Catalytic Hydroetherification of Unactivated Alkenes Enabled by Proton-Coupled Electron Transfer

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Supporting Information

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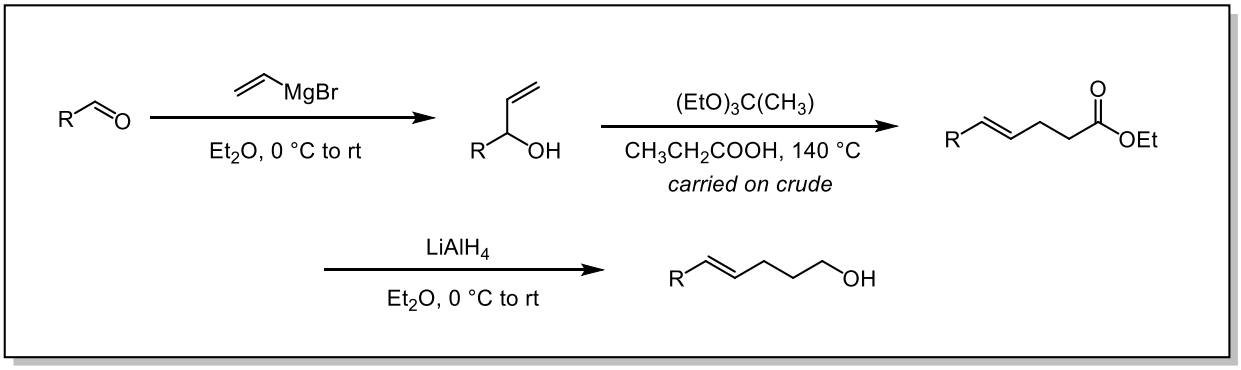
General Information

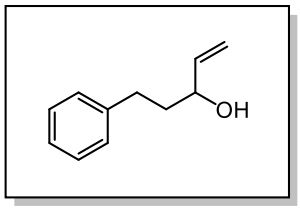
Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] All solvents were purified according to the method of Grubbs.[2] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath. Chromatographic purification of products was accomplished by flash chromatography on a Biotage Isolera One with Biotage SNAP Ultra cartridges packed with HP-Sphere 25 μm spherical silica. Thin-layer chromatography (TLC) was performed on Silicycle 250 μm silica gel plates or Sorbent Technologies 250 μm neutral alumina plates. Visualization of the developed chromatogram was performed by irradiation with UV light or treatment with a solution of potassium permanganate, ceric ammonium molybdate, *p*-anisaldehyde, or 2,4-dinitrophenylhydrazine stain followed by heating when necessary. Ether products characterized herein stained best using a fresh solution of *p*-anisaldehyde, followed by adequate heating. Yields refer to purified compounds unless otherwise noted.

All ^{1}H, NOESY, COSY, ^{13}C{^{1}H}, ^{19}F{^{1}H}, and ^{31}P{^{1}H} NMR spectra were recorded on Bruker Avance II 500 (500, 126, and 202 MHz for ^{1}H, ^{13}C, and ^{31}P, respectively), Bruker Avance III 400 (400, 101, and 376 MHz for ^{1}H, ^{13}C, and ^{19}F, respectively), and Bruker Avance III 300 (282 MHz for ^{19}F). The ^{1}H and ^{13}C NMR spectra were referenced to residual protio- and ^{13}C solvent signals: $CDCl_3$ at δ 7.26 and 77.16 ppm, C_6D_6 at δ 7.16 and 128.06 ppm, and DMSO-d_6 at δ 2.50 and 39.52 ppm; or to added tetramethylsilane signal at δ 0.00 ppm. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, m = multiplet), coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. NMR characterization of mixtures of *E*/*Z* isomers and of diastereomers are reported with ratios of major to minor isomers indicated where appropriate. In certain starting materials and products, the presence of the *N*-Boc group resulted in rotameric products, and, for selected compounds, the NMR spectral data were acquired in DMSO-d_6 at 70 °C; otherwise, characterization of a mixture of rotamers was reported. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at Princeton University Mass Spectrometry Facility using an Agilent 6210 TOF LC/MS (Electrospray Ionization, ESI) or an Agilent 7200 Q-TOF GC/MS (Electron Ionization, EI).

Synthesis of Starting Materials

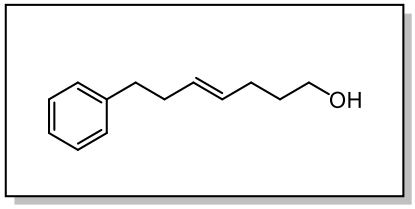
General Procedure A





5-phenylpent-1-en-3-ol

To a flame-dried 100-mL round-bottom flask equipped with a stir bar was added 20 mL dry Et_2O and commercially available 3-phenylpropionaldehyde (20.0 mmol, 1.0 equiv, 2.64 mL). The reaction mixture was stirred under nitrogen and cooled to 0 °C, and a solution of commercially available vinylmagnesium bromide (26.0 mmol, 1.3 equiv, 1 M in THF, 26.0 mL) was added dropwise to the flask over 30 minutes to give an opaque pale yellow-orange solution. The reaction was warmed to room temperature and allowed to stir under nitrogen for 24 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl, stirred for 15 minutes, and acidified with 1 M HCl solution. The mixture was diluted with Et_2O, washed with brine, and dried over anhydrous Na_2SO_4. The crude product was concentrated *in vacuo* and purified *via* silica gel chromatography (gradient from 15% to 20% EtOAc in hexanes) to give the titled compound (2.33 g, 72% yield). Spectra are consistent with reported literature values.[3]



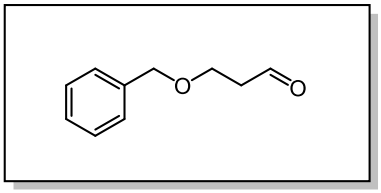
(*E*)-7-phenylhept-4-en-1-ol

To a flame-dried 50-mL round bottom flask equipped with a stir bar and dried distillation apparatus was added triethyl orthoacetate (99.3 mmol, 7.0 equiv, 18.2 mL), propionic acid (0.425 mmol, 0.030 equiv, 32.0 μL), and 5-phenylpent-1-en-3-ol (14.2 mmol, 1.0 equiv, 2.30 g). The reaction mixture was heated to 140 °C with stirring, and intense bubbling of the mixture and

distillation of ethanol were observed. After 4 hours at reflux, the reaction mixture was cooled to room temperature, quenched with saturated aqueous $NaHCO_3$, and diluted with CH_2Cl_2. Excess triethylorthoacetate was hydrolyzed by addition of 1 M HCl. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to yield a yellow oil. The crude product was carried onto the next step without further purification.

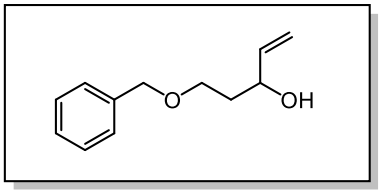
To a flame-dried 250-mL round bottom flask equipped with a stir bar was added $LiAlH_4$ (25.8 mmol, 2.0 equiv, 0.980 g) suspended in 40 mL dry Et_2O. Once the suspension was cooled to 0 °C, crude *(E)*-ethyl 7-phenylhept-4-enoate (12.9 mmol, 1.0 equiv, 3.00 g) dissolved in 10 mL dry Et_2O was added dropwise to the reaction. After 30 minutes, the reaction was warmed to room temperature and allowed to stir overnight. The reaction mixture was diluted with Et_2O and quenched with 1 mL water, 1 mL 1 M NaOH, and 3 mL water added dropwise sequentially at 0 °C. The reaction was warmed to room temperature and stirred for 15 minutes. Anhydrous $MgSO_4$ was added to the mixture and stirred for 15 minutes. The reaction was filtered through Celite and concentrated *in vacuo*. The crude product was purified *via* silica gel chromatography (gradient from 10% to 15% EtOAc in hexanes) to afford the titled compound (2.15 g, 87% yield). Spectra are consistent with reported literature values.[3]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 7.20–7.14 (m, 3H), 5.53–5.38 (m, 2H), 3.60 (t, *J* = 6.5 Hz, 2H), 2.67 (dd, *J* = 8.8, 6.7 Hz, 2H), 2.35–2.27 (m, 2H), 2.07 (tdd, *J* = 7.6, 6.3, 1.0 Hz, 2H), 1.65–1.56 (m, 2H), 1.35 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 142.2, 130.4, 130.3, 128.6, 128.4, 125.9, 62.6, 36.1, 34.5, 32.5, 29.0. **IR (neat):** 3327, 3027, 2929, 2852, 1604, 1496, 1453, 1056, 1031, 967, 913, 744, 696 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{18}O$) from $[M+Na]^+$ is 190.13577, found 190.13576, difference of 0.02 ppm.



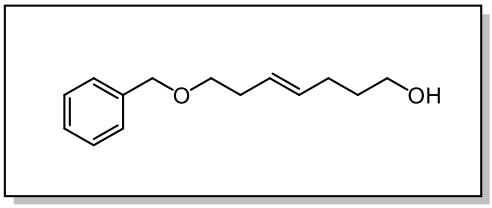
3-(benzyloxy)propanal

The titled compound was synthesized following a literature procedure.[4] Spectra are consistent with reported literature values.



5-(benzyloxy)pent-1-en-3-ol

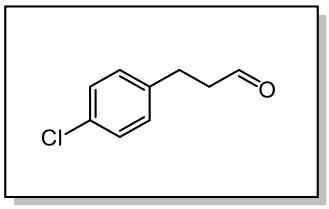
The titled compound was synthesized from 3-(benzyloxy)propanal following the Grignard reaction outlined in General Procedure A. The product was purified *via* silica gel chromatography (gradient from 20% to 30% EtOAc in hexanes) to give the titled compound. Spectra are consistent with reported literature values.[5]



(*E*)-7-(benzyloxy)hept-4-en-1-ol

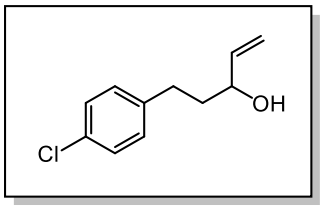
The titled compound was synthesized following General Procedure A using *(E)*-ethyl 7-(benzyloxy)hept-4-enoate, which was synthesized from 5-(benzyloxy)pent-1-en-3-ol and carried onto the next step without further purification. The final product was purified *via* silica gel chromatography (gradient from 25% to 30% EtOAc in hexanes) to give the titled compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.32 (m, 4H), 7.31–7.27 (m, 1H), 5.58–5.41 (m, 2H), 4.51 (s, 2H), 3.64 (t, J = 6.4 Hz, 2H), 3.48 (t, J = 6.8 Hz, 2H), 2.36–2.28 (m, 2H), 2.14–2.05 (m, 2H), 1.69–1.59 (m, 2H), 1.49 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 138.6, 131.9, 128.5, 127.8, 127.7, 127.3, 73.0, 70.2, 62.7, 33.2, 32.4, 29.3. **IR (neat):** 3376, 3030, 2932, 2858, 1496, 1454, 1362, 1206, 1099, 1029, 970, 737, 698 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{14}H_{20}O_2$) from $[M+Na]^+$ is 220.14633, found 220.14638, difference of 0.22 ppm.



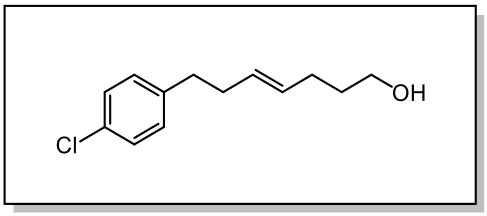
3-(4-chlorophenyl)propanal

The titled compound was synthesized following a literature procedure.[6] Spectra are consistent with reported literature values.[7]



5-(4-chlorophenyl)pent-1-en-3-ol

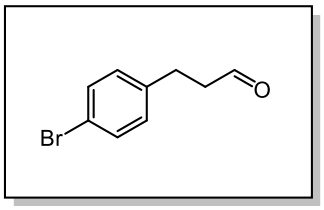
The titled compound was synthesized from 3-(4-chlorophenyl)propanal following the Grignard reaction outlined in General Procedure A. The product was purified *via* silica gel chromatography (gradient from 20% to 30% EtOAc in hexanes) to give the titled compound. Spectra are consistent with reported literature values.[8]



(*E*)-7-(4-chlorophenyl)hept-4-en-1-ol

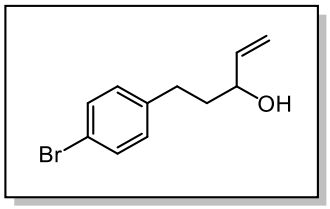
The titled compound was synthesized following General Procedure A using (*E*)-ethyl 7-(4-chlorophenyl)hept-4-enoate, which was synthesized from 5-(4-chlorophenyl)pent-1-en-3-ol and carried onto the next step without further purification. The final product was purified *via* silica gel chromatography (gradient from 20% to 30% EtOAc in hexanes) to give the titled compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.21 (m, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 5.44 (q, *J* = 5.5 Hz, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.63 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.28 (m, 2H), 2.07 (m, 2H), 1.61 (p, *J* = 6.8 Hz, 2H), 1.38 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 140.5, 131.6, 130.7, 130.0, 129.8, 128.5, 62.6, 35.5, 34.4, 32.5, 29.0. **IR (neat):** 3334, 2931, 1492, 1444, 1407, 1092, 1057, 1015, 969, 816, 660 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{17}ClO$) from $[M+H]^+$ is 224.09679, found 224.09666, difference of 0.60 ppm.



3-(4-bromophenyl)propanal

The titled compound was synthesized following a literature procedure.[9] Spectra are consistent with reported literature values.[10]

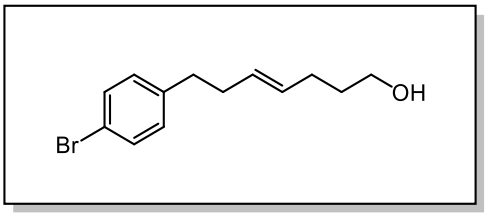


5-(4-bromophenyl)pent-1-en-3-ol

The titled compound was synthesized from 3-(4-bromophenyl)propanal following the Grignard reaction outlined in General Procedure A. The product was purified *via* silica gel chromatography (gradient from 10% to 20% EtOAc in hexanes) to give the titled compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.37 (m, 2H), 7.10–7.05 (m, 2H), 5.89 (ddd, *J* = 17.0, 10.4, 6.3 Hz, 1H), 5.24 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.14 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.15–4.06 (m, 1H), 2.68 (qdd, *J* = 14.0, 9.0, 6.8 Hz, 2H), 1.89–1.75 (m, 2H), 1.54 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 141.0, 140.9, 131.6, 130.4, 119.7, 115.3, 72.4, 38.4, 31.2. **IR (neat):** 3351, 2927, 2862, 1488, 1424, 1404, 1312, 1279, 1179, 1120, 1095, 1072, 1047, 1009, 991, 924, 830, 814, 800,

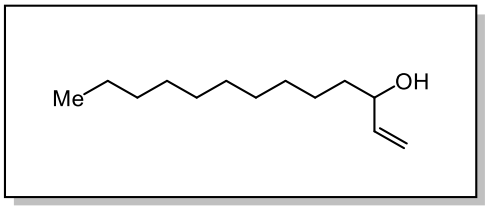
713, 668 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{13}BrO$) from $[M+Na]^+$ is 240.01496, found 240.01459, difference of 1.54 ppm.



(*E*)-7-(4-bromophenyl)hept-4-en-1-ol

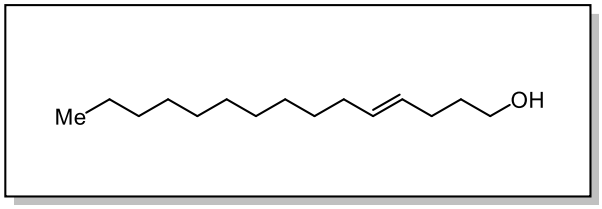
The titled compound was synthesized following General Procedure A using (*E*)-ethyl 7-(4-bromophenyl)hept-4-enoate, which was synthesized from 5-(4-bromophenyl)pent-1-en-3-ol and carried onto the next step without further purification. The final product was purified *via* silica gel chromatography (gradient from 20% to 30% EtOAc in hexanes) to give the titled compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.36 (m, 2H), 7.07–7.00 (m, 2H), 5.43 (q, *J* = 5.3 Hz, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.62 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.34–2.22 (m, 2H), 2.07 (dt, *J* = 8.4, 6.0 Hz, 2H), 1.66–1.54 (m, 2H), 1.35 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 141.2, 131.4, 130.8, 130.4, 129.8, 119.6, 62.6, 35.5, 34.3, 32.5, 29.0. **IR (neat):** 3336, 2931, 1488, 1444, 1403, 1072, 1011, 969, 813 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{17}BrO$) from $[M+H]^+$ is 268.04628, found 268.04605, difference of 0.84 ppm.



Tridec-1-en-3-ol

The titled compound was synthesized from commercially available undecanal following the Grignard reaction outlined in General Procedure A. The product was purified *via* silica gel chromatography (gradient from 10% to 40% EtOAc in hexanes) to give the titled compound. Spectra are consistent with reported literature values.[11]

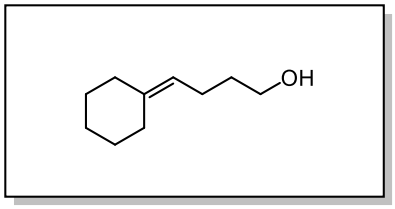


(*E*)-pentadec-4-en-1-ol

The titled compound was synthesized following General Procedure A using (*E*)-ethyl pentadec-4-enoate, which was synthesized from tridec-1-en-3-ol and carried onto the next step without

further purification. The final product was purified *via* silica gel chromatography (gradient from 0% to 20% EtOAc in hexanes) to give the titled compound. Spectra are consistent with reported literature values.[12]

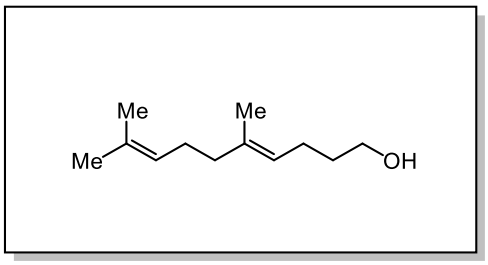
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50–5.35 (m, 2H), 3.66 (t, *J* = 6.5 Hz, 2H), 2.11–2.03 (m, 2H), 1.97 (q, *J* = 6.4 Hz, 2H), 1.64 (p, *J* = 6.7 Hz, 2H), 1.42 (s, 1H), 1.26 (s, 16H), 0.88 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 131.5, 129.5, 62.8, 32.7, 32.6, 32.1, 29.8, 29.8, 29.7, 29.7, 29.5, 29.3, 29.1, 22.8, 14.3. **IR (neat):** 3335, 2922, 2853, 1461, 1057, 966, 721 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{15}H_{30}O$) from $[M+H]^+$ is 226.22967, found 226.22945, difference of 0.95 ppm.



4-cyclohexylidenebutan-1-ol

The titled compound was synthesized following General Procedure A using ethyl 4-cyclohexylidenebutanoate, which was synthesized from commercially available 1-vinylcyclohexanol and carried onto the next step without further purification. The final product was purified *via* silica gel chromatography (gradient from 10% to 20% EtOAc in hexanes) to give the titled compound. Spectra are consistent with reported literature values.[13]

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (t, *J* = 7.4 Hz, 1H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.13 (*J* = 5.9 Hz, 2H), 2.11–2.03 (m, 4H), 1.61 (p, *J* = 6.9 Hz, 2H), 1.57–1.46 (m, 6H), 1.40 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 140.7, 120.6, 62.9, 37.3, 33.2, 28.8, 28.8, 28.0, 27.1, 23.6. **IR (neat):** 3318, 2922, 2853, 1446, 1047, 1032, 936, 895, 842, 825 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{10}H_{18}O$) from $[M+H]^+$ is 154.13577, found 154.13564, difference of 0.84 ppm.

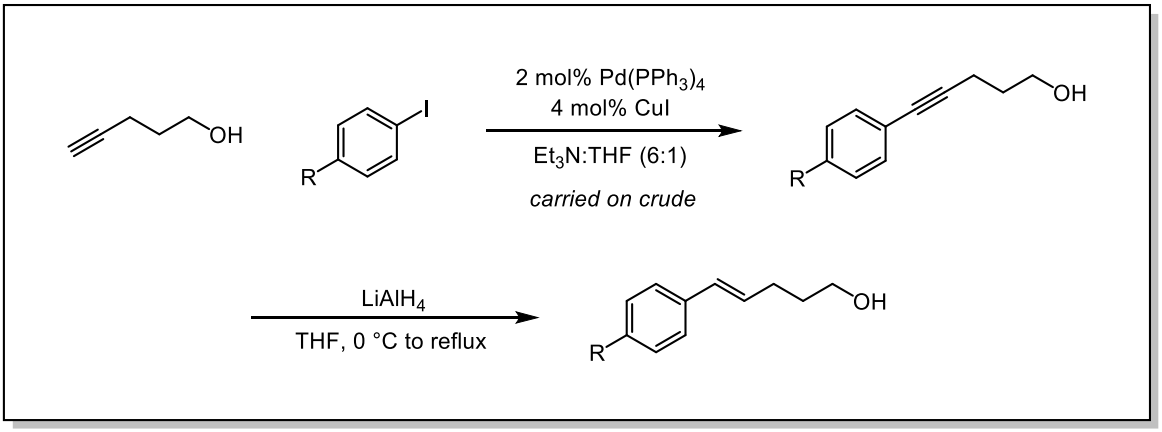


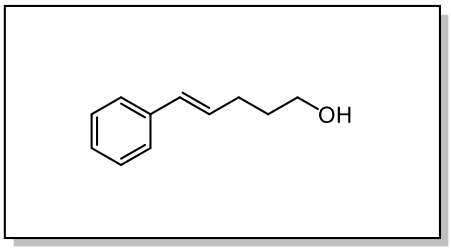
(*E*)-5,9-dimethyldeca-4,8-dien-1-ol

The titled compound was synthesized following General Procedure A using (*E*)-ethyl 5,9-dimethyldeca-4,8-dienoate, which was synthesized from commercially available (*R*)-3,7-dimethylocta-1,6-dien-3-ol ((–)-linalool) and carried onto the next step without further purification. The final product was purified *via* silica gel chromatography (20% EtOAc in hexanes) to give the titled compound as an inseparable mixture of *E* and *Z* isomers. Spectra are consistent with reported literature values.[14]

^{1}H NMR (400 MHz, $CDCl_3$, mixture of *E*/*Z* products) δ 5.18–5.05 (m, 2H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.12–2.03 (m, 5H), 1.99 (dd, *J* = 9.0, 6.4 Hz, 1H), 1.70–1.67 (m, 4H), 1.65–1.56 (m, 7H), 1.33 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$, mixture of *E*/*Z* products)** δ 136.1, 136.0, 131.8, 131.6, 124.7, 124.4, 124.4, 123.9, 62.9, 62.9, 39.9, 33.1, 32.9, 32.1, 26.8, 26.7, 25.8, 24.4, 24.3, 23.5, 17.8, 17.8, 16.1. **IR (neat):** 3329, 2962, 2923, 2856, 1445, 1376, 1058, 829 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{12}H_{22}O$) from $[M+H]^+$ is 182.16707, found 182.16724, difference of 0.99 ppm.

General Procedure B





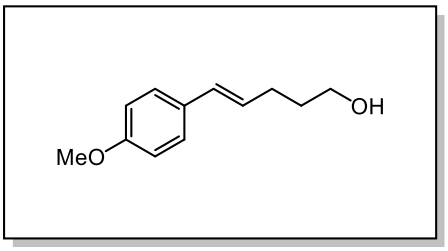
(*E*)-5-phenylpent-4-en-1-ol

To a flame-dried 250-mL round bottom flask equipped with a stir bar was added pent-4-yn-1-ol (15.0 mmol, 1.0 equiv, 1.40 mL) and iodobenzene (16.5 mmol, 1.1 equiv, 1.84 mL) in 44 mL Et_3N and 7.4 mL THF (6:1 Et_3N:THF). CuI (0.600 mmol, 0.04 equiv, 0.114 g) and $Pd(PPh_3)_4$ (0.300 mmol, 0.020 equiv, 0.347 g) were added to the solution, and the reaction mixture was allowed to stir at room temperature overnight. The product was filtered through Celite, and the filtrate was concentrated *in vacuo*. The crude product was carried onto the next step without further purification.

To a flame-dried 100-mL round bottom flask equipped with a stir bar was added $LiAlH_4$ (13.5 mmol, 3.0 equiv, 0.512 g) suspended in 8 mL dry THF. Once the suspension was cooled to 0 °C, crude 5-phenylpent-4-yn-1-ol (4.50 mmol, 1.0 equiv, 0.721 g) dissolved in 5 mL dry THF was added dropwise to the reaction. The reaction was warmed to room temperature and heated at reflux overnight. The reaction mixture was worked up by diluting the mixture with Et_2O and adding 1 mL water, 1 mL 1 M NaOH, and 3 mL water dropwise sequentially at 0 °C. The reaction was warmed to room temperature and stirred for 15 minutes. Anhydrous $MgSO_4$ was

added to the mixture and stirred for 15 minutes. The reaction was filtered and concentrated *in vacuo*. The crude product was purified using silica gel chromatography (30% EtOAc in hexanes) to afford the titled compound (0.600 g, 82% yield). Spectra are consistent with reported literature values.[15]

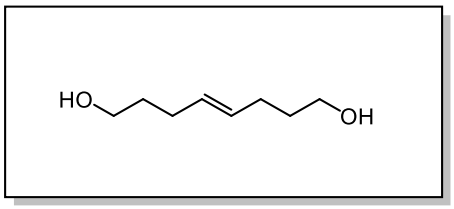
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2H), 7.29 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.22–7.17 (m, 1H), 6.42 (dt, *J* = 15.8, 1.6 Hz, 1H), 6.24 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.72 (q, *J* = 6.2 Hz, 2H), 2.32 (qd, *J* = 7.1, 1.5 Hz, 2H), 1.81–1.70 (m, 2H), 1.30 (t, *J* = 5.3 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 137.7, 130.5, 130.2, 128.7, 127.1, 126.1, 62.6, 32.4, 29.5. **IR (neat):** 3335, 3025, 2934, 2866, 1494, 1447, 1057, 965, 741, 690 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{14}O$) from $[M+H]^+$ is 162.10447, found 162.10415, difference of 1.97 ppm.



(*E*)-5-(4-methoxyphenyl)pent-4-en-1-ol

The titled compound was synthesized following General Procedure B using 5-(4-methoxyphenyl)pent-4-yn-1-ol, which was synthesized from commercially available pent-4-yn-1-ol and 1-iodo-4-methoxybenzene and carried onto the next step without further purification. The final product was purified *via* recrystallization in hexanes and Et_2O to give the titled compound. Spectra are consistent with reported literature values.[16]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.9 Hz, 2H), 6.87–6.79 (m, 2H), 6.37 (dt, *J* = 15.8, 1.6 Hz, 1H), 6.09 (dt, *J* = 15.8, 7.0 Hz, 1H), 3.80 (s, 3H), 3.71 (q, *J* = 6.2 Hz, 2H), 2.29 (qd, *J* = 7.2, 1.5 Hz, 2H), 1.75 (dt, *J* = 7.9, 6.6 Hz, 2H), 1.28 (t, *J* = 5.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.9, 130.6, 129.9, 128.0, 127.2, 114.1, 62.6, 55.4, 32.5, 29.5. **IR (neat):** 3358, 3281, 2934, 2863, 1606, 1511, 1459, 1443, 1242, 1173, 1029, 970, 833, 800 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{12}H_{16}O_2$) from $[M+H]^+$ is 192.11503, found 192.11482, difference of 1.09 ppm.



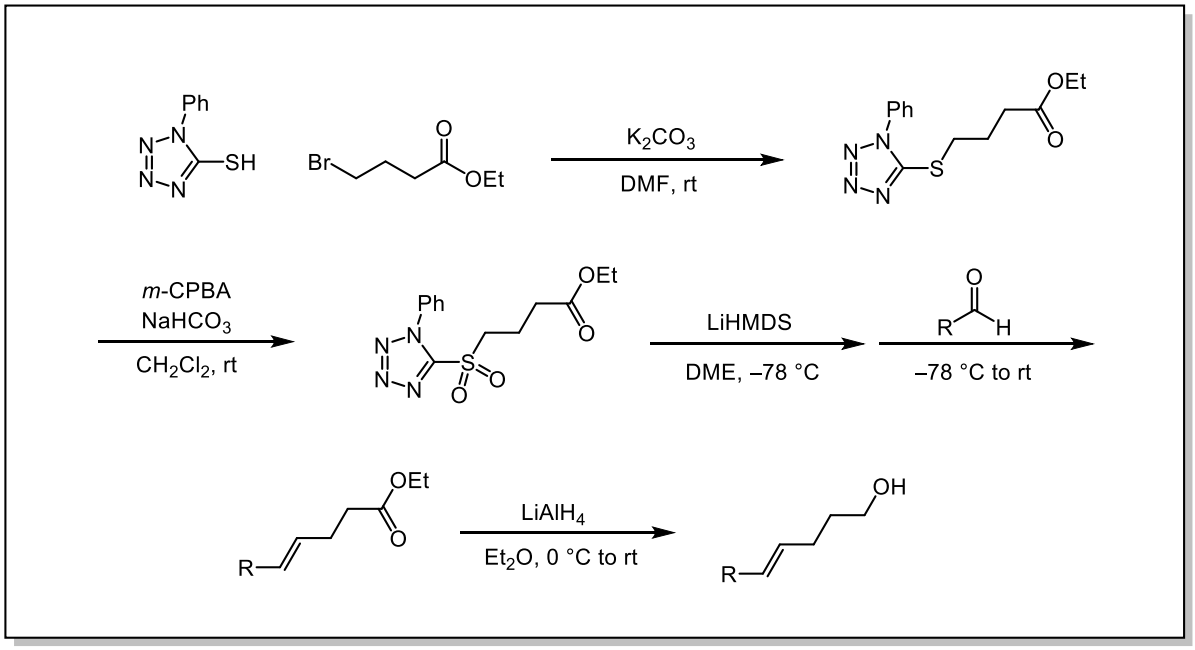
(*E*)-oct-4-ene-1,8-diol

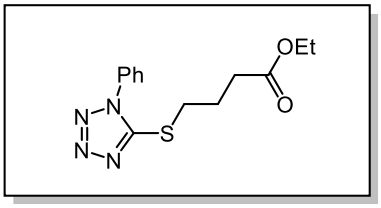
The titled compound was synthesized following a literature procedure.[17] Spectra are consistent with reported literature values with a 5:1 ratio of inseparable *E*:*Z* product.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of *E*/*Z* products) δ 5.66–5.33 (m, 2H), 3.65 (t, *J* = 6.5 Hz, 4H), 2.22–2.05 (m, 4H), 1.69–1.59 (m, 6H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of *E*/*Z***

products) δ 130.4, 130.0, 62.6, 62.1, 32.5, 32.4, 29.0, 23.4. **IR (neat):** 3310, 2931, 2866, 1441, 1050, 1034, 967, 915 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_8H_{16}O_2$) from $[M+H]^+$ is 144.11503, found 144.11511, difference of 0.54 ppm.

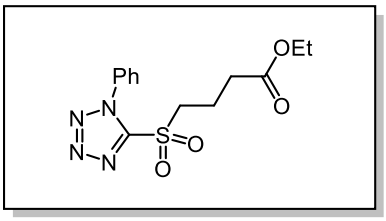
General Procedure C





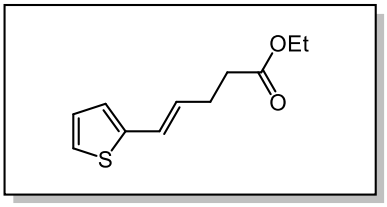
Ethyl 4-((1-phenyl-1*H*-tetrazol-5-yl)thio)butanoate

To a flame-dried 250-mL round bottom flask was added 1-phenyl-1*H*-tetrazole-5-thiol (22.4 mmol, 1.0 equiv, 4.00 g) and K_2CO_3 (44.9 mmol, 2.0 equiv, 6.20 g). The flask was evacuated and backfilled with nitrogen, and 30 mL anhydrous DMF was added. To the flask was added ethyl 4-bromobutanoate (24.7 mmol, 1.1 equiv, 3.53 mL), and the reaction was allowed to stir at room temperature overnight. The reaction was quenched with water and CH_2Cl_2, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with 5% aqueous LiCl solution, brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified *via* silica gel chromatography (gradient from 20% to 40% EtOAc in hexanes) to give the titled compound (6.60 g, 100% yield). Spectra are consistent with reported literature values.[18]



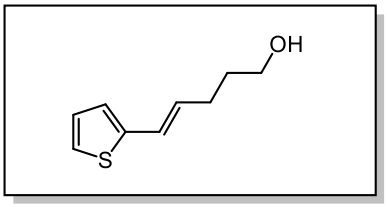
Ethyl 4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butanoate

To a flame-dried 250-mL round bottom flask was added ethyl 4-((1-phenyl-1*H*-tetrazol-5-yl)thio)butanoate (23.9 mmol, 1.0 equiv, 7.00 g), *m*-CPBA (≤77% purity) (120 mmol, 5.0 equiv, 20.7 g), and $NaHCO_3$ (59.9 mmol, 2.5 equiv, 5.03 g). The flask was evacuated and backfilled with nitrogen, and 60 mL CH_2Cl_2 was added. The reaction was allowed to stir at room temperature overnight, with a large amount of precipitate crashing out of solution. The reaction was quenched with saturated aqueous $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc, washed with saturated aqueous $Na_2S_2O_3$, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using silica gel chromatography (gradient from 10% to 30% EtOAc in hexanes) to yield the titled compound as a white solid (5.88 g, 76% yield). Spectra are consistent with reported literature values.[18]



(*E*)-ethyl 5-(thiophen-2-yl)pent-4-enoate

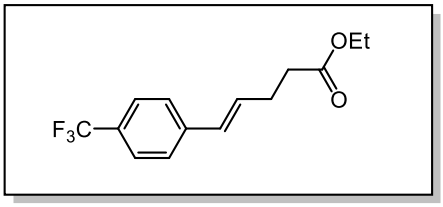
To a flame-dried 100-mL round bottom flask was added ethyl 4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butanoate (4.93 mmol, 1.0 equiv, 1.60 g). The flask was evacuated and backfilled with nitrogen, and 20 mL anhydrous DME was added. The reaction mixgture was then cooled to –78 °C. A solution of LiHMDS (5.43 mmol, 1.1 equiv, 1 M in THF, 5.43 mL) was added dropwise to the reaction, which was allowed to stir for 30 minutes. Then, commercially available thiophene-2-carbaldehyde (4.93 mmol, 1.0 equiv, 0.46 mL) dissolved in 10 mL DME was added dropwise to the reaction, which was slowly warmed to room temperature and allowed to stir overnight. The reaction was quenched with water and EtOAc, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and purified using silica gel chromatography (gradient from 0% to 10% EtOAc in hexanes) to give the titled compound (0.936 g, 90% yield). Spectra are consistent with reported literature values.[18]



(*E*)-5-(thiophen-2-yl)pent-4-en-1-ol

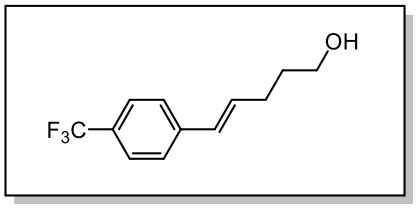
To a flame-dried 50-mL round bottom flask equipped with a stir bar was added $LiAlH_4$ (8.84 mmol, 2.0 equiv, 0.336 g) suspended in 15 mL anhydrous Et_2O. Once the suspension was cooled to 0 °C, (*E*)-ethyl 5-(thiophen-2-yl)pent-4-enoate (4.42 mmol, 1.0 equiv, 0.930 g) dissolved in 10 mL anhydrous Et_2O was added dropwise to the reaction. After 30 minutes, the reaction was warmed to room temperature and allowed to stir overnight. The reaction mixture was worked up by diluting the mixture with Et_2O and adding 0.4 mL water, 0.4 mL 1 M NaOH, and 1.2 mL water dropwise sequentially at 0 °C. The reaction was warmed to room temperature and stirred for 15 minutes. Anhydrous $MgSO_4$ was added to the mixture and stirred for 15 minutes. The reaction was filtered through Celite and concentrated *in vacuo*. The crude product was purified using silica gel chromatography (gradient from 10% to 30% EtOAc in hexanes) to afford the titled compound (0.381 g, 51% yield) with a 7:1 ratio of inseparable *E*:*Z* product. Spectra are consistent with reported literature values.[19]

^{1}H NMR (500 MHz, $CDCl_3$, mixture of *E*/*Z* products) δ 7.29–7.22 (m, 0.1H), 7.13–7.05 (m, 0.9H), 7.03–6.97 (m, 0.2H), 6.93 (dd, *J* = 5.1, 3.6 Hz, 0.9H), 6.87 (d, *J* = 3.5 Hz, 0.9H), 6.61–6.49 (m, 1H), 6.07 (dt, *J* = 15.7, 7.0 Hz, 0.9H), 5.59 (dt, *J* = 11.4, 7.3 Hz, 0.1H), 3.70 (t, *J* = 6.5 Hz, 2H), 2.52 (qd, *J* = 7.4, 1.8 Hz, 0.2H), 2.35–2.21 (m, 1.8H), 1.86–1.68 (m, 2H), 1.30 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of *E*/*Z* products)** δ 143.0, 130.2, 130.1, 127.4, 127.4, 126.9, 125.2, 124.6, 123.8, 123.4, 122.5, 62.7, 62.5, 32.5, 32.2, 29.2, 25.7. **IR (neat):** 3314, 2933, 2875, 1435, 1204, 1056, 1040, 954, 852, 831, 693 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_9H_{12}OS$) from $[M+H]^+$ is 168.06089, found 168.06076, difference of 0.73 ppm.



(*E*)-ethyl 5-(4-trifluoromethyl)phenyl)pent-4-enoate

The titled compound was synthesized following General Procedure C for the olefination of commercially available 4-(trifluoromethyl)benzaldehyde. The crude product was purified *via* silica gel chromatography (gradient from 0% to 10% EtOAc in hexanes) to give the titled compound with a 6:1 ratio of inseparable *E*:*Z* products. Spectra are consistent with reported literature values.[20]

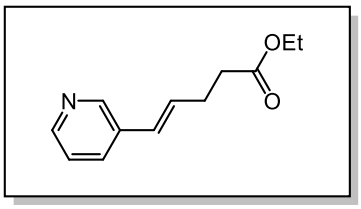


(*E*)-5-(4-(trifluoromethyl)phenyl)pent-4-en-1-ol

The titled compound was synthesized following General Procedure C for the reduction of (*E*)-ethyl 5-(4-trifluoromethyl)phenyl)pent-4-enoate. The crude product was purified *via* silica gel chromatography (gradient from 20% to 30% EtOAc in hexanes) to give the titled compound with

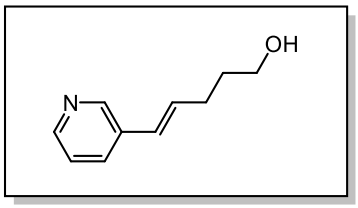
pure *E* isomer isolated. Spectra are consistent with reported literature values.[21]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.34 (dt, *J* = 15.8, 6.5 Hz, 1H), 3.72 (t, *J* = 6.4 Hz, 2H), 2.35 (q, *J* = 7.1 Hz, 2H), 1.78 (dt, *J* = 8.0, 6.6 Hz, 2H), 1.38 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 141.2, 133.1, 129.4, 128.9 (q, *J* = 31.5 Hz), 126.2, 125.6 (q, *J* = 5.0 Hz), 124.4 (q, *J* = 272.2 Hz), 62.5, 32.2, 29.5. **^{19}F NMR (282 MHz, $CDCl_3$)** δ –62.41. **IR (neat):** 3352, 2934, 2876, 1652, 1615, 1415, 1323, 1161, 1115, 1065, 1016, 967, 852, 806, 763 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{12}H_{13}F_3O$) from $[M+H]^+$ is 230.09185, found 230.09184, difference of 0.04 ppm.



(*E*)-ethyl 5-(pyridin-3-yl)pent-4-enoate

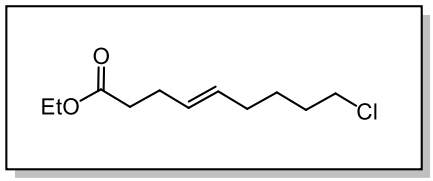
The titled compound was synthesized following General Procedure C for the olefination of commercially available nicotinaldehyde. The crude product was purified *via* silica gel chromatography (gradient from 80% to 100% EtOAc in hexanes) to give the titled compound with a 6:1 ratio of inseparable *E*:*Z* products. Spectra are consistent with reported literature values.[22]



(*E*)-5-(pyridin-3-yl)pent-4-en-1-ol

The titled compound was synthesized following General Procedure C for the reduction of (*E*)-ethyl 5-(pyridine-3-yl)pent-4-enoate. The crude product was purified *via* silica gel chromatography (gradient from 70% to 100% EtOAc in hexanes) to give the titled compound with a 4:1 ratio of inseparable *E*:*Z* products.

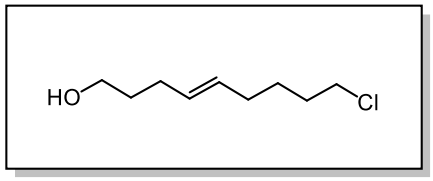
^{1}H NMR (500 MHz, $CDCl_3$, mixture of *E*/*Z* products) δ 8.55 (dd, *J* = 9.5, 2.3 Hz, 1H), 8.44 (ddd, *J* = 12.7, 4.8, 1.7 Hz, 1H), 7.66 (dt, *J* = 7.9, 2.0 Hz, 0.8H), 7.60 (dt, *J* = 7.9, 2.0 Hz, 0.2H), 7.28–7.19 (m, 1H), 6.44–6.37 (m, 1H), 6.32 (dt, *J* = 15.9, 6.7 Hz, 0.8H), 5.82 (dt, *J* = 11.6, 7.4 Hz, 0.2H), 3.72 (t, *J* = 6.4 Hz, 1.6H), 3.69 (t, *J* = 6.4 Hz, 0.4H), 2.41 (qd, *J* = 7.4, 1.8 Hz, 0.4H), 2.35 (td, *J* = 8.0, 7.5, 6.2 Hz, 1.6H), 1.81–1.71 (m, 2H), 1.81–1.52 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of *E*/*Z* products)** δ 150.0, 148.1, 148.0, 147.7, 135.9, 134.7, 133.3, 132.8, 132.6, 127.0, 126.0, 123.6, 123.3, 62.4, 32.8, 32.2, 29.6, 25.1. **IR (neat):** 3285, 3027, 2930, 2862, 1651, 1571, 1479, 1416, 1056, 1025, 965, 922, 827, 790, 701 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{10}H_{13}NO$) from $[M+H]^+$ is 163.09971, found 163.09953, difference of 1.15 ppm.



(*E*)-ethyl 9-chloronon-4-enoate

The titled compound was synthesized following General Procedure C for the olefination of commercially available 5-chloropentanal. The crude product was purified *via* silica gel chromatography (gradient from 0% to 10% EtOAc in hexanes) to give the titled compound with a 4:1 ratio of inseparable *E*:*Z* products.

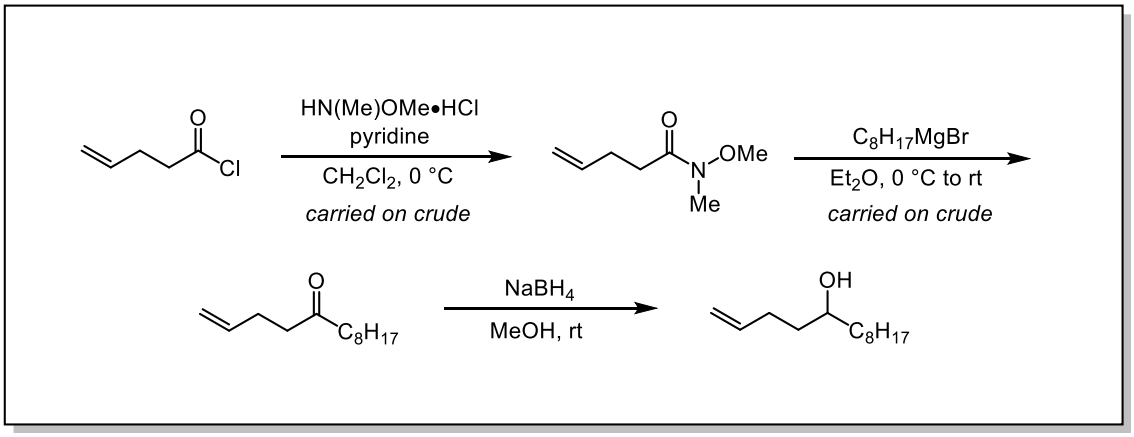
^{1}H NMR (500 MHz, $CDCl_3$, mixture of *E*/*Z* products) δ 5.51–5.32 (m, 2H), 4.16–4.09 (m, 2H), 3.53 (q, *J* = 6.7 Hz, 2H), 2.39–2.28 (m, 4H), 2.09 (q, *J* = 7.1 Hz, 0.4H), 2.04–1.98 (m, 1.6H), 1.77 (dq, *J* = 15.1, 6.7 Hz, 2H), 1.55–1.45 (m, 2H), 1.26 (td, *J* = 7.1, 2.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of *E*/*Z* products)** δ 173.3, 173.2, 131.0, 130.6, 128.9, 128.3, 60.5, 60.4, 45.1, 34.5, 32.3, 32.1, 31.8, 28.0, 26.9, 26.7, 26.5, 23.0, 14.4, 14.3. **IR (neat):** 2982, 2935, 2860, 1732, 1445, 1372, 1345, 1301, 1250, 1173, 1164, 1096, 1039, 969, 857, 724, 652 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{19}ClO_2$) from $[M+H]^+$ is 218.10736, found 218.10739, difference of 0.16 ppm.

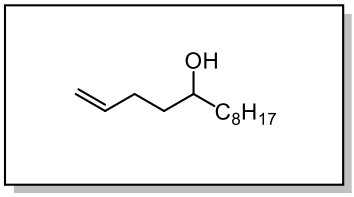


(*E*)-9-chloronon-4-en-1-ol

The titled compound was synthesized following General Procedure C for the reduction of (*E*)-ethyl 9-chloronon-4-enoate. The crude product was purified *via* silica gel chromatography (gradient from 15% to 20% EtOAc in hexanes) to give the titled compound with a 6:1 ratio of inseparable *E*:*Z* products.

^{1}H NMR (500 MHz, $CDCl_3$, mixture of *E*/*Z* products) δ 5.49–5.36 (m, 2H), 3.65 (td, *J* = 6.5, 3.6 Hz, 2H), 3.54 (td, *J* = 6.7, 3.9 Hz, 2H), 2.16–1.99 (m, 4H), 1.82–1.73 (m, 2H), 1.67–1.60 (m, 2H), 1.54–1.46 (m, 2H), 1.37 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of *E*/*Z* products)** δ 130.4, 130.4, 129.9, 129.8, 62.7, 62.7, 45.2, 32.7, 32.5, 32.3, 32.2, 31.9, 29.0, 27.0, 26.8, 26.5, 23.7. **IR (neat):** 3331, 2932, 2860, 1443, 1306, 1056, 969, 916, 723 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_9H_{17}ClO$) from $[M+H]^+$ is 176.09679, found 176.09686, difference of 0.40 ppm.





Tridec-1-en-5-ol

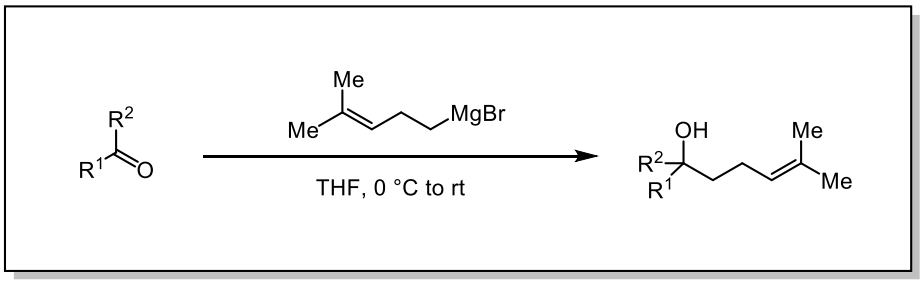
To a flame-dried 250-mL round bottom flask was added *N,O*-dimethylhydroxylamine hydrochloride (27.8 mmol, 1.1 equiv, 2.71 g), pyridine (63.3 mmol, 2.5 equiv, 5.12 mL), and 40 mL CH_2Cl_2. The mixture was cooled to 0 °C, and to the mixture was slowly added pent-4-enoyl chloride (25.3 mmol, 1.0 equiv, 2.79 mL) dissolved in 10 mL of CH_2Cl_2. The reaction mixture was warmed to room temperature and allowed to stir for 4 hours. The crude reaction was diluted with EtOAc and washed with 1 M HCl. The organic layer was further washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give *N*-methoxy-*N*-methylpent-4-enamide as a brown oil. The crude product was carried onto the next step without further purification.

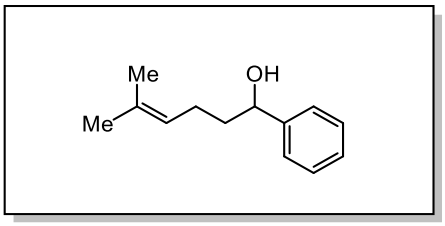
To a flame-dried 100-mL round bottom flask was added crude *N*-methoxy-*N*-methylpent-4-enamide (6.98 mmol, 1.0 equiv, 1.00 g) and 20 mL anhydrous Et_2O. The mixture was cooled to 0 °C, and to the mixture was added a commercially available solution of octylmagnesium bromide (8.38 mmol, 1.2 equiv, 2 M in Et_2O, 4.19 mL) dropwise. The reaction mixture was slowly warmed to room temperature and allowed to stir overnight. The crude reaction was quenched with saturated aqueous NH_4Cl at 0 °C, acidified with 1 M HCl, extracted with Et_2O, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give tridec-1-en-5-one. The crude product was carried onto the next step without further purification.

To a flame-dried 100-mL round bottom flask equipped with a stir bar was added crude tridec-1-en-5-one (7.13 mmol, 1.0 equiv, 1.40 g) and 25 mL methanol. To the reaction was added $NaBH_4$ (9.27 mmol, 1.3 equiv, 0.351 g) at 0 °C, and the reaction was allowed to stir overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl and water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified *via* silica gel chromatography (gradient from 5% to 10% EtOAc in hexanes) to give the titled compound (1.25 g, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.9 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 3.62 (tt, *J* = 8.6, 4.3 Hz, 1H), 2.26–2.08 (m, 2H), 1.62–1.38 (m, 6H), 1.34–1.22 (m, 11H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 138.8, 114.9, 71.7, 37.7, 36.6, 32.0, 30.3, 29.8, 29.7, 29.4, 25.8, 22.8, 14.3. **IR (neat):** 3343, 2926, 2855, 1642, 1462, 991, 910 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{26}O$) from $[M+Na]^+$ is 198.19835, found 198.19872, difference of 1.87 ppm.

General Procedure D

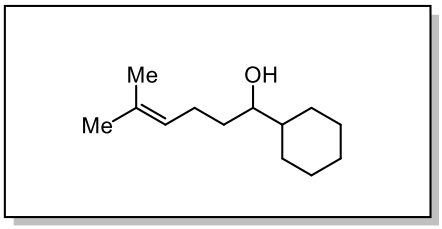




5-methyl-1-phenylhex-4-en-1-ol

To a flame-dried 100-mL round bottom flask equipped with a condenser and stir bar was added magnesium turnings (14.0 mmol, 1.4 equiv, 0.340 g) and a catalytic amount of iodine. The solids were stirred under nitrogen for 4 hours to achieve activation. To the mixture was added 5-bromo-2-methylpent-2-ene (12.0 mmol, 1.2 equiv, 1.61 mL) dissolved in 20 mL anhydrous THF, first portion-wise and then dropwise. The reaction mixture was stirred at reflux for 2 hours. The reaction was cooled to room temperature and then 0 °C, after which commercially available benzaldehyde (10.0 mmol, 1.0 equiv, 1.02 mL) dissolved in 6 mL THF was added dropwise. The reaction was allowed to stir under nitrogen overnight. The reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl, extracted with Et_2O, washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford a clear oil. The crude product was purified *via* silica gel chromatography (gradient from 5% to 10% EtOAc in hexanes) to give the titled compound (0.747 g, 39% yield). Spectra are consistent with reported literature values.[23]

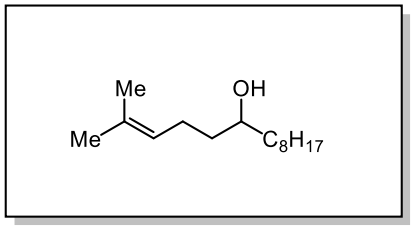
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.4 Hz, 4H), 7.30–7.24 (m, 1H), 5.14 (ddq, *J* = 8.7, 6.0, 1.5 Hz, 1H), 4.68 (dd, *J* = 7.8, 5.4 Hz, 1H), 2.14–2.00 (m, 2H), 1.89–1.71 (m, 3H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.59 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 144.9, 132.5, 128.6, 127.6, 126.0, 123.9, 74.4, 39.2, 25.9, 24.6, 17.9. **IR (neat):** 3354, 3029, 2966, 2920, 2857, 1604, 1494, 1451, 1377, 1200, 1060, 1015, 915, 832, 760, 698 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{18}O$) from $[M+Na]^+$ is 190.13577, found 190.13541, difference of 1.87 ppm.



1-cyclohexyl-5-methylhex-4-en-1-ol

The titled compound was synthesized following General Procedure D for the Grignard addition to commercially available cyclohexanecarbaldehyde. The crude product was purified *via* silica gel chromatography (gradient from 5% to 10% EtOAc in hexanes) to give the titled compound. Spectra are consistent with reported literature values.[24]

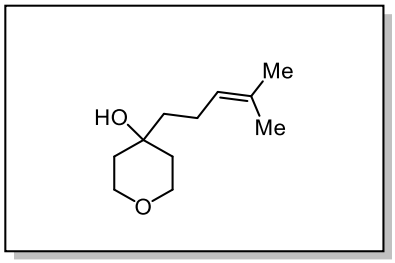
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (tp, *J* = 7.3, 1.4 Hz, 1H), 3.37 (ddd, *J* = 8.9, 5.4, 3.3 Hz, 1H), 2.14 (dt, *J* = 14.7, 7.3 Hz, 1H), 2.05 (dq, *J* = 14.8, 7.6 Hz, 1H), 1.84–1.61 (m, 11H), 1.57–1.49 (m, 1H), 1.47–1.38 (m, 2H), 1.35–0.95 (m, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 132.2, 124.5, 76.2, 43.8, 34.3, 29.4, 27.9, 26.7, 26.5, 26.4, 25.9, 24.8, 17.9. **IR (neat):** 3360, 2922, 2852, 1449, 1376, 1265, 1086, 1063, 1047, 966, 892, 831 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{24}O$) from $[M+H]^+$ is 196.18272, found 196.18296, difference of 1.25 ppm.



2-methyltetradec-2-en-6-ol

The titled compound was synthesized following General Procedure D for the Grignard addition to commercially available nonanal. The crude product was purified *via* silica gel chromatography (gradient from 5% to 20% EtOAc in hexanes) to give the titled compound.

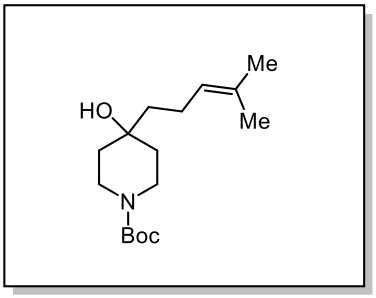
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (ddt, *J* = 7.2, 5.7, 1.5 Hz, 1H), 3.60 (tt, *J* = 8.6, 4.2 Hz, 1H), 2.17–2.01 (m, 2H), 1.69 (d, *J* = 1.5 Hz, 3H), 1.6 (s, 3H), 1.55–1.38 (m, 6H), 1.34–1.21 (m, 11H), 0.88 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 132.2, 124.4, 72.0, 37.7, 37.5, 32.0, 29.9, 29.7, 29.4, 25.9, 25.8, 24.6, 22.8, 17.8, 14.3. **IR (neat):** 3339, 2927, 2854, 1454, 1377, 1074, 989, 832, 722 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{15}H_{30}O$) from $[M+H]^+$ is 226.22967, found 226.22942, difference of 1.08 ppm.



4-(4-methylpent-3-en-1-yl)tetrahydro-2*H*-pyran-4-ol

The titled compound was synthesized following General Procedure D for the Grignard addition to commercially available tetrahydropyran-4-one. The crude product was purified *via* silica gel chromatography (gradient from 5% to 40% EtOAc in hexanes) to give the titled compound.

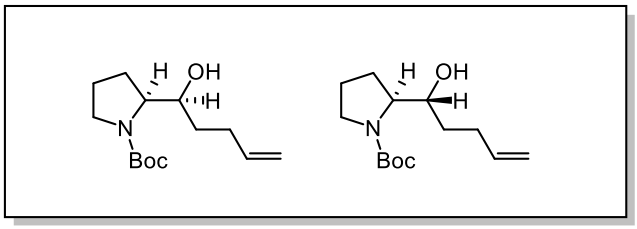
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (tt, *J* = 7.3, 1.6 Hz, 1H), 3.80–3.71 (m, 4H), 2.10 (q, *J* = 7.7 Hz, 2H), 1.73–1.66 (m, 5H), 1.63 (s, 3H), 1.56–1.47 (m, 4H), 1.33 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 132.4, 124.3, 69.3, 64.0, 43.1, 37.8, 25.9, 21.5, 17.8. **IR (neat):** 3420, 2927, 2865, 1446, 1384, 1300, 1239, 1179, 1098, 1017, 985, 933, 843 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{20}O_2$) from $[M+Na]^+$ is 184.14633, found 184.14617, difference of 0.85 ppm.



***tert*-butyl 4-hydroxy-4-(4-methylpent-3-en-1-yl)piperidine-1-carboxylate**

The titled compound was synthesized following General Procedure D for the Grignard addition to commercially available *tert*-butyl 4-oxopiperidine-1-carboxylate. The crude product was purified *via* silica gel chromatography (gradient from 5% to 40% EtOAc in hexanes) to give the titled compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (tdd, *J* = 5.6, 2.9, 1.5 Hz, 1H), 3.80 (dt, *J* = 13.3, 4.1 Hz, 2H), 3.16 (ddd, *J* = 13.3, 9.3, 5.6 Hz, 2H), 2.08 (q, *J* = 7.6 Hz, 2H), 1.69 (d, *J* = 1.5 Hz, 3H), 1.62 (s, 3H), 1.55–1.49 (m, 5H), 1.45 (s, 10H), 1.42–1.34 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 155.0, 132.5, 124.2, 79.5, 70.1, 42.8, 39.9, 36.9, 28.6, 25.9, 21.7, 17.8. **IR (neat):** 3438, 2971, 2922, 2880, 1694, 1666, 1425, 1365, 1278, 1246, 1166, 1148, 1083, 1009, 966, 864, 768 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{16}H_{29}NO_3$) from $[M+Na]^+$ is 283.21474, found 283.21452, difference of 0.77 ppm.



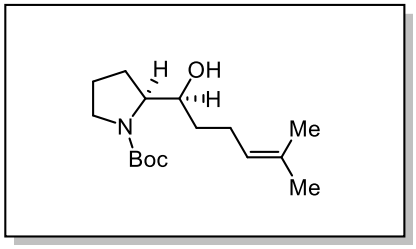
***tert*-butyl (*S*)-2-((*S*)-1-hydroxypent-4-en-1-yl)pyrrolidine-1-carboxylate**
***tert*-butyl (*S*)-2-((*R*)-1-hydroxypent-4-en-1-yl)pyrrolidine-1-carboxylate**

To a flame-dried 100-mL round bottom flask equipped with a condenser and stir bar was added magnesium turnings (11.2 mmol, 1.4 equiv, 0.272 g) and a catalytic amount of iodine. The solids were stirred under nitrogen for 4 hours to achieve activation. To the mixture was added 4-bromobut-1-ene (9.60 mmol, 1.2 equiv, 0.974 mL) dissolved in 16 mL anhydrous THF, first

portion-wise and then dropwise. The reaction mixture was stirred at reflux for 2 hours. The reaction was cooled to room temperature and then 0 °C, after which commercially available (*S*)-*tert*-butyl 2-formylpyrrolidine-1-carboxylate (8.00 mmol, 1.0 equiv, 1.50 mL) dissolved in 4 mL THF was added dropwise. The reaction was allowed to stir under nitrogen overnight. The reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl, extracted with Et_2O, washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford a clear oil. The crude product was purified *via* silica gel chromatography (gradient from 20% to 40% EtOAc in hexanes) to give the *S*,*S*-diastereomer (0.796 g, 39% yield) and the *S*,*R*-diastereomer (0.741 g, 36% yield).

^{1}H NMR (500 MHz, $CDCl_3$, *S*,*S*-diastereomer) δ 5.84 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.04 (dq, *J* = 17.2, 1.8 Hz, 1H), 4.96 (ddt, *J* = 10.2, 2.2, 1.4 Hz, 1H), 3.88 (t, *J* = 7.2 Hz, 1H), 3.79 (t, *J* = 6.6 Hz, 1H), 3.55 (ddd, *J* = 10.5, 7.3, 4.9 Hz, 1H), 3.23 (dt, *J* = 10.6, 7.1 Hz, 1H), 3.18, (br, 1H), 2.33 (dq, *J* = 14.2, 7.1, 6.6 Hz, 1H), 2.18–2.08 (m, 1H), 2.01–1.92 (m, 1H), 1.91–1.82 (m, 1H), 1.79–1.67 (m, 2H), 1.46 (s, 9H), 1.45–1.39 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$, *S*,*S*-diastereomer)** δ 156.6, 139.0, 114.8, 80.1, 73.3, 63.4, 48.3, 31.4, 30.6, 28.6, 28.0, 24.4. **IR (neat):** 3425, 2975, 2932, 2881, 1689, 1670, 1478, 1398, 1366, 1252, 1166, 1113, 995, 909, 875, 772 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{14}H_{25}NO_3$) from $[M+Na]^+$ is 255.18344, found 255.18318, difference of 1.02 ppm.

^{1}H NMR (500 MHz, $CDCl_3$, *S*,*R*-diastereomer) δ 5.84 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.04 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.95 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 3.81 (td, *J* = 8.3, 4.2 Hz, 1H), 3.48 (tt, *J* = 7.8, 4.8 Hz, 2H), 3.28 (ddd, *J* = 10.9, 7.3, 5.6 Hz, 1H), 2.37–2.26 (m, 1H), 2.23–2.14 (m, 1H), 1.95 (dq, *J* = 12.5, 7.8 Hz, 1H), 1.89–1.72 (m, 2H), 1.69–1.61 (m, 1H), 1.60–1.52 (m, 1H), 1.46 (s, 11H). **^{13}C NMR (126 MHz, $CDCl_3$, *S*,*R*-diastereomer)** δ 158.2, 139.0, 114.0, 80.6, 75.3, 62.9, 47.4, 34.5, 29.6, 28.8, 28.6, 24.3. **IR (neat):** 3411, 2976, 2932, 2881, 1693, 1666, 1478, 1399, 1366, 1253, 1166, 1109, 909, 774 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{14}H_{25}NO_3$) from $[M+Na]^+$ is 255.18344, found 255.18308, difference of 1.44 ppm.

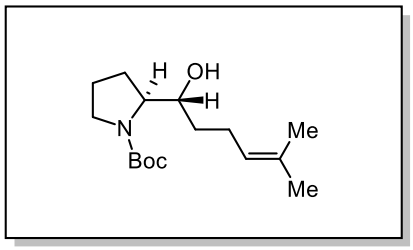


***tert*-butyl (*S*)-2-((*S*)-1-hydroxy-5-methylhex-4-en-1-yl)pyrrolidine-1-carboxylate**

To a flame-dried 25-mL round bottom flask was added Grubbs Catalyst 2nd Generation (11.7 μmol, 0.01 equiv, 10.0 mg) in neat 2-methyl-2-butene (47.2 mmol, 40 equiv, 5.00 mL). This solution was degassed for five minutes, and to this mixture was added *tert*-butyl (*S*)-2-((*S*)-1-hydroxypent-4-en-1-yl)pyrrolidine-1-carboxylate (1.17 mmol, 1.0 equiv, 0.300 g). The reaction mixture was allowed to stir overnight under nitrogen. The solvent was evaporated *in vacuo*, and the product was purified using silica gel chromatography (gradient from 5% to 20% EtOAc in hexanes) to give the titled compound (0.312 g, 94% yield).

^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 5.19–5.11 (m, 1H), 4.16–3.89 (m, 1H), 3.79–3.48 (m, 2H), 3.30–3.19 (m, 1H), 2.37–2.18 (m, 1H), 2.14–2.06 (m, 1H), 2.04–1.95 (m,

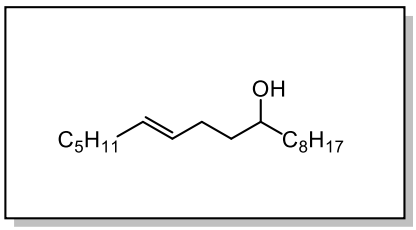
1H), 1.93–1.84 (m, 1H), 1.79–1.67 (m, 5H), 1.64 (s, 3H), 1.48 (s, 10H), 1.41–1.30 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of rotamers)** δ 156.6, 132.1, 124.6, 80.0, 73.5, 63.4, 48.3, 32.2, 28.6, 28.0, 25.9, 25.0, 24.4, 17.8. **IR (neat):** 3429, 2972, 2927, 2879, 1692, 1669, 1478, 1453, 1395, 1365, 1251, 1164, 1109, 1065, 908, 872, 853, 771 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{16}H_{29}NO_3$) from $[M+H]^+$ is 283.21474, found 283.21418, difference of 1.97 ppm.



***tert*-butyl (*S*)-2-((*R*)-1-hydroxy-5-methylhex-4-en-1-yl)pyrrolidine-1-carboxylate**

To a flame-dried 25-mL round bottom flask was added Grubbs Catalyst 2nd Generation (19.6 μmol, 0.01 equiv, 16.6 mg) in neat 2-methyl-2-butene (58.7 mmol, 30 equiv, 6.22 mL). This solution was degassed for five minutes, and to this mixture was added *tert*-butyl (*S*)-2-((*R*)-1-hydroxypent-4-en-1-yl)pyrrolidine-1-carboxylate (1.96 mmol, 1.0 equiv, 0.500 g). The reaction mixture was allowed to stir overnight under nitrogen. The solvent was evaporated *in vacuo*, and the product was purified using silica gel chromatography (gradient from 5% to 20% EtOAc in hexanes) to give the titled compound (0.520 g, 94% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (tdd, *J* = 7.1, 3.0, 1.5 Hz, 1H), 3.81 (td, *J* = 8.2, 4.3 Hz, 1H), 3.49 (d, *J* = 9.6 Hz, 2H), 3.29 (ddd, *J* = 10.9, 7.3, 5.6 Hz, 1H), 2.28–2.17 (m, 1H), 2.11 (dq, *J* = 15.0, 7.7 Hz, 1H), 1.95 (dq, *J* = 12.3, 7.8 Hz, 1H), 1.89–1.72 (m, 2H), 1.71–1.58 (m, 7H), 1.53–1.43 (m, 11H), 1.38 (dtt, *J* = 13.6, 8.7, 4.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.1, 131.9, 124.5, 80.5, 75.5, 62.9, 47.3, 35.3, 28.8, 28.6, 25.9, 24.3, 23.8, 17.8. **IR (neat):** 3415, 2972, 2928, 2881, 1694, 1667, 1478, 1449, 1400, 1366, 1253, 1167, 1108, 908, 874, 773 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{16}H_{29}NO_3$) from $[M+Na]^+$ is 283.21474, found 283.21499, difference of 0.87 ppm.

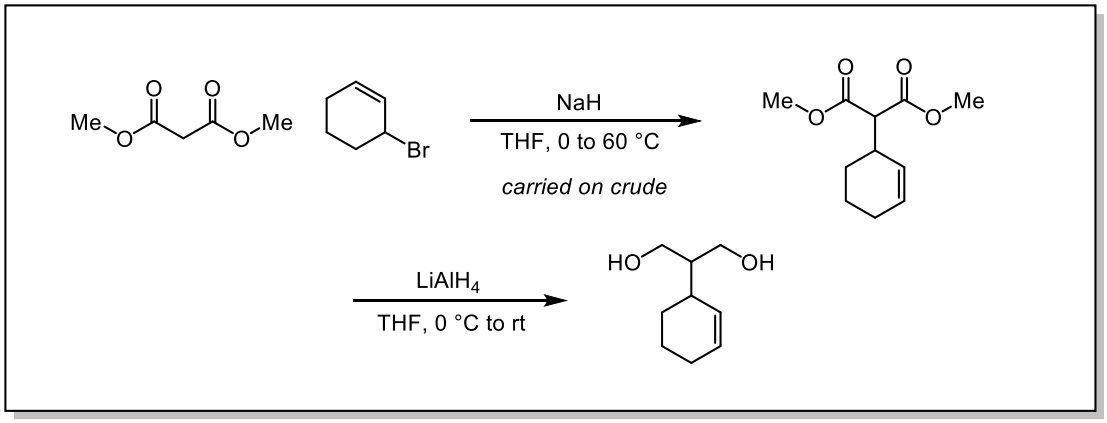


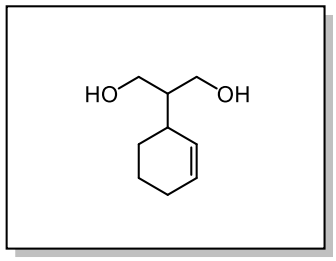
(*E*)-octadec-12-en-9-ol

To a flame-dried 100-mL round bottom flask was added (*E*)-dec-4-enal (9.72 mmol, 1.0 equiv, 1.50 g) and 32 mL anhydrous Et_2O. The mixture was cooled to 0 °C, and to the mixture was added a solution of commercially available octylmagnesium bromide (11.7 mmol, 1.2 equiv, 2 M in Et_2O, 5.83 mL) dropwise. The reaction mixture was slowly warmed to room temperature and allowed to stir overnight. The crude reaction was quenched with saturated aqueous NH_4Cl at 0 °C, acidified with 1 M HCl, extracted with Et_2O, washed with brine, dried over anhydrous

Na_2SO_4, and concentrated *in vacuo*. The crude product was purified using silica gel chromatography (gradient from 5% to 20% EtOAc in hexanes) to give the titled compound (2.32 g, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51–5.35 (m, 2H), 3.61 (tt, *J* = 8.6, 4.1 Hz, 1H), 2.18–2.01 (m, 2H), 1.97 (q, *J* = 6.6 Hz, 2H), 1.57–1.38 (m, 7H), 1.37–1.22 (m, 16H), 0.88 (t, *J* = 6.9 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 131.3, 129.9, 71.8, 37.6, 37.3, 32.7, 32.0, 31.6, 29.9, 29.7, 29.4, 29.4, 29.1, 25.8, 22.8, 22.7, 14.3, 14.2. **IR (neat):** 3333, 2956, 2916, 2854, 1462, 1378, 1081, 967, 723 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{18}H_{36}O$) from $[M+H]^+$ is 268.27662, found 268.27613, difference of 1.83 ppm.





2-cyclohex-2-en-1-ylpropane-1,3-diol

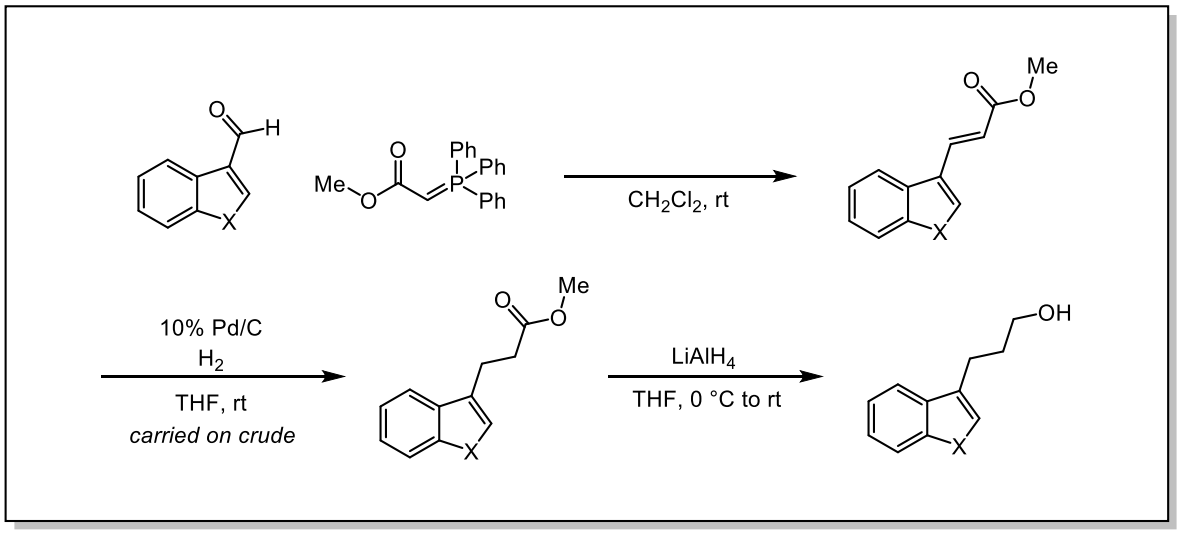
To a flame-dried 100-mL round bottom flask equipped with a stir bar was added NaH (12.5 mmol, 1.1 equiv, 60% dispersion in mineral oil, 0.498 g) and 25 mL anhydrous THF. The mixture was cooled to 0 °C, and to the mixture was added dimethyl propanedioate (11.4 mmol, 1.0 equiv, 1.29 mL) dropwise. The reaction was stirred at 0 °C for 1 hour, and then, 3-bromocyclohexene (12.5 mmol, 1.1 equiv, 1.44 mL) was added. The reaction mixture was refluxed overnight. The crude reaction was quenched with saturated aqueous NH_4Cl, extracted with Et_2O, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was carried onto the next step without further purification.

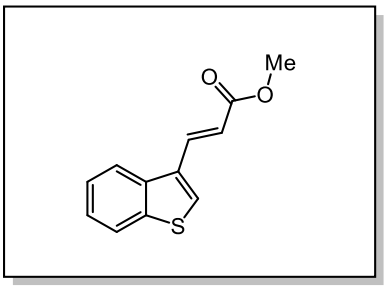
To a flame-dried 100-mL round bottom flask equipped with a stir bar was added $LiAlH_4$ (12.4 mmol, 1.1 equiv, 0.472 g) suspended in 23 mL dry THF. Once the suspension was cooled to 0 °C, crude dimethyl 2-cyclohex-2-en-1-ylpropanedioate (11.3 mmol, 1.0 equiv, 2.40 g) dissolved in 23 mL dry THF was added dropwise to the reaction. The reaction was warmed to room temperature and allowed to stir for 2 hours. The reaction mixture was worked up by diluting the mixture with Et_2O and adding 1 mL water, 1 mL 1 M NaOH, and 1 mL water dropwise

sequentially at 0 °C. The reaction was warmed to room temperature and stirred for 15 minutes. Anhydrous $MgSO_4$ was added to the mixture and stirred for 15 minutes. The reaction was filtered and concentrated *in vacuo*. The crude product was purified using silica gel chromatography (20% to 60% EtOAc in hexanes) to afford the titled compound (0.796 g, 45% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dq, *J* = 10.0, 3.3 Hz, 1H), 5.60 (dq, *J* = 10.2, 2.4 Hz, 1H), 3.89–3.79 (m, 4H), 2.30 (ddq, *J* = 8.6, 5.6, 2.8 Hz, 1H), 2.15–1.85 (m, 4H), 1.81–1.69 (m, 3H), 1.57–1.48 (m, 1H), 1.39–1.31 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 129.6, 128.8, 65.4, 65.2, 46.8, 34.5, 26.3, 25.3, 22.0. **IR (neat):** 3330, 2926, 2886, 1446, 1031, 979, 722, 673 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_9H_{16}O_2$) from $[M+Na]^+$ is 156.11503, found 156.11506, difference of 0.22 ppm.

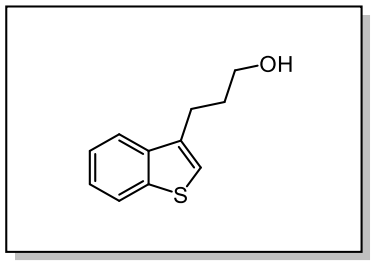
General Procedure E





Methyl (*E*)-3-(benzothiophen-3-yl)prop-2-enoate

To a flame-dried 100-mL round bottom flask equipped with a stir bar was added methyl (triphenylphosphoranylidene)acetate (15.0 mmol, 1.5 equiv, 5.02 g) in 25 mL CH_2Cl_2. The resulting slurry was allowed to stir at room temperature as benzothiophene-3-carbaldehyde (10.0 mmol, 1.0 equiv, 1.62 g) was added portion-wise as a solid. The reaction mixture was stirred overnight, after which it was concentrated *in vacuo* and purified *via* silica gel chromatography (gradient from 0% to 25% EtOAc in hexanes) to provide the titled compound (1.92 g, 88% yield). Spectra are consistent with reported literature values.[25]

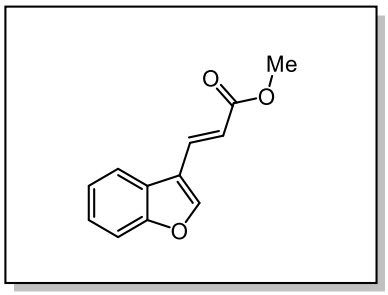


3-(benzothiophen-3-yl)propan-1-ol

To a flame-dried 100-mL round bottom flask equipped with a stir bar was added methyl *(E)*-3-(benzothiophen-3-yl)prop-2-enoate (8.81 mmol, 1.0 equiv, 1.92 g) and 10 wt% Pd/C in 44 mL THF. The flask was evacuated and backfilled with H_2 from a balloon five times, and the black suspension was allowed to stir at room temperature overnight under an atmosphere of H_2. The reaction was filtered through Celite washing with EtOAc. The filtrate was concentrated *in vacuo* to provide crude methyl 3-(benzothiophen-3-yl)propanoate. The crude product was carried onto the next step without further purification.

To a flame-dried 100-mL round bottom flask equipped with a stir bar was added $LiAlH_4$ (26.4 mmol, 3.0 equiv, 1.00 g) suspended in 30 mL dry THF. Once the reaction vessel was cooled to 0 °C, crude methyl 3-(benzothiophen-3-yl)propanoate (8.81 mmol, 1.0 equiv, 1.94 g) dissolved in 5 mL dry THF was added dropwise to the reaction. The reaction was warmed to room temperature and allowed to stir for 3 hours. The reaction mixture was worked up by diluting the mixture with Et_2O and adding 1 mL water, 1 mL 1 M NaOH, and 3 mL water dropwise sequentially at 0 °C. The reaction was warmed to room temperature and stirred for 15 minutes. Anhydrous $MgSO_4$ was added to the mixture and stirred for 15 minutes. The reaction was filtered and concentrated *in vacuo*. The crude product was purified using silica gel chromatography (5% to 40% EtOAc in hexanes) to afford the titled compound (1.06 g, 63% yield). Spectra are consistent with reported literature values.[25]

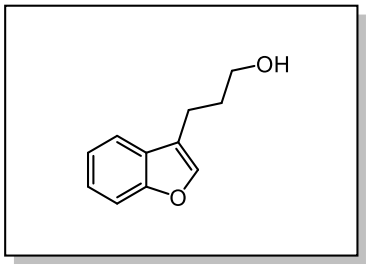
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.83 (m, 1H), 7.81–7.73 (m, 1H), 7.43–7.32 (m, 2H), 7.12 (d, J = 1.1 Hz, 1H), 3.75 (t, J = 6.4 Hz, 2H), 2.96 (td, J = 7.6, 1.1 Hz, 2H), 2.07–1.97 (m, 2H), 1.48 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 140.6, 139.1, 136.3, 124.3, 124.0, 123.0, 121.8, 121.4, 62.5, 32.1, 24.9. **IR (neat):** 3338, 2937, 2871, 1456, 1427, 1257, 1158, 1057, 918, 853, 761, 733 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{12}OS$) from $[M+H]^+$ is 192.06089, found 192.06058, difference of 1.61 ppm.



Methyl (*E*)-3-(benzofuran-3-yl)prop-2-enoate

The titled compound was synthesized following General Procedure E for the olefination of commercially available benzofuran-3-carbaldehyde. The crude product was purified *via* silica gel chromatography (gradient from 0% to 25% EtOAc in hexanes) to give the titled compound.

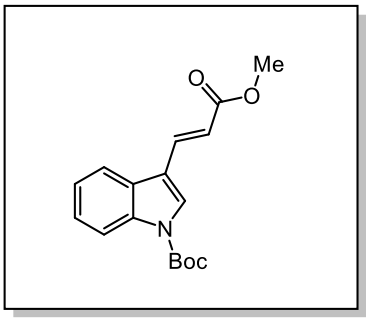
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.86–7.83 (m, 1H), 7.80 (d, J = 16.0 Hz, 1H), 7.56–7.52 (m, 1H), 7.41–7.32 (m, 2H), 6.57 (d, J = 16.1 Hz, 1H), 3.83 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 167.7, 156.3, 148.0, 134.9, 125.6, 124.9, 123.9, 121.1, 118.1, 118.0, 112.2, 51.9. **IR (neat):** 3132, 2944, 2840, 1705, 1626, 1584, 1448, 1433, 1320, 1308, 1246, 1195, 1170, 1149, 1132, 1082, 1018, 1009, 997, 931, 866, 856, 831, 781, 743, 728, 701 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{12}H_{10}O_3$) from $[M+H]^+$ is 202.06299, found 202.06319, difference of 0.96 ppm.



3-(benzofuran-3-yl)propan-1-ol

The titled compound was synthesized following General Procedure E for the reduction of methyl 3-(benzofuran-3-yl)propanoate, which was synthesized from methyl (*E*)-3-(benzofuran-3-yl)prop-2-enoate and carried onto the next step without further purification. The crude product was purified *via* silica gel chromatography (gradient from 5% to 40% EtOAc in hexanes) to give the titled compound. Spectra are consistent with reported literature values.[26]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.55 (m, 1H), 7.47 (dt, J = 8.2, 0.9 Hz, 1H), 7.43 (d, J = 1.2 Hz, 1H), 7.29 (ddd, J = 8.3, 7.2, 1.4 Hz, 1H), 7.24 (td, J = 7.4, 1.1 Hz, 1H), 3.74 (t, J = 6.3 Hz, 2H), 2.79 (td, J = 7.5, 1.2 Hz, 2H), 2.02–1.94 (m, 2H), 1.51 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 155.5, 141.3, 128.3, 124.3, 122.4, 120.0, 119.7, 111.6, 62.4, 32.0, 19.9. **IR (neat):** 3333, 2936, 2866, 1452, 1277, 1183, 1089, 1057, 1009, 918, 857, 741, 701 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{12}O_2$) from $[M+H]^+$ is 176.08373, found 176.08371, difference of 0.11 ppm.

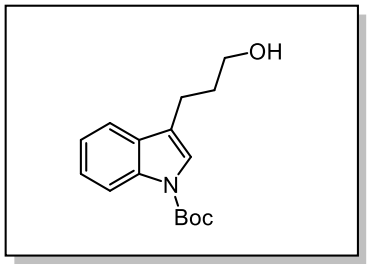


***tert*-butyl 3-[(*E*)-3-methoxy-3-oxo-prop-1-enyl]indole-1-carboxylate**

The titled compound was synthesized following General Procedure E for the olefination of

commercially available *tert*-butyl 3-formylindole-1-carboxylate. The crude product was purified *via* silica gel chromatography (gradient from 0% to 25% EtOAc in hexanes) to give the titled compound.

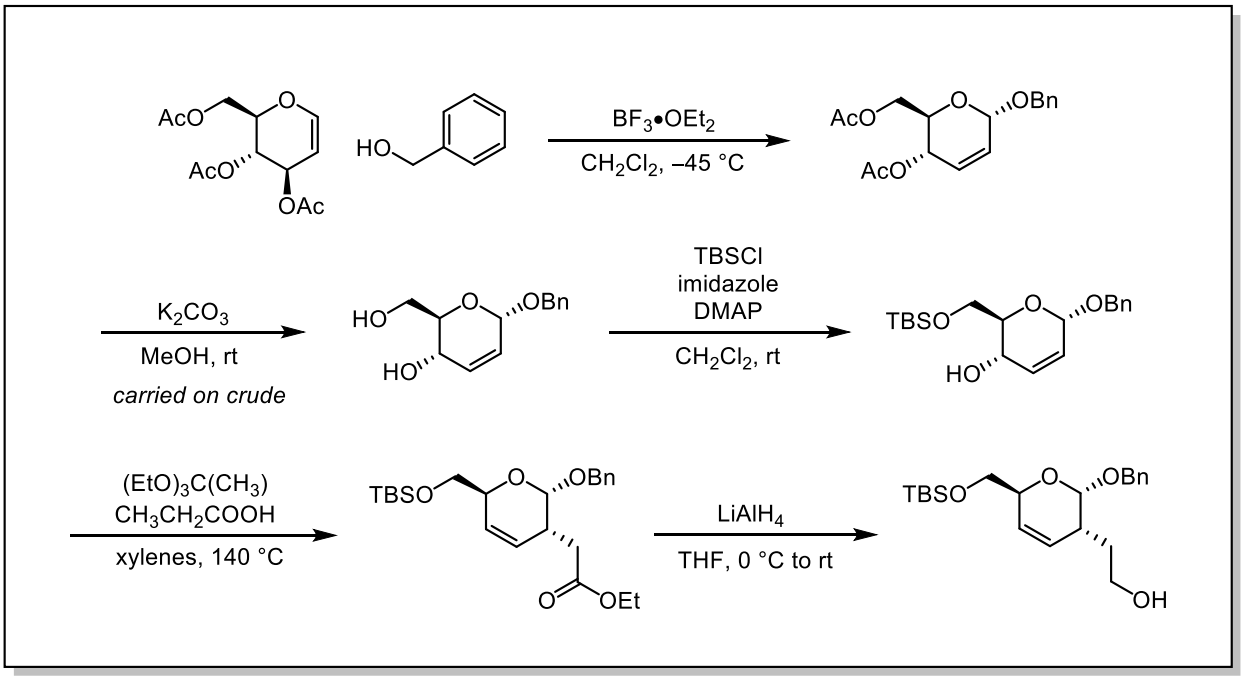
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.88–7.84 (m, 2H), 7.84–7.80 (m, 1H), 7.39 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.33 (td, *J* = 7.5, 1.2 Hz, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 3.82 (s, 3H), 1.68 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.0, 149.3, 136.8, 136.3, 128.9, 128.0, 125.4, 123.7, 120.4, 117.1, 116.8, 115.7, 84.8, 51.8, 28.3. **IR (neat):** 2981, 2950, 1737, 1716, 1635, 1452, 1434, 1364, 1309, 1250, 1237, 1151, 1095, 1083, 1024, 976, 856, 837, 763, 744 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{17}H_{19}NO_4$) from $[M+H]^+$ is 301.13141, found 301.13170, difference of 0.97 ppm.

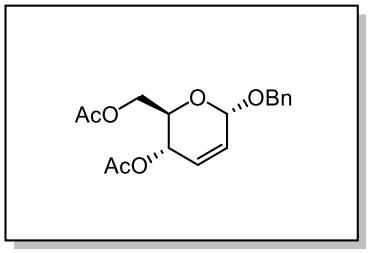


***tert*-butyl 3-(3-hydroxypropyl)indole-1-carboxylate**

The titled compound was synthesized following General Procedure E for the reduction of *tert*-butyl 3-(3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate, which was synthesized from *tert*-butyl 3-formylindole-1-carboxylate and carried onto the next step without further purification. The crude product was purified *via* silica gel chromatography (gradient from 10% to 60% EtOAc in hexanes) to give the titled compound. Spectra are consistent with reported literature values.[27]

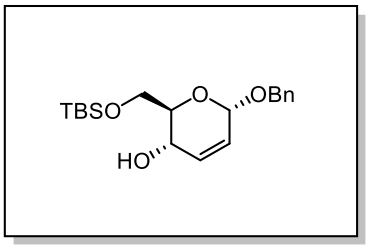
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.54 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.38 (s, 1H), 7.31 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.23 (td, *J* = 7.5, 1.1 Hz, 1H), 3.75 (t, *J* = 6.3 Hz, 2H), 2.80 (td, *J* = 7.6, 1.2 Hz, 2H), 1.99 (ddt, *J* = 8.5, 7.5, 6.4 Hz, 2H), 1.67 (s, 9H), 1.35 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 150.0, 135.7, 130.8, 124.4, 122.6, 122.5, 120.6, 119.1, 115.4, 83.5, 62.5, 32.2, 28.4, 21.3. **IR (neat):** 3357, 2978, 2935, 1726, 1475, 1452, 1369, 1252, 1151, 1089, 1047, 1017, 856, 766, 743 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{16}H_{21}NO_3$) from $[M+Na]^+$ is 275.15214, found 275.15181, difference of 1.21 ppm.





(2*R*,3*S*,6*R*)-3-acetoxy-6-(benzyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate

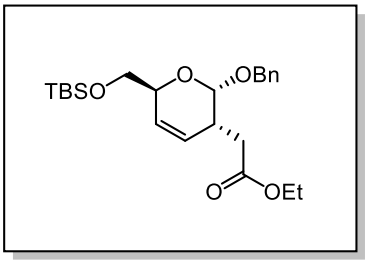
To a flame-dried 250-mL round bottom flask equipped with a magnetic stir bar was added (2*R*,3*S*,4*R*)-2-(acetoxymethyl)-3,4-dihydro-2*H*-pyran-3,4-diyl diacetate (20.0 mmol, 1.0 equiv, 5.45 g). The white solid was dissolved in 80 mL CH_2Cl_2, and benzyl alcohol (24.0 mmol, 1.2 equiv, 2.50 mL) was added. The solution was cooled to –45 °C, and BF_3•OEt_2 (2.00 mmol, 0.10 equiv, 0.253 mL) was added *via* syringe. The reaction was stirred at –45 °C for 4 hours. The reaction was then quenched by addition of water, extracted with CH_2Cl_2, and washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* silica gel chromatography (gradient from 25 to 40% EtOAc in hexanes) to give the titled compound (4.42 g, 69% yield) as an 11:1 mixture of α/β anomers. Spectra are consistent with reported literature values.[28]



(2*R*,3*S*,6*S*)-6-(benzyloxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,6-dihydro-2*H*-pyran-3-ol

To a 250-mL round bottom flask equipped with a magnetic stir bar was added (2*R*,3*S*,6*R*)-3-acetoxy-6-(benzyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate (13.7 mmol, 1.0 equiv, 4.40 g) and 28 mL methanol. K_2CO_3 (82.0 mmol, 6.0 equiv, 11.4 g) was added as a solid, and the heterogeneous mixture was allowed to stir at room temperature overnight. Once complete, the reaction mixture was filtered through Celite washing with MeOH. The filtrate was concentrated *in vacuo* to provide an orange-colored waxy solid. The crude deacetylated product was carried onto the next step without further purification.

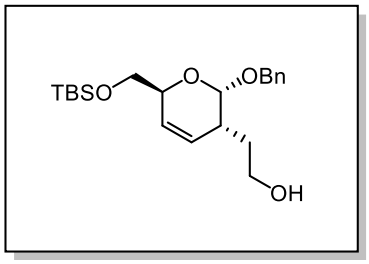
To a 100-mL round bottom flask containing a magnetic stir bar was added (2*R*,3*S*,6*S*)-6-(benzyloxy)-2-(hydroxymethyl)-3,6-dihydro-2*H*-pyran-3-ol (12.3 mmol, 1.0 equiv, 2.91 g), imidazole (30.8 mmol, 2.5 equiv, 2.10 g), and *N*,*N*-dimethylpyridin-4-amine (2.47 mmol, 0.20 equiv, 0.301 g). The solid mixture was suspended in 30 mL CH_2Cl_2 and allowed to stir at room temperature. *tert*-Butyldimethylsilyl chloride (14.8 mmol, 1.2 equiv, 2.23 g) was added next portion-wise, and the resulting slurry was allowed to stir overnight. The reaction solution was diluted with CH_2Cl_2 and washed twice with 1 M HCl and twice with brine. The resulting reaction mixture was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide a yellow oil. The crude product was purified *via* silica gel chromatography (gradient from 10% to 40% EtOAc in hexanes) to give the titled compound (2.21 g, 51% yield). Spectra are consistent with reported literature values.[28]



Ethyl 2-[(2*S*,3*R*,6*S*)-2-benzyloxy-6-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3,6-dihydro-2*H*-pyran-3-yl]acetate

To a flame-dried 50-mL round bottom flask equipped with a stir bar and dried distillation apparatus was added triethyl orthoacetate (28.5 mmol, 10 equiv, 5.23 mL), propionic acid (1.43 mmol, 0.50 equiv, 0.107 mL), and (2*R*,3*S*,6*S*)-6-(benzyloxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,6-dihydro-2*H*-pyran-3-ol (2.85 mmol, 1.0 equiv, 1.00 g) in 10 mL xylenes. The reaction mixture was heated to 140 °C with stirring, and intense bubbling of the mixture and distillation of ethanol were observed. After 36 hours of reflux, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2. Excess triethylorthoacetate was

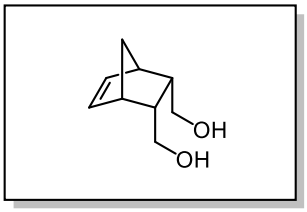
hydrolyzed by adding 1 M HCl. The aqueous phase was extracted with CH_2Cl_2, the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and the mixture was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield a yellow oil. The crude material was purified *via* silica gel chromatography (gradient from 0% to 5% EtOAc in hexanes) to give the titled compound (0.298 g, 25% yield). Spectra are consistent with reported literature values.[29]



2-[(2*S*,3*R*,6*S*)-2-benzyloxy-6-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3,6-dihydro-2*H*-pyran-3-yl]ethanol

To a flame-dried 50-mL round bottom flask equipped with a stir bar was added $LiAlH_4$ (3.35 mmol, 3.0 equiv, 0.127 g) suspended in 8 mL anhydrous THF. Once the suspension was cooled to 0 °C, ethyl 2-[(2*S*,3*R*,6*S*)-2-benzyloxy-6-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3,6-dihydro-2*H*-pyran-3-yl]acetate (1.12 mmol, 1.0 equiv, 0.470 g) dissolved in 4 mL anhydrous THF was added dropwise to the reaction. The reaction was warmed to room temperature and allowed to stir overnight. The reaction mixture was diluted with Et_2O, and 0.2 mL water, 0.2 mL 1 M NaOH, and 0.6 mL water were added dropwise sequentially at 0 °C. The reaction was warmed to room temperature and stirred for 15 minutes. Anhydrous $MgSO_4$ was added to the mixture and stirred for 15 minutes. The reaction was filtered through Celite and concentrated *in vacuo*. The crude product was purified *via* silica gel chromatography (gradient from 10% to 20% EtOAc in hexanes) to afford the titled compound (0.260 g, 61% yield). Spectra are consistent with reported literature values.[29]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.78 (dt, *J* = 10.4, 2.3 Hz, 1H), 5.68–5.62 (m, 1H), 4.98 (d, *J* = 4.1 Hz, 1H), 4.83 (d, *J* = 12.1 Hz, 1H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.25 (dtd, *J* = 6.1, 3.9, 1.8 Hz, 1H), 3.75 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.70–3.57 (m, 3H), 2.65–2.55 (m, 1H), 1.82–1.71 (m, 1H), 1.65 (dq, *J* = 13.2, 6.5 Hz, 1H), 1.50 (t, *J* = 5.4 Hz, 1H), 0.91 (s, 9H), 0.08 (d, *J* = 2.4 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 137.9, 128.6, 128.2, 127.9, 126.9, 126.2, 96.8, 69.9, 69.2, 65.8, 60.6, 35.6, 33.3, 26.1, 18.5, –5.1, –5.1. **IR (neat):** 3382, 2952, 2929, 2856, 1459, 1254, 1095, 1023, 836, 777, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{21}H_{34}O_4Si$) from $[M+Na]^+$ is 378.22264, found 378.22247, difference of 0.43 ppm.

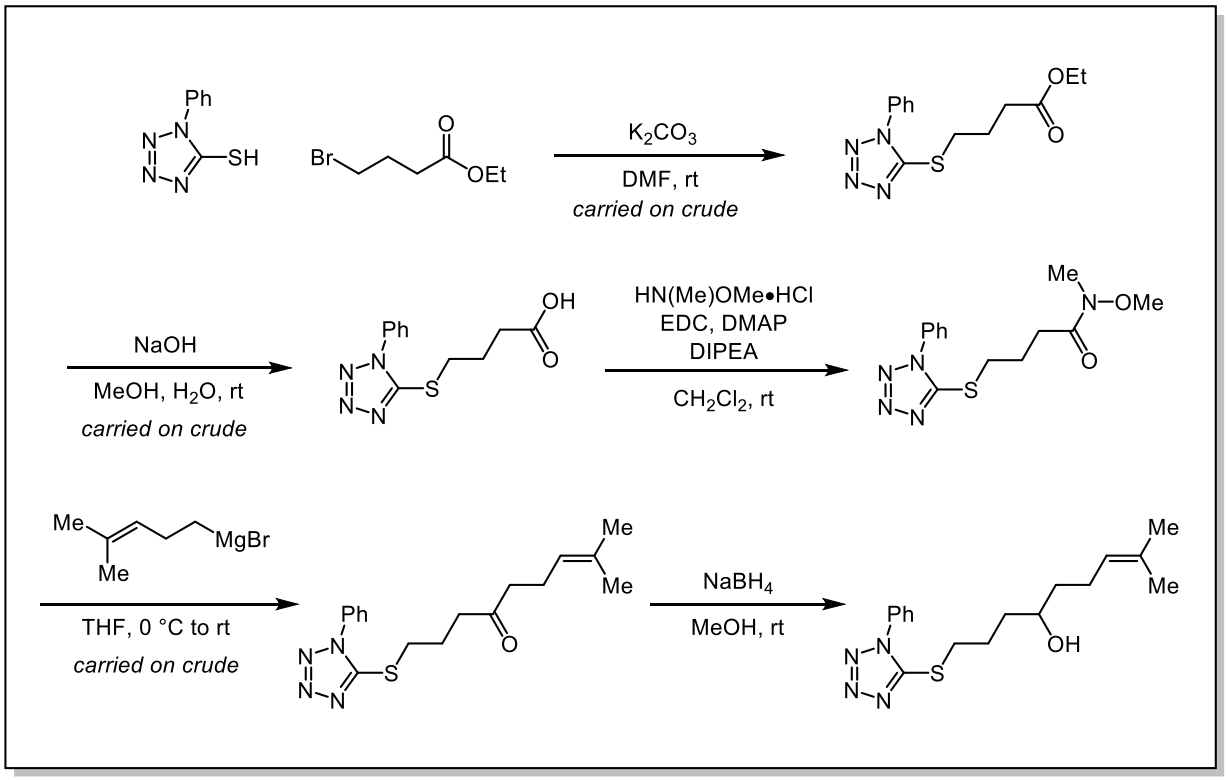


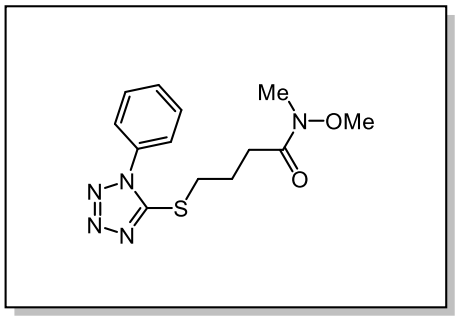
((1*R*,2*S*,3*R*,4*S*)-bicyclo[2.2.1]hept-5-ene-2,3-diyl)dimethanol

To a flame-dried 100-mL round bottom flask equipped with a stir bar was added $LiAlH_4$ (36.6

mmol, 3.0 equiv, 1.39 g) suspended in 30 mL dry THF. Once the suspension was cooled to 0 °C, carbic anhydride (12.2 mmol, 1.0 equiv, 2.00 g) dissolved in 10 mL dry THF was added dropwise to the reaction. The reaction was warmed to room temperature and allowed to stir for 4 hours. The reaction mixture was worked up by diluting the mixture with Et_2O and adding 1.4 mL water, 1.4 mL 1 M NaOH, and 4.2 mL water dropwise sequentially at 0 °C. The reaction was warmed to room temperature and stirred for 15 minutes. Anhydrous $MgSO_4$ was added to the mixture and stirred for 15 minutes. The reaction was filtered and concentrated *in vacuo*. The crude product was purified using silica gel chromatography (100% EtOAc) to afford the titled compound (1.50 g, 80% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (t, *J* = 1.9 Hz, 2H), 3.66 (dd, *J* = 11.1, 3.3 Hz, 2H), 3.47–3.32 (m, 2H), 2.95 (s, 2H), 2.82 (hept, *J* = 1.6 Hz, 2H), 2.62–2.48 (m, 2H), 1.41 (qt, *J* = 8.2, 1.7 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.0, 63.8, 50.1, 46.7, 45.4. **IR (neat):** 3289, 3058, 2961, 2933, 2869, 1451, 1340, 1167, 1042, 1021, 916, 780, 721 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_9H_{14}O_2$) from $[M+H]^+$ is 154.09938, found 154.09965, difference of 1.74 ppm.





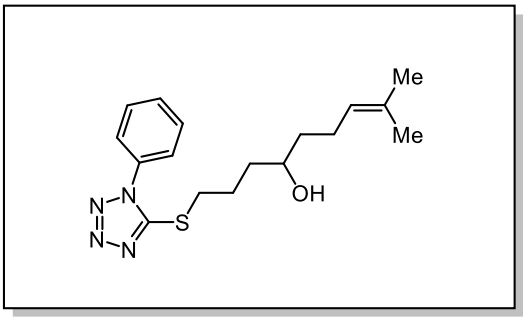
***N*-methoxy-*N*-methyl-4-(1-phenyltetrazol-5-yl)sulfanyl-butanamide**

To a flame-dried 100-mL round bottom flask was added 1-phenyl-1*H*-tetrazole-5-thiol (11.2 mmol, 1.0 equiv, 2.00 g) and K_2CO_3 (22.4 mmol, 2.0 equiv, 3.10 g). The flask was evacuated and backfilled with nitrogen, and 20 mL anhydrous DMF was added. To the flask was added ethyl 4-bromobutanoate (12.3 mmol, 1.1 equiv, 1.77 mL), and the reaction was allowed to stir at room temperature overnight. The reaction was quenched with water and CH_2Cl_2, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with 5% aqueous LiCl solution, brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude substitution product was carried onto the next step without further purification.

To a 100-mL round bottom flask was added crude ethyl 4-(1-phenyltetrazol-5-yl)sulfanylbutanoate (10.3 mmol, 1.0 equiv, 3.00 g) in 32 mL methanol and a solution of NaOH (30.8 mmol, 3.0 equiv, 1.23 g) in 8 mL water. The reaction was allowed to stir at room temperature for 3 hours. The reaction was quenched with water and CH_2Cl_2, and the aqueous layer was extracted once with CH_2Cl_2. The aqueous layer was acidified with 1 M HCl until a pH of 1 was reached, at which point it was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to yield a clear, yellow-brown oil. The crude carboxylic acid product was carried onto the next step without further purification.

To a 100-mL round bottom flask was added crude 4-(1-phenyltetrazol-5-yl)sulfanylbutanoic acid (7.57 mmol, 1.0 equiv, 2.00 g), *N*,*O*-dimethylhydroxylamine hydrochloride (22.7 mmol, 3.0 equiv, 2.21 g), and *N*,*N*-dimethylpyridin-4-amine (9.08 mmol, 1.2 equiv, 1.11 g) in 40 mL CH_2Cl_2. The mixture was allowed to stir at room temperature as EDC (9.08 mmol, 1.2 equiv, 1.74 g) was added portion-wise to the reaction mixture. Next, *N*,*N*-diisopropylethylamine (18.2 mmol, 2.4 equiv, 3.10 mL) was added, and the reaction was allowed to stir overnight. The reaction was quenched with water and CH_2Cl_2, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified *via* silica gel column chromatography (gradient from 20% to 60% EtOAc in hexanes) to give the titled compound (2.10 g, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.48 (m, 5H), 3.68 (s, 3H), 3.48 (t, J = 7.3 Hz, 2H), 3.18 (s, 3H), 2.62 (t, J = 7.1 Hz, 2H), 2.19 (p, J = 7.2 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.3, 154.4, 133.8, 130.2, 129.9, 124.0, 61.4, 32.8, 32.3, 30.5, 24.2. **IR (neat):** 2938, 1656, 1597, 1499, 1413, 1385, 1242, 1178, 1091, 1014, 994, 762, 695 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{17}N_5O_2S$) from $[M+H]^+$ is 307.11029, found 307.11031, difference of 0.05 ppm.

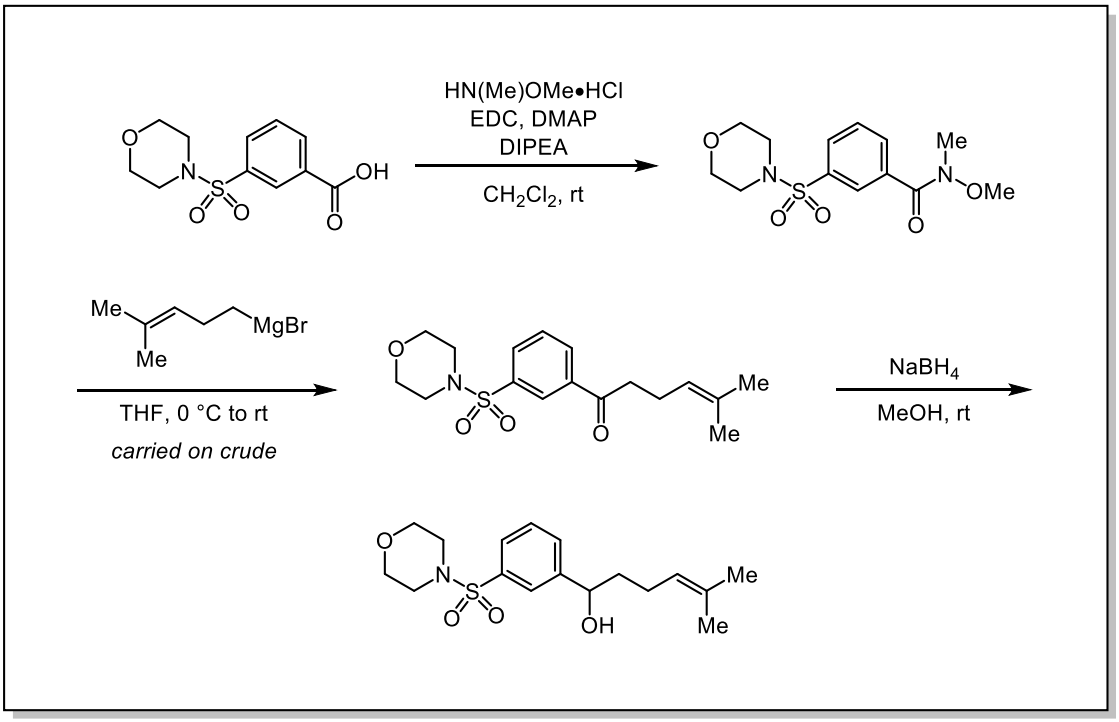


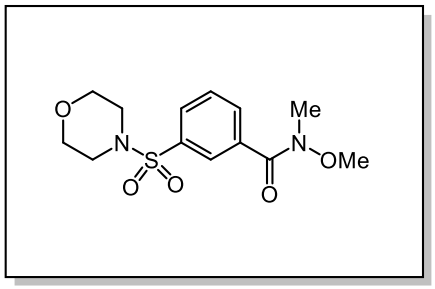
8-methyl-1-(1-phenyltetrazol-5-yl)sulfanyl-non-7-en-4-ol

To a flame-dried 100-mL two-neck round bottom flask equipped with a condenser and stir bar was added magnesium turnings (9.11 mmol, 1.4 equiv, 0.221 g) and a catalytic amount of iodine. The solids were mixed under nitrogen for 2 hours to activate the magnesium. 5-Bromo-2-methyl-pent-2-ene (7.81 mmol, 1.2 equiv, 1.04 mL) in 20 mL THF was added next, first portion-wise and then dropwise. The reaction mixture was allowed to stir at reflux for 2 hours. The reaction was cooled to room temperature and then to 0 °C, after which *N*-methoxy-*N*-methyl-4-(1-phenyltetrazol-5-yl)sulfanyl-butanamide (6.51 mmol, 1.0 equiv, 2.00 g) dissolved in 6 mL THF was added dropwise. The reaction was allowed to stir at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl, extracted with Et_2O, washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford a clear oil. The crude Grignard product was carried onto the next step without further purification.

To a flame-dried 100-mL round bottom flask equipped with a stir bar was added crude 8-methyl-1-(1-phenyltetrazol-5-yl)sulfanyl-non-7-en-4-one (6.51 mmol, 1.0 equiv, 2.15 g) and 25 mL methanol. To the reaction was added $NaBH_4$ (7.81 mmol, 1.2 equiv, 0.295 g) at 0 °C, and the reaction was allowed to stir for 3 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl and water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified *via* silica gel chromatography (gradient from 20% to 40% EtOAc in hexanes) to give the titled compound (1.59 g, 73% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.52 (m, 5H), 5.13 (ddt, *J* = 8.6, 5.8, 1.4 Hz, 1H), 3.68 (tt, *J* = 8.5, 4.6 Hz, 1H), 3.51–3.34 (m, 2H), 2.10 (dq, *J* = 14.6, 7.3 Hz, 2H), 2.04–1.91 (m, 2H), 1.87 (br, 1H), 1.69 (d, *J* = 1.5 Hz, 3H), 1.67–1.52 (m, 5H), 1.53–1.47 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 154.6, 133.8, 132.5, 130.3, 129.9, 124.0, 124.0, 71.1, 37.6, 36.1, 33.2, 25.9, 25.8, 24.5, 17.9. **IR (neat):** 3411, 2920, 2856, 1597, 1499, 1450, 1411, 1385, 1242, 1075, 1015, 981, 759, 691 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{17}H_{24}N_4OS$) from $[M+H]^+$ is 332.16708, found 332.16659, difference of 1.48 ppm.



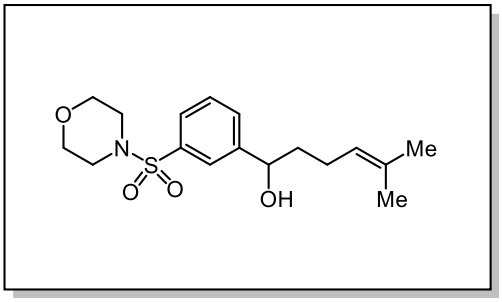


***N*-methoxy-*N*-methyl-3-morpholinosulfonyl-benzamide**

To a 100-mL round bottom flask was added commercially available 3-morpholinosulfonylbenzoic acid (7.37 mmol, 1.0 equiv, 2.00 g), *N*,*O*-dimethylhydroxylamine hydrochloride (22.1 mmol, 3.0 equiv, 2.16 g), and *N*,*N*-dimethylpyridin-4-amine (8.85 mmol, 1.2 equiv, 1.08 g) in 40 mL CH_2Cl_2. The mixture was allowed to stir at room temperature as EDC (8.85 mmol, 1.2 equiv, 1.70 g) was added portion-wise to the reaction mixture. Next, *N*,*N*-diisopropylethylamine (17.7 mmol, 2.4 equiv, 3.08 mL) was added, and the reaction was allowed to stir overnight. The reaction was quenched with water and CH_2Cl_2, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified *via* silica gel column chromatography (gradient from 80% to 100% EtOAc in hexanes) to give the titled compound (2.16 g, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (t, *J* = 1.9 Hz, 1H), 8.00–7.92 (m, 1H), 7.85 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 3.75 (t, *J* = 4.7 Hz, 4H), 3.54 (s, 3H), 3.40 (s, 3H), 3.02 (dd, *J* = 5.7, 3.4 Hz, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.3, 167.9, 135.3, 133.0, 129.7, 129.2, 127.8, 66.2, 61.4, 46.1, 33.4. **IR (neat):** 2975, 2898, 2858, 1643, 1454, 1348, 1261, 1158, 1112, 1070, 981, 942, 791, 721, 692 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{18}N_2O_5S$) from

$[M+H]^+$ is 314.09364, found 314.09362, difference of 0.07 ppm.

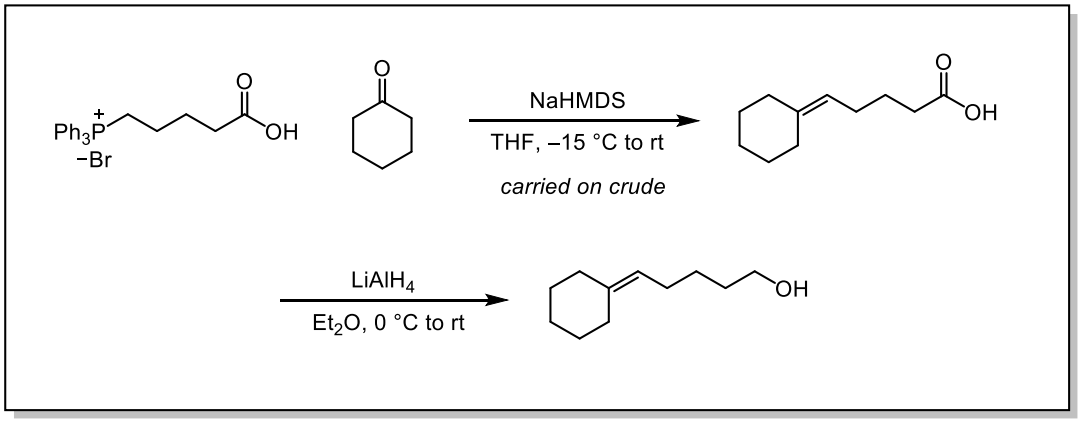


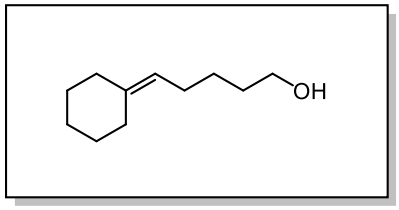
5-methyl-1-(3-morpholinosulfonylphenyl)hex-4-en-1-ol

To a flame-dried 100-mL two-neck round bottom flask equipped with a condenser and stir bar was added magnesium turnings (4.45 mmol, 1.4 equiv, 0.108 g) and a catalytic amount of iodine. The solids were mixed under nitrogen for 2 hours to activate the magnesium. 5-Bromo-2-methyl-pent-2-ene (3.82 mmol, 1.2 equiv, 0.51 mL) in 20 mL THF was added next, first portion-wise and then dropwise. The reaction mixture was allowed to stir at reflux for 2 hours. The reaction was cooled to room temperature and then 0 °C, after which *N*-methoxy-*N*-methyl-3-morpholinosulfonyl-benzamide (3.18 mmol, 1.0 equiv, 1.00 g) dissolved in 6 mL THF was added dropwise. The reaction was allowed to stir at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl, extracted with Et_2O, washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford a clear oil. The crude Grignard product was carried onto the next step without further purification.

To a flame-dried 100-mL round bottom flask equipped with a stir bar was added crude 5-methyl-1-(3-morpholinosulfonylphenyl)hex-4-en-1-one (3.17 mmol, 1.0 equiv, 1.07 g) and 25 mL methanol. To the reaction was added $NaBH_4$ (3.81 mmol, 1.2 equiv, 0.144 g) at 0 °C, and the reaction was allowed to stir for 3 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl and water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified *via* silica gel chromatography (gradient from 20% to 40% EtOAc in hexanes) to give the titled compound (0.614 g, 57% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 1.8 Hz, 1H), 7.63 (ddt, *J* = 15.2, 7.8, 1.5 Hz, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 5.14 (tdd, *J* = 7.1, 2.9, 1.4 Hz, 1H), 4.79 (dd, *J* = 8.1, 4.9 Hz, 1H), 3.80–3.69 (m, 4H), 3.04–2.95 (m, 4H), 2.10 (q, *J* = 7.5 Hz, 2H), 2.05 (br, 1H), 1.87–1.73 (m, 2H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.60 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 146.7, 135.3, 133.1, 130.7, 129.3, 126.9, 125.3, 123.4, 73.6, 66.2, 46.1, 39.4, 25.9, 24.5, 17.9. **IR (neat):** 3475, 2968, 2918, 2858, 1601, 1453, 1347, 1329, 1261, 1157, 1112, 1069, 941, 731, 699 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{17}H_{25}NO_4S$) from $[M+Na]^+$ is 339.15043, found 339.15045, difference of 0.06 ppm.





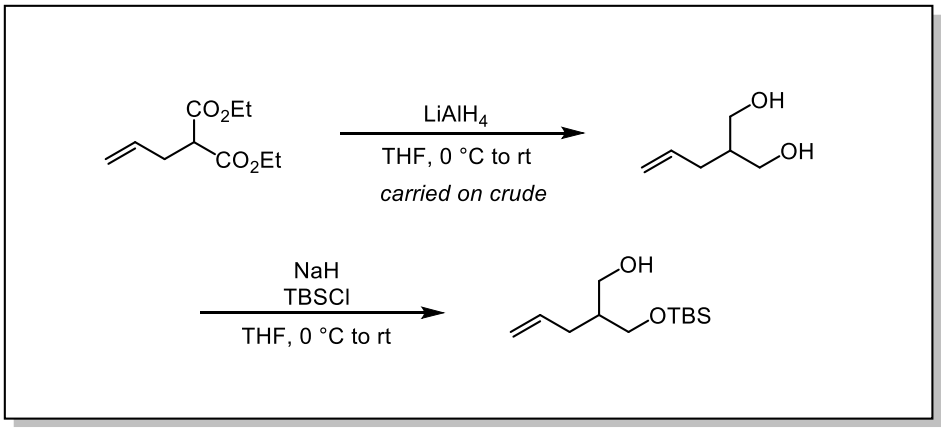
5-cyclohexylidenepentan-1-ol

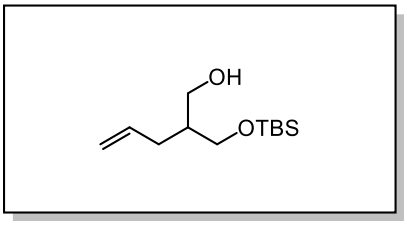
To a flame-dried 250-mL round bottom flask equipped with a stir bar was added (4-carboxybutyl)triphenylphosphonium bromide (11.0 mmol, 1.1 equiv, 4.88 g) and 20 mL anhydrous THF. The mixture was cooled to –10 °C, and to the mixture was added a solution of NaHMDS (24.0 mmol, 2.4 equiv, 1 M in THF, 24.0 mL) dropwise over 15 minutes. The reaction was stirred at –10 °C for 30 minutes, and then, cyclohexanone (10.0 mmol, 1.0 equiv, 1.04 mL) dissolved in 2 mL anhydrous THF was added. The reaction mixture was warmed to room temperature and allowed to stir overnight. The crude reaction was diluted with 50 mL water and washed with CH_2Cl_2. The aqueous phase was acidified to pH = 1 by 1 M HCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was carried onto the next step without further purification.

To a flame-dried 100-mL round bottom flask equipped with a stir bar was added $LiAlH_4$ (20.0 mmol, 2.0 equiv, 0.758 g) suspended in 30 mL dry Et_2O. Once the suspension was cooled to 0 °C, crude 5-cyclohexylidenepentanoic acid (10.0 mmol, 1.0 equiv, 1.82 g) dissolved in 10 mL dry Et_2O was added dropwise to the reaction. The reaction was warmed to room temperature and allowed to stir for 2 hours. The reaction mixture was worked up by diluting the mixture with Et_2O and adding 1 mL water, 1 mL 1 M NaOH, and 1 mL water dropwise sequentially at 0 °C. The reaction was warmed to room temperature and stirred for 15 minutes. Anhydrous $MgSO_4$ was added to the mixture and stirred for 15 minutes. The reaction was filtered and concentrated *in vacuo*. The crude product was purified using silica gel chromatography (10% to 25% EtOAc in hexanes) to afford the titled compound (1.25 g, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (tt, J = 7.3, 1.2 Hz, 1H), 3.65 (t, J = 6.6 Hz, 2H), 2.14–2.08 (m, 2H), 2.08–2.04 (m, 2H), 2.02 (q, J = 7.4 Hz, 2H), 1.61–1.45 (m, 8H), 1.39 (tt, J = 10.2, 6.3 Hz, 2H), 1.25 (br, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 140.1, 121.1, 63.2, 37.3, 32.5, 28.8, 28.0, 27.1, 26.9, 26.4. **IR (neat):** 3319, 2922, 2853, 1447, 1059, 846 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{20}O$) from $[M+H]^+$ is 168.15141, found 168.15172, difference of 1.84

ppm.





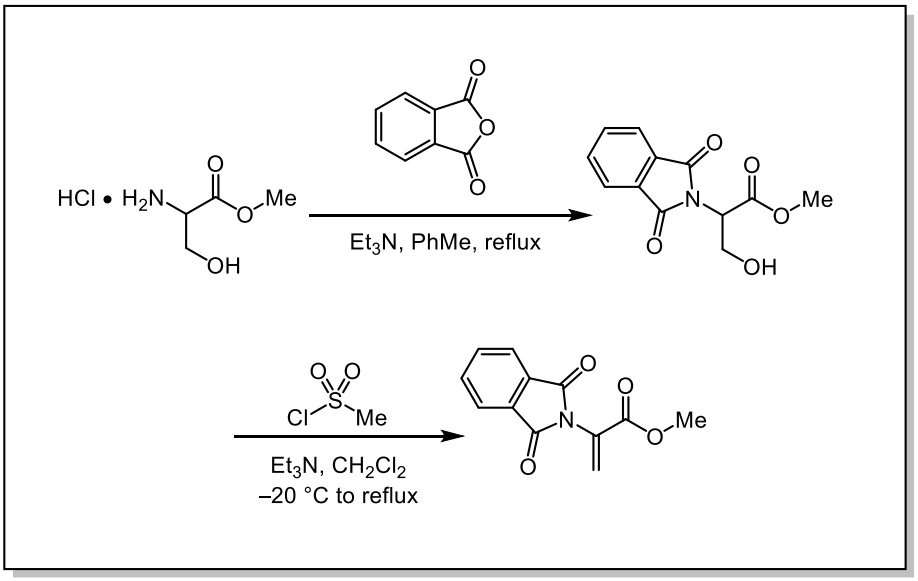
2-(((*tert*-butyldimethylsilyl)oxy)methyl)pent-4-en-1-ol

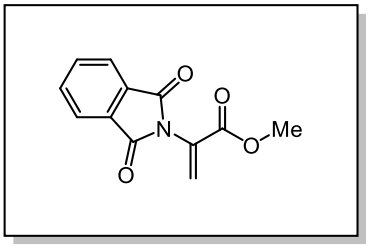
To a flame-dried 250-mL round bottom flask equipped with a stir bar was added $LiAlH_4$ (60.0 mmol, 2.0 equiv, 2.28 g) suspended in 90 mL dry THF. Once the suspension was cooled to 0 °C, diethyl 2-allylmalonate (30.0 mmol, 1.0 equiv, 5.92 mL) dissolved in 10 mL dry THF was added dropwise to the reaction. The reaction was warmed to room temperature and allowed to stir for 4 hours. The reaction mixture was worked up by diluting the mixture with Et_2O and adding 2.3 mL water, 2.3 mL 1 M NaOH, and 6.9 mL water dropwise sequentially at 0 °C. The reaction was warmed to room temperature and stirred for 15 minutes. Anhydrous $MgSO_4$ was added to the mixture and stirred for 15 minutes. The reaction was filtered and concentrated *in vacuo*. The crude diol product was carried onto the next step without further purification.

To a 100-mL round bottom flask containing a magnetic stir bar was added NaH (5.00 mmol, 1.0 equiv, 60% dispersion in mineral oil, 0.120 g) in 10 mL anhydrous THF, and then, crude 2-allylpropane-1,3-diol (5.00 mmol, 1.0 equiv, 0.581 g) was added at 0 °C. After stirring for 15 minutes, *tert*-butyldimethylsilyl chloride (5.00 mmol, 1.0 equiv, 0.754 g) was added slowly, and the resulting slurry was allowed to stir for 4 hours at room temperature. The reaction solution was quenched with water and extracted with Et_2O. The organics were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified *via* silica gel chromatography (10% EtOAc in hexanes) to give the titled compound (0.613 g, 53% yield). Spectra are consistent with reported literature values.[30]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.09–4.99 (m, 2H), 3.82–3.70 (m, 2H), 3.68–3.59 (m, 2H), 2.71 (dd, *J* = 6.4, 4.8 Hz, 1H), 2.05 (tt, *J* = 7.1, 1.3 Hz, 2H), 1.8 (ddp, *J* = 10.5, 7.1, 3.6 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.6, 116.5, 66.7, 66.4, 41.9, 32.6, 26.0, 18.3, –5.4, –5.5. **IR (neat):** 3367, 2954, 2929, 2858,

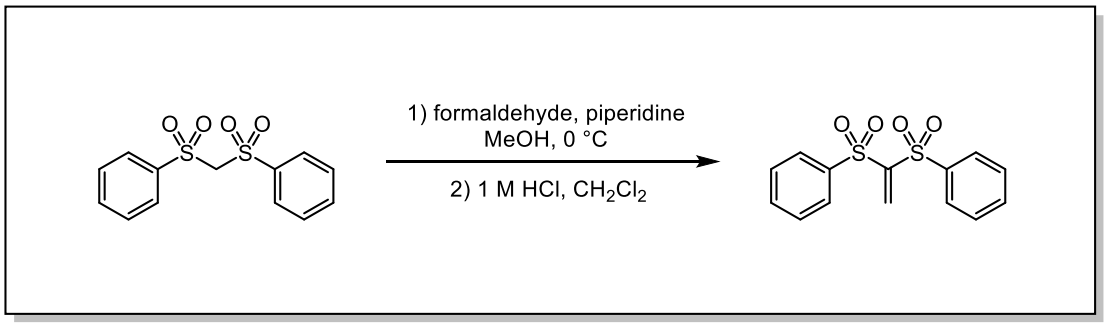
1641, 1472, 1361, 1253, 1089, 1038, 912, 832, 774 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{12}H_{26}O_2Si$) from $[M+H]^+$ is 230.17021, found 230.17059, difference of 1.69 ppm.

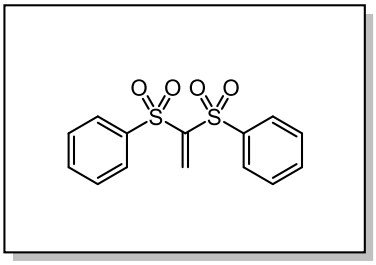




Methyl 2-(1,3-dioxoisoindolin-2-yl)prop-2-enoate

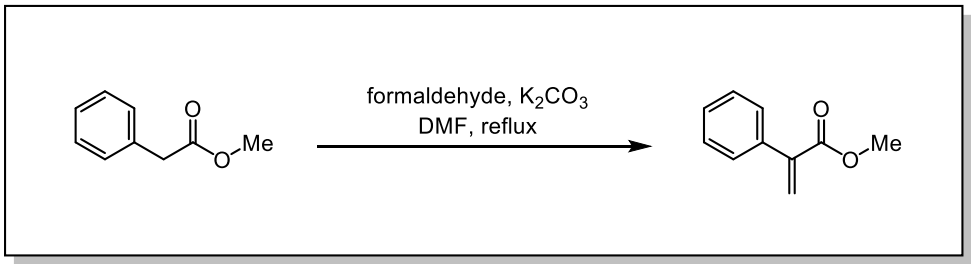
The titled compound was prepared as previously reported in the literature.[31] Spectra are consistent with reported literature values.

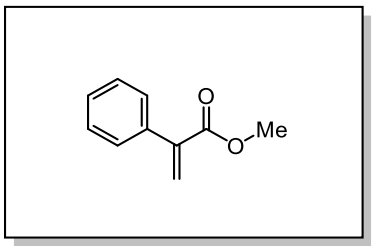




1-(benzenesulfonyl)vinylsulfonylbenzene

The titled compound was prepared as previously reported in the literature.[32] Spectra are consistent with reported literature values.





Methyl 2-phenylprop-2-enoate

The titled compound was prepared as previously reported in the literature.[33] Spectra are consistent with reported literature values.

Reaction Optimization

A. General Screening Procedure for Hydroetherification Reactions

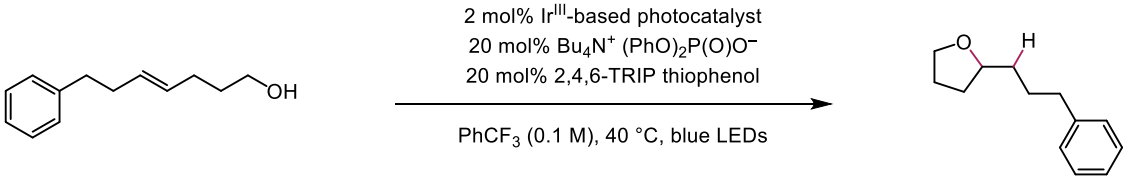
An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with the alcohol substrate (0.050 mmol, 1.0 equiv) and an Ir(III)-based photocatalyst (0.0010 mmol, 2 mol%). The vial was brought into a glove box under an atmosphere of N_2, where the appropriate Brønsted base (0.010 mmol, 20 mol%) was added. The vial was then sealed with a cap outfitted with a PTFE septum and removed from the glovebox. The vial was sealed with electrical tape, and an N_2 inlet needle was added through the septum. Anhydrous $PhCF_3$ (0.5 mL, 0.1 M) was added *via* syringe, followed by the appropriate HAT co-catalyst (0.010 mmol, 20 mol%) *via* microsyringe. The vial was placed on a stir plate approximately 2 cm away from Kessil H150B LED lamps, and the reaction solution was allowed to stir under blue light irradiation (~450 nm) for 24 hours. The average temperature of the reaction setup was 40 °C with cooling fans running constantly; variations of up to ±5 °C were observed. After 24 h, irradiation was ceased, and biphenyl (0.050 mmol, 1.0 equiv, 7.7 mg) was added as a standard. A small amount of CH_2Cl_2 was added to the vial to ensure that the crude mixture was homogeneous. An aliquot of the crude mixture was then filtered through a pipette silica plug containing ~2 cm of silica gel eluting with ~1.5 mL of acetone. Yields were directly quantified using gas chromatography.

NOTE: The Brønsted base was added *via* microsyringe outside of the glovebox (under positive N_2 pressure) before the addition of the HAT co-catalyst when the base was a volatile liquid (*e.g.,* collidine, *N*-methylimidazole, 2-methyloxazoline).

NOTE: For screening with 4-penten-1-ol as a terminal olefin model substrate, the alcohol was also delivered *via* microsyringe outside of the glovebox (under positive N_2 pressure) before the addition of the HAT co-catalyst.

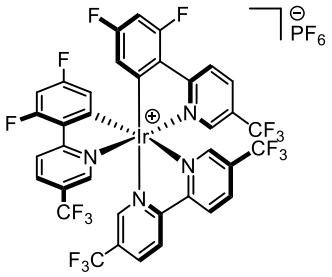
B. Optimization Data

Table S1: Photocatalyst Optimization

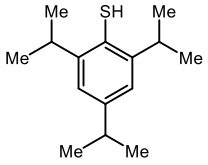


Entry	Photocatalyst	$E^{o}(Ir^{III*/II})$ (V vs. Fc^{+}/Fc)[a]	$E^{o}(Ir^{III/II})$ (V vs. Fc^{+}/Fc)[a]	Effective 'BDFE' (kcal/mol)[b]	GC Yield[c]
1	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$	+0.94	–1.75	95.8	0%
2	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	+0.83	–1.75	91.9	0%
3	$[Ir(d(CF_3)(Me)ppy)_2(dtbbpy)]PF_6$	+1.22	–1.35	92.0	0%
4	$[Ir(dF(CF_3)ppy)_2(4,4'\text{-}d(CF_3)bpy)]PF_6$	+1.27	–1.18	102.0	27%
5	$[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$	+1.30	–1.07	102.7	31%
6	$[Ir(d(CF_3)(CF_3)ppy)_2(dtbbpy)]PF_6$	+1.11	–1.43	98.3	0%

[a]Potentials measured in MeCN. [b]Effective BDFEs were calculated using the Bordwell equation: 'BDFE' = 1.37pK_a(B–H) + 23.06$E^{\circ}(Ir^{III*/II})$ + 54.9. The pK_a of $(PhO)_2P(O)O^-$ in MeCN is ~13.0. [c]GC yields determined relative to biphenyl as an internal standard.

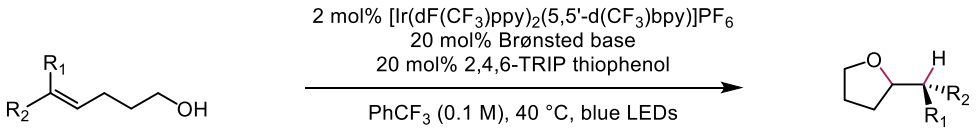


$[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$



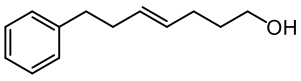
2,4,6-TRIP thiophenol

Table S2: Optimization of Brønsted Base for Three Different Olefin Classes

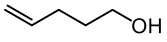


Entry	Brønsted Base	pK_a[a]	Effective 'BDFE' (kcal/mol)[b]	Disubstituted Olefin (R_1 = H, R_2 = $(CH_2)_2Ph$)[c]	Terminal Olefin (R_1 = R_2 = H)[c]	Trisubstituted Olefin (R_1 = R_2 = $(CH_2)_5$)[c]
1	Bu_4N^+ $(PhO)_2P(O)O^-$	13.0	102.7	31%	23%	31%
2	Bu_4P^+ $(PhO)_2P(O)O^-$	13.0	102.7	71%	26%	39%
3	Bu_4P^+ (*n*-BuO)$_2$P(O)O$^-$	13.0	102.7	48%	23%	32%
4	Bu_4P^+ (*t*-BuO)$_2$P(O)O$^-$	13.0	102.7	33%	15%	46%
5	Bu_4P^+ $(MeO)_2P(O)O^-$	13.0	102.7	55%	27%	52%
6	Bu_4N^+ $CF_3C(O)O^-$	12.7	102.3	58%	25%	54%
7	Bu_4P^+ $CF_3C(O)O^-$	12.7	102.3	54%	29%	48%
8	imidazole	15.1	105.6	1%	0%	6%
9	*N*-methylimidazole	15.1	105.6	14%	5%	71%
10	2-methyloxazoline	13.2[d]	103.0	45%	6%	80%
11	collidine	15.0	105.4	23%	3%	75%

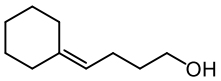
[a]pK_a values estimated in MeCN. [b]Effective BDFEs were calculated using the Bordwell equation: 'BDFE' = 1.37pK_a(B–H) + 23.06$E°$($Ir^{III*/II}$) + 54.9, where $E°$($Ir^{III*/II}$) = +1.30 V vs. Fc^+/Fc in MeCN. [c]GC yields determined relative to biphenyl as an internal standard. [d]p*K*a value in MeCN estimated from value in H_2O using p*K*a shift parameters (see Rossini, E.; Bochevarov, A. D.; Knapp, E. W. *ACS Omega* **2018**, *3*, 1653–1662)



disubstituted olefin

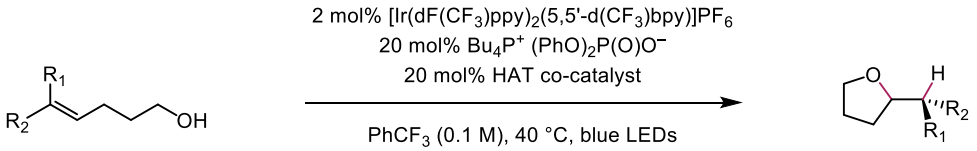


terminal olefin



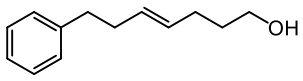
trisubstituted olefin

Table S3: Optimization of HAT Co-Catalyst for Three Different Olefin Classes

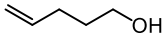


Entry	HAT Co-Catalyst	Disubstituted Olefin (R_1 = H, R_2 = $(CH_2)_2Ph$)[a]	Terminal Olefin (R_1 = R_2 = H)[a]	Trisubstituted Olefin (R_1 = R_2 = $(CH_2)_5$)[a]
1	2,4,6-TRIP-thiophenol	71%	45%	23%
2	2,4,6-trimethylthiophenol	57%	26%	39%
3	thiophenol	45%	30%	56%
4	2-naphthalene thiol	43%	26%	43%
5	pentafluorothiophenol	69%	38%	45%
6	4-methoxythiophenol	41%	51%	39%
7	4-(trifluoromethyl)thiophenol	45%	27%	69%
8	4-fluorothiophenol	59%	37%	42%
9	3-fluorothiophenol	47%	24%	42%
10	2-fluorothiophenol	75%	29%	63%
11	3,4-difluorothiophenol	81%	31%	57%
12	2,4-difluorothiophenol	55%	35%	62%
13	disulfide of best thiol	74%[b]	55%[c]	62%[d]

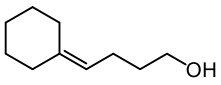
[a]GC yields determined relative to biphenyl as an internal standard. [b]Bis(2-fluorophenyl) disulfide used as HAT co-catalyst. [c]Bis(4-methoxyphenyl) disulfide used as HAT co-catalyst. [d]Bis(4-trifluoromethylphenyl) disulfide used as HAT co-catalyst.



disubstituted olefin

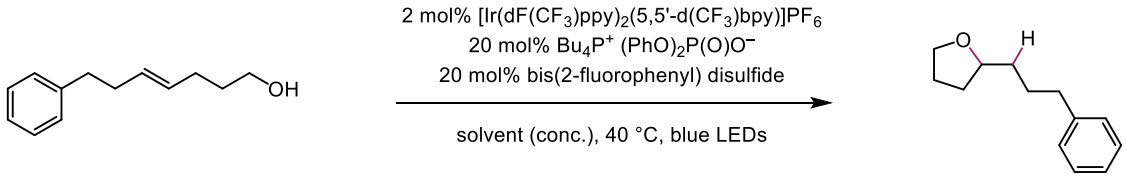


terminal olefin



trisubstituted olefin

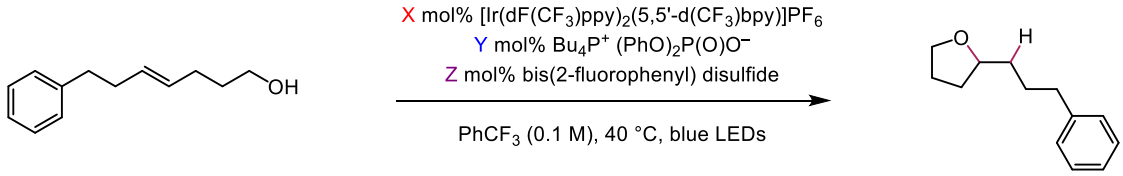
Table S4: Optimization of Solvent & Reaction Concentration



Entry	Solvent	Solvent Source/Quality[a]	Substrate Concentration	GC Yield[b]
1	$PhCF_3$	Sure-Seal bottle	0.1 M	67%
2	PhMe	solvent system[c]	0.1 M	58%
3	PhF	glass bottle	0.1 M	53%
4	CH_2Cl_2	solvent system[c]	0.1 M	49%
5	$(CH_2Cl)_2$	Sure-Seal bottle	0.1 M	27%
6	1,4-dioxane	solvent system[c]	0.1 M	20%
7	$PhCF_3$	Sure-Seal bottle	0.2 M	70%
8	$PhCF_3$	Sure-Seal bottle	0.05 M	80%
9	$PhCF_3$	Sure-Seal bottle	0.025 M	71%
10	$PhCF_3$	new Sure-Seal bottle	0.1 M	74%
11	$PhCF_3$	new Sure-Seal bottle, run in sealed vial (no N_2 inlet)	0.1 M	69%
12	$PhCF_3$	dried & degassed solvent	0.1 M	72%
13	$PhCF_3$	wet & aerated solvent	0.1 M	55%
14	$PhCF_3$	new Sure-Seal bottle, run open to air	0.1 M	3%

[a]Standard reactions are run under positive pressure of N_2 with the inlet needles (22 G) perforating the septa of the vials. [b]GC yields determined relative to biphenyl as an internal standard. [c]Solvents from the solvent system are dried over an alumina column and stored under Ar.

Table S5: Optimization of Catalyst Loadings



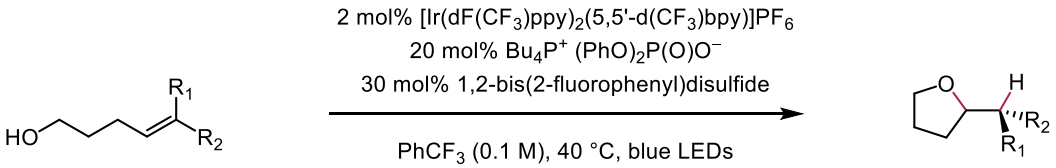
Entry	Photocatalyst Loading (X)	Brønsted Base Loading (Y)	HAT Co-Catalyst Loading (Z)	GC Yield[a]
1	1 mol%	20 mol%	20 mol%	58%
2	2 mol%	20 mol%	20 mol%	74%
3	3 mol%	20 mol%	20 mol%	77%
4	5 mol%	20 mol%	20 mol%	80%
5	2 mol%	5 mol%	20 mol%	59%
6	2 mol%	10 mol%	20 mol%	60%
7	2 mol%	30 mol%	20 mol%	50%
8	2 mol%	50 mol%	20 mol%	53%
9	2 mol%	20 mol%	5 mol%	42%
10	2 mol%	20 mol%	10 mol%	56%
11	2 mol%	20 mol%	30 mol%	85%
12	2 mol%	20 mol%	50 mol%	64%

[a]GC yields determined relative to biphenyl as an internal standard.

NOTE: Even though 3 mol% and 5 mol% loadings of photocatalyst gave a slight boost in yield, it was decided that a 2 mol% loading would be used for all preparative scale reactions for practical reasons.

Table S6: Optimized Conditions

General Optimized Conditions:

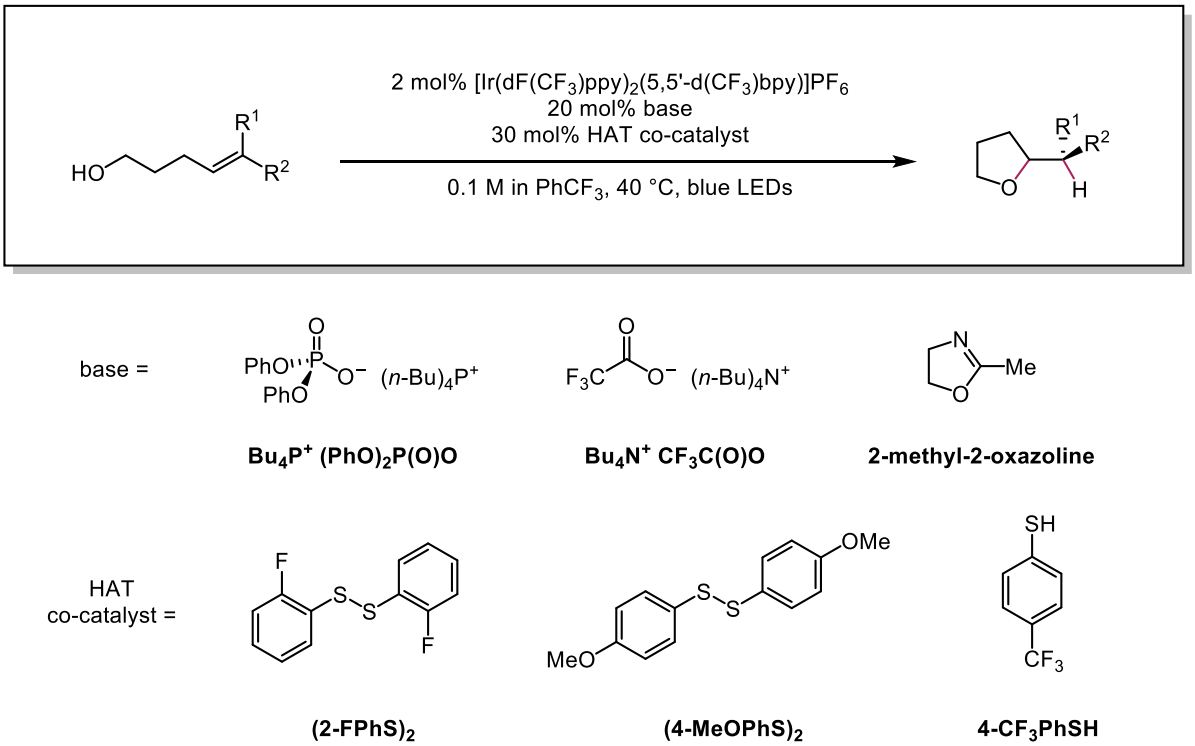


Tailored Catalyst Combinations:

disubstituted alkenes	monosubstituted alkenes	trisubstituted alkenes
20 mol% Bu_4P^+ $(PhO)_2P(O)O^-$ 30 mol% 1,2-bis(2-fluorophenyl) disulfide	20 mol% Bu_4P^+ $(PhO)_2P(O)O^-$ 30 mol% 1,2-bis(4-methoxyphenyl) disulfide	20 mol% 2-methyl-2-oxazoline 30 mol% 4-trifluoromethyl thiophenol

During our substrate scope studies, we found that different classes of alkenols with respect to the olefin substitution pattern perform optimally when tailored catalyst combinations are used. The highest yields for terminal olefins are obtained when 1,2-bis(4-methoxyphenyl)disulfide, a more electron-rich HAT co-catalyst, is employed, while trisubstituted olefins prefer heterocyclic bases, such as 2-methyl-2-oxazoline, and electron-deficient thiols, such as 4-trifluoromethylthiophenol. While our general optimization parameters can be used for a broad scope of substrates, these substrate-specific conditions provide a meaningful improvement in yield for some cases and are listed in the footnotes of Table 2.

Synthesis of Products



A. General Procedure for Preparative Hydroetherification Reactions:

Method A (Preparative Scale for General Hydroetherification Reactions):

An oven-dried 2-dram vial was charged with a magnetic stir bar, substrate (0.500 mmol, 1.0 equiv) and $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$ (0.0100 mmol, 2 mol%, 11.5 mg). The vial was brought into a glove box where Bu_4P^+ $(PhO)_2P(O)O^-$ (0.100 mmol, 20 mol%, 50.9 mg) or, in some noted cases, Bu_4N^+ $CF_3C(O)O^-$ (0.100 mmol, 20 mol%, 35.5 mg) was added. The vial was then sealed with a Teflon septum and removed from the glovebox. With an N_2 inlet in the vial, 5 mL (0.1 M) anhydrous $PhCF_3$ was added *via* syringe, followed by $(2\text{-FPhS})_2$ (0.150 mmol, 30 mol%, 30.3 μL). The reaction was irradiated by blue LED lamps (Kessil H150B LED Grow Light) and stirred for 48–60 hours at an average of 40 °C with cooling fans running constantly. Variations of up to ±5 °C were observed. The solvent was removed under reduced pressure, and the crude product was purified by silica gel flash chromatography on a Biotage Isolera One instrument (Biotage SNAP Ultra 25 g column, eluted with hexane/Et_2O) to afford the titled compound below. All scale-ups were run in duplicates, and the average yields are reported. Diastereomeric ratios were determined by ^1H NMR of the crude reaction mixtures.

Method B (Preparative Scale for Hydroetherification of Trisubstituted Alkenes):

An oven-dried 2-dram vial was charged with a magnetic stir bar, substrate (0.500 mmol, 1.0 equiv) and $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$ (0.0100 mmol, 2 mol%, 11.5 mg). The vial was

sealed with a Teflon septum inside a glove box and then brought out. With an N_2 inlet in the vial, 5 mL (0.1 M) anhydrous $PhCF_3$ was added *via* syringe, followed by 2-methyl-2-oxazoline (0.10 mmol, 20 mol%, 8.5 µL) and 4-CF_3PhSH (0.150 mmol, 30 mol%, 20.3 µL). The reaction was irradiated by blue LED lamps (Kessil H150B LED Grow Light) and stirred for 48–60 hours at an average of 40 °C with cooling fans running constantly. Variations of up to ±5 °C were observed. The solvent was removed under reduced pressure, and the crude product was purified by silica gel flash chromatography on a Biotage Isolera One instrument (Biotage SNAP Ultra 25 g column, eluted with hexane/Et_2O) to afford the titled compound below. All scale-ups were run in duplicates, and the average yields are reported. Diastereomeric ratios were determined by ^{1}H NMR of the crude reaction mixtures.

Method C (Preparative Scale for Hydroetherification of Monosubstituted Alkenes):

An oven-dried 2-dram vial was charged with a magnetic stir bar, substrate (0.500 mmol, 1.0 equiv), [Ir(dF(CF_3)ppy)$_2$(5,5′-d(CF_3)bpy)]PF_6 (0.0100 mmol, 2 mol%, 11.5 mg), and (4-MeOPhS)$_2$ (0.150 mmol, 30 mol%, 41.8 mg). The vial was brought into a glove box where Bu_4P^+ $(PhO)_2P(O)O^-$ (0.100 mmol, 20 mol%, 50.9 mg) was added. The vial was then sealed with a Teflon septum and removed from the glovebox. With an N_2 inlet in the vial, 5 mL (0.1 M) anhydrous $PhCF_3$ was added *via* syringe. The reaction was irradiated by blue LED lamps (Kessil H150B LED Grow Light) and stirred for 48–60 hours at an average of 40 °C with cooling fans running constantly. Variations of up to ±5 °C were observed. The solvent was removed under reduced pressure, and the crude product was purified by silica gel flash chromatography on a Biotage Isolera One instrument (Biotage SNAP Ultra 25 g column, eluted with hexane/Et_2O) to afford the titled compound below. All scale-ups were run in duplicates, and the average yields are reported. Diastereomeric ratios were determined by ^{1}H NMR of the crude reaction mixtures.

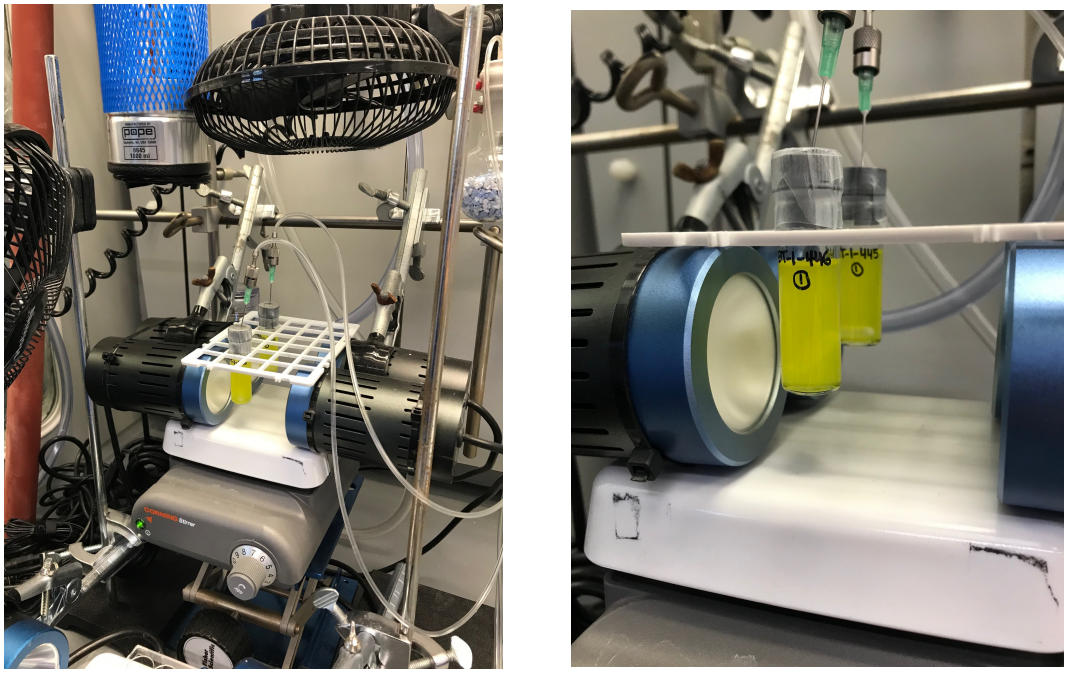


Figure S1. Set-up for preparative scale hydroetherification reactions.

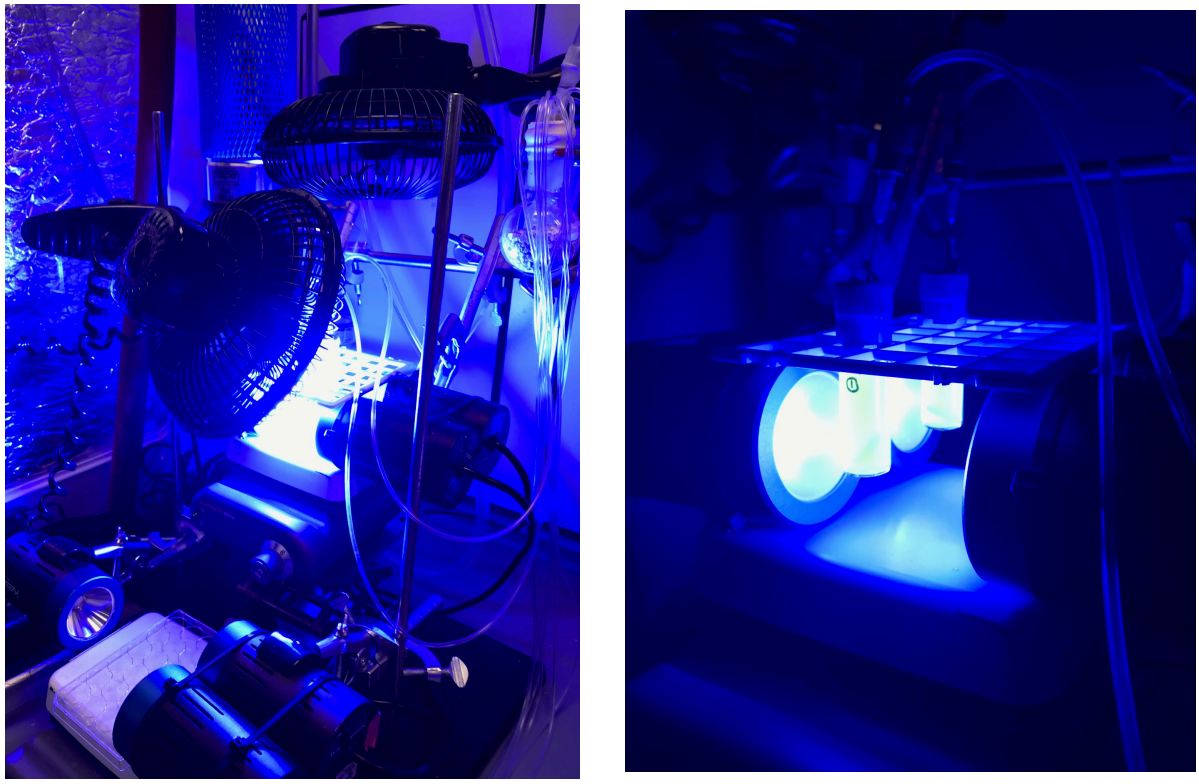
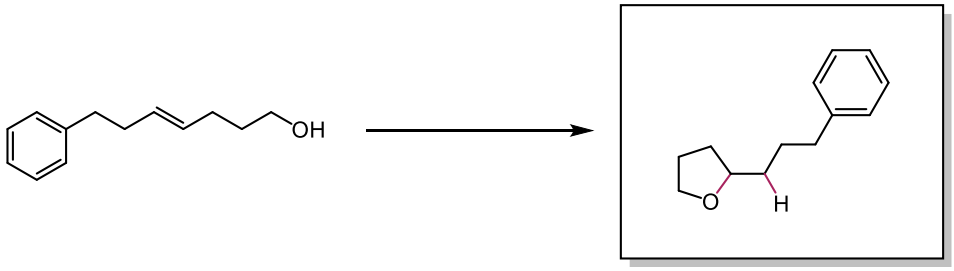


Figure S2. Set-up for preparative scale hydroetherification reactions under blue light irradiation.

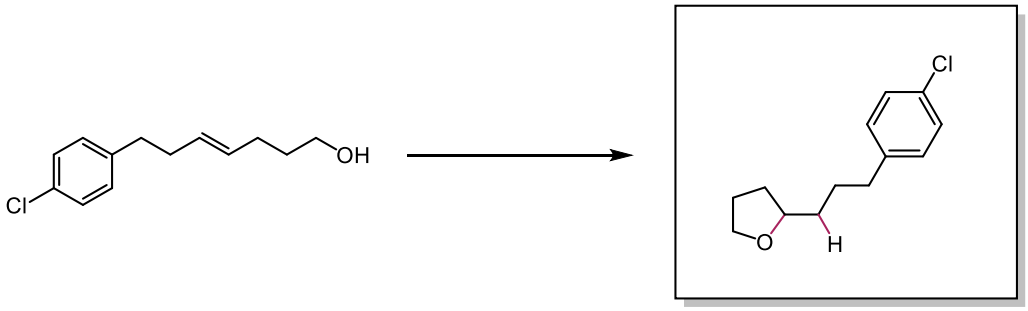
B. Characterization of Hydroetherification Products:



2-(3-phenylpropyl)tetrahydrofuran (2)

The titled compound was synthesized following General Procedure A using (*E*)-7-phenylhept-4-en-1-ol with a reaction time of 48 h. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 20% Et_2O in hexanes) to afford the titled compound (77.0 mg, 81% yield).

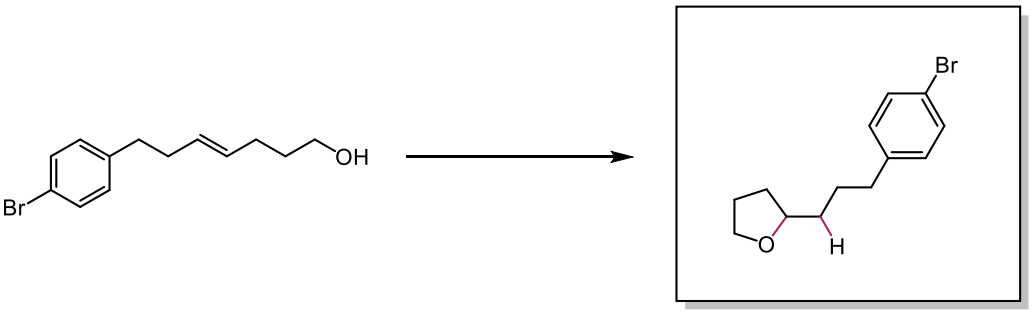
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 7.21–7.14 (m, 3H), 3.88–3.77 (m, 2H), 3.71 (td, J = 8.0, 6.3 Hz, 1H), 2.69–2.59 (m, 2H), 2.00–1.92 (m, 1H), 1.91–1.70 (m, 3H), 1.70–1.58 (m, 2H), 1.55–1.38 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 142.5, 128.5, 128.3, 125.7, 79.3, 67.7, 36.0, 35.3, 31.4, 28.3, 25.8. **IR (neat):** 3026, 2932, 2858, 1603, 1496, 1454, 1382, 1067, 1030, 921, 748 cm^{-1}. **HRMS (EI):** *m/z* calculated for $C_{13}H_{18}O$ ($[M]^{\bullet+}$) is 190.13522, found 190.13517, difference of 0.26 ppm.



2-(3-(4-chlorophenyl)propyl)tetrahydrofuran (3)

The titled compound was synthesized following General Procedure A using (*E*)-7-(4-chlorophenyl)hept-4-en-1-ol with a reaction time of 48 h. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 20% Et_2O in hexanes) to afford the titled compound (108.3 mg, 97% yield).

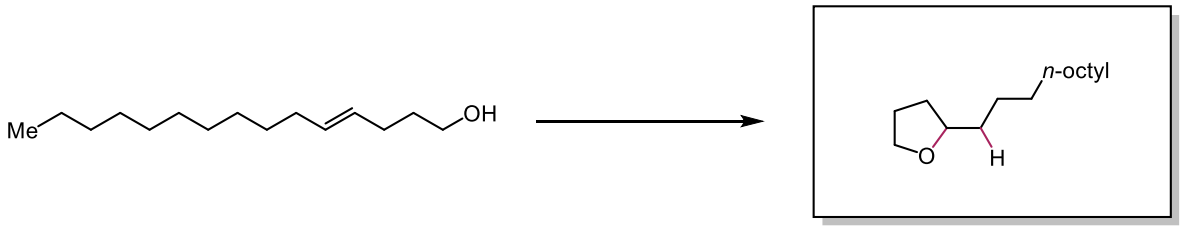
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.21 (m, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 3.88–3.75 (m, 2H), 3.70 (td, *J* = 7.9, 6.2 Hz, 1H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.01–1.91 (m, 1H), 1.91–1.79 (m, 2H), 1.79–1.69 (m, 1H), 1.68–1.53 (m, 2H), 1.53–1.37 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 140.9, 131.4, 129.8, 128.4, 79.1, 67.7, 35.3, 35.2, 31.4, 28.1, 25.7. **IR (neat):** 2934, 2859, 1574, 1493, 1474, 1460, 1407, 1091, 1069, 1015, 922, 819, 758, 662 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{17}ClO$) from $[M+H]^+$ is 224.09679, found 224.09640, difference of 1.73 ppm.



2-(3-(4-bromophenyl)propyl)tetrahydrofuran (4)

The titled compound was synthesized following General Procedure A using (*E*)-7-(4-bromophenyl)hept-4-en-1-ol with a reaction time of 48 h. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% Et_2O in hexanes) to afford the titled compound (109.7 mg, 81% yield).

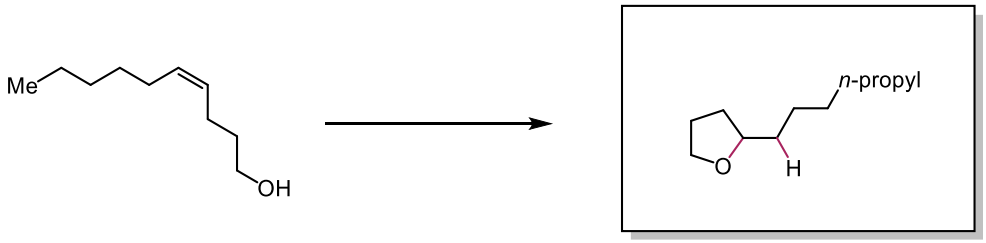
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.35 (m, 2H), 7.05 (d, *J* = 8.3 Hz, 2H), 3.88–3.75 (m, 2H), 3.70 (td, *J* = 8.0, 6.3 Hz, 1H), 2.59 (t, *J* = 7.4 Hz, 2H), 2.00–1.91 (m, 1H), 1.91–1.80 (m, 2H), 1.80–1.68 (m, 1H), 1.67–1.53 (m, 2H), 1.53–1.37 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 141.5, 131.4, 130.3, 119.5, 79.3, 67.8, 35.5, 35.3, 31.5, 28.1, 25.9. **IR (neat):** 2935, 2859, 1488, 1460, 1403, 1071, 1011, 816 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{17}BrO$) from $[M+H]^+$ is 268.04628, found 268.04625, difference of 0.12 ppm.



2-undecyltetrahydrofuran (5)

The titled compound was synthesized following General Procedure A using (*E*)-pentadec-4-en-1-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% Et_2O in hexanes) to afford the titled compound (97.1 mg, 86% yield).

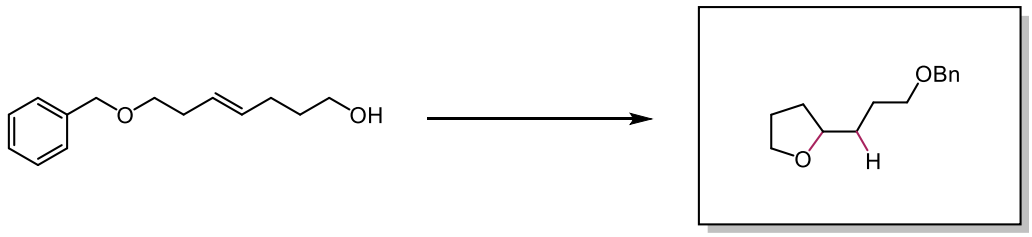
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89–3.83 (m, 1H), 3.77 (dt, *J* = 7.9, 6.2 Hz, 1H), 3.71 (td, *J* = 8.0, 6.2 Hz, 1H), 2.00–1.92 (m, 1H), 1.92–1.79 (m, 2H), 1.47–1.37 (m, 3H), 1.32–1.22 (m, 18H), 0.88 (t, *J* = 6.9, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 79.6, 67.8, 35.9, 32.1, 31.5, 29.9, 29.8, 29.8, 29.8, 29.8, 29.5, 26.6, 25.9, 22.8, 14.3. **IR (neat):** 2923, 2853, 1464, 1378, 1070, 919, 757, 722 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{15}H_{30}O$) from $[M+H]^+$ is 226.22967, found 226.22968, difference of 0.06 ppm.



2-hexyltetrahydrofuran (6)

The titled compound was synthesized following General Procedure A using commercially available (*Z*)-dec-4-en-1-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% Et_2O in hexanes) to afford the titled compound (59.6 mg, 76% yield).

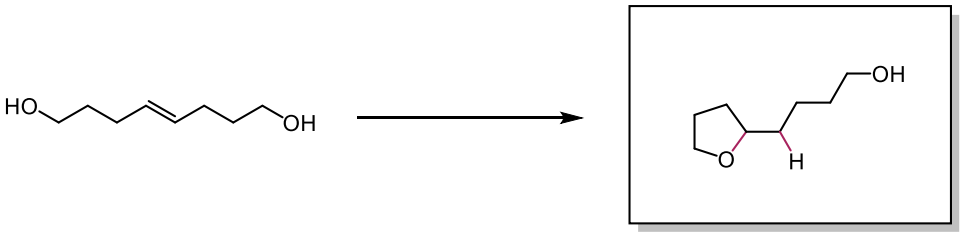
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (td, *J* = 7.9, 6.2 Hz, 1H), 3.81–3.74 (m, 1H), 3.71 (td, *J* = 8.0, 6.3 Hz, 1H), 2.01–1.92 (m, 1H), 1.92–1.80 (m, 2H), 1.63–1.51 (m, 1H), 1.48–1.35 (m, 3H), 1.35–1.23 (m, 7H), 0.91–0.85 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 79.5, 67.6, 35.8, 31.9, 31.4, 29.5, 26.4, 25.7, 22.6, 14.1. **IR (neat):** 2957, 2922, 2856, 1462, 1379, 1326, 1067, 1049, 921, 758, 724 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{10}H_{20}O$) from $[M+H]^+$ is 156.15142, found 156.15134, difference of 0.47 ppm.



2-(3-benzyloxy)propyl)tetrahydrofuran (7)

The titled compound was synthesized following General Procedure A using (*E*)-7-(benzyloxy)hept-4-en-1-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% Et_2O in hexanes) to afford the titled compound (89.5 mg, 81% yield).

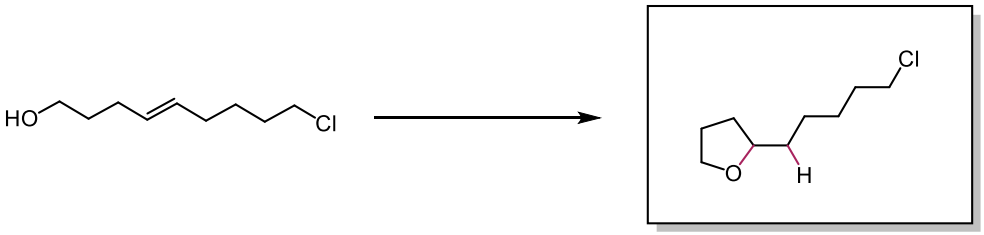
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.6 Hz, 4H), 7.30–7.24 (m, 1H), 4.50 (s, 2H), 3.90–3.75 (m, 2H), 3.71 (td, *J* = 8.0, 6.2 Hz, 1H), 3.50 (qt, *J* = 9.4, 6.2 Hz, 2H), 2.02–1.92 (m, 1H), 1.92–1.80 (m, 2H), 1.80–1.70 (m, 1H), 1.70–1.53 (m, 3H), 1.45 (ddt, *J* = 11.9, 8.9, 7.6 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 138.7, 128.4, 127.6, 127.5, 79.2, 72.9, 70.3, 67.7, 32.3, 31.4, 26.6, 25.8. **IR (neat):** 3030, 2940, 2856, 1496, 1454, 1363, 1205, 1096, 1029, 934, 736, 698 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{14}H_{20}O_2$) from $[M+H]^+$ is 220.14633, found 220.14613, difference of 0.89 ppm.



4-(tetrahydrofuran-2-yl)butan-1-ol (8)

The titled compound was synthesized following General Procedure A using (*E*)-oct-4-ene-1,8-diol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 100% Et_2O in hexanes) to afford the titled compound (56.8 mg, 79% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89–3.83 (m, 1H), 3.80 (qd, *J* = 7.4, 5.2 Hz, 1H), 3.71 (td, *J* = 8.0, 6.3 Hz, 1H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.02–1.93 (m, 1H), 1.93–1.80 (m, 2H), 1.65–1.54 (m, 4H), 1.54–1.38 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 79.5, 67.8, 63.0, 35.5, 32.9, 31.5, 25.9, 22.7. **IR (neat):** 3388, 2935, 2863, 1460, 1378, 1358, 1072, 1052, 918, 862 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_8H_{16}O_2$) from $[M+H]^+$ is 144.11503, found 144.11503, difference of 0.04 ppm.

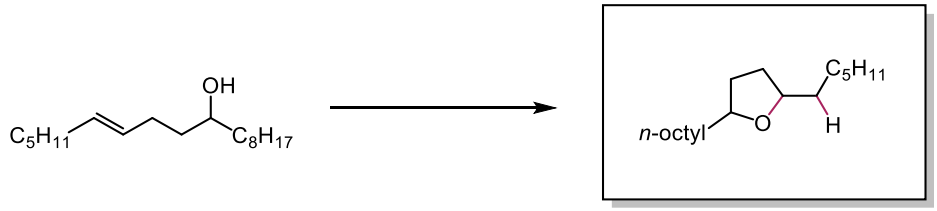


2-(5-chloropentyl)tetrahydrofuran (9)

The titled compound was synthesized following General Procedure A using (*E*)-9-chlorononen-4-en-1-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% Et_2O in hexanes) to afford the titled compound (70.9 mg, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (ddd, *J* = 8.4, 7.3, 6.1 Hz, 1H), 3.82–3.74 (m, 1H), 3.71 (td, *J* = 8.0, 6.3 Hz, 1H), 3.54 (t, *J* = 6.7 Hz, 2H), 2.01–1.93 (m, 1H), 1.93–1.82 (m, 2H), 1.79 (dq, *J* = 8.7, 6.8 Hz, 2H), 1.62–1.54 (m, 1H), 1.51–1.41 (m, 5H), 1.40–1.30 (m, 1H). **^{13}C NMR**

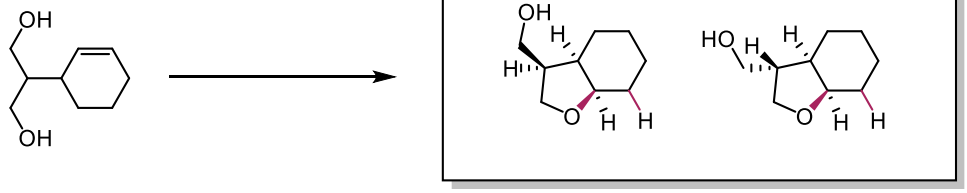
(126 MHz, $CDCl_3$) δ 79.4, 67.8, 45.2, 35.7, 32.7, 31.6, 27.1, 25.9, 25.9. **IR (neat):** 2933, 2859, 1462, 1446, 1310, 1074, 921, 759, 729 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_9H_{17}ClO$) from $[M+Na]^+$ is 176.09679, found 176.09657, difference of 1.26 ppm.



2-hexyl-5-octyltetrahydrofuran (10)

The titled compound was synthesized following General Procedure A using (*E*)-octadec-12-en-9-ol with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 10% Et_2O in hexanes) to afford the titled compound (62.2 mg, 47% yield, 1.3:1 dr).

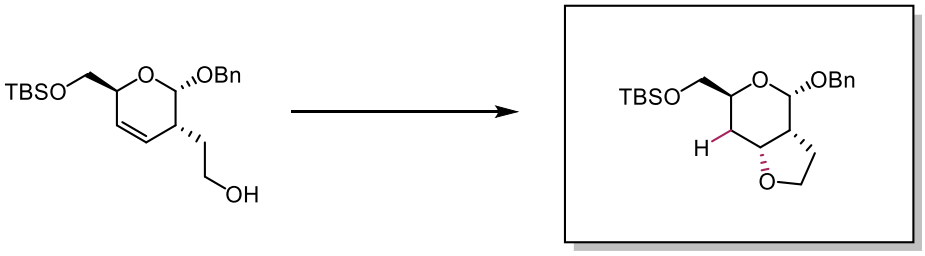
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 3.90 (p, *J* = 6.2 Hz, 1H), 3.77 (qd, *J* = 7.1, 6.7, 2.1 Hz, 1H), 2.04–1.87 (m, 2H), 1.64–1.54 (m, 2H), 1.51–1.34 (m, 6H), 1.33–1.20 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 79.5, 78.8, 36.3, 36.3, 32.3, 32.0, 32.0, 32.0, 31.2, 30.0, 29.9, 29.8, 29.7, 29.6, 29.6, 29.4, 26.4, 26.4, 26.4, 22.8, 22.8, 14.3, 14.3. **IR (neat):** 2957, 2925, 2856, 1465, 1378, 1091, 896, 757 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{18}H_{36}O$) from $[M+H]^+$ is 268.27662, found 268.27655, difference of 0.23 ppm.



2-(cyclohex-2-en-1-yl)propane-1,3-diol (11)

The titled compound was synthesized following General Procedure A using racemic 2-cyclohex-2-en-1-ylpropane-1,3-diol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 80% to 100% Et_2O in hexanes) to afford the titled compound (73.5 mg, 94% yield, 1:1 dr).

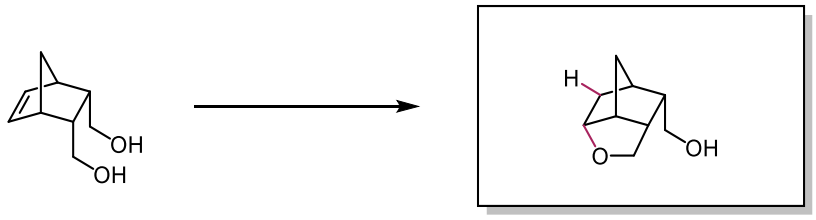
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 4.14 (dd, *J* = 9.1, 8.0 Hz, 0.5H), 4.01–3.93 (m, 1H), 3.89 (q, *J* = 4.4 Hz, 0.5H), 3.77 (dd, *J* = 10.5, 8.1 Hz, 0.5H), 3.71–3.58 (m, 1.5H), 3.57–3.50 (m, 1H), 2.72–2.54 (m, 0.5H), 2.24–2.13 (m, 0.5H), 2.08–1.96 (m, 1H), 1.93–1.80 (m, 1H), 1.76–1.67 (m, 0.5H), 1.65–1.44 (m, 4H), 1.42–1.10 (m, 3.5H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 78.5, 76.4, 69.3, 68.6, 65.0, 61.5, 47.5, 46.7, 40.3, 39.1, 28.5, 28.2, 27.9, 24.6, 24.0, 22.1, 21.1, 20.6. **IR (neat):** 3378, 2927, 2857, 1446, 1366, 1331, 1156, 1122, 1056, 1017, 944, 887, 855, 805, 687 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_9H_{16}O_2$) from $[M+H]^+$ is 156.11503, found 156.11523, difference of 1.28 ppm.



(((3a*R*,4*S*,6*S*,7a*R*)-4-(benzyloxy)hexahydro-4*H*-furo[3,2-c]pyran-6-yl)methoxy)(*tert*-butyl)dimethylsilane (12)

The titled compound was synthesized following General Procedure A using 2-[(2*S*,3*R*,6*S*)-2-benzyloxy-6-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3,6-dihydro-2*H*-pyran-3-yl]ethanol with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 40% Et_2O in hexanes) to afford the titled compound (94.7 mg, 51% yield, >20:1 dr).

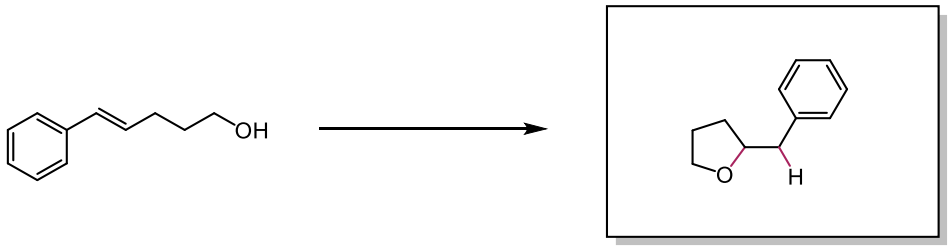
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H), 4.90 (d, *J* = 5.6 Hz, 1H), 4.79 (d, *J* = 12.3 Hz, 1H), 4.43 (d, *J* = 12.3 Hz, 1H), 4.11–4.02 (m, 2H), 3.99 (td, *J* = 4.3, 2.4 Hz, 1H), 3.82 (ddd, *J* = 9.9, 7.5, 3.6 Hz, 1H), 3.68–3.60 (m, 2H), 2.36–2.29 (m, 1H), 2.09–2.01 (m, 1H), 1.97–1.87 (m, 2H), 1.69 (ddd, *J* = 14.3, 11.8, 3.9 Hz, 1H), 0.90 (s, 9H), 0.06 (d, *J* = 6.1 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 138.5, 128.4, 127.6, 127.5, 97.4, 74.5, 68.8, 68.2, 66.5, 63.7, 39.9, 29.2, 28.0, 26.1, 18.5, –5.1, –5.2. **IR (neat):** 2947, 2928, 2857, 1472, 1389, 1360, 1253, 1138, 1093, 1075, 1025, 837, 777, 734, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{21}H_{34}O_4Si$) from $[M+Na]^+$ is 378.22264, found 378.22217, difference of 1.24 ppm.



10-oxatricyclononan-8-ylmethanol (13)

The titled compound was synthesized following General Procedure A using [3-(hydroxymethyl)-2-bicyclo[2.2.1]hept-5-enyl]methanol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 10% to 50% acetone in hexanes) to afford the titled compound (75.8 mg, 98% yield, >20:1 dr).

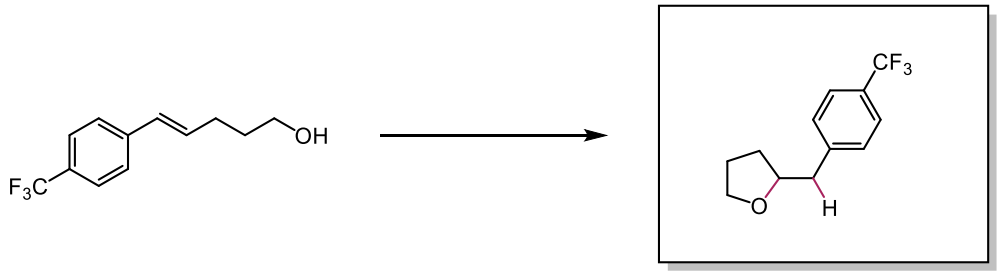
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (dd, *J* = 7.5, 5.1 Hz, 1H), 3.77–3.65 (m, 3H), 3.62 (dd, *J* = 8.9, 4.4 Hz, 1H), 2.69 (dt, *J* = 4.9, 3.2 Hz, 1H), 2.44 (dt, *J* = 9.5, 4.5 Hz, 1H), 2.22–2.15 (m, 1H), 2.14 (br, 1H), 1.59 (ddt, *J* = 10.4, 3.3, 1.6 Hz, 1H), 1.51–1.44 (m, 1H), 1.44–1.34 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 79.6, 68.0, 61.5, 47.9, 45.1, 39.7, 37.3, 36.0, 36.0. **IR (neat):** 3378, 2948, 2873, 1469, 1441, 1331, 1224, 1098, 1071, 1004, 949, 888, 797, 734 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_9H_{14}O_2$) from $[M+H]^+$ is 154.09938, found 154.09965, difference of 1.75 ppm.



2-benzyltetrahydrofuran (14)

The titled compound was synthesized following General Procedure A using (*E*)-5-phenylpent-4-en-1-ol and Bu_4N^+ $CF_3C(O)O^-$ as the base with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% Et_2O in hexanes) to afford the titled compound (61.1 mg, 75% yield).

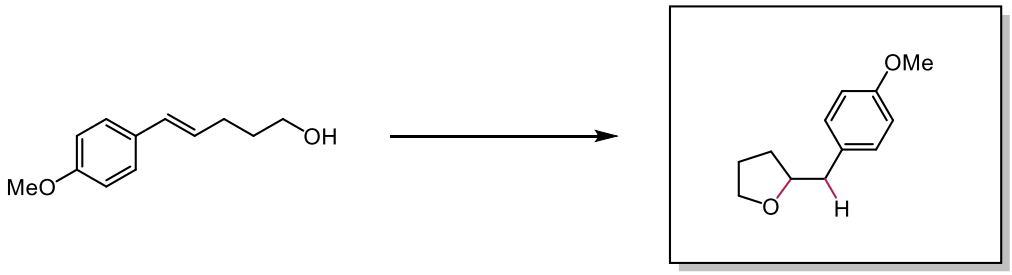
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.25–7.18 (m, 3H), 4.06 (dt, *J* = 7.9, 6.1 Hz, 1H), 3.93–3.86 (m, 1H), 3.74 (td, *J* = 7.9, 6.1 Hz, 1H), 2.93 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.74 (dd, *J* = 13.6, 6.5 Hz, 1H), 1.96–1.79 (m, 3H), 1.61–1.51 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 139.1, 129.4, 128.5, 126.3, 80.2, 68.1, 42.1, 31.1, 25.7. **IR (neat):** 3028, 2970, 2937, 2863, 1604, 1497, 1474, 1454, 1370, 1178, 1065, 1030, 1011, 920, 823, 746, 698 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{14}O$) from $[M+H]^+$ is 162.10447, found 162.10454, difference of 0.49 ppm.



2-(4-(trifluoromethyl)benzyl)tetrahydrofuran (15)

The titled compound was synthesized following General Procedure A using (*E*)-5-(4-(trifluoromethyl)phenyl)pent-4-en-1-ol and Bu_4N^+ $CF_3C(O)O^-$ as the base with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% Et_2O in hexanes) to afford the titled compound (90.1 mg, 78% yield).

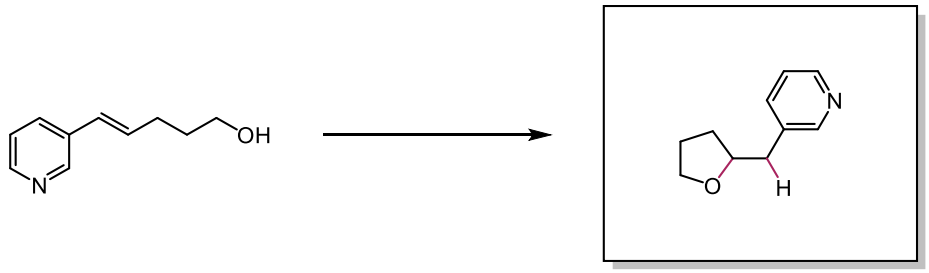
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 4.07 (ddd, *J* = 13.4, 7.2, 5.9 Hz, 1H), 3.89 (dt, *J* = 8.3, 6.7 Hz, 1H), 3.74 (td, *J* = 8.0, 6.4 Hz, 1H), 2.92 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.84 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.01–1.92 (m, 1H), 1.92–1.82 (m, 2H), 1.60–1.51 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.3, 129.7, 128.6 (q, *J* = 31.5 Hz), 125.4 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 272.2 Hz), 79.6, 68.2, 41.8, 31.2, 25.8. **^{19}F NMR (282 MHz, $CDCl_3$)** δ –62.38. **IR (neat):** 2945, 2869, 1619, 1418, 1322, 1161, 1116, 1065, 1019, 846, 809, 759 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{12}H_{13}F_3O$) from $[M+H]^+$ is 230.09185, found 230.09183, difference of 0.08 ppm.



2-(4-methoxybenzyl)tetrahydrofuran (16)

The titled compound was synthesized following General Procedure A using (*E*)-5-(4-methoxyphenyl)pent-4-en-1-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% Et_2O in hexanes) to afford the titled compound (81.9 mg, 85% yield).

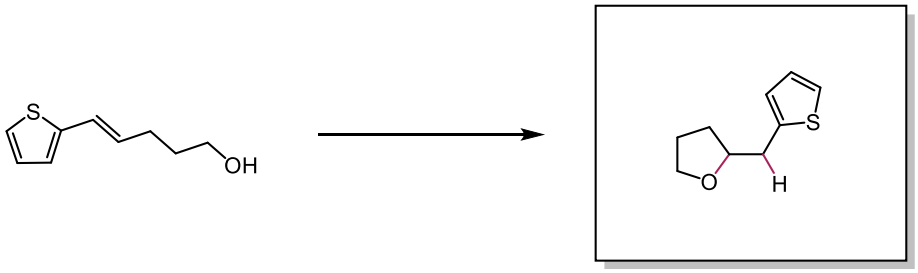
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.12 (m, 2H), 6.86–6.81 (m, 2H), 4.02 (dq, *J* = 7.9, 6.3 Hz, 1H), 3.88 (ddd, *J* = 8.3, 7.1, 6.0 Hz, 1H), 3.78 (s, 3H), 3.76–3.70 (m, 1H), 2.85 (dd, *J* = 13.7, 6.4, 1H), 2.69 (dd, *J* = 13.7, 6.5, 1H), 1.95–1.79 (m, 3H), 1.58–1.50 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.2, 131.2, 130.3, 113.9, 80.4, 68.1, 55.4, 41.1, 31.0, 25.8. **IR (neat):** 2939, 2861, 1612, 1583, 1512, 1464, 1443, 1300, 1245, 1178, 1061, 1036, 833, 806, 754 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{12}H_{16}O_2$) from $[M+H]^+$ is 192.11503, found 192.11471, difference of 1.66 ppm.



3-((tetrahydrofuran-2-yl)methyl)pyridine (17)

The titled compound was synthesized following General Procedure A using (*E*)-5-(pyridine-3-yl)pent-4-en-1-ol and Bu_4N^+ $CF_3C(O)O^-$ as the base with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (100% Et_2O) to afford the titled compound (68.4 mg, 84% yield).

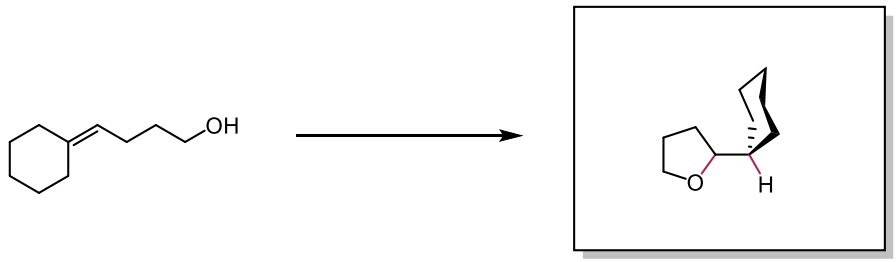
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50–8.43 (m, 2H), 7.58 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.22 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.06 (p, *J* = 6.5 Hz, 1H), 3.88 (dt, *J* = 8.4, 6.7 Hz, 1H), 3.74 (dt, *J* = 8.4, 6.9 Hz, 1H), 2.86 (dd, *J* = 13.9, 6.8, 1H), 2.79 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.00–1.92 (m, 1H), 1.90–1.82 (m, 2H), 1.55 (dq, *J* = 11.9, 7.9 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 150.7, 147.8, 136.9, 134.4, 123.3, 79.4, 68.1, 39.0, 31.0, 25.7. **IR (neat):** 2971, 2937, 2866, 1575, 1479, 1424, 1372, 1188, 1058, 1028, 921, 828, 789, 715 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{10}H_{13}NO$) from $[M+H]^+$ is 163.09971, found 163.09961, difference of 0.66 ppm.



2-(thiophen-2-ylmethyl)tetrahydrofuran (18)

The titled compound was synthesized following General Procedure A using (*E*)-5-(thiophen-2-yl)pent-4-en-1-ol and Bu_4N^+ $CF_3C(O)O^-$ as the base with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% Et_2O in hexanes) to afford the titled compound (48.6 mg, 58% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 5.2, 1.3 Hz, 1H), 6.93 (dd, *J* = 5.2, 3.4 Hz, 1H), 6.87–6.82 (m, 1H), 4.14–4.06 (m, 1H), 3.91 (dt, *J* = 8.3, 6.8 Hz, 1H), 3.77 (dt, *J* = 8.3, 6.9 Hz, 1H), 3.09 (dd, *J* = 14.8, 6.1 Hz, 1H), 2.99 (dd, *J* = 14.8, 6.1 Hz, 1H), 1.98 (ddd, *J* = 12.1, 7.5, 6.0 Hz, 1H), 1.91–1.82 (m, 2H), 1.64–1.54 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 141.0, 126.8, 125.6, 124.0, 79.7, 68.3, 36.1, 30.9, 25.9. **IR (neat):** 2970, 2927, 2865, 1440, 1370, 1063, 923, 851, 824, 695 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_9H_{12}OS$) from $[M+H]^+$ is 168.06089, found 168.06100, difference of 0.67 ppm.

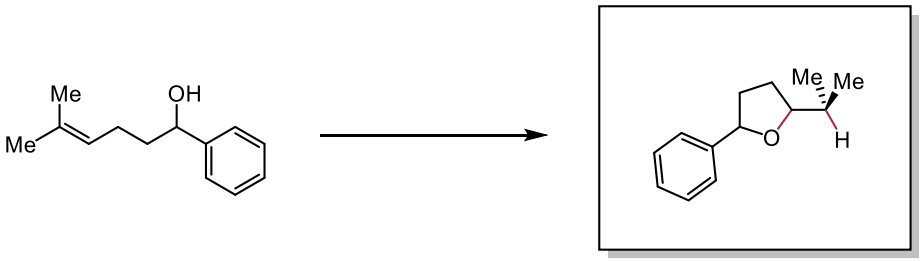


2-cyclohexyltetrahydrofuran (19)

The titled compound was synthesized following General Procedure A using 4-cyclohexylidenebutan-1-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 40% Et_2O in hexanes) to afford the titled compound (48.8 mg, 63% yield). Due to volatility of the product, the yield was also determined by GC (69% yield) against an authentically synthesized sample of the titled compound.

Alternatively, the titled compound was synthesized following General Procedure B with a reaction time of 48 hours. These conditions resulted in an increase in yield (58.0 mg, 75% yield).

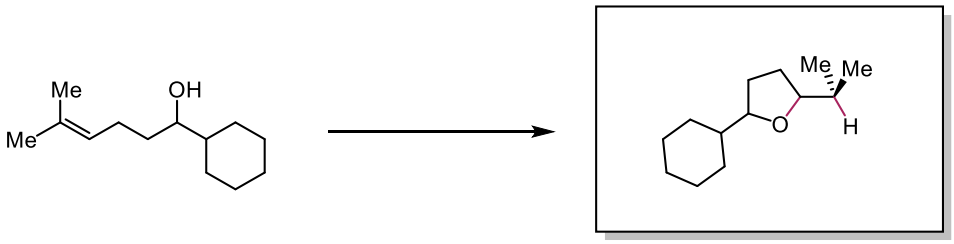
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (dt, *J* = 8.3, 6.9 Hz, 1H), 3.71 (td, *J* = 7.8, 6.0 Hz, 1H), 3.49 (td, *J* = 8.0, 6.1 Hz, 1H), 1.97–1.79 (m, 4H), 1.77–1.69 (m, 2H), 1.68–1.59 (m, 2H), 1.50 (dq, *J* = 11.1, 8.2 Hz, 1H), 1.34 (tdt, *J* = 11.2, 7.1, 3.4 Hz, 1H), 1.29–1.11 (m, 3H), 0.98 (qdd, *J* = 12.4, 5.5, 3.5 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 84.2, 67.8, 43.2, 30.1, 29.3, 29.3, 26.7, 26.3, 26.1, 26.0. **IR (neat):** 2922, 2851, 1448, 1382, 1354, 1262, 1183, 1060, 978, 923, 886, 758 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{10}H_{18}O$) from $[M+H]^+$ is 154.13577, found 154.13549, difference of 1.76 ppm.



2-isopropyl-5-phenyl-tetrahydrofuran (20)

The titled compound was synthesized following General Procedure B using 5-methyl-1-phenyl-hex-4-en-1-ol with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 5% Et_2O in hexanes) to afford the titled compound (65.7 mg, 69% yield, 1.2:1 dr).

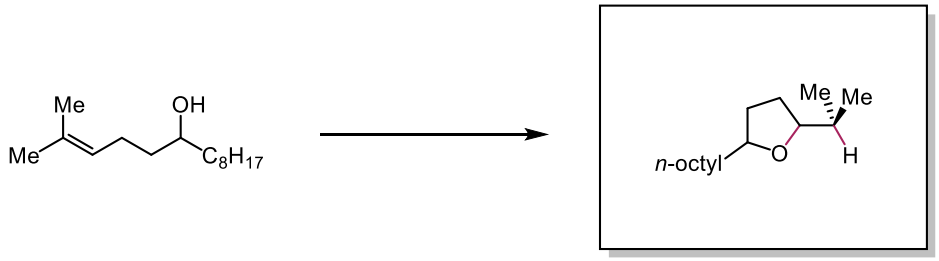
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.37–7.30 (m, 4H), 7.25–7.21 (m, 1H), 4.96 (dd, *J* = 8.5, 6.2 Hz, 0.5H), 4.86 (t, *J* = 7.1 Hz, 0.5H), 3.88 (ddd, *J* = 8.6, 7.1, 5.8 Hz, 0.5H), 3.72 (q, *J* = 7.1 Hz, 0.5H), 2.38–2.30 (m, 0.5H), 2.30–2.23 (m, 0.5H), 2.08–2.01 (m, 0.5H), 2.01–1.94 (m, 0.5H), 1.88–1.64 (m, 3H), 1.05 (d, *J* = 6.7 Hz, 1.5H), 1.02 (d, *J* = 6.7 Hz, 1.5H), 0.95 (d, *J* = 6.8 Hz, 1.5H), 0.92 (d, *J* = 6.8 Hz, 1.5H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 144.3, 143.7, 128.4, 128.3, 127.2, 127.1, 125.9, 125.3, 85.6, 85.5, 80.8, 80.6, 35.9, 34.8, 33.5, 33.4, 30.0, 28.9, 19.6, 19.5, 18.8, 18.4. **IR (neat):** 3030, 2959, 2872, 1689, 1603, 1494, 1469, 1451, 1386, 1365, 1328, 1215, 1083, 1059, 1028, 949, 753, 698 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{18}O$) from $[M+H]^+$ is 190.13576, found 190.13573, difference of 0.18 ppm.



2-cyclohexyl-5-isopropyltetrahydrofuran (21)

The titled compound was synthesized following General Procedure B using 1-cyclohexyl-5-methylhex-4-en-1-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 10% Et_2O in hexanes) to afford the titled compound (81.0 mg, 83% yield, 1.2:1 dr).

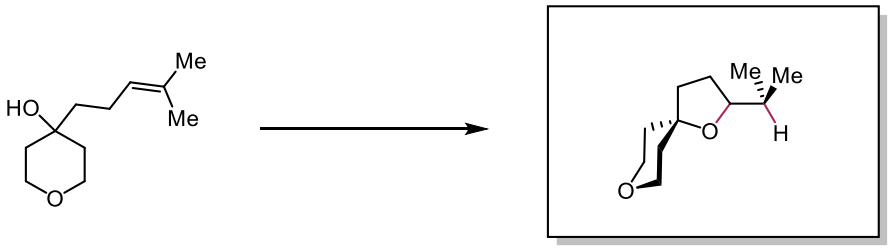
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 3.60–3.46 (m, 2H), 1.98–1.78 (m, 3H), 1.76–1.69 (m, 2H), 1.68–1.57 (m, 3H), 1.56–1.46 (m, 2H), 1.33 (dtq, *J* = 11.1, 7.0, 3.4 Hz, 1H), 1.28–1.10 (m, 3H), 1.01–0.88 (m, 5H), 0.84 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 84.5, 84.3, 83.8, 83.6, 43.5, 43.3, 33.5, 33.3, 30.3, 30.2, 30.1, 29.8, 29.1, 28.9, 28.8, 28.5, 26.8, 26.8, 26.3, 26.3, 26.2, 26.1, 19.7, 19.6, 18.5, 18.4. **IR (neat):** 2924, 2852, 1470, 1449, 1384, 1365, 1263, 1080, 1063, 978, 889, 757 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{24}O$) from $[M+H]^+$ is 196.18271, found 196.18302, difference of 1.58 ppm.



2-isopropyl-5-octyltetrahydrofuran (22)

The titled compound was synthesized following General Procedure B using 2-methyltetradec-2-en-6-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 10% Et_2O in hexanes) to afford the titled compound (80.2 mg, 71% yield, 1.1:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 3.86 (dq, *J* = 8.3, 6.0 Hz, 0.5H), 3.79 (p, *J* = 6.6 Hz, 0.5H), 3.61 (td, *J* = 8.0, 6.0 Hz, 0.5H), 3.51 (q, *J* = 7.1 Hz, 0.5H), 2.02–1.79 (m, 2H), 1.70–1.62 (m, 1H), 1.62–1.48 (m, 2H), 1.48–1.33 (m, 3H), 1.32–1.20 (m, 11H), 0.95 (dd, *J* = 6.8, 1.3 Hz, 3H), 0.86 (dt, *J* = 13.2, 6.7 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 84.8, 84.2, 79.4, 79.2, 36.2, 36.2, 33.5, 33.3, 32.6, 32.0, 31.3, 30.0, 29.9, 29.7, 29.7, 29.7, 29.4, 28.5, 26.4, 26.4, 22.8, 19.6, 19.6, 18.5, 18.4, 14.3. **IR (neat):** 2957, 2922, 2855, 1466, 1382, 1323, 1070, 899, 723 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{15}H_{30}O$) from $[M+H]^+$ is 226.22967, found 226.22993, difference of 1.16 ppm.

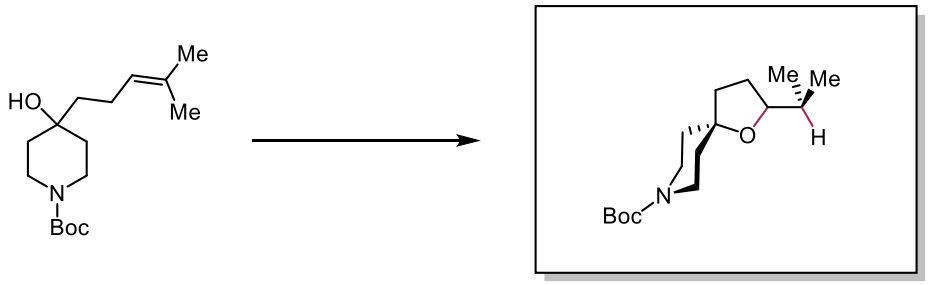


2-isopropyl-1,8-dioxaspiro[4.5]decane (23)

The titled compound was synthesized following General Procedure A using 4-(4-methylpent-3-en-1-yl)tetrahydro-2*H*-pyran-4-ol and Bu_4N^+ $CF_3C(O)O^-$ as the base with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% Et_2O in hexanes) to afford the titled compound (68.6 mg, 75% yield).

Alternatively, the titled compound was synthesized following General Procedure B with a reaction time of 48 hours. These conditions resulted in a comparable yield (68.0 mg, 74% yield).

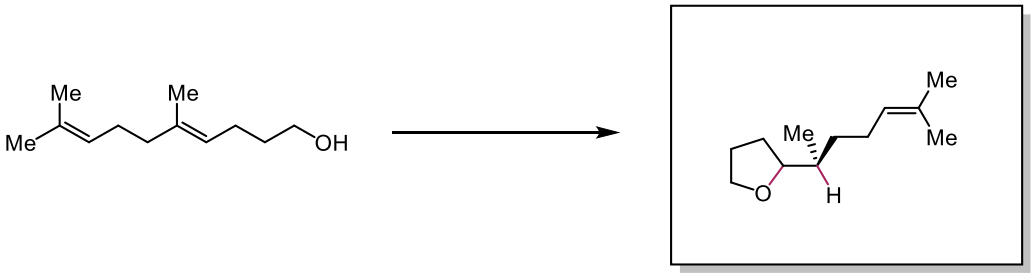
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (ddd, *J* = 11.8, 6.8, 5.1 Hz, 2H), 3.67–3.60 (m, 3H), 1.94–1.87 (m, 1H), 1.78–1.68 (m, 2H), 1.67–1.59 (m, 6H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 83.8, 78.9, 65.7, 65.6, 38.7, 37.8, 37.1, 33.6, 28.4, 19.6, 18.3. **IR (neat):** 2955, 2863, 1574, 1470, 1446, 1387, 1361, 1306, 1227, 1164, 1103, 1048, 1012, 967, 930, 897, 843, 760 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{20}O_2$) from $[M+H]^+$ is 184.14633, found 184.14629, difference of 0.21 ppm.



***tert*-butyl 2-isopropyl-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (24)**

The titled compound was synthesized following General Procedure B using *tert*-butyl 4-hydroxy-4-(4-methylpent-3-enyl)piperidine-1-carboxylate with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 20% Et_2O in hexanes) to afford the titled compound (111.8 mg, 79% yield).

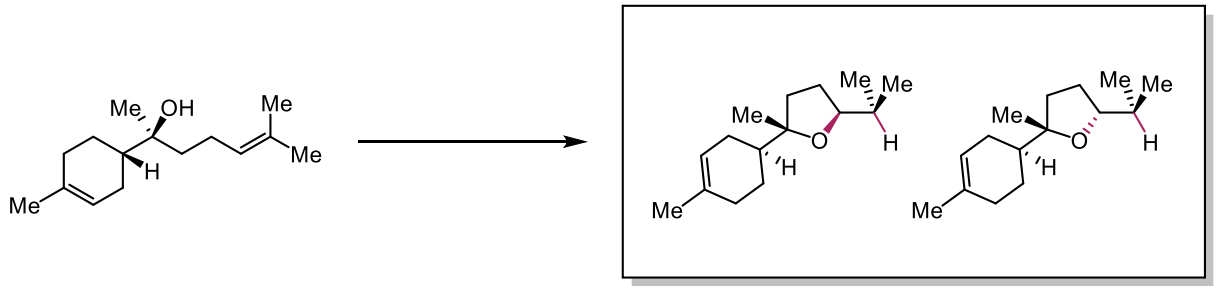
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65–3.59 (m, 1H), 3.59–3.51 (m, 2H), 3.39–3.31 (m, 2H), 1.94–1.86 (m, 1H), 1.75–1.47 (m, 8H), 1.45 (s, 9H), 0.95 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 155.1, 83.9, 79.6, 79.3, 41.4, 37.6, 36.9, 36.7, 33.6, 28.6, 28.5, 19.6, 18.4. **IR (neat):** 2957, 2871, 1696, 1420, 1365, 1278, 1242, 1176, 1153, 1048, 959, 866 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{16}H_{29}NO_3$) from $[M+Na]^+$ is 283.21474, found 283.21447 difference of 0.96 ppm.



2-(6-methylhept-5-en-2-yl)tetrahydrofuran (25)

The titled compound was synthesized following General Procedure A using (*E*)-5,9-dimethyldeca-4,8-dien-1-ol and Bu_4N^+ $CF_3C(O)O^-$ as the base with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 20% Et_2O in hexanes) to afford the titled compound (63.8 mg, 70% yield, 1:1 dr).

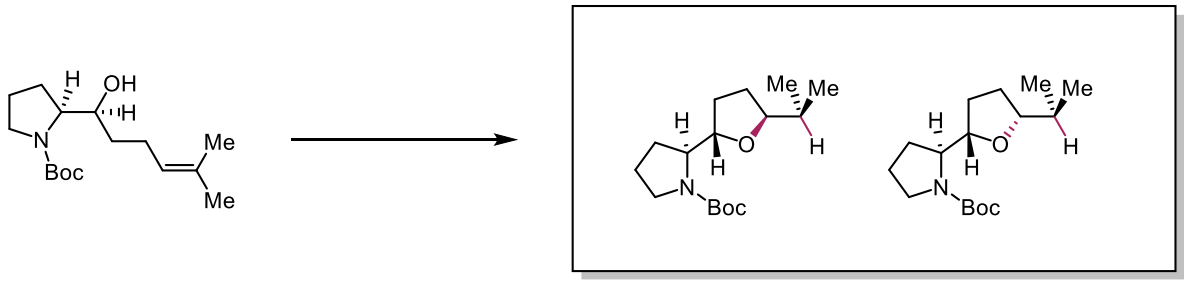
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 5.11 (q, J = 7.2 Hz, 1H), 3.87–3.80 (m, 1H), 3.75–3.69 (m, 1H), 3.62–3.55 (m, 1H), 2.07 (dq, J = 15.1, 6.9 Hz, 1H), 1.99–1.79 (m, 4H), 1.68 (s, 3H), 1.61 (s, 3H), 1.59–1.40 (m, 3H), 1.16–1.06 (m, 1H), 0.95 (d, J = 6.6 Hz, 1.5H), 0.86 (d, J = 6.5 Hz, 1.5H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 131.5, 131.3, 125.0, 124.9, 83.9, 68.0, 68.0, 37.5, 33.9, 33.2, 29.1, 28.6, 26.1, 26.1, 25.9, 25.9, 25.7, 25.6, 17.8, 15.9, 15.2. **IR (neat):** 2966, 2923, 2856, 1782, 1581, 1473, 1446, 1378, 1261, 1223, 1168, 1067, 924, 891, 825, 757 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{12}H_{22}O$) from $[M+H]^+$ is 182.16707, found 182.16687, difference of 1.06 ppm.



(2*S*)-5-isopropyl-2-methyl-2-((*S*)-4-methylcyclohex-3-en-1-yl)tetrahydrofuran (26)

The titled compound was synthesized following General Procedure B using commercially available (–)-α-bisabolol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 10% Et_2O in hexanes) to afford the titled compound (86.5 mg, 78% yield, 1.1:1 dr).

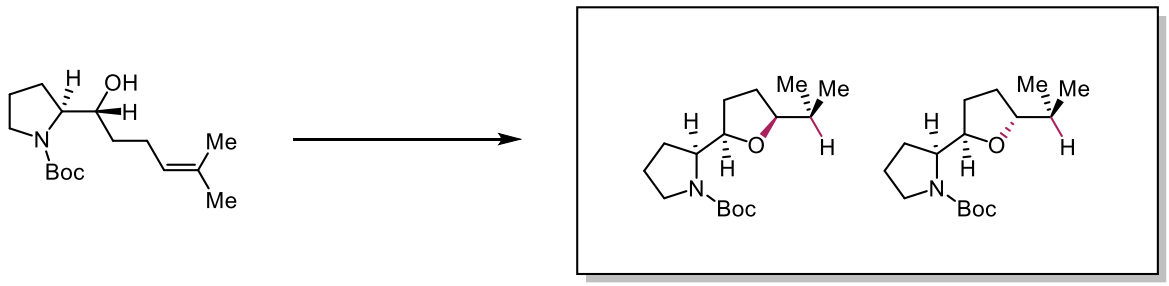
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 5.44–5.37 (m, 1H), 3.69 (q, *J* = 6.8 Hz, 0.5H), 3.58 (qd, *J* = 6.3, 3.8 Hz, 0.5H), 2.08–1.74 (m, 7H), 1.73–1.52 (m, 7H), 1.34–1.24 (m, 1H), 1.14 (s, 1.5H), 1.11 (s, 1.5H), 0.95 (dd, *J* = 6.8, 2.8 Hz, 3H), 0.87 (dd, *J* = 6.8, 4.8 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 134.3, 134.2, 120.9, 120.9, 84.8, 84.6, 84.5, 83.1, 44.0, 43.9, 35.7, 35.1, 33.3, 33.2, 31.1, 31.1, 28.7, 28.6, 27.5, 27.2, 24.5, 24.5, 23.8, 23.6, 23.6, 22.8, 19.8, 19.5, 18.3, 18.0. **IR (neat):** 2960, 2926, 2872, 1581, 1471, 1447, 1374, 1307, 1261, 1226, 1153, 1109, 1071, 1049, 961, 898, 865, 800, 756 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{15}H_{26}O$) from $[M+H]^+$ is 222.19837, found 222.19841, difference of 0.22 ppm.



***tert*-butyl (2*S*)-2-[(2*S*)-5-isopropyltetrahydrofuran-2-yl]pyrrolidine-1-carboxylate (27)**

The titled compound was synthesized following General Procedure B using *tert*-butyl (*S*)-2-((*S*)-1-hydroxy-5-methylhex-4-en-1-yl)pyrrolidine-1-carboxylate with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 40% Et_2O in hexanes) to afford the titled compound (111.2 mg, 78% yield, 2:1 dr).

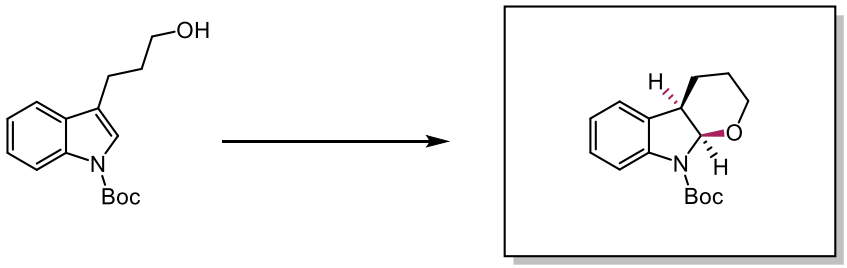
^{1}H NMR (400 MHz, DMSO-d_6, 70 °C, mixture of diastereomers) δ 3.97 (ddd, *J* = 8.3, 6.1, 5.0 Hz, 0.7H), 3.88 (td, *J* = 6.8, 5.1 Hz, 0.3H), 3.78–3.68 (m, 1H), 3.55 (ddd, *J* = 8.6, 7.1, 5.8 Hz, 0.7H), 3.47 (dt, *J* = 8.1, 6.5 Hz, 0.3H), 3.37–3.27 (m, 1H), 3.23–3.14 (m, 1H), 1.97–1.78 (m, 4H), 1.78–1.46 (m, 5H), 1.41 (s, 9H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.83 (dd, *J* = 12.5, 6.8 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-d_6, 70 °C, mixture of diastereomers)** δ 153.6, 153.6, 84.2, 83.8, 79.1, 79.0, 77.9, 77.9, 59.8, 59.4, 46.0, 32.4, 32.3, 28.9, 28.7, 27.9, 27.8, 27.4, 25.8, 22.8, 18.6, 18.0, 17.8. **IR (neat):** 2966, 2931, 2875, 1694, 1456, 1388, 1365, 1254, 1171, 1106, 1059, 882, 772 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{16}H_{29}NO_3$) from $[M+H]^+$ is 283.21474, found 283.21496, difference of 0.77 ppm.



***tert*-butyl (2*S*)-2-[(2*R*)-5-isopropyltetrahydrofuran-2-yl]pyrrolidine-1-carboxylate (28)**

The titled compound was synthesized following General Procedure B using *tert*-butyl (*S*)-2-((*R*)-1-hydroxy-5-methylhex-4-en-1-yl)pyrrolidine-1-carboxylate with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 40% Et_2O in hexanes) to afford the titled compound (110.5 mg, 78% yield, 1.3:1 dr).

^{1}H NMR (400 MHz, DMSO-d_6, 70 °C, mixture of diastereomers) δ 4.02–3.84 (m, 2H), 3.55 (ddd, J = 8.7, 7.1, 5.9 Hz, 0.5H), 3.49–3.35 (m, 1.5H), 3.22–3.12 (m, 1H), 1.96–1.77 (m, 4H), 1.77–1.43 (m, 5H), 1.41 (s, 9H), 0.89 (dd, J = 6.7, 3.7 Hz, 3H), 0.83 (dd, J = 7.8, 6.7 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-d_6, 70 °C, mixture of diastereomers)** δ 153.9, 153.8, 83.6, 83.5, 80.2, 79.9, 77.8, 77.7, 58.7, 58.3, 46.4, 46.1, 32.3, 32.2, 28.7, 27.8, 27.7, 27.6, 27.2, 27.0, 26.7, 23.1, 22.9, 18.6, 18.5, 18.0, 17.9. **IR (neat):** 2965, 2875, 1694, 1461, 1390, 1365, 1254, 1171, 1104, 1073, 905, 771 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{16}H_{29}NO_3$) from $[M+H]^+$ is 283.21474, found 283.21458, difference of 0.56 ppm.

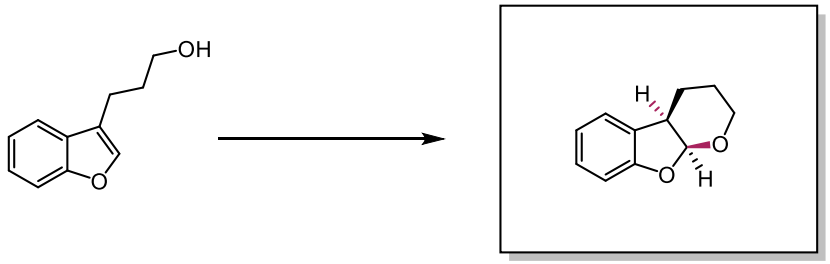


***tert*-butyl 3,4,4a,9a-tetrahydro-2*H*-pyrano[2,3-*b*]indole-9-carboxylate (29)**

The titled compound was synthesized following General Procedure B using *tert*-butyl 3-(3-hydroxypropyl)indole-1-carboxylate with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 40% Et_2O in hexanes) to afford the titled compound (124.4 mg, 90% yield, >20:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (br, 1H), 7.21 (td, J = 7.7, 1.3 Hz, 1H), 7.18–7.14 (m, 1H), 7.02 (td, J = 7.4, 1.0 Hz, 1H), 5.69 (br, 1H), 3.79–3.71 (m, 1H), 3.52 (ddd, J = 11.6, 9.3, 4.4 Hz, 1H), 3.24 (t, J = 6.0 Hz, 1H), 2.32 (ddt, J = 13.8, 4.9, 2.1 Hz, 1H), 2.07 (ddt, J = 14.2, 11.8, 6.1 Hz, 1H), 1.59 (s, 9H), 1.55–1.46 (m, 2H). **^{13}C NMR (101 MHz, DMSO-d_6, 70 °C)** δ 151.1, 141.9, 132.0, 126.8, 122.7, 122.2, 113.9, 86.6, 80.4, 61.8, 38.1, 27.7, 20.2, 19.9. **IR (neat):** 2967, 2936, 2867, 1707, 1606, 1479, 1462, 1389, 1368, 1335, 1275, 1257, 1162, 1115, 1084, 1055,

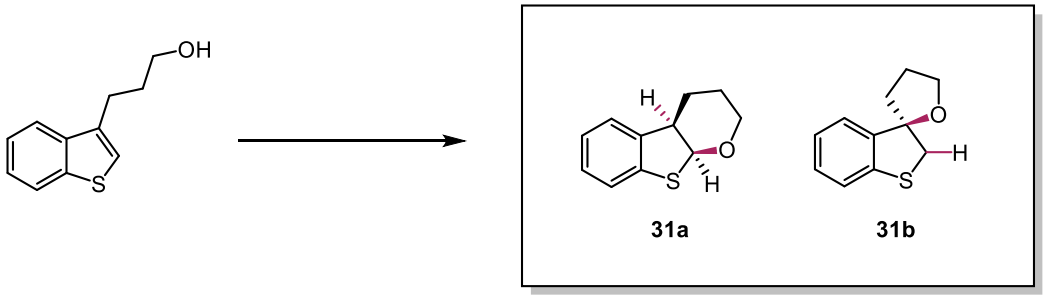
1040, 1020, 943, 896, 856, 751, 699 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{16}H_{21}NO_3$) from $[M+Na]^+$ is 275.15214, found 275.15259, difference of 1.63 ppm.



3,4,4a,9a-tetrahydro-2*H*-pyrano[2,3-*b*]benzofuran (30)

The titled compound was synthesized following General Procedure B using 3-(benzofuran-3-yl)propan-1-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 10% Et_2O in hexanes) to afford the titled compound (61.5 mg, 70% yield, >20:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.13 (m, 2H), 6.91 (td, *J* = 7.4, 1.0 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 5.89 (d, *J* = 6.3 Hz, 1H), 3.79 (ddd, *J* = 12.0, 7.1, 5.2 Hz, 1H), 3.71 (dt, *J* = 11.6, 5.9 Hz, 1H), 3.32 (q, *J* = 5.9 Hz, 1H), 2.11–2.03 (m, 1H), 1.94–1.87 (m, 1H), 1.68–1.59 (m, 1H), 1.56–1.48 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 158.5, 129.6, 128.4, 124.0, 121.2, 109.9, 104.3, 61.2, 38.9, 22.8, 20.1. **IR (neat):** 2935, 2866, 1613, 1597, 1475, 1460, 1400, 1325, 1277, 1255, 1227, 1209, 1154, 1113, 1078, 1041, 1019, 972, 946, 932, 896, 883, 869, 858, 751, 714 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{12}O_2$) from $[M+H]^+$ is 176.08373, found 176.08371, difference of 0.11 ppm.



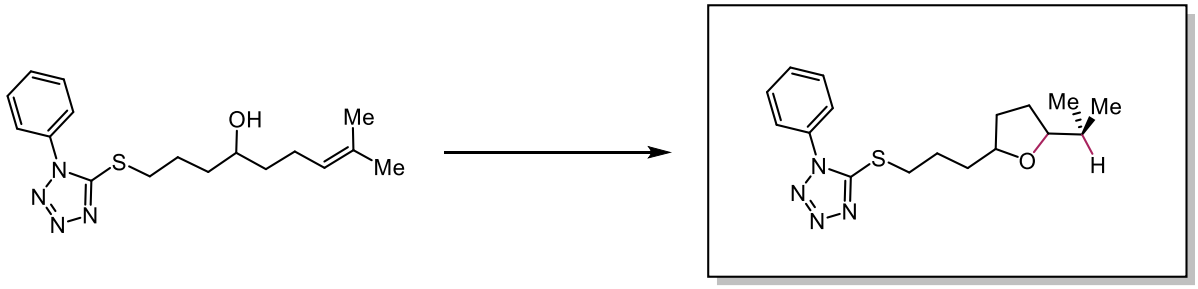
3,4,4a,9a-tetrahydro-2*H*-benzothiopheno[2,3-*b*]pyran (31a)
spiro[2*H*-benzothiophene-3,2'-tetrahydrofuran (31b)

The titled compounds were synthesized following General Procedure B using 3-(benzothiophene-3-yl)propan-1-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 10% Et_2O in hexanes) to afford the titled compounds (81.9 mg, 85% yield, 2.5:1 6-*endo*:5-*exo*, >20:1 dr for **31a**).

^{1}H NMR (500 MHz, $CDCl_3$, 6-*endo*) δ 7.32–7.27 (m, 1H), 7.20–7.15 (m, 2H), 7.14–7.09 (m, 1H), 5.62 (d, *J* = 4.4 Hz, 1H), 3.91–3.86 (m, 1H), 3.59 (ddd, *J* = 11.7, 9.2, 3.0 Hz, 1H), 3.29 (q, *J* = 4.8 Hz, 1H), 2.37–2.29 (m, 1H), 2.09–2.01 (m, 1H), 1.68–1.58 (m, 1H), 1.55–1.49 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$, 6-*endo*)** δ 140.4, 139.8, 127.7, 124.8, 123.8, 123.5, 88.8, 65.9, 47.2, 24.0, 21.2. **IR (neat):** 3059, 2938, 2860, 1589, 1459, 1446, 1357, 1325, 1252, 1236, 1223, 1167, 1104, 1080, 1057, 1034, 982, 920, 885, 847, 799, 775, 746, 735, 694 cm^{-1}. **HRMS**

(ESI): *m/z* calculated for [M] ($C_{11}H_{12}OS$) from $[M+H]^+$ is 192.06089, found 192.06062, difference of 1.37 ppm.

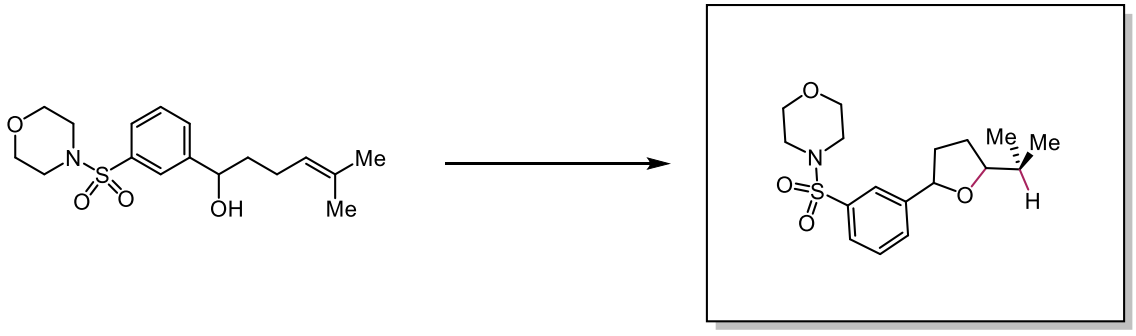
^{1}H NMR (500 MHz, $CDCl_3$, 5-*exo*) δ 7.23–7.18 (m, 3H), 7.10 (dt, *J* = 7.3, 4.2 Hz, 1H), 4.12–4.00 (m, 2H), 3.43 (d, *J* = 11.2 Hz, 1H), 3.18 (d, *J* = 11.2 Hz, 1H), 2.36 (ddd, *J* = 12.1, 7.3, 4.4 Hz, 1H), 2.20–2.01 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, 5-*exo*)** δ 142.7, 140.1, 129.1, 124.9, 123.6, 123.0, 94.0, 68.9, 44.3, 37.1, 26.4. **IR (neat):** 3061, 2971, 2927, 2870, 1590, 1459, 1447, 1314, 1264, 1135, 1073, 1044, 979, 955, 752, 732, 706 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{12}OS$) from $[M+H]^+$ is 192.06089, found 192.06075, difference of 0.71 ppm.



5-[3-(5-isopropyltetrahydrofuran-2-yl)propylsulfanyl]-1-phenyl-tetrazole (32)

The titled compound was synthesized following General Procedure B using 8-methyl-1-(1-phenyltetrazol-5-yl)sulfanyl-non-7-en-4-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 40% Et_2O in hexanes) to afford the titled compound (158.3 mg, 95% yield, 1.5:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.61–7.50 (m, 5H), 3.91 (tt, *J* = 7.6, 5.5 Hz, 0.6 H), 3.86–3.79 (m, 0.4 H), 3.60 (td, *J* = 8.0, 6.1 Hz, 0.6 H), 3.50 (q, *J* = 7.2 Hz, 0.4 H), 3.45 (t, *J* = 7.3 Hz, 2H), 2.04–1.81 (m, 4H), 1.74–1.58 (m, 3H), 1.57–1.42 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.84 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 154.6, 133.9, 130.2, 129.9, 124.0, 85.0, 84.4, 78.5, 78.4, 34.9, 34.9, 33.6, 33.5, 33.4, 33.3, 32.6, 31.4, 29.7, 28.5, 26.3, 26.1, 19.6, 19.5, 18.6, 18.4. **IR (neat):** 2957, 2870, 1597, 1500, 1465, 1411, 1385, 1278, 1242, 1073, 1015, 978, 759, 694 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{17}H_{24}N_4OS$) from $[M+H]^+$ is 332.16708, found 332.16716, difference of 0.23 ppm.

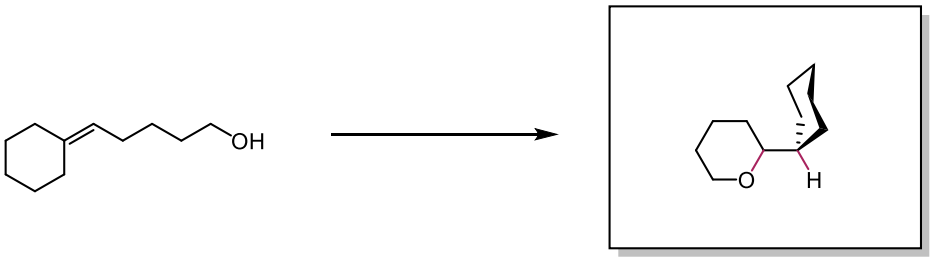


4-[3-(5-isopropyltetrahydrofuran-2-yl)phenyl]sulfonylmorpholine (33)

The titled compound was synthesized following General Procedure B using 5-methyl-1-(3-morpholinosulfonylphenyl)hex-4-en-1-ol with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 20% acetone in

hexanes) to afford the titled compound (78.3 mg, 46%, 1:1 dr).

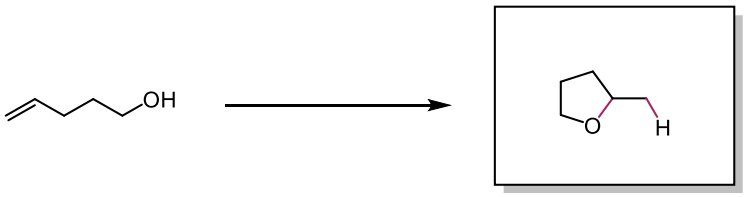
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.72 (dt, *J* = 14.7, 1.9 Hz, 1H), 7.65–7.59 (m, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 5.02 (dd, *J* = 8.3, 6.2 Hz, 0.5H), 4.94 (t, *J* = 7.0 Hz, 0.5H), 3.94–3.86 (m, 0.5H), 3.78–3.71 (m, 4.5H), 3.02–2.97 (m, 4H), 2.45–2.32 (m, 1H), 2.10–1.98 (m, 1H), 1.87–1.66 (m, 3H), 1.06 (d, *J* = 6.7 Hz, 1.5H), 1.03 (d, *J* = 6.7 Hz, 1.5H), 0.95 (d, *J* = 6.8 Hz, 1.5H), 0.93 (d, *J* = 6.8 Hz, 1.5H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 146.2, 145.6, 135.2, 135.1, 130.6, 130.4, 129.3, 129.2, 126.6, 126.6, 125.2, 125.0, 86.0, 85.9, 79.9, 79.8, 66.3, 46.1, 36.1, 34.9, 33.4, 30.0, 28.9, 19.5, 19.4, 18.8, 18.4. **IR (neat):** 2964, 2864, 1454, 1351, 1329, 1261, 1164, 1115, 1070, 945, 800, 742, 697 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{17}H_{25}NO_4S$) from $[M+H]^+$ is 339.15043, found 339.15097, difference of 1.60 ppm.



2-cyclohexyltetrahydropyran (34)

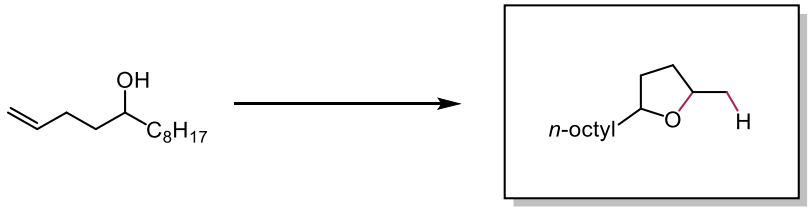
The titled compound was synthesized following General Procedure B using 5-cyclohexylidenepentan-1-ol with a reaction time of 48 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 5% Et_2O in hexanes) to afford the titled compound (61.6 mg, 73% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (ddt, *J* = 11.4, 4.2, 2.0 Hz, 1H), 3.39 (td, *J* = 11.5, 2.6 Hz, 1H), 2.98 (ddd, *J* = 11.0, 6.4, 2.0 Hz, 1H), 1.93–1.80 (m, 2H), 1.76–1.39 (m, 8H), 1.36–1.09 (m, 5H), 1.04–0.91 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 82.5, 68.9, 43.4, 29.3, 28.8, 28.8, 26.8, 26.6, 26.5, 26.4, 23.9. **IR (neat):** 2923, 2851, 1449, 1209, 1090, 1052, 1032, 879 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{11}H_{20}O$) from $[M+H]^+$ is 168.15141, found 168.15158, difference of 1.01 ppm.



2-methyltetrahydrofuran (35)

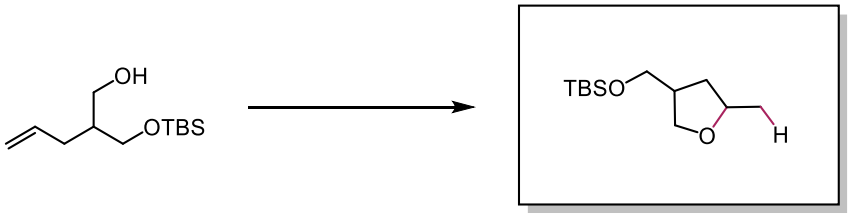
The titled compound was synthesized following General Procedure A using commercially available pent-4-en-1-ol with a reaction time of 48 hours. Due to volatility of the product, the yield was determined by GC (71% yield) against a commercial sample of the titled compound.



2-methyl-5-octyltetrahydrofuran (36)

The titled compound was synthesized following General Procedure C using tridec-1-en-5-ol with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 20% Et_2O in hexanes) to afford the titled compound (51.8 mg, 52% yield, 1.7:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 4.10 (dp, *J* = 8.1, 6.0 Hz, 0.6H), 4.03–3.90 (m, 1H), 3.80 (p, *J* = 6.5 Hz, 0.4H), 2.11–1.89 (m, 2H), 1.72–1.36 (m, 5H), 1.35–1.21 (m, 14H), 0.90 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 79.8, 79.0, 75.2, 74.6, 36.4, 36.4, 34.2, 33.0, 32.5, 32.0, 31.4, 30.0, 29.9, 29.7, 29.7, 29.4, 26.4, 26.4, 22.8, 21.6, 21.5, 14.3. **IR (neat):** 2960, 2927, 2855, 1462, 1376, 1093, 889, 722 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{13}H_{26}O$) from $[M+H]^+$ is 198.19837, found 198.19874, difference of 1.89 ppm.

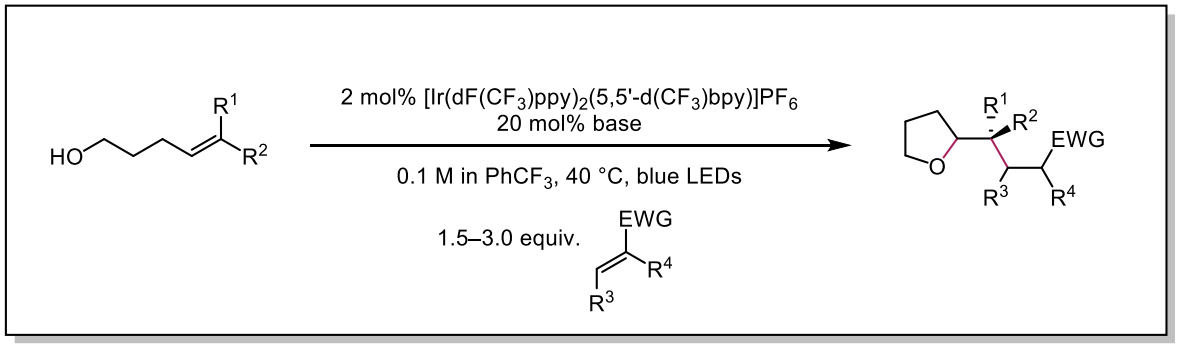


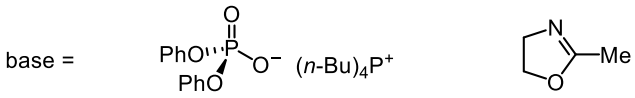
***tert*-butyl-dimethyl-[(5-methyltetrahydrofuran-3-yl)methoxy]silane (37)**

The titled compound was synthesized following General Procedure C using 2-(((*tert*-butyldimethylsilyl)oxy)methyl)pent-4-en-1-ol with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 20% Et_2O in hexanes) to afford the titled compound (61.2 mg, 53% yield, 2:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 4.03–3.96 (m, 0.67 H), 3.92 (dt, *J* = 9.1, 6.0 Hz, 0.67H), 3.78–3.69 (m, 1.32H), 3.60–3.55 (m, 0.33H), 3.55–3.47 (m, 2H), 2.54–2.39 (m, 1H), 2.07 (ddd, *J* = 12.3, 8.2, 6.0 Hz, 0.67H), 1.79 (ddd, *J* = 12.5, 6.6, 4.6 Hz, 0.33H), 1.52 (ddd, *J* = 12.4, 9.1, 7.6 Hz, 0.33H), 1.25 (d, *J* = 6.0 Hz, 2H), 1.22 (d, *J* = 6.1 Hz, 1H), 1.08 (ddd, *J* = 12.4, 9.2, 7.7 Hz, 0.66H), 0.89 (s, 9H), 0.04 (s, 6H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 75.8, 74.9, 70.6, 70.5, 65.7, 65.0, 42.8, 42.0, 36.8, 36.2, 26.0, 21.3, 21.1, 18.4, –5.2, –5.2, –5.2, –5.3. **IR (neat):** 2955, 2930, 2886, 2857, 1471, 1463, 1252, 1095, 836, 776 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{12}H_{26}O_2Si$) from $[M+H]^+$ is 230.17021, found 230.17036, difference of 0.68 ppm.

C. General Procedure for Carboetherification Reactions:



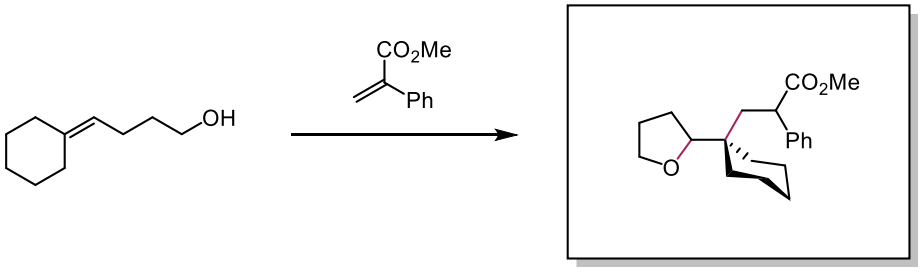


Bu_4P^+ $(PhO)_2P(O)O$ **2-methyl-2-oxazoline**

Method D (Preparative Scale for General Carboetherification Reactions):

An oven-dried 2-dram vial was charged with a magnetic stir bar, substrate (0.500 mmol, 1.0 equiv) and $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$ (0.0100 mmol, 2 mol%, 11.5 mg). The vial was sealed with a Teflon septum inside a glove box and then brought out. With an N_2 inlet in the vial, 5 mL (0.1 M) anhydrous $PhCF_3$ was added *via* syringe, followed by 2-methyl-2-oxazoline (0.10 mmol, 20 mol%, 8.5 µL) and the appropriate electron-deficient alkene (0.750–1.50 mmol, 1.5–3.0 equiv). The reaction was irradiated by blue LED lamps (Kessil H150B LED Grow Light) and stirred for 48–60 hours at an average of 40 °C with cooling fans running constantly. Variations of up to ±5 °C were observed. The solvent was removed under reduced pressure, and the crude product was purified by silica gel flash chromatography on a Biotage Isolera One instrument (Biotage SNAP Ultra 25 g column, eluted with hexane/Et_2O) to afford the titled compound below. All scale-ups were run in duplicates, and the average yields are reported. Diastereomeric ratios were determined by ^1H NMR of the crude reaction mixtures.

D. Characterization of Carboetherification Products:

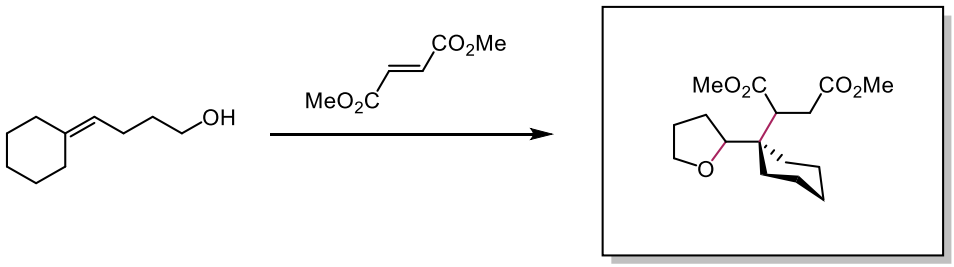


Methyl 2-phenyl-3-(1-tetrahydrofuran-2-ylcyclohexyl)propanoate (38)

The titled compound was synthesized following General Procedure D using 4-cyclohexylidenebutan-1-ol as the alkenol (0.500 mmol, 1.0 equiv) and methyl 2-phenylprop-2-

enoate (α-phenyl methacrylate) (1.00 mmol, 2.0 equiv) as the electron-deficient alkene with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 20% Et_2O in hexanes) to afford the titled compound (93.3 mg, 59% yield, 1:1 dr).

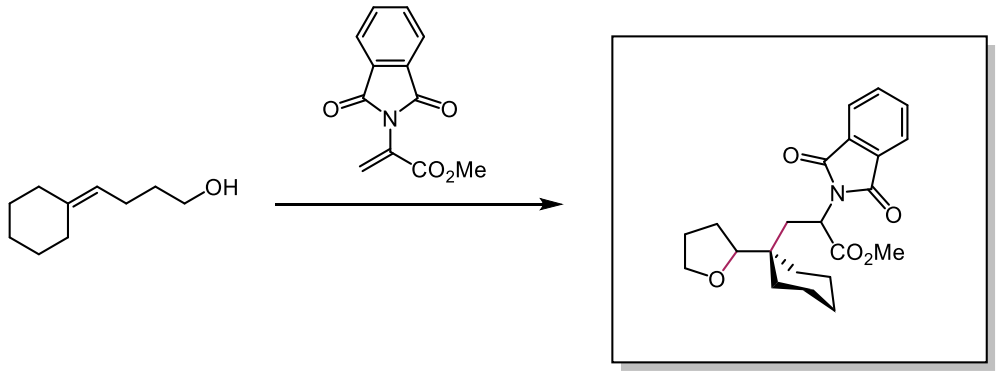
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.35–7.27 (m, 4H), 7.25–7.20 (m, 1H), 3.89 (dd, *J* = 9.4, 3.0 Hz, 0.5H), 3.83 (dd, *J* = 7.9, 3.9 Hz, 0.5H), 3.81–3.73 (m, 1.5H), 3.71–3.63 (m, 1.5H), 3.62 (d, *J* = 2.5 Hz, 3H), 2.61 (dd, *J* = 14.9, 8.0 Hz, 0.5H), 2.34 (dd, *J* = 14.7, 9.4 Hz, 0.5H), 1.90–1.59 (m, 5H), 1.52–1.21 (m, 10H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 175.6, 175.4, 142.0, 141.8, 128.8, 128.7, 128.0, 127.9, 127.1, 127.0, 85.2, 84.6, 68.0, 67.9, 52.1, 52.1, 47.1, 47.0, 38.9, 38.9, 38.1, 37.2, 33.1, 31.7, 31.7, 31.1, 26.4, 26.3, 26.0, 25.7, 25.5, 25.2, 21.6, 21.5, 21.3, 21.3. **IR (neat):** 2929, 2859, 1735, 1454, 1435, 1269, 1247, 1232, 1201, 1156, 1063, 1030, 730, 699 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{20}H_{28}O_3$) from $[M+H]^+$ is 316.20384, found 316.20368, difference of 0.51 ppm.



Dimethyl 2-(1-tetrahydrofuran-2-ylcyclohexyl)butanedioate (39)

The titled compound was synthesized following General Procedure D using 4-cyclohexylidenebutan-1-ol (0.750 mmol, 1.5 equiv) as the alkenol and dimethyl (*E*)-but-2-enedioate (dimethyl fumarate) (0.500 mmol, 1.0 equiv) as the electron-deficient alkene with a reaction time of 48 hours. Dimethyl fumarate was used as the limiting reagent in this case for purification purposes. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 50% Et_2O in hexanes) to afford the titled compound (96.5 mg, 65% yield, 1:1 dr).

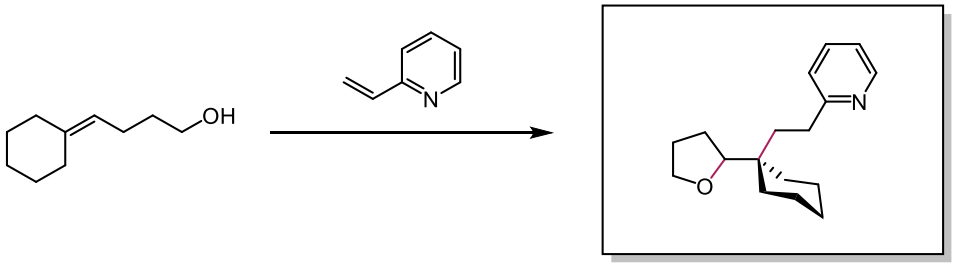
^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 3.93 (dd, *J* = 9.5, 6.2 Hz, 0.5H), 3.78–3.69 (m, 1.5H), 3.69–3.63 (m, 7H), 3.23 (dd, *J* = 12.2, 2.8 Hz, 0.5H), 3.18 (dd, *J* = 12.0, 3.0 Hz, 0.5H), 3.05 (dd, *J* = 17.4, 12.2 Hz, 0.5H), 2.86 (dd, *J* = 16.7, 12.0 Hz, 0.5H), 2.74 (dd, *J* = 17.4, 2.8 Hz, 0.5H), 2.45 (dd, *J* = 16.7, 3.0 Hz, 0.5H), 1.91–1.63 (m, 5H), 1.60–1.30 (m, 9H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 175.4, 175.0, 174.2, 173.6, 82.7, 82.3, 68.0, 67.7, 51.9, 51.8, 51.6, 51.6, 44.0, 43.0, 41.6, 40.7, 32.9, 32.1, 31.0, 30.6, 29.8, 29.1, 26.4, 26.0, 25.8, 21.4, 21.2, 21.2, 21.0. **IR (neat):** 2946, 2933, 2867, 1733, 1435, 1343, 1256, 1196, 1161, 1063, 846 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{16}H_{26}O_5$) from $[M+H]^+$ is 298.17802, found 298.17858, difference of 1.87 ppm.



Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(1-tetrahydrofuran-2-ylcyclohexyl)propanoate (40)

The titled compound was synthesized following General Procedure D using 4-cyclohexylidenebutan-1-ol as the alkenol (0.500 mmol, 1.0 equiv) and methyl 2-(1,3-dioxoisoindolin-2-yl)prop-2-enoate (0.750 mmol, 1.5 equiv) as the electron-deficient alkene with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 30% acetone in hexanes) to afford the titled compound (173.4 mg, 90% yield, 1.5:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.86 (ddd, *J* = 5.3, 4.4, 3.0 Hz, 2H), 7.73 (td, *J* = 5.5, 3.0 Hz, 2H), 5.36 (dd, *J* = 9.5, 2.3 Hz, 0.6H), 5.08 (dd, *J* = 8.0, 3.3 Hz, 0.4H), 3.79–3.72 (m, 1H), 3.71 (d, *J* = 6.0 Hz, 3H), 3.64–3.54 (m, 1H), 3.53–3.45 (m, 0.6H), 3.28 (dt, *J* = 8.0, 6.2 Hz, 0.4H), 2.65–2.46 (m, 1.4H), 2.41 (dd, *J* = 15.8, 9.5 Hz, 0.6H), 1.88–1.60 (m, 4H), 1.58–1.27 (m, 9H), 1.25–1.14 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 171.2, 171.1, 168.0, 167.8, 134.2, 134.1, 132.2, 132.1, 123.6, 123.5, 85.2, 84.6, 68.0, 68.0, 53.1, 53.0, 49.3, 48.6, 38.3, 38.2, 32.4, 31.7, 31.7, 31.2, 31.0, 26.4, 26.3, 25.9, 25.7, 25.6, 25.3, 21.5, 21.5, 21.4, 21.2. **IR (neat):** 2930, 2860, 1775, 1742, 1711, 1467, 1436, 1385, 1256, 1217, 1087, 1060, 898, 721 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{22}H_{27}NO_5$) from $[M+H]^+$ is 385.18892, found 385.18921, difference of 0.74 ppm.

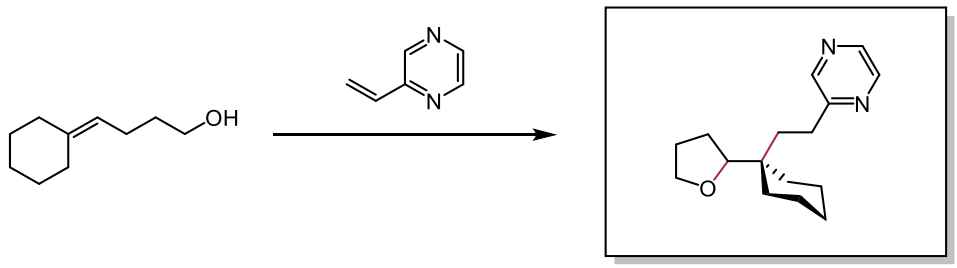


2-[2-(1-tetrahydrofuran-2-ylcyclohexyl)ethyl]pyridine (41)

The titled compound was synthesized following General Procedure D using 4-cyclohexylidenebutan-1-ol as the alkenol (0.500 mmol, 1.0 equiv) and 2-vinylpyridine (1.50 mmol, 3.0 equiv) as the electron-deficient alkene with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 50% to 100% Et_2O in hexanes) to afford the titled compound (45.2 mg, 35% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.58 (td, *J* = 7.7, 1.9 Hz, 1H), 7.16 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.08 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 3.82 (ddd, *J* = 15.3, 8.8, 6.7 Hz, 2H), 3.74 (dt, *J* = 8.0, 6.3 Hz, 1H), 2.81 (td, *J* = 13.0, 5.1 Hz, 1H), 2.72 (td, *J* = 13.0, 4.9 Hz, 1H), 1.93 (ddd, *J* = 14.1, 12.7, 5.1 Hz, 1H), 1.89–1.78 (m, 3H), 1.77–1.64 (m, 2H), 1.61–

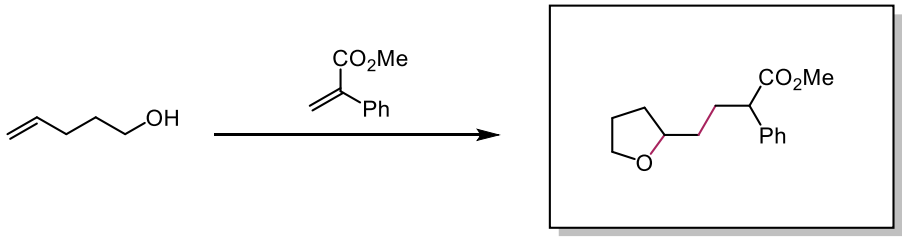
1.52 (m, 2H), 1.52–1.40 (m, 7H), 1.30–1.20 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 163.6, 149.4, 136.4, 122.8, 120.9, 84.9, 68.2, 38.5, 33.3, 32.8, 31.8, 30.6, 26.5, 26.4, 25.5, 21.7, 21.4. **IR (neat):** 2927, 2858, 1590, 1569, 1474, 1459, 1434, 1063, 773, 749 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{17}H_{25}NO$) from $[M+H]^+$ is 259.19361, found 259.19316, difference of 1.76 ppm.



2-[2-(1-tetrahydrofuran-2-ylcyclohexyl)ethyl]pyrazine (42)

The titled compound was synthesized following General Procedure D using 4-cyclohexylidenebutan-1-ol as the alkenol (0.500 mmol, 1.0 equiv) and 2-vinylpyrazine (1.50 mmol, 3.0 equiv) as the electron-deficient alkene with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 50% to 100% Et_2O in hexanes) to afford the titled compound (49.7 mg, 38% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51–8.45 (m, 2H), 8.38 (d, *J* = 2.5 Hz, 1H), 3.86–3.78 (m, 2H), 3.74 (dt, *J* = 8.1, 6.3 Hz, 1H), 2.86 (td, *J* = 13.1, 5.0 Hz, 1H), 2.76 (td, *J* = 13.2, 4.9 Hz, 1H), 1.98–1.78 (m, 4H), 1.75–1.67 (m, 2H), 1.62–1.37 (m, 9H), 1.30–1.22 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 159.2, 144.8, 144.1, 142.1, 85.0, 68.1, 38.5, 32.9, 31.7, 30.8, 30.1, 26.4, 26.3, 25.5, 21.6, 21.4. **IR (neat):** 2926, 2857, 1474, 1459, 1402, 1060, 1017, 834 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{16}H_{24}N_2O$) from $[M+H]^+$ is 260.18886, found 260.18885, difference of 0.05 ppm.

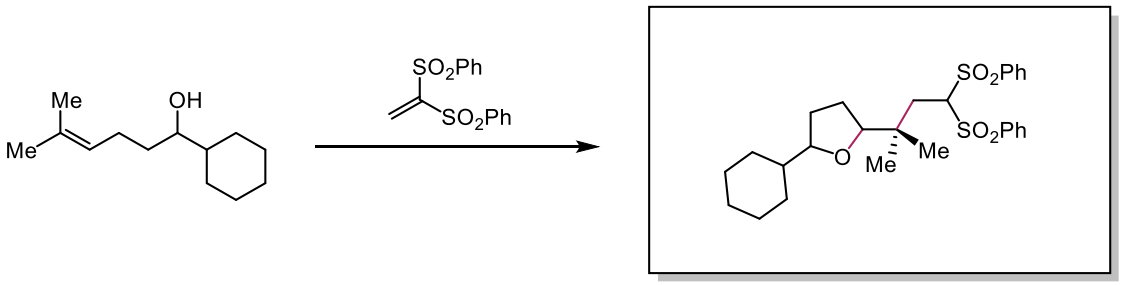


Methyl 2-phenyl-4-tetrahydrofuran-2-yl-butanoate (43)

The titled compound was synthesized following General Procedure D using pent-4-en-1-ol as the alkenol (0.500 mmol, 1.0 equiv) and methyl 2-phenylprop-2-enoate (α-phenyl methacrylate) (1.00 mmol, 2.0 equiv) as the electron-deficient alkene with a reaction time of 60 hours. Bu_4P^+ $(PhO)_2P(O)O^-$ (0.100 mmol, 20 mol%, 50.9 mg) was used as the base instead of 2-methyl-2-oxazoline because the alkenol substrate is monosubstituted rather than trisubstituted. The crude material was purified by silica gel flash column chromatography (20% Et_2O in hexanes) to afford the titled compound (83.2 mg, 67% yield, 1:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.34–7.28 (m, 4.5H), 7.25–7.21 (m, 0.5H), 3.86–3.75 (m, 2H), 3.73–3.67 (m, 1H), 3.65 (d, *J* = 1.6 Hz, 3H), 3.57 (t, *J* = 7.8 Hz, 1H),

2.19 (dddd, J = 12.8, 10.7, 7.6, 5.1 Hz, 0.5H), 2.10 (dddd, J = 13.6, 10.1, 8.2, 5.7 Hz, 0.5H), 2.01–1.77 (m, 4H), 1.58–1.32 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 174.6, 174.5, 139.2, 139.1, 128.8, 128.1, 128.0, 127.4, 79.1, 79.0, 67.8, 67.8, 52.1, 51.7, 51.7, 33.7, 33.6, 31.4, 31.4, 30.5, 30.3, 25.8. **IR (neat):** 2951, 2863, 1734, 1454, 1435, 1255, 1219, 1197, 1159, 1070, 734, 700 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{15}H_{20}O_3$) from $[M+H]^+$ is 248.14124, found 248.14155, difference of 1.24 ppm.



2-[3,3-bis(benzenesulfonyl)-1,1-dimethyl-propyl]-5-cyclohexyl-tetrahydrofuran (44)

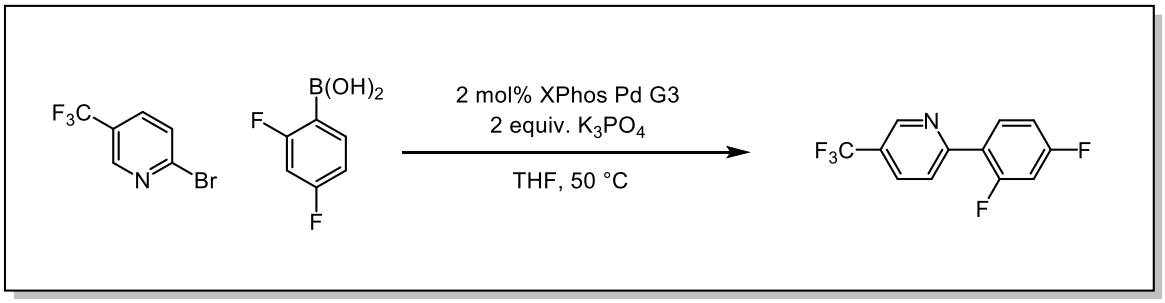
The titled compound was synthesized following General Procedure D using 1-cyclohexyl-5-methyl-hex-4-en-1-ol as the alkenol (0.250 mmol, 1.0 equiv) and 1-(benzenesulfonyl)vinylsulfonylbenzene (1,1-bis(phenylsulfonyl)ethylene) (0.500 mmol, 2.0 equiv) as the electron-deficient alkene with a reaction time of 60 hours. The crude material was purified by silica gel flash column chromatography (gradient from 0% to 50% Et_2O in hexanes) to afford the titled compound (72.2 mg, 57% yield, 1.3:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 8.00–7.95 (m, 2H), 7.95–7.89 (m, 2H), 7.69–7.62 (m, 2H), 7.55–7.49 (m, 4H), 5.45 (t, J = 4.0 Hz, 0.5H), 5.39 (t, J = 4.0 Hz, 0.5H), 3.73 (dd, J = 10.0, 6.2 Hz, 0.5H), 3.51–3.37 (m, 1.5H), 2.38 (ddd, J = 20.3, 16.4, 3.6 Hz, 1H), 2.24 (ddd, J = 16.3, 11.8, 4.3 Hz, 1H), 1.91–1.77 (m, 2H), 1.77–1.57 (m, 6H), 1.54–1.10 (m, 5H), 0.97–0.88 (m, 2H), 0.86 (s, 1.5H), 0.83 (s, 1.5H), 0.81 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers)** δ 138.8, 138.7, 138.7, 138.6, 134.4, 134.3, 134.3, 130.1, 130.0, 130.0, 129.9, 129.0, 129.0, 128.9, 85.4, 85.4, 85.1, 83.7, 81.1, 80.9, 43.4, 43.2, 37.9, 37.0, 35.1, 34.8, 30.9, 30.3, 30.0, 29.3, 29.0, 28.1, 28.0, 26.7, 26.7, 26.6, 26.3, 26.3, 26.2, 26.2, 26.1, 25.4, 20.2, 20.0. **IR (neat):** 2925, 2852, 1471, 1448, 1328, 1312, 1153, 1080, 1061, 1046, 1026, 889, 756, 730, 688 cm^{-1}. **HRMS (ESI):** *m/z* calculated for [M] ($C_{27}H_{36}O_5S_2$) from $[M+H]^+$ is 504.20042, found 504.20064, difference of 0.45 ppm.

Synthesis of Catalysts

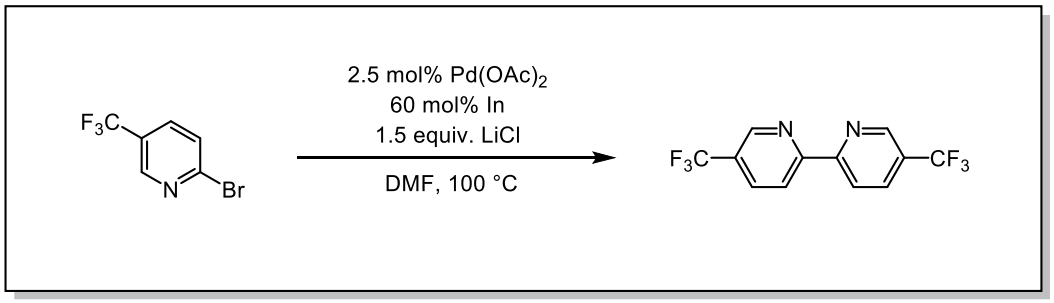
A. Photocatalyst Synthesis

Synthesis of Ligands



2-(2,4-difluorophenyl)-4-(trifluoromethyl)pyridine

To a flame-dried 250-mL round bottom flask charged with a stir bar was added 2-bromo-5-(trifluoromethyl)pyridine (22.1 mmol, 1.0 equiv, 5.00 g), (2,4-difluorophenyl)boronic acid (33.2 mmol, 1.5 equiv, 5.24 g), potassium phosphate (44.2 mmol, 2.0 equiv, 10.2 g), and XPhos Pd G3 (0.442 mmol, 2 mol%, 0.375 g). The flask was evacuated and backfilled with argon three times, and 45 mL anhydrous THF was added to the reaction mixture, which was allowed to stir at 50 °C overnight. The reaction was cooled to room temperature, and water was added to quench the reaction. The organic phase was extracted with Et_2O, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified *via* silica gel chromatography (gradient from 2% to 20% EtOAc in hexanes) to give the titled compound (4.89 g, 85% yield). Spectra are consistent with reported literature values.[34]

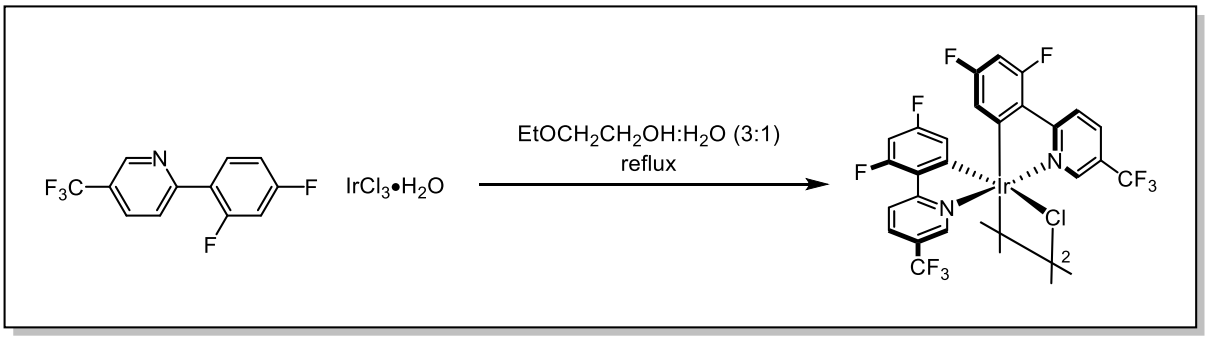


5,5′-bis(trifluoromethyl)-2,2′-bipyridine

To a flame-dried 500-mL round bottom flask charged with a stir bar was added indium (26.5 mmol, 0.60 equiv, 3.05 g), 2-bromo-5-(trifluoromethyl)pyridine (44.2 mmol, 1.0 equiv, 10.0 g), $Pd(OAc)_2$ (1.11 mmol, 2.5 mol%, 0.248 g), and LiCl (66.4 mmol, 1.5 equiv, 2.81 g). The flask was evacuated and backfilled with argon three times, and 90 mL anhydrous DMF was added to the reaction mixture, which was allowed to stir at 100 °C overnight. The reaction was cooled to room temperature, and saturated aqueous $NaHCO_3$ was added slowly to quench the reaction. The reaction mixture was diluted with EtOAc and water, and it was filtered through a pad of Celite. The organic phase was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified *via* silica gel chromatography

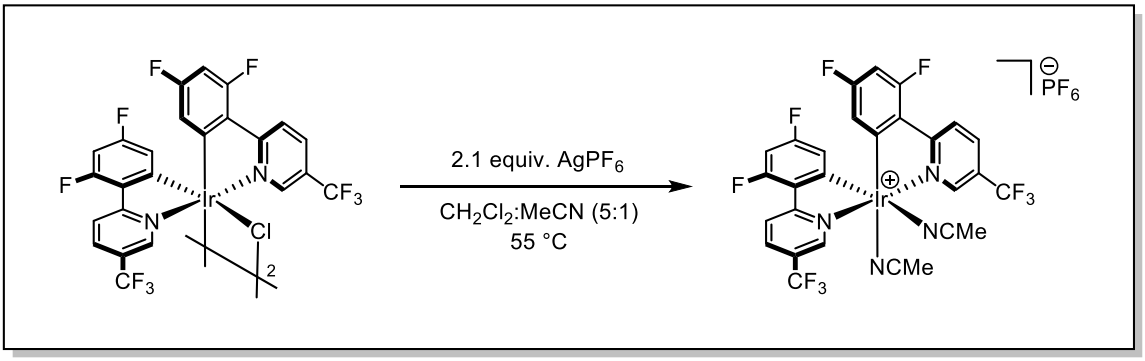
(gradient from 2% to 10% EtOAc in hexanes) to give the titled compound (1.93 g, 30% yield). Spectra are consistent with reported literature values.[34]

Synthesis of [Ir(dF(CF$_3$)ppy)$_2$Cl]$_2$-dimer



To a flame-dried 250-mL three-neck round bottom flask containing a stir bar and equipped with a reflux condenser was added 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine (16.6 mmol, 2.05 equiv, 4.30 g) and $IrCl_3 \bullet H_2O$ (8.09 mmol, 1.0 equiv, 2.56 g). The flask was evacuated and backfilled with argon, and 76 mL 2-ethoxyethanol and 25 mL water (3:1 ratio) were added. The reaction mixture was degassed for 30 minutes. The reaction was heated to 135 °C for 40 hours. The reaction mixture turned from opaque dark red to transparent light red to transparent yellow during the course of the reaction. The mixture was cooled to room temperature, which resulted in the formation of a large amount of yellow precipitate. The solid was filtered and washed with water three times. The crude dimer was carried onto the next step without further purification.

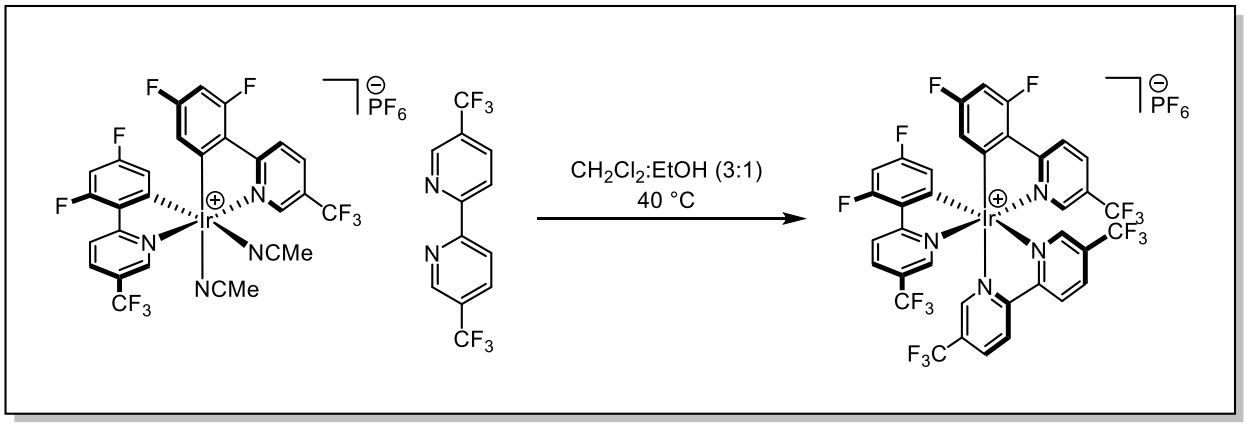
Synthesis of [Ir(dF(CF$_3$)ppy)$_2$(MeCN)$_2$]PF$_6$



To a flame-dried 100-mL round bottom flask equipped with a reflux condenser and stir bar was added [Ir(dF(CF$_3$)ppy)$_2$Cl]$_2$-dimer (1.01 mmol, 1.0 equiv, 1.50 g) and, in the glove box, was added $AgPF_6$ (2.12 mmol, 2.1 equiv, 0.535 g). The flask and reflux condenser were evacuated and backfilled with argon three times. Next, 21 mL anhydrous CH_2Cl_2 and 4.2 mL anhydrous MeCN (5:1 ratio) were added, and the reaction mixture was heated to 55 °C overnight. The reaction was cooled to room temperature, and the precipitated AgCl was filtered out of the product. The filtrate was concentrated *in vacuo*, leaving behind a yellow solid, which was re-dissolved in hot CH_2Cl_2. The mixture was allowed to cool to room temperature, and pentane was

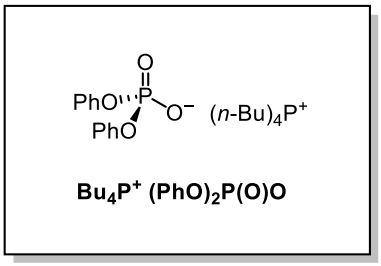
added to afford pale yellow crystals of the cationic iridium complex. The crystals were filtered and washed with pentane to give the crude product, which was carried onto the next step without further purification.

Synthesis of [Ir(dF(CF$_3$)ppy)$_2$(5,5′-d(CF$_3$)bpy)$_2$]PF$_6$



To a flame-dried 100-mL round bottom flask equipped with a reflux condenser and stir bar was added [Ir(dF(CF$_3$)ppy)$_2$(MeCN)$_2$]PF$_6$ (2.67 mmol, 1.0 equiv, 2.50 g) and 5,5′-bis(trifluoromethyl)-2,2′-bipyridine (2.94 mmol, 1.1 equiv, 0.859 g). The flask was evacuated and backfilled with argon three times, and 32 mL CH_2Cl_2 and 11 mL EtOH (3:1 ratio) were added. The reaction was heated to 40 °C and allowed to stir under argon overnight. The reaction mixture was cooled to room temperature and filtered. Copious amounts of CH_2Cl_2 were used to wash the filter to ensure dissolution of the crude iridium complex. The filtrate was concentrated *in vacuo*. The crude product was purified using silica gel chromatography (gradient from 100% CH_2Cl_2 to 25% acetone/CH_2Cl_2) to afford a yellow-red solid. The solid was dissolved in a minimal amount of acetone and recrystallized using pentane to give a fine, bright yellow powder (2.01 g, 66% yield). Spectra are consistent with reported literature values.[34]

B. Phosphate Base Synthesis



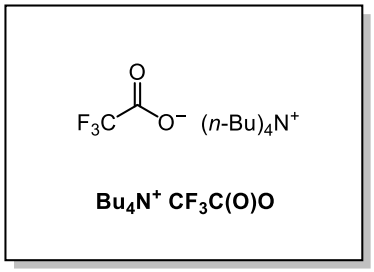
Bu_4P^+ $(PhO)_2P(O)O$

<u>Tetrabutylphosphonium diphenyl phosphate</u>

To a 100-mL round-bottom flask was added commercially available diphenyl phosphate (14.7 mmol, 1.05 equiv, 3.68 g) and 30 mL MeOH. Tetrabutylphosphonium hydroxide (14.0 mmol, 1.00 equiv, 9.78 mL, 40% w/w solution in water) was added in portions. The mixture was stirred at room temperature overnight. The mixture was concentrated *in vacuo*, dried azeotropically with toluene, concentrated to a small volume, and further dried on high vacuum at 60 °C for 5 days to

obtain the titled compound initially as a clear oil. The oil may crystallize upon introduction of a nucleation site (*e.g.*, a pipette tip) to give a white solid, which was stored at low temperature in the glovebox. Spectra are consistent with reported literature values.[35]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 4H), 7.19 (t, *J* = 7.7 Hz, 4H), 6.95 (t, *J* = 7.3 Hz, 2H), 2.36–2.23 (m, 8H), 1.52–1.37 (m, 16H), 0.98–0.86 (m, 12H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 154.0 (d, *J* = 7.2 Hz), 129.0, 122.2, 120.5 (d, *J* = 5.2 Hz), 24.1 (d, *J* = 15.3 Hz), 24.0 (d, *J* = 4.9 Hz), 18.9 (d, *J* = 47.3 Hz), 13.6. **^{31}P NMR (202 MHz, $CDCl_3$)** δ 32.92, –10.61.



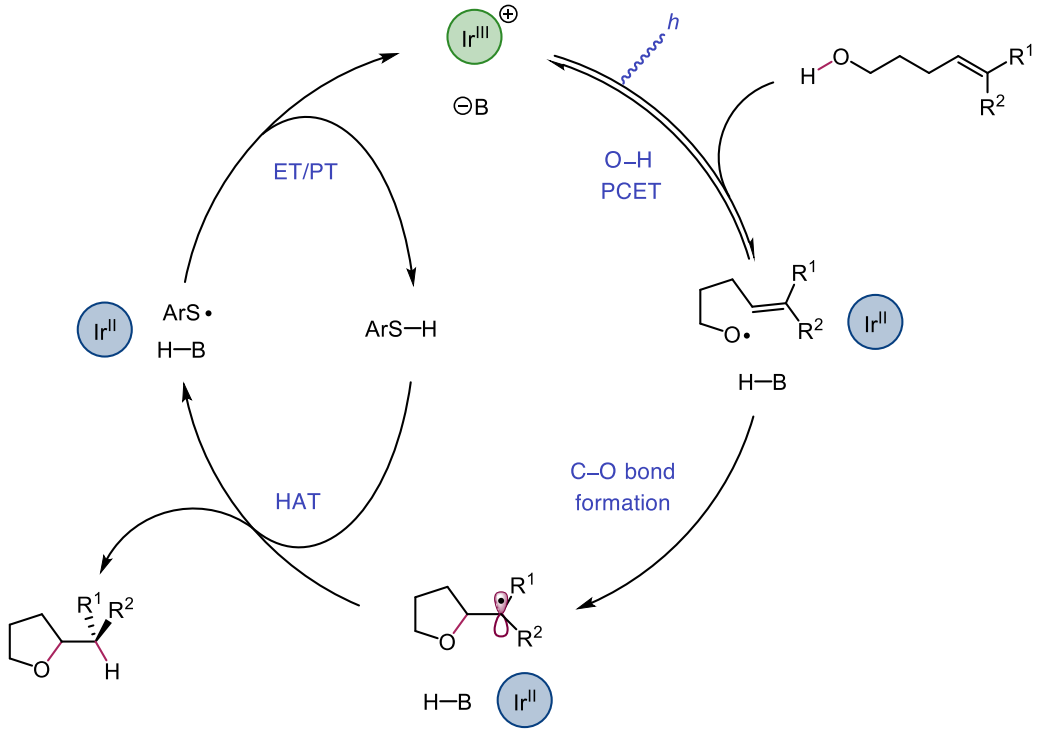
Tetrabutylammonium 2,2,2-trifluoroacetate

The titled compound was synthesized in a similar fashion to tetrabutylphosphonium diphenyl phosphate but using tetrabutylammonium hydroxide and trifluoroacetic acid as the reagents. After drying on high vacuum at 60 °C for 5 days, the titled compound was obtained as a white solid, which was stored at low temperature in the glovebox.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33–3.24 (m, 8H), 1.70–1.58 (m, 8H), 1.43 (h, *J* = 7.4 Hz, 8H), 1.00 (t, *J* = 7.4 Hz, 12H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 160.8 (q, *J* = 32.8 Hz), 117.5 (q, *J* = 297.4 Hz), 58.8, 24.1, 19.8, 13.7. **^{19}F NMR (376 MHz, $CDCl_3$)** δ –74.80.

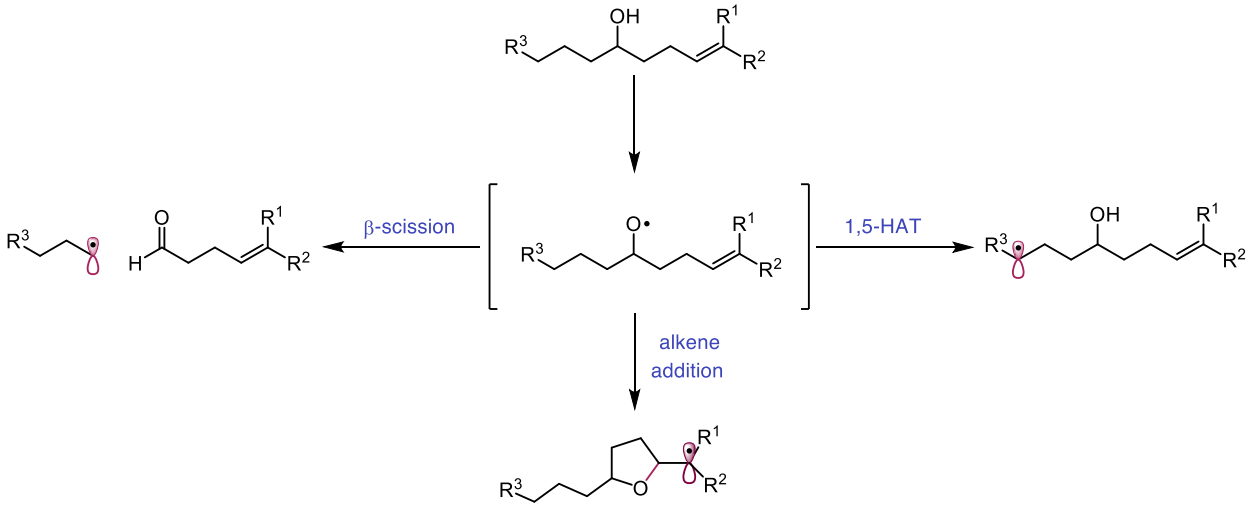
Mechanistic Proposal

A. Proposed Catalytic Cycle



Scheme S1. Proposed catalytic cycle for hydroetherification enabled by proton-coupled electron transfer (PCET).

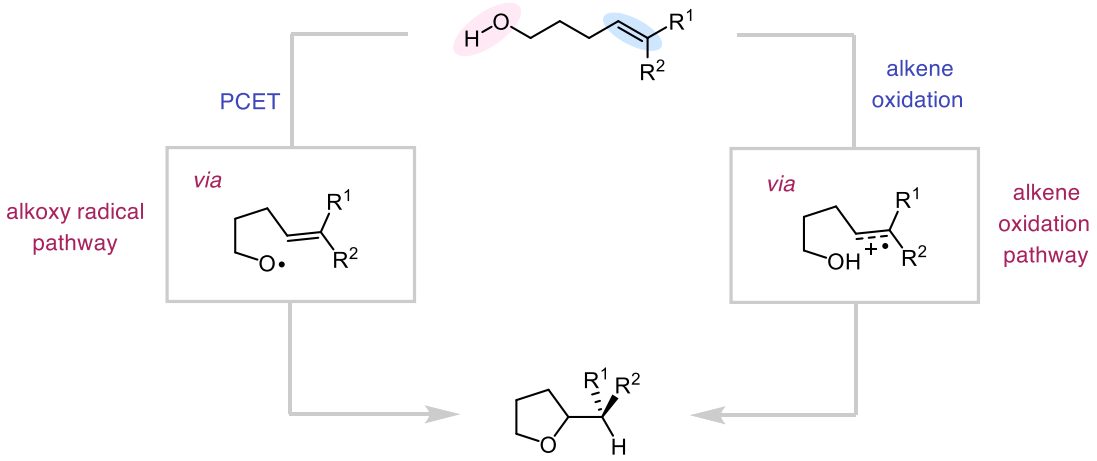
B. Possible Competing Pathways



Scheme S2. Competing alkoxy radical pathways.

Alkoxy radicals are known to undergo three types of reactions: β-scission, alkene addition/cyclization, and 1,5-hydrogen atom transfer (1,5-HAT). Depending on the substrate, these processes can have comparable rates ($k = 10^7$ to 10^8 s^{-1}).[36]

C. Alkene Oxidation Pathway

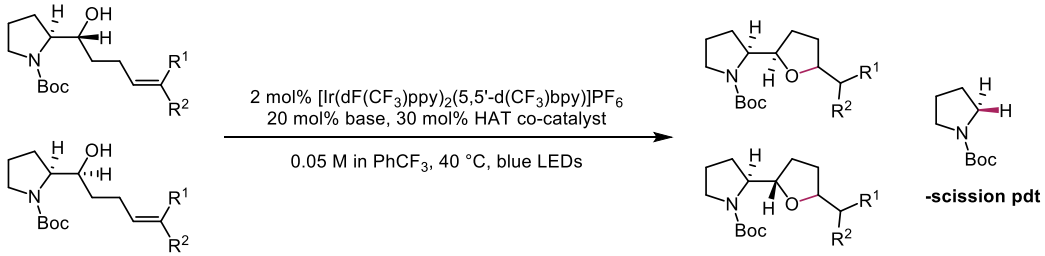


Scheme S3. Cyclization occurring through an alkoxy radical pathway or an alkene oxidation pathway.

Oxidizable alkenes, such as styrenyl or trisubstituted olefins, show diminished but meaningful yields in the absence of base, suggesting that an alkene oxidation mechanism may be operative under these conditions. The optimized photocatalyst $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)]PF_6$ has an excited-state potential of $E^{III*/II} = +1.30$ V vs. Fc^+/Fc in MeCN, while generic trisubstituted alkene 2-methyl-2-butene has a potential of $E^{\bullet+/0} = +1.60$ V vs. Fc^+/Fc and generic β-methylstyrene has a potential of $E^{\bullet+/0} = +1.36$ V vs. Fc^+/Fc.[37] While the oxidation of trisubstituted olefins by this photocatalyst is endergonic by 300 mV, the oxidation of styrenes is certainly possible using this photocatalyst in the absence of base. However, this does not preclude the viability of a dominant alkoxy radical-mediated mechanism under the optimal PCET conditions.

As shown in Table S7, while investigating **27** and **28**, we found that the mass balance is composed primarily of the cyclized ether product as well as the β-scission product *N*-Boc-pyrrolidine. The presence of β-scission, a process that can only occur through an alkoxy radical-mediated mechanism, suggests that a discrete alkoxy radical is formed and is consistent with cyclization through an alkoxy radical.

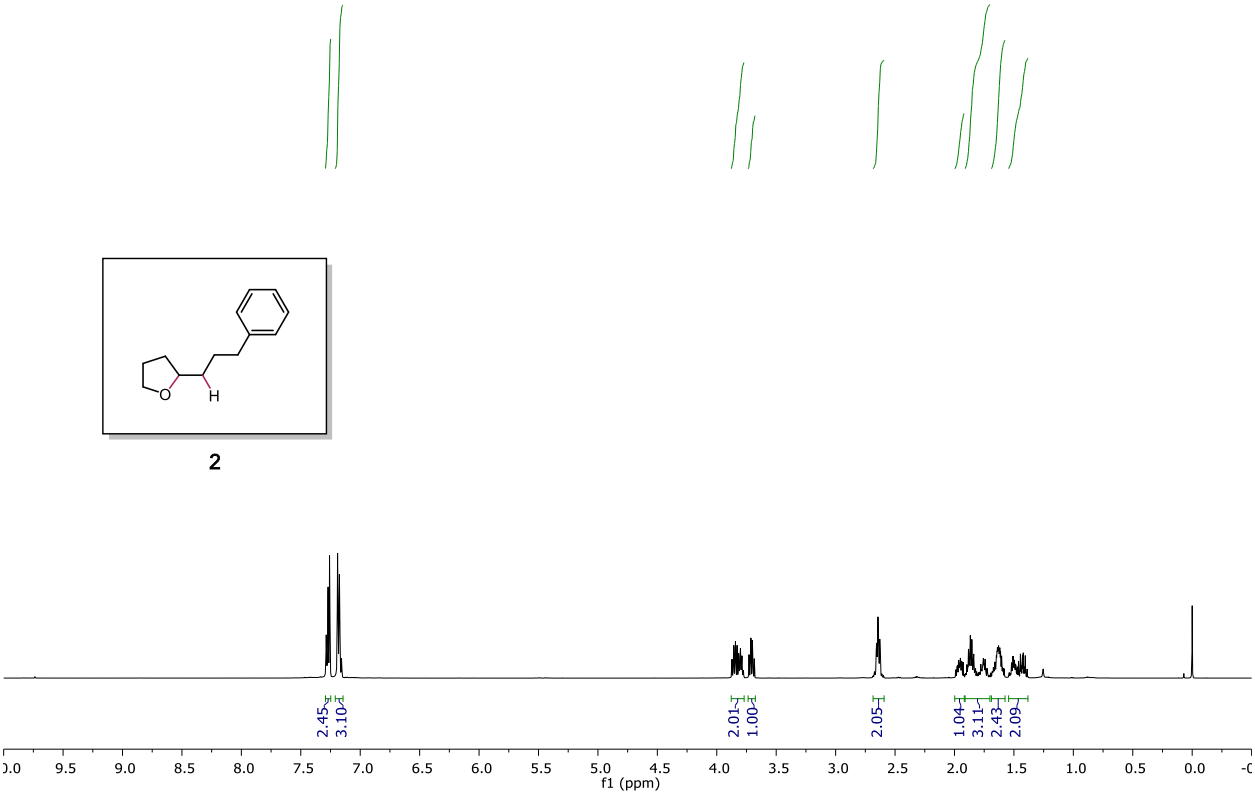
Table S7: *N*-Boc-L-Prolinol Cyclization and β-Scission Competition

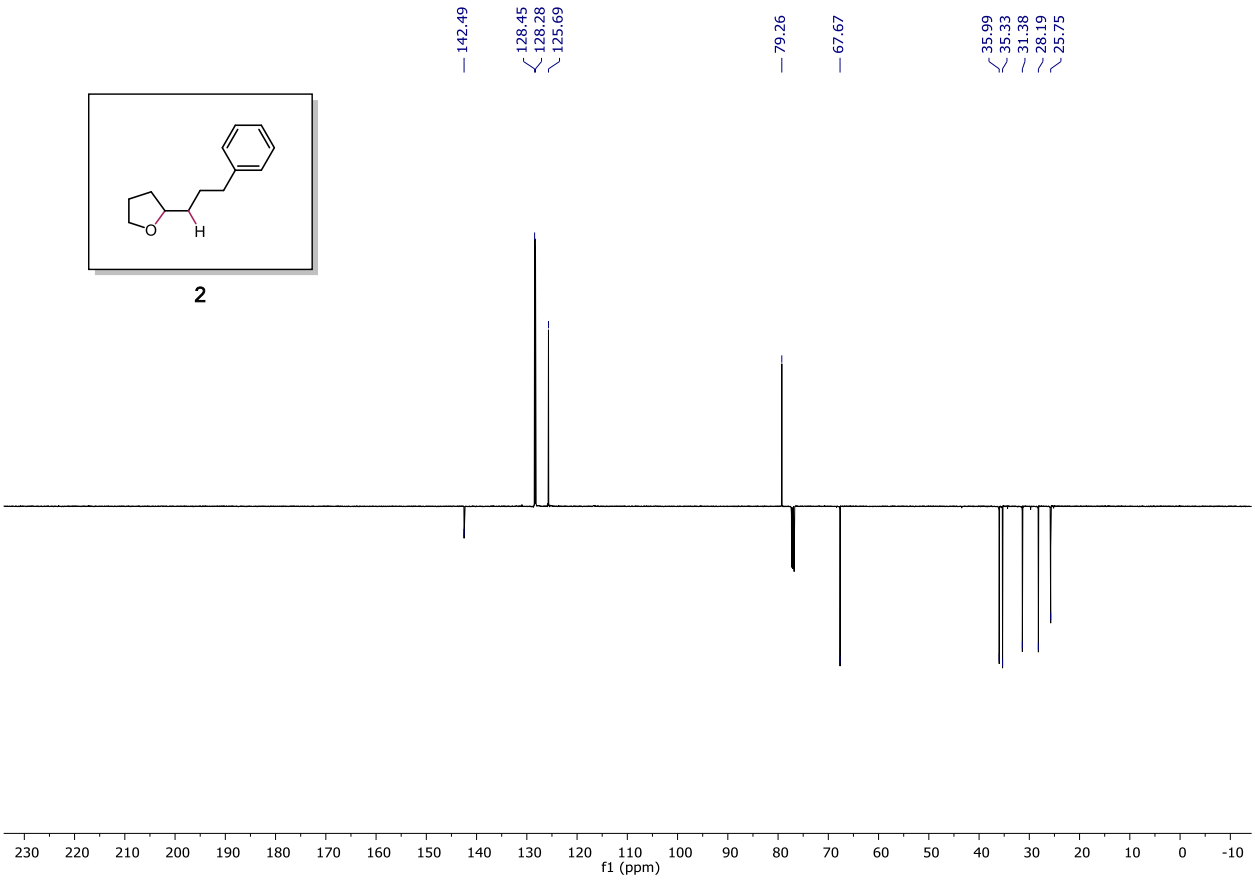


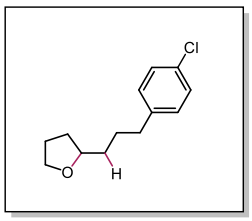
Entry	R^1	R^2	Diastereomer of Alkenol	Brønsted Base	HAT Co-Catalyst	Yield of Cyclized Pdt[a]	Yield of -scission Pdt[a]
1	H	H	*trans* (*S*,*R*)	Bu_4P^+ $(PhO)_2P(O)O^-$	$(2\text{-FPhS})_2$	0%	83%
2	H	H	*trans* (*S*,*R*)	Bu_4P^+ $(PhO)_2P(O)O^-$	$(4\text{-MeOPhS})_2$	0%	80%
3	H	H	*cis* (*S*,*S*)	Bu_4P^+ $(PhO)_2P(O)O^-$	$(2\text{-FPhS})_2$	0%	77%
4	H	H	*cis* (*S*,*S*)	Bu_4P^+ $(PhO)_2P(O)O^-$	$(4\text{-MeOPhS})_2$	0%	75%
5	H	C_3H_7	*cis* (*S*,*S*)	Bu_4P^+ $(PhO)_2P(O)O^-$	$(2\text{-FPhS})_2$	0%	91%
6	CH_3	CH_3	*trans* (*S*,*R*)	Bu_4P^+ $(PhO)_2P(O)O^-$	$(2\text{-FPhS})_2$	19%	69%
7	CH_3	CH_3	*trans* (*S*,*R*)	2-methyl-2-oxazoline	$4\text{-CF}_3\text{PhSH}$	65%	34%

[a]NMR yields determined relative to DMF as an internal standard. Reactions performed on a 0.05 mmol scale.

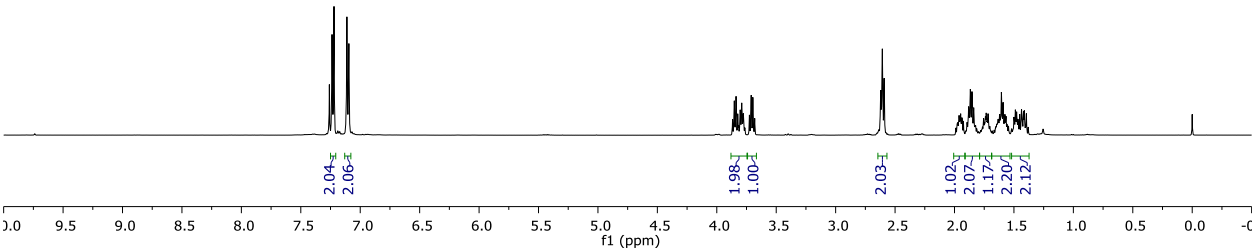
^{1}H and ^{13}C NMR Spectra of Products



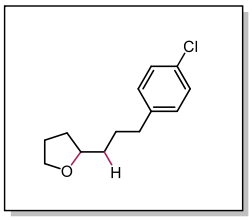



Cl
O
H

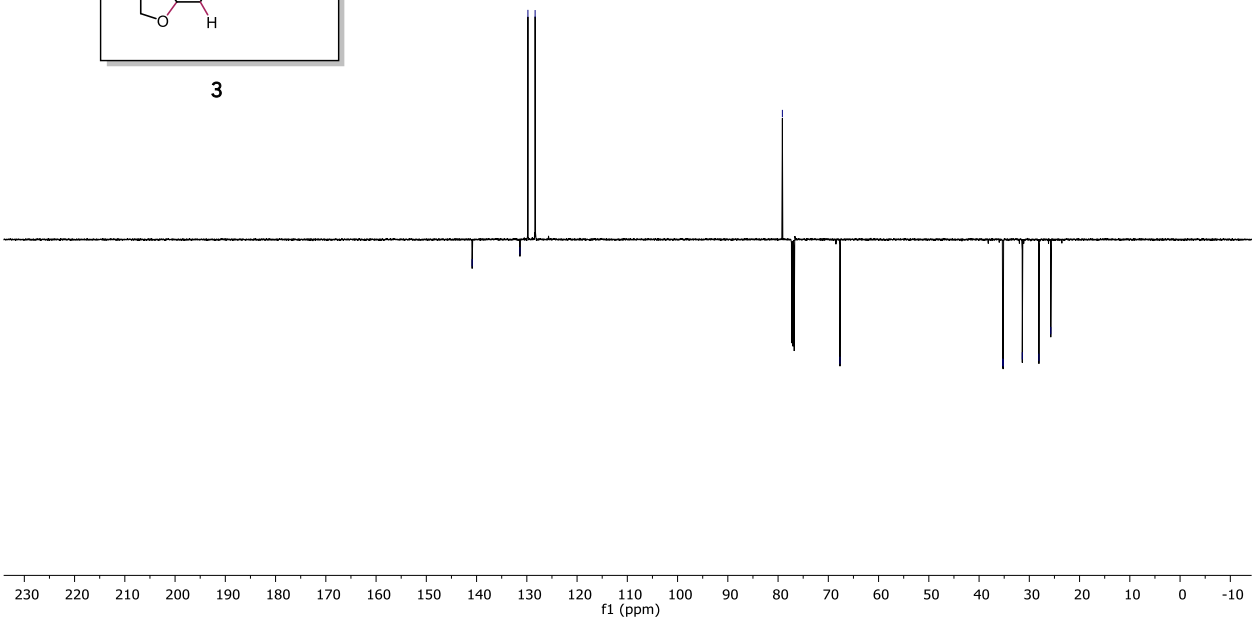
3

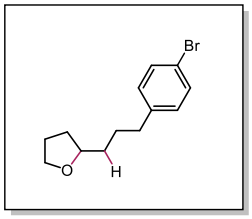

2.04
2.06
1.98
1.00
2.03
1.02
2.07
1.17
2.20
2.12
f1 (ppm)


140.88
131.37
129.78
128.35
79.14
67.68
35.29
35.18
31.40
28.09
25.73

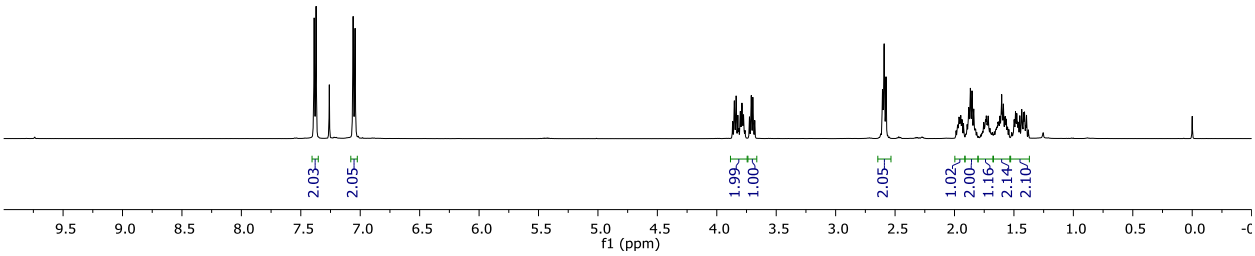

Cl
O
H

3

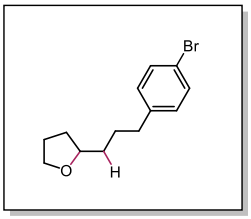

f1 (ppm)


Br
O
H

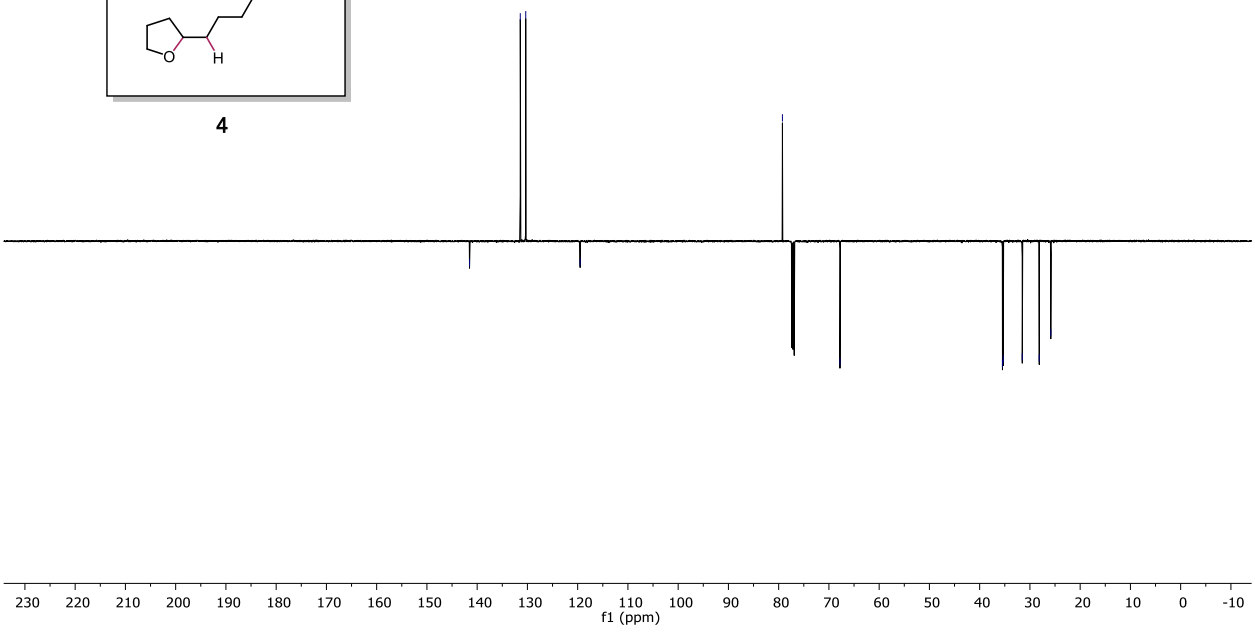
4

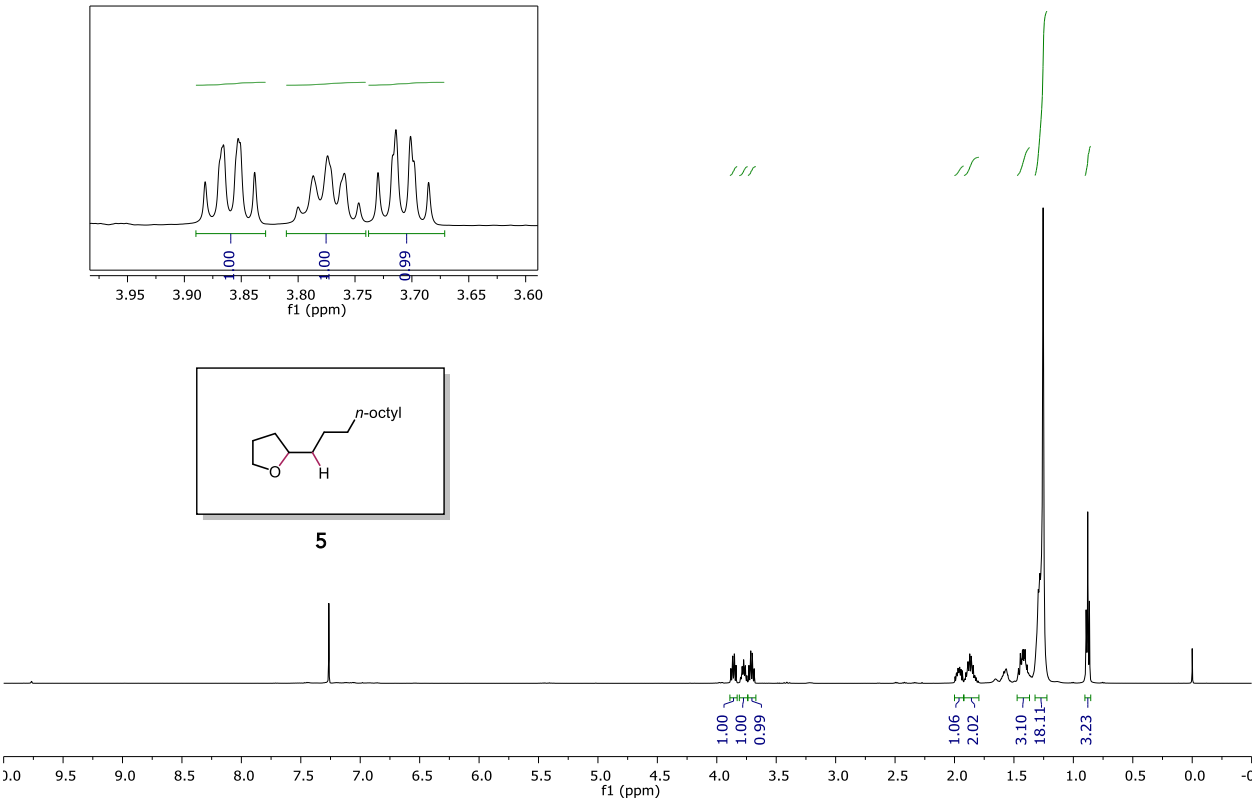

2.03
2.05
1.99
1.00
2.05
1.02
2.00
1.16
2.14
2.10
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


141.52
131.42
130.33
119.51
79.25
67.80
35.46
35.30
31.52
28.14
25.85

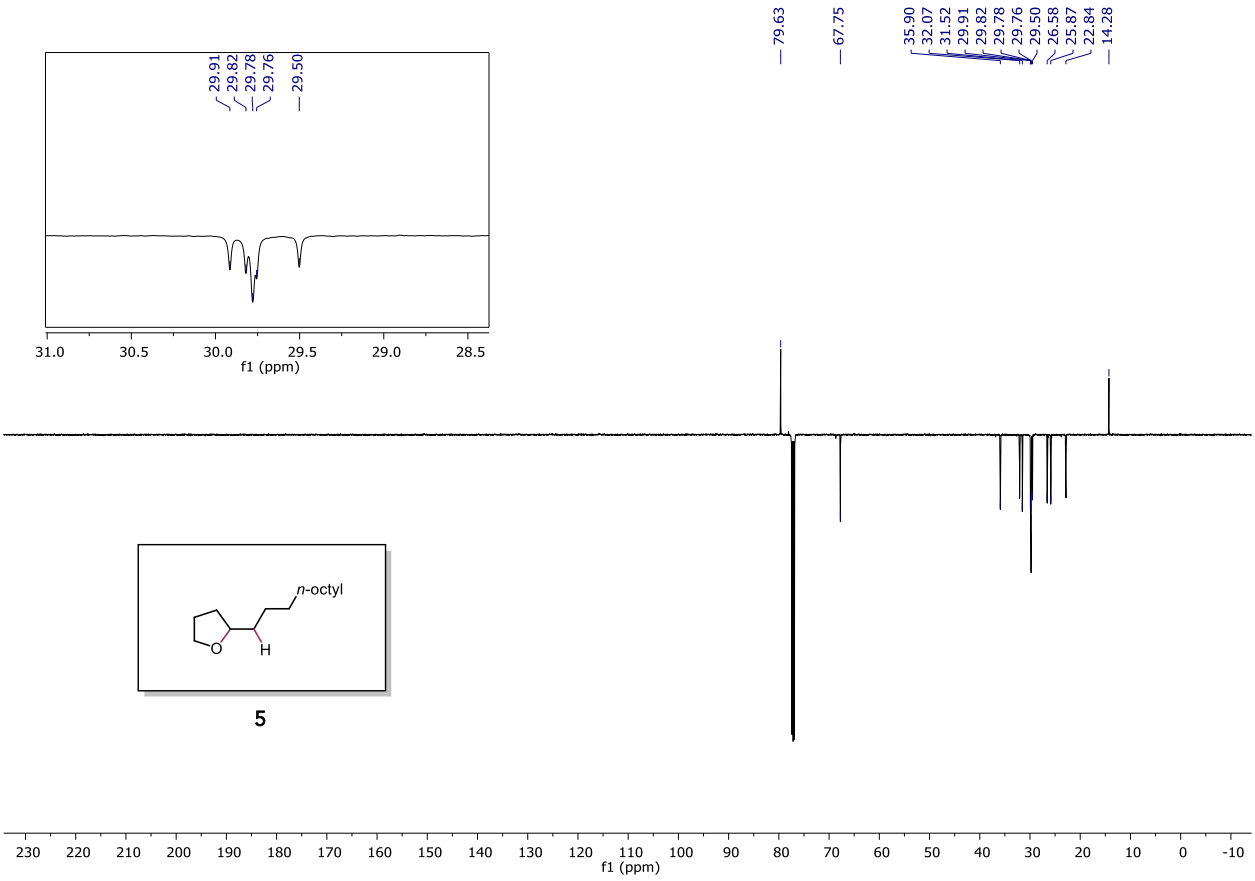

Br
O
H

4

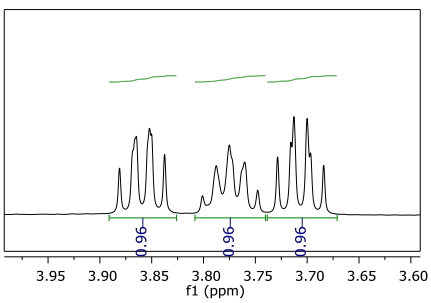

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

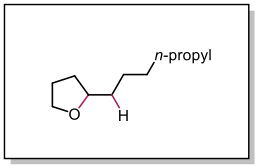

1.00
1.00
0.99
3.95 3.90 3.85 3.80 3.75 3.70 3.65 3.60
f1 (ppm)
n-octyl
O
H
1.00
1.00
0.99
1.06
2.02
3.10
18.11
3.23
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

5


79.63
67.75
35.90
32.07
31.52
29.91
29.82
29.78
29.76
29.50
26.58
25.87
22.84
14.28
29.91
29.82
29.78
29.76
29.50
31.0 30.5 30.0 29.5 29.0 28.5
f1 (ppm)
n-octyl
O
H
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

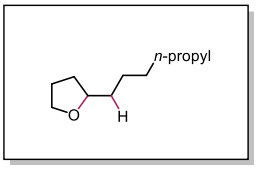
5


0.96
0.96
0.96
3.95 3.90 3.85 3.80 3.75 3.70 3.65 3.60
f1 (ppm)


n-propyl
O
H

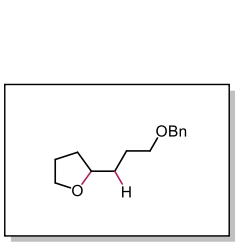
6

0.96
0.96
0.96
1.05
1.95
1.04
3.10
7.25
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


n-propyl
O
H

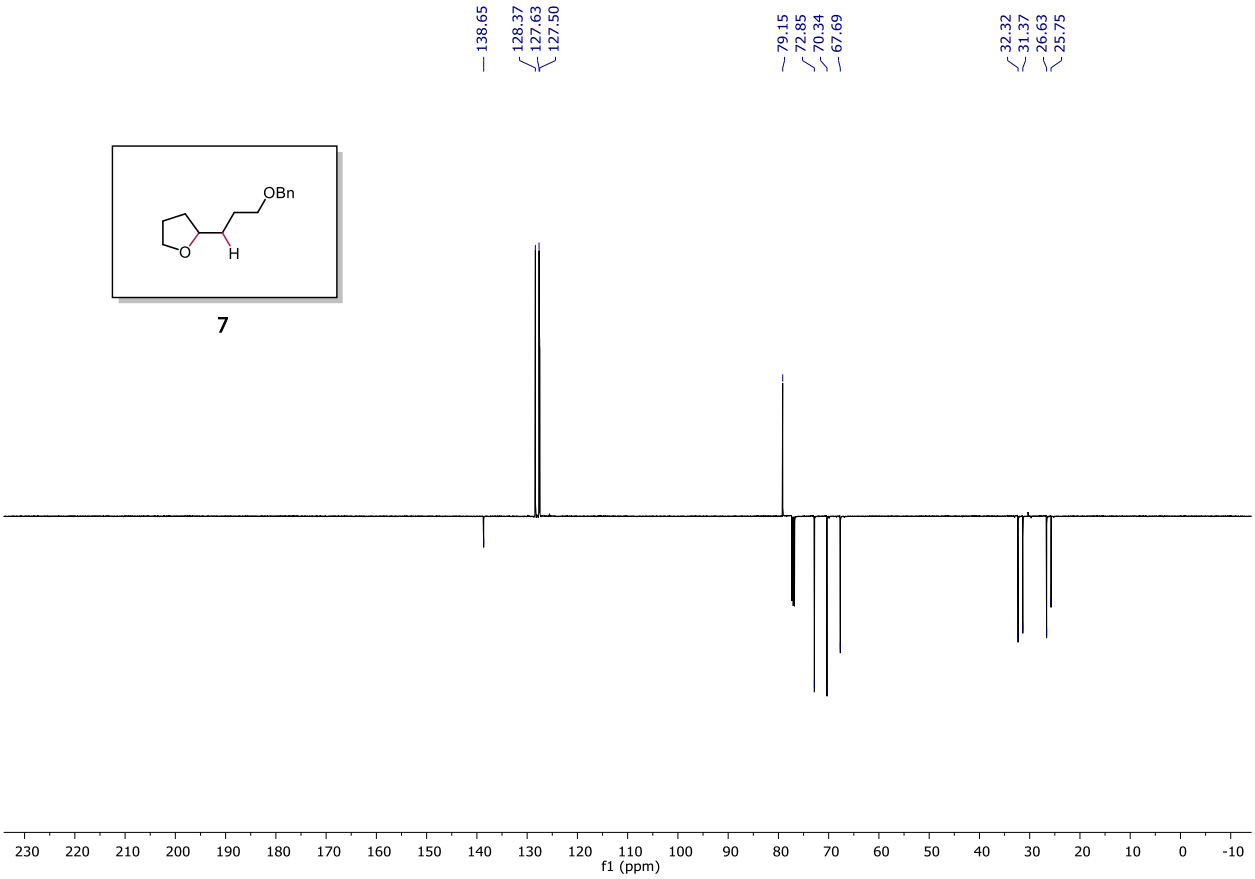
6

79.49
67.61
35.78
31.86
31.40
29.45
26.40
25.74
22.63
14.11
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OBn
O
H

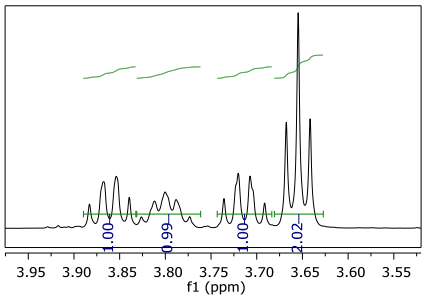
7

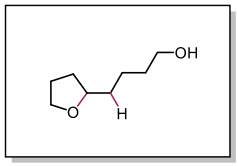
3.97
1.25
2.00
1.98
1.02
2.02
1.05
2.09
1.11
3.04
1.11
f1 (ppm)


138.65
128.37
127.63
127.50
79.15
72.85
70.34
67.69
32.32
31.37
26.63
25.75
f1 (ppm)

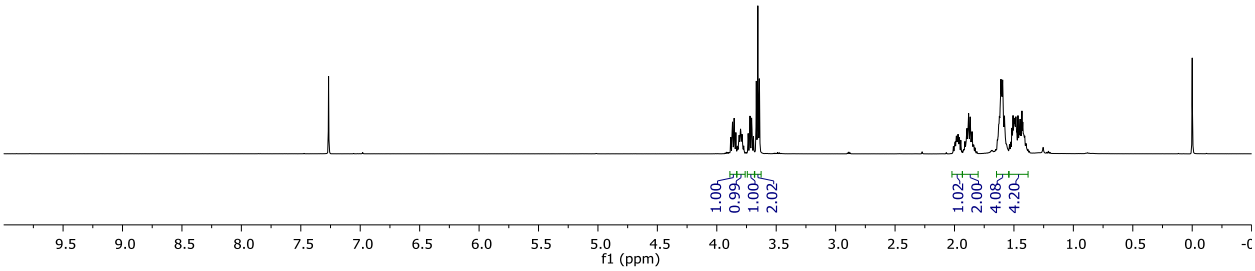
OBn
O
H

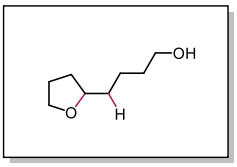
7


1.00
0.99
1.00
2.02
3.95 3.90 3.85 3.80 3.75 3.70 3.65 3.60 3.55
f1 (ppm)


OH
O
H

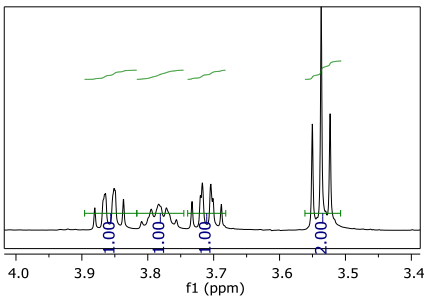
8

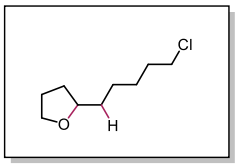

1.00
0.99
1.00
2.02
1.02
2.00
4.08
4.20
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


OH
O
H

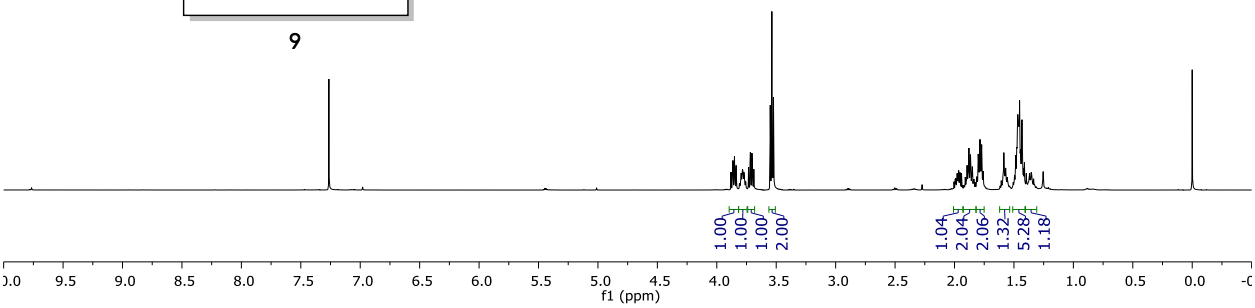
8

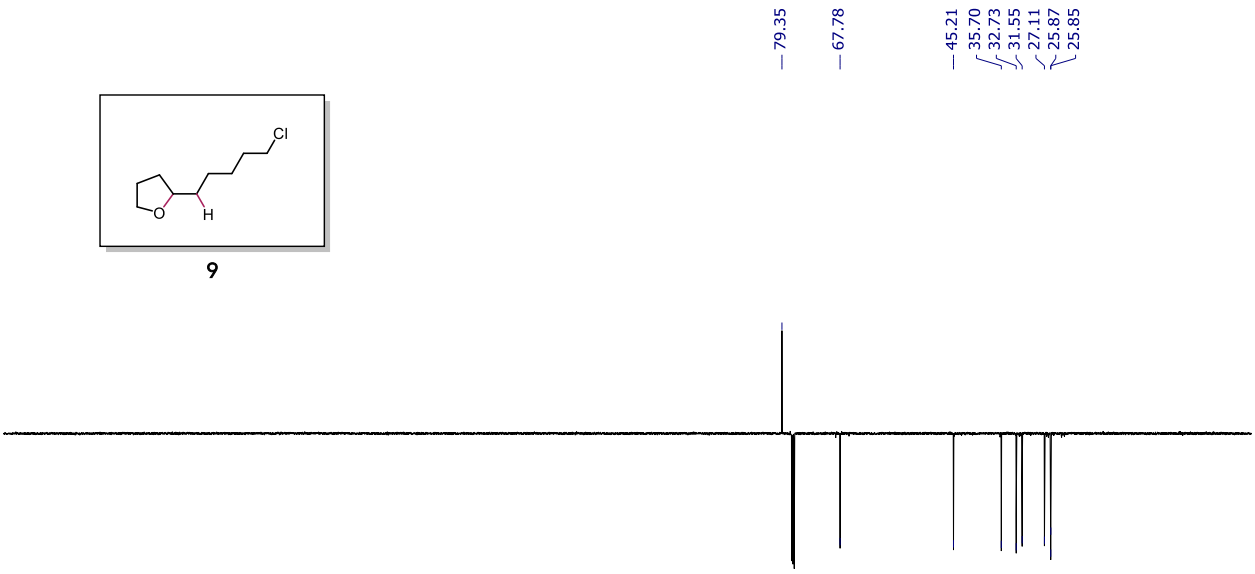
79.45
67.79
62.99
35.46
32.87
31.51
25.85
22.70
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


1.00
1.00
1.00
2.00
4.0
3.9
3.8
3.7
3.6
3.5
3.4
f1 (ppm)


Cl
O
H

9

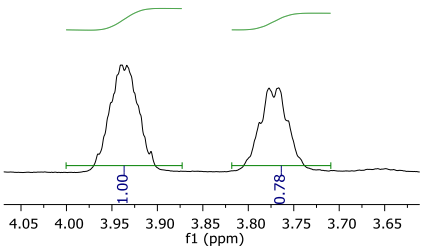

1.00
1.00
1.00
2.00
1.04
2.04
2.06
1.32
5.28
1.18
f1 (ppm)

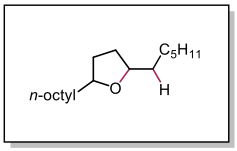

79.35
67.78
45.21
35.70
32.73
31.55
27.11
25.87
25.85
f1 (ppm)

Cl
O
H

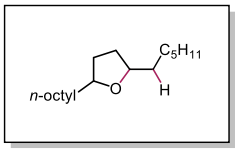
9

Inset from crude NMR in C_6D_6 at 500 MHz (1.3:1 dr)

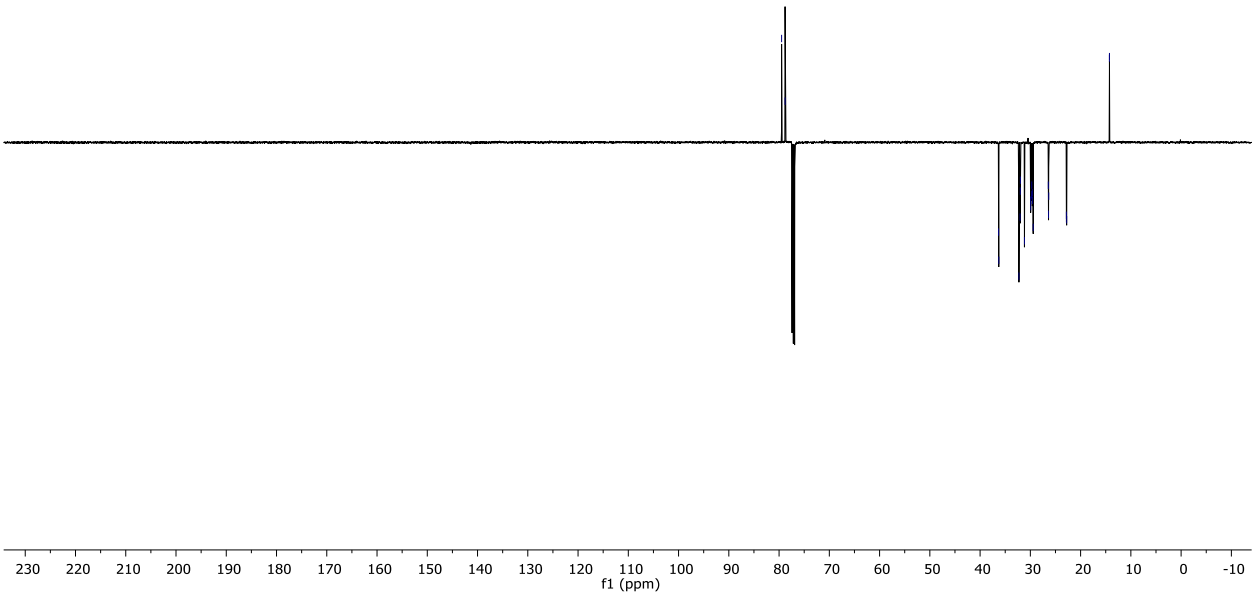




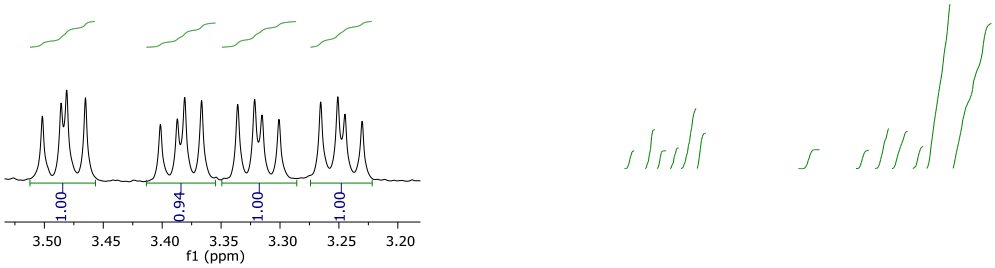
10

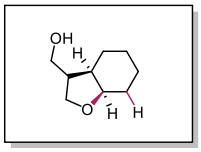


10

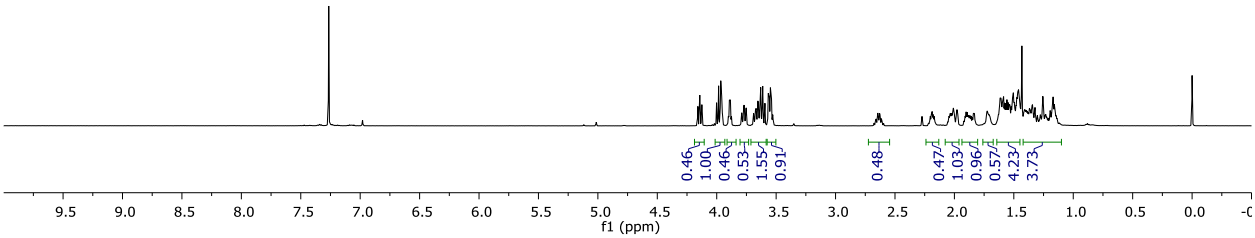


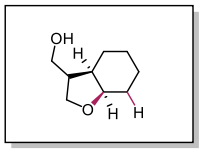
Inset from crude NMR in
C_6D_6 at 500 MHz
(1:1 dr)



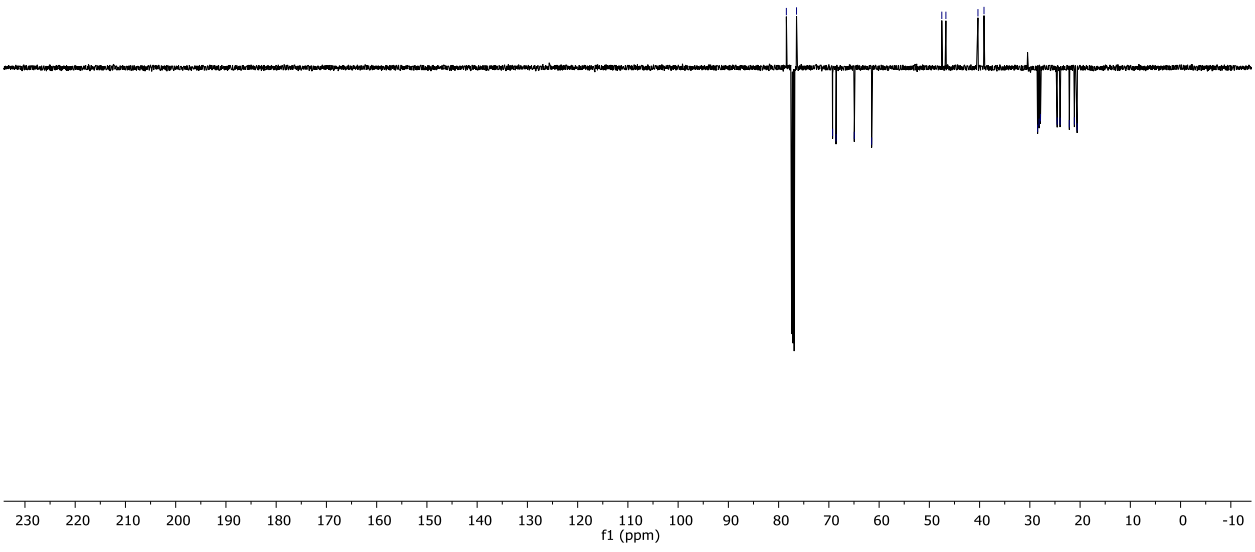


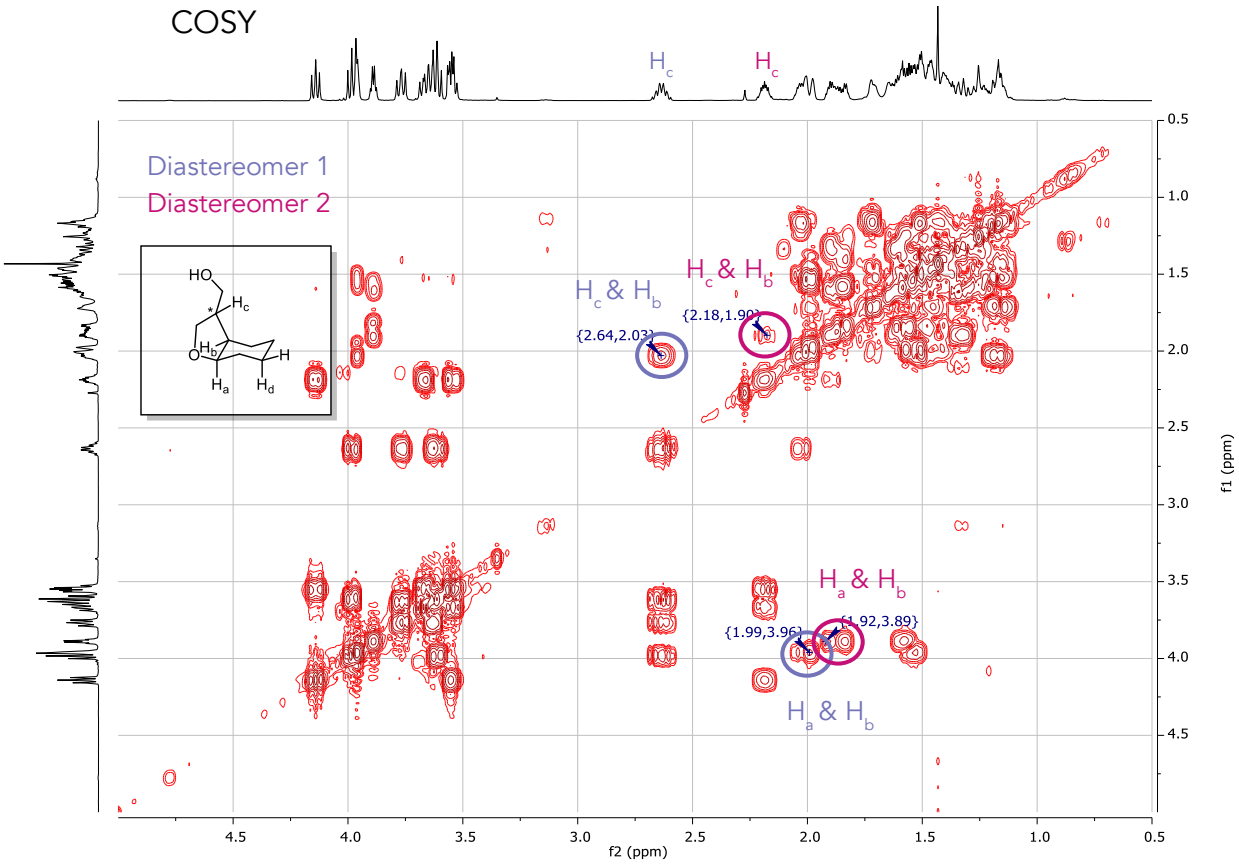
11

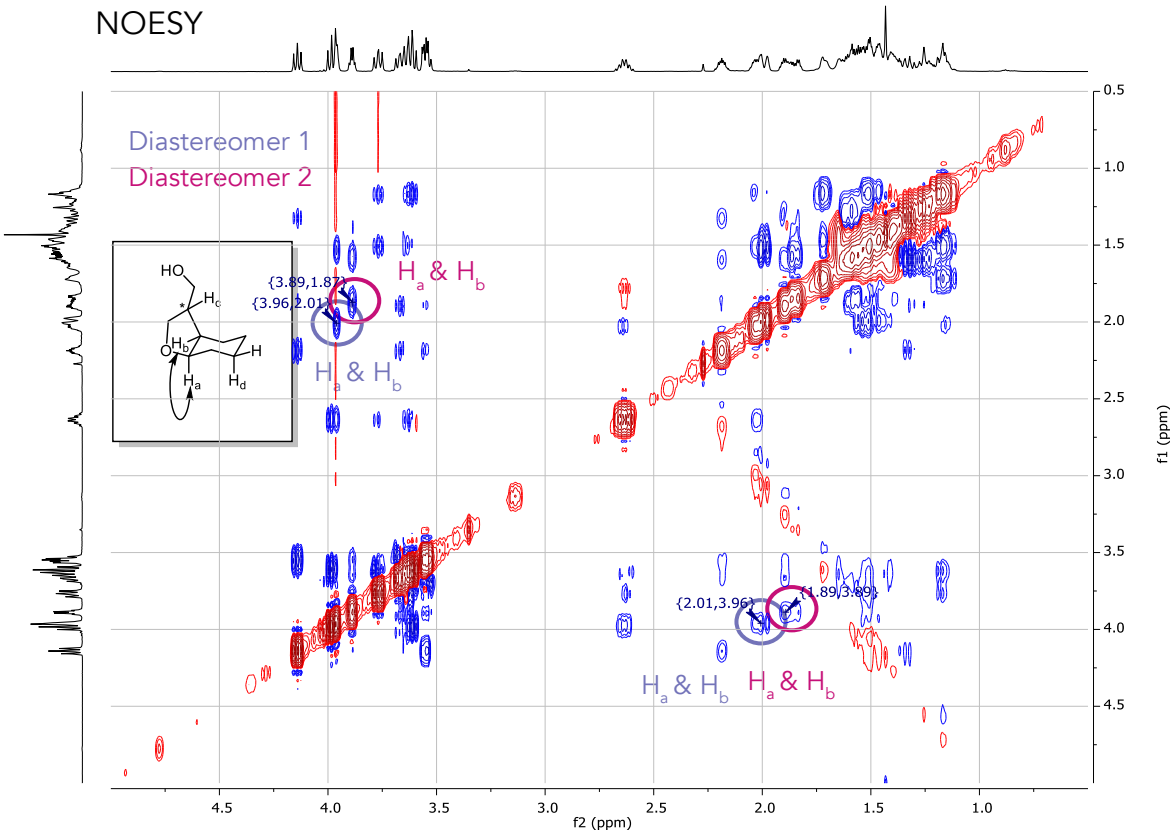


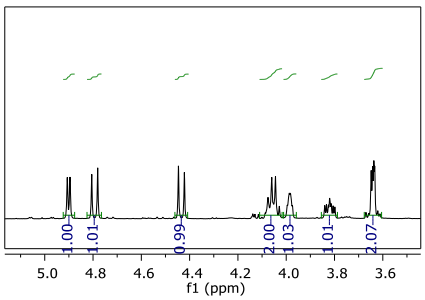


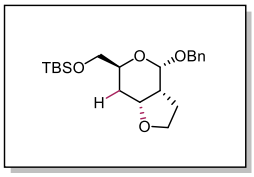
11




COSY
Diastereomer 1
Diastereomer 2
Hc & Hb
{2.64,2.03}
Hc & Hb
{2.18,1.90}
Ha & Hb
{1.99,3.96}
{1.92,3.89}
Ha & Hb
f2 (ppm)
f1 (ppm)

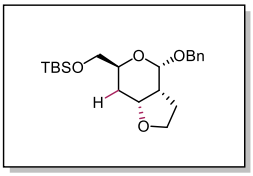

NOESY
Diastereomer 1
Diastereomer 2
{3.89,1.87}
{3.96,2.01}
Ha & Hb
Ha & Hb
{2.01,3.96}
{1.89,3.89}
Ha & Hb
Ha & Hb
f2 (ppm)
f1 (ppm)


1.00
1.01
0.99
2.00
1.03
1.01
2.07
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
f1 (ppm)


TBSO
O
OBn
H
O

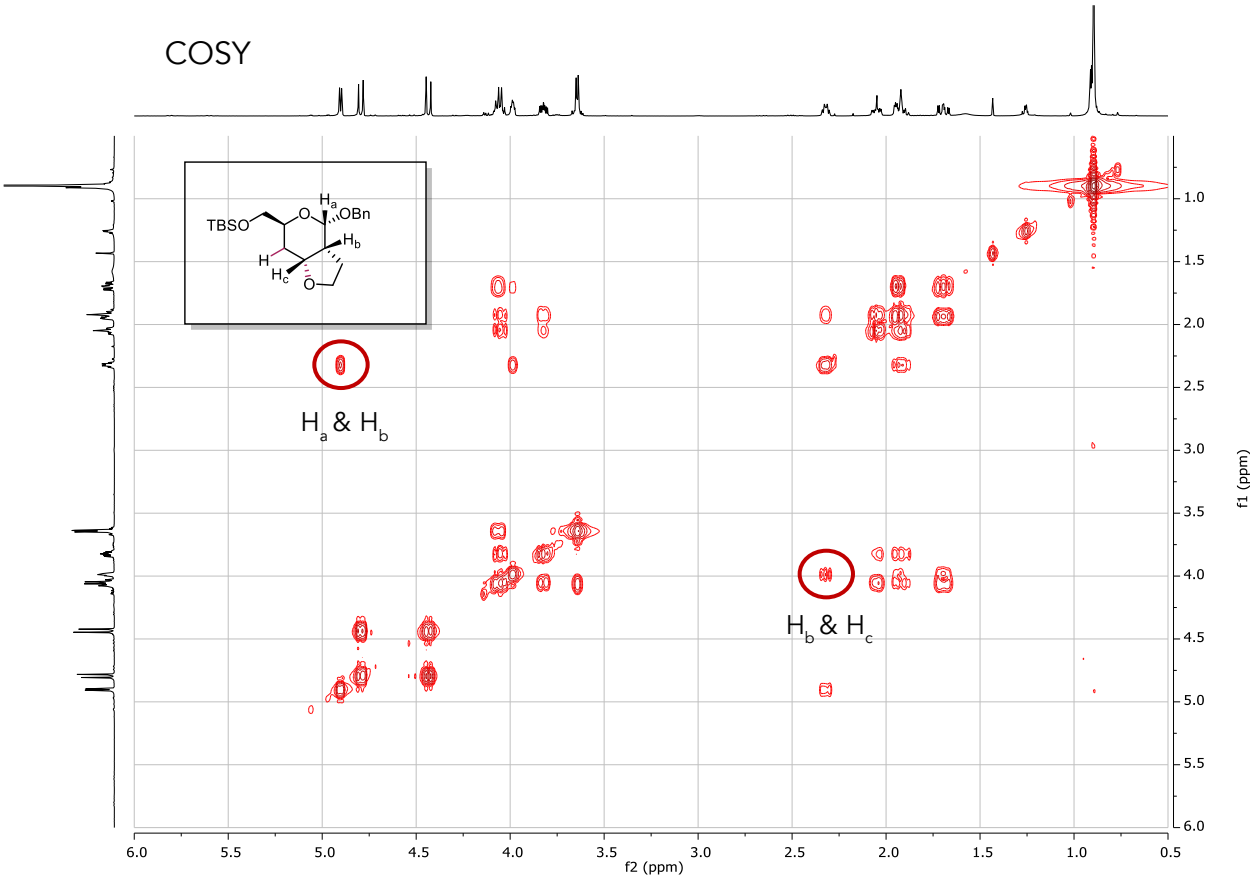
12

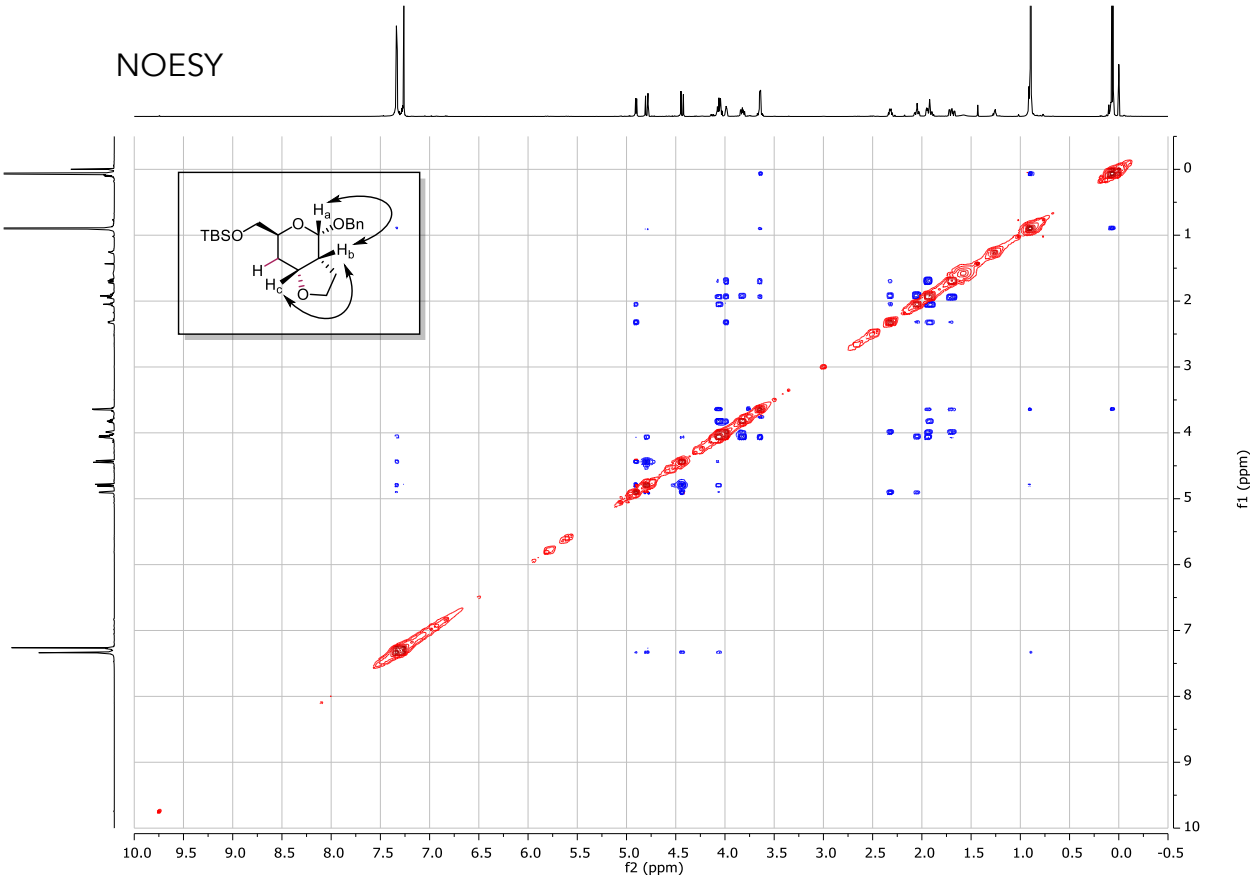
5.01
1.00
1.01
0.99
2.00
1.03
1.01
2.07
0.97
1.19
2.04
1.01
9.02
6.01
f1 (ppm)


TBSO
O
OBn
H
O

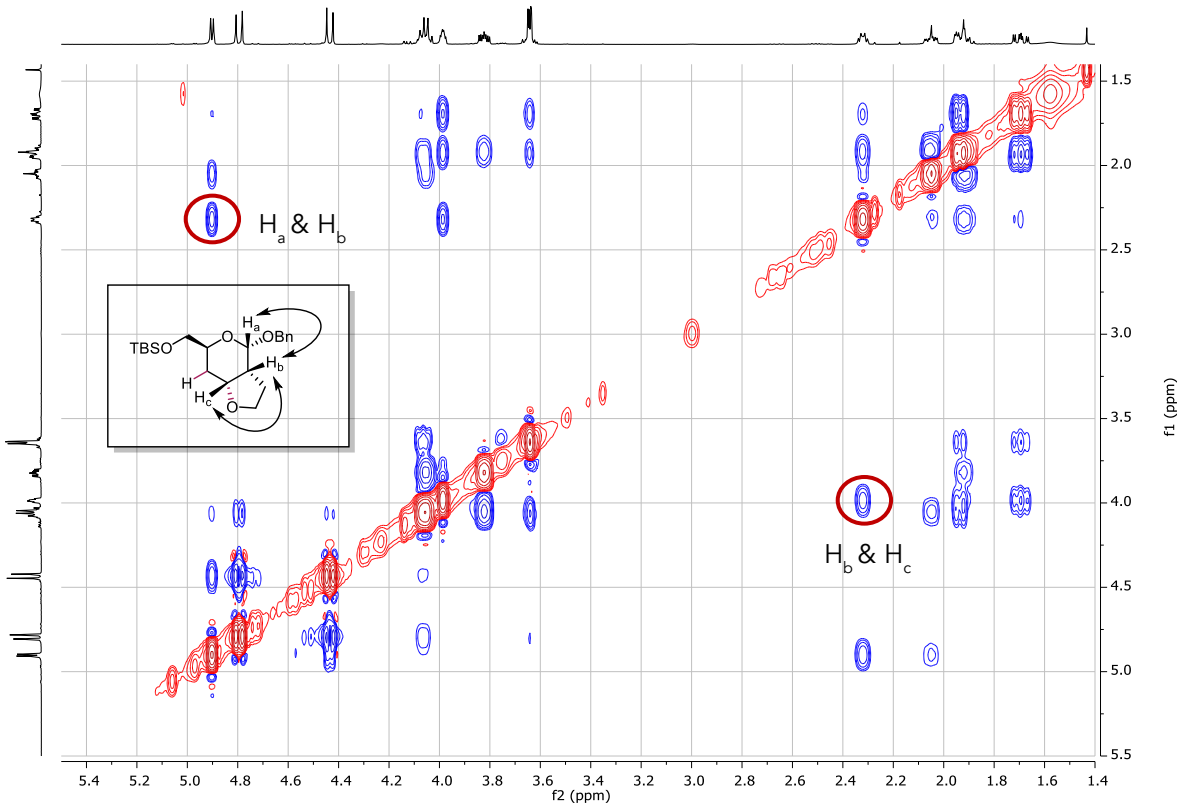
12

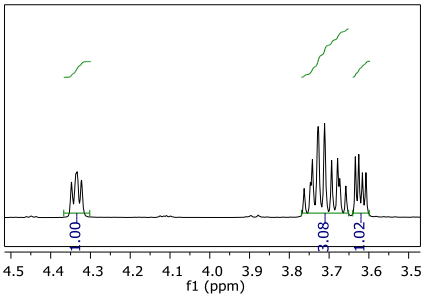
138.54
128.41
127.62
127.45
97.39
74.48
68.84
68.18
66.46
63.69
39.86
29.21
27.95
26.10
18.53
-5.13
-5.18
f1 (ppm)

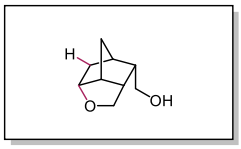

COSY
TBSO
OBn
H
H_a & H_b
H_b & H_c
f2 (ppm)
f1 (ppm)


NOESY
TBSO
OBn
H
f2 (ppm)
f1 (ppm)

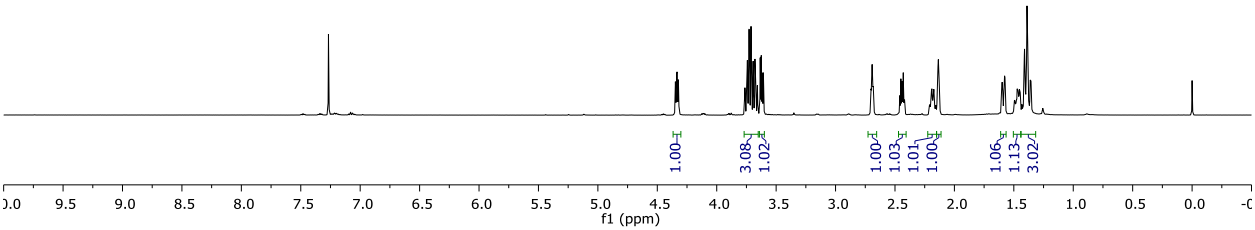
NOESY


H_a & H_b
H_b & H_c
TBSO
OBn
H_a
H_b
H
H_c
O
O
f2 (ppm)
f1 (ppm)
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4
1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5

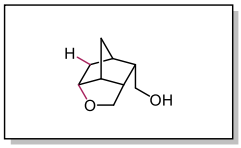

1.00
3.08
1.02
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5
f1 (ppm)


H
O
OH

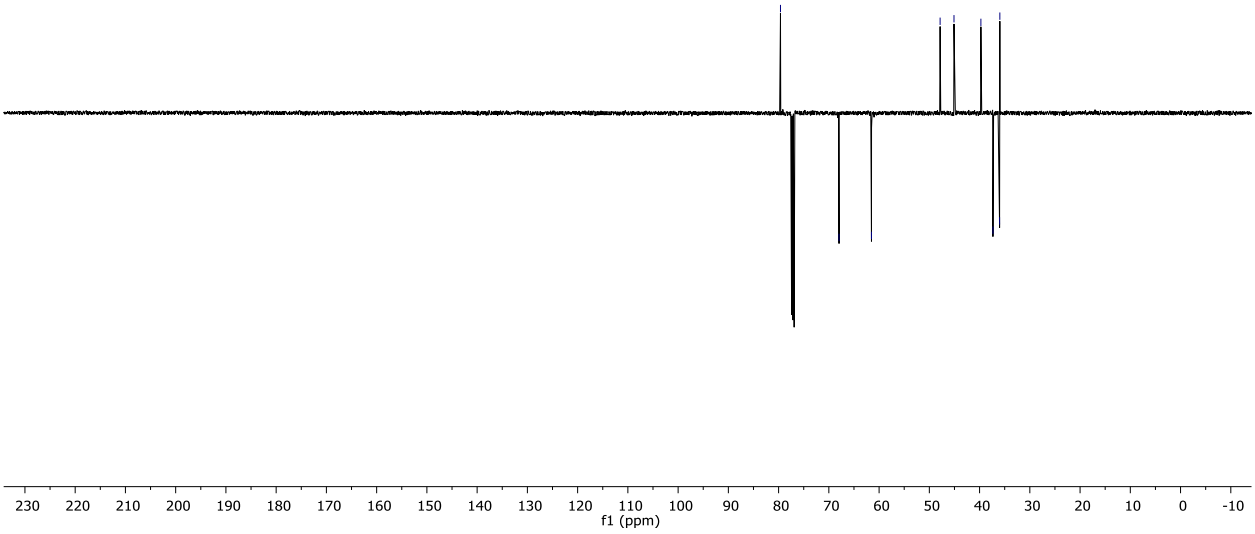
13

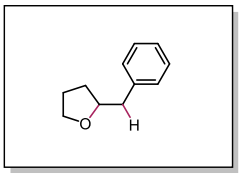

1.00
3.08
1.02
1.00
1.03
1.01
1.00
1.06
1.13
3.02
f1 (ppm)


79.63
67.97
61.52
47.86
45.09
39.74
37.34
36.02
35.97

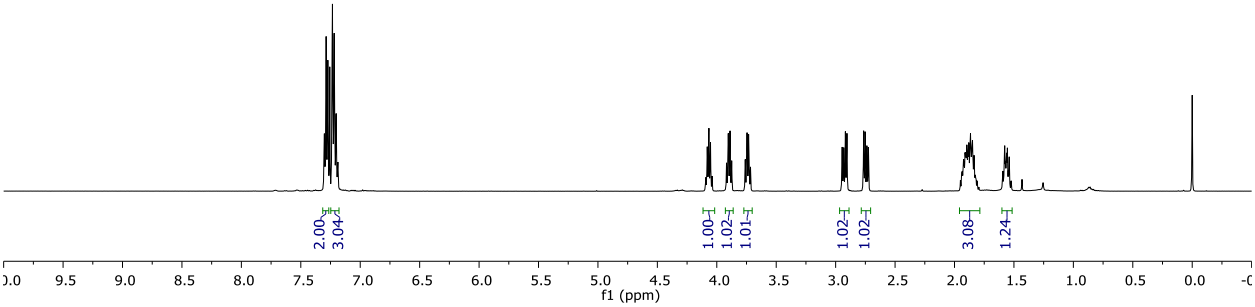

H
O
OH

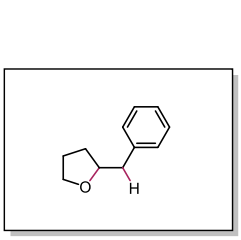
13


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



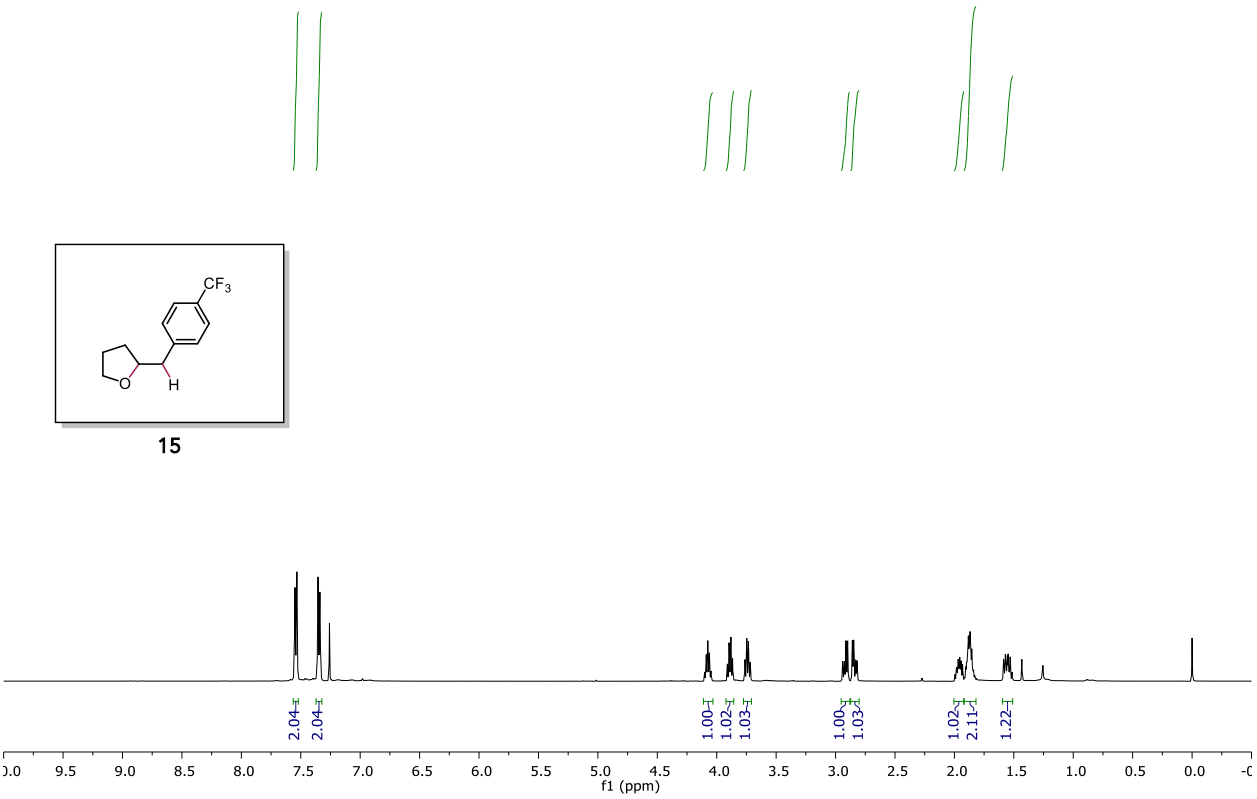
14

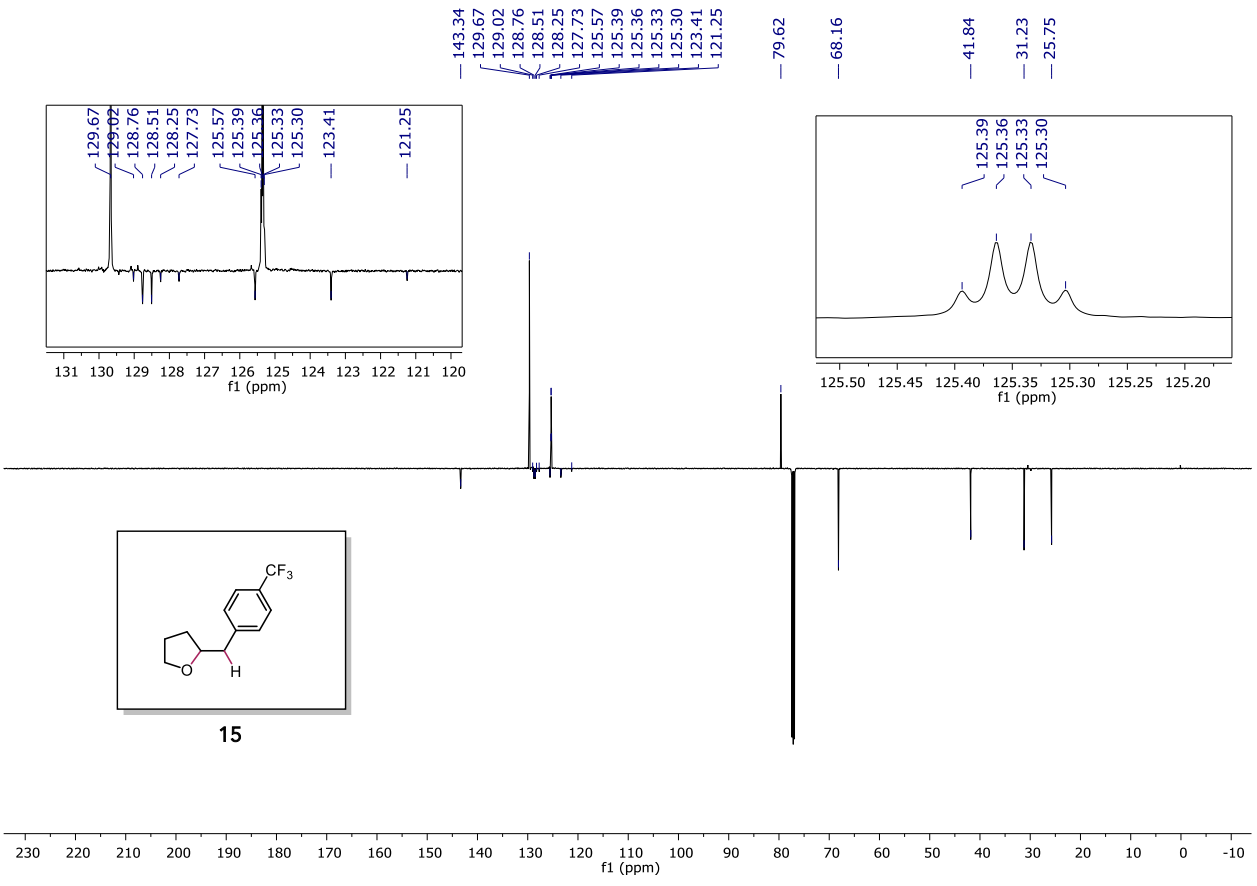

2.00
3.04
1.00
1.02
1.01
1.02
1.02
3.08
1.24
f1 (ppm)

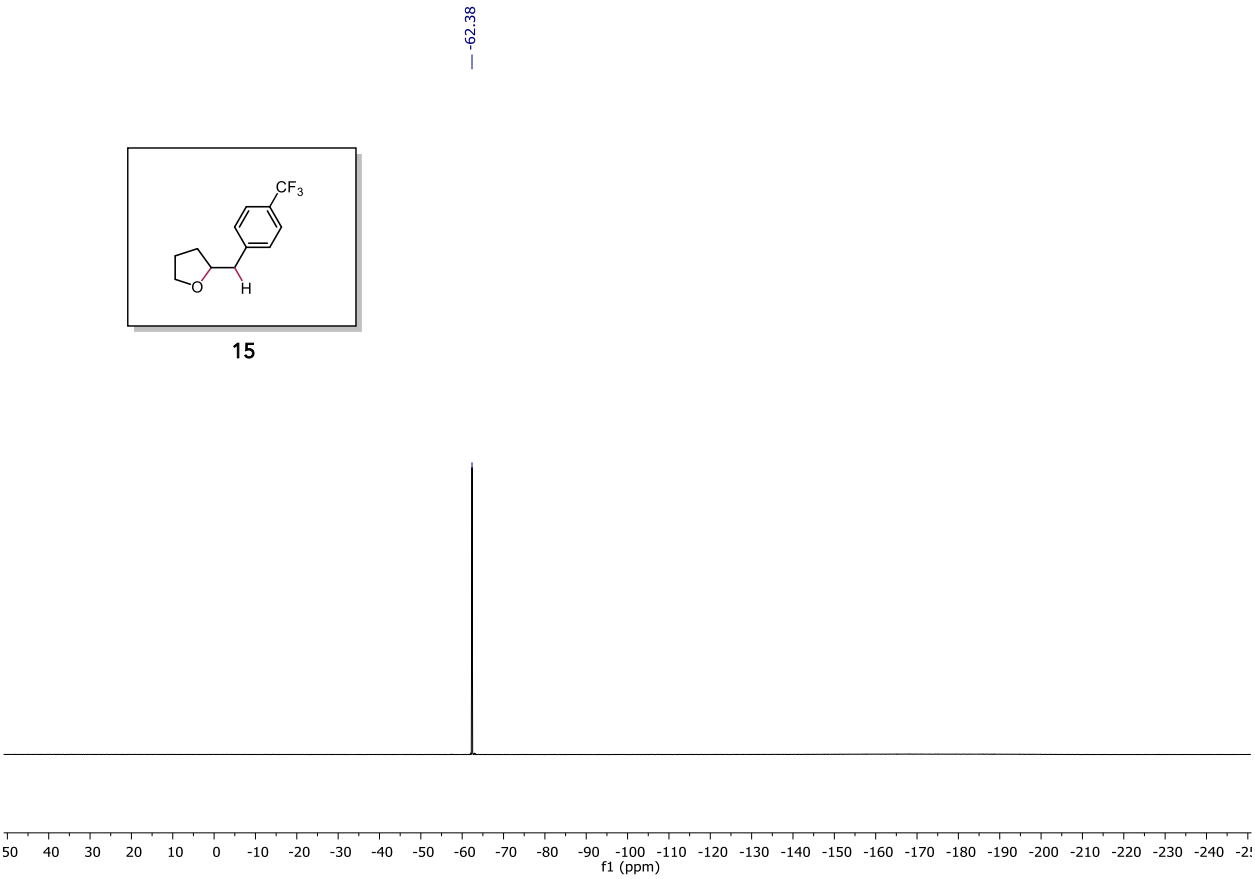


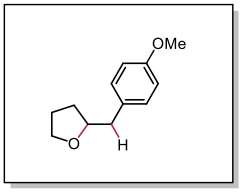
14

139.13
129.35
128.45
126.29
80.19
68.08
42.07
31.12
25.74
f1 (ppm)


CF3
O
H
15
2.04
2.04
1.00
1.02
1.03
1.00
1.03
1.02
2.11
1.22
f1 (ppm)

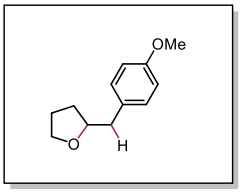

143.34
129.67
129.02
128.76
128.51
128.25
127.73
125.57
125.39
125.36
125.33
125.30
123.41
121.25
79.62
68.16
41.84
31.23
25.75
f1 (ppm)
CF3
O
H
15


-62.38
CF3
O
H
15
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)


OMe
O
H

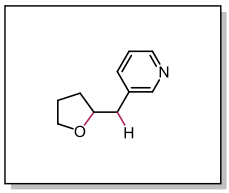
16

2.04
2.02
1.00
1.03
3.01
1.06
1.02
1.02
3.07
1.02
f1 (ppm)

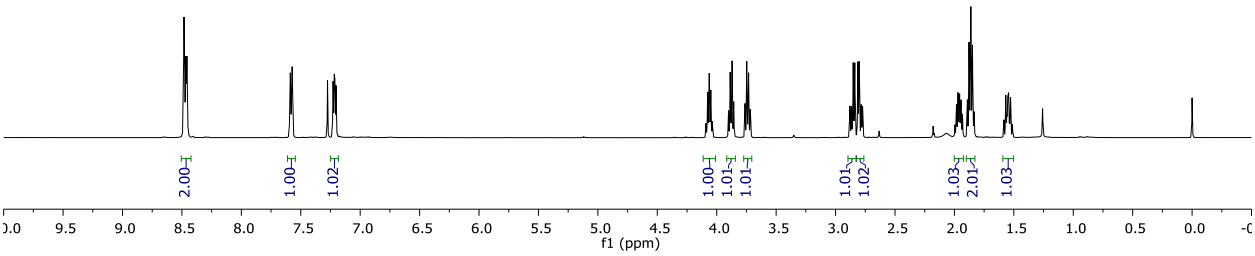

OMe
O
H

16

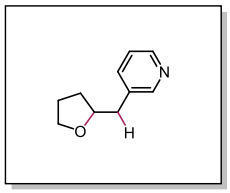
158.15
131.22
130.25
113.87
80.37
68.06
55.37
41.12
31.04
25.75
f1 (ppm)


N
O
H

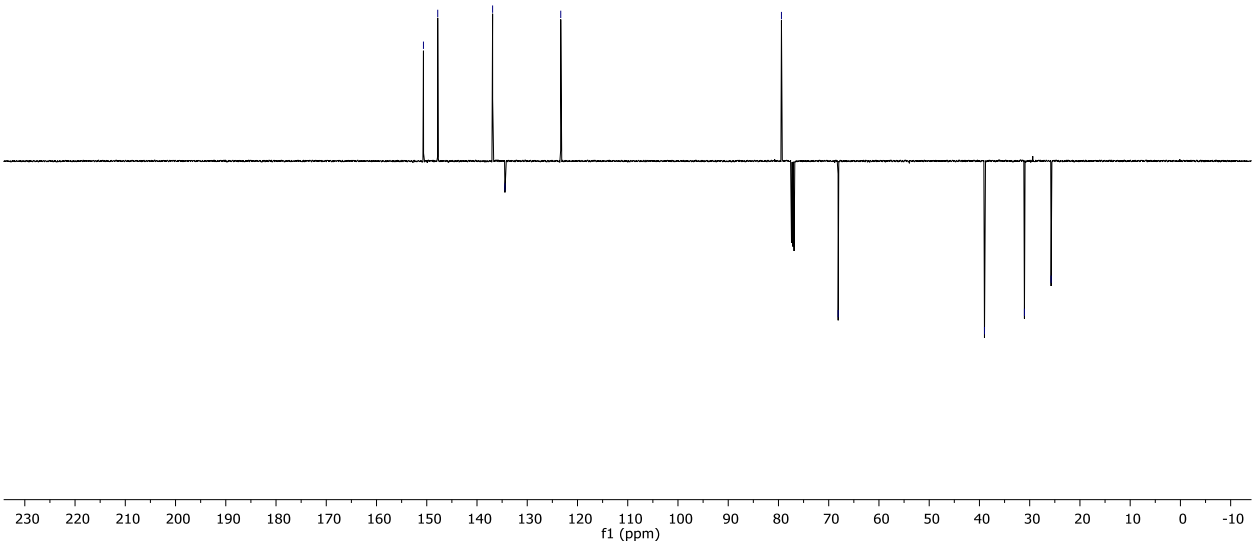
17

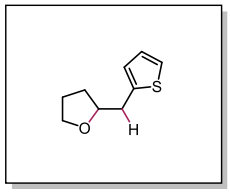

2.00
1.00
1.02
1.00
1.01
1.01
1.01
1.02
1.03
2.01
1.03
f1 (ppm)


150.66
147.82
136.89
134.44
123.33
79.40
68.12
39.00
31.04
25.74

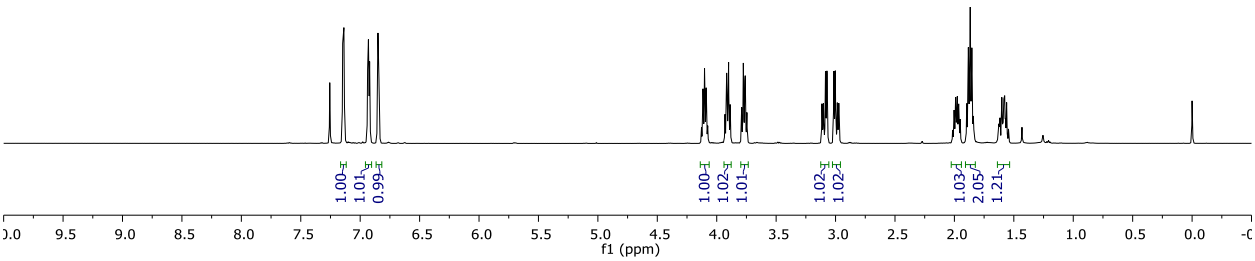

N
O
H

17

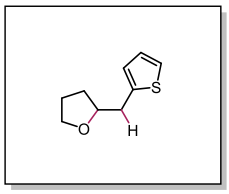

f1 (ppm)


S
O
H

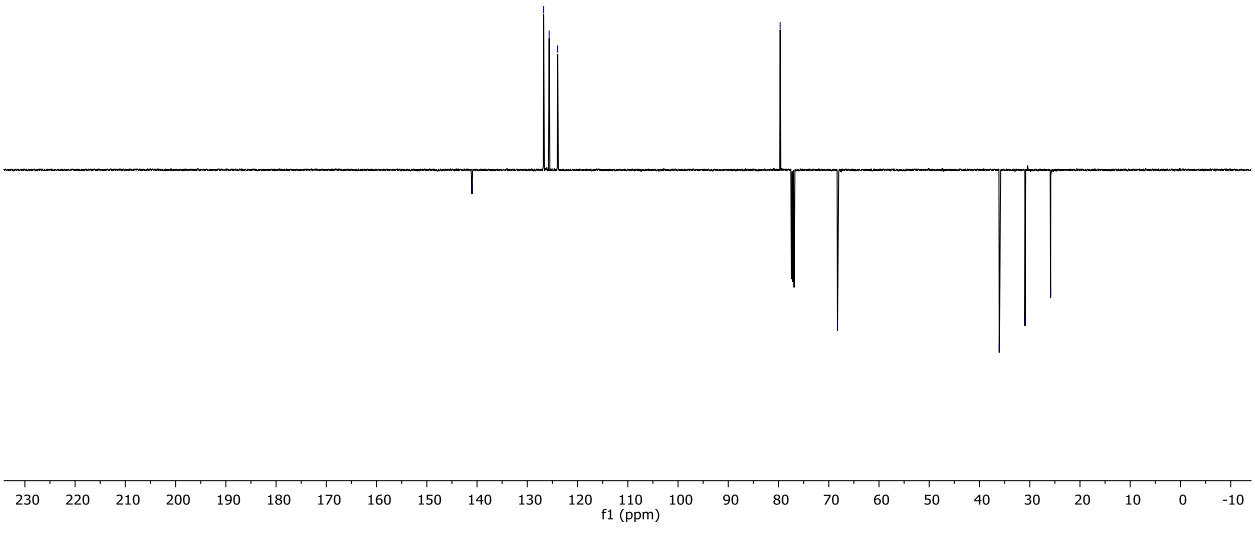
18

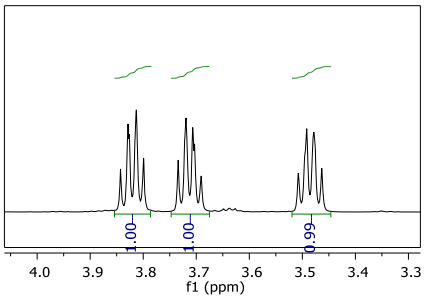

1.00
1.01
0.99
1.00
1.02
1.01
1.02
1.02
1.03
2.05
1.21
f1 (ppm)

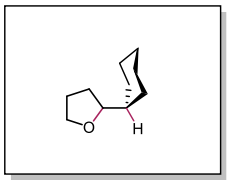

141.01
126.76
125.64
123.97
79.66
68.26
36.05
30.94
25.85


S
O
H

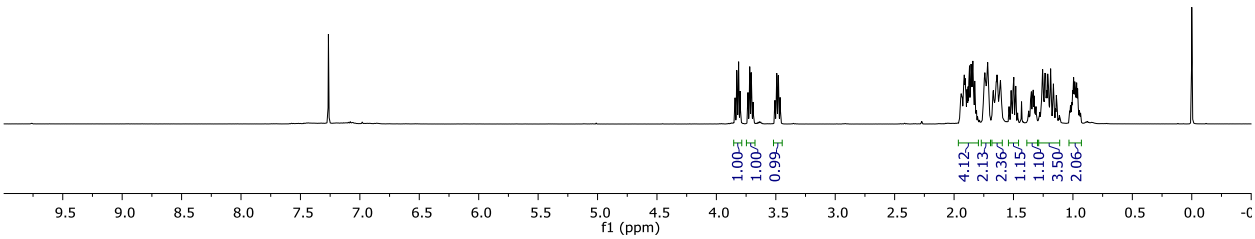
18

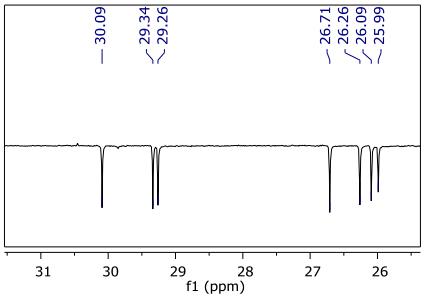

f1 (ppm)


1.00
1.00
0.99
4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3
f1 (ppm)


O
H

19


1.00
1.00
0.99
4.12
2.13
2.36
1.15
1.10
3.50
2.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

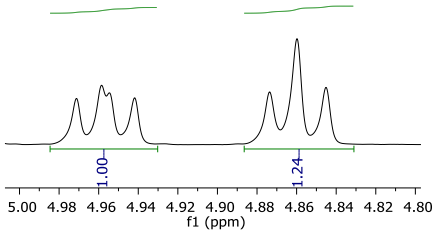

30.09
29.34
29.26
26.71
26.26
26.09
25.99
31 30 29 28 27 26
f1 (ppm)

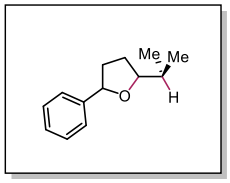
84.15
67.83
43.22
30.09
29.34
29.26
26.71
26.26
26.09
25.99
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

O
H

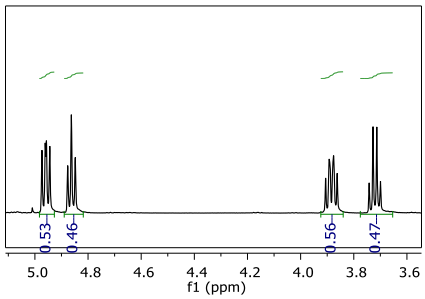
19

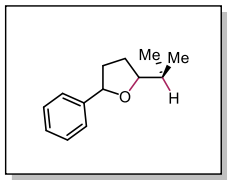
Inset from crude NMR in $CDCl_3$ at 500 MHz (1.2:1 dr)



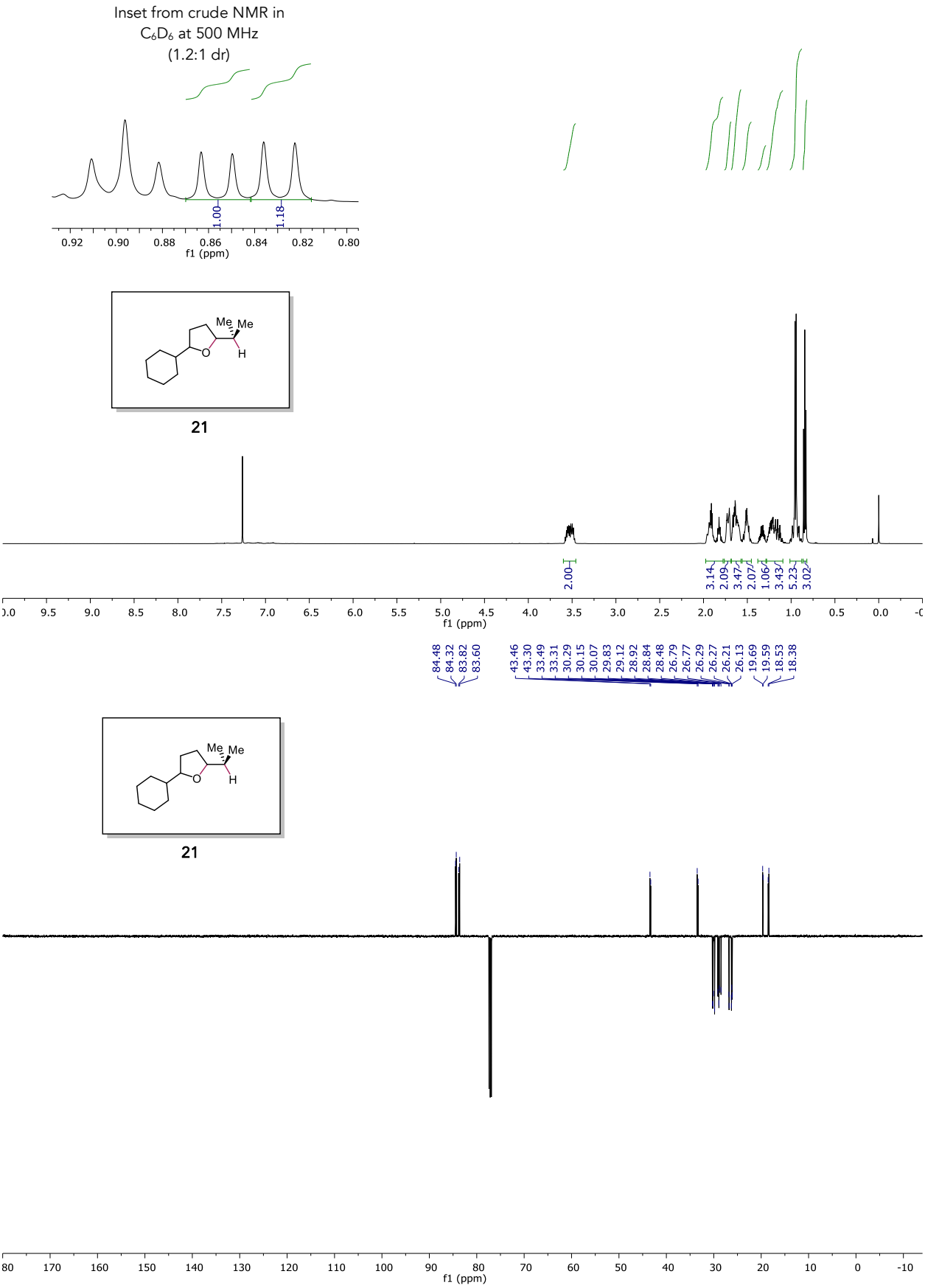


20

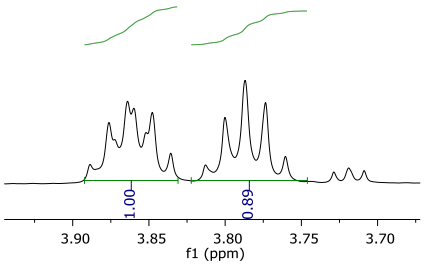


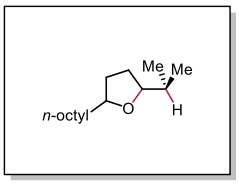


20

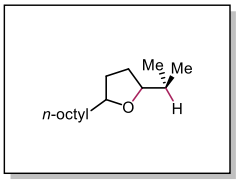

Inset from crude NMR in
C6D6 at 500 MHz
(1.2:1 dr)
1.00
1.18
f1 (ppm)
Me
Me
O
H
21
2.00
3.14
2.09
3.47
2.07
1.06
3.43
5.23
3.02
f1 (ppm)
84.48
84.32
83.82
83.60
43.46
43.30
33.49
33.31
30.29
30.15
30.07
29.83
29.12
28.92
28.84
28.48
26.79
26.77
26.29
26.27
26.21
26.13
19.69
19.59
18.53
18.38
Me
Me
O
H
21
f1 (ppm)

Inset from crude NMR in $CDCl_3$ at 500 MHz (1.1:1 dr)

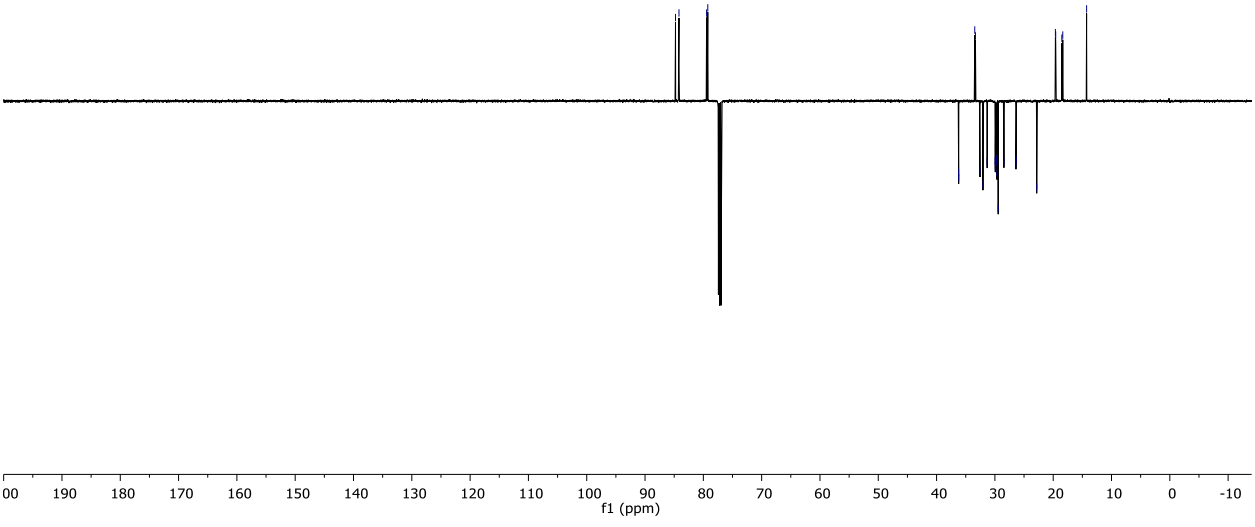


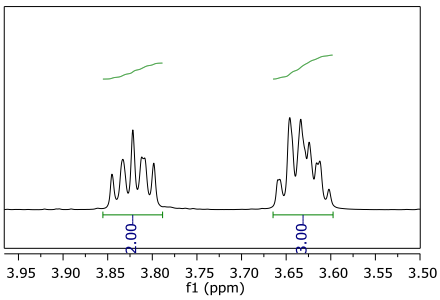


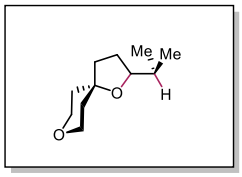
22



22



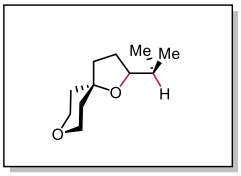

2.00
3.00
3.95 3.90 3.85 3.80 3.75 3.70 3.65 3.60 3.55 3.50
f1 (ppm)


Me
Me
H
O
O

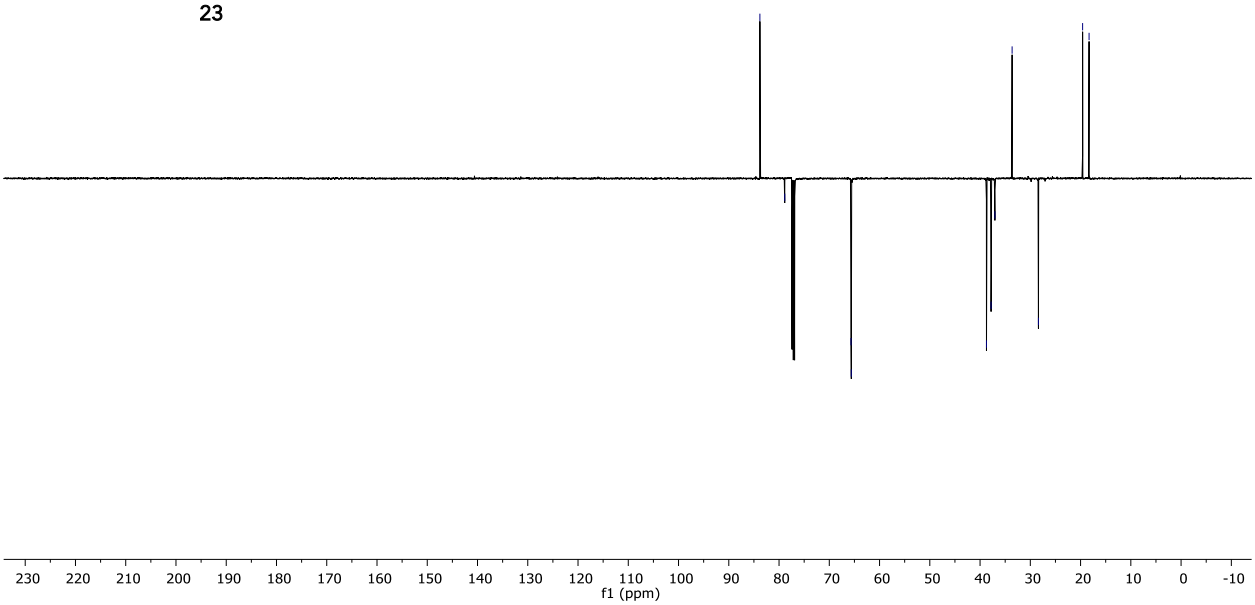
23

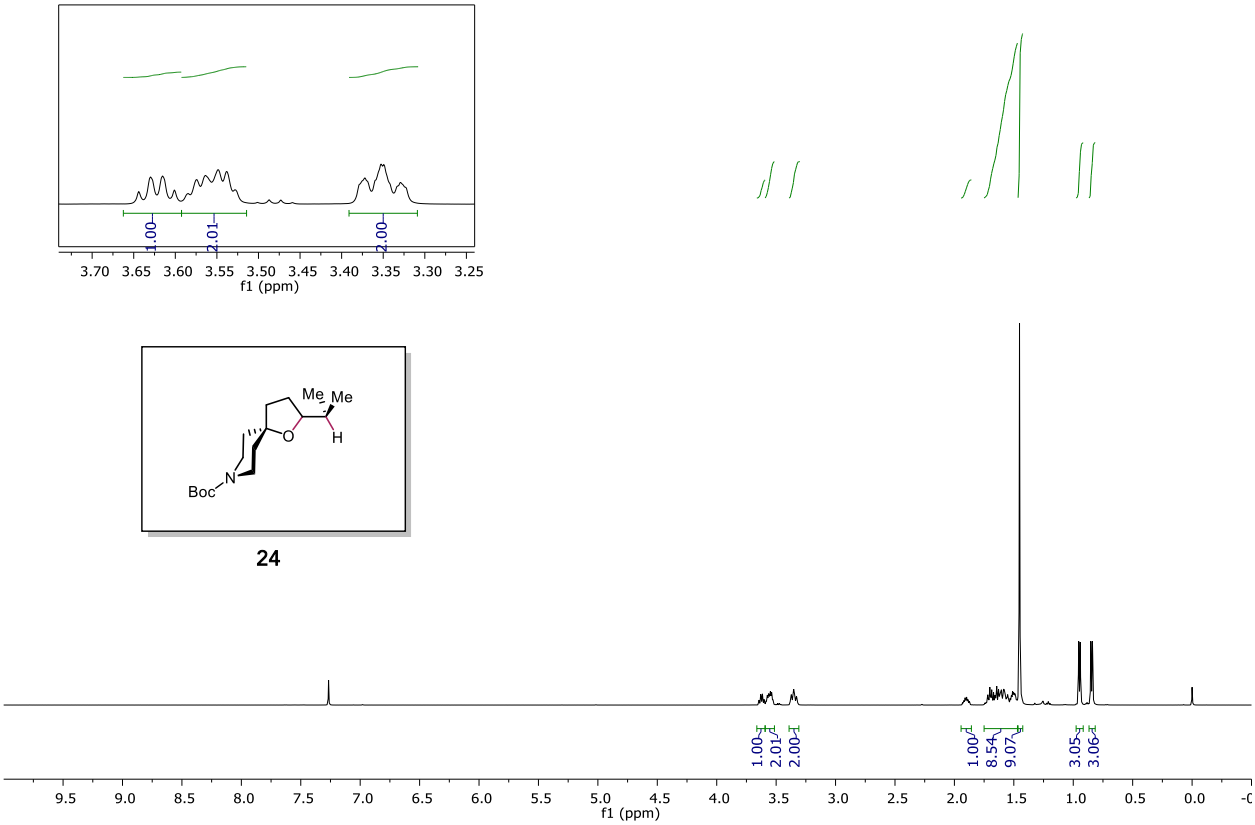
2.00
3.00
1.00
2.08
6.04
3.00
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


83.81
78.87
65.68
65.62
38.72
37.81
37.05
33.62
28.38
19.59
18.31

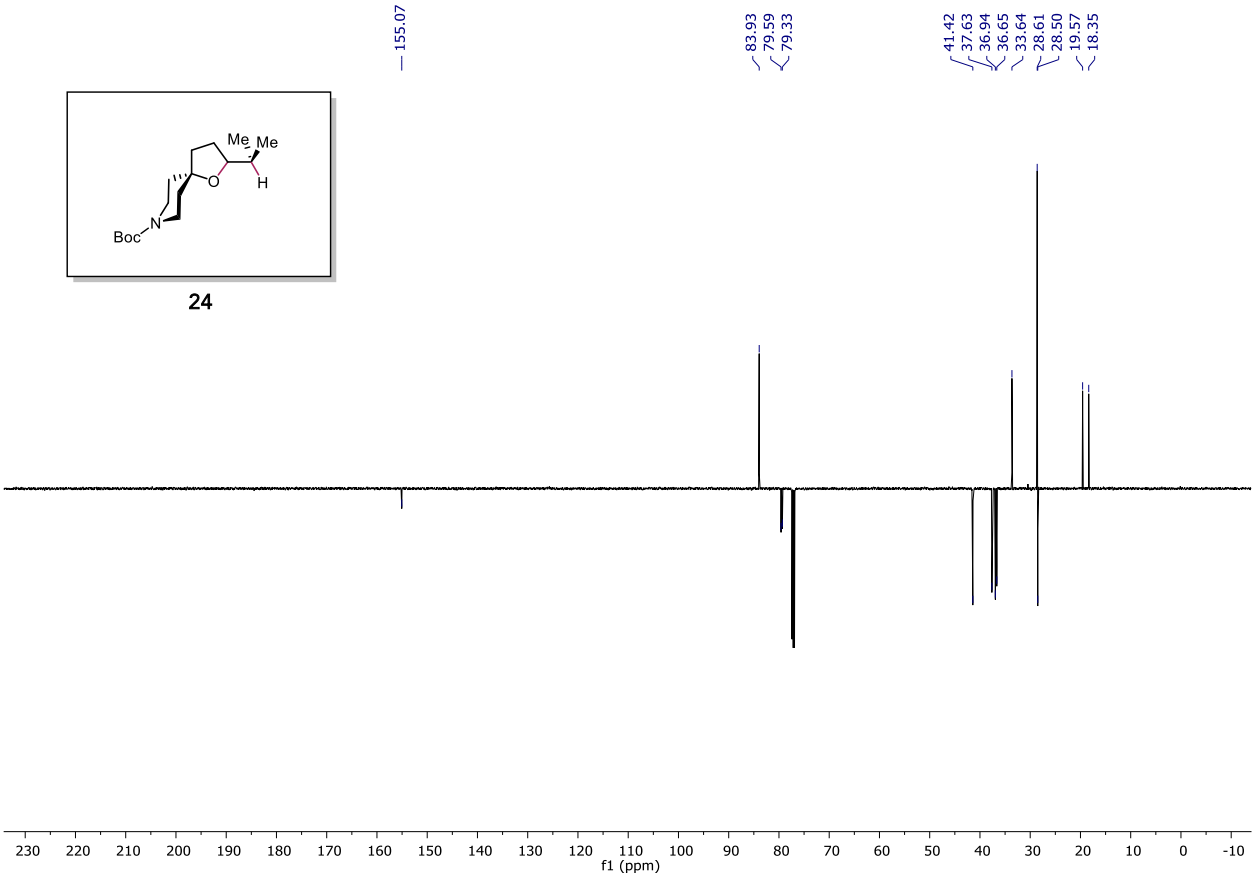

Me
Me
H
O
O

23


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

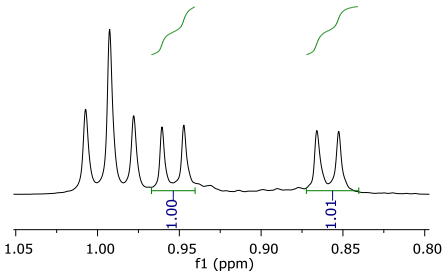

1.00
2.01
2.00
3.70 3.65 3.60 3.55 3.50 3.45 3.40 3.35 3.30 3.25
f1 (ppm)
Me
Me
H
O
N
Boc
1.00
2.01
2.00
1.00
8.54
9.07
3.05
3.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

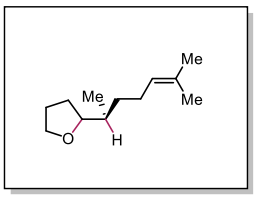
24


155.07
83.93
79.59
79.33
41.42
37.63
36.94
36.65
33.64
28.61
28.50
19.57
18.35
Me
Me
H
O
N
Boc
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

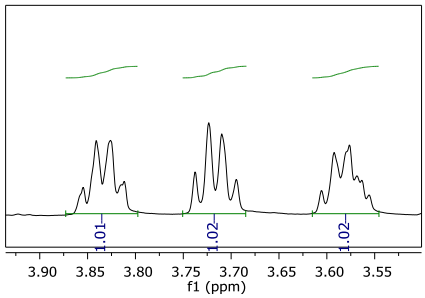
24

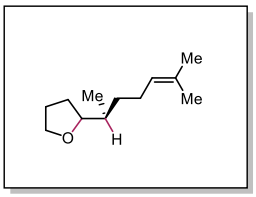
Inset from crude NMR in $CDCl_3$ at 500 MHz (1:1 dr)





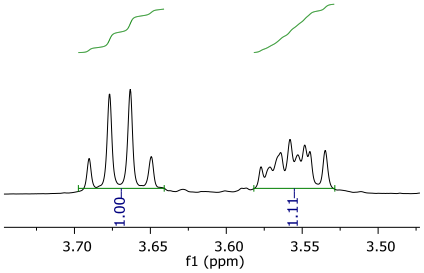
25

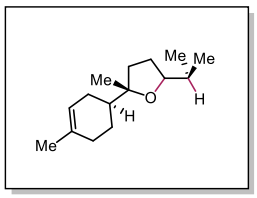




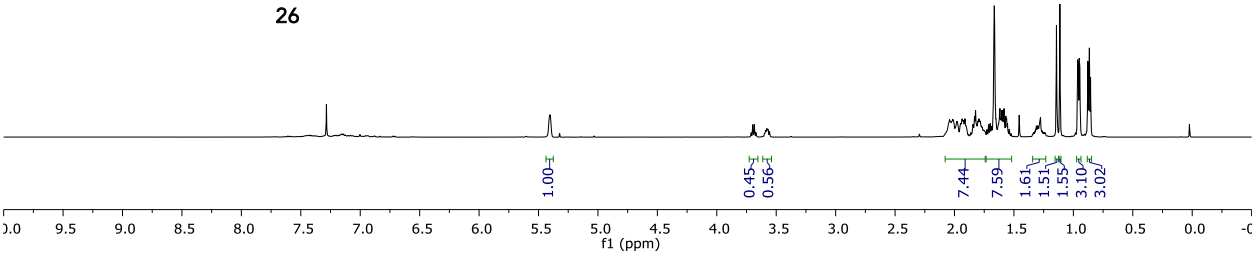
25

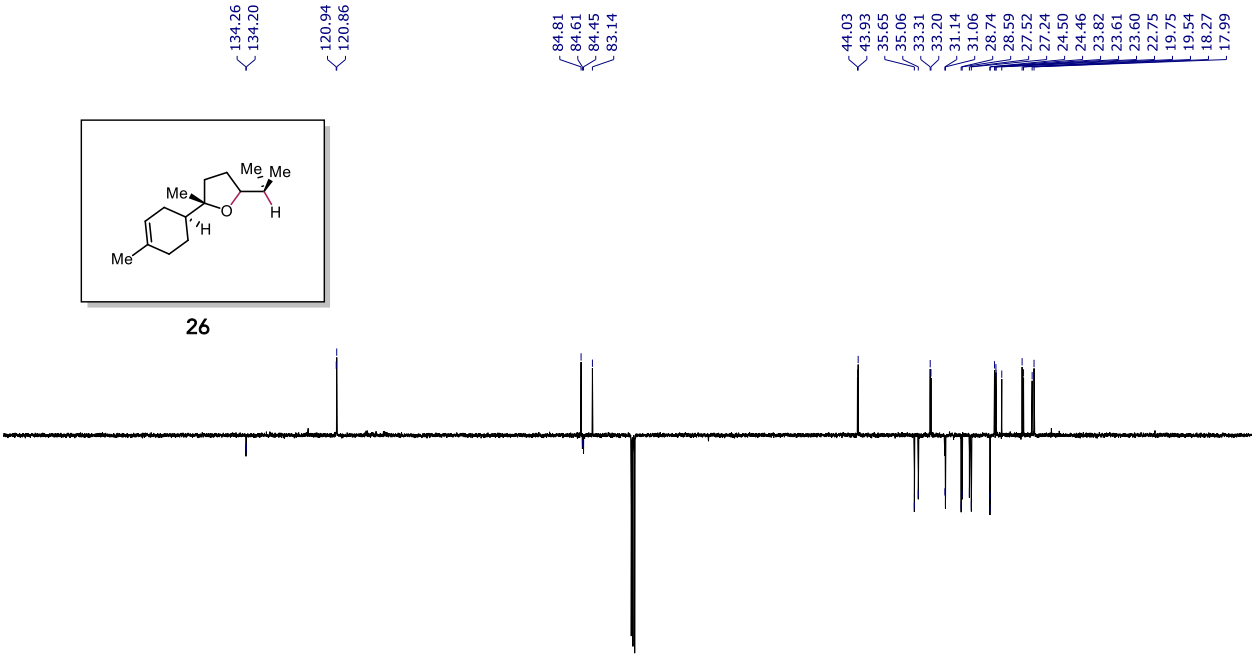
Inset from crude NMR in $CDCl_3$ at 500 MHz (1.1:1 dr)





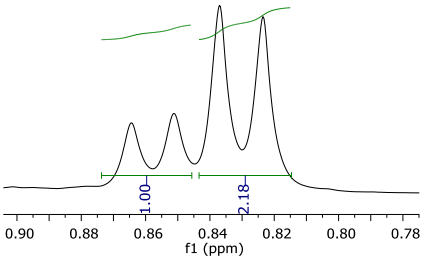
26

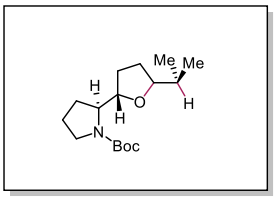




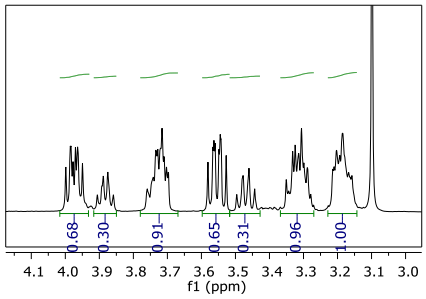
26

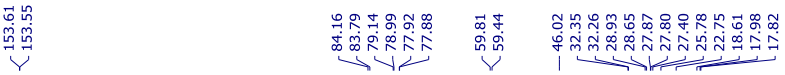
Inset from crude NMR in $CDCl_3$ at 500 MHz (2:1 dr)

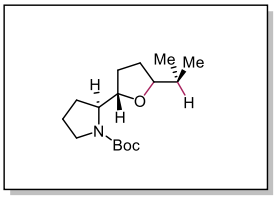




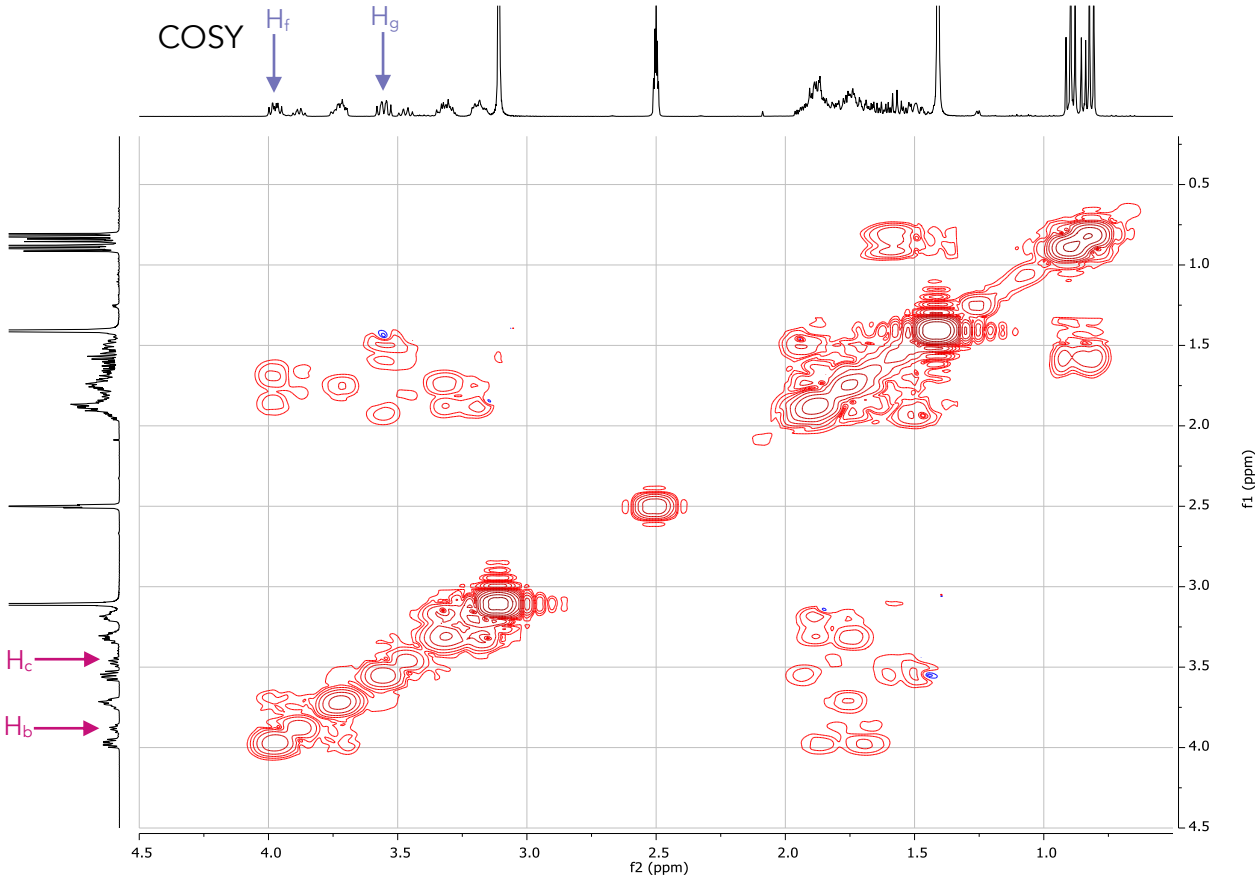
27

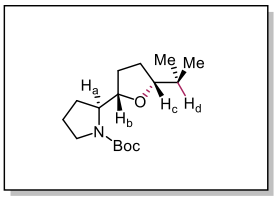




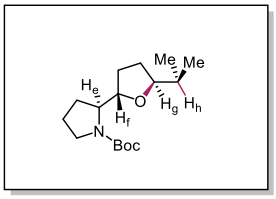


27

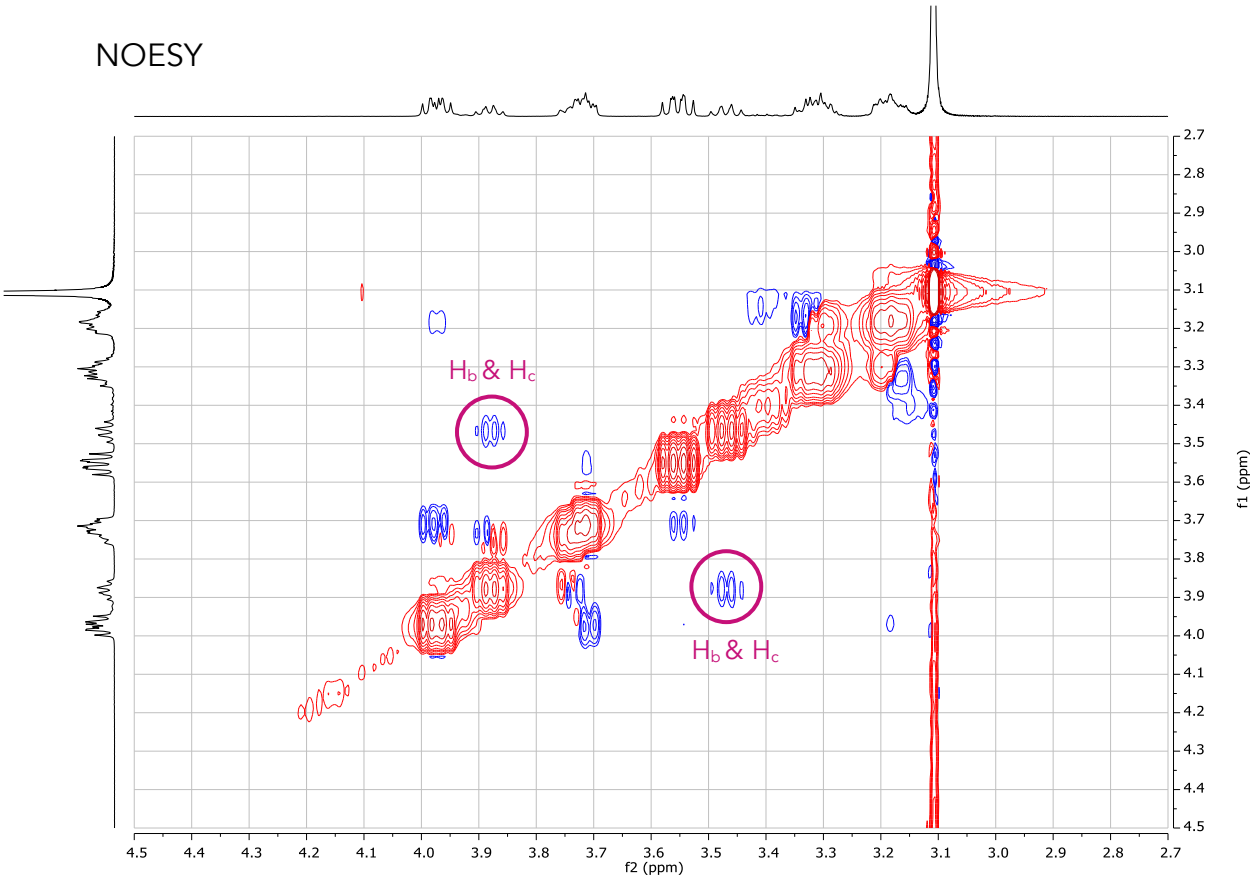


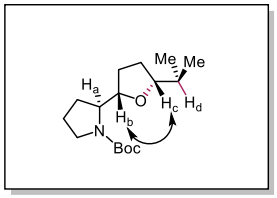


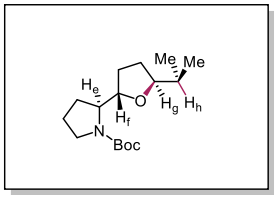
Minor Diastereomer



Major Diastereomer



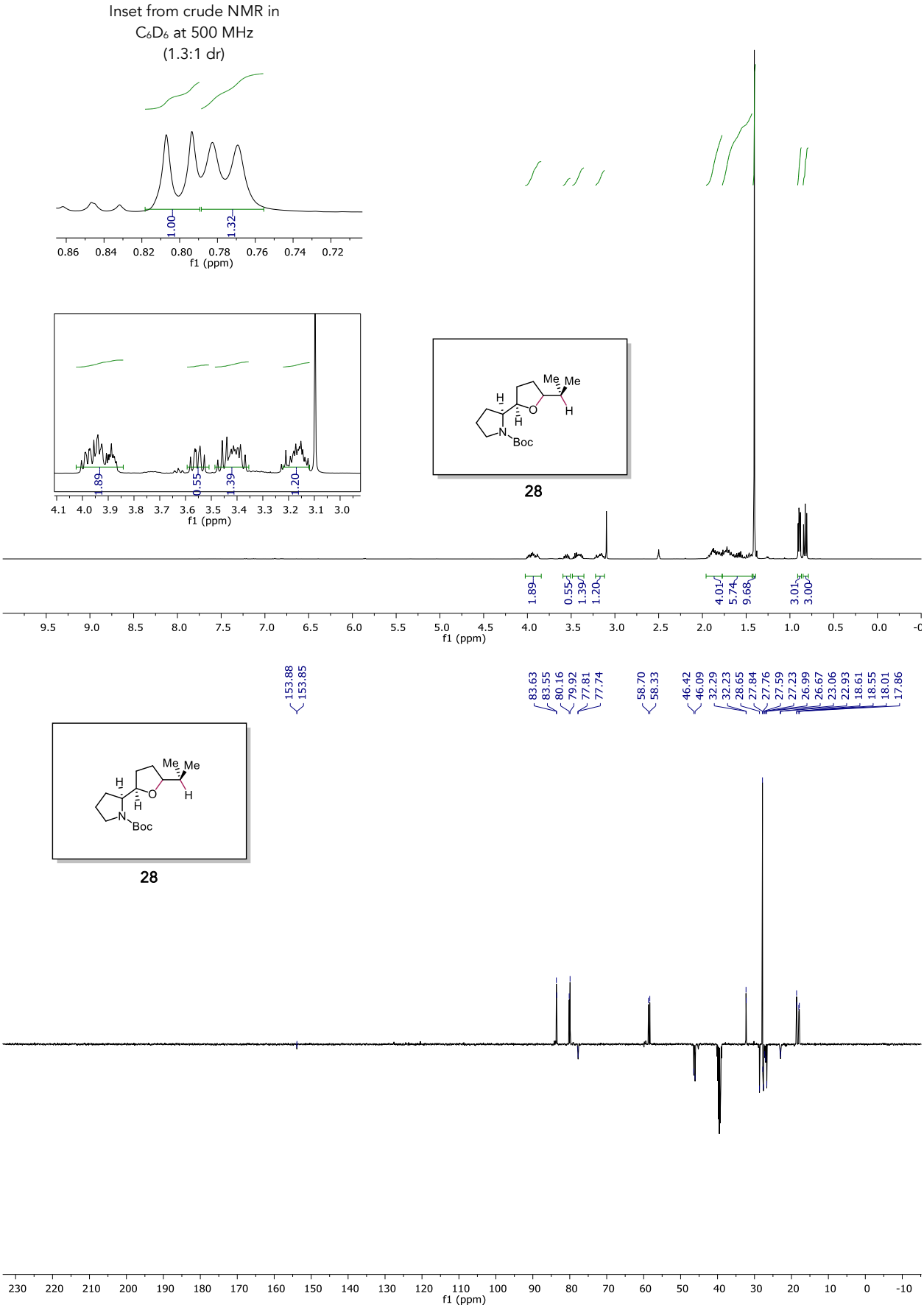


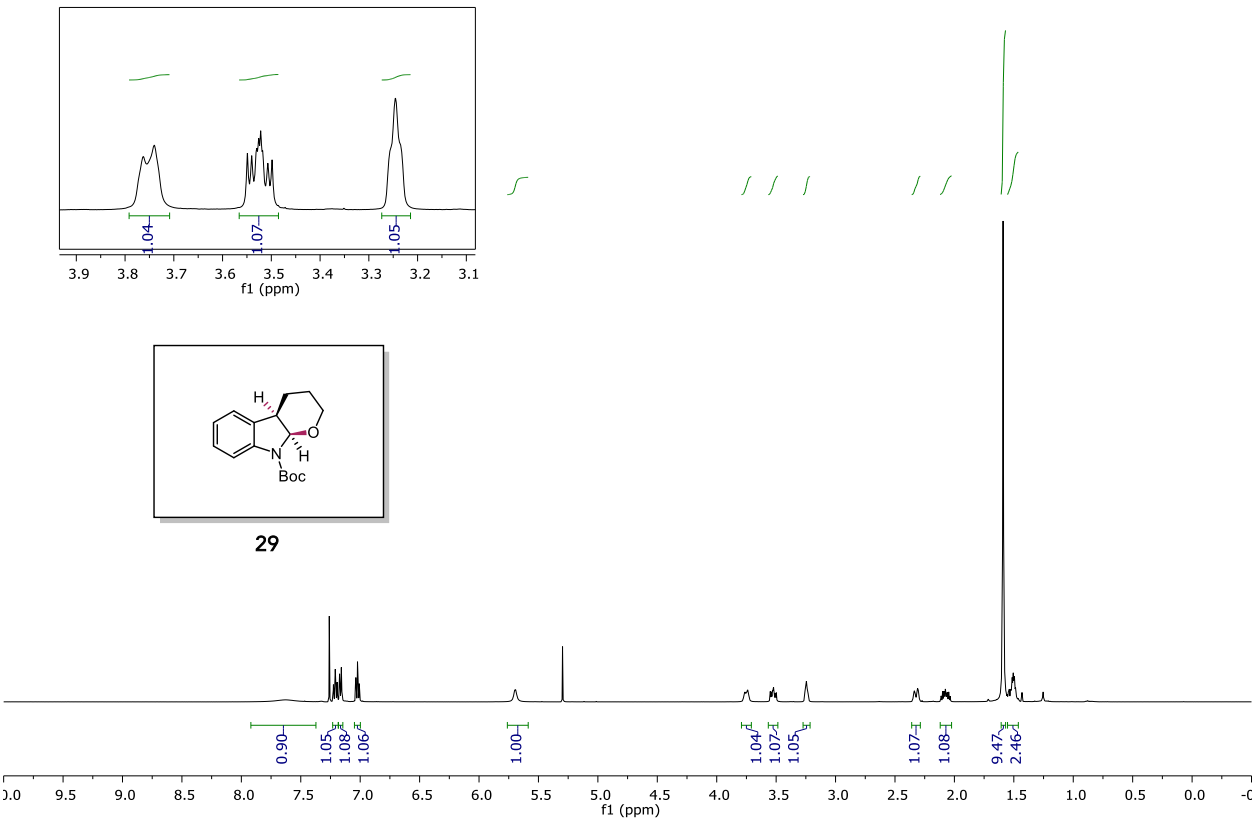


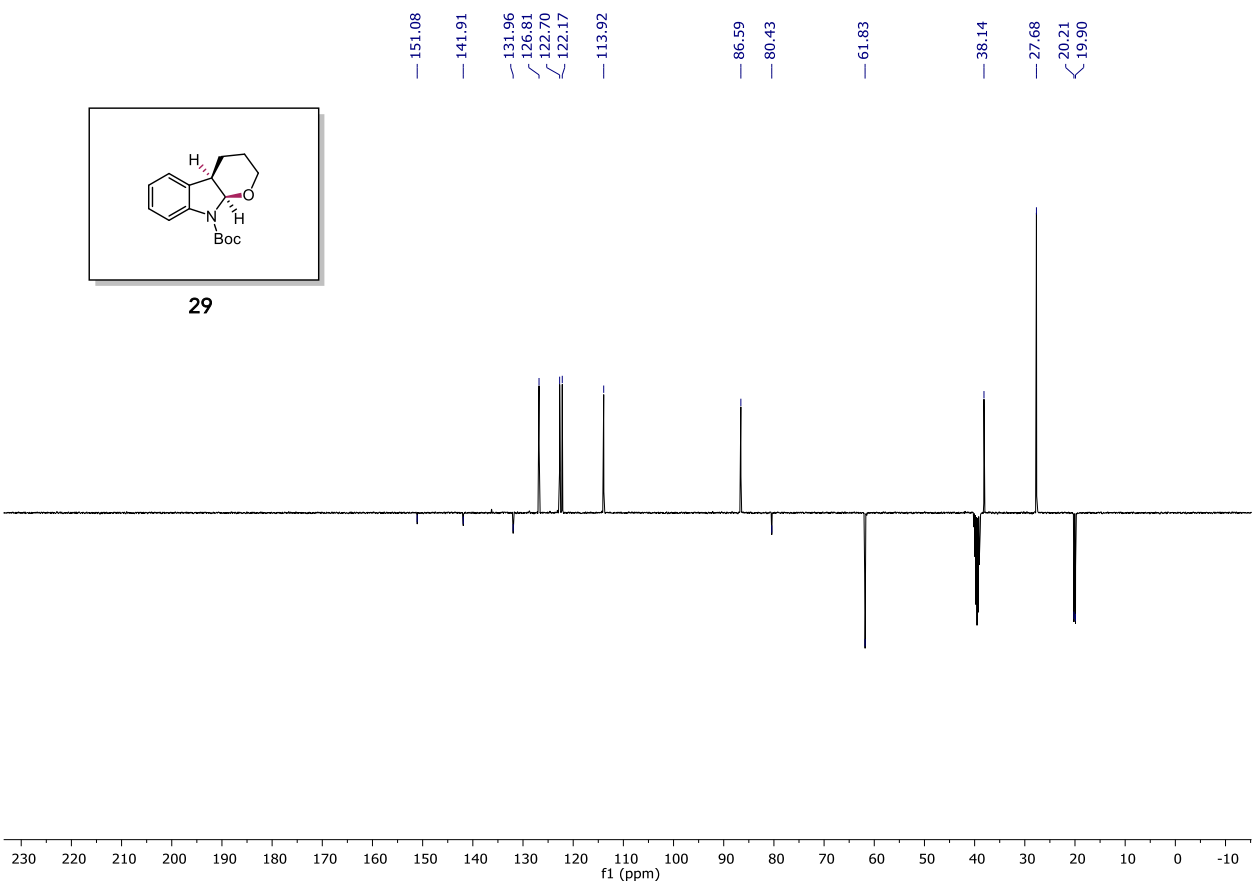
Minor Diastereomer

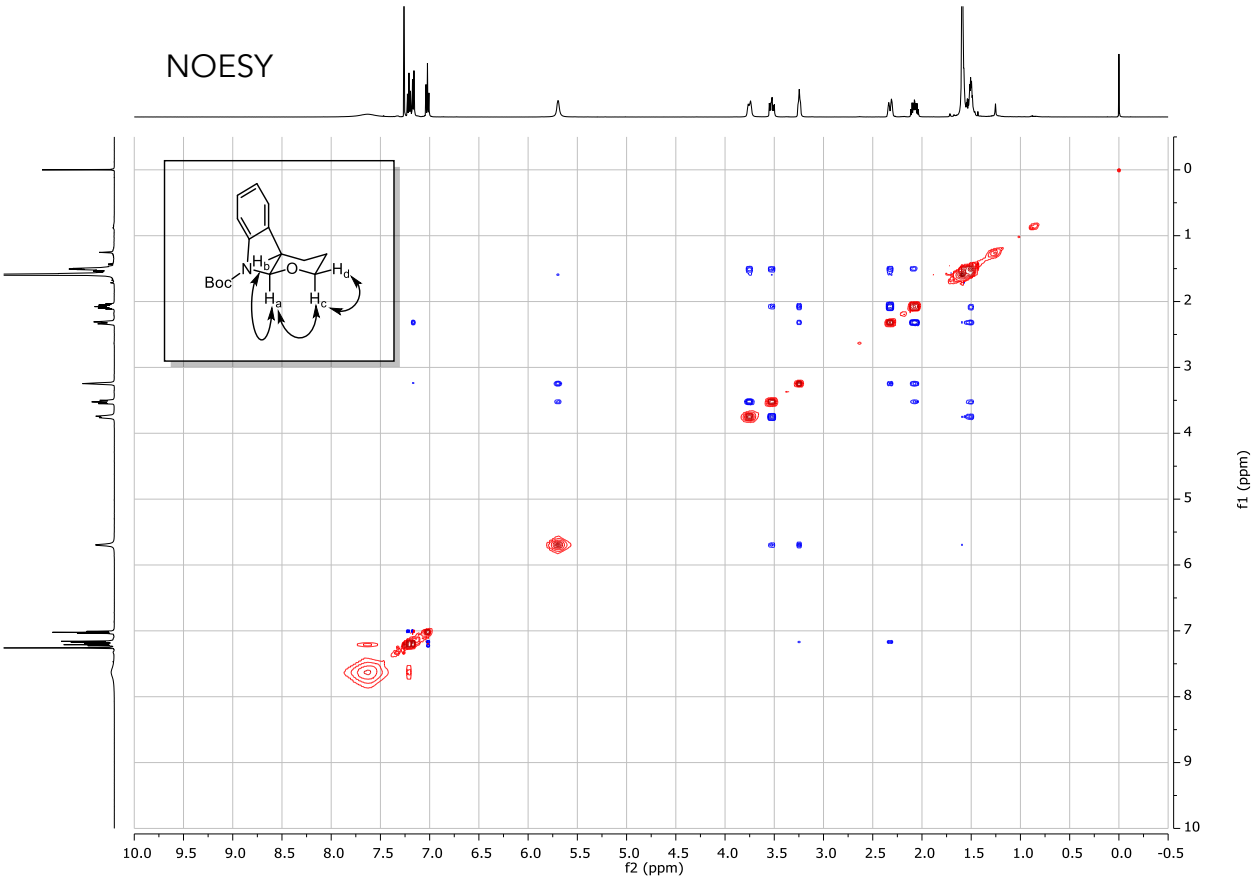
Major Diastereomer

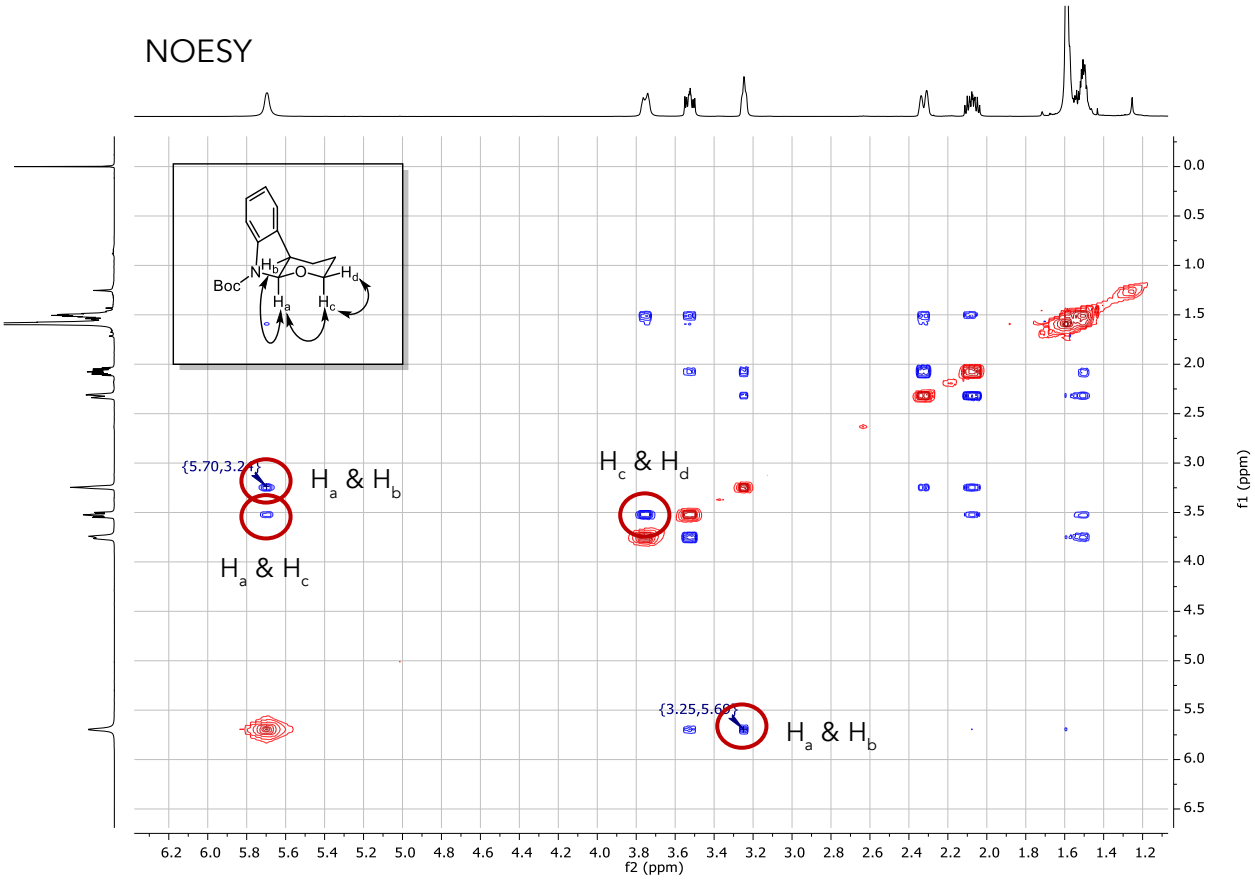
H_b is observed to have an NOE with H_c, whereas no significant NOE is observed between H_f and H_g. This suggests that the minor diastereomer has H_b and H_c *syn* to each other, and the major diastereomer has H_f and H_g *anti* to each other.

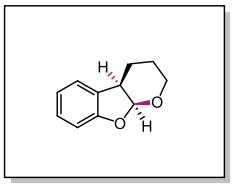

Inset from crude NMR in
C6D6 at 500 MHz
(1.3:1 dr)
1.00
1.32
0.86 0.84 0.82 0.80 0.78 0.76 0.74 0.72
f1 (ppm)
1.89
0.55
1.39
1.20
4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0
f1 (ppm)
Me
Me
H
O
H
H
N
Boc
28
1.89
0.55
1.39
1.20
4.01
5.74
9.68
3.01
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
153.88
153.85
83.63
83.55
80.16
79.92
77.81
77.74
58.70
58.33
46.42
46.09
32.29
32.23
28.65
27.84
27.76
27.59
27.23
26.99
26.67
23.06
22.93
18.61
18.55
18.01
17.86
Me
Me
H
O
H
H
N
Boc
28
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


1.04
1.07
1.05
f1 (ppm)
H
O
N
H
Boc
29
0.90
1.05
1.08
1.06
1.00
1.04
1.07
1.05
1.07
1.08
9.47
2.46
f1 (ppm)

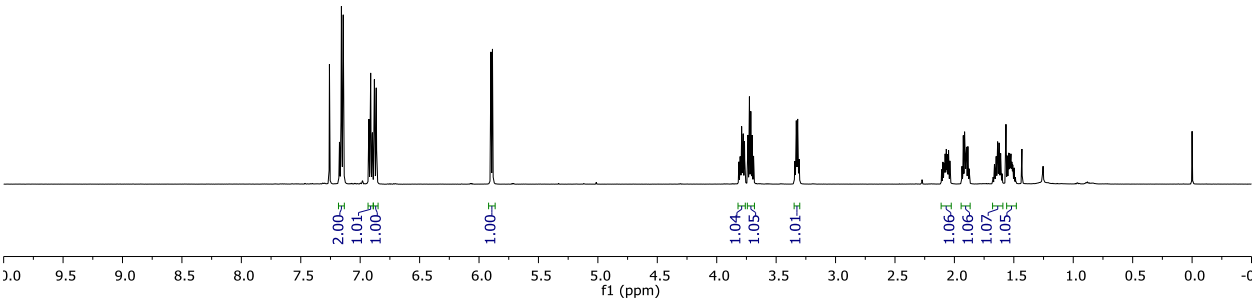

151.08
141.91
131.96
126.81
122.70
122.17
113.92
86.59
80.43
61.83
38.14
27.68
20.21
19.90
H
O
N
H
Boc
29
f1 (ppm)

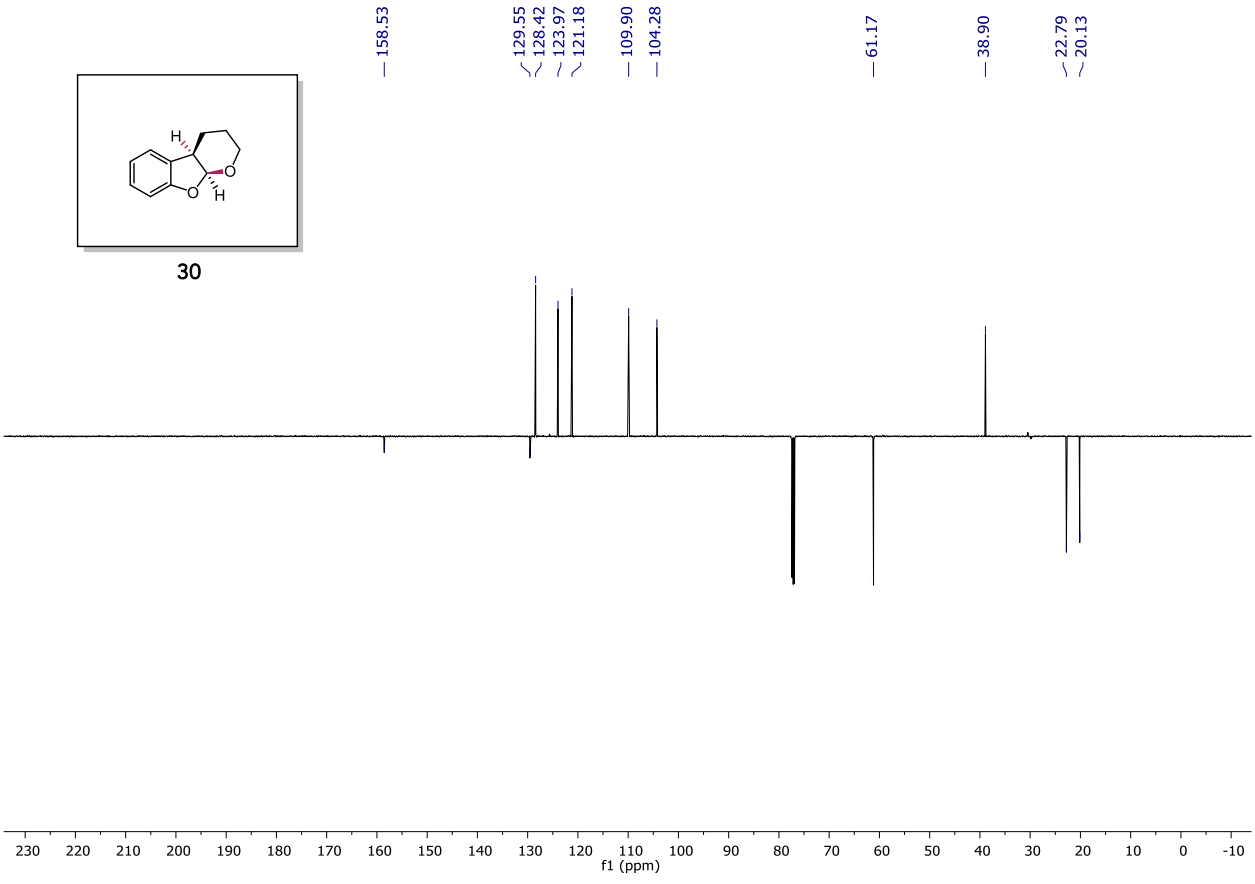

NOESY
Boc
N
O
H_a
H_b
H_c
H_d
f2 (ppm)
f1 (ppm)


NOESY
Boc
N
O
H_a
H_b
H_c
H_d
{5.70,3.21}
H_a & H_b
H_a & H_c
H_c & H_d
{3.25,5.69}
H_a & H_b
f2 (ppm)
f1 (ppm)

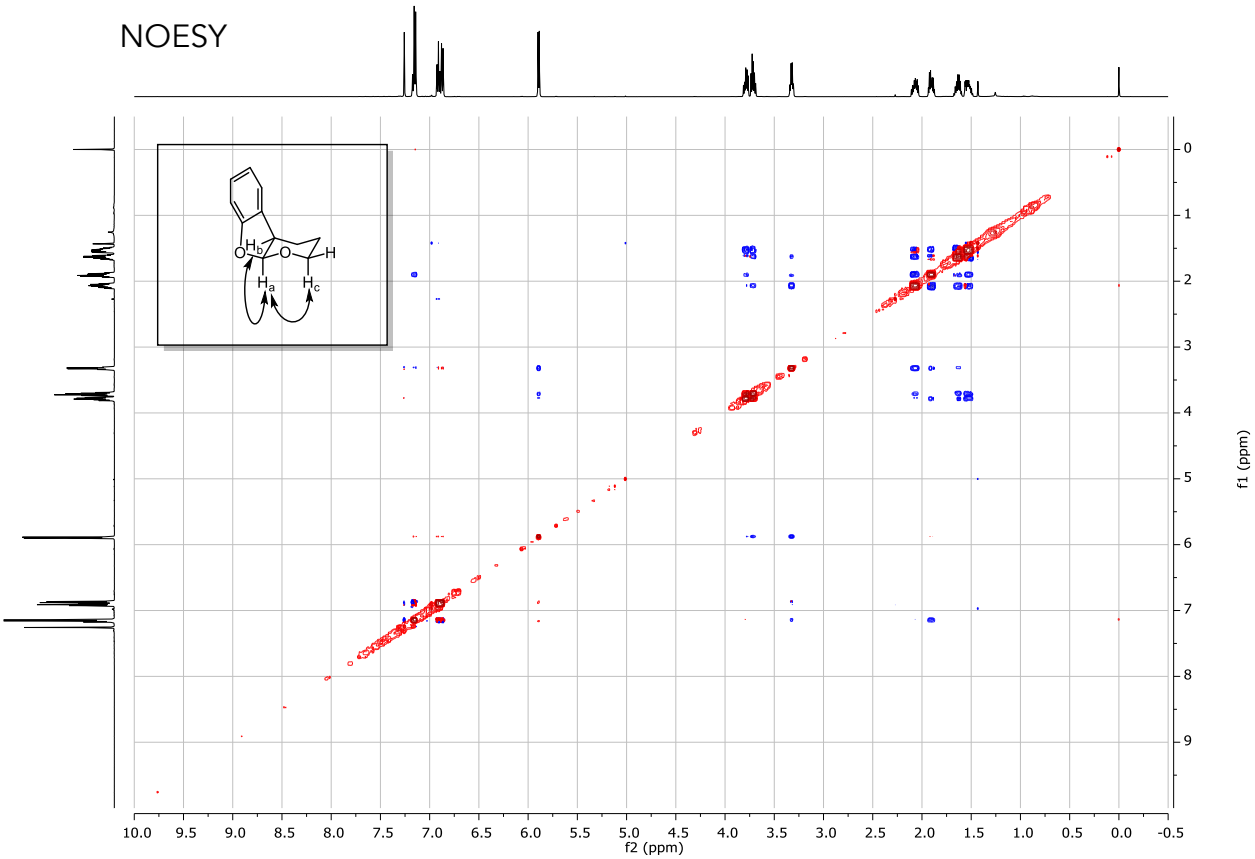


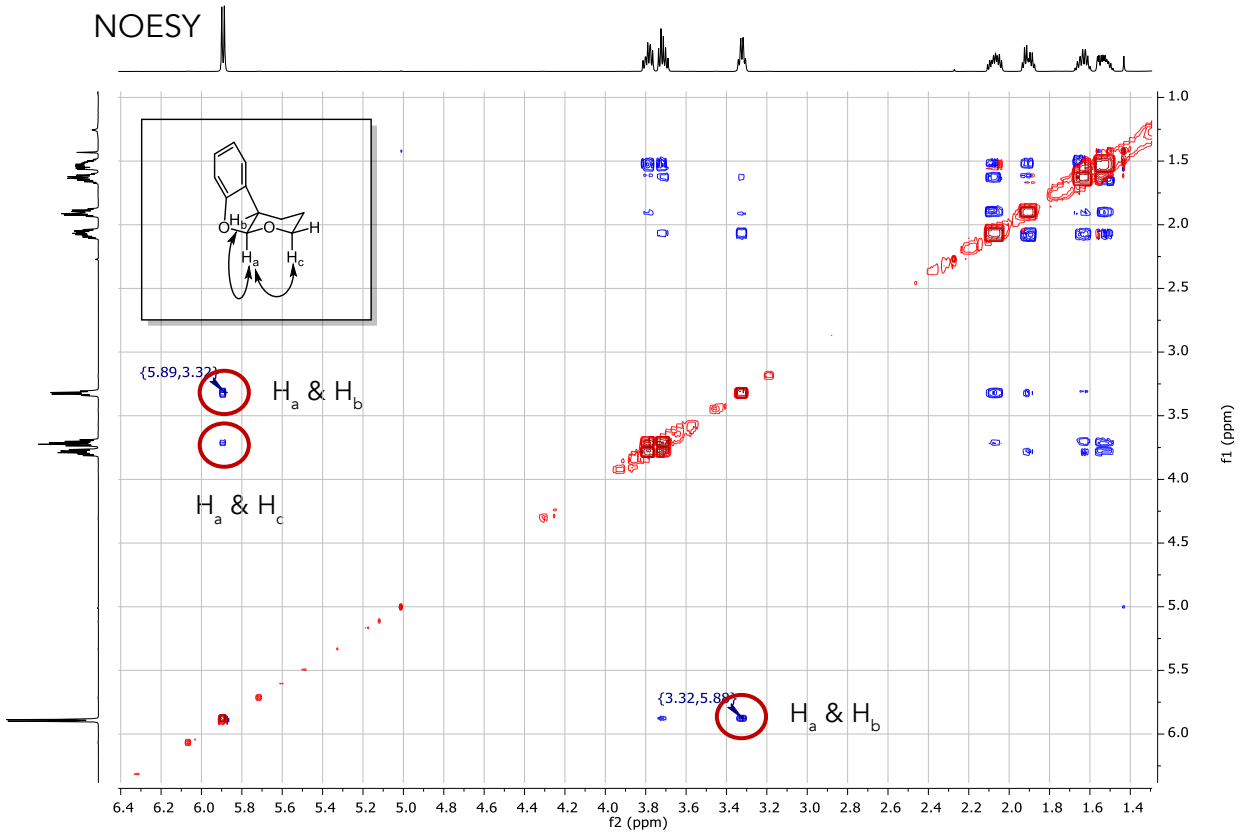
30

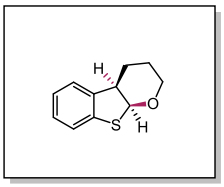

2.00
1.01
1.00
1.00
1.04
1.05
1.01
1.06
1.06
1.07
1.05
f1 (ppm)


158.53
129.55
128.42
123.97
121.18
109.90
104.28
61.17
38.90
22.79
20.13
f1 (ppm)

30

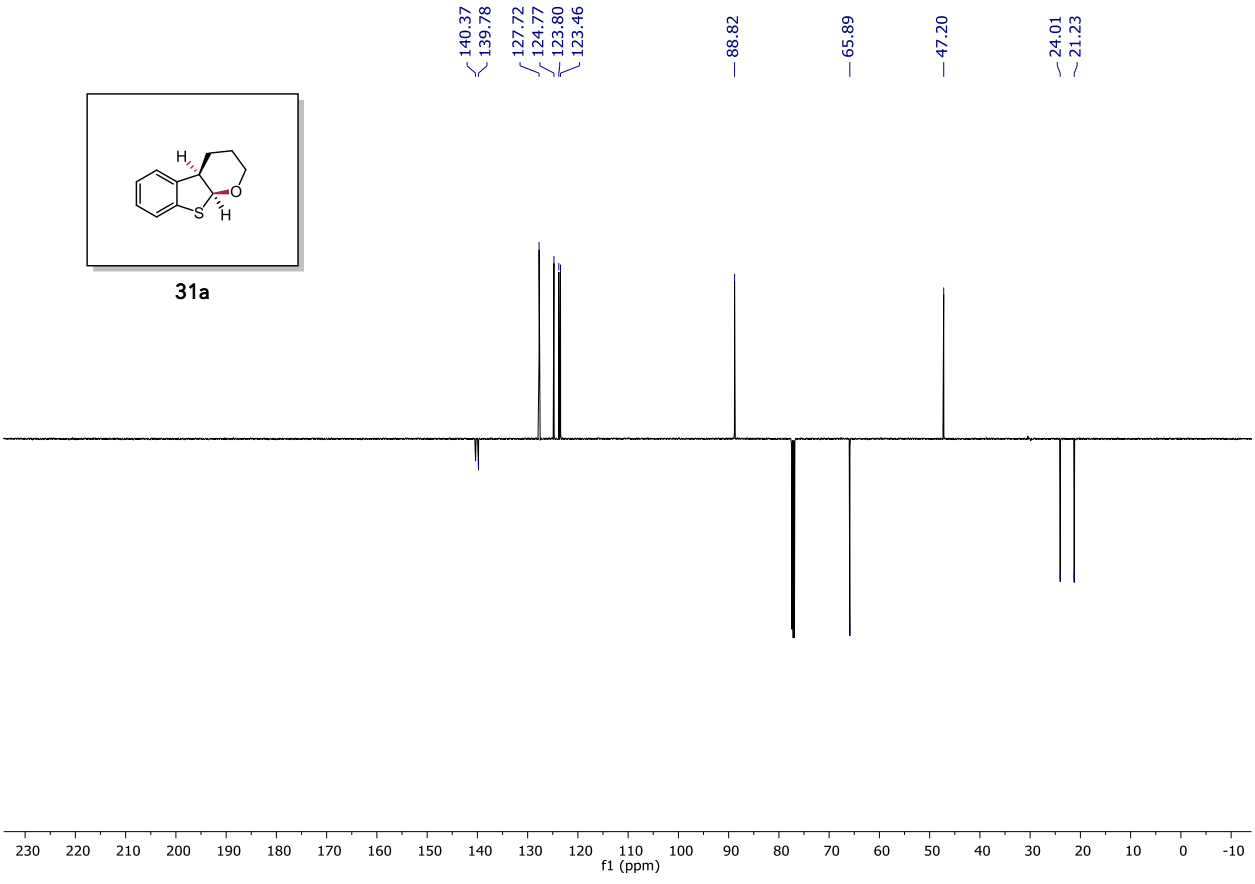

NOESY
f2 (ppm)
f1 (ppm)


NOESY
{5.89,3.32}
Ha & Hb
Ha & Hc
{3.32,5.89}
Ha & Hb
f2 (ppm)
f1 (ppm)

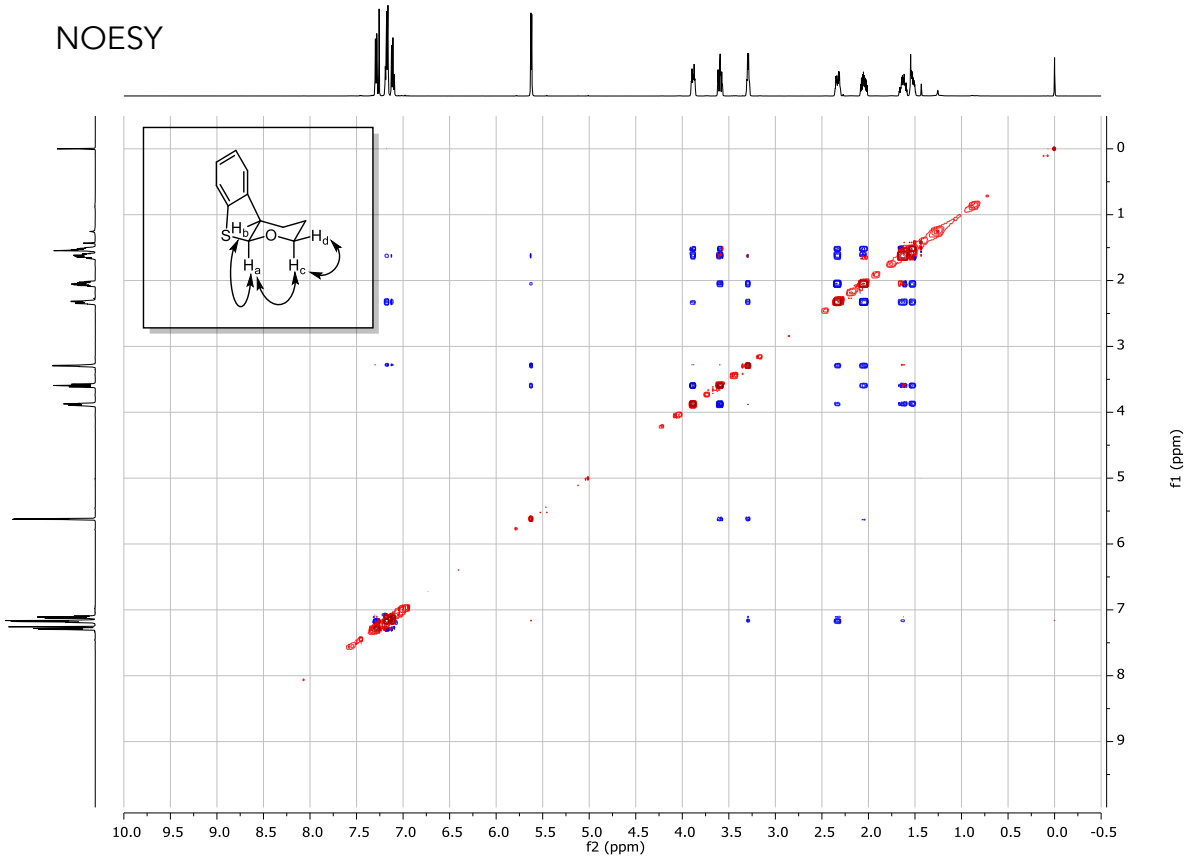


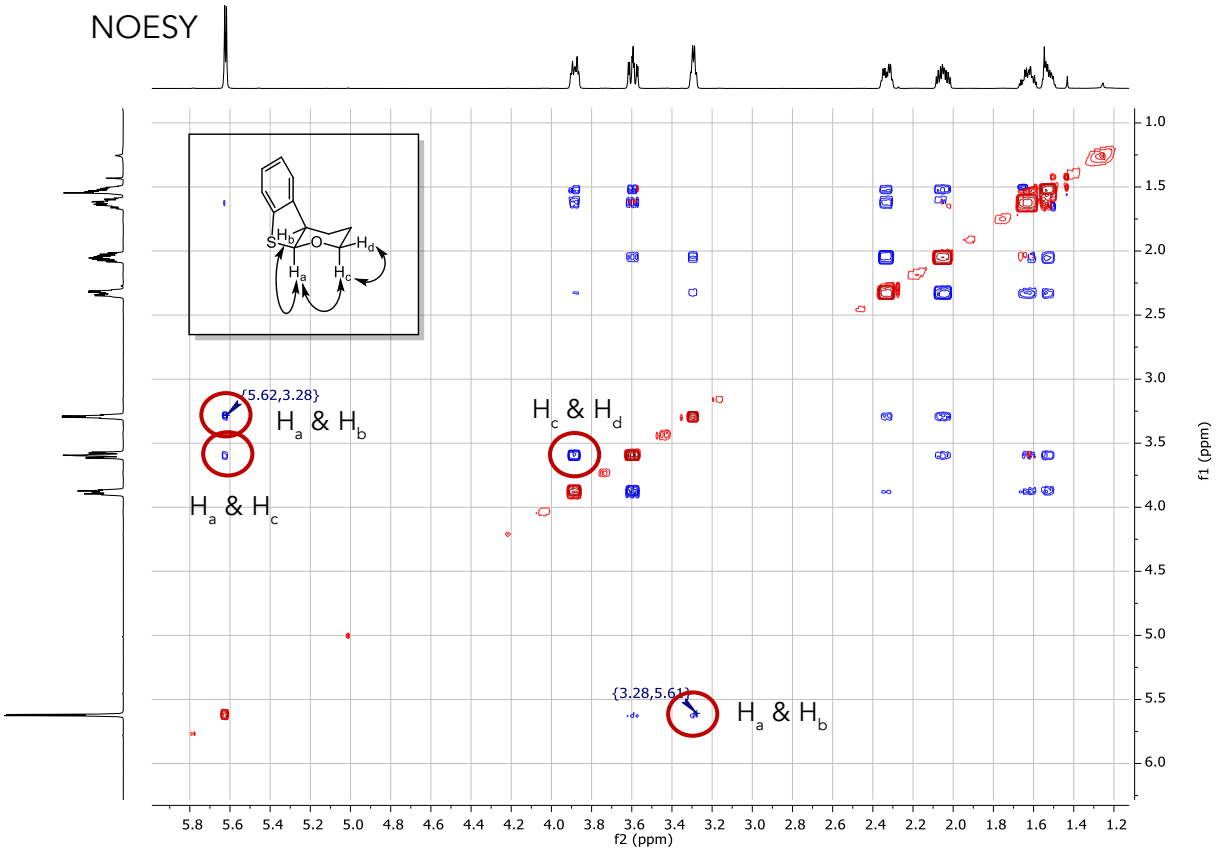
31a

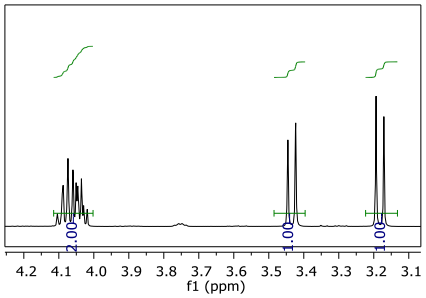
1.00
2.02
1.01
1.00
1.03
1.04
1.01
1.05
1.05
1.06
0.98
f1 (ppm)

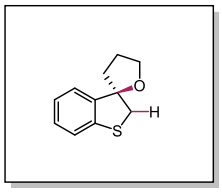

140.37
139.78
127.72
124.77
123.80
123.46
88.82
65.89
47.20
24.01
21.23
f1 (ppm)

31a

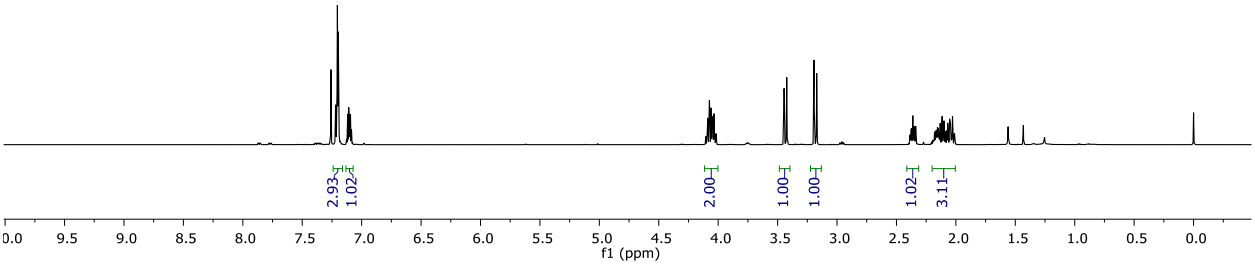

NOESY
f2 (ppm)
f1 (ppm)


NOESY
{5.62,3.28}
Ha & Hb
Ha & Hc
Hc & Hd
{3.28,5.61}
Ha & Hb
f2 (ppm)
f1 (ppm)

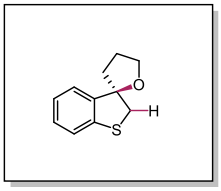

2.00
1.00
1.00
4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1
f1 (ppm)


O
H
S

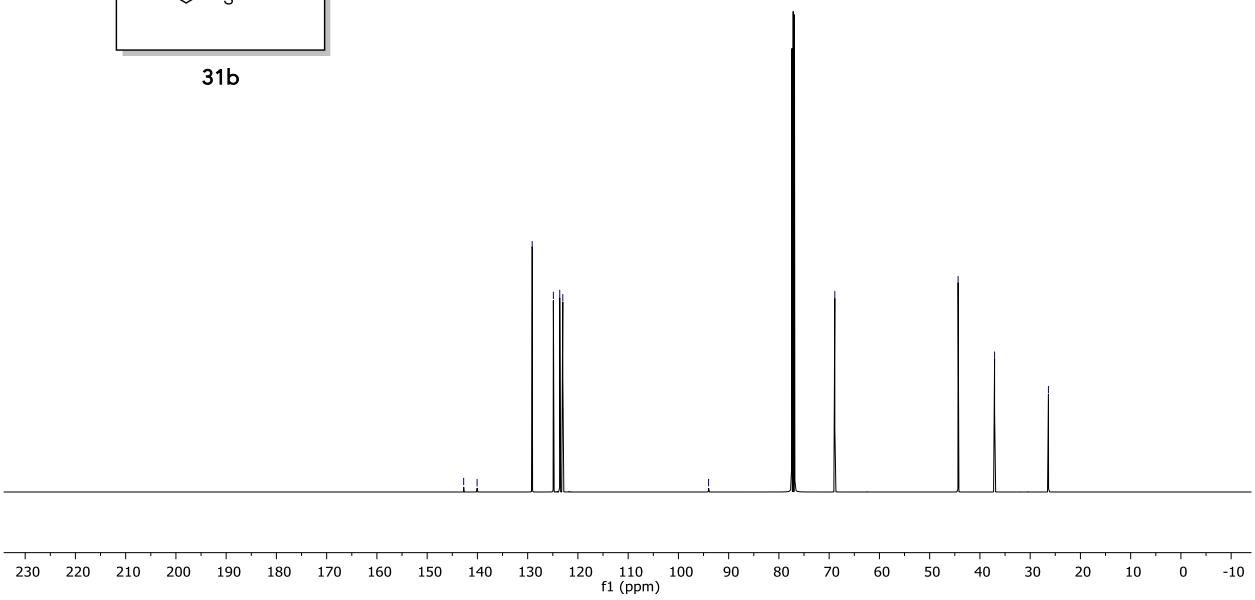
31b


2.93
1.02
2.00
1.00
1.00
1.02
3.11
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

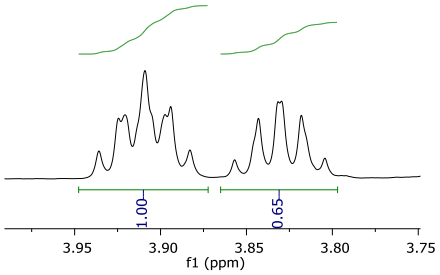

142.74
140.06
129.10
124.88
123.62
123.01
94.00
68.88
44.34
37.08
26.36

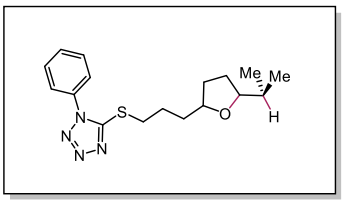

O
H
S

31b

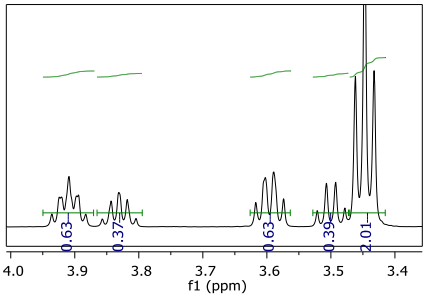

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

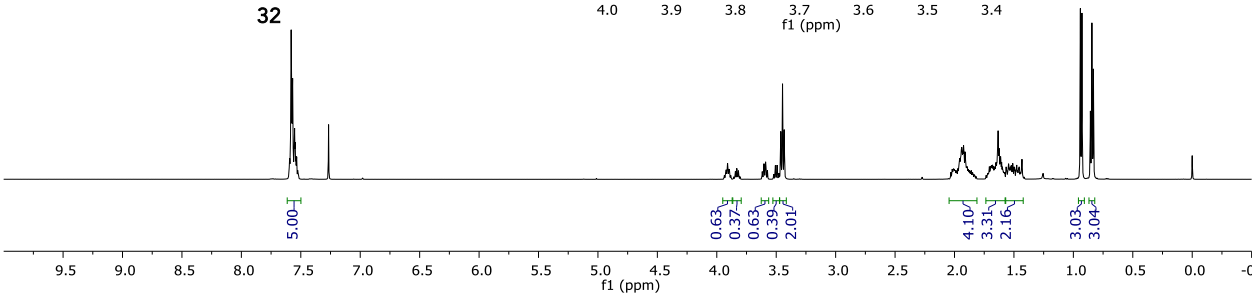
Inset from crude NMR in
$CDCl_3$ at 500 MHz
(1.5:1 dr)

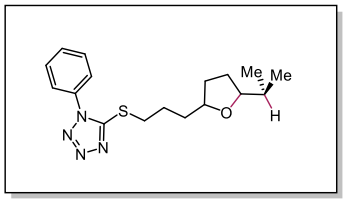




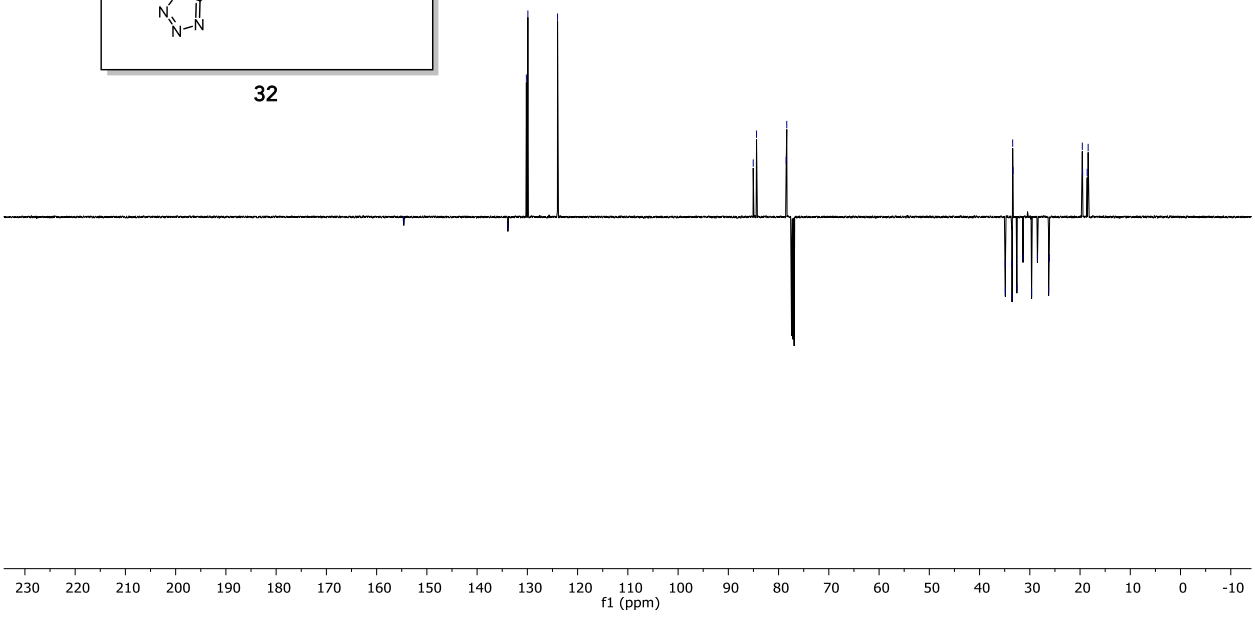
32



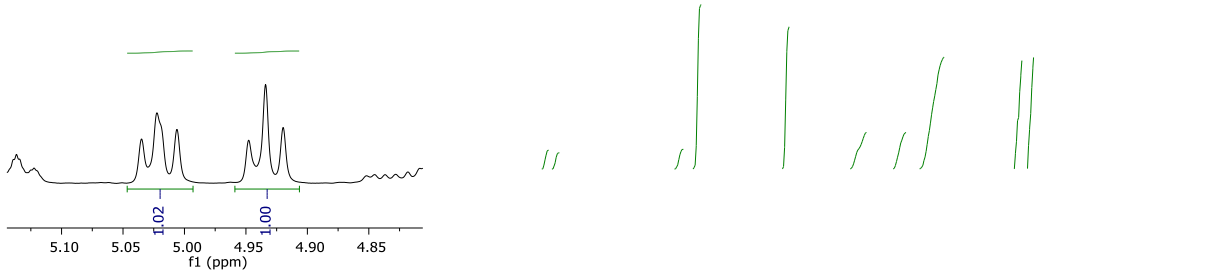


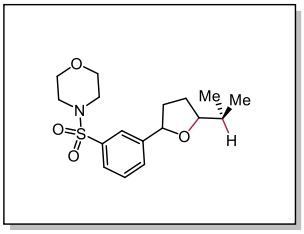


32

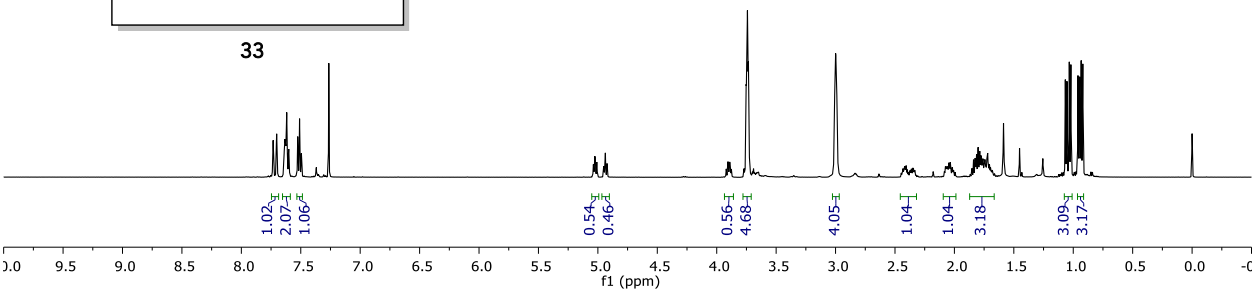


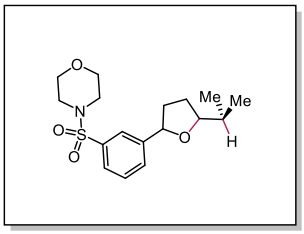
Inset from crude NMR in
$CDCl_3$ at 500 MHz
(1:1 dr)



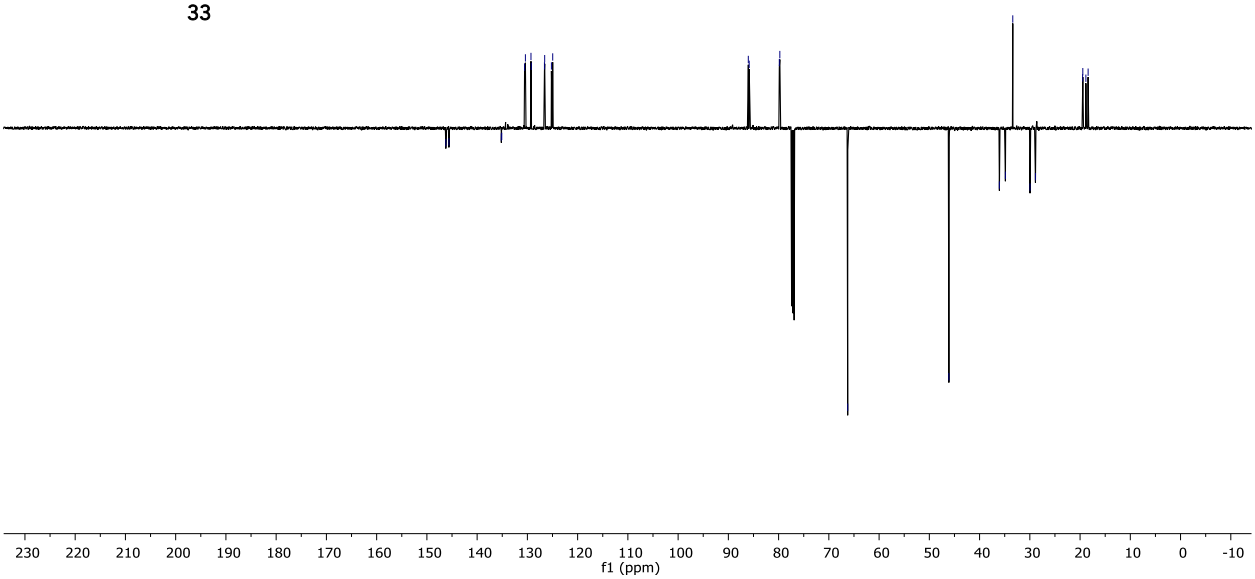


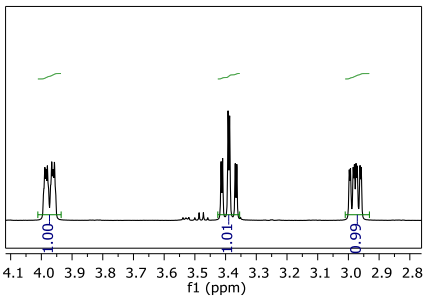
33

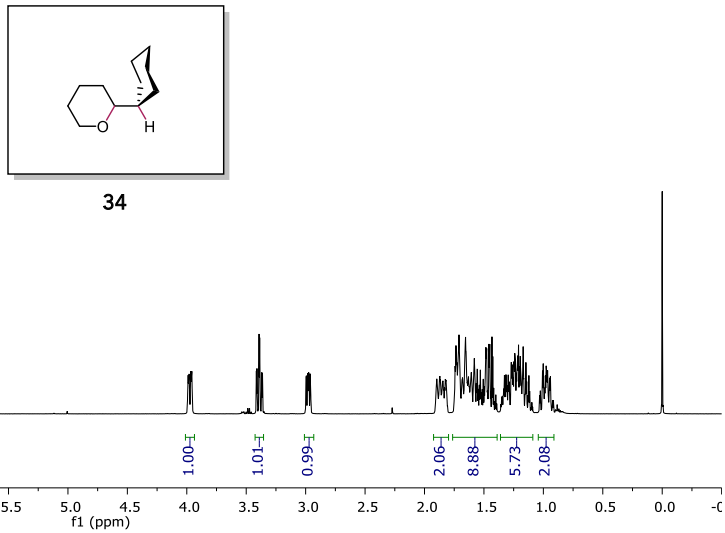




33



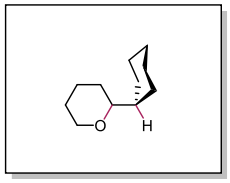

1.00
1.01
0.99
4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8
f1 (ppm)


O
H

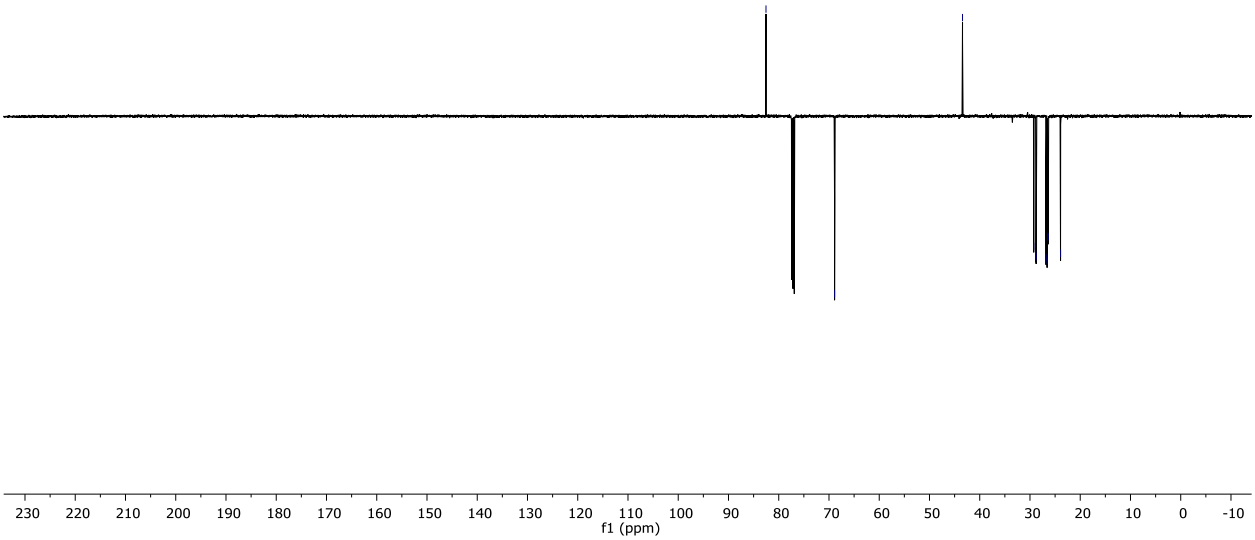
34

1.00
1.01
0.99
2.06
8.88
5.73
2.08
f1 (ppm)

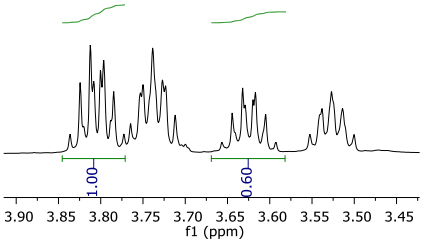

82.54
68.89
43.43
29.25
28.83
28.77
26.80
26.59
26.46
26.37
23.92

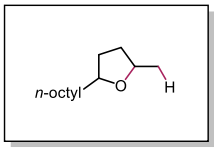

O
H

34

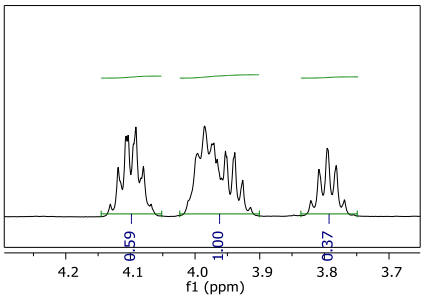

f1 (ppm)

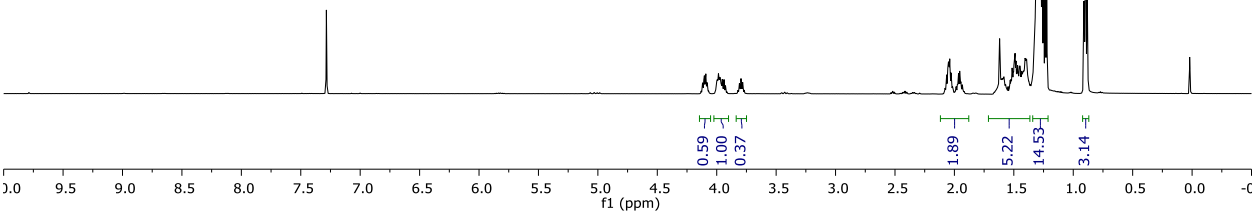
Inset from crude NMR in
C_6D_6 at 500 MHz
(1.7:1 dr)

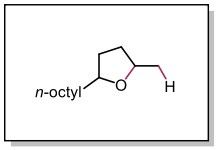




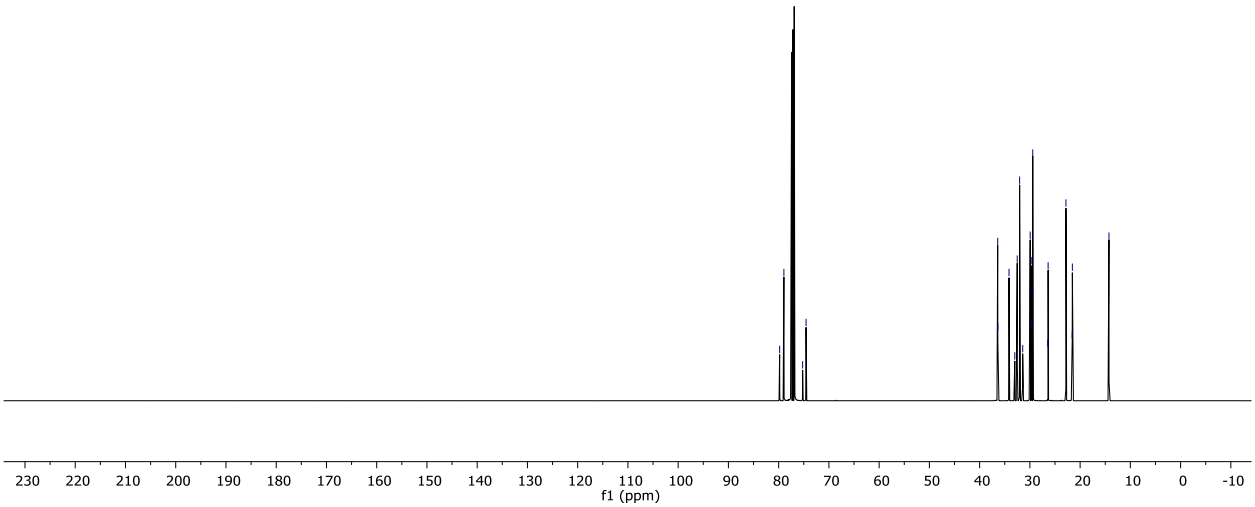
36

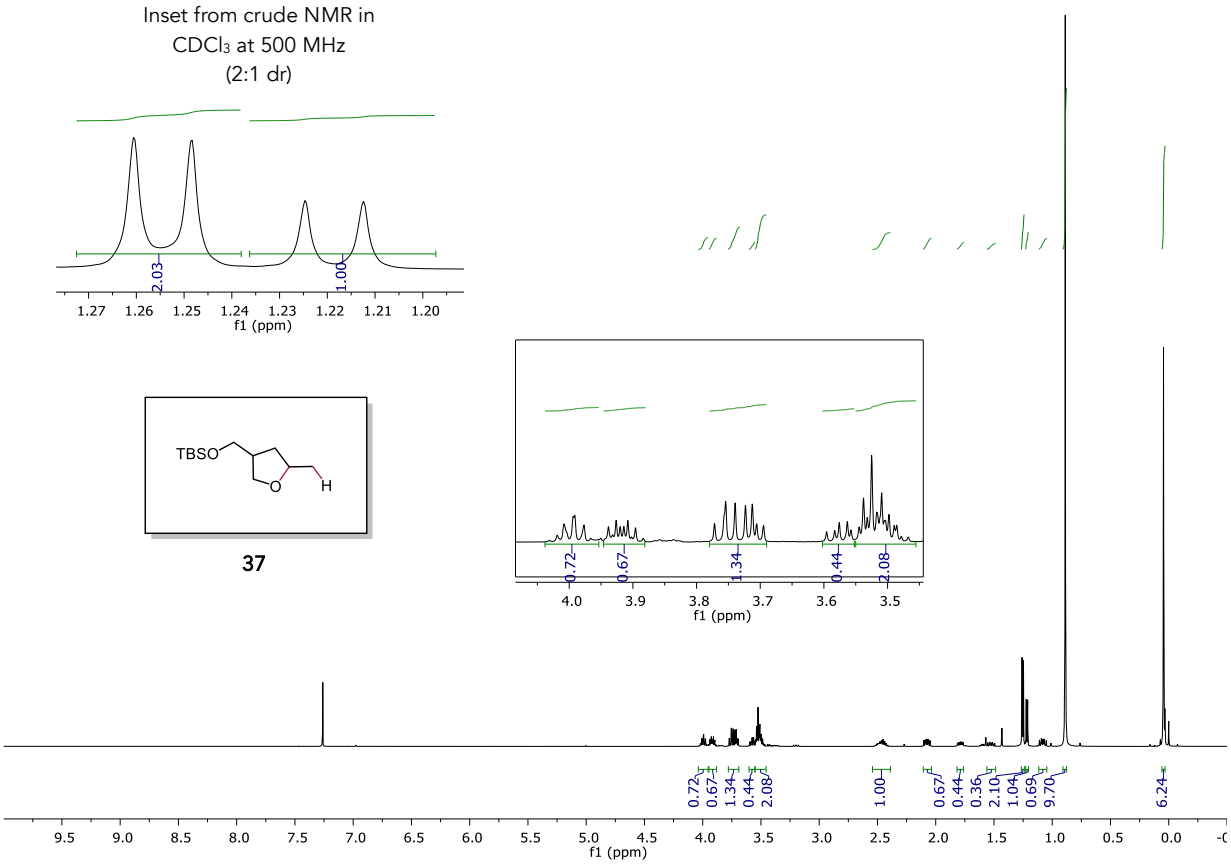


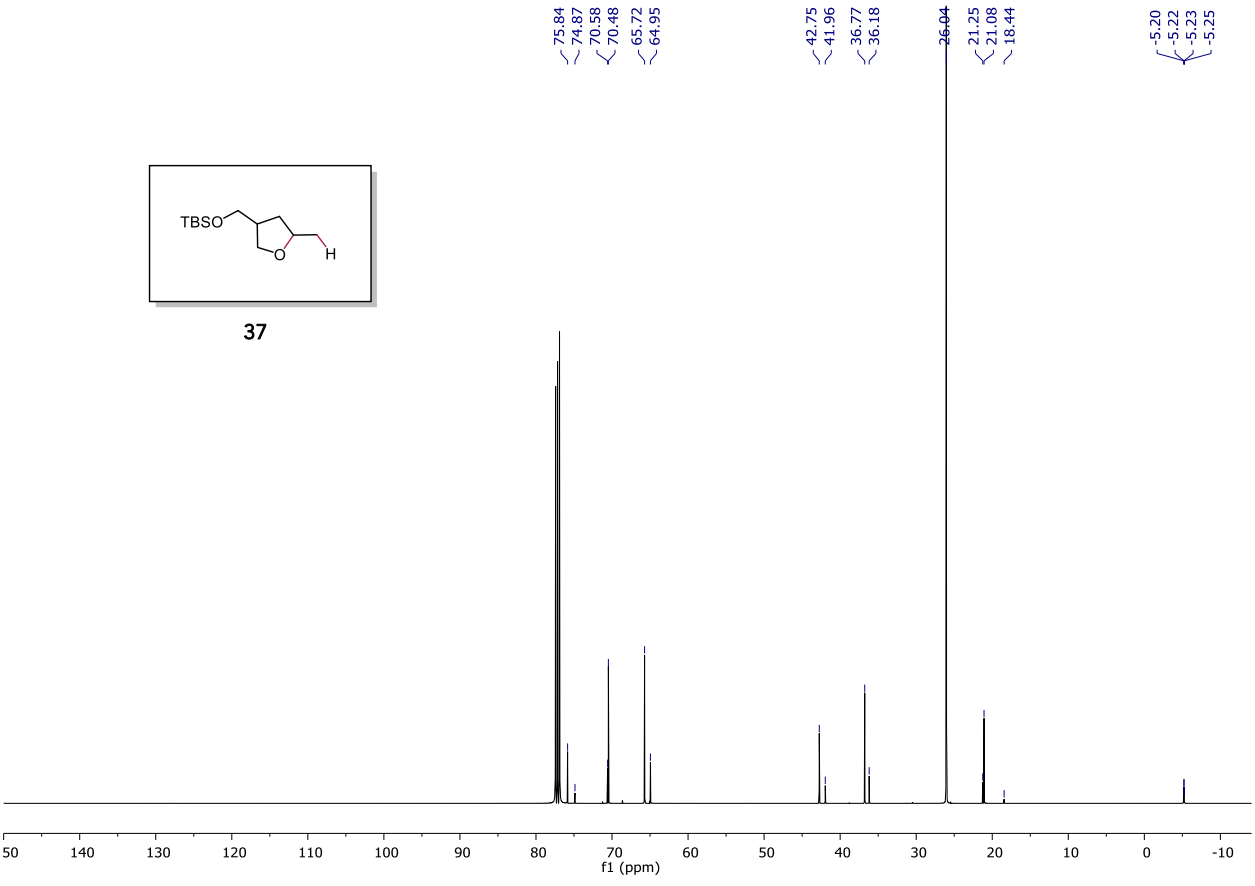


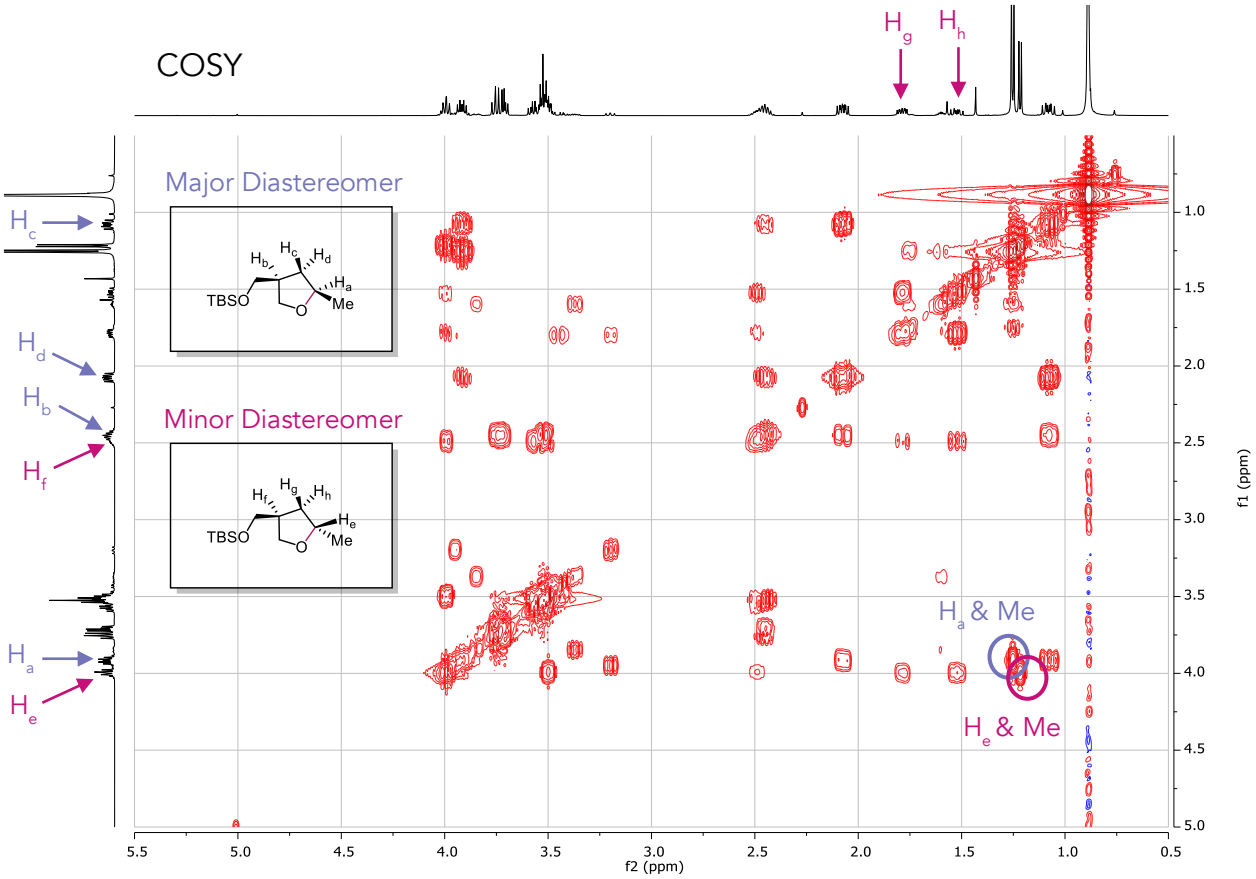


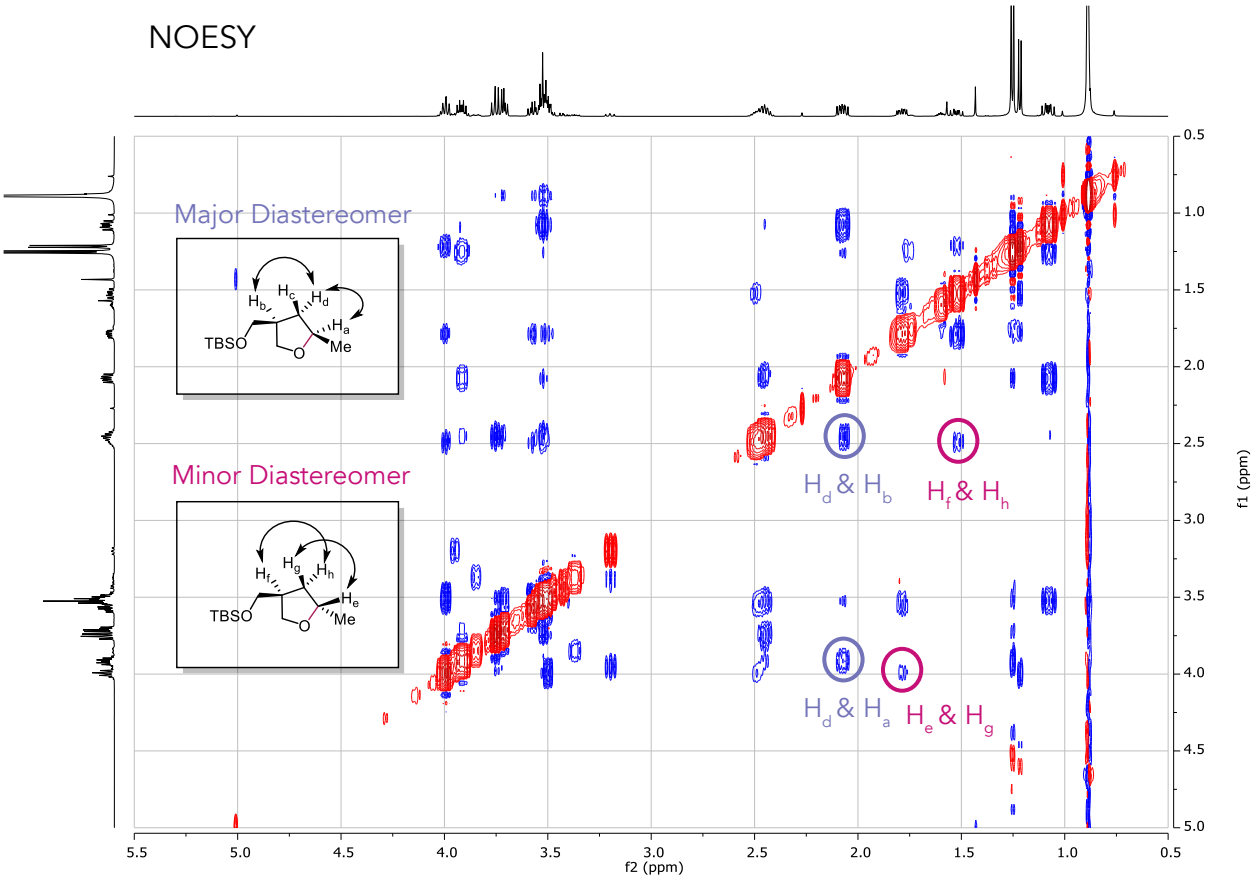
36




Inset from crude NMR in
CDCl3 at 500 MHz
(2:1 dr)
2.03
1.00
1.27 1.26 1.25 1.24 1.23 1.22 1.21 1.20
f1 (ppm)
TBSO
O
H
37
0.72
0.67
1.34
0.44
2.08
4.0 3.9 3.8 3.7 3.6 3.5
f1 (ppm)
0.72
0.67
1.34
0.44
2.08
1.00
0.67
0.44
0.36
2.10
1.04
0.69
9.70
6.24
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

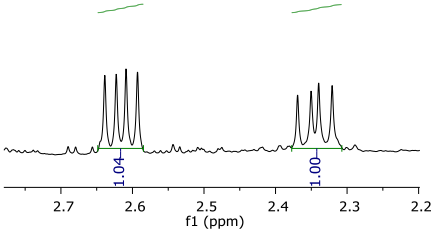

75.84
74.87
70.58
70.48
65.72
64.95
42.75
41.96
36.77
36.18
26.04
21.25
21.08
18.44
-5.20
-5.22
-5.23
-5.25
TBSO
O
H
37
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

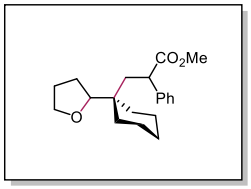

COSY
H_g
H_h
Major Diastereomer
TBSO
Me
Minor Diastereomer
TBSO
Me
H_c
H_d
H_b
H_f
H_a
H_e
H_a & Me
H_e & Me
f2 (ppm)
f1 (ppm)



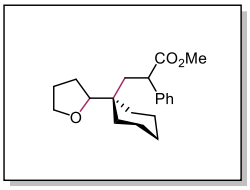
H_c has no significant NOE correlation with H_a or H_b. H_f has an NOE correlation with H_h but not with H_g, while H_e correlates with H_g but not with H_h. These results suggest that the major diastereomer is the *syn* diastereomer (H_a and H_b are *syn* to each other).

Inset from crude NMR in
$CDCl_3$ at 500 MHz
(1:1 dr)

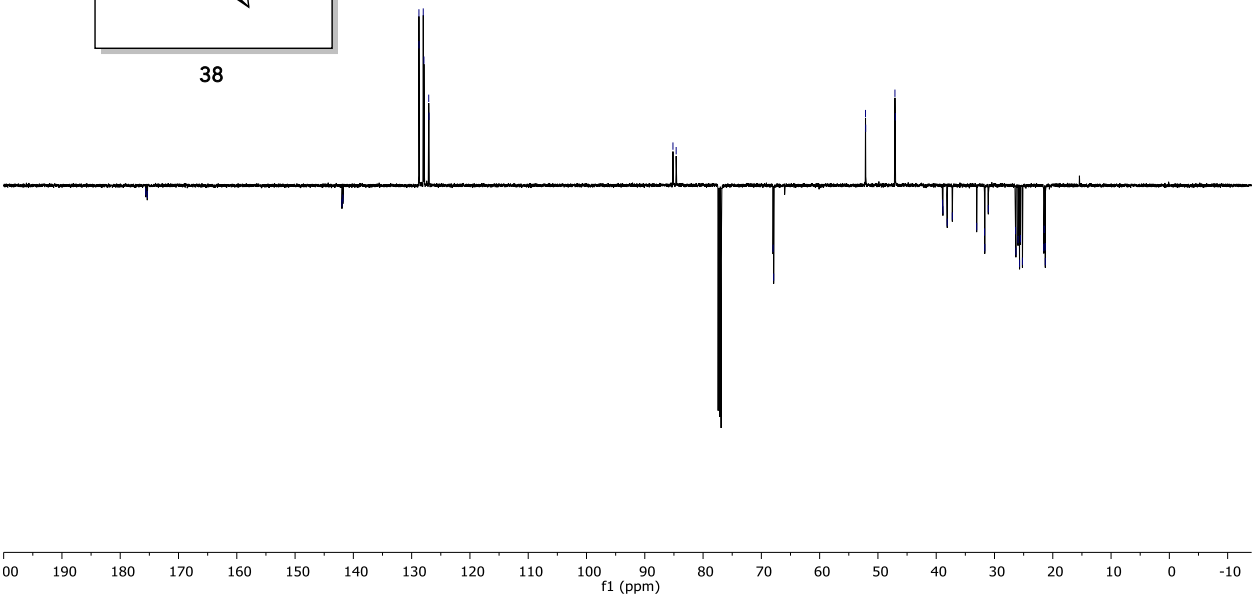




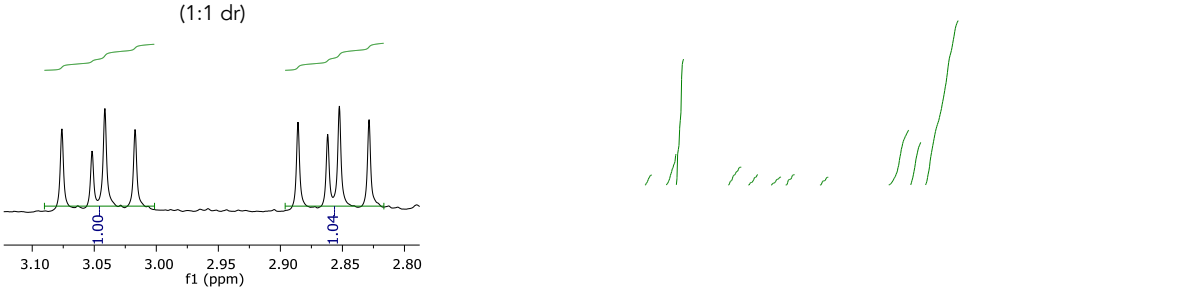
38

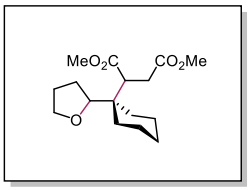


38

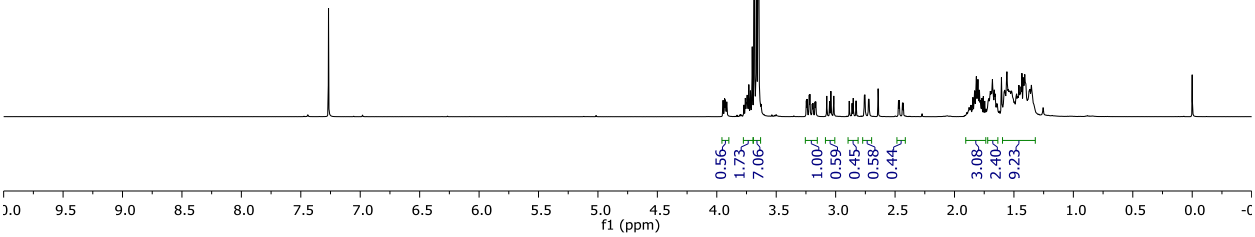


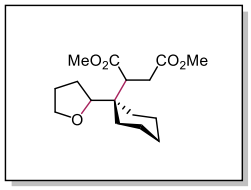
Inset from crude NMR in
$CDCl_3$ at 500 MHz
(1:1 dr)



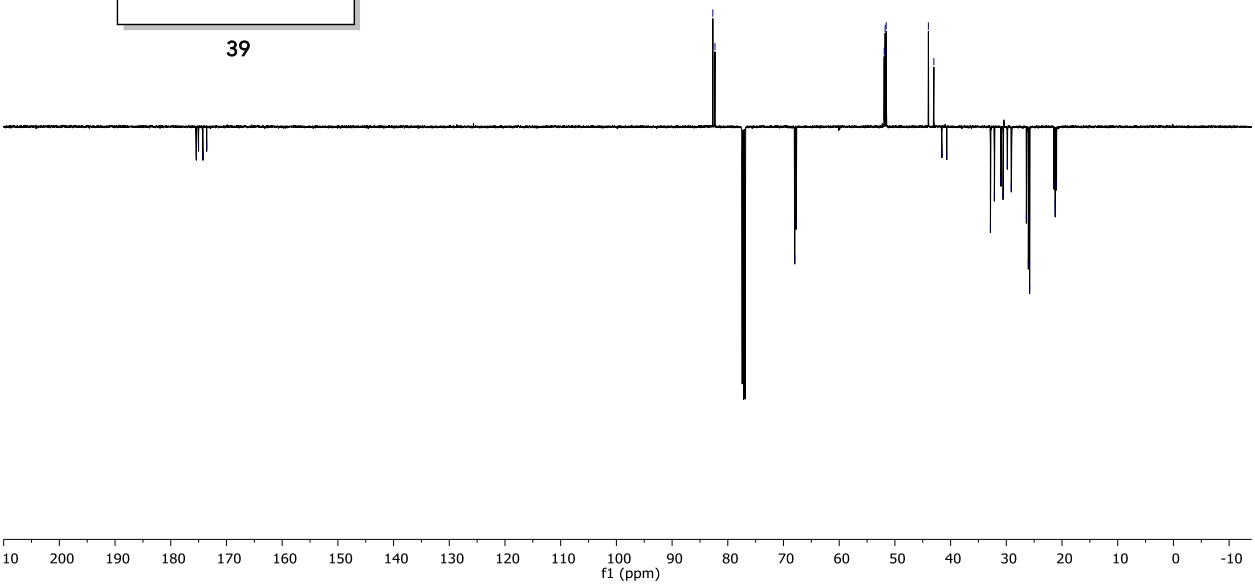


39

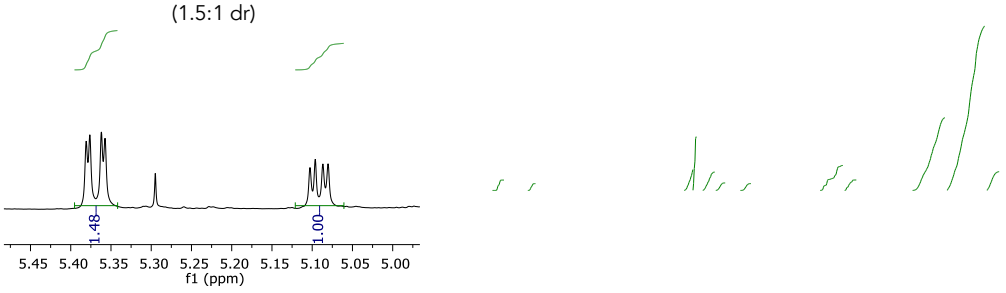


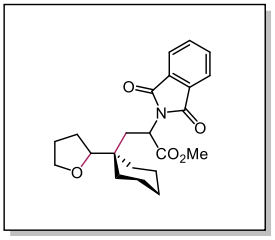


39

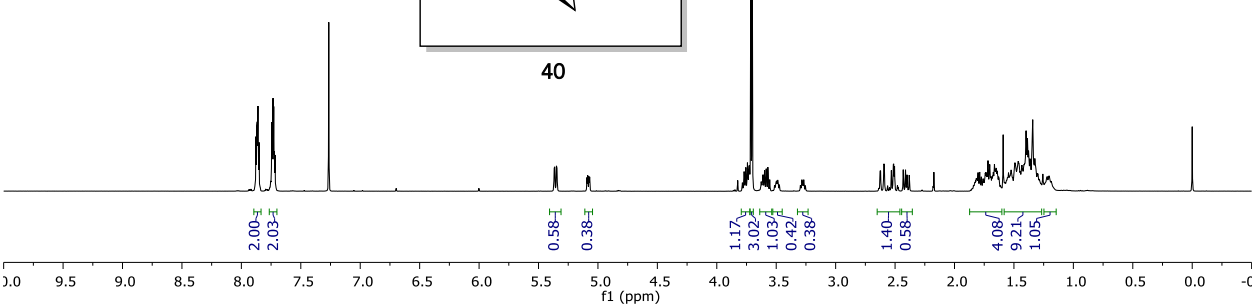


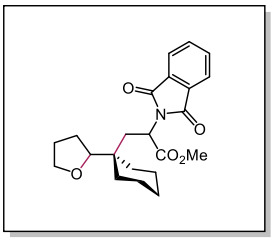
Inset from Crude NMR in $CDCl_3$ at 500 MHz (1.5:1 dr)



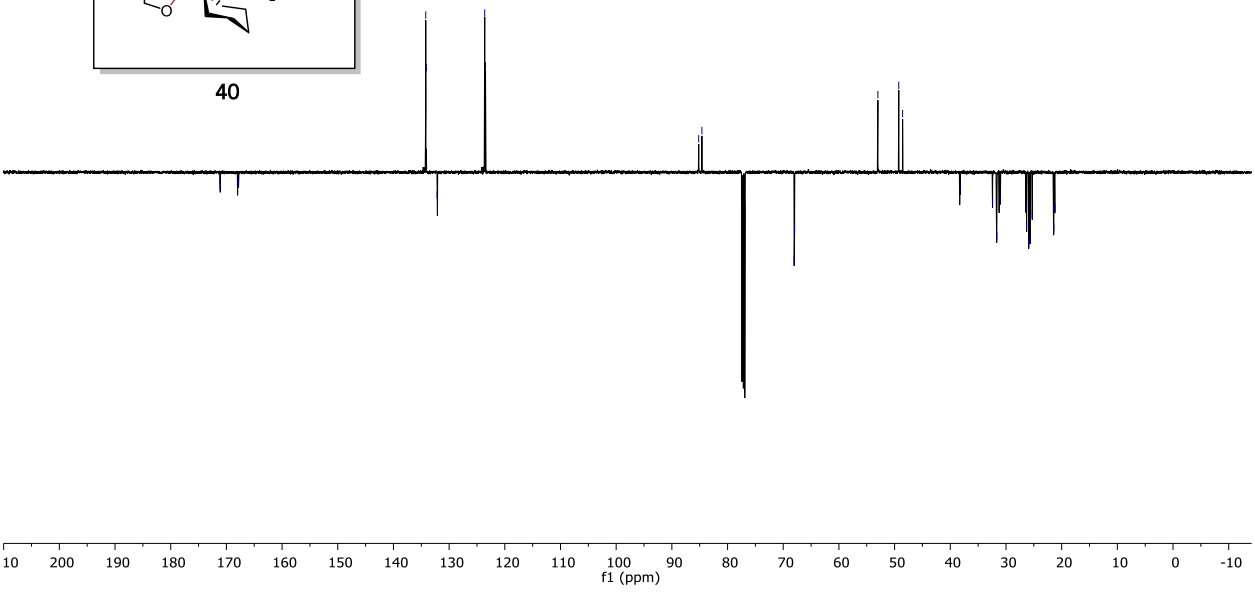


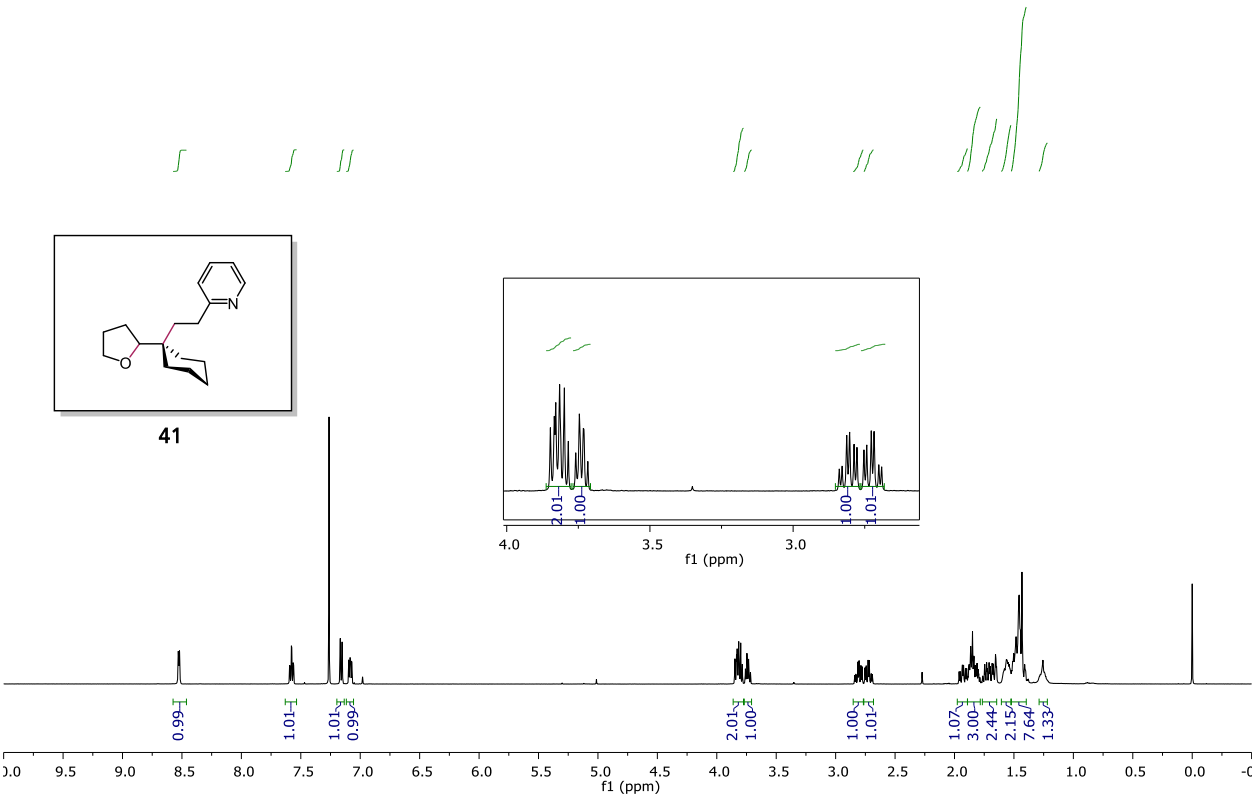
40

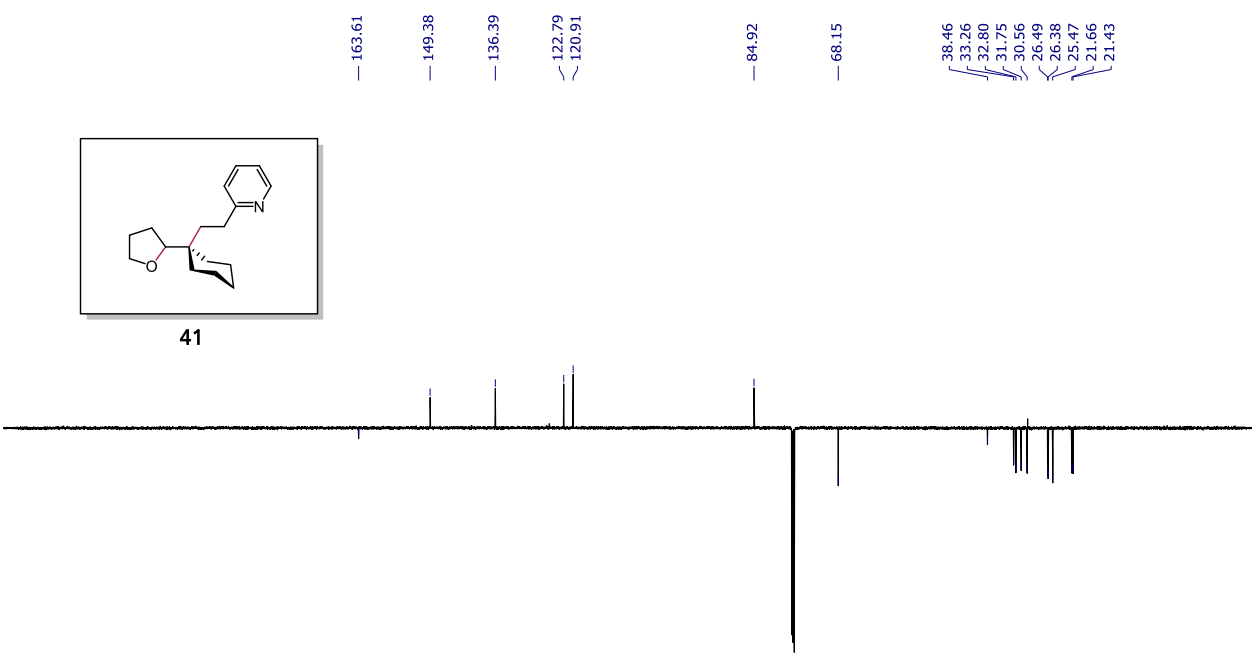


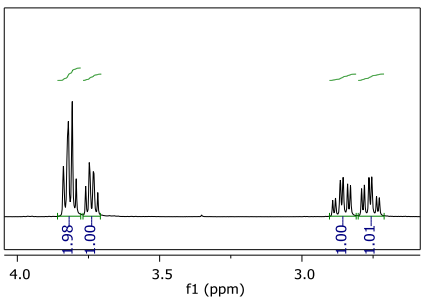


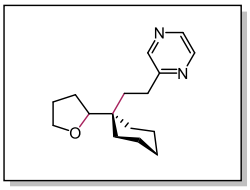
40



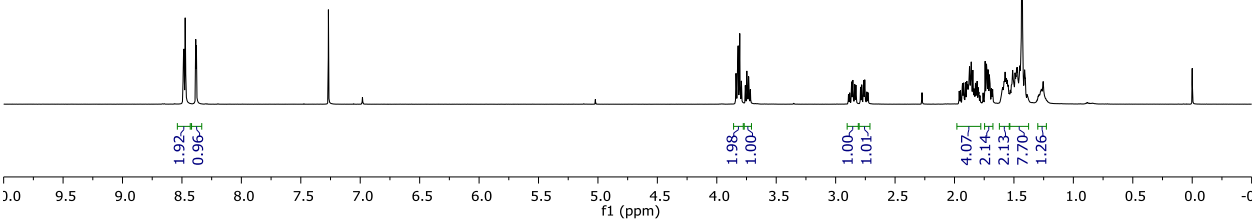

41
2.01
1.00
1.00
1.01
4.0
3.5
3.0
f1 (ppm)
0.99
1.01
1.01
0.99
2.01
1.00
1.00
1.01
1.07
3.00
2.44
2.15
7.64
1.33
f1 (ppm)


163.61
149.38
136.39
122.79
120.91
84.92
68.15
38.46
33.26
32.80
31.75
30.56
26.49
26.38
25.47
21.66
21.43
41
f1 (ppm)

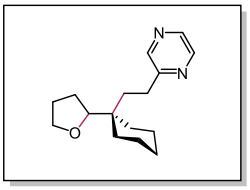

1.98
1.00
1.00
1.01
4.0
3.5
3.0
f1 (ppm)



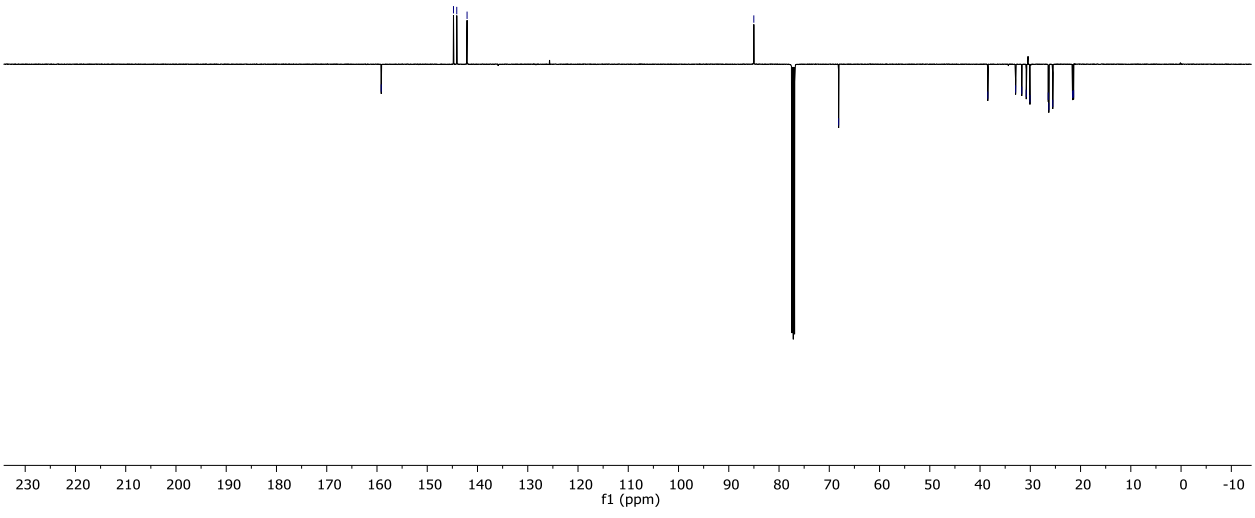
42

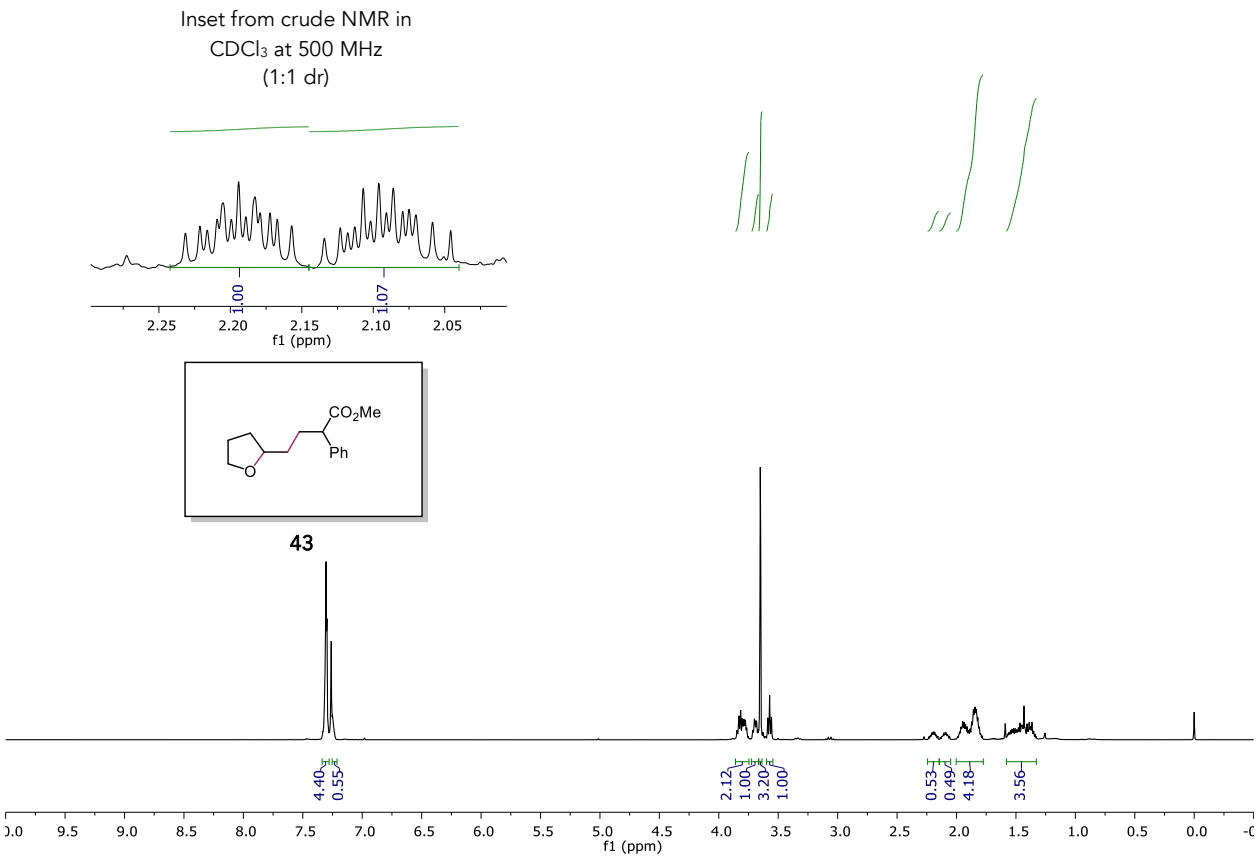

1.92
0.96
1.98
1.00
1.00
1.01
4.07
2.14
2.13
7.70
1.26
f1 (ppm)

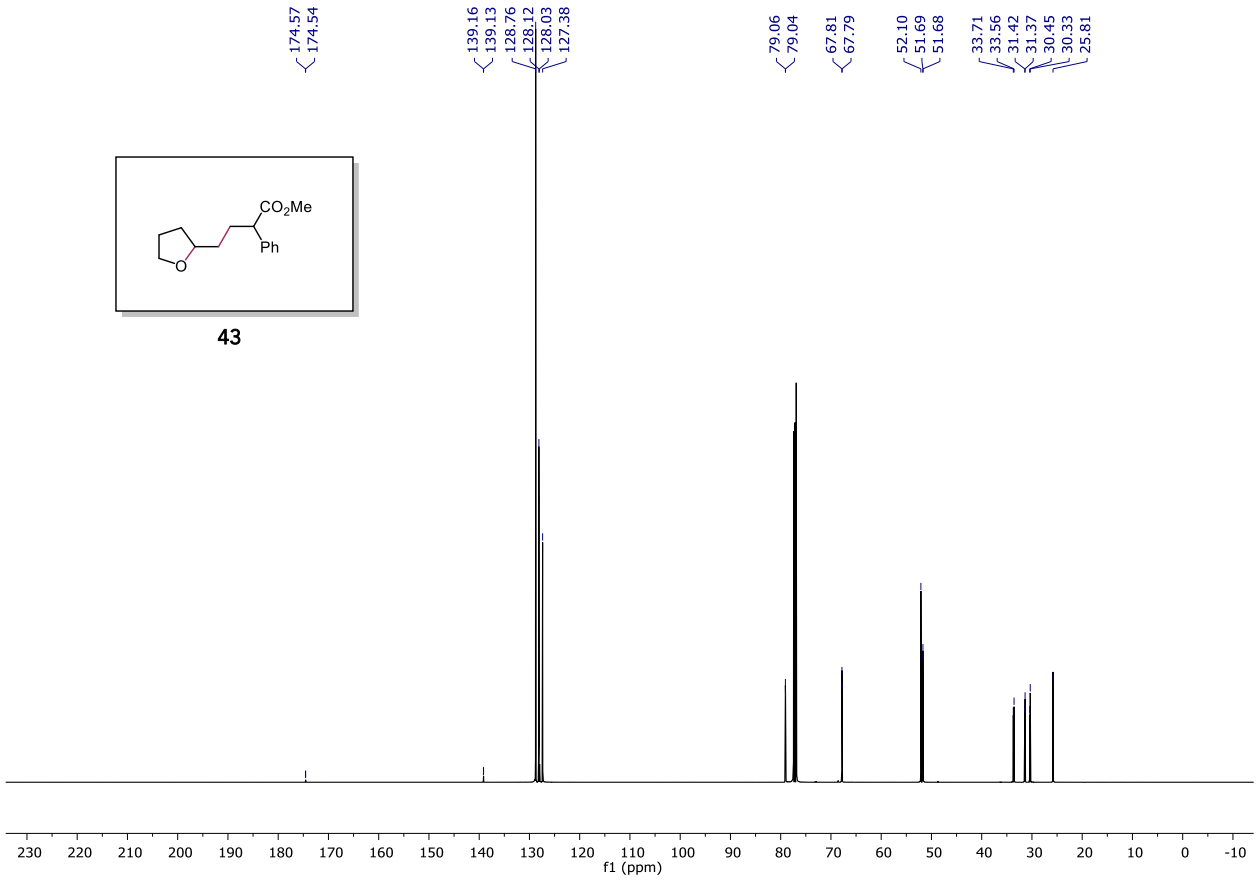

159.15
144.78
144.13
142.08
85.02
68.14
38.46
32.92
31.70
30.81
30.07
26.42
26.32
25.53
21.58
21.38

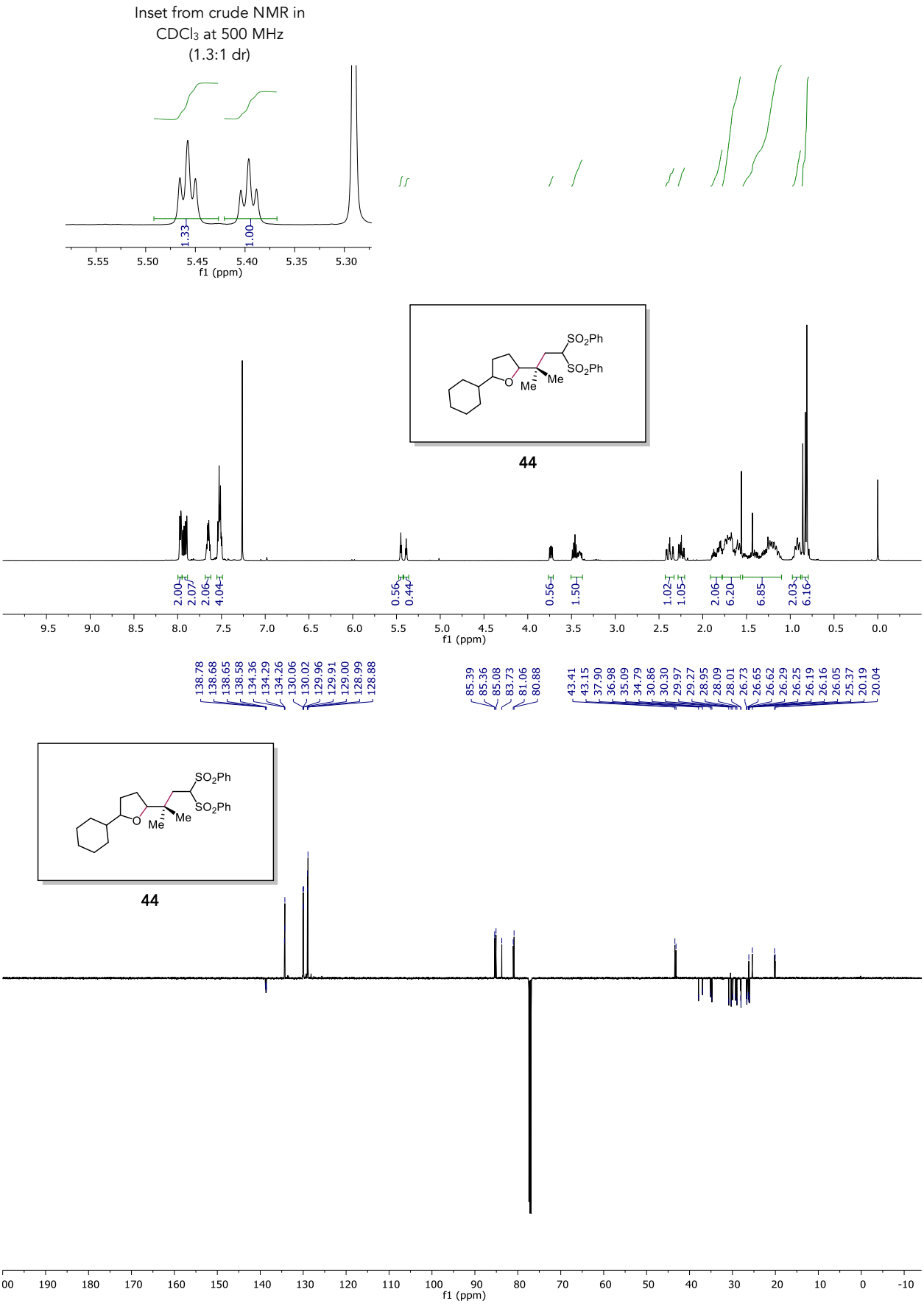


42


f1 (ppm)


Inset from crude NMR in
CDCl3 at 500 MHz
(1:1 dr)
1.00
1.07
2.25
2.20
2.15
2.10
2.05
f1 (ppm)
CO2Me
Ph
O
43
4.40
0.55
2.12
1.00
3.20
1.00
0.53
0.49
4.18
3.56
f1 (ppm)


174.57
174.54
139.16
139.13
128.76
128.12
128.03
127.38
79.06
79.04
67.81
67.79
52.10
51.69
51.68
33.71
33.56
31.42
31.37
30.45
30.33
25.81
CO2Me
Ph
O
43
f1 (ppm)


Inset from crude NMR in
CDCl3 at 500 MHz
(1.3:1 dr)
1.33
1.00
5.55 5.50 5.45 5.40 5.35 5.30
f1 (ppm)
SO2Ph
SO2Ph
Me
Me
O
44
2.00 2.07 2.06 4.04 0.56 0.44 0.56 1.50 1.02 1.05 2.06 6.20 6.85 2.03 6.16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
138.78 138.68 138.65 138.58 134.36 134.29 134.26 130.06 130.02 129.96 129.91 129.00 128.99 128.88
85.39 85.36 85.08 83.73 81.06 80.88
43.41 43.15 37.90 36.98 35.09 34.79 30.86 30.30 29.97 29.27 28.95 28.09 28.01 26.73 26.65 26.62 26.29 26.25 26.19 26.16 26.05 25.37 20.19 20.04
SO2Ph
SO2Ph
Me
Me
O
44
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

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