
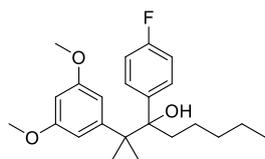
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **8e**



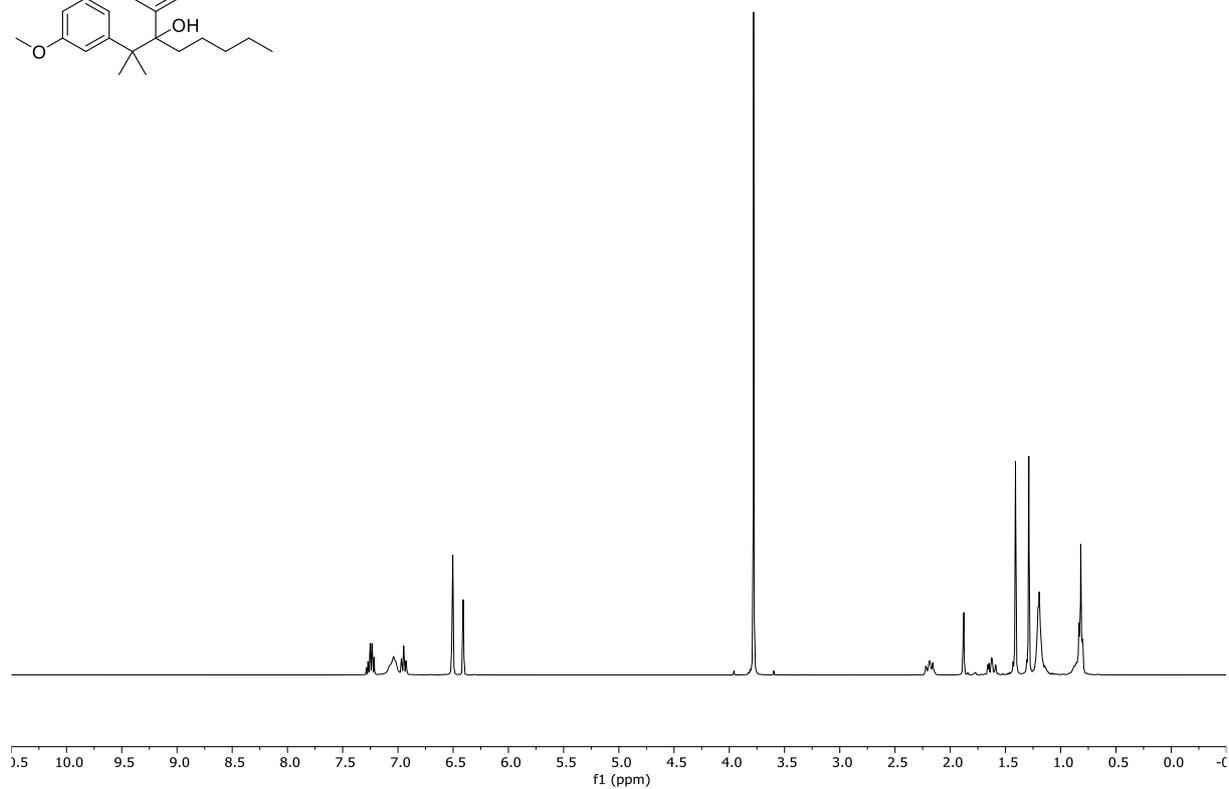
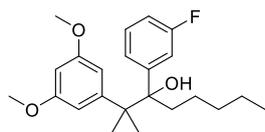
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **8e**



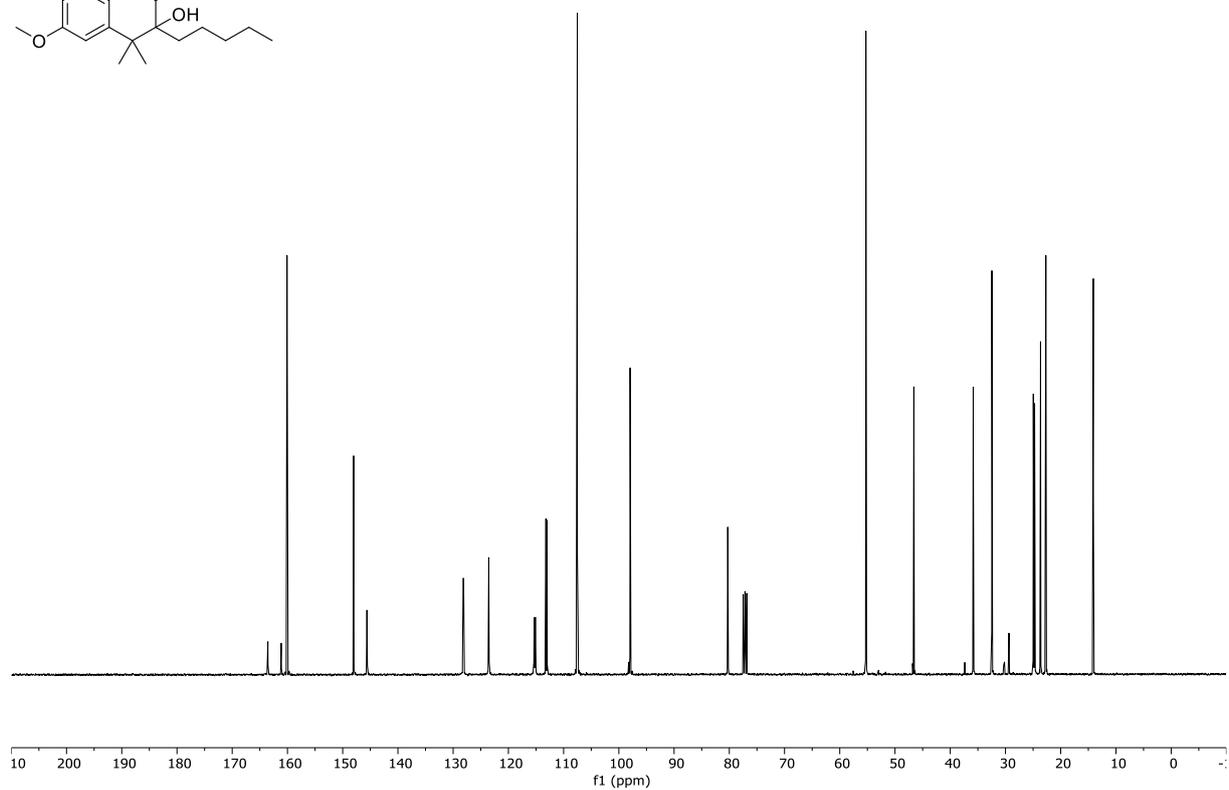
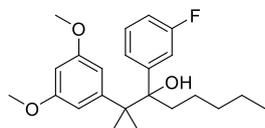
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of **8e**



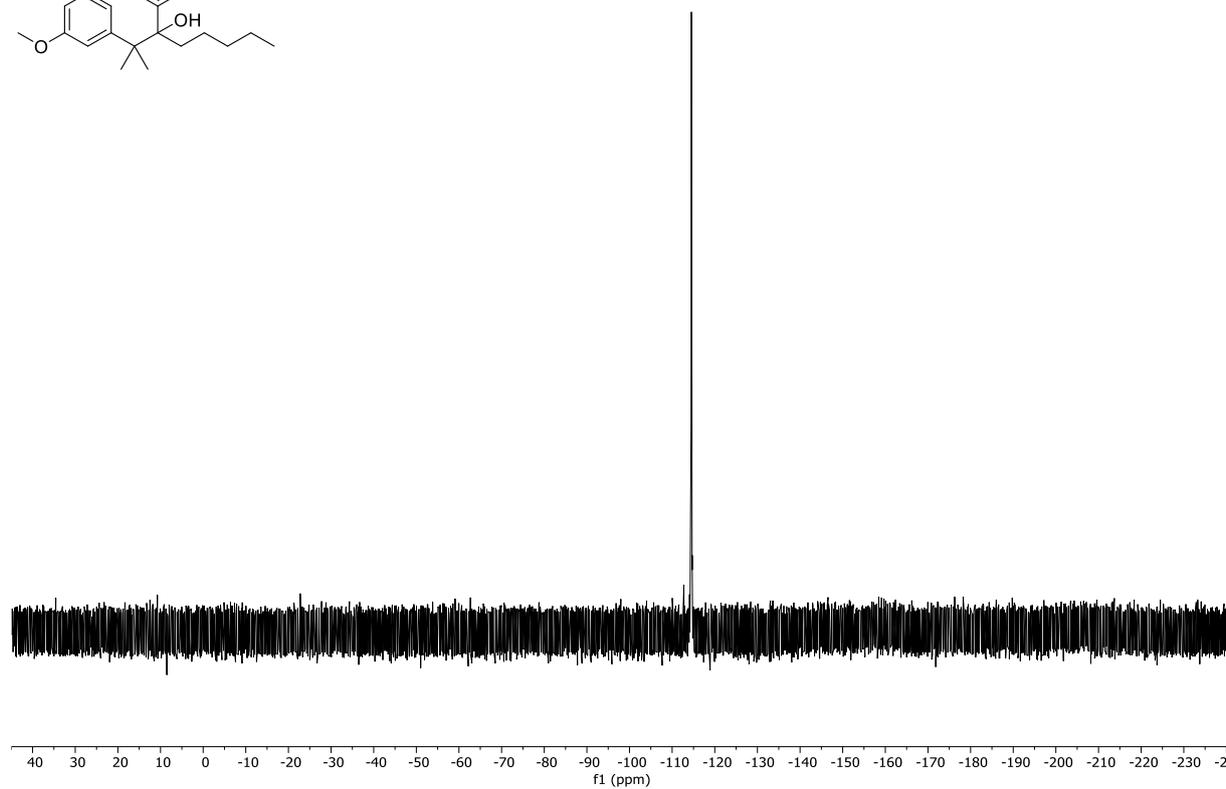
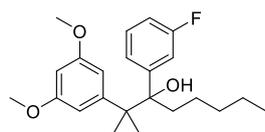
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **8f**



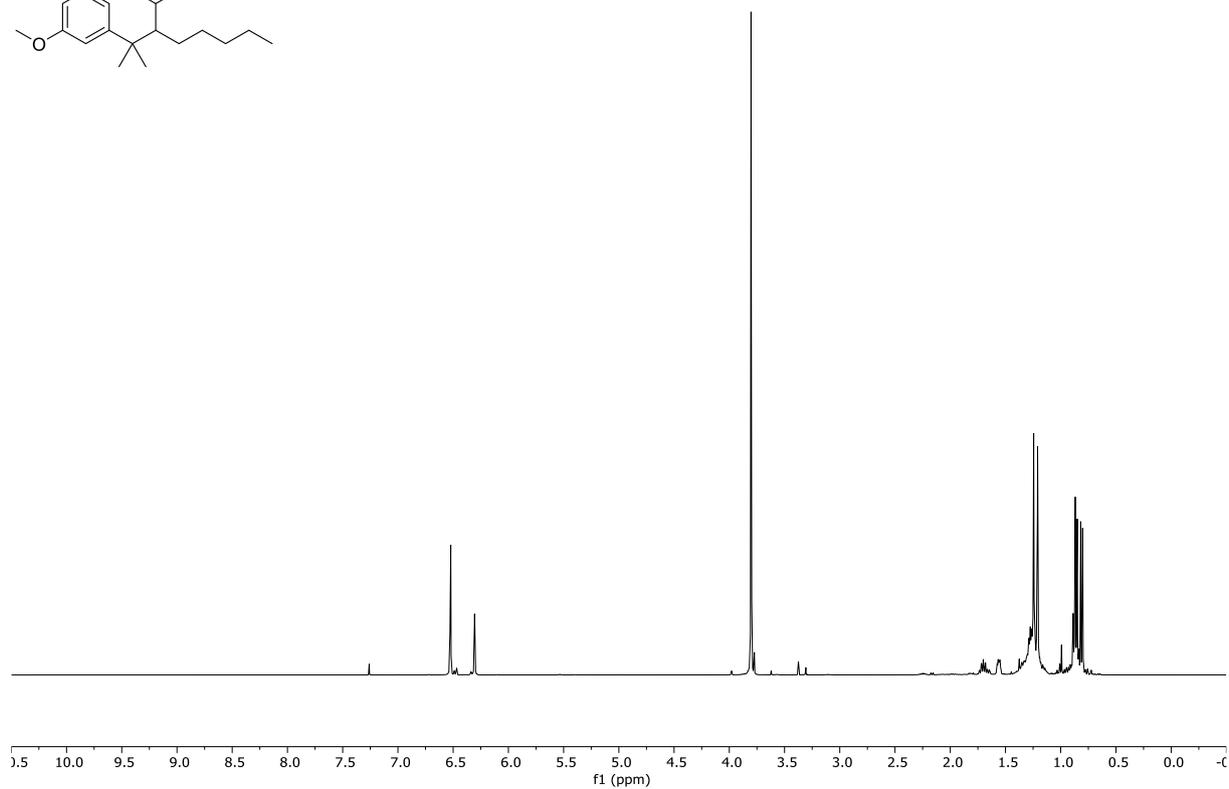
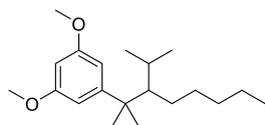
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **8f**



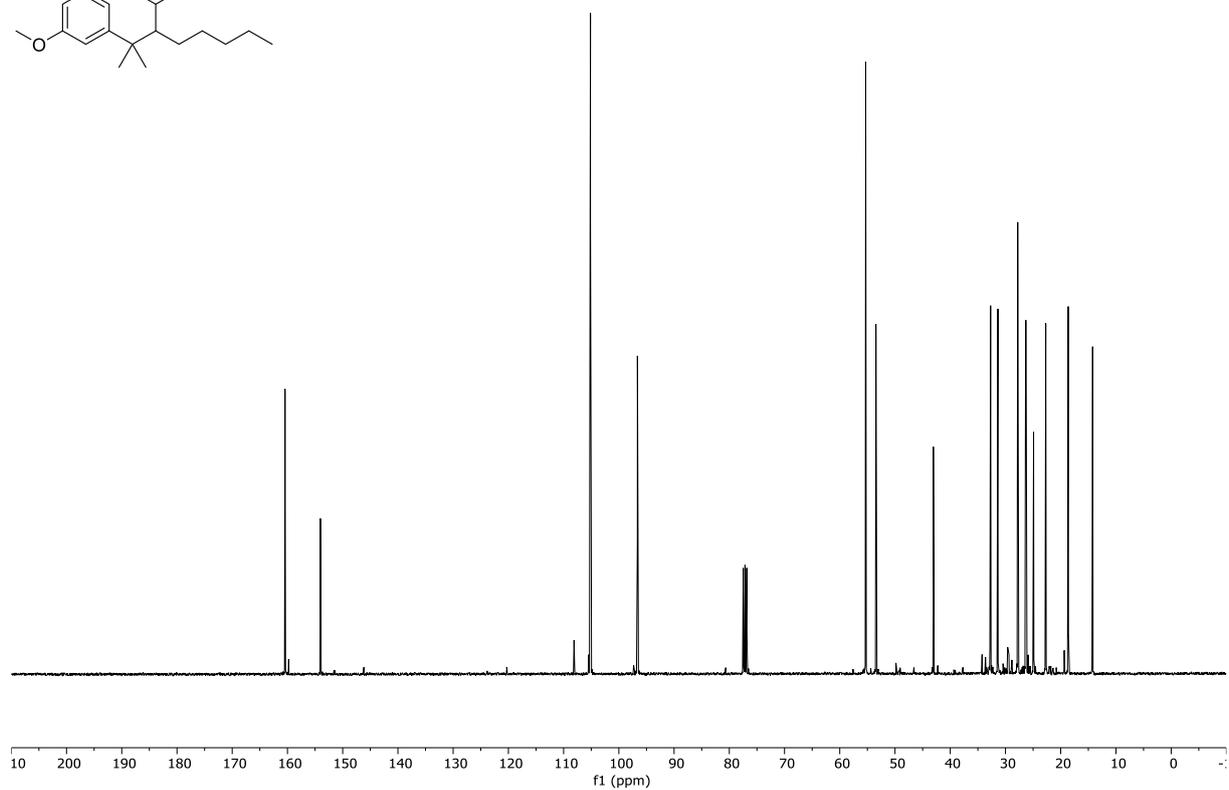
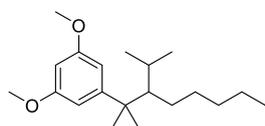
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of **8f**



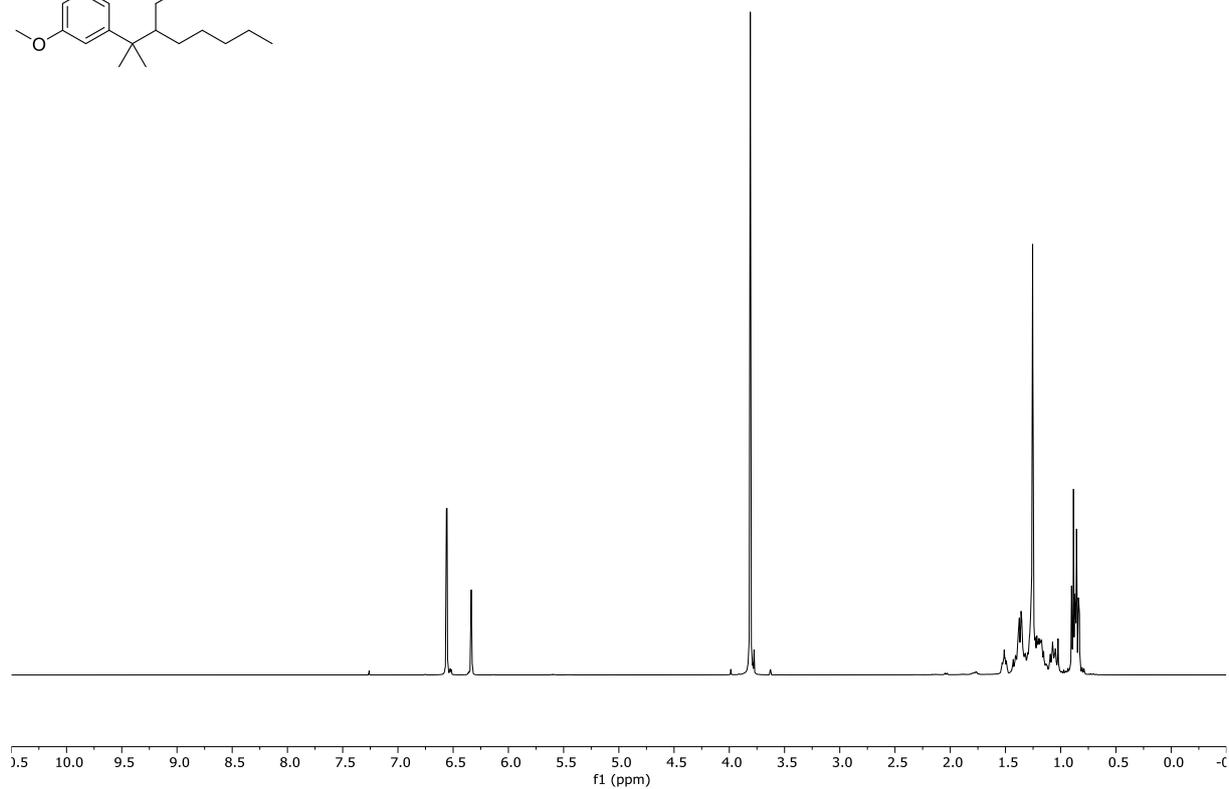
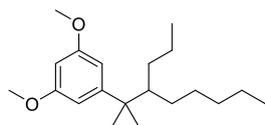
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **SI-15a**



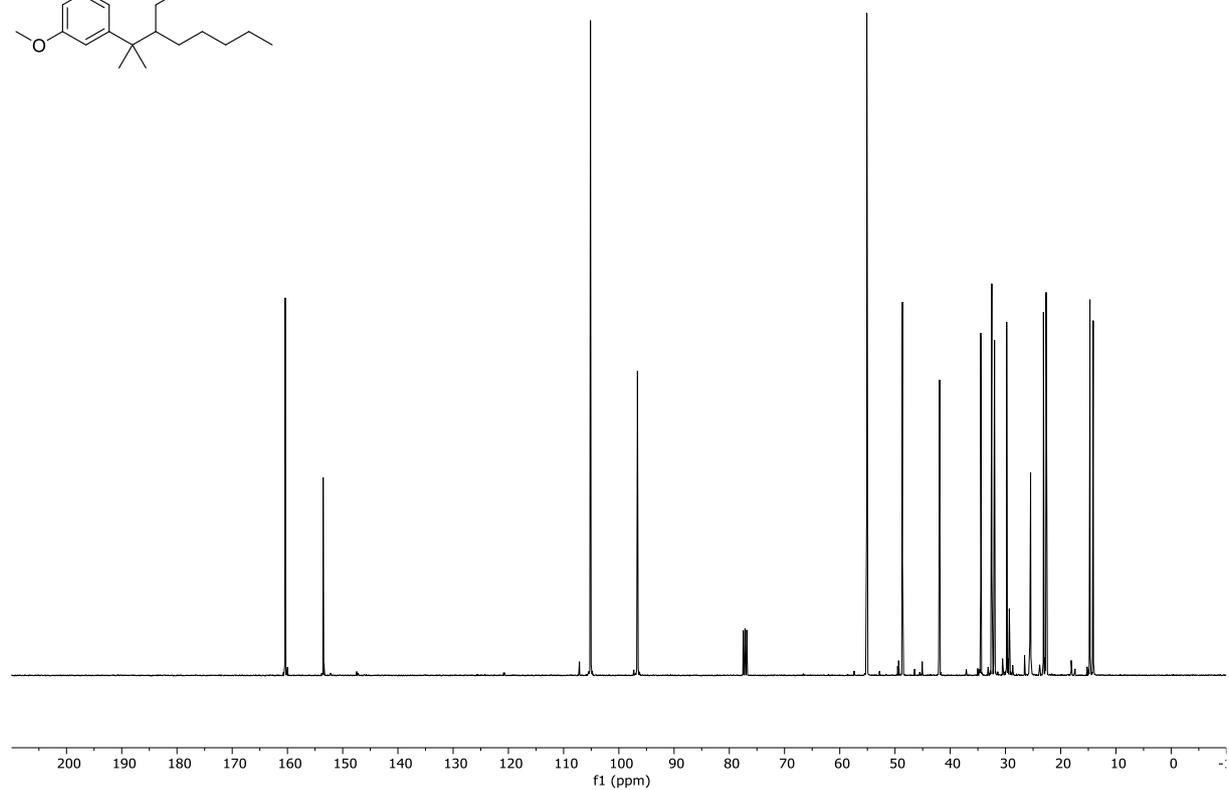
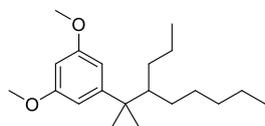
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **SI-15a**



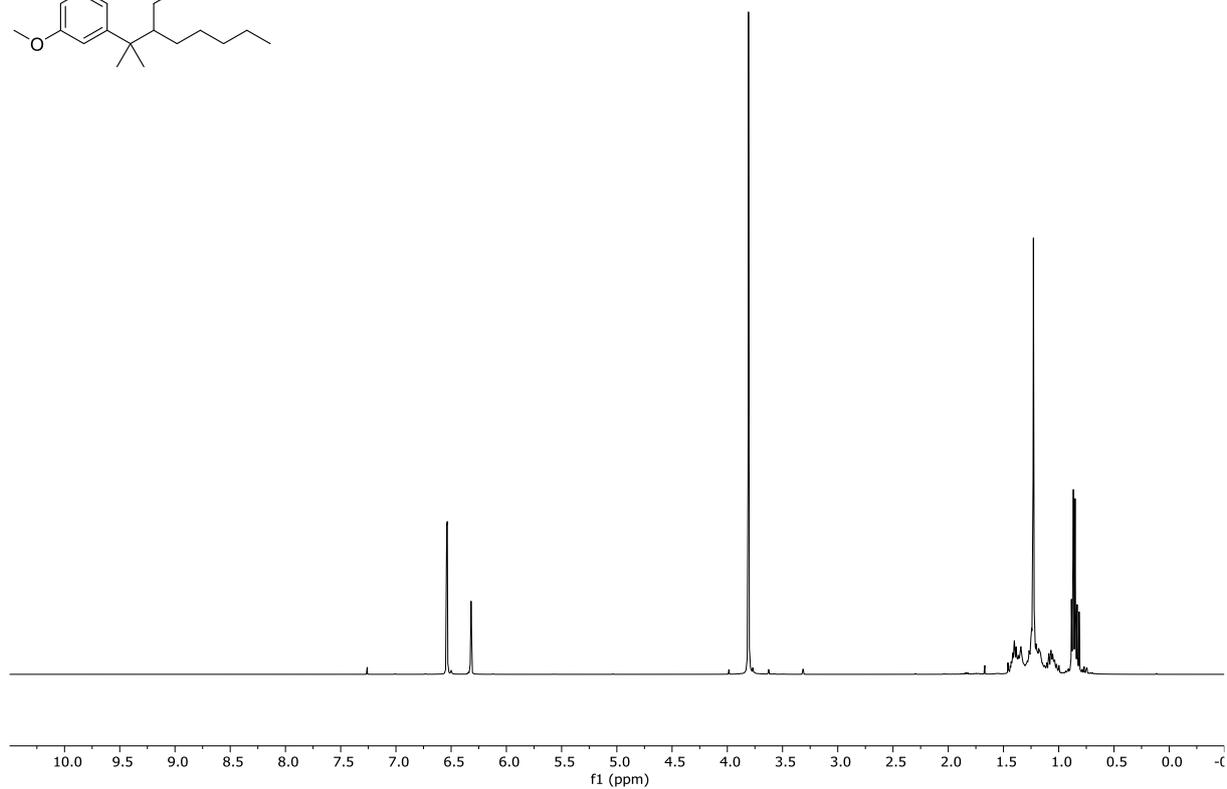
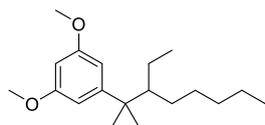
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **SI-15b**



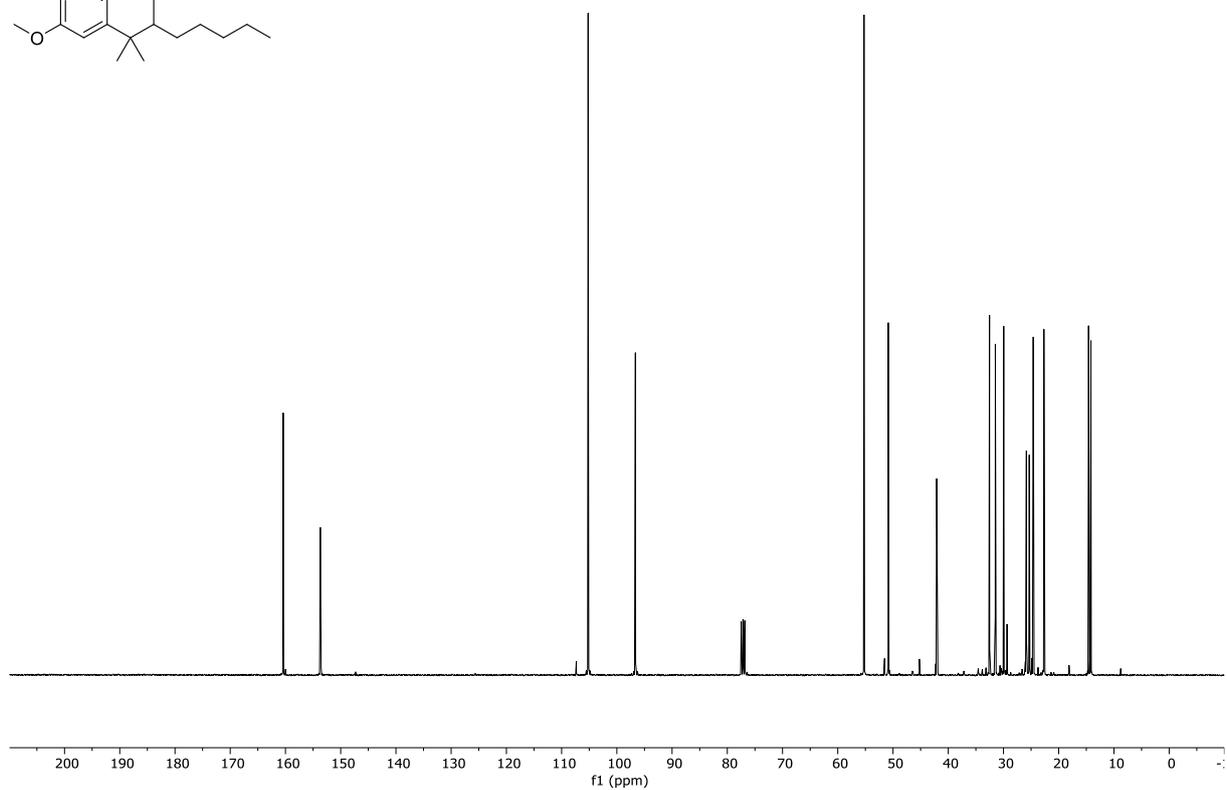
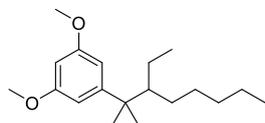
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **SI-15b**



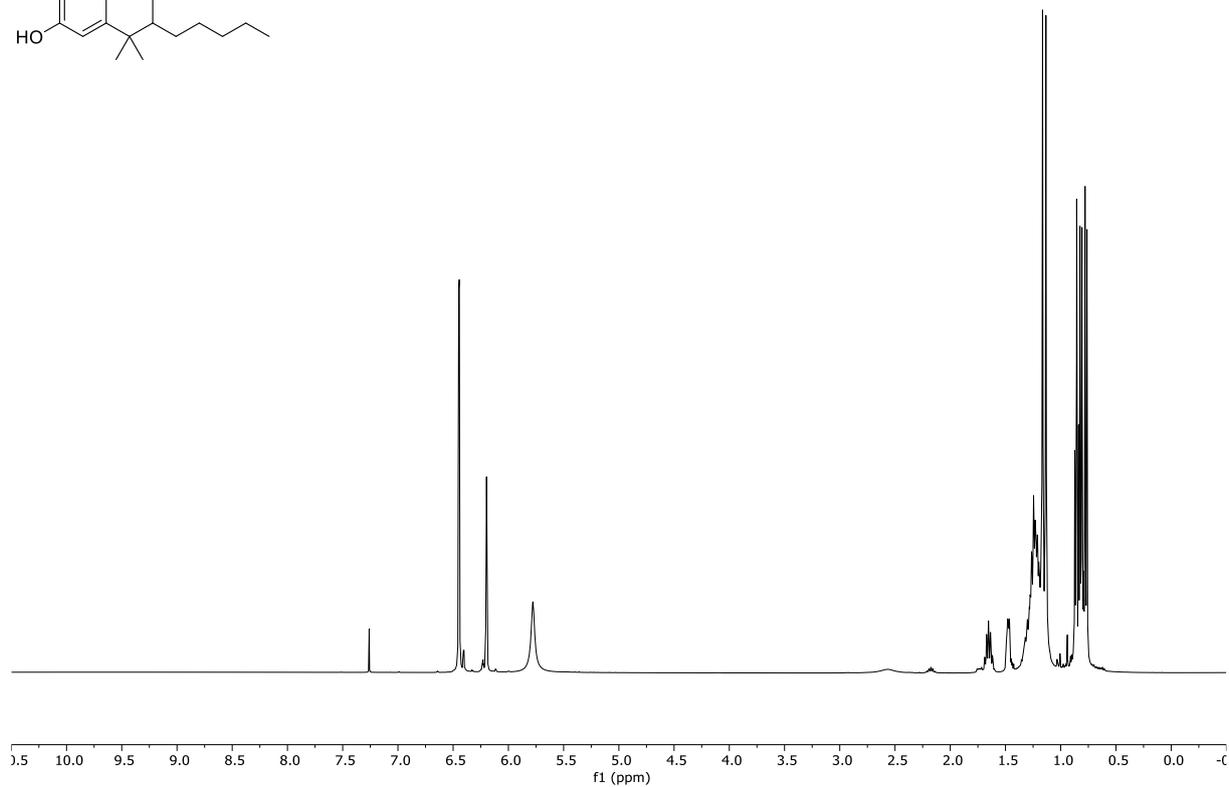
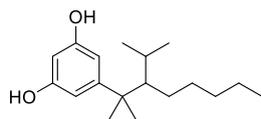
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **SI-15c**



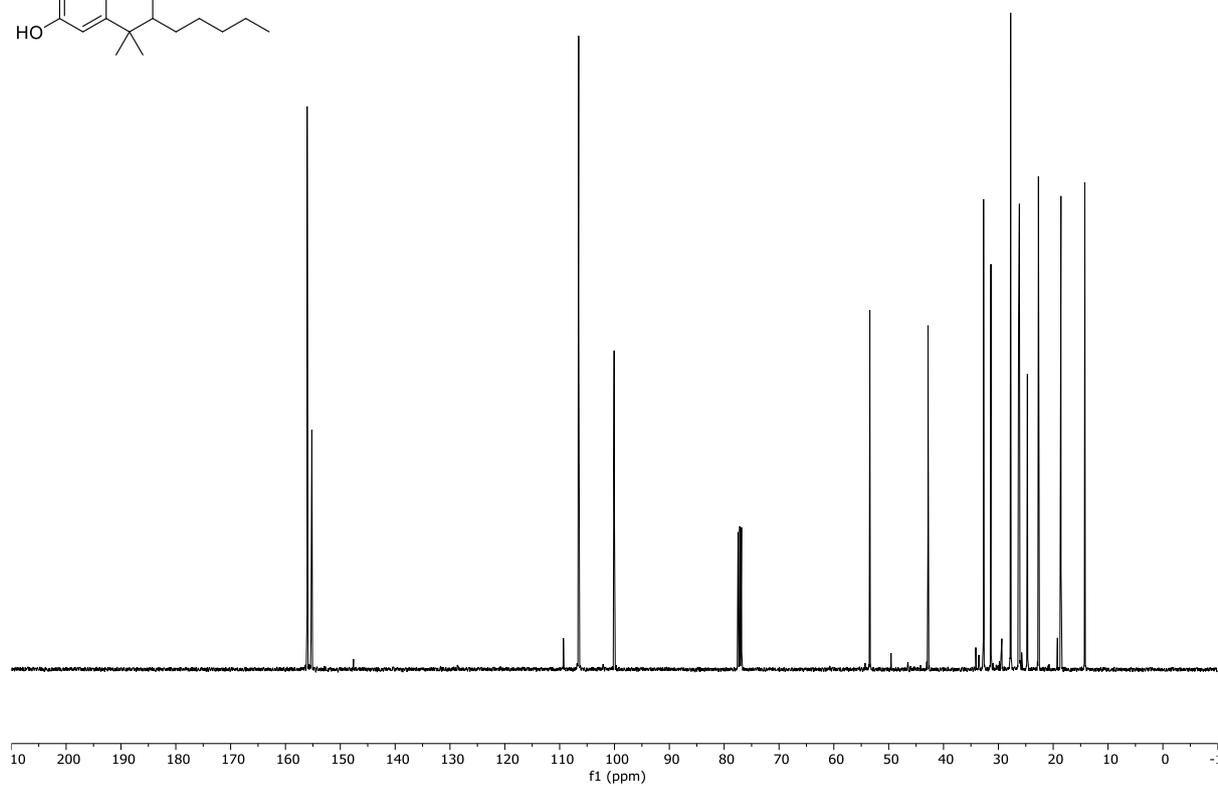
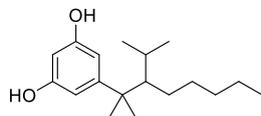
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **SI-15c**



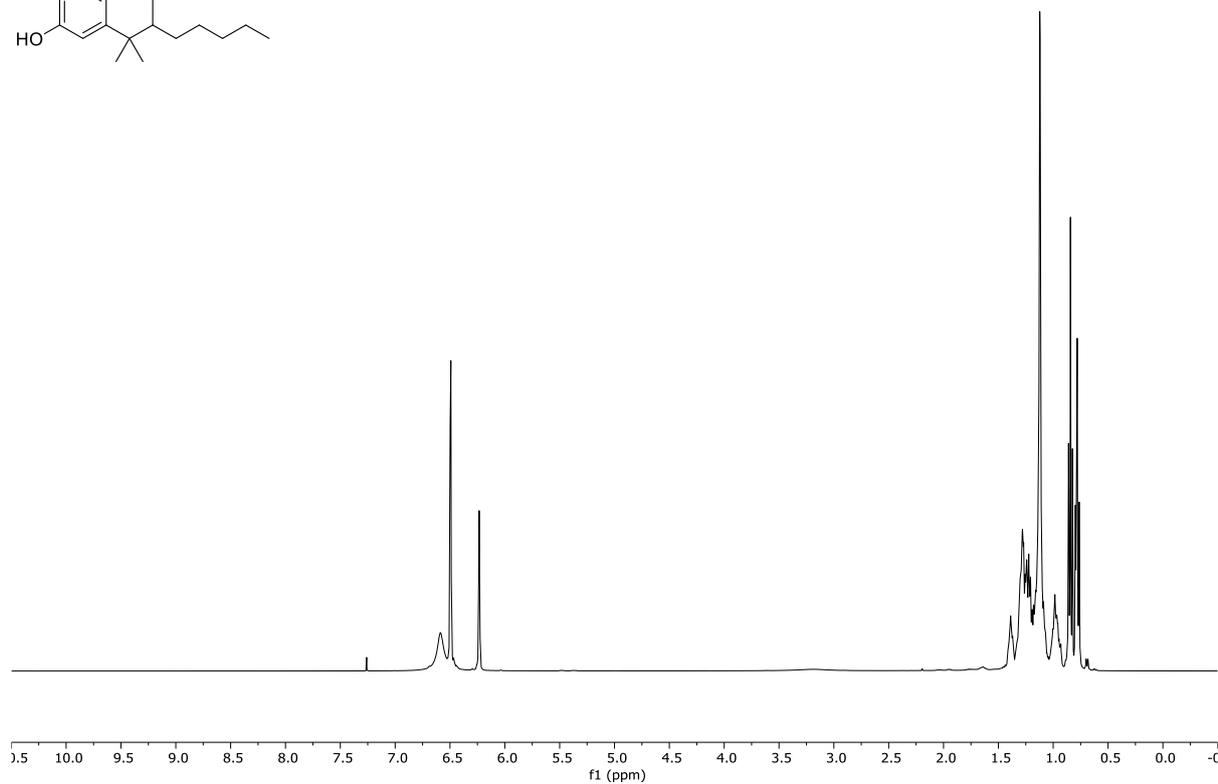
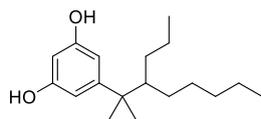
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **9a**



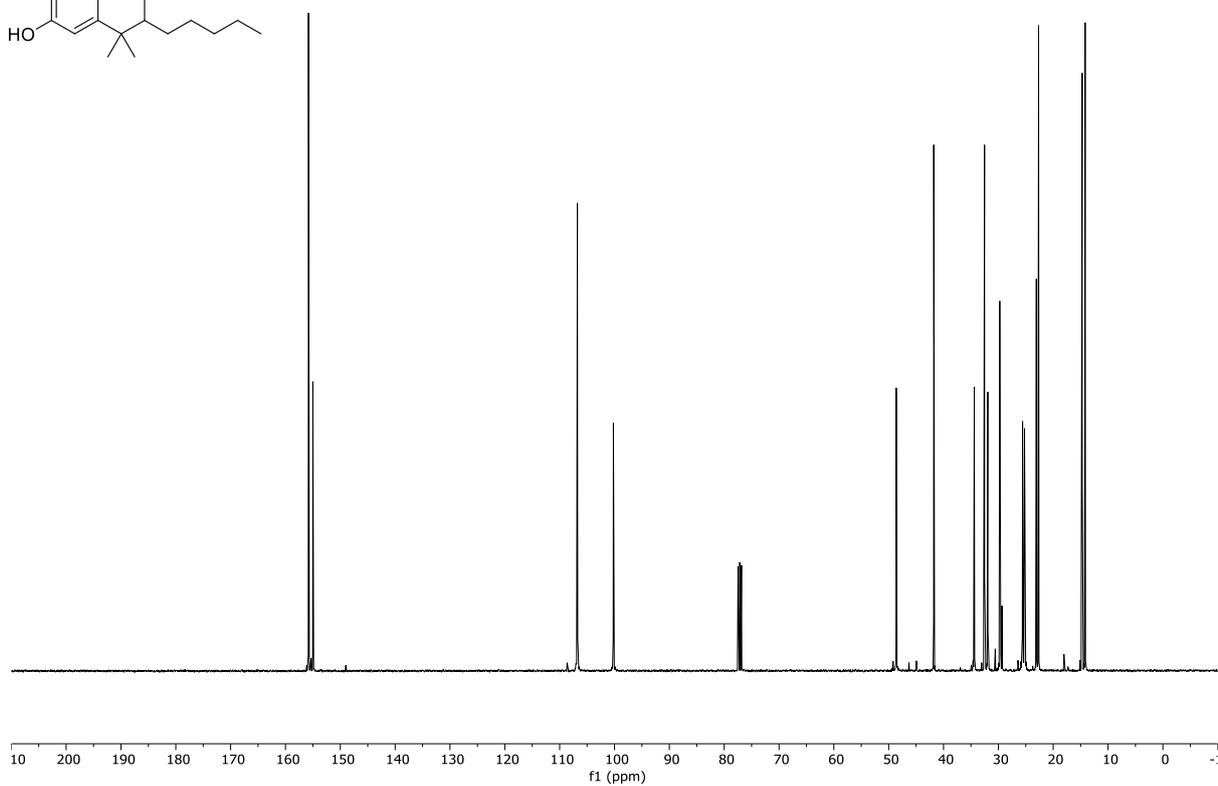
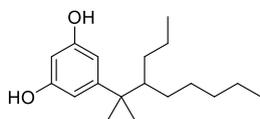
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **9a**



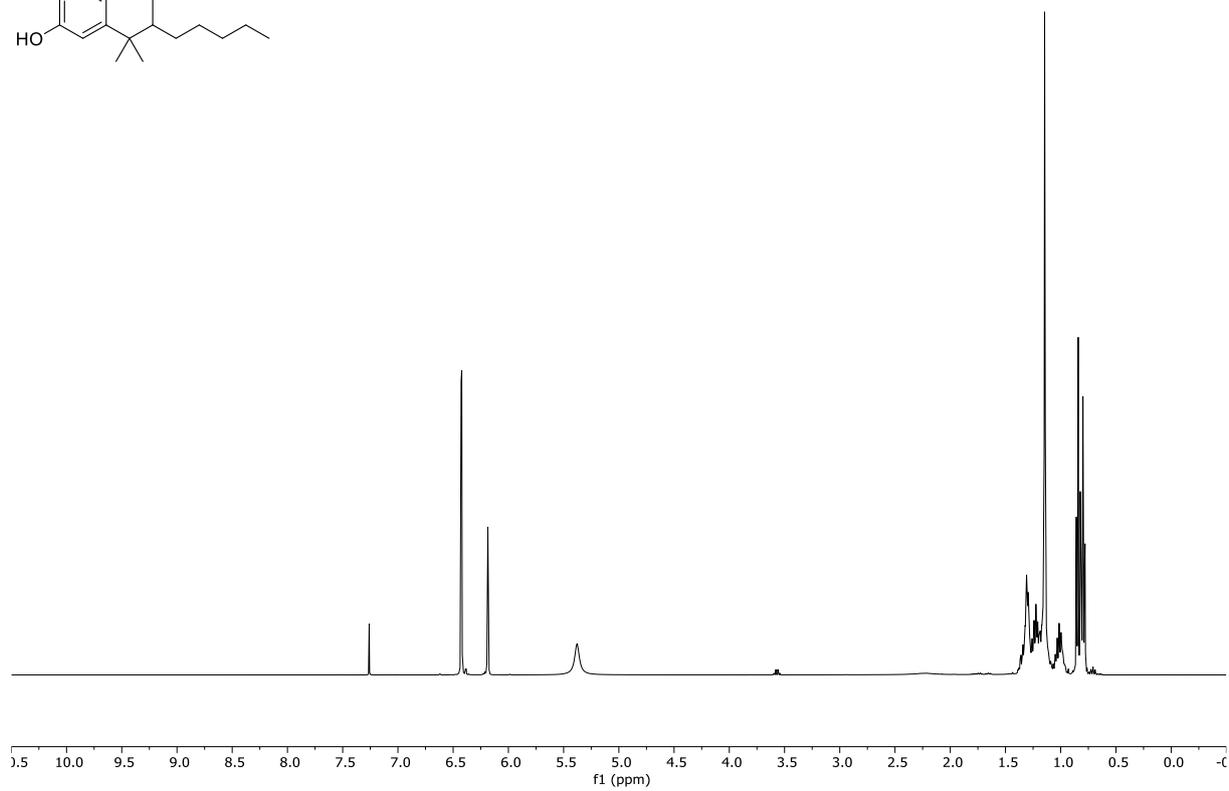
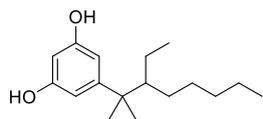
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **9b**



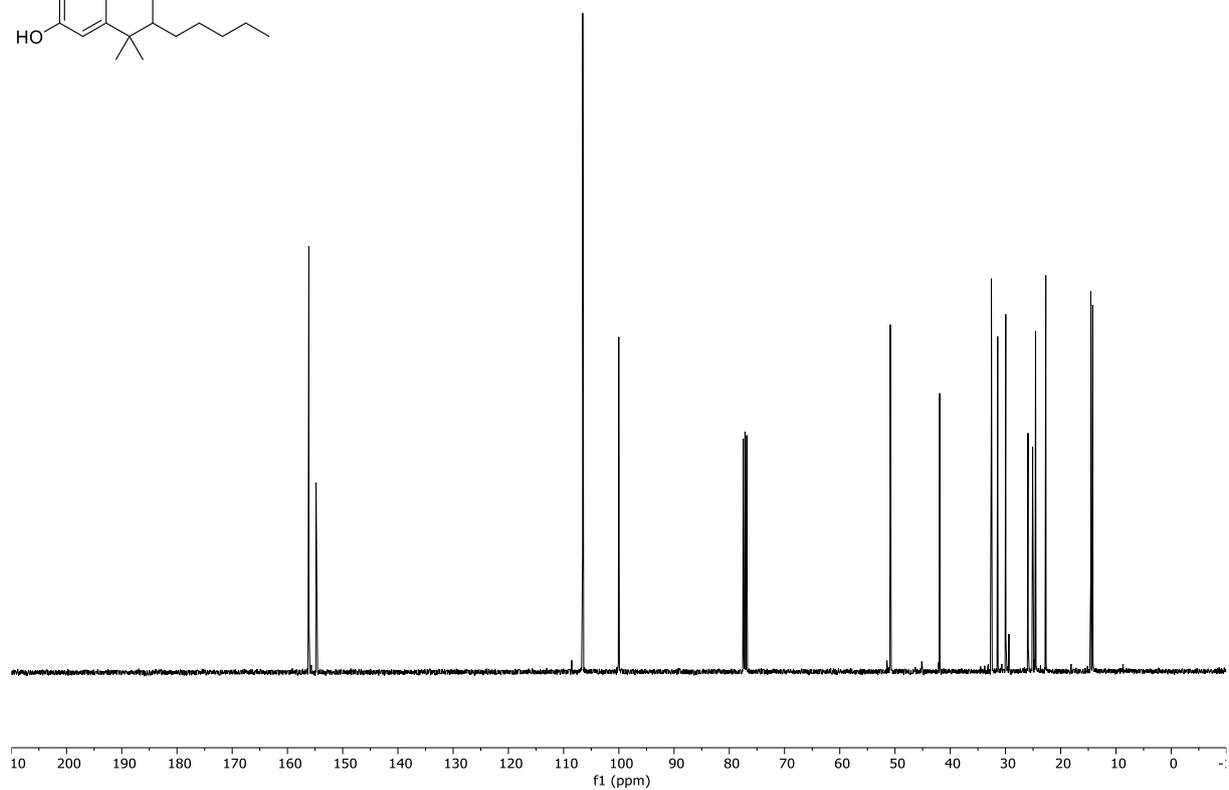
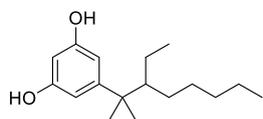
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **9b**



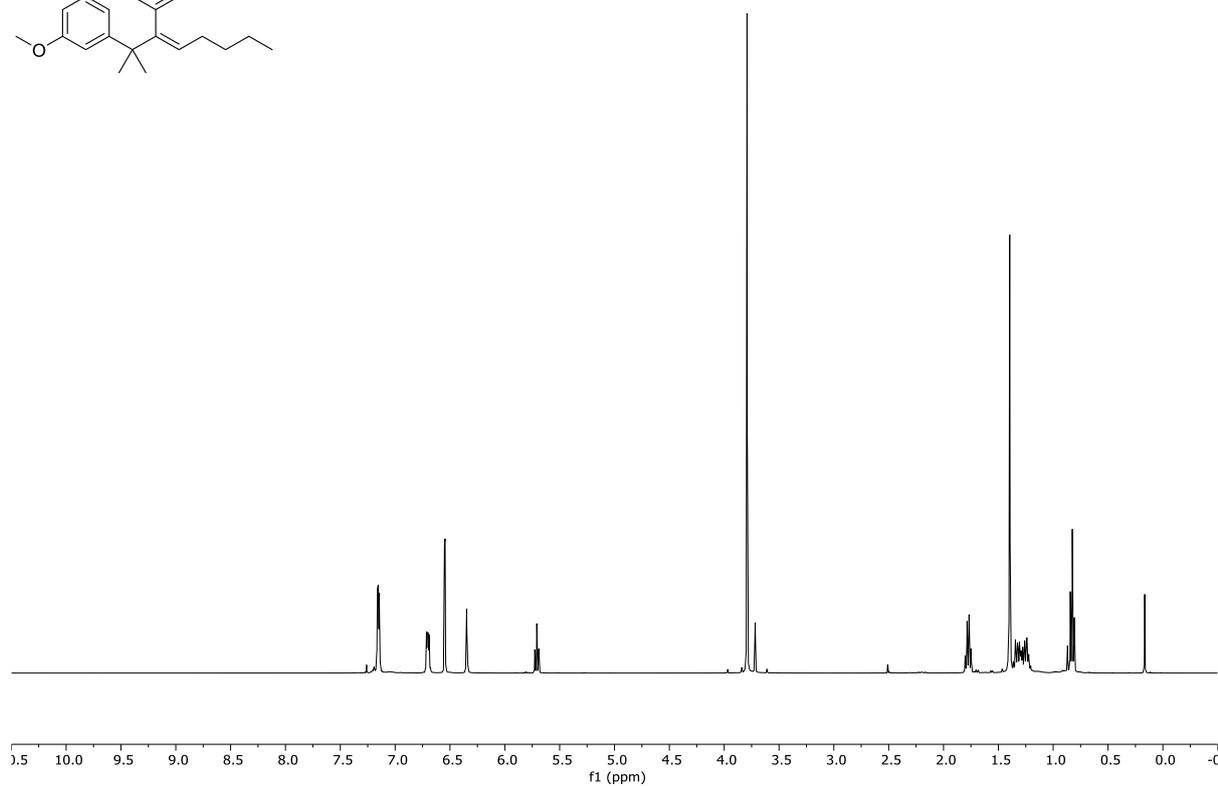
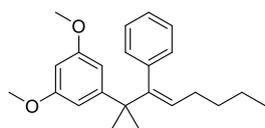
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **9c**



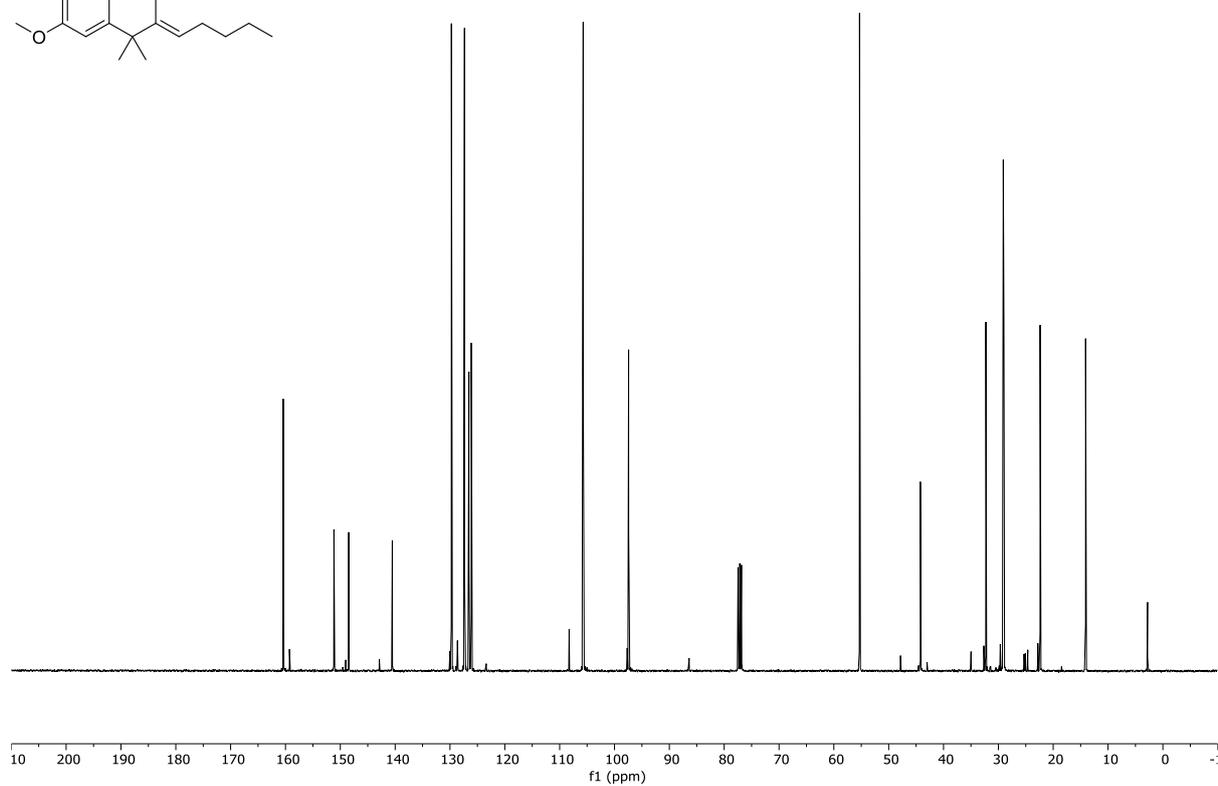
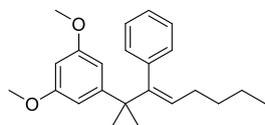
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **9c**



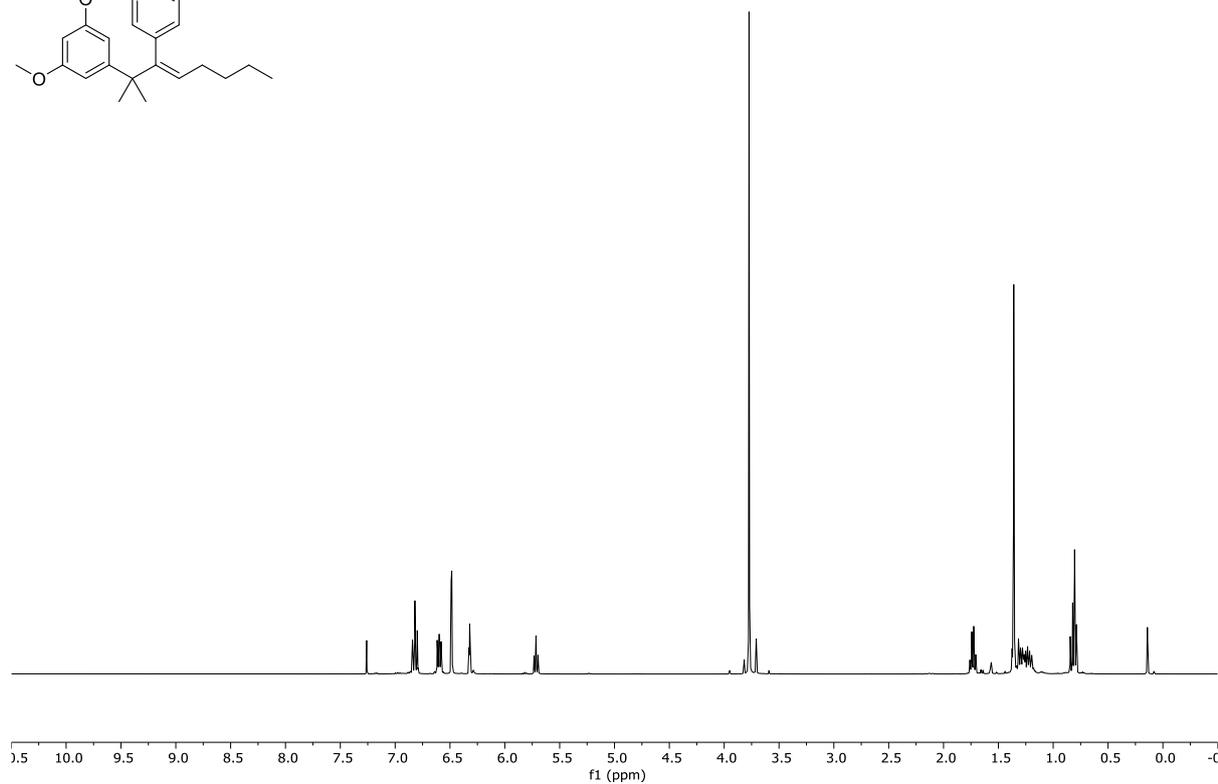
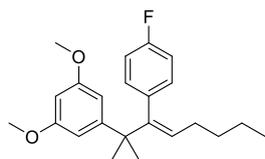
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **SI-16d**



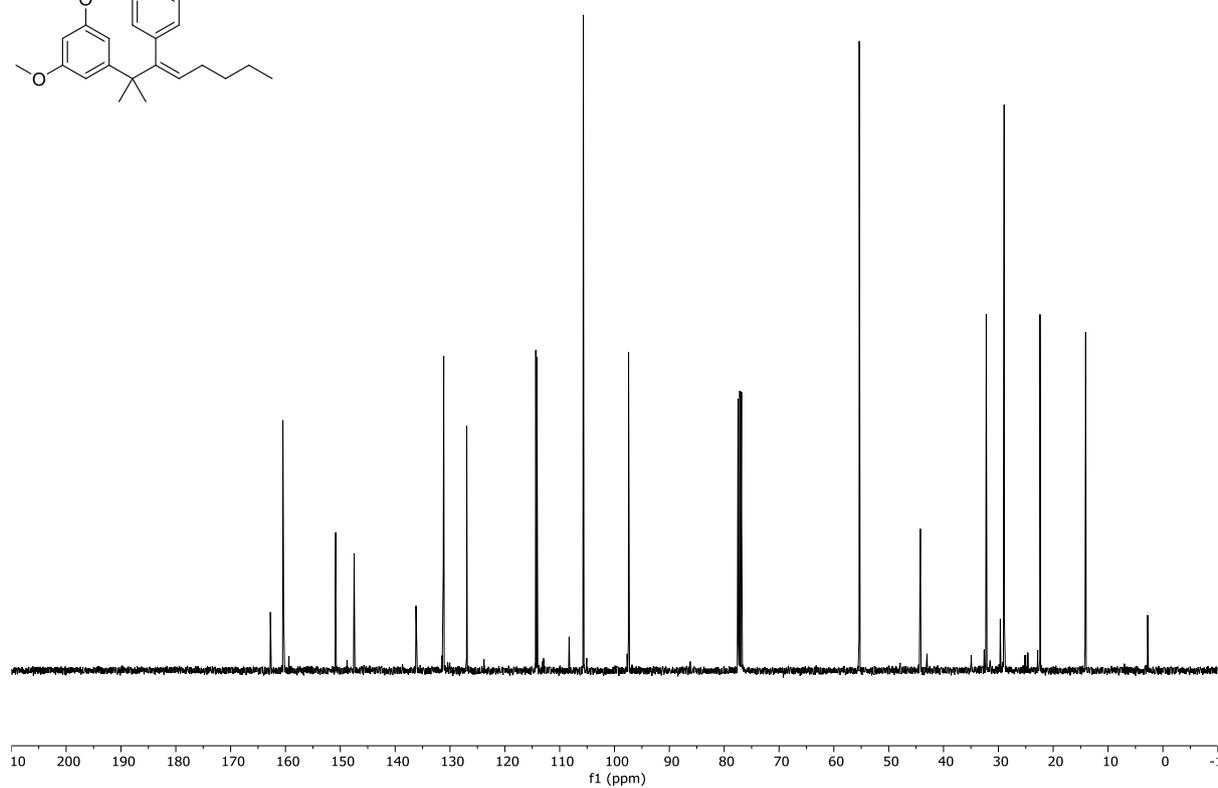
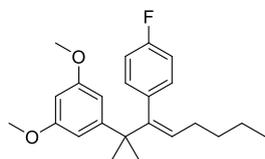
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **SI-16d**



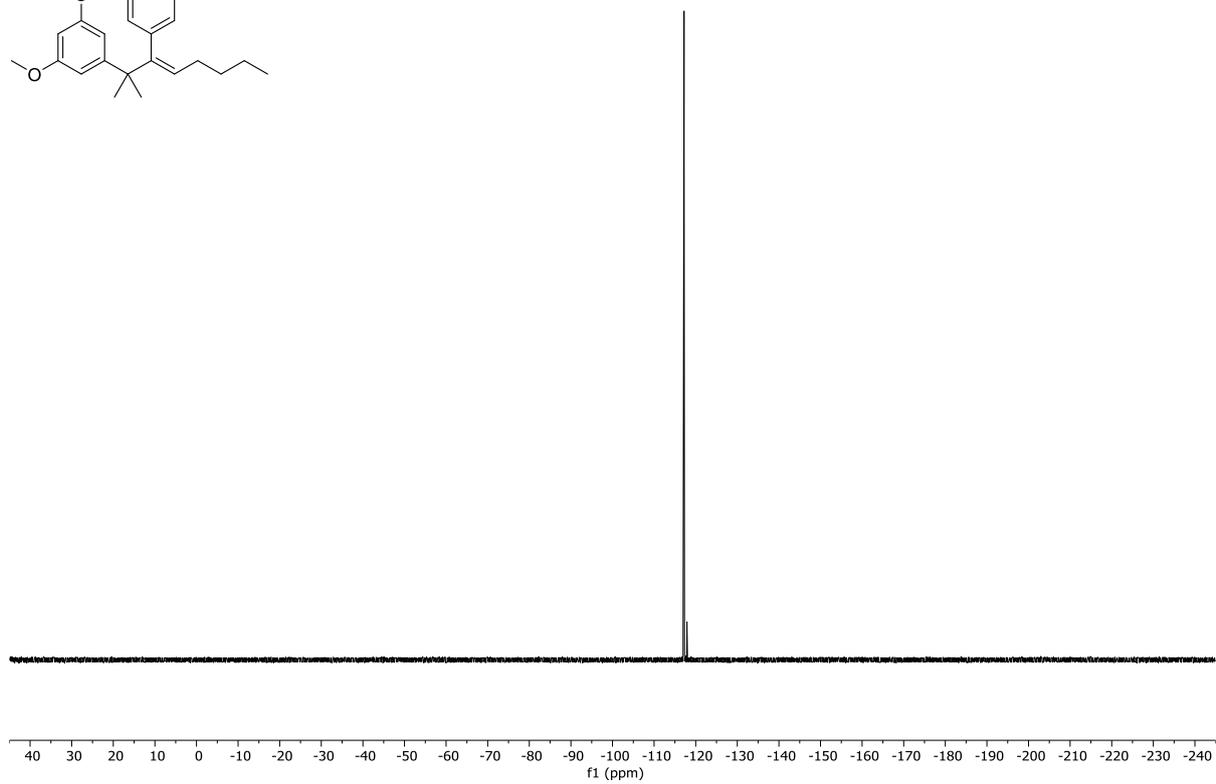
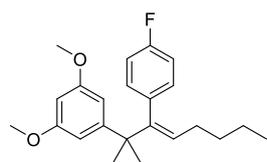
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **SI-16e**



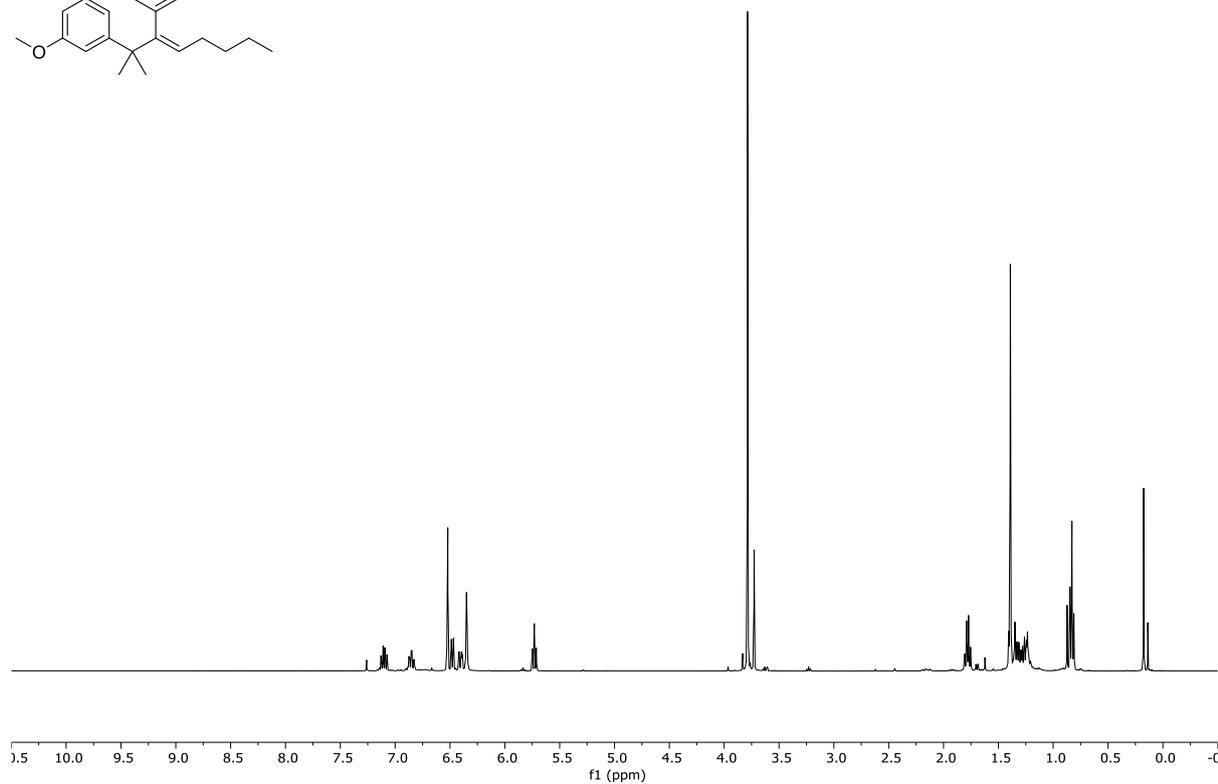
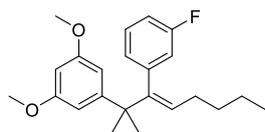
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **SI-16e**



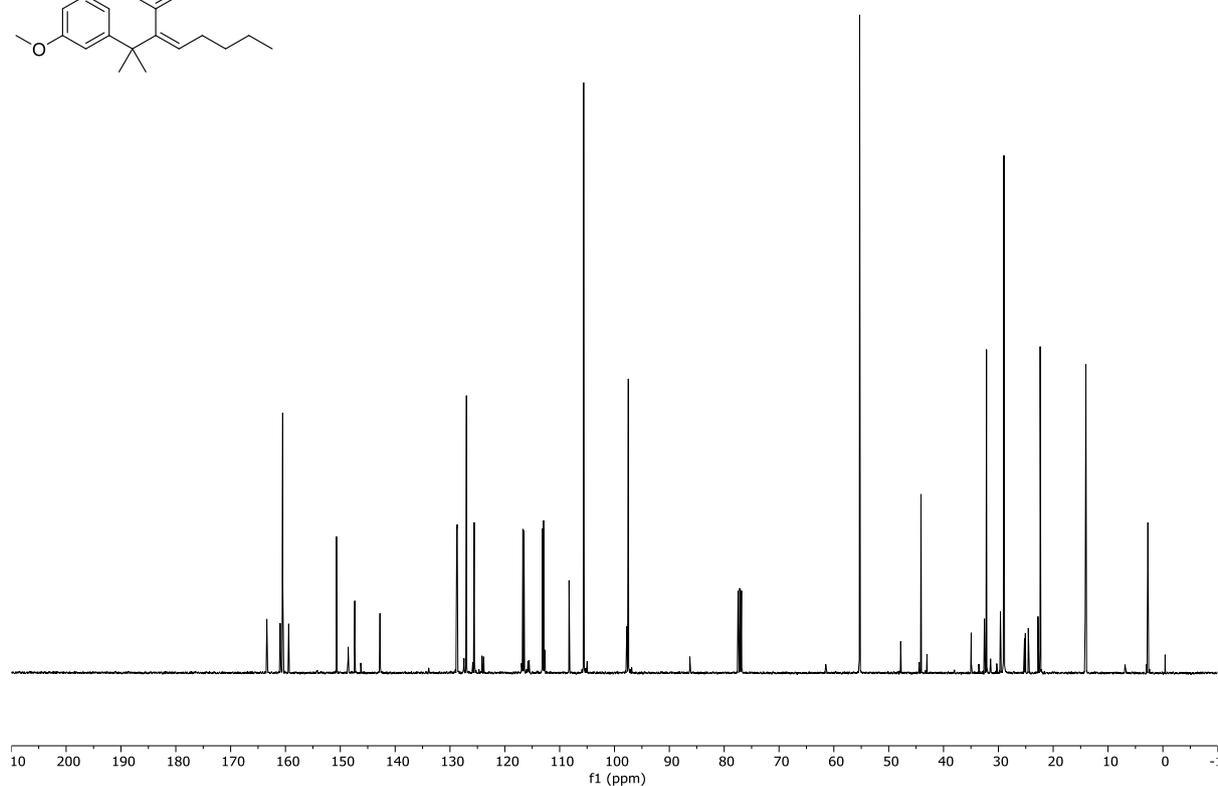
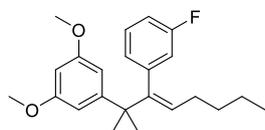
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of **SI-16e**



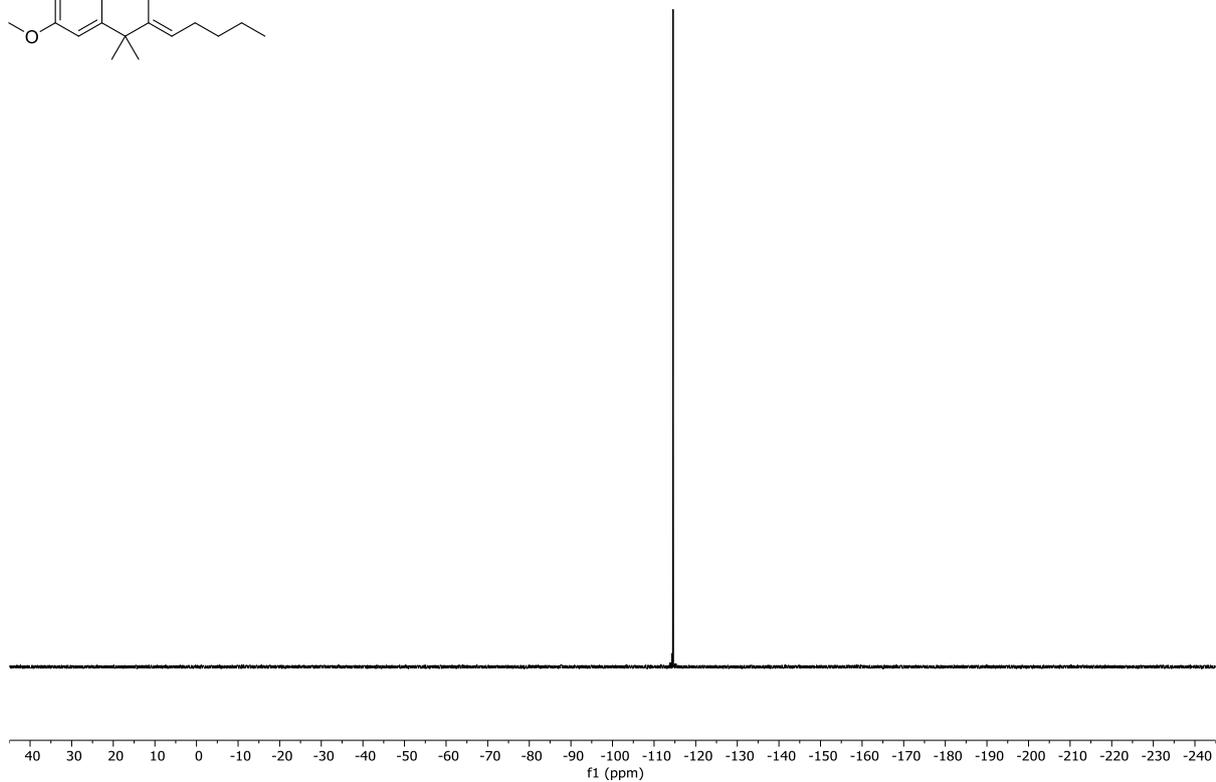
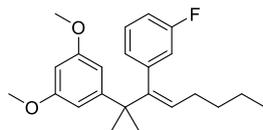
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **SI-16f**



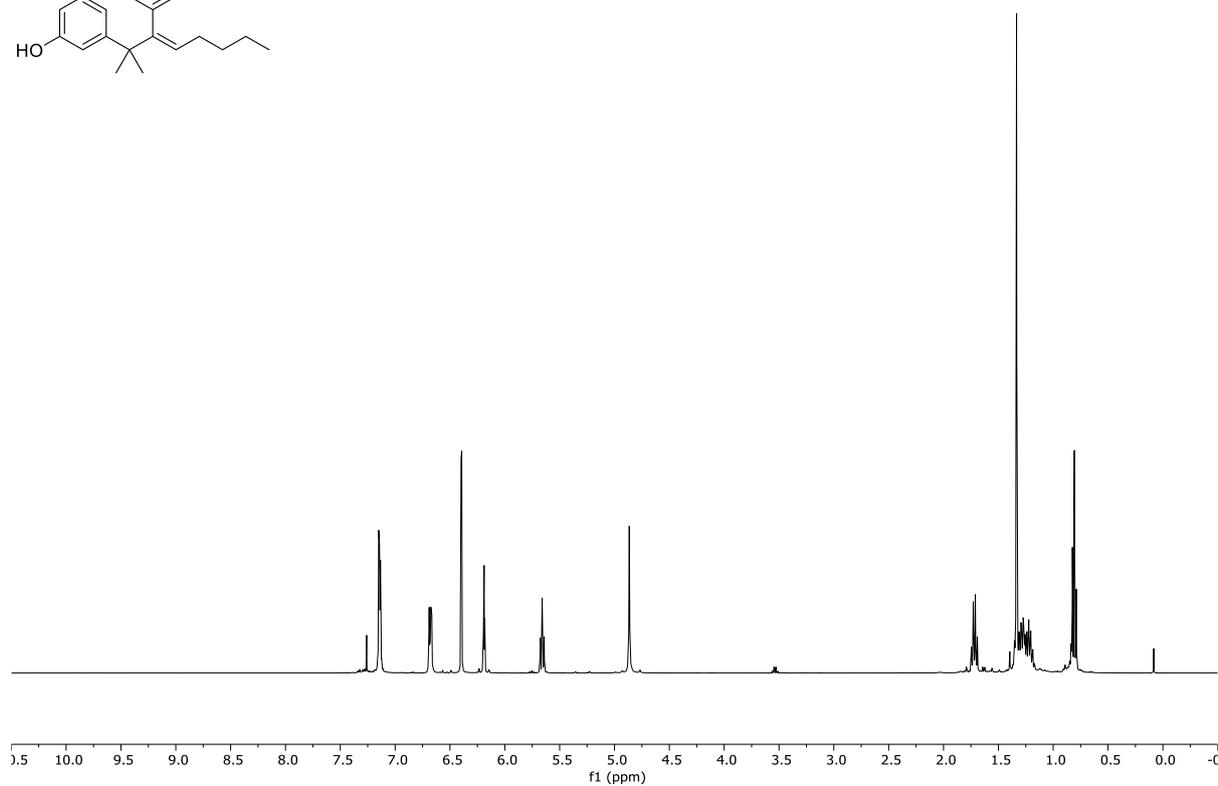
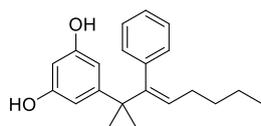
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **SI-16f**



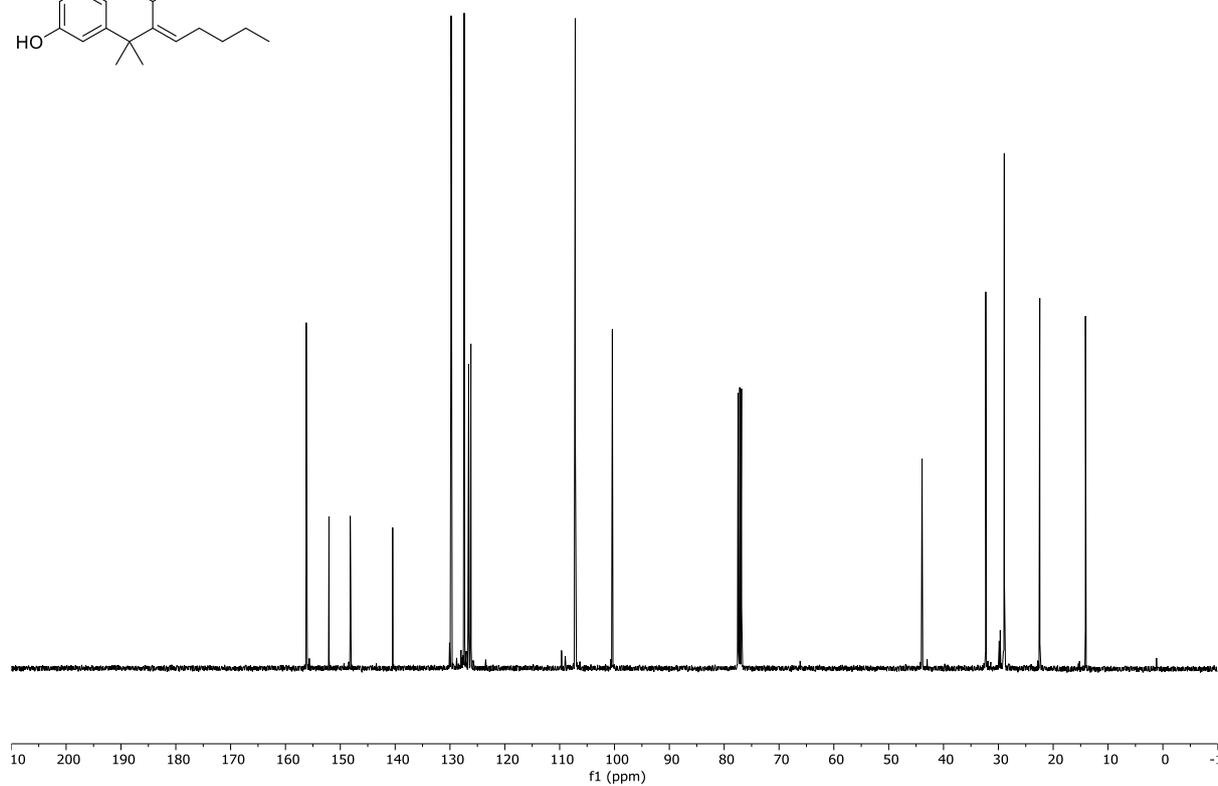
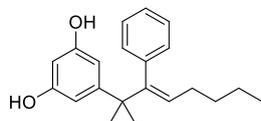
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of **SI-16f**



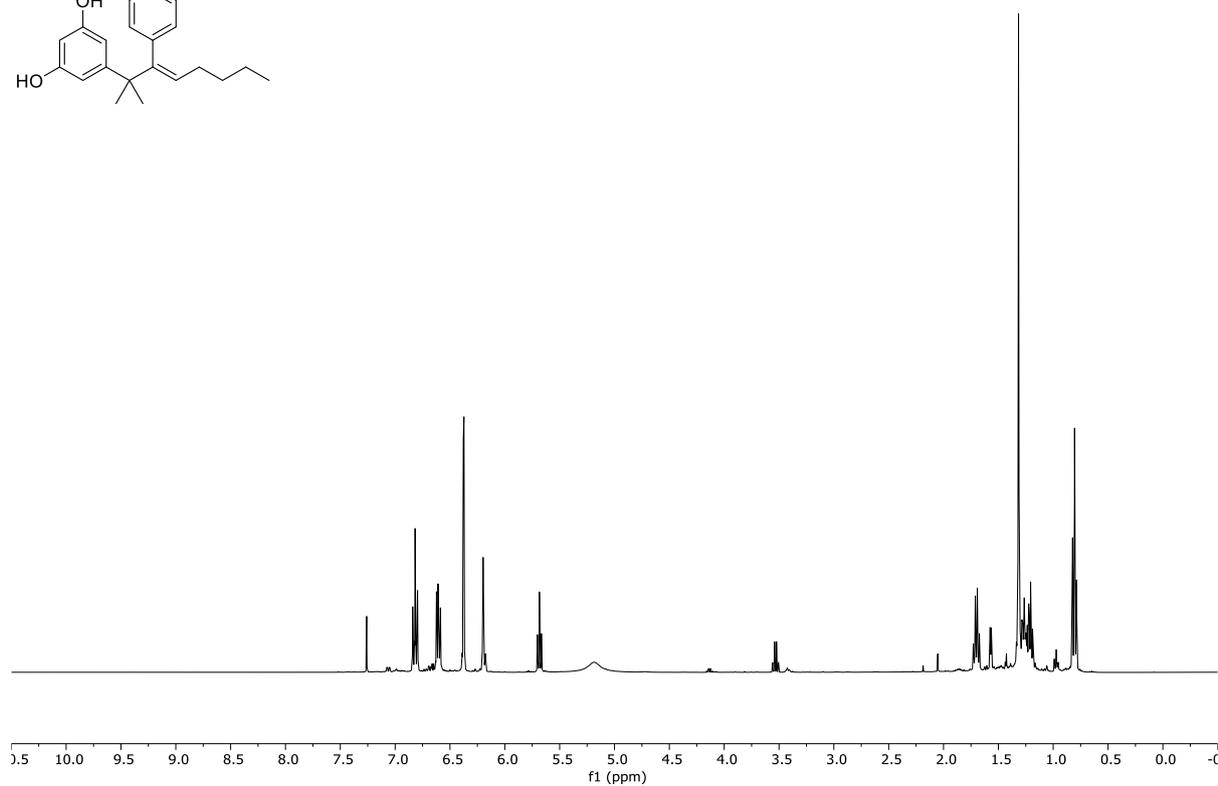
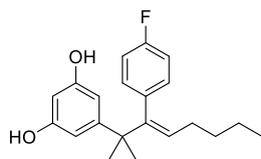
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of SI-17d



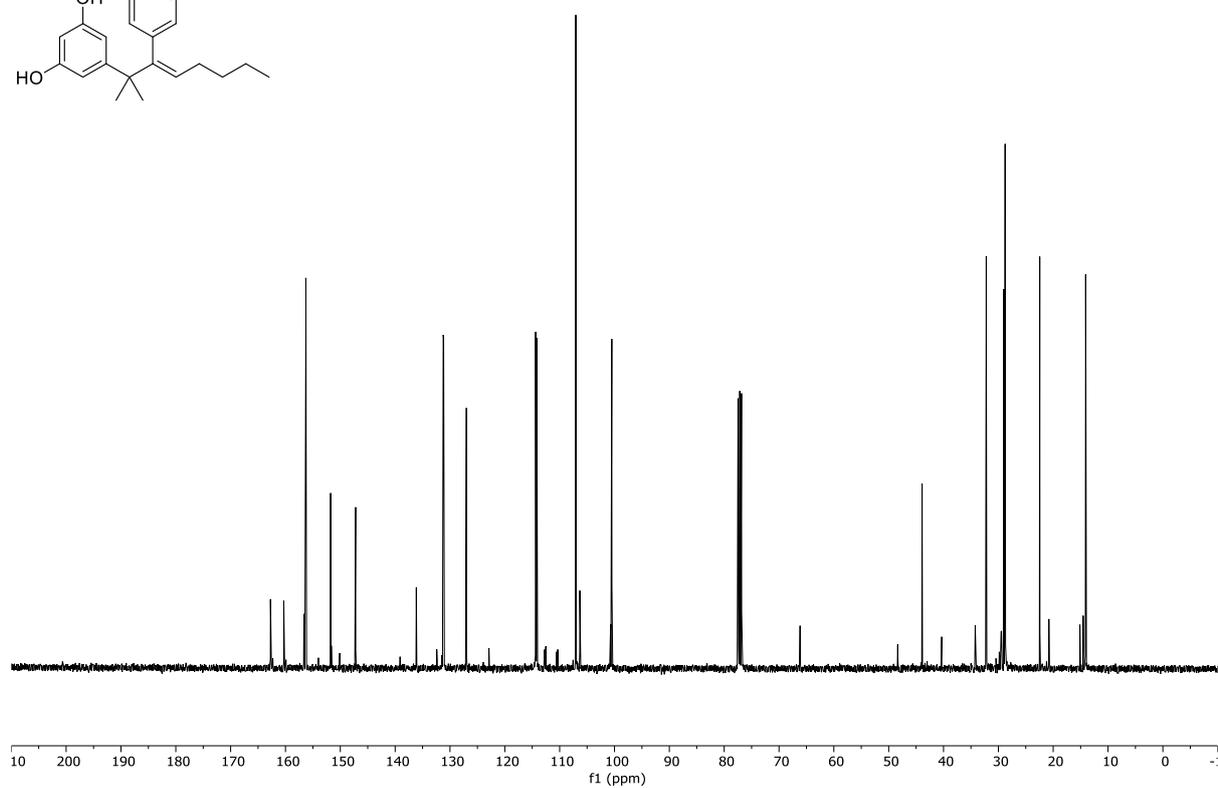
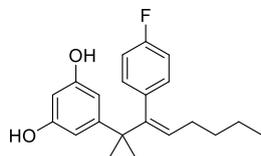
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of SI-17d



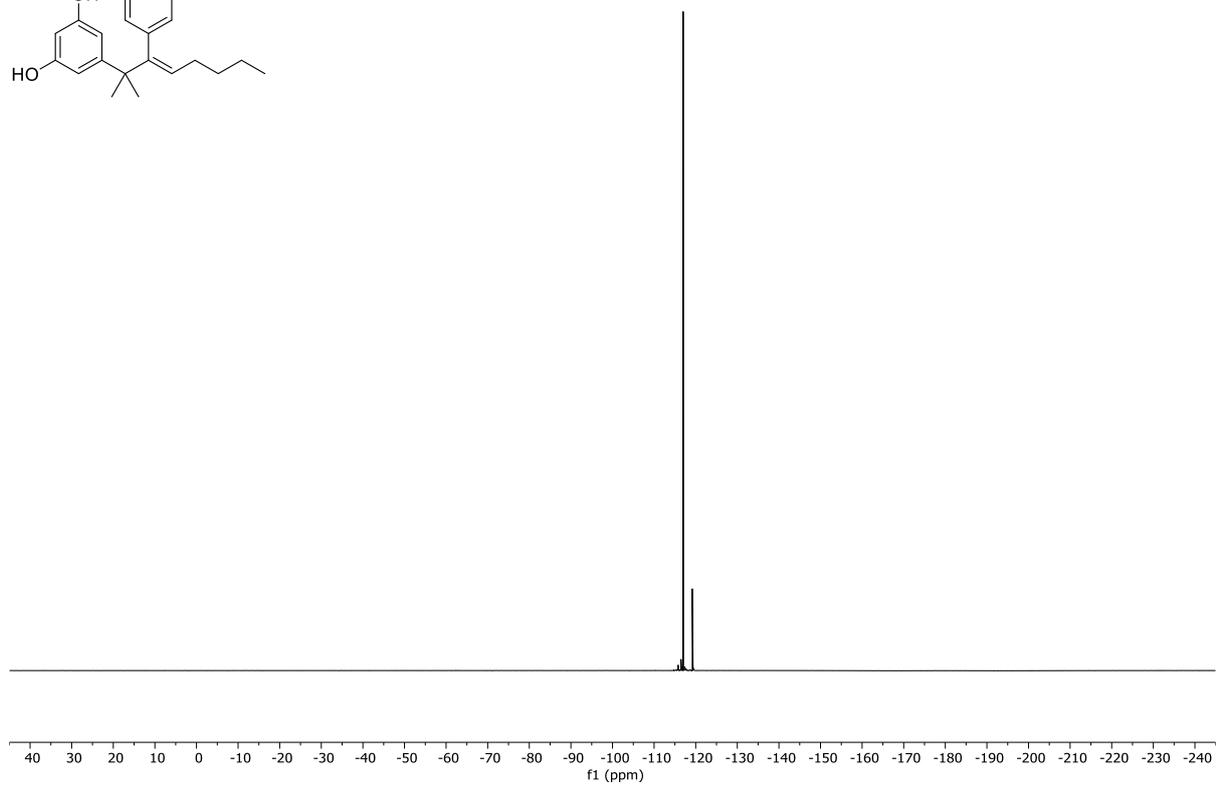
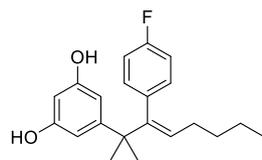
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of SI-17e



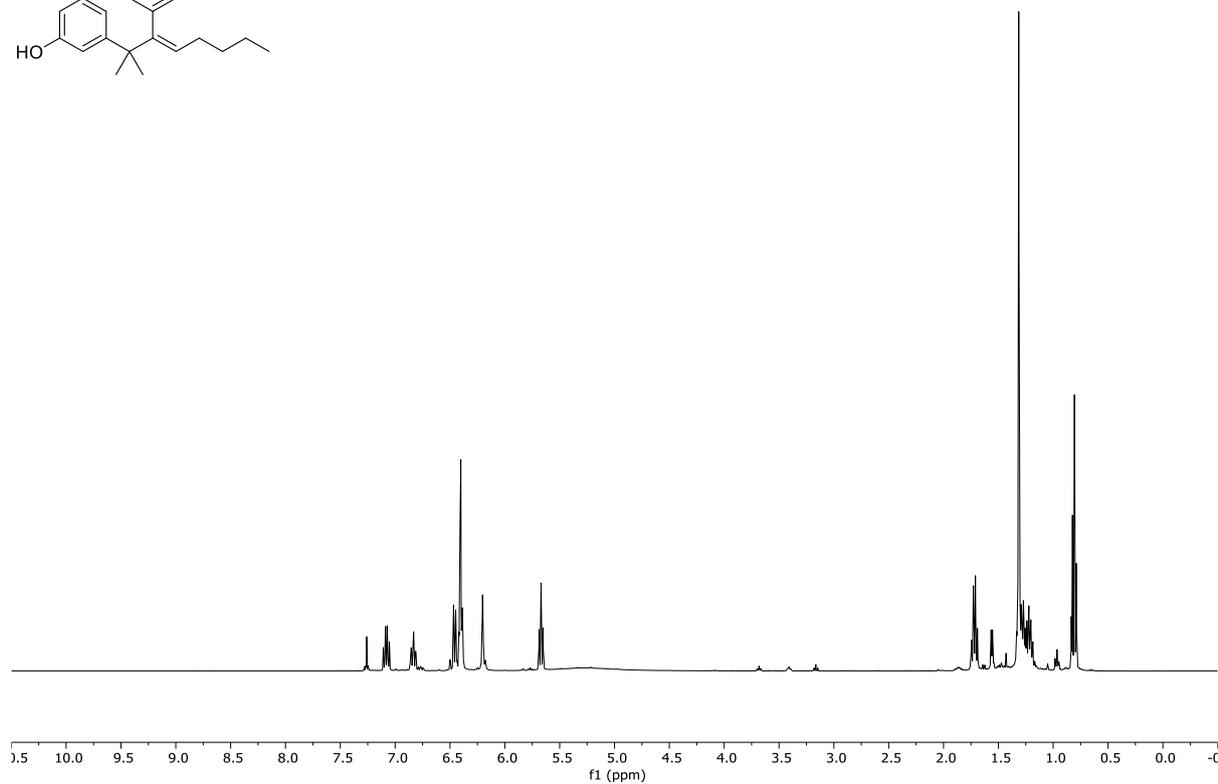
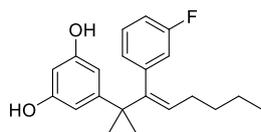
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of SI-17e



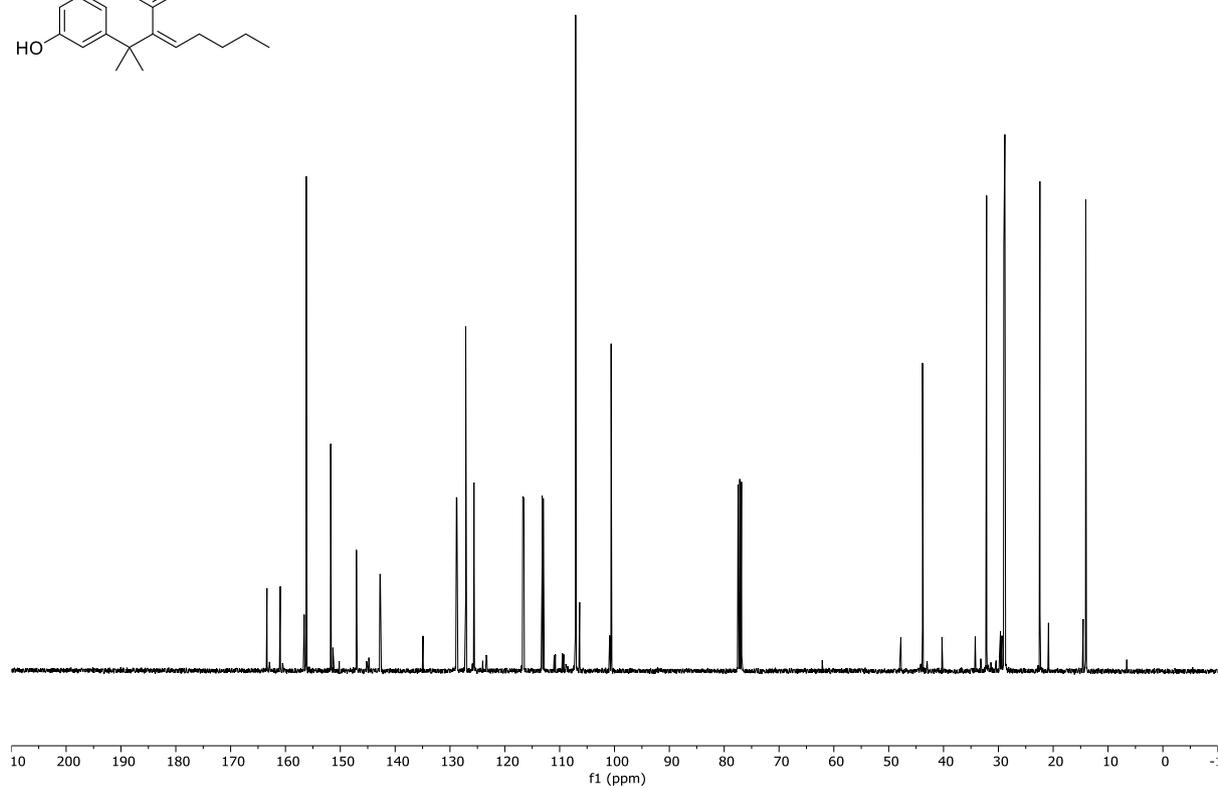
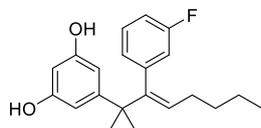
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of **SI-17e**



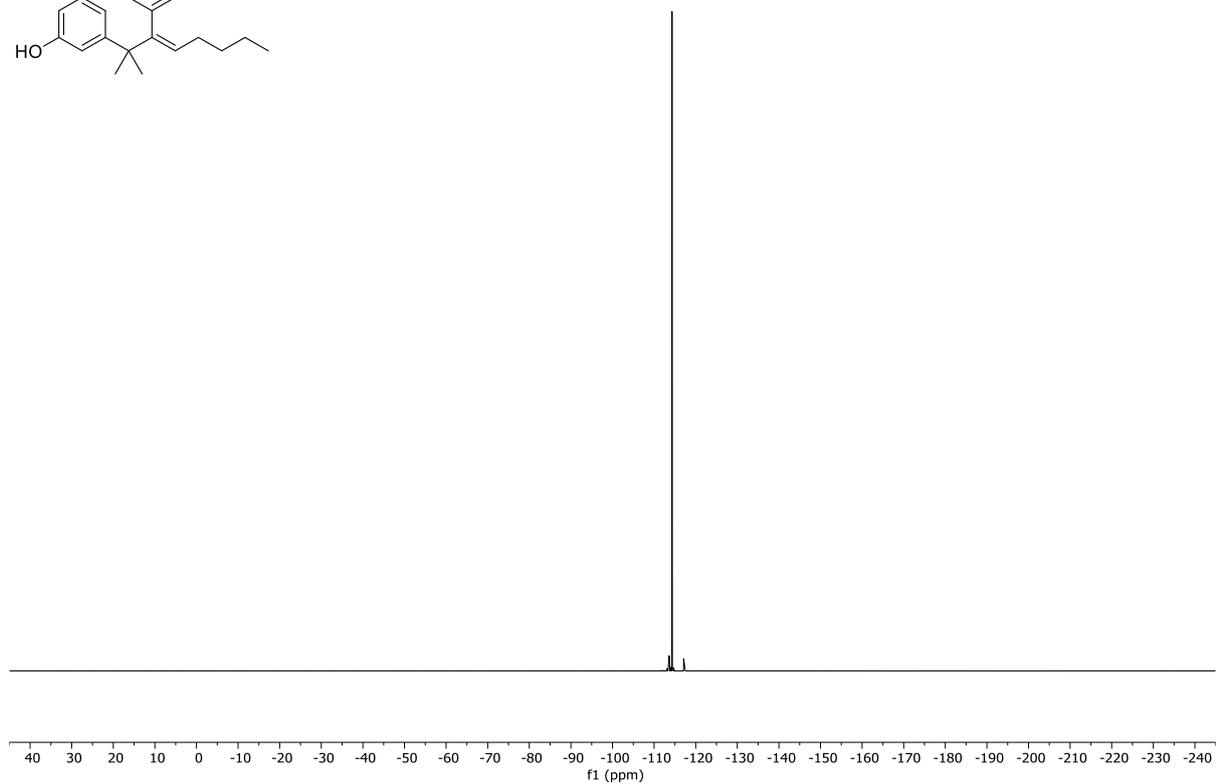
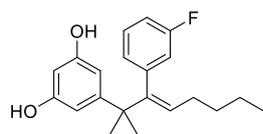
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of **SI-17f**



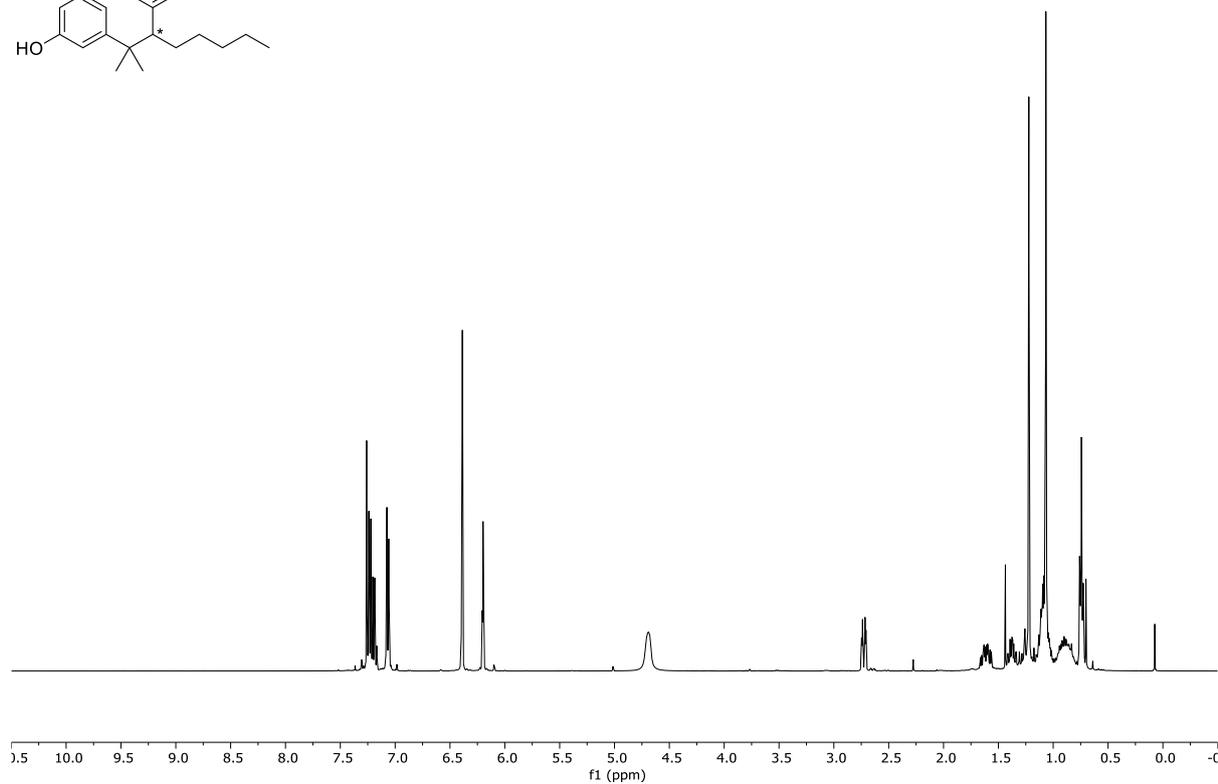
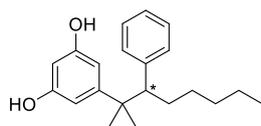
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of **SI-17f**



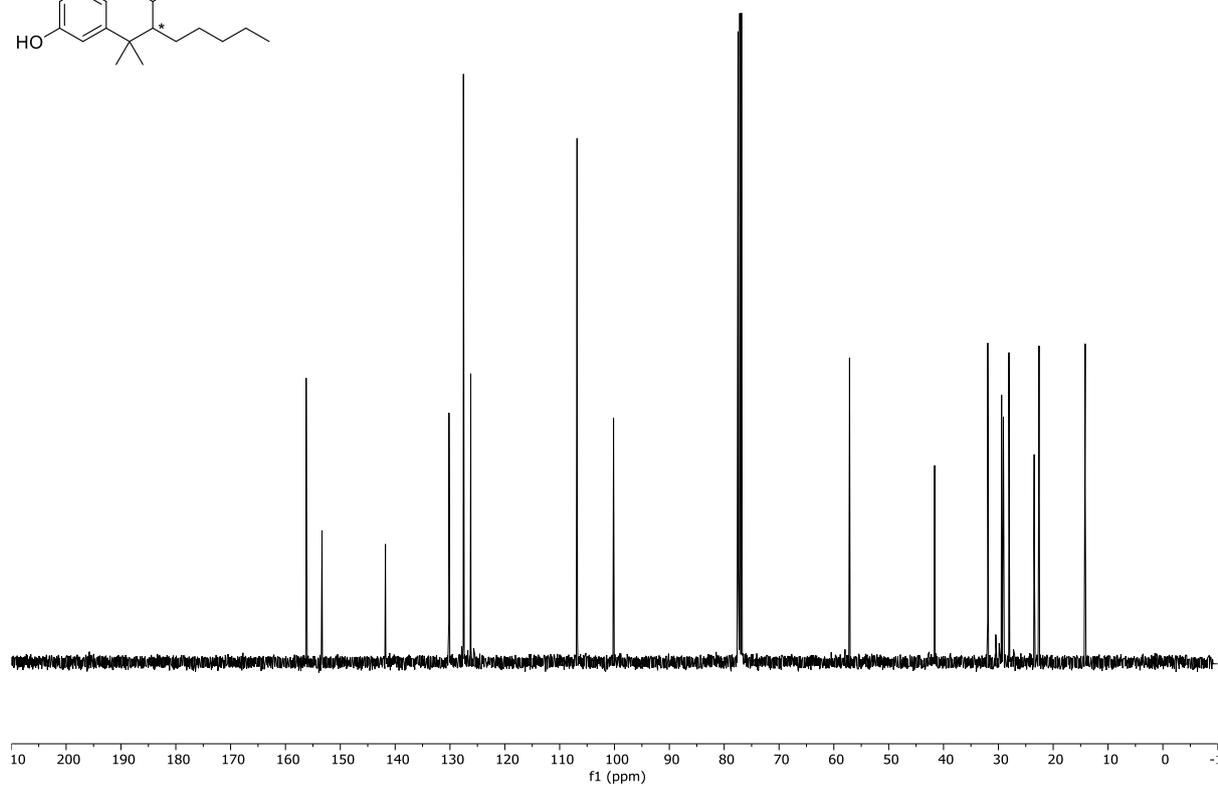
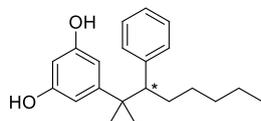
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of **SI-17f**



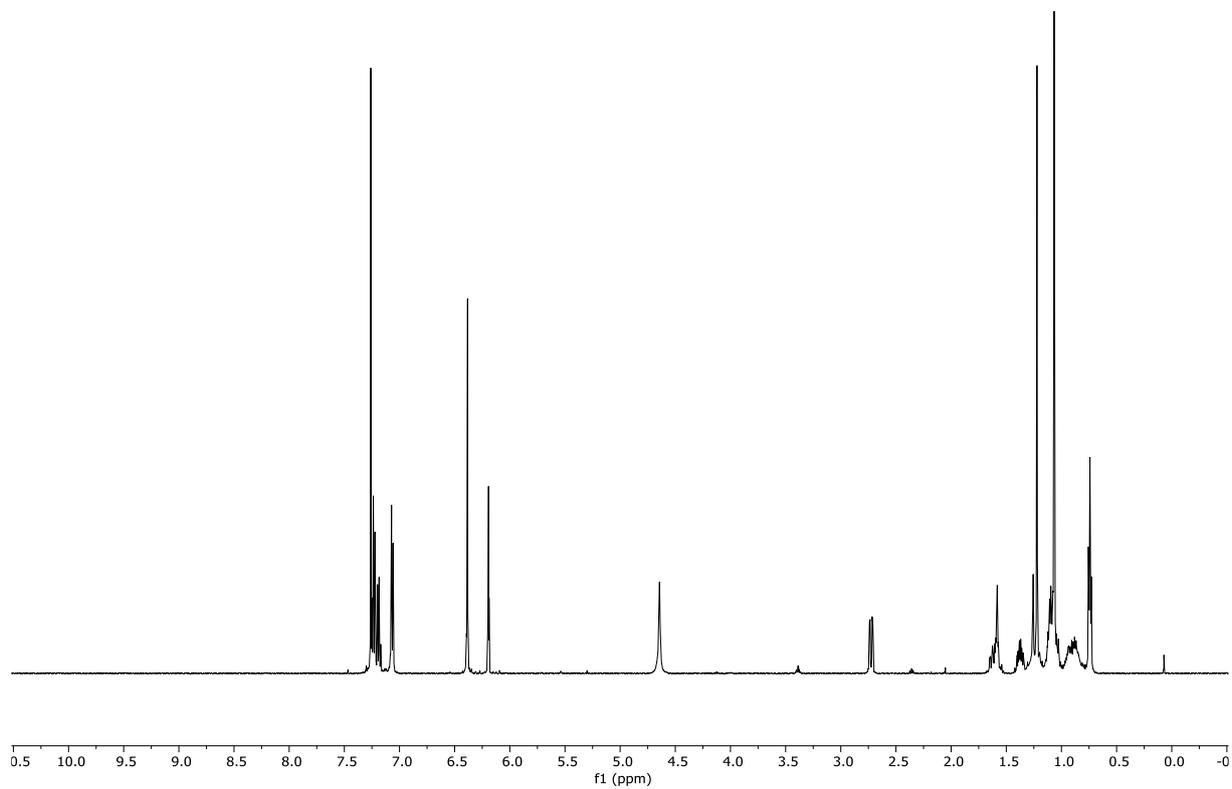
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (-)-(*S*)-**9d** & (+)-(*R*)-**9d**



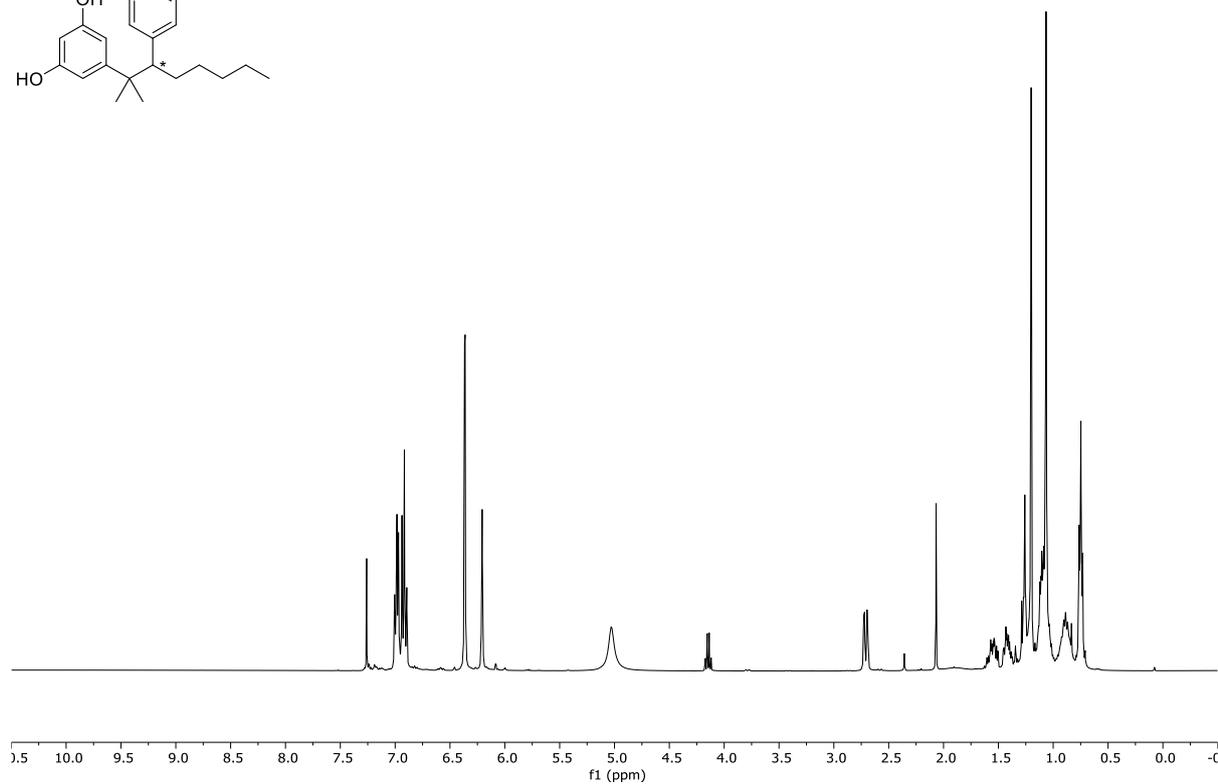
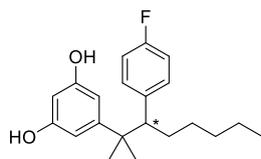
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (-)-(*S*)-**9d** & (+)-(*R*)-**9d**



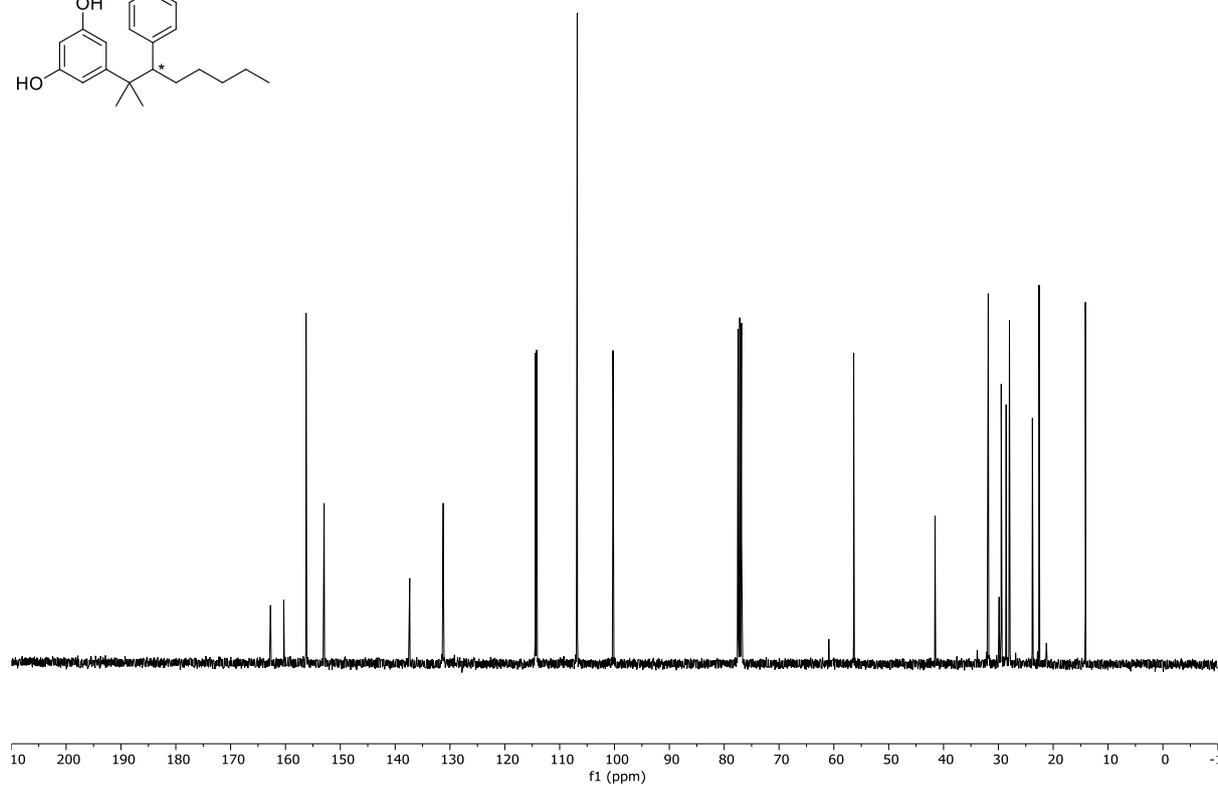
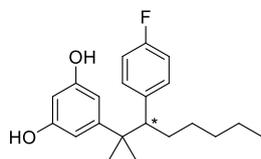
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) independent synthesis of (*S*)-**SI-18**/(A)-**9** = (–)-(*S*)-**19**



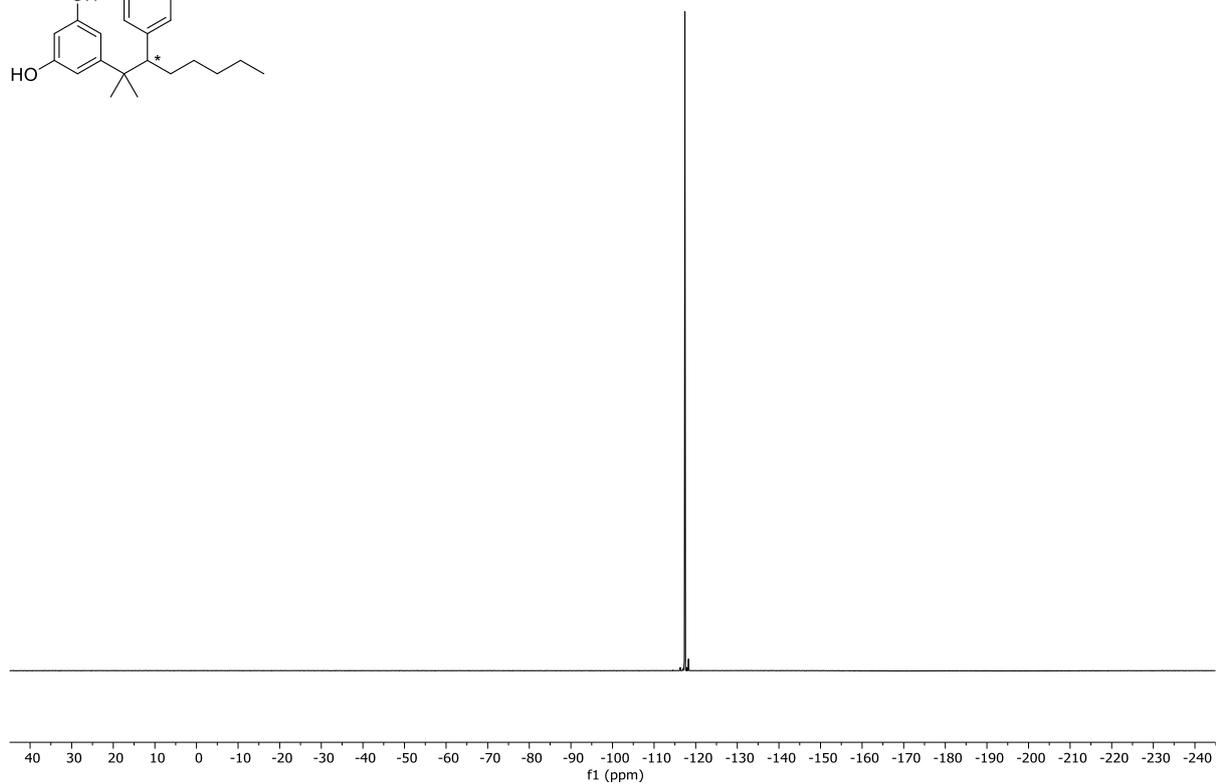
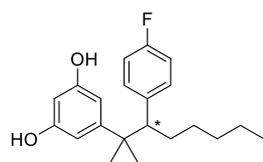
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (-)-(*S*)-**9e** & (+)-(*R*)-**9e**



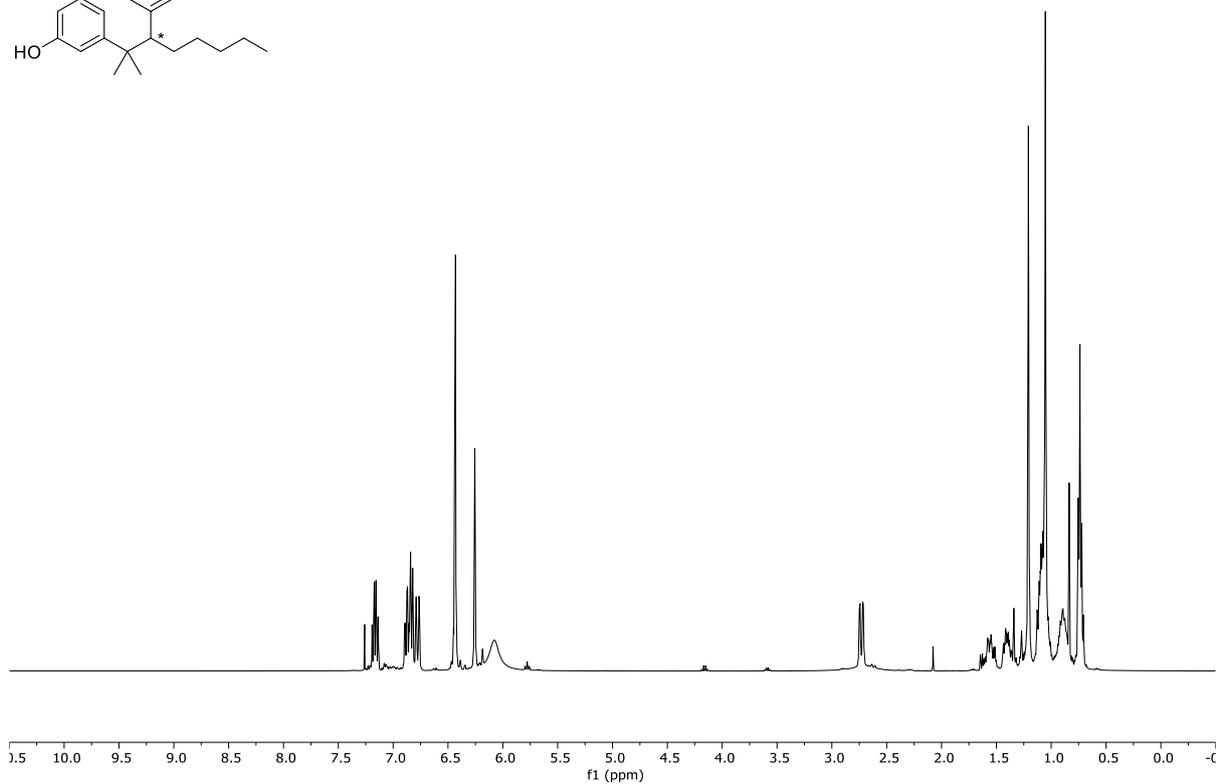
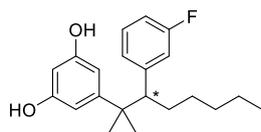
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (-)-(*S*)-**9e** & (+)-(*R*)-**9e**



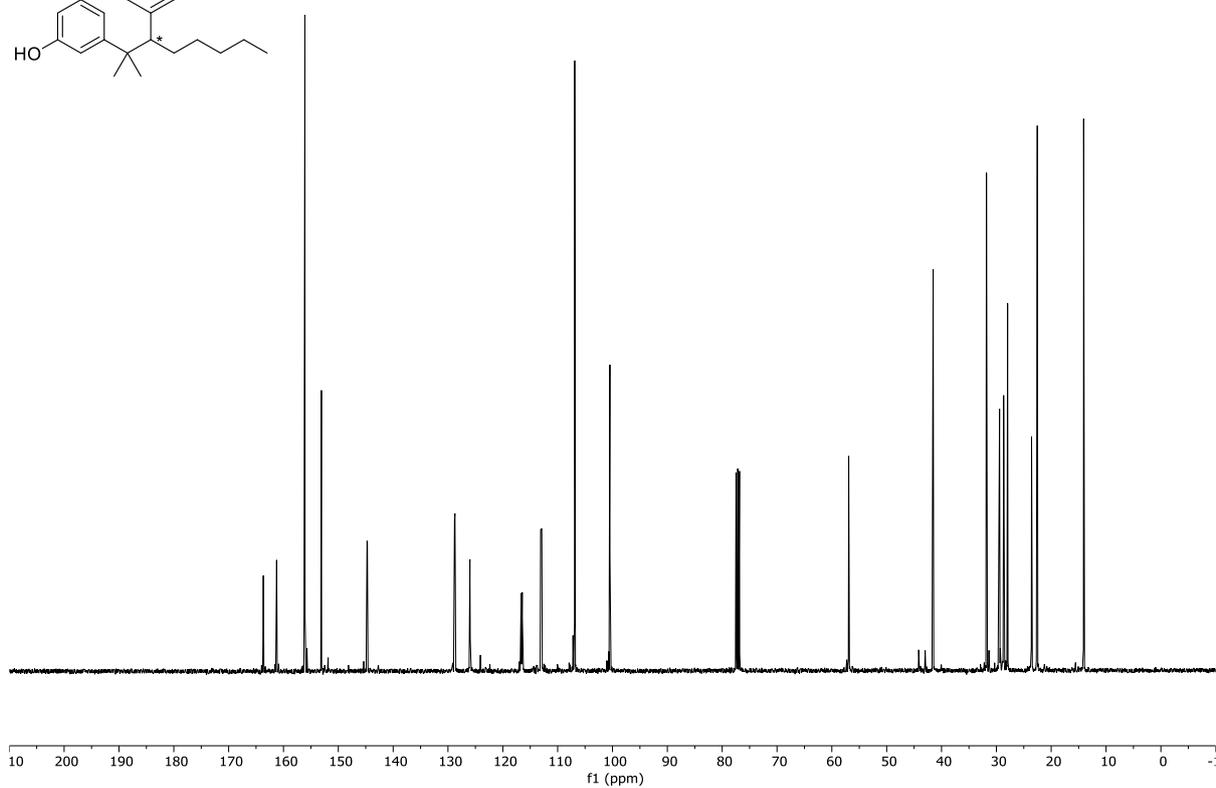
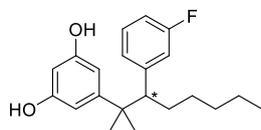
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of (-)-(*S*)-**9e** & (+)-(*R*)-**9e**



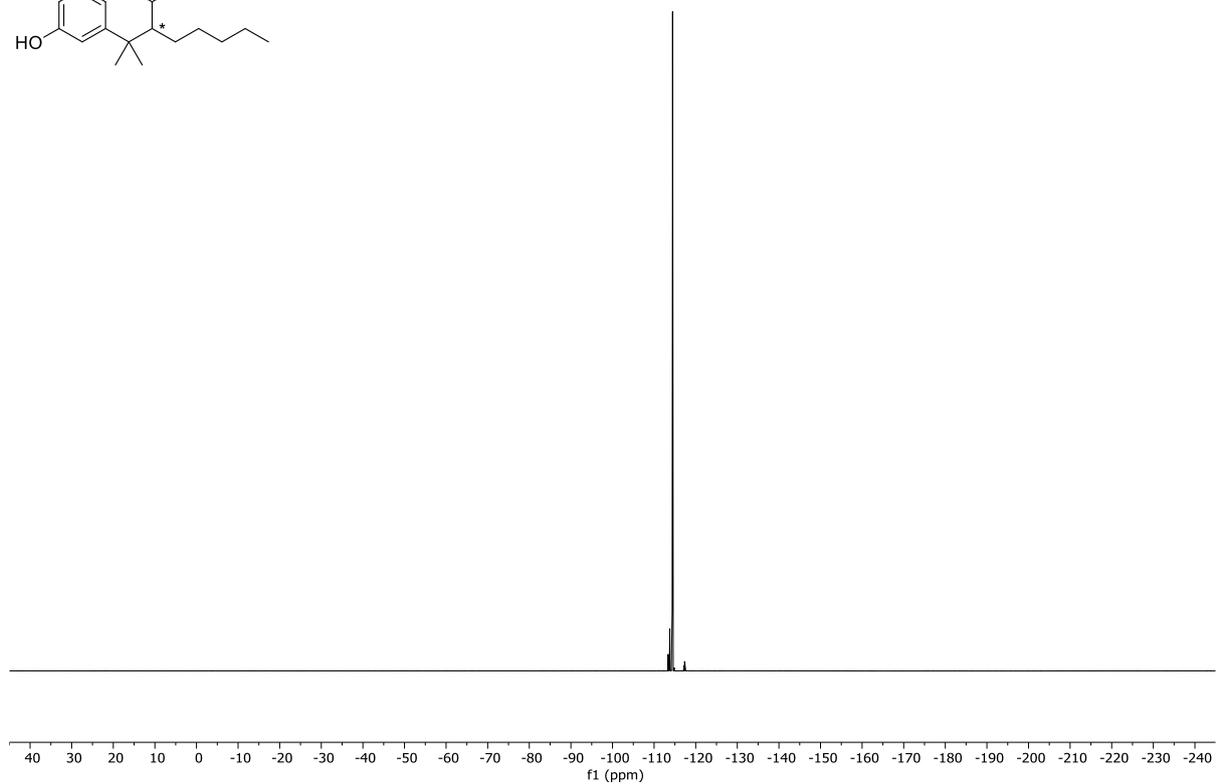
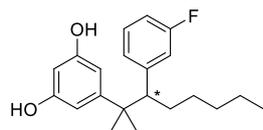
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (-)-(*S*)-**9f** & (+)-(*R*)-**9f**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (-)-(*S*)-**9f** & (+)-(*R*)-**9f**

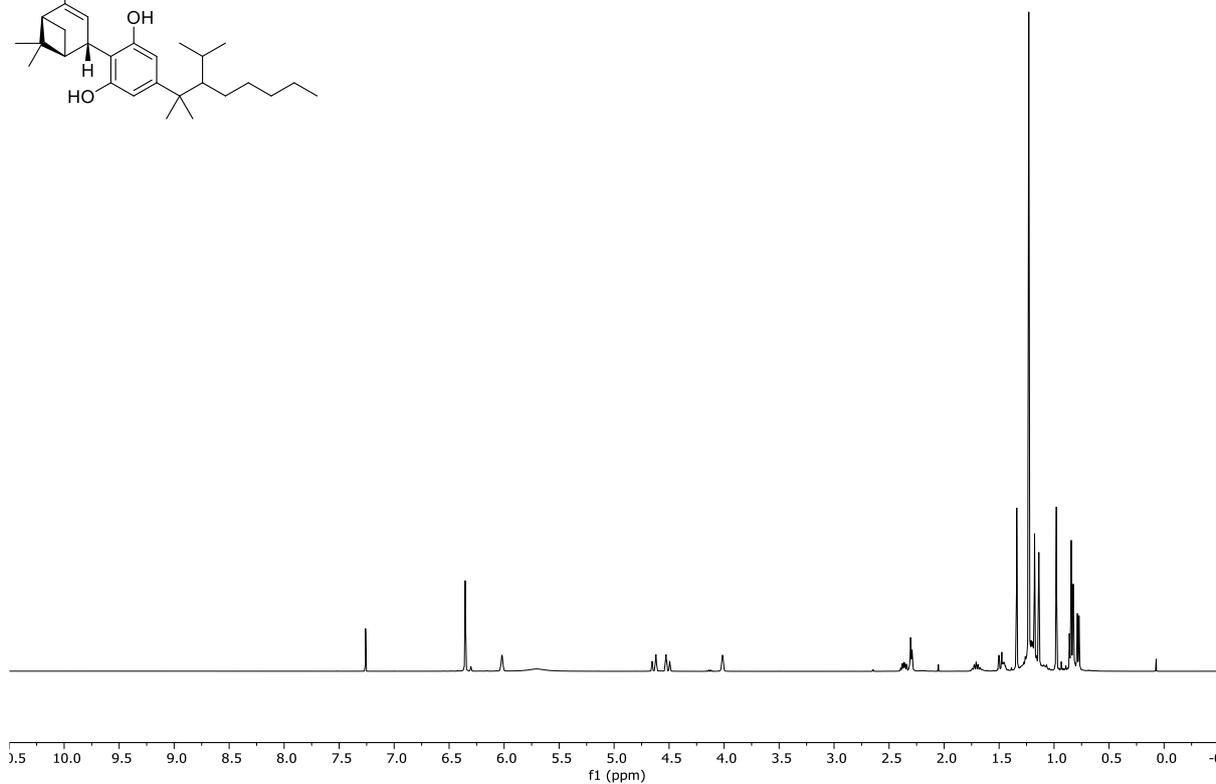
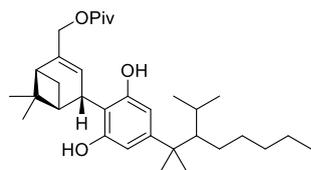


$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of (-)-(*S*)-**9f** & (+)-(*R*)-**9f**

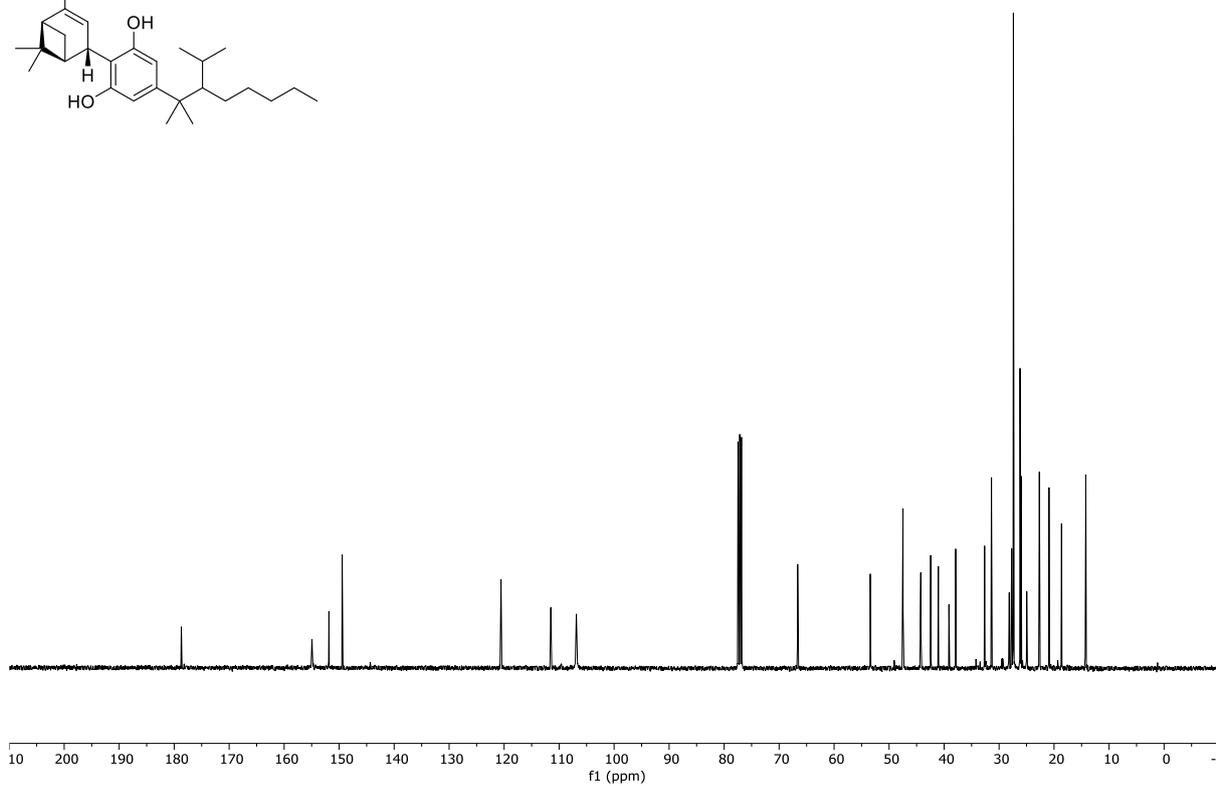
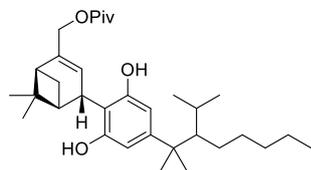




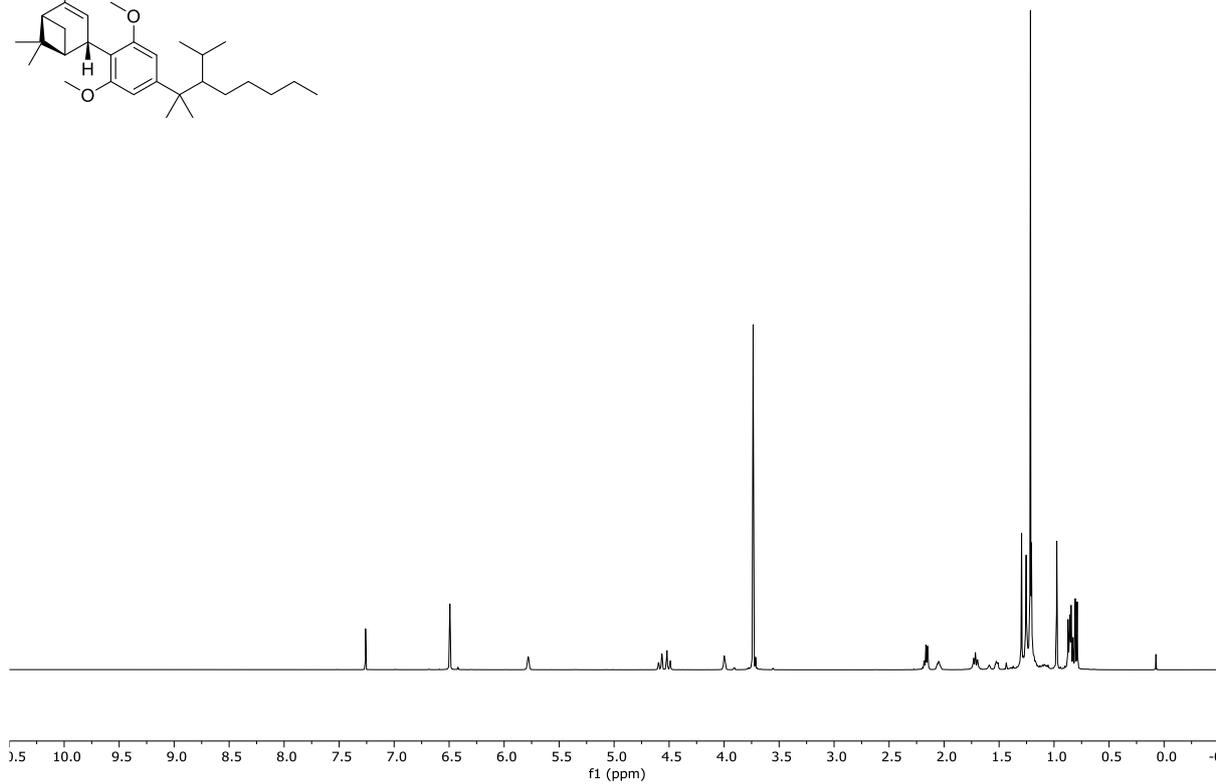
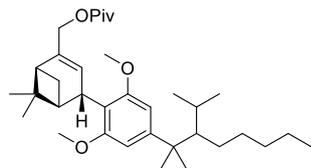
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**SI-20a**



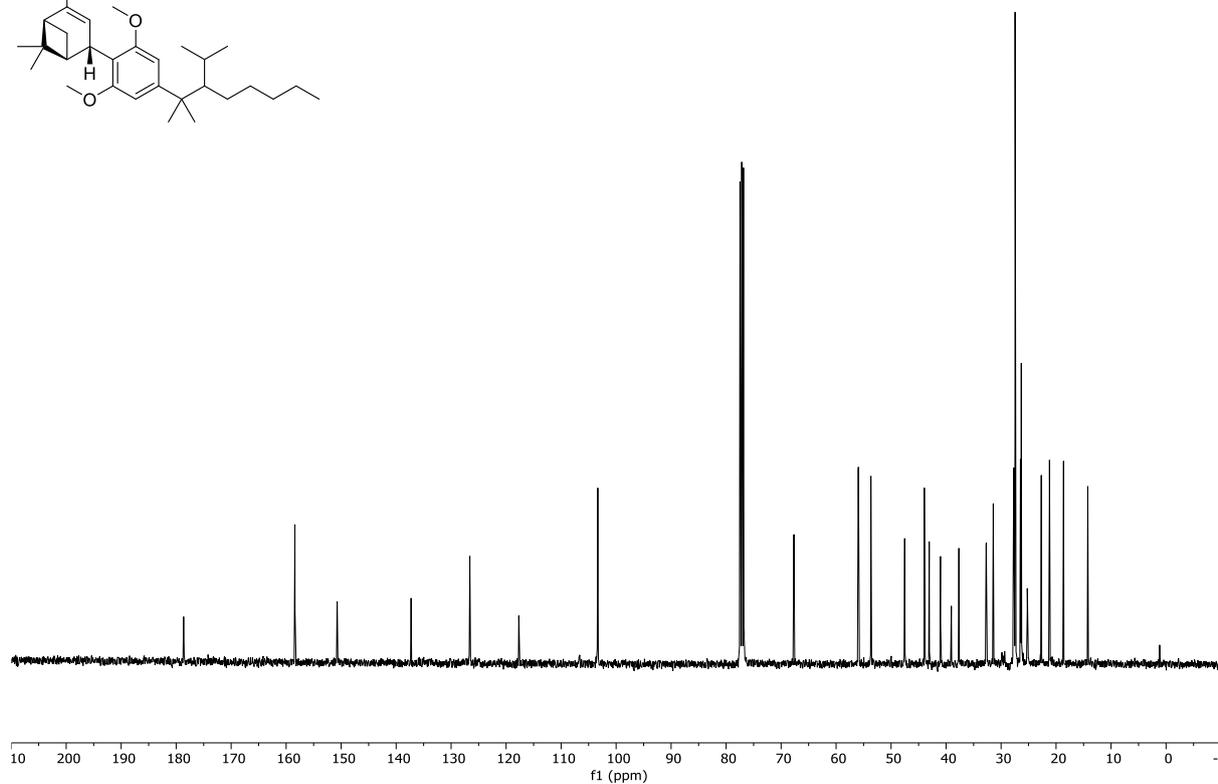
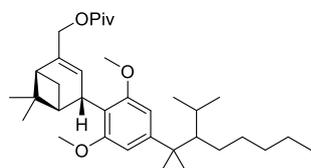
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**SI-20a**



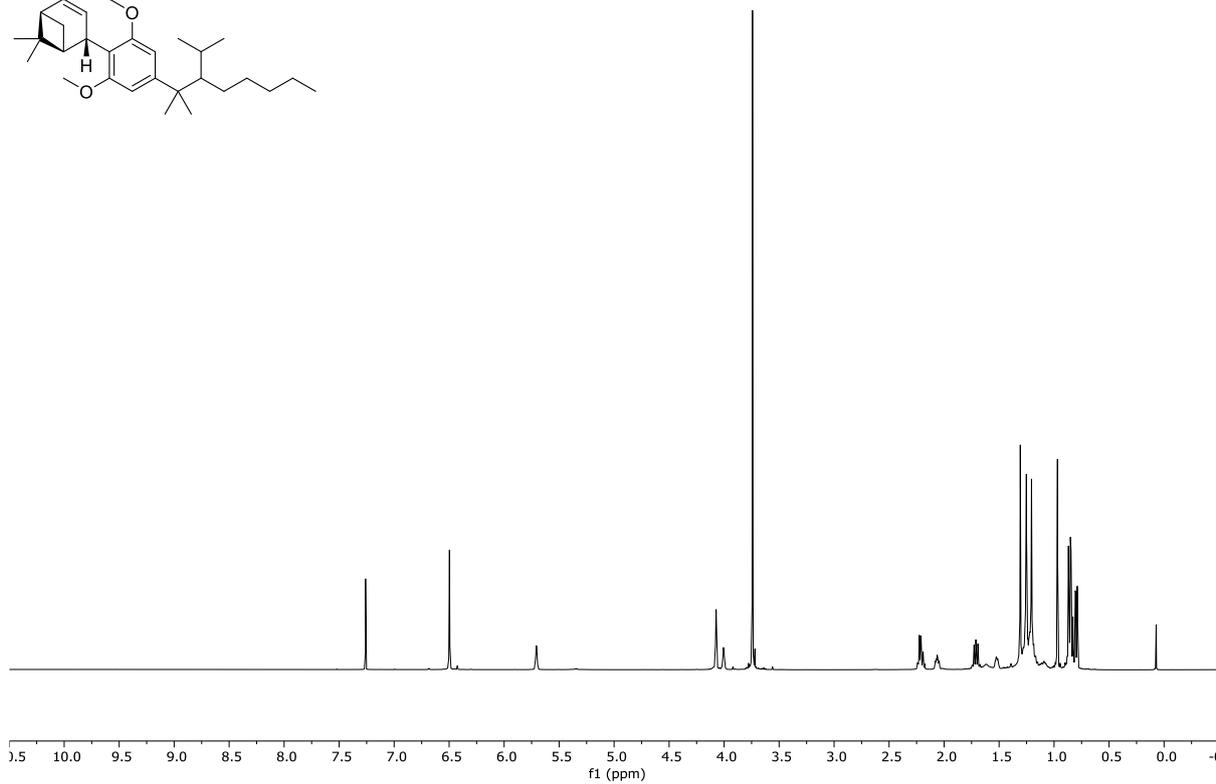
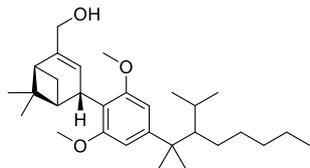
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**10a**



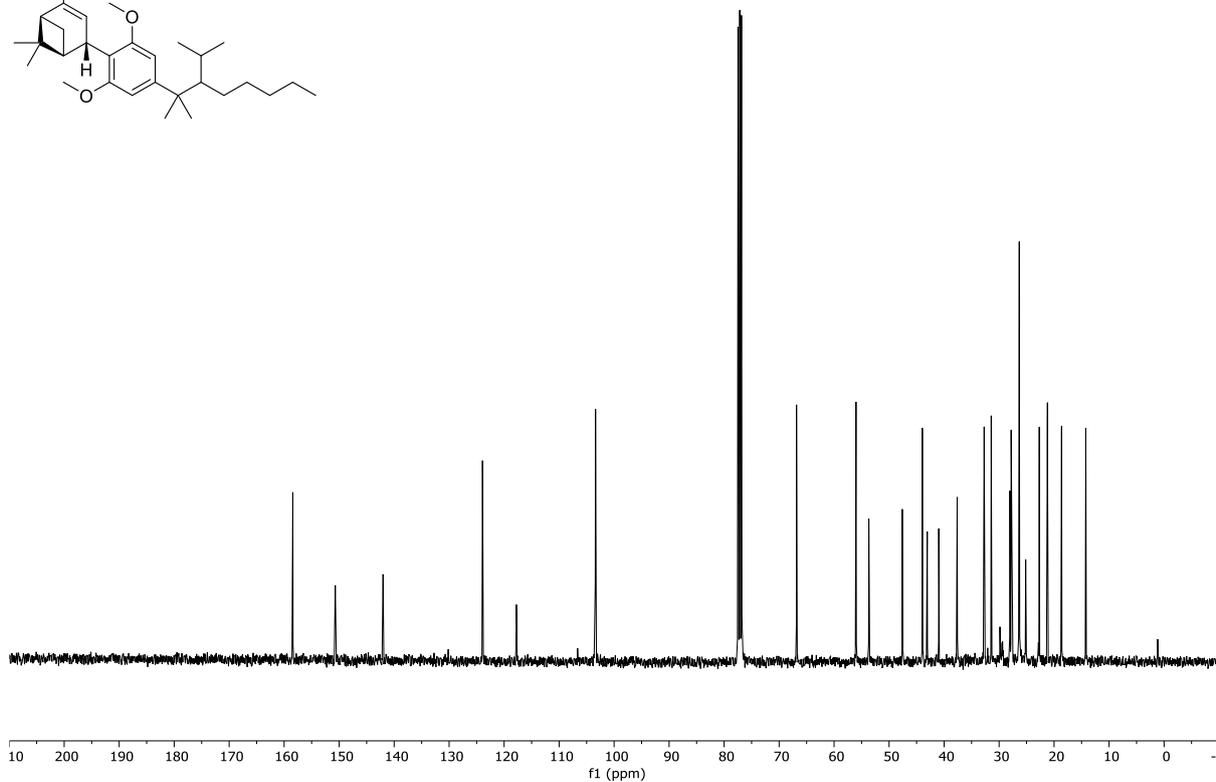
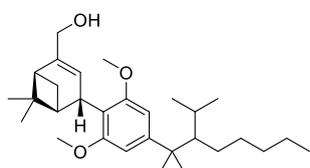
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**10a**



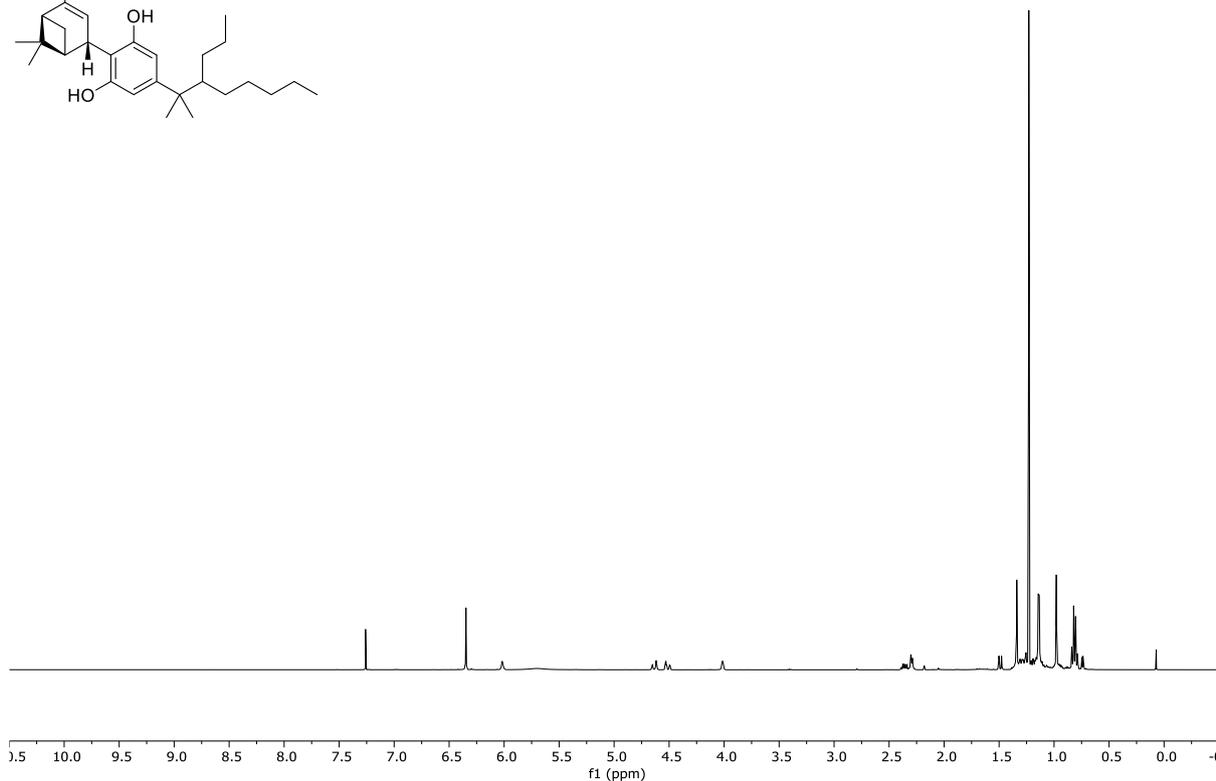
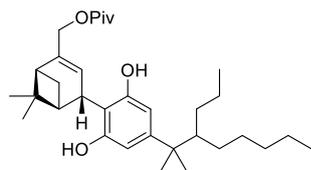
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of (*S/R*)-**6a**



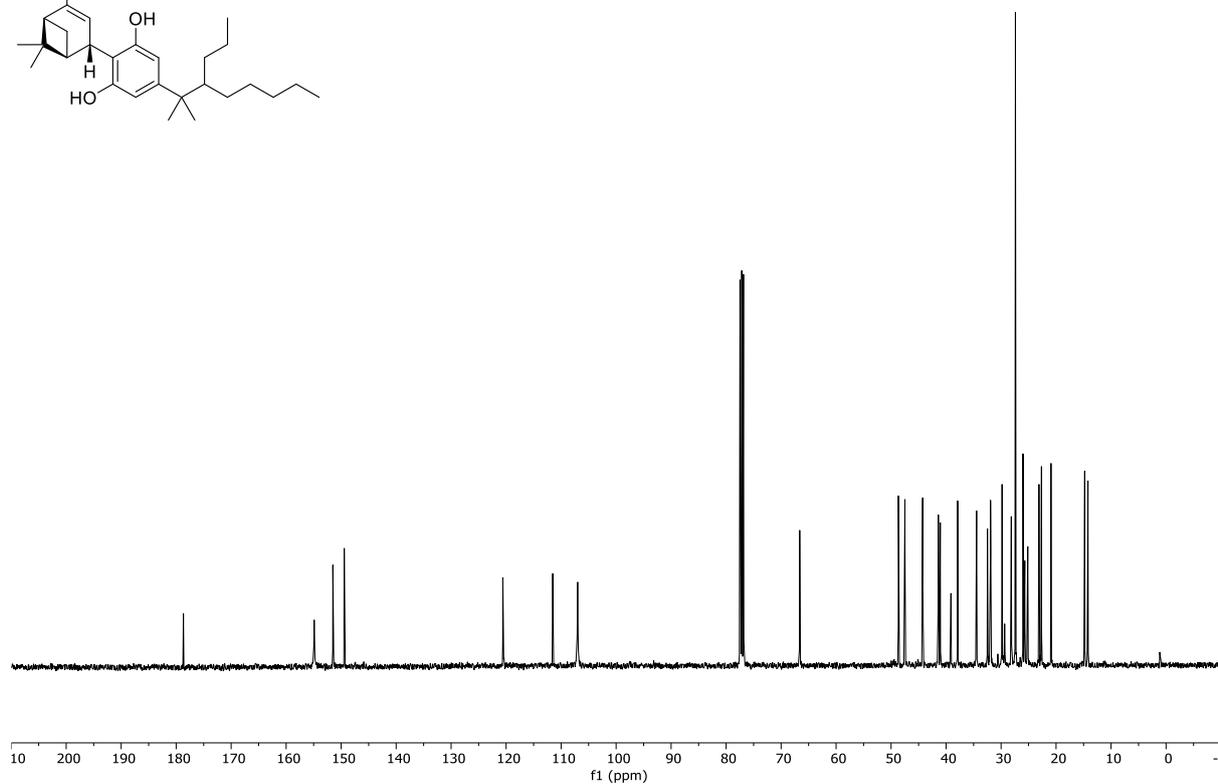
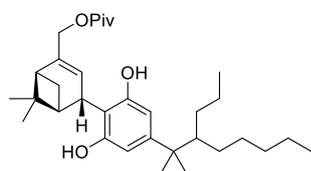
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of (*S/R*)-**6a**



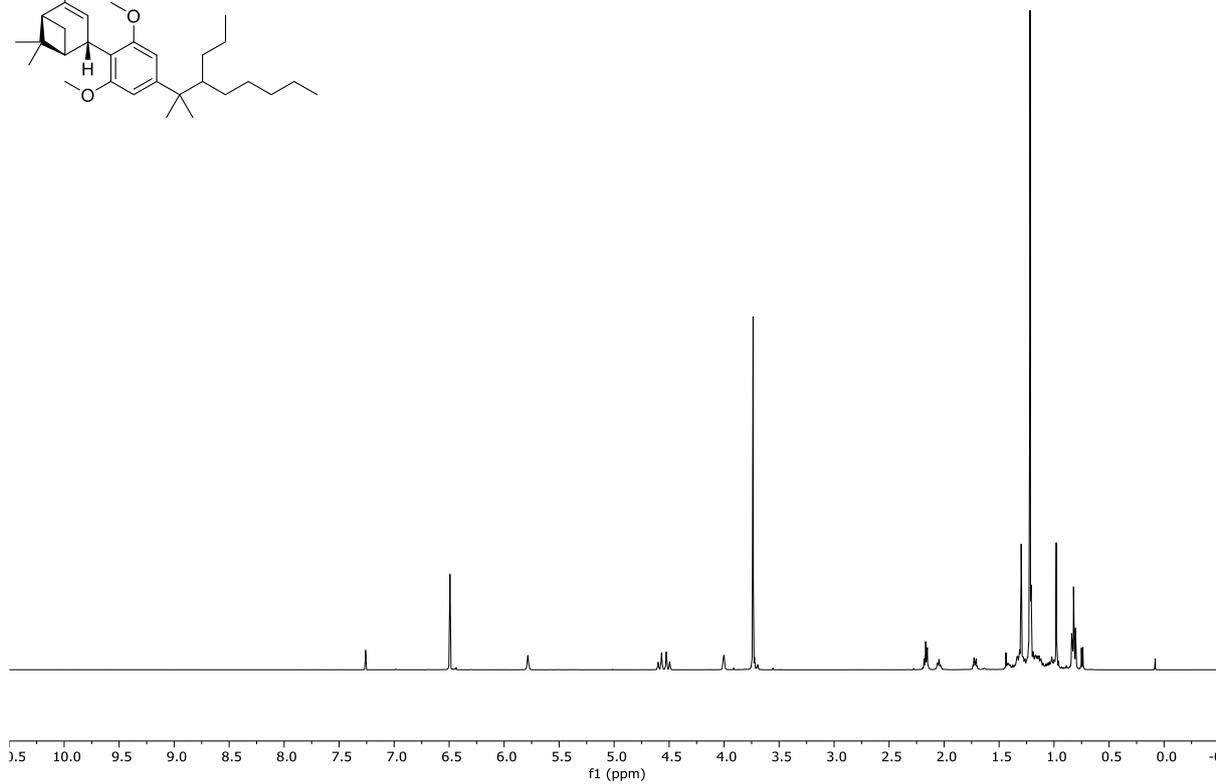
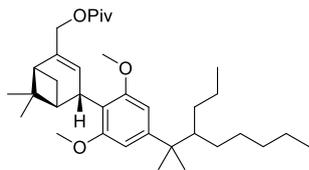
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of (*S/R*)-SI-20b



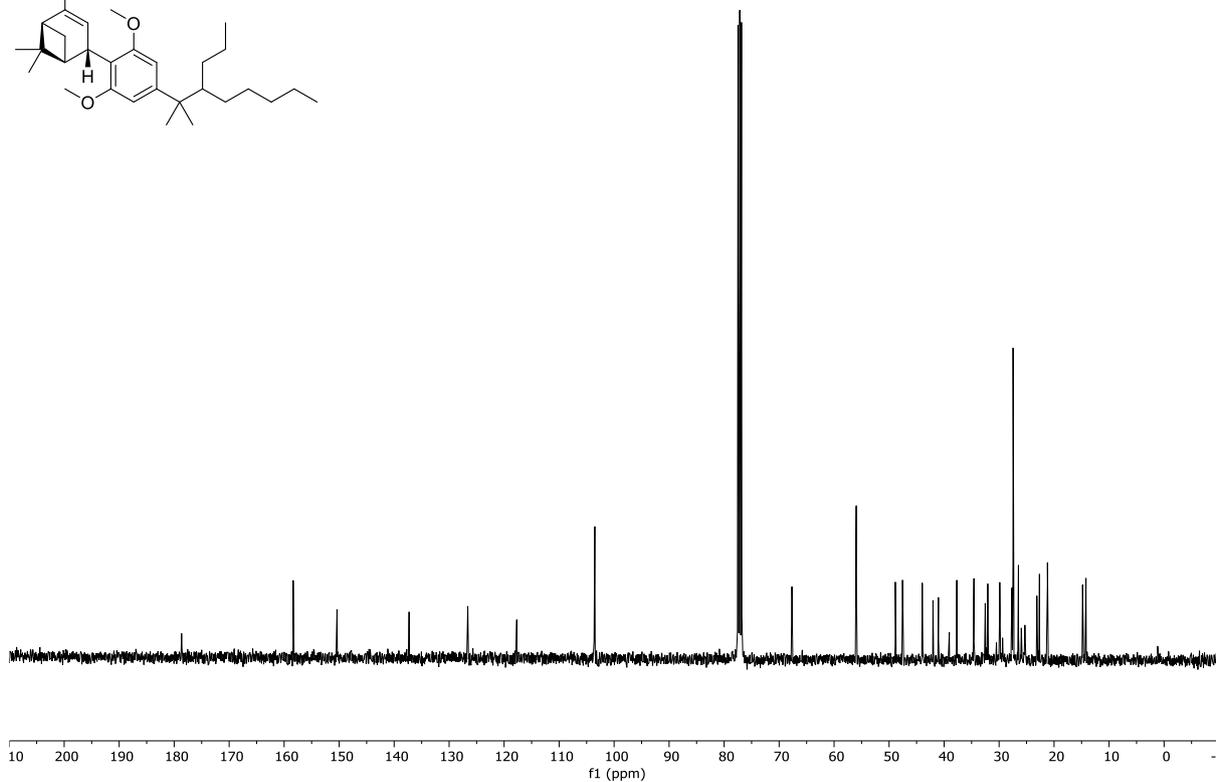
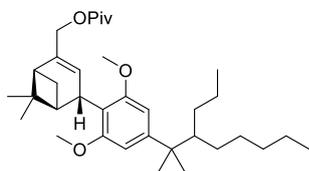
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of (*S/R*)-SI-20b



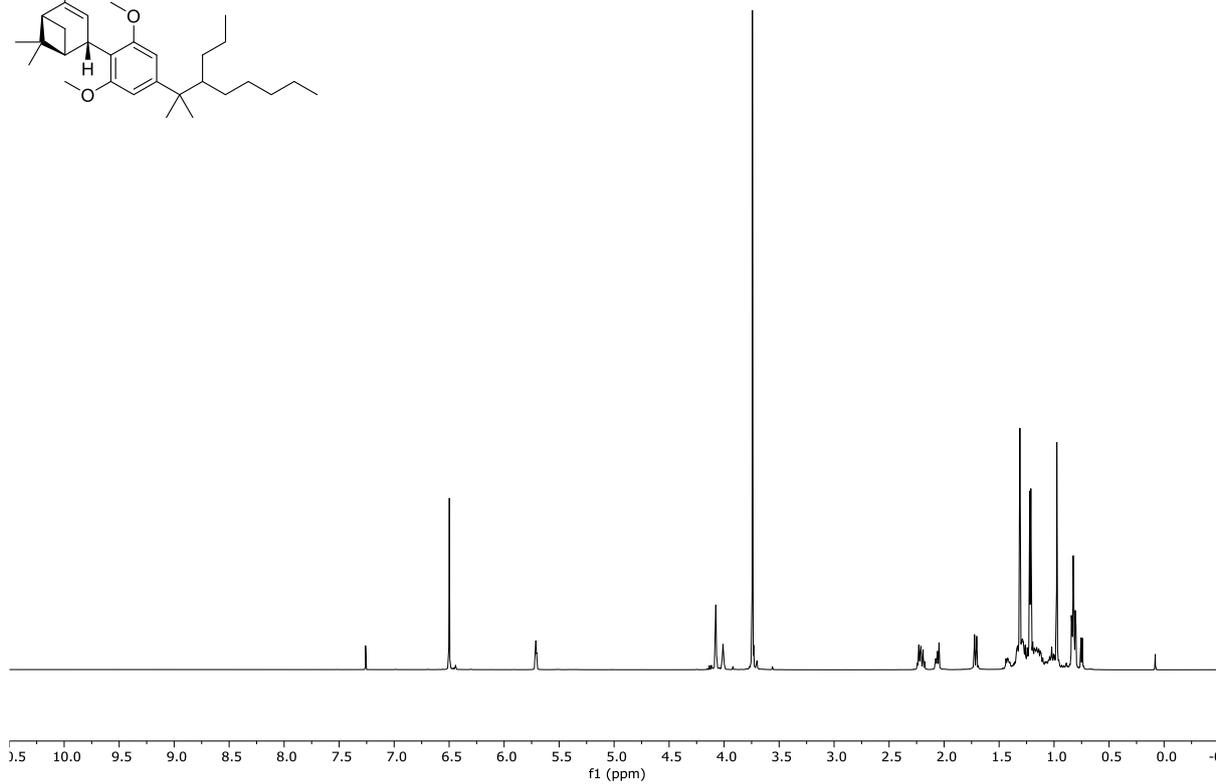
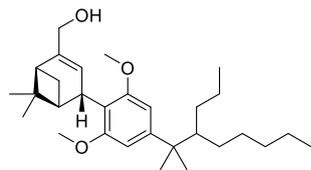
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of (*S/R*)-**10b**



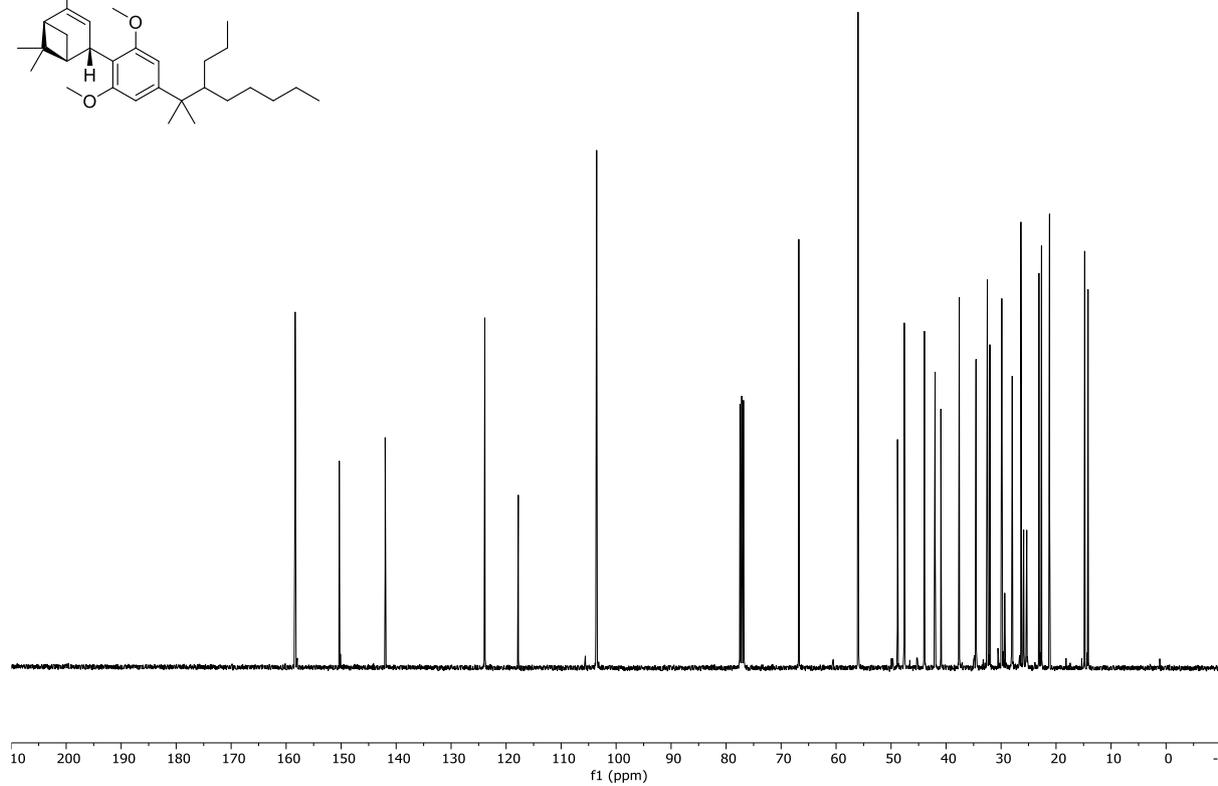
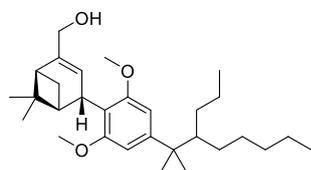
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of (*S/R*)-**10b**



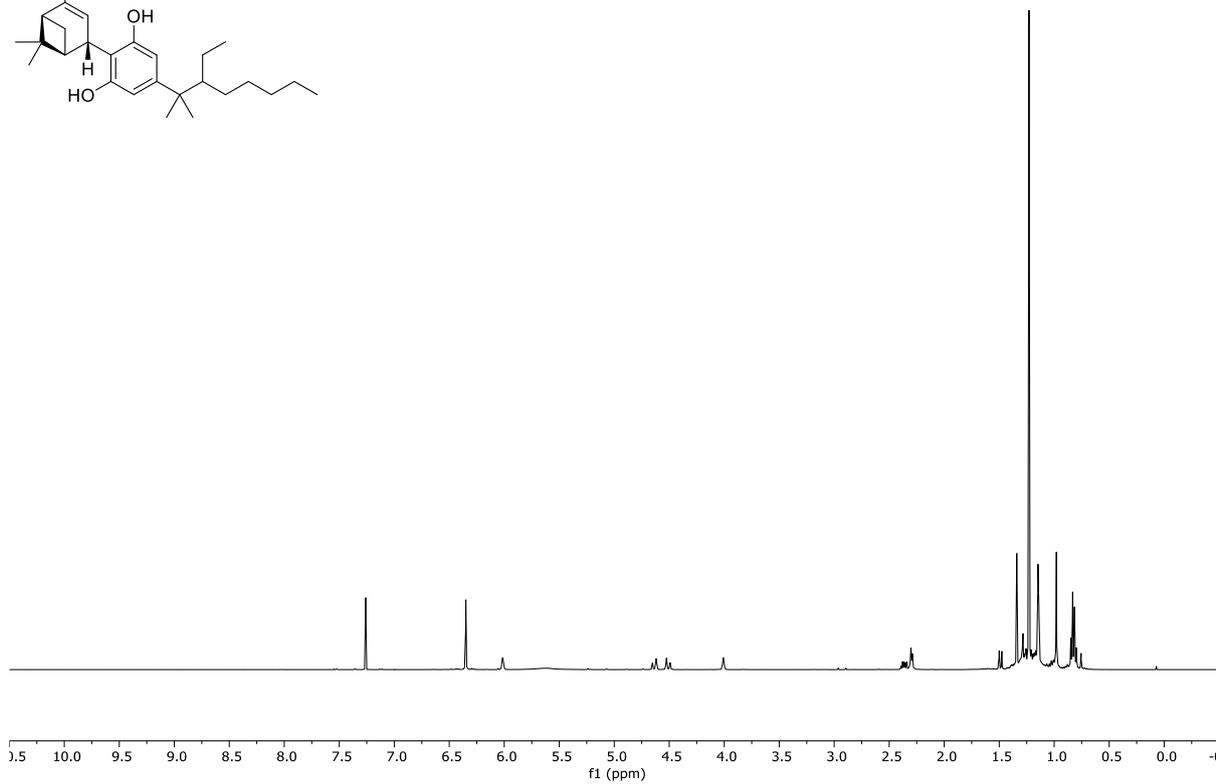
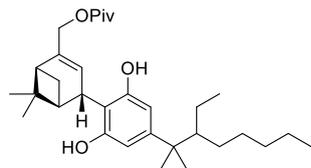
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**6b**



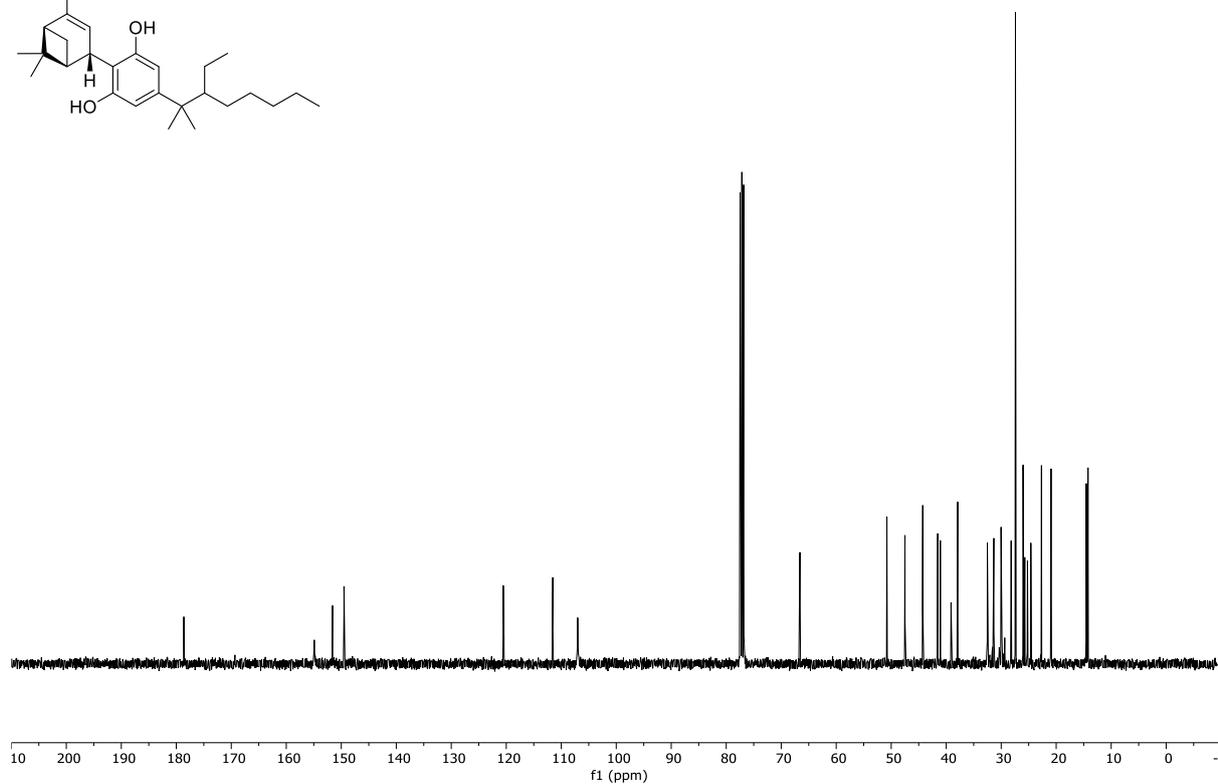
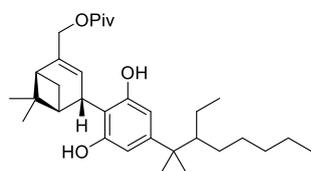
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**6b**



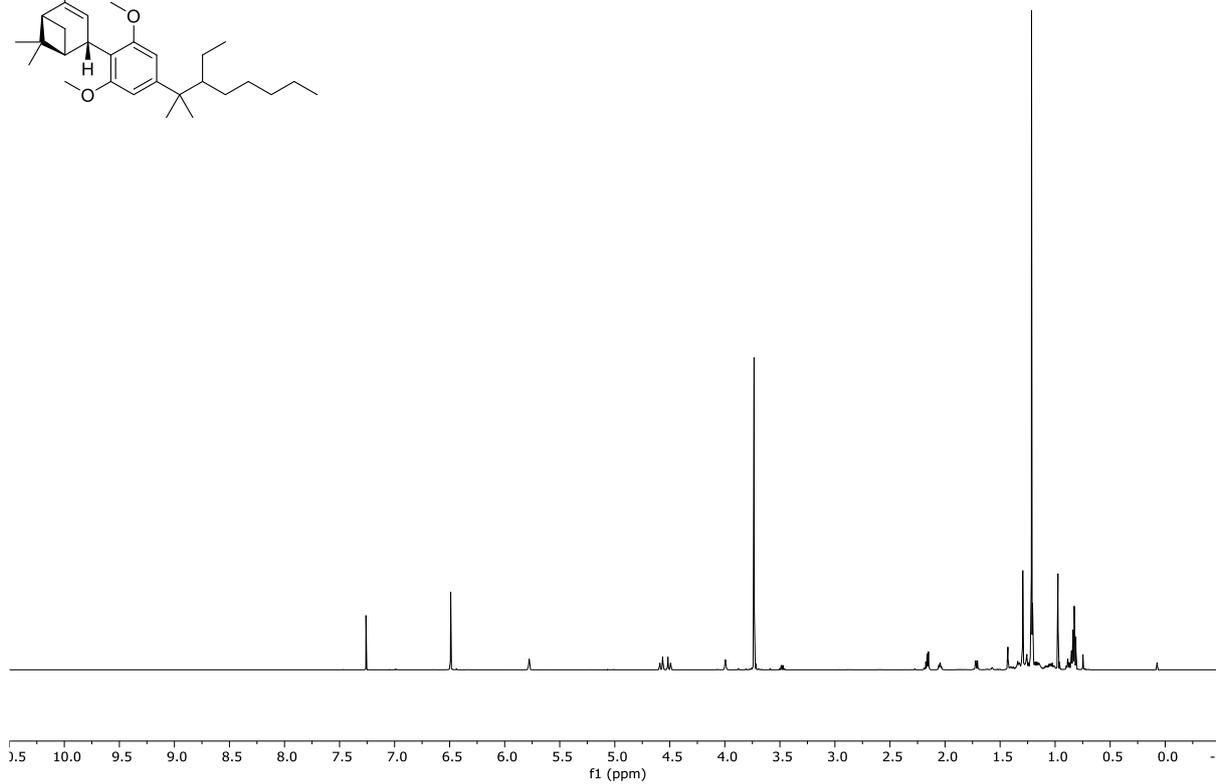
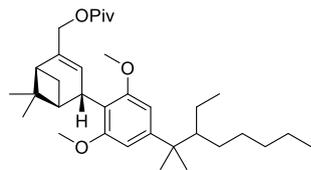
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**SI-20c**



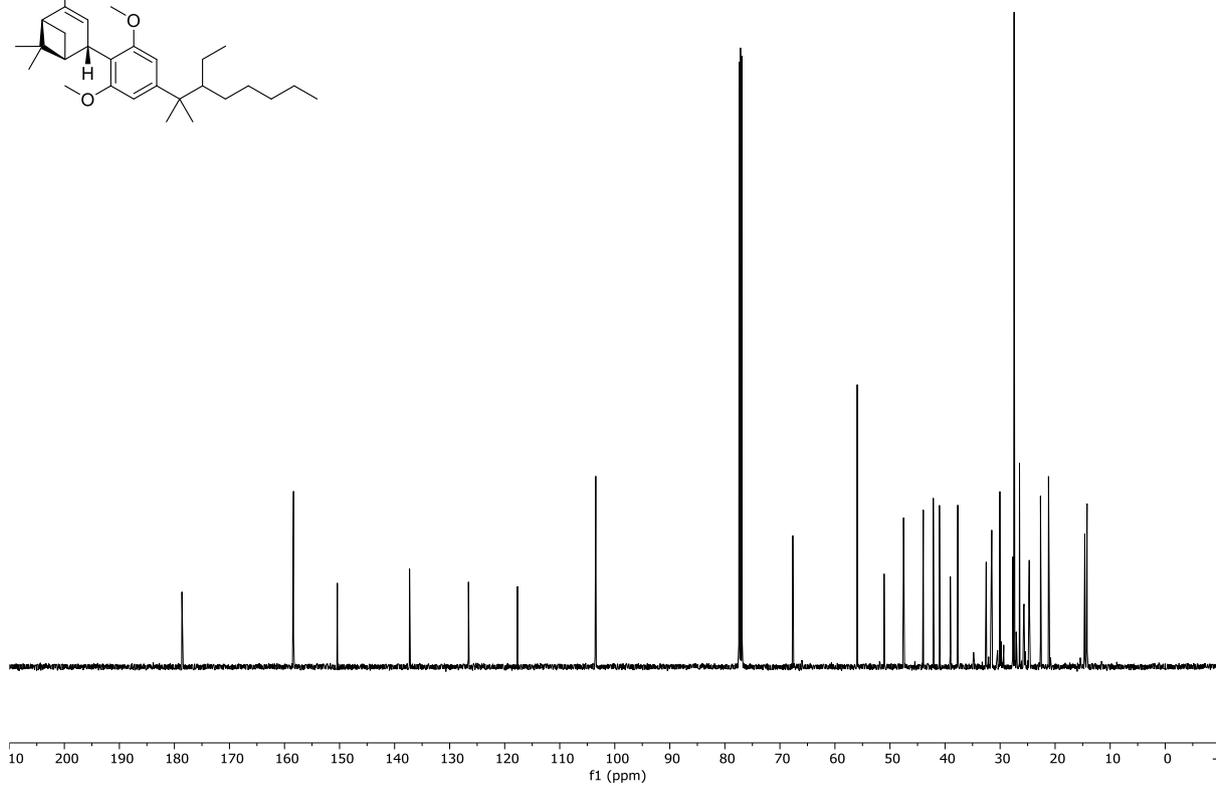
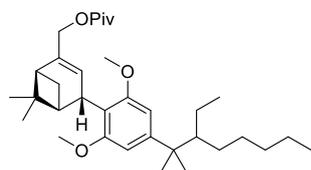
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**SI-20c**



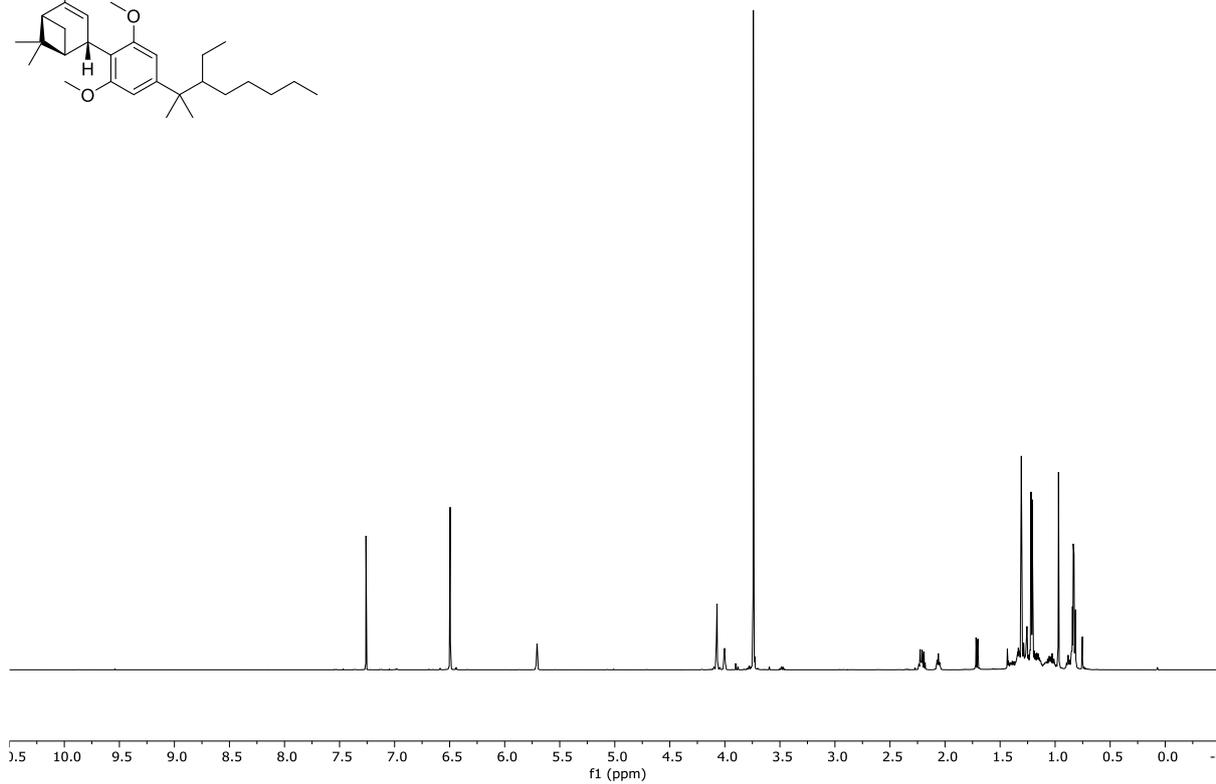
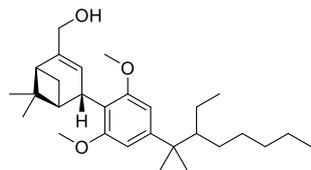
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**10c**



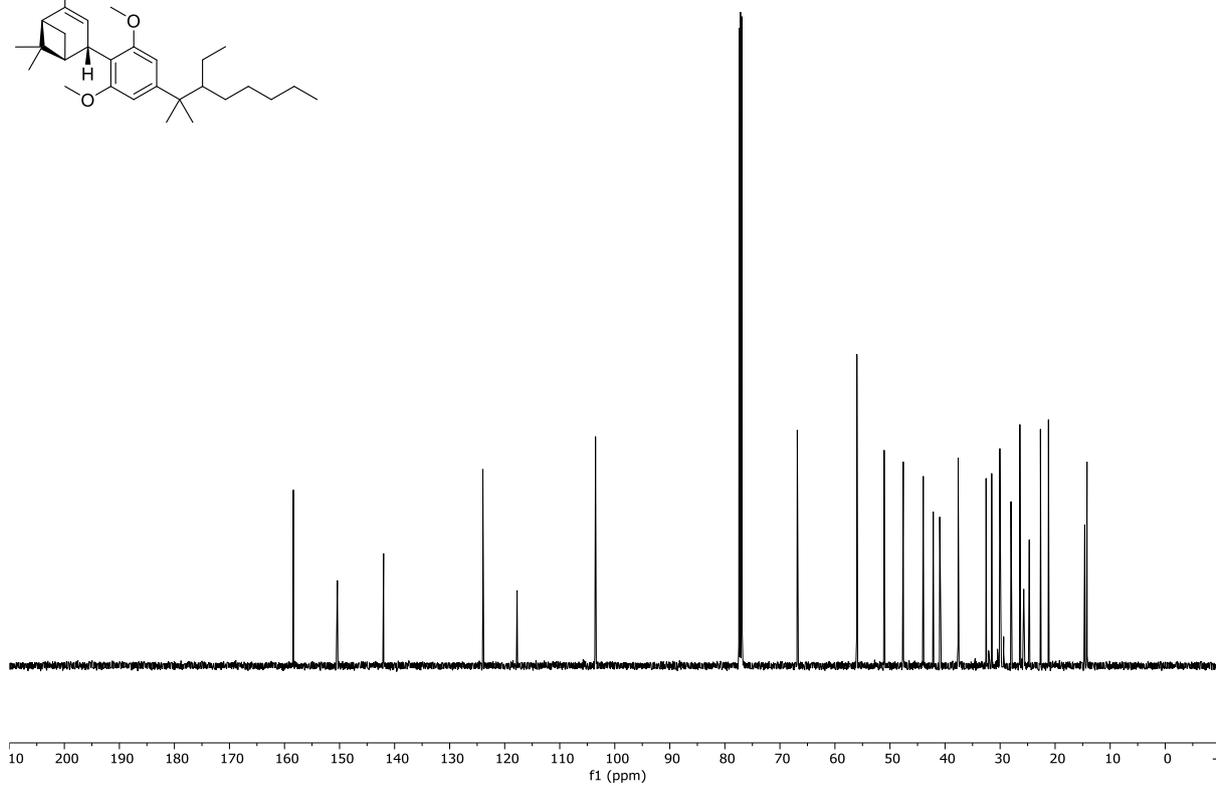
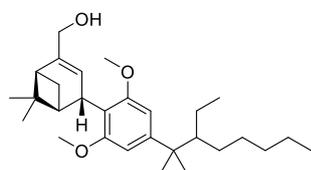
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**10c**



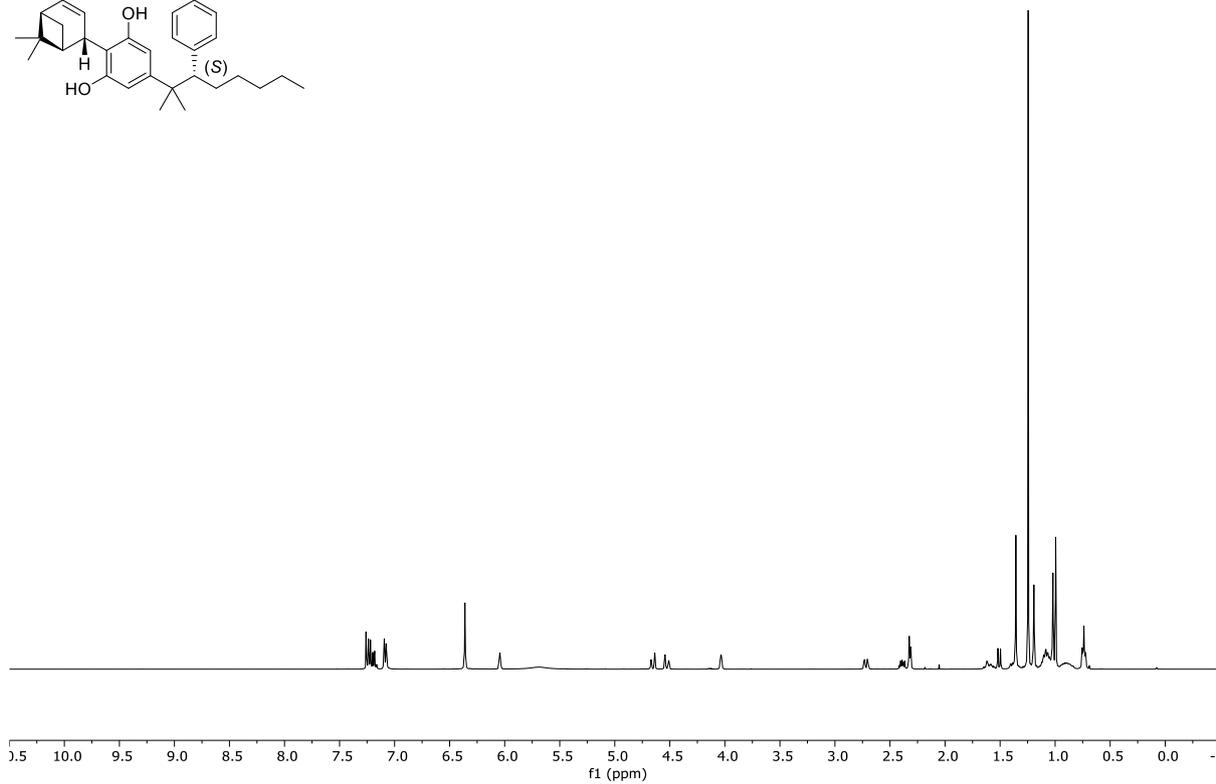
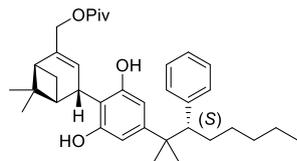
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**6c**



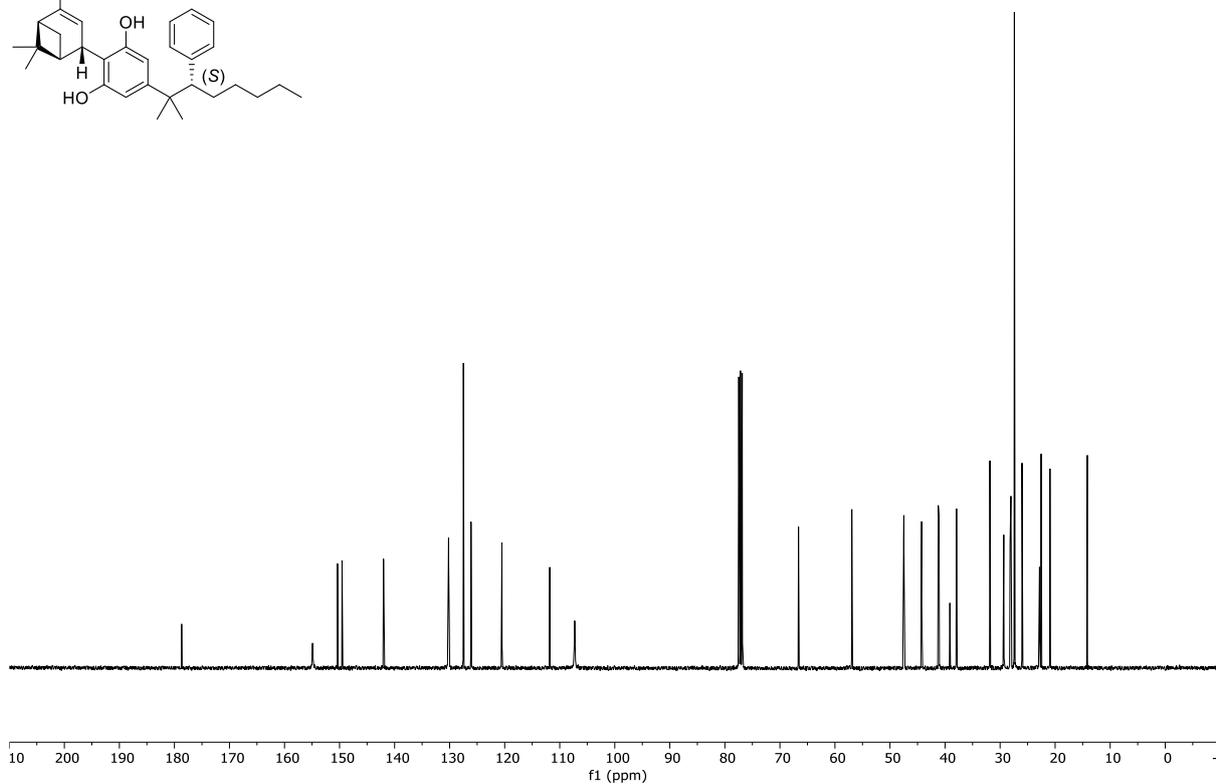
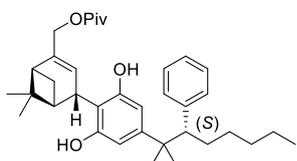
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S/R*)-**6c**



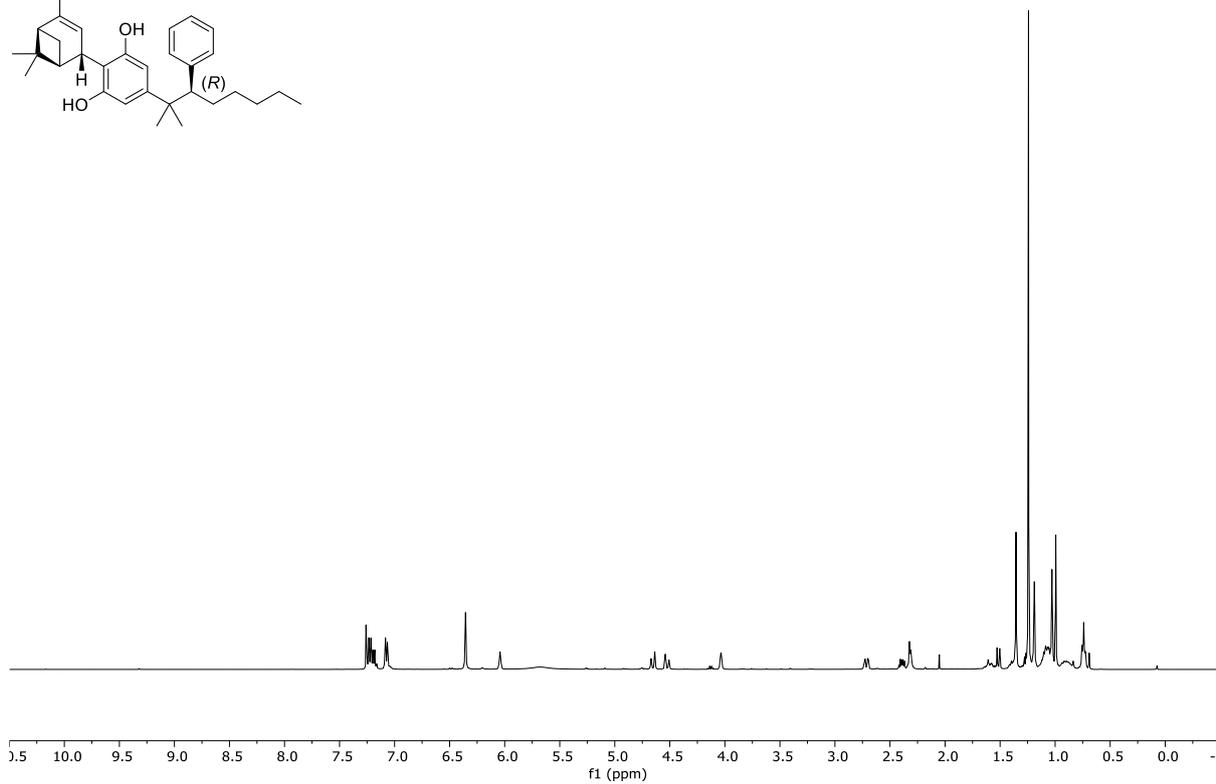
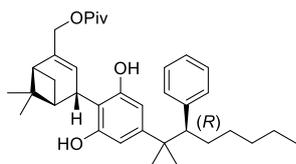
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of (*S*)-SI-20d



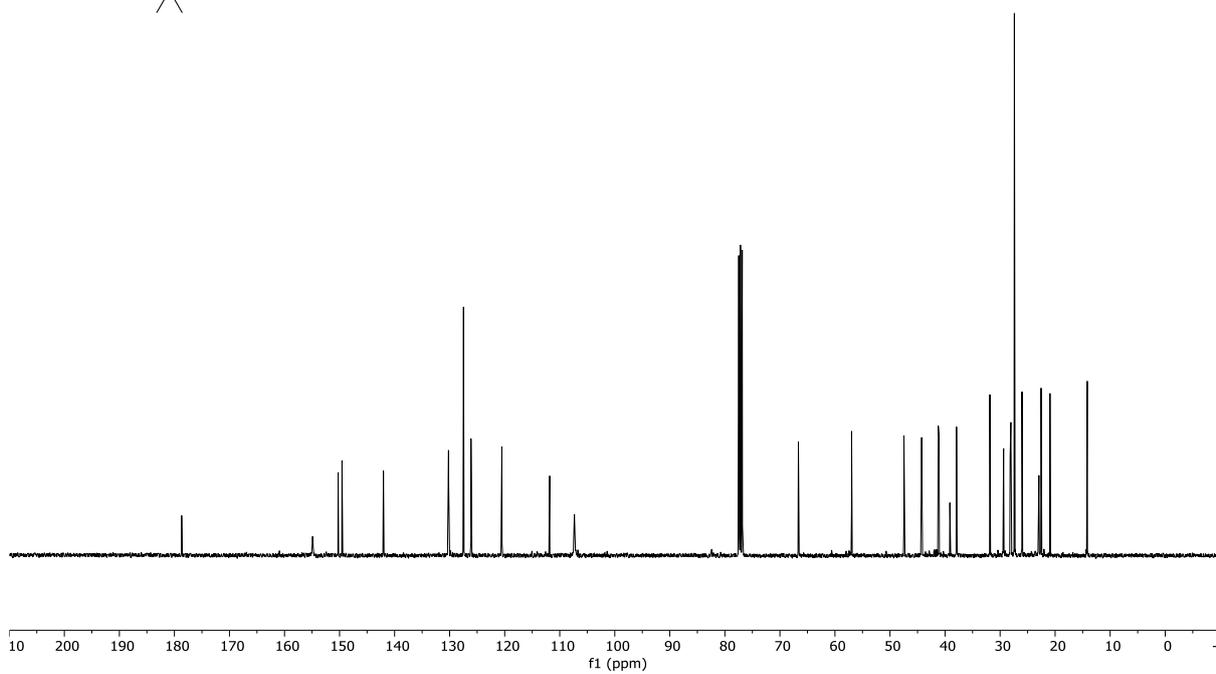
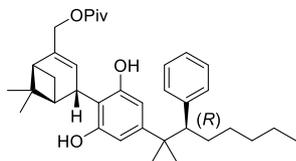
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of (*S*)-SI-20d



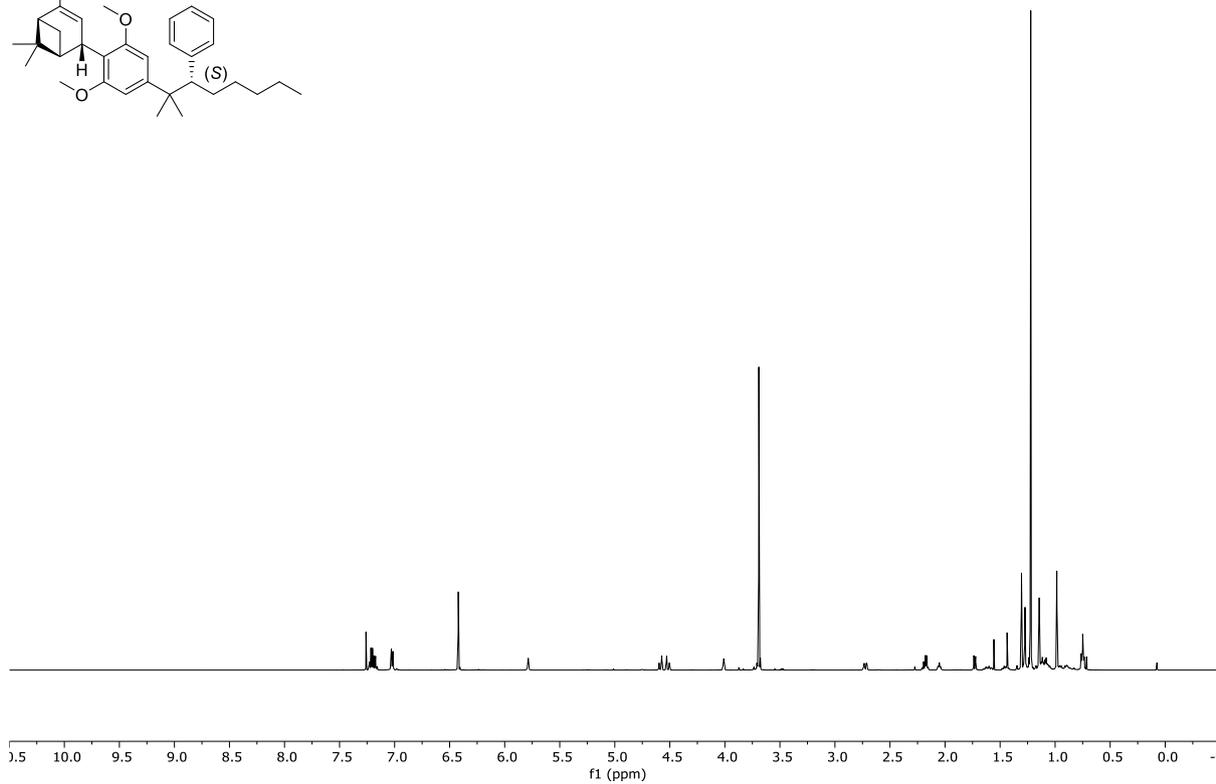
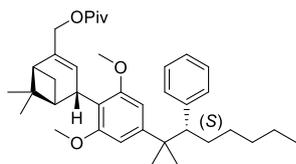
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*R*)-**SI-20d**



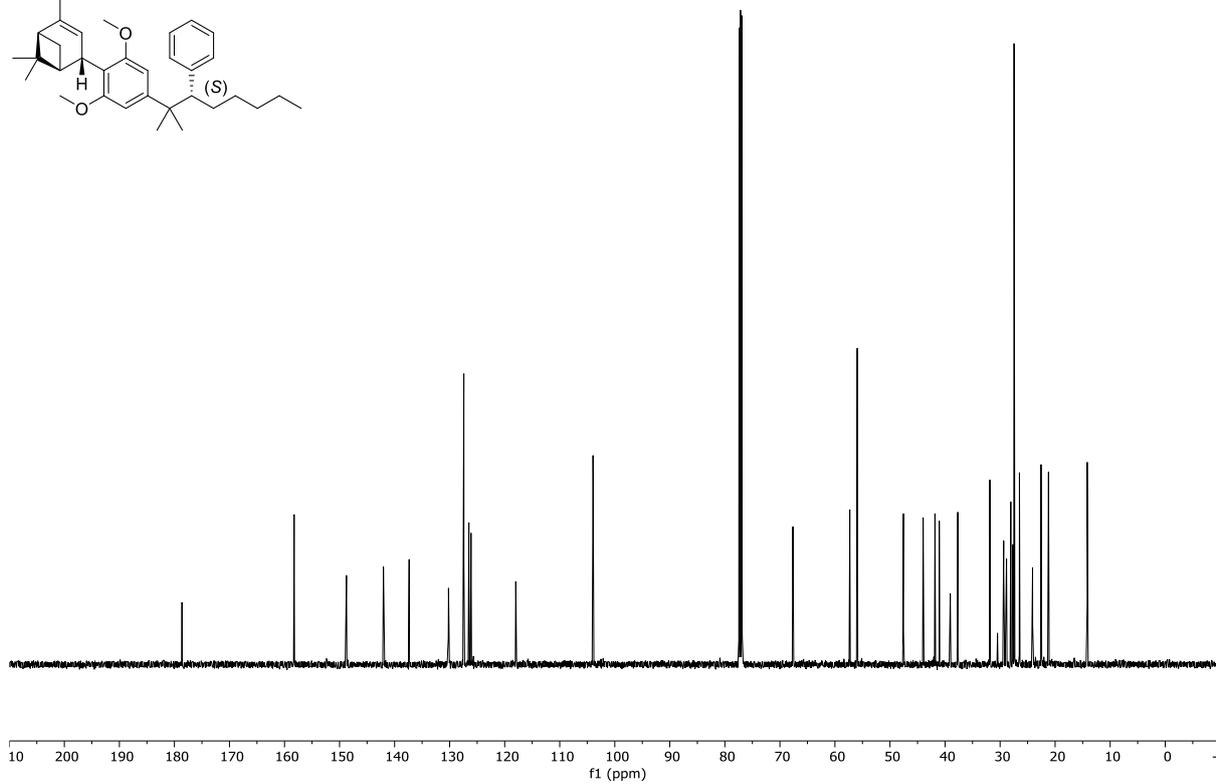
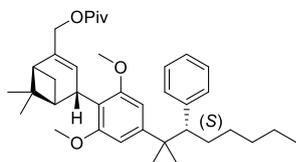
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*R*)-**SI-20d**



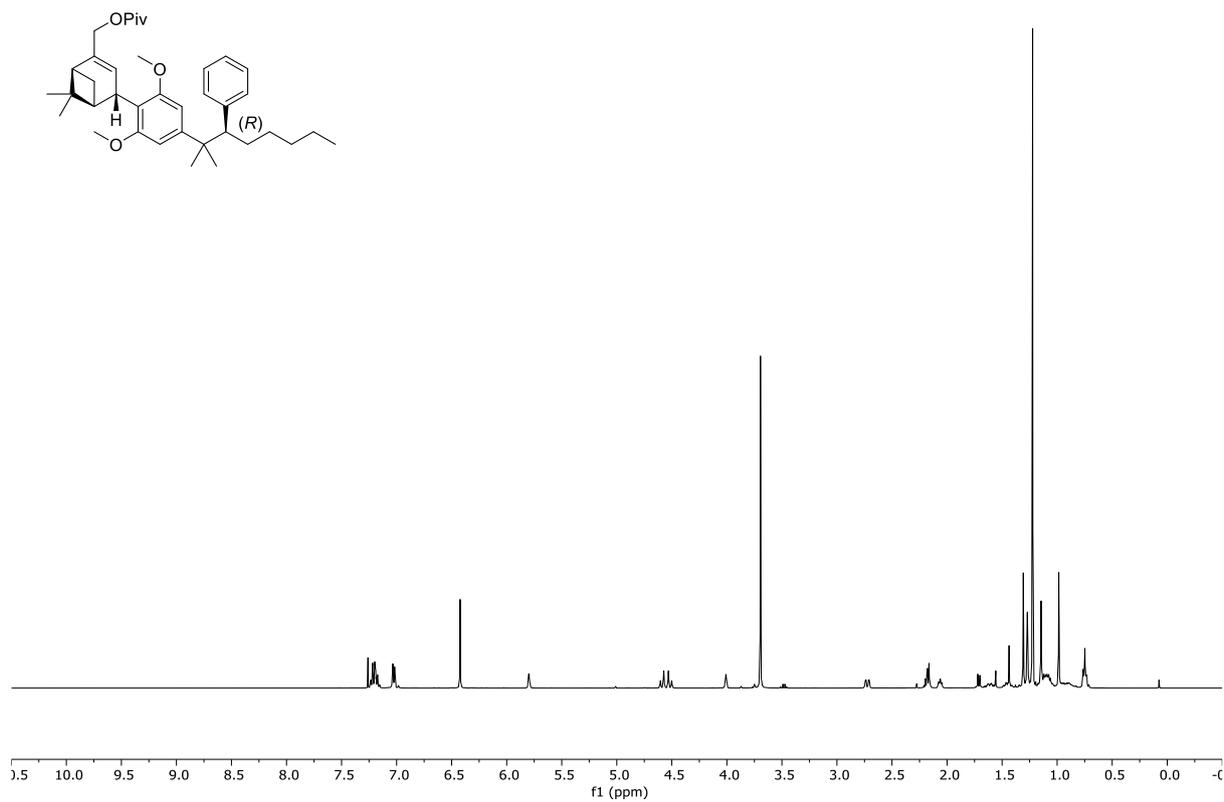
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (*S*)-**10d**



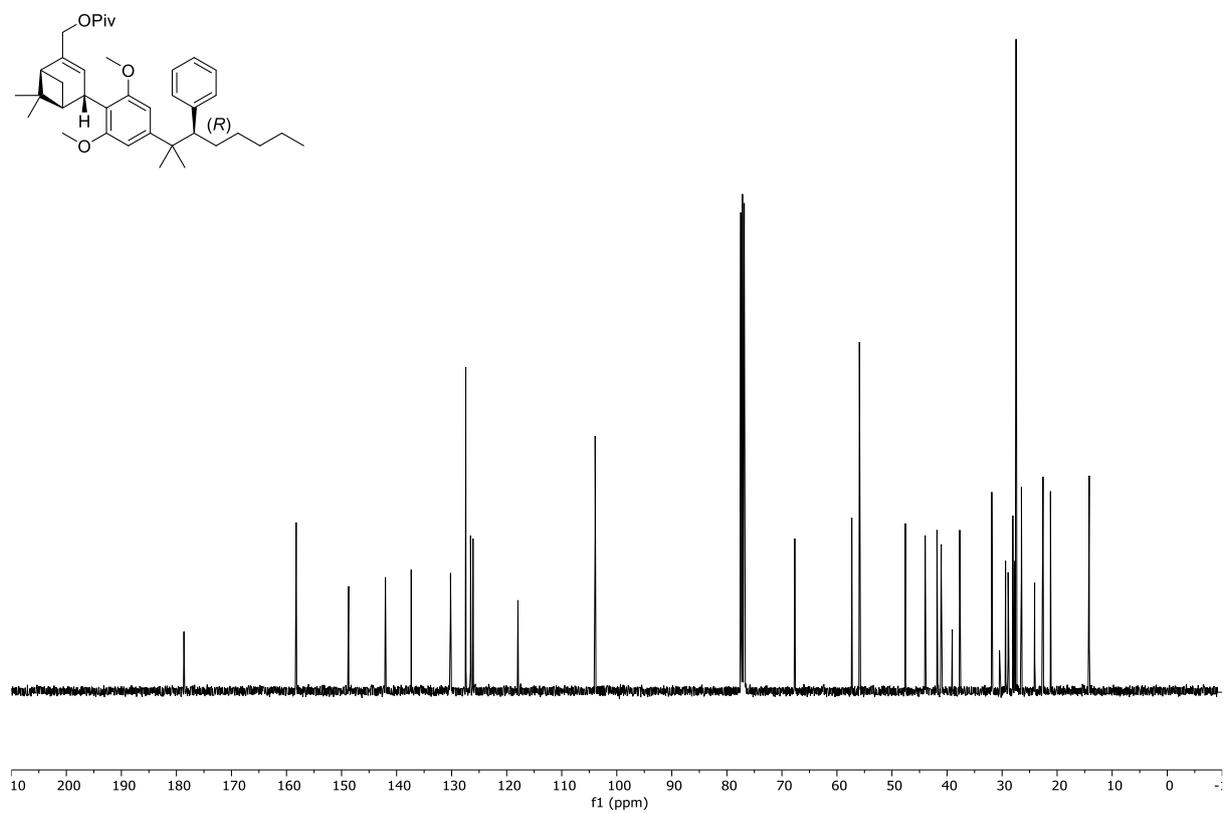
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) of (*S*)-**10d**



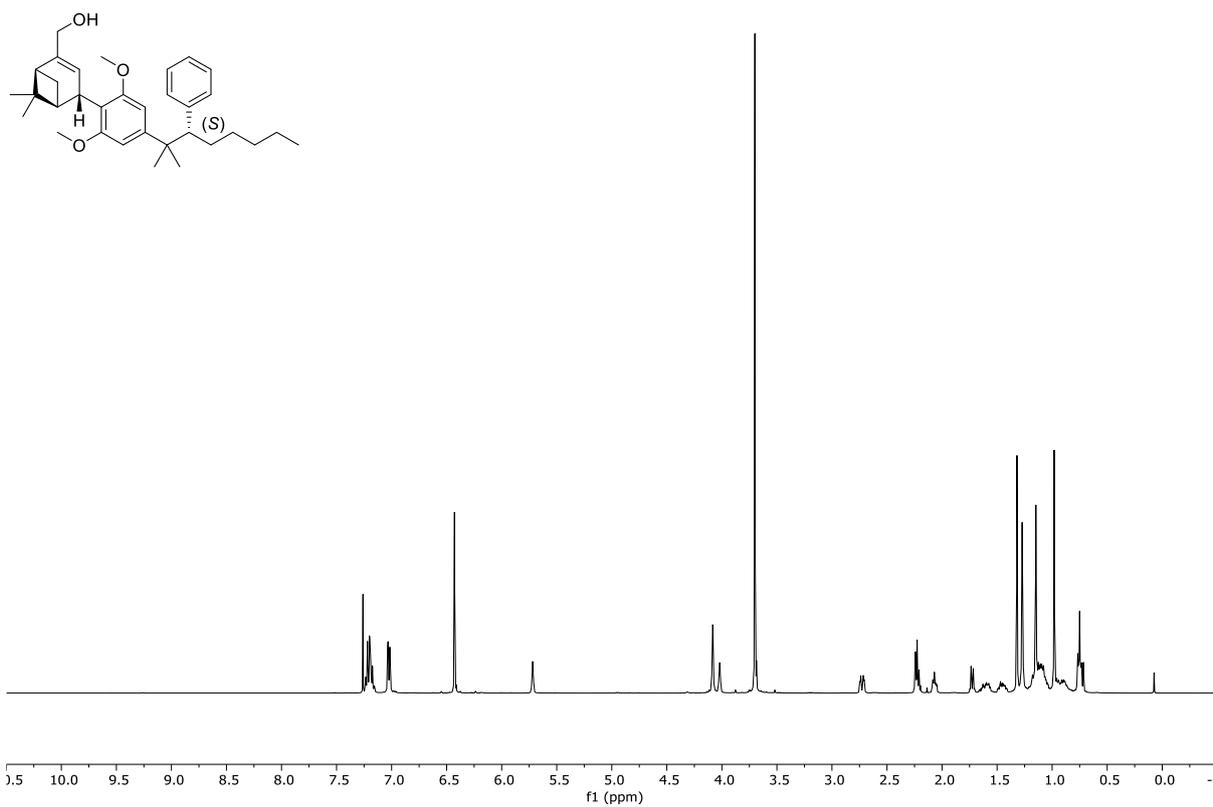
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*R*)-**10d**



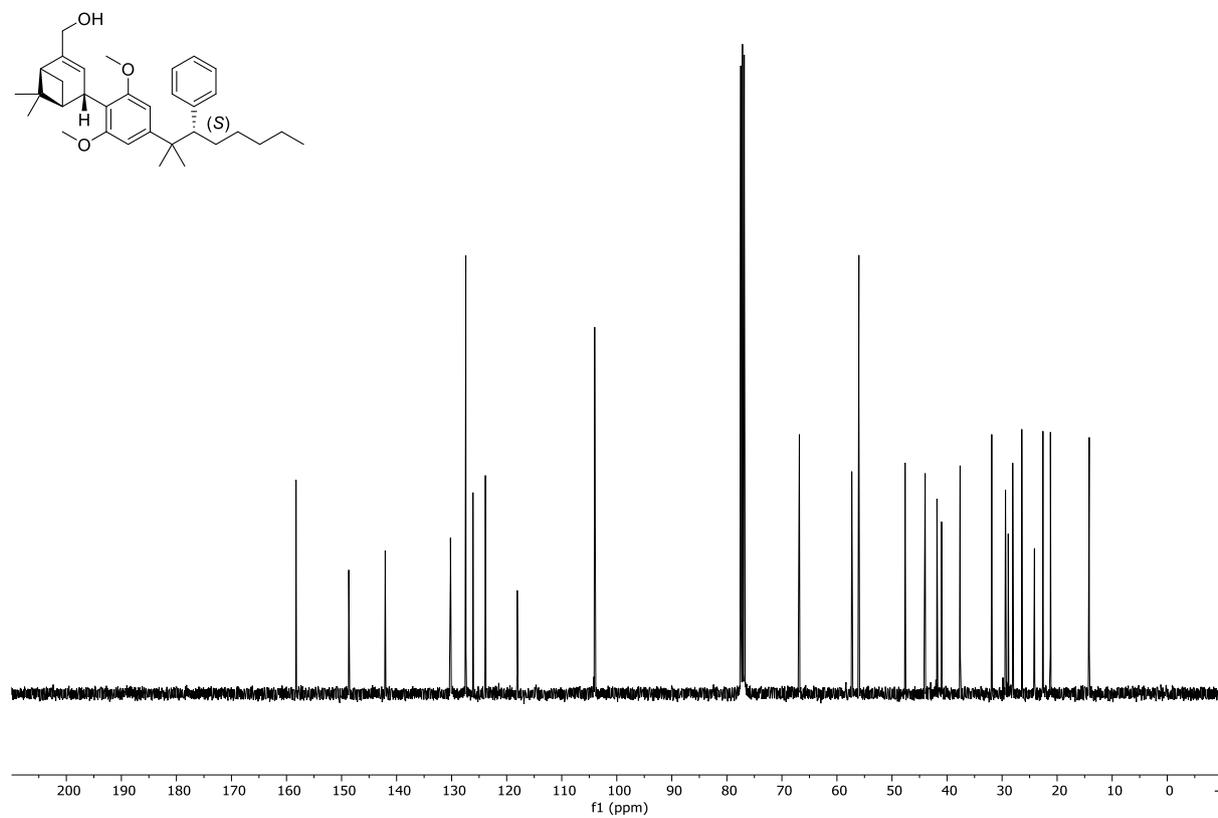
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*R*)-**10d**



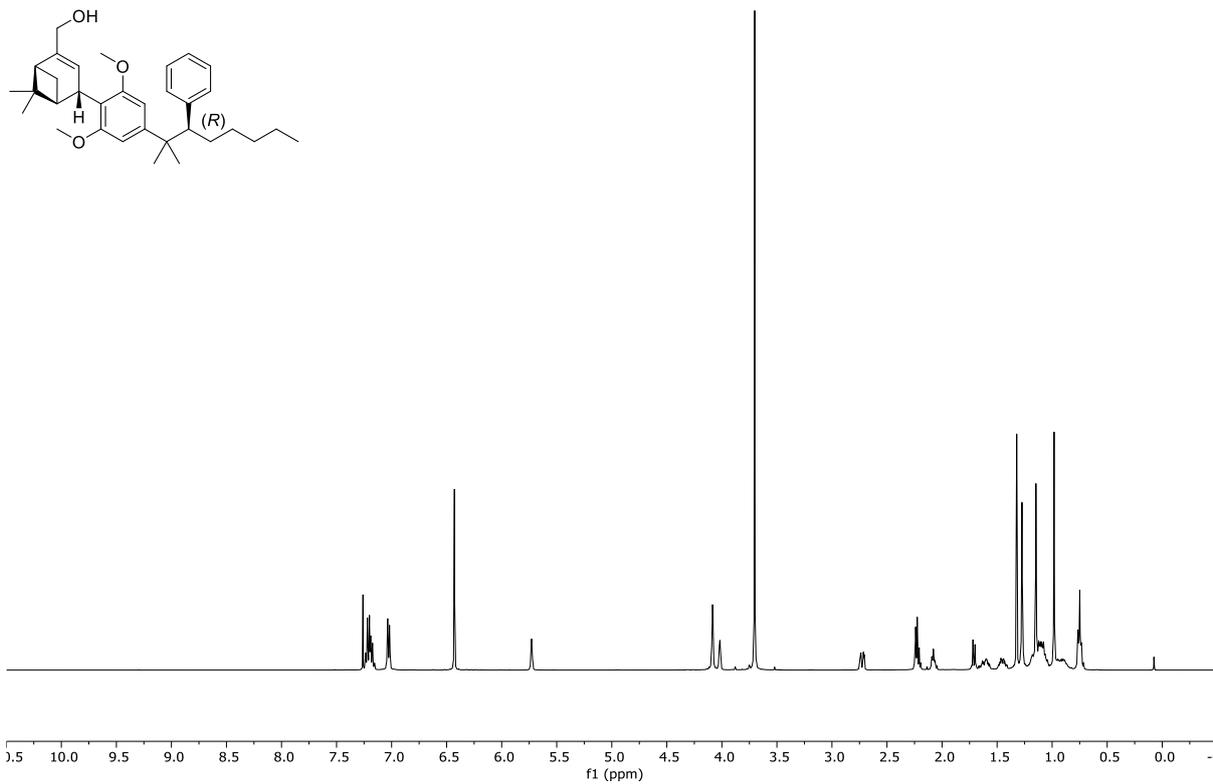
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S*)-**6d**



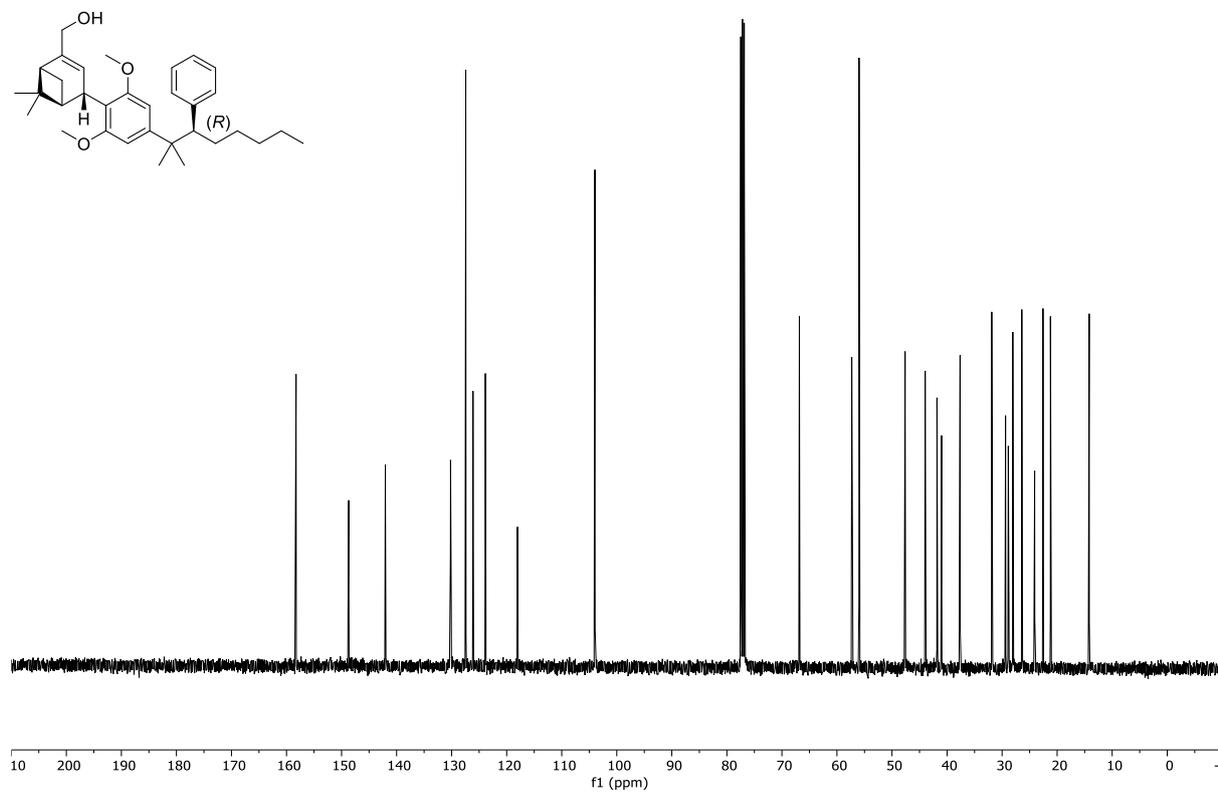
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S*)-**6d**



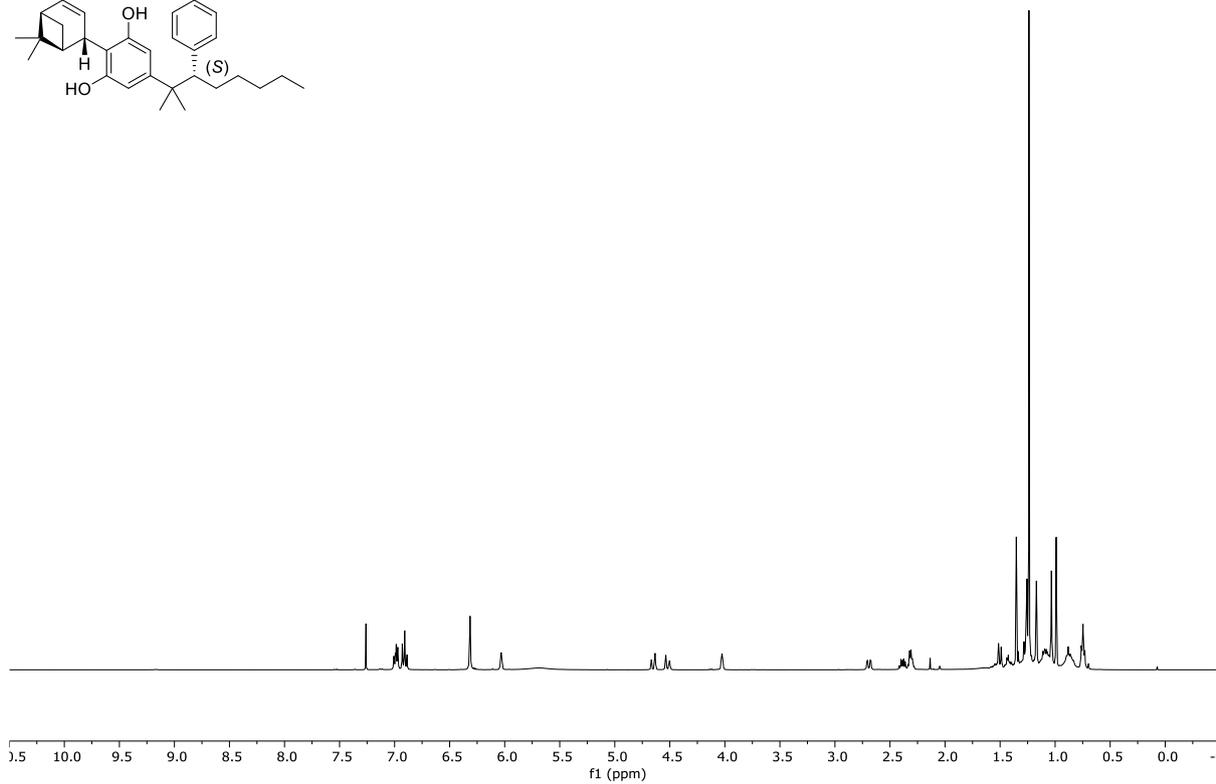
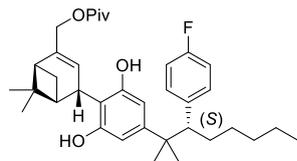
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*R*)-**6d**



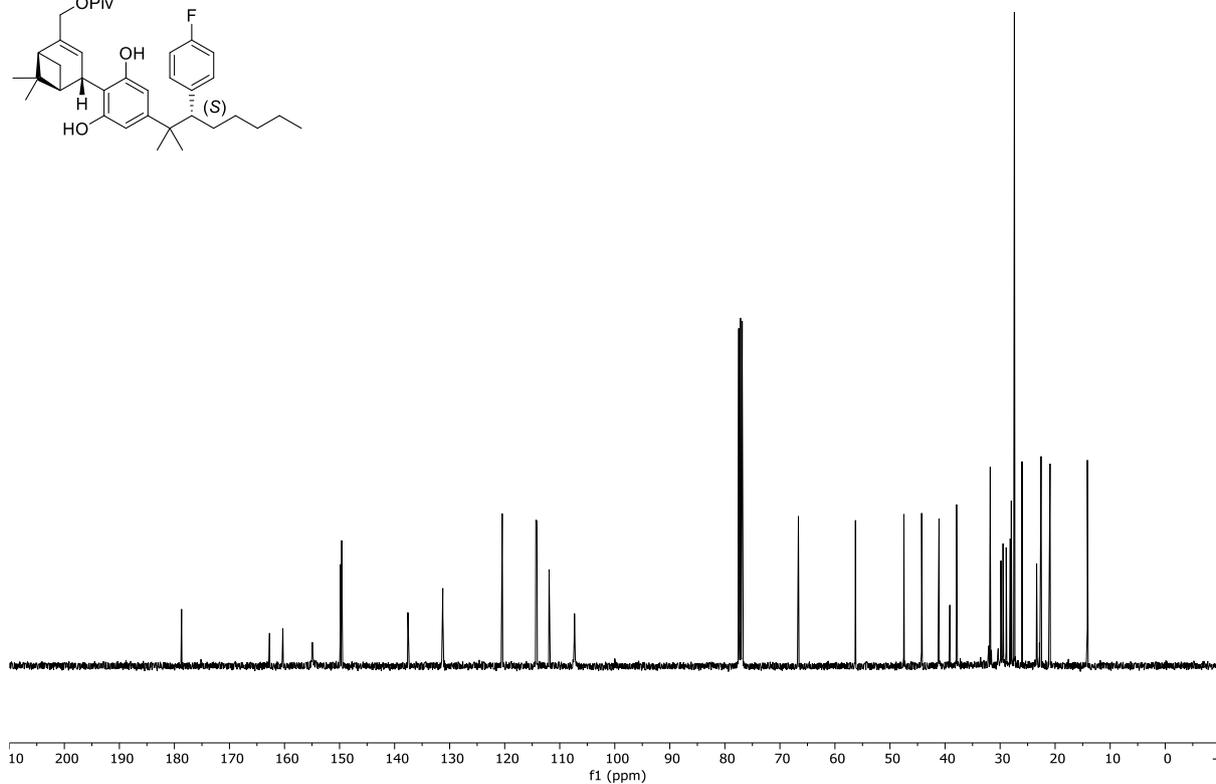
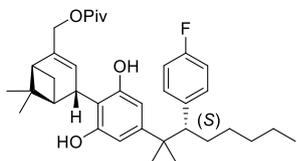
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*R*)-**6d**



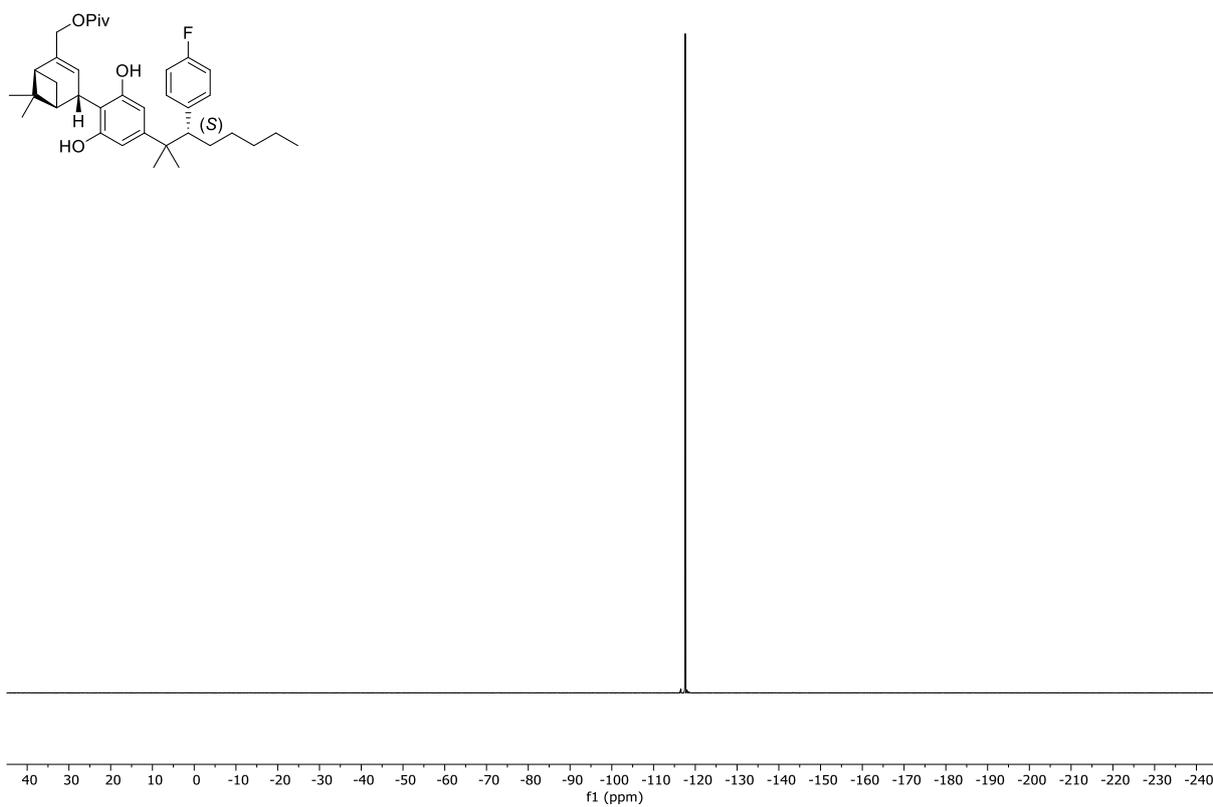
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S*)-**SI-20e**



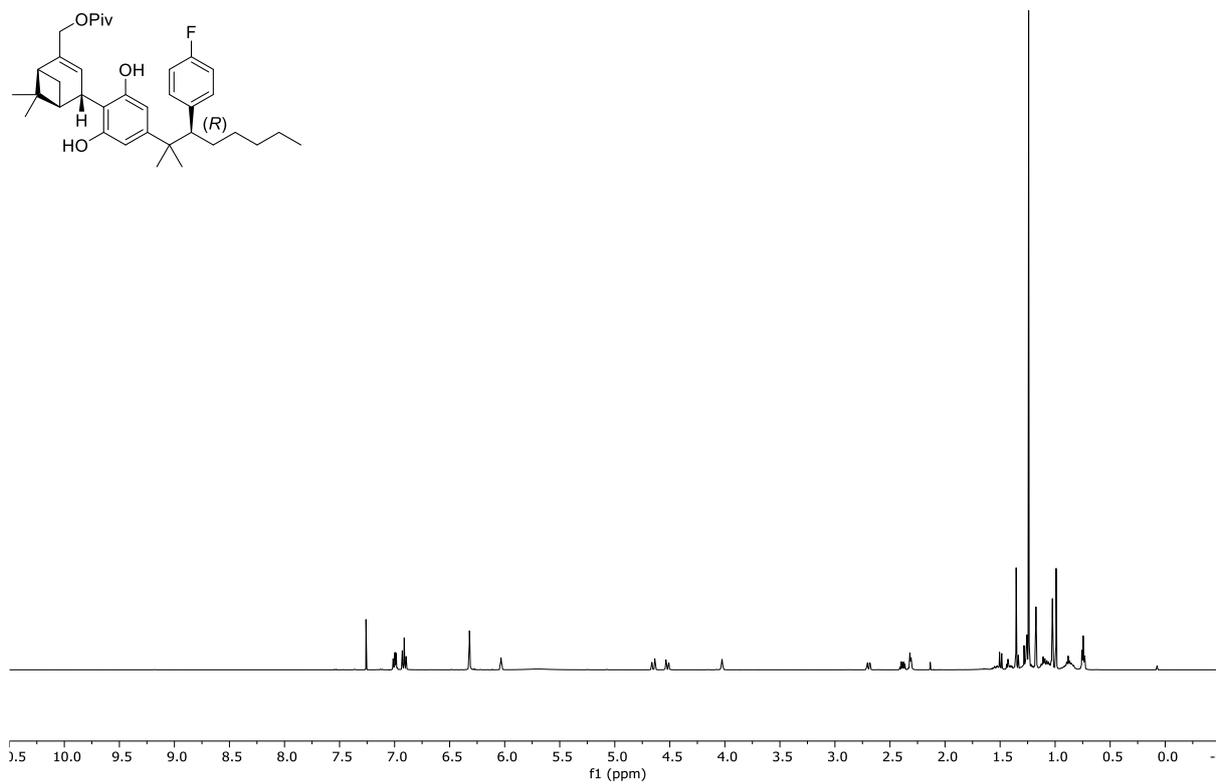
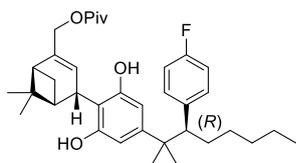
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S*)-**SI-20e**



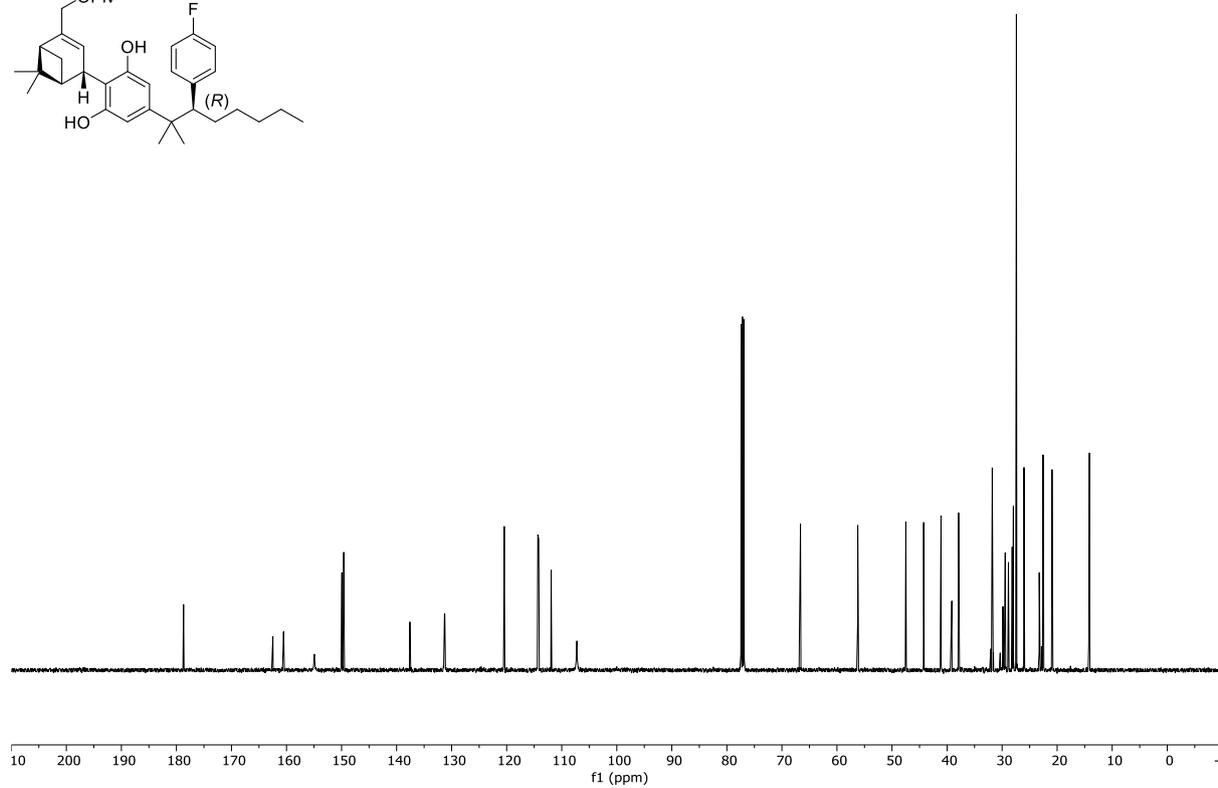
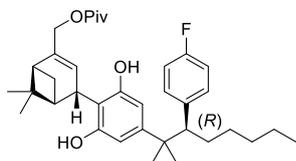
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of (*S*)-**SI-20e**



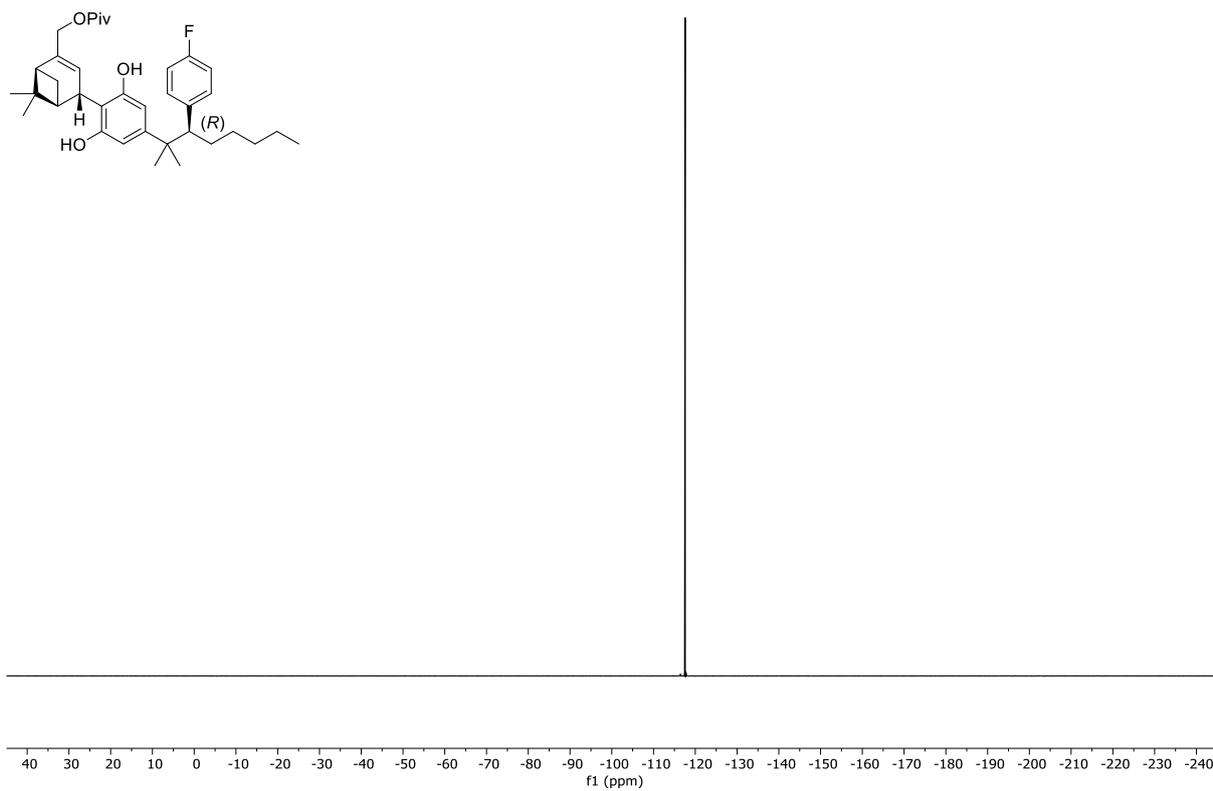
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) of (*R*)-**SI-20e**



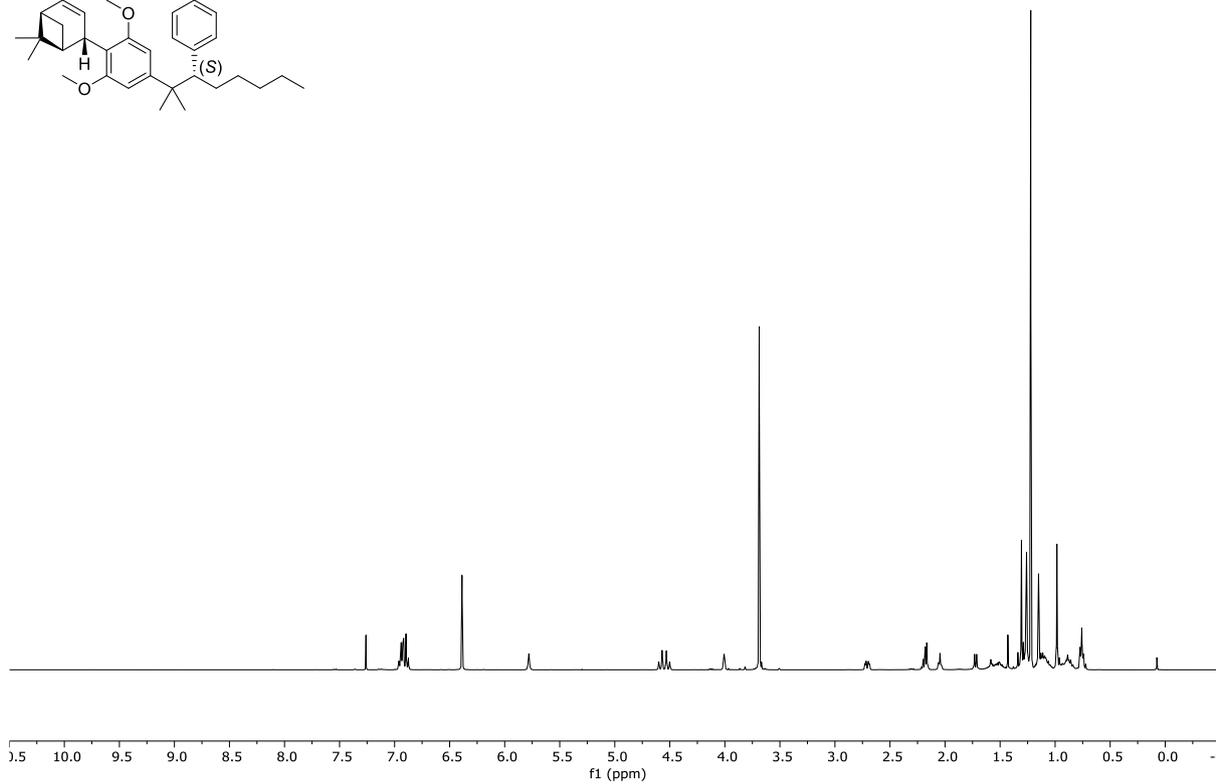
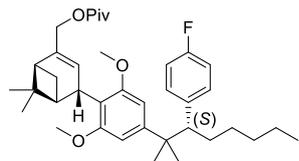
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) of (*R*)-**SI-20e**



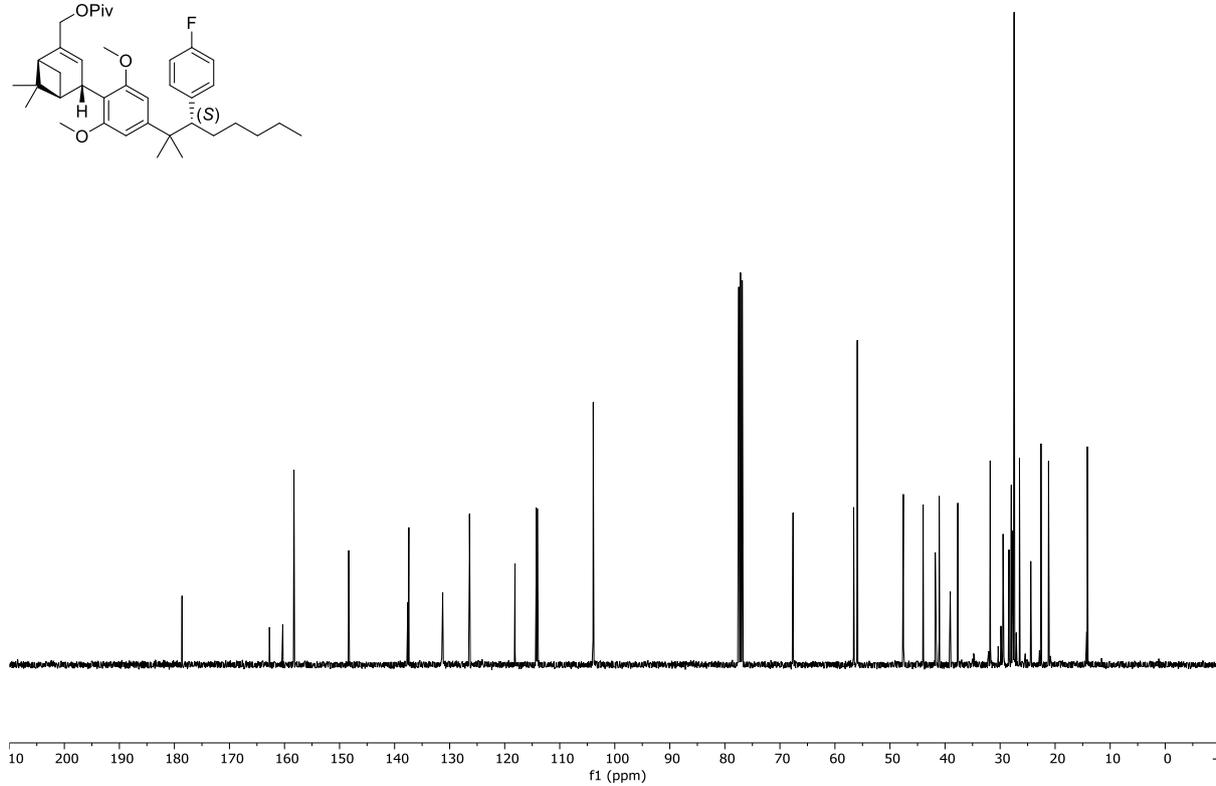
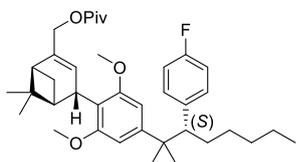
$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ) of (*R*)-**SI-20e**



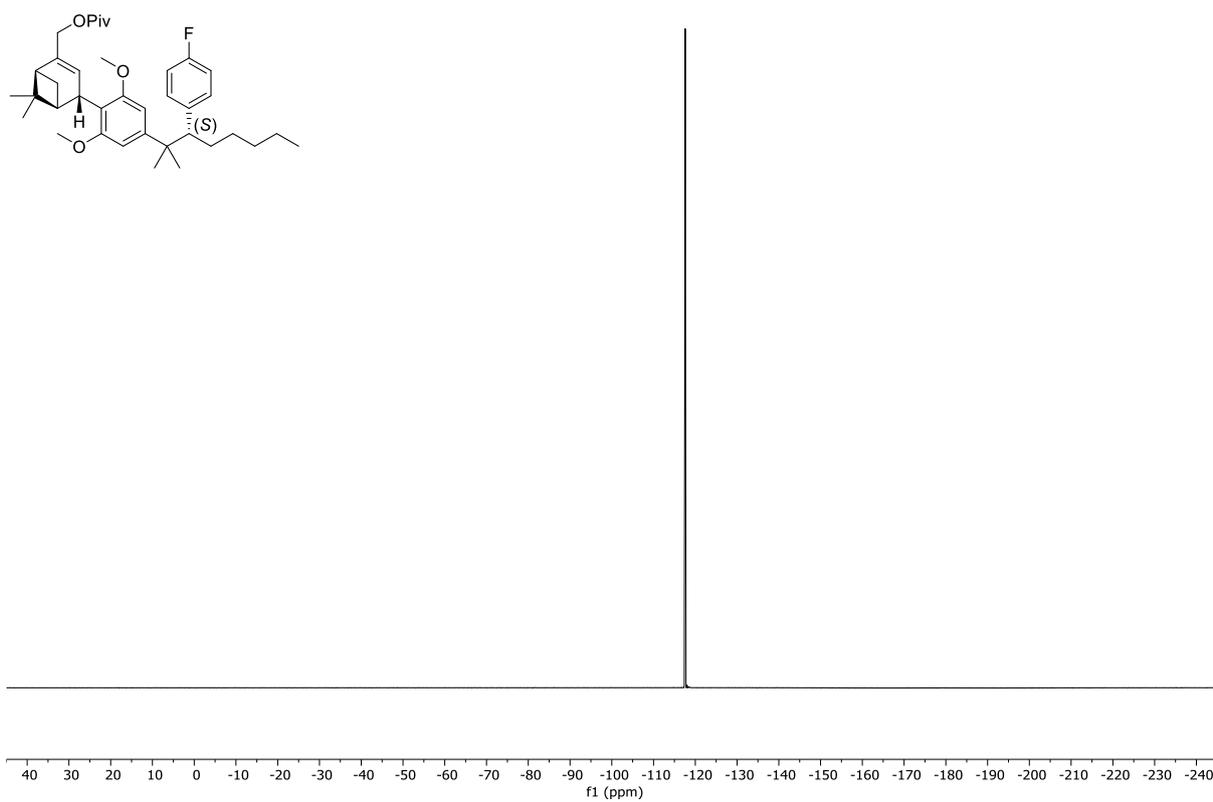
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S*)-**10e**



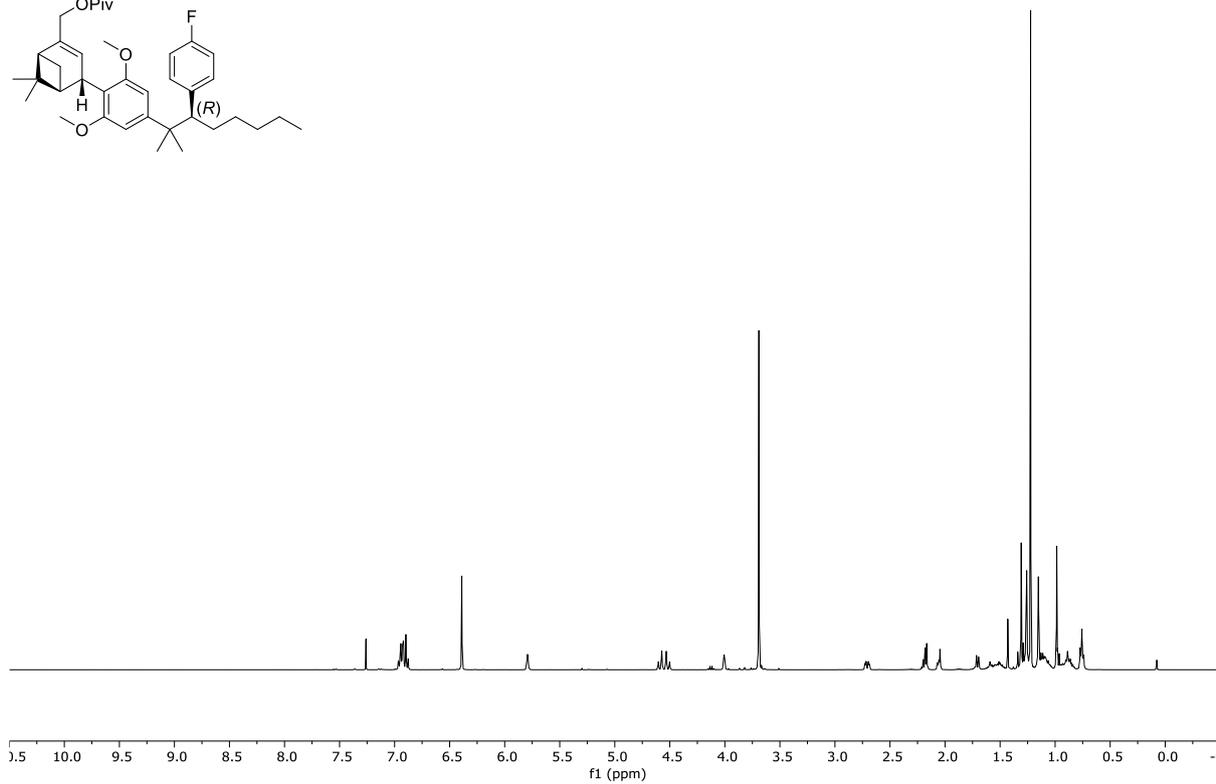
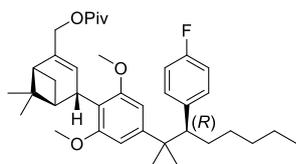
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S*)-**10e**



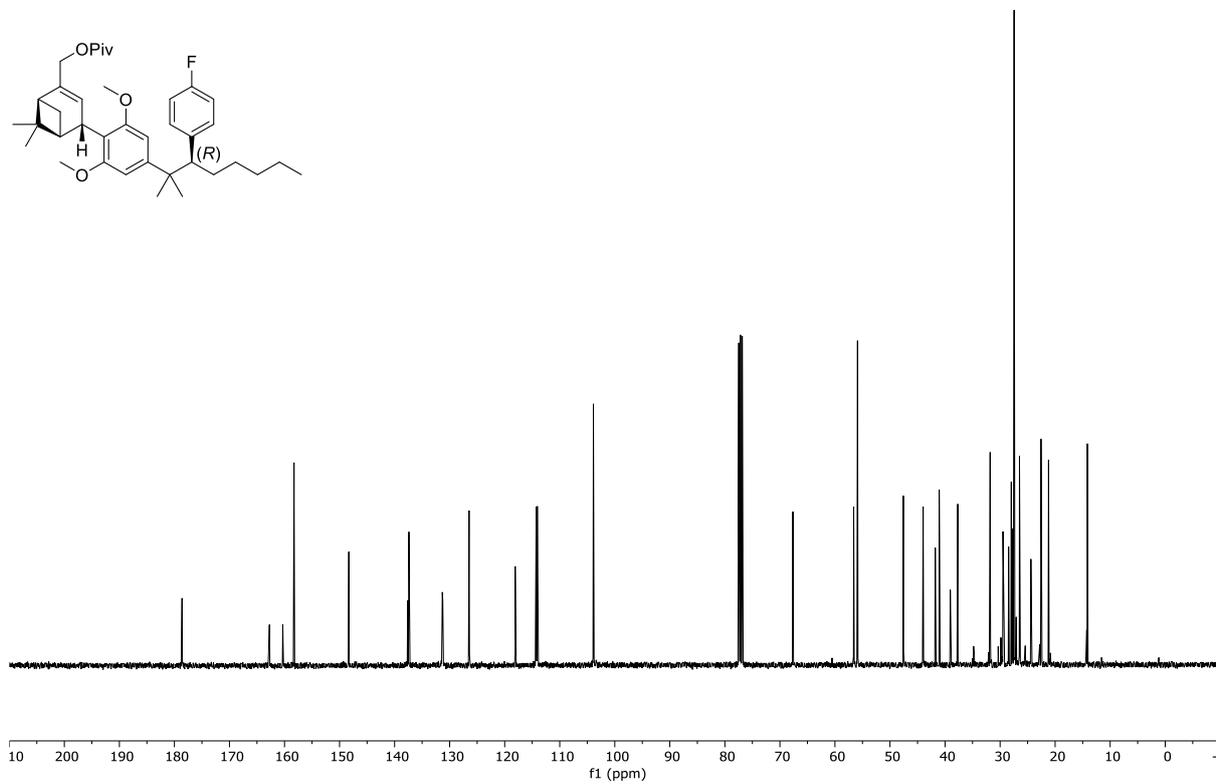
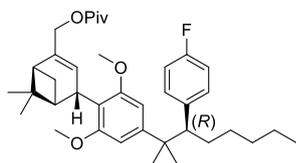
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of (*S*)-**10e**



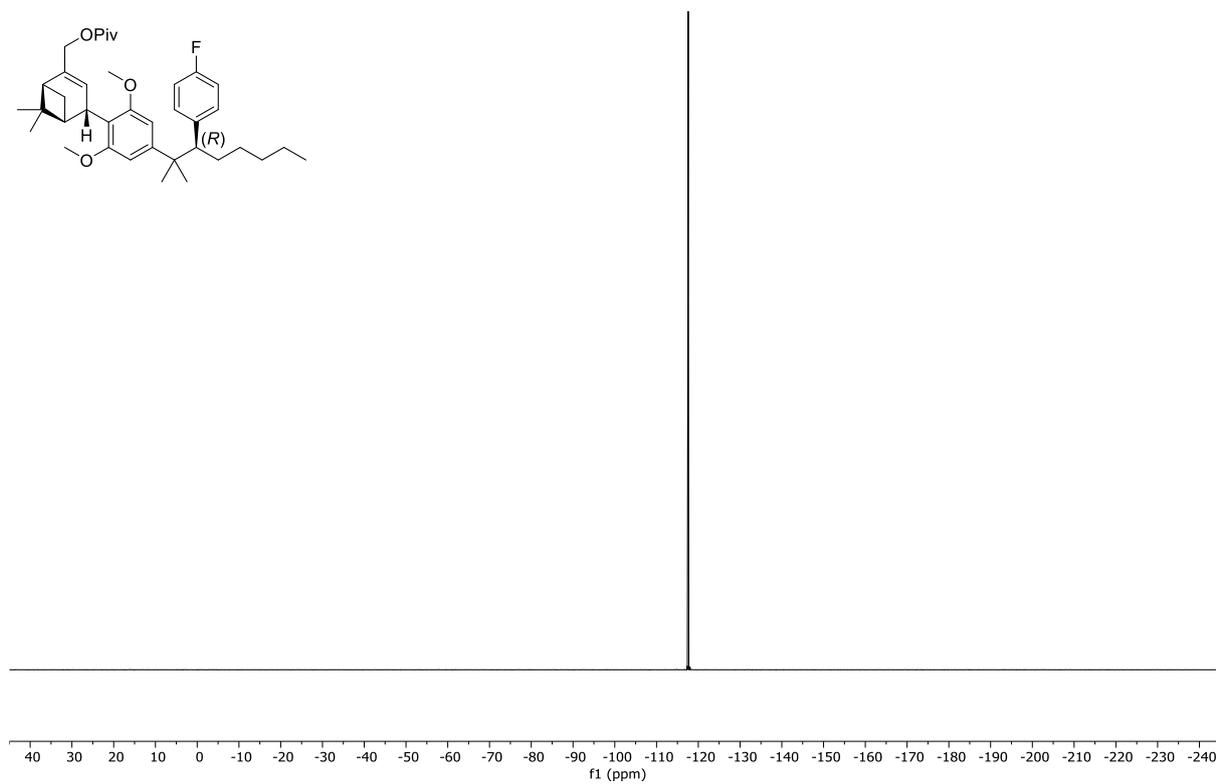
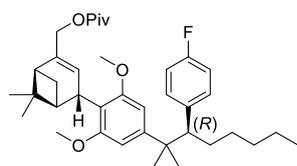
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*R*)-**10e**



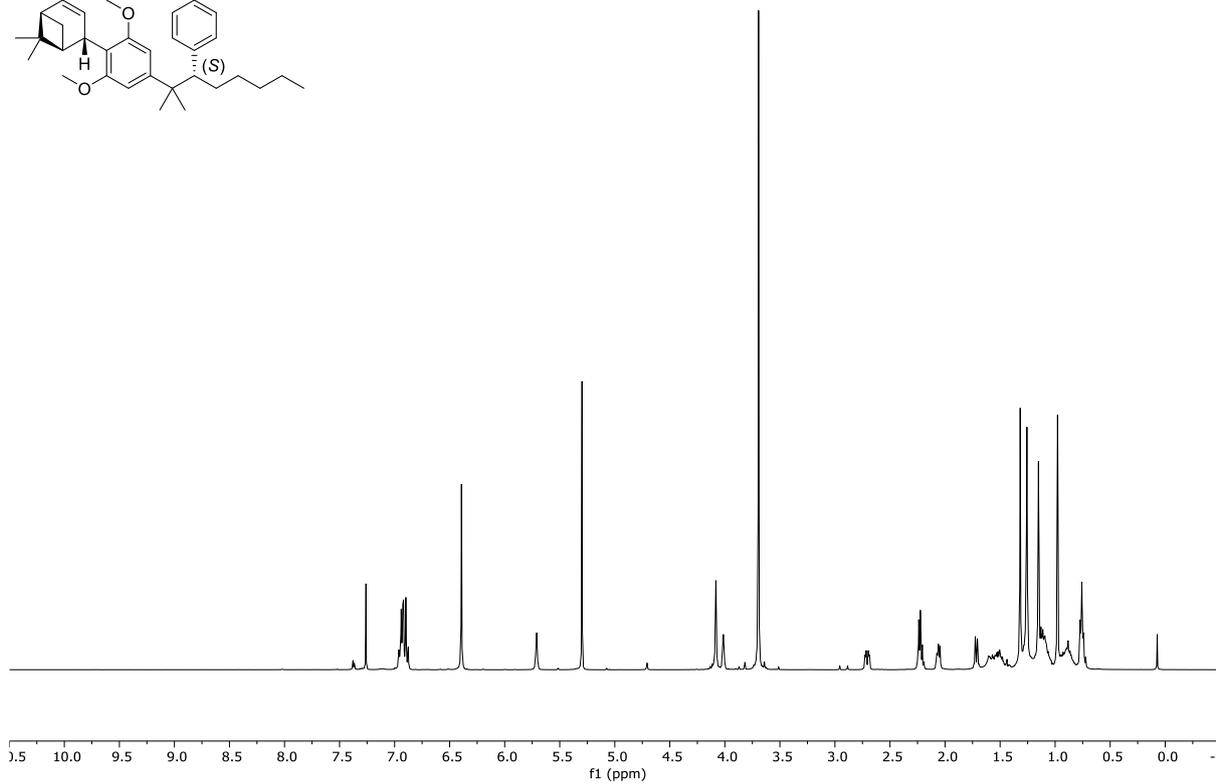
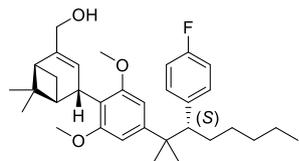
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*R*)-**10e**



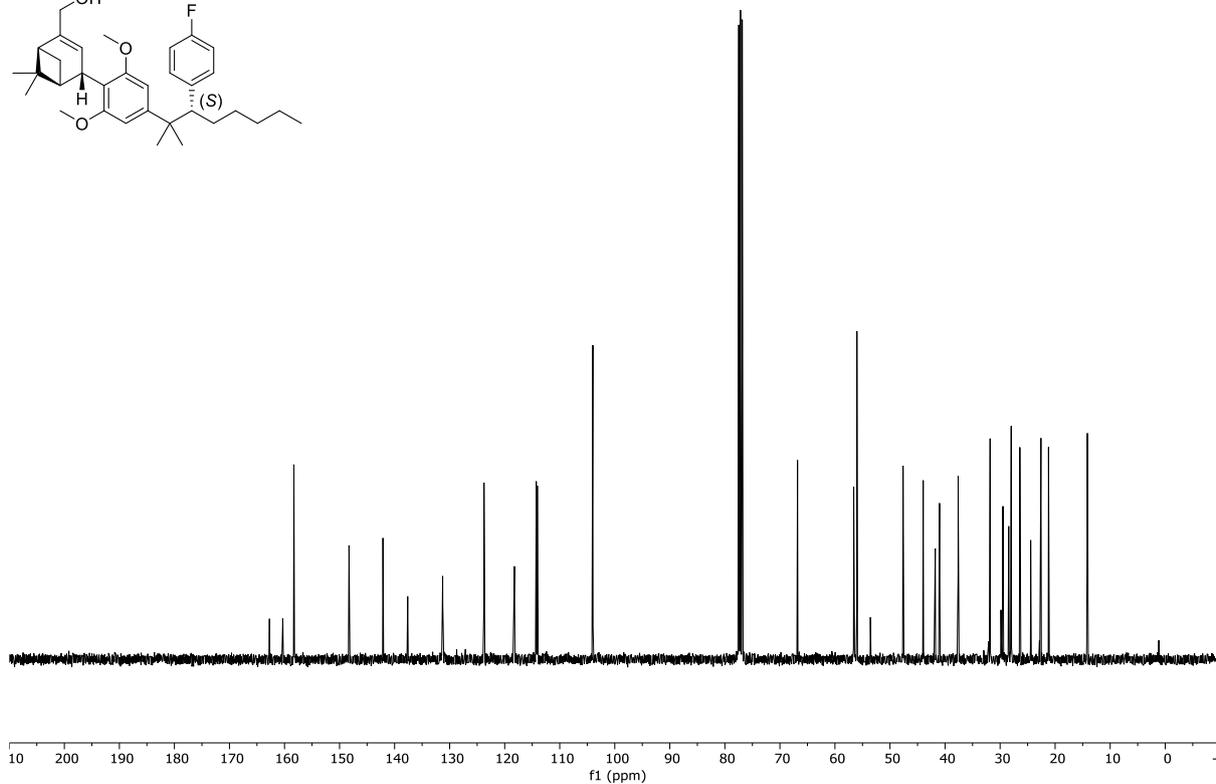
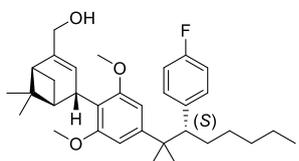
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of (*R*)-**10e**



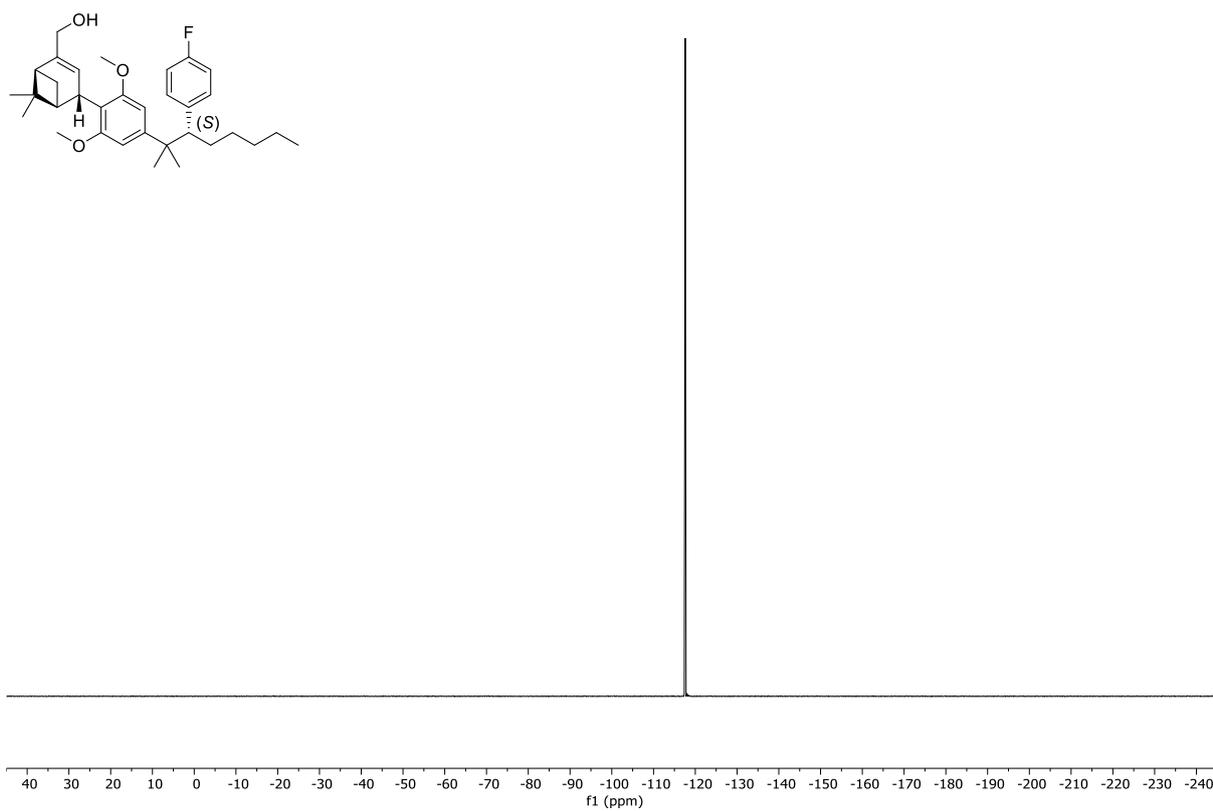
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S*)-**6e**



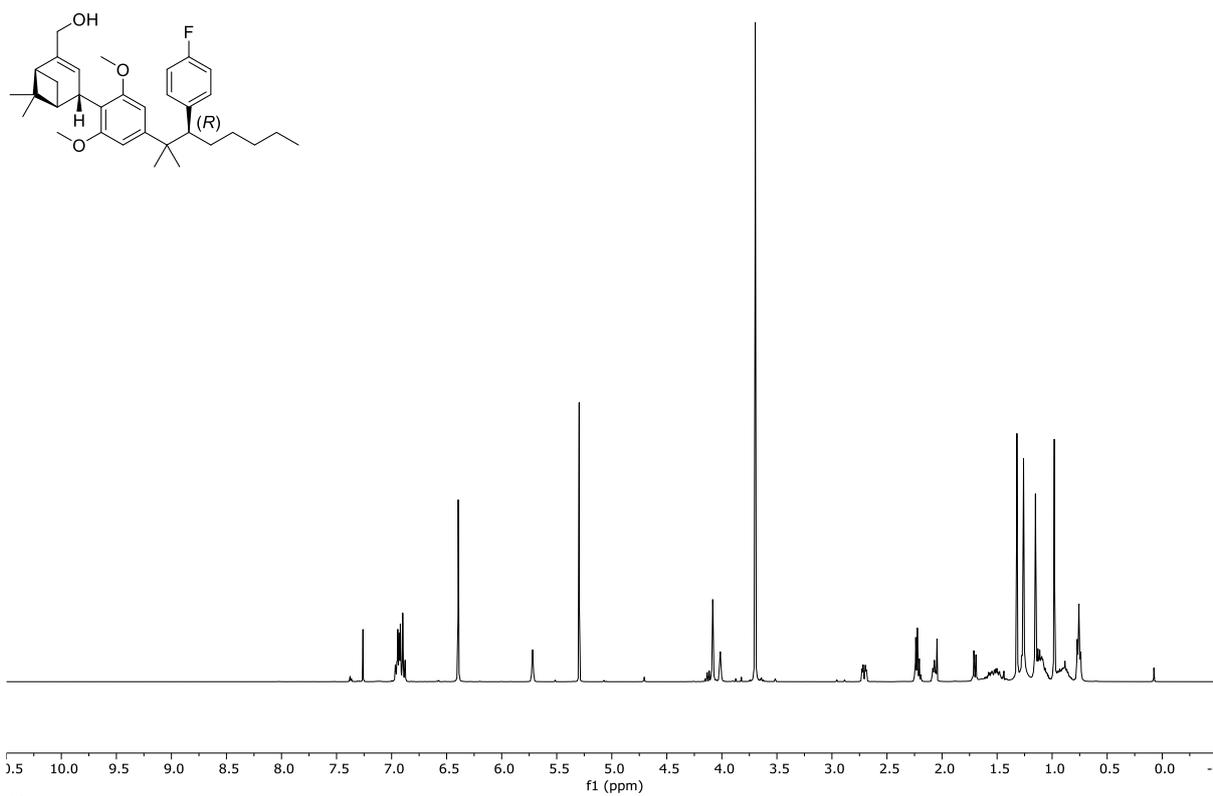
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S*)-**6e**



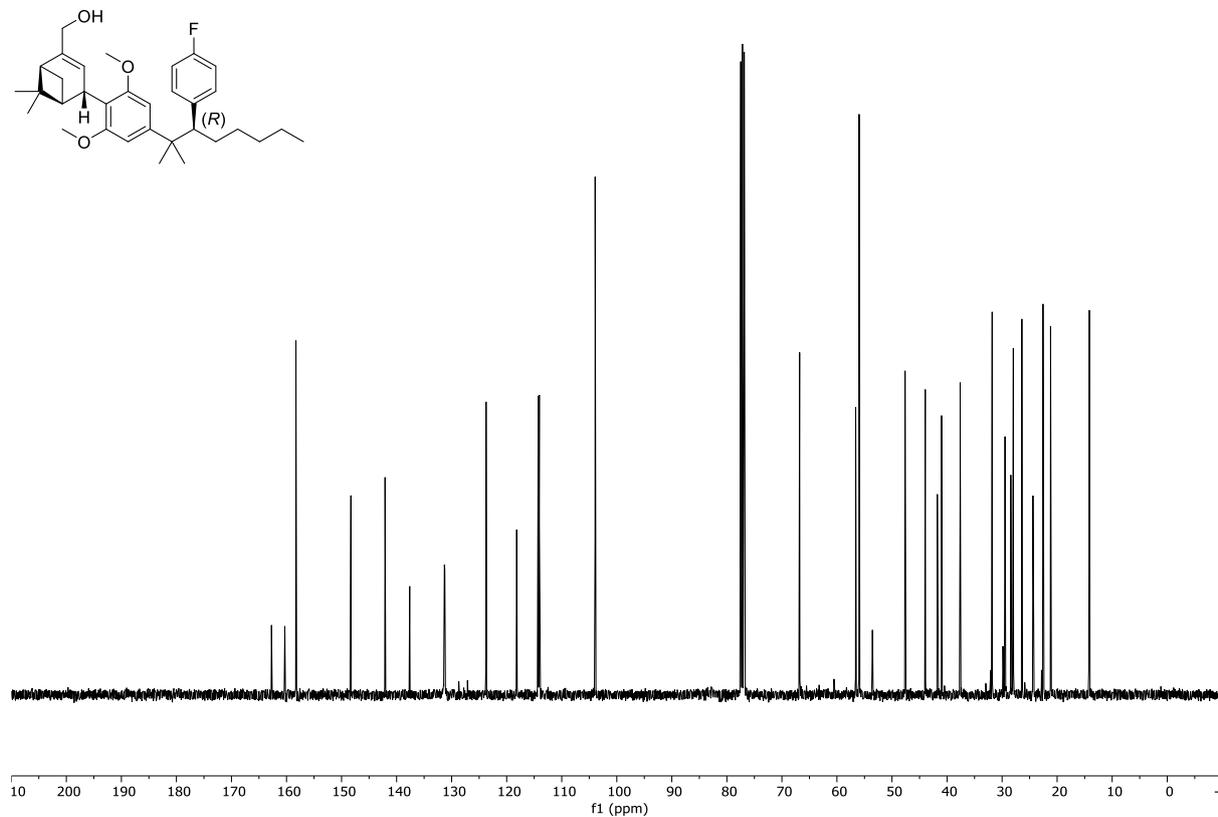
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of (*S*)-**6e**



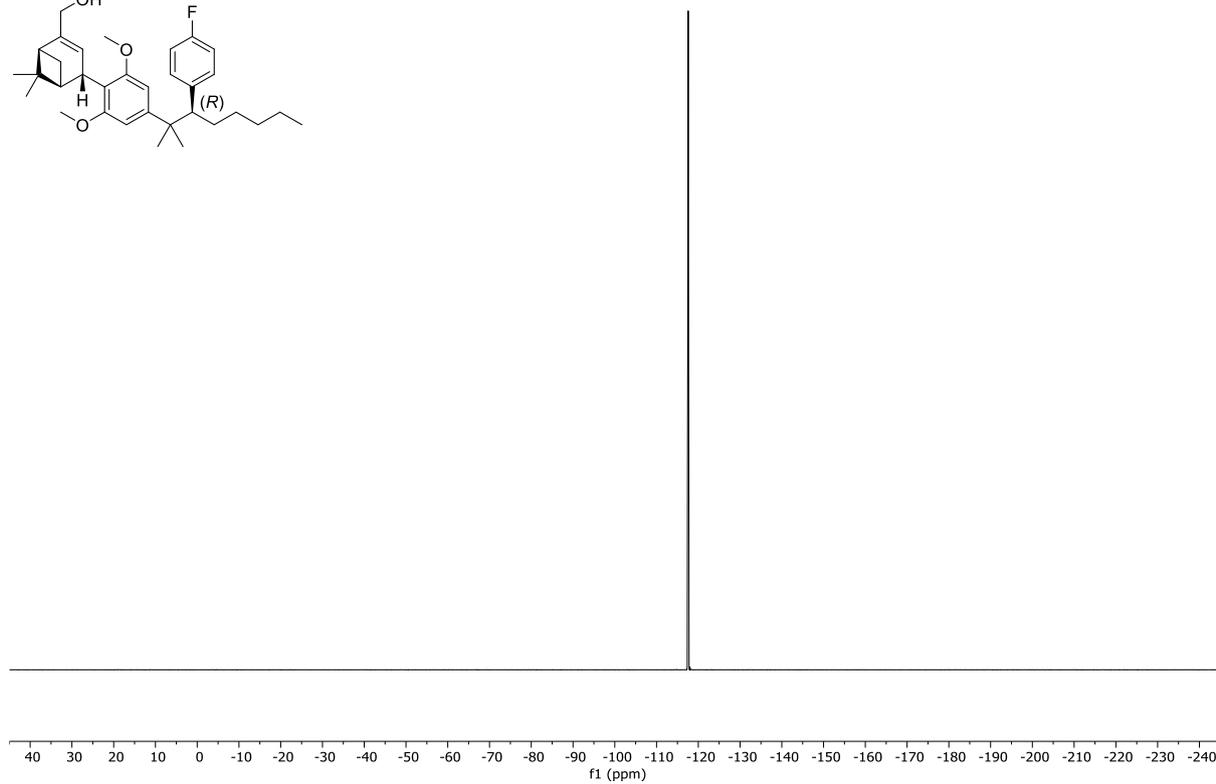
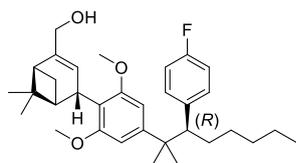
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*R*)-**6e**



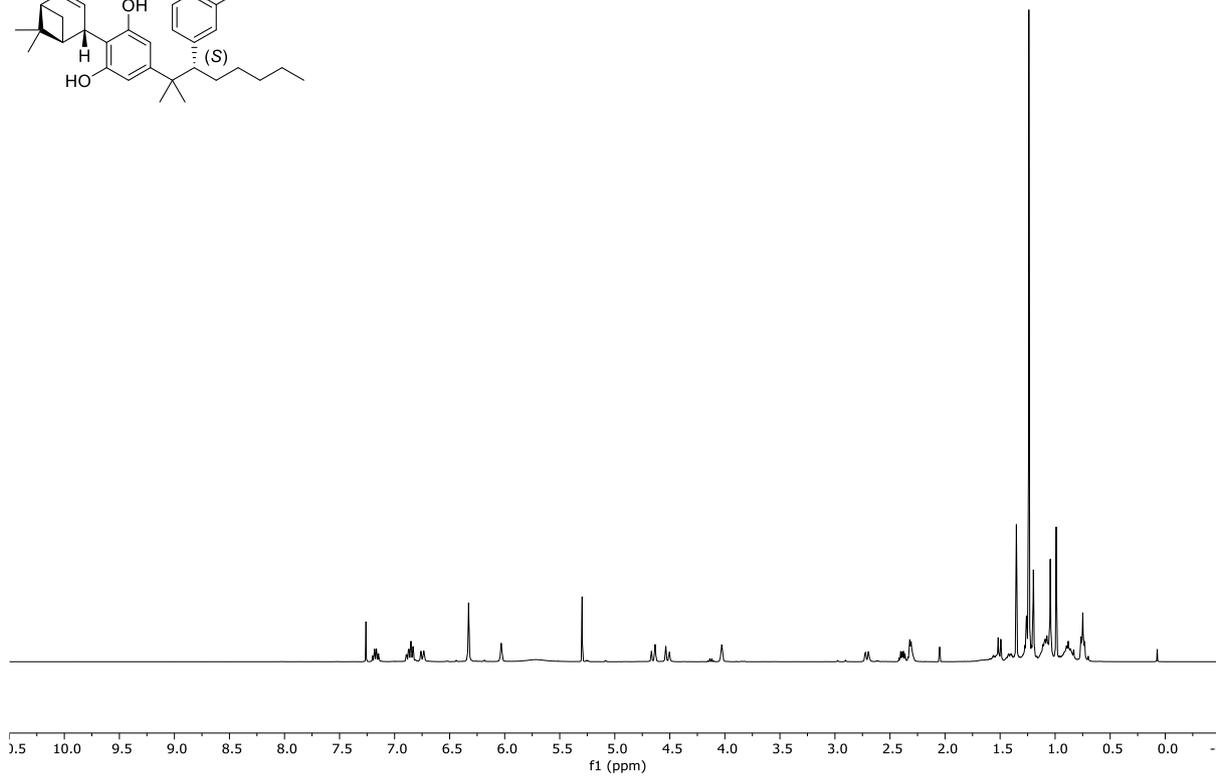
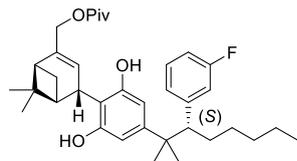
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*R*)-**6e**



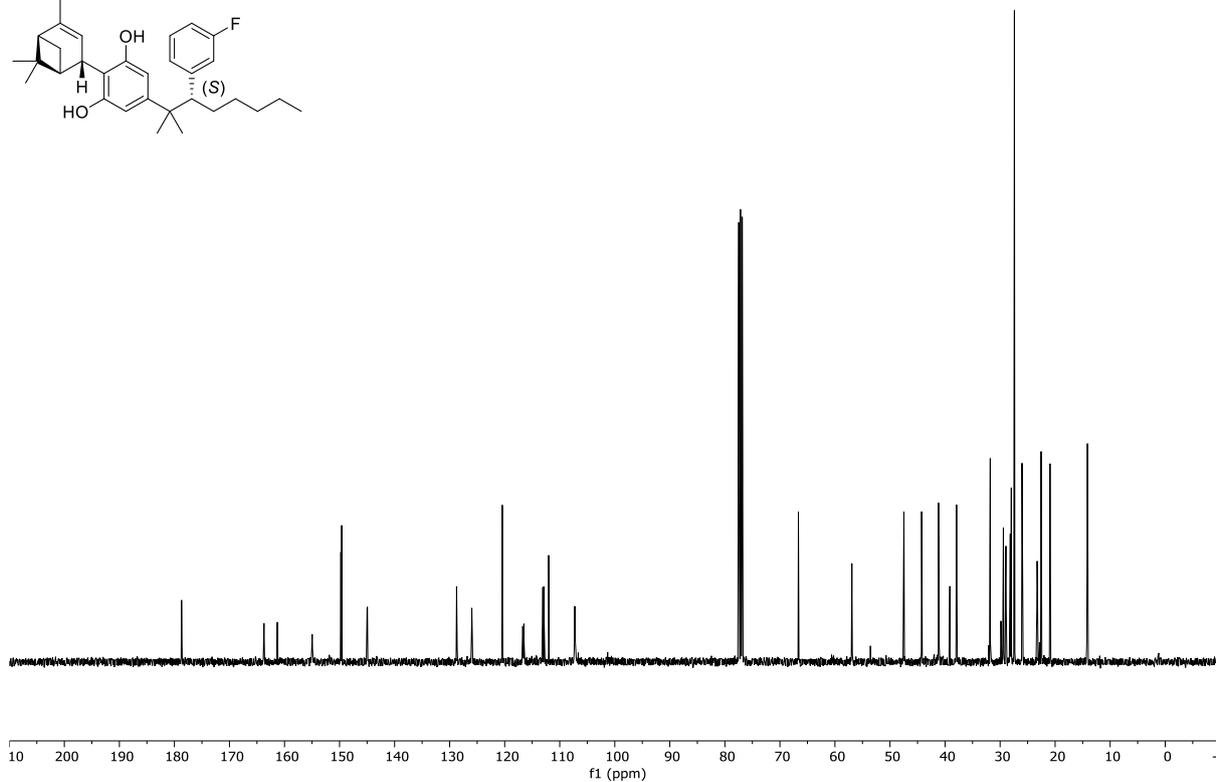
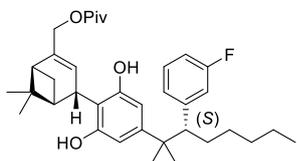
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of (*R*)-**6e**



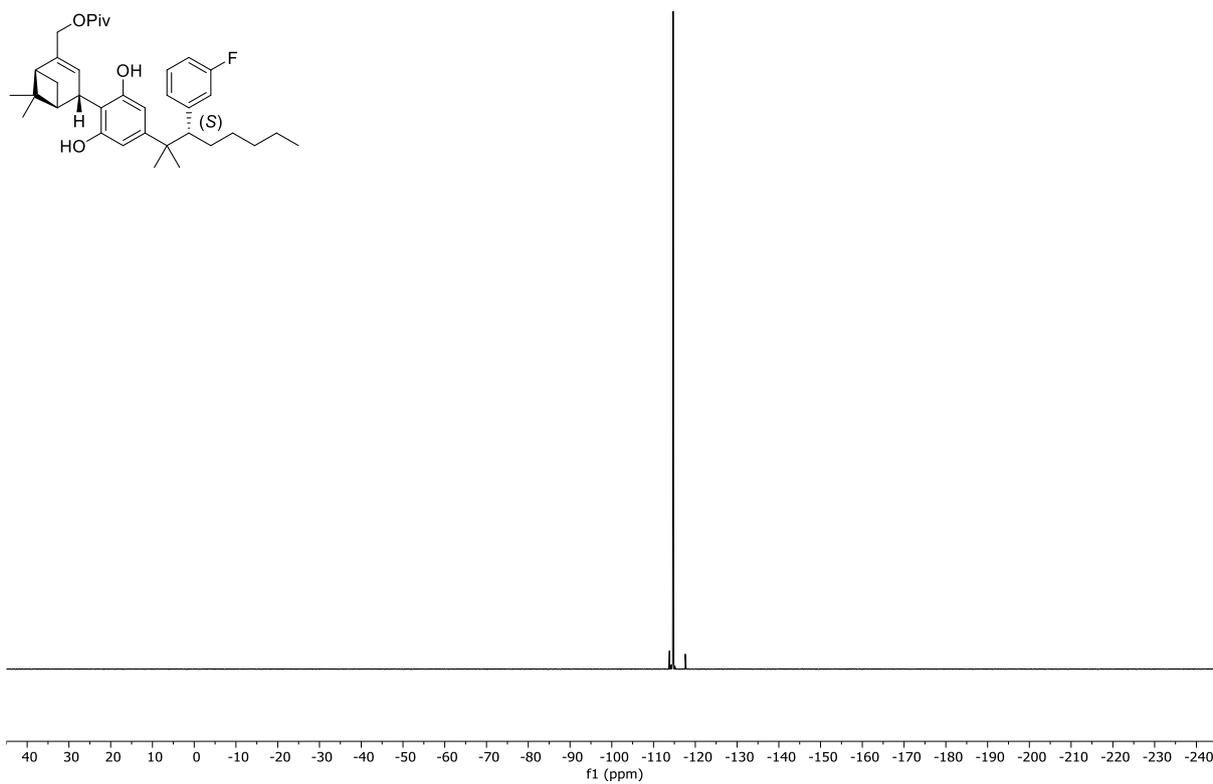
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of (*S*)-SI-20f



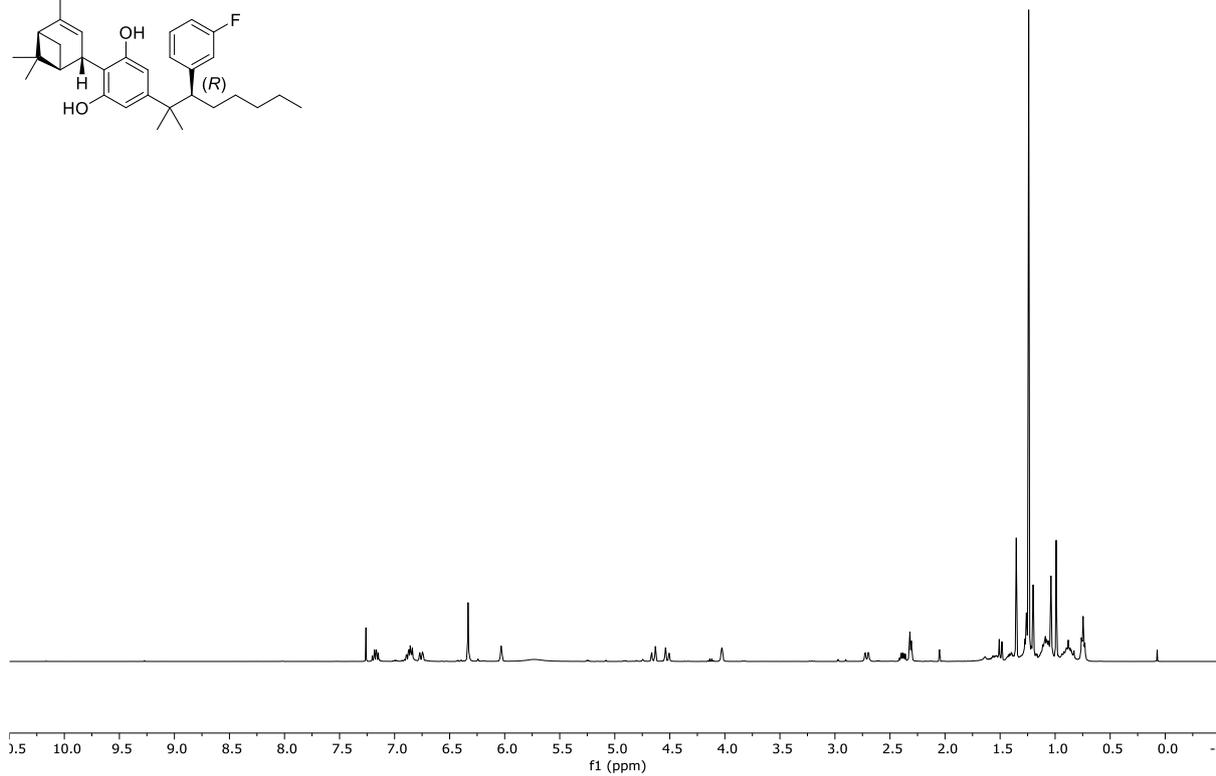
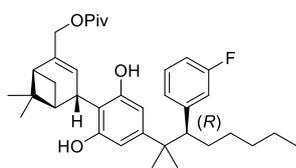
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) of (*S*)-SI-20f



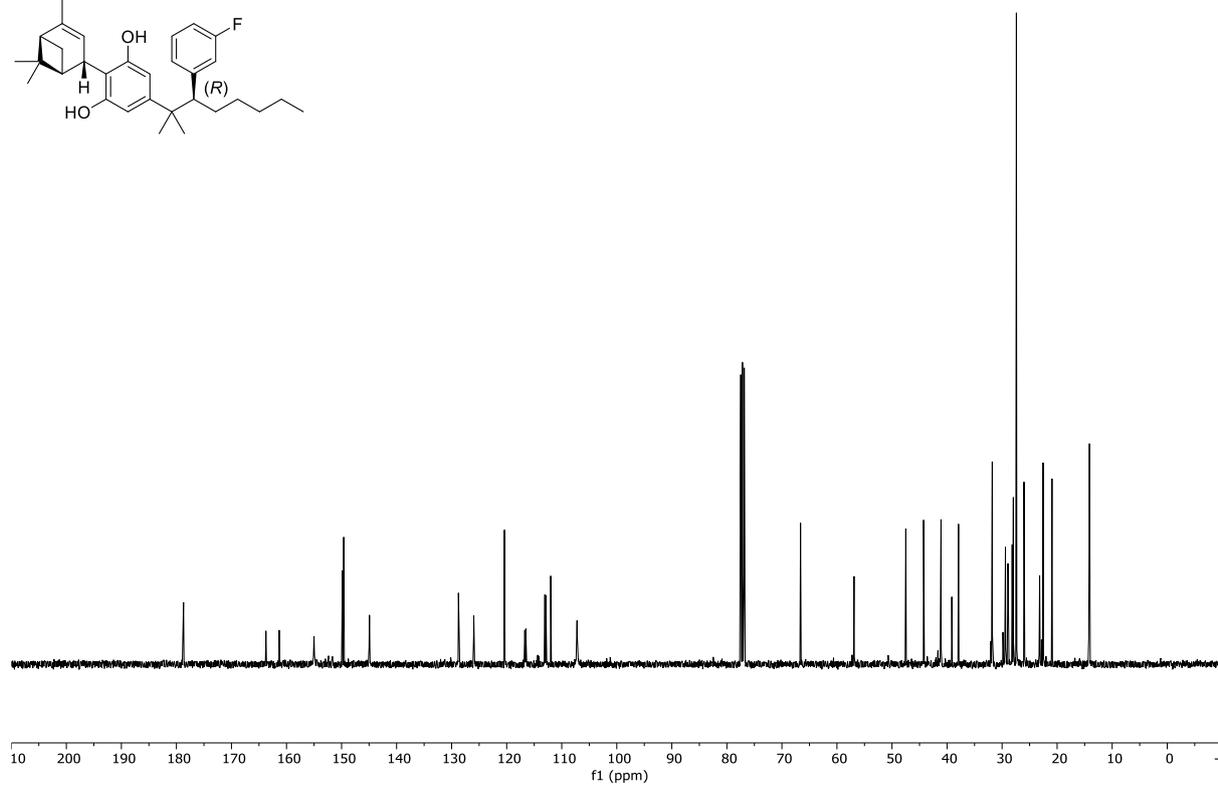
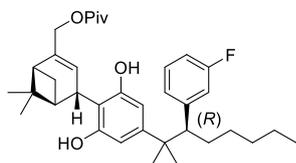
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of (*S*)-**SI-20f**



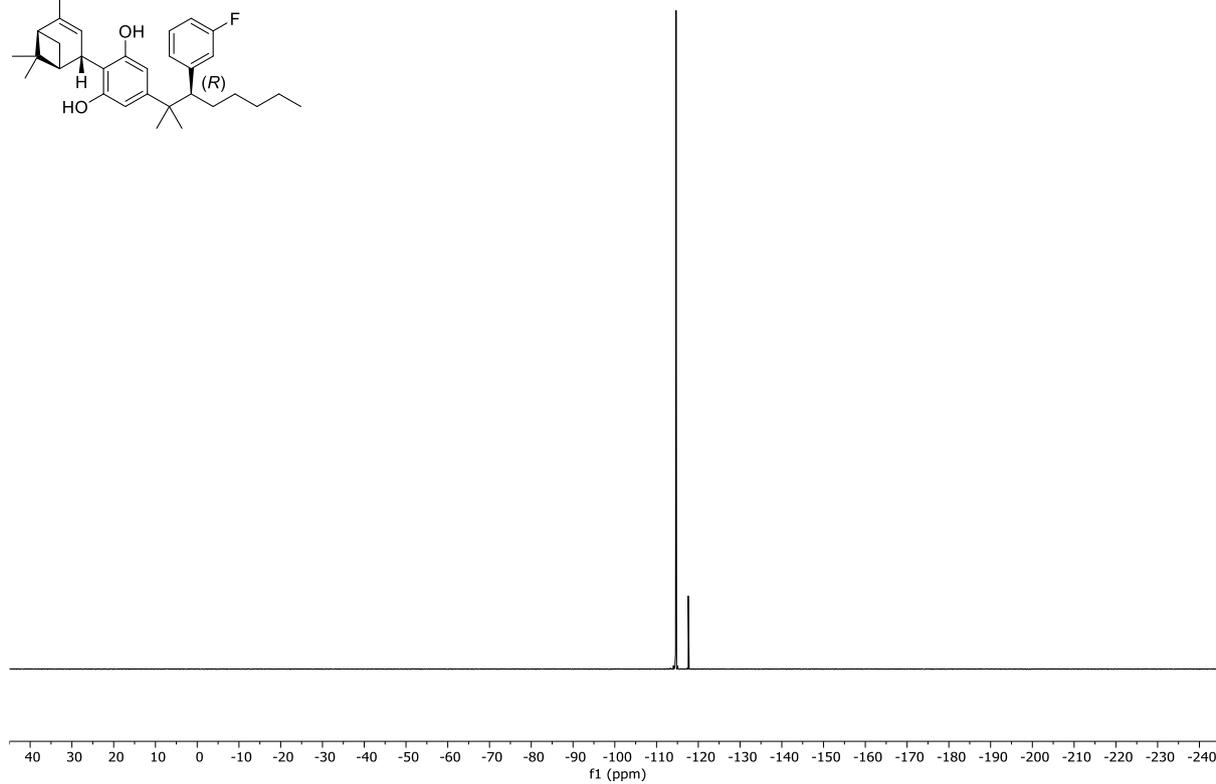
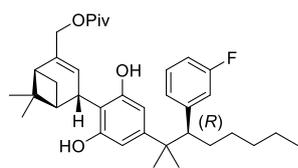
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*R*)-**SI-20f**



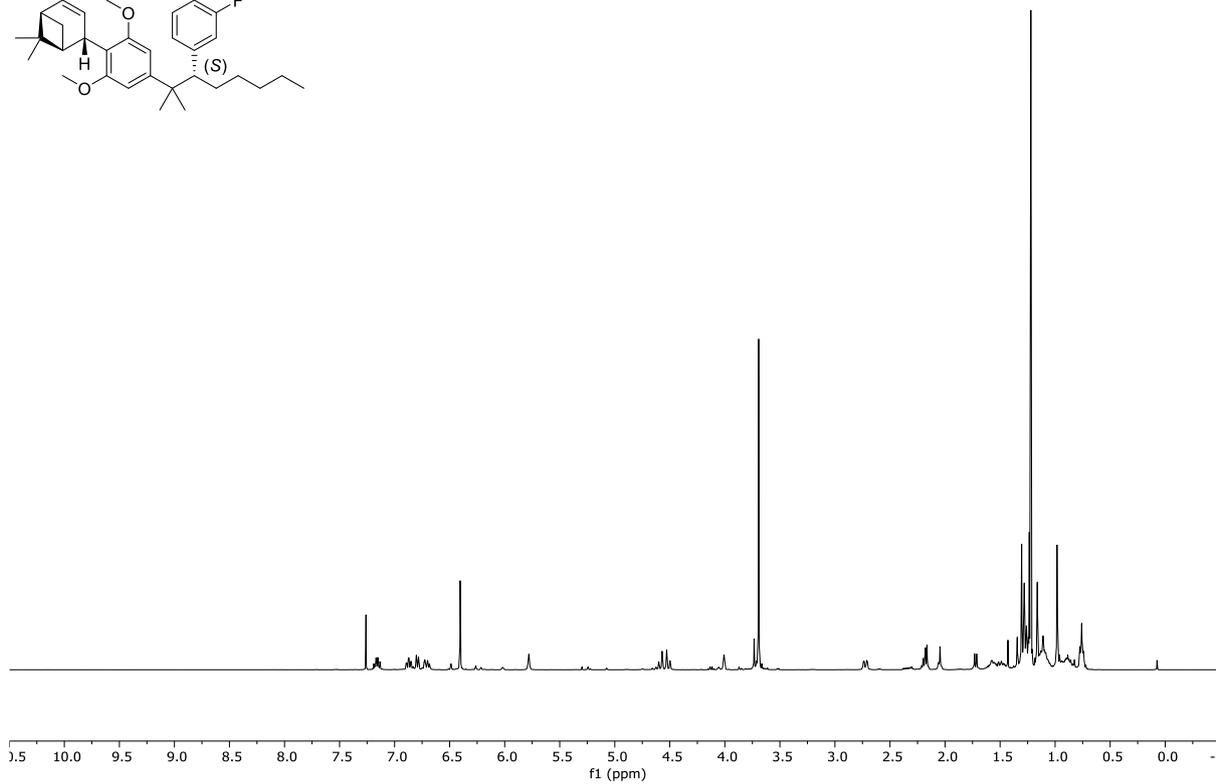
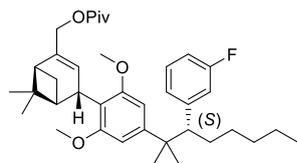
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*R*)-**SI-20f**



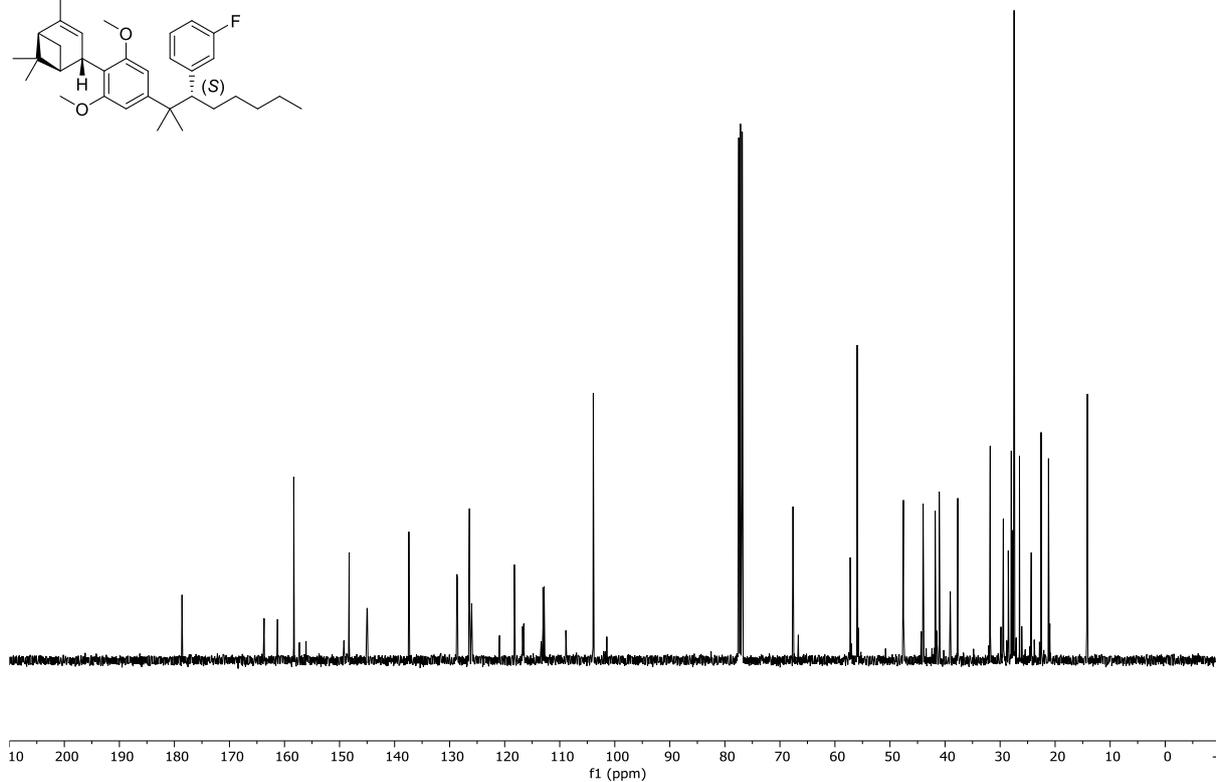
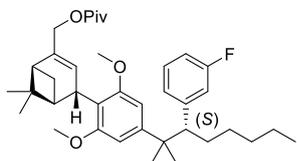
$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ) of (*R*)-**SI-20f**



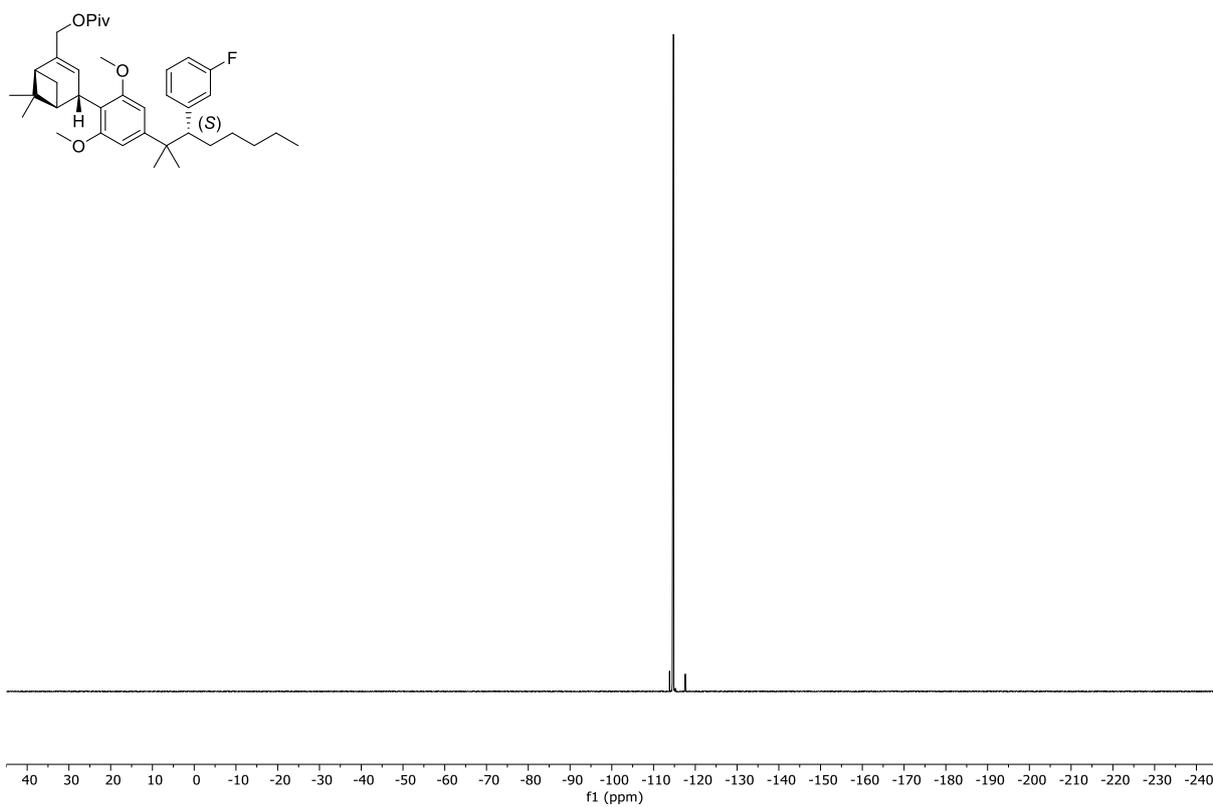
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S*)-**10f**



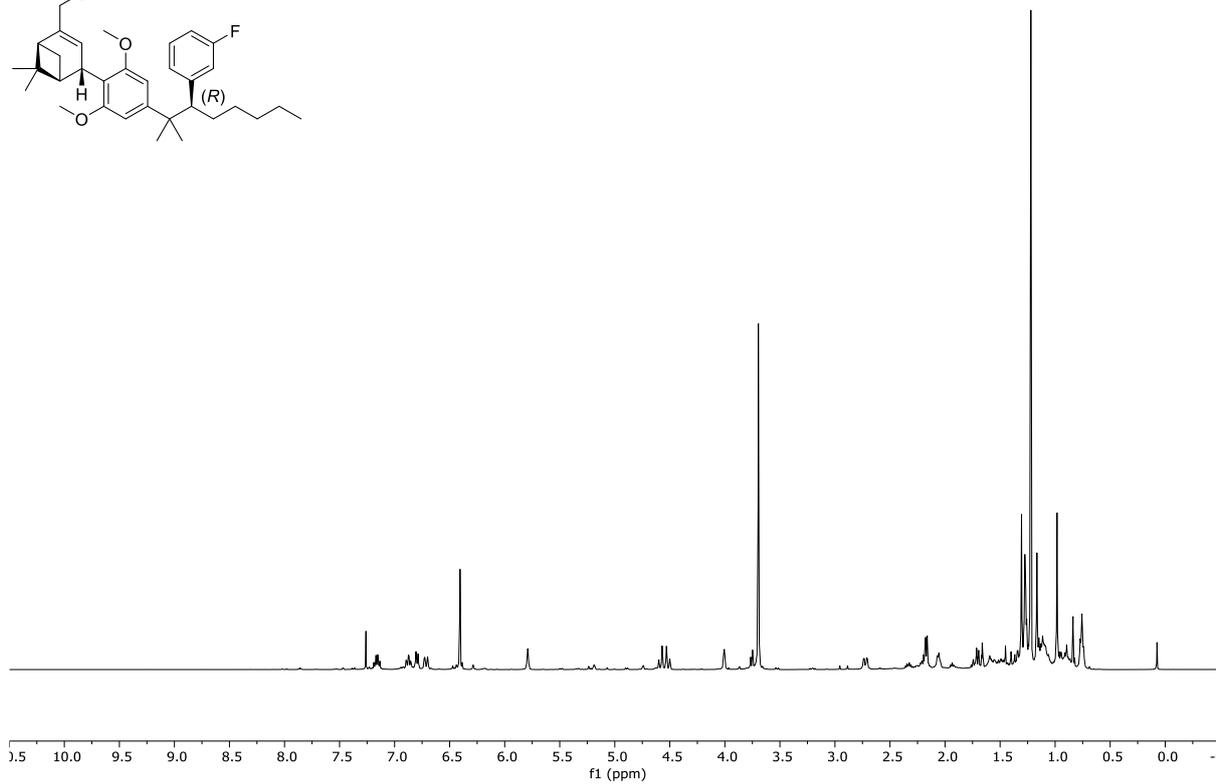
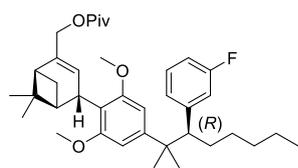
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S*)-**10f**



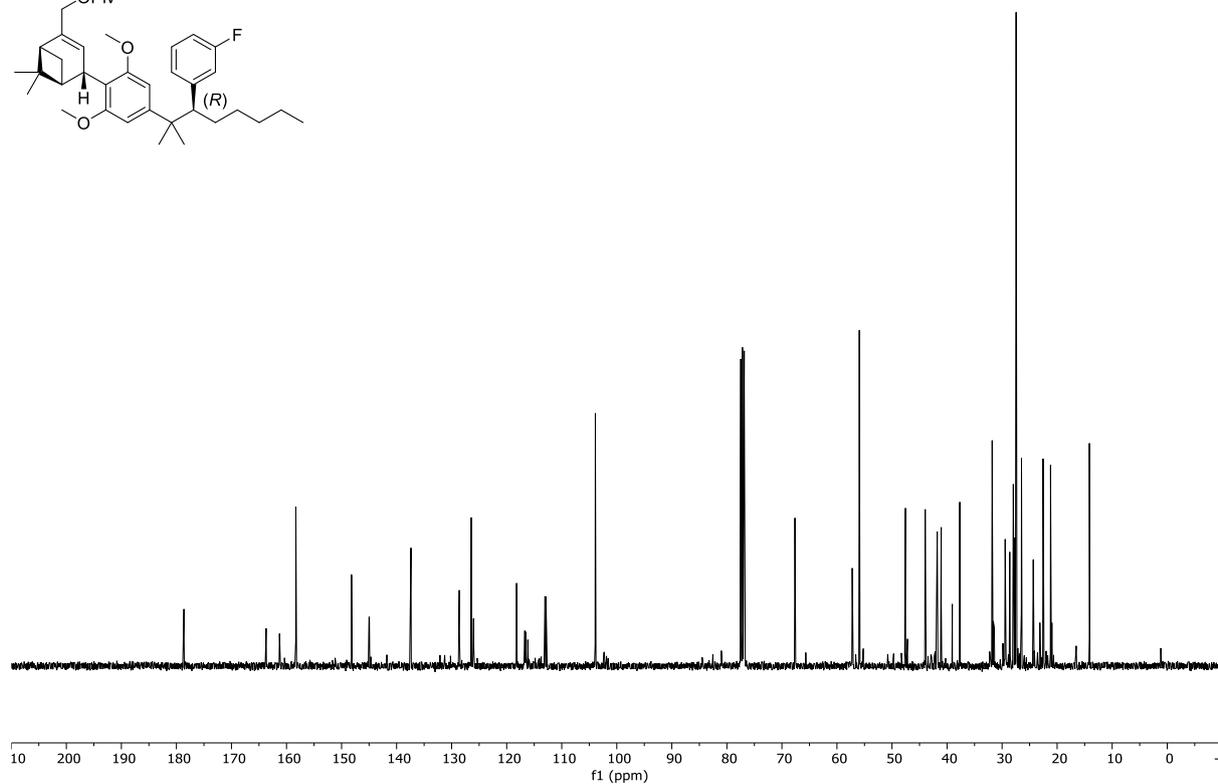
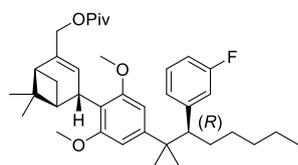
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of (*S*)-**10f**



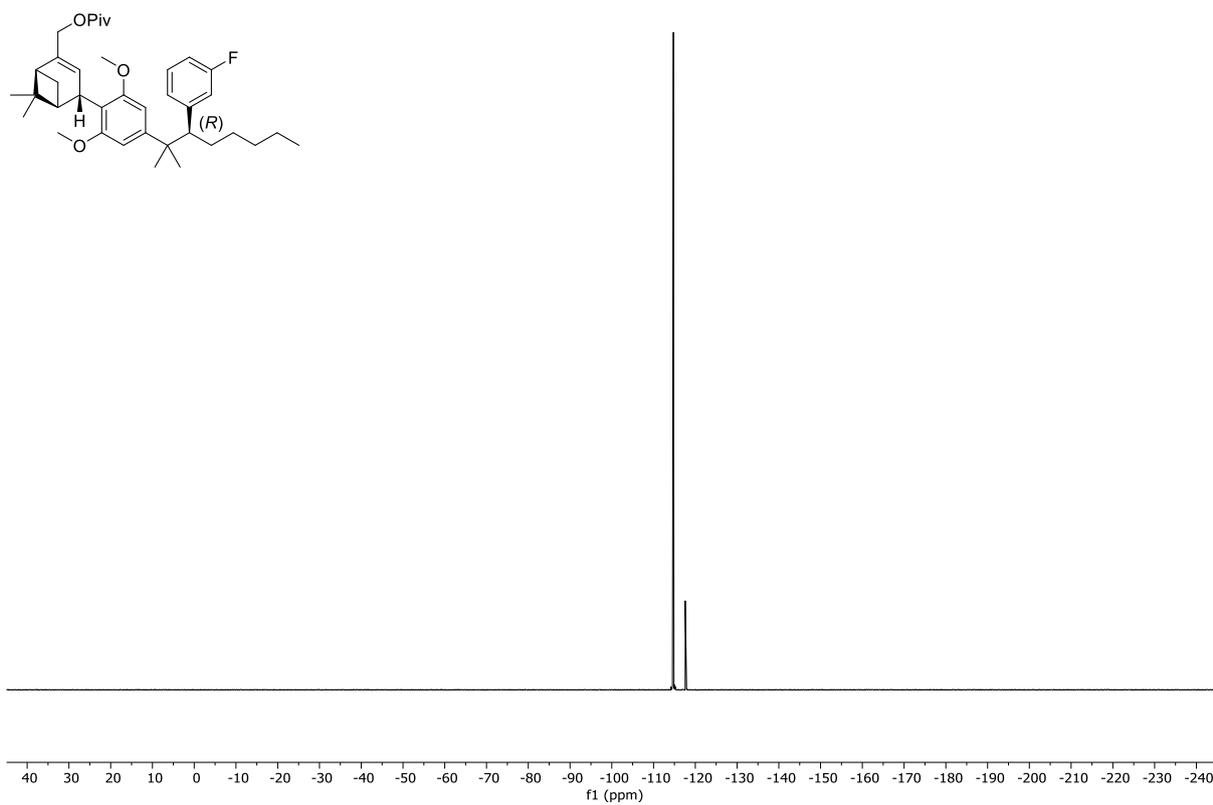
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*R*)-**10f**



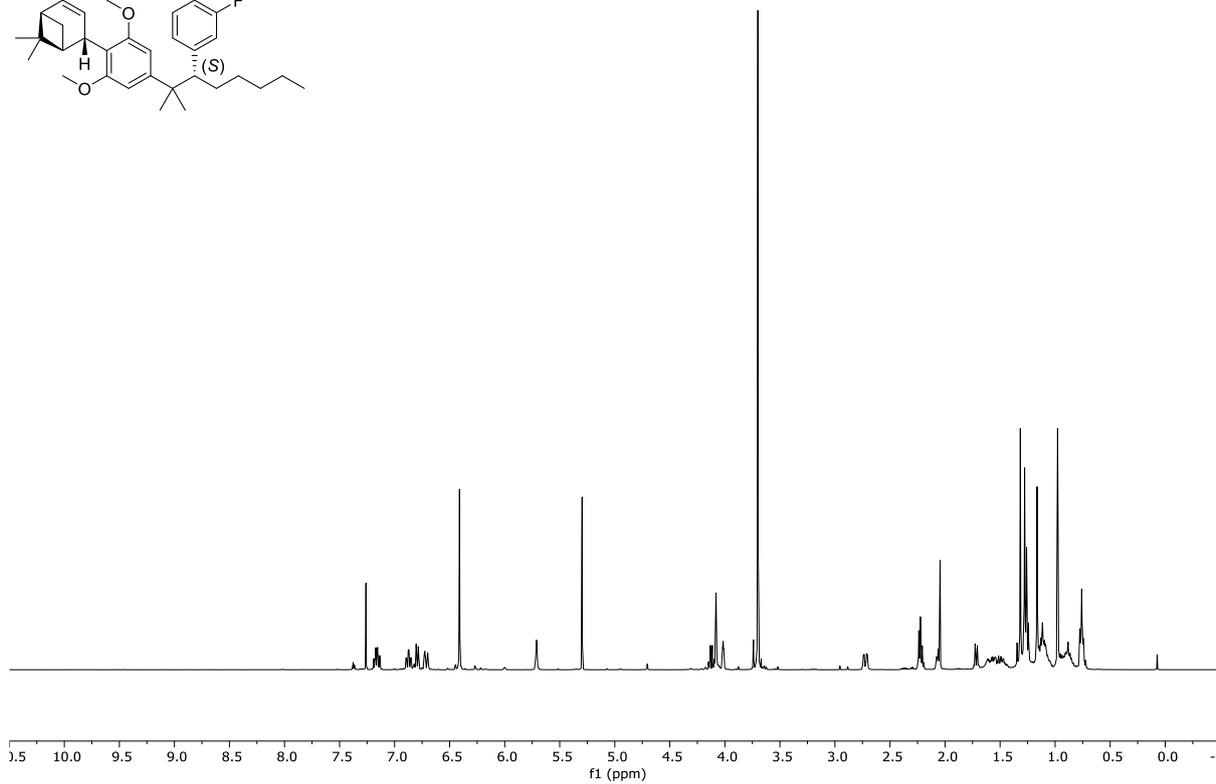
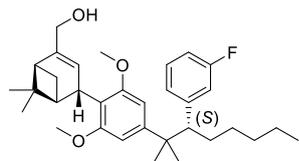
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*R*)-**10f**



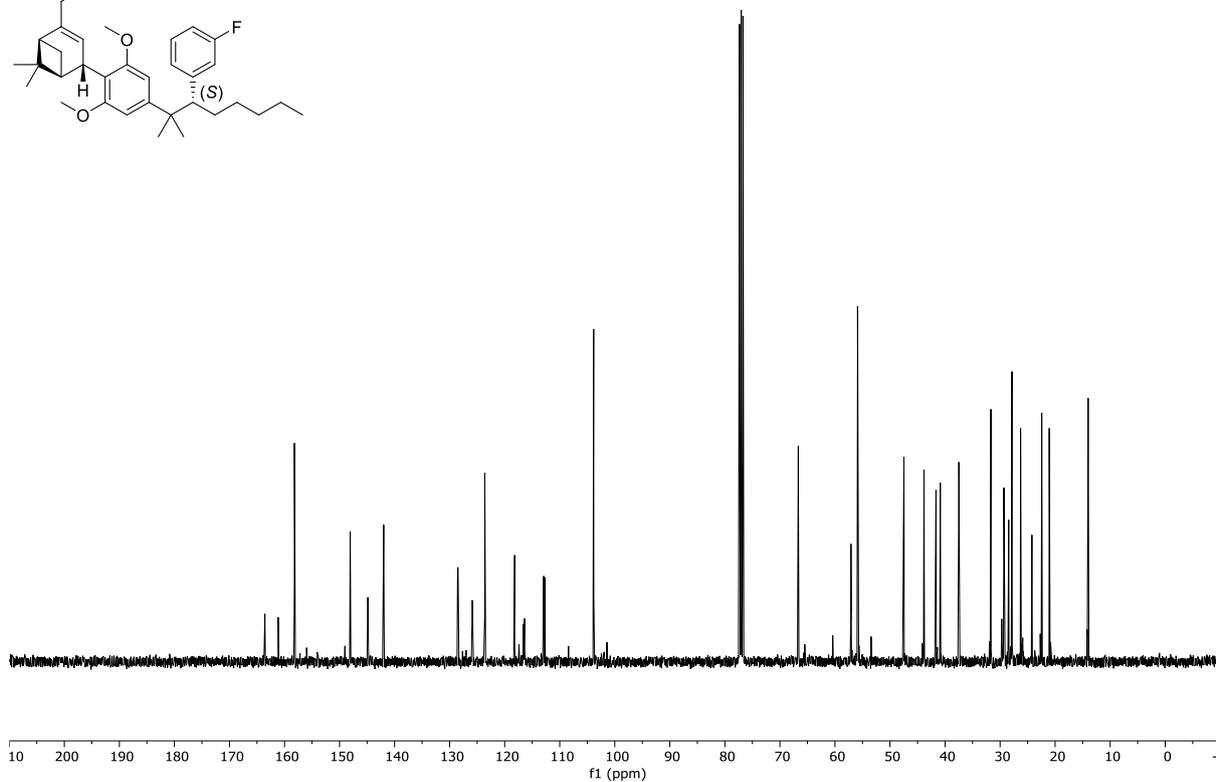
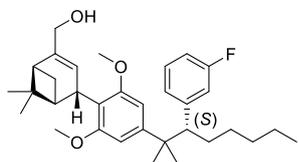
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of (*R*)-**10f**



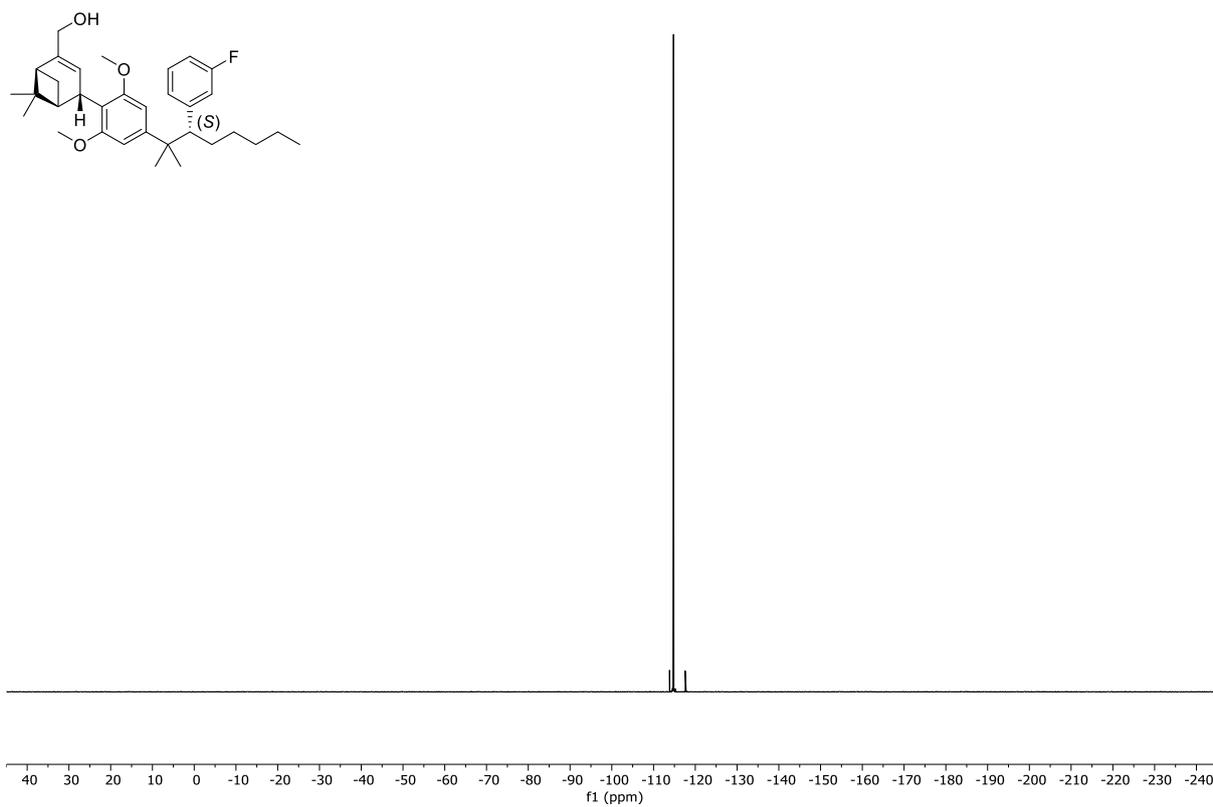
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*S*)-**6f**



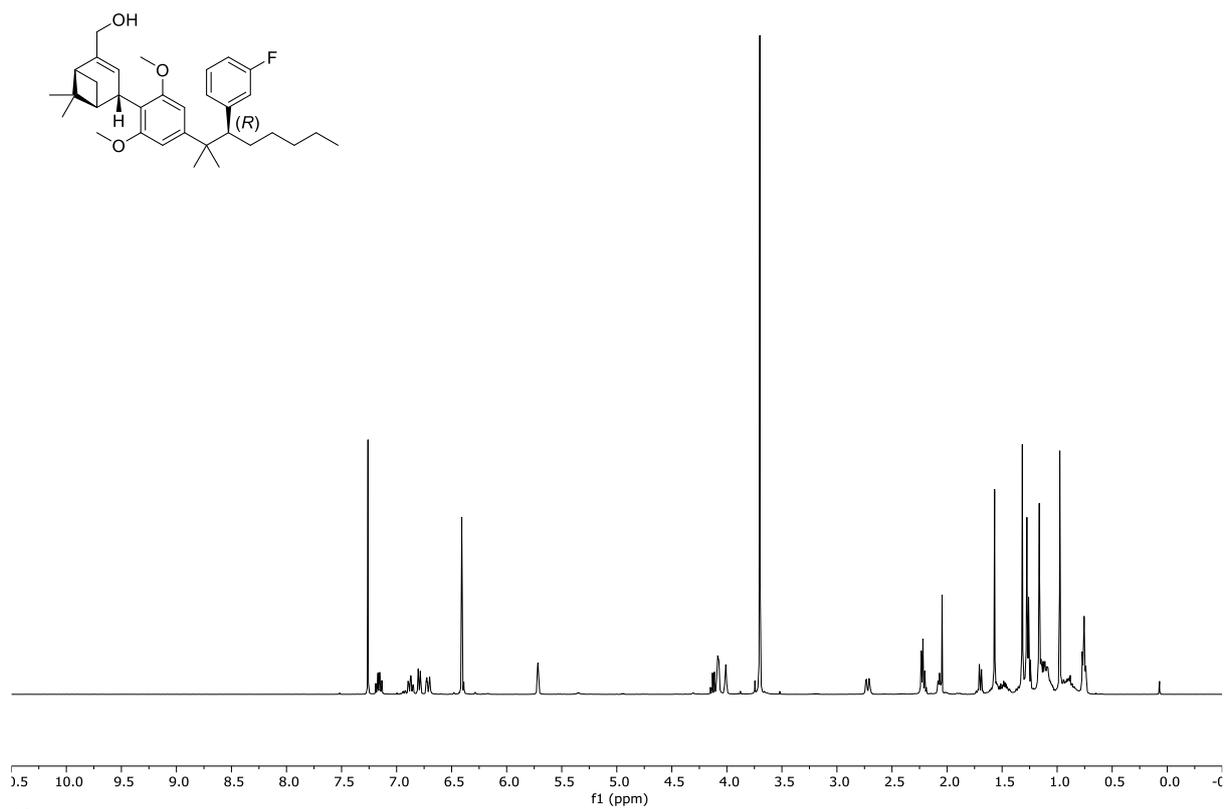
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*S*)-**6f**



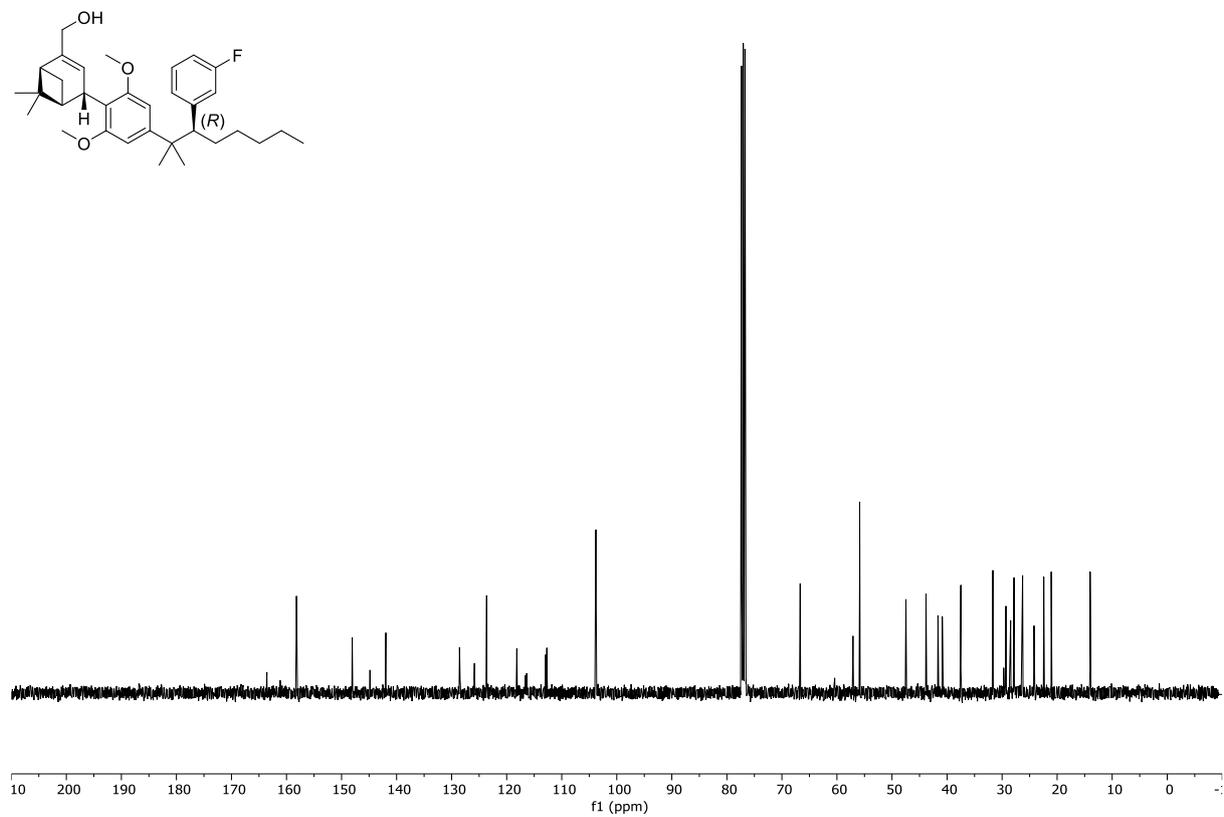
$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of (*S*)-**6f**



$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of (*R*)-**6f**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of (*R*)-**6f**

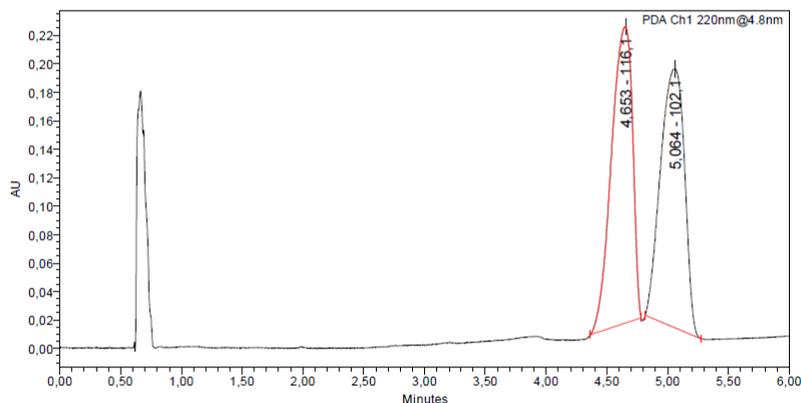
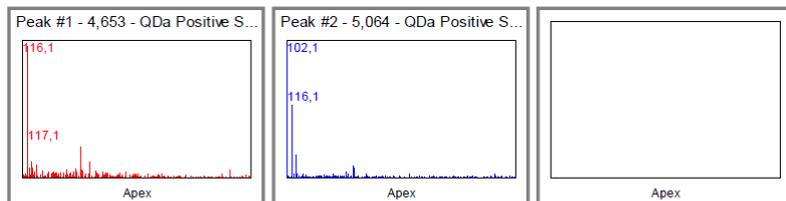


$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of (*R*)-**6f**



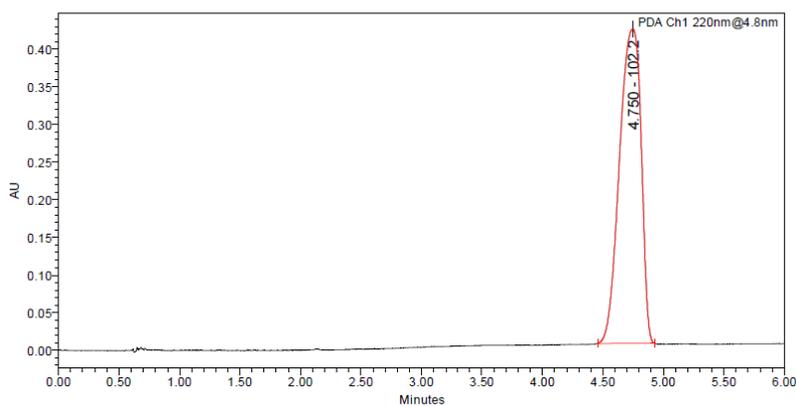
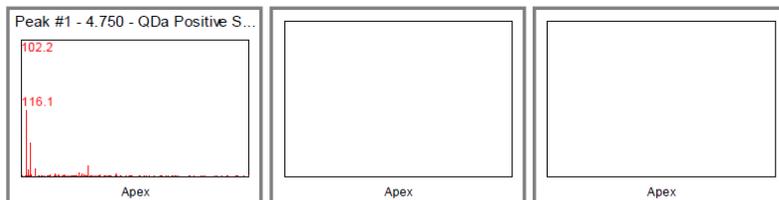
# SFC Traces

## SFC trace of racemate 4



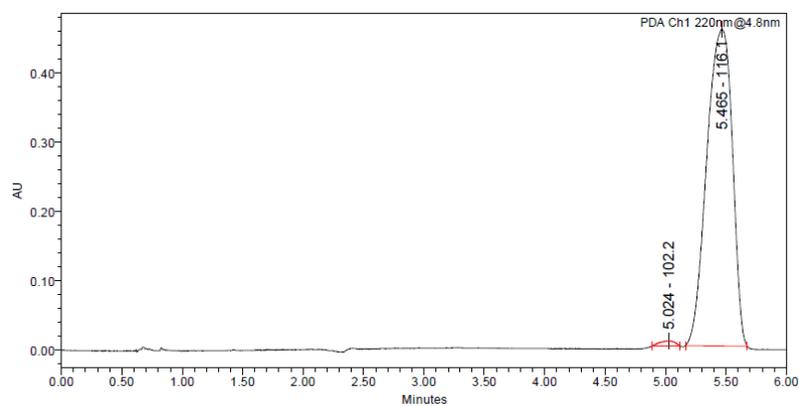
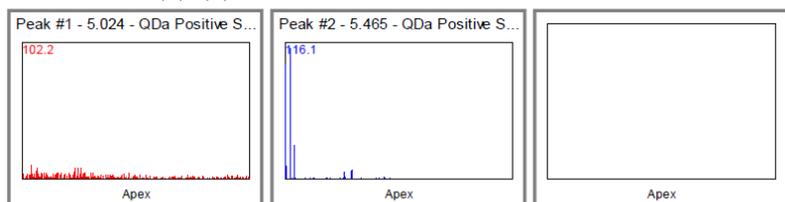
Peak Results				
RT	Area	% Area	Base Peak (m/z)	
1	4.653	2517147	50.35	116.1
2	5.064	2482332	49.65	102.1

## SFC trace of (+)-(R)-4



Peak Results				
RT	Area	% Area	Base Peak (m/z)	
1	4.750	5180871	100.00	102.2

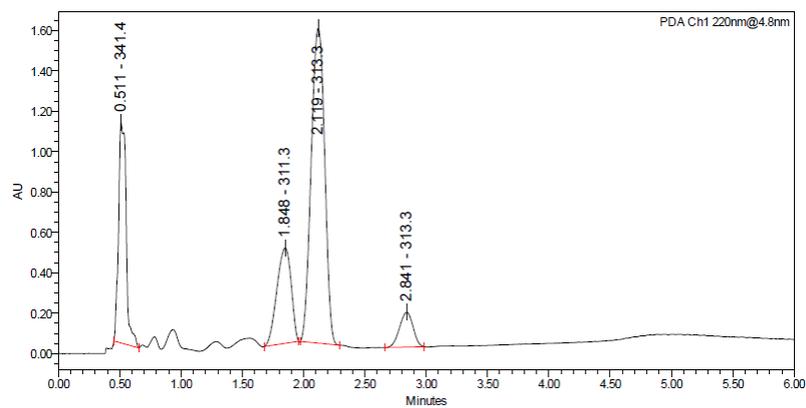
### SFC trace of (-)-*S*-4



Peak Results

	RT	Area	% Area	Base Peak (m/z)
1	5.024	64599	0.96	102.2
2	5.465	6699611	99.04	116.1

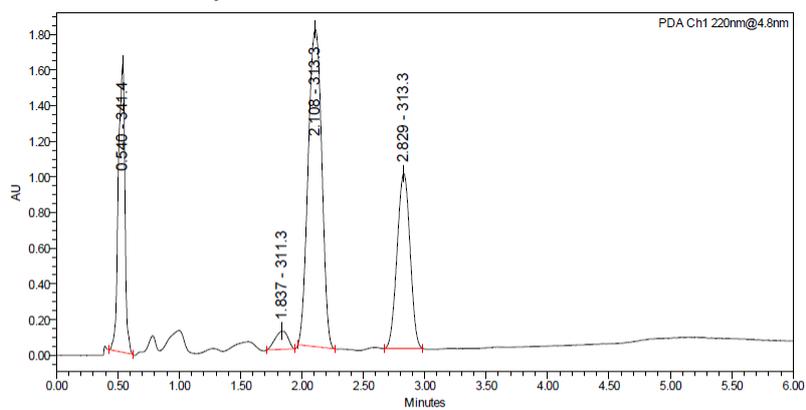
### SFC trace of Entry 1 from Table S2



Peak Results

	RT	Area	% Area	Base Peak (m/z)
1	0.511	4728576	21.70	341.4
2	1.848	3813868	17.50	311.3
3	2.119	11925976	54.73	313.3
4	2.841	1320516	6.06	313.3

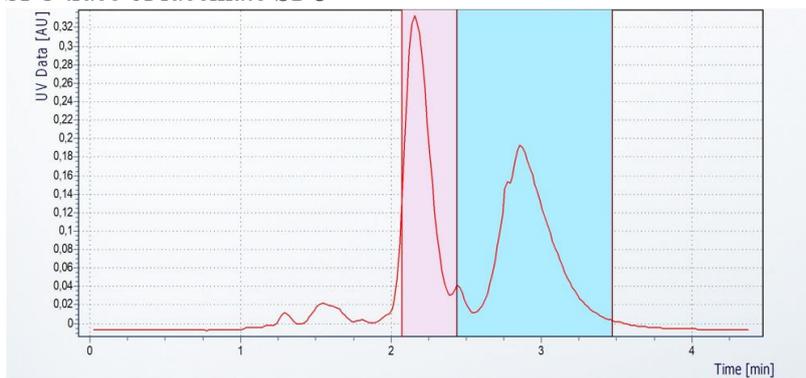
SFC trace of Entry 11 from Table S2.



**Peak Results**

	RT	Area	% Area	Base Peak (m/z)
1	0.540	5946443	21.56	341.4
2	1.837	743517	2.70	311.3
3	2.108	13710163	49.70	313.3
4	2.829	7186666	26.05	313.3

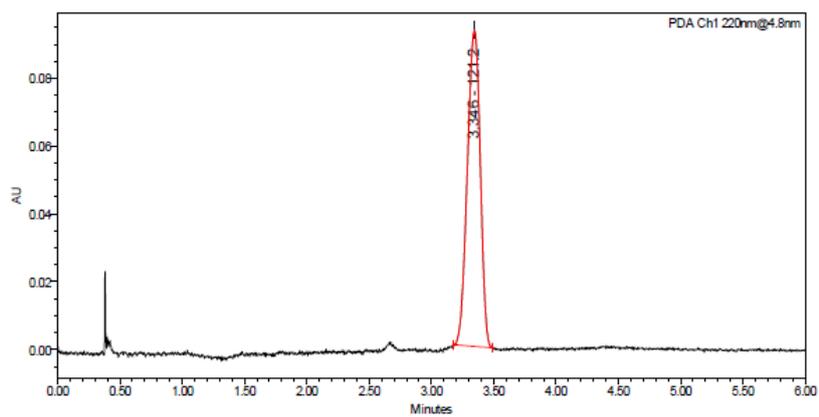
### SFC trace of racemate SI-8



Peak Number Peak Start Peak Stop Vial No.

1	2,07	2,44	1
2	2,44	3,47	2

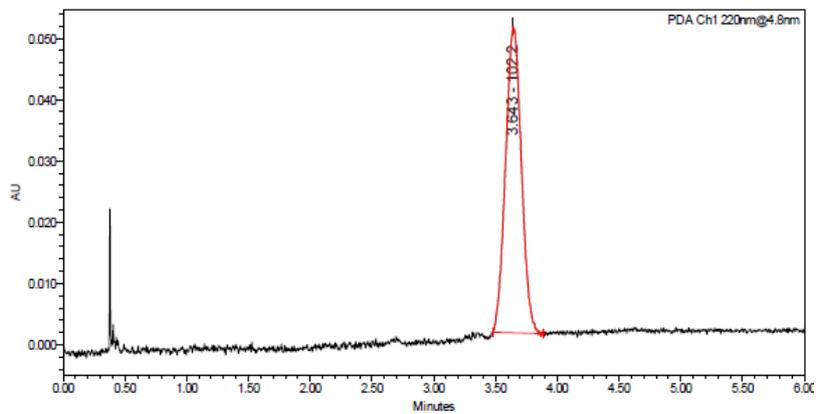
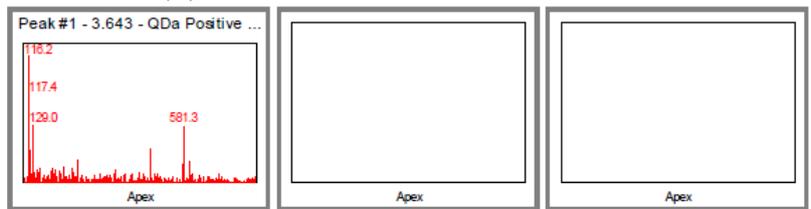
### SFC trace of (A)-SI-8



Peak Results

RT	Area	% Area	Base Peak (m/z)
1 3.346	669130	100.00	121.2

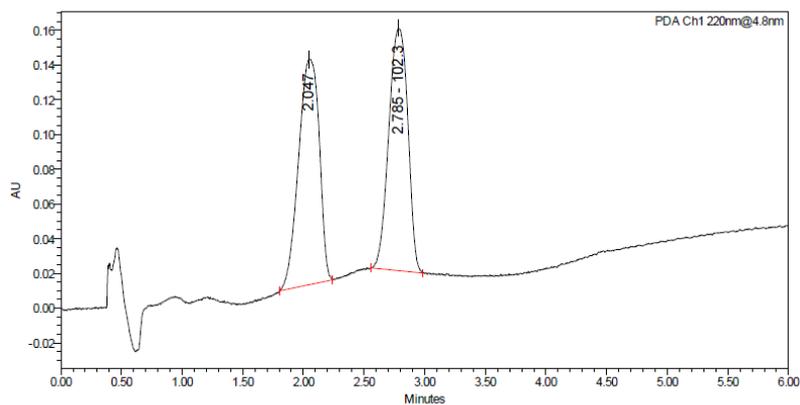
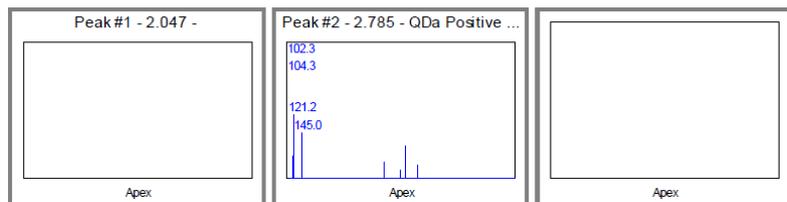
SFC trace of (B)-SI-8



Peak Results

	RT	Area	% Area	Base Peak (m/z)
1	3.643	444337	100.00	102.2

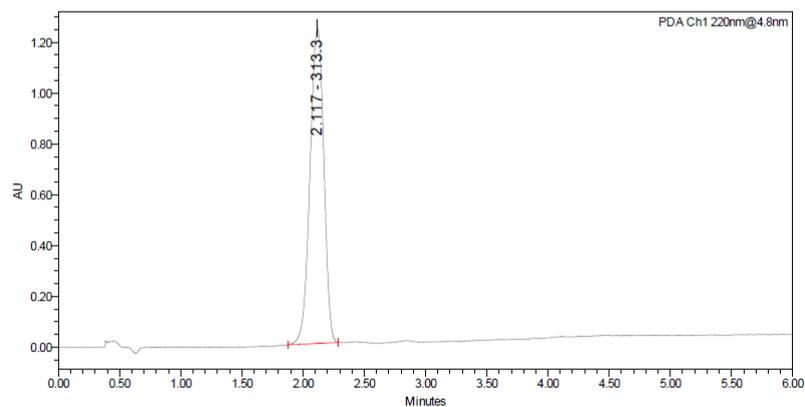
### SFC trace of racemate **9d**



**Peak Results**

RT	Area	% Area	Base Peak (m/z)
1 2.047	1548661	50.37	
2 2.785	1525983	49.63	102.3

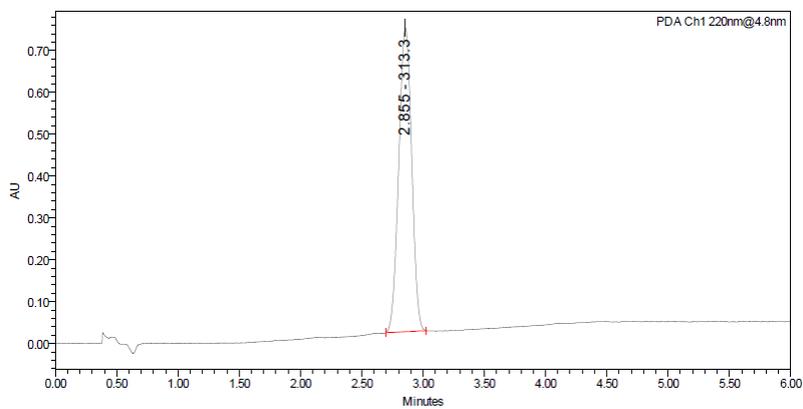
### SFC trace of (-)-(*S*)-**9d**



**Peak Results**

RT	Area	% Area	Base Peak (m/z)
1 2.117	9741544	100.00	313.3

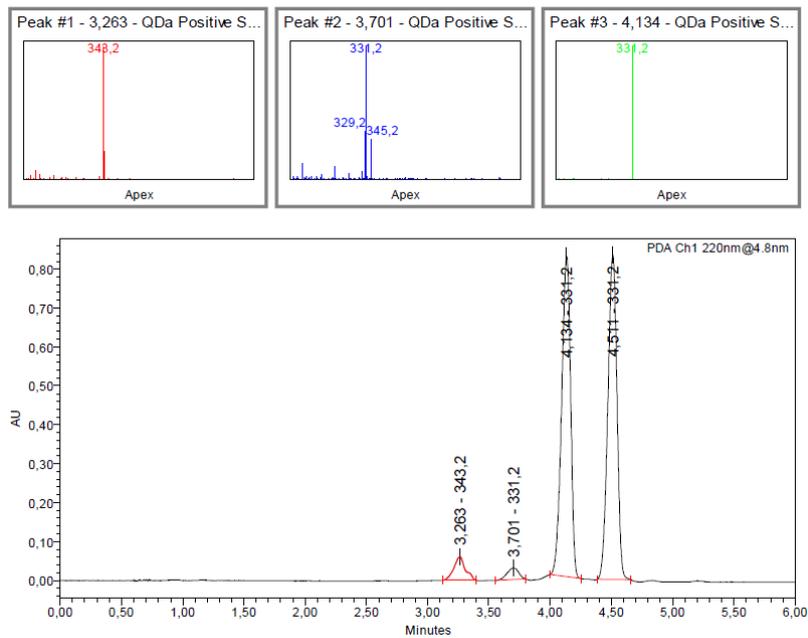
### SFC trace of (+)-(R)-9d



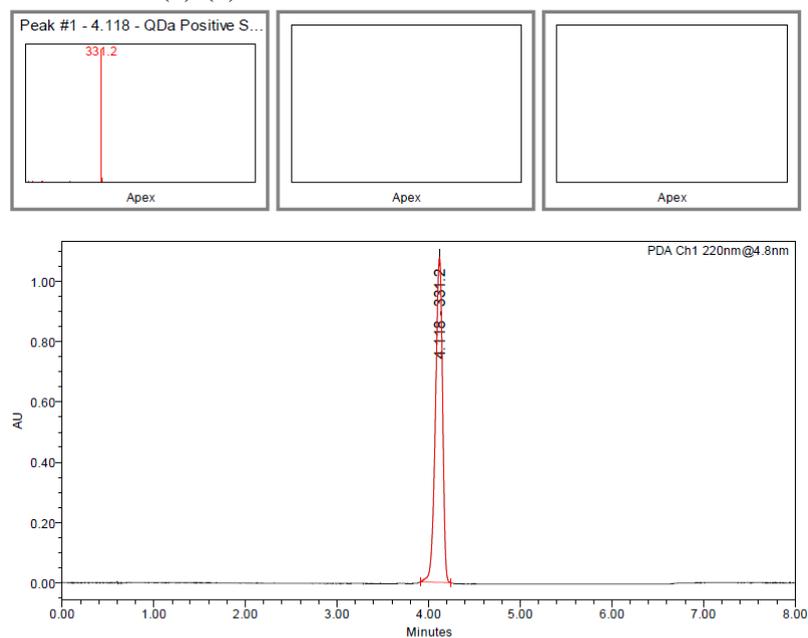
**Peak Results**

RT	Area	% Area	Base Peak (m/z)
1 2.855	5305780	100.00	313.3

### SFC trace of racemate **9e**

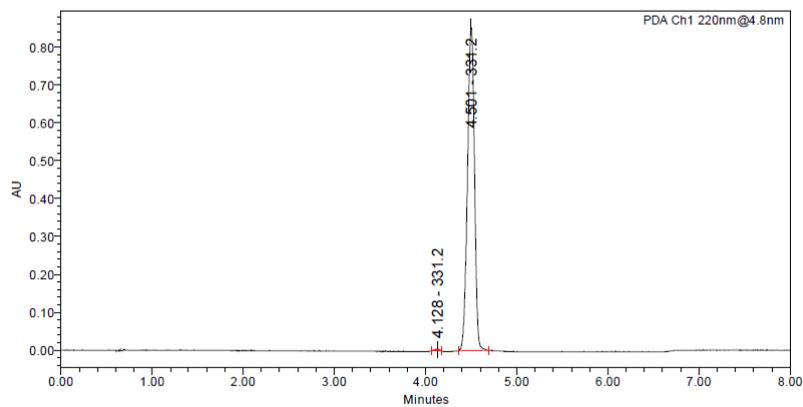
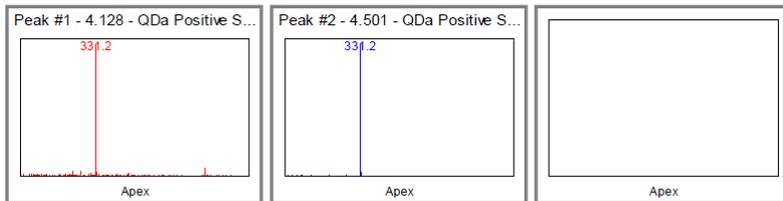


### SFC trace of (-)-(*S*)-**9e**



Peak Results			
RT	Area	% Area	Base Peak (m/z)
1 4.118	5751146	100.00	331.2

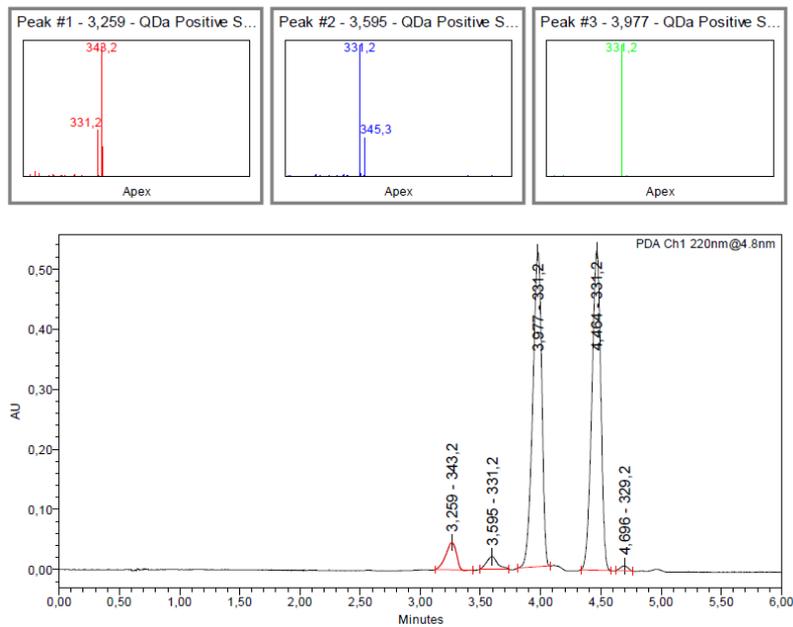
SFC trace of (+)-(*R*)-**9e**



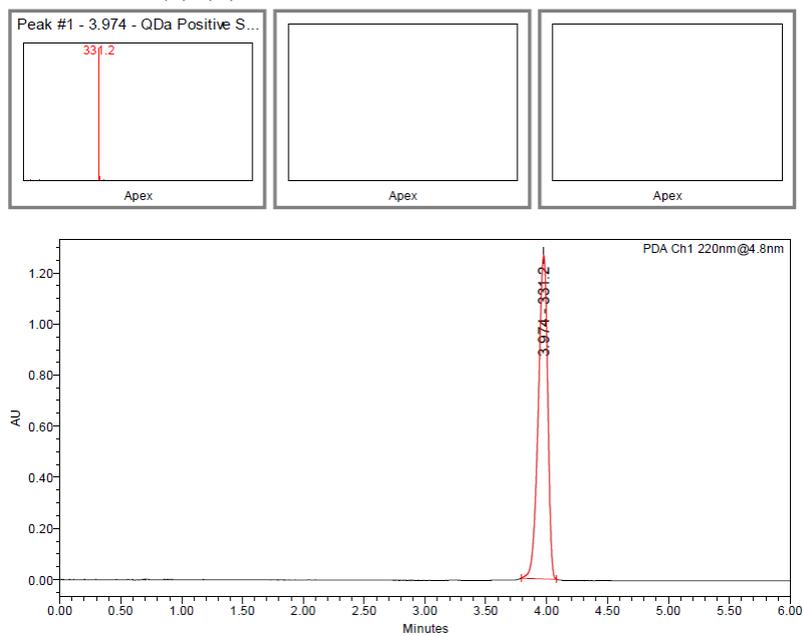
Peak Results

	RT	Area	% Area	Base Peak (m/z)
1	4.128	13746	0.30	331.2
2	4.501	4543976	99.70	331.2

### SFC trace of racemate **9f**

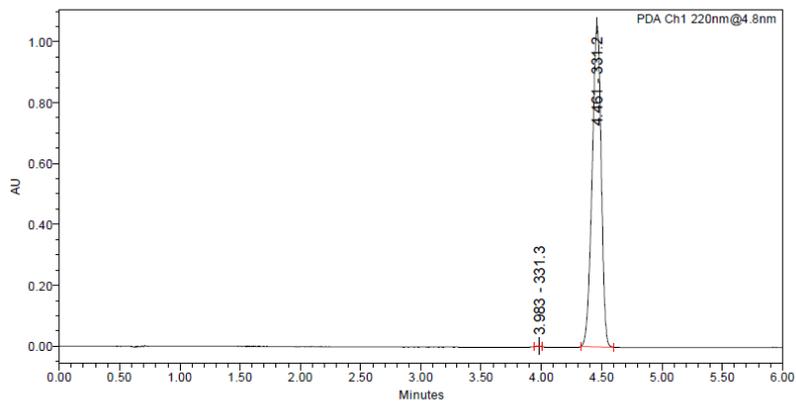
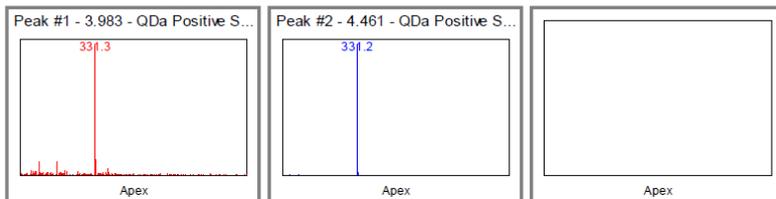


### SFC trace of (-)-(R)-**9f**



Peak Results			
RT	Area	% Area	Base Peak (m/z)
1 3.974	6754335	100.00	331.2

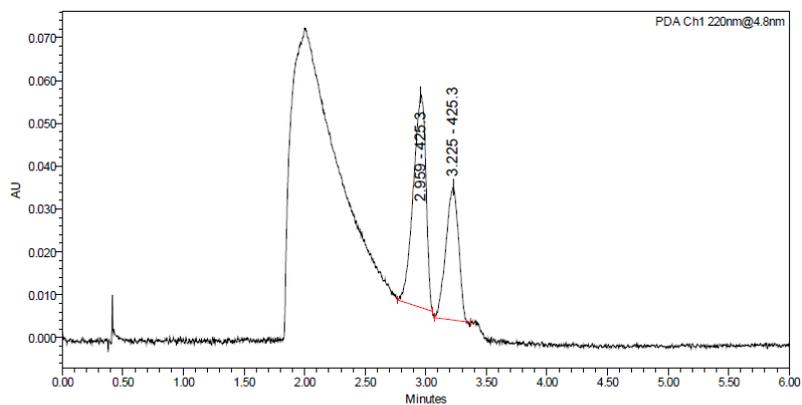
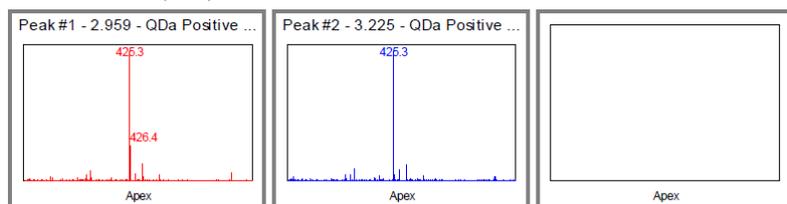
SFC trace of (+)-(*R*)-**9e**



Peak Results

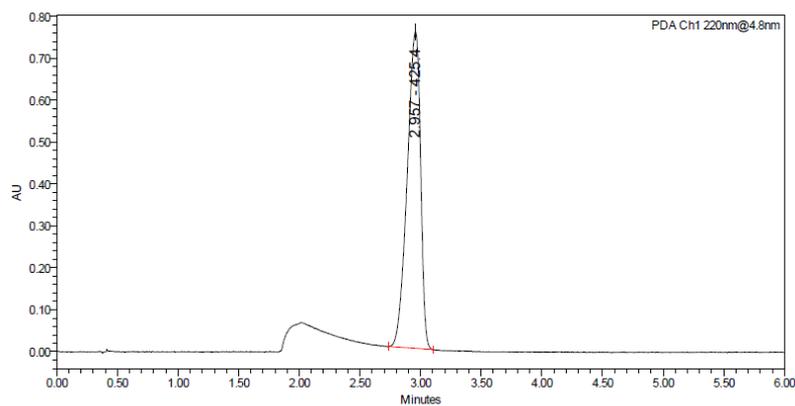
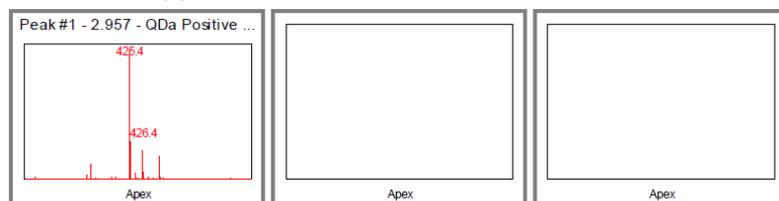
RT	Area	% Area	Base Peak (m/z)
1 3.983	3237	0.06	331.3
2 4.461	5541013	99.94	331.2

### SFC trace of (S/R)-6c



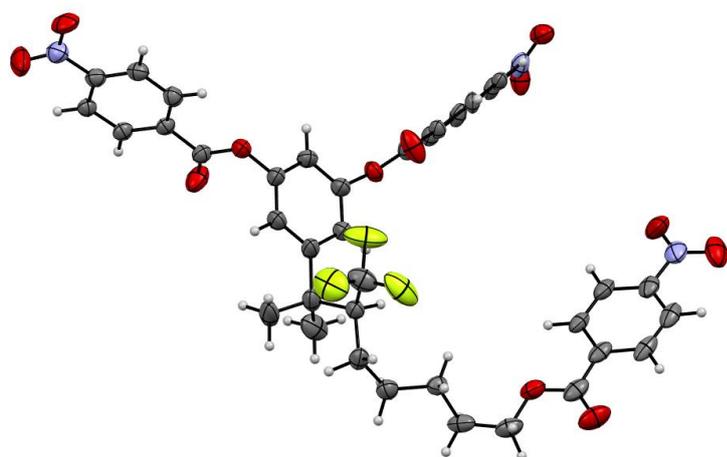
Peak Results				
	RT	Area	% Area	Base Peak (m/z)
1	2.959	358897	61	425.3
2	3.225	226044	39	425.3

### SFC trace of (S)-6c



Peak Results				
	RT	Area	% Area	Base Peak (m/z)
1	2.957	5777565	100	425.4

## Crytallographic Data



**Figure S8.** (*S*)-5-(2-methyl-8-((4-nitrobenzoyl)oxy)-3-(trifluoromethyl)octan-2-yl)-1,3-phenylene bis(4-nitrobenzoate). ORTEP diagram of (*S*)-**SI-9**. Thermal ellipsoids are displayed at 50% probability level. Hydrogen atoms are displayed as spheres with fixed radius (0.15Å)

CCDC number	2450722
Empirical formula	C <sub>37</sub> H <sub>32</sub> N <sub>3</sub> O <sub>12</sub> F <sub>3</sub>
Formula weight	767.65
Temperature/K	100.0(1)
Crystal system	triclinic
Space group	P1
a/Å	7.01380(10)
b/Å	14.10450(10)
c/Å	19.1791(2)
α/°	109.9170(10)
β/°	99.2180(10)
γ/°	92.2350(10)
Volume/Å <sup>3</sup>	1751.82(4)
Z	2
ρ <sub>calc</sub> /cm <sup>3</sup>	1.455
μ/mm <sup>-1</sup>	1.028
F(000)	796.0
Crystal size/mm <sup>3</sup>	0.15 × 0.098 × 0.031
Radiation	Cu Kα (λ = 1.54184)
2θ range for data collection/°	6.7 to 149.694
Index ranges	-8 ≤ h ≤ 8, -17 ≤ k ≤ 17, -23 ≤ l ≤ 23
Reflections collected	13737
Independent reflections	13737 [R <sub>int</sub> = 0.0214, R <sub>sigma</sub> = 0.0123]
Data/restraints/parameters	13737/4082/1540
Goodness-of-fit on F <sup>2</sup>	1.019
Final R indexes [I >= 2σ (I)]	R <sub>1</sub> = 0.0428, wR <sub>2</sub> = 0.1171
Final R indexes [all data]	R <sub>1</sub> = 0.0462, wR <sub>2</sub> = 0.1206
Largest diff. peak/hole / e Å <sup>-3</sup>	0.59/-0.24
Flack parameter	0.03(5)

## References

1. L. Borrega-Roman, B. L. Hoare, M. Kosar, R. C. Sarott, K. J. Patej, J. Bouma, M. Scott-Dennis, E. J. Koers, T. Gazzì, L. Mach, S. Barrondo, J. Salles, W. Guba, E. Kuszniir, M. Nazare, A. C. Rufer, U. Grether, L. H. Heitman, E. M. Carreira, D. A. Sykes and D. B. Veprintsev, A universal cannabinoid CB1 and CB2 receptor TR-FRET kinetic ligand-binding assay, *Front. Pharmacol.*, 2025, **16**, 1469986.
2. M. Kosar, R. C. Sarott, D. A. Sykes, A. E. G. Viray, R. M. Vitale, N. Tomasevic, X. Li, R. L. Z. Ganzoni, B. Kicin, L. Reichert, K. J. Patej, U. Gomez-Bouzo, W. Guba, P. J. McCormick, T. Hua, C. W. Gruber, D. B. Veprintsev, J. A. Frank, U. Grether and E. M. Carreira, Flipping the GPCR Switch: Structure-Based Development of Selective Cannabinoid Receptor 2 Inverse Agonists, *ACS Cent. Sci.*, 2024, **10**, 956-968.
3. M. Scott-Dennis, F. A. Rafani, Y. Yi, T. Perera, C. R. Harwood, W. Guba, A. C. Rufer, U. Grether, D. B. Veprintsev and D. A. Sykes, Development of a membrane-based Gi-CASE biosensor assay for profiling compounds at cannabinoid receptors, *Front. Pharmacol.*, 2023, **14**, 1158091.
4. Optimal for sensitivity of the assay
5. Y. Cheng and W. H. Prusoff, Relationship between the inhibition constant (K<sub>1</sub>) and the concentration of inhibitor which causes 50 per cent inhibition (I<sub>50</sub>) of an enzymatic reaction, *Biochem. Pharmacol.*, 1973, **22**, 3099-3108.
6. F. J. Ehlert, M. T. Griffin, G. W. Sawyer and R. Bailon, A simple method for estimation of agonist activity at receptor subtypes: comparison of native and cloned M3 muscarinic receptors in guinea pig ileum and transfected cells, *J. Pharmacol. Exp. Ther.*, 1999, **289**, 981-992.
7. D. Winpenny, M. Clark and D. Cawkill, Biased ligand quantification in drug discovery: from theory to high throughput screening to identify new biased mu opioid receptor agonists, *Br J Pharmacol*, 2016, **173**, 1393-1403.
8. X. Li, H. Chang, J. Bouma, L. V. de Paus, P. Mukhopadhyay, J. Paloczi, M. Mustafa, C. van der Horst, S. S. Kumar, L. Wu, Y. Yu, R. van den Berg, A. P. A. Janssen, A. Lichtman, Z. J. Liu, P. Pacher, M. van der Stelt, L. H. Heitman and T. Hua, Structural basis of selective cannabinoid CB(2) receptor activation, *Nat. Commun.*, 2023, **14**, 1447-1463.
9. X. Li, T. Hua, K. Vemuri, J. H. Ho, Y. Wu, L. Wu, P. Popov, O. Benchama, N. Zvonok, K. Locke, L. Qu, G. W. Han, M. R. Iyer, R. Cinar, N. J. Coffey, J. Wang, M. Wu, V. Katritch, S. Zhao, G. Kunos, L. M. Bohn, A. Makriyannis, R. C. Stevens and Z. J. Liu, Crystal Structure of the Human Cannabinoid Receptor CB2, *Cell*, 2019, **176**, 459-467.
10. ULC, C. C. G. Molecular Operating Environment (MOE), 2022.02, 1010 Sherbrooke St. West, Suite 910, Montreal, QC, Canada, 2022
11. G. Jones, P. Willett, R. C. Glen, A. R. Leach and R. Taylor, Development and validation of a genetic algorithm for flexible docking, *J. Mol. Biol.*, 1997, **267**, 727-748.
12. E. F. Pettersen, T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng and T. E. Ferrin, UCSF Chimera--a visualization system for exploratory research and analysis, *J. Comput. Chem.*, 2004, **25**, 1605-1612.
13. M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis and J. A. Montgomery Jr, General atomic and molecular electronic structure system, *J. Comput. Chem.*, 1993, **14**, 1347-1363.
14. G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell and A. J. Olson, AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility, *J. Comput. Chem.*, 2009, **30**, 2785-2791.

15. T. Fox and P. A. Kollman, Application of the RESP Methodology in the Parametrization of Organic Solvents, *J. Phys. Chem. B*, 1998, **102**, 8070-8079.
16. D.A. Case, K. Belfon, I.Y. Ben-Shalom, S.R. Brozell, D.S. Cerutti, T.E. Cheatham, III, V.W.D. Cruzeiro, T.A. Darden, R.E. Duke, G. Giambasu, M.K. Gilson, H. Gohlke, A.W. Goetz, R. Harris, S. Izadi, S.A. Izmailov, K. Kasavajhala, A. Kovalenko, R. Krasny, T. Kurtzman, T.S. Lee, S. LeGrand, P. Li, C. Lin, J. Liu, T. Luchko, R. Luo, V. Man, K.M. Merz, Y. Miao, O. Mikhailovskii, G. Monard, H. Nguyen, A. Onufriev, F. Pan, S. Pantano, R. Qi, D.R. Roe, A. Roitberg, C. Sagui, S. Schott-Verdugo, J. Shen, C.L. Simmerling, N.R. Skrynnikov, J. Smith, J. Swails, R.C. Walker, J. Wang, L. Wilson, R.M. Wolf, X. Wu, Y. Xiong, Y. Xue, D.M. York and P.A. Kollman (2020), AMBER 2020, University of California, San Francisco.
17. B. R. Miller, 3rd, T. D. McGee, Jr., J. M. Swails, N. Homeyer, H. Gohlke and A. E. Roitberg, MMPBSA.py: An Efficient Program for End-State Free Energy Calculations, *J Chem Theory Comput*, 2012, **8**, 3314-3321.
18. J. Mongan, C. Simmerling, J. A. McCammon, D. A. Case and A. Onufriev, Generalized Born model with a simple, robust molecular volume correction, *J Chem Theory Comput*, 2007, **3**, 156-169.
19. J. Weiser, P. S. Shenkin and W. C. Still, Approximate atomic surfaces from linear combinations of pairwise overlaps (LCPO), *J. Comput. Chem.*, 1999, **20**, 217-230.
20. CrysAlisPro and ABSPACK. Rigaku Oxford Diffraction, 2016.
21. G. M. Sheldrick, SHELXT - integrated space-group and crystal-structure determination, *Acta Crystallogr A Found Adv*, 2015, **71**, 3-8.
22. G. M. Sheldrick, A short history of SHELX, *Acta Crystallogr A*, 2008, **64**, 112-122.
23. G. M. Sheldrick, Crystal structure refinement with SHELXL, *Acta Crystallogr C Struct Chem*, 2015, **71**, 3-8.
24. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program, *J. Appl. Crystallogr.*, 2009, **42**, 339-341.
25. S. P. Nikas, R. Sharma, C. A. Paronis, S. Kulkarni, G. A. Thakur, D. Hurst, J. T. Wood, R. S. Gifford, G. Rajarshi, Y. Liu, J. G. Raghav, J. J. Guo, T. U. Jarbe, P. H. Reggio, J. Bergman and A. Makriyannis, Probing the carboxyester side chain in controlled deactivation (-)-delta(8)-tetrahydrocannabinols, *J. Med. Chem.*, 2015, **58**, 665-681.
26. C. Nilewski, N. R. Deprez, T. C. Fessard, D. B. Li, R. W. Geisser and E. M. Carreira, Synthesis of undecachlorosulfolipid A: re-evaluation of the nominal structure, *Angew Chem Int Ed Engl*, 2011, **50**, 7940-7943.
27. M. Soethoudt, S. C. Stolze, M. V. Westphal, L. van Stralen, A. Martella, E. J. van Rooden, W. Guba, Z. V. Varga, H. Deng, S. I. van Kasteren, U. Grether, I. J. AP, P. Pacher, E. M. Carreira, H. S. Overkleeft, A. Ioan-Facsinay, L. H. Heitman and M. van der Stelt, Selective Photoaffinity Probe That Enables Assessment of Cannabinoid CB2 Receptor Expression and Ligand Engagement in Human Cells, *J. Am. Chem. Soc.*, 2018, **140**, 6067-6075.
28. T. L. Church and P. G. Andersson, Iridium catalysts for the asymmetric hydrogenation of olefins with nontraditional functional substituents, *Coord. Chem. Rev.*, 2008, **252**, 513-531.