# Enantioselective Catalytic Transannular Ketone-Ene Reactions

Naomi S. Rajapaksa and Eric N. Jacobsen*

*Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138*

jacobsen@chemistry.harvard.edu

**Supporting Information**

**A. General Information**

Unless otherwise noted, all reactions were performed under a positive pressure of anhydrous nitrogen or argon in flame- or oven-dried glassware. Moisture- and air-sensitive reagents were dispensed using oven-dried stainless steel syringes or cannulae and were introduced to reaction flasks through rubber septa. Reactions conducted below ambient temperature were cooled by external baths (dry ice/acetone for −78 °C and ice/water for 0 °C). Reactions conducted above ambient temperature were heated by an oil bath.

Analytical thin layer chromatography (TLC) was performed on glass plates pre-coated with silica 60 $F_{254}$ (0.25 mm) or on aluminum sheets pre-coated with neutral aluminum oxide 60 $F_{254}$ (0.2 mm). Visualization was carried out by exposure to a UV-lamp (short wave 254 nm, long wave 365 nm), and by heating after staining the plate with a ceric ammonium molybdate, potassium permanganate, or phosphomolybdic acid solution. Extraction and chromatography solvents were reagent or HPLC grade and were used without further purification. Flash column chromatography was carried out over silica gel (60 Å, 230–400 mesh) from EM Science, Davisil™ (Grade 643, 150 Å, 200–425 mesh) from Aldrich, or activated neutral aluminum oxide (Brockman I standard grade, 58 Å, 150 mesh) from Aldrich. Flash column chromatography was conducted on a Biotage Isolera automated chromatography system.

***Materials.***

Commercial reagents and solvents were used with the following exceptions: tetrahydrofuran, diethyl ether, toluene, and dichloromethane employed as reaction solvents were dried by passage through columns of activated alumina. Triethylamine was distilled from calcium hydride at 760 torr prior to use. Chloroform-d was treated with and stored over anhydrous potassium carbonate prior to use. Powdered 4Å MS were purchased from Sigma-Aldrich and activated by heating in a commercial microwave oven, and stored in a vial sealed with parafilm in a desiccator. 4,4-dimethyl-cyclohexanone was prepared according to the reported procedure.[1] Intermediates **S10**, **S11**, and **S12** were prepared according to reported procedures.[2,3,4]

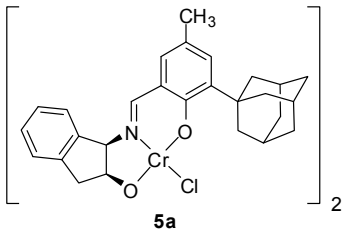
***Instrumentation.***

Proton nuclear magnetic resonance ($^1$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Varian Mercury-400 (400MHz), Inova-500 (500MHz), or an Inova-600 (600MHz) spectrometer at 23 °C, unless otherwise noted. Chemical shifts for protons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: 7.26 ppm). Chemical shifts for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the NMR solvent ($CDCl_3$: 77.16 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constant (*J*) in Hertz (Hz). Infrared (IR) spectroscopy was performed on the neat compounds on a Brucker Tensor 27 FT-IR Spectrometer using OPUS software. Data are represented as follows: frequency of absorption ($cm^{-1}$),

[1] Meyer, W. L.; Brannon, M. J.; Burgos, C. d. G.; Goodwin, T. E.; Howard, R. W. *J. Org. Chem.* **1985**, *50*, 438.
[2] Reetz, M. T.; Kindler, A. *J. Organomet. Chem.* **1995**, *502*, C5.
[3] Grisé, C. M.; Rodrigue, E. M.; Barriault, L. *Tetrahedron* **2008**, *64*, 797.
[4] Clément, R.; Grisé, C. M.; Barriault, L. *Chem. Commun.* **2008**, 3004.

intensity of absorption (s = strong, m = medium, w = weak). Mass spectra were obtained on an Agilent 1200 series 6120 Quadrupole LC/MS. Optical rotation data were collected using a 1-mL cell using a 0.5 dm path length on a Jasco P-2000 polarimeter and are reported as $[\alpha]_D^{23}$ (concentration in grams/100 mL solvent). Reported rotations are the average of 3–5 measurements per sample.

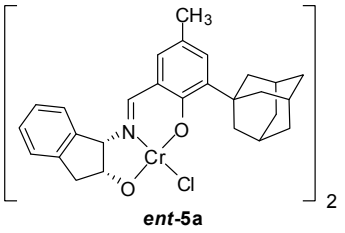
**B. Catalyst Preparation and Characterization**




**5a**

**Chromium(III) Chloride Complex (5a)**

Catalyst **5a** was prepared according to the published procedure.[5]



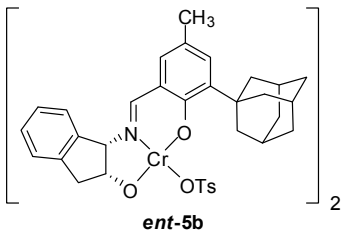

***ent*-5a**

**Chromium(III) Chloride Complex (*ent*-5a)**

Catalyst ***ent*-5a** was prepared according to the published procedure.[5]

**General Procedure A – Counteranion Exchange**

A flame-dried 50 mL round-bottom flask equipped with a stir bar and septum was wrapped with aluminum foil and charged with a silver salt bearing the desired counterion (0.0924 mmol, 0.95 equiv). To this flask was added complex **5a** (50 mg, 0.097 mmol, 1 equiv). To the flask, under an atmosphere of argon, was added TBME (16.2 mL). The reaction mixture was stirred at room temperature for 3 h, after which the contents were filtered through Celite®. The pad of Celite® was rinsed with an additional portion of TBME (16.2 mL). The filtrate was concentrated to afford the desired complex, which was used without further purification.

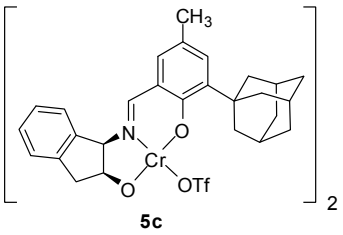



***ent*-5b**

**Chromium(III) Tosylate Complex (*ent*-5b):**

Following General procedure A, the counterion exchange was performed with ***ent*-5a** (100 mg, 0.19 mmol, 1 equiv) and AgOTs (50.5 mg, 0.18 mmol, 0.95 equiv) to provide catalyst ***ent*-5b** as a brown powder (84%). FTIR (neat, $cm^{-1}$) 3198 (br m) 2902 (m) 1616 (s) 1538 (m) 1434 (m) 1307 (w) 1229 (s) 1169 (m) 1078 (m) 1010 (m) 945 (w) 812 (m) 744 (s).

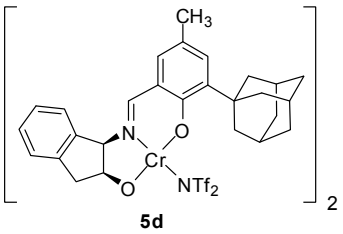
[5] Chavez, D. E.; Jacobsen, E. N. *Org. Synth.* **2005**, *82*, 34.




**5c**

**Chromium(III) Triflate Complex (5c):**

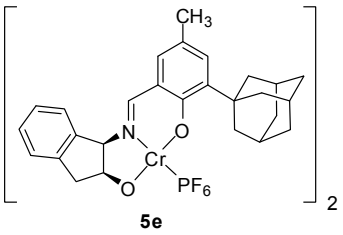
Following General Procedure A, the counterion exchange was performed with **5a** (200 mg, 0.39 mmol, 1 equiv) and AgOTf (95 mg, 0.37 mmol, 0.95 equiv) to provide catalyst **5c** as a brown powder (244 mg, 98%). FTIR (neat, $cm^{-1}$) 3271 (br w) 2902 (m) 2845 (w) 1614 (m) 1538 (m) 1453 (w) 1294 (m) 1227 (s) 1170 (s) 1026 (s) 980 (w) 811 (w) 746 (s).




**5d**

**Chromium(III) Triflimide Complex (5d)**

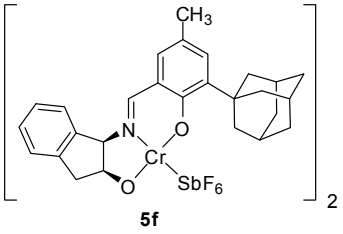
Following General Procedure A, the counterion exchange was performed with **5a** (50 mg, 0.097 mmol, 1 equiv) and $AgNTf_2$ (35.9 mg, 0.0924 mmol, 0.95 equiv) to provide catalyst **5d** as a brown powder (62.3 mg, 83%). FTIR (neat, $cm^{-1}$) 3538 (br w) 2905 (w) 2850 (w) 1614 (m) 1541 (m) 1431 (w) 1349 (m) 1298 (m) 1227 (m) 1188 (s) 1135 (m) 1057 (s) 981 (m) 748 (m).




**5e**

**Chromium(III) Hexafluorophosphate Complex (5e)**

Following General Procedure A, the counterion exchange was performed with **5a** (50 mg, 0.097 mmol, 1 equiv) and $AgPF_6$ (23.4 mg, 0.0924 mmol, 0.95 equiv) to provide catalyst **5e** as a brown powder (50.3 mg, 82%). FTIR (neat, $cm^{-1}$) 3532 (br w) 2901 (m) 2848 (w) 1614 (m) 1538 (m) 1431 (w) 1300 (w) 1228 (m) 1151 (m) 1054 (m) 839 (s) 749 (m).



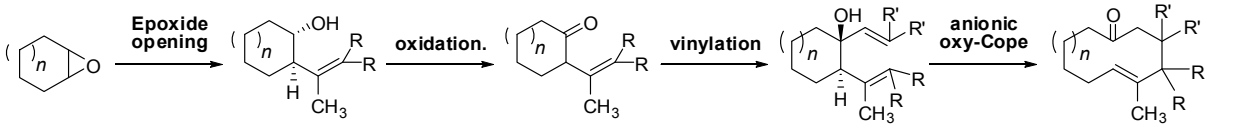

**5f**

**Chromium(III) Hexafluoroantimonate Complex (5f)**

Following General Procedure A, the counterion exchange was performed with **5a** (50 mg, 0.097 mmol, 1 equiv) and AgSbF6 (31.8 mg, 0.0924 mmol, 0.95 equiv) to provide catalyst **5f** as a brown powder (67.4 mg, 96%). This complex has previously been characterized.[5]

**C. Substrate Syntheses**

**General Synthetic Scheme for Transannular Ketone-Ene Substrates 1a, 1c, 1d, and 8**




**S1a**: R=H, n=1
**S1c**: R=$CH_3$, n=1
**S8**: R=H, n=0

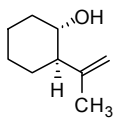
**2**: R=H, n=1
**S2c**: R=$CH_3$, n=1

**3**: R=R'=H, n=1
**S3c**: R=$CH_3$,R'=H, n=1
**S3d**: R=H, R'=CH3, n=1
**S9**: R=H, n=0

**1a**: R=R'=H, n=1
**1c**: R=$CH_3$,R'=H, n=1
**1d**: R=H, R'=CH3, n=1
**8**: R=H, n=0

**General Procedure B – copper-catalyzed addition of Grignard reagents to meso epoxides[6]**

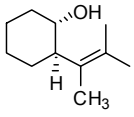
A flame-dried 3 L round-bottom flask under $N_2$ was charged with CuI (2.9g, 15.3 mmol, 0.15 equiv) and THF (1 L) and cooled to –30 °C (dry ice/acetone). To this suspension was added a solution of Grignard in THF (150 mmol, 1.5 equiv) over a period of 30 m. After another 10 m at –30 °C, meso epoxide (100 mmol, 1 equiv) was added dropwise, neat, over 10 m, and the reaction mixture was allowed to gradually warm to room temperature overnight. The dark reaction mixture was cooled to 0 °C and quenched by slow addition of saturated aqueous $NH_4Cl$ (200 mL). The contents were diluted with DI $H_2O$ (200 mL) and extracted with $Et_2O$ (3 x 500 mL). The combined organics were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was re-dissolved in $CH_2Cl_2$, dried over $Na_2SO_4$, filtered, and concentrated to afford crude alcohol that, unless otherwise noted, was carried on to the next reaction without further purification.



**S1a**

**(±)-(1S,2R)-2-(prop-1-en-2-yl)cyclohexanol (S1a)[7]**

This compound was prepared according to General Procedure B, with cyclohexene oxide (9.8 g, 100 mmol, 1 equiv) and isopropenylmagnesium bromide (0.5 M in THF, 300mL, 150 mmol, 1.5 equiv). The known alcohol **S1a** was obtained as a yellow oil (12.7 g) that was carried forward to the following reactions without further purification.

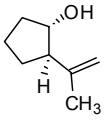


**S1c**

**(±)-(1S,2R)-2-(3-methylbut-2-en-2-yl)cyclohexanol (S1c)**

This compound was synthesized according to General Procedure B, with cyclohexene oxide (600 mg, 6.11 mmol, 1 equiv) and (3-methylbut-2-en-2-yl)magnesium bromide (0.25 M, 30mL, 1.5 equiv). The crude product was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 50% $Et_2O$/hexanes) to afford **S1c** (698mg, 4.15 mmol, 68%) as a clear oil. R*f*=0.2 (50% $Et_2O$/hexanes); $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 3.43 (td, *J*=9.84, 4.58 Hz, 1 H) 2.45 (ddd, *J*=11.79, 9.96, 3.89 Hz, 1 H) 2.02 - 2.09 (m, 1 H) 1.75 - 1.82 (m, 1 H) 1.73 (s, 3 H) 1.71 (s, 3 H) 1.64 - 1.70 (m, 2 H) 1.58 (s, 3 H) 1.44 - 1.52 (m, 1 H) 1.18 - 1.39 (m, 4 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ ppm 128.7, 127.6, 71.2, 49.1, 34.3, 29.3, 26.0, 25.1, 21.4, 20.4, 13.1; FTIR (neat, $cm^{-1}$) 3417 (br m) 2929 (s) 2857 (m) 1449 (m) 1375 (w) 1272 (w) 1162 (w) 1146 (w) 1060 (s) 1010 (m) 962 (m) 852 (m). MS (APCI) *m/z* calc'd for $C_{11}H_{19}$ $[M–H_2O+H]^+$: 151.1; found: 151.1.

[6] This procedure is adapted from Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *17*, 1503.
[7] Warrington, J. M.; Yap, G. P. A.; Barriault, L. *Org. Lett.* **2000**, *2*, 663.



S8

**(±)-(1S,2R)-2-(prop-1-en-2-yl)cyclopentanol (S8)**

This compound was prepared according to General Procedure B with cyclopentene oxide (8.4 g, 100 mmol, 1 equiv) and isopropenylmagnesium bromide (0.5M in THF, 300 mL, 1.5 equiv). The crude product was obtained as a yellow oil (8.6 g) and was carried forward to the following reaction without further purification.

**General Procedure C – Swern oxidation to generate β-γ unsaturated ketone intermediates**

An oven-dried 250 mL round-bottom flask under argon was charged with a stir bar, $CH_2Cl_2$ (39 mL), and oxalyl chloride (3.5 mL, 40.9 mmol, 1.2 equiv) and cooled to –78 °C. To this solution was added dropwise a solution of DMSO (6.0 mL, 85.2 mmol, 2.5 equiv) in $CH_2Cl_2$ (39 mL). After the mixture was stirred for 5 m, a solution of alcohol (34.1 mmol, 1.0 equiv) in $CH_2Cl_2$ (30 + 2 x 5 mL rinses) was added dropwise. The reaction mixture was stirred 1 h at –78 °C, at which point it was quenched by addition of $NEt_3$ (23.8 mL, 170 mmol, 5.0 equiv) and immediately warmed to room temperature. The contents were diluted with DI $H_2O$ (50 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organics were dried over $Na_2SO_4$, filtered, and concentrated. To remove amine salts, the crude residue was twice suspended in 5% $Et_2O$/hexanes, filtered, and concentrated to isolate the β-γ unsaturated ketone. This product was carried forward without further purification.[8]

**General Procedure D – Grignard addition to β-γ unsaturated ketone intermediates**

A flame-dried 500 mL round-bottom flask was charged with a stir bar, β-γ unsaturated ketone (14.5 mmol, 1 equiv) and THF (145 mL) and cooled to 0 °C. A solution of Grignard in THF (17.4 mmol, 1.2 equiv) was added dropwise under argon. The reaction was allowed to warm to room temperature overnight and was then quenched by slow addition of saturated aqueous $NH_4Cl$ (50 mL). The crude mixture was diluted with DI $H_2O$ (50 mL) and extracted with $Et_2O$ (3 x 100 mL). The combined organics were diluted with $CH_2Cl_2$, dried over $Na_2SO_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography to afford the divinyl alcohol.

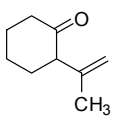
**General Procedure E – Cerium trichloride mediated Grignard addition to β-γ unsaturated ketone[9]**

A flame-dried 100 mL round-bottom flask was charged with anhydrous cerium trichloride (2.1 g, 8.5 mmol, 2.5 equiv) and THF (17 mL), and the resultant suspension was stirred for 2 h at room temperature. The flask was cooled to –78 °C, and *t*-butyllithium (1.7 M in pentane) was added dropwise until the suspension took on a persistent faint pink color (~5 drops). The flask was brought to room temperature, and β-γ unsaturated ketone (3.4 mmol, 1.0 equiv) was added as a solution in THF (10 mL + 2 x 3.5 mL rinses). The suspension was stirred under $N_2$ at room temperature for an additional 2 h. The flask was cooled to –78 °C and the reaction mixture was stirred at this temperature for 8 h, at which point saturated aqueous $NH_4Cl$ was added (20 mL) and the flask was brought to room temperature. The resultant emulsion was treated with 1 N HCl (10 mL) and was extracted with $Et_2O$ (3x20 mL).

[8] Attempted purification of some β-γ unsaturated ketone intermediates resulted in partial isomerization to the conjugated enone.

[9] Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568.

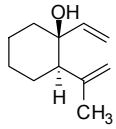
The combined organics were diluted with $CH_2Cl_2$, dried over $Na_2SO_4$, filtered, and concentrated to afford the crude product which was purified by flash column chromatography to afford the desired divinyl alcohol.



**2**

**2-(prop-1-en-2-yl)cyclohexanone (2)**[7]

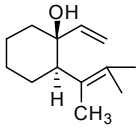
Alcohol **S1a** (4.78g, 34.1 mmol, 1 equiv) was oxidized according to General Procedure C to afford known ketone **2** as a dark orange oil (4.2 g). This product was carried forward without further purification.



**3**

**(±)-(1*S*,2*R*)-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (3)**[7]

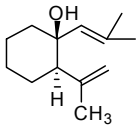
According to General Procedure D, crude ketone **2** (2.0 g, 14.5 mmol) was reacted with vinylmagnesium bromide (1.0 M in THF, 17.4 mL, 17.4 mmol, 1.2 equiv) to afford the crude addition product in 20:1 dr in favor of the title compound. The crude residue was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 6% $Et_2O$/hexanes) to afford the divinyl alcohol **3** (1.32 g, 7.9 mmol, 55% yield) as a pale yellow oil. R*f*=0.34 (10% $Et_2O$/hexanes, $KMnO_4$); $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 5.87 (ddd, *J*=17.17, 10.76, 1.37 Hz, 1 H) 5.11 - 5.23 (m, 1 H) 4.92 - 5.02 (m, 1 H) 4.81 - 4.89 (m, 1 H) 4.73 (d, *J*=0.92 Hz, 1 H) 2.04 (dd, *J*=12.59, 3.43 Hz, 1 H) 1.74 (s, 3 H) 1.71 - 1.80 (m, 2 H) 1.58 - 1.71 (m, 2 H) 1.49 - 1.57 (m, 1 H) 1.39 - 1.49 (m, 2 H) 1.21 - 1.30 (m, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 148.4, 146.5, 111.8, 110.7, 72.8, 52.5, 38.1, 27.4, 26.2, 25.7, 21.3; FTIR (neat, $cm^{-1}$) 3551 (m), 3482 (br m), 3082 (w), 2933 (s), 2856 (m), 2671 (w), 1638 (m), 1447 (m), 1373 (m), 1285 (m), 1197 (w), 1077 (m), 997 (m), 971 (s), 916 (s), 856 (m), 838 (m), 666 (m), 611 (m). MS (APCI) *m/z* calc'd for $C_{11}H_{17}$ $[M–H_2O+H]^+$: 149.1; found: 149.1.



**S3c**

**(±)-(1*S*,2*R*)-2-(3-methylbut-2-en-2-yl)-1-vinylcyclohexanol (S3c)**

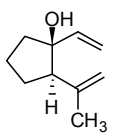
Alcohol **S1c** (650 mg, 3.9 mmol, 1 equiv) was oxidized according to General Procedure C to afford ketone **S2c**, which was carried forward without purification. According to General Procedure E, ketone **S2c** was reacted with vinylmagnesium bromide (1.0 M in THF, 9.6 mL, 9.6 mmol, 2.5 equiv) to afford the crude addition product in >19:1 dr in favor of the title compound. The crude residue was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 25% $Et_2O$/hexanes) to afford **S3c** as a clear oil (518 mg, 2.7 mmol, 68% yield over 2 steps). R*f* = 0.37 (10% $Et_2O$/hexanes) $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 5.86 (dd, *J*=17.40, 10.99 Hz, 1 H) 5.12 (dd, *J*=16.94, 1.37 Hz, 1 H) 4.91 (dd, *J*=10.99, 1.37 Hz, 1 H) 2.55 (dd, *J*=12.59, 2.98 Hz, 1 H) 1.84 - 1.97 (m, 1 H) 1.75 - 1.83 (m, 1 H) 1.66 - 1.74 (m, 1 H) 1.64 (br. s., 3 H) 1.62 (s, 6 H) 1.51 - 1.61 (m, 3 H) 1.18 - 1.39 (m, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 148.4, 146.5, 111.8, 110.7, 72.8, 52.5, 38.1, 27.4, 26.2, 25.7, 21.3; FTIR (neat, $cm^{-1}$) 3491 (br m) 3084 (w) 2929 (s) 2959 (m) 1640 (w) 1447 (s) 1413 (m) (1375 (m) 1268 (m) 1244 (m) 1164 (m) 1150 (m) 1056 (w) 992 (m) 963 (s) 916 (s) 859 (w) 816 (m) 668 (m). MS (APCI) *m/z* calc'd for $C_{13}H_{21}$ $[M–H_2O+H]^+$: 177.2; found: 177.2.



**S3d**

**(±)-(1S,2R)-1-(2-methylprop-1-enyl)-2-(prop-1-en-2-yl)cyclohexanol (S3d)**

According to General Procedure D, crude ketone **S2a** (1.0 g, 7.2 mmol, 1 equiv) was reacted with 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 17.4 mL, 17.4 mmol, 1.2 equiv) to afford the crude addition product in 6:1 dr in favor of the title compound. The crude product was purified by flash column chromatography (Davisil®, Biotage, 0 to 25% $Et_2O$/hexanes) to afford **S3d** (452 mg, 2.3 mmol, 32% yield) as a pale yellow oil. R*f*=0.75 (10% $Et_2O$/hexanes, $KMnO_4$); $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 5.19 (s, 1 H) 4.88 (s, 1 H) 4.78 (s, 1 H) 2.06 (dd, *J*=12.36, 2.75 Hz, 1 H) 1.88 (d, *J*=14.19 Hz, 1 H) 1.83 (s, 3 H) 1.81 (s, 3 H) 1.69 - 1.78 (m, 3 H) 1.67 (s, 3 H) 1.35 - 1.63 (m, 4 H) 1.23 (qt, *J*=13.58, 3.20 Hz, 1 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ ppm 149.2, 132.49, 132.46, 112.2, 73.5, 53.5, 38.5, 27.8 (2 C) 26.3, 25.7, 21.6, 18.8; FTIR (neat, $cm^{-1}$) 3559 (m) 3502 (br m) 2078 (w) 2930 (s) 2855 (s) 1667 (m) 1637 (m) 1447 (s) 1375 (m) 1323 (w) 1286 (m) 1212 (w) 1179 (w) 1069 (m) 978 (s) 949 (m) 895 (s) 863 (m) 734 (m). MS (ESI) *m/z* calc'd for $C_{13}H_{21}$ $[M–H_2O+H]^+$: 177.1638; found: 177.1637.



**S9**

**(±)-(1S,2R)-2-(prop-1-en-2-yl)-1-vinylcyclopentanol (S9)**

Alcohol **S8** (1.0g, 7.9 mmol, 1 equiv) was dissolved in $CH_2Cl_2$ (80 mL) in a 200 mL round-bottom flask. Dess–Martin periodinane (4.0 g, 9.4 mmol, 1.2 equiv) was added as a solid in one portion. The reaction was stirred at room temperature under $N_2$ for 1 h, at which point the contents of the flask were poured into a 1 L Erlenmeyer flask containing a large stir bar and $Et_2O$ (80 mL). A 10% aqueous sodium thiosulfate solution (80 mL) and saturated aqueous $NaHCO_3$ (80 mL) were added to the flask, and the contents were vigorously stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organics were dried over $Na_2SO_4$, filtered, and concentrated. The crude ketone was taken forward without purification.

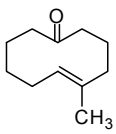
According to General Procedure D, the intermediate ketone was reacted with vinylmagnesium bromide (1.0 M in THF, 9.5 mL, 9.5 mmol, 1.2 equiv) to afford the crude addition product in 9:1 dr in favor of the title compound. The crude product was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 25% $Et_2O$/hexanes) to afford divinyl alcohol **S9** as a yellow oil (497 mg, 3.2 mmol, 41% over 2 steps). Characterization data matches reported values.[10]

**General Procedure F – Anionic oxy-Cope rearrangement**

A flame-dried 250 mL round-bottom flask was charged with KH (866 mg, 21.7 mmol, 2.4 equiv), 18-crown-6 (6.8 g, 25.7 mmol, 2.8 equiv), and THF (150 mL) and cooled to 0 °C under an atmosphere of argon. A solution of divinyl alcohol (9.0 mmol, 1 equiv) in THF (30 mL + 10 mL rinse) was added dropwise via cannula. The reaction was stirred at 0 °C for 30 m, after which it was warmed to room temperature. The reaction was determined to be complete by TLC analysis after 2 h at room temperature. The flask was cooled to 0 °C and quenched by slow addition of saturated aqueous $NH_4Cl$ (10 mL). The reaction was further diluted with 100 mL DI $H_2O$ and extracted

[10] Tomooka, K.; Ezawa, T.; Inoue, H.; Uehara, K.; Igawa, K. *J. Am. Chem. Soc.* **2011**, *133*, 1754.

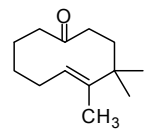
with $Et_2O$ (3 x 100 mL). The combined organics were diluted with $CH_2Cl_2$, dried over $Na_2SO_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography to afford the keto-olefin.



**1a**

**(*E*)-5-methylcyclodec-5-enone (1a)**[11]

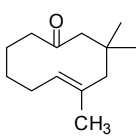
According to General Procedure F, divinyl alcohol **3** (1.5g, 9.0 mmol, 1 equiv) underwent an anionic oxy-Cope rearrangement. The crude product was purified by flash column chromatography (neutral $Al_2O_3$, Biotage, 0 to 10% $Et_2O$/hexanes) to afford cyclodecenone **1a** (978 mg, 5.9 mmol, 65% yield). The product is a clear oil at room temperature and freezes to a white solid upon storage at 5 °C. R*f*=0.26 (10% $Et_2O$/hexanes, CAM); $^1$H NMR (500 MHz, 23 °C,$CDCl_3$) δ ppm 5.17 (t, *J*=7.10 Hz, 1 H) 1.47 (s, 3 H) 1.12 - 2.81 (m, 14 H); $^1$H NMR (500 MHz, –20 °C, $CDCl_3$) δ ppm 5.18 (dd, *J*=10.07, 3.20 Hz, 1 H) 2.64 (dd, *J*=16.25, 9.84 Hz, 1 H) 2.25 - 2.47 (m, 3 H) 2.17 (dd, *J*=12.36, 5.95 Hz, 1 H) 1.97 - 2.12 (m, 3 H) 1.52 - 1.89 (m, 5 H) 1.46 (s, 3 H) 1.20 - 1.40 (m, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 209.6, 137.9, 126.8, 45.3, 43.4, 41.4, 29.0, 28.6, 26.0, 22.5, 16.0; FTIR (neat, $cm^{-1}$) 3392 (w), 2922 (s), 2852 (m), 2678 (w), 1703 (s), 1443 (s), 1425 (s), 1359 (m), 1181 (w), 1096 (s), 1017 (w), 924 (m), 859 (m), 809 (m), 774 (m), 733 (w). MS (ESI) *m/z* calc'd for $C_{11}H_{19}O$ $[M+H]^+$: 167.1430; found: 167.1425.



**1c**

**(*E*)-4,4,5-trimethylcyclodec-5-enone (1c)**

According to General Procedure F, divinyl alcohol **S3c** (388 mg, 2.0 mmol, 1 equiv) underwent an anionic oxy-Cope rearrangement. The crude product was purified by flash column chromatography (neutral $Al_2O_3$, Biotage, 0 to 50% $Et_2O$/hexanes and $SiO_2$, Biotage, 0 to 10% $Et_2O$/hexanes) to afford cyclodecenone **1c** (294 mg, 0.1.5 mmol, 76% yield) as a pale yellow oil. $^1$H NMR (500 MHz, 23°C, $CDCl_3$) δ ppm 5.24 (td, *J*=7.33, 0.92 Hz, 1 H) 2.18 - 2.81 (m, 4 H) 2.09 (br. s., 3 H) 1.48 - 1.97 (m, 5 H) 1.45 (s, 3 H) 1.07 (s, 6 H); $^1$H NMR (500 MHz, –40 °C, $CDCl_3$) δ ppm 5.19 (d, *J*=10.74 Hz, 1 H) 2.57 (dd, *J*=16.36, 10.01 Hz, 1 H) 2.49 (t, *J*=13.70 Hz, 1 H) 2.26 - 2.38 (m, 2 H) 2.06 - 2.17 (m, 1 H) 1.95 - 2.05 (m, 1 H) 1.90 (dd, *J*=14.89, 4.64 Hz, 1 H) 1.66 - 1.82 (m, 2 H) 1.51 - 1.63 (m, 1 H) 1.39 (s, 3 H) 1.23 - 1.35 (m, 2 H) 1.06 (s, 3 H) 0.97 (s, 3 H); $^{13}$C NMR (126 MHz, –40 °C, $CDCl_3$) δ ppm 210.2, 143.0, 124.4, 45.8, 39.3, 39.1, 39.0, 29.3, 28.6, 28.0, 24.8, 22.1, 13.6; FTIR (neat, $cm^{-1}$) 2921 (m) 1705 (s) 1446 (m) 1370 (m) 1355 (m) 1179 (w) 1132 (s) 1080 (w) 1064 (w) 1040 (m) 1000 (w) 910 (m) 853 (m) 807 (m) 733 (m); MS (ESI) *m/z* calc'd for $C_{13}H_{21}$ $[M–H_2O+H]^+$: 177.1638; found: 177.1642.



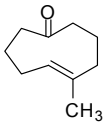
**1d**

**(*E*)-3,3,5-trimethylcyclodec-5-enone (1d)**

According to General Procedure F, divinyl alcohol **S3d** (200 mg, 1.03 mmol, 1 equiv) underwent an anionic oxy-Cope rearrangement. The crude product was purified by flash column chromatography (neutral $Al_2O_3$, Biotage, 0 to 5% $Et_2O$/hexanes) to afford cyclodecenone **1d** (120 mg, 0.61 mmol, 61% yield) as a white crystalline solid. R*f*=0.4 (10% $Et_2O$/hexanes); $^1$H NMR (500 MHz, –40 °C, $CDCl_3$) δ ppm 5.20 (t, *J*=6.80 Hz, 1 H) 2.60 (dd, *J*=16.36, 10.50 Hz, 1 H) 2.40 (d, *J*=14.65 Hz, 1 H) 2.27 (dd, *J*=16.36, 9.03 Hz, 1

[11] Bluthe, N.; Malacria, M.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 1157.

H) 1.95 - 2.03 (m, 3 H) 1.92 (d, *J*=14.65 Hz, 1 H) 1.85 (d, *J*=12.21 Hz, 1 H) 1.68 - 1.78 (m, 2 H) 1.55 (s, 3 H) 1.45 - 1.57 (m, 1 H) 1.36 (s, 3 H) 1.24 - 1.33 (m, 1 H) 0.91 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 209.9, 138.6, 129.0, 54.1, 53.0, 46.4, 43.3, 34.8, 28.5 (2C), 27.1, 22.2, 18.8; FTIR (neat, $cm^{-1}$) 2952 (s) 2925 (m) 1703 (s) 1447 (m) 1365 (m) 1286 (w) 1152 (m) 1109 (m) 1057 (m) 979 (m) 890 (w) 793 (m) 735 (m). MS (APCI) *m/z* calc'd for $C_{13}H_{23}O$ $[M+H]^+$: 195.2; found: 195.2.

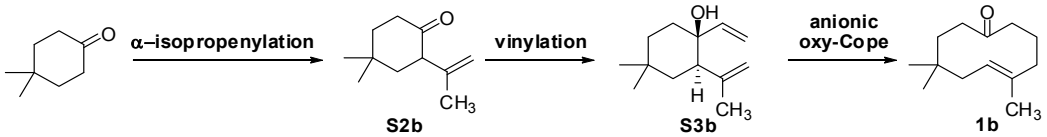


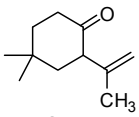
**8**

**(*E*)-5-methylcyclonon-5-enone (8)**

According to General Procedure F, divinyl alcohol **S9** (200 mg, 1.32 mmol, 1 equiv) underwent an anionic oxy-Cope rearrangement. The crude product was purified by flash column chromatography (neutral $Al_2O_3$, Biotage, 0 to 5% $Et_2O$/hexanes) to afford cyclononenone **8** (83 mg, 0.54 mmol, 42% yield) as a pale yellow solid. Characterization data matched reported values.[10]

**Scheme for the Synthesis of Transannular Ketone-Ene Substrate 1b**



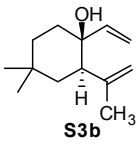



**S2b**

**4,4-dimethyl-2-(prop-1-en-2-yl)cyclohexanone (S2b)[12]**

A thick-walled vial was charged with a stir bar, 4,4-dimethyl cyclohexanone (252 mg, 2.0 mmol, 1 equiv), and $[(t\text{-}Bu_3P)PdBr]_2$ (19 mg, 0.025 mmol, 1.25 mol%) and sealed with a pressure septum cap. Under a positive pressure of $N_2$, toluene (4 mL) was added followed by a solution of LHMDS (1.0 M in toluene, 5 mL, 5 mmol, 2.5 equiv). The resultant suspension was stirred for 5 m at room temperature, after which 2-bromopropene (262 μL, 3.0 mmol, 1.5 equiv) was added in a single portion. The $N_2$ inlet was removed, and the vial was immersed in a 80 $^oC$ oil bath and stirred at this temperature for 24 h. The vial was cooled to room temperature and the contents were poured into $Et_2O$ (10 mL) and washed with saturated aqueous $NH_4Cl$ (5 mL) and DI water (5mL). The organic layer was diluted with $CH_2Cl_2$, dried over $Na_2SO_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 40% $Et_2O$/hexanes) to afford **S2b** (146 mg, 0.88 mmol, 44% yield) as a clear oil. R*f*=0.45 (20% $Et_2O$/hexanes); $^1$H NMR (600 MHz, $CDCl_3$) δ ppm 4.90 - 4.97 (m, 1 H) 4.72 (dt, *J*=1.76, 0.88 Hz, 1 H) 3.15 (dd, *J*=13.33, 5.42 Hz, 1 H) 2.44 - 2.55 (m, 1 H) 2.29 (ddd, *J*=14.64, 4.69, 2.90 Hz, 1 H) 1.79 (t, *J*=13.47, 1H) 1.61 - 1.76 (m, 3 H) 1.72 (s, 3 H) 1.23 (s, 3 H) 1.05 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 211.3, 143.5, 113.1, 54.1, 44.8, 39.7, 38.5, 31.6, 30.7, 24.4, 21.2; FTIR (neat, $cm^{-1}$) 2955 (m), 2925 (m), 2865 (m), 1712 (s), 1649 (w), 1462 (m), 1446 (m), 1308 (w), 1153 (m), 1099 (m), 1009 (w), 890 (s), 828 (w), 732 (w); MS (ESI) *m/z* calc'd for $C_{11}H_{19}O$ $[M+H]^+$: 167.1430; found: 167.1422.

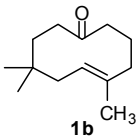
[12] This procedure was adapted from: Huang, J.; Bunel, E. Faul, M. M. *Org. Lett.* **2007**, *9*, 4343.



S3b

**(±)-(1S,2R)-4,4-dimethyl-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (S3b)**

According to General Procedure E, ketone **S2b** (267.3 mg, 1.6 mmol, 1.0 equiv) was reacted with vinylmagnesium bromide (1.0 M in THF, 4.0 mL, 4.0 mmol, 2.5 equiv) to afford the crude addition product in 4.6:1 dr in favor of the title compound. The crude residue was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 5% $Et_2O$/hexanes) to afford **S3b** (114 mg, 0.58 mmol, 36% yield) as a pale yellow oil. R*f*=0.59 (5% $Et_2O$/hexanes, $KMnO_4$); $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 5.90 (dd, *J*=17.09, 10.74 Hz, 1 H) 5.19 (dd, *J*=17.09, 0.98 Hz, 1 H) 4.99 (dd, *J*=10.74, 0.98 Hz, 1 H) 4.90 (t, *J*=1.47 Hz, 1 H) 4.75 (s, 1 H) 2.23 (dd, *J*=13.67, 3.42 Hz, 1 H) 1.75 (s, 3 H) 1.58 - 1.72 (m, 4 H) 1.48 (dt, *J*=12.94, 3.05 Hz, 1 H) 1.19 (ddd, *J*=12.21, 5.37, 2.44 Hz, 1 H) 1.12 (dt, *J*=13.18, 2.93 Hz, 1 H) 0.96 (s, 3 H) 0.94 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ ppm 147.9, 146.2, 111.8, 110.9, 72.3, 47.8, 40.0, 34.1, 33.7, 33.0, 30.2, 25.7, 23.9; FTIR (neat, $cm^{-1}$) 3553 (m), 3482 (br m), 3083 (m), 2951 (s), 2865 (m), 1638 (m), 1449 (m), 1365 (m), 1283 (m), 1099 (m), 992 (m), 962 (s), 917 (s), 897 (s), 668 (m); MS (ESI) *m/z* calc'd for $C_{13}H_{21}$ $[M–H_2O+H]^+$: 177.1638; found: 177.1639.

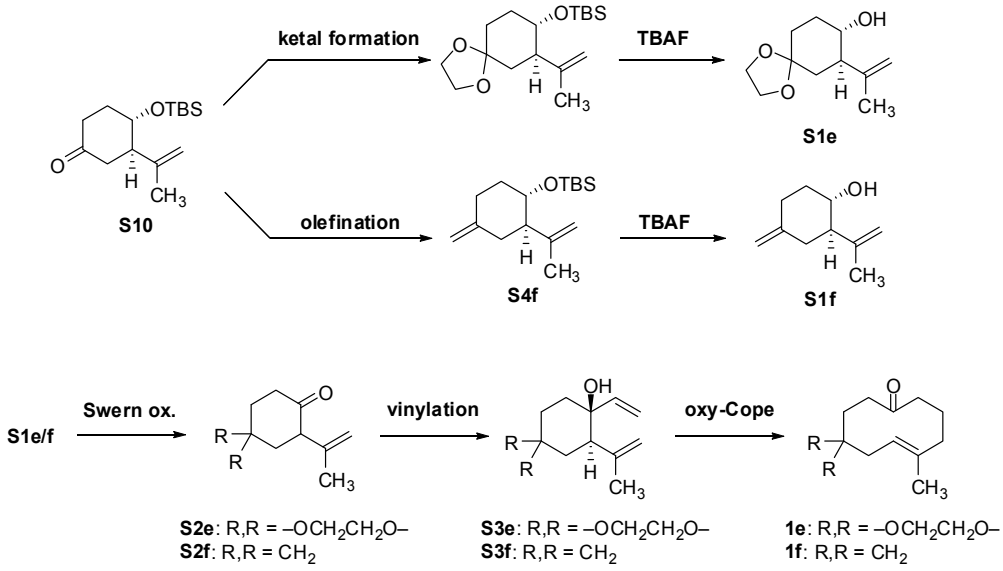


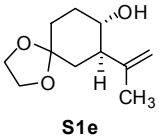
1b

**(*E*)-5,8,8-trimethylcyclodec-5-enone (1b)**

According to General Procedure F, divinyl alcohol **S3b** (110 mg, 0.57 mmol, 1 equiv) underwent an anionic oxy-Cope rearrangement. The crude product was purified by flash column chromatography (Davisil®, Biotage, 0 to 7% $Et_2O$/hexanes) to afford cyclodecenone **1b** (55 mg, 0.28 mmol, 50% yield) as a white crystalline solid. R*f*=0.24 (10% $Et_2O$/hexanes, $KMnO_4$); $^1H$ NMR (500 MHz, 23 °C,$CDCl_3$) δ ppm 5.30 (t, *J*=7.33 Hz, 1 H) 1.51 - 3.09 (m, 12 H) 1.41 (s, 3 H) 0.97 (br. s., 6 H); $^1H$ NMR (500 MHz, –40 °C, $CDCl_3$) δ ppm 5.30 (d, *J*=11.87 Hz, 1 H) 2.85 (dd, *J*=16.65, 10.20 Hz, 1 H) 2.23 - 2.35 (m, 2 H) 2.16 (dd, *J*=12.13, 6.20 Hz, 1 H) 2.03 - 2.13 (m, 2 H) 1.99 (dd, *J*=14.07, 12.26 Hz, 1 H) 1.76 - 1.90 (m, 2 H) 1.60 - 1.72 (m, 2 H) 1.41 (s, 3 H) 1.19 (t, *J*=12.39 Hz, 1 H) 1.00 (s, 3 H) 0.91 (s, 3 H); $^{13}C$ NMR (126 MHz, –40 °C, $CDCl_3$) δ ppm 210.0, 138.6, 123.4, 43.4, 41.5, 40.7, 40.0, 34.3, 34.2, 33.1, 26.4, 24.3, 16.0; FTIR (neat, $cm^{-1}$) 2951 (m) 2928 (m) 2868 (w) 1707 (s) 1472 (w) 1443 (m) 1426 (m) 1386 (m) 1363 (m) 1173 (w) 1108 (s) 910 (w) 839 (w) 740 (w). MS (ESI) *m/z* calc'd for $C_{13}H_{23}O$ $[M+H]^+$: 195.1743; found: 195.1739.

**Schemes for the Synthesis of Transannular Ketone-Ene Substrates 1e and 1f**



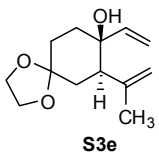



**S1e**

**(±)(7R,8S)-7-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (S1e)**

An oven-dried 50 mL round-bottom flask fitted with a Dean-Stark trap and reflux condenser was charged with **S10** (1.4 g, 5.2 mmol, 1 equiv), ethylene glycol (294 μL, 5.2 mmol, 1 equiv), benzene (10.4 mL) and pTsOH•$H_2O$ (15 mg, cat.). The side arm of the Dean-Stark trap was filled with benzene (10 mL), and the flask was immersed in a 80°C oil bath under $N_2$ overnight. The contents of the flask were concentrated to afford the crude acetal an orange oil that was carried forward without purification.

An oven-dried 50 mL round-bottom flask was charged with the intermediate silyl ether and THF (5 mL) and cooled to 0 °C. To this was added a solution of TBAF (1.0M in THF, 10.4 mL, 10.4 mmol, 2 equiv). The ice bath was removed and the reaction was stirred at room temperature for 48 h. The reaction was quenched with DI water and extracted with $Et_2O$ (3 x 5 mL). The combined organics were diluted with $CH_2Cl_2$, dried over $Na_2SO_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography ($SiO_2$, Biotage, 20 to 100% $Et_2O$/hexanes) to afford **S1e** (681mg, 3.44 mmol, 66% yield, 2 steps) as a pale yellow oil. R*f*=0.28 (50% $Et_2O$/hexanes, CAM); $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 4.93 (s, 1 H) 4.91 (s, 1 H) 3.90 - 4.00 (m, 4 H) 3.44 - 3.55 (m, 1 H) 2.33 (ddd, *J*=13.18, 9.77, 3.91 Hz, 1 H) 1.98 - 2.09 (m, 1 H) 1.83 (d, *J*=1.95 Hz, 1 H) 1.78 (dt, *J*=9.40, 2.87 Hz, 1 H) 1.71 (s, 3 H) 1.67 - 1.73 (m, 1 H) 1.58 - 1.67 (m, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 145.32, 113.97, 108.42, 69.90, 64.59, 64.55, 51.26, 37.98, 33.23, 31.03, 18.93; FTIR (neat, $cm^{-1}$) 3454 (br m), 3073 (w), 2946 (m), 2881 (m), 1646 (w), 1361 (m), 1142 (m), 1142 (m), 1088 (s), 1022 (s), 947 (m), 924 (s); MS (ESI) *m/z* calc'd for $C_{11}H_{19}O_3$ $[M+H]^+$: 199.1329, found: 199.1338.



**S3e**

**(±)-(7R,8S)-7-(prop-1-en-2-yl)-8-vinyl-1,4-dioxaspiro[4.5]decan-8-ol (S3e)**

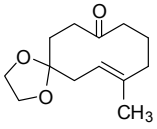
Alcohol **S1e** (681 mg, 3.4 mmol, 1.0 equiv) was oxidized according to General Procedure C to afford the corresponding β,γ-unsaturated ketone **S2e** that was carried forward without further

purification.

According to General Procedure E, crude ketone **S2b** (267.3 mg, 1.6 mmol, 1.0 equiv) was reacted with vinylmagnesium bromide (1.0 M in THF, 8.4 mL, 8.4 mmol, 2.5 equiv) to afford the crude addition product as a yellow oil and in 9.7:1 dr in favor of the title compound. The crude residue was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 40% $Et_2O$/hexanes) to afford **S3e** (441 mg, 2.0 mmol, 57% yield over 2 steps) as a clear oil. R*f*=0.54 (50% Et2O/hexanes, CAM); $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 5.88 (dd, *J*=17.17, 10.76 Hz, 1 H) 5.20 (d, *J*=17.40 Hz, 1 H) 5.01 (d, *J*=10.53 Hz, 1 H) 4.91 (d, *J*=1.37 Hz, 1 H) 4.74 (s, 1 H) 3.80 - 4.11 (m, 4 H) 2.44 (dd, *J*=13.74, 3.66 Hz, 1 H) 2.06 (t, *J*=13.28 Hz, 1 H) 1.96 (td, *J*=13.39, 4.35 Hz, 1 H) 1.70 - 1.85 (m, 2 H) 1.74 (s, 3 H) 1.61 - 1.68 (m, 1H) 1.55 - 1.60 (m, 1 H) 1.51 (dt, *J*=12.82, 2.98 Hz, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 146.81, 145.41, 112.44, 111.50, 109.08, 72.03, 64.39, 49.60, 35.80, 35.60, 30.03, 25.58, 25.55; FTIR (neat, $cm^{-1}$) 3483 (br w), 2965 (m), 2883 (w), 1683 (w), 1438 (w), 1343 (m), 1272 (m), 1211 (w), 1180 (m), 1101 (s), 1037 (m), 992 (s), 953 (s), 917 (s), 733 (s). MS (ESI) *m/z* calc'd for $C_{13}H_{19}O_2$ $[M–H_2O+H]^+$: 207.1380, found: 207.1377; calc'd for $C_{13}H_{20}NaO_3$ $[M+Na]^+$ 247.1305, found 247.1313.

**General Procedure G – Palladium-Catalyzed oxy-Cope Rearrangement**

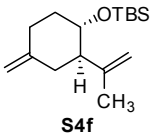
A flame-dried 50 mL round-bottom flask was charged with a stir bar, divinyl alcohol (1.79 mmol, 1 equiv), and THF (17.9 mL). To the resultant solution was added $(C_6H_5CN)_2PdCl_2$ (69 mg, 0.18 mmol, 0.1 equiv) as a solid. The flask was capped with a plastic stopper and was stirred at room temperature overnight. The reaction mixture was concentrated to afford the crude product, which was purified by flash column chromatography.



**1e**

**(*E*)-12-methyl-1,4-dioxaspiro[4.9]tetradec-12-en-8-one (1e)**

According to General Procedure G, divinyl alcohol **S3e** (401 mg, 1.79 mmol, 1 equiv), underwent the palladium-catalyzed oxy-Cope rearrangement. The crude product, an orange solid, was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 50% EtOAc/hexanes) to afford **1e** (234 mg, 1.04 mmol, 58% yield) as a white crystalline solid. R*f*=0.24 (20% EtOAc/hexanes, CAM); $^1$H NMR (500 MHz, $CDCl_3$, 23 °C) d ppm 5.29 (t, *J*=6.87 Hz, 2 H) 3.84 - 4.02 (m, 4 H) 3.04 (br. s., 1 H) 1.49 - 2.55 (m, 11 H) 1.44 (s, 3 H); $^1$H NMR (500 MHz, $CDCl_3$, –40 °C) δ ppm 5.26 (d, *J*=11.23 Hz, 1 H) 3.84 - 4.05 (m, 4 H) 3.03 (dd, *J*=17.09, 10.25 Hz, 1 H) 1.97 - 2.47 (m, 8 H) 1.81 (td, *J*=12.21, 3.40 Hz, 1 H) 1.65 (d, *J*=10.25 Hz, 1 H) 1.51 - 1.61 (m, 1 H) 1.41 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$, 23 °C) δ ppm 208.66, 139.99, 121.42, 109.78, 64.33, 42.86, 40.97, 39.00, 37.84, 31.10, 25.17, 15.79; FTIR (neat, $cm^{-1}$) 2936 (M), 2904 (m) 2882 (m), 1696 (s), 1428 (m), 1363 (m), 1261 (m), 1173 (w), 1107 (s), 1033 (s), 983 (m), 915 (s), 888 (s), 673 (w). MS (ESI) *m/z* calc'd for $C_{13}H_{21}O_3$ $[M+H]^+$: 225.1485, found: 225.1499; calc'd for $C_{13}H_{20}NaO_3$ $[M+Na]^+$ 247.1305, found 247.1319.

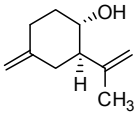


**S4f**

**(±)-tert-butyldimethyl((1R,2S)-4-methylene-2-(prop-1-en-2-yl)cyclohexyloxy)silane (S4f)**

To an oven-dried 25 mL round-bottom flask containing a stir bar and methyltriphenylphosphonium bromide (845 mg, 2.25 mmol, 1.5 equiv) was added $Et_2O$ (10 mL) under nitrogen. The white suspension was cooled to 0 ºC, and after 5 m at this temperature, KO*t*-Bu (236 mg, 2.1 mmol, 1.4 equiv) was added

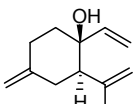
as a solid, portion-wise (roughly thirds) over 10 m, resulting in the formation of a bright yellow suspension. After stirring the reaction mixture at 0 °C for an additional 30 m, a solution of ketone **S10** (402 mg, 1.5 mmol, 1 equiv.) in $Et_2O$ (2 mL + 2 x 1 mL rinses to complete the transfer) was added dropwise. The reaction mixture was stirred under nitrogen allowing the temperature to gradually reach room temperature. After 16 h, the pale orange reaction mixture was quenched by addition of saturated aqueous $NH_4Cl$ (5 mL). The reaction mixture was diluted with $H_2O$ (15 mL) and extracted with $Et_2O$ (3 x 10 mL). The combined organics were diluted with $CH_2Cl_2$, dried over $Na_2SO_4$, filtered, and concentrated to provide a yellow solid which was purified by flash column chromatography (silica gel, Biotage, 0 to 4% $Et_2O$ in hexanes) to provide the desired silyl ether **S4f** as a clear oil (385 mg, 1.44 mmol, 96% yield). R*f* = 0.9 (5% $Et_2O$ in hexanes) $^1$H NMR (500 MHz, $CDCl_3$) d ppm 4.78 (d, *J*=5.37 Hz, 1 H), 4.78 (d, *J*=5.37 Hz, 1 H), 4.64 (d, *J*=6.35 Hz, 1 H), 4.64 (d, *J*=6.35 Hz, 1 H), 3.63 (td, *J*=9.16, 4.15 Hz, 1 H) 2.29 (dt, *J*=14.16, 3.90 Hz, 1 H) 2.22 (dd, *J*=8.79, 1.95 Hz, 1 H) 2.00 - 2.14 (m, 3 H) 1.95 (dq, *J*=12.57, 3.95 Hz, 1 H) 1.71 (s, 3 H) 1.33 - 1.45 (m, 1 H) 0.85 (s, 9 H) 0.03 (s, 3 H) 0.01 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) d ppm 147.72, 147.22, 111.69, 108.05, 72.98, 54.23, 38.44, 36.33, 32.76, 25.96 (3 C), 20.98, 18.23, -3.85, -4.70; FTIR (neat, $cm^{-1}$) 2937 (m), 2857 (m), 1650 (w), 1462 (w), 1362 (w), 1255 (m), 1101 (s), 1055 (w), 1006 (w), 886 (s), 834 (s), 773 (s), 670 (m); MS (ESI) *m/z* calc'd for $C_{16}H_{31}OSi$ $[M+H]^+$: 267.2139, found: 267.2140; calc'd for $C_{16}H_{30}KO$ $[M+K]^+$ 305.1698, found 305.1699.



**S1f**

**(±)-(1S,2R)-4-methylene-2-(prop-1-en-2-yl)cyclohexanol (S1f)**

An oven-dried 25 mL round-bottom flask under nitrogen was charged with a stir bar, **S4f** (755.1 mg, 2.83 mmol, 1 equiv), and $Et_2O$ (2.8 mL), in that order. The resultant solution was cooled to 0 °C, and after stirring for 5 m at this temperature, TBAF (5.7 mL, 1 M solution in THF, 5.7 mmol, 2.0 equiv.) was added dropwise. The flask was brought to room temperature and the reaction mixture was stirred for 48 h, at which point it was returned to 0 °C and quenched by the addition of DI $H_2O$ (5 mL). The mixture was diluted with $H_2O$ (5 mL) and extracted with $Et_2O$ (3 x 10 mL). The combined organics were diluted with $CH_2Cl_2$, dried over $Na_2SO_4$, filtered, and concentrated to provide the crude product as an orange oil, which was purified by flash column chromatography (silica, Biotage, 0 to 40% $Et_2O$/hexanes) to provide **S1f** as a clear oil (412 mg, 2.7 mmol, 96% yield) R*f* = 0.12 (20% $Et_2O$ in hexanes, $KMnO_4$); $^1$H NMR (500 MHz, $CDCl_3$) d ppm 4.89 (quin, *J*=1.60 Hz, 1 H) 4.84 (s, 1 H) 4.64 - 4.67 (m, 1 H) 4.63 (d, *J*=1.37 Hz, 1 H) 3.55 (td, *J*=10.07, 4.12 Hz, 1 H) 2.26 - 2.33 (m, 1 H) 2.19 - 2.24 (m, 1 H) 1.97 - 2.14 (m, 5 H) 1.70 (s, 3 H) 1.27 - 1.37 (m, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) d ppm 146.82, 145.86, 113.40, 108.66, 70.37, 55.03, 37.93, 34.63, 32.73, 18.99; FTIR (neat, $cm^{-1}$) 3404 (br, m), 3073 (w), 2938 (m), 1647 (m), 1439 (m), 1253 (w), 1067 (s), 1043 (m), 1021 (m), 888 (s), 834 (w), 654 (s). MS (ESI) *m/z* calc'd for $C_{10}H_{17}O$ $[M+H]^+$: 153.1274, found: 153.1273; calc'd for $C_{10}H_{16}NaO$ $[M+Na]^+$ 175.1093, found 175.1101.

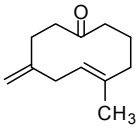


**S3f**

**(±)-(1S,2R)-4-methylene-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (S3f)**

Alcohol **S1f** (400 mg, 2.63 mmol, 1.0 equiv) was oxidized according to General Procedure C to afford the corresponding β,γ-unsaturated ketone **S2f** that was carried forward without further purification.

According to General Procedure E, ketone **S2f** was reacted with vinylmagnesium bromide (1.0 M in THF, 6.5 mL, 6.5 mmol, 2.5 equiv) to afford the crude addition product as a yellow oil and in >19:1 dr in favor of the title compound. The crude material was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 10% $Et_2O$/hexanes) to provide **S3f** as a pale yellow oil (246 mg, 1.4 mmol, 52% yield, 2 steps). R*f* = 0.43 (10% $Et_2O$ in hexanes, $KMnO_4$); $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 5.85 (dd, *J*=17.17, 10.76 Hz, 1 H) 5.20 (dd, *J*=17.40, 1.37 Hz, 1 H) 5.00 (dd, *J*=10.53, 1.37 Hz, 1 H) 4.89 - 4.94 (m, 1 H) 4.77 (s, 1 H) 4.65 - 4.68 (m, 1 H) 4.62 - 4.65 (m, 1 H) 2.54 (td, *J*=13.05, 1.37 Hz, 1 H) 2.38 - 2.50 (m, 1 H) 2.17 (dd, *J*=13.28, 3.66 Hz, 1 H) 2.13 (dquin, *J*=13.28, 1.83 Hz, 1 H) 2.05 (ddd, *J*=13.30, 3.66, 1.83 Hz, 1 H) 1.82 (d, *J*=1.83 Hz, 1 H) 1.75 (s, 3 H) 1.72 (dd, *J*=4.81, 2.52 Hz, 1 H) 1.56 (tdd, *J*=13.74, 4.58, 1.83 Hz, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) d ppm 148.70, 147.41, 145.50, 112.07, 111.33, 107.32, 72.68, 53.60, 39.12, 36.12, 30.05, 25.54; FTIR (neat, $cm^{-1}$) 3547 (br, m), 3072 (m), 2981 (m), 2938 (m), 2918 (m), 2849 (w), 1843 (w), 1786 (w), 1650 (m), 1639 (m), 1438 (m), 1374 (m), 1281 (m), 1135 (m), 997 (m), 950 (s), 888 (s). MS (APCI) *m/z* calc'd for $C_{12}H_{16}$ $[M–H_2O+H]^+$: 161.1; found: 161.1.

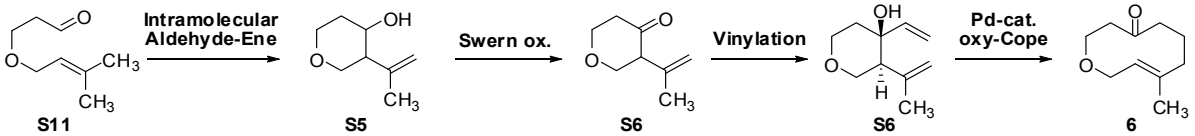


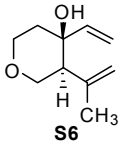
**1f**

**(*E*)-5-methyl-8-methylenecyclodec-5-enone (1f)**

According to General Procedure F, divinyl alcohol **S3f** (200 mg, 1.12 mmol, 1 equiv) underwent an anionic oxy-Cope rearrangement. The crude material was purified by flash column chromatography (Davisil$^{TM}$, Biotage, 0 to 5% $Et_2O$/hexanes) to provide cyclodecenone **1f** as a clear oil (95 mg, 0.53 mmol, 47 yield). R*f* = 0.31 (5% $Et_2O$/hexanes, $KMnO_4$); $^1$H NMR (500 MHz, 23 °C, $CDCl_3$) δ ppm 5.09 (t, *J*=7.33 Hz, 1 H) 4.73 - 4.76 (m, 1 H) 4.72 (s, 1 H) 1.54 - 3.14 (m, 12 H) 1.46 (s, 3 H); $^1$H NMR (399 MHz, –20 °C, $CDCl_3$) δ ppm 5.08 (d, *J*=10.53 Hz, 1 H) 4.73 (s, 1 H) 4.70 (s, 1 H) 2.71 - 2.86 (m, 1 H) 2.51 - 2.71 (m, 2 H) 2.41 (dd, *J*=14.43, 9.75 Hz, 2 H) 2.10 - 2.34 (m, 4 H) 2.04 (d, *J*=12.48 Hz, 1 H) 1.77 (td, *J*=12.48, 3.51 Hz, 1 H) 1.57 - 1.70 (m, 1 H) 1.44 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 209.2, 149.2, 138.8, 124.9, 113.0, 45.2, 43.0, 41.0, 37.8, 30.9, 25.0, 15.8; FTIR (neat, $cm^{-1}$) 3071 (w), 2924 (m), 2856 (m), 1703 (s), 1638 (m), 1443 (m), 1426 (m), 1381 (w), 1351 (m), 1260 (w), 1175 (w), 1103 (s), 1081 (m), 1020 (w), 907 (s), 846 (m), 804 (m), 633 (m). MS (ESI) *m/z* calc'd for $C_{12}H_{18}ONa$ $[M+Na]^+$ 201.1250, found 201.1259.

**Scheme for the Synthesis of Transannular Ketone-Ene Substrate 6**



**S6**

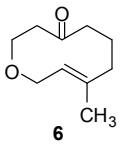
**(±)-(3*S*,4*S*)-3-(prop-1-en-2-yl)-4-vinyltetrahydro-2H-pyran-4-ol (S6)**

A 200 mL round-bottom flask was charged with a stir bar and powdered 4Å MS. The sieves were activated by flame-drying under reduced pressure (1 torr) and cooled under argon. $CH_2Cl_2$ (86 mL) was added by syringe, followed by aldehyde **S11** (6.1 g, 43 mmol, 1 equiv). The resultant suspension was cooled to –78 °C, and $SnCl_4$ (4.4 mL, 38 mmol, 0.90 equiv) was added neat, dropwise. The flask was transferred to a –60 °C cryocool and the mixture was stirred at this temperature overnight. The flask was transferred to a 0 °C bath, and the

reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ (50 mL). The contents were diluted with an additional 50 mL DI $H_2O$, and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organics were dried over $Na_2SO_4$, filtered, and concentrated to afford the crude product as a yellow oil and a 1.8:1.0 mixture of diastereomeric alcohols (**S5**, 2.8 g). This crude product was taken on to the next step without further purification.[3]

The crude product **S5** was oxidized according to General Procedure C to afford **S6**, which was carried forward without further purification.[3]

According to General Procedure D, the intermediate ketone **S6** was reacted with vinylmagnesium bromide (1.0 M in THF, 23.6 mL, 23.6 mmol, 1.2 equiv) to afford the crude addition product in 3.9:1 dr in favor of the title compound. The crude product was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 50% EtOAc/hexanes) to afford divinyl alcohol **S6** as a clear oil (1.2 g, 7.1 mmol, 17% over 3 steps). R*f*=0.32 (20% EtOAc/hexanes); $^1$H NMR (600 MHz, $CDCl_3$) δ ppm 5.89 (dd, *J*=17.13, 10.69 Hz, 1 H) 5.25 (dd, *J*=17.13, 1.03 Hz, 1 H) 5.07 (dd, *J*=10.69, 1.03 Hz, 2 H) 4.97 (d, *J*=1.17 Hz, 1 H) 4.69 (s, 1 H) 3.74 - 3.86 (m, 2 H) 3.61 - 3.72 (m, 2 H) 2.37 (dd, *J*=11.42, 4.69 Hz, 1 H) 1.89 (d, *J*=2.34 Hz, 1 H) 1.83 (dddd, *J*=13.95, 11.31, 6.66, 2.34 Hz, 1 H) 1.77 (s, 3 H) 1.52 (d, *J*=13.77 Hz, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 144.8, 143.9, 113.0, 112.1, 70.6, 66.8, 63.5, 50.9, 37.0, 26.6; FTIR (neat, $cm^{-1}$) 3436 (br m) 3085 (w) 2954 (m) 2869 (m) 1639 (m) 1374 (m) 1289 (w) 1215 (w) 1114 (s) 968 (s) 917 (s) 867 (s) 815 (m) 734 (m); MS (APCI) *m/z* calc'd for $C_{10}H_{15}O$ $[M–H_2O+H]^+$ 151.1; found 151.2.

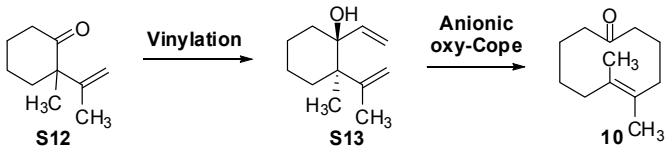


**6**

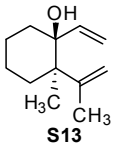
**(*E*)-8-methyl-5,6,7,10-tetrahydro-2H-oxecin-4(3H)-one (6)**

According to General Procedure G, divinyl alcohol **S6** (1.1 g, 6.5 mmol, 1.0 equiv) underwent the palladium-catalyzed oxy-Cope rearrangement. The crude product was purified by flash column chromatography (neutral $Al_2O_3$, 0 to 40% EtOAc/hexanes) to afford keto-olefin **6** (528 mg, 3.14 mmol, 48%) as a white solid. R*f*=0.56 (25% EtOAc/hexanes, $Al_2O_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 5.22 - 5.40 (m, 1 H) 4.13 (d, *J*=12.70 Hz, 1 H) 3.86 - 3.98 (m, 2 H) 3.59 - 3.77 (m, 1 H) 2.94 (dd, *J*=15.38, 8.55 Hz, 1 H) 2.36 - 2.50 (m, 2 H) 2.31 (dd, *J*=15.14, 7.81 Hz, 1 H) 2.16 - 2.26 (m, 1 H) 2.10 (d, *J*=11.23 Hz, 1 H) 1.83 - 1.99 (m, 1 H) 1.78 (d, *J*=11.72 Hz, 1 H) 1.51 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 208.6, 143.1, 123.9, 68.6, 66.8, 47.4, 43.5, 41.1, 26.3, 16.3; FTIR (neat, $cm^{-1}$) 2931 (m) 2868 (m) 1692 (s) 1422 (w) 1354 (m) 1297 (m) 1259 (m) 1241 (m) 1103 (s) 1071 (s) 1044 (s) 859 (m) 808 (m) 791 (m); MS (ESI) *m/z* calc'd for $C_{10}H_{17}O_2$ $[M +H]^+$ 169.1223, found 169.1227; calc'd for $C_{10}H_{15}O$ $[M–H_2O+H]^+$ 151.1117, found 151.1114.

**Scheme for the Synthesis of Planar Chiral Transannular Ketone-Ene Substrate 10**



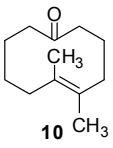
**S12** **S13** **10**



S13

**(±)-(1S,2R)-2-methyl-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (S13)**

According to General Procedure F, ketone **S12** (1.16 g, 7.62 mmol, 1 equiv) was reacted with vinylmagnesium bromide (1.0 M in THF, 18.8 mL, 18.8 mmol, 2.5 equiv) to afford the desired divinyl alcohol in >19:1 dr. The crude product was purified (neutral $Al_2O_3$, Biotage, 0 to 10% $Et_2O$/hexanes) to afford divinyl alcohol **S13** (476 mg, 2.64 mmol, 35%) as a yellow oil. Rf=0.34 (10% $Et_2O$/hexanes, $Al_2O_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 6.10 (dd, *J*=17.09, 10.74 Hz, 1 H) 5.19 (dd, *J*=17.09, 1.46 Hz, 1 H) 5.07 (t, *J*=1.50 Hz, 1 H) 5.00 (dd, *J*=10.74, 1.47 Hz, 1 H) 4.96 (s, 1 H) 2.18 (td, *J*=12.45, 5.37 Hz, 1 H) 2.07 (d, *J*=2.44 Hz, 1 H) 1.79 (s, 3 H) 1.72 - 1.78 (m, 1 H) 1.65 - 1.71 (m, 1 H) 1.53 - 1.59 (m, 2 H) 1.47 - 1.53 (m, 1 H) 1.39 - 1.46 (m, 1 H) 1.22 (s, 3 H) 1.13 - 1.20 (m, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 151.0, 144.4, 114.1, 112.0, 74.2, 46.4, 33.2, 32.9, 23.9, 21.5, 20.9, 19.3; FTIR (neat, $cm^{-1}$) 3540 (br m) 2088 (w) 2929 (s) 2966 (m) 1623 (m) 1447 (m) 1379 (m) 1315 (m) 1195 (w) 1088 (m) 1040 (m) 1000 (m) 975 (s) 917 (s) 901 (s) 888 (s) 684 (m). MS (APCI) *m/z* calc'd for $C_{12}H_{19}$ $[M–H_2O+H]^+$: 163.1; found: 163.2.



10

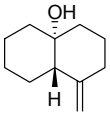
**(±)-(*E*)-5,6-dimethylcyclodec-5-enone (10)**

According to General Procedure F, divinyl alcohol **S13** (243 mg, 1.34 mmol, 1 equiv) underwent an anionic oxy-Cope rearrangement. The crude residue was purified by flash column chromatography (neutral $Al_2O_3$, 0 to 10% $Et_2O$/hexanes) to afford planar chiral cyclodecenone **10** (124 mg, 0.69 mmol, 51%) as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 2.52 (ddt, *J*=16.03, 8.70, 0.90, 0.90 Hz, 1 H) 2.33 - 2.48 (m, 3 H) 2.22 - 2.30 (m, 2 H) 2.00 (dd, *J*=14.65, 6.41 Hz, 1 H) 1.82 (s, 3 H) 1.50 - 1.86 (m, 7 H) 1.48 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 208.5; 132.0, 129.1, 43.1, 41.5, 34.4, 34.2, 26.5, 26.0, 22.4, 19.1, 18.8; FTIR (neat, $cm^{-1}$) 3382 (br m) 2958 (m) 2952 (s) 2861 (s) 1701 (s) 1445 (m) 1428 (m) 1372 (m) 1353 (m) 1199 (w) 1126 (s) 1061 (m) 893 (w) 788 (w). MS (ESI) *m/z* calc'd for $C_{12}H_{19}$ $[M–H_2O+H]^+$ 163.1481; found 163.1484; calc'd for $C_{12}H_{20}NaO$ $[M+Na]^+$ 203.1406; found 203.1418.

**D. Enantioselective Transannular Ketone-Ene Reactions**

**General Procedure H – Enantioselective Cr(III)-Catalyzed Transannular Ketone-Ene Reaction**

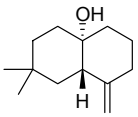
An oven-dried 0.5 dram screw-top vial was charged with a stir bar, activated 4 Å MS (10 mg) and was sealed with a cap containing a Teflon-lined septum. The sieves were flame-dried under vacuum (1 torr) and allowed to cool to room temperature under $N_2$. To the cooled vial was added catalyst **5c** (12.7 mg, 0.02 mmol, 5 mol %, which is 10 mol % based on Cr). The keto-olefin substrate (either **1b**, **1d**, **1e**, **6**, or **8**) (0.2 mmol) was added as a solid to the vial, followed by toluene (50 μL) by microliter syringe. For keto-olefin substrates **1a**, **1c**, and **1f**: toluene (50 μL) was first added, followed by the substrate, which was added neat by microliter syringe. The $N_2$ line was removed, the cap was wrapped with parafilm, and the reaction mixture was stirred at room temperature for 48 h. At this point, an aliquot (~2 μL) was removed from the vial and diluted into an NMR tube with $CDCl_3$ to determine the product diastereomeric ratio. The NMR sample along with the remainder of the crude reaction mixture was directly loaded onto a column ($SiO_2$, neutral $Al_2O_3$, or Davisil$^{TM}$) and eluted to isolate the bicyclic alcohol product.



**4a**

**(4a*R*,8a*S*)-1-methylenedecahydronaphthalen-4a-ol (4a)**

Following General Procedure H, cyclodecenone **1a** (33.3 mg, 0.2 mmol, 1 equiv) underwent a transannular ketone-ene rearrangement to afford **4a** as a single diastereomer. The crude product was purified by flash column chromatography (neutral $Al_2O_3$, Biotage, 0 to 10% $Et_2O$/hexanes, followed by 10% to 50% EtOAc/hexanes) to afford **4a** (27.1 mg, 0.163 mmol, 81% yield) as a pale yellow oil. R*f*=0.16 (10% $Et_2O$/hexanes, $SiO_2$, $KMnO_4$). $[\alpha]_D^{23}$= +33.2° (c=0.82, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 4.86 - 4.92 (m, 1 H) 4.63 (d, *J*=0.98 Hz, 1 H) 2.33 (dquin, *J*=12.70, 2.40, 1 H) 1.92 - 2.06 (m, 2 H) 1.80 (dquin, *J*=13.18, 3.40 Hz, 1 H) 1.66 - 1.75 (m, 2 H) 1.54 - 1.66 (m, 3 H) 1.38 - 1.54 (m, 4 H) 1.33 (td, *J*=13.31, 4.15 Hz, 1 H) 1.21 - 1.37 (m, 1 H) $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 150.4, 108.6, 72.0, 49.5, 40.0, 38.7, 36.7, 26.1, 24.0, 23.9, 21.4; FTIR (neat, $cm^{-1}$) 3474 (br m), 2930 (s) 2853 (m) 1643 (w) 1446 (m) 1251 (w) 1186 (w) 1089 (m) 949 (s) 893 (m) 756 (m) 700 (m). MS (APCI) *m/z* calc'd for $C_{11}H_{19}O$ $[M+H]^+$: 167.2; found: 167.1. The enantiomeric excess was determined to be 93% by chiral GC analysis (CHIRALDEX β-PH, 100 °C, 14 psi, 20:1 split) $t_R$(minor) = 21.47 min, $t_R$(major) = 22.60 min..

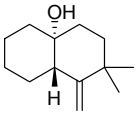


**4b**

**(4a*S*,8a*S*)-7,7-dimethyl-1-methylenedecahydronaphthalen-4a-ol (4b)**

Following General Procedure H, cyclodecenone **1b** (38.9 mg, 0.2 mmol, 1 equiv) underwent a transannular ketone-ene rearrangement to afford **4b** as a single diastereomer. The crude product was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 10% $Et_2O$/hexanes) to afford **4b** as a clear oil (37.7 mg, 0.19 mmol, 97% yield). R*f*=0.34 (10% $Et_2O$/hexanes, $KMnO_4$). $[\alpha]_D^{23}$= +17.4° (c=0.43, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 4.90 (q, *J*=1.53 Hz, 1 H) 4.65 (d, *J*=0.92 Hz, 1 H) 2.36 (ddt, *J*=12.93, 4.01, 2.06, 2.06 Hz, 1 H) 2.18 (d, *J*=14.19 Hz, 1 H) 2.04 (td, *J*=13.16, 4.81 Hz, 1 H) 1.53 - 1.78 (m, 7 H) 1.41 - 1.50 (m, 2 H) 1.15 - 1.21 (m, 2 H) 0.99 (s, 3 H) 0.94 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 150.3, 108.5, 71.6, 45.1, 39.6, 36.83, 36.75, 34.9, 34.0, 33.4, 30.6, 24.3, 24.0; FTIR (neat, $cm^{-1}$) 3471 (br m), 3083 (w), 2931 (s), 1644 (m), 1441 (m), 1364 (m), 1252 (w), 1194 (w), 1093 (m), 1039 (w), 970 (m), 948 (m), 923 (m), 893 (s), 758 (w). MS (ESI) *m/z* calc'd for

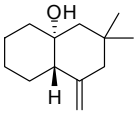
$C_{13}H_{23}O$ $[M+H]^+$: 195.1743; found: 195.1736; calc'd for $C_{13}H_{26}NO$ $[M+NH_4]^+$ 212.2009; found 212.2007. The enantiomeric excess was determined to be 94% by chiral GC analysis (CHIRALDEX β-PH, 100 °C, 14 psi, 20:1 split) $t_R$(minor) = 28.24 min, $t_R$(major) = 30.18 min.



**4c**

**(4a*R*,8a*S*)-2,2-dimethyl-1-methylenedecahydronaphthalen-4a-ol (4c)**

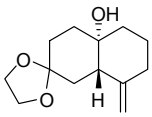
Following General Procedure H, cyclodecenone **1c** (38.9 mg, 0.2 mmol, 1 equiv) underwent a transannular ketone-ene rearrangement to afford **4c** as a single diastereomer. The crude product was purified by flash column chromatography (neutral $Al_2O_3$, Biotage, 0 to 10% $Et_2O$/hexanes, followed by 10% to 50% EtOAc/hexanes) to afford **4c** (32.8 mg, 0.169 mmol, 84% yield) as a pale yellow oil. $[\alpha]_D^{24}$= +16.2° (c=1.0, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 4.91 - 4.98 (m, 1 H) 4.70 (s, 1 H) 2.19 - 2.29 (m, 1 H) 1.78 - 1.87 (m, 1 H) 1.72 (dquin, *J*=13.74, 2.30 Hz, 1 H) 1.54 - 1.69 (m, 2 H) 1.42 - 1.54 (m, 4 H) 1.33 - 1.40 (m, 2 H) 1.22 - 1.33 (m, 2 H) 1.12 (s, 3 H) 1.08 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 156.8, 106.9, 72.1, 45.3, 38.9, 36.99, 36.93, 36.4, 29.7, 26.3, 26.0, 24.7, 21.5; FTIR (neat, $cm^{-1}$) 3474 (br m) 3096 (w) 2930 (s) 2854 (m) 1707 (w) 1632 (m) 1449 (m) 1364 (m) 1179 (w) 1081 (m) 990 (m) 955 (s) 915 (m) 898 (s) 857 (m); MS (ESI) *m/z* calc'd for $C_{13}H_{21}$ $[M-H_2O+H]^+$: 177.1638; found: 177.1639; calc'd for $C_{13}H_{22}NaO$ $[M+Na]^+$ 217.1563; found 217.1567. The enantiomeric excess was determined to be 94% by chiral GC analysis (CHIRALDEX β-PH, 100 °C, 14 psi, 20:1 split) $t_R$(minor) = 40.28 min, $t_R$(major) = 41.89 min.



**4d**

**(4a*R*,8a*S*)-3,3-dimethyl-1-methylenedecahydronaphthalen-4a-ol (4d)**

Following General Procedure H, cyclodecenone **1d** (38.9 mg, 0.2 mmol, 1 equiv) underwent a transannular ketone-ene rearrangement to afford **4d**, as a single diastereomer but as a mixture of regioisomers. The crude product was purified by flash column chromatography (neutral $Al_2O_3$, Biotage, 0 to 10% $Et_2O$/hexanes, followed by 10% to 50% EtOAc/hexanes). The product was isolated as a mixture with an inseparable olefin isomer in a combined yield of 32% (12.5 mg) and was formed as a racemate. The characterization data provided here were measured on a racemic sample. $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 4.85 (d, *J*=1.83 Hz, 1 H) 4.71 (s, 1 H) 2.04 (dd, *J*=12.82, 2.29 Hz, 1 H) 1.99 (d, *J*=12.82 Hz, 0 H) 1.90 (dd, *J*=10.99, 4.58 Hz, 1 H) 1.74 - 1.86 (m, 1 H) 1.64 - 1.72 (m, 1 H) 1.41 - 1.64 (m, 5 H) 1.36 (d, *J*=14.19 Hz, 1 H) 1.15 - 1.33 (m, 3 H) 1.01 (s, 3 H) 0.95 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 148.4, 109.3, 73.0, 52.2, 50.4, 49.4, 39.7, 34.0, 33.4, 27.4, 26.1, 23.7, 21.1; FTIR (neat, $cm^{-1}$) 3491 (br m) 2081 (w) 2927 (s) 2861 (m) 1648 (m) 1450 (m) 1365 (m) 1162 (m) 1073 (m) 972 (s) 156 (m) 889 (s) 812 (m) 697 (w). MS (ESI) *m/z* calc'd for $C_{13}H_{21}$ $[M-H_2O+H]^+$: 177.2, found: 177.1.

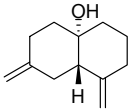


**4e**

**(4a'*S*,8a'*S*)-8'-methyleneoctahydro-1'H-spiro[[1,3]dioxolane-2,2'-naphthalen]-4a'-ol (4e)**

Following General Procedure H, cyclodecenone **1e** (44.9 mg, 0.2 mmol, 1 equiv) underwent a transannular ketone-ene rearrangement to afford **4e** as a single diastereomer. The crude product was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 25% EtOAc/hexanes) to afford **4e** (38.9 mg, 0.173 mmol, 87% yield) as a clear oil.; $[\alpha]_D^{23}$= +58.3° (c=0.107, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ

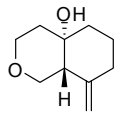
ppm 4.89 (d, *J*=1.37 Hz, 1 H) 4.59 (s, 1 H) 3.84 - 4.06 (m, 3 H) 2.32 (dd, *J*=13.05, 1.60 Hz, 2 H) 1.86 - 2.06 (m, 2 H) 1.81 (t, *J*=12.82 Hz, 1 H) 1.63 - 1.76 (m, 3 H) 1.50 - 1.63 (m, 3 H) 1.44 (td, *J*=13.30, 4.12 Hz, 1 H) 1.47 (br. s., 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 149.2, 109.7, 108.8, 71.1, 64.4, 46.9, 38.9, 36.1, 36.0, 32.9, 30.2, 23.8; FTIR (neat, $cm^{-1}$) 3491 (br w), 2932 (s) 2879 (m) 1646 (w) 1441 (w) 1358 (m) 1296 (m) 1270 (m) 1153 (m) 1091 (s) 1031 (m) 988 (m) 965 (m) 950 (m) 932 (m) 898 (m) 836 (m) 757 (m); MS (ESI) *m/z* calc'd for $C_{13}H_{19}O_2$ [M–$H_2O$+H]$^+$: 207.1380; found: 207.1370; calc'd for $C_{13}H_{20}NaO_3$ [M+Na]$^+$ 247.1305; found 247.1297. The enantiomeric excess was determined to be 96% by chiral GC analysis (CHIRALDEX β-Cyclodex, 140 °C, 14 psi, 20:1 split) $t_R$(minor) = 38.63 min, $t_R$(major) = 40.96 min.



**4f**

**(4a*S*,8a*S*)-1,7-dimethylenedecahydronaphthalen-4a-ol (4f)**

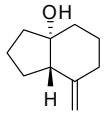
Following General Procedure H, cyclodecenone **1f** (35.7 mg, 0.2 mmol, 1 equiv) underwent a transannular ketone-ene rearrangement to afford **4f** as a single diastereomer. The crude product was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 5% $Et_2O$/hexanes) to afford **4f** (22.2 mg, 0.124 mmol, 62% yield) as a clear oil.; $[\alpha]_D^{24}$= +107.8° (c=0.66, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 4.93 (d, *J*=1.46 Hz, 1 H) 4.66 - 4.69 (m, 2 H) 4.64 - 4.66 (m, 1 H) 2.42 (tdd, *J*=13.70, 13.70, 4.88, 1.95 Hz, 1 H) 2.35 (dquin, *J*=13.18, 2.00 Hz, 1 H) 2.26 - 2.38 (m, 1 H) 2.04 - 2.17 (m, 3 H) 1.98 (td, *J*=13.18, 4.39 Hz, 1 H) 1.85 (ddd, *J*=13.43, 4.88, 2.20 Hz, 1 H) 1.65 - 1.78 (m, 2 H) 1.49 - 1.65 (m, 2 H) 1.43 (tdd, *J*=13.49, 13.49, 9.16, 4.39 Hz, 2 H)$^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 149.7, 148.9, 108.9, 107.5, 71.8, 50.6, 39.8, 39.4, 36.3, 32.9, 30.2, 23.7; FTIR (neat, $cm^{-1}$) 3471 (br m) 3071 (w) 2932 (s) 2850 (m) 1724 (w) 1648 (m) 1441 (m) 1270 (m) 1095 (m) 937 (s) 887 (s) 838 (w) 655 (m). MS (ESI) *m/z* calc'd for C12H17 (M–$H_2O$+H)$^+$: 161.1325; found: 161.1325. The enantiomeric excess was determined to be 94% by chiral GC analysis (CHIRALDEX β-Cyclodex, 100 °C, 14 psi, 20:1 split) $t_R$(minor) = 44.84 min, $t_R$(major) = 48.31 min.



**7**

**(4a*S*,8a*R*)-8-methyleneoctahydro-1H-isochromen-4a-ol (7)**

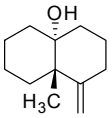
Following General Procedure H, with the exception of a 24 h reaction time, ether **6** (33.6 mg, 0.2 mmol, 1 equiv) underwent a transannular ketone-ene rearrangement to afford **7** as a single diastereomer. The crude product was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 40% EtOAc/hexanes) to afford **7** (4.4 mg, 0.026 mmol, 13% yield) as a clear oil. R*f*=0.40 (25% EtOAc/hexanes, CAM); $[\alpha]_D^{23}$= +15.3° (c=0.36, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 4.90 (s, 1 H) 4.40 (s, 1 H) 3.71 - 3.85 (m, 3 H) 3.66 (t, *J*=11.20 Hz, 1 H) 2.26 - 2.36 (m, 2 H) 2.06 (td, *J*=13.18, 4.88 Hz, 1 H) 1.54 - 1.80 (m, 6 H) 1.42 - 1.54 (m, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 146.5, 108.9, 69.9, 65.0, 64.0, 48.6, 38.9, 38.2, 36.3, 23.5; FTIR (neat, $cm^{-1}$) 3448 (br m) 2934 (m) 2867 (m) 1647 (m) 1439 (w) 1391 (w) 1250 (w) 1170 (m) 1120 (m) 1081 (s) 1025 (m) 967 (s) 945 (m) 888 (s) 854 (s) 832 (w). MS (APCI) *m/z* calc'd for $C_{10}H_{15}O$ [M–$H_2O$+H]$^+$: 151.1; found: 151.1. The enantiomeric excess was determined to be 49% by chiral GC analysis (CHIRALDEX γ-TA, 100 °C, 14 psi, 20:1 split) $t_R$(major) = 26.30 min, $t_R$(minor) = 29.25 min.



**9**

**(3a*R*,7a*S*)-7-methyleneoctahydro-1H-inden-3a-ol (9)**

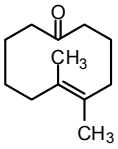
Following General Procedure H, with the exception of a 24 h reaction time, cyclononenone **8** (30.4 mg, 0.2 mmol, 1 equiv) underwent a transannular ketone-ene rearrangement to afford **9** as a single diastereomer. The crude product was purified by flash column chromatography ($SiO_2$, Biotage, 0 to 10% $Et_2O$/hexanes) to afford **9** (5.6 mg, 0.037 mmol, 18% yield) as a clear oil. R*f*=0.42 (10%$Et_2O$/hexanes); $[\alpha]_D^{23}$= +6.1° (c=0.17, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$) δ ppm 4.93 (q, *J*=1.76 Hz, 1 H) 4.69 (q, *J*=1.76 Hz, 1 H) 2.32 (ddd, *J*=15.55, 3.81, 1.76 Hz, 1 H) 2.13 (dd, *J*=12.03, 6.16 Hz, 1 H) 1.90 - 2.01 (m, 2 H) 1.72 - 1.87 (m, 4 H) 1.63 - 1.71 (m, 2 H) 1.60 (dt, *J*=13.50, 4.40 Hz, 1 H) 1.52 - 1.57 (m, 1 H) 1.43 (td, *J*=13.21, 4.70 Hz, 1 H) 1.34 (br. s., 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 148.5, 108.5, 80.5, 53.9, 38.0, 36.3, 35.2, 24.0, 23.7, 20.3. FTIR (neat, $cm^{-1}$) 3476 (br m), 2930 (s) 1650 (m) 1439 (m) 1287 (w) 1246 (m) 1188 (w) 1056 (m) 964 (s) 893 (s) 873 (s) 756 (s). MS (APCI) *m/z* calc'd for $C_{10}H_{15}$ $[M–H_2O+H]^+$: 135.1; found: 135.1. The enantiomeric excess was determined to be 68% by chiral GC analysis (CHIRALDEX β-Cyclosil, 90 °C, 14 psi, 100:1 split) $t_R$(minor) = 29.16 min, $t_R$(major) = 29.62 min.



**11**

**(4a*R*,8a*S*)-8a-methyl-1-methylenedecahydronaphthalen-4a-ol (11)**

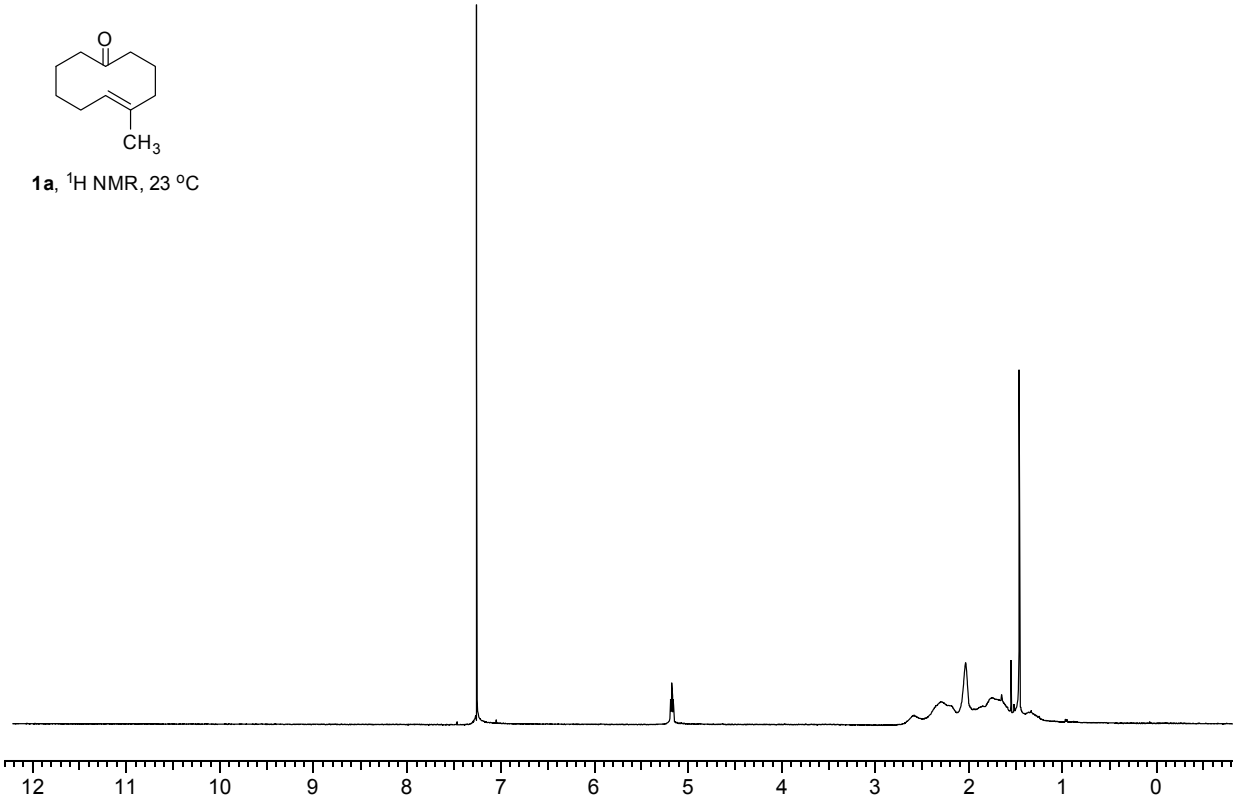
An oven-dried 0.5 dram screw-top vial was charged with a stir bar, activated 4 Å MS (10 mg) and was sealed with a cap containing a Teflon-lined septum. The sieves were flame-dried under vacuum (1 torr) and allowed to cool to room temperature under $N_2$. To the cooled vial was added catalyst **5c** (12.7 mg, 0.02 mmol, 5 mol %, which is 10 mol % based on Cr). Toluene (50 μL) was first added, followed by the cyclodecenone **10** (36.0 mg, 0.2 mmol, 1 equiv), which was added neat by microliter syringe. The $N_2$ line was removed, the cap was wrapped with electrical tape, and the vial was immersed in an oil bath at 50 °C and stirred at this temperature for 24 h. 1,3,5-trimethoxybenzene (3.4 mg, 0.02 mmol, 0.1 equiv) was added as a solid followed by $CDCl_3$ (~1 mL). The conversion was determined to be 19%, based on integration of the $^1$H NMR spectrum. The crude product was purified by flash column chromatography (neutral $Al_2O_3$, Biotage, 0 to 10% $Et_2O$/hexanes). Recovered **10** eluted first and was isolated as a clear oil (24.6 mg, 0.137 mmol, 69%), and decalinol **11** was isolated as a clear oil (4.3 mg, 0.024 mmol, 12% yield). R*f*=0.3 (10% $Et_2O$/hexanes). $^1$H NMR (600 MHz, $CDCl_3$) δ ppm 4.90 (t, *J*=1.76 Hz, 1 H) 4.72 (s, 1 H) 2.40 - 2.54 (m, 1 H) 2.10 - 2.17 (m, 1 H) 1.82 - 1.93 (m, 1 H) 1.64 - 1.80 (m, 3 H) 1.53 - 1.63 (m, 3 H) 1.44 - 1.52 (m, 1 H) 1.40 (m, *J*=13.50 Hz, 1 H) 1.23 - 1.32 (m, 3 H) 1.19 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 154.9, 109.3, 74.1, 44.0, 34.2, 33.2, 31.8, 30.8, 29.8, 23.3, 22.7, 21.4; FTIR (neat, $cm^{-1}$) 3433 (br w) 2922 (s) 2852 (m) 1718 (w) 1642 (w) 1462 (m) 1377 (w) 1260 (w) 1103 (m) 803 (w). MS (APCI) *m/z* calc'd for $C_{12}H_{19}$ $[M–H_2O+H]^+$ 163.1; found 163.2. The enantiomeric excess was determined to be 73% by chiral GC analysis (CHIRALDEX γ-TA, 90 °C, 14 psi, 20:1 split) $t_R$(minor) = 33.28 min, $t_R$(major) = 34.94 min.



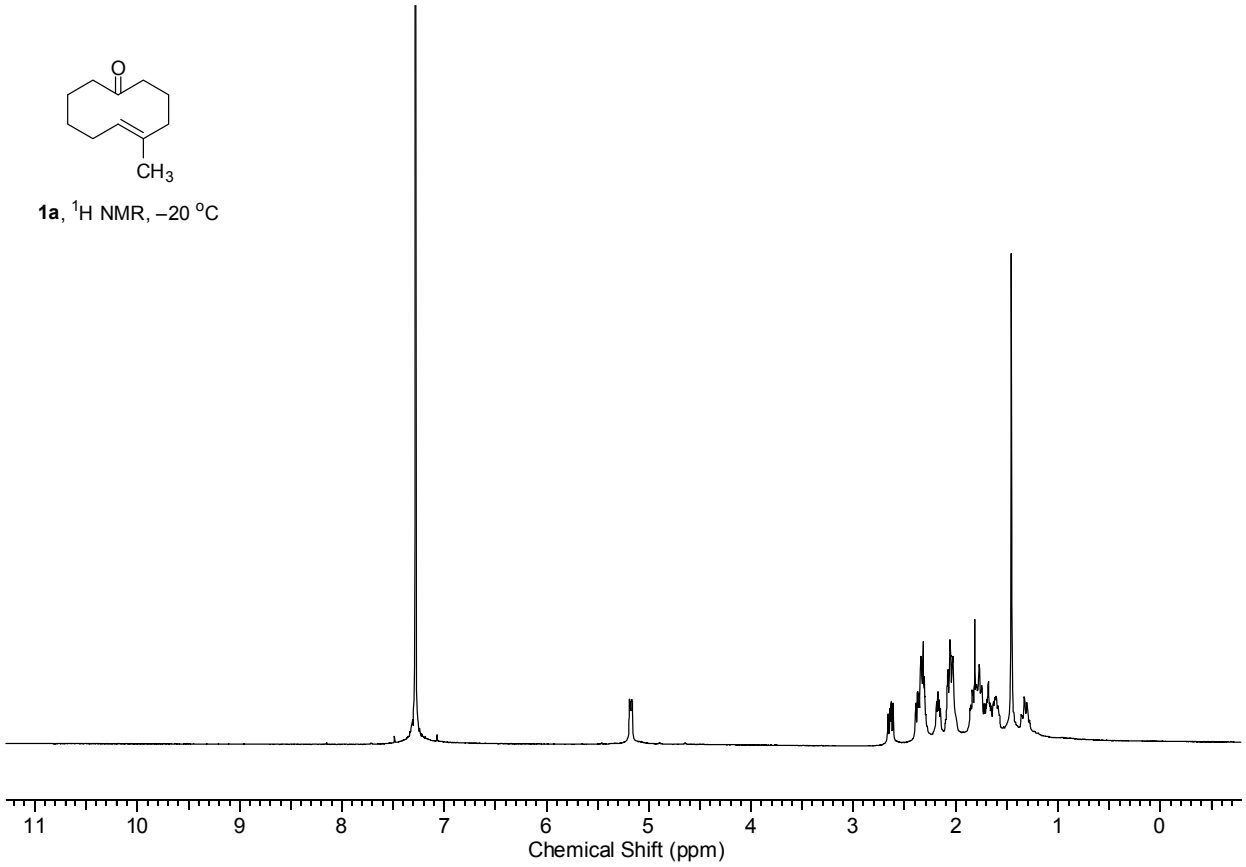
recovered **10**

Characterization for recovered **10**: $[\alpha]_D^{23}$= +2.4° (c=0.68, $CHCl_3$), The enantiomeric excess was determined to be 10% by chiral HPLC analysis (CHIRALCEL OD-H, 2% IPA/hexanes, 1 mL/min, 210 nm) $t_R$(major) = 5.89 min, $t_R$(minor) = 6.32 min.

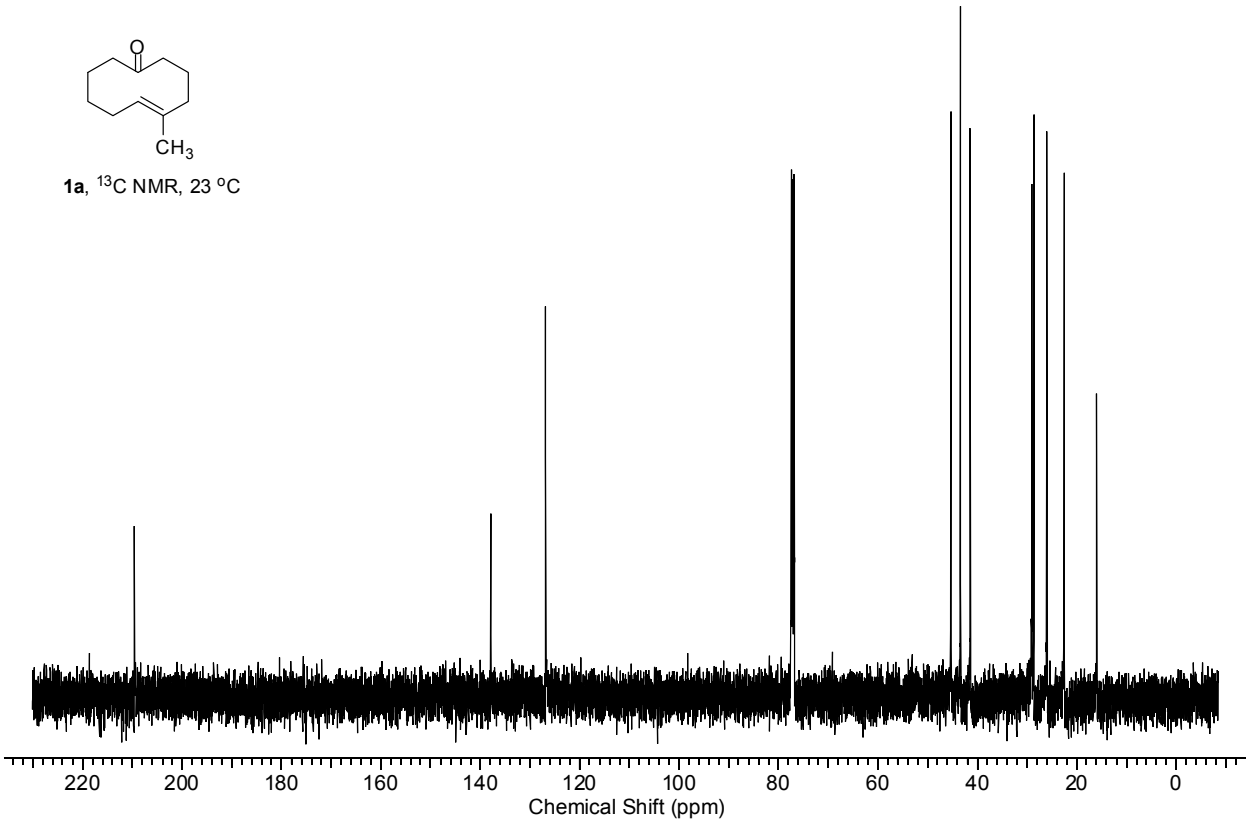
**E. $^{1}$H and $^{13}$C NMR of Substrates for the Transannular Ketone-Ene Reaction**



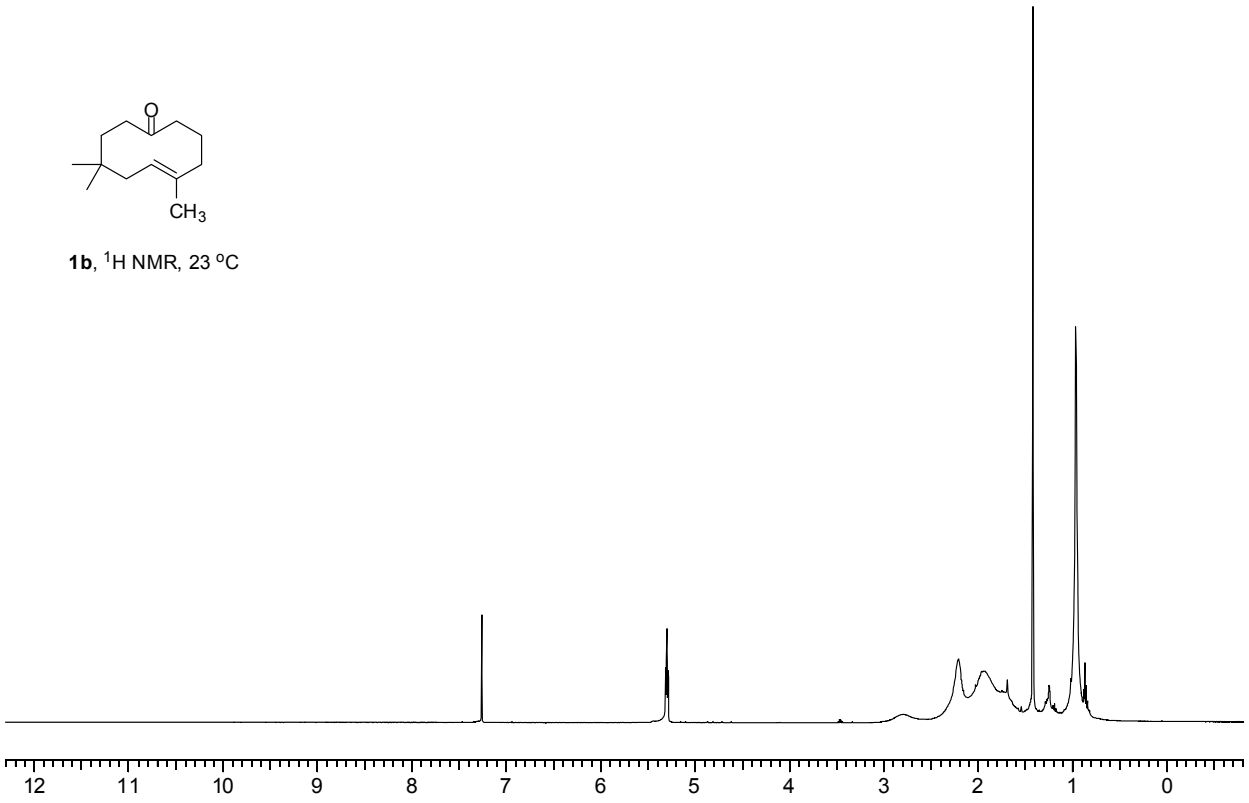

**1a**, $^{1}$H NMR, 23 $^{o}$C



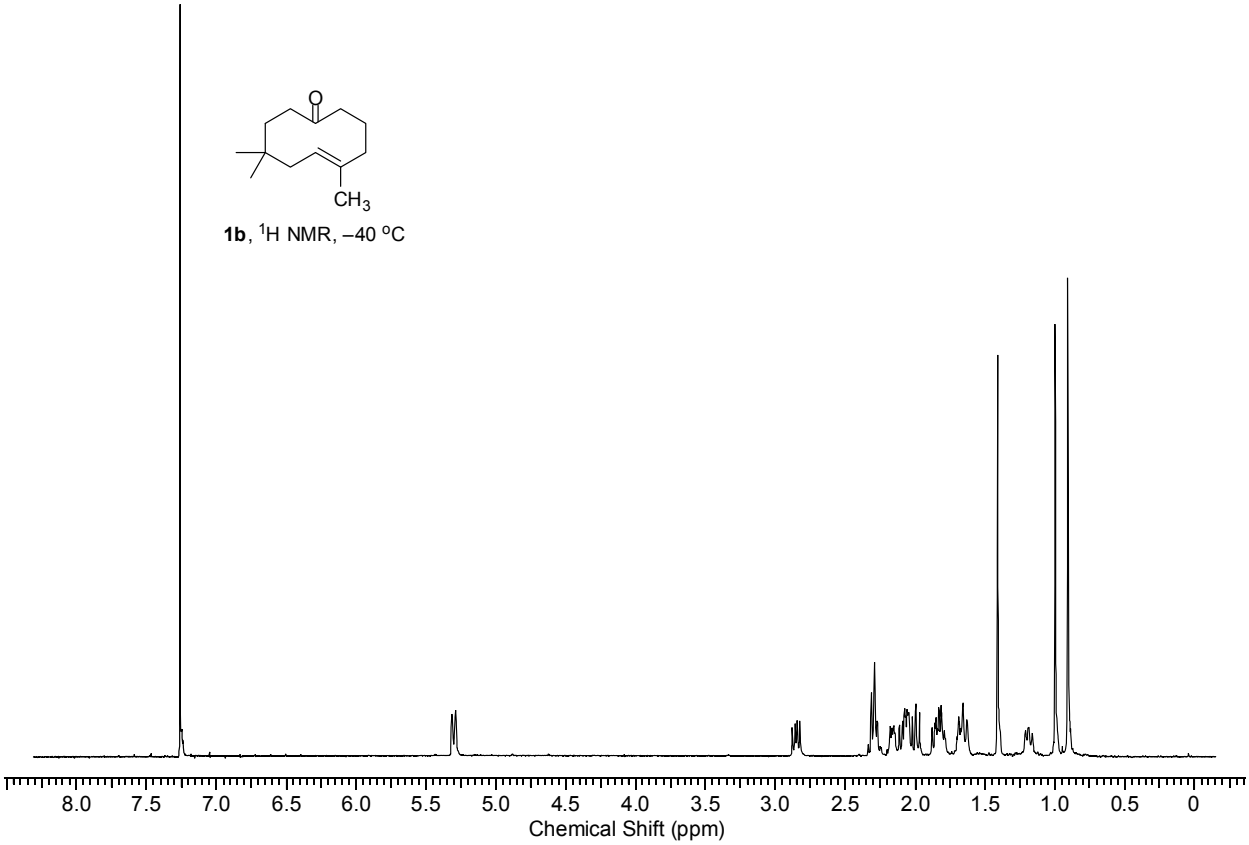

**1a**, $^{1}$H NMR, –20 $^{o}$C



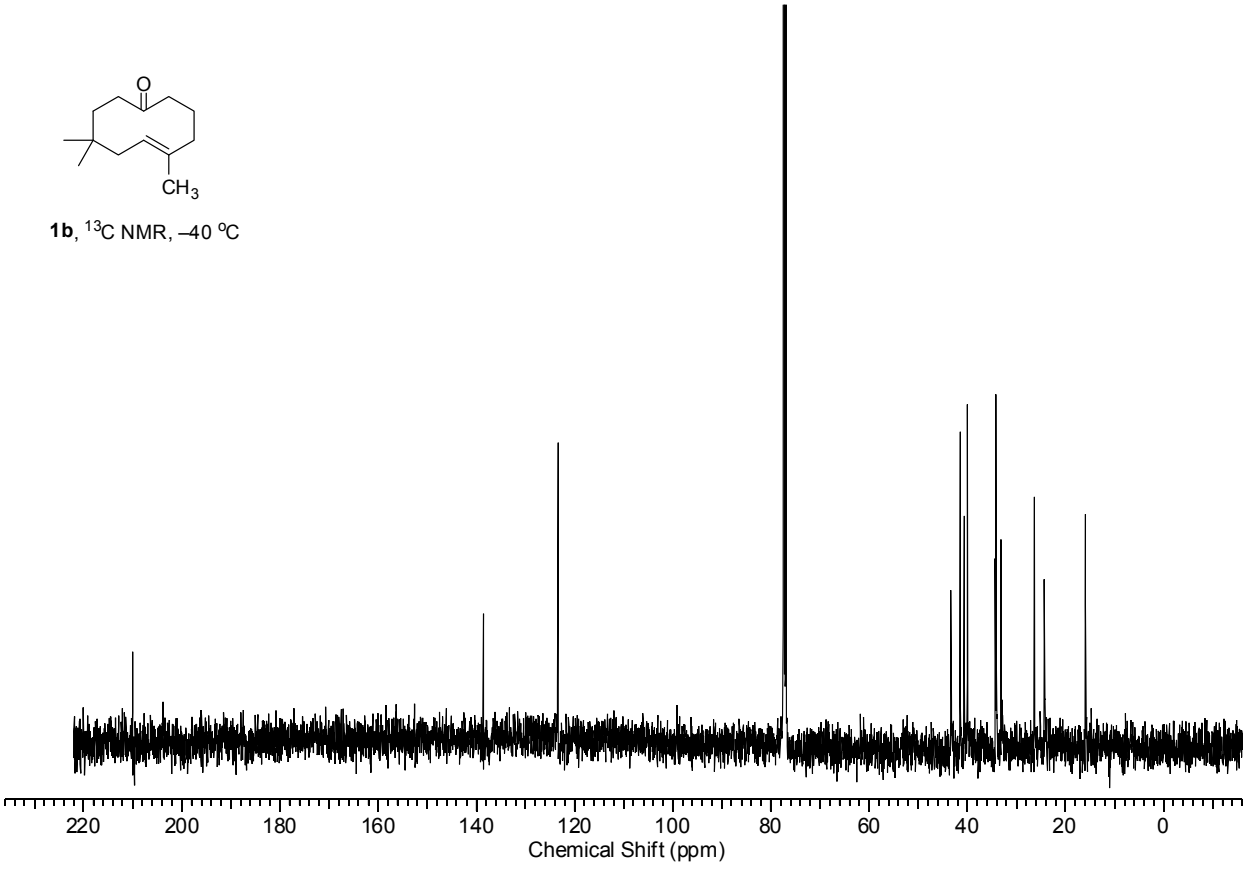

**1a**, $^{13}C$ NMR, 23 $^{o}C$



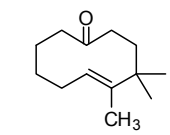

**1b**, $^{1}H$ NMR, 23 $^{o}C$




**1b**, $^{1}$H NMR, –40 $^{o}$C

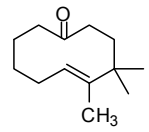



**1b**, $^{13}$C NMR, –40 $^{o}$C

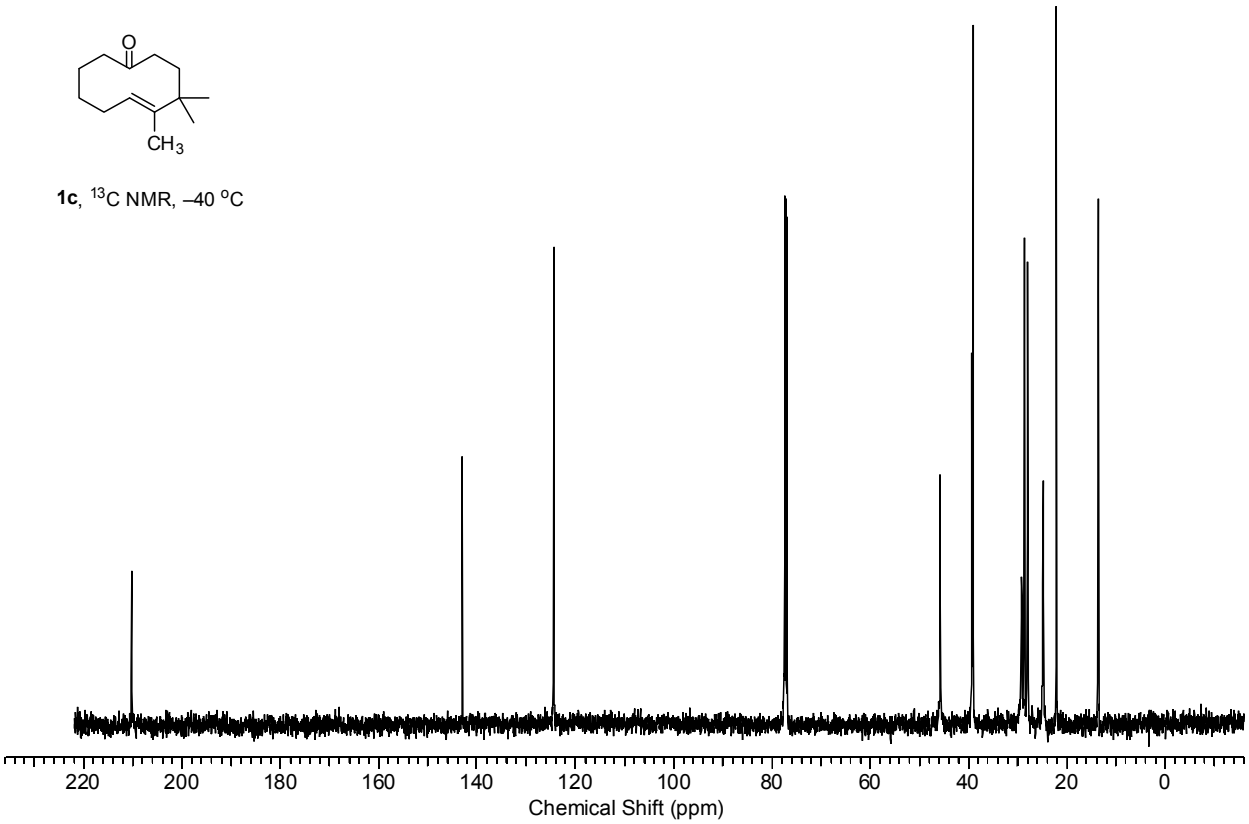



**1c**, $^{1}$H NMR, 23 $^{o}$C

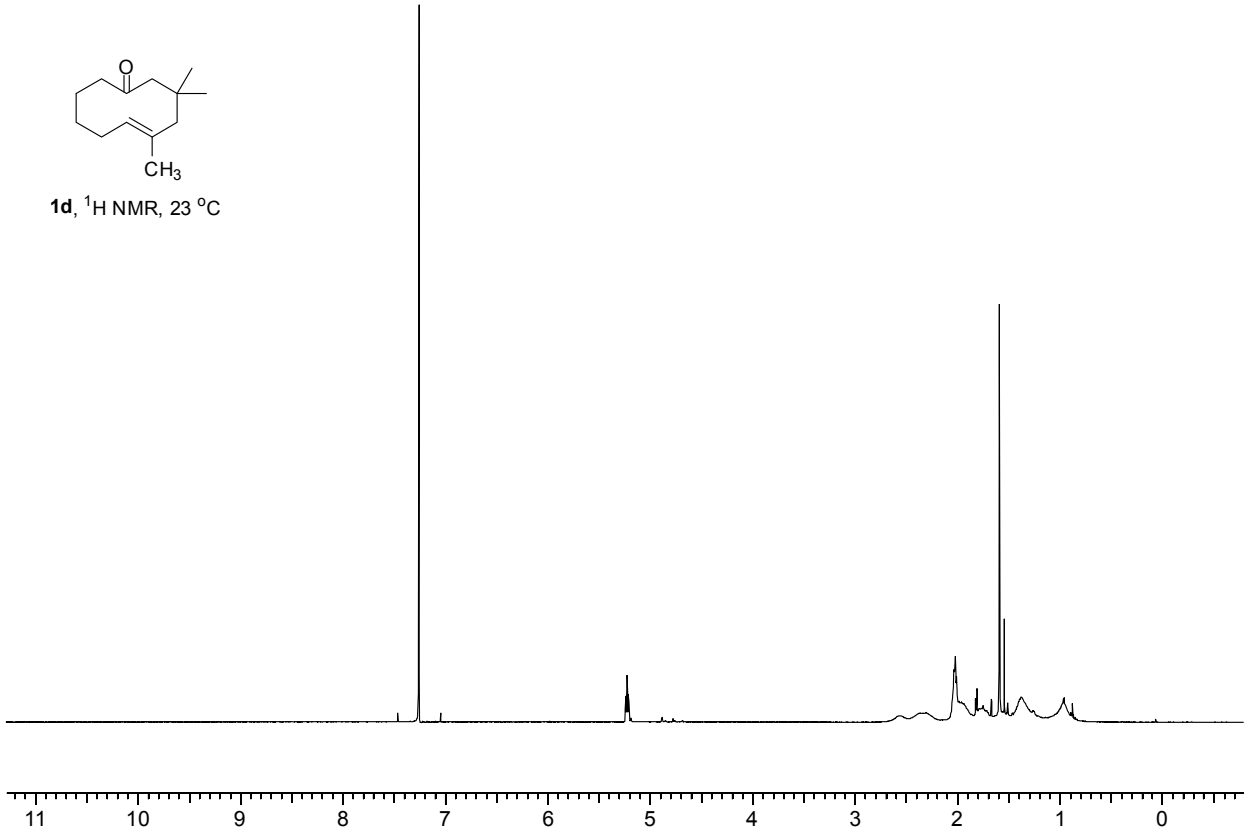


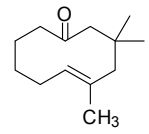

**1c**, $^{1}$H NMR, –40 $^{o}$C




**1c**, $^{13}C$ NMR, –40 °C

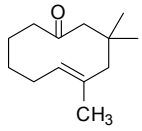



**1d**, $^{1}H$ NMR, 23 °C

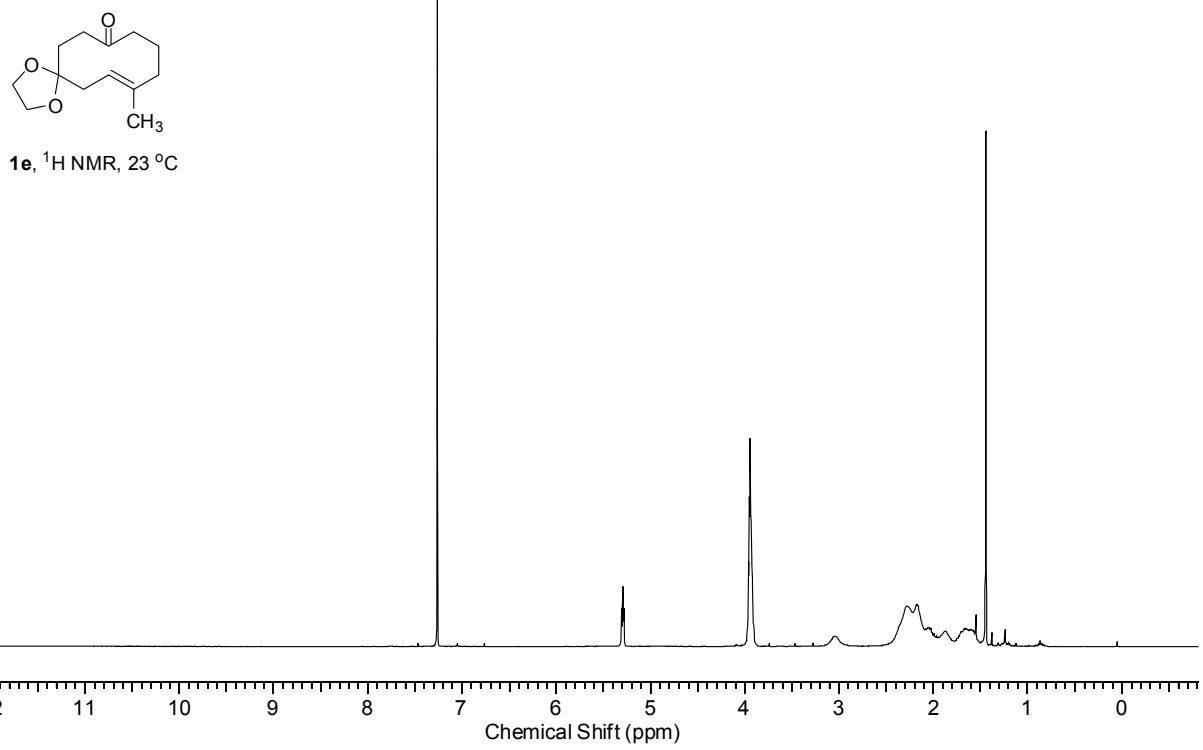



**1d**, $^{1}$H NMR, –40 $^{o}$C

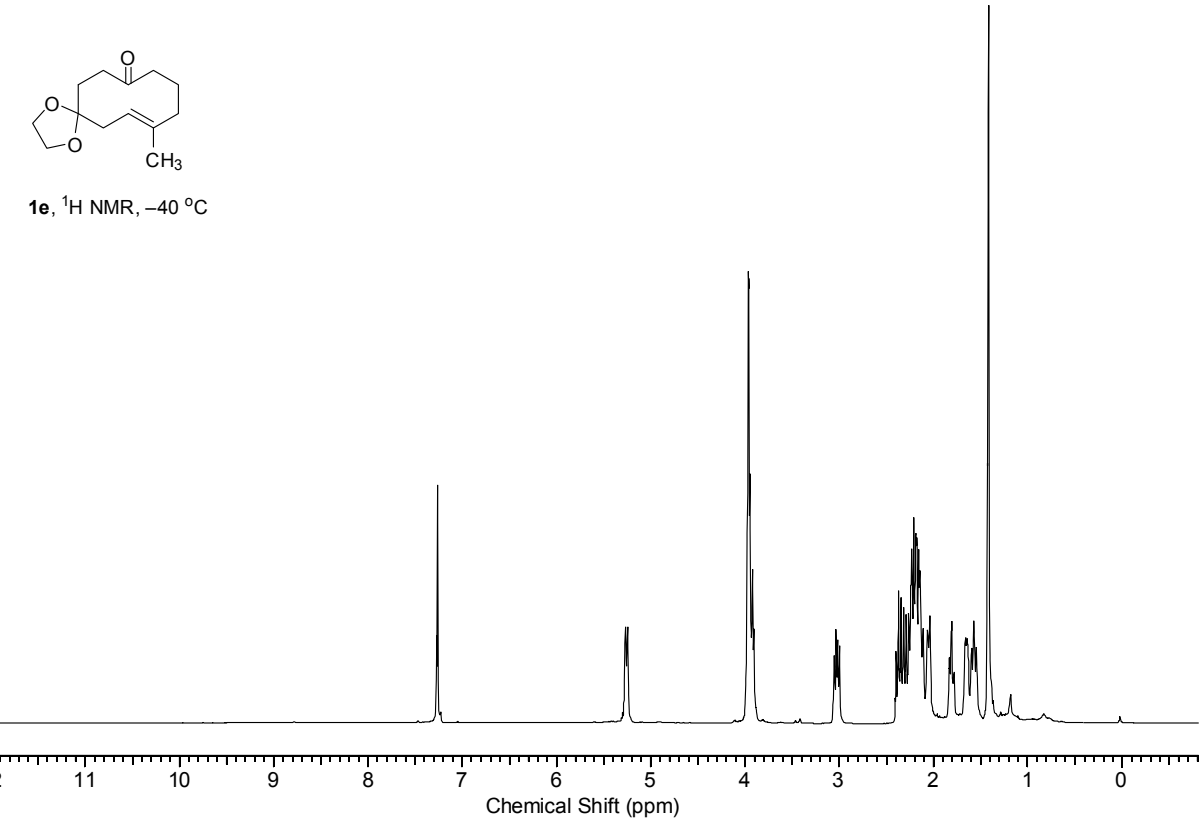


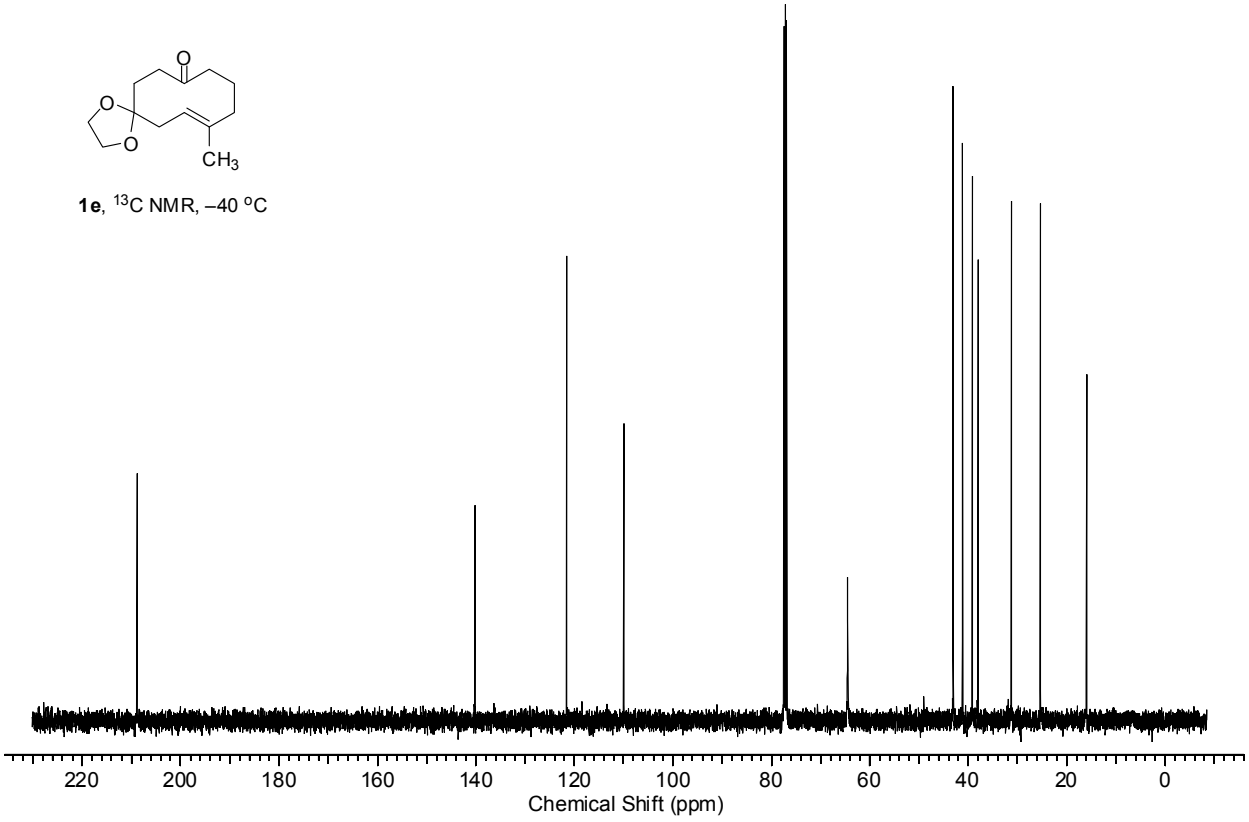

**1d**, $^{13}$C NMR, 23 $^{o}$C



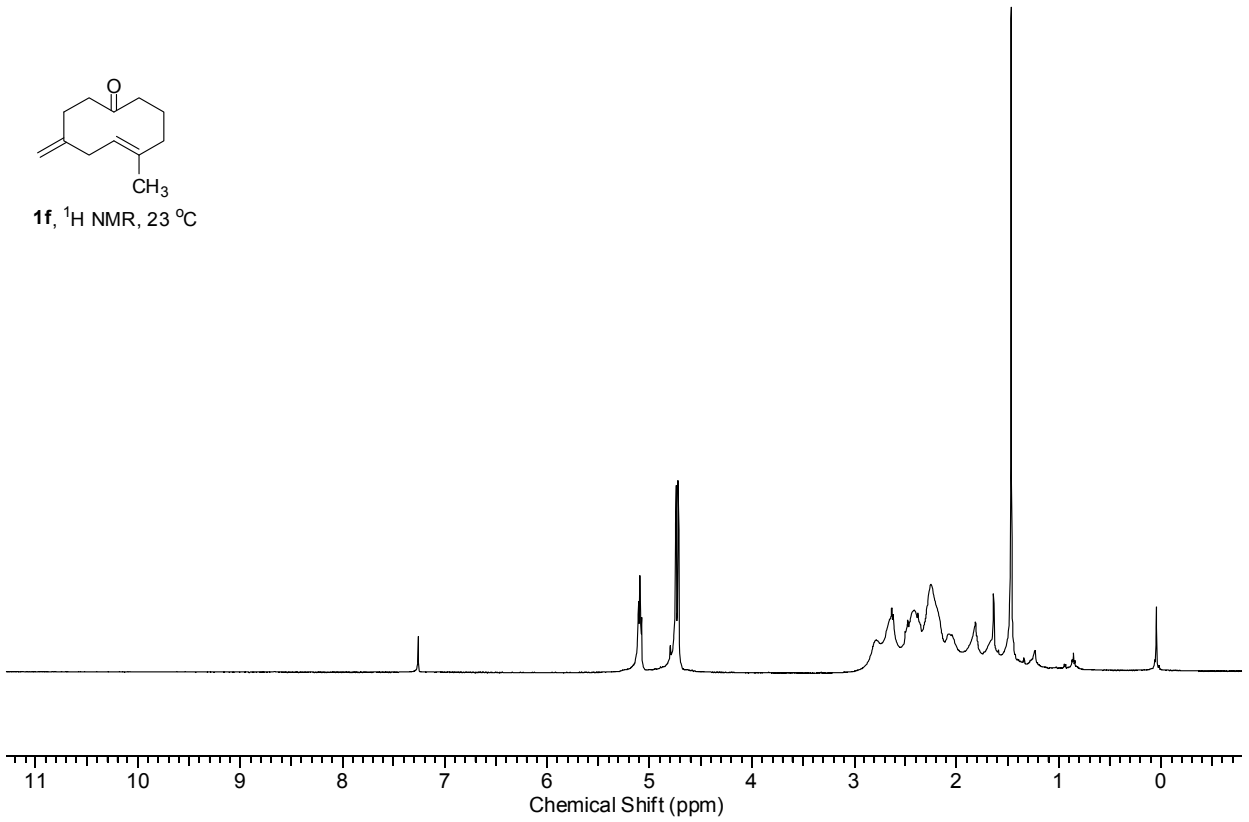

**1e**, $^{1}$H NMR, 23 $^{o}$C



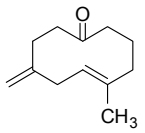

**1e**, $^{1}$H NMR, –40 $^{o}$C




**1e**, $^{13}$C NMR, –40 $^{o}$C

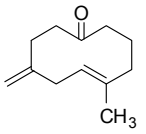



**1f**, $^{1}$H NMR, 23 $^{o}$C

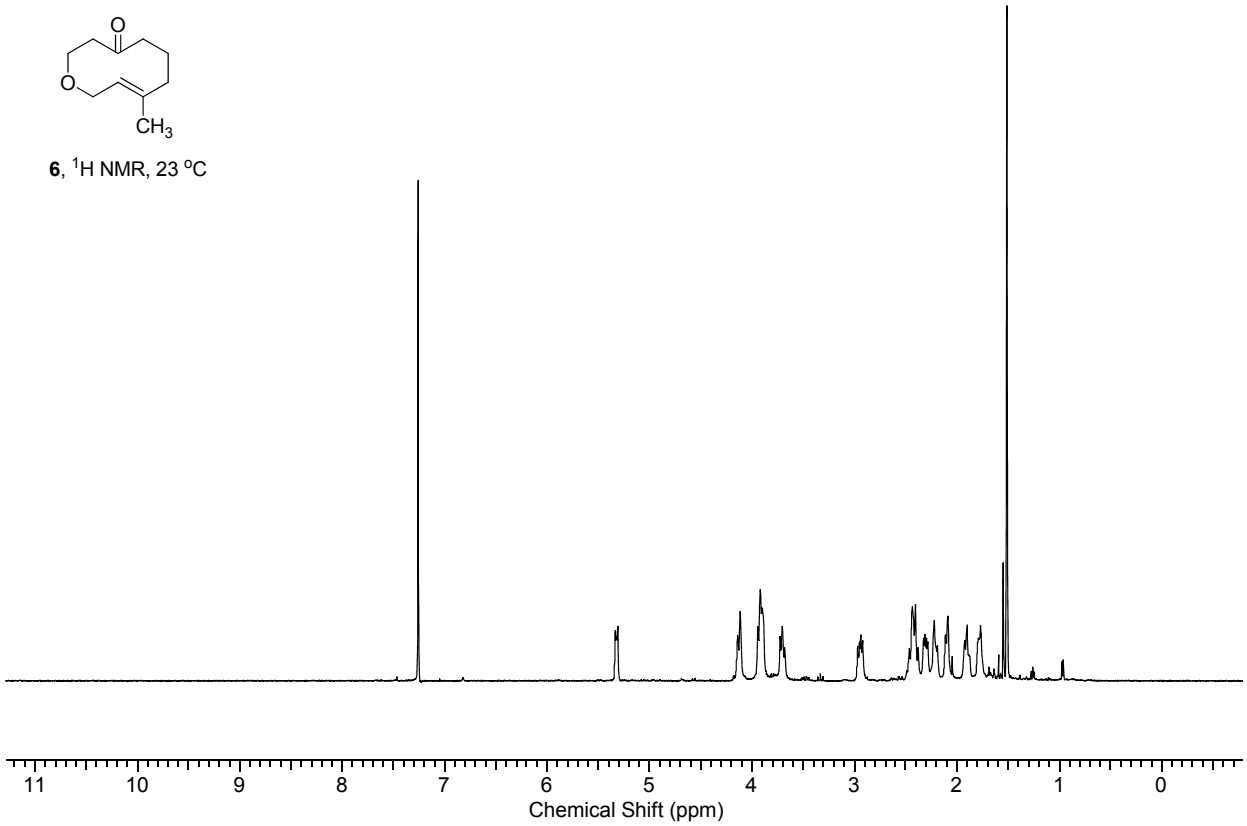



**1f**, $^{1}$H NMR, –20 $^{o}$C

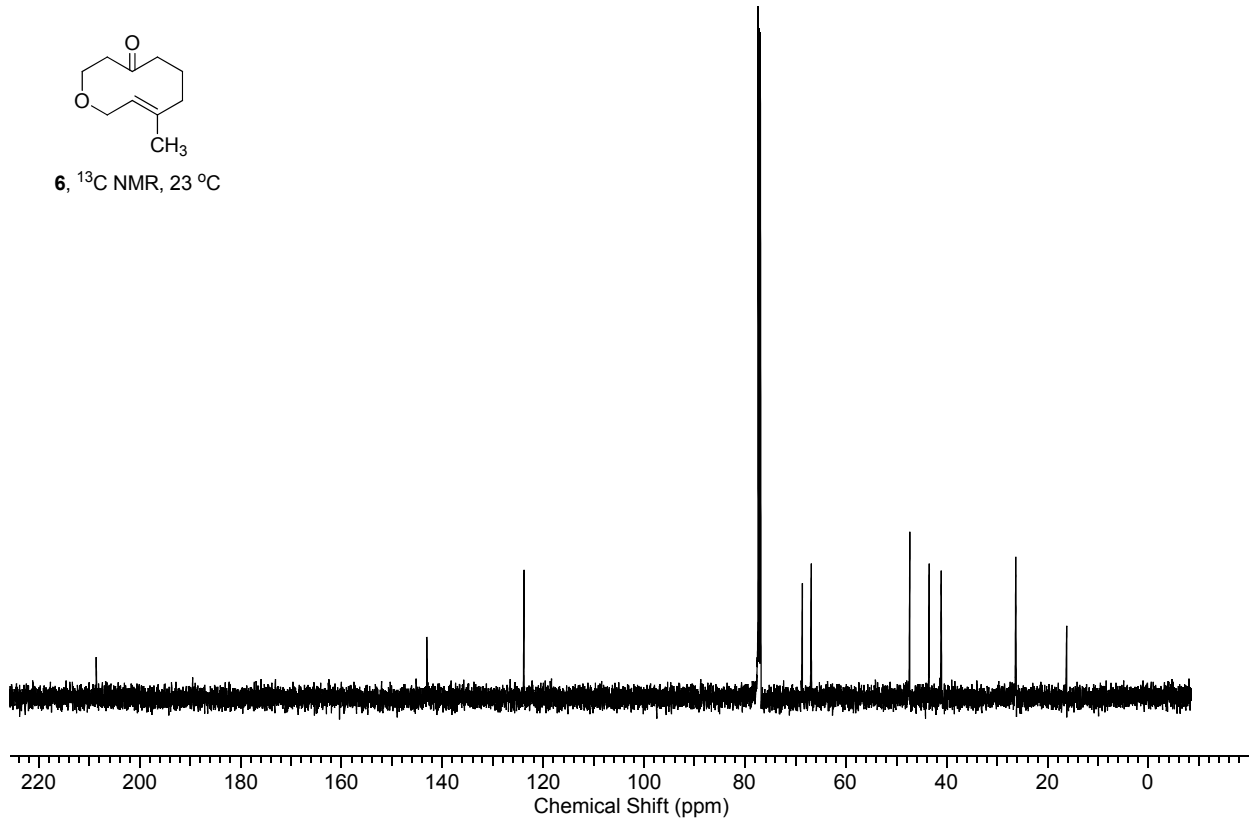


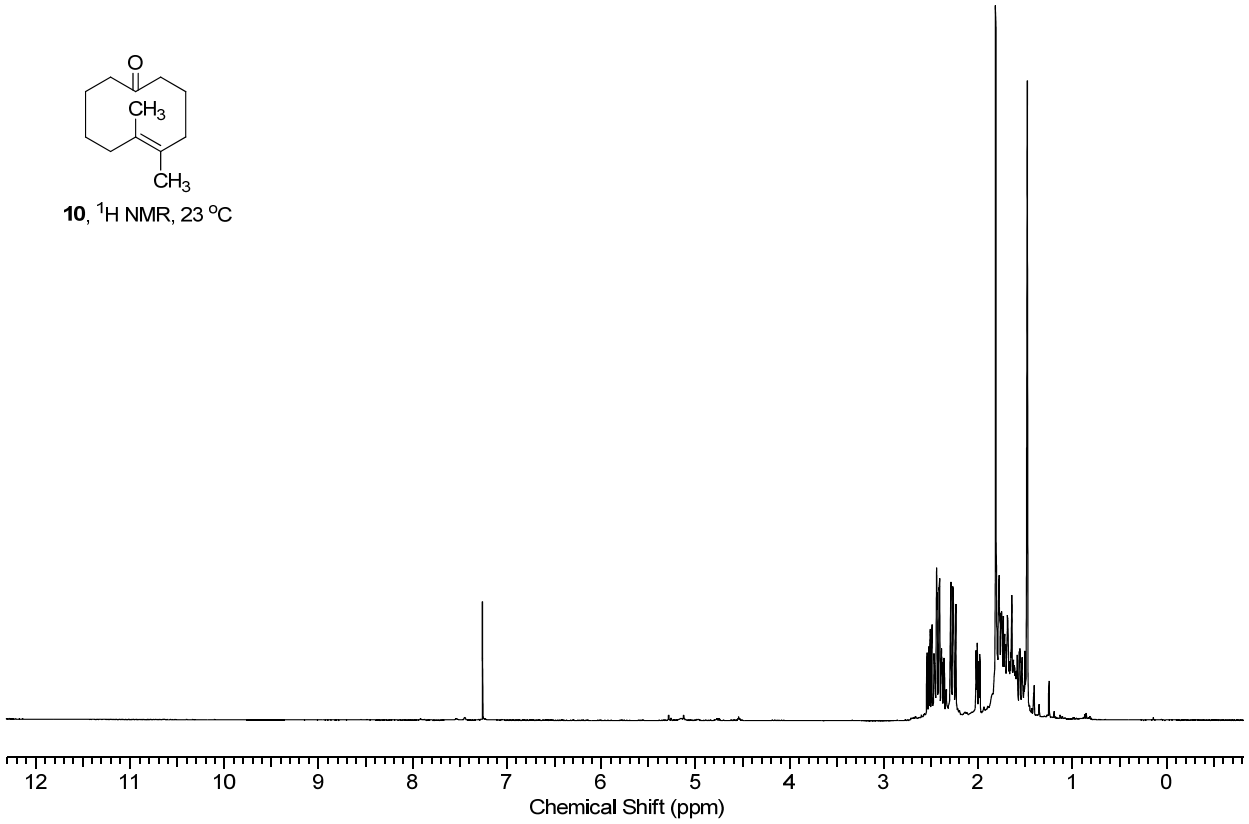

**1f**, $^{13}$C NMR, 23 $^{o}$C



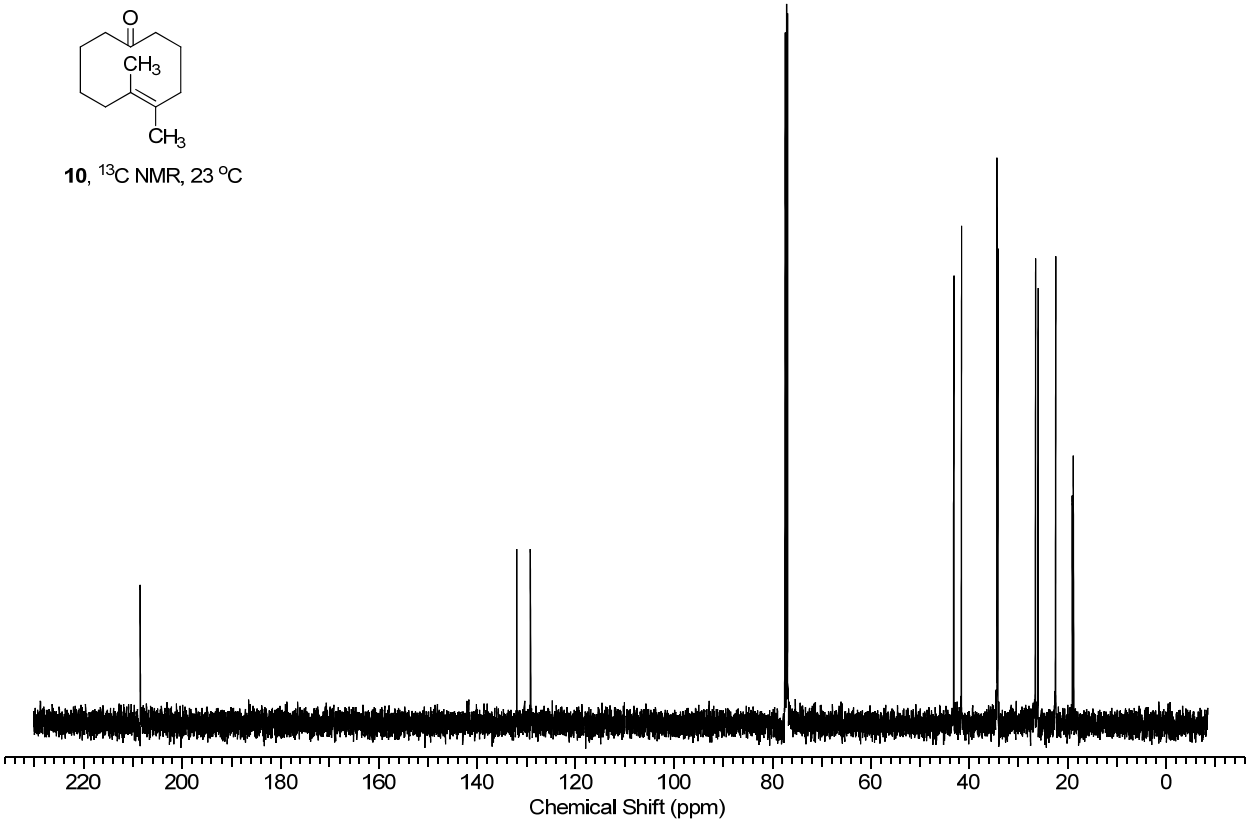

**6**, $^{1}$H NMR, 23 $^{o}$C




**6**, $^{13}$C NMR, 23 $^{o}$C

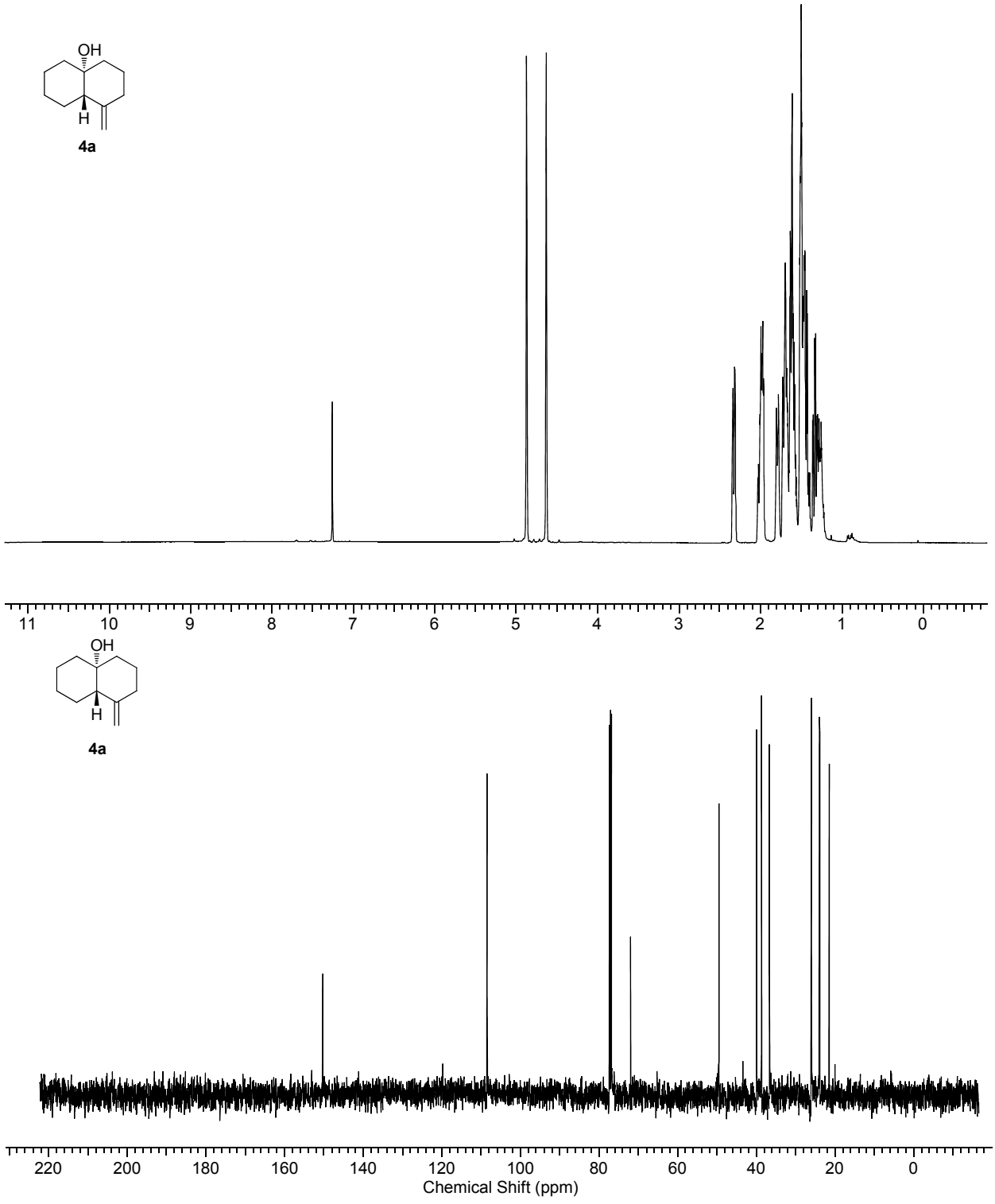



**10**, $^{1}$H NMR, 23 $^{o}$C

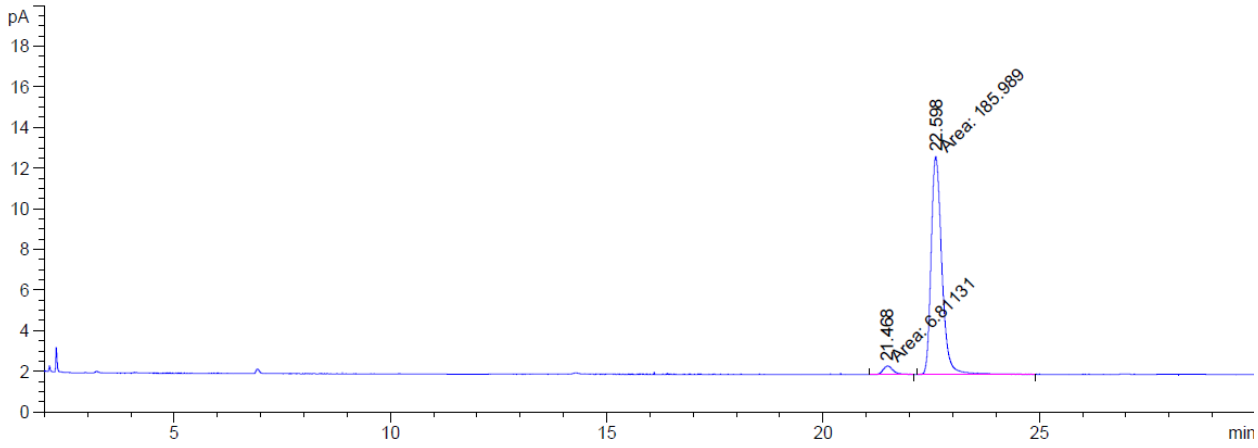



**10**, $^{13}$C NMR, 23 $^{o}$C

**F. Characterization Data of Transannular Ketone-Ene Products**

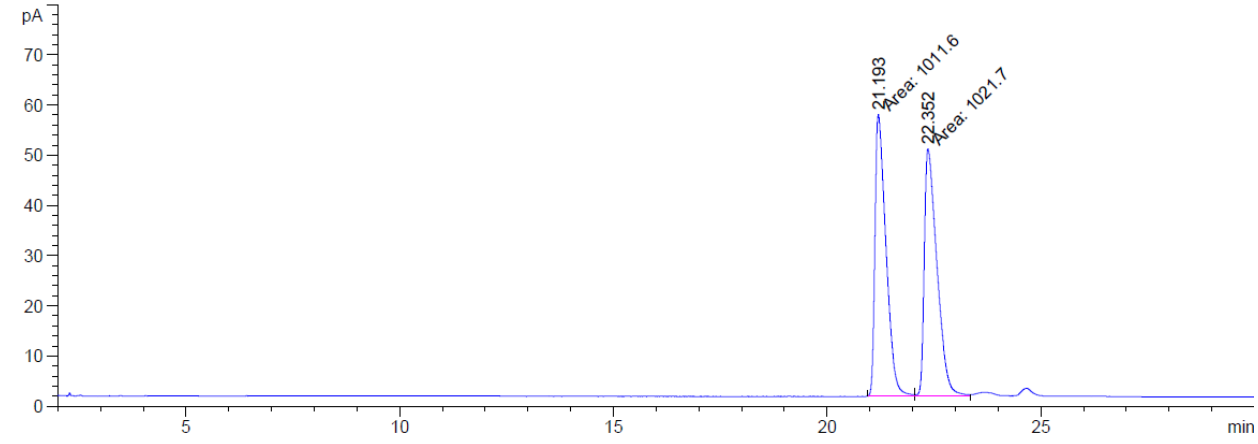


**Enantioenriched Sample**: GC (CHIRALDEX β-PH, 100 °C, 14 psi, 20:1 split), 93% ee (**4a**)

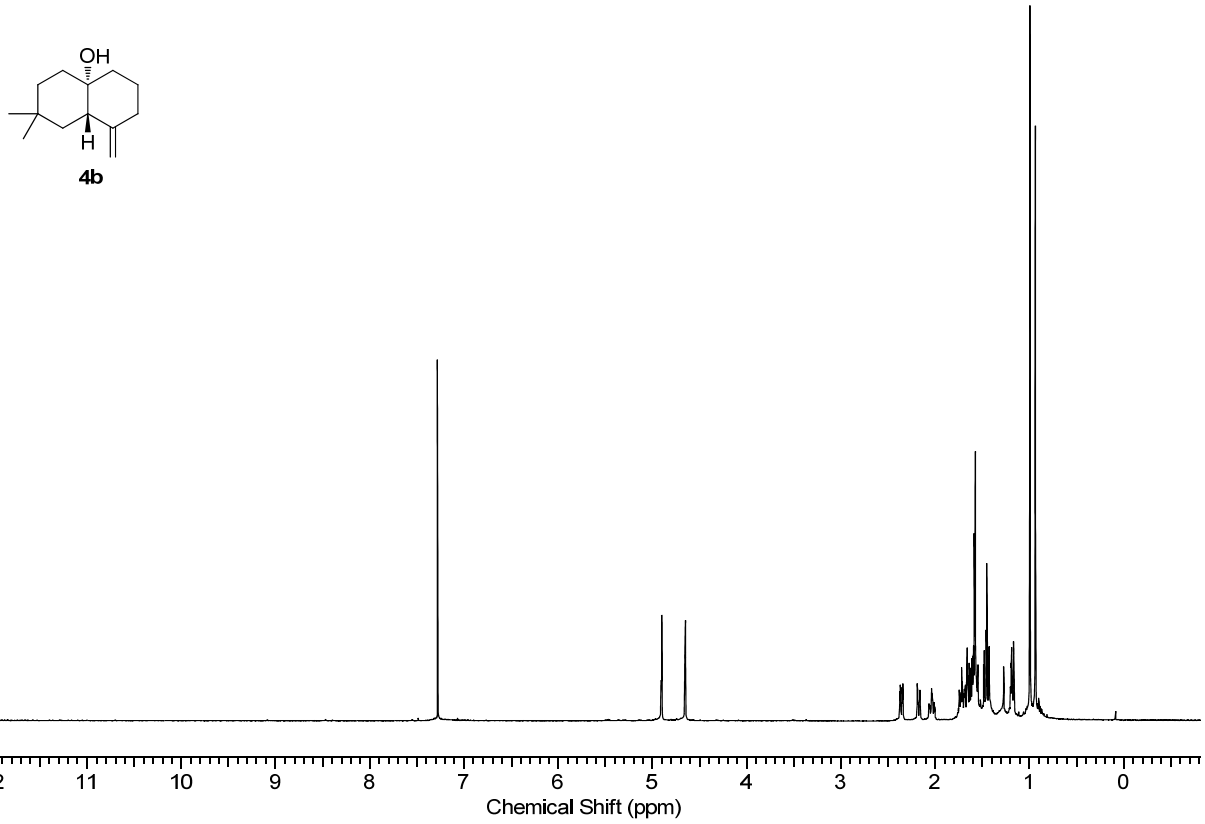


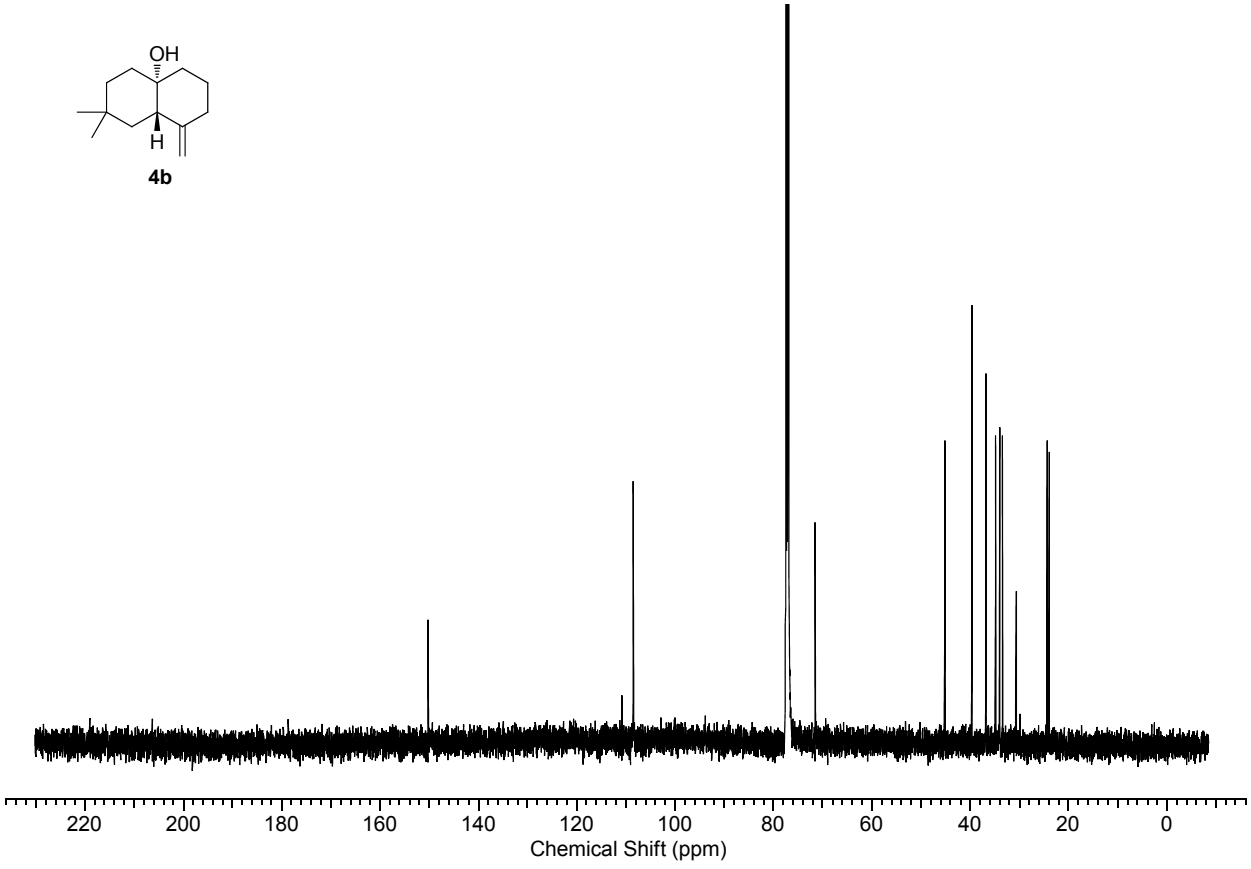

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 21.468 | MM | 0.2689 | 6.81131 | 4.22207e-1 | 3.53283 |
| 2 | 22.598 | MM | 0.2887 | 185.98906 | 10.73842 | 96.46717 |

**Racemic Sample**: GC (CHIRALDEX β-PH, 100 °C, 14 psi, 20:1 split) (**4a**)

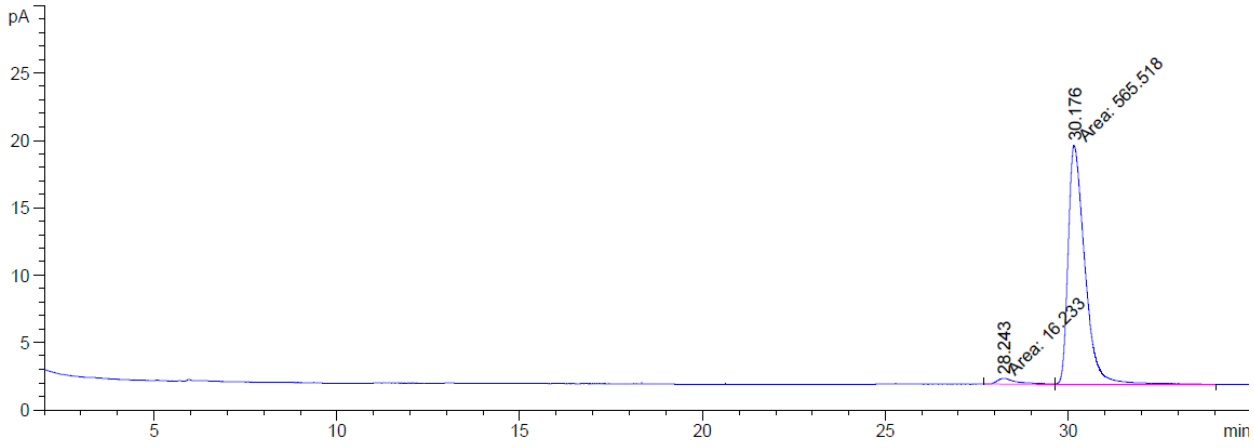



| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 21.193 | MF | 0.3000 | 1011.60272 | 56.19423 | 49.75173 |
| 2 | 22.352 | FM | 0.3451 | 1021.69873 | 49.33677 | 50.24827 |


OH
H
4b
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

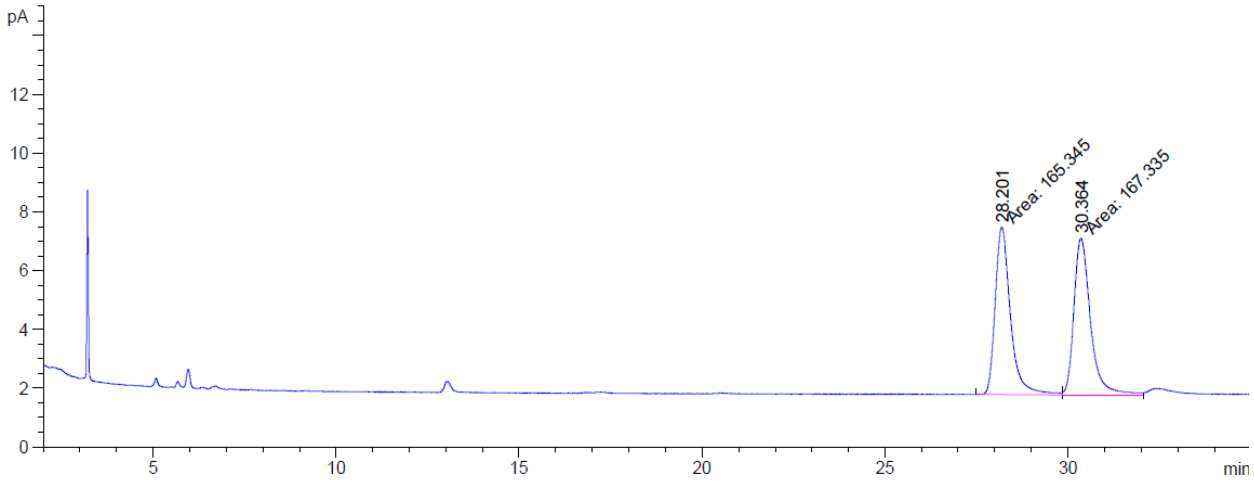

OH
H
4b
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

**Enantioenriched Sample**: GC (CHIRALDEX β-PH, 90 °C, 14 psi, 20:1 split), 94% ee (**4b**)

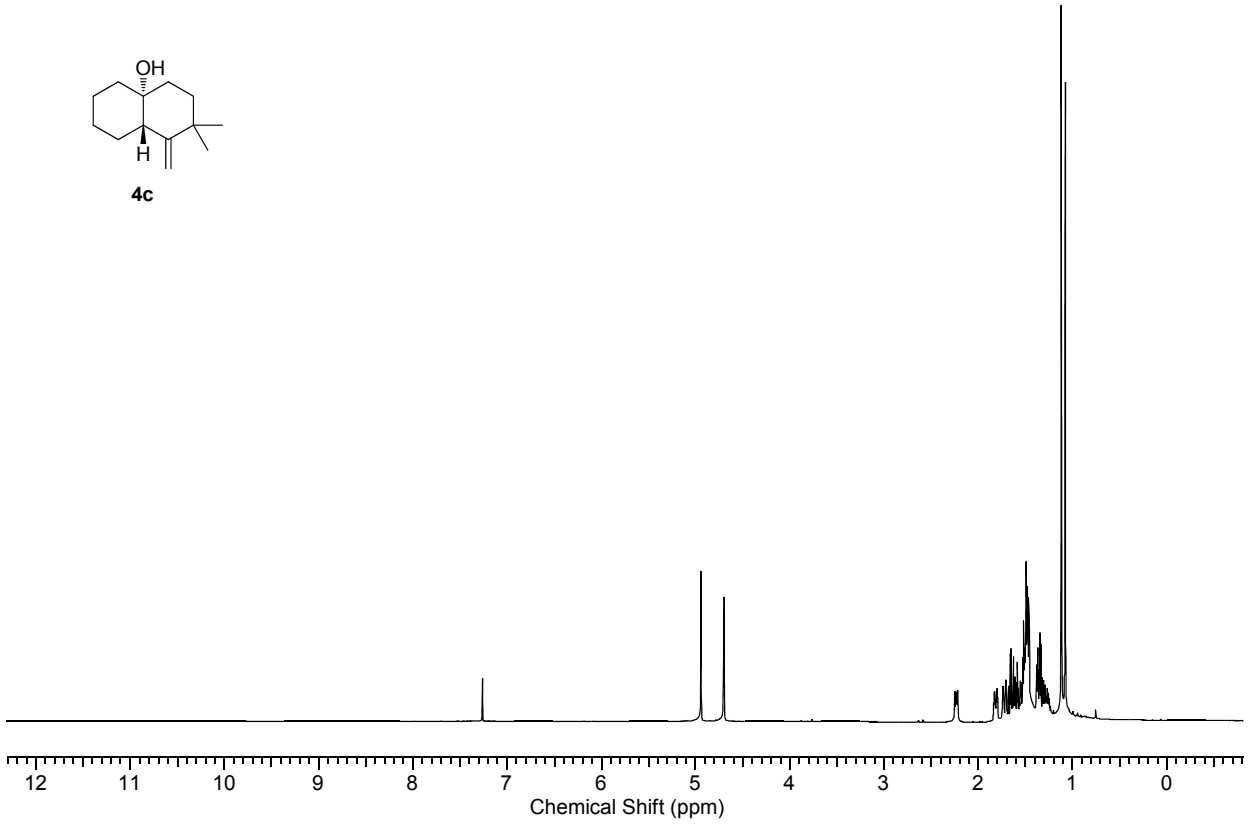


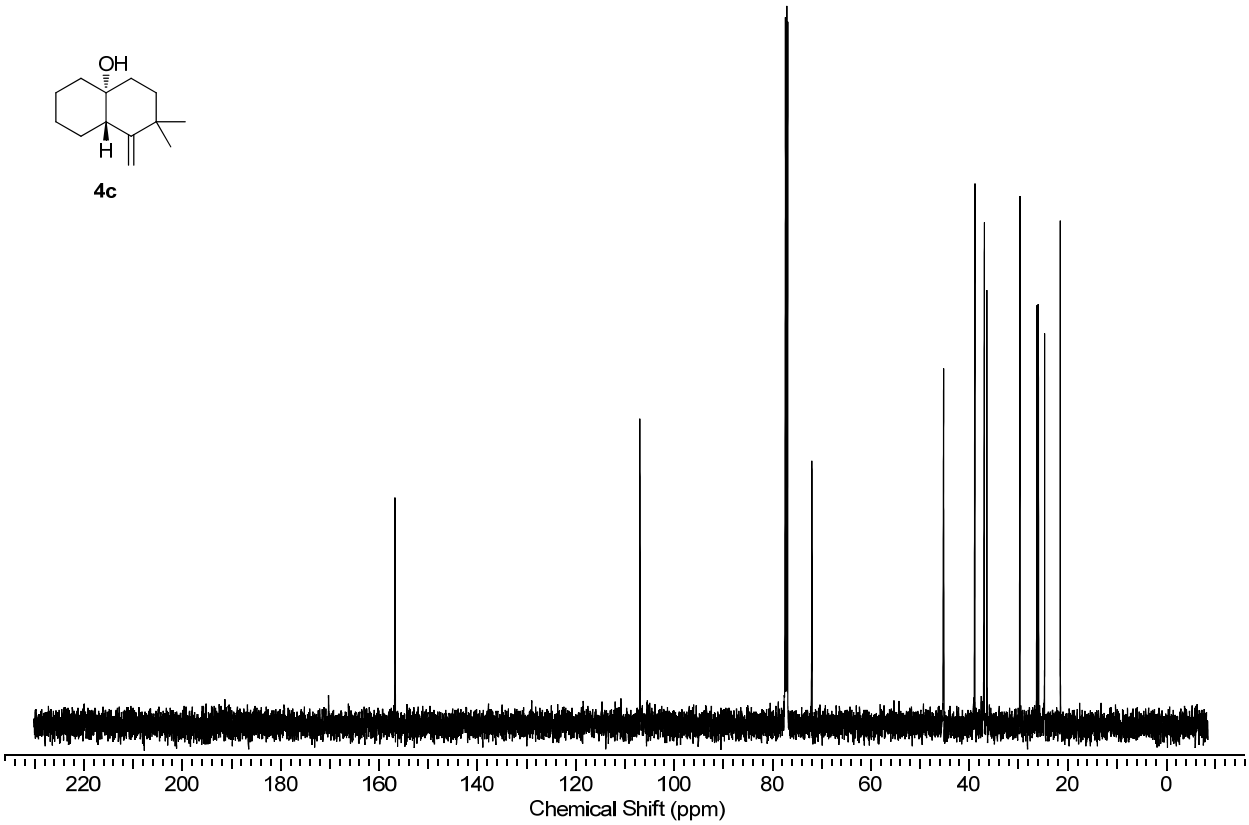

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 28.243 | MF | 0.6259 | 16.23298 | 4.32253e-1 | 2.79036 |
| 2 | 30.176 | FM | 0.5320 | 565.51837 | 17.71748 | 97.20964 |

**Racemic Sample**: GC (CHIRALDEX β-PH, 90 °C, 14 psi, 20:1 split) (**4b**)

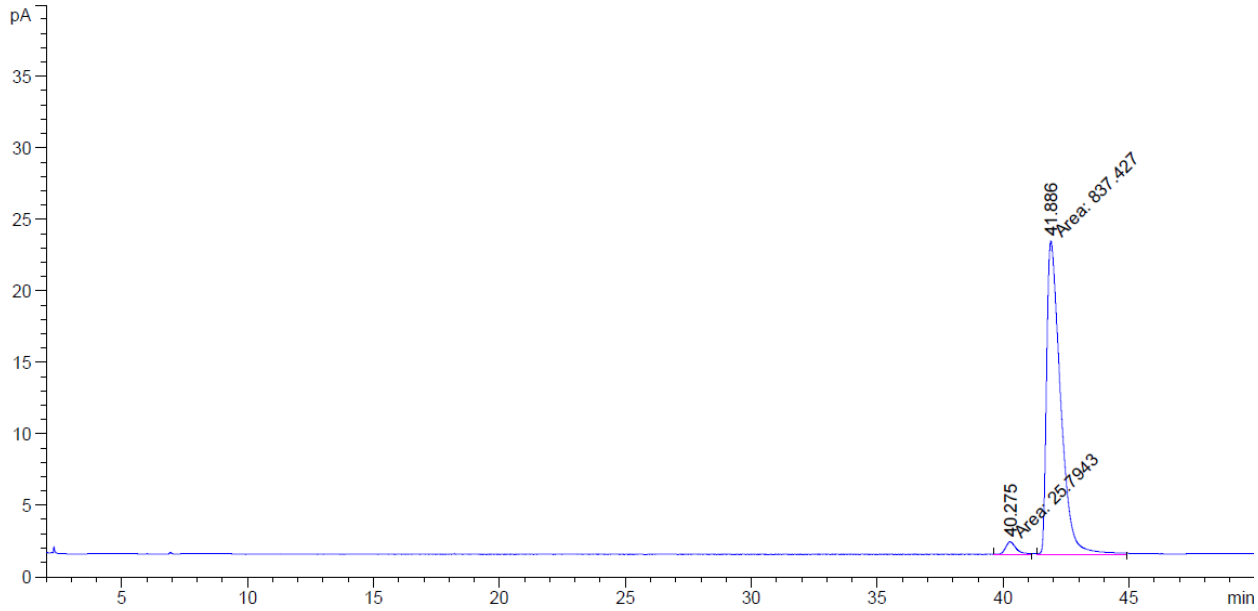



| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 28.201 | MF | 0.4838 | 165.34515 | 5.69549 | 49.70100 |
| 2 | 30.364 | FM | 0.5226 | 167.33459 | 5.33684 | 50.29900 |


OH
H
4c
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

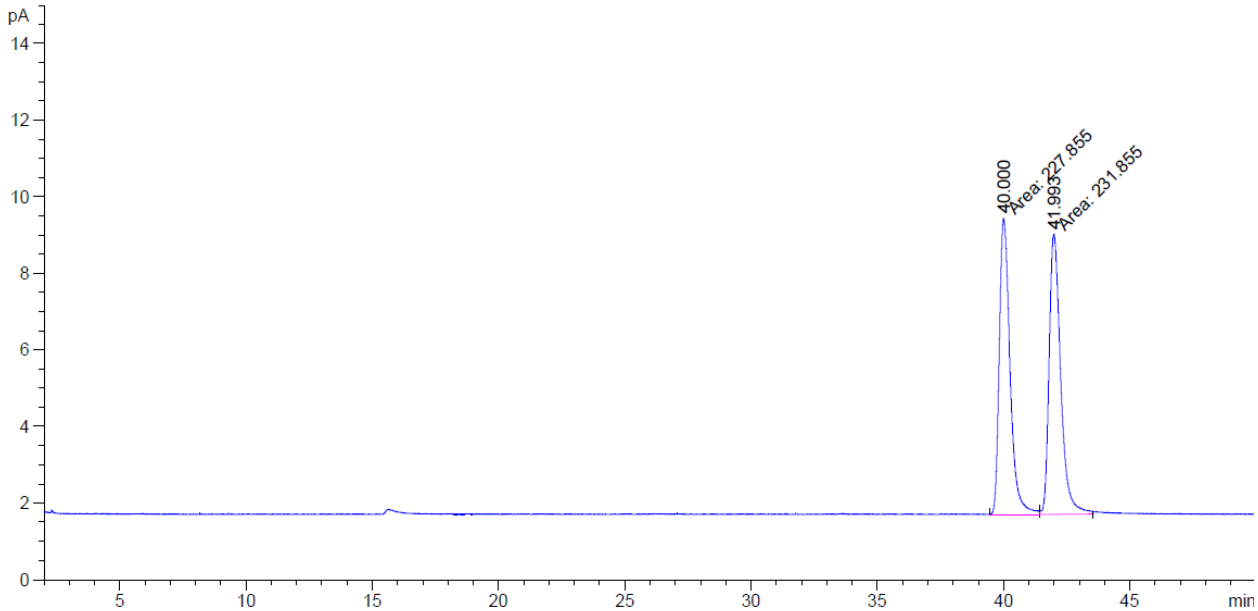

OH
H
4c
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

**Enantioenriched Sample**: GC (CHIRALDEX β-PH, 100 °C, 14 psi, 20:1 split), 94% ee (**4c**)

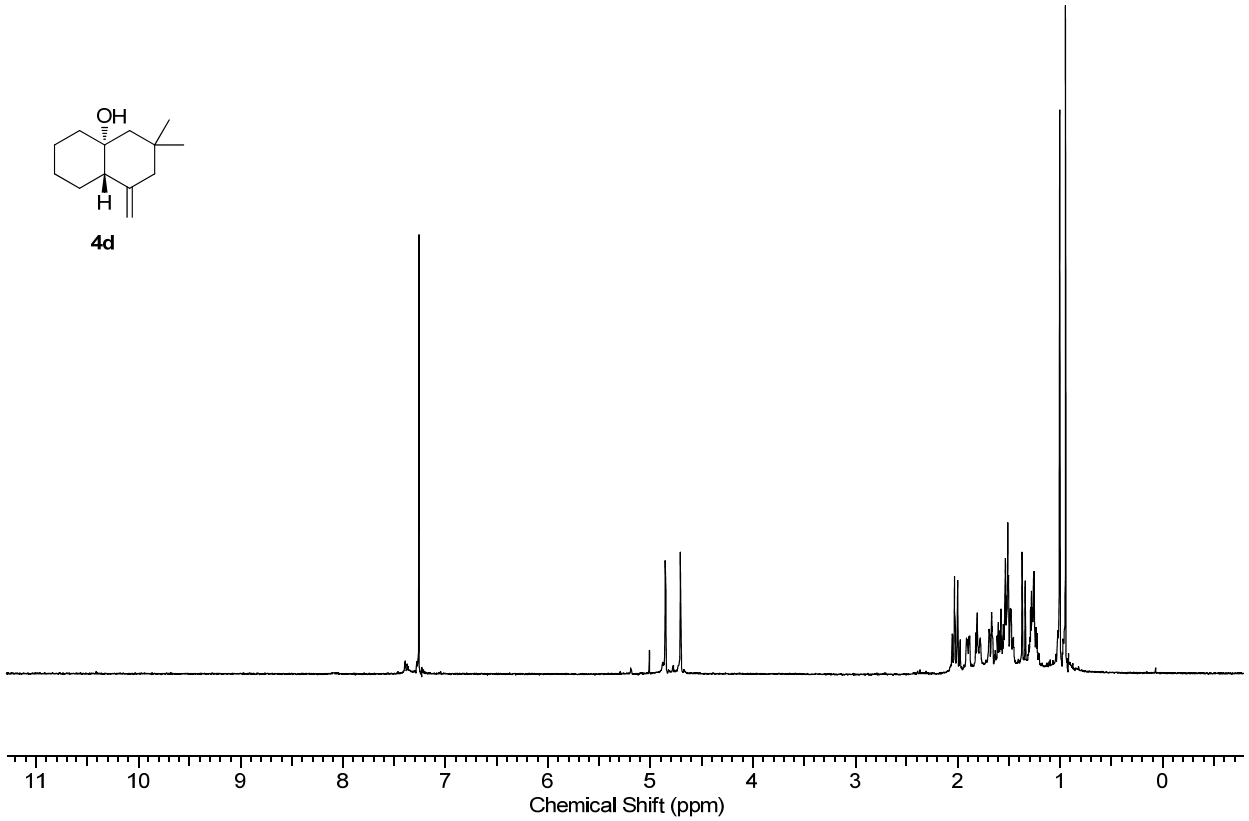


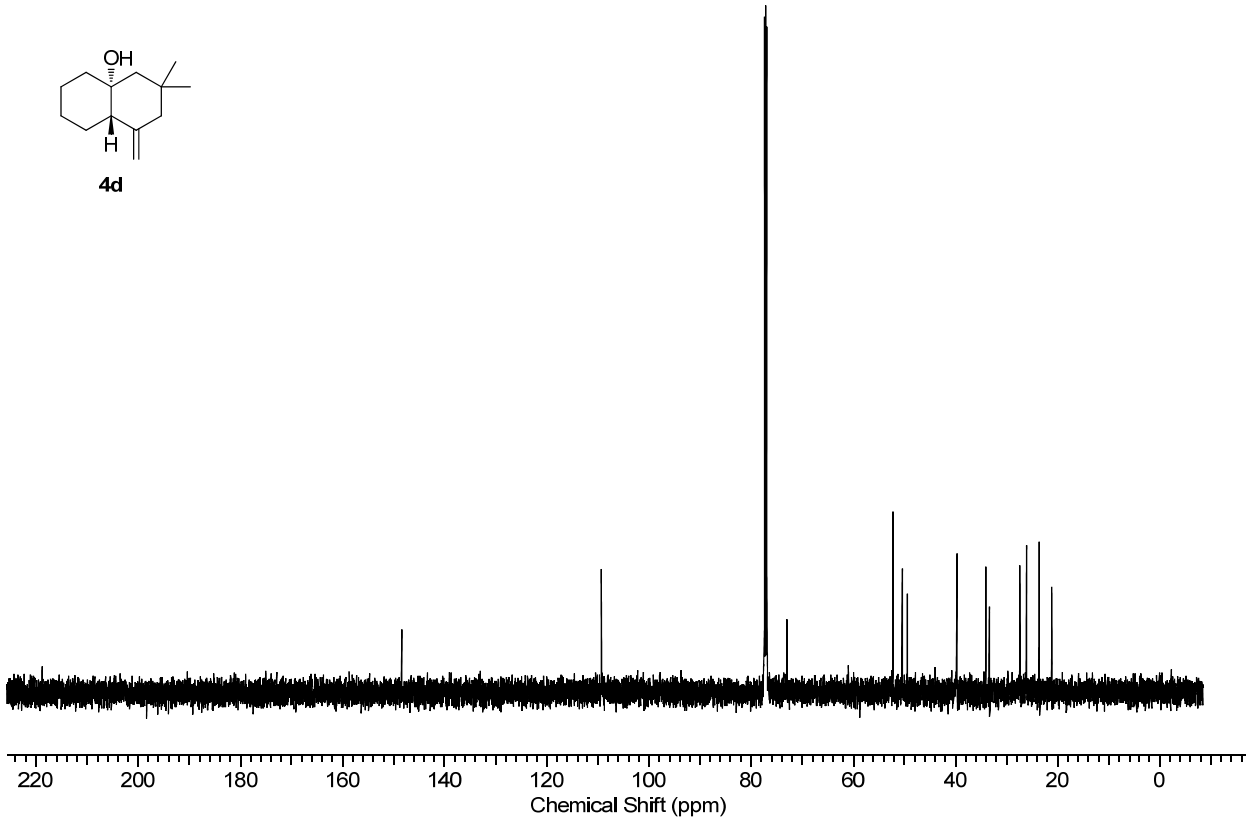

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 40.275 | MM | 0.4945 | 25.79430 | 8.69292e-1 | 2.98815 |
| 2 | 41.886 | MM | 0.6363 | 837.42682 | 21.93381 | 97.01185 |

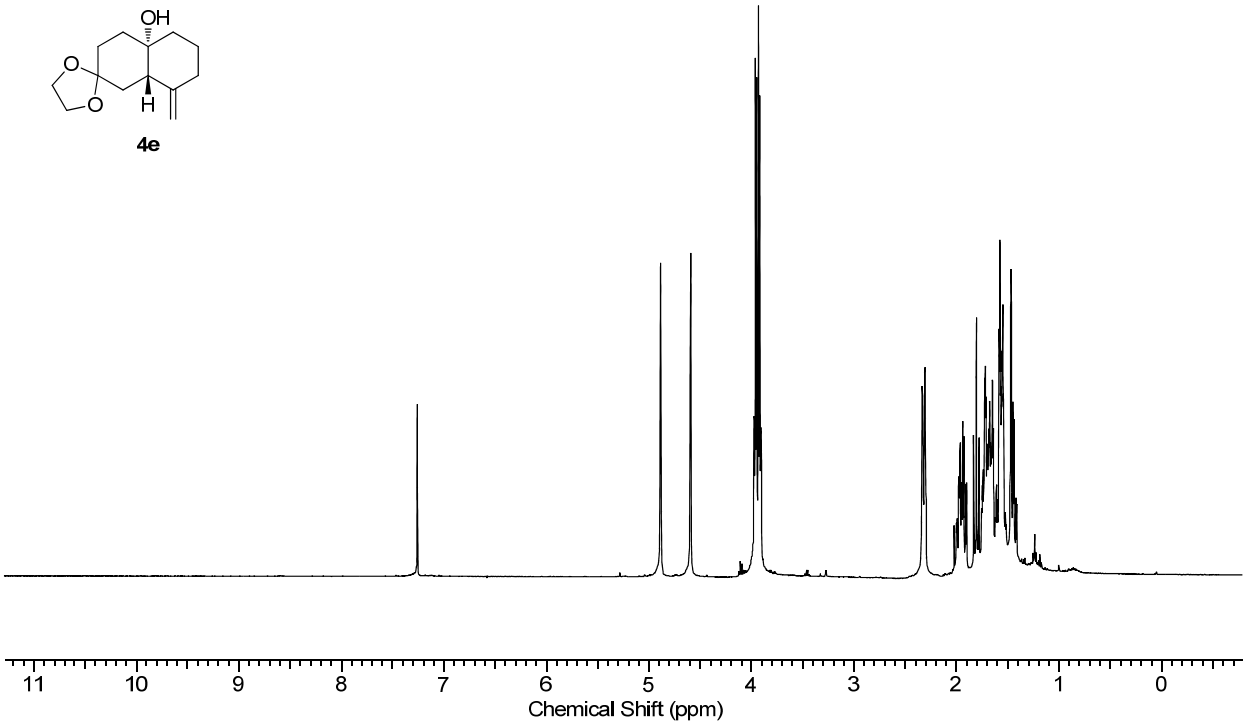
**Racemic Sample**: GC (CHIRALDEX β-PH, 100 °C, 14 psi, 20:1 split) (**4c**)

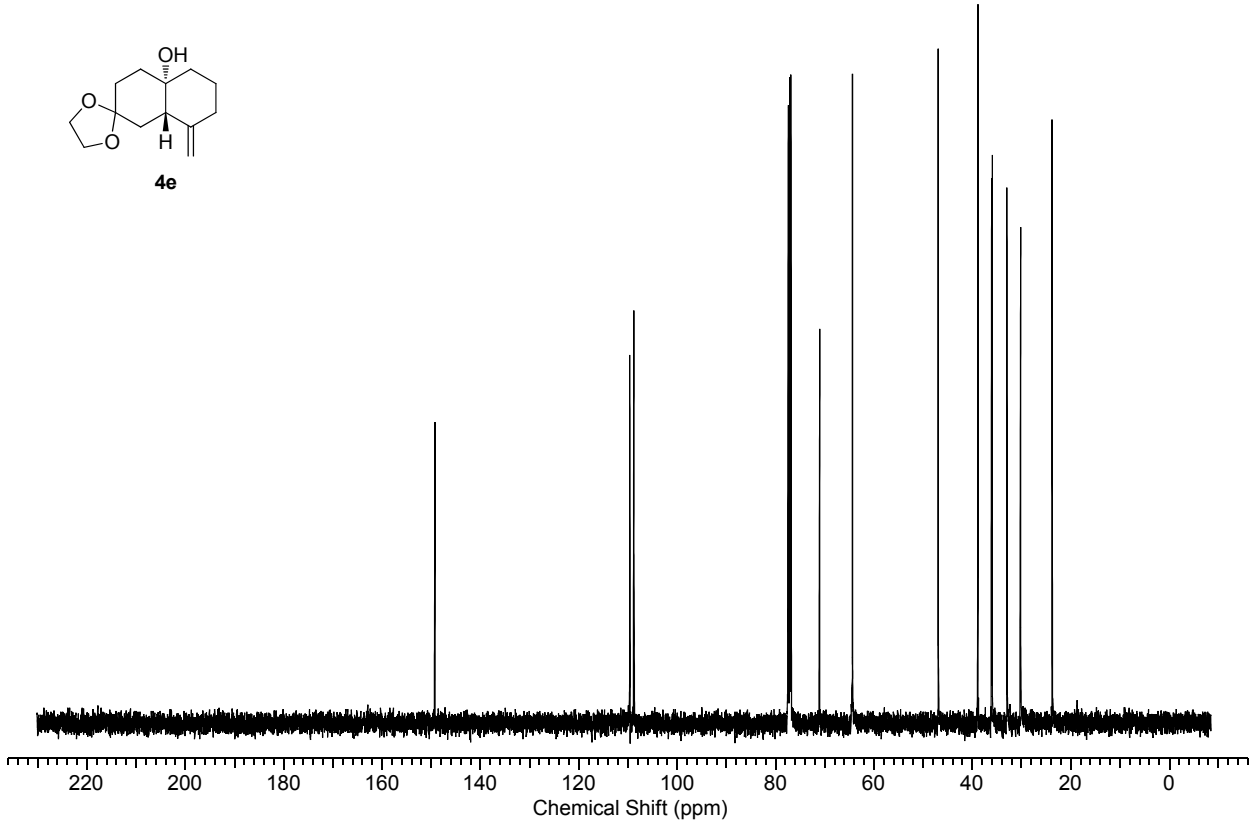



| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 40.000 | MF | 0.4907 | 227.85464 | 7.73971 | 49.56489 |
| 2 | 41.993 | FM | 0.5274 | 231.85510 | 7.32652 | 50.43511 |

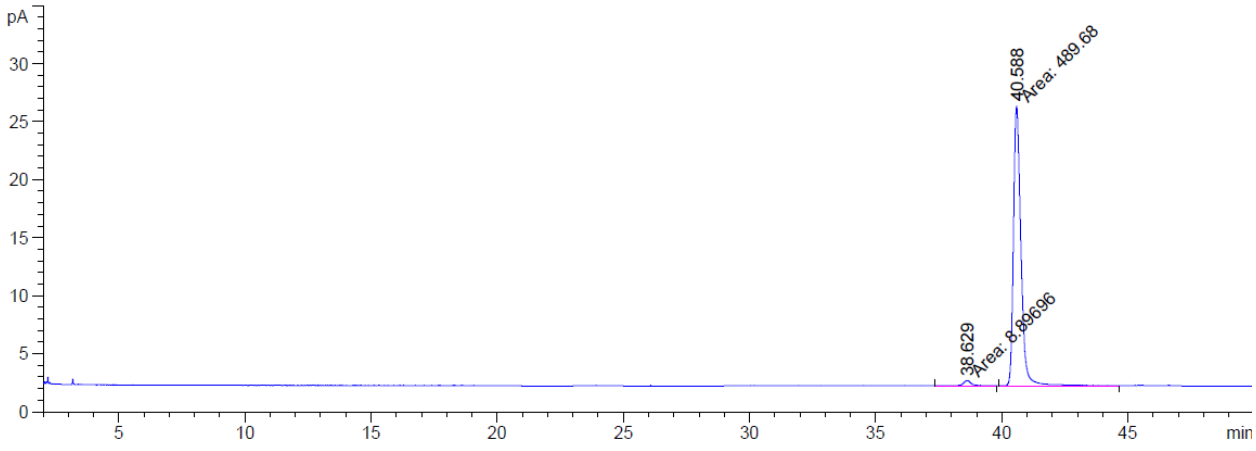

OH
H
4d
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


OH
H
4d
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


OH
O
O
H
4e
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

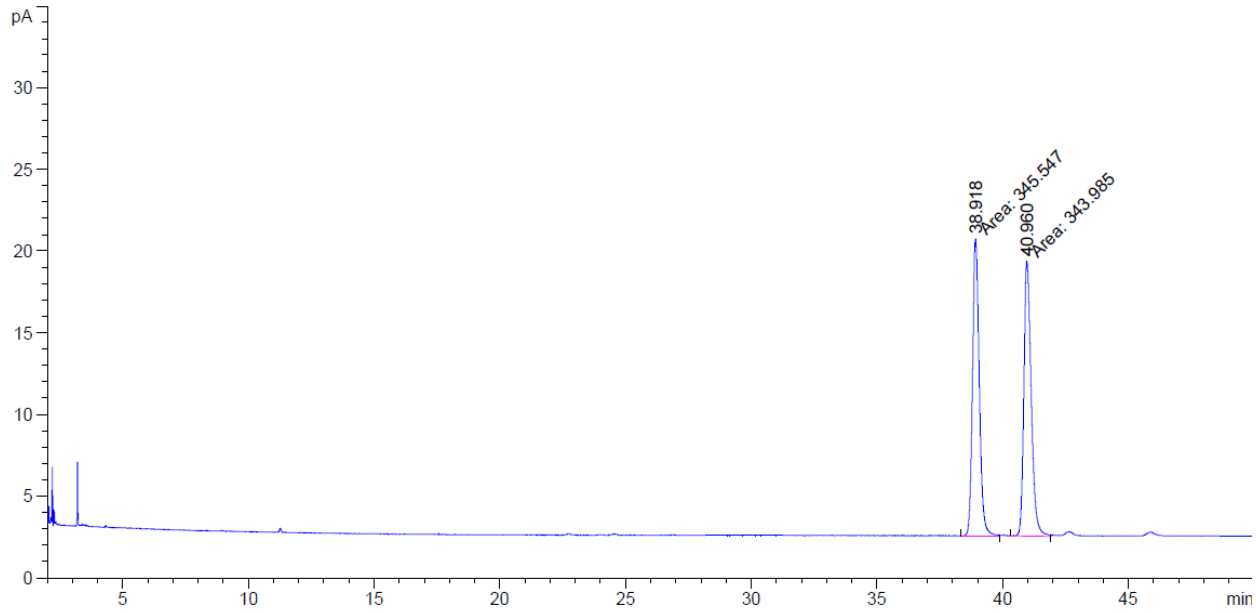

OH
O
O
H
4e
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

**Enantioenriched Sample**: GC (CHIRALDEX β-Cyclodex, 140 °C, 14 psi, 20:1 split), 96% ee (**4e**)

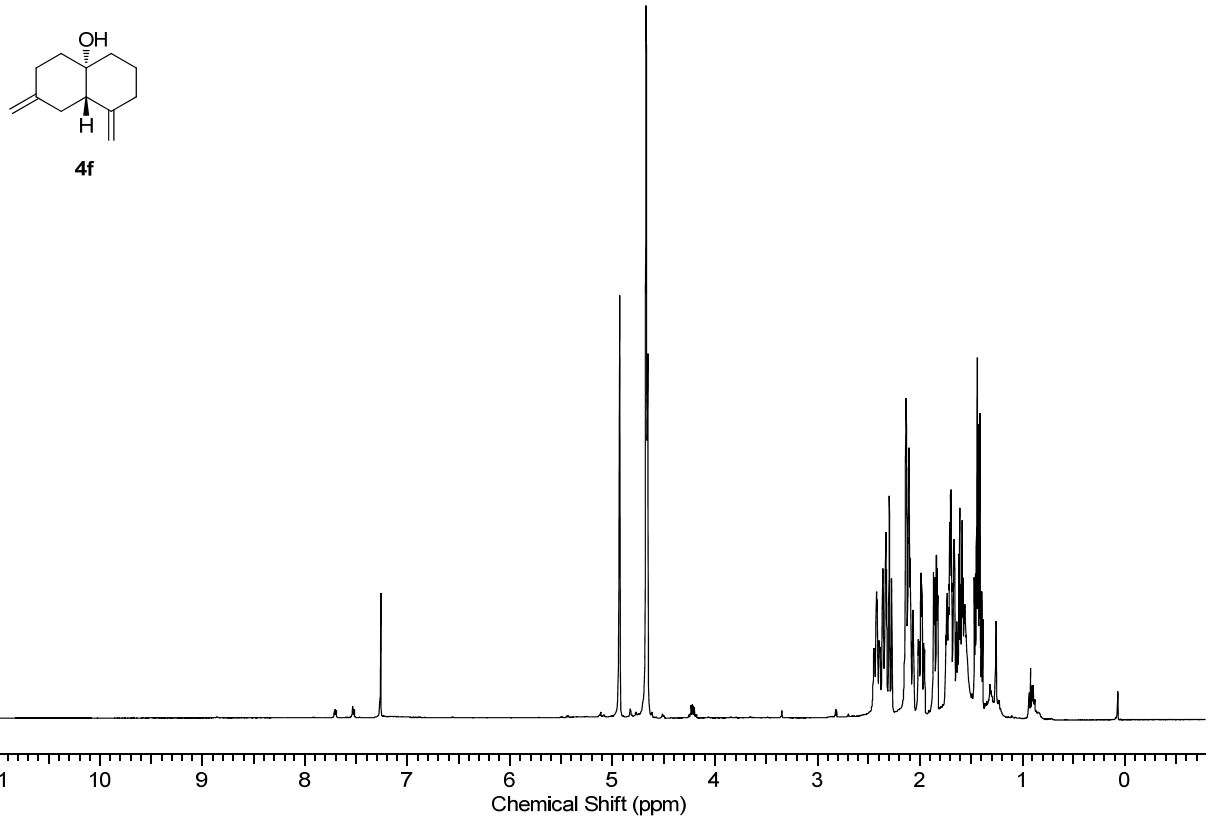


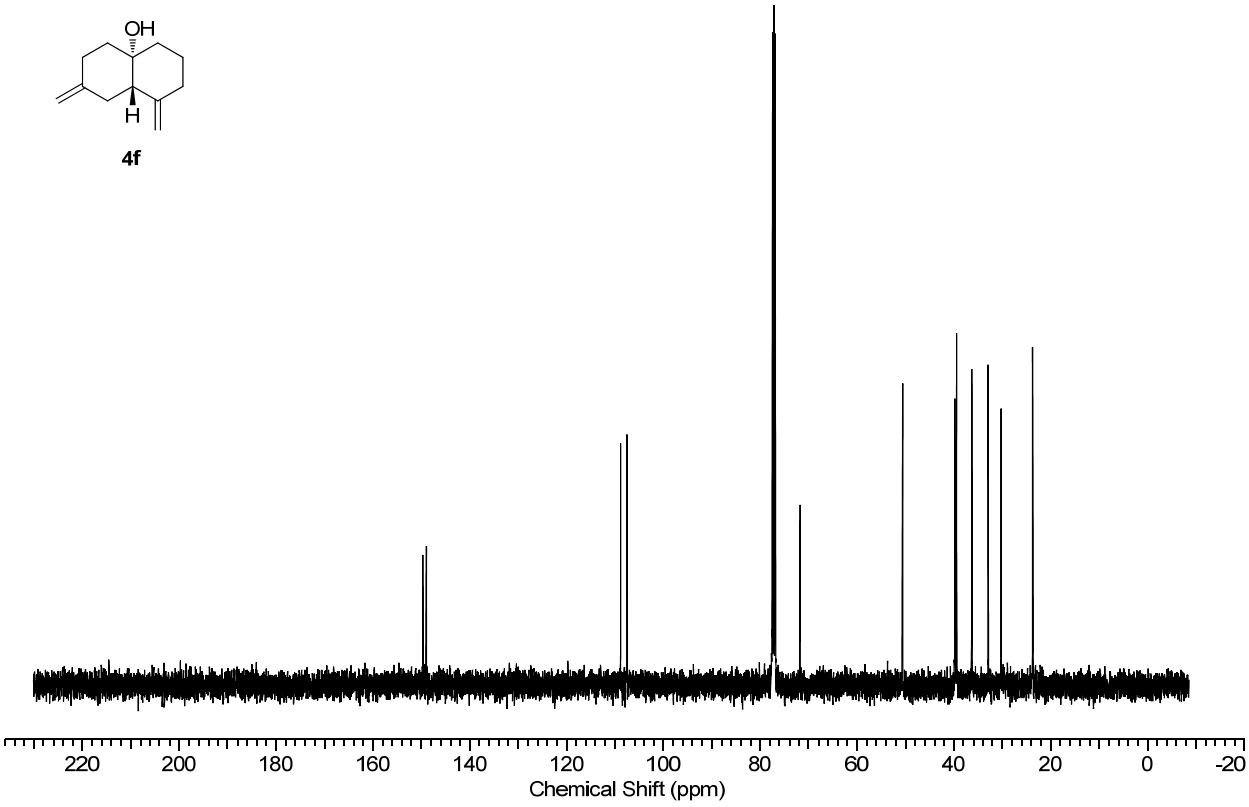

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 38.629 | MM | 0.3398 | 8.89696 | 4.36353e-1 | 1.78447 |
| 2 | 40.588 | MM | 0.3382 | 489.68005 | 24.13474 | 98.21553 |

**Racemic Sample**: GC (CHIRALDEX β-Cyclodex, 140 °C, 14 psi, 20:1 split) (**4e**)

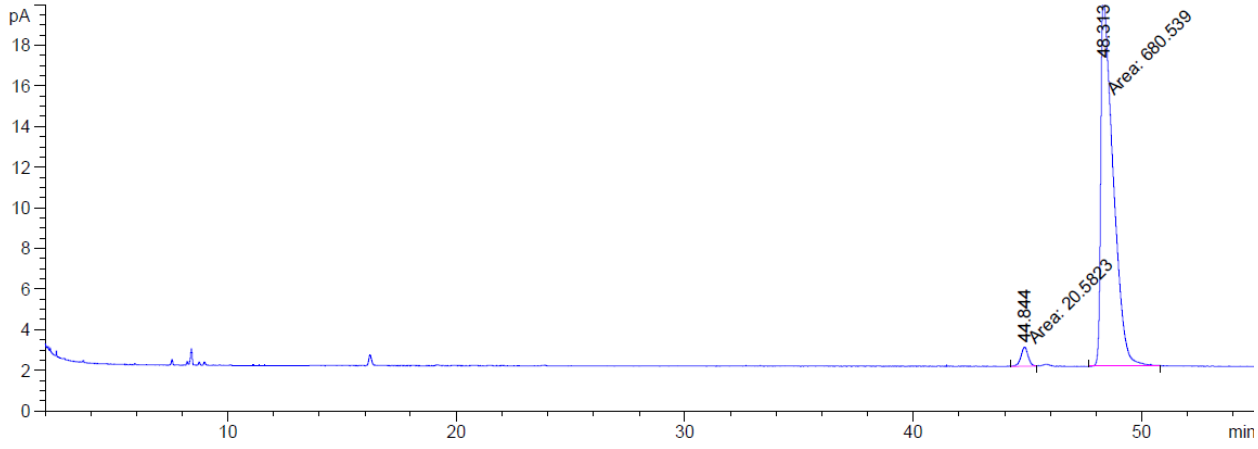



| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 38.918 | MM | 0.3161 | 345.54706 | 18.22182 | 50.11326 |
| 2 | 40.960 | MM | 0.3404 | 343.98514 | 16.84392 | 49.88674 |


OH
H
4f
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

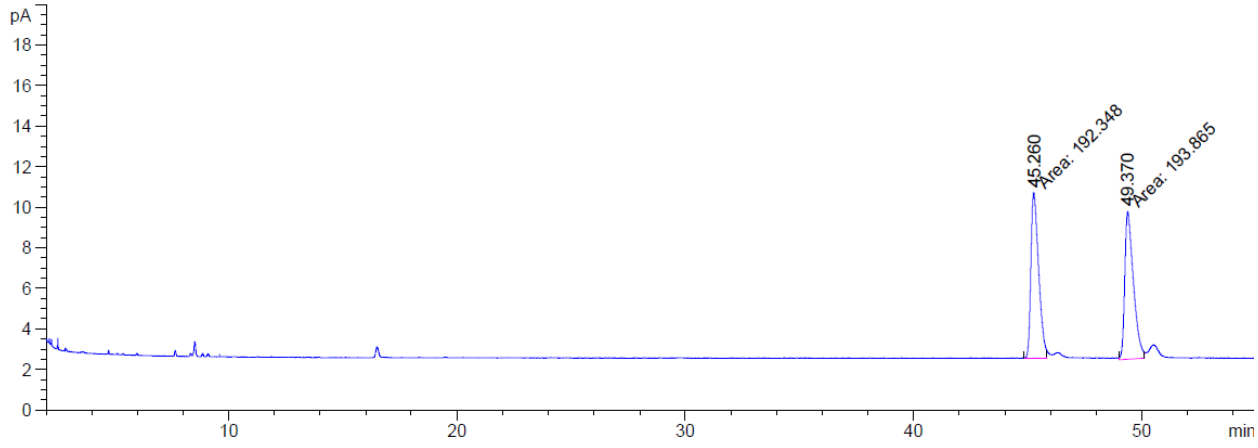

OH
H
4f
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

**Enantioenriched Sample**: GC (CHIRALDEX β-Cyclodex, 100 °C, 14 psi, 20:1 split), 94% ee (**4f**)

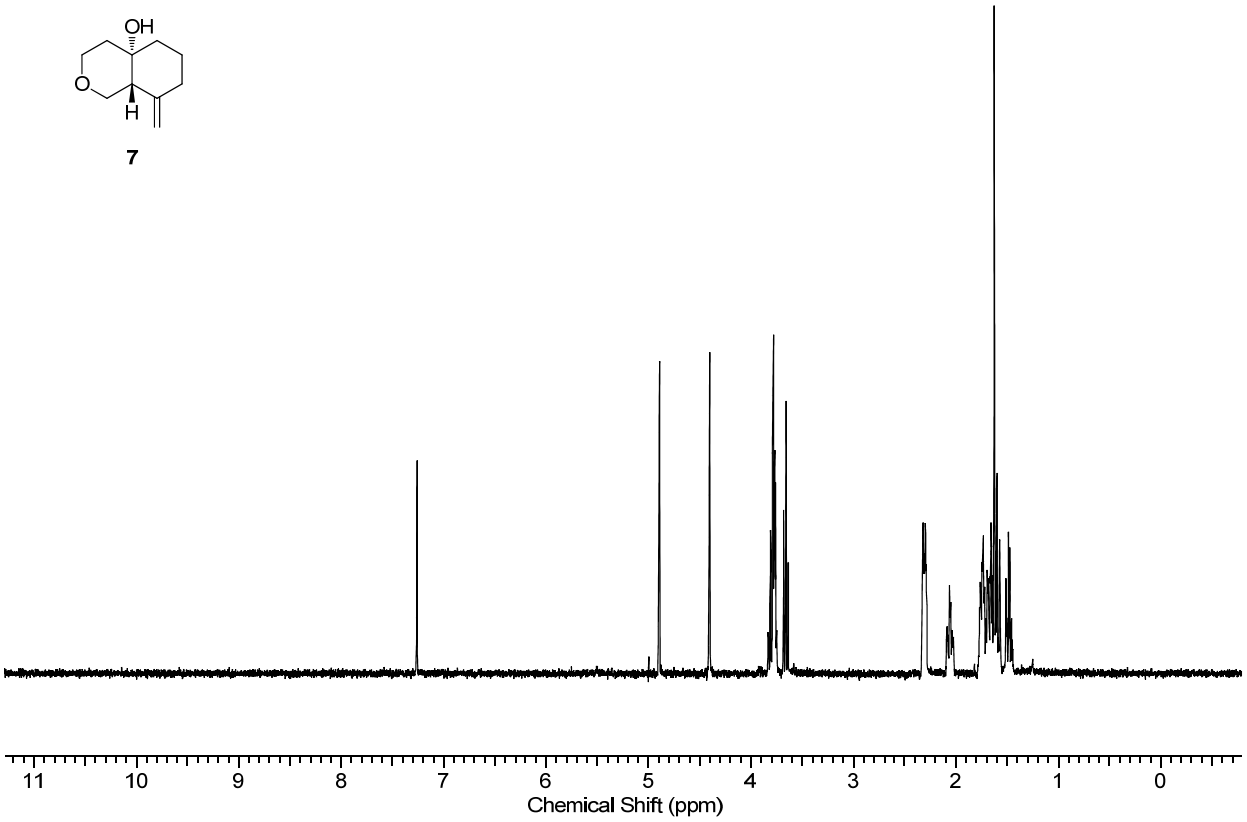


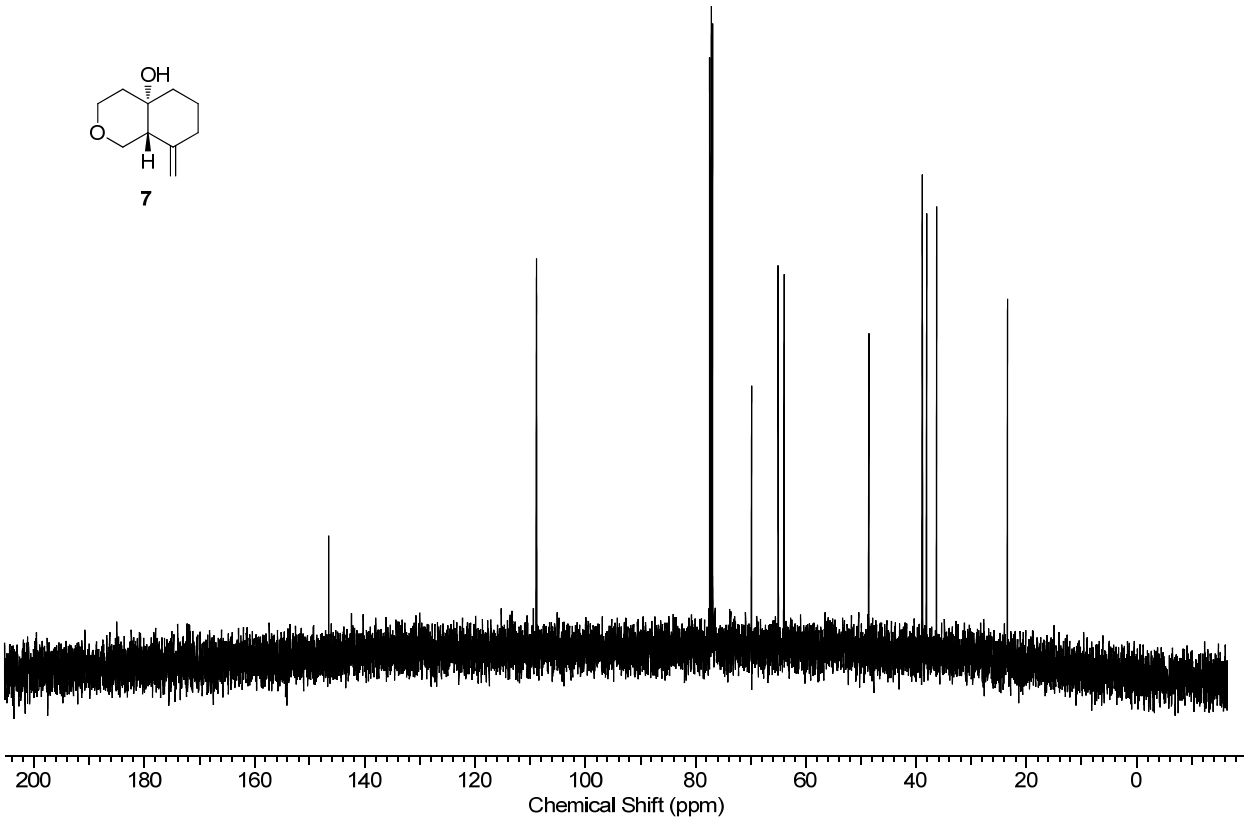

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 44.844 | MM | 0.3666 | 20.58225 | 9.35815e-1 | 2.93562 |
| 2 | 48.313 | MM | 0.6184 | 680.53912 | 18.34250 | 97.06438 |

**Racemic Sample**: GC (CHIRALDEX β-Cyclodex, 100 °C, 14 psi, 20:1 split) (**4f**)

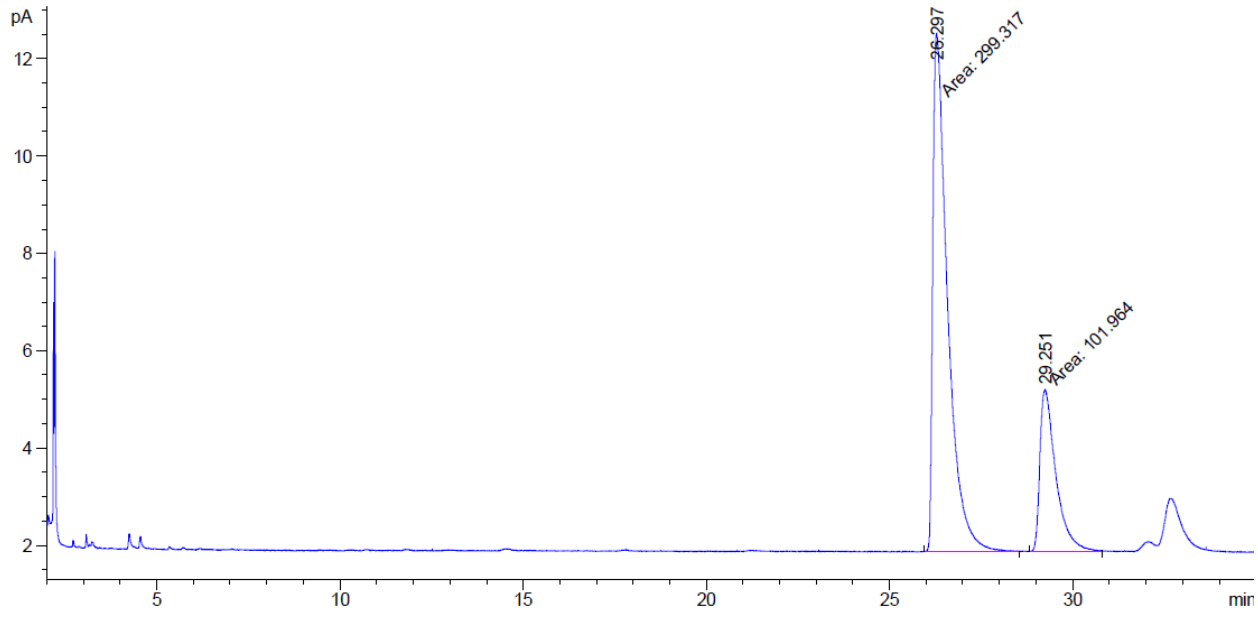



| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 45.260 | MM | 0.3893 | 192.34784 | 8.23389 | 49.80364 |
| 2 | 49.370 | MM | 0.4405 | 193.86458 | 7.33464 | 50.19636 |


OH
O
H
7
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

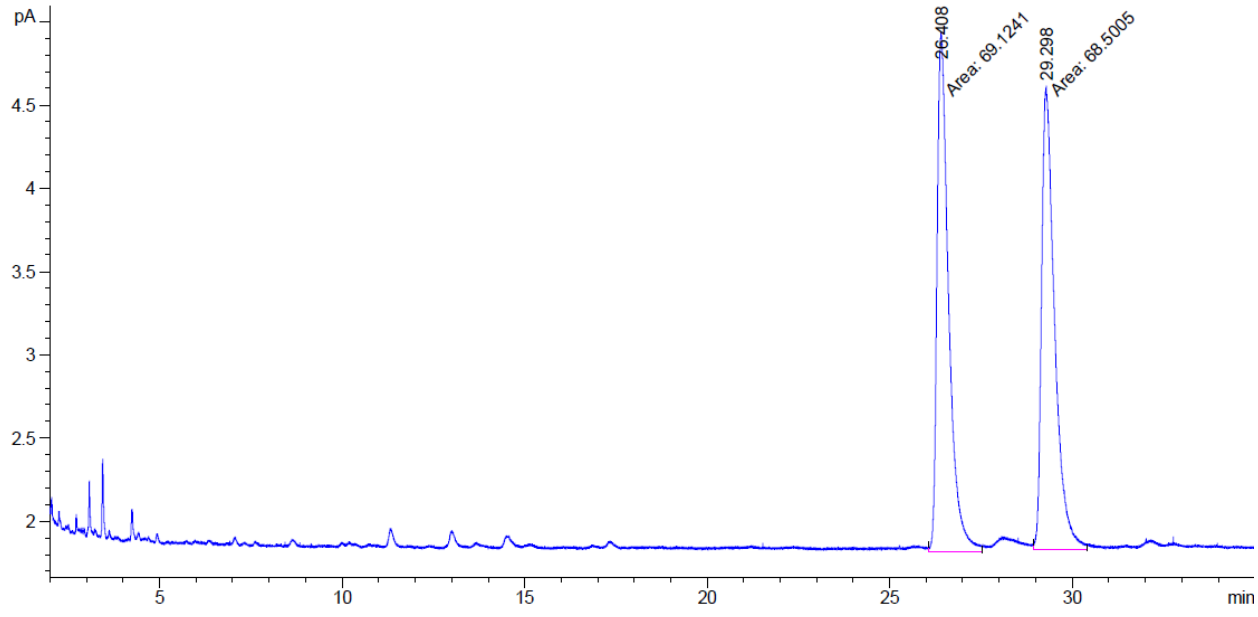

OH
O
H
7
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

**Enantioenriched Sample**: GC (CHIRALDEX γ-TA, 100 °C, 14 psi, 20:1 split) (**7**), 49% ee

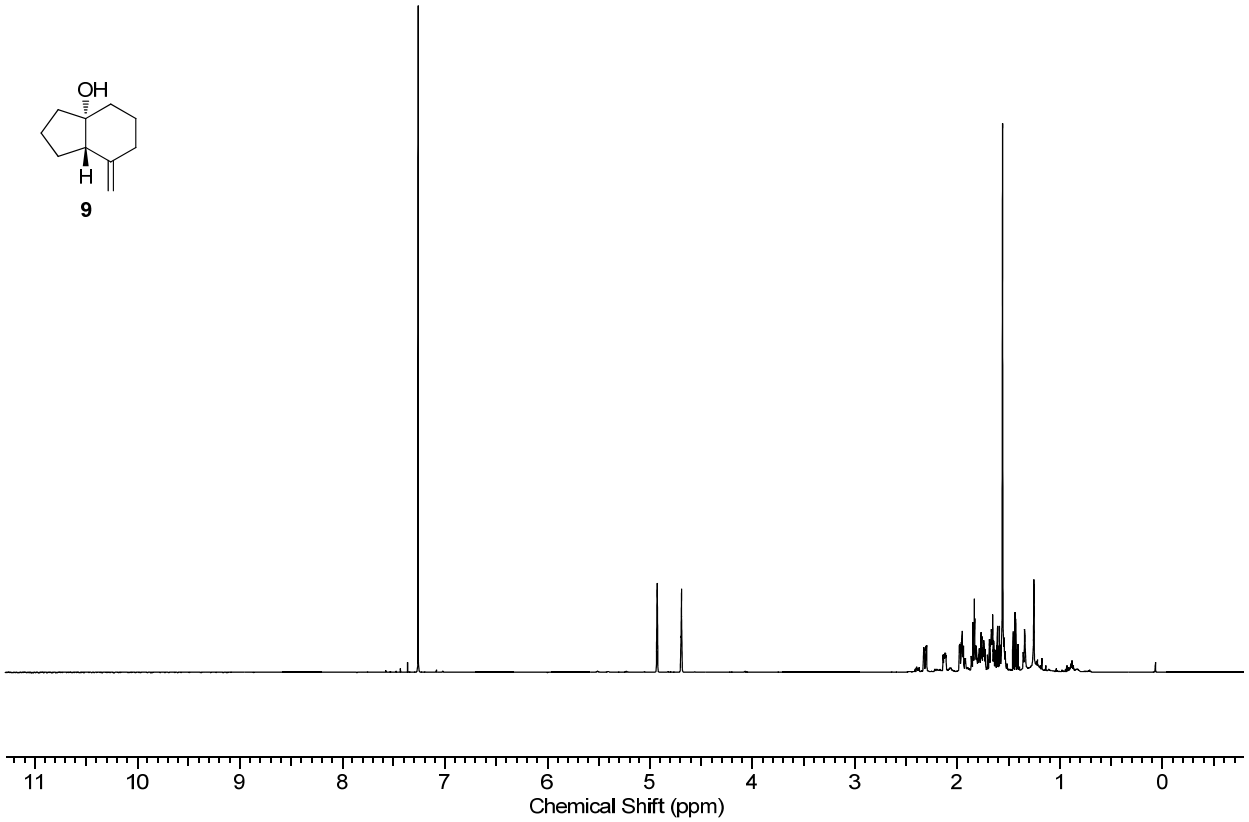


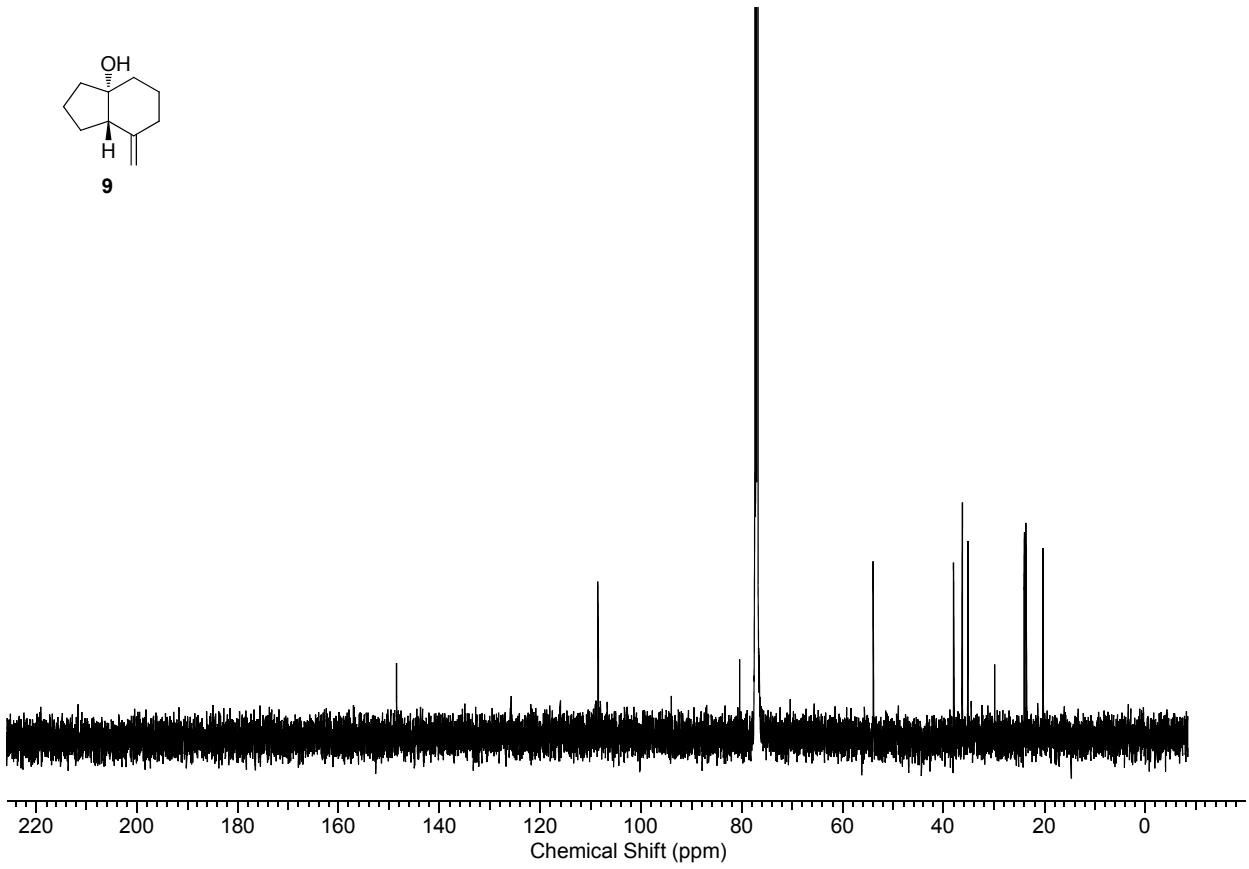

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 26.297 | MM | 0.4684 | 299.31699 | 10.65121 | 74.59040 |
| 2 | 29.251 | MM | 0.5076 | 101.96384 | 3.34772 | 25.40960 |

**Racemic Sample**: GC (CHIRALDEX β-Cyclodex, 100 °C, 14 psi, 20:1 split) (**7**)

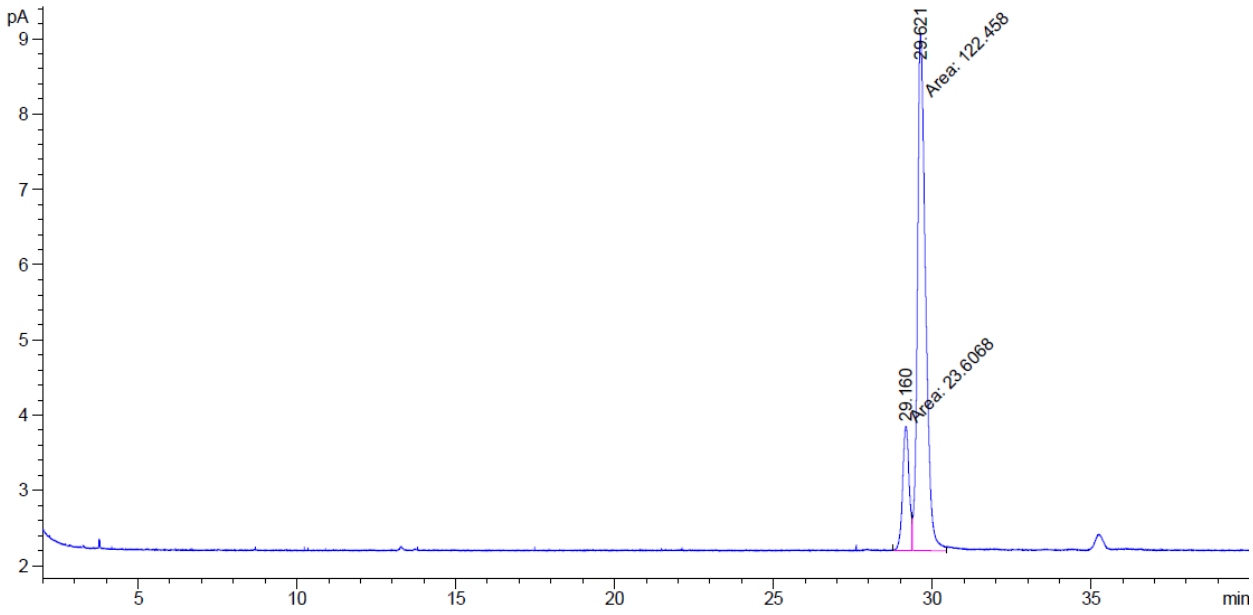



| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 26.408 | MM | 0.3691 | 69.12410 | 3.12137 | 50.22655 |
| 2 | 29.298 | MM | 0.4099 | 68.50053 | 2.78531 | 49.77345 |


OH
H
9
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

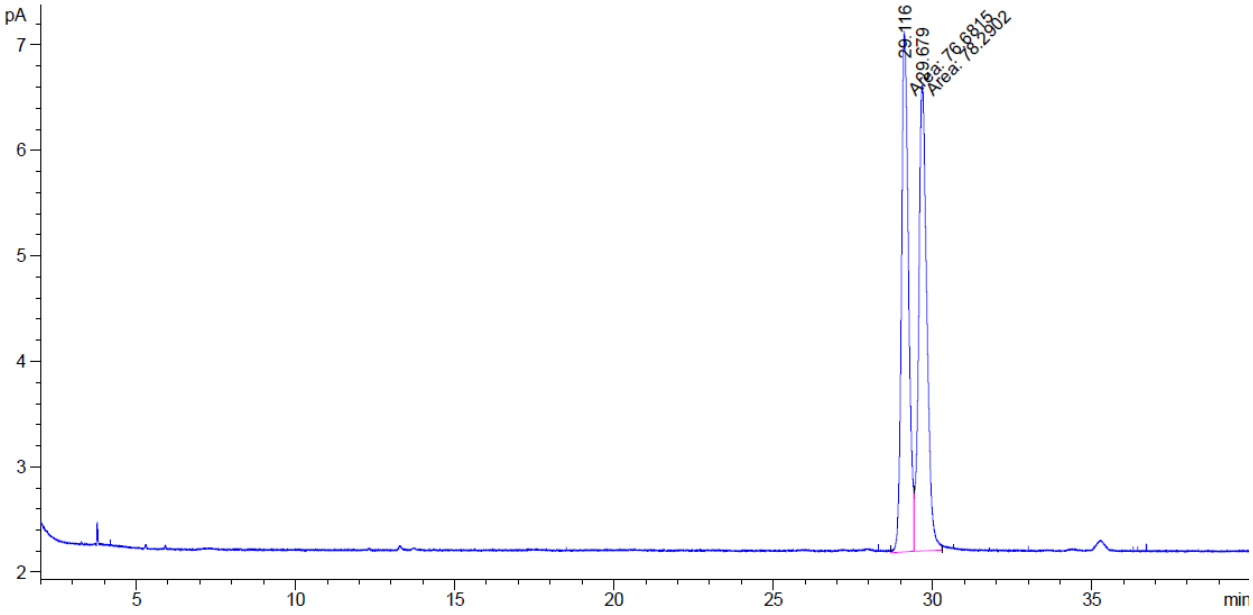

OH
H
9
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

**Enantioenriched Sample**: GC (CHIRALDEX β-Cyclosil, 90 °C, 14 psi, 100:1 split) (**9**), 68% ee

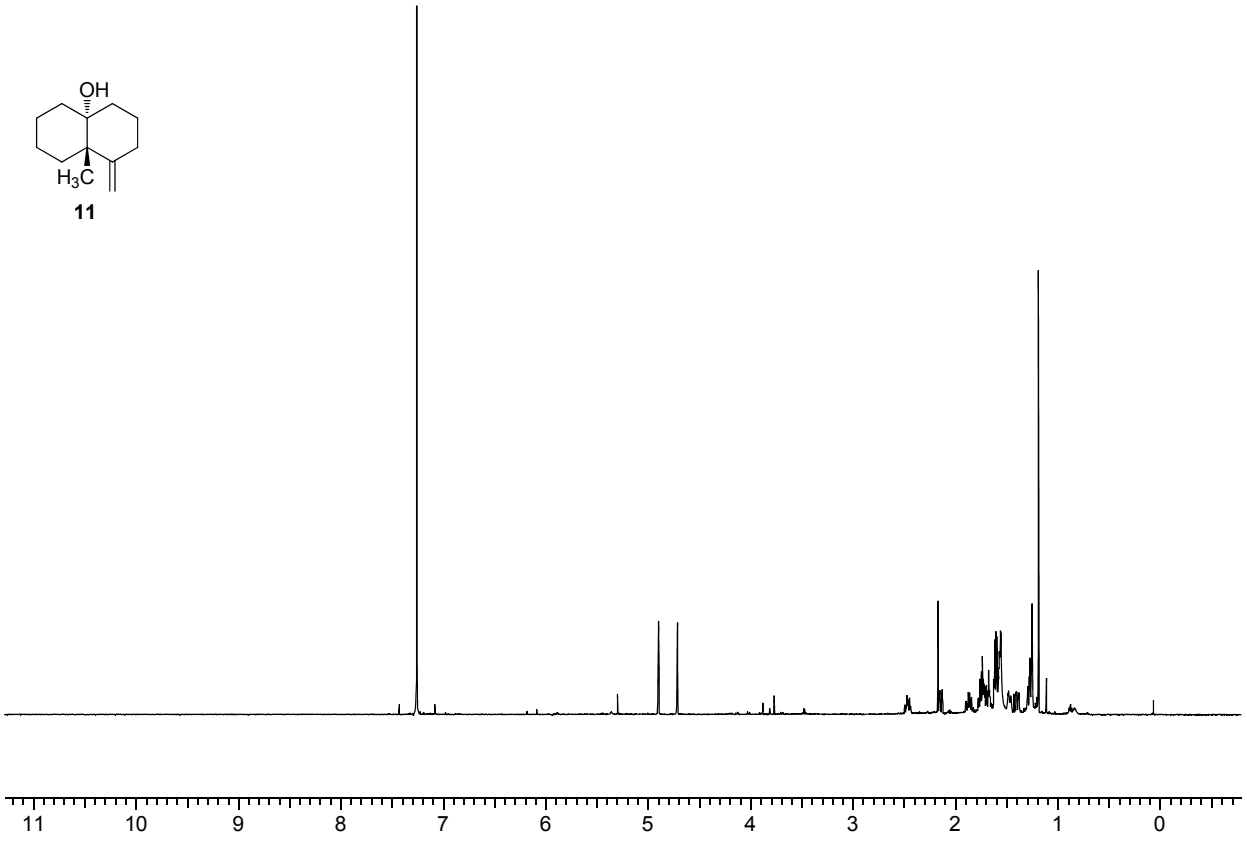


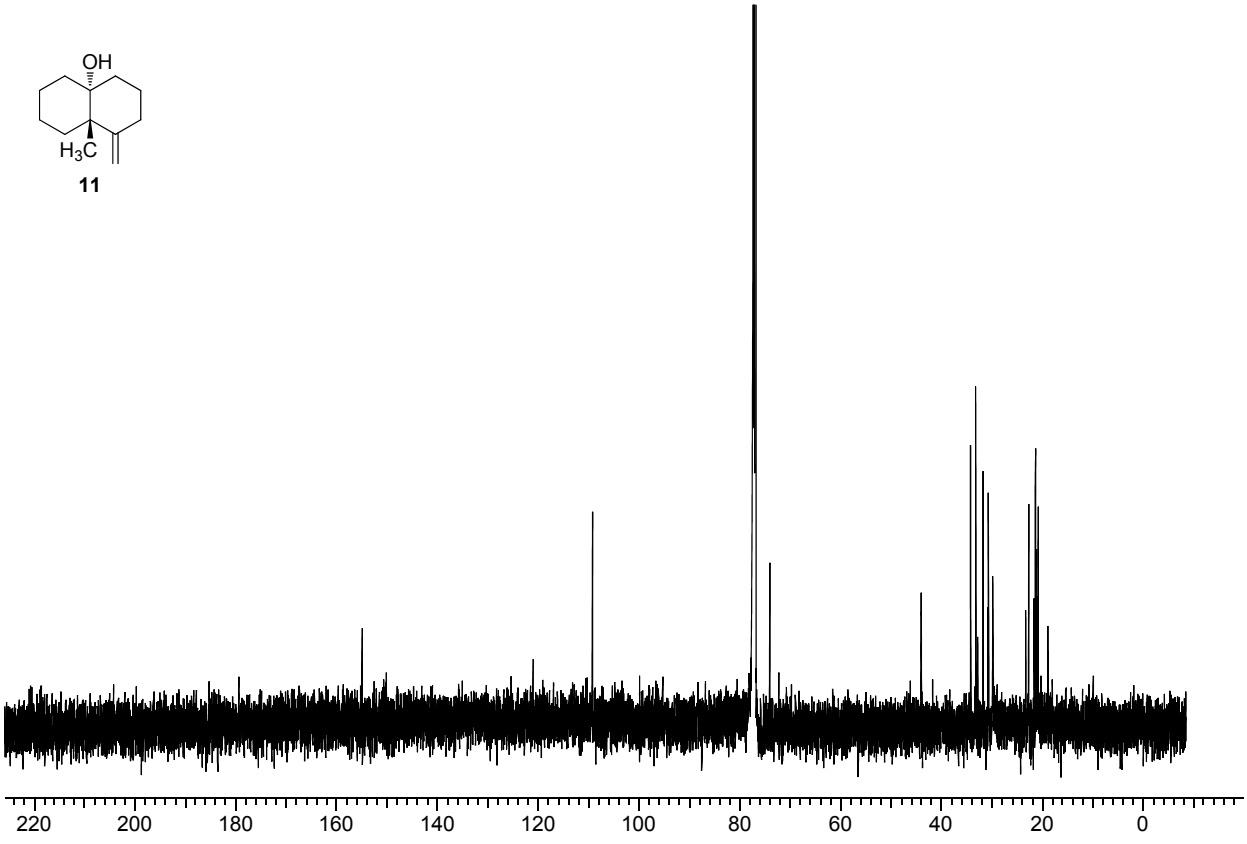

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 29.160 | MF | 0.2379 | 23.60683 | 1.65363 | 16.16185 |
| 2 | 29.621 | FM | 0.2968 | 122.45834 | 6.87763 | 83.83815 |

**Racemic Sample**: GC (CHIRALDEX β-Cyclosil, 90 °C, 14 psi, 100:1 split) (**9**)

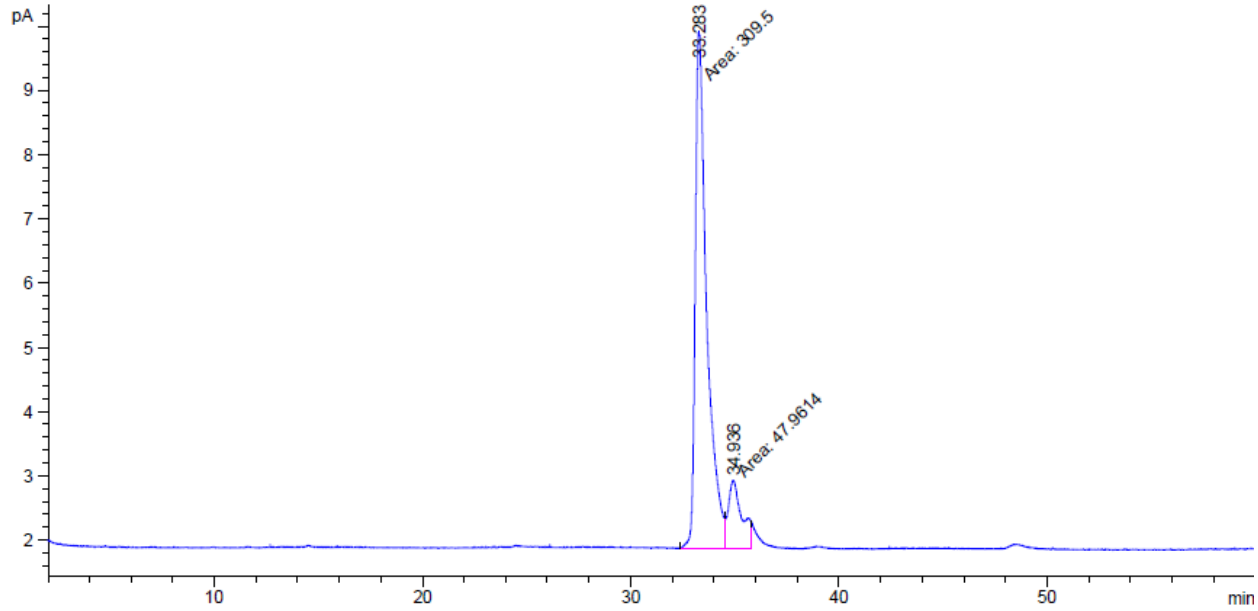



| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 29.116 | MF | 0.2596 | 76.68148 | 4.92253 | 49.48095 |
| 2 | 29.679 | FM | 0.2956 | 78.29025 | 4.41420 | 50.51905 |


OH
H3C
11
11
10
9
8
7
6
5
4
3
2
1
0

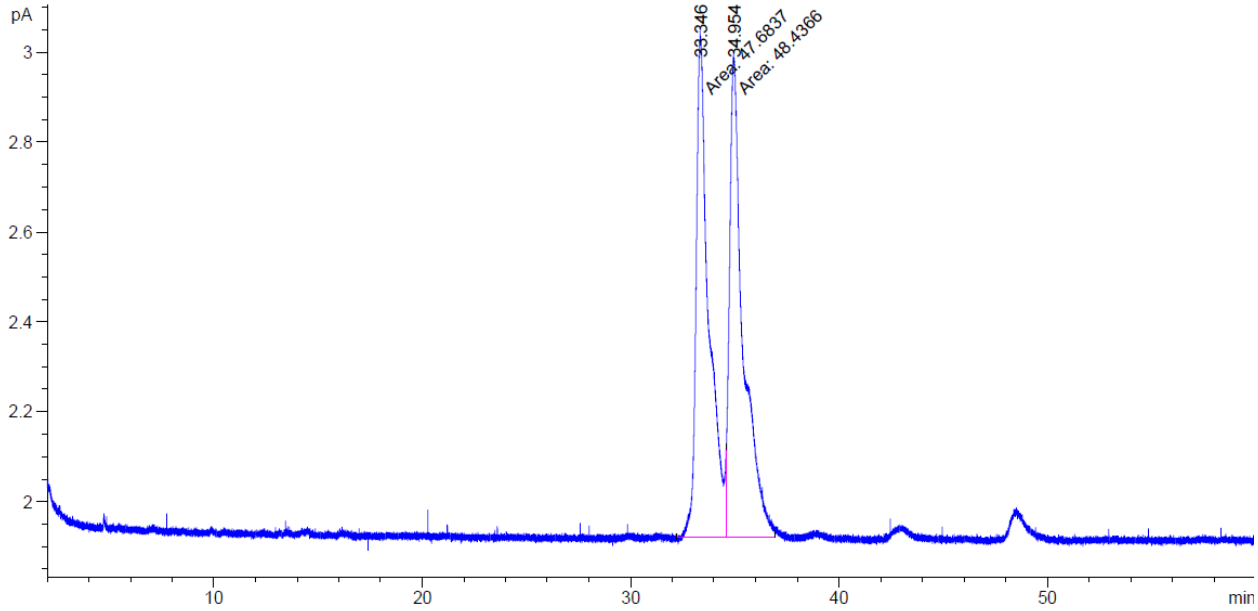

OH
H3C
11
220
200
180
160
140
120
100
80
60
40
20
0

**Enantioenriched Sample**: GC (CHIRALDEX γ-TA, 90 °C, 14 psi, 20:1 split) (**11**), 73% ee




| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 33.283 | MF | 0.6404 | 309.49951 | 8.05479 | 86.58276 |
| 2 | 34.936 | FM | 0.7558 | 47.96137 | 1.05756 | 13.41724 |

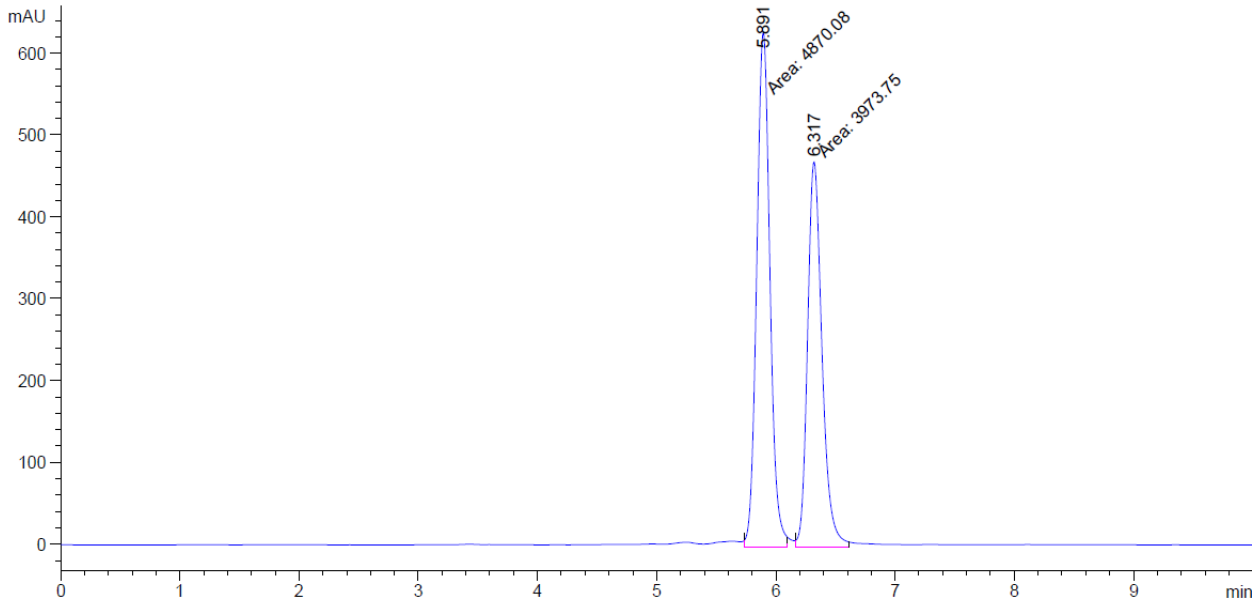
**Racemic Sample**: GC (CHIRALDEX γ-TA, 90 °C, 14 psi, 20:1 split) (**11**)




| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 33.346 | MF | 0.7056 | 47.68370 | 1.12627 | 49.60836 |
| 2 | 34.954 | FM | 0.7530 | 48.43658 | 1.07215 | 50.39164 |

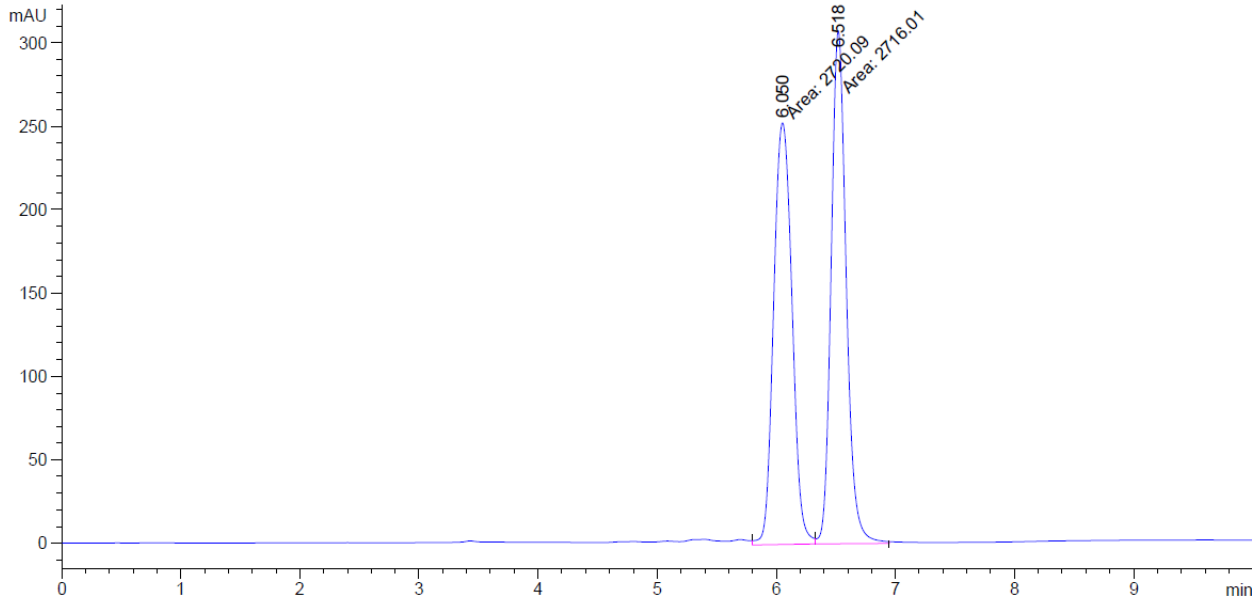
**Recovered 10**

**Enantioenriched Sample**: HPLC (CHIRALCEL OD-H, 2% IPA/hexanes, 1 mL/min, 210 nm), 10% ee



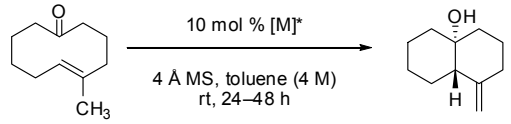

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.891 | MM | 0.1286 | 4870.08203 | 631.02441 | 55.0676 |
| 2 | 6.317 | MM | 0.1403 | 3973.74756 | 472.06912 | 44.9324 |

**Racemic Sample**: HPLC (CHIRALCEL OD-H, 2% IPA/hexanes, 1 mL/min, 210 nm) (**10**)

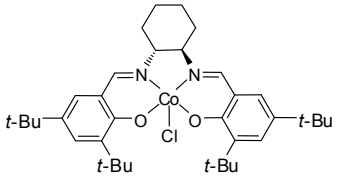



| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 6.050 | MF | 0.1791 | 2720.08545 | 253.08800 | 50.0375 |
| 2 | 6.518 | FM | 0.1470 | 2716.00781 | 308.03268 | 49.9625 |

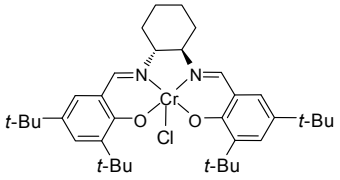
## G. Initial Screen of Chiral Lewis Acids for the Transannular Ketone-Ene Reaction



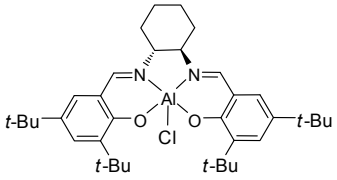

**1a** **4a**



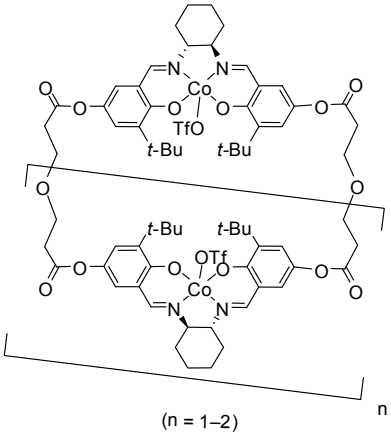

0% (14%)[a]



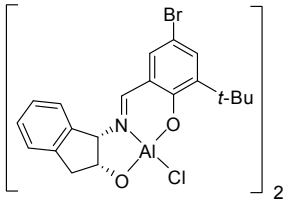

0% (11%)[a]



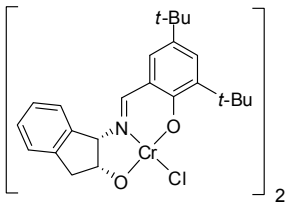

5% (9%)[a]
dr ND, ee ND




(n = 1–2)
0% (14%)[a]

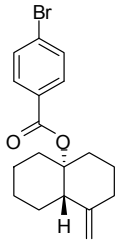



4% (8%)[a]
dr ND, ee ND




62% (100%)[b]
> 19 : 1 dr,[c] –79% ee[d]

[a]Yields and conversions (in parantheses) were deteremined by $^1$H NMR analysis of crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. [b] **1a** was completely consumed, and afforded **4a** as a single regioisomer and diastereomer, as deteremined by $^1$H NMR analysis of the crude reaction mixture. Yield was determined by isolation. [d]Determined by GC analysis using commercial chiral columns.



**S14**

**H. Determination of Absolute Configuration**

A solution of KHMDS in THF (1.0 M, 0.36 mL, 0.36 mmol, 5 equiv) was added dropwise to a stirred solution of enantioenriched **(+)-4a** (93% ee, 12 mg, 0.072 mmol, 1 equiv) in THF at 0 $^{o}$C and under a positive pressure of $N_2$. The resultant solution was stirred at 0 $^{o}$C for 30 m, at which point a solution of *p*-bromo-benzoyl chloride in THF (0.86 M, 0.5 mL, 0.43 mmol, 6 equiv) was added in one portion. The reaction vial was sealed with parafilm and stirred at 4 $^{o}$C for 16 h, after which it was quenched by slow addition of DI $H_2O$ (1 mL) and extracted with $Et_2O$ (3 x 0.5 mL). The combined organics were diluted with dichloromethane (1 mL), dried with $Na_2SO_4$, filtered, and concentrated to afford a white solid. The crude product was purified by column chromatography (Biotage, $SiO_2$, 0 to 5% $Et_2O$/hexanes) to afford a clear oil, which was re-evaporated from hexanes twice to afford the desired benzoate **S14** as a white solid (13.3 mg, 0.038 mmol, 53% yield). R*f*=0.53 (5% $Et_2O$/hexanes); $^{1}$H NMR (500 MHz, $CDCl_3$) δ ppm 7.87 (d, *J*=8.30 Hz, 2 H) 7.55 (d, *J*=8.79 Hz, 2 H) 4.87 (d, *J*=1.46 Hz, 1 H) 4.76 (d, *J*=1.46 Hz, 1 H) 2.82 - 2.98 (m, 2 H) 2.33 - 2.45 (m, 1 H) 2.11 (td, *J*=12.70, 4.88 Hz, 1 H) 1.96 (t, *J*=7.81 Hz, 1 H) 1.82 (dd, *J*=12.21, 3.42 Hz, 1 H) 1.71 - 1.79 (m, 2 H) 1.62 - 1.70 (m, 1 H) 1.52 - 1.60 (m, 1 H) 1.27 - 1.51 (m, 5 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ ppm 164.5, 149.4, 131.7 (2 C), 131.3 (2 C), 127.7, 107.5, 85.5, 50.1, 36.5, 34.5, 34.4, 25.8, 24.4, 23.2, 21.5; FTIR (neat, cm$^{-1}$) 2932 (s) 2855 (m) 1715 (s) 1590 (m) 1484 (w) 1446 (m) 1397 (w) 1279 (s) 1259 (s) 1225 (w) 1173 (m) 1070 (m) 1012 (s) 911 (m) 848 (w) 758 (s). MS (ESI) *m/z* calc'd for $C_{18}H_{21}BrO_2$ $[M+H]^+$: 349.0798; found: 349.0803. $[\alpha]_D^{25}$= –17.1$^{o}$ (c=0.41, $CHCl_3$).

Slow evaporation of a hexanes solution of **S14** at room temperature afforded single crystals (white needles) suitable for X-ray analysis.